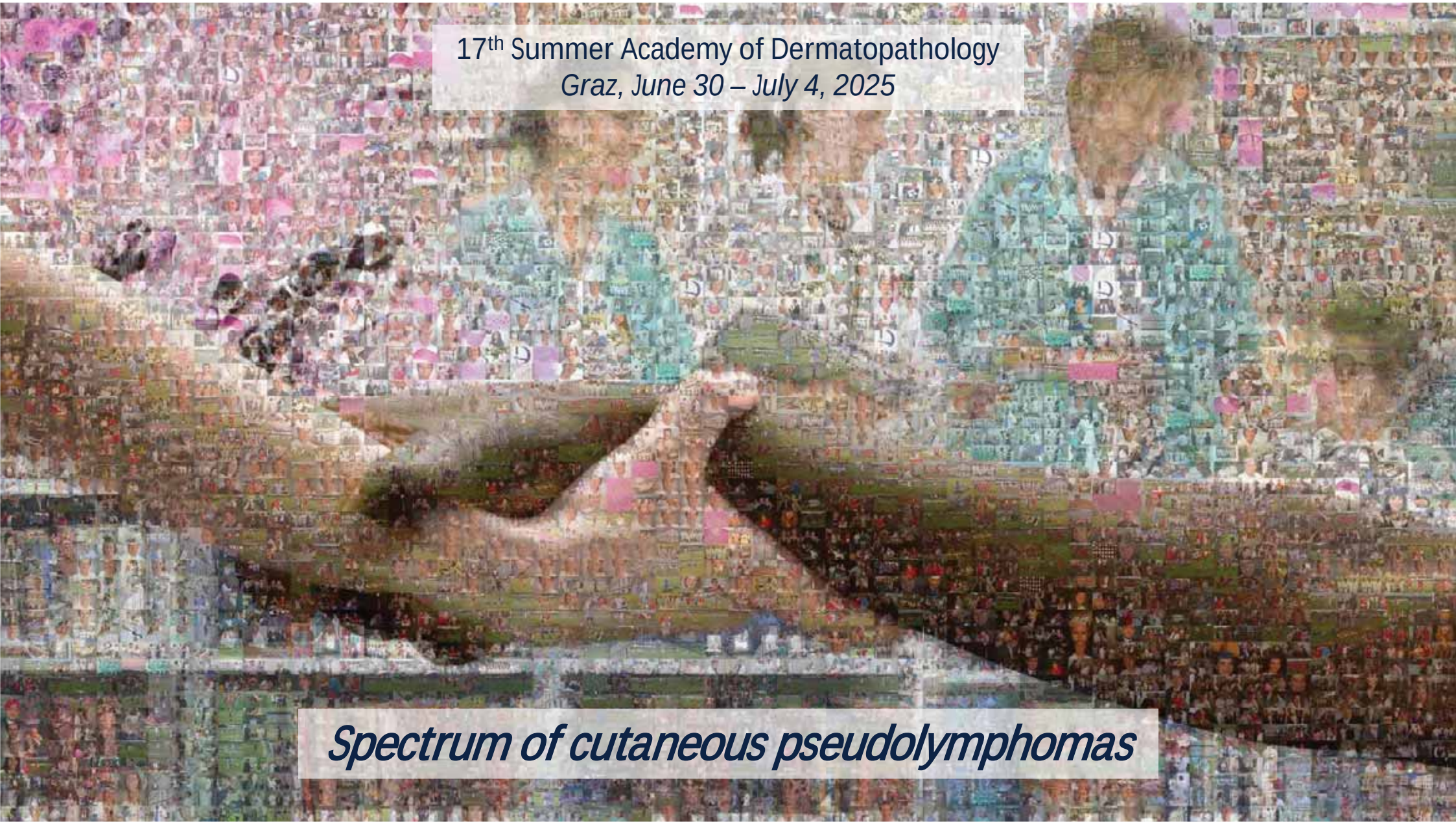
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Spectrum of cutaneous pseudolymphomas

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REVIEW

WILEY

Cutaneous pseudolymphoma—A review on the spectrum and a proposal for a new classification

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Abstract

Cutaneous pseudolymphomas (PSLs) belong to a group of lymphocytic infiltrates that histopathologically and/or clinically simulate lymphomas. Different causative agents (e.g., Borrelia sp., injected substances, tattoo, arthropod bite) have been described, but in many cases no cause can be identified, hence the term idiopathic PSL. Clinicopathological correlation is important to make the diagnosis. Four main groups of cutaneous PSL can be distinguished based on histopathologic and/or clinical presentation: (a) nodular PSL; (b) pseudo mycosis fungoides (pseudo-MF) and simulators of other CTCLs; (c) other PSL (representing distinct clinical entities); and (d) intravascular PSL. This article gives an overview of the histopathologic and clinical characteristics of cutaneous PSLs and proposes a new classification.

KEYWORDS
B-cell lymphoma, Borreliosis, clonality, cutaneous pseudolymphoma, infection, T-cell lymphoma, tattoo

1 | INTRODUCTION

1.1 | Definition

Cutaneous pseudolymphoma (PSL) is described in the literature as a reactive lymphoproliferation that histopathologically and/or clinically imitates cutaneous lymphomas.[1–3] Based on this wide definition it is clear that many processes fulfill the criteria of PSL. Not surprisingly, the term PSL defined in this way seems to have been overstretched in the literature. Many infectious and non-infectious diseases are characterized by atypical lymphocytic infiltrates, which can be easily misinterpreted as cutaneous lymphoma based on histopathologic features alone. To limit the usage of the term cutaneous PSL, we suggest a narrower definition. In analogy to cutaneous lymphomas, clinical information is essential in arriving at the diagnosis. By histopathology alone, the diagnosis of cutaneous pseudolymphoma can, in many cases, only be suspected. Additional clinical information and further diagnostic work-up are necessary to confirm the suspected diagnosis. Therefore, the term cutaneous PSL should be restricted to cases that histopathologically simulate cutaneous lymphomas and do not fit into any other diagnosis after clinical correlation. Figure 1 illustrates this approach.

1.2 | Etiology

The literature documents a wide range of causes of PSL, broadly divided into infections, drugs, and foreign agents (Table 1). Miguel et al[4] summarized the frequency of different causes of PSL (Figure 2). Despite the wide range of agents, in many PSL cases no trigger can be found; such cases are designated as idiopathic PSL.

1.3 | Classification

The literature describes many approaches to classify cutaneous PSL. These include a separation according to the predominating immunophenotype (T-cell, B-cell, or mixed), the histoarchitectural growth pattern, the etiology, or distinct clinical features (reviewed in Refs. 1,2,5). None of these approaches allows a consideration of overlapping features. Moreover, the phenotype and etiology are not evident, at first glance; further diagnostic work-up is essential. The composition of the infiltrate is variable, being influenced by genetic and immunological factors of the host, as reflected in the observation that identical agents (e.g., Borrelia sp.) can induce either B-PSL or T-PSL.

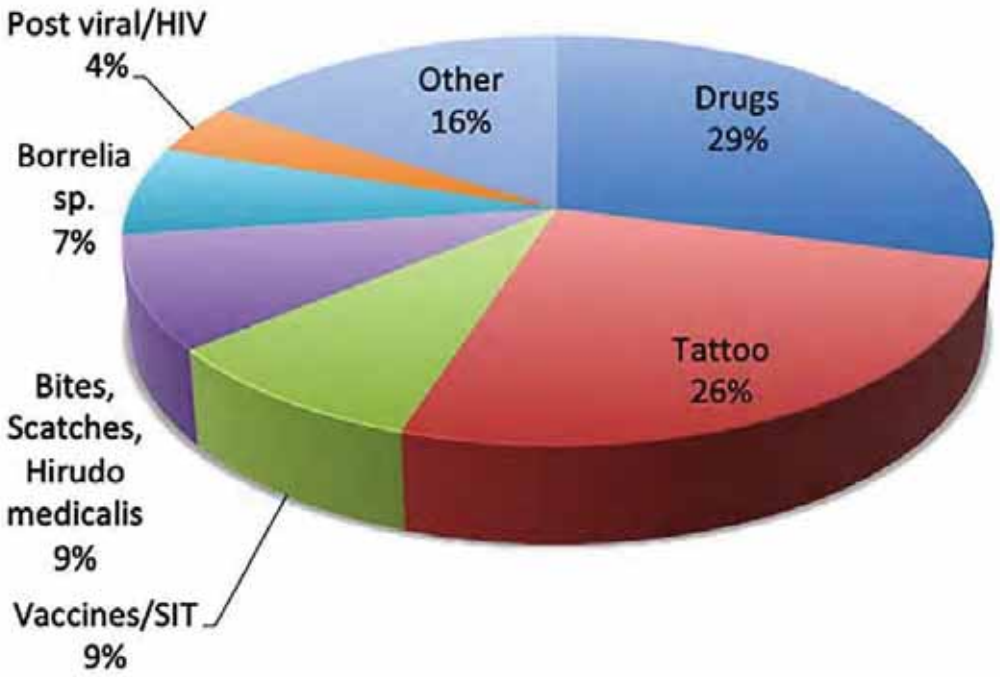
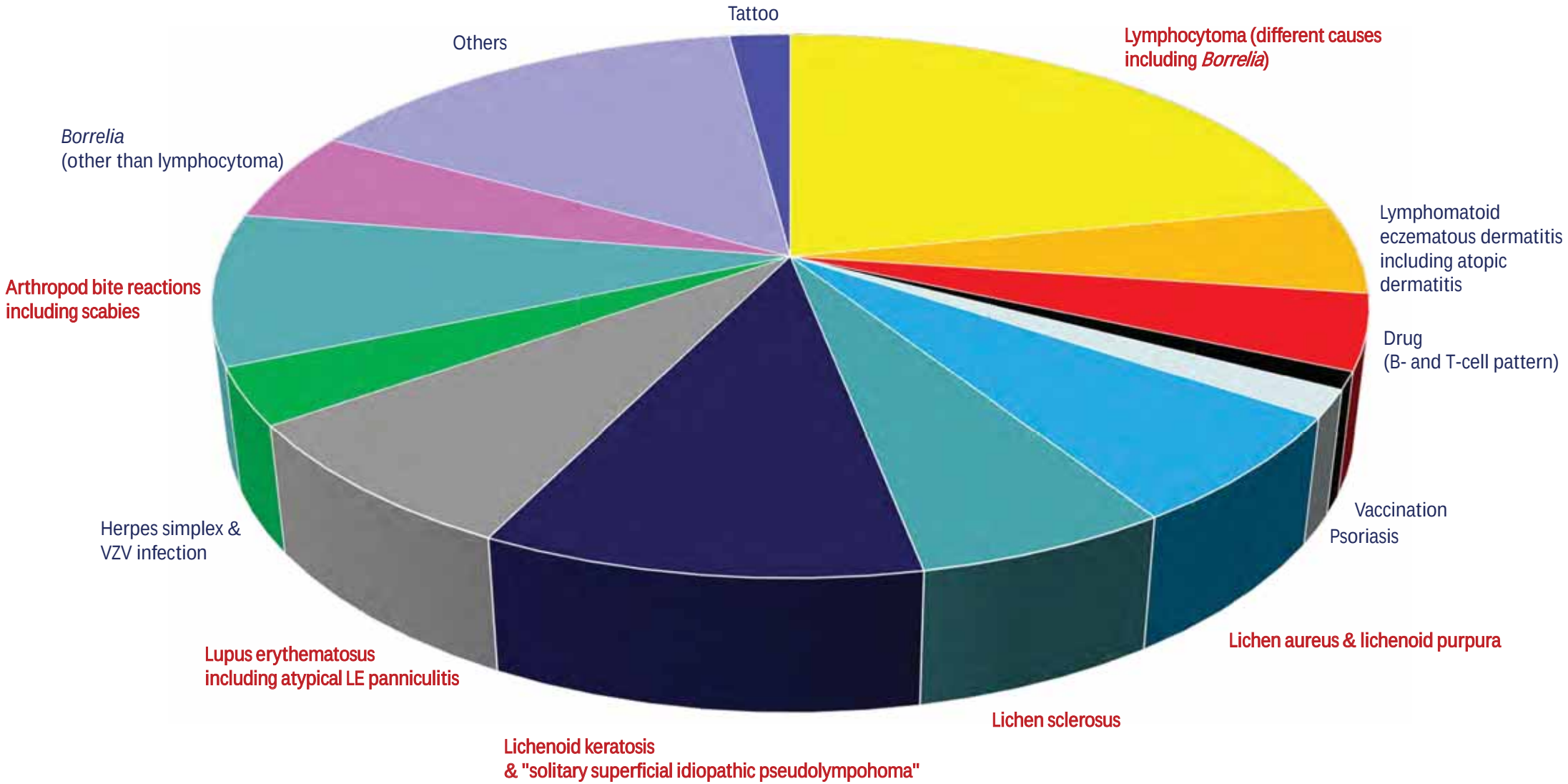


FIGURE 2 Frequency of different causes of cutaneous pseudolymphomas, modified after Miguel et al[4]

Cutaneous pseudolymphomas (my experience on >1200 cases)



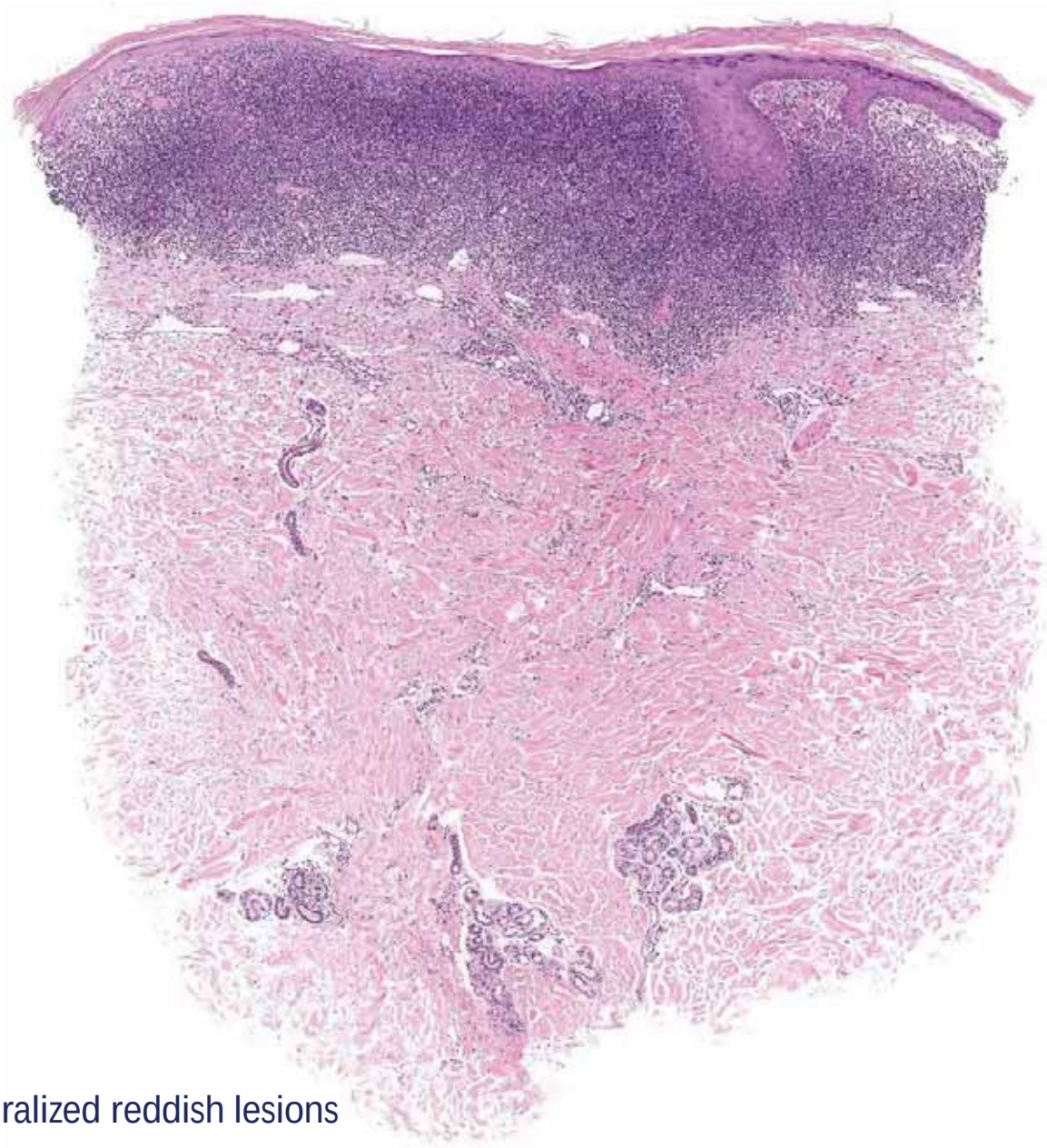
Cutaneous Pseudolymphomas

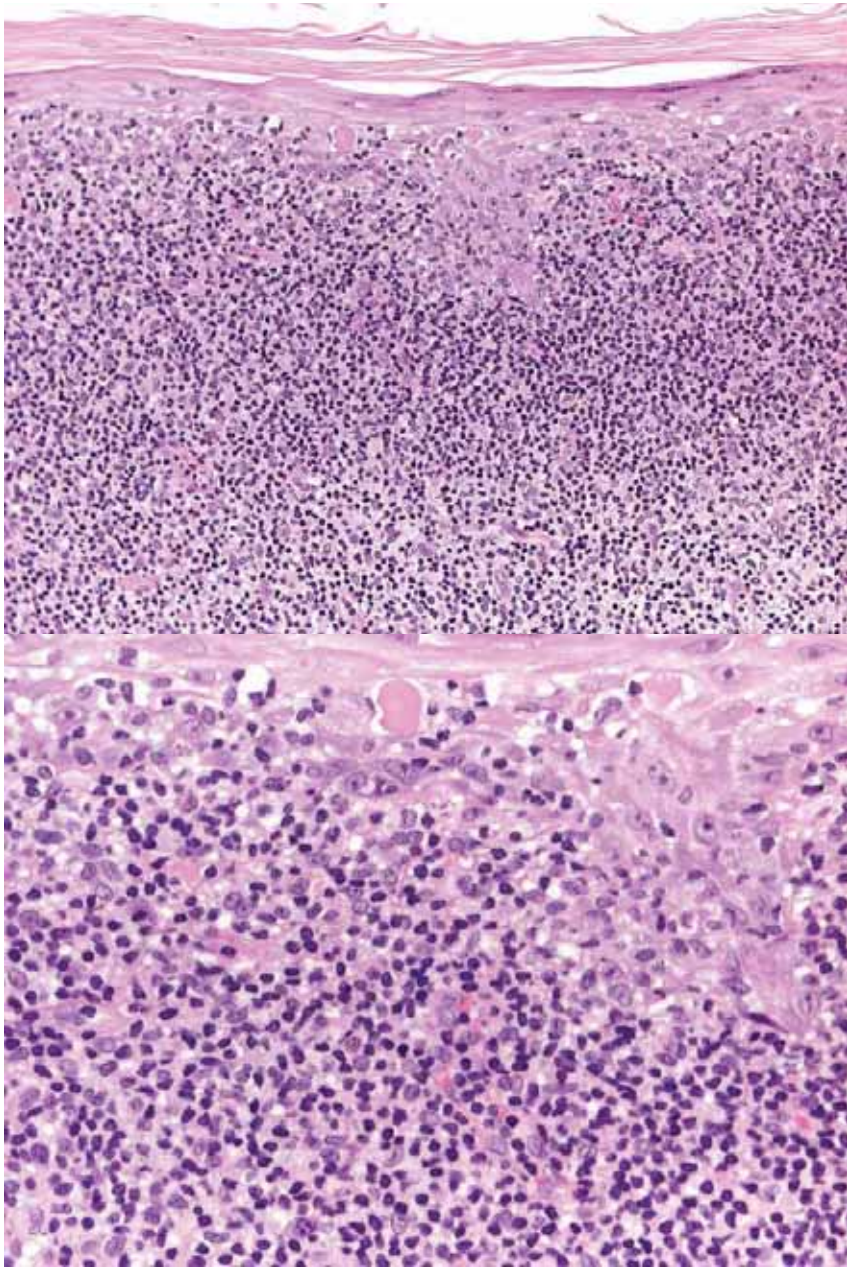
General Histopathologic Remarks

- A band-like T-cell infiltrate with intraepithelial lymphocytes is not restricted to MF or other CTCLs, and is not uncommon in several inflammatory disorders (e.g., lichenoid dermatoses)
- Low-grade malignant cutaneous B-cell lymphomas are usually characterized by a prominent population of reactive lymphocytes that may be the predominant one
- Identification of the neoplastic population crucial for proper diagnosis and classification (phenotype, proliferation pattern)
- kappa/lambda ratio for detection of monoclonality: 10:1; lambda/kappa: 4:1

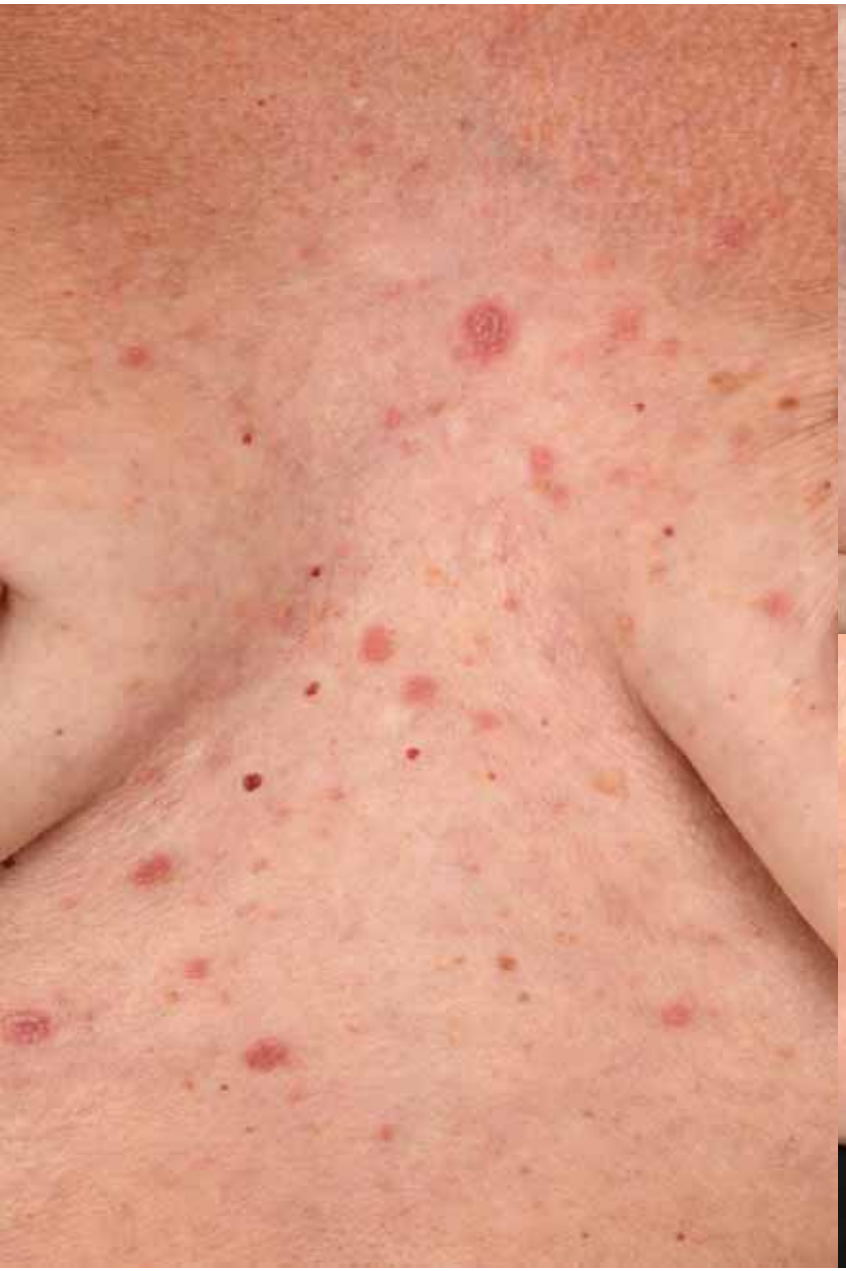
Mimickers of mycosis fungoides

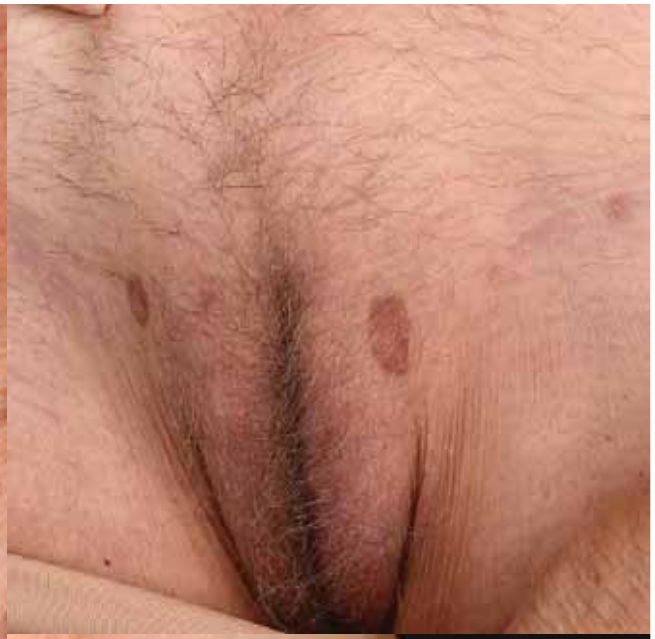
Always	Sometimes to Frequently	Rarely
Lichen aureus	Actinic reticuloid	Lichen planus
Non-MF-associated follicular mucinosis	Eczematous dermatoses	LE, superficial variant
Lymphomatoid keratosis	Psoriasis	Bullous pemphigoid
Superficial idiopathic pseudolymphoma	Lichen sclerosus (genital)	ACA, superficial variant
Annular lichenoid dermatitis of youth	Vitiligo, inflammatory stage	Drug eruption, T-cell type
	CD8+ dermatitis in HIV+	Tattoos, lichenoid type
	CD8+ dermatitis in mogamulizumab	Lichen striatus
	Pityriasis lichenoides	Nevoid hyperkeratosis of nipple
	Syphilis, superficial variant	
	HTLV-I infectious dermatitis	
	Immune response to epithelial tumors	

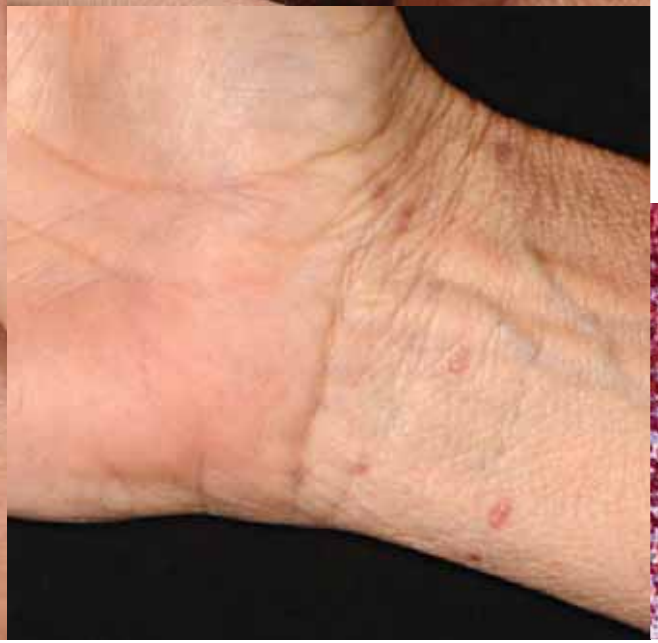


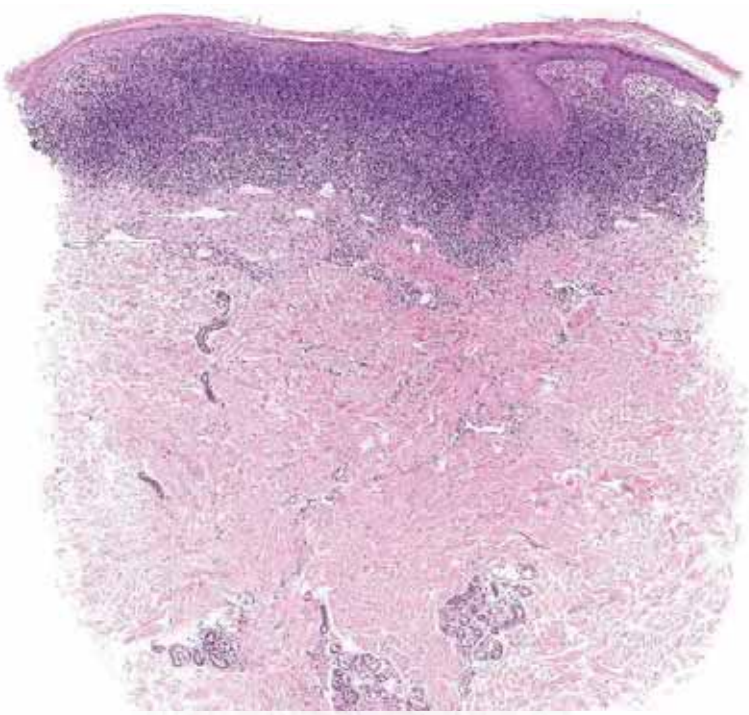


F, 58
Generalized reddish lesions

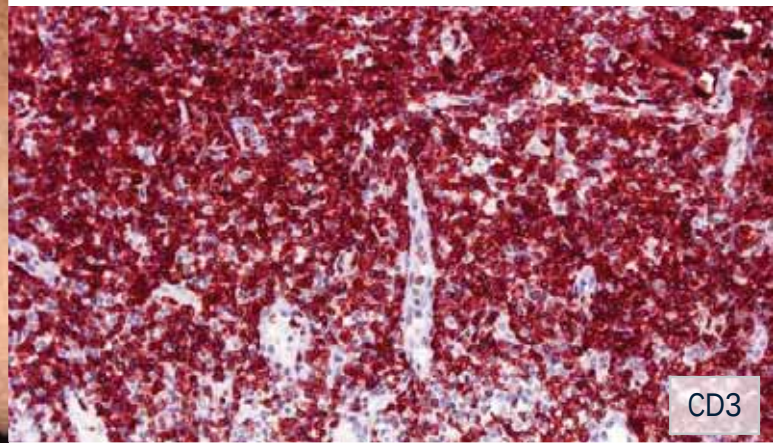


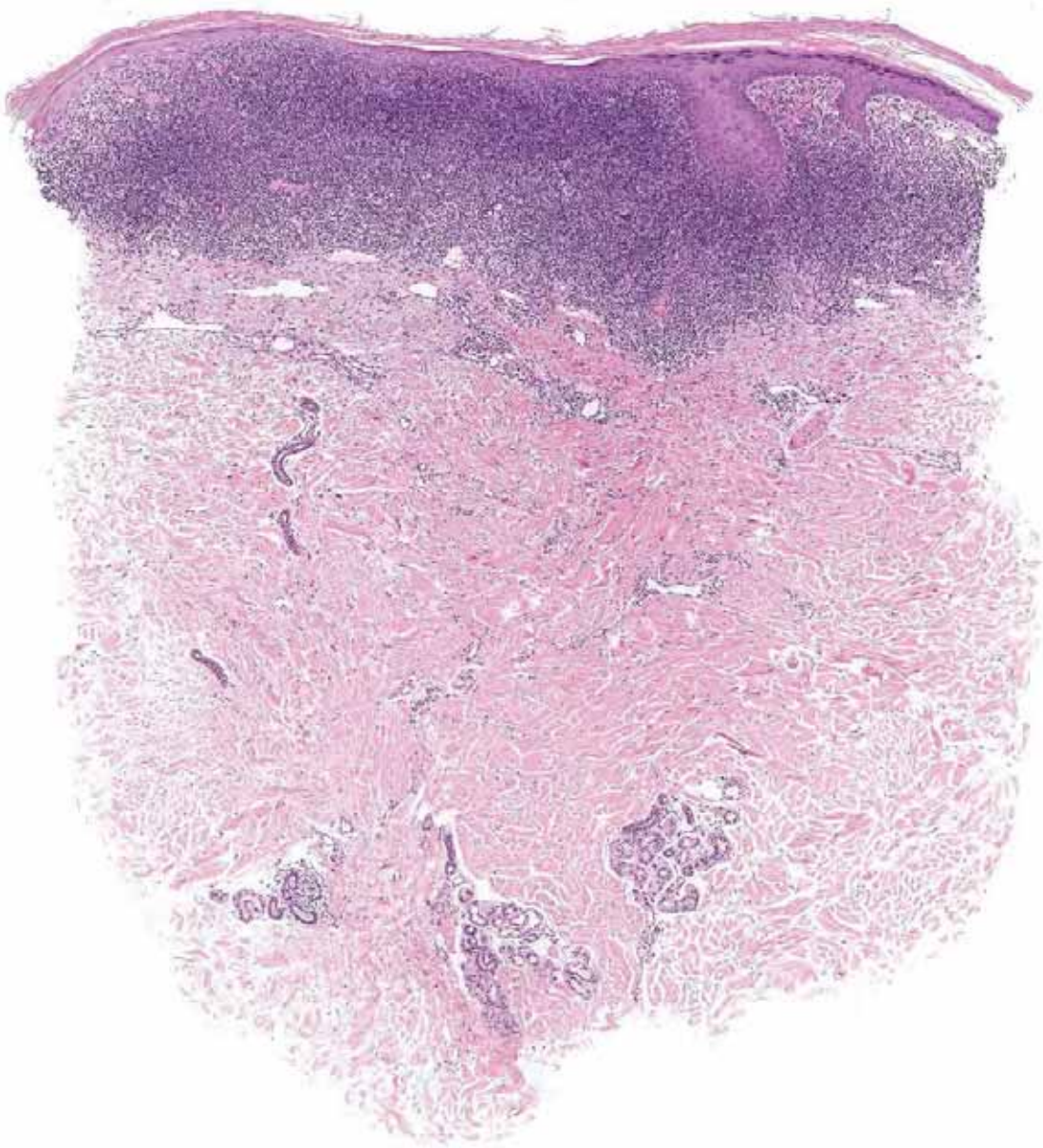


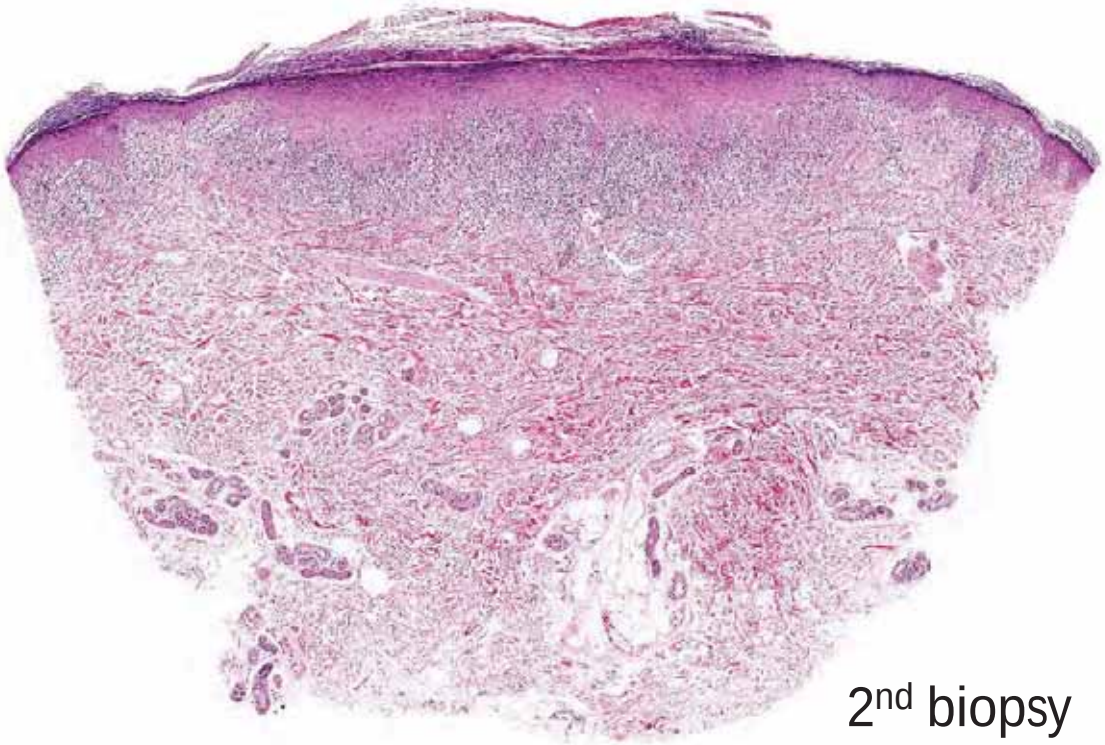




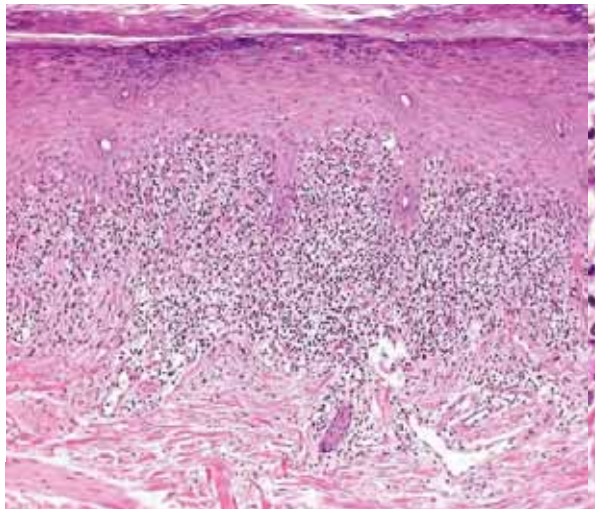
Lichen planus

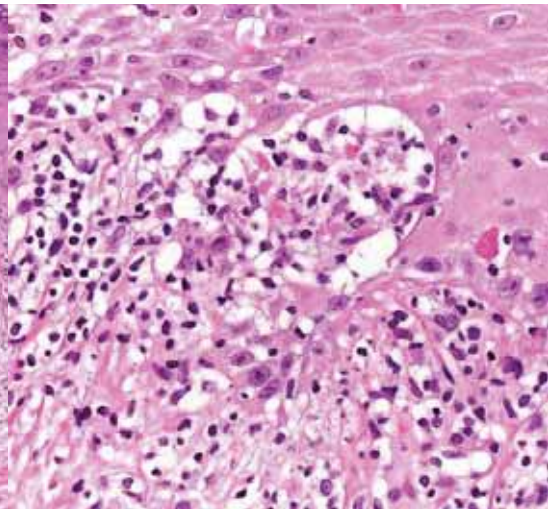






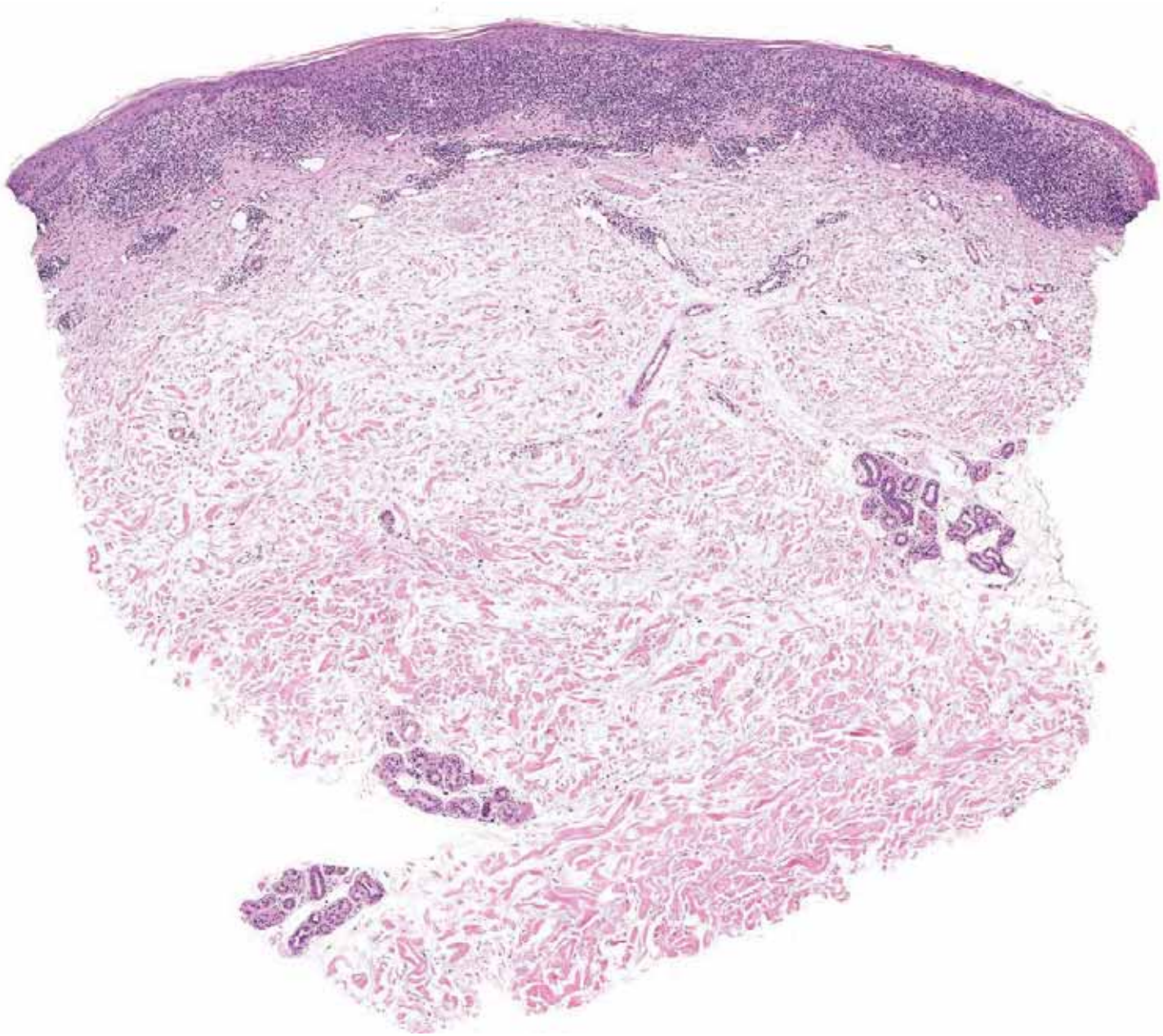
2nd biopsy



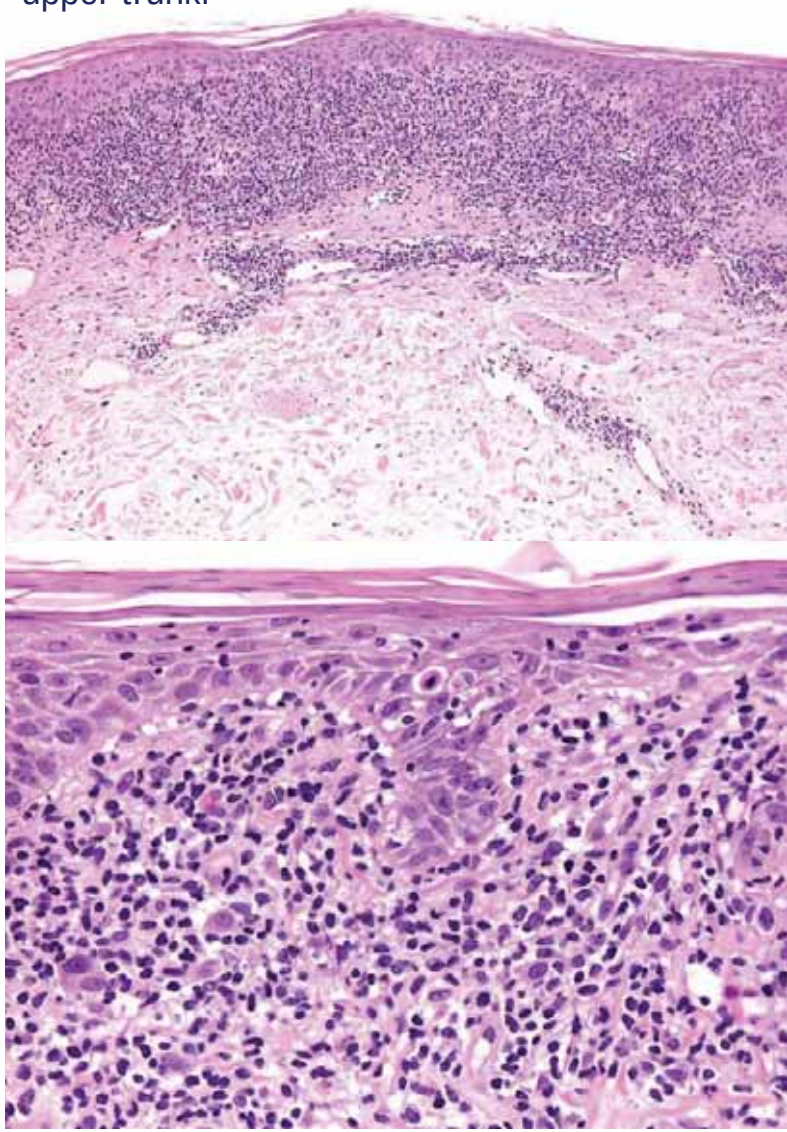


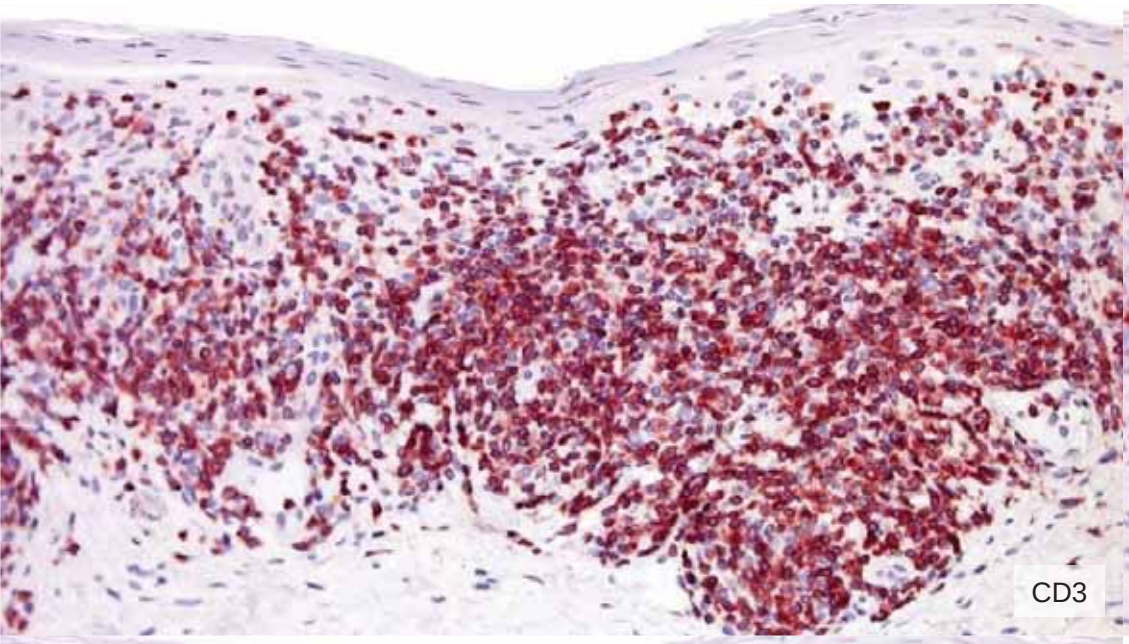
Pseudolymphomatous lichen planus

- The lichenoid infiltrate of lichen planus is easily distinguished from band-like infiltrates of MF in the vast majority of cases
- In some cases lack of other typical histopathological features of lichen planus (e.g., epithelial hyperplasia, hypergranulosis) and presence of epidermotropic lymphocytes may be the reason for concern
- Phenotypic features of these cases do not provide differential diagnostic criteria; correlation with the clinical picture and/or repeat biopsies allow a precise diagnosis



F, 69.
Infiltrated, reddish papules and plaques on the upper trunk.

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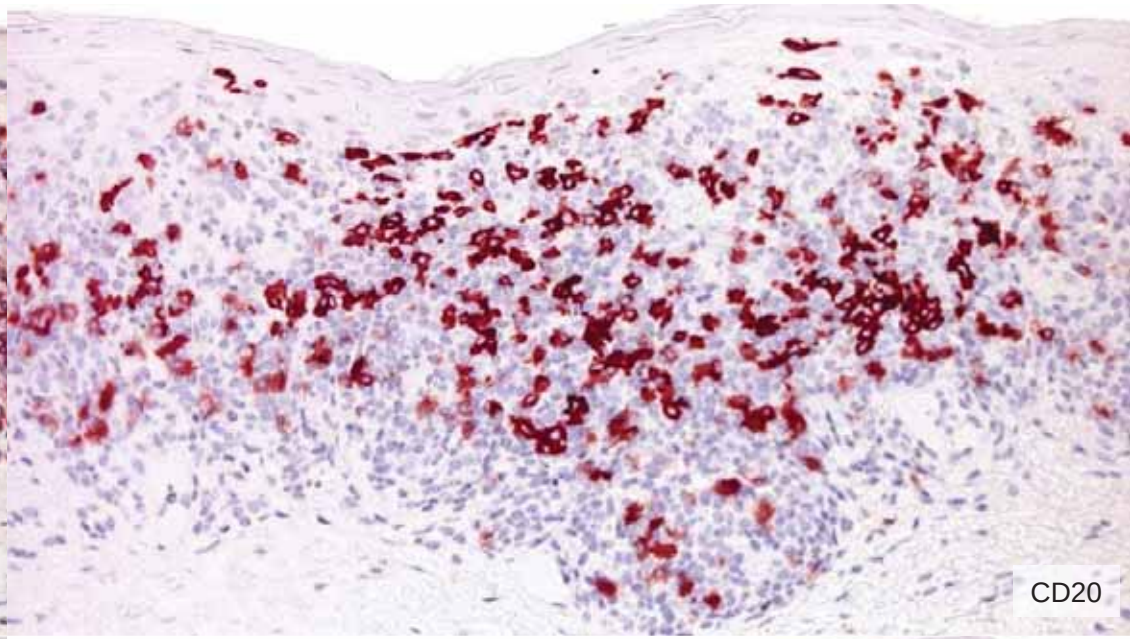
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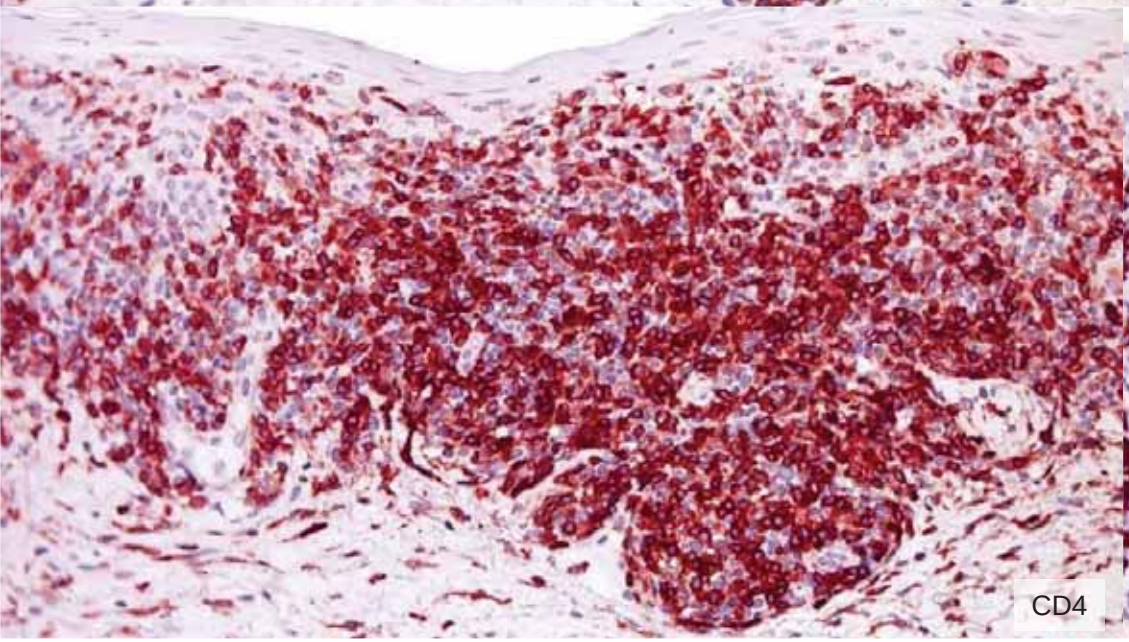
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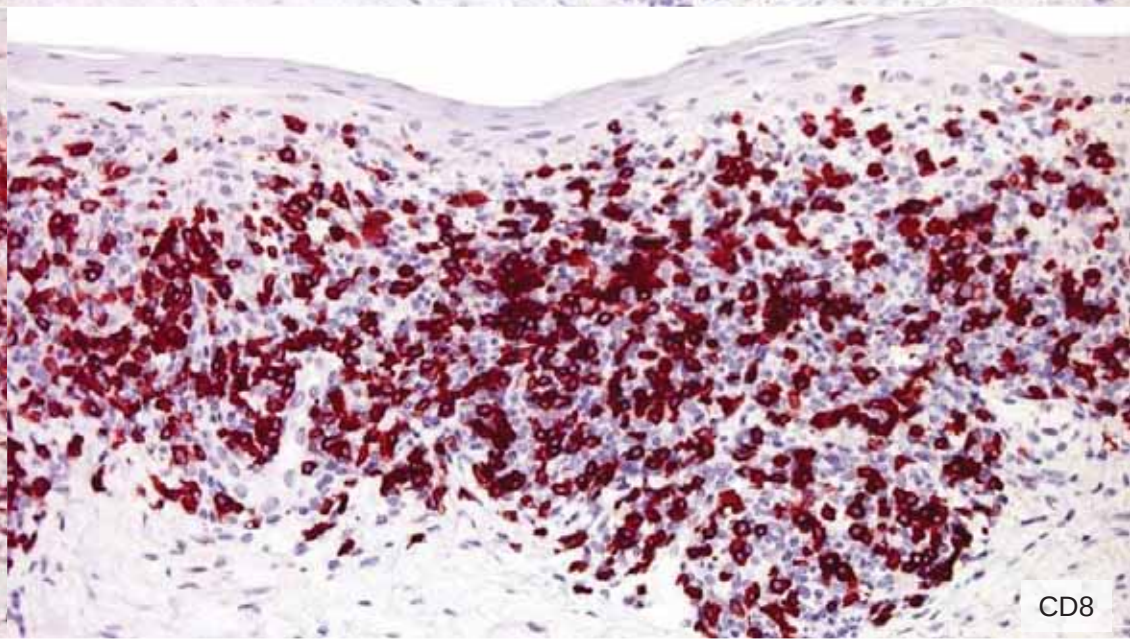
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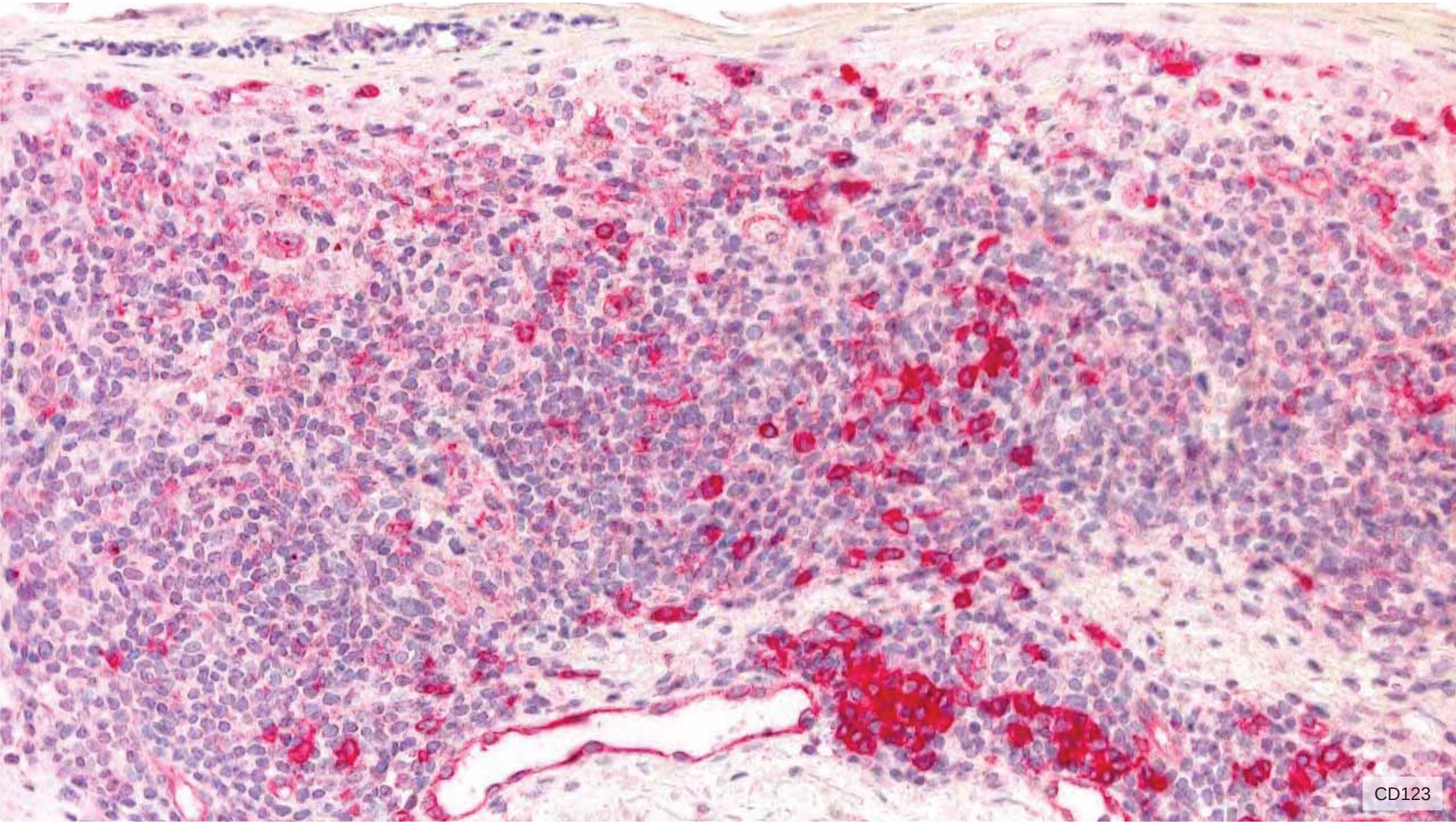
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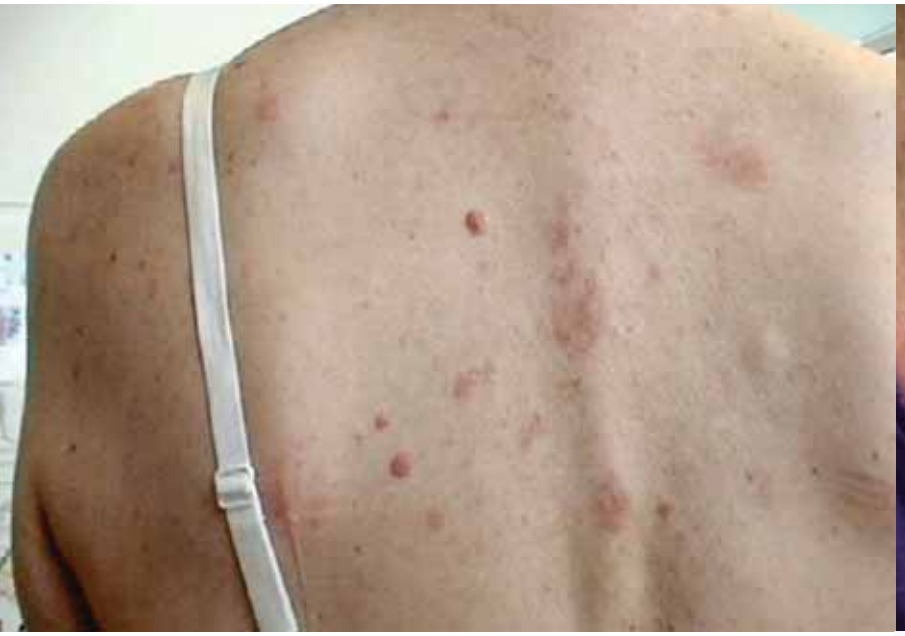

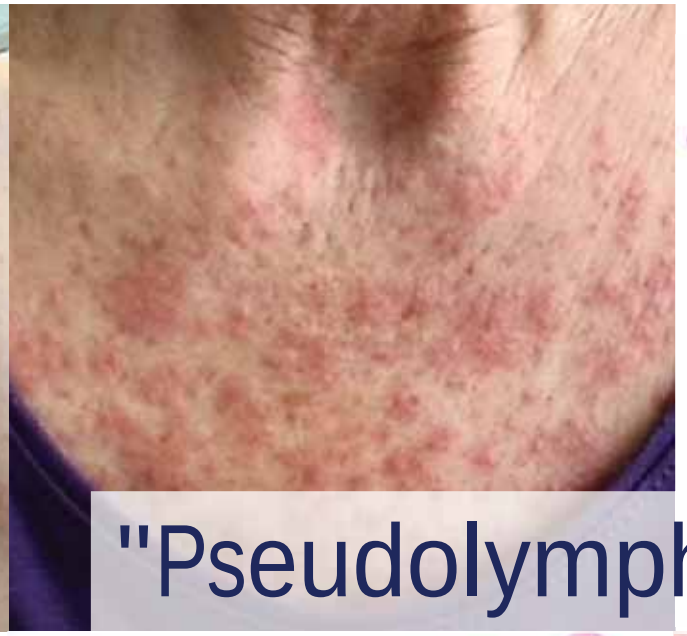

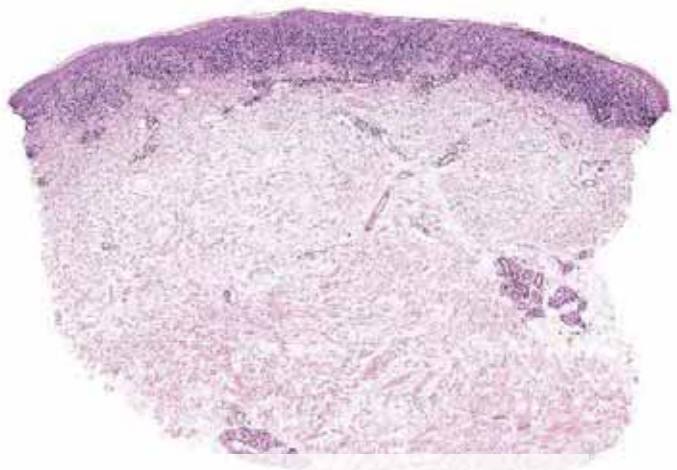

"Pseudolymphomatous" LE

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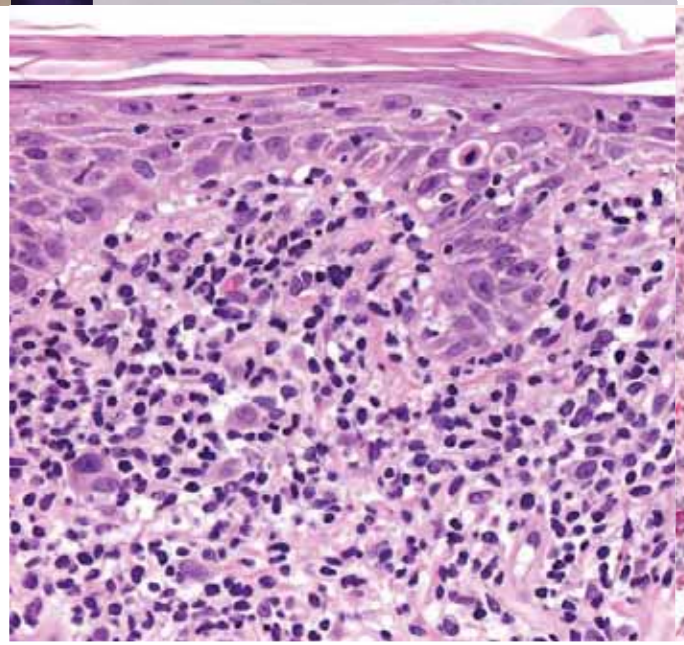
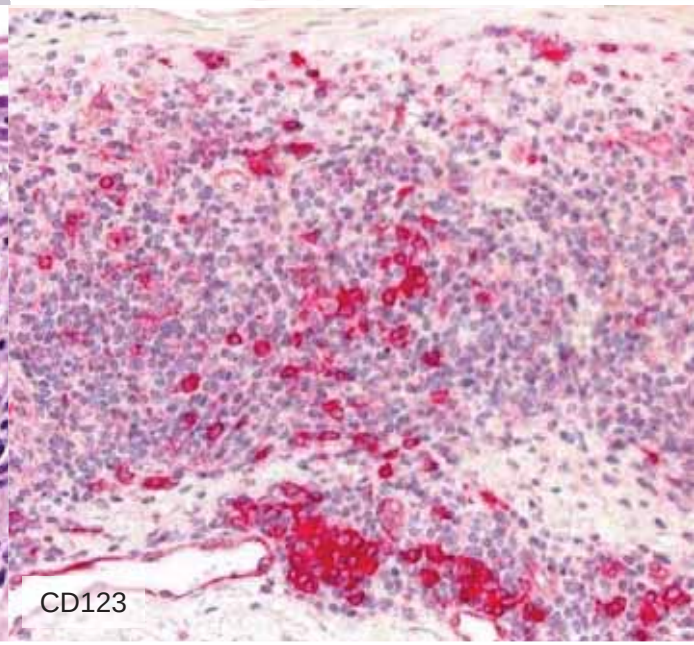
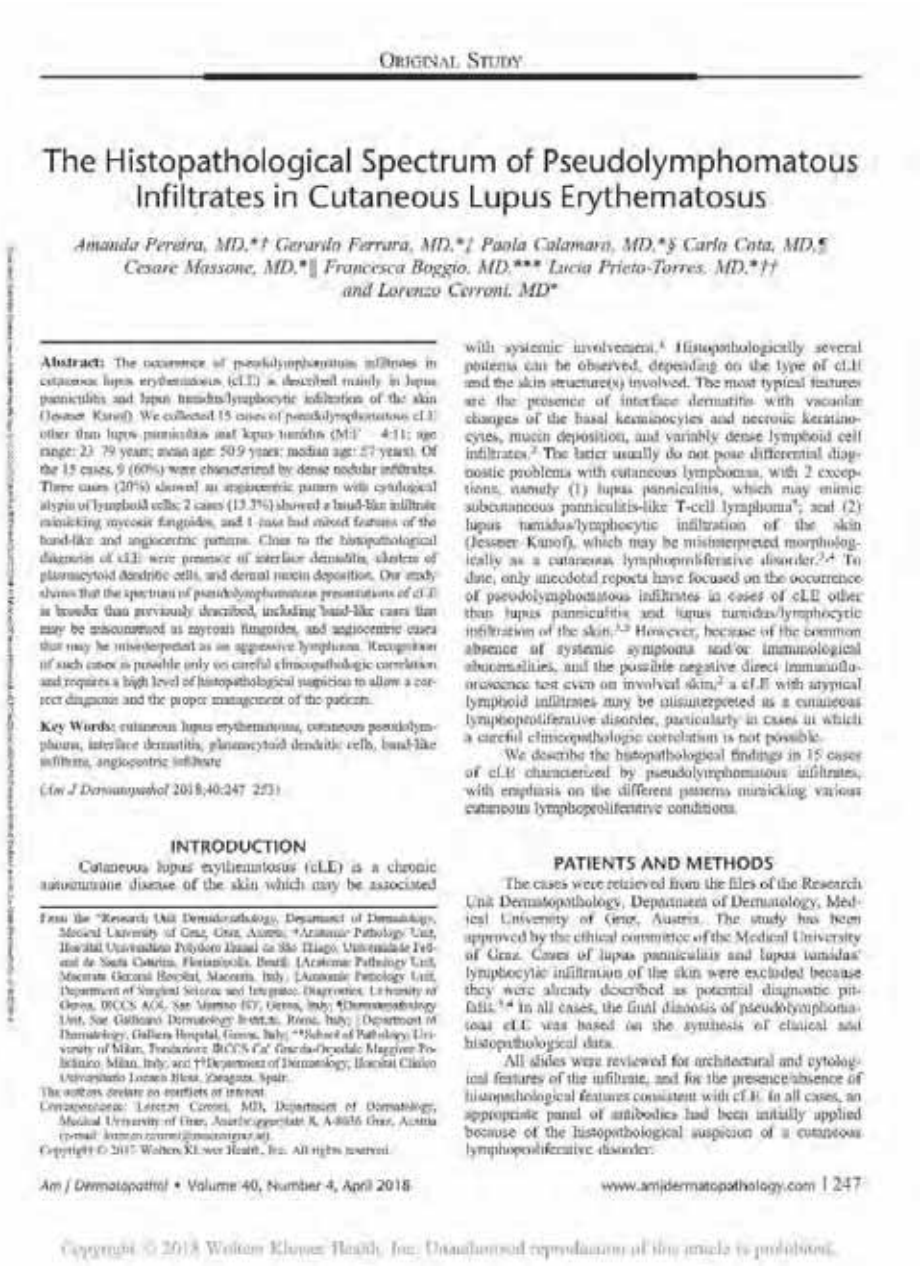
ENA >32.0 U/ml (0 – 1)
Ro-Abs >240.0 U/ml (0 – 10)
Ro 52-Abs >240.0 U/ml (0 – 10)
Ro 60-Abs >282.0 U/ml (0 – 10)
La-Abs 19.0 U/ml (0 – 10)







ORIGINAL STUDY

The Histopathological Spectrum of Pseudolymphomatous Infiltrates in Cutaneous Lupus Erythematosus

Amanda Pereira, MD.† Gerardo Ferrara, MD.*‡ Paola Calamaro, MD.*§ Carlo Cota, MD.¶ Cesare Massone, MD.*‖ Francesca Boggio, MD.*** Lucia Prieta-Torres, MD.*†† and Lorenzo Cerroni, MD**

Abstract: The occurrence of pseudolymphomatous infiltrates in cutaneous lupus erythematosus (cLE) is described mainly in lupus panniculitis and lupus tumidus/lymphocytic infiltration of the skin (Jessner–Kanof). We collected 15 cases of pseudolymphomatous cLE other than lupus panniculitis and lupus tumidus (M:F = 4:11; age range: 23–79 years; mean age: 50.9 years; median age: 57 years). Of the 15 cases, 9 (60%) were characterized by dense nodular infiltrates. Three cases (20%) showed an angiocentric pattern with cytological atypia of lymphoid cells; 2 cases (13.3%) showed a band-like infiltrate mimicking mycosis fungoides, and 1 case had mixed features of the band-like and angiocentric patterns. Clues to the histopathological diagnosis of cLE were presence of interface dermatitis, clusters of plasmacytoid dendritic cells, and dermal mucin deposition. Our study shows that the spectrum of pseudolymphomatous presentations of cLE is broader than previously described, including band-like cases that may be misconstrued as mycosis fungoides, and angiocentric cases that may be misinterpreted as an aggressive lymphoma. Recognition of such cases is possible only on careful clinicopathologic correlation and requires a high level of histopathological suspicion to allow a correct diagnosis and the proper management of the patient.

Key Words: cutaneous lupus erythematosus, cutaneous pseudolymphoma, interface dermatitis, plasmacytoid dendritic cells, band-like infiltrate, angiocentric infiltrate

(*Am J Dermatopathol* 2018;40:247–253)

INTRODUCTION

Cutaneous lupus erythematosus (cLE) is a chronic autoimmune disease of the skin which may be associated with systemic involvement.[1] Histopathologically several patterns can be observed, depending on the type of cLE and the skin structure(s) involved. The most typical features are the presence of interface dermatitis with vacuolar changes of the basal keratinocytes and necrotic keratinocytes, mucin deposition, and variably dense lymphoid cell infiltrates.[2] The latter usually do not pose differential diagnostic problems with cutaneous lymphomas, with 2 exceptions, namely (1) lupus panniculitis, which may mimic subcutaneous panniculitis-like T-cell lymphoma[3]; and (2) lupus tumidus/lymphocytic infiltration of the skin (Jessner–Kanof), which may be misinterpreted morphologically as a cutaneous lymphoproliferative disorder.[3,4] To date, only anecdotal reports have focused on the occurrence of pseudolymphomatous infiltrates in cases of cLE other than lupus panniculitis and lupus tumidus/lymphocytic infiltration of the skin.[3,5] However, because of the common absence of systemic symptoms and/or immunological abnormalities, and the possible negative direct immunofluorescence test even on involved skin,[2] a cLE with atypical lymphoid infiltrates may be misinterpreted as a cutaneous lymphoproliferative disorder, particularly in cases in which a careful clinicopathologic correlation is not possible.

We describe the histopathological findings in 15 cases of cLE characterized by pseudolymphomatous infiltrates, with emphasis on the different patterns mimicking various cutaneous lymphoproliferative conditions.

PATIENTS AND METHODS

The cases were retrieved from the files of the Research Unit Dermatopathology, Department of Dermatology, Medical University of Graz, Austria. The study has been approved by the ethical committee of the Medical University of Graz. Cases of lupus panniculitis and lupus tumidus/lymphocytic infiltration of the skin were excluded because they were already described as potential diagnostic pitfalls.[3,4] In all cases, the final diagnosis of pseudolymphomatous cLE was based on the synthesis of clinical and histopathological data.

All slides were reviewed for architectural and cytological features of the infiltrate, and for the presence/absence of histopathological features consistent with cLE. In all cases, an appropriate panel of antibodies had been initially applied because of the histopathological suspicion of a cutaneous lymphoproliferative disorder.

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The authors declare no conflicts of interest.

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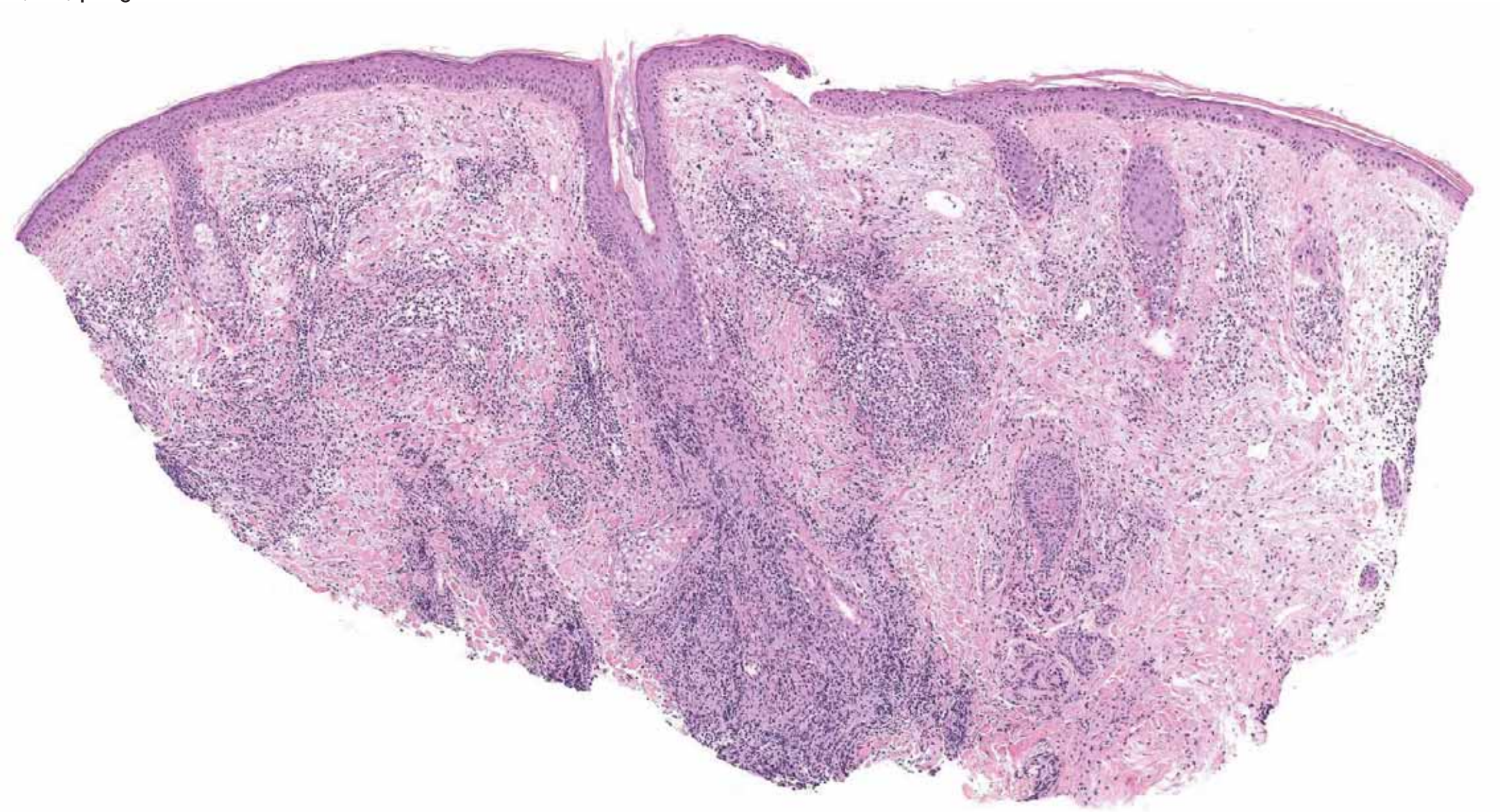
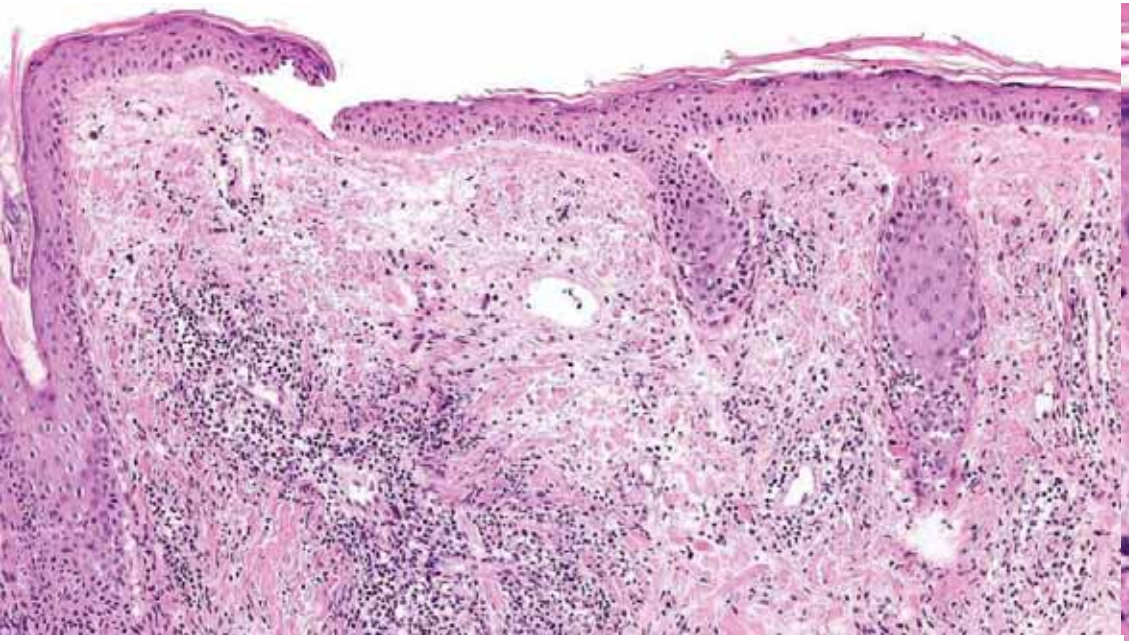
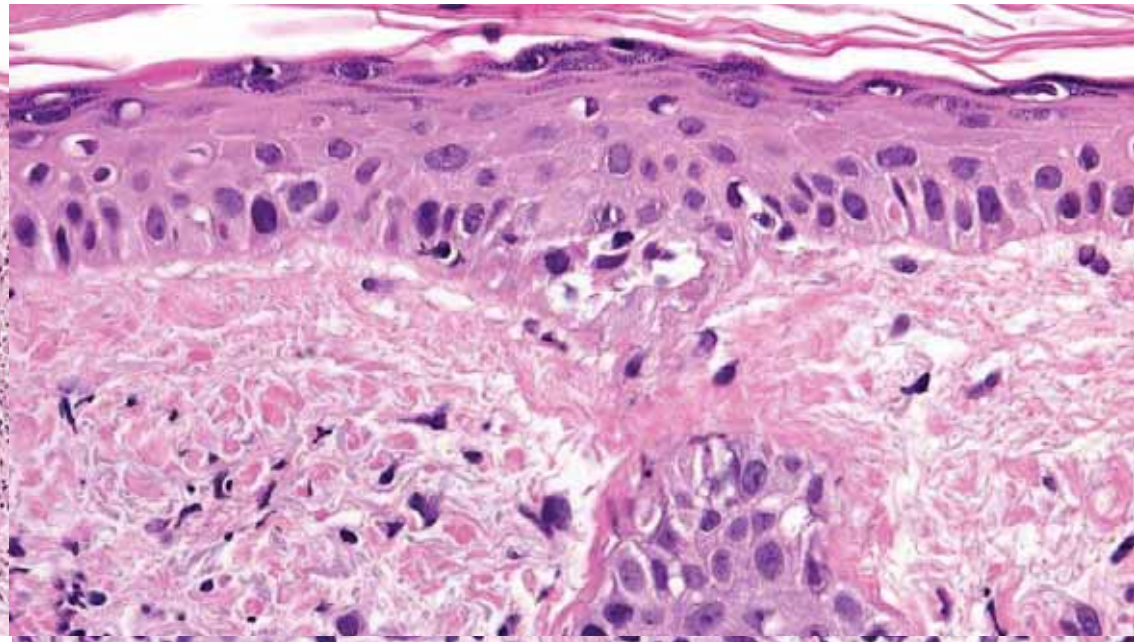
15 cases

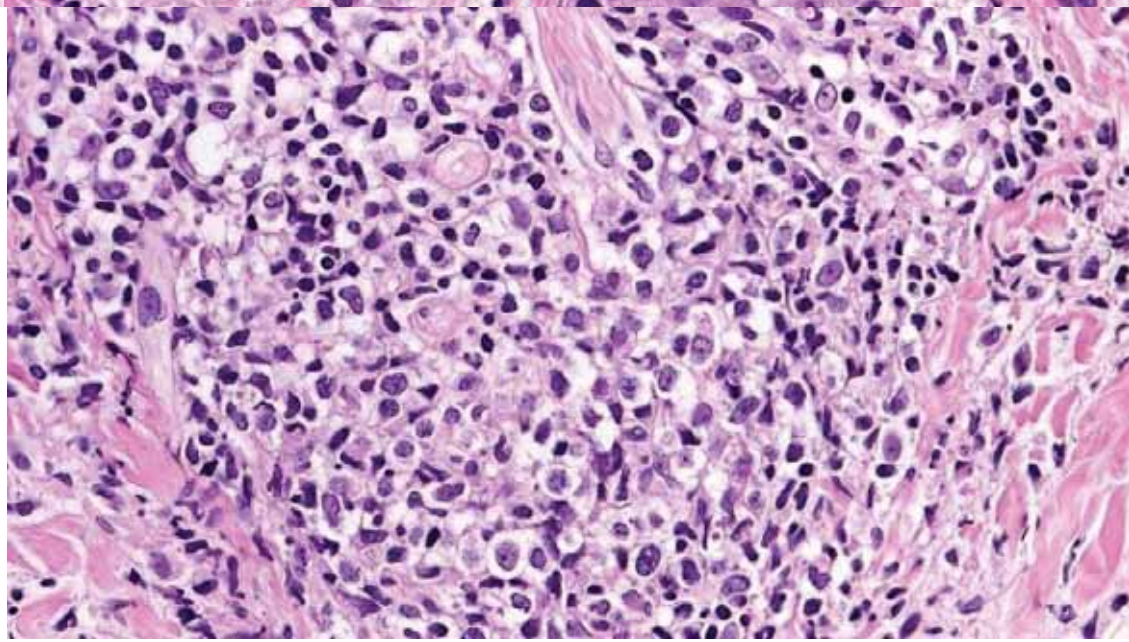
9 cases: dense nodular infiltrates
3 cases: angiocentric pattern
2 cases: band-like pattern
1 case: band-like + angiocentric pattern

F, 35, pregnant.









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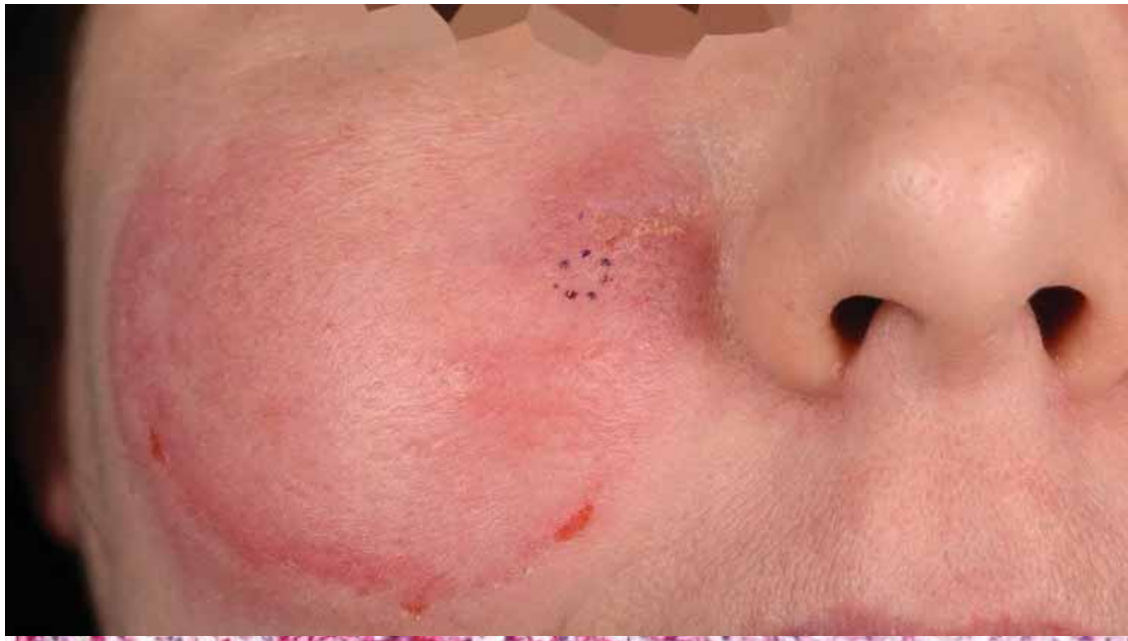
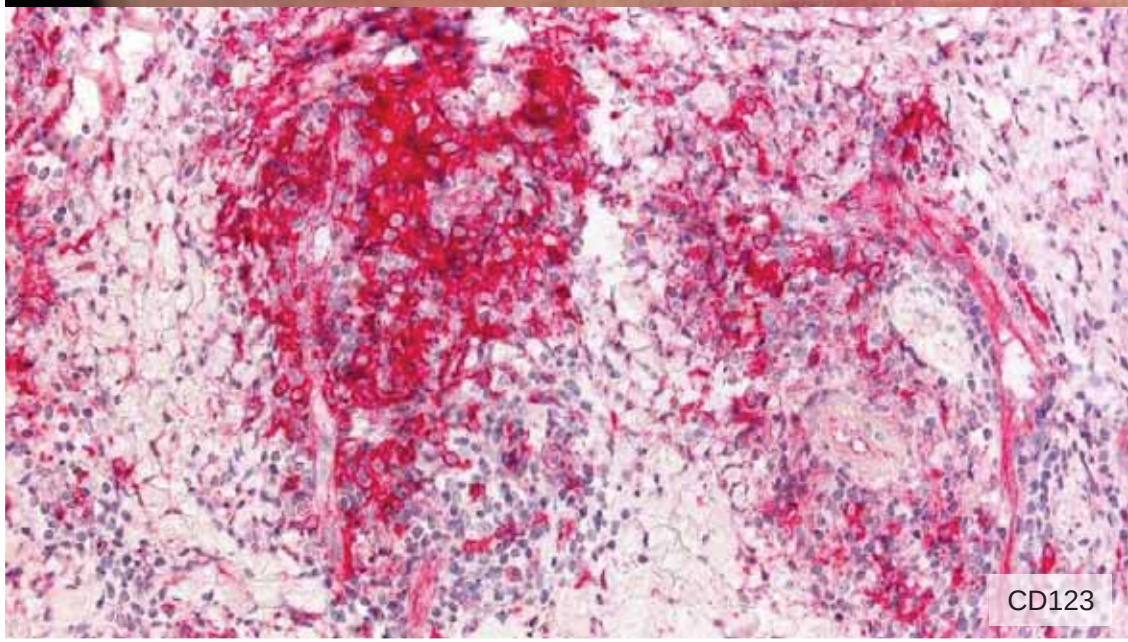
Ro52-AK	>240.0 U/mL (-10.0)
Ro60-AK	>282.0 U/mL (-10.0)
La-AK	290.0 U/mL (-10.0)

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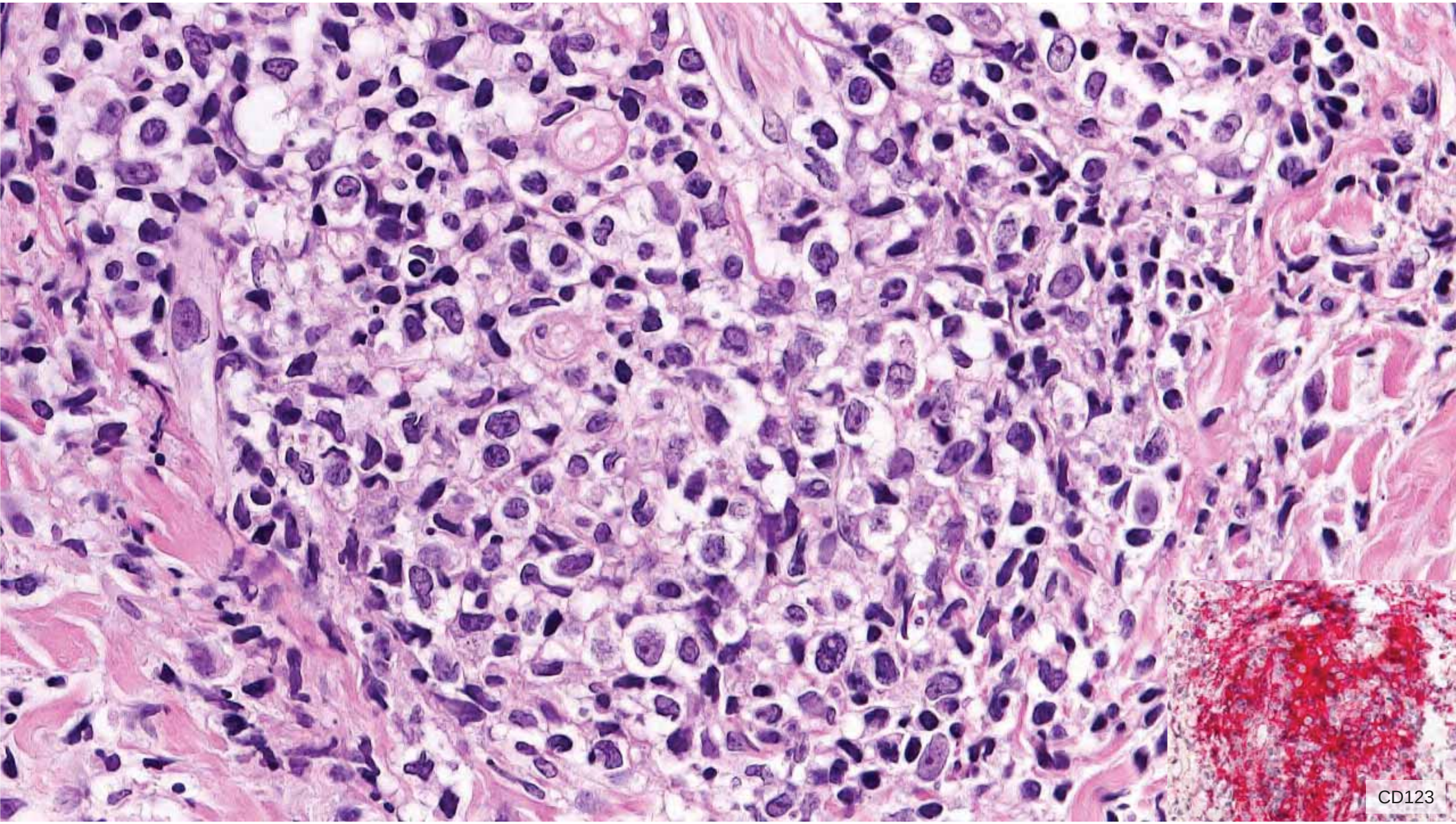
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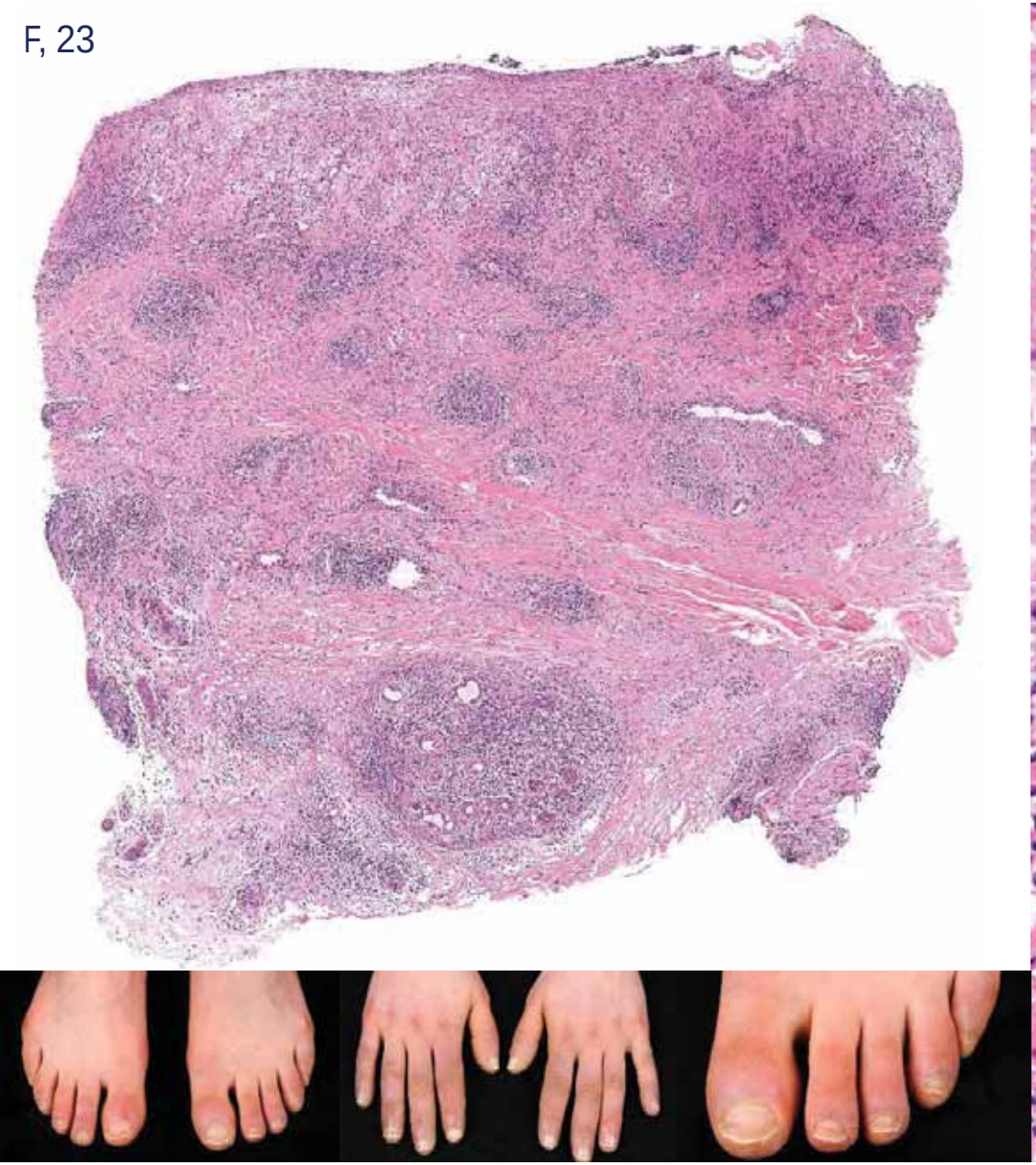
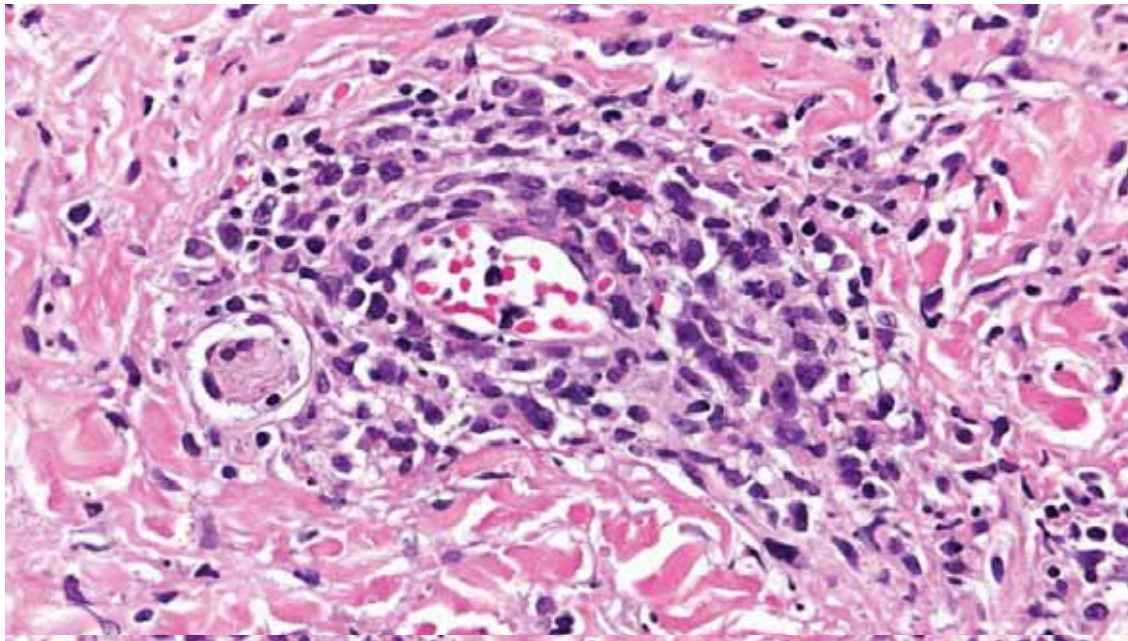
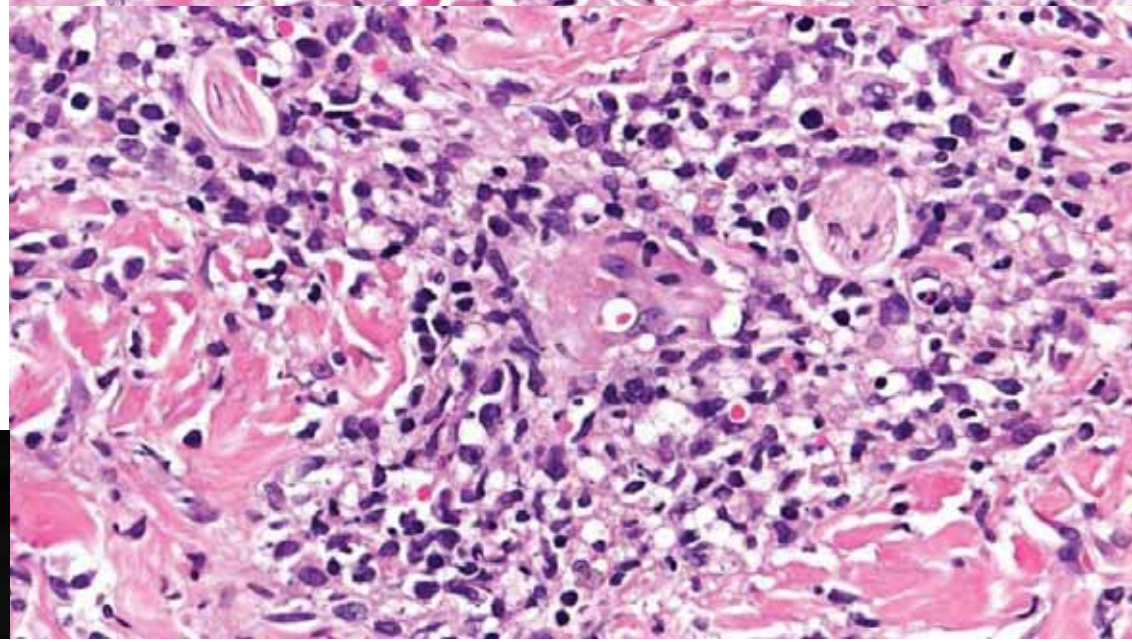
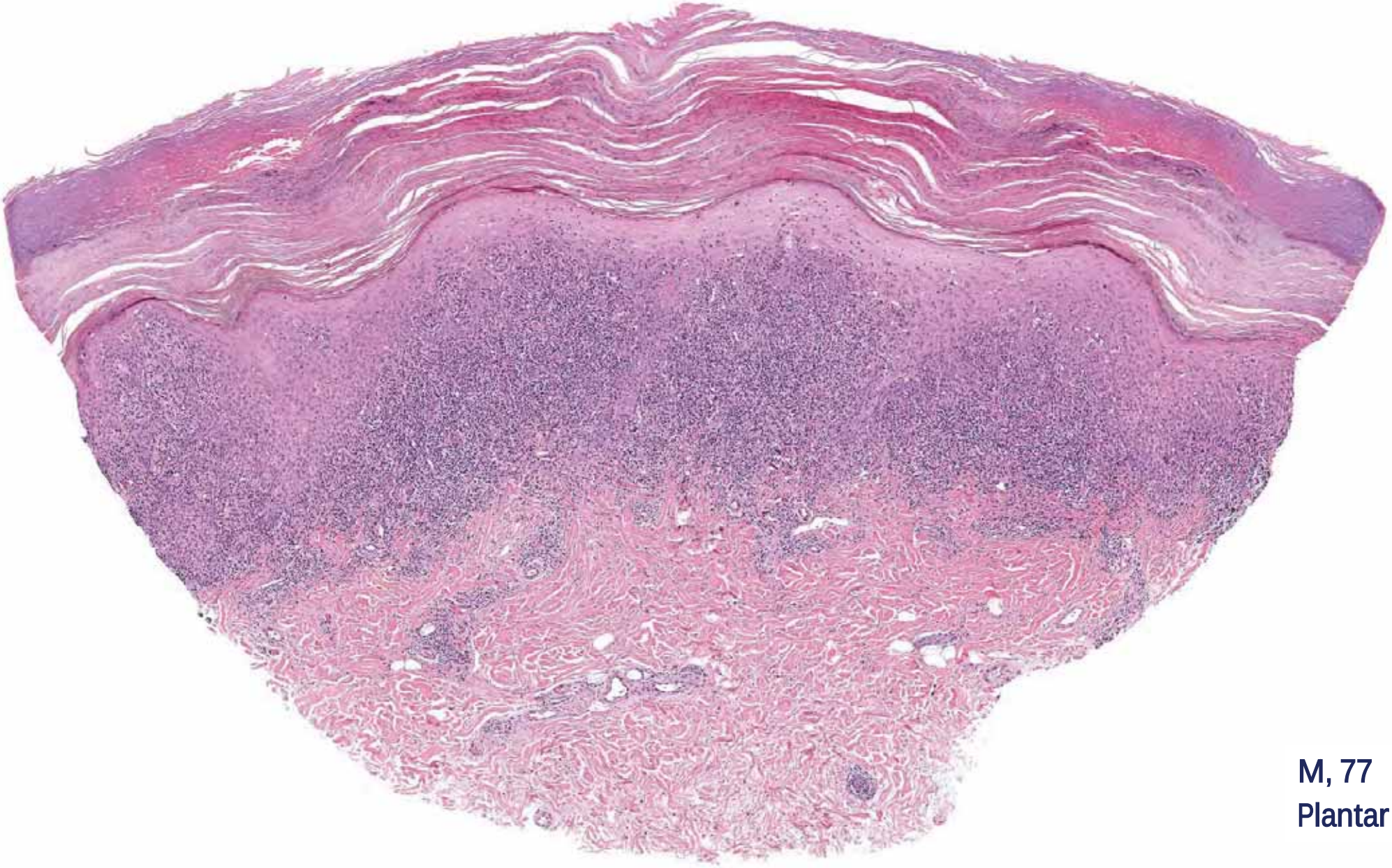
F, 23

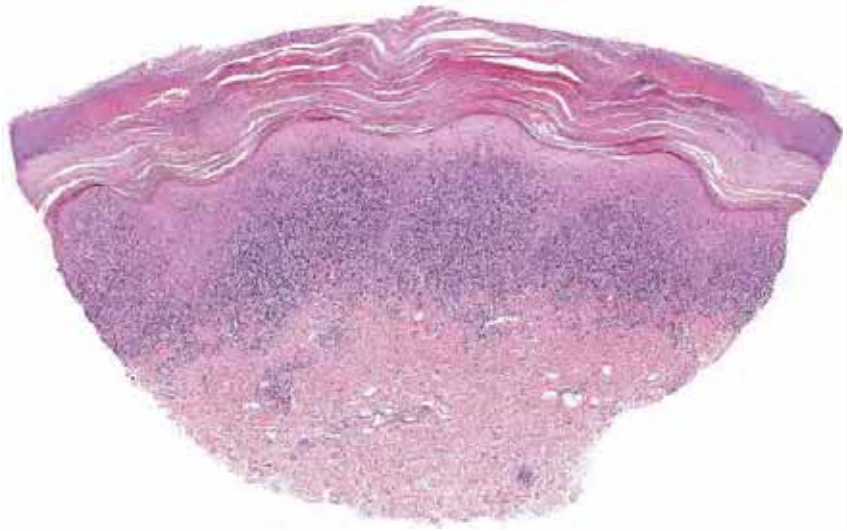








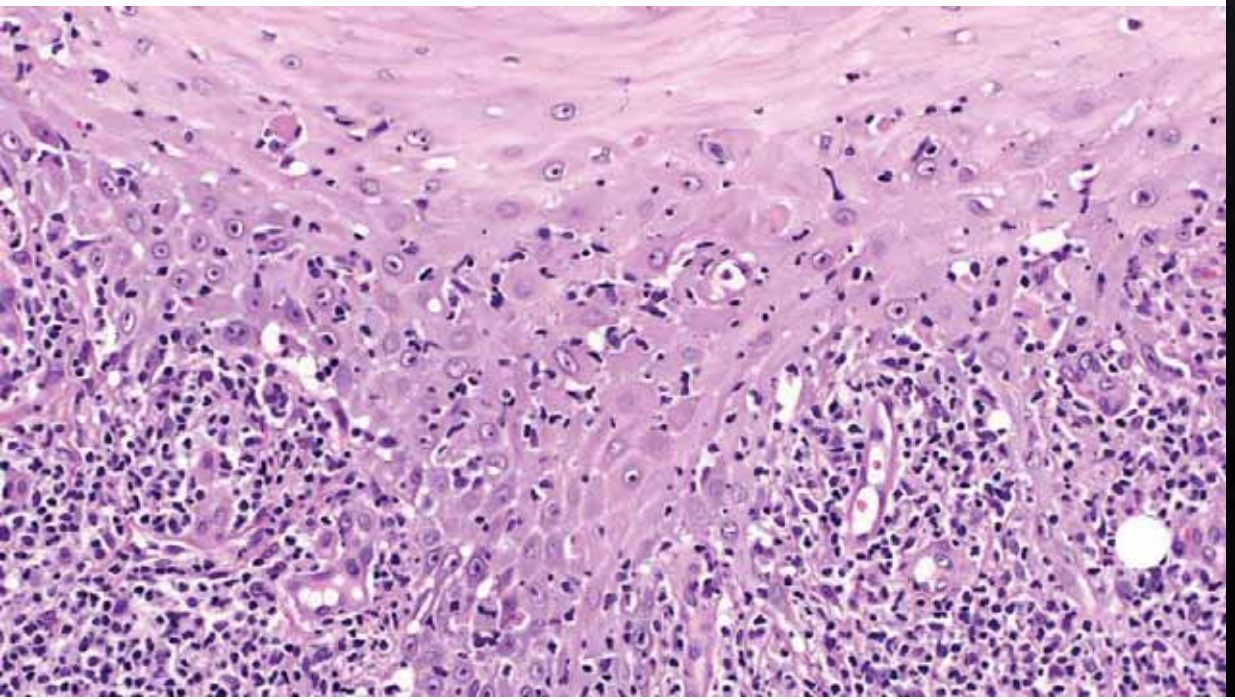
M, 77
Plantar region

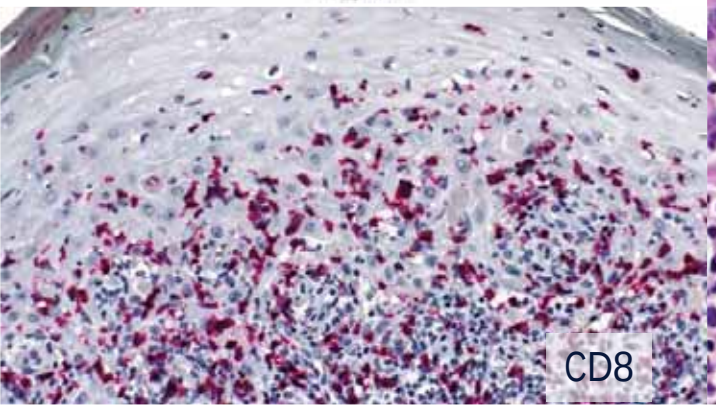


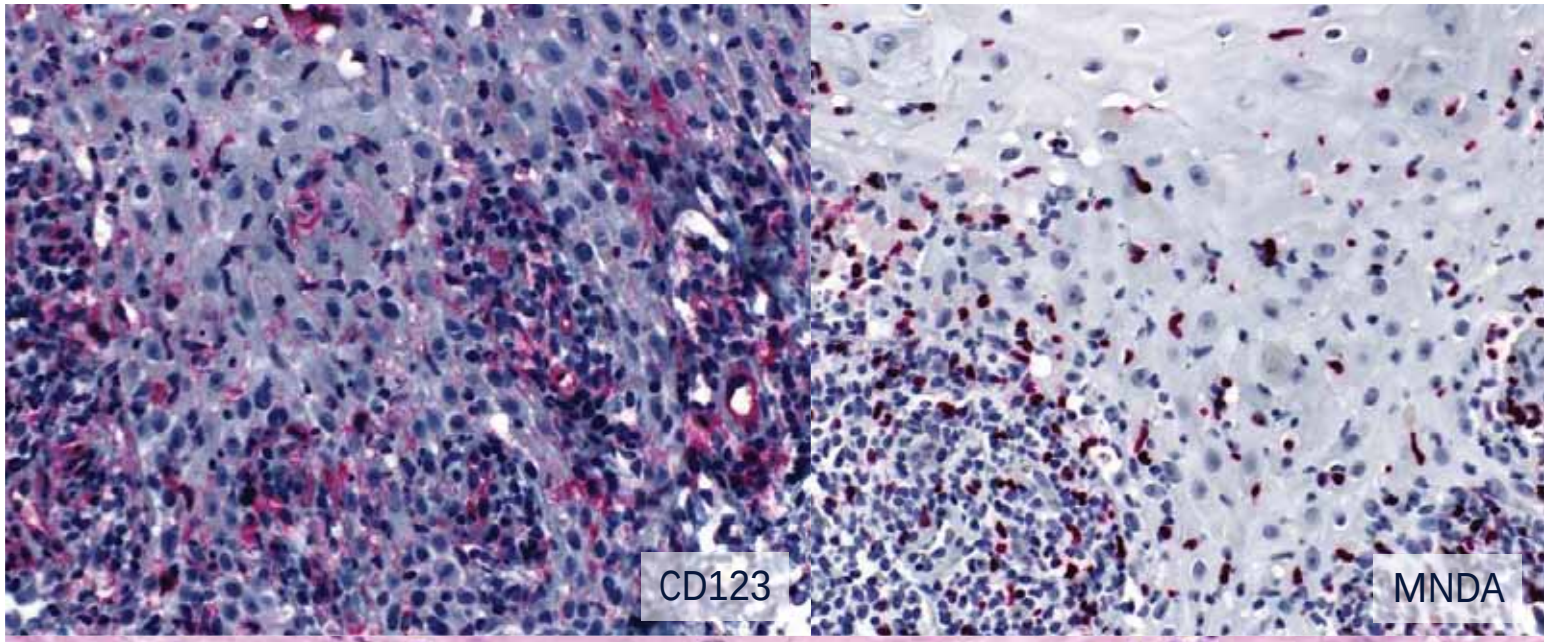
M, 77

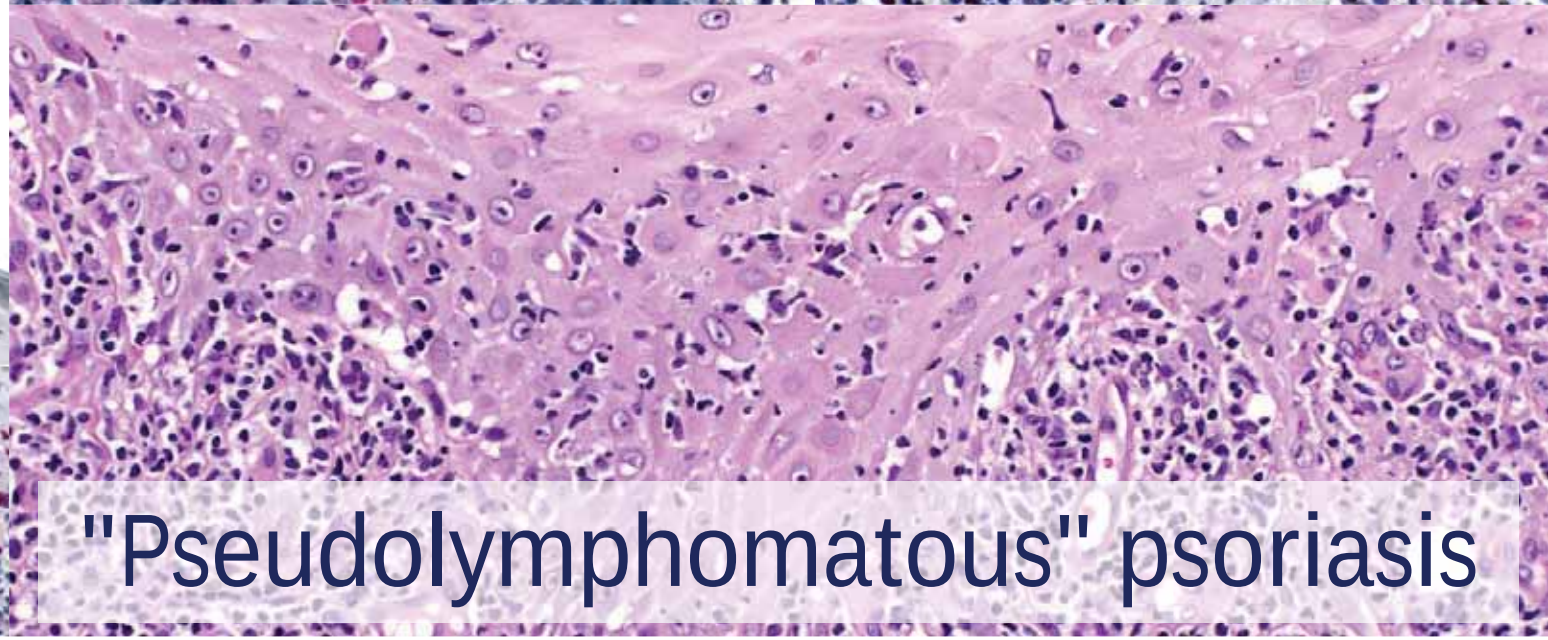
According to the patient lesions on the soles for approximately 3 years. Mostly asymptomatic, sometimes mild pruritus.

Last sexual intercourse 12 years previously. Screening for syphilis negative.









"Pseudolymphomatous" psoriasis

Hyperkeratotic mycosis fungoides restricted to the palms*

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San Antonio, TX

The case of a 45-year-old Latin American man, who presented to the Dermatology Clinic with a 6-month history of hyperkeratotic lesions confined to the palms and the palmar aspects of the digits of both hands, is discussed. Biopsy of these lesions revealed the classic histologic findings of mycosis fungoides. The clinical and histologic differential diagnosis of mycosis fungoides is considered. (J Am Acad Dermatol 7:792-796, 1982.)

The clinical diagnosis of mycosis fungoides may at times be difficult because of the variability of its clinical presentation and course. The histologic diagnosis can also, at times, be difficult, and several entities have been described which cannot be separated histologically from mycosis fungoides.[1-3] The biologic behavior of the lesions in any given patient is the ultimate confirmation of the correct diagnosis. We present a patient with unusual clinical and histologic findings and discuss the difficulty of prospective analysis of a patient with premycotic stage mycosis fungoides.

CASE REPORT

A 45-year-old Mexican American man presented to the Dermatology Clinic at Audie Murphy Veterans Hospital with a 6-month history of hyperkeratotic lesions confined to the palms and the palmar aspects of the digits of both hands. The patient had previously been treated for several months with various topical steroids without improvement. The patient denied any history of extensive exposure to petrochemicals, frequent contact with irritants, or any history of contact allergy. Medications at the time of presentation included NPH insulin, 40 units each morning, for adult-onset diabetes mellitus present since 1975; aminophylline, 200 mg four times a day, and metaproterenol sulfate inhaler, 1.3 mg four times a day, for chronic asthma and chronic obstructive pulmonary disease; and chlordiazepoxide hydrochloride (Librium) for a long-standing anxiety neurosis.

The lesions consisted of small hyperkeratotic pits and small hyperkeratotic plaques. These lesions were predominantly located on the palmar aspect of the digits. Clinically the lesions resembled a hand eczema (Fig. 1).

A biopsy was taken which revealed a psoriasiform epidermis with a dense lichenoid infiltrate of mononuclear cells (Fig. 2). Closer examination showed the infiltrate to contain predominantly lymphocytes, many with large, atypical nuclei. No spongiosis of the epidermis was observed. Large, atypical mononuclear cells could be seen within the epidermis, singly and in groups. In some areas, small, nonspongiotic abscesses filled with atypical mononuclear cells could be seen (Fig. 3).

Since the patient lived quite a distance from San Antonio, an interval of approximately 2 months elapsed before his next visit. During this period, the patient was treated with keratolytics and high-potency topical steroids. On return his lesions had worsened slightly.

A biopsy was again obtained. Histologic findings were identical to those of the previous sample. A specimen was also submitted for electron microscopy.

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*The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Air Force or the Department of Defense.

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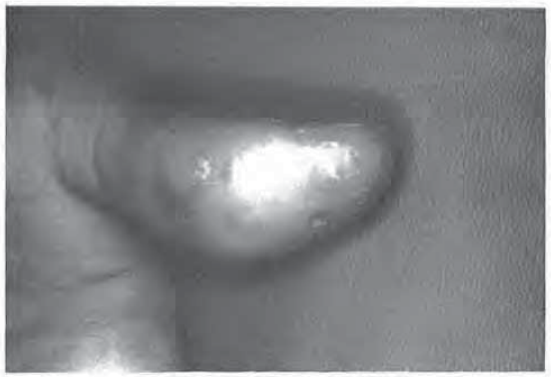

Fig. 1. Small hyperkeratotic pits and plaques confined to the hands.

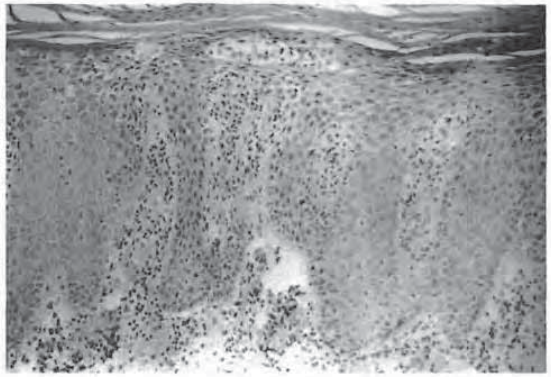

Fig. 2. Psoriasiform epidermis with dense lichenoid infiltrate of mononuclear cells. (Hematoxylin-eosin stain; original magnification, ×100.)

This examination revealed in the dermis the presence of lymphocytes with large hyperconvoluted nuclei (Fig. 4).

Complete physical examination at this time was unremarkable except for the lesions on the hands. In particular, there was no palpable adenopathy and no palpable increase in liver or spleen size. Patch testing was performed with the standard tray of the North American Patch Test Kit, with negative results. A blind axillary node biopsy was performed, and no tumor was found

"Our case may be distinguished from psoriasis by the density and bandlike characteristics of the lymphohistiocytic infiltrate and the lack of polymorphonuclear cells in the dermal papillae. The cells seen in the epidermis and in the abscesses are atypical mononuclear cells rather than polymorphonuclear cells."

Clinicopathologic features and T-cell receptor gene rearrangement findings of mycosis fungoides palmaris et plantaris

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Busan, South Korea

Background: Mycosis fungoides palmaris et plantaris (MFPP), characterized by hyperkeratotic patches or plaques confined to the palms and soles, is rare and easy to misdiagnose because of the clinical similarity to psoriasis, cutaneous inflammatory dermatoses, and dermatophytic infections. The literature about MFPP mostly consists of case reports with short-term follow-up.

Objective: Our purpose was to evaluate the clinicopathologic features, T-cell receptor (TCR) gene rearrangement findings, and prognosis of MFPP.

Patients and methods: This retrospective study has been reviewed in the clinicopathologic, TCR γ gene rearrangement findings and follow-up study of 12 patients with MFPP.

Results: The duration of diseases ranged from 9 months to 25 years with a mean duration of 5.3 years. Clinically, hyperkeratotic patches and plaques were observed in all cases, with 6 cases having developed on the palms and soles and 6 cases on the palms only. In TNM classifications, all cases were confined to T1N0M0 (stage IA) showing an early stage of mycosis fungoides (MF). Histopathologic findings revealed marked hyperkeratosis, parakeratosis with plasma, epidermotropism, convoluted lymphocytes, haloed lymphocytes, dense infiltrate of lymphocytes in all 12 cases (100%), Pautrier's microabscess in 9 cases (75%), a wire bundle of collagen in 11 cases (91.7%) and basilar epidermotropism in 3 cases (25%). TCR γ gene rearrangement was performed except for one case and monoclonality was detected in 10 of 11 cases. In the comparison group with cutaneous inflammatory dermatoses, all cases showed polyclonality. Treatment was done with Re-PUVA (acitretin and PUVA), ultraviolet A1, as well as systemic acitretin and methotrexate. Most patients showed a good response. In the follow-up study of 9 cases for a mean period of 47.6 months, only one patient's skin lesions were extended to the trunk and face, but the other patients had no sign of extracutaneous involvement.

Limitations: These results were obtained from patients with MFPP in Korea. A cooperative study with other ethnic groups will be helpful.

Conclusions: If a patient has recalcitrant palmoplantar dermatosis, MFPP should be suspected and histopathologic studies with TCR gene rearrangement should be done for early diagnosis of MFPP. (J Am Acad Dermatol 2006;54:466-71.)

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0190-9622/$32.00

doi:10.1016/j.jaad.2005.11.1055

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma, which has 3 clinical stages of patch, plaque, and tumor. Histopathologic findings of early MF are quite similar to other cutaneous inflammatory dermatoses, unlike the plaque and tumor stage of MF, making the diagnosis difficult. T-cell receptor (TCR) γ gene rearrangement analysis on lesional skin using polymerase chain reaction (PCR) may be helpful as an adjunct to the histopathologic features of early MF. TCR gene rearrangement analysis has been performed using Southern blot technique or PCR

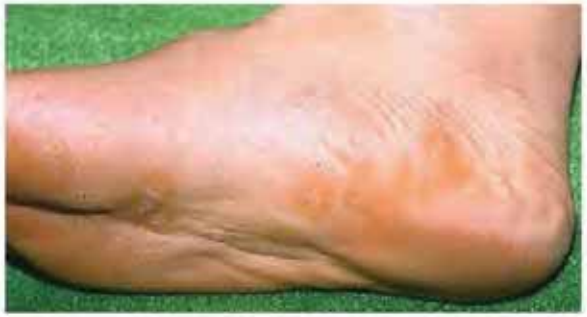


Fig 1. Case 1. Relatively well-demarcated, erythematous to brownish, hyperkeratotic plaques on the foot.

and face. However, to date, the remaining cases showed no further development of the skin lesions and no extracutaneous involvement (Table I).

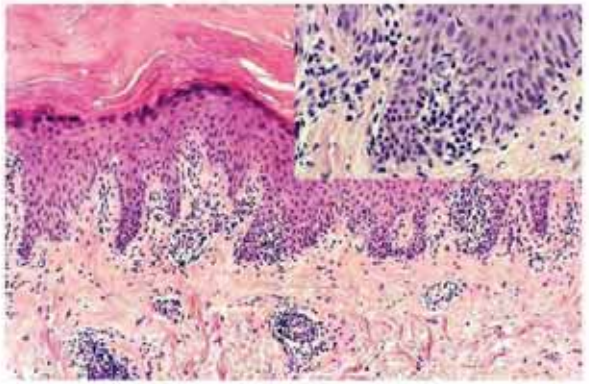
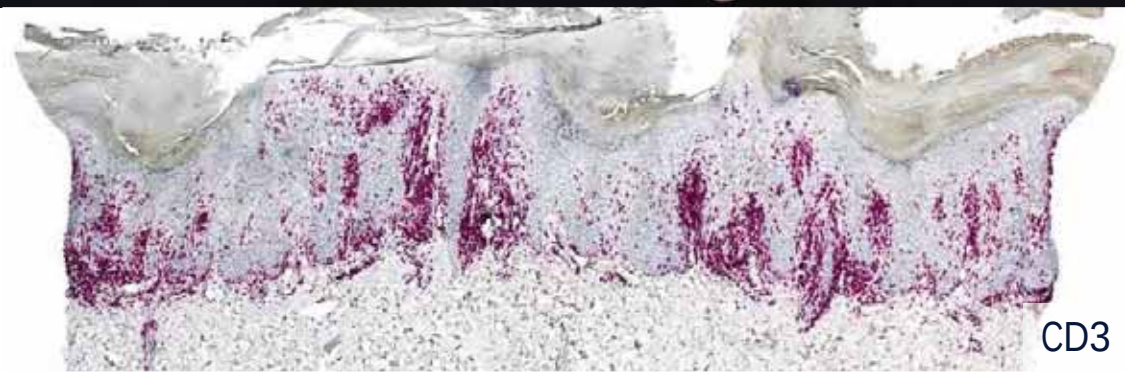
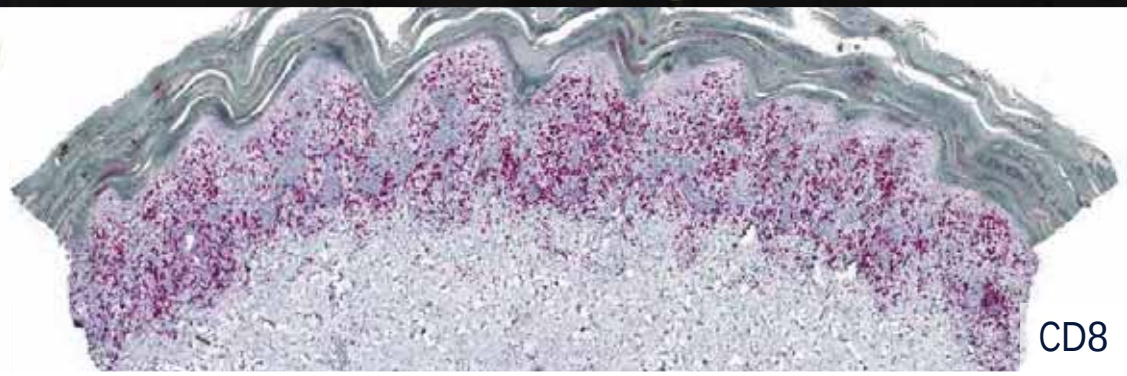


Fig 2. Case 2. Skin biopsy specimen reveals epidermotropism and coarse papillary dermal collagen. Epidermotropism composed of atypical hyperchromatic lymphocytes are seen *(inset)*. (Hematoxylin-eosin stain; original magnification: ×100; *inset*, ×400.)

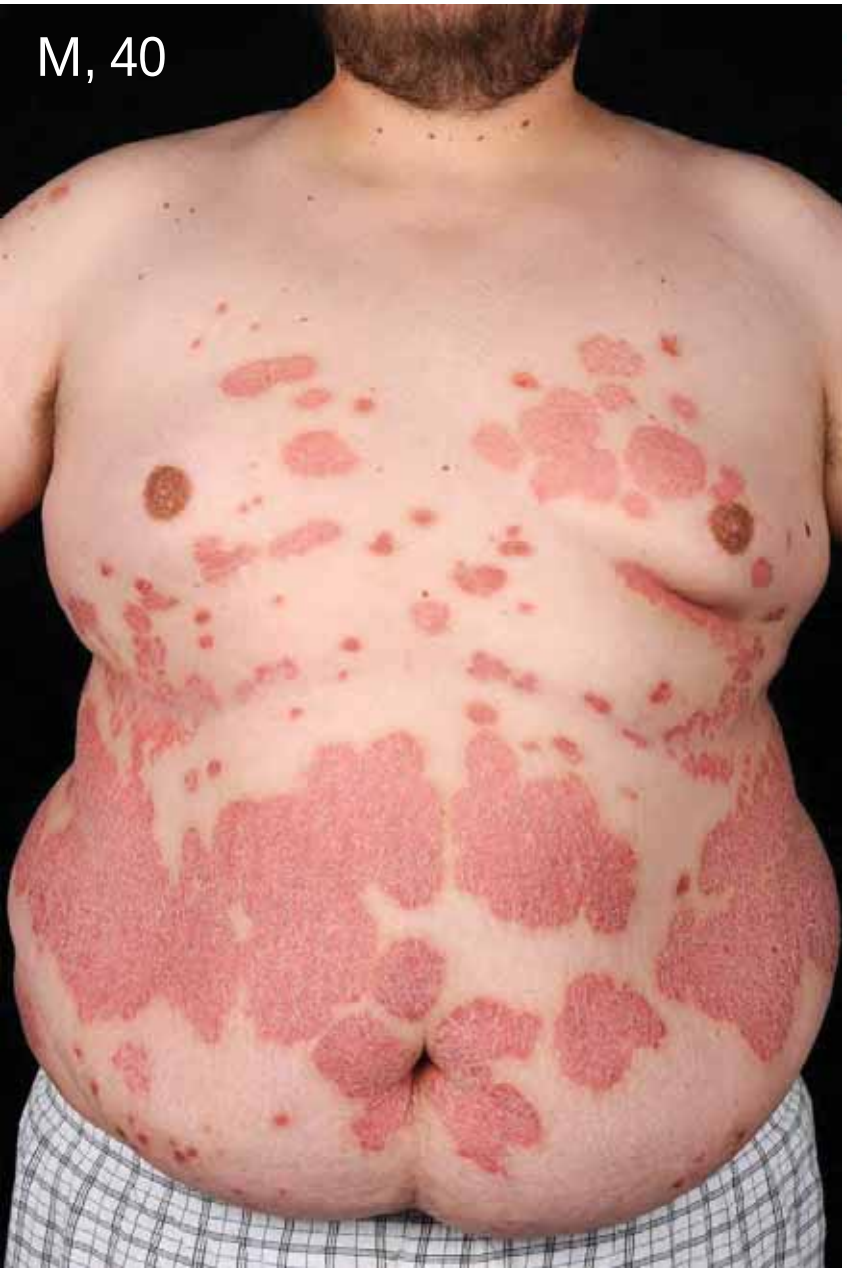


CD3



CD8

Palmoplantar psoriasis (and other variants of the disease as well) may present with band-like lymphocytic rather than neutrophil-rich infiltrates. A diagnosis of MF in a patient with lesions confined to the palms and/or soles should be made only when features are compelling; positivity of some of the mononuclear cells for MNDA may represent a clue.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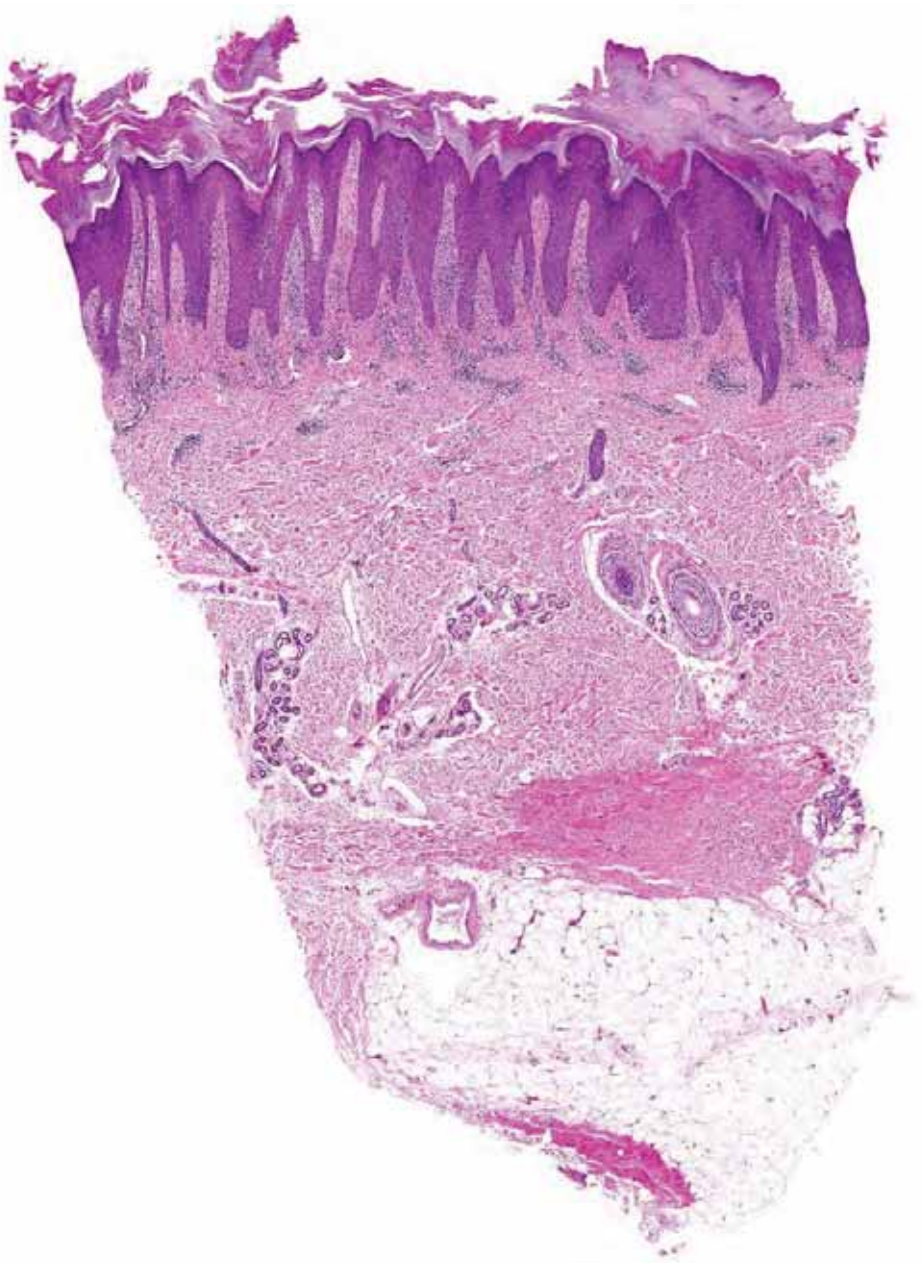
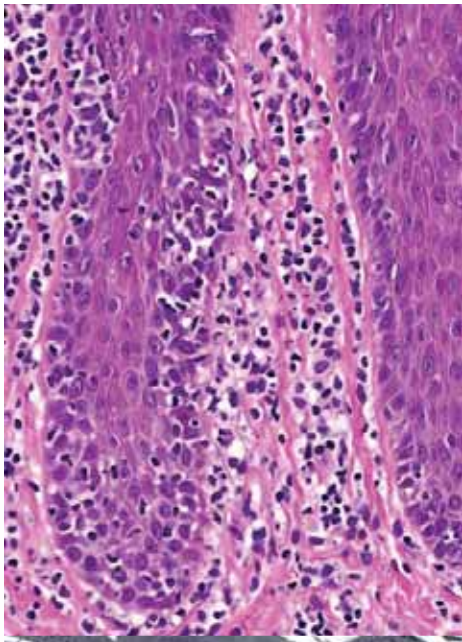
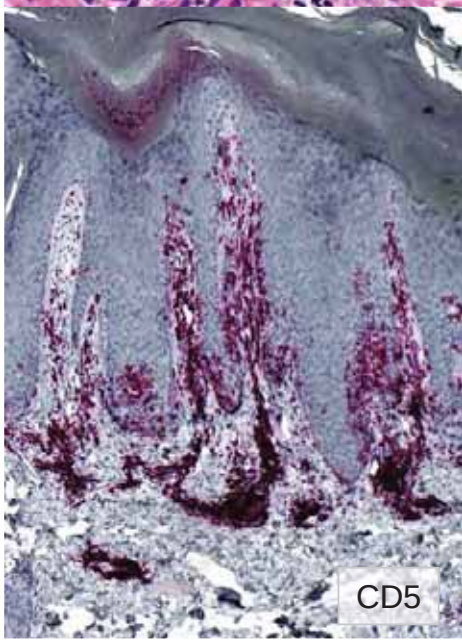


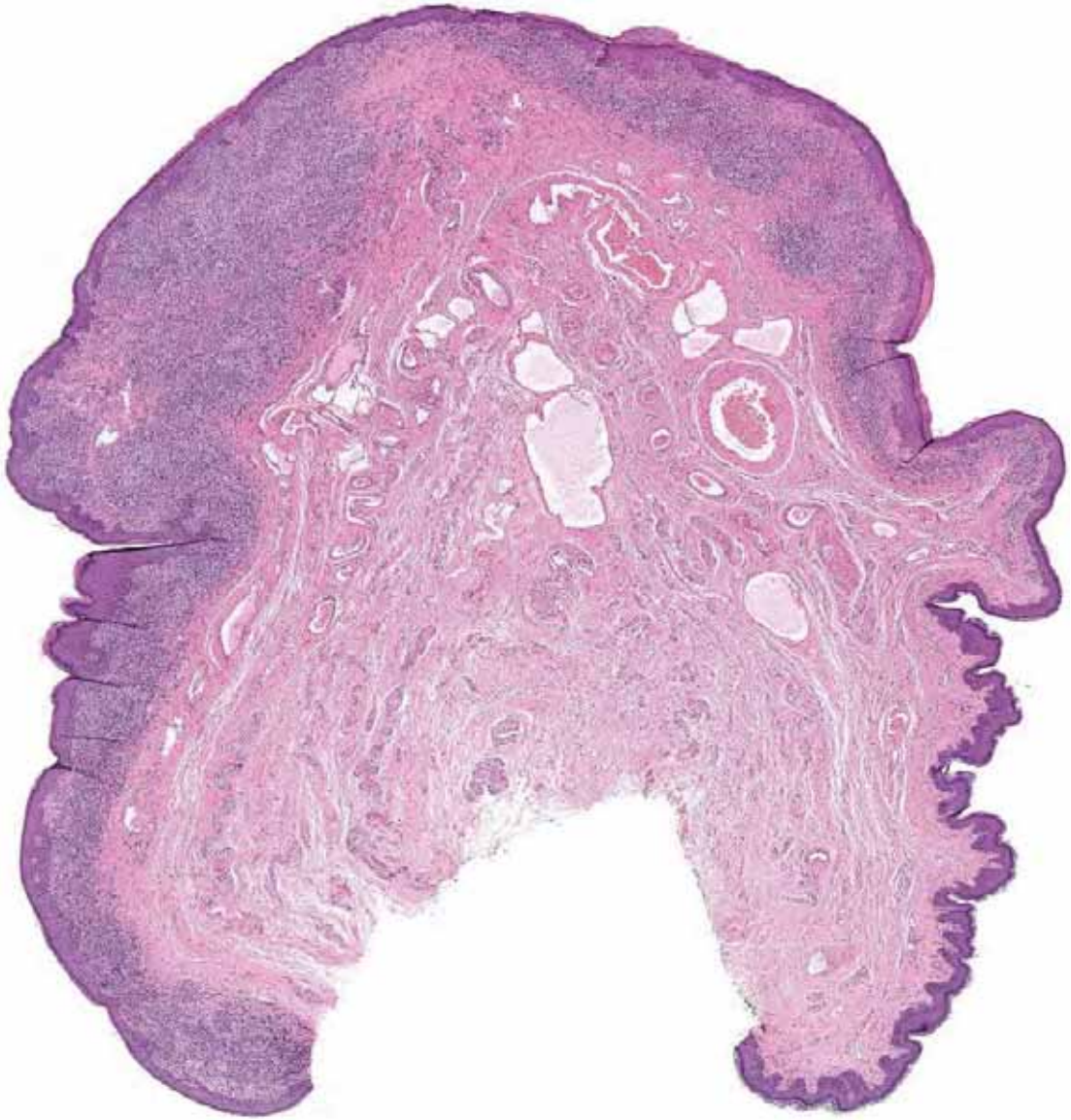


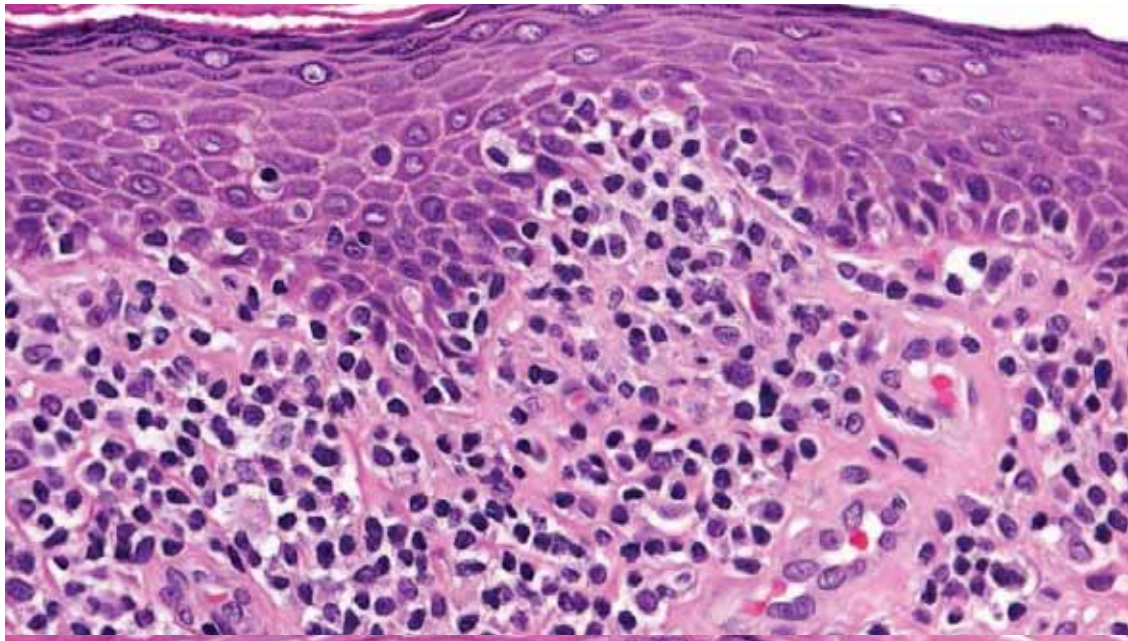

CD5

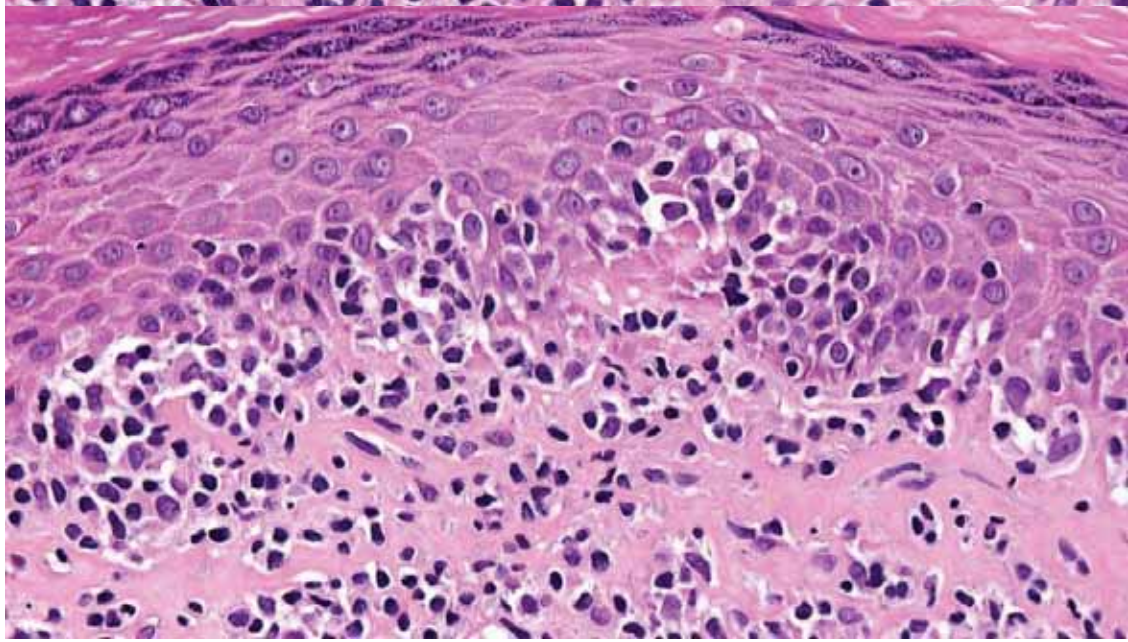
Psoriasis mimicking mycosis fungoides

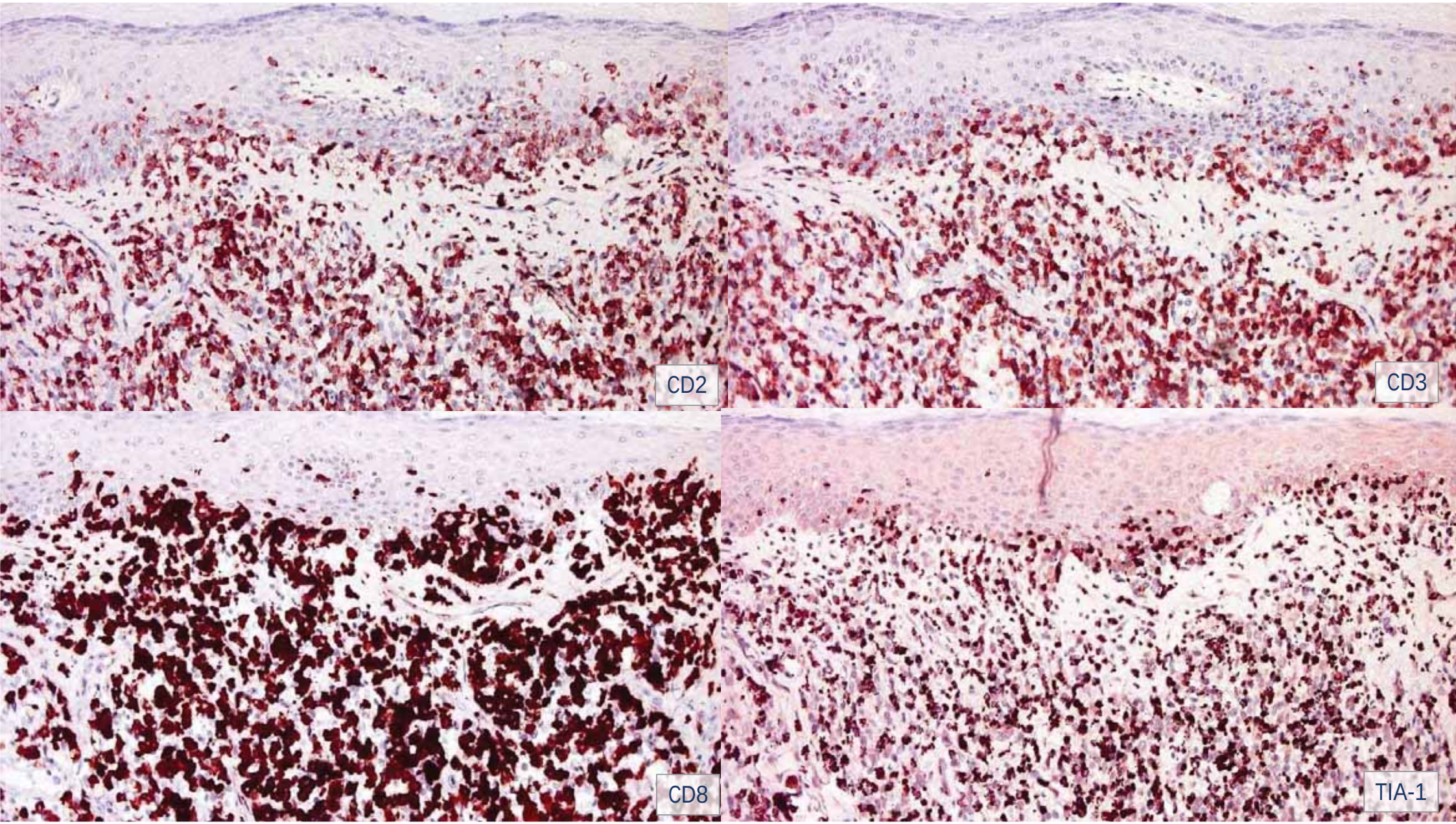
- A variant of mycosis fungoides restricted to the palms and soles has been described in the literature as "mycosis fungoides palmaris et plantaris"; in my opinion ***this variant does not exist***, and these cases are examples of psoriasis with a band-like infiltrate of lymphocytes and many epidermotropic cells
- Variable numbers of intraepidermal lymphocytes may be observed also in psoriasis at sites other than palms and soles
- MF, of course, may involve the palms and soles as any other part of the body, but never the palms and soles only

8-year-old boy with phymosis.








CD2
CD3
CD8
TIA-1

Lichen Sclerosus with Histopathologic Features Simulating Early Mycosis Fungoides

Luigi Citarella, MD, Cesare Massone, MD, Helmut Kerl, MD, and Lorenzo Cerroni, MD

Abstract: Mycosis fungoides (MF) is a cutaneous T-cell lymphoma characterized in its early stages by a superficial band-like infiltrate with epidermotropism of lymphocytes without particularly atypical cytologic features. Even though clinicopathologic presentation is diagnostic in typical cases, some inflammatory skin disorders can simulate the histopathologic features of early MF. In this study we present data on 9 patients affected by lichen sclerosus (LS) (M:F ratio 8:1; age range 7–75 years; mean age 31.3 years; median age 13 years), who presented with histopathologic features simulating early lesions of MF. The histopathologic picture was characterized in all cases by a dense, band-like infiltrate of lymphocytes within the superficial dermis, with exocytosis of lymphocytes within the lower part of the epidermis. The papillary dermis was expanded and showed focally coarse bundles of collagen simulating MF. The typical signs of LS were either absent or present only focally. Molecular analyses of the TCRγ gene rearrangement performed with the polymerase chain reaction (PCR) technique revealed a polyclonal smear in eight cases, and a monoclonal band in one. Our study shows that LS can present with histopathologic features simulating early MF. Especially in cases revealing a monoclonal population of T lymphocytes by PCR, the correct diagnosis may be overlooked without proper clinical information and clinicopathologic correlation. Lichen sclerosus should be added to the list of cutaneous T-cell pseudolymphomas.

Key Words: histopathologic simulator, mycosis fungoides, lichen sclerosus, pseudolymphoma

(*Am J Dermatopathol* 2003;25:463–465)

Mycosis fungoides (MF) is characterized histologically in its early stages by a patchy lichenoid lymphohistiocytic infiltrate in the papillary dermis with epidermotropism of lymphocytes. Although this pattern is typical of MF, some inflammatory diseases may display similar histopathological changes, and differentiation of MF from these simulators is one of the most vexing problems in dermatopathology.[1,2] The best known among these benign cutaneous diseases are actinic reticuloid,[3–5] lymphomatoid contact dermatitis,[2,6] lymphomatoid drug eruption, T-cell type,[7,8] and lymphomatoid keratosis.[9,10]

We report on 9 patients with lichen sclerosus (LS) showing histopathologic features simulating early MF.

PATIENTS AND METHODS

Nine patients (M:F ratio 8:1; age range 7–75 years; mean age 31.3 years; median age 13 years) presenting with LS that showed histopathologic features simulating MF have been included in our study (Table 1).

Histology and Molecular Biology

In every case histopathologic examination of the biopsy specimen was performed on sections of tissue stained with hematoxylin and eosin. Molecular analysis of the T-cell receptor-γ (TCR-γ) gene rearrangement was performed in all cases with a standard PCR technique described previously.[11]

RESULTS

All patients had lesions clinically diagnostic of LS characterized by itching, atrophic, partly whitish, partly erythematous patches. In 6 patients the lesions were located on the foreskin, in 2 on the glans and in 1 on the labia minora. A punch biopsy was performed in 5 patients; in the other 4 patients histopathologic sections were prepared from surgical specimens after circumcision. The histopathologic picture was characterized in all cases by a dense band-like lymphocytic infiltrate located in the superficial dermis (Fig.1A). Intraepidermal small- to medium-sized lymphocytes were observed in all specimens (Fig.1B), located within the lower layers of the epidermis and focally arranged in irregular clusters. Some lymphocytes showed nuclei surrounded by a clear halo (Fig.1C). The papillary dermis was expanded and filled by lymphocytes; in addition, thickened bundles of collagen could be observed focally. The horny layer in some areas was thickened and showed orthokeratosis and parakeratosis. The typical signs of LS (homogenization of collagen bundles and sclerosis in the upper part of the dermis) were either completely absent or present only focally, even in cases where a large excisional biopsy

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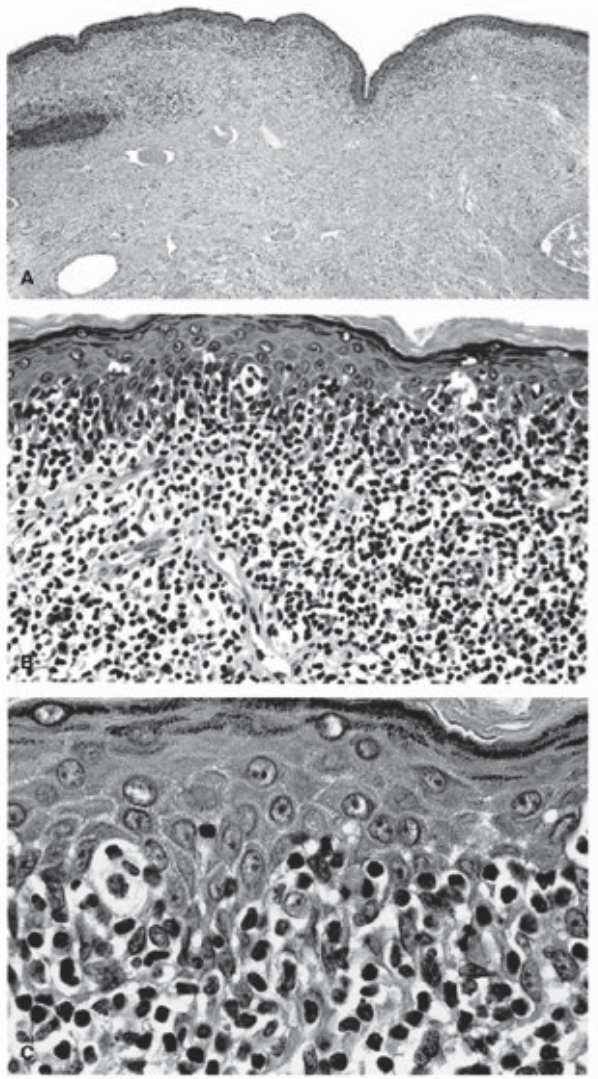

FIGURE 1. A, Dense band-like infiltrate in the superficial dermis. B, The infiltrate obscures the dermo-epidermal junction and involves the epidermis. C, Note intraepidermal lymphocytes with "haloed" nuclei resembling epidermotropic lymphocytes in MF.

Lichen Sclerosus et Atrophicus With Histopathologic Features Mimicking Mycosis Fungoides

A Large Series of Cases Comparing Genital With Extragenital Lichen Sclerosus

Eleonora Leoni, MD, Werner Kempf, MD,†‡ and Lorenzo Cerroni, MD§*

Abstract: Lichen sclerosus et atrophicus (LSA) is a chronic inflammatory dermatosis of unknown etiology involving the genital and/or extragenital area, showing histopathologically a characteristic homogenization and sclerosis of the superficial collagen with variably dense lymphoid infiltrates. Intraepidermal lymphocytes may be observed, and in some cases may pose differential diagnostic problems with mycosis fungoides (MF). We studied the histopathologic features of 121 cases of LSA with dense lymphoid infiltrates (genital: 94; male:female: 93:1; age range: 2 to 87 y; median age: 11 y; extragenital: 27; male:female: 0.1:1; age range: 11 to 79 y; median age: 59 y), to better characterize the intraepidermal lymphoid infiltrate and to compare genital with extragenital cases. Epidermotropic lymphocytes mimicking the histopathologic features of MF were present in 93.6% of the genital specimens but none of the extragenital cases. Interestingly, typical features of LSA were missing in 39.4% of genital LSA, and in a further 25.5% were present only focally. Immunohistochemical analyses showed a predominance of $CD8^+$ T-lymphocytes within the epidermis. Molecular studies of the T-cell receptor genes revealed a monoclonal population of T-lymphocytes in nearly half of the cases. Our study shows that MF-like histopathologic features are extremely common in genital LSA but are never encountered in extragenital cases. A diagnosis of MF in the genital area should be made only upon compelling features, keeping in mind the frequent pseudolymphomatous aspects of LSA.

Key Words: lichen sclerosus, mycosis fungoides, cutaneous T-cell pseudolymphoma, cutaneous T-cell lymphoma, cutaneous pseudolymphoma, extragenital lichen sclerosus

(*Am J Surg Pathol* 2021;00:000–000)

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Lichen sclerosus et atrophicus (LSA) is a chronic inflammatory dermatosis of unknown etiology involving the genital mucosa or the extragenital skin. The typical histopathologic findings are characterized by atrophic epidermis with orthohyperkeratosis overlying a papillary dermis showing homogenized, sclerotic collagen, and a variably dense lymphocytic infiltrate. In typical cases, the histopathologic diagnosis of LSA is not problematic; some cases, however, may lack typical features being characterized instead by a dense lymphocytic infiltrate with prominent exocytosis of lymphocytes within the epidermis, thus mimicking mycosis fungoides (MF).[1–3]

We studied the clinicopathologic features of LSA with particular emphasis on histopathologic features mimicking MF, and with comparison of genital with extragenital cases.

PATIENTS AND METHODS

One hundred twenty-one patients (male:female = 3.8:1; age range: 2 to 87 y; mean age: 30.6 y; median age: 15 y) presenting with LSA have been included in our study. Ninety-four cases were from the anogenital area (male:female = 93:1; age range: 2 to 87 y; median age: 11 y), and 27 from the extragenital area (male:female = 0.1:1; age range: 11 to 79 y; median age: 59 y). The cases were collected at the Department of Dermatology of the Medical University of Graz and at the Kempf und Pfaltz Histologische Diagnostik, Zürich, Switzerland. Variably dense lymphoid infiltrates were present in all cases (cases devoid of lymphoid infiltrates were excluded). Partial data on 9 cases had been published previously.[1] The study has been approved by the ethical committee of the Medical University of Graz.

A total of 123 formalin-fixed, paraffin-embedded biopsy specimens were available for histopathologic analysis. Following histopathologic features were evaluated: presence of typical aspects of LSA; presence of epidermotropic lymphocytes (pseudo-MF aspects); presence of pronounced hemorrhage (pseudovascular aspects); presence of associated morphea; presence of granulomatous phlebitis; presence of germinal centers; presence of perineural inflammatory infiltrates.

In 69 cases (27 from the extragenital, 42 from the genital area), immunohistochemical analyses were performed with a standard immunoperoxidase technique using

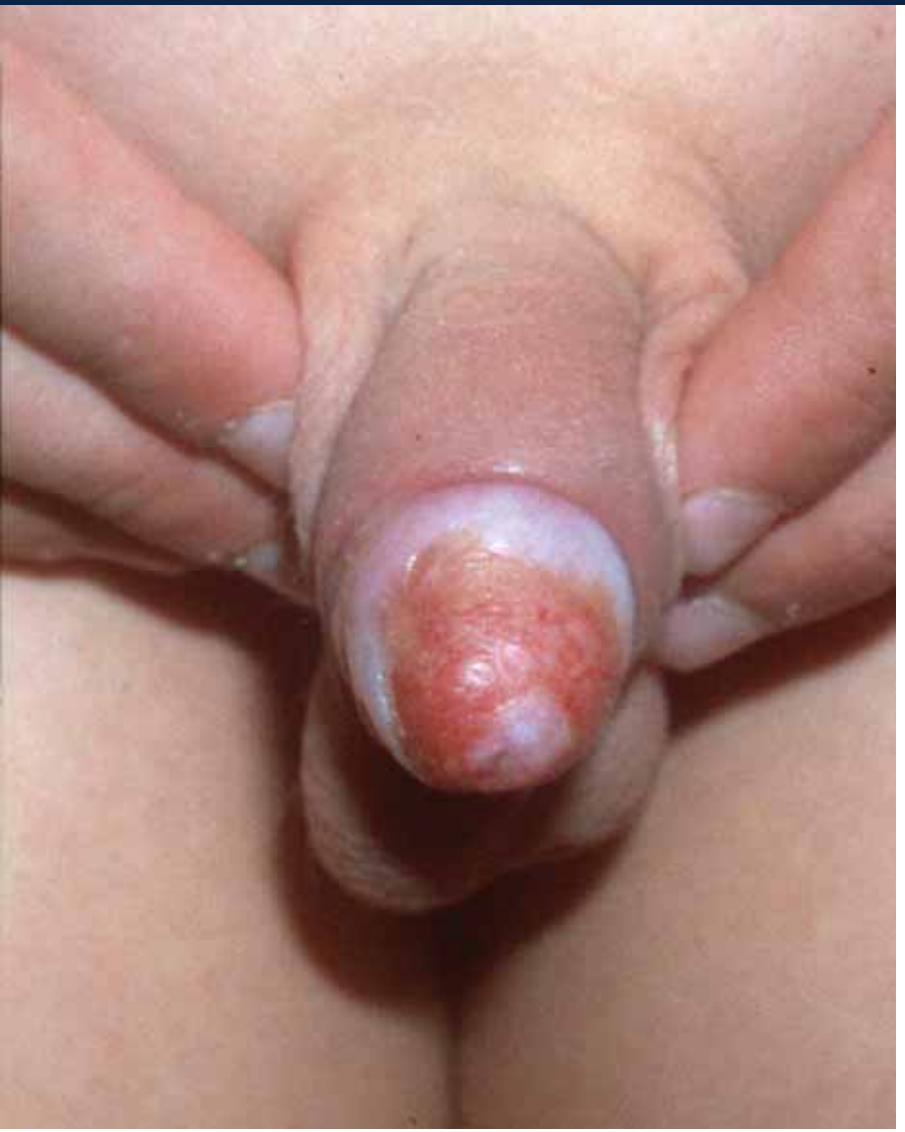
121 cases of LSA with dense lymphoid infiltrates (genital: 94; M:F: 93:1; age range: 2-87; median age: 11; extragenital: 27; M:F: 0.1:1; age range: 11-79; median age: 59).

Epidermotropic lymphocytes mimicking the histopathological features of MF were present in 93.6% of the genital specimens but none of the extragenital cases.

Interestingly, typical features of LSA were missing in 39.4% of genital LSA, and in a further 25.5% were present only focally.

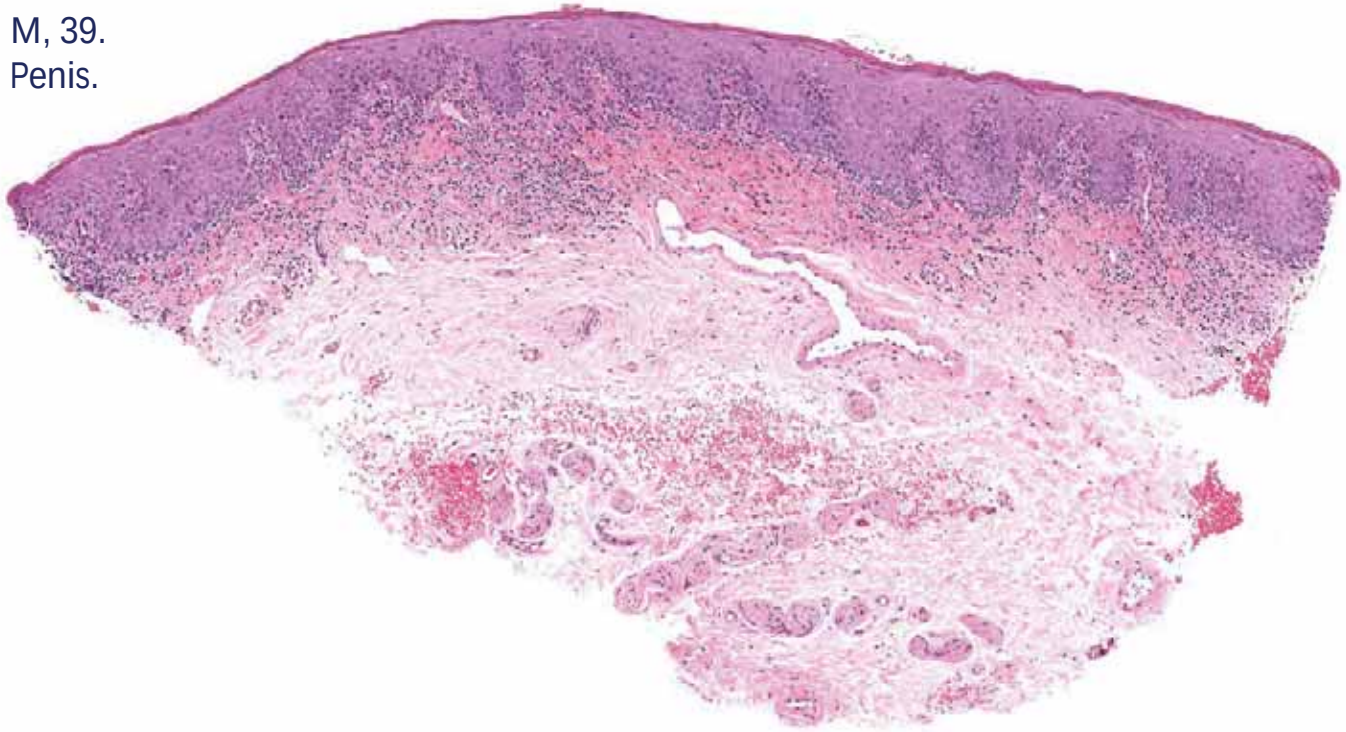
In genital "pseudo-MF" cases, immunohistochemical analyses showed a predominance of CD8+ T lymphocytes within the epidermis. Molecular studies of the T-cell receptor genes revealed a monoclonal population of T lymphocytes in nearly half of the cases.

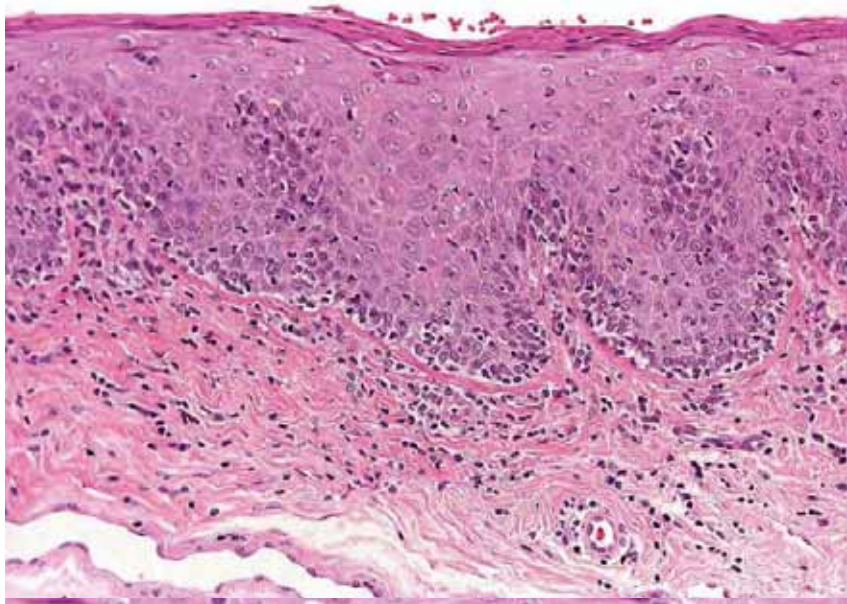
Lichen sclerosus, inflammatory stage

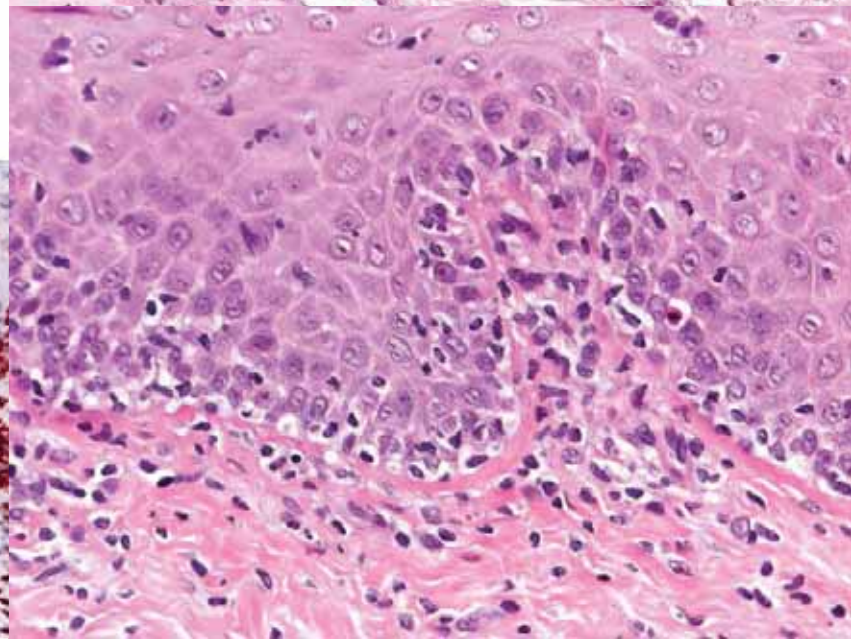


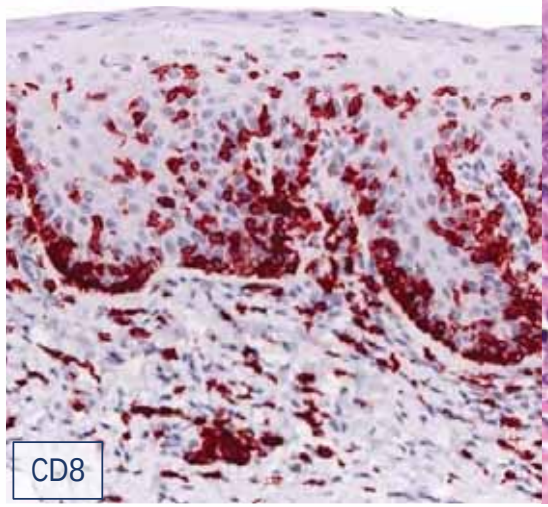
- Pseudolymphomatous features are observed almost exclusively in genital LSA
- Most frequent presentation is phymosis in male children
- Band-like infiltrate of T-lymphocytes with variable numbers of epidermotropic 'haloed' cells; CD8+
- Conventional histopathological features of LSA are often missing or present only focally; clinicopathologic correlation crucial

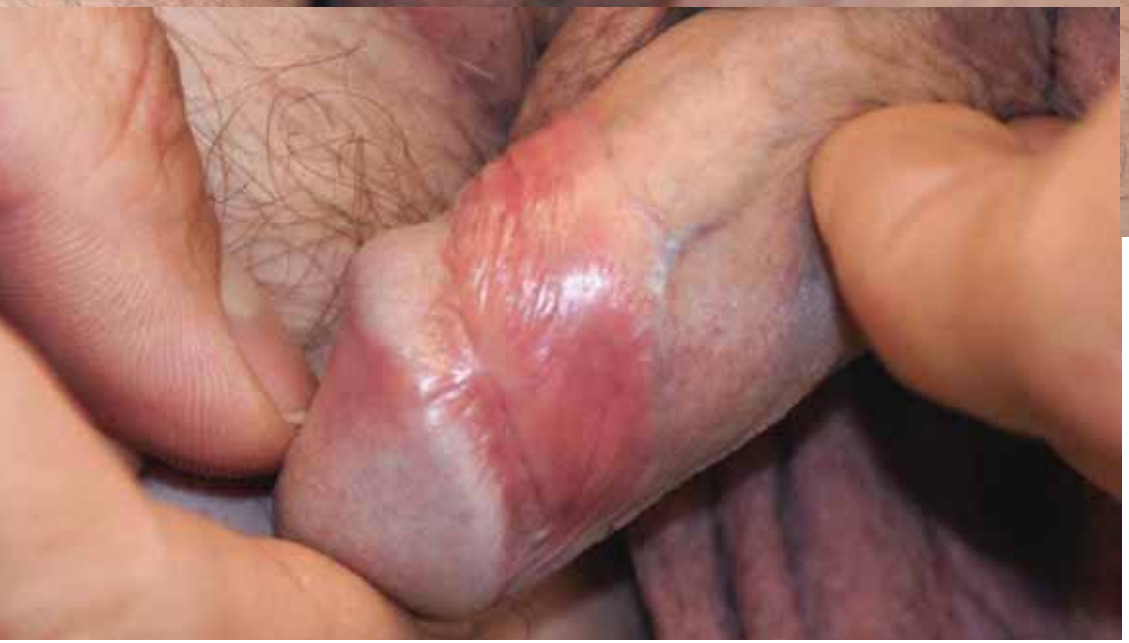
M, 39.
Penis.







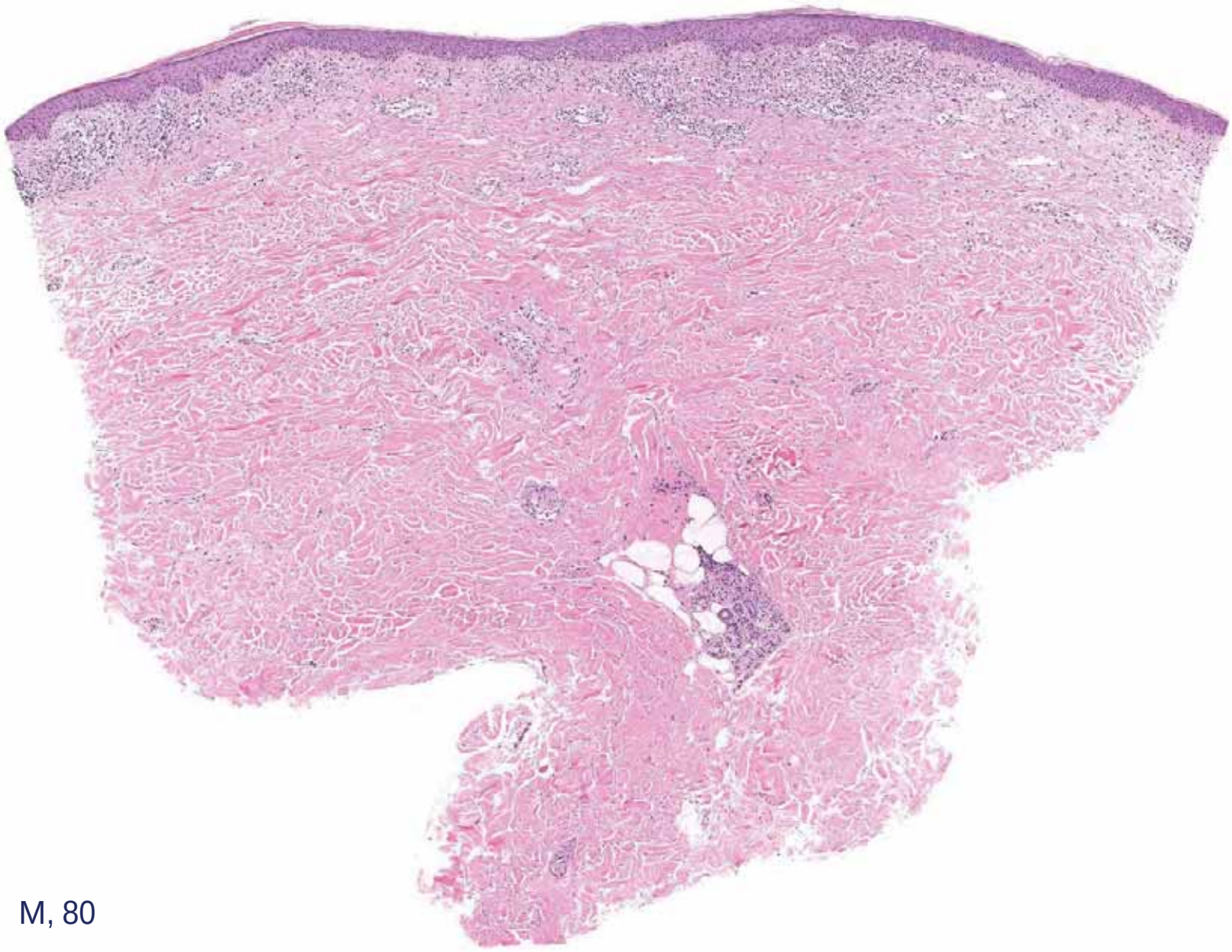




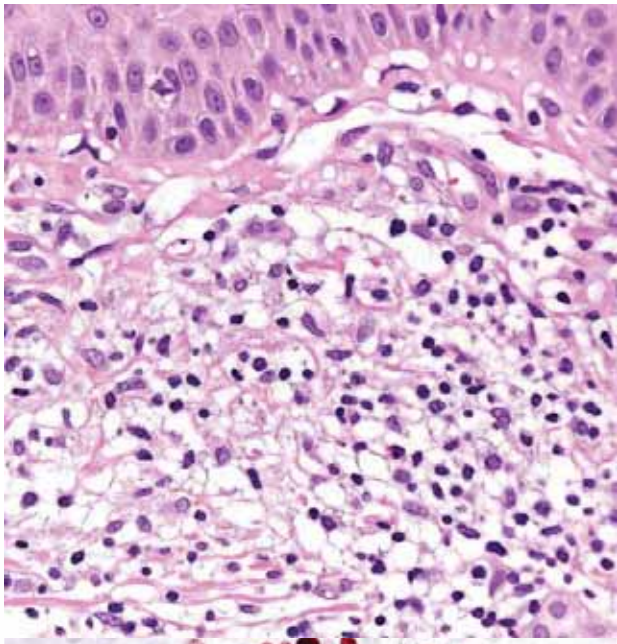
Picture taken after 10d of local steroids with partial resolution (achieved after 3 weeks); No clinical signs of LSA or of MF. A&W (32 months).

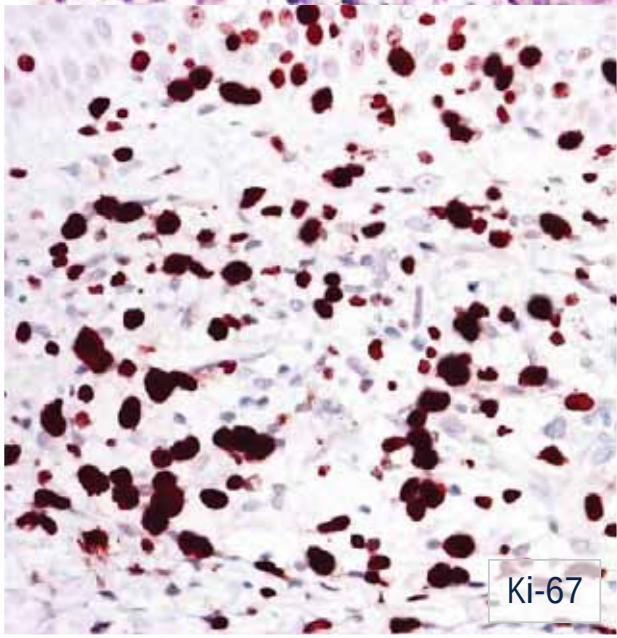
Pseudo-MF features on genital skin

- MF-like histopathological features are very common in genital lichen sclerosus and may be observed rarely also in balanitis / balanoposthitis / vulvitis
- In all such conditions presence of intraepidermal (epidermotropic) lymphocytes, usually with cytotoxic phenotype (CD8+)
- The genital area may be a special site for MF-like cytotoxic T-cell infiltrates
- A diagnosis of MF on genital skin should be made only upon compelling evidence

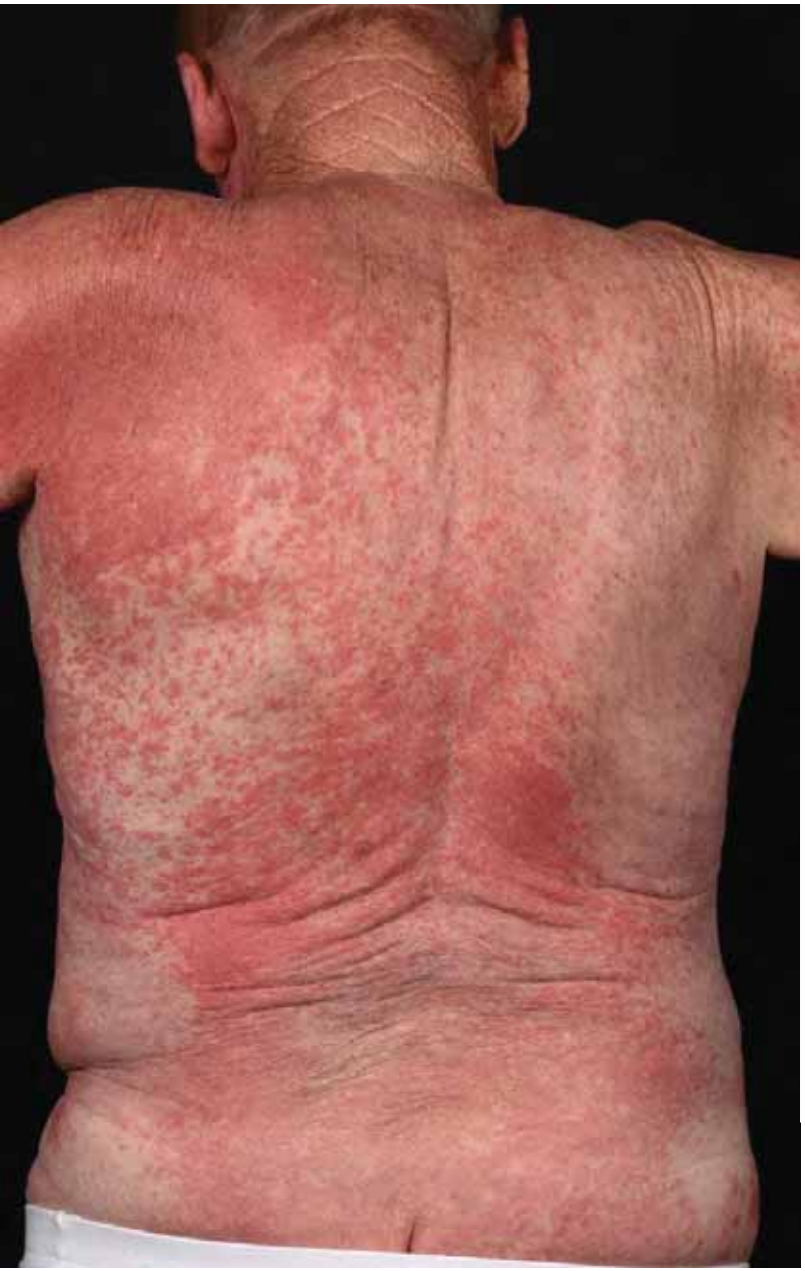


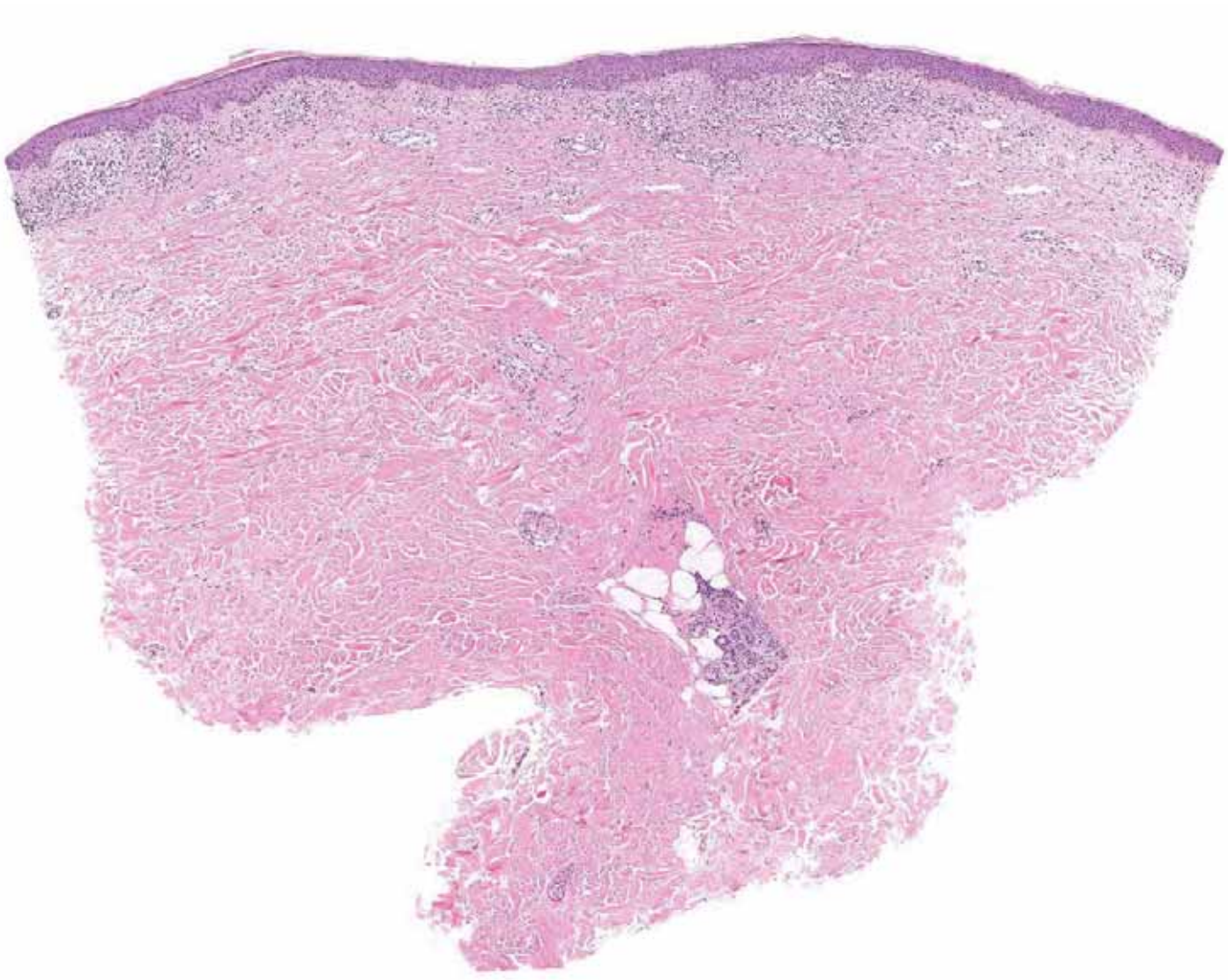
M, 80



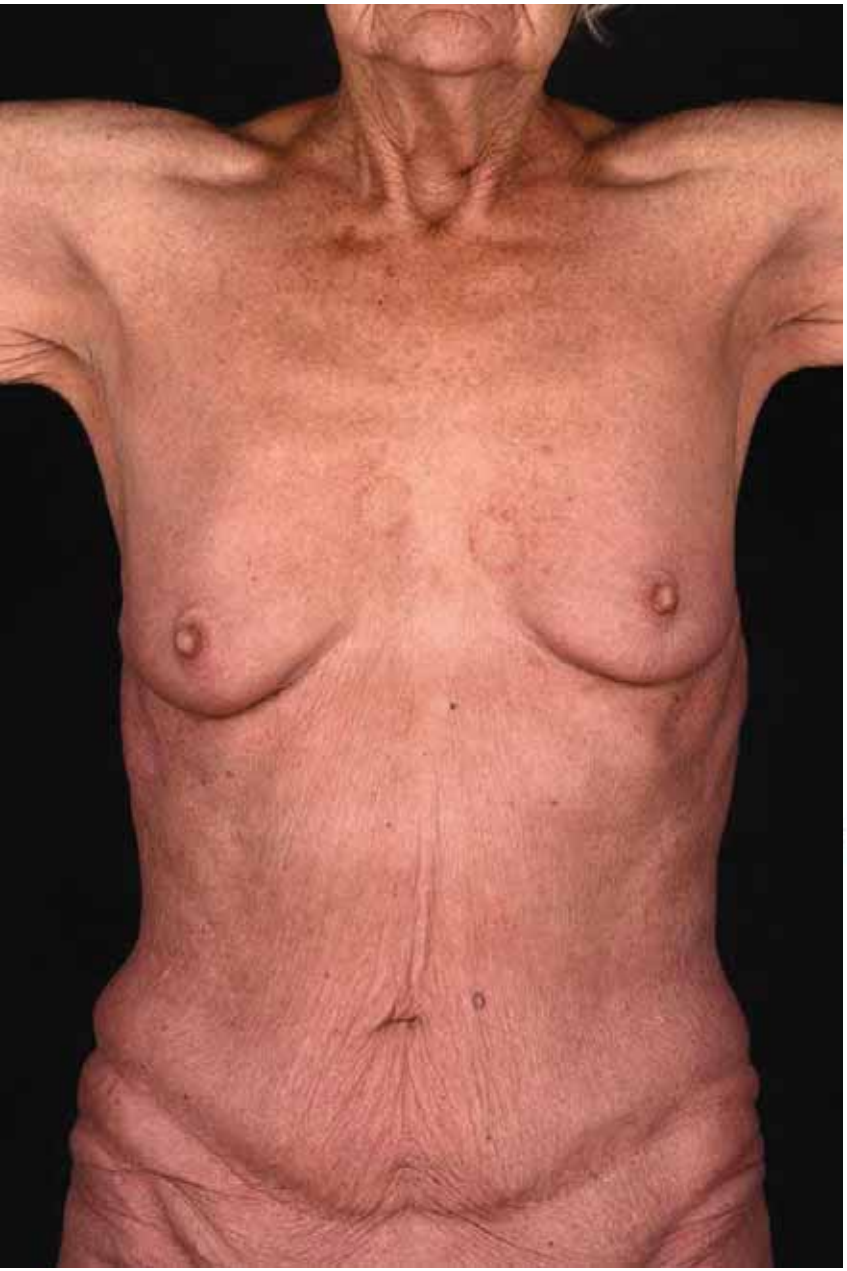


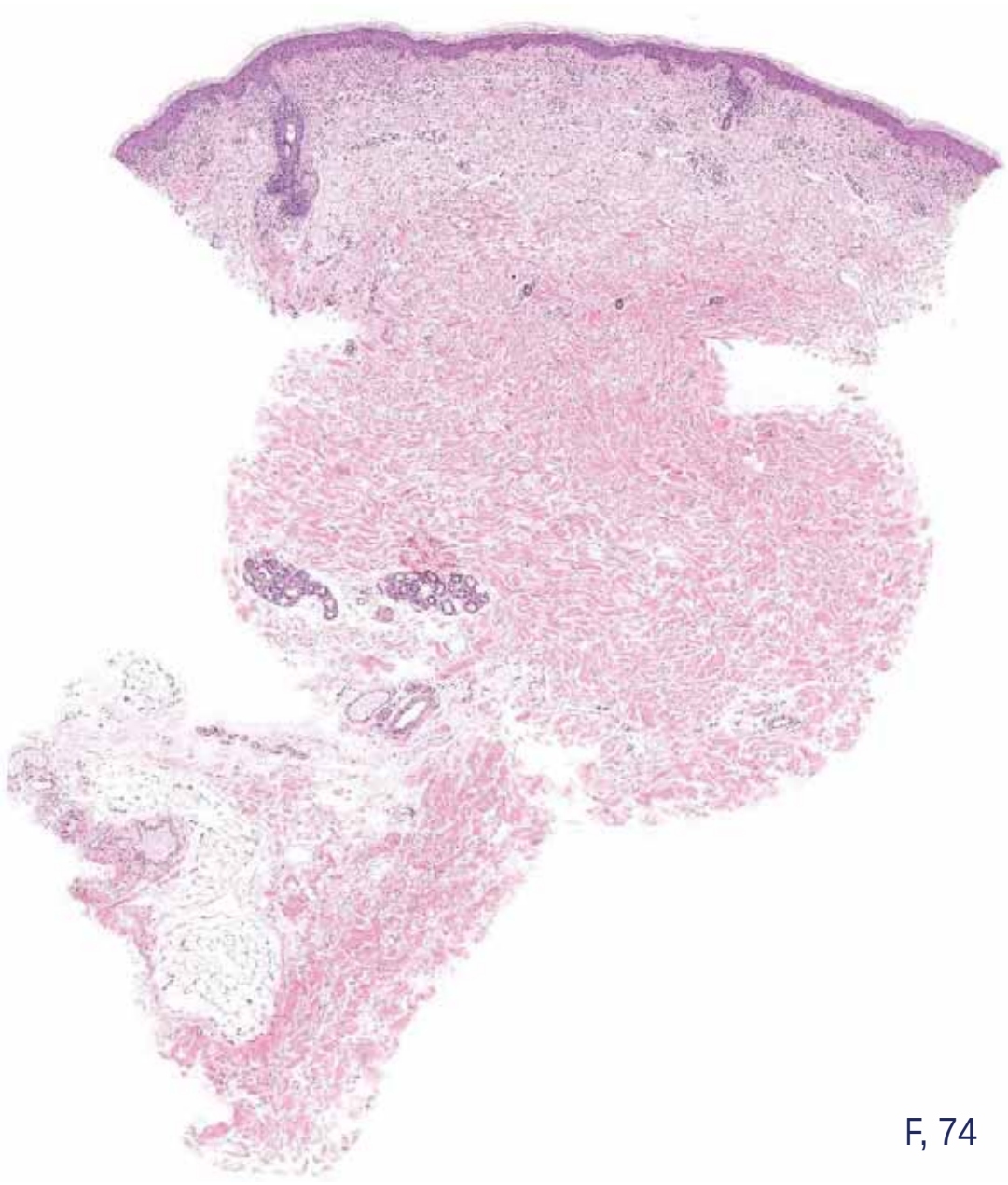
Ki-67



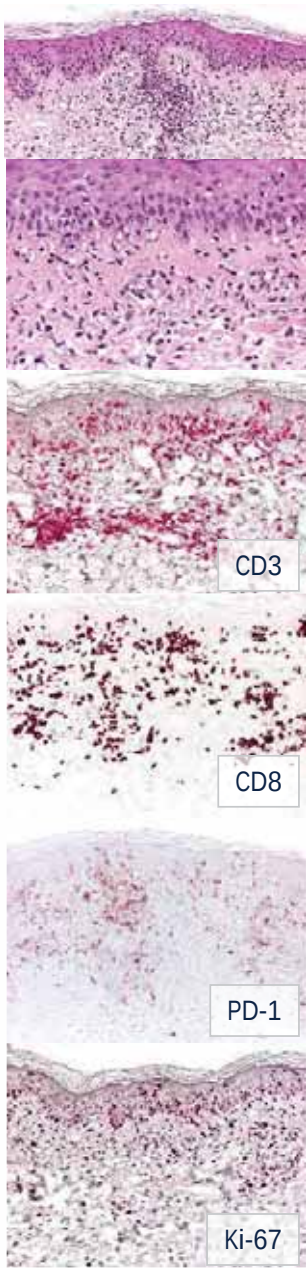


Lymphomatoid drug eruption





F, 74



Lymphomatoid drug eruption (T-cell pattern)

- Drug eruptions may occasionally mimic histopathologically a cutaneous T-cell lymphoma (MF-like or lymphomatoid papulosis-like)
- Sudden onset, generalized distribution; Resolution upon discontinuation of the offending drug
- Cases with T-cell pattern show band-like lymphoid infilrates with several activated cells and often with high proliferation (>90%); Epidermotropism usually minimal but atypia may be striking
- Cases with CD30+ activated lymphocytes usually characterized by mostly perivascular rather than interstitial CD30+ cells

Drug-Induced Immune Dysregulation As a Cause of Atypical Cutaneous Lymphoid Infiltrates:

A Hypothesis

CYNTHIA M. MAGRO, MD, AND A. NEIL CROWSON, MD

The authors encountered 22 patients in whom a skin biopsy showed atypical lymphoid hyperplasia and in whom a subsequent drug history showed ingestion of one or more agents before lesional onset. In 13 patients, the biopsy had been performed to rule out a diagnosis of malignant lymphoma, whereas in the other nine the clinical impression was that of a drug eruption. Among the more frequently prescribed agents were calcium-channel blockers, angiotensin-converting enzyme (ACE) inhibitors, antidepressants, antihistamines, β-blockers, benzodiazepines and lipid-lowering agents, all of which are either known to perturb lymphocyte function or have been implicated as a cause of pseudolymphomata. Twelve of the patients were on two or more of these drugs. The effect of drug modulation on the clinical course was assessed. The clinical presentations were as one or more erythematous plaques or multiple infiltrative papules, or as solitary nodules. The patients had been on one or more of the aforementioned drugs from 2 weeks to 5 years before developing the lesions. Resolution of the eruptions occurred in 17 patients within 4 to 32 weeks (mean, 7 weeks) of discontinuing the medication. Five additional patients had complete excision of solitary lesions without recurrence. A history of atopy, autoimmune disease, or previous carcinoma was elicited in five patients. All biopsy specimens showed atypical lymphoid infiltrates, which assumed one or more of the following patterns: mycosis fungoides (MF)–like, a lymphomatoid vascular reaction, lymphocytoma cutis, and follicular mucinosis. Based on the histopathology of the biopsied lesions and the clinical course being one of lesional resolution after cessation of drug therapy or excision of a solitary lesion without subsequent recurrence, a diagnosis of drug-associated lymphomatoid hypersensitivity was established in all specimens. A diagnosis of drug-associated pseudolymphoma should be excluded before a diagnosis of cutaneous lymphoma is rendered, and should be considered if the patient is on a drug known to alter lymphocyte function, particularly in the setting of systemic immune dysregulation or multidrug therapy where agents may act synergistically or cumulatively to alter lymphoid function. The authors postulate that the drug may promote an aberrant immune response to an antigen that may be the drug itself or some other stimulus. A skin biopsy may be particularly helpful, as the lesions of drug-associated pseudolymphoma have a morphology distinctive from malignant lymphoma. HUM PATHOL 27:125–132. Copyright © 1996 by W.B. Saunders Company

Key words: drug-induced lymphoid hyperplasia, immune dysregulation.

Abbreviations: ACE, angiotensin-converting enzyme; MF, mycosis fungoides; LYP, lymphomatoid papulosis; LyVR, lymphomatoid vascular reaction; AIL, angioimmunoproliferative lesions; DTH, delayed type hypersensitivity.

Cutaneous pseudolymphomata are benign infiltrates that mimic malignant lymphoma and encompass a spectrum of entities including actinic reticuloid, Kikuchi's disease, Rosai-Dorfman disease, Jessner's lymphocytic infiltrate of skin, lymphomatoid papulosis (LYP), pseudolymphomatous angiokeratoma of children,[1] and hypersensitivity reactions to antigens such as viruses,[2] *Borrelia burgdorferi*,[3] arthropods,[1] contactants,[5] or drugs.[6,7] An aberrant immune response to microbial or other antigens may reflect a state of systemic immune dysregulation as is proposed for eosinophilic pustular follicular reactions,[8] diphenylhydantoin (Dilantin)-associated pseudolymphoma,[9] and pseudolymphomata developing in the setting of leukemia.[2] The distinction between pseudolymphoma and malignant lymphoma may be problematic, because a pseudolymphoma can mimic both cutaneous T-cell and B-cell lymphoma.[10] Furthermore, a pseudolymphoma may progress to malignant lymphoma.[11]

The authors describe 22 patients who developed drug-associated atypical cutaneous lymphoid infiltrates consistent with pseudolymphomata. Certain stereotypic light microscopic features enabled the distinction of these infiltrates from malignant lymphoma. A role for drug-induced immune dysregulation is proposed as the pathogenetic basis for the evolution of these lesions.

MATERIALS AND METHODS

Twenty-three skin biopsies from 22 patients were selected from 70,000 specimens accessioned over a 10-month period in the dermatopathology laboratories of Pathology Services, Inc. (Cambridge, MA) and Central Medical Laboratories (Winnipeg, Canada), and examined by conventional light microscopy. In 10 of the specimens, the clinician questioned a drug eruption, and in two a specific drug was mentioned. In all specimens, a complete drug history was obtained by the authors before finalizing the biopsy report, revealing drug ingestion before lesional onset. In all specimens, although an atypical lymphoid infiltrate was observed, the authors rendered a final diagnosis of probable drug-associated lymphomatoid hypersensitivity based on specific histological criteria outlined later. In 12 specimens, malignant lymphoma was the stated histological differential diagnosis. Cessation of drug therapy was recommended by the authors, and in 20 of 22 specimens, this advice was acted on by the clinician. The clinical courses of all patients were followed for up to 1.5 years after cessation of drug therapy.

From the Department of Pathology, Beth Israel Hospital, Harvard Medical School, Boston, and Pathology Services, Inc, Cambridge, MA; Central Medical Laboratories and Department of Laboratories, Misericordia General Hospital, Winnipeg, Manitoba, Canada. Accepted for publication October 2, 1995.

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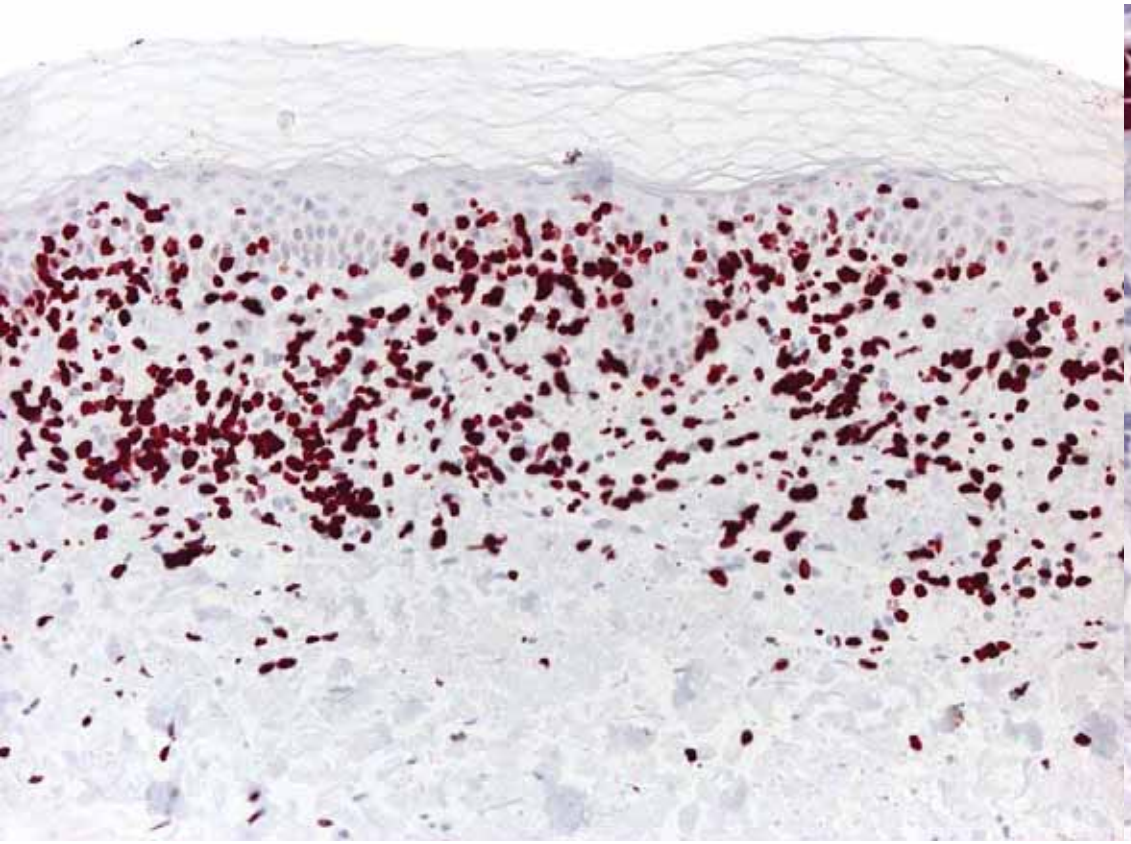
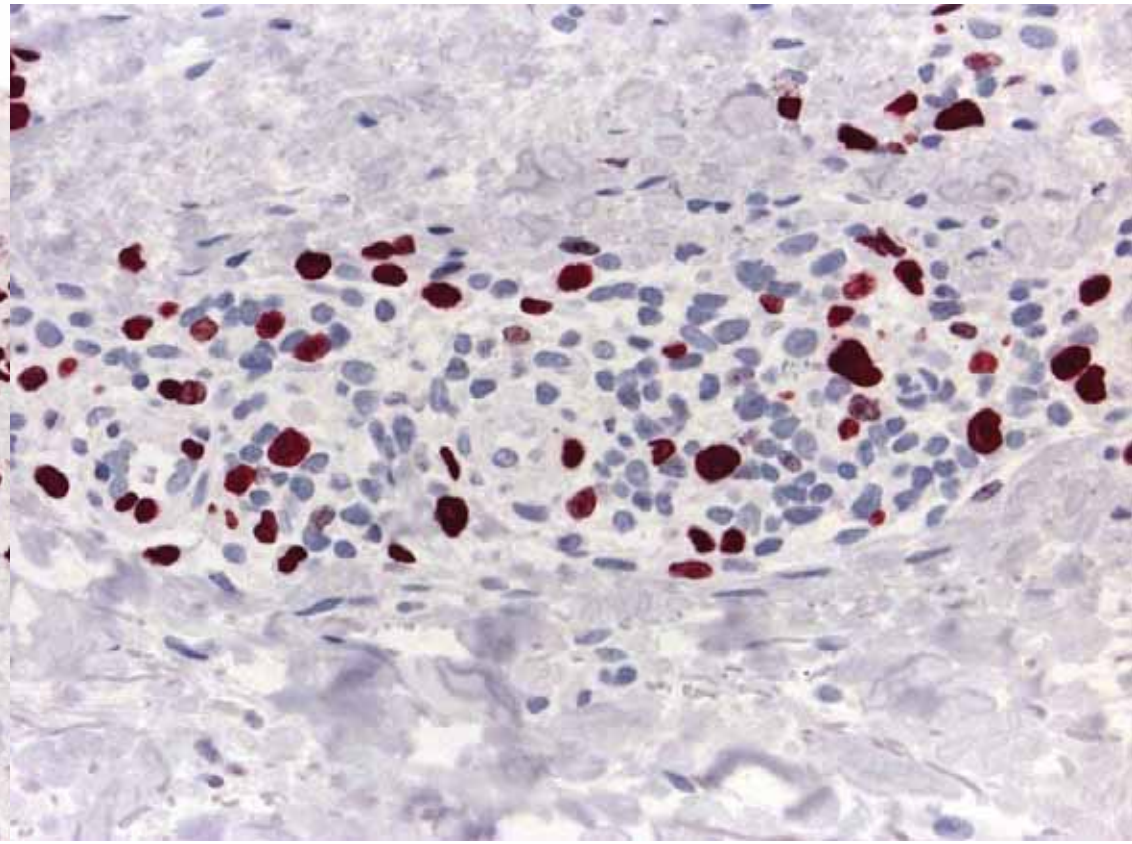
Pattern		
MF-like	69,6%	(n= 16)
Angiocentric	39,1%	(n= 9; 8 with MF-like features)
Folliculotropic	8,7%	(n=2)
Lymphocytoma	17,4%	(n=4)

Clue: Proliferation rate (Ki-67) too high for early MF

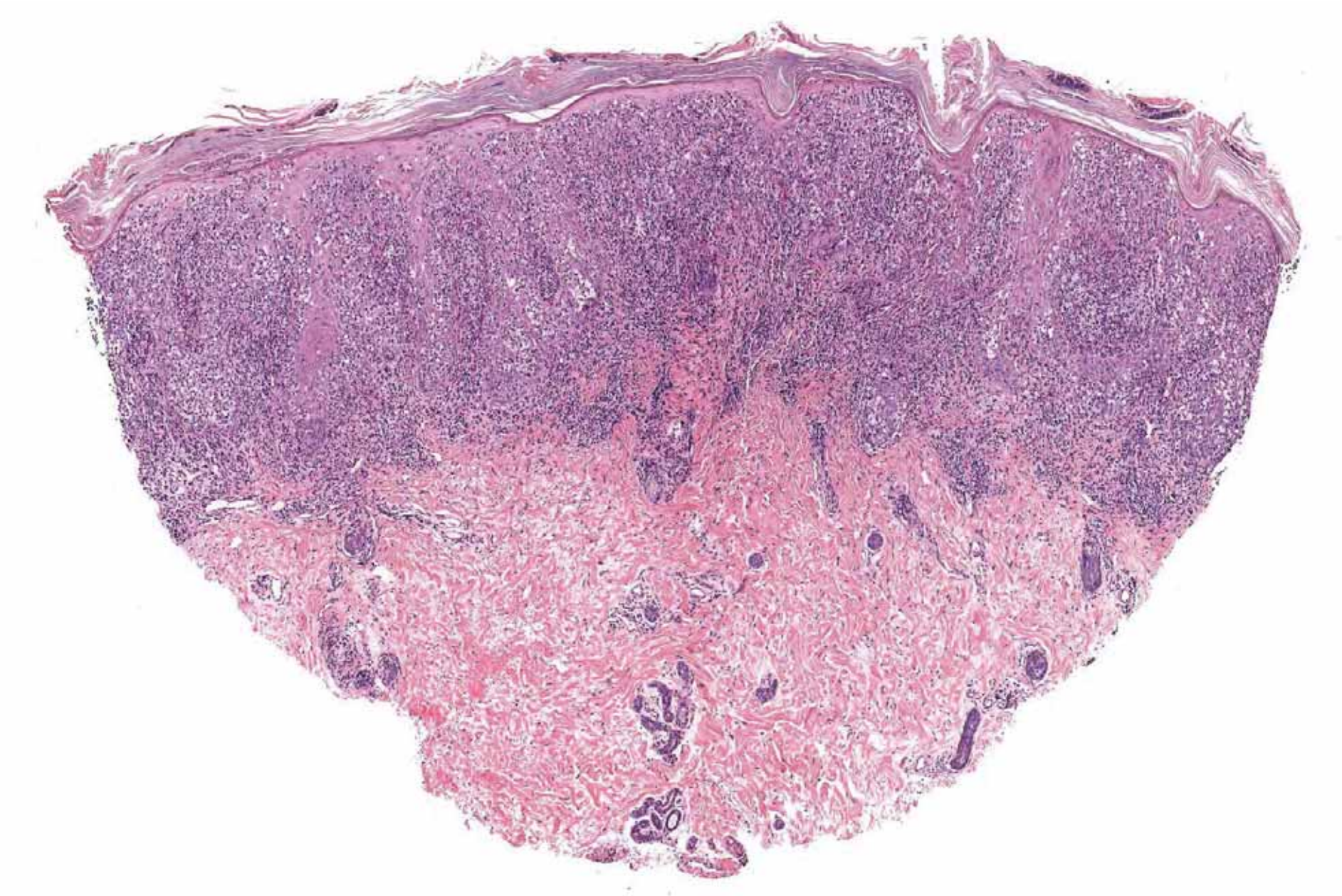


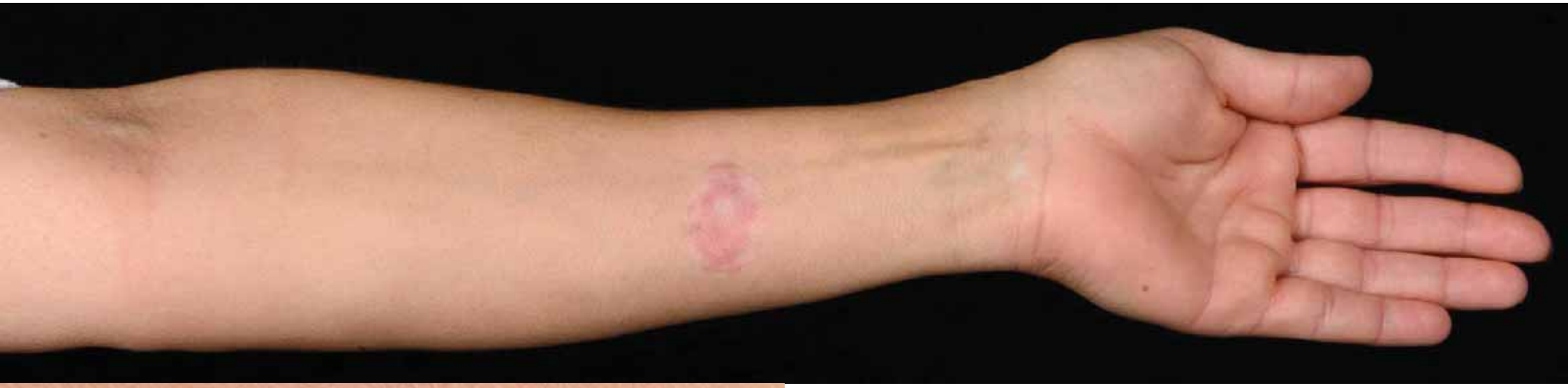
Lymphomatoid drug eruption

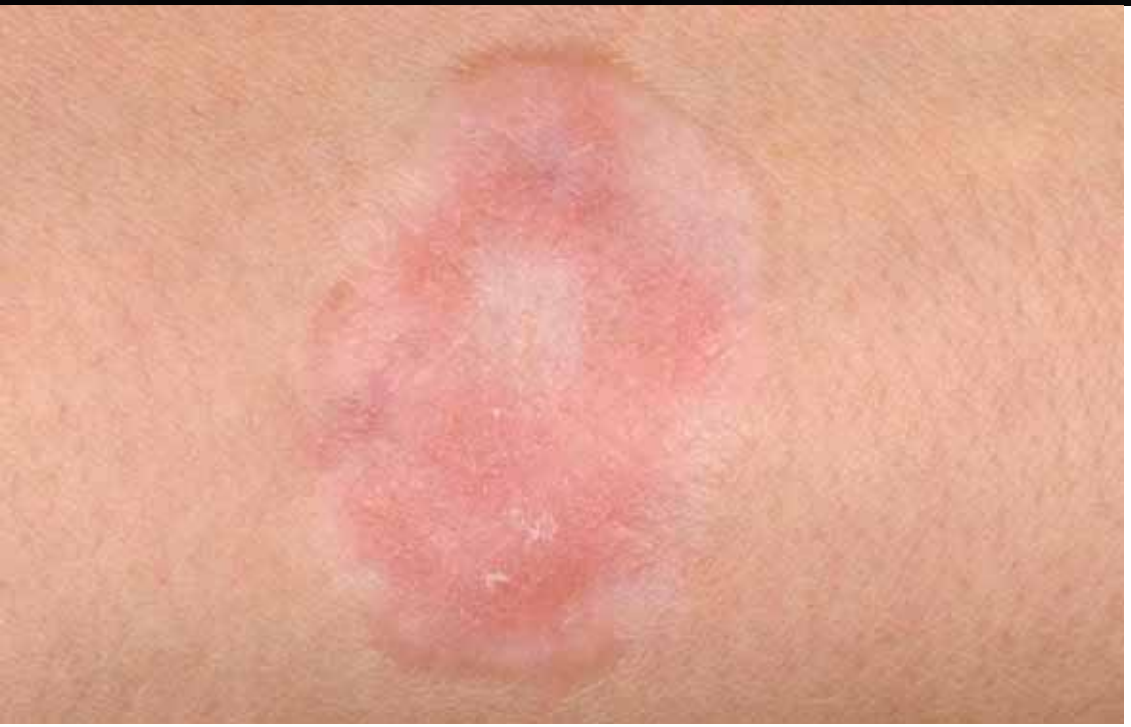


Mycosis fungoides / Sézary

F, 44
Lower arm

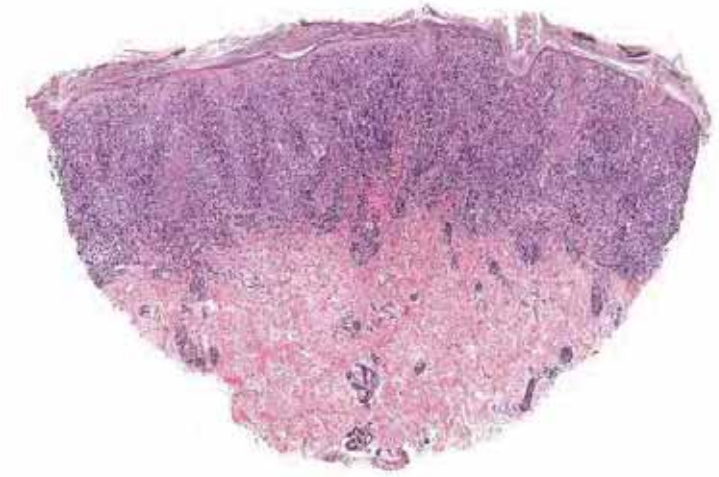


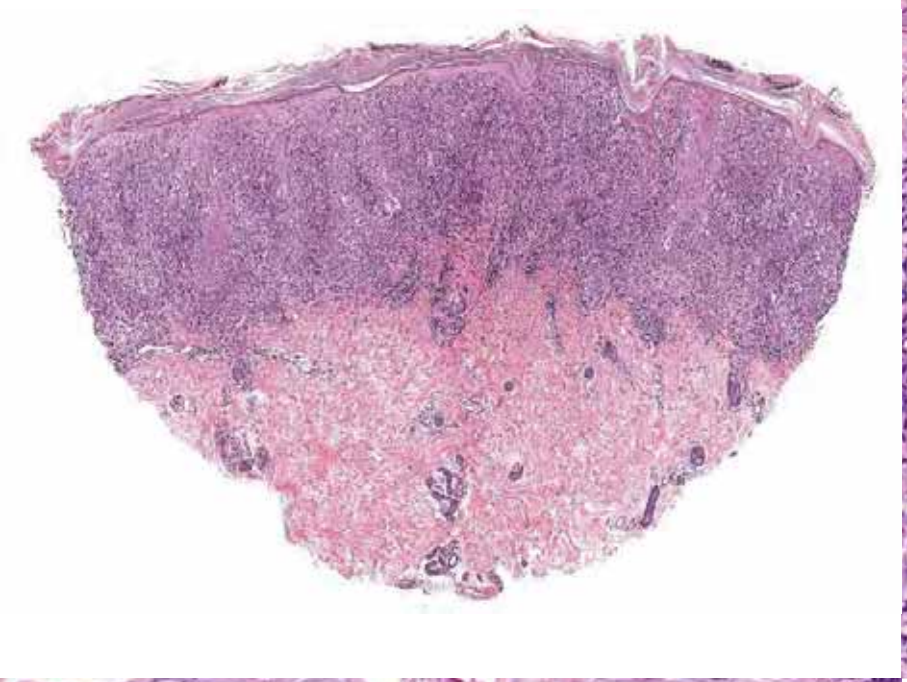


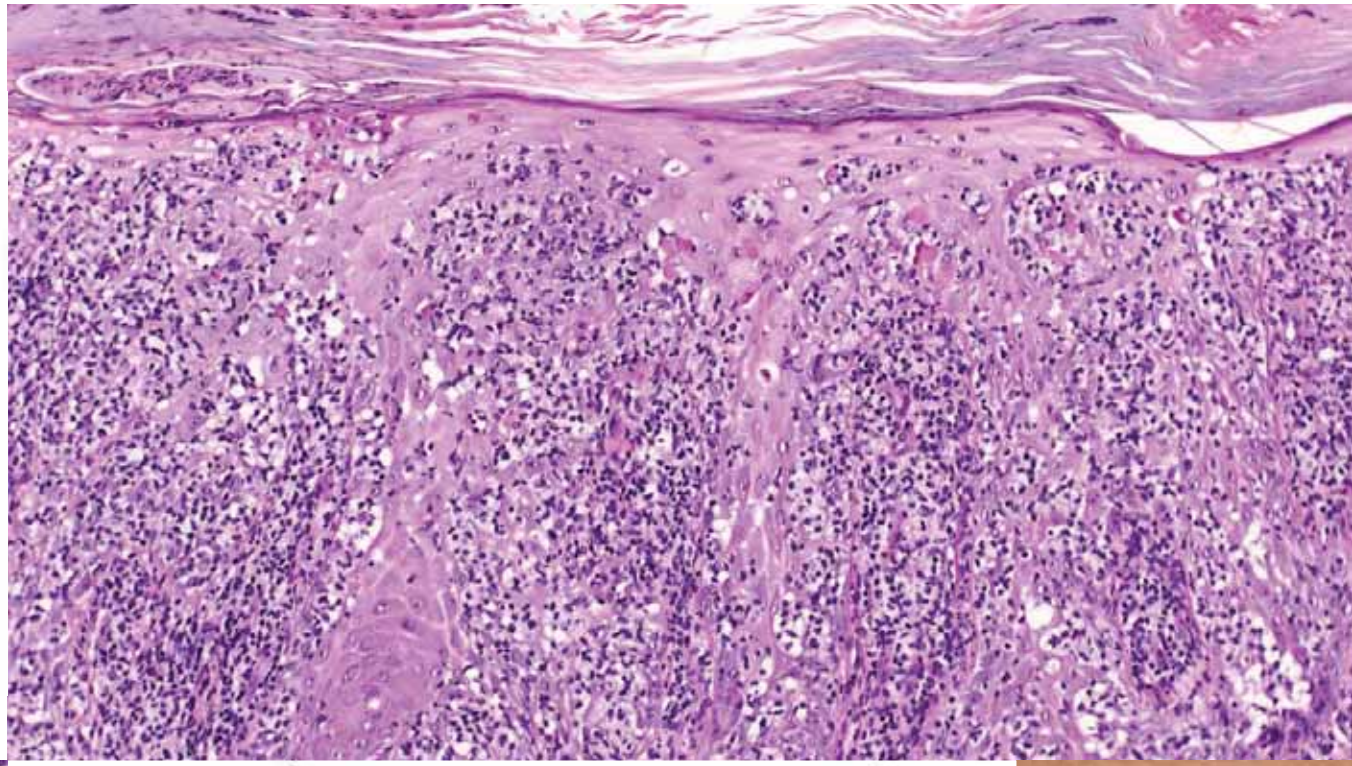


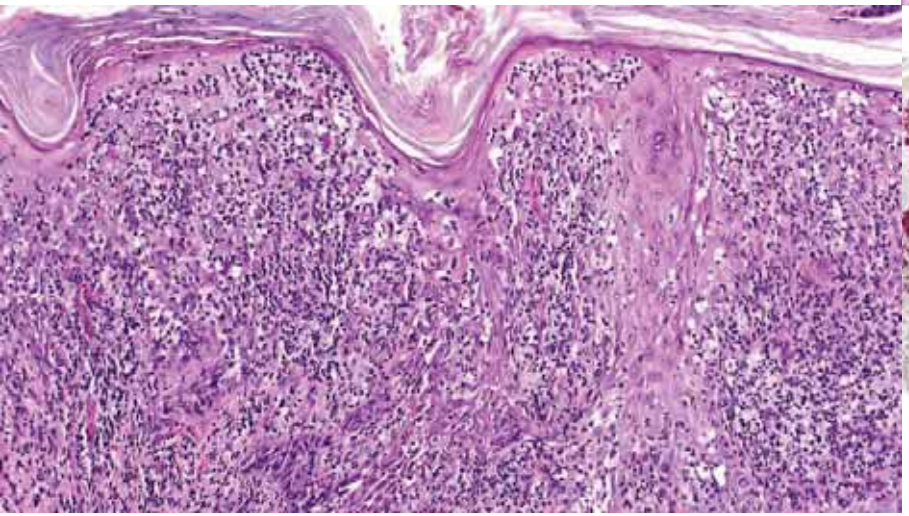
F, 44

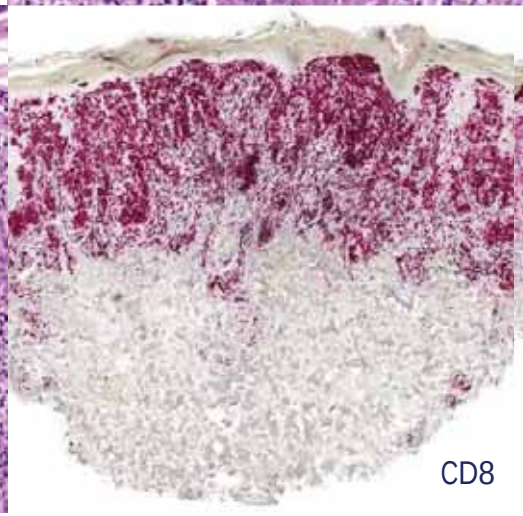
According to the patient asymptomatic skin lesion on the left lower arm for approximately 9 months (picture taken after a punch biopsy).



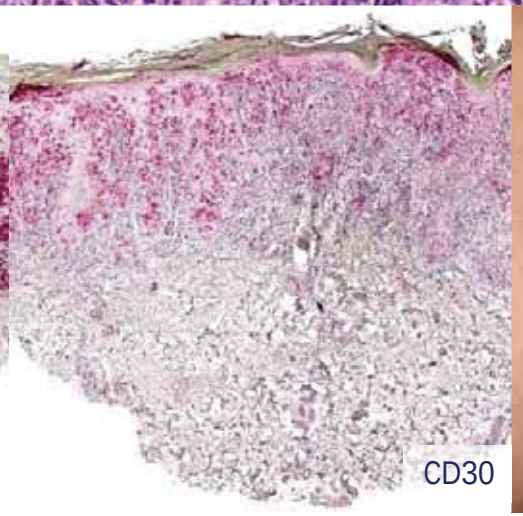




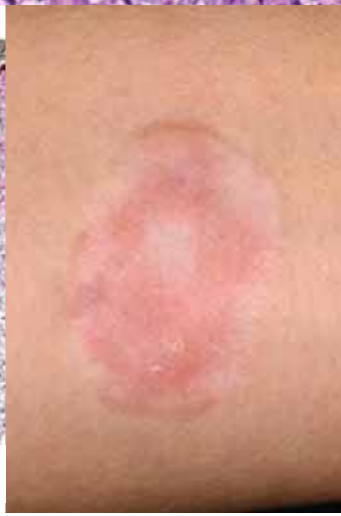


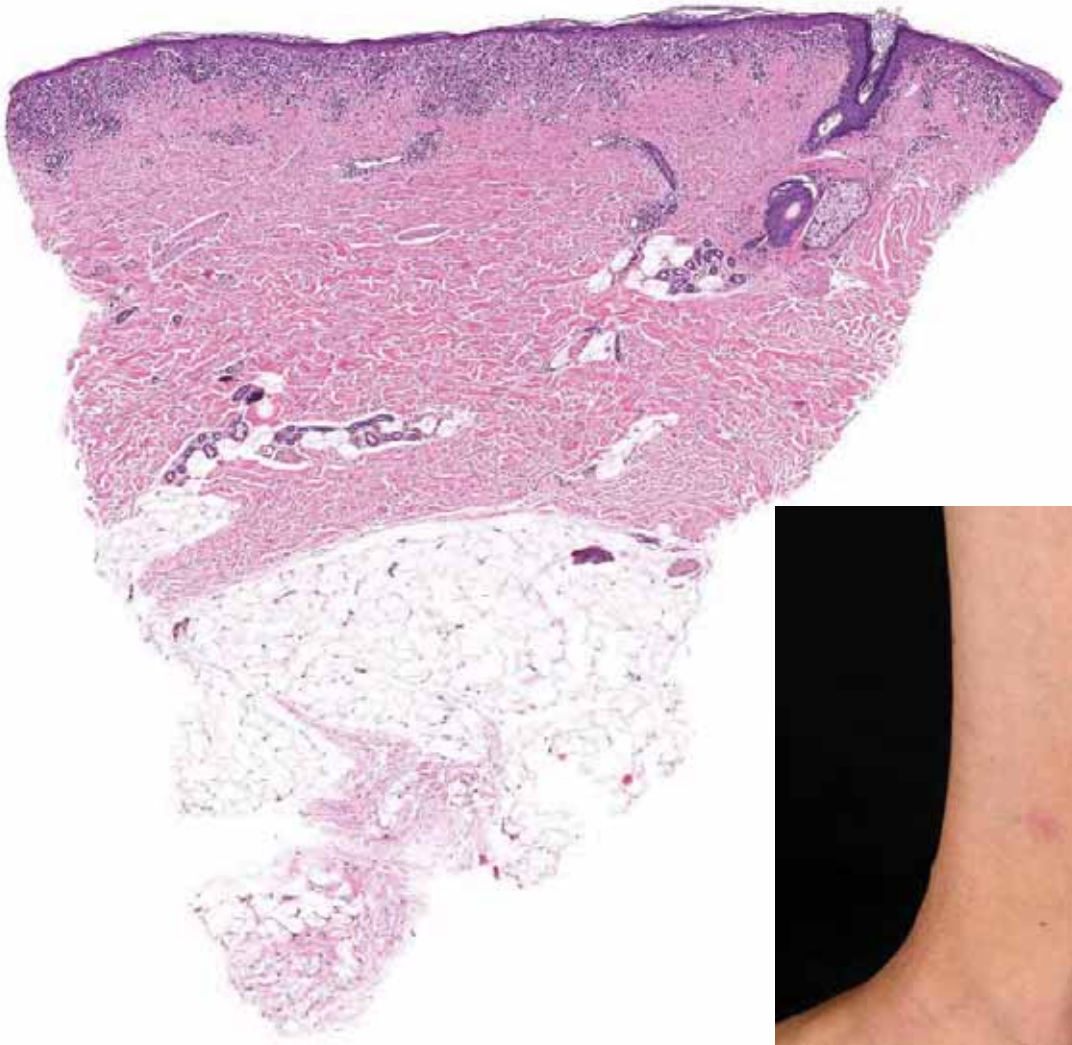


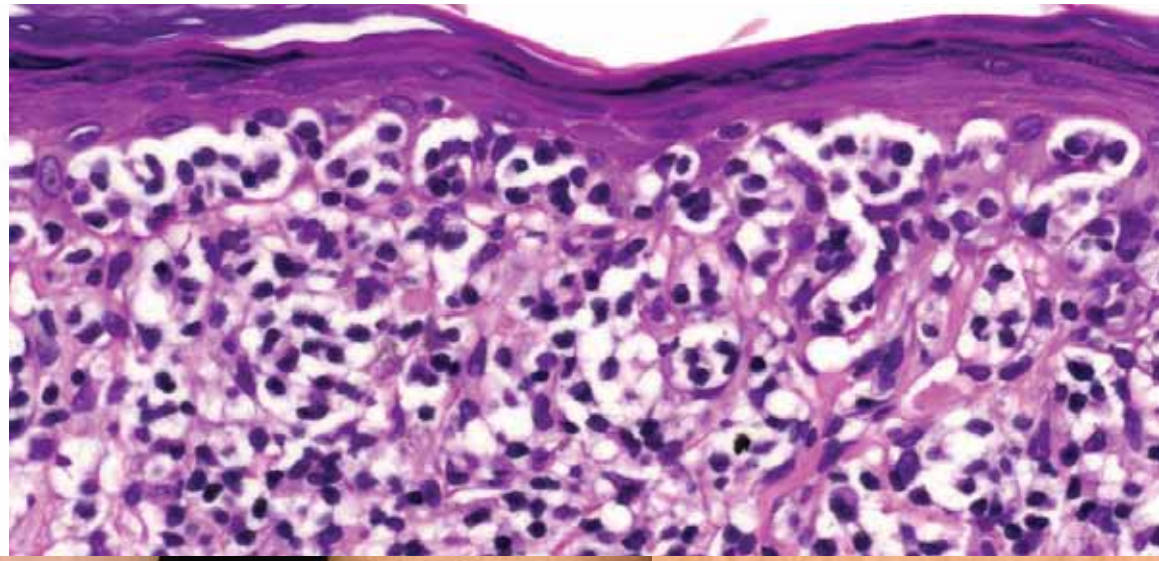
CD8

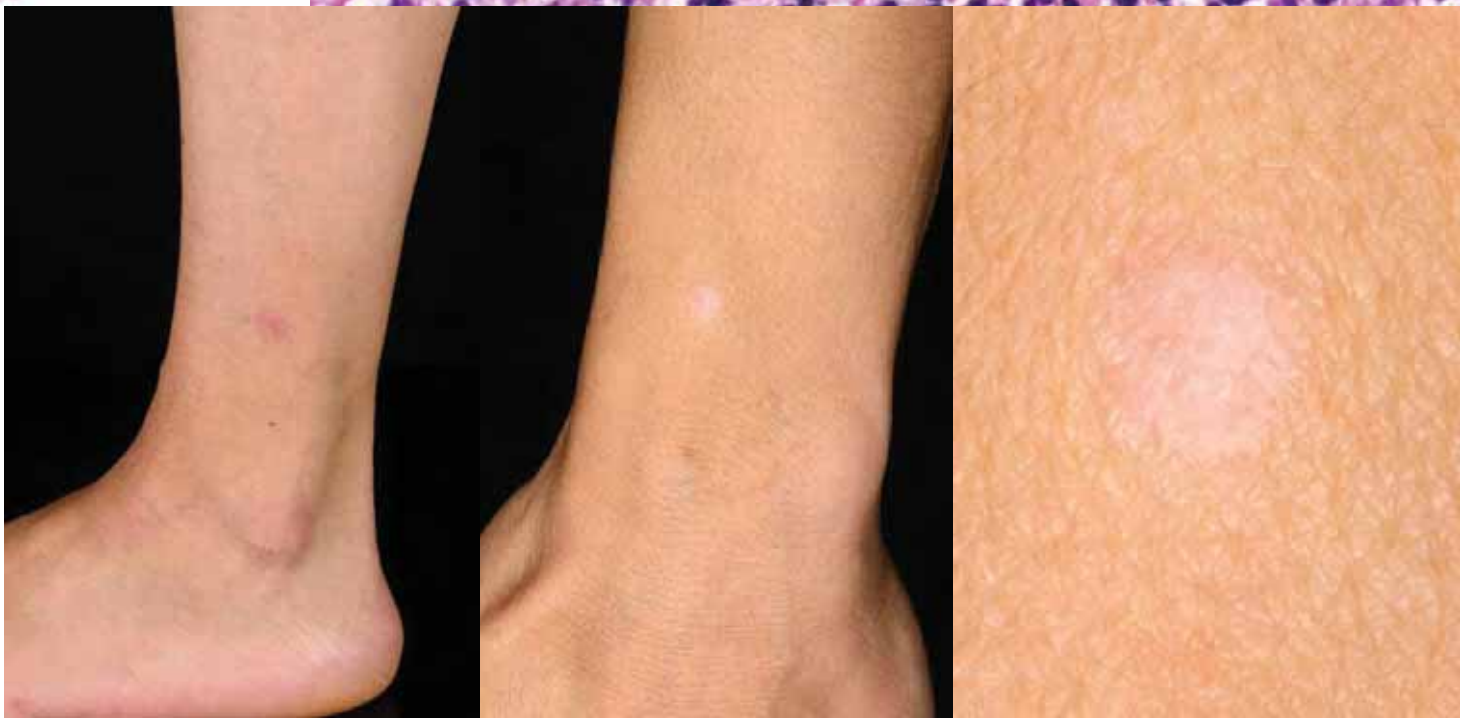


CD30

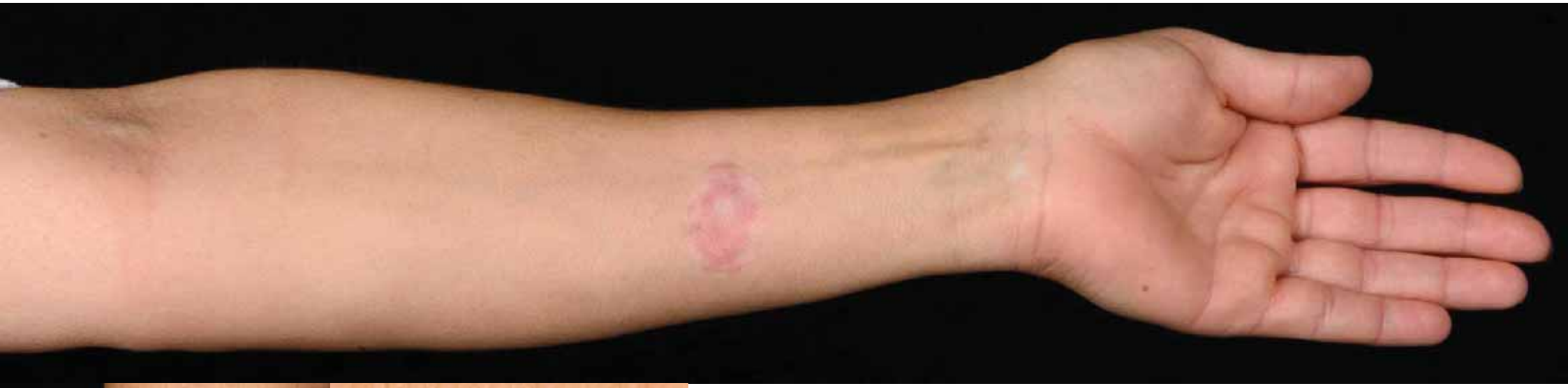


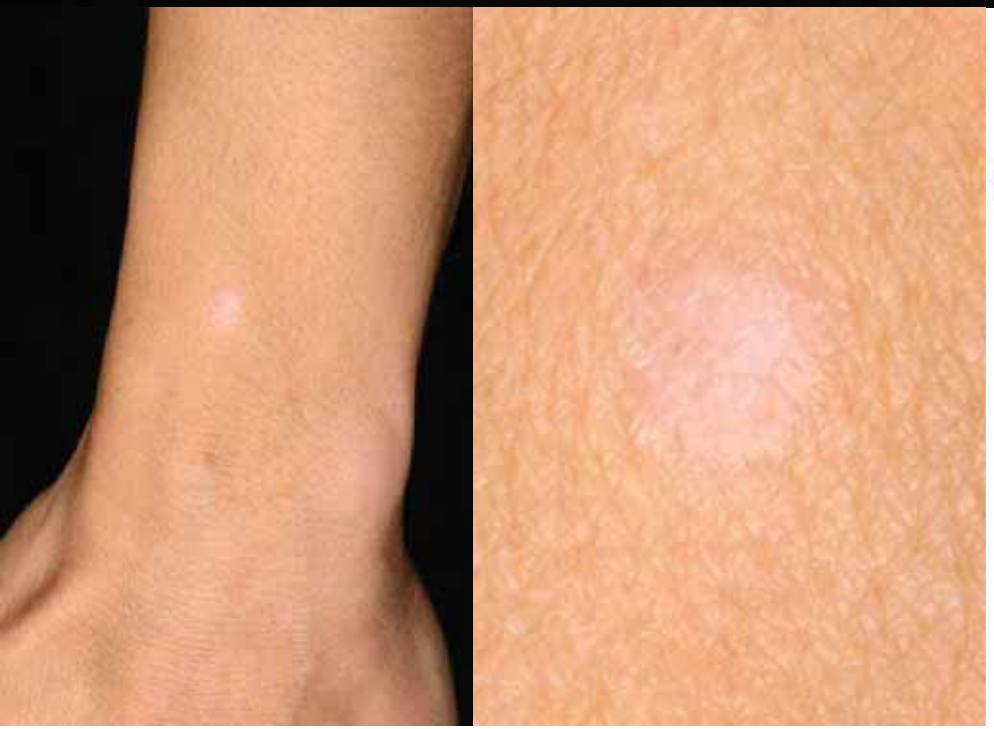


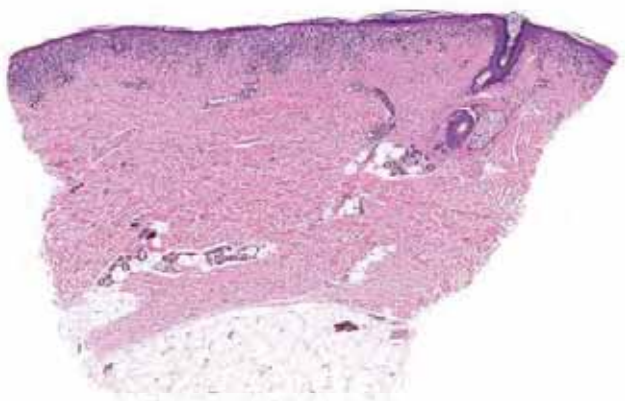


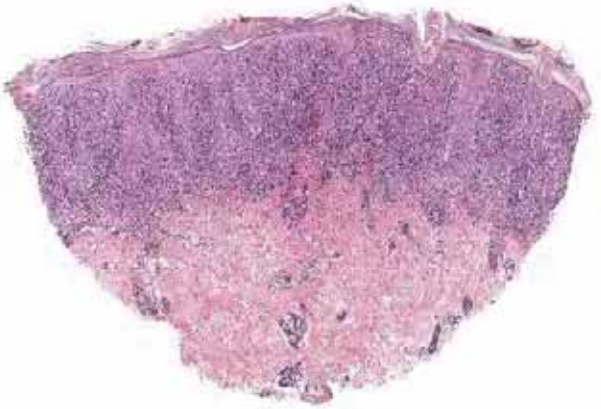


Two further lesions on the lower leg and left arm (biopsy from the arm).



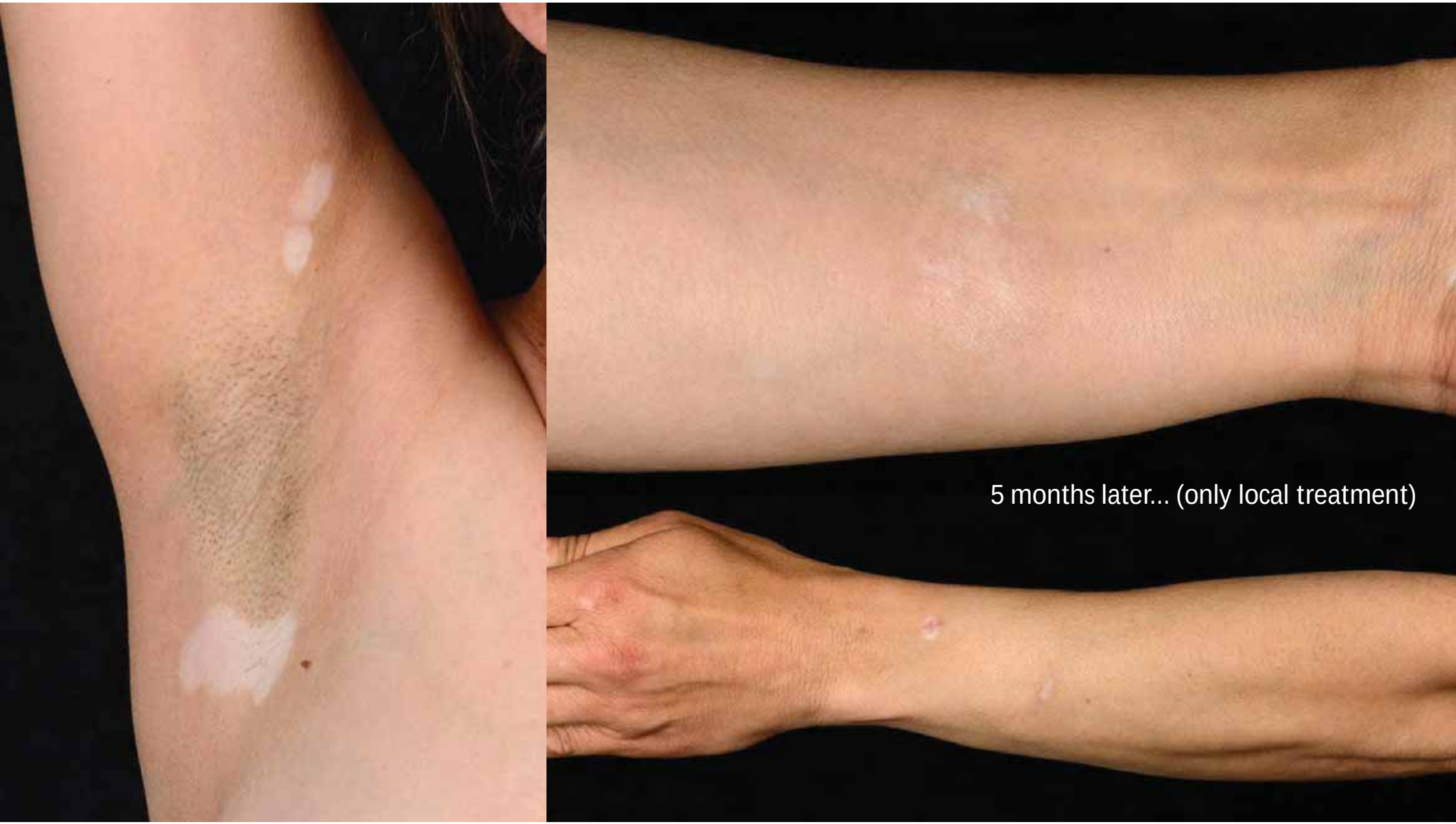


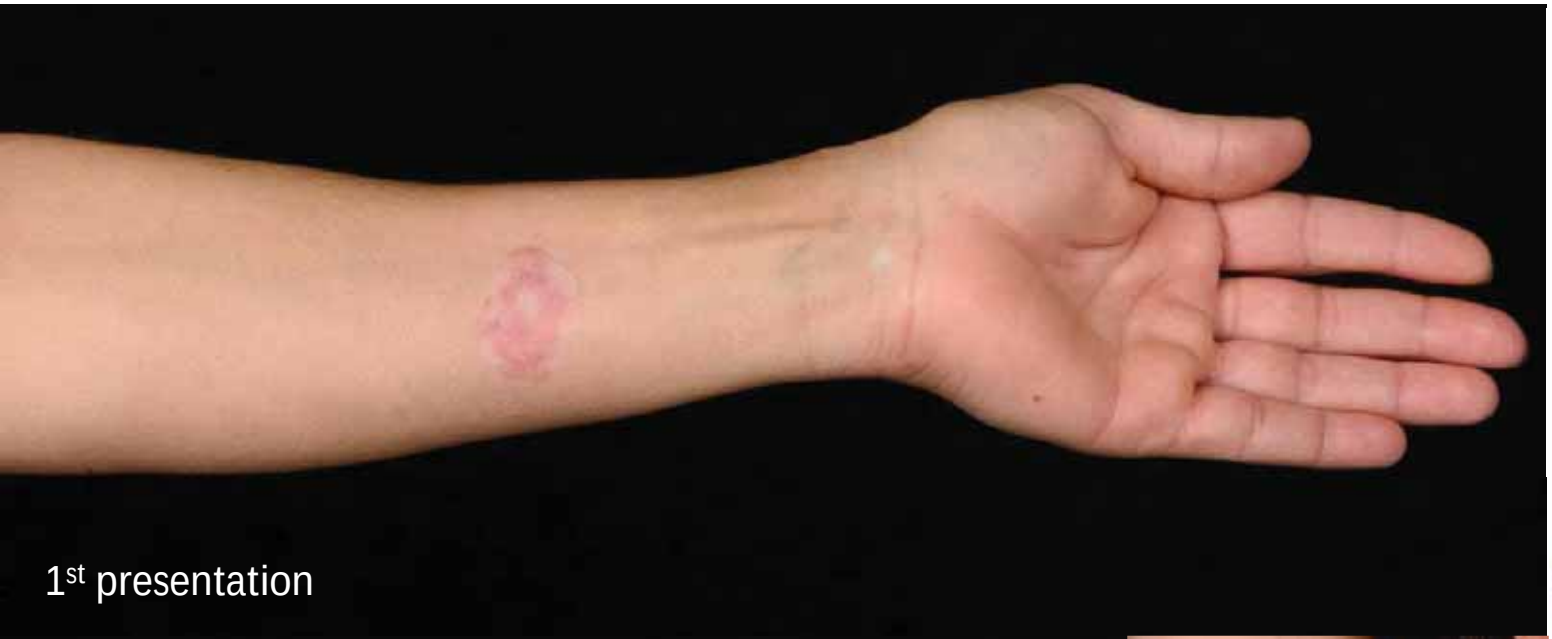




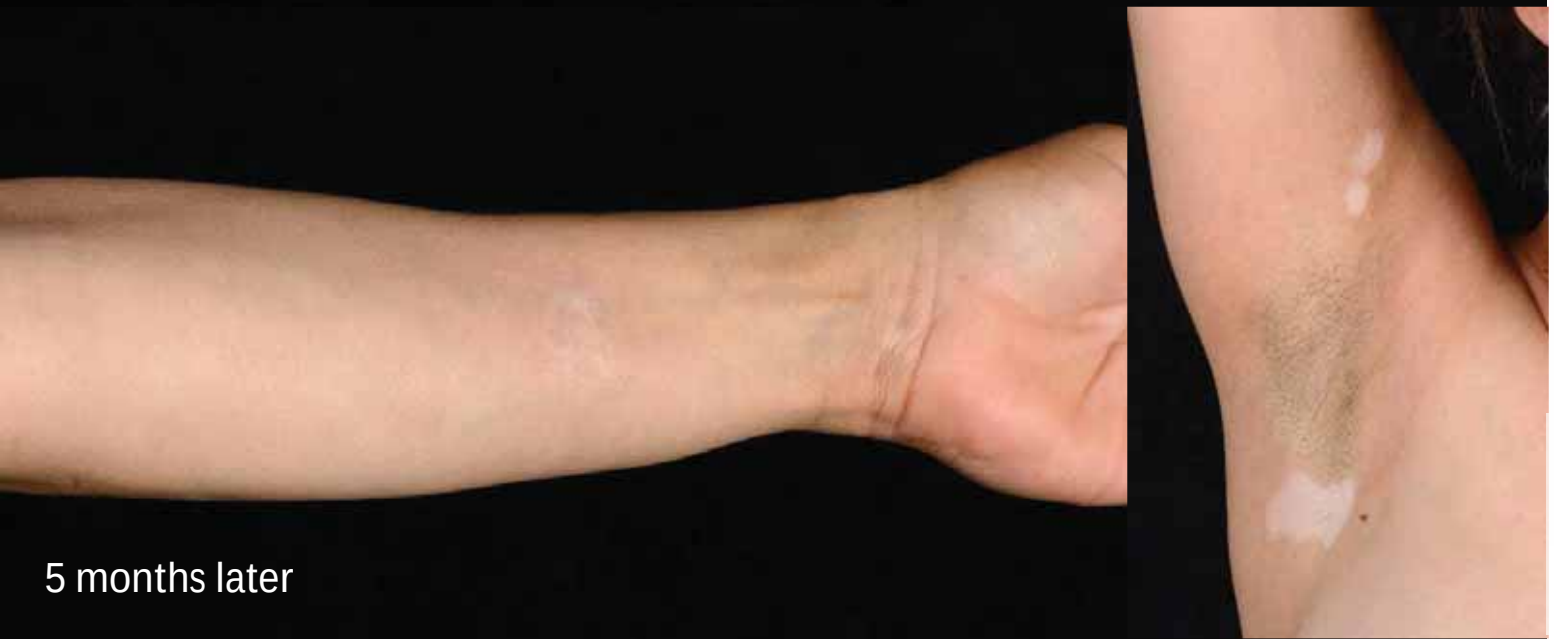
Reported as mycosis fungoides...

(pagetoid reticulosis-like)

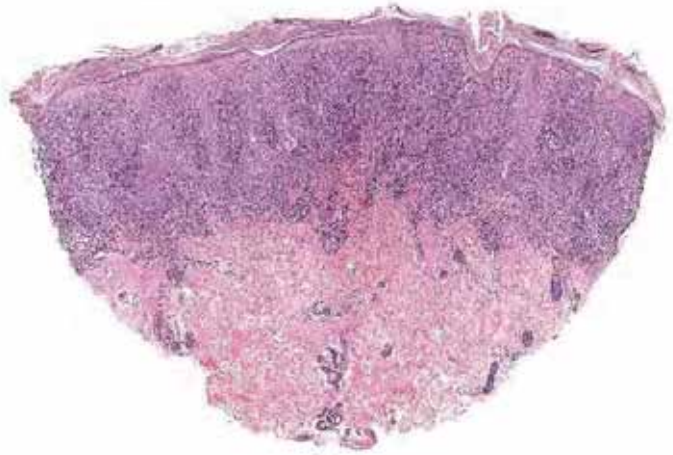

5 months later... (only local treatment)

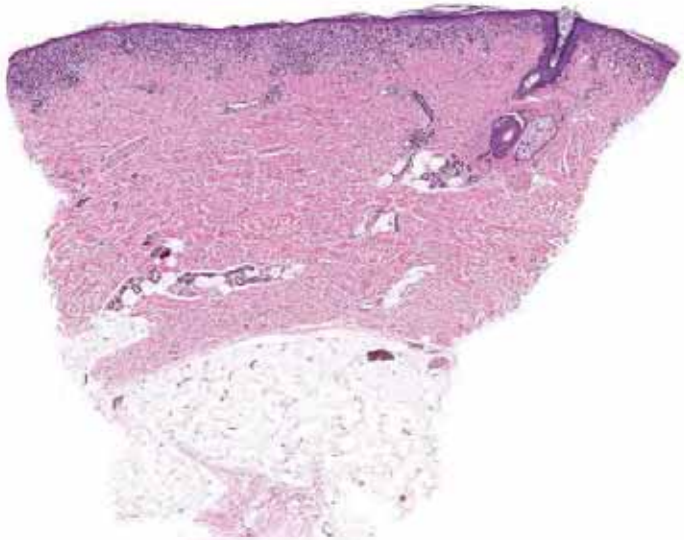


1st presentation



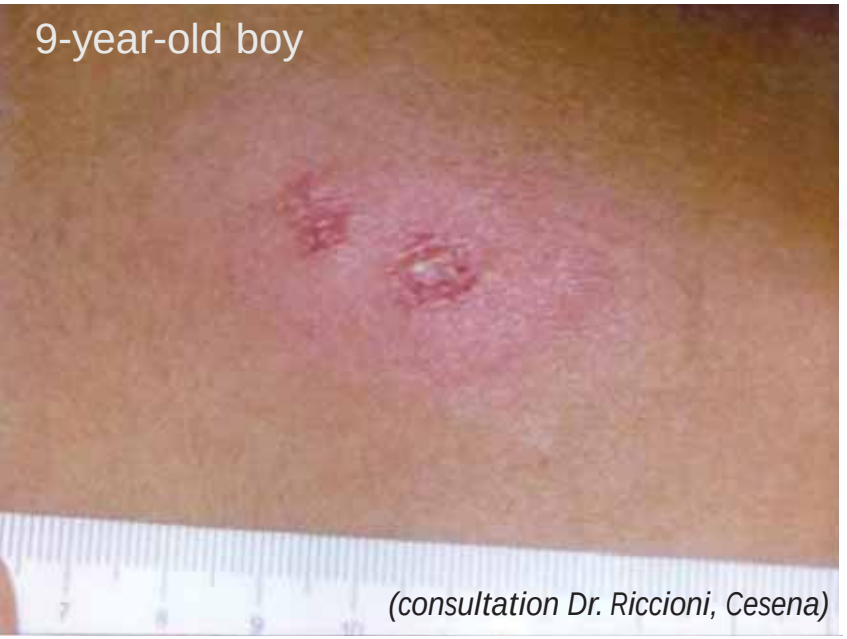
5 months later

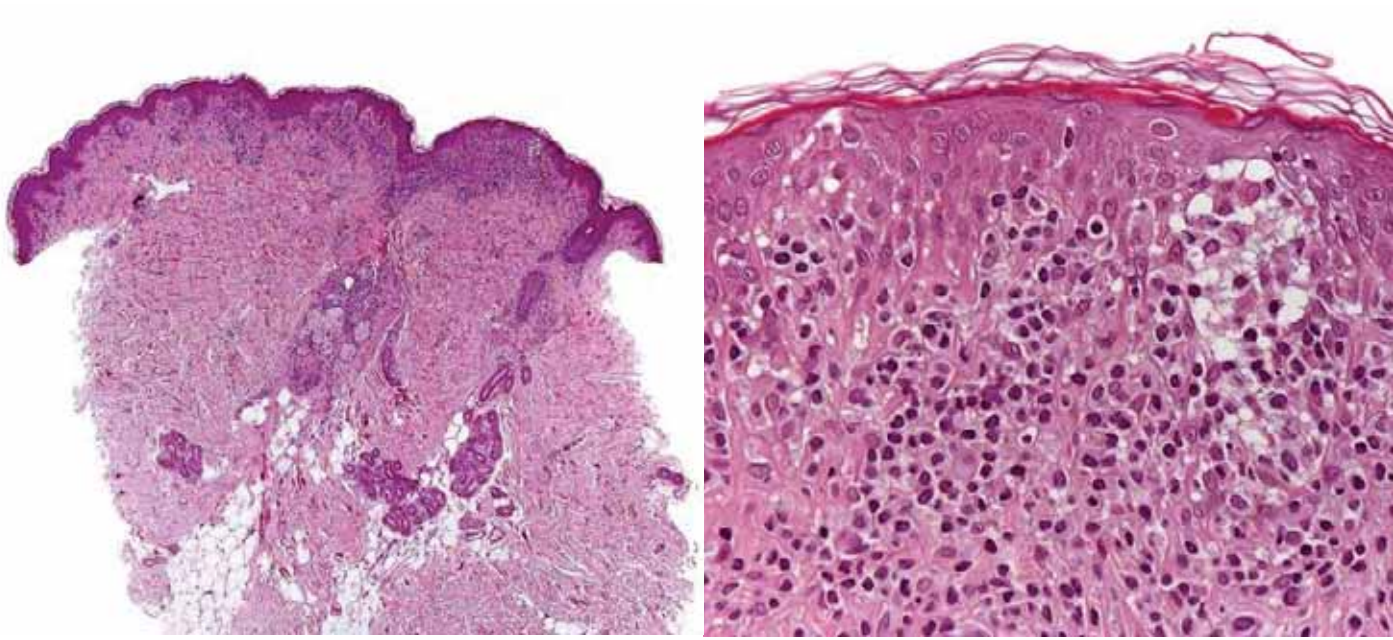




... vitiligo

(pagetoid reticulosis-like)





Vitiligo – Inflammatory stage

- Erythematous patches with evolving central depigmentation; borders not as sharply demarcated as in later stages; "inflammatory" borders may persist around central depigmentation
- Band-like infiltrate of lymphocytes; several epidermotropic lymphocytes
- Cytotoxic lymphocytes (CD8+) predominate (similar to cases of hypopigmented MF)
- A source of dermatopathological mistakes
  (my humble experience: 3 out of 3 (100%) "MF-like" cases missed...)

Baby Wet Wipes: An Unusual Culprit of Lymphomatoid Contact Dermatitis Mimicking Mycosis Fungoides

Emily Coleman, MD and Jag Bhawan, MD

Abstract: Lymphomatoid contact dermatitis (LCD) is a rare, benign pseudolymphoma with clinicopathologic features of both allergic contact dermatitis and cutaneous T-cell lymphoma (CTCL). In this article, we report a fascinating case of LCD secondary to chronic baby wet wipe use with clinical features of allergic contact dermatitis and histopathologic changes of mycosis fungoides, a subtype of CTCL. We argue that LCD should be added to the list of mimickers of mycosis fungoides, a subtype of CTCL.

Key Words: lymphomatoid contact dermatitis, mycosis fungoides, cutaneous T cell lymphoma, allergic contact dermatitis, clinicopathologic correlation

(*Am J Dermatopathol* 2022;44:205–206)

BACKGROUND

Lymphomatoid contact dermatitis (LCD) is a rare, benign pseudolymphoma with overlapping clinical and pathologic features of allergic contact dermatitis and cutaneous T-cell lymphoma (CTCL) that often represents a diagnostic challenge.[1] Clinicopathologic correlation is essential in the diagnosis of LCD. In this article, we report a case of baby wet wipes use as the culprit of LCD showing typical histopathologic changes of mycosis fungoides (MF). LCD should be added to the list of mimickers of MF.[2,3]

REPORT OF A CASE

An African American woman in her 50s with well-controlled hypertension presented with a history of discoloration of the inguinal and intergluteal areas. Initially she was seen by a gynecologist who performed a biopsy that was reported as nondiagnostic. Two years later, she presented to dermatology for evaluation of the persistent lesions. Medications and family history were noncontributory. Clinical examination revealed hypopigmented, minimally scaly patches with focal erosion and erythema overlying the suprapubic, intergluteal, and bilateral inguinal areas (Fig. 1). Two 3-mm punch biopsies revealed abundant lymphocytic epidermotropism with occasional Pautrier microabscesses (Fig. 2A), an interstitial proliferation of lymphocytes, and papillary dermal fibrosis (Fig. 2B). There was a preponderance of $CD8^+$ and $CD4^-$ lymphocytes in the epidermis (Fig. 3A) and dermis (Fig. 3B), respectively. A mild decrease in epidermal melanocytes was noted on MART-1 staining. T-cell receptor (TCR) gene rearrangement polymerase chain reaction studies demonstrated a clonal T-cell population, supporting a diagnosis of hypopigmented MF. However, given a lack of clinicopathologic correlation for MF, additional probing revealed frequent cleansing with baby wet wipes. Topical corticosteroids and cessation of baby wet wipes led to complete resolution of the lesions without recurrence.

DISCUSSION

Although histologic and polymerase chain reaction findings were consistent with MF, the lack of clinical evidence of MF led to the conclusion that this case represented LCD. Furthermore, given resolution of the lesions with cessation of baby wet wipes, we concluded that these were the etiologic agent of LCD. In addition, we would not expect to see clinical resolution of MF with cessation of baby wet wipes, which further supports the diagnosis of LCD.

First coined in 1976 after 4 patients with CTCL had positive patch tests for phosphorus sesquisulfide secondary to matchbox use, LCD is a pseudolymphoma with clinicopathologic features of both allergic contact dermatitis and CTCL.[4] The distribution of lesions of LCD along the buttocks, pelvis, and upper legs more closely mirrors the so-called "bathing trunk" distribution of the lesions MF, which often clouds diagnosis.[1] In addition to the initial report of phosphorous sesquisulfide,[4] other causative allergens identified include dimethyl fumarate, ethylenediamine dihydrochloride, azo dyes, gold sodium thiosulfate, cobalt naphthenate, nickel sulfate, *N*-isopropyl-*N*′-phenyl-*p*-phenylenediamine, *p*-phenylenediamine, *Tectona grandis*, *para*-tertyl-butyl phenol, methylchloroisothiazolinone/methylisothiazolinone and parabens, benzalkonium hydrochloride, and methylchloroisothiazolinone quaternium-15.[5] Similar to our case, moist wipes were the causative agent of LCD on the buttock, genitals, or interglueal cleft in 2 reported cases, with methylchloroisothiazolinone as a common underlying allergen identified by patch testing in both cases.[1,5] Although we did not conduct patch testing, this agent may have been the allergen in our case as well.

Although LCD may have features of MF,[1,4] none of the previously reported cases had the extent and intensity of epidermotropism as seen in our case. Our case is unique in that the histopathological features were indistinguishable from MF. Furthermore, LCD rarely shows TCR gene

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The authors declare no conflicts of interest.

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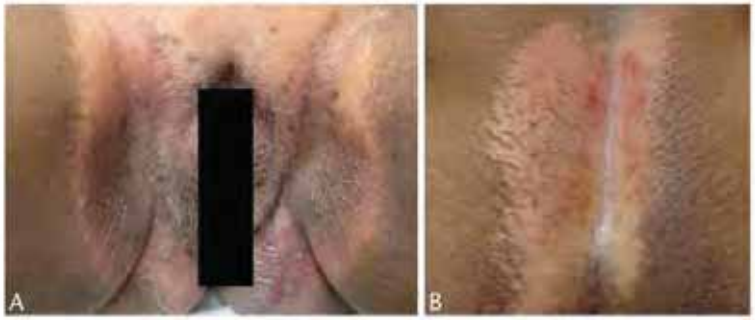


FIGURE 1. A, The inguinal and genital regions demonstrated a hypopigmented, minimally scaly plaque with a mildly erosive plaque posteriorly. B, The intergluteal cleft was notable for a hypopigmented patch with a cluster of 0.1–0.3 mm erythematous macules coalescing into a patch centrally.

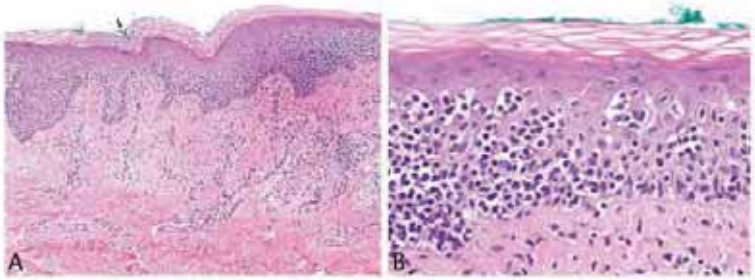
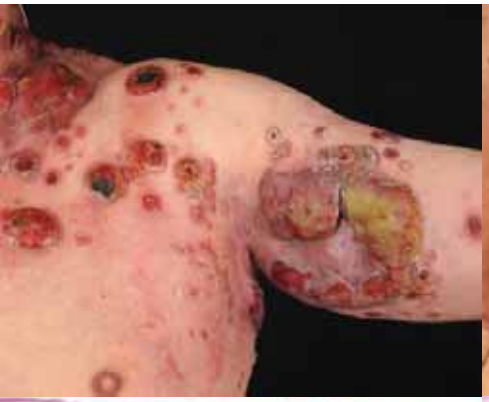
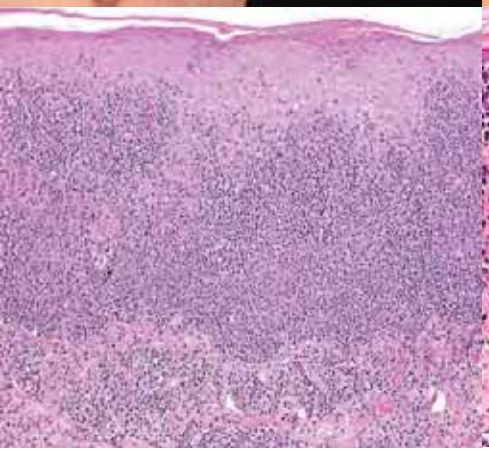


FIGURE 2. A, Hemotoxylin and eosin revealed abundant lymphocytic epidermotropism with occasional Pautrier microabscesses, an interstitial proliferation of lymphocytes, and papillary dermal fibrosis ×10. B, Epidermotropism with Pautrier microabscesses are easily seen in higher magnification ×40.

Prominent ("pagetoid") epidermotropism

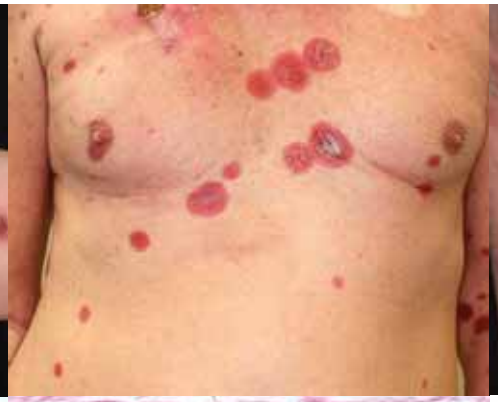
Aggressive T-cell lymphomas

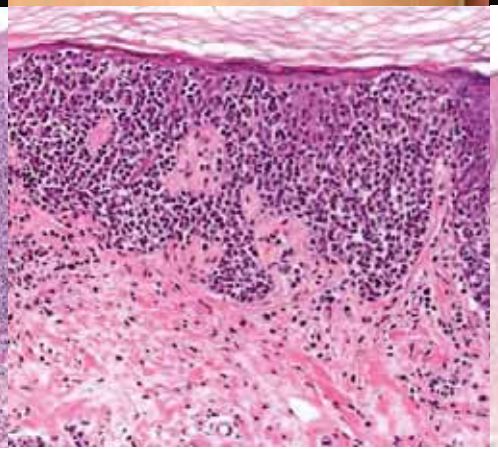




Aggressive epidermotr. CD8+ cytotoxic T-cell ly

Generalized, partly ulcerated plaques and tumors. CD8+ by definition; CD30 usually negative (Ddx from LyP type D); TCRß+ / TCRγ/δ–.

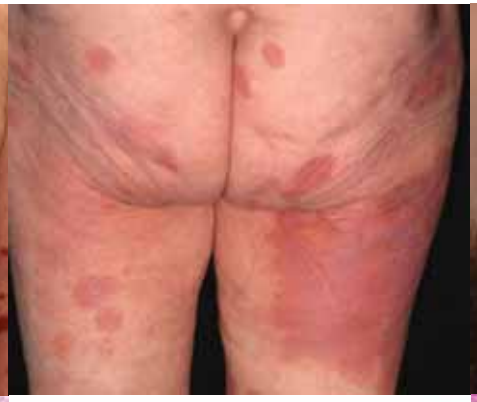


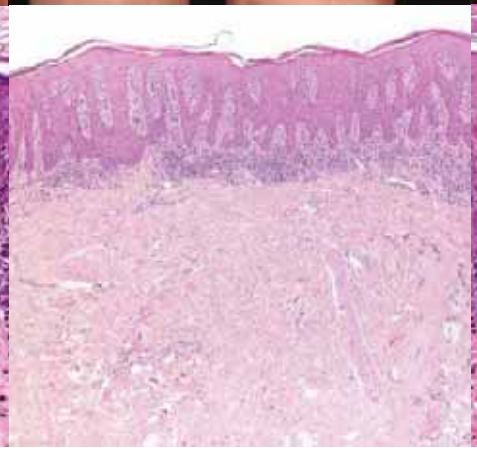


Cutaneous γ/δ T-cell lymphoma

Generalized, partly ulcerated plaques and tumors. TCRγ/δ cytotoxic phenotype pre-requisite for diagnosis; TCRß may be coexpressed. Angiocentricity, concomitant subcutaneous involvement; Haemophagocytosis.

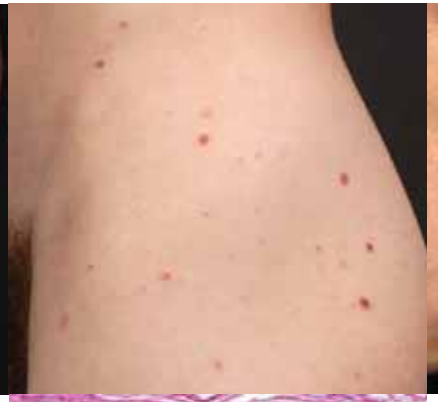
Indolent T-cell lymphomas

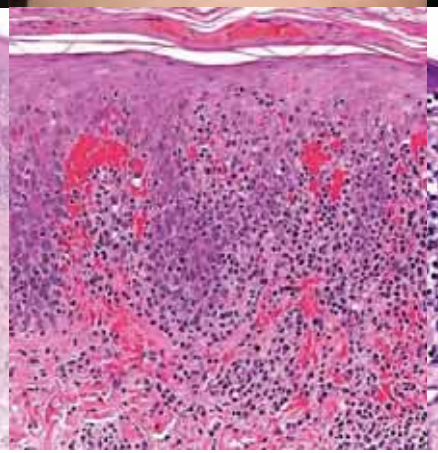




Mycosis fungoides

Conventional clinical presentation or features of solitary pagetoid reticulosis. Pagetoid epidermotropism mostly in cases with cytotoxic phenotype.

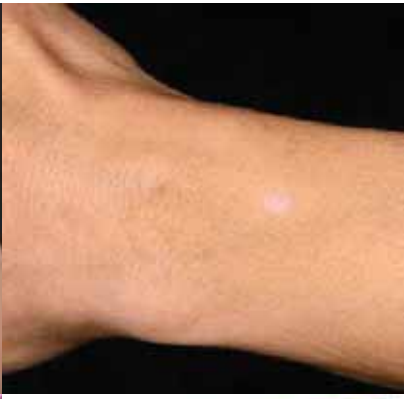


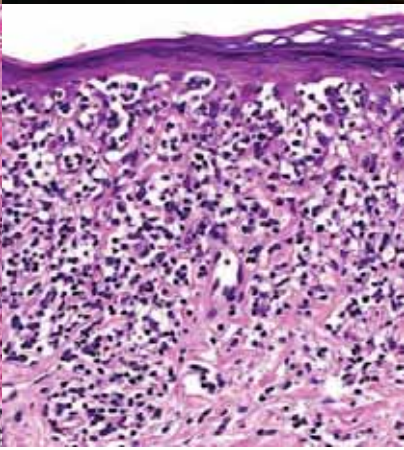


Lymphomatoid papulosis, type B or D

Waxing and waining papules and small nodules. Positivity for CD30 and CD4 (type B) or CD8 (type D) are a pre-requisite for the diagnosis; may be positive for TCRγ/δ .

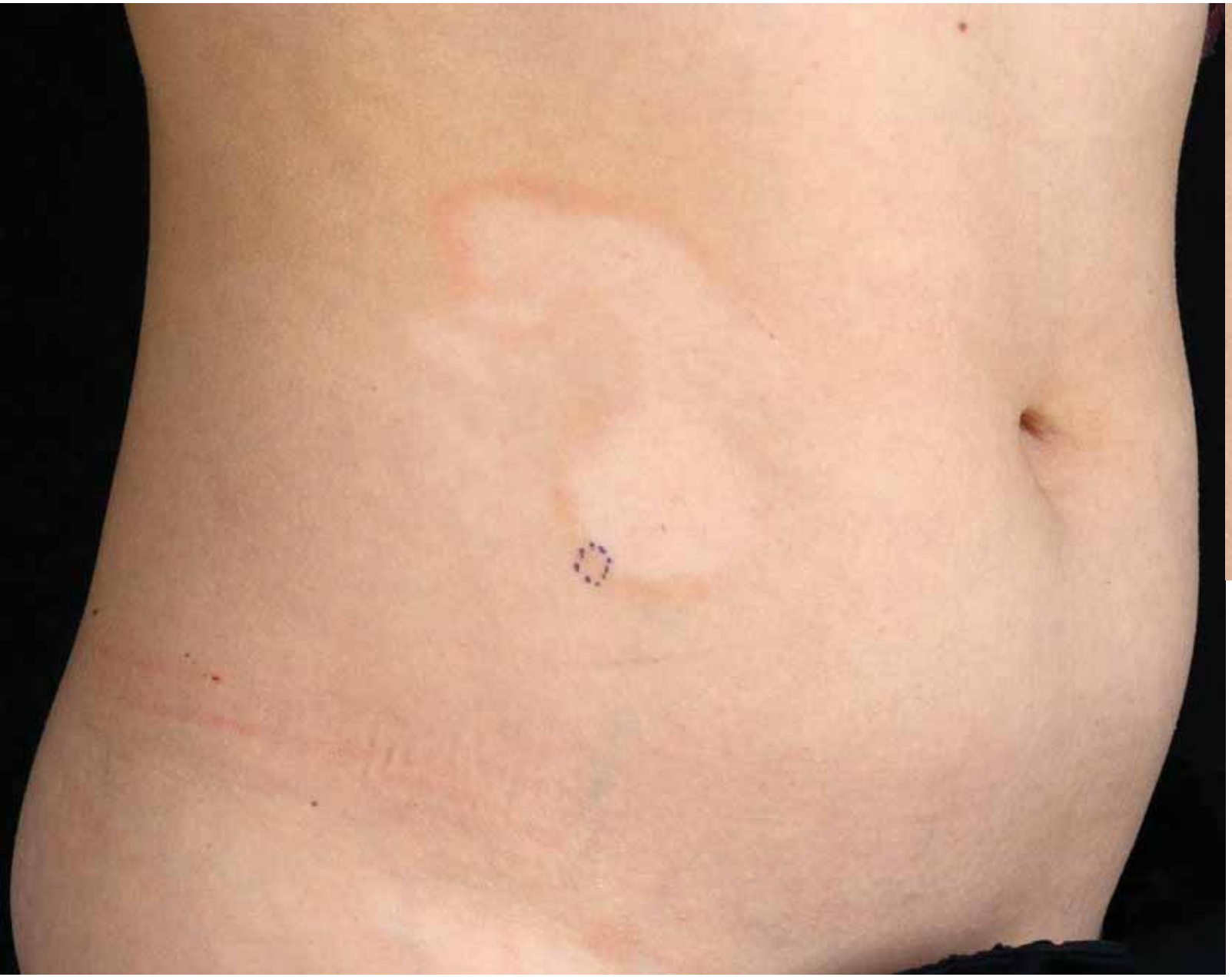
Pseudolymphomas

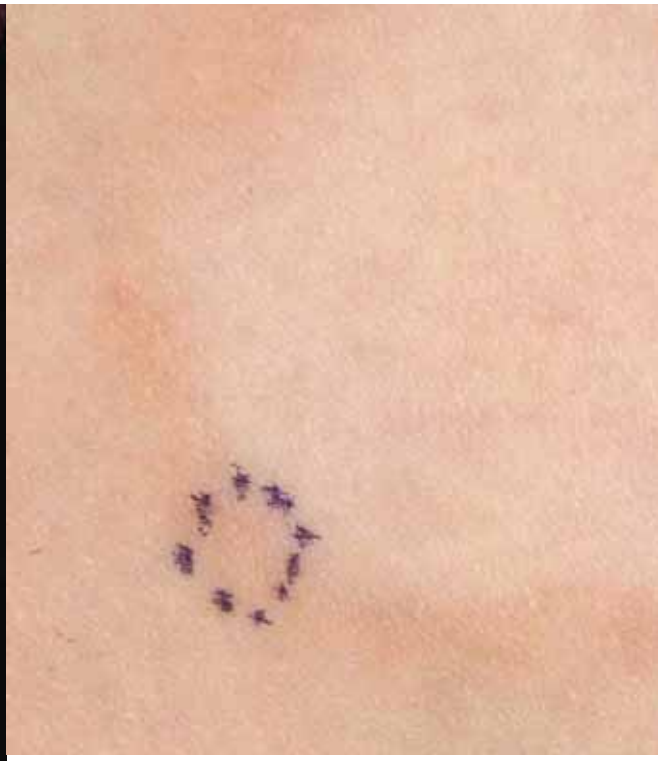




Exceedingly rare

Vitiligo.
Lymphomatoid contact dermatitis.
Lichen sclerosus.
Usually predominance of CD8+ T lymphocytes.

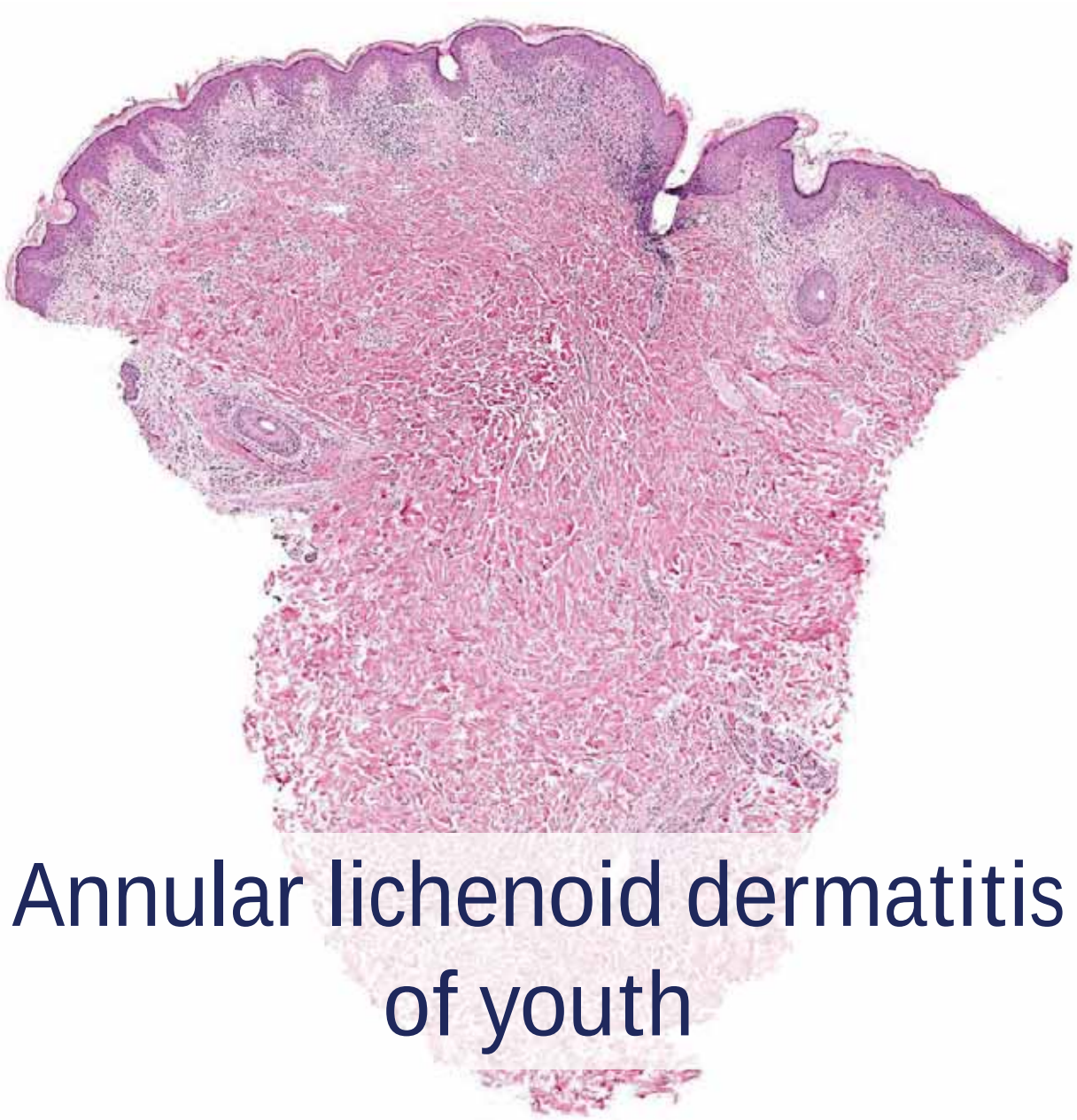


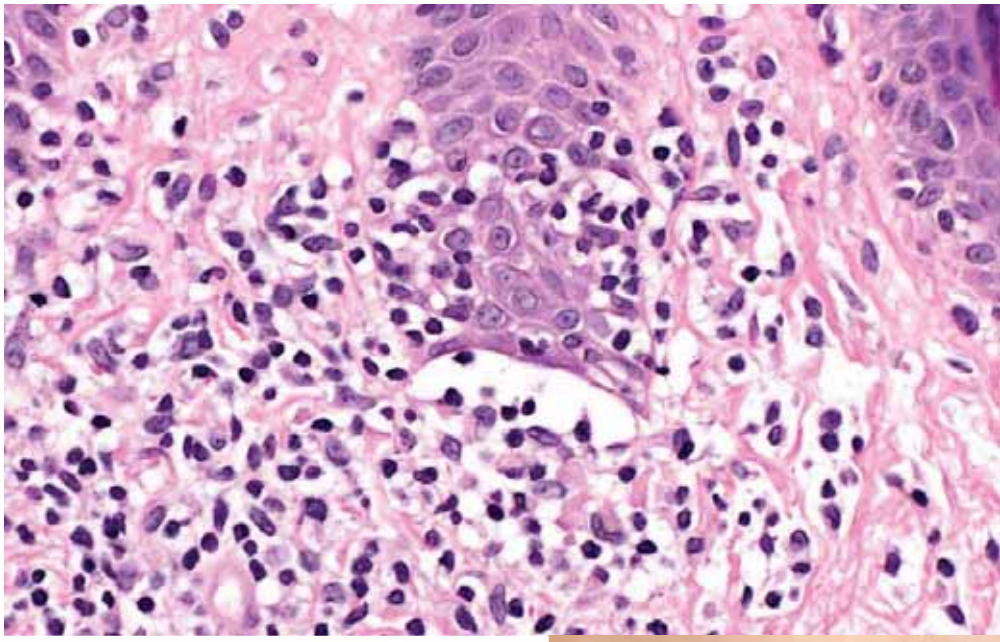


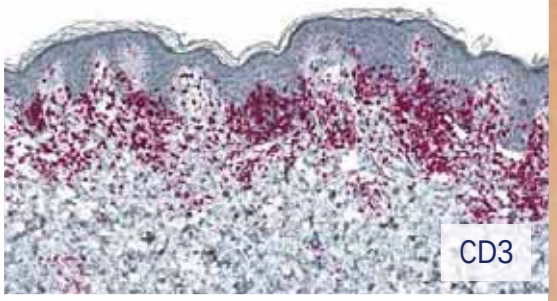
F, 10

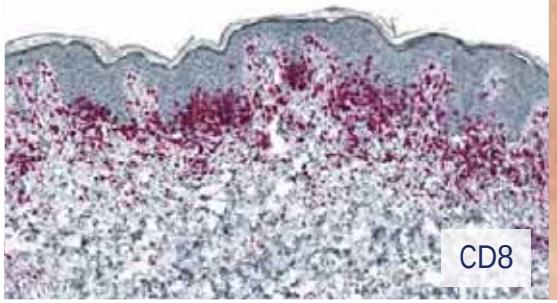
According to the mother asymptomatic skin lesion on the abdomen for 3 years. Improvement with local steroids, yet no complete clearance. Recent enlargement.

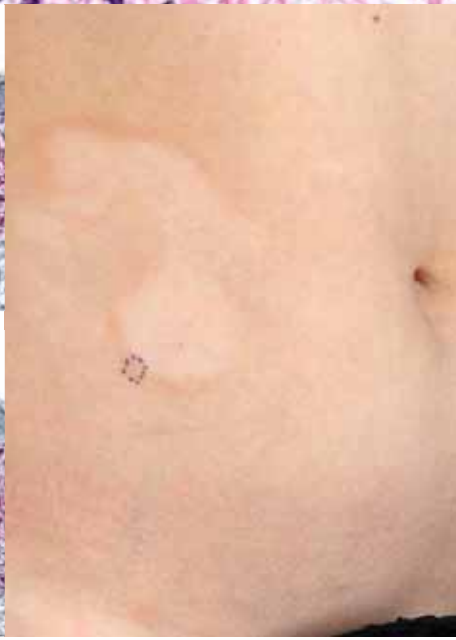
A biopsy is taken.











Annular lichenoid dermatitis of youth

Annular lichenoid dermatitis of youth

Giorgio Annessi, MD, Mauro Paradisi, MD, Corrado Angelo, MD, Marie Perez, PhD, Pietro Puddu, MD, and Giampiero Girolomoni, MD
Rome, Italy

Background: Lichenoid dermatoses are composed of a wide spectrum of disorders with a common histopathologic interface pattern but diverse causes and pathophysiology.

Objective: We describe a series of young patients with a peculiar annular lichenoid dermatitis, the clinical appearance of which initially suggested diagnoses of morphea, mycosis fungoides, or annular erythema.

Results: The study involved 23 patients (median age 10 years; age range 5-22 years). Lesions consisted of persistent asymptomatic erythematous macules and round annular patches with a red-brownish border and central hypopigmentation, mostly distributed on the groin and flanks. Histology revealed a peculiar lichenoid dermatitis with massive necrosis/apoptosis of the keratinocytes limited to the tips of rete ridges, in the absence of dermal sclerosis and epidermotropism of atypical lymphocytes. The infiltrate was composed mainly of memory $CD4^+$ $CD30^-$ T cells with few B cells and macrophages. Analysis of T-cell receptor-γ-chain gene rearrangement in skin biopsy specimens revealed polyclonality in all the 15 cases studied. Topical and systemic corticosteroids or phototherapy were effective in most patients with relapse after treatment withdrawal.

Conclusions: We suggest that this is a distinctive inflammatory condition, and we propose to term it "annular lichenoid dermatitis of youth." (J Am Acad Dermatol 2003;49:1029-36.)

Lichenoid dermatoses are composed of a wide spectrum of disorders characterized histologically by vacuolar alteration and necrotic/apoptotic keratinocytes in the basal layer of the epidermis together with a bandlike lymphohistiocytic infiltrate obscuring the dermoepidermal junction. These histologic changes are associated with disparate clinical lesions, including erythematous macules, flat-topped violaceous papules, papulovesicles, and plaques that can be arranged in linear or, more rarely, annular pattern.[1]

During the last 6 years we have observed a series of young patients with peculiar skin changes consisting of persistent erythematous macules and annular patches mostly localized on the groin and flanks. In all cases the clinical picture was suggestive of inflammatory morphea, patch-/plaque-stage mycosis fungoides, or annular erythema. However, all 3 of these diagnoses were excluded histologically with a distinctive superficial lichenoid dermatitis with massive necrosis/apoptosis of the keratinocytes situated at the tips of rete ridges.

In this study we describe the clinical, histologic, immunohistochemical, and molecular characteristics of this condition, which we have termed "annular lichenoid dermatitis of youth" (ALDY), and discuss the differential diagnosis with morphea, patch-/plaque-stage mycosis fungoides, and annular erythemas.

PATIENTS AND METHODS

Patient selection

We reviewed the history, clinical photographs, and histologic slides of 25 cases of ALDY, which have been seen during the last 6 years at our institution.

Histology and immunohistochemistry

From 23 patients, 32 biopsy specimens were collected for histologic study. In each case 2 hematoxylin and eosin sections were prepared. In all, 2 biopsy specimens from lesions at different stages of evolution were acquired from 6 patients; in another 5 patients, skin samples were obtained from both initial lesions and lesions recurring after 6 to 12

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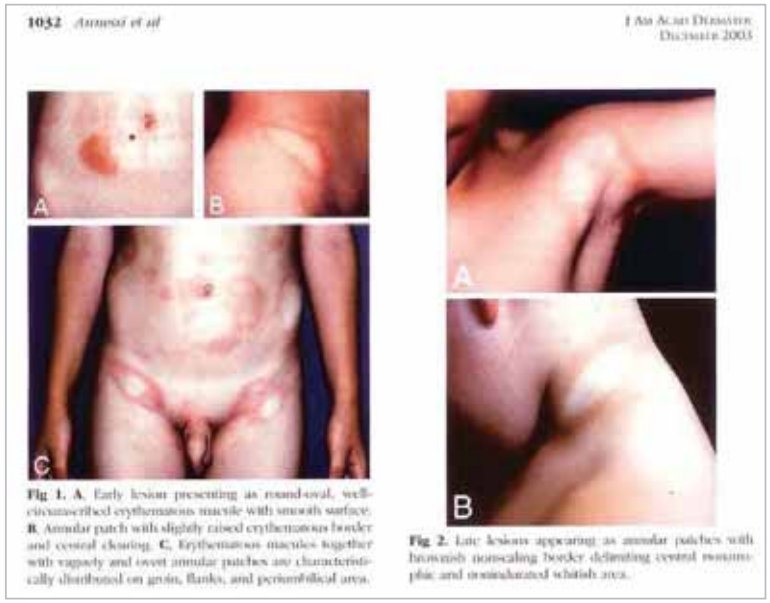
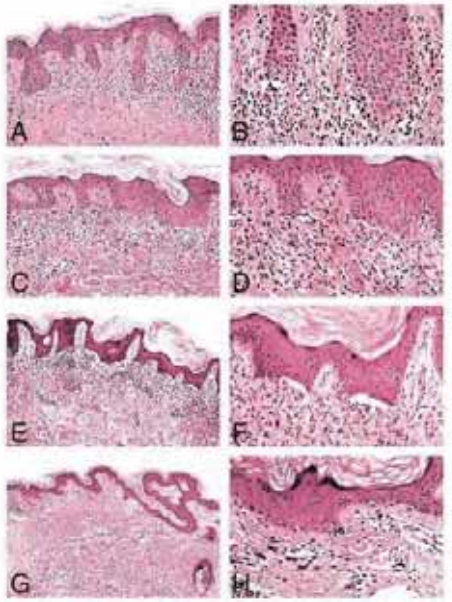


Fig 1. A. Early lesion presenting as round-oval, well-circumscribed erythematous macule with smooth surface. **B.** Annular patch with slightly raised erythematous border and central clearing. **C.** Erythematous macules together with vaguely and overt annular patches are characteristically distributed on groin, flanks, and periumbilical area.

Fig 2. Late lesions appearing as annular patches with brownish noncaling border delimiting central normochromic and noninducated whitish area.



- 23 patients (median age 10 years; age range 5-22 years)
- Characteristic clinical presentation resembling morphea or MF
- Histopathologic features mimic MF; necrosis of keratinocytes at tip of rete ridges ("squaring" of rete ridges) typical of ALDY
- Polyclonal pattern of TCR genes rearrangement
- Benign behaviour (yet few cases described, relatively short follow-up)
- Long-term follow-up advisable

Annular Lichenoid Dermatitis of Youth … and Beyond: A Series of 6 Cases

Anna Maria Cesinaro, MD, Pamela Sighinolfi, MD,* Antonietta Greco, MD,† Lorella Garagnani, BsPhD,* Andrea Conti, MD,† and Fabrizio Fantini, MD†*

Abstract: Annular lichenoid dermatitis of youth (ALDY) is a clinicopathologic entity described in children and young patients, clinically reminiscent of morphea, annular erythema, vitiligo or mycosis fungoides. We report on six patients presenting single or multiple lesions, distributed particularly on the flanks and abdomen, with clinical and histologic features consistent with ALDY. Two patients were young girls and four were adults males. Three patients received topical therapy and four showed complete resolution of the lesions after a 24–65 months follow-up. Analogously to the cases reported so far, immunohistochemistry showed a T cell infiltrate with a predominance of CD8+ lymphocytes, while T cell receptor rearrangement was absent in all cases. It seems appropriate to include annular lichenoid dermatitis of youth among the dermatoses with a lichenoid pattern. For the first time, we found that it can affect also adult patients, therefore we propose to rename the disease annular lichenoid dermatitis. The differential diagnosis with mycosis fungoides, especially in adult patients, is particularly crucial for their proper management and treatment.

Key Words: annular lichenoid dermatitis, age, histology, immunohistochemistry, molecular analysis

(*Am J Dermatopathol* 2009;31:263–267)

INTRODUCTION

Annular lichenoid dermatitis of youth (ALDY) is a clinicopathologic entity described in 2003 by Annessi et al[1] in children and young patients. It is characterized by clinical features suggesting inflammatory morphea, mycosis fungoides, vitiligo, or annular erythema, whereas histologically the main differential diagnosis includes mycosis fungoides, particularly the hypopigmented variant.

The differential diagnosis in most cases is not difficult. Clinically, morphea is characterized by indurated plaques and histologically by thickened collagen fascicles and lymphoplasmacytic perivascular inflammatory infiltrate.[2] Classic erythema annulare presents as lesions with scaling erythematous borders, whereas histologically it shows foci of parakeratosis and a superficial or superficial and deep perivascular lymphocytic infiltrate.[3] Vitiligo can present as inflammatory lesions mimicking ALDY both clinically and histologically,[1] but unlike to vitiligo, no loss of melanocytes leading to permanent depigmentation has been observed in ALDY.[1,4] The main problem is the differential diagnosis between ALDY and mycosis fungoides, although histopathology, immunohistochemistry, and molecular analysis seemed to be able to differentiate the 2 diseases.[5]

Few more cases have been reported so far, always in young patients.[4–7] We describe herein 6 patients with clinicopathologic features consistent with ALDY. For the first time, we found that the disease can develop also in adulthood; the differential diagnosis with mycosis fungoides in these patients is particularly crucial for their proper management and treatment.

MATERIALS AND METHODS

Patients

The cases were collected in a 6-year period, from 2003 throughout 2008. Two patients were young girls, aged 10 and 12 years, and 4 were adult males, age ranging from 33 to 45 years. Lesions consisted of asymptomatic rounded or oval patches, developed by initial erythematous macules with peripheral spreading. Most lesions showed the characteristic annular shape, with a raised erythematous border and a hypopigmented center. In 2 patients, only 1 lesion was present, whereas 4 patients had multiple lesions. In 5 patients, the lesions developed on the trunk, particularly on the flanks and the abdomen; in the last patient, the lesions were localized on the trunk, axillary regions, groin, and neck (Figs. 1A–C). The duration of the lesions before the biopsy ranged between 1 and 15 months. The clinical diagnosis included "eczema," morphea, mycosis fungoides, granuloma annulare, and vitiligo. The patients were otherwise healthy. Testing for autoimmunity, infections, and allergy and collection of relevant clinical information about their families disclosed no putative etiologic factors. Patient 5 revealed an atopic condition, whereas patient 1 had a sister suffering from atopy. A 1 or 2-month course of topical therapy was given to 3 patients (2 patients with corticosteroids and 1 patient with tacrolimus), whereas the others did not receive any therapy. No remission of the lesions was observed during and after therapy. Spontaneous resolution was observed at follow-up in 4 of 6 patients after 24–65 months (Fig. 1D). Clinical data are

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TABLE 1. Clinical Features in 6 Cases of Annular Lichenoid Dermatitis

Case No./Sex	Age at Onset (yrs)	Site	No. Lesions	Type of Lesions	Therapy	Follow-up
1/F	12	Left flank	1	Annular erythematous plaque with central hypopigmentation	None	NED after 65 mo
2/M	34	Abdomen, thorax	Multiple symmetric	Erythematous annular plaques	Topical corticosteroid	NED after 46 mo
3/M	33	Right flank	1	Ovalar brownish plaque with erythematous border	Topical corticosteroid	NED after 48 mo
4/M	39	Abdomen	Multiple	Ovalar desquamative pigmented plaques	None	Lost at FU
5/M	45	Flanks	3	Rounded erythematous plaques	Topical tacrolimus	NED after 24 mo
6/F	10	Abdomen, flanks, groin, neck, axillary region	Multiple	Annular erythematous plaques with central hypopigmentation	None	Recent case

F, female; M, male; NED, no evidence of disease; FU, follow-up.

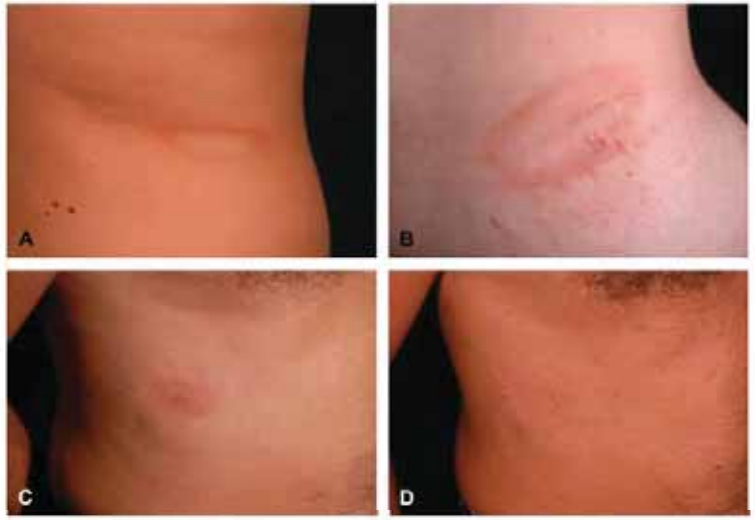


FIGURE 1. Clinical presentation in case 6 (A), case 1 (B), and case 5 (C). D, Complete resolution in patient 5 at the 24-month follow-up.

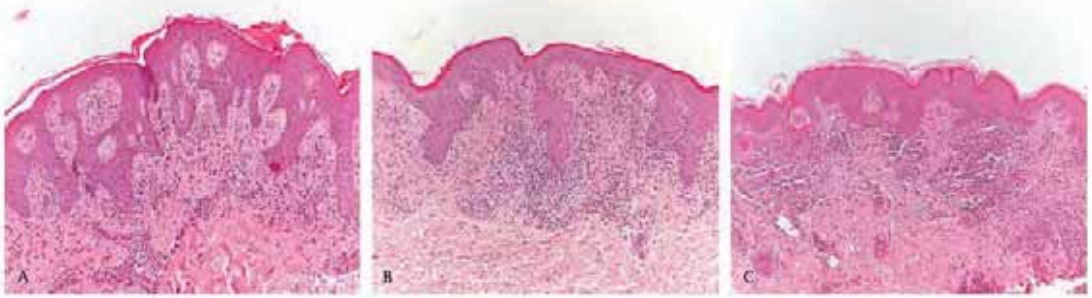
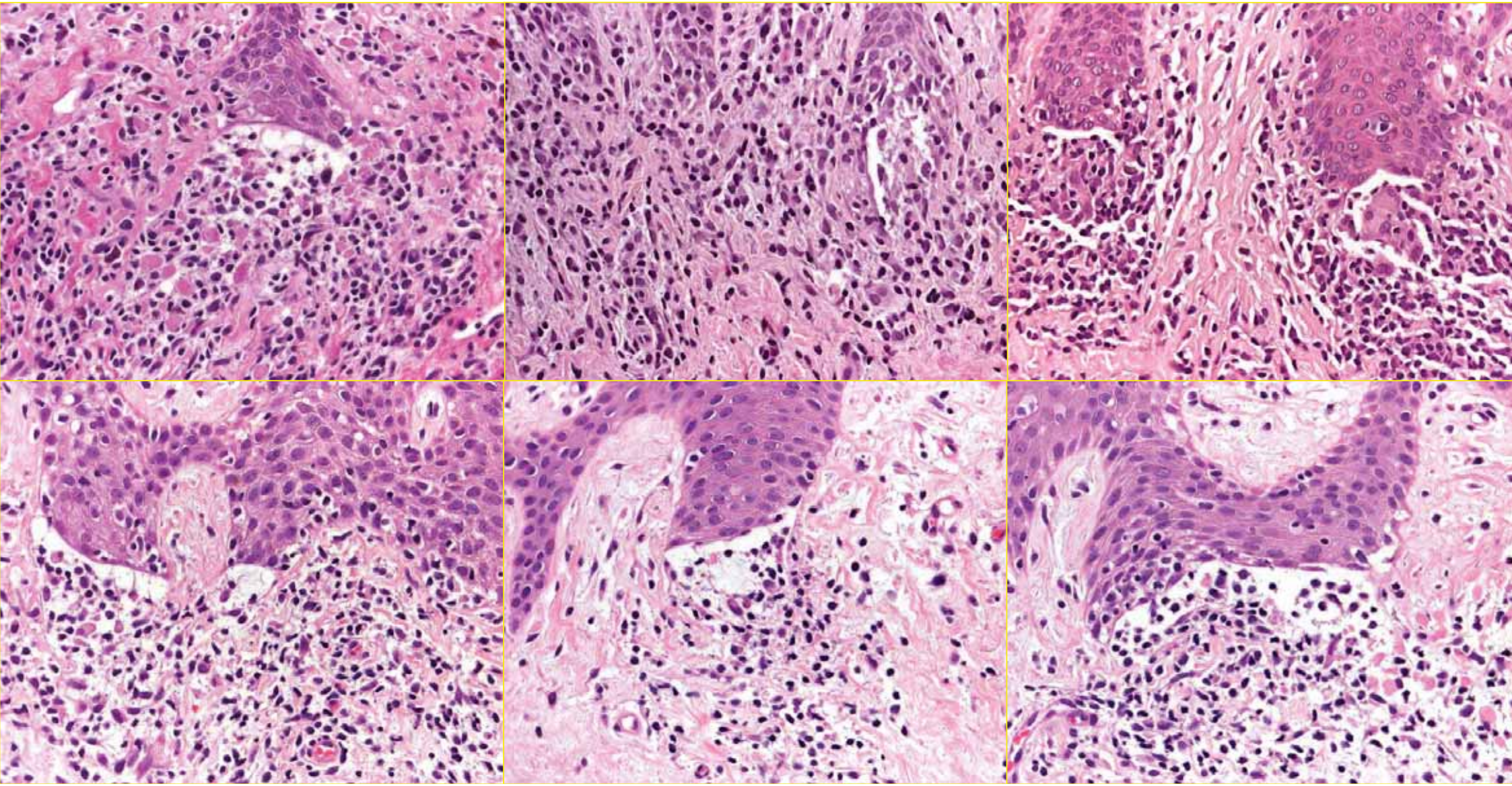


FIGURE 2. Lichenoid lymphocytic infiltrate with basal vacuolization in case 3 (A), case 5 (B), and case 1 (C) (hematoxylin and eosin, ×100).

Clue: "squaring" of tip of rete ridges by lymphoid infiltrate



Annular Lichenoid Dermatitis (of Youth) Immunohistochemical and Serological Evidence for Another Clinical Presentation of Borrelia Infection in Patients of Western Austria

Michael Wilk, MD, Bettina G. Zelger, MD,† Michael Emberger, MD,‡ and Bernhard Zelger, MD, MSc§*

Abstract: Annular lichenoid dermatitis of youth (ALDY) is a most recently described inflammatory disease of the skin of unknown etiology with clinical similarities to morphea. The authors clinically, histopathologically, and immunohistochemically investigated 14 biopsies from 12 patients in western Austria with this disease. There were 6 female and 6 male patients with solitary (n = 7) and multiple lesions (n = 5) affecting the trunk (n = 11), upper arm (n = 2), thigh (n = 1), and calf (n = 1). Clinically, early lesions were erythematous in nature leading to central paleness, scaling, wrinkling, dermal atrophy, slight pigmentation, and telangiectasia later on. Histopathologically, all specimens showed the typical features of ALDY with a superficial lichenoid process with sprinkling of lymphocytes along the basal cell layer and within the epidermis accompanied by mild fibrosis. Pigment incontinence, superficial fibrosis, and dilatation of superficial capillary vessels are prominent features in more advanced stages of disease. Immunohistologically, using a polyclonal antibody against *Borrelia*, 11/14 specimens revealed spirochetes, either vital (n = 4) or degenerated (n = 7), in close proximity to collagen bundles. Thirteen of 14 specimens in addition showed focal (n = 4) or clustered (n = 9) positivity for CD20 in the papillary dermis. Nine of 12 sera tested for *Borrelia* with an enzyme-linked immunosorbent assay were positive. Lichen sclerosus et atrophicus and morphea have previously been reported to be possibly related to *Borrelia* infection. We postulate that a similar relationship to *Borrelia* infection may be true for ALDY implying that ALDY may be an early superficial stage of morphea.

Key Words: annular lichenoid dermatitis, ALDY, morphea, lichen sclerosus et atrophicus, dermatopathology

(*Am J Dermatopathol* 2017;39:177–180)

INTRODUCTION

Annular lichenoid dermatitis of youth (ALDY) belongs to the more recently described inflammatory dermatoses of the skin only published in 2003 by Annesi et al[1] in a series of 23 patients. Since then, also older patients have been reported to suffer from this disease.[2,3] Both sexes are equally affected. Clinically, patients present with round to oval, often annular patches with a characteristic erythematous border, and a hypopigmented center mainly involving the groin and trunk. The patches may be solitary or multiple, gradually enlarge in a centrifugal growth pattern, and typically are persistent. The etiology of the disease is still obscure.

In recent years, the spectrum of clinical manifestations of *Borrelia* infection has expanded considerably. With the advent of immunohistochemistry and molecular genetic methods, diseases such as granuloma anulare, necrobiosis lipoidica, morphea,[4] lichen sclerosus et atrophicus,[5] and even necrobiotic xanthogranuloma[6] have been reported to be possibly in part caused by *Borrelia*. In this regard, the immunohistological investigation of tissue of morphea and lichen sclerosus using focus floating microscopy (FFM) has been found to be more sensitive than the use of polymerase chain reaction. Positive results with FFM were especially observed in inflammatory morphea and early lichen sclerosus et atrophicus.[4,5]

To investigate the nature of ALDY, biopsies from patients with this disease have been investigated histopathologically and immunohistochemically for *Borrelia* using FFM supplemented by blood investigation for *Borrelia* antibodies.

MATERIALS AND METHODS

A total of 14 biopsies from 12 patients of western Austria with the typical clinical presentation of ALDY have been investigated histologically and immunohistochemically. Four μm thick sections were cut and stained with hematoxylin and eosin, periodic acid-Schiff (PAS), elastic stain, as well as immunohistologically with a Ventana autostainer (Tucson, AZ) and a polyclonal antibody against *Borrelia*/*Borrelia*-like organisms (Quartett immunodiagnostics, Berlin, Germany) as described previously.[7] In addition, sections were investigated for CD20-positive lymphocytes (L26, Dako, Glostrup, Denmark). Two specimens (case no. 2 and 8) were seen in consultation (see acknowledgment). In addition, blood samples were investigated for antibodies against *Borrelia* using an enzyme-linked immunosorbent assay.

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The authors declare no conflicts of interest.

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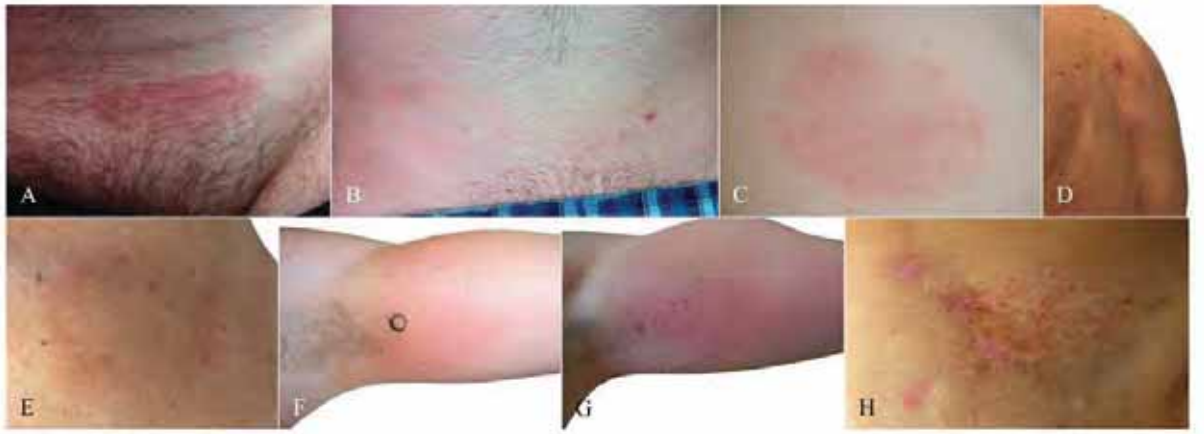
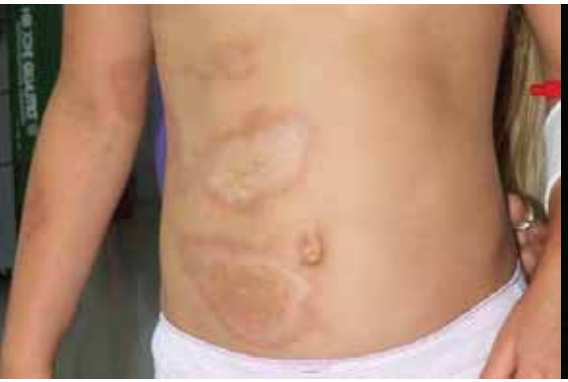


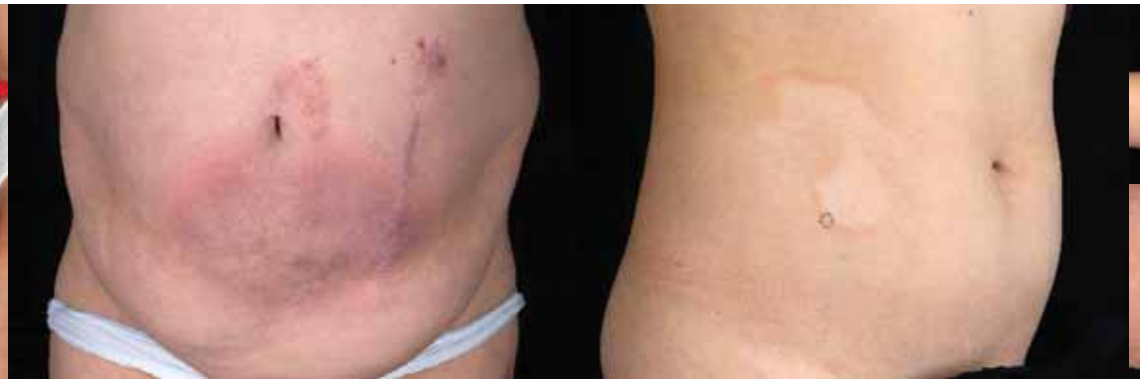
FIGURE 1. A–H, Early erythematous lesion on the left lower abdomen close to pubic area, later on enlarged and multifocal with a pale center resembling erythema migrans. Left laterally, there is a small scar after biopsy (A, B; case no. 2). More advanced lesions may additionally reveal slight scaling, wrinkling, and brownish pigmentation (C; case no. 3). Multifocal erythematous lesions in this case present with central paleness, atrophy, and wrinkling. There is a small scar after biopsy at the upper part of the back (D, E; case no. 11). Erythema and wrinkling are present on this patient's left armpit leading to atrophy, prominent wrinkling, and telangiectasia later on. The biopsy site is marked in black (F, G; case no. 1). Telangiectasia, atrophy, and fibrosis resembling chronic irradiation dermatitis may be the predominant clinical feature in very old lesions (H; case no. 5).

To my eyes, not a single one among these 12 cases is a true ALDY
"Positive *Borrelia* serology" not specified (IgG+ alone not diagnostic)
PCR for *Borrelia* on tissue not tested
"Floating" microscopy a completely useless technique (my opinion)

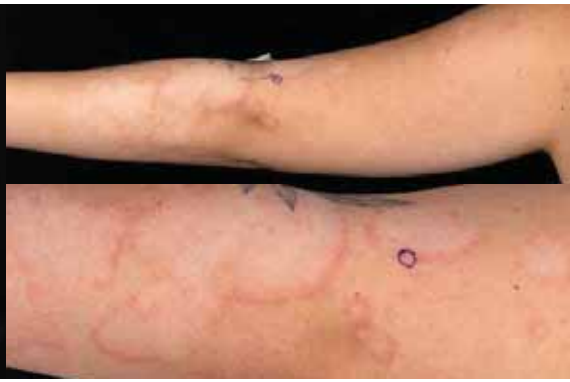
Genuine ALDY has nothing to do with *Borrelia* (my opinion)



Scleroderma

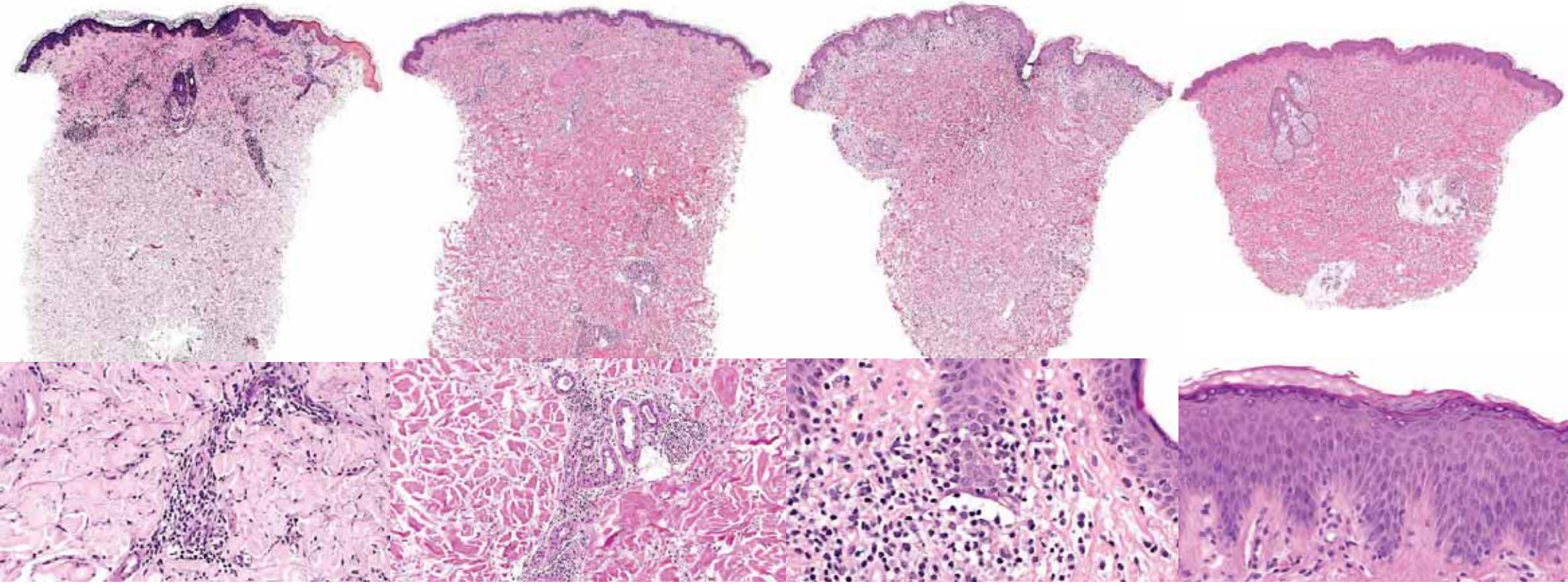


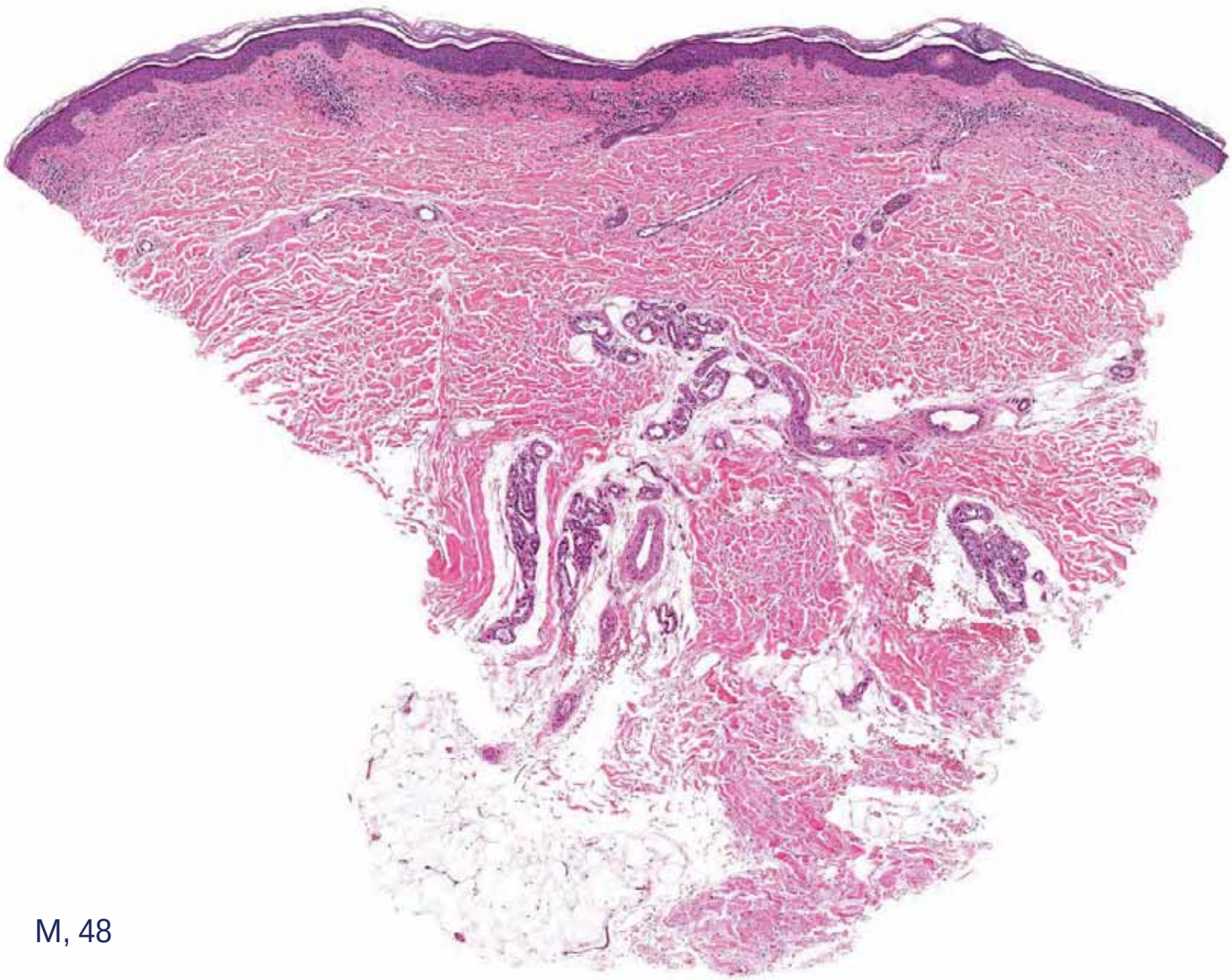
Erythema chronicum migrans

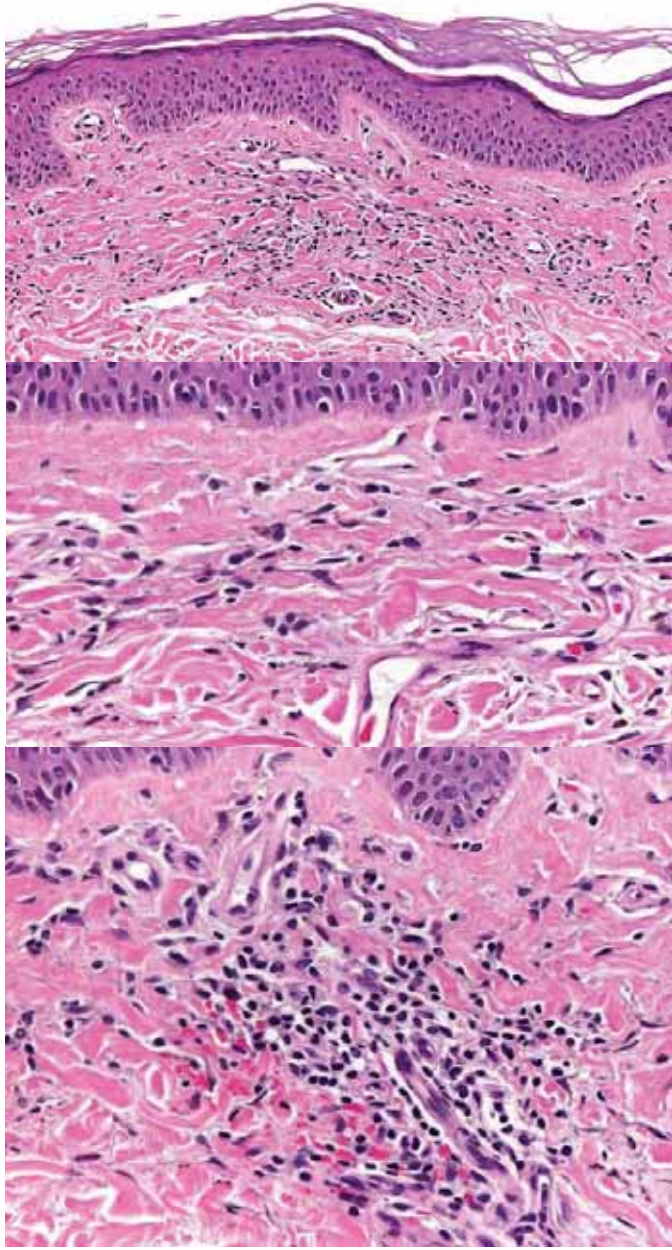


Annular lichenoid dermatitis of youth

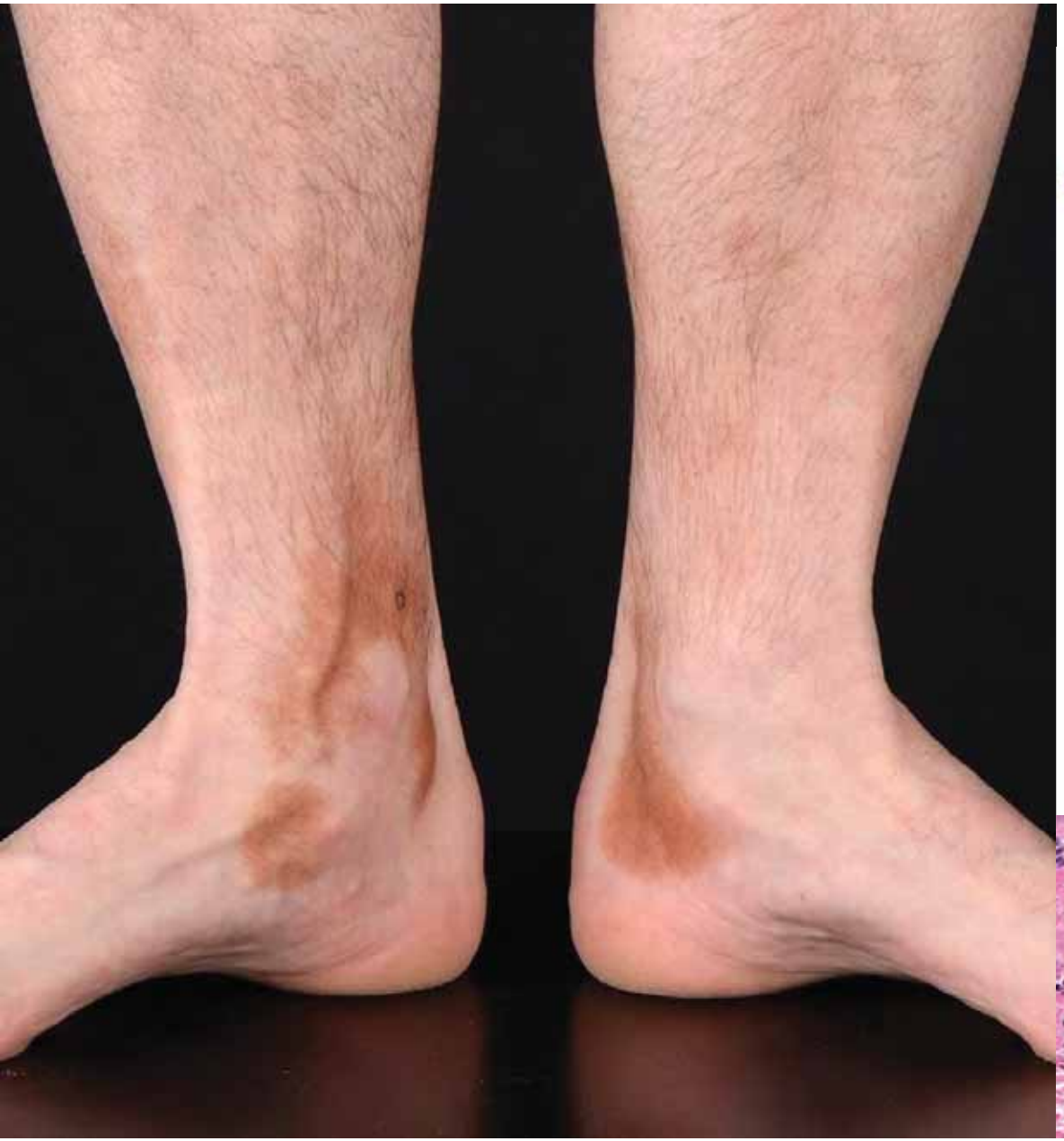
Atopic dermatitis with hypopigmentation

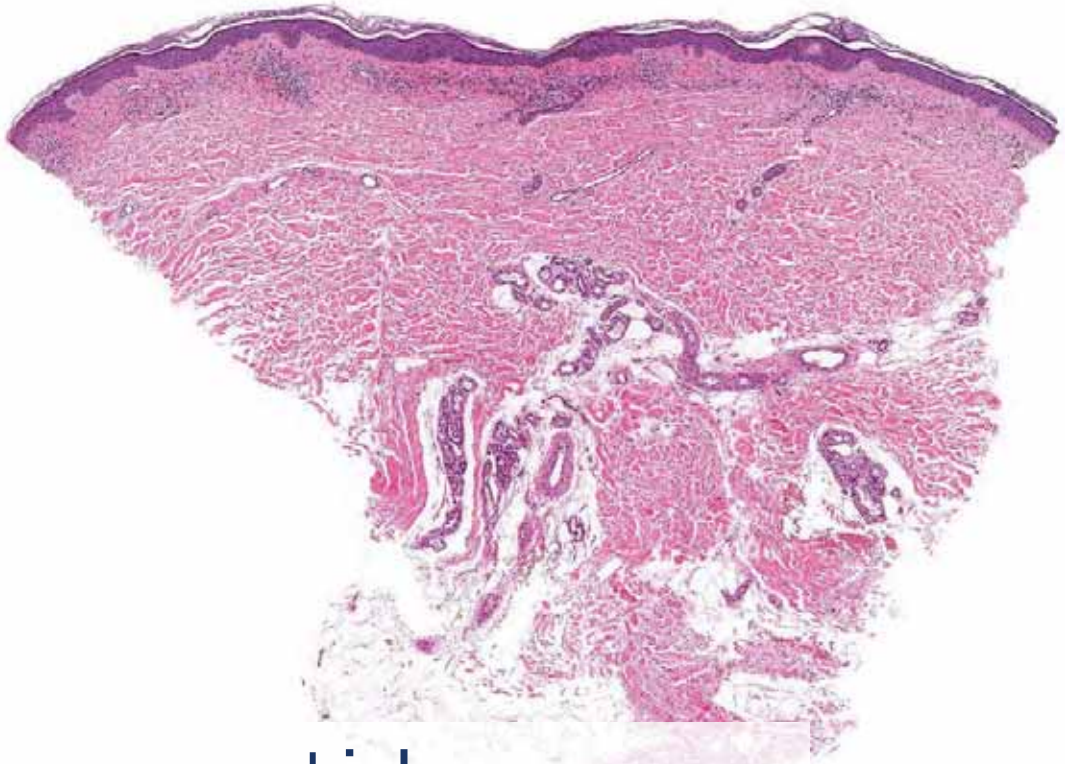




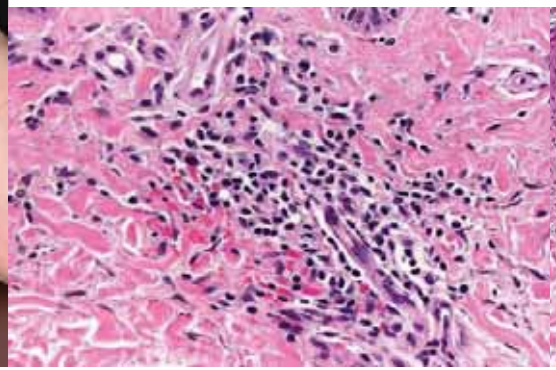


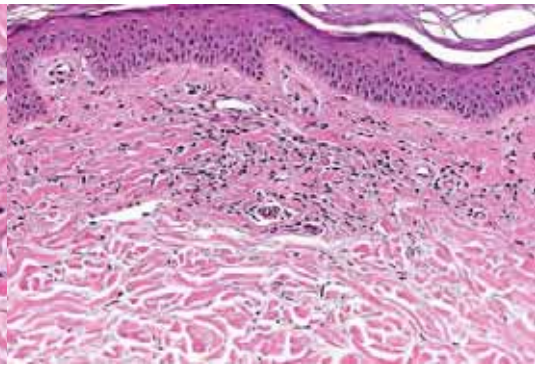
M, 48

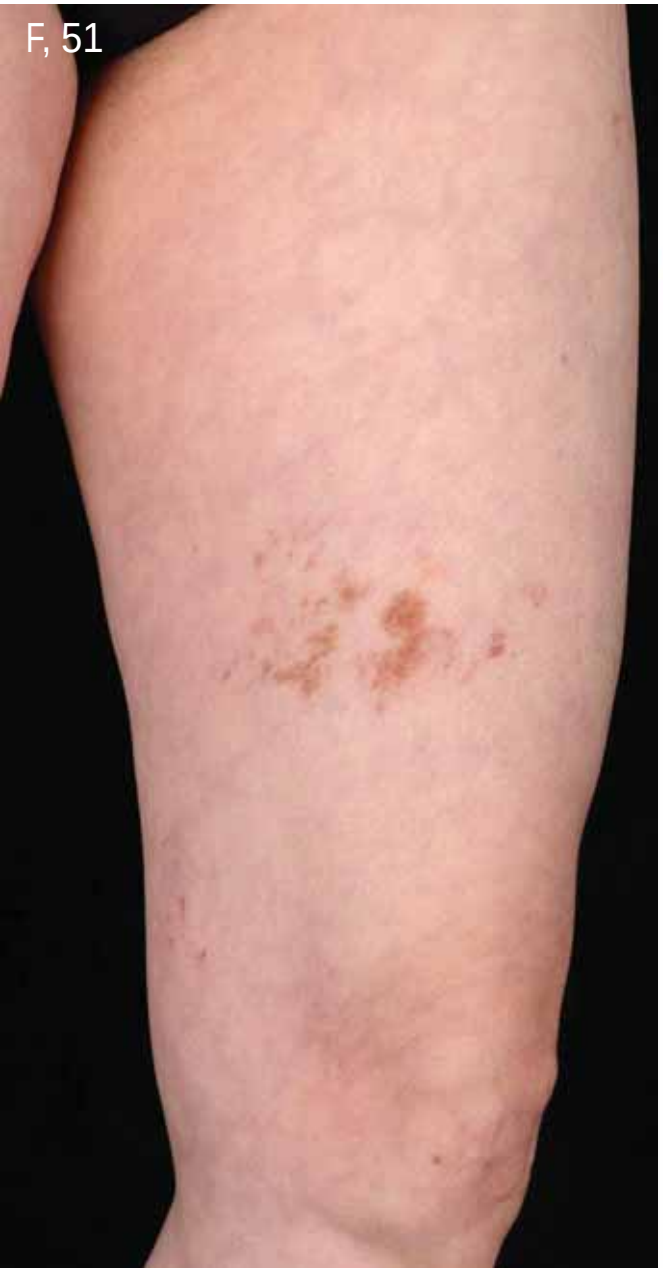


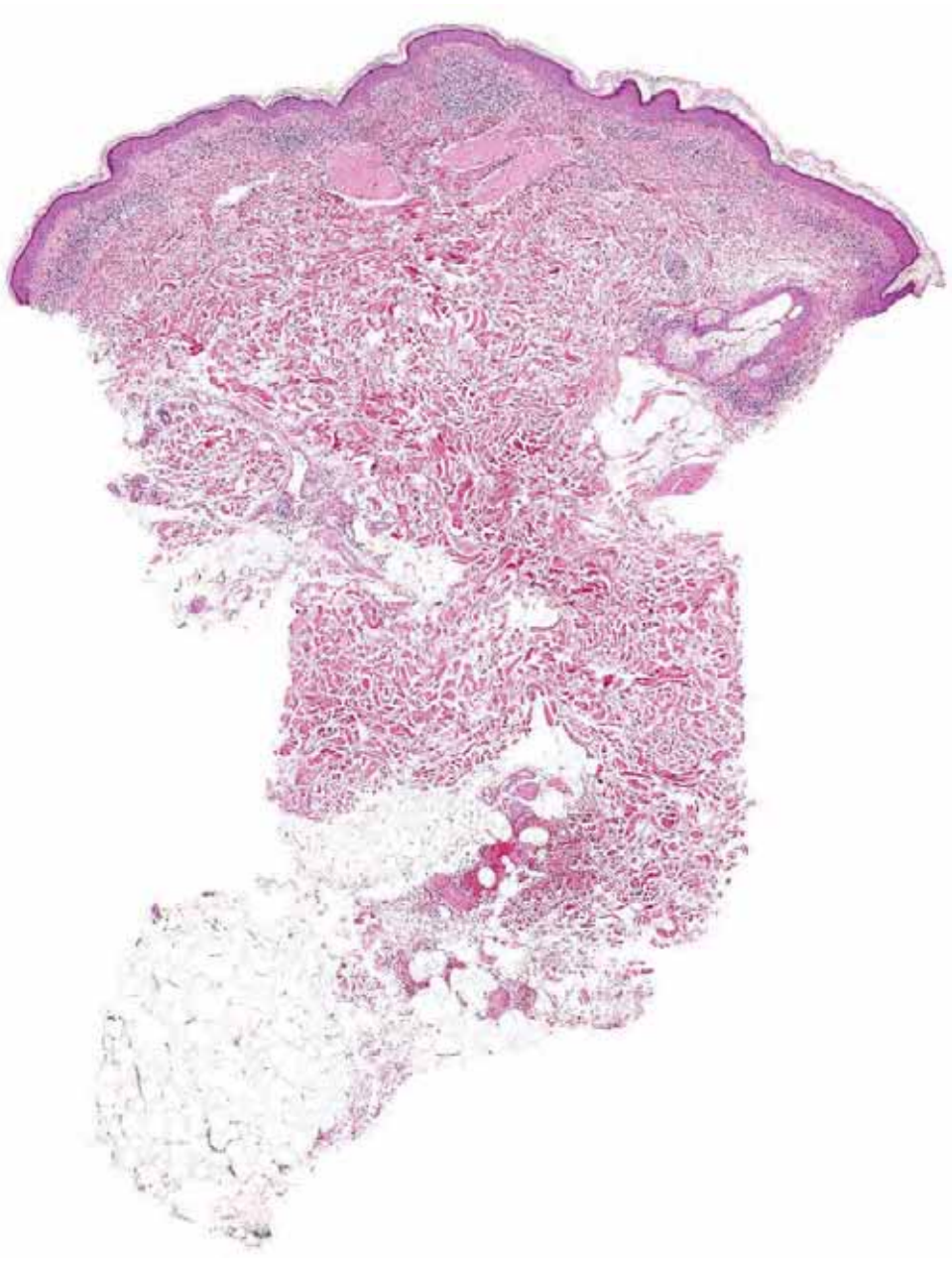


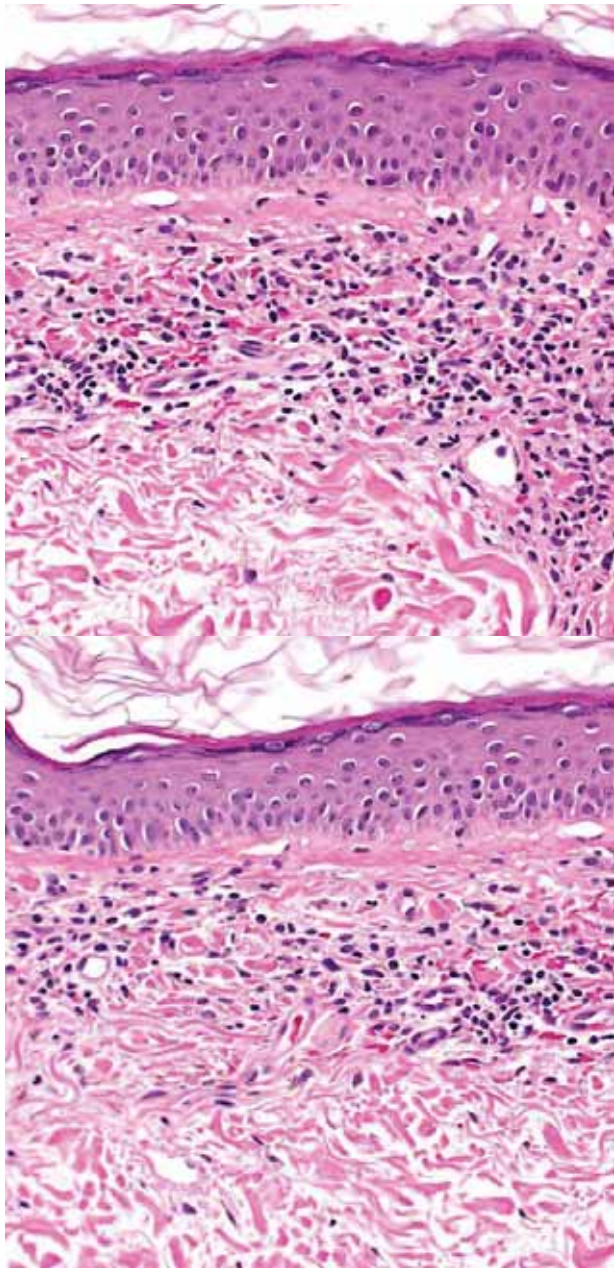
Lichen aureus

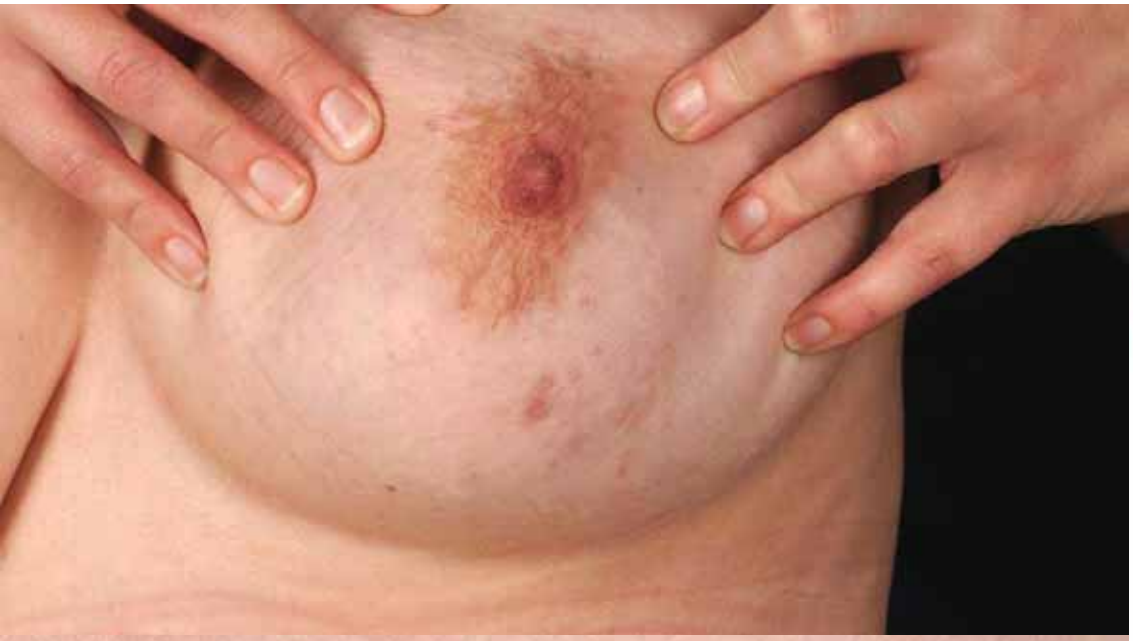


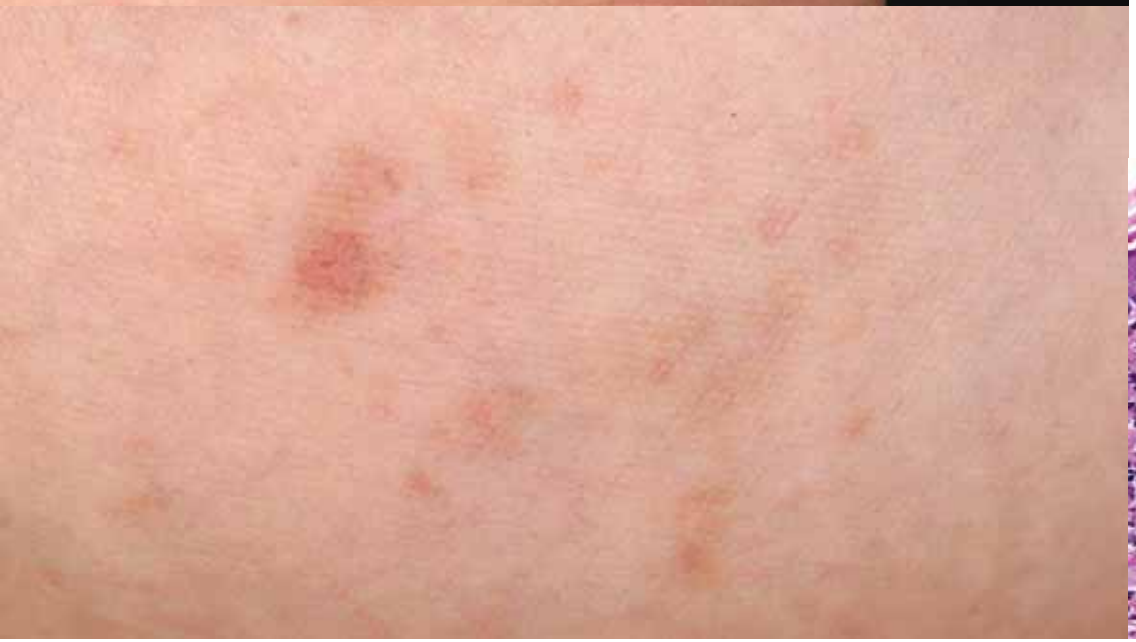



F, 51

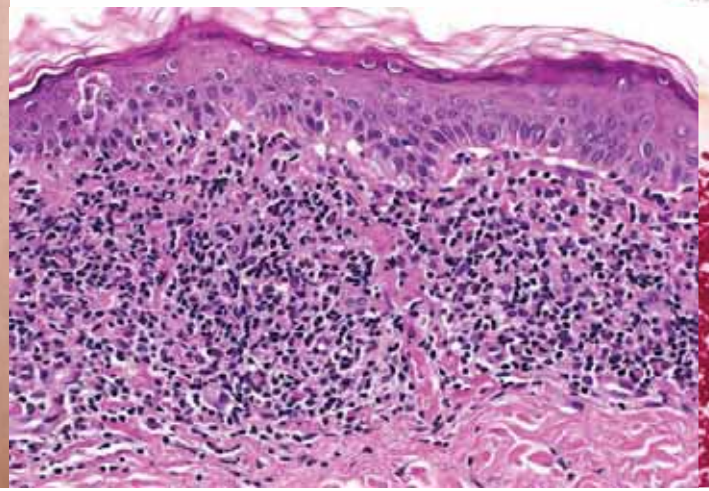


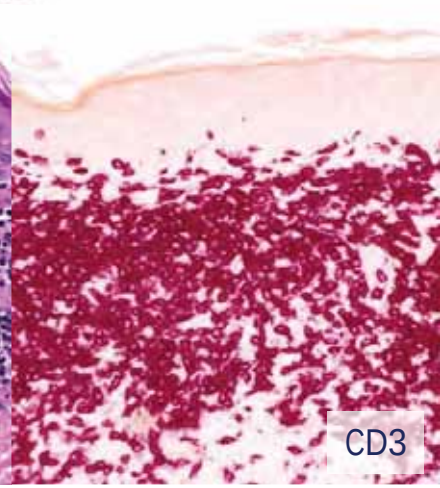






Same patient,
11 years previously





CD3

Lichen Aureus

- Persistent, localized form of "pigmented purpuric dermatitis"
- Spontaneous resolution observed in >50% of cases; in some case lesions persist unchanged for years, or recur at the same or at different sites
- T-cell monoclonality in ~50% of cases
- No relationship between treatment / clonality and outcome
- Probably represents one of so-called "clonal dermatoses" – follow-up advisable

The American Journal of Dermatopathology 1992; 108–118, 1997

Persistent Pigmented Purpuric Dermatitis and Mycosis Fungoides: Simulant, Precursor, or Both?

A Study by Light Microscopy and Molecular Methods

Jorge R. Toro, M.D., Christian A. Sander, M.D., and Philip E. LeBoit, M.D.

Mycosis fungoides (MF) can present with purpuric lesions, and rare patients who seemed to have persistent pigmented purpuric dermatitis (PPPD) have developed MF. We recently encountered two patients referred to our cutaneous lymphoma clinic who had PPPD rather than MF and two others who appeared to have both conditions, leading us to explore the histologic similarities of these diseases. We examined specimens from 56 patients with PPPD to determine the frequency of MF-like histologic configurations, namely, the psoriasiform lichenoid, psoriasiform spongiotic lichenoid, and atrophic lichenoid patterns. We also noted the degree of spongiosis, epidermotropism, papillary dermal fibrosis, lymphocytic atypia, and epidermal hyperplasia, the number of extravasated erythrocytes and siderophages, and the distribution of lymphocytic infiltrate within the epidermis. In 29 of 56 patients, there were patterns typically seen in MF. PPPD can feature lymphocytes aligned along the epidermal side of the dermoepidermal junction, with few necrotic keratinocytes, as can MF. Papillary dermal edema occurred frequently in PPPD but not in MF, while lymphocytes in MF but not PPPD had markedly atypical nuclei and had ascended into the upper spinous layer. Given these similarities, we tested for clonality of the T-cell population using a polymerase chain reaction assay for γ-chain rearrangements. Clonal populations were present in three of three and one of two specimens from patients with both PPPD and MF, but also in 8 of 12 specimens typical of lichenoid patterns of PPPD. These findings raise the possibility that the lichenoid variants of PPPD are biologically related to MF.

Key Words: Mycosis fungoides—Persistent pigmented purpuric dermatitis—T-cell gene rearrangements—Lichenoid purpura—Schamberg's disease—Cutaneous T-cell lymphoma.

The many clinical and histological features of mycosis fungoides (MF) are more than curiosities because MF is one of the most common non-Hodgkin's lymphomas. The profusion of variants may be due to the admixture of non-neoplastic inflammatory cells in many lesions of MF and the skin's large repertoire of reaction patterns (1). Among the variants of MF is one in which purpuric areas develop within lesional skin (2–4).

Several considerations led us to examine the relationship between MF and the group of conditions known as persistent pigmented purpuric dermatitis (PPPD). Purpuric lesions can occur in MF. The first patient reported in the American literature as having lichen aureus (5) later proved to have MF (6). The diagnosis of several patients referred to our cutaneous lymphoma clinic was changed from MF to PPPD following review of sections from their skin biopsies. Last, we have seen two patients with both conditions; in one, PPPD preceded MF. We therefore examined sections from a large group of cases of PPPD to determine how often MF-like patterns of lymphocytic infiltration were present and ascertained the degree to which other features characteristic of MF, such as papillary dermal fibrosis and lymphocytes aligned along the epidermal side of the dermoepidermal junction, were present. Upon determining that MF-like histopathologic features were common in PPPD, we used the polymerase chain reaction (PCR) to test for clonal rearrangement of the T-cell receptor γ-chain gene.

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Dr. Toro was a fellow in the Department of Dermatology at the University of California, San Francisco, California, U.S.A., at the time this study was performed. He is currently a resident in the Division of Dermatology at Southern Illinois State University School of Medicine in Springfield, Illinois, U.S.A.

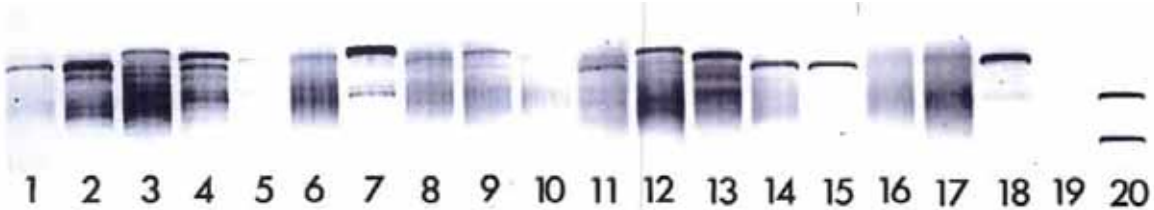
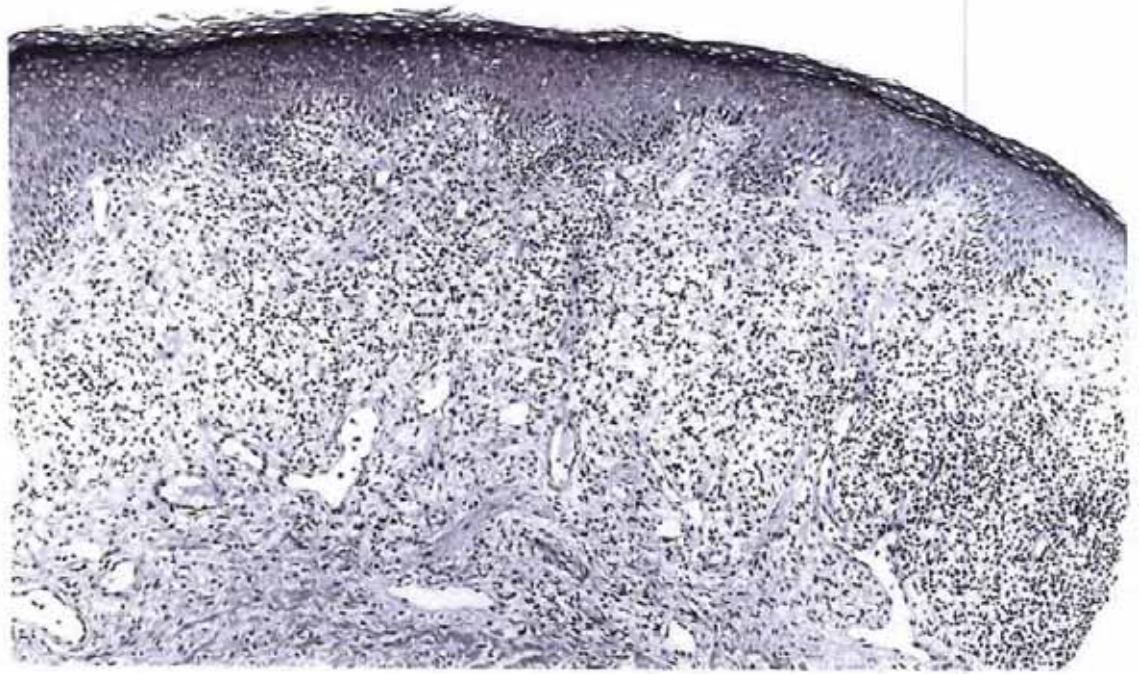


FIG. 6. Results of PCR reaction for T-cell γ-chain gene rearrangement using the Vγ10 probe. Positive control is in lane 18, negative control lane 19, and molecular standards lane 20. Bands signifying rearrangements are present in lanes 1,2,4,7, and 12–15. Smears or faint bands are present in the remaining lanes.



ORIGINAL OBSERVATION

Lichen Aureus

Clinicopathologic Features, Natural History, and Relationship to Mycosis Fungoides

Regina Fink-Puches, MD; Peter Wolf, MD; Helmut Kerl, MD; Lorenzo Cerroni, MD

Background: A possible association between lichen aureus (LA) and mycosis fungoides (MF) has been suggested in the past. We evaluated the clinicopathologic features of LA and its relationship to MF. Data from 23 patients with a clinicopathologic diagnosis of LA were reviewed.

Observations: Lesions were asymmetrically localized on 1 area of the body (mostly 1 extremity) and were characterized histologically by dense, bandlike lymphocytic infiltrates. A monoclonal T-cell population was detected in half of the cases. After a mean follow-up of 102.1 months, 14 patients had no signs of skin disease, 7 patients had unmodified skin lesions, and 2 other patients with unmodified skin lesions had died of unrelated conditions. Treatment modalities did not affect the outcome. There was no relationship between the presence or absence of monoclonality and patient status at follow-up assessment.

Conclusion: Patients with classic lesions of LA do not show progression to MF.

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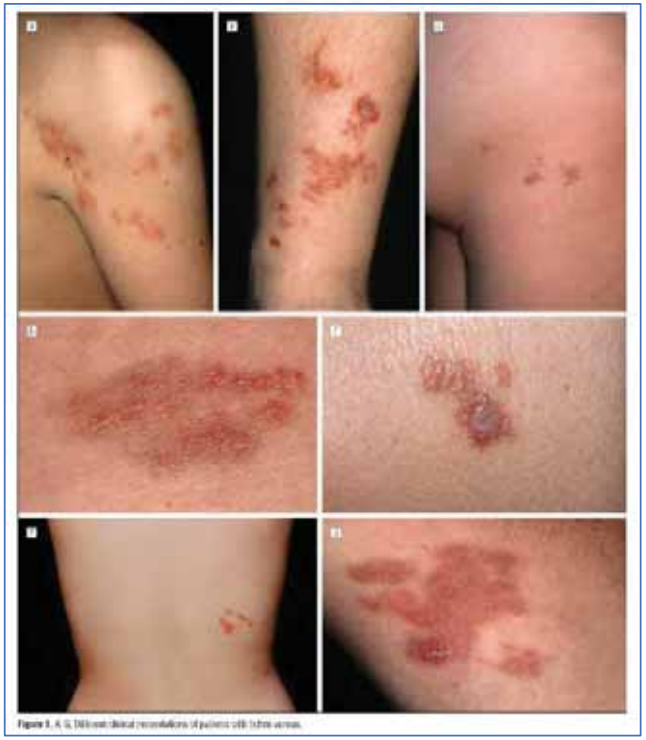

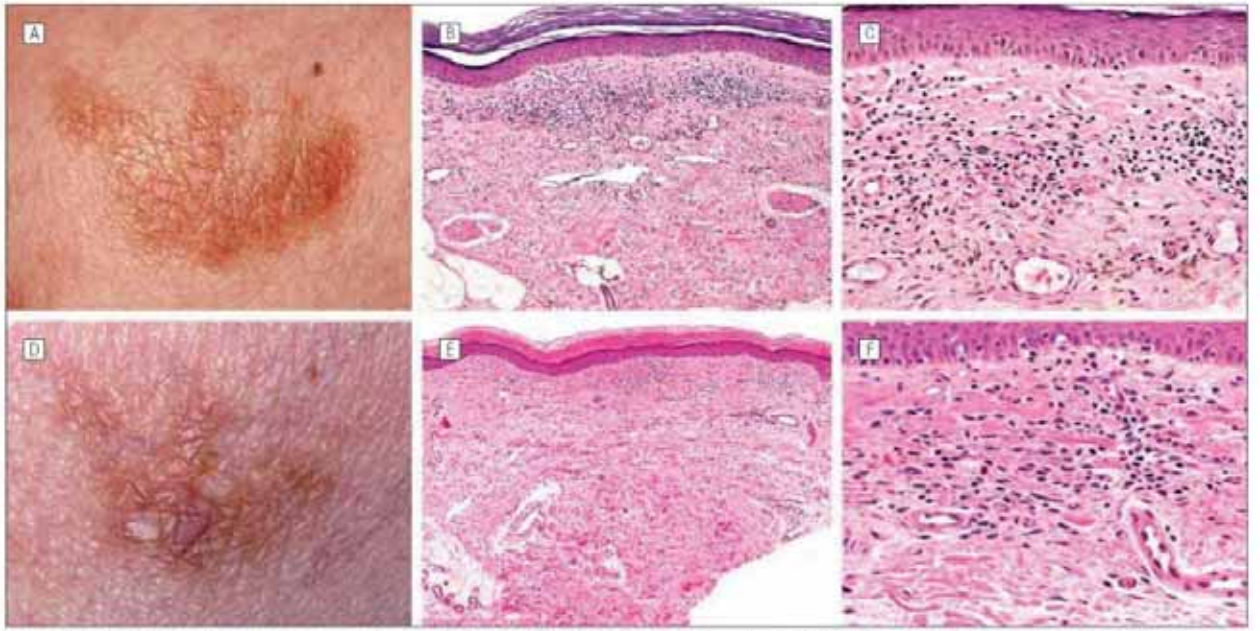

Figure 3. Patient 3 in the Table. A, Appearance of skin lesion in 1990. B, A biopsy specimen obtained in 1990 showed a bandlike infiltrate. C, Note sparse hemorrhage and coarse bundles of collagen in the papillary dermis. D, Appearance of the lesion in 2007. E, A biopsy specimen obtained in 2007 revealed persistence of the lymphocytic infiltrate. F, Note features similar to those of the biopsy specimen obtained in 1990. Hematoxylin-eosin, original magnification ×10 (B), ×20 (C and F), and ×4 (E).

23 patients (F:M=1.1:1; median age: 47 range: 1-77)
Monoclonal: 8/16 (50%)
Persistent disease: 9/23 (39,1%)
(range: 20-204 months; median: 41)

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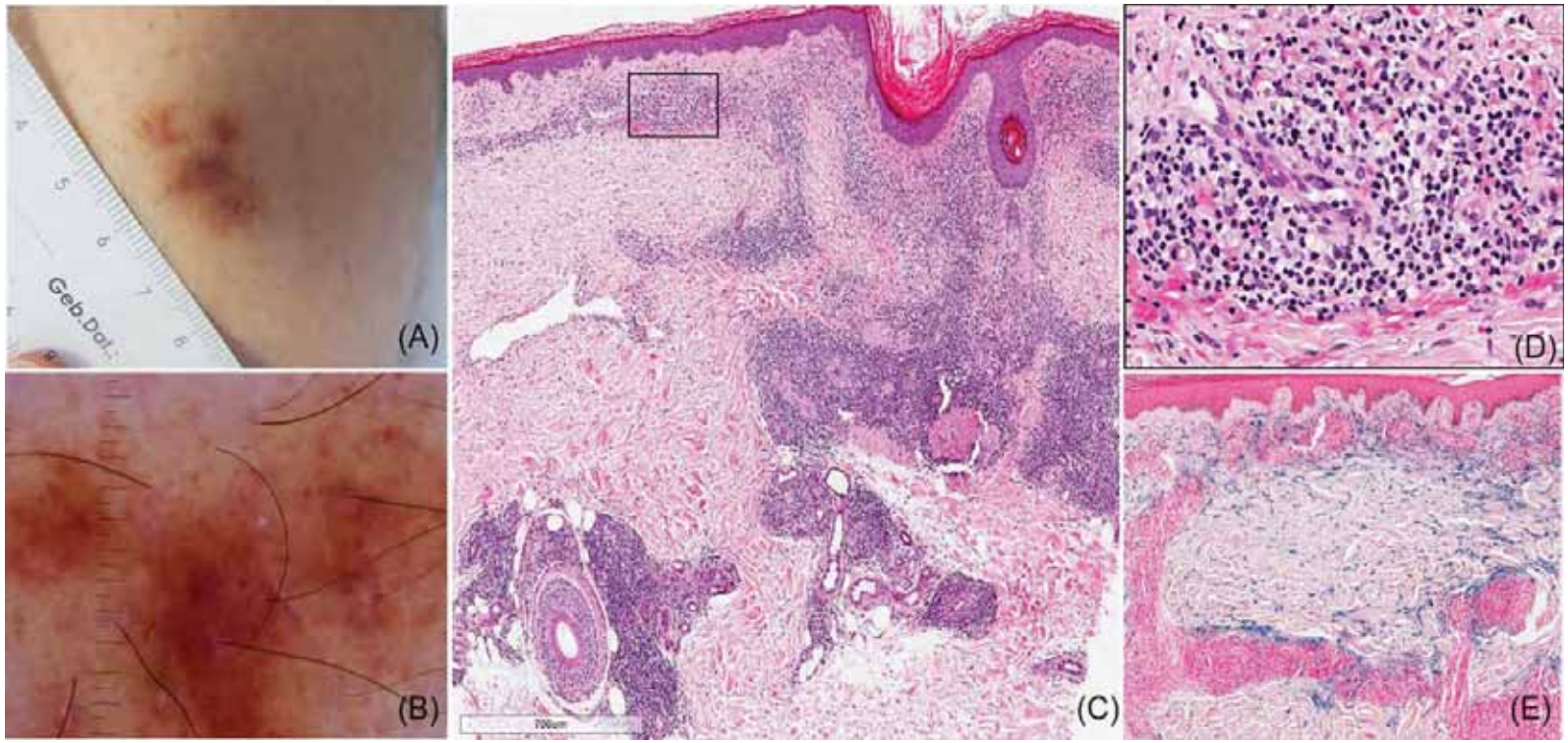
DOI: 10.1111/cup.13948

CASE REPORT

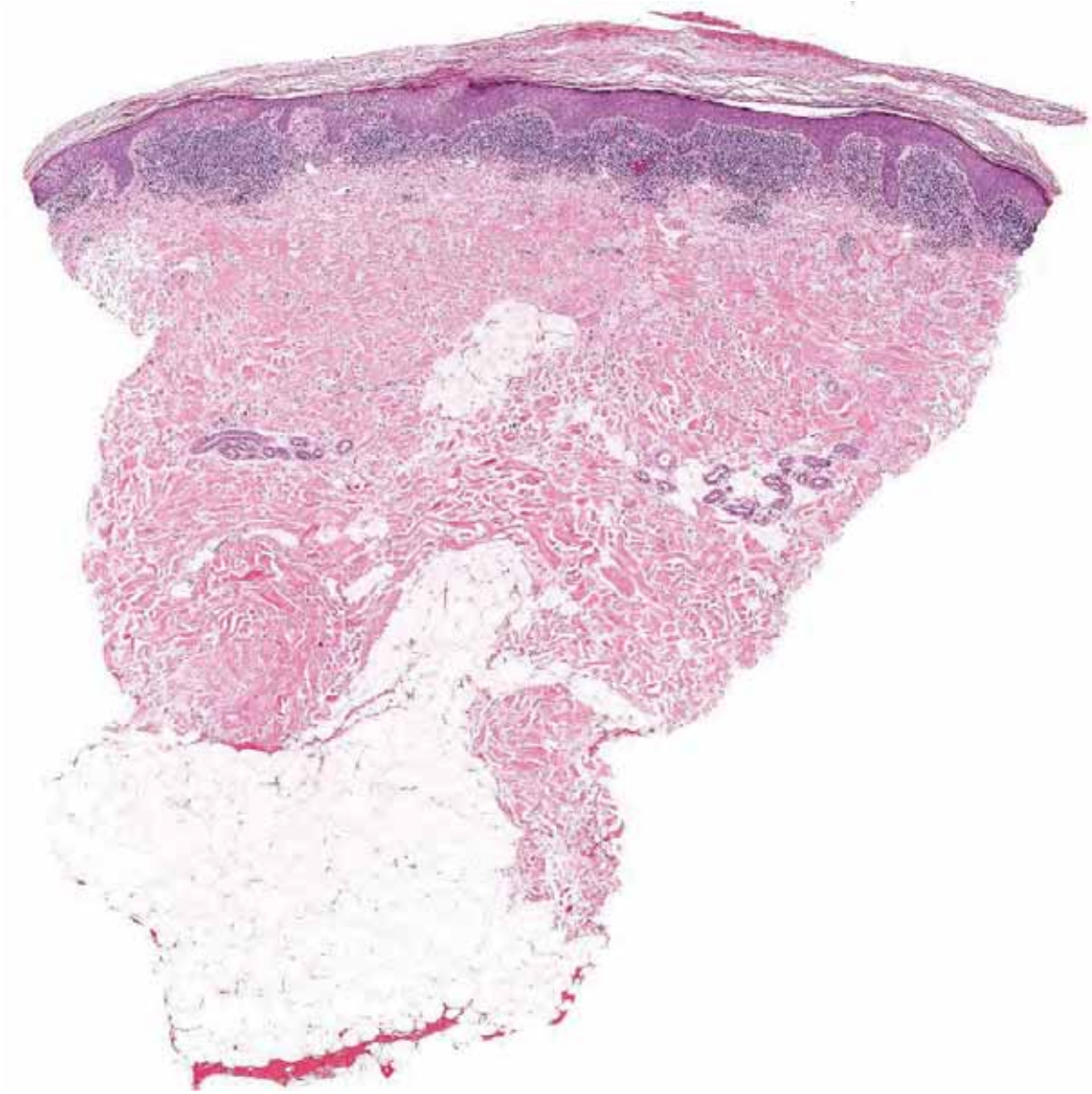
JCP WILEY

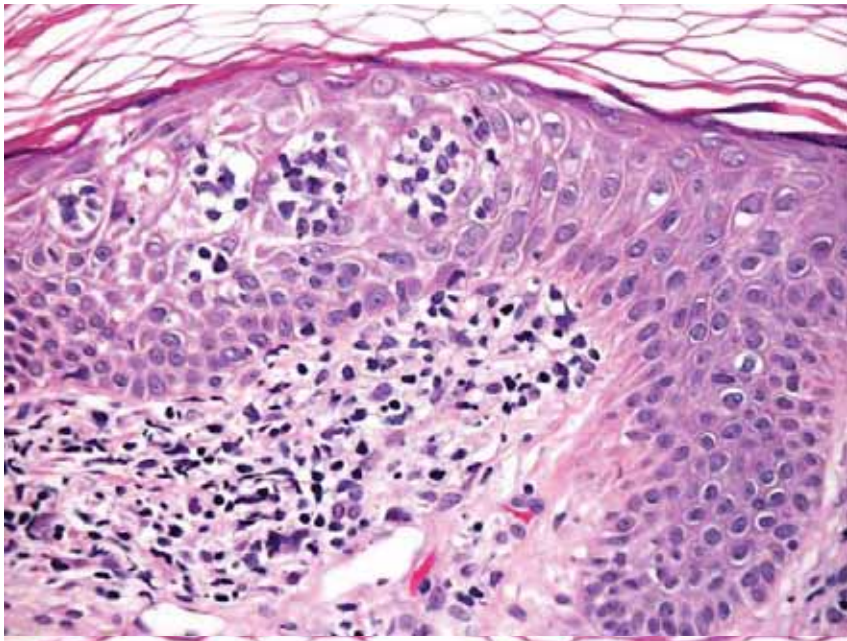
Lichen aureus with pseudolymphomatous infiltrate

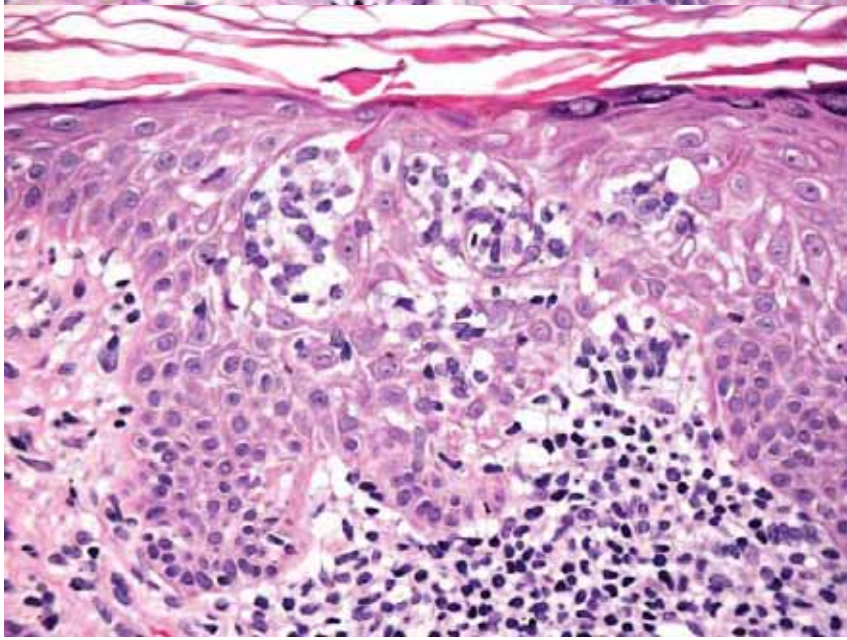
Isabel Kolm[1] | Caroline Buset[1,2] | Ursula Flury[3] | Daniel Nosek[4] | Dmitry V. Kazakov[5] | Werner Kempf[1,6]

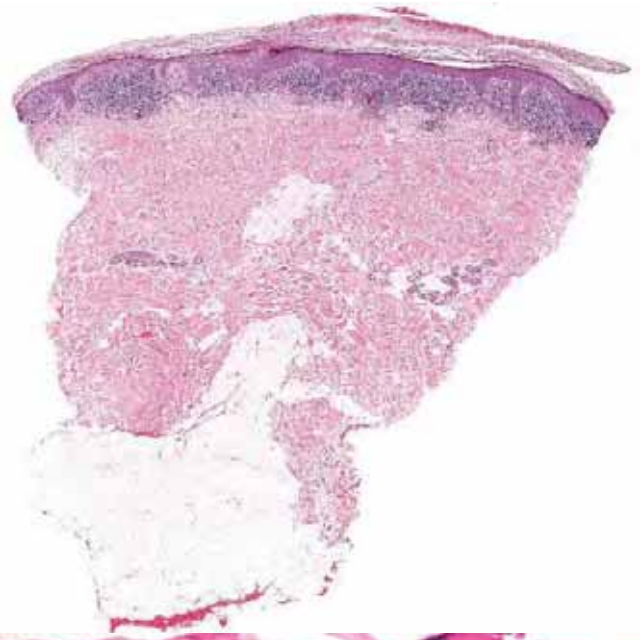


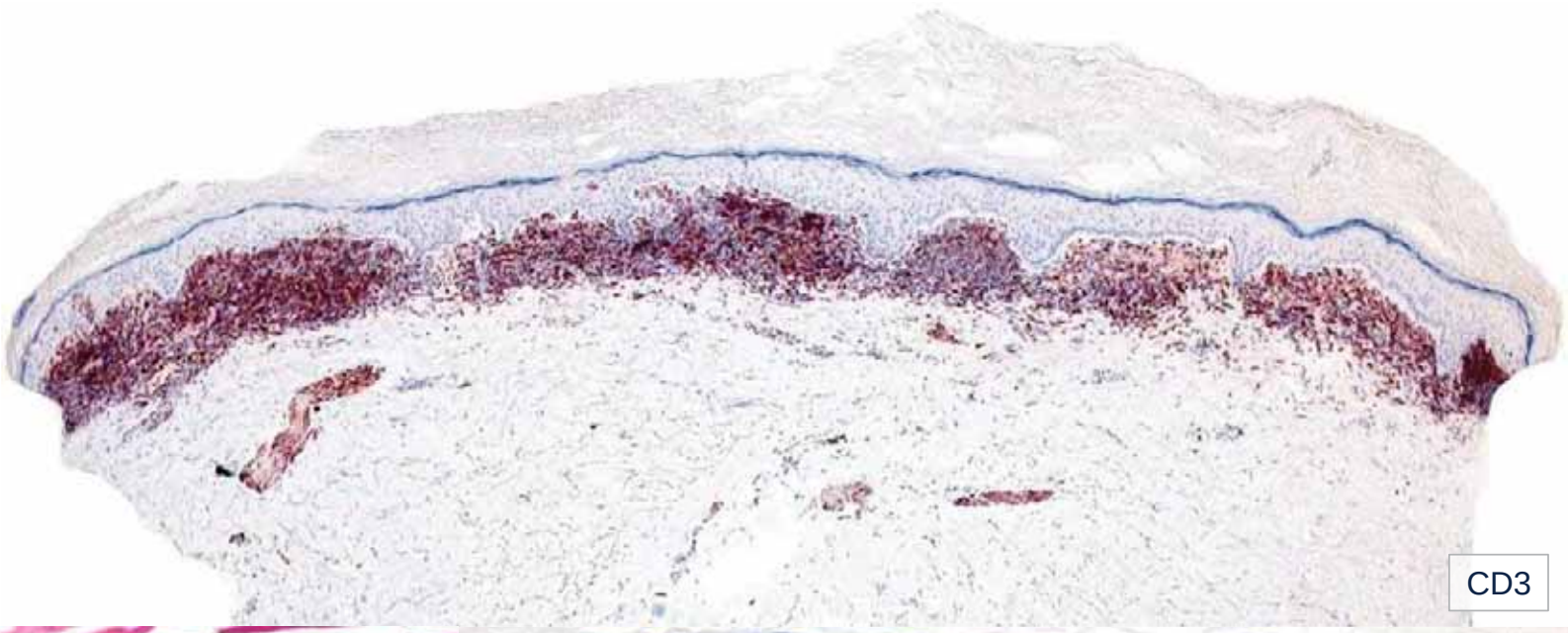
70-year-old woman with a scaly, solitary lesion on the breast.

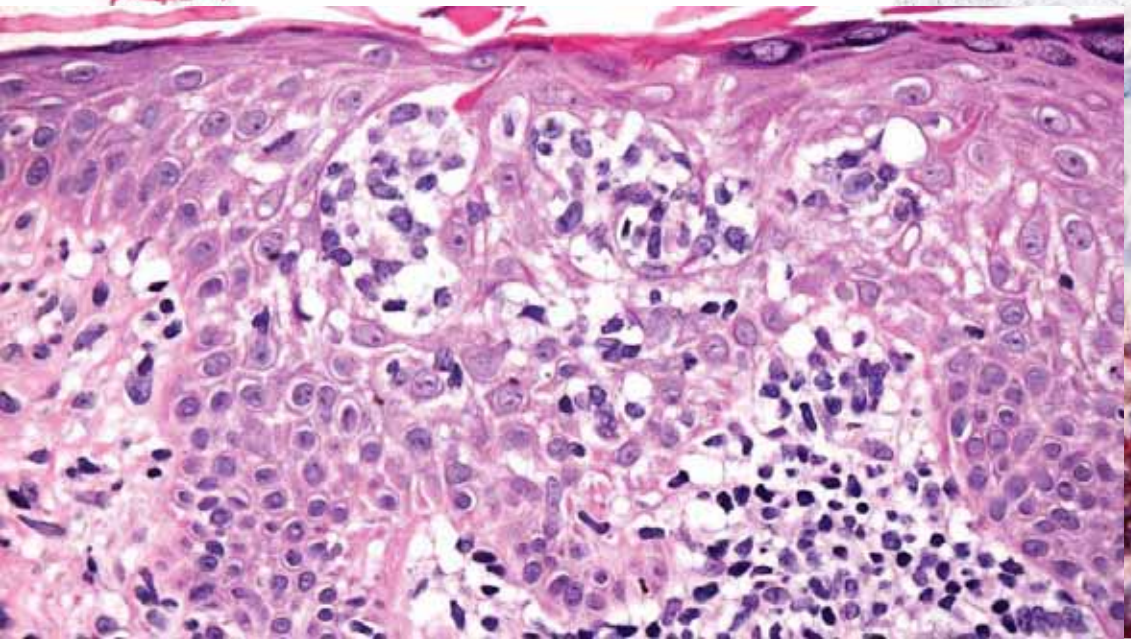


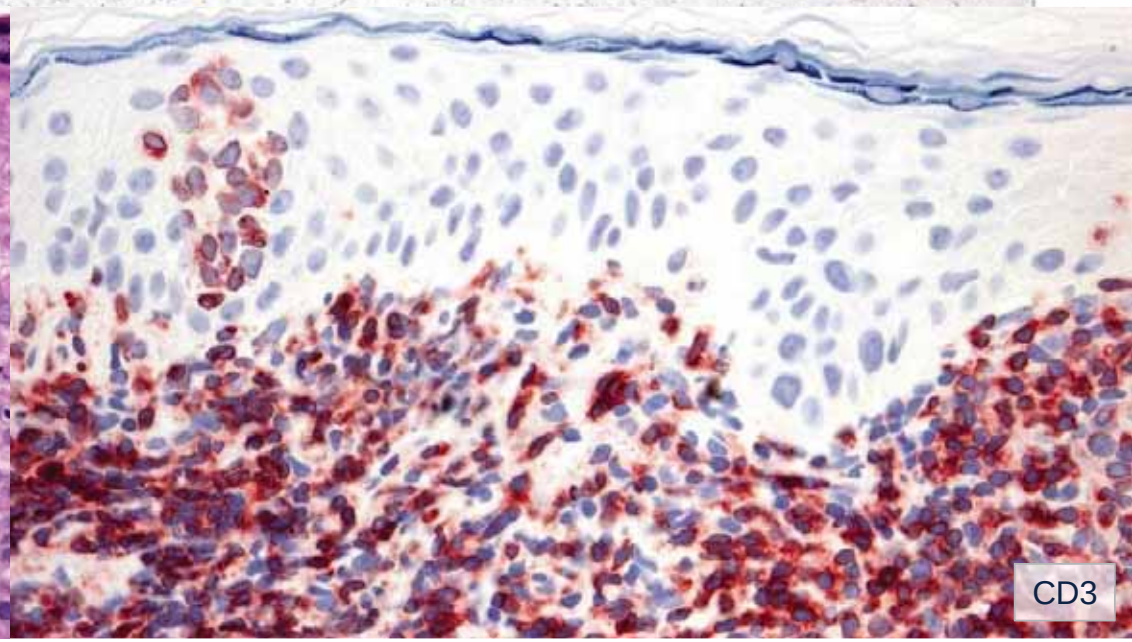







CD3

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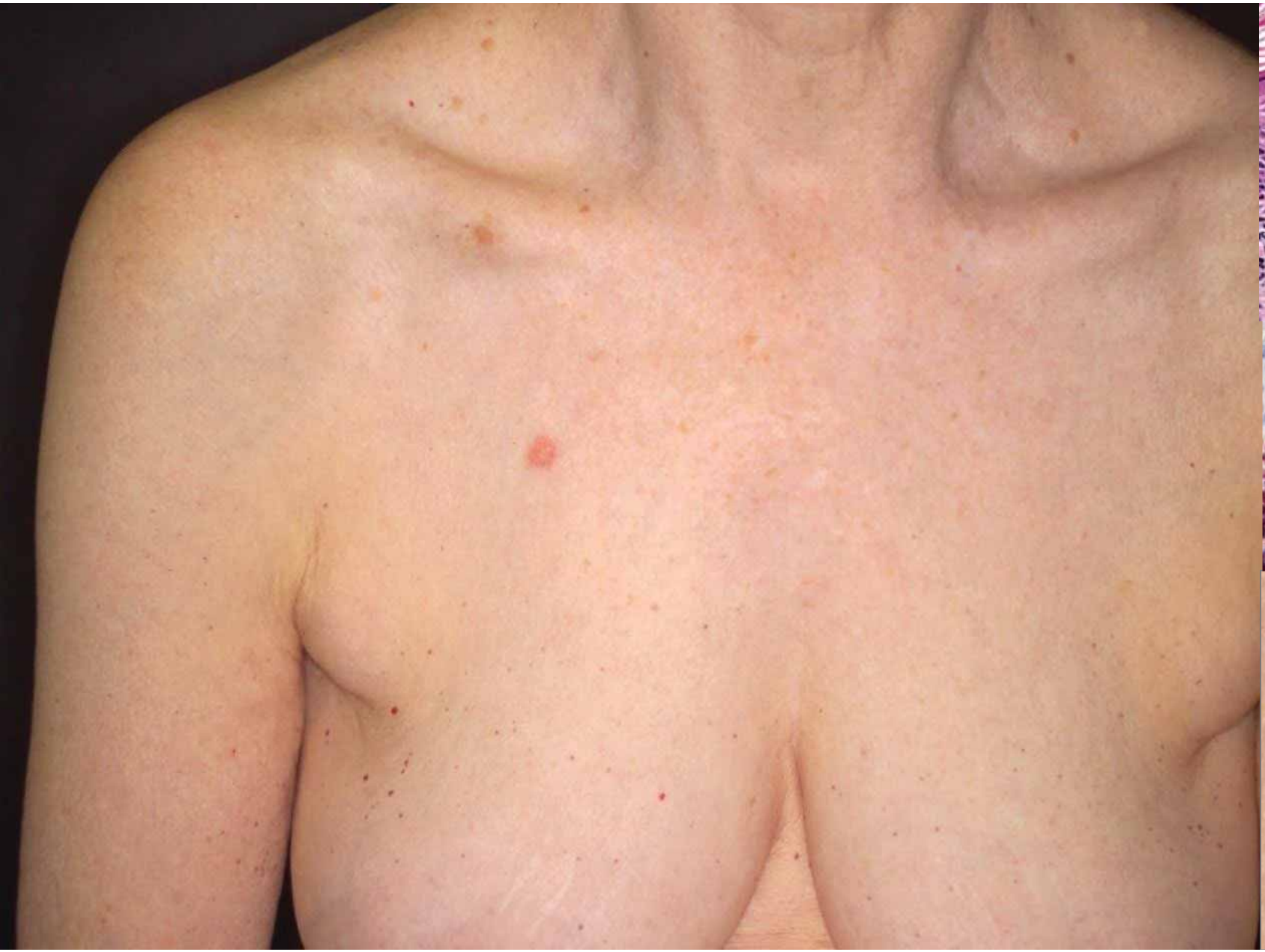

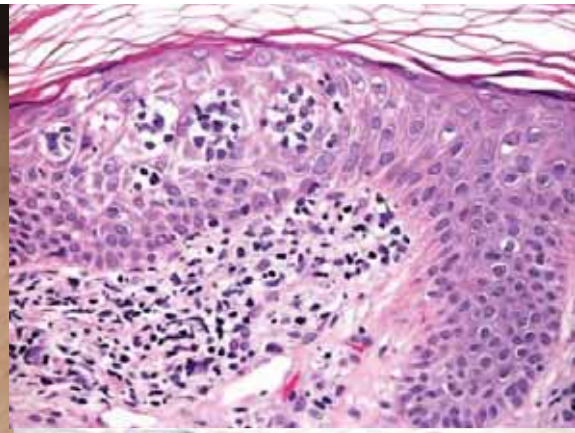

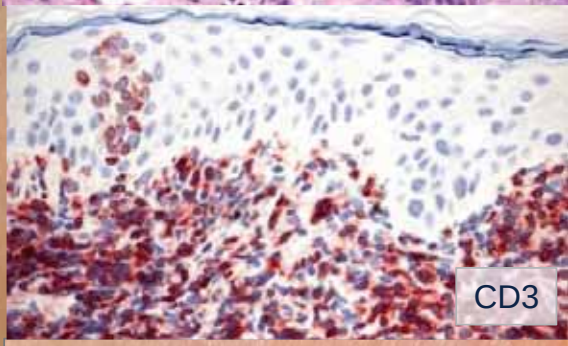
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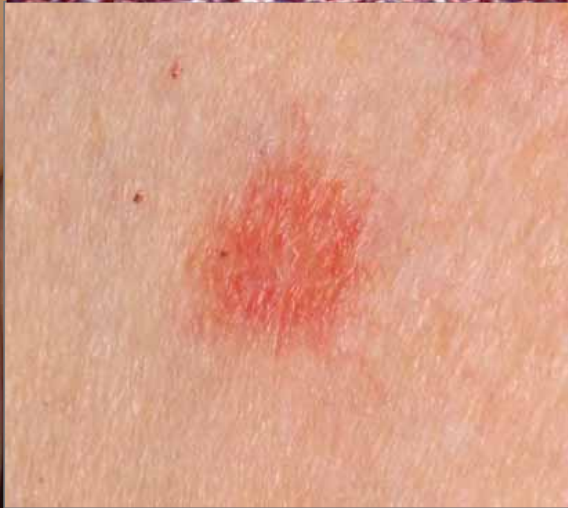

Lichenoid (lymphomatoid) keratosis

- Dense, band-like infiltrate with sharp lateral circumscription *(not visible on partial biopsies!)*
- Epithelial hyperplasia (variable); sometimes remnants of an epithelial tumor *(e.g., lentigo actinica, seborrheic keratosis)*
- Mixed infiltrate of T-cells (predominant) and B-cells
- Lack or minimal fibrosis of papillary dermis
- Variable numbers of intraepithelial ("epidermotropic") lymphocytes; may be larger than normal
- In the past reported often (and published) as "solitary" MF *(also by me...)*

The American Journal of Dermatopathology 21(6): 518–524, 1999

Solitary Skin Lesions With Histopathologic Features of Early Mycosis Fungoides

Lorenzo Cerroni, M.D., Regina Fink-Puches, M.D., Laila El-Shabrawi-Caelen, M.D., H. Peter Soyer, M.D., Philip E. LeBoit, M.D., and Helmut Kerl, M.D.

Mycosis fungoides (MF) is a cutaneous T-cell ly
usually begins with cutaneous patches that evolve
and tumors. A few recent reports describe a solit
MF distinct from localized pagetoid reticulosis,
which solitary verrucous lesions occur on acral
skin lesions with some of the histopathologic fe
rarely occur during treatment with several drug
antidepressants or antihistamines. We analyzed th
ologic features of 20 patients with solitary skin les
histopathologic features of patch- or early plaq
Eight men and 12 women (mean age 50.6, range 2
49) had solitary, small erythematous patches or pl
on the trunk (16 cases, 6 of them on the breast), u
ties (3 cases), and inguinal region (1 case). Ten
treated with one or more drugs; only two of t
antidepressants or antihistamines. Histopathologic
revealed in all cases a band-like infiltrate in the
frequently with epidermotropism of solitary
Atypical lymphocytes were present in a minority
munohistology showed a predominance of CD3
cytes, in most cases admixed with clusters of CI
Only a small proportion of the infiltrate was CD8
analysis of the rearrangement of the T-cell recep
performed in 16 cases using the polymerase c
(PCR) technique and revealed a monoclonal band
After surgical excision, 2/14 patients had a recur
surgical scar. In 18 patients with complete follo
evidence of "classic" MF could be observed afte
low-up of 31.9 months. Solitary skin lesions w
pathologic features of MF can be considered as a
scopathologic entity, probably representing a solit
mycosis fungoides.

Key Words: Solitary mycosis fungoides—Cut
lymphoma—Cutaneous T-cell pseudolympho
lymphomatous drug eruptions.

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TABLE 1. *Clinical data, drug history, and results of PCR analysis of TCR genes*

Patient no	Sex	Age	Location	Drugs	PCR analysis of TCR genes	Treatment	Follow-up (months)	
1	F	59	back	no	P	TE	A&W (45)	A&W (83)
2	F	53	breast	[illegible]	M	TE	A&W (50)	A&W (176)
3	F	45	breast	Developed new lesions	P	TE	A&W (26)	A&W (194)
4	F	23	breast	no	M	TE	A&W (76)	A&W (258)
5	F	44	inguinal	unknown	nd	TE	LFU	LFU
6	M	63	breast	no	P	TE	A&W (7)	A&W (27)
7	M	71	flank	no	nd	TE	A&W (38)	A&W (196)
8	M	47	arm	unknown	P	TE	LFU	D- (30)
9	M	47	back	no	M	TE	A&W (75)	A&W (239)
10	M	75	flank	Isosorbide 5-mononitrat	M	TE	A&W (48)	A&W (48)
11	M	36	back	Clofibrate; Atenololi, Allopurinol	M	local steroids	A&D (15)	A&W (35)
12	F	51	breast	Developed new lesions & LyP	P	local steroids	A&D (8)	A&W (167)
13	F	58	back	Enalapril; Coumecin; Hydrochlorothiazide Sucralfate; Ranitidine; Famotidine	P	local steroids	A&D (11)	A&W (176)
14	F	58	breast	Levothyroxine	M	local steroids	A&D (57)	A&W (118)
15	F	29	abdomen	Levothyroxine	P	TE	A&W (23)	A&W (184)
16	F	70	arm	Levothyroxine; Isradipine; Allopurinol; Bisoprolol; Terbutaline; Chlordiazepoxide; Amitriptyline; Ketotifene	P	TE	A&W (22)	A&W (207)
17	F	34	back	no	M	TE	recurrence (36)	
18	F	43	back	Fluoxetine	M	local steroids	A&D (18)	
19	M	24	back	no	P	local steroids	A&D (8)	
20	M	82	arm	[illegible] Naproxen; Acetyl Salicylic acid; Acetaminophen	P	TE	recurrence (12)	

PCR, polymerase chain reaction; TCR, T-cell receptor; nd, not done; TE, total excision; recurrence, recurrence within surgical scar; PB, punch biopsy; M, monoclonal band; P, polyclonal smear; A&W, alive and well; A&D, alive with persistent disease; LFU, lost to follow-up.

San Francisco

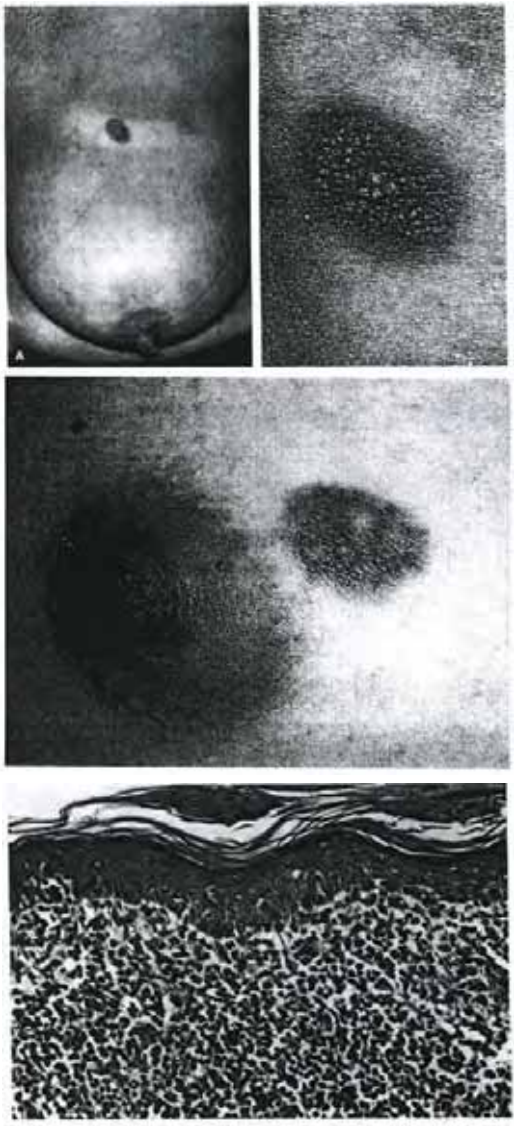
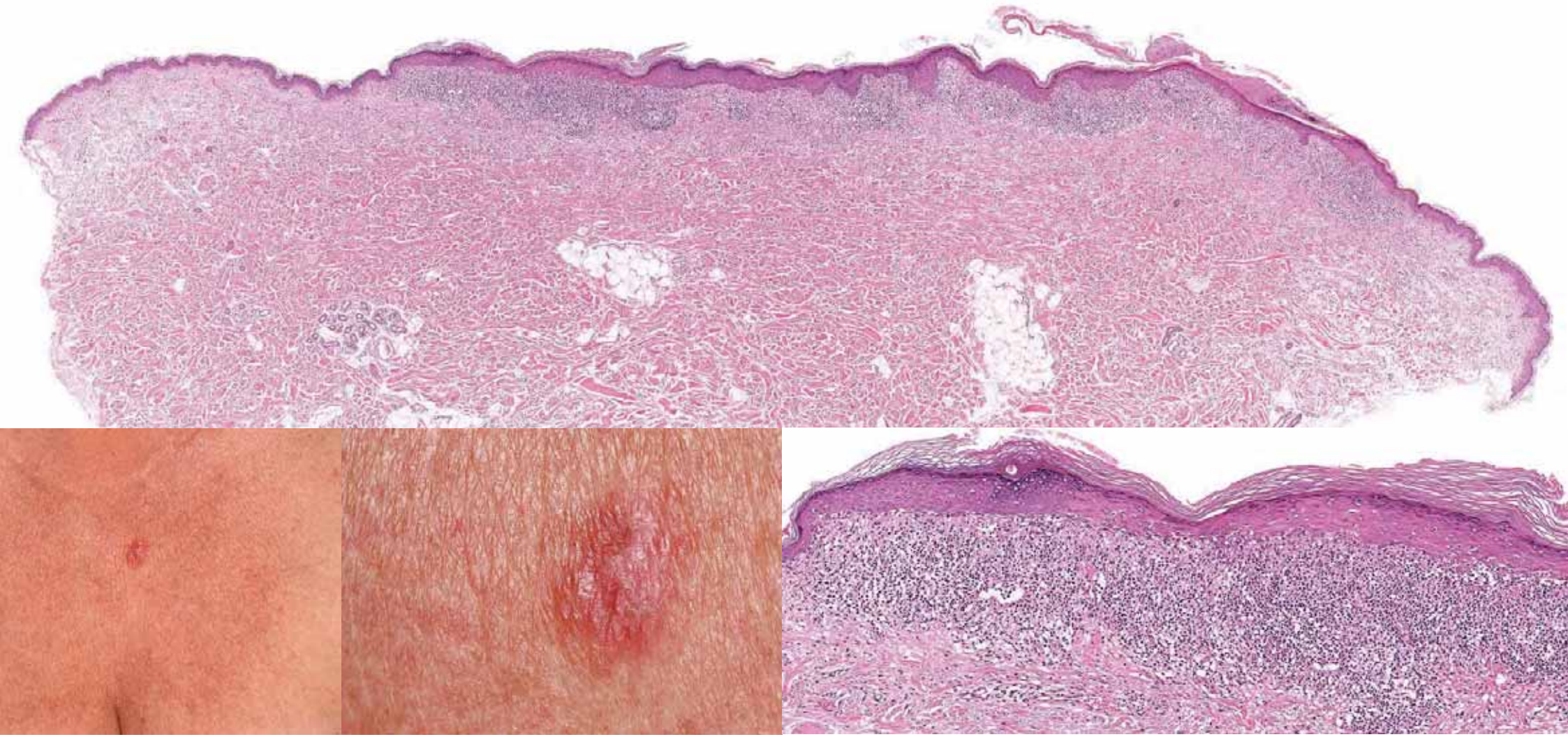
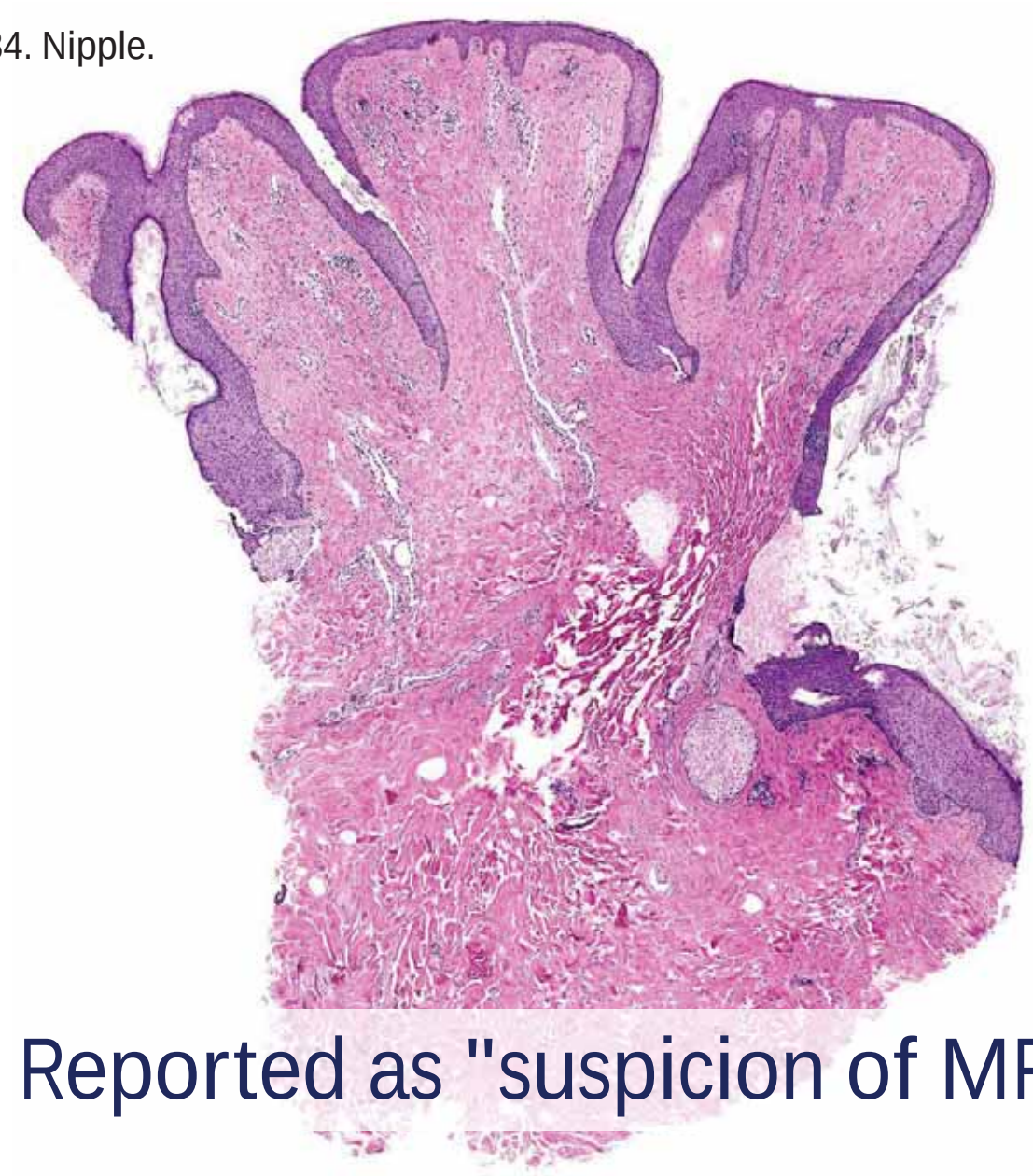


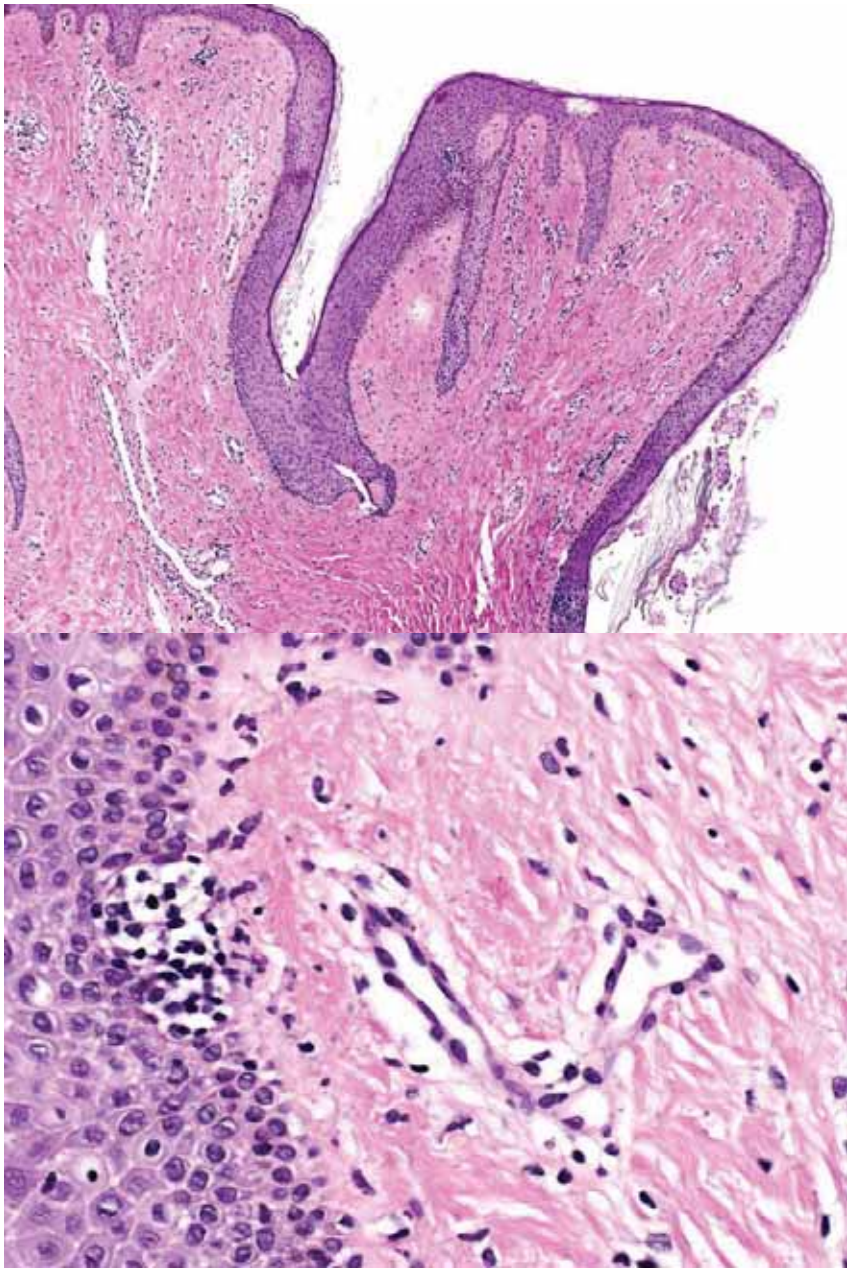
FIG. 5. Small lymphocytes predominate; note small intraepidermal collection of lymphocytes.

Clue: sharp circumscribed, dense infiltrate; mixed T- and B-lymphocytes; in many cases focal rests of an epithelial tumor, often seborrheic keratosis



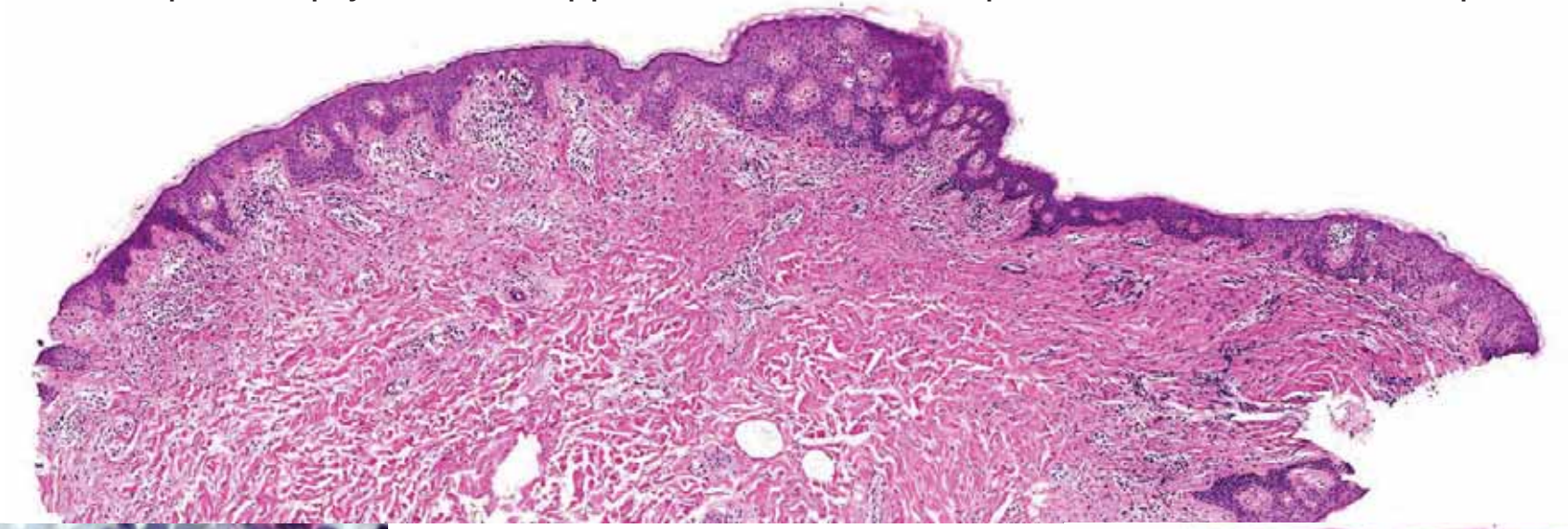
F, 34. Nipple.

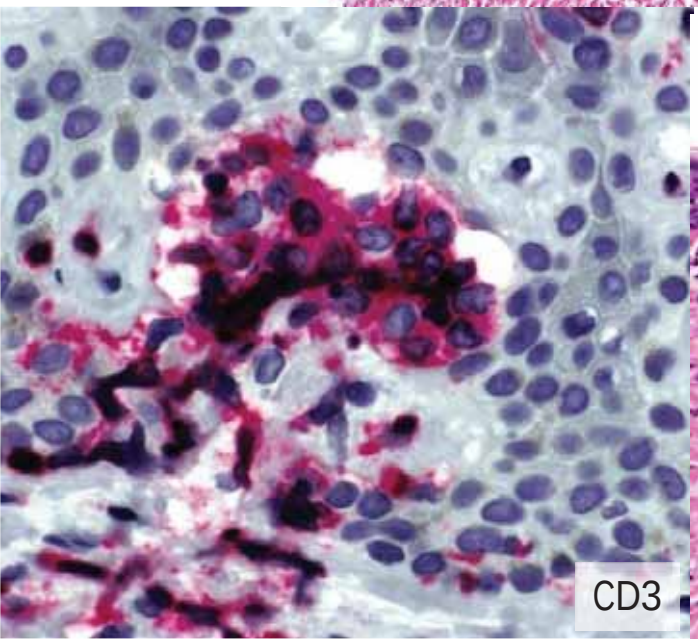


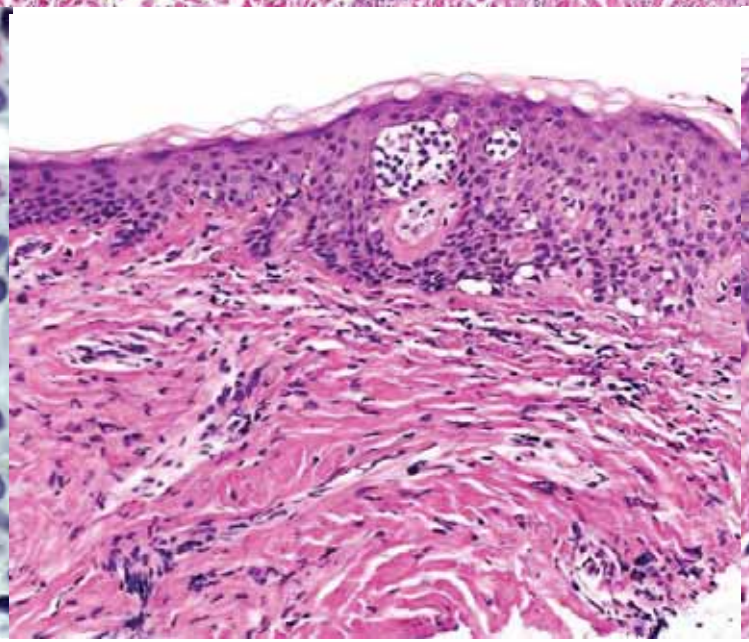


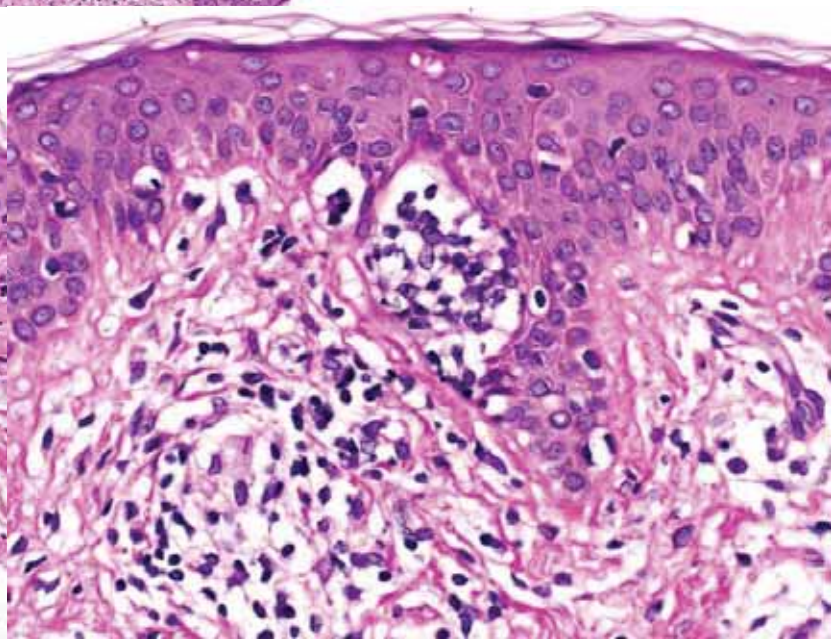
Reported as "suspicion of MF"

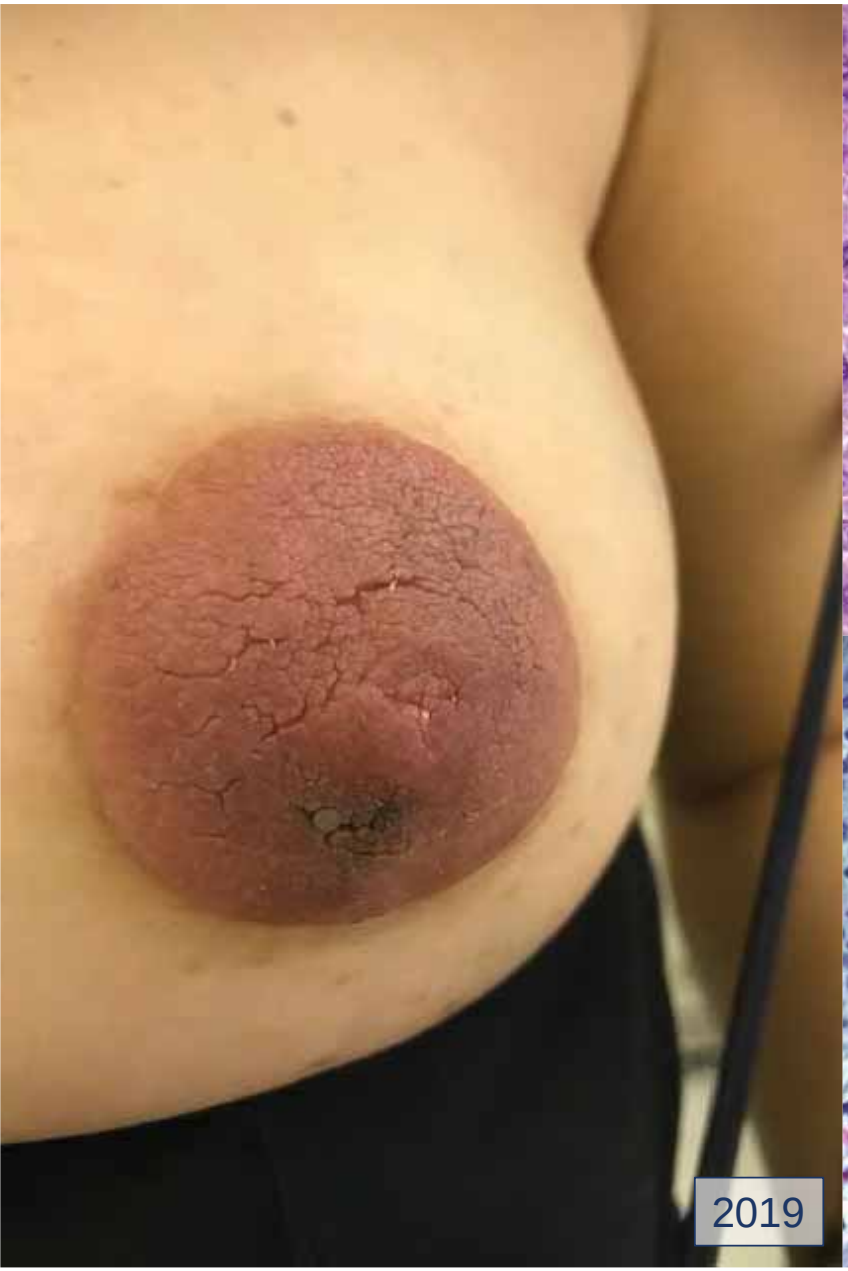
One year later repeat biopsy on same nipple to confirm the "suspicion of MF" made on the previous biopsy.

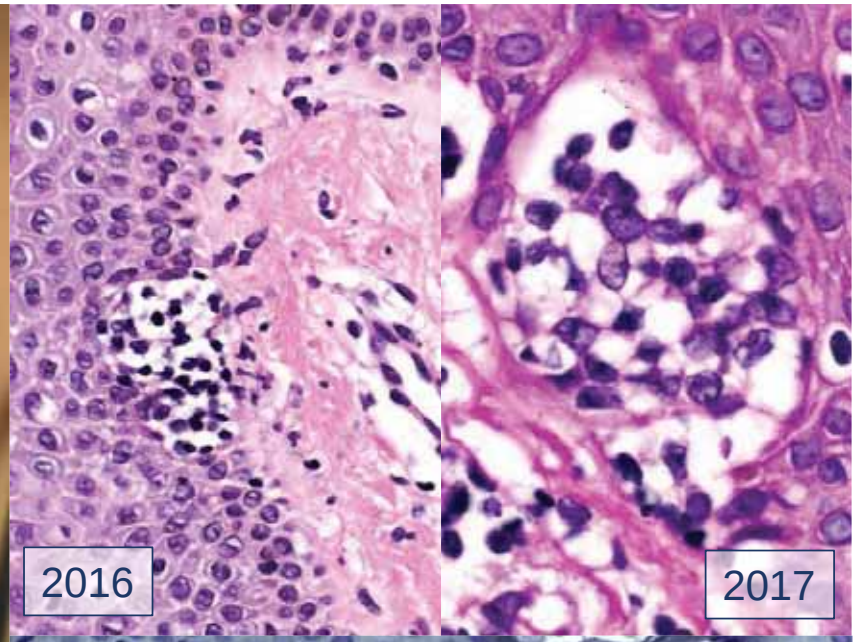


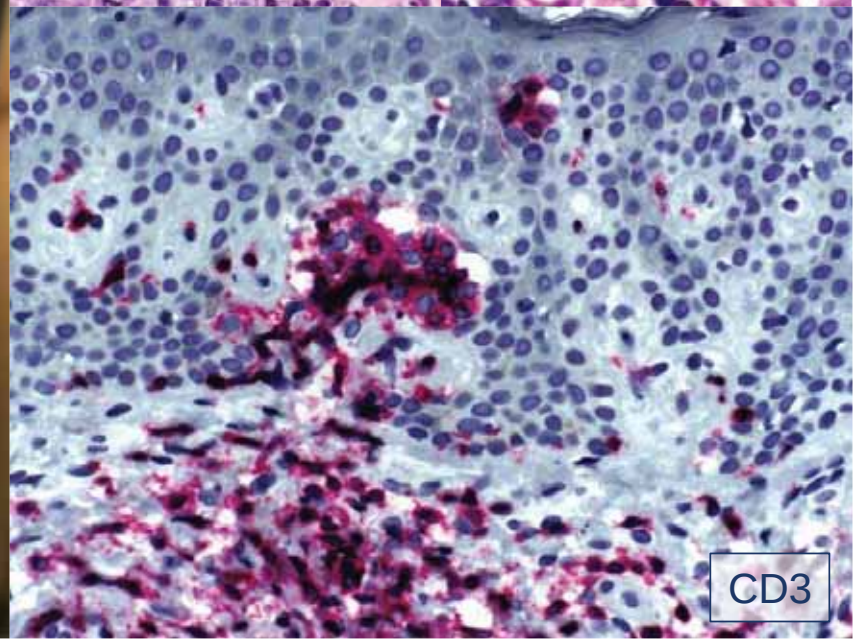












Clinical correlation (available only 2 years after the second biopsy, 3 years after the first one).

Nevoid hyperkeratosis of the nipple

J Cutan Pathol 2012: 39: 545–548
doi: 10.1111/j.1600-0560.2012.01885.x
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Journal of
Cutaneous Pathology

Nevoid hyperkeratosis of the areola misinterpreted as mycosis fungoides

Nevoid hyperkeratosis of the nipple and areola is a benign condition with fewer than 70 cases reported in the literature. We report a case of unilateral nevoid hyperkeratosis of the areola with intraepidermal lymphocytes that resembled Pautrier's microabscesses on histological examination. This is the third report of mycosis fungoides-like changes in nevoid hyperkeratosis of the nipple and areola. In addition, this is the first case to present immunohistochemical and T-cell gene rearrangement studies of the intraepidermal lymphocytes. This case highlights a potential histopathological pitfall in the diagnosis of nevoid hyperkeratosis of the nipple and areola.

Keywords: mycosis fungoides, nevoid hyperkeratosis, pitfall, simulant

Rosman IS, Hepper DM, Lind AC, Anadkat MJ. Nevoid hyperkeratosis of the areola misinterpreted as mycosis fungoides. J Cutan Pathol 2012; 39: 545–548. © 2012 John Wiley & Sons A/S.

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Nevoid hyperkeratosis of the nipple and areola is a rare benign condition with fewer than 70 cases reported in the literature. Nevoid hyperkeratosis presents as asymptomatic verrucous plaques on the nipples and/or areolae and is characterized histopathologically by hyperkeratosis, acanthosis, papillomatosis and keratin plugging or hyperkeratosis.

We report a case of unilateral nevoid hyperkeratosis of the areola with intraepidermal lymphocytes that resembled Pautrier's collections on microscopic examination. To our knowledge, this is the third report of mycosis fungoides-like changes in nevoid hyperkeratosis of the nipple and areola. In addition, this case is the first to present immunohistochemical studies of the intraepidermal lymphocytes and the results of T-cell gene rearrangement analysis.

Case report

A 43-year-old Caucasian woman with no significant medical history presented with a 4-year history of thickening of the right areola. She had no history of treatment with oral contraceptives or other hormonal agents. Three years prior, the area had been biopsied and diagnosed as mycosis fungoides by dermatopathologists at an outside institution. The lesion had remained stable over the subsequent years with only occasional pruritus. Intermittent treatment with a topical corticosteroid was employed without benefit. She presented to our clinic for a second opinion prior to undergoing further treatment for mycosis fungoides.

On physical examination, an irregular verrucous plaque was present on the right areola with extension of a velvety tan plaque beyond the margin of the areola (Fig. 1). There was no lymphadenopathy, and no other cutaneous lesions were evident.

Two 4-mm punch biopsies of the right areola were performed during her visit to our institution. The findings from both showed similar features, including hyperkeratosis, papillomatosis and acanthosis (Fig. 2). There were occasional small aggregates of mononuclear cells within the epidermis, and the superficial dermis was sclerotic with stellate-appearing fibroblasts (Figs. 3 and 4). A CD3 immunohistochemical stain highlighted the mononuclear cells, including the epidermal aggregates.

Dermato pathology

Dermatopathology 2015;2:61–66

Karger Open Access

Case Studies

The Dilemma of Coexisting Nevoid Hyperkeratosis of the Nipple and Areola in Mycosis Fungoides: A Report of Three Cases

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Can Baykal[a]

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Key Words
Nevoid hyperkeratosis of the nipple and the areola · Mycosis fungoides

Abstract
Nevoid hyperkeratosis of the nipple and areola (NHNA) is a rare clinicopathological entity showing persistent and strictly localized hyperkeratotic lesions of the nipple, areola or both with unknown etiopathogenesis. A similar clinical appearance may also be seen in different diseases with specific histopathological features. There are a few anecdotal reports on the association of NHNA with mycosis fungoides (MF), but they do not describe a uniform condition. In this report, we present 3 patients with hyperkeratotic lesions of the nipple and areola associated with MF, but showing different histopathological features. We also review similar cases in the literature and discuss possibilities concerning this association. Two of our cases represent the association between MF and NHNA without histopathological features of MF on the nipple-areola complex. The other case represents hyperkeratosis of the nipple and areola with specific histological and immunohistochemical features of MF. Hence, we would like to hypothesize that MF may involve the nipple and areola and have an appearance similar to NHNA. Intriguingly, however, NHNA may occasionally also be seen in association with MF. However, this peculiar association requires further explanation.

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KARGER 125

Dermatologica 155: 268–274 (1977)

Mycosis fongoïde et mucinose folliculaire avec très importantes lésions papillomateuses et verruqueuses

C. KANITAKIS et G. TSOÏTIS

Clinique des maladies cutanées et syphilitiques de l'Université «Aristotelion» de Salonique (Directeur: Prof. C. KANITAKIS), Salonique

Key Words. Mycosis fungoides · Follicular mucinosis · Papillomatous and verrucous lesions

Mycosis fungoides and Follicular Mucinosis with Very Prominent Papillomatous and Verrucous Lesions

Abstract. An exceptional case of mycosis fungoides and follicular mucinosis with very prominent papillomatous and verrucous lesions in a 20-year-old woman is reported. Papillomatous and verrucous lesions have not been described, so far as we know, in lymphomas.

Nous avons eu l'occasion d'observer un cas de mycosis fongoïde associé à une mucinose folliculaire avec lésions papillomateuses et verruqueuses très importantes chez une femme de 20 ans. Il nous a semblé intéressant de rapporter cette observation, à cause de la présence des lésions papillomateuses et verruqueuses, qui, à notre connaissance, ne sont pas décrites dans les hématodermies.

Observation personnelle

La malade E.S., âgée de 20 ans, est entrée dans notre Service le 24 février 1975 pour des lésions cutanées très étendues; elles ont débuté 1 an auparavant et ont commencé à s'aggraver progressivement à partir du 3e mois d'une grossesse terminée 15 jours avant son entrée dans le Service, par opération césarienne.

Reçu: le 21 février 1977; accepté: le 16 avril 1977.

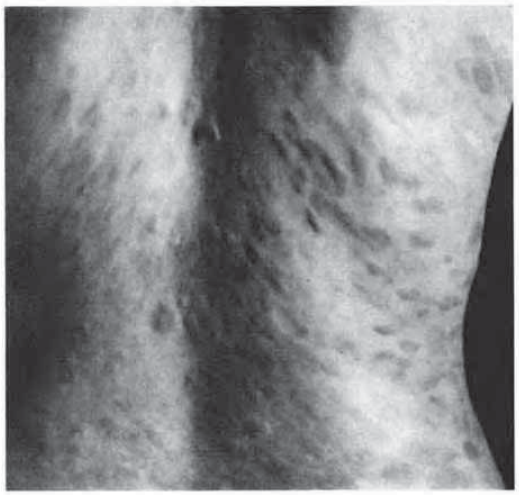


Fig. 1. Lésions de la face postérieure du tronc.

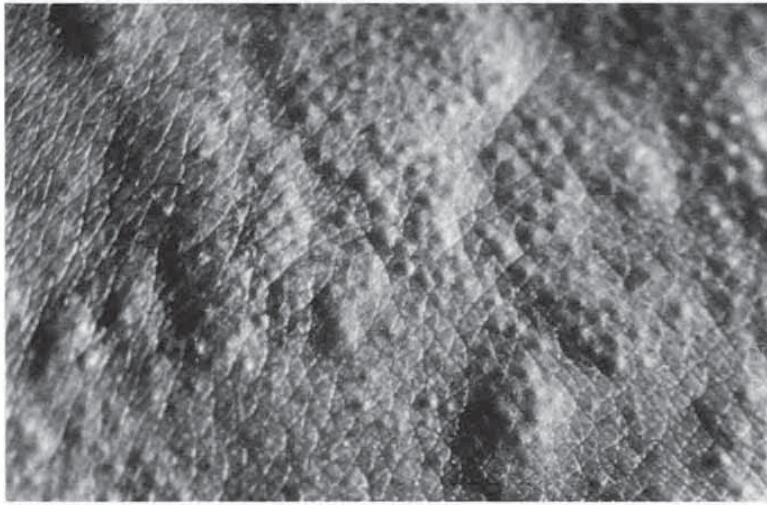


Fig. 2. Papules folliculaires sur des placards infiltrés du dos.

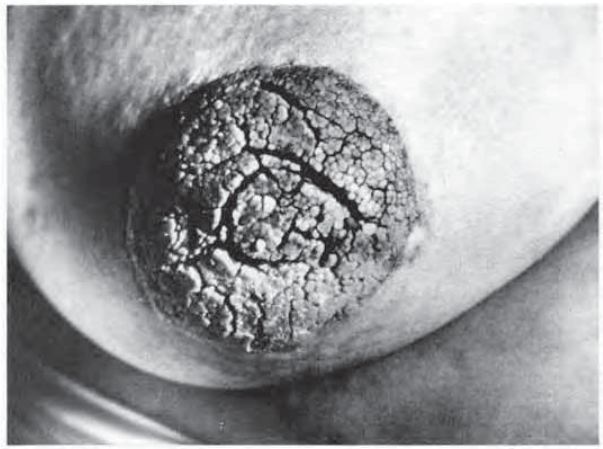


Fig. 5. Lésions papillomateuses et verruqueuses du mamelon et de l'aréole.

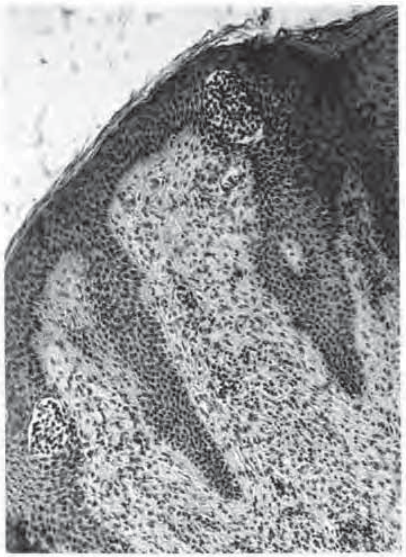
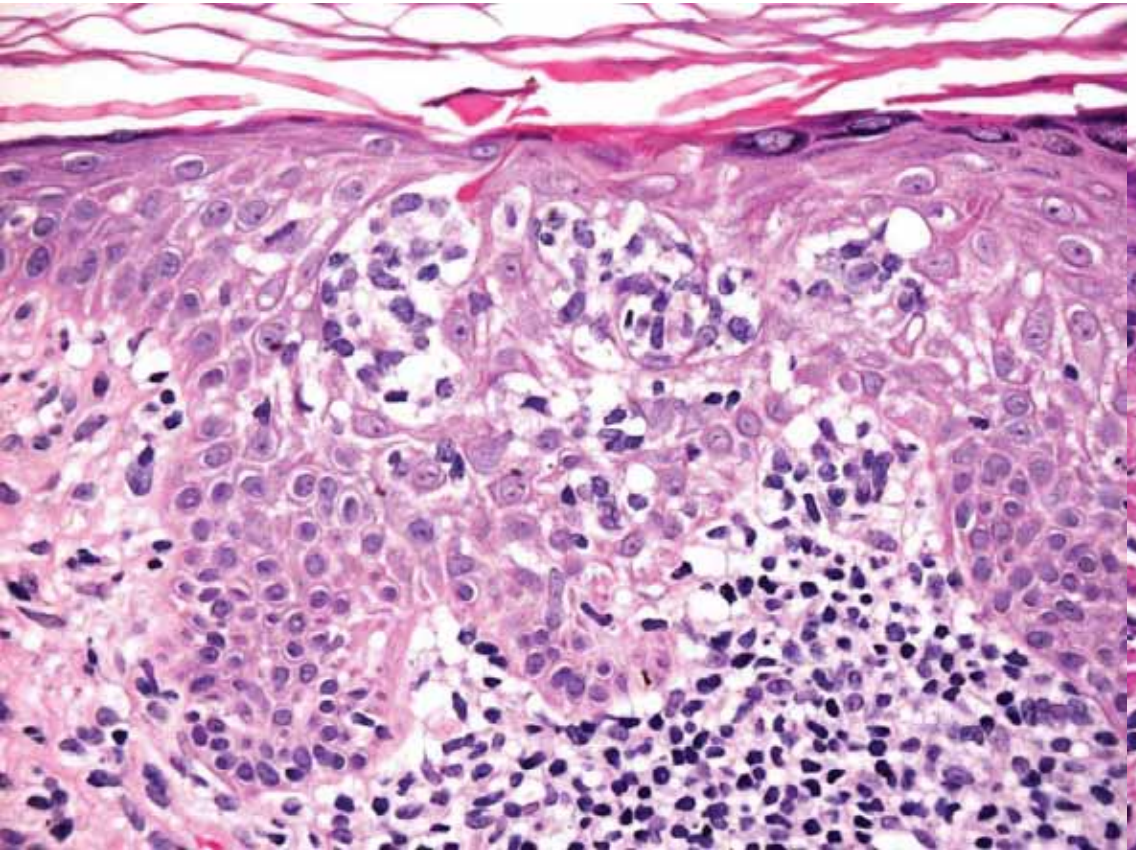


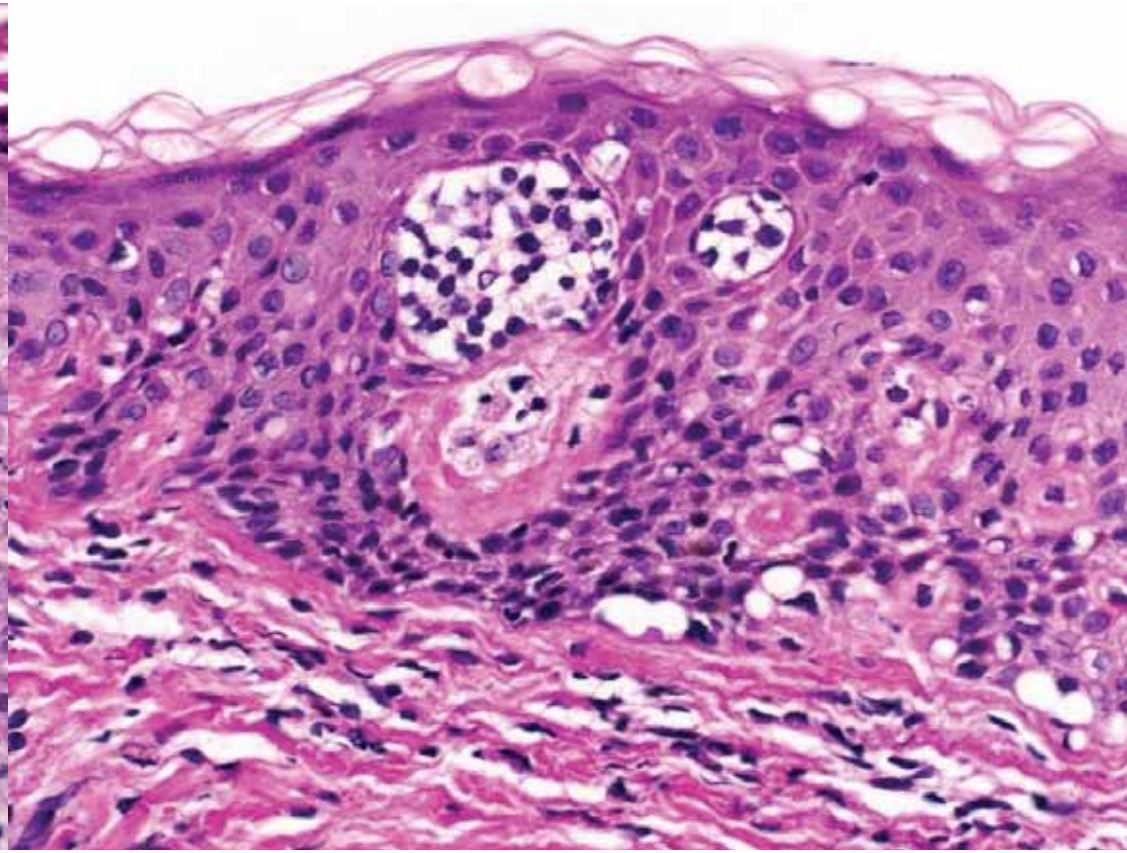
Fig. 6. Acanthose et papillomatose très importantes, thèques intraépidermiques et infiltrat cellulaire du derme papillaire.

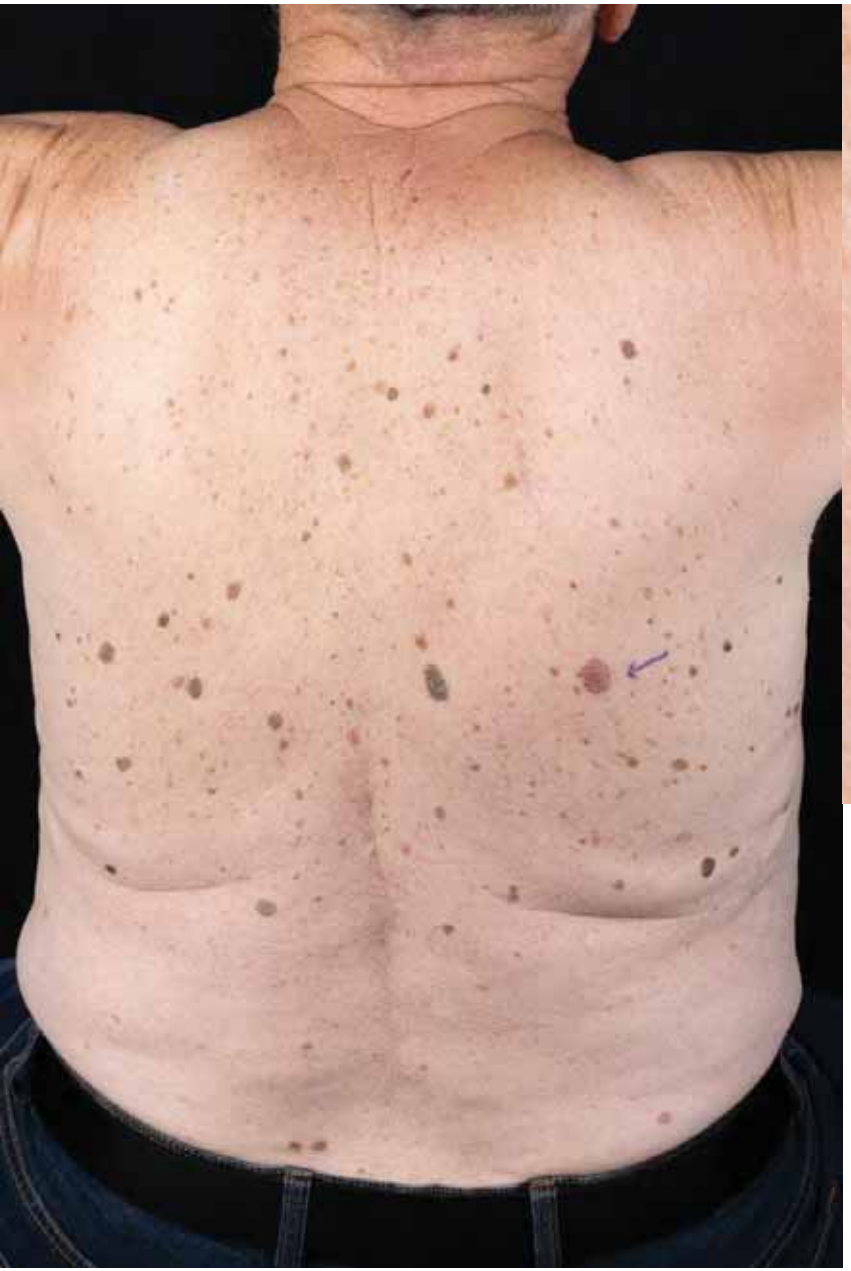
Benign intraepidermal collections of lymphocytes ("pseudo"-Darier nests / Pautrier microabscesses)

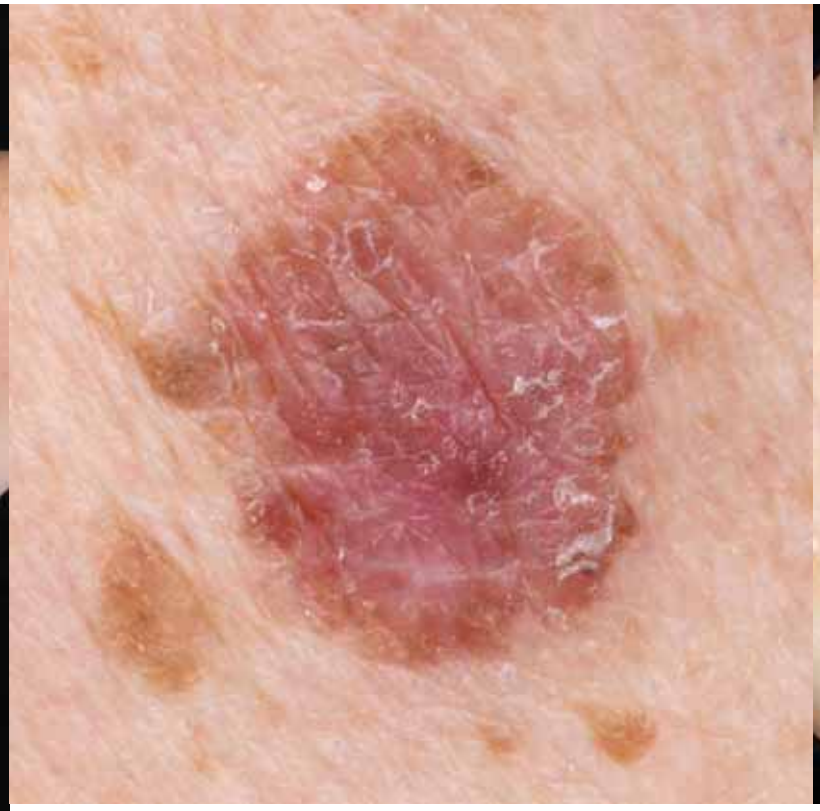
Lichenoid keratosis

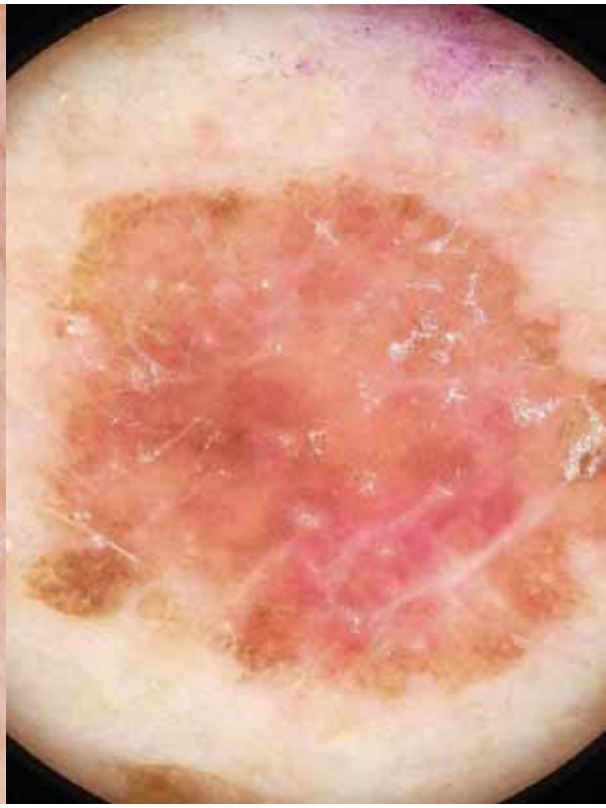


Nevoid hyperkeratosis of the nipple





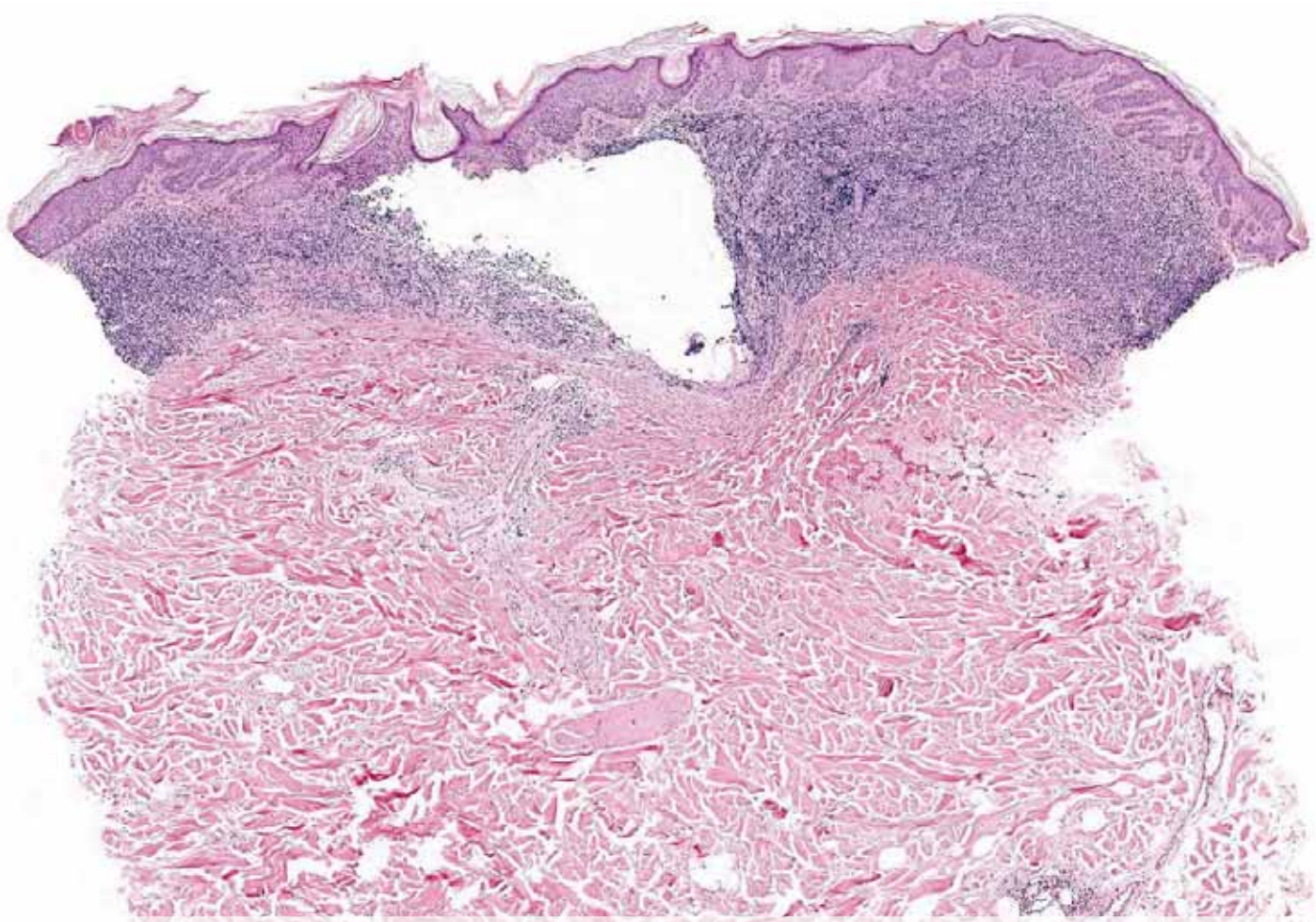


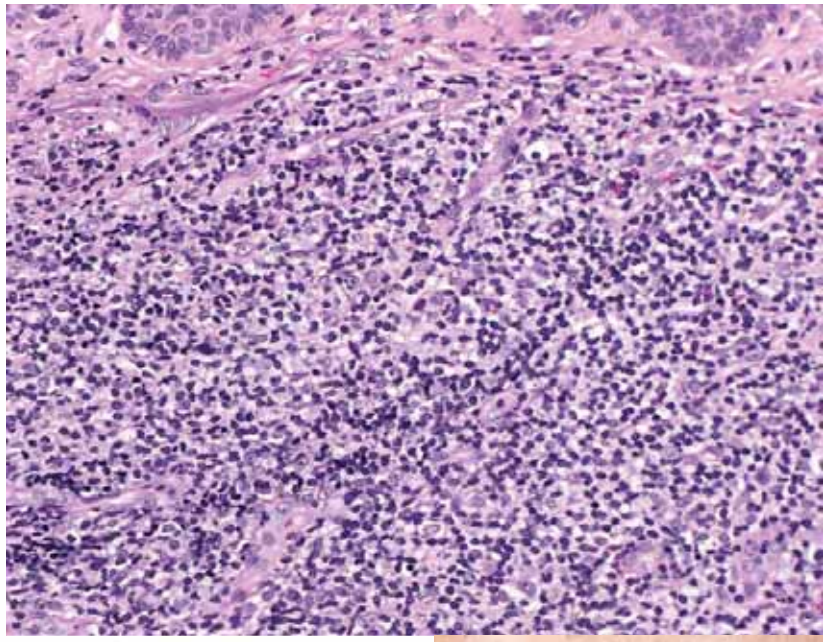


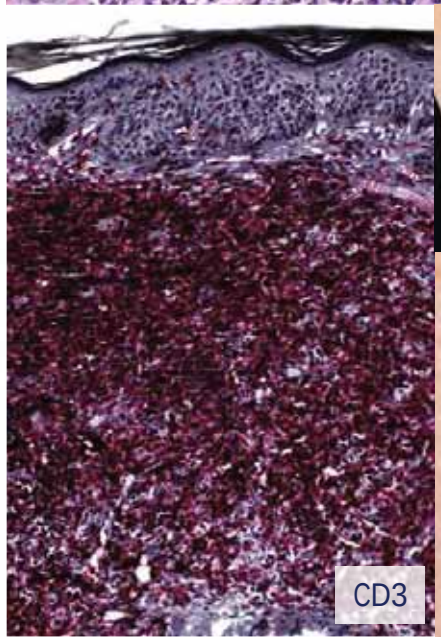
M, 79

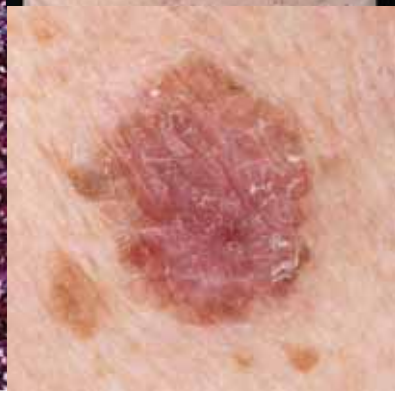
History of non-melanoma skin cancers. According to the patient "new" lesion on the right back (not mentioned in the chart 16 months previously).

A biopsy is taken.









Seborrheic keratosis with pseudolymphomatous infiltrate

Seborrheic keratoses with inflammatory infiltrate

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CLINICAL LETTER

Seborrheic keratosis-like mycosis fungoides: A rare variant with clinical, dermatoscopic, and dermatopathological features

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Dear Editors,

Classic mycosis fungoides (MF) is characterized by patches, plaques, and tumor lesions in sun-protected areas. MF can mimic many inflammatory diseases and present with different morphological findings.[1] Seborrheic keratosis (SK)-like MF is a rare clinicopathological variant of MF, which has been reported in only two cases to date. SK-like MF can be considered when epidermal atypical lymphocytes accompany histopathological findings similar to SK.[2,3] Also in patients with MF, SK may manifest as Leser-Trélat sign or in the form of collisions.[4–6]

A 38-year-old woman presented with erythematous patches extending from the left breast to the back, accompanied by SK-like papules (Figure 1a,b), initially appearing a decade ago with recent progression. Similar lesions emerged in the pubic and left inguinal regions over the past 2–3 months. Erythematous patches were noted in the right axilla and neck during examination. Dermatoscopy revealed milia-like cysts, comedo-like openings, and well-demarcated borders, suggestive of SK (Figure 1c,d). Biopsies of the lesions on the left back showed basaloid proliferation resembling SK, along with keratin cysts, and atypical lymphocytes in the epidermis and dermis. A few cells in the dermis were CD30-positive (Figure 2). The biopsy from the right axilla was consistent with the patch phase of MF and showed large-cell transformation. Monoclonal T-cell receptor rearrangement was observed. Laboratory tests, lymph node ultrasound, peripheral smear, and peripheral blood flow cytometric examination revealed no abnormalities. No additional malignancies beyond MF were detected. The patient was diagnosed with SK-like MF, with an affected surface area of 8% and classified as stage 1A MF (T1N0M0B0).

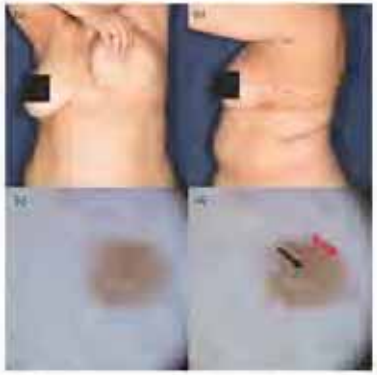


FIGURE 1 (a, b) Papules resembling SK on an erythematous patch extending from the lateral aspect of the left breast to the back. (c) The dermatoscopic appearance of a SK-like lesion in polarized mode. (d) In the non-polarized mode, comedo-like openings (black arrow) and milia-like cysts (red arrow).

We initiated a combination therapy of pegylated interferon alfa-2a (180 μg/week), as recommended by EORTC and German guidelines, along with narrowband ultraviolet B three times weekly.[7,8] By the four-month follow-up, patch lesions had regressed, and most SK-like papules had flattened or regressed.

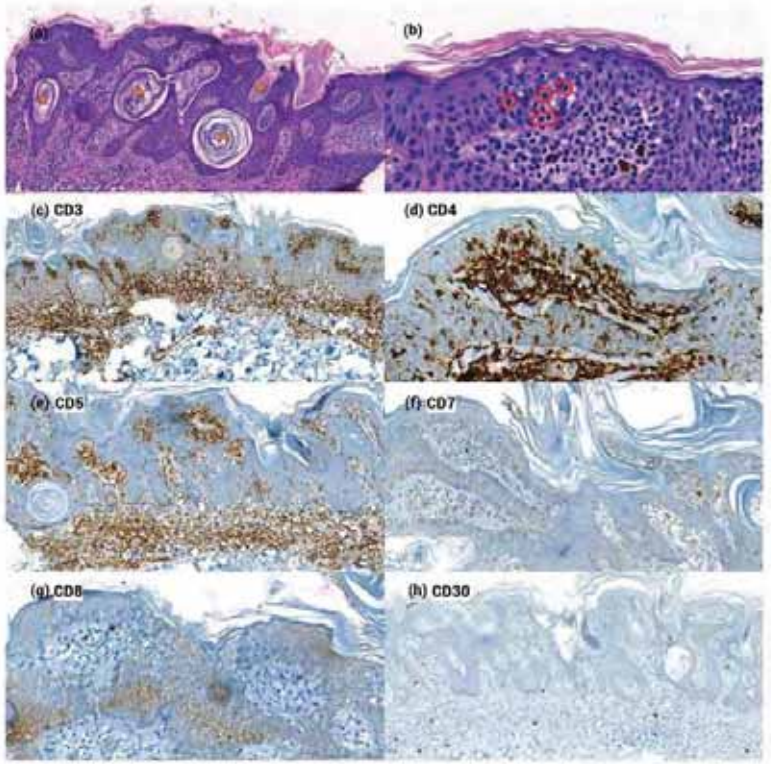
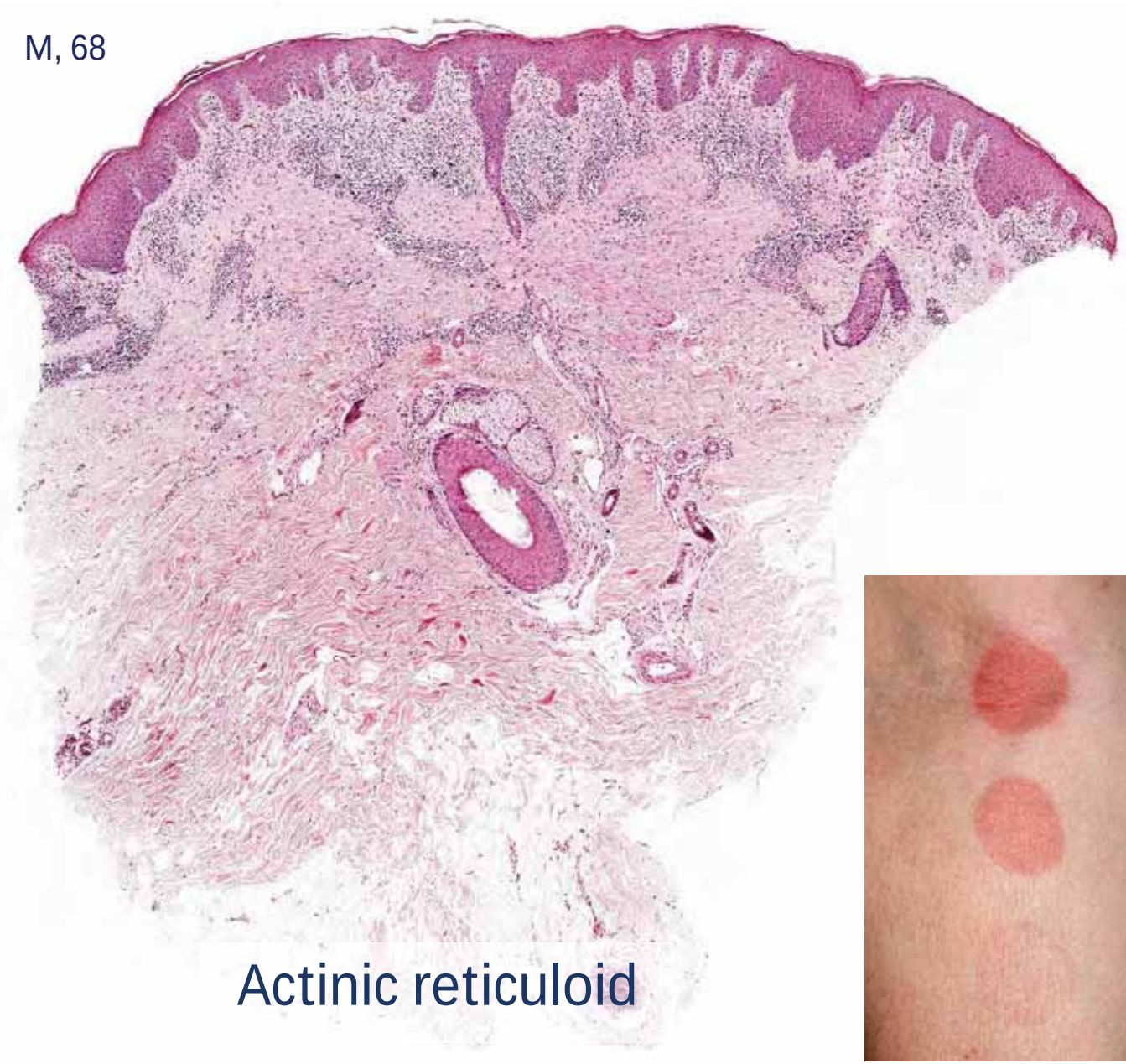


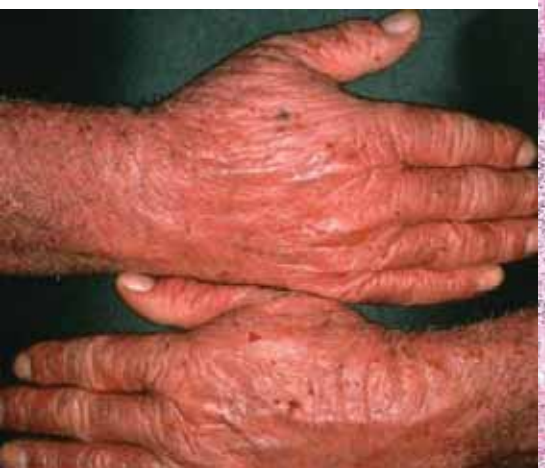
FIGURE 2 (a) Basaloid proliferation resembling SK in the epidermis and keratin cysts within it (stars), along with perivascular and scattered moderate lymphoid cells in the fibrotic appearance of the dermis (hematoxylin and eosin stain [HE], original magnification x 13.3). (b) Small to medium-sized, hyperchromatic, irregular nuclei atypical lymphoid cells within the epidermis (enclosed in red circles) (HE, x 59.8). (c) Nearly all of the lymphoid cells in the epidermis and dermis are $CD3^+$ T cells (Immunohistochemical [IHC] CD3 staining x 6.8). (d, g) The majority of T cells are $CD4^+$ and $CD8^-$ (IHC CD4 staining x 34, IHC CD8 staining x 35). (e) There is no loss of expression with CD5 (IHC CD5 staining x 14). (f) There is loss of expression with CD7 (IHC CD7 staining x 22). (h) There is scattered positivity for CD30 in the dermis with very few cells (IHC CD30 staining x 9).

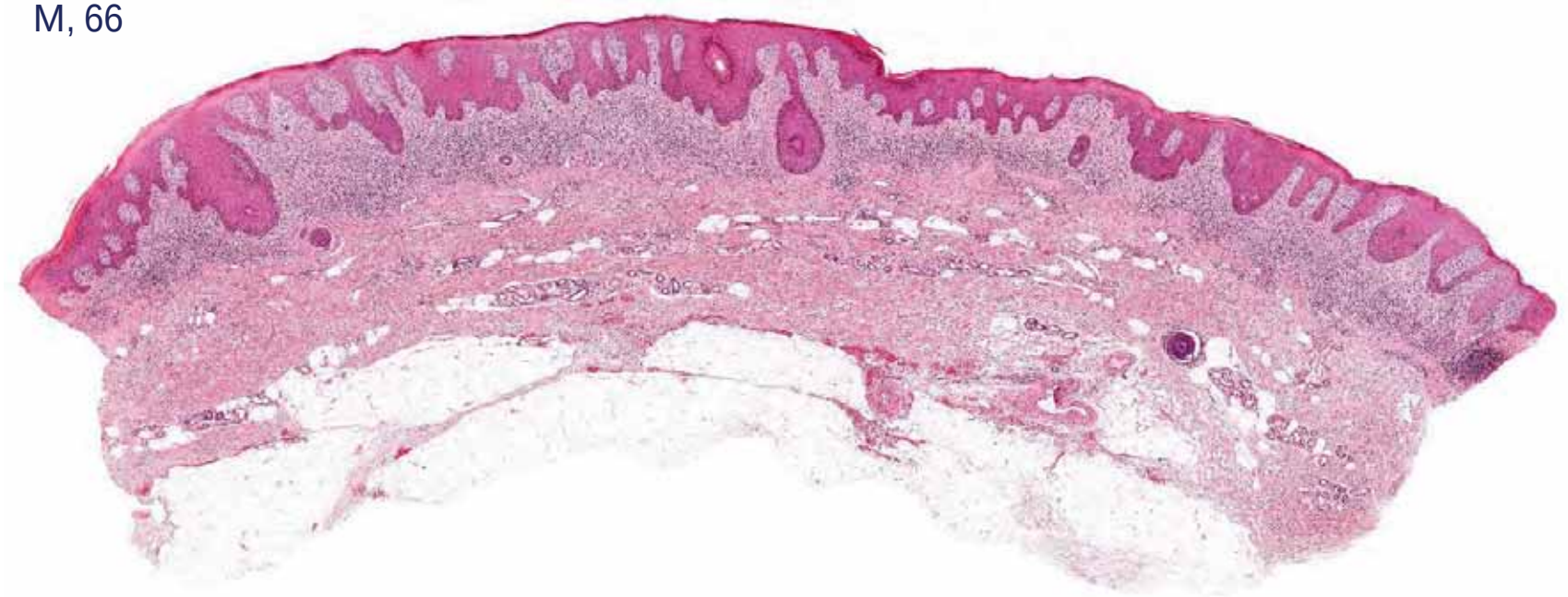
M, 68

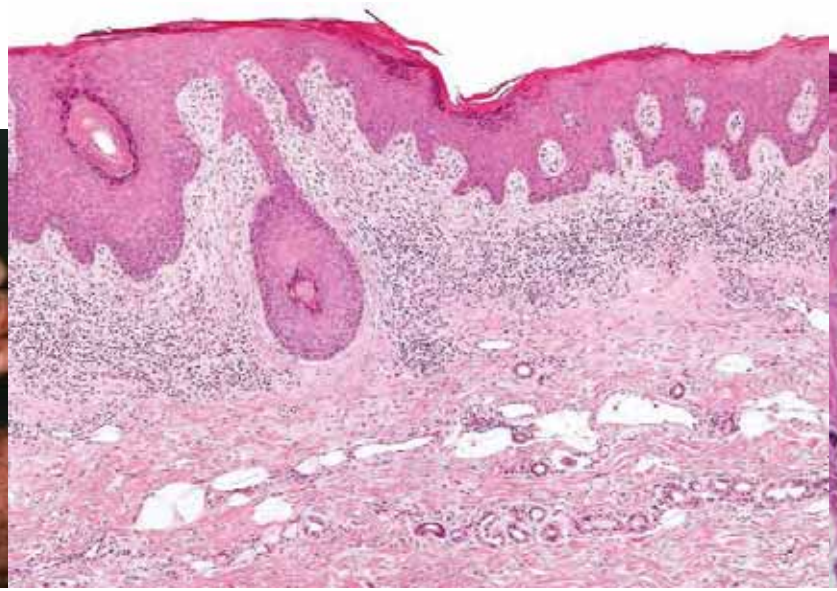


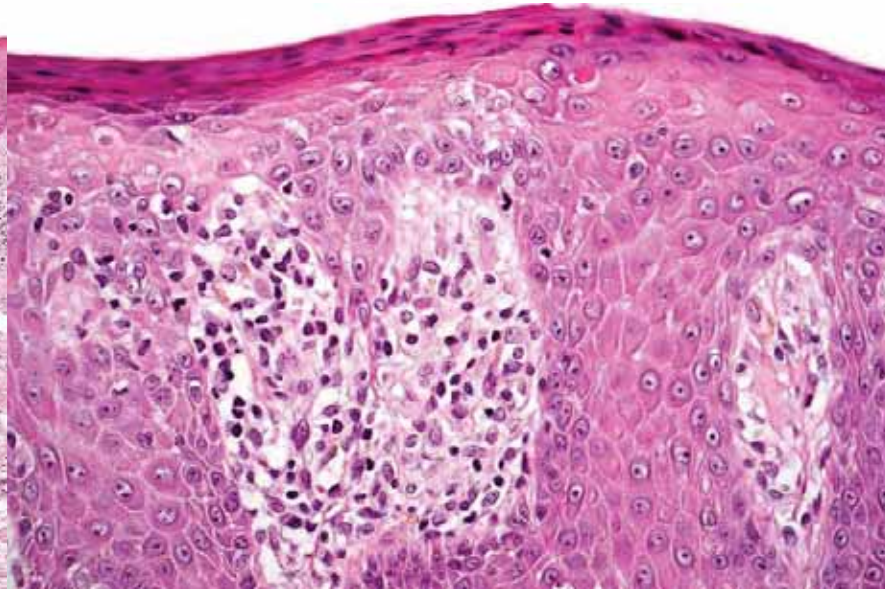
Actinic reticuloid

M, 66









J Clin Pathol 1998;51:154–158

Differentiation between actinic reticuloid and cutaneous T cell lymphoma by T cell receptor γ gene rearrangement analysis and immunophenotyping

V Bakels, J W van Oostveen, A H Preesman, C J L M Meijer, R Willemze

Abstract

***Aims*—Differentiation between actinic reticuloid and cutaneous T cell lymphoma can be extremely difficult. Demonstration of clonal T cell receptor (TCR) gene rearrangements has been suggested as a potential diagnostic criterion, but the results obtained thus far have been conflicting. This study investigated whether TCRγ gene rearrangement analysis, using polymerase chain reaction (PCR) in combination with denaturing gradient gel electrophoresis (DGGE) and immunohistochemistry, can serve as a diagnostic criterion.**

***Methods*—PCR/DGGE was performed on skin, peripheral blood mononuclear cells, and/or lymph nodes of seven patients with actinic reticuloid, 11 patients with Sézary syndrome, and 15 patients with a benign form of erythroderma. The results of PCR/DGGE and Southern blot analysis of TCRβ gene rearrangements were compared. In addition, CD4:CD8 ratios in skin and peripheral blood samples were inves-**

analysis, in combination with immunohistochemistry, may be an important adjunct in differentiating between actinic reticuloid and cutaneous T cell lymphoma. In patients suspected of having actinic reticuloid, application of both techniques is recommended.

(*J Clin Pathol* 1998;51:154–158)

Keywords: actinic reticuloid; T cell receptor gene rearrangement; cutaneous T cell lymphoma; polymerase chain reaction/denaturing gradient gel electrophoresis

Actinic reticuloid is a severe, chronic photosensitivity disorder, first described by Ive.[1] The clinical picture is characterised by an eczematous, pruritic eruption, predominantly present on light exposed areas of skin. Frequently, lesions spread to covered areas, leading to erythroderma. This erythrodermic variant of actinic reticuloid can resemble Sézary syndrome, a type of cutaneous T cell lymphoma. Apart from erythroderma, pruritus, lymphadenopathy, and the presence of atypical lymphocytes in the peripheral blood, patients with the erythrodermic form of actinic reticuloid and patients with Sézary syndrome may also have alopecia, palmoplantar hyperkeratosis, or onychodystrophy.[2 3]

Histologically, actinic reticuloid is characterised by the presence of extensive dermal infiltrates of medium sized lymphoid cells with cerebriform or convoluted nuclei. These cells show epidermotropism and sometimes even form Pautrier-like microabcesses.[1 3] These cellular and histological features are also characteristic for mycosis fungoides, the most common variant of cutaneous T cell lymphoma.

and the results have been conflicting.[8 12 13]

Therefore, we investigated the presence of clonal T cell populations in skin, lymph node and/or peripheral blood samples of patients with actinic reticuloid, Sézary syndrome, or a benign form of erythroderma, by means of polymerase chain reaction (PCR) amplification of the TCRγ gene in combination with denaturing gradient gel electrophoresis (DGGE). In addition, immunophenotypic analysis was performed on skin and peripheral blood samples to assess the proportions of $CD4^+$ and $CD8^+$ T cells.

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Immunophenotypic analysis demonstrated increased proportions of CD8+ T cells in the skin in seven of seven cases of patients with actinic reticuloid.

Chronic Actinic Dermatitis/Actinic Reticuloid: A Clinicopathologic and Immunohistochemical Analysis of 37 Cases

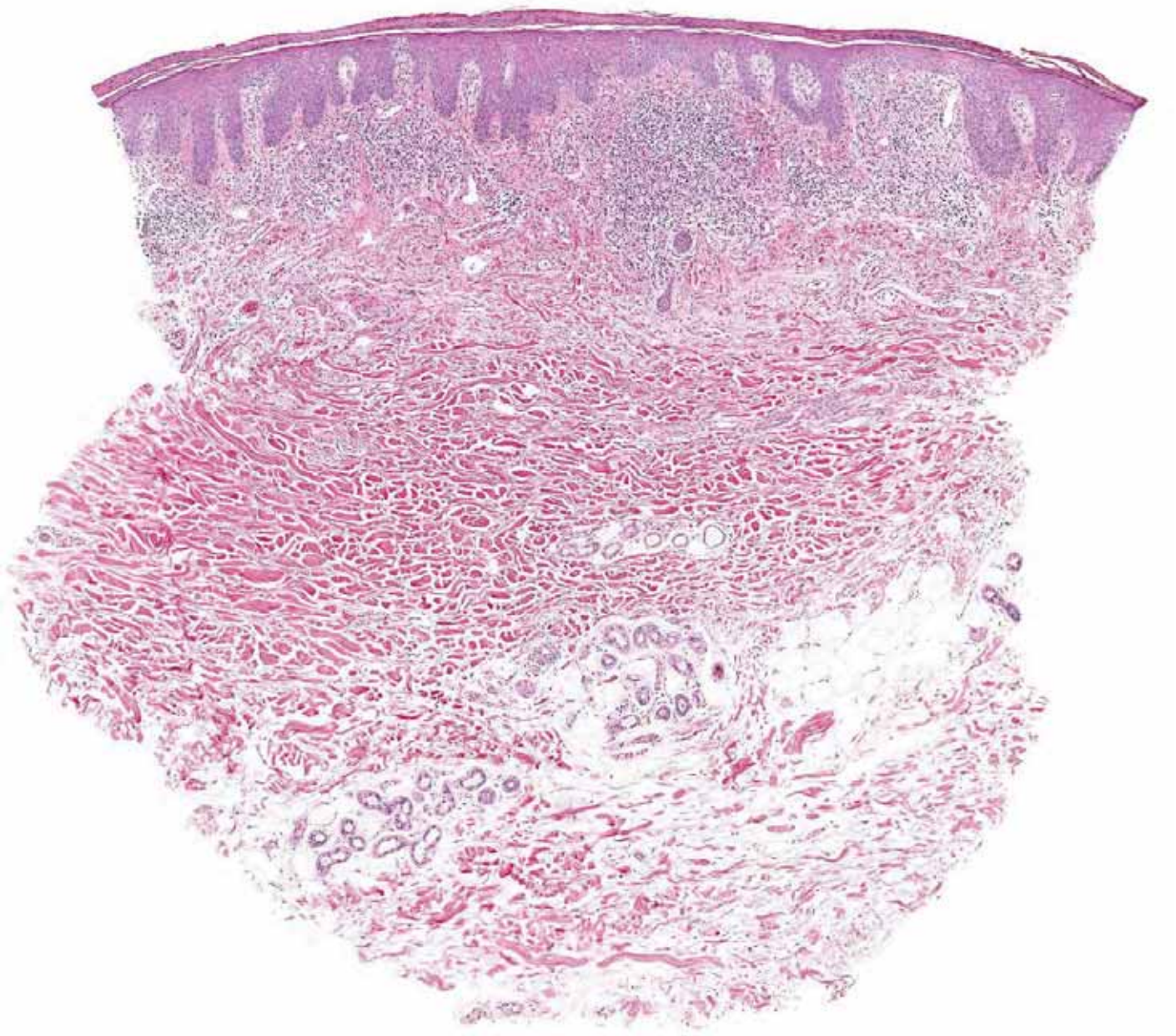
Michael Sidiropoulos, MD, MSc, Janyana Deonizio, MD,* M. Estela Martinez-Escala, MD,* Pedram Gerami, MD,*† and Joan Guitart, MD*†*

TABLE 2. Summary of Pathologic Data

Characteristic	Total Sample (%)
Acanthosis	37/37 (100)
Spongiosis	37/37 (100)
Dermal lymphocytic infiltrate	37/37 (100)
Papillary dermal fibroplasias	37/37 (100)
Melanin-laden macrophages	37/37 (100)
Prominent stellate dermal dendrocytes	37/37 (100)
Multinucleated dendritic cells	35/37 (95)
Plasma cells	33/37 (89)
Eosinophils	33/37 (89)
Parakeratosis	31/37 (84)
Medium-large reactive lymphocytes	25/37 (68)
Follicular infundibulum spongiosis and exocytosis	18/27 (67)
Exocytosis	23/37 (62)
Solar elastosis	23/37 (62)
Superficial serous exudate	18/37 (49)
Pautrier-like microabscesses	13/37 (35)
Epidermal infiltrate	
$CD8^+$	20/25 (80)
$CD4^+$	5/25 (20)
CD4:CD8 ratio	
<1:1	9/25 (36)
1:1	11/25 (44)
>1:1	5/25 (20)

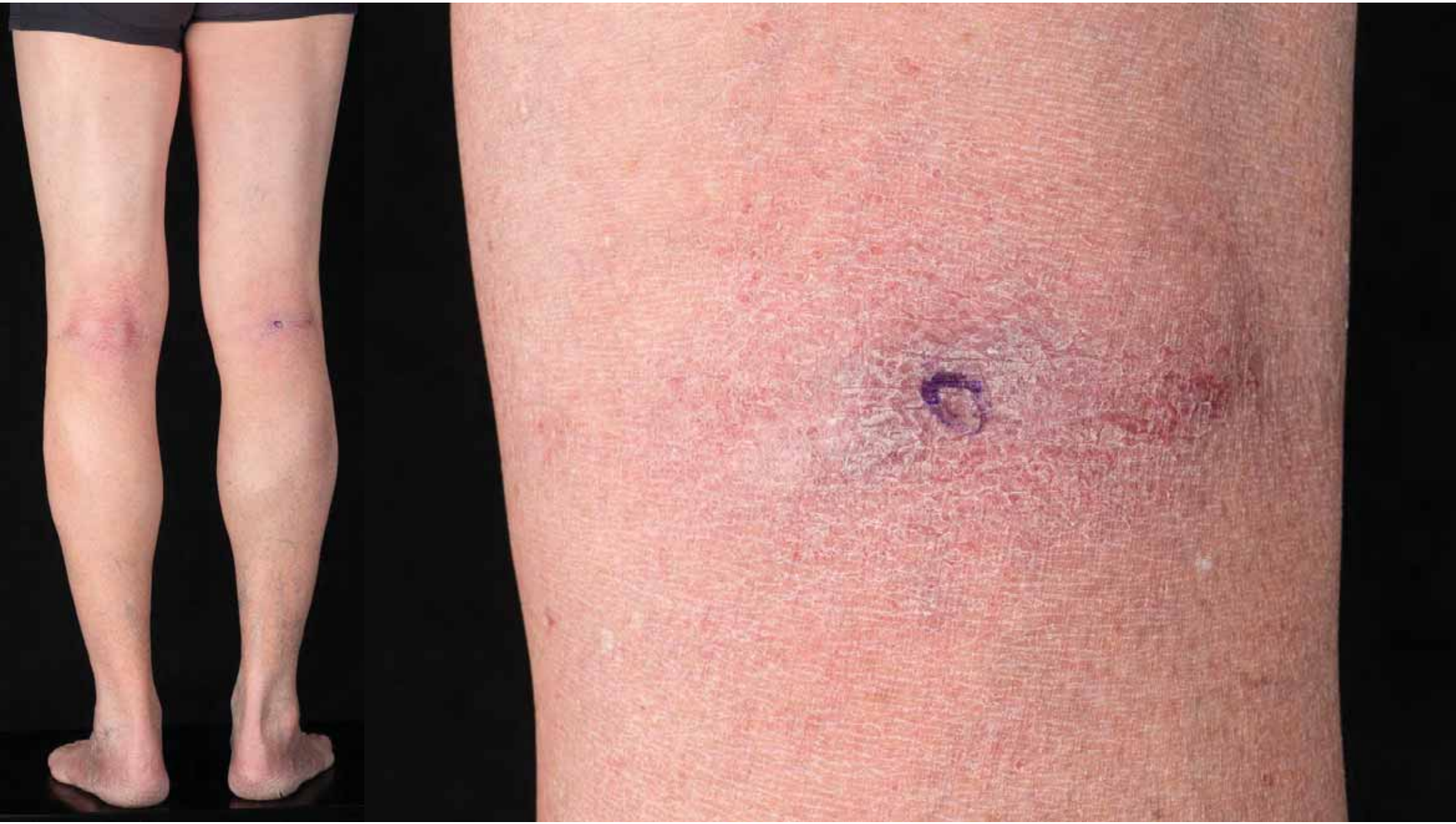
Actinic reticuloid

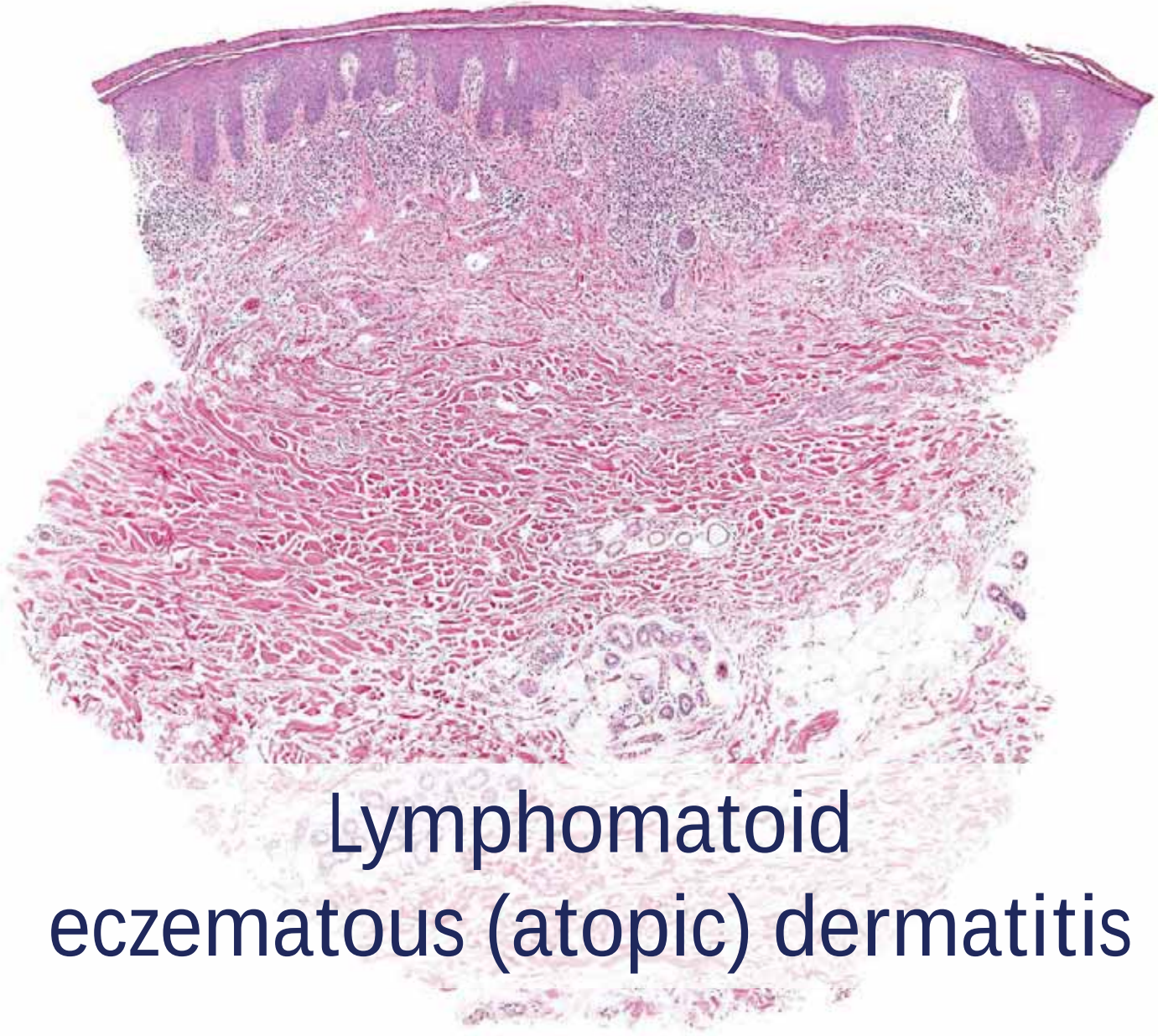
- Considered as a "prototypic" T-cell pseudolymphoma, yet most cases do not resemble histopathologically mycosis fungoides or other CTCLs (it may be indistinguishable from a chronic eczematous dermatitis)
- Clinically may become erythrodermic
- Hyperplastic epidermis with variable spongiosis, similar to lichen simplex chronicus
- "Bizarre" fibroblasts in the superficial dermis
- UV test necessary to confirm the diagnosis

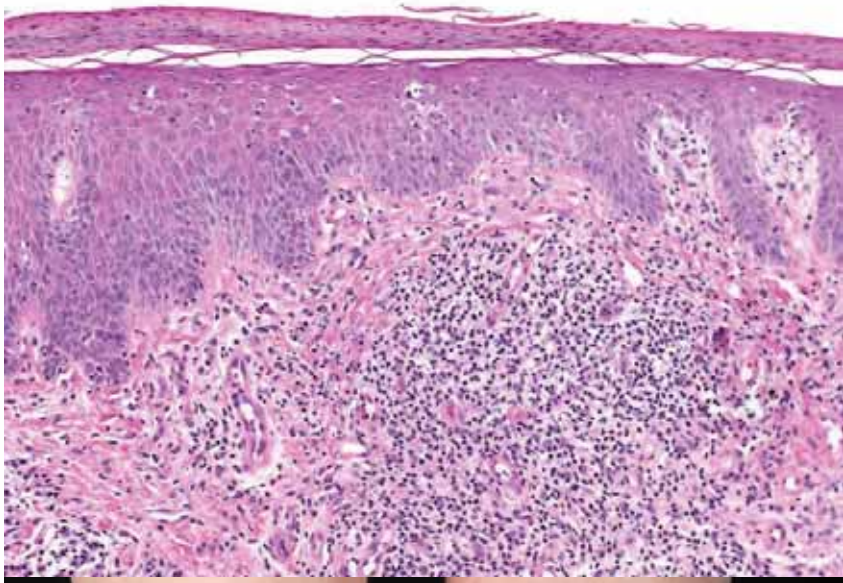


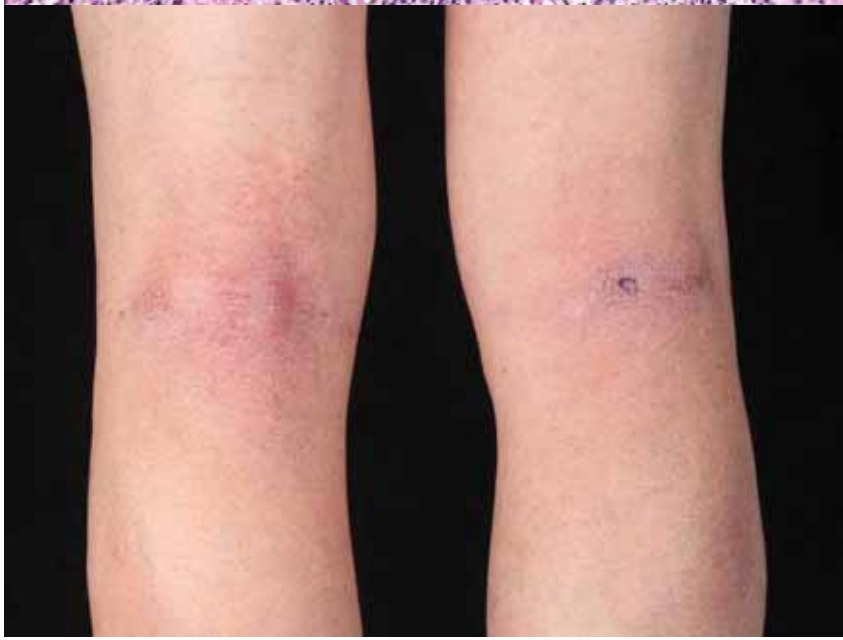
M, 72

Referred by a private dermatologist for further evaluation of itchy skin lesions on the lower extremities and elevated serum tryptase (41,3 μg/L; normal value: 0-11,4). No gastrointestinal symptoms; no other complaints.

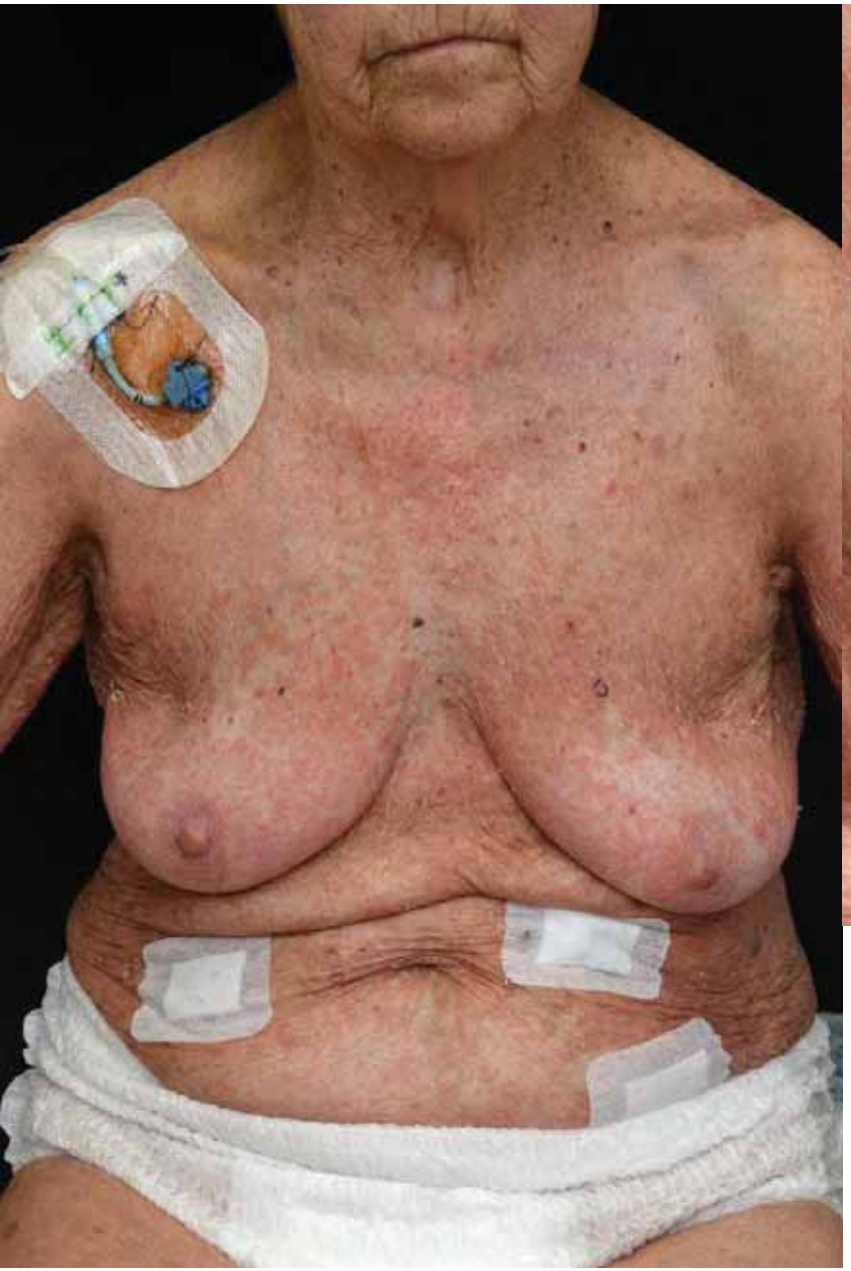


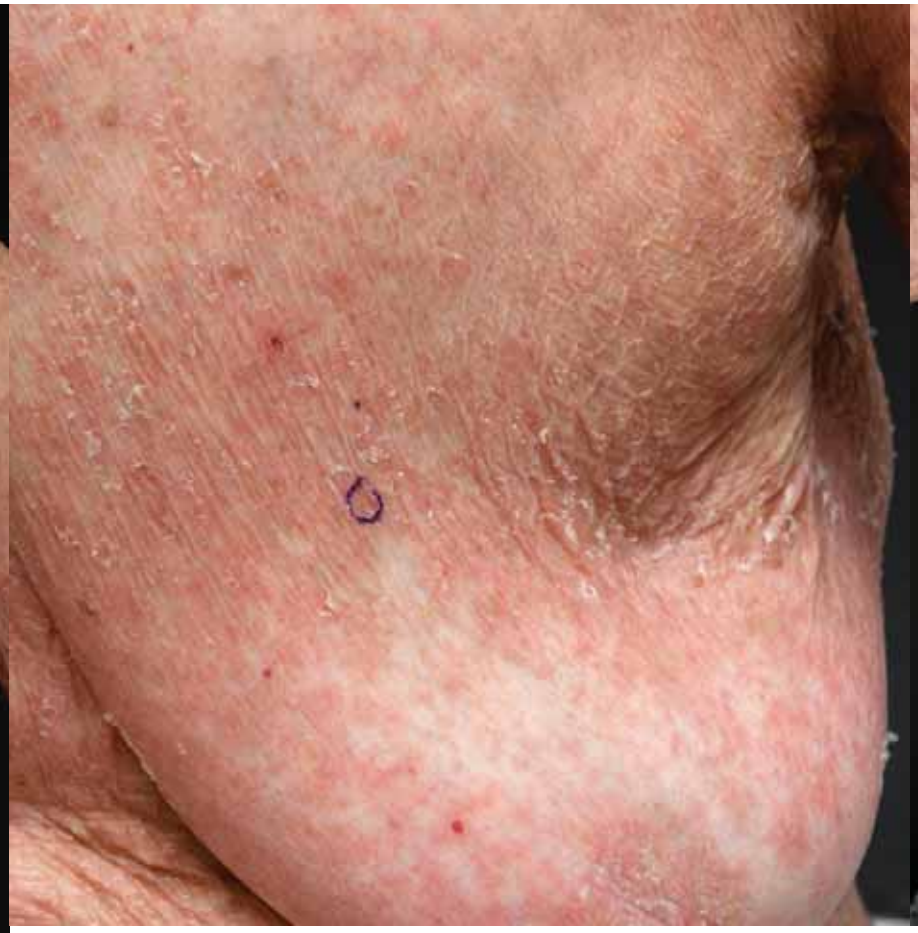


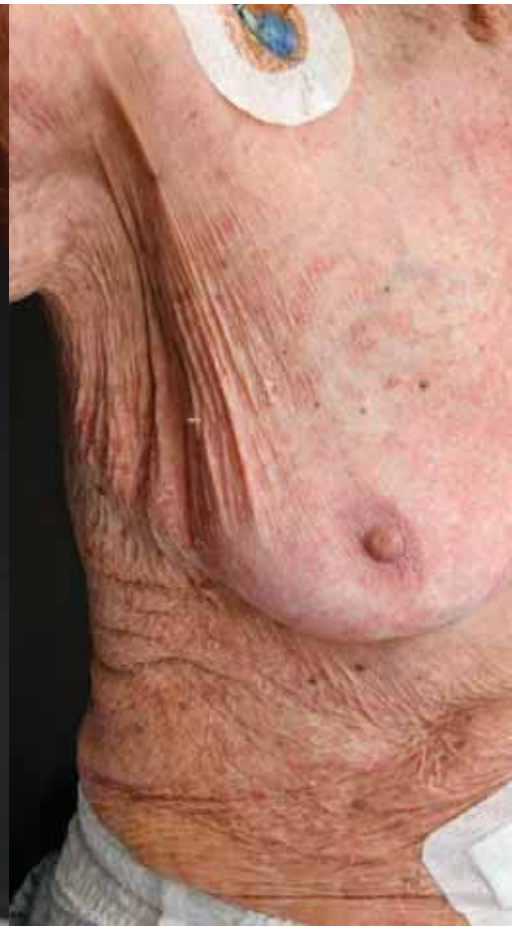




Lymphomatoid
eczematous (atopic) dermatitis



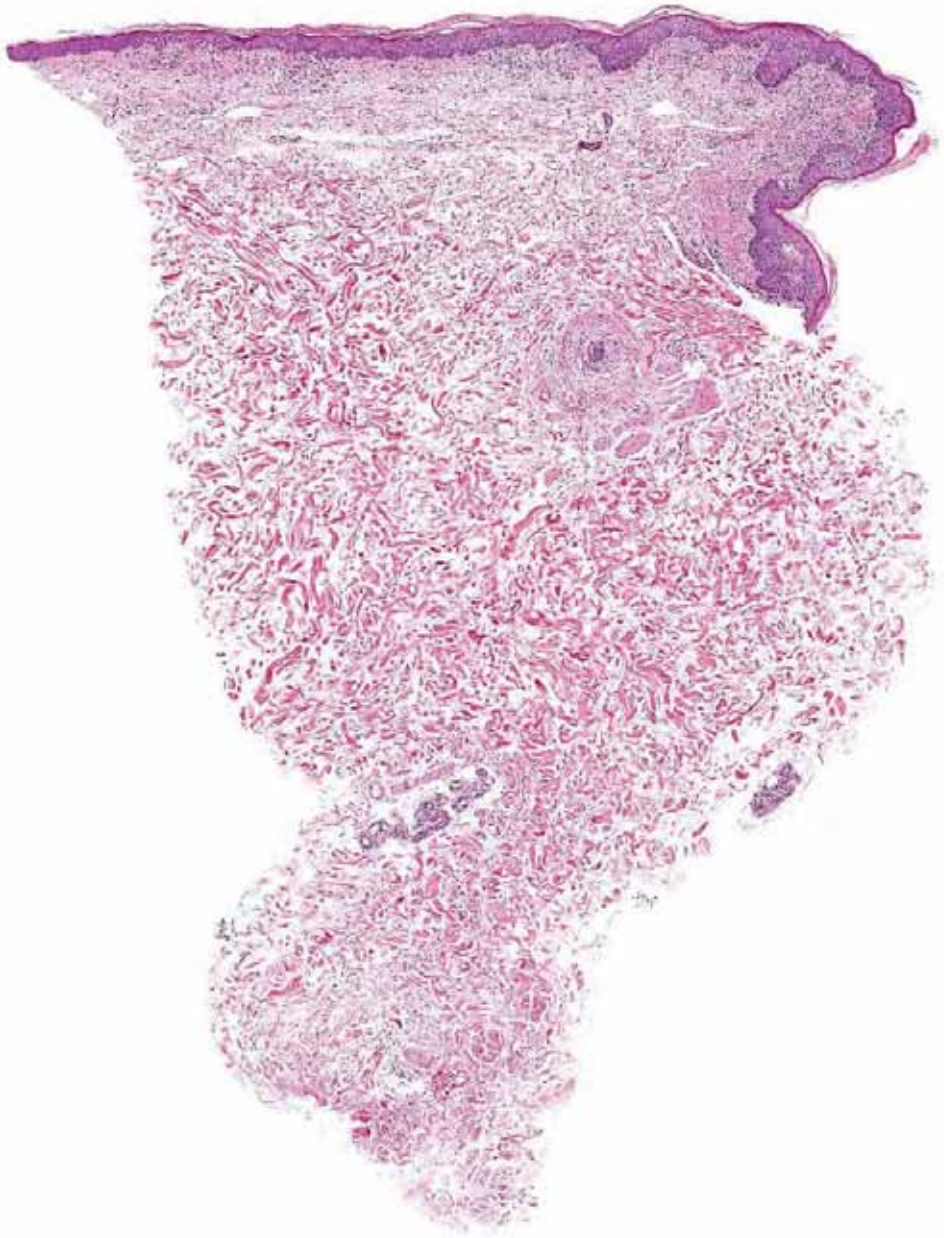


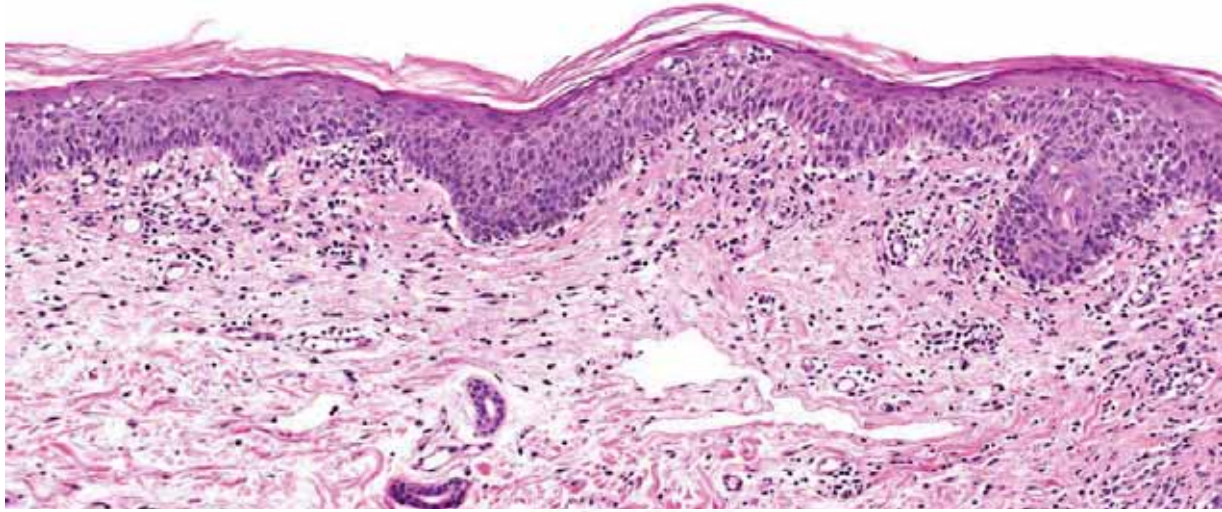


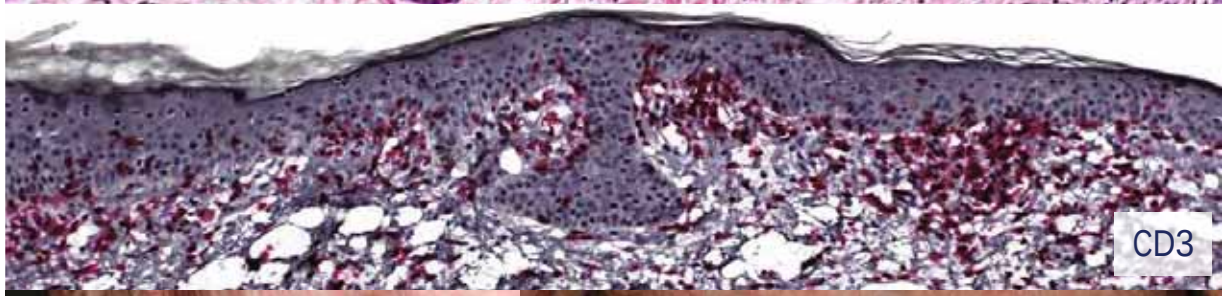
F, 85

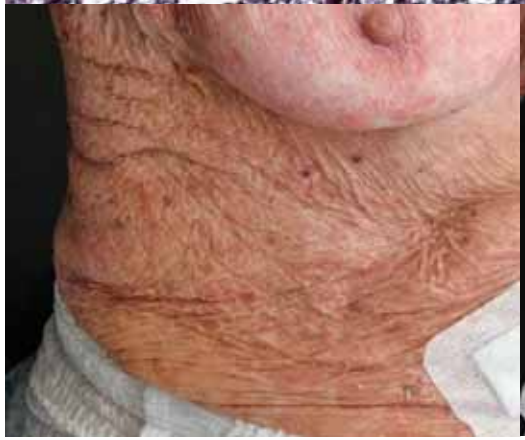
History of B-CLL stage IV, managed with ibrutinib. Itchy exanthema "for a few days".

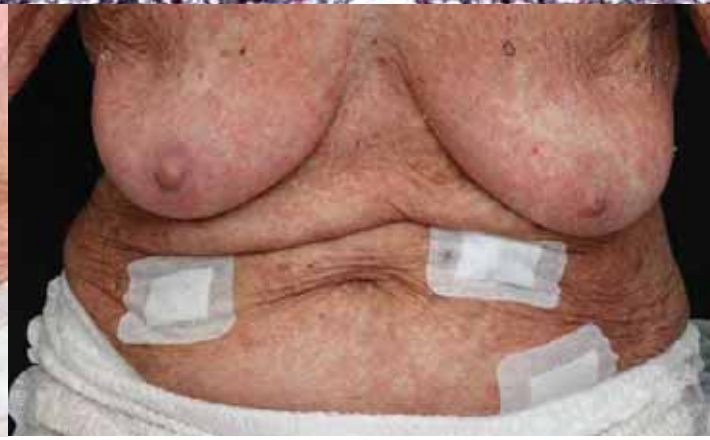
Two biopsies are taken.

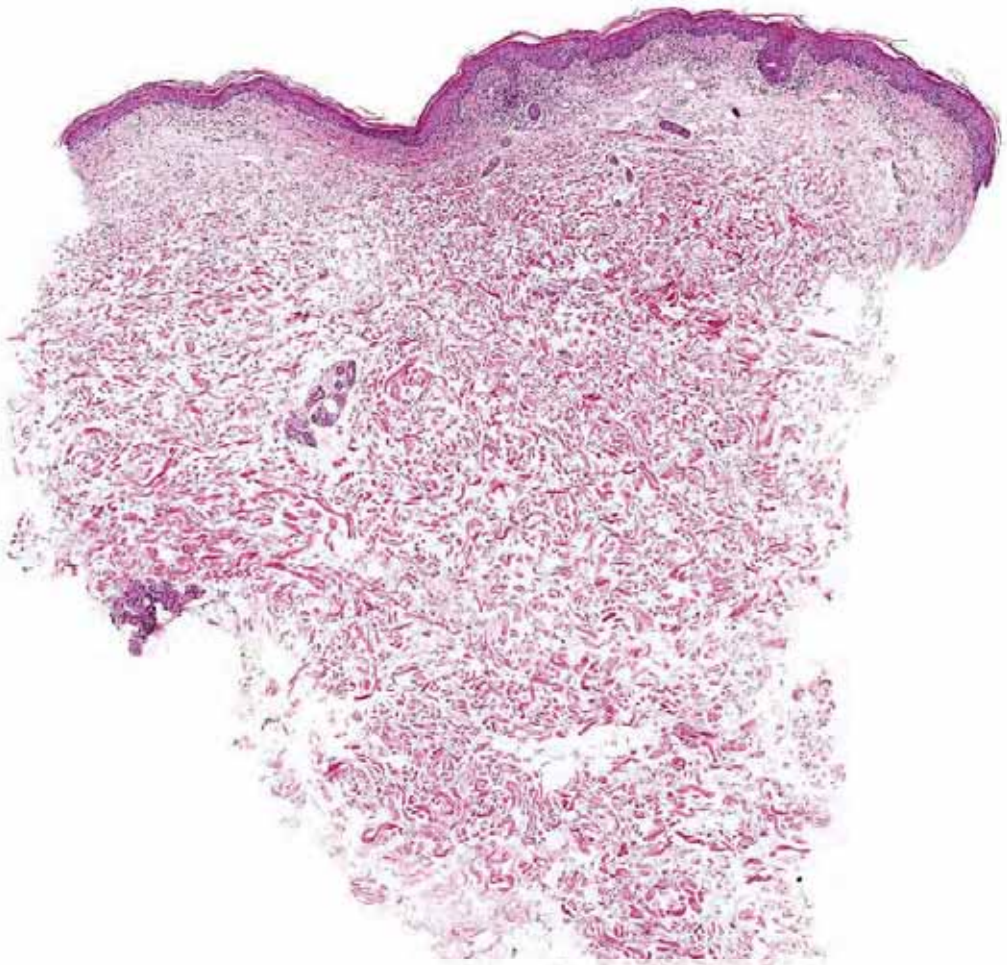


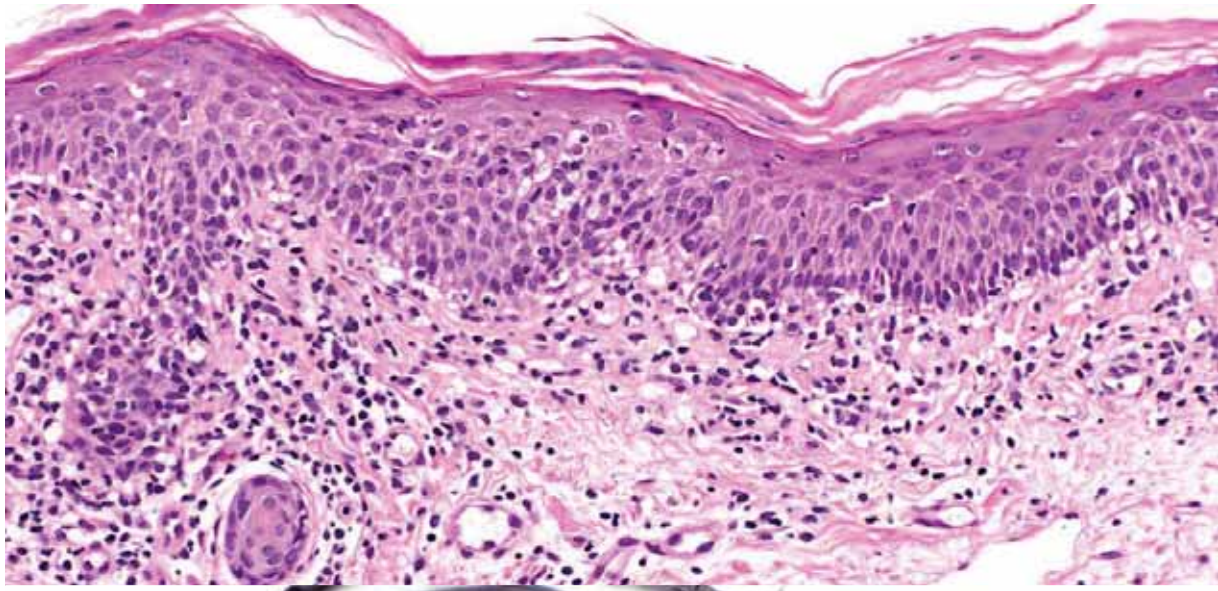


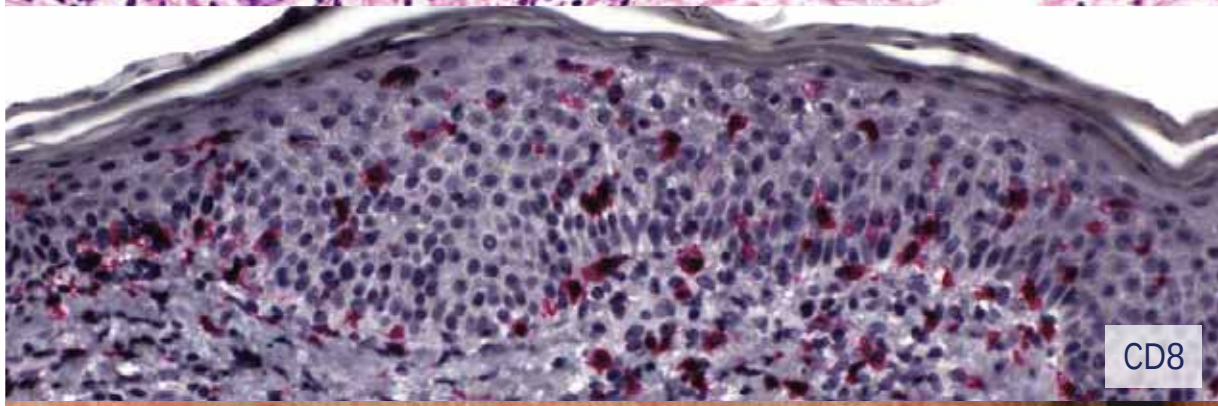

CD3

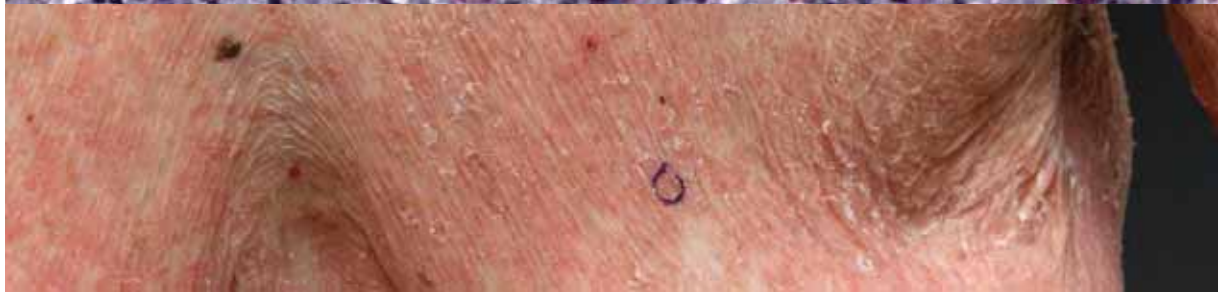












Lymphomatoid eczematous dermatitis

Contact Dermatitis 1976: 2: 139–143

Lymphomatoid contact dermatitis

A syndrome produced by epicutaneous hypersensitivity with clinical features and a histopathologic picture similar to that of mycosis fungoides

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Four cases have been studied which were clinically suggestive of mycosis fungoides because of their infiltrated plaque-like lesions, but in which the suspicion of a topical hypersensitivity arose when a positive patch test was obtained with the striker part of a box of matches.

Key words: contact dermatitis – mycosis fungoides.

Received for publication October 30, 1975

We have had occasion to observe several cases which could be interpreted clinically, from the morphological character and persistence of the lesions, as a form of xanthoerythrodermia perstans or parapsoriasis-en-plaques; with their complaint of intense pruritus they were reminiscent of mycosis fungoides. Several cases were histologically diagnosed as such. We consider it important to report these cases because they are caused by a hypersensitivity reaction.

Case histories

Case 1. A 54-year-old male had noticed a dry, pruritic erythematous plaque about the size of the palm of his hand on his right thigh about four months earlier. The plaque grew progressively in area and in depth. Some time later, a similar lesion appeared on his left thigh. The first lesion appeared in August 1973. During the ensuing months, there arose multiple erythematous, oedematous, ill-defined lesions all over the face, retroauricular areas and the sides of the neck. Their course was one of remissions and exacerbations. Topical treatment with corticosteroids did not produce any improvement. Later, he developed another lesion on the left pectoral area. Examination showed on both thighs two plaque-like lesions, about 10 cm wide, which were erythematous, scaly, intensely infiltrated and with well-defined borders. Violaceous erythematous, scaly infiltrated plaques were also found on the face, behind the ears and on the neck. There was another plaque, the size of the palm of a hand, on the left pectoral region; it had the same features as the others. Multiple biopsies were obtained which showed a dense infiltrate, band-like with histiocytes, lymphocytes and some eosinophils. There was lymphocytic exocytosis, sometimes forming nests and in some areas, limited spongiosis. The histologic picture and its clinical counterpart were like that of infiltrated mycosis fungoides.

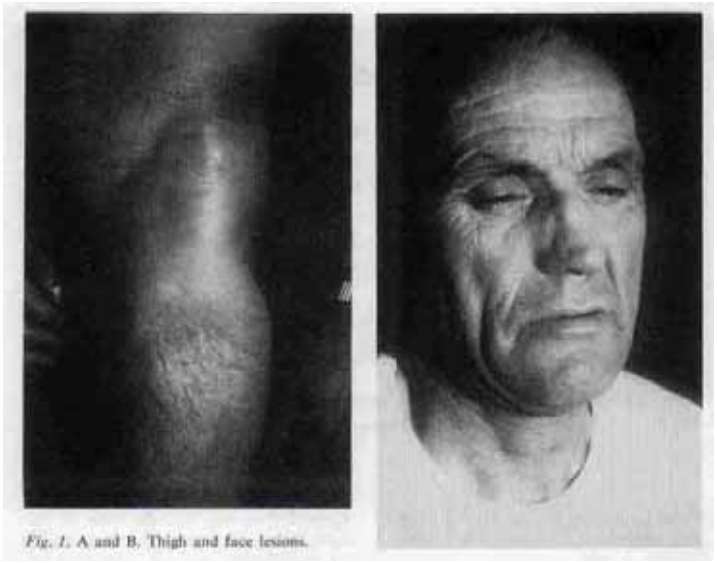


Fig. 1. A and B. Thigh and face lesions.

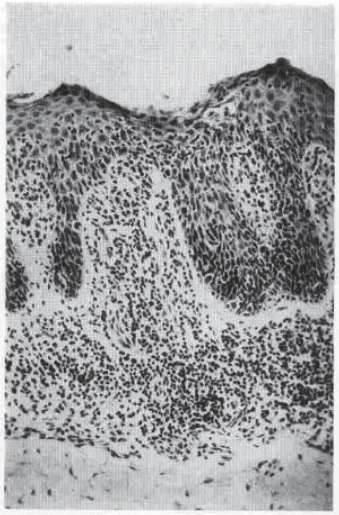


Fig. 2. Acantholytic epidermis. In the dermis there is a dense infiltrate in the form of a superficial band.

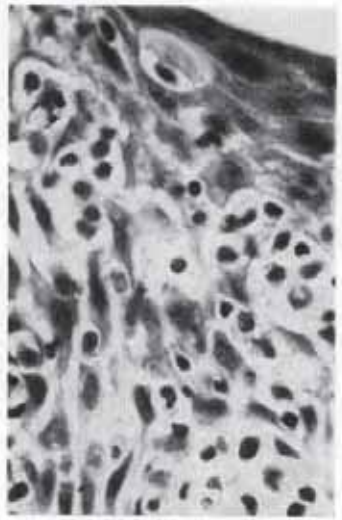


Fig. 3. Lymphocytic exocytosis sometimes forming nests, and limited spongiosis.

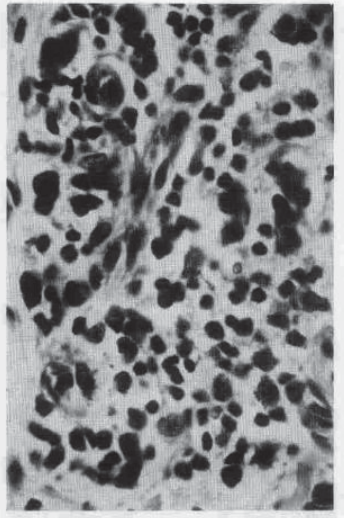
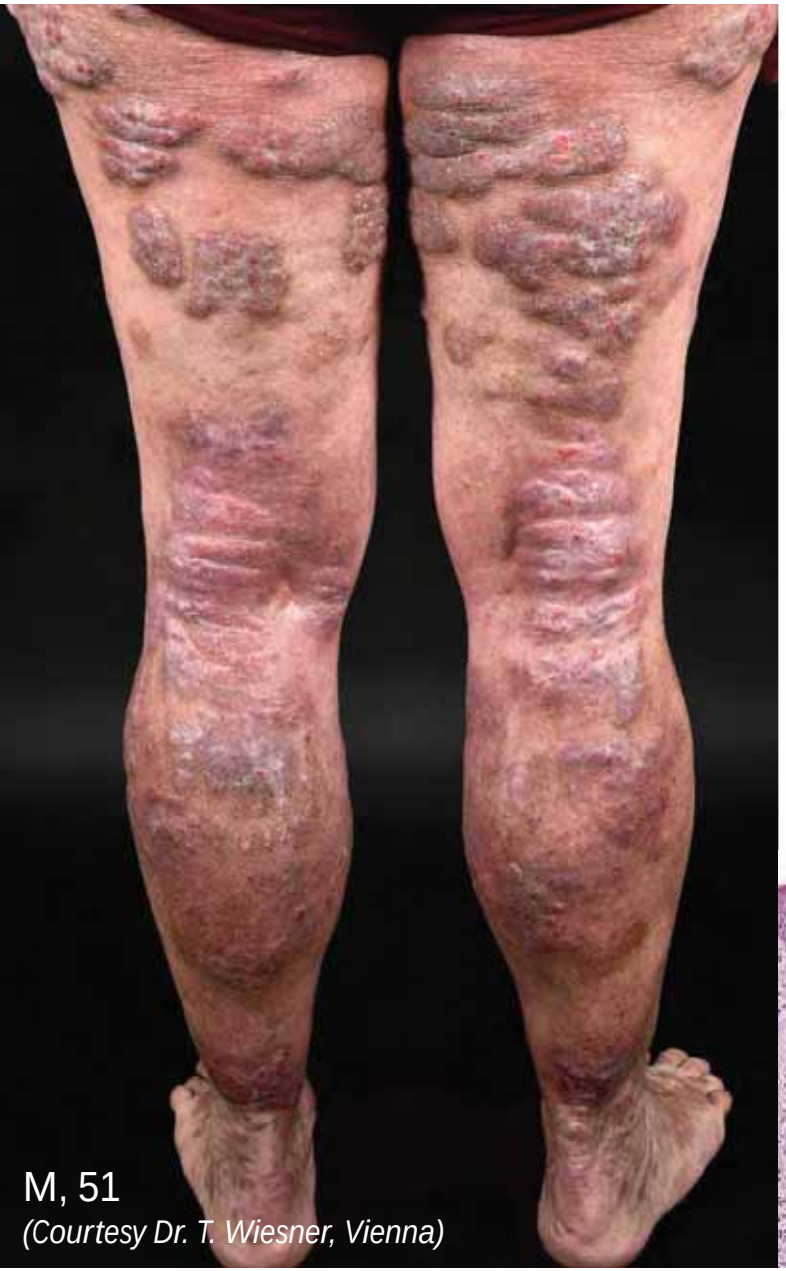


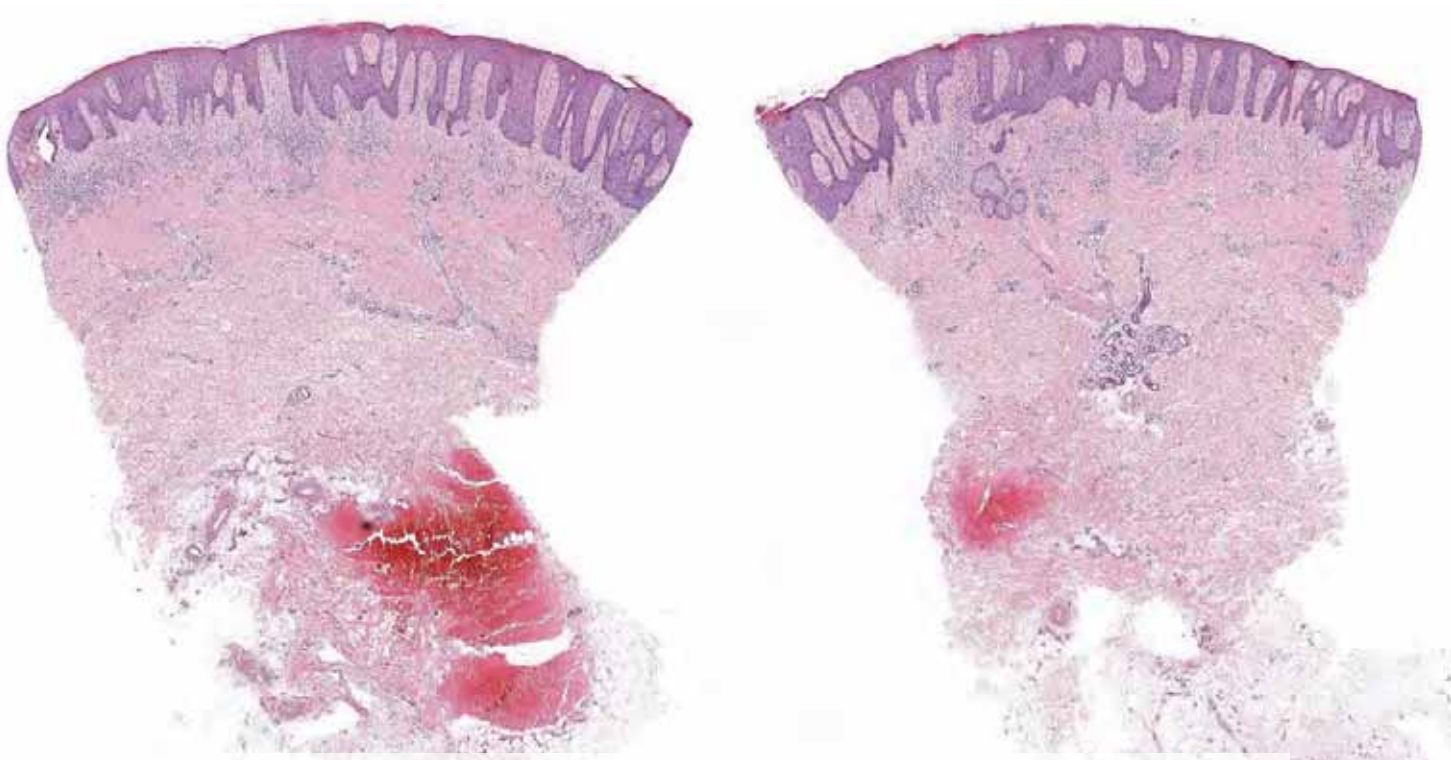
Fig. 4. Dense infiltrate of histiocytes and lymphocytes, some of which are hyperchromatic.

In my experience not restricted to contact dermatitis; may be observed in any "eczematous" dermatitis, including atopic dermatitis, xerosis cutis, and lichen simplex chronicus among others.

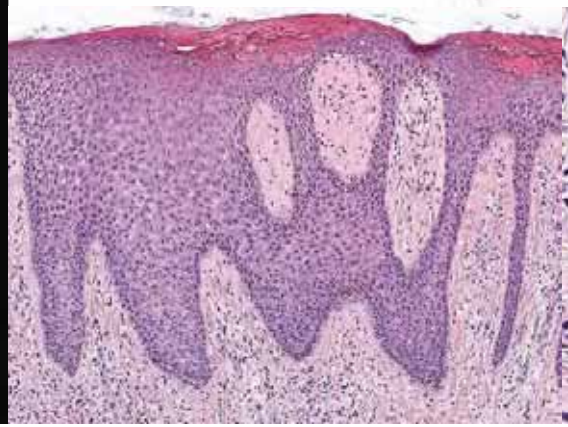


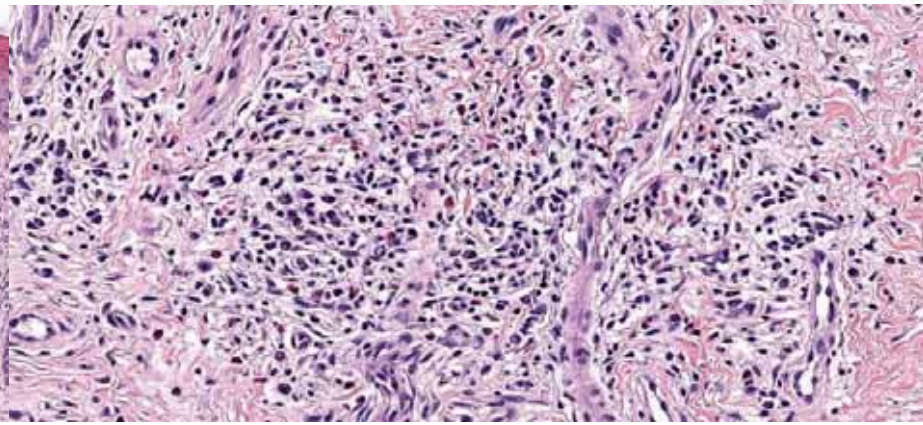
M, 51

(Courtesy Dr. T. Wiesner, Vienna)



"Pseudotumoral" eczematous dermatitis

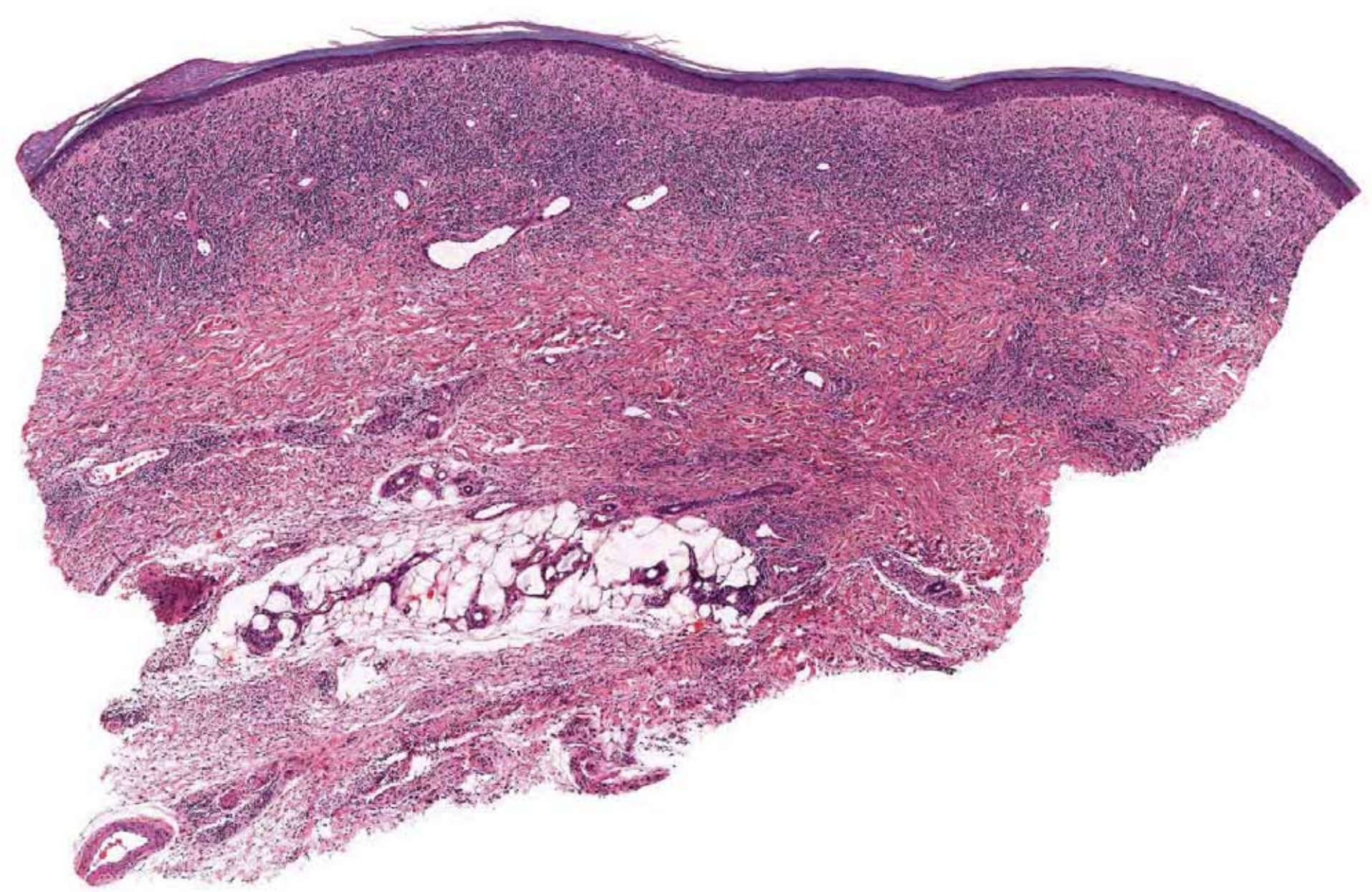


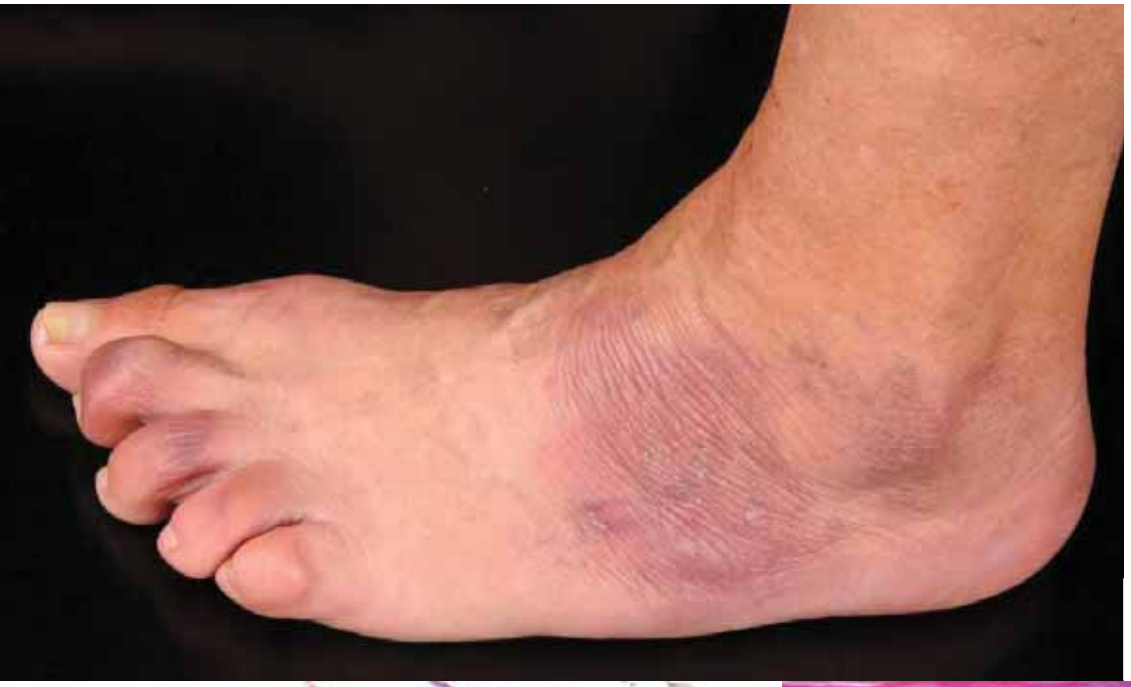


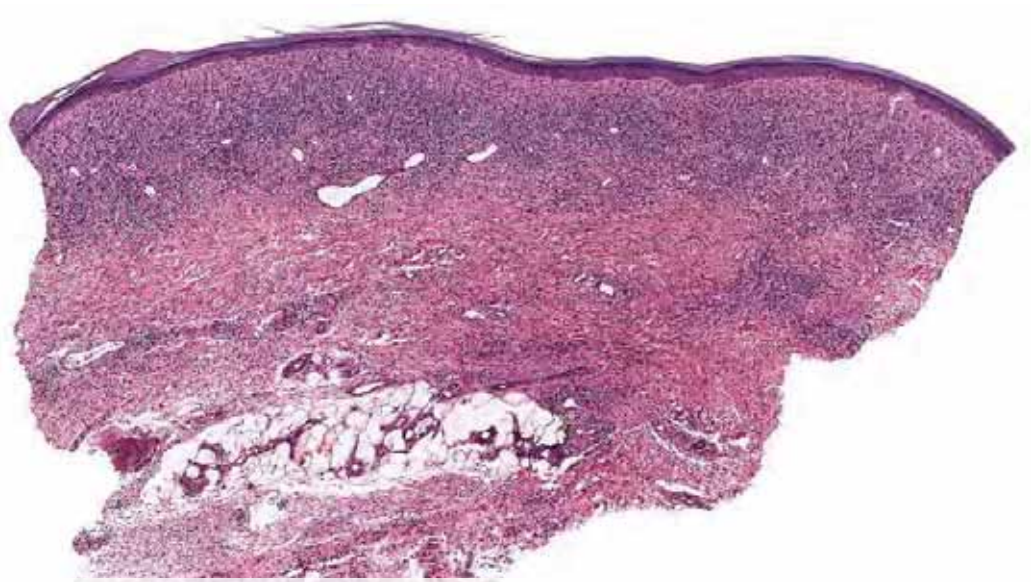
Lymphomatoid eczematous dermatitis

- Eczematous conditions may present with dense lymphoid infiltrates, potentially mimicking histopathologically mycosis fungoides
- Eczematous histopathological features (e.g., irregular acanthosis, spongiosis, parakeratosis, serum in horny layer, eosinophils in the infiltrate) usually prominent – yet similar features may be observed sometimes in mycosis funbgoides or Sèzary syndrome
- Intraepidermal lymphocytes usually positive for CD8 in eczematous dermatoses

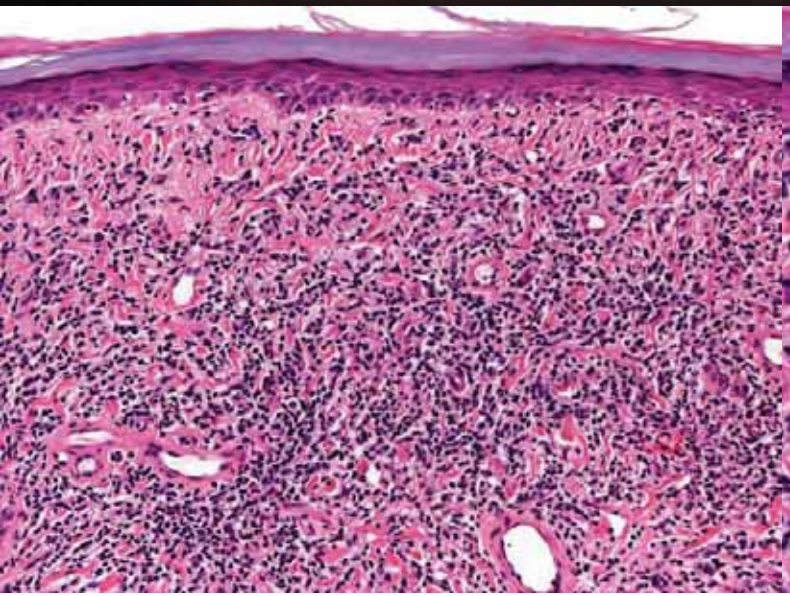
F, 68

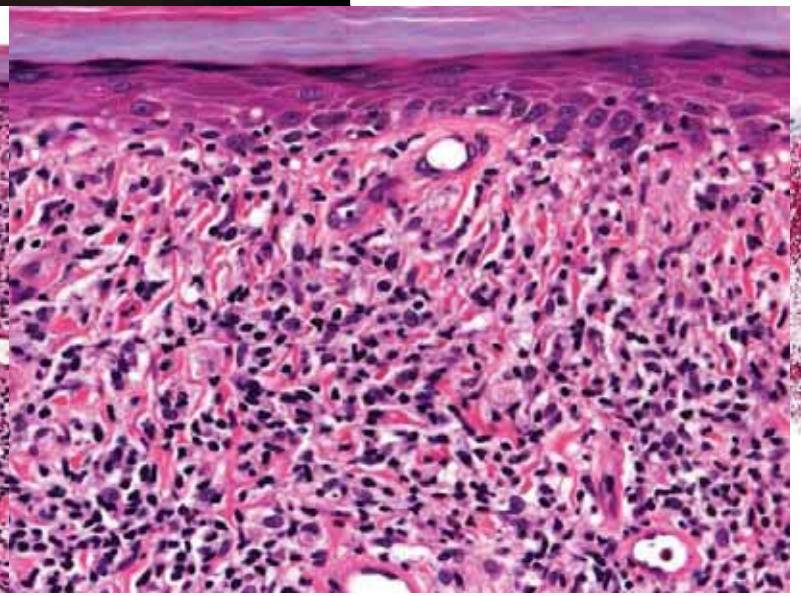


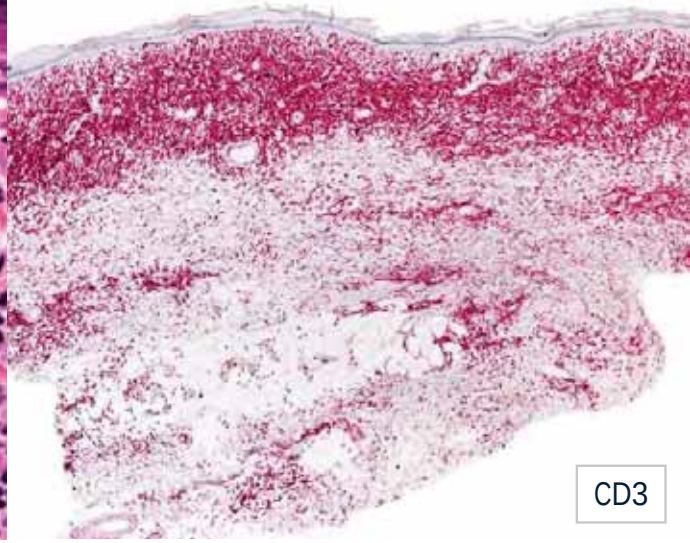




Acrodermatitis chronica atrophicans







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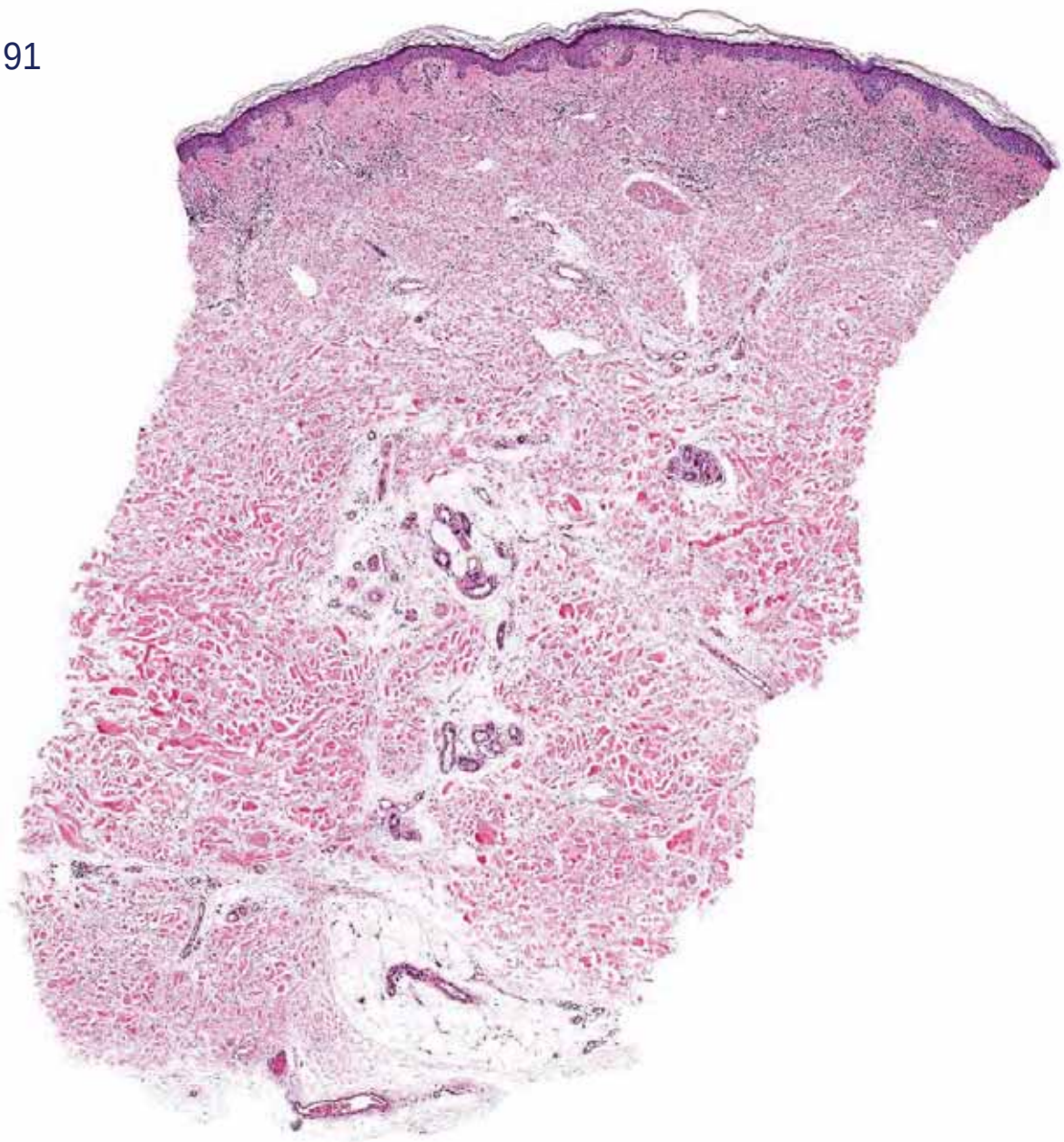

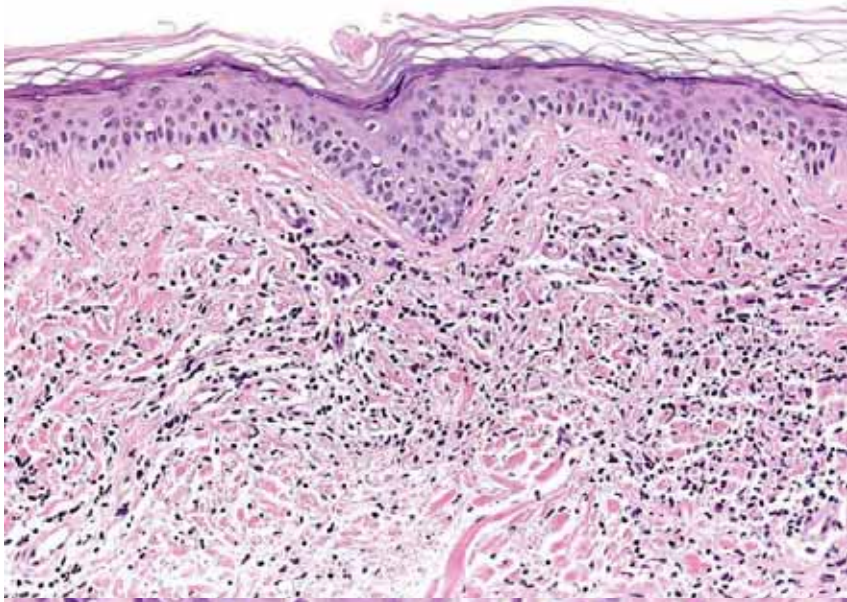

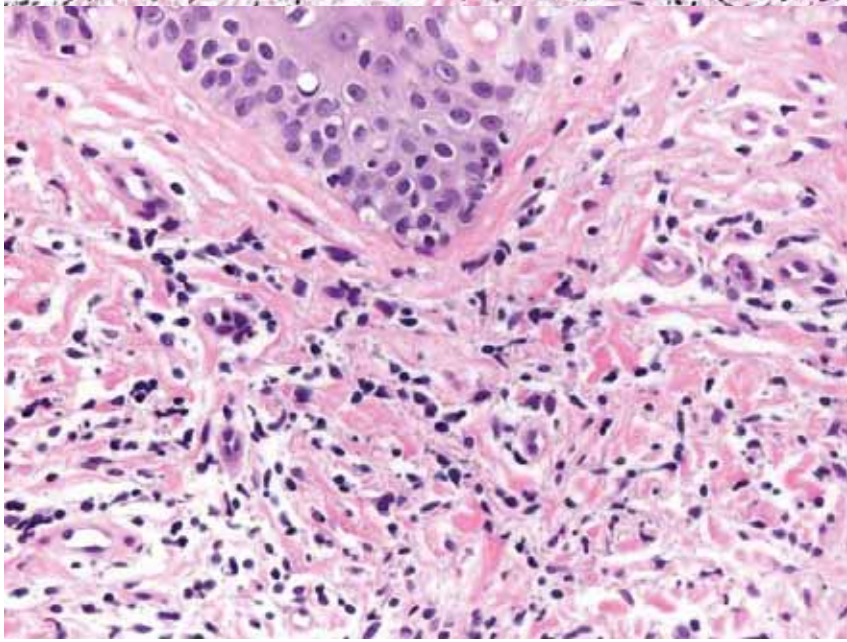

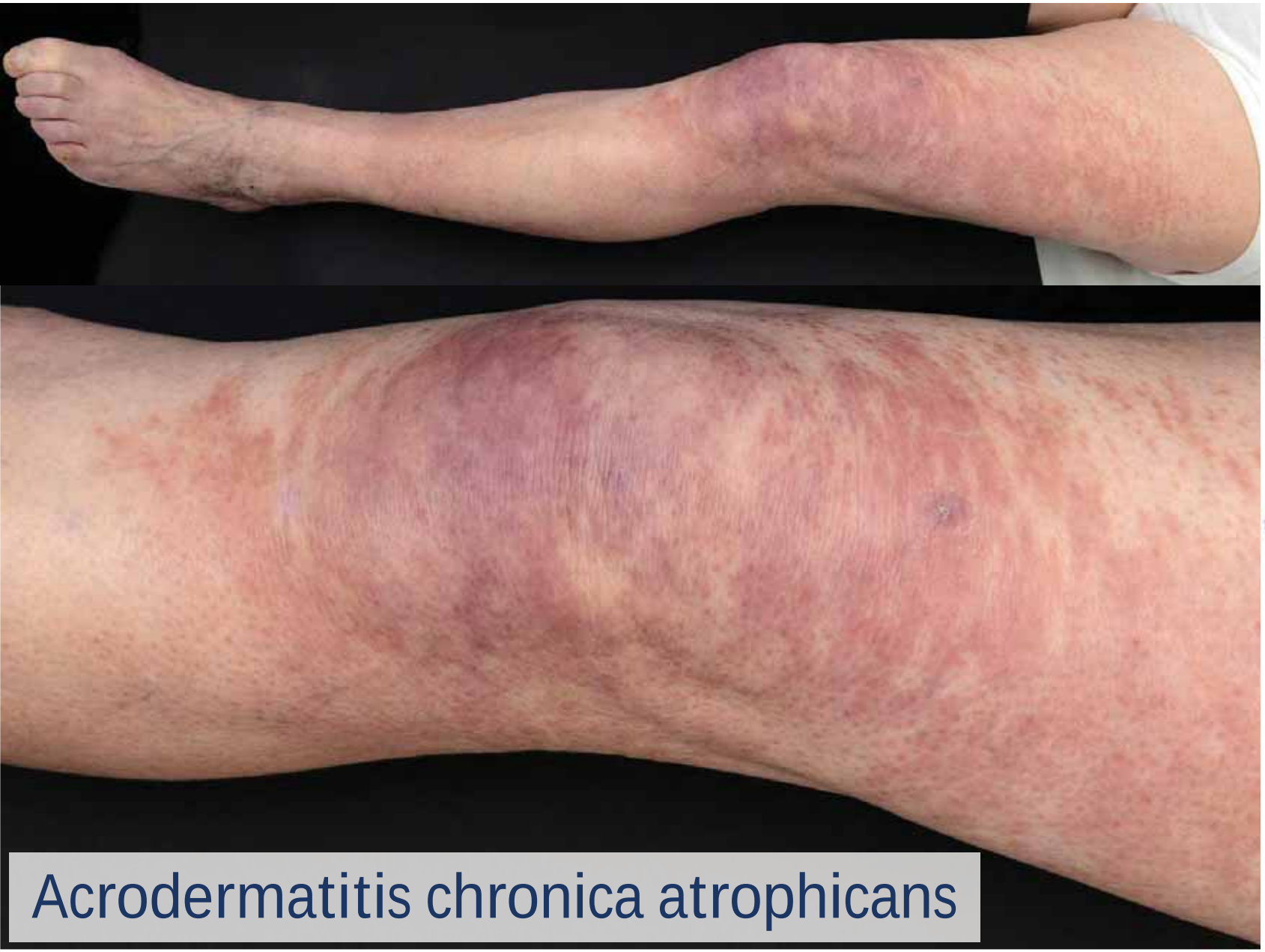

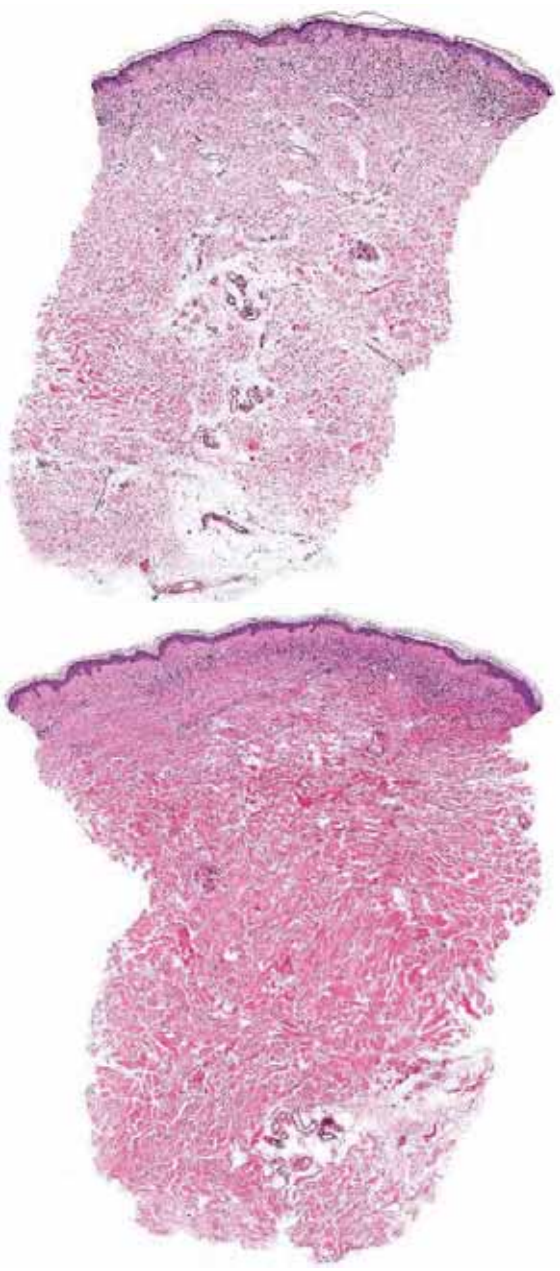

Acrodermatitis chronica atrophicans

Pseudolymphomatous ACA

- Acral sites (particularly leg, foot); usually asymmetrical distribution; may simulate histopathologically either MF or MZL
- Dense inflammatory infiltrates; frequent band-like arrangement
- T lymphocytes predominate in some cases; plasma cells reveal a polyclonal pattern
- Positive *Borrelia* serology; PCR positive for *Borrelia*
- Resolution with antibiotic treatment

Acrodermatitis Chronica Atrophicans With Pseudolymphomatous Infiltrates

Shang-Ian Tee, MRCP,† Marcela Martinez-Escanamé, MD,* Daniel Zuriel, MD,*‡ Isabella Fried, MD,* Ingrid Wolf, MD,* Cesare Massone, MD,* and Lorenzo Cerroni, MD**

Abstract: In this study, we describe the clinicopathologic features of pseudolymphomatous infiltrates found within lesions of acrodermatitis chronica atrophicans (ACA). We studied 11 patients (10 females, 1 male, age range 60–88 years). The diagnosis of ACA in all cases was confirmed by clinicopathologic correlation and positive serology for *Borrelia*. Histopathologic examination revealed prominent, pseudolymphomatous inflammatory cell infiltrates in all cases, with 2 distinct patterns. Eight of 11 cases showed a band-like lymphocytic infiltrate, exocytosis of lymphocytes and a fibrotic papillary dermis, similar to features seen in mycosis fungoides. The other 3 cases showed dense, nodular-diffuse dermal infiltrates with many plasma cells and without germinal centers. The plasma cells expressed both kappa and lambda immunoglobulin light chains with a polyclonal pattern in all 3 cases. In conclusion, ACA may present with pseudolymphomatous infiltrates showing both a T-cell and, less frequently, a B-cell pattern. These lesions need to be distinguished from a cutaneous lymphoma. In the context of the knowledge of *Borrelia*-associated cutaneous lymphomas, follow-up seems advisable in these cases.

Key Words: acrodermatitis chronica atrophicans, pseudolymphoma, *Borrelia*

(*Am J Dermatopathol* 2013;35:338–342)

INTRODUCTION

Acrodermatitis chronic atrophicans (ACA) is a late cutaneous manifestation of infection by *Borrelia afzelii*.[1] It typically affects elderly women, usually involving the dorsal surfaces of acral sites. After an initial inflammatory phase characterized by edematous swelling and bluish-red discoloration, the skin becomes atrophic, dry, and wrinkled with prominent telangiectasias, dermal sclerosis, and loss of appendageal structures. The diagnostic evaluation of suspected cases commonly includes a histopathological examination. Characteristic histopathologic changes of ACA include (1) a superficial and deep, perivascular, and interstitial dermal inflammatory infiltrate composed of lymphocytes, histiocytes and plasma cells; (2) atrophic dermis with reduction in size and number of adnexal structures; (3) thinning of the epidermis with flattened rete ridges; (4) variable dermal edema.[2]

Rarely, prominent dermal lymphoid infiltrates may be present within lesions of ACA, which may mimic a cutaneous lymphoma. In this study, we present the clinicopathologic features of 11 cases of ACA with pseudolymphomatous infiltrates.

PATIENTS AND METHODS

Patients

We reviewed the database of the Research Unit Dermatopathology, Department of Dermatology, Medical University of Graz for cases of ACA containing dense lymphoid infiltrates. In all cases, the diagnosis of ACA was confirmed clinically and by positive serology for *Borrelia*. We excluded cases in which histopathological specimens were inadequate, or in which complete clinical information was unavailable.

Histopathology

All specimens were fixed in 4% buffered formalin, routinely processed and embedded in paraffin. Sections were subsequently stained with hematoxylin and eosin for routine histopathologic analysis.

Immunohistology

Immunohistology was performed in 4 cases on routinely fixed, paraffin-embedded tissue sections according to a previously described 3-step immunoperoxidase technique.[3] The panel of monoclonal antibodies included the following markers: CD3 (Novocastra, clone PS1, dilution 1:100), CD4 (Novocastra, clone 1F6, dilution 1:30), CD8 (Dako, Dakopatts, clone C8/144b, dilution 1:25), CD20 (Dako, Dakopatts, clone L26, dilution 1:500), kappa and lambda light chains (both Dako, Dakopatts, clones R10/2-1/3 and N10/2, respectively, dilution 1 drop in 500 μL). Biopsy specimens of tonsil tissue were used as positive controls. Negative controls were obtained by omitting the primary antibody or replacing it with normal human serum. Heat-induced antigen retrieval was performed for all the antibodies.

Molecular Biology

In 3 cases, analysis of *Borrelia* DNA was performed by polymerase chain reaction (PCR) with standard methods.

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Funding sources: none.

Conflict of interests: None.

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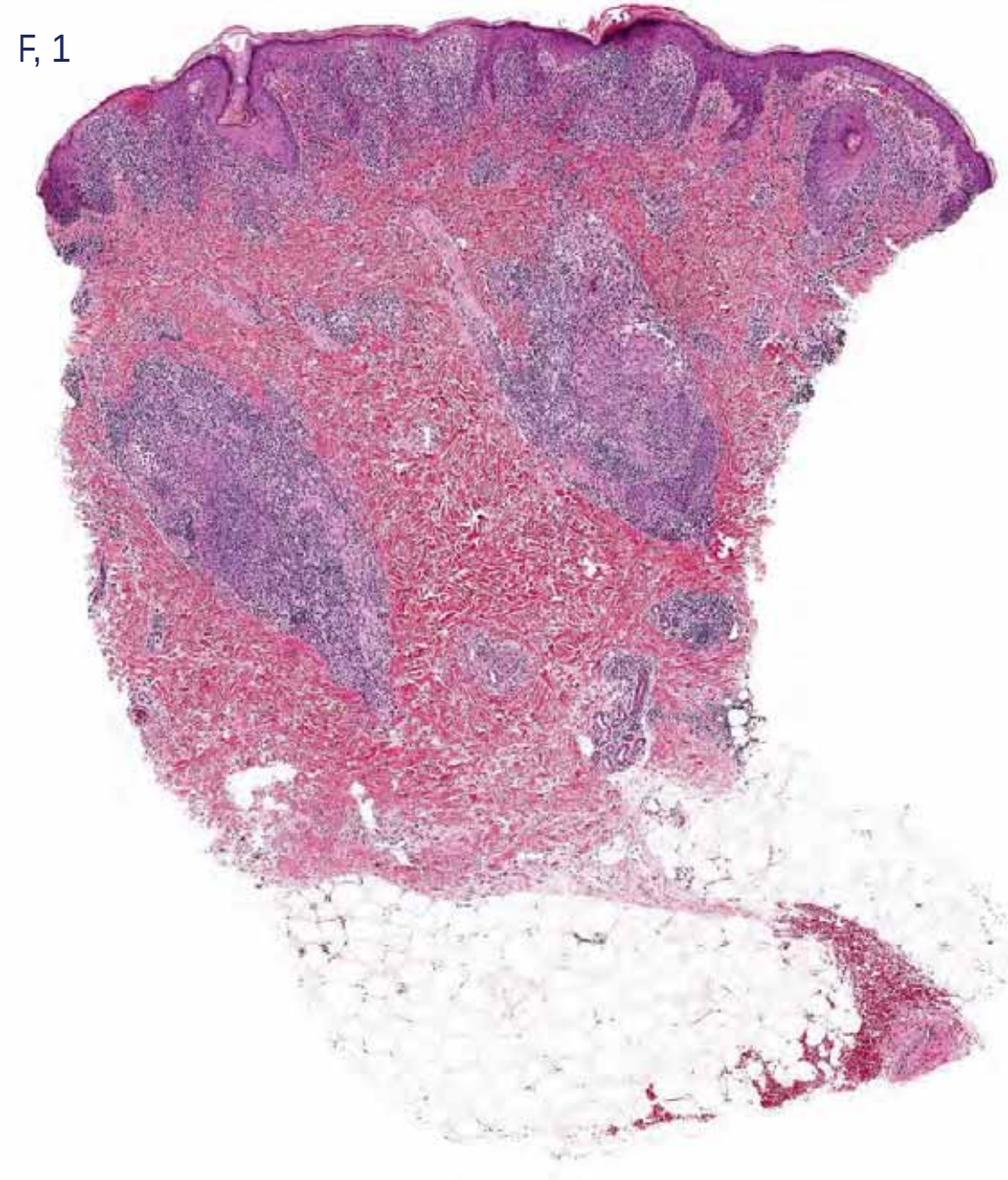
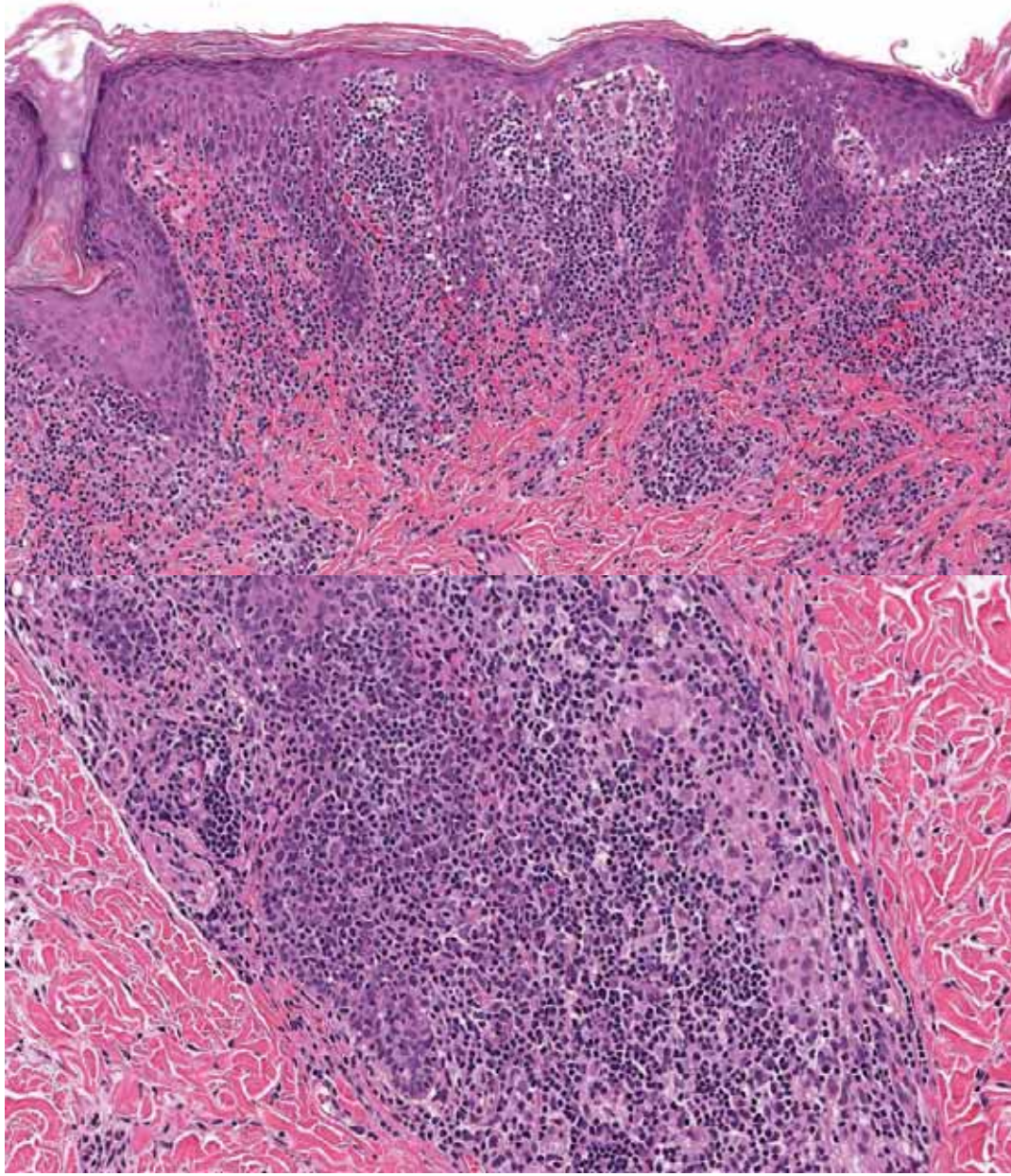
TABLE 1. Clinical Data of the Patients and Histopathologic Pattern

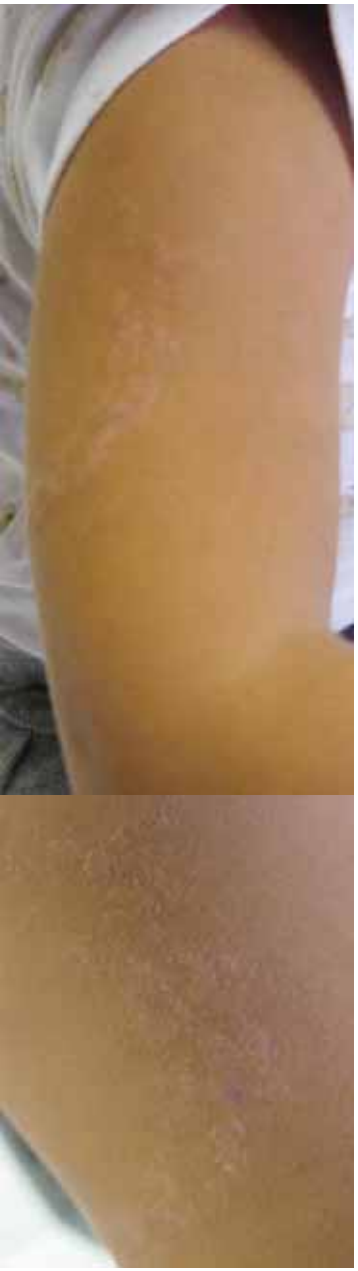
No	Sex, Age (yrs)	Location	Histological Pattern	*Borrelia* PCR	*Borrelia* Serology	Follow-up (Time)
1	F, 70	Foot	Band-like	ND	IgG and IgM	NA
2	F, 68	Foot	Band-like	Positive	IgG and IgM	CR (2 mos)
3	F, 64	Foot	Band-like	ND	IgG and IgM	CR (13 yrs)
4	F, 68	Leg	Band-like	ND	IgG and IgM	CR (8 mos)
5	F, 77	Leg	Superficial and deep, diffuse with plasma cells	Positive	IgG and IgM	CR (8 yrs)
6	F, 60	Leg	Band-like	ND	IgG and IgM	CR (8 yrs)
7	M, 88	Hand	Band-like	ND	IgG and IgM	NA
8	F, 60	Hand	Superficial and deep, diffuse with plasma cells	ND	IgG and IgM	CR (22 yrs)
9	F, 77	Leg	Band-like	Positive	IgG	Almost CR (16 mos)
10	F, 61	Leg	Band-like	ND	IgG and IgM	CR (2 mos)
11	F, 74	Leg	Superficial and deep, diffuse with plasma cells	ND	IgG and IgM	CR (2 mos)

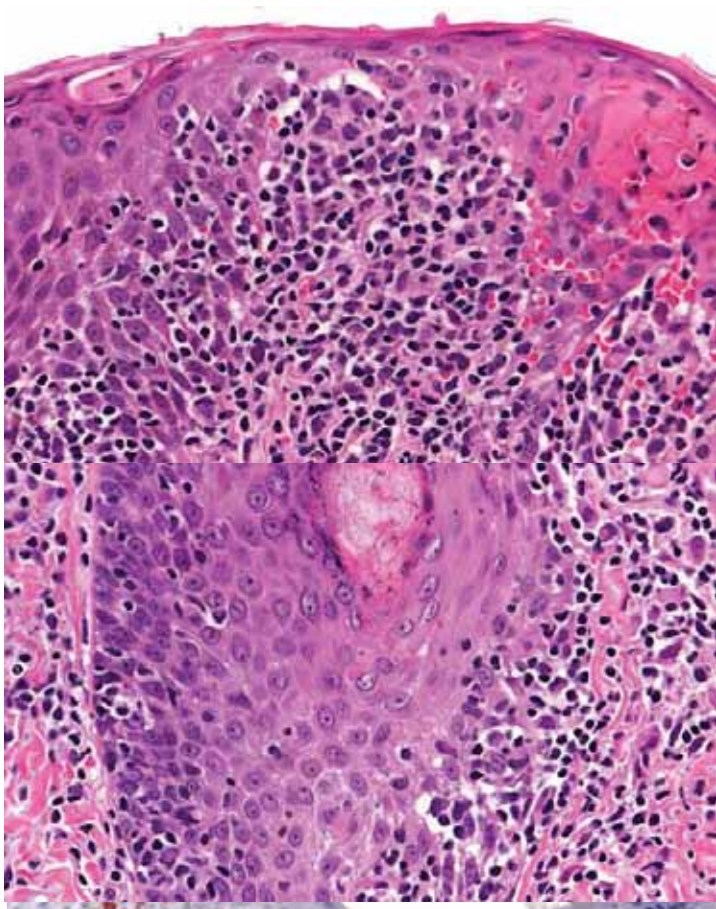
CR, complete remission; F, female; M, male; NA, not available; ND, not done; PR, partial remission.

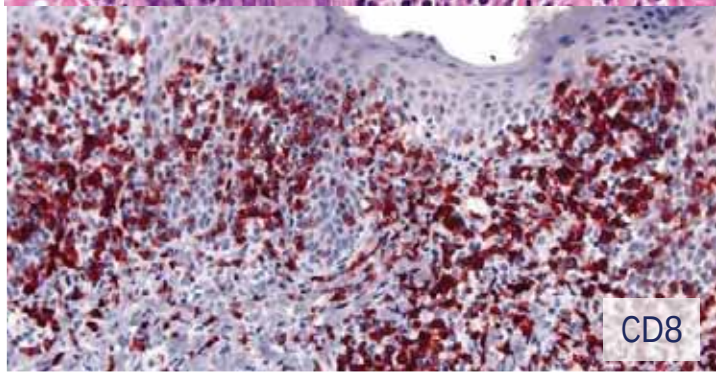
F, 1











Lichen striatus

Lichen Striatus

- A prototypic example of the "linear dermatoses"
- Psoriasiform epidermal hyperplasia and variably dense lichenoid infiltrate, involving the deep dermis growing along the adnexal structures
- Epitheliotropism may be prominent
- Phenotype not studied in detail; some cases are positive for CD8

Mimickers of cALCL / LyP

Sometimes to Frequently	Rarely
HSV1, HSV2, VZV infection	Tattoo
Milker's nodule & Orf	Syphilis II (lues maligna)
Molluscum contagiosum	Leishmaniasis
Arthropod bite reactions including scabies	Inflammatory infiltrates in various conditions
Pityriasis lichenoides	
Syphilis I	

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Journal of
Cutaneous Pathology

Large CD30-positive cells in benign, atypical lymphoid infiltrates of the skin

Background: Cutaneous infectious and inflammatory diseases may contain a significant number of CD30-positive cells, thus mimicking lymphomatoid papulosis (LyP) or anaplastic large cell lymphoma.
Methods: We reviewed our cases of non-neoplastic skin conditions with large, CD30-positive cells and searched the literature for similar cases.
Results: A total of 28 cases were included in the study: Milker's nodule (n = 8), Herpes simplex virus infection (n = 7), lymphomatoid drug reaction (n = 3), molluscum contagiosum (n = 3), nodular scabies (n = 2), leishmaniasis (n = 1), syphilis (n = 1), pernio (n = 1), ruptured infundibular cyst (n = 1) and pseudolymphoma in a scar (n = 1). CD30-positive cells were often arranged in clusters and revealed both Golgi and membrane positivity, similar to what was observed in LyP and CD30+ anaplastic large T-cell lymphoma.
Conclusions: Analysis of our data and of those published in the literature shows that viruses and drugs are the most common cause for occurrence of large CD30-positive cells in cutaneous pseudolymphomatous infiltrates. Arrangement of these large, CD30-positive cells in small clusters is not unique to cutaneous CD30-positive lymphomas, and in many cases a precise diagnosis can be made only upon accurate clinicopathological correlation or using ancillary methods such as polymerase chain reaction analysis for viral DNA.

Werner B, Massone C, Kerl H, Cerroni L. Large CD30-positive cells in benign, atypical lymphoid infiltrates of the skin.
J Cutan Pathol 2008; 35: 1100–1107. © Blackwell Munksgaard 2008.

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Expression of the CD30 antigen is the hallmark of a group of primary cutaneous T-cell lymphomas including the spectrum ranging from lymphomatoid papulosis (LyP) to primary cutaneous anaplastic large T-cell lymphoma (cALCL).[1,2] CD30-positivity on neoplastic cells of cutaneous malignant lymphomas, however, is not a feature exclusive to LyP and cALCL, as it can be observed in cases of Hodgkin's lymphoma involving secondarily the skin[3] as well as in several T-cell[4,5] and B-cell lymphomas,[6–8] natural-killer cell lymphomas[9,10] or even in granulocytic sarcoma.[11] Furthermore, in the past years, CD30-positive cells have been detected in several reactive lymphocytic infiltrates of the skin[12–32] and oral mucosa.[33]

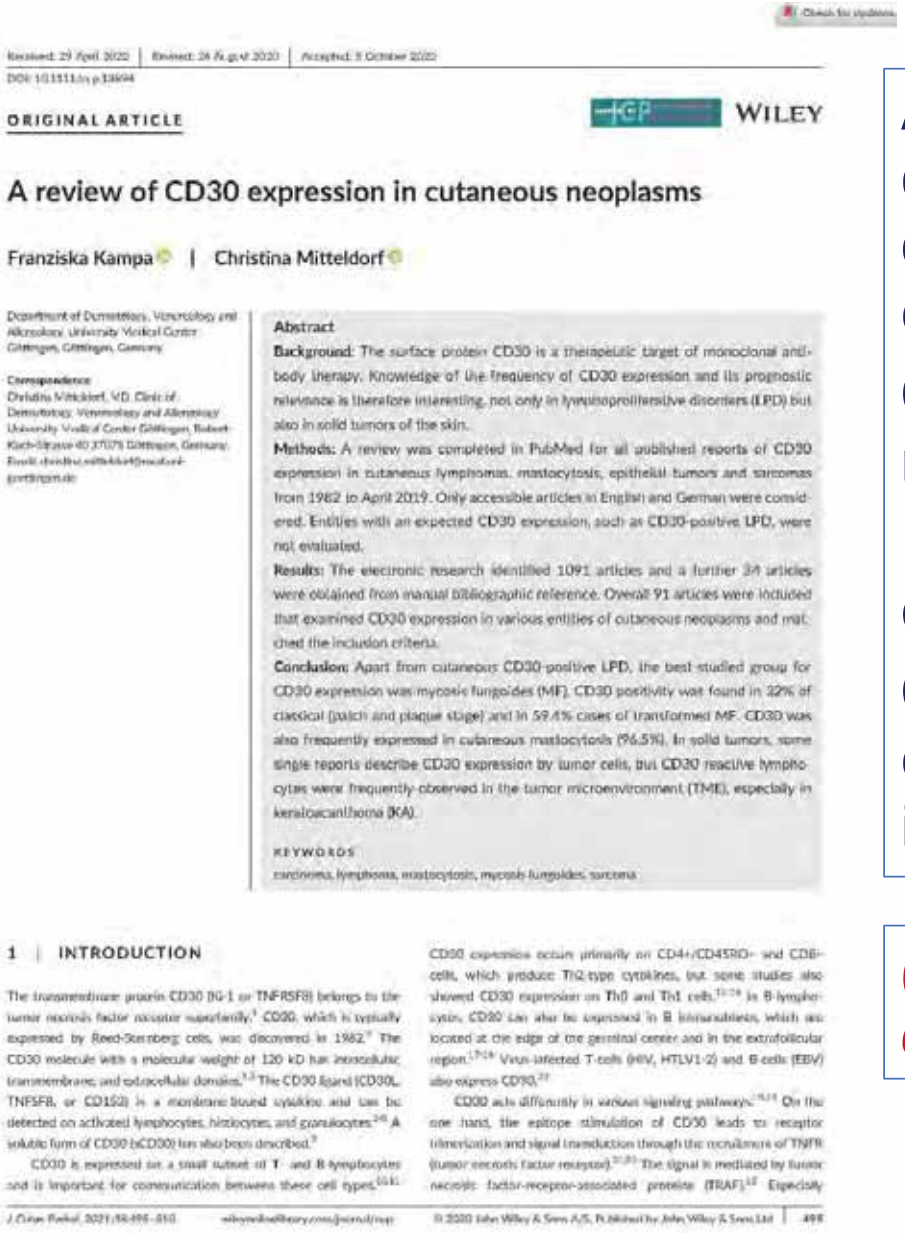
We reviewed our cases of non-neoplastic (inflammatory or infectious) skin conditions in which large CD30-positive cells were detected among the infiltrating lymphocytes, analyzing the pattern of cell positivity and discussing the significance of the finding of CD30-positive lymphocytes in cutaneous lymphoid infiltrates.

Material and methods

Files from the Research Unit of Dermatopathology, Department of Dermatology, Medical University of Graz, Austria and cases sent in consultation to one of us (L. C.) were searched for pseudolymphomas (reactive benign inflammatory or infectious conditions) showing presence of large CD30-positive cells within the infiltrate. Biopsy specimens obtained in Graz were fixed in 10% buffered formalin and

Table 1. Reactive cutaneous infiltrates containing large CD30-positive lymphocytes included in our study

Condition	Number of cases
Milker's nodule	8
Herpes simplex virus or Varicella-Zoster virus infection	7
Lymphomatoid drug reaction	3
Molluscum contagiosum	3
Nodular scabies	2
Cutaneous leishmaniasis (oriental sore)	1
Syphilis (stage I)	1
Pernio	1
Re-excision scar of basal cell carcinoma	1
Ruptured infundibular cyst	1
Total	28



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ORIGINAL ARTICLE

WILEY

A review of CD30 expression in cutaneous neoplasms

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Abstract

Background: The surface protein CD30 is a therapeutic target of monoclonal antibody therapy. Knowledge of the frequency of CD30 expression and its prognostic relevance is therefore interesting, not only in lymphoproliferative disorders (LPD) but also in solid tumors of the skin.

Methods: A review was completed in PubMed for all published reports of CD30 expression in cutaneous lymphomas, mastocytosis, epithelial tumors and sarcomas from 1982 to April 2019. Only accessible articles in English and German were considered. Entities with an expected CD30 expression, such as CD30-positive LPD, were not evaluated.

Results: The electronic research identified 1091 articles and a further 34 articles were obtained from manual bibliographic reference. Overall 91 articles were included that examined CD30 expression in various entities of cutaneous neoplasms and matched the inclusion criteria.

Conclusion: Apart from cutaneous CD30-positive LPD, the best studied group for CD30 expression was mycosis fungoides (MF). CD30 positivity was found in 32% of classical (patch and plaque stage) and in 59.4% cases of transformed MF. CD30 was also frequently expressed in cutaneous mastocytosis (96.5%). In solid tumors, some single reports describe CD30 expression by tumor cells, but CD30 reactive lymphocytes were frequently observed in the tumor microenvironment (TME), especially in keratoacanthoma (KA).

KEYWORDS
carcinoma, lymphoma, mastocytosis, mycosis fungoides, sarcoma

1 | INTRODUCTION

The transmembrane protein CD30 (Ki-1 or TNFRSF8) belongs to the tumor necrosis factor receptor superfamily.[1] CD30, which is typically expressed by Reed-Sternberg cells, was discovered in 1982.[2] The CD30 molecule with a molecular weight of 120 kD has intracellular, transmembrane, and extracellular domains.[1,3] The CD30 ligand (CD30L, TNFSF8, or CD153) is a membrane-bound cytokine and can be detected on activated lymphocytes, histiocytes, and granulocytes.[3-6] A soluble form of CD30 (sCD30) has also been described.[7]

CD30 is expressed on a small subset of T- and B-lymphocytes and is important for communication between these cell types.[3,5,6] CD30 expression occurs primarily on CD4+/CD45RO+ and CD8- cells, which produce Th2-type cytokines, but some studies also showed CD30 expression on Th0 and Th1 cells.[3,7,8] In B-lymphocytes, CD30 can also be expressed in B immunoblasts, which are located at the edge of the germinal center and in the extrafollicular region.[3,7,9] Virus-infected T-cells (HIV, HTLV1-2) and B-cells (EBV) also express CD30.[10]

CD30 acts differently in various signaling pathways.[4,11] On the one hand, the epitope stimulation of CD30 leads to receptor trimerization and signal transduction through the recruitment of TNFR (tumor necrosis factor receptor).[11,12] The signal is mediated by tumor necrosis factor-receptor-associated proteins (TRAF).[12] Especially

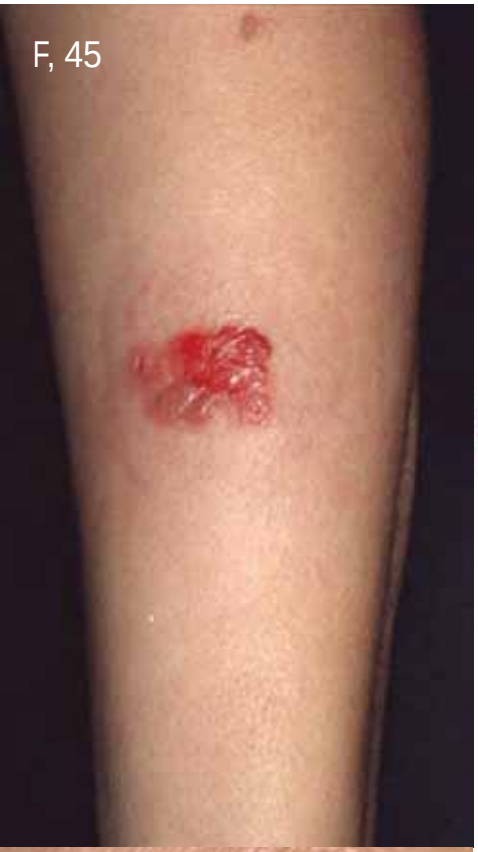
Apart from cutaneous CD30+ lymphoproliferative disorders, CD30 positivity was found in 32% of classical (patch and plaque stage) and in 59.4% cases of transformed MF.

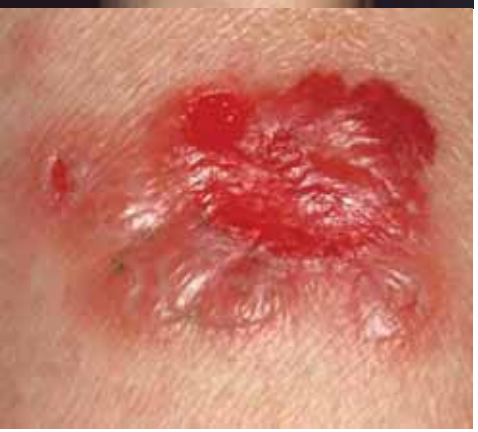
CD30 was also frequently expressed in cutaneous mastocytosis (96.5%).

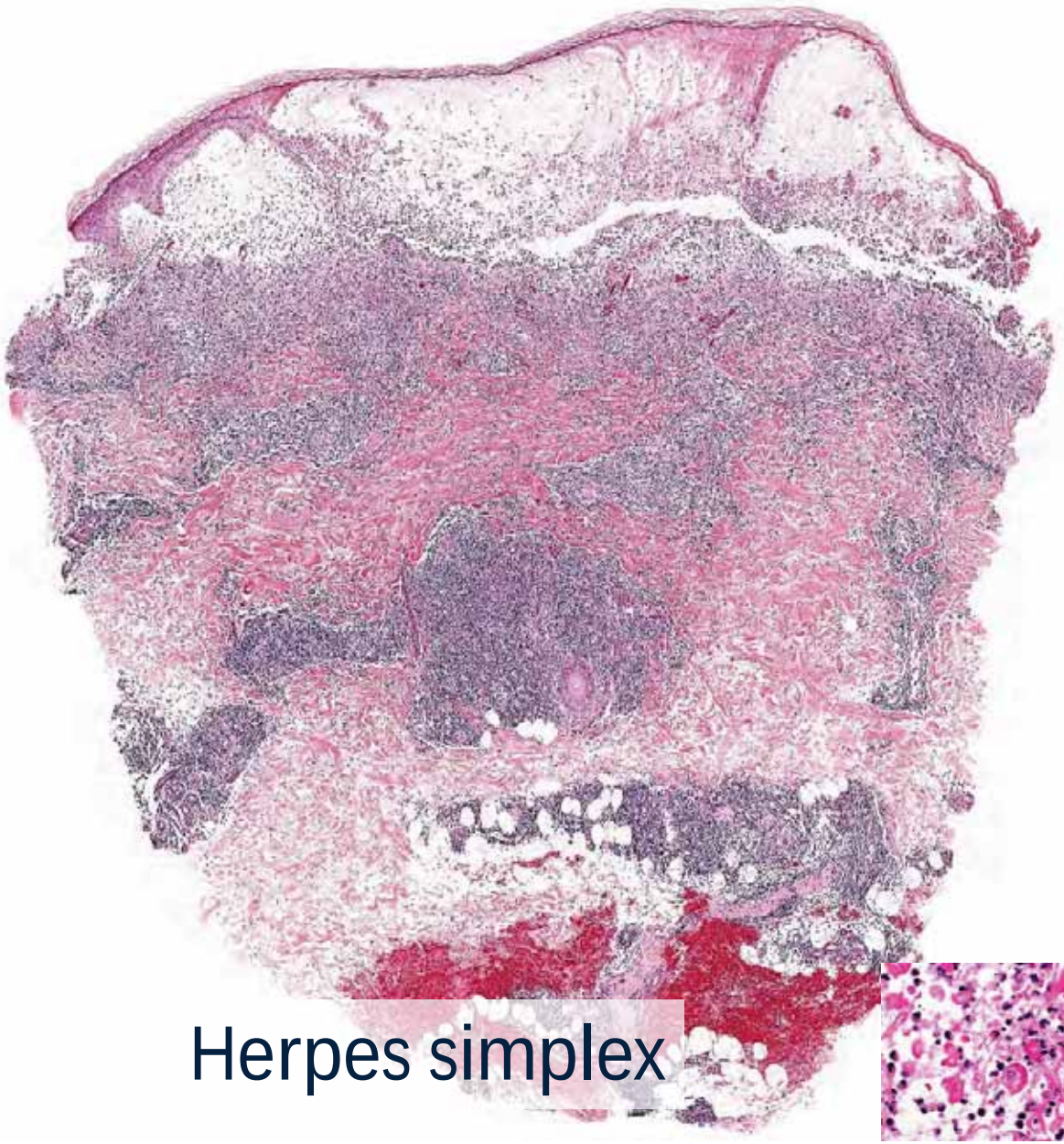
In solid tumors, some single reports describe CD30 expression by tumor cells.

CD30+ reactive lymphocytes were frequently observed in the tumor microenvironment, especially in keratoacanthoma. (*)

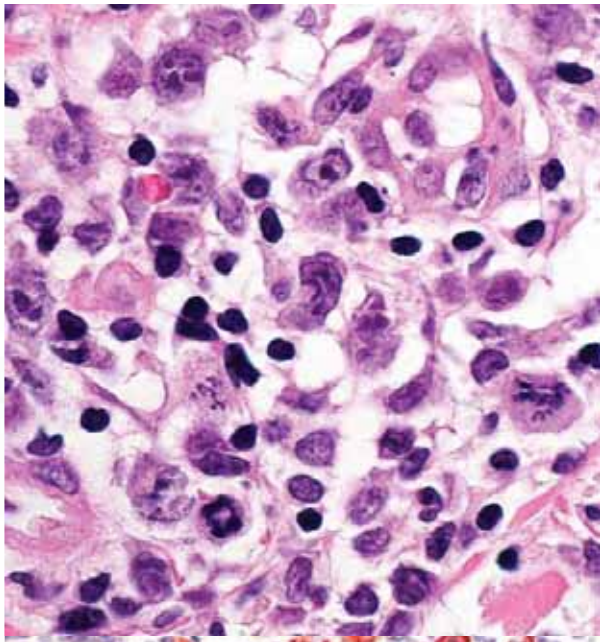
(*) beware of "keratoacanthomatous" LyP and cALCL !!

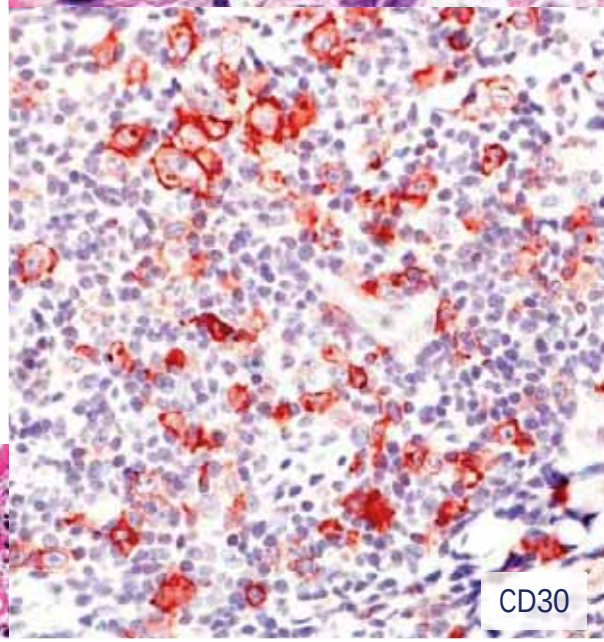




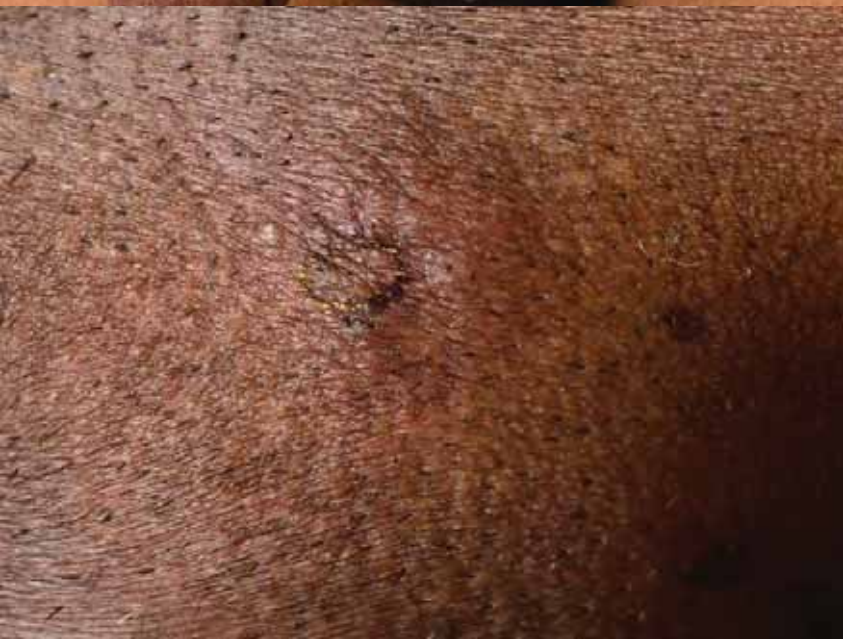


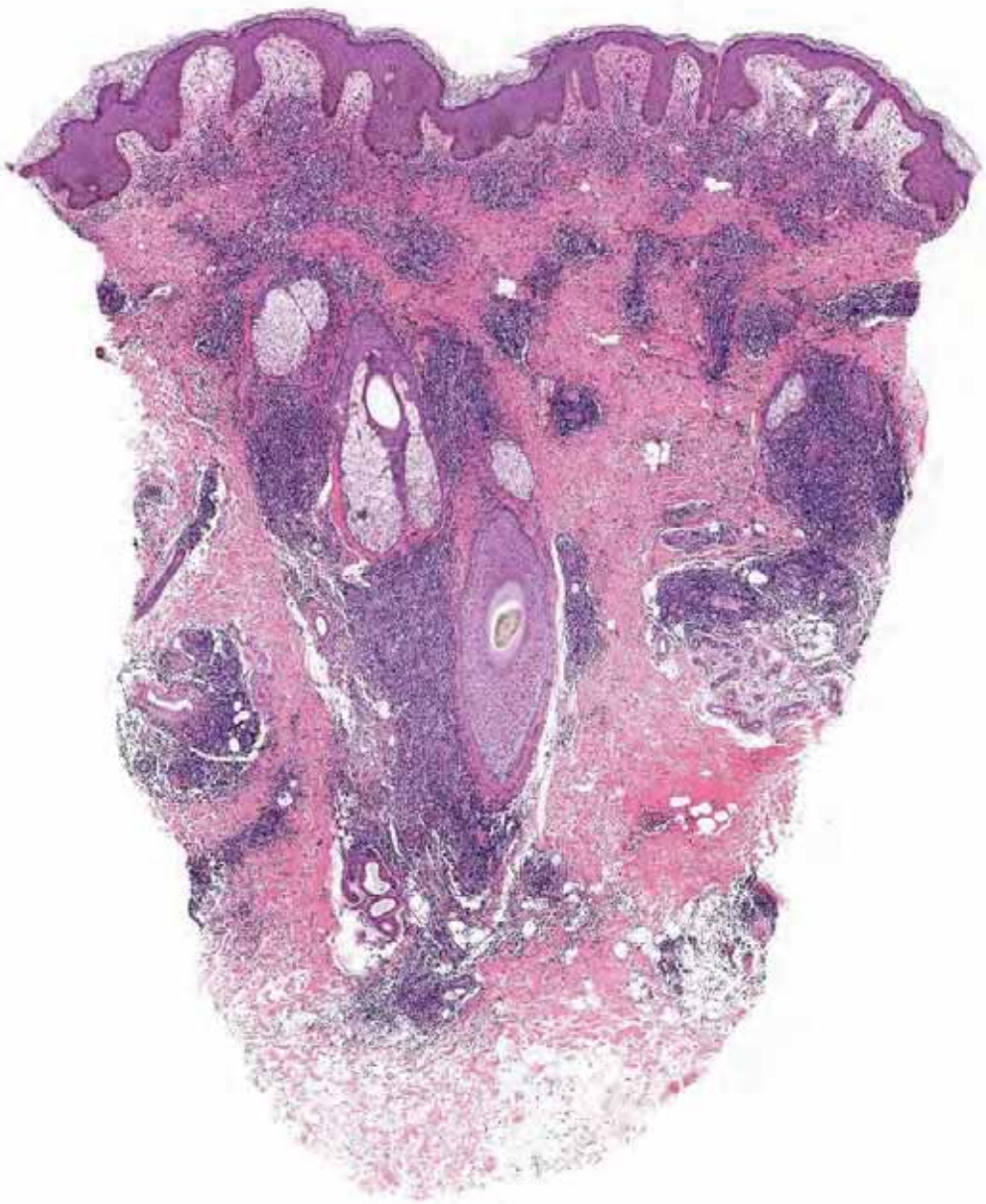
Herpes simplex

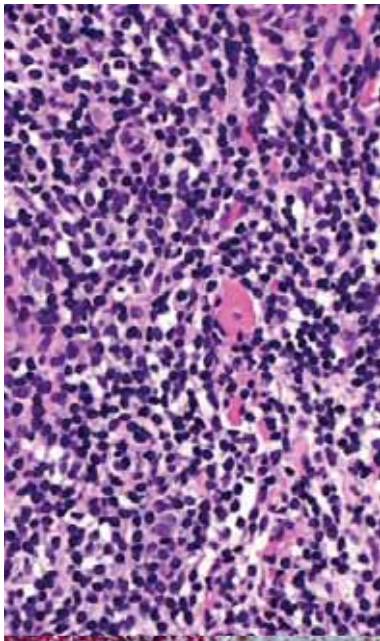


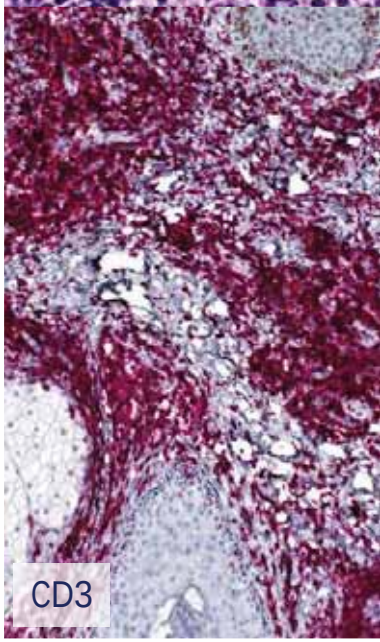


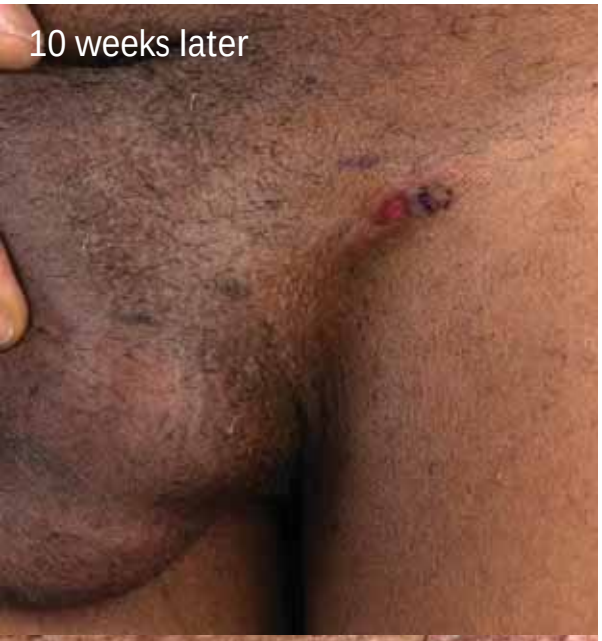

M, 53

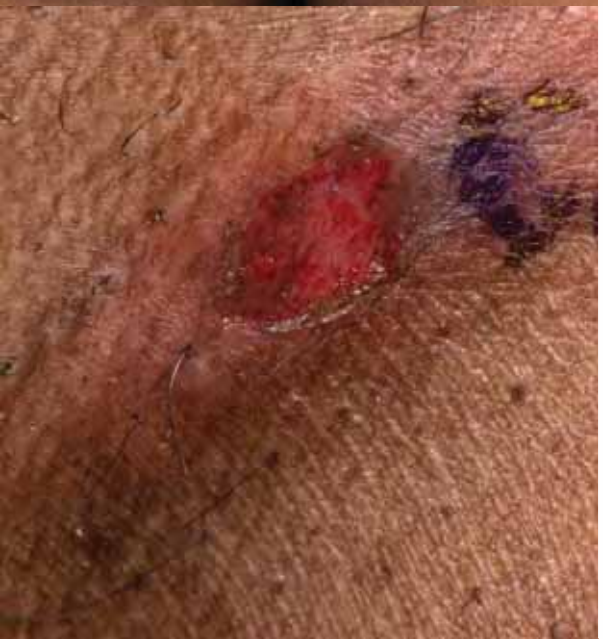


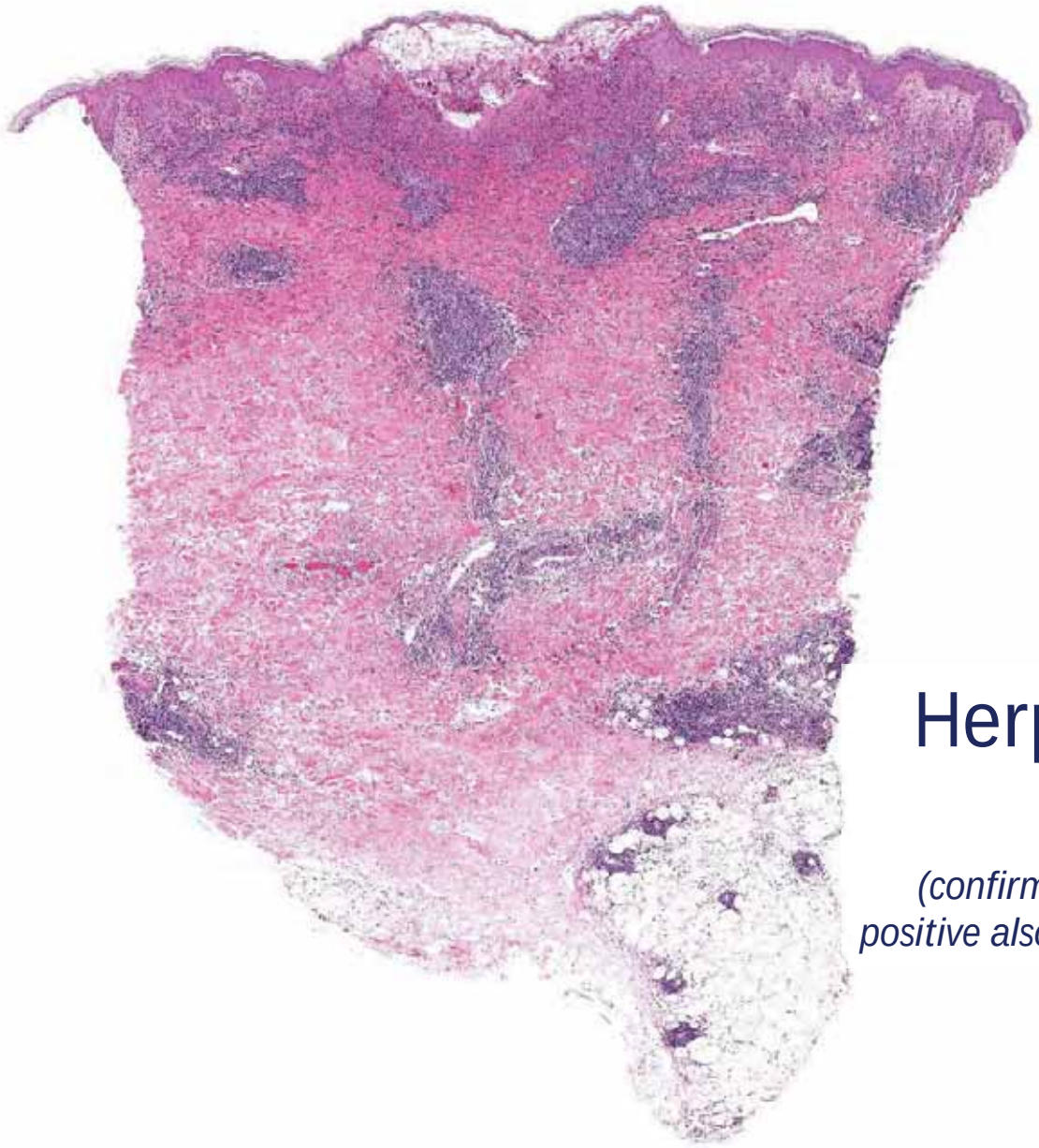


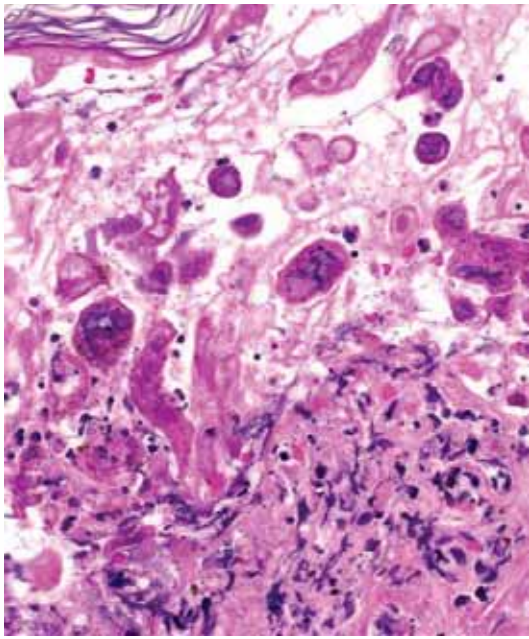



CD3



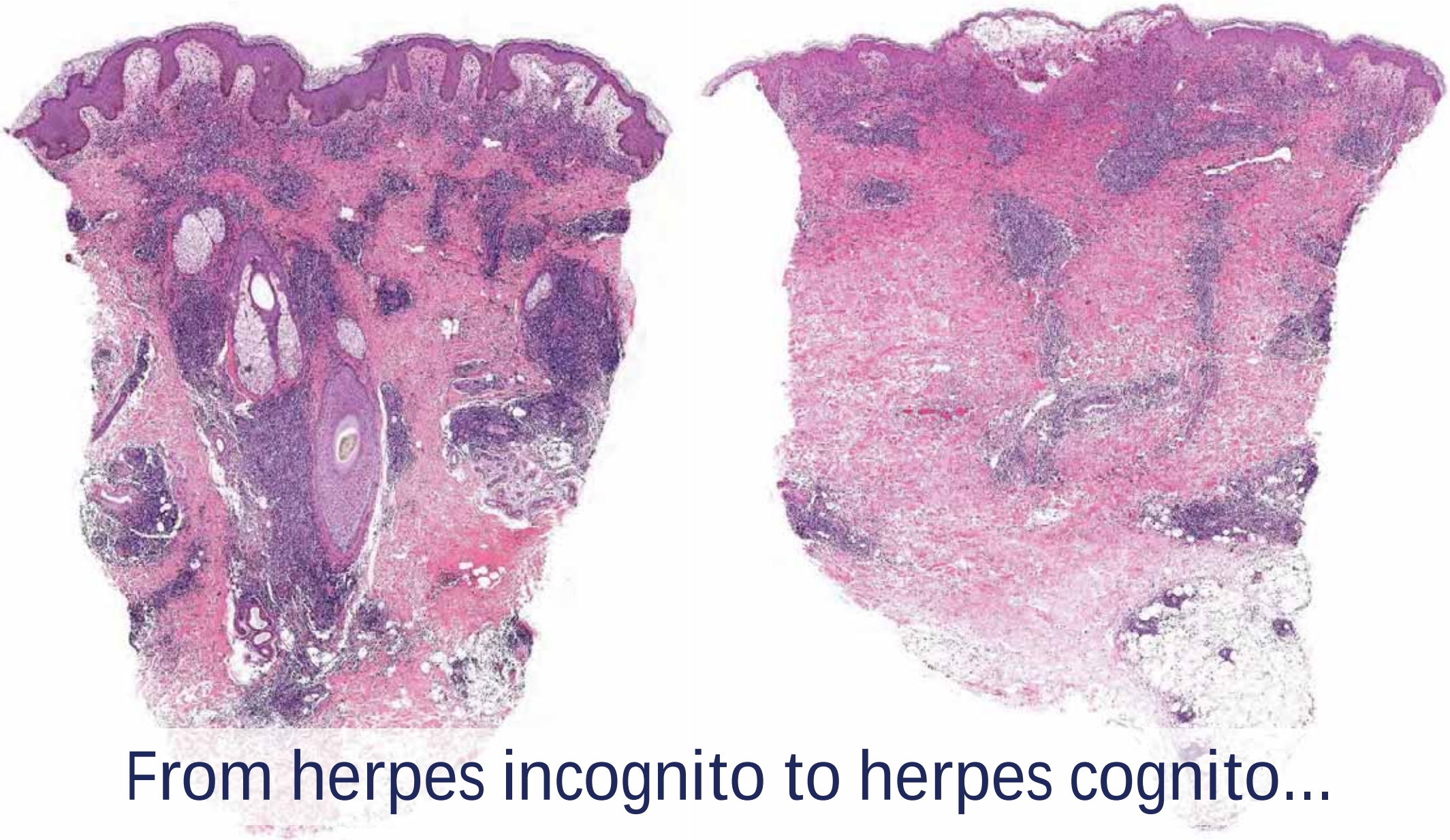






Herpes simplex 1 infection

(confirmed by PCR, retrospectively positive also on the first biopsy specimen)



From herpes incognito to herpes cognito...

Histopathologic Features of Cutaneous Herpes Virus Infections (Herpes Simplex, Herpes Varicella/Zoster)

A Broad Spectrum of Presentations With Common Pseudolymphomatous Aspects

Bernd Leinweber, MD, Helmut Kerl, MD, and Lorenzo Cerroni, MD

Abstract: Cutaneous eruptions caused by herpes simplex 1/2 (HSV-1/2) and herpes varicella/zoster (VZV) represent common dermatoses. In some cases, they present with atypical clinical and/or histopathologic features, including presence of dense lymphoid infiltrates with atypical lymphocytes simulating cutaneous lymphomas. In this study, we reviewed the biopsy specimens of 65 patients (33 males, 32 females; mean age, 61.2 years; median age, 62 years; age range, 19–96 years) with cutaneous eruptions caused by HSV-1/2 or VZV. Histologic examination revealed several atypical findings, including presence of dense lymphoid infiltrates, angiotropism, and atypical lymphocytes simulating malignant lymphoma. Immunohistochemistry performed in 22 cases showed a predominant T-cell infiltrate, in the majority of cases with variable numbers of CD30+ and CD56− cells. Two cases with a pseudolymphomatous appearance and small clusters of CD30+ cells revealed a monoclonal population of T lymphocytes by PCR analysis, underlying the difficulties in classifying some of these cases correctly. Our study indicates that cutaneous herpes infections can exhibit several atypical histopathologic, immunohistochemical, and molecular features, and that in given cases accurate clinicopathologic correlation and short-term follow-up controls are necessary for differentiation from cutaneous lymphomas.

Key Words: herpes simplex, herpes varicella/zoster, cutaneous pseudolymphoma

(*Am J Surg Pathol* 2006;30:50–58)

Cutaneous eruptions caused by herpes simplex 1/2 (HSV-1/2) and herpes varicella/zoster (VZV) represent common dermatoses. In most cases, a correct diagnosis can be made based on the characteristic clinical findings, and usually skin lesions are biopsied only in patients with uncommon clinical presentations.[1–3] In this context, it is well known that cutaneous herpes infections can present with atypical clinical features in patients with immunosuppression or with underlying hematologic diseases.[2,3,22,23] In these instances, the clinical diagnosis may be problematic, and the differential diagnosis includes cutaneous lymphoma or pseudolymphoma among others. In addition, histology of cutaneous herpes infections can vary to a great extent, ranging from lesions with purely epithelial involvement and sparse to absent inflammatory infiltrates, to cases with a florid pseudolymphomatous pattern simulating a malignant lymphoma. Indeed, in a recent article, Taddesse-Heath et al reported a case of an obstructive mass in the nasopharynx caused by infection with HSV-1/2, with a clinical presentation simulating a malignant tumor, and a preliminary pathologic diagnosis of extranodal NK/T-cell lymphoma, nasal-type.[25]

Occasionally, patients without coexisting diseases present with cutaneous HSV-1/2 or VZV infections that display atypical clinical and histologic findings suggestive of a cutaneous lymphoma. Indeed, in the past few months, one of us (L.C.) received 5 such cases for consultation (case nos. 27, 31, 49, 53, and 54), which had been previously misdiagnosed as malignant lymphoma (cutaneous CD30+ lymphoproliferative disorders, spectrum lymphomatoid papulosis/anaplastic large cell lymphoma). In this study, we analyzed retrospectively the histopathologic features of 65 cases of cutaneous HSV-1/2 and VZV infections.

MATERIALS AND METHODS

Biopsy specimens from 65 patients (33 males, 32 females; mean age, 61.2 years; median age, 62 years; age range, 19–96 years) with cutaneous HSV-1/2 and VZV were included in the study (Table 1). All cases were retrieved from the files of the Division of Dermatopathology, Department of Dermatology, Medical University of Graz, Graz, Austria. Some of the cases had been sent as consultation cases. All diagnoses were reviewed by at least two independent dermatopathologists (B.L., L.C.). Diagnoses were based on clinical, histologic, immunohistochemical, molecular, and follow-up data.

Histology

All biopsy specimens were fixed in 10% buffered formalin, routinely processed, and subsequently embedded in paraffin. Sections were stained with hematoxylin and eosin and analyzed for the presence of several histopathologic features listed in Table 1.

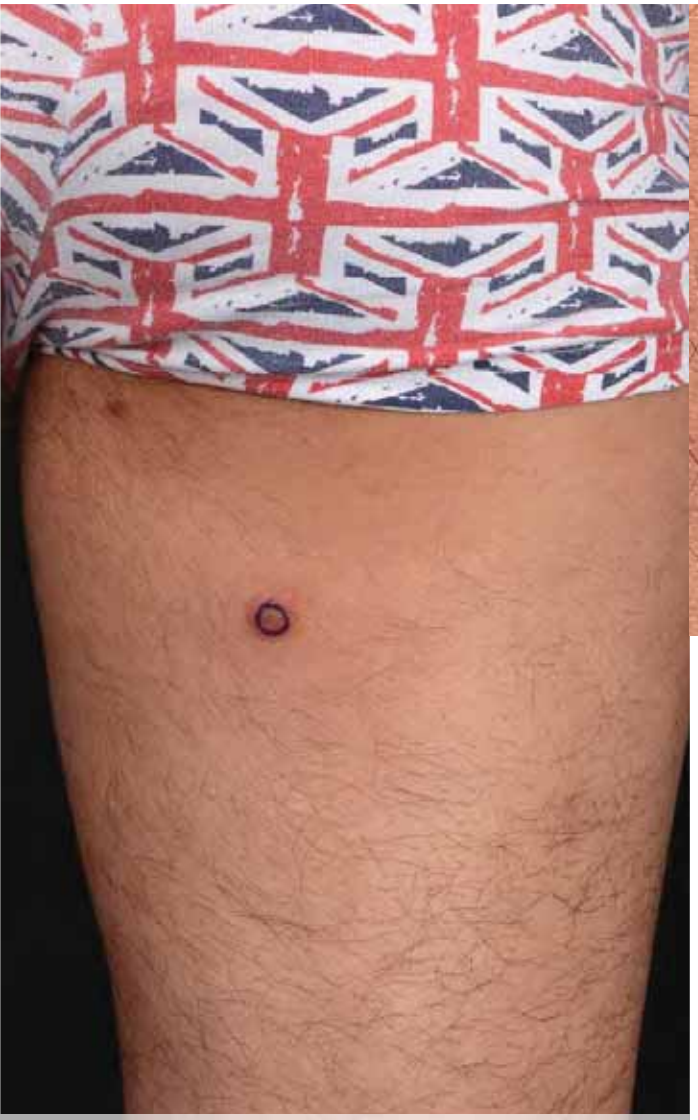
From the Department of Dermatology, Medical University of Graz, Graz, Austria.

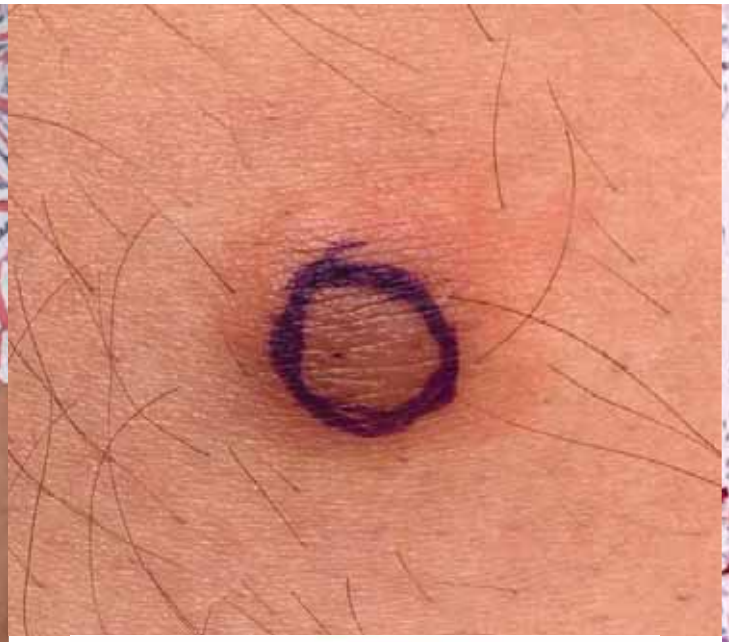
Reprints: Lorenzo Cerroni, MD, Department of Dermatology, Medical University of Graz, Auenbruggerplatz 8, A-8036 Graz, Austria (e-mail: lorenzo.cerroni@meduni-graz.at).

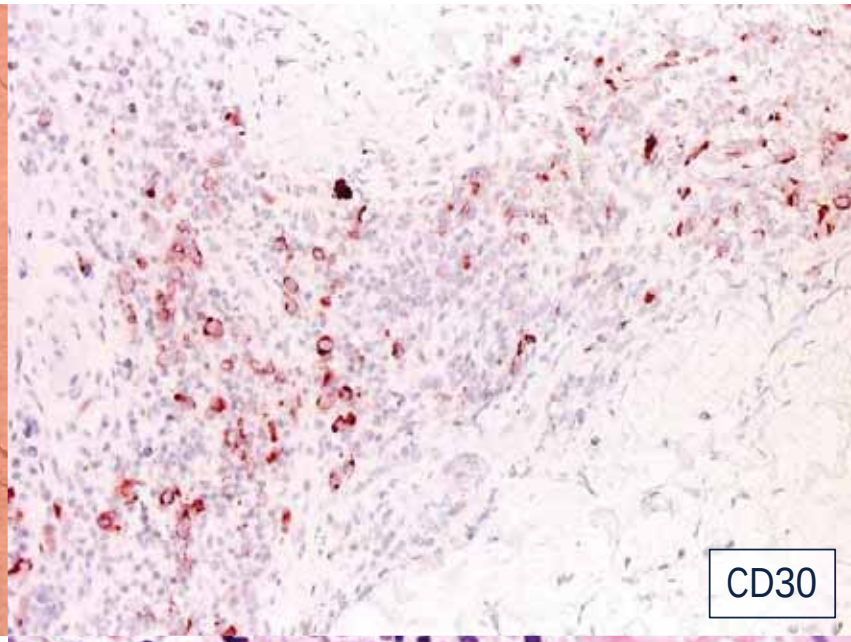
TABLE 2. Summary of Results of Immunohistologic and PCR Analyses

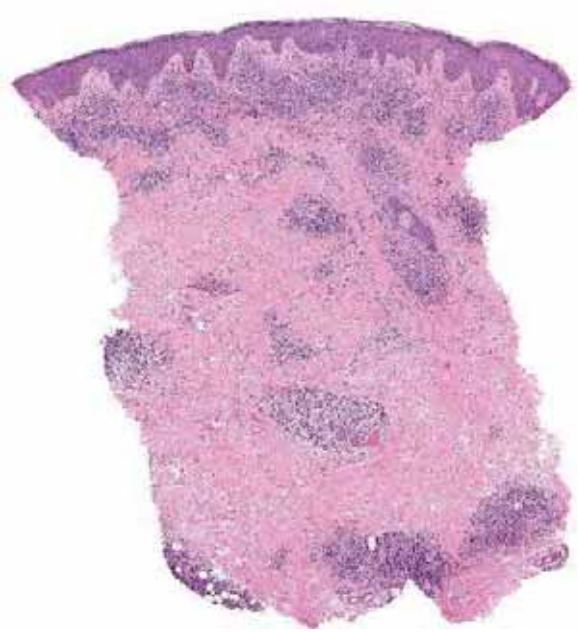
	Immunohistochemistry*								PCR		
Case No.	CD3	CD4	CD8	CD20	CD30	CD56	TIA1	CD123	Herpes Type	TCR	IgH
1	+++	++	+++	+	+/–	+/–	++	–	ND	ND	ND
5	ND	ND	ND	ND	ND	ND	ND	ND	VZV	ND	ND
8	+	+/–	+	+	+/–	+/–	++	–	ND	ND	ND
11	+++	+	++	+	+/–	+	++	–	ND	ND	ND
15	++	+	++	+	+/–	+/–	++	–	ND	ND	ND
16	++	++	++	+	–	+/–	++	–	ND	ND	ND
17	+++	+++	++	+	+/–	+/–	++	+/–	ND	ND	ND
18	+++	+++	++	+	+/–	+†	++	–	ND	ND	ND
24	+++	++	++	++	–	+	++	–	ND	ND	ND
25	+++	+	+++	+	+	–	++	–	ND	ND	ND
27	+++	ND	ND	++	+	+	ND	ND	HSV–1/2	P	P
28	+++	++	+++	++	+	+	+++	–	ND	ND	ND
29	ND	ND	ND	ND	ND	ND	ND	ND	HSV–1/2 & VZV	ND	ND
31	+++	+	++	+/–	+/–	+	++	ND	VZV	P	P
34	ND	ND	ND	ND	ND	ND	ND	ND	HSV–1/2	ND	ND
36	ND	ND	ND	ND	ND	ND	ND	ND	HSV-1/2	ND	ND
37	+++	+	+++	+	+/–	–	+++	+/–	ND	ND	ND
39	+++	+	++	+	–	+/–	+	–	ND	ND	ND
40	+	+/–	+	+	+/–	–	+	–	ND	ND	ND
43	+++	++	++	+	+/–	+	++	–	ND	ND	ND
44	ND	ND	ND	ND	ND	ND	ND	ND	HSV–1/2 & VZV	ND	ND
46	++	+	++	++	+	+/–	++	–	HSV–1/2	P	P
48	+++	++	++	+	+	+/–	++	–	VZV	ND	ND
49	ND	ND	ND	ND	+†	ND	ND	ND	HSV–1/2	M	P
50	+++	++	++	+	+	+	++	+/–	ND	ND	ND
53	+++	++	++	+	+†	–	++	ND	HSV–1/2	M	P
54	+++	++	+	+	+/–	ND	ND	ND	HSV–1/2	P	P
56	+++	ND	ND	+	–	ND	ND	ND	HSV–1/2	ND	ND
61	ND	ND	ND	ND	ND	ND	ND	ND	HSV–1/2	ND	ND
62	ND	ND	ND	ND	ND	ND	ND	ND	HSV–1/2	ND	ND
63	ND	ND	ND	ND	ND	ND	ND	ND	HSV–1/2	ND	ND
64	ND	ND	ND	ND	ND	ND	ND	ND	HSV–1/2	ND	ND

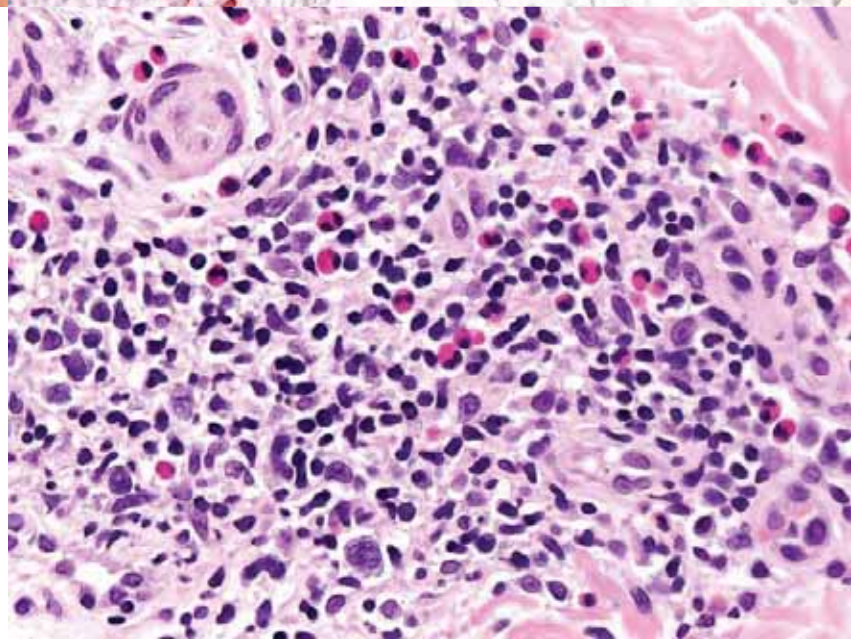
HSV-1/2, herpes simplex 1/2; VZV, varicella zoster virus; PCR, polymerase chain reaction; TCR, T-cell receptor; P, polyclonal; M, monoclonal; ND, not done.
*Rating immunohistochemistry: –, none; +/–, scattered to 5%; +, >5% to 25%; ++, >25% to 50%; +++, >50%.
†Clusters of positive cells.



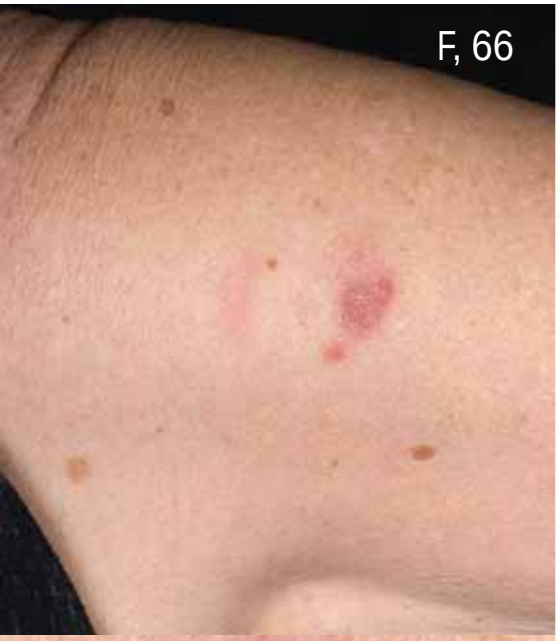


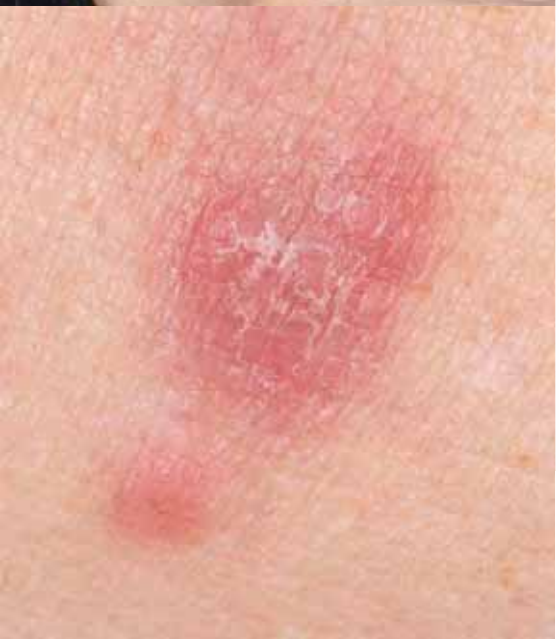


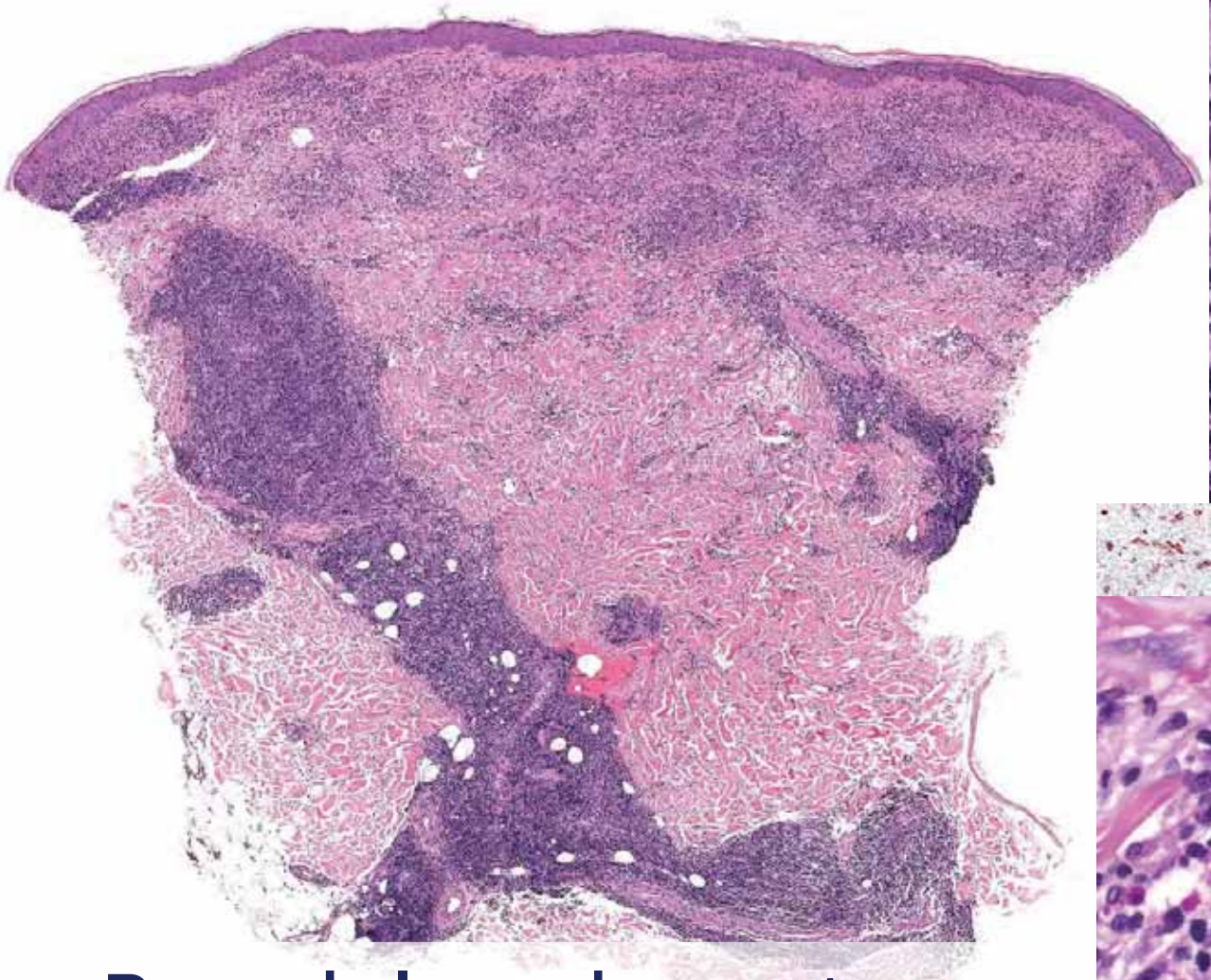


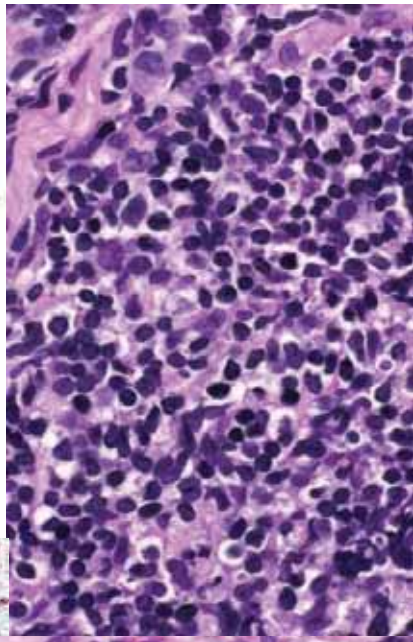


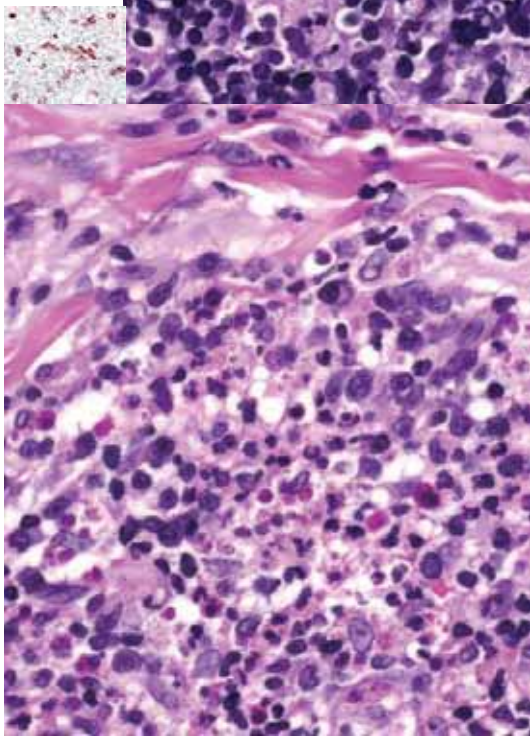
Pseudolymphomatous reaction to artrhropod bite



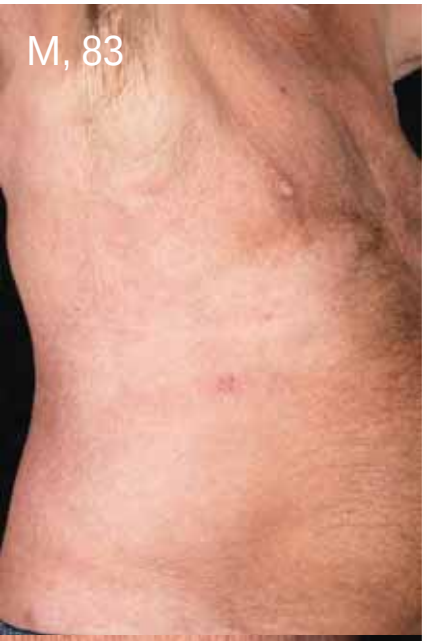


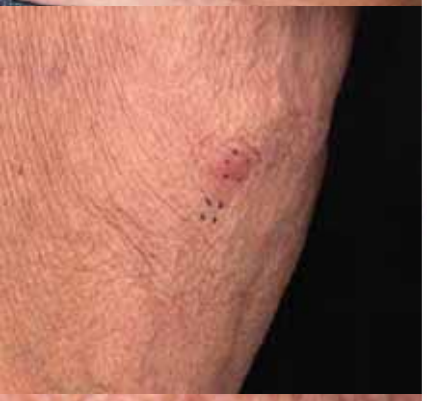


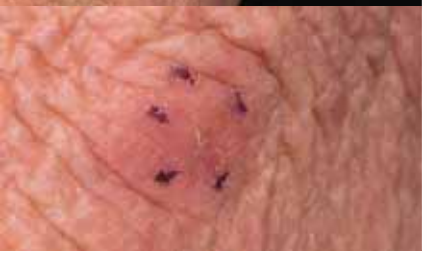


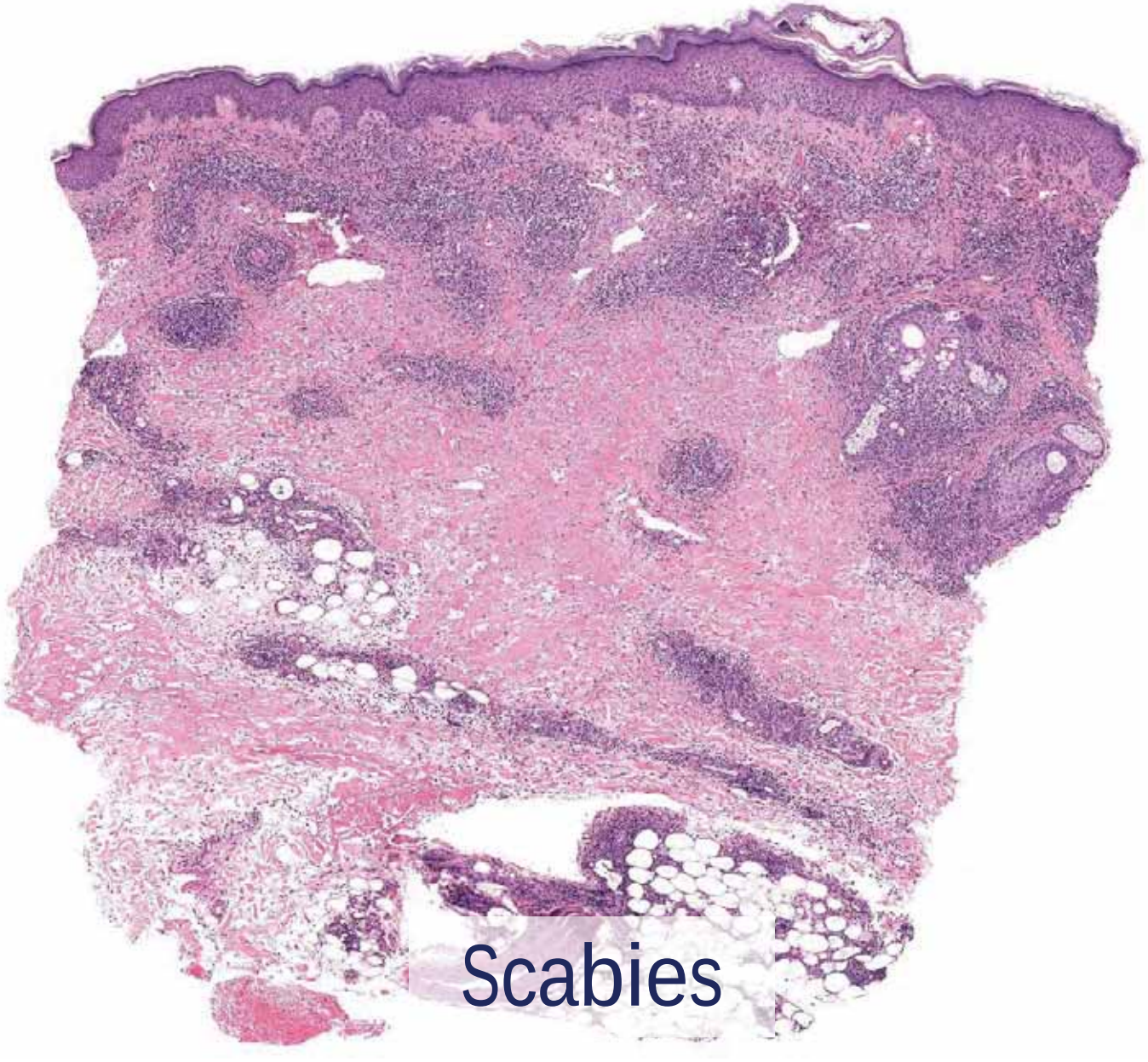


Pseudolymphomatous reaction to artrhropod bite

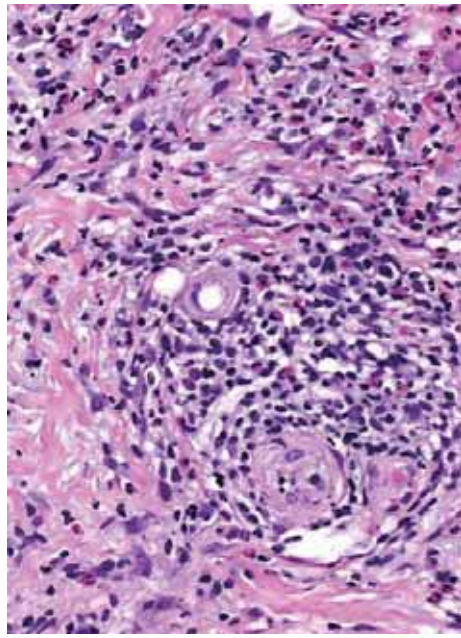


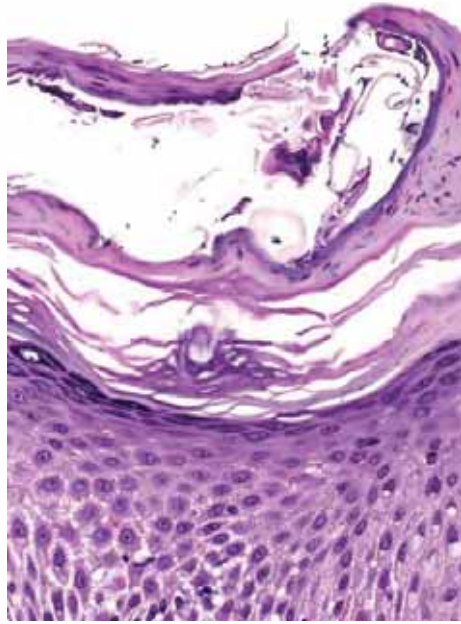


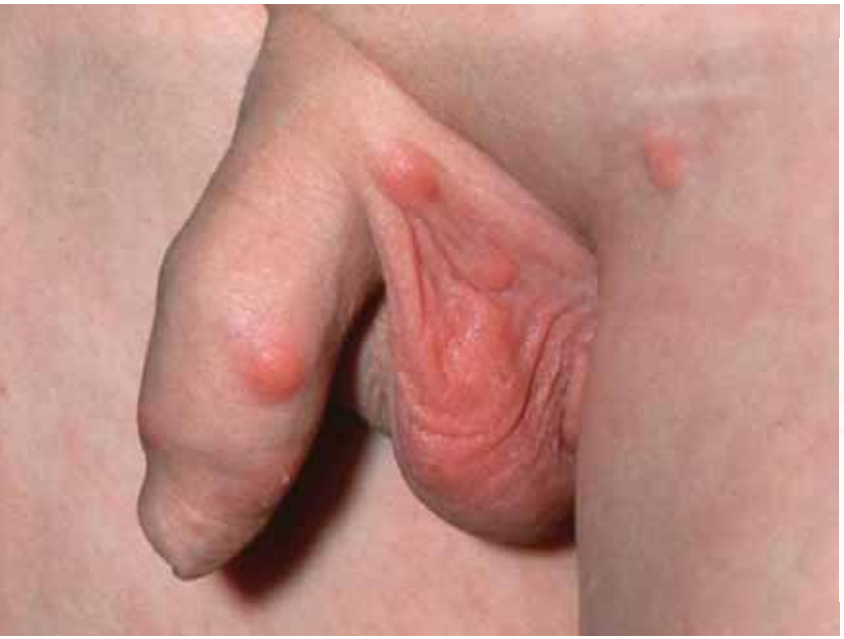


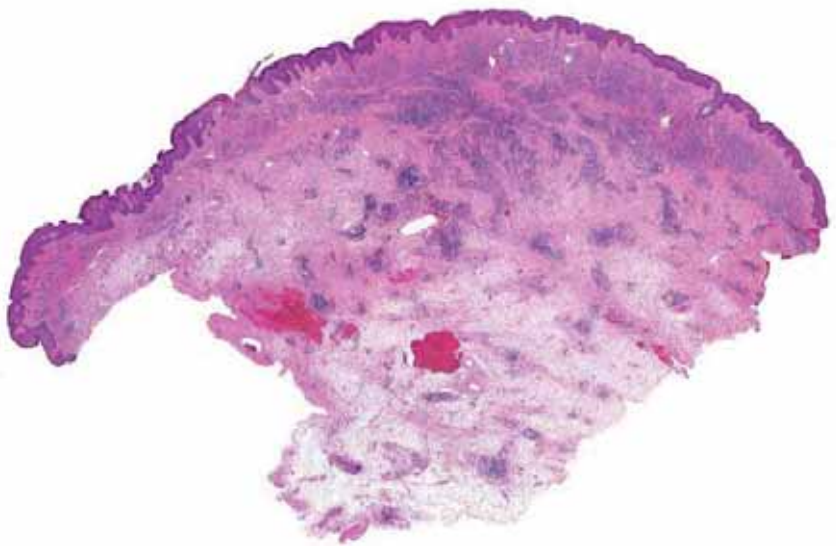


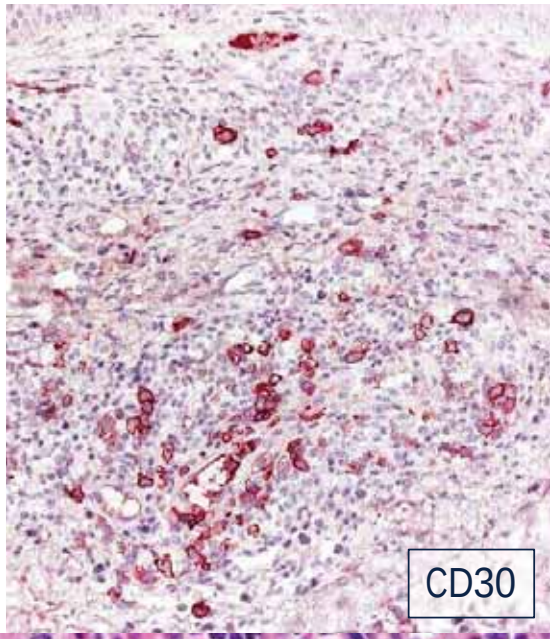
Scabies





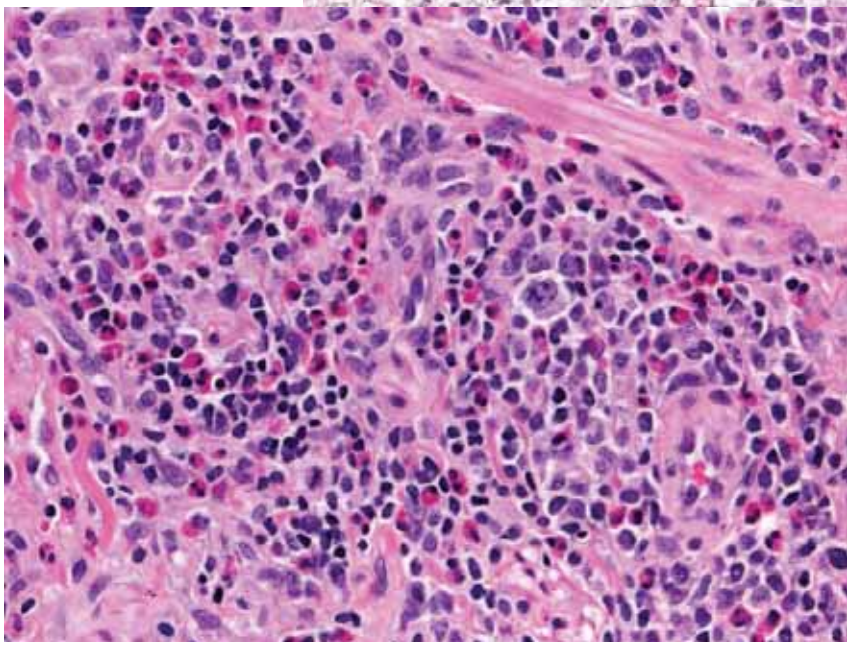


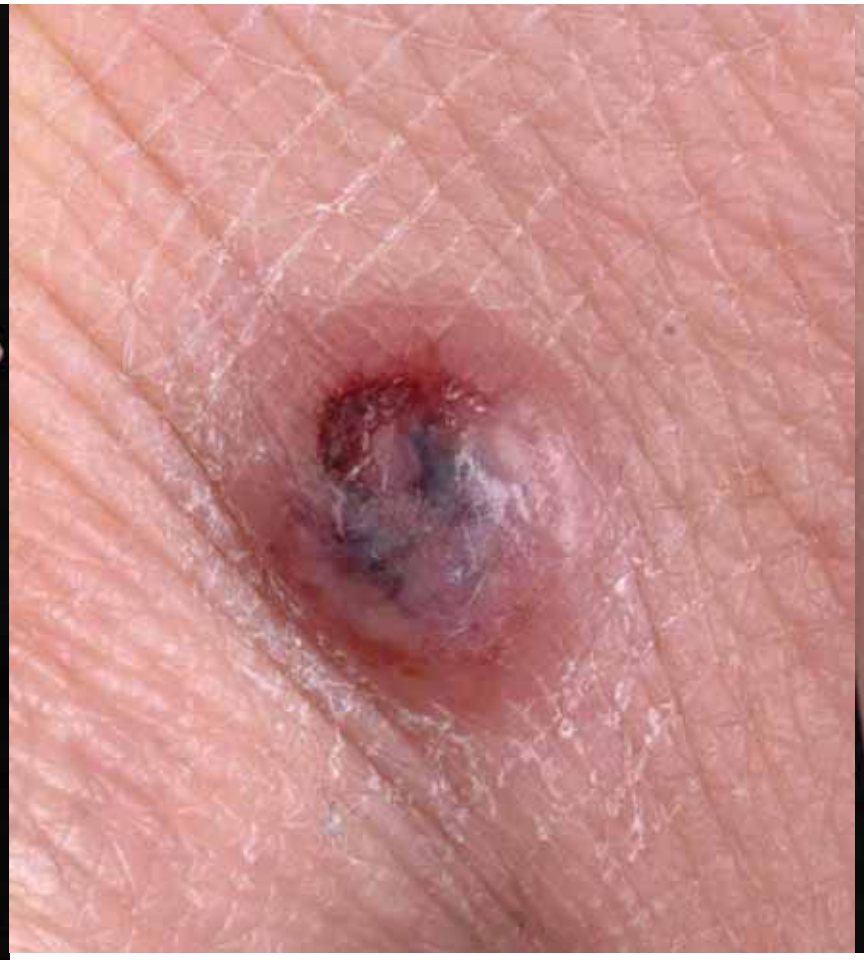


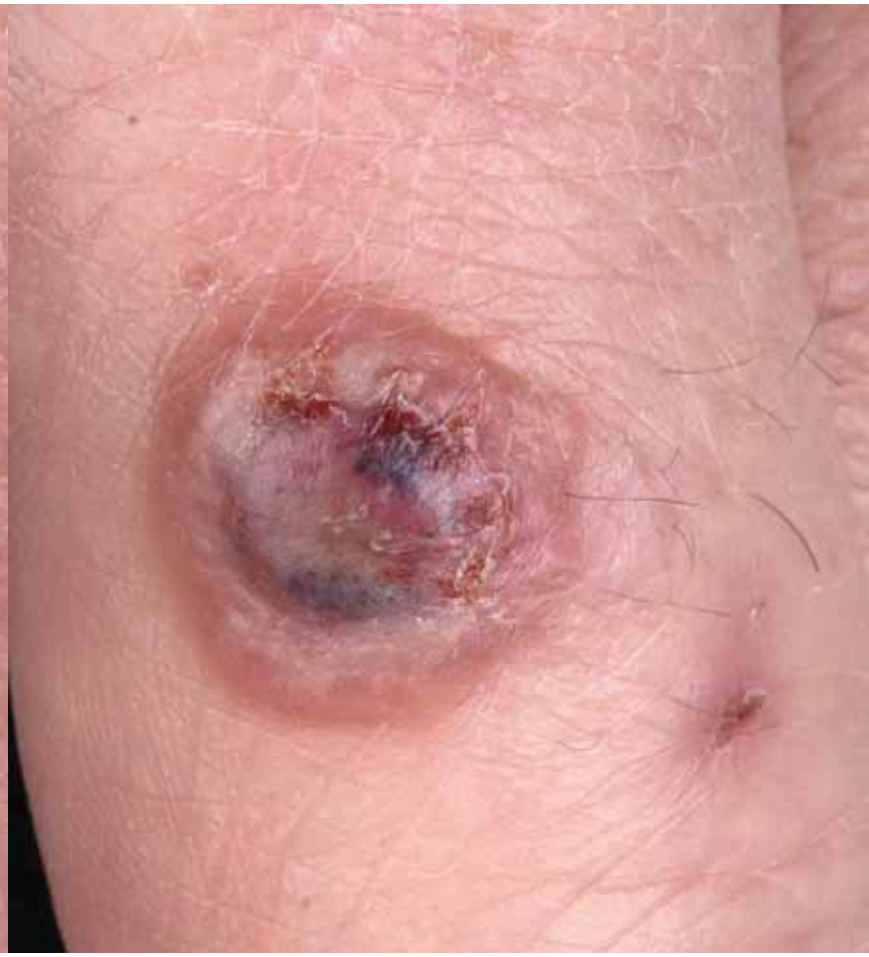


Nodular scabies

- Pruritic papules and small nodules with a predilection for the lower trunk, scrotum, and thighs; commonly observed in children
- May persist for several months and be not responsive to conventional treatment
- Mites are found in a minority of cases; it may represent a delayed hypersensitivity reaction similar to that found following other arthropod bites
- Activated, CD30+ cells may mimic lymphomatoid papulosis



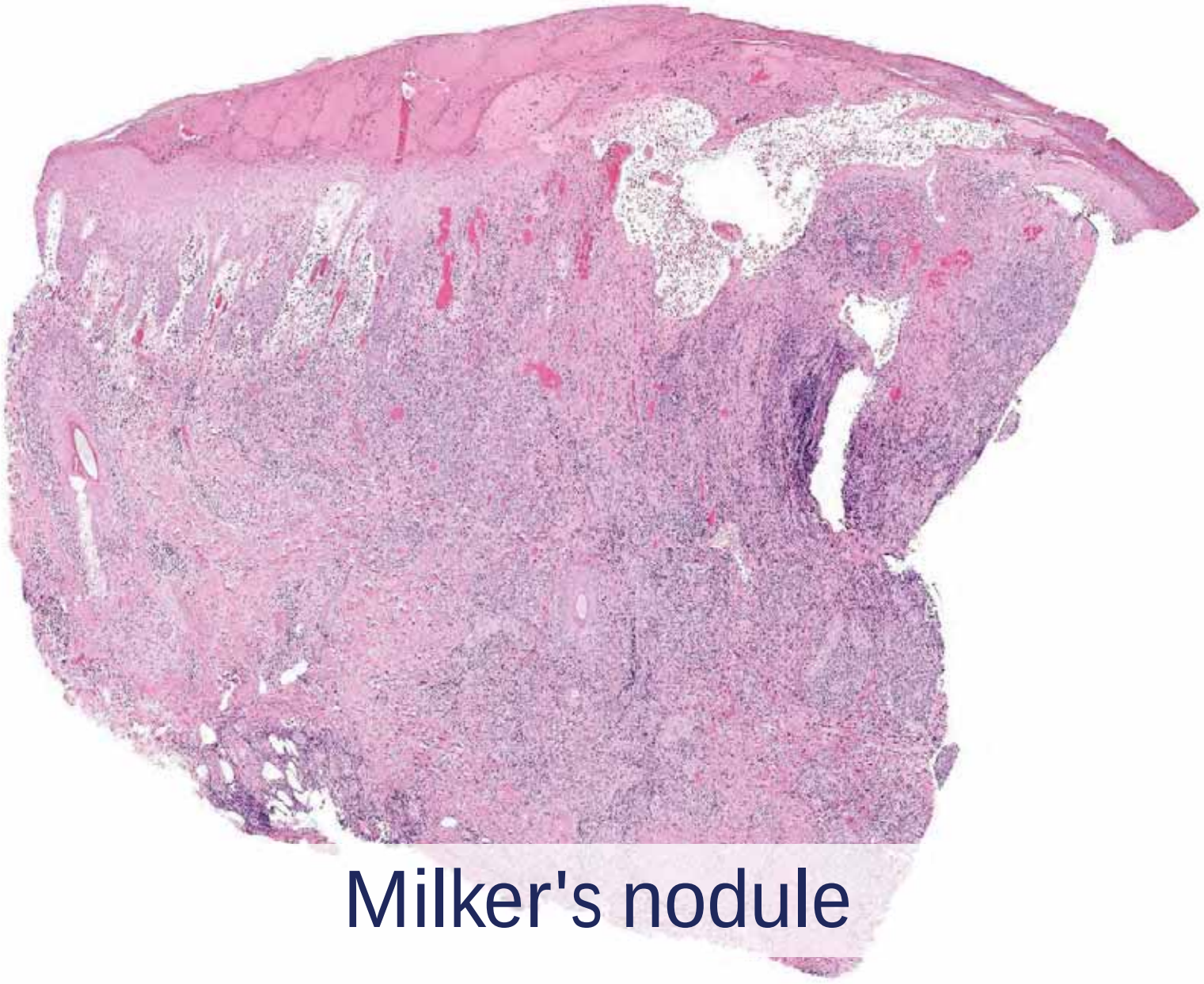




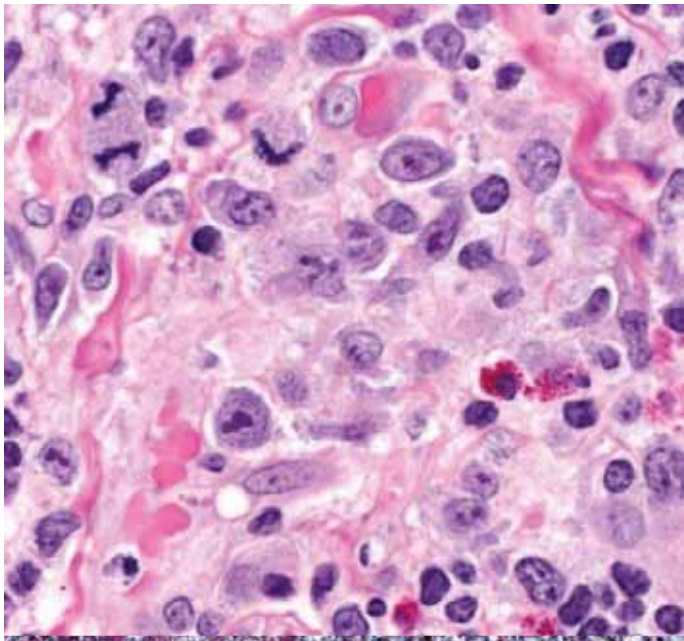
F, 44

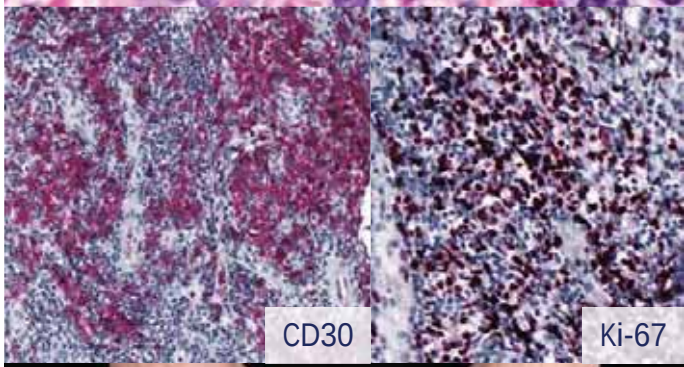
The patient is a nurse and also has a small farm with cows and rabbits (a cow was recently ill). Two itchy lesions on right and left hands for 3 days.

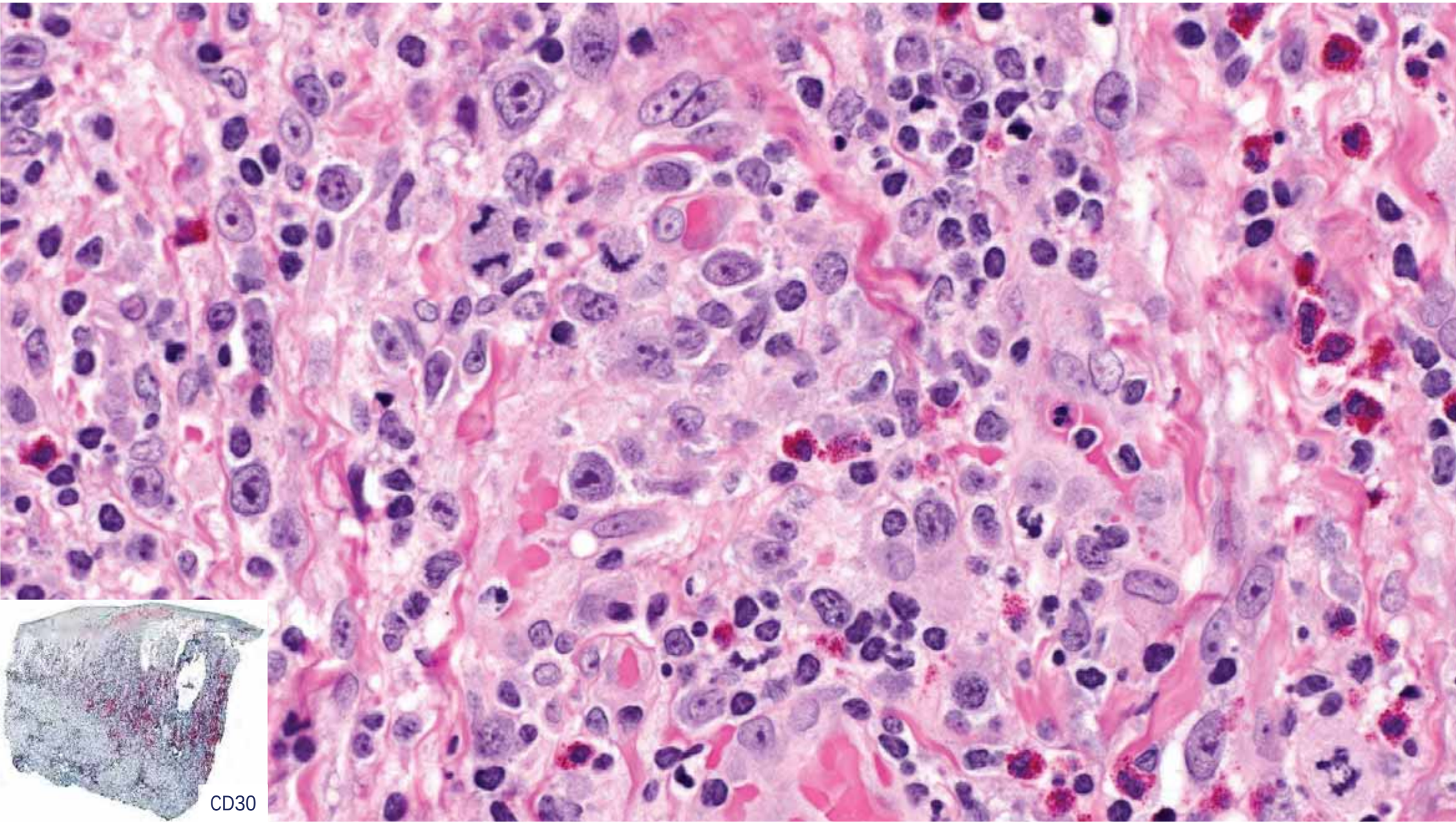
A biopsy is taken.

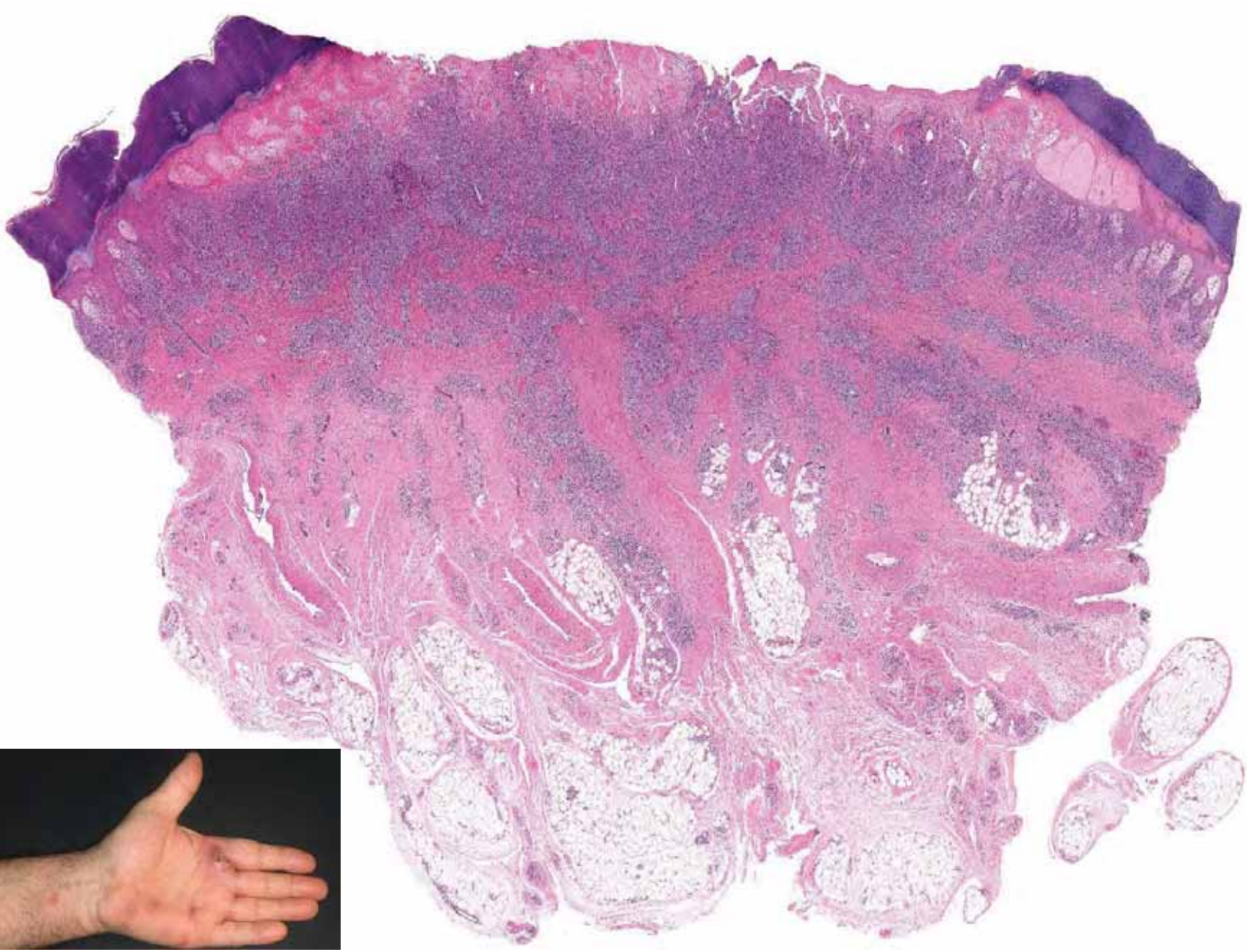


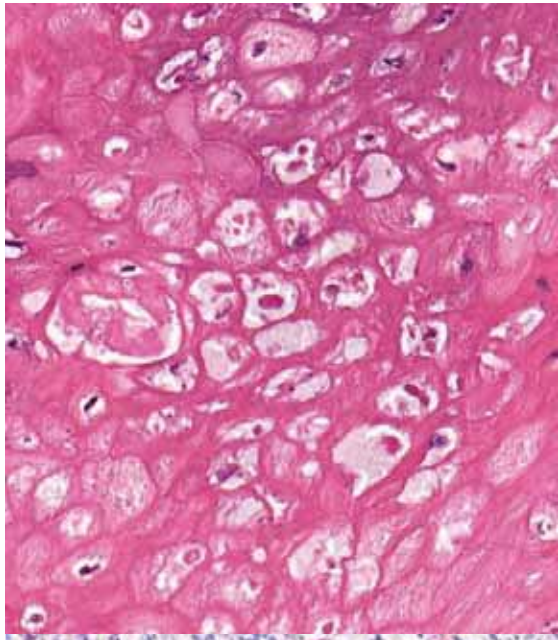
Milker's nodule

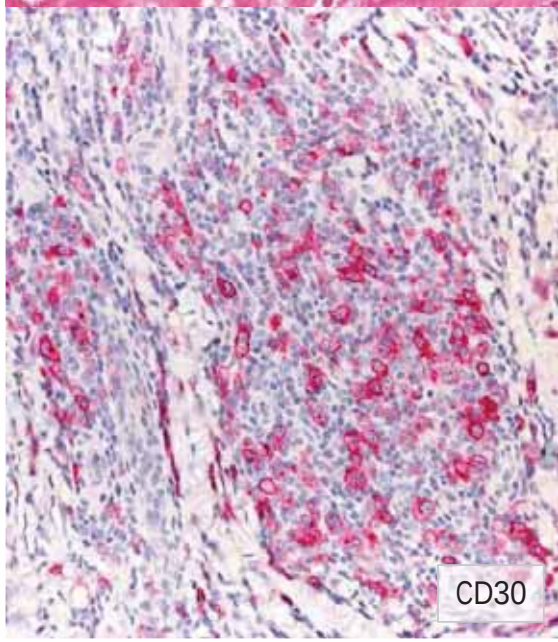




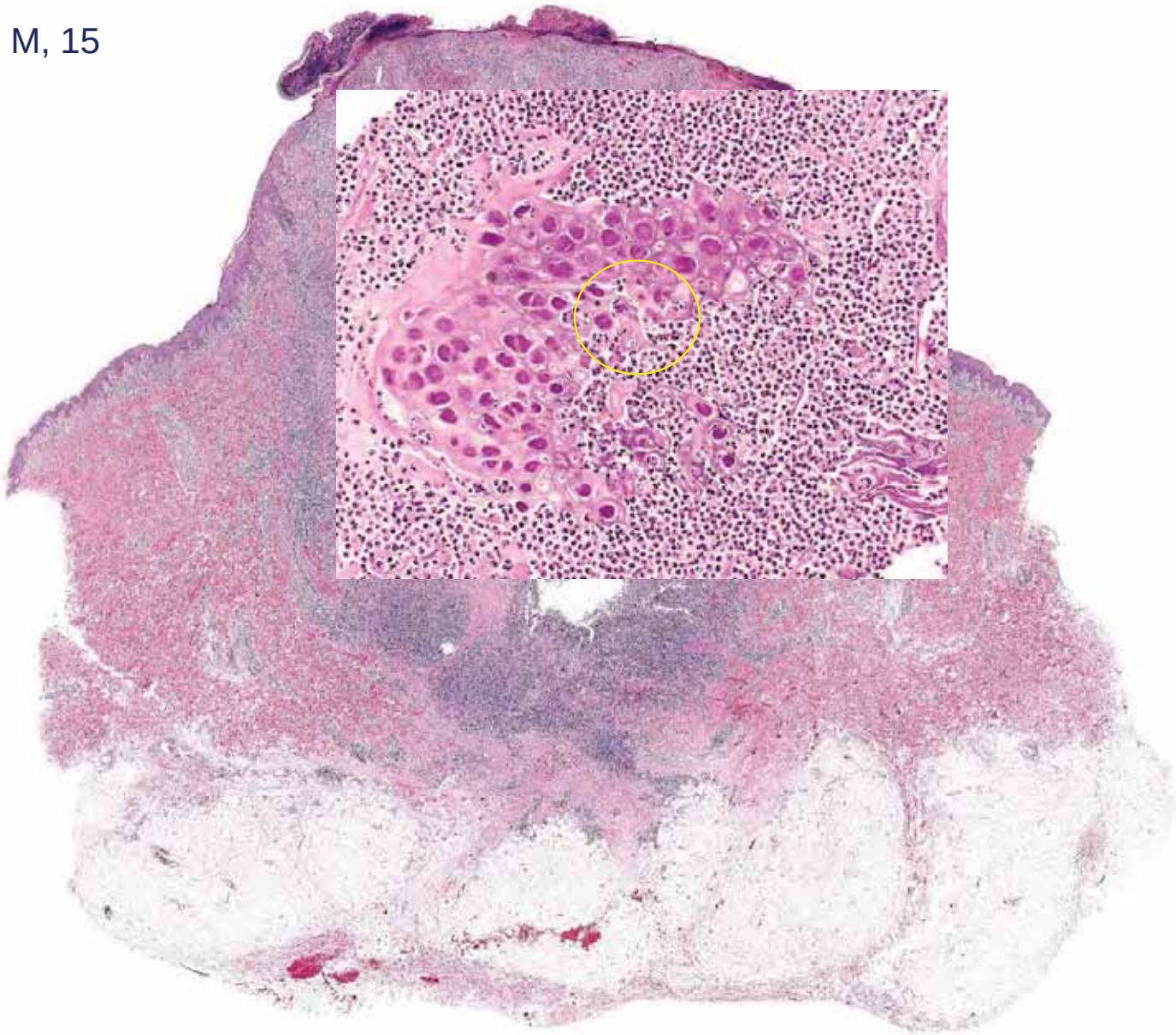

CD30

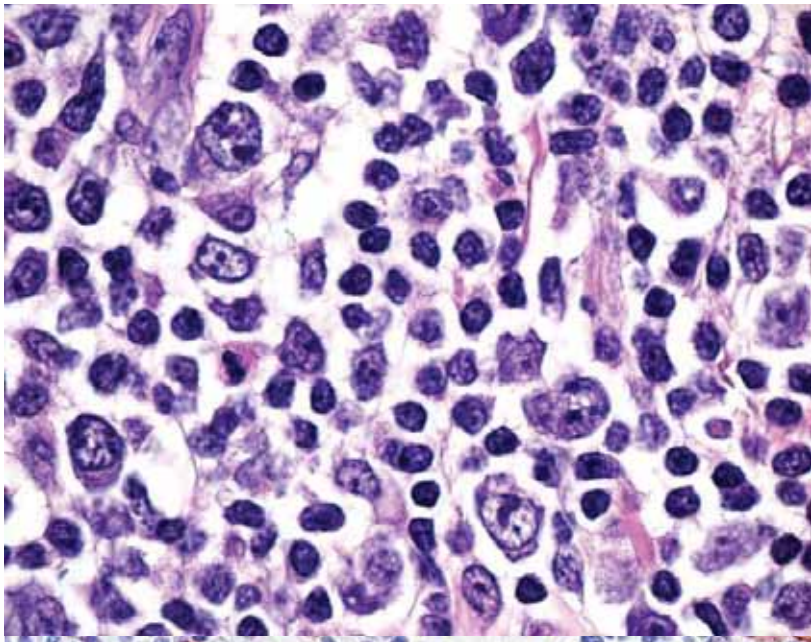


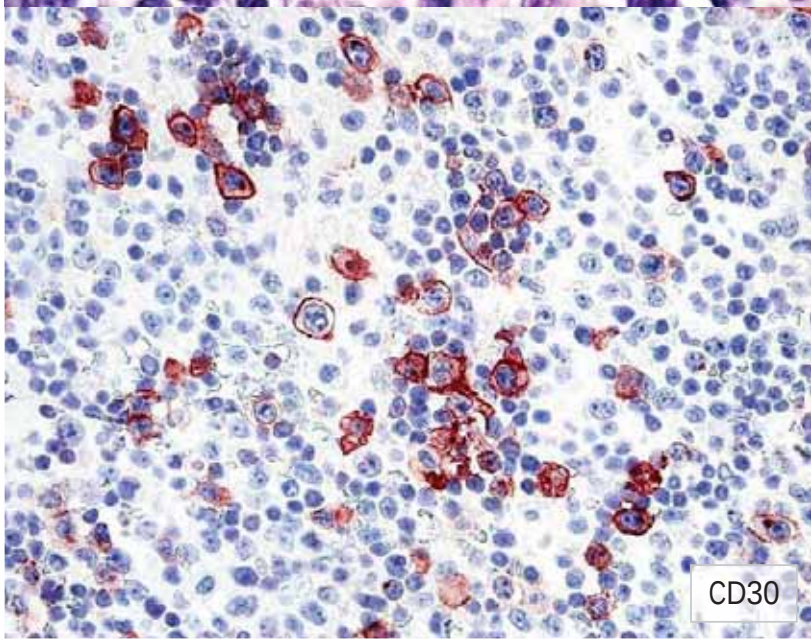



CD30

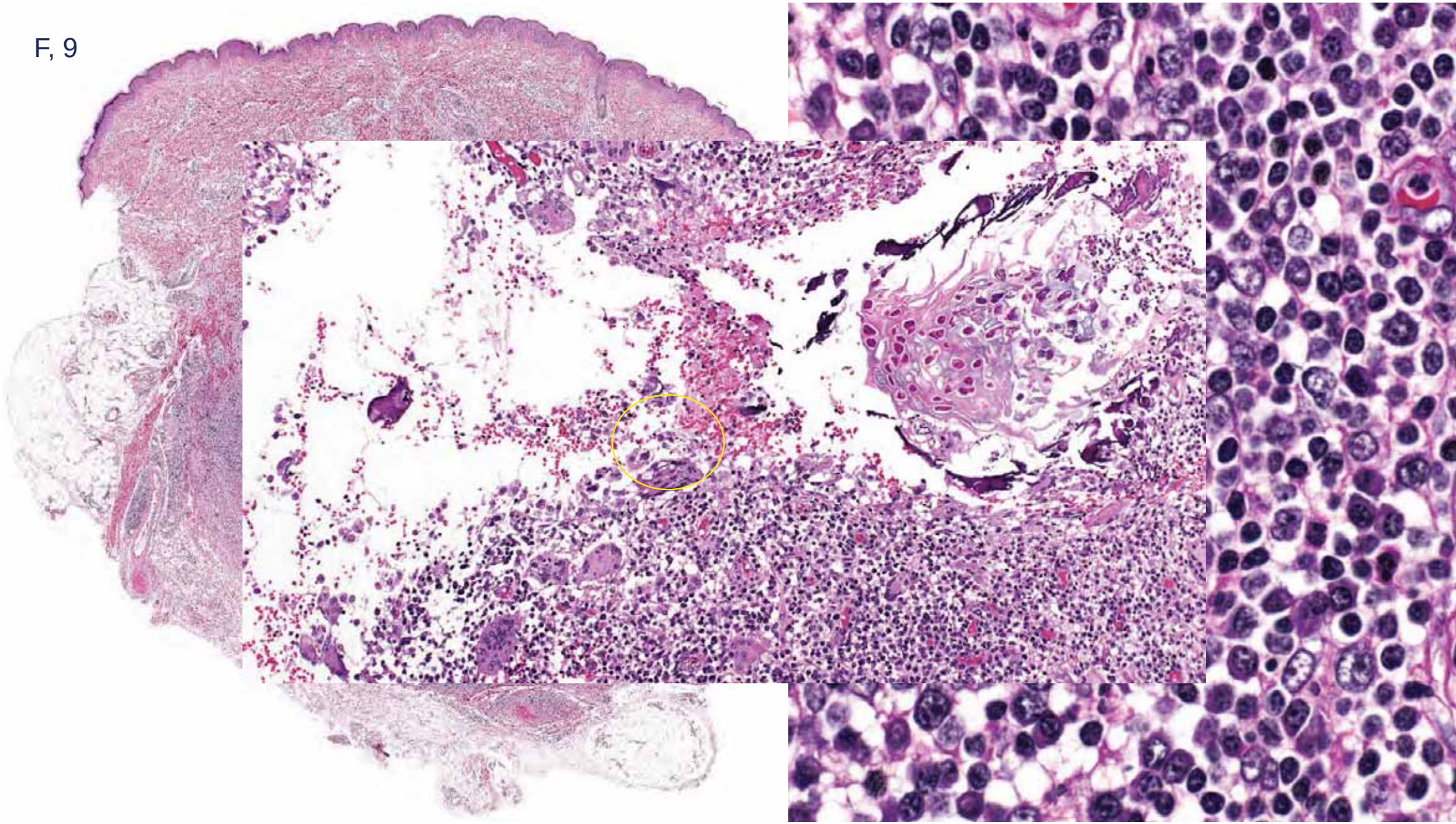
M, 15







F, 9



The American Journal of Dermatopathology 20(5):518–521, 1998

Cutaneous Pseudolymphoma in Association With Molluscum Contagiosum

Julia de Diego, M.D., Daniel Berridi, M.D., Nieves Saracibar, M.D., and Luis Requena, M.D.

Cutaneous pseudolymphomas have been defined as benign lymphocytic infiltrates of the skin that simulate cutaneous lymphoma clinically or histologically. The authors report on a 2-year-old boy with a lesion of molluscum contagiosum in which the inflammatory infiltrate that surrounded a cystlike structure containing molluscum bodies consisted of atypical hyperchromatic mononuclear cells with abundant mitotic figures, some of them atypical. Immunohistochemical investigation demonstrated that the infiltrate was predominantly composed of T lymphocytes. A previous report documented pseudoleukemia cutis associated with molluscum contagiosum, and this report expands the spectrum of histopathologic pseudomalignancies that may be seen in lesions of molluscum contagiosum.

Key Words: Pseudolymphoma—Molluscum contagiosum.

Cutaneous pseudolymphomas are commonly defined as benign hyperplastic lymphoproliferative reactions that simulate cutaneous malignant lymphomas clinically or histologically (1,2). Because these pseudolymphomas can mimic cutaneous B-cell lymphomas or cutaneous T-cell lymphomas, they often are divided into B-cell pseudolymphomas and T-cell pseudolymphomas according to the architectural pattern of the cutaneous infiltrates (3–5) (Table 1). Thus, cutaneous B-cell pseudolymphomas are characterized by nodular infiltrates throughout the entire dermis, a pattern similar to that of the cutaneous lesions of malignant B lymphomas. In contrast, cutaneous T-cell pseudolymphomas show a dense, bandlike infiltrate in the upper parts of the dermis, mimicking plaque-stage lesions of mycosis fungoides.

The authors describe a striking example of cutaneous T-cell pseudolymphoma associated with a cystic lesion of molluscum contagiosum in 2-year-old boy. In their review of the literature, the authors found a previous report of pseudoleukemia cutis in association with molluscum contagiosum (6). The current case expands the spectrum of histopathologic pseudomalignancies that may be seen in lesions of molluscum contagiosum.

CASE REPORT

A 2-year-old boy had a pedunculated lesion on the anterior aspect of the chest that had been present for several months. He was born from a normal delivery, and family history was not contributory. He was in good health until 6 months of age, when he showed an episode of laryngitis and acute gastroenteritis. He was therefore admitted to the hospital, receiving treatment with adrenaline inhalations and intravenous administration of fluids and desoxymetasone. The infant recovered in a few days and was discharged with no additional problems until the cutaneous lesion appeared.

Examination revealed an erythematous pedunculated lesion of 1 cm on the anterior aspect of the chest. The

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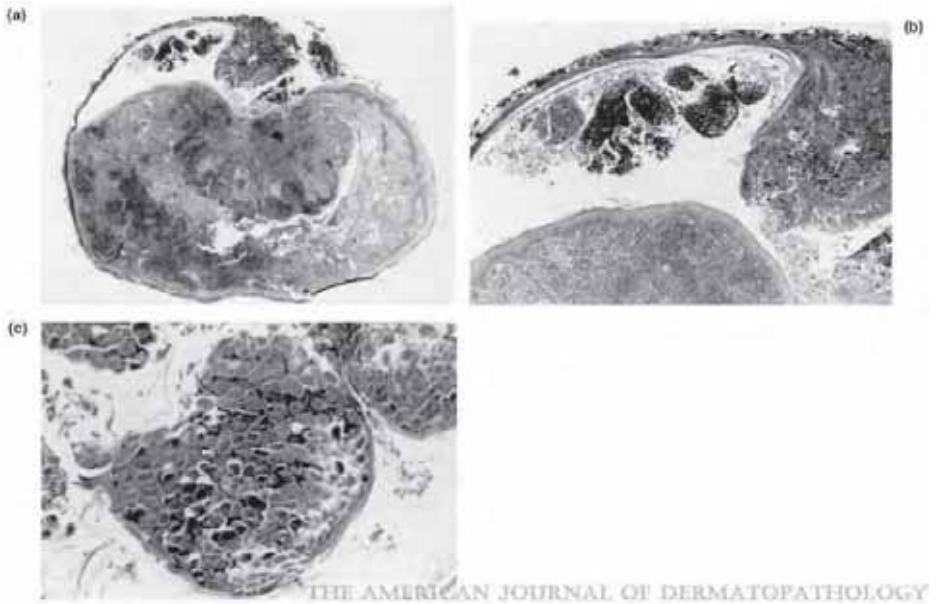
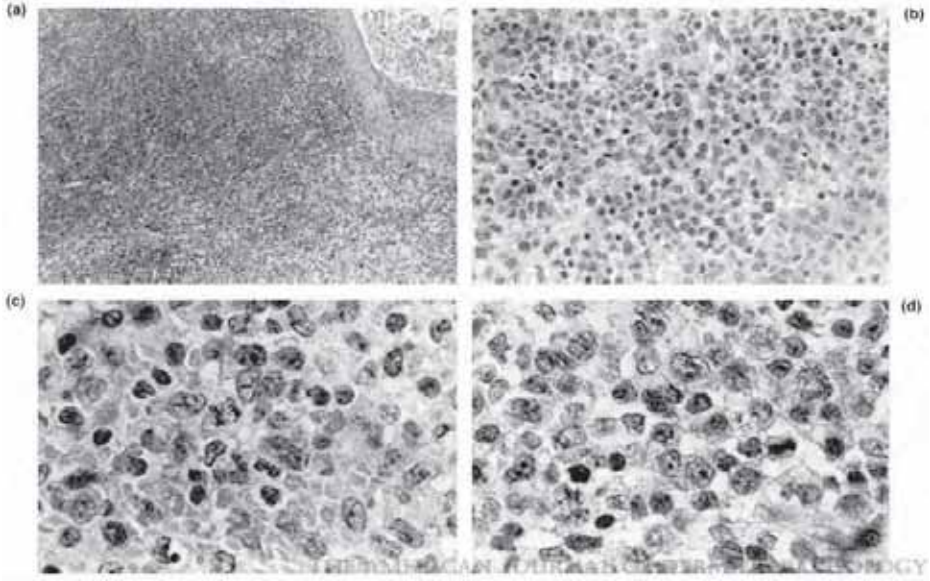
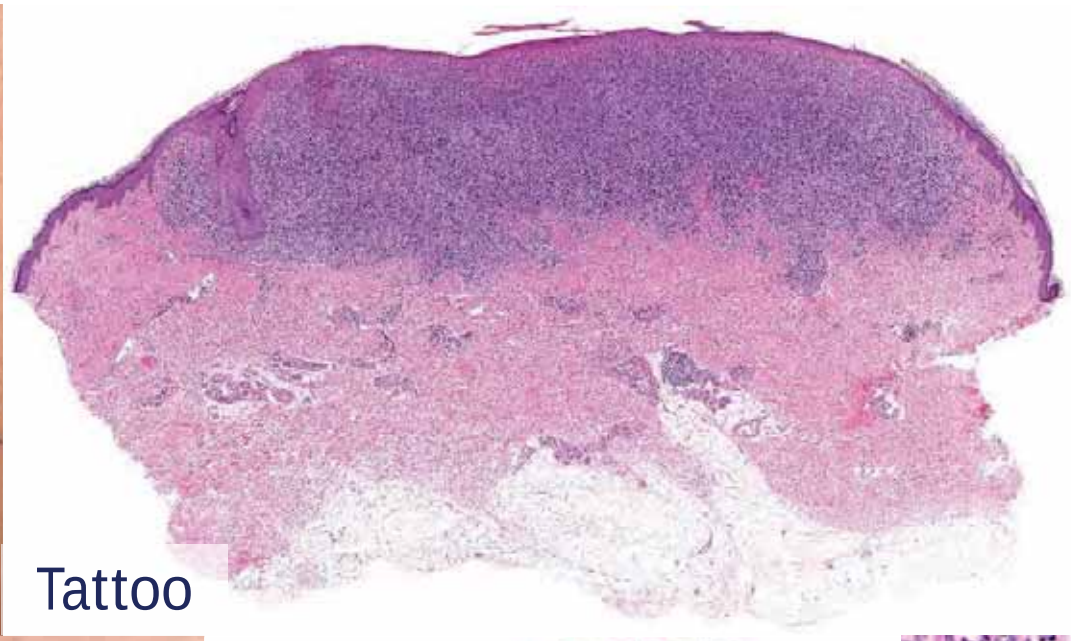
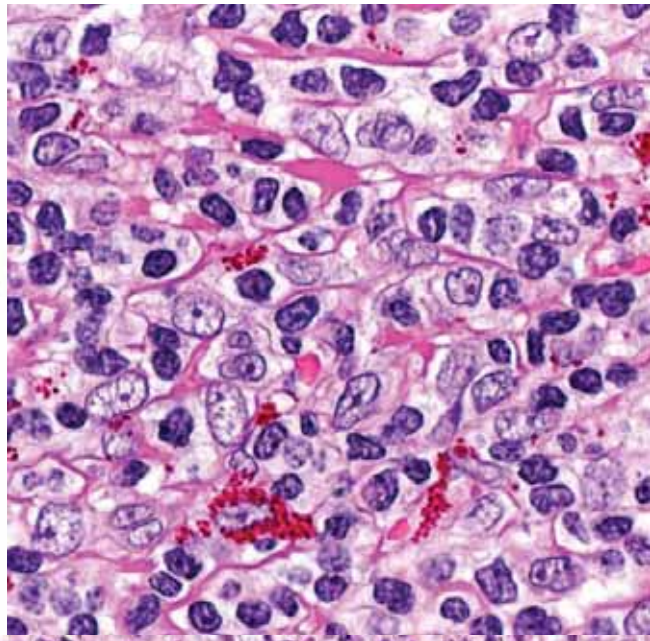
Address correspondence and reprint requests to Dr. Luis Requena, Department of Dermatology, Fundación Jiménez Díaz, Avda. Reyes Católicos 2, 28040, Madrid, Spain.

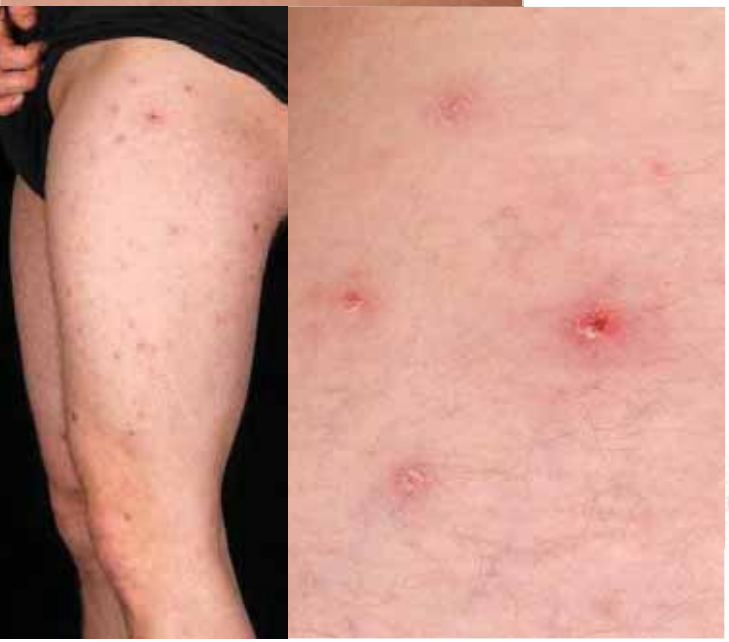


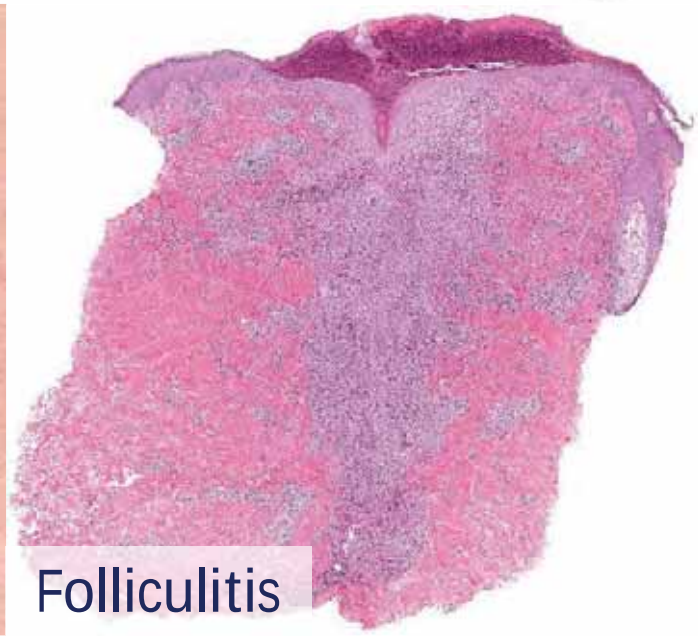




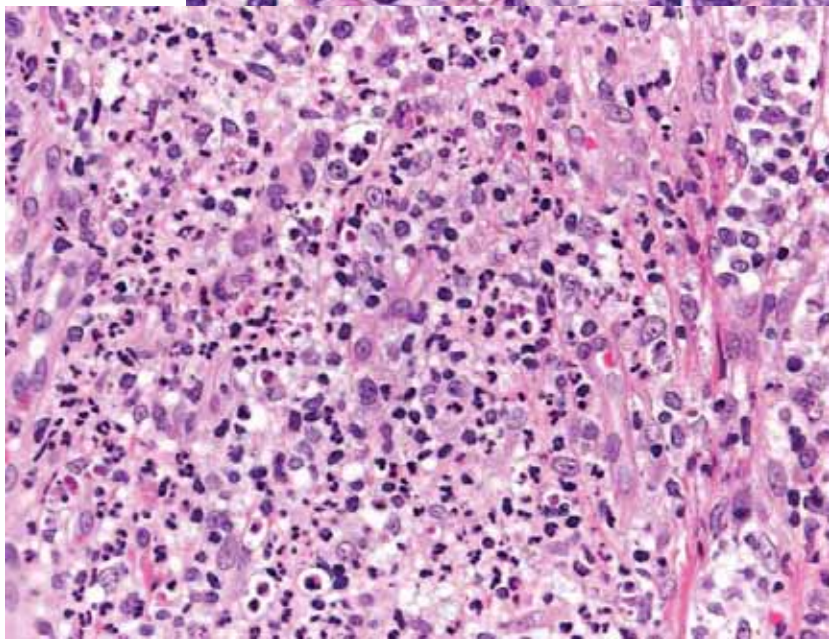
Tattoo







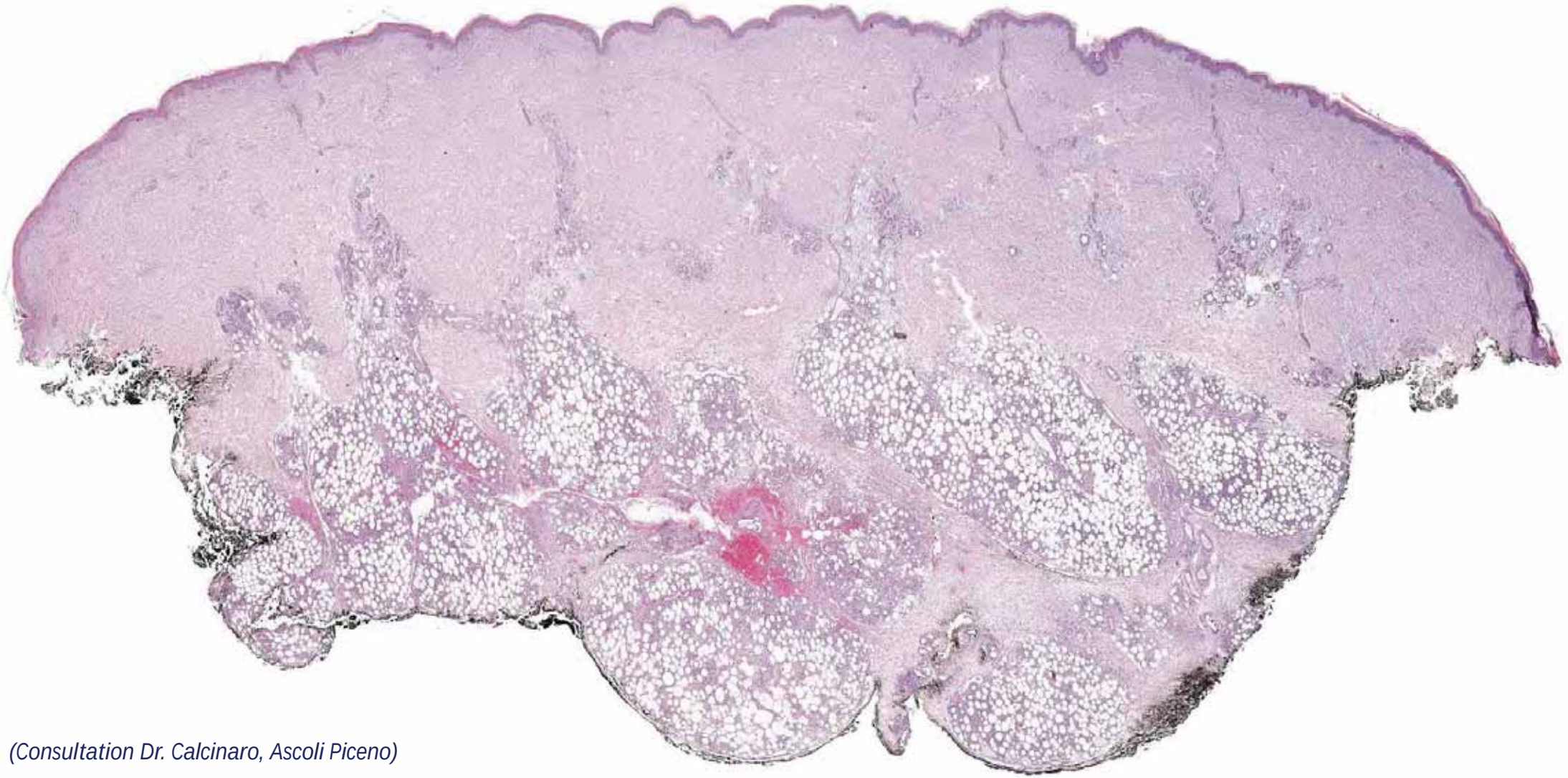
Folliculitis



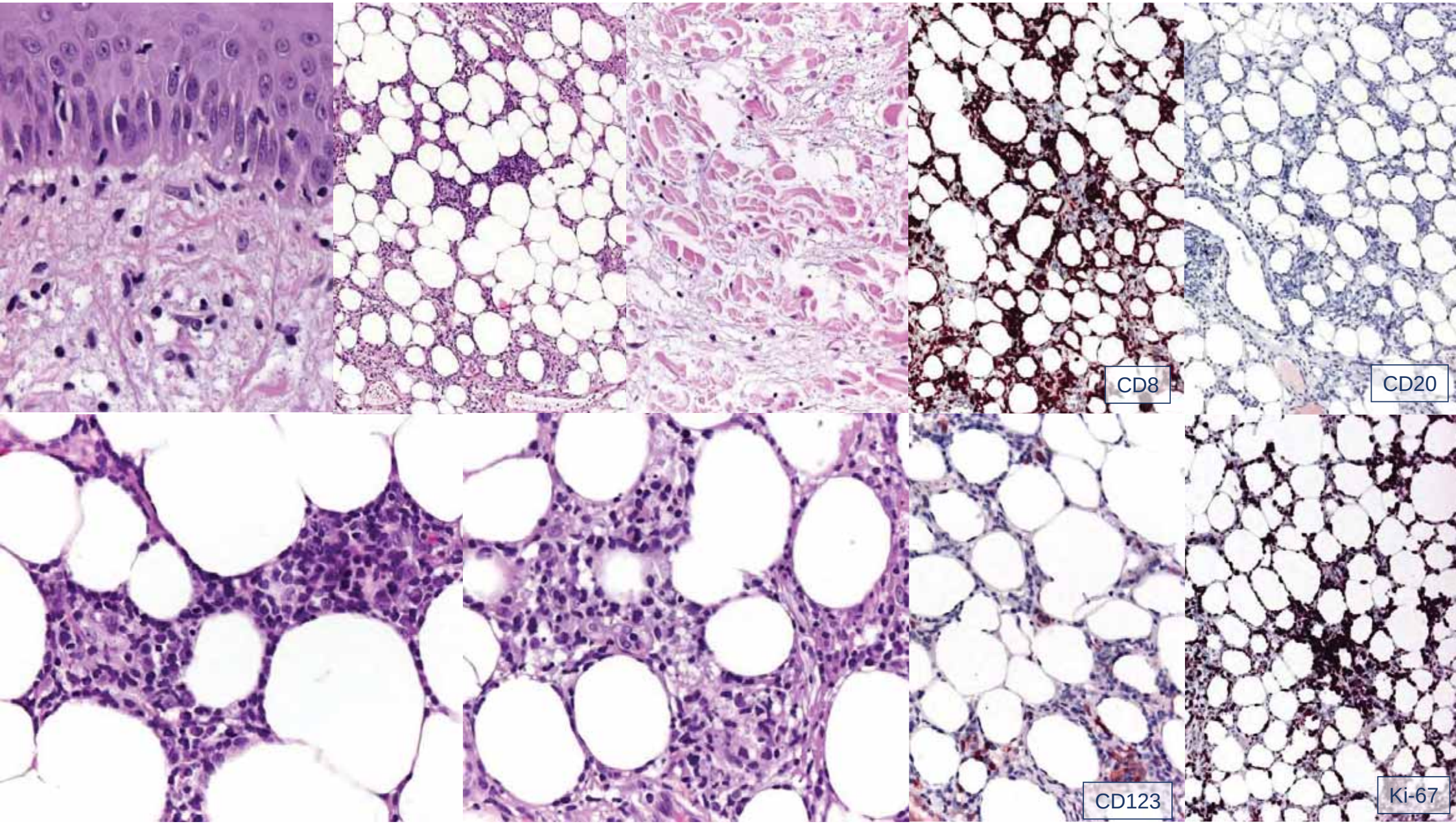
CD30+ pseudolymphomas – Histopathological clues

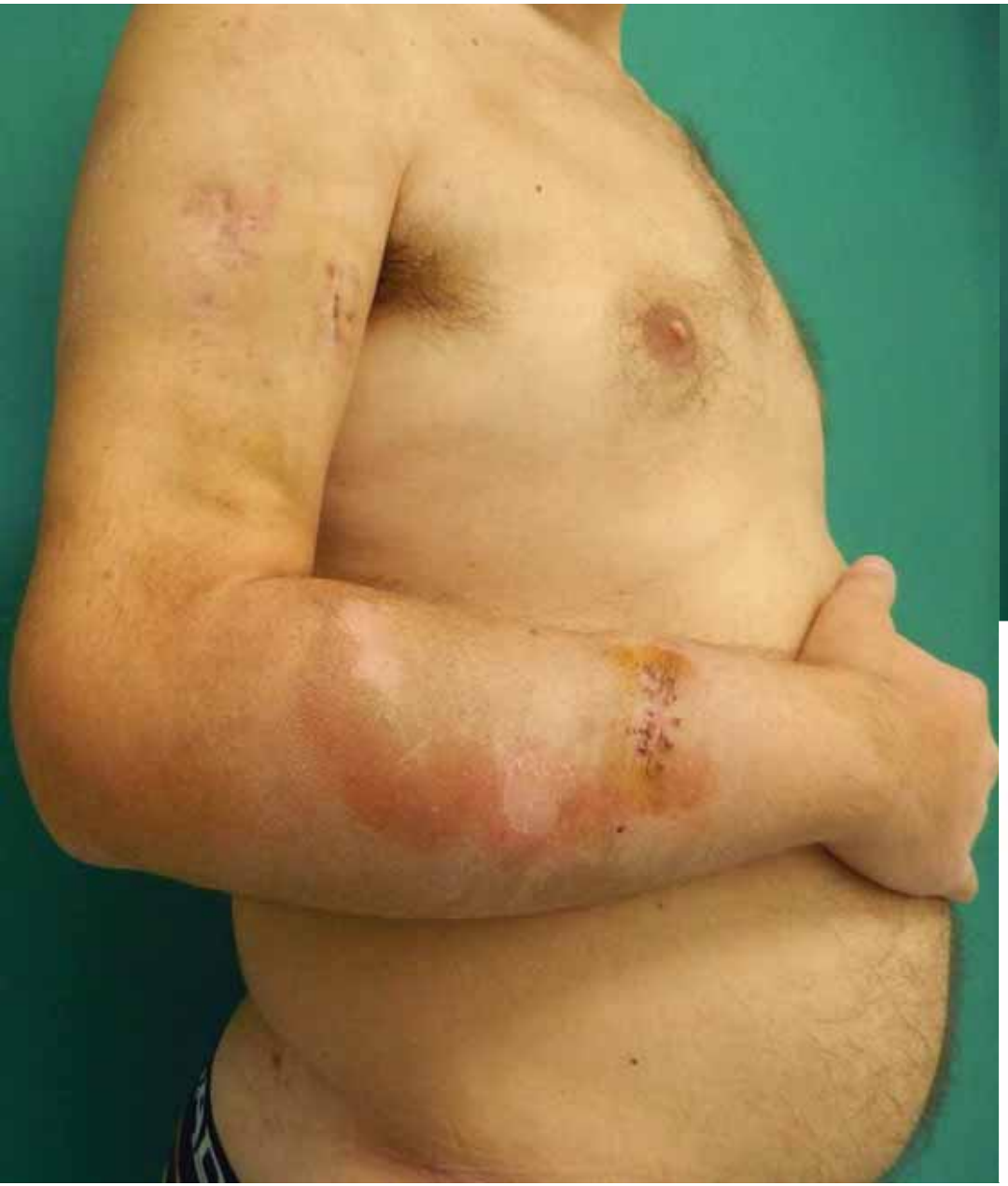
- ***Arthropod bites with CD30+ cells:*** infiltrate wedge-shaped, may resemble LyP type A but limited number of atypical cells; usually no clusters of CD30+ cells; sometimes central scale crust; intracorneal cuniculum in scabies (rare!)
- ***Herpes infections:*** necrotic keratinocytes within epithelial structures (sometimes confined to follicles, eccrine coils)
- ***Parapox virus:*** large areas of haemorrhage, dilated vessels, irregular epithelial hyperplasia with focal areas of necrosis
- ***Molluscum contagiosum:*** typical molluscum bodies (may be found only in deeper sections!)
- ***Drug eruptions with CD30+ cells:*** infiltrate superficial, may resemble MF but more "atypical" than early MF

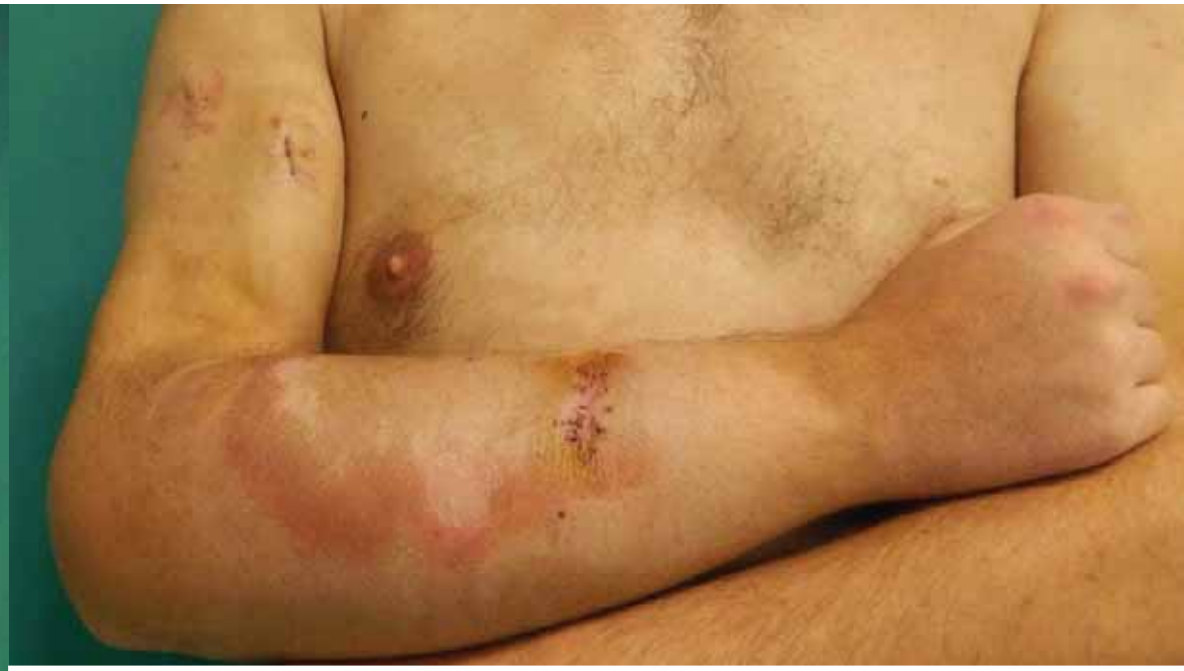
M, 36. Recurrent subcutaneous nodules, some with atrophic scars, for the last 14 years.



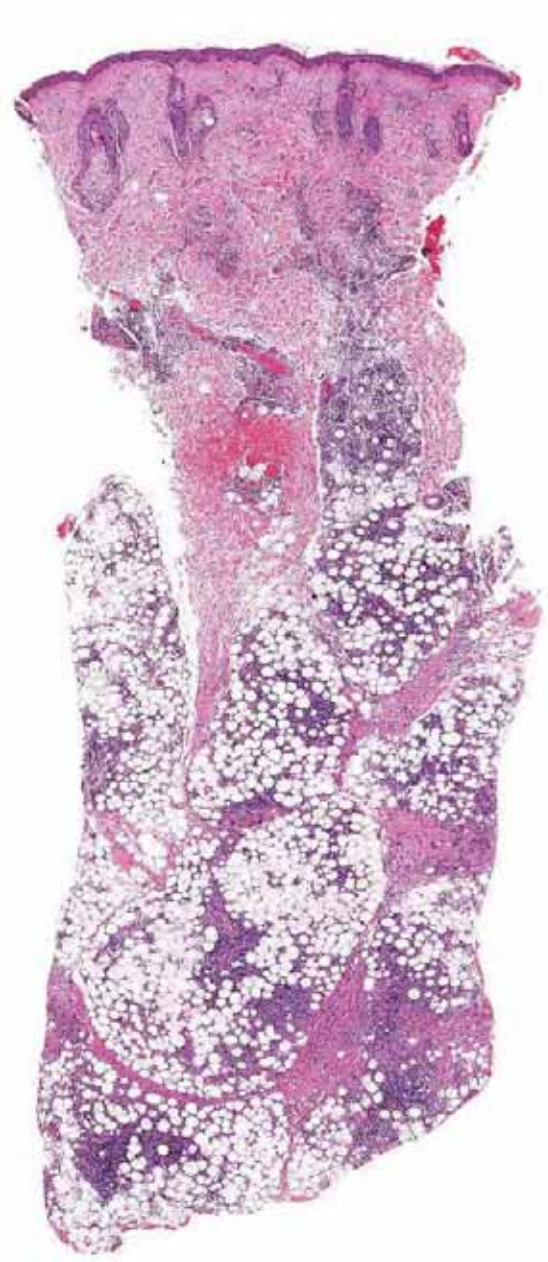
(Consultation Dr. Calcinaro, Ascoli Piceno)

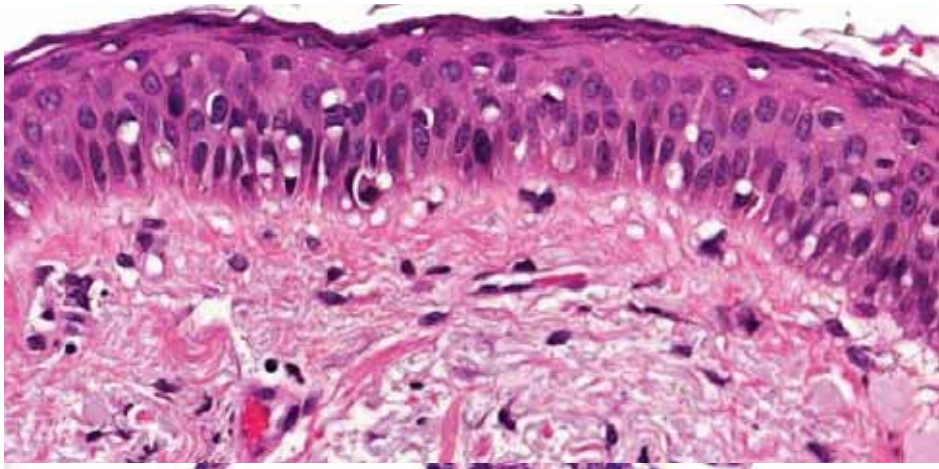

CD8
CD20
CD123
Ki-67

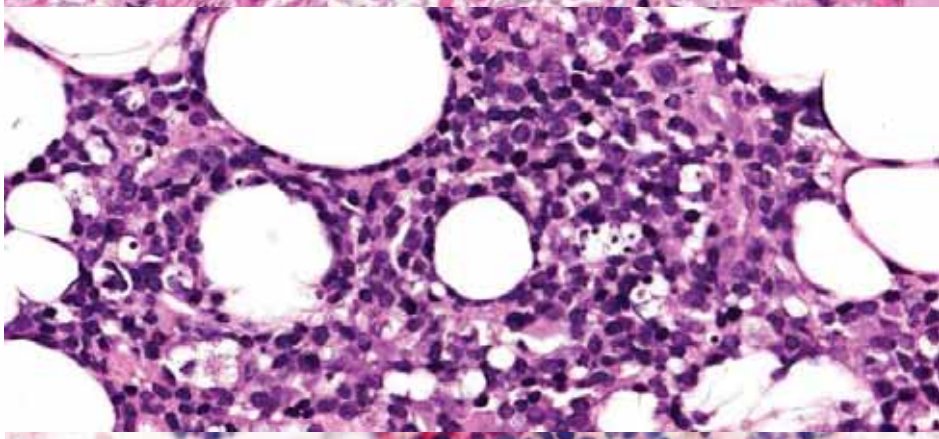


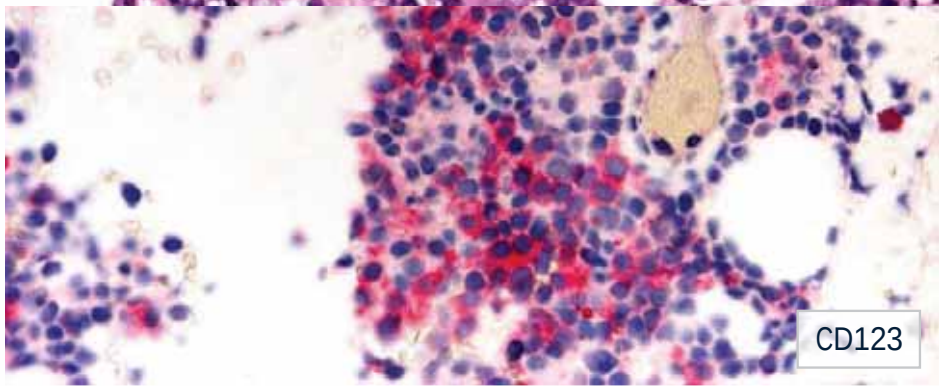


LE panniculitis








CD123

Panniculitis in lupus erythematosus (lupus profundus)

- Patients with cLE may show prominent involvement of the subcutaneous fat (lupus profundus)
- May be concomitant to more conventional lesions of cLE (particularly CDLE but also SLE)
- The overlying skin may show features of cLE
- Histopathologically, pattern of a mainly lobular panniculitis with variable involvement of the septae ("mixed panniculitis") and with hyaline necrosis of the fat lobules
- Distinction from SPTCL is traditionally considered difficult; some biopsies show overlapping histopathological features of the two entities

Subcutaneous Panniculitis-Like T-Cell Lymphoma Versus Lupus Erythematosus Panniculitis: Distinction by Means of the Periadipocytic Cell Proliferation Index

Panitta Sitthinamsuwan, MD, Pornvadee Pattanaprichakul, MD,† Jitsupa Treetipsatit, MD,* Tawatchai Pongpruttipan, MD,* Sanya Sukpanichnant, MD,* Laura B. Pincus, MD,‡ and Timothy H. McCalmont, MD‡*

Abstract: The distinction between subcutaneous panniculitis-like T-cell lymphoma (SPTCL) and lupus erythematosus (LE) panniculitis is remarkably challenging. Rimming by lymphocytes with an elevated Ki-67 cell proliferation index has been forwarded as a potential diagnostic finding in biopsies of SPTCL but has not been rigorously compared with biopsies from patients with LE panniculitis. Nineteen and 17 examples of SPTCL and LE panniculitis, respectively, were evaluated for periadipocytic rimming by lymphocytes expressing Ki-67, CD8, and βF1 and for attributes associated with LE, including clusters of CD123-positive cells. The identification of periadipocytic rimming using Ki-67, CD8, and βF1 held sensitivity of 79%, 100%, and 89.5% and specificity of 100%, 52.9%, and 88.2%, respectively ($P < 0.01$). CD123-positive cells were in both disorders. LE-like histopathology was commonly encountered in SPTCL. In conclusion, an elevated Ki-67 cell proliferation index with rimming is useful for distinguishing SPTCL from LE panniculitis. Notably, many features of LE panniculitis can also be encountered in SPTCL.

Key Words: subcutaneous panniculitis-like T-cell lymphoma, lupus erythematosus panniculitis, periadipocytic rimming, Ki-67 (MIB-1), CD123

(*Am J Dermatopathol* 2018;0:1–5)

INTRODUCTION

Periadipocytic rimming, defined as a string of lymphocytes that encircle individual adipocytes, is considered a significant diagnostic finding but is not a pathognomonic finding in subcutaneous panniculitis-like T-cell lymphoma (SPTCL) because this feature can be seen in other cutaneous lymphomas[1] and in some forms of lymphocytic panniculitis.[2] The distinction between SPTCL and lymphocytic panniculitis, in particular lupus erythematosus (LE) panniculitis, is often challenging. As an illustration of this difficulty, cases with overlapping features of both of these entities have been described.[3–7]

SPTCL is defined by the World Health Organization (WHO)/the European Organization for Research and Treatment of ...

Immunoreagents	SPTCL (n = 19)	LE (n = 17)	*P*	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)	PPV (95% CI) (%)	PLR (95% CI)
Ki-67 periadipocytic rimming, n (%)							
Positive	15 (78.9)	0 (0)	<0.001	79 (54.4–94)	100 (80.5–100)	100 (–)	—
Negative	4 (21.1)	17 (100)					
CD8 periadipocytic rimming, n (%)							
Positive	19 (100)	8 (47.1)	<0.001	100 (82.4–100)	52.9 (27.8–77)	70.4 (58.9–79.7)	2.1 (1.3–3.5)
Negative	0 (0)	9 (52.9)					
βF1 periadipocytic rimming, n (%)							
Positive	17 (89.5)	2 (11.8)	<0.001	89.5 (66.9–98.7)	88.2 (63.6–98.5)	89.5 (69.6–96.9)	7.6 (2–28.2)
Negative	2 (10.5)	15 (88.2)					
CD123 positive in clusters, n (%)							
Positive	7 (36.8)	12 (70.6)	0.04	70.6 (44–89.7)	63.2 (38.4–83.7)	63.2 (46.9–76.9)	1.9 (1–3.7)
Negative	12 (63.2)	5 (29.4)					

TABLE 3. Calculated Sensitivity, Specificity, PPV, and PLR of Immunoreagents for Distinction of SPTCL and LE Panniculitis

... protocol at the University of California, San Francisco (UCSF #11-07951).

A search of the pathology files of the Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University was performed from January 1999 to December 2009 for cases of SPTCL and LE panniculitis. The study consisted of 19 SPTCL and 17 LE panniculitis specimens retrieved from 18 and 17 patients, respectively.

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The authors declare no conflicts of interest.

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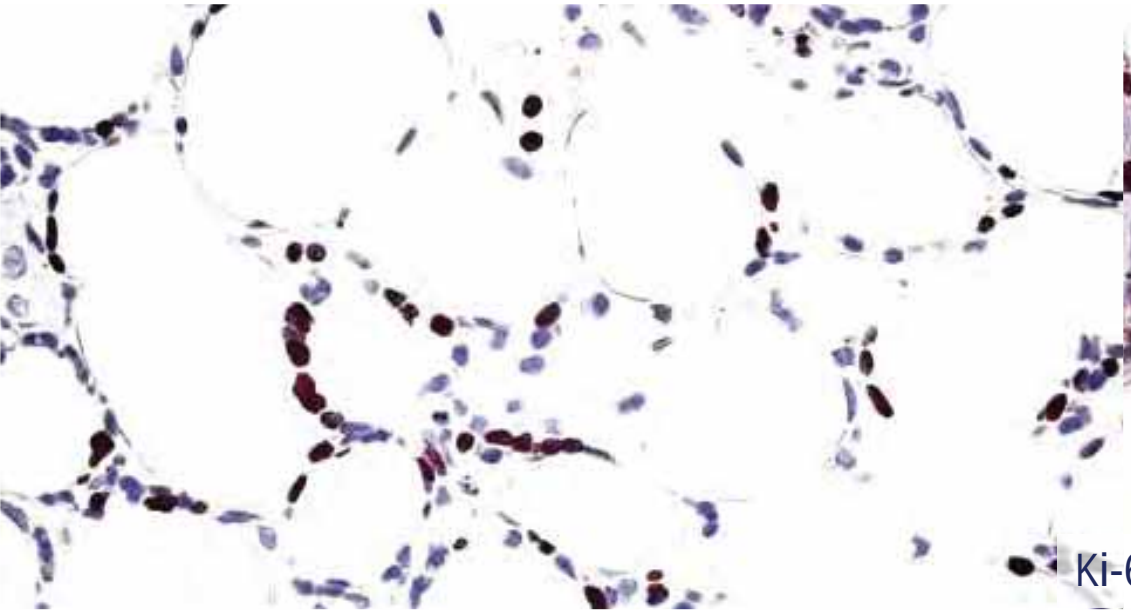
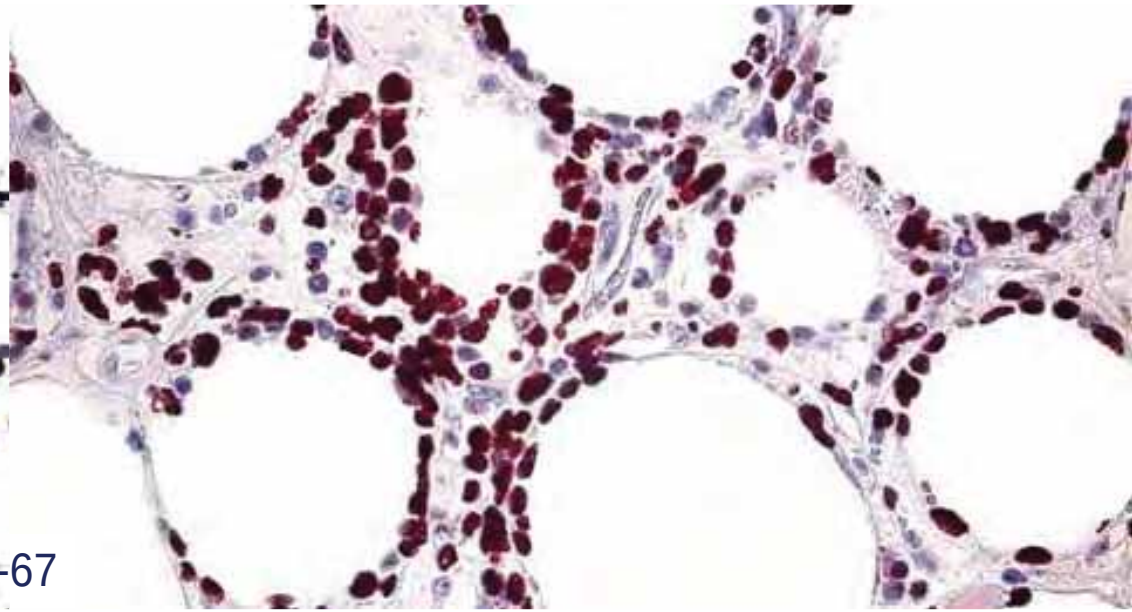
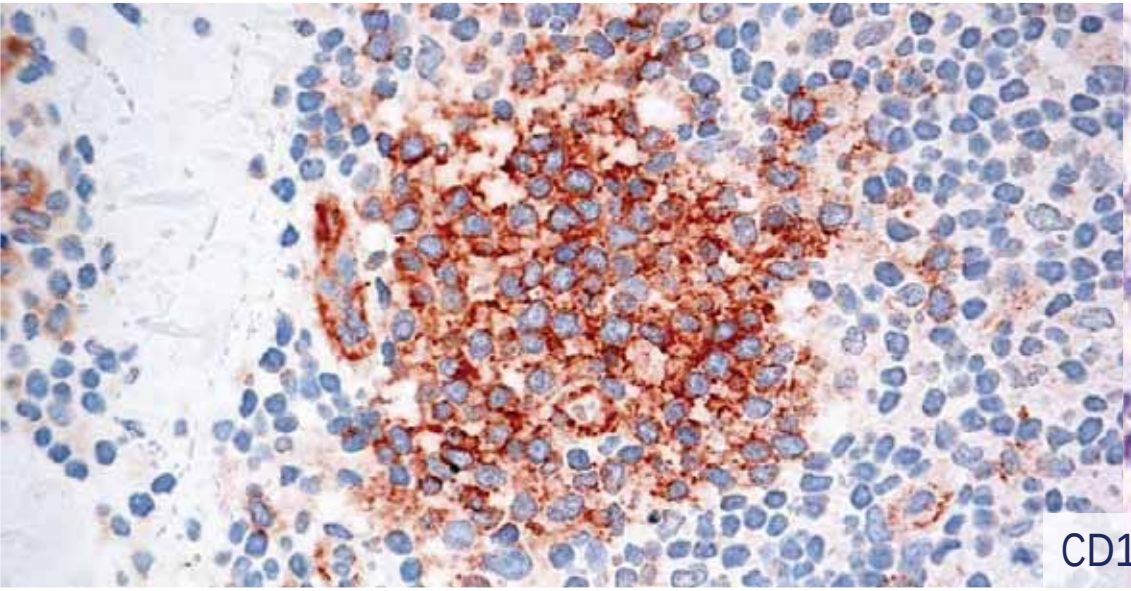


Ki-67

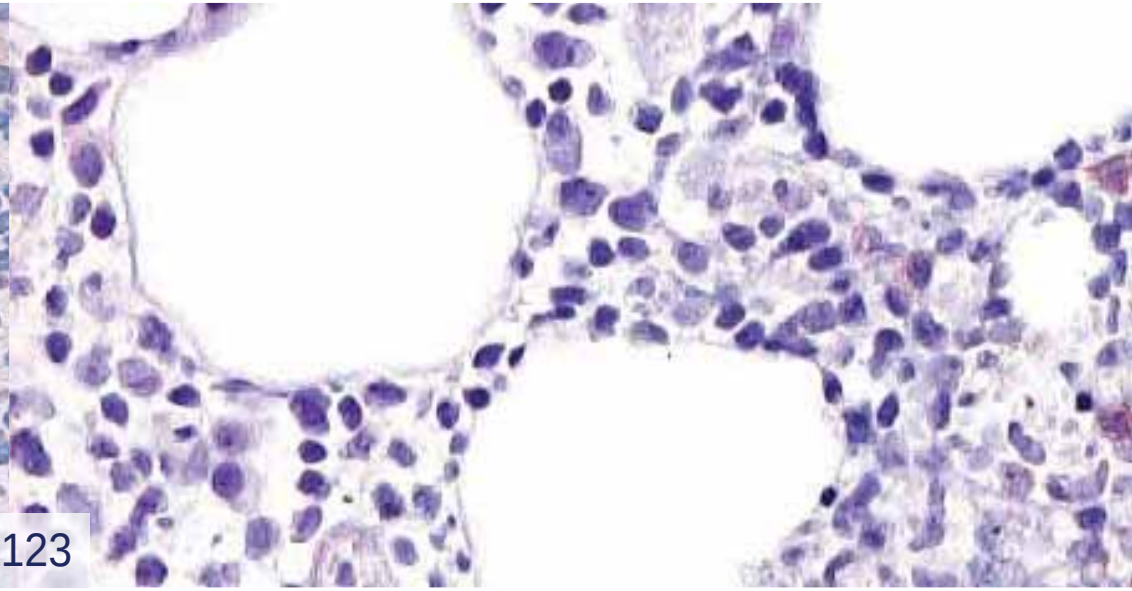
Lupus panniculitis



Subcutaneous panniculitis-like T-cell lymphoma



CD123



Lupus panniculitis	Subcutaneous T-cell lymphoma
• Mostly lobular paniculitis	• Mostly lobular panniculitis
• Prominent necrosis	• Prominent necrosis
• Nuclear debris, degenerative changes	• Nuclear debris, degenerative changes
• Rimming of adipocytes by different cell types	• Rimming of adipocytes by atypical lymphocytes
• Nodules of B lymphocytes at the periphery of lobules	• B lymphocytes few or absent
• Germinal centers frequent	• Germinal centers absent
• Mixed cell infiltrate; plasma cells frequent	• Monomorphous lymphocytes; clusters of atypical cells
• Fibrotic, enlarged septae	• Septae minimally or not enlarged
• Proliferation (Ki-67) low	• Proliferation (Ki-67) high
• No proliferation "rimming"	• Proliferation "rimming"
• Clusters of CD123+ cells	• No (or small) clusters of CD123+ cells
• TCR: polyclonal	• TCR: monoclonal

Subcutaneous Panniculitis-Like T-Cell Lymphoma With Overlapping Clinicopathologic Features of Lupus Erythematosus: Coexistence of 2 Entities?

Laura B. Pincus, MD, Philip E. LeBoit, MD,*† Timothy H. McCalmont, MD,*† Roberto Ricci, MD,‡ Carlo Buzio, MD,§ Lindy P. Fox, MD,* Fergus Oliver, MD,¶ and Lorenzo Cerroni, MD‖*

Abstract: We observed 5 patients with subcutaneous panniculitis-like T-cell lymphoma (SPTCL) who were unusual, in that they also exhibited features of lupus erythematosus (LE). This observation is in keeping with a recent study that reported an increased rate of autoimmune disease, including systemic lupus erythematosus (SLE), among patients with SPTCL. In all cases, attributes indicating SPTCL included an infiltrate of lymphocytes with pleomorphic nuclei involving subcutaneous lobules exhibiting a cytotoxic T-cell (CD3$^+$CD8$^+$βF1$^+$) immunophenotype. Additionally, a high proliferation rate and a monoclonal T-cell receptor-γ gene rearrangement were observed in most cases. The manifestations of LE in these patients included a spectrum of clinical and histopathological abnormalities. Clinical manifestations of LE included, in some patients, morphologic evidence of lupus erythematosus panniculitis (LEP) with subcutaneous nodules that healed with lipoatrophy on the face. In addition, all the patients exhibited serologic and/or extracutaneous end-organ abnormalities seen in patients with SLE, with 2 patients having sufficient findings to meet American College of Rheumatology criteria for SLE. Histopathological evidence of LE included vacuolar change at the dermal–epidermal interface in 3 patients, 2 of whom also showed interstitial deposition of mucin in the reticular dermis. One of these patients also had findings of LEP in the subcutaneous lobules with clusters of CD20$^+$ B cells partially arranged within germinal centers. In 2 patients in which neither the epidermis nor dermis was available for review, histopathological features of LE included, in one patient, a few small clusters of CD123$^+$ plasmacytoid dendritic cells within the adipose tissue and, in the other patient, a positive direct immunofluorescence test (lupus band) on clinically uninvolved and lesional skin. Our study shows that some patients show overlap between SPTCL and LE. We suspect that these patients may suffer from both diseases concomitantly. Furthermore, patients with LE, particularly LEP, should be monitored for evolution into SPTCL with biopsy of any subcutaneous lesion that is not typical of LEP. Additionally, screening for cutaneous LE and SLE could be considered in patients with SPTCL.

Key Words: cutaneous T-cell lymphoma, lupus erythematosus, lupus panniculitis, lupus profundus, subcutaneous panniculitis-like T-cell lymphoma

(*Am J Dermatopathol* 2009;31:520–526)

INTRODUCTION

A recent large European Organization for Research and Treatment of Cancer study of 63 patients with subcutaneous panniculitis-like T-cell lymphoma (SPTCL) indicated that 19% had an associated autoimmune disease, including 4 with systemic lupus erythematosus (SLE).[1] We encountered 5 patients in routine practice or in consultation who exhibited typical features of SPTCL but were unusual, in that they also had manifestations of lupus erythematosus (LE). The features of LE included a spectrum of findings from typical clinical cutaneous lesions, to serologic and extracutaneous end-organ abnormalities typical of SLE, to findings of LE seen on histopathological sections from skin biopsies.

Reports addressing a relationship between SPTCL and LE have focused primarily on delineating histopathological and clinical features that distinguish SPTCL from lupus erythematosus panniculitis (LEP).[2–5] Indeed, it can be very challenging to differentiate between SPTCL and LEP on histopathological grounds.[6,7] Microscopically, LEP is typically characterized by a lymphocytic infiltrate within subcutaneous lobules with little septal involvement, fat necrosis, and the presence of histiocytes containing karyorrhectic debris although these features can also be seen in SPTCL. Microscopic findings that can help to distinguish LEP from SPTCL include features typical of cutaneous LE in the epidermis and dermis, including vacuolar change at the dermal–epidermal interface, perifollicular lymphocytic infiltrates, and interstitial deposition of mucin in the reticular dermis. The presence in the subcutis of lymphoid follicles with reactive germinal centers, clusters of B lymphocytes, and a mixed infiltrate with prominent plasma cells also favors LEP.[4] A recently elucidated clue to LEP is presence of clusters of CD123$^+$ plasmacytoid dendritic cells (pDCs) within the subcutaneous lobules and, if present, within the dermal infiltrates,

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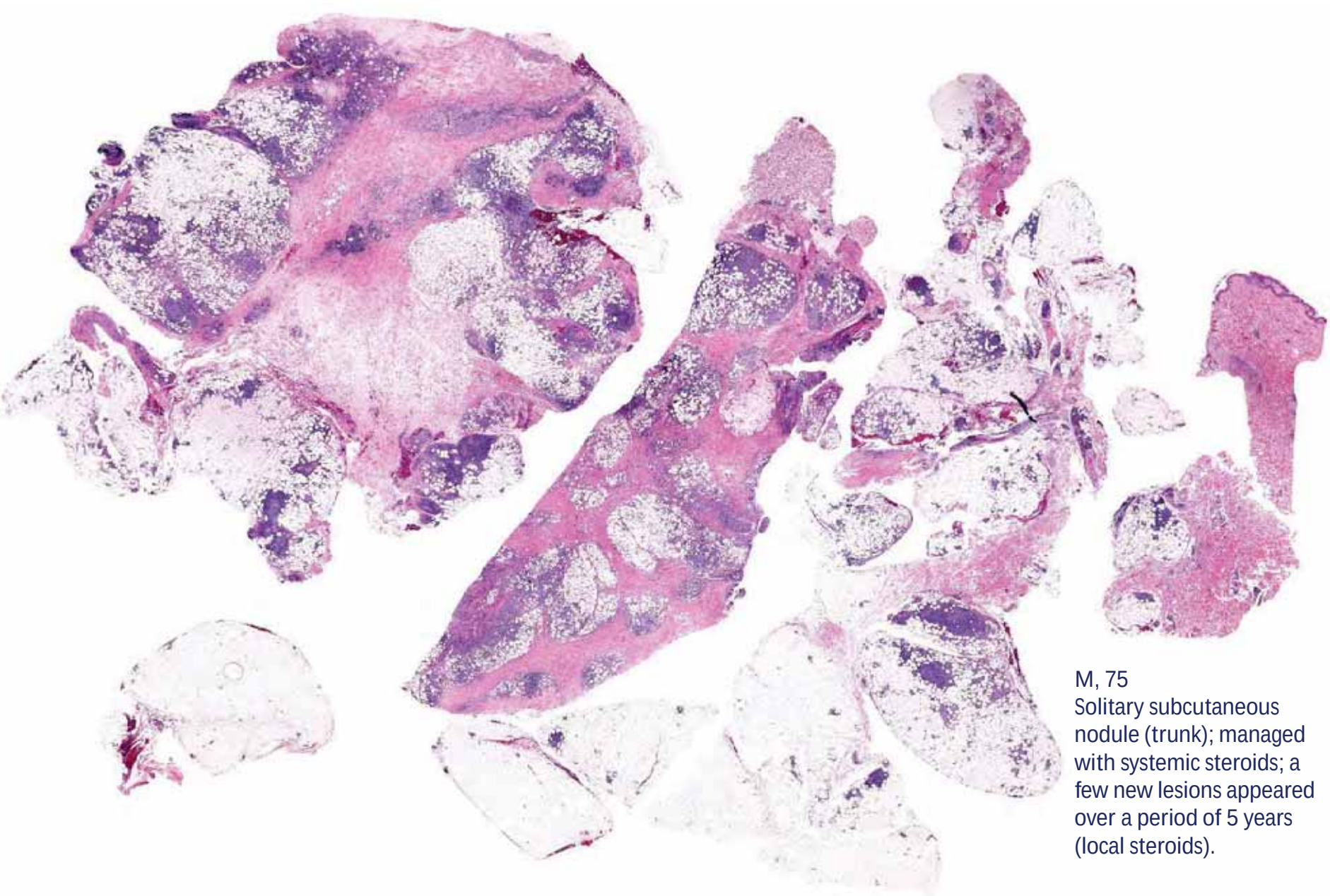
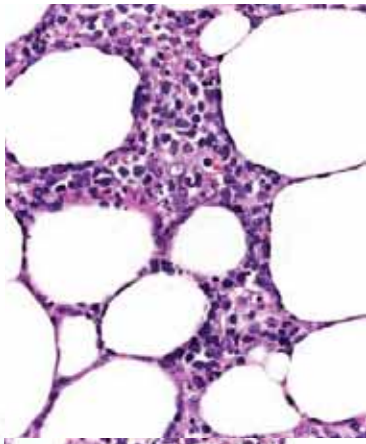
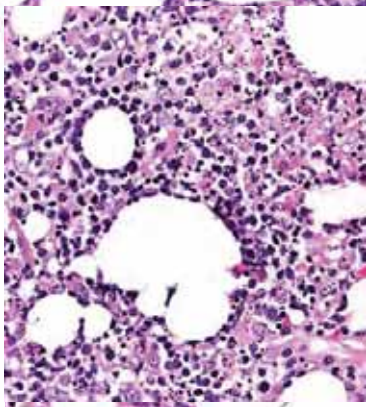
TABLE 1. Patient Data

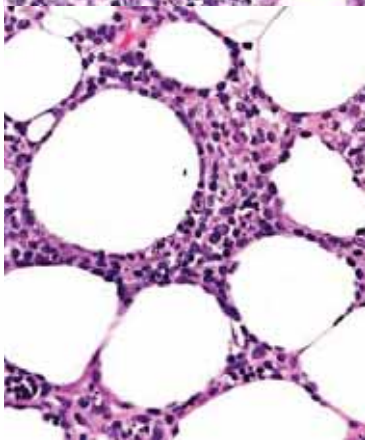
	Patient				
	1	2	3	4	5
Age at diagnosis of SPTCL (yrs)/sex	52/F	22/M	22/F	20/F	20/F
Age at first presentation of clinical lesions (yrs)	37	20	NA	NA	15
Follow-up (mo)	A− (18): clinical remission after treatment with hydroxychloroquine 200 mg/d and methylprednisolone 1 mg/d	A− (19): clinical remission after treatment with hydroxychloroquine 200 mg/d	D+ (41)	NA	A− (30): clinical remission after treatment with vorinostat and currently on low-dose prednisone
Location/morphology of skin lesions	Extremities and face/ "panniculitis" with evolution in lipoatrophy	Bilateral cheeks/facial swelling with evolution in lipoatrophy	Extremities and face/ "panniculitis" with evolution in lipoatrophy	Extremities/ subcutaneous lesions	Abdomen and extremities/ subcutaneous nodules; focal erosions
Clinical features of LE	Skin lesions eventuated in lipoatrophy involving the face	Skin lesions eventuated in lipoatrophy involving the face	Skin lesions eventuated in lipoatrophy involving the face	dsDNA+	Episodic fevers
	ANA+	Episodic fevers	ANA+ 1:2560		Elevated ESR
	dsDNA+ (titer 1:80)	Lymphadenopathy	dsDNA+		Coombs-positive hemolytic anemia
	Interstitial nephropathy with proteinuria	Anemia	Episodic fevers		IgA nephropathy
	Anemia	Neutropenia	Renal failure requiring dialysis		Bilateral parotitis
	Anti-Ro+ (meets ACR criteria for LE)		Coombs-positive hemolytic anemia (meets ACR criteria for LE)		ASMA + (1:40 titer)
Histopathological features of LE seen in skin biopsies	DIF: junctional deposits of IgM and IgG on clinically uninvolved and lesional skin	A few small clusters of CD123 staining pDCs	Interface dermatitis	Interface dermatitis	Interface dermatitis
				Mucin deposition	Mucin deposition
				Substantial CD20$^+$ B-cell population, partially arranged within germinal centers	DIF: junctional deposits of IgG and C3 on lesional skin

A−, alive without signs of SPTCL; Anti-Ro, Anti-Ro antibodies; ASMA, anti–smooth muscle antibodies; D+, dead of hemophagocytic syndrome with SPTCL; ESR, erythrocyte sedimentation rate; F, female; M, male; NA, not available.

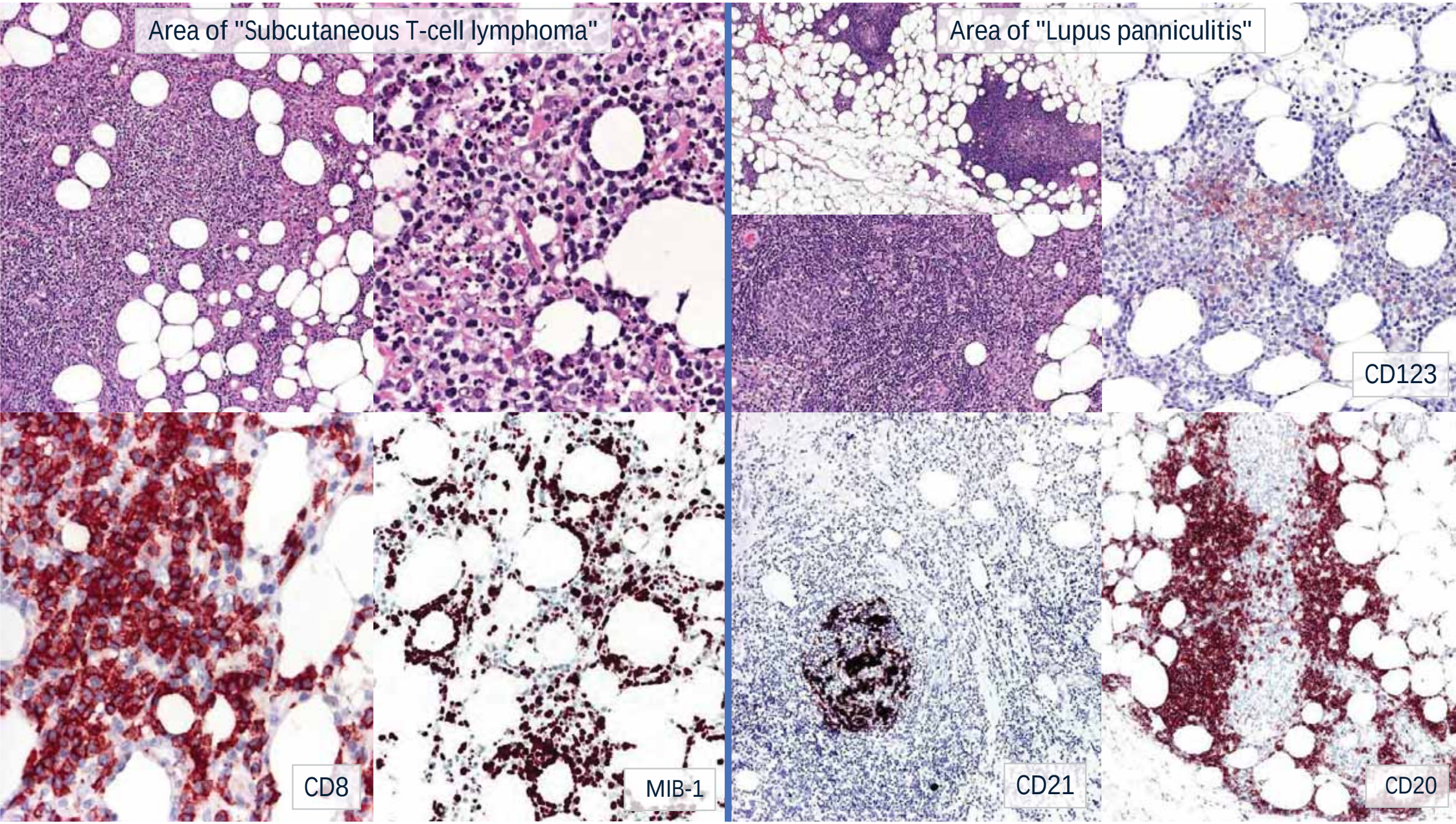








M, 75
Solitary subcutaneous nodule (trunk); managed with systemic steroids; a few new lesions appeared over a period of 5 years (local steroids).


Area of "Subcutaneous T-cell lymphoma"
Area of "Lupus panniculitis"
CD123
CD8
MIB-1
CD21
CD20

Lobular Panniculitic Infiltrates With Overlapping Histopathologic Features of Lupus Panniculitis (Lupus Profundus) and Subcutaneous T-cell Lymphoma

A Conceptual and Practical Dilemma

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Abstract: Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is characterized by panniculitic infiltrates that may be difficult to distinguish from inflammatory disorders, particularly lupus erythematosus profundus (LEP). We report on 11 patients (M:F = 5:6; median age: 49 y; range: 20 to 75 y) presenting with lobular panniculitic infiltrates showing histopathologic features of both SPTCL and LEP in different parts of the same biopsy specimen. The areas showing aspects of SPTCL revealed dense infiltrates of small and medium-sized, atypical α/β T-cytotoxic lymphocytes with focal rimming of the adipocytes and high proliferation. In other areas the infiltrate was composed of nodules of B lymphocytes arranged characteristically at the periphery of the fat lobules and in the septa and showing a low proliferation rate. CD123-positive plasmocytoid dendritic cells arranged in small clusters could be observed in 3 cases. Our observation raises an important question concerning the relationship between SPTCL and LEP. A simple chance overlap of 2 unrelated pathologies seems unlikely, as we could observe these unusual features in 11 cases, much more than mere chance would justify. Three other hypotheses may explain the features observed in our patients: (1) these are examples of SPTCL with focal histologic features mimicking those of LEP; (2) these are examples of LEP with focal atypical histologic features mimicking those of SPTCL; (3) SPTCL and LEP may represent 2 ends of a spectrum, a hypothesis that may be supported by the frequent association of the 2 diseases.

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Conflicts of Interest and Sources of Funding: The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

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Key Words: subcutaneous panniculitis-like T-cell lymphoma, lupus erythematosus, lupus panniculitis, lupus profundus, atypical lymphocytic lobular panniculitis

(*Am J Surg Pathol* 2015;39:206–211)

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is defined in the World Health Organization (WHO)-European Organization for Research and Treatment of Cancer (EORTC) classification of primary cutaneous lymphomas and in the 2008 WHO classification of tumors of hematopoietic and lymphoid tissues as a primary cutaneous lymphoma of T-cell lineage that involves the subcutaneous tissue, expressing an α/β cytotoxic T-cell phenotype.[1,2] Lupus erythematosus profundus (LEP) is characterized by a lobular panniculitis with aspects that may mimic those of SPTCL[3] and represents its most important differential diagnosis. A further problem is represented by the knowledge that in a distinct proportion of cases SPTCL is associated with various autoimmune disorders,[1,4] and that an interface dermatitis has been observed in a minority of SPTCL cases,[5] thus showing that overlapping features between these 2 conditions may exist. However, histopathologic analysis of any given biopsy is aimed at differentiation of the 2 diseases, and overlapping histopathologic features on the same biopsy specimen have not been described. We report on 11 patients with lobular panniculitic infiltrates showing features of both SPTCL and LEP and discuss the implications of this unusual finding.

PATIENTS AND METHODS

Patients

Data from 11 patients with overlapping histopathologic features of SPTCL and LEP in the same biopsy specimen were collected from the files of the Research Unit Dermatopathology, Department of Dermatology, Medical University of Graz, Austria. When available, clinical and follow-up data were obtained from the referring physicians. The study was approved by the Ethic Committee of the Medical University of Graz

11 patients

(M:F=5:6; median age: 49 y; range: 20 to 75 y)

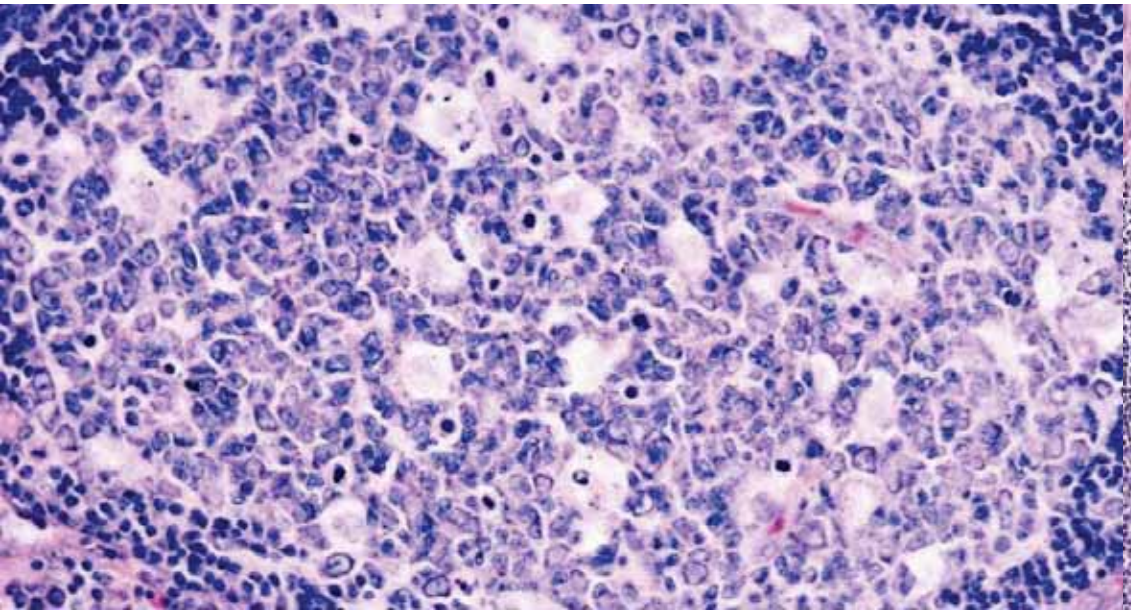
A simple chance overlap of 2 unrelated pathologies seems unlikely, as we could observe these unusual features in 11 cases, much more than mere chance would justify. Three other hypotheses may explain the features observed in our patients: (1) these are examples of SPTCL with focal histologic features mimicking those of LEP; (2) these are examples of LEP with focal atypical histologic features mimicking those of SPTCL; (3) SPTCL and LEP may represent 2 ends of a spectrum, a hypothesis that may be supported by the frequent association of the 2 diseases.

Mimickers of CBCLs (FCL, MZLD)

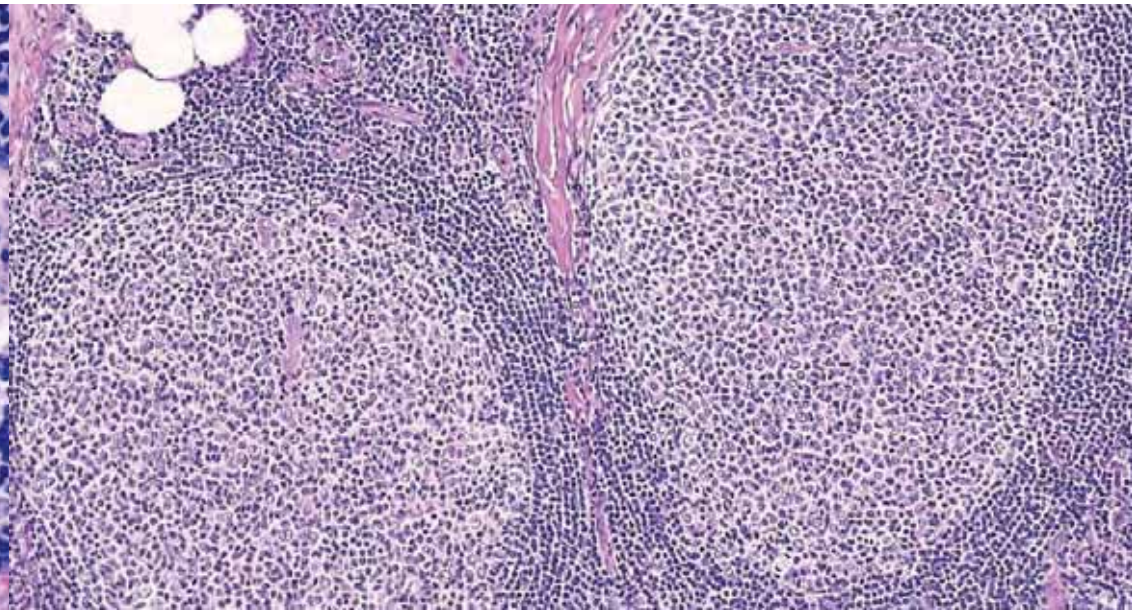
Sometimes to Frequently	Rarely
Borrelia & other lymphocytomas	Syphilis II
Local reaction to vaccination	Leishmaniasis
ACA, plasma cell-rich variant	Drug eruptions, B-cell type
Cutaneous plasmacytosis	Reactions to tattoo
	Localized scleroderma

Differential diagnosis of cutaneous lymphoid infiltrates with follicular pattern

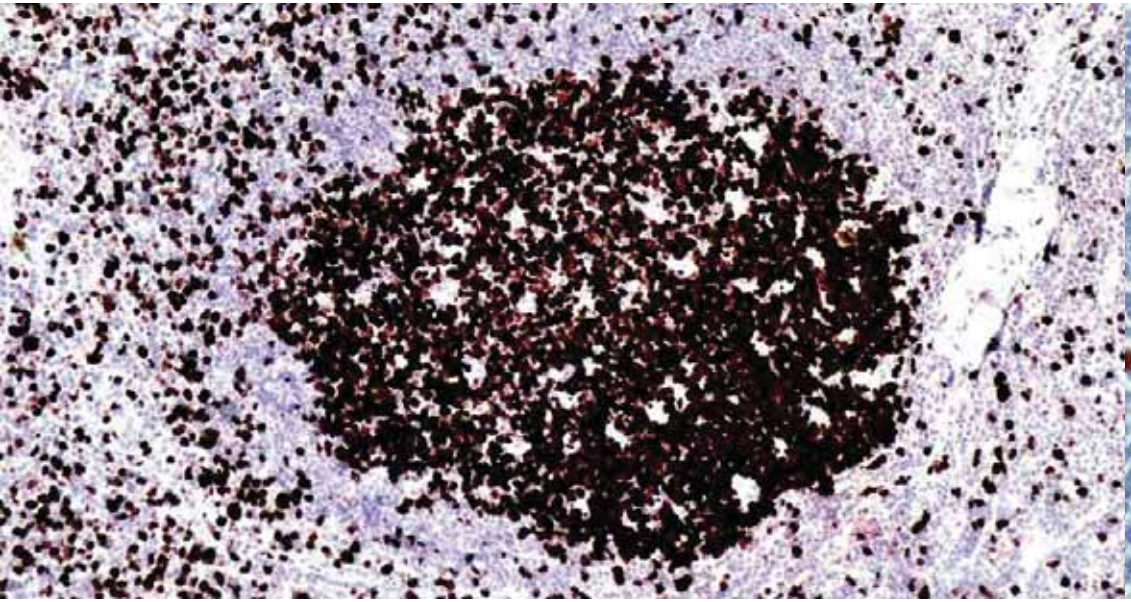
- ***Reactive germinal centers:***
- Large numbers of tingible body macrophages and normal, well-formed mantle zone
- Clusters of Bcl6+ cells confined to the germinal centers
- High proliferation of the germinal centers
- Other clues specific to particular types of lymphocytoma (e.g., focal necrosis and histiocytes with a granular, basophilic cytoplasm in vaccination-induced pseudolymphoma)
- Beware special locations in *Borrelia*-related lymphocytoma (e.g., earlobe, nipple, genital area)

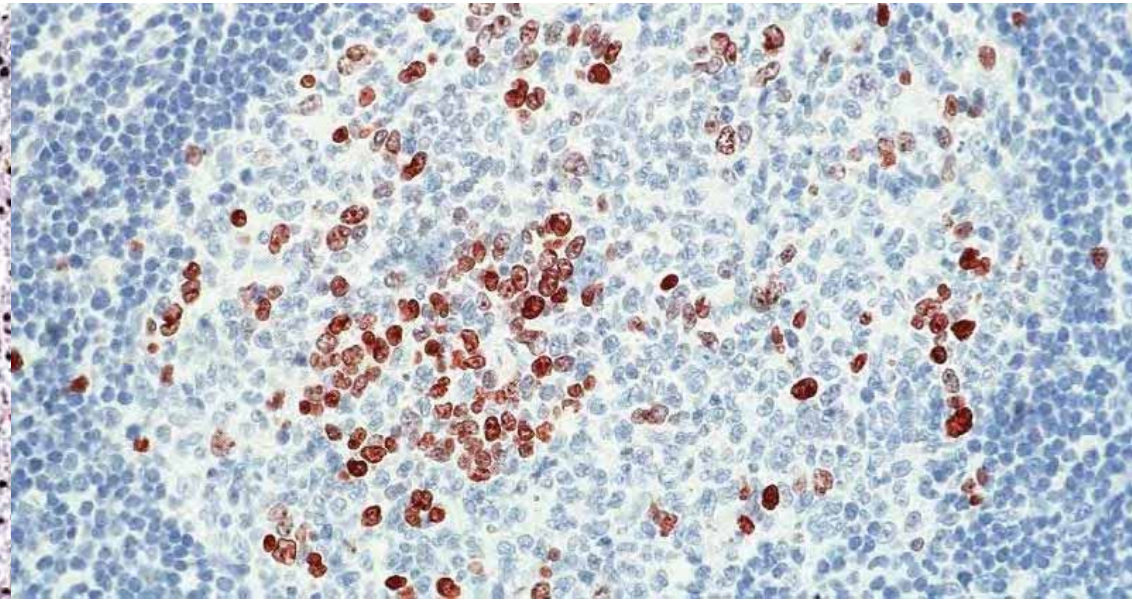


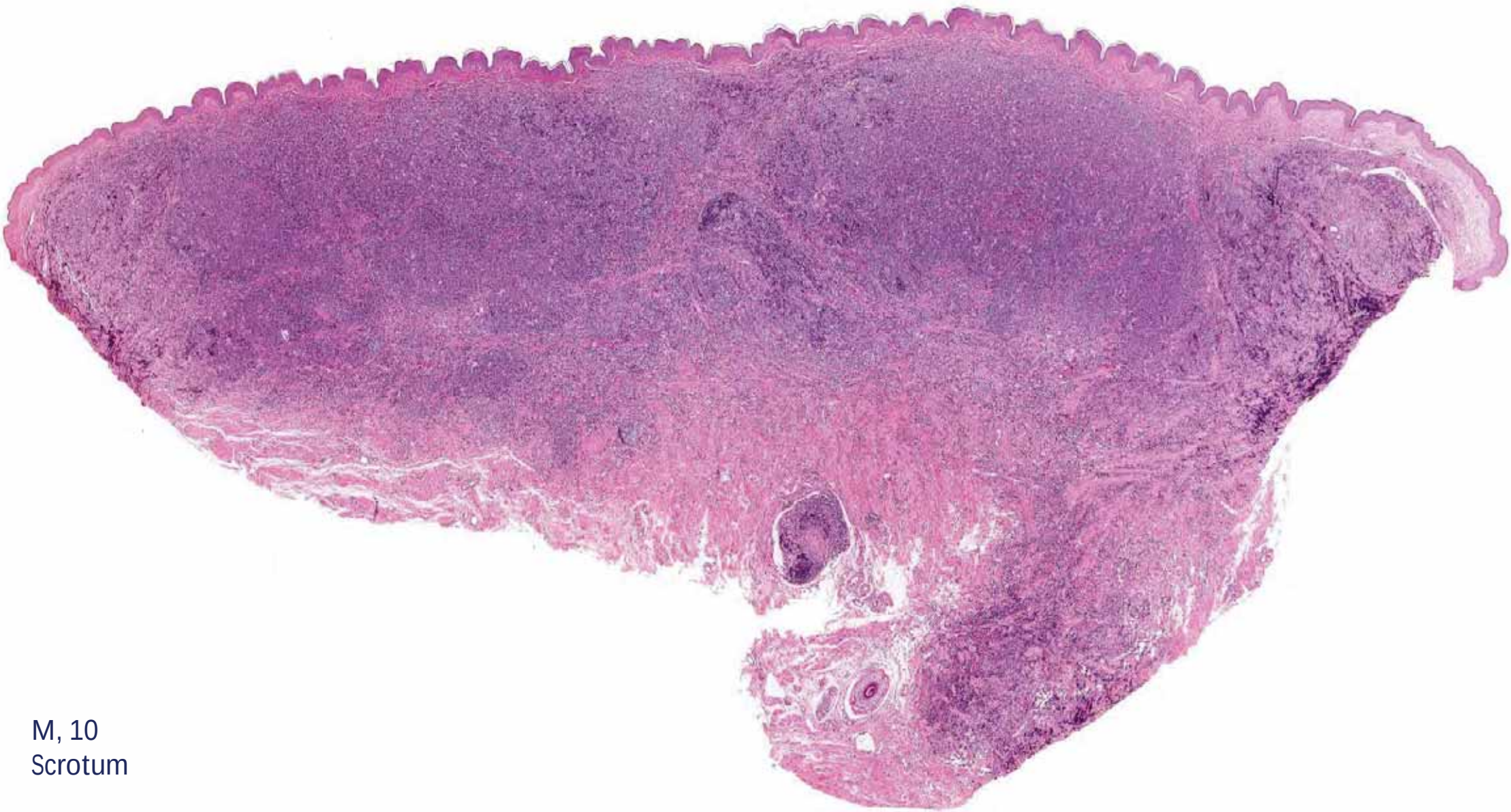
Reactive follicle



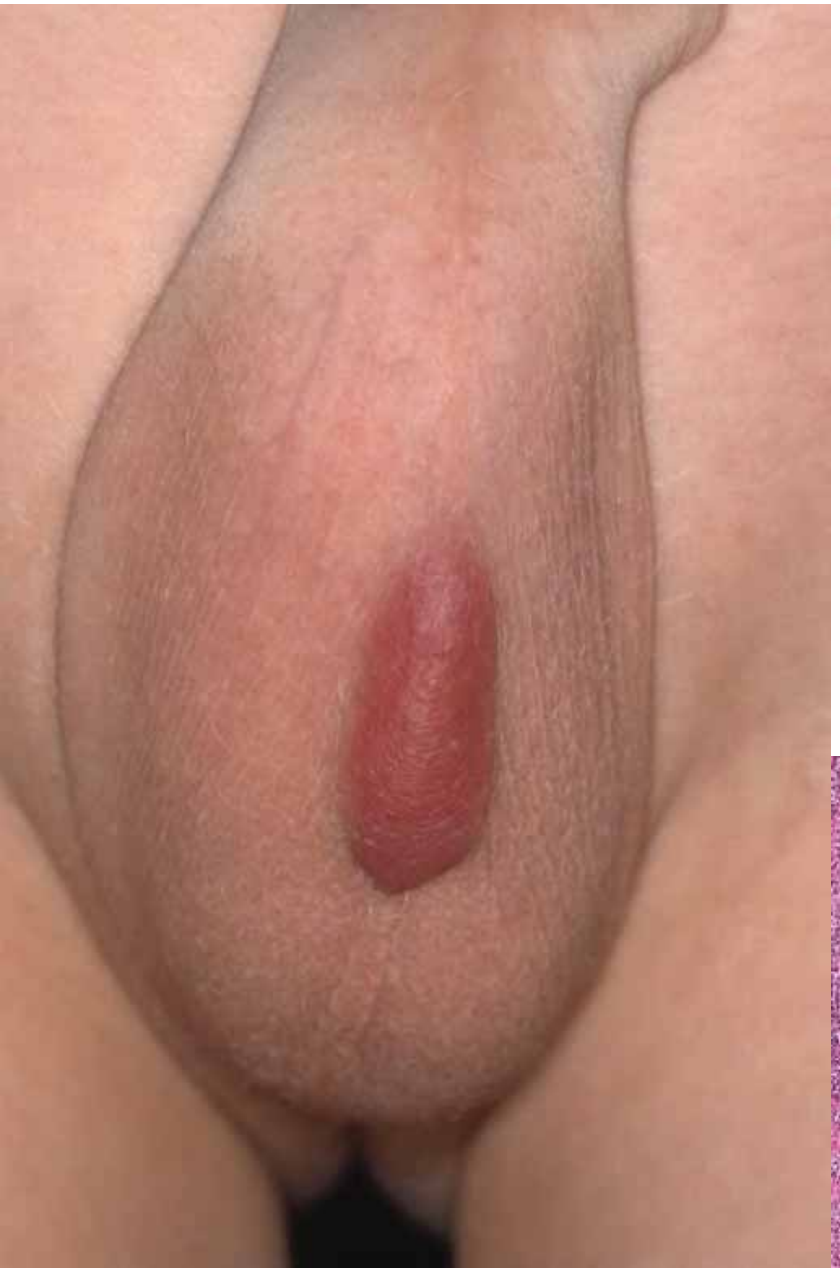
Neoplastic follicle

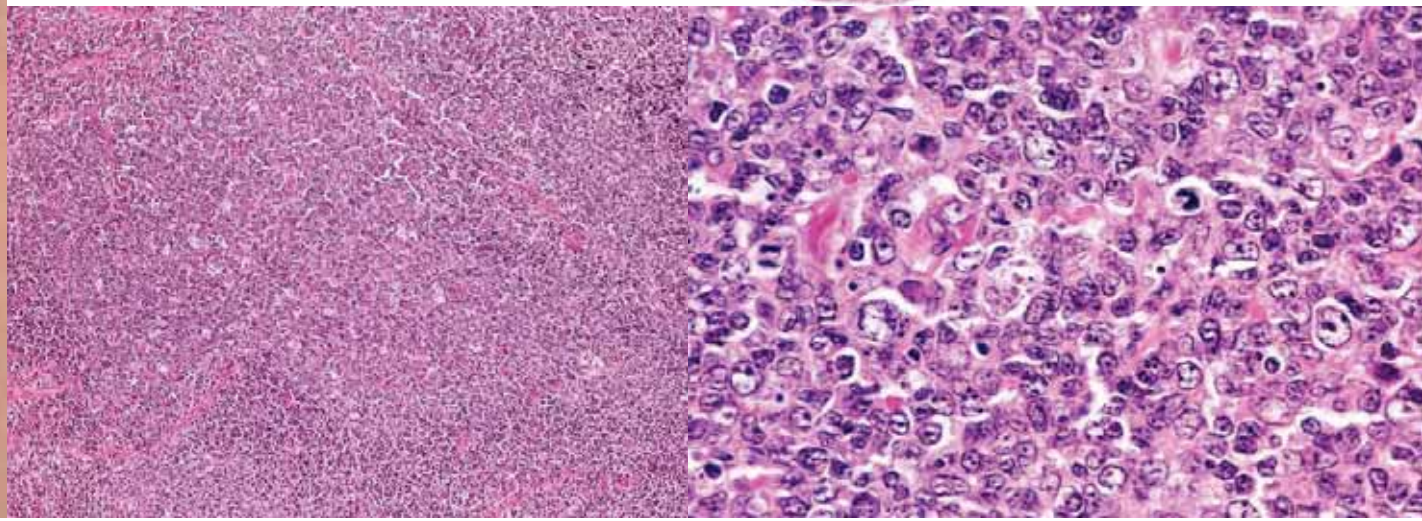


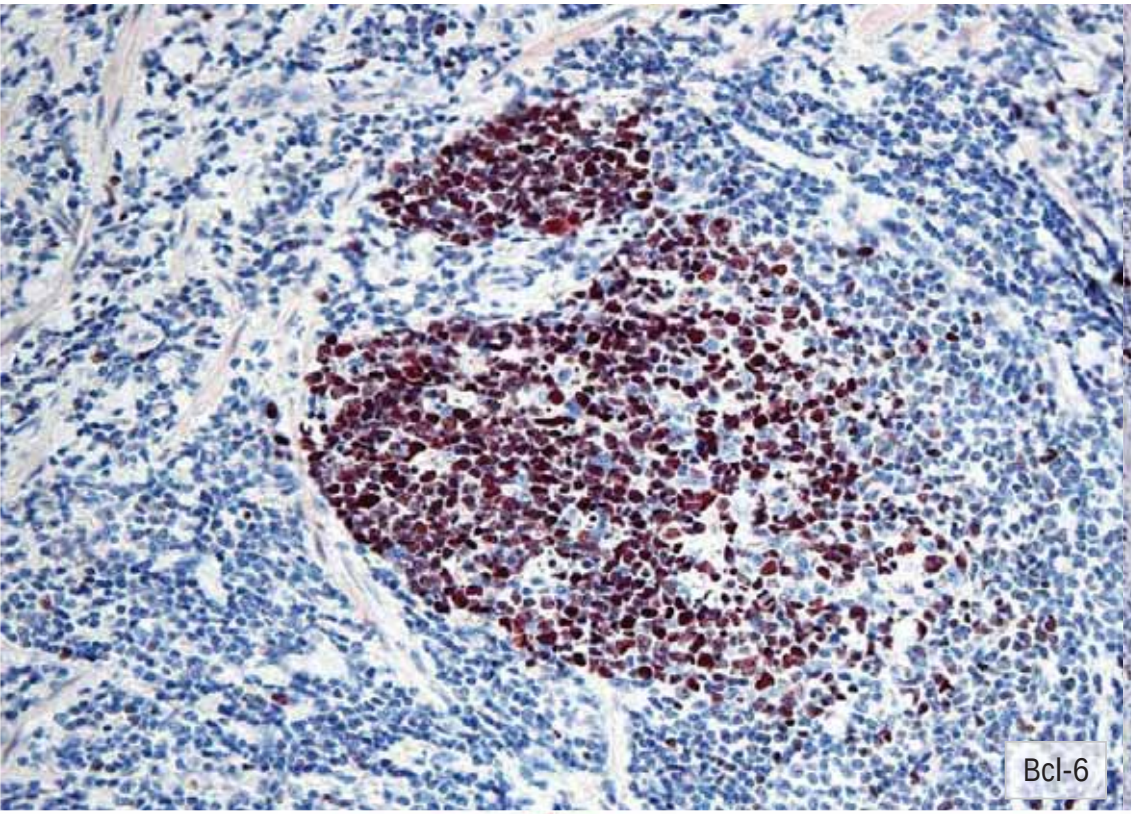


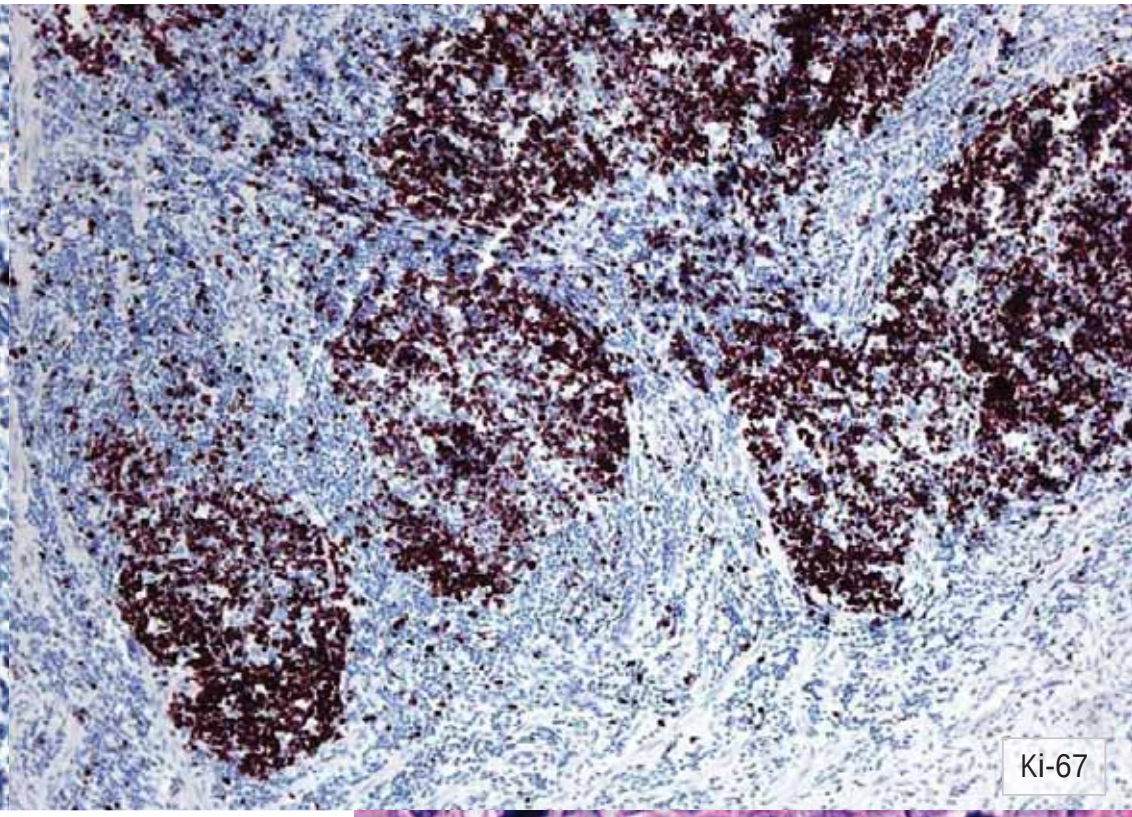


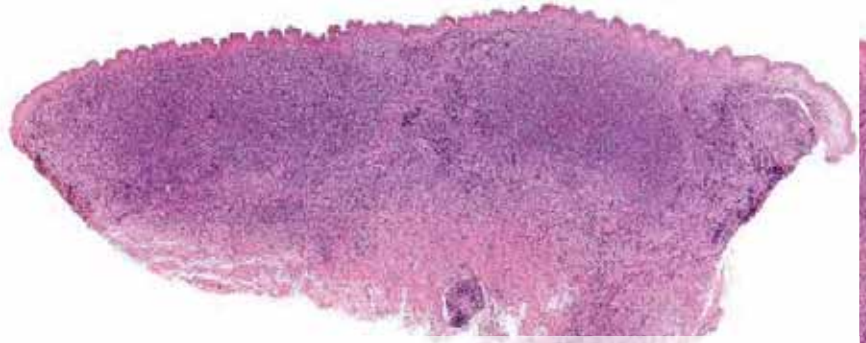
M, 10
Scrotum

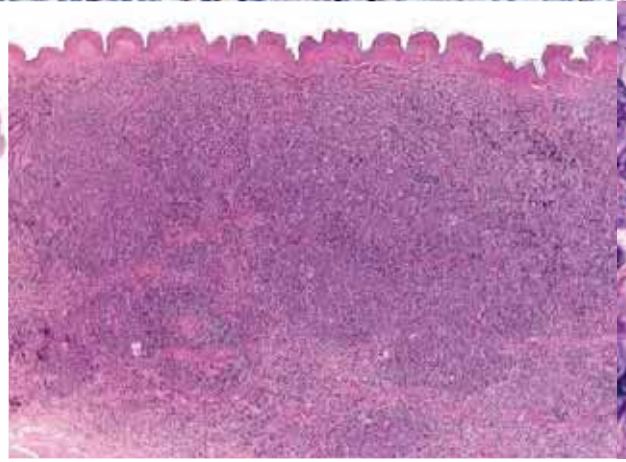


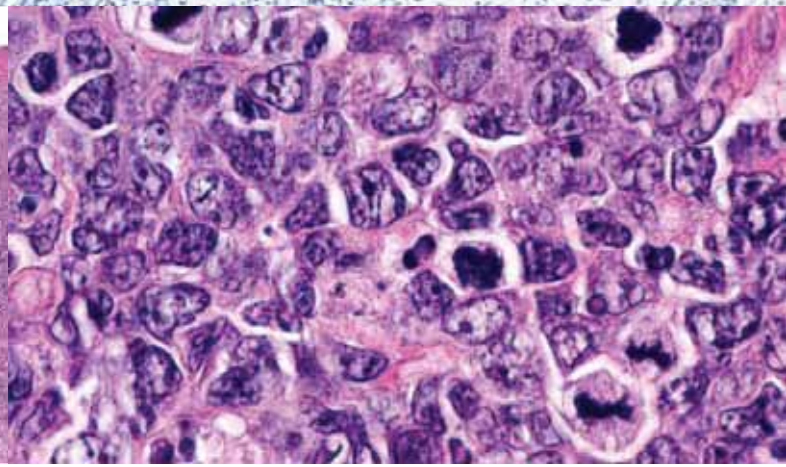












Borrelia lymphocytoma

Borrelia burgdorferi–associated lymphocytoma cutis simulating a primary cutaneous large B-cell lymphoma

Florent Grange, MD, PhD,[a] Janine Wechsler, MD,[b] Jean-Claude Guillaume, MD,[a] Jacques Tortel, MD,[a] Marie-Claire Tortel, MD,[c] Bruno Audhuy, MD,[d] Benoit Jaulhac, MD, PhD,[e] and Lorenzo Cerroni, MD[f] *Colmar, Créteil, and Strasbourg, France; and Graz, Austria*

The distinction between primary cutaneous B-cell lymphoma and B-cell pseudolymphoma on a histologic basis may be difficult, particularly in some cases of *Borrelia burgdorferi*-associated lymphoid proliferations. We report two cases of *B burgdorferi*-associated pseudolymphoma that showed a dense infiltrate with a predominance of large atypical B cells. Because of this misleading histologic feature, a diagnosis of primary cutaneous large B-cell lymphoma was first suspected in both cases. In one case, successive recurrences led to aggressive therapies before the *B burgdorferi* infection was recognized. However, a detailed review of histologic and immunohistochemical features was finally suggestive of a *B burgdorferi*-associated pseudolymphoma in both cases. The etiologic role of *B burgdorferi* was confirmed by serology, polymerase chain reaction analysis of *B burgdorferi* DNA within the lesional skin, and response to antibiotic therapy. Because the distinction between *B burgdorferi*-associated pseudolymphoma and primary cutaneous B-cell lymphomas may be difficult and true *B burgdorferi*-associated B-cell lymphomas have been described, we suggest that antibiotic therapy should be considered as a first-line treatment in suspected or confirmed cases of primary cutaneous B-cell lymphoma in regions with endemic *B burgdorferi* infection. (J Am Acad Dermatol 2002;47:530-4.)

The distinction between primary cutaneous B-cell lymphoma and B-cell pseudolymphoma on a histologic basis may be difficult, particularly in some cases of *Borrelia burgdorferi*-associated lymphoid proliferations. We report two cases of *B burgdorferi*-associated cutaneous pseudolymphomas that were initially diagnosed as primary cutaneous B-cell lymphomas (PCBCLs) because of misleading histologic features.

CASE REPORTS

Case 1

A 26-year-old man presented in December 1995 to his dermatologist with an infiltrated plaque on the scrotum, which had developed progressively for 2 months. He had no history of tick bite. A course of potent local corticosteroid was ineffective, and a skin biopsy was performed. Histologic examination showed in the entire dermis a dense, diffuse infiltrate mainly composed of centroblasts admixed with large centrocytes and small lymphocytes. Most cells expressed the B-cell-associated antigen CD20. Few reactive CD3+ T cells were present. A diagnosis of centroblastic-centrocytic lymphoma (type F in the Working Formulation for Clinical Usage) was made, and the patient was referred for treatment to the Department of Dermatology of Pasteur Hospital in Colmar, France, in March 1996. Clinical examination showed a deeply infiltrated plaque of 45 × 25 mm in diameter on the anterior part of the scrotum (Fig 1). Staging investigations revealed no evidence of extracutaneous manifestations of lymphoma. Histologic examination of a new biopsy specimen showed features similar to those observed in the previous specimen (Figs 2 and 3). Clear-cut germinal centers could not be identified by standard histologic examination or immunophenotyping with CD3 and CD20 antibodies. No immunoglobulin expression could be detected in the infiltrate on paraffin sections. A diagnosis of primary cutaneous follicle center cell lymphoma according to the European Organization for Research and Treatment of Cancer

From the Department of Dermatology,[a] Hôpital Pasteur, Colmar; Department of Pathology,[b] Hôpital Henri-Mondor, Créteil; Department of Pathology,[c] Hôpital Pasteur, Colmar; Department of Hematology,[d] Hôpital Pasteur, Colmar; Institute of Bacteriology,[e] Louis Pasteur University and Hôpitaux universitaires de Strasbourg; and Department of Dermatology,[f] University of Graz, Austria.

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doi:10.1067/mjd.2002.120475

"Because of this misleading histologic feature, a diagnosis of primary cutaneous large B-cell lymphoma was first suspected in both cases. In one case, successive recurrences led to aggressive therapies before the *B burgdorferi* infection was recognized."

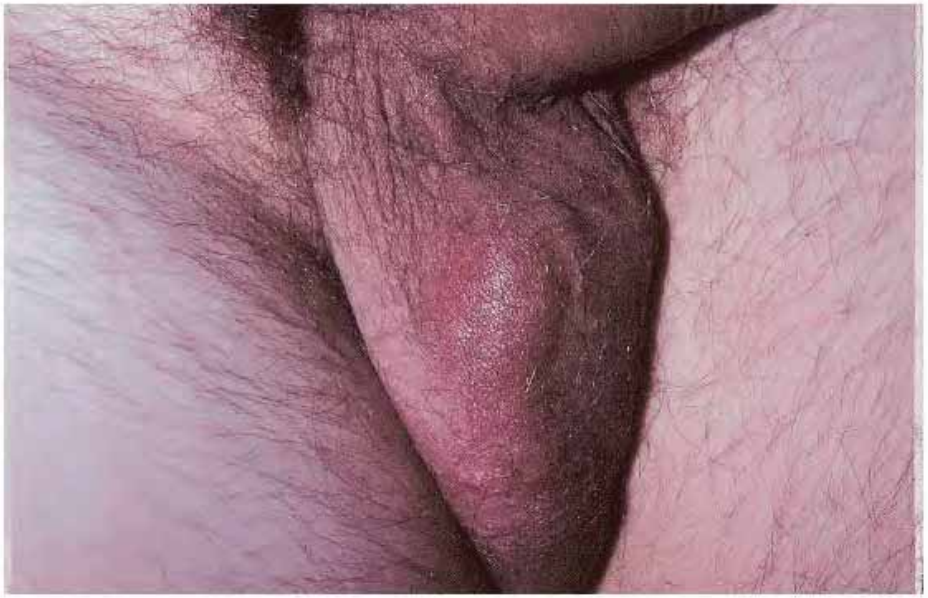


Fig 1. Case 1. Deeply infiltrated plaque on anterior part of scrotum.

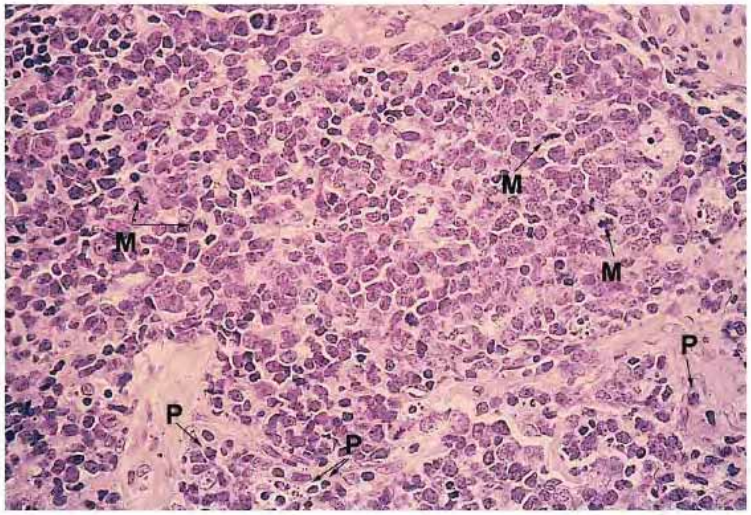
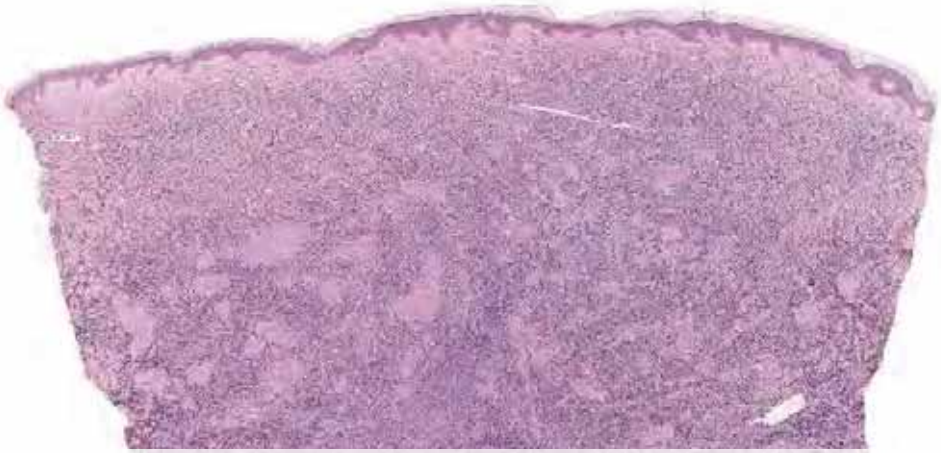
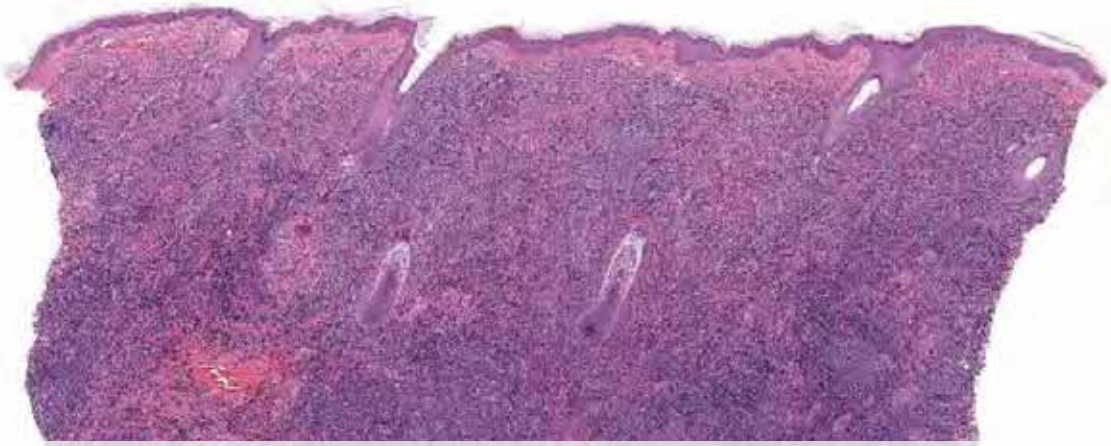


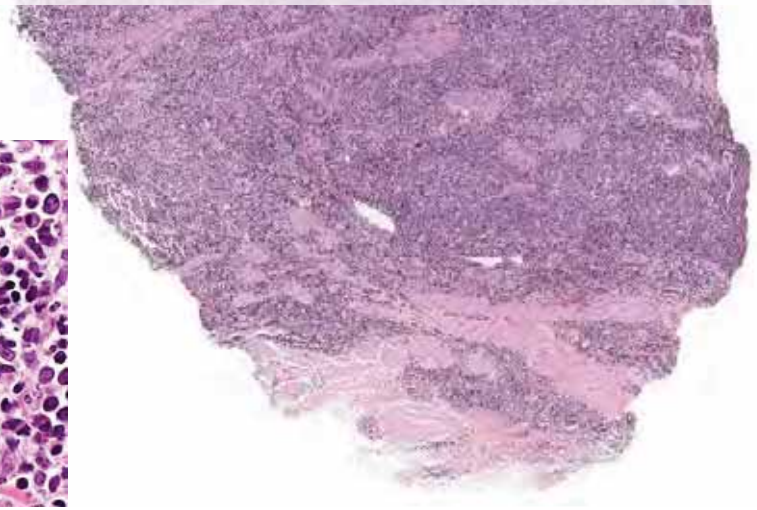
Fig 3. Case 1. Detail of Fig 2. Infiltrate is mainly composed of centroblasts; few immunoblasts and numerous mitoses *(M arrows)* are present. Some lymphocytes exhibit a plasmacytic differentiation *(P arrows)*. (Hematoxylin-eosin stain; original magnification ×200.)

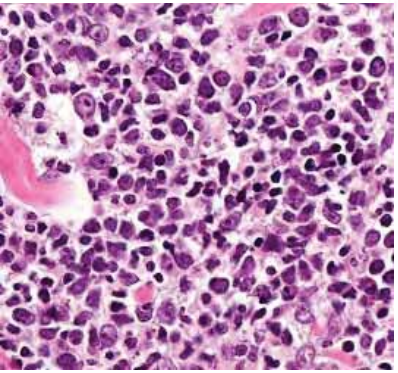
"A **surgical cutaneous excision associated with a testis biopsy** was performed. (...) After a 15-month disease-free interval, the patient presented in July 1997 with an infiltrated plaque of 15x10 mm in diameter on the anterior part of the scrotum. A biopsy specimen confirmed the **recurrence** of the previously diagnosed tumor. **Radiation therapy** was performed in September 1997 with 6 meV for a total dose of 44 Gy in 20 fractions and resulted in a slow and complete resolution of the skin lesion within 2 months. However, a **local recurrence** with similar histologic features occurred 3 months later in the radiation field. The patient received **6 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy**. A complete response was achieved in July 1998. However, a **scrotal nodule again reappeared** in March 1999. (...) **A complete resolution of the skin lesion was achieved after 3 weeks of therapy with amoxicillin, 3 g, administered daily.** No relapse was observed after a follow-up period of 27 months."

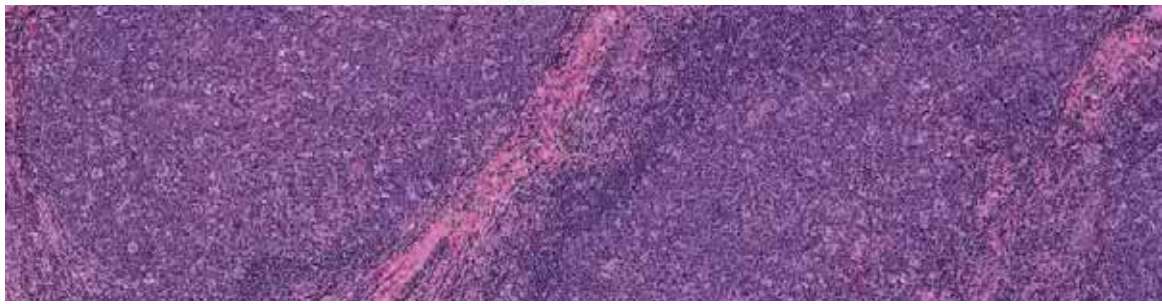




Germinal centers in *Borrelia* lymphocytoma at special sites (nipple, genital area, sometimes also earlobe) are commonly "naked", and may become confluent mimicking a diffuse large B-cell lymphoma







J Cutan Pathol 2004: 31: 232–240
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Journal of
Cutaneous Pathology

Borrelia burgdorferi-associated lymphocytoma cutis: clinicopathologic, immunophenotypic, and molecular study of 106 cases

Lymphocytoma cutis (LC) is considered as the stereotypical example of the cutaneous B-cell pseudolymphomas. It can be induced by various antigenic stimuli including arthropod bites, vaccination, and drugs among others. In endemic regions, *Borrelia burgdorferi* is the principal causative agent for LC. We studied retrospectively 108 biopsies from 106 patients (male : female, 48 : 58; mean age, 44.6; median, 51.5; range, 3–81) with *B. burgdorferi*-associated LC retrieved from the files of the Department of Dermatology of the University of Graz (Austria). Only cases with a *B. burgdorferi* etiology (typical locations, positivity of serologic and/or polymerase chain reaction (PCR) tests, clinical history) were included in the study. Lesions were located on the nipple (63 cases), earlobe (18 cases), genital region (9 cases), and trunk or extremities (16 cases). PCR analysis of *B. burgdorferi* DNA was positive in 54 of 80 cases tested (67.5%). In 47 cases, we could retrieve data on serologic examination for *B. burgdorferi* antibodies performed at the time of diagnosis of LC. Positivity was found in 45 patients (IgG /IgM , 5 cases; IgG /IgM , 37 cases; IgG /IgM$^+$, 3 cases; IgG /IgM , 2 cases). Histology revealed dense lymphoid infiltrates with prominent germinal centers (GCs) in all cases. Atypical morphologic and/or immunophenotypic features of the GCs were commonly observed. In 5 cases, due to confluence of large follicles, the histopathologic pattern simulated that of a large B-cell lymphoma. PCR analysis of the IgH gene rearrangement performed in 33 cases showed a polyclonal pattern in 31 cases and a monoclonal band in 2. In summary, *B. burgdorferi*-associated LC can present with misleading histopathologic, immunophenotypic, and molecular features, and integration of all data is necessary for a correct diagnosis.

Colli C, Leinweber B, Müllegger R, Chott A, Kerl H, Cerroni L. *Borrelia burgdorferi*-associated lymphocytoma cutis: clinicopathologic, immunophenotypic, and molecular study of 106 cases
J Cutan Pathol 2004; 31: 232–240. © Blackwell Munksgaard 2004.

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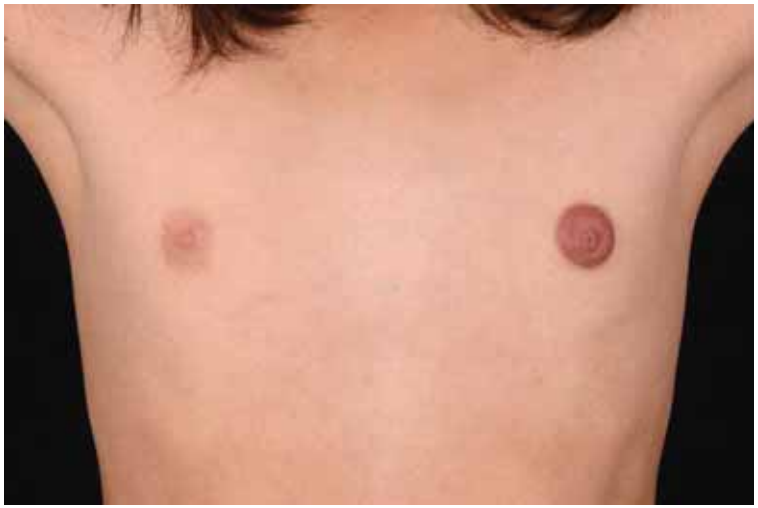
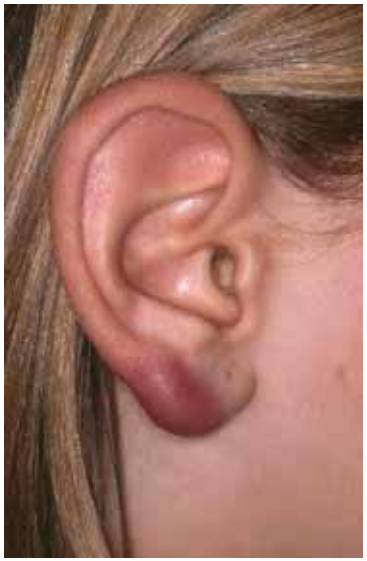
Lymphocytoma cutis (LC) is one of the most common types of cutaneous B-cell pseudolymphoma.[1,2] It can be induced by various antigenic stimuli, including arthropod bites,[3] vaccination,[4] and drugs[5] among others. In endemic regions, *Borrelia burgdorferi* infection is the most common causative factor.[6,7] These lesions are also designated '*Borrelial* lymphocytoma', and represent the least common manifestation within the

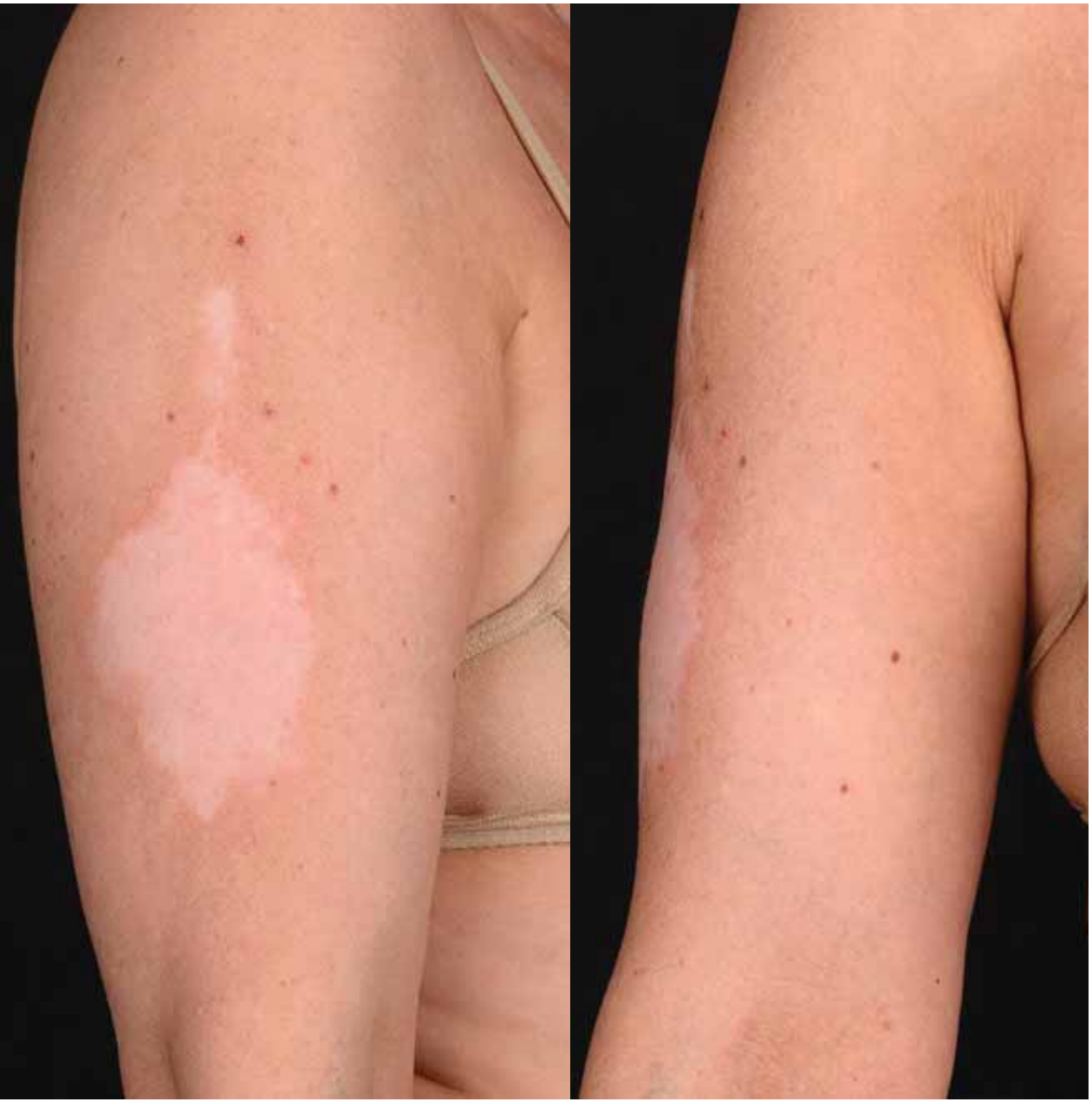


Nipple	59,4%
Earlobe	16,7%
Genital	8,5%
Other	10,0%



Exception to the rules

- Reactive germinal centers in *Borrelia*-induced lymphocytoma may lack a well-formed mantle and show confluence, mimicking the histopathological features of a diffuse large B-cell lymphoma
- High proliferation is usually a feature of malignant tumors, yet in lymphoid infiltrates with follicular pattern *reduced* proliferation of the lymphoid follicles is a clue for malignancy, whereas high (nearly 100%) proliferation is typical of reactive germinal centers



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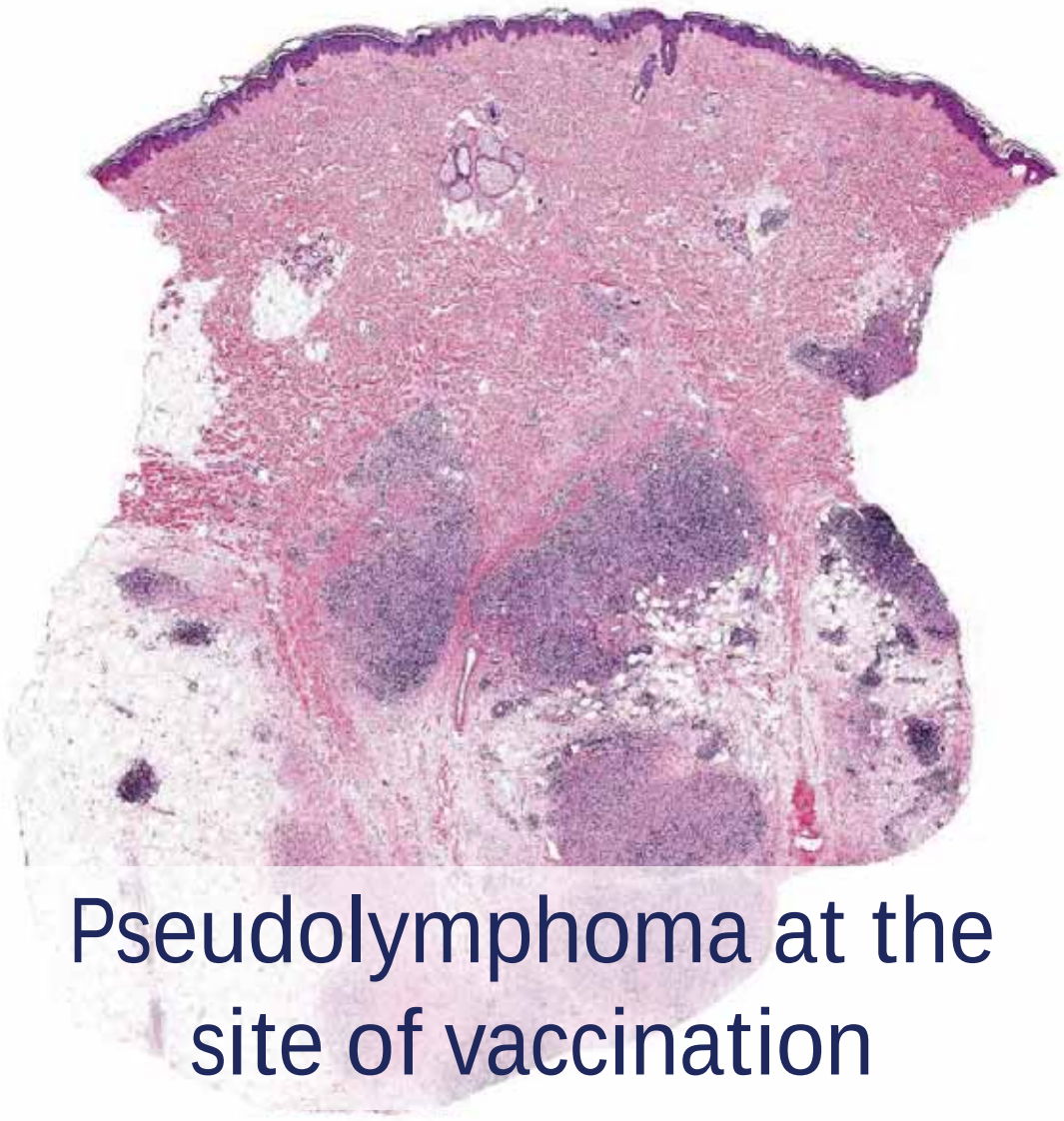
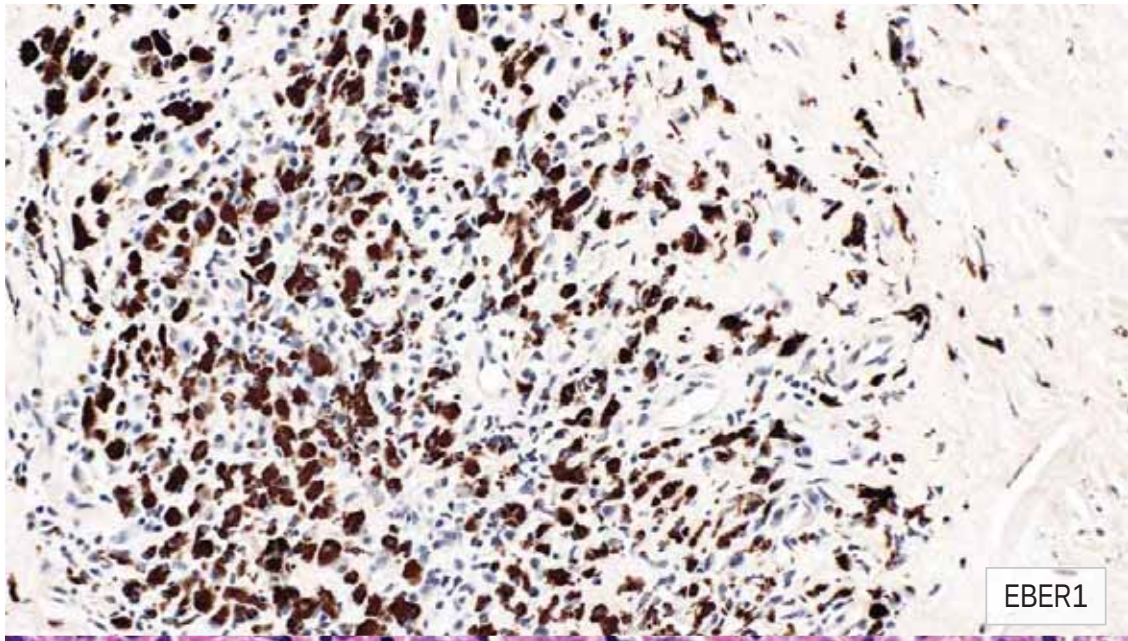
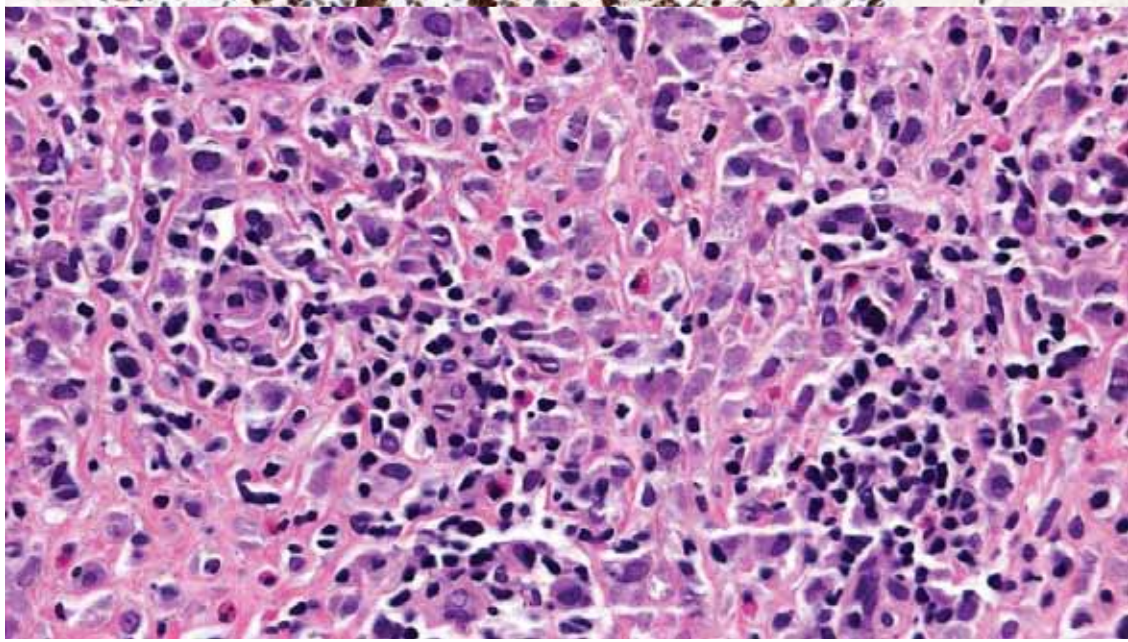
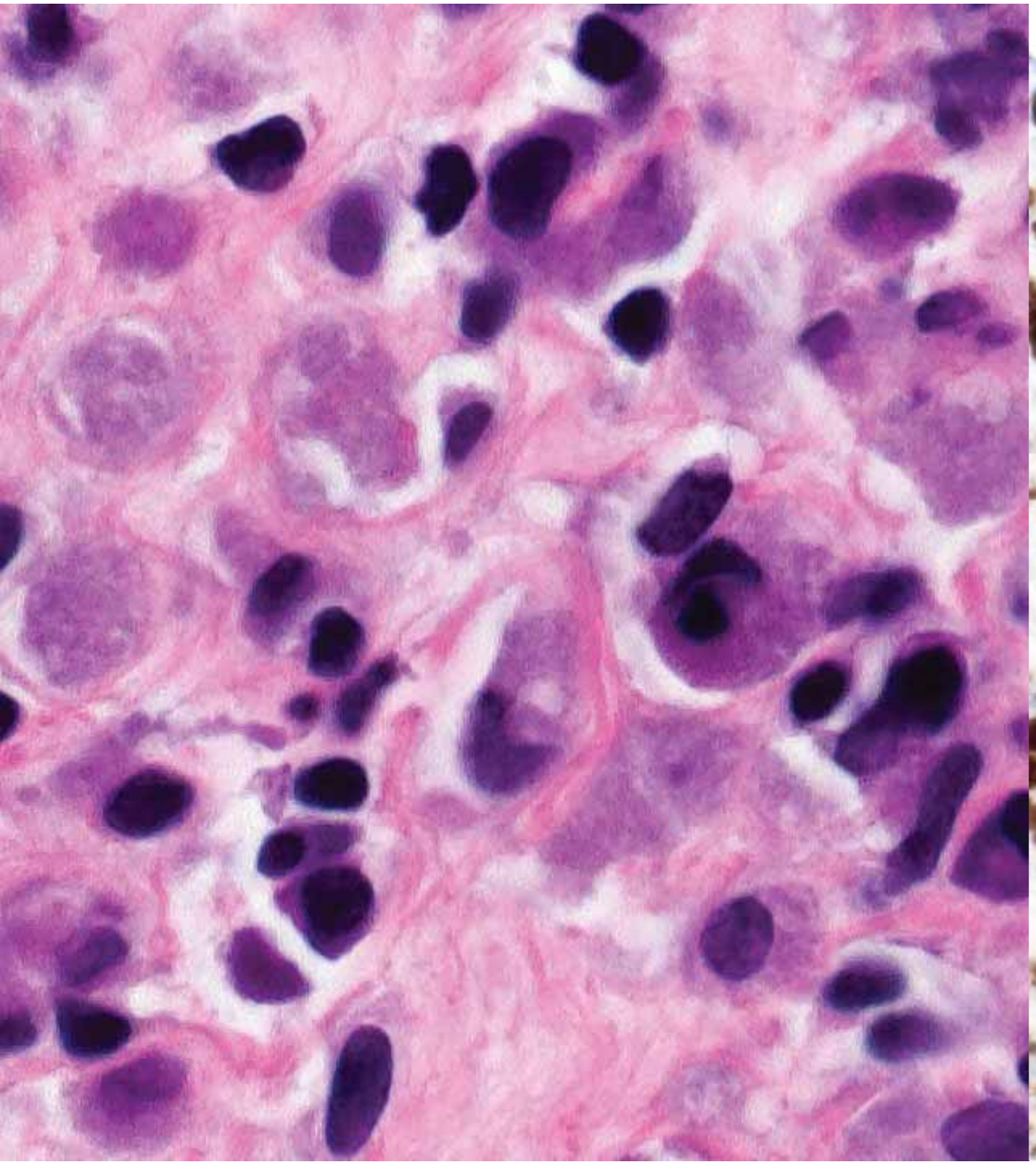
Subcutaneous nodule at the site of a hyposensitivity treatment.

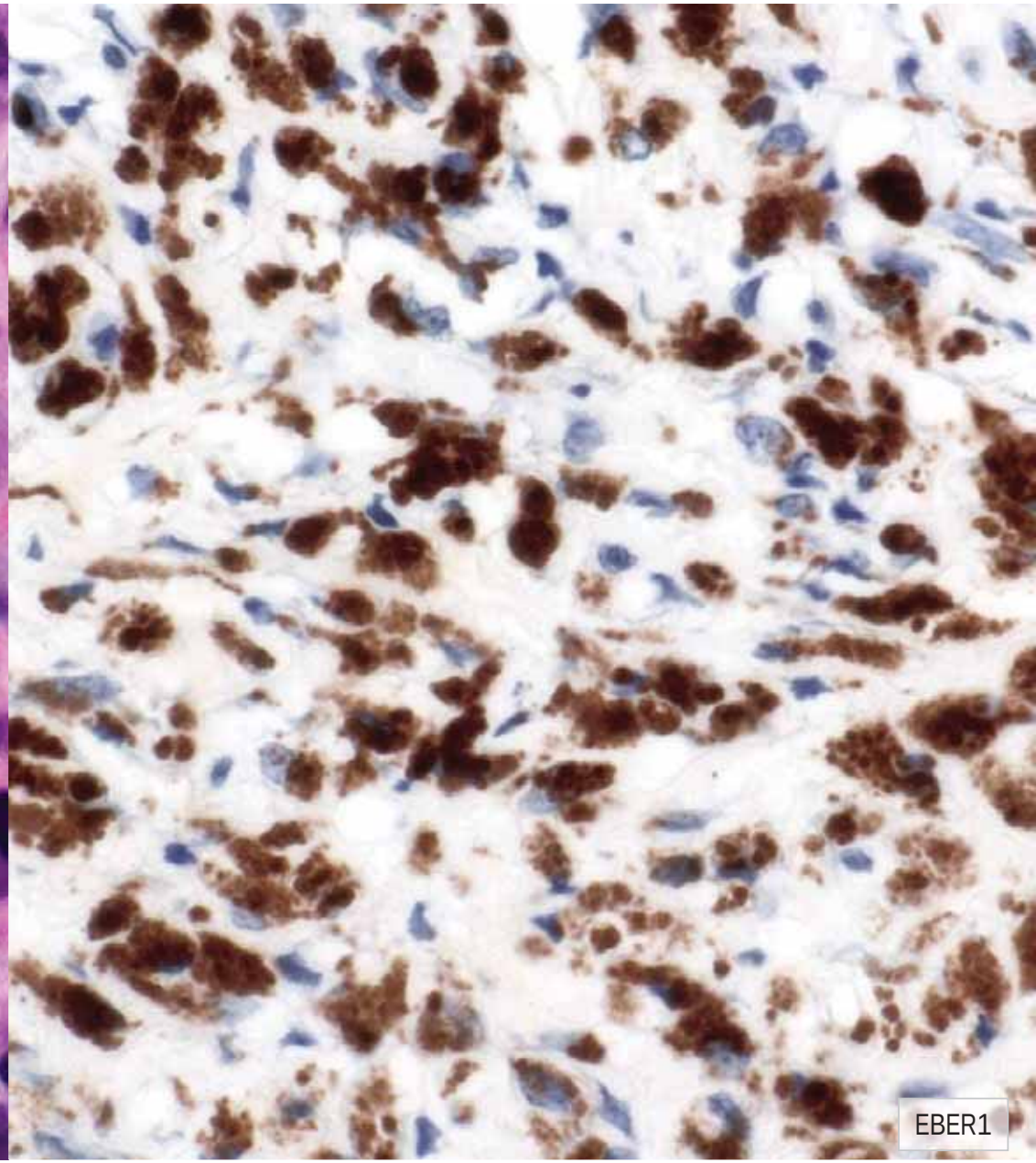


Pseudolymphoma at the site of vaccination








EBER1

Cutaneous B-cell Pseudolymphoma at the Site of Vaccination

Lorenzo Cerroni, MD, Riccardo G. Borroni, MD,*† Cesare Massone, MD,* Andreas Chott, MD,‡ and Helmut Kerl, MD**

Abstract: Pseudolymphomas are a rare complication of vaccination, presenting with dense lymphoid infiltrates and prominent follicular pattern. We report our observations on 4 patients with vaccination-induced B-cell pseudolymphoma (all females; age range 19 to 60 years; median: 34.5 years). Clinically 3 patients presented with subcutaneous nodules and 1 presented with a large, indurated, erythematous plaque. Histology revealed in all cases dense lymphoid infiltrates in the subcutaneous fat with prominent follicular pattern. The follicles displayed features of reactive germinal centers (normal mantle zone, presence of tingible body macrophages, normal proliferation). Necrotic areas surrounded by palisaded histiocytes were seen in 3 biopsies from 2 patients. A mixed-cell infiltrate with eosinophils and plasma cells was present in all cases. In addition, histiocytes with granular basophilic cytoplasm could be observed around the focal area of necrosis or within the inflammatory infiltrate. Follow-up was available for 3 patients. One patient was alive with persistent disease 6 months after the first observation. Two patients were treated with local radiotherapy and are alive and free of disease after 12 and 72 months, respectively. One of these two patients had a second pseudolymphoma on the contralateral arm after a new injection of vaccine. Cutaneous pseudolymphoma after vaccination should be distinguished histopathologically from low-grade cutaneous B-cell lymphomas (follicle center cell lymphoma, marginal zone lymphoma) and from other B-cell pseudolymphomas with prominent follicular pattern requiring different treatment (eg, *Borrelia burgdorferi*-induced lymphocytoma cutis).

Key Words: B-cell pseudolymphoma, vaccination, follicular pseudolymphoma, lymphocytoma, lymphadenosis benigna cutis

(*Am J Dermatopathol* 2007;29:538–542)

Adverse cutaneous effects of vaccinations include widespread and localized reactions. Mild erythema, edema, pain, and induration limited to the site of injection are commonly observed immediately after immunization and usually heal spontaneously. Less frequently, papules or subcutaneous nodules arise at the site of vaccination and may persist for months or years.[1,2] Histopathologically, they are characterized by either granulomas or lymphoid infiltrates with prominent germinal centers.[3–5] Typically, pseudolymphomas at the site of injection have been reported following administration of vaccines or allergens adsorbed to aluminum.[1,6,8,9]

We describe the clinical, histopathologic, immunophenotypic, and molecular biologic findings of 4 patients who developed cutaneous B-cell pseudolymphoma at the site of vaccination.

PATIENTS AND METHODS

Patients

Four patients with a diagnosis of pseudolymphoma occurring at the site of vaccination were included in the study. The diagnosis of pseudolymphoma was based on clinicopathologic features. Association with previous vaccination was documented in all patients.

Histology, Immunohistology, and Molecular Biology

All biopsy specimens were fixed in 4% buffered formalin, routinely processed, and subsequently embedded in paraffin. For routine histopathologic analysis, sections were stained with hematoxylin and eosin. All histopathologic sections were reviewed by at least two of us (L.C., R.G.B.). The following features were analyzed: location of the infiltrate, presence or absence of necrosis, sarcoidal or tuberculoid granulomas, germinal centers, degenerative fat changes, eosinophils, plasma cells, and histiocytes with granular basophilic cytoplasm. Standard immunohistology and molecular biology techniques [polymerase chain reaction (PCR) analysis of immunoglobulin (Ig) H gene rearrangement] were used as described previously.[10,11]

RESULTS

Clinical Features

The clinical features of our patients are summarized in Table 1. All patients included were women. Age ranged from 19 to 60 years (median: 34.5 years). The vaccine administered was for early summer meningoencephalitis (ESME) in 2 of 4 patients, tetanus in 1 patient, and hepatitis B virus in 1 patient. The site of injection, thus the site of occurrence of skin lesions, was the upper arm in all patients. Patient 2 presented with a pseudolymphoma after ESME vaccination on the left upper arm. She subsequently received a second injection of the

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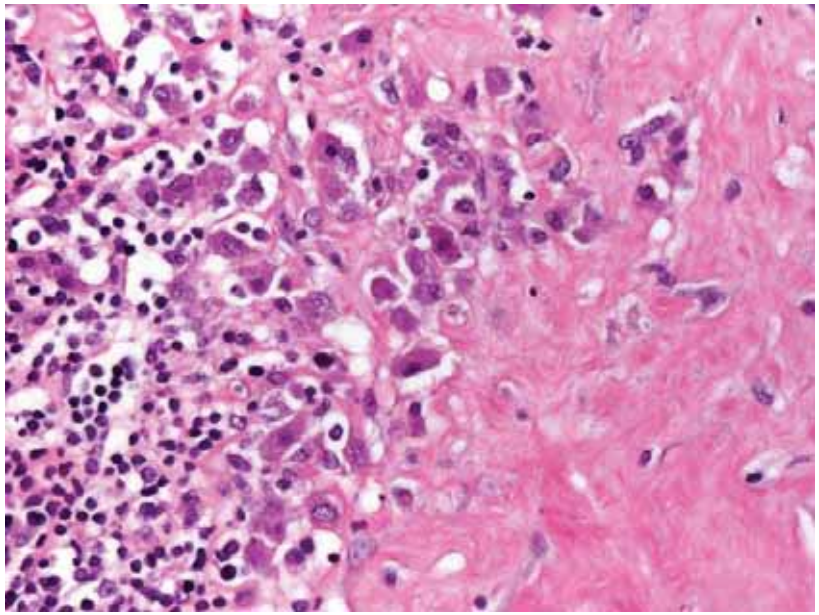
TABLE 2. Histopathologic Features of Pseudolymphomas at Site of Vaccination

Patient	Necrosis	Sarcoidal or Tuberculoid Granulomas	Germinal Centers	Eosinophils	Plasma Cells	Histiocytes With Granular Basophilic Cytoplasm	Degenerative Fat Changes	Polymerase Chain Reaction
1	—	—	+	+	+	+	+	P
2	—	—	+	+	+	+	+	P
2*	+	—	+	+	+	+	+	ND
2†	+	—	+/−	+	+	+	+	P
3	—	—	+	+	+	+/−	—	P
3*	+	—	+	+	+	+	+	ND
4	—	—	+	+	+	+	+	P

ND, not done; P, polyclonal smear.
*Persistent lesion at the same location.
†New lesion on the contralateral arm after a second injection of vaccine.

"Histiocytes with a granular, basophilic cytoplasm were observed in clusters and scattered throughout the infiltrates in all cases."



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ORIGINAL ARTICLE

WILEY

EBER in situ hybridization in subcutaneous aluminum granulomas/lymphoid hyperplasia: A diagnostic clue to differentiate injection-associated lymphoid hyperplasia from other forms of pseudolymphomas and cutaneous lymphomas

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Abstract

Background: Subcutaneous vaccination or desensitization may induce persistent nodules at the injection sites. Without the knowledge of prior injection, histopathological work up may be challenging.

Objective: Aim of this study was to contribute to the histopathological work up of unclear subcutaneous nodules, especially their differentiation from cutaneous lymphoma.

Methods: We retrospectively reviewed clinical data and histopathological slides of four patients with subcutaneous nodules, which were suspected to suffer from cutaneous T- or B-cell lymphoma. Sections of these cases and 12 negative controls were stained with hematoxylin and eosin and a standardized immunohistochemical panel of B- and T-cell markers including EBER in situ hybridization as well as electron microscopy.

Results: In all cases, large histiocytes with granular cytoplasm compatible with intracellular aluminum hydroxide were present. EBER in situ hybridization revealed positive staining of these granular histiocytes while staining was absent in negative controls.

Limitations: Post hoc completion of medical history revealed that vaccination or specific immunotherapy had been applied before at the biopsy site in only three out of four patients; one patient was lost to follow-up.

Conclusion: EBER in situ hybridization is an adjunctive tool to differentiate aluminum induced granuloma/lymphoid hyperplasia from other forms of pseudolymphoma and cutaneous B- or T-cell lymphomas.

KEYWORDS
aluminum granuloma, EBER in situ hybridization, lymphoid hyperplasia, pseudolymphoma, RNA probe

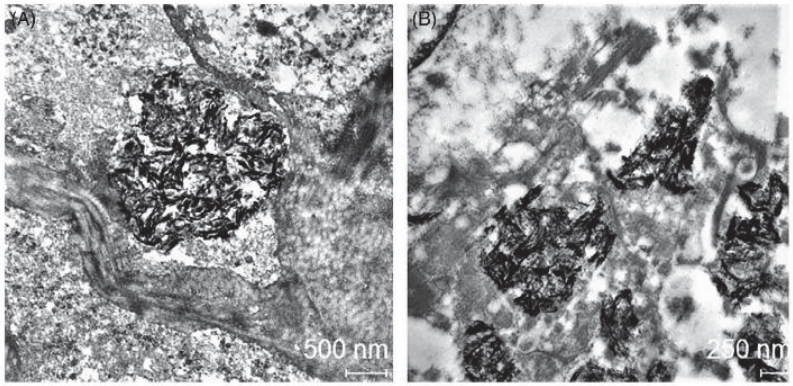
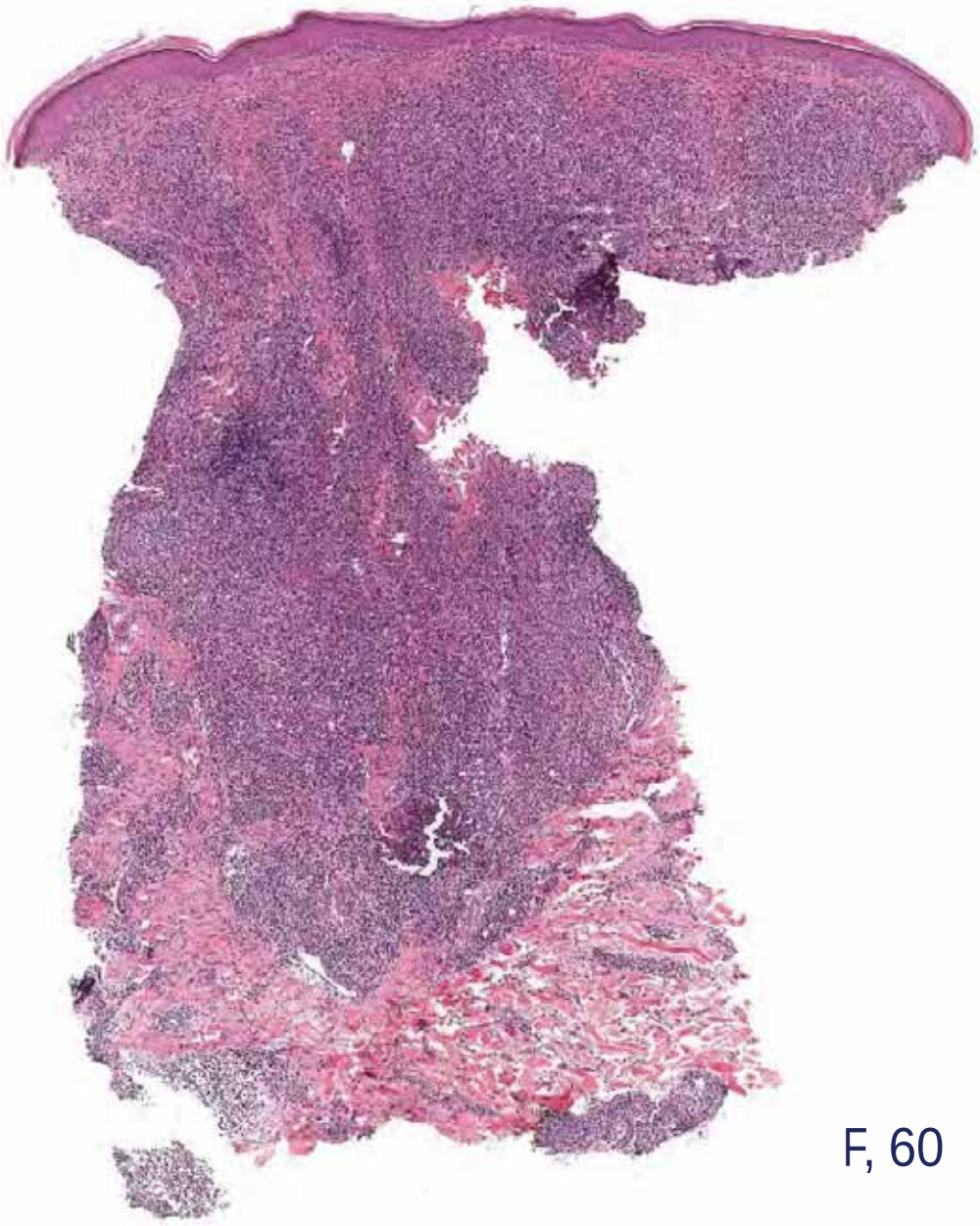


FIGURE 2 Aluminum granuloma. Electron microscopy exemplified by case 1. (A, B) In the cytoplasm of the histiocytes there are interwoven, filamentary or crystalline structures that correspond to the EBER positive signals



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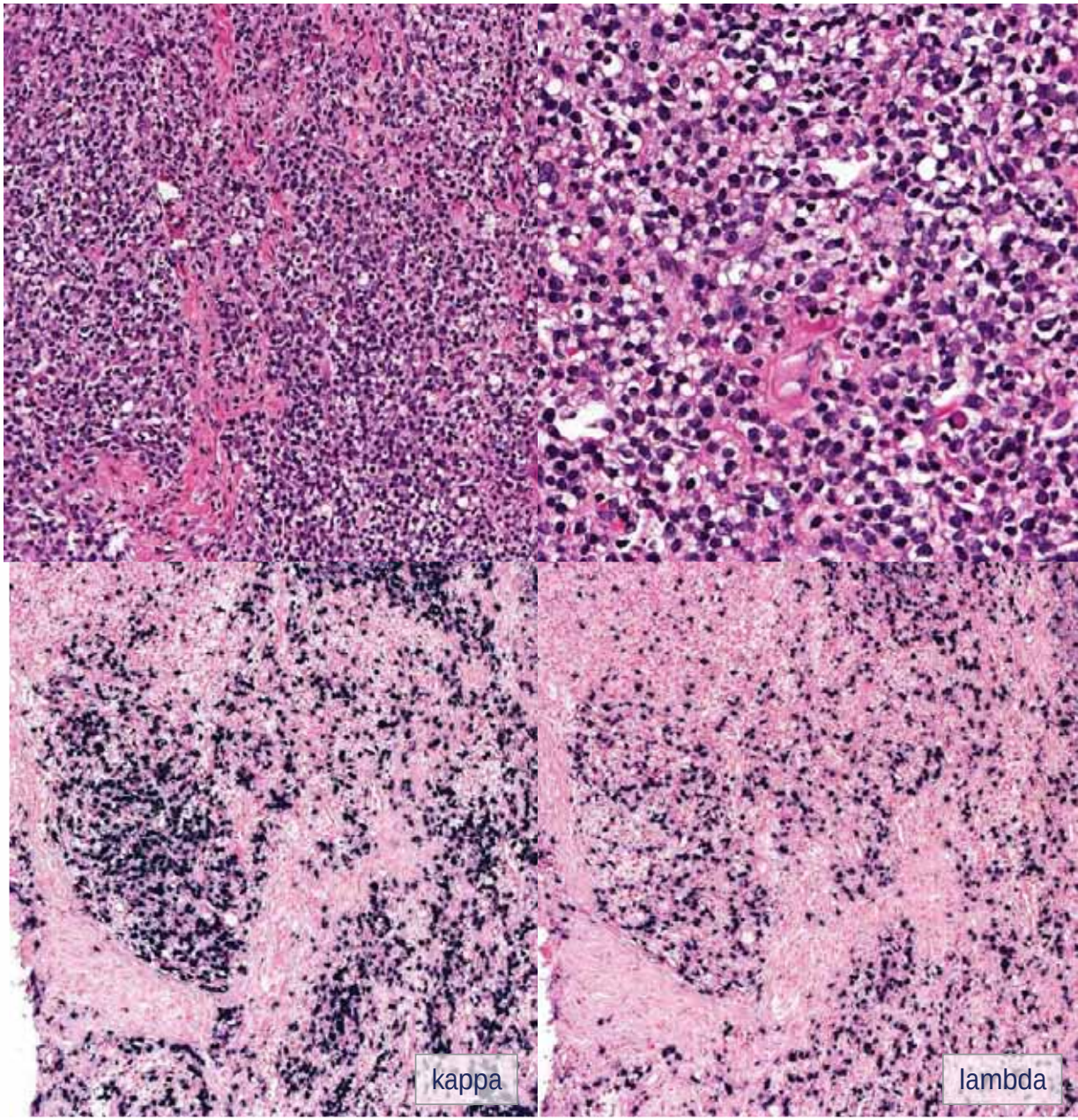
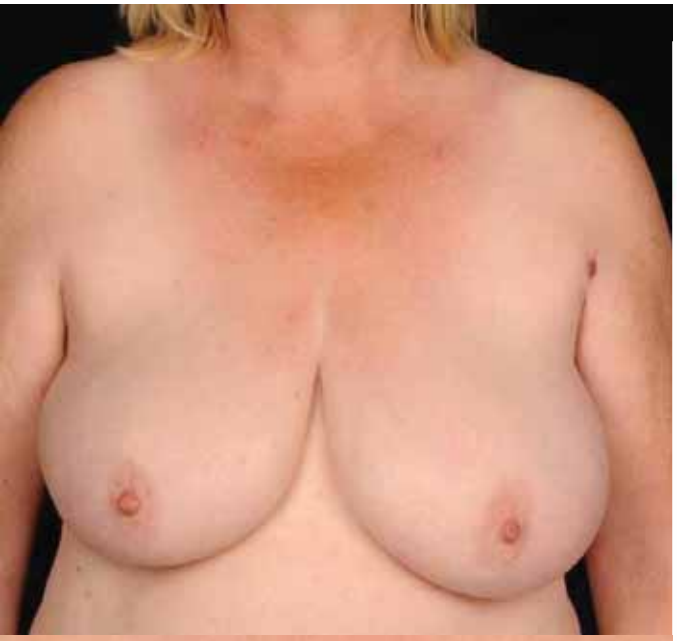
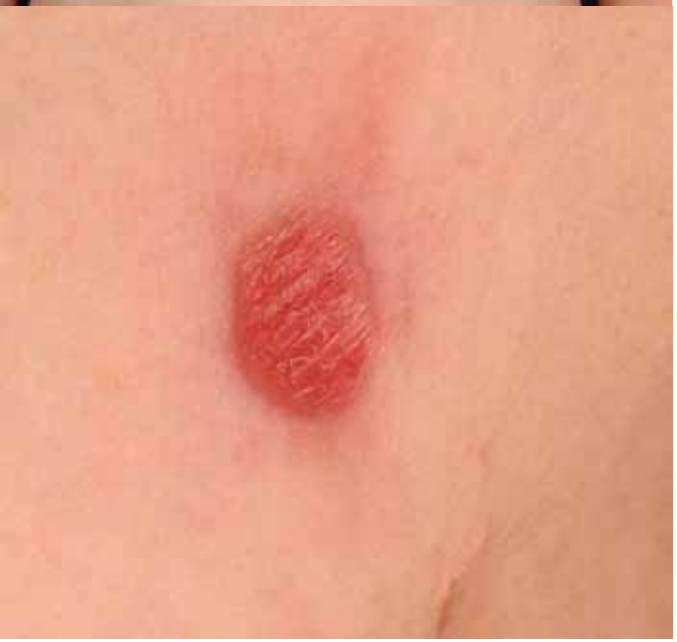
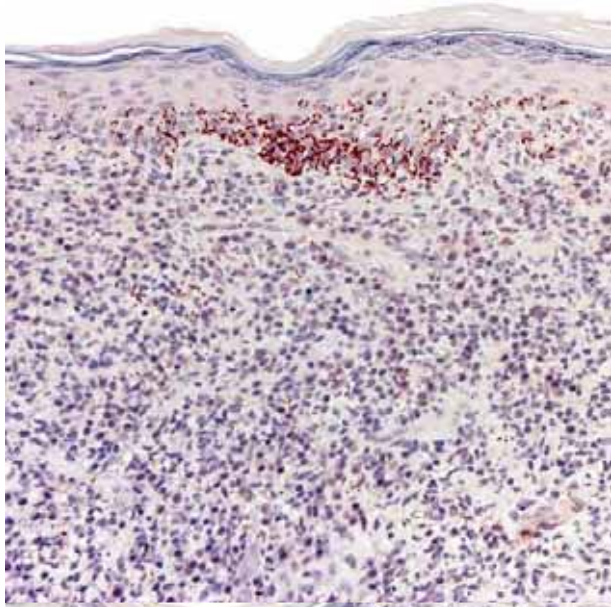
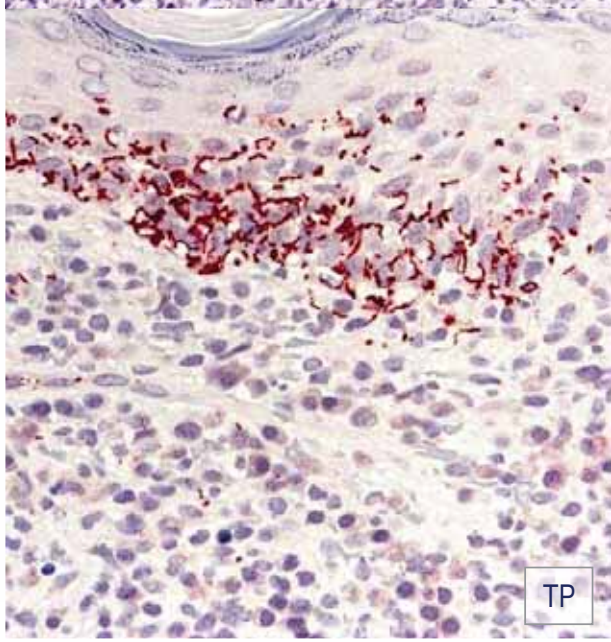


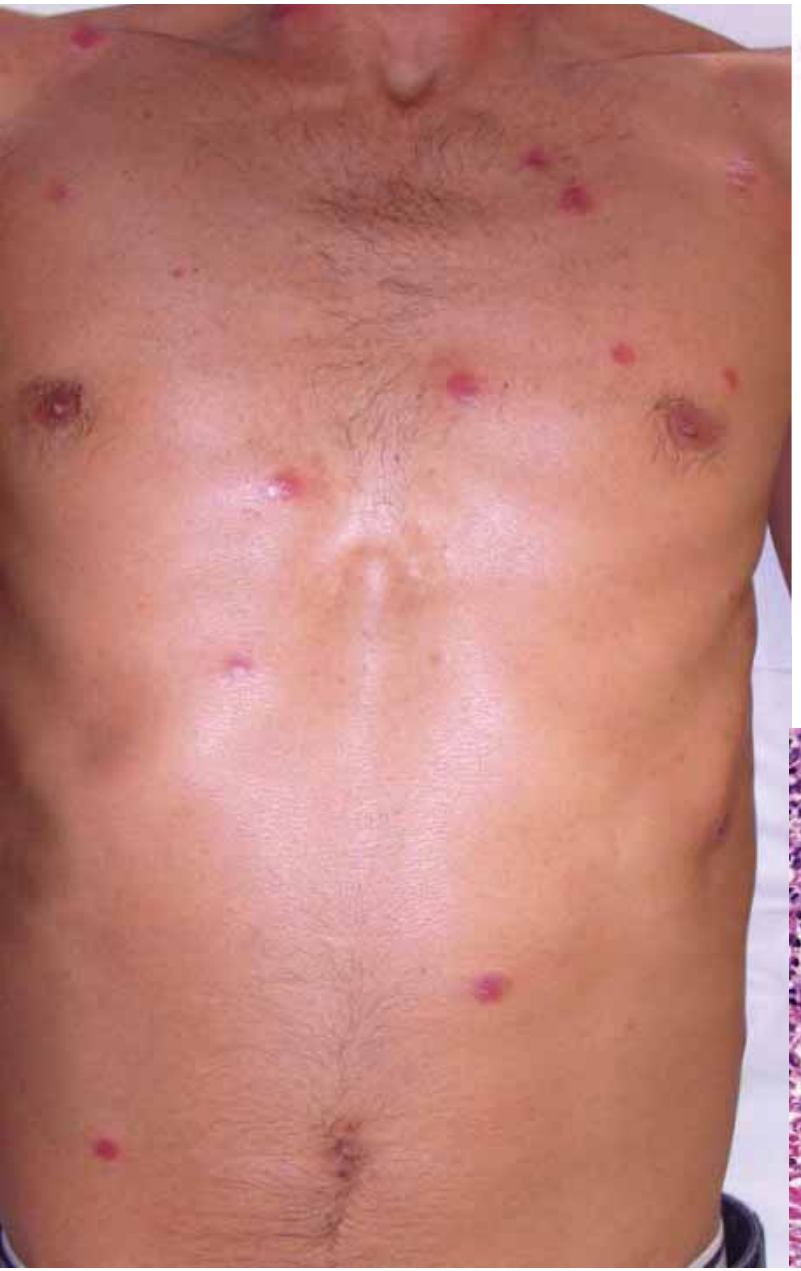


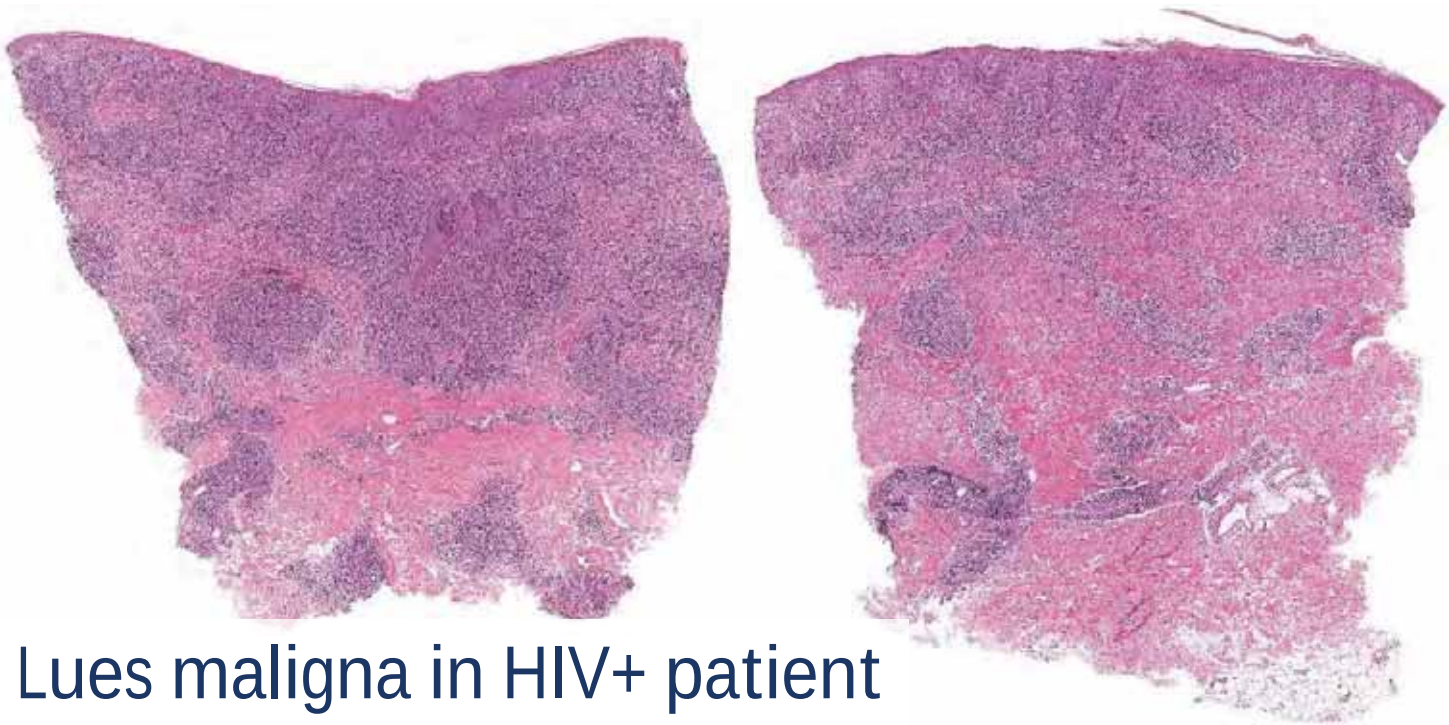


Secondary syphilis

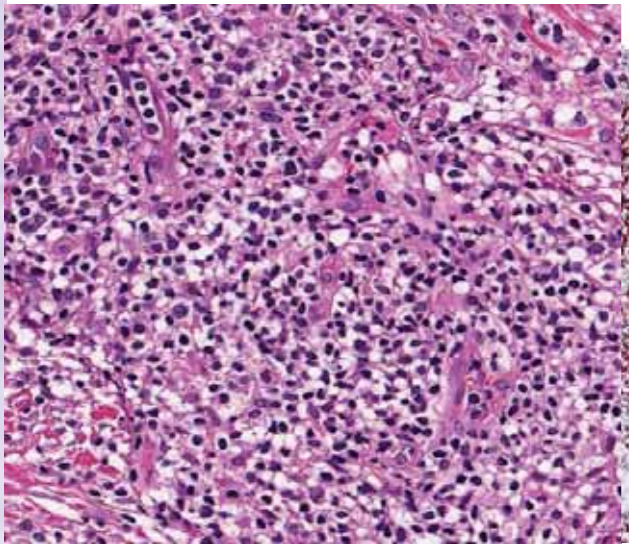


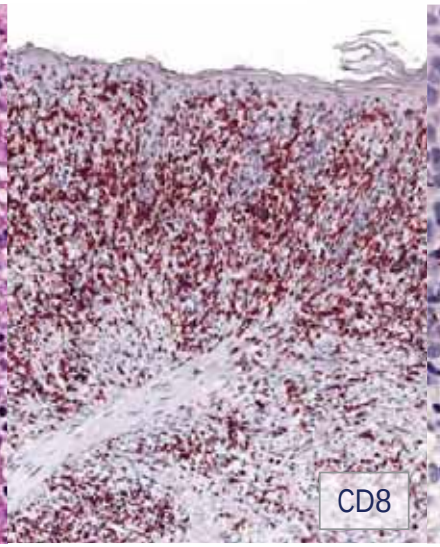


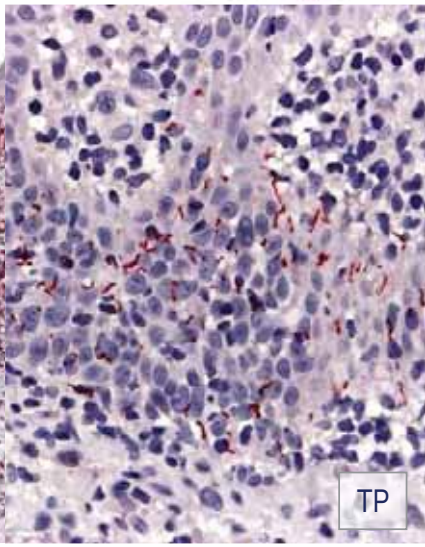




Lues maligna in HIV+ patient







Secondary Syphilis Misdiagnosed as Lymphoma

D. R. Goffinet, M.D., C. Hoyt, M.D., and J. R. Eltringham, M.D., *Stanford*

In 1968 Symmers reviewed the histologic material of 600 patients with an initial biopsy diagnosis of Hodgkin's disease and found that three of the patients actually had either primary or tertiary syphilis as the correct diagnosis.[1] However, 25 years have elapsed since the generalized lymphadenopathy of secondary syphilis was last reported to have been misdiagnosed as one of the lymphomas, in particular giant follicle lymphoma.[2]

Since 1944 a new generation of physicians has been trained, some of whom have never seen a case of secondary syphilis. Therefore, attention is again called to the fact that syphilis is still a common disease that should be considered in the differential diagnosis of generalized lymphadenopathy. This report describes two patients seen recently, both of whom had syphilis, misdiagnosed in one case as giant follicle lymphoma and in the other confused with Hodgkin's disease.

Report of First Case

Case 1. A 31-year-old Negro man noted tender right inguinal lymphadenopathy in January 1968, but no penile lesions were present and a VDRL report was negative. Erythromycin was given orally for five days with prompt disappearance of all palpable lymph nodes.

The patient was then well until October 1968 when a slightly pruritic widespread papular skin eruption appeared, followed in about two weeks by generalized lymphadenopathy. The skin lesions were treated with cornstarch soaks. Biopsy of material from axillary and inguinal nodes in November was interpreted as giant follicle lymphoma, and the patient was subsequently referred to the Division of Radiation Therapy at Stanford University Medical Center for further evaluation and treatment. He was taking no medications, had not used Dilantin® and had no history of mononucleosis, cat scratches, sweats, or fevers.

The patient, who was healthy-appearing, had generalized lymphadenopathy, including palpable epitrochlear nodes, all less than 2.5 cm in size. There was a generalized papulo-squamous eruption, most prominent on the palms and trunk. The remainder of the examination, including neurological, disclosed no abnormality.

The Venereal Disease Research Laboratory Test (VDRL) was reactive to 1:128 dilution and the Fluorescent Treponema Antibody Test (FTA) was also positive. The Stanford surgical pathologists were of the opinion that the lymph node biopsy sections showed reactive hyperplasia.

The patient was sent back to the referring physician with a diagnosis of secondary syphilis. A Jarisch-Herxheimer reaction developed during penicillin therapy, and palpable adenopathy disappeared within three weeks. A repeat VDRL was nonreactive within three months.

Report of Second Case

Case 2. A 41-year-old single white man was well until January 1968 when he first noted small, painless, slowly enlarging masses on both sides of the neck. A generalized, erythematous and pruritic skin eruption was also noted. It cleared completely, without treatment, in a few days. There was no history of fevers, night sweats, diphenylhydantoin (Dilantin®) intake, cat scratches, mononucleosis, or penile lesions. A VDRL test had been negative in 1966, but the patient admitted to having both homosexual and heterosexual relations since that time.

After a March 1969 cervical lymph node biopsy was interpreted as showing Hodgkin's disease, the patient was transferred to the Palo Alto Veterans Administration Hospital for consideration of radiation therapy.

Except for generalized lymphadenopathy, including palpable epitrochlear nodes, no abnormality was noted on physical examination. All nodes were less than 2 cm in diameter. The liver and spleen were not palpable, and there were no skin lesions.

Results of blood cell count, urinalysis, determination of blood urea nitrogen, SGOT and electrolyte contents, and an x-ray film of the chest were all within normal limits. A VDRL test was reactive at 1:128 dilution and an FTA test was also positive.

The studies described in this paper were supported by research grants CA 08122 and CA 05858 from the National Cancer Institute.

From the Departments of Surgery (Dr. Goffinet), Medicine (Dr. Hoyt), and Radiology (Dr. Eltringham, Advanced Clinical Fellow, American Cancer Society), Stanford University Medical Center.

Submitted October 8, 1969.

Reprint requests to: Department of Surgery, Stanford University Medical Center, Stanford, Ca. 94305 (Dr. Goffinet).

Biopsies of lymph nodes interpreted as lymphoma

British Journal of Dermatology (1976) **95**, 251.

Histology simulating reticulosis in secondary syphilis

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SUMMARY

Three cases of secondary syphilis are described in whom a skin biopsy was performed. In all, the histology bore a striking resemblance to that of malignant lymphoid neoplasm.

The classical cutaneous manifestations of secondary syphilis are usually easy to diagnose, especially when there is a good clinical history and the appropriate investigations are positive. If, however, the eruption is not characteristic, a skin biopsy may be carried out. We should like to report three cases where the histological appearances in isolation would have been misleading.

CASE REPORTS

Case 1

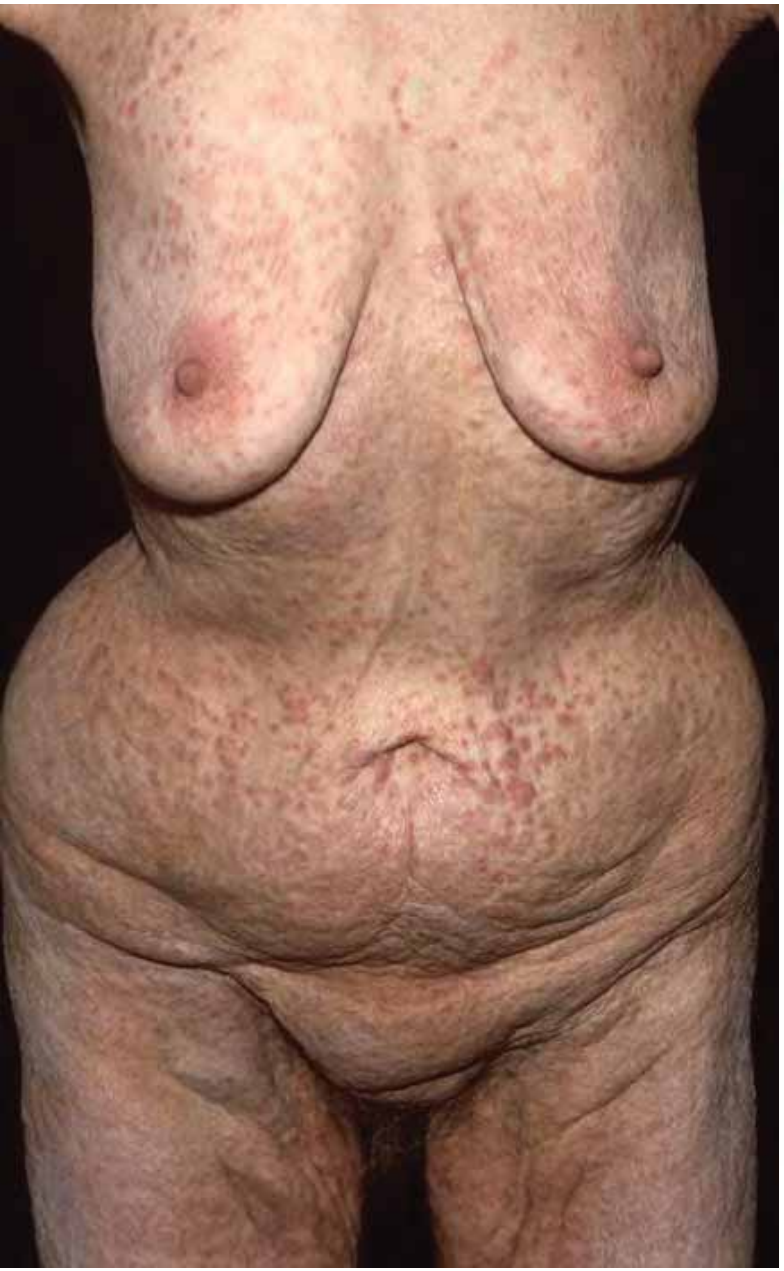
The patient , a 16-year-old girl, was admitted to hospital with a pyrexia and symptoms suggestive of a urinary tract infection. She was noted to have a widespread erythematous papular eruption involving face, trunk and limbs, which had been present for 3 weeks. There were no mucosal lesions. The inguinal lymph nodes were palpable.

Specific serology was as follows: VDRL slide test—positive. Cardiolipin Wassermann reaction—positive. Reiter protein complement fixation test—positive. A skin biopsy was reported as follows: The epidermis is hyper- and parakeratotic with marked epidermotropism of mononuclear lymphoid cells which are forming micro-abscesses in areas. There is inter- and intracellular oedema in the epidermis. In the dermis there is a dense infiltrate which predominantly is perivascular. There is no evidence of a vascular lesion. The infiltrate is composed of histiocytic cells, mononuclear cells, plasma cells and occasional neutrophil polymorphs. Scattered throughout there are large pleomorphic mononuclear cells with hyperchromatic nuclei and prominent nucleoli. Mitotic figures are occasionally found. These findings in the absence of a clinical history are compatible with the diagnosis of cutaneous lymphoid neoplasm.

Skin biopsies interpreted as lymphoma

Pseudolymphomatous syphilis

- Rare clinicopathologic presentation of secondary syphilis
- Solitary (rarely) or multiple papules, nodules and small tumors; may simulate MZLD, but plasma cells polyclonal
- In HIV+ patients with low CD4+ count may simulate a T-cell lymphoma (lues maligna)
- Some ulcera of primary syphilis may also be characterized by florid, pseudolymphomatous infiltrates
- Staining for *Treponema pallidum* represents a useful tool, but microorganisms may be only a few



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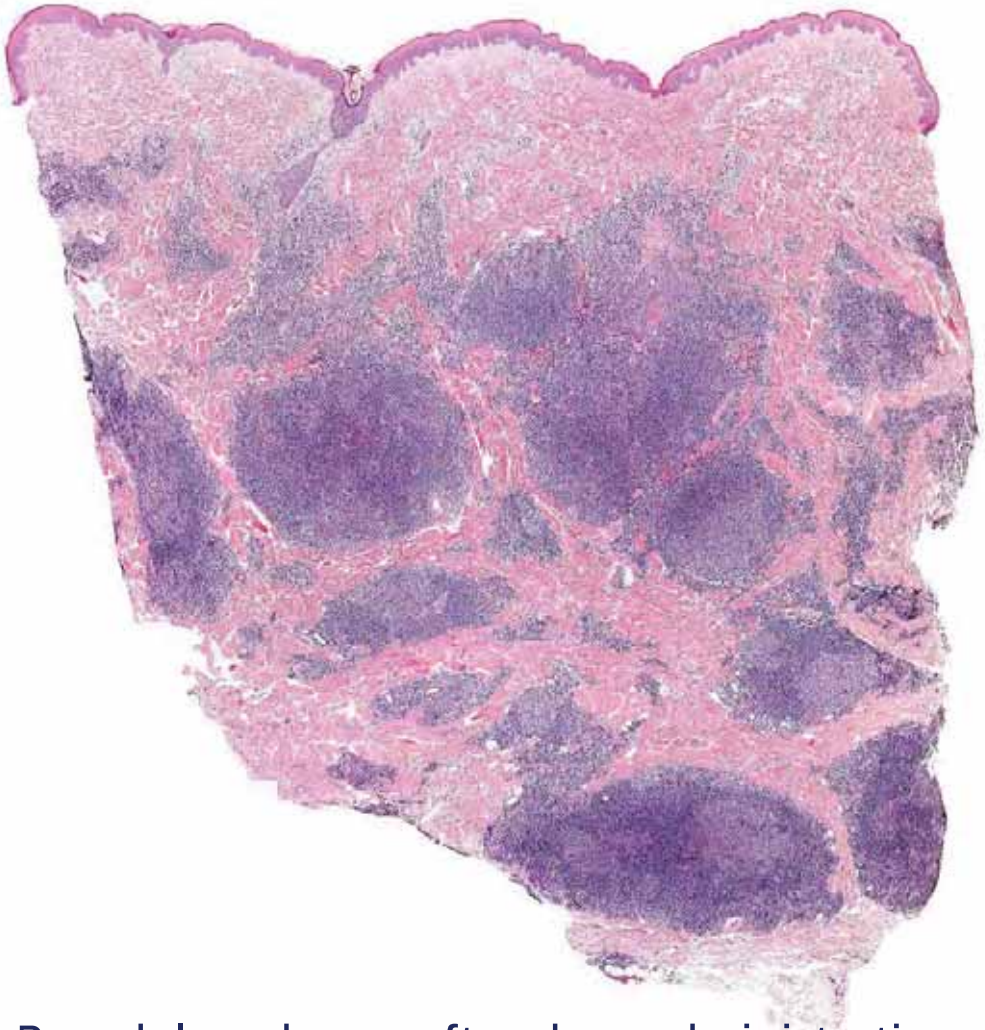

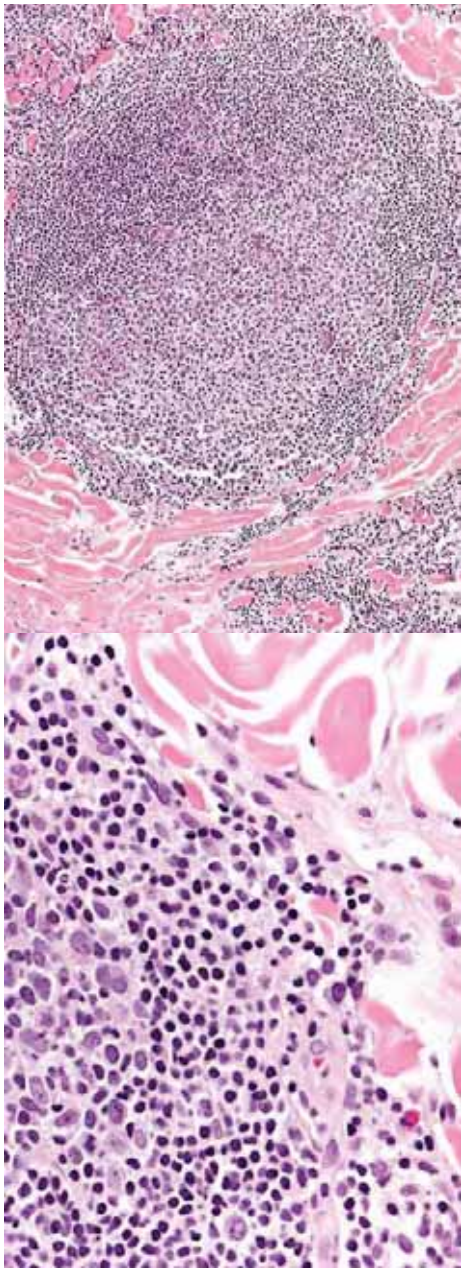

Pseudolymphoma after drug administration,
B-cell type

Lymphomatoid drug eruption (B-cell pattern)

- Drug eruptions may occasionally mimic a cutaneous B-cell lymphoma (FCL-like or MZLD-like); The B-cell pattern is much less frequent than the T-cell pattern of drug-induced pseudolymphoma
- Sudden onset, localized or generalized distribution; Resolution upon discontinuation of the offending drug
- Cases with B-cell pattern present with nodular infiltrates, either with germinal centers or with clusters/sheets of monotypic plasma cells
- The germinal centers reveal reactive morphologic and phenotypic features

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REVIEW ARTICLE

Australasian Journal of Dermatology

Drug-induced cutaneous pseudolymphoma: A systematic review of the literature

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Abstract

Drug-induced cutaneous pseudolymphoma (CPL) is a common form of pseudolymphoma and there are numerous drugs associated with it. In this study, we performed a systematic review of the literature by searching PubMed/Medline and Embase databases to determine the most common drugs responsible for CPL and to define the demographic, clinical, histopathological and immunopathological characteristics of patients (updated on 30 December 2020). From 883 initially found articles, 56 studies (89 reported cases) were included. The mean age of patients was 54.4 ± 17.7 (ranging 8–86) years, and 46 (51.7%) were men. The median time interval between drug intake and CPL occurrence was 120 days (range 1–7300 days). The shortest median time interval between taking the drug and the onset of the disease was observed among patients taking antidepressants (60 days) (range 7–540) and the longest median time interval was observed in individuals using immunomodulators (300 days) (range 3–7300). The most-reported drug categories causing CPL were anti-hypertensives (17.9%), anti-convulsants (14.6%), monoclonal antibodies (13.4%) and antidepressants (11.2%). Moreover, the most common drugs were phenytoin (6.7%), amlodipine (5.6%), fluoxetine (5.6%) and carbamazepine (4.4%). Histopathological evaluation of 76 cases revealed 62 (81.5%) reports of T-cell infiltrations. Furthermore, positive reports of CD4 (94.0%), CD8 (93.0%) and CD30 (87.5%) were noted. The lowest prevalence of CD30-positive reports was observed among monoclonal antibodies. In conclusion, anti-hypertensives, anti-convulsants, monoclonal antibodies and anti-depressants are the most common drugs responsible for CPL. It mostly presents in middle-aged patients with almost no gender difference as pruritic papules, nodules and plaques.

KEYWORDS

amlodipine, cutaneous pseudolymphoma, drug-induced, fluoxetine, phenytoin

Name of the institution: Tehran University of Medical Sciences (TUMS), Department of dermatology, Razi hospital.

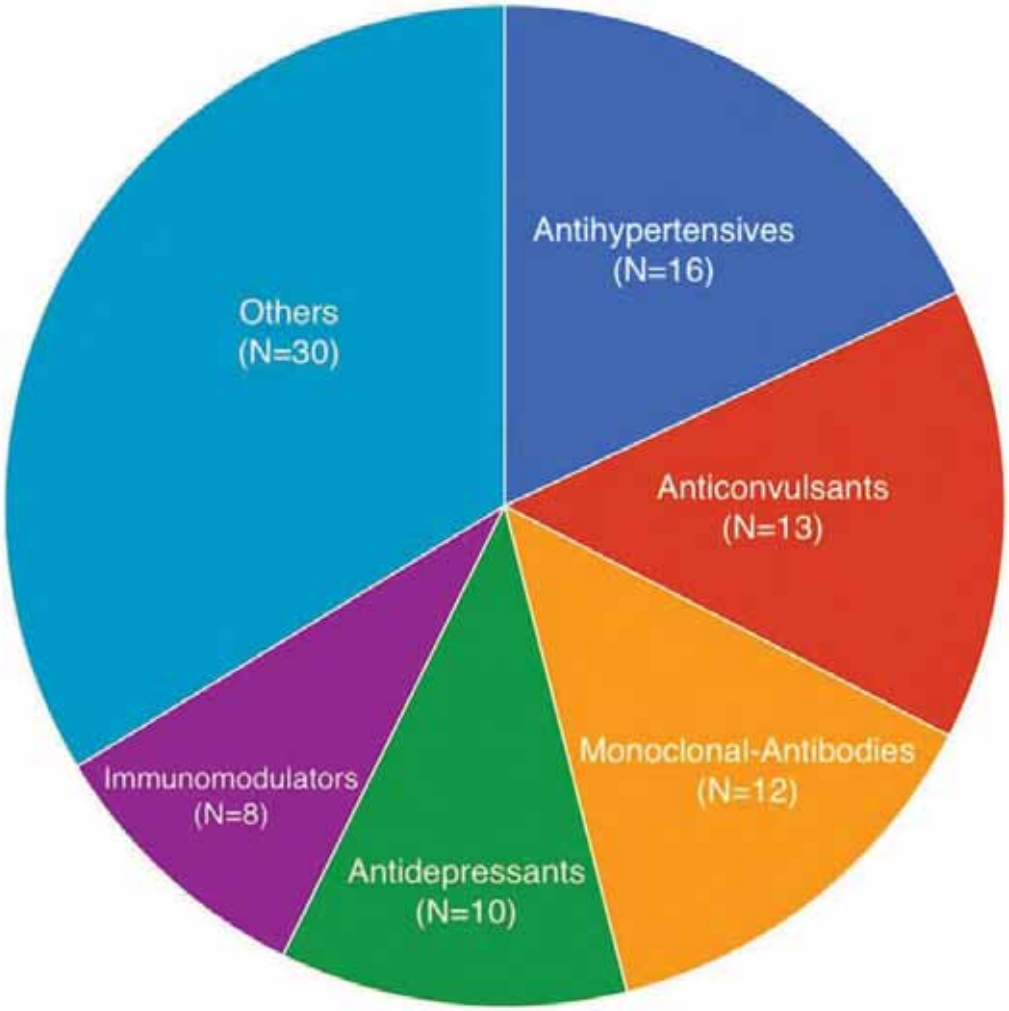
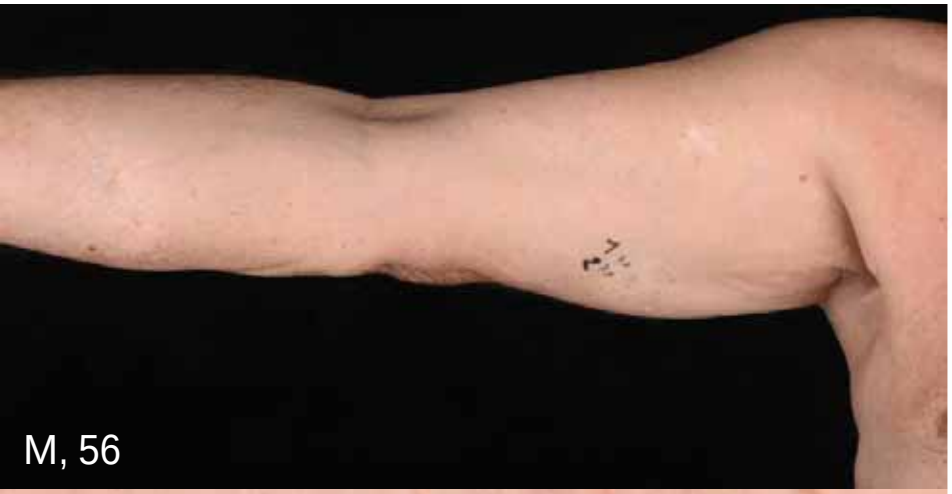
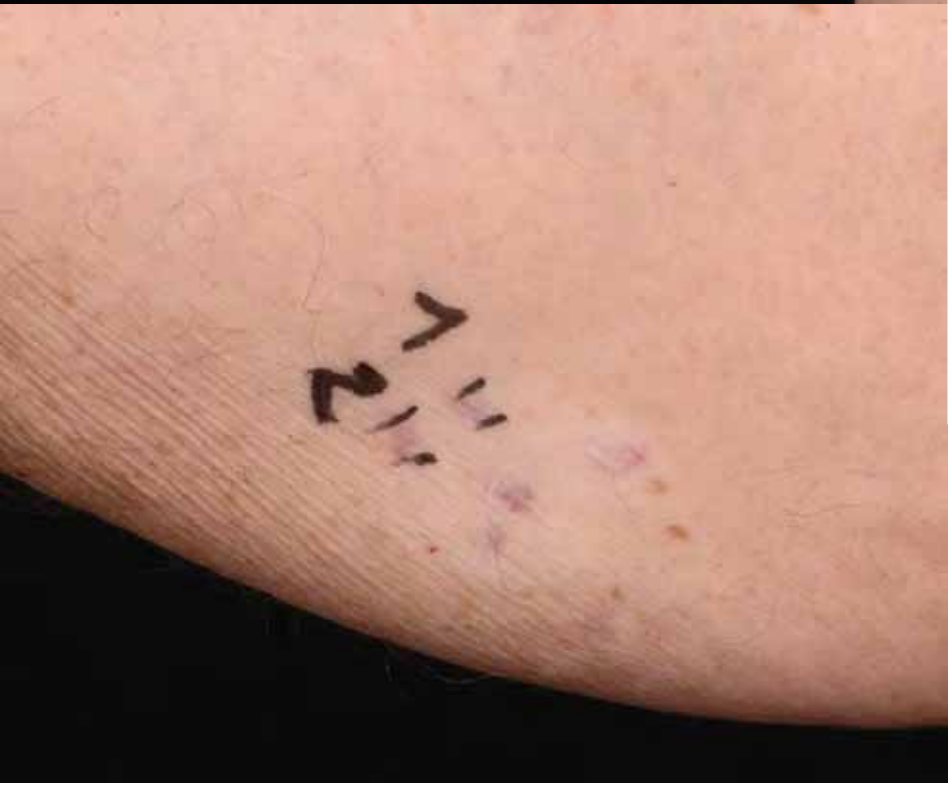
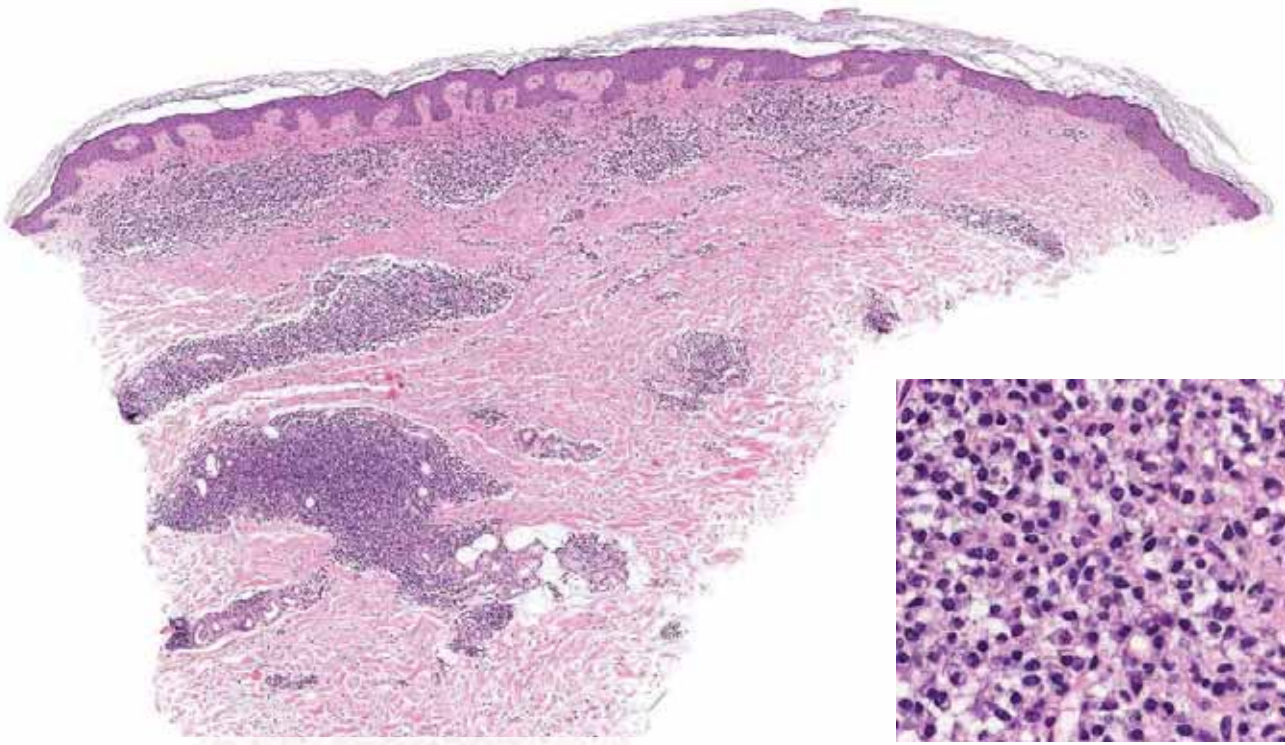


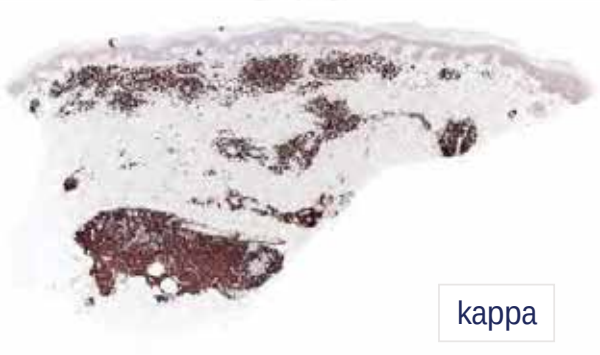
FIGURE 1 The culprit drug categories

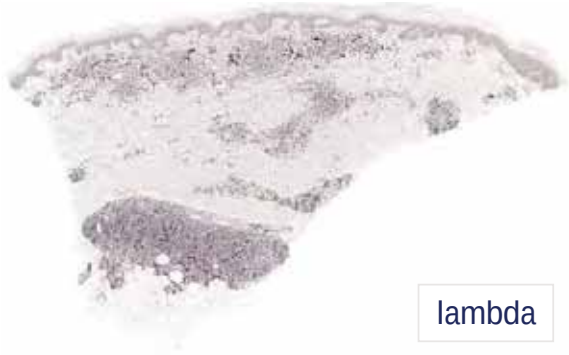


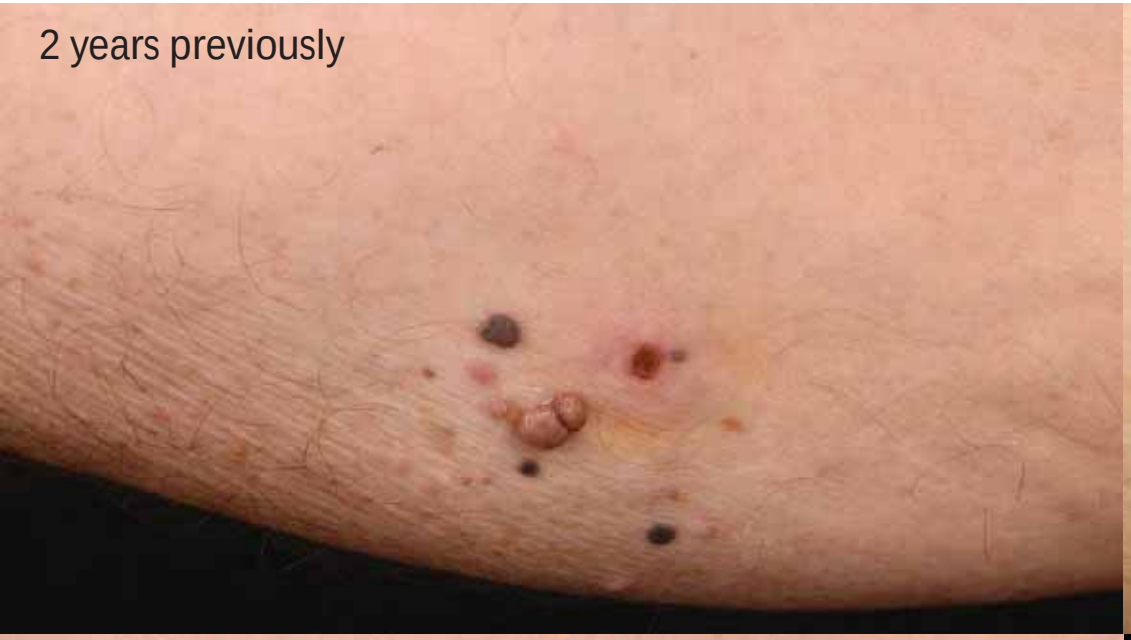




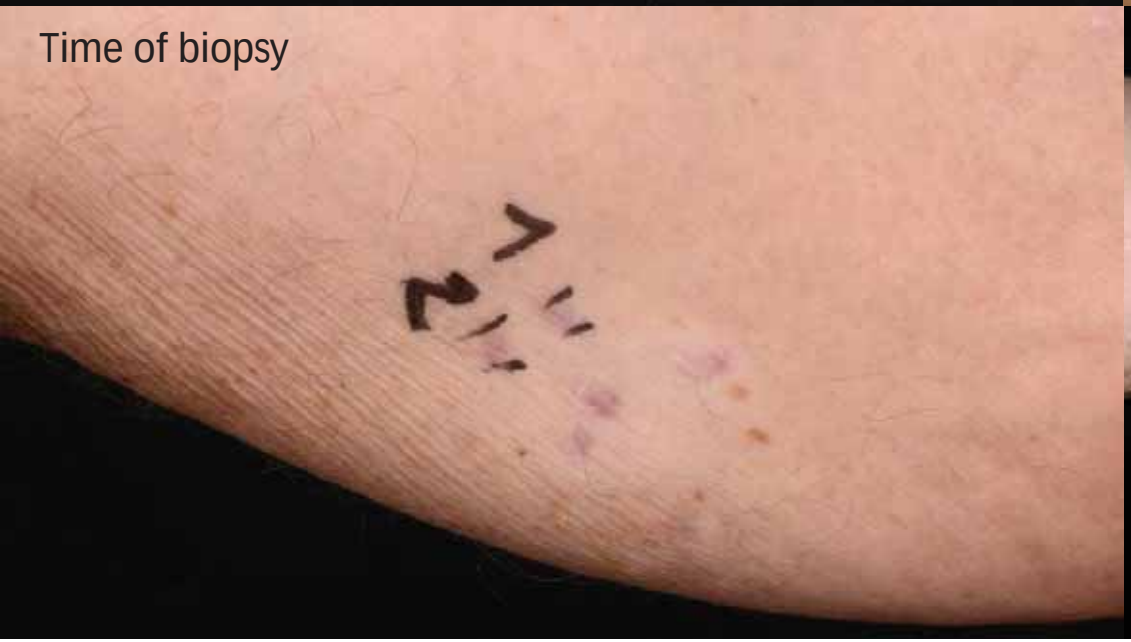
Pseudolymphoma after talimogene laherparepvec treatment for metastatic melanoma






2 years previously


1 year previously (during treatment)


Time of biopsy


2 years later

personal fees from Berlin-Chemie Menarini, personal fees from Merck, personal fees from Regeneron, personal fees from Sanofi-Genzyme, personal fees from Amgen, personal fees from Boehringer Ingelheim, personal fees from Galapagos, personal fees from InflaRX, personal fees from Pfizer, personal fees from UCB, personal fees from Incyte and personal fees from Helm; outside the submitted work, and is a co-author of the article on development of the InToDermQoL questionnaire.

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Talimogene laherparepvec can initiate plasma cell invasion into infiltrated melanoma lesions – a case series

Editor

Talimogene laherparepvec (T-VEC) is a genetically engineered herpes simplex virus type 1 (HSV-1) and used in locally advanced melanoma patients. Its mode of action is not fully understood.[1,2] We present three cases where T-VEC caused monoclonal as well as polyclonal B-cell infiltration.

Case 1: A 56-year-old male patient presented with several firm black-bluish papules on his right upper arm after a history of nodular melanoma (2.06 mm) on his right lower arm 2 years prior (Fig. 1a). Histopathology revealed cutaneous *BRAF*[V600E] mutated melanoma metastases. Due to no signs of distant metastases, treatment with T-VEC (IMLYGIC®) was administered intralesionally according to recommended guidelines. Within 4 months, all lesions regressed leaving flat greyish macules that were excised (Fig. 1b).

Histology revealed dense infiltrates composed almost entirely of mature plasma cells located in the entire dermis and superficial subcutis (Fig. 1c). Focal fibrosis and superficial clusters of melanophages were observed, and complexes of melanocytes were absent (Fig. 1d). By in situ hybridization and immunohistochemistry, the plasma cells were clonal, expressing light chain kappa and heavy chain IgG (Fig. 1e,f). Nine months later, two new papules on the right upper arm were excised. They showed the same infiltrate as mentioned above. Serum and urine protein electrophoresis was polyclonal. Quantification of IgG, IgA and IgM immunoglobulins as well as measurement of the serum free light chains lambda and kappa showed no pathologic findings. A

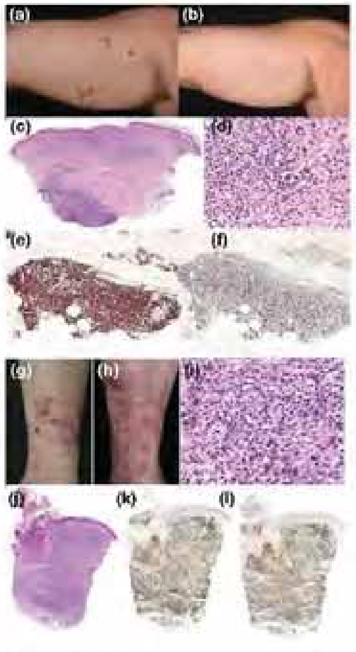

Figure 1 Clinical images and immunohistochemical pictures of case 1 and 2. (a) Black-bluish papules on right upper arm representing cutaneous melanoma metastases in December 2016. (b) Regression of all marked lesions in May 2017. (c) Histology showing dense infiltrates composed almost entirely of mature plasma cells located in the entire dermis and superficial subcutis (original magnification 20×). (d) Focal fibrosis and small clusters of melanophages admixed with plasma cells, but no complexes of melanocytes (original magnification 200×). (e) Plasma cells are positive for kappa light chain (in situ hybridization; original magnification 100×). (f) Plasma cells are mostly negative for lambda light chain (in situ hybridization; original magnification 100×). (g) Red and black-bluish macules and papules on the left lower leg representing cutaneous melanoma metastases in August 2018. (h) Regressive lesions in Mai 2019. (i) Histology showing dense infiltrates composed almost entirely of mature plasma cells located in the entire dermis (original magnification 20×). (j) Focal fibrosis and small clusters of melanophages admixed with plasma cells and lymphocytes, but no complexes of melanocytes (original magnification 200×). Polyclonal expression of kappa (k) and lambda (l) light chains of plasma cells (in situ hybridization; original magnification 20×).

Figure 2 Clinical images and immunohistochemical pictures of case 3. (a) Black-bluish papules on the left lower leg representing cutaneous melanoma metastases in December 2017. (b) Regressive lesions in December 2018. (c) Histology showing dense infiltrates composed almost entirely of mature plasma cells located in the entire dermis (original magnification 20×). (d) Focal fibrosis and plasma cells, but no complexes of melanocytes (original magnification 200×). (e) Plasma cells are positive for kappa light chain (in situ hybridization; original magnification 20×). (f) Plasma cells are mostly negative for lambda light chain (in situ hybridization; original magnification 20×).

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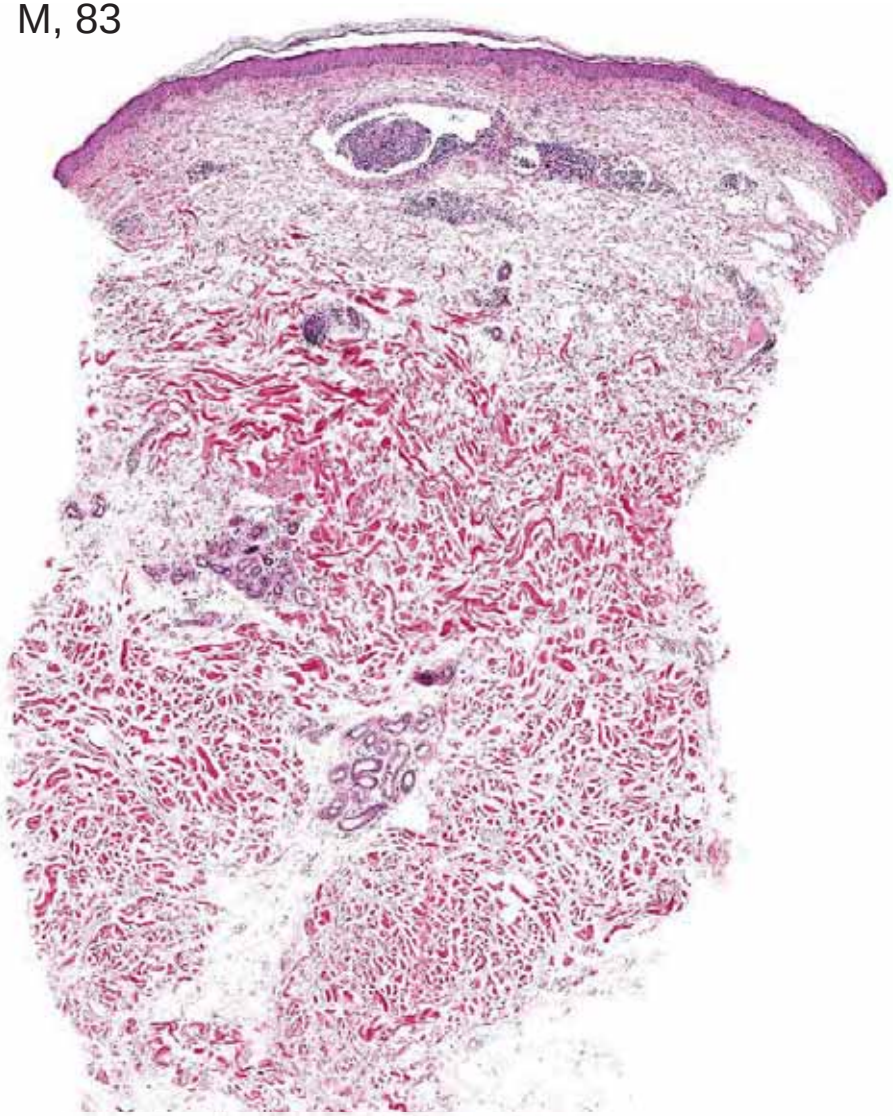
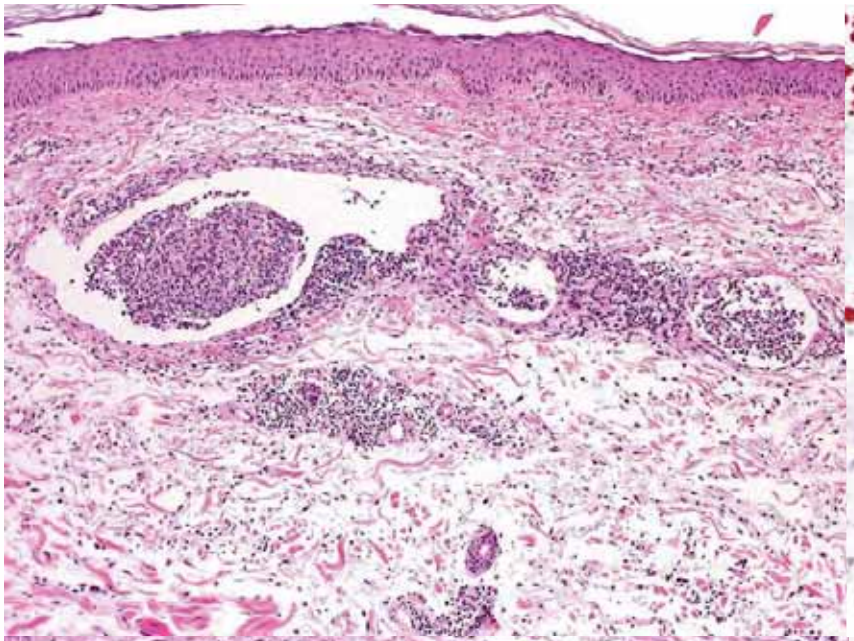
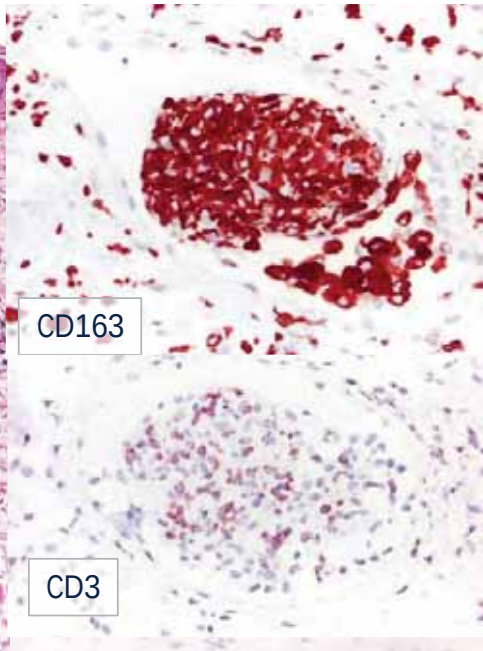
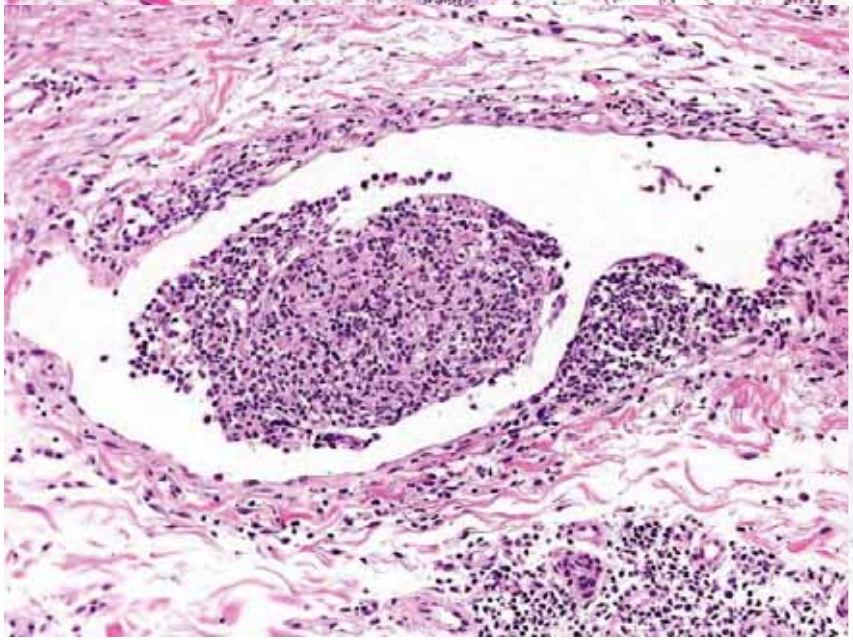
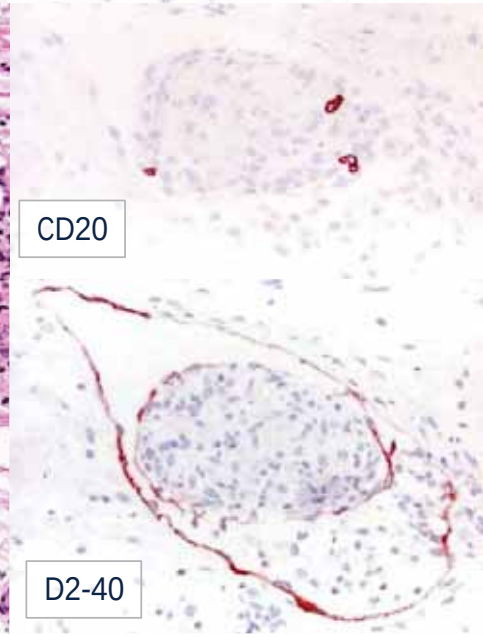


Intralymphatic histiocytosis

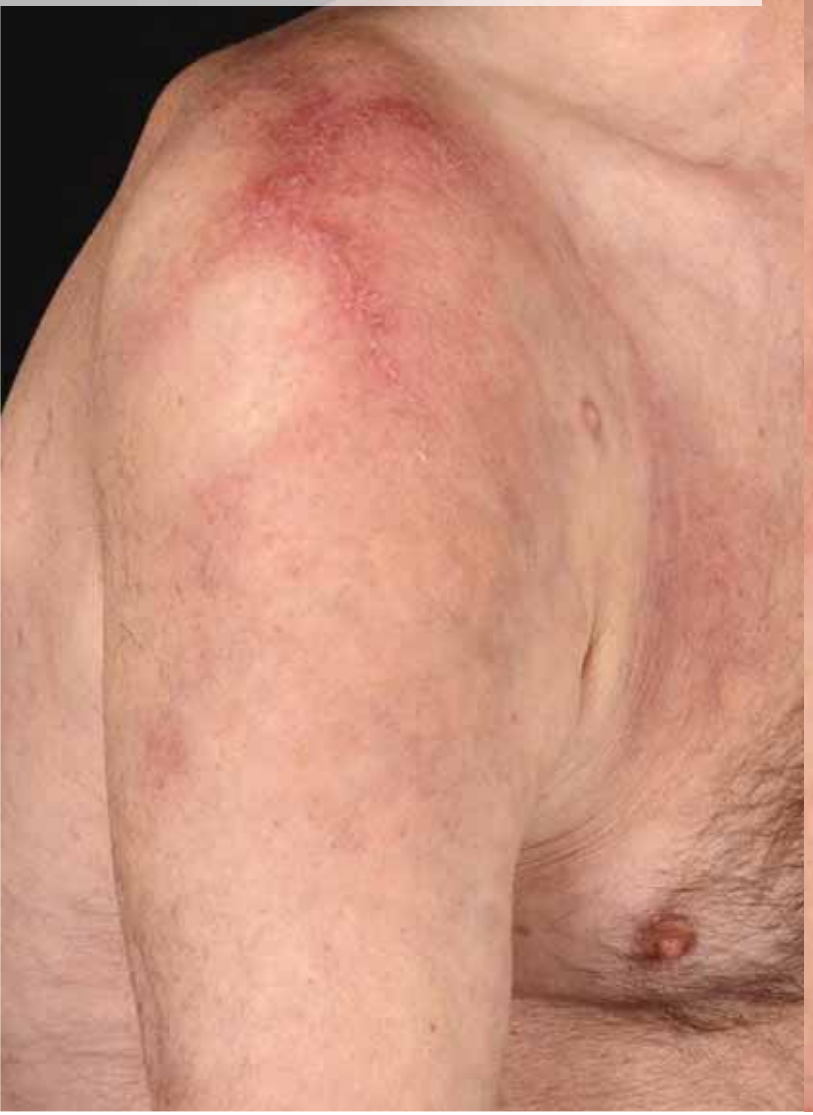


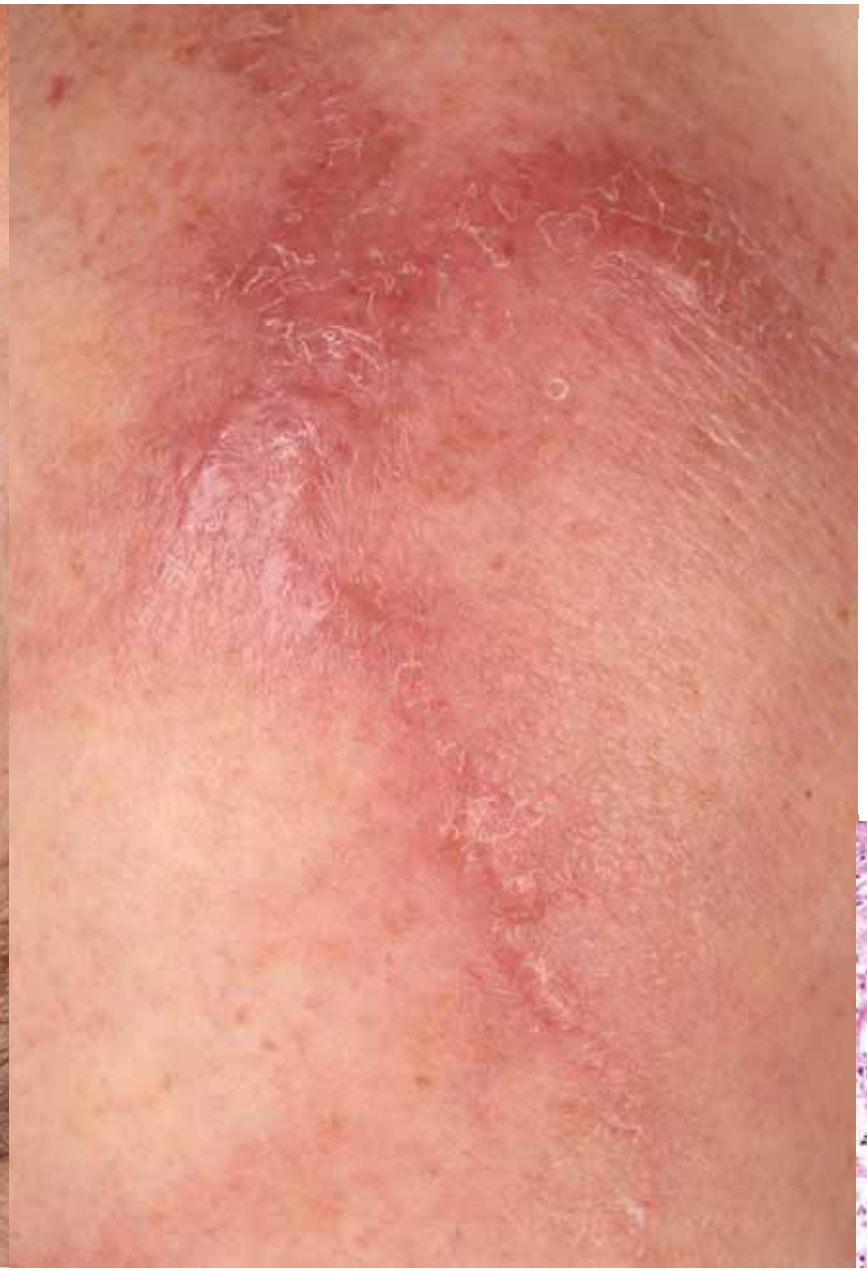


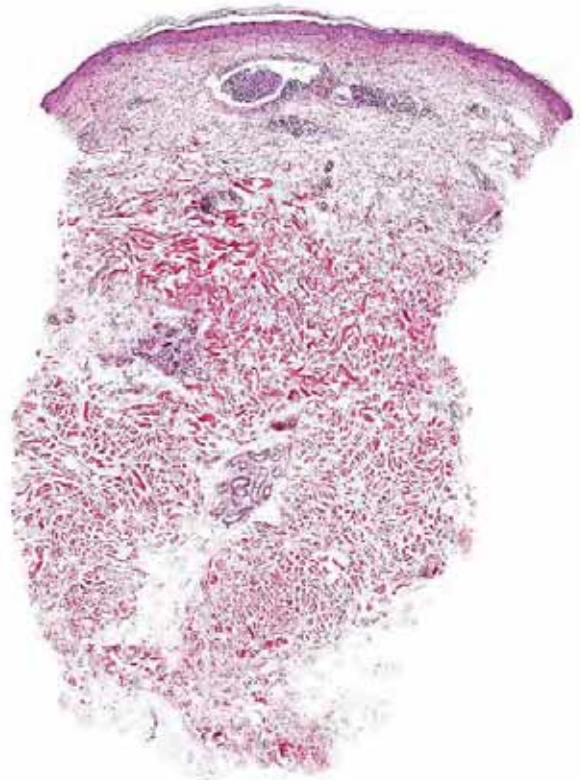


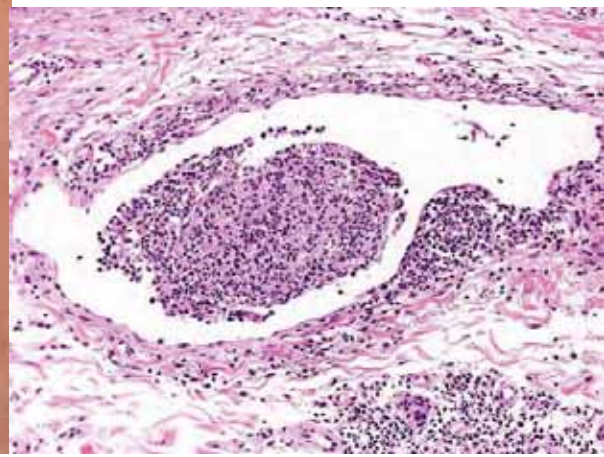


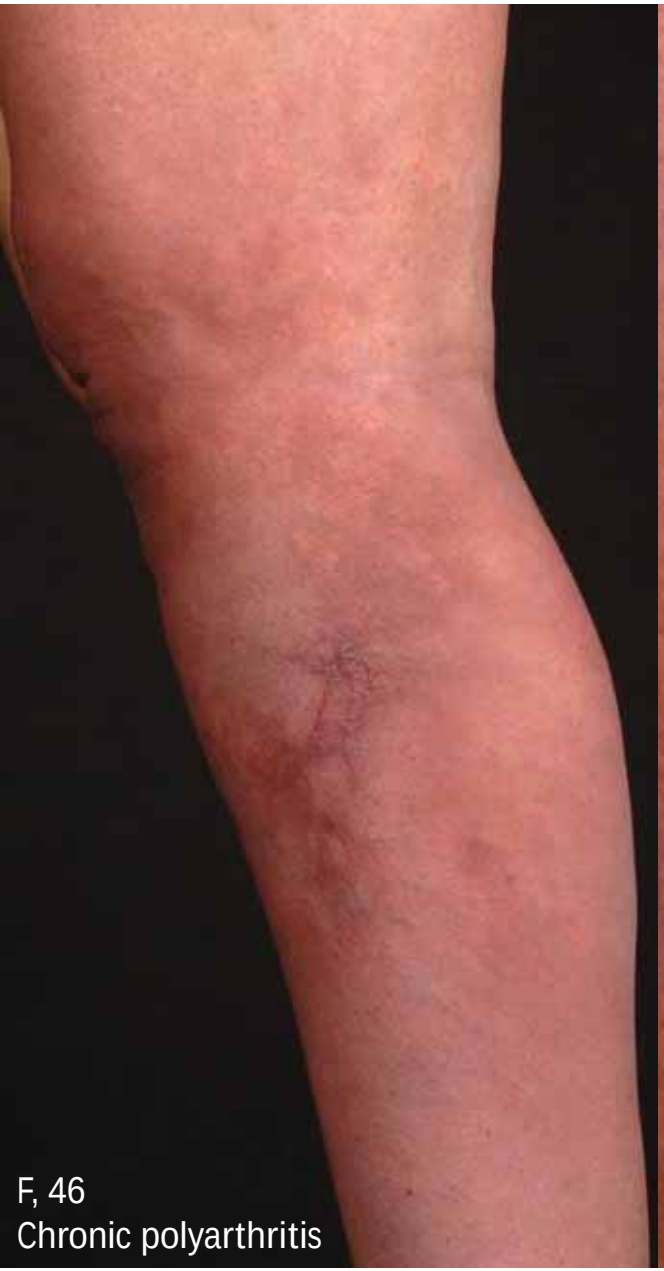
- Known seronegative chronic polyarthritis
- Elevated CRP (111,1 mg/L)
- Duration of the skin lesions unknown

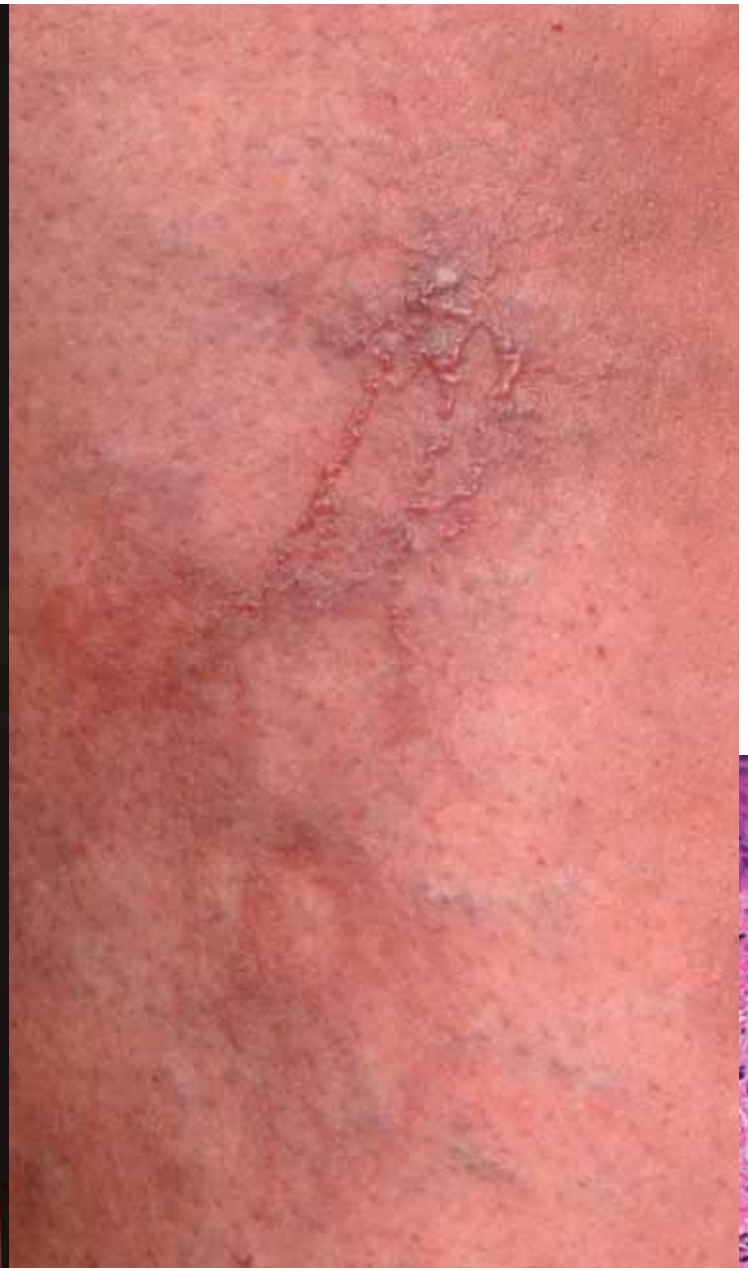


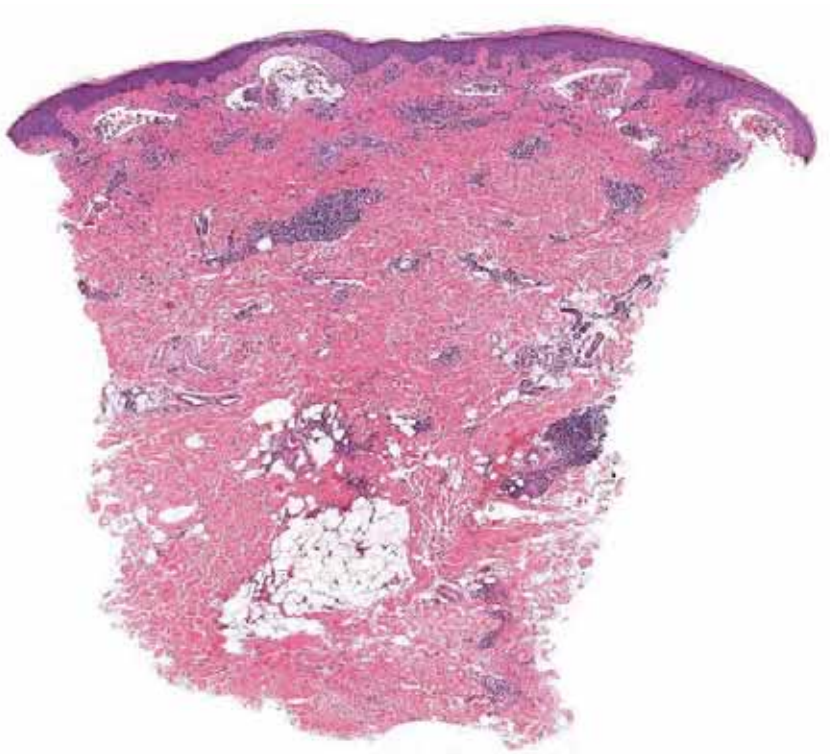


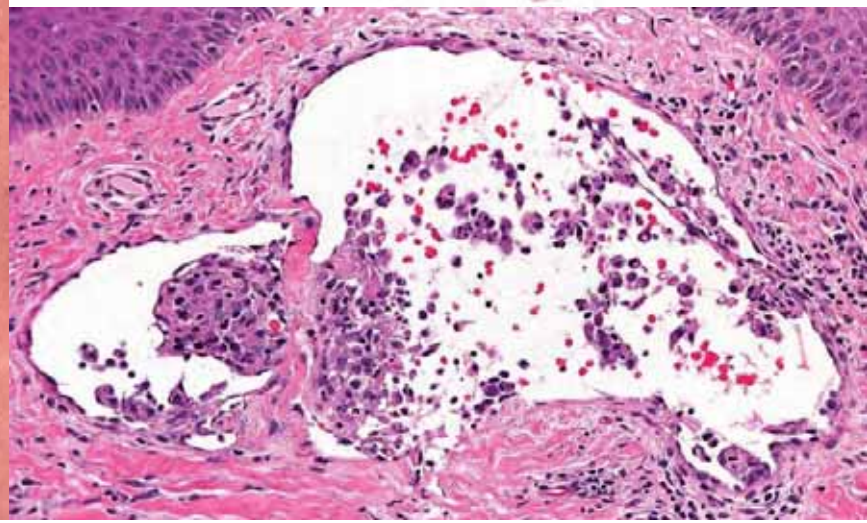












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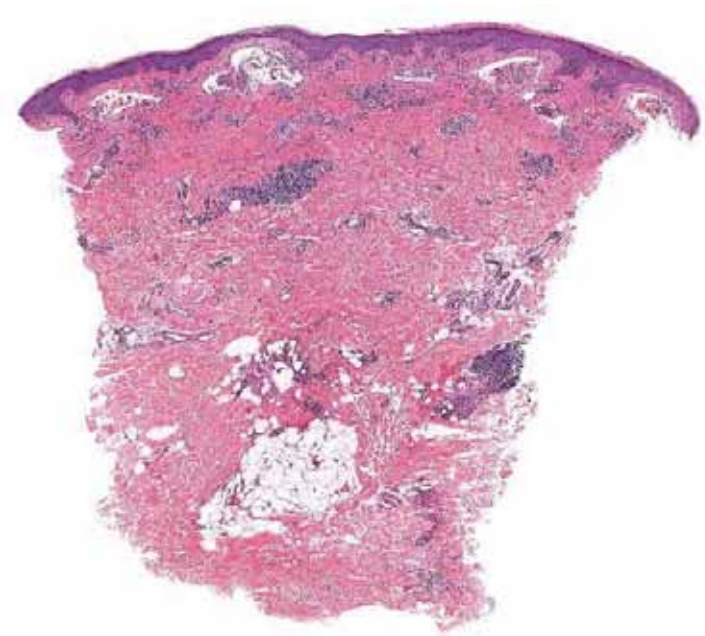
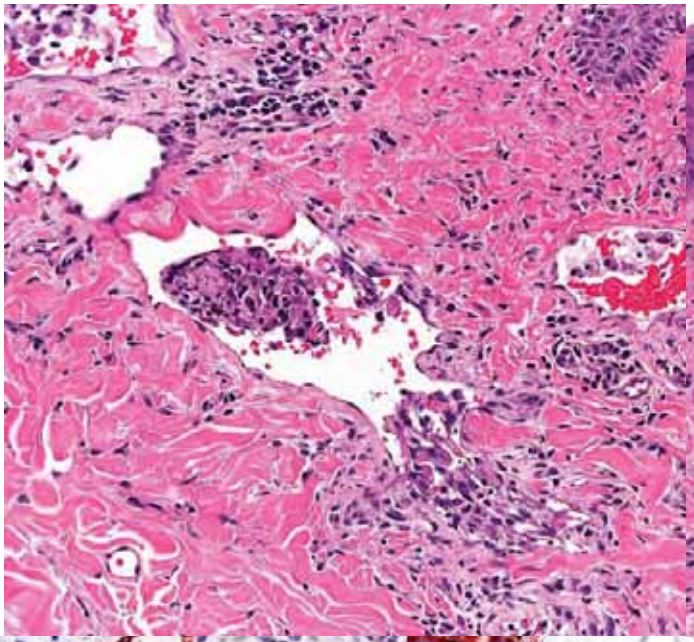
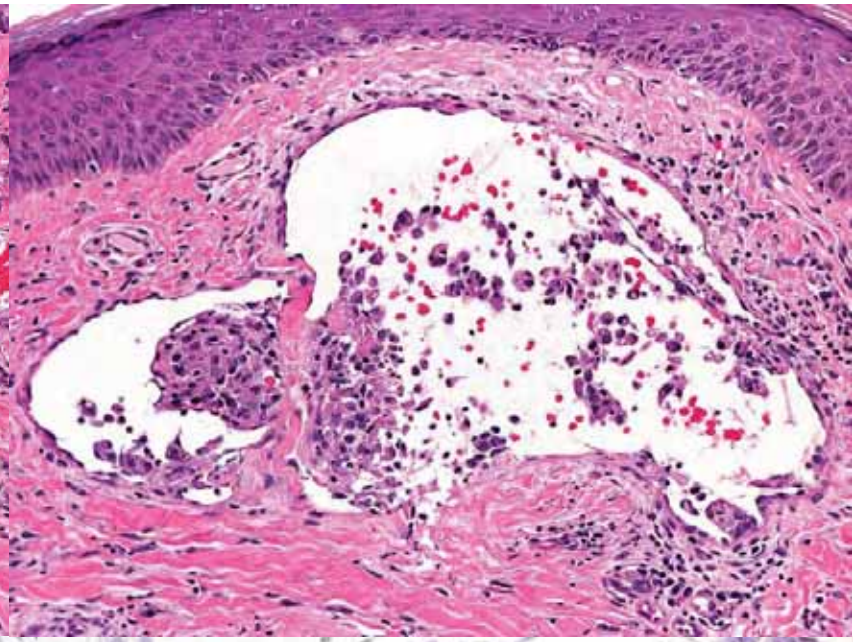
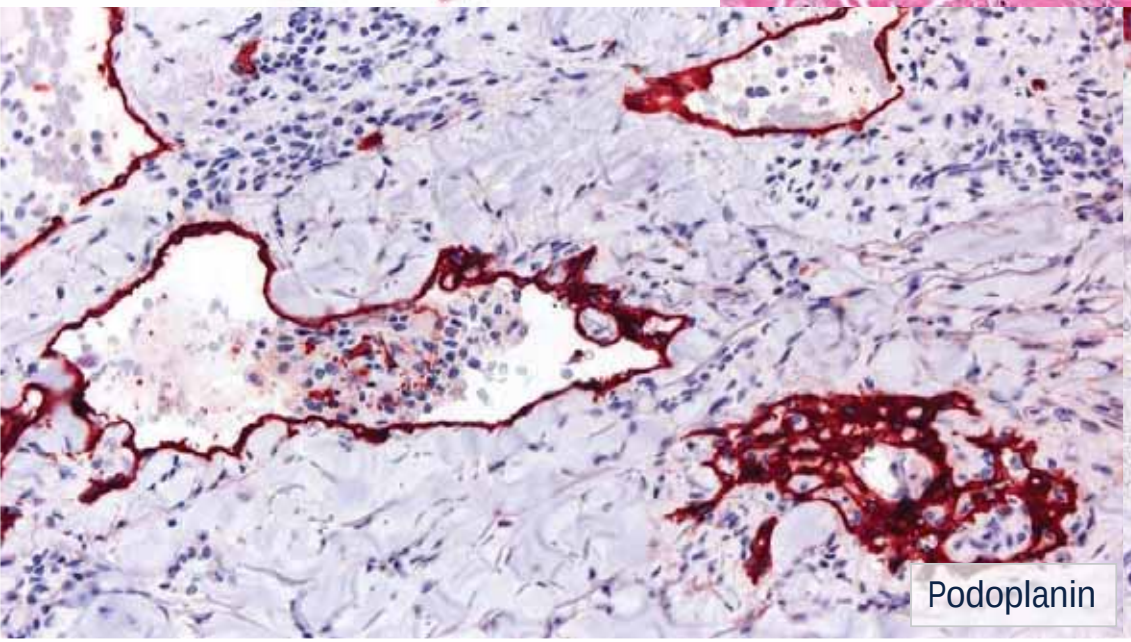
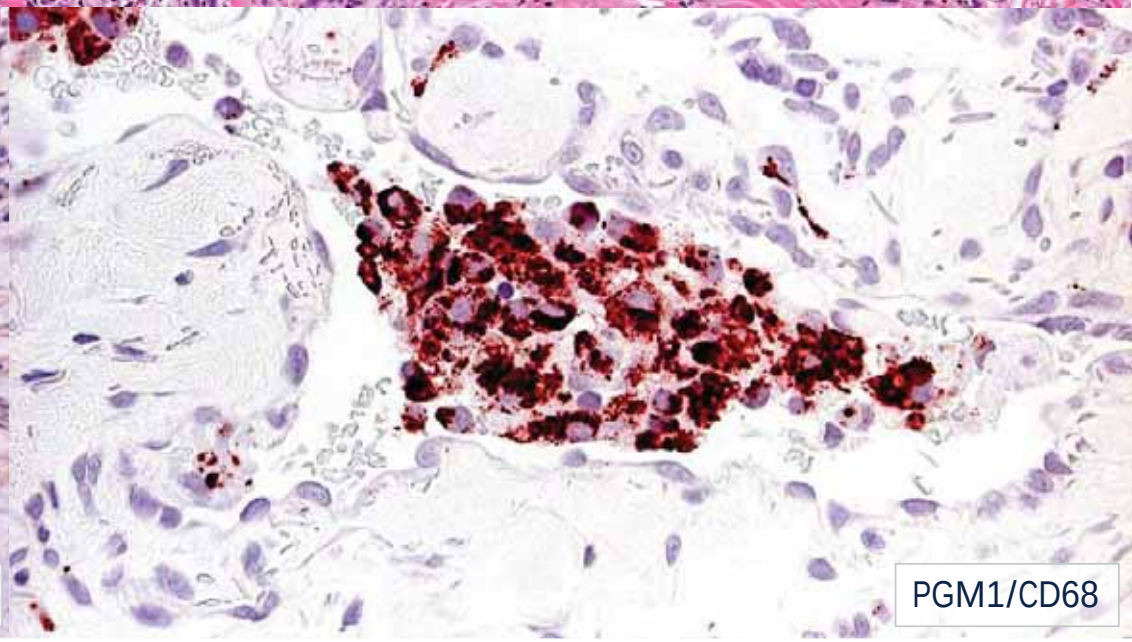
Chronic polyarthritis








Podoplanin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Intralymphatic Histiocytosis. A Clinicopathologic Study of 16 Cases

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*Sonia Segura, MD,|| Mirjana Ziemer, MD,** Mark A. Hurt, MD,¶*
Omar P. Sangüeza, MD,‡§ and Heinz Kutzner, MD††

Abstract: Intralymphatic histiocytosis is a rare condition characterized by the presence of dilated lymphatic vessels containing aggregates of mononuclear histiocytes (macrophages) within their lumina. The phenomenon seems to occur almost exclusively within the reticular dermis. Although its pathogenesis remains uncertain, findings expand on the previously described morphologic and immunohistochemical features of intravascular histiocytosis. We also discuss the possible relationship between intralymphatic histiocytosis and the so-called reactive intravascular angioendotheliomatosis.

Key Words: intralymphatic histiocytosis, intralymphatic macro-

TABLE 1. Clinical Data of 16 Patients With Intralymphatic Histiocytosis

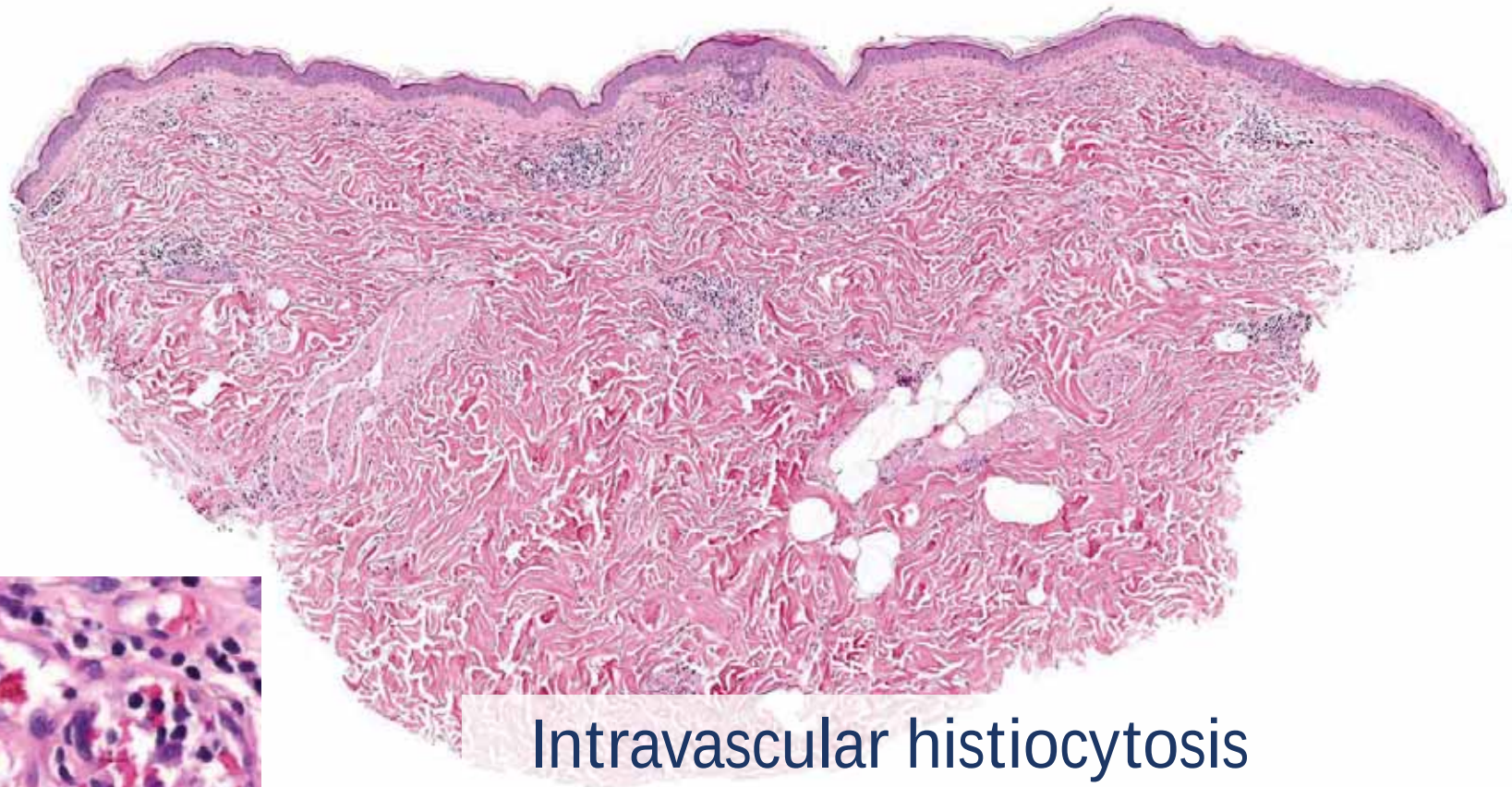
Case	Sex	Age (yrs)	Lesion Location	Clinical Features	Associated Diseases or Findings	Follow-up
1	F	79	Thighs, knees	Erythematous violaceous confluent patches	Rheumatoid arthritis	Lesions disappeared after knee joint replacement
2	F	46	Left lower leg	Poorly demarcated erythema	Rheumatoid arthritis Klippel–Trenaunay syndrome	N/a
3	M	48	Left chest, left thigh	N/a	N/a	N/a
4	F	84	Right arm	Indurated plaque: intravascular lymphoma?	None	Lesions have persisted
5	F	57	Left thigh	Erythema and induration	Merkel cell carcinoma at the same site of the original biopsy, rheumatoid arthritis, PCR negative for EBV, *Borrelia*, and *Treponema pallidum*	N/a
6	M	79	Abdominal skin	Multiple excoriated papules: scabies?	None	N/a
7	F	69	Right breast	Erythema on the surgical scar: carcinoma erysipeloides?	Previous right breast carcinoma	N/a
8	F	85	Left upper arm	Livic erythema: dermatomyositis?	PCR negative for *Borrelia*, *Streptococcus*, *Staphylococcus*, and *Bartonella*	N/a
9	F	66	Left breast	Livid erythematous patch	Excision of left breast carcinoma 9 yrs ago	N/a
10	F	78	Right elbow	Scaly induration: granuloma annulare, allergic eczema, herpes simplex?	None	N/a
11	M	63	Right hip	Indurated erythema of the surgical scar	The lesions developed on the scar after hip joint replacement with a metal prosthesis	N/a
12	F	75	Right upper arm	Livic erythema after insect bite: mycosis fungoides?	PCR negative for *Borrelia*and HHV-8, polyclonality of light chain expression (kappa and lambda light chains)	N/a
13	M	65	Right thigh	Erythema on the surgical scar	The lesions developed on the surgical scar after hip joint replacement with a metal prosthesis	N/a
14	F	84	Right upper arm	Persistent reticulate erythema	Rheumatoid arthritis, PCR negative for *Borrelia*, IgH and TCR clonality	N/a
15	M	68	Upper eyelid	Melkersson–Rosenthal syndrome?	Melanoma in situ in the overlying epidermis Unilateral eyelid swelling histopathologically showing suppurative granuloma	N/a
16	M	73	Left upper arm	Large vascular radiating patch present for 2 months: angiosarcoma, inflammatory carcinoma, Kaposi's sarcoma?	Rheumatoid arthritis, malignant melanoma S/P lymphadenectomy	N/a

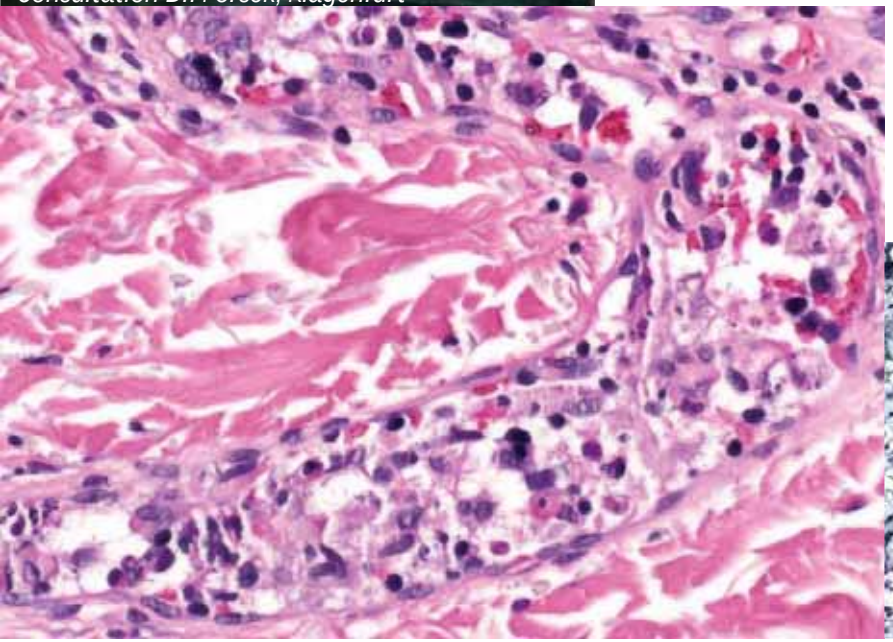
HHV-8, human herpesvirus 8; N/a, Not available; PCR, polymerase chain reaction; TCR, T-cell receptor; EBV, epstein-barr virus.

TABLE 2. Summary of the Cases of Intralymphatic Histiocytosis Previously Described in Literature

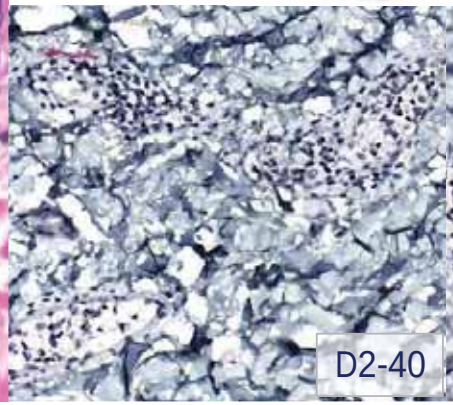
Case, Reference	Age (yrs)/Sex	Clinical Diagnosis	Histopathology/Immunohistochemistry	Associated Diseases
1, O'Grady et al[1]	70/F	Erythematous rash below the left knee	Intravascular collections of histiocytes (Mac 387 and Kp1 + histiocytes and F-VIII + endothelial cells)	ND
2, Rieger et al[2]	80/F	Red macules and plaques on face and arms	Intravascular collections of histiocytes (Mac 387 and PGM1 + histiocytes and CD31, F-VIII, and *Ulex europaeus* + endothelial cells	Cardiac insufficiency osteoporosis, positive rheumatoid factor
3, Rieger et al[2]	77/F	Violaceous patches with livedo-like erythema on both elbows	Intravascular collections of histiocytes (Mac 387 and PGM1 + histiocytes and CD31, F-VIII, and *U. europaeus* + endothelial cells)	Rheumatoid arthritis, bilateral breast cancer
4, Pruim et al[3]	63/M	Violaceous lesions with livedo-like erythema on the left elbow	Intravascular collections of histiocytes (HAM 56 and CD68 + histiocytes and CD31, CD34 + endothelial cells)	Rheumatoid arthritis
5, Pruim et al[3]	59/F	Erythematous rash on the left wrist	Intravascular collections of histiocytes (HAM 56 and CD68 + histiocytes and CD31, CD34 + endothelial cells)	Rheumatoid arthritis
6, Magro and Crowson[4]	82/M	Contact dermatitis on shoulder	Intravascular collections of histiocytes	Rheumatoid arthritis
7, Magro and Crowson[4]	46/M	Urticaria on buttocks, thighs, and lower back	Intravascular collections of histiocytes	Rheumatoid arthritis
8, Magro and Crowson[4]	41/F	Lymphoma on forearm	Intravascular collections of histiocytes	Rheumatoid arthritis
9, Takiwaki et al[5]	69/F	Indurated erythema and papules on the elbow	Intravascular or intralymphatic collections of histiocytes (CD68 + histiocytes and CD31, CD34, and F-VIII + endothelial cells)	Rheumatoid arthritis
10, Takiwaki et al[5]	74/M	Livedo-like erythema on the elbow and forearm	Intravascular or intralymphatic collections of histiocytes (CD68 + histiocytes and CD31, CD34, and F-VIII + endothelial cells)	Rheumatoid arthritis
11, Takiwaki et al[5]	66/F	Livedo-like erythema on the elbow and forearm	Intravascular or intralymphatic collections of histiocytes (CD68 + histiocytes and CD31, CD34, and F-VIII + endothelial cells)	Rheumatoid arthritis
12, Takiwaki et al[5]	62/F	Erythema and confluent papules on forearm	Intravascular or intralymphatic collections of histiocytes (CD68 + histiocytes and CD31, CD34, and F-VIII + endothelial cells)	Rheumatoid arthritis
13, Okazaki et al[6]	52/M	Livedo-like erythema with vesicles on lower leg	Intralymphatic collections of histiocytes (CD68 + histiocytes and D2-40 + endothelial cells)	Rheumatoid arthritis
14, Asagoe et al[7]	17/M	Painful induration of the scrotum	Intravascular collections of histiocytes (CD68 + histiocytes and CD31 + D2-40 endothelial cells)	Tonsillitis
15, Catalina-Fernández et al[8]	50/F	Erythematous plaques with livedo-like pattern on shins	Intralymphatic collections of histiocytes (CD68 + histiocytes and D2-40 + endothelial cells)	Rheumatoid arthritis, fibromyalgia
16, Okamoto et al[9]	75/F	Violaceous, infiltrated erythema on left forearm	Intralymphatic collections of histiocytes (PGM-1 + histiocytes and D2-40 + endothelial cells)	Rheumatoid arthritis, lymphedema
17, Mensing et al[10]	68/F	Reticular, bizarre-shaped livid macules on the face, livid macules on the face, back, and thighs	Intravascular collections of histiocytes (CD68 + histiocytes and CD31, CD34, and F-VIII + endothelial cells	Heart attack, diabetes
18, Waranabe et al[11]	75/M	Erythematous nodules on the left knee	Intravascular collections of histiocytes (PGM-1 + histiocytes and D2-40 + endothelial cells)	Orthopedic metal implants

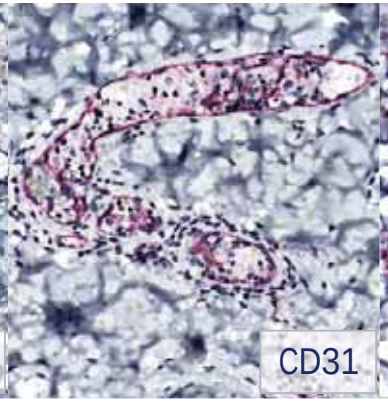
F-VIII, factor-VIII–related antigen; F, female; M, male; ND, not described.

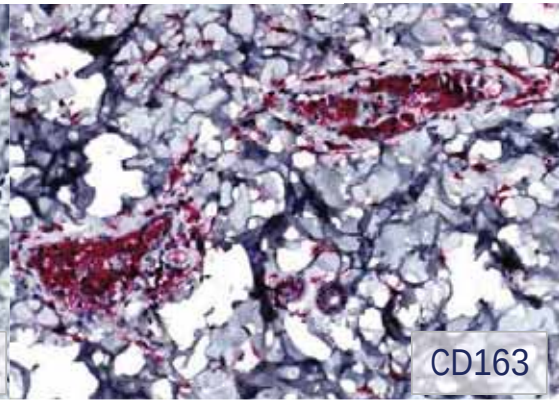




Intravascular histiocytosis







Histopathology

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SHORT REPORT

Intravascular (blood vessel) histiocytosis with haemophagocytosis

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Intravascular (blood vessel) histiocytosis with haemophagocytosis

Aims: Many types of intravascular lymphohistiocytic proliferation have been described recently; this was previously an unnoticed or misinterpreted phenomenon. Intralymphatic lymphohistiocytic aggregates are relatively common, and include benign, malignant and indeterminate conditions. In contrast, all non-endothelial proliferations in the lumina of blood vessels have been interpreted so far as malignant. Herein, we present three cases of histiocytic proliferations in the lumen of blood vessels associated with intracytoplasmic granulocyte debris (haemophagocytosis), a previously undescribed entity.

Methods and results: We identified three patients from two institutions with similar cutaneous lesions, both clinically and microscopically. Information regarding clinical history, histological features and immunoprofiles were obtained. The three cases presented intravascular histiocytosis with haemophagocytosis involving blood vessels of the dermis, a process that may be representative of a new entity. The patients were two women and one man who presented a symmetrical reticulated erythema with a tendency to involve the skin of the breasts. The lesions were indolent, did not ulcerate and followed a benign course.

Conclusions: This seemingly novel condition is characterised by the presence of histiocytic cells inside blood vessels, where they have not been described previously as an entity. The most reasonable explanation for this process is an origin from the non-classical subset of monocytes that 'patrol' the inner face of blood vessels acting as macrophages. The existence of this entity should be kept in mind to avoid overdiagnosis of malignancy.

Keywords: blood vessel, breast, hemophagocytosis, histiocytosis, intravascular, non-classical monocytes

Introduction

Intralymphatic lymphohistiocytic proliferations are relatively common, and different types have been described in recent years. In most cases the cause is intralymphatic histiocytosis (ILH), that may be either primary (idiopathic) or secondary to neoplastic diseases or inflammatory conditions, and is particularly

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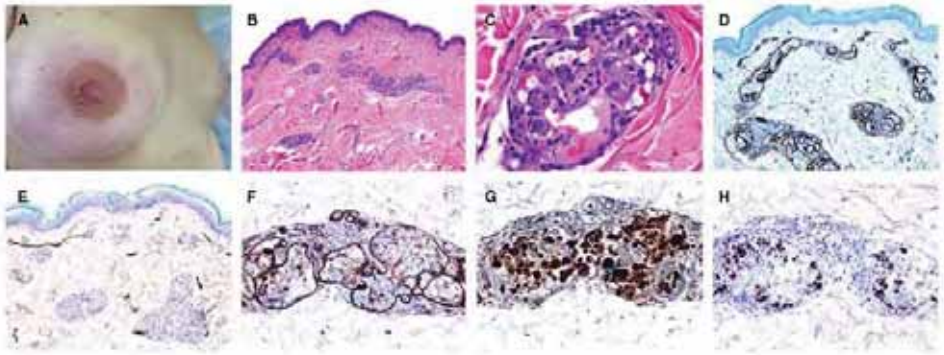


Figure 1. Clinicopathological features of case 1. **A**, Four months after presentation the patient showed intense reticular erythema with a violaceous hue surrounding the areola of both breasts. **B**, Superficial proliferation of capillary vessels that form cohesive aggregates, mainly in the upper dermis. **C**, Capillary vessels filled with large histiocytes showing fragmented granulocytes in their cytoplasm (haemophagocytosis). **D**, CD34 staining highlights the well-demarcated areas of vascular proliferation and is negative in the intravascular cell collections. **E**, D2-40 immunoreactivity demonstrates the presence of a small number of lymphatic vessels but is negative in the vascular proliferation. **F**, CD31 is positive in the vessel walls and also in many histiocytes. **G**, CD68-KP1-positive intravasenlar histiocytes. **H**, Myeloperoxidase staining positive in the partially digested granulocytes present in the cytoplasm of most macrophages.

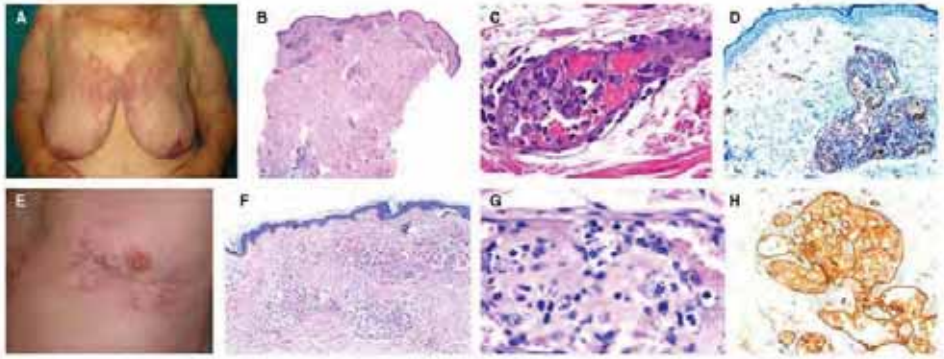
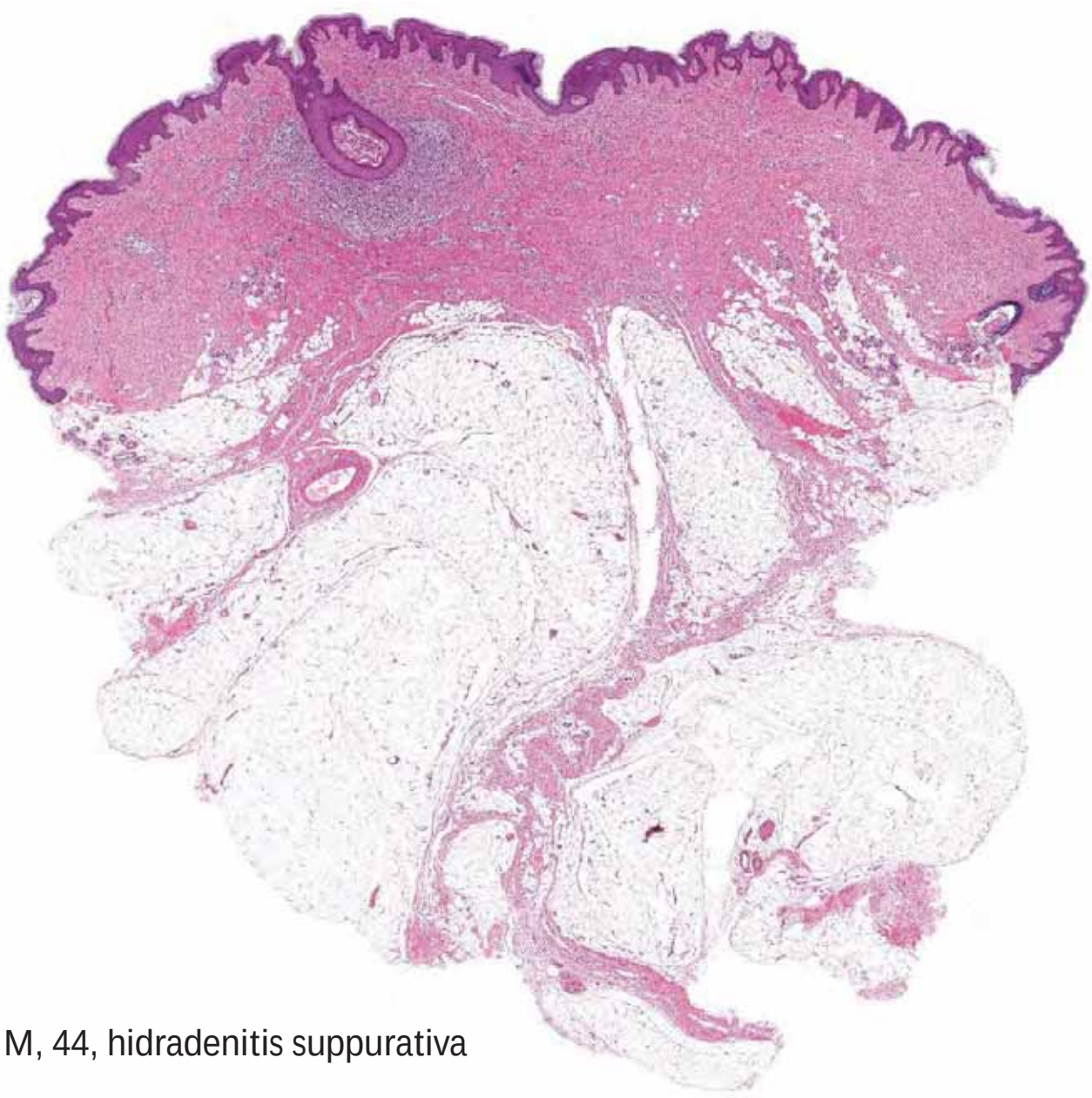


Figure 2. Clinicopathological features of cases 2 (**A–D**) and 3 (**E–H**). **A**, The patient presented with reticular erythema involving the anterior and posterior aspects of the thorax, including her breasts as well as the proximal upper limbs. **B**, Proliferation of capillary vessels forming cohesive aggregates in the upper and deep dermis. **C**, Capillary vessel with dilated lumina containing many histiocytes with fragmented granulocytes in their cytoplasms (haemophagocytosis). **D**, CD31 immunohistochemical staining in blood vessel and some histiocytes. **E**, Telangiectatic confluent erythema in the upper chest area of case 3. **H**, Interconnected capillary vessels and venules in the upper and mid dermis were filled with histiocytes. **G**, Dilated capillary vessels filled with histiocytes containing fragments of granulocytes cells in their cytoplasm. **H**, CD31 immunohistochemical staining was taken up by both histiocytes and blood vessel endothelial cells.

Intravascular (intralymphatic) histiocytosis

- Clusters of histiocytes within lymphatic vessels (in rare cases within blood vessels); may mimic intravascular large cell lymphoma
- Cells CD68+, CD163+ and negative for lymphoid markers; vessels positive for podoplanin in the vast majority of cases
- Association with rheumatoid arthritis more common than mere chance would explain (part of a macrophage activation syndrome?)
- "Localized" cases observed in different settings (particularly in chronic recurrent infections / inflammation, e.g. recurrent erysipelas)



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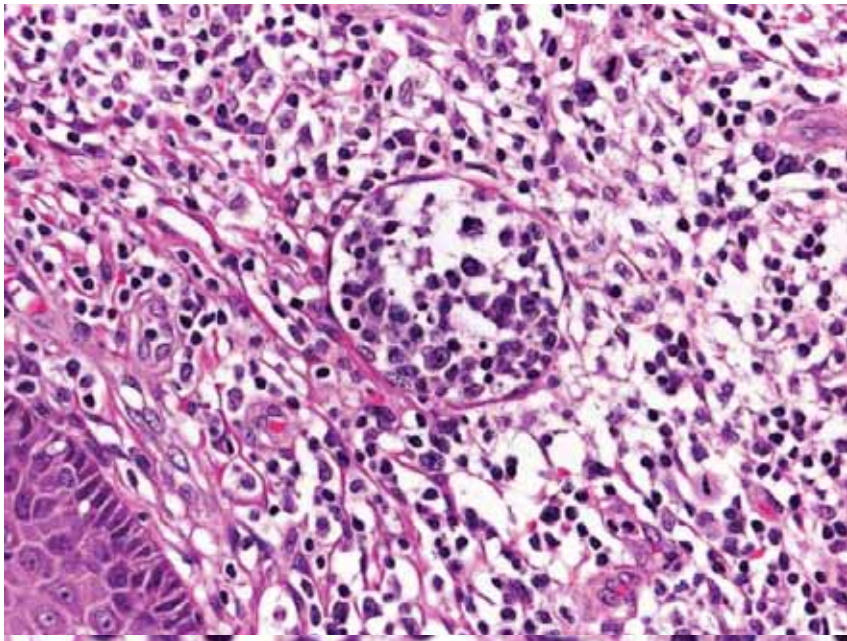
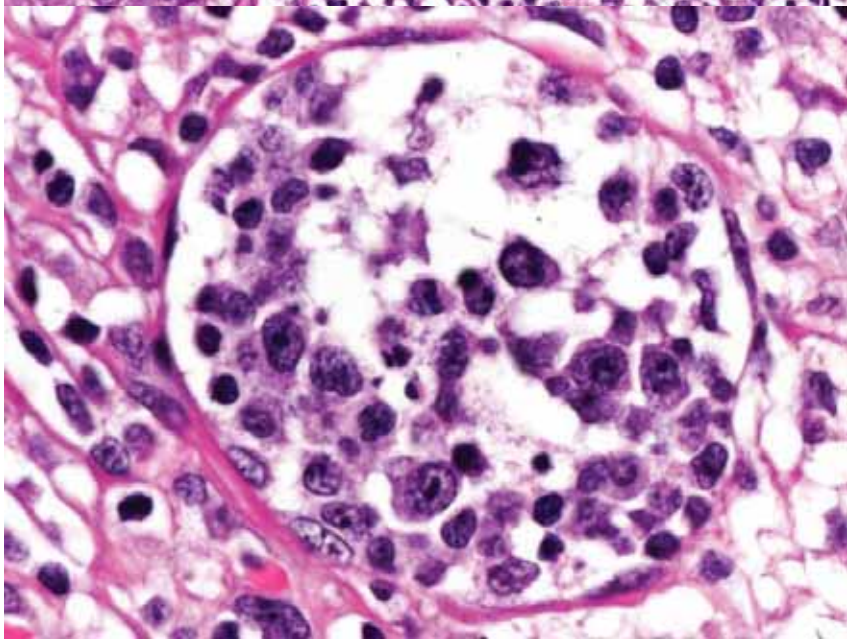
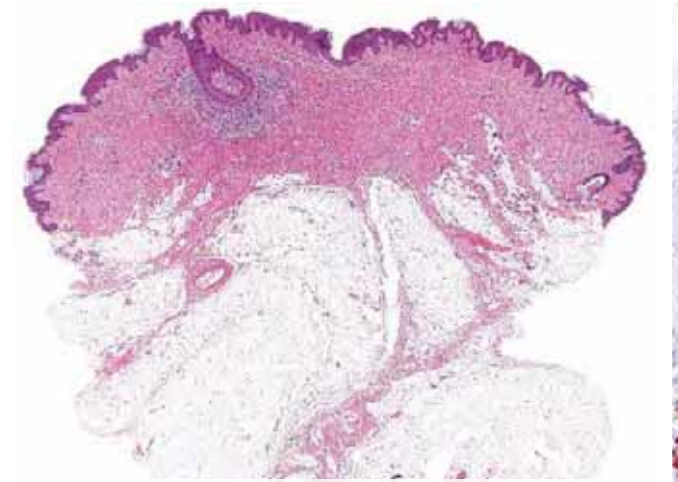
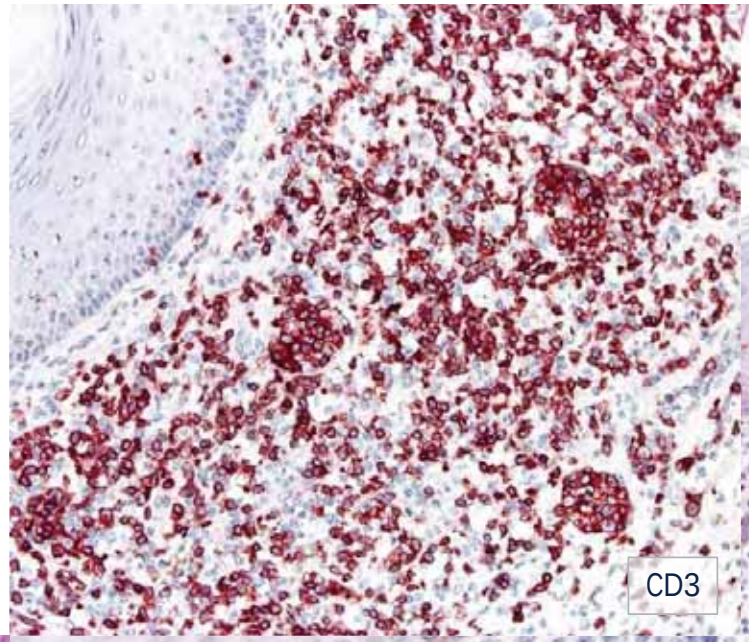
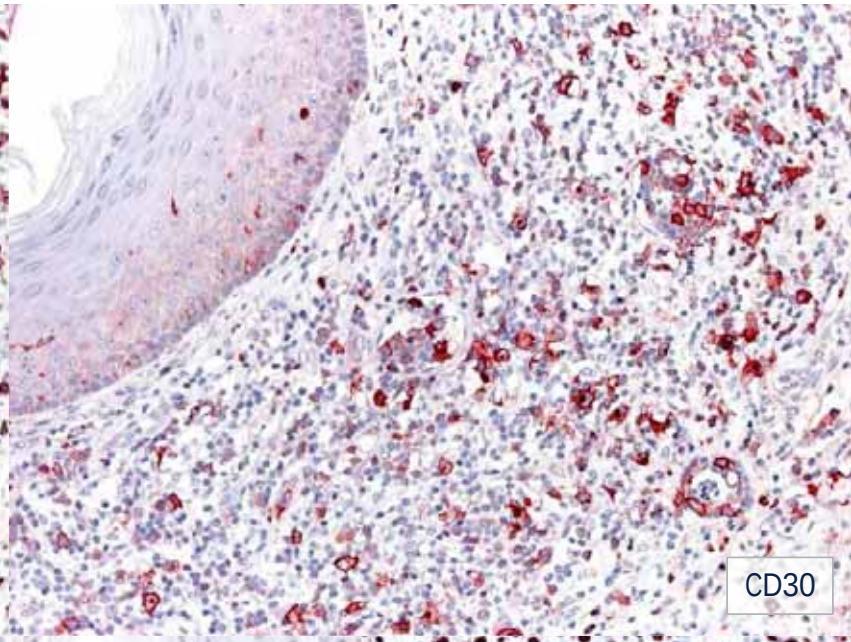


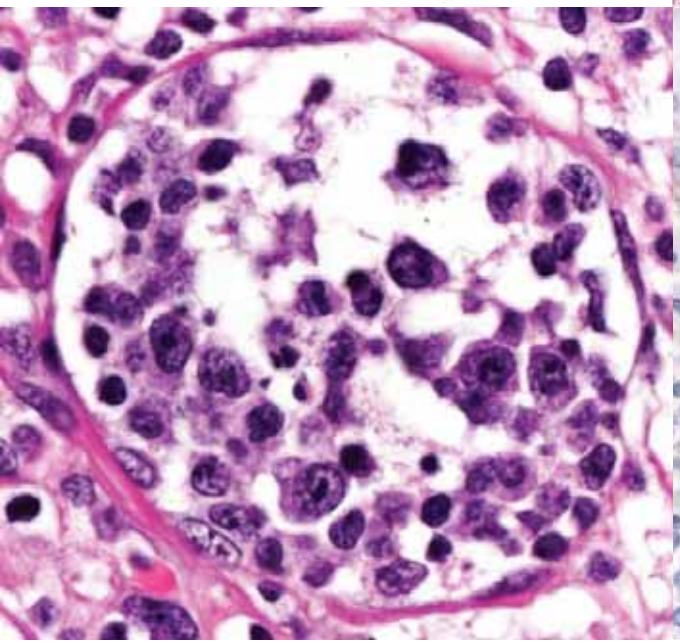


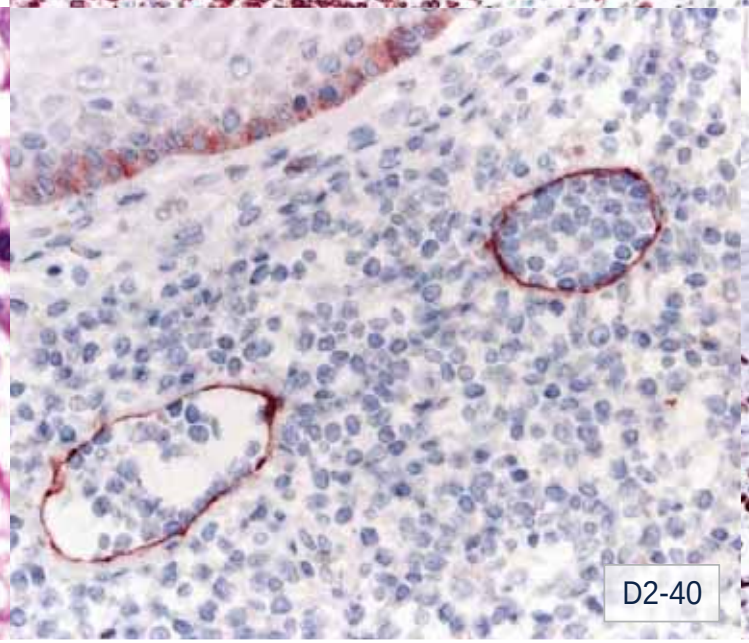


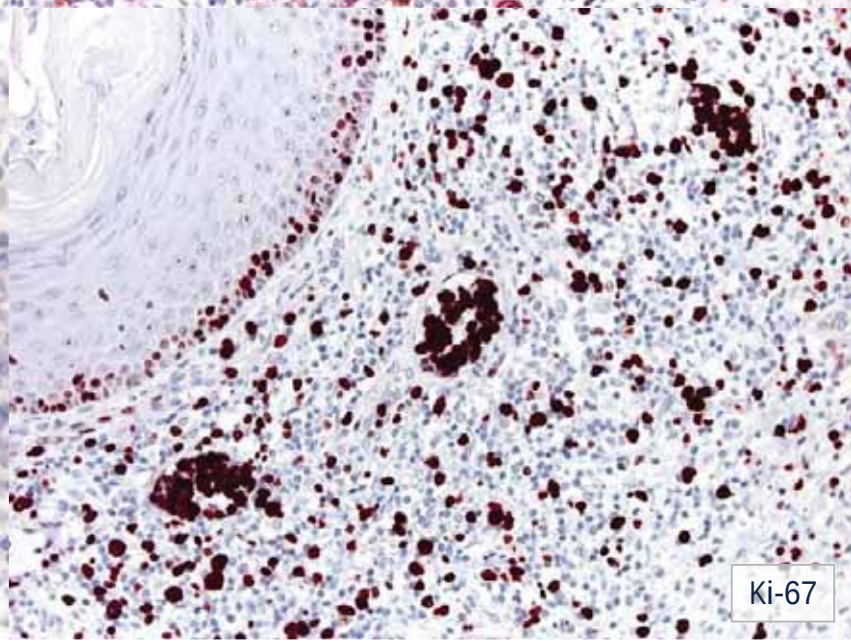
Benign intralymphatic proliferation of T-cell blasts











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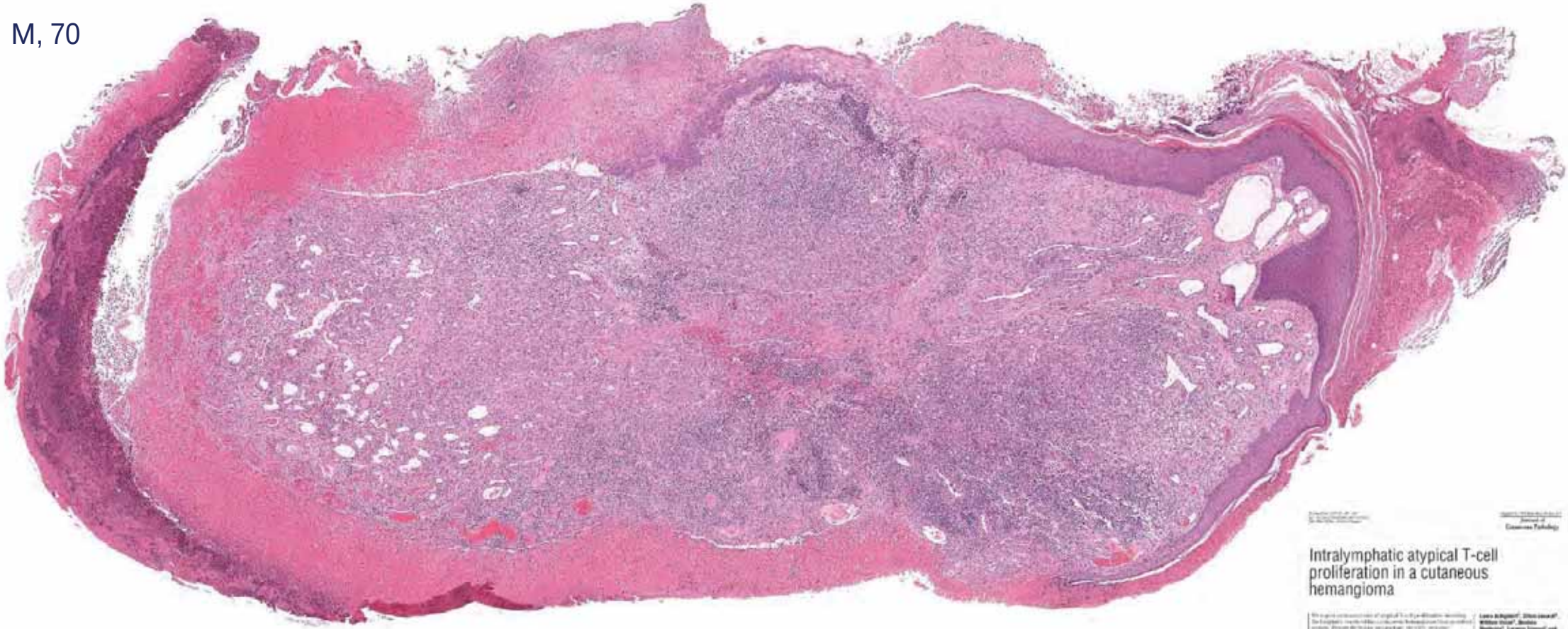

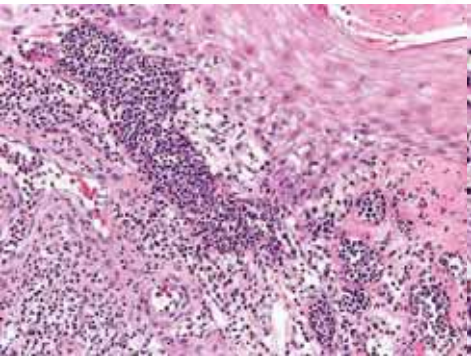

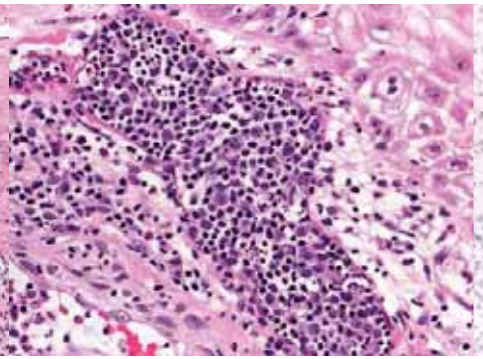

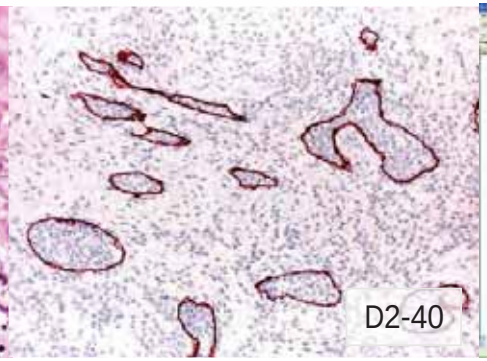

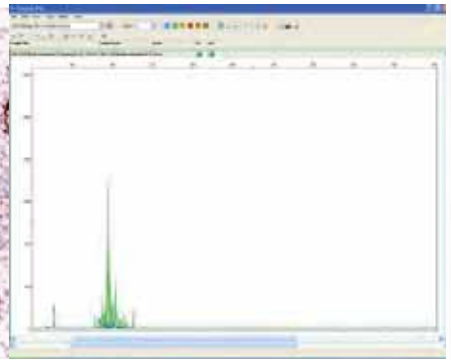

Intralymphatic atypical T-cell proliferation in a cutaneous hemangioma

Benign intralymphatic proliferation of T-cell blasts

- Most reported cases observed in a "microorganism-rich" environment
- May be related to a local infection triggering the activation and proliferation of a T-cell subclone trafficking to and from the regional lymph nodes
- Usually CD30+ T-cell phenotype with high Ki-67; cytotoxic markers negative; no association with EBV; polyclonal pattern of the TCR genes
- Positive staining for podoplanin in affected vessels rules out intravascular large cell lymphoma
- Presence of a prominent inflammatory response outside of the affected vessels rules out intralymphatic cALCL (LyP may remain a differential diagnosis, but features of the background condition usually allow a clear-cut distinction)

PSEUDOLEUKEMIA CUTIS

Report of a Case in Association with Molluscum Contagiosum

A. BERNARD ACKERMAN, MD, AND EUGENE V. TANSKI, MD

Histologic sections from a solitary cystic cutaneous lesion that showed atypical mononuclear cells in the dermis and within blood vessels were diagnosed by several general pathologists and dermatopathologists as leukemia cutis. The patient, who had no other cutaneous lesions, was consequently submitted to an extensive investigation for leukemia, which proved negative. Additional and deeper sections from the original block revealed that the cellular infiltrate so suspicious of leukemia cutis was secondary to rupture of a lesion of molluscum contagiosum. The correct histopathologic diagnosis, therefore, was pseudoleukemia cutis. The lessons of the case are that 1) further study of the specimen, solitary as it was and asymptomatic as the patient was, would have obviated worry and the expense and inconvenience of an extensive systemic investigation, and that 2) the diagnosis of leukemia cutis should never be made solely on the basis of histologic sections of skin, but rather after examination of blood and bone marrow.

Cancer 40:813–817, 1977.

CERTAIN CAVEATS PERTAINING TO THE INTERpretation of histopathology of the skin cannot be emphasized too firmly or too often. One such caution relates to making an unqualified diagnosis of leukemia cutis solely on the basis of histologic findings in a lesion of the skin. The consequences of such premature conclusions are here reported in a case that may be as instructive to others as it was to us.

CASE REPORT

A 37-year-old woman had a "cyst" of 11 months duration on the right lower eyelid. It was removed *in toto* by surgical excision and histologic sections were interpreted by a general pathologist as leukemia cutis. For greater certainty, the slides were sent in consultation to the Armed Forces Institute of Pathology (AFIP Accession No. 1475626) where a diagnosis of "malignant neoplastic infiltrate, probably granulocytic leukemia, eyelid" was also made. A diagnosis (#1122-74) of "metastatic lesion, lymphoma or lymphomatoid papulosis" was rendered by the Department of Eye Pathology of the Northwestern University School of Medicine. The Dermatopathology Section of the Skin and Cancer Unit of New York University School of Medicine also interpreted the changes as those of leukemia cutis. All saw a moderately dense, mixed infiltrate of lymphocytes, histiocytes, plasma cells, eosinophils, and especially atypical mononuclear cells throughout the dermis. In addition to their interstitial distribution, the atypical mononuclear cells were found in large numbers within widely dilated endothelial-lined spaces (Fig. 1a & b)

Despite the fact that the cutaneous lesion was solitary, and solely on the basis of the histologic diagnosis of leukemia cutis, which had been concurred in by most of the pathologists who had examined the tissue, the patient (a doctor's wife) was admitted to the M.D. Anderson Tumor Institute for thorough systemic investigation. Findings of complete routine examination and special studies of the blood and bone marrow were completely normal.

Perplexed by the contradiction between the dire histologic interpretation and the negative clinical and other laboratory findings, we obtained the original block of the cutaneous specimen and cut deeper sections through it. To our amazement, and embarassment, those sections revealed molluscum bodies within the cornified cells of an epithelial, cyst-like structure (Fig. 2) that had ruptured. In these sections, too, within the lumina of the dilated blood vessels surrounding the cystlike lesion of molluscum contagiosum, there were many of those atypical mononuclear cells that were previously so misleading (Fig. 3a & b)

DISCUSSION

One may only wonder worriedly about the phenomenon of rupture of a lesion of molluscum

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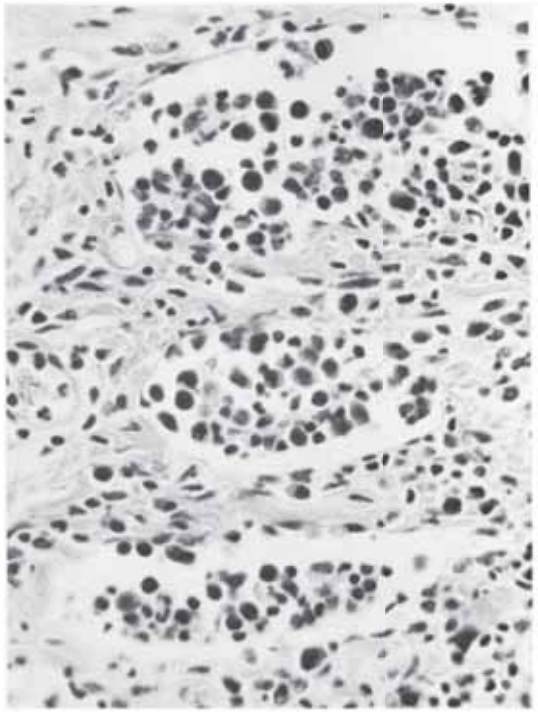

FIG. 1b. Higher power of Fig. 1a showing atypical mononuclear cells in the stromal infiltrate and within three vascular spaces (×680).

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Blackwell Munksgaard, Printed in Singapore

Journal of
Cutaneous Pathology

Atypical intravascular CD30+ T-cell proliferation following trauma in a healthy 17-year-old male: first reported case of a potential diagnostic pitfall and literature review

Herein, we present the first report of a reactive atypical intravascular CD30+ T-cell proliferation. Our patient developed the condition after trauma, and he has followed a benign clinical course. This observation represents a potential diagnostic pitfall for intravascular lymphoma and adds to the list of reactive conditions that may be associated with an atypical CD30+ T-cell infiltrate.

Baum CL, Stone MS, Liu V. Atypical intravascular CD30+ T-cell proliferation following trauma in a healthy 17-year-old male: first reported case of a potential diagnostic pitfall and literature review. J Cutan Pathol 2009; 36: 350–354. © Blackwell Munksgaard 2008.

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A number of cutaneous entities have been described in which the corresponding histology shows a population of CD30+ lymphocytes. These conditions may be categorized within a spectrum according to density of the atypical infiltrate and clinical prognosis. The end of the spectrum with a benign prognosis includes inflammatory conditions such as atopic dermatitis[1] and arthropod bite reactions.[2] In the middle are forms of CD30+ lymphoproliferative disorders, which include lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma.[3] The end of the spectrum with the least favorable prognosis includes cutaneous Hodgkin's lymphoma[4] and cutaneous involvement of nodal anaplastic large cell lymphoma.[5]

Intravascular lymphoma is a rare condition with myriad clinical manifestations. In general, it affects patients in the sixth or seventh decade of life and portends a poor prognosis. Often, patients present with advanced disease or the diagnosis is made at autopsy.[5,6–8] The vast majority of cases involve malignant B cells, although T-cell variants have been reported.[6–8] A recent review examining all reports of intravascular lymphoma in the literature identified 224 patients; approximately 10% of patients had cutaneous manifestations of the disease. Of 119 cases of intravascular lymphoma reported since 1986, 72% (n = 86) were B-cell lymphoma and 23% (n = 33) were T-cell lymphoma.[7]

To our knowledge, there are no reports in the literature describing intravascular atypical CD30+ lymphocytic proliferations associated with a benign clinical course. There are two case reports of CD30+ T-cell intravascular lymphoma in the literature and both were associated with an aggressive clinical course.[9,10] Herein, we report a case of a 17-year-old male who developed a solitary plaque after trauma that histologically showed an atypical CD30+ intravascular proliferation. This case is noteworthy because of its benign clinical course, its expansion of the spectrum of cutaneous reactive states with CD30+ T-cell infiltrates and because it highlights a potential histologic diagnostic pitfall.

Case report

A 17-year-old Caucasian male presented to his primary physician for a 7- to 8-week history of a lesion

Benign Atypical Intravascular CD30+ T-Cell Proliferation: A Recently Described Reactive Lymphoproliferative Process and Simulator of Intravascular Lymphoma

Report of a Case Associated With Lichen Sclerosus and Review of the Literature

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Key Words: CD30; T-cell; Lymphoproliferation; Intravascular; Benign; Atypical; Lymphomatoid Skin

ABSTRACT

Objectives: *Intravascular accumulations of atypical large lymphoid cells are a rare finding in skin biopsy specimens and raise the suspicion for intravascular lymphoma. The intravascular accumulation of atypical large CD30+ T cells, however, as a reactive process is very uncommon in the skin, with only four cases documented so far in the literature. This condition, referred to as benign intravascular atypical CD30+ T-cell proliferation, has been associated with chronic inflammation after trauma.*

Methods: *We report on a case of atypical intravascular CD30+ T-cell proliferation in a patient with ulcerated lichen sclerosus on the foreskin, discuss the differential diagnoses, propose diagnostic criteria, and review the literature on this uncommon reactive intralymphatic CD30+ T-cell lymphoproliferation.*

Results: *The atypical intravascular CD30+ T-cell proliferation is characterized by the accumulation of large CD30+ polyclonal T cells within lymphatics in close vicinity to ulceration or an inflammatory skin disease. There is no association with Epstein-Barr virus infection.*

Conclusions: *This benign cutaneous lymphoproliferation needs to be distinguished from intravascular T-cell lymphoma, particularly from the intravascular variant of anaplastic large cell lymphoma. Obstruction of lymphatics due to lichen sclerosus with disrupted immune cell trafficking may result in the accumulation of activated CD30+ lymphocytes.*

The presence of intravascular large atypical lymphocytes raises the suspicion for intravascular lymphoma (IVL) or leukemia. IVL is an aggressive disease, which most commonly represents a diffuse large B-cell lymphoma with predominantly intravascular growth, but a very rare T-cell variant has been described, including cases with expression of CD30 by tumor cells.[1,2] On the other hand, primary cutaneous CD30+ lymphoproliferative diseases (CD30+ LPDs) encompass a spectrum of diseases such as lymphomatoid papulosis (LyP), primary cutaneous anaplastic large-cell lymphoma (ALCL), and so-called borderline lesions, with all exhibiting an excellent prognosis.[3–5] The tumor cells in CD30+ LPDs mostly are large pleomorphic or anaplastic T cells. The expression of CD30, however, is not restricted to lymphomas. An increasing number of reactive conditions are known to harbor atypical medium- to large-sized CD30+ T cells, such as infestations, viral infections, and drug eruptions.[6,7] Recently, benign proliferation of intravascular atypical CD30+ T cells as a reactive process due to trauma was described, but so far, only a few cases have been reported.[8,9] We present a case of benign atypical intravascular CD30+ T-cell proliferation occurring in a patient with focally ulcerated lichen sclerosus (LS) on the foreskin and review the literature on this reactive lymphoproliferation, which may mimic IVL.

Case Report

A 46-year-old man had LS with white, sclerotic, focally eroded areas (up to 1 cm in diameter) on the prepuce, which slowly had increased to 7 cm in diameter over several months, before seeking treatment at the department of urology to

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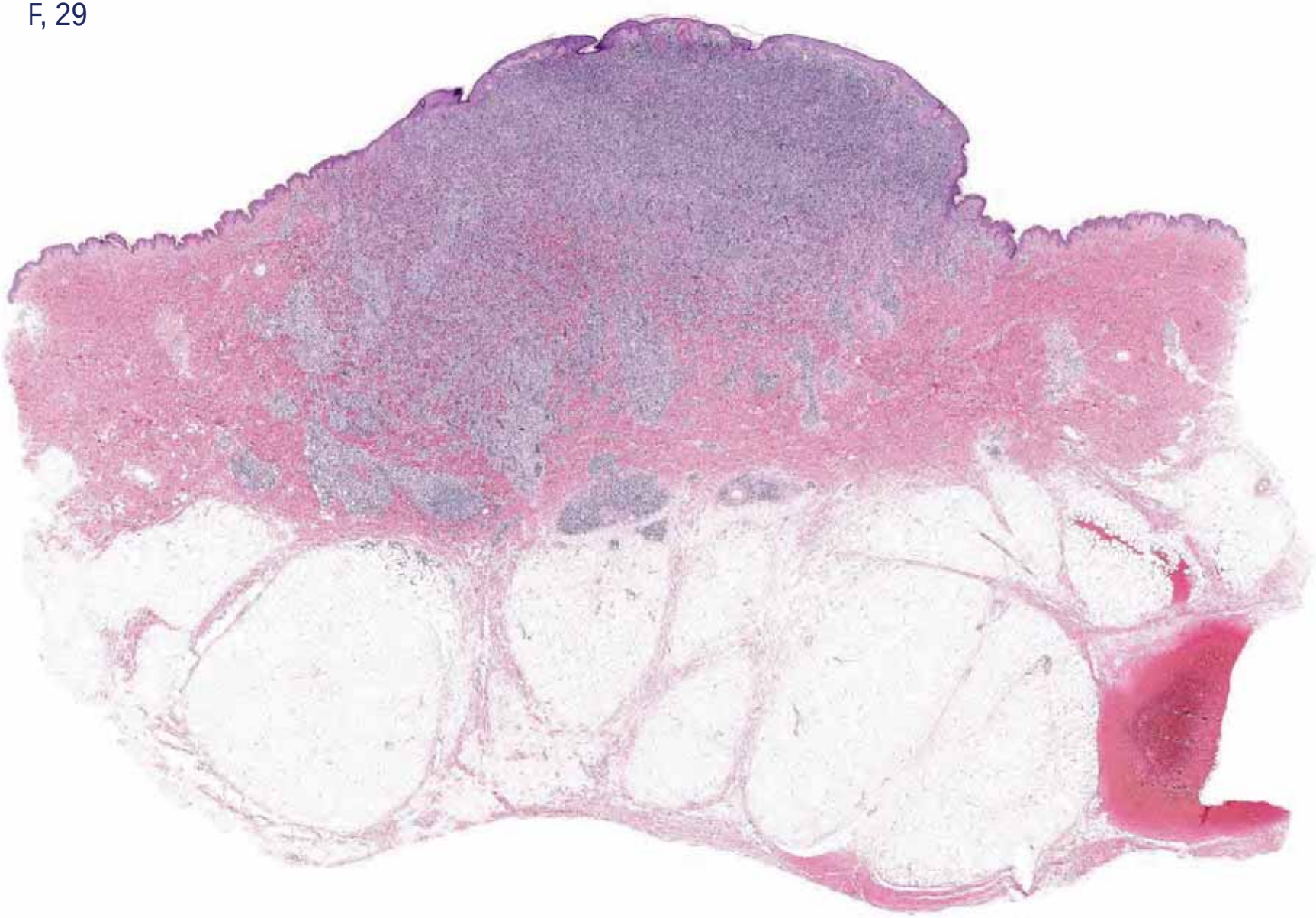
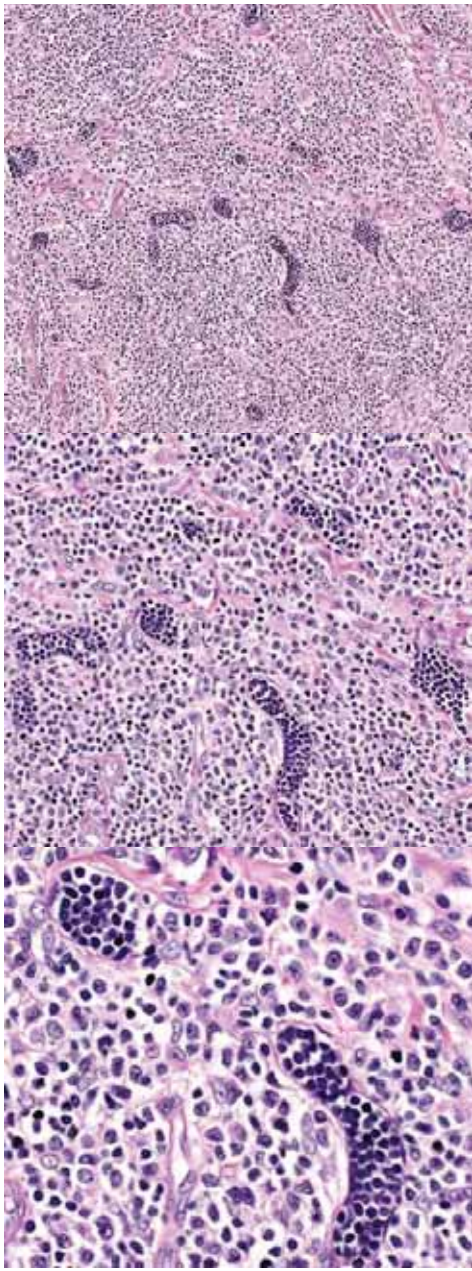
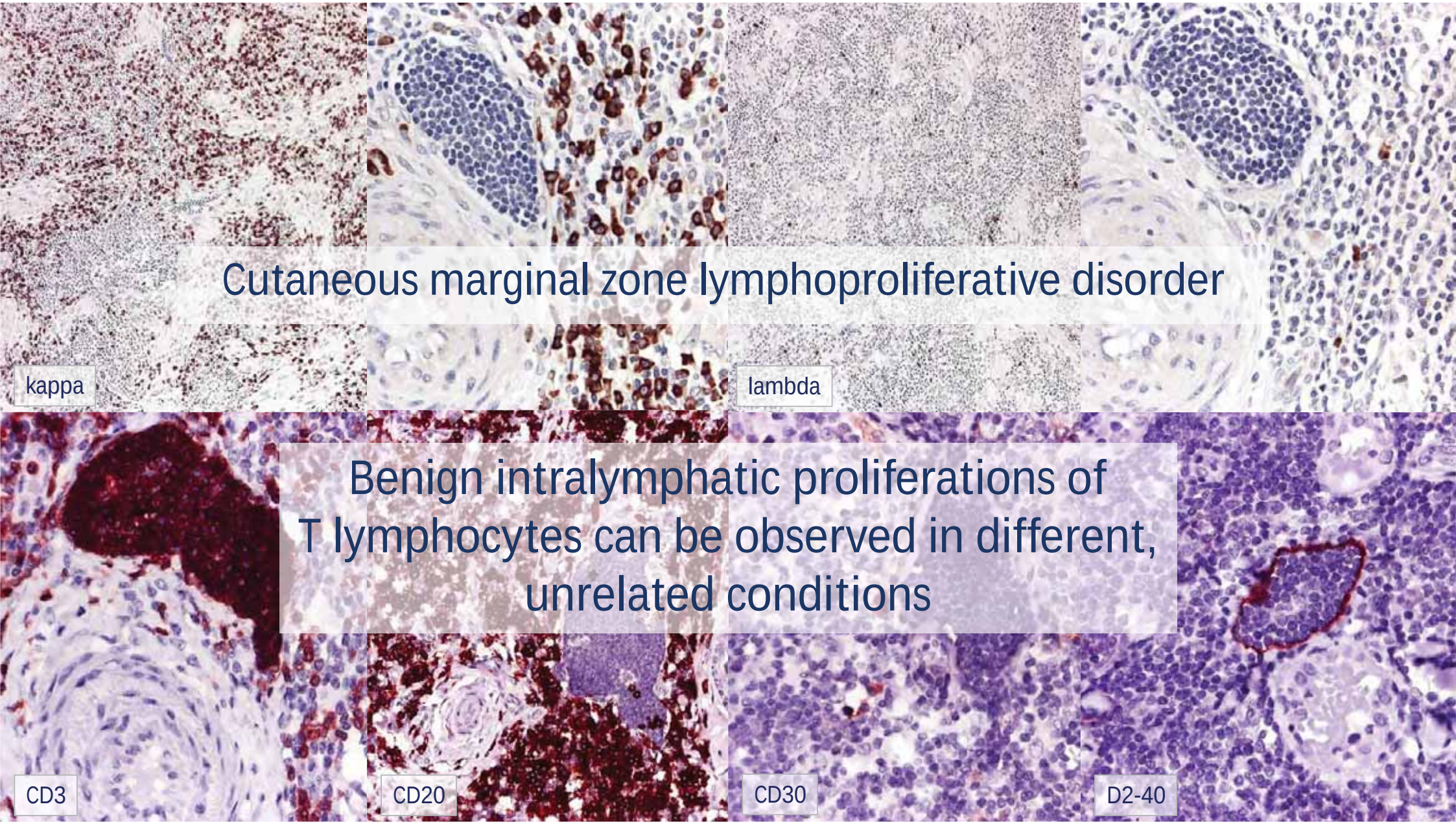





Cutaneous marginal zone lymphoproliferative disorder
kappa
lambda
Benign intralymphatic proliferations of
T lymphocytes can be observed in different,
unrelated conditions
CD3
CD20
CD30
D2-40

Main "intravascular" proliferation of cells

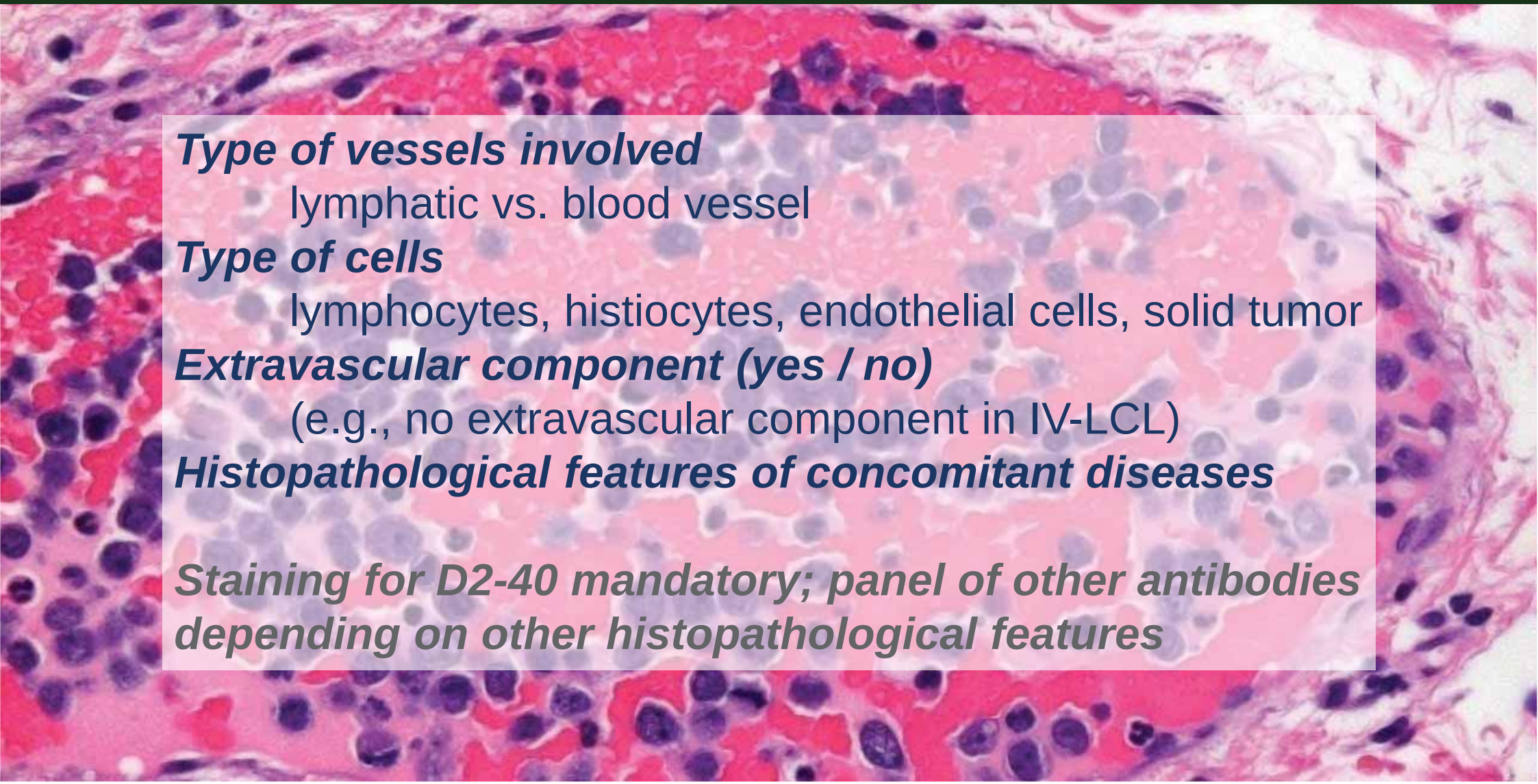
Within blood vessels

- B- and NK/T-cell intravascular diffuse large cell lymphoma
- Diffuse large B-cell lymphoma with intravascular component
- Intravascular angiosarcoma
- Reactive angioendotheliomatosis
- Rare cases of intravascular histiocytosis
- Merkel cell carcinoma (rare)

Within lymphatic vessels

- Intralymphatic cut. anaplastic large cell lymphoma / lymphomatoid papulosis
- Benign intralymphatic proliferation of large T-cell lymphoid blasts
- Intralymphatic histiocytosis
- Merkel cell carcinoma (common)
- Metastases of different types of carcinoma and of other malignant neoplasms

Approach to diagnosis of intraluminal cells



Type of vessels involved

lymphatic vs. blood vessel

Type of cells

lymphocytes, histiocytes, endothelial cells, solid tumor

Extravascular component (yes / no)

(e.g., no extravascular component in IV-LCL)

Histopathological features of concomitant diseases

Staining for D2-40 mandatory; panel of other antibodies depending on other histopathological features