Overexpression of STAT4 at early stages of mycosis fungoides: coincidence or not?

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INTRODUCTION

Mycosis fungoides (MF) is the most common subtype of cutaneous T-cell lymphomas (CTCL). The early diagnosis of MF is challenging due to the existence of different clinical forms and absence of definitive diagnostic criteria.[1,2] The molecular pathogenesis of CTCL is only partially understood.[3-7] Activation of the signal transducers and activators of transcription (STAT) protein family has been involved in the pathogenesis of leukemias, Hodgkin lymphomas and CTCL.[2-5] In particular, STAT4 is essential for T-helper (Th) 1 differentiation which is induced by IL-12 cytokine. Previous studies showed that expression of STAT3, STAT4 and STAT5 has potential diagnostic and prognostic value in CTCL patients.[7,8]

METHODS

In order to monitor T-cell infiltration, the expression of STAT4 was identified relative to CD3 expression. RNA expression of STAT4 and CD3 was evaluated by quantitative real-time PCR (qPCR) using FAM-labeled hydrolysis probes (Bio-Rad, USA) at the Laboratory for Medical Genetics, Sechenov University. To normalize the level of STAT4 gene expression in each individual sample, we used B2M and ACTB reference genes with stable expression during cell activity as endogenous control. Three replicates of each sample were examined to assess the reproducibility of the results.
A p value of 0.05 was chosen as a threshold for statistical significance. To detect statistically significant differences between the groups, the Mann-Whitney U test was used.

MEASURES

The study included patients with early MF (stages I-IIA; n=19), advanced MF (stages IIB-IV; n=10), benign dermatoses that may mimic CTCL (atopic dermatitis, chronic eczema, psoriasis) (n=13) and healthy controls (n=10). The patients received treatment in the Department of Dermatology and Venereology, Sechenov University, over the period of 2 years (2017–2019). MF was diagnosed using clinical examination and skin biopsies for histological, immunohistochemical and molecular tests. Molecular tests entailed detection of TCRγ gene rearrangement by PCR.

RESULTS

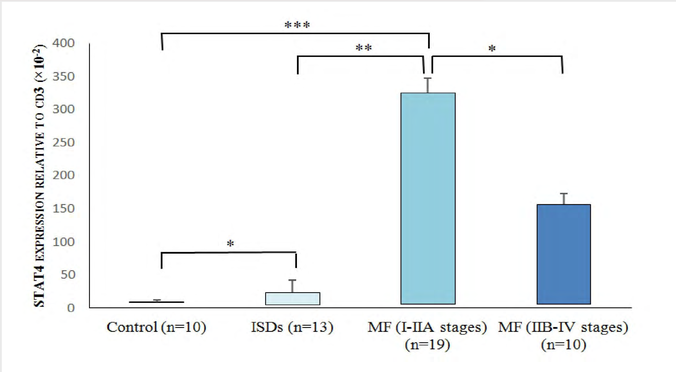

Figure 1: Quantitative real-time PCR expression of STAT4 relative to CD3 in healthy controls and patients with MF and benign dermatoses.

CONCLUSIONS

Our study showed that STAT4 was significantly elevated in early MF lesional skin compared to healthy skin ($p<0.001$), as well as benign dermatoses skin samples ($p<0.01$).
Litvinov I et al. showed that STAT signaling appears to play a central role in the pathogenesis of CTCL. They demonstrated that STAT4 is one of the targets for miR-155,[7] which provokes a switch from the Th1 to Th2 phenotype. At later stages, activation of STAT3 increases survival, resistance to apoptosis, expression of miR-21 and upregulation of IL-5 and IL-10 signaling, all working together to promote carcinogenesis.7 Johnson V et al. observed that increased expression of IL-4 and decreased expression of STAT4 and FOXP3 relative to CD3 expression levels were associated with progression of early MF.[8] Our results revealed no such correlation.
Thus, our pilot study showed that overexpression of STAT4 was associated with early stages of MF which means it may become a potentially useful diagnostic marker. However, our findings are limited by a small number of patients and single-center nature of the study. Further research may fully assess the utility of STAT4 in early diagnosis of MF.

BIBLIOGRAPHY

Differences in Th Phenotypes between Granulomatous and Classic Mycosis Fungoides

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INTRODUCTION

- Granulomatous Mycosis Fungoides (GMF) is a rare subtype of mycosis fungoides (MF) that histopathologically is characterized by a granulomatous infiltrate associated with the neoplastic lymphoid population
- GMF appears to have a poorer response to skin-directed therapy than classic MF (CMF)
- The pathophysiological mechanisms of the granulomatous reaction in MF are not elucidated
- We characterized the T helper profile by immunohistochemistry (IHC) of GMF and compared it with that of CMF

METHODS

- 52 patients: 30 GMF, 12 CMF, 10 MF with large cell transformation (MF-LCT)
- T helper profile was assessed by immuno-histochemistry, using Tbet (TBX21), GATA3, RORγT, and additional pathways were explored with Foxp3, PD-1, and PD-L1 antibodies
- The percentage of positive dermal cells (both neoplastic and from microenvironment) was evaluated by two pathologists and scored with 10% increments
- The intensity of the stain was recorded as 0+ (negative stain), 1+ (mild), 2+ (moderate), and 3+ (intense)
- Statistical differences in expression of Th markers were determined by Chi-square and Mann-Whitney test ($p<0.05$). Overall survival (OS) was estimated using the Kaplan-Meier method

RESULTS

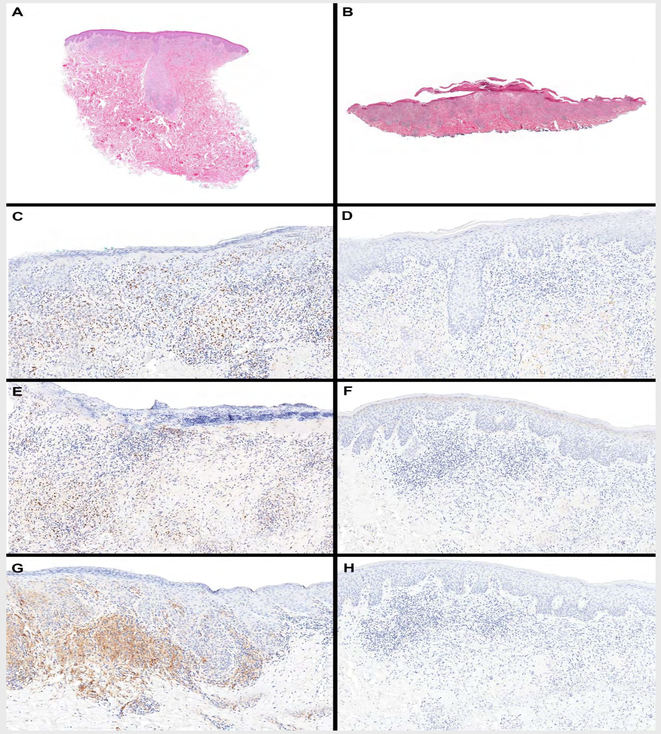

Figure 1. Histologic sections on panoramic view reveal dense dermal infiltrate composed of atypical lymphocytes and granulomas in GMF **(A)** while no granulomas are seen in the CMF **(B)** (H&E, 20x). A higher expression of Tbet **(C, D)**, RORγT **(E, F)**, and PD-L1 **(G, H)** is observed in GMF (immunohistochemistry, 100x).

Table 1. Baseline characteristics (age, sex, ethnicity, and medial overall survival) and median percentage of IHC expression of Tbet, GATA-3, RORγT, Foxp3, PD-1, PD-L1 in dermal cells in skin biopsies from patients with Classic Mycosis Fungoides/Mycosis Fungoides with large cell transformation, and Granulomatous Mycosis Fungoides.

	CMF and MF-LCT	GMF	p-value
Median Age (years)	61.5	64.5	p= 0.9231
Male:Female	1.1:1	1.4:1	p= 0.2810
Ethnicity			
Caucasian	16	16	p= 0.2840
African-American	4	9	p= 0.2355
Hispanic	1	1	p= 0.8771
N/A	1	4	N/A
% dermal positive cells, median (range)			
Tbet	0% (0-70%)	20% (0-70%)	***p= 0.0232***
GATA-3	40% (0-90%)	40% (0-80%)	p= 0.8556
RORγT	0% (0-60%)	20% (0-40%)	***p= 0.0008***
Foxp3	10% (0-60%)	20% (0-50%)	p= 0.0636
PD-1	10% (0-80%)	10% (0-80%)	p= 0.5271
PD-L1	0% (0-100%)	10% (0-90%)	***p= 0.0098***
Overall survival (OS) in months, median (95%CI)	71 months (54.8-87.1)	134 months (81.4-186.5)	***p= 0.009***

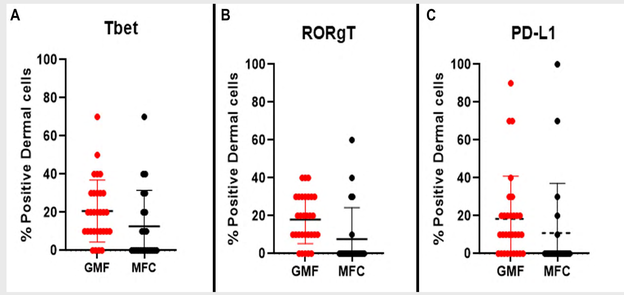

Figure 2. GMF cases showed higher expression of **(A)** Tbet (p= 0.0232), **(B)** RORγT (p= 0.0008), and **(C)** PD-L1 (p= 0.0098).

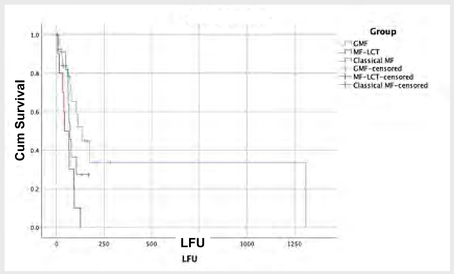

Figure 3. Kaplan-Meier curve shows better OS of GMF when compared to CMF and MF-LCT, p= 0.009.

CONCLUSIONS

- GMF shows upregulation of the axis Th1/Th17/PD-L1 in tumor cells and tumor microenvironment, in contrast to CMF
- In our series, GMF appears to have better OS survival than CMF and MF-LCT
- Th1 and Th17 phenotype, seen in early MF and granulomatous processes respectively, may explain the biological behavior of GMF
- Further studies involving larger series of cases and more sensitive techniques, such gene expression profiling, and single-cell RNA-sequencing assays are warranted

BIBLIOGRAPHY

Epidemiologic Trends of Mycosis Fungoides and Sezary Syndrome in Arkansas Reveal Increasing Incidence and Disparities

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INTRODUCTION

Cutaneous T-cell lymphomas (CTCL) are rare non-Hodgkin's lymphomas from skin-homing T cells, most represented by mycosis fungoides (MF) and Sezary syndrome (SS). With fluctuating population demographics in the US, we compare the population of MF and SS from 2013-2020 in Arkansas to the SEER's cohort representing 36% of the US population based on 2010 census from 2000-2017 to gain insight into trends in prevalence and incidence. We present demographics analysis from a single academic center in relation to the SEER database with the focus on updating trends to better understand geographic factors and other variables that affect disparities of this rare malignancy.

METHODS

A retrospective chart review of patients diagnosed from 2014 to 2020 at UAMS dermatology Clinic in Little Rock, Arkansas. 150 charts were reviewed.

Analysis was applied to national data obtained from 21 population-based cancer registries of the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute from 2000 through 2017. Criteria used for data selection: Malignant behavior, Known age, Site and morphology, Primary site = skin (codes 440-449), and ICD-O-3 Histology/behavior (codes): 9700/3: Mycosis fungoides, 9701/3: Sezary syndrome, and 9709/3: Primary cutaneous T-cell lymphoma.

Texas A&M Geoservices and Tableau Custom Geocoding were used to obtain and plot address geocodes on the map.

MEASURES

- Incidence and mortality rates are per 100,000 and age-adjusted to the 2000 US Standard Population (19 age groups - Census P25-1130) standard; Confidence intervals (Tiwari mod) are 95% for rates.
- For trends analysis, percent changes were calculated using 1 year for each end point
- APCs (Annual Percent Change) were calculated using weighted least squares method. Confidence intervals are 95% for trends.
- APCs were significantly different from zero ($p<0.05$).

RESULTS

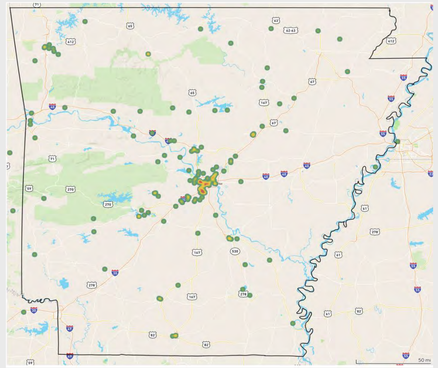

Figure 1: Spatial Distribution of patients in Arkansas

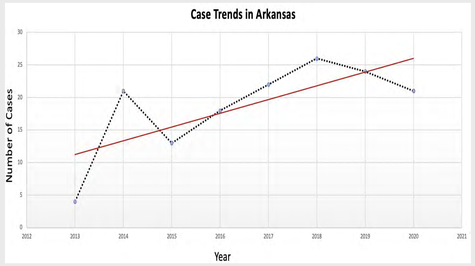

Figure 2: Arkansas Incidence Trends

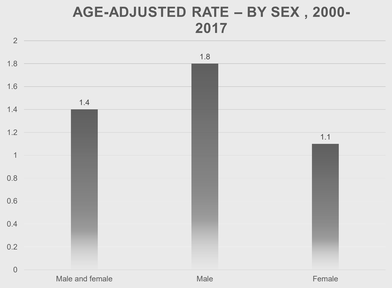

Figure 3: Mortality Rates in the US by Sex

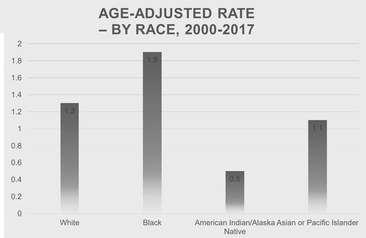

Figure 4: Mortality Rates in the US by Race

CONCLUSIONS

- There was a significant increase in mortality rates of CTCL in the US; between 2000-2017, with a male predominance in all sex groups and races, but disproportionately affecting young Black males. The rate ratio indicates that the mortality rate in Blacks is significantly different than the rate for White.
- Incidence rates ratio are significantly higher for Male than for Female sex. Mycosis Fungoides incidence rates were the highest amongst Black Males followed by Black Females. Mycosis Fungoides and Primary Cutaneous -Cell Lymphoma occurs earlier in Blacks than other races.
- Population-adjusted rates indicate that in Arkansas, CTCL is 2.23 times more prevalent in metropolitan than non-metropolitan areas. Our observational estimates were consistent with the 2.38 ratio calculated using SEERS data. An analysis of spatial distribution revealed that most patients live near major interstates and near chemical emitting facilities. This geographic pattern indicates that traffic-related and other pollutants may be a risk factor in the development of CTCLs.

BIBLIOGRAPHY

Phenotypes of alopecia from mogamulizumab therapy: A multi-institutional case series

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INTRODUCTION

Mogamulizumab is a humanized anti-CC chemokine receptor 4 (CCR4) monoclonal antibody approved for the treatment of Mycosis Fungoides/Sezary Syndrome (MF/SS). Cutaneous adverse events (e.g., rash, pruritus) remain a frequent issue. We characterize two distinct phenotypes of mogamulizumab-related alopecia.

METHODS

We conducted a retrospective chart review of MF/SS patients treated with mogamulizumab at two academic centers.

MEASURES

Parameters collected:

- MF/SS diagnostic information
- Prior systemic therapies
- Best lymphoma response to mogamulizumab
- Clinical features of alopecia (time-to-onset, distribution)
- Skin biopsy findings
- Alopecia-directed treatments

RESULTS

Four cases were identified, 3 female and 1 male (Table 1). All experienced either partial or complete lymphoma response to mogamulizumab by the global response score. Time-to-onset of alopecia ranged from 10 to 23 months. Three patients developed a scarring alopecia in an area of cutaneous drug eruption. Clinical exam features included well-demarcated plaques with erythema, loss of follicular ostia, and overlying scale (Figure 1). Rash biopsies demonstrated granulomatous infiltration around hair follicles. One patient developed alopecia areata universalis, with biopsy showing an overall decreased follicle count, all in telogen phase (Figure 2). Targeted therapies included high-potency topical corticosteroids for the rash-associated phenotype and intralesional corticosteroid for the alopecia areata phenotype. Alopecia was refractory to treatment in the rash-associated phenotype, but the patient with AU has had significant eyebrow/scalp hair regrowth.

Table 1. Clinical and Histologic Characteristics of Mogamulizumab-associated Alopecia

Characteristic	Case			
	1	2	3	4
Prior therapies	Methotrexate and vorinostat	Photopheresis, romidepsin, and vorinostat	Romidepsin, bexarotene, carfilzomib, acitretin, ECP	Bexarotene
TTO (months)	10.0	10.3	23.0	16.0
Clinical presentation	Well-demarcated alopecic plaques with overlying scale, loss of follicular ostia	Well-demarcated alopecic plaques with overlying scale, loss of follicular ostia	Well-demarcated pink-purple alopecic plaques with thin overlying scale	Rapid development of annular alopecic patches
Distribution	Vertex and frontal scalp	Right occipital/parietal scalp	Right occipital/parietal scalp → bilateral posterior scalp	Total body hair loss including scalp, eyebrows, eyelashes, and pubic hair
Best response				
Blood	CR	CR	CR	CR
Skin	CR	CR	CR	CR
Lymph node(s)	CR	PR	CR	CR
Global	CR	PR	CR	CR
Histologic findings	Granulomatous and spongiotic dermatitis with eosinophils	Lymphoid infiltrate with focal atypia and granulomatous component	Dermal granulomas with eosinophilic perivascular infiltrate and without atypia	Decreased number of hair follicles all in the telogen phase
Treatments for alopecia	Topical Clobetasol 0.05% ointment	Topical Clobetasol 0.05% ointment	Topical Betamethasone dipropionate 0.05% ointment	Intralesional corticosteroid (triamcinolone acetonide)

Abbreviations: CR, complete response, ECP, extracorporeal photopheresis; PR, partial response; TTO, time-to-onset

RESULTS

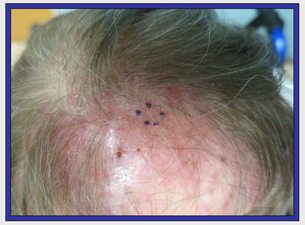

Figure 1: Mogamulizumab-associated rash phenotype

progression over 2 months

Figure 2: Alopecia areata universalis phenotype

CONCLUSIONS

Alopecia from mogamulizumab may represent an inflammatory phenomenon occurring as a consequence of depleting CCR4-expressing cells, including T helper 2 cells (Th2) and regulatory T cells (Treg). In the rash-associated phenotype, we hypothesize the preferential depletion of Th2-polarized cells leads to unopposed Th1-mediated inflammation, as suggested by the granulomatous infiltrate. The reduction of Tregs, a lineage involved in preventing autoimmunity, represents a separate pathophysiologic mechanism that could explain the development of alopecia areata. Regardless, skin biopsies of involved plaques can serve to rule out progression of disease.

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SCAN ME

MOGAMULIZUMAB-ASSOCIATED RASH FREQUENTLY MIMICS CTCL RECURRENCE BUT HERALDS DESIRABLE RESPONSE

N.A. Trum, BS, MD student[1,4], J. Zain, MD[1], X.U. Martinez, MD[1], V. Parekh, MD[1], M. Afkhami, MD[1], F. Abdulla, MD[1], K.R. Carson, MD[3], S.T. Rosen, MD[1,2], C.L. Bennett, MD PhD MPP[1,2], C. Querfeld, MD, PhD[1,2]

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INTRODUCTION

Mogamulizumab is a humanized antibody targeting chemokine receptor type 4 (CCR4) for relapsed/refractory mycosis fungoides (MF)/Sezary syndrome (SS), the most common subtypes of cutaneous T-cell lymphoma (CTCL). Mogamulizumab associated rashes (MARs) are the most common adverse events reported[1]; however, the clinical, histopathological, and molecular nature of these eruptions remains unclear[2,3]. We aim to report our experience of all 25 patients treated with mogamulizumab at our center since its approval in 2018, and to define clinical, histopathologic, and molecular patterns associated with MAR.

METHODS

Retrospective case series; includes all T cell lymphoma (TCL) patients treated with mogamulizumab at a single tertiary referral center since its approval as standard of care. Study approval was obtained by the City of Hope Cancer Protocol Review and Monitoring Committee and Institutional Review Board.

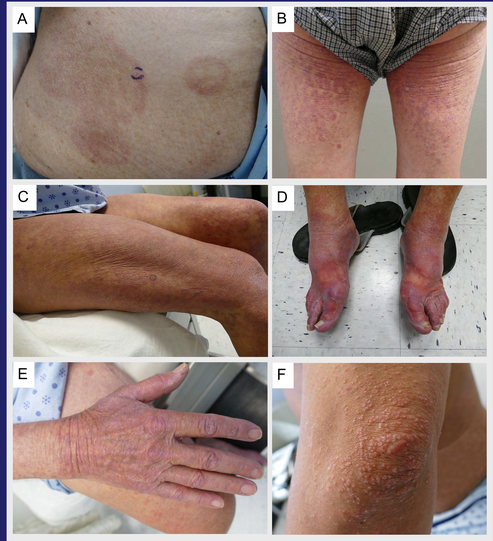

Figure 1. Clinical MAR morphologies included mycosis fungoides-like patches/plaques (**A**; n=7), psoriasiform eruptions (**B**; n=7), erythroderma (**C**; n=3), photodermatitises (**D**, **E**; n=7), and lichenoid eruptions (**F**; n=8).

RESULTS

25 TCL (16 SS, 8 MF, 1 ATLL) patients were included. 17 developed MAR (68%). Median MAR time to onset (TTO) was 2.1 mo. (0.7-9.0). Median time to resolution (TTR) was 6.6 mo. (3.5-9.3). Global ORR among patients with MAR was 88% (9 CR, 5 PR) versus 25% (2/8) among those without MAR, suggesting that MAR may underscore a desirable clinical response. Median disease-free survival (DFS) was 7.9 mo. (4.2-16.3+). Median follow-up time was 11.5 months (5.3-28.8+). Five distinct but frequently concurrent clinical patterns were identified (**Figure 1**). Histopathological patterns (**Figure 2**) included spongiotic (n=21), lichenoid (n=14), psoriasiform (n=10), and interface (n=8) features across 26 skin biopsies. Eosinophils (n=15), epithelioid granulomas (n=4), and bizarre bi- and multinucleated cells (n=6) that may represent highly activated macrophages were also noted. Epidermotropism (n=10) or exocytosis (n=12) and lymphoid atypia (n=16), key CTCL histology features, were found in all clinical morphologies (**Figure 3**). Concomitant flow cytometry for circulating SS cells and TCR rearrangement studies in skin and blood were negative during evaluation for MAR with rare exception.

CONCLUSIONS

MAR may be characterized by distinct clinical and histopathological patterns. Patients with SS may be more likely to develop both MAR and a durable clinical response to moga, underscoring its efficacy in this population. Furthermore, MAR can clinically mimic CTCL lesions, highlighting the need for clinicians to rule out progressive disease vs. drug eruption in treating a condition that historically suffers from poor outcomes and treatment response.

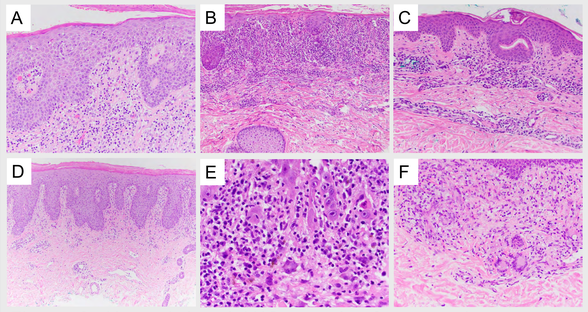

Figure 2. Histopathological MAR examples. Spongiotic dermatitis with eosinophils (**A**), lichenoid interface dermatitis with dermal eosinophils (**B**), lichenoid dermatitis (**C**) psoriasiform dermatitis (**D**), highly activated macrophages (**E**), and rare granulomas with multinucleated giant cells in papillary dermis in the setting of a lichenoid interface dermatitis (**F**). Hematoxylin and eosin (H&E) staining.

Table 2. Baseline vs. MAR histopathological, molecular, and clinical characteristics, case-by-case.

Prior to mogamulizumab baseline						Evaluation of suspected MAR								
Case	Dx	TNMB stage	Baseline Sézary cell count (cells/μL)	Skin lesion	TCR rearrangement studies	Skin lesion		Peripheral blood		Best response		Moga infusions		Best global response in relation to MAR onset (months)
				CD4:CD8	γ/β peaks	CD4:CD8	γ/β peaks	CD4:CD8	γ/β peaks	Skin	Blood	Until MAR	Total	
1	SS	T4N3M0B2	2808	>10:1	1/2	-	-	-	-	PD	SD	5	9	-
2	SS	T4N2M0B2	7812	10:1	2/4	<1:1	0/0	<1:1	-	CR	CR	3	3	After (9.0)
3	SS	T4N1M0B2	21	6:1	+	<1:1	0/0	2:1	0/0	CR	CR	5	5	After (0.2)
4	SS	T4N1M0B2	5549	8:1	1/2	-	0/0	10:1	0/0	CR	CR	10	11	After (2.8)
5	SS	T4N0M0B1b	25	10:1	2/2	2:1	0/1	8:1	0/0	CR	CR	5	13	After (12.9)
6	SS	T4N2M0B2	1407	NR	2/1	5:1	0/0	2:1	0/0	PR	CR	22	22	After (3.4)
7	SS	T4N0M0B2	567	>10:1	2/1	4:1	0/0	3:1	0/0	CR	CR	9	12	Simul. (0)
8	SS	T4N1M0B2	2001	>10:1	2/1	<1:1	1/0	>10:1	2/1	SD	PR	4	10	-
9	SS	T4N3M0B2	7896	>10:1	1/2	5:1	0/0	2:1	0/0	PR	CR	8	10	Simul. (0)
10	SS	T4N0M0B2	1584	8:1	2/1	2:1	0/0	<1:1	0/2	CR	PR	6	7	After (1.2)
11	SS	T4N1M0B2	3243	8:1	2/3	<1:1	0/0	1:1	0/0	CR	CR	15	15	Before (0.9)
12	SS	T4NxM0B2	589	2:1	1/1	6:1	0/0	<1:1	0/1	CR	PR	10	11	Before (0.5)
13	SS	T4N3M0B2	356	6:1	1/2	4:1	0/0	<1:1	-	CR	CR	12	12	Before (2.3)
14	SS	T4N3M0B1b	322	8:1	1/3	8:1	0/0	7:1	0/0	CR	CR	3	23	After (14.5)
15	EMF	T4N0M0B1b	278	-	2/2	8:1	0/0	1:1	0/0	PR	CR	3	7	After (2.5)
16	MF	T2bN0M0B0a	-	-	2/2	2:1	0/0	2:1	0/0	PR	-	9	11	Simul. (0)
17	MF	T2bN0M0B0b	-	>10:1	3/1	-	-	-	-	PD	-	-	-	-

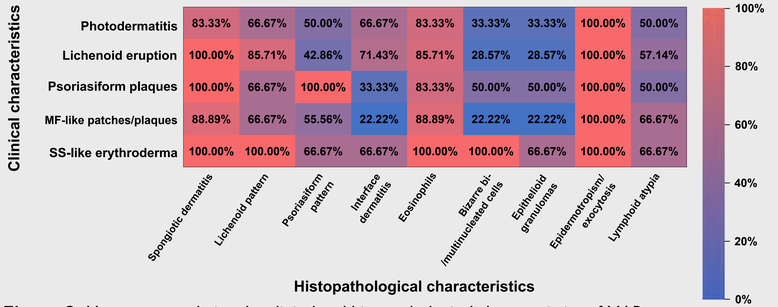

Figure 3. Heatmap correlating the clinical and histopathological characteristics of MAR.

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Evaluating the ISCL Algorithm for the Diagnosis of Early Stage Mycosis Fungoides (MF)

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INTRODUCTION

- In 2005, the ISCL proposed a diagnostic algorithm for early MF that incorporates clinical and histopathologic characteristics in addition to immunohistochemistry (IHC) and T-cell receptor gene rearrangement studies.
- Each set of criteria is assigned a point value and when a sum of four or more points is achieved, the diagnosis of MF is made.
- A recent case series highlights that despite incorporation of IHC and molecular studies, diagnostic criteria for MF underscoring epidermotropism in the absence of spongiosis may contribute to missed and delayed diagnosis of MF.
- We examined the diagnostic utility of the ISCL algorithm by applying it to patients with a known diagnosis of MF and evaluated how modifying the algorithm's histologic criterion regarding spongiosis influenced its sensitivity.

METHODS

- We retrospectively identified patients diagnosed with early stage (IA-IIA) MF between 1/1/2013-12/31/2019 who had at least one skin biopsy with histopathology performed at their initial visit and continued to carry a confirmed diagnosis of MF at two-year follow-up.
- We applied the ISCL algorithm using clinical, immunohistochemical and molecular data obtained from medical records and histopathological data generated by dermatopathologist blinded review.
- IHC and T cell receptor gene rearrangement studies were not performed for all patients, so we subsequently performed a subgroup analysis including patients in whom both studies had been performed.
- Finally, we examined how modifying the histopathologic criterion of the proposed ISCL algorithm influenced the sensitivity of the algorithm.

RESULTS

- 28 patients matched the eligibility criteria. Of these, 43% (12/28) met the algorithm's 4-point threshold to achieve a diagnosis of MF. (Table 1)
- 18 of the 28 patients had both IHC and molecular studies performed, in addition to basic histopathology. Of these, 50% (9/18) met the diagnostic threshold of MF. (Table 1)
- 85.7% (24/28) of the entire cohort and 89% (16/18) of the subgroup had at least one skin biopsy exhibiting epidermotropism but none of demonstrated epidermotropism without spongiosis. (Table 2)
- When we modified the algorithm to award a point for epidermotropism irrespective of spongiosis, 71% (20/28) of patients in the whole cohort and 89% (16/18) of patients in the subgroup met the algorithm's threshold for MF. (Table 2)

		Entire Cohort	Subgroup
	Value	n(%); N=28	n(%); N=18
Total Score	2	5 (17.9)	1 (5.6)
	3	11 (39.3)	8 (44.4)
	4	12 (42.9)	9 (50)
Clinical Score	1	0 (0)	0 (0)
	2	28 (100)	18 (100)
Persistent and progressive plaques	Yes	28 (100)	18 (100)
Non-sun exposed	Yes	28 (100)	18 (100)
Size/shape variation	Yes	28 (100)	18 (100)
Poikiloderma	Yes	3 (10.7)	1 (5.6)
Histopathology Score	0	10 (35.7)	5 (28)
	1	18 (64.3)	13 (72)
	2	0 (0)	0 (0)
Superficial Lymphoid Infiltrate		27 (96.4)	18 (100)
Epidermotropism without spongiosis		0 (0)	0 (0)
Atypia		18 (64.3)	13 (72)
Immunohistochemistry Score	0	20 (71.4)	12 (67)
	1	8 (28.6)	6 (33)
<50% CD2, CD3, &/or CD5	Yes	2 (7.1)	2 (11.1)
<10% CD7	Yes	6 (21.4)	5 (27.8)
Discordance	Yes	6 (21.4)	4 (22.2)
Molecular Score	0	18 (64.3)	10 (55.6)
	1	10 (35.7)	8 (44.4)
Total Score ≥4	Yes	12 (43)	9 (50)

Table 1: Scores obtained when ISCL algorithm applied to entire cohort and subgroup

		Entire Cohort		Subgroup	
		ISCL Algorithm	Modified Algorithm	ISCL Algorithm	Modified Algorithm
	Value	n (%); N=28	n (%); N=28	n (%); N=18	n (%); N=18
Total Score	2	5 (17.9)	1 (3.6)	1 (5.6)	0 (0)
	3	11 (39.3)	7 (25.0)	8 (44.4)	2 (11.1)
	4	12 (42.9)	9 (32.1)	9 (50)	8 (44.4)
	5	0 (0)	11 (39.3)	0 (0)	8 (44.4)
Histopathology Score	0	10 (35.7)	3 (10.7)	5 (28)	1 (5.6)
	1	18 (64.3)	10 (35.6)	13 (72)	6 (33.3)
	2	0 (0)	15 (53.6)	0 (0)	11 (61.1)
Superficial Lymphoid Infiltrate	Yes	27 (96.4)	Unchanged	18 (100)	Unchanged
Epidermotropism without spongiosis	Yes	0 (0)	---	0 (0)	---
Epidermotropism	Yes	---	24 (85.7)	---	16 (89)
Atypia	Yes	18 (64.3)	Unchanged	13 (72)	Unchanged
Total Score ≥4	n/N	12/28 (42.8)	20/28 (71)	9/18 (50)	16/18 (89)

Table 2: Comparison of scores obtained with the ISCL algorithm and the modified algorithm in the entire cohort and the subgroup

CONCLUSIONS

- While the ISCL algorithm is useful in the diagnosis of early stage MF, its sensitivity remains suboptimal.
- In our cohort, all skin biopsies that exhibited epidermotropsim had some degree of spongiosis.
- In this small study, modifying the algorithm to award a point for epidermotropism irrespective of spongiosis, increased the algorithm's diagnostic sensitivity.
- Clarification regarding the degree of spongiosis permitted or further refinement of the algorithm's histologic criterion to capture spongiotic subtypes of MF, may improve its diagnostic value.
- Considering the healthcare costs, morbidity and mortality associated with advanced MF, accurate and timely diagnosis and treatment is important.
- Future large scale studies are needed to identify highly specific and sensitive diagnostic criteria that reliably distinguish early spongiotic MF from benign dermatoses.

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QR code for Abstract and References

Proteomic Identification of New Diagnostic Biomarkers of Early-stage Mycosis Fungoides

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INTRODUCTION

Mycosis fungoides (MF), the most common subtype of cutaneous T-cell lymphoma is a rare disease. Patients with early-stage MF suffer poor quality of life from painful, itchy and disfiguring lesions, further, advanced-stage MF shows aggressive progression. Early-stage MF is characterized by a favorable prognosis with long-term survival similar to or slightly lower than that of age-matched healthy people. In contrast, advanced-stage MF shows aggressive progression, yet there are few specific biomarkers for the early diagnosis and prognosis of MF. In this study, we described the pathological features of MF during the early and advanced stages through proteomics technology, providing clues for the pathogenesis of MF as well as biomarkers for malignant tumors in the early stage.

METHODS

In this study, we collected tissue samples of skin lesions from early- and advanced-stage MF patients and used proteomics to identify biomarkers of early- and advanced-stage MF as well as early-stage MF that may progress to an advanced stage.

Human participants: Fourteen patients diagnosed with MF based on WHO-EORTC classifications were recruited, including 4 early-stage and 10 advanced-stage MF patients. The patients in the benign inflammatory disease (BID) control group were diagnosed with psoriasis and eczema according to clinical manifestatiequippedons and histopathological results. The foreskin tissues from the healthy control group were obtained through circumcision.

Mass spectrometry: The peptide mixtures were analyzed using an Orbitrap Q-Exactive HF mass spectrometer with an Easy-nLC nanoflow liquid chromatography system.

RESULTS

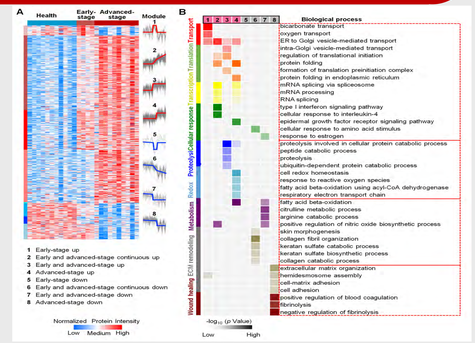

Figure 1: Proteomics features during tumor development. (A) Eight protein modules reveal protein specificity based on statistical analysis. (B) Biological process analyses of the proteins enriched in the eight modules.

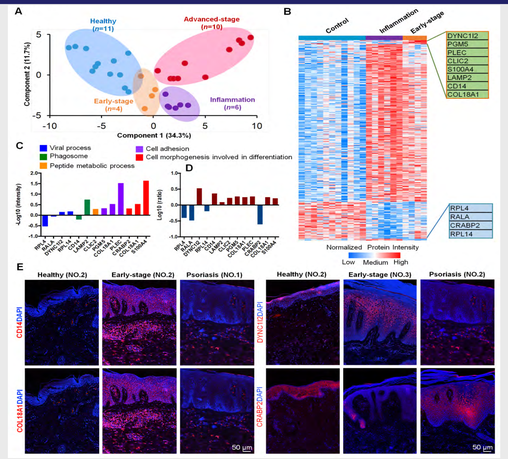

Figure 2: Biomarker identification for early-stage MF. (A) PCA of the proteome profile of different groups. (B) Heatmap analysis of the differentially expressed proteins. (C) Expression of upregulated and downregulated proteins in the early-stage MF samples. (D) Ratio of the protein expression of early-stage MF samples to that of inflammatory samples. (E) Immunofluorescence of CD14, COL18A1and so on.

CONCLUSIONS

First, we found that there were two characteristics of highly expressed proteins in skin tissues of MF patients: (i) The proteins that were only highly expressed in early-stage MF patients may assist in the clinical identification of biomarkers of early-stage MF that is not likely to develop into advanced-stage. Most of the biological processes mediated by these proteins are transport-related processes, such as bicarbonate transport, oxygen transport, and ER to Golgi vesicle-mediated transport. (ii) The expression of some proteins were gradually increased from early- to advanced-stage MF. These proteins are involved in many biological processes, including translation, proteolysis and redox. They are not only biomarkers for early-stage MF that could develop into malignant tumors but also potential initiating factors for the tumor development.

Next, we found proteins with significant differences in expression between early-stage MF and BID that can be used as potential biomarkers. Based on that, we conducted a large number of validations in a new population and found that CD14, DYNC1I2, et al. can distinguish early-stage MF from BID. Among them, CD14 and DYNC1I2 exhibited low expression in epithelial-derived tumor tissues, indicating that the biomarkers we have identified may be used as effective markers for the diagnosis of early-stage MF.

BIBLIOGRAPHY

Lead Contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the Lead Contact, Jie Liu, MD. (Liujie04672@pumch.cn) and Ling Leng, Ph.D. (lengling@pumch.cn, zhenlinger@126.com).

Materials Availability

There are no tangible materials produced by this study that are available for distribution.

Data and Code Availability

All proteomic data have been deposited to the ProteomeXchange Consortium via the iProX partner repository with the dataset identifier PXD022798. (https://www.iprox.org/page/PSV023.html;?url=1606568096317yqtW, Nvbj).

Primary cutaneous lymphoma cases visited during 2019 in a referral italian center: retrospective analysis of disease subtypes and staging, disease course, survival, treatment performed, comorbidities and associated symptoms

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INTRODUCTION

Primary cutaneous lymphomas (PCL) are extremely rare diseases, characterised by different subtypes, disease presentations, clinico-pathologic features, disease curse and survival. Limited data are reported in literature and the international guidelines report numerous therapeutic options, without recommending any specific order.

OBJECTIVES

1) to describe patients and disease entities visited during 1 year at a referral PCL centre.
2) to identify comorbidities/associated cancers, staging, high-grade transformation, and stage progression, with a focus on treatment and responses in Cutaneous and T-cell lymphoma (CTCL).
3) to identify in multivariate analysis, the possible predictors of complete remission (CR) in CTCL.

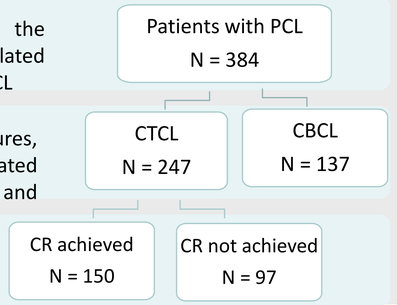
METHODS

This retrospective study collects data from 384 patients seen from January to December 2019 at the Cutaneous Lymphoma Center, Dermatology Clinic, University of Turin. Follow-up data are updated at December 2020.

Descriptive analysis of the the different types and the related demographic characteristics of PCL

CTCL analysis: clinical features, comorbidities and associated neoplasms, staging, evolution and treatment.

Sub-analysis of the population with CTCL



RESULTS

❖ Descriptive analysis

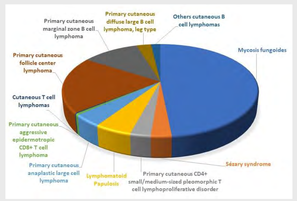
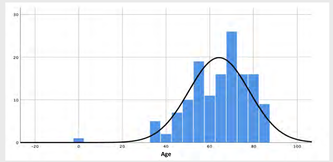


Figure 1: Different types of Primary Cutaneous Lymphoma



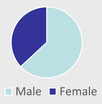
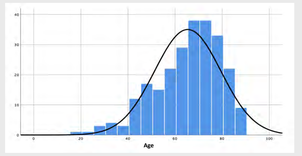


Figure 2: Age and gender distribution B-cell lymphoma



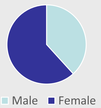


Figure 3: Age and gender distribution T-cell lymphoma

❖ T-cell Lymphoma sample analysis

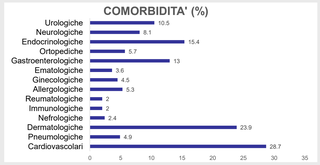


Figure 4: Distribution of comorbidities

STAGING (MF and SS)	N = 197
IA	106 (53.8)
IB	58 (29.4)
IIA	6 (3.0)
IIB	12 (6.1)
IIIA	2 (1.0)
IIIB	1 (0.5)
IVA	6 (3.0)
NA	6 (3.0)
Progression at any stage	29 (14.7)
Progression at advanced stage	17 (8.6)
High grade trasformation	8 (4.1)

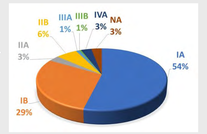


Figure 5: Staging at diagnosis and progression

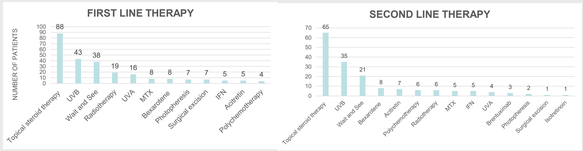


Figure 6: Analysis of treatment

The choice of therapy in the first lines of treatment which resulted, most of the time, the **topical steroid therapy**, able of leading to complete or partial remission in **more than half of the patients**, followed by UVB phototherapy.

❖ **Sub-analysis** of the population with T-cell lymphoma

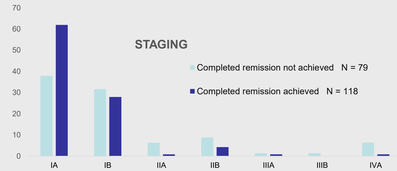


Figure 7: Comparative analysis of staging

Stage IA is associated with a greater tendency to **remission**, patients in stage **IB** are **equally distributed**, while from the stage **IIA** there is a greater tendency for **non-remission**.

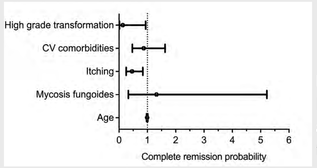


Figure 8: Multivariate analysis of treatment

A correlation emerged between the presence of an **itchy symptomatology and/or high grade transformation and a complete remission not achieved**.

CONCLUSIONS

- **The prognosis worsens as early as stage IB in CTCL**, therefore differentiated therapeutic strategies should be defined
- The presence of **itchy symptoms and high-grade lymphoma transformation represent negative independent prognostic factors for CTCL.**
- These data provide an insight into the characteristics of cutaneous lymphoma patients seen in real life setting as well as their treatment approaches and identify new potential predictive parameters to be considered in clinical practice.

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PATIENTS WITH PRIMARY CUTANEOUS LYMPHOMA ARE AT RISK FOR SEVERE COVID-19. DATA FROM THE SPANISH PRIMARY CUTANEOUS LYMPHOMA REGISTRY

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INTRODUCTION

- While some papers report an increased risk of COVID-19 and worse outcomes in oncological patients[1], others have found no differences[2].
- The objectives of our study:
  - Evaluate the **incidence of COVID-19** and **severe outcomes** in a cohort of PCL patients.
  - **Compare it to the general population.**
  - Describe **changes in lymphoma staging** eight weeks after COVID-19.

METHODS

- Registro Español de Linfomas Cutaneos (RELC) is a **cohort study** recruiting **all patients with PCL** referred to 27 participating dermatology departments.
- In May 2020, we collected all patients with COVID-19 and described their clinical data and evolution.
- We defined COVID-19 cases, according to the European Centre for Disease Prevention and Control[3], as possible, probable or confirmed. COVID-19 outcomes included asymptomatic or mild, hospitalized, intensive care unit (ICU) and deaths
- We described age-specific cumulative incidences of COVID-19 and COVID-19 related events, and compared them with the general population by means of the overall SIRs.

MEASURES

We estimated cumulative incidences, 95% Confidence Intervals (CI), and standardized incidence ratios (SIR) by age, sex and geographical area, corresponding to the same period (January-November 2020) of Spanish general population data published by the Spanish Ministry of Health[4].

RELC included 1542 patients (56% Mycosis fungoides/Sézary (MF/SS), 44% non-MF/SS primary cutaneous lymphomas). 20% were in T3 and T4 stages. 60 patients (3.9 %) suffered from COVID-19, median age of 59.1 years (SD=13.1); 50% of them MF/SS, and 50% non-MF/SS. 42 patients had a microbiologically confirmed infection (70%), 7 of them being probable cases (12%) and 11 possible cases (18%). Most patients (65%) experienced mild disease, 25% required hospitalization, 5% needed ICU and 5% died. 82% of patients reported stability of their PCLs, 9% improvement and 9% worsening.

RESULTS

- None of the SIRs are statistically significant, but they increase with the severity of COVID-19 disease.
- **Patients in the 60-69 years stratum show a strongly increased risk of hospitalization (SIR: 4.81 (95%CI: 2.2-9.12)) and need for intensive care (SIR: 12.41 (95%CI: 1.5-45) compared to general population**
- **In surviving patients, the oncological disease remained stable.**

CONCLUSIONS

- **THIS STUDY IS THE FIRST TO DESCRIBE THE INCIDENCE AND SEVERITY OF COVID-19 AMONG PCL PATIENTS.**
- Strengths of our study are that **it is based on a previously defined and closely followed prospective cohort**, and has **comparable data for the general population.**
- We could not detect increased risks of hospitalization and severe outcomes in all PCL patients compared to the general population, especially for rare outcomes such as mortality.
- However, **we found an augmented risk of severe disease compared to general population among those of 60 to 69 years of age** (this group included more patients and outcomes, thus, offering more statistical power). The insufficient number of total cases didn't allow us further subdivision of the PCL group.

OUR STUDY SUGGESTS THAT PCL PATIENTS SHOULD BE CONSIDERED AT RISK FOR SEVERE COVID-19, REQUIRING REINFORCED PREVENTIVE MEASURES AND PRIORITIZATION IN VACCINATION STRATEGIES

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Spontaneous Remission of Advanced Untreated Sezary Syndrome after SARS COVID-19

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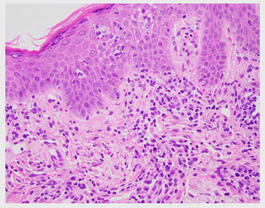
Northwestern Medicine®
Feinberg School of Medicine

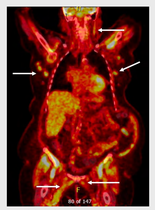
INTRODUCTION

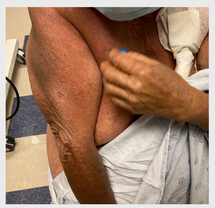
- Sezary Syndrome (SS) is a leukemic subtype of cutaneous T-cell with a median survival time of less than five years [1].
- Therapies for SS include interferon (alpha and gamma), retinoids, chemotherapy, biologics and extracorporeal photopheresis [2].
- During the global COVID-19 pandemic, a subset of patients undergo Severe Acute Respiratory Syndrome (SARS), which includes systemic cytokine storm [3].
- Few cases of COVID-19 in patients with Sezary syndrome have been reported in the literature.

CLINICAL PRESENTATION

- This is the case of a 66-year-old woman who experienced a marked improvement in her Sezary syndrome after an episode of SARS-Covid-19.
- Past Medical History: Type 2 diabetes, uncontrolled hypertension and end-stage renal disease (CKD stage 5) on hemodialysis
- Initial presentation in September 2019: Diffuse pruritus, 90% BSA erythroderma with minimal overlying scale.
- Diagnosis: Mycosis fungoides with Sezary Syndrome, stage T4NXM0B2



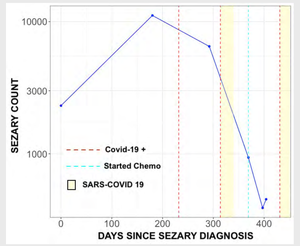




LEFT: Pathology image taken upon presentation to Northwestern. CENTRAL: PET with bilateral axillary, cervical and inguinal lymphadenopathy. RIGHT: 90% BSA erythroderma

CLINICAL PRESENTATION

- Due to COVID restrictions and a lack of transportation, the patient was lost to follow-up.
- April 2020: The patient was presented to the emergency department afebrile with shortness of breath. She was COVID-19 positive but received only supportive care.



- June 2020: A PET scan shows continued lymphadenopathy; Sezary count remains elevated at 6494
- July 2020: The patient presented with chills and a fever to101.3°. She becomes hypoxemic and is admitted to the ICU.
- A 25-day hospital course included two stays (8 days total) in the ICU for BiPAP respiratory support, empiric antibiotics (azithromycin, vancomycin/piperacillin/tazobactam, vancomycin/cefepime) and one week of dexamethasone upon initial admission.
- September 2020: The patient's Sezary count had decreased to 936 (<10% of peak) with a record low lymphocyte count.
- The patient began romidepsin/granisetron/methylprednisolone and her Sezary counts continued to drop.
- Erythema improves; axillary and inguinal lymphadenopathy resolves.
- November 2020: The patient was admitted with SARS-COVID+ a second time and succumbed to cardiac arrest.

Days From Diagnosis	Sezary Count	Lymphocyte Count	CD4:CD8 Ratio
0	2312	5508	6
180	11132	14274	22.5
DAY 232: COVID-19+, MILD SYMPTOMS			
292	6494	7595	23
DAYS 314-339: SARS-COVID-19			
369	936	3436	
DAY 369: START ROMIDEPSIN THERAPY			
397	389	1776	6.3
404	452	1435	
DAY 431: SARS-COVID-19 DAY 443: CARDIAC ARREST			

DISCUSSION

- Our patient experienced remission of her Sezary Syndrome after suffering from SARS COVID-19. This remission continued after she began chemotherapy.
- Cases of cancer remission after SARS COVID-19 have been reported, including for Hodgkin's lymphoma and metastatic lung cancer. [4,5]
- Heterologous immune response to viral infection has been shown in the literature to reduce cancer burden [6].
- COVID-19 infection is known to cause a cytokine storm with increased levels of IL-2, IL-6, IL-7, and TNF, as well as interferon gamma (IFNG). IFNG is sometimes used to treat SS [2, 7].
- New literature suggests that COVID-19 infection may induce a diverse array of autoantibodies corresponding to disease severity [8].

CONCLUSION

- Our patient experienced a partial "spontaneous" remission of her Sezary Syndrome that we believe may have been due to heterologous immune response to SARS COVID-19.

BIBLIOGRAPHY

Abstract

Bibliography

Near infrared photoimmunotherapy targeting the cutaneous lymphocyte antigen for mycosis fungoides

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INTRODUCTION

Mycosis fungoides (MF) is a low-grade T-cell lymphoma with primary cutaneous involvement accounting for more than half of all primary cutaneous lymphomas. The treatment of MF is very challenging due to the limited therapies available. Near-infrared photoimmunotherapy (NIR-PIT) is a newly developed and highly selective cancer treatment that employs a monoclonal antibody conjugated to a photo-absorber dye, the hydrophilic phthalocyanine IRdye 700DX® (IR700), and near infrared light. In this study, we investigated the effect of NIR-PIT on MF targeting the cell-surface antigen cutaneous lymphocyte antigen (CLA).

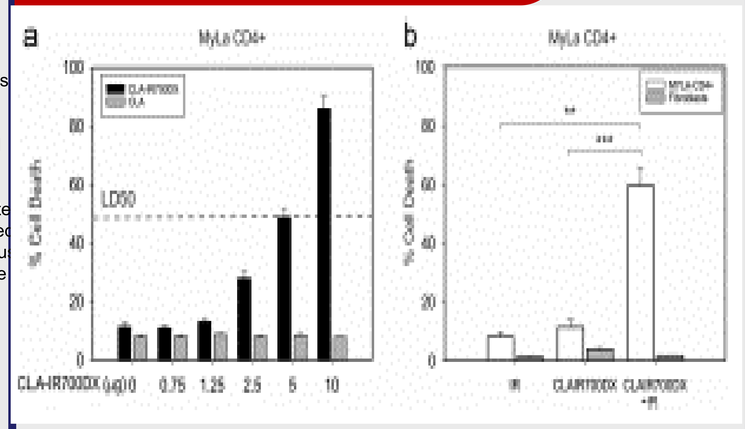
METHODS

The IRDye®700DX Protein Conjugation Kit, (LI-COR Biosciences, Lincoln, NE, USA) was used to conjugate the antibody anti-CLA (Miltenyi Biotec, Bergisch Gladbach, Germany) with the IRDye®700DX dye (LI-COR Biosciences, Lincoln, NE, USA). The obtained conjugated IR700DX-CLA-antibody was quantified with the BiochromTM GeneQuantTM spectrophotometer (Fisher Scientific Waltham, Massachusetts, USA)
My-La CD4+ cells (0.6 x106) were seeded into 24-well plates in 1 ml of complete RPMI 1640 medium. Cells were incubated with CLA-IR700 antibody at 37°C for 30 minute before 5 minutes irradiation with a MIC-LED-690 M (Prizmatix Ltd., Israel). The lamp used irradiation is based on a single-chip LED (Light Emitting Diode) with incorporated an adju aspheical lens collimator. The irradiance on the samples was 35 mW/cm2; samples were exposed for 300 seconds so that a total dose of 10 J/cm2 was released After 24 hours of incubation, 200 µl of cells were collected and stained with 400 ng of propidium iodide (Sigma-Aldrich, St. Louis, Missouri, U.S.A.). After 10 minutes' incubation at room temperature, cells were analyzed by flow cytometry using a LSRII flow cytometer and Diva software (BectonDickinson Franklin Lakes, New Jersey USA). Ten thousand ungated events were analyzed. Normal fibroblasts were used as off-target control.

RESULTS

Quantitative evaluation of cell death in response to increasing doses of CLA-IR700DX revealed a lethal dose 50 (LD50) of approximately 5 µg of antibody per 10 at 6 cells (Figure 1 a black). Interestingly, anti-CLA antibody did not affect cell death per se (Figure 1a gray irradiation on cell death in My-La CD4+ cells and normal fibroblasts used as off-target control.
Results showed that treatment with anti-CLA (Figure 1 (a,b)) or light irradiation exhibited very modest pro-death effects, while the combination of the two induced a substantial increase in death in the MF cell line, but not in normal fibroblasts, which do not express the CLA antigen (Figure 1(b)).

RESULTS



CONCLUSIONS

This is the first study investigating NIR-PIT in a skin neoplasm. In particular, given that there is no molecular-targeted therapy in the standard of care for MF patients and that CLA is selectively expressed in MF skin infiltrating lymphocytes, CLA-targeted NIRPIT is an attractive candidate for in vivo studies and ultimately clinical trials. NIR-PIT targeting CLA to treat MF was very feasible and showed marked antitumour effects which is indicative of the Translation al potential of this approach.
Limitations of the study were the utilization of only one cell line and, moreover, the lack of in vivo experiments. Therefore, if validated in an in vivo system, CLA-targeted NIR-PIT could be a promising treatment for MF and, possibly, for other neoplastic and inflammatory skin conditions characterized by the cutaneous infiltration of CLA+ T-cells.

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Increased chlormethine-induced DNA double-stranded breaks in malignant T cells from mycosis fungoides skin lesions

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INTRODUCTION

- Cutaneous T cell lymphoma (CTCL) is a heterogeneous group of extra-nodal non-Hodgkin's lymphoma.
  - Mycosis fungoides (MF) is the most common type of CTCL[1] and is considered a malignancy of skin-resident T cells.
  - Sézary syndrome (SS) is an aggressive variant type of CTCL with blood diseases.
- Chlormethine (CL) is a bifunctional alkylating agent that inhibits rapidly proliferating cells.
- CL is the first chemotherapy agent that has been effectively used for decades to treat lymphoid malignancies, including MF-CTCL.
- A novel CL gel formulation was purposely developed to treat MF-CTCL and is currently endorsed by international guidelines for use in MF-CTCL adults as first line therapy.[2–5]

METHODS

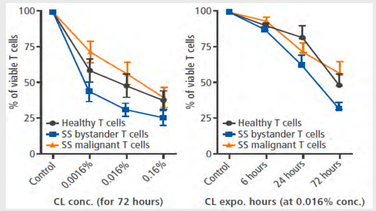
- To investigate the impact of CL on malignant skin T cells regarding their susceptibility to treatment, proliferation, deoxyribonucleic acid (DNA) double-stranded breaks and the expression of alkylated-nucleotide-excision genes.
- Patients with MF or SS and specific T-cell receptor (TCR) Vβ⁺ T-cell population in their skin and blood were included.
  - Healthy T cells from blood and skin of healthy individuals and bystander T cells were used as controls.
- Blood T cells were purified by pan T-cell isolation and TCR Vβ⁺ tumour T cells by magnetic-activated cell sorting.
- Skin biopsies were taken, and T cells isolated using collagen-coated cellfoam matrices.

MEASURES

- Blood/skin T cells were exposed to CL and monitored for:
  - Viability – MTT assay
  - Proliferation – Bromodeoxyuridine (BrdU) assay
  - DNA double-stranded breaks – γH2AX Ser139 expression by flow cytometry
  - Alkylated-nucleotides-excision gene expression – reverse transcription quantitative polymerase chain reaction.
- Values were calculated using a paired t test; $p \leq 0.05$ were considered significant for control-versus CL-treated, or bystander versus malignant T cells.

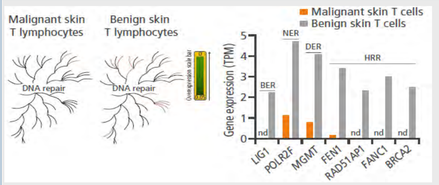
RESULTS

Figure 1: Time- and dose-dependent decrease in clonal malignant, bystander, and healthy T-cell viability by CL exposure



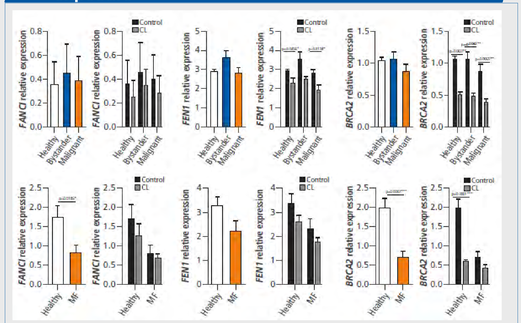
CL: chlormethine; **conc.:** concentration; **expo.:** exposure; **SS:** Sézary syndrome.

Figure 2: Lower expression of DNA-repair pathways in skin tumour T cells from patients with MF



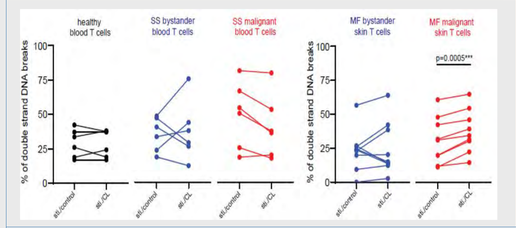
BER: base excision repair; **NER**: nucleotide excision repair; **DER**: direct enzymatic repair; **HRR**: homologous recombination repair.

Figure 3: DNA repair genes were down-regulated in malignant T cells and decreased after CL exposure



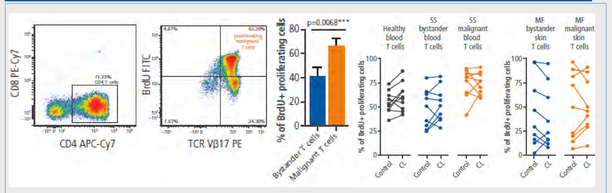
BRCA2: breast cancer 2 gene; **CL**: chlormethine; ***FANC1***: fanconi anaemia complementation 1; ***FEN1***: flap structure-specific endonuclease 1; **MF**: mycosis fungoides; **SS**: Sézary syndrome.

Figure 4: Double-stranded DNA breaks in skin T cells from patients with MF



CL: chlormethine; **MF**: mycosis fungoides; **SS**: Sézary syndrome.

Figure 5: CL exposure did not significantly influence blood or skin T cell proliferation



PMA, ionomycin, and PHA stimulation[4] was used after CL exposure.
CL: chlormethine; **MF**: mycosis fungoides; **PHA**: Phytohemagglutinin; **PMA**: Phorbol 12-myristate 13-acetate; **SS**: Sézary syndrome.

CONCLUSIONS

- This study highlights the anti-tumour effects of CL on MF skin T cells, inducing DNA double-stranded breaks predominantly in the subpopulation of malignant skin T cells.
- CL also decreases the expression of genes involved in alkylated nucleotides' excision.
- These data provides a rationale for CL as an early and valuable skin-directed treatment option for cutaneous lymphoma.

BIBLIOGRAPHY

Abstract

Research Group

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Enhancement of antibody-dependent cellular cytotoxicity is associated with treatment response to extracorporeal photopheresis in Sézary syndrome

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INTRODUCTION

- The Sézary syndrome (SS) is a rare and aggressive disease from the group of cutaneous T cell lymphomas.
- It is a tumour of the immune system which itself has strong immunomodulatory effects.
- Extracorporeal photopheresis (ECP) is the current first-line therapy with which the disease can be controlled, yet not cured.
- Despite being successfully applied for over 30 years remains the exact mechanism of action poorly understood and there are no reliable biomarkers to monitor response to therapy.

METHODS

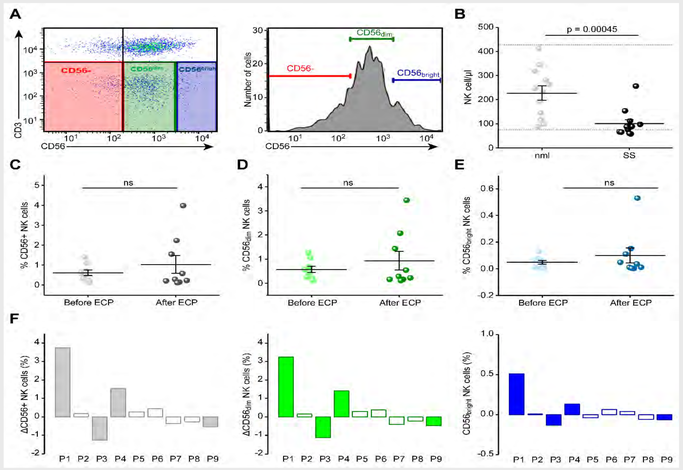
- We aimed to answer the question whether ECP affects NK cell numbers and the efficacy of NK-mediated antibody-dependent cellular cytotoxicity (ADCC).
- NK cells from healthy doners and 13 SS patients (UHZ Dermatology biobank) where counted and compared before and after the start of ECP.
- Analysis of samples by flow cytometry and an LDH assay was done according to established workflows
- NK cells were isolated from blood as PBMCs, Rituximab-coated Raji cells served as target cells.

Measures

- FACS measure:
  - number of NK cells in healthy doner, SS
  - percentage of CD56+, CD56dim and CD56bright
- LDH assay:
  - release of LDH measured by absorption
- clinical response to treatment according to the consensus statement of the ISCL, the USCLC and the EORTC

RESULTS I

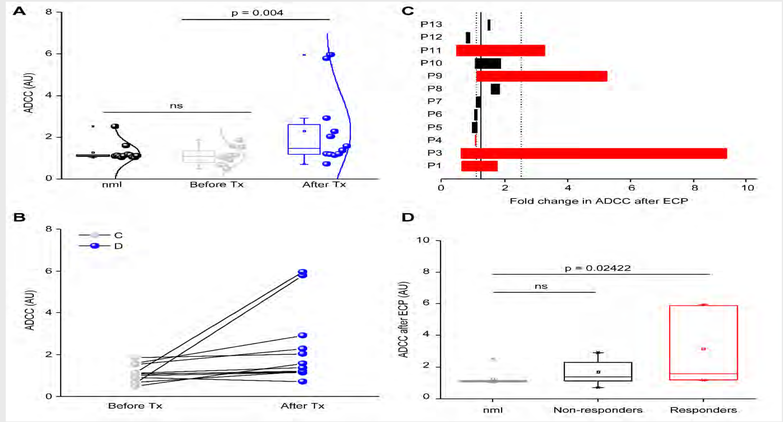
NK cell numbers are reduced in SS compared to healthy and show a tendency of recovery after ECP treatment.



CD3: cluster of differentiation 3; **CD56**: neural cell adhesion molecule; **nml:** healthy doner sample; **SS**: sézary syndrome; **ECP**: extracorporeal photopheresis; **pX**: patient number X

Results II

ADCC is enhanced in ECP responders



nml: healthy donor sample; **ADCC(AU)**: antibody dependent cellular cytotoxicity measured in arbitrary unit; **Tx**: therapy; **pX**: patient number X

CONCLUSIONS

- Long-term ECP only marginally changes the number of NK cells.
- The NK cells ability to facilitate ADCC increases significantly with ECP and selectively in responders to ECP.
- Increase in ADCC can serve as a reliable biomarker to objectively monitor responses to ECP in patients with SS.

BIBLIOGRAPHY

Abstract and References

Research Groupe

Suspicion comes first: Blastic plasmacytoid dendritic cell neoplasm

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INTRODUCTION

- Blastic plasmocytoid dendritic cell neoplasia (BPDCN) is a rare, agressive malignancy (1).
- It originates from transformed plasmacytoid dendritic cells (pDCs) (2).
- pDCs regulate immune response via type I IFN production (3).
- BPDCN incidence: 0.4/100000, M>F, primarily affects older, white adults (4).
- Cutaneous involvement is common, often preceding bone marrow involvement. The skin is often the initial presenting symptom (5).
- Challenging diagnosis, delays are common.
- Differential diagnoses: traumatic ecchymoses, purpuric disorders, angiosarcoma, Kaposi's sarcoma, neuroblastoma, vascular metastases, extramedullary hematopoiesis and skin involvement by other hematologic malignancies (6).
- Immunohistochemical and flow-cytometry are essential for diagnosis. pDC markers: CD4, CD56, CD123, TCL1, CD303 and TCF4 (6).

CASE PRESENTATION

- 68 year-old woman
- 5 cm violaceous nodule on the dorsum of right foot (Fig. 1a)
- First appeared a year ago and increased in size during the last two months
- Dermatologic examination:
  - pale erythematous patches with thin scales on the gluteal region
  - petechial and purpuric macules on the trunk (Fig 1b)
- 1 to 4 cm lymph nodes in cervical, axillary and inguinal areas - USG: lymph nodes that lost their oval contours with asymmetrical cortical hypertrophy.
- Abdominal USG: periportal, celiac, interaortacaval, paracaval and periaortic lymph nodes (the largest 14x24 mm in size).
- Bone marrow biopsy: blastic cell infiltration.

CLINICAL FINDINGS

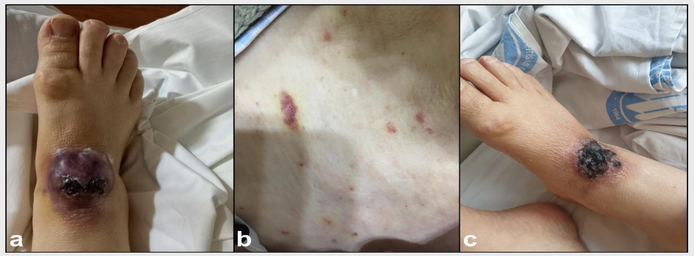

Figure 1. Clinical photographs. a. Violaceous nodule on right foot that ulcerated after biopsy. b. Purpuric macules on trunk. c. Lesion shrank with a crust after first course of chemotherapy.

HISTOPATHOLOGICAL FINDINGS

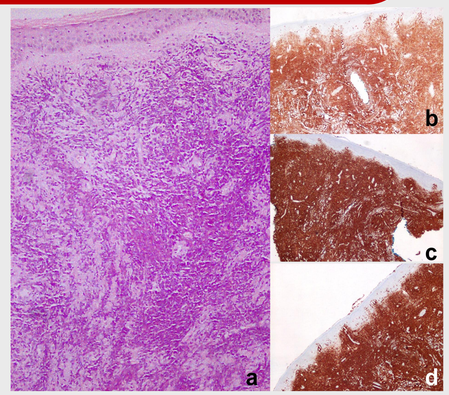

Figure 2: Histopathological photographs. a. Dense monomorphous blastic cell infiltration in dermis with some crush artefact. b. Strong CD4, c. CD56 and d. CD43 positivity.

CONCLUSIONS

The skin is the most common extra-medullary organ involvement of BPDCN (5), and differential diagnosis depends on the quite variable clinical presentation, thus making it harder to think of this diagnosis at first. Cutaneous manifestations include deep purple or brown patches, plaques, or tumors on the skin. Skin lesions may be disseminated or limited to a single location. Disseminated lesions tend to concentrate on the upper trunk while single lesions may be anywhere in the body (5). Our patient's most prominent lesion was a nodule, but she also had patches on the trunk and gluteal region.

BPDCN is a rapidly progressive neoplasm with high mortality and often delayed diagnosis due to diagnostic pitfalls. Our patient's diagnostic process was also prolonged, involving consultations with multiple clinics at different centers. Although this is not a primary cutaneous neoplasm, skin biopsies are often key to diagnosis and should include deep dermis, and shave biopsies should be avoided (4). Since markers for this disorder are uncommonly used by the pathologists, it is essential for the dermatologist to keep this entity in mind and to add it among the differential diagnosis to guide the pathologist, to prevent delayed diagnoses in this aggressive malignancy with short survival rates.

BIBLIOGRAPHY

To see bibliography

To read full text

To reach corresponding author

CD8+ Pseudolymphoma in Two Patients with Idiopathic CD4+ Lymphopenia

Christopher Chung BS[1], Tessa LeWitt BS[1], Joan Guitart MD[1]

[1]Northwestern University

Introduction

Epidermotropic CD8+ pseudolymphoma can arise secondary to CD4+ lymphopenia. This phenomena is thought to be due to homeostatic expansion of a diminished CD4+ T-cell population[1]. The proliferation of these CD4+ T-cells may trigger the activation of CD8+ T-cells leading to a pseudolymphoma[1]. Rarely, this condition can be found in patients with advance HIV with low CD4+ counts. In these cases, highly active antiretroviral therapy can restore the CD4+ count and resolve the pseudolymphoma[2]. In patients with idiopathic CD4+ lymphopenia and CD8+ pseudolymphoma, an exhaustive workup must be done.

Presentation

Case 1 A 58-year-old man with a history of autoimmune enteropathy and erosive lichen planus presented to our clinic with 4-5 years of a gradually worsening rash, mucositis, and constitutional symptoms. His rash began on his torso and slowly spread to his entire body. It had been treated as psoriasis with TNF-α inhibitors, secukinumab, and ustekinumab without improvement. Physical examination revealed near-complete desquamative erythroderma with associated scaling (Figure 1). Mild inguinal lymphadenopathy was present. The patient was admitted to the hospital for supportive care and workup.

The patient was treated with intravenous immunoglobulin, light therapy, acitretin, corticosteroids, thalidomide, tofacitinib, and romidepsin without success. After an 18-month follow-up, the patient received a haploidentical hematopoietic stem cell transplant but died shortly afterwards due to sepsis.

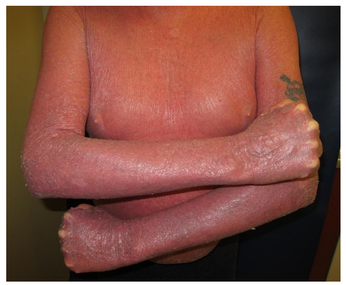

Figure 1. Patient 1 Initial Presentation

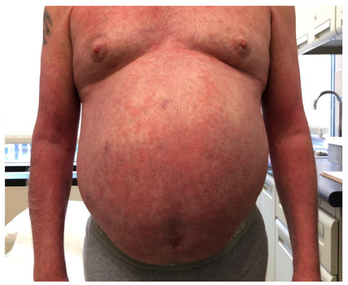

Figure 2. Patient 2 Initial Presentation

Case 2 A 63-year-old man with a history of hypothyroidism, presented to our clinic with a 2-year history of a pruritic, burning rash on the trunk and extremities, exacerbated by ultraviolet light. He had been diagnosed with eczema by an outside dermatologist and was treated unsuccessfully with dupilumab. He had moderate improvement with topical and oral corticosteroids, however the rash flared upon discontinuation. Physical examination revealed pink scaly confluent papules and plaques diffusely involving the chest, abdomen, back, and extremities (Figure 2). No lymphadenopathy was identified.

The patient was started on methotrexate 10mg weekly with improvement of existing lesions but continued to development of new lesions. The dose was escalated to 12.5mg weekly with mild improvement in BSA (~50% at 4-month follow-up) (Figure 4). Repeat flow cytometry demonstrated an absolute CD4+ T-cell count of 84 cells/uL. The patient was only on methotrexate and was not on any prophylactic medications.

Diagnostic Workup

	Case 1	Case 2
CBC	Hb 10.2 g/dL (L), normocytic Slightly absolute lymphopenia 0.9 K/UL	Within normal limits
BMP	Within normal limits	Within normal limits
LDH	Within normal limits	Within normal limits
ANA	1:80	1:160 with negative panel
HIV	Negative	Negative
HTLV1	Negative	Negative
CMV	Negative	IgG positive
EBV	Positive at 500 IU/mL	Negative
Sezary Count	No sezary cells identified	No sezary cells identified
Flow Cytometry	Inverted CD4:CD8 ratio of 0.2. T-cells did not show loss or decreased expression of pan T-cell antigens.	Discrete abnormal CD8+ T-cell population with loss of CD26, and dimmer CD7 expression.
T-Cell Counts	CD4+ 54 cells/mm3 CD8+ 330 cells/mm3	Within normal limits initially, Then, CD4+ 84 cells/uL
Imaging	CT negative	n/a
Skin Biopsy	A pagetoid pattern of atypical small/medium CD8+ lymphocytes (Figure 3)	A pagetoid pattern of atypical CD8+ lymphocytes (Figure 4)
TCR Gamma	Negative	Negative

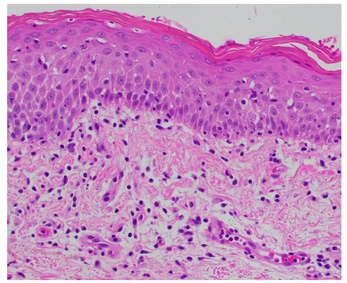

Figure 3. Patient 1 Abdomen Punch Biopsy 20X H&E

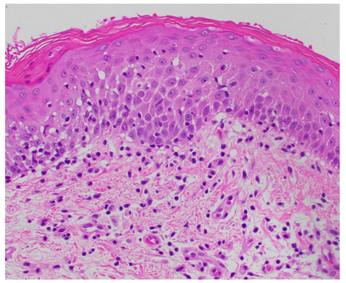

Figure 4. Patient 2 Chest Punch Biopsy 20X H&E

Next Generation Gene Sequencing

Sequencing was performed using Invitae primary immunodeficiency panel of 452 genes

	Gene	Known Immune Function[3-8]	Variant
Case 1	RELA	NF-κB activation	c617G>A, p.Cys206Tyr
	TCIRG1	T-cell Activation	c.2116G>A, p.Glu706Lys
Case 2	RNU4ATAC	snRNA involve in U12 dependent splicing of many genes	n.46G>A, RNA change
	CD3D	T-cell development and signaling	c.356C>A, p.Ala119Asp
	DOCK2	Lymphocyte migration	c.148A>C, p.Ile50Leu
	MTHFD1	De novo purine synthesis	c.1543A>T, p.Ile515Leu

Discussion

These are two patients presenting with (near) erythroderma found to have CD8+ pseudolympoma in the setting of CD4+ lymphopenia. After an exhaustive workup, acquired immunodeficiency is ruled out and adult-onset primary immunodeficiency is presumed. In these cases, stem cell transplant is the only definitive treatment. While the genetic variants identified may be the cause of the patient's lymphopenia, a definitive link cannot be established. Of note, TCIRG1 is involved in T-cell immune regulation, and mutations of this gene have been associated with oral ulcers[9]. CD3D is involved in the development and signal transduction in T-cells while DOCK2 is involved in lymphocyte migration. Further research of these variants is needed.

References (Click Here)

Cutaneous pseudolymphoma caused by Poly Implant Prothèse breast implants

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INTRODUCTION

Cutaneous pseudolymphoma (C-PSL) is not an uncommon condition. C-PSLs may arise in response to a wide variety of foreign antigens or factors: acupuncture, drugs, Borrelia burgdorferi, body piercing, tattoos, insect bites and specific immunotherapy.[1-4] It is important to note that histologically and immunohistochemically identical lesions develop far from the implants, as in the previously described clinical cases of pseudolymphoma caused by specific immunotherapy.[4,5]
Cutaneous pseudolymphoma usually resembles lymphoma morphologically, but in some cases, it may also mimic lymphoma clinically. Consequently, C-PSL could potentially progress to true cutaneous lymphoma with permanent antigenic stimulation.

METHODS

We present a 41-year-old woman with itching polymorphic skin lesions involving the trunk and extremities which first appeared in September 2011 (7 years ago). Physical examination revealed multiple erythematous, scaly macules and patches, indurated red plaques and purplish red and smooth surfaced nodules. Over the period of seven years, the skin lesions grew slowly and spread across the body but sometimes they regressed either spontaneously or after insolation. An excisional biopsy taken from the lesion revealed massive lymphocytic infiltrationwith few plasma cells, histiocytes and eosinophils in the upper and mid-dermis. Immunohistochemistry for CD3, CD4, CD8, CD20 and Ki-67 was performed revealing T-cell predominance (CD3+). Moreover, polymerase chain reaction demonstrated clonal T-cell receptor (TCR)-Cβ1 gene rearrangement in a skin sample

MEASURES

The patient was treated with psoralen plus ultraviolet A (PUVA) photochemotherapy. Oral 8-methoxypsoralen (0.8 mg/kg) was given 2 hours before UVA radiation, three times a week. Overall, the patient underwent 20 procedures with the lesions showing no improvement. We took a careful clinical history that revealed prior breast augmentation surgery with Poly Implant Prothèse breast implants seven years ago. Consequently, the patient underwent implant removal, and as a result, within three weeks the number of lesions and the size of the rash had decreased,and blanching was observed with a 65% regression in mSWAT (modified Severity Weighted Assessment Tool) index.

RESULTS

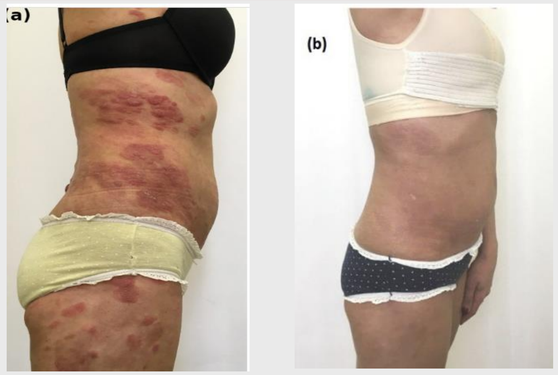

Figure 1. Clinical findings. (a) Multiple polymorphic skin lesions (patches, plaques and nodules) on the thoracolumbar region. (b) Clinical findings 1 year after PIP breast implant removal.

CONCLUSIONS

We reviewed articles identified by searches of Medline, PubMed up to January 2017 using the terms "Poly Implant Prothèse"("PIP"), and discovered that PIP breast implants were more likely to cause adverse effects and complications than other implants.
According to Greco C. et al, the PIP company is known to manufacture breastimplants using unapproved industrial grade silicone (dimethylsiloxane). Their products havebeen banned after numerous studies reporting an increased risk of complications such asbreast carcinoma, xanthoma, mesenchymal tumors, and anaplastic large cell lymphoma.1,9,10Over 400,000 PIP implants have been used for breast augmentation worldwide. We believethat PIP implants were the antigenic stimulus for the development of C-PSL as removal of theimplants caused the rash to decrease.In the present case we describe a unique C-PSL caused by PIP breast implants. To ourknowledge, there are currently no reports on such an association. It's important to rely onclinical, histopathological and molecular biology data. Moreover, accurate history taking iscritical for prompt identification of the causative factor.

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Ichthyosiform lesions: think “lymphomatously”

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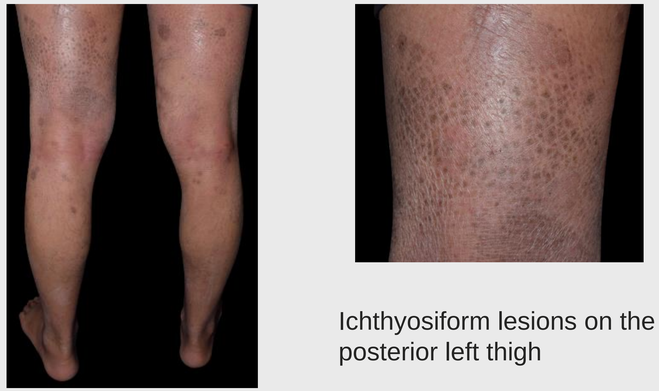
INTRODUCTION

Cutaneous lymphomas represent a heterogeneous group, with mycosis fungoides (MF) being the most common subtype. Apart from the classic Alibert-Bazin disease, many atypical variants of MF have been described. Ichthyosiform MF (IFM) is a very rare variant, with few cases reported in the medical literature.

CASE REPORT

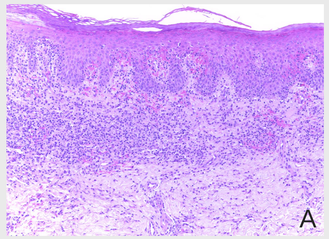
A 45-year-old male had a diagnosis of eritrodermic MF (T4N0M0) in June 2018. He was treated with radiotherapy (20 sessions of total skin irradiation and 10 sessions of localized radiotherapy) until January 2019. Methotrexate has been part of the treatment since the beginning and interferon was initiated in May 2019. There was improvement of his clinical picture until July, when he got COVID-19 and had to discontinue interferon. Thereafter, slightly ictiosiform lesions which had been already observed in his lower limbs became exuberant. New histopathological analysis revealed superficial lymphomatous infiltration in sub-epidermal band, with expression of CD2, CD3, CD4, CD5 and low expression of CD7, confirming the hypothesis of IMF.

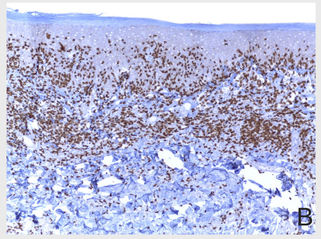
CLINICAL FINDINGS

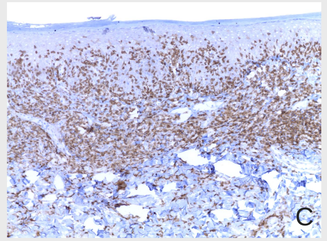


Ichthyosiform lesions on the posterior left thigh

HISTOLOGICAL FINDINGS







Hematoxylin and eosin 100x (A); Immunohistochemistry 100x - CD3 (B) and CD4 C)

DISCUSSION

Acquired ichthyosis usually begins in adult life and constitutes a cutaneous sign of a variety of underlying causes, mostly malignancies. Ichthyosiform eruption as a MF variant is rare, representing about 1.8% of MF cases. It may coexist with other classical or atypical variants of MF or be isolated expressed. It usually presents as widespread ichthyosiform lesions associated with comedo-like lesions and/or follicular keratotic papules, although limbs may exhibit a more striking picture. Histologically, ichtyosiform areas demonstrate compact orthokeratosis, hypogranulosis and an infiltrate composed of small cerebriform lymphocytes with epidermotropism. Therefore, when examining patients with acquired ichthyosiform lesions, biopsies should be performed to rule out, among other causes, the possibility of IMF.

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An Unexpected Case of Adult T-cell Leukaemia–Lymphoma

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The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

INTRODUCTION

Adult T-cell leukaemia-lymphoma (ATLL) is a rare and often aggressive T cell neoplasm. It is aetiologically linked with Human T-cell lymphotrophic virus-1 (HTLV-1) with a distinct geographic distribution. HTLV-1 is endemic in certain parts of the world including Japan, the Caribbean basin, and parts of central Africa and South America.

The virus can be transmitted from mother to child, through unprotected sexual contact and via contaminated blood products.

CASE PRESENTATION

A 29 year old Caucasian man from the UK with no past medical history and no history of foreign travel, was referred to the dermatology department with a three year history of slowly progressive facial lesions involving the periorbital and nasal sidewall regions. These were initially asymptomatic but gradually increased in size to cause symptoms of nasal obstruction. (Figure 1)

Figure 1: Periorbital and nasal sidewall lesions on presentation and in 2018

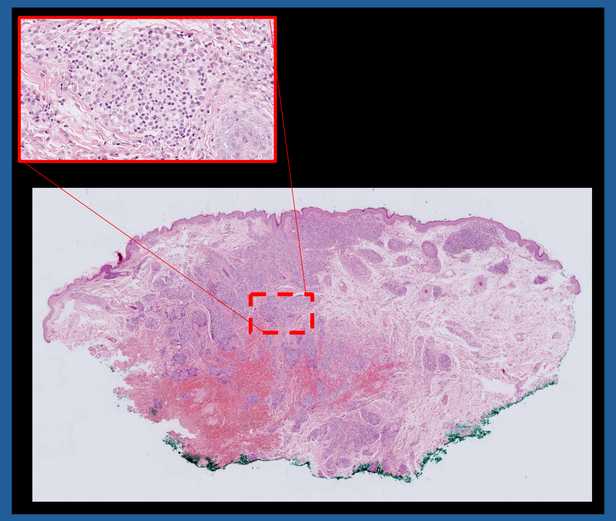

Figure 2: Histology demonstrating dermal and perivascular lymphoid infiltrate

INVESTIGATIONS

Biopsy showed a prominent dermal, predominantly perivascular lymphoid infiltrate composed of medium-sized and occasional large atypical lymphocytes. (Figure 2) Epidermotropism was present. Immunostaining showed the atypical lymphoid cells to express CD2, CD3, CD5 and TCR beta with equal numbers of CD4 and CD8 positive cells.

Blood tests including full blood count, lactate dehydrogenase and calcium were normal. Human immunodeficiency virus was negative. Computed tomography scanning of thorax, abdomen and pelvis was normal.

Human T-cell Lymphotrophic virus-1 was detected, with a blood viral load of 7% and a skin viral load of 100%.

His results were consistent with adult T-cell leukaemia-lymphoma, smouldering variant.

MANAGEMENT

Following multidisciplinary input from different specialities including infectious diseases and the national HTLV-1 clinic, he was commenced on zidovudine 250mg twice daily and interferon alpha 3mg three times per week and remains under review by the national HTLV-1 clinic.

Since his initial contact with health services he failed to attend multiple appointments and lacked compliance with treatment. This was a challenging aspect in the provision of his care.

DISCUSSION

This patient had no identifiable risk factors of HTLV-1 and his diagnosis was unexpected. We hypothesise he may have contracted the virus vertically given his young age and the long latency period seen with ATLL. Unfortunately, his parents were not alive to investigate this further.

The smouldering variant which this patient has can have a prolonged course with a 65% five year survival rate. However, there is a recognized risk of disease progression to the acute variant which has a poor prognosis with less than 10% five year survival.[1]

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Micropapular Sézary syndrome and nodal follicular lymphoma

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Case presentation

A 42-year-old female patient presented a diffuse micropapular erythema on the trunk, upper and lower limbs, including the palms, for three years (Figure 1). She reported no new medications nor exposition to possible allergens. A 3cm lymph node was detected on the left axillary region.

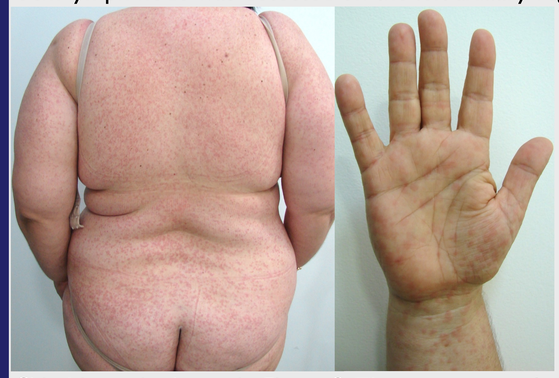

Fig. 1. Diffuse micropapular erythema on the back, upper limbs, and buttocks (A). Erythematous papules on the palm (B).

Skin biopsy is shown in Figure 2. The same monoclonal T-cell population was detected on skin and blood. Increased lactate dehydrogenase (289U/L, reference 135-214U/L), lymphocytosis (5,030/mm^3), CD4/CD8 = 8, CD4+C26- = 55% (2,766/mm^3) and CD4+CD7- = 68% (3,420/mm^3) were observed. Diagnosis of Sézary syndrome was made.

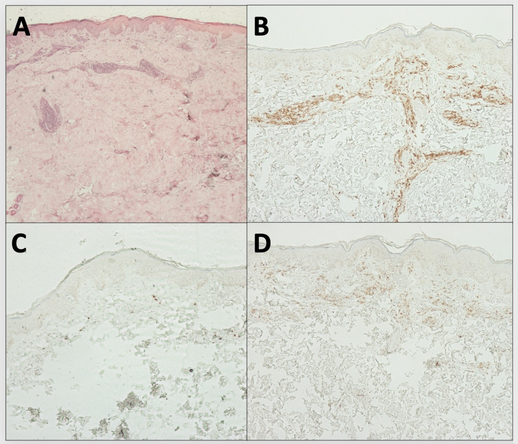

Fig. 2. Skin histopathology.
(A)Superficial perivascular dermatitis (hematoxylin eosin, 40x)
(B) CD4 (100x)
(C) CD8 (100x)
(D) CD7 (100x)

Hypothesis of nodal involvement by Sézary syndrome was not confirmed. Lymph node biopsy showed an atypical lymphocytic infiltrate with CD20+ and BCL-2+ cells, compatible with follicular lymphoma (Figure 3).

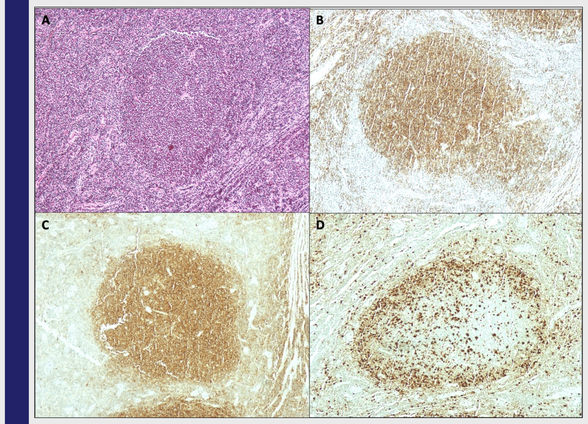

Fig. 3. Lymph node biopsy.
(A)Atypical lymphocytic infiltrate (hematoxylin eosin, 100x)
(B) CD20 (100x)
(C) BCL-2 (100x)
(D) Ki-67 (100x)

Computed tomography showed no visceral lesions. After four cycles of rituximab for treatment of follicular lymphoma, no improvements in skin lesions or lymph node size were observed. Thus, pegylated interferon and PUVA were started for treatment of Sézary syndrome, and complete remission of erythroderma, reduction on lymph node size, and complete blood clearing after 18 months were achieved (2,000 lymphocytes/mm^3, CD4/CD8 ratio 3.1, CD4+CD7- 4.9%, CD4+CD26- 14.7%).

Skin lesions relapsed three other times after using amoxicillin for a dental procedure, nonsteroidal anti-inflammatory drug for back pain, and clindamycin for another dental procedure. On the relapses, no lymph node or blood alterations were detected. However, the same monoclonal T-cell population was observed on skin and blood samples collected in each relapse. Skin biopsies revealed superficial perivascular dermatitis, except for the last relapse when a dense lymphocytic infiltrate with epidermotropism and Pautrier microabscesses were detected (Figure 4).

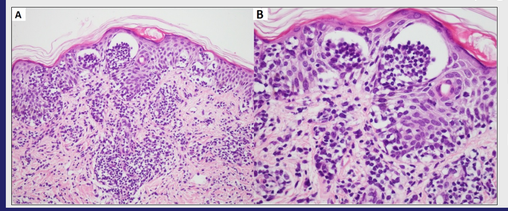

Fig. 4. Dense lymphocytic infiltrate (A); Pautrier microabscesses (B)

CONCLUSIONS

In our patient, some intriguing points may be raised: (1) the micropapular exanthem presentation of Sézary syndrome, which first raised the hypothesis of drug eruption; (2) the lymph node biopsy showing features suggestive of follicular lymphoma; (3) the lack of response to rituximab and excellent response to pegylated interferon for presumed follicular lymphoma; (4) the long remission of Sézary syndrome, an aggressive leukemic variant of cutaneous T-cell lymphoma; (5) the clinical significance of a residual T-cell clone on blood; (6) the relapses of micropapular exanthem with a positive T-cell clone on the skin and the blood after the use of amoxicillin, nonsteroidal anti-inflammatory drug, and clindamycin, and the rapid response with prednisone, that raised the suspicion of a pseudolymphomatous drug eruption; and (7) the skin histology compatible with mycosis fungoides, presence of the same clone on the skin and the blood, and clearing of skin lesions after a short course of prednisone.

We speculate if lymph node biopsy represents a true follicular lymphoma or if it represents an inflammatory pattern secondary to Sézary syndrome, since no response was observed with rituximab and complete regression of lymph node enlargement was achieved with interferon.

The etiopathogenesis of lymphomas is still mostly unknown, and more studies are needed to elucidate the role of genetic/epigenetic predisposition and environmental exposure as possible triggers in lymphomagenesis.

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Progression of Mycosis Fungoides in Patient with Lamellar Ichthyosis

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Introduction

Mycosis fungoides is the most common cutaneous T-Cell lymphoma (CTCL), presenting clinically with scaly erythematous patches/plaques and histologically with superior lymphoid infiltrate and epidermotropism of lymphocytes. Lamellar ichthyosis (LI) is a nonsyndromic autosomal recessive congenital ichthyosis (ARCI) and presents at birth with collodion membrane, which later sheds to reveal red scaly skin with large plate-like scales.

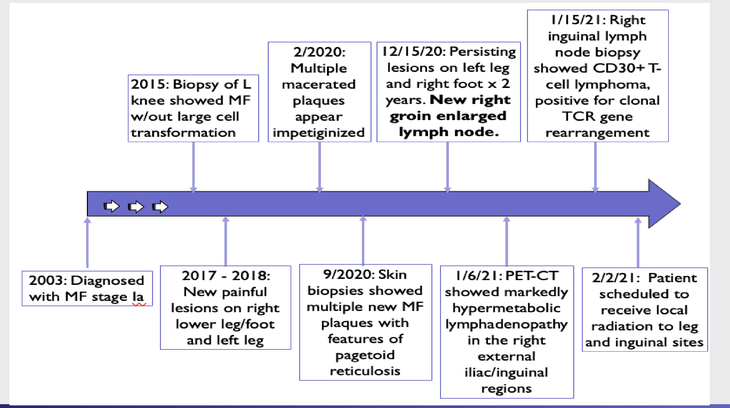
Our challenging case focuses on possible challenges and complications in treating patients with MF upon a background of lamellar ichthyosis.

Challenges

Despite re-initiation of antibacterial soaks, increased acitretin dosage and addition of methotrexate and oral doxycycline, his disease progressed with development of larger thicker plaques and new right inguinal lymphadenopathy. Lymph node biopsy was consistent with CD30+ T cell lymphoma.

Though the patient is scheduled for targeted radiation to the largest plaques on the legs and right groin lymph node, further management steps beyond this are unclear. Options include increasing the dose of acitretin or methotrexate, brentuximab vedotin, HDAC inhibitors, anti-PD1 immunotherapy and even aggressive antibiotic therapy.

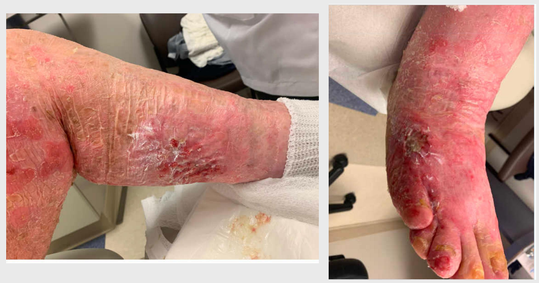
Disease Progression Timeline



Case Presentation

A 66-year-old male with lamellar ichthyosis and a 20-year history of stage IA mycosis fungoides (MF) managed with oral retinoids, phototherapy, topical steroids, and bleach and vinegar soaks presented with non-healing ulcers on the bilateral lower extremities. Recent biopsies of his MF have increasingly been characterized by pagetoid epidermotropism of atypical lymphocytes that are TIA1 positive, and negative for CD4 and CD8. Over the past year, due to access and social issues during the COVID19 pandemic, he stopped narrowband UVB therapy and antibacterial soaks, which corresponded with worsening ulcerated plaques that demonstrated blastomycosis-like pyoderma and MF.

Clinical Images



Most recent clinical images taken 02/2021: Persisting MF plaques on left leg (left) and right foot (right) despite treatment regimen of antibacterial soaks, increased acitretin dosage, addition of methotrexate and oral doxycycline

Discussion

We present a case of previously stable stage IA mycosis fungoides progressing to plaques with double negative phenotype and pagetoid pattern, now with nodal involvement, complicated by a background of lamellar ichthyosis and multiple skin infections. The patient's underlying lamellar ichthyosis causes impaired skin barrier, likely leading to bacterial impetiginization and increased susceptibility to infection. We hypothesize that certain bacterial infections may even drive progression of disease. Finally, severe xerosis and skin barrier defects in ichthyosis and long-term acitretin use may present unique challenges when treating with systemic therapies and radiation for cutaneous T cell lymphoma.

There is lack of existing literature on management of patients with both lamellar ichthyosis and MF or any information on susceptibility for MF in those with lamellar ichthyosis.

PRIMARY CUTANEOUS T-CELL LYMPHOMA SHOWING GAMMA/DELTA PHENOTYPE

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INTRODUCTION

Primary cutaneous gamma/delta T-cell lymphoma (PCGDTCL) is a rare and very aggressive cutaneous T-cell lymphoma (CTCL) subtype composed of a clonal proliferation of mature activated T cells expressing TCRγδ chains. PCGDTCL accounts for approximately 1% of all primary cutaneous lymphomas, mainly in middle-aged to elderly patients (1). Five-year overall survival rates range between 11% to 33% and the median survival is 15 months (2). In some cases, MF-like lesions may be initially noticed and later evolve into an aggressive disease with ulceration (3). Lymph node and bone marrow are mostly uninvolved (1). B symptoms, including fevers, night sweats and weight loss are not uncommon. In skin biopsies, variable epidermotropic, dermal or subcutaneous lymphoid infiltrate patterns can be seen (2,5,6). Although the presence of γδ T-cells is typically aggressive and associated with poor prognosis, rare cases presenting with indolent behavior have been reported (5,7).

Expression of TCRγδ has also been found in rare cases of otherwise classic MF or LyP. These cases can be clinically and histopathologically similar, and the way that these lymphomas should be classified remains to be clarified. In our case differential diagnosis between gamma/delta MF and primary gamma/delta lymphoma was a big challenge, and diagnosis was based more on clinical grounds and disease course whereas histology could not add to the differentiation between the 2 entities.

CASE REPORT

A 58-year-old man was referred to our Cutaneous Lymphoma Centre in 2019 with multiple violet-to-red patches and plaques, located mainly on trunk, chest, back, lower and upper limbs (figure 1), clinically resembling MF.

He has a 6-year personal history of Ca of the larynx, treated with surgery, radiation therapy and chemotherapy and was left with a permanent tracheostomy. In 2014 he was diagnosed with histologically confirmed MF plaque stage and initial treatments involved PUVA and topical steroids with PR In 2017 he developed a progressive skin disease and histology was supportive of of gamma/delta lymphoma superficial type. He was treated with CHOEP (6 sessions), autologous stem cell transplantation (BEAM), chemotherapy with gemcitabine (4 sessions), topical radiotherapy and very potent topical steroids (near CR), and had one-year progression free survival.

A new skin biopsy was performed in our center in 2019. Histopathological and immunohistochemical analysis displayed an atypical lymphoid infiltrate, involving epidermis and dermis(figure 2a), consisting of CD3+CD4-CD5-CD8+CD56- small to medium-size cells, a strong expression of TCRγ+ and a high Ki-67 60-70% (figure 2b). Absence of large-size cells but with a strong expression of TCRγ+ made the diagnosis of MF with a gamma/delta phenotype more likely. Blood work and PET-CT scan were negative. TSEB was initiated with very good partial but short-term response. Then, the patient received Peginterferon alpha-2a, for only two months and finally stopped due to side effects and cytopenia. We initiated treatment with monochemotherapy Doxorubicin (45MG) with very good response, nearCR. After the 6th cycle of Doxorubicin and approximately four months progression free survival, the patient presented again with increased disease activity and aggressive course having violaceous infliltrated plaques located on trunk, back and legs(figure 3). New biopsy confirmed an aggressive CTCL, either an indolent PCGDTCL or MF with a gamma/delta phenotype, showing an aggressive course, which does not respond anymore to skin-directed therapies. Patient underwent allogeneic hematopoietic stem cell transplantation (HSCT) three months ago (2021) and he is in close monitoring.

PHOTOS

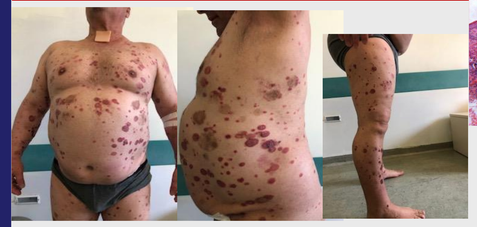

Figure 1

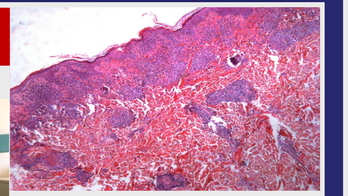

Figure 2a: Dermis and epidermis infiltrated by atypical cells. H&E, microscopic magnification.

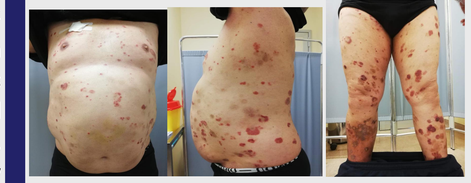

Figure 3

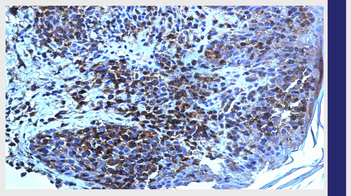

Fig 2b: Expression of TCRγ+ cells.

CONCLUSION

Our patient's disease course and survival is not consistent with an aggressive gamma delta lymphoma but more with a gamma delta CTCL with more indolent course most likely a gamma/delta MF. The diagnostic dilemma in our case lays between a primary cutaneous gamma-delta T-cell lymphoma with a more indolent course of superficial type, and gamma-delta MF showing an aggressive course. The identification of a gamma/delta phenotype in a case clinically and histopathologically resembling MF requires a close monitoring and awareness of potential aggressive behavior and suggests the need of further classification based on clinical, histopathological and molecular studies.

Due to the rarity of these disorders and clinicopathologic overlap, there is limited data to guide therapeutic approaches and treatment recommendations are primarily based upon data from small series. All therapies in cases of cutaneous T-cell lymphomas with a gamma/delta phenotype have shown modest effectiveness, and disease resistance to multi-agent chemotherapy is not uncommon. HSCT is considered a last treatment option and has been successful in some patients.

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