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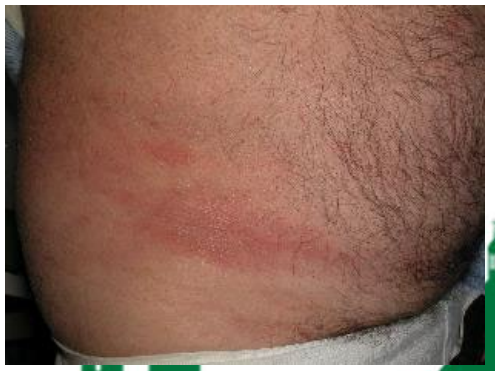
29 novembre 2023

Valeria Brazzelli

La micosi fungoide e i farmaci biologici: una difficile convivenza



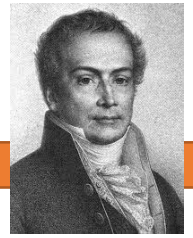
Micosis Fungoide→ consensus points

- **La MF è il linfoma cutaneo primitivo a cellule T più comune**
- La MF rappresenta dallo 0,5% al 3% di tutti i linfomi non Hodgkin
- L'incidenza annuale è di circa 0,2-0,4 casi ogni 100.000 abitanti
- La MF ha un'ampia distribuzione per età al momento della diagnosi, con la maggior parte dei pazienti diagnosticati di età compresa tra 40 e 60 anni
- Colpisce principalmente gli anziani con un rapporto maschi/femmine da 1,6:1 a 2:1

- La maggior parte dei pazienti con MF conclamata ha una storia di malattia con minime chiazze eritematose di lunga data

- **Willenze R**, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, et al. WHO-EORTC classification of cutaneous lymphomas. Blood. 2005; 105:3768-85
- **Bradford PT**, Devesa SS, Anderson WF et al. Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. Blood 2009;113:5064–5073.
- **Willemze R**. et Al. Classification of cutaneous T-cell lymphoma: from Alibert to WHO-EORTC. J Cutan Pathol 2006: 33 (Suppl. 1): 18–26
- **Wilcox R**. Cutaneous T-cell lymphoma: 2017 update on diagnosis, risk-stratification, and management. Am J Hematol. 2017;92:1085–1102.
- **Trautinger F. et Al. E**uropean Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sezary syndrome e Update 2017. Eur J Cancer 77 (2017) 57e74

Storia della MICOSI FUNGOIDE

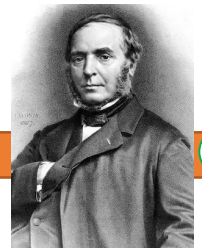


1806

The **French dermatologist** **Jean Luis Alibert** first described mycosis fungoides as “pian fungoide

1835

In 1835, Alibert used the terms “mycosis fungoides” to describe the clinical presentation of mushroom-like tumors characteristic of this entity.



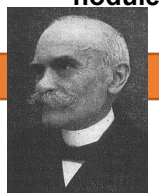
1862

Ernest Bazin (1807-1878) described the natural evolution of the disease and defined its stages integrated into the **staging: patch, plaque and nodules**

1885

Louis Brocq coined the term “Parapsoriasis” and described 2 distinct variants

Vidal and Brocq introduced the term MF d’emble´e for patients s presenting with skin tumors



1885

Heinrich Auspitz introduced the term “granuloma fungoides” because he believed that this disease represented an inflammatory reaction of the reticuloendothelial system

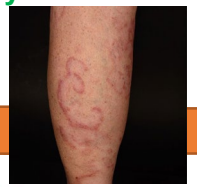
1936

the Italian dermatologist **Aldo Baccaredda-Boy** described for the first time the circulating cells characteristic of this syndrome, which were then, undeservedly, called Sézary cells

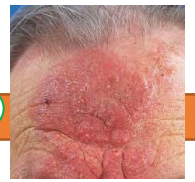
1938

Sézary syndrome (SS) was first described by **Albert Sézary**

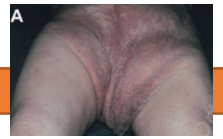
1939



1957



1970



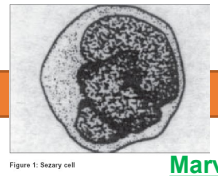


Figure 1: Sezary cell

1975

Marvin Lutzner coined the term **“cutaneous T-cell lymphoma”** to refer to both MF andSS, malignant tumors of T lymphocyte origin closely related to each other, representing theaccording to the leukemic form of the first

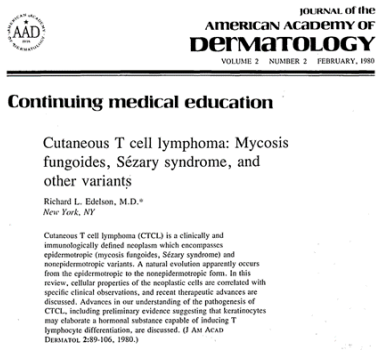
1968. Thus, in the early 1970s, MF, SS, and some related conditions were the only types of cutaneous lymphoma that had been rather well described.[4] Reports on cutaneous lymphomas other than MF/SS were few. Moreover, they were firmly believed to represent skin manifestations of a systemic lymphoma and treated consistently.

Other variants described included **pagetoid reticulosis** in 1939, **folliculotropic variant** in 1957, and the **granulomatous variant** in 1970

Willemze R, Meijer CJLM. Classification of cutaneous T-cell lymphoma: from Alibert to WHO-EORTC. J Cutan Pathol 2006; 33 (Suppl. 1): 18–26.

1975

Richard Edelson introduced the unifying concept of **Cutaneous T Cell Lymphoma (CTCL)**, as a malignancy of skin-homing malignant CD4 T cells. Second, he devised Extracorporeal Photochemotherapy, which became the first FDA-approved immunotherapy for any cancer.



JOURNAL of the AMERICAN ACADEMY OF DERMATOLOGY
VOLUME 2 NUMBER 2 FEBRUARY, 1980

Continuing medical education

Cutaneous T cell lymphoma: Mycosis fungoides, Sézary syndrome, and other variants

Richard L. Edelson, M.D.*
New York, NY

Cutaneous T cell lymphoma (CTCL) is a clinically and immunologically defined neoplasm which encompasses epidermotropic (mycosis fungoides, Sézary syndrome) and nonepidermotropic variants. A natural evolution apparently occurs from the epidermotropic to the nonepidermotropic form. In this review, cellular properties of the neoplastic cells are correlated with specific clinical observations, and recent therapeutic advances are discussed. Advances in our understanding of the pathogenesis of CTCL, including preliminary evidence suggesting that keratinocytes may elaborate a hormonal substance capable of inducing T lymphocyte differentiation, are discussed. (J Am Acad Dermatol 2:89-106, 1980.)

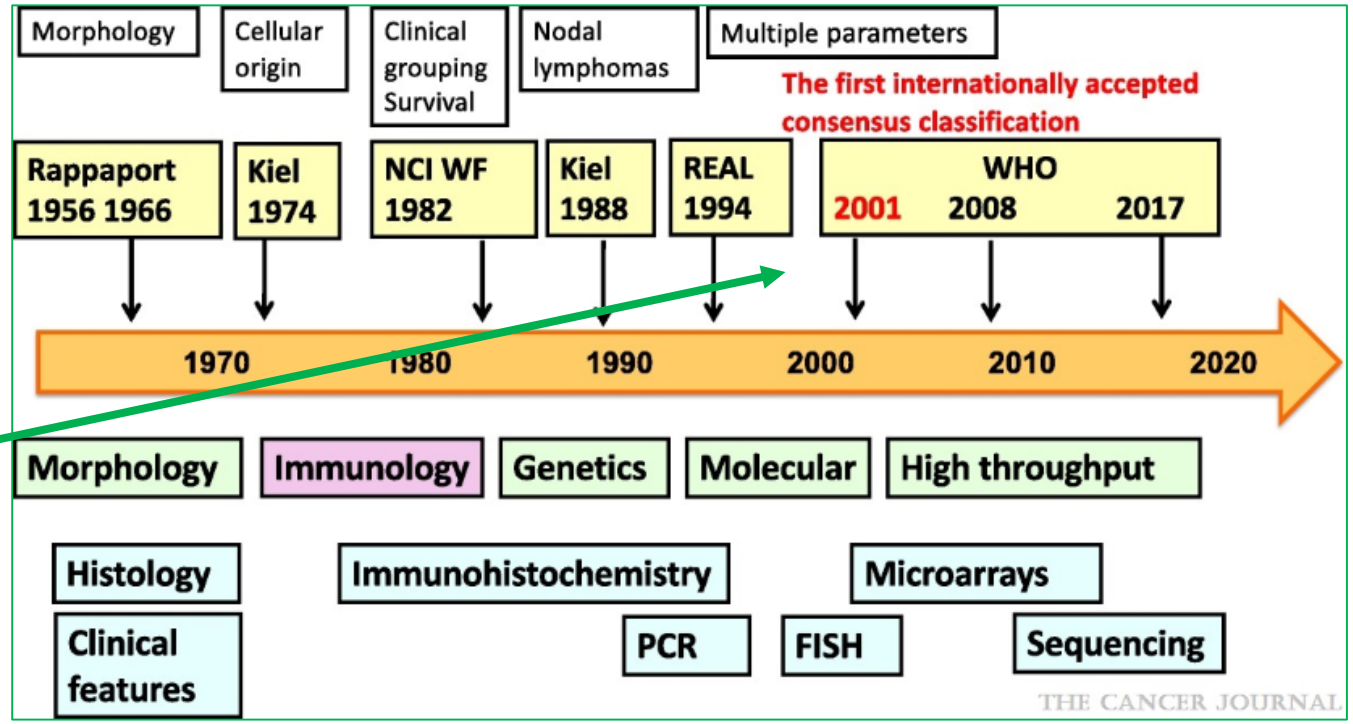
1980'

Table 1. Classification of Cutaneous T-cell lymphoma (CTCL) in WHO-EORTC classification with corresponding categories in the EORTC and WHO classifications, frequency and disease-specific 5-year-survival data

WHO-EORTC Classification	Corresponding categories in the EORTC Classification	Corresponding categories in the WHO Classification	Frequency (%)*	5-year survival (%)
Indolent clinical behavior	*Indolent clinical behavior*	*Indolent clinical behavior*		
Mycosis fungoides	Mycosis fungoides	Mycosis fungoides	54	88
Folliculotropic MF	MF-associated follicular mucinosis	MF-associated follicular mucinosis	6	80
Pagetoid reticulosis	Pagetoid reticulosis	Pagetoid reticulosis	1	100
Granulomatous slack skin	Granulomatous slack skin	Granulomatous slack skin	<1	100
Primary cutaneous CD30+ LPD		Primary cutaneous CD30+ LPD		
Primary cutaneous anaplastic large-cell lymphoma	Primary cutaneous CD30+ large T-cell lymphoma	Primary cutaneous anaplastic large-cell lymphoma	10	95
Lymphomatoid papulosis	Lymphomatoid papulosis	Lymphomatoid papulosis	16	100
Subcutaneous panniculitis-like T-cell lymphoma†	Subcutaneous panniculitis-like T-cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma	1	82
Primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma‡	Primary cutaneous small/medium pleomorphic T-cell lymphoma	Peripheral T-cell lymphoma, unspecified	3	75
Aggressive clinical behavior	*Aggressive clinical behavior*	*Aggressive clinical behavior*		
Sézary syndrome	Sézary syndrome	Sézary syndrome	4	24
Extranodal NK/T-cell lymphoma, nasal-type		Extranodal NK/T-cell lymphoma, nasal type	<1	NR
Primary cutaneous aggressive CD8+ T-cell lymphoma§	Primary cutaneous CD30- negative large T-cell lymphoma	Peripheral T-cell lymphoma, unspecified	1	18
Cutaneous / T-cell lymphoma§	or	Peripheral T-cell lymphoma, unspecified	1	NR
Primary cutaneous peripheral T-cell lymphoma, unspecified‡	Primary cutaneous small/medium pleomorphic T-cell lymphoma	Peripheral T-cell lymphoma, unspecified	3	16

NR, not reached.
*Data are based on 1476 CTCL patients registered at the Dutch and Austrian Cutaneous Lymphoma Group classified according to the WHO-EORTC classification.[3]
†Includes only cases with an α/β^+ T-cell phenotype.
‡Primary cutaneous T-cell lymphoma, unspecified excluding the three provisional entities indicated with †.

Willemze R, Kerl H, Sterry W, et al. EORTC classification for primary cutaneous lymphomas. A proposal from the Cutaneous Lymphoma Study Group of the European Organization for Research and Treatment of Cancer (EORTC). Blood 1997; 90: 354.



Willemze R, Meijer CJLM. Classification of cutaneous T-cell lymphoma: from Alibert to WHO-EORTC. J Cutan Pathol 2006 Lymphoma Classification de Leval, L; Jaffe, ES. Cancer J 2020.

Haematolymphoid Tumours
Lymphoid Neoplasms
CTCLS

World Health Organization

- **Micosi Fungoide (MF) (>50-55% di tutti CTCLS)**
- Sindrome di Sezary
- Disord. Linfoprolif. cutanei CD30+
  - Papulosi linfomatoide (LyP)
  - Linfoma a grandi cellule anaplastiche CD30+
- Linfoma T sottocutaneo simil-panniculitico
- Disord. linfoprolif. cutaneo, piccole/medie cellule CD4+
- Disord. linfoprolif. cutaneo acrale CD8+
- Linfoma primitivi cut. gamma/delta
- Linfoma cut. T CD8+ citotossico, epidermotropo, aggressivo
- Linfoma cutaneo T periferico NOS

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REVIEW ARTICLE OPEN

LYMPHOMA

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms

Rita Alaggio[1], Catalina Amador[2], Ioannis Anagnostopoulos[3], Ayoma D. Attygalle[4], Iguaracyra Barreto de Oliveira Araujo[5], Emilio Berti[6], Govind Bhagat[7], Anita Maria Borges[8], Daniel Boyer[9], Mariarita Calaminici[10], Amy Chadburn[11], John K. C. Chan[12], Wah Cheuk[12], Wee-Joo Chng[13], John K. Choi[14], Shih-Sung Chuang[15], Sarah E. Coupland[16], Magdalena Czader[17], Sandeep S. Dave[18], Daphne de Jong[19], Ming-Qing Du[20,21], Kojo S. Elenitoba-Johnson[22], Judith Ferry[22,23], Julia Geyer[11], Dita Gratzinger[23], Joan Guitart[24], Sumeet Gujral[25], Marian Harris[26], Christine J. Harrison[27], Sylvia Hartmann[28], Andreas Hochhaus[29], Patty M. Jansen[30], Kennosuke Karube[31], Werner Kempf[32], Joseph Khoury[33], Hiroshi Kimura[34], Wolfram Klapper[35], Alexandra E. Kovach[36], Shaji Kumar[37], Alexander J. Lazar[38], Stefano Lazzi[39], Lorenzo Leoncini[39], Nelson Leung[40], Vasiliki Leventaki[41], Xiao-Qiu Li[42], Megan S. Lim[21], Wei-Ping Liu[43], Abner Louissaint Jr.[22], Andrea Marcogliese[44], L. Jeffrey Medeiros[33], Michael Michal[45], Roberto N. Miranda[33], Christina Mitteldorf[46], Santiago Montes-Moreno[47], William Morice[48], Valentina Nardi[22], Kikkeri N. Naresh[49], Yasodha Natkunam[23], Siok-Bian Ng[50], Ilske Oschlies[35], German Ott[51,52], Marie Parrens[52], Melissa Pulitzer[53], S. Vincent Rajkumar[54], Andrew C. Rawstron[55], Karen Rech[48], Andreas Rosenwald[3], Jonathan Said[56], Clémentine Sarkozy[57], Shahin Sayed[58], Caner Saygin[59], Anna Schuh[60], William Sewell[61], Reiner Siebert[62,63], Aliyah R. Sohani[22], Reuben Tooze[63], Alexandra Traverse-Glehen[64], Francisco Vega[33], Beatrice Vergier[65], Ashutosh D. Wechalekar[66], Brent Wood[36], Luc Xerri[67] and Wenbin Xiao[53]

Review > Eur J Dermatol. 2023 Aug 1;33(4):360-367. doi: 10.1684/ejd.2023.4531.

Epidemiology of cutaneous T-cell lymphomas: state of the art and a focus on the Italian Marche region

Alessandro Pileri [1], Erika Morsia [2], Corrado Zengarini [1], Elena Torre [3], Gaia Goteri [4], Pietro Quaglino [5], Nicola Pimpinelli [6], Marco Paulli [7], Stefano A Pileri [8], Pier Luigi Zinzani [9], Serena Rupoli [3]

Affiliations + expand

PMID: 37823487 DOI: 10.1684/ejd.2023.4531

Abstract

Among primary cutaneous T-cell lymphomas (CTCL), mycosis fungoides (MF) is the most frequent and, along with Sézary syndrome (SS), the best-studied subtype. Most available studies on epidemiology of MF and SS are based on small cohorts or different inclusion criteria. Moreover, although this has become a hot topic, most studies show limitations, such as selection bias and lack of clinical information or follow-up data. Therefore, no reliable conclusions can be drawn. This paper reviews the current data underpinning our understanding of the epidemiology of MF and SS, and presents some original findings based on data retrieved from the cutaneous lymphoma registry of the Italian Marche region. The Marche Regional Cutaneous Lymphoma Registry is a multidisciplinary team founded 27 years ago to share the management of these rare disorders. All patients with a clinical and histologically confirmed diagnosis of primary cutaneous lymphoma are centralized in Ancona (Italy) at the Haematology Clinic, Polytechnic University of Marche, for clinical evaluation, staging, treatment, and follow-up. This paper emphasizes the need for a national registry of pCLs in Italy, as no detailed epidemiological information is available in the country except for the Marche Regional Cutaneous Lymphoma Registry. A national registry would allow for more comprehensive data collection from all over Italy and could provide more accurate information on incidence and epidemiology. This would be beneficial for understanding the pathogenesis and diagnostic procedures of these diseases and could improve patient outcomes. Therefore, we advise the creation of a national registry of pCLs in

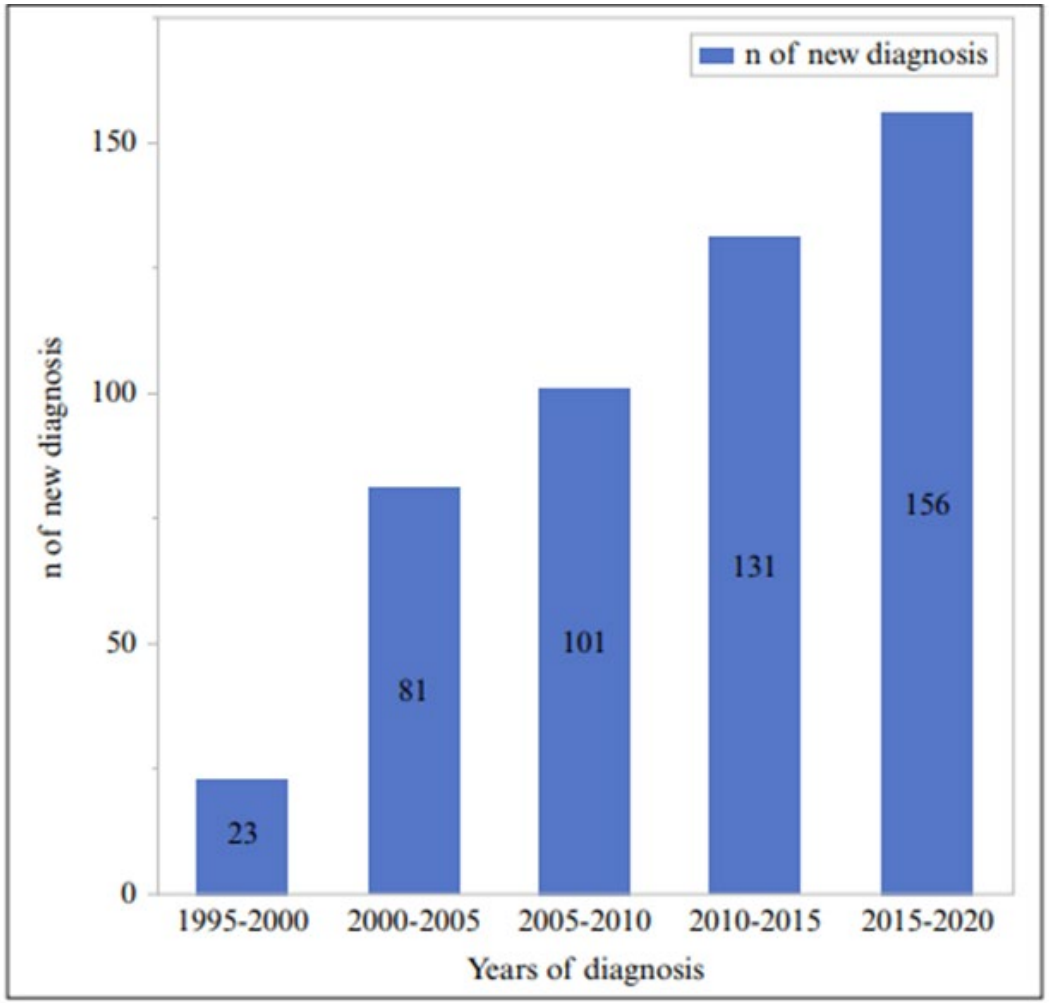

Figure 1. Registration of the MDT Registry (1995-2020).

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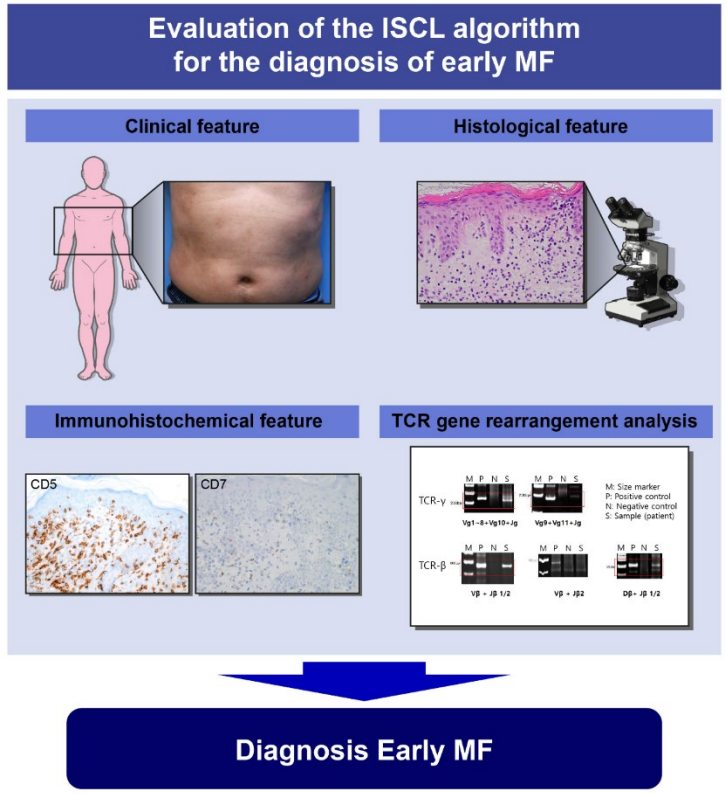
Early diagnosis

Defining early mycosis fungoides

Nicola Pimpinelli, MD,[a] Elise A. Olsen, MD,[c] Marco Santucci, MD,[b] Eric Vonderheid, MD,[d] Andreas C. Haeffner, MD,[e] Seth Stevens, MD,[f] Guenter Burg, MD,[e] Lorenzo Cerroni, MD,[g] Brigitte Dreno, MD,[h] Earl Glusac, MD,[i] Joan Guitart, MD,[j] Peter W. Heald, MD,[i] Werner Kempf, MD,[e] Robert Knobler, MD,[k] Stuart Lessin, MD,[l] Christian Sander, MD,[m] Bruce S. Smoller, MD,[n] Gladys Telang, MD,[o] Sean Whittaker, MD,[p] Keiji Iwatsuki, MD, PhD,[q] Erik Obitz, MD,[r] Masahiro Takigawa, MD,[s] Maria L. Turner, MD,[t] and Gary S. Wood, MD,[u] for the International Society for Cutaneous Lymphoma

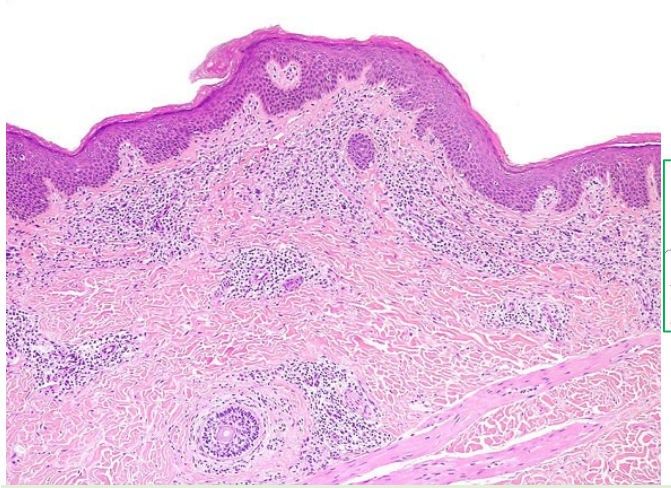


- To arrive at a diagnosis, combine:
  - ❑ Histology
  - ❑ **Clinical presentation**
  - ❑ Immunophenotype
  - ❑ Molecular features

Table I. Algorithm for diagnosis of early MF*

Criteria	Scoring system
Clinical	
Basic	2 points for basic criteria and two additional criteria
Persistent and/or progressive patches/thin plaques	1 point for basic criteria and one additional criterion
Additional	
1) Non-sun exposed location	
2) Size/shape variation	
3) Poikiloderma	
Histopathologic	
Basic	2 points for basic criteria and two additional criteria
Superficial lymphoid infiltrate	1 point for basic criteria and one additional criterion
Additional	
1) Epidermotropism without spongiosis	
2) Lymphoid atypia†	
Molecular biological	
1) Clonal TCR gene rearrangement	1 point for clonality
Immunopathologic	
1) <50% CD2+, CD3+, and/or CD5+ T cells	1 point for one or more criteria
2) <10% CD7+ T cells	
3) Epidermal/dermal discordance of CD2, CD3, CD5, or CD7‡	

2021

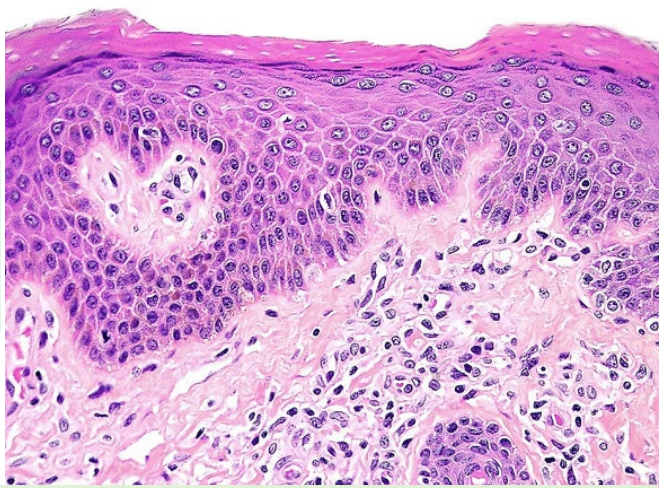


PRIMER

Check for updates

Cutaneous T cell lymphoma

Reinhard Dummer[1,2]✉, Maarten H. Vermeer[3], Julia J. Scarisbrick[4], Youn H. Kim[5], Connor Stonesifer[6], Cornelis P. Tensen[3], Larisa J. Geskin[6], Pietro Quaglino[7] and Egle Ramelyte[1,2]



- **80-90% T-CD4+ «memory, skin-resident»:** CD2, CD3, TCR-β, rar. **CD8**; -/+ espress. molecole citotossiche
- 3/4 casi **delez. antigeniche**: CD7 (64%); CD3 (59%); CD5 (40%); CD2 (14%); CD7 perso anche in disordini infiammatori benigni (DIB)
- **CD30 variabilità**: intra/inter-lesionale; positiv. CLA, CCR4, talora PD1; TOX (?), CADM1 (?)
- Riarrang. **TCR < 50%** MF «early» (dato tecnica correlato)

Leukemia. 2004 Sep;18(9):1531-8. doi: 10.1038/sj.leu.2403428.

f BIOMED-2 multiplex PCR tubes for TCRB gene rearrangements in T-cell s

ak, P J T A Groenen, M Brüggemann, P Neumann, I L M Wolvers-Tettero ba, J J M van Dongen

Received: 17 February 2021

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REVIEW

Clinicopathologic Variants of Mycosis Fungoides☆

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Received 17 May 2016; accepted 4 August 2016
Available online 28 February 2017

KEYWORDS
Cutaneous lymphomas;
Mycosis fungoides;
Variants;
Dermatopathology

Abstract Mycosis fungoides (MF) is the most common primary cutaneous T-cell lymphoma. The clinical course of the disease is typically characterized by progression from a nonspecific phase of erythematous macules to the appearance of plaques and ultimately, in some patients, tumors. However, numerous clinical and histopathologic variants of MF with specific therapeutic and prognostic implications have been described in recent decades. Clarification of the differential diagnosis can be frustrated by the wide range of clinical manifestations and histopathologic patterns of cutaneous infiltration, particularly in the early phases of the disease. In this paper, we review the main clinical, histopathologic, and immunohistochemical characteristics of the variants of MF described in the literature in order to facilitate early diagnosis of the disease.

Table 2 Clinical, Clinicopathologic, and Histologic Variants of Mycosis Fungoides.

Clinical Variants
Hypopigmented mycosis fungoides
Erythrodermic mycosis fungoides
Ichthyosiform mycosis fungoides
Mycosis fungoides palmaris et plantaris
Papillomatous mycosis fungoides
Papular mycosis fungoides
Solitary or unilesional mycosis fungoides
Invisible mycosis fungoides
Clinicopathologic variants
Folliculotropic mycosis fungoides
Mycosis fungoides with eruptive infundibular cysts
Syringotropic mycosis fungoides
Granulomatous slack skin
Pagetoid reticulosis or Woringer-Kolopp disease
Poikilodermal mycosis fungoides (poikiloderma vasculare atrophicans)
Bullous mycosis fungoides and dyshidrotic mycosis fungoides
Anetodermic mycosis fungoides
Hyperpigmented mycosis fungoides
Purpuric mycosis fungoides
Pustular mycosis fungoides
Verrucous mycosis fungoides
Histopathologic variants
Granulomatous mycosis fungoides
Interstitial mycosis fungoides
Mycosis fungoides with large-cell transformation

Hydroa vacciniforme-like lymphoproliferative disorder

Dermatol Ther (Heidelb) (2021) 11:1931–1951
https://doi.org/10.1007/s13555-021-00625-6

REVIEW

A Comprehensive Update of the Atypical, Rare and Mimicking Presentations of Mycosis Fungoides

Eve Lebas · Patrick Collins · Joan Somja · Arjen F. Nikkels

Received: August 9, 2021 / Published online: October 28, 2021

ABSTRACT

Introduction: Mycosis fungoides (MF) is the most frequent subtype of primary cutaneous T cell lymphomas (pCTCL). The diagnosis may be particularly difficult in the early stages as well as in atypical and rare clinical presentations. Furthermore, MF may simulate a large variety of common dermatologic disorders and patterns, both histopathologically and clinically.
Methods: A literature search was performed to provide a comprehensive update on the rare and atypical MF manifestations as well as the dermatoses and dermatological patterns that could be imitated by MF.
Results: A total of 114 publications were found describing a series of different dermatoses and dermatological patterns mimicked by MF, as well as some particular localizations of MF lesions and dermatoses that occur in preexisting MF lesions.
Conclusions: The number of dermatoses that can be imitated by MF is ever-increasing. Patients with common dermatologic conditions that prove to be treatment refractory should be biopsied without delay, and sequentially as necessary, to prevent delay in diagnosis and progression of disease. Clinicopathologic correlation is the best way of diagnosis.

Keywords: Mycosis fungoides; Primary cutaneous T cell lymphoma; pCTCL dermatology; Atypical manifestations; Diagnostic delay

Key Summary Points
Why carry out this study?
Mycosis fungoides may present many atypical and rare forms, often imitating other dermatoses, delaying diagnosis.
What was learned from the study?
This study presents an update of the dermatological manifestations of mycosis fungoides and their corresponding histological presentations.
The number of dermatoses that can be imitated by mycosis fungoides is ever-increasing.
Patients with common dermatologic conditions that prove to be treatment refractory should be biopsied without delay, and sequentially as necessary, to prevent delay in diagnosis and progression of disease. Clinicopathologic correlation is the best way of diagnosis.

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Department of Dermatopathology, CHU du Sart Tilman, University of Liège, 4000 Liège, Belgium

Table 1 continued

Mimicking disease	Histological subtype of MF	References
Perioral dermatitis	Folliculotropic MF	[44]
Pigmented purpuric dermatosis	Pigmented purpuric dermatitis with classic MF	[31, 45–52]
Pityriasis alba	Classic MF with epidermotropic atypical Lc	[8, 53]
Pityriasis lichenoides	Classic MF, lymphocytic epidermotropism, and Lc tagging the dermo-epidermal junction. Hyperchromatic and irregular nuclei of atypical Lc, the infiltrating lymphocytes: CD2, CD3, CD5, CD7, and CD8: +. CD4, CD20, CD30, CD68, and CD163: −. TCR: rearrangement of the gamma chain	[54, 55]
Pseudolymphomatous angiokeratoma	Granulomatous MF	[14]
Psoriasis inversa	Classic MF; marked psoriasiform epidermal hyperplasia with epidermotropic atypical Lc	Figures 7, 8
Psoriasis vulgaris	Classic MF; marked psoriasiform epidermal hyperplasia with epidermotropic atypical Lc	[31, 56, 57]
Pyoderma gangrenosum	Neutrophil-rich MF	[58] Figure 9
Reticular erythematous mucinosis	Classic MF	[59]
Rosacea	Folliculotropic MF	Figure 10
Sarcoidosis	Granulomatous MF. Granulomatous infiltrate rich in giant cells, emperipolesis, histiocytic cells, and scattered eosinophils, sometimes reaching the fascia and muscle; the absence of elastic fibers or their phagocytosis by giant cells; and Lc with atypia and epidermotropism	[60, 61]
Seborrheic dermatitis	Classic MF	Figure 11
Urticaria	Classic MF	[62]
Varicous eczema	Classic MF	Figure 12
Skin diseases		
Infectious		
Facial erysipelas	Classic MF with cellulitis, with only focal epidermo- and folliculotropism of atypical Lc	[63]
Tinea pedis	Folliculotropic MF	[64, 65] Figure 13
Gangrene	Classic MF with epidermal vesiculation	[66]

UN CRESCENTE ARMAMENTARIO DI FARMACI BIOLOGICI PER IL TRATTAMENTO DELLA PSORIASI E DELLA DERMATITE ATOPICA

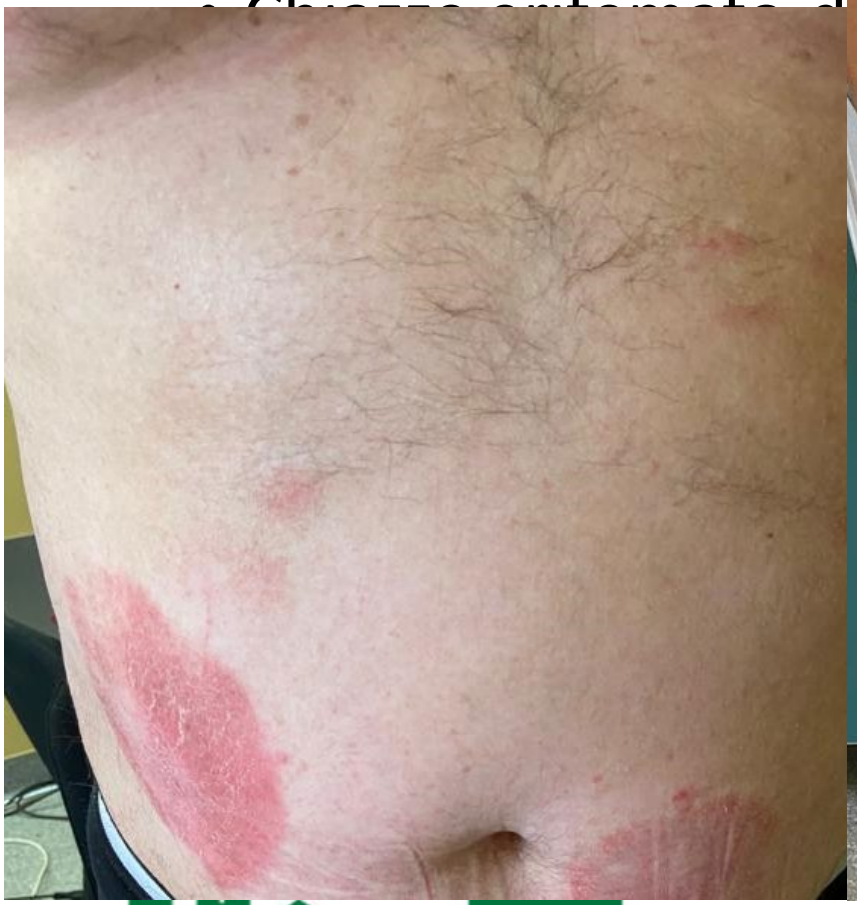
Trial clinici per futuri trattamenti biologici della psoriasi

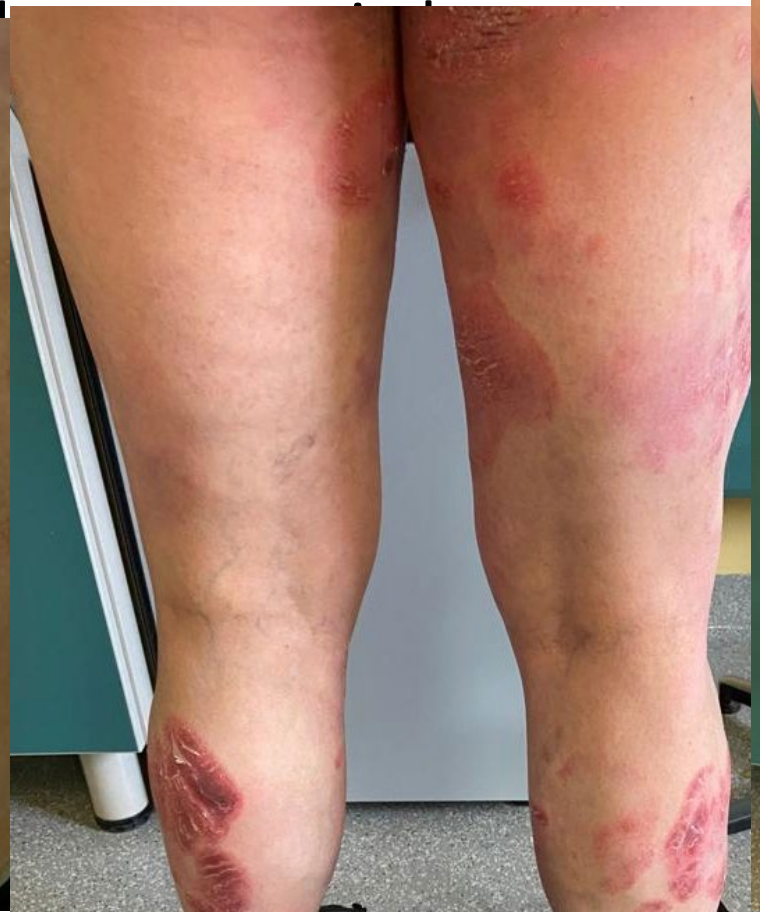
Therapeutic agent	Mechanism of action	Trial (status)	ClinicalTrials.gov identifier
Tofacitinib	JAK1 and JAK3 inhibition	Randomized trial versus etanercept (completed)	NCT01241591
Ruxolitinib (topical treatment)	JAK1 and JAK3 inhibition	Randomized vehicle controlled safety and efficacy trial (completed)	NCT00820950
Pazopanib (topical treatment)	VEGF antagonist	Randomized efficacy trial (completed)	NCT00358384
Ponesimod	S1P1 receptor inhibition	Randomized safety and efficacy trial (completed)	NCT01208090
Guselkumab	IL-23 inhibitor	Randomized trial versus adalimumab (ongoing)	NCT02207244
Tildrakizumab	IL-23 inhibitor	Randomized trial versus etanercept (ongoing)	NCT01729754
Risankizumab	IL-23 inhibitor	Open-label safety and efficacy trial (recruiting)	NCT02772601
IMO-8400	TLR7, TLR8 and TLR9 inhibitor	Randomized dose-ranging trial (completed)	NCT01899729
Namilumab	GM-CSF receptor antagonist	Randomized safety and efficacy trial (completed)	NCT02129777
Piclidenoson (also known as CF101)	Adenosine A3 receptor agonist	Randomized safety and efficacy trial (completed)	NCT00428974

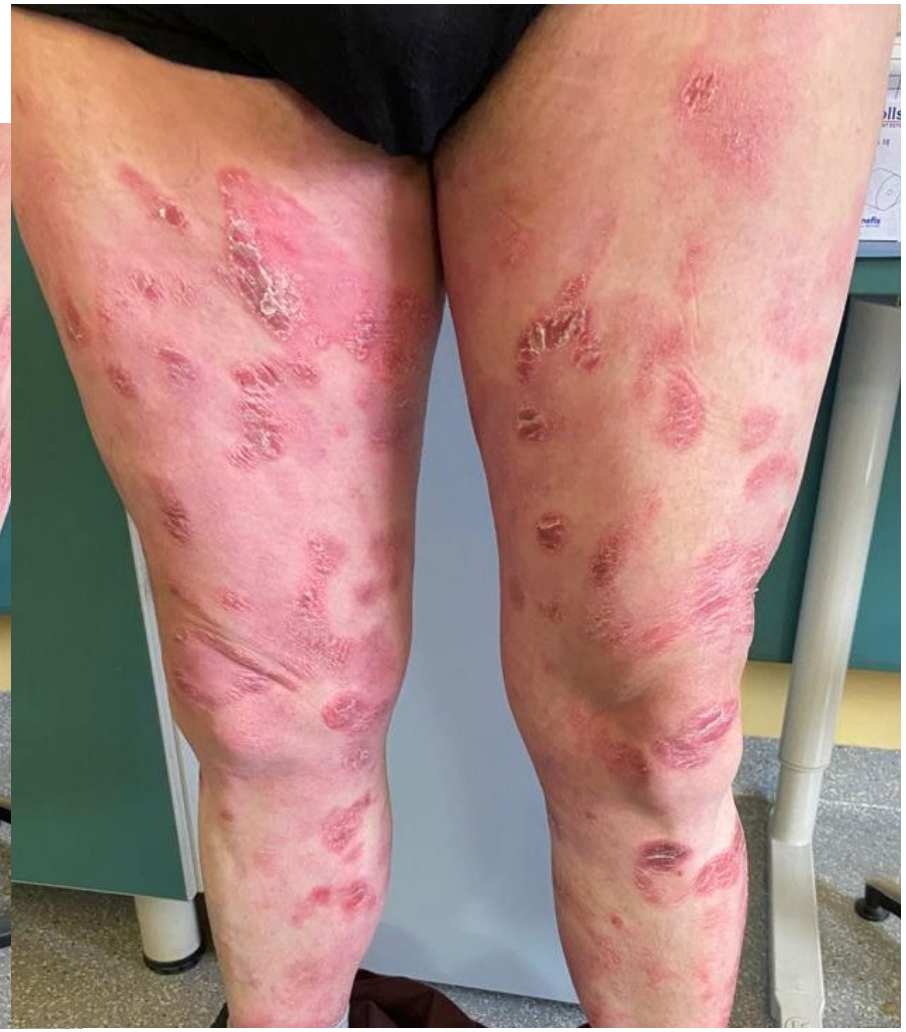
Trial clinici per futuri trattamenti biologici della dermatite atopica

Target	Drug	Biologic or SMA	Symptom severity indication	Notes	Refs
Systemic					
Anti-T_H2 cell signalling					
IL-13	Tralokinumab	Biologic	Moderate to severe	• Humanized monoclonal antibody • Phase II trials completed • Modest effect on EASI and IGA measures compared with the placebo group after 16 weeks • Possible confounding effect of concomitant use of TCSs in both arms	229
	Lebrikizumab	Biologic	Moderate to severe	• Humanized monoclonal antibody • Phase II trials completed • Modest benefit in EASI50 compared with placebo after 12 weeks • Possible confounding effect of concomitant use of TCSs in both arms	230
TSLP	Tezepelumab	Biologic	Moderate to severe	• Phase IIa study failed to meet primary end point of improvement in EASI after 12 weeks	231
IL-33	ANB020	Biologic	Moderate to severe	• Monoclonal antibody • In phase IIa trial, 75% of patients ($n=9$) achieved an EASI50 by day 15, with efficacy sustained for >4 months • Well-tolerated; headache most common adverse event	232
OX40	GBR830	Biologic	Moderate to severe	• Monoclonal antibody • Greater proportion of patients achieving EASI50 and EASI75 than the control arm at day 71 • Headache most common adverse event	233
CRTH2	Fevipiprant	SMA	Moderate to severe	• Phase II trials completed • Minimal benefit	107
	Timapiprant	Biologic	Moderate to severe	• Phase II trials completed • Minimal benefit	107
Anti-T_H22 cell signalling					
IL-22	Fezakinumab	Biologic	Moderate to severe	• Monoclonal antibody • Significant reductions in body surface area affected but not in SCORAD after 12 weeks	234
Anti-pruritic					
IL-31Rα	Nemolizumab	Biologic	Moderate to severe	• Monoclonal antibody • In a phase II trial, significant reductions in itch (VAS), but not in EASI or body surface area affected, compared with placebo after 12 weeks • Discontinuation owing to exacerbation of atopic dermatitis, peripheral oedema and elevated creatine kinase levels more common in the treatment arm than in the placebo arm	107
IL-31	BMS-981164	Biologic	Moderate to severe	• Dose-escalation phase I study completed; results not yet available	NA
NK1R	Tradipitant	SMA	Moderate to severe	• Phase II study completed • Significant reductions in itch (VAS) and SCORAD after 8 weeks • Well-tolerated	235
Anti-inflammatory					
JAK1 and JAK2	Baricitinib	SMA	Moderate to severe	• Phase II study completed • EASI50 achieved by 61% of patients treated with baricitinib + TCSs compared with 37% of patients in the control arm (TCSs alone) ($P=0.027$) • Significant improvement in SCORAD • Possible confounding effect of concomitant use of TCSs in both arms • Most common adverse events were headache, increased creatine kinase levels and nasopharyngitis	236
JAK1	Upadacitinib	SMA	Moderate to severe	• Phase II study completed • Clinical and patient-reported outcomes • 74% reduction in EASI score compared with 23% in the placebo arm • IGA0 or IGA1 achieved by 50% of patients treated with upadacitinib compared with 2% of patients in the placebo arm • Detailed results not yet available	237
	PF-04965842	SMA	Moderate to severe	• Phase IIa study completed • 82% reduction in EASI score compared with 35% in the placebo arm • IGA0 or IGA1 achieved by 44.5% of patients treated with PF-04965842 compared with 6.3% of patients in the placebo arm ($P<0.003$) • Detailed results not yet available	238
JAK and SYK	ASN002	SMA	Moderate to severe	• Phase IIa study completed • EASI75 achieved by 63% of patients treated with ASN002 • Detailed results not yet available	239

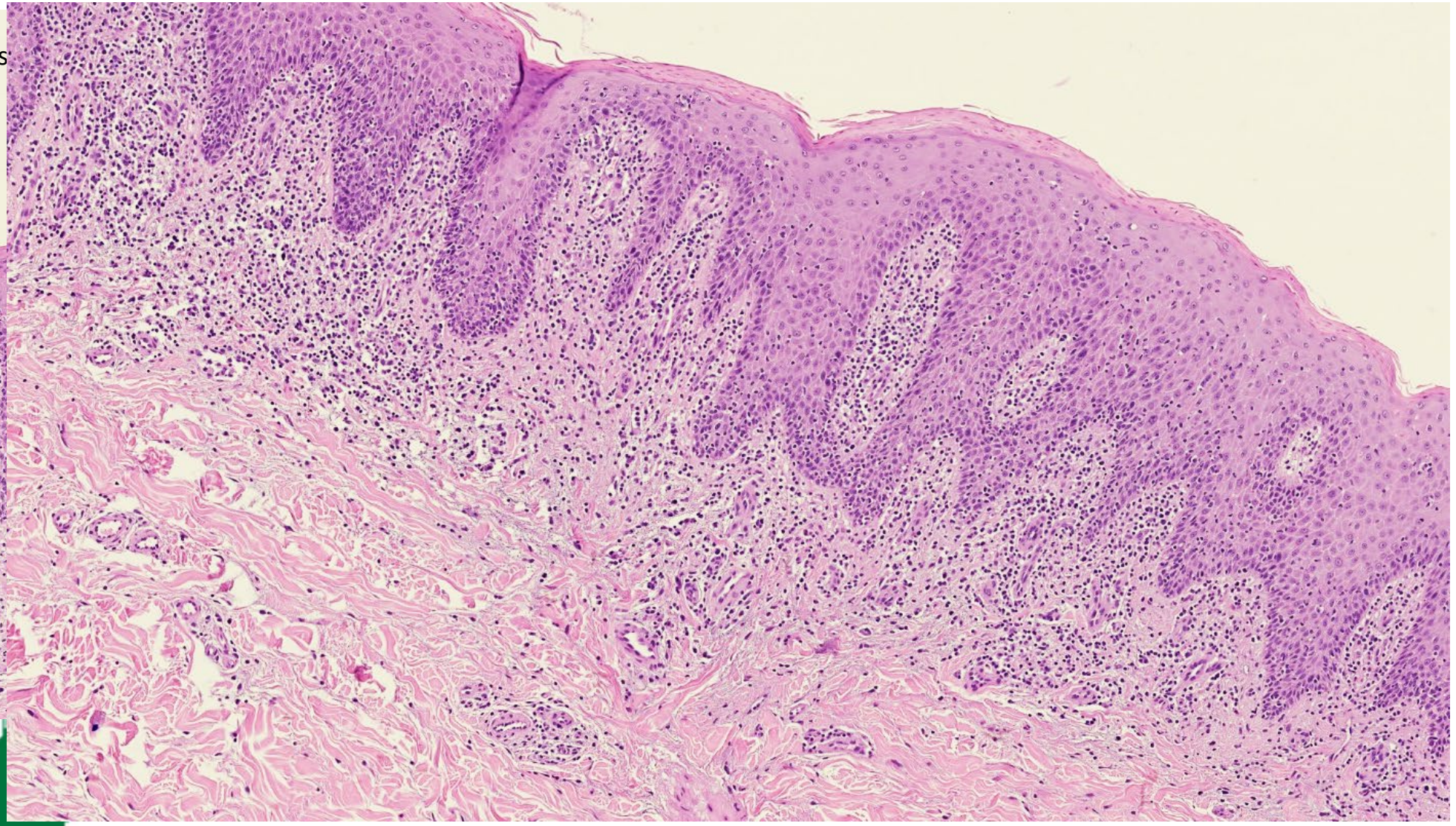
Caso 1, uomo 56 anni





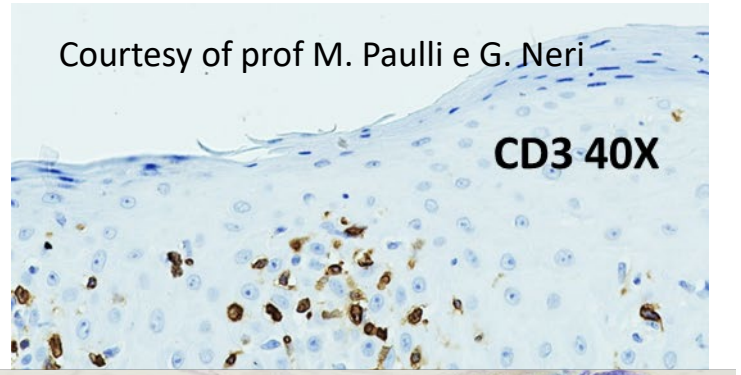


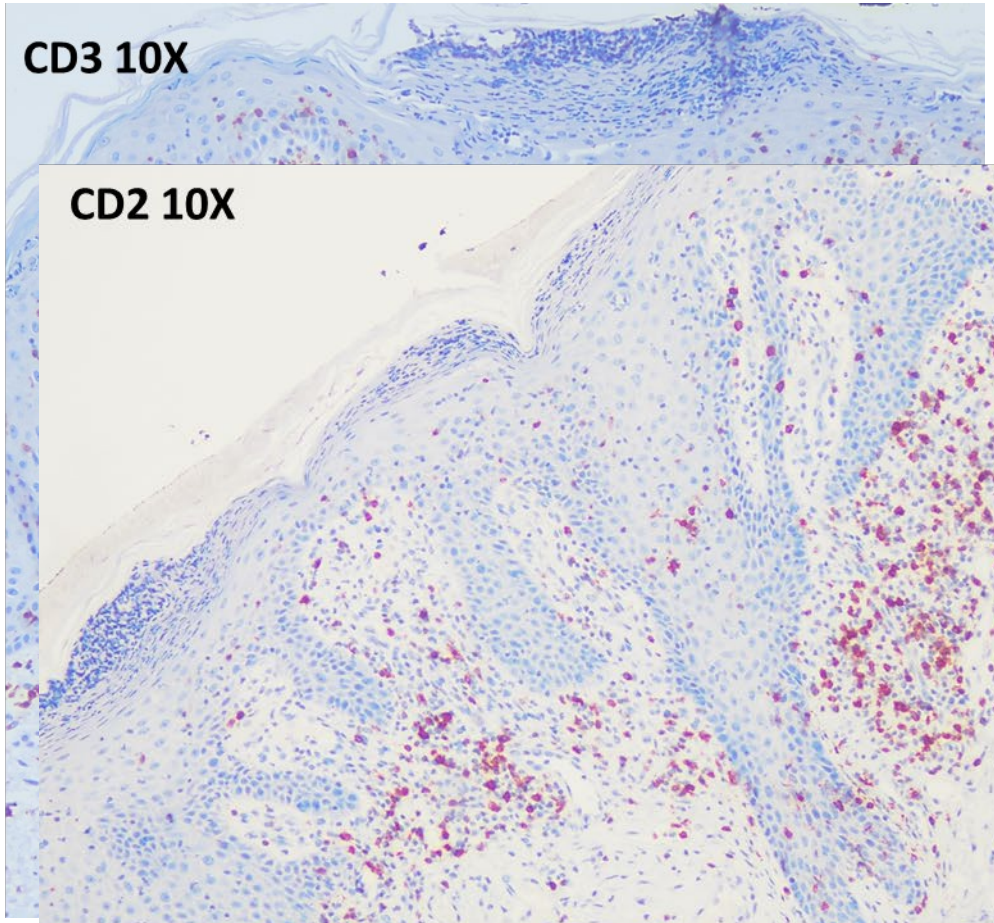
Courtes

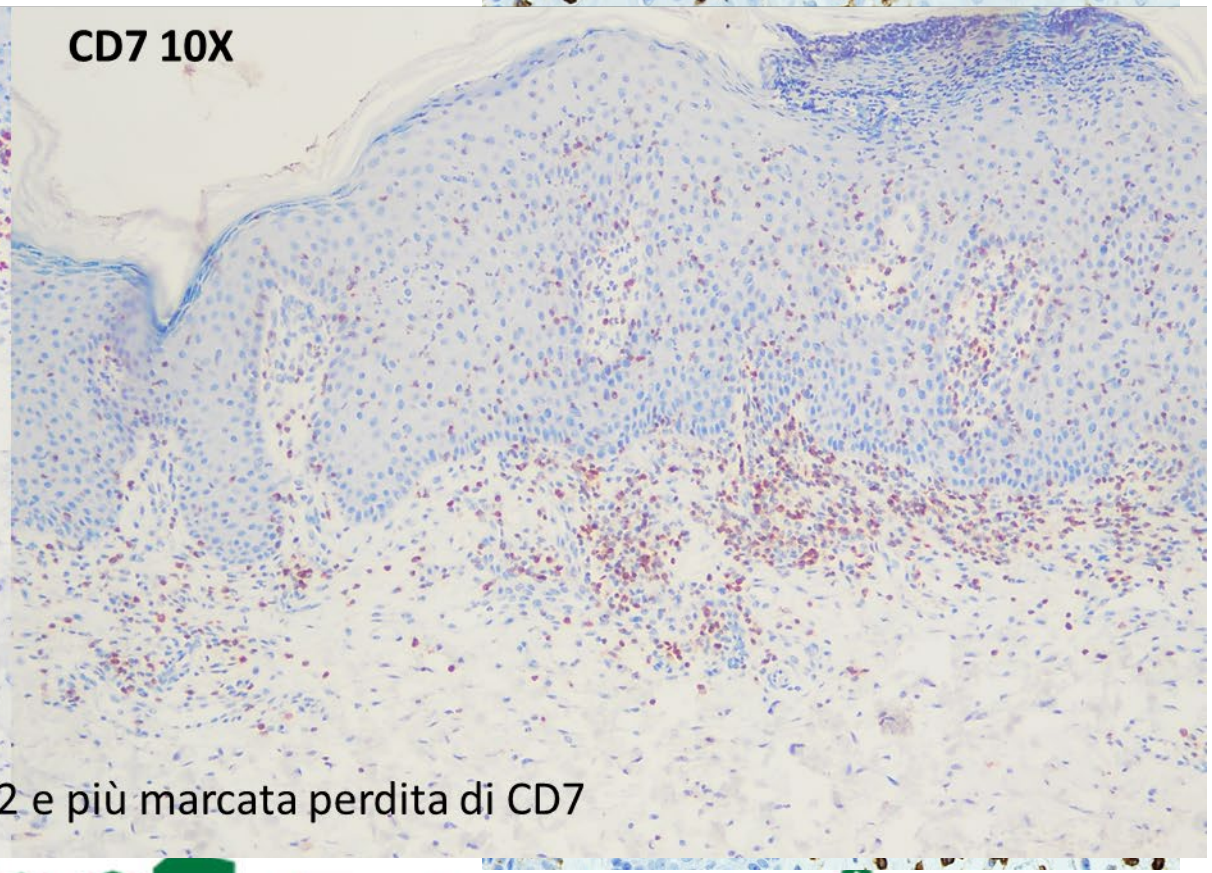


Iperplasia epidermica con papillomatosi allungamento delle papille acantosi regolare minima paracheratosi; iniziale disposizione in banda dell'infiltrato con piccoli linfociti ed esocitosi di singoli linfociti

Infiltrato a disposizione prevalente in banda con iniziale epidermotropismo
L'alto ingrandimento mostra soprattutto l'esocitosi dei singoli elementi

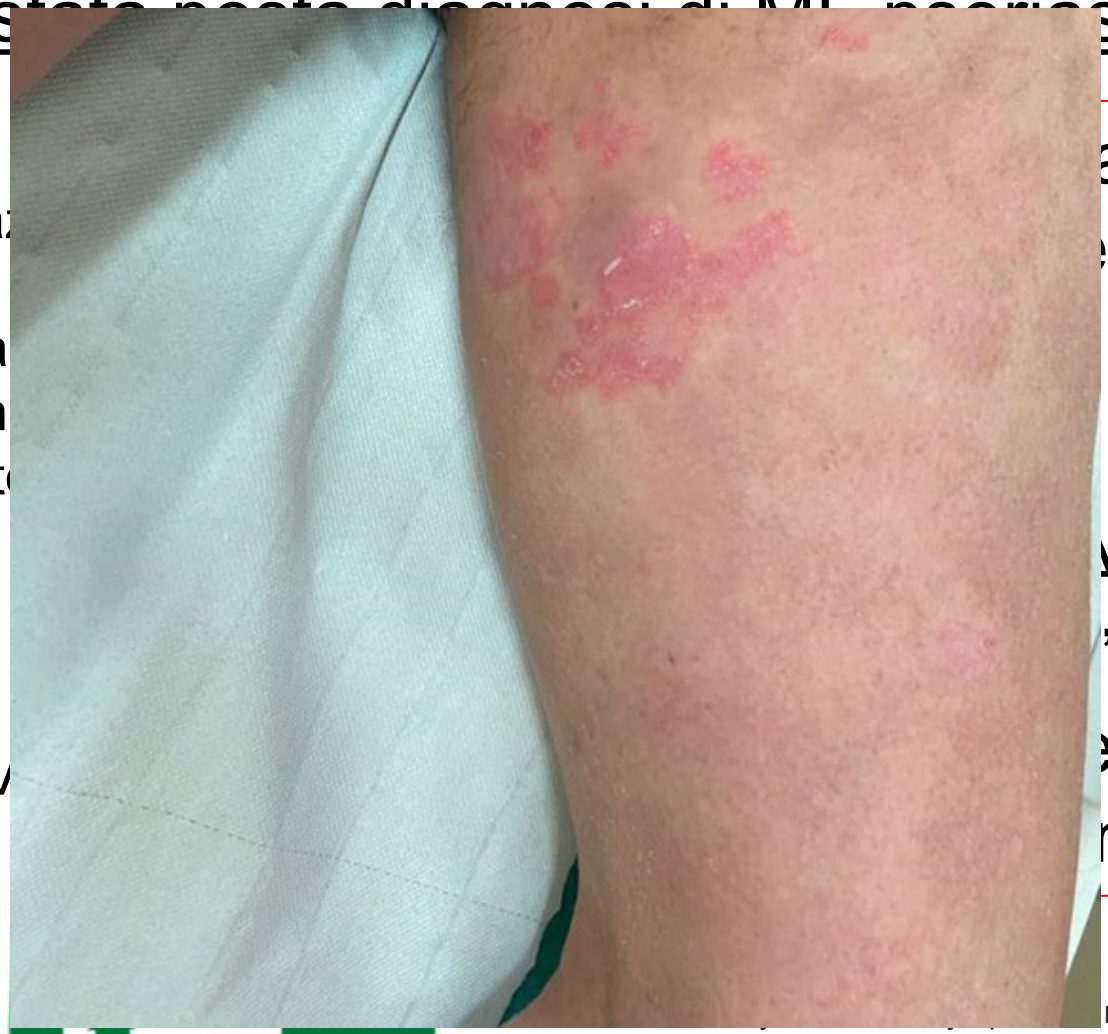


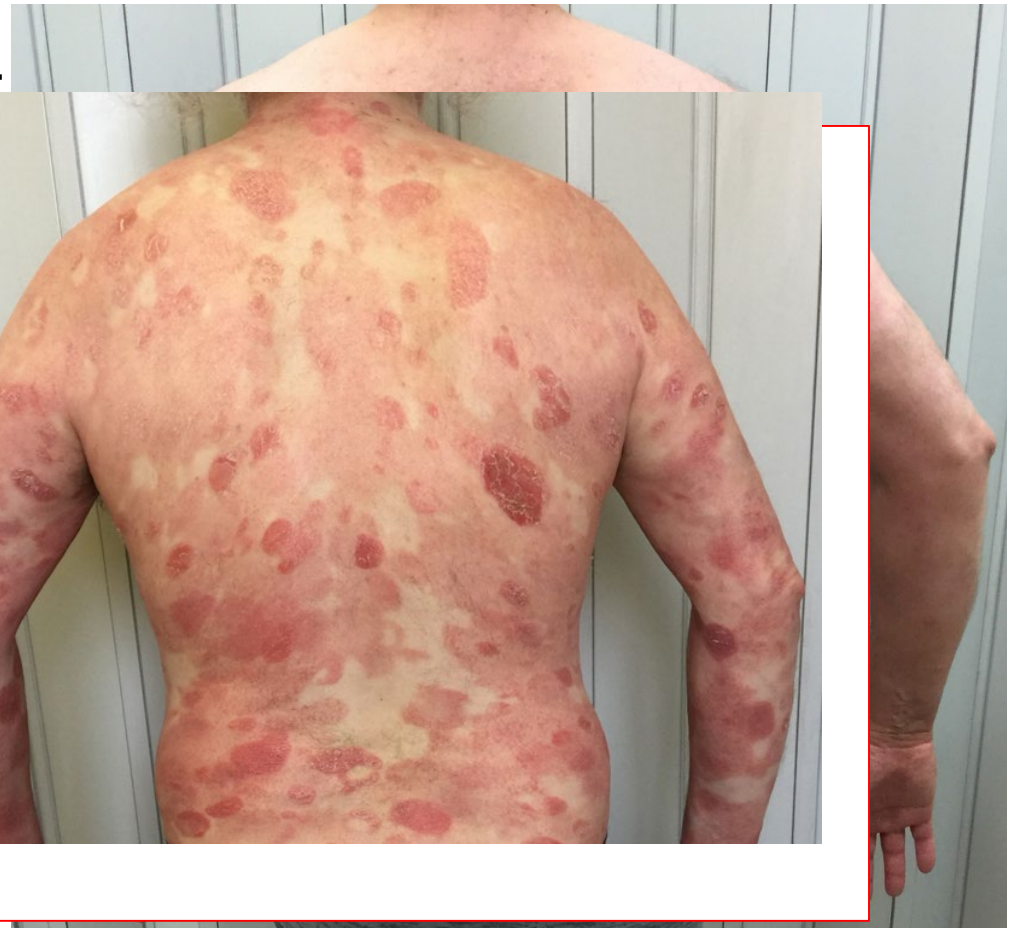




Lievissima perdita di CD2 e più marcata perdita di CD7

E’ s siforme.





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recommendations for clinical trial design and staging update from the ISCL, USCLC, and EORTC blood 2022 Aug 4;140(5):419-437.

IMMUNOISTOCHIMICA: piccoli linfociti T a fenotipo "peripheral" CD3+, CD2+, CD5+, CD7+/-, presenza di entrambe le popolazioni CD4 e CD8. Positività per anti-CD30 in circa il 5% della popolazione

n sede

Epide
iperpa
Intens
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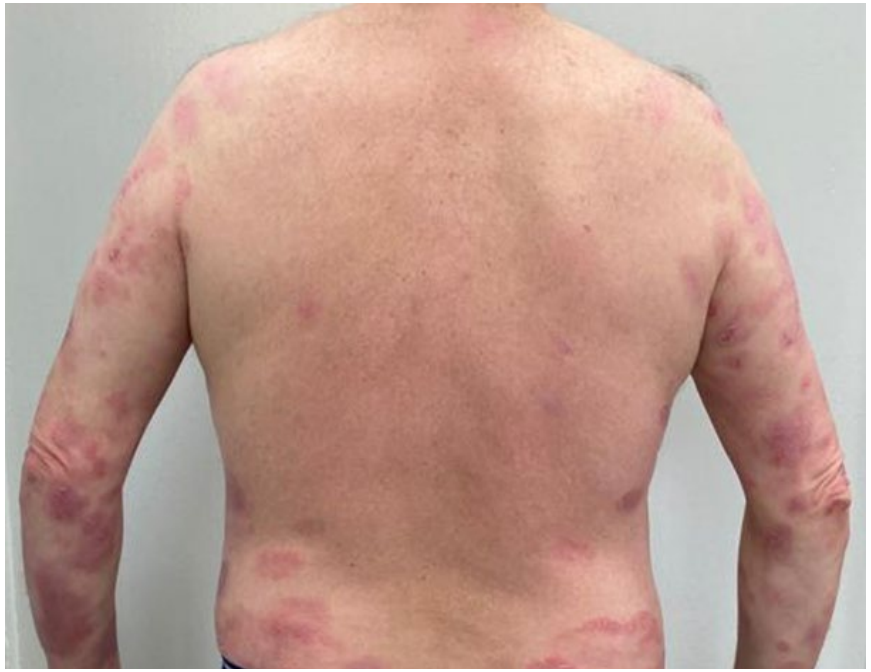
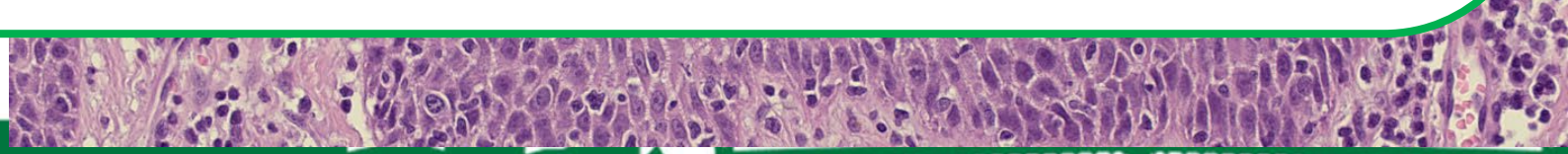
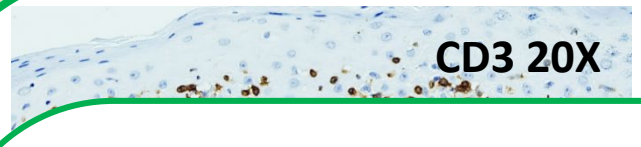
Dopo 1 anno da TSEB-→Recidiva







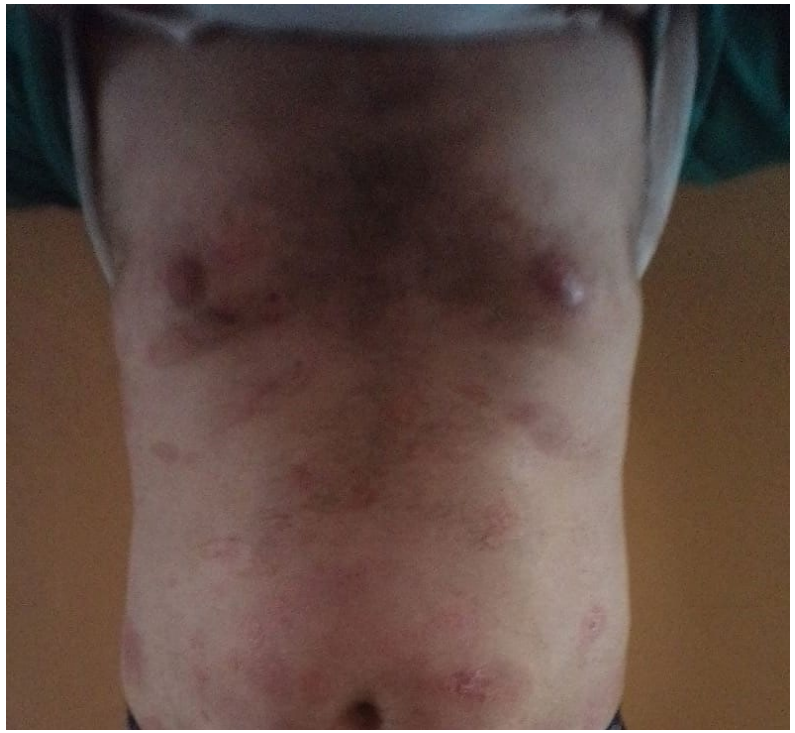
Esami ematochimici nella norma

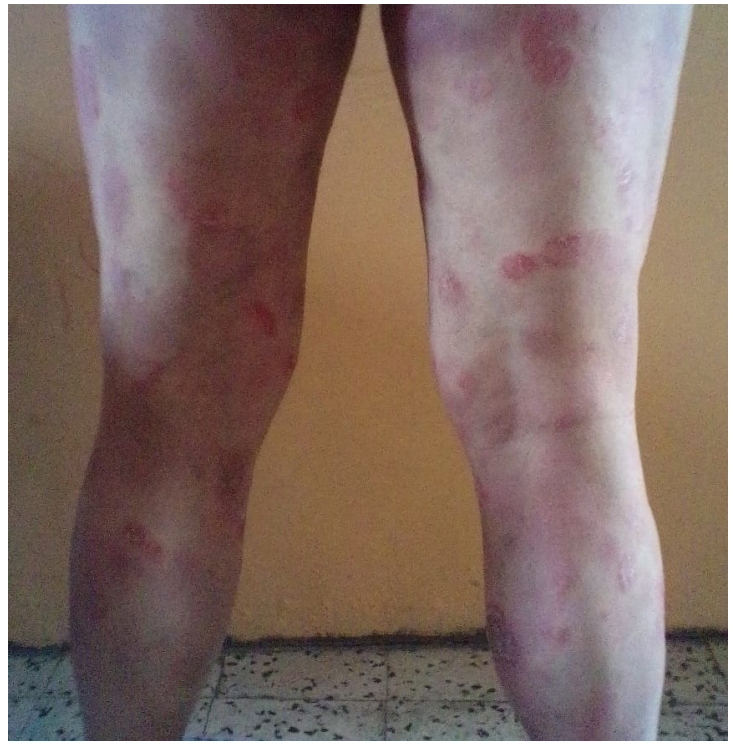
Analisi citofluorimetrica su sangue periferico:
sottopopolazioni T con conservato rapporto CD4/CD8 , segnalata popolazione aberrante CD3+, CD2+, CD5+, CD7+ (debole)pari al 20% dei linfociti; allo studio delle regioni variabili del TCR alfa/beta evidenza di lieve espansione della regione variabile Vb13.2

Tc total body: negativa

T_2b, N_0 M_0 B_1

Peginterferon 90 mcg/sett

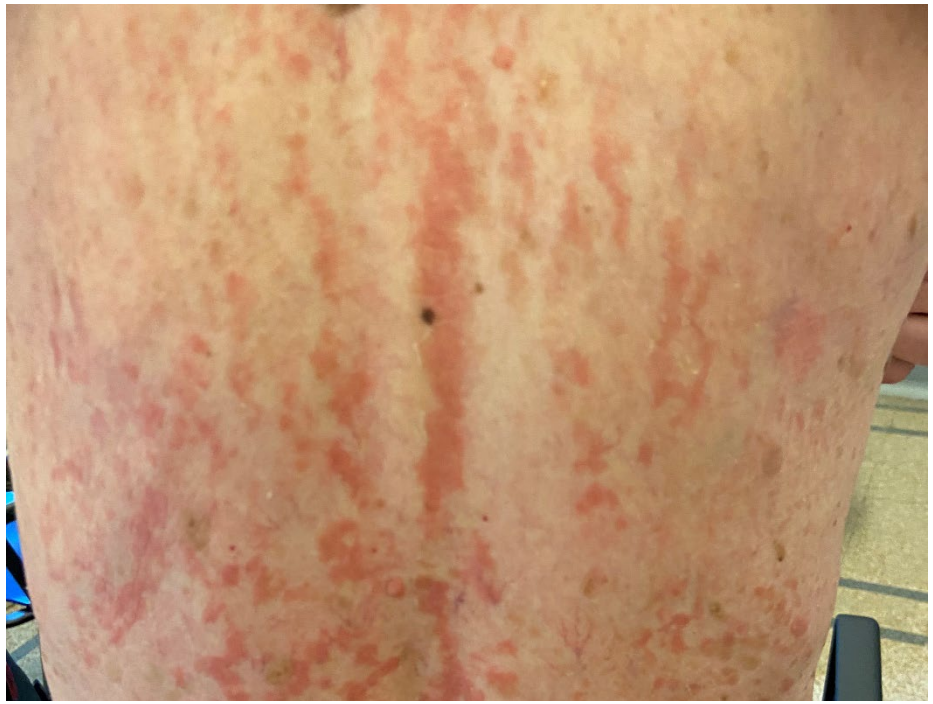


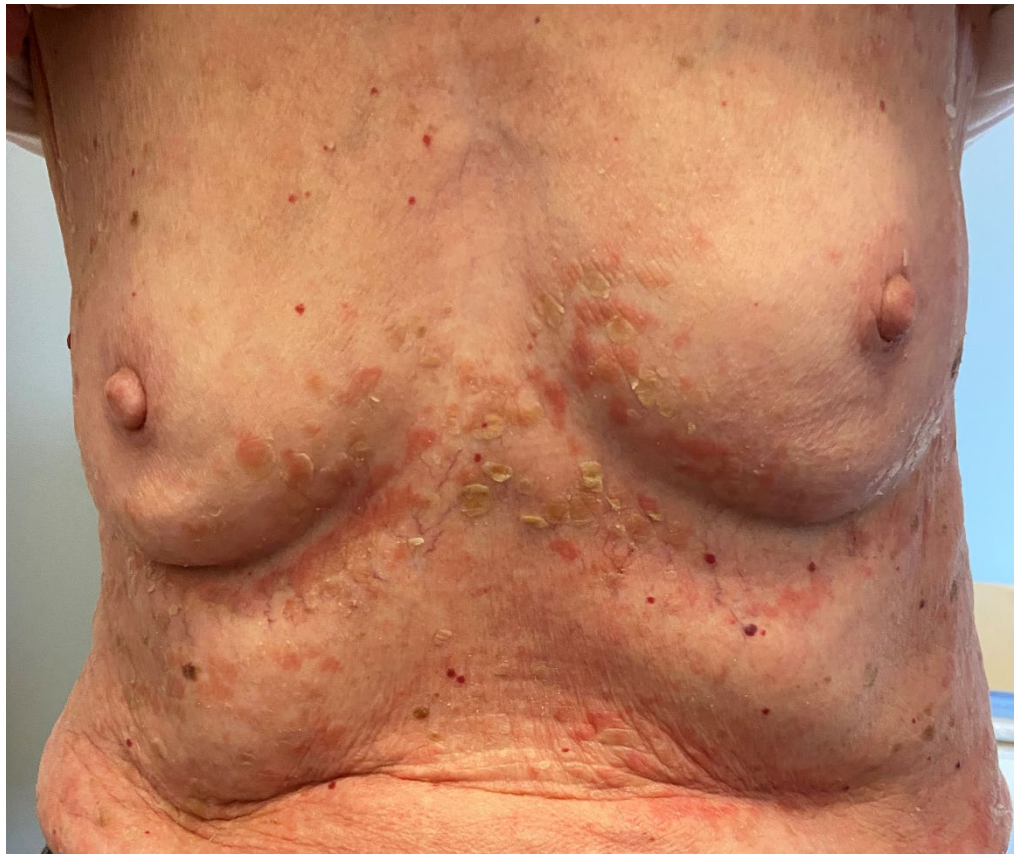


Caso 2, donna 76 anni

- Giunta a valutazione Dermatologica dopo gestione in ambito Reumatologico
- Riferito peggioramento della componente cutanea in «artropatia psoriasica»

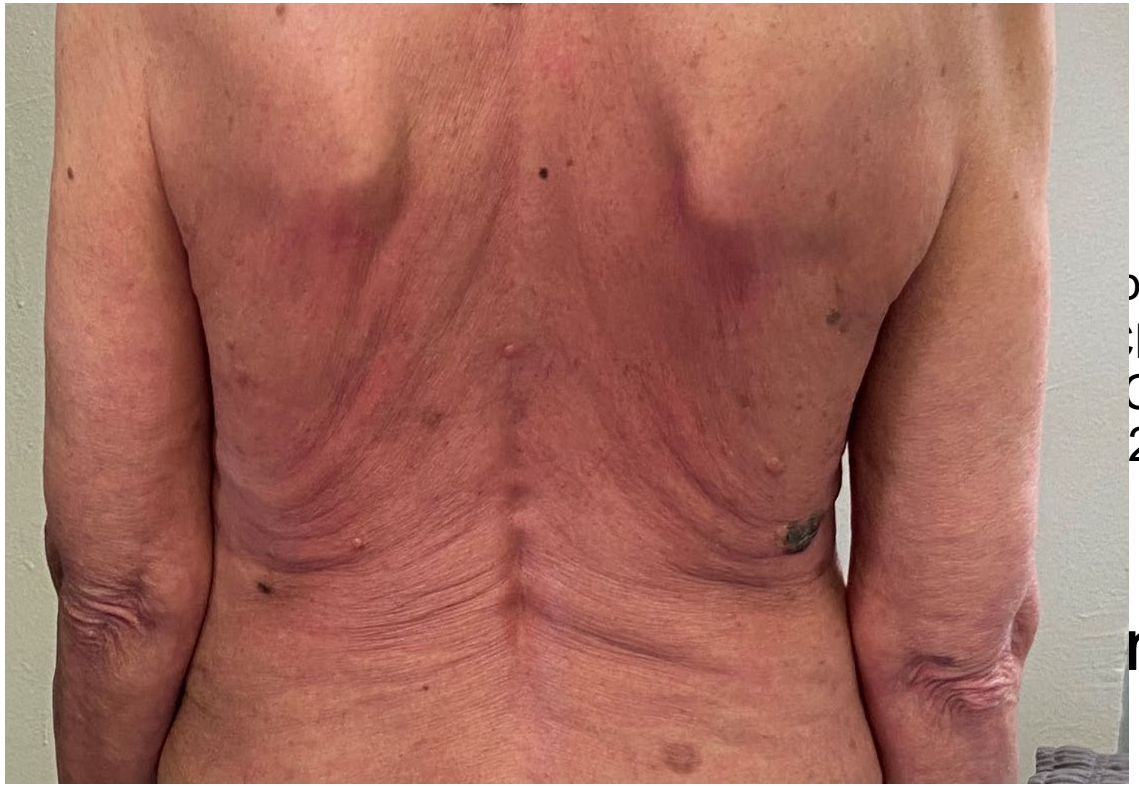
- La paziente era in tp con Guselkumab, MTX, FANS per sintomi articolari





Chiazze e piccole chiazze eritemato-desquamanti al tronco

DIAGNOSI: MICOSI FUNGOIDE PSORIASIFORME



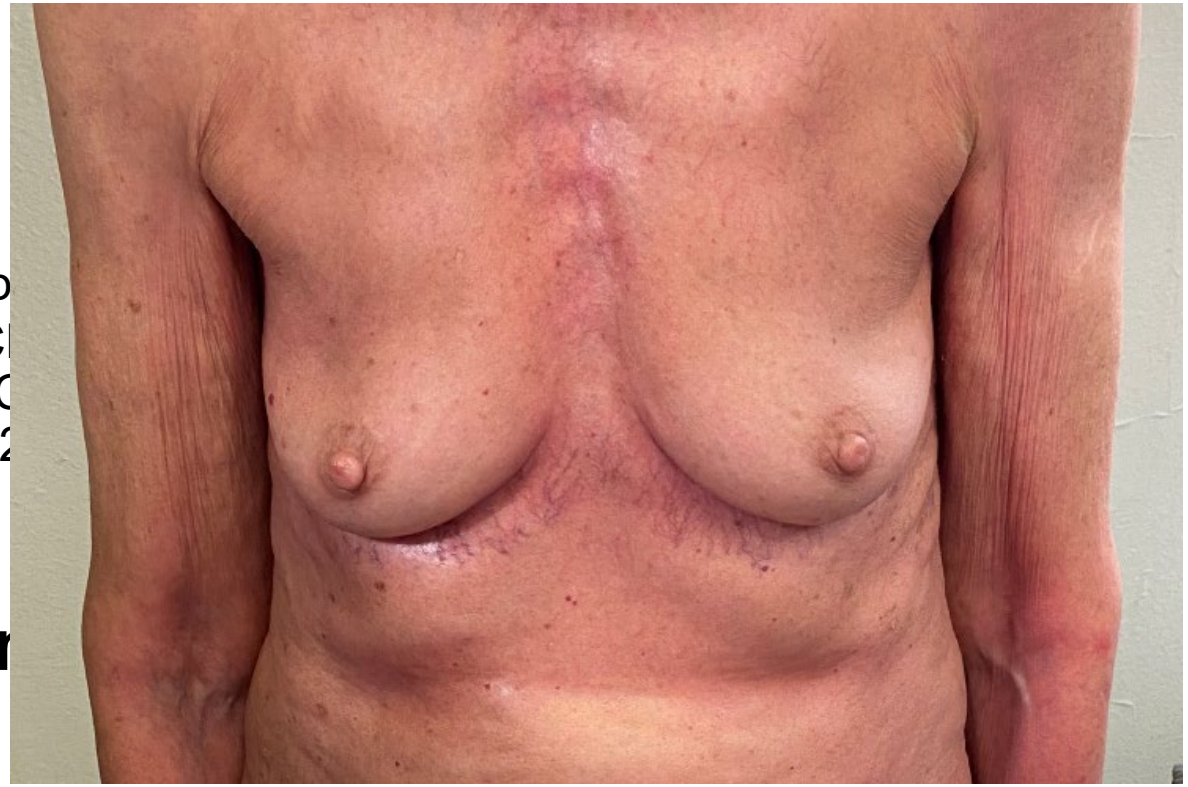


Table 1. *Clinical and immunohistochemical features of psoriasiform MF cases in this study, and previous studies.*

Study(year)	Case	Age (sexF/M)	Clinical presentation at the time of last visit	Ulceration (YES/NO)	Duration of skin disease treated as psoriasis(year or month)	Previous treatments	IHC	Outcome
Zackheim et al. (2002) [4]	1	52(F)	Palmoplantar desquamation Widespread erythematous patches and plaques	No	9(y)	Topical steroids, calcipotriene, MTX, cyclosporine	N/A	Death due to highly aggressive large cell lymphoma
Lafaille et al. (2009) [3]	2	47(M)	Generalized erythematous scaly plaques, alopecia, large ulcerating plaque on scalp	Yes	5(y)	MTX, NBUV-B, PUVA, Etanercept	CD4+ Tcells	Final Dx: MF, Improved with a combination of NBUVB, IFN alfa-2b & bexarotene 2-year F/u: stable
	3	52(M)	widespread ulceration with red, indurated borders	Yes	20(y)	Topical steroids, acitretin, alefacept	CD2,3,5,7+	finalDx:CTCL Thx:syst.CS+IFN alpha2a. Death due to multisystem organ failure
Weenig et al. (2009) [6]	4	75(M)	generalized, indurated, and erythematous plaques. Many were ulcerated	Yes	2(y)	Topical steroids, acitretin	CD3,5,7,8+	Final DX:CTCL PUVA+Gemcitabine Death:sepsis
	5	67(M)	Widespread ulceration	Yes	20(y)	Topical CS, cyclosporine, MTX	CD2,3,5,7+	Final Dx:CTCL Thx:Gemcitabine Death:MI

Dermatology Online Journal | Case Presentation
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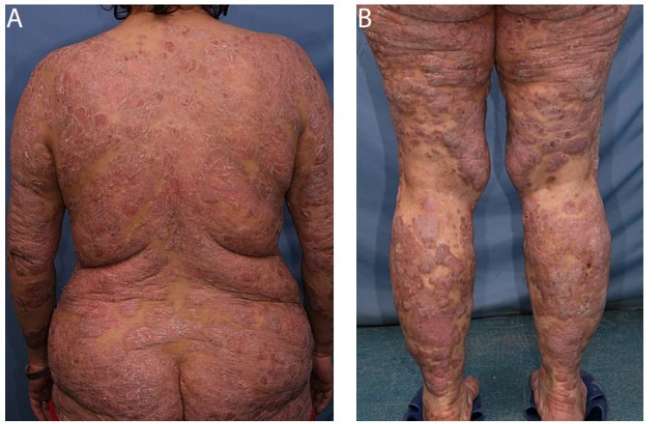
DOJ 23 (9): 15

Study(year)	Case	Age (sexF/M)	Clinical presentation at the time of last visit	Ulceration (YES/NO)	Duration of skin disease treated as psoriasis(year or month)	Previous treatments	IHC	Outcome
Dakouki et al. (2009) [7]	6	52(M)	Red-brown ulcerated tumors, indurated erythematous plaques with superficial erosion	Yes	6(y)	Topical CS	CD3, 4+	N/A
Jinno et al. (2015) [8]	7	54(M)	erythema with pityroid scales, indurated, well demarcated erythema with thick scales	No	N/A	Topical CS, Cyclosporine	CD3,CD4+	Final Dx:MF Thx: improvement with phototherapy+ topical CS
Our study	8	46(F)	Well demarcated red-brown plaques with thick scale	No	13(y)	Topical CS	CD3,4,5,8,30+	Final Dx:MF Thx:marked improvement with PUVA+ acitretin



ıltiple well demarcated erythematous plaques with psoriasiform scales on her back (A), extremities (B)

Histological examination shows:

1. Marked psoriasiform epidermal hyperplasia with elongation of the rete ridges with regular acanthosis, hyperkeratosis with parakeratosis, thinning, or total effacement of the granular layer and Munro microabscesses
2. Epidermotropic atypical lymphocytes and scant spongiosis.
3. The epidermis revealed many intraepidermal atypical medium-sized lymphocytes with perinuclear halo and convoluted nuclei linearly arranged along the basal layer.
4. The papillary dermis was filled by a dense infiltration of lymphocytes, which were smaller than the intraepidermal lymphocytes and associated with marked lamellar fibroplasia of the upper dermis Immunohistochemical staining showed that atypical lymphocytes were positive for CD3, CD4, CD8, and CD5

Progression of undiagnosed cutaneous lymphoma after anti–tumor necrosis factor-alpha therapy

Maria Estela Martinez-Escala, MD, PhD,[a] Alba L. Posligua, MD,[a] Heather Wickless, MD,[b] Audrey Rutherford, BA,[b] Kimberly A. Sable, MS,[a] Belen Rubio-Gonzalez, MD,[c,d] Xiaolong A. Zhou, MD,[a] Jason B. Kaplan, MD,[c] Barbara Pro, MD,[c] Jaehyuk Choi, MD, PhD,[a] Christiane Querfeld, MD, PhD,[c,d] Steven T. Rosen, MD,[c,d] and Joan Guitart, MD[a]

Chicago, Illinois; Dallas, Texas; and Duarte, California

Background: Cutaneous lymphoma diagnosed after anti–tumor necrosis factor-α therapy (anti–TNF-α) has been reported in the literature, yet a clear link between both events remains elusive.

Objective: To review our experience with cutaneous lymphoma diagnosed during or after the use of anti–TNF-α therapies.

Methods: This is a multicenter retrospective study and a literature review.

Results: A total of 22 cases, including 20 cutaneous T-cell lymphomas (CTCLs) and 2 cutaneous B-cell lymphomas, were identified. In the CTCL group, 75% of the patients received an anti–TNF-α agent for a presumed inflammatory skin condition. Mycosis fungoides and Sézary syndrome were the most common subtypes of CTCL diagnosed. Advanced disease (stage IIB to IVA) was commonly seen at time of diagnosis and required aggressive therapy, including stem cell transplant in 3 patients; 2 patients in whom cutaneous B-cell lymphomas was diagnosed had an indolent course. A total of 31 cases were gathered from a literature search.

Limitations: This is a retrospective study.

Conclusions: Our findings suggest that the disease of most of the identified patients was misdiagnosed as psoriasis or eczema; therefore, a comprehensive morphologic and molecular review of skin biopsy specimens and peripheral blood samples should be considered before initiation of anti–TNF-α therapy in patients with poorly defined dermatitis or atypical presentations of psoriasis. (J Am Acad Dermatol 2018;78:1068-76.)

CAPSULE SUMMARY

- Cutaneous lymphoma (CL) diagnosed after anti–tumor necrosis factor-α (anti–TNF-α) therapy is most commonly associated with a misdiagnosis of psoriasis.
- Anti–TNF-α therapy can accelerate the course of CL.
- Before initiation of anti–TNF-α therapy, skin biopsy and peripheral blood analysis should be considered in patients with atypical presentation of psoriasis to exclude CL.

The Course of Mycosis Fungoides under Cytokine Pathway Blockers: A Multicentre Analysis of Real-life Clinical Data*

Iris AMITAY-LAISH[1,2], Emmanuella GUENOVA[3], Pablo L. ORTIZ-ROMERO[4], Cristina VICO-ALONSO[4], Sima ROZATI[5], Larisa J. GESKIN[6], Vasiliki NIKOLAOU[7], Evangelia PAPADAVID[8], Aviv BARZILAI[2,9], Lev PAVLOVSKY[1,2], Elena DIDKOVSKY[2,10], Hadas PRAG NAVEH[1], Oleg E. AKILOV[11#] and Emmilia HODAK[1,2#]

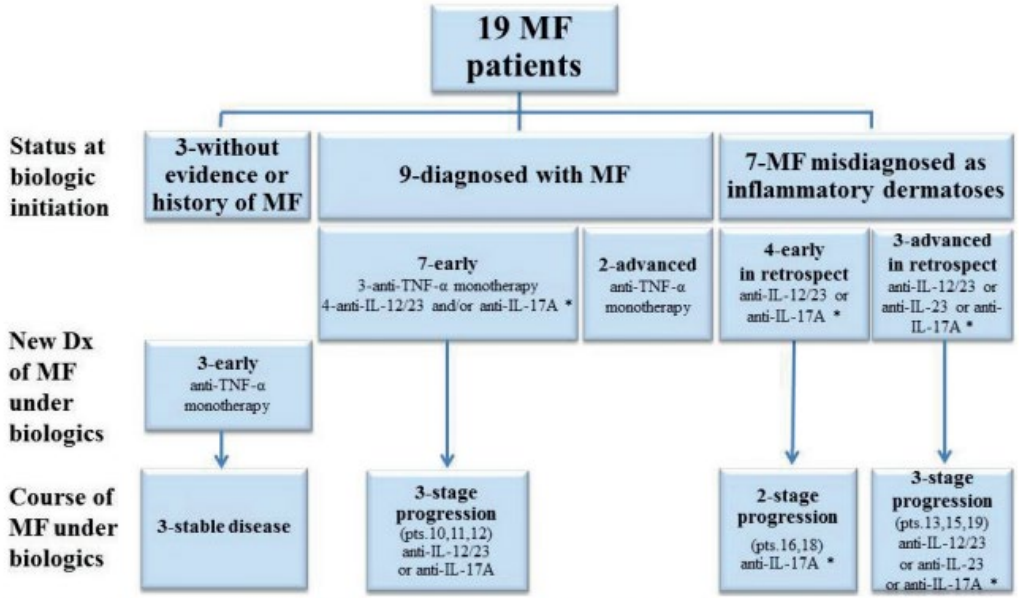
[1]Division of Dermatology and [10]Institute of Pathology, Rabin Medical Center – Beilinson Hospital, Petach Tikva, [2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [3]Department of Dermatology, University Hospital Zürich & Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland, [4]Department of Dermatology, 12 de Octubre Hospital, CIBERONC, Institute i+12, Medical School, University Complutense, Madrid, Spain, [5]Department of Dermatology, Johns Hopkins Medicine, Baltimore, MD, USA, [6]Department of Dermatology, Columbia University, New York, NY, USA, [7]Department of Dermatology, Andreas Sygros Hospital, [8]Department of Dermatology, Attikon General Hospital, University of Athens Medical School, Athens, Greece, [9]Department of Dermatology, Sheba Medical Center, Ramat-Gan, Israel, and [11]Cutaneous Lymphoma Program, Department of Dermatology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
#These authors contributed equally to this work.

Literature regarding the effect of biologics on the course of mycosis fungoides (MF) is scarce. This multicentre study analysed retrospective data on 19 patients with MF, who were treated with biologics; 12 for inflammatory conditions coexisting with MF, and 7 for MF misdiagnosed as an inflammatory skin disease. Eight patients were treated with anti-tumour necrosis factor-α-monotherapy; 6 had early-stage MF, in 3 patients MF preceded and in 3 MF was diagnosed after initiation of biologics, with no stage-progression or with stable disease, respectively (median treatment time concurrent with MF 57 months). Two patients had advanced stage MF: IIB, treated for 15 months with no stage-progression, and IVA1, treated for 8 months, died of disease 10 months later. The other 11/19 patients received anti-interleukin-17A and/or anti-interleukin-12/23 or anti-interleukin-23 (with/without anti-tumour necrosis factor-α/anti-interleukin-4/13), with stage-progression in 8 patients after a median of 8 months' treatment. Although, in general, biologics should be avoided in patients with MF, these results indicate that anti-tumour necrosis factor-α-monotherapy might not aggravate the disease course in early-stage patients. Interleukin-17A, interleukin-12/23 and interleukin-23 pathway-blockers may prompt progression of MF.

SIGNIFICANCE

Since, almost as a rule, the treatment of patients with inflammatory conditions with biologics is terminated on diagnosis of mycosis fungoides, information on the course of mycosis fungoides under biologic treatment is scarce. Analysis of real-life data for 19 patients with mycosis fungoides being treated with biologics, revealed that anti-tumour necrosis factor-α-monotherapy may not always adversely affect early-stage disease. In contrast, in the vast majority of patients with mycosis fungoides, continuation of treatment with interleukin-17A, -12/23, and -23 pathway-blockers led to prompt progression of the disease. These observations may guide clinicians in considering the advantages and disadvantages in continuation of tumour necrosis factor-α-blockers in the rare co-occurrence of early-stage mycosis fungoides and inflammatory conditions.

anti-interleukin (IL)-17, anti-IL-12/23 and anti-IL-23, has revolutionized the management of autoimmune and inflammatory diseases (1–3). Patients with psoriasis, one of the most common inflammatory dermatoses, affecting 2–4% of the population in Western countries, now receive biologic treatment sooner in the course of their disease, following treatment with fewer conventional agents (3).



…s and stage of mycosis fungoides (MF) at initiation and during the course of biologic therapy. *Some were also tr…
…s. anti-TNF-α: anti-tumour necrosis factor-α; IL: interleukin; pts: patients; Dx: diagnosis.

Conclusion

Several conclusions may be drawn from this study. First, before considering biologics for benign cutaneou… inflammatory disorders, clinicians should re-thin… the indication, take a second look for clinical clues o… MF, revise the histology or take another biopsy, an… consider blood assessment, including flow cytometry. Secondly, although similar to other immunosuppres… sant treatments, biologics in general should be avoide… in cases of MF. Nevertheless, based on our experience… together with the few cases reported in the literature, … seems that anti-TNF-α may not always adversely affe… the course of unequivocal early-stage MF, and the pro… and cons of anti-TNF-α-therapy should be considere… on a case-by-case basis. Further studies are needed t… search for a biomarker to assist in predicting the risk of MF aggravation under anti-TNF-α or other biologics. Thirdly, we found that anti-IL-17 and/or anti-IL-12/23 or anti-IL-23treatment/s were associated with rapid aggravation of diagnosed and undiagnosed MF in several patients, all with at least stage IB MF. Whether the course of unequivocal classic very early-stage MF-IA might also progress under these treatments is not known and requires further study. A large international observational study is needed to fully clarify the complex relationship between MF and biologic agents and to guide clinical decisions.

Safety and danger of biologic treatments in psoriasis in context of cutaneous T-cell lymphoma (CTCL)

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DOI: https://doi.org/10.5114/ada.2021.107553

Abstract

Microenvironment has a significant impact on the pathogenesis of cutaneous T-cell lymphoma (CTCL), especially in the context of new emerging biologic therapies. Our aim was to review the literature on interleukins 12, 17, 23 and tumour necrosis factor-α in mycosis fungoides in order to clarify the safety of using biologics in the treatment of psoriasis. Our analysis suggests that these drugs may have an impact on the progression of CTCL. Concluding, in case of uncertain psoriatic lesions, a biopsy followed by pathologic examination should exclude the possibility of co-existence of a primary cutaneous lymphoma before administration of therapies affecting cytokine profiles.

Key words: cutaneous T-cell lymphoma, mycosis fungoides, biologic treatment, psoriasis, interleukin-12, interleukin-17, tumour necrosis factor-α.

Conclusions

Interleukin-17 is detectable in MF lesions, sometimes with the elevated level, but it does not seem to be the main player of MF. We show it not to be as important in the pathogenesis of CTCLs as it is in the pathogenesis of psoriasis, nevertheless using IL-17 or IL-17RA blockers (bimekizumab, brodalumab, ixekizumab, secukinumab) may cause a progression of MF in case of an overlap or a misdiagnosis of the mentioned autoimmune disease. Based on the literature, we have also described the beneficial effects of IL-12 on MF, therefore the agents blocking both IL-12/IL-23 pathway (ustekinumab) should be avoided in patients, who have a suspicion or a diagnosed MF. Lastly, the overall contribution of TNF-α to creating cell mediated cytotoxic Th1 microenvironment seems to outweigh the negative effects of TNF-a on the lymphoma, which was reported. TNF-α-inhibitors and TNF-α-receptor inhibitors (e.g. adalimumab, etanercept, infliximab) should not be used if CTCL cannot be ruled out. Before introducing the biological treatment, in case of advanced to severe psoriasis, we recommend performing a biopsy from the skin lesion followed up by a close pathological examination to exclude the possibility of MF misdiagnosis. We believe that further research is necessary to clarify the role of IL-17, IL-23 and TNF-α in MF and new immunosuppressive drugs should be used carefully in order not to aggravate the plausible lymphoma.

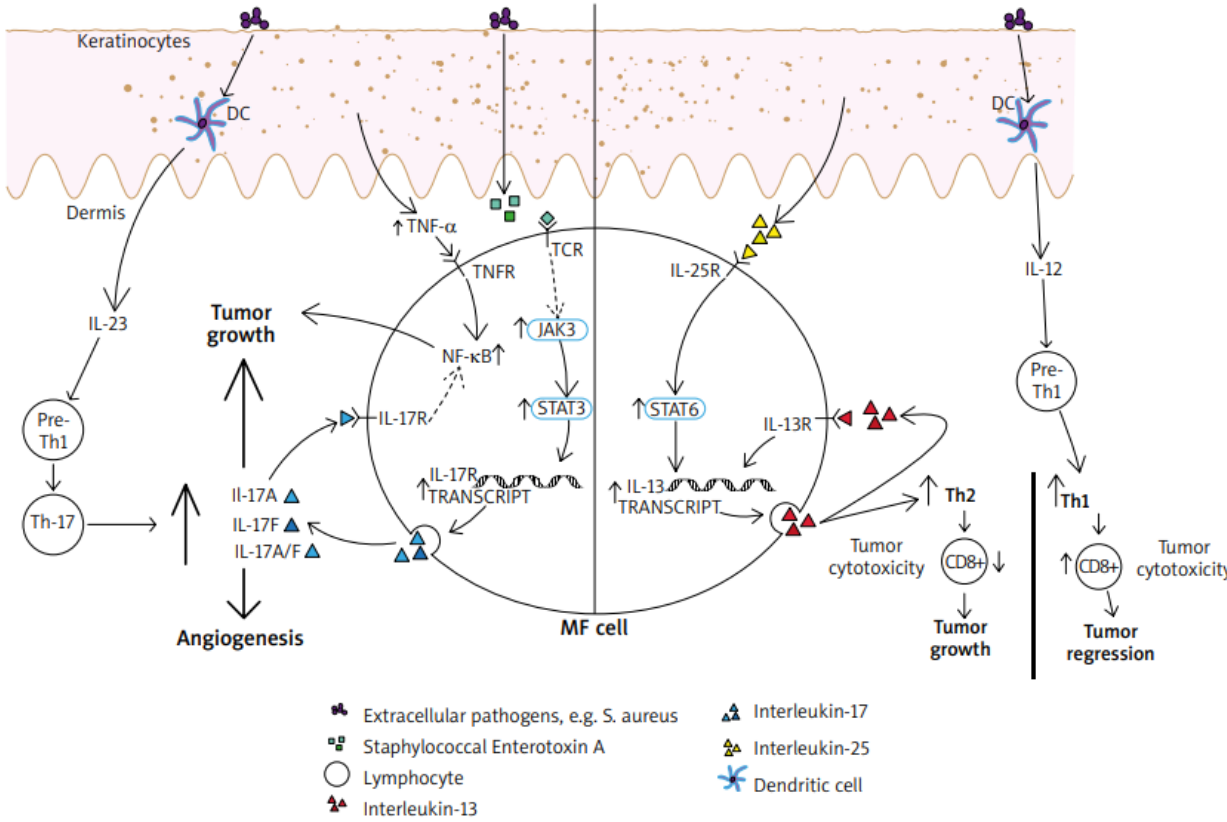
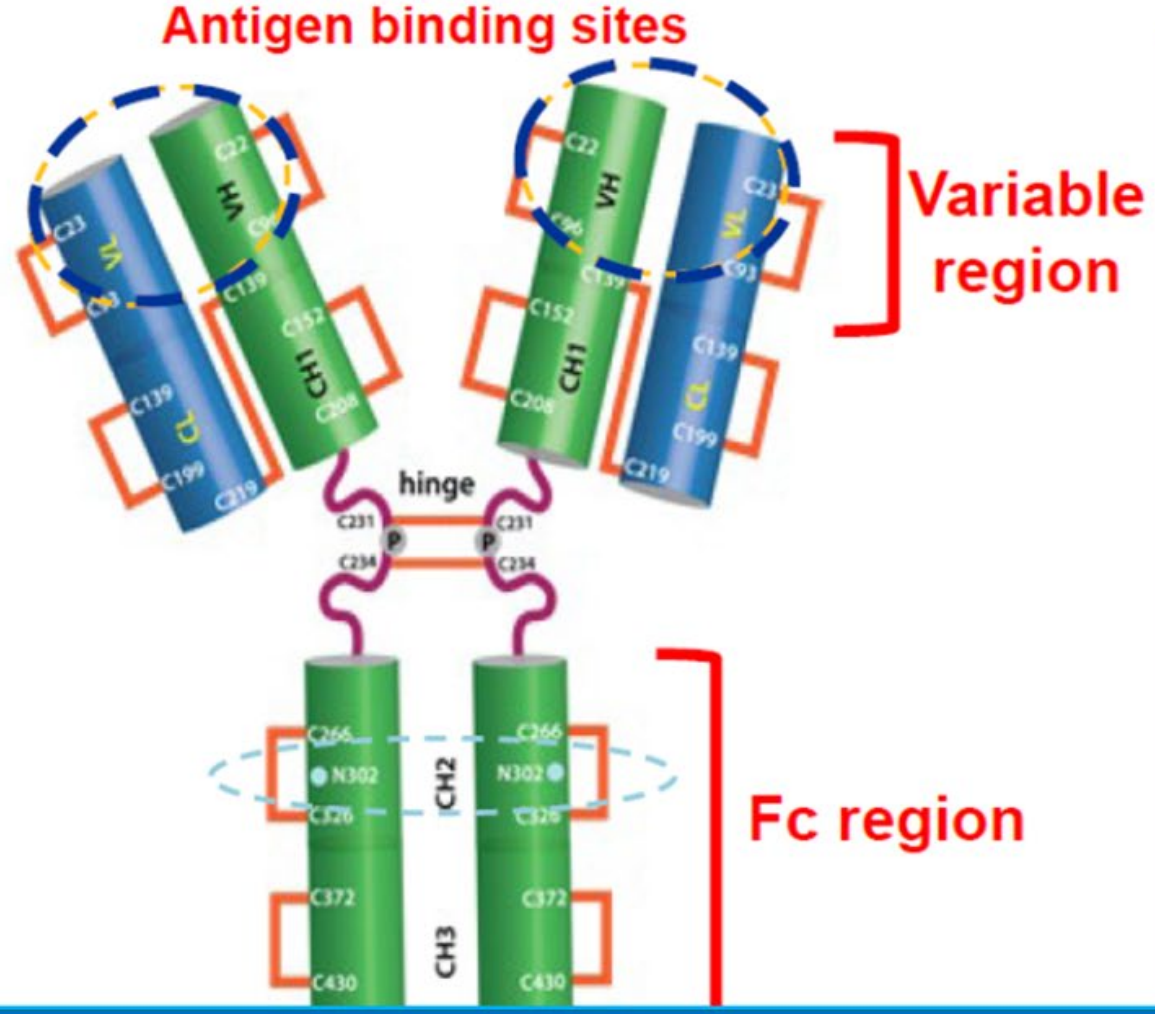


Figure 1. The contribution of interleukins (IL) 12, 17, 23 and tumour necrosis factor α (TNF-α) to the tumour microenvironment in mycosis fungoides (MF). IL-12 has been indirectly restoring the cytotoxic mediated CD8(+) answer and promoting tumour regression by stimulating the differentiation of pre-T-helper 1 lymphocytes. IL-23 can stimulate pre-T-helper 1 lymphocytes, followed by creating T-helper 17 cells subset and increased secretion of IL-17 proinflammatory cytokines. MF cell is also able to secrete IL-17A, IL-17F and IL-17A/IL-17F heterodimers. It is reinforced by upregulated JAK3/STAT3 pathway, which has been shown to be promoted by activated T-cell receptor (TCR), which is necessary for malignant transformation in MF to occur. One of the possible ways of activating TCR is related to Staphylococcal enterotoxin A. NF-kB upregulation, with its anti-apoptotic effect on lymphoma cells, seems to be important and relevant in the pathogenesis of CTCL. It has been promoted by TNF-α as well as proinflammatory IL-17 cytokines. IL-25 (IL-17E) is promoting STAT6 pathway. Those interactions result in increased IL-13 secretion (also in autocrine manner). Especially in the advanced stage of the disease it contributes to forming Th-2 cytokine profile, what results in decreased cytotoxic immunosurveillance and tumour growth

TNF-α nella Micosi fungoide:.da un lato sostiene un microambiente Th1-biased dall'altro è implicato nel sostenere la sovravvivenza delle cellule tumorali
La prima funzione sarebbe prevalente

Dupilumab: Molecular Structure

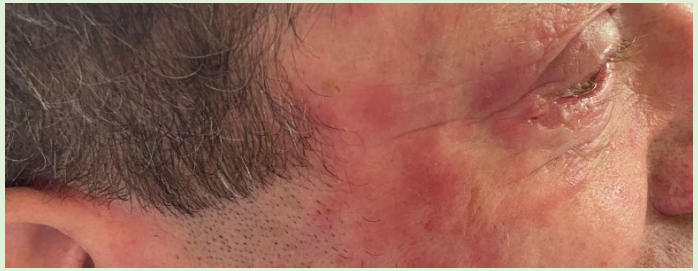
Fully human IgG4 monoclonal antibody



- Two complete heavy chains
- Two complete κ light chains
- Molecular weight: 147 kDa
- One N-linked glycosilation site in each heavy chain (Fc region)
- Target antigenic binding site: alpha subunit of the IL-4 receptor (IL-4Rα)
- High binding affinity for IL-4Rα

DUPILUMAB

Dopo 9 mesi di terapia con Dupilumab



BIOPSIA CUTANEA

Paziente 3

infiltrato linfocitario costituito da linfociti di piccole e medie dimensioni distribuiti nel derma superficiale
epidermotropismo e follicolotropismo
C3+ positive con parziale perdita di C7+.

Riarrangiamento TCRγ: negativo

I reperti, anche alla luce del quadro clinico, depongono per una micosi fungoide in fase iniziale; aspetti suggestivi per variante follicolare o con note di follicolotropismo.

Naranjo algorithm

	Yes	No	Do not know	Score
1. Are there previous *conclusive* reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	−1	0	
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	
4. Did the adverse reaction reappear when the drug was readministered?	+2	−1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0	
6. Did the reaction reappear when a placebo was given?	−1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
			Total score	

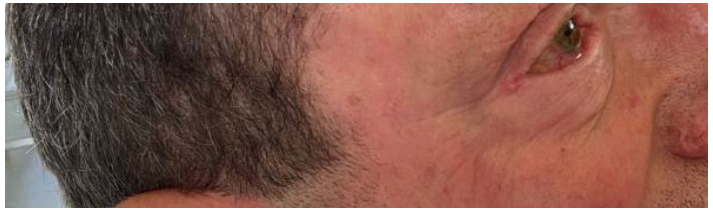
6 → ADR probabile

SOSPENSIONE DUPILUMAB

Naranjo CA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981 Aug;30(2):239-45. doi: 10.1038/clpt.1981.154.

E’ stata posta diagnosi di MF in paziente grande atopico→Dupilumab sospeso

BEXAROTENE 150 mg + UVBnb



STADIAZIONE

- TAC TB: negativa
- Immunofenotipo su sangue: negativo

In corso NGS

più sensibile in fasi iniziali di MF

Sufficool, K. E., et al. (2015). JAAD, 73(2), 228-236.e2. https://doi.org/10.1016/j.jaad.2015.04.030

DALLA LETTERATURA

Editorial

October 18, 2023

Dupilumab, Atopic Dermatitis, and Mycosis Fungoides—New Insights on an Evolving Story

Joan Guitart, MD[1]

» Author Affiliations

JAMA Dermatol. 2023;159(11):1177-1178. doi:10.1001/jamadermatol.2023.3846

I commend Boesjes et al[1] for their astute observation. We have certainly observed similar cases at the Northwestern Cutaneous Lymphoma Clinic with resolution on discontinuation of dupilumab, but concerns for the several reports of irreversible and often aggressive disease acceleration in previously undiagnosed patients with MF remains.[8,9,15] Furthermore, the cohort[1] included a patient with both MF and LR, raising concerns that LR may not be reversible in all cases, but rather an initial step toward lymphoma. This latter case revealed a complex story beyond a simple diagnostic dilemma of MF vs LR, suggesting that an initial workup and long follow-up may be required to identify and treat these more nuanced, indeterminate cases.

Given the widespread and growing use of dupilumab in eczema and the increasing interest for its use in other TH2-mediated disease indications, it is crucial to recognize and better understand a potential association between dupilumab and MF progression or to unmask individuals with previously undiagnosed MF. Although clinical and pathologic resolution of the eruption after discontinuation of dupilumab in most LR cases is reassuring, such patients deserve a comprehensive workup including skin biopsy with T-cell receptor clonality assay, blood cell counts with flow cytometry analysis, serum lactate dehydrogenase, and documentation of possible adenopathy, followed with imaging studies and/or nodal biopsies in cases with abnormal results.

Despite the encouraging outcome of this case series,[1] dermatologists should remain vigilant in ruling out MF, particularly in atypical presentations such as adult-onset AD, cases without personal or familial atopic medical history, erythrodermic and other uncharacteristic presentations like plaques, nodules, or sparing flexural sites. In such cases, skin biopsy should be the first step prior to dupilumab prescription. The detection of an atypical T-cell infiltrate regardless of the final pathologic diagnosis should be followed by a comprehensive workup or referral to an academic center with expertise in cutaneous lymphomas.

Clin Exp Dermatol. 2023 Nov 16;48(12):1376-1378. doi: 10.1093/ced/llad277.

Mycosis fungoides and Sézary syndrome following dupilumab treatment: experience of two Italian tertiary care centres

Stefano Buffon [1 2], Silvia Alberti Violetti [1 2], Gianluca Avallone [3], Luigia Venegoni [2], Angelo V Marzano [1 2], Luca Mastorino [3], Paolo Fava [3], Simone Ribero [3], Pietro Quaglino [3], Michela Ortoncelli [3], Silvia M Ferrucci [1]

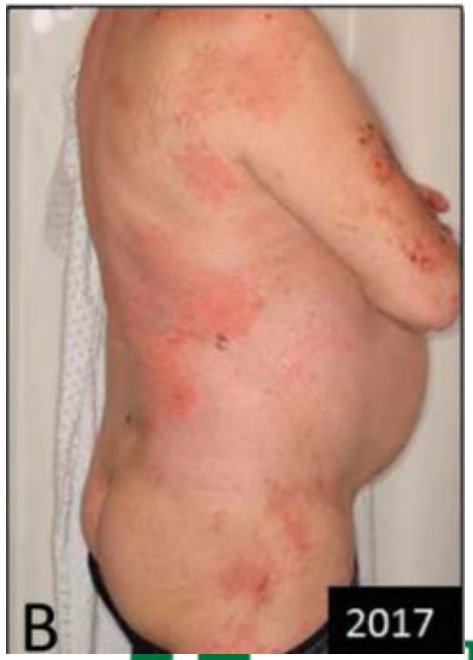
In our multicentre experience, based on a large sample of patients and long-term follow-up, dupilumab appears to be a safe drug. AD progression and CTCL induction seem extremely rare, even in cases of nonmalignant T-cell clonal proliferation in the peripheral blood. We could not ascertain whether our MF/SS cases depend on an initial misdiagnosis or dupilumab-induced progression. As both worsened during treatment, we recommend dupilumab discontinuation in case of CTCL diagnosis, as previously reported.[4] Moreover, prompt execution of skin biopsies and TCRG analysis is mandatory when AD is unresponsive to dupilumab or in cases of late-onset AD with no history of atopic diathesis, in order to minimize the risk of delayed CTCL diagnosis and treatment.

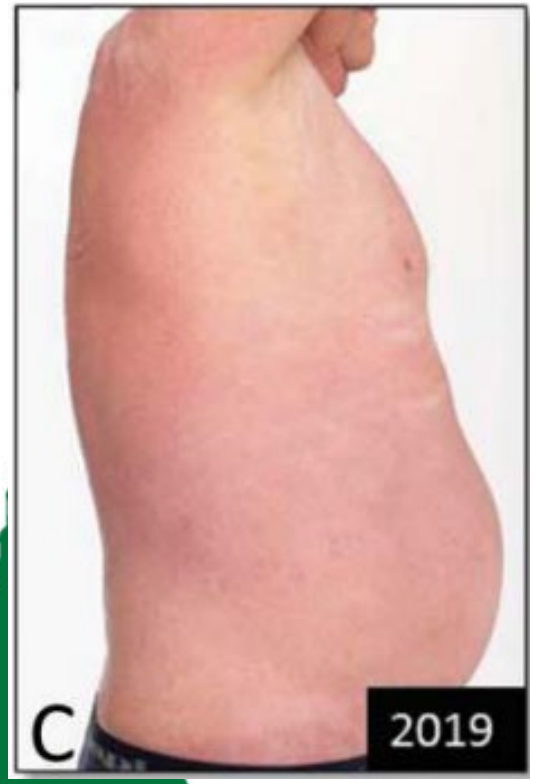
Evolution of Dupilumab-Associated Cutaneous Atypical Lymphoid Infiltrates

Olayemi Sokumbi, MD, Huma Shamim, MBBS,† Mark Dennis P. Davis, MD,† David A. Wetter, MD,† Catherine C. Newman, MD,† and Nneka Comfere, MD†‡*

(*Am J Dermatopathol* 2021;43:714–720)

- Età media 60.4 anni (range, 27–74)
- Esordio di dermatite eczematosa in età adulta
- Biopsie precedenti non sospette per MF
- TCRγ negativo in 6/7 casi





Am J Clin Dermatol. 2023 Jan 10. doi: 10.1007/s40257-022-00749-1. Online ahead of print.

Development of Cutaneous T-Cell Lymphoma Following Biologic Treatment: A Systematic Review

Lauren Schaefer [1], Nneka Comfere [2 3], Olayemi Sokumbi [4 5]

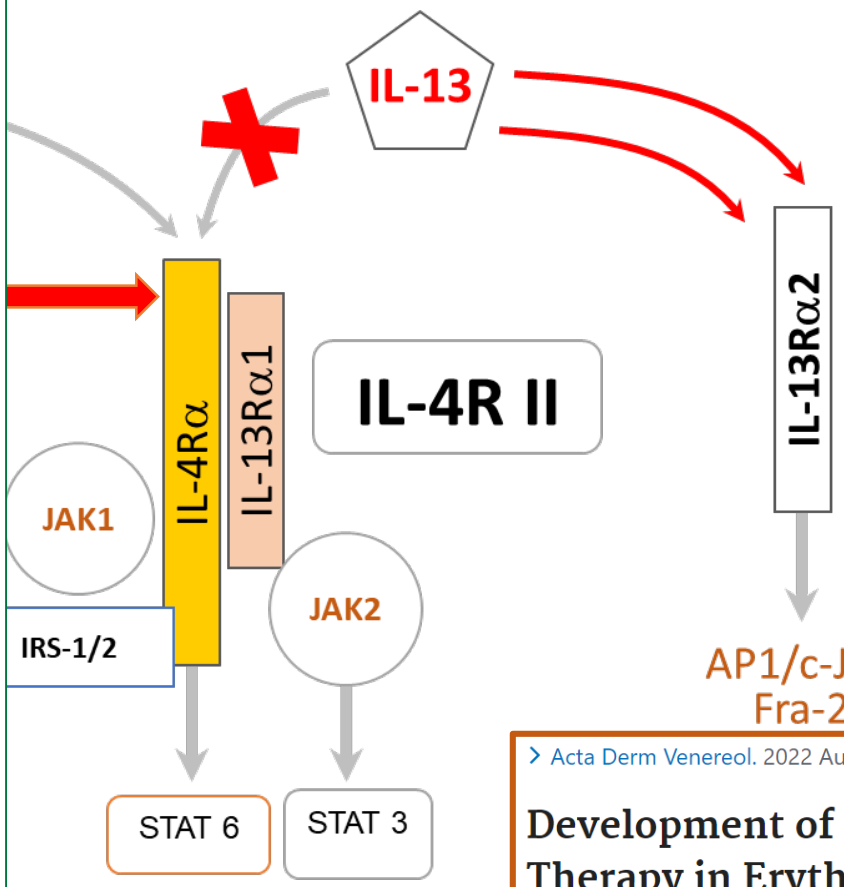
Within our cohort, most patients were treated with a biologic agent due to a primary dermatologic indication that possibly was misdiagnosed, considering that CTCL, especially MF, has the propensity to clinically and histologically mimic atopic dermatitis and psoriasis. It has been proposed

Meccanismo molecolare

Hollins LC, et al. Cutis. 2020 Jaén, M., et al. 2022). In Biochimica et Biophysica Acta - Reviews onCancer

IL-13 along with its signalling (IL-13Rα1) and decoy (IL-13Rα2) receptors are **overexpressed in CTCL** cells, and IL-13 promotes tumor cell growth and guarantees immune evasion in CTCL. Hence, increased availability of IL-13 following IL-4Rα1 inhibition might result in CTCL progression.

On the other hand, IL-4/IL-13 inhibition could theoretically reverse Th2 polarization, which is typical of the advanced-stage CTCL microenvironment, but progression to MF during dupilumab therapy appears to occur through an alternate, IL-13-independent pathway.



Legame ad alta affinità

Iperespresso in numerose neoplasie

- glioblastoma
- K ovarico
- K mammario

Dupilumab può favorire la progressione di un CTCL

> Acta Derm Venereol. 2022 Aug 24;102:adv00766. doi: 10.2340/actadv.v102.2234.

Development of Nodular Lesions after Dupilumab Therapy in Erythrodermic Mycosis Fungoides with Interleukin-13 Receptor alpha2 Expression

Mina Hashimoto, Tomomitsu Miyagaki [1], Reo Komaki, Sora Takeuchi, Takafumi Kadono

Affiliations + expand

PMID: 36000994 PMCID: PMC9593494 DOI: 10.2340/actadv.v102.2234

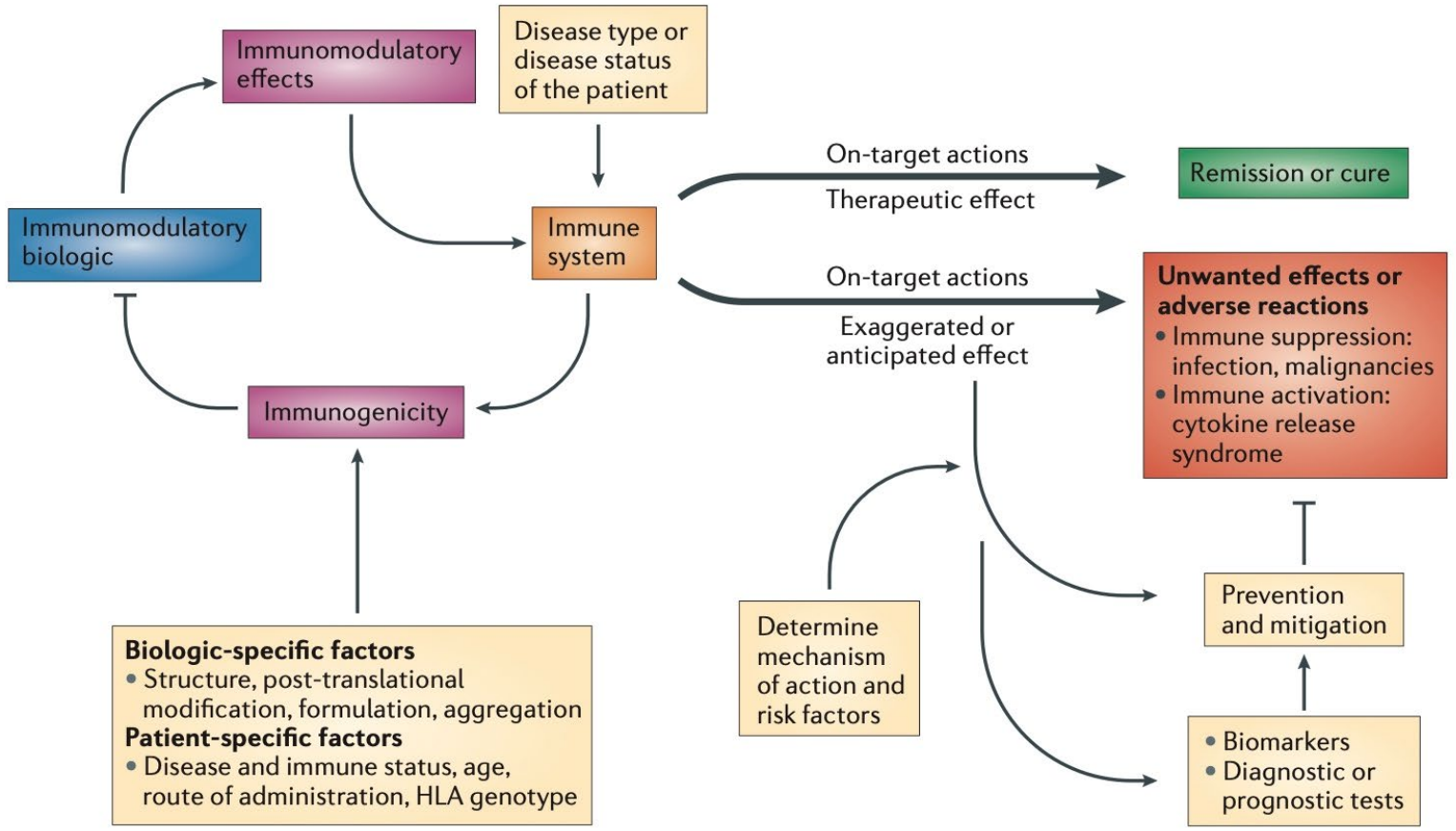
Challenges and approaches for the development of safer immunomodulatory biologics 2013

Jean G. Sathish[1], Swaminathan Sethu[1]*, Marie-Christine Bielsky[2], Lolke de Haan[3], Neil S. French[1], Karthik Govindappa[1], James Green[4], Christopher E. M. Griffiths[5], Stephen Holgate[6], David Jones[2], Ian Kimber[7], Jonathan Moggs[8], Dean J. Naisbitt[1], Munir Pirmohamed[1], Gabriele Reichmann[9], Jennifer Sims[10], Meena Subramanyam[11], Marque D. Todd[12], Jan Willem Van Der Laan[13], Richard J. Weaver[14] and B. Kevin Park[1]*

- I farmaci biologici ad oggi rappresentano più del 30% dei prodotti farmaceutici autorizzati

- Tra il 1993 e il 2011, 174 nuovi farmaci biologici sono stati autorizzati dall'EMA per una grande varietà di malattie, incluse quelle immuno-mediate e neoplasie.

- La comprensione delle complesse interazioni tra stati di malattia, sistema immunitario del ricevente, target dell'immunomodulazione è necessaria per mitigare i rischi di effetti avversi.



L'interazione dei farmaci biologici immunomodulatori può infatti risultare sia in un'efficace risposta terapeutica targettizzata, sia in reazioni avverse ed effetti indesiderati

Review > Front Oncol. 2023 Sep 7:13:1235711. doi: 10.3389/fonc.2023.1235711. eCollection 2023.

Role of cytokine in malignant T-cell metabolism and subsequent alternation in T-cell tumor microenvironment

Megha Yadav [1], Blessi N Uikey [1], Shantnu Singh Rathore [1], Priyanka Gupta [1], Diksha Kashyap [1], Chanchal Kumar [1], Dhananjay Shukla [2], Vijayamahantesh [3], Arvind Singh Chandel [4], Bharti Ahirwar [5], Ashish Kumar Singh [6], Shashi Shekhar Suman [7], Amit Priyadarshi [8], Ajay Amit [1]

Affiliations + expand

PMID: 37746258 PMCID: PMC10513393 DOI: 10.3389/fonc.2023.1235711

Free PMC article

Abstract

T cells are an important component of adaptive immunity and T-cell-derived lymphomas are very complex due to many functional sub-types and functional elasticity of T-cells. As with other tumors, tissues specific factors are crucial in the development of T-cell lymphomas. In addition to neoplastic cells, T- cell lymphomas consist of a tumor micro-environment composed of normal cells and stroma. Numerous studies established the qualitative and quantitative differences between the tumor microenvironment and normal cell surroundings. Interaction between the various component of the tumor microenvironment is crucial since tumor cells can change the microenvironment and vice versa. In normal T-cell development, T-cells must respond to various stimulants deferentially and during these courses of adaptation. T-cells undergo various metabolic alterations. From the stage of quiescence to attention of fully active form T-cells undergoes various stage in terms of metabolic activity. Predominantly quiescent T-cells have ATP-generating metabolism while during the proliferative stage, their metabolism tilted towards the growth-promoting pathways. In addition to this, a functionally different subset of T-cells requires to activate the different metabolic pathways, and consequently, this regulation of the metabolic pathway control activation and function of T-cells. So, it is obvious that dynamic, and well-regulated metabolic pathways are important for the normal functioning of T-cells and their interaction with the microenvironment. There are various cell signaling mechanisms of metabolism are involved in this regulation and more and more studies have suggested the involvement of additional signaling in the development of the overall metabolic phenotype of T cells. These important signaling mediators include cytokines and hormones. The impact and role of these mediators especially the cytokines on the interplay between T-cell metabolism and the interaction of T-cells with their micro-environments in the context of T-cells lymphomas are discussed in this review article.

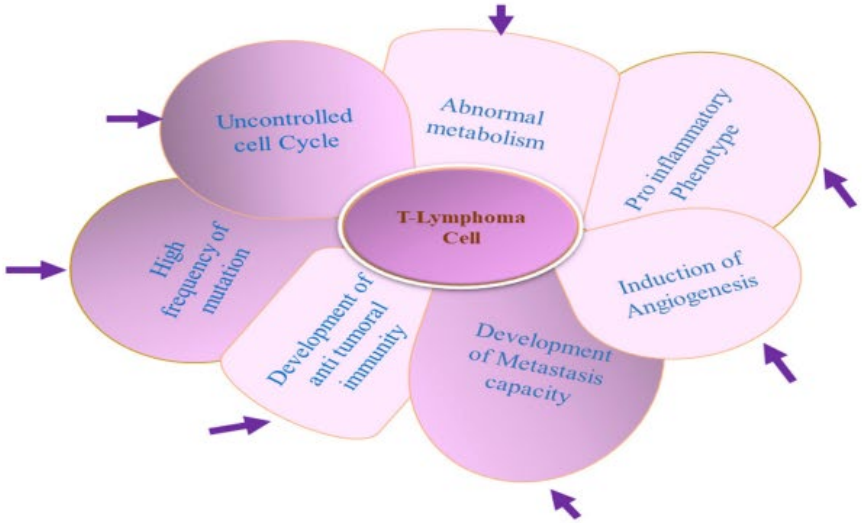


FIGURE 1
Unusual properties of T-lymphoma cell: T-lymphoma cell's unusual properties is dictated by an interwoven complex signaling network between T lymphoma cell and other normal constituent cells of the tumor microenvironment (TME).

cells

MDPI

Review

The Microenvironment's Role in Mycosis Fungoides and Sézary Syndrome: From Progression to Therapeutic Implications

Alessandro Pileri [1,2,*], Alba Guglielmo [1], Vieri Grandi [3], Silvia Alberti Violetti [4], Daniele Fanoni [4], Paolo Fava [5], Claudio Agostinelli [2,6], Emilio Berti [4], Pietro Quaglino [5] and Nicola Pimpinelli [3]

Mycosis fungoides: The great imitator

Herschel S. Zackheim, MD,[a] and Timothy H. McCalmont, MD[a,b] *San Francisco, California*

A considerable number of reports have documented mycosis fungoides (MF) mimicking other dermatoses, but a comprehensive review has not been published. Our aim was to comprehensively review reports of various dermatoses simulated by MF. Additionally, 2 cases in which MF simulated diseases not previously documented (psoriasis and erythema annulare centrifugum) are presented. A literature search of all case reports of MF cited in the MEDLINE database from 1966 through 2000 plus those in one of the author's (H. Z.) files was performed. A total of 23 reported cases of dermatoses mimicked by MF were found. With the additional 2 dermatoses now presented, this yields a total of at least 25 diseases that can be simulated by MF. In view of the considerable number of dermatoses simulated by MF, the term *the great imitator* is appropriate for MF. (J Am Acad Dermatol 2002;47:914-8.)

In years past, syphilis was called *the great imitator*.[1] However, clinical evidence strongly suggests that in the present era this appellation best fits mycosis fungoides (MF). Vonderheid[2] has noted that early lesions of MF are frequently confused with other dermatoses. Koh, Charif, and Weinstock[3] remark that MF may resemble chronic eczematous or atopic dermatitis, neurodermatitis, psoriasis, nummular dermatitis, or tinea corporis; however, a comprehensive review of the tendency of MF to mimic other dermatoses has not been published.

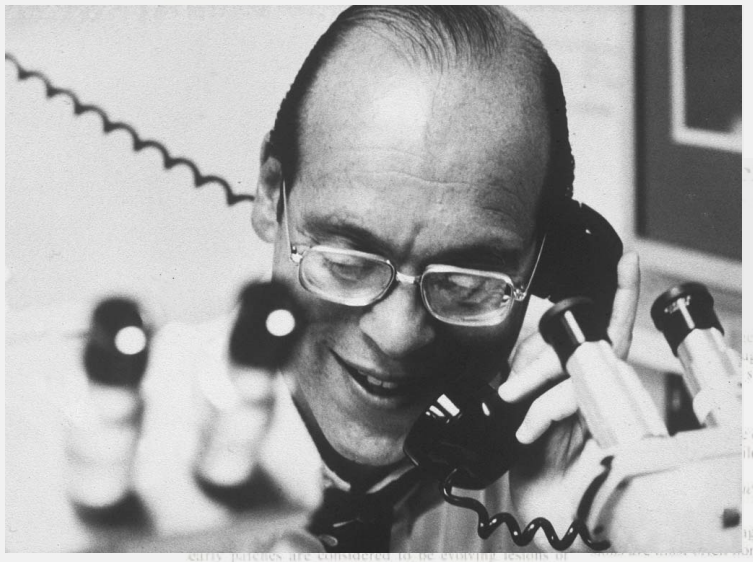
MF is the most common form of cutaneous T-cell lymphoma and represents an epidermotro
plasm composed of $CD4^+$ (helper) cells.[3]
uncommon disease; the most recent US d
1991 to 1992 indicate an annual incidenc
cases/million.[4] Although a number of fac
chronic antigenic stimulation; atopy; biolog
ical, or chemical exposures; and viral infecti
been postulated as causative agents, none
definitively confirmed.[3]

Over the past several decades, one autho
has been struck by the multiform morphol
sentations of MF and the frequent instances
well-known dermatoses have been simulat
cally by MF. A computerized literature searc
LINE since 1966) was done to supplement this personal experience. A total of 23 dermatoses were reported (Table I). In all instances the diagnosis of MF was not suspected clinically but was based on histopathologic findings. These include acanthosis nigricans,[5] alopecia,[6-8] bullous eruption,[9] comedones and epidermal cysts,[7,8,10-12] dissecting cellulitis of the scalp,[13] dyshidrosis,[14] erythema multiforme,[15] gangrene,[16] acquired ichthyosis,[17] invisible dermatosis,[18] ischemic foot,[19] keratosis lichenoides chronica,[20] necrobiosis,[21] perioral dermatitis,[22] pigmented purpuric dermatitis,[23-25] pityriasis alba,[26] po-
rokeratosis,[27,28] palmarplantar pustulosis,[29-31] pyo-

Table I. Dermatoses simulated clinically by mycosis fungoides (MF)

	Presence of other clinical manifestations of MF	Type	References
Acanthosis nigricans	Yes	PL	Willemze et al[5]
Alopecia	Yes	PA	Kossard et al[6]
Alopecia	No		Peris et al[8]
Bullous eruption	Yes	PA/PL, tumors	Roenigk and Castrovinci[9]
Comedones, epidermal cysts	No		Oliwiecki, Ashworth[7]
Comedones, epidermal cysts	No		Peris et al[8]
Comedones, epidermal cysts	Yes	PL	Lacour et al[10]
Cysts (epidermal)	Yes	PL	Radeff et al[11]
Cysts (epidermal), comedones	Yes	PA/PL	Aloi et al[12]
Dissecting cellulitis of the scalp	Yes	PA/PL	Gilliam et al[13]
Dyshidrosis	Yes	PL	Soyer et al[14]
Erythema annulare centrifugum	Yes	PA	Zackheim and McCalmont (this report)
Erythema multiforme	No		Krebs et al[15]
Gangrene	No		Lund et al[16]
Ichthyosis, acquired	No		Kutting et al[17]
Invisible dermatosis	No		Pujol et al[18]
Ischemic foot	No		Goldstein et al[19]
Keratosis lichenoides chronica	No		Bahadoran et al[20]
Necrobiosis	Yes	PA/PL, tumors	Woolons et al[21]
Perioral dermatitis	Yes	PA/PL	Wolf et al[22]
Pigmented purpuric dermatitis	Yes	PA	Barnhill and Braverman[23]
Pigmented purpuric dermatitis	No		Cather et al[24]
Pigmented purpuric dermatitis	No		Martinez et al[25]
Pityriasis alba	No		Whitmore et al[26]
Porokeratosis	No		Hsu et al[27] (case 2)
Porokeratosis	Yes	PA	Breneman and Breneman[28]
Psoriasis, plaque-type	Yes	PL, tumor	Zackheim and McCalmont (this report)
Pustulosis, palmoplantar	Yes	PA/PL, tumors	Ohkohchi et al[29]
Pustulosis, palmoplantar	Yes	PA/PL, tumors	Moreno et al[30]
Pustulosis, palmoplantar	Yes	PA/PL	Camisa and Aulisio[31]
Pyoderma gangrenosum	Yes	PL	Ho et al[32]
Sarcoidosis	No		Bessis et al[33]
Sarcoma	Yes	PA/PL	Machler et al[34]
Vesicular eruption	Yes	PL	McBride et al[35]
Vesiculobullous eruption	Yes	PA/PL	Maeda et al[36]
Vesiculobullous eruption	Yes	PL, tumors	Cordoba et al[37]
Vitiligo	Yes	PA	Zackheim et al[38] (case 3)
Vitiligo	No		Cooper et al[39]
Vitiligo	No		Lambroza et al[40]

MF, Mycosis fungoides; *PA*, patch stage; *PL*, plaque stage.



Mycosis fungoides“Neoplastic but with an Inflammatory Attitude”

Sanchez JL, Ackerman AB. The patch stage of mycosis fungoides. Am J Dermatopathol. 1979;1:5–26.

Ackerman AB, Denianke K, Sceppa J, et al. Mycosis Fungoides: Perspective Historical Allied With Critique Methodical for Illumination Maximal. New York: Ardor Scribendi; 2007.

RINGRAZIAMENTI

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Dipartimento di Scienze Clinico-Chirurgiche, Diagnostiche e Pediatriche

Fondazione IRCCS Policlinico San Matteo

Università di Pavia

"There is an art to science, and a science in art; the two are not enemies, but different aspects of the whole." Science fiction writer Isaac Asimov mirrors