Final Program

2nd

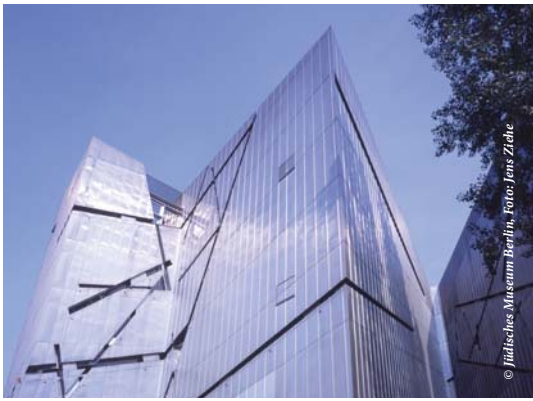
WCCL

2nd World Congress
of Cutaneous Lymphomas

6th

ISBICL

6th International Symposium on the Biology
and Immunology of Cutaneous Lymphoma



CUTANEOUS LYMPHOMAS

February 6–9
2013
Berlin, Germany

www.cutaneouslymphomas2013.com

Acknowledgements
The organizers gratefully acknowledge the support of the following companies:

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The 2nd World Congress of Cutaneous Lymphomas and the 6th International Symposium on the Biology and Immunology of Cutaneous Lymphoma was made possible by funds of the

DFG – Deutsche Forschungsgemeinschaft

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Venue
Langenbeck-Virchow-Haus
Luisenstrasse 58/59
10117 Berlin

The congress is supported by:

WELCOME ADDRESS

Dear Colleagues,

Following the immensely successful 1st World Congress of Cutaneous Lymphomas (WCCL) in Chicago with its clinical emphasis and the 5th International Symposium on the Biology and Immunology of Cutaneous Lymphoma (ISBICL) with its focus on basic and translational research, we are most delighted to invite you to join us at the 2nd WCCL/6th ISBICL 2013 in Berlin. This unique meeting will review both the latest research and development relating to cutaneous lymphomas and the clinical practice including new therapies and clinical trials. The congress is supported by the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium and the EORTC Cutaneous Lymphoma Task Force.

In addition to a rewarding congress program, the visit to Berlin will bring you right into touch with the profound political changes of recent years and into one of the most vibrant cultural centers of the world with numerous concerts, operas, theaters, cabarets, museums, exhibitions, fairs and off-stage events. All who have visited the city before will be amazed of the rapid developments and will find ever new paths to explore.

We look forward to welcoming you in Berlin for a certainly most exciting congress and a rich personal experience.

Yours cordially,

The International Program Committee
The Local Organizing Committee

WELCOME ADDRESS

Dear Colleagues,

It is a great pleasure to welcome you on behalf of the EORTC Cutaneous Lymphoma Task Force Board to the second World Congress of Cutaneous Lymphoma 2013 in Berlin.

The first World Congress has proven to be an exceptional periodical meeting worldwide for physicians and researchers interested in cutaneous lymphoproliferative disorders. Our host in Chicago created an exciting atmosphere at Lake Michigan that stimulated every participant in the field of lymphoma and initiated a number of international co operations. I am sure that the spirit and the unique world city Berlin will provide the fascinating platform to enrich personal contacts, to exchange scientific ideas and to offer an ideal opportunity to build collaborations and social contacts among all participants. Meanwhile, the EORTC Lymphoma Board has established a clinical study platform for CTCL all over Europe. This is the first promising step for developing translational research and therapeutic progress. We invite everybody to participate in our engagement for lymphoproliferative disorders. I am sure that Prof. Wolfram Sterry and Prof. Peter Walden with their team created a most interesting scientific program that will give you all the information on the latest developments. I personally thank both of them for their outstanding engagement in scientific research and their willingness to host and welcome the lymphoma world in Berlin.

We are all looking forward to exciting days among friends in the centre of Europe.

Cordially yours,

Rudolf Stadler
EORTC CLTF President

WELCOME ADDRESS

Dear Colleague,

Welcome to the 2nd World Congress of Cutaneous Lymphomas/6th International Symposium on the Biology and Immunology of Cutaneous Lymphoma! On behalf of the Board of Directors of the International Society for Cutaneous Lymphomas (ISCL), we wish to thank you for your support and participation.

If you are not currently a member of the ISCL, we would like to take this opportunity to encourage you to consider joining. For convenience, an application is included on page 183.

The ISCL was founded in 1992 at the World Congress of Dermatology in New York to foster communication and stimulate interactions among regional and national groups and individuals interested in cutaneous lymphomas.

The aims of the society are to:

A. Increase knowledge of lymphoproliferative and related disorders of the skin.
B. Foster collaboration among clinicians, scientists and regional or national groups by being sponsor of an international registry of cutaneous lymphomas.
C. Promote dissemination of scientific information by organizing meetings.
D. Favor consensus about diagnosis, management and treatment of cutaneous lymphoma.

You may join as a:

- **General Member** (physician or scientist actively involved in the care of patients with lymphoproliferative skin disorders or engaged in research in this or a related area);
- **Associate Member** (allied healthcare professional, an individual or entity that grants financial support to the Society or an individual involved in a cutaneous lymphoma patient support group who is interested in, and supports, the purposes of the Society); or
- **Resident Member** (granted to any physician in good standing who is in a residency program or post-residency fellowship and is interested in the field of cutaneous lymphoproliferative disorders).

Thank you and sincere regards,

Sean Whittaker, MD
President

Youn H. Kim, MD
Secretary-Treasurer

Program Schedule

Room: Auditorium

Wednesday, February 6, 2013		Thursday, February 7, 2013			Friday, February 8, 2013		Saturday, February 9, 2013	
		08:30–10:10	Genomics and Genetics		08:30–10:20	Immunology I	08:30–10:00	Molecular Cell Biology (Cell Signaling)
		10:10–10:40	Coffee Break		10:20–10:50	Coffee Break	10:00–10:25	Coffee Break
		10:40–12:30	Genetics and Epigenetics		10:50–12:30	Immunology II	10:25–11:45	Molecular Cell Biology (Apoptosis)
13:00–13:05	Welcome	12:30–14:00	Lunch and Symposium Teva		12:30–13:30	Lunch and Symposium Millennium	11:45–12:15	Coffee Break
13:05–15:00	Diagnostic in Cutaneous Lymphomas	14:00–15:40	Targeted Therapies for Cutaneous Lymphomas		13:30–15:00	Current Therapies I	12:15–13:25	On-Going and Prospective Clinical Trials
15:00–15:25	Coffee Break	15:40–16:10	Coffee Break		15:00–15:30	Coffee Break	13:45–14:00	Valediction
15:25–17:05	Biomarkers (Diagnostic and Prognostic)	16:10–17:40	Difficult to Treat/Rare Lymphomas		15:30–17:00	Current Therapies II		
17:05–17:30	Coffee Break	17:40–18:10	Coffee Break		17:00–17:30	Coffee Break		
17:30–19:00	Systems Medicine: Prospects for the Therapy and Management	18:10–19:30	Society Meeting Poster Session		17:30–19:00	Cutaneous Lymphomas Disease Management		
19:00	Poster Session with Wine and Cheese Welcome Party (Get Together)	19:30	Poster Session Social Gathering		19:30	Conference Dinner		

13:00–13:05 Welcome
Sterry W

13:05–15:00 Diagnostics in Cutaneous Lymphomas

Chairs: Cozzio A, Whittaker S, Humme D

O-001 Mycosis fungoides and sèzary syndrome: different stages of the same disease or distinct entities? 15 + 5
Willemze R

O-002 Histopathology of sèzary syndrome in contrast to other erythrodermic skin diseases 15 + 5
Klemke C-D, Booken N, Goerdt S, Felcht M, Nicolay JP, Géraud C, Kempf W, Assaf C, Ortonne N, Batistella M, Bagot M, Knobler R, Quaglino P, Arheiliger B, Santucci M, Jansen P*, Willemze R*, Vermeer MH**

O-003 Diagnostic issues raised by the presence of CD20-positive cells in transformed mycosis fungoides 8 + 4
Jullie ML, Prochaskova-Carlotti M, Beylot-Barry M, Ortonne N, Frouin E, Carlotti A, de Muret A, Balme B, Merlio JP, Vergier B

O-004 Primary cutaneous B large cell lymphomas: A spectrum of histologic subtypes ranging from follicular to diffuse large B-cell lymphoma subtype – clinico-pathologic and molecular analysis of 173 caases 8 + 4
Lucioni M, Berti E, Arcaini L, Tomasini C, Quaglino P, Goteri G, Pimpinelli N, Gambacorta M, Santucci M, Paulli M

O-005 High rate of TCRγ gene rearrangement with clonal identity in microdissected CD30+ cells from lymphomatoid papulosis 8 + 4
Riboni R, Lucioni M, Arcaini L, Nicola M, Maffi A, Dallera E, Arra M, Molo S, Berti E, Paulli M

O-006 Spectrotyping of rearranged T-cell receptor Vβ genes in folliculotropic mycosis fungoides does not show restricted gene rearrangements 8 + 4
Mantaka P, Malecka A, Trøen G, Helsing P, Gjersvik P, Delabie J

O-007 Cutaneous follicular helper T-cell lymphomas: a series of 6 cases highlighting new clinical-pathological aspects and the possible occurrence of ITK-SYK rearrangements 8 + 4
Ortonne N, Martin N, Chatelain D, Chaby G, Carlotti A, Lecaudey-Hansen MH, Comoz F, Gaulard P

O-008 Phenotype instability in sèzary cells: follow-up results in 107 patients 8 + 4
Fierro MT, Novelli M, Ponti R, Savoia P, Fava P, La Selva R, Sarda C, Quaglino P, Bernengo MG

15:00–15:25 Coffee Break

15:25–17:05 Biomarkers (Diagnostic and Prognostic)

Chairs: Kempf W, Wong H, Hwang S

O-009 Insights into cutaneous T-cell lymphomas 15 + 5
Whittaker S

O-010 KIR3DL2/CD158K as diagnostic marker and new therapeutic target for cutaneous T-cell lymphomas 15 + 5
Bagot M, Michel L, Marie-Cardine A, Bensusann A

O-011 Immunocytochemical P63 expression in primary cutaneous B-cell lymphoma; further evidence for pathogenetic heterogeneity 8 + 4
Shukur Z, Coates P, Goodlad J, Sahni D, Robson A

O-012 Validation of diagnostic and prognostic biomarkers for sèzary syndrome 8 + 4
Zoutman WH, Boonk SE, van der Fits L, Whittaker S, Bagot M, Klemke C-D, Ranki A, Bernengo MG, Willemze R, Vermeer MH

O-013 A recurrent rearrangement of 6p25.3 and unique pathology identify a previously unrecognized subtype of lymphomatoid papulosis 8 + 4
Karai LJ, Kadin ME, Hsi ED, Sluzevich JC, Ketterling RP, Knudson RA, Feldman AL

O-014 BAP1 Protein expression is frequently lost in cutaneous lesions of blastic plasmacytoid dendritic cell neoplasm and chronic myelomonocytic leukemia 8 + 4
Gammon B, Kim J

O-015 Immediate-early gene reactivation signal, BZLF1 expression, is a molecular marker for a poor prognosis of epstein-barr virus-associated T/NK lymphoproliferative skin diseases 8 + 4
Iwatsuki K, Yamamoto T, Hirai Y, Miyake T

17:05–17:30 Coffee Break

17:30–19:00 Systems Medicine: Prospects for the Therapy and Management

Chairs: Sterry W, Duvic M, Walden P

O-016 The future of medicine (and health) 20 + 3
Lehrach H

O-017 So many data – and so few consequences: can a "medical cloud" help to bridge the gap between advances In research and clinical work? 20 + 3
Dress A

O-018 Personalized medicine: epigenetic and genetic features that modulate the effects of methotrexate and interferon-alpha in CTCL 20 + 3
Wood GS, Wu J, Stutz N, Salva K, Nihal M

O-019 Systematic toponome decoding of disease machanisms in human tissues 20 + 3
Schubert W

19:00 Poster Session with Wine and Cheese, Welcome Party (Get Together)

08:30–10:10 Genomics and Genetics

Chairs: Tensen C, Vandersee S, Möbs M

O-020 Whole exome sequencing provides insights in driver mutations, clonal architecture and genomic evolution in multiple myeloma 20 + 5
Bolli N

O-021 Chromosomal rearrangements at 6p25.3 in cutaneous T-cell lymphomas highlight the role of the DUSP22 phosphatase in oncogenesis 20 + 5
Cappellen D, Idrissi Y, Prochazkova-Carlotti M, Laharanne E, De Souza Goes AC, Chevret E, Moreau-Gaudry F, Pham-Lédard A, Beylot-Barry M, Merlio J-P

O-022 A novel (recurrent) translocation in C-ALCL 8 + 4
Benner MF, Van den Burg M, Ngarmlertsirichai P, Przybylski GK, Grabarczyk P, Vermeer MH, Willemze R, Szuhai K, Schmidt CA, Tensen CP

O-023 Cytogenetic stability of sèzary syndrome in sequential samples 8 + 4
Prochazkova-Carlotti M, Laharanne E, Pham-Ledard A, Soler G, Chevret E, Beylot-Barry M, Merlio J-P

O-024 Identification of multiple complex rearrangements associated with deletions in the 6q23-27 region in sèzary syndrome 8 + 4
Iżykowska K, Zawada M, Nowicka K, Grabarczyk P, Braun FCM, Delin M, Möbs M, Beyer M, Sterry W, Schmidt CA, Przybylski GK

O-025 ARRAY-CGH analysis and microrna profiling in a cohort of sèzary syndrome patients 8 + 4
Corti L, Fanoni D, Saporiti G, Venegoni L, Narducci MG, Cristofoletti C, Russo G, Cortelezzi A, Onida F, Berti E

10:10–10:40 Coffee Break

10:40–12:30 Genetics and Epigenetics

Chairs: Wasik MA, Hummel M, Gniadecki R

O-026 Genome-wide analysis of DNA methylation in sèzary syndrome 20 + 5
Vermeer MH, Boonk S, van der Fits L, Zoutman W, Goeman J, Heijmans B, van Doorn R

O-027 Mutational studies in mycosis fungoides 20 + 5
Ortiz Romero PL, Vaqué JP, Gómez-López G, Monsálvez V, de Benito SG, Varela I, Martínez N, Cereceda L, del Olmo SC, Domínguez O, Graña O, Rodríguez-Peralto JL, Rodríguez-Pinilla SM, González-Vela C, Requena L, Rubio-Camarillo M, Martín E, Papadavid E, Papadaki T, Méndez M, García-Marco JA, Provencio M, Hospital M, Suárez L, Postigo C, Piris MA, Sánchez-Beato M

O-028 What can we learn from telomeres status and telomerase functions in primary cutaneous T-cell lymphoma? 8 + 4
Chevret E, Andrique L, Prochazkova-Carlotti M, Ferrer J, Cappellen D, Laharanne E, Idrissi Y, Pham-Ledard A, Beylot-Barry M, Merlio J-P

O-029 Primary cutaneous diffuse large B-cell lymphoma, leg-type harbours the genetic profile of noda activated B-cell diffuse large B-cell lymphoma 8 + 4
Pham-Ledard A, Carlotti M, Cappellen D, Martinez F, Gachard N, Deveza M, Feuillard J, Vergier B, Beylot-Barry M, Merlio J-P

O-030 Molecular analysis of primary cutaneous aggressive T-cell lymphomas: aggressive epidermotropic CD8+ lymphoma and peripheral T-cell lymphoma, unspecified 8 + 4
Fanoni D, Tensen CP, Novara F, Venegoni L, Corti L, Violetti SA, Onida F, Paulli M, Willemze R, Berti E

O-031 Aberrant gene expression and promoter methylation as biomarker for sèzary syndrome 8 + 4
Mishra A, Hake T, Gibson H, Sullivan L, Porcu P, Wong HK

O-032 HERV-W transcription and SYNCYTIN-1 expression in mycosis fungoides provides new insight into cutaneous T-cell lymphoma pathogenesis 8 + 4
Maliniemi P, Vincendeau M, Mayer J, Frank O, Hahtola S, Karenko L, Carlsson E, Mallet F, Seifarth W, Leib-Mösch C, Ranki A

12:30–14:00 Lunch Break

12:30–14:00 Symposium
TEVA GmbH: Retinoids and Novel Treatment Perspectives in CTCL

Chair: Jürgen Becker, Graz, Austria

The optimal use of bexarotene in CTCL
Gniadecki R

Combination therapy in CTCL using retinoids
Stadler R

Bexarotene side effect management and maintenance therapy in CTCL
Assaf C

Effect of Bexaterone in CTCL other than classical MF
Weichenthal M

Programmed death 1 expression in CTCL – implications for diagnosis and treatment
Willemze R

14:00–15:40 Targeted Therapies for Cutaneous Lymphomas

Chairs: Kim Y, Guitart J, Prince M

O-033 Targeting signaling pathways in lymphoid malignancies: applications for cutaneous lymphomas 20 + 5
Horwitz S

O-034 Monoclonal antibodies and fusion proteins in cutaneous lymphomas 20 + 5
Geskin LJ

O-035 CD30+ cutaneous T-cell lymphoma and response to brentuximab vedotin: three illustrative cases 8 + 4
Knackstedt T, Mody K, Zug K, Lansigan F

O-036 Targeting signaling pathways in mycosis fungoides and sèzary syndrome 8 + 4
Ai W, Rakhshandhroo T, Pincus L, McCormick F, Bandyopadhyay S

O-037 CD40-activated B-cells as cellular adjuvants: lymphnode homing and T-cell interaction 8 + 4
von Bergwelt-Baildon M, Klein-Gonzalez N, Schlaak M, Theurich S

O-038 Exploring the IL-21 – STAT3 axis as therapeutic target for sèzary syndrome 8 + 4
van der Fits L, Out-Luiting JJ, Zoutman WH, Willemze R, Vermeer MH

15:40–16:10 Coffee Break

16:10–17:40 Difficult to Treat/Rare Lymphomas

Chairs: Willemze R, Assaf C, Foss F

O-039 Cutaneous manifestations of extranodal NK/T-cell lymphoma, nasal-type — 20 + 5
Cerroni I, Fried I

O-040 Adult T-cell leukaemia/Lymphoma: impaired innate immunity of the skin — 20 + 5
Tokura Y

O-041 Clinicopathologic features, prognosis, and therapeutic responses in patients with grannulomatous mycosis fungoides: results of a united states case-control study — 8 + 4
Querfeld C, Li JY, Dusza SW, Myskowski PL, Horwitz S, Moskowitz A, Pulitzer MP

O-042 Blastic plasmacytoid dentritic cell neoplasm: Clinical features in 90 patients — 8 + 4
Julia F, Petrella T, Beylot-Barry M, Bagot M, Lipsker D, Machet L, Joly P, Dereure O, Wetterwald M, d'Incan M, Grange F, Cornillon J, Tertian G, Maubec E, Saiaiag P, Dalac S, Dalle S

O-043 Subcutaneous panniculitis-like t-cell lymphoma: a multicentric clinical and pathologic report of the french cutaneous lymphoma group (GFELC) experience — 8 + 4
Michonneau D, Bruneau J, Boccara O, Hermine O, Maynadié M, Petrella T, Brousse N, Fraitag S

17:40–18:10 Coffee Break

18:10–19:30 Society Meetings
Poster Session

19:30 Poster Session
Social Gathering

08:30–10:20 Immunology I

Chairs: Rook A, Clark R, Klemke C-D

O-044 The role of macrophages in a murine model of inflammation-dependent T-cell lymphoma in skin — 20 + 5
Hwang S

O-045 A New Mouse Model for studying NF-kB Effects in CTCL — 8 + 4
Nicolay JP, Müller-Decker K, Krammer PH, Gülow K

O-046 CD8 + cytotoxic action combined with changes in paracrine microenvironment of epidermal melanocytic unit collaborate for melanogenesis inhition in hypopigmented mycosis fungoides — 8 + 4
Furlan FC, Pereira BAP, Silva LFF, Sanches JA

O-047 Th1, Th2, Th17 and T reg expression in cutaneous T-cell lymphoma patients: modulation of master gene targets — 8 + 4
Quaglino P, Ponti R, Bergallo M, Fierro MT, Fava P, Barberio E, Terlizzi ME, Astegiano S, Bernengo MG

O-048 CD30 lymphoproliferative disorder with pseudoepitheliomatous hyperplasia: possible role of TH17 cytokines, neutrophils and eosinophils — 8 + 4
Guitart J, Deonizio J, Kadin ME

O-049 Genetic association between TLR9/MyD88 polymorphisms and sézary syndrome risk — 8 + 4
Tamouza R, Michel L, Busson M, Jean-Louis F, Amokrane K, Charron D, Bensussan A, Bagot M, Toubert A

O-050 CD160 and CD158k are unique markers for CD4+ cutaneous T-lymphocytes — 8 + 4
Schmitt C, Michel L, Schiavon V, Dessirier V, Marie-Cardine A, Olive D, Bagot M, Bensussan A

O-051 An angiopoietin-2^{high} Tie2^{low} endothelial phenotype correlates with an aggressive clinical course in primary cutaneous B-cell lymphoma — 8 + 4
Stumpf C, Teichert M, Booken N, Wobser M, Nashan D, Dippel E, Müller CSL, Becker JC, Sachse MM, Nicolay JP, Goerdt S, Thomas M, Klemke C-D, Augustin HG, Felcht M

10:20–10:50 Coffee Break

10:50–12:30 Immunology II

Chairs: Bensussan A, Vermeer M, Nicolay JP

O-052 The importance of the host immune response in the treatment of cutaneous T-cell lymphoma 20 + 5
Rook AH, Wysocka M, Benoit B, Vittorio CC, Stephen S, Kim EJ, French LE

O-053 CTCL immunobiology: how an understanding of T-cell recirculation can guide therapy 20 + 5
Clark R

O-054 Immunotherapy strategies in cutaneous T-cell lymphoma 20 + 5
Kim YH

O-055 Expression of follicular helper T-cell marker PD-1 in cutaneous B-cell lymphomas – correlation with biologic behavior 8 + 4
Mitteldorf C, Bieri M, Wey N, Pfaltz M, Kutzner H, Roncador G, Tomasini D, Kempf W

O-056 Programmed death-1 expression in cutaneous B-cell lymphomas 8 + 4
Çetinözman F, Koens L, Jansen PM, Willemze R

12:30–13:30 Lunch Break

12:30–13:30 Lunch Symposium
Millennium – The Takeda Oncology Company: Advanced-stage mycosis fungoides and Sézary syndrome – an unmet medical need

Chair: Sean Whittaker (Chairman)

Introduction

Outcomes for advanced disease
Whittaker S

Treatment approaches/Case studies:

Stage IIB mycosis fungoides
Hoppe R

Stage IVA mycosis fungoides
Prince M

Stage IVA Sézary syndrome
Zinzani PL

Panel discussion

Future role for radiotherapy
Hoppe R

Future role for chemotherapy
Prince M

Future role for biologic therapy
Zinzani PL

Summary and close
Whittaker S

13:30–15:00 Current Therapies I

Chairs: Stadler R, Horwitz S, Zinzani P

O-057 Therapy of advanced CTCL: what we know and what we need to know 20 + 5
Dummer R, Goldinger SM, Kempf W, Cozzio A

O-058 A novel non-myeloablative allogeneic transplant induces molecular remission assessed by high-throughput sequencing of T-cell receptor in mycosis fungodies and sèzary syndrome 8 + 4
Weng W-K, Armstrong R, Arai S, Krathan M, Million L, Hoppe R, Kim YH

O-059 Low dose total skin electron beam radiotherapy for mycosis fungoides. Initial experience of 12Gy in 8 fractions over 2 weeks 8 + 4
Morris S, Attard N, Child F, Whittaker S

O-060 Allogeneic stem cell transplantation in advanced stage mycosis fungoides and sèzary syndrome after non myeloablative conditioning with pentostatin and TBI200 8 + 4
Onida F, Saporiti G, Tagliaferri E, Annaloro C, Corti L, Grifoni F, Olivares C, Mometto G, Cortelezzi A, Berti E

O-061 Comorbidities, secondary cancers and mortality associated with nitrogen mustard therapy in patients with mycosis fungoides: a 30-year population-based cohort study 8 + 4
Lindahl LM, Fenger-Grøn M, Iversen L

O-062 Cutaneous toxicity associated with pralatrexate in cutaneous and peripheral T-cell lymphoma 8 + 4
Parker TL, Girardi M, Edelson R, Subtil A, Wilson LD, Barbarotta L, Foss F

15:00–15:30 Coffee Break

15:30–17:00 Current Therapies II

Chairs: Porcu P, Ranki A, Zic J

O-063 The future of HDAC inhibitors in cutaneous T-cell lymphomas 20 + 5
Stadler R

O-064 Total skin electron beam therapy can improve peripheral blood disease burden in sèzary syndrome and leukemic mycosis fungoides 8 + 4
Klein R, Samimi S, Morrissey KA, Evans KG, Gardner JM, Introcaso CE, Vittorio CC, Rook AH, Micaily B, Kim EJ

O-065 Total skin electron therapy for mycosis fungoides: a single centre experience 8 + 4
Scarisbrick J, Jayawardena S, Morris S, Grieve R

O-066 Multi-center results on the effect of different phototherapeutic modalities in lymphomatoid papulosis 8 + 4
Wolf P, Calzavara-Pinton P, Cozzio A, Querfeld C, Wolf E-V, Dummer R, Cerroni L, Kempf W

O-067 Extracorporeal photopheresis for the treatment of erythrodermic cutaneous T-cell lymphoma: over-view of the literature and clinical experience with long-term follow-up data 8 + 4
Quaglino P, Knobler R, Fierro MT, Savoia P, Marra E, Fava P, Bernengo MG

O-068 Extracorporeal photopheresis in erythrodermic CTCL: the UK experience 8 + 4
Scarisbrick J, Taylor P, Parry E, Cowan R, Douglas K, Child F, Aguilar-Duran S, Whittaker S, Morris S

17:00–17:30 Coffee Break

17:30–19:00 Cutaneous Lymphomas Disease Management

Chairs: Geskin L, Quaglino P, Beyer M

O-069 Primary cutaneous marginal zone lymphoma: a critical review 20 + 5
Guitart J, DeonizioJ, Bloom T, Kwasny MJ, Rosen S

O-070 Primary cutaneous small/medium-sized CD4+ pleomorphic T-cell lymphoma: Retrospective case series of 22 patients 8 + 4
James E, Sokhn J, Subtil A, Girardi M, Edelson R, Wilson LD, Foss F

O-071 Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma: Clinical and histological characteristics 8 + 4
Csomor J, Erős N, Kontár O, Hársing J, Szepesi A, Kárpáti S, Matolcsy A, Marschalkó M

O-072 Long term outcome of 61 patients with primary cutaneous anaplastic large cell lymphoma: the stanford experience 8 + 4
Million L, Kim YH, Bashey S, Krathen M, Hoppe R

O-073 Management and patterns of relapse for primary cutaneous B-cell lymphomas at the multimodality cutaneous lymphoma clinic at the Ohio State University. A series update 8 + 4
Winardi FK, Elkins C, Frederickson J, Peters S, Wong H, Porcu P

O-074 Heterogeneity in tumor stage mycosis fungoïdes correlates with prognosis 8 + 4
Boonk SE, Putter H, Koolhof L, Willemze R, Vermeer MH

19:30 Conference Dinner

08:30–10:00 Molecular Cell Biology (Cell Signaling)

Chairs: Wood G, French L, Eberle J

O-075 Identification of deregulated transcription factors in human lymphoma — 15 + 5
Mathas S

O-076 Micro RNAs regulate the effect of chemotherapy in CTCL — 15 + 5
Gniadecki R

O-077 Activation of phosphatidylinositol-3 kinase (PI3K)/SerineE/Threonine protein kinase (AKT) pathway in mycosis fungoides — 8 + 4
Papadavid E, Korkolopoulou P, Levidou G, Saetta AA, Papadaki T, Siakantaris M, Nikolaou V, Economidi A, Kolialexi A, Marinos L, Chatziandreou I, Psyrri A, Patsouris E, Antoniou C

O-078 Nuclear factor-κB signaling pathway-related gene aberrancies in primary cutaneous large B-cell lymphomas, leg type — 8 + 4
Koens L, Zoutman WH, Ngarmlertsirichai P, Przybylski GK, Grabarczyk P, Vermeer MH, Willemze R, Jansen PM, Schmidt CA, Tensen CP

O-079 The importance of notch signalling in peripheral T-cell lymphomas — 8 + 4
Kamstrup MR, Rahbek Gjerdrum LM, Biskup E, Ralfkiaer E, Niazi O, Gniadecki R

O-080 Three components Of TOX-RUNX3 pathway are differentially expressed in CTCL — 8 + 4
O'Neill-Dulmage BL, Mirvish ED, Vu JR, Falo LD, Jr., Geskin LJ

10:00–10:25 Coffee Break

10:25–11:45 Molecular Cell Biology (Apoptosis)

Chairs: Ortiz-Romero P, Girardi M, Mathas S

O-081 Regulation of apoptosis by bcl-2 proteins — 15 + 5
Daniel PT

O-082 Apoptosis regulation in cutaneous T-cell lymphoma – ritical roles of TRAIL resistance, cFLIP expression and lack of bid — 15 + 5
Braun FK, Al-Yacoub N, Möbs M, Sterry W, Eberle J

O-083 HSP 70 kDa protein 1A inhibits histone deacetylase inhibitor-induced apoptosis through mitochondrial pathway — 8 + 4
Fujii K, Suzuki N, Kaji T, Hamada T, Idogawa M, Kondo T, Iwatsuki K

O-084 Tax can Induce PD-1 expression but apoptosis is inhibited by PD-1 promoter methylation in HTLV-1-infected T-cells — 8 + 4
Shimauchi T, Sakabe JI, Qin Y, Sawada Y, Nakamura M, Tokura Y

O-085 Cutaneous T-cell lymphoma cells release proapoptotic fas ligand (CD178) in lysosomal secretory vesicles — 8 + 4
Jean-Louise F, Chauvel C, Raposo G, Bagot M, Bachelez H, Bensussan A, Michel L

11:45–12:15 Coffee Break, Snacks

12:15–13:25 On-going and Prospective Clinical Trials

Chairs: Olsen E, Bagot M, Pro B

O-086 Phase II trial of brentuximab vedotin (SGN-35) for CD30+ cutaneous T-cell lymphomas and lymphoproliferative disorders — 15 + 5
Duvic M, Tetzlaff M, Gangar P, Talpur R

O-087 Phase II multicenter trial of oral quisinostat, a histone deacetylase inhibitor, in patients with previously treated stage IB-IVA cutaneous T-cell lymphoma — 8 + 4
Zinzani PL, Child F, Ortiz-Romero P, Alvarez R, Bagot M, Stadler R, Weichenthal M, Alves R, Bernengo MG, Beylot-Barry M, Cowan R, Geskin LJ, Pérez Ferriols A, Hellemans P, Elsayed Y, Phelps C, Forslund A, Kamida M

O-088 Brentuximab vedotin demonstrates clinical activity in mycosis fungoides and sèzary syndrome irrespective of Tissue CD30 Expression by routine immunohistostaining — 8 + 4
Krathen MS, Bashey S, Salva K, Wood GS, Sundram U, Nagpal S, Advani R, Hoppe R, Reddy S, Pulitzer M, Horwitz S, Kim YH

O-089 Multicenter, randomized, phase I/II study evaluating the safety and efficacy of low-dose total skin electron beam therapy vs. low-dose TSEBT combined with vorinostat in mycosis fungoides — 8 + 4
Bashey S, Krathen MS, Million L, Duvic M, Dabaja B, Wilson L, Girardi M, Foss F, Hoppe R, Kim YH

O-090 Immunomodulatory effects of lenalidomide: Results from a multicenter phase II trial — 8 + 4
Querfeld C, Guitart J, Rosen ST, Dusza SW, Duvic M, Kim YH, Kuzel TM

13:25–13:30 Valediction
P Walden

Poster

Cell Biology

P-001

RECURRENT LOSS OF TNFAIP3 IN SÉZARY SYNDROME

FLORIANE C.M. BRAUN[1], PIOTR GRABARCZYK[1], MARKUS MÖBS[2], MAARTEN H VERMEER[3], CORNELIS P. TENSEN[3], GRZEGORZ K. PRZYBYLSKI[4], CHRISTIAN A. SCHMIDT[1]

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Despite recent therapeutic improvements, the prognosis for patients suffering from Sézary syndrome (SS), a leukemic form of cutaneous T-cell lymphomas (CTCL), is still poor. In previous work we identified bi- and monoallelic deletions of the tumor necrosis factor alpha induced protein 3 gene (TNFAIP3; A20) in a high proportion of SS patients as well as biallelic A20 deletion in the SS-derived cell line SeAx. Furthermore, we demonstrated that inhibition of A20 activates the NF-κB pathway thereby increasing the proliferation of normal T lymphocytes. On the other hand, the reconstitution of A20 expression slowed down the cell cycle in SeAx cells. These observations suggest that A20 functions as a tumor suppressor gene in Sézary syndrome. In this study we extended the number of Sézary syndrome patient samples and determined gene copy number of A20 using an optimized competitive PCR assay. In this independent group of SS patients deletions were found in nine out of 17 (53%) Sézary syndrome samples. These results underscore the relevance of A20 deletion in this tumor entity.

P-002

NOTCH-1 INDUCTION VIA P53 STRONGLY RESTRAINS NUTLIN-3A CYTOTOXICITY IN CUTANEOUS T-CELL LYMPHOMA

VALENTINA MANFÈ[1], MARIA KAMSTRUP[1], EDYTA BISKUP[1], OMID NIAZI[1], ANDREAS WILLERSLEV-OLSEN[2], NIELS ØDUM[2], ROBERT GNIADECKI[1,3]

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[3] Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark

Strategies aimed to induce p53 activation, such as the inhibition of the MDM2/p53 interaction using nutlin-3a, are promising in the preclinical treatment of cutaneous T-cell lymphomas (CTCL). Here, we investigated the mechanisms able to restrict the therapeutic efficacy of nutlin-3a in CTCL cells. We demonstrated that *NOTCH-1* is a transcriptional target of p53 and that nutlin-3a induces Notch-1 protein accumulation in CTCL cell lines carrying wild-type *P53*. This effect was abolished whenever p53 was silenced by specific siRNA. Moreover, knockdown of Notch-1 increased the cytotoxicity of nutlin-3a, in the presence of a functional p53, and accounted for a larger extend to the apoptosis induced by inhibition of the transcriptional activity of p53. Consistent with these observations, we reported that γ-radiation also induces Notch-1 accumulation concomitant with p53 increase, in $P53^{\text{wild-type}}$ CTCL cells, but not in cells lacking a functional p53.

P-003

MAB- OR CPG ODN-ENGAGEMENT OF KIR3DL2 DRIVES DISTINCT CELLULAR PATHWAYS IN SÉZARY SYNDROME MALIGNANT T-CELLS

GHAZI BOUCHRA[1], THONNART NICOLAS[1], BAGOT MARTINE[1], BENSUSSAN ARMAND[1], MARIE-CARDINE ANNE[1]
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We previously identified the NK cell receptor KIR3DL2 as a valuable diagnostic and prognostic marker for the detection of the tumoral t-cell burden of Sézary syndrome patients. However, the function of this receptor on the malignant T lymphocyte population remained unexplored. We demonstrate that triggering of KIR3DL2 with the monoclonal antibody AZ158 results in a strong inhibition of the CD3-mediated proliferation and cell death of the CD4+ KIR3DL2+ cells that is correlated to a down-modulation of CD3-ζ phosphorylation and Erk1/2 activation. Unexpectedly, engagement of KIR3DL2 by its newly identified ligand CpG ODN-C does not promote the delivery of such negative signals. However, we here report that CpG ODN binding induces the internalization of the receptor and leads to a caspase-dependent apoptosis of the malignant T-cells. This process of cellular death is correlated to a dephosphorylation of the transcription factor STAT3, which is found constitutively phosphorylated and activated in Sézary cells. Our results indicate that according to its ligand recruitment, KIR3DL2 can act as a co-inhibitory receptor or specifically promote Sézary syndrome malignant cell death.

P-004

DIFFERENTIAL PROTEOMIC ANALYSIS IN PRIMARY CUTANEOUS MARGINAL ZONE LYMPHOMA

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[2] Karl Landsteiner Institute of Dermatological Research, St.Pölten, Austria

Proteome profiling is an unbiased screening method with the potential to identify as yet unknown molecular mechanisms and biomarkers in human disease. This technique has not yet been applied in cutaneous lymphomas and we describe here initial results of the proteomic analysis in a primary cutaneous marginal zone lymphoma.
Tissue was obtained from a cutaneous tumor of a 70-year-old male patient with primary cutaneous marginal zone lymphoma (pcMZL) and the whole sample was used for further analysis. Reference proteome profiles of fibroblasts, endothelial cells, and leukocytes were used for differential display of pcMZL specific proteins. Proteins were separated and identified by SDS page, proteolytic digest, nano-LC separation of peptides, and fragmentation analysis using an ion trap mass spectrometer. 30 proteins with a high specificity for the investigated tissue were identified. Among others these proteins included enzymes (Cathepsin G, Lysozyme C), kinases (mitogen activatd protein kinase 4, dual specificity protein kinase CLK3, tyrosin protein kinase BTK), cytokines (interleukin-18), proteoglykanes (decorin, osteoglycin), a DNA repair protein, and surface receptors (CD14, toll-like-receptor 4). These results provide the basis for further verification of the identified candidate proteins and for analysis for their relevance in the pathophysiology of pcMZL and related diseases.

P-005

MICRORNA PROFILING OF PRIMARY CUTANEOUS LARGE B-CELL LYMPHOMAS

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MicroRNAs are small non-coding RNAs that regulate gene expression at a posttranscriptional level. Their aberrant expression is known to be pathogenetically involved in many diseases. Although a role of microRNAs in nodal diffuse large B-cell lymphomas (DLBCLs) is generally recognized, the presence and function of microRNAs in primary cutaneous large B-cell lymphomas (PCLBCLs) are not yet described. The two types of PCLBCL, primary cutaneous diffuse large B-cell lymphoma, leg type (PCBCL-LT) and primary cutaneous follicle center lymphoma (PCFCL) are characterized by an activated B-cell (ABC) genotype and a germinal center B-cell (GCB) genotype, respectively. By performing high-throughput next generation sequencing analysis, the microRNA profiles of frozen tumour biopsies from 11 cases of PCBCL-LT and 6 cases of PCFCL were established. Quantitative analysis for differential expression of microRNAs between the two tumour types was performed. For a selection of these microRNAs real-time qPCR on both internal and external validation groups was performed, along with a set of microRNAs known to be involved in the pathogenesis of nodal DLBCLs. The sequence data showed 16 microRNAs that were differentially expressed between PCBCL-LT and PCFCL ($p<0.05$, Benjamini-Hochberg corrected). However, 5 microRNAs commonly described to be differentially expressed between GCB and ABC type nodal DLBCL were not amongst them. Higher expression of miR-9, miR-31, miR-129-2 and miR-214 in PCFCL compared to PCBCL-LT was confirmed by qPCR. This approach allowed the identification of a microRNA signature discriminating PCFCL from PCBCL-LT. These results show substantial differences as compared to the previously described signature(s) discriminating GCB from ABC type nodal DLBCLs.

P-006

ROLE OF VERSICAN IN SKIN HOMING OF SÉZARY CELLS

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Sézary syndrome is characterized by erythroderma, lymphadenopathy and the presence of neoplastic T lymphocytes, termed Sézary cells (SéCs) in the blood. We performed microarray analysis on purified CD4+ SéCs from patients, which were additionally sorted according to patient-specific TCR-Vgamma expression (Vgamma+). The effects of a candidate gene defined by this analysis were then tested on CD4+Vgamma+ SéCs from patients and cutaneous lymphoma (CL) cell lines. We obtained expression profiles of tumor CD4+ Vgamma+ T-cells from patients and compared those to non-clonal CD4+ Vgamma- T-cells obtained from the same patient. We identified versican as the highest differentially up-regulated gene in clonal CD4+Vgamma+ SéCs population. Versican is a large chondroitin-sulphate proteoglycan that

occurs in four different isoforms (V0-V3), depending on the splicing. Investigation of versican expression pattern revealed preferential expression of versican V1 isoform in the sorted SéCs from patients and also in the CL cell lines. Different cytokines (PDGF, TGF-beta) influenced versican expression in a different manor. Furthermore, we assessed the effects of versican expression on the motility of CL cell lines to cytokines and skin homing chemokines and could show that versican V1 expression could modulate their motility. Our experiments imply versican as a new factor regulating skin homing of SéC.

Immunology

P-007

TARGETED THERAPY OF CD30-POSITIVE LYMPHOMAS WITH BRENTUXIMAB VEDOTIN AND DLI FOLLOWING ALLOGENEIC STEM CELL TRANSPLANTATION: INDUCTION OF SUSTAINED CLINICAL REMISSIONS AND CELLULAR IMMUNITY

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The expression of CD30 is a characteristic feature of a variety of nodal and primary cutaneous lymphomas or lymphoproliferative disorders. Since the clinical introduction of brentuximab vedotin, a monoclonal anti-CD30 antibody-drug conjugate, targeted therapy of CD30+ lymphomas is possible and has revealed suprisingly high efficacy even in heavily pretreated patients. However, to the current knowledge the median duration of response is limited.
In contrast, allogeneic hematopoietic stem cell transplantation (alloSCT) has shown curative potential in patients with relapsed CD30+ lymphomas such as Hodgkin lymphoma and also in progressive primary cutaneous t-cell lymphoma. Thereby, the therapeutic principle relies primarily on the graft-versus-lymphoma (GvL) effect which needs time to evolve and strategies are lacking that focus alloimmunity towards the tumor sparing healthy tissue from the development of graft-versus-host disease (GvHD).
However, in a significant number of patients the lymphoma relapses shortly after alloSCT due to a weak cellular immunosystem but also to factors of the lymphoma microenvironment which can suppress GvL reactivity. In this situation, classic cytotoxic treatment options are very limited due to side effects and efficacy. Donor lymphocyte infusions (DLI) are a therapeutic option but bear the risk of unspecific immune responses such as GvHD and the effect of DLI is also hampered by suppressive effects of the tumor microenvironment.
Here, we propose brentuximab vedotin combined with and without DLI as a new treatment option in patients with relapsed CD30+ lymphoma following alloSCT. In a series of patients we could demonstrate that targeted treatment with brentuximab vedotin increased cellular immunity and induced lymphoma specific T-cells most likely due to immunogenic cell death. Moreover, in these patients the median duration of disease control was remarkably higher compared to the published data in a non-alloSCT setting.

P-008

TUMOR INFILTRATING B CELLS IN PRIMARY CUTANEOUS T-CELL LYMPHOMAS CORRELATE WITH DISEASE PROGRESSION AND MIGHT REPRESENT A POTENTIAL TARGET FOR THERAPY

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B cells have been recently described to mediate tumor biology but so far their role as tumor promoting or tumor repressing lymphocyte population remains controversial. Mycosis fungoides (MF) and other primary cutaneous t-cell lymphomas (CTCL) are characterized by an indolent course in early stages. However, advanced stage MF (≥ EORTC Stage IIB) and the follicular MF subtype (FMF) as well as Sézary syndrome (SS) show a more aggressive pattern with a median survival of less than two years. The pathogenesis of these more aggressive courses is still incompletely understood. Anecdotal reports have previously described CD20 positive cells in CTCL but further characterization of these cells have not been performed.
We systematically analyzed the B cell infiltrate in paraffin samples of CTCL patients by immunohistochemistry (CD20 and CD79a) and correlated these data with the stage, subtype and clinical course. Advanced stage MF, FMF and SS samples contained significantly increased numbers of infiltrating B cells per lymphoma infiltrate. Moreover, time to progression showed a significant inverse relationship with the density of the B cell infiltrate.
Based on our results, we hypothesized that infiltrating B cells might be a therapeutic target. In a 77-year old patient suffering from advanced stage FMF with a significant B-cell infiltration and progression after standard treatments, intralesional B-cell depletion with the anti-CD20 monoclonal antibody rituximab resulted in a sustained local tumor regression.
In summary, we present first evidence on the potential tumor promoting role of infiltrating B cells in CTCL which warrants further study as a potential therapeutic strategy.

P-009

NOVEL THERAPEUTIC AND DIAGNOSTIC ANTIBODIES AGAINST KIR3DL2, A UNIQUE TUMOR ANTIGEN OVEREXPRESSED ON SUBTYPES OF CTCLS

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KIR3DL2 belongs to the killer immunoglobulin (Ig)-like receptors (KIRs) family and is composed of three extracellular Ig-like domains. KIR3DL2 is naturally expressed on some NK cells and minor subpopulations of CD8+ and CD4+ T-cells. Physiologically, KIRD3L2 is an inhibitory receptor for human leukocyte antigen (HLA) class I molecules regulating NK cell activation. Remarkably, KIR3DL2 is also aberrantly overexpressed on several subtypes of T lymphomas/leukemias, such as Sezary Syndrome, transformed Mycosis Fungoides and HTLV1+ Adult t-cell Leukemia, making it a unique therapeutic target in cancer. We have generated a series of anti-KIR3DL2 monoclonal antibodies (mAbs) binding selectively to KIR3DL2, spanning epitopes on each of the three Ig domains. Their efficacy was evaluated in vitro and in vivo against KIR3DL2-expressing tumors and Sezary cell lines as disease model. Various modes of action, such as complement-dependent cytotoxicity (CDC) and antibody-dependent cell cytotoxicity (ADCC) were found involved in their anti-tumor activity. In parallel, anti-KIR3DL2 mAbs were also developed as unique and sensitive tools for the detection by immunohistochemistry of KIR3DL2 on tumor biopsies. Owing to the promising efficacy profile of our anti-KIR3DL2 mAb candidates and to the highly restricted expression pattern of the target on some T leukemia/lymphoma cells, an antibody-based therapy targeting KIR3DL2 stands as a potentially unequalled strategy in several orphan diseases with critical unmet medical need.

P-010

STUDY OF REACTIVE B AND CD8+ T LYMPHOCYTES IN PROGRESSION AND EVOLUTION OF CLASSIC MYCOSIS FUNGOIDES

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INTRODUCTION: Mycosis Fungoides (MF) is the most common subtype of primary Cutaneous T-cell Lymphoma. CD4+, CD45RO+ T malignant-cells of MF are accompanied by different types of reactive lymphocytes, including B and CD8+ T-cells. CD8+ T-cells seem to relate to a state of early immunosurveillance, but the role of B-cells in the pathogenesis and progression of the disease is not entirely clear.
The aim of this study was to analyze reactive B and CD8+ T-lymphocytes in two stages of MF progression and their relationship with clinical behavior.

MATERIALS AND METHODS: Twenty samples of plaque stage MF (PMF) and seven of tumor stage MF (TMF) obtained from fifteen patients with a follow-up of 4 to 20 years, were studied retrospectively. The study was approved by the institutional Ethics Committee. CD20, CD8 and IL-10 expression was assessed using immunohistochemical methods. Double label Immunoperoxidase for Ki-67 and CD20 were performed in selected samples. The percentage of CD20+ or CD8+ cells over total number of skin-infiltrating cells and the pattern of the infiltrate (scattered cells, groups/focal pattern, or large aggregates/nodular pattern) were correlated with follow-up data (survival <5 years, resistance to treatment or risk factors).
RESULTS: In general, CD20+ cells showed low basal levels (<10%). In PMF CD8 expression (4.91±2.58) was higher than CD20 (1.21±0.84, p<0.001). Only CD20+ cells showed focal (2PMF, 1TMF) or nodular (2TMF, 1PMF) patterns without reactive germinal centers. In nodular pattern, CD20+ cells were also Ki-67+ and IL10+. Six (40%) of 15 patients had poor evolution and 4 of 6 (3 PMF and 1TMF) had nodular o focal pattern with CD20 increased (16.5±9.69 vs. 1.21±0,84, p=0.001).
CONCLUSIONS: These preliminary results show different amount of B and CD8+ T-cells in PMF and raise the possibility that activated B cells expressing IL10 associated with nodular pattern could be related with progression and poor prognosis of MF.

P-011

CORRELATION BETWEEN IMMUNOPHENOTYPE AND T-CELL RECEPTOR γ-CHAIN GENE REARRANGEMENT IN MYCOSIS FUNGOIDES

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Mycosis fungoides (MF) is the most common form of cutaneous T-cell lymphoma and is characterized by the clonal expansion of a dominant T-cell clone.
To find a correlation between immunphenotype and the presence of clonality, we used laser-capture microdissection (LCM) to evalute T-cell receptor (TCR) γ chain gene rearrangement in separately microdissected T-cells expressing CD3, CD4, CD5, CD7 or CD8. As each immunophenotype correlates with a specific stage of maturity, a pattern might lead towards the stage of T-cell development at which the clonal expansion of malignant-cells occurs.
13 biopsies diagnosed MF were included in the study. After immunohistochemistry, the labelled lymphocytes (CD3, CD4, CD5, CD7, CD8) were separately microdissected and subjected to TCR γ clonality analysis.
Investigating certain subgroups of lymphocytes, we detected more than one single clone in 11 of 13 biopsies. A correlation between immunophenotype and clonality could not be drawn, as all stages of lymphocytic development expressed clonality. Finding a clonal dominance in both CD4 and CD8 positive T-lymphocytes describes very early occurence of clonality, as only thymocytes express both CD4 and CD8 simultaneously.
The combination of immunohistochemistry and microdissection showing clonal heterogenity in one single biopsy in early stages of MF can hint towards the evolution of monoclonality from the stage of polyclonality and oligoclonality.

Due to the independence of clonality and CD4 expression in several cases, the dogma of MF being a disease of a CD4 phenotype has to be critically reconsidered.
We therefore postulate that MF in early stages with multiple clones or few dominant clones evolve from a benign lymphocytic infiltrate. During disease progression MF turns to an eventually monoclonal disease unrelated to CD4 expression. The entire infiltrate, consisting both of neoplastic and reactive T-cells, however, always seems to be dominated by CD4 positive cells.

P-012

SPECTRUM OF IMMUNOPHENOTYPES OF EARLY MYCOSIS FUNGOIDES AND THEIR CLINICAL CORRELATES

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Although the neoplastic cells in early mycosis fungoides (MF) characteristically have a mature CD3+, CD4+, CD8- phenotype, cases of a CD3+ CD4-CD8+ or a CD4-CD8- phenotype are being increasingly recognized as rare immunohistochemical variants of the disease. The relative frequency of the different immunophenotypes and their correlation with the clinical presentations of the disease have never been addressed in a large study. In the present study, 234 biopsy specimens from 234 patients (149 male, 85 female; median age 50 years, age range 2-90 years) with early MF were analyzed. All diagnoses were made in our cutaneous lymphoma clinic. Immunophenotyping of the intraepidermal lymphocytes yielded 3 groups: CD4+CD8-, 60% of patients; CD8+CD4-, 20%; CD4-CD8-, 20%. To correlate the immunophenotypes with the clinical presentations, we used only lesion samples from patients with the four most common clinical phenotypes in our study population: classical patch/plaque disease, 105 patients; folliculotropic variant, 40 patients; hypopigmented variant, 21 patients, and hyperpigmented variant, 17 patients (total, 183). The remaining 51 patients were excluded because they had less common variants (unilesional, ichthyosiform, poikilodermal, psoriasiform) or the clinical type could not be determined from the biopsy report. Main findings were as follows: CD4+ group: overrepresentation of the folliculotropic variant and underrepresentation of the hypo- and hyperpigmented variants ($p<0.05$); CD8+ group: overrepresentation of the hypo- and hyperpigmented variants ($p<0.05$); CD4- CD8- group: no correlation with any of the 4 clinical presentations of MF in this series. These results indicate that although the majority of cases of MF are characterized by the CD4+ immunophenotype, a significant fraction have unusual immunophenotypes. The immunophenotype of early MF correlates with specific clinical presentations.

P-013

THE EXPRESSION OF CXCL10, CXCL9 AND CCL17 CHEMOKINES IN MYCOSIS FUNGOIDES IS REDUCED IN SKIN TREATED BY PUVA AND INTERFERON-α2B

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BACKGROUND AND AIMS: The interferon-inducible protein-10 (IP10)/CXCL10, the monokine induced by interferon-γ (MIG)/CXCL9 and the thymus and activation-regulated chemokine (TARC)/CCL17 are Th1 and Th2 chemokines that regulate skin selective T lymphocyte trafficking and recruitment in Mycosis Fungoides (MF). In a previous study we have observed that cutaneous T cell-attracting chemokine (CTACK)/ CCL27 expression in the skin is increased at diagnosis, remains abnormal also after therapy, even if complete histological remission is recorded, and seems to be correlated with an higher probability to have a relapse.
The aims of our study were to evaluate the expression of CXCL10, CXCL9 and CCL17 chemokines at diagnosis and after combination of PUVA and interferon-α2b (PUVA/IFNα2b) and if variations of expression are clinically relevant.
PATIENTS AND METHODS: Tissue skin biopsy specimens were collected from 22 MF patients at an early stage (IB-IIA) at the time of the diagnosis and after treatment with PUVA/IFNα2b combination therapy. Immunostaining for CXCL10, CXCL9 and CCL17 was performed on formalin and paraffin-embedded tissue sections.
RESULTS: At diagnosis, a high number of cells positive for the chemokines CXCL10 and CXCL9 was present in the skin, both in the epidermis, particularly in the foci of lymphoid infiltration, and in the dermis. A lower number of cells reactive for CCL17 was found. Expression was found in keratinocytes, dendritic cells and macrophages. Treatment with PUVA plus interferon-α2b reduced significantly the number of cells reactive for all the chemokines, but the cases showing a clinical and histological partial response showed a higher expression of CXCL10, CXCL9 and CCL17 than those achieving a complete response ($P<0.05$). The expression of the chemokines was not correlated with the event-free survival.
CONCLUSIONS: PUVA and interferon-α2b induces a reduction of CXCL10, CXCL9 and CCL17 expression in MF, expecially in those achieving a complete response, but the variations of expression are not clinically relevant to predict the event-free survival.

Diagnostics

P-014

ERYTHROCYTE SEDIMENTATION RATE AS A PROGNOSTIC FACTOR IN MYCOSIS FUNGOIDES

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INTRODUCTION: Mycosis fungoides has a characteristically indolent clinical course, with a slow progression from patches over plaques to tumours. In advanced stages, with generalized skin involvement or tumours, the prognosis is poor. Well defined prognostic parameters for the individual risc stratifications are rare.
OBJECTIVES: To determine a correlation between elevated erythrocyte sedimentation rate (ESR) and advanced stages of mycosis fungoides.
METHODS: In a retrospective monocenter study, we reevaluated 54 consecutive cases of mycosis fungoides seen at our clinic (16 women and 38 men) with a mean age of 59 years. Various parameters were recorded: sex, age at time of diagnosis, age-adjusted erythrocyte sedimentation rate and anemia. Advanced stages of mycosis fungoides were identified from stage IIB (T3N0-1M0).
RESULTS: There is a significant correlation ($p=0.027$) between the advanced stages of mycosis fungoides and accelerated ESR. This parameter (accelerated ESR) could learn as soon as the diagnosis of mycosis fungoides, the prognosis of this disease.
CONCLUSION: We identified ESR as a significant prognostic marker for mycosis fungoides. Further studies on ESR and survival rate could provide more relevant results.

P-015

GAMMA DELTA T-CELL LYMPHOMA MIMICKING SÉZARY SYNDROME

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Cutaneous t-cell lymphomas (CTCLs) are a heterogeneous group of lymphoproliferative disorders of the skin. Sézary syndrome is a rare variant with an aggressive clinical behaviour presenting with erythroderma, generalized lymphadenopathy and leukemic blood involvement. The neoplastic T-cells are considered to be CD4+ TCRgamma delta+ memory cells with skin-homing properties and a Th2 phenotype.
Other forms of CTCL frequently show expression of a cytotoxic phenotype (e.g. primary cutaneous CD30+ lymphoproliferative disorders, subcutaneous panniculitis-like lymphoma, extranodal NK/T cell lymphoma). Among them primary cutaneous TCRgamma/delta+ t-cell lymphomas (PCGD-TCL) encompass a rare new entity in the current WHO-EORTC

classification. They are clinically characterized by disseminated plaques, nodules or tumors with a poor prognosis.
Here, we present a case of a peripheral TCRgamma/delta T-cell lymphoma with a Th2 phenotype and a clinical manifestation resembling Sézary syndrome.

P-016

DIAGNOSTIC CHALLENGES: DIFFERENTIATING ALLERGIC CONTACT DERMATITIS AND EARLY CUTANEOUS T-CELL LYMPHOMA

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Early lesions of allergic contact dermatitis (ACD) and cutaneous T-cell lymphoma (CTCL) can overlap in clinical morphology and histopathology. We describe 2 cases to illustrate this diagnostic challenge.
The first patient was diagnosed with unilesional, clonal Stage 1A CD8+ CTCL on his buttock and treated with radiation therapy. Six months after initial clearance, a rash and biopsy were consistent with disease recurrence. At that time, the patients habitual use of baby wipes containing methylparaben and methylisothiazolinone became apparent. Prior positive patch tests to these substances was identified and the lymphomatoid rash resolved with allergen avoidance. In the second patient, a 2-3 year history of dermatitis and positive patch testing to multiple preservatives was reported on consultation. Work-up revealed no clear correlation between exposures and allergens and a family history of CTCL. Biopsy was consistent with follicular mucinosis and concerning for folliculotropic mycosis fungoides.
ACD classically presents with an eczematous rash and marked spongiosis on biopsy. Patch testing is performed to identify allergens. Early or isolated lesions of CTCL may mimic the clinical and histological morphology of ACD. Atypical T-cells are characteristically present in CTCL but can also be seen in reactive processes. Features such as T-cell clonality are nonspecific and can be present in benign lymphomatoid contact dermatitis. The established progression of certain reactive processes to malignancy via chronic antigen stimulation further blurs the overlap between early CTCL and ACD.
CTCL and ACD are commonly encountered by dermatologists and differentiating between the two diseases in some cases is challenging. This presentation will review lymphomatoid contact dermatitis, chronic antigen stimulation, and the clinical overlap between CTCL and ACD to highlight the challenges in formulating and applying current diagnostic criteria.

P-017

A CASE OF PRIMARY CUTANEOUS FOLLICLE CENTER LYMPHOMA MISDIAGNOSED AS HERPES ZOSTER

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Primary cutaneous follicle center lymphoma (PCFCL), is the most common type of primary cutaneous B-cell lymphomas with a predilection for the scalp, forehead and trunk.

A 46-year old man referred to our clinic with asymptomatic, firm 0.5-2cm wide pink papulonodular lesions distributed over the skin corresponding to left scapula. Patient could not be able to confirm the duration of the lesion. When he first noticed the lesion 3 weeks earlier, he had been diagnosed as herpes zoster and treated with valacyclovir at a different medical care unit, by a dermatologist. Upon examination, two groups of clustured nodular lesions were detected nearby erythematous plaque lesions, together showing a serpiginous pattern over the scapula of the patient. Routine blood screening and serology for Hepatitis-C, Borrelia burgdorferi and HIV were within normal ranges. Histopathologically, punch biopsy of one of the erythematous papules revealed a dense lymphoid infiltrate in papillary demis extending into the deep dermis consisting of centrocytes and centroblasts. The immunostaining showed that this infiltrate was positive for CD20, BCL-6 and Lambda light chain antibodies. Average Ki-67 proliferation index was 25%. After excluding systemic nodal lymphoma we confirmed the diagnosis of PCFCL. For this isolated lesion, our treatment protocol was 18 sessions of local radiotherapy after the primary excision of the lesion. After the treatment, he showed both clinical and histological remission without relapse at 11 months follow-up.
In summary, herein we report a case of PCFCL misdiagnosed as herpes zoster in the early phase of the disease, by a dermatologist. By reporting this case, our aim is to be the part of growing awareness that PCFCL can present with a zosteriform morphology.

P-018

FOLLICULAR LYMPHOCYTE EXOCYTOSIS IN PERSISTENT/NODULAR ARTHROPOD REACTIONS MAY MIMIC FOLLICULOTROPIC MYCOSIS FUNGOIDES

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Follicular exocytosis of atypical lymphocytes is a feature of folliculotropic mycosis fungoides/cutaneous T-cell lymphoma (MF/CTCL), which exhibits more aggressive behavior and poorer prognosis than classic MF. Therefore, follicular lymphocyte exocytosis can be a concerning feature in any skin biopsy with a florid lymphocytic infiltrate. A search of Yale Dermatopathology Laboratory archives identified 8 patients with persistent/nodular arthropod reaction (7 to scabies and 1 to a tick) and associated florid lymphocytic inflammation. Specimens lacking hair follicles on multiple sections were excluded. Review of 11 specimens from 8 patients identified: follicular exocytosis in 81% (9/11), atypical lymphocytes in 27% (3/11), and sebaceous gland exocytosis in 27% (3/11). Sebaceous gland atrophy was detected in all specimens. Mitotic figures were abundant in one case (9%) and occasionally identified in 10/11 (91%). In summary, follicular lymphocyte exocytosis was identified commonly in persistent/nodular arthropod reactions. Frequent follicular exocytosis along with occasional lymphocytic atypia may mimic lymphoma and could pose a diagnostic pitfall in cases of persistent/nodular arthropod reactions with florid lymphocytic inflammation.

P-019

LOW FREQUENCY OF ABERRANT CD56 EXPRESSION IN CUTANEOUS MARGINAL ZONE B-CELL LYMPHOMA

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CD56 has been shown to be positive in up to 78% of cases of plasma cell myeloma, but not in normal and reactive plasma cells. Primary cutaneous marginal zone lymphoma (PCMZL) is a type of cutaneous B-cell lymphoma composed predominantly of small lymphocytes and a variable subset of monotypic plasma cells. In some cases, plasma cells predominate in the infiltrate. Primary cutaneous plasmacytoma (without underlying plasma cell myeloma) has been included in the category of PCMZL in the WHO-EORTC (World Health Organization-European Organization for Research and Treatment of Cancer) Classification for cutaneous lymphomas. We examined 8 cases of PCMZL with a significant subset of monotypic plasma cells to assess for aberrant CD56 expression. Only one case of PCMZL (12.5%) showed prominent CD56 expression by neoplastic plasma cells. Extensive laboratory and radiographic studies and close follow-up in this case were negative for evidence of an underlying plasma cell dyscrasia. In summary, aberrant CD56 expression may occur in PCMZL but is uncommon.

P-020

COMBINATION OF PLS3, TWIST, CD158K/KIR3DL2 AND NKP46 GENE EXPRESSION FOR THE DIAGNOSIS OF SEZARY SYNDROME

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Several molecular markers including T-plastin (PLS3), transcription factor Twist, CD158k/KIR3DL2 and NKp46 (CD335) have been specifically identified in patients with Sézary Syndrome (SS), the erythrodermic and leukemic form of cutaneous T-cell lymphoma (CTCL). Our purpose was to investigate whether the expression profiling of these 4 genes by quantitative Real-time PCR (qRT-PCR) can be employed for the SS diagnosis. A cohort of 81 patients with SS was investigated for tumor burden and mRNA expression quantification of PLS3, Twist, KIR3DL2 and NKp46 in CD4+-purified T-cells from blood samples using SYBR Green qPCR and specific primer pairs. CD4+-purified t-cells from 12 healthy donors were studied as controls, with qRT-PCR mean values (±SD) of PLS3, Twist, KIR3DL2, and NKp46 mRNA levels reaching 2.4±2.5, 6.6±8, 22.5±20.4, and 2.6±2.8, respectively. A respective threshold of 95% significance was set up at 5, 10, 25 and 25, and any value less than the respective threshold was considered as negative. As positive controls we used mRNA mean levels (±SD) detected in SS HuT-78 cell line cultures (n=3) with 128±65 for PLS3, 13155±3000 for Twist, 316±40 for KIR3DL2, and 7.3±1.9 NKp46, respectively, as mRNA mean levels (±SD) in NK-purified cells (n=3) reaching 0.4±0.1, 0.5±0.15, 684±80.3, and 371±80.2, respectively. Our results demonstrated that qRT-PCR data accurately classified 100% of 81 SS patients with high blood tumor burden. CD4+-purified t-cells from SS patients expressed PLS3, Twist, KIR3DL2, and NKp46 mRNA mean levels (±SEM) of 706±133, 1440±292, 843±96, and 7.1±1.7, respectively. The accuracy was 100% in identifying these samples as SS patients since the four markers were detected in 20% CD4+-purified t-cell samples, three ones in 53%, two ones 20% and only one marker (Twist, PLS3 or Nkp46) in 7%. These results demonstrate that gene expression profiling by quantitative PCR on a selected number of 4 critical genes can be employed for the molecular diagnosis of SS.

P-021

CHARACTERIZATION OF CUTANEOUS LYMPHOMAS AT PONTIFICIA UNIVERSIDAD CATÓLICA DE CHILE (1986-2012)

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INTRODUCTION: Cutaneous lymphomas (CL) are a heterogeneous group of cutaneous neoplasms. A high clinical suspicion and adequate histopathologic techniques are important to a correct and timely diagnosis to prevent the progression.
OBJECTIVE: To analyze epidemiological, clinical and histopathological features of patients with diagnosis of primary and secondary CL at the Pontificia Universidad Católica de Chile (PUC).
PATIENTS AND METHODS: Clinical cases, demographic characteristics and histopathology of patients with diagnosis of primary and secondary CL at PUC between 1986 and 2012 were analyzed.
RESULTS: 161 cases of primary (139 CTCLs and 22 CBCLs) and 19 cases of secondary CL were found. Of the CTCLs 64.7% were mycosis fungoides (MF), 18% lymphomatoid papulosis, 4.3% Sézary syndrome, 3.6% NK/T-cell lymphomas, 2.2% subcutaneous panniculitis-like, 1.4% primary cutaneous anaplastic large cell lymphomas, 1.4% pleomorphic T-cell lymphomas and 4.3% unspecified cutaneous peripheral T-cell lymphomas. Of the MF 64% were classical MF, 21% hypopigmented, 11% folliculotropic, 2% pagetoid reticulosis, 1% plantar and 1% syringotropic. The patients with hypopigmented MF had a mean age of 13 years compared with 55 years in the classical MF. The patients with folliculotropic MF had the worst prognosis of the MF showing recurrences and needing more than one treatment modality. Of the CBCLs 64% were marginal zone B-cell lymphomas, 27% diffuse large B-cell lymphomas (leg type) and 9% follicle center lymphomas. Of the secondary CL 63% were NHL, 26% adult T-cell leukemia lymphoma, 5.5% HL and 5.5% leukemia cutis.
CONCLUSION: This casuistic depicts an idea of the incidence and epidemiology of CL in Chile and Latin America. The incidence of CL is increasing and at earlier age. The most frequent CL was MF with an important proportion of hypopigmented MF at a younger age. We observed a higher proportion of diffuse large B-cell lymphomas than reported in the literature.

P-022

SKIN ULCER AS PRESENTATION OF A T-CELL LYMPHOMA WITH VASCULAR INVOLVEMENT

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Cutaneous t-cell lymphomas (CTCL) are a diverse group of lymphoid neoplasms with heterogeneous clinical manifestations, whose classification has been greatly improved in the last years. Nevertheless, there are still cases that cannot be classified according to the current EORTC/WHO classification. Although patients with CTCL may present skin ulcers, they usually occur in advanced disease stages.
We describe a clinical case of a 29-year-old Caucasian man who presented with a painful cutaneous ulcer on his left leg since the last three months. He denied trauma or application of irritant local topical products. His past medical history was otherwise unremarkable and he was not taking any medications.
Physical examination revealed a well-circumscribed cutaneous ulcer with purple edges covered with thick crust on the anterior left lower extremity, measuring approximately 4x3 cm in diameter. The ulcer was surrounded by multiple small purpuric macules and there were no other relevant findings on physical examination.
Based on the clinical findings a diagnosis of vasculitis was hypothesized and extensive laboratory studies were done in order to exclude this entity. Also, a skin biopsy was performed showing the presence of a perianexial and perivascular lymphocytic infiltrate with predominance of small sized atypical t-cells within the vessels, although without vasculitis. The flow cytometry of the skin biopsy revealed a t-cell lymphoma showing that 12% of the mature t-cells were small CD4+ alpha/beta+ lymphocytes with an abnormal phenotype: CD2 positive (pos); CD3 weakly pos; CD5 positive, CD7 negative, CD26, CD27 and CD28 pos. The blood counts and the biochemical parameters were normal.
Infiltration of the small vessels by lymphoma is a rare event, occurring mainly in the setting of specific large cell lymphoma subtypes, such as intravascular large B cell lymphoma, nasal type T/NK cell lymphoma and anaplastic large cell lymphomas.

P-023

ATYPICAL PRESENTATION OF MYCOSIS FUNGOIDES PILOTROPIC

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INTRODUCTION: Pilotropic mycosis fongoides is a particular form of the disease, because of its clinical and histological aspects, its poor prognosis and its resistance to treatment. We report a case of pilotropic mycosis fongoides with atypical presentation, without mucinosis, whose evolution was favorable with methotrexate.

CASE REPORT: We report a case of 53-year-old man, consulted for hyperpigmented follicular papules, plaques and keratotic pruritic in the extensor surface of limbs, back and abdomen evolving for four years. The cutaneous histology was in favor of Pilotropic mycosis fongoides. After staging, the diagnosis was that of pilotropic mycosis fongoides stage Ib. The patient was put on Methotrexate intramuscularly at a dose of 20 mg/week with a favorable outcome
DISCUSSION: Before the character hyperpigmented, lichenified and keratotic lesions, it can evoke a lichen pigmentosa papular amyloidosis, chronic eczema or parapsoriasis. However, given the presence of follicular papules and keratosis pilaris, a cutaneous lymphoma was considered, including mycosis fungoides in its pilotropic. Clinicopathological confrontation in this observation allowed to retain the diagnosis of mycosis fungoides(MF) in its pilotropic forme. The peculiarities of our observation are the clinical presentation of this type of lymphoma, in its rarity and the favorable methotrexate.

P-024

WHAT IS YOUR DIAGNOSIS? HYPOCHROMIC MACULES

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We report the case of a 53-year-old man, who consulted for facial lesions hypochromic evolving for 5 years with the appearance of secondary lesions diffuse erythematous, scaly. The cutaneous histology was in favor of mycosis fungoides (MF). After staging, the diagnosis was that of a hypopigmented MF in its classic stage IIa. Regarding the presence of hypopigmented lesions, diagnoses were mentioned leprosy, vitiligo, or even a parapsoriasis, eczematides achromiantes. The absence of sensory disturbances and disturbances of sweating has eliminated leprosy. The appearance of erythematous, scaly plaques infiltrated led to the diagnosis of MF. The delayed diagnosis observed in our case is mainly due to the indolence of the disease, lack of functional symptoms including itching and chronic course of the lesions.
The peculiarities of this observation are mainly the occurrence of hypopigmented MF in a patient older than 50 years and phototype clear.

P-025

FOLLICULOTROPIC MYCOSIS FUNGOIDES. SINGLE-CENTER EXPERIENCE OF TEN CASES

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Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma. Folliculotropic Mycosis fungoides (FMF) is an uncommon subtype of MF, characterized by folliculotropic infiltrates of neoplastic T cells, with or without follicular mucinosis. Clinically it presents with grouped follicular papules, acneiform lesions, plaques and occasionally

tumors. The head and neck area is most commonly involved. Several studies report an impaired prognosis compared to classic MF.
We report the clinical, histological, immunophenotypic and genotypic characteristics of ten cases of FMF seen in our department. All patients were diagnosed between 2000 and 2012 at Department of Dermatology, Pontificia Universidad Católica de Chile.
There were ten patients with FMF (six men and four women), aged 23 to 64 years. The mean age at diagnosis was 42.3 years. Five patients (3 males and 2 females) were younger than 40 years at the time of diagnosis.
Clinically the lesions presented as plaques with follicular plugging, papules, nodules and tumors. Involvement of the face or scalp was seen in 7 patients. Three cases had lesions limited to the torso or extremities; 3 patients had significant associated pruritus. One patient developed Hodgkin´s disease 5 years after diagnosis of FMF.
Histopathological examination revealed perifollicular infiltrate with atypical lymphocytes. Some cases showed follicular mucinosis, cystic formation and epidermotropism.
The immunohistochemical analysis was performed in 9 cases. In each case the atypical t-cells showed a CD4+, CD8- immunophenotype. Polymerase chain reaction studies for T-cell receptor (TCR) gene rearrangement were available in 4 cases; a monoclonal TCR rearrangement was identified in 2 patients.

P-026

ACQUIRED ICHTHYOSIS: A NEW REVELATION OF MYCOSIS FUNGOIDES

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INTRODUCTION: Cutaneous lymphoproliferations are rarely associated with acquired ichthyosis, in the particular case of mycosis fungoides, it can correspond, in rare cases, to a rare and special entity called ichthyosiform MF.
CASE REPORT: A 56 year-old man, presented with ichthyosiform eruption of the lower limbs lasting for two years associated with maculopapular pruritic papules of the trunk appeared more recently and lymphadenopathy. Skin biopsy revealed ichthyosiform mycosis fungoides in lesions of ichthyosis and classic mycosis fungoides in lesions on the trunk. CD3 and CD4 were positive and CD8 was negative. The diagnosis was that of a mycosis fungoides stage IIA in its classical form on the trunk and its ichthyosiform type on the legs.
DISCUSSION: Ichthyosis is rarely associated with cutaneous lymphomas. Isolated, it would often suggest first paraneoplastic hypothesis. In the particular context of mycosis fungoides, ichthyosiform eruption may correspond in rare cases, such as our patient, to a particular entity called ichthyosiform mycosis fungoides. This new and rare variant of mycosis fungoides is defined by clinical feature suggestive of ichthyosis vulgaris and histology associating a specific aspect of mycosis fungoides and ichthyosis vulgaris.
CONCLUSION: It seems wise to perform a skin biopsy to a patient with isolated acquired ichthyosis or associated with specific lesions.

P-027

A FOUR YEAR SERIES OF PATIENTS WITH HYPOPIGMENTED MYCOSIS FUNGOIDES IN CHILE

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INTRODUCTION: Hypopigmented Mycosis Fungoides (MF) is an unusual variant of t-cell primary cutaneous lymphoma. It is more common in young patients. Histopathological diagnosis may be delayed for several years.
OBJECTIVE: To describe the experience of patients with hypopigmented MF of the Dermatology Department of the Pontificia Universidad Católica de Chile.
MATERIALS AND METHODS: Medical history and histopathology specimens of patients with hypopigmented MF diagnosed at the Dermatology Department, Pontificia Universidad Católica de Chile from August 2008 to October 2012 were analyzed. Patient demographics, histopathology, immunohistochemistry, t-cell receptor gene rearrangement (TCR) and monitoring were reviewed.
RESULTS: 19 cases of patients with hypopigmented MF were found, 15 patients were under 20 years and 4 over 20 years, 9 women and 10 men. The age range was 4-40 years. In 11 of 19 patients the initial diagnosis was different from MF. Time to definitive diagnosis of MF ranged from 4 months to 3 years. Histopathological examination revealed mild to moderate lymphocytic infiltrates, perivascular and superficial, with epidermotropism of large lymphocytes with convoluted nuclei and occasional Pautrier's microabscesses. Immunohistochemical studies showed loss of CD7 in 13 of 19 patients, the predominant immunophenotype was CD4+ in 4 cases and CD8+ in 11 cases; 2 cases showed CD4+ and CD8+ phenotype, one patient had CD7 50% and CD4 50% and one patient CD7 90% and CD8 90%; 10 of 19 cases showed monoclonal TCR rearrangement by PCR. 17 patients were treated at this center. All cases showed initially a good response.
CONCLUSION: The diagnosis of hypopigmented MF may be delayed due to a reluctance to diagnose this disease. However, MF must always be considered in the differential diagnosis of multiple hypopigmented macules. The biopsy should include conventional analysis, immunohistochemistry and TCR rearrangement.

P-028

TRANSFORMED MYCOSIS FUNGOIDES/SEZARY SYNDROME. REPORT OF ELEVEN CASES

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BACKGROUND: Transformation of mycosis fungoides (T-MF) occurs in 8-55% of MF patients. It is generally associated with an aggressive clinical course and poor survival, requiring aggressive therapeutic approach.
OBJECTIVES: We analyzed the clinical, histological and immunophenotypical features of T-MF in our patient population.

METHODS: We performed a retrospective analysis of the database of the Department of Dermatology. All patients meeting the clinicopathologic criteria of anaplastic large cell lymphoma (ALCL) occurring after mycosis fungoides (T-MF) from 1995 to 2012 were included.
RESULTS: We diagnosed 150 CTCL, 111 were MF. Among these patients we found 11 cases of T-MF (9.9%). Ten were male and one female. Two patients presented folliculotropic MF (FMF) and one patient bullous MF (BMF). Mean age at diagnosis of T-MF was 59.3 years (range 44-76 years). Median time from diagnosis of MF to transformation was 53.9 months. Mean follow up time was 74.9 months. At time of transformation, 90.9% of the patients were in tumor stage (T3); (only two patients had localized lesions and one of this had complete response to treatment and is still alive, the other one was lost to follow up), 1 patient had nodal involvement and 1 had a Sezary Syndrome. Only one patient had complete response and 6 disease progression despite treatment. Eigth patients died (72.7%), deaths were directly related to the lymphoma in 6 cases (including patients with FMF and BMF) and most of them were CD 30+. Two patients were lost of follow up. Mean survival from transformation to death was 16.3 months (11 in patient with nodal involvement).
CONCLUSIONS: In our report T-MF had a high mortality rate (72.7%) related to disease progression and lack of response to treatments. Pathological and immunopathological documentation of progressive MF is important in order to identify T-MF at an early stage; however, an accurate diagnosis is sometimes difficult.

P-029

PRIMARY CUTANEOUS ANAPLASTIC LARGE CELL LYMPHOMA AND CD30+ LARGE-CELLS TRANSFORMED MYCOSIS FUNGOIDES: COMPARATIVE STUDY OF 81 CASES

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Primary cutaneous anaplastic large cell lymphoma (cALCL) is the second most common cutaneous lymphoma after mycosis fungoides (MF) and has an excellent prognosis. MF can undergo a process of large-cell transformation, where large-cells may express or not CD30 antigen. Transformed MF (TMF) has an aggressive course and a poor prognosis. The differential diagnosis between CD30+ TMF and cALCL is a major issue for an appropriate treatment but may be difficult, especially when tumor clinical presentation and histological features raise the question of CALCL associated to MF rather than CD30+ TMF.
We conducted a retrospective study of 2 groups of "typical" cases (32 cALCL and 34 CD30-rich TMF) and a group of 15 "borderline" cases for which the diagnosis was found difficult and controversial between cALCL and TMF. Clinical, histological and molecular features were analyzed to identify markers than may help for the differential diagnosis and/or have a prognostic value.
We confirm the good prognosis of cALCLCL while it was less favorable than expected (77.4% 5-year survival). Stage T3, up to 5 skin lesions and lower limb involvement were associated with a decrease of overall and disease free survival. For CD30+ TMF, (20.7% 5-year survival), stage T4, extra cutaneous involvement, B symptoms and high levels of LDH were associated with poor overall and disease free survival. Comparison between the 2 groups showed that age over 60, up to 5 skin lesions, early progression, absence of spontaneous regression and trunk involvement were significantly associated with the diagnosis of TMF.
Cytotoxic markers were partially informative, with a perforin expression being more frequent in cALCL than in TMF (53% vs 10%, p=0.00065). Finally, translocation of the IRF4/DUSP22 locus was more frequent in cALCL (22%) than TMF (12%) but this difference was not significant (p=0.16) without any prognostic significance in our series.
Thanks to French Study Group of Cutaneous Lymphoma for the TMF group.

P-030

IMMUNOISTOCHEMICAL, CYTOFLUORIMETRIC AND MOLECULAR PROFILES OF CUTANEOUS BLASTIC PLASMACYTOID DENTRITIC CELL NEOPLASM. REPORT OF TWO CASES

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Blastic plasmacytoid dentritic cell neoplasm (BPDCN) is a rare, aggressive hematological malignancy derived from precursors of plasmacytoid dendritic cells. This tumor preferentially involves the skin and presents with solitary or multiple cutaneous involvement as first manifestation, with subsequent/simultaneous spread to bone marrow and peripheral blood. BPDCN exhibits a clinically aggressive course with leukemic dissemination. Initially it was considered a neoplasia of natural killer cells because of the expression of CD56 and terminal deoxynucleotidyl transferase (TdT); now it has been proved that BPDCN is derived from the precursors of plasmacytoid dentritic cell (a specialized subset of dendritic cells known as professional type I interferon-producing cells). We observed two cases.
Case 1: A 75 years old man came to the Hospital complaining diffuse nodular lesions, on the face, neck and trunk, enlarged lymph nodes and hepato-splenomegaly. Clinically the lesions were popular and nodular, red to purple, not ulcerated and measured from cm 0.5 to 2.5. The patient referred the onset of the disease with only a few nodules one month before, followed by a rapid dissemination. The skin biopsy showed neoplastic cells phenotypically positive for CD45, CD4, CD56, TdT and CD33 and negativity for CD20, CD3 and MPO. The molecular analysis showed a polyclonal rearrangement. The patient underwent CHT cycles and had a partial remission followed by a relapse, and died after 10 months from the diagnosis.
Case 2: A 70 years old man came to the Hospital complaining two nodular lesions on the back that were previously been diagnosed as Herpesvirus infections and treated with Acyclovir. As the lesions didn't resolve he was sent to a dermatologic consult and a biopsy was made. The histological and immunohistochemical pictures were similar to case 1. The molecular analysis showed a double rearrangement for the B- and T-lymphocyte. The patient is currently under CHT.

P-031

ZOSTERIFORM HEMATODERMIA OF A CHRONIC LYMPHOCYTIC LEUKEMIA

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BACKGROUND: Cutaneous manifestations of chronic lymphocytic leukemia (CLL) are present in 25%. However, rarely this manifestation came first and exceptionally this skin lesion has a zosteriforme distribution. We report a case of a LLC with an inaugural hematodermia having a dermatomal distribution with no history of herpes zoster or preexistant lesion or surgery.
CASE: Mr MK, 69 year old, with no medical history, presented since 2 months and at the same time asthenia, dyspnea, cervical lymphadenopathies with erythematous skin lesions within a context of fever and weight loss. The examination of the skin objectified on the trunk a zosteriform eryhtematous eruption dotted of pseudo-comedones and infiltrated. These lesions were asymptomatic. The physical examination revealed diffuse peripheral lymphadenopathies. Two biopsies were made: one on skin trunk, and the other of a lymph nod. Histological studies and immunohistochemical showed the same aspect of B lymphocytic infiltration tumor expressing CD20, CD79a, CD5 and CD23. The blood count showed hyperlymphocytosis >5G/l, anemia 90g/l with thrombocytopenia <100G/l. CT of the neck, trunk and pelvis revealed multiple lymphadenopathies in more than 3 lymph node areas with splenomegaly. Matutes score was 5. The patient is classified as Binet stage C and received R-CHOP chemotherapy with good evolution.
CONCLUSION: The skin metastases of chronic lymphocytic leukemia don't seem affecting the prognosis even though they contribute to the tumoral mass.

P-032

PALMOPLANTAR KERATODERMA REVEALING MYCOSIS FUNGOIDES: REPORT OF 4 CASES

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INTRODUCTION: Mycosis fungoides (MF) is the most common variant of cutaneous T-cell lymphoma (CTCL). The localization on the palms and soles is rare and clinically non-specific. Even more, a many inflammatory dermatitis can be evoked.
The purpose of this study is to determin the clinical, histological and evolving characteristics of MFPP collected in our training.
MATERIALS AND METHODS: A retrospective study conducted at the dermatology department of the Ibn Sina University hospital in Rabat, Morocco, covering a 11-year period and including 4 patient presenting MFPP.
RESULTS: Three men and one woman were included with a mean age of 57 years. The mean time to onset of lesions was 18 months. After staging, all cases were classified Ia. Three patients were treated with local puvatherapy. Methotrexate was required in two of them. One patient was treated with topical corticosteroid. The outcome was favorable in all patients

CONCLUSION: The MFPP is an atypical clinical variant of mycosis fungoides. Few studies have published on this subject. The diagnosis is based on histological data, hence the interest to perform a skin biopsy to all palmoplantar keratoderma therapy resistant. The therapeutic management is not codified. The evolution of MFPP is often insidious.

P-033

VALUE OF DIAGNOSTIC PROCEDURES IN PRIMARY CUTANEOUS T AND B CELL LYMPHOMA

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Primary cutaneous T (CTCL) and B cell lymphomas (CBCL) are defined as cutaneous lymphomas that exclusively present to the skin at the time of diagnosis. To rule out extracutaneous manifestations of CTCL and CBCL both EORTC and German guidelines recommend staging diagnostics (chest x ray, abdominal and lymph-node sonography) and in cases of CBCL bone marrow biopsy or serology for Borrelia burgdorferi.
In an attempt to evaluate the significance of these recommended procedures to rule out extracutaneous involvement, we retrospectively analyzed 70 patients with mycosis fungoides (MF), 8 with primary cutaneous anaplastic CD30 postive t-cell lymphoma, 17 follicle center B cell lymphomas (PCFCL) and 14 patients suffering form marginal zone B cell lymphoma (PCMZL). While sonography of the skin draining lymphnodes was helpful in MF to confirm dermopathic lymphadenopathy in 16/21 cases presenting with enlarged palpable lymph-nodes, chest x ray and abdominal sonography in all 58 cases of MF did not detect any lymphoma infiltration. In CD30 positive lymphoma however, we could detect one suspicious lymph-node enlargement in the 8 cases analyzed leading to the detection of extracutaneous disease, which was confimed histologically. In PCFCL, one chest x ray indicated a CT scan which then finally ruled out extracutaneous lymphoma, all remaining PCFCL (16) and PCMZL (10) chest x rays and sonographies were considered normal. Interestingly, in low malignant B cell lymphoma, Borrelia titers were positive in 4/29 (14%) of all cases with a postive IgG in 3/29 and both IgM and IgG in 1/29 cases. Bone marrow histology was performed in 7 patients with PCMZL and in 20 patients with PCFCL, not generating any pathological results.
In summary, our data indicate to consider a diagnostic regimen adapted to the clinical stage to increase sensitivity and specificity of the diagnostic means rather than screening all patients at the time of diagosis with sonography, x ray or bone marrow biopsy.

P-034

CD8-POSITIVE PRIMARY CUTANEOUS T-CELL LYMPHOMA WITH PERIPHERAL AND CENTRAL NERVOUS SYSTEM INVOLVEMENT

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A 67-year-old man was referred to our department with large erythematous patches and plaques on his trunk and extremities. A histopathologic examination was consistent with

mycosis fungoides and phototherapy was started. Three months later, a non-ulcerated tumoral lesion appeared in a previous patch on his back. An histopathologic examination revealed a massive atypical lymphoid infiltrate occupying the entire dermis. The infiltrate comprised small and medium-sized lymphoid cells with irregular, indented nuclei, dense chromatin and large, retracted cytoplasms. The lymphocytes were positive for CD3, CD4 and CD8 but were negative for CD7, CD56, CD30, CD20, CD79a, CD10, Bcl6 and PD1. In situ hybridization for the detection of EBV-encoded RNAs (EBERs) was negative. The CD4/CD8 ratio was within the normal range. A Southern blot hybridization analysis demonstrated a monoclonal rearrangement of the T-cell receptor (TCR) beta- and gamma-chain genes. On the basis of these findings, the patient was diagnosed with primary cutaneous T-cell lymphoma, unspecified (PTLU), with a CD8-positive phenotype. Gradually the patient developed a sensitive and motor axonal peripheral polyneuropathy. A lumbar puncture demonstrated the presence of numerous atypical CD8 lymphocytes in the cerebrospinal fluid. Vertebral nuclear magnetic resonance (NMR) demonstrated a tumoral leptomeningeal infiltrate. Skin biopsies were performed again, and the specimens displayed large, epidermotropic, atypical CD8 cells, with neural, muscular and subcutaneous fat infiltration. Based on the presumption that these CD8-positive cells represented peripheral nervous system and central nervous system (CNS) involvement, the patient was treated with systemic gemcitabine and high-dose methotrexate. Intrathecal chemotherapy with MTX and ARA-C was also started to treat CNS involvement. The patient died several weeks later.

P-035

FOUR CASES OF "CUTANEOUS TYPE" ADULT T-CELL LEUKEMIA/LYMPHOMA

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Adult T-cell leukemia/lymphoma is a hematological malignancy caused by human T-cell lymphotropic virus type I (HTLV-I) with heterogeneous clinical presentation and outcome. ATLL is divided into four clinical variants: acute, lymphomatous, chronic, and smoldering (Shimoyama classification), and this classification is useful for estimating prognosis. Cutaneous involvement is frequent in all types of ATLL. Clinical manifestations include patch, plaque, nodule, multiple papules, erythroderma, and purpura. It is recently reported that the type of skin eruption is an independent prognostic factor for ATLL. In particular, erythrodermic and purpuric types have very poor prognosis. Some patients with indolent ATLL (chronic and smoldering types) suffer from cutaneous lesions without extracutaneous disease until the advanced stage. These cases have been called "cutaneous type", although the term has not been formally accepted. Herein, we present our experience with four cases of "cutaneous type" ATLL. All patients were HTLV-I seropositive and diagnosed as having skin infiltration of ATLL tumor cells by histopathological analysis of biopsy specimens. Clinical presentations were multiple reddish papules (two cases), erythroderma (one case), and multiple violaceous plaques (one case). The erythrodermic patient met the criteria for chronic type ATLL and the others were smoldering type ATLL. All patients have been treated only with skin-targeted therapies such as topical steroid and ultraviolet therapy. None of them has exhibited disease progression during the observation period (13-41 months). Relatively indolent clinical courses of our patients suggest that it is important to analyze the prognosis of "cutaneous type" ATLL on the basis of the skin manifestations.

P-036

ANGIOINVASIVE LYMPHOMATOID PAPULOSIS (TYPE E) – A NEW VARIANT SIMULATING AGGRESSIVE LYMPHOMAS

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Lymphomatoid papulosis (LyP) belongs to the spectrum of primary cutaneous CD30-positive lymphoproliferative disorders and is clinically characterized by papulo-nodular lesions with spontaneous regression and the typical waxing and waning course. Histologically, five types (A, B, C, D, E) have been delineated. We report the clinicopathological features of 16 patients with the most recently reported angioinvasive variant (or LyP type E). Clinically, angioinvasive LyP is characterized by oligolesional papules that rapidly ulcerate and evolve into large necrotic eschar-like lesions with a diameter of 1-4 cm. Median age at diagnosis was 52 years (range 8-72 years). Histologically, predominantly angiotropic and angiodestructive infiltrates of mostly medium-sized lymphoid cells within the walls of veins and small arterioles in the mid and deep dermis were found. Ulceration, necrosis and extensive hemorrhage were usually present. The lymphoid cells expressed CD2, CD3, CD4 or CD8, CD30, beta-F1 and TIA-1, but were negative for CD56 (except for one case) and EBER. There was a predominance of CD8+ cells in half of the cases. Monoclonal TCR gamma gene rearrangements was found in 9 of the 15 cases (60%) studied. As in other forms of LyP, the lesions underwent spontaneous regression after a few weeks leaving behind scars. Recurrences were common, but the prognosis was excellent with no extracutaneous spread or disease-related deaths. Complete remission was observed in 9 out of 16 patients (56%) after a median follow-up of 3 years.
In regard to the low-malignant course with the proclivity of the lesions to undergo spontaneous regression and the excellent prognosis, it is crucial to differentiate this LyP variant from primary cutaneous lymphomas with angiocentric infiltrates and/or a cytotoxic CD8+ or CD56+ phenotype with poor outcome such as extranodal T/NK-cell lymphoma and cutaneous gamma/delta lymphoma.

P-037

PRIMARY CUTANEOUS CD8+ SMALL TO MEDIUM-SIZED LYMPHOPROLIFERATIVE DISORDER IN EXTRAFACIAL SITES – CLINICOPATHOLOGICAL FEATURES AND CONCEPTS ON THEIR CLASSIFICATION

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Cutaneous CD8+ lymphoproliferations have been reported on the face and particularly on the ears. They exhibit an indolent course and share features with primary cutaneous CD4+ small to medium-sized pleomorphic T-cell lymphoma (CD4+ SMPTL) except for the phenotype (expression of CD8 instead of CD4). So far, only a few cases of CD8+ lymphoproliferations arising at extrafacial sites have been described. The classification of these proliferations pose difficulties. We report the clinicopathological features of three cases with cutaneous CD8+ proliferations of small to medium-sized lymphocytes occuring at extrafacial sites. Clinically, the patients presented with papulo-nodular or plaque-like lesions without preceding patches. Histopathologically, the non-epidermotropic nodular or diffuse dermal infiltrates were composed of clonal small to medium-sized pleomorphic lymphocytes which expressed CD8 (more than 80% of the cells) and granzyme B (60-70% of the cells), but were negative for CD4, CD30, CD56 and EBER. In the two patients with solitary lesions complete remission after radiation therapy was observed, whereas one patient with multifocal lesions experienced several recurrences. Based on our observations and the reports in the literature, small to medium-sized pleomorphic lymphoproliferations presenting with solitary lesions show an indolent course and an excellent prognosis independent of their phenotype (CD4 or CD8). In contrast, patients with multiple lesions are at risk for a less indolent course with relapses and should most probably be treated with chemotherapy or other intense regimens. These findings indicate that small to medium-sized pleomorphic lymphoproliferations may represent a phenotypically and prognostically heterogeneous group.

P-038

LYMPHOMATOID PAPULOSIS MIMICKING SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA

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Patient, 72 years, female, caucasian, born and raised in São Paulo capital, came to Hospital A.C. Camargo in July 2010, for her first visit. She had a skin biopsy from another clinical center that histology revealed an atypical lymphoid proliferation infiltrating the dermis and subcutaneous tissue that may correspond to subcutaneous panniculitis-like t-cell lymphoma. At the first consultation, the patient told that the skin lesions had begun 4 months ago. The accompanying daughter reported that the patient had ulcerated lesions with crustings on the eyelid and cheek that improved spontaneously and showed full resolution retaining only residual erythema. The dermatological exam showed infiltrated and erythematous plaque with crusts on the surface on the submandibular region. At upper eyelid and on the cheek there were only residual erythematous macules. The staging tests CT scans of the abdomen, pelvis, complete blood count, LDH, liver function, renal and serology for hepatitis, HIV, HTLV I and II and EBV and bone marrow biopsy were normal. Computer tomography of the chest showed lung nodes. The review of the first biopsy was made and new sample from submandibular region was performed in our service. This exam showed that CD3+, CD4+, CD8+, CD30+ neoplastic cells, CD20 positive B lymphocyte reactional, CD7 and CD21 negative, CD1a positive focal. Cyclin D1, CD10 and Bcl2 negative in neoplastic cells; Ki67+ in 80% of neoplastic cells, perforin, granzyme B and TIA-1 were positive in scattered lymphoid cells allowed to conclude that it was malignant lymphoma CD30+/lymphomatoid papulosis. The patient was referred to the thoracic surgery team and underwent biopsy and subsequent lobectomy D due to the diagnosis of adenocarcinoma acinar of the lung. The skin lesions were treated with corticosteroids and topical antibiotics with full resolution.

P-039

FOLLICULOTROPIC MYCOSIS FUNGOIDES MIMICKING HANSEN'S DISEASE

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A female patient, aged 42, came to our clinic complaining of itching for 5 years, had been diagnosed with leprosy (Hansen's disease) and was in the seventh month of treatment with multi-drug therapy. She was referred to the clinic of Santa Casa with the hypothesis of Type I reaction. The first consultation in June 2007 showed diffuse cutaneous infiltration of the face, generalized pruritus, madarosis, frontal alopecia, follicular hyperkeratosis, generalized xerosis and hypochromic macules by the trunk. In addition, general exams showed only increase of LDH and smear negative. Because of the hypothesis of Type I reaction the authors initiated systemic corticosteroid treatment and maintained regimen for leprosy. Patient progressed without improvement and held new smear negative also. Because of the skin lesions and smear negative, a new biopsy of the face was performed and the result was follicular mucinosis, a characteristic that could be observed in mycosis fungoides. The immunohistochemistry revealed positive immunohistochemical expression of CD5 and CD3 CD4 diffusedly, rare cells CD7 positive, CD8 and CD 20 focally negative. The immunohistochemical profile and histology were compatible with the hypothesis of folliculotropic mycosis fungoides. Serologically tested were negative (HIV, HTLV, hepatitis B and C). Exams for staging (CT scans of the chest, abdomen and pelvis) confirmed cutaneous exclusive involvement.

P-040

SKIN LESIONS AS FIRST SIGN OF LENNERT LYMPHOMA – DESCRIPTION OF TWO CASES

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INTRODUCTION: Lennert's lymphoma is a peripheral T-cell lymphoma that only rarely (in about 7%) involves the skin and may follow a variable course. In the new WHO-EORTC classification of cutaneous lymphoma (vers. 10, 15.02.2005) it has been placed in the subgroup – "primary cutaneous peripheral T-cell lymphoma- unspecified".
MATERIALS AND METHODS: We describe a 61-year-old female patient with a one year history of grouped follicular papules, cysts and comedo – like lesions and some superficial, erythematous, mildly scaling plaques, localized on the trunk and the extremites. Findings of a biopsy specimen showed perifollicular as well as intrafollicular infiltrates of atypical lymphocytes. In some of the biopsed lesions were found groups of epithelioid cells. The infiltrates were predominantly composed of CD3+, CD4+ cells. The patient was considered as having follicular mycosis fungoides. Four months later the patient developed a swelling of tonsils and submandibular lymph nodes, histologically and immunohistochemically diagnosed as Lennert's lymphoma. A second case of a 61-year old male patient presented at our department with erythematous macules on the whole body, severe headache, change in the perception of tastes, swelling of the left tonsila, left cervical lymphadenopathy, loss of weight (10kg in two months) and dysphagia. Hystological findings from a skin, tonsilar and lymph node biopsies showed infiltration from a periferal T-cell lymphoma, not otherwise specified.
RESULTS: The patients ware successfully treated by polychemotherapy with complete regression of the tonsilar changes and reduction of skin lesions.
DISCUSSION: Cutaneous manifestations in Lennert's lymphoma have only rarely been reported and include atypical granuloma anulare, erythroderma, erythema nodosum, chronic pyoderma, neurodermitis, and prurigo nodularis. To our knowledge there is no literature data of Lennert's lymphoma presenting with follicular skin lesions.

P-041

LENNERT LYMPHOMA WITH SKIN INVOLMENT

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A 27 year-old woman presented with a 3-month history of intermittent fever, splenomegaly, hepatomegaly, and 2 weeks of a papular and nodular skin rash that started in her back that later became widespread. The skin lesions consisted of nodules and papules with central necrotic crust initially; later, she developed erythematous edematous plaques on the abdominal wall. A skin biopsy was performed which showed granulomatous reaction without B lymphocytes. Immunohistochemistry confirmed a reactive granulomatous disorder with histiocytes and CD8 positive T cells. A month later, the patient returned with fevers and lymphadenopaty.

An excisional biopsy of a lymph-node showed CD3 and perforin positivity. These findings, together with a >50% Ki67, loss of T lymphocyte markers (CD5, CD7) and an altered CD4/CD8 ratio, favor the diagnosis of a peripheral lymphoma T-type lymphoproliferative disorder. The abundance of histiocytes, epithelioid cells and formation of microgranulomas suggest Lennert lymphoma. Only a small percentage of patients with Lennert lymphoma reported in the literature have cutaneous manifestations. She was started on CHOP chemotherapy which led to resolution of the skin lesions. We declare no conflics of interest.

P-042

A CASE OF MYCOSIS FUNGOIDES WITH MANIFESTATION IN THE ORAL CAVITY

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BACKGROUND: Diagnosis of mycosis fungoides (MF) can be difficult due to its highly variable presentation and sometimes nonspecific nature of the histological and molecular findings.
CLINICAL CASE: A 74-year-old male presented to our centre with an 11-month history of progressing right cheek deformation. Three operations were performed at the department of facial-maxilliar surgery during 8 months. A diagnosis of the right chronic necrotic maxillar sinusitis and osteomyelitis was established. Physical examination revealed a 4 cm diameter hole-defect, slight swelling, erythema, necrotic crusts of the right side of oral mucosa membrane. Additionally, red, slightly scaling patches on the right side of neck and armpits were noticed. Peripherial lymph nodes were not palpable. Laboratory tests revealed a mild anaemia, leucocytosis and trombocytosis, elevated ESR and CRB. Serology, biochemistry, and screening tests – within normal ranges. CT scan of the face revealed that almost all right side sinuses were filled with heterogenic content. A deep skin biopsy from mucosal lesion showed mixed dermal infiltration, arteriitis of medium size arteries. The biopsy from the skin lesion revealed dermal perivascular, interstitional infiltrate of atypical T-lymphocytes (CD4+, CD8+) without epidermotropism. The phenotype of the oral mucosa and cutaneous lesions was different, but both biopsies were the same clonal rearrangement of t-cell receptor gamma gene. The patient was treated with 30mg of prednisolone per day and 500mg of ciprofloxacine 3 times a day, for two weeks. After few months, the patient stopped any treatment, he passed away 14 months later.
CONCLUSION: Oral involvement is uncommon in cutaneous T-cell lymphomas and usually associated with poor prognosis. In our case, the presence of the same clonal population of T lymphocytes at both sites support the diagnosis of MF with involvement of the oral cavity.

P-043

NECROTIZING ULCERATIVE TUMOR CHIN

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INTRODUCTION: We report the case of a man presented a mycosis fungoides (MF) tumor immediately transformed in T-cell lymphoma with large CD30+ cells.
CASE REPORT: Mr M. B 61-years-old consulted in July 2008 for an ulcerative crusty tumor on the chin. The diagnosis of mycosis fungoides tumor stage IIB was accepted. Treatment with chemotherapy was called. A year later, he has presented an infiltrated lesions evolving rapidly towards a state of erythroderma. The skin histology was in favor of T-cell lymphoma CD30+ anaplastic. The patient had died a few days after his admission in an array of shock.
DISCUSSION: The peculiarity of our observation is the rarity of the location of the MF on the chin, uniqueness, revelation at the outset by a tumor lesion, rapid development and transformation into aggressive lymphoma CD30+ anaplastic large cell.

P-044

CHARACTERISTICS OF 39 CASES OF PRIMARY CBCL: CORRELATION OF TNM STAGING WITH OUTCOME

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Thirty-nine patients with primary CBCL were identified from the histopathology database at University Hospital Birmingham since 2000. Case notes and pathology were reviewed.19 were male and 20 female.The mean age at diagnosis was 62 years (range 20-90 years). Subtypes included 18 with follicular centre (FCC),13 marginal zone (MZL) & 8 diffuse large B-cell (DLBCL).
Sites involved were head & neck in 8, trunk in 7, upper limbs in 5, lower limbs in 5 (3x DLBCL) and multiple sites in 14 (36%). Pruritis or pain were reported by 5 and the rest were asymptomatic. 21 (54%) patients had single skin lesions and 18 had multiple (46%). Morphology of lesions was nodular in 25, patches & plaques in 12 and large tumours >15cm in 2 (both DLBCL). LDH was raised in 4 patients. 3 had bone marrow involvement.
First line treatments included superficial radiotherapy in 17 patients(47%), surgical excision in 7, chemotherapy in 8, topical steroid in 2, PUVA in 1 and expectant policy in 4 patients.
Relapse occurred in 17 patients (44%); 4/8 with DLBCL, 8/18 FCC & 5/13 MZL. 7 of these had extra-cutaneous disease. 6 patients died from lymphoma(15%),15 are alive and disease free,14 alive with disease and 4 were lost to follow up. The mean follow up was 4 years.
In 2007 EORTC/ISCL published a TNM classification for CBCL. All patients were staged retrospectively at diagnosis. Among 20 with T1a/b disease, 5 had nodal disease, 2 died (both DLBCL, N0) & 6 had recurrence, mean FU 76 months. All 6 patients with T2 (all N0) were alive, 4 recurrences. 13 had T3, 2 died both had nodal disease (DLBCL & FCC) & 7 recurrences, mean FU 54 months. Of the 9 patients with nodal disease; 4 died (2 FCC & 2 DLBCL) and 3 others recurred, mean FU 32 months. No patients with MZL including 7 with T3 died. This trend may suggest some prognostic value from this staging system but early stage DLBCL may still have an aggressive course. Larger studies comparing stage & outcome in DLBCL would be informative.

P-045

CASE REPORT: PRIMARY CUTANEOUS CD30 ANAPLASTIC LARGE CELL LYMPHOMA

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Primary cutaneous CD30+ lymphoproliferative disorders, accounts for 30% of the primary cutaneous T-cell lymphomas and includes the spectrum between primary cutaneous anaplastic large cell lymphoma (PCALCL) and lymphomatoid papulosis. PCALCL has variable clinicopathologic and immunologic features. It is characterized by the absence of systemic involvement at presentation, an indolent course, spontaneous remissions, and low recurrence rate after therapy and infrequent dissemination.
A 75-year-old male presented with a 1-year history of an asymptomatic, irregularly shaped erythematous nodule at the nose. This enlarged for the past 3 months. Physical examination revealed one erythematous to violaceous indurated tumor over the nose measuring 2.5×3.5cm. There were no lymphadenopathies or hepatosplenomegaly. Review of systems was unremarkable. Work-ups were negative for extracutaneous involvement. Skin punch biopsy showed dense infiltrates of non-epidermotropic, large, irregularly-shaped lymphocytes with hyperchromatic nuclei and mitoses extending from the superficial to deep dermis. Immunohistochemistry revealed that these atypical cells are CD30+, CD3+, CD4+ and CD20- Clinical, histopathological and immunohistochemical findings were consistent with PCALCL. Due to cartilage involvement, proximity to central nervous system and rapid progression, chemotherapy was performed. He was treated with six months of CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) achieving total resolution of skin lesions.
Primary cutaneous anaplastic large cell lymphoma (PCALCL) is a rare type of non-Hodgkin's lymphoma comprising approximately 0.9-9.0% of all cutaneous lymphomas. The clinical presentation of PCALCL can be variable, so a high index of suspicion is necessary in patients presenting with tumors and nodules unresponsive to topical or oral medications. PCALCL has a favorable prognosis with 5- and 10-year survival rate of 91 to 100%.

P-046

MYCOSIS FONGOIDES PRESENTING AS HYPOPIGMENTED AND PIGMENTED PURPURA-LIKE LESIONS

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BACKGROUND: Mycosis fungoides (MF) has a heterogeneous clinical presentation. We report an unusual case of hypopigmented variant associated with pigmented purpuric dermatitis-like (PPD-like) MF in a young patient.
CASE REPORT: A 25-year-old male, Fitzpatrick skin phototype IV, presented with an 8-year history of asymptomatic hyperpigmented macules. He had numerous brownish-purplish patches on his trunk and limbs. He also had widespread hypopigmented rounded macules and 3 scaly erythematous slightly infiltrated patches on his trunk. Two biopsy specimens were obtained from erythematosquamous and purpuric lesions. The histopathological examination combined with immunophenotypic evaluation confirmed the diagnosis of MF. Blood analysis and thoracoabdominopelvis scan was normal. The patient's disease was at stage T2bN0M0. He was treated with PUVAtherapy, three times a week for 3 months, which induced complete remission of the hypopigmented patches and desinfiltration of eryhtematosquamous lesions but was ineffective for the purpuric lesions. The patient begins injectable weekly methotrexate.
DISCUSSION: In our patient we noticed hypopigmented and pigmented PPD-like MF despite the fact that these two clinical variants are very rare conditions. PPD-like MF is characterized by persistent pigmented purpuric lesions associated with the histopathological hallmark of small cerebriform lymphocytes exhibiting epidermotropism. MF, manifesting as hypopigmented patches, occurs in young dark-skinned patients. It may be confused initially with a lot of other pathologies. The cause of hypopigmentation may be due to a decreased transfer of melanosomes from melanocytes to keratinocytes, as a non-specific response to inflammation. Both the treatment and prognosis of these forms are the same as in classical MF.
CONCLUSION:The possibility of the coexistance of atypical variants must be kept in mind even though rare, and skin biopsies must be done for early diagnosis of the disease.

P-047

SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA AND LUPUS PROFUNDUS: AN ILLUSTRATIVE CASE

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The distinction between subcutaneous panniculitis-like T-cell lymphoma (SPTL) and lupus profundus is sometimes extremely difficult. Patient: Female, 34 years old, had a subcutaneous nodule on her left arm in 2004 with a biopsy compatible with lupus profundus. She developed new subcutaneous plaques and nodules on face and arms, and alopecic plaques on scalp. A new biopsy from the arm in 2012 revealed hyaline necrotising lobular panniculitis with an oligoclonal atypical lymphoid infiltrate with an T-suppressor phenotype, rimming of adipocytes by neoplastic t-cells (Mib-1/Ki-67+), some bean-bag histiocytes and DIF-, all findings suggestive of SPTL. A biopsy from the scalp showed overlapping features of lupus and SPTL on the scalp. ANA was +1/80 (speckled) and antidsDNA+. She was treated with a course of systemic prednisolone and maintenance with methotrexate with excellent response (8 months). The nature of SPTL and lupus profundus has been studied and some authors think that they form a spectrum of disease while others believe that they are distinct entities with some overlapping cases, and evidence of one disease cannot be used to rule out presence of the second.

Therapy

P-048

LEUKEMIA CUTIS IN ACUTE LYMPHATIC LEUKEMIA (ALL)

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BACKROUND: Leukemia cutis (LC) is an uncommon manifestation of leukemia that is strongly associated with the presence of further extramedullary disease manifestation. Patients usually present with leukemia cutis synchronously with time of first diagnosis of systemic leukemia or after leukemia has already been diagnosed.
CASE REPORT: After conditioning chemotherapy with the FBTT-protocol (fludarabine, BCNU and thiotepa) the acute lymphatic leukemia (ALL) of a 60-year old patient was treated with allogeneic stem cell transplantation of his HLA-identical brother. Four months later erythematous painful solid tumour nodes on the forehead developed. Beside macrocytic anemia (erythrocyte count 2.86 Mio/µl, haemoglobin 10.2g/dl) leucocytes and thrombocytes were normal. The histological evaluation revealed an extensive infiltrate of large mitotic cells with dense chromatin rich nuclei. Based on staging examinations the cutaneous infiltrate was the solitary sign of relapse of the ALL. A complete remission of these chloromas was achieved by imatinib therapy with 400mg/d, but lasted only for three months. Then the patient developed a new chloroma and one month later he developed further nodular cutaneous leukemia infiltrations. These nodules were treated with radiotherapy, followed by chemotherapy with vincristin in combination with nilotinib, cytosine-arabinosid and idarubicin. Due to constant clinical progress with 60% of blast cells in the peripheral blood (without bone marrow involvement) he finally received another allogeneic stem cell transplantation.
CONCLUSION: The lesions of leukemia cutis show a variable morphology and it can be difficult to distinguish both clinically and histopathologically from nonspecific lesions. Differential diagnoses of chloromas include primary cutaneous tumours like basal cell carcinoma, merkel cell carcinoma and adnexal tumours like zylindroma. The prognosis once leukemia cutis has occured is … (abstract truncated).

P-049

TOTAL SKIN ELECTRON BEAM FOR CUTANEOUS T-CELL LYMPHOMAS: A RETROSPECTIVE STUDY FROM 3 HOSPITALS IN BARCELONA FROM 1999 TO 2012

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INTRODUCTION: Total skin electron beam (TSEB) is palliative treatment used mainly in primary cutaneous T-cell lymphomas (CTCL). The aim of this study is to retrospectively assess the outcome and toxicity of a TSEB in patients with CTCL.
MATERIAL AND METHODS: We included 19 patients with CTCL (median of age 56.6 years; 12 males and 7 females) visited in the Dermatology departments of 3 hospitals in Barcelona who received TSEB between 1999 and 2012. Sixteen patients were diagnosed of mycosis fungoides, two patients had CTLC not-otherwise-specified, and one patient had Sézary syndrome. Four patients were classified as I stage, thirteen as II, one as III and one as IV stage. All patients had received multiple treatments before TSEB.
RESULTS: Complete response was achieved in 68.42% of patients, and the overall response rate (complete response + partial response) was reached in 100% of patients. The median of dose received was 34 Gy. 36.8% of patients received a supplemental irradiation to treat shadowed areas, with a median dose of 30 Gy. 36.8% of patients relapsed with a median of time to relapse of 2.33 months, which was mainly treated with different chemotherapy schemes. 47.37% of patients (nine patients) died with an overall survival of 16.4 months after having received TSEB. Six of these nine patients died due to progression of the primary cutaneous T-cell lymphoma. The remaining ten patients are nowadays alive, one patient had a partial response and the remaining nine patients are free from disease. All patients suffered from acute adverse events; 78.95% of patients suffered from grade 1 or 2 epithelitis, and 21.05% had grade 3 or 4 epithelitis. Long-term adverse events including asymptomatic cataract and constant tearing were only documented in two patients.
DISCUSSION: TSEB is an effective treatment for refractory lymphomas, with good initial response. Folliculotropic mycosis fungoides is the subtype of CTCL with better overall response rate in our study

P-050

DOES PREEMPTIVE LEUCOVORIN USE COMPROMISE THE EFFICACY OF PRALATREXATE IN CTCL

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Pralatrexate (PDX) is a novel FDA-approved antifolate for the treatment of relapsed/refractory PTCL and transformed Mycosis Fungoides (T-MF) with an overall response rate of 29% in the pivotal Phase II "PROPEL" clinical trial. Symptomatic mucositis, the most common treatment-related adverse event (AE), affected more than 70% of the patients and in 22% it was the dose limiting toxicity.

PDX has a higher affinity for the reduced folate carrier (RFC) and the folylpolyglutamate synthetase enzyme (FPGS), therefore, a more selective accumulation in cells than other antifolate agents. In some cell cultures PDX was up to 100 times more potent in terms of cell killing. Due to this increased uptake and prolonged intracellular activity 30mg/m^2 of PDX may be akin to ~300mg/m^2 or more of methotrexate (MTX) at the cellular level. Leucovorin (LV) rescue is the standard of care with high dose MTX to prevent side effects while preserving efficacy, but in PDX therapy it is recommended only for overdose and has not been studied for preemptive use. In our clinical experience the vast majority of CTCL patients on PDX develop significant mucositis leading to dose reduction or discontinuation of treatment.
LV bypasses the antifolate blocked dihydrofolate reductase enzyme (DHFR) as it is not dependent on the DHFR to participate in "one carbon" reactions for DNA synthesis. As a whole, studies of other antifolates in combination with LV have had mixed results in determining any compromise in efficacy due to LV use. Efficacy of PDX after LV administration may be related to several factors including timing of a subsequent PDX infusion, route of administration, dosage, and form of LV given. All of these effect the intracellular accumulation of LV and thus the affect it can have on the efficacy of PDX. We have used the PDX-LV combination efficaciously while essentially eliminating mucositis and other AEs and recommend further randomized clinical trials to evaluate this combination therapy.

P-051

HYPOPIGMENTED MYCOSIS FUNGOIDES IN A CAUCASIAN WOMAN – SHORT REMISSION AFTER TRADITIONAL PHOTOTHERAPY PROTOCOL

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INTRODUCTION: Hypopigmented Mycosis fungoides is a rare clinical variant of cutaneous T-cell lymphoma associated with good prognosis. Only few cases are reported in Caucasians patients.
MATERIALS AND METHODS: We present a case of a 26-year old Caucasian woman who presented at our clinic with multiple disseminated hypopigmented macules on the trunk and extremities since more than 4-years. Skin biopsy from affected and non-affected skin has been performed revealing exocytosis of lymphocytes, marked epidermotropism and single atipical T-cells in the epidermis. Clinical and histological diagnosis of Mycosis fungoides-hypopigmented variant has been established.
RESULTS: Narrow Band Ultraviolet B- Treatment has been initiated according to the phototherapy protocol at our clinic with 4 sessions/weekly with initial dose of 0.3J/cm^2 and incensement of the dose with 0.05 at each session after good tolerence of the previous dose. A total number of 27 sessions has been performed with complete clinical response (disappearance of all existing lesions for at least one month) has been achieved after the 22nd session. Total UV dose was 17.5J/cm^2 and complete clinical response was achieved at a dose of 11.85J/cm^2. No maintenance phototherapy has been administered according to the protocol. Skin biopsy after the end of the treatment revealed lower than the initial number atipical CD3+ mostly CD4+ T-cells in the epidermis. The disease-free interval was 2.5 months.

DISCUSSION: We presented a case of complete clinical remission of a patient with hypopigmented Mycosis fungoides with a significantly low cumulative dose of NB-UVB (17.5J/cm^2) with a 4 times/weekly regiment. Although there was complete clinical response, histological remission was not achieved and the disease-free interval was short. Traditional phototherapy protocols for Mycosis fungoides have to be challenged in the hypopigmented variant of this entity.

P-052

CUTANEOUS T-CELL LYMPHOMA – LIBYAN EXPERIENCE OF MANAGEMENT

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BACKROUND: Mycosis fungoides (MF) represents the commonest form of cutaneous T-cell lymphoma subsets. No available data from Libya about Mycosis fungoides.
OBJECTIVE: To study the clinicopathologic features, treatment, and coarse of mycosis fungoides among Libyan patients.
PATIENTS & METHODS: Fourteen patients diagnosed as MF according to the clinical, histological, immune-histochemistry findings, peripheral blood smear for atypical lymphocytes and further staging. The result of treatment options according to clinical staging and follow up were analyzed.
RESULTS: A fourteen patients with proven diagnosis of mycosis fungoides. Six were females and eight were males, with a male to female ratio of 1.3:1. Age ranged (16-60 year), mean of age ±SD of 48.3±14.3 years. Eight patients had diseases duration of less than five years, while six had a disease duration of more than five years. One patient (7%) had tumour presentation, three patients (21%) presented with piokilodermatous MF, and two patients (14%) with generalized scaly atrophic patches, while the remaining eight patients (58%) presented with scaly patches and plaques. One female patients had also lymphomatoid papulosis. TNMB classification of the patients revealed that nine (64%) patients had stage IB MF, four (29%) patients had stage IIA, and one (7%) male patient had stage IIB. Five patients received systemic PUVA therapy, five patients receive narrowband UVB and three patients received weekly oral methotrexate and narrowband UVB. One patient developed severe photosensitivity with phototherapy, he received short course of systemic steroids and then shifted to systemic retinoid. Two patients lost follow up, while the remaining patients still under follow up with good response to treatment.
CONCLUSIONS: Mycosis fungoides is not uncommon in Libyans and need awareness from dermatologists.

P-053

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P-054

TOTAL SKIN ELECTRON BEAM THERAPY FOR PRIMARY CUTANEOUS LYMPHOMA

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PURPOSE: To document the outcomes of a series of 79 patients treated with total or near total skin electron beam therapy (TSEB) between 1987 and 2011.
PATIENTS/METHODS: There were 49 males (62%) and 30 females (38%), with median age 61.4 years (range 23.5-83.5). Diagnoses were mycosis fungoides (59%), Sezary syndrome (30%), other t-cell skin lymphoma subtypes (8%) and primary cutaneous B cell lymphoma (3%). In patients with t-cell disease, 33% had Stage 1 disease at commencement of TSEB, with 21% stage 2, 21% stage 3, and 20% stage 4. Four patients (5%) treated post-auto/allograft had no detectable disease at commencement of TSEB. The median number of prior therapies was 2 (range 0-11). All patients were treated with a 6MeV rotational technique, with direct electron boosts to areas of concern underdosed by the rotational technique (axillae, upper thighs etc). The majority of patients (86%) received 30-36 Gy in 20-24 fractions over 7 weeks.
RESULTS: All patients had an objective response during treatment, but in some this was very short-lived. At one month post-TSEB, 84% had achieved a complete or partial response, but 13% had progressive disease. Pruritis was improved in 88% of patients with this symptom pre-TSEB. The median time to progression post-TSEB was 5.2 months (stage 1-22.2 months). Eight patients remain in remission at a median of 17.2 months post-TSEB. Median survival from diagnosis for the entire group was 13.0 years.
CONCLUSION: Results of TSEB are less favourable than previous literature suggests. We hypothesize that the emergence of effective systemic agents over the last ten years had led to TSEB being more frequently deferred until late in the course of the disease, with consequent poorer results. We are therefore increasingly using a combined modality "maintenance" approach to maximise the duration of response post-TSEB. TSEB continues to provide valuable symptom palliation in appropriate patients.

P-055

HISTONE ACETYLATION AND DNA DEMETHYLATION IN CUTANEOUS T CELL LYMPHOMA

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Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of malignancies derived from skin-homing T cells. CTCL is a chronic and at times debilitating disease with many open questions regarding its pathogenesis and an ultimate successful therapy regimen. Relapse is common during the disease course, which is difficult to treat and curative therapy remains elusive. HDAC inhibitors can synergize with demethylating agents and are shown to be effective in hematological malignancies. Here, we hypothesized that the combination of Romidepsin and Azacytidine is synergistic in well-characterized CTCL cell lines and SS patients' PBL. In addition, we analyze the molecular basis for this synergistic effect by evaluating gene and protein expression for the cells treated with the single and combination agents in CTCL. To determine the effect of the combination treatment with Romidepsin and Azacytidine compared to single agent or untreated cells we performed MTT for cell viability and Annexin V assay via flow cytometry. Indeed, the combination treatment showed a noticeable change of cell viability due to an increase in apoptosis and necrosis in a time and dose dependent manner. Furthermore, we observed a more pronounced increase cell cycle arrest by induction of cell cycle regulators such as p15, p16, p21 and in acetylation of H3 in the combination treatment than either drug alone suggesting that this combination treatment counteracts the loss of cell cycle control in CTCL more efficiently. Addtionally, the combination treatment effectively triggered cell-death signalling pathways by demostrating an increased cleavage caspase 9 as well as the effector caspases 3 and 7 and increase in cleavage of PARP1 more so than single agents. Our investigation will not only help elucidate the epigenetic control of CTCL pathogenesis in vitro and in vivo but also provides a platform to identify biomarkers that could be used in clinical studies evaluating efficacy of this combination.

P-056

MYCOSIS FUNGOIDES MIMICKING ABSCESS FORMATION

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Diagnosing Mycosis Fungoides (MF) remains a challenge due to diverse clinical presentations and subtle microscopic features. Molecular diagnostic techniques have improved the diagnostic accuracy. A 65-year-old man with MF stage 1B maintained on interferon alpha therapy developed painless, firm nodules on his right forearm and wrist, which slowly enlarged and ulcerated. There was no response to numerous courses of antibiotics. An ultrasound scan revealed the masses to be solid. Three incisional biopsies and complete excision of the largest nodule on the right forearm consistently demonstrated dermal suppurative abscesses with surrounding granulation tissue and failed to confirm cutaneous T-cell lymphoma (CTCL). The epidermis was acanthotic, but otherwise unremarkable. Marked dermal fibrosis and scarring was interspersed with an extensive inflammatory infiltrate composed of neutrophils and eosinophils. Giant cells and granuloma formation were not a feature. Ziehl-Neelsen, Gram, Periodic Acid Schiff and Grocott stains were repeatedly negative for micro-organisms, as were microbacterial PCR, acid fast bacilli and fungal culture. Some histological sections revealed a lymphoid infiltrate composed of B-cell follicles, T lymphocytes and macrophages. The T-cells were predominantly $CD4^+$ and included activated forms, felt to be commensurate with the degree of inflammation. No convincing evidence of MF was seen in any biopsy, although low-grade lymphoma could not be definitively excluded. CD30 staining was negative. The excised lesion the regrew within 3 months. Assessment by the Infectious Diseases team excluded infection. A single fraction of radiotherapy (8Gy) was given to each of the lesions. There was an excellent clinical response which has been sustained, further supporting the diagnosis of tumour-stage MF. This is the first reported case of tumour stage MF mimicking

abscess formation and highlights that patients with CTCL may present with new atypical lesions posing difficult diagnostic questions.

P-057

TOTAL SKIN ELECTRON BEAM RADIATION THERAPY IN CUTANEOUS T-CELL LYMPHOMA: A RETROSPECTIVE ANALYSIS.

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AIM: Total Skin Electron beam Therapy (TSET) is an effective therapeutic strategy in the management of advanced Cutaneous T-cell lymphoma. The presents study reports the retrospective analysis of patients treated with TSET at our centre.
MATERIAL AND METHODS: A total of 5 patients of Cutaneous T-cell lymphoma were analyzed from January 2004 to March 2011. All the patients were treated with Elekta Precise Linear accelerator with high dose rate mode of 3000cGy/min at isocenter. All the patients were treated as per the Stanford technique, delivering a total dose of 36Gy with a dose of 1.2Gy/f/day using 4MeV electron beam. Out of six fields planned, three fields per day were delivered alternatively. In all the sessions nails and eyes were shielded with 3mm lead shield. Boost dose of 10 Gy was delivered to the self-shielded regions.
RESULTS: Out of 5 patients studied, 4 had stage IIB disease. One patient achieved complete remission following TSET while 2 patients died of progressive disease during treatment. After completion of radiation, 2 patients continued on PUVA therapy. The main complication observed were non hematological toxicities: four patients had grade III skin reaction and rest patients had grade II dermatitis. At median follow up time of 3.5 years, two patients were alive without any disease. Three patients died due to relapse in non cutaneous sites within 2 years.
CONCLUSION: Total Skin Electron Beam Therapy was well tolerated and effective treatment of advanced Cutaneous T-cell lymphoma.

P-058

EXTRACORPOREAL PHOTOPHERESIS: THE EXPERIENCE OF A PIONEER DERMATOLOGY UNIT IN ARGENTINA

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Extracorporeal Photopheresis (ECP) is an approved FDA treatment for cutaneous lymphoma and Sezary Syndrome. Since July 2011 we have been working on ECP, as a pioneer Dermatology Unit in our country, Argentina. We already treated six patients (3 males) who suffered from cutaneous lymphoma. Mean age was 66 years (48 to 78), clinical diagnosis were: Sezary Syndrome stage IVb, erithrodermic mycosis fungoides (MF) with follicular mucinosis stage III, erithrodermic MF stage III, and three relapsed and resistant MF stage IIa. Two IIa stage patients were not included in the analysis since they were in an early part of their treatment. The length of the treatment was related with the severity of the condition and its evolution. The number of sesions performed were between 8 to 58 (twice a month). Three patients started the treatments as monotherapy and one, combined with bexarotene (eritrodermic MF with FM). The stage IIa patient improved more thant 50% his lesions, but after he was submitted to an aortic aneurysm surgery, his limphoma worsened and it was added PUVA therapy, with significant improvement. Stage III MF patient stabilized her disease after five month treatment, and now is in plan of adding other immunomodulatory therapy. SS patient was a male that did not respond to four month of ECP, so the treatment was changed for vorinostat, he died four month later. The patient with erithrodermic MF with follicular mucinosis improved (pruritus, cutaneous erithema and infiltration below the neck), but conversely he developed facial tumours needing polychemotherapy after six month of ECP. No adverse effect secondary to ECP was documented.
Since we have just initiated our experience in ECP in our country, it is very important for us to share our experience in this field.

P-059

LOW DOSE HIGH-DOSE-RATE BRACHYTHERAPY IN THE TREATMENT OF FACIAL LESIONS IN CUTANEOUS T-CELL LYMPHOMA

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BACKGROUND: Mycosis fungoides (MF) is the most common subtype of cutaneous T-cell lymphoma (CTCL), and describes a malignancy of CD4+ mature skin-homing T-cells with characteristic immunophenotypic changes. It is not unusual for patients with MF to develop facial lesions which are uniquely burdensome and refractory to treatment. Moreover, the use of many of the standard skin directed MF therapies on facial skin may be limited by site-specific increased risks of side effects, excessive inflammation and ocular toxicity.

OBJECTIVE: Our study aimed to describe the levels of erythema, scale, and induration of facial lesions in MF before and after low dose high dose rate (HDR) surface applicator brachytherapy and to examine the overall clinical response to brachytherapy.
METHODS: A total of 23 facial MF lesions in 10 patients were treated with HDR brachytherapy doses of 4 Gy per session for a total of 2 fractions at our multidisciplinary cutaneous oncology clinic between 08/17/2009 and 03/12/2012.
RESULTS: In all 23 lesions, dramatic clinical improvement was observed. Patients were followed for a median of 6.3 months. No recurrences were reported in the follow-up period.
LIMITATIONS: Long term follow up is lacking. Reassessment of all included patients at annual intervals for a period of at least 5 years is the authors' goal.
CONCLUSION: Low dose HDR brachytherapy utilizing custom-made surface molds is a highly efficacious therapy in the treatment of facial lesions in MF.

P-060

CASE REPORT: FOLLICULAR MYCOSIS FUNGOIDES TREATED WITH BEXAROTENE PLUS INTRALESIONAL INTERFERON

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There is no therapy that is considered the treatment of choice for follicular mycosis fungoides (F-MF)and sometimes it is also difficult to realize a good staging of the disease.
We describe a patient with F-MF with predominantly affectation of the face and excellent response to intralesional interferon alpha-2a (IFN) and oral bexarotene.
A 36-years-old woman presented with a two years history of a pruritic rash that began on her arms. The eczematous plaques rapidly developed into a progressive lesions with infiltrated plaques showing numerous enlarge tumoral lesions with an important face affectation. We did several skin biopsies that suggested F-MF. Laboratory examination and Computerized tomography were normal. The diagnosis of F-MF IIB (T3, N0, M0) was made.
The patient began treatment with PUVA therapy plus oral bexarotene but about 3 weeks we discontinued PUVA therapy because she did had not well evolution. She developed multiple comedo-like follicular lesions. So, we proposed she was treated with a combination therapy consisting of intralesional IFN (3 million three days a week) and bexarotene 300mg/m2/daily for 3 months with total remision. She continued with low maintenance doses of bexarotene.
There is no therapy that is considered the treatment of choice for F-MF. In general, patients responded poorly to skin-directed therapy possibly due to the deep follicular localization of the malignant T cells. The mechanism of action of this combined therapy on cutaneous lesions remains unclear. In vitro, a synergistic effect of retinoid on IFN antiviral activity has been demonstrated and in vivo and inmunohistochemical study showed that the combined therapy modulates antigens expressed by keratinocytes and increases cytotoxic cells in dermis without modifying the number of Langerhans cell in epidermis.
The results suggest bexarotene and IFN to be an effective and well tolerated combination treatment of F-MF

P-061

CUTANEOUS LYMPHOMA MULTIDISCIPLINARY CLINIC: 14 YEARS EXPERIENCE

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INTRODUCTION: Primary cutaneous lymphomas are rare diseases that often present diagnostic difficulties and challenging complex therapeutic issues. Thus, optimal patient care requires the cooperation of several medical specialties and it is accepted that these patients are best managed in the setting of multidisciplinary clinics.
OBJECTIVES: To present the data of the patients managed in our Multidisciplinary Cutaneous Lymphoma Clinic between 1996 and 2010.
MATERIALS AND METHODS: Retrospective analysis of 240 patients followed-up from January 1996 to August 2010. They were divided by subtype of cutaneous lymphoma (according to the WHO-EORTC 2005 classification) and treatment options, clinical status and causes of death. The 5 year overall survival rate was evaluated.
RESULTS: Of 240 patients, 166 (69.2%) had cutaneous T-cell lymphoma (CTCL), 66 (27.5%) cutaneous B-cell lymphoma (CBCL) and 8 (3.3%) blastic plasmacytoid dendritic cell neoplasm (BPDCN). In the CTCL group 103 (62%) patients had mycosis fungoides (MF), 27 (16%) Sézary syndrome (SS), 18 (11%) primary cutaneous CD30+ lymphoproliferative disorders and 18 (11%) presented with other subtypes of CTCL. All patients were submitted to skin-targeted therapies and additional one or more systemic treatments in 116 cases. Of the patients who died, 43 (26%) had CTLC, 6 (9%) had CBCL and 7 (87.5%) had BPDCN. The cause of death was directly related to disease progression in 63% of the patients with CTCL and in 16% with CBCL. The 5-year overall survival rates were: 83% in MF; 41% in SS; 93% in CD30+ CTCL; 64% in other subtypes of CTCL and 95% in CBCL.
CONCLUSIONS: The majority of our patients presented with CTCL with a T/B proportion similar to that reported in the literature. Most of the CTCL patients that died was attributed to disease progression. Of the BPDCN cases, the clinical course was uniformly fatal regardless of therapeutic modality. Our patients with MF, CD30+ lymphoproliferative disorders and CBCL presented a 5-year overall survival similar to other international centres published data.

P-062

TREATMENT OF MYCOSIS FUNGOIDES WITH BEXAROTENE: AN OBSERVATIONAL STUDY IN TERTIARY HOSPITALS IN THE CANARY ISLANDS

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BACKGROUND: Bexarotene (BEX) selectively activates retinoid X receptors. It has activity in cutaneous T-cell lymphoma and has been approved by the European Medicines Agency since 1999 for treatment of the skin manifestations of advanced stage of MF. At doses of 300mg/m^2/day in early-stage disease (IA–IIA) response rates of 54% were noted while patients with advanced MF (stages IIB–IVB) showed response rates of 45% with a notable reduction in

pruritus in stage III disease. In responders treatment is continued indefinitely. BEX may also be safely combined with other CTCL therapies. Side-effects are transient and generally mild but most patients require treatment for hyperlipidaemia and central hypothyroidism.
OBJETIVE: To analyze demographic and clinical data, side effects and clinical response of the patients treated with oral BEX.
METHODS: We retrospectively reviewed the medical records of 25 patients with MF treated with BEX followed at 2 Hospitals in Canary Islands.
RESULTS: GLOBAL: Males, 71%. Mean age at diagnosis, 54.4 years. Early stage disease, 54%. Previous treatments, 87%. Mean initial dose, 253mg/day (75-675). Mean maximum dose, 337 mg/day (150-675). Mean time on BEX treatment (months): 27 (1.5-92). Combined treatment: 87% (PUVA 54%). Response: CR, 33%; PR, 42%. Maintenance treatment: 54%. Mean maintenance dose, 219mg/day. Statins and/or fibrates: 88%. T4: 67%. No withdrawal due to BEX adverse effects. BEX MONOTHERAPY: 11 (3CR+4PR). 6/7 responders showed early stage MF. Mantenance treatment: 4/7. Progression rate: 5/7.
CONCLUSIONS: BEX is a well-tolerated and effective treatment for MF, even at lower than standard doses. It should be considered a useful alternative in patients refractory to skin-directed therapy (at least PUVA), patients with recurrent lesions and in cases with folicullar MF. Side-effects are transient, generally mild, dose dependent and may be controlled with corrective therapy or doses adjustments.

P-063

NARROW-RANGE UVA1 PHOTOTHERAPY IN MYCOSIS FUNGOIDES

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Mycosis fungoides is the most common form of the primary cutaneous lymphoma, characterised by a malignant proliferation of CD4+ cells. Narrow-range UVA1 irridiation is used in the treatment of skin diseases aetiologicaly linked to T-cell, such as atopic dermatitis.
METHODS: We present a case report of seven patients with histopathologically confirmed MF. UVA1 phototherapy was conducted using GP-24H Cosmedico device (Germany). The histopatologically examination was performed at least twice: prior to the treatment and after it was concluded, each time in the same location.
RESULTS: The patients were treated with 1430-2730j/cm 2 UVA1 given in 29-40 fractions. Biopsies were taken in all of the patients before and after UVA1 therapy and histopatologically remission was observed. in all cases complete clinical remission was atchived. The follow up was between 10 and 24 months, everidge remision rate was 9 months.
CONCLUSION: The presented case shows the posibility of treatmant in MF.

P-064

"A NEVER ENDING STORY"

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HISTORY/CLINICAL SIGNS: In 1995 a 70 year old male presented with several erythematous partly grouped, partly exulcerated papulo-nodular lesions on his torso, his hands and proximal lower extremities.
DIFFERENTIAL DIAGNOSES: Prurigo simplex subacuta; Pityriasis lichenoides chronica; Pseudolymphoma, Insect bites; Syphilis; large cell, CD30-positive cutaneous T-Cell-Lymphoma.
RESULTS: 1995: Sonography of abdomen and lymphnodes: unconspicuous; Lab results (FBC, U&E, LFT, Electrophoresis): unconspicuous; Histology: Lymphomatoid Papulosis, Type A; Immunohistochemistry: CD30 pos.; Immunophenotyping peripheral blood (FACS-Analysis): normal. 1999: Molecular Typing: Blood: no clonal TCR rearrangement; Tissue: clonal TCR rearrangement. 2012: No significant changes in results compared to 1995. No hint for a transition into a secondary large cell, anaplastic malignant lymphoma.
THERAPY: 1995-1999: Isotretinoin (up to 1mg/kgKG), PUVA, Excision of single lesions. 2000: Methotrexate (MTX), (20mg/week s.c.)/Isotretinoin (0,3mg/kgKG). 2001-2002: Isotretinoin (0,6mg/kgKG) monotherapy. 2003: restarting MTX/Isotretinoin. 2004: UVB; due to newly diagnosed papillous urothel carcinoma, transurethral resection of the urinal bladder, no tx for >1 year. 2006: Interferon alpha (3x/week 3 Mio. IE s.c.), stopped after 4 weeks because of depression), local x-ray (20Gy total). 2007: Fast electrons (6MeV, 12Gy total), topical steroids. 2009: PUVA. 2011-2012: Radiation of single lesion(30Gy), Bexarotene (450mg/d), cessation of therapy at request of patient due to elevated lipids, excision of single lesions. 2012: Narrowband-UVB (3x/Wk), topical steroids.
CONCLUSION: According to the literature there are no defined therapy guidelines, because of lack of controlled trials. We conclude that an exact risk-benefit-analysis of treatment modalities is critical for therapy success as well as patient´s compliance.

P-065

A CASE OF FOLLICULOTROPIC MYCOSIS FUNGOIDES; A TREATMENT CHALLENGE

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We present a 52 year old male with an 18 month history of erythematous patches over the pubic area, thighs and forehead along with scarring alopecia. Skin histology was consistent with Folliculotropic Mycosis Fungoides (FMF). The patient was treated with ultraviolet-B (UVB) and topical steroids, which halted hair loss. Two episodes of disease progression ensued in the following four years, with involvement of the lower face and limbs. Temporary remission was achieved with topical steroids and psoralen combined with ultraviolet-A (PUVA) on both occasions. Seven years into diagnosis, patches and plaques developed on the neck, lower face and both cheeks, which completely cleared after localised radiotherapy.Disease progressed quickly thereafter and was refractory to PUVA. Alpha Interferon was not tolerated.

The patient developed a transient mandibular nodule which we postulate represented a FMF-related tumour. 11 years into diagnosis, methotrexate (up to 25mg weekly) offered no benefit therefore the patient was started on a trial of oral retinoid (Neotigasone at 30mg daily) in combination with PUVA. Future treatment options would include a Bexarotene and localised radiotherapy to plaques and patches, and topical Imiquimod and localised radiotherapy to tumours. FMF is an aggressive variant of classical mycosis fungoides (CMF) with low overall survival, characterised by the presence of perifollicular neoplastic T-cells. Current management is based on treatments designed for CMF; skin-targeted therapies in early stages and systemic treatment for advanced disease. Some studies suggest these patients should be treated as having tumour-stage disease. The European Organization for Research and Treatment of Cancer proposed that TSEBI (total systemic electron beam irradiation) may need to be considered earlier in the course of disease. Our case portrays difficulties encountered in the managing FMF. Including these patients in clinical trials may help improve treatment regimes.

P-066

SYSTEMIC CHEMOTHERAPY IN PATIENTS WITH SEZARY SYNDROME: A 43 CASES RETROSPECTIVE STUDY

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BACKGROUND: Mycosis fungoide (MF) and Sezary syndrome (SS) are the most frequent entities of cutaneous T-cell lymphomas. Given the absence of controlled trials we have no evidence of response and survival rates using systemic chemotherapy.
OBJECTIVE: To evaluate clinical features, response rates and survival of patients treated with systemic chemotherapy.
MATERIALS AND METHODS: We reviewed medical records of the cutaneous network of Barcelona's Hospital de Bellvitge-Institut Catala d'Oncologia and Clinic Hospital, from May 1980 to April 2011. We applied the EORTC / ISCL new staging system and ISCL cutaneous and hematologic response criteria. Survival curves were estimated by the Kaplan-Meier method and compared using the log-rank test.
RESULTS: Forty-three patients were included in the study, 22 (51.2%) were male, the median age was 64.2 years (range: 30-90). Staging at chemotherapy was: IIIB 6 (14%); IVA1 22 (51%); IVA2 12 (28%); IVB 3 (7%). Eight (18.6%) patients had large cell transformation, 33 (76.7%) elevated LDH and 9 (20.9%) of 31, elevated beta2-microglobulin. Thirty-seven (86%) patients received systemic chemotherapy as first treatment. Thirty-one (72%) patients were treated with chlorambucil (23.7% in IVA1 stage or lower), 10 (23.2%) with CHOP or CHOP-like (4, 40% with stage IVA1 or lower), 2 (4.6%) with other types of chemotherapy. The overall response in peripheral blood was 41.8% and 46.4% skin. Two (4.6%) patients achieved complete response (CR) and 13 (30.2%) had partial response (RP) in both locations. The response rate did not differ significantly according to the stages. Thirty-three (76.7%) patients relapsed or progressed. With a median follow up of 44 months, 36 (83.7%) died. The median event-free survival (DFS) was 8 months with no statistically significant differences by stage or by type of treatment. The median overall survival of patients treated with CHOP and/or derivatives was 14 months and 31 months.

P-067

MONOCHEMOTHERAPY ASSOCIATED WITH LOW-DOSE BEXAROTENE: A USEFUL COMBINATION TREATMENT IN ADVANCED/AGGRESSIVE CUTANEOUS T CELL LYMPHOMA

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Primary cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of extranodal non-Hodgkin lymphomas primarily presenting in the skin, without extracutaneous involvement at the time of diagnosis. The treatment choice depends on clinical entity and disease stage. Early stage mycosis fungoides (MF) (I-IIA) is treated with skin directed therapies in first line, whereas advanced stage MF (IIB-IV) and most peripheral T-cell lymphoma, not otherwise specified (PTL, NOS) require radiotherapy and/or systemic therapy, including mono/polichemotherapy and biologic response modifiers.
The aim of this study was to investigate the role of low dose, oral bexarotene in association with scarcely immunosuppressive monochemotherapy (gemcitabine, GEM; pegylated liposomal doxorubicin, PEG-DOXO) in both induction and maintenance/consolidation treatment in advanced/aggressive CTCL relapsed after monoCT. Primary endpoints were ORR and PFS. Clinical response, valued as the best clinical response ever reached (CR, complete remission; VGPR, very good partial remission, >75%; PR, partial remission, >50%; SD, stable disease, <20 to >20%) and overall survival (OS) were also assessed.
Fifteen patients were enrolled: 11 patients (6 MF stage IIB and 5 PTL, NOS) were treated with bexarotene plus PEG-DOXO, 4 patients (2 MF stage IIB and 2 PTL, NOS) with bexarotene plus GEM. With bexarotene/PEG-DOXO combination, 9/11 patients achieved response (3 CR, 4 VGPR, 2 PR), and 1 patient remained in SD. One patient was discontinued because of an idiosyncrasic reaction. To date, median PFS and median OS are 15 months and 20 months, respectively. In bexarotene/GEM group, clinical response was obtained in 3/4 patients (1 VGPR, 2 PR); one patient reached SD. To date, median PFS and median OS are 8 months and 11 months, respectively. No AE were observed. All considered, ORR was 80%. PFS achieved with bexarotene in consolidation after induction with Peg-DOXO was the same as that obtained with PEG-DOXO alone; Treatment schedule was well tolerated due to prophylaxis of bexarotene SE and of PPE.
Our preliminary experience confirms the key role of bexarotene in association with monochemotherapy, both in induction and consolidation treatment in advanced/aggressive CTCL.

P-068

ALLOGENIC HEMATOPOIETIC STEM-CELL TRANSPLANTATION IN ADVANCED MYCOSIS FUNGOIDES: PRESENTATION OF TWO CASES WITH OPPOSED OUTCOME.

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Advanced-stage primary cutaneous T-cell lymphoma (CTCL) has an unfavorable prognosis and low survival rates and nowadays there is no effective treatment. Usually aggressive treatment with chemotherapy is the most used therapy but it is not curative and causes considerable side effects. In the last years some reports have shown good results with allogenic hematopoietic stem-cell transplantation (Allo-HCT). This therapy may overcome chemotherapy resistance via graft-versus-lymphoma effects and result in long-term disease control, even in poor-risk and chemotherapy-refractorypatients. Nonmyeloablative conditioning regimens allow allogeneic engraftment with reduced morbidity and mortality, even in older and heavily pretreated patients. Allogeneic transplantation in mycosis fungoides (MF)/Sézary syndrome (SS) offers an estimated overall survival of 66% at 1 year and 54% at 3 years (data from the European Group for Blood and Marrow Transplantation), primarily driven by donor type, disease phase, and type of conditioning. Some patients who experience relapse can successfully undergo rescue treatment with donor lymphocyte infusions. We present two female patients (32 and 53 years-old) with advanced and heavily pretreated MF, treated in two different centers with nonmyeloablative conditioning regimens prior their allo-HCT. The first patient died four moths after transplantation due to an acute post- transplantation lymphoproliferative syndrome and the second one is still alive but with a chronic graft-versus-host syndrome. We discuss both cases with their different outcomes.

P-069

PRIMARY CUTANEOUS FOLLICLE CENTER LYMPHOMA OF THE SCALP TREATED WITH SYSTEMIC RITUXIMAB

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Male patient, 25 years old, born and raised in São Paulo capital, with a history of tumor in the scalp for 3 years. He was evaluated by a dermatologist that decided to perform a biopsy. The diagnostic of the histological exam was pseudolymphomatous folliculitis. After 2 years of the first lesion on the scalp, the patient noticed increasing of the initial lesion and new lesions surged that affected the parietal region of the scalp. Again, the patient decided to visit his doctor and because of the worsening of the lesions two new biopsies were performed. Histological examination associated with immunohistochemical study confirmed the diagnosis of primary cutaneous follicle center cell lymphoma. The staging exams, CT scans of the abdomen, pelvis and chest, PET scan and bone marrow biopsy have shown no alteration. The serology for Borrelia Burgdorferi was negative. Because of the large number of lesions, the authors opted for systemic treatment with Rituximab. It was administered systemically

375mg/m^2 intravenously once a week for 8 weeks. After the treatment the patient reached a complete response.

P-070

IMIQUIMOD AND MYCOSIS FUNGOIDES: A LITERATURE REVIEW

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Our experience in treating patients with Cutaneous t-cell Lymphoma (CTCL) demonstrates a clinical use of imiquimod (IMQ) for early stage mycosis fungoides (MF), especially in combination or alternation with topical corticosteroids. We therefore performed a literature review on this clinical application. MF is the commonest type of primary CTCL. For early stage disease skin-directed therapies are preferred but are, however, not always uniformly effective, and can be associated with significant adverse events. IMQ is a topical immunomodulator which acts by stimulating a T helper 1 cell-mediated response and inhibiting the clonal T helper 2 cells which predominates in MF, through release of proinflammatory cytokines. In a small double blind placebo controlled pilot study of 4 patients with stage IB MF (Chong et al. 2004), IMQ was used once daily for 16 weeks. In the treatment group a mean decrease in MF lesions surface area of 8.9% and a mean increase in surface area of 39.9% in control areas were observed. This preliminary study, although small, suggested that IMQ is safe and well tolerated and may have some therapeutic benefit in early stage MF. Martinez-Gonzalez et al. (2008) provided a summary of cases reported to date, amounting a total of 20 patients with clinical stage IA to IIB MF. The dosing schedule varied from 3 times a week to once daily. The number of lesions treated, where stated, ranged from 1 to 5. A clinical response was seen in 85% of patients, being complete in 70% and partial in 15%. Where pathological examination was performed, 69% showed complete histological clearance. Most patients had previously received one or more treatment modality (topical and/or systemic). The longest follow up following remission with IMQ was of six months, and clearance was maintained. In all patients IMQ appeared to be well tolerated. Side effects reported included local irritation, pain, vesiculation and ulceration. Severe … (abstract truncated).

P-071

MONOCHEMOTHERAPY WITH GEMCITABINE IN A PATIENT WITH PRIMARY CUTANEOUS AGGRESSIVE EPIDERMOTROPIC CD8+ T-CELL LYMPHOMA

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BACKGROUND: Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma is a rare entity and often refractory to the usual treatment options for the more frequent CD4+ cutaneous T-cell lymphoma. We report a case of this entity with healing of tumor manifestations under a treatment with gemcibatine monochemotherapy.
CASE REPORT: A 76 year old male patient presented with a 12 month history of initially pruritic red and scaling skin lesion on extremities and trunk rapidly progressing into violaceous colored and partly ulcerating nodular lesions. Histology showed a dense lymphocytic

infiltrate of the entire dermis with epidermotropism. The immunohistochemical examination showed a CD3+, CD8+, CD45RO+ infiltrate with high positivity for TIA-1+, granzyme B and Ki-67. CD4, CD20, CD30 and CD 56 were negative. Staging examinations revealed no signs of organ or lymph node involvement leading us to the diagnosis of a primary cutaneous aggressive epidermotropic CD8+ T-cell Lymphoma without organ involvement (T3bN0M0, stage IIb). Previous treatments with systemic PUVA and low dose interferone-γ showed no success. We decided to initiate a monochemotherapy with gemcitabine, thus inducing a complete response with regression of the nodules and healing of the ulcerations within the first treatment cycle. Recurrence was observed two weeks after termination of the first cycle and a second cycle hat to be terminated after day one due to side effects with major deterioration of the patient's general condition, severe anemia, recurrent diarrhea, fever, hypoproteinemia, renal insufficiency and generalized edema.
CONCLUSION: In this case of primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma without further organ involvement we observed a good response to the treatment with monochemotherapy with gemcitabine. However this response was limited to the treatment period and side effects of subsequent therapy may require termination of the treatment.

P-072

A CASE OF SUCCESSFUL TREATMENT WITH TOPICAL CORTICOSTEROIDS OF SOLITARY FOLLICULOTROPIC MYCOSIS FUNGOIDES IN A TEENAGE BOY

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INTRODUCTION: Mycosis fungoides (MF), the most common form of cutaneous T-cell lymphoma (CTCL), occurs rarely in childhood. Folliculotropic MF is a rare variant of MF, which histopathologically is characterized by pronounced folliculotropism of neoplastic T-cells, with or without follicular mucinosis, and clinically by a poor prognosis compared to classic MF. We present a case of solitary folliculotropic MF of the face in a young patient successfuly treated with topical corticosteroids.
CASE REPORT: A 14-year-old boy presented to our centre with an 8-week history of a slowly enlarging, coin shape (2×1,8 cm), infiltrated, erythematous and slightly pruritic lesion on his glabella area. The patient was otherwise healthy. Laboratory tests revealed a mild lymphocytosis, eosinophilia and elevated IgE titers. Other laboratory, serology and screening tests were within normal ranges. A histological examination of biopsy specimen from the lesion revealed dermal perivascular, interstitional and periadnexal infiltrate of atypical T-lymphocytes (most population CD4+) with eosinophils; the CD4+ T-lymphocytes invasion to the epithelium of hair follicles without epidermotropism, and massive follicular mucinosis. After staging examination and repeated biopsy the diagnosis of IA stage folliculotropic MF was established. The patient was treated with the potent topical corticosteroid Clobetasol propionate 0.05% ointment twice daily for 2 weeks, then once daily for 3 months. After 2 weeks infiltration of the lesion markedly decreased, and the lesion completely disappeared after 2 months. After a 3-year follow-up, our patient was still in complete remission.

CONCLUSIONS: The combination of juvenile, folliculotropic and solitary MF is very unusual. Its clinical behavior and prognosis is still uncertain. In our case, a complete remision with potent topical corticosteroid was achieved, no relapse or stage progression were observed, however a long-term follow-up is highly recommended.

P-073

PRIMARY CUTANEOUS MARGINAL ZONE B-CELL LYMPHOMA: RESPONSE TO TREATMENT AND DISEASE FREE SURVIVAL IN A SERIES OF 137 PATIENTS

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Primary cutaneous marginal zone B-cell lymphomas (PCMZBCL) are low grade B-cell lymphomas that primarily arise in the skin. Although a high number of cutaneous relapses have been observed, there is little information about disease free survival (DFS) in these patients. One hundred and thirty seven PCMZBCL cases were reviewed from 1991 to 2011. The mean age at diagnosis was 49 years (range 20-87). Solitary lesions were the most common clinical presentation observed in 70 cases (51%). Most patients were classified at diagnosis as T1 (n=70; 51%), followed by T2 (n=40; 29%) and T3 (n=27; 20%). Surgical excision, local radiotherapy or a combination of both treatments were the preferred initial treatment used in 118 patients (86%), resulting in complete remission (CR) in all but two patients. Cutaneous relapses were observed in 53 patients (44%). The median DFS for all patients was 47 months. Five and 10-year DFS were 46% and 17%, respectively. Patients with multifocal lesions or T3 disease showed significantly higher relapse rate and shorter DFS compared to solitary or localized disease. No significant differences were observed between patients treated initially with surgery or radiotherapy in terms of relapse rate or DFS but surgery alone were associated with more recurrences at initial site. The present study is the largest published series focused exclusively on PCMZBCL patients with long follow-up period. Our results demonstrate that although a significant number of PCMZBCL could be virtually cured a high proportion of them will relapse even more than 10 years after initial CR. We add evidence that only those patients with disseminated skin lesion have higher relapse rate and shorter DFS supporting the need for further investigation in the use of systemic therapies in such a group of patients.

P-074

PERIPHERAL T-CELL LYMPHOMA – NOT OTHERWISE SPECIFIED

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BACKGROUND: Lymphoid neoplasm classified as peripheral T-cell lymphoma (PTCL) "not otherwise specified" (NOS) are rare and known to have a poor prognosis. They do not match other more clearly defined lymphoma entities in terms of clinical and histologic criteria.

Despite insufficient treatment studies CHOP combination chemotherapy or bone marrow transplantation are considered treatments of choice. The 5-year survival rate is 20-30%.
CASE REPORT: 62 year old male patient developed within three months a painless exophytic 6 x 7 cm measuring irregularly shaped erythematous, partly ulcerated mass on the left side of the chin. Histology revealed a transdermal infiltration with atypical lymphocytes. Nuclei being small to medium in part large sized, partially with marked nuclear atypia. Intermingled a remarkable number of eosinophils. The lymphocytes are predominantly positive for CD2, CD3, CD4, a subpopulation of large lymphocytes being positive for CD30. CD56 and ALK1 negative. In addition, the imaging showed an involvement of the mandible and maxilla. A biopsy of a lymph node confirmed nodal expansion of PTCL. Subsequently, a local radiation therapy including the regional lymph nodes of the head and neck was performed. After complete remission (CR) new lesions arose on the right elbow, a generalized lymphadenopathy developed. CR after 6 cycles of CHOP. 11 months later again erythematous nodes occurred. Neither bath PUVA, nor alitretinoin and a new radiation therapy showed significant improvement. Finally, during a three-week oral treatment with prednisone 100 mg/d the tumours disappeared. Three years after the first diagnosis, the patient is free of symptoms, taking prednisone 200 mg/d for 7 days with a subsequent three-week break.
CONCLUSION: Currently, there is no sufficient evidence for a fundamental superiority of aggressive therapies in PTCL-NOS.

P-075

AN EARLY INFANT CASE OF SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA (SPTCL)

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INTRODUCTION: SPTCL is a rare type of cutaneous lymphoma in childhood, which especially affects infants. We herein present an infant case of SPTCL who had extensive subcutaneous nodules and received systemic prednisolone monotherapy. To the best of our knowledge, this patient is the youngest SPTCL case reported in the literature.
CASE: A 7-month-old male presented with a 6-month history of multiple erythematous subcutaneous nodules on his cheeks, hips, and both upper and lower extremities. A nodule had first been noted on his left earlobe at 1 month of age. A histopathological examination of a skin biopsy showed a lobular panniculitis composed of small and medium-sized atypical lymphoid cells, small normal lymphocytes, and histiocytes. Fat cell rimming by the atypical cells were seen. Immunohistochemistry revealed the atypical cells to express CD3, CD4, CD8 and TIA. The MIB-1 labeling index was approximately 60%. An analysis of TCR-beta gene rearrangement was positive. Because he had no clinical findings except broad skin involvements, we decided to manage him with oral prednisolone (2 mg/kg/daily) first. After two weeks of treatment, we observed rapid improvement of his skin nodules. Although these nodules continued to improve during a drug tapering for four months, a few nodules persisted and gradually spread.

DISCUSSION: After a diagnosis of SPTCL, we commonly provide initial therapy using a corticosteroid, with or without anti-neoplastic agents. In this case, we selected prednisolone monotherapy for the initial management because his disease was of the indolent type and he was very young. Unfortunately, his skin nodules persisted and spread after he was tapered off prednisolone. We just plan to treat him with combination chemotherapy consisting of prednisolone, vincristine, cyclophosphamide and doxorubicin. More aggressive management may be needed for extensive skin-limited SPTCL cases, even if they have no systemic symptoms.

P-076

CUTANEOUS VARIANT OF INTRAVASCULAR LARGE B-CELL LYMPHOMA SUCCESSFULLY TREATED WITH R-CHOP

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Intravascular large B-cell lymphoma (IVLBCL) is a rare type of extranodal diffuse large B-cell lymphoma (DLBCL). It is characterized by the proliferation of tumor cells exclusively in the lumen of small blood vessels in different organs. The clinical manifestation depends on the type of organ involved, additionally, a haemophagocytic syndrom can be observed especially in patients from Asia.
We report on a 73 year-old Caucasian woman who presented to our department with a five-month history of painful bilateral erythema and thickening of the subcutaneous tissue of the medial thighs and lower legs with prominent teleangiectasias.
Histologic analysis of a skin biopsy revealed the presence of large atypical lymphocytes in dermal and subcutaneous blood vessels. Theses cells stained positive for CD19, CD20, CD79a, MUM1, BCL2, BCL6, CD5 and FOXP1, and negative for CD10. Staging with whole body PET-CT, MRI of the brain and a bone marrow biopsy did not reveal any further organ involvement. The patient responded well to a chemotherapeutic regimen consisting of six cycles of R-CHOP, with no evidence of further disease as confirmed by skin biopsy and diagnostic imaging. Two years after initial diagnosis the patient still remains disease free.
Despite the advanced age of our patient this case highlights the good prognosis in patients with IVLBCL confined to the skin.

P-077

EXPERIENCE OF THE USE OF BEXAROTENE GEL IN THE TREATMENT OF MYCOSIS FUNGOIDES. INSTITUTE OF BIOMEDICINE

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Mycosis fungoides (MF) are a type of cutaneous T-cell lymphoma (CTCL), chronic and indolent course where the prevalence of early stages and long duration of disease allows the use of sequential therapy to decrease side effects and improve quality of life of patients. Bexarotene, the RXR-selective retinoid, is the most modern retinoid for the treatment of CTCL and has been used both topically and systemically for this condition. Yet there are few reports in the literature of its use topically for early stages of the disease. It describes the experience of using bexarotene topical at the Institute of Biomedicine, Hospital Vargas de Caracas. We conducted a retrospective study reviewed the records of patients evaluated and record the clinical and epidemiological characteristics of patients and the therapies used for your response. We obtained a total of 63 patients aged between 9 and 77 years to 48.8 years and average ratio F: M 1.5:1. The most prevalent were stages IA and B (89%). The most commonly used treatment options for patients in stages IA and IB were topical steroids, bexarotene gel, alone or combined PUVA and nitrogen mustard. Bexarotene gel represented a valid option for early stage (IA, IB) alone or in combination with other systemic therapies, reducing the degree of infiltration and in some cases achieved remission. Conclusion: Bexarotene has been shown in our clinic to be an important option for the treatment of mycosis fungoides stage I, showing very few side effects and medication adherence.
Keywords: bexarotene gel, mycosis fungoides

Patient Care

P-078

A FIVE YEAR RETROSPECTIVE ANALYSIS OF THE CUTANEOUS T-CELL LYMPHOMA AT THE CENTRE OF DERMATOVENEROLOGY IN VILNIUS, LITHUANIA

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The epidemiological and clinicopathological characteristics of cutaneous T-cell lymphomas (CTCL) vary according to geography and have not been previously investigated in Lithuania. The aim of this study was to review the data of newly diagnosed CTCL cases from 1 January 2007 to 31 June 2012 at Vilnius University Hospital, Centre of Dermatovenerology. A retrospective analysis of data abstracted from the medical documentaries was performed. Eighty six patients with CTCL (59.3% men, 40.7% women) were investigated. Mean age was 56.6 years (ranging from 14 to 85 years). According to WHO-EORTC classification, the most commonly mycosis fungoides (MF) (95.3%) was diagnosed, followed by Sezary syndrome (1.2%), primary cutaneous CD30+ lymphoma (2.3%), angioimmunoblastic T-cell lymphoma (1.2%). MF consisted from 77.9% classic, 11.6% folliculotropic, 9.3% erythrodermic, 1.2% poikilodermatous subtypes. Morbidity lasted from 1 to 480 months (average 7 months), the majority of the patients (77.6%) had pruritus. Laboratory tests did not significantly correlated with pruritus, CTCL forms and MF subtypes. 9.3% of patients presented with other malignancies. Majority of patients (40.7%) were treated with combined PUVA and topical corticosteroids therapy, only 11% with PUVA monotherapy. 9.3% of patients required treatment with PUVA and other systemic drugs. Remission was achieved in 20.9% of patients, in 11.6% of cases the disease progressed, 5.8% of patients died from CTCL. There was statistically significant (p=0.019) correlation between combined PUVA and topical corticosteroids treatment and remission rate. Currently, only 39.5% of the patients are followed-up and continuously treated in our center. This study revealed that MF is the most common manifestation of CTCL in our center, moreover, the frequency of folliculotropic MF is high. A combined therapy, long-term follow-up and periodical examination is highly recommended for the patients with CTCL.

P-079

BREAST IMPLANT ASSOCIATED ALCL – A UNIQUE ENTITY IN THE SPECTRUM OF CD30+ LYMPHOPROLIFERATIVE DISORDERS

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CD30+ lymphoproliferative disorders (LPD) represent a spectrum of diseases with distinct phenotypes ranging from reactive conditions to systemic anaplastic large cell lymphoma (ALCL). In January 2011, FDA announced a possible association between breast implants and ALCL, which was likened to the systemic ALK- ALCL and treated accordingly. We conducted a systematic review of all publications relating to ALCL and breast implantation between 1990

and 2012, contacting corresponding authors to obtained follow-up where available. Thirty-nine unique cases of iALCL were identified and analyzed to see if implant associated ALCL (iALCL) may represent a distinct, reactive entity, different from the aggressive systemic ALCL. There are unique features of iALCL which put it apart from systemic ALCL: 1) it demonstrates an indolent course and excellent prognosis (only two deaths have been reported since 1990), similar to primary cutaneous indolent ALK- ALCL with an overall 5 year survival of 90%, in stark contrast to systemic ALK- ALCL at approximately 40%; 2) their course points toward their reactive nature – spontaneous remission after removal of the implant and very strong association with late-onset seroma formation have been reported. Seroma was present in majority of the cases where the records were available. In contrast, incidence of seroma after any breast augmentations is only 0.05-0.1%. It appears that iALCL may demonstrates an indolent, often relapsing course; with a morphology, cytokine profile and biological behavior similar to primary cutaneous ALCL. Our literature review revealed that iALCL may start as a reactive process which has the rare potential to progress and acquire an aggressive phenotype typical of its systemic counterpart. Larger data set analysis and prospective evaluation and follow-up of iALCL patients are necessary to definitively resolve the issue of natural course and best therapeutic approaches for these patients.

P-080

GUIDELINES FOR THE MANAGEMENT OF CUTANEOUS LYMPHOMAS (2011): A CONSENSUS STATEMENT BY JAPANESE SKIN CANCER SOCIETY – LYMPHOMA STUDY GROUP

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In 2010, the first Japanese edition of guidelines for the management of cutaneous lymphoma was published jointly by the Japanese Dermatological Association (JDA) and the Japanese Skin Cancer Society (JSCS)-Lymphoma Study Group. Since the guidelines were revised in 2011 based on the most recent data, we summarized the revised guidelines in English for two reasons: 1) to inform overseas clinicians about our way of managing common types of cutaneous lymphomas such as mycosis fungoides/Sézary syndrome, and 2) to introduce Japanese guidelines for lymphomas peculiar to Asia, such as adult T-cell leukemia/lymphoma and extranodal NK/T-cell lymphoma, nasal type. References that provide scientific evidence for these guidelines have been selected by JSCS-Lymphoma Study Group. These guidelines, together with the degrees of recommendation, have been made in the context of limited medical treatment resources, and standard medical practice within the framework of the Japanese National Health Insurance system.

P-081

CLINICOPATHOLOGICAL CHARACTERISTICS ARE ASSOCIATED WITH THE PRESENCE OF NEOPLASTIC LYMPHOPROLIFERATIVE DISORDERS IN PATIENTS WITH LYMPHOMATOID PAPULOSIS

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Lymphomatoid papulosis (LyP) refers to a cutaneous lymphoma with excellent overall prognosis. The association with a second hematologic malignancy has been reported, however the rates of increased disease activity and progressive disease have not yet been determined. We aimed to identify any association between clinicopathological characteristics and the occurrence of lymphoproliferative disorders in LyP. The prognostic effect of clinicopathological characteristics and first line treatment were evaluated in 24 LyP patients (16 females, 8 males) using logistic regression models and generating survival curves. One or more concurrent lymphomas were diagnosed in 8 (33%) patients; namely mycosis fungoides in 6 patients (one had mycosis fungoides and anaplastic lymphoma) and non-Hodgkin lymphoma in 2 patients. Lymphoma occurrence was associated with: 1) a lower mean age of initial LyP symptoms (mean age: 31.38±16.6 versus 45.81±15.2 years in non-lymphoma patients), 2) histological types B & C (p=0.04), 3) head-located LyP lesions (p=0.05) 4) a higher frequency of LyP exacerbations (p=0.04). Fewer LyP patients with histologic type A (14.2%) presented a second lymphoma comparing to those with histologic type B and C (50% and 75% respectively, p=0.032). In multivariate analysis histologic type A remained associated with a lower risk of second lymphoma adjusting for age of LyP first symptomatology (OR=0.11, 95% C.I.0.013-0.96; p=0.04) as well as with increased lymphoma-free survival rate was (long-rank test; p=0.05).

The occurence of lymphoproiferative disorder in patients with LyP is high and significantly associated with histological types B and C as well as certain clinical features such as lower mean age of LyP onset, higher frequency of LyP exacerbations and head located lesions. Future larger studies are needed to confirm these associations and to explore underlying mechanisms.

P-082

SÉZARY SYNDROME AFTER TREATMENT WITH ETANERCEPT AND ADALIMUMAB

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We report two patients who developed Sézary syndrome soon after starting on TNF-inhibitors. A 24-year old female was started on etanercept for presumed widespread psoriasis. Within a few weeks, she developed erythroderma and eventually was diagnosed with Sézary syndrome. The second patient was a 54 year-old male who was treated with adalimamab after an initial biopsy suggested psoriasis. While he had an initial transient improvement, he then rapidly declined and developed Sézary syndrome.
Seventeen patients who developed cutaneous T-cell lymphomas (CTCL) while on TNF-inhibitors have been reported in the literature. In these patients, the TNF-inhibitors likely caused decreased tumor surveillance eventuating in either the unmasking or worsening of latent lymphoma. The majority of the reported patients (8/17) have exhibited forms of mycosis fungoides. Only 3/17 patients have had Sézary syndrome, and thus this report adds an additional two cases. In addition, the first case is remarkable for the young age of the patient since the previously reported patients were all over 60 years of age. This report aims to make practitioners aware that Sézary syndrome can be the manifestation of CTCL in patients who have CTCL unmasked by TNF-inhibitors, and that this can occur in young patients.

P-083

ACUTE LEUKEMIC TRANSFORMATION OF MYCOSIS FUNGOIDES/SÉZARY SYNDROME

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Cutaneous t-cell Lymphoma (CTCL) is a heterogeneous group of skin neoplasms usually without extracutaneous involvement at the time of diagnosis. The most common subtypes are mycosis fungoides (MF) and Sézary syndrome (SS). Several studies have shown that the overall survival (OS) depends primarily on the stage of disease at the time of presentation, but large cell transformation can herald a more aggressive course, particularly if associated with generalized skin lesions, folliculotropism, CD30- status, or extracutaneous transformation. Unlike nodal LCT, acute leukemic transformation is a relatively rare occurrence. Here we report a case series of 4 MF/SS patients with abrupt marked leukocytosis and elevated lactate dehydrogenase in conjunction with rapid progression of their disease.
All 4 CTCL patients (1 Stage IA MF, 3 Stage IVA SS) with mean age 69 y.o. (range, 62-75 y.o.), had prior normal or upper limit normal WBC at diagnosis. They experienced sudden increase in WBC, median: 84,200 ul (range, 62,000-96,000ul); markedly elevated LDH, median: 3037.5U/L (range, 350-7639U/L) and development of generalized lymphadenopathy or visceral disease in conjunction with deterioration of clinical course within weeks of onset of the abrupt lymphocytosis, median: 8.75 weeks (range, 4-16 weeks). The median interval from diagnosis to acute leukemic transformation was 9.5 months (range, 1-96 months). 3 patients transformed while on active therapy, 1 patient transformed within one month of diagnosis, before treatment onset. 2 patients (1 MF, 1 SS) succumbed to disease despite chemotherapy within a few months of progression, 1 SS patient has partially responded to gemcitabine, 1 SS patient has responded to multimodality treatment.
These cases demonstrate that MF/SS can rarely transform in the blood compartment with markedly elevated/increasing WBC count and LDH. Such disease transformation presents with rapid clinical progression requiring aggressive treatment.

P-084

CLINICOPATHOLOGIC FEATURES, TREATMENTS AND OUTCOMES IN FOLLICULOTROPIC MYCOSIS FUNGOIDES IN 37 PATIENTS IN A SINGLE-CENTER RETROSPECTIVE STUDY

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BACKGROUND: Folliculotropic mycosis fungoides (FMF) is a distinct variant of MF with a predilection for hair follicles, reported decreased patient survival and resistance to therapy.
METHODS: A single-center retrospective study followed 37 patients with FMF seen at the Vanderbilt Cutaneous Lymphoma Clinic over the last 17 years.
RESULTS: Thirty-seven mainly Caucasian (97%) patients (15/41% male; 22/59% female) with a mean age of 50 years (10-88 years) met study criteria. The mean time to diagnosis was 3.4 years and the mean follow up time was 3 years. The most common clinical features were: patches (60%), papules (41%), plaques (35%), alopecia (22%) and acneiform eruption (11%) on the head and neck (76%), extremities (60%) and back (49%) associated with pruritus in 55%. Histopathology at diagnosis showed folliculotropism (34/92%), ceribriform lymphocytes (25/68%), epidermotropism (21/57%), mucin deposits (11/30%), eosinophils (13/35%), loss of CD7 (17/20; 85%), CD4 predominance (30/32; 94%) and T-cell receptor gene rearrangement (21/30; 70%). The clinical stage at diagnosis was IA (75%), IB (22%) and IIB (3%). Disease has progressed to a more advanced stage in 6/37 or 16% and large cell transformation was noted in 8%. Survival rates for 3, 5 and 10 years were 91.5% (95% CI 82.7-1), 88% (95% CI 77.5-99.9) and 78.8% (95% CI 64.6-96.1) respectively. Durable (complete or partial) response to treatments was 14/19 or 74% for phototherapy; 14/16 or 87.5% for radiation therapy (11/14; 78.6% for EBRT; 5/5; 100% for TSEBRT), 2/9 or 22% for bexarotene capsules, 4/5 or 80% for systemic therapy (including chemotherapy, immunotherapy and photopheresis), 11/21 or 52.4% for topical treatments (topical steroids 6/14 or 43%; fluorouracil 3/3 or 100%; pimecrolimus 1/4 or 25%; targretin gel 2/9 or 22%).
DISCUSSION: This study showed overall survival rate of 95%. Radiation therapy and phototherapy showed the highest rates of durable response at 88% and 74% respectively.

P-085

NOVEL NURSING ROLES IN THE CUTANEOUS LYMPHOMA SETTING IN MELBOURNE, AUSTRALIA

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Nursing roles within the Cutaneous Lymphoma setting in Melbourne are evolving in response to unique patient needs and demands. The physiological and physical distress experienced by many patients with Cutaneous Lymphoma from around Australia prompted the development of these unique and specialised nursing roles.

The Cutaneous Lymphoma Nurse roles based at Peter Mac Callum Cancer Centre and St Vincent's Hospital Melbourne were developed to address the complex patient needs. The roles include the Dermatology Lead Nurse Role (St Vincent's Hospital), Skin Lymphoma Support Nurse Role (Peter MacCallum Cancer Centre) and the Skin Lymphoma Nurse Practitioner Role.

The Skin Lymphoma Nurse Consultancy Role was established in 2006 and developed into the Skin Lymphoma Nurse Practitioner Role. The candidate undertook extensive specialised training in order to gain Nurse Practitioner status.

The Dermatology Lead Nurse role at St Vincent's Hospital. The Skin Lymphoma Nurse Practitioner Role and the Skin Lymphoma Support Nurse Role's are all involved in triaging patients together with the Haematologists and Dermatologists. All nursing roles are unique and have different skill sets.

The Dermatology Lead Nurse manages the clinic patient list, triaging, light testing and UV treatments based at St Vincent's Hospital. The Skin Lymphoma Support Nurse manages the Skin Lymphoma Data Base and organises web based Multidisciplinary Team meetings once per month. Specialists from around Australia virtually attend this meeting. On occasion specialists from New Zealand also attend.

The Skin Lymphoma Nurse Practitioner conducts a Nurse Led Clinic once per week and can see patients four days per week. The Skin Lymphoma Nurse Practitioner has the ability to prescribe diagnostics and medications within the scope of the Skin Lymphoma setting. This nurse also attends local and interstate requests for patient, nursing, community, and medical education pertaining to Cutaneous Lymphoma.

P-086

UNILESIONAL FOLLICULOTROPIC MYCOSIS FUNGOIDES: A TRUE RARITY IN THE CLINICO-PATHOLOGIC SPECTRUM?

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The term unilesional mycosis fungoides MF (UMF) encompasses cases characterised by a solitary lesion with clinical and histological features of MF. Since 1981, over 100 cases have been reported. However, there is no consensus about criteria characterising UMF: according to some authors, the term can be applied to all cases with a single lesion at presentation, while for others UMF corresponds to a single area of involvement by MF covering less than 5% of the body surface. In this setting, patients featured by a folliculotropic involvement by UMF (UFMF) are even rarer, only 10 cases having so far been quoted in the literature. Conversely, the incidence and prevalence of "classical" Alibert-Bazin type has increased over the past 3 decades. Looking for folliculotropic MF (FMF) cases in the database of the Dermatological Divisions of Bologna (12 patients) and Florence University (16 patients) over the last 10 years, 4 UFMF patients (2 males and 2 females, mean age 46 years; median age: 41 years) were retrieved. UFMF diagnosis was made based both on clinical features and on the histological criteria of the 4th edition of the WHO Classification of Haematopoietic and Lymphoid Tumours. Notably, two patients showed a solitary, alopecic lesion on the face, another one on the forehead, and the fourth on the periorbital area. Patient no. 1 was initially treated with phototherapy (UVB nb) plus methotrexate (10mg/week) for 3 months, showing a slight improvement. Thereafter, radiotherapy was started (total dose of 24 Gy) with complete remission (CR), lasting from the last ten months. Patient no. 2 received a cycle of RE-PUVA therapy (starting dose: 0.5 J/cm^2, 3 days/week, plus acitretin 10mg per day) for 5 months, obtaining a CR still stable after a one-year-follow up. Patient no. 3 was treated with PUVA therapy (starting dose: 0.5 J/cm^2, 3 days per week for 4 months) and topical clobetasol plus tazarotene (the latter once a day for 6 months), achieving CR which is ongoing 6 months after stopping treatment. Patient no. 4 was treated with surgical excision, with CR still stable after a 3-year-follow up. In our databases, UFMF represent 14.3% of the total 28 FMF cases. These data are in line with those previously reported about UFMF incidence, suggesting that this disease should be considered as a true rarity in MF clinico-pathologic spectrum.

P-087

MYCOSIS FUNGOIDES – 3-MONTHS EVOLUTION IN TUMOR STAGE

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We present a 65-year-old female patient with 5-year history of clinically, histologically and immunohistochemically confirmed mycosis fungoides. In 2007, the disease presented with multiple erythematous plaques over the trunk, arms and legs. The patient was treated with PUVA and topical steroids with partial remission. In 2011, the patient presented with exacerbated erythematous plaques over the trunk and arms. Additionally, a new nodular lesion appeared over the left arm with 3-month rapid progression to ulcerated tumor formation. After clinical, histological, and immunohistochemical investigation, IIB stage of mycosis fungoides was determined. Percutaneous radiotherapy was conducted with subsequent therapy with Interferon-α without any clinical improvement. The tumor formation regressed following 10-week treatment with Methotrexate of 100mg weekly. Mycosis fungoides is a cutaneous T-cell lymphoma that should be clinically, histologically, and immunohistochemically verified for appropriate staging and treatment. Although we consider that non-aggressive maintenance therapy is beneficial for the long-term prognosis of the disease, chemotherapy with Methotrexate is crucial in this case of rapid progression of mycosis fungoides.

P-088

MYCOSIS FUNGOIDES: A SERIES OF SEVEN PATIENTS

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INTRODUCTION: Mycosis fungoides (MF) represent about 50% of all primary cutaneous lymphomas.The purpose of this study is to analyze the clinical and biological characteristics, to assess response to therapy and survival in a series of seven patients
Patients and methods: Retrospectivestudy (2006-2010), patients (pts) are MF whose diagnosis is retained after a histological study. ISL/EORTC staging of MF / Sezary syndrome has been used on our patients.
RESULTS: Over a period of 4 years were recruited 7 pts whose sex ratio 1.34 (4 men, 3 women), median age 62 years (29-69 years), 2 pts (28.6%) of patients with a history of eczema. The reason for consultation was pruritic eczematous lesions in 42.9% of pts (3 cases), plates tumors 42.9% of cases (3 pts) and one patient (14.3%) to skin ulceration. Clinically, general symptoms were found in 71.4% (5 cases), pruritus 71.4% (5 pts), eczematous lesions 71.4% (5 cases), tumors plates 42.9 % (3 pts), erythroderma 28.6% (2 qt), skin ulceration in one patient (14.3%) and lymphadenopathy in 5 pts (71.4%). Biologically, the rate of FSP Sezary cells is <5% in all our patients, an LDH greater than normal was found in 4 pts (57.1%), 2 pts (28.6%) have had visceral involvement. A classification, 4 pts (57.1%) were classified stage IIA, one patient (14.3%) stage IIB, 3 pts (42.9%) stage IVB. 5 pts were treated with chemotherapy and

2pts by interferon alpha, were obtained 2 complete remission (CR) (28.6%), 3 partial response (PR) (42.9%), 2 stable disease (SD) (28.6%), the current A, 4 pts (57.1%) are living with two (28.6%) and in RC 2 (28.6%) PR, 3pts (42, 9%) were dead, including 2 by disease progression and severe sepsis by a door skin.
CONCLUSION: MF is an indolent-behaving subtype with slow progression over a period of many years, Clinical presentation is mainly skin, the presence of erythroderma and invasion of viscera worsens the prognosis, hence the importance of diagnosis and therapeutic management early.

P-089

CUTANEOUS LYMPHOMA T: AN OBSERVATION ABOUT AN UNUSUAL

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INTRODUCTION: Cutaneous t-cell lymphoma is the most frequent of lymphomas. Its evolution is slow, usually several years and the prognosis depends on the stage of evolution. We relate a case that illustrates the rapid passage has an aggressive rapidly fatal.
OBSERVATION: It is the patient bm age of 67, a miner by profession, retired for 11 years, without antecedents individuals, phototype ii. seems to date back to the early 04 years, marked by the appearance of a generalized pruritus, which is why the patient has consulted on several occasions where he was put under trt symptomatic [anti h1]. two months before his hospitalization, the patient introduced a facial erythema and edema erosive lesions superinfected with fierce itching, followed one month after papular lesions of the limbs and trunk notion of figure 10 kg weight loss over a period of 04 years. STAGE cutaneous biopsy with microscopic study finds a superficial and deep dermal infiltrate, polymorphous, made of elements and mature lymphoid cells of small size core has hyper chromatic basophilic, irregular, indented, the histopathological appearance is evocative of a coating cutaneous lymphoma cutaneous seat of t. The immunohistochemical study revealed a positivity of the tumor population with anti-cd3, which directs to the diagnosis of cutaneous lymphoma type t. Evolution after chemotherapy after the first treatment were: a slight improvement lesions – appearance of a macro cheilitis – appearance of hyperkeratosis Soles. Pruritus is still present and insomiant. A broad spectrum antibiotic treatment was established, but unfortunately the patient dies following a septic shock.
CONCLUSION: the peculiarity of our patient is passing quickly aggressive view deadly 2 months after the discovery of this condition is often poor prognosis despite the precocity of the introduction of poly chemotherapy with wholes side effects they cause.

P-090

GRAFT OF ANGIOSARCOME ON A SECONDARY BREAST CANCER LYMPHOEDEME

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INTRODUCTION: The lymphangiosarcome is a tumour which develops on a primitive or secondary chronic lymphoedeme. We bring back a secondary lymphangiosarcome on lymphoedeme to unilateral carcinoma of the upper limb.
OBSERVATION: Patient 60 years old consults for invalidating pain of the left upper limb. It was operated in 1988, by a radical mastectomy of the left centre with ganglion clearing out for an invasive galactophoric adenocarcina differentiated grade I from SBR without ganglion invasion (23N-/23N). In 1994, she presents a repetition on the operational scar. An exerese followed by radiotherapy on the thoracic wall and the ganglion (sus claviculaire, axillaire, chain mammaire intern) were carried out. No treatment by chemotherapy or hormonotherapy was recommended. With the clinical examination, the left upper limb is the seat of a lymphoedeme interesting all the member with circumferential purplish colouring blue of the arm. The echography and the IRM of the left upper limb showed a thickening of cutaneous fabrics with the presence of some nodules will infra centimetric. A biopsy of the cutaneous lesions was carried out. The histological examination finds the aspect of an angiosarcome confirmed by immunohistochemical. An amputation of the upper limb is carried out. Six days after the intervention, it presented a left hemothorax. The cytology of the pleural liquid finds the presence of tumoral cells. The patient dies one month after the intervention.
DISCUSSION: The angiosarcome is rare, accounting for 1% of the sarcomas. It is grafted on a primitive chronic lymphoedeme or secondary with radiotherapy, a mastectomy with ganglion clearing out, or with a filariose. Stevens and Trevens described for the first the secondary lymphangiosarcome grafted on lymphoedème with a mastectomy in 1948. In the majority of the cases, the angiosarcome is relatively diagnosed at a late stage. The treatment of the syndrome Stevens Trevens consists of a … (abstract truncated).

P-091

T-CELL LYMPHOMA SUBCUTANEOUS PANNICULITIS IS A TYPE OF RAPID IMPROVEMENT – ABOUT ONE CASE

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INTRODUCTION: T-cell lymphomas are the most common cutaneous lymphoma. Forms preferentially affecting the hypodermis are rare and pose the problem of differential diagnosis with other causes of panniculitis.
MATERIALS AND METHODS: We report a case of T-cell lymphoma subcutaneous panniculitis a type of indolent.
OBSERVATION: Patient KM 27 years old without a history notable was hospitalized for a dermo-hypodermal afebrile lasting for four months. His general condition was maintained.

Clinical examination objectified nodules dermo-hypodermic 2-3 cm in diameter, infiltrated, firm, painful, adhering to the deep layers, the upper limb and lower right.
RESULT: There was an inflammatory syndrome and increased lacticodésydrogénases (LDH 694 U/L). Deep skin biopsy showed an atypical lymphoid proliferation of the hypodermis, composed of cells of small and medium-sized, with, in places, cytophagie images. The immunostainings were positive for CD3, CD8 and negative for CD4, CD56, with positivity for granzyme B. FNA lymph adenitis was a reaction. The diagnosis of T-cell lymphoma Subcutaneous panniculitis has type was selected. The patient received a course of chemotherapy (CHOP) followed by oral corticosteroids at 0.5mg/kg/day of prednisone, which resulted in complete regression of lesions after two months.
THREAD: T-cell lymphoma Subcutaneous panniculitis to type is a rare form of cutaneous lymphoma. Clinically he made a picture of panniculitis affecting preferentially root members. The clinical, histological, phenotype, and evolutionary profile distinguish two entities subcutaneous T-cell lymphoma. T-cell lymphomas phenotype CD4-CD8-CD56 ±, gamma delta, they have a poor prognosis. T-cell lymphomas phenotype CD4-/CD8+/CD56-, alpha beta, their evolutionary potential is low, with a survival rate at 5 years was 82%. In our case it was T-cell lymphoma in cutaneous CD4-/CD8+/CD56-, a good prognosis. The outcome was good in low dose corticosteroids stopped after 3 … (abstract truncated)

P-092

QUALITY OF LIFE (QOL) AND IMPACT OF AN EDUCATION SESSION IN PATIENTS WITH CUTANEOUS LYMPHOMA: WESTMEAD HOSPITAL EXPERIENCE (AUSTRALIA)

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INTRODUCTION: Lymphomas may have a profound impact on patient's QoL and psychological well-being, but there is limited information about QoL in cutaneous lymphomas. Our aims were to determine the level of impairment by using skin-specific (Skindex-16) and psychological-specific (DASS-21) questionnaires, before and after an Education Session.
METHODS: The questionnaires and an Education Session (ES) invitation were mailed in August 2011 to patients attending to our Cutaneous Lymphoma Clinic. The ES for patients consisted of general information about the disease and its potential emotional impact and social concerns. Patients were invited to mail new-answered questionnaires, two weeks after the ES.
RESULTS: 23 out of 49 patients (47%) returned the questionnaires. Twelve assisted and answered post ES questionnaires. There were 18 patients with mycosis fungoides (MF), 2 with Sézary Syndrome (SS), 2 primary cutaneous CD30+ lymphoproliferative disorders, and 1 unspecified cutaneous t-cell lymphoma. The mean score of symptoms, emotions and functioning domain scales in Skindex-16 were 32, 47 and 19, respectively. In the DASS-21, mean depression, anxiety and stress scores were 9.6, 5.9 and 12.7, respectively. Patients with advanced MF and SS showed worse scores in symptoms and functioning in Skindex-16

(P<0.05), but not in DASS-21. After the ES, there was a small reduction in the Emotions domain in Skindex-16, but not significant. Other domains in Skindex-16 and DASS-21 did not change. CONCLUSIONS: Cutaneous lymphoma can have a significant impact on patients' emotional state, as compared to their symptoms and functional aspects, regardless of the disease severity. Only symptoms and functions domains were worse in advanced MF/SS. We did not find a significant change in scores after the ES, but this could be related with small sample size. We believe that Health-related QoL assessment should be incorporated as a routine part of evaluating patients with cutaneous lymphoma.

P-093

PRIMARY CUTANEOUS PLASMABLASTIC LYMPHOMA OF THE LOWER LEG IN AN HIV NEGATIVE PATIENT

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Plasmablastic lymphoma (PBL) is referred to as a rare subtype of diffuse large B-cell lymphoma (DLBCL) characterized by an immunoblastic morphology and an immune phenotype of differentiated plasma cells, mainly in the setting of underlying human immune deficiency virus (HIV) and Epstein-Barr-Virus (EBV) infections. While PBL limited to the skin was reported to be less aggressive, systemic involvement is associated with a lethal course within months. Thus accurate clinical and histopathological diagnosis is essential given their significantly more favorable prognosis when compared to systemic forms according to the present literature. Here, we report a case of EBV associated PBL limited to the skin localized to a non-healing leg ulcer in a 67-year-old HIV-negative women with one year of follow-up.

P-094

EBV-NEGATIVE DIFFUSE LARGE B-CELL LYMPHOMA WITH CONCURRENT CUTANEOUS AND OCULAR INVOLVEMENT, AND SUBSEQUENT INFILTRATION TO THE CENTRAL NERVOUS SYSTEM

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Primary cutaneous diffuse large B cell lymphomas (pcDLBCL) unlike other cutaneous lymphomas are more likely to disseminate to other organs but concurrent ocular involvement and/or infiltration of the tumor to the central nervous system(CNS) is very rare.
A 67 year-old female, presented with a slowly enlarging, gyrated and erythematous infiltrate on the left arm. Histopathology of the biopsied skin lesion showed a dense confluent lymphocytic infiltration of the entire dermis with large centroblasts and immunoblast-like cells. Immunohistochemistry revealed $CD10^-$, $CD20^+$, $CD79a^+$, $BCL\text{-}2^+$, $BCL\text{-}6^-$ and $MUM1/IRF4^+$ tumor cells suggesting diagnosis of DLBCL, leg type. PCR analysis for IgH rearrangement demonstrated a monoclonal rearrangement. EBER in situ staining for EBV was negative.
Patient also complaint of recent blurry vision and her eye exam was noticeable for pseudophakia and a vitreous opacity in the right eye. The histopathology from the right vitrectomy showed B-cell tumor cells similar to the skin biopsy.The complete staging work up was unremarkable. Head and neck MRI did not reveal any involvement of central nervous system. Considering all findings the diagnosis of diffuse large B-cell lymphoma with concurrent cutaneous and ocular involvement was made.Over the next two years the multiple local recurrences on the left arm were locally treated. Eventually, 4 years after initial diagnosis, patient presented with signs and symptoms of multifocal CNS metastasis. MRI of head and neck revealed cerebral infiltrates and CSF cytology showed tumor cells of B cell origin identical to the skin and ocular specimens. Complete staging remained negative for any further systemic involvement. Patient underwent total brain irradiation, intrathecal depocyte and systemic treatment with R-CHOP without success. Rare cases such as this represent possibility of aggressive transformation and rapid clinical progression in cutaneous B cell lymphoma.

P-095

RISK OF SECOND CANCERS IN MYCOSIS FUNGOIDES

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BACKGROUND: The increased risk of second malignancies in CTCL patients has been well documented. The most frequent malignant tumors associated with CTCL are Hodgkin and non-Hodgkin lymphoma and lung cancer. Altered immune response in CTCL and effects of MF therapies suggest that these patients may present an increased risk of second primary malignancy.
OBJECTIVE: The aim of this study was to evaluate the relative frequency of second malignant neoplasms in patients with MF, their clinical features and the relationship with the disease outcome.
METHODS: We searched a database of 155 patients with primary cutaneous lymphoma (PCL) seen in the Oncology Section of the Dermatology Department of the "Hospital General de Agudos Dr. Cosme Argerich", registered from November 1995 to November 2012, to identify patients with diagnoses of both MF and a second cancer.
RESULTS: Of the 155 patients with PCL, 150 had CTCL; of this group, 111 were MF. We identified 32 second malignancies in 23 (20.7%) patients with MF. Twelve second malignancies were diagnosed before confirmation of MF, and twenty cases after. We found 16 skin cancers and 16 internal malignant neoplasm. No correlation between the presence of a second cancer and the outcome of the MF could be achieved.
CONCLUSION: We found an elevated incidence 20.7% of second malignancy in our series of patients with MF. Compared with other series where they found 6 to 15 %, the frequency of second malignancy occurring after the diagnosis of MF (18%) in the present series is similar. Further studies including a large number of patients are necessary.

P-096

"SEE YOU AT THE CLINIC"

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The Cutaneous Lymphoma Service in Melbourne has expanded in an effort to address the growing demands for patient consultations regarding management for this unique, rare and complex disease. The Cutaneous Lymphoma Service health professionals recognise the importance of haematological, dermatological and multi disciplinary input to enhance patient experiences.
Initially the Cutaneous Lymphoma Service began at St. Vincent's Hospital in Melbourne. Over time patient numbers increased as did their unique Haematological and Dermatological needs. In an effort to address these needs there are now 4 clinics in Melbourne specifically for patients with Cutaneous Lymphoma. These clinics consist of the St Vincent's/ Peter MacCallum Cancer Centre Multidisciplinary Clinic once per month, Peter MacCallum Cancer Centre Haematology Clinic weekly, Haematology Skin Lymphoma Nurse Led Clinic (weekly) conducted by a Skin Lymphoma Nurse Practitioner and the Private Caulfield Dermatology Clinic (monthly).
The St Vincent's/Peter MacCallum Cancer Centre Multidisiplinary monthly clinic has become a learning platform for health professionals throughout Australia. This clinic is often now attended by visiting dermatology and haematology teams from around Australia. These teams in addition to the Melbourne teams aim to improve knowledge, management and awareness of Cutaneous Lymphoma throughout Australia.
A team of haematologists, specialist histopathologists, radiation oncololgist, dermatologists, nurses, and an administrative assistant triage referrals between St Vincent's Hospital, Peter MacCallum Cancer Centre and Private consultation rooms.

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SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA IN AN AFRICAN WOMAN

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We present a 42-year-old woman, who developed fever and disseminated subcutaneous nodules several months after returning from a stay in Kenya. Due to her African descent and the fact that she was seen by internal medicine specialists, she was suspected to have an infectious problem. A thorough work-up excluding all major possibly inflicting infections was performed, producing negative results. A fine needle puncture from a breast nodule revealed granulomatous inflammation, without finding the cause in the subsequent investigations. During several months the number of subcutaneous nodules progressively increased, with another fine needle puncture with similar result and a monoclonal TCR-rearrangement. An appropriate biopsy followed suspecting a subcutaneous panniculitis-like T-cell lymphoma (SPTCL) or lupus panniculitis. She was referred to our department for further investigations. A diagnosis of alpha-beta SPTCL was made in June 2011, without evidence of systemic involvement. Lupus panniculitis or other manifestations of lupus erythematosus could be excluded. Systemic corticosteroids were initiated and have resulted in a complete morphological and metabolic clearance of the SPTCL in February 2012. The patient has been lymphoma-free since.

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FOLLICULOTROPIC MYCOSIS FUNGOIDES MIMICKING VARIOUS DERMATOSIS

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Mycosis fungoides (MF) has numerous clinical and histologic variants. Folliculotropic MF (FMF) is characterized by involvement of hair follicles, and epidermotropism is often lacking. A 77 years old men presented with 6-month history of exudative ear oedema, associated with eczematiform features, including fissures and itching and painful cervical lymphadenopathy, was initial treated for eczema with topical corticosteroids with partial improvement. Due to indurated papules and plaques in the entire face with scale-crust surface, clindamycin and terbinafine were prescribed with no clinical response. He presented to the emergency department after 4 days of fever and complaining of exudative facial infiltration and hearing impairment. On admission, facial cellulitis was diagnosed, however, during physical examination, he had auscultatory crackles and x-ray evidences of pneumonia. He had complete resolution of fever and inflammatory parameters with antibiotherapy, but the skin condition remained. Skin biopsy revealed dermal perifollicular infiltration of lymphocytes with atypical hyperchromatic nucleus, destruction of follicular epithelium and extension to subcutaneous fat. Lymphocyte populations in blood were 30,6% CD3+/CD4+ and 46,4% CD3+/CD8+ and a CD45+ atypical intensity subpopulation was found. Immunophenotypical analysis on blood and skin demonstrate respectively 6% and 91% of CD3+/CD4+/CD8-/CD30- t-cells with TCR-Vbeta 7.1 clonality. Ultrasound showed enlarged cervical lymph nodes with loss of normal morphology, and a biopsy confirmed involvement by T-cell lymphoma. He was staged as IVa2 and started CHOP therapy, therapy was effective and the lesions of the forehead became less indurated.
FMF is clinically characterized by papules and plaques on head and upper trunk, but it can presents acneiform, rosaceiform or eczematiform features. MF variants, can sometimes lead to late diagnose once the presentation is clinically different.

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CUTANEOUS SUBTYPE OF ADULT T-CELL LEUKEMIA/LYMPHOMA (ATLL)

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Adult T-cell leukemia/lymphoma (ATLL) is a malignant lymphoproliferative disorder caused by human T-cell lymphotropic virus type 1 (HTLV-1). It is endemic in south-western Japan and

the Caribbean basin. There are several subtypes of HTLV-1-induced ATLL; acute, lymphoma, chronic, and smoldering. Chronic and smoldering type ATLL have a relatively good prognosis, even without treatment. These types can, however, evolve to acute type ATLL, which has a poor prognosis: the median survival time (MST) after ATLL diagnosis is only 6 months. Specific skin lesions are caused by infiltration of the skin by the tumor cells and have been described in about half of patients with ATLL. In 1992, differences in HTLV-1 integration patterns between skin lesions and peripheral blood lymphocytes of ATLL patients with cutaneous involvements. Later, some reports have described patients who presented with only the cutaneous lesions without either leukemic change or visceral invasion for many years. We previously studied 124 cases of ATLL with specific skin manifestations. The MST of smoldering type ATLL was 16 months. We found that the smoldering type ATLL with skin involvements may have a worse prognosis than that without skin lesions, and proposed a fifth category; namely, cutaneous type ATLL, which has less than 5% abnormal T lymphocyte in peripheral blood, a normal lymphocyte count (i.e. $<4\times10^9$/L), no hypercalcemia and lactate dehydrogenase values of up to 1.5 times the normal upper limit. There is at least one of the histologically proven skin lesions in the cutaneous involvements. However, individual patients of ATLL showed considerable fluctuation in abnormal lymphocyte in peripheral blood over a prolonged period of time. The definition of primary cutaneous lymphomas has been changed "no extracutaneous manifestations of the disease at presentation". We propose a new definition of cutaneous subtype of ATLL, which show less than 4×10^9/L

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AN UNUSUAL SÉZARY SYNDROME : A FOLLICULOTROPIC FORM WITH CONCOMITANT PULMONARY LOCALIZATION

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Mycosis fungoides (MF) and Sézary syndrome are the most common clinical variants of cutaneous T-cell lymphoma (CTCL): they account for approximately 65% of CTCLs. The WHO-EORTC (World-Health-Organization-European-Organization for Research and Treatment of Cancer) has included a follicular variant of MF. This variant has been reported to have a more aggressive clinical course, with a poorer prognosis, and to be refractory to usual therapies.
Folliculotropic Sézary syndrome is exceptional, and we report here a folliculotropic Sézary syndrome with concomitant pulmonary localization.
A 64-year-old-man had a pruritic eruption for one month. An infiltrated leonine facies, follicular papules of the head and neck, alopecia of the scalp, abdominal non-tumoral infiltrated plaques, and multiple lymphadenopathy, suggested a folliculotropic Sézary syndrome, in line with the biological and histological results. A Computed-Tomography scan showed a bilateral reticular syndrome. The analyses of bronchoalveolar fluid using flow cytometric immunophenotyping showed the same T-cell clone as in the skin, blood and lymph nodes.

Our patient presented an exceptional folliculotropic form of Sézary syndrome with concomitant pulmonary lymphoma localization. To our knowledge, this is the first description of pulmonary involvement in folliculotropic Sézary syndrome. Only 7 previous cases of folliculotropic Sézary syndrome have been reported. In these cases, an extracutaneous involvement was present in 42%, whereas extracutaneous localization is rare in CTCL. Our case and previous data suggest that folliculotropism is particularly aggressive. They raise the question of the molecular characteristics of T-lymphocytes, currently unknown in the setting of folliculotropism, as compared to T-lymphocytes involved in CTCL without pillotropism.

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PRIMARY CUTANEOUS FOLLICULAR HELPER T-CELL LYMPHOMA – CASE REPORT AND DIAGNOSTIC PITFALLS OF THIS NEW LYMPHOMA SUBTYPE

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The recently proposed entity of cutaneous T-cell lymphoma of follicular helper T-cell type (CTFHCL) harbors distinct clinical as well as histological features and sheds new light on the spectrum of cutaneous peripheral t-cell lymphomas not otherwise specified (CPTCL-NOS).
We report on a 45-year-old patient who was initially diagnosed with cutaneous follicle center B-cell lymphoma on upper arms and buttock. Consequently, intravenous rituximab 375 mg/m2 infusions once weekly were started, but did not result in clinical remission. Therefore, repetitive skin biopsies were obtained with all of them revealing a CD3+CD4+CD8- cutaneous T-cell lymphoma of follicular helper T-cell type (CTFHCL). Interestingly, the prima vista PD-1- and CD10-positive tumor cells lost PD-1 expression in the follow-up biopsies while retaining a stable CD10 expression. All biopsy specimens studied for T-cell receptor gamma gene rearrangements displayed an identical biclonal T-cell population.
The nodules limited to trunk and extremities were initially well controlled by local radiotherapy as well as oral PUVA therapy for plaques. However, during maintenance therapy with oral PUVA disease recurred and progressed rapidly with numerous nodules. Treatment with bexarotene, methotrexate and, finally, polychemotherapy (CHOP) failed to stop disease progression. At that time, the patient suffered from numerous plaques and tumors on trunk, extremities and face. Modified total skin electron beam radiation (18 Gy) resulted in complete remission. Finally, disease stabilized on maintenance therapy with bexarotene in combination with UVA therapy (currently 10 months).
In summary, CTFHCL usually evokes strong and persistent B-cell responses which histologically might be mistaken – as in our case – for cutaneous follicle center lymphoma. Clinically, CTFHCL shows a distinct course with rapid progress despite aggressive treatment. Strikingly, prognosis seems to be not as poor as assumed from clinical course.

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PRIMARY CUTANEOUS B CELL LYMPHOMA LOCALISED ON THE FACE AND HARD PALATE – REPORT OF A CASE

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ABSTRACT: We report here a case of a woman with a cutaneous nodular B-cell lymphoma of the face. Upon presentation in our department, the patient presented two non-ulcerated nodules on the left part of the face. A histological examination on both pieces, following surgical excision showed a diffuse infiltrate of atypical B cells. The patient was subsequently directed to the Oncology Department for futher investigation, but she died soon after.
CASE REPORT: A 54-year old woman was referred to our Department, for a one year long history of two red or bluish-red nodular lesions, of about 4-5 cm of diameters, located on the left side of the face. The lesions were asymptomatic, non-ulcerated, with very slow growth in size, no submandibular adenopathy. On physical examination we noticed the two nodules of different size, not painful nor adherent to subcutis. The patient was in good health condition, but she informed us of the appearance of a small ulceration, one year ago, on the hard palate, in the same time with the nodules on the face. In the recent past, she has several times adressed to Oro-Laryngology Department, where she was diagnosed with aphtous ulceration and nodular fibroma of the face. She underwent many laboratory investigations and topical treatments with no improvement. Her past medical history included systemic blood hypertension, with good control upon systemic medication. Both lesions from the face were excised and a small punch-biopsy was taken from the lesion on the hard palate. The histopatologicl examinatin of the three lesions came with the same result: diffuse large B-cell lymphomas. The histologic examination provided the following observations: 1) normal epidermis, 2) diffuse non-epidermotropic infiltrates, predominantly made up of lymphocytes, with perivascular, periadnexial disposition and some involvment of nervous fibers; small and medium lymphocytes, some monocitoid-like or plasmocytoid-like, with atypical nuclei and frecquent mytosis. Imunohistochemistry of the biopsies revealed the modifications and established the final diagnosis of cutaneous lymphoma (CD20 positive, Vimentin focally positive and Ki67 positive on nuclear level in 46% of tumoral cell). The diagnosis of primary cutaneous B cell lymphoma localised on the face and hard palate was accepted. The patient was imediatly sent to the Oncology Department for further investigations, for stadialisation and treatment, but 24 hours after hospitalisation she died of pulmonary embolism.
DISCUSSIONS: Our patient was a relatively young woman of 54 years old, with three lesions on the head (face and hard palate), with a one-year period of course evolution of the disease and a fulminant ending.
This case report describes therefore a very unusual initial clinical presentation and strongly suggests consideration upon malignant nature of the lesion, when facing any apparent benign skin disorder.

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PARANEOPLASIC ACANTHOSIS NIGRICANS FOLLOWING DISEASE PROGRESSION IN A PATIENT WITH MYCOSIS FUNGOIDES

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A 33 year-old man presented to our clinic with a history of developing erythematous patches and plaques and then tumors over a three-year period. Shortly after tumors appeared, the patient also noticed brown, hyperpigmented and velvety plaques on his hands, feet, groin and axillae. Skin biopsies of the erythematous patches, plaques and tumors confirmed the diagnosis of mycosis fungoides (MF). A skin biopsy from a brown, velvety plaque revealed characteristic features of acanthosis nigricans (AN) without a concomitant lymphomatous T-cell infiltration. A staging evaluation was negative for systemic involvement and the patient was diagnosed with both stage IIB MF and AN.
Paraneoplastic AN mainly occurs in the course of adenocarcinomas located in the abdomen (70-90%), and it is rarely seen in patients with nonepithelial tumors such as sarcomas or lymphomas. In the few reported patients with both MF and AN, most of the biopsies showed features of both AN and MF in the same specimen. By contrast, in the case presented herein, the biopsy from the AN lesion was pauci-inflammatory and thus there was no evidence of malignant T-cell infiltration within this specimen. Thus, to our knowledge, our case is the second case reported of authentic paraneoplastic AN in the setting of MF.
It has been suggested that transforming growth factor α (TGF-α) is involved in the pathogenesis of paraneoplastic AN. Epidermal growth factor α (EGF-α) interacts with the same receptors on actively proliferating basal keratinocytes as TGF-α. Since epidermal expression of EGF-α and TGF-α appears stronger in MF than in normal human skin, and lymphomatous t-cells also express EGF-α and TGF-α, some authorities have suggested that this cytokine is involved in the epidermal hyperplasia sometimes seen in biopsies of MF. Thus, we hypothesize that expression of EGF-α and TGF-α by both epithelial cells and neoplastic lymphocytes is involved in the pathogenesis of paraneoplastic AN secondary to MF.

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NASAL-TYPE EXTRANODAL NATURAL KILLER/T-CELL LYMPHOMA WITH LONG-TERM SURVIVAL PRESENTING AS GENITAL ULCERS

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A 50-year-old Mexican woman attended our institute with an 18-month history of recurrent vulvar and perianal ulcers. Upon admission, she had several atrophic scars on labial and perianal skin along with a superficial perianal ulcer. A biopsy showed a pandermal, and subcutaneous angiocentric infiltrate with no epidermotropism composed of intermediate andlarge-sized atypical lymphocytes. Immunohistochemical positivity for CD2, CD3ε, CD56,

TIA-1, perforin and Granzyme B, along with the detection of the Epstein-Barr virus-encoded small RNA (EBER) by in situ hybridization, was consistent with extranodal natural killer/T cell lymphoma (NK/TCL). A staging evaluation was negative for systemic and nasopharyngeal involvement. The patient underwent superficial radiotherapy followed by 8 cycles of 3 different schemes of combination chemotherapy before achieving clinical remission. However, 6 months latter vulvar ulcers recurred and a new ulcer appeared in her right helix, which showed similar histopathologic findings. After 3 new cycles of chemotherapy the genital ulcers healed but not the one on the ear and there is still no evidence of systemic involvement 42 months after the beginning of her disease.
Extranodal NK/TCL is an extremely rare entity that classically affects the upper respiratory tract. Skin is the second most common site and lesions most often present on the trunk and extremities. Seven cases affecting female internal genital organs have been reported but none involved external genitals or perianal skin. Furthermore, albeit its clinical heterogeneity, the presence of ulcers as the sole primary lesion is exceedingly uncommon in NK/TCL.
The clinical course is aggressive and conveys a poor prognosis. The median survival for cases presenting in the skin is less than 12 months. However, in accordance to the case presented herein, an "indolent" subtype with long-term survival (median survival of 66 months) in spite of frequent relapses has recently been described.

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SECONDARY MALIGNANCIES IN PATIENTS WITH MYCOSIS FUNGOIDES (MF) AND SÉZARY SYNDROME (SS)

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BACKGROUND: An increase in the incidence of secondary malignancies has been reported in both MF and SS. Immunosuppression, as a result of both the disease and treatment may play a role in their development.
METHODS: We report a single-centre retrospective study of 1736 patients with MF and 252 patients with SS and associated secondary and multiple malignancies. Epidemiological features as well as types of secondary malignancy were collected and compared between both cohorts. Clinical information was collected from the patients' medical records and our clinical database.
RESULTS: 135 (7.7%) patients with MF and 30 (11.9%) patients with SS developed secondary or multiple malignancies. The median age of diagnosis was 65 (Interquartile range (IQR) 53-73) for MF and 72 (IQR 63-77) for SS (p=0.01). Overall 50% of MF patients were stage IB and 41% of SS patients were stage IVA1 at diagnosis (p<0.01). Of those MF patients with secondary malignancies, 36% had only cutaneous malignancies, but these were less common in SS (20%). Systemic malignancies represented 48% of secondary malignancies in MF and 53% in SS. 16% patients with MF had multiple cutaneous and systemic malignancies concurrently but the incidence increased to 27% in SS patients. There was no significant difference between the incidence of haematologic (including Hodgkin´s disease, non-Hodgkin lymphomas and leukaemia), gastrointestinal, gynecologic, urinary tract, pulmonary and endocrine malignancies in either cohort.

CONCLUSION: This study shows that in our cohort of patients, the frequency of secondary malignancy is similar in patients with MF and SS in spite of the different prognosis, stage and age at diagnosis.

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CUTANEOUS T-CELL LYMPHOMAS AND SECOND PRIMITIVE MALIGNANCIES

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INTRODUCTION: The occurrence of a T-cell lymphoma and another primary neoplasm in a same patient is rare.
Material and methods: Descriptive and retrospective study including patients with a documented TCL associated with other cutaneous or extracutaneous neoplasms over 12 year (2001-2012).
RESULTS: 120 patients with TCL were collected. Five of them had associated neoplasm: 2 men and 3 women, mean age 53.4. The TCL was mycosis fungoide (3 cases), Sezary syndrome (2 cases). Associated neoplasia was: lung adenocarcinoma, melanoma, larynx carcinoma, B-leukemia, Hodgkin's disease. These tumors preceded the TCL in 2 patients, and were simultaneous in two cases and 6 years later in one patient. Treatment of associated tumor was possible in 4 cases, with a good improvement.
DISCUSSION: Association of TCL and other primary malignancies remains is rare. These are most often solid neoplasms. These associations may result from environmental factors (smoking), genetic predisposition to develop malignancies, an underlying infection by an oncogenic virus or immunosuppressive treatment, by the mutagenic effect of anticancer drugs used to treat the first of the two malignant syndrome or abnormal functioning of t-cell or cytokines system. Alteration of a stem cell could explain the association of B and t-cell lymphomas.
CONCLUSION: Initial exploration and monitoring regiment of primary cutaneous lymphomas are not yet standardized. Regular periodic monitoring is necessary for early detection of these associations and their individual and environmental risk factors.

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PRIMARY CUTANEOUS ANAPLASTIC CD30+ LARGE CELL LYMPHOMA ASSOCIATED WITH HEMOPHAGOCYTIC SYNDROME: FATAL ASSOCIATION

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INTRODUCTION: The primary cutaneous anaplastic CD30+ large cell lymphoma (PCALCL) is a rare type of cutaneous lymphoma with a good prognosis. The association with a hemophagocytic syndrome is exceptional.
CASE REPORT: We report an unusual presentation of PC-ALCL. A 37-year-old man, presented with a four months history of subcutaneous nodules of the limbs. The hospitalization was indicated to febrile disorders of consciousness. Skin histology confirmed the diagnosis of

PCALCL. The diagnostic of hemophagocytis syndrome was made on results of the laboratory data and myelogram. The patient died on the third day of his hospitalization in an array of multiple organ failure.
DISCUSSION: The originality of our observation lies is the clinical presentation of this type of lymphoma, the rarity, the fatal evolution and the association the PCALCL and HPS. This association is a special and rare entity. We discuss the particularity of diagnosis, prognosis and the recent data on this association.
KEYWORDS: Subcutaneous nodules; Primary cutaneous T anaplastic CD30+ large cell lymphoma (PCALCL); Hemophagocytic syndrome (HPS).

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BULLOUS MYCOSIS FUNGOIDES: REPORT OF A NEW OBSERVATION

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INTRODUCTION: Mycosis fungoides, the most common type of cutaneous T-cell lymphoma, can manifest in a variety of clinical and histological forms. Bulla formation is an uncommon finding in mycosis fungoides and only approximately 20 cases have been reported in the literature.
CASE REPORT: We present a case of rapidly progressive mycosis fungoides in a 85-year-old moroccan man, who had initially a history of erythrodermic mycosis fungoides stage III (T4N0M0) since 2008, for which he was treated with methotrexate 25 mg/week with no real improvement. After 3 years of evolution, he presented a relapse of erythroderma accompanied by the appearance of vesiculous and bullous lesions of the trunk and limbs. Skin biopsy was in favor of a bullous mycosis fungoides with epidermotropism of atypical lymphocytes without acantholysis, large coalescing Pautrier's microabscesses were also noted. Findings from immunohistochemical analysis showed that the infiltrate was predominantly composed of t-cells CD3 positive and CD30 negative. Direct and indirect immunofluorescence for bullous pemphigoid and pemphigus antibodies were negative. The search for Sezary cells in the blood was also negative.
DISCUSSION: Mycosis fungoides is the most common type of cutaneous T-cell lymphoma. Vesiculobullous lesions represent an extremely rare manifestation of mycosis fungoides. Bowman and al. have proposed criteria for its diagnosis. The appearance of bullous lesions in a patient with mycosis fungoides seems to be a harbinger of a poor prognosis. Treatment of bullous mycosis fungoides is similar to that of a conventional mycosis fungoides and depends on the stage of lymphoma.
CONCLUSION: Although mycosis fungoides bullosa is extremely rare, it has to be regarded as an important clinical subtype of cutaneous T-cell lymphoma. Mycosis fungoides bullosa represents a particularly aggressive form of mycosis fungoides and is associated with a poor prognosis.

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CLINICOEPIDEMIOLOGICAL FEATURES OF MYCOSIS FUNGOIDES IN 61 TURKISH PATIENTS

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Mycosis fungoides is the most common cutaneous T-cell lymphoma characterized by proliferation of T lymphocytes with cerebriform nuclei. Its annual incidence reported as 0.13 to 0.9 cases per 100,000 persons. Although clinicoepidemiological features of mycosis fungoides well defined in previous studies, its features in Turkish population have yet to be determined. In this study we retrospectively analyzed the clinicoepidemiological features of 61 patients diagnosed as mycosis fungoides between December 2001 and December 2012.
A total of 61 histopathologically confirmed mycosis fungoides with a mean age at diagnosis 36.8 years involved in this study. Of 61 patients, 17 patients were female and 44 patients were male. The mean age at onset of skin lesion was 32.8 years. Mean duration of disease before diagnosis was 4 years. All patients were evaluated by TNMB staging and 17 patients had stage IA disease, 18 patients had stage IB disease, 23 patients had stage IIA disease and 3 patients had stage IIB disease. At diagnosis most prevalent skin lesions were patches which is followed by plaques, follicular lesions and erythroderma respectively. Patients were treated with various treatment options including topical steroids, oral isotretinoin, PUVA therapy, NBUVB therapy, PUVA plus acitretine, PUVA plus bexarotene, oral bexarotene, topical bexarotene, radiation therapy, and chemotherapy. At final assessment, patients showed remission duration up to 8 years. Death from disease occurred in 1 patient which shows progression from stage IIB to IVB.
In conclusion, mycosis fungoides seem to affect younger individuals in Turkish population. Duration of disease before diagnosis was also lower than previous studies. Only one patient had progressed to advanced stage. Other patients showed remission and relapses which are controlled by conventional therapies.

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HYPOPIGMENTED MYCOSIS FUNGOIDES: DEMOGRAPHY, CLINICAL, HISTOPATHOLOGY PROGRESS AND RESPONSE TO TREATMENT

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OVERVIEW & INTRODUCTION: the hypopigmented Mycosis Fungoides is a rare presentation of Mycosis Fungoides. Mostly affects children and adults young people of dark skin and asians, without preference for gender; presents as asymptomatic macules hypopigmented, or slightly itchy, slowly progressive. Histologically presents the same alterations observed in the classical MF stage patch. Methodology: We performed a retrospective, descriptive study where demographic parameters, behavior is analyzed clinical-histopathological and response to the established treatment for patients with diagnosis of hypopigmented Mycosis Fungoides studied in the Institute of biomedicine between the years 1992-2009.

RESULTS: were they included 16 patients, 13 female and 3 male, with an average age of 24 years. The initial lesion was hypopigmented maculae in 100% of cases, asymptomatic in 31% and mild itching in 69%, to dominate the phototypes III-V, average duration of illness >5 years, 100% of the biopsies concluded: Mycosis Fungoides. The most commonly used treatment modalities were: PUVA, UVB, nitrogen mustard, Bexarotene, inducing repigmentation in 100%, with high rates of recurrence, but with good response to reinstate the treatment.
DISCUSSION: Hypopigmented Mycosis Fungoides is a clinical modality rare Mycosis Fungoides, rarely reported, probably underdiagnosed. Occurs in children and young dark-skinned adults, such as asymptomatic hypopigmented macules or itchy lesions can be kept its character macular by years, slow, not aggressive, with good response to treatment. With frequent recurrences. We emphasize on the importance of hypochromic macules that do not respond to conventional treatments skin biopsies, sometimes repeated to achieve the early diagnosis.
KEYWORDS: Hypopigmented Mycosis Fungoides

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LYMPHOMATOÏD PAPULOSIS AND BREAST ADENOCARCINOMA: MORE THAN A SIMPLE COÏNCIDENCE

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INTRODUCTION: Patients with lymphomatoïd papulosis (LyP) seem to have an increased risk of malignancies. We report an unusual association of both lymphomatoïd papulosis and breast carcinoma.
CASE REPORT: A 50-year-old woman sought care for a six-year history of a reccurent, slightly pruritic and disseminated skin eruption. Her medical history was otherwise unremarkable. The dermatological examination revealed 0,5cm to 1cm in diameter necrotic papulonodules and crusty papules affecting the face, the trunk and the limbs. The right breast examination displayed a tumor about 6cm in diameter. No nodes were found. The histopathologic examination of the skin biopsy showed a marked epidermal acanthosis with irregular papillomatosis and a parakeratosis topped with central ulcerations. The dermal infiltrate had a roughly triangular-based epidermal architecture, and was composed of inflammatory cells mainly represented by small mature lymphocytes, histiocytes, neutrophils and eosinophils. Atypical multinucleate large cells resembling Reed Sternberg cells were found preferentially around the vessels. An immunohistochemical study revealed abnormal lymphocytes expressing the antibodies CD30 (Ber-H2) and CD4 (clone Ab-8). This aspect was concluding to a lymphomatoïd papulosis type A. In search of an associated lymphoma, additional laboratory tests were normal. However, scans of the chest and the mammographic aspect of the right breast were disturbing. A micro-biopsy of the breast tumor showed an invasive ductal carcinoma. A neoadjuvant chemotherapy was established. The evolution was charactized by the stabilisation of cutaneous lesions.

DICUSSION: The association between LyP and lymphoïd malignancy is well established. Nevertheless, the risk of developing a visceral cancer in patients affected by LyP is underreported in literature.
CONCLUSION: Patients with LyP should be regularly monitored not only to detect hematologic malignancies but also to look for other visceral tumors.

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HYPOPIGMENTED MYCOSIS FUNGOIDES VERSUS MYCOSIS FUNGOIDES WITH CONCOMITANT HYPOPIGMENTED LESIONS: A CLINICAL AND EPIDEMIOLOGICAL COMPARATIVE STUDY

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BACKGROUND: Hypopigmented mycosis fungoides (HMF) is a rare subtype of mycosis fungoides (MF); however, there are no criteria to define a typical case: patients with other morphologic subtypes of MF lesions and concomitant hypopigmented ones are usually diagnosed as HMF patients.
OBJECTIVE: We aim to analyze and compare a group of MF patients who presented only hypopigmented lesions with a group of MF patients who presented, besides hypopigmented lesions, another morphologic variant.
METHODS: 20 patients with MF presenting exclusive hypopigmented patches (exclusively hypopigmented MF – eHMF) and 14 patients with MF presenting hypopigmented lesions concomitant to other types of lesions (mixed hypopigmented MF – mHMF) were selected. Clinic-epidemiological analysis, histologic and immunochemic study were performed.
RESULTS: Our findings show that eHMF and mHMF can preserve some similarities: younger patients (compared to classic MF), striking predilection for dark-skinned persons, female predominance, histopathological features and relative good prognosis (most patients presented stage I disease – ISCL staging). They can also present differences: exclusive hypopigmented variant is associated with early onset (24.5 vs. 27.5 years, median, $p<0.05$) and a clear CD8+ immunophenotype (16/20 vs. 4/14 cases, $p=0.005$, considering hypopigmented lesions). However, epidermal CD8 + lymphocytes were identified in all CD4+ immunophenotype cases. Disease duration was higher in mHMF group than eHMF one (12 vs.8.5 years, median, $p<0.05$).
CONCLUSION: Hypopigmentation could represent a protective immune response: neoplastic or reactive CD8+ t-cells from cellular infiltrates guarantee an indolent course, preventing disease progression. Therefore, hypopigmented MF lesions could be considered as a marker of good prognosis, independently whether exclusively or mixed hypopigmented variant.

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EVALUATION OF ITCH-INDUCING MEDIATORS IN CTCL

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Chronic pruritus is a common symptom affecting many individuals with lymphoma, particularly those with cutaneous t-cell lymphoma and Sezary syndrome. Effective control of pruritus in those patients is often difficult to achieve as antihistamines may show little benefit. Newer therapies, including aprepitant, have been proposed as effective measures, working outside of the classical histamine pathway. However, the identification and characterization of non-histaminergic pathways relevant to itch have not been defined. Nociceptors in the skin (dorsal root ganglion neurons) have been identified as the relevant pathway carrying messages of itch and pain to the brain. Measurement of neuronal activity can be assessed in vitro using primary dorsal root ganglion (DRG) neurons from mice. Stimulation of particular subsets of ion channels (TRP, transient receptor potential channels) causes neuronal activation and action potential generation. Here we evaluate the distribution and activity of candidate TRP-family ion channels in mouse skin and DRG neurons. Additionally, the effects of non-histaminergic pathways leading to nociceptor activation were investigated, including relevant itch-associated cytokines.

Clinical Trials

P-115

PHASE 3 STUDY OF BRENTUXIMAB VEDOTIN VERSUS PHYSICIAN'S CHOICE OF METHOTREXATE OR BEXAROTENE IN PATIENTS (PTS) WITH CD30-POSITIVE (CD30+) CUTANEOUS T-CELL LYMPHOMA (CTCL). THE ALCANZA STUDY

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Brentuximab vedotin is a CD30-targeted antibody conjugated by a protease-cleavable linker to a microtubule-disrupting agent, monomethyl auristatin E. Overall response rate (ORR) of 75% in CD30+ relapsed/refractory (RR) Hodgkin lymphoma and ORR of 86% in RR systemic anaplastic large cell lymphoma (sALCL) has been reported. The latter trial also reported resolution of cutaneous lesions in 93% of pts (Advani EHA 2011). Some clinical activity has also been noted in RR CD30+ mycosis fungoides (MF; ORR 68%; Krathen ASH 2012) and CD30+ CTCL and lymphoproliferative disorders (ORR 63%; Duvic ASH 2012). This randomized, open-label, multicenter study (NCT01578499) will assess the efficacy of brentuximab vedotin in 124 CD30+ CTCL pts, including primary cutaneous ALCL (pcALCL) and MF. Primary endpoint: ORR lasting >=4 months. Key secondary endpoints: complete response (CR) rate, progression-free survival, and burden of symptoms. All randomized pts will be followed for survival. Key inclusion criteria: histologically-confirmed CD30+ (>=10% total lymphocytes or neoplastic cells) pcALCL or MF and >=1 prior systemic therapy. Pts will be stratified by diagnosis and randomized to receive brentuximab vedotin 1.8 mg/kg every 3 weeks (wks) for up to 16 cycles (48 wks), or physician's choice (methotrexate or bexarotene) up to 48 wks. Pts with partial response or CR at cycle 3 may continue study drug for up to 48 wks. Pts with stable disease and evidence of benefit may continue for a further 3 cycles. Pts with increasing skin score (modified severity weighted assessment tool; mSWAT) prior to cycle 3 may continue until cycle 3 if it is due to tumor flare. Response assessments: skin (mSWAT), nodal and visceral radiographic assessments, detection of circulating Sézary cells (MF only). ORR will be evaluated until disease progression or study closure. Safety assessments: incidence and severity of adverse events, changes to physical and laboratory tests. Enrollment into this study is ongoing.

Abstracts

Wednesday, February 6, 2013

O-001

MYCOSIS FUNGOIDES AND SEZARY SYNDROME: DIFFERENT STAGES OF THE SAME DISEASE OR DISTINCT ENTITIES?

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Since the early description of Sezary syndrome (SS) in 1938, there has been continued discussion regarding the relationship between SS and mycosis fungoides (MF). With the introduction of the term cutaneous T-cell lymphoma (CTCL), emphasizing the morphological and phenotypical similarities between MF and SS (skin homing T-cells with cerebriform nuclei), distinction became just a matter of stage, and in many textbooks and review articles SS is simply considered as a leukemic variant or leukemic phase of MF. However, there is accumulating evidence to suggest that MF and SS are distinct entities. Apart from differences in clinical presentation and clinical behavior, there are also histological, phenotypical and genetic differences between these conditions. Histologically, the neoplastic t-cells in early stage MF preferentially colonize the basal layers of the epidermis, while the neoplastic t-cells in SS show a preferential perivascular distribution, reflecting the leukemic nature of the disease. Recent phenotypical studies suggest that the neoplastic T-cells in SS and MF arise from distinct functional T-cell subsets: circulating tumor cells in SS from central memory T-cells and T-cells isolated from MF skin lesions from skin resident effector memory T-cells. In addition, SS consistently has a mature $CD4^+$ T-cell phenotype and shows expression of programmed death 1 (PD-1; CD279). Also in MF a $CD4^+$ phenotype is most common, but patients may also present with a $CD4^-$ $CD8^+$ or a $CD4^-$ $CD8^-$ T-cell phenotype, and expression of PD-1 is uncommon. Recent molecular genetic studies also showed marked differences between MF and SS. These studies suggest differences in the pathways involved in the development and progression of these two types of CTCL, which may imply different responses to (novel) treatments. Therefore, in future clinical trials, patients with MF and SS should be entered separately, or the results of these trials should at least be stratified according to CTCL type.

O-002

HISTOPATHOLOGIC CRITERIA FOR THE DIAGNOSIS OF SÉZARY SYNDROME IN DIFFERENTIATION FROM OTHER ERYTHRODERMIC SKIN DISEASES: AN EORTC CUTANEOUS LYMPHOMA GROUP STUDY OF 101 CASES

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Erythrodermic patients are a diagnostic challenge regarding the clinical and histological differential diagnosis. 101 cases of erythroderma were collected by the EORTC CLTF histopathology group in order to describe diagnostic criteria. Skin biopsies from 3 different groups of erythroderma were investigated: Sézary syndrome (SS, n=54), erythrodermic mycosis fungoides (EMF, n=7) and reactive erythrodermas (RE; n=40; e.g. atopic dermatitis, psoriasis, drug eruptions etc.). The following criteria were evaluated during 2 histopathology workshops: epidermal and dermal changes, morphology of the infiltrate, immunohistochemical analysis of marker loss (CD2, CD3, CD4, CD5 and CD7), bystander infiltrate by stainings for CD8, FOXP3 and CD25 and expression of Ki-67, CD30, PD-1 and MUM-1. Then, the expert panel made a diagnosis based on histology and immunohistochemistry which was then correlated with clinical data including molecular biology data. The mean age for all 3 groups of erythroderma was 66 years. The male to female ratio was 1:1 (SS), 7:0 (EMF) and 4.7:1 (RE). Epidermal changes were seen in 88% (SS), 86% (EMF) and 80% (RE) of the cases. Pautrier microabscesses were found in 22% (SS) and 29% (EMF) of the CTCL skin biopsies and in none of the RE samples. All cases demonstrated an upper dermal infiltrate of lymphocytes which were admixed with large or small blasts in 35% (SS), 0% (EMF) and 15% (RE) of the cases. 59% (SS), 14% (EMF) and 10% (RE) of the samples showed an antigen loss for at least one of the t-cell markers investigated. There was no difference in the bystander infiltrate (CD8+, FOXP3+ and CD25+ cells) between the 3 groups and none of the CTCL cases had FOXP3+ tumor cells. Also the expression levels of CD30, Ki67 and MUM-1 were similar for the 3 groups. 74% of the SS samples (57% [EMF], 43% [RE]) had more than 50% PD-1+ lymphocytes in their skin infiltrate. Based on these criteria the workshop expert panel established a diagnosis of RE in 6% of the SS cases, 29% of EMF samples and 80% of biopsies from RE. A number of different histopathological and immunohistochemical criteria are required to differentiate between the different types of erythroderma investigated.

O-003

DIAGNOSTIC ISSUES RAISED BY THE PRESENCE OF CD20-POSITIVE CELLS IN TRANSFORMED MYCOSIS FUNGOIDES

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Mycosis fungoides (MF) can undergo transformation in about 10% of cases (T-MF) that may be associated with the presence of CD20+-cells as observed in 18 out of 40 cases of a previous series of our group in 2000. The aim of this study was to analyze the prevalence of such phenomenon and to determine whether the CD20 antigen was expressed by reactive or lymphomatous cells.

Among 311 T-MF from the GFELC, we studied 148 cases for which we had complete clinical and pathological data. Out of these 148 T-MF cases, CD20 was found expressed by more than 10% of cells in 88 cases (59%). Indeed, the proportion of CD20+ cells among the infiltrate was 10 to 49% for 71 (50%) cases and more than 50% in 17 (12%) cases without impact on prognosis. Thereafter, we focused our study on 23 cases containing more than 50% of CD20+ cells with large ones. To confirm the expression of CD20 antigen and to rule out cross-reactivity, we used two anti-CD20 antibodies (L26 and 7D1 clones). To define the B-cell or T-cell origin of cells expressing CD20, we also used antibodies against CD3, CD22 and PAX5. We also used immunofluorescence staining (using anti-CD20 and anti-CD3 antibodies) and determination of B-cell clonality by IGH gene rearrangement study.

In 15 out of the 23 cases, the CD20+ cells corresponded to reactive B cells, sometimes with large cell and dendritic morphology. In 6 cases, CD20 protein was aberrantly expressed by large lymphomatous T-cells as determined by double immunofluorescence staining. Lastly we found two composite lymphomas combining T-MF lesions and a follicular center B-cell lymphoma with monoclonal IGH rearrangement.

Based on our data, we have built a simple algorithm in order to help the pathologist to solve diagnostic issues raised by the presence of the CD20+ cells associated with MF transformation.

O-004

PRIMARY CUTANEOUS B LARGE CELL LYMPHOMAS: A SPECTRUM OF HISTOLOGIC SUBTYPES RANGING FROM FOLLICULAR TO DIFFUSE LARGE B-CELL LYMPHOMA SUBTYPE – CLINICO-PATHOLOGIC AND MOLECULAR ANALYSIS OF 173 CASES

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BACKGROUND: Classification of primary cutaneous B-cell lymphoma (PCBCL) with predominant diffuse large cell histology is still matter of debate. Such cases are classified either as follicle centre cell lymphoma (FCCL) or as diffuse large B-cell lymphoma leg type (DLBCL-LT), based on cytologic features (round vs cleaved cells). However the histologic criteria to distinguish between these two subtypes need to be precised.
PATIENTS AND METHODS: 173 cases of PCBCL diagnosed between 1993 and 2010 in 9 centers (Ancona, Firenze, Milano, Novara, Padova, Pavia, Terni, Torino, Vercelli) referring to GILC, were reviewed by a panel of expert pathologists and dermatopathologists to reach a consensus diagnosis according to the 2008 WHO Lymphoma Classification. Histogenesis was defined by immunohistochemistry for CD10, Bcl6, MUM1. BCL2 rearrangement was tested by FISH.
RESULTS: 105/173 (61%) cases were classified as FCCL; 22/173 (13%) cases as DLBCL-LT. 42/173 (24%) cases showed intermediate features between FCCL and DLBCL. They had a diffuse growth pattern and consisted of monomorphic centroblasts (28/173, 16%) or of an admixture of centroblasts and large cleaved cells (14/173, 8%). Most DLBCL-LT (15/22, 67%) had a non-germinal centre (GC) profile, whereas the majority of cases with intermediate features had a GC phenotype (17/33 53%). BCL2 rearrangement was found in 14/72 (19%) FCCLs, in 1/6 (1,6%) DLBCLs-LT and in 2/16 (12,5%) cases with intermediate features. Two cases of FCCL progressed to large cell lymphoma and patients died of disease. BCL2 rearrangement did not affect prognosis. DLBCL-LT pursued a more aggressive course (30% of patients died of lymphoma). Within the group of FCCLs, the cases with a predominance of large cells (centroblasts and large cleaved cell) had frequent cutaneous relapses (60% vs 43% in FCCL), with 4/42 (9%) patients dead of disease. Our data seem to delineate a subgroup of PCBCL with intermediate clinico-pathologic features between FCCL and DLBCL-LT.

O-005

HIGH RATE OF TCRΓ GENE REARRANGEMENT WITH CLONAL IDENTITY IN MICRODISSECTED CD30+ CELLS FROM LYMPHOMATOID PAPULOSIS (LYP)

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INTRODUCTION: Lymphomatoid papulosis (LyP) belongs to the spectrum of primary cutaneous CD30+ T-cell lymphoproliferative disorders, that have been included within the peripheral T-cell lymphomas in the WHO lymphoma classification. LyP cellular infiltrate consists of scattered CD30+ atypical cells, resembling Hodgkin and Reed-Sternberg cells, intermingled with polymorphous inflammatory background. Despite its malignant histology, LyP lesions regress spontaneously, and 5-year-survival is close to 100%, thus raising questions about LyP nature (neoplastic vs reactive). Literature reported TCRγ clonal rearrangements in 40% of LyPs in which clonality assays have been performed using DNA from whole lesional paraffin sections. Similarly to the findings in previous studies on Hodgkin lymphoma, the few atypical cells and the rich inflammatory background may be responsible for low clonality rate. We compared the rate of TCRγ clonal rearrangement in LyPs, employing DNA extracted respectively, from whole sections and CD30+ microdissected cells.
MATERIALS AND METHODS: Individual biopsies from 12 LyP cases were tested for TCRγ rearrangements by PCR on DNA extracted respectively from whole-tissue sections and a pool (50-100 cells) of CD30+ microdissected cells (ZEISS-PALM Robot-MicroBeam System). PCR products were sequenced and compared with each other and published data base sequences.
RESULTS: TCR clonality assessment revealed a 92% of monoclonal rearrangement in microdissected CD30+ cells vs a 42% in whole tissue sections. Sequencing of PCR products showed a high degree of matching rearrangements, suggesting clonal identity. No clonal rearrangement was found in a pool of microdissected cells from CD30 negative areas. The high rate of TCR clonality in LyP microdissected cases corroborates the neoplastic nature of LyP. The laser microdissection remains the most valuable tool to assess clonality in lymphomas showing rich inflammatory background but few lymphoma cells.

O-006

SPECTROTYPING OF REARRANGED T-CELL RECEPTOR VB GENES IN FOLLICULOTROPIC MYCOSIS FUNGOIDES DOES NOT SHOW RESTRICTED GENE REARRANGEMENTS

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Folliculotropic mycosis fungoides (FMF) is a variant of cutaneous t-cell lymphoma characterized by predominant infiltration of hair follicles by lymphoma cells. Folliculotropism

may suggest that antigen-stimulation by particular antigens present in the hair follicle may contribute to the pathogenesis of FMF. To test this hypothesis, we identified the rearranged T-cell receptor (TCR) Vβ genes in a series of 20 cases (21 samples) with clinically and histologically well-characterized FMF as well as 10 control cases (10 samples) of conventional mycosis fungoides (MF)[1]. The analysis was performed by using a multiplex PCR and BIOMED-2 primers, followed by sequencing of the monoclonal PCR products.
No restricted use of TCR Vβ genes in FMF was demonstrated. Similarly, control cases of conventional MF showed non-restricted TCR Vβ gene rearrangements, as has been demonstrated before. Our results indicate that FMF, as has been demonstrated for MF before, does not arise from TCR Vβ-restricted T cells, including NKT cells. Whether antigen-stimulation plays a role in the pathogenesis of FMF is still an open question, but our results do not indicate the involvement of restricted antigens.

O-007

CUTANEOUS FOLLICULAR HELPER T-CELL (TFH) LYMPHOMAS: A SERIES OF 6 CASES HIGHLIGHTING NEW CLINICAL-PATHOLOGICAL ASPECTS AND THE POSSIBLE OCCURRENCE OF ITK-SYK REARRANGEMENTS

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A subset of cutaneous lymphomas that cannot be classified using the current WHO 2008 scheme (PTCL, NOS) express TFH markers, recently considered to represent a distinct sub-group and termed primary cutaneous TFH lymphomas (PCTFHL). PCTFHL may be related to the previously described nodal peripheral T-cell lymphomas (PTCL),NOS follicular variants, that can be associated with a t(5;9)(q32;q22) translocation with ITK-SYK rearrangement, shown to promote T-cell lymphoproliferations in transgenic mice models.
We reviewed 6 PCTFHL, focusing on T-cell and TFH related markers and ITK-SYK rearrangements using FISH.
The patients had multiple nodules (n=4), an ulcerated tumour or a maculo-papular rash. One had a regional enlarged lymph node, showing partial involvement by the lymphoma, another a polyadenopathy and 2 a leukemic component. Epidermotropic neoplastic TFH cells were evidenced in 2 cases and in one the neoplastic cells were large and CD30+. T-cell antigen loss were found in 3 cases (CD2 or CD5). The architecture of the infiltrates varied from a perivascular infiltrate (n=2) to a diffuse (n=3) or nodular infiltrate with follicular dendritic cells hyperplasia (n=1). The neoplastic T-cells were CD4+ with variable expression CXCL13, PD1, ICOS and BCL6 (<5% to over 50%), while CD10+ lymphocytes were rare (n=2). Plasma cells were present in 3 cases, with a monotypic Kappa light chain expression in one. Three had EBV+ B-cells and in two cases, there was an associated EBV+ diffuse large B-cell lymphoma (skin or lymph node). All had a dominant cutaneous T-cell clone and two an associated B-cell clone. Interestingly, ITK-SYK fusion signals were identified in two cases.

PCTFHL may histologically present as an epidermotropic T-cell lymhoma and may be composed of large atypical CD30+ cells. They may be associated with EBV+ B-cells and with EBV+ DLBCL. As in nodal PTCL,NOS follicular variant, some PCTFHL are associated with ITK-SYK rearrangements.

O-008

PHENOTYPE INSTABILITY IN SÉZARY CELLS: FOLLOW-UP RESULTS IN 107 PATIENTS

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Sézary cells (SC) display a "central memory" T helper phenotype characterized by specific markers such as CD158K and T-plastin, often with CD3 or CD4 dim expression, and a variable lack of CD7. Anti-TCR-Beta chain antibodies may be helpful for identifying SC. CD26 negativity still constitutes the one of the more reliable and easier to use phenotypic parameter for SC identification and quantification. However, few data are available on SC phenotypic stability during follow-up. In order to ascertain the SC phenotypic plasticity during follow-up, we retrospectively revised our casistic consisting of 2,434 serial cytometric analyses performed in 107 patients with Sézary syndrome (7 B1 and 100 B2) from 1985 to 2012. A lack of CD26 was detected at diagnosis in 97 cases (90.7%), whereas 9 patients (8.4%) showed a variable CD26+ SC population and 1 case was totally CD26+. Regarding follow-up, 86 out of 97 CD26- cases at diagnosis (80.4%) as well as 7 out of 9 patients with a CD26+ subset maintained this stable phenotype. Conversely, 13 patients (12.1%) exhibited a phenotypic change with a CD26+ subset appearence or disappearence. CD7 expression showed a higher degree of variability: 46 patients (49.2%) were permanently CD7-, 25 (26.8%) CD7+ and 27 (28.9%) showed the simultaneous presence of CD7+ and CD7- SC. Nine patients (9.6%) developed phenotypic changes during follow-up. Regarding CD2 expression, 23 patients (24.6%), showed a complete or partial CD2 loss. Changes over time were observed in 6 cases. Dim or bright CD3+ and/or CD4+ populations were present in 72/91 cases (79.1%) with a general stable fluorescence intensity over time. CD158k was positively expressed in about 40% of cases. In conclusion, a significant percentage of patients with Sézary syndrome developed phenotypic changes during follow-up, with increase or decrease of different subsets. An intriguing hypothesis is that CD26 gene CpG islands methylation or demethylation could explain this phenomenon.

O-009

INSIGHTS INTO CUTANEOUS T-CELL LYMPHOMAS

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Different genomic platforms have characterized complex and heterogenous patterns of somatic copy number variations (CNV) in mycosis fungoides and Sezary syndrome (MF/SS). In addition abnormal gene expression, often associated with aberrant methylation, and

aberrant microRNA expression has been identified in both MF and SS but questions still remain about the relationship between these abnormalities and the T-cell differentiation status of the tumour cells. Constitutive expression of several key transcription factors such as NFkB and STAT3 has also been defined, particularly in SS, and are likely to affect tumour cell survival and proliferation. However at present there is a paucity of data on somatic driver mutations in both MF/SS and indeed which somatic mutations might underline these abnormalities of gene regulation.
Transcriptome and whole exome sequencing technologies are now starting to identify key gene expression and somatic genomic abnormalities in CTCL and are illustrating the complexity and marked heterogeneity of gene variants. These datasets will now form the basis for more extensive prevalence screens in both MF and SS which hopefully will provide more insight to enable identification of new therapeutic targets and pathways. A specific example are genes on chromosome 9p21 encoding genes including *MTAP* which has been shown to be deleted in some malignancies including CTCL and there is now evidence that that this region may also be inactivated through promotor hypermethylation but with no evidence for somatic mutation in CTCL.

O-010

KIR3DL2/CD158K AS DIAGNOSTIC MARKER AND NEW THERAPEUTIC TARGET FOR CUTANEOUS T-CELL LYMPHOMAS

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KIR3DL2/CD158k has been shown to be a valuable diagnostic marker for the identification of tumor T lymphocytes in skin and blood of patients with Sézary syndrome. CD158k has also been shown to be expressed by tumor t-cells in flow cytometric studies in mycosis fungoides and other types of cutaneous and nodal t-cell lymphomas. Expression of CD158k by qRT-PCR in the skin can be helpful for the differential diagnosis of lymphoma in erythrodermic patients. We recently investigated the value of a combination of four markers for the diagnosis of Sézary syndrome by RT-PCR in the blood. On a series of 81 Sézary patients, we showed that gene expression profiling by quantitative RT-PCR on a combination of the four markers T-plastin (PLS3), Twist, CD158k/KIR3DL2 and NKp46 (CD335) could allow a reliable molecular diagnosis of Sézary syndrome. The function of KIR3DL2 was further studied by triggering KIR3DL2 with the monoclonal antibody AZ158. This triggering strongly inhibits the CD3-mediated proliferation and cell death of the CD4+ KIR3DL2+ cells. This effect also induces a down-modulation of CD3-zeta phosphorylation and Erk1/2 activation. These negative signals are not induced if KIR3DL2 is engaged by its newly identified ligand CpG ODN-C. However, binding of CpG ODN-C to KIR3DL2 induces the internalization of the receptor and leads to a caspase-dependent apoptosis of the malignant T cells. STAT3 has been shown to be constitutively phosphorylated and activated in Sézary cells. Binding of CpG ODN-C to KIR3DL2 induces a dephosphorylation of this transcription factor. Therefore, the type of engagement of KIR3DL2 may vary according to the type of engagement, either by monoclonal antibody or by CpG ODN-C. Following engagement, KIR3DL2 can act as a co-inhibitory receptor or specifically promote cell death of Sézary cells.

O-011

IMMUNOCYTOCHEMICAL P63 EXPRESSION IN PRIMARY CUTANEOUS B-CELL LYMPHOMA; FURTHER EVIDENCE FOR PATHOGENETIC HETEROGENEITY

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p63 belongs to a family of transcriptional activators which includes p53. The p63 gene is an important regulator of epithelial development. Over-expression of p63 has been demonstrated in various tumours, although it is not clear whether p63 serves to halt or enhance tumour growth. Through the use of alternate promoters certain isoforms (TAp63) transactivate p53 target genes and induce apoptosis, whereas other isoforms (delta-Np63) appear to convey a dominant-negative effect on p53. p63 expression in nodal follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL) has been observed and correlated with proliferative index and mortality. The role of p63 in cutaneous B-cell lymphoma has yet to be elucidated. This study assessed p63 expression in primary cutaneous follicle centre cell lymphoma (pcFCCL) and diffuse large B-cell lymphoma, leg type (DLBCLL), two tumours which differ morphologically, immunophenotypically and prognostically. A similar division that exists in systemic nodal lymphomas can be made; pcFCCL is derived from germinal centre cells, having a bcl-6+ CD10+/- MUM-1- immunophenotype, DLBCLL has a post-germinal phenotype, which is bcl-6+/- MUM- 1+. Using an antibody that recognizes both p63 isoforms, 16 of 21 of DLBCLL had diffuse strong expression. Of 16 pcFCCL, 11 were completely negative, with focal expression in 2. Further labeling of 8 cases of DLBCLL and 5 pcFCCL using an antibody specific to the delta-Np63 isoform of p63 failed to show expression, indicating the observed expression in the positive cases was of the TAp63 isoform. This pilot study further emphasises the different biology of these lymphomas, and might reflect one mechanism for their differing clinical behavior.

O-012

VALIDATION OF DIAGNOSTIC AND PROGNOSTIC BIOMARKERS FOR SÉZARY SYNDROME

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Sézary syndrome (SS) is an aggressive type of cutaneous T-cell lymphoma with a poor prognosis. Differentiation between SS and other conditions presenting with erythroderma, including benign inflammatory dermatoses, may be extremely difficult. Also identification and quantification of tumor cells is often difficult, thereby hampering (early) diagnosis and monitoring of progression. Several small, single center studies reported potential biomarkers for Sézary cells on genomic, transcriptional and translational level, but these markers have not been evaluated in independent studies. In this prospective, multicenter study we evaluate the

diagnostic and prognostic value of these potential markers that were previously described in literature.We collected peripheral blood mononuclear cells, cDNA and genomic DNA from SS patients (as defined by WHO criteria, 2008) and patients with benign erythroderma. CD4+ t-cells were analyzed for expression of cell surface proteins by flow cytometry. Gene expression and copy number alterations were evaluated by using custom made quantitive PCR platforms. Experimental data are correlated with clinical information at inclusion of the study and after 12, 24, 36, and 48 months follow up. During the first two years of this study, samples from 105 individuals were included and clinical data from 86 patients have been collected. Characteristic alterations in copy number for MYC and MNT were observed in respectively 44% and 65% of the SS patients. Flow cytometry revealed aberrant expression of CD2, CD7, CD26, CD158b and/or CD45RA in >90% of patients. In addition, upregulation of DNM3, EPHA4, PLS3 and TWIST1 and downreguation of STAT4 in 65 to 95% of SS patietns was confirmed by RT-qPCR.
Our data demonstrate that Sézary cells can be identified by (combinations of) specific biomarkers using different techniques. The prognostic significance of those markers is currently under investigation with the sample data of all included patients.

O-013

A RECURRENT REARRANGEMENT OF 6P25.3 AND UNIQUE PATHOLOGY IDENTIFY A PREVIOUSLY UNRECOGNIZED SUBTYPE OF LYMPHOMATOID PAPULOSIS

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LyP is a complex cutaneous lymphoproliferative disease with diverse histologies. The pathogenesis remains unknown. In few cases studied by cytogenetics, non-repetitive chromosomal abnormalities were found. Here we present a cohort of 11 elderly patients whose atypical LyP cells harbor a recurrent rearrangement of the DUSP22-IRF4 locus at 6p25.3. Lesions were restricted to a single body area in all but 2 patients who each had isolated papules on the back and arm. Untreated lesions regressed spontaneously. No patient developed disseminated skin disease or extracutaneous spread. Lesions ranged from 0.3 cm to 1.0 cm in diameter and had variable scale but no ulceration. Histology was remarkably similar and differed from previously described LyP subtypes. Each demonstrated a biphasic growth pattern with a dense dermal infiltrate of large blasts and prominent epidermotropism of small cerebriform cells, imparting a pagetoid appearance. Mitotic figures and apoptotic bodies were abundant within the dermal infiltrate; necrosis was absent. Eosinophils and neutrophils were absent in most specimens. Atypical cells in all cases expressed at least one T-cell antigen. CD30 showed an unusual, biphasic pattern of expression in most cases, with strong diffuse staining in the dermis and weaker staining in the epidermis. ALK was uniformly absent. FISH analysis of the DUSP22-IRF4 locus showed 6p25.3 rearrangements in all cases. At last follow-up only 1 patient had active lesions: these were confined to the presenting site. The remaining 10 patients had been disease-free from 2 to 32 months. In conclusion, we present a series of LyP cases with unique clinical, histologic, immunophenotypic and genetic features suggesting these cases comprise a distinct clinicopathogic entity for which we propose the designation "LyP with 6 p25.3 rearrangement" to describe this new subtype.

O-014

BAP1 PROTEIN EXPRESSION IS FREQUENTLY LOST IN CUTANEOUS LESIONS OF BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM AND CHRONIC MYELOMONOCYTIC LEUKEMIA

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It has been recently reported that loss of the deubiquitinating enzyme BAP1 within the hematopoietic compartment is sufficient to induce a myelodysplasia resembling chronic myelomonocytic leukemia (CMML) in a murine model. The investigators further report that a patient with de novo myelodysplastic syndrome demonstrated an inactivating BAP1 mutation, and that, as a group, MDS patients expressed significantly lower levels of BAP1 protein.
CMML is known to transform into acute myeloid leukemia (AML) and leukemia cutis (LC) is a frequent finding in patients with AML. Accurate diagnosis is essential as LC is a poor prognostic indicator. Unfortunately, LC due to AML may be challenging to differentiate from cutaneous lesions of blastic plasmacytoid dendritic cell neoplasm (BPDCN) 3. We hypothesized that loss of BAP1 protein expression might be a more frequent finding in cases of CMML LC than in other AMLs.
Using immunohistrochemistry according to previously reported methods, we assessed BAP1 protein expression in 13 cases of LC, including 2 cases of CMML, 10 cases of AML and 1 case of JMML, and 12 cases of cutaneous BPDCN. We found that BAP1 protein expression was decreased in 1 of 10 cases of AML. The cases of cutaneous CMML and JMML both showed loss of BAP1 expression. Four of 12 cases (33%) of BPDCN cases showed decreased BAP1 protein expression.
Our results provide further evidence for the role of loss of BAP1 in the development of CMML in a subset of patients with myeloid leukemias. Interestingly, low BAP1 protein expression is also a frequent finding in cutaneous BPDCN. It is known that clonal proliferations of plasmacytoid dendritic cell nodules are present in CMML and BPDCN. Therefore, the finding of a similar expression pattern of BAP1 in these two related disorders is an expected finding and merits further investigation.

O-015

IMMEDIATE-EARLY (IE) GENE REACTIVATION SIGNAL, BZLF1 EXPRESSION, IS A MOLECULAR MARKER FOR A POOR PROGNOSIS OF EPSTEIN-BARR VIRUS-ASSOCIATED T/NK LYMPHOPROLIFERATIVE SKIN DISEASES

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BACKGROUND: Epstein-Barr virus (EBV)-associated T/NK lymphoproliferative disorders (LPDs) are a group of diseases including hydroa vacciniforme (HV) and hypersensitivity to mosquito bites (HMB). Unlike classical HV, patients with HV-like eruptions with systemic symptoms and/or abnormalities in routine laboratory tests, and patients with HMB may often result in a fatal outcome. However, little has been known about the cellular and molecular events leading to the poor prognosis.
OBJECTIVES: To clarify molecular markers related to the prognosis of EBV-associated T/NK LPDs.
PATIENTS AND METHODS: A total of 46 patients with HV and HMB were categorized into 4 groups by the following criteria: 1) classical HV, 2) HV-like eruptions with systemic clinical symptoms and/or abnormalities in routine laboratory findings (systemic HV), 3) HMB only, and 4) HMB associated with HV-like eruptions (HMB+HV). In addition to EBV-infected lymphocyte subsets, EBV DNA load and the expression of EBV-encoded gene products including EBER, BARTs and BZLF1 mRNA were examined in comparison with the prognosis of each group.
RESULTS: The majority of patients with classical HV and HMB presented with clinical symptoms in the first decade. Patients with classical and systemic HV were associated with increased numbers of γδT cells in the peripheral blood, while patients with HMB were associated with increased NK cell numbers. Patients with classical HV showed a favorable prognosis with 100% survival in our series. The other 3 groups including systemic HV, HMB, and HMB+HV revealed unfavorable survival rates, especially in the patients with onset age of over 9 years, and/or BZLF1 mRNA expression. BZLF1 mRNA, or an EBV immediate-early (IE) gene product, was detected in the skin lesions: 3 of 7 systemic HV, and 2 of 5 HMB. No BZLF1 mRNA was detected in skin lesions of classical HV or peripheral blood samples from all types of HV and HMB. A follow-up study revealed that BZLF1 mRNA-positive cases showed poorer prognoses than BZLF1 mRNA-negative ones. No significant correlation was observed between the EBV DNA load and prognosis.
CONCLUSION: The expression of BZLF1 in the skin lesions was closely related to the poor prognosis as well as severe clinical symptoms in systemic HV and HMB.

O-016

THE FUTURE OF MEDICINE (AND HEALTH)

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The solution of many medically important problems depends primarily on being able to predict the behaviour of complex networks (e.g. the biological networks acting within a tumor, but also in the other tissues of the patient) under complex disturbances (e.g. a particular therapy). Targeted drugs used in oncology therefore typically help only one quarter of the patients they are used on, with the others suffering from severe side effects, without any medical benefits. Decades of molecular cancer research, but also the recent genome revolution, have however still not been able to provide this urgently needed power to predict the response of individual patients. We are currently sequencing the genome and transcriptome of the tumor and the genome of the patient for individual cancer patients, as the basis of a 'virtual patient' models, which can then be used to predict effect and side effects of specific therapies on the individual patient (www.treat1000.org). In addition, we have proposed IT Future of Medicine (ITFoM), www.ITFoM.eu), with the goal to develop integrated molecular/physiological/anatomical models of every individual in the health care system, on the basis of -omics (genomics, epigenomics, transcriptomics, proteomics, metabolomics, metagenomics etc), imaging and sensor data, as the basis of a new, data rich, computation based individualised medicine of the future.

O-017

SO MANY DATA – AND SO FEW CONSEQUENCES: CAN A "MEDICAL CLOUD" HELP TO BRIDGE THE GAP BETWEEN ADVANCES IN RESEARCH AND CLINICAL WORK?

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Well-known and much deplored facts are that 1) in spite of great efforts, much of the overwhelming current progress in the medical and life sciences does not easily find its way to the bed side in our hospitals, 2) hospital information systems (while well-developed for their actual task of managing information flow and storage in routine administrative hospital services) are not – and never were – designed to bridge scientific progress and clinical work, 3) while tools for generating ever better information regarding the individual makeup of a patient are becoming available, the shear amount of the data these tools produce easily becomes awesome and cannot be interpreted and processed for clinical application by medical practitioners and 4) further and further improving and prolonging medical education has its limits as nobody can encompass and comprehend all relevant new medical insights coming along year by year.
So, biomedical researchers and medical practitioners should perhaps be better equipped with means to 1) easily exchange their views regarding new bio-medical developments, 2) obtain, annotate and interpret their patients' data in the light of the latest bio-medical insights, 3) specifically search for the most relevant insights exactly when needed, and 4) discuss the implications of such insights for their clinical work on basis of ALL that can be learned from the various bio-databases and bio-informatics tools.
Remarkably, this can be achieved using modern ICT-technology including specifically designed service-oriented architectures (SOAs) supporting a „medical cloud" and grid-based computations.
Using such technology, medical professionals can, in spite of limited time and computer literacy, be equipped with means for effortless search for pertinent insights and to discuss resulting implications in the daily routine.

In the lecture, I will try to exemplify this claim by outlining a research project with the Charité and others to develop a systems-biology model for cutaneous T-cell lymphoma.

O-018

PERSONALIZED MEDICINE: EPIGENETIC AND GENETIC FEATURES THAT MODULATE THE EFFECTS OF METHOTREXATE AND INTERFERON-ALPHA IN CTCL

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The FAS pathway is a major mediator of T-cell apoptosis. FAS expression is low in the majority of CTCL patients. Demethylation of the FAS promoter restores FAS expression and enhances apoptotic sensitivity. We observed that methotrexate (MTX) functions as a demethylator probably by depleting S-adenosyl methionine (SAM), the principal methyl donor for DNA methyltransferases. Other folate analogs (pemetrexed, aminopterin) have the same effect. Exogenous SAM reverses this effect. MTX reduces FAS promoter methylation and increases FAS expression by FAS-low HH, SZ4 and CTCL blood cells. Interferon-alpha (IFNa) increases FAS expression by a different mechanism. STAT1 induced by IFNa binds to a non-methylated FAS promoter element involving nt -671 that can be either A (wildtype) or G (SNP). CTCL cells with the -671GG genotype fail to up-regulate FAS in response to IFNa whereas those with at least one A allele do up-regulate FAS. A significant minority of CTCL patients bear the -671GG genotype. These results demonstrate that MTX and IFNa can augment FAS expression via two distinct promoter mechanisms, one involving epigenetic methylation and the other involving a germline SNP. This may help explain the previously reported high response rate of advanced CTCL to MTX/IFNa therapy (Aviles et al. Cancer Biother Radiopharm 22:836, 2007). In order to quantitatively monitor the effects of MTX and IFNa on CTCL in-vitro and in-vivo, we measured Fas promoter methylation using pyrosequencing with or without laser capture microdissection. We measured FAS protein expression using immunostaining and Nuance spectral analysis. We observed significant reduction of Fas promoter methylation and increased protein expression. This method works for archival pathology specimens and leukemic blood. It will allow us to determine if we can predict response to MTX/IFNa therapy based on FAS methylation and/or SNP status, and to monitor DNA methylation/protein expression relationships more generally.

O-019

SYSTEMATIC TOPONOME DECODING OF DISEASE MACHANISMS IN HUMAN TISSUES

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The recent development of parameter-unlimited functional super-resolution microscopy TIS™ (Toponome Imaging System) provides direct access to protein neworks at nanometer 2D and 3D resolution in a single tissue section. TIS™ is a device that overcomes both the spectral and the resolving power of a conventional light microscopy without having to change hardware. It is the first ready-to-use technology for dimension- and parameter-unlimited histological

diagnostics and systematic decoding of the toponome at super-resolution (toponome: defined as the spatial protein network code in morphologically intact cells and tissues). Using TIS™ data it will be shown that large arrays of supermolecules, detected here for the first time, together forming a network of several million multi protein clusters inside one single tissue section, can be directly imaged by TIS™ leading to direct subellular and transcellular disease mechanisms, which were hitherto undetectable. TIS™ is a highly flexible machine that can adapt to the needs of the researcher: a 4-in-one microscope including (1) routine transmitted light functions, (2) conventional fluorescence functionalities, (3) paramater-unlimited visualization of protein networks composed of millions of multi protein clusters in real time, and (4) super-resolution of subcellular structures and multi protein clusters in tissue sections (subnanometer to 40 nm resolution). The human toponome project based on TIS™ has at its goal to unravel the complete toponome in all cell types and tissues in health and disease (www.huto.toposnomos.com). The technology is scalable as large cooperative parallel screening devices (large TIS™ clusters) extracting the most relevant disease targets from protein network hierarchies in situ: a novel efficient way to find selective drugs, by escaping the present low content trap in drug target and diagnostic marker discovery. Genome sequencing and functional disease mechanism decoding are now done in parallel.

Thursday, February 7, 2013

O-020

WHOLE EXOME SEQUENCING PROVIDES INSIGHTS IN DRIVER MUTATIONS, CLONAL ARCHITECTURE AND GENOMIC EVOLUTION IN MULTIPLE MYELOMA

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Multiple myeloma (MM) is an incurable plasma cell malignancy with only partially understood pathogenesis. Chromosomal abnormalities like hyperdiploidy and recurrent immunoglobulin locus rearrangements are frequent but insufficient for malignant transformation as also observed in a pre-malignant syndrome, MGUS. Malignant progression is associated with additional hits, implying that the genetic landscape of MM changes over time with events defining its symptomatic emergence and progression. In this study we aimed at investigating driver and passenger mutational events underlying MM biology, with focus on its clonal architecture and evolution over time. We confirmed some of the genes previously identified, with mutations deregulating the pERK pathway most prevalent. KRAS and/or NRAS activating mutations were present in 47.8% of patients, interestingly co-existed in one of them. BRAF mutations were present in 14.5% of cases but only 30% of them were V600E, thus amenable to targeted treatment. BRAF and KRAS mutations co-existed in 3 patients, further suggesting that BRAF inhibitors may have little role in MM. Clonal analysis showed that, when two mutations of the pERK pathway were present in the same patient, they likely belonged to different subclones. We described 2481 mutated genes in our cohort (range 1-484 per patient, mean 65). 430 were recurrent, suggesting a role in MM pathogenesis, many are previously unreported, among them genes involved in the NF-kB pathway, histone-modifying enzymes, cyclins and cyclin-dependent kinases. Clonal analysis showed a complex subclonal structure, with at least one additional subclone, in 67/69 (97%) patients. The burden of at least some mutations changed over time in 12/15 patients (80%), highlighting ongoing clonal evolution in serial samples. The tumour burden of each variant was compared between early and late sample in each patient to obtain "2D plots", summarizing clonal evolution. Four main patterns where found: no change; linear evolution, where only new changes were acquired; differential subclonal response, where the burden of a cluster of variants changed over time; and branching evolution, where the late sample showed loss of some variants and gain of others compared with the early one. The patterns of response correlated with the karyotypic subgroup but not with treatment response. Our findings refine the current understanding of the pathogenesis of myeloma providing new insights into diver mutations and clonal evolution. As our data will help identify molecular alterations associated with disease progression and chemoresistance, they may also have a therapeutic impact. The presence of branching evolution could change the definition of partial or good disease response, currently insufficient where all subclones were ablated by treatment except for one, chemoresistant from the start, eventual source of aggressive disease relapse. Similarly, in light of our results and given the availability of highly effective treatment regimens, the concept of expectant management of smouldering myeloma could be challenged, in cases where early treatment of a less complex disease could result in eradication of the tumour before its evolution to a more resistant subclonal architecture.

O-021

CHROMOSOMAL REARRANGEMENTS AT 6P25.3 IN CUTANEOUS T-CELL LYMPHOMAS HIGHLIGHT THE ROLE OF THE DUSP22 PHOSPHATASE IN ONCOGENESIS.

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Recurrent chromosomal rearrangements or imbalances have been identified in primary cutaneous T-cell lymphomas (CTCL) but this has not led to the functional identification of a candidate gene. We and others previously identified heterozygous translocations at chromosome 6p25.3 particularly those with a large cell CD30+/IRF4+/ALK- phenotype. The fluorescence in situ hybridization (FISH) study of 6p25.3 status was extended on 23 cases of cutaneous anaplastic large cell lymphoma (CALCL), 16 cases of transformed mycosis fungoides and 6 cases of CD30+ borderline lesions between these two entities. About 39% of ALCL cases and 12.5% of TMF displayed 6p25 rearrangement with half of these cases involving a reciprocal translocation with chromosome 7q32.3. The mapping of the breakpoints at 6p25.3 was found variable between cases involving several regions around or between the DUSP22, IRF4 and EXOC2 genes.

Using our array-CGH data, we also found a SS case with focal 6p25.3 hemizygous cryptic deletions without translocation encompassing the DUSP22 (Dual Specificity Phosphatase 22) gene as well as one ALCL cases with 6p25.3 and rearrangement DUSP22 loss. DUSP22, but not IRF4 or EXOC2 was found silenced in all CTCL cases with 6p25.3 translocation or deletion, indicating that these alterations inactivate the expression of the gene. We also investigated the possible implication of epigenetic silencing and observed methylation of CpG island in the 5' region of DUSP22. Functional assays testing proliferation, migration or clonogenicity were undertaken in T-cell lines with either lentiviral ectopic expression or inhibition by shRNA targeting DUSP22 transcripts. Our data indicate that DUSP22 loss contributes to oncogenesis. Overall, our results identify DUSP22 as a new tumor suppressor gene inactivated by genetic or epigenetic mechanisms. Deciphering the molecular pathways involved in DUSP22 signaling will help to ultimately find relevant therapies in tumors with DUSP22 loss.

O-022

A NOVEL (RECURRENT) TRANSLOCATION IN C-ALCL

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Primary cutaneous anaplastic large cell lymphoma (C-ALCL) is a non-Hodgkin lymphoma of t-cell origin that presents in the skin without evidence of extracutaneous disease at the time of diagnosis.

It is characterized by large cells with an anaplastic, pleomorphic, or immunoblastic cytomorphologic presentation and by expression of the CD30 antigen by more than 75% of the tumor cells. Recent FISH screens for IRF4 rearrangements in C-ALCL identified (putative) non-TCR-related IRF4 translocations in 25 % of the patients. Although for a subgroup of C-ALCL a translocation of the DUSP22 phosphatase gene, located immediately telomeric to IRF4, and the FRA7H fragile site was demonstrated (resulting in a balanced translocation t(6;7)(p25.3;q32.3)) IRF4 translocation partner(s) are not identified in C-ALCL.
In search for IRF4 partners we screened 12 cases of C-ALCL with FISH and found putative IRF4 alterations in 3 patients (25%). Using Fine-Tiling arrays and ligation mediated PCR we were able to map the location of breakpoints for 2 patients. One case turned out to represent a hitherto unrecognized structural variation in the genome involving a region telomeric to IRF4. In the other patient we identified an inversion/translocation involving genomic regions immediately centromeric from IRF4 and 6q21. Close inspection of the literature revealed that the identified rearrangement is in perfect agreement with a previously suggested but not resolved inversion in C-ALCL (involving IRF4 and the long arm of 6q) suggesting recurrence in (a subpopulation of) C-ALCL patients.

O-023

CYTOGENETIC STABILITY OF SÉZARY SYNDROME IN SEQUENTIAL SAMPLES

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This study was designed to characterise the karyotype of malignant T-cells in Sézary syndrome and to follow if cytogenetic changes occur during the course of the disease. Therefore, during 6 years we collected 39 samples from 23 patients. In twelve patients, we obtained between two and four peripheral blood samples (median time lapse 22 months). Samples were analysed by multicolour fluorescence in situ hybridisation (mFISH) and high-density oligonucleotide array CGH (aCGH).
Cell culture was successful in 34 from 39 samples (87%) and mFISH karyotype was found abnormal in 27 samples (15 patients, 65%). The most frequently observed inter-chromosome rearrangements involved chromosomes 1 and 10 (80%), chromosome 14 (73%) and chromosome 2 (67%). All in all complex karyotypes with translocations involving 5 to 16 chromosomes per patient (median 7 chromosomes) were established. Furthermore, we clearly identified in eight cases (53%) the presence of two or three cytogenetic subclones sharing most of their chromosome abnormalities. In consecutive samples, these subclones co-existed but their proportion in patient varied between samples.
Array CGH revealed abnormal karyotype in 35 samples (22 patients, 96%). As previously published, losses were more frequent than gains and the most rearranged chromosomes were chromosome 10 (73%), chromosome 8 (69%), chromosomes 1, 7 and 17 (61%). aCGH profile remained stable in patients with consecutive samples. However, fluctuation of the subclones proportion between sequential samples accounted for some variation of aCGH profile. Interestingly, some translocations revealed by mFISH were also found associated with microdeletions by aCGH.
In conclusion, thanks to improved cell culture protocol we have increased the rate of tumour metaphases and were able to compare global genomic data with individual karyotype of Sézary cells. Although karyotype of Sézary cells is complex, we have demonstrated its stability during the course of the disease.

O-024

IDENTIFICATION OF MULTIPLE COMPLEX REARRANGEMENTS ASSOCIATED WITH DELETIONS IN THE 6Q23-27 REGION IN SÉZARY SYNDROME

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Chromosomal instability is a characteristic of Sézary syndrome (SS), but only few abnormalities directly involved in its development have been found so far. In this study we characterized at the molecular level the 6q23-27 region, reported to be recurrently deleted, in 13 SS patients and SS cell line SeAx. Using Fine-Tiling Comparative Genomic Hybridization (FT-CGH) deletions within the 6q23-27 region were detected in half of the samples (six patients and SeAx). All samples with deletions were further analyzed by ligation-mediated PCR (LM-PCR). Additionally, in one patient sample and in SeAx paired-end next-generation sequencing was performed on the HiSeq2000 Illumina platform. Using those techniques 23 new rearrangements associated with deletions in 6q23-27 were identified. The majority of rearrangements showed enormous complexity and diversity, including eight inversions, three transpositions and four translocations (with chromosomes 3, 17, 10 and 12). Fifteen genes were disrupted by those rearrangements; among them the MYB proto-oncogene three times and the interleukin-22 receptor subunit alpha-2 gene (IL22RA2) twice. Five gene fusions were identified, of which two were in the same orientation, and one, between the androgen-induced 1 gene (AIG1) and the Golgi SNAP receptor complex member 1 gene GOSR1, was expressed on the mRNA level.

O-025

ARRAY-CGH ANALYSIS AND MICRO-RNA PROFILING IN A COHORT OF SÉZARY SINDROME PATIENTS

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Sézary Syndrome (SS) is an aggressive leukemic variant of cutaneous T-cell lymphoma associated with a poor clinical outcome. Improvements in diagnosis/prognosis may strongly ameliorate the management of SS patients. In the last years several papers described recurrent allelic imbalances in SS, such as gains in 8q and 17q and losses in 10q and 17p. MiRNA expression profiles in SS have been more recently investigated and their role in the pathogenesis is still unknown.
In this study we recruited 33 SS patients, all with typical phenotype CD4+/CD26-, while CD7 was variably expressed. Peripheral blood CD4+ lymphocytes were analyzed by array-CGH and in a subgroup of 14 patients we also studied miRNA expression profile.
We found recurrent chromosomal alterations: gains in various regions of 17q in up to 72% of cases and del17p13.1 (TP53) in 66%; losses of chromosome 10 in 5 regions, ranging from 42% to 60%; gains in 8q24.3 (51%), 7q11.23 and 7q21.3-22.1 (48%), 7q34, 12q13 and 19q13.3-13.41 (45%), 7p22.1 and 19p13.11 (39%). 9p21 loss was present in 9 patients, 6 showing a very aggressive course. Amp8q24 was seen in most patients after 3 years of evolution. We compared genomic data, blood prognostic markers and clinical details: no significative correlations were found.
MiRNA expression profiles revealed 24 miRNAs differentially expressed in SS. Most of them were overexpressed and only 6 downregulated, 8 have never been described previously. Unsupervised hierarchical clustering analysis identified 4 subgroups of SS samples. Comparison of miRNA and CGH data showed that all patients with amp8q have also miR-29b, miR-21-3p, miR-214-5p overexpression and let-7b downregulation, while aberrations in chromosome 17 were associated with miR-29b and miR-214-3p upregulation. Overexpressed miR-21 and miR-142 are located in chromosomal regions involved in gains, both in 17q.
Our array data could be preliminar to identify new tools to better manage diagnosis and theraphy in SS patients.

O-026

GENOME-WIDE ANALYSIS OF DNA METHYLATION IN SÉZARY SYNDROME

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Sézary syndrome (SS) is an aggressive type of CTCL characterized by erythroderma, generalized lymphadenopathy, and the presence of neoplastic t-cells (Sézary cells) in the skin, lymph nodes and peripheral blood. The overall prognosis of patients with SS is poor with a median survival between 2 and 4 years after diagnosis and a disease-specific 5-year survival around 20%. The implication of epigenetic alterations such as aberrant DNA methylation in the pathogenesis of haematopoietic malignancies is increasingly recognized. Promoter hypermethylation is associated with transcriptional downregulation affecting a multitude of genes in cancer cells. DNA methylation often manifests in tumor type-specific patterns and we have previously shown that also in CTCL established tumor suppressor genes are affected by promoter hypermethylation. In this study we have characterized the DNA methylomes of malignant t-cells from peripheral blood of 15 SS patients and benign t-cells from 4 healthy individuals and 3 patients with benign erythroderma using beadchip technology interrogating the methylation status of 485,000 methylation sites at single-nucleotide resolution. The epigenomic landscapes revealed a multitude of differentially methylated sites in SS versus benign T cells. Statistical analysis identified 272 gene promoters that were significantly and frequently hypermethylated in SS. These included multiple established tumor suppressor genes and 20 target genes of the oncogenic STAT3 transcription factor that is constitutively activated in SS. Clinically, the differentially methylated sites in SS could be applied as epigenetic biomarkers in the early diagnosis of this disease. The epigenetic instability of SS cells provides a rationale for its sensitivity to epigenetic drugs. Our study demonstrates an array of highly recurrent DNA methylation alterations in SS with potential diagnostic applications and suggests that aberrant DNA methylation contributes to the pathogenesis of SS.

O-027

MUTATIONAL STUDIES IN MYCOSIS FUNGOIDES

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BACKGROUND: Mycosis fungoides and Sézary syndrome are the most frequent primary cutaneous T-cell lymphomas. The molecular pathogenesis of CTCL is largely unknown, although neoplastic cells show increased signaling from T-cell receptors (TCR) and acquire Treg and the TH17 phenotype. Aggressive forms of CTCL lack effective treatment.
METHODS: DNA from 11 MF/SS patients, both normal and tumoral, were processed, target-enriched and sequenced by massive parallel sequencing. Identified variants were manually reviewed and validated by capillary sequencing. Immunohistochemical analysis for NFAT, p50, and p52 was also performed. Specific variants were qPCR-genotyped in a new cohort of 42 CTCL patients.
RESULTS: Multiple mutations were found in essential genes from pathways involved in Treg and Th17 regulatory pathways, among others. PLCG1 was mutated in three samples, two of which shared a mutation in exon 11 that affects the PLCx protein catalytic domain. This mutation was analyzed further by qPCR-genotyping in the new series of patients, where it was found in 22.6% of samples. PLCG1-mutated cases had strong paraffin immunostaining for nuclear NFAT, p50 and p52. Functional studies showed that PLCG1 mutants can increase NFAT activity and are highly sensitive to specific inhibition.
CONCLUSIONS: Increased survival signaling in CTCL might partially depend on the acquisition of somatic mutations in PLCG1 and other genes that are essential to T-cell differentiation processes and acquisition of TH17 and Treg phenotypes.

O-028

WHAT CAN WE LEARN FROM TELOMERES STATUS AND TELOMERASE FUNCTIONS IN PRIMARY CUTANEOUS T-CELL LYMPHOMA?

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Telomeres protect chromosomal ends and are maintained functional by telomerase (TERT), a reverse transcriptase, active in cells with high replicative demands and in 90% of tumor cells. To date, sparse information is available regarding telomere length (TL) and telomerase activity (TA) in primary cutaneous T-cell lymphomas (CTCL). We evaluated in CTCL the relevance of TL and TA as target-candidates for diagnostic and therapeutic purposes. We focused on common subtypes of CTCL using either cell lines (HUT78, Se-Ax, My-La, FE-PD) or patient cells (24 Sézary syndromes, SS, 19 transformed mycosis fungoides, T-MF and 14 anaplastic large cell lymphomas, ALCL). The relative TL was estimated in CTCL in comparison with age-matched healthy donors by quantitative polymerase chain reaction (Q-PCR) and quantitative FISH assays. TERT mRNA expression was measured by real-time Q-PCR, and TA was assessed using a Telomeric Repeat Amplification Protocol (TRAP) assay. The impact of telomerase down-regulation and over-expression on tumorigenicity was tested in vitro by a soft agar assay, and in vivo by xenografts in immunodeficient mice.
Our results indicated that CTCL cells exhibit shorter TL than controls. Short telomeres were hallmark of aggressive CTCL subtypes. A TA was detectable in CTCL cell lines and in SS patient cells. To understand the role of telomerase in CTCL, we manipulated its expression levels in CTCL cell lines. Telomerase inhibition rapidly impeded in vitro cell proliferation and led to cell death, while telomerase overexpression stimulated in vitro proliferation, clonogenicity properties and favored tumor development in immunodeficient mice. Further investigations are now necessary to improve our understanding on the molecular pathways implicated in these telomerase functions. Nevertheless, the present data provide evidence that telomerase is a promising target offering therapeutic possibilities to decrease cells viability, especially in aggressive CTCL cells.

O-029

PRIMARY CUTANEOUS DIFFUSE LARGE B-CELL LYMPHOMA, LEG-TYPE (PCDLCBCL-LT) HARBOURS THE GENETIC PROFILE OF NODAL ACTIVATED B-CELL DIFFUSE LARGE B-CELL LYMPHOMA (ABC-DLBCL)

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PCDLBCL-LT is a separate entity sharing histological and phenotypical features of nodal ABC-DLBCL, especially IRF4 expression. The objective of this study was to screen PCDLBCL-LT for genetic alterations described in nodal ABC-DLBCL.
Skin biopsies from 23 patients with PCDLBCL-LT were analyzed retrospectively. FISH testing for BCL2, BCL6, MYC split, p16 and BLIMP1 deletion was performed on skin sections. Sequential FISH on the same slide with different probes was realized in order to relocalize tumour area on the slide and to better characterize samples with multiple FISH alterations. We searched for MYD88 mutation by Sanger sequencing.
Among 23 patients, we detected cytogenetic or MYD88 alterations in all patients but one. Five patients exhibited only one anomaly, and 17 were harbouring multiples anomalies. We observed a BCL2/BCL6/MYC split in 1/23 (4.3%), 6/23 (26%) and 3/23 (13%) of cases, respectively. None patient was harbouring a double-hit lymphoma (BCL2 and MYC split) and cases with BCL2, BCL6 or MYC breakpoint were mutually exclusive. p16 deletion was observed in 7/23 (30.4%) and BLIMP1 deletion on 10/20 (50%). FISH relocalization of abnormal nuclei showed that several FISH alterations were carried by the same nuclei.
The L265PMYD88 mutation was found in 11/18 (61%) of cases .The study of somatic hypermutation and CDR3 IGH length also confirmed the post-GC origin of most cases.
Contrary to most cutaneous lymphomas that rarely harbour the same genetic alteration of their nodal histological equivalent, PCDLBCL-LT seems to be a “cutaneous counterpart” of ABC-DLBCL with similar genetic loci alterations and concomittant MYD88 oncogenic L265P mutation. In such small series, we did not find prognosis impact of each mutation. The similarity with ABC-lymphomas is incentive to further explore common signaling pathways.

O-030

MOLECULAR ANALYSIS OF PRIMARY CUTANEOUS AGGRESSIVE T-CELL LYMPHOMAS: AGGRESSIVE EPIDERMOTROPIC CD8+ LYMPHOMA AND PERIPHERAL T-CELL LYMPHOMA, UNSPECIFIED (PTL-NOS).

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Primary cutaneous aggressive epidermotropic CD8-positive cytotoxic T-cell lymphoma (AECTCL) and primary cutaneous peripheral T-cell lymphoma, unspecified (PTL-NOS) (both CD4+ and CD8+ phenotypes) are a very aggressive tumors with poor outcome in adults. In these rare CTCL subtypes few reports have been published dealing with oncogenomic investigations. In this study, by array-based comparative genomic hybridization (a-CGH), we aimed to explore genomic alterations possibly involved in tumorigenesis of these entities. We focused on 17 cases of CD8+ AECTCL, 4 cases of CD8+ PTL-NOS and 3 cases of CD4+ PTL-NOS. By a-CGH investigations, we found some alterations present in all entities such as loss of 9p21.3 and gains of 11q12.3-q13.2 and 17q. Some aberrations seems to be more frequent in CD8+ lymphomas (both AECTCL and PTL-NOS-CD8+) (gains of 3p21.33-p21-2, 7q21.2-q22.1, 8q24.3, 11pter and trisomy 19) while others were found only in CD4+ lymphomas (losses of 2p24.2-p21, 6q24.2-q27, 10p). Gains of 7q36.1-q36.3, 16p13.3 and trisomy 22 as well as loss of 8p22 were found only in AECTCLs and should be related to epidermotropism, while loss of 13q were observed only in PTL-NOS (both CD8+ and CD4+). 9p21.3, harbouring CDKN2A and CDKN2B genes, and 17q (STAT3 and STAT5) regions were imbalanced in all three entities studied and they may be involved in aggressiveness of tumors and poor outcome. Trisomy of chr19 (JAK3) was shared by CD8+ lymphomas suggesting a possible role of JAK3/STATs pathway in the pathogenesis of these malignancies. Although some genetic aberrations detected in our study have already been described in tumoral stage of mycosis fungoides, we conclude that the combination of aberrations appear characteristic in these aggressive disorders. Further studies should be directed to better define subgroups of patients with different prognosis by gene expression profiling (GEP), miRNA and next generation sequencing techniques (whole exome and whole genome).

O-031

ABERRANT GENE EXPRESSION AND PROMOTER METHYLATION AS BIOMARKER FOR SEZARY SYNDROME

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Sézary Syndrome (SS) is a variant of Cutaneous T-cell lymphoma (CTCL) characterized by erythroderma, lymphadenopathy, and circulating malignant T-cells in the peripheral blood. Since SS can have a highly variable morphology, phenotype, and clinical course, biomarkers have become increasingly important in diagnosis of the disease and its treatment. In this study, using microarray analysis we report a set of genes for diagnosing patients with SS, which was also confirmed via qRT-PCR. We observed significant overexpression (fold change) of PLS3 (330.5+10.12), TWIST1 (30.90+10.12), GATA3 (5.67+0.86), and GATA6 (17.49+5.68) in SS (N=5) relative to normal donors (ND) CD4+ T-cells (P<0.002). To investigate potential mechanism for altered expression, we analyzed the methylation status of the SS DNA samples and found significant genomic DNA hypomethylation in SS patients (ND vs. SS patients = 74.58±0.63 vs. 61.23±4.064, N=6 each, P=0.008). Since aberrant methylation results in abnormal gene expression in malignancies, we next examined the methylation patterns of the promoter regions of these genes in SS patients. We found significant hypomethylation (% methylation in ND vs. SS patients, N=6 each) in the promoter regions of TWIST1 (6.86±0.85 vs. 4.01±0.53, P=0.01), PLS3 (6.56±0.93 vs. 2.71±0.90, P=0.01), and GATA6 (9.70±0.63 vs. 6.86±1.08, P=0.04). Next we examined known CpG regions mapped to the promoter regions to determine the methylation status of each individual CpG islands. Analysis demonstrated that 11 of 22 (50%) CpG islands were hypomethylated in the TWIST1 promoter, 3 of 13 (23.1%) in GATA3, 2 of 7 (28.6%) in GATA6, and 8 of 11 (72.7%) in PLS3. In summary, we identify a set of genes increased significantly in SS, and show that these genes are associated with promoter hypomethylation. We propose that the epigenetic changes in SS play an important role in the pathogenesis and that these genes may serve as biomarkers for SS.

O-032

HERV-W TRANSCRIPTION AND SYNCYTIN-1 EXPRESSION IN MYCOSIS FUNGOIDES PROVIDES NEW INSIGHT INTO CUTANEOUS T-CELL LYMPHOMA PATHOGENESIS.

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Mycosis fungoides (MF) is the most common type of primary cutaneous T-cell lymphomas (CTCLs). The pathomechanism of MF is unknown albeit underlying viral infections have been sought for. Human endogenous retroviruses (HERVs) are ancient retroviral sequences in the human genome and their transcription is often deregulated in cancers.

We explored the transcriptional activity of HERV sequences in a total of 34 samples comprising MF and psoriasis skin lesions, as well as corresponding non-malignant skin using a retrovirus-specific microarray and quantitative RT-PCR. Furthermore, transcribed HERV loci were identified.

Firstly, a distinct, skin-specific transcription profile consisting of five constitutively active HERV groups was established. Although individual variability was common, HERV-W showed significantly increased transcription in MF lesions compared to intact skin from the same patient. Predominantly transcribed HERV-W loci were found to be located in chromo-somes 6q21 and 7q21.2, chromosomal regions typically altered in CTCL. The latter locus (also called ERVWE1) encodes for a functional protein, Syncytin-1. We found Syncytin-1 expressed in MF lymphocytes, especially in the epidermal microabscesses of malignant cells.

We conclude that differences in the HERV-W transcription levels between lesional MF and non-malignant skin are significant. Expression of HERV-W-derived Syncytin-1 offers a new perspective into the pathogenesis of CTCL.

O-033

TARGETING SIGNALING PATHWAYS IN LYMPHOID MALIGNANCIES: APPLICATIONS FOR CUTANEOUS LYMPHOMAS

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Signaling pathways play a significant role in lymphoma growth and survival. Multiple novel agents are in development targeting signaling through the b-cell receptor. Ibrutinib targeting Bruton's tyrosine kinase and GS1101 targeting Pi3K delta have both shown promise in a wide range of B-cell lymphomas. Similarly inhibition of spleen tyrosine kinase (syk) and downstream steps in the PI3K/AKT/mTOR have showed activity in indolent B-cell lymphomas. While not specifically studied, these agents may be applied to cutaneous B-cell lymphomas. Many of these agents may have at least theoretical activity in cutaneous T-cell lymphomas as well. Syk in over-expressed in many t-cell lymphomas and targeting Pi3K gamma signaling may be an important strategy in T-cell malignancies. IPI-145, a novel Pi3K inhibitor blocks Pi3K gamma at physiologic achievable concentrations and is currently being studied in a phase 1 study in B and T-cell lymphomas including mycosis fungoides and Sezary syndrome. Other novel targeted therapies agents aurora kinase, Alisertib, and the BCL-2 inhibitor, ABT-199 are also promising and maybe rationally applied to the treatment of cutaneous lymphomas.

O-034

MONOCLONAL ANTIBODIES AND FUSION PROTEINS IN CUTANEOUS LYMPHOMAS

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Monoclonal antibody-based (mAb) therapies are well-established and successful strategies for treating patients with hematological malignancies, including cutaneous lymphomas. The

mechanisms of action of such mAb-based approaches are varied and may include changing of agonist or antagonist functions of a receptor, modulation of the immune system, such as activation of tumor-specific T cells, or delivering a conjugated drug capable of specific cell killing, among others. There are numerous challenges in developing potent antibodies capable of effective tumor cell killing, including identifying and selecting suitable tumor targets as well as physical properties of the antibodies. This review will summarize the recent advances in monoclonal therapies in cutaneous lymphomas and describe future directions in the development of this important therapy.

O-035

CD30+ CUTANEOUS T-CELL LYMPHOMA AND RESPONSE TO BRENTUXIMAB VEDOTIN: THREE ILLUSTRATIVE CASES

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Cutaneous T-cell lymphomas (CTCL) are a heterogeneous set of disorders that include mycosis fungoides (MF) and primary cutaneous anaplastic large cell lymphoma (ALCL). With the emergence of therapy targeting the CD30 antigen, treatment with brentuximab vedotin (BV) in CTCL is an evolving option for select patients that cannot tolerate or are refractory to chemotherapy. The efficacy of BV in the treatment of CTCL has recently been demonstrated this year with a 63-68% response rate by Duvic et al. and Krathen et al. We report 3 additional cases to validate the high response rate of CD30(+) CTCL to BV therapy.
The first patient was a 75-year-old man with transformation of his patch-plaque MF in the axilla to CD30(+) large-cell disease. The second patient was an 87 year-old-man presenting with a small cell variant of ALCL on his extremities. The final case was a 59-year-old man with widespread tumor stage CD30 (+) folliculotropic MF. Work-up in all cases included a skin biopsy with molecular and immunohistochemical studies and a bone marrow biopsy which was negative in each patient. Prior to BV therapy, imaging (CT or PET/CT) was negative for extracutaneous disease in the first 2 patients and had shown progressive axillary and inguinal lymphadenopathy in the third patient. All 3 patients had previously received skin direct (PUVA, narrow-band UVB, steroids) and systemic (CHOP, gemcitabine, liposomal doxorubicin) treatment prior to starting BV at 1.2-1.8mg/kg every 3 weeks.
After 2 cycles of BV, the patient with transformed MF had complete response. Similarly, after just 1 cycle of BV, the patients with cutaneous ALCL and tumor stage MF both had a partial response. Side effects were limited to mild grade 1 fatigue, taste alterations and gastric discomfort.
As large studies are underway for the use of BV for CD30(+) CTCL, we demonstrate that for patients with CD30(+) CTCL, BV is active, effective, and a well-tolerated emerging option.

O-036

TARGETING SIGNALING PATHWAYS IN MYCOSIS FUNGOIDES AND SEZARY SYNDROME

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BACKGROUND: Mycosis fungoides /Sezary syndrome (MF/SS) is a group of heterogeneous diseases. Although generally indolent at early stage, approximately 40-50% patients with advanced stage disease eventually succumb to the illness. Recent studies demonstrated dysregulation of signaling pathways in MF/SS, including PI3K/Akt, jak/stat, RAS and NFkB pathways. Here, we performed a high throughput drug screening to identify new therapeutic agents targeting signaling pathways in MF/SS.
METHODS: We compiled a drug library of 94 compounds comprising of inhibitors for all major signaling pathways as well as HDAC, proteosome, tyrosine kinases, DNA repair and apoptosis. We then evaluated anti-proliferation effect of these compounds on 4 MF/SS cell lines in high throughput proliferation assays. In addition, we tested the effect of combining BKM120, a PI3K inhibitor, with the rest of 93 compounds in the drug library in high throughput proliferation assays.
RESULTS: We identified 14 active compounds, including inhibitors for PI3K, mTOR, HDAC, proteosome, and heat shock proteins. Of these compounds, BKM120 exerted cytotoxic effect by inducing apoptosis in MF/SS cell lines. Combination studies revealed additive effect of BKM120 with several other agents with known clinical activities in MF/SS.
CONCLUSION: BKM120 is a promising new cytotoxic agent targeting the PI3K/Akt pathway in MF/SS.

O-037

CD40-ACTIVATED B CELLS AS CELLULAR ADJUVANTS: LYMPHNODE HOMING AND T-CELL INTERACTION

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We have previously introduced an alternative cellular adjuvant that could be integrated into immunotherapy of cutaneous malignancies. B cells when activated via CD40-L/IL-4 (CD40-B) can be expanded from small amounts of peripheral blood in 12–14 days. At day 14 these cells are >95% $CD20^+$ and CD80/83/86/MHCI/$MHCII^{hi}$. CD40-B take up antigen independent of the B-cell receptor via endocytosis, process it via the classical and an alternative MHC II pathway and prime naïve T cells. They have a doubling time of 3–4 days and can be used to efficiently expand $CD4^+$ and $CD8^+$ t-cells in a highly differentiated *in vitro* system. Nevertheless, it remains unclear whether such cells have the property to colocalize and interact with t-cells in a physiological context i.e. after injection.

Here, we show that CD40-B express the full lymph node homing triad including CD62L, CCR7/CXCR4 and LFA1. Murine and human CD40-B migrate towards cognate ligands such as CCL19, CCL21 and CXCL12. Furthermore, such CD40-B express several T-cell chemoattractants and induce t-cell chemotaxis *in vitro*.
To dissect T cell/APC interaction on a single cell we analyzed three-dimensional migration in collagen matrix. Interestingly, antigen-loaded CD40-B differ from immature and mature DC by displaying a rapid migratory pattern undergoing promiscuous, short-lived (7.5min) but stable interactions with cognate T cells. Furthermore, upon injection GFP+ CD40-activated B cells home to secondary lymphoid organs. Taken together, these data suggest that CD40-B are equipped with the receptors and migratory capacity necessary to home to secondary lymphoid organs and have the property to attract and enter into stable contacts with T cells.

O-038

EXPLORING THE IL-21 – STAT3 AXIS AS THERAPEUTIC TARGET FOR SÉZARY SYNDROME

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Sézary syndrome is an aggressive cutaneous t-cell lymphoma with malignant cells in skin, lymph nodes and blood. The transcription factor STAT3 is constitutively activated in Sézary cells. We recently showed that IL-21 activates STAT3 in Sézary cells, and that the IL-21 gene itself is a STAT3 target gene, thereby creating an autocrine positive feedback loop. The aim of current study is to explore this IL-21 – STAT3 loop as therapeutic target for Sézary syndrome. Freshly isolated Sézary cells underwent apoptosis when incubated with Stattic, a selective inhibitor of STAT3 dimerization. Since STAT3 target genes previously described for other tumour and/or cell types include (proto)onocgenes and anti-apoptotic proteins, expression of these genes was investigated. Interestingly, STAT3 activation in primary Sézary cells did not affect expression of anti-apoptotic genes BCL2, BCL-xL, MCL-1 and Survivin, whereas expression of (proto)oncogenes miR-21, TWIST1, MYC and PIM1 was significantly increased. Blocking IL-21 by adding an IL-21receptor-IgG fusion protein did not cause apoptosis of Sézary cells, probably due to the inert state of the cells in culture. To circumvent this, we polyclonally activated Sézary cells using CD3/CD28-coated beads. This resulted in increased cell proliferation, accompanied by activation of STAT3 and elevated expression of IL-21. Blocking IL-21 in CD3/CD28-stimulated Sézary cells had no effects, whereas inhibition of STAT3 in CD3/CD28-stimulated cells abrogated IL-21 expression, as well as cell proliferation.
Thus, specific inhibition of the STAT3 pathway induces apoptosis of Sézary cells, likely mediated via the regulation of (proto)oncogenes rather than anti-apoptotic genes. The role of IL-21 in regulation of cell proliferation and/or apoptosis seems redundant. Therefore, therapeutic targeting of STAT3 in Sézary syndrome seems a promising approach, in contrast to the specific targeting of IL-21 or its receptor.

O-039

CUTANEOUS MANIFESTATIONS OF EXTRANODAL NK/T-CELL LYMPHOMA, NASAL-TYPE

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Extranodal NK/T-cell lymphoma, nasal type (ENKTCL-NT) is a highly aggressive lymphoma usually presenting in the upper respiratory tract, especially the nasal cavity. The skin is the second most affected organ and may also be the primary site of onset. Precise diagnosis rests on a constellation of clinicopathologic, immunohistochemical and molecular findings, and on demonstration of Epstein-Barr virus (EBV) integration within tumor cells. It should be emphasized that on clinicopathologic grounds alone primary cutaneous lesions of ENKTCL-NT may be indistinguishable from those of mycosis fungoides (MF), and many cases probably have been wrongly classified in the past as "aggressive" or "tumeur d'emblee" MF. Although prognosis was considered to be almost invariably poor, new treatment modalities have allowed a better course in recent years. However, without aggressive treatment only a few patients show a prolonged survival. Prognosis is related mainly to the stage of disease at first diagnosis, and precise prognostic criteria for primary cutaneous cases are still lacking.

O-040

ADULT T-CELL LEUKAEMIA/LYMPHOMA: IMPAIRED INNATE IMMUNITY OF THE SKIN

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Adult t-cell leukemia/lymphoma (ATLL) is a malignancy of mature $CD4^+CD25^+$ t-cells caused by HTLV-1. ATLL is divided into four clinical categories: acute, lymphoma, chronic, and smoldering types. Cutaneous involvement can be recognized in ~50% of ATLL patients. The eruptions are categorized into patch, plaque, multipapular, nodulotumoral, erythrodermic, and purpuric types, which are an independent prognostic factor for ATLL. ATLL patients often suffer from various infections, such as pneumocystis carinii, pathogenic fungi, viruses, and parasites. In particular, superficial dermatophytosis is quite common in ATLL patients, as approximately 50% of the ATLL patients have *tinea pedis/unguium/corporis*, candidiasis and other cutaneous mycotic infection. However, the pathomechanism of dysfunction of cutaneous innate immunity in ATLL patients remains elusive. We have shown that Th17 cells play an important role in cutaneous innate immunity. The frequencies of circulating $CD4^+CD25^+$ t-cells and Th17 cells were inversely correlated in ATLL patients. Whereas peripheral Th17 cells and serum IL-17 were significantly decreased, serum IL-10 and TGF-β1 were increased in ATLL as compared to healthy controls. Furthermore, ATLL patients with dermatophytosis had higher IL-10 and TGF-β1 levels and lower IL-17 levels than did those without dermatophytosis. Immunohistochemical study revealed that the epidermal expression of both HBD-2 and LL-37 were significantly lower in ATLL patients with dermatophytosis than in non-ATLL patients with dermatophytosis or healthy controls. Thus, the Th17 cell-enhanced expression of antimicrobial peptides in keratinocytes is decreased in ATLL patients, leading to the perturbed innate immunity and frequent occurrence of superficial dermatophytosis. This is

the first step to elucidate the pathomechanism of the impaired cutaneous innate immunity in ATLL patients and to potentially improve the infections and the patients' prognosis.

O-041

CLINICOPATHOLOGIC FEATURES, PROGNOSIS, AND THERAPEUTIC RESPONSES IN PATIENTS WITH GRANULOMATOUS MYCOSIS FUNGOIDES: RESULTS OF A UNITED STATES CASE-CONTROL STUDY

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Granulomatous mycosis fungoides (GMF) is an unusual MF variant. The prognostic significance of granuloma formation in MF is controversial. A retrospective case-control study was performed of 430 patients with a diagnosis of MF between Jan 1981 and April 2012. Histopathology slides were reviewed for granulomas or histiocytes comprising ≥25% of the atypical infiltrate. Each identified case was randomly matched with 2 classic MF cases via age and TNMB stage.
RESULTS: 27 pts with GMF were identified representing 6.3% of all MF pts. Most GMF pts were Caucasian with a median age of 56 years (range; 25-83) and had early stage IA-IIA disease (70%).The time from disease onset to diagnosis was longer in the GMF group compared to the control group (mean 8.0 vs. 4.3 years, p=0.04). Skin manifestations of GMF were similar to classic MF with granuloma-annulare like lesions seen in a minority of pts. The most common histologic pattern was an atypical lichenoid CD4+CD8- lymphocytic infiltrate with interstitial histiocytes and/or perivascular granulomas with giant cells. Fewer GMF pts achieved a PR or CR with topical therapy (57% vs 83%; p=0.002) or phototherapy (62% vs 90%; p=0.006). More GMF pts required systemic therapy compared to classic MF patients (66.7 vs. 32.7%; p=0.006). Progression to higher stage was higher among GMF pts compared to classic MF (46% vs 30%, p=0.23). The 5-y and 10-y progression-free survival rates were significantly lower in GMF pts (59% vs. 33%) compared to classic MF pts (84% vs. 56%; p=0.02), but overall survival rates were similar between groups (86% and 72 vs. 85% and 85%; p=0.54). Our study presents the largest series on GMF to date. More frequent disease progression and poorer response to therapies are seen in GMF pts compared to classic MF. The majority of GMF pts present with granulomatous features at initial diagnosis and in subsequent biopsies suggesting that this entity has a unique relationship with its microenvironment.

O-042

BLASTIC PLASMACYTOID DENTRITIC CELL NEOPLASM: CLINICAL FEATURES IN 90 PATIENTS

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Blastic plasmacytoid Dentritic Cell Neoplasm is, as defined in the new 2008 World health Organized classification of tumors of hematopoietic and lymphoid tissue, a rare disease characterized by malignant proliferation of a contingent blastic plasmacytoid dendritic cell. This rare entity is mostly revealed and diagnosed on cutaneous spreading associated d'emblée or not with a leukaemic component. We herein studied a large cohort of 90 patients with BPDCN and defined additional clues to coin earlier the correct diagnosis and manage accordingly such patients. We retrospectively reviewed BPDCN cases registered in the French Study Group on Cutaneous Lymphoma database from November 1995 to January 2012. Demographic data, clinical presentation, initial staging, and outcome were recorded.The studied group contained 62 male and 28 female patients (sex ratio 2.2).Three major different clinical presentations were identified: Sixty six patients (73.2%) presented with nodular lesions only, 11 patients with "bruise-like" patches (12.2%).The remaining ones showed disseminated lesions (patches and nodules). In 13 (14.6%) patients, lesions were disseminated. Mucosal lesions were notified in five patients (5.6%) The mean survival in patients with BPDCN was 15.3 months (95% confidence interval CI: 12.7–17.9 months). BPDCN is a dismal disease in all cases, even patients with an initial localized disease do not benefit so far of a better outcome. We here distinct three different clinical presentation of BPDCN. Nodular pattern is actually a more common feature than the originally reported "bruise-like" pattern. Although useful to diagnose earlier this very severe condition, the clinical staging is not a reliable prognosis factor. Beyond the fact that BPDCN may initial appear as a localized tumor, an aggressive management including bone marrow transplantation should be considerd'emblée since it is so far the only one option with long term survival.

O-043

SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA: A MULTICENTRIC CLINICAL AND PATHOLOGIC REPORT OF THE FRENCH CUTANEOUS LYMPHOMA GROUP (GFELC) EXPERIENCE

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Subcutaneous panniculitis-like t-cell lymphoma (SPTCL) is a rare entity individualized from cutaneous gamma/delta t-cell lymphoma. Surprisingly, despite well-described lymphoma criteria, SPTLC frequently affect young women and children. Prognosis is considered as favorable and whether the best treatment should be chemotherapy or immunosuppressive-based is still debated.

All SPTCL cases diagnosed since 2000 were reviewed by GFELC dermatopathologists. We retrospectively analyzed clinical, biological and pathological data of 27 patients with a confirmed SPTCL diagnosis.

Median age was 31.1yo and F/M ratio was 22/5. Five cases occurred in children of whom three were under 3yo. 47% of patients had an autoimmune disease medical past and 24% were previously diagnosed for another panniculitis. Three cases occurred just after pregnancy and the three young children cases after infectious events. Hemophagocytic syndrome was present in 35% of cases. Beta2-microglobulin was elevated in 83% of cases (4.51±2mg/L). Autoantibodies were positive in 65% of cases. All biopsies showed a panniculitis features with lymphoid infiltration by CD3+CD8+granzyme+CD30-CD56- cells, with rimming, apoptosis and hemophagocytosis. B cells were rare but plasma cells were frequently found in septa surrounding fat lobules (35%). Ki67 was usually elevated (86%). Diagnosis was confirmed by betaF1 expression (66%) and/or monoclonal TCR rearrangement (89%). Median follow-up was 20.5 months. Complete remission (CR) was reached in 74% of cases. 69.5% were treated with immunosuppressive treatment (group 1) and 30.5% received chemotherapy (group 2). In both groups respectively, CR was 77.7% and 37.5% (p=0.07) and progression was only observed with chemotherapy (37.5%, p=0.02).

In conclusion, SPTLC is frequently associated with autoimmunity or infections. Because of their efficiency and low toxicity, immunosuppressive treatment should be considered as a first-line treatment in young patients.

Friday, February 8, 2013

O-044

WHAT WE CAN LEARN FROM MURINE MODELS OF CUTANEOUS T-CELL LYMPHOMA

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Murine models of cancer have markedly advanced our knowledge of many human cancers, but mouse models of CTCL have been lacking. Several murine models of CTCL will be described in this presentation along with their corresponding advantages and disadvantages. Because the inflammatory microenvironment likely plays a role in the pathogenesis of CTCL, including mycosis fungoides, we have sought to develop a murine skin t-cell lymphoma model in which inflammation is a critical regulator of tumorigenesis. To this end, we have developed a model in which MBL2 T lymphoma cells are injected into the ear skin of syngeneic C57BL/6 mice. In the absence of topical application of di-nitro-fluorobenzene (a well known contact allergen), no tumor formation is observed and the MBL2 cells gradually die. With a single topical application of DNFB, however, immediately after MBL2 implantation, high grade tumors develop in the ear skin within 14-20 days. Several known topical treatments for early stage MF (specifically, corticosteroids and imiquimod) block tumor development in this model. Using this model, we have found a requirement for macrophages and have identified cytokine expression pathways that are expressed early during tumorigenesis. This murine model of CTCL, albeit having its own limitations, is simple, highly reproducible, and bears similarities to plaque/tumor development in humans with CTCL. This model may be a convenient means to identify novel agents that will improve therapy for CTCL.

O-045

A NEW MOUSE MODEL FOR STUDYING NF-κB EFFECTS IN CTCL

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Cutaneous t-cell lymphoma (CTCL) represent a heterogeneous group of lymphoid malignancies that are characterized by proliferation of CD4+ T cells. CTCL challenge both basic and clinical research for two reasons: first, their pathogenesis is unknown, second, the disease is not curable so far. Thus, there is urgent need to develop new therapeutic approaches.

Animal models are a powerful tool in the development of new therapies in oncology, as they represent the missing link between promising effects gathered by *in vitro* experiments and the initiation of clinical studies. The peculiarity of CTCL is that the proliferation of malignant CD4+ t-cells usually affects different organ systems by lymphogenic progression from the skin and is thus not limited to distinct solid tumour manifestations. This phenomenon has proven to be difficult to replicate in mouse models when tumour cells are injected subcutaneously. It is thus not yet completely captured in existing xenograft mouse models. We used a human

CTCL cell line with high constitutive NF-κB activity which, after subcutaneous injection, induces a fast-growing solid tumour and subsequently infiltrates different organs such as lymph nodes and liver. This model reflects the complex clinical phenotype of CTCL as a systemic disease in more detail than other established models. In addition the used cell line shows high constitutive NF-κB activity which is described as a major hallmark of CTCL. This model enables us to study therapeutic targets which aim at suppressing NF-κB activity thus inducing apoptosis of CTCL cells.

O-046

CD8+ CYTOTOXIC ACTION COMBINED WITH CHANGES IN PARACRINE MICROENVIRONMENT OF EPIDERMAL MELANOCYTIC UNIT COLLABORATE FOR MELANOGENESIS INHITION IN HYPOPIGMENTED MYCOSIS FUNGOIDES

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OBJECTIVE: To investigate possible depigmentation mechanisms of hypopigmented mycosis fungoides (HMF) lesions through a comparative immunohistochemical study of hypopigmented lesions from HMF patients, non-hypopigmented lesions from patients with classic mycosis fungoides (CMF), and normal skin samples from the same HMF patients.
METHODS: We selected 18 HMF patients and 8 CMF patients. We performed immunohistochemical analysis for infiltration immunophenotyping; for the melanocytic function study, reactions were conducted with Melan-a, tyrosinase, stem cell factor (SCF), stem cell factor receptor (CD117), and microphthalmia associated transcription factor (MITF).
RESULTS: We found a predominance of CD8+ T immunophenotype in HMF cases (14/18 patients), whereas most cases in the CMF group (7/8) presented a CD4+ immunophenotype (p=0.003); it corresponds with the theory that the cytotoxic activity of suppressor lymphocytes towards melanocytes can result in hypopigmentation. Melanocytic function analysis revealed a significant decrease in the immunostaining of melanocytes by Melan-A, tyrosinase, MITF, and CD117 in hypopigmented lesions. Keratinocyte SCF expression was irregular in hypopigmented lesions and significantly different from the expression in normal skin and non-hypopigmented lesions. These results confirm previous findings comparing HMF pathogenesis to vitiligo: besides the decrease in melanocytes and melanocytic CD117 receptor, we also described decreased expression of MITF in HMF lesions, a factor crucial for the function and survival of melanocytes. We also demonstrated an imbalance in melanogenic cytokine production by keratinocytes (by SCF) as a possible mechanism of depigmentation.
CONCLUSION: Similar to vitiligo, the pathogenesis of HMF hypopigmentation seems to be a combination of interdependent mechanisms involving neoplastic or reactive CD8+ t-cells with cytotoxic actions on melanocytes and inhibitory effects on keratinocytic paracrine function.

O-047

TH1, TH2, TH17 AND TREG EXPRESSION IN CUTANEOUS T-CELL LYMPHOMA PATIENTS: MODULATION OF MASTER GENE TARGETS.

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Mycosis fungoides (MF), the most common type of primary Cutaneous T-Cell Lymphomas (CTCL), represents a malignant CD4+ t-cell proliferation. Different studies suggested that gene expression analysis in lesional skin biopsies can improve the understanding of disease origin and its clinical behaviour. Data about molecular pattern of tumour-stage MF are heterogeneous and a general agreement on which molecular signature can characterize MF in tumour stage is still lacking. Master and Stat are genes involved in the CD4 naïve cell differentiation. We utilized RT-PCR to detect transcriptional profiles in Master and Stat gene involved in the CD4 differentiative lineage Th1 (Tbet/Stat4), Th2 (Gata3/Stat6), Th17(RORγt/Stat3) and Treg (Foxp3) with the aim to better clarify if these parameters can impact on clinical manifestations and natural history of the disease. We collected and analysed a total of 70 skin biopsy and 78 peripheral blood samples from 62 MF patients at different disease stage. All data were compared with those obtained from blood samples of a cohort of healthy donors. In peripheral blood analyses, gene profiles of STAT4 and GATA3 and resulted under expressed in CTCL patients when compared with healthy donors, whereas FOXp3 appeared to be over expressed. When skin and blood data were analyzed on the basis of disease stage, a lower expression of FOXp3 and Tbet was observed together with the cutaneous disease progression. Conversely STAT3 resulted with higher expression in advanced stage disease, but not RORγt probably depending on the difference in the mechanism of action of Master and Stat genes.
In conclusion we confirm the prognostic role of regulatory T-Cell Subsets (Treg and Th17) in MF patients. The better definition of the molecular signature in the different disease stages could lead to a better understanding of risk subset and prognosis of MF patients.

O-048

CD30 LYMPHOPROLIFERATIVE DISORDER WITH PSEUDOEPITHELIOMATOUS HYPERPLASIA: POSSIBLE ROLE OF TH17 CYTOKINES, NEUTROPHILS AND EOSINOPHILS

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Pseudoepitheliomatous hyperplasia (PEH) has been reported in CTCL and CD30+ cutaneous lymphoproliferative disorders (CLPD). The mechanism, in particular whether epidermal growth factor or transforming growth factor alpha are involved remains controversial. Instead, we propose the hypothesis that PEH is caused by Th17/Th22 cytokines produced by tumor cells; these cytokines are known to stimulate keratinocyte hyperplasia in vitro and are increased in psoriasis. To test our hypothesis, we examined cytokine expression

by IHC in FFPE tissue sections from skin lesions of 17 patients with CD30+ CLPD with PEH. the group includes 9 F and 8M with median age of 52 (11-89). No patient thad MF or other lymphomas. Lesions were often ulcerated (12) and corrugated with hemorrhagic features (6) resembling conditions like pyogenic granuloma or blastomycosis. Lesions were large, often >1 cm and up to 8cm, and clusters or satellite lesions were common. Most cases had numerous neutrophils and eosinophils. Two distinct patterns of PEH were noted: a follicular pattern resembling keratoacanthoma, with neutrophils > eosinophils, and a more broad and superficial epithelial pattern, with more eosinophils. Tumor cells contained IL-17F in 10/14 tested cases and IL-22 in 9/12. Four cases had few or no IL-17F+ cells; only one of these was positive for IL-22. Thus Th17 or Th22 cytokines were detected in tumor cells in 13 of 16 (81%) cases tested. Tumor cells in none of 7 cases tested had Th2 transcription factor GATA3, 2 of 7 expressed Th17 transcription factor ROR, and one was positive for Aryl Hydrocarbon Receptor which enhances IL-22 expression. Ten of twelve cases tested had strong expression of cytokeratin 17 known to be inducible by Th17 cytokines. We conclude that Th17/Th22 cytokines produced by tumor cells play a major role in the development of PEH in CD30+ CLPD.

O-049

GENETIC ASSOCIATION BETWEEN TLR9/MYD88 POLYMORPHISMS AND SÉZARY SYNDROME RISK

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Sézary syndrome is characterized by neoplastic T-cells expressing the NK cell surface receptor KIR3DL2 that bind CpG oligo-deoxynucleotides. Into NK cells intracellular early endosome compartment KIR3DL2 delivers CpG ODNs to its specific toll like receptor-9, which after recruitment of the myeloid differentiation factor 88, mediate interferon-γ upregulation. TLR-9 and MyD88 molecules are encoded by two polymorphic genes, widely implicated in infection and cancer settings. As bacterial/viral infections are believed to mediate the early phases of tumorigenic process leading to SS, we hypothesized that a genetically-driven differential expression of TLR-9/MyD88 could contribute to the individual susceptibility and undertook a genetic association study involving relevant TLR-9/MyD88 polymorphisms under a case-control design.
MATERIAL AND METHODS: 82 patients along with 250 healthy controls were genotyped for six well documented SNPs i.e. TLR-9 -1486 T/C, -1237 T/C, +1174 G/A, +2848 A/G and MyD88 -938C/A, +1944C/G. Genetic associations between TLR-9 and MYD88 alleles, genotypes, haplotypes and SS as well as relationship with demographic and/or clinical variables were examined.
RESULTS AND DISCUSSION: We found that the TLR9 -1237 TT and +1174 AA genotypes were significantly more prevalent in patients as compared to controls and hence considered as risk genotypes (p=.0021, OR=2.13, and p=.007, OR=2.6 respectively) and that the MyD88 -938 CC and MyD +1944 CC genotypes were higher in controls as compared to patients and behaves as protective genotypes (p=0.001 OR=0.33, and p= 0.003, OR=0.38 respectively). Given the

linkage disequilibrium between the SS-associated TLR-9 polymorphisms and that the -1237 dimorphism has been shown to affect promoter activity and IFNγ production, our finding could fit with our previous hypothesis speculating that SS tumorigenic process might be initiated by a chronic triggering of KIR3DL2 mediated T-cell proliferation by infectious agents

O-050

CD160 AND CD158K ARE UNIQUE MARKERS FOR CD4+ CUTANEOUS T-LYMPHOCYTES

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CD160 is a GPI-anchored Ig-like receptor expressed by circulating CD56dim+ NK cells and TCRγδ lymphocytes, identified by the monoclonal antibody BY55. Whereas most intestinal T lymphocytes express it, only a minor circulating CD4+ or CD8+ T lymphocyte subset is CD160+, although it has been reported on most of these cells following their activation. Here we describe CD4+CD160+ T lymphocytes that can be isolated from the peripheral blood of normal individuals and correspond to less than 1% of the whole CD4+ T cells. This unique T lymphocyte subset, which exhibits a limited TCR-Vß repertoire, co-expresses CD8αα, CD244, perforin but lacks CD28 expression, corresponding to an effector memory cytotoxic T-lymphocyte phenotype. Functional studies performed with purified CD4+CD160+ circulating cells confirmed their cytotoxic potential, significant proliferative capacity in response to CD3/TcR engagement and lack of immunoregulatory functions. These cells are also distinct from circulating precursors of intra-epithelial intestinal lymphocytes as they lack CD103 expression associated with this population. Finally and importantly, CD4+CD160+ were found to represent a mean of about 35% (and up to 80%) of the cutaneous CD4+ T lymphocytes present in the normal skin were they are often associated with the unique KIR marker CD158k. These cells might represent specialized cutaneous lymphocytes devoted to immune surveillance of the skin barrier, and from which could originate some cutaneous T-lymphomas such as mycosis fungoides or Sézary those malignant cells expressed the CD158k marker in the skin.

O-051

AN ANGIOPOIETIN-2 HIGH TIE2 LOW ENDOTHELIAL PHENOTYPE CORRELATES WITH AN AGGRESSIVE CLINICAL COURSE IN PRIMARY CUTANEOUS B-CELL LYMPHOMA

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Angiopoietin-2 (Ang-2), the ligand of Tie2 receptor, represents a pivotal molecule during angiogenesis. However Ang-2 signaling is dichotomous with a destabilizing effect in $Tie2^{high}$ stalk/phalanx endothelial cells (EC) and a sprouting effect in $Tie2^{low}$ tip cells during physiological angiogenesis. Ang-2 induced sprouting in $Tie2^{low}$ tip cells requires expression of the angiogenic integrins αvβ3/αvβ5/α5β1 and is accompanied by FAK phosphorylation at Tyrosine397 (p-FAK[Tyr397]). $Tie2^{low}$ EC have been described in several malignancies but the relevance of Ang-2 stimulation of $Tie2^{low}$ EC in tumors remains an enigmatic question in the understanding of tumor angiogenesis. The aim of this study was to investigate if tumor malignancy correlates with Ang-2 signaling in $Tie2^{low}$ EC. Primary cutaneous B-cell lymphoma (PCBCL) of indolent behavior were compared with aggressive PCBCL for their vascular network morphology, Tie2, Ang-2, angiogenic integrin and p-FAK[Tyr397] expression. Aggressive PCBCL showed significant smaller, more often non-lumenized vessels defining tip cell morphology. Abundant Ang-2, significant more $Tie2^{low}$ EC and significant higher EC expression of the angiogenic integrins were observed in aggressive PCBCL. Enriched p-FAK[Tyr397] in sprouting vessels was only detectable in aggressive PCBCL. Concordantly, significant more sprouting vessels were found in aggressive PCBCL. In summary, an aggressive clinical course correlates with an Ang-2 induced $Tie2^{low}$ EC phenotype in PCBCL.

O-052

THE IMPORTANCE OF THE HOST IMMUNE RESPONSE IN THE TREATMENT OF CUTANEOUS T-CELL LYMPHOMA

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Substantial data has emerged supporting the critical role of the host immune response in the control of CTCL progression. Data include the rapid progression of advanced stage CTCL following the administration of calcineurin inhibitors and other drugs that suppress cell-mediated immunity. Moreover, therapeutic agents which augment cell-mediated immunity play an important role in mediating disease resolution. Most notably, interferon alpha is especially therapeutically active. Trials with other immune potentiating agents such as interleukin-12 and interferon gamma as well as Toll-like receptor agonists that trigger TLR 7, 8 or 9 have demonstrated significant clinical activity in CTCL. Substantial evidence has been obtained for the induction of tumor infiltrating cytotoxic T-cells during use of immune stimulatory treatments. These observations are relevant in the context of new drugs, such as histone deacetylase inhibitors, which appear to suppress cell-mediated immunity, as well as in the use of proapoptotic treatments that do not significantly alter immunity. Our observations will be reviewed.

O-053

CTCL IMMUNOBIOLOGY: HOW AN UNDERSTANDING OF T-CELL RECIRCULATION CAN GUIDE THERAPY

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Cutaneous t-cell lymphoma (CTCL) is a malignancy of skin tropic t-cells that can present as leukemic CTCL (L-CTCL), which we have reported to be a malignancy of central memory t-cells (T_{CM}), or mycosis fungoides (MF), a malignancy of non-recirculating skin resident t-cells (T_{RM}).

We have found that understanding the recirculation patterns of the malignant t-cells of origin can have significant impacts on therapy. For example, MF represents a malignancy of sessile, non-recirculating $T_{RM.}$ We have treated patients with debilitating, refractory syringotropic CTCL with low dose radiation consisting of two 4GY sessions, delivered either by brachytherapy or electron beam therapy, and found that this therapy induces long-standing remission and has the additional benefit of inducing long-term improvements in coexisting hand/foot dermatitis. In contrast, L-CTCL is a malignancy of highly migratory T_{CM}, cells that in mouse models actively recirculate between the skin, lymph nodes and blood. We find that low dose alemtuzumab (αCD52) is an effective therapy for refractory L-CTCL that depletes t-cells in blood but not in skin. Alemtuzumab depletes all t-cells from blood and selectively depletes T_{CM} from skin, leaving the benign skin resident T_{RM} intact. Because alemtuzumab only depletes circulating T cells, this has provided the first evidence in humans that T_{CM} recirculate

whereas skin resident T_{RM} are a sessile, non-recirculating t-cell population. We observed a remarkable lack of infections in treated patients despite the complete absence of t cells in blood, suggesting that skin resident T_{RM} can protect the skin from pathogens even in the absence of t-cell recruitment from the circulation. In short, we find that alemtuzumab is an effective therapy for refractory L-CTCL that depletes malignant t-cells while sparing the local skin immunity provided by T_{RM}. In summary, we describe effective therapies for refractory MF and L-CTCL that are based on a clearer understanding of the biology and recirculation patterns of the malignant t-cells of origin. In addition to improving therapies for patients with CTCL, these studies also highlight biologic differences between T_{CM} and T_{RM}, demonstrating that T_{CM} are migratory but skin resident T_{RM} are non-recirculating and capable of protecting the skin from infection, even in the absence of t-cell recruitment from blood.

O-054

IMMUNOTHERAPY STRATEGIES IN CUTANEOUS T-CELL LYMPHOMA (CTCL)

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Cancer immunotherapy practicum started with William Coley in his quest to immune-stimulate with intratumoral injection of bacterial products, later known as Coley's toxin. After a decade later, Coley's strategy has been made current leading to various immunotherapy strategies ranging from nonspecific immune stimulation such as cytokine therapy to highly specific strategies utilizing monoclonal antibodies. After years of disappointment in efficacy of cancer immunotherapy, meaningful successes were achieved based on the advances in understanding of the toleragenic nature of cancer and the key role of tumor immune microenvironment in suppressing antitumor immunity. This has led to advances in strategies that break tolerance and reactivate antitumor immune responses. A notable proof of concept was demonstrated in melanoma with ipilimumab showing that an active immune therapy in concert with molecular targeted agent may provide the solution towards long-lasting responses in cancer therapy. With demonstration of immune dysregulation in MF/SS and improved clinical outcome associated with tumor infiltrating CD8+ T cells, immunotherapy has long been employed in MF/SS. Immunotherapy developments in CTCL have included cytokine therapeutics, harnessing innate immunity with potent TLR-agonists used alone or as part of vaccine strategies, monoclonal antibodies to generate ADCC. Methods to augment ADCC by defucosylation of Fc region or by boosting NK activity with agonistic anti-CD137 antibody have been explored. Blockade of immune checkpoints with antibodies against CTLA-4 or PD-1/PD-L1 to break tolerance and reactivate antitumor immune responses are being explored in hematolymphoid malignancies including CTCL. Finally, successful graft versus lymphoma effect with allogeneic HSC transplantation has further reaffirmed the importance of optimizing immunotherapy strategies in CTCL to attain a long-lasting if not curative outcome.

O-055

EXPRESSION OF FOLLICULAR HELPER T-CELL MARKER PD-1 (CD279) IN CUTANEOUS B-CELL LYMPHOMAS – CORRELATION WITH BIOLOGIC BEHAVIOR

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BACKGROUND: Programmed death-1 (PD-1/CD279) is a cell surface protein expressed in a subset of T lymphocytes including follicular helper T-cells. The interaction between PD-1 and its ligands (PD-L1 and PD-L2) plays a role in normal immune response, but also in immune evasion of malignancies. In nodal follicular lymphoma, the number of PD-1 positive lymphocytes is associated with overall survival. Our aim was to investigate the presence of PD-1 positive lymphocytes in the different forms of primary cutaneous B-cell lymphomas (PCBCL) in correlation with biologic behavior.
MATERIAL & METHODS: We investigated 35 blinded cases of PCBCL including primary cutaneous follicle center lymphoma (PCFCL; n=11), primary cutaneous marginal zone lymphoma (PCMZL; n=11) and primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT; n=13) for the number and density of PD-1 positive cells using image analysis software and correlated these data with the clinical outcome.
RESULTS: The PD-1 positive cells represented tumor infiltrating T-cells (TIL). The tumor-cells were negative for PD-1. Patients with PCDLBCL-LT had a significant lower number of PD-1 TILs than PCMZL (p=0.012) and PCFCL (p=0.002) or both groups together (p=0.002). The difference between PCMZL and PCFCL reached borderline significance (p=0.059).
DISCUSSION: High number of PD-1 expressing follicular helper T-cells correlate with the favorable prognosis of PCMZL and PCFCL. The tumor cells in all investigated types of PCBCL did not show aberrant PD-1 expression.

O-056

PROGRAMMED DEATH-1 (PD-1) EXPRESSION IN CUTANEOUS B-CELL LYMPHOMAS

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Programmed Death-1 (PD-1; CD279) is a member of the CD28 costimulatory receptor family and is involved in down regulation of T-cell responses. PD-1 is specifically expressed by germinal center-associated T-cells (follicular helper T-cells; TFH cells), which are considered to play an important role in B-cell differentiation and plasma cell development. Recent studies demonstrated that PD-1 is expressed by the neoplastic t-cells in several types of (cutaneous) T-cell lymphoma, including Sézary syndrome, but data on PD-1 expression in cutaneous B-cell lymphomas (CBCL) are almost lacking. In one report PD-1 positivity was found in primary follicle center lymphoma (PCFCL), but not in primary cutaneous marginal zone lymphomas

(PCMZL) and primary cutaneous diffuse large B-cell lymphoma, leg type (PCLBCL, LT). In the present study we investigated PD-1 expression in skin biopsies of nine patients with a PCMZL, 13 patients with a PCFCL and 12 patients with a PCLBCL–LT; skin biopsies from five patients with a pseudo B-cell lymphoma and from two patients with a B-CLL were included as (positive) controls. In PCMZL and PCFCL PD-1 was expressed by 25-50% (PCMZL) and 50-75% (PCFCL) of the reactive CD3+ T-cells. These PD-1 positive T-cells were mostly located within or around reactive (PCMZL) or neoplastic (PCFCL) germinal centers. In PCMZL PD-1 positive T-cells were spatially not associated with plasma cells, and in both types of CBCL PD-1 was not expressed by the neoplastic B-cells. In patients with PCLBCL, LT PD-1 was expressed by the neoplastic B-cells in 2 of 12 cases. The number of admixed CD3+ T-cells was generally low (always less than 25%) and PD-1 was expressed by only a small minority of these T-cells.
In conclusion, PD-1 positive reactive t-cells are most abundant PCFCL and uncommon in PCLBCL, LT. The neoplastic B-cells in CBCL do not express PD-1, except for some cases of PCLBCL–LT.

O-057

THERAPY OF ADVANCED CTCL: WHAT WE KNOW AND WHAT WE NEED TO KNOW

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Primary cutaneous T-cell lymphomas (CTCL) are a very heterogeneous group of skin neoplasia. In general, most CTCL patients respond very rapidly and consistently to several non-specific treatment strategies including corticosteroids, retinoids, interferons and cytostatic drugs.
However, there is also an agreement that most responses are of limited duration and that most of the drugs mentioned also affect the survival and the function of normal T-lymphocytes. There is an urgent need to determine the optimal sequence of therapeutic options adapted to the stage and the type of the CTCL. In addition, there is an urgent need to develop powerful maintenance therapies. Finally, we still do not know whether any systemic therapy can definitely cure CTCL patients.

O-058

A NOVEL NON-MYELOABLATIVE ALLOGENEIC TRANSPLANT INDUCES MOLECULAR REMISSION ASSESSED BY HIGH-THROUGHPUT SEQUENCING OF T-CELL RECEPTOR (TCR) IN MYCOSIS FUNGODIES (MF) AND SEZARY SYNDROME (SS)

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We have performed allogeneic transplant in 21 patients with advanced stage MF or SS using a novel preparative regimen with total skin electron beam therapy (TSEBT) + total lymphoid irradiation (TLI)/anti-thymocyte globulin (ATG) in an attempt to provide prolonged disease control. The median age was 64 years (range 20-74). All but three had stage IV disease and 19 patients had active but non-progressive disease prior to TSEBT. In the 17 evaluable patients, 14 achieved CR and 2 had PR (ORR 94%). Neither median OS nor PFS was reached with a median13.6 month follow-up. Patients tolerated transplant extremely well with a 0% one-year non-relapse mortality. Three patients had grade 2 acute GVHD (skin, skin, GI), and one developed chronic GVHD. The current monitoring method using flow cytometry, review of skin samples and TCR PCR lacks sensitivity or specificity in detecting minimal residual disease (MRD). Here, we applied high-throughput sequencing in monitoring MRD using Illumina GA2 system to generate 1,000,000 reads of TCR CDR3 region. This TCR sequencing method detected spiked Sezary cells in whole blood as low as 1 in 50,000 PBMC (or 1 in 140,000 leukocytes). Malignant clone was identified in blood samples from the first 8 SS cases by a dominant unique TCRβ CDR3 sequence. Before TSEBT, 3 patients had measurable circulating Sezary cells by flow cytometry. The other five had no detectable disease by flow cytometry. However, 8.47%, 0.38%, 0.22%, 0.08% and 0.02% of the TCR sequences were of malignant clones in these cases. The percentage of malignant clones decreased in all cases immediately post transplant. Four patients eventually achieved molecular remission (at days +30, +30, +270, +270, respectively). Preliminary data from TCR sequencing of skin samples showed that one patient also achieved molecular remission in skin. The follow-up is still short to determine whether achieving molecular remission, assessed by TCR sequencing, correlates with better clinical outcome.

O-059

LOW DOSE TOTAL SKIN ELECTRON BEAM RADIOTHERAPY (TSEB) FOR MYCOSIS FUNGOIDES. INITIAL EXPERIENCE OF 12GY IN 8 FRACTIONS OVER 2 WEEKS

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INTRODUCTION: Total skin Electron Beam radiotherapy (TSEB) is one of the most effective therapies for Mycosis Fungoides. This study presents the results of a low dose schedule.
METHODS: In August 2011 we introduced a low dose 12Gy in 8 fraction over 2 weeks schedule of TSEB. TSEB was delivered using the modified Stanford technique. Data was collected prospectively on response, duration of response, survival and toxicity according to the EORTC and ISCL recommendations on end points. Response assessments were made using the mSWAT score. Toxicity was recorded according to the CTCAE v 4.0.
RESULTS: We have treated 26 patients with the low dose schedule and only 7 patients with the standard full dose schedule. The low dose schedule over 2 weeks is more acceptable to patients when given the choice. Of these 26 patients 19 have completed treatment with follow up allowing assessment of response. The median follow up is 7 months (range 1.3 to 12.4). The stage of MF prior to TSEB was IB in 9, IIB in 5, IIIA in 3 and IIIB in 2 patients. 4 patients had a CR, 10 a PR, 4 SD and 1 had PD during treatment giving an ORR of 73%, CR rate of 21% and PR rate 52%. 4 patients have relapsed (median duration of response 6.9 months, range 4.4 to 10.6 months). 14 patients have not relapsed with a median follow up of 5.2 months (range 0 to 10.3 months) Of the 4 patients who achieved CR none have relapsed at 5.7, 4.8, 3.7 and 0 months) The low dose schedule was very well tolerated. Grade 2 fatigue was reported in 2 patients. Grade 1 leg oedema was reported in 4 patients and grade 2 in 1 patient. No

patients developed blisters on their feet or hands. 3 patients reported a Grade 2 skin reaction. There were 3 grade 3 toxicities which recovered completely.
CONCLUSION: Our initial experience is that this low dose schedule of TSEB is more acceptable to patients with a low side effect profile, and similar response rates and duration of response to higher dose schedules. Further follow up is needed.

O-060

ALLOGENEIC STEM CELL TRANSPLANTATION IN ADVANCED STAGE MYCOSIS FUNGOIDES AND SÉZARY SYNDROME AFTER NON MYELOABLATIVE CONDITIONING WITH PENTOSTATIN AND TBI200

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Advanced tumor-stage MF and Sézary syndrome are CTCL characterized by very poor prognosis. Allogeneic haematopoietic stem cell transplantation (allo-SCT) has been shown to be very effective in achieving long lasting complete remission, possibly leading to cure in selected pts. However, high transplant-related mortality (TRM) limit its feasibility in the vast majority of pts with CTCL. Reduced-intensity (RIC) or non myeloablative (NMA) conditioning regimens have been demonstrated to decrease TRM, allowing gradual establishment of full donor chimerism and graft-versus-lymphoma effect.
In our Institution, between 09/2002 and 10/2012, 18 pts underwent allo-HSCT after pentostatin/TBI200 NMA regimen. Graft-versus-Host Disease (GvHD) prophylaxis included CsA and MMF (+ ATG in MUD transplants).
At the time of transplant all pts (11 M and 7 F; median age 52 years, range 27-66) had stage III/IV refractory MF (n=13) or SS (n=5). Median time from diagnosis to HSCT was 42 months (range 13-252). Donors were HLA-identical sibling in 13 pts and HLA-matched unrelated (MUD) in 5. Source of stem cells was peripheral blood in all pts but one, who received a single umbilical cord blood unit.
Full donor chimerism was obtained in 16/17 evaluable pts, in a median time of 2 months (range 1-12). Acute GvHD occurred in 8 pts (4 grade I-II, 3 grade III and 1 grade IV), whereas chronic GvHD was observed in 6 (extensive in 3). Six pts died, 1 in complete remission (CR) for aGvHD and 5 with progressive disease.
Overall, clinical CR was obtained in 13 pts. With a median follow-up of 84 months (range 2-122), 12 pts are currently alive and disease-free. Of note, all pts who died in progression had chemoresistant disease at time of transplant.
In conclusion, alloHSCT after pentostatin/TBI200 NMA regimen is feasible and represents a highly effective strategy of cure in pts with advanced stage refractory MF/SS, with a key role of immunomediated graft-versus-lymphoma in maintaining remissions.

O-061

COMORBIDITIES, SECONDARY CANCERS AND MORTALITY ASSOCIATED WITH NITROGEN MUSTARD THERAPY IN PATIENTS WITH MYCOSIS FUNGOIDES: A 30-YEAR POPULATION-BASED COHORT STUDY

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BACKROUND: Topical nitrogen mustard (mechlorethamine hydrochloride) is a widely used therapy in patients with mycosis fungoides (MF). However, it remains controversial whether nitrogen mustard therapy in patients with MF is associated with secondary cancers and induction of chronic pulmonary diseases.
The aim of the present study was to determine the risk of comorbidities, subsequent cancers, mortality and causes of death in MF patients treated with nitrogen mustard compared with MF patients not receiving this treatment.
METHODS: We conducted a 30-year population-based cohort study by linking the Danish nationwide registries and identified 110 MF patients treated with nitrogen mustard (cohort 1) and 193 MF patients, who did not receive nitrogen mustard (cohort 2). The two cohorts were compared by Cox-regression.
RESULTS: During an average follow-up time of 6.6 years in cohort 1 and 6.1 years in cohort 2, we found no significantly increase in all types of comorbidities, including chronic pulmonary diseases, in patients treated with nitrogen mustard. The risk of all secondary cancers was not significantly increased, hazard ratio: 0.78 (0.45-1.38), and subanalysis showed no significantly increased risk of non-melanoma skin cancers, malignant melanomas, colorectal cancers and cancers in the respiratory organs in patients treated with nitrogen mustard. Furthermore, we found no significant differences in mortality and causes of death between the two cohorts.
CONCLUSION: This study demonstrate that topical nitrogen mustard therapy is not associated with increased risk of comorbidities and secondary cancers in patients with MF and that nitrogen mustard does not influence mortality and causes of death in these patients. Thus, our findings strongly indicate that topical nitrogen mustard is a safe therapy in patients with MF.

O-062

CUTANEOUS TOXICITY ASSOCIATED WITH PRALATREXATE IN CUTANEOUS AND PERIPHERAL T-CELL LYMPHOMA

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Pralatrexate is a folate analogue metabolic inhibitor that has clinical activity in both peripheral T-cell lymphoma (PTCL) (O'Connor, et al. JCO. 2011;29(9):1182-9) and relapsed/refractory cutaneous T-cell lymphoma (CTCL) (Horowitz, et al. Blood. 2012 119: 4115-22). The most commonly reported adverse events (AE) observed with pralatrexate are mucositis, fatigue,

nausea, and cutaneous toxicity. To further characterize the incidence and clinical features of cutaneous toxicity, we retrospectively analyzed the data of 22 consecutively treated patients at the Yale Cancer Center. Of the 22 patients (4 PTCL, 18 CTCL), there was 1 PTCL patient who developed toxic erythema of chemotherapy. In the CTCL cohort, the large majority of treated patients (14/18, 78%) developed cutaneous toxicity, and this manifested as worsening erythema, skin breakdown, ulceration, and/or pain at CTCL lesion sites. The majority of these patients (10/14, 71%) developed the toxicity following cycle 1 week 1. Eight patients had received a dose of 15mg/m2, 3 patients received 10mg/m2 and 2 patients had doses of 17.5mg/m2 and 20mg/m2 respectively. Of those patients who developed cutaneous toxicity, 8 (57%) required the pralatrexate to be held, and 2 patients (14%) required hospitalization and treatment with intravenous antibiotics. In 7 patients, pralatrexate was restarted at a lower dose; 3 patients were changed to an every other week dosing schedule; and 2 patients continued on pralatrexate with no dosage change following resolution of their symptoms. In all 12 patients who were retreated with pralatrexate, cutaneous toxicity did not recur. We conclude that skin toxicity from pralatrexate is common, occurs early, and is typically observed at the sites of CTCL lesions as a skin flare. Cutaneous skin toxicity was not dose dependent or associated with disease response, and most patients were able to continue on therapy.

O-063

THE FUTURE OF HDAC INHIBITORS IN CUTANEOUS T-CELL LYMPHOMAS

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The regulation of gene expression in many biological processes involves various epigenetic mechanisms. Apparent histone acetylation is frequently observed in human cancers, HDAC are considered a promising target for cancer therapy and HDAC inhibitors are being developed.
HDAC are a family of enzymes that catalyze the removal of acetyl a group on lysine residues of proteins including the core nuclesomal histones H2A, H2B, H3, and H4. The balance of acetylation of nuclesomal histones plays an important regulatory role in the transcription of many genes including nuclear receptors, p53, C-myc, nuclear factor κ B, hypoxia inducible factor 1 α (HIF-1α), STAT3, as well as α-tubolin and H-schock protein 90 (HSP 90). In addition, HDAC inhibition up regulates the intrinsic apoptosis pathway via the up regulation of pro-apoptotic proteins in the Bcl2 family.
Due to this variety of cell functions that are involved in cell survival, cell cycle progression, angiogenesis, and immunity HDAC are considered promising targets, especially for cutaneous T-cell lymphomas.
Several structural distinct classes of HDAC inhibitors have been developed, including hydroxamid acid, cyclic peptide, eletrophylic ketons, short-chain fatty acid, benzamides, and recently second generation hydroxamate, a potent orally available pan HDAC inhibitor. HDACs are currently being studied in clinical trials as monotherapy or in combination with other anti-cancer agents; however, only two inhibitors – vorinostat and romidepsin – have been approved by the US Food and Drug Administration for use in the treatment of relapsed cutaneous T-cell lymphomas. Other HDAC inhibitors such as belinostat, mocetinostat, panobinostat, and recently trinolquisinostat have demonstrated therapeutic potential as monotherapies in patients with relapsed lymphomas. However, the response rates are around 20-30 % with maximum medium progression-free survival up to 15 months. In addition to these clinical results, it has been shown that HDAC inhibitors act immunosuppressive.
All these findings raise the question whether HDAC inhibitors will play a significant role in the treatment of cutaneous T-cell lymphomas.

O-064

TOTAL SKIN ELECTRON BEAM THERAPY CAN IMPROVE PERIPHERAL BLOOD DISEASE BURDEN IN SEZARY SYNDROME AND LEUKEMIC MYCOSIS FUNGOIDES

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There is a paucity of effective therapies for patients with Sézary syndrome and advanced mycosis fungoides with peripheral blood involvement. Total skin electron beam radiation therapy is an extremely effective skin directed therapy for these patients, but until recently, was thought not to affect the peripheral blood malignant T-cell population.
We present a retrospective case series of 11 patients with advanced mycosis fungoides or Sézary syndrome in our Photopheresis Service at the University of Pennsylvania who underwent total skin electron beam radiation therapy between January 2008 and October 2011 at Temple University Hospital and examined the therapeutic effect on their peripheral blood malignant T-cell population, as documented by flow cytometry.
Two patients had B1 blood involvement/Stage IIIB disease and 9 had B2/Stage IVA disease. All patients were on extracorporeal photopheresis-based combination therapy prior to TSEBT (typically interferon alpha and/or gamma and retinoids) and 5 of 11 patients remained on these therapies during TSEBT. Total dose of radiation ranged from 1200-3800 cGy. Overall, six out of eleven patients achieved ≥50% decrease in their peripheral blood malignant T-cell population following total skin electron beam therapy, for an overall peripheral blood response rate of 55% assessed on average at 7 weeks after TSEBT (range 1-16 weeks) . Within the group of patients that had a response in the skin (82% skin overall response rate), 67% also had a response in the peripheral blood. Out of the 6 peripheral blood responders, 3 patients have maintained response (average 23 months follow up), 2 have relapsed (at 5 and 6 months follow up), 1 patient was lost to follow up.
CONCLUSION: This current series further substantiates our prior report that patients with advanced mycosis fungoides and Sézary syndrome can show improvement in their peripheral blood disease following a skin directed therapy such as total skin electron beam therapy.

O-065

TOTAL SKIN ELECTRON THERAPY FOR MYCOSIS FUNGOIDES: A SINGLE CENTRE EXPERIENCE

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Data was collected from hospital notes, radiotherapy notes, electronic system & general practitioners.
44 patients with mycosis fungoides from 13 centres were treated with total skin electron beam therapy (TSEB) at University Hospitals Coventry NHS Trust since 1997: 33 males (75%) & 11 females (25%). Mean age was 59yrs (range 31-88). Staging at diagnosis ranged from IA-IVA (4xIA,13xIB,3xIIA,11xIIB,3xIII,1xIVA). Stage at referral included patients with at least stage IB disease.
Most patients (93%) had received prior therapy. 13/36 (36%) had received skin directed therapy alone (PUVA, carmustine, local radiotherapy). 57% had received systemic therapy (interferon, bexarotene or methotrexate). 19% had prior intravenous chemotherapy.
Mean time from diagnosis to TSEB was 58 months (range 3-240). Dose fractionation included 11x 30Gy in 20 fractions(25%), 30x 24Gy in 3 fractions (68%) & 3x 12Gy in 8 fractions (7%). Fractionation had been changed as toxicity profile was better with increased fractionation.
Survival data was available in all patients. 18/44 (40%) were alive with median FU 168 months (mean 163, range 33-348) and 26/42 (60%) had died with median FU 92 months (mean 80, range 6-336). Of 15 patients with early stage disease(ESD:stage IA-IIA): 8 were alive, mean FU 156 months and 7 had died, mean survival 124 months. Of 15 patients with late stage disease (LSD) at diagnosis: 6 were alive, mean FU 128 months & 9 had died, mean survival 53 months. 5 yr survival rates were 80% in ESD & 47% in LSD. 10 yr survival was 27% in all stages.
There is a small cohort of patients with advanced disease in whom survival is improved (all IIB survival >10yrs) but to determine if TSEB plays a role would require a prospective multicentre study. There is a need for a unified prospective national audit in order to maximise the information especially as newer shorter fractionation schedules (12Gy in 8 fractions over 2 weeks) are now being introduced in the UK.

O-066

MULTI-CENTER RESULTS ON THE EFFECT OF DIFFERENT PHOTOTHERAPEUTIC MODALITIES IN LYMPHOMATOID PAPULOSIS

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BACKROUND: The purpose of this study was to evaluate and compare the efficacy of different phototherapeutic modalities in lymphomatoid papulosis (LyP).
METHODS: Data from 5 centers on a total of 40 patients treated with phototherapy for LyP (type A, B or C) between 1997 and 2012 were available for retrospective analysis. The patients included 26 men and 14 women (age range, 14 to 85 years) with LyP (range of disease duration, 1 month to 15 years). Twenty-one patients had been treated with psoralen plus UVA (PUVA) photochemotherapy, 4 patients with UVA-1, 1 patient with UVA/B, and 14 patients with 311-nm UVB. If a patient had received several cycles of phototherapy, only the first cycle was included in the analysis. Analysis was intention-to-treat and patients with unknown result after treatment were considered as non-responders.
RESULTS: The short-term complete responder (CR), partial responder (PR), and non-responder (NoR) numbers (percentages) were as follows: oral PUVA, 8/8/4 (40/40/20); bath PUVA, 0/1/0 (0/100/0); UVA-1, 2/1/1 (50/25/25); UVA/B, 0/1/0 (0/100/0); and 311-nm UVB, 11/2/1 (78/14/7). The statistical comparison of the CR rate of 311nm UVB (78%) to that of oral PUVA (40%) indicated that the former may be more effective than the later in clearing LyP (p=0.0364; Fisher exact test). A limitation of the study is that the allocation to the different phototherapeutic treatment modalities varied widely among the different participating centers.
CONCLUSIONS: PUVA, UVA-1 and 311-nm UVB can lead to complete clearance of LyP. A prospective study is needed to clarify whether on the short-term 311-nm UVB may indeed be more effective than other phototherapeutic modalities. In addition, predictive factors of response as well as long-term outcomes need to be determined.

O-067

EXTRACORPOREAL PHOTOPHERESIS FOR THE TREATMENT OF ERYTHRODERMIC CUTANEOUS T-CELL LYMPHOMA: OVER-VIEW OF THE LITERATURE AND CLINICAL EXPERIENCE WITH LONG-TERM FOLLOW-UP DATA

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Extracorporeal photopheresis (ECP) is a well-established therapeutic procedure in which leukapheresed peripheral blood mononuclear cells are exposed to UVA in the presence of the photosensitizer 8-methoxypsoralen (8-MOP) and then reinfused. ECP has been recommended by several guidelines as a first-line treatment in erythrodermic primary cutaneous T-cell lymphomas (E-CTCL). The rarity of these disease and the lack of randomised controlled trials implies however a low level of evidence.
We performed a review of the English literature, restricting our analysis to studies including erythrodermic patients and more than 10 cases. Based on these criteria, 28 studies were identified, with a total of 407 patients. The median response rate in erythrodermic patients was 63% (range 31%-86%), with a complete response rate ranging between 0 and 62% (median 20%). The duration of responses ranges widely but it appears that a significant percentage of patients can experience long term remissions.
In our experience, 51 E-CTCL patients have been treated since 1992. A clinical response was obtained in 32 patients (63%), with 16% complete response rate. The median time for response induction was 8 months (range: 1-23). The median response duration was 22.4 months (range 6 months–11 years). The treatment was generally well tolerated without

systemic toxicities grade III-IV. The pre-treatment parameters significantly associated with a higher likelihood to obtain a clinical response were the B-score in the peripheral blood, the CD4/CD8 ratio and the amount of circulating CD3+CD8+ cells.
Literature data together with our personal experience clearly support the clinical activity and tolerability of ECP in E-CTCL patients. In patients with a high tumour burden, a treatment able to induce a significant reduction in circulating leukemic cells should be performed before initiating ECP. Prospective controlled clinical trials are recommended to better document these evidences.

O-068

EXTRACORPOREAL PHOTOPHERESIS IN ERYTHRODERMIC CTCL: THE UK EXPERIENCE

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Extracorporeal photopheresis(ECP) is available at selected UK centres for treating erythrodermic CTCL. ECP has reported response rates in eCTCL ~60%. UK, European & US guidelines recommend ECP as first line systemic treatment in CTCL. However data on median length of treatment & number of treatments is lacking. This data is essential to determine cost implications for commissioners & to aid service development. Data on ECP patients was requested from all UK sites. Fifty-three patients were identified from 4 treatment centres. Eight had erythrodermic mycosis fungoides (4x stageIII,4x IVA) & 45 Sezary syndrome (35x stage III, 3x IVA, 1x stageIVB). This included 37 men & 16 women. The median time from diagnosis to ECP was 6 months (mean=8.9 months, range: 1-39 months.) In 24 patients ECP was used as first systemic therapy. The median number of systemic therapies prior to ECP was 1, mean 1.6 & range 0-8. 18 patients commenced treatment with adjuvant therapy: 5 with bexarotene & interferon, 7 with interferon only & 6 with bexarotene only. 10 further patients had adjuvant treatment after commencement of ECP: 8 with bexarotene, 1 with interferon & 1 with methotrexate. Median time from commencing ECP to addition of adjuvant therapy was 8 months (mean=9.2 months, range:3-22). The median duration of ECP therapy was 17 months(mean=21.3months, range:1-66) & median number of treatments 28(mean=26, range 1-72). A global physician score was available on 51 patients at 3-6 months. 42/51 (82%) responded to ECP: 31 had a good response, 11 a partial response & 9 had no response, 6 of whom received <6 months of therapy. In the UK ECP is used as first & second line therapy in eCTCL stage III-IVA. The majority of patients respond to ECP & responses may be improved by combination with bexarotene/interferon. The median number of ECP treatment was 28 over 17 months. Defining the median number of treatments required aids future planning of ECP services.

O-069

PRIMARY CUTANEOUS MARGINAL ZONE LYMPHOMA: A CRITICAL REVIEW

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PCMZL is recognized as an indolent lymphoproliferative condition of the skin. Preexisting chronic inflammation (infection or autoimmunity) resulting in accumulation of extranodal lymphoid tissue is common in MALT lymphomas, and Borrelia has been associated to PCMZL in Europe. However other possible co-morbidities in PCMZL are not known. A case-control epidermiologic assessment was performed using a questionnaire and chart review of a cohort of 70 PCMZL and control subjects (CG) matched for age, sex and race. None of the patients had systemic disease and skin staging included: 19 T1, 28 T2 and 23 T3 subjects. The median age was 60 years (range 23-87) and the average follow up was 3.5 years. At the time of the survey 47% were in CR and only 1 had disease progression. We found a high incidence of past or present history of GI problems in 66% (46) of the cohort in contrast with 36% (25) in CG (P<0.001). Gastroesophageal reflux was reported in 54% (38 vs. 22 CG P=0.01); gastric ulcers in 11% (8 vs. 3 in CG); 19% of cohort had positive H pylori serology (12 vs. 2 CG P=0.003). Colon pathology including irritable bowel syndrome and IBD were more common in the cohort (20 vs. 7 CG P=0.005). Other notable morbidities did not reach statistical significance including dry mouth in 21% (15 vs.9 in CG) and 37% with dry eyes (26 vs. 16 in CG). Both symptoms were present in14% (10 vs 2 CG). Three of these patients had a positive ANA and only one patient carried the diagnosis of lupus erythematosus and another one Sjögren syndrome diagnosis. 3 patient related history of hepatitis. Together 19% with autoimune conditions (13 vs. 10 CG) . History of non-cutaneous malignancies was observed in 21% of the cases (15 vs. 7 CG). Our results indicate a high incidence of systemic pathology in PCMZL, especially involving the GI tract, but also autoimmunity and cancer.

O-070

PRIMARY CUTANEOUS SMALL/MEDIUM-SIZED CD4+ PLEOMORPHIC T-CELL LYMPHOMA: RETROSPECTIVE CASE SERIES OF 22 PATIENTS

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BACKGROUND: Primary cutaneous small/medium-sized CD4+ pleomorphic T-cell lymphoma (PCSM-TCL) is a rare and provisional subcategory of cutaneous T-cell lymphoma associated with a favorable prognosis. Methods: A retrospective study of a series of 22 patients diagnosed with PCSM-TCL between 2006 and 2012 and evaluated at the Yale Cancer Center was conducted. All patients met the clinical, histopathologic and molecular criteria for PCSM-TCL as defined by WHO-EORTC.
RESULTS: Average and median age at diagnosis were 55 and 63 years. Only 3 patients had multifocal lesions involving the neck and trunk. The head and neck was the most commonly affected location (13 patients) followed by the trunk (6 patients). Two patients

had lesions involving the neck and shoulder and 1 patient had a lesion in the lower extremity. Immunohistochemistry demonstrated that all tumors were CD3+ and CD4+ and 17 were CD2+. No tumor was CD8+. Only 1 patient had partial expression of CD30, and Ki-67 was <50% in the majority of cases, further confirming the less aggressive nature of these tumors. The average follow up was 34.7 months. Eleven patients received excisional biopsy only. Spot radiation alone was used in 5 patients, and 2 received excision and spot radiation. CHOP chemotherapy and spot radiation was used in one patient with aggressive and invasive features, and intralesional triamcinolone was used in one. All therapeutic modalities employed were successful and recurrence was noted in only one patient.
CONCLUSION: Our case series provides further evidence that PCSM-TCL is a generally indolent type of T-cell lymphoma and can be treated with local modalities.

O-071

PRIMARY CUTANEOUS CD4+ SMALL/MEDIUM-SIZED PLEOMORPHIC T-CELL LYMPHOMA: CLINICAL AND HISTOLOGICAL CHARACTERISTICS

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INTRODUCTION: Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma is an uncommon provisional cutaneous lymphoma of follicular T helper cell origin with a benign course. The aim of our study was to clarify the frequency of the disease and to determine clinical and histological characteristics of this provisional entity.
MATERIAL AND METHODS: Since 2006, thirty-seven cases – 28 % of all 130 cases with cutaneous lymphoma – have been found in the archives of I. Dept. Pathology. 22 cases were investigated using CD3, CD4, CD7, CD8, PD1, CXCL13, bcl6, CD20, CD21, CD23, CD30, Ki67 and CLA. 15 cases were examined with CD3, CD4, CD8, CD20 and Ki67. TCRγ gene rearrangement analysis was performed in all samples.
RESULTS: Skin lesions were on the upper half of the body in 31/37 cases. Except for 2 cases with multiple lesions, all patients presented with solitary papule or nodule. Staging examinations excluded systemic involvement in all patients. Spontaneous regression was observed in 2 cases. All the other patients were treated with surgical excision. During the follow-up lymph node or visceral manifestation was not observed. Histological results similar to previous reports showed CD4+ PD1+ t-cells 20-30 % of all cells of the infiltrate. Double staining with bcl6 and PD1 showed three populations. Nearly one third of PD1+ cells were also bcl6+. B-cells were integral part of the tumor, however follicle formation, dendritic cell compartment and plasma cells were not found. Proliferation rate was less than 20% in all cases. TCRγ gene was monoclonal in 16/37, polyclonal in 15/37cases and in 4 cases DNA was not amplifiable.
CONCLUSION: Based on our observation CD4+ small/medium-sized pleomorphic T-cell lymphoma seems to be more frequent than previously reported. Lack of plasma cells, dendritic reticulum cells and follicle formation suggest impaired function of follicular helper T- cells, and indicates further investigation of the origin of this entity.

O-072

LONG TERM OUTCOME OF 61 PATIENTS WITH PRIMARY CUTANEOUS ANAPLASTIC LARGE CELL LYMPHOMA (PCALCL): THE STANFORD EXPERIENCE

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We reviewed 61 patients (pts) identified in the Stanford dermatopathology-clinical database with CD 30+ pcALCL from 1990-2012 to determine the long term outcome of pcALCL managed with contemporary therapies including excision, radiation therapy (RT), chemotherapy (topical or systemic), biologic therapies, and stem cell transplant (SCT). Potential prognostic factors including age, gender, T classification and progression to extra cutaneous disease (ECD) were analyzed for local control and time to first relapse after complete response (CR). Disease specific survival (DSS) and overall survival (OS) hazard ratios were calculated using the Cox regression model. Univariate analysis demonstrates T classification and age as significant prognostic factors for OS while T classification and progression to ECD are significant for DSS. In multivariate analysis, age at diagnosis remained significant for OS (HR, 1.03; 95% confidence interval (CI), 1.00-1.06; p2=.02). The table below shows DSS and OS based on prognostic factors.
CR was achieved in 50/61 (82%) after the first course of treatment. CR was maintained in 22/50 with initial therapy including RT (8), excision only (8), RT/excision (2), chemotherapy (3) and RT/chemotherapy (1). Of 50 with CR, 56% had a cutaneous relapse at a median of 5 months. Only 11% of those relapsing progressed to ECD, including 5/37 with T1, 1/14 with T2 and 6/10 with T3 disease. Two pts unresponsive to conventional management underwent SCT and are alive without disease at 10 and 14 year follow-up. We confirm excellent 10 year DSS for limited stage pcALCL; the majority managed with EXC or RT. Although cutaneous relapse is frequent, few progress to ECD. Progression to ECD is associated with a significantly worse outcome.

O-073

MANAGEMENT AND PATTERNS OF RELAPSE FOR PRIMARY CUTANEOUS B-CELL LYMPHOMAS (PCBCL) AT THE MULTIMODALITY CUTANEOUS LYMPHOMA CLINIC (MCLC) AT THE OHIO STATE UNIVERSITY. A SERIES UPDATE

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Primary cutaneous B-cell lymphomas (PCBCL) comprise ~25% of cutaneous lymphomas and have an indolent course, though a subset experiences skin relapses. The impact of treatment on risk of recurrence is not well known and treatment guidelines are vague. We describe clinicopathologic features and outcomes, and correlate stage and treatment with relapse. Cases were identified for the period 1998-2012. For the MCLC, we searched electronic medical records (EMR). For pathology, we queried CoPath v.4.1. Histology and immunohistochemistry were reviewed at OSU. CT or PET imaging was done in all cases, bone marrow (BM) biopsy in

most (81%). ISCL/EORTC staging criteria were used. Analysis of time-to-first-recurrence was performed using a log rank test. All tests were two-tailed. Overall 14 patients had systemic disease, despite skin-limited presentation (3 MZL, 6 FCL, 5 DLBCL) and 62 had PCBCL (no systemic/nodal disease at diagnosis or within 6 months), 39 men, 23 women. Median age for PCFCL and PCMZL was 48 yrs. Most presented with nodules or papules in the head and neck (67% of PCFCL, 28% of PCMZL), trunk (25% PCFCL, 28% PCMZL), and extremities (15% PCFCL, 4% PCMZL, 2/2 DLBCL, leg type). Multifocal skin lesions were found in 28% of MZL and 4% of FCL. The majority of patients (PCFCL, PCMZL were stage T1 (58%). Treatments included topical steroids, radiation, prednisone, rituximab, and chemotherapy. For all subtypes, with median follow-up 32.6 months (range 0.8-19 yrs) 35 patients (56%) were alive relapse free, while 24 (40%) were alive with $\geq$1 relapse. One patient (DLBCL, leg type) died of disease, one (PCFCL) died of unrelated causes, and one (DLBCL, leg type) was lost to follow up. To assess differences in time to first recurrence according to treatment, patients were split into an observation (post biopsy), and a treatment group. Of the patients with Stage T1 PCFCL and PCMZL 70% did not recur (observed 21%, treated 39%) and 30% recurred, with no statistically significant difference in time to first recurrence between observation and treatment (P=0.75). In conclusion, imaging and bone marrow biopsy staging showed that a significant number of patients with skin-limited presentation of B-cell NHL have systemic disease. Laboratory and clinical factors predictive of extracutaneous disease will be discussed. For PCBCL, there was no difference in the risk of relapse, or time to relapse between patients observed after excisional biopsy and treated.

O-074

HETEROGENEITY IN TUMOR STAGE MYCOSIS FUNGOÏDES CORRELATES WITH PROGNOSIS

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Mycosis fungoïdes (MF) is the most common type of cutaneous lymphoma. The disease course is clinically characterized by progression from patches to plaques to tumors and in a minority of patients extracutaneous localizations develop. MF is classified by type and extent of skin lesions using the tumor-node-metastasis (TNM) staging system as described by the International Society for Cutaneous Lymphomas (ISCL) and the European Organization of Research and Treatment of Cancer (EORTC) in 2007. However, within tumor stage MF considerable heterogeneity in the number of tumors and time interval between development of tumors is observed. It is unknown if this clinical heterogeneity correlates with differences in disease course and survival. The aim of this retrospective follow up study was to get a better insight into the heterogeneity in tumor development and prognosis in tumor stage MF. Of 46 MF patients who developed stage IIB during their follow up each period of tumor growth was registered with dates. The number of tumors and interval between tumor development were visualized using timeline templates. A statistical frailty model was fitted on the basis of the number of tumors developed during follow up leading to a numerical frailty score for each patient. The frailty score was divided into 3 groups containing high (n=15), median (n=15) and low (n=16) frailty, which correlated with disease progression and survival using the Kaplan Meier method. The differences in numbers of (new) tumors and interval between tumor growth between all patients were statistically significant (p=0.00). The group with the high, median and low frailty score showed a 2-year overall survival (OS) of 13%, 50% and 94%, respectively, and a 5-year OS of 0%, 29% and 71%, respectively. Our results show that tumor stage MF is a heterogeneous disease stage. Within this stage patients with a high frailty score have a more adverse prognosis.

Saturday, February 9, 2013

O-075

IDENTIFICATION OF DEREGULATED TRANSCRIPTION FACTORS IN HUMAN LYMPHOMA

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Oncogenic transformation is not only characterized by an enhanced proliferative capacity and/or higher apoptosis resistance of malignant cells, but also by a disruption of the physiological differentiation process. During the last two decades, it has become increasingly clear that disruption of cellular differentiation is intimately linked to lineage infidelity, cellular reprogramming and eventually tumor development in the hematopoietic system. As a consequence, hematopoietic tumor cells can display features of lineage infidelity or cellular reprogramming that might open up alternative growth and survival pathways for transformed cells. A number of lymphoid malignancies display a phenotype that is in accordance with such a process, including anaplastic large cell lymphoma (ALCL), primary effusion lymphoma (PEL) and classical Hodgkin lymphoma (cHL). Among these, cHL constitutes the most prominent example for lineage infidelity: in striking contrast to their origin from B-cells, the malignant Hodgkin-/Reed-Sternberg (HRS) cells of cHL have almost completely lost their B-cell-specific gene expression program and acquired expression of genes characteristic for other hematopoietic lineages, the so called expression of lineage-inappropriate genes. We have previously shown that the aberrant expression of such lineage-inappropriate genes is indeed required for growth and survival of malignant lymphoid cells. In order to extend our current model of deregulated transcription factor activities in cHL, we performed a genome-wide analysis of accessible chromatin regions in cHL in comparison to non-Hodgkin lymphoma cell lines, analyzed these regions for enriched transcription factor binding motifs and integrated these data with gene expression data derived from cHL cells and functional analyses. As a result, we identified a key regulator of HRS cell-specific gene expression which synergistically interacts with and contributes to the activation of transcription factors NF-κB and AP-1, both known to be required for HRS cell survival and gene expression. These data thus describe a powerful method for the identification of deregulated TF activities in human lymphoma.

O-076

MICRO RNAS REGULATE THE EFFECT OF CHEMOTHERAPY IN CTCL

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miRNAs are not only major physiological regulators of gene expression but are also involved in all stages of cancer development. miRNAs regulate tumor development, tumor growth and apoptosis, maintenance of cancer phenotype and the metastatic potential. We have focused on the role of selected miRNAs as regulators of the response to chemotherapy in cutaneous T-cell lymphoma (CTCL). Our approach was to measure the alterations in miRNA expression during in CTCL cell lines in response to chemotherapy and test the functional involvement of the promising miRNA species in the regulation of proliferation and apoptosis induced by cytotoxic drugs. We have identified miR-122 and miR-125b as possible new regulators of drug response in CTCL. MiR-122 and miR-125b were expressed in vitro in CTCL cell lines (SeAx, MyLa, Mac2a, Mac1 and Hut-78) and in vivo in lesional skin in mycosis fungoides (MF) and in Sézary cells purified from peripheral blood. MiR-122 promoted chemoresistance in CTCL via a signalling pathway involving Akt and p53, and its inhibition augmented chemotherapy-induced apoptosis. miR-125b-5p overexpression blocked the apoptotic response to the anticancer proteasome inhibitor bortezomib in vitro and enhanced tumor growth in a mouse model of T-cell lymphoma produced by xenotransplantation of MyLa cells to NOD/SCID gamma mice. We showed an auto regulative circuit in which miR-125b-5p modulates cMyc accumulation that in turn repressed transcriptionally miR-125b-5p. This auto regulative loop is likely to operate in vivo since we found an inverse relationship between cMyc and miR-125b-5p levels in the lesions of MF. Thus miR-122 and miR-125b-5p regulate the apoptotic responses to chemotherapy in CTCL via reciprocal interactions with key oncogenes and tumor suppressor genes such as p53 and cMyc. Since miRNAs are pharmacologically targetable, these studies may contribute to the rational development of new, miRNA based therapies for the yet incurable cutaneous T-cell lymphomas.

O-077

ACTIVATION OF PHOSPHATIDYLINOSITOL-3 KINASE (PI3K) /SERINE/THREONINE PROTEIN KINASE (AKT) PATHWAY IN MYCOSIS FUNGOIDES

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The serine/threonine protein kinase Akt, a downstream target of phosphatidylinositol 3-kinase (PI3K), is involved in various cellular processes linked to tumorigenesis.
We analysed immunohistochemically the expression of phosphorylated AKT (pAKT), p85 subunit of PI3K and PTEN in a panel of 54 samples (33 plaques and 21 tumors) from 50 MF patients stages I-IV (T1-T2-T3). The immunoreactivity of these molecules was correlated with clinicopathological features and disease, progression-free, and disease specific survival (DFS, PFS, CSS). Forty five cases were screened for activating mutations in exons 9,20 of PIK3CA, exon 4 of AKT1 and exons 5,7 and 8 of PTEN by Real Time PCR-High Resolution Melting Analysis (HRMA), sequencing and/or Pyrosequencing and 30 cases for PI3KCA gene amplifcation using the dual colour PIK3CA/CEN3q FISH probe. Cytoplasmic p-AKT immunoreactivity was seen in 53/54 (98.1%), nuclear p85apI3K immunoreactivity in 70.3% (38/54) and cytoplasmic PTEN in 25/53 (47.2%) of the cases. p85apI3K H-score was higher in tumours when compared to plaques (Mann Whitney U test, p=0.0233). PTEN immunoreactivity was inversely correlated

with clinical stage (Mann Whitney U test, I/IA vs IIB/III/IV, p=0.0744). All three cases with a PTEN mutation displayed negative or very low PTEN immunoexpression (H-score 1.5) and were positive for p-AKT (H-score 20-60). Univariate survival analysis in the entire cohort CD30 positivity was the only parameter that was adversely correlated with CSS (p=0.0006) and DFS (p=0.0059) and presence of PTEN mutations was correlated with shorter DFS and PFS (p=0.0253 and p<0.0001 respectively). In multivariate survival analysis p-AKT overexpression retained its statistical significance (HR=1.012, p=0.0017) for CSS as well as CD30 positivity regarding CSS (HR=5.89, p=0.003) and DFS (HR=2.53, p=0.009).Our findings implicate PI3K/AKT pathway in the aggressiveness of MF.

O-078

NUCLEAR FACTOR-κB SIGNALING PATHWAY-RELATED GENE ABERRANCIES IN PRIMARY CUTANEOUS LARGE B-CELL LYMPHOMAS, LEG TYPE

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Primary cutaneous large B-cell lymphoma, leg type (PCLBCL-LT) is an aggressive cutaneous lymphoma with a 5 year overall survival of less than 50%. At gene expression level, PCLBCL-LT resembles the activated B-cell (ABC) type of nodal diffuse large B-cell lymphoma (DLBCL). In ABC-DLBCL a role for constitutive nuclear factor (NF)-κB pathway activation in tumour cell survival is generally recognized and specific therapies targeting this pathway are being developed. In this research we screened PCLBCL-LT for genetic alterations leading to aberrant NF-κB activation. Of 10 cases of PCLBCL-LT DNA and RNA were isolated from frozen tumour biopsy samples with at least 75% tumour cells. The tumour suppressor gene TNFAIP3/A20 (an inhibitor of the NF-κB pathway) was analyzed using fine-tiling custom designed genomic DNA arrays, along with methylation specific melting curve analysis, mutation analysis for intron 3 splice site mutations and PCR to detect possible alternative splicing. Mutations resulting in activation of the NF-κB pathway genes CD79b and MYD88 were analyzed by PCR on DNA and cDNA followed by Sanger sequencing. Four cases showed heterozygous deletions of TNFAIP3, but none showed additional silencing through hypermethylation, presence of splice site mutations or alternative splicing. At DNA level, the oncogenic MYD88 L265P c.794T>C mutation was found in 4 cases, of which 3 showed the same mutation in cDNA. A CD79b ITAM Y196 mutation was found at DNA and cDNA in 2 cases. Overall, seven out of 10 cases of PCLBCL-LT showed genetic alterations converging on the NF-κB pathway. These findings strongly suggest a role for constitutive activation of the NF-κB pathway in PCLBCL-LT and provide the rationale to explore the possibility of using specific therapy targeted at components of the NF-κB pathway in this type of lymphoma.

O-079

THE IMPORTANCE OF NOTCH SIGNALLING IN PERIPHERAL T-CELL LYMPHOMAS

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Deregulation of Notch signalling has been linked to the pathogenesis of several different kinds of cancers, including haematopoietic malignancies. We have previously demonstrated an increased expression of Notch1 in primary cutaneous T-cell lymphomas and that its' inhibition potently induces apoptosis. In this study, we focused on the expression of Notch-1 in other peripheral T-cell lymphomas (PTL). We performed immunohistochemical staining for Notch-1 in 52 cases of PTL, including 33 patients with PTL not otherwise specified (PTL NOS) and 19 patients with systemic anaplastic large cell lymphoma (ALCL). Five cases had primary manifestation of PTL in the skin.
Of the 19 cases with systemic ALCL, 11 were positive and 8 were devoid of the ALK protein. Notch1 labeling in tumor cells was scored as negative (no visible staining or positive staining in <10%), moderately positive (positive staining in 10–50% of the tumor cells) and positive in a majority (>50%) of the tumor cells. We found that the distribution of Notch-1 was the same among the 3 different categories analyzed: PTL NOS, ALCL ALK+ and ALCL ALK-. The percentage of biopsies with negative, moderate and strong Notch-1 was respectively 21%, 26% and 53% for PTL NOS, respectively 9%, 18% and 73% for ALCL ALK+ and respectively 25%, 50% and 25% for ALCL ALK- (p>0.05 determined by Kruskal-Wallis test for non-parametric data). In regard to the functional consequences of Notch inhibition in cultured cells derived from PTL, we focused on the cell line Karpas-299 (ALK-+ ALCL cell line). We demonstrated that pharmacological inhibition of Notch signalling with gamma-secretase inhibitor (GSI) I (EC_{50}=0.48□M) is far more potent than GSI IX, XX and XXI (EC_{50}>20□M) in regard to cell viability and induces apoptosis. The mechanism of action for GSI I involved proteasome inhibition. In conclusion, there is a prominent expression of Notch-1 on tumor cells derived from PTL and a cytotoxic effect of treatment with Notch inhibitors.

O-080

THREE COMPONENTS OF TOX-RUNX3 PATHWAY ARE DIFFERENTIALLY EXPRESSED IN CTCL

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Though studies have examined gene expression changes in Sézary syndrome (SS), the pathogenesis of the disease remains largely unknown. TOX is a transcription factor involved in CD4+ T-cell development during which it increases the expression of ThPOK, a zinc-finger transcriptional regulator which in turn represses RUNX3, a known tumor suppressor gene. GATA3, an important regulator of T-cell development and promoter of Th2 responses, also contributes ThPOK upregulation and RUNX3 downregulation. Upregulation of GATA3 was previously shown in CTCL.

Here we sought to evaluate malignant lymphocytes of MF and SS patients for expression of factors responsible for RUNX3 downregulation, specifically TOX and GATA3. We also evaluated TOX protein expression in routine biopsy specimen from patients with MF/SS by immunohistochemistry (IHC) to assess its suitability as a diagnostic marker.
We previously demonstrated with sequencing-based transcriptome analysis that TOX is upregulated in CD4+ T-cells from SS and MF patients. Using qRT-PCR we confirmed upregulation of both TOX and GATA3 in malignant lymphocytes isolated from peripheral blood of SS patients, while RUNX3 expression was consistently downregulated. Moreover, TOX and RUNX3 expression were significantly inversely proportional. ThPOK expression in SS CD4+ cells did not vary significantly compared with controls. To assess TOX protein expression and its suitability as a biomarker, we performed IHC staining for TOX protein in MF/SS skin biopsies. We observed a non-uniform nuclear staining of the infiltrates, suggesting that TOX may be a candidate diagnostic biomarker for MF and SS.
Evaluation of gene expression in the ↑TOX→↓RUNX3←↑GATA3 pathway revealed that three components are differentially expressed in CTCL, implicating this pathway as a component of disease pathogenesis and a potential therapeutic target. Prospective studies validating our findings and evaluating usefulness of TOX as a disease marker are warranted.

O-081

REGULATION OF APOPTOSIS BY BCL-2 PROTEINS

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No abstract available.

O-082

APOPTOSIS REGULATION IN CUTANEOUS T-CELL LYMPHOMA: CRITICAL ROLES OF TRAIL RESISTANCE, CFLIP EXPRESSION AND LACK OF BID

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Suppression of apoptosis is critical in cancerogenesis, and therapeutic strategies aim at an induction of apoptosis or an overcoming of apoptosis deficiency. Extrinsic proapoptotic pathways are induced by binding of death ligands (TNF-α, CD95L/FasL, TRAIL) to death receptors, formation of death-inducing signaling complexes and activation of a caspase-8/caspase-3 cascade. Intrinsic apoptosis pathways enclose mitochondrial activation, controlled by Bcl-2 proteins, and activate a caspase-9/caspase-3 cascade. Death ligands may also trigger intrinsic pathways due to caspase-8-mediated processing of the proapoptotic Bcl-2 protein Bid. Proapoptotic pathways may be interrupted at defined levels, enclosing expression of cFLIP (cellular FLICE-inhibitory protein), which blocks caspase-8, by cIAPs (inhibitory proteins of apoptosis), which block caspase-3 or by changes of pro- and antiapoptotic Bcl-2 proteins. Our studies have proven the decisive role of extrinsic apoptosis pathways in cutaneous T-cell lymphoma (CTCL). Thus, 8/8 CTCL cell lines revealed expression of cFLIP, and activation of mitochondrial pathways by death ligands was further abrogated by lacking Bid expression (5/8 cell lines). These changes correlated with resistance to the death ligand TRAIL. The critical role of cFLIP in suppressing apoptosis in CTCL became obvious by applying different drugs in cell culture. Both SAHA (suberoylanilide hydroxamic acid) and NSAIDs (acetylsalicylic acid, sodium salicylate, diclofenac) strongly induced apoptosis and decreased CTCL cell proliferation. Importantly, they resulted in significant downregulation of cFLIP, and the proapoptotic effects were prevented by retroviral cFLIP overexpression. Also intrinsic apoptosis pathways were activated, as seen by caspase-9 processing, loss of mitochondrial membrane potential and cytochrome c release, which correlated to downregulation of the antiapoptotic Bcl-2 protein Mcl-1. Comparable proapoptotic responses were obtained in ex vivo tumor cells of CTCL patients. These studies provide an understanding on CTCL apoptosis resistance and on the mode of action of therapeutic drugs. FLIP appears as a marker for monitoring proapoptotic efficacy.

O-083

HSP 70 KDA PROTEIN 1A INHIBITS HISTONE DEACETYLASE INHIBITOR-INDUCED APOPTOSIS THROUGH MITOCHONDRIAL PATHWAY

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The anticancer effects of histone deacetylase inhibitors (HDACi) are often limited, while its molecular background is largely unknown. To reveal the molecular mechanisms of response to anticancer effects of HDACi, we investigated proteomic features of the 33 lymphoid cell lines, which exhibited the different sensitivity to the valproic acid (VPA). The expression level of 10 protein species (8 unique genes) showed the significant correlation with chemosensitivity. Among these protein species, heat shock 70 kDa protein 1A (HSPA1A, also known as HSP72) was further examined because it showed the most dominant up-regulation in the resistant cell line group. First, we examined the combined effects of HDACi and a heat shock protein inhibitor, KNK437. Treatment with KNK437 alone did not have cytotoxic effects on either Jurkat (sensitive cell) or TL-SU (resistant cell). In contrast, cotreatments with VPA and KNK437 resulted in considerable increase of annexin V-positive cells, compared with the treatments with VPA alone. KNK437 also significantly enhanced the apoptotic effects of vorinostat. Next, we established stably transfected Jurkat cells, and assessed the functional role of HSPA1A in HDACi (vorinostat and VPA) treatment. HDACi-induced apoptosis, detected by annexin V assay, active caspase-3 staining, cleaved PARP and subG1 fraction, were significantly decreased in HSPA1A overexpressed cells compared to MOCK cells. HDACi-induced upregulation of caspase-9 activity and reduction of mitochondrial membrane potential were also suppressed. Bad, a proapoptotic molecule, expression was increased after treatment in control cells, while that in the transfected cells was not changed. On the other hand, base line level of bcl-2, phosphorylated bad and X-linked inhibitor-of-apoptosis

protein expression was increased in transfected cells. In conclusion, HSPA1A inhibit HDACi-induced apoptosis through intrinsic apoptotic pathway.

O-084

TAX CAN INDUCE PD-1 EXPRESSION BUT APOPTOSIS IS INHIBITED BY PD-1 PROMOTER METHYLATION IN HTLV-1-INFECTED T CELLS

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The engagement of programmed cell death-1 (PD-1) and its ligands contribute directly to T-cell dysfunction. However, it remains unclear whether human T-lymphotropic virus type 1 (HTLV-1) or its oncogene Tax can regulate PD-1 expression and how malignant t-cells can expand despite their PD-1 expression. To elucidate these issues, we used JPX-9 cells, expressing Tax under the control of Cd2+ inducible promoter, and MT-2 cells, a representative HTLV-1-infected cell line. Since PD-1 is involved in apoptosis, the role of Tax or HTLV-1 was evaluated in an UVB-induced apoptotic condition. In UVB-irradiated JPX-9 cells, Tax augmented apoptosis with increased expression of PD-1 and caspase-3. Despite HTLV-1 integration and Tax expression, however, MT-2 cells showed neither enhanced apoptosis nor augmented expression of PD-1 upon UVB irradiation. To address the mechanisms underlying the apoptosis resistance of MT-2 cells, we then investigated PD-1 gene methylation and found that PD-1 promoter region was methylated in MT-2 cells. Furthermore, PD-1 expression in UVB-irradiated MT-2 cells was significantly increased by pretreatment with DNA demethylation agent. These results suggest that Tax can induce apoptosis via PD-1, but apoptosis may be inhibited in HTLV-1-infected cells by downregulation of PD-1 due to DNA methylation of its promoter region.

O-085

CUTANEOUS T-CELL LYMPHOMA CELLS RELEASE PROAPOPTOTIC FAS LIGAND (CD178) IN LYSOSOMAL SECRETORY VESICLES

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Although the expression of the death-promoting molecule CD95L/CD178 by cutaneous t-cell lymphomas (CTCL) has already been described, the subcellular localisation and the functional consequences of this expression remain unknown. We investigated herein the synthesis and the presence of FasL/CD178 in the secretory vesicles of tumor CTCL cells, and its proapoptotic properties in vitro. CTCL cell lines and peripheral blood lymphocytes (PBL) isolated from circulating blood of patients with Sezary Syndrome (SS), the leukemic variant of CTCL, were stimulated by PMA and ionomycine for 16h. Microvesicule fractions were obtained after ultracentrifugation of cell supernatants. The presence of microvesicle-associated FasL was studied by Western blots and immunoelectron microscopy. Biological activities of microvesicles were tested including the ability to induce apoptosis of Jurkat cells. Our results confirm synthesis of FasL/CD178 by malignant SS cells as shown by qRT-PCR. Flow cytometry analysis allowed detection of intracellular expression of FasL/CD178, but not at the cell membrane of PB-malignant cells from SS patients and in CTCL lines. Confocal microscopic analysis of CD95L//CD178 and CD63 double staining showed that intracellular FasL/CD178 colocalised with the lysosomal secretory vesicles. Immunoelectronic microscopy confirmed lysosomal FasL/CD178 expression and evidenced a staining under cell membrane. Western-blot analysis of ultracentrifugated supernatant from PMA/ionomycin-stimulated CTCL lines and PBLs from SS patients showed predominant expression of the 37KDa form of FasL/CD178 in the exosomal fraction, while the soluble form was barely detected. Finally, we found that exosomal fractions from CTCL lines and PB-malignant cells were able to induce apoptosis of the Fas-expressing Jurkat cell line, as shown by flow cytometry analysis of annexin staining. Therefore, bioactive FasL expressed in lysosomal secretory vesicles of CTCL induce apoptosis following release.

O-086

PHASE II TRIAL OF BRENTUXIMAB VEDOTIN (SGN-35) FOR CD30+ CUTANEOUS T-CELL LYMPHOMAS AND LYMPHOPROLIFERATIVE DISORDERS

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Brentuximab vedotin (SGN-35), a CD30 monoclonal antibody (cAC10) conjugated to microtubule disrupting agent, monomethyl auristatin E (MMAE), targets the CD30 surface receptor. Safety and efficacy of SGN-35 was evaluated in a Phase II open-label trial conducted in CD30+ lymphoproliferative disorders (lymphomatoid papulosis (LyP) or primary cutaneous pc-ALCL) or CD30+ mycosis fungoides (MF) ± large cell transformation. SGN-35 dosing was 1.8 mg/kg for 30 min every 21 days for up to 8 doses or patients who responded or had stable disease could receive additional 8 doses. Response assessment required > 2 doses and a 50% decrease in active LyP number, pc-ALCL tumor measurement, or modified skin weighted assessment tool (MF). Twenty-one F and 25 M with median age of 59.5 years (range 31-86 years) were evaluable. Overall responses were seen in 31/46 (67.3%) with CR of 32% (15/46). LyP (n=9) and pc-ALCL (n=3) had 100% CR rates. Twenty-seven MF patients had ORR of 44% which varied based on low (<10%), medium (10-50%) or high (>50%) expression of CD30. Time to response for LyP and pc-ALCL was only 3 weeks (range 3-6); median duration of response (DOR) was 22 weeks (range 9-38). Time to response for MF was 12 wks (range 3-25); mDOR was 12 wks (range 6-48). Adverse events (related, any grade) were neuropathy (59%), drug rash (27%), diarrhea (22%), fatigue (30%), alopecia (14%), myalgias and nausea (18%). Grade 3-4 events were neutropenia (n=3), nausea (n=2), chest pain (n=2), deep vein thrombosis (n=1), transaminitis (n=1) and dehydration (n=1). Dose reductions to 1.2 mg/kg were for grade 2 neuropathy (n=15), and transaminitis, arthralgias, and fatigue (n=1 each). Withdrawals were for neuropathy (n=2), drug rash (n=3), lack of efficacy (n=1), and infusion

reaction (n=1). In conclusion, this phase II clinical trial demonstrates that Brentuximab vedotin is an effective, safe targeted therapy for CD30+ CTCLs - MF, pc-ALCL, and LyP with high overall response rate of 67.3%, including100% in LyP/pc-ALCL, and 44% in CD30+ patch/plaque MF regardless of CD30 expression.

O-087

PHASE 2 MULTICENTER TRIAL OF ORAL QUISINOSTAT, A HISTONE DEACETYLASE INHIBITOR, IN PATIENTS WITH PREVIOUSLY TREATED STAGE IB-IVA CUTANEOUS T-CELL LYMPHOMA

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BACKGROUND: Mycosis fungoides (MF) and Sézary syndrome (SS) are the most common variants of cutaneous T-cell lymphoma (CTCL). This phase 2 trial evaluated the efficacy and safety of quisinostat, a potent and orally active hydroxamate pan-histone deacetylase (HDAC) inhibitor, in patients with previously treated CTCL.
METHODS: Patients with relapsed or refractory, confirmed stages IB to IVA MF/SS were treated with oral quisinostat on days 1, 3 and 5 of each week in 21-day treatment cycles at 8 mg and 12mg, which was changed to 12mg after protocol amendment. The primary efficacy endpoint was overall cutaneous response rate (cRR) measured by the modified Severity Weighted Assessment Tool (mSWAT). Key secondary endpoints included global response rate (gRR), duration of response (DOR) in skin, pharmacodynamic markers, severity of pruritus, and safety profile.
RESULTS: The total 26 enrolled patients (8mg dose group: 6 patients, 12 mg dose group: 20 patients) included 81% males; median age=61 years (range 32-80 years); 96% white; MF/SS stage: IB/IIA=35% (n=9) and IIB/III/IVA=65% (n=17); CTCL type: MF=96% (n=25), and SS=4% (n=1); mean pruritus intensity score=5.1. Eight patients achieved ≥50% reduction in mSWAT score at least once, with confirmed cutaneous response in 6 patients: 1 complete response and 5 partial responses. The overall cRR=24%, with 95% CI: 9.4% to 45.1%. Gradual onset of response was observed. The gRR=23%, with 95% CI: 7.8% to 45.4%, and the DOR in skin ranged from 2.79 to 6.93 months. Stable disease lasting ≥12 weeks was observed in 28% of patients. A reduction in mSWAT score was associated with a decrease in pruritus intensity.

The most common (≥5% of patients) drug-related adverse events have been nausea (23%), diarrhea (19%), asthenia (15%), hypertension (12%), thrombocytopenia (12%), vomiting (12%), lethargy (8%), palpitations (8%), and pruritus (8%). There were no observations of dose limiting neutropenia or thrombocytopenia, or ≥Grade 2 QTc prolongation. Serial tumor biopsies revealed an increase in acetylated tubulin, indicating a target effect of HDAC6.
CONCLUSION: Quisinostat at 12 mg dose on a 3 times weekly schedule is active in the treatment of patients with relapsed or refractory MF/SS, and has an acceptable safety profile.

O-088

BRENTUXIMAB VEDOTIN DEMONSTRATES CLINICAL ACTIVITY IN MYCOSIS FUNGOIDES (MF) AND SEZARY SYNDROME (SS) IRRESPECTIVE OF TISSUE CD30 EXPRESSION BY ROUTINE IMMUNOHISTOSTAINING

MICHAEL S KRATHEN[1], SAMEER BASHEY[1], KATRIN SALVA[2], GARY WOOD[2], UMA SUNDRAM[1], SEEMA NAGPAL[1], RANJANI ADVANI[1], RICHARD HOPPE[1], SUNIL REDDY[1], MELISSA PULITZER[3], STEVEN HORWITZ[3], YOUN H KIM[1]

[1] Stanford Cancer Institute, Stanford University Medical Center, [2] Department of Dermatology, University of Wisconsin, [3] Memorial Sloan-Kettering Cancer Center

We explored the clinical activity of brentuximab vedotin in MF/SS irrespective of baseline CD30 immunohistochemistry expression levels. Patients age≥18 with MF/SS stages IB-IV, ECOG≤2, and failing at least 1 prior systemic therapy were enrolled in this investigator-initiated, phase II, single-arm exploratory study. Subjects were treated with planned 8 cycles of brentuximab vedotin (1.8 mg/kg) with optional extension for responders. Independent review confirmed responses.
20 subjects, the majority with advanced disease and/or adverse prognostic risk factors, were consented and received at least one dose of BV; median age was 59.5y (range 20-88) with median of 4 prior systemic therapies (range: 1-15).
The overall response rate was 70% (14/20). Median best mSWAT reduction was 65%. Responses were observed in all clinical stages. Median time to response was 6 weeks (range 3-18). Kaplan-Meier (KM) estimates at 6 months demonstrate 78% of responses ongoing with median follow-up 46 weeks (range 6-66). The median event free survival (excludes topical steroid use) was 31 weeks (range 4-61+). Related grade 1 or 2 adverse events (AEs) occurring in >20% were peripheral neuropathy (70%), fatigue (60%), decreased appetite (30%), and nausea (25%). The most frequent related grade 3-4 AEs included neutropenia and rash. Quantitative multi-spectral image analysis (Nuance imaging system, CRi, Woburn, MA) identified CD30 expression above background in 9/9 screening biopsies initially read as 'non-detectable' per routine IHC. Clinical response did not correlate with CD30 expression levels by routine IHC (p>0.99) nor image analysis (p=0.71).
Our exploratory study demonstrates significant clinical activity of brentuximab vedotin in heavily pre-treated MF/SS with mostly grade 1/2 related AEs. Clinical responses were observed throughout spectrum of CD30 expression levels. Target detection by multispectral image analysis is more sensitive and quantitative than routine IHC.

O-089

MULTICENTER, RANDOMIZED, PHASE I/II STUDY EVALUATING THE SAFETY AND EFFICACY OF LOW-DOSE TOTAL SKIN ELECTRON BEAM THERAPY (TSEBT) VS. LOW-DOSE TSEBT COMBINED WITH VORINOSTAT IN MYCOSIS FUNGOIDES

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Low-dose (10-15 Gy) TSEBT produces reliable and efficient responses with minimal toxicity in MF. This multicenter study was designed to investigate the potential TSEBT-enhancing clinical activity of vorinostat (Vor), and the safety of the combination therapy.
TSEBT naive patients with MF stages IB-IIIB who failed 1 prior treatment were eligible. Patients were randomized by stage and institution to receive TSEBT ± Vor. Patients received TSEBT (12Gy in 1 Gy fractions over 3 wks) ± Vor 400mg daily for 8 wks. In the TSEBT arm (n=14) the median age was 59 yrs (26-73 yrs); 7 male; 9 stage IB, 2 IIA, 2 IIB, 1 III; 3 large cell transformation (LCT), and 4 folliculotropic MF (F-MF). In the TSEBT+ Vor arm (n=13), median age was 53yrs (37–65 yrs); 7 male; 8 stage IB, 2 IIA, 2 IIB, 1 III; 2 LCT, and 2 F-MF. Primary endpoint was complete response (CR) at wk 8. Unplanned interim analysis revealed 71% (10/14) response rate (RR) with 36% CR in TSEBT arm vs. 85% RR (11/13) with 23% CR in TSEBT + Vor arm. A new endpoint, duration of clinical benefit (DOCB), defined as the duration from response to initiation of next "TSEBT equivalent treatment" (whole-body topical therapy, phototherapy, systemic therapy) or progressive disease. Median DOCB for TSEBT vs. TSEBT + Vor was 91 vs. 28 wks, respectively (p=0.037). Kaplan-Meier estimate of those maintaining clinical benefit at 6 months was 86% in TSEBT vs. 67% in TSEBT + Vor. Median event-free survival of TSEBT vs. TSEBT+ Vor was 99 vs. 34 wks (p=0.080). No significant differences in the number or severity of radiation-related adverse events (AE's) were noted: radiation dermatitis (p=0.33), alopecia (p=0.24), nail changes (p=0.33), extremity pain (p=0.45), and xerosis (p=0.60). Treatment related AE's were all grade 1-2.
At present, our data support that the combination of low-dose TSEBT + Vor is well tolerated without increased radiation toxicity; however, a radiation-enhancing clinical activity or benefit is not demonstrated.

O-090

IMMUNOMODULATORY EFFECTS OF LENALIDOMIDE: RESULTS FROM A MULTICENTER PHASE II TRIAL

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Lenalidomide has demonstrated clinical activity in CTCL. In a phase II trial with heavily pretreated CTCL patients the overall response rate with single agent lenalidomide was 32% (9 patients). Similar to findings observed in CLL patients, one of the key features of lenalidomide's clinical activity in CTCL is that patients tolerate poorly the dose (25mg) used in other hematologic malignancies such as multiple myeloma. A contributing factor to this difference is a "tumor flare" reaction. A significant number of CTCL patients (25%) experienced a tumor flare after starting treatment with lenalidomide, characterized by increased circulating Sezary cell counts, lymphadenopathy and/or associated inflammation of skin lesions. Seven patients went off study as a result of constitutional symptoms noted within several wks of drug initiation. Therefore, gradual dose escalation may be an alternative strategy. The tumor flare reaction, however, appeared to correlate with clinical outcome suggesting that mechanisms underlying these reactions may present an anti-tumor response. We evaluated the immunologic component of blood samples and skin lesions in 10 patients treated after one month of lenalidomide and compared to baseline data. Our data suggest that the immunomodulatory effects of lenalidomide could be associated with decreased circulating CD25+ T-cells and correlated with decreased CD4+ T-cell number in peripheral blood samples. In contrast, the skin lesions showed a trend for increased CD25 and FoxP3 expression with decreased CD4:CD8 ratios. There was also a decrease in mast cells (CD117+), but no change in other immunologic cells such as Langerhans cells, or dendritic cell subsets. The decline in circulating CD25+ T-cells and CD4+ T-cells may represent a direct cytotoxic impact against CTCL and/or an effect on normal T-cells influencing the response. Future investigations will focus on co-stimulatory molecules which may help explain the phenomena.

Congress Venue
Langenbeck-Virchow-Haus
Luisenstrasse 58/59
10117 Berlin

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Registration
You can register for the conference on-site. The registration desk is located in the foyer on the ground floor to the following opening hours:

Opening Hours

Wednesday, February 6, 2013	11:30–21:00
Thursday, February 7, 2013	07:30–19:00
Friday, February 8, 2013	07:30–19:00
Saturday, February 9, 2013	07:30–14:40

Times are subject to change

Registration Fees

Member of ISCL/USCLC	€ 360.–
Non-Member of ISCL/USCLC	€ 480.–
Trainee*	€ 180.–
Students*	€ 180.–
Accompanying Person	€ 40.–

**I certify to be entitled to the reduced registration fee. An appropriate proof of status is attached to the registration form.*

The registration fee includes tuition for the 3.5 day conference, the welcome reception (Thursday), handout materials, lunch snack (Thursday–Saturday) and the German VAT. Accompanying persons are not allowed access to the scientific program.

Name Badge
The badge will be the official meeting document and should be worn at all times in order to access the meeting rooms and the exhibition hall. Name changes will be charged with € 16.– per registration. In case of lost or forgotten badges, an administration fee of € 16.– will be charged.

Cloakroom
The cloakroom is located in the foyer on the ground floor to the following opening hours:

Opening Hours

Wednesday, February 6, 2013	11:30–22:00
Thursday, February 7, 2013	07:30–22:30
Friday, February 8, 2013	07:30–19:30
Saturday, February 9, 2013	07:30–15:00

Industrial Exhibition
The industrial exhibition is located in the Foyer on the ground floor.

Opening Hours

Wednesday, February 6, 2013	13:00–22:00
Thursday, February 7, 2013	08:00–19:00
Friday, February 8, 2013	08:00–19:00
Saturday, February 9, 2013	08:00–15:00

GENERAL INFORMATION

Media Check
The media check is located in the "Referentenraum" on the first floor and is equipped with computer projection. Speakers are asked to hand in their presentations at least 3 hours before their talk. Speaker holding their presentation during the first time slot in the morning are asked to hand in their slides the day before.

Opening Hours

Wednesday, February 6, 2013	12:00–19:00
Thursday, February 7, 2013	07:30–19:00
Friday, February 8, 2013	07:30–19:00
Saturday, February 9, 2013	07:30–13:00

Times are subject to change

Poster Session
Posters shall be prepared in DIN A0, portrait format and in English language. Scientific posters will be displayed in the foyer on the second floor. Posters should be mounted on Wednesday, February 6, 2013 by 13:00 and will remain accessible to all attendees until Saturday, February 9, 2013, 13:00.

Certificate of Attendance
All registered participants receive a certificate of attendance.

Catering
Beverages and lunch snacks will be served from designated stations in the foyer.

Program Changes
The organizer reserves the right to make changes if necessary. No full or partial refunds are available in the event of cancellations by speakers or other change in the main program. Please note that changes will be posted at the registration desk and at the entrance of the session halls. The participants will be informed about the changes.

Smoking
Smoking is prohibited within the congress center.

Emergency and First Aid
In any case of emergency please contact the local organizer in the foyer or call 112.

Important Dates

Wednesday, February 6, 2013	13:00–13:15	Welcome
Wednesday, February 6, 2013	19:00	Poster Sessions & Get Together
Thursday, February 7, 2013	12:15–13:45	Symposium TEVA
Friday, February 8, 2013	12:30–13:30	Lunch Symposium Takeda Millennium
Friday, February 8, 2013	19:30	Conference Dinner
Saturday, February 9, 2013	13:45–14:00	Valediction

GENERAL INFORMATION

Congress Venue

Langenbeck-Virchow-Haus
Luisenstrasse 58/59
10117 Berlin

Arriving by Plane

Airport Berlin Tegel

- From Tegel Airport take the TXL bus to "Karlplatz"; from here it is approx. 3 minutes by foot in the direction of the Charité.

Airport Schönefeld

- From Airport Schönefeld you can take the train in the direction "Nauen" until the train station "Friedrichstrasse". From here you can take the bus 147 in the direction "Hauptbahnhof" until "Charité – Campus Mitte". The station is directly in front of the Langenbeck-Virchow-Haus.

Arriving by Train

- From "Hauptbahnhof" you can take the bus 147 in the direction "Friedrichstrasse".
- From "Friedrichstrasse" you can take bus 147 in the direction "Hauptbahnhof".
- The station is directly in front of the Langenbeck-Virchow-Haus.

Arriving by Car

- You can take the motorway A100 driving north. Please use the exit *Kaiserdamm* in direction *Ernst-Reuter-Platz*. Please use the second exit to *Berliner Siegesäule* and leave the roundabout through the second exit to *Brandenburger Tor*. Turn left into *Ebertstrasse* and the next right again into *Dorothenstrasse*. After that please turn left at the next street and go straight on to Langenbeck-Virchow-Haus.
- You can take the motorway A114/ B109 driving south. Turn right from the *Prenzlauer Alle* into *Torstrasse*. Turn left into *Friedrichstrasse* and please use the second exit right into *Reinhardstrasse*. Then use the second right to Langenbeck-Virchow-Haus.

Please note that the Langenbeck-Virchow-Haus does not have any parking facilities.

Taxi

Phone: +49 (0)30 21 01 01

Transfer times by taxi:

- Airport Berlin Tegel: approx. 20 minutes
- Airport Schönefeld: approx. 50–60 minutes

INTERNATIONAL SOCIETY FOR CUTANEOUS LYMPHOMAS

Membership Application Form

The International Society for Cutaneous Lymphomas (ISCL) was organized in December 1992 to foster communication and stimulate interactions among regional and national groups and individuals interested in cutaneous lymphomas. Membership Applications will be reviewed by the ISCL Board of Directors and the applicant will be notified of its decision by e-mail. Thank you for your interest in the ISCL.

General Member: Physician or scientist actively involved in the care of patients with lymphoproliferative skin disorders or engaged in research in this or a related area

Associate Member: Allied healthcare professional, an individual or entity that grants financial support to the Society or an individual involved in a cutaneous lymphoma patient support group who is interested in, and supports, the purposes of the Society

Resident Member: Physician in good standing who is in a residency program or post-residency fellowship and is interested in the field of cutaneous lymphoproliferative disorders

Check Category: ❑ General ❑ Associate ❑ Resident

Name: _____ Credentials (e.g., MD, PhD, MBBS): _____

Title: _____

Specialty: _____

Institution: _____

Street Address: _____

City: _____ State: _____

Country: _____ Postal/Zip Code: _____

E-mail: _____

Telephone: _____ Fax: _____
(include country code)

Number of cutaneous lymphoma patients followed: _____

Research Interests: _____

_____

Representative Publications: _____

_____

_____

Please send the completed application and application fee ($50, which also serves as first year's dues) to:

By mail and check (made out to: *International Society for Cutaneous Lymphomas*)
International Society for Cutaneous Lymphomas
303 West State Street
Geneva, IL 60134 USA

Electronically:
Submit payment of application fee by PayPal at www.cutaneouslymphoma.org and e-mail application to: info@cutaneouslymphoma.org

For questions, please e-mail Dr. Youn Kim, Secretary/Treasurer, at: younkim@stanford.edu

You will be notified of membership application status by email. Thank you!

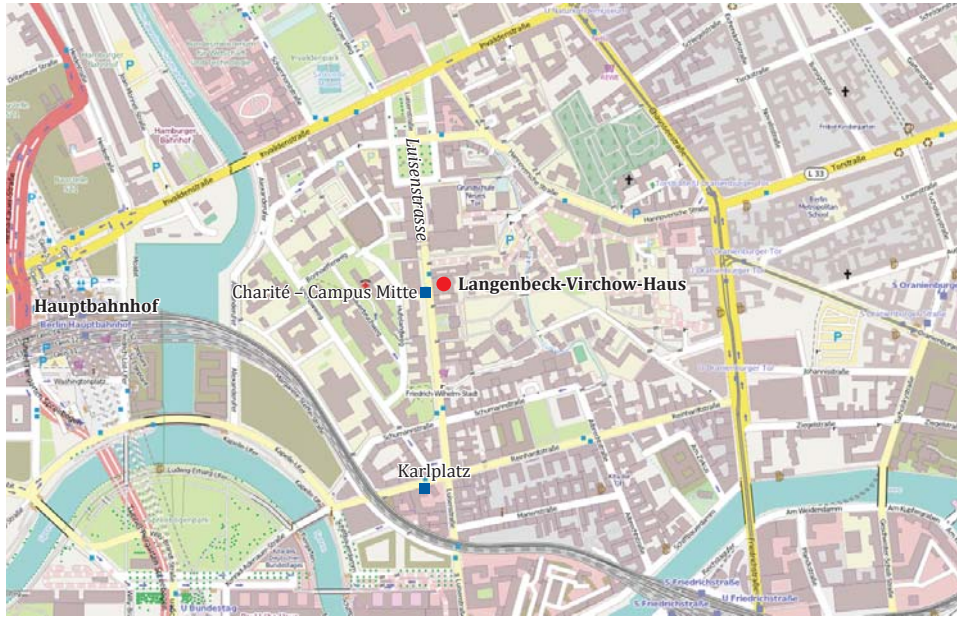
IMPRINT

Publisher
The International Program Committee
The Local Organizing Committee

Editors
The International Program Committee
The Local Organizing Committee
MCI Deutschland GmbH, Berlin

Graphic Design
MCI Deutschland GmbH, Berlin

Editorial Deadline
January 18, 2013



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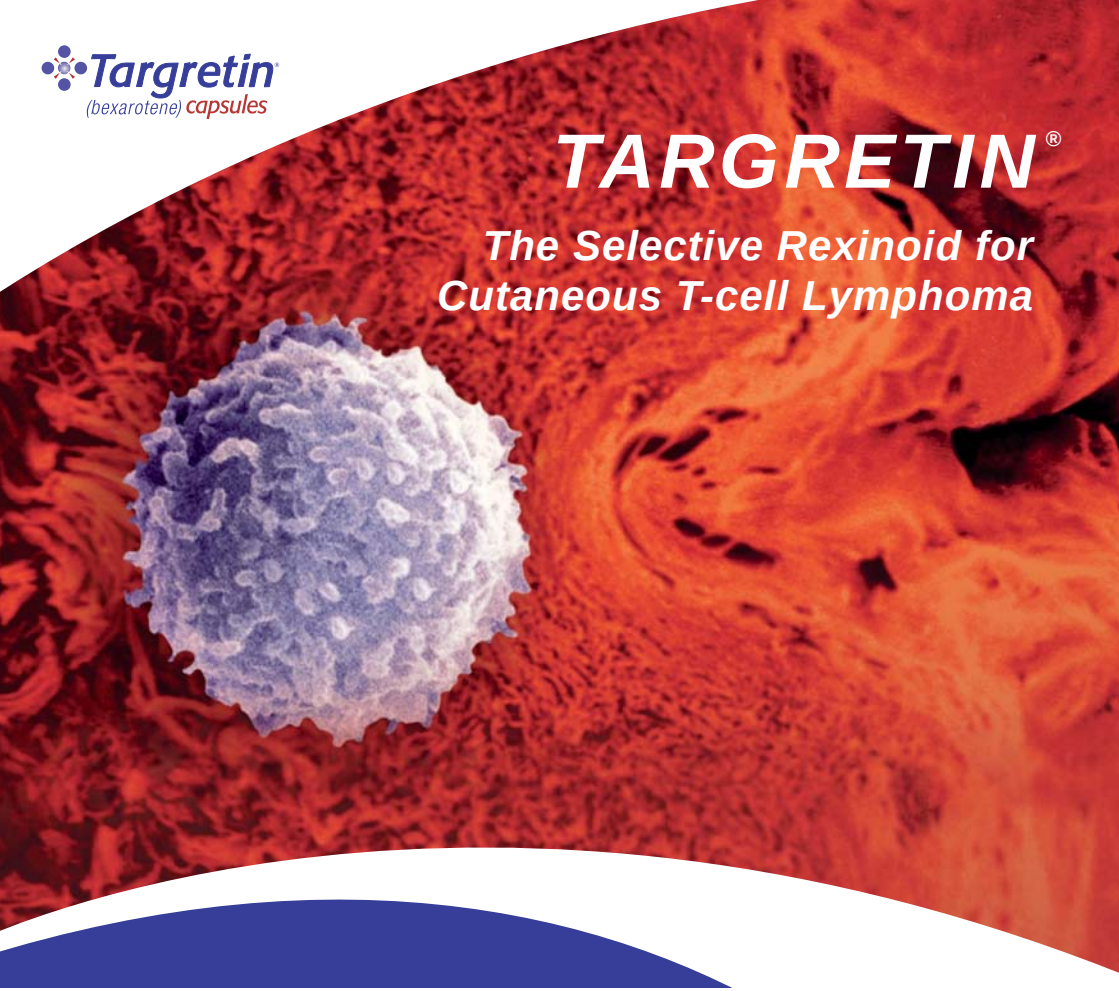
The Selective Rexinoid for Cutaneous T-cell Lymphoma



Targretin® 75 mg Weichkapseln. Wirkstoff: Bexaroten. **Zus.setzung:** Jede Kapsel enthält 75 mg Bexaroten. **Sonst. Bestandt.:** Kapselinhalt: Macrogol, Polysorbat 20, Povidon, Butylhydroxyanisol (Ph.Eur.); Kapselhülle: Gelatine, Sorbitol-Spezialglycerolmischung (Glycerol, Sorbitol, Sorbitolanhydrid (1,4-Sorbitan), Mannitol (Ph.Eur.), Wasser), Titandioxid (E 171), Druckertinte (SDA 35A Alkohol (Ethanol und Ethylacetat), Propylenglycol (E 1520), Eisen(II,III)-oxid (E 172), Polyvinylacetatphthalat, gereinigtes Wasser, Isopropylalkohol, Macrogol 400, Ammoniumhydroxid 28 %). **Anw.gebiete:** Zur Behandl. v. Hautmanifestationen b. Pat. mit CTCL im fortgeschr. Stadium, d. auf mind. eine system. Behandl. nicht angesprochen haben. **Gegenanzeigen:** Überempfindlichkeit gegen Bexaroten od. e. d. sonst. Bestandt., Schwangerschaft u. Stillzeit, Frauen im gebärfähigen Alter ohne effektive Empfängnisverhütung, Vorgeschichte e. Pankreatitis, unkontrollierte Hypercholesterinämie/Hypertriglyceridämie, Hypervitaminose A, unkontrollierte Schilddrüsenerkrank., Leberinsuff., bestehende system. Infekt. **Nebenw.:** Sehr häufig: Leukopenie, Hypothyreose, Hyperlipämie, Hypercholesterinämie, exfoliative Dermatitis, Pruritus, Hautausschlag, Schmerzen, Kopfschmerzen, Asthenie; Häufig: lymphomähnl. Reakt., Lymphadenopathie, hypochrome Anämie1,2,3, Stör. d. Schilddrüsenfkt., Gewichtszunahme, erhöh. GOT, erhöh. GPT, erhöh. LDH, erhöh. Kreatinin, Hypoproteinämie, Schwindelgefühl, Hypästhesie, Schlaflosigkeit, trockene Augen, Augenstör., Taubheit, periph. Ödem, Erbrechen, Diarrhoe1,3, Übelkeit3, Anorexie1, abnormale Leberfkts.tests, Cheilitis2, trockener Mund2,3, Verstopfung, Blähungen, Hautulzera, Alopezie1, Hypertrophie d. Haut, Hautknötchen, Akne, Schwitzen, trockene Haut2,3, Hautstör., Knochenschmerzen, Arthralgie, Myalgie, allerg. Reakt., Infekt., Schüttelfrost1, Bauchschmerzen, veränd. Hormonspiegel1; Gelegentlich: Blutdyskrasie, Purpura, Koagulationsstör., erhöh. Koagulationszeit2,3, Anämie1, Thrombozytopenie3, Thrombozythämie, Eosinophilie1, Leukozytose2, Lymphozytose, Hyperthyreose, Gicht, Bilirubinämie1,3, erhöh. Bluthamstoffwerte1, herabgesetztes HDL, Ataxie, Neuropathie, Gleichgewichtsstör., Hyperästhesie, Depression1,2,3, Erregung, spez. Linsentrübung1,2,3, Amblyopie3, Gesichtsfeldausfall, Hornhautverletzung, abnorm. Sehvermögen1,2,3, Blepharitis, Bindehautentzünd.3, Ohrenstör., Tachykardie, Hämorrhagien, Bluthochdruck, Ödem3, Vasodilatation1,2,3, Krampfadern, Pankreatitis1,3, Leberversagen, gastrointest. Stör.1, seröse Wundabsonderungen1, Herpes simplex, pustulöser Ausschlag, Hautverfärbung3, Haar-1, Nagelstör.1,3, Myasthenie1, Albuminurie1,3, abnorm. Nierenfkt., Neoplasma, Fieber1,2,3, Cellulitis, Parasiteninfekt., Stör. d. Schleimhäute3, Rückenschmerzen1,2,3, abnorm. Laborergebnisse [1NW mit erhöh. Häufigkeit festgestellt, wenn Bexaroten-Dos. > 300 mg/m2/Tag; 2NW mit erhöh. Häufigkeit festgestellt, wenn Bexaroten-Dos. > 300 mg/m2/Tag an Tumorpat. ohne CTCL; 3NW mit erhöh. Häufigkeit festgestellt, wenn Bexaroten-Dos. > 300 mg/m2/Tag (im Vergl. zur Verabreichung e. Dos. v. 300 mg/m2/Tag an Pat. mit CTCL) an Tumorpat. ohne CTCL]; NW b. Anfangsdos. >300 mg/m2/Tag od. b. Tumorind. ohne CTCL: Neu beobacht.: Ekchymose, Petechien, abnorm. Leukozyten, herabgesetztes Thromboplastin, abnorm. Erythrozyten, Dehydratation, erhöh. gonadotropes LH, Gewichtsverlust, erhöh. alkal. Phosphatase, erhöh. Kreatininphosphokinase, erhöh. Lipase, Hyperkalzämie, Migräne, periph. Neuritis, Parästhesie, Hypertonie, Verwirrung, Angstzustände, emotion. Labilität, Schläfrigkeit, herabgesetzte Libido, Nervosität, Nachtblindheit, Nystagmus, Tränenflussstör., Tinnitus, Geschmackssinnstör., Brustschmerzen, Arrhythmie, periph. Gefäßstör., allg. Ödem, Hämoptyse, Dyspnoe, verstärkter Hustenreiz, Sinusitis, Pharyngitis, Dysphagie, Mundulzerierungen, orale Moniliasis, Stomatitis, Dyspepsie, Durst, abnorm. Stuhl, Aufstoßen, Ausschlag (vesikobullöser, makulopapulärer), Beinkrämpfe, Hämaturie, Grippesyndr., Beckenschmerzen, Körpergeruch; Vereinzelte Berichte: Knochenmarkdepressionen, herabgesetztes Prothrombin, herabgesetztes gonadotropes LH, erhöh. Amylase, Hyponatriämie, Hypokaliämie, Hyperurikämie, Hypocholesterinämie, Hypolipämie, Hypomagnesiämie, abnorm. Gang, Stupor, zirkumorale Parästhesie, abnorm. Denken, Augenschmerzen, Hypovolämie, Subduralhämatom, kongestive Herzinsuff., Palpitation, Epistaxis, Gefäßanomalien u.-stör., Blässe, Pneumonie, Erkrank. d. Atemwege, Lungen- u. Brustfellerkrank., Cholezystitis, Leberschäden, (Cholestase-) Ikterus, Teerstuhl, Erbrechen, Laryngismus, Tenesmus, Rhinitis, erhöh. Appetit, Gingivitis, Herpes zoster, Psoriasis, Furunkulose, Kontaktdermatitis, Seborrhoe, flechtenähnl. Dermatitis, Arthritis, Gelenkerkrank., Urinretention, gestör. Harnlassen, Polyurie, Nykturie, Impotenz, Urinabnormalitäten, Brustvergrößerung, Karzinom, photosensible Reakt., Gesichtsödem, Unwohlsein, Virusinfekt., geschwollenes Abdomen. Verkehrshinweis! **Verschreibungspflichtig. Zulassungsinhaber:** Eisai Ltd., European Knowledge Centre, Mosquito Way, Hatfield, Hertfordshire, AL10 9SN, Vereinigtes Königreich. **Örtlicher Vertreter:** Teva GmbH, Graf-Arco-Str. 3, 89079 Ulm. Stand: April 2009.

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