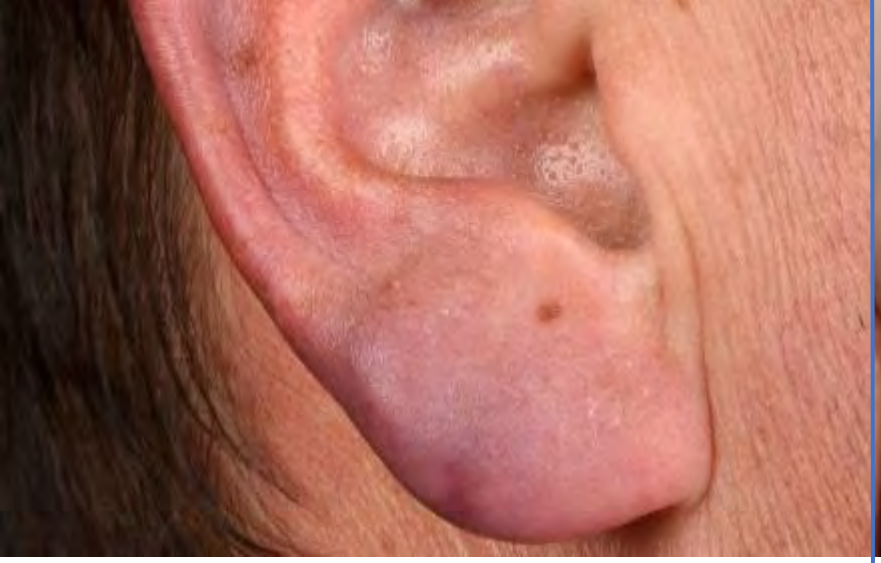
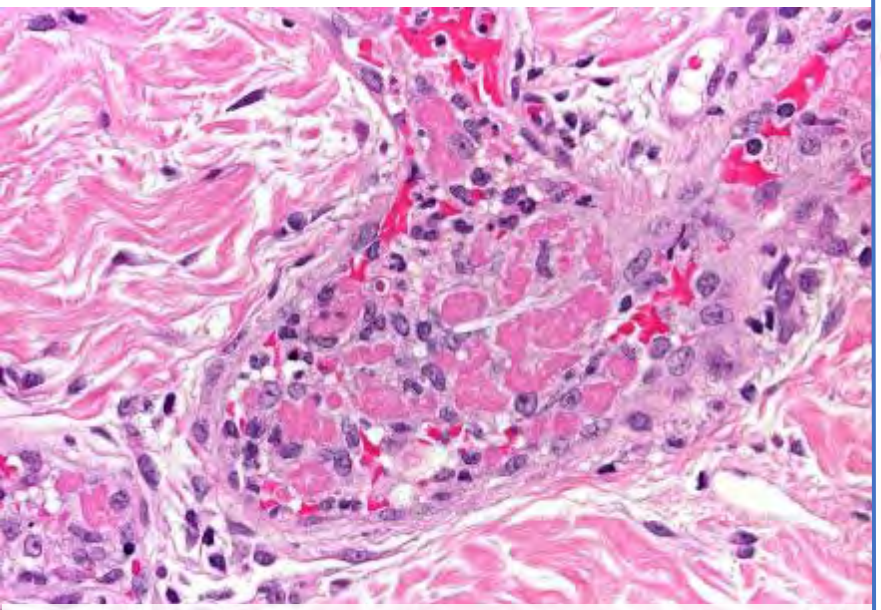
18th Summer Academy of Dermatopathology
Graz, July 6 – 10, 2026

Protean clinicopathological manifestations of skin involvement in leukemia & related disorders

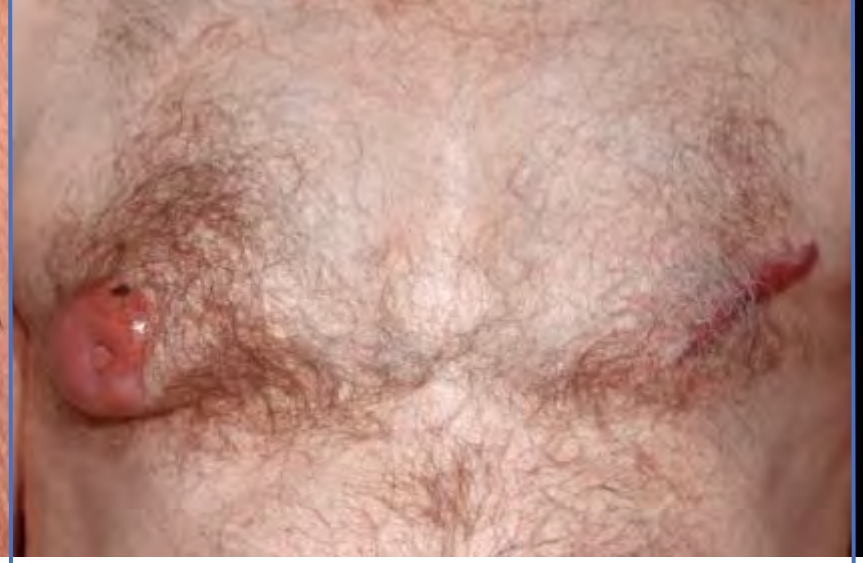
Lorenzo Cerroni



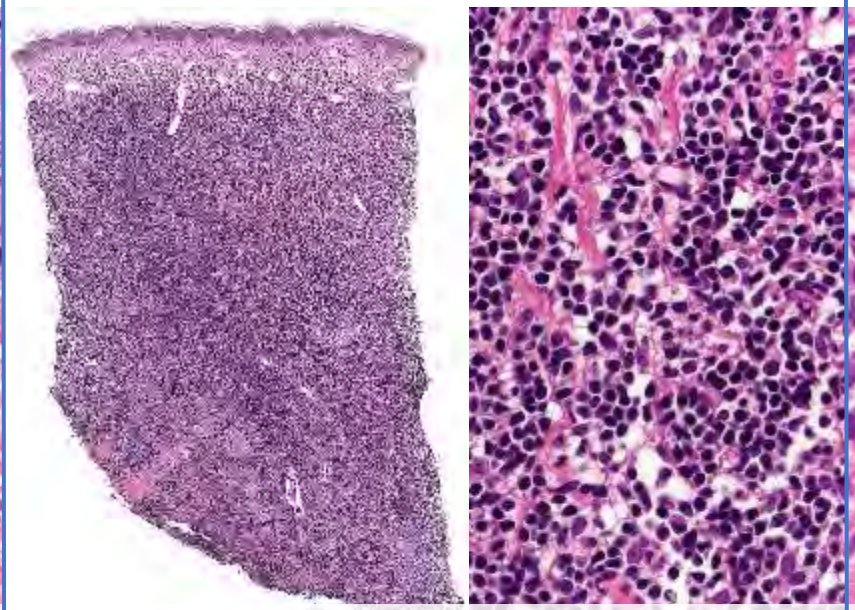
Inflammatory conditions related to hematological malignancies, without specific infiltrates



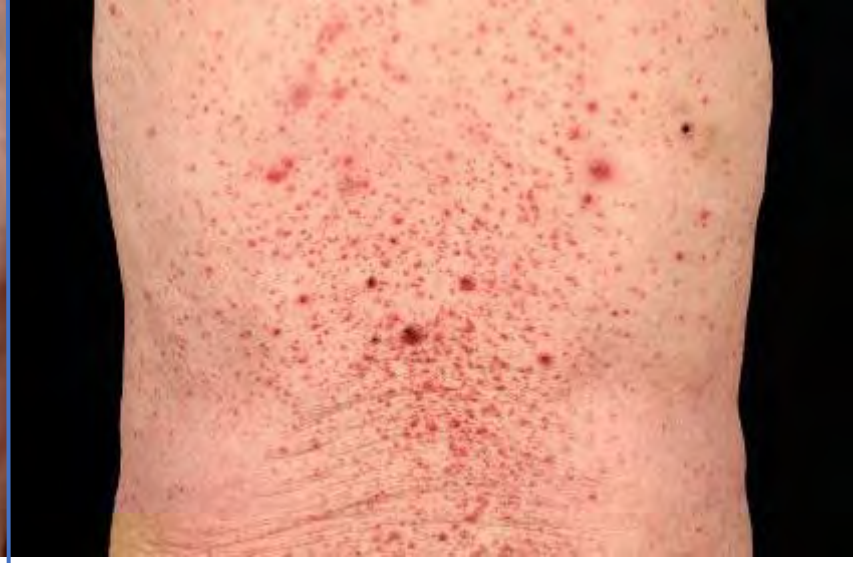
Monoclonal cryoglubulinemia



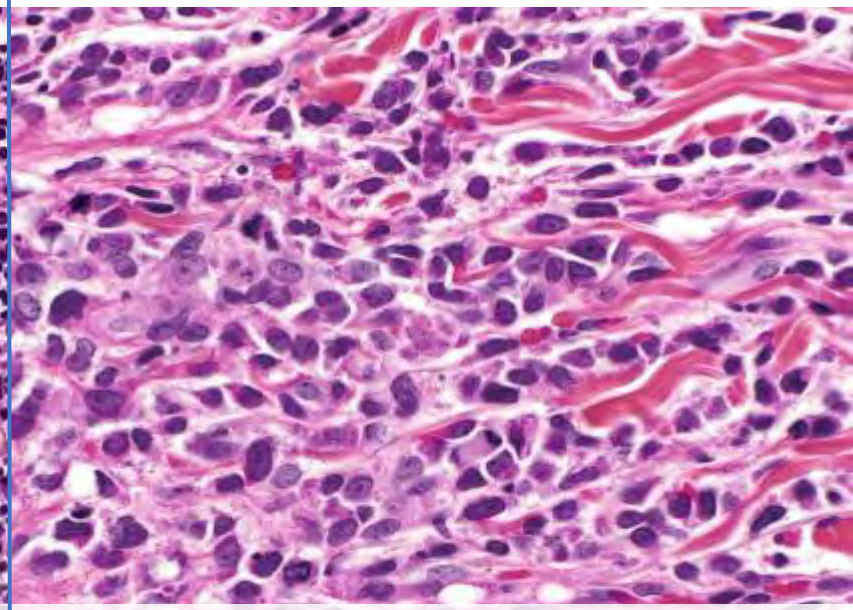
Specific skin infiltrates of a leukemia at sites of cutaneous inflammation / neoplasms



Borrelia-associated B-CLL

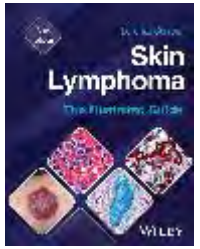


Specific skin infiltrates of a leukemia unrelated to cutaneous inflammation / neoplasms



Cutaneous manifestation of acute myeloid leukemia

Mucocutaneous signs and symptoms that may be associated with systemic lymphomas and leukemias (#)



Associated with tumor-induced or treatment-related bone marrow suppression and resulting cytopenia
Pallor; Bruising; Ecchymoses; Persistent hemorrhages; Purpura, especially petechial; Gingival hemorrhage; Epistaxis; Prolonged bleeding after minor injuries; Oral ulcerations in neutropenic patients

Associated with either tumor-specific or treatment-related immune dysregulation
Opportunistic infections; Unusual presentations of common infections (e.g., vegetating lesions, severe demodicosis – demodex folliculitis; prolongued duration of self-limited infections; severe manifestations of otherwise banal infections)
Trichodysplasia spinulosa
Infection-induced panniculitis
Septic vasculitis (either bacterial or fungal, particularly *aspergillus* sepsis)
Neutrophilic eccrine hidradenitis
Gout due to hyperuricemia in tumor lysis syndrome (after chemotherapy for a rapidly dividing chemosensitive malignancy) (elevated levels of uric acid in the urine are associated with uric acid nephrolithiasis and may cause acute renal failure) ($)
Development of multiple melanocytic nevi after chemotherapy

Associated with autoantibodies produced by the hematologic neoplasm
Paraneoplastic pemphigus ($)
Associa
Cutaneo
Associa
Nodular
Light- a
Crystal
Reactive
Acquire
Associa
Cryoglobulinemic obstructive vasculopathy (type I/II cryoglobulinemia)
Crystalglobulinemia (cryocrystalglobulinemia)
Interstitial crystalglobulinosis
Cryokeratotic follicular spicules

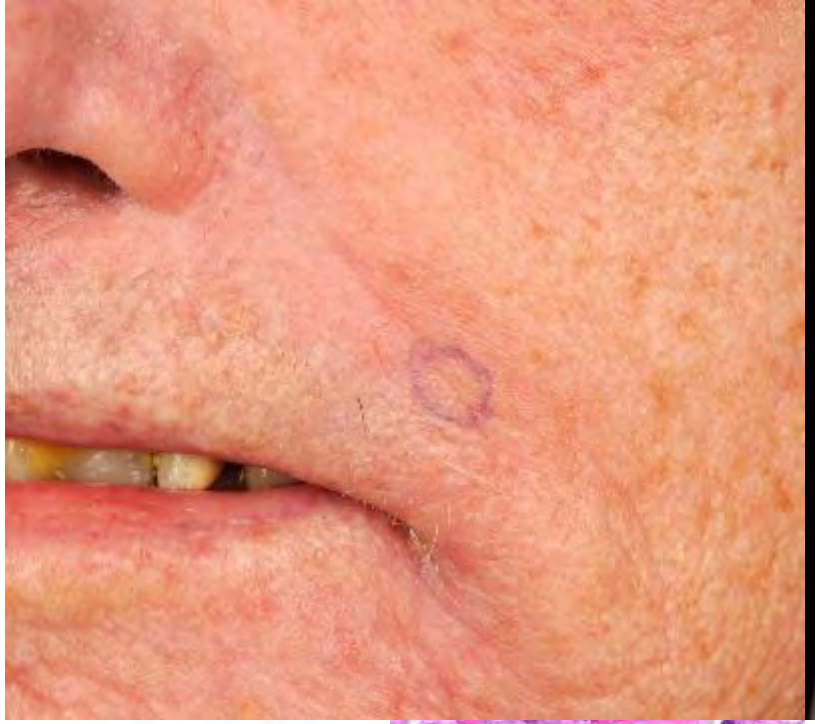
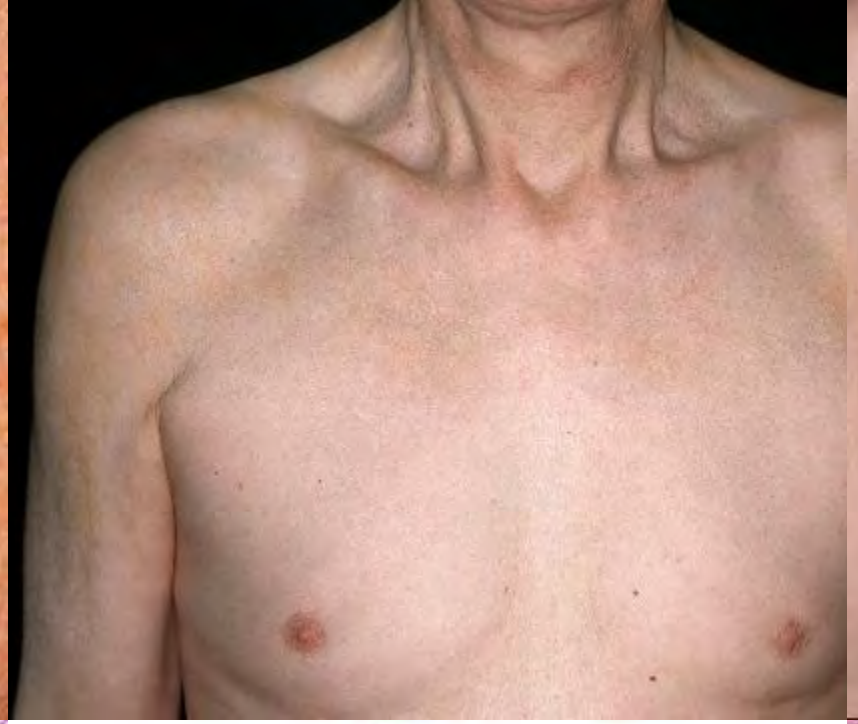
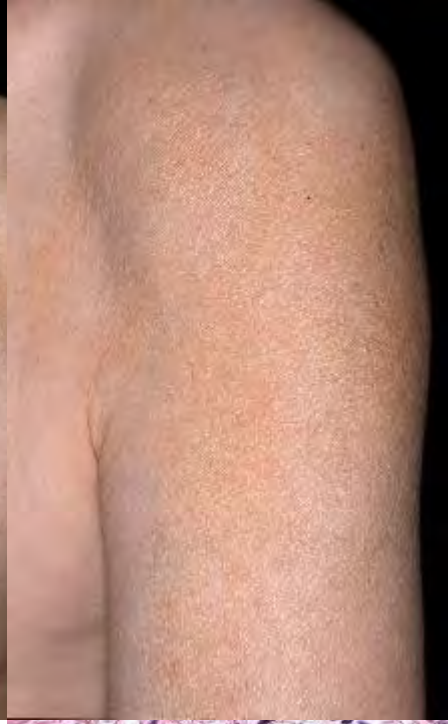
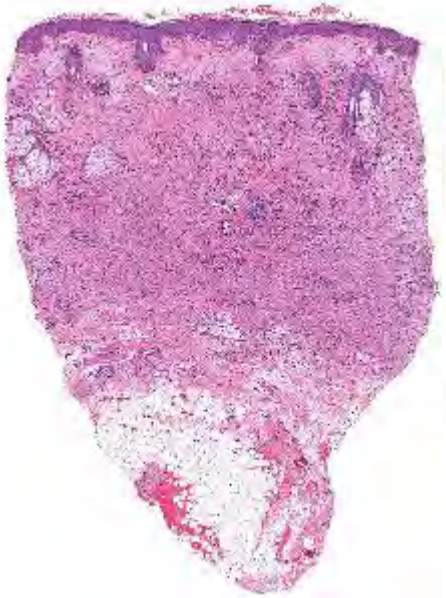
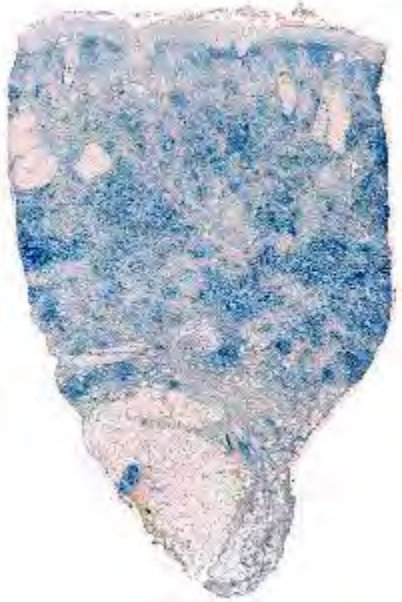
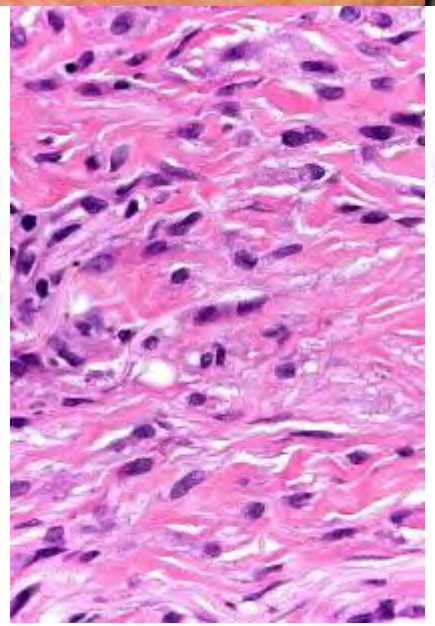
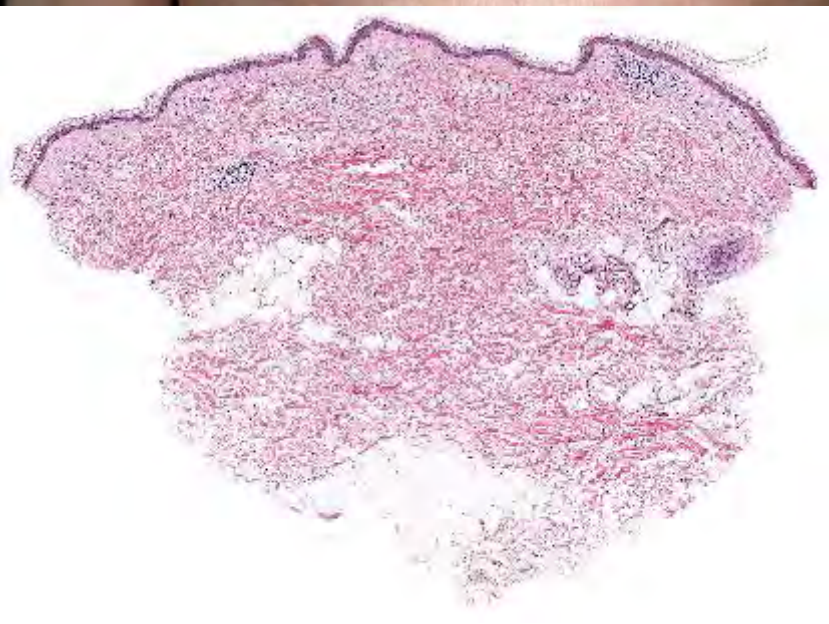
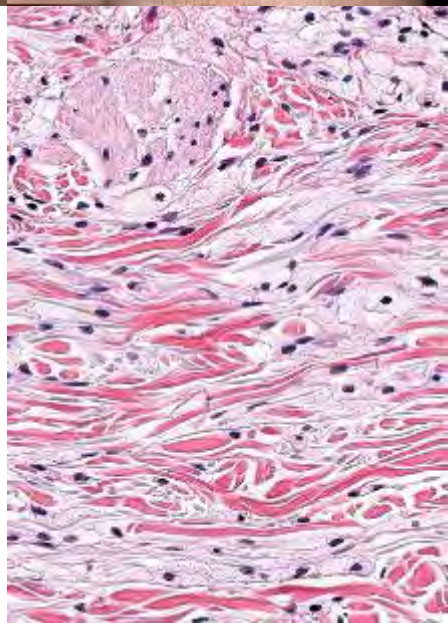
Often / constantly associated with paraproteinemia (without deposition of M-protein) ($)
Scleromyxedema
Scleredema (type 2)
Normolipemic plane xanthomas
Necrobiotic xanthogranuloma
POEMS syndrome *(Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin changes – particularly hyperpigmentation and angiomas)*
AESOP syndrome *(Adenopathy and Extensive Skin Patch Overlying a Plasmacytoma)*
TEMPI syndrome *(Telangiectasias, Elevated erythropoietin and erythrocytosis, Monoclonal gammopathy, Perinephric fluid collection, and Intrapulmonary shunting)*
Schnitzler's syndrome
Subepidermal bullous dermatosis associated with IgM gammopathy
Systemic capillary leak syndrome (Clarkson syndrome)

Occasionally associated with paraproteinemia (without deposition of M-protein)
Sneddon-Wilkinson disease
Localized lichen myxedematosus in HIV-infected patients

Other cutaneous conditions often or occasionally associated with hematological malignancies
Generalized "pruritus sine materia" (particularly in Hodgkin lymphoma)
Sweet syndrome (acute febrile neutrophilic dermatosis), especially the "histiocytoid" variant (particularly in myeloid leukemia) (§)
VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic mutations) syndrome (§)
Bullous pyoderma gangrenosum
Eosinophilic dermatosis of hematological malignancy (exaggerated insect bite-like reaction) ($)
Wells syndrome
Juvenile xanthogranuloma
Generalized eruptive histiocytoma
Xanthoma disseminatum
Langerhans cell histiocytosis
Indeterminate cell histiocytosis
Acquired ichthyosis
Spiny keratoderma
Acquired angioedema due to C1 esterase inhibitor dysfunction
Linear IgA bullous dermatosis
Epidermolysis bullosa acquisita
Calcinosis cutis
Annular elastolytic giant cell granuloma
Cutis verticis gyrata
Paraneoplastic scleroderma-like syndrome (similar to systemic sclerosis, but older age at onset; seen in association with a monoclonal gammopathy, hairy cell leukemia, and solid tumors (e.g. breast, lung)
Papuloerythroderma of Ofuji (in some patients with B-cell chronic lymphocytic leukemia, acute myeloid leukemia, Hodgkin lymphoma or other systemic lymphomas) ($)

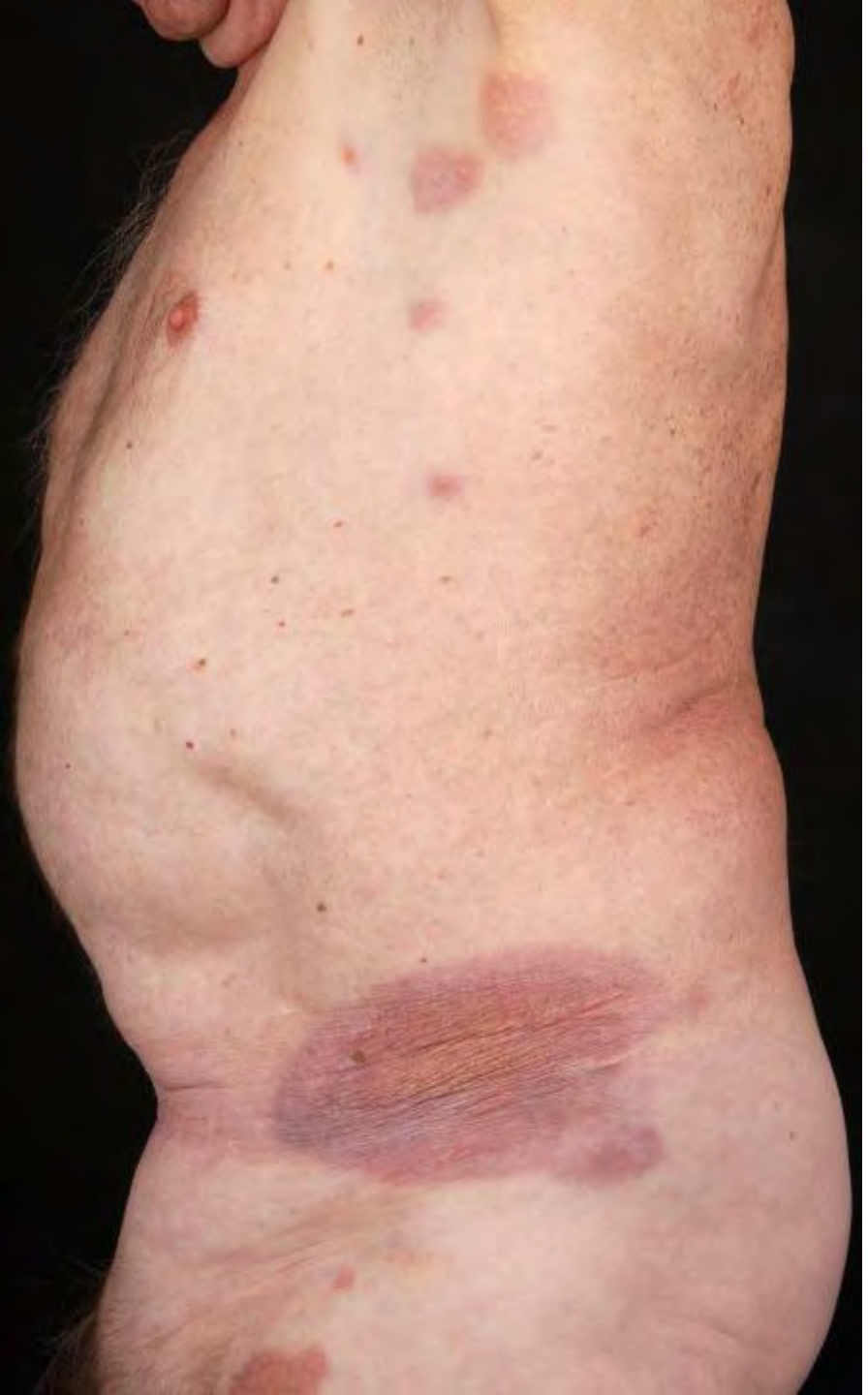
Many skin conditions may be associated with an underlying hematological malignancy

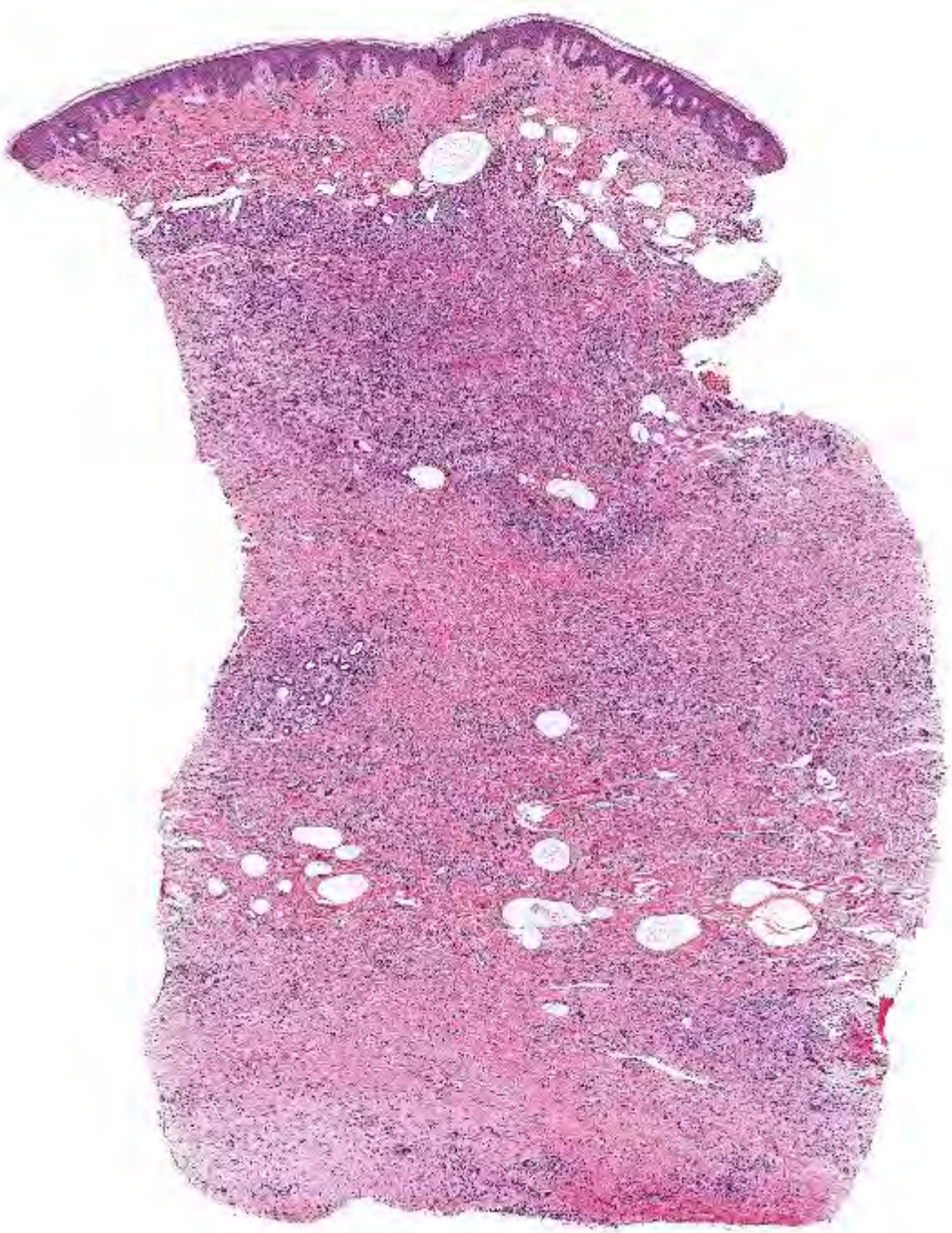
(#) Most of these conditions may be observed also in settings other than hematological neoplasms
($) Observed mostly in the setting of hematological malignancies
(ϕ) Sarcoidosis may antedate the diagnosis of non-Hodgkin lymphoma ("sarcoidosis-lymphoma syndrome") or arise during the course of the disease
(§) Neoplastic cells clonally related to the underlying myeloid neoplasm can be found within the cutaneous infiltrate

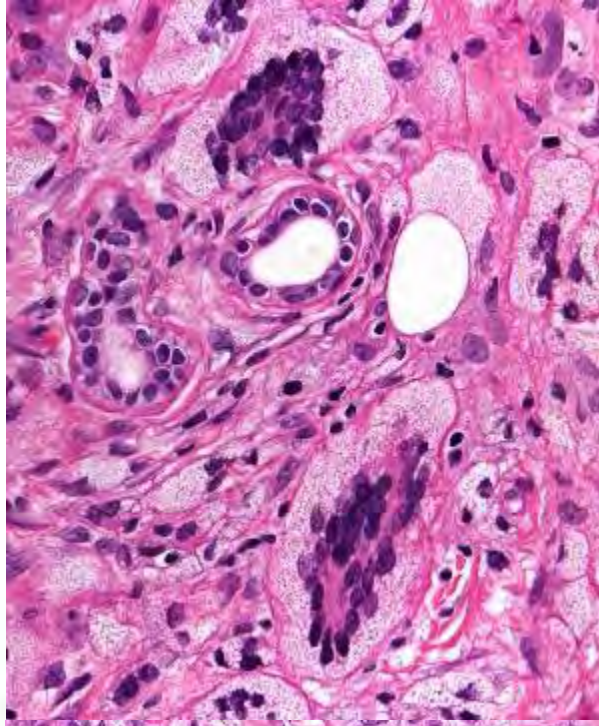









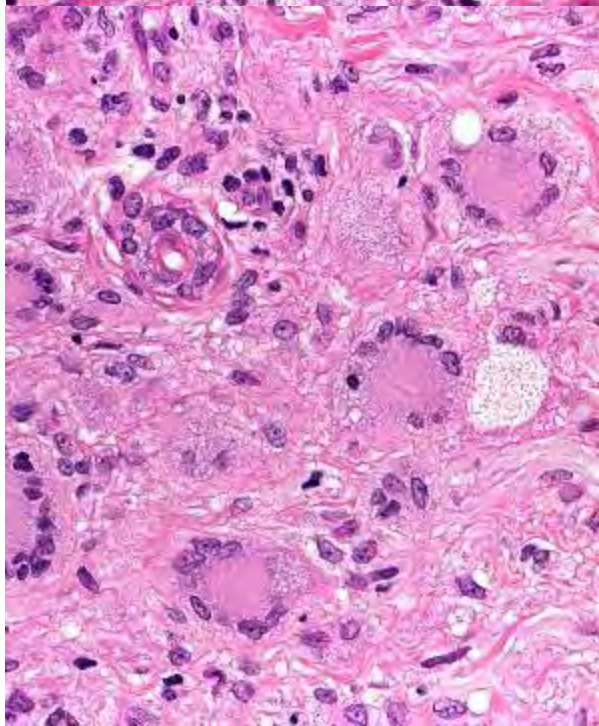
Scleromyxedema

Normolipemic plane xanthomas

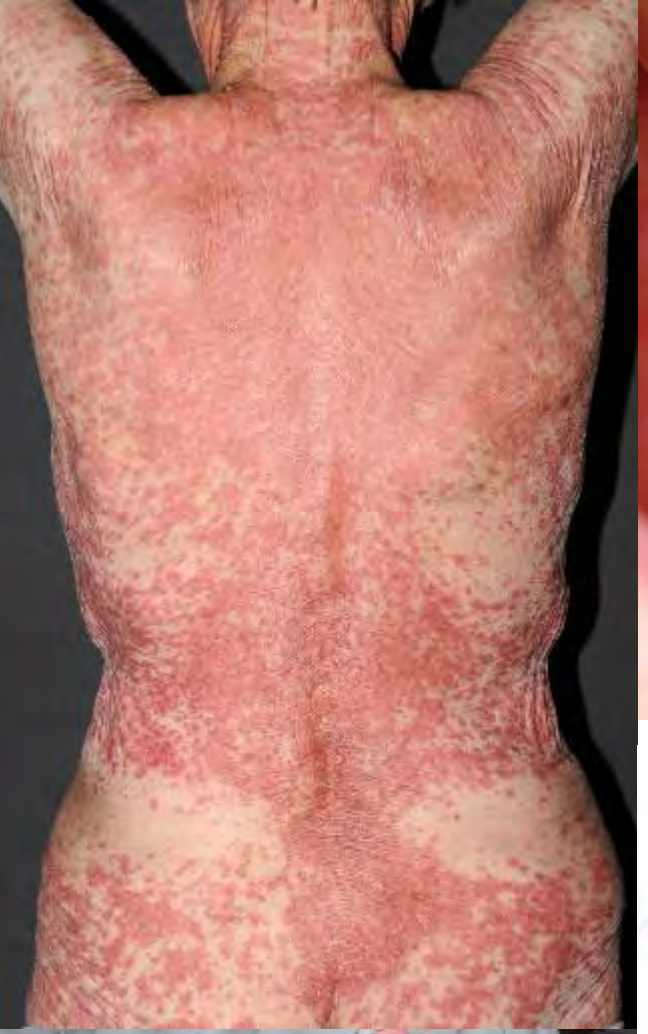


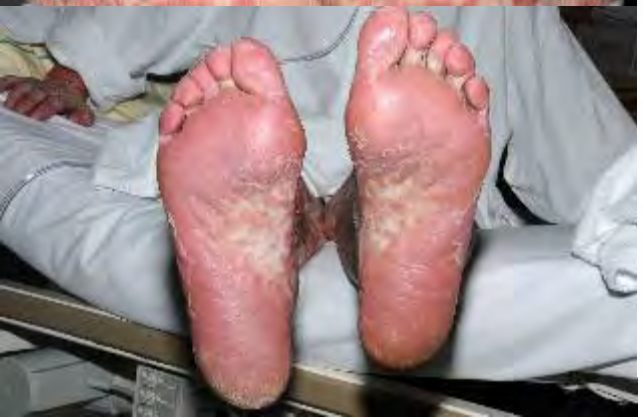


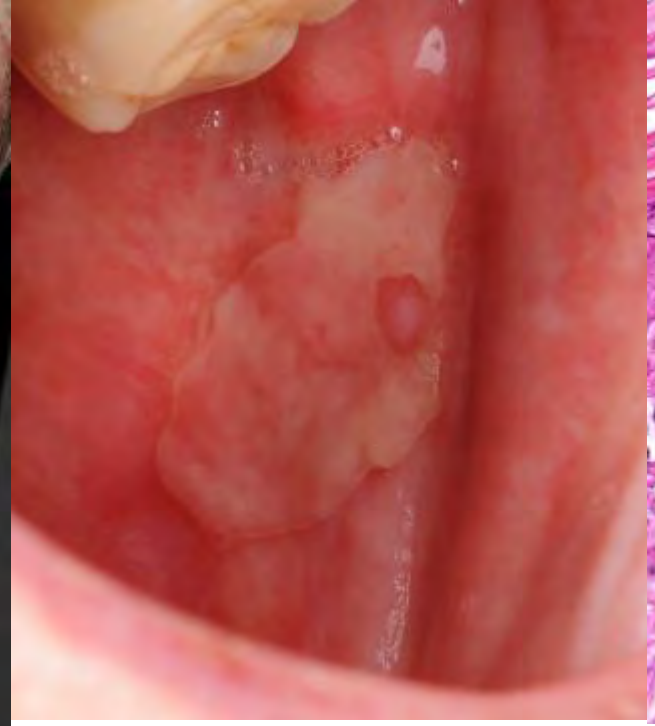


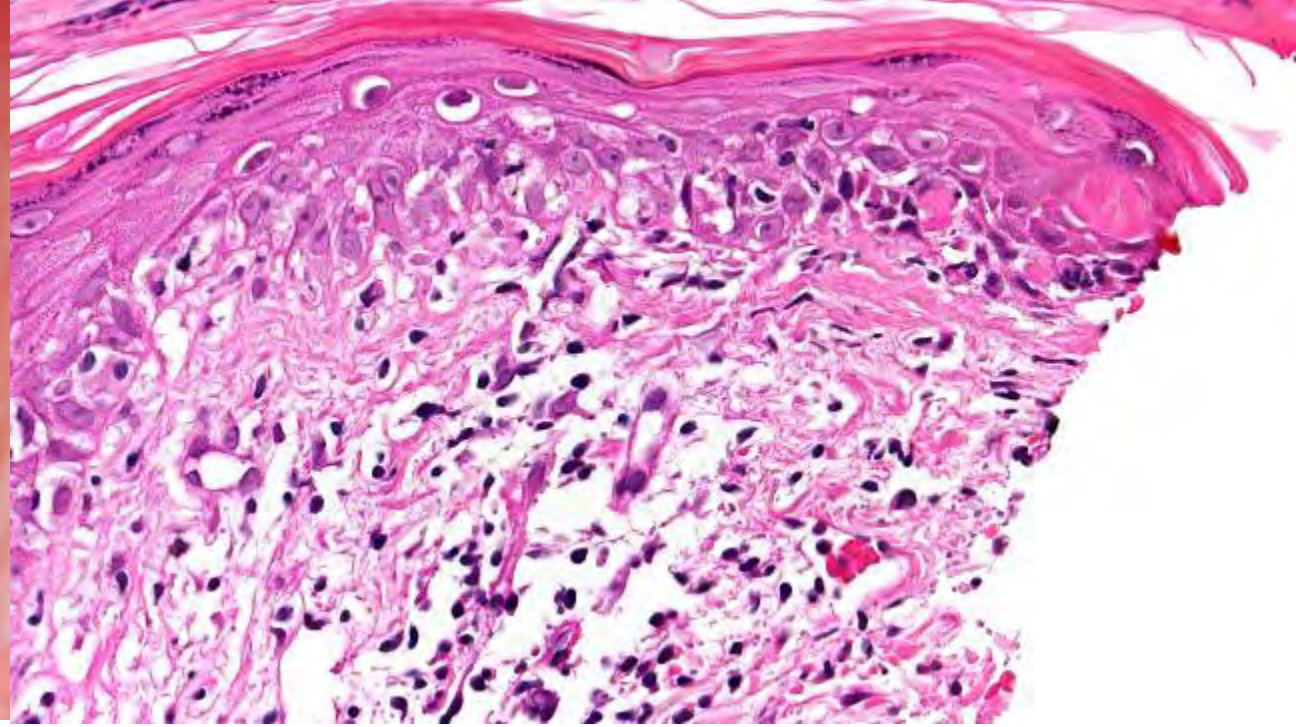


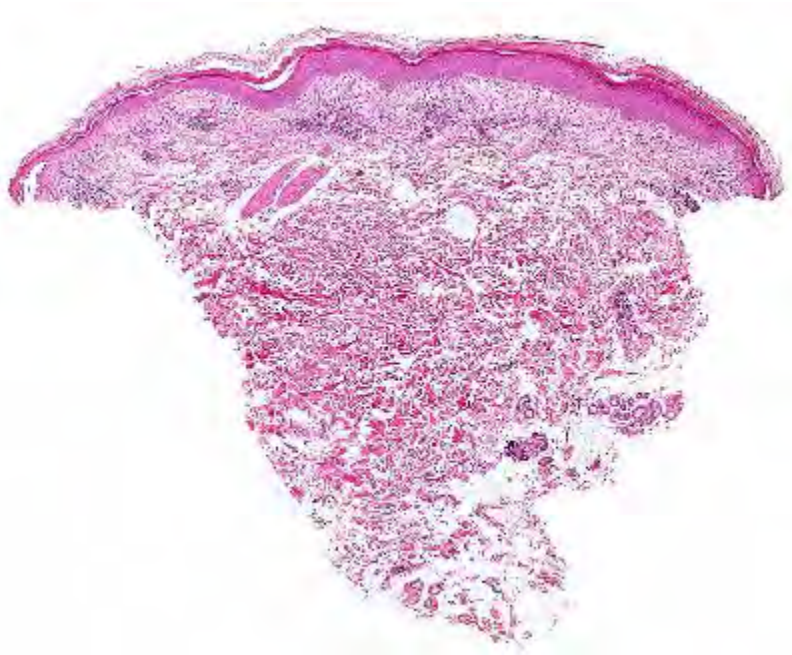
Necrobiotic xanthogranuloma











Paraneoplastic pemphigus

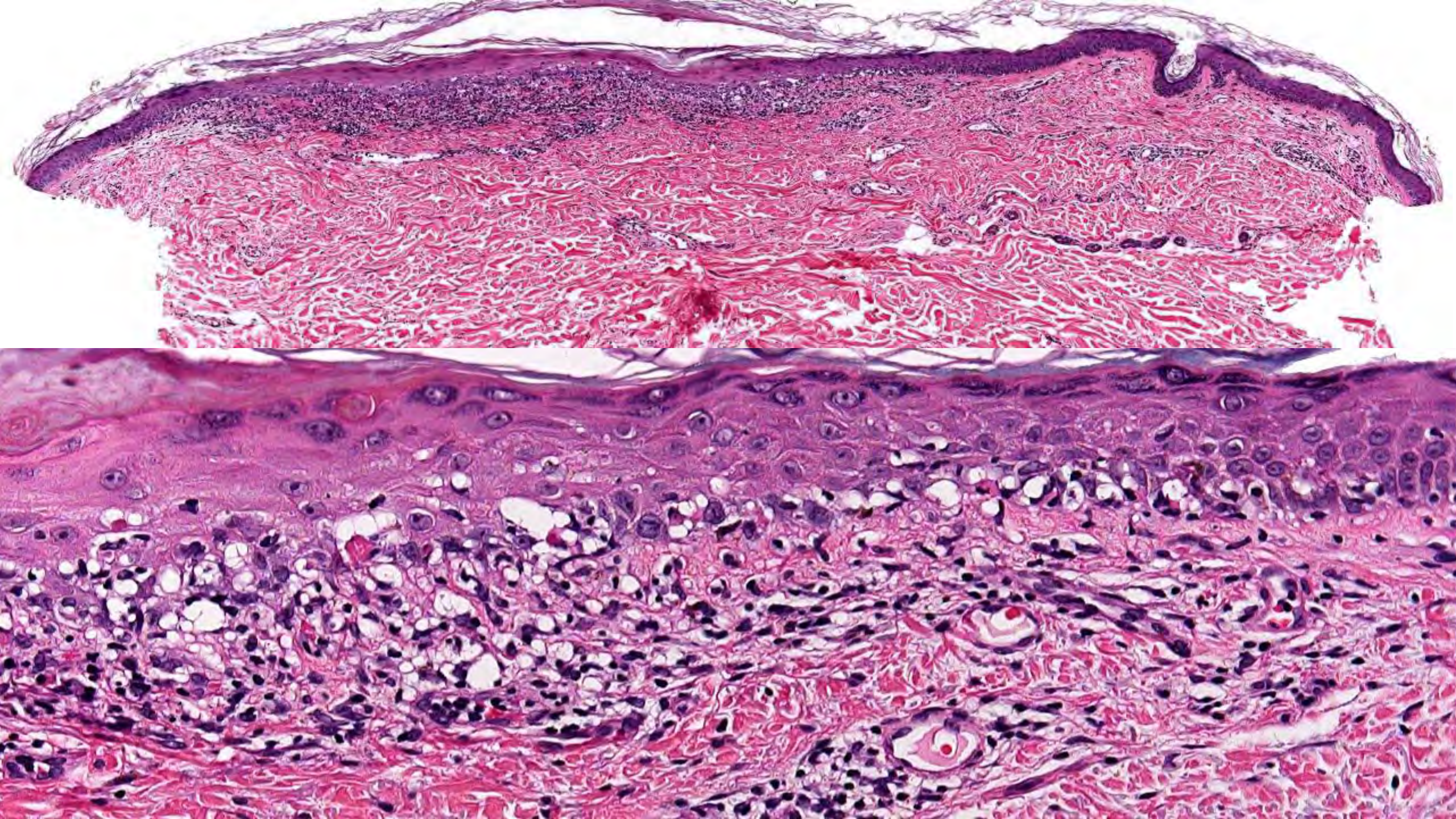
Mostly associated with B-CLL, NHL, Castleman's disease.

Cutaneous involvement common but not obligatory (epithelia of eyes, respiratory tract, thyroid, kidney – "*Paraneoplastic autoimmune multiorgan syndrome*", PAMS).

Auto-abs. against desmoglein 1 & 3 , plakin proteins, alpha-2-macroglobulin-like 1.

Cutaneous involvement characterized by severe lesions on mucosal surfaces and on palms & soles.

Refractory to treatment.

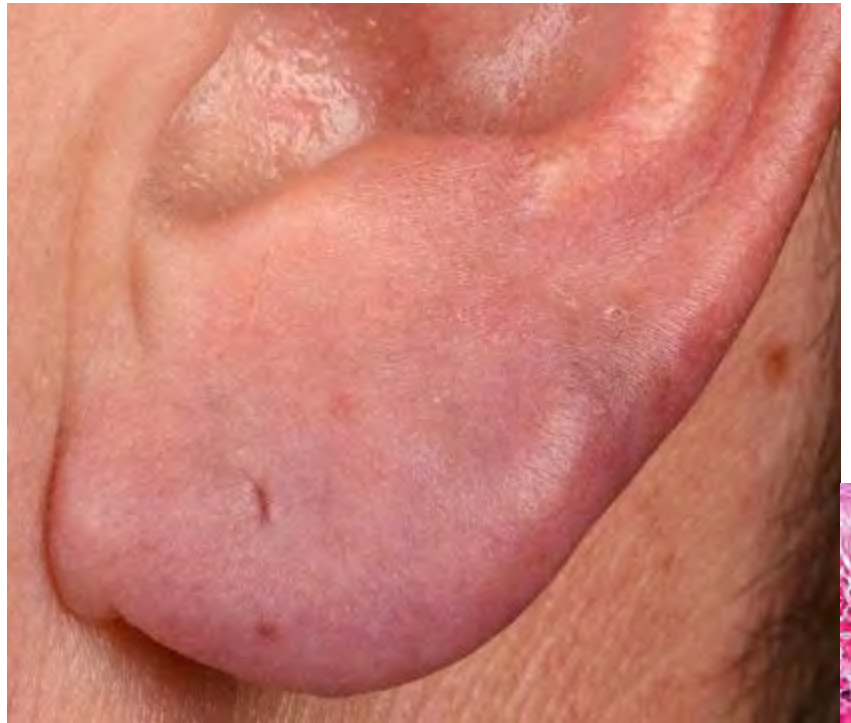


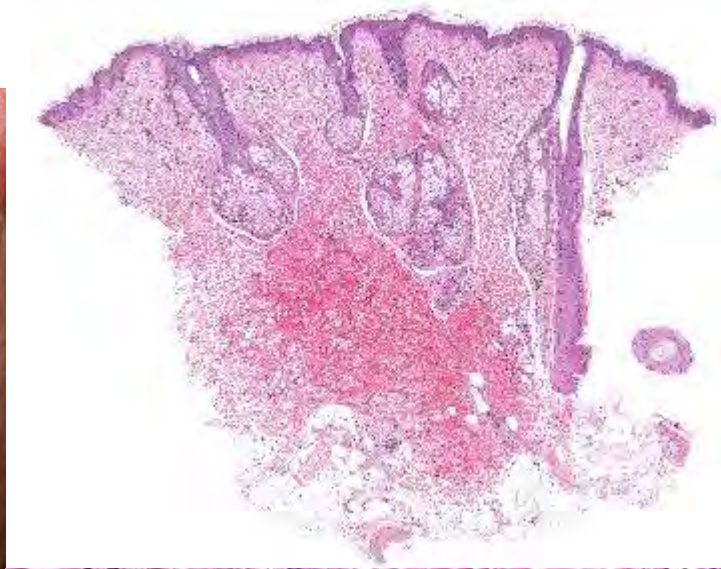
M, 40

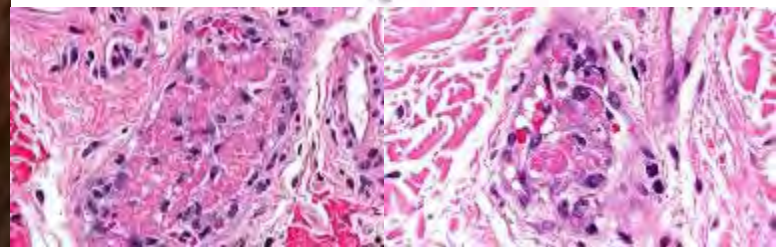
One day before presentation fever and swelling of the face; admitted to Dermatology as in-patient with the diagnosis of erysipelas.

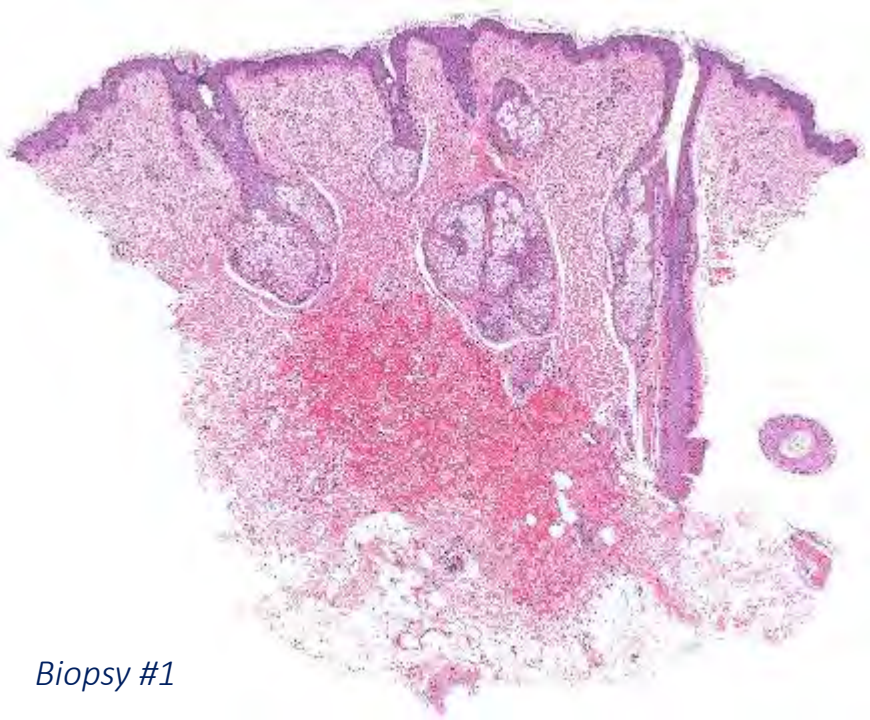
Blood tests show hemolytic anemia with mild hyperbilirubinemia (1,48), and elevated LDH (621) and CRP (97).

Two biopsies are performed.

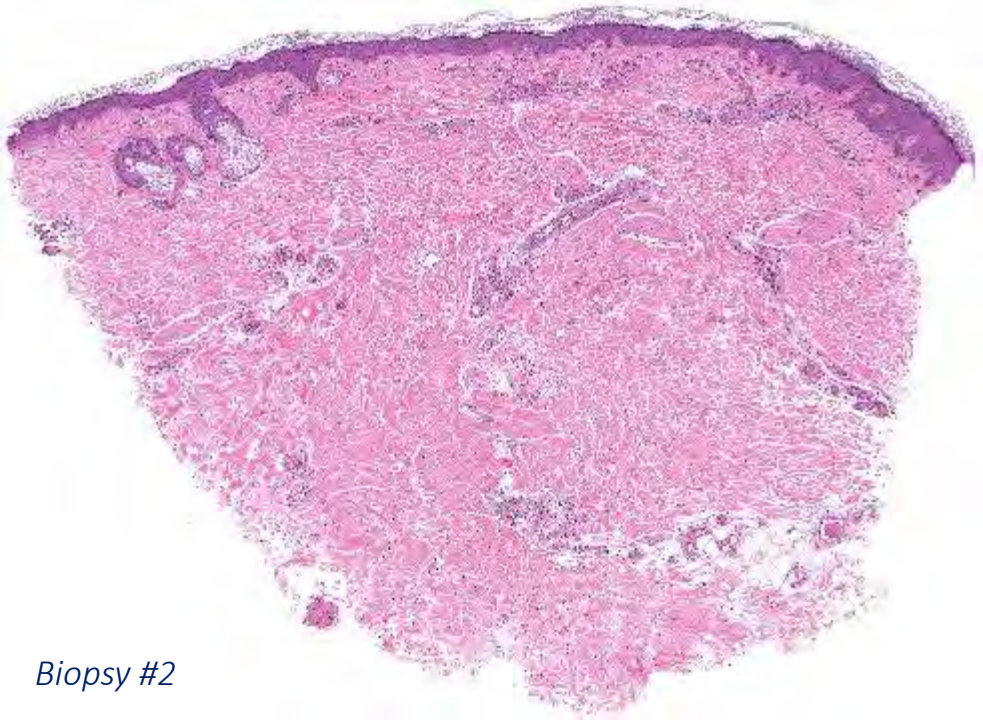




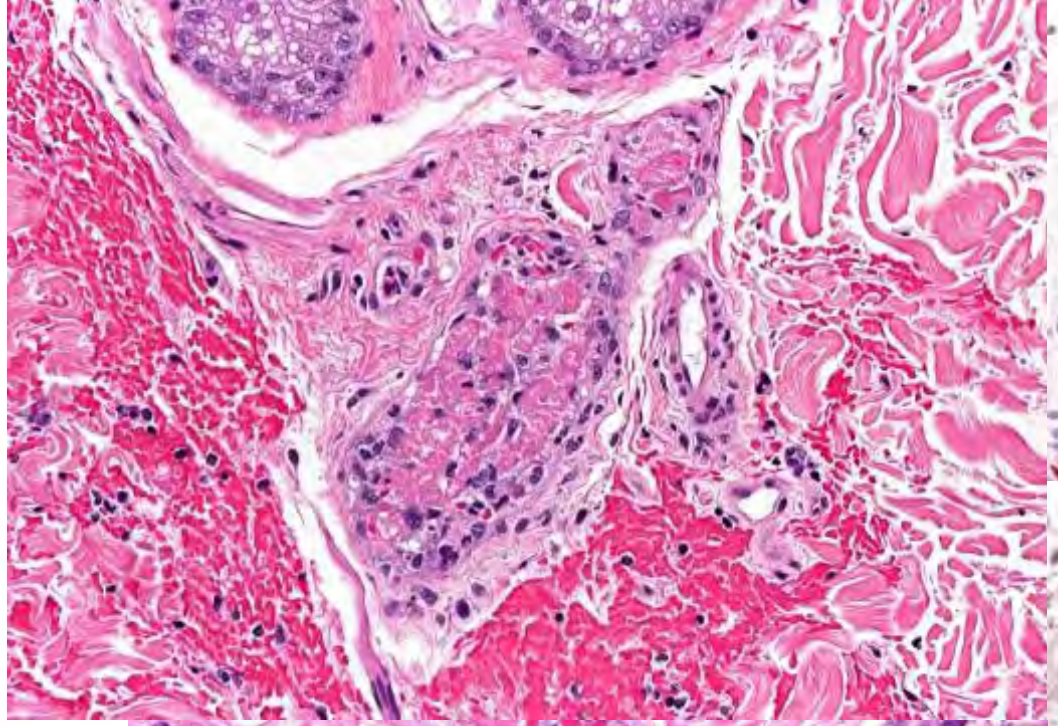


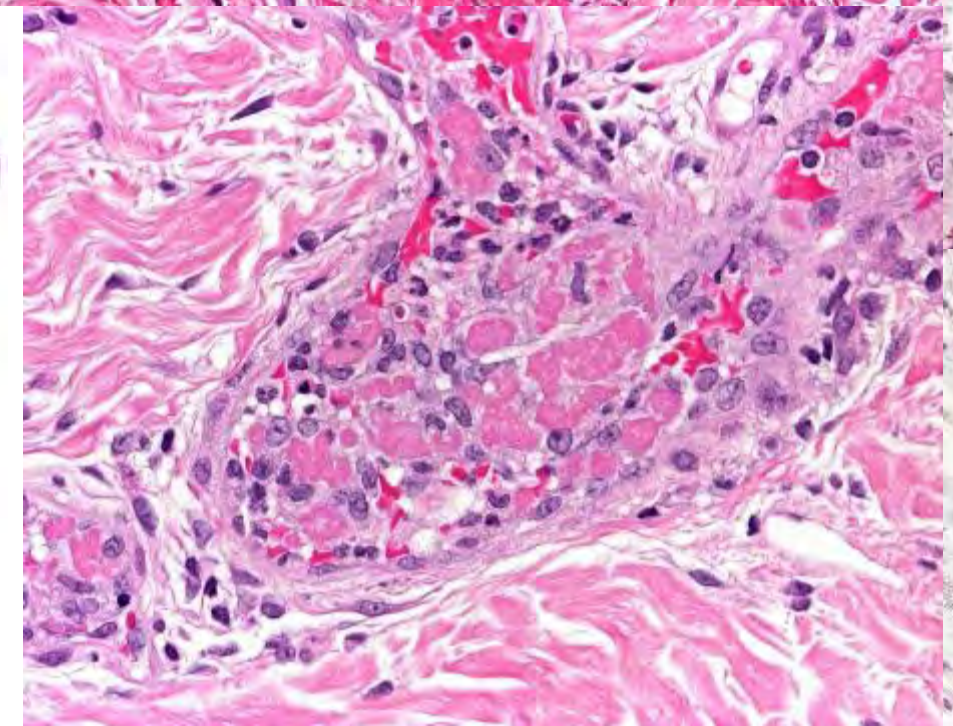


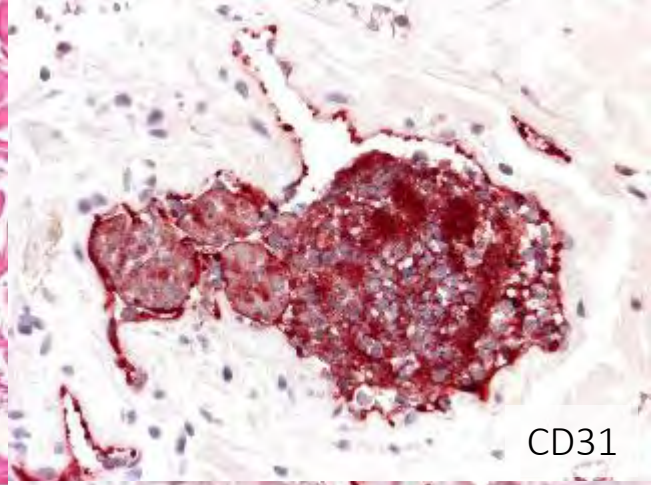
Biopsy #1



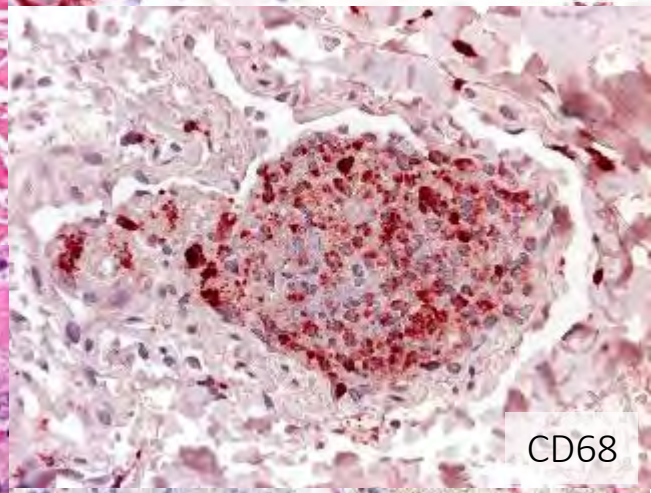
Biopsy #2



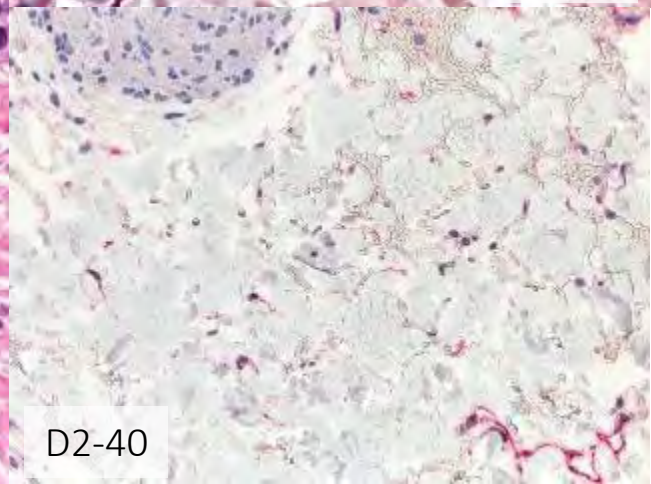




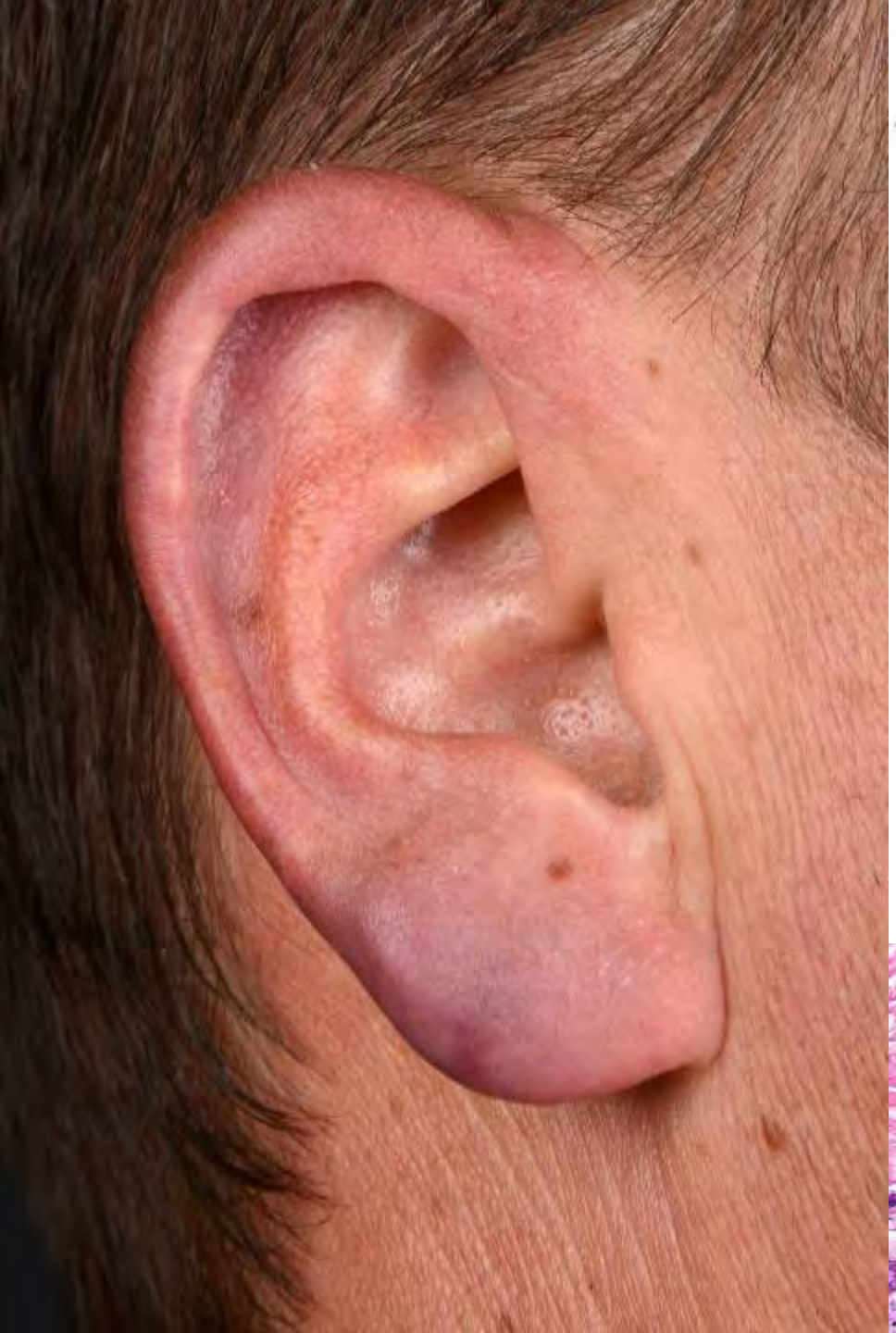
CD31

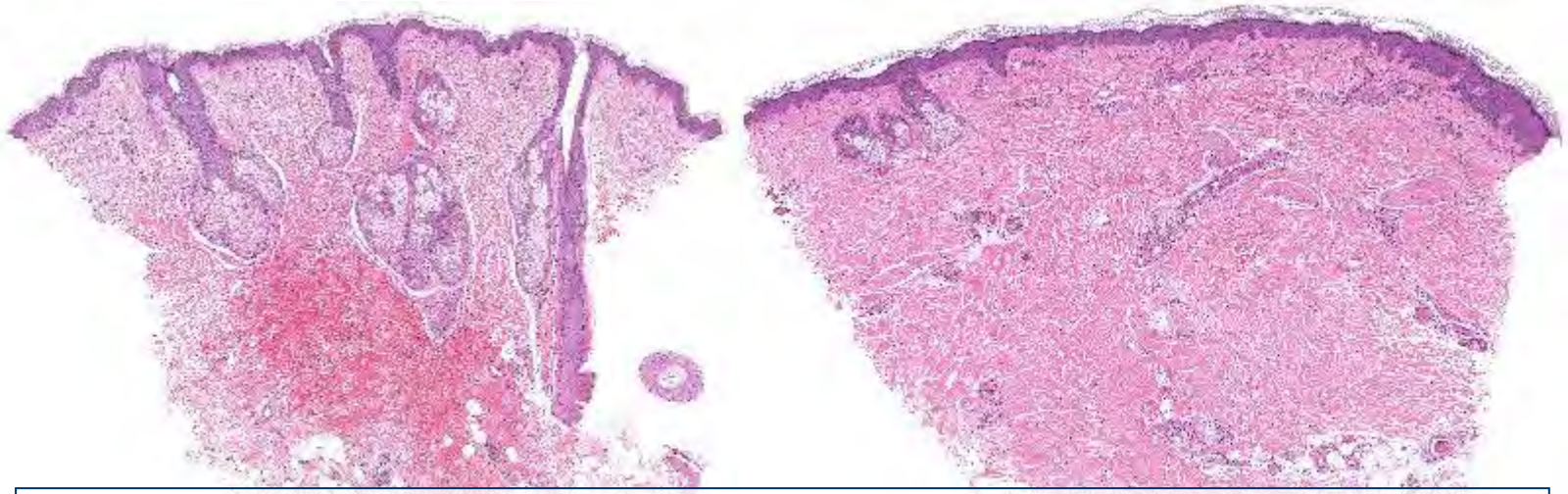


CD68



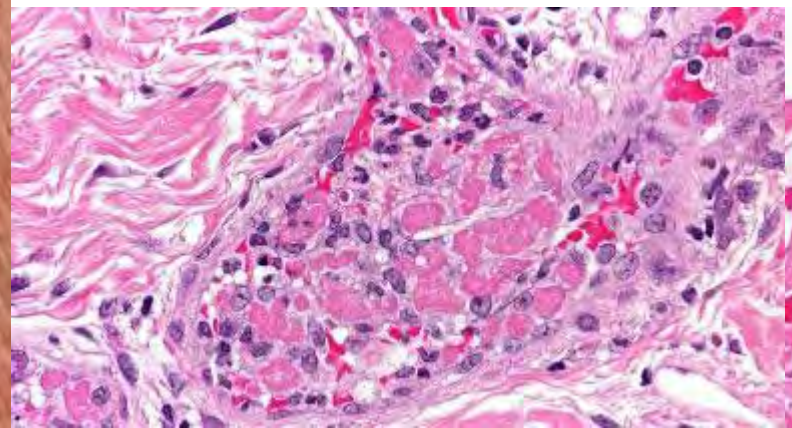
D2-40

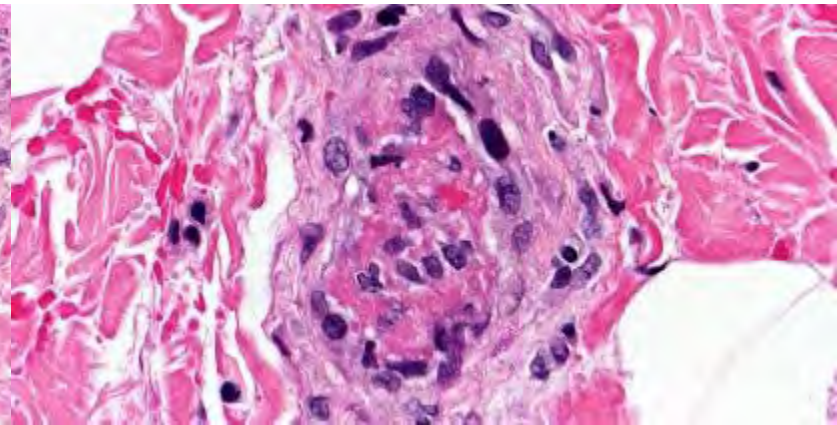




Monoclonal cryoglobulinemia with reactive angioendotheliomatosis

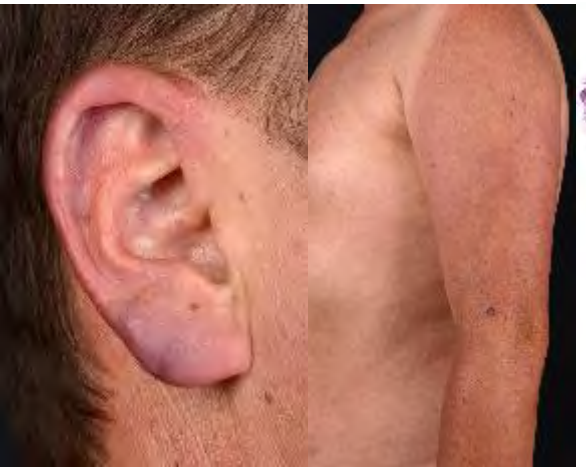
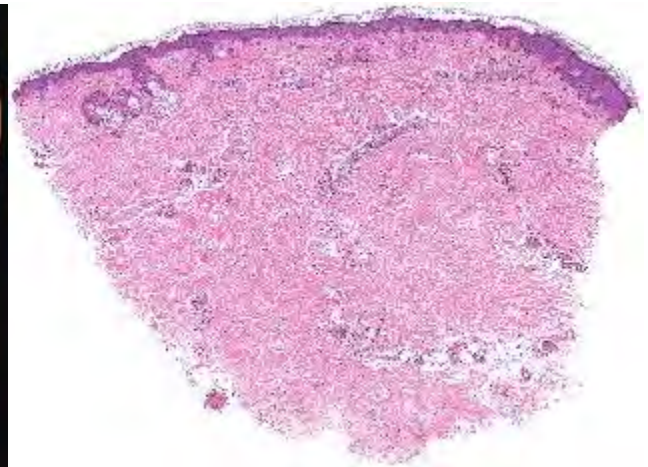
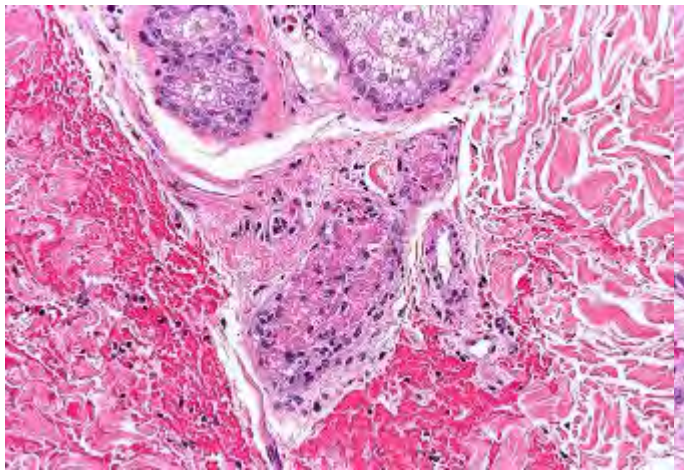
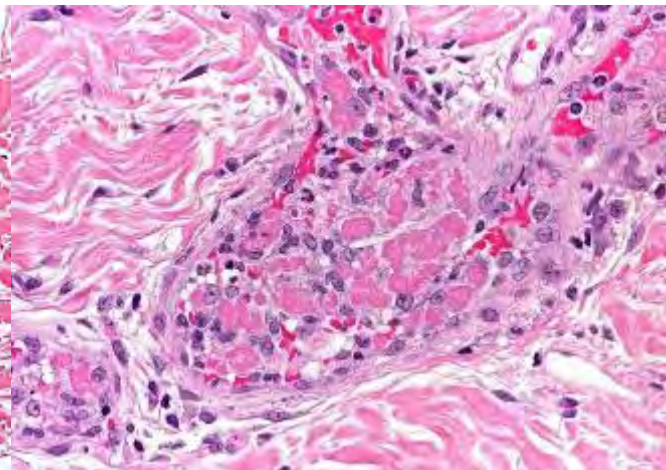
(cold agglutinin autoimmune hemolytic anemia and lymphoma)
High-grade B-NHL found on Jamshidi; Rapid deterioration, intensive care, death 11 days after admission to Dermatology





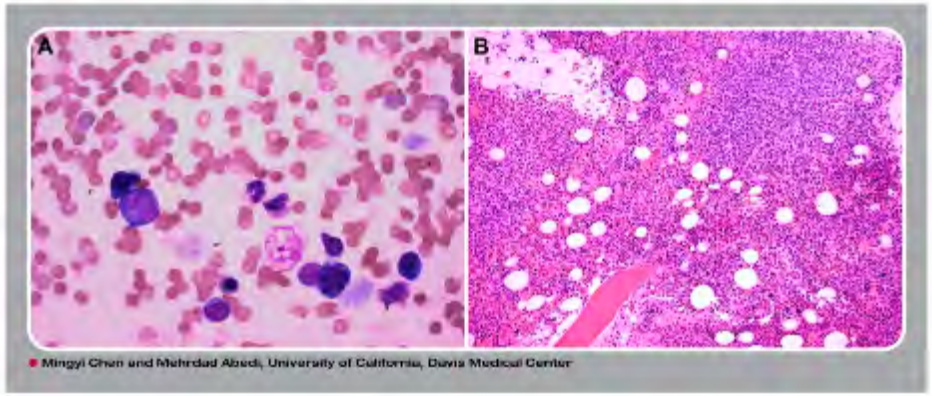
Cryoglobulinemia

- Monoclonal (usually in the setting of hematological disorders; intravascular deposits)
- Mixed (often in association with hepatitis C; acute vasculitis with variable leucocytoclasia)
- Immunoglobulin and complement found often within the vessel walls in mixed cryoglobulinemia

bloodwork
IMAGES IN HEMATOLOGY

Atypical lymphocytosis, cold agglutinin hemolytic anemia, and monoclonal gammopathy in an HIV patient with marrow involvement by diffuse large B-cell lymphoma



Mingyi Chen and Mehrdad Abedi, University of California, Davis Medical Center

A 43-year-old man presented with fever, fatigue, and shortness of breath. Physical examination revealed bilateral axillary lymphadenopathy. Complete blood count showed hemoglobin of 9.8 g/dL, a white cell count of 4.4 × 10^9/L, and a platelet count of 195 × 10^9/L. Blood smear showed increased red blood cell agglutination, polychromasia with nucleated red cells, and atypical lymphocytosis (panel A). Hemolysis was evident, with raised serum bilirubin (2.3 mg/dL), low serum haptoglobin (4 mg/dL), high serum lactate dehydrogenase, direct Coombs test positive, and cold agglutinins (1:256). Serology studies for hepatitis B or hepatitis C were negative. Laboratory work-up detected hypergammaglobulinemia (3.9 g/dL) with increased serum immunoglobulin G (IgG) (2408 mg/dL), IgM (599 mg/dL), and IgE (175 mg/dL) with an IgG κ monoclonal paraprotein. A bone marrow biopsy revealed dense nodular atypical lymphoid infiltrates, plasmacytosis, and megakaryocytic hyperplasia (panel B). Biopsy of the axillary lymph nodes showed diffuse large B-cell lymphoma. Subsequently, the patient was discovered to be positive for HIV type 1, with a viral load of 485 315 copies per microliter, and a CD4 cell count of 215 per microliter.

All patients with unexplained cold agglutination and hypergammaglobulinemia associated with lymphoma should undergo screening for HIV infection; peripheral blood analysis may be useful in the diagnosis of marrow involvement by lymphoma.

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- *Autoimmune hemolytic anemia* usually presents in the context of autoimmune disorders, drug ingestion or infections
- Autoimmune hemolytic anemia due to cold agglutinins (cold agglutinin disease – COD) is often associated with lymphoproliferative disorders (usually MGUS or B-CLL, rarely high-grade lymphomas)
- Usually responds to lymphoma-specific treatment

Autoimmune cytopenias in patients with malignant lymphoma: A multicenter report by the Polish Lymphoma Research Group

Magdalena Witkowska, Joanna Druzd-Sokolowska, Anna Waszczuk-Gajda, Agnieszka Giza, Barbara Lewicka, Joanna Zdziarska, Damian Mikulski, Piotr Smolewski

Address for correspondence:

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Conflict of interest

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Accepted:
Published online:

Abstract

Background.

Objectives.

Materials and methods.

Results.

Conclusions.

Key words:

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DOI

Publication info

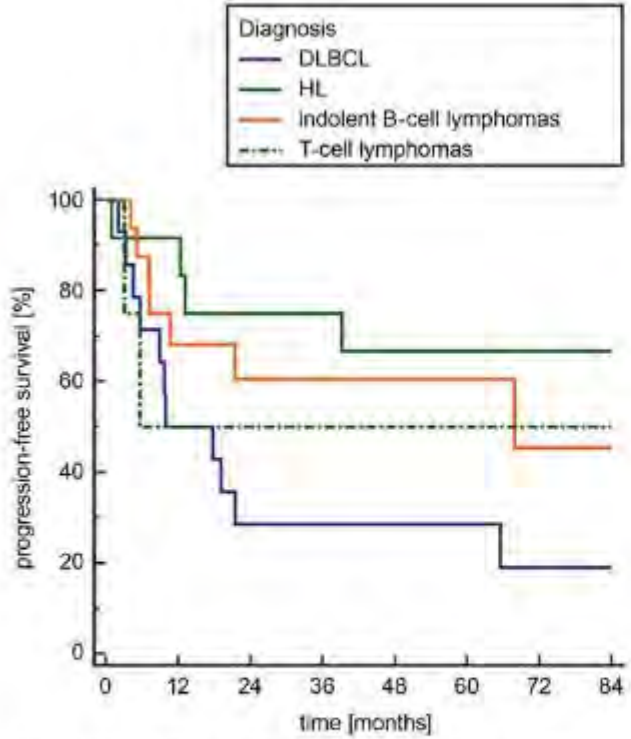

Fig. 2. Progression-free survival (PFS) in the studied groups of patients. Patients with DLBCL had a trend into poorer PFS compared to the other diagnosis groups, but the difference did not yield statistical significance (log-rank p-value = 0.062).

DLBCL – diffuse large B-cell lymphoma; HL – Hodgkin lymphoma.

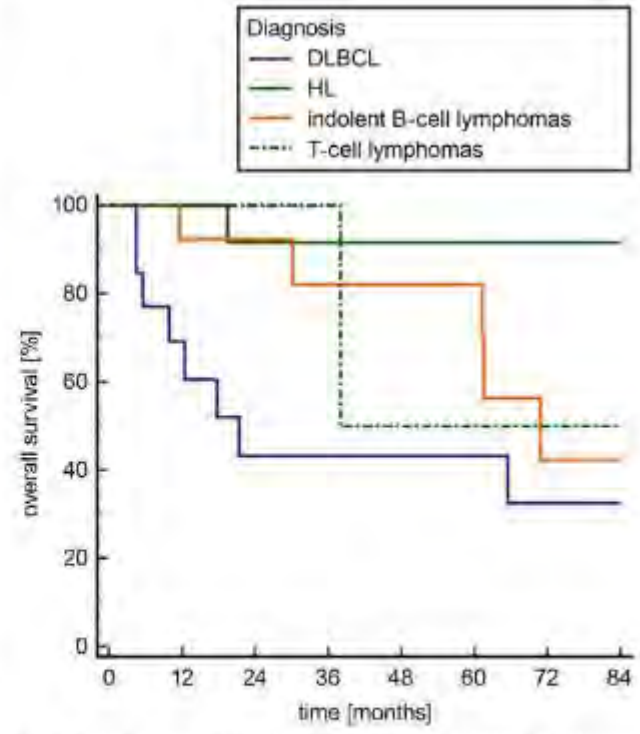

Fig. 3. Overall survival (OS) in the studied groups of patients. Patients with Hodgkin lymphoma (HL) had a significantly better outcome in terms of OS (median not reached) compared to other groups: DLBCL (median OS: 1.8 years), indolent B-cell lymphoma (median OS: 3.9 years) and T-cell lymphoma (median OS: 3.2 years). Log-rank p-value = 0.008.

DLBCL – diffuse large B-cell lymphoma.

Follicular spicules of the nose: A peculiar cutaneous manifestation of multiple myeloma with cryoglobulinemia

Luis Requena, MD,[a] José Luis Sarasa, MD,[b] Fernando Ortiz Muelloves, MD,[c] Lucía Martín, MD,[a] Enric Piqué, MD,[a] Mercedes Olivares, MD,[a] María Carmen Fariña, MD,[a] Elena Prieto, MD,[c] Lloy Pacho, MD,[c] and Juan Gómez Oliveiro, MD[a] *Madrid, Spain*

We describe a patient with multiple myeloma and cryoglobulinemia who had spicules with a horny appearance in the follicular openings of the face, particularly on the nose. Histopathologic study demonstrated that these spicules consisted of eosinophilic homogeneous deposits in the intercellular spaces between keratinocytes in the upper layers of the follicular infundibulum. Direct immunofluorescence, ultrastructural, and biochemical investigations revealed that these eosinophilic deposits were cryoprecipitates composed of IgG-κ with electrophoretic characteristics identical to those of the paraproteín present in the serum of the patient. Hence we believe that these lesions are best referred to as pseudoperforating spicules of the nose, and that they are a characteristic cutaneous manifestation of patients with multiple myeloma and cryoglobulinemia. (J Am Acad Dermatol 1995;32:834-9.)

Cutaneous manifestations in patients with multiple myeloma have been classified as specific and nonspecific.[1] The specific skin lesions include extramedullary plasmocytomas and secondary cutaneous involvement by direct extension from underlying bone tumors. The nonspecific manifestations include cutaneous findings that occur as a result of abnormal levels of proteins, cytopenia, or myelomatous involvement of internal organs. Since Bluefarb's publication,[1] several reports have described additional cutaneous findings in patients with multiple myeloma. These findings include pyoderma gangrenosum,[2-4] leukocytoclastic vasculitis,[5] necrobiotic xanthogranuloma,[6] scleromyxedema,[7] Sweet's syndrome,[8,9] subcorneal pustular dermatosis,[10,11] POEMS syndrome,[12-14] scleredema,[15] angioedema with C1 inhibitor deficiency,[16] and plane xanthoma.[17] All these cutaneous manifestations have recently been reviewed.[18] A characteristic, although uncommon, cutaneous manifestation in patients with multiple myeloma and cryoglobulinemia consists of spicules with horny appearance that develop in follicular openings of the face, particularly on the nose.

We describe a 79-year-old man with IgG-κ multiple myeloma and cryoglobulinemia who had follicular spicules, composed mostly of IgG-κ, on his face.

CASE REPORT

A 79-year-old man had multiple filiform spicules on his face. The patient had a 10-year history of chronic obstructive airway disease. His medications included fenoterol, budesonide, and theophylline. Examination revealed multiple, minute follicular spicules, mostly on the nose (Fig. 1), forehead, cheeks, chin, and, to a lesser extent, on the shoulders, arms, and upper portions of the back. These spicules could be removed easily without bleeding. Scattered on the scalp, many hair shafts showed tiny white adherent particles of the same material, mimicking nits of hair casts. A mottled, red to blue, reticulated vascular pattern suggestive of livedo reticularis was evident on the anterior aspect of the knees and purpuric lesions, some with a necrotic surface and covered by hemorrhagic crusts, were present on both ankles.

Roentgenographic examination showed small osteolytic defects in the skull and in two vertebrae that were

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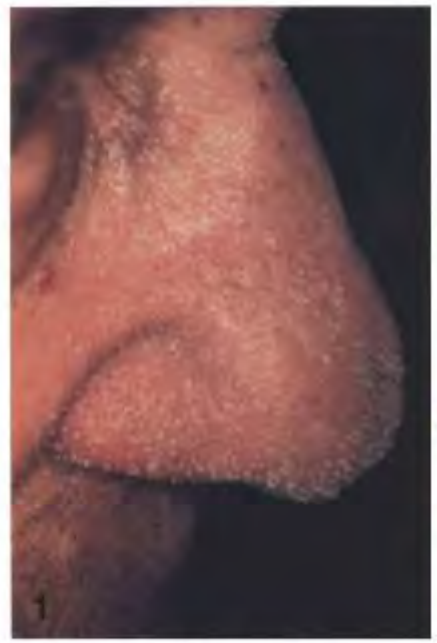


Fig. 1. Follicular spicules on nose.

Fig. 2. Light microscope examination of hair shafts of scalp shows white particles adhered to their surface.

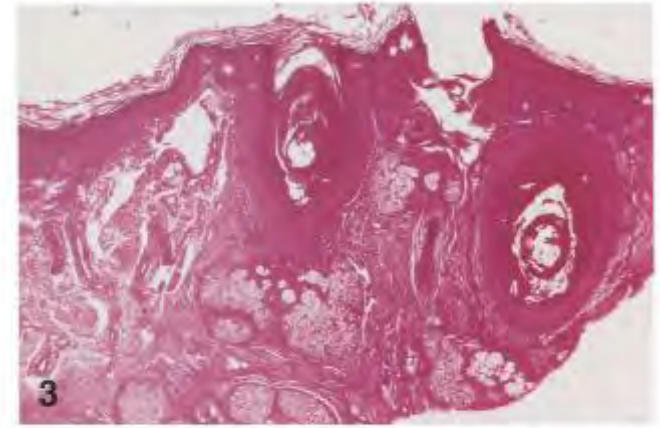


Fig. 3. Lesion on the nose shows follicular plugs of eosinophilic compact homogeneous material.

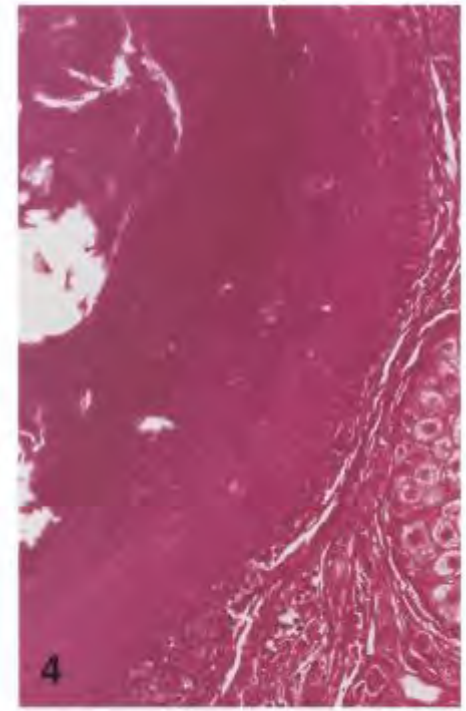
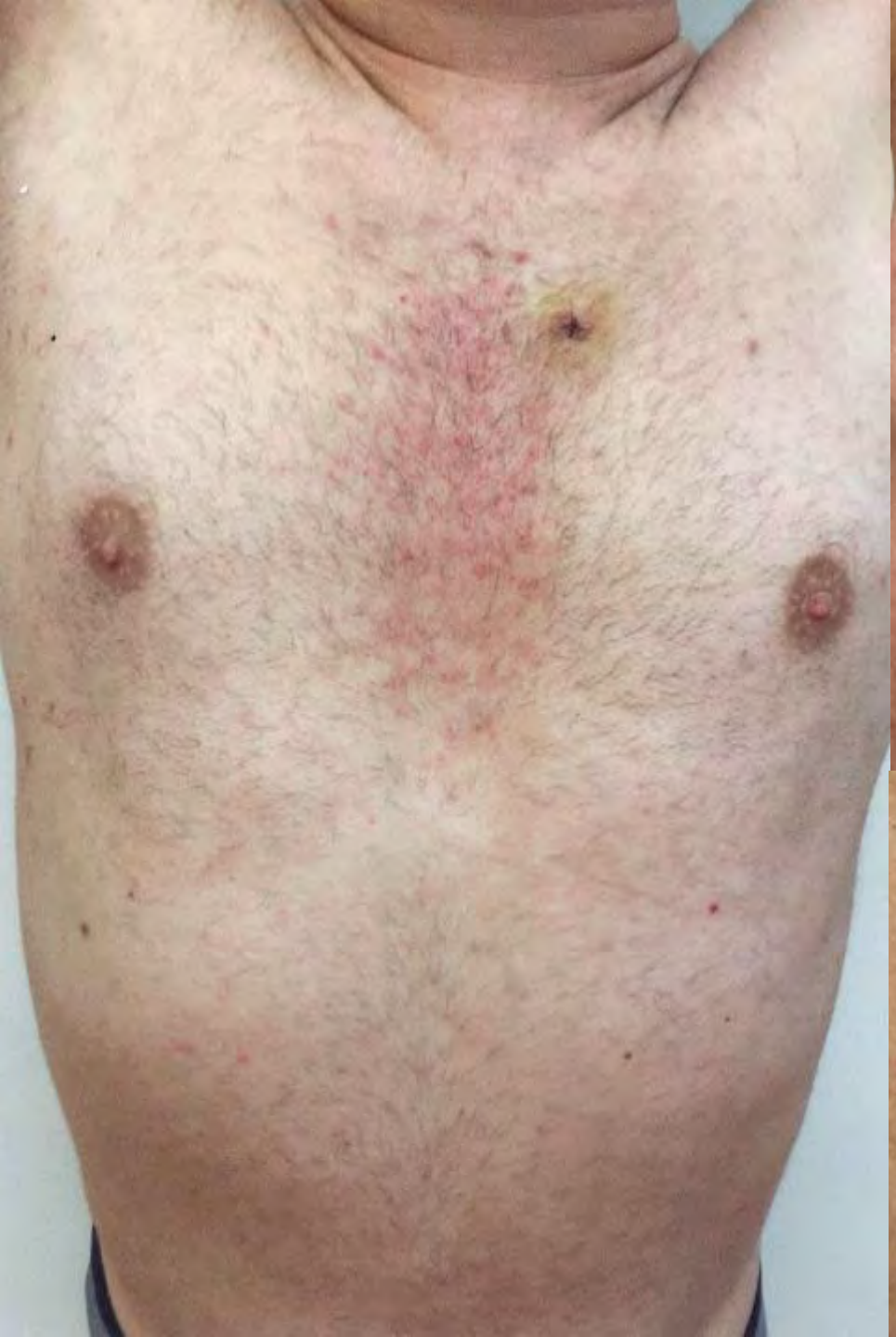
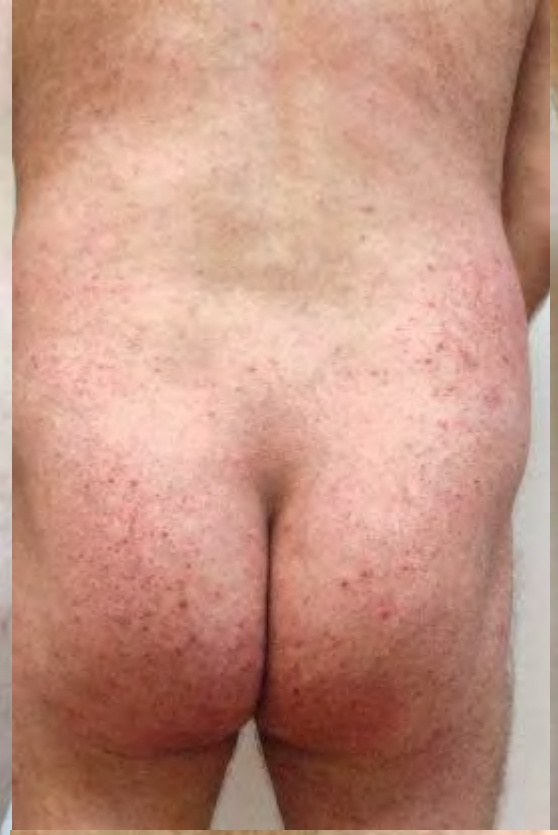


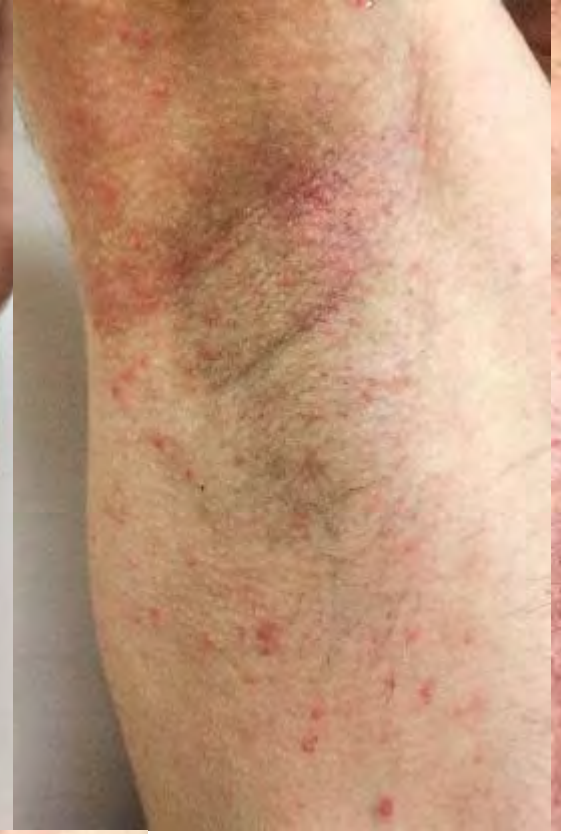
Fig. 4. Higher magnification shows intercellular eosinophilic deposits between keratinocytes of upper layers of infundibulum.

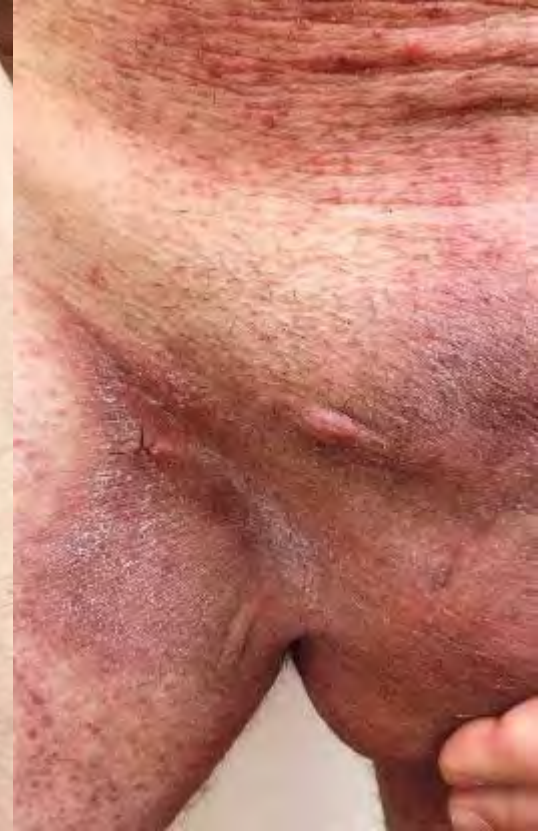
Follicular spicules of the nose / face

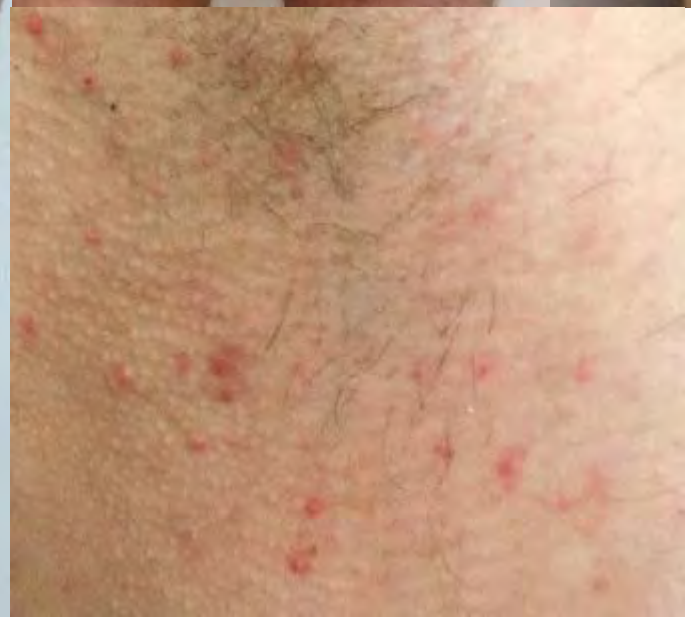
- Mostly in the setting of multiple myeloma, due to transfollicular extrusion of cryoglobulins (onset of follicular spicules may precede the diagnose of multiple myeloma)
- Some cases "idiopathic" or associated with drugs (particularly sorafenib), Crohn disease, or non-neoplastic hematological disorders
- Histopathological features are characterized by hyperkeratotic follicular plugs composed of a homogenous, eosinophilic material









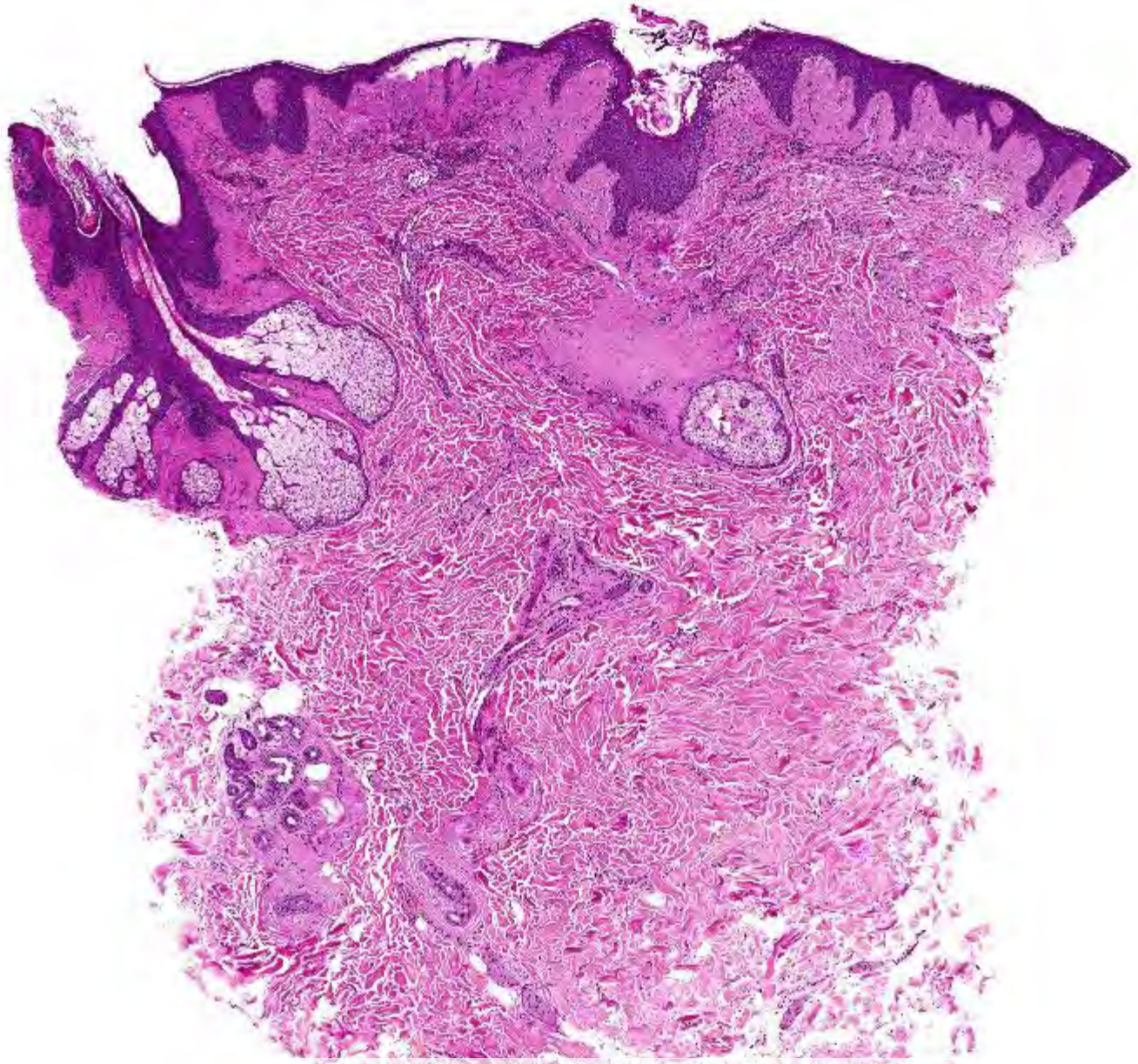


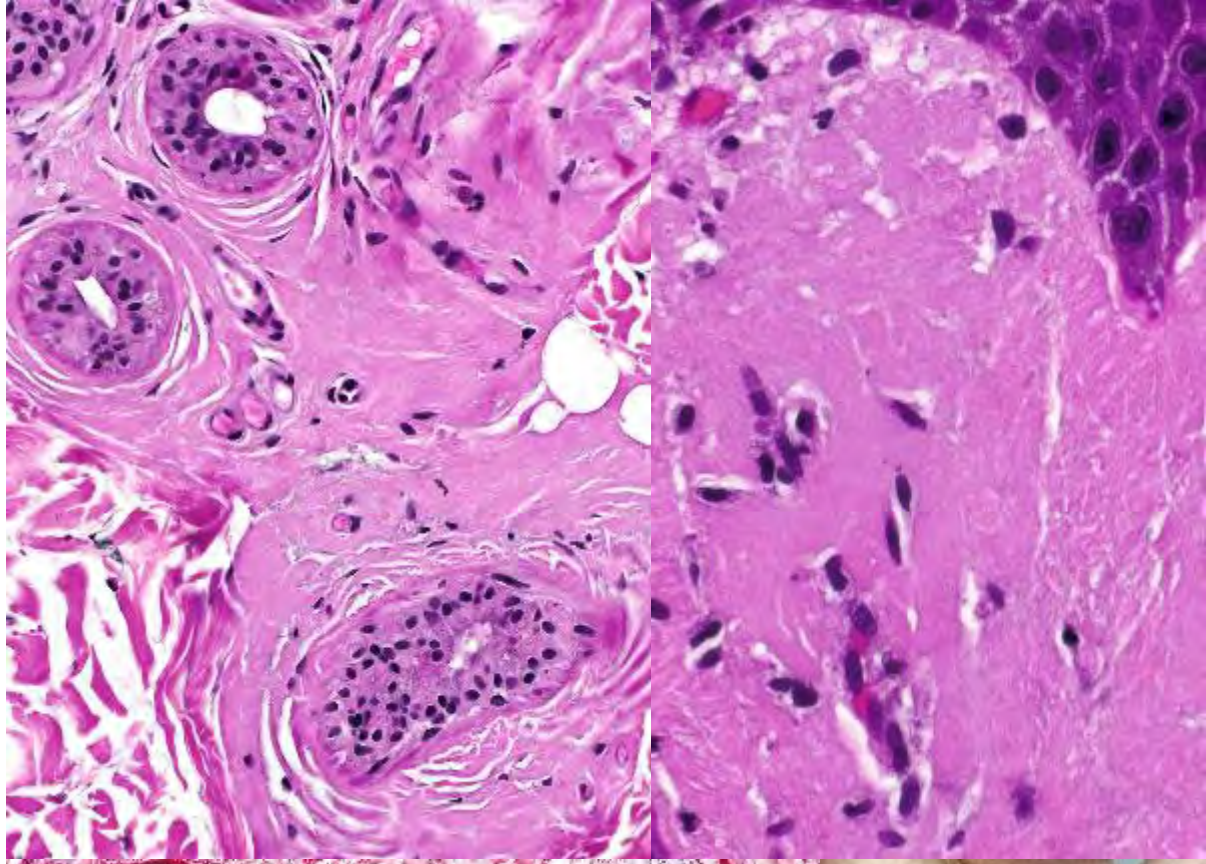
M, *age unknown*

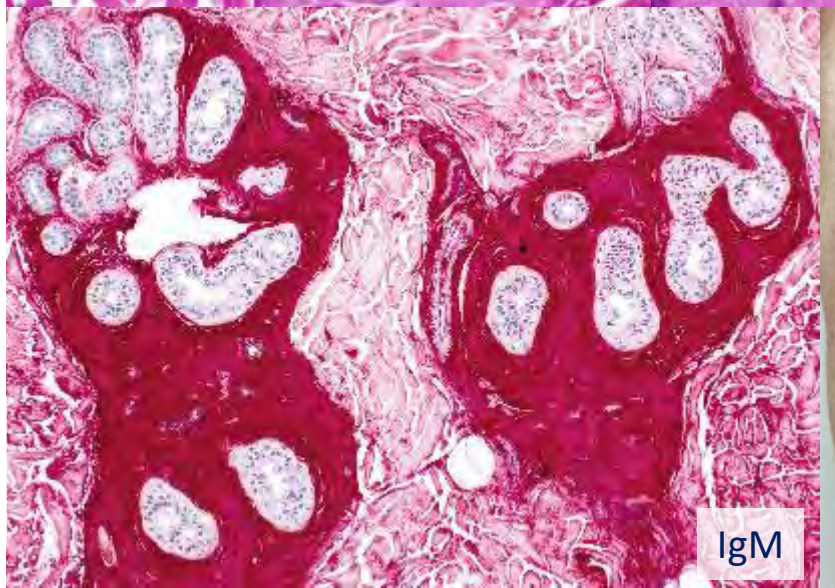
Cutaneous eruption of lasting a few weeks.

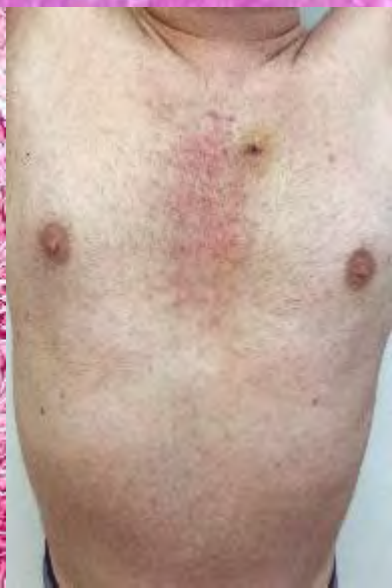
A biopsy is taken from the chest (clinical pictures taken after the biopsy).

(Case courtesy Dr. H. Kutzner, Friedrichshafen)









Cutaneous macroglobulinosis

Cutaneous macroglobulinosis

- In the setting of Waldenström macroglobulinemia / IgM-type lymphoplasmacytic lymphoma
- Considered as a specific cutaneous manifestation of the disease, usually characterized clinically by a papular rash
- Histopathologically, the substrate is characterized by monoclonal IgM deposits (PAS positive but negative for amyloid stains), that may encase the adnexal structures
- Different from another specific cutaneous manifestation of the disease characterized by an infiltrate of lymphoplasmacytoid cells that may mimic the histopathological picture of cutaneous marginal zone lymphoproliferative disorder / lymphoma

Journal of Cutaneous Pathology

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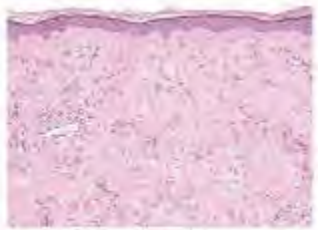
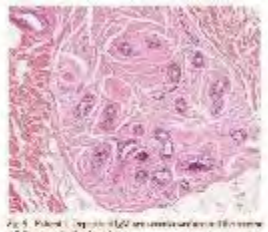
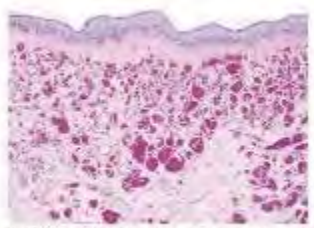
Cutaneous macroglobulinosis: a case series

Brendan J. Camp and Cynthia M. Magro







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F, 41. Monoclonal IgM-kappa gammopathy.
F, 83. Monoclonal IgM-lambda paraproteinemia.
M, 80. Waldenstrom macroglobulinemia.

Coexisting cutaneous macroglobulinosis and scleredema of Buschke in a patient with a Waldenström Macroglobulinemia

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Editor

The presence of a serum monoclonal immunoglobulin can lead to complications related to the physicochemical properties of circulating immunoglobulin and/or its deposition in different tissues, such as kidney, peripheral nervous system and skin. Specific

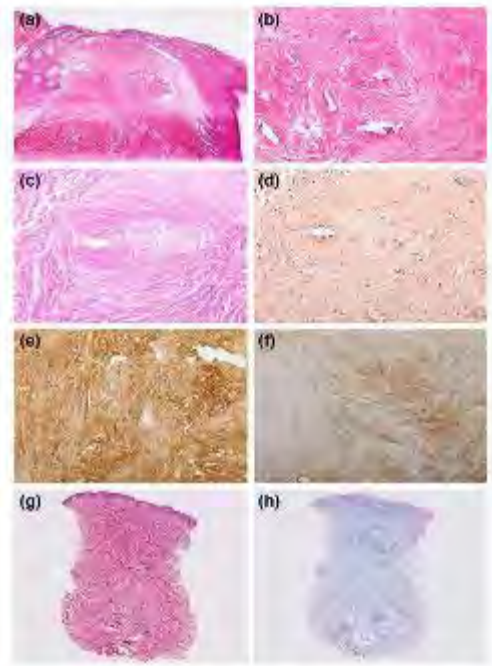
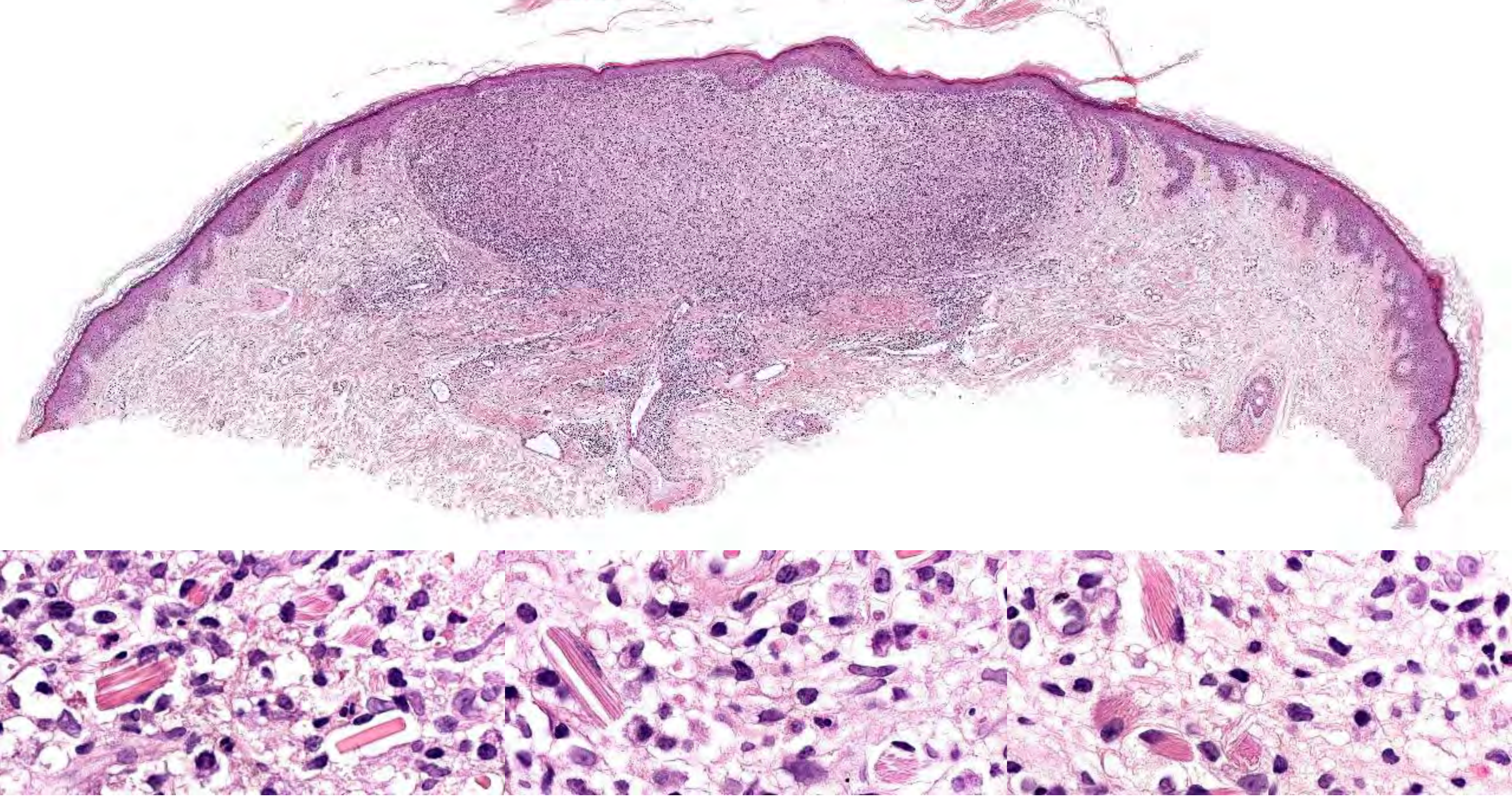
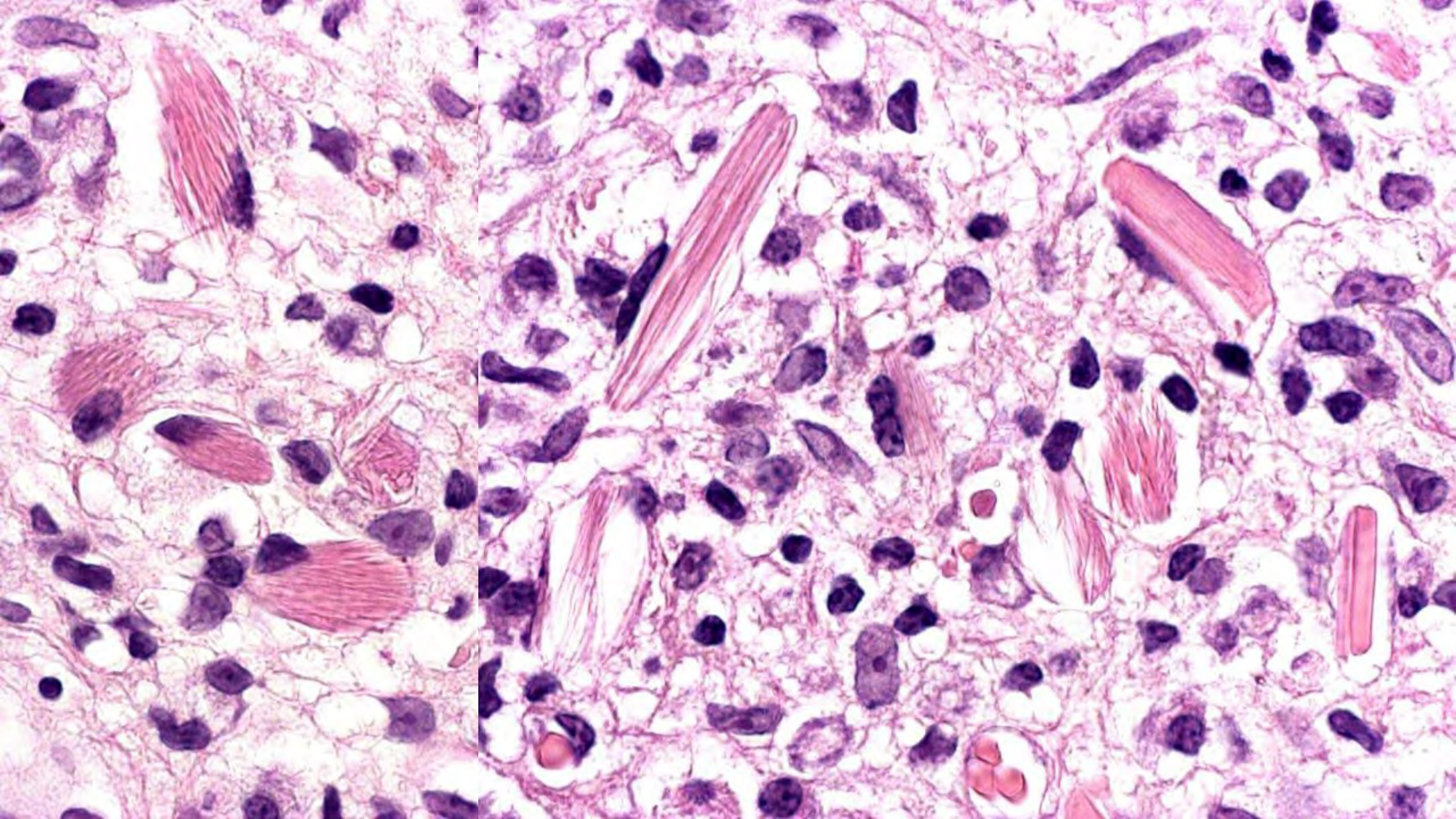


Figure 2 Histopathology of the lesions – biopsy of a papule on the side of the foot (a–f), biopsy of the neck (g, h). (a, b) Eosinophilic amorphous material deposited in the dermis, peri- and intra-vascular space (Haematoxylin/eosin stain, ×50 (a), ×200 (b)). (c) Material positively stained with periodic acid–Schiff (PAS, ×200). (d) Material negative with Congo red staining (Congo Red, ×200). (e) Positive immunostaining with IgM (×200). (f) Positive immunostaining with lambda light chain (×200). (g) Dermal sclerosis and light perivascular lymphocytic infiltrate. (H/E × 2.5). (h) Light interstitial mucin deposits with alcian blue staining (×2.5).

EADV 2018, 33, e92–e143



Crystal storing histiocytosis



OBSERVATIONS

Cutaneous Crystalline Deposits in Myeloma

Rachel E. Jenkins, BSc, MRCP, Eduardo Calonje, MD, Hilary Lawson, MRCP, Malcom W. Greaves, MD, FRCP, Edward Wilson-Jones, FRCP, MRCPath

Background: Myeloma is a plasma cell malignancy that usually presents with systemic manifestations or symptoms related to bone involvement. We describe the first case of crystalline protein deposition in the skin as the initial manifestation of myeloma.

Observations: Crystals were found mainly in the extracellular spaces in the dermis of both involved and uninvolved skin in the absence of plasma cell infiltration. Crystals were also found in conjunctival tissue and bone marrow.

Conclusions: We have described a unique case of myeloma that presented as facial and eyelid swelling. There were crystalline deposits in the skin and conjunctivae, but mechanisms of crystal formation and the factors causing local deposition were not established. However, treatment of the underlying disorder leads to resolution of the cutaneous features of crystal deposition.

(Arch Dermatol. 1998;134:489-490)

MYELOMA is a plasma cell malignancy typically occurring in patients aged 40 to 70 years. It usually presents with systemic manifestations or symptoms related to bone involvement. Various cutaneous lesions have been associated with myeloma.[1] Specific manifestations include extramedullary plasmacytomas of the skin and mucous membranes and tumors of the skin that have developed as extensions from the bone or bone marrow.[2] Nonspecific manifestations include pyoderma gangrenosum,[3] leukocytoclastic vasculitis,[4] necrobiotic xanthogranuloma,[5] scleromyxedema,[6] Sweet's syndrome[7] and subcorneal pustulosis.[8]

We describe the first case of crystalline protein deposition in the skin as the initial manifestation of myeloma. Crystals were found predominantly in the extracellular space in the dermis of both involved and uninvolved skin in the absence of plasma cell infiltration. The presence of cutaneous crystals, although reported, is rare. Protein crystal deposition has been found in necropsy studies, but there are no previous descriptions of antemortem crystal deposition in the skin in the absence of local plasma cell infiltration.

From the St Johns Institute of Dermatology, St Thomas' Hospital, London, England (Drs Jenkins, Calonje, Greaves, and Wilson-Jones); and Hinchingbrooke Hospital, Huntingdon, England (Dr Lawson). Dr Jenkins is now with the Department of Dermatology, General Hospital, Birmingham, England.

REPORT OF A CASE

A 61-year-old man was referred with a 3.5-year history of intermittent facial swelling. He had initially reported bilateral periorbital swelling that settled spontaneously after a few weeks, with no cause being identified. He then had two similar episodes, at approximately 1-year intervals, each resolving after a short course of oral prednisolone. However, in the 16 months prior to his referral, despite steroid therapy, he had developed persistent swelling of the right side of the face and slight swelling on the left side. He had also experienced night sweats and was lethargic. On examination, there was a tender, yellowish, and indurated dermal swelling of the right side of the face, extending from the supraorbital ridge down to the lower margin of the cheek. There were many telangiectasias over both cheeks (**Figure 1**). General examination revealed normal results; there was no lymphadenopathy and no bone tenderness.

The clinical differential diagnosis included, initially, recurrent angioedema and, subsequently, malignant infiltrates and cel-

Photos courtesy of Dr. E. Wilson-Jones, London, UK

M, 61 with a 3.5-year history of intermittent facial swelling that settled spontaneously after a few weeks or with short courses of systemic steroids. Investigations revealed the presence of a multiple myeloma. Several biopsies were taken from the skin, showing eosinophilic-shaped crystals located mostly, but not exclusively, in the cytoplasm of histiocytes.

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CASE STUDY

WILEY

Cutaneous crystal storing histiocytosis: A case series with review of literature

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Abstract

Crystal storing histiocytosis (CSH) is a rare condition in which crystals accumulate in the cytoplasm of histiocytes and is usually associated with a lymphoplasmacytic neoplasm. Cutaneous CSH is extraordinarily rare and limited to case reports in the literature. We report two cases of this disease with cutaneous involvement. Case 1 was a 65-year-old male with a 4-month history of a pruritic eruption that started as a solitary pink to skin-colored indurated plaque on the anterior neck before progressing to involve the whole neck, chest wall, and face. Case 2 was a 54-year-old woman with a history of unspecified lymphoma who presented with a soft nodule on the forearm. Biopsies from both cases had similar findings and showed a proliferation of epithelioid cells with pink cytoplasm and intracellular crystalline structures infiltrating the dermis and subcutaneous fat. In the first case, the cells were positive for CD163, CD15, CD68, and IgG kappa, and in the second case, the crystals were positive for IgG lambda. Based on these findings, the patients were diagnosed with cutaneous CSH. We highlight this rare diagnosis and the importance of investigating an underlying lymphoplasmacytic neoplasm.

KEYWORDS
crystals, histiocytic lesions, lymphoplasmacytic neoplasm

1 INTRODUCTION

Crystal-storing histiocytosis (CSH) is a rare condition caused by the accumulation of crystalline structures within the cytoplasm of histiocytes.[1] CSH is usually a result of the deposition of light-chain immunoglobulins, specifically kappa. However, cases with lambda have been reported. Other non-immunoglobulin crystalline structures can occur within histiocytes, including cholesterol crystals, Charcot-Leyden crystals, cystinosis, and silica-associated crystals.[2] Cases of immunoglobulin storing histiocytosis without a crystalized pattern of the deposited immunoglobulins have also been rarely described.[3] CSH can be localized (involving one site) or generalized (involving two or more sites). The most frequently involved sites include bone, head and neck, kidney, and lung.[1] Cutaneous involvement is extremely rare; we are aware of only 13 cases reported in the literature.[1,4] The most frequent clinical association is an underlying lymphoproliferative or plasma cell disorder (LP-PCD), including multiple myeloma (MM), monoclonal gammopathy of undetermined significance (MGUS), and lymphoplasmacytic lymphoma (LPL). Here we present two cases of

[illegible] at the [illegible] Society of Dermatopathology in Chicago, October 20–21, 2023.

FIGURE 1 Case 1 Clinical presentation. (A) Plaque-like lesion on the anterior neck. (B) Expansion of lesion to involve the whole neck and chest wall.

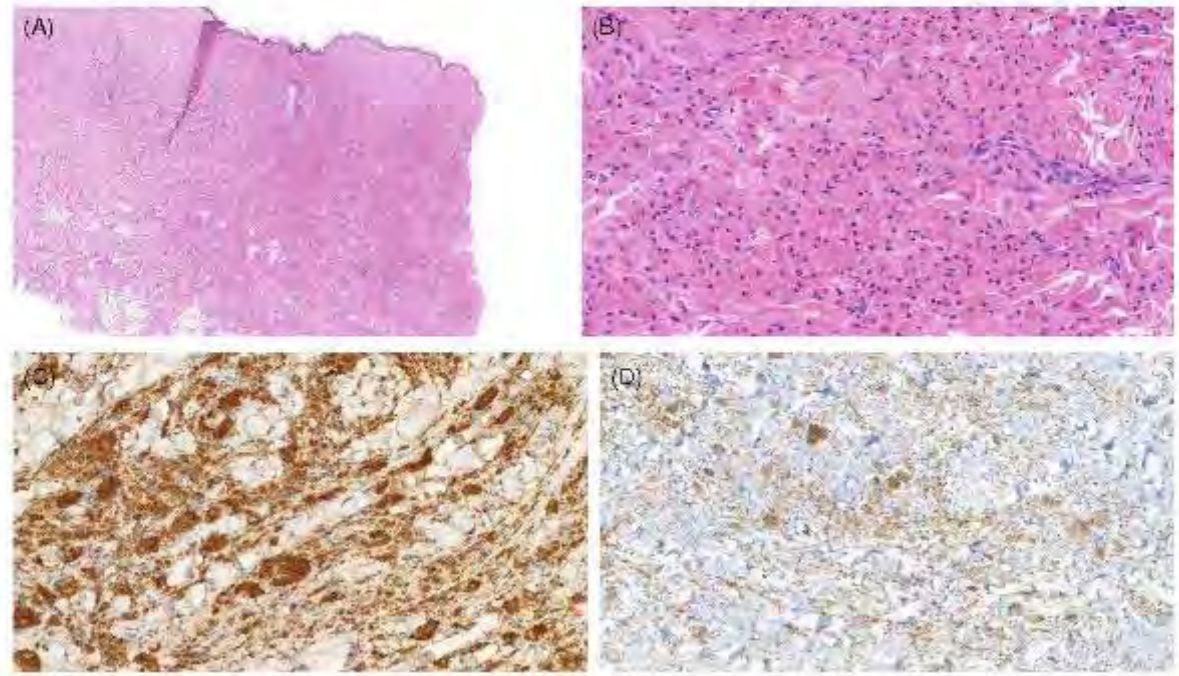

FIGURE 2 Case 1—Histopathologic features and immunohistochemical findings. (A) Histologic sections demonstrated epithelioid cells intercalating through dermal collagen bundles. (B) The cells had mildly irregular hyperchromatic nuclei with variable small prominent nucleoli and abundant cytoplasm with pink crystalline structures. (C) Histiocytes were kappa light chain restricted (D) and are highlighted by CD68 immunohistochemical stains (A, B: H&E; C, D: Immunohistochemistry; A: ×10; B, C: ×200; D: ×100).

Journal of Cutaneous Pathology

WILEY

CASE STUDY

Cutaneous Crystal-Storing Histiocytosis With Marginal Zone Lymphoma. A Case Report With A Striking Clinical Presentation

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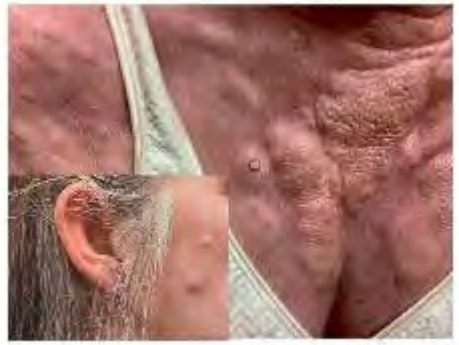

FIGURE 1 | Clinical presentation of CSH. Numerous large confluent nodules and plaques with [illegible] appearance.

[illegible] histopathologic finding of histiocytes [illegible] crystals [illegible] plasmacytic infiltrates. It commonly presents in a wide [illegible] lymphoproliferative disorder. Dermatologic examination typically [illegible] on the trunk, proximal extremities, head, and neck, [illegible] CD68-positive histiocytes with a wavy-granular appearance [illegible] needle-like or rhomboid crystals in the cytoplasm. The [illegible] is [illegible] associated monotypic B-cell population, often lymphoplasmacytic [illegible] with a striking clinical presentation of cutaneous CSH. [illegible] year-old female with a history of marginal zone [illegible] comprised of confluent nodules and plaques with an infiltrated dermis and the subcutaneous fat, producing a marked 'peau d'orange' appearance of the affected skin on the face, neck, chest, and upper extremities. Histopathologic examination confirmed kappa light chain–restricted cutaneous CSH with a monoclonal lymphoplasmacytic infiltrate consistent with cutaneous MZL.

1 | Introduction

[illegible] described in the United States in a case report published in 1987 by Tateishi et al. in a patient with multiple myeloma [1]. In large series of CSH, cutaneous involvement [illegible] approximately 8% of cases [2]. The dermatopathology literature is limited, including the initial case report, only 15 cases have been described in the literature to date worldwide [3–7]. Overall, cases of cutaneous CSH are predominantly associated with multiple myeloma, lymphoplasmacytic lymphoma, and aqueous kappa light chains. This case is significant and unique in that it is the only reported study of cutaneous CSH with kappa light chains and extranodal MZL in the other than cutaneous MZL occurs most often [3, 6, 7]. Herein, we describe extensive cutaneous involvement,

2 | Case Report

A 61-year-old female with a prior history of extranodal MZL was referred to the dermatology clinic in March 2025 with multiple new cutaneous lesions on her neck, chest, shoulders, face, and upper arms that had been intermittently appearing within the past month. Previously in September 2022, she had presented with a gradually enlarging mass on her left neck. She had been present

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CASE STUDY

A Rare Case of Cutaneous Crystal-Storing Histiocytosis With Kappa Light Chain Restriction and Unusual BCL6 Expression

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Correspondence: Jonathan L. Curry (jlcurry@mdanderson.org) | Phyu T. Aung (ptaung@mdanderson.org)

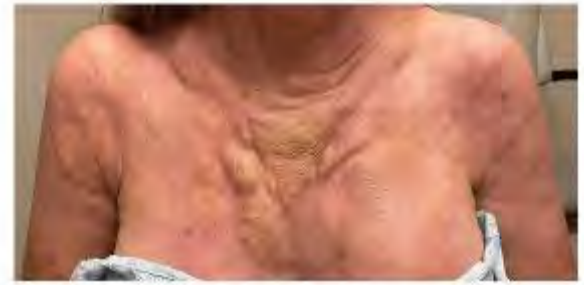


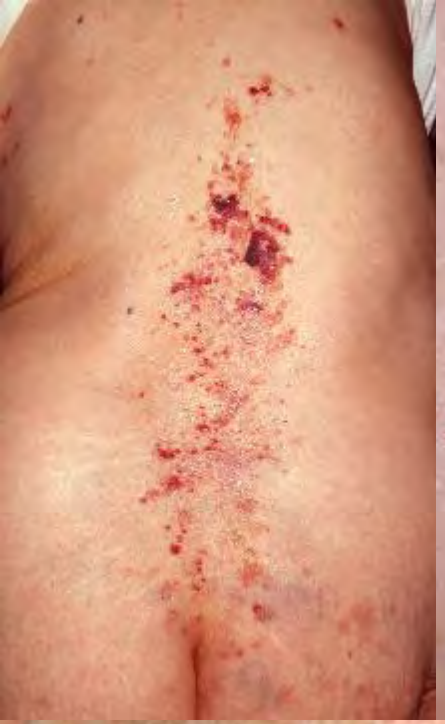
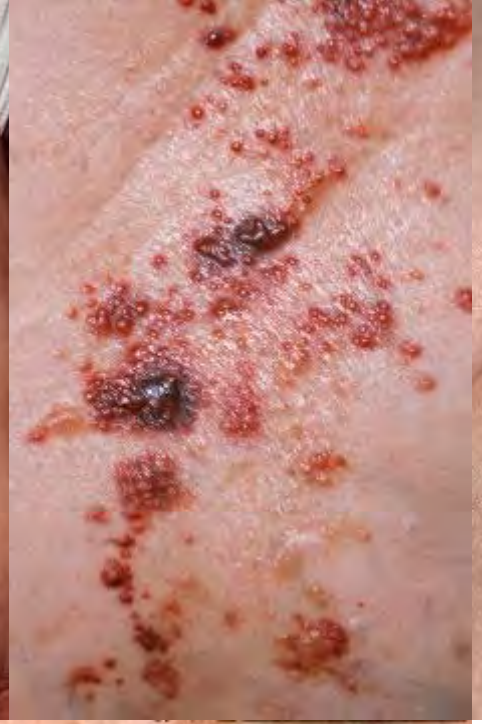
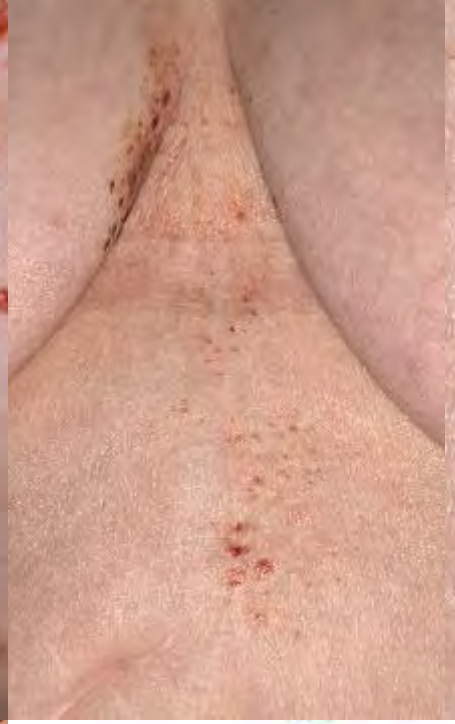
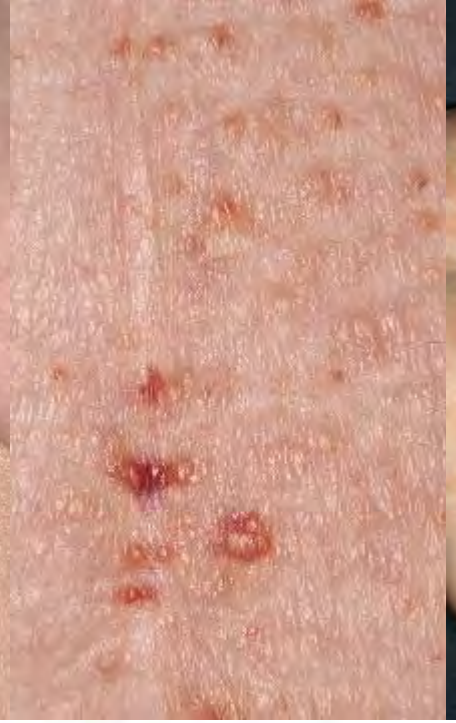
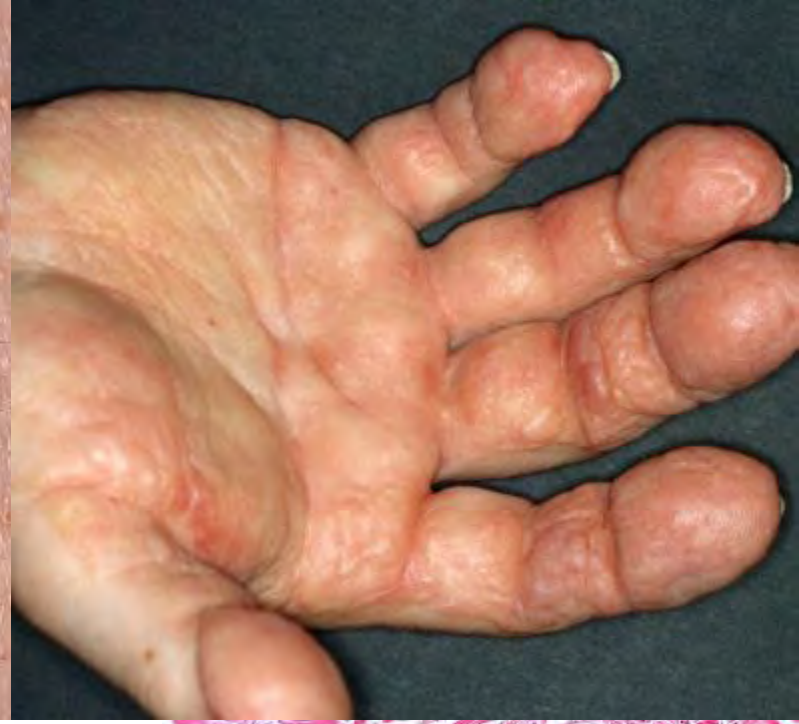
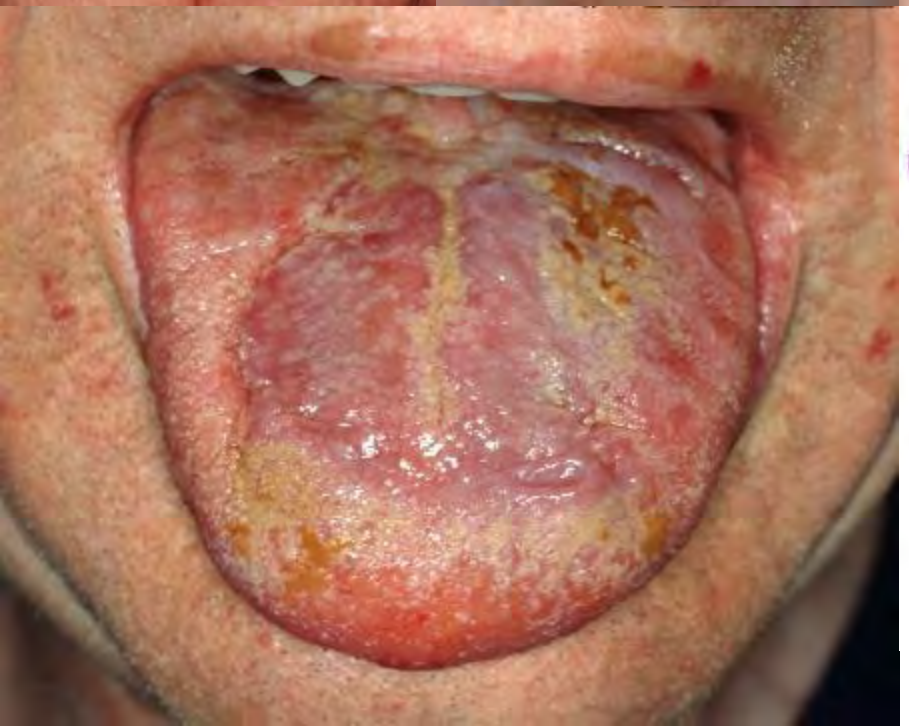
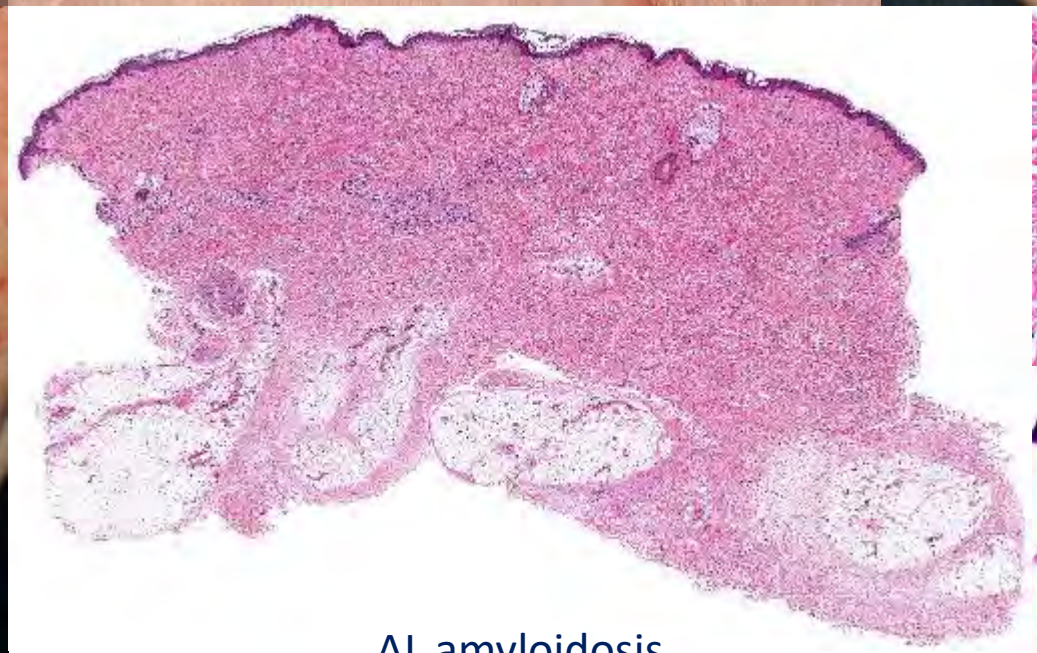
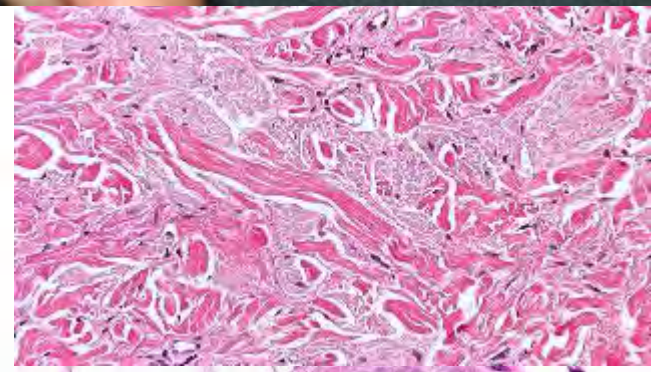
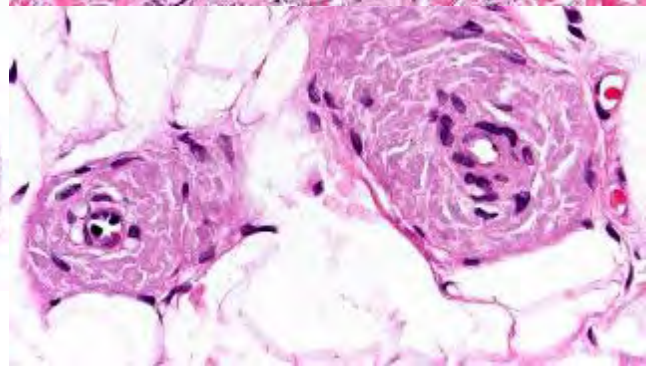
FIGURE 1 | Cutaneous crystal-storing histiocytosis. Representative clinical picture showing ill-defined pink to flesh-colored indurated plaques and cutaneous lesions on the chest and proximal upper extremities.

[illegible] characterized by the accumulation of crystalline [illegible] or plasma cell neoplasms. Cutaneous involvement is [illegible] with [illegible] plaques involving the face, [illegible] histiocytes containing intracytoplasmic crystals. [illegible] were positive for CD68 and CD163. Flow cytometry demonstrated a monoclonal immunoglobulin kappa light chain [illegible] gammopathy, supporting a diagnosis of cutaneous involvement with localized CSH. Weak, nonspecific [illegible] expression [illegible] sequencing did not identify a BRAF V600E mutation. Histiocytes showed weak BCL6 expression of uncertain significance in CSH, emphasizing [illegible] for an underlying lymphoplasmacytic [illegible] may complicate interpretation.

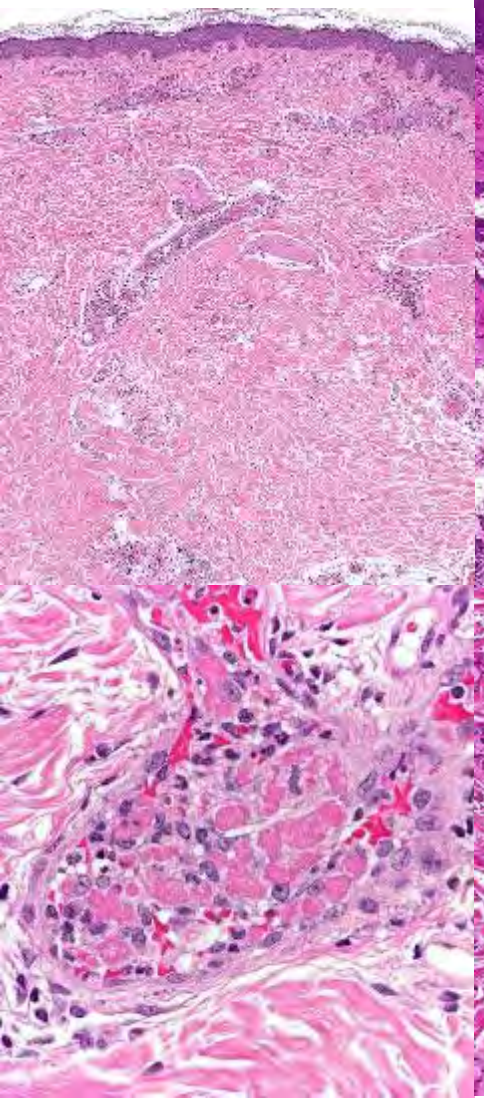
1 | Introduction

Crystal-storing histiocytosis (CSH) is a rare condition that was first described by Glass in 1917 [1]. Histologically, it is defined by the presence of cytoplasmic crystalline inclusions within [illegible] histiocytes, which can accumulate across various organ systems. CSH most commonly results from the intracellular deposition of immunoglobulin light chains—particularly kappa light chains—less frequently, it may involve Charcot-Leyden crystals, silica, or drug-related crystalline material [2, 3]. The majority of reported cases are associated with underlying lymphoproliferative or plasma cell neoplasms, including multiple myeloma, marginal zone lymphoma, lymphoplasmacytic lymphoma, and monoclonal gammopathy of undetermined significance [3, 4]. In a minority of cases, CSH has been reported in the context of reactive inflammatory conditions, autoimmune diseases, metabolic disorders, or medication-induced crystal deposition [2].

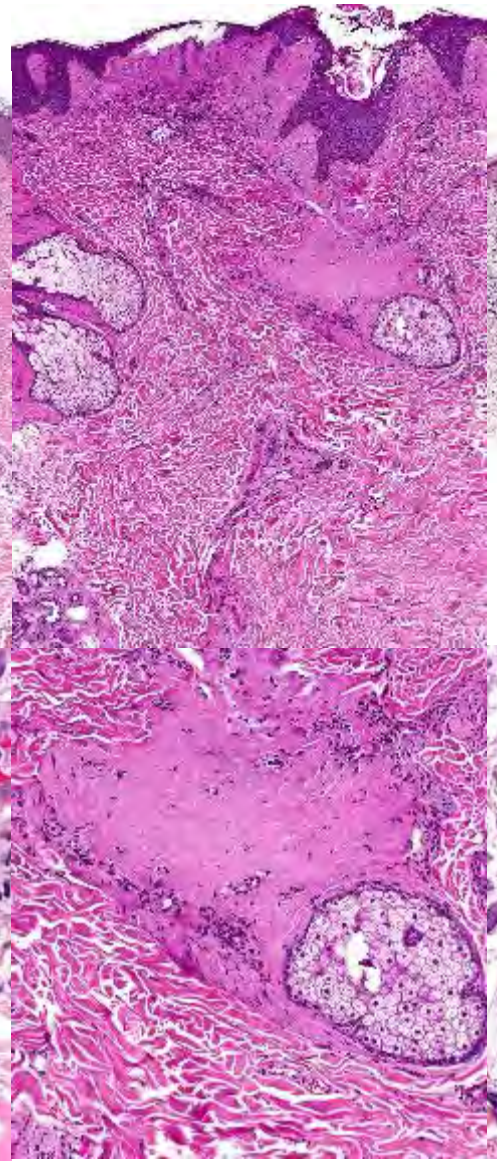
CSH may present as either a localized process—restricted to a single organ or site—or as a generalized condition involving multiple organ systems. Reported sites of involvement include bone marrow, kidney, lung, lymph nodes, skin, ocular tissue, and the gastrointestinal tract, while cutaneous involvement is








AL amyloidosis



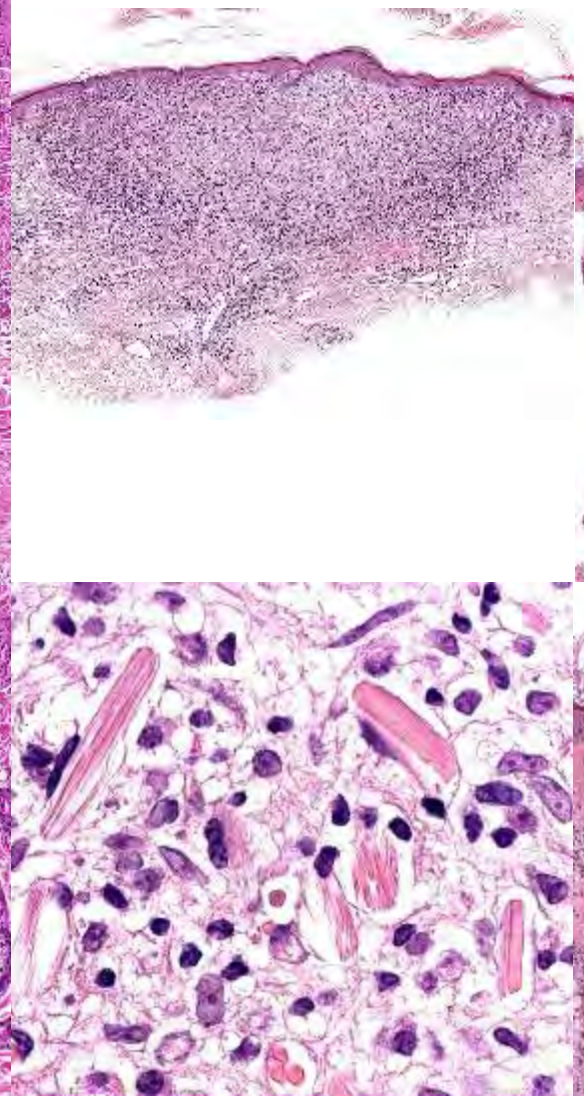
Different faces of immunoglobulins' deposition in the skin



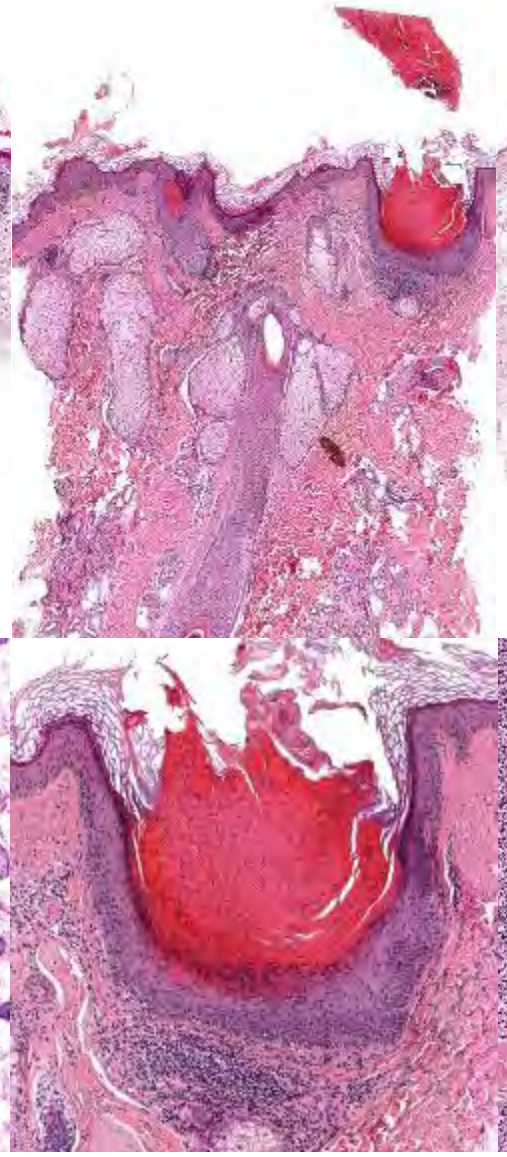
Monoclonal cryoglobulinemia



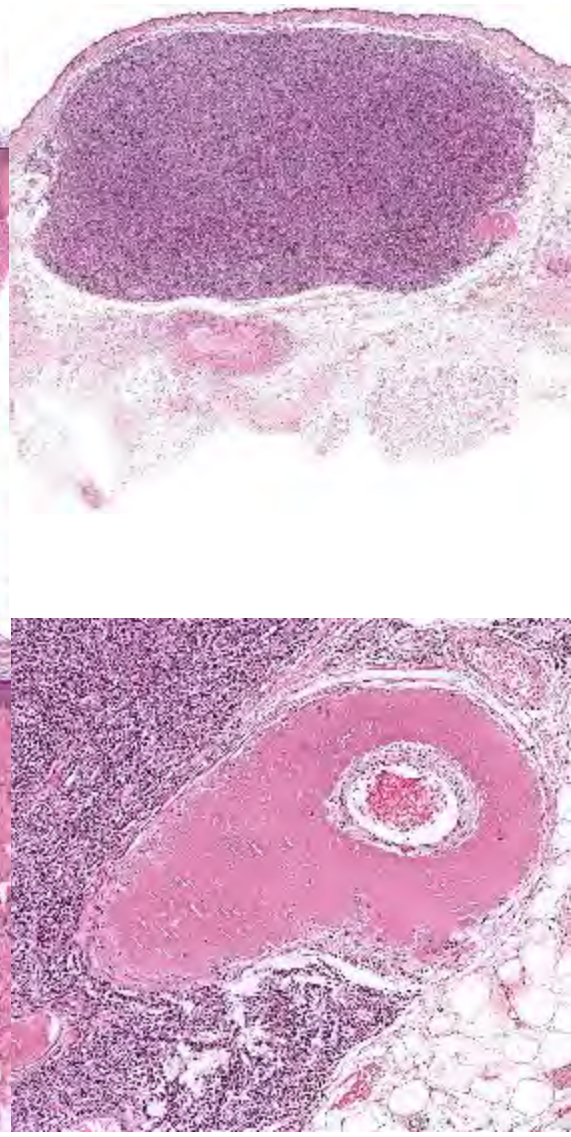
Macroglobulinosis



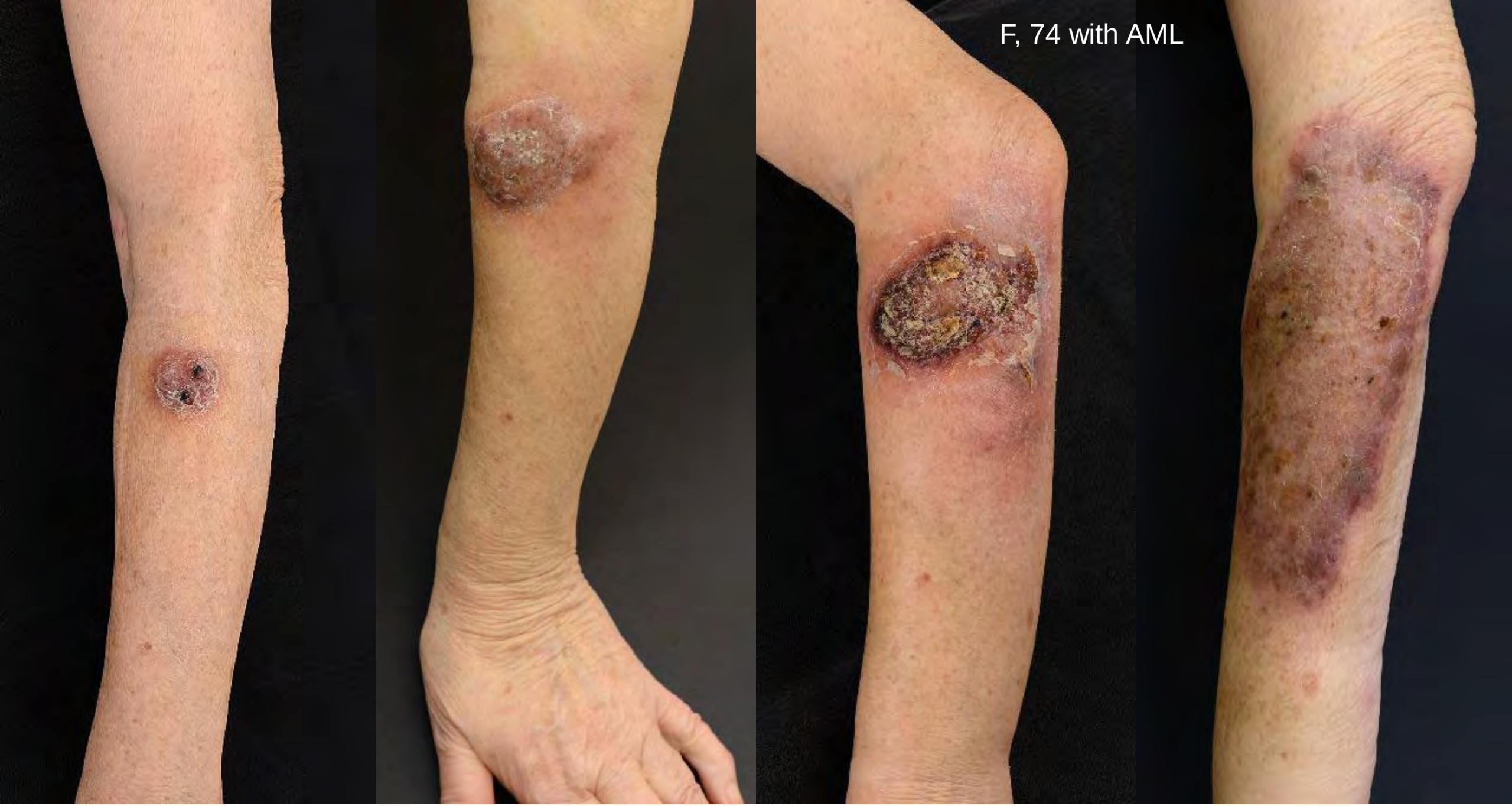
Crystal storing histiocytosis



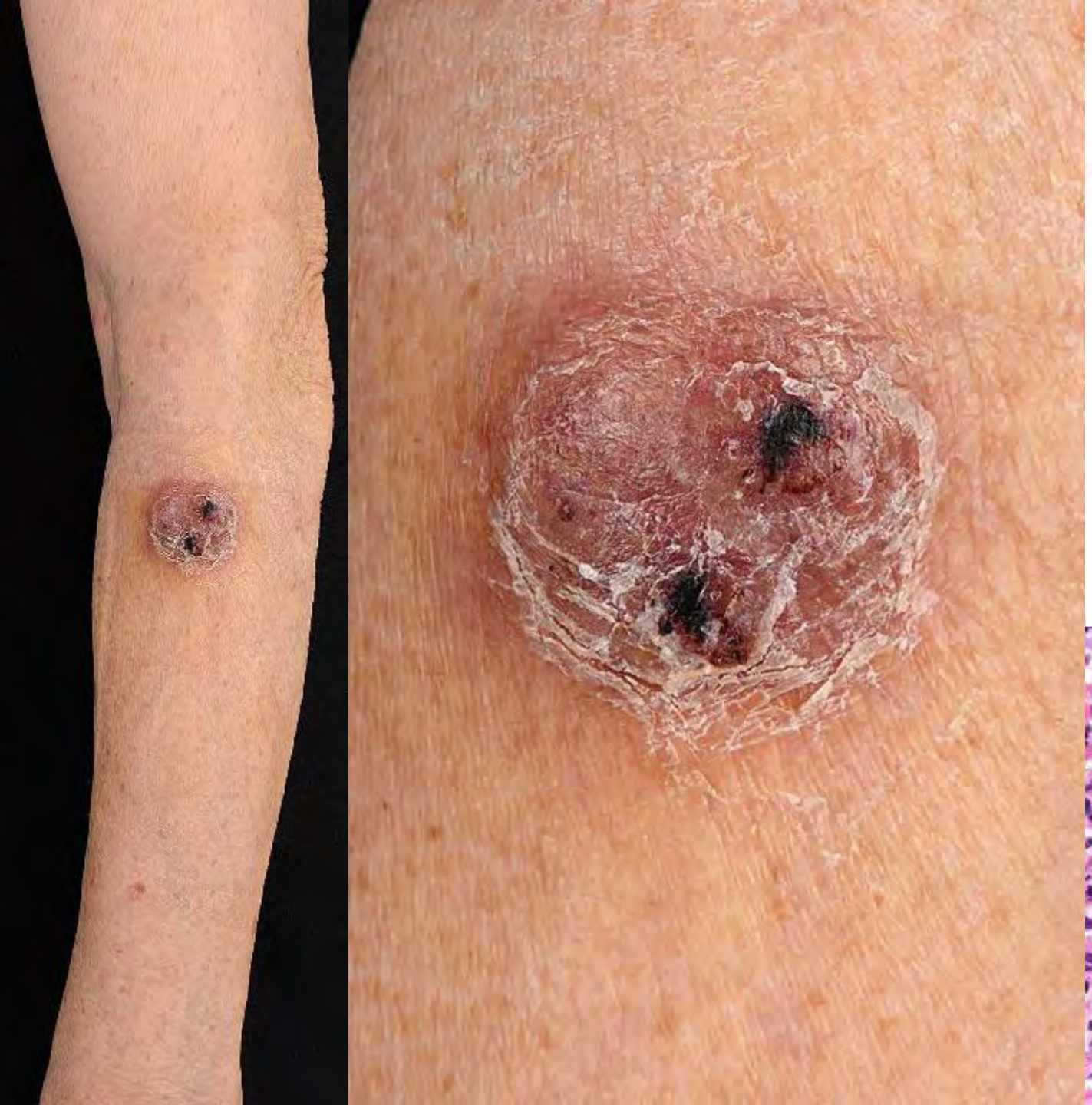
Follicular hyperkeratotic spicules

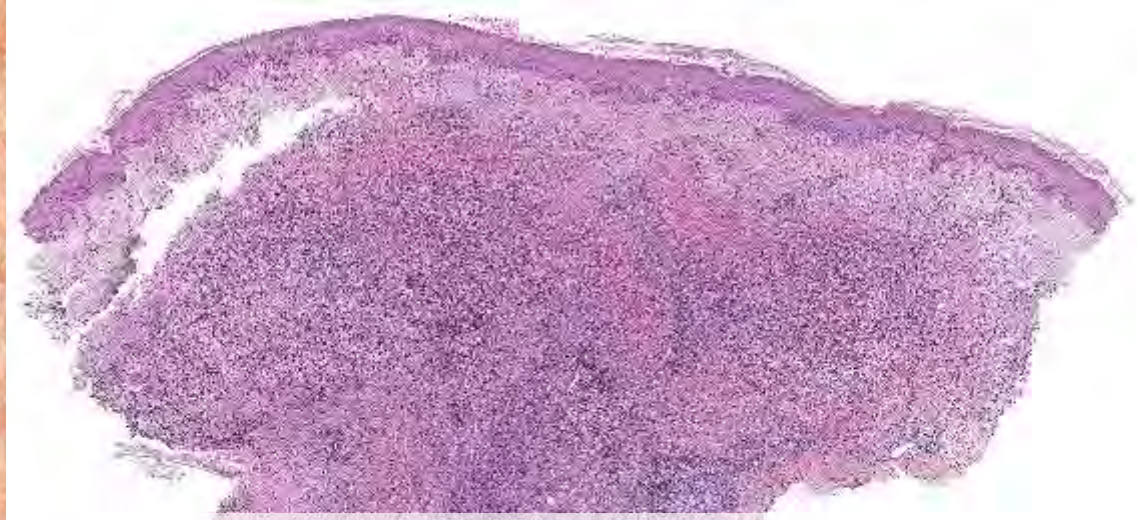


AL amyloid in myeloma

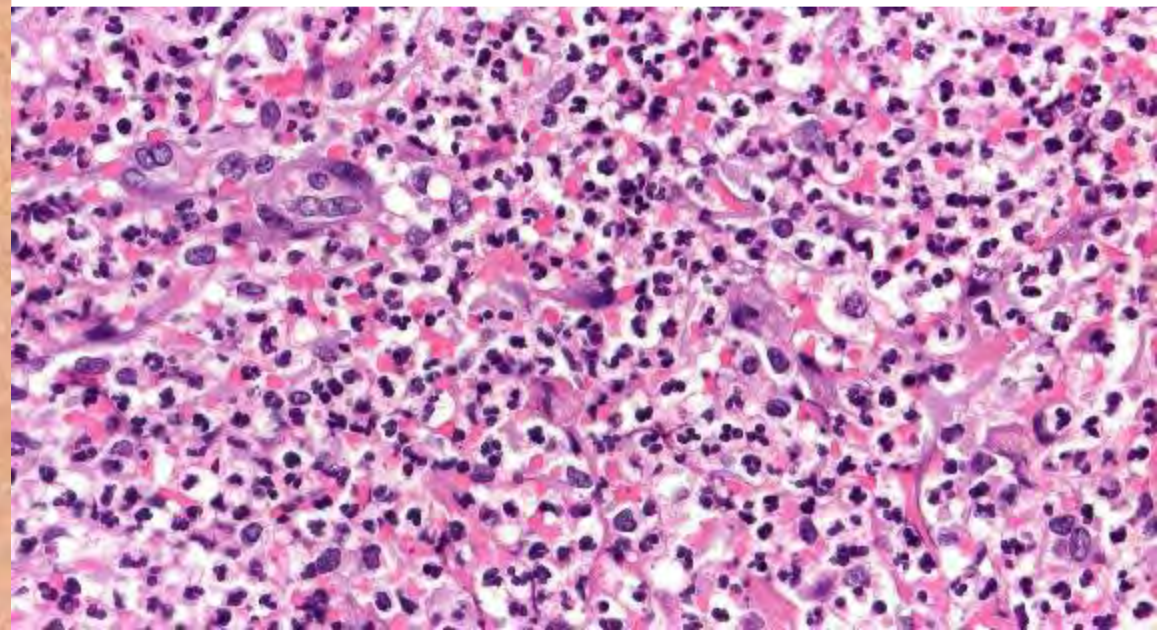


1st presentation + 17 days + 26 days + 54 days





Bullous pyoderma gangrenosum in AML



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Atypical bullous pyoderma gangrenosum associated with myeloid malignancies

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SUMMARY Atypical bullous pyoderma gangrenosum was diagnosed during the course of a myeloid malignancy in three patients. One patient had chronic myeloid leukaemia, one acute myeloid leukaemia, and the third, refractory anaemia with excess of blasts. This atypical form of pyoderma gangrenosum has been specifically associated with myeloid malignancies. The atypical appearance of the skin lesions and the clinical context in which they arose caused the true diagnosis to be delayed in all cases. Treatment with steroids was associated with rapid healing of the skin lesion. The histopathological changes in the skin biopsy specimens from these cases were non-specific, and although the histology was considered to be atypical of pyoderma gangrenosum in one case, the unusual features could be attributed to the patient's neutropenia. (Skin biopsy was performed to exclude other specific pathology).

Atypical bullous pyoderma gangrenosum is an uncommon association of the myeloid malignancies. It may remain unrecognised and should be considered more often.

Pyoderma gangrenosum is a clinical diagnosis largely based on the appearance of the typical lesion. This has a raised plaque with progressive central necrosis and a bluish-red necrotising border. A rapid response to steroids lends further support to the diagnosis and is thought to be an essential diagnostic criterion by some authors.[1] Although a skin biopsy specimen is usually obtained, it does not provide independent confirmation of the diagnosis. The histopathological features are non-specific and variable. Some features remain in dispute[2-4]: the presence of vasculitis, in particular, is thought by some authors to exclude pyoderma gangrenosum.[3]

Fifty per cent of cases are associated with bowel disease,[4] and when seen in this clinical context, the diagnosis is easy. Diagnostic difficulty may arise in the absence of systemic disease or with less well known associations such as myeloid malignancies. Pyoderma gangrenosum has been observed in patients with myeloproliferative disorders,[4,5] myelodysplasia,[2,6] and acute myeloid leukaemia.[4,7] Though it has been associated with blast crisis and poor prognosis, it may arise at any stage of the disease, even as the presenting complaint.[7] As skin lesions in myeloid malignancies are usually caused by haemorrhage, infection, or leukaemia cutis the true diagnosis of pyoderma gangrenosum may be delayed or missed. Additional problems may arise because the atypical bullous variant of pyoderma gangrenosum associated with myeloid malignancies[1,4,6] is often unfamiliar and may not be recognised.

We describe three cases presenting over 12 months to draw attention to the association between pyoderma gangrenosum and the myeloid malignancies, and also to illustrate the characteristic clinical features and natural history. The value of skin biopsy in this situation and the range of histopathological changes are also reviewed.

Case reports

CASE 1

A 26 year old salesman with a lifelong history of mild eczema, presented with classical Philadelphia chromosome positive chronic myeloid leukaemia in 1975. Although he had massive splenomegaly and a presenting white cell count of 455 × 10^9/l, his leukaemia was sensitive to busulphan and he remained well for a number of years. By 1983 increasing splenomegaly, resistance to busulphan, and additional

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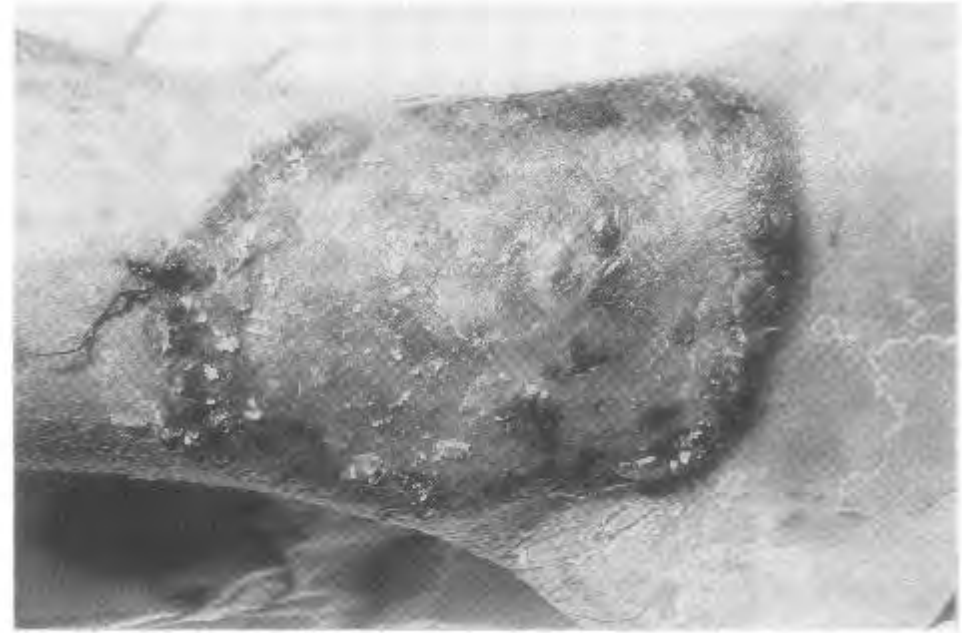


Fig 1 *Rapidly extending ulcer over medial malleolus from case 1 showing bluish-grey undermined margin and surrounding erythema.*

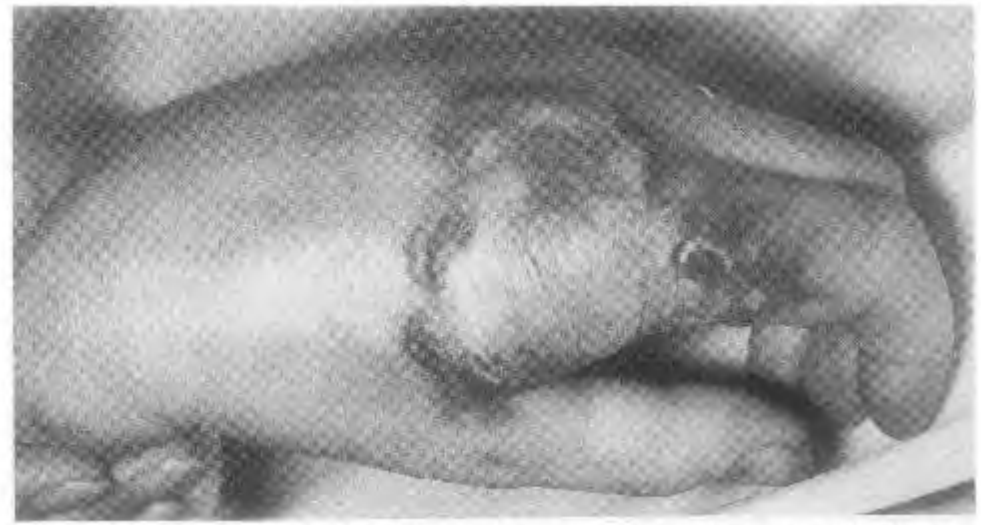
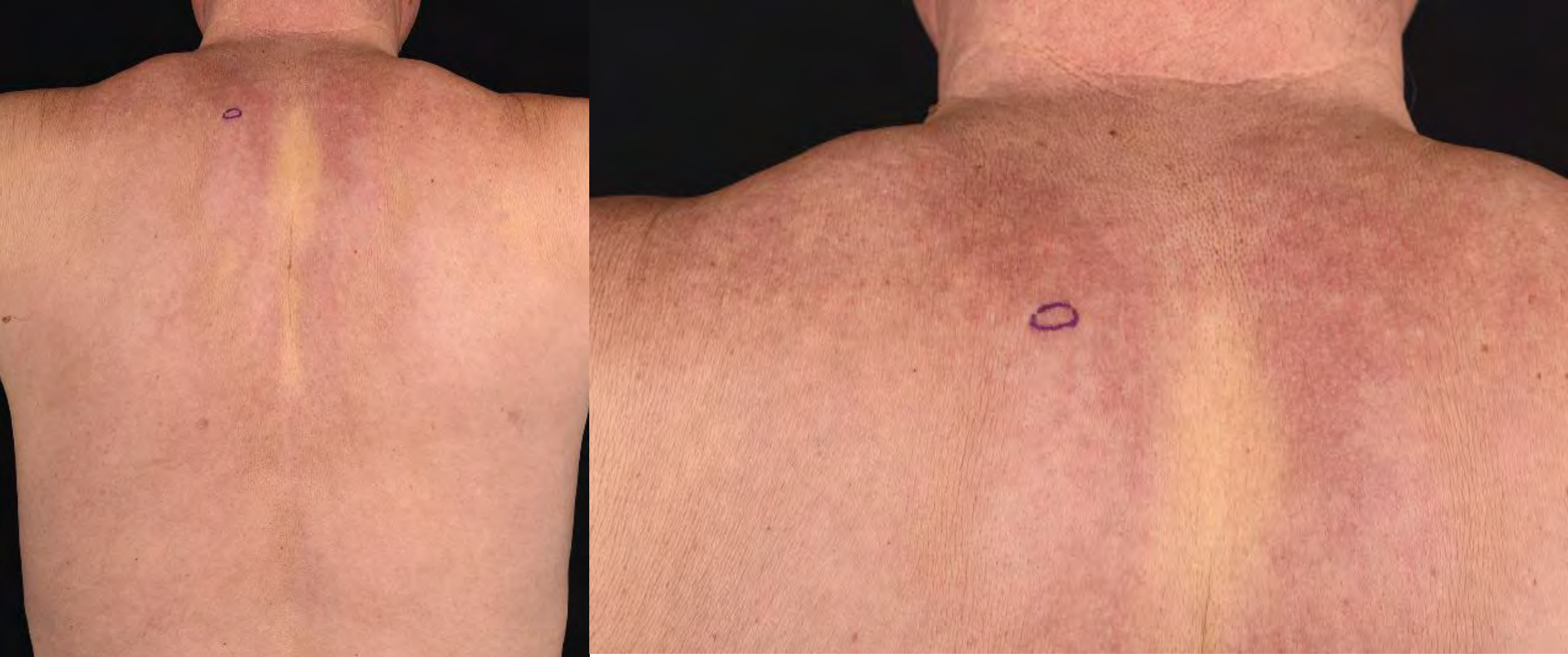


Fig 4 *Painful bullus arising on back of left hand from case 3, photographed 36 hours after appearance of initial area of erythema, showing raised pale bluish-grey margin and surrounding erythema.*

Skin conditions mostly associated with hematological malignancies

- *Scleromyxedema, normolipemic plane xanthomas, necrobiotic xanthogranuloma:* in the setting of paraproteinemia, without deposition of paraproteins in the skin
- *Cristal storing histiocytosis, cutaneous macroglobulinosis:* in the setting of paraproteinemia, with deposition of paraproteins in the skin
- *Monoclonal cryoglobulinemia:* intravascular deposits of immunoglobulins resulting in an occlusive vasculopathy
- *Follicular spicules of the nose / face:* extrusion of cryoglobulins through the hair follicles
- *Paraneoplastic pemphigus:* production of autoantibodies, occurring mainly in hematological (mostly B-cell) malignancies and Castleman's disease
- *AL amyloidosis:* In the setting of plasma cell disorders (e.g., multiple myeloma, MGUS, Waldenstrom macroglobulinemia)
- *Bullous pyoderma gangrenosum:* A variant of pyoderma gangrenosum associated mostly with myeloproliferative disorders

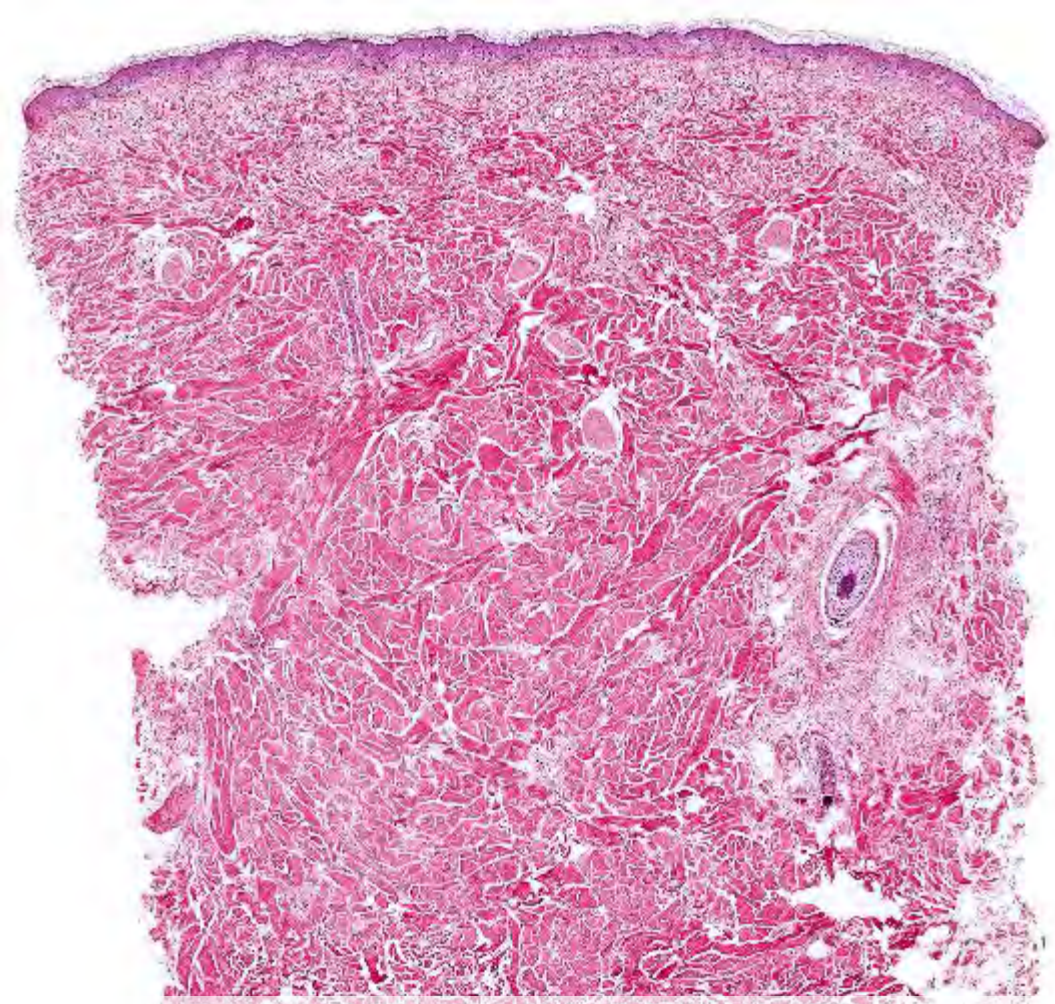


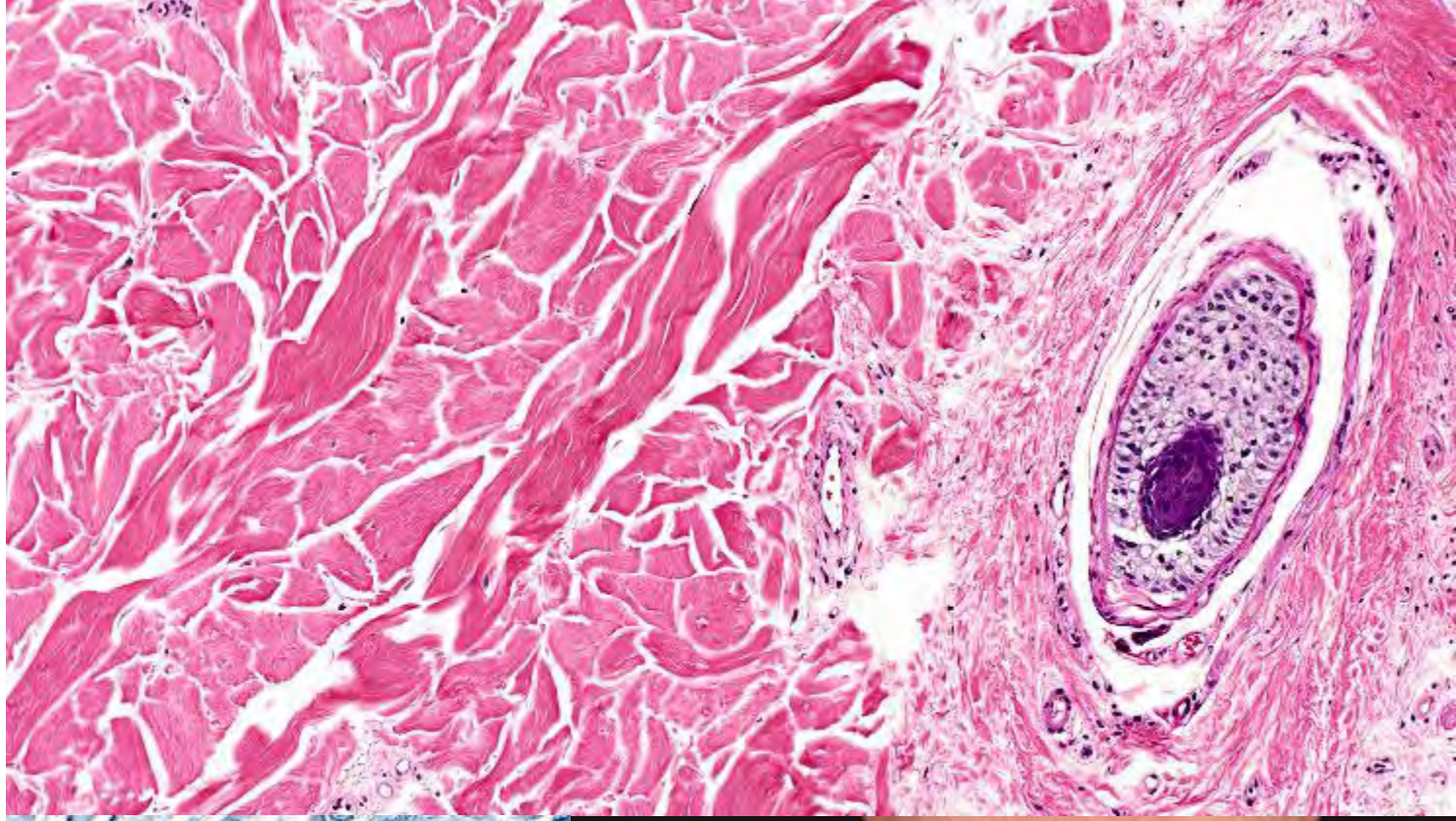
M, 58

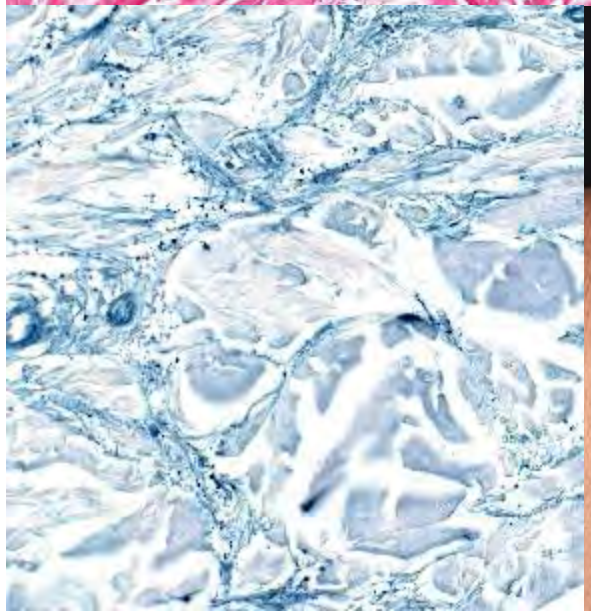
History of recurrent infections of the upper respiratory tract.

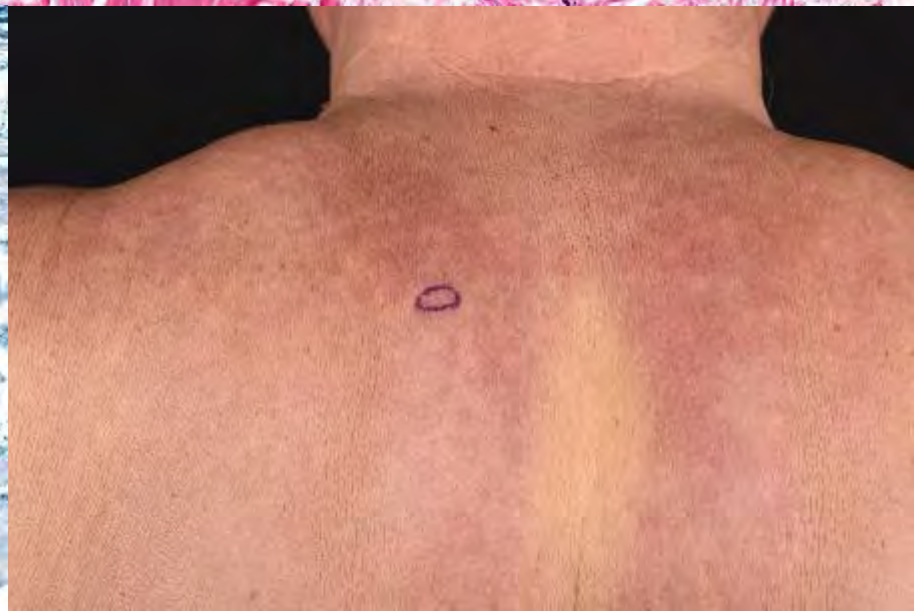
According to the patient slowly increasing, indurated lesions on the upper back for 2-3 years.

A biopsy is taken.







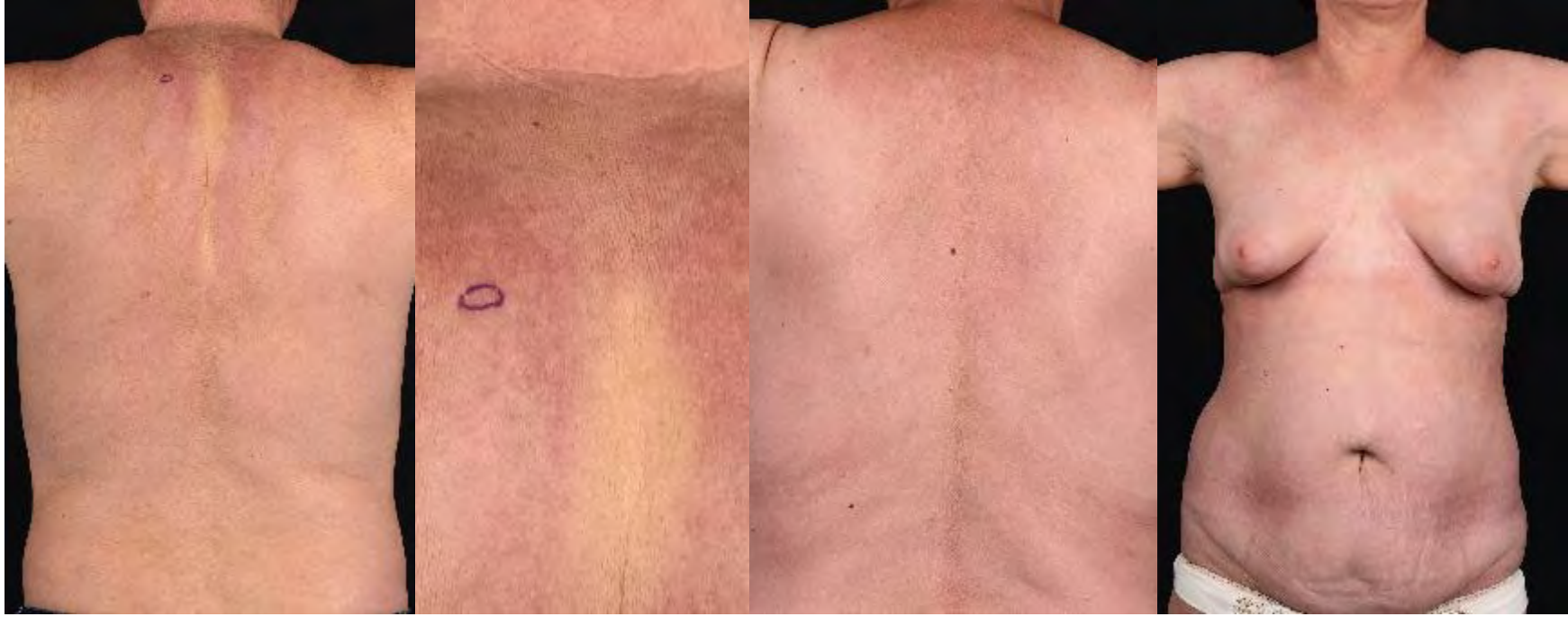


Scleredema adultorum (Buschke)

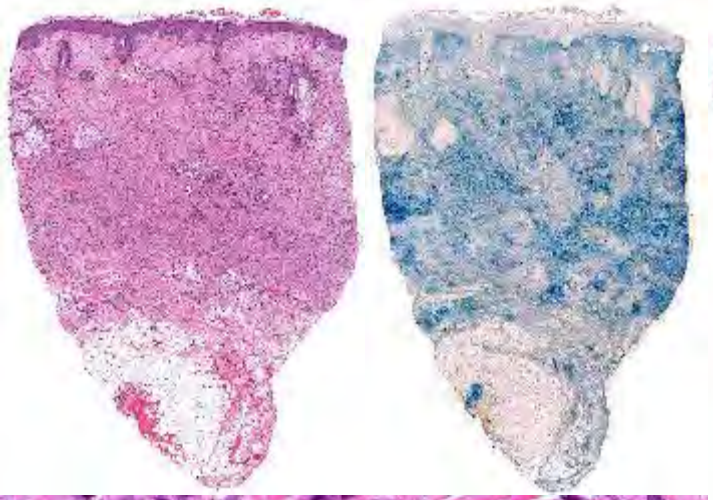
Normal glycemia, no paraproteins

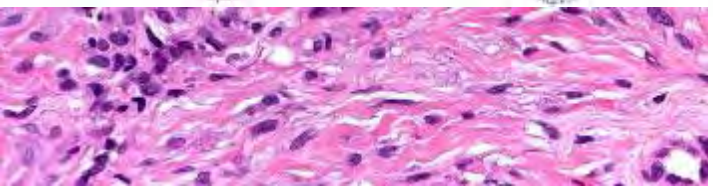
Scleredema adultorum (Buschke)

- Mostly associated with adult-onset diabetes mellitus or after infections (particularly upper respiratory tract or viral infections); can be observed in patients with monoclonal gammopathies / paraproteinemia
- Thickened dermis with "fenestrated" pattern and interstitial deposits of mucin, without increase in the number of fibroblasts and without inflammation
- Must be differentiated from morphea (mucin deposition not uncommon in morphea, yet usually presence of an inflammatory infiltrate, sometimes with plasma cells)

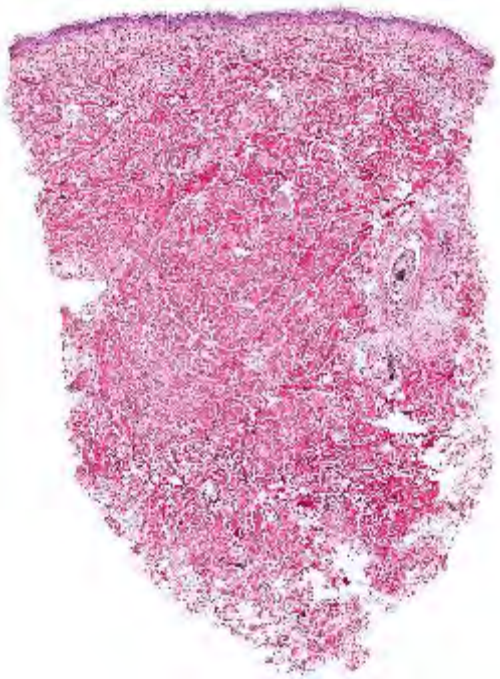


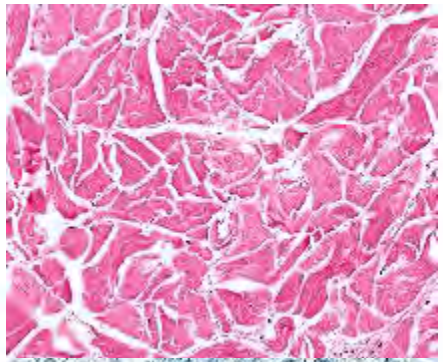
Scleromyxedema



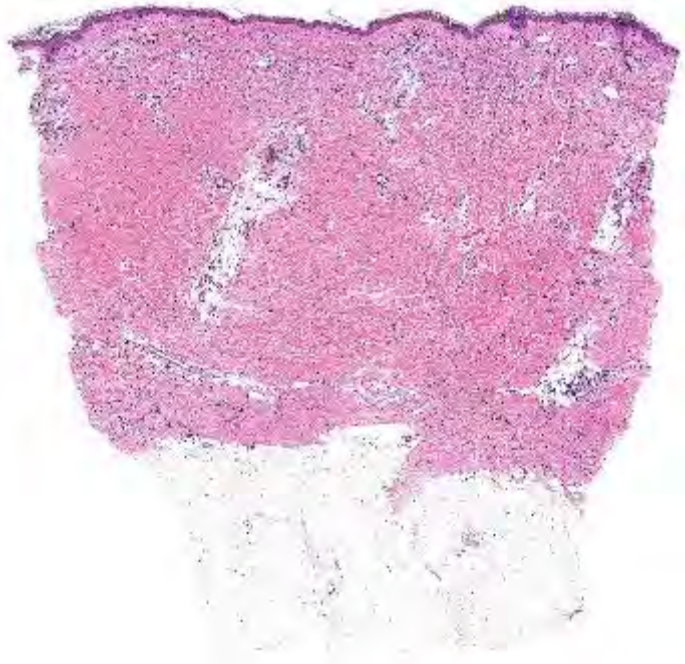


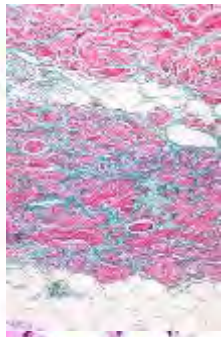
Scleredema adultorum (Buschke)

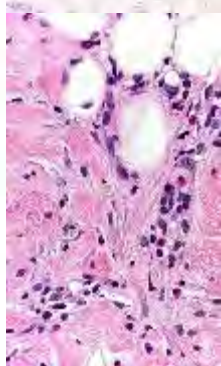


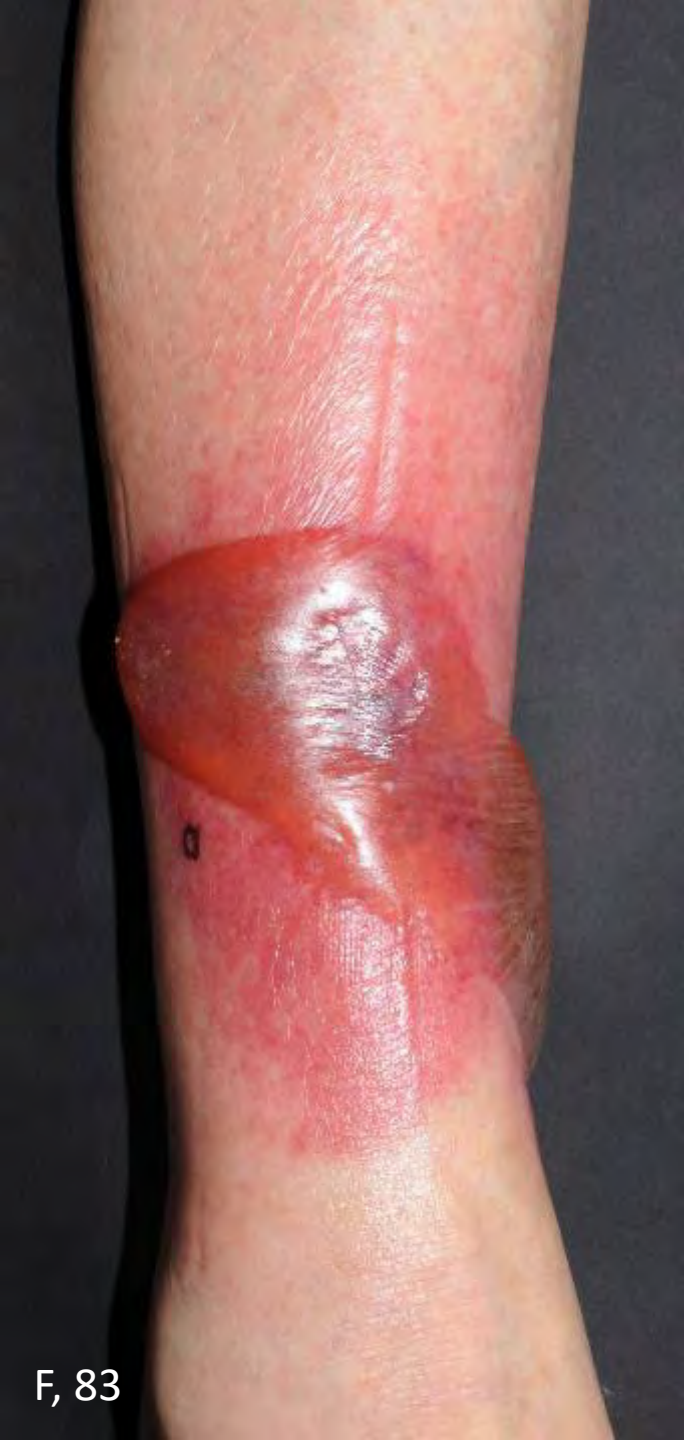


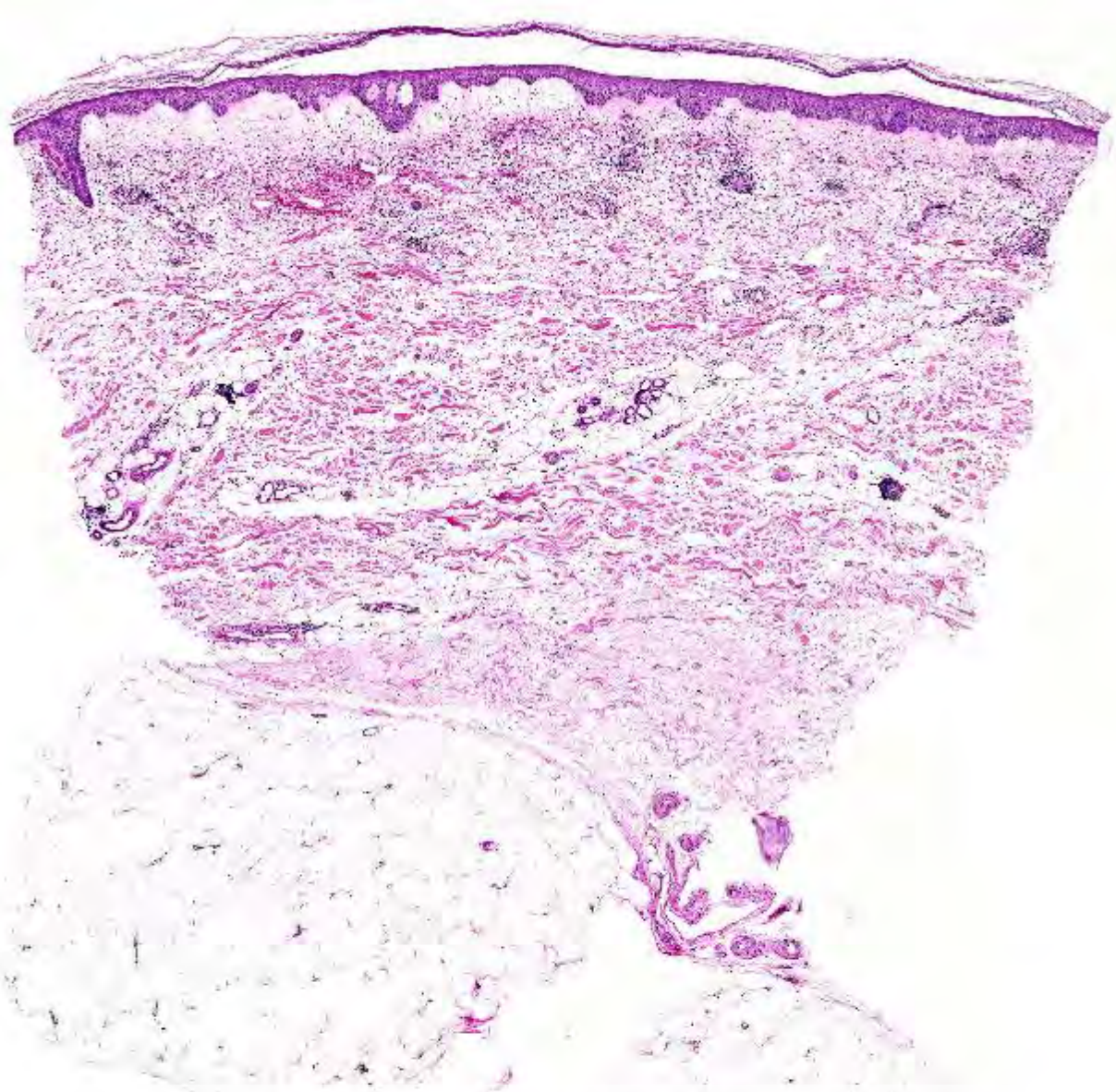
Morphea

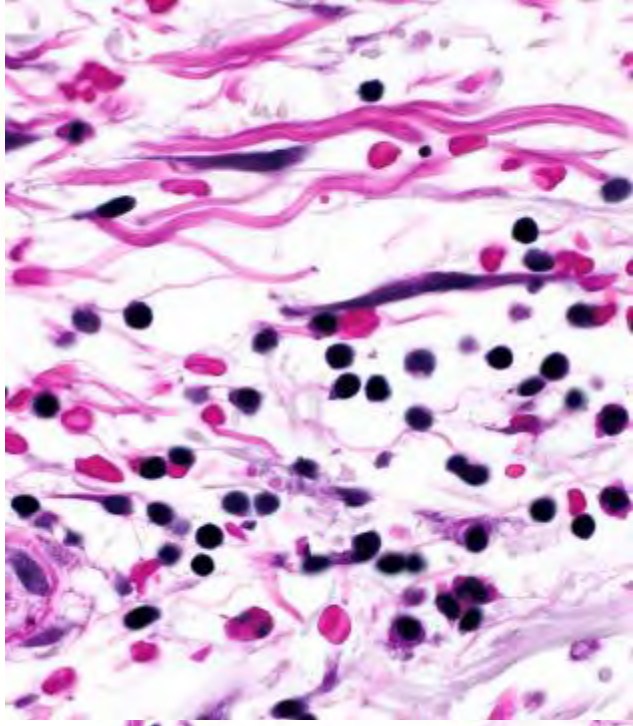


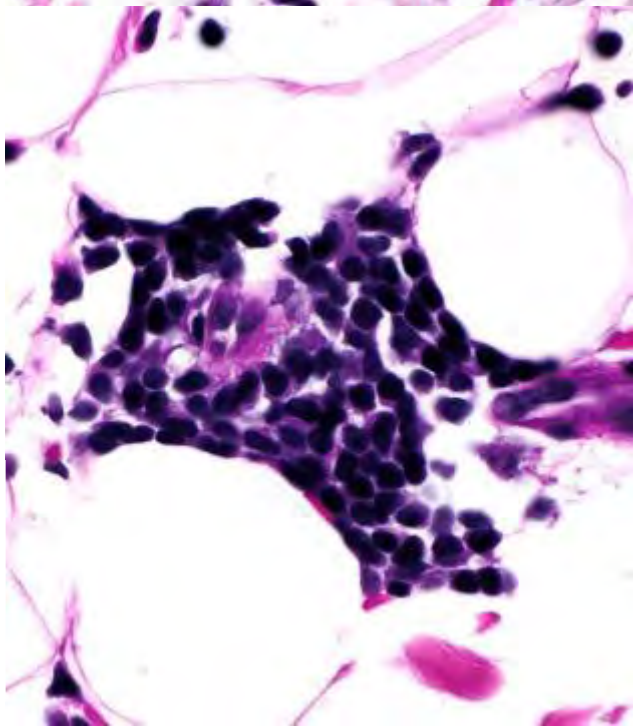












Exaggerated arthropod bite-like reaction in B-CLL

8 individuals with B-CLL, who were found to have severe troublesome local reactions to insect bites, usually mosquito.

Exaggerated Delayed Hypersensitivity to Mosquito Bites in Chronic Lymphocytic Leukemia

By Robert L. Wood

IT IS THE PURPOSE of this report to describe the occurrence of unusual cutaneous hyperreactivity phenomena in certain patients having chronic lymphocytic leukemia. These reactions are consistent with an exaggerated delayed hypersensitivity type of response to insect bites, inoculated mosquito antigen and to certain other delayed hypersensitivity antigens.

The mosquito is an example of certain insects whose bites are capable of evoking both immediate and delayed hypersensitivity types of cutaneous response.[1] Exaggerated delayed response may occur after initial sensitization and it is occasionally seen in children, but repeated exposure to the antigen seems to moderate the response. Spontaneous development of exaggerated delayed hypersensitivity to the mosquito is exceedingly rare in individuals past middle age. However, out of 97 cases of chronic lymphocytic leukemia that were seen between 1950 and 1963 at Strong Memorial Hospital, there were 8 individuals who were found to have severe troublesome local reactions to insect bites, usually mosquito. Such reactions display features consistent both with delayed cutaneous hypersensitivity and with leukemia cutis. The enhanced delayed hypersensitivity has led to further evaluation of the immunologic competency of these individuals.

Clinical Features

Gross and Histologic Appearance of the Insect Bite Lesions

Each of these patients had the cutaneous reactions on several occasions, but only those reactions with a definite history of an observed antecedent insect bite and/or evidence of a puncture wound in the center of the lesion are reported here. All of the patients who were able to identify the insect reported a mosquito as the offender. The reactions to the bites developed slowly, reaching their peak in from 12 to 24 hours and they were characterized by induration, edema, erythema and intense pruritis. The most severe lesions progressed to the development of bulla, up to 10 cm. in diameter surrounding the puncture. Figure 1 illustrates such a severe reaction to a known mosquito bite, resulting in hemorrhagic bullous formations. Resolution occurs spontaneously within 2 to 14 days.

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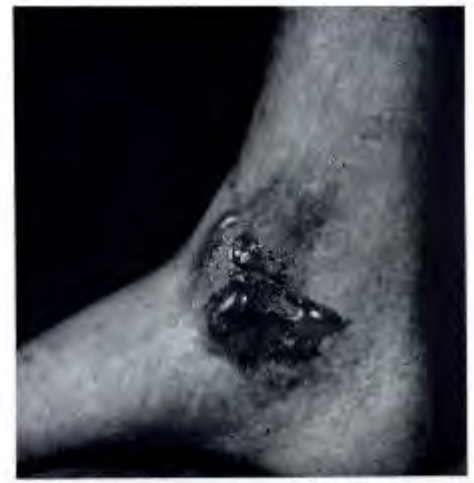
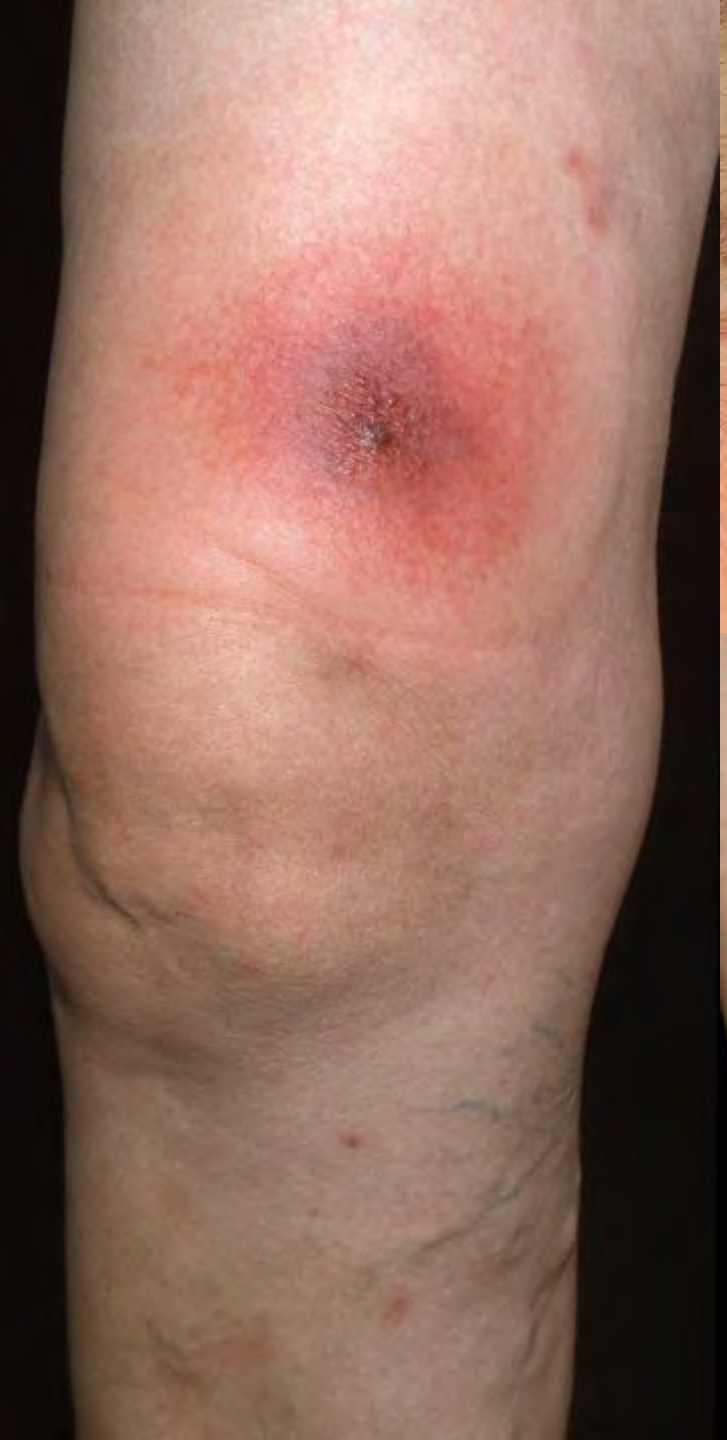
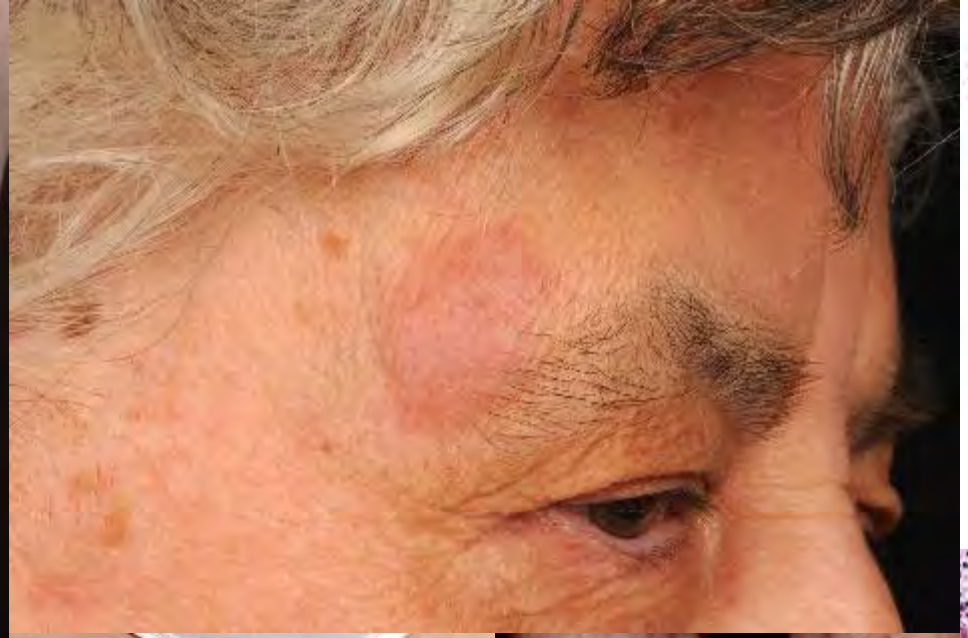
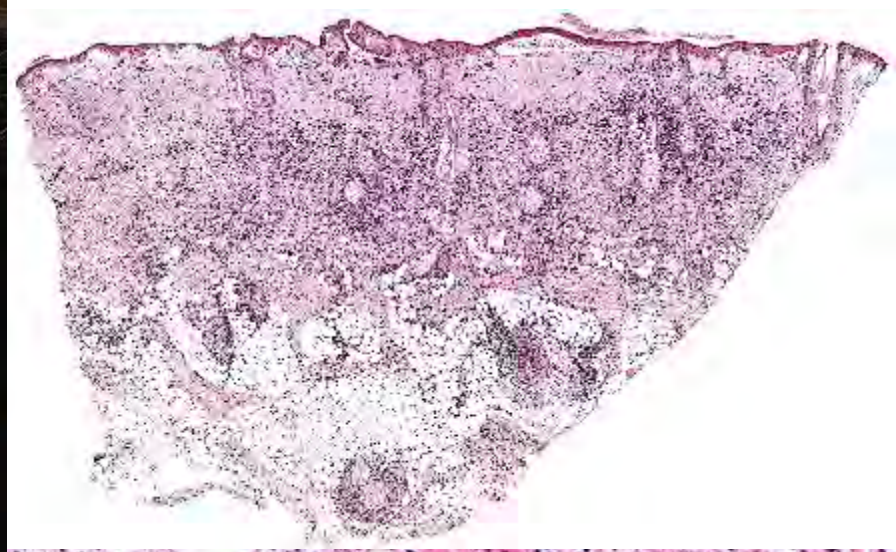
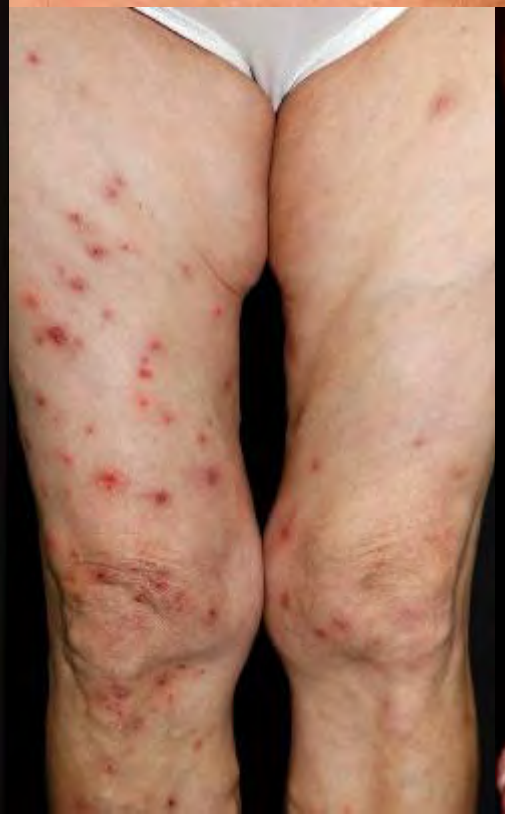
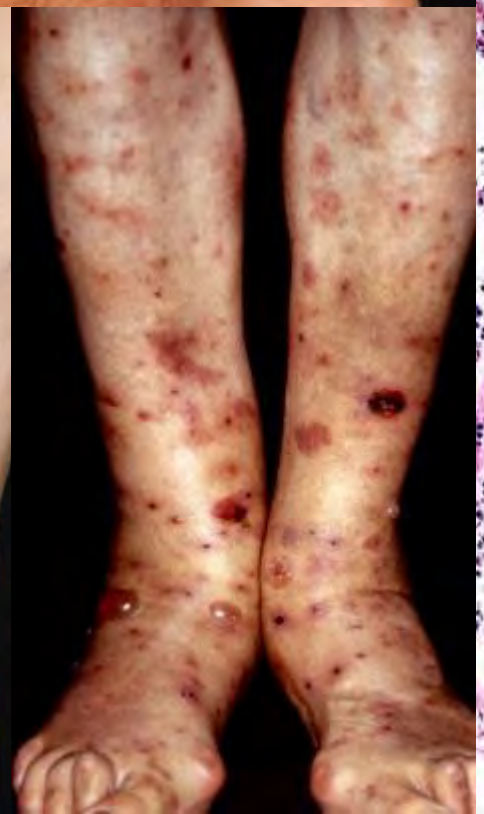
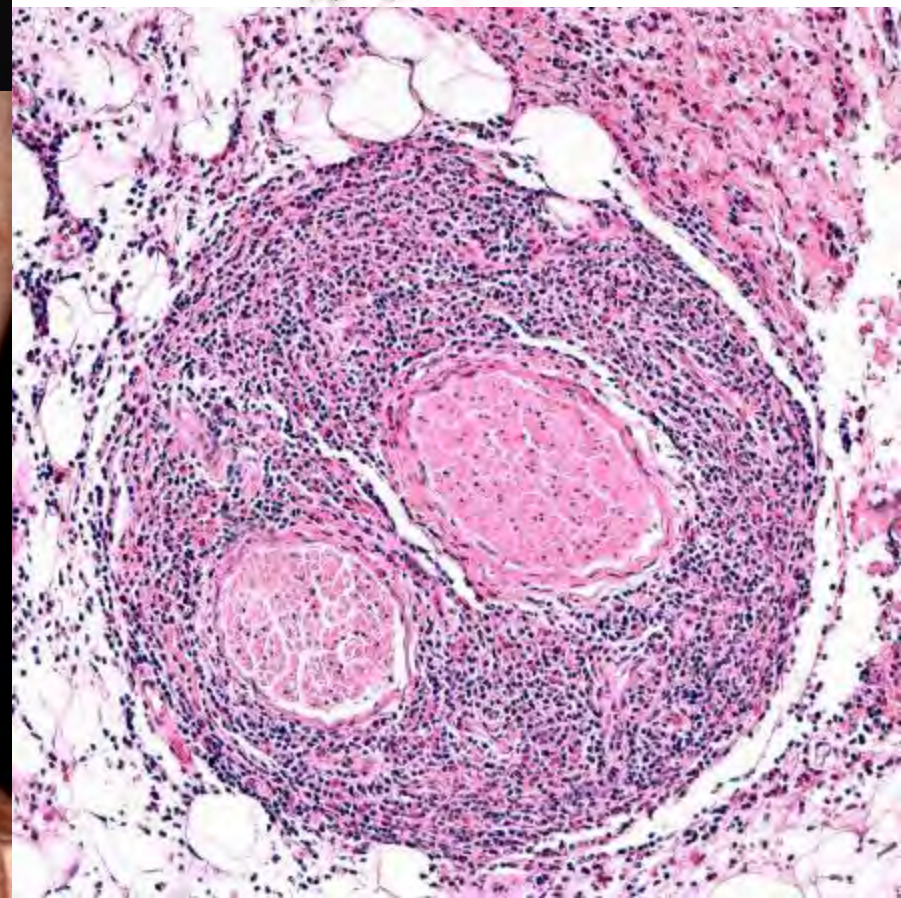


Fig. 1.—Gross appearance of severe hemorrhagic bullous lesion following mosquito bite in Patient No. 4 (I. J.) with chronic lymphocytic leukemia.

Table 4.—*Skin Tests in Patients with Hyper-reactivity to Insect Bites*

Patient No.	Prednisone When Tested	Ragweed 15 min.	P-K Transfer of Ragweed Immune Serum	Mosquito Antigen 1/1000	Mosquito Antigen 1/100	Monilia	Hormodendron	Cottonseed	Tobacco	Other
M. S. 3	no	0	+++	++	++++					
I. J. 4	yes	0	+++	0	+++					
H. B. 5	yes	0	++	0	+++					Had inactive tuberculosis
H. K. 6	no	0	+++	0	+++	0	0	+++	+	++++
S. C. 7	yes			+++	+++	+	++	0	0	Tuberculin
S. Y. 8	no	0	+++	0	+++	+	0	0	0	PPD and 1/10,000 OT negative

Immediate hypersensitivity (Bugweed) was read at 15 minutes and graded 1+ for erythema and edema confined to area of injection, 2+ for extension beyond area of injection and 3+ if pseudopods were identifiable. Delayed hypersensitivity reactions were read at 24 and 48 hours, with the more positive being reported: 1+, 5–10 mm. induration; 2+, 10–20 mm. induration; 3+, greater than 20 mm. induration, and 4+, necrosis

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Eosinophilic Dermatosis of Myeloproliferative Disease: Characterization of a Unique Eruption in Patients With Hematologic Disorders

Blood dyscrasias include a variety of malignant and premalignant conditions of blood or bone marrow such as leukemias, myelodysplasia, and myeloproliferative disorders. These disorders are associated with a broad range of cutaneous findings, ranging from recurrent cutaneous infections to malignant cell invasion. However, these eruptions are not associated with tissue eosinophilia, as seen in immunobullous diseases, parasitic infections, drug reactions, and cutaneous T-cell lymphoma. We describe 4 patients with blood dyscrasias who presented with a persistent, erythematous, pruritic, papulonodular eruption characterized by dermal lymphocytic and eosinophilic infiltrates. As our patients share many features with patients described elsewhere,[1-7] we have named this unique eruption *eosinophilic dermatosis of myeloproliferative disease*.

Report of Cases. The histories and clinical courses of our patients are summarized in **Table 1**. All were men, with hematologic disorders and a persistent, pruritic, papulonodular dermatosis characterized by prominent dermal eosinophilia. None of them reported an associated drug exposure, insect bite, parasitic infection, or collagen-vascular disease. On examination, the cutaneous lesions were erythematous papules and nodules distributed on the face, scalp, torso, extremities, and buttocks (**Figure 1**). No vesicles or bullae were present. In 2 cases, the eruption developed before the hematologic neoplasia was diagnosed; in 1 case, the eruption developed after the initiation of chemotherapy for chronic lymphocytic leukemia. In general, the lesions and associated pruritus were difficult to treat, being recalcitrant to numerous therapies. Two patients experienced complete clearing after systemic chemotherapy for leukemia, with prompt reappearance of the papulonodular eruption on discontinuation of the chemotherapy. In these 2 patients, chemotherapy was later reinstituted specifically to control the skin eruption. Recently, 2 patients have responded to narrowband UV-B phototherapy.

Skin biopsy specimens were obtained from each patient (1-6 per patient). Fifteen specimens were blindly reviewed by a dermatopathologist (M.L.C.) to evaluate qualitatively the extent and nature of the infiltrates. All specimens showed a superficial and deep lymphohistiocytic infiltrate that was perivascular in 15 (100%), periadnexal in 10 (67%), and perifollicular in 14 (93%). Diffuse dermal eosinophilia was noted in all specimens (**Figure 2**).

Comment. The differential diagnosis of the eosinophilic dermatosis seen in our 4 patients includes leukemia cutis and various reactive dermatoses. The most similar reactive process is eosinophilic pustular folliculitis, which has been associated with human immunodeficiency vi-

Table 1. Clinical Data on Index Cases of Eosinophilic Dermatosis of Myeloproliferative Disease*

Age, y	Diagnosis/Treatment	Onset	Location/Morphologic Findings	Pathological Findings	Course of Pruritic Eruption	Status
71	CLL (B cell)/ chemotherapy	8 y after CLL diagnosis	Face and scalp/erythematous nodules	Perivascular and periadnexal lymphocytic infiltrate with numerous eosinophils	Improved after chemotherapy; no response to topical or systemic steroids, antibiotics, antifungals, isotretinoin, or colchicine	Died of sepsis
53	CLL (B cell)/ chemotherapy	After first chemotherapy	Face, scalp, and torso/erythematous nodules	Perivascular and periadnexal lymphocytic infiltrate with numerous eosinophils	Improved after NBUVB; no response to antihistamines, topical steroids, or colchicine; partial response to oral steroids and dapsone	Alive with active disease
81	AML/chemotherapy	2 y before diagnosis of AML	Trunk, buttock, and extremities/ erythematous nodules	Perivascular and periadnexal lymphocytic infiltrate with numerous eosinophils	Improved after chemotherapy	Died of AML
71	MDS anemia with excess blasts/none	Several months before diagnosis of MDS	Scalp and extremities/ erythematous and hemorrhagic papules	Perivascular lymphocytic infiltrate with numerous eosinophils	Improved after NBUVB; no response to steroids, cyclosporine, hydroxyurea, or hydroxychloroquine sulfate	Alive with active disease

*CLL indicates chronic lymphocytic leukemia; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; and NBUVB, narrowband UV-B.

Eosinophilic dermatosis of *myeloproliferative* disease ??

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*CLL indicates chronic lymphocytic leukemia; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; and NBUVB, narrowband UV-B.

Journal of
Cutaneous Pathology

Eosinophilic dermatosis of hematologic malignancy

Michele J Farber[1], Sal La Forgia[2], Joya Sahu[3] and Jason B. Lee[3]

Cutaneous involvement by an eosinophil-rich process (eosinophilic dermatosis) may be encountered in the setting of various hematologic malignancies, including mantle cell lymphoma, acute monocytic leukemia, acute lymphoblastic leukemia, large cell lymphoma, myelofibrosis and chronic lymphocytic leukemia (CLL). Of the various hematologic malignancies, eosinophilic dermatosis has been most frequently described in association with CLL. Published previously as insect bite-like reaction and eosinophilic dermatosis of myeloproliferative disease, this rare cutaneous process presents as a pruritic, papular and occasionally vesicular eruption associated with an eosinophil-rich infiltrate histopathologically. Although clinical and histopathologic features are similar to insect bites, affected patients frequently deny a history of insect bites. We report a case of eosinophilic dermatosis of hematologic malignancy in a patient with known history of CLL.

Keywords: chronic lymphocytic leukemia; eosinophilic dermatosis; eosinophilia; hematologic malignancy; insect bite-like reaction

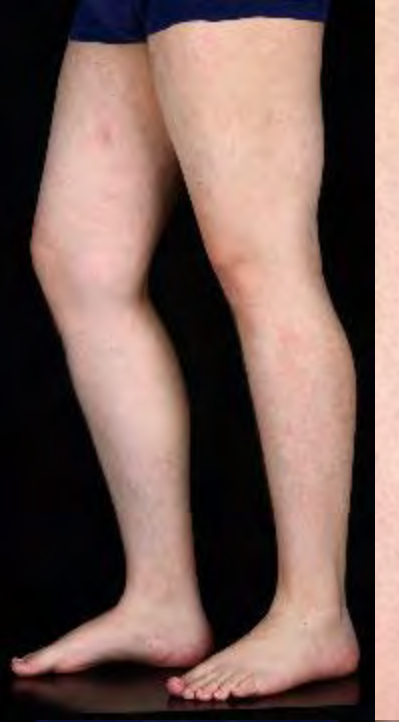
Farber MJ, La Forgia S, Sahu J. Eosinophilic dermatosis of hematologic malignancy. J Cutan Pathol 2012; 39: 690–695. © 2012 John Wiley & Sons A/S.

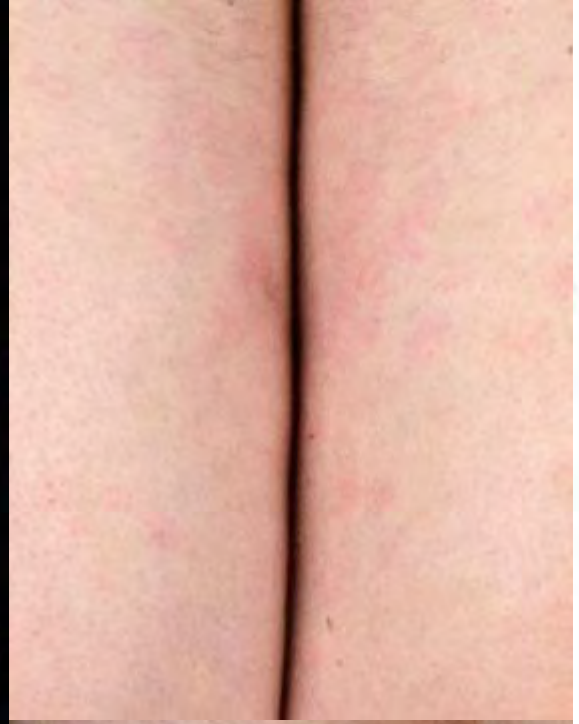
Chronic lymphocytic leukemia (CLL) represents a hematologic malignancy characterized by proliferation of monoclonal B-cells in the peripheral blood. A number of cutaneous reactions have been described in patients with CLL and have been classified as either specific or non-specific lesions. Specific lesions result from leukemic cell infiltration, while the more frequently encountered non-specific category refers to non-metastatic secondary lesions that are infectious, hemorrhagic or hypersensitive in nature. Specific CLL manifestations are defined histopathologically by the presence of leukemic cells in leukemia cutis, and present clinically as red-brown papules or nodules in 8.3% of patients with CLL. Non-specific eruptions, seen in approximately 45% of CLL patients, include petechiae, purpura, urticaria, erythema multiforme, exfoliative dermatitis, paraneoplastic pemphigus, vasculitis and eosinophilic dermatosis.[1] As reported herein, eosinophilic dermatosis of hematologic malignancy or insect bite-like reaction is a rare cutaneous eruption seen in CLL patients presenting as a pruritic papular eruption, which histologically and clinically mimics insect bites, and other eosinophil-rich dermatoses.[2–5] Although most frequently associated with CLL, eosinophilic dermatosis has been described in other hematologic malignancies, primarily in patients with B-cell hematologic malignancies such as mantle cell lymphoma, acute lymphoblastic leukemia and large cell lymphoma, as well as in acute monocytic leukemia and myelofibrosis.[5,6–9]

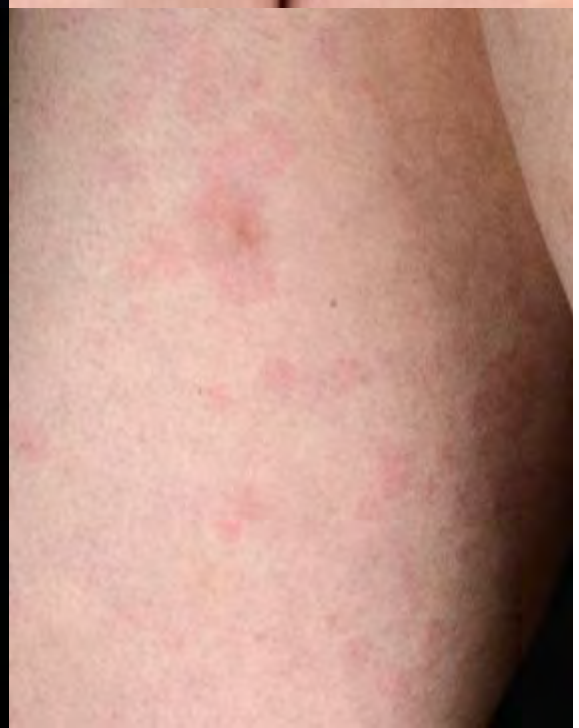
Case Report

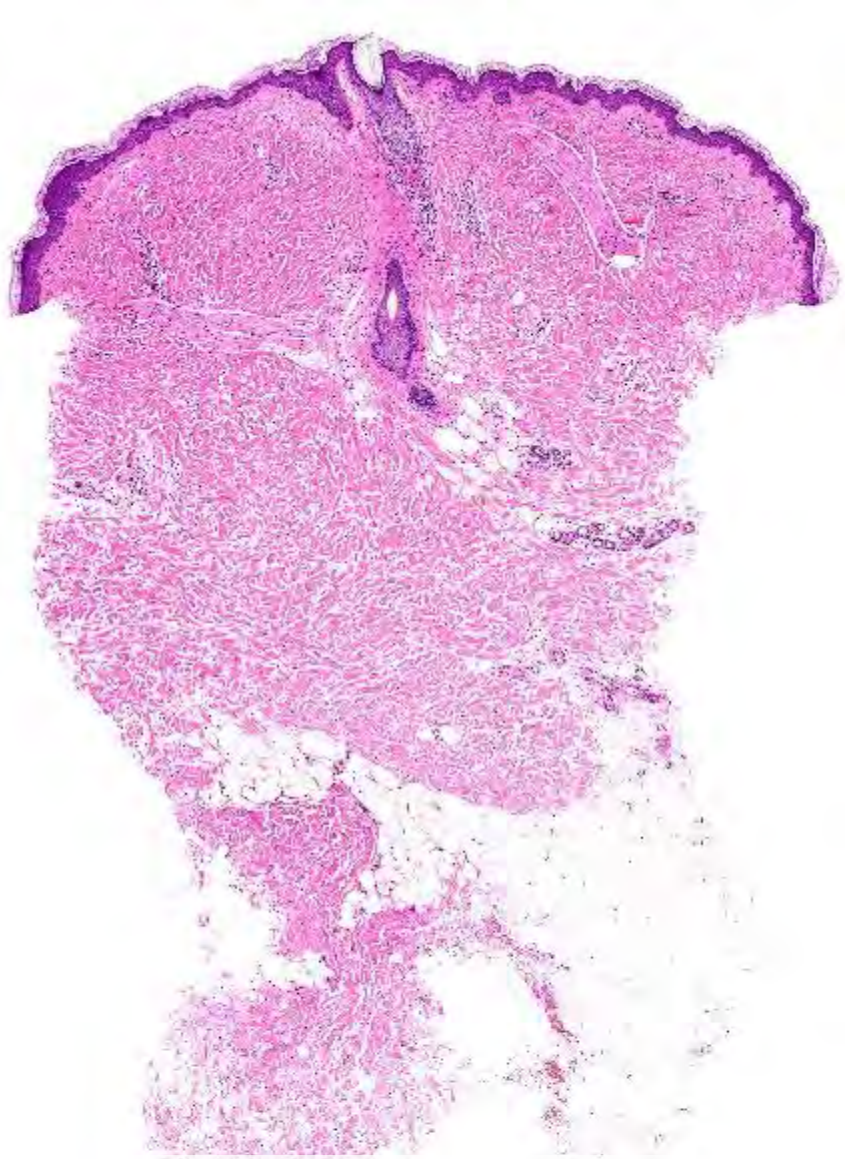
The patient was a 78-year-old man who presented with a 1-year history of a recurrent, pruritic eruption. Significant past medical history included CLL, diagnosed in 2005 and treated with a 6-month

"We prefer the designation eosinophilic dermatosis of hematologic malignancy rather than insect bite-like reaction or eosinophilic dermatosis of myeloproliferative disease, because it is a better descriptor of the pathologic process that encompasses the various hematologic malignancies associated with the eruption."



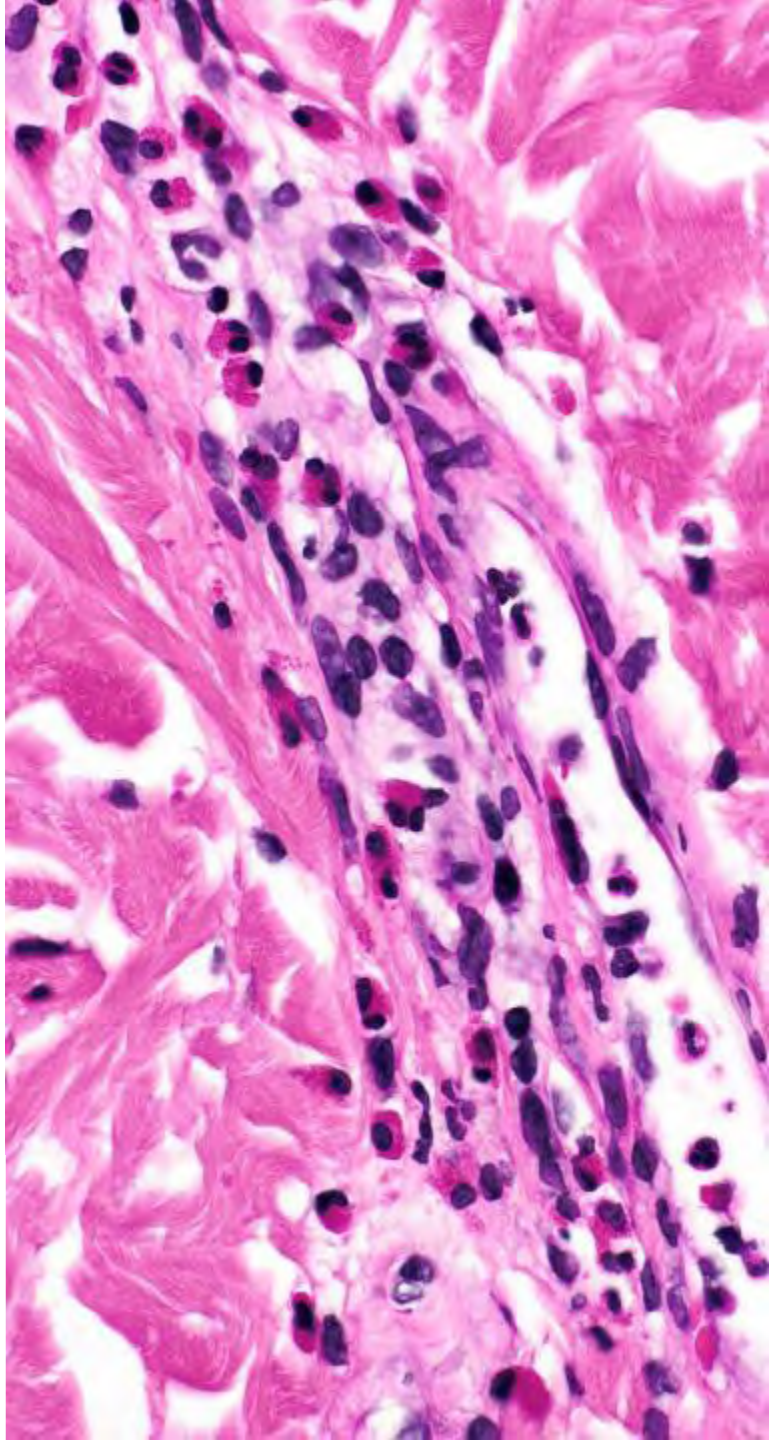






M, 24

History of acute B lymphoblastic leukemia; minimal residual disease after modified German ALL protocol followed by allogeneic stem cell Tx. Skin lesions for a few days.



Hematologic-Related Malignancy-Induced Eosinophilic Dermatosis (He Remained): An eosinophilic dermatosis predominantly associated with chronic lymphocytic leukemia

To the Editor: I read with interest the enlightening research letter by Grandi et al[1] and the accompanying astute clinician's perspective by Heyuasu.[2]

Table I. Hematologic malignancies associated with eosinophilic dermatosis*

Malignancy	Patients, No. (%) (N = 206)
Chronic lymphocytic leukemia	158 (76.7)
Lymphomas	34 (16.5)
Non-Hodgkin lymphoma	14 (6.8)
Mantle cell lymphoma	9 (4.3)
MALT lymphoma	3 (1.4)
Diffuse large B-cell lymphoma	1 (0.5)
Follicular lymphoma	1 (0.5)

From San Diego Family Dermatology, National City; Touro University California College of Osteopathic Medicine, Vallejo; Scripps Family Medicine Residency, Scripps Mercy Hospital Chula Vista, Chula Vista; and Family Medicine Residency, Family Health Centers of San Diego, San Diego, California.

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What's in a name? a new nomenclature has been proposed For eosinophilic dermatosis of hematologic malignancy (EDHM): hematologic-related malignancy-induced eosinophilic dermatosis (He Remained)

Philip R Cohen MD[1-4]

Affiliations: [1]San Diego Family Dermatology, National City, California, USA, [2]Touro University California College of Osteopathic Medicine, Vallejo, California, USA, [3]Scripps Family Medicine Residency, Scripps Mercy Hospital Chula Vista, Chula Vista, California, USA, [4]Family Medicine Residency, Family Health Centers of San Diego, San Diego, California, USA

I respectfully suggest to stop proposing new, fancy names for dermatological conditions that are already plagued by a plethora of names (my personal, humble opinion)

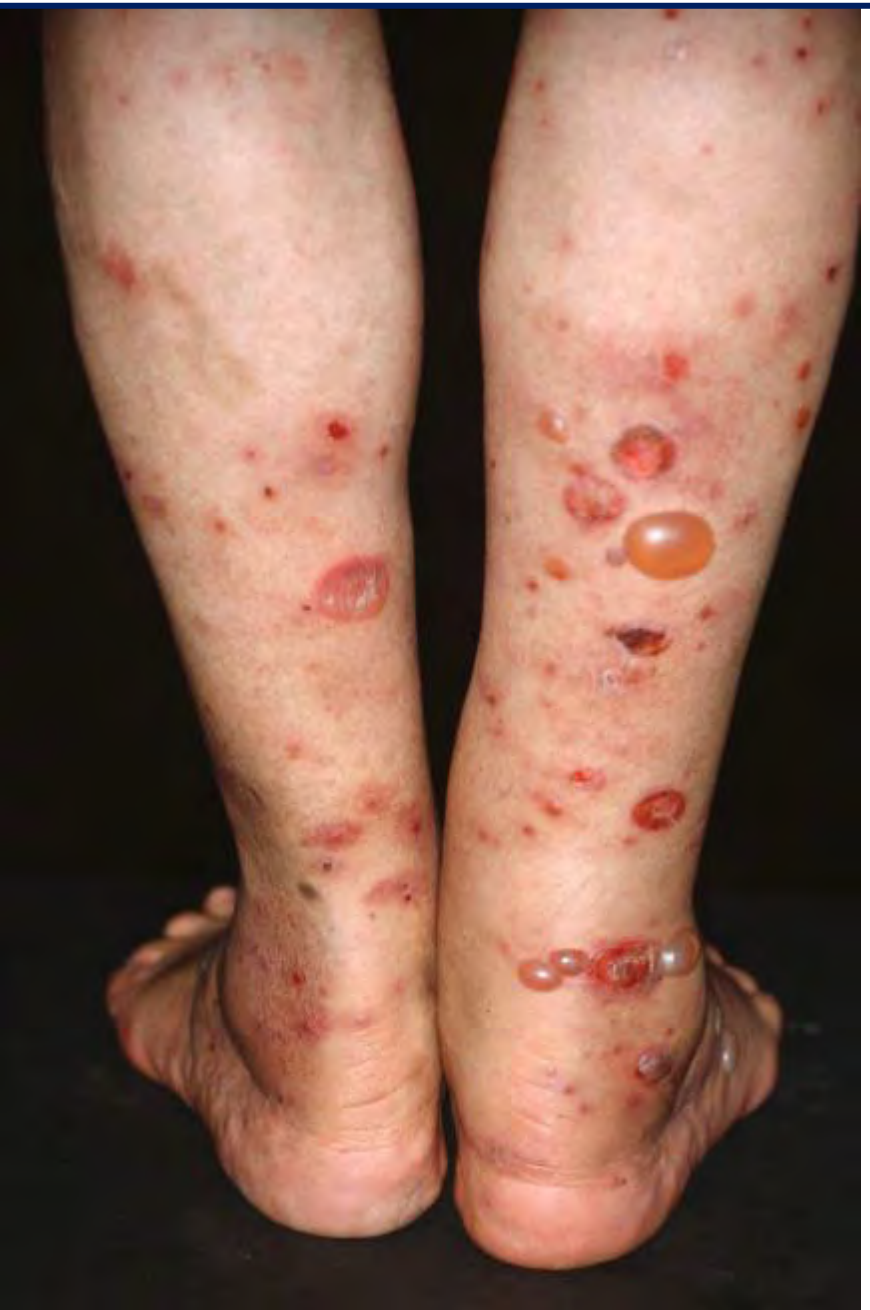
secondary to an immune shift toward a T helper 2 type response possibly caused by the neoplastic cells, that results in these T cells producing interleukin 4. Clinical observations, currently based on the prompt (within four weeks) and sustained (at least 12 weeks to 6 months) resolution of *He Remained* in two elderly men with *He Remained*, suggests that dupilumab may be the treatment of choice in chronic lymphocytic leukemia patients with this condition.

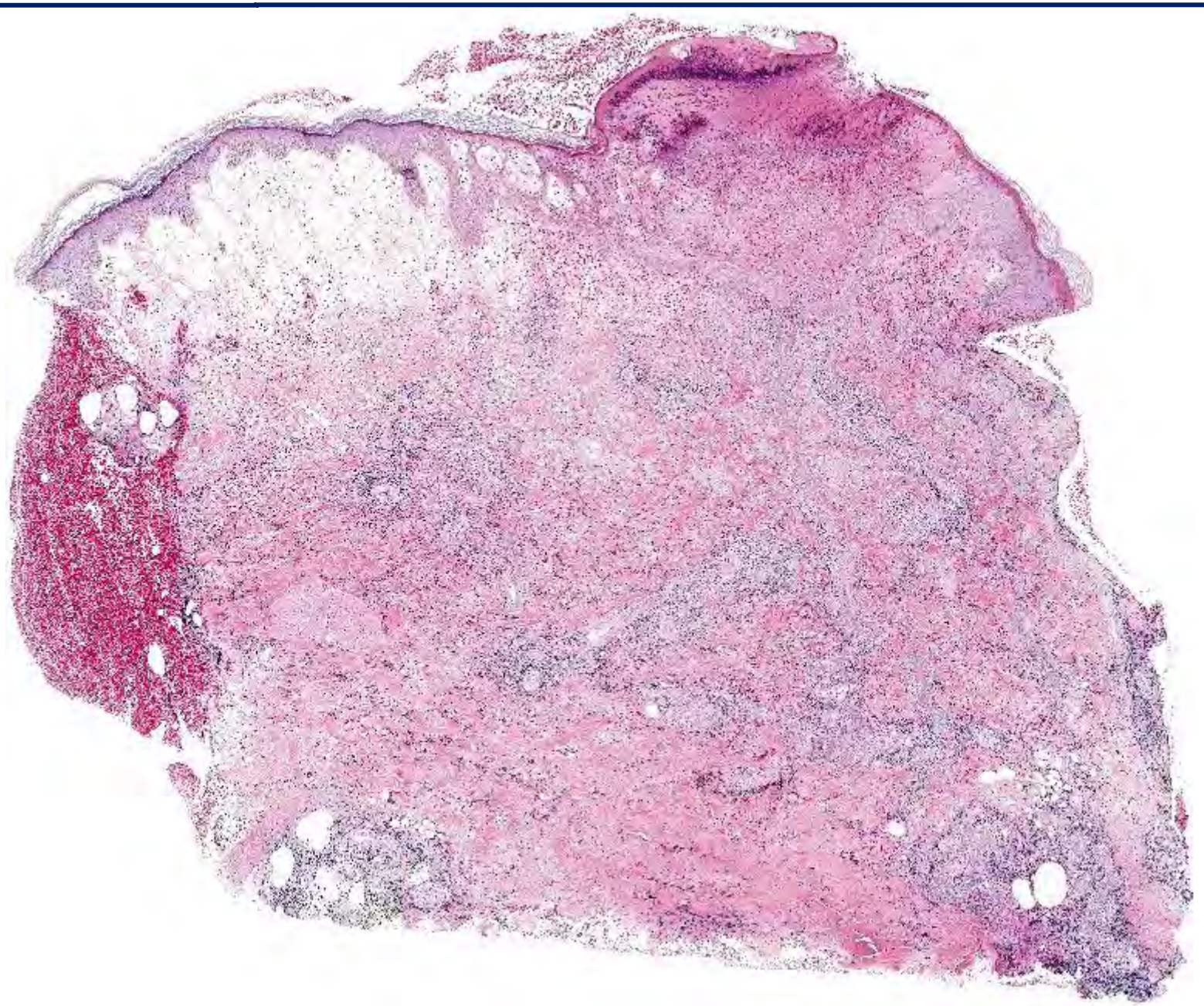
Keywords: chronic, dermatosis, dupilumab, eosinophil, eosinophilic, he, hematologic, leukemia, lymphocytic, malignancy, remained

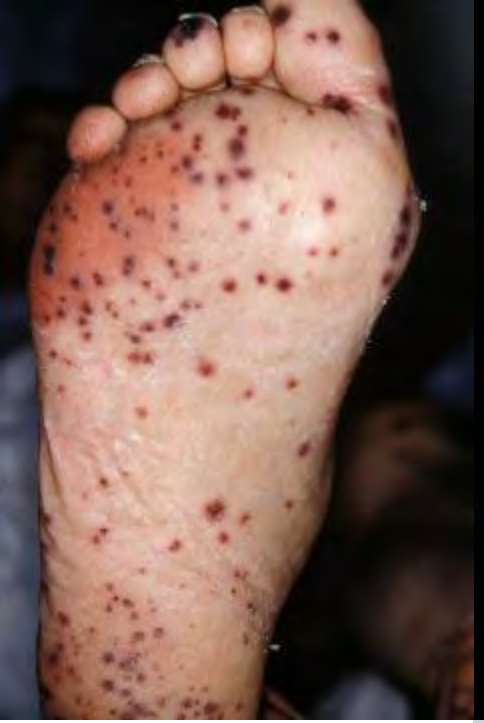
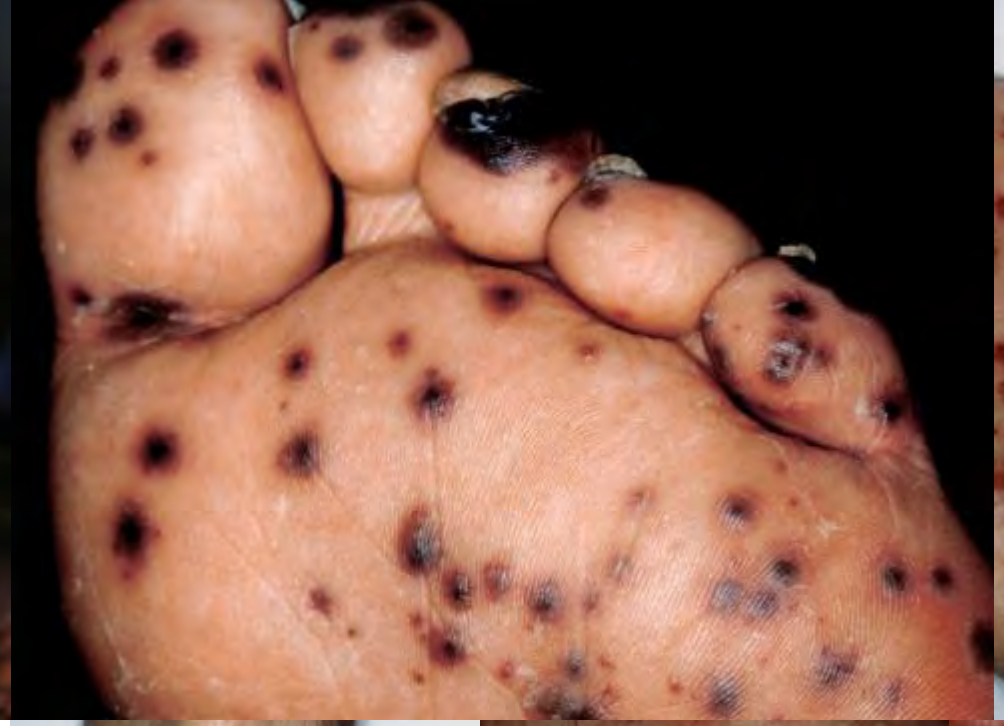
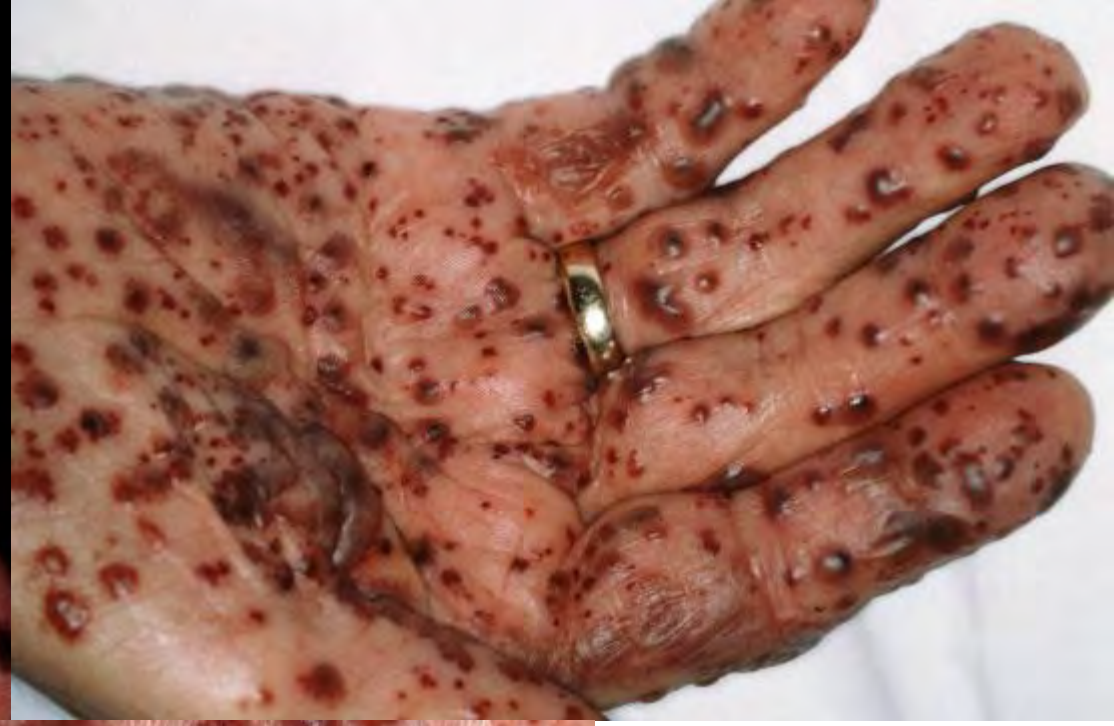
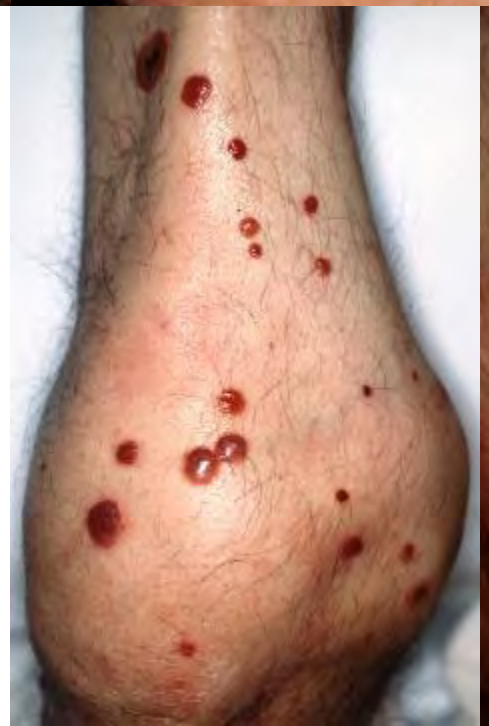
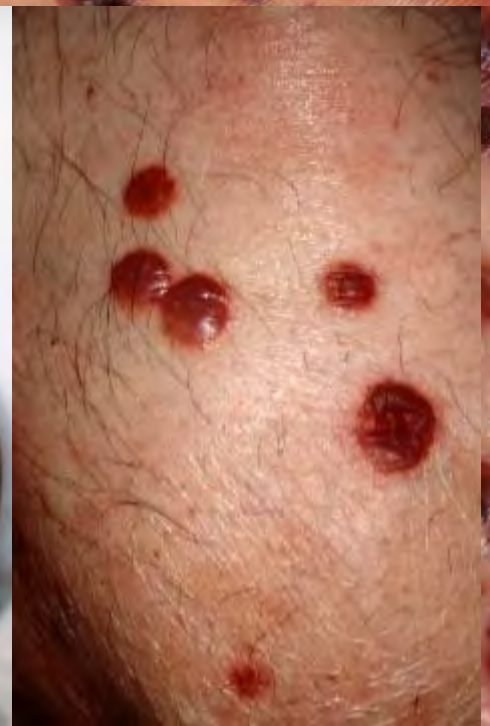
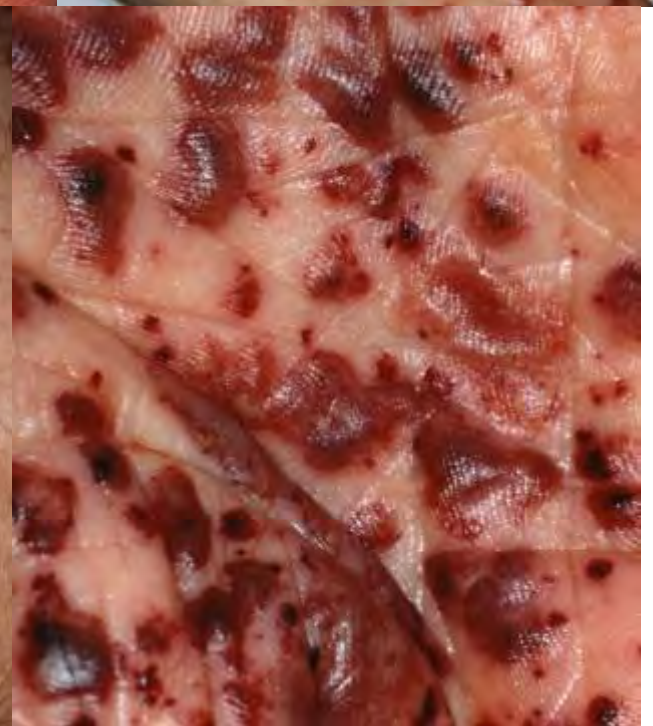
biopsy for direct immunofluorescence and bullous pemphigoid antigen-1 and enzyme-linked immunosorbent assays for bullous pemphigoid antigen-2) that established a diagnosis of eosinophilic dermatosis of hematologic malignancy. He received symptomatic treatment for his skin condition with oral antihistamines; however, his condition rapidly deteriorated and he died. The authors emphasize that more effective treatment modalities for this condition need to be investigated [1].

The term eosinophilic dermatosis of hematologic malignancy (EDHM) was proposed by Farber et al. [2] in 2012. However, the condition was originally

Exaggerated insect bite-like reactions in hematologic malignancies



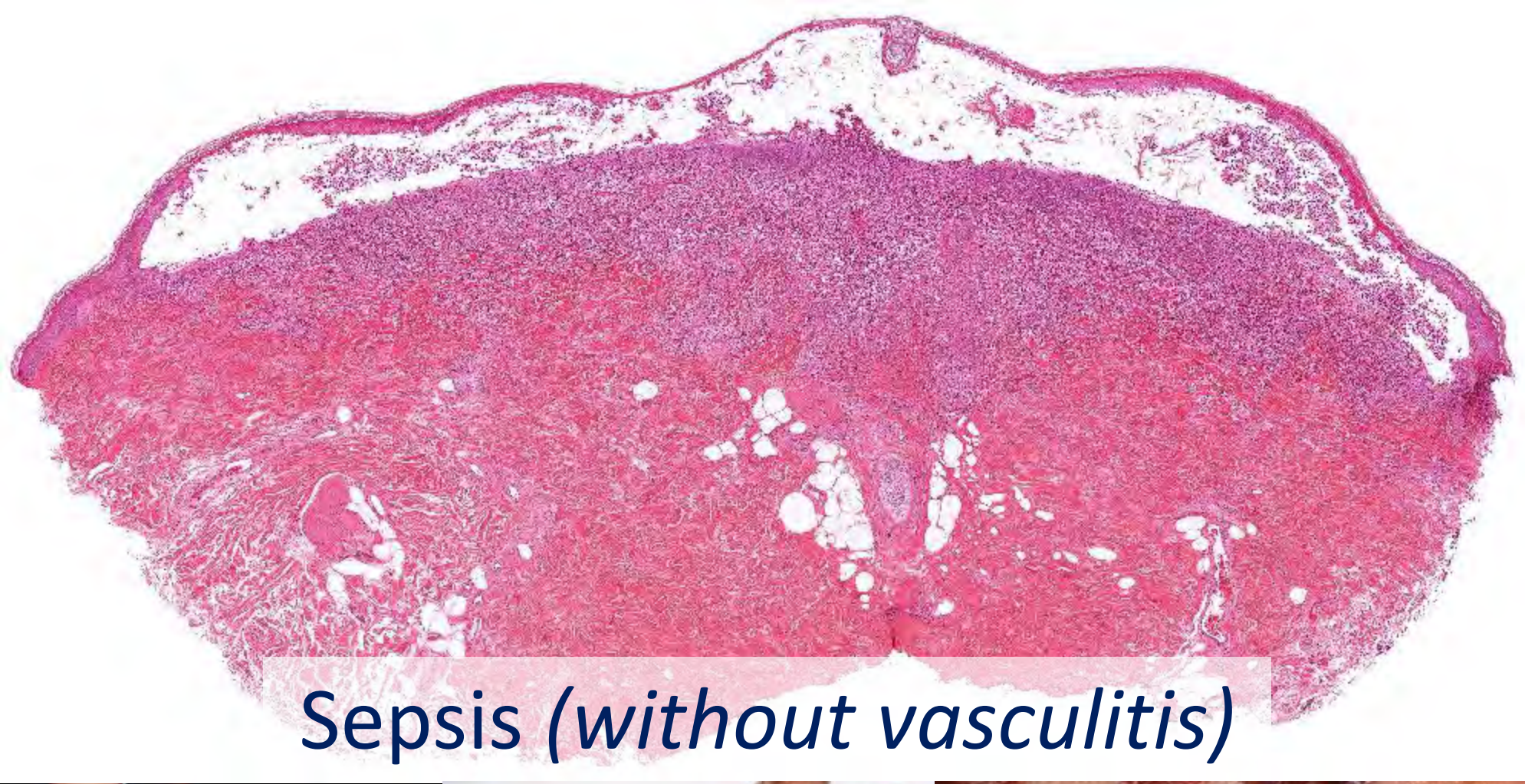


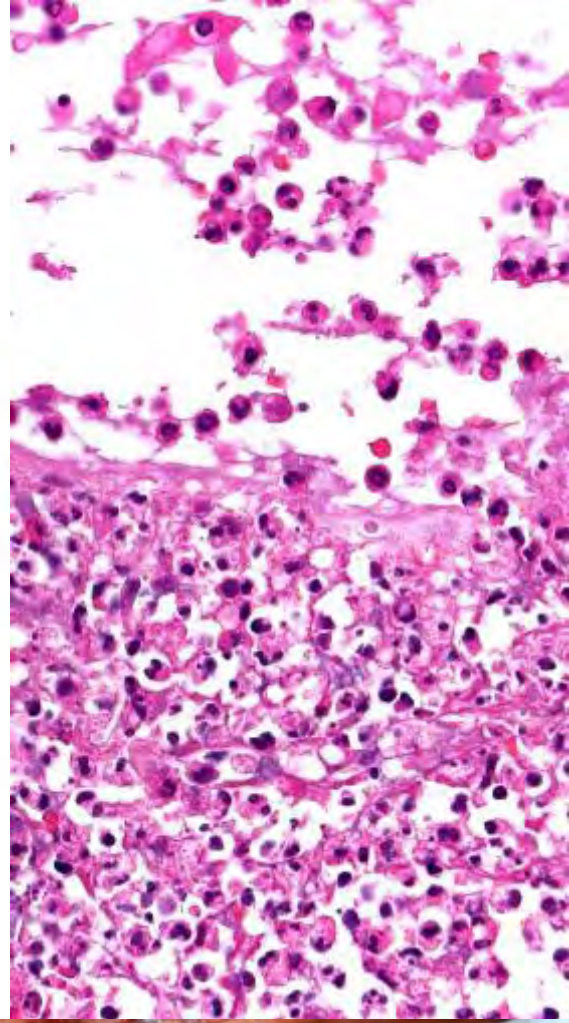







M, 82

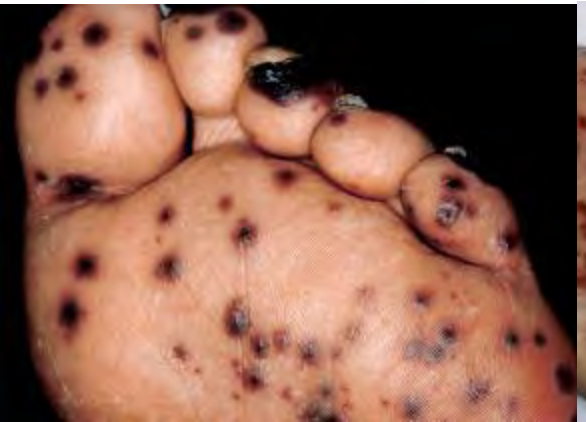
History of AML. Onset of hemorrhagic vesiculo-pustules within a few days. Fever, malaise, reduced general conditions.

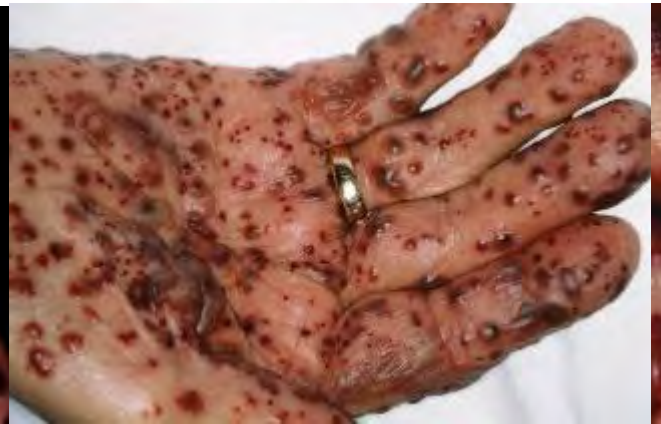
A biopsy is taken.

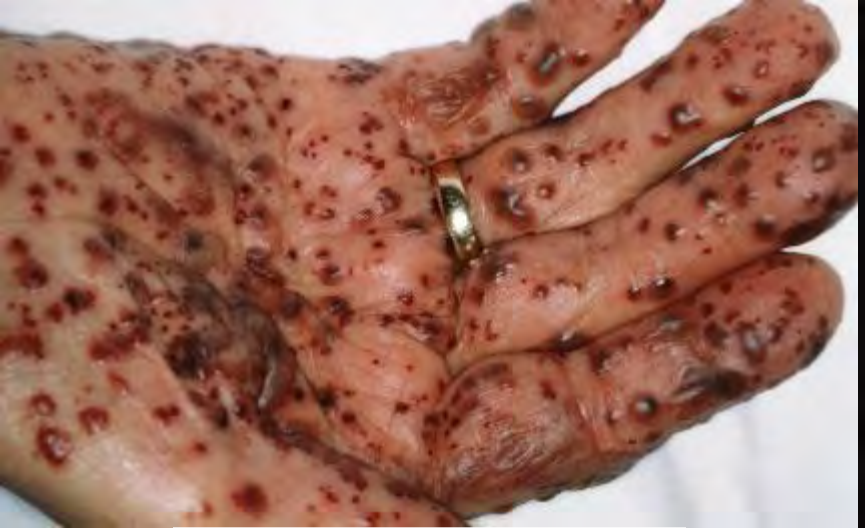




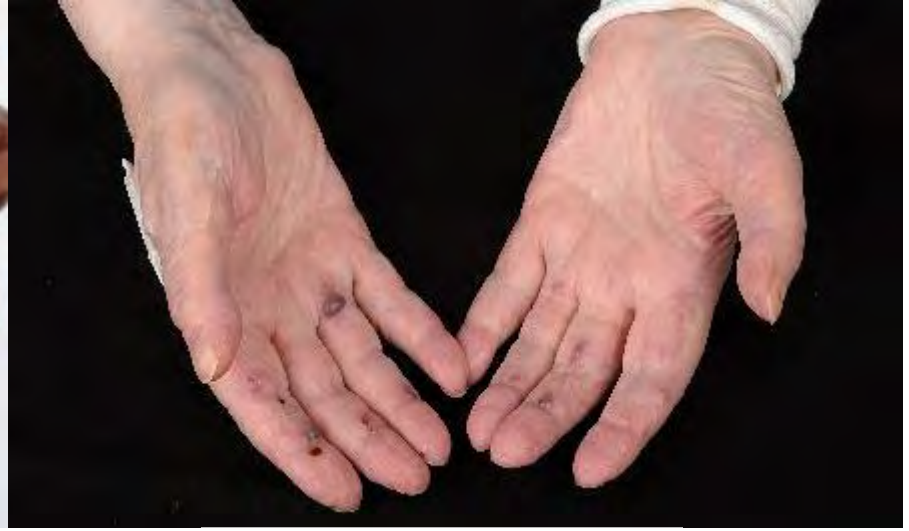
Sepsis *(without vasculitis)*





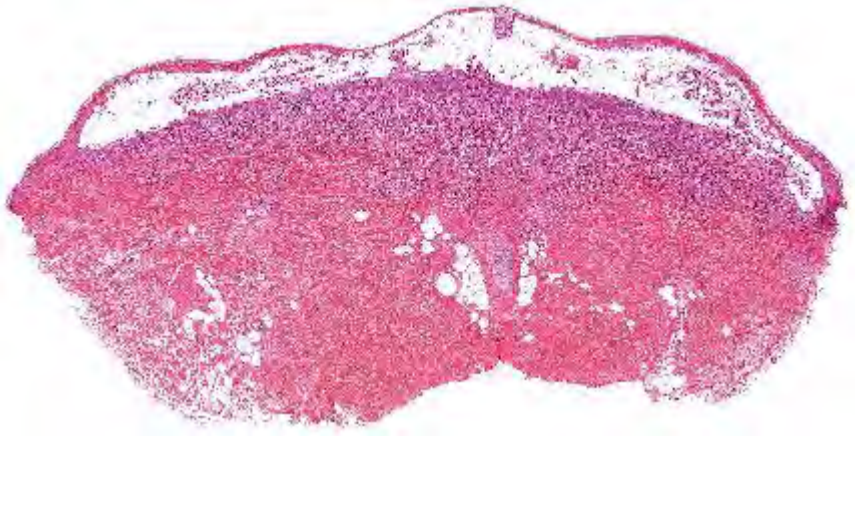


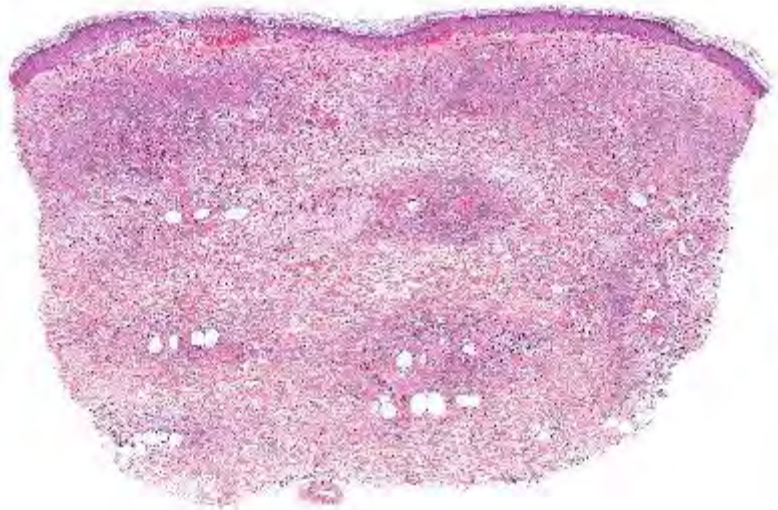
Sepsis, vesiculo-pustular

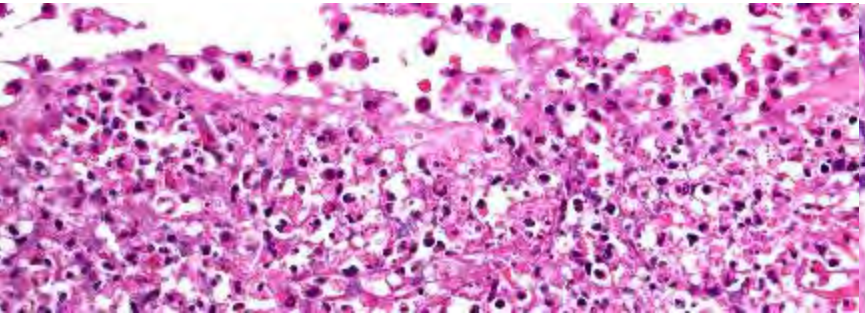


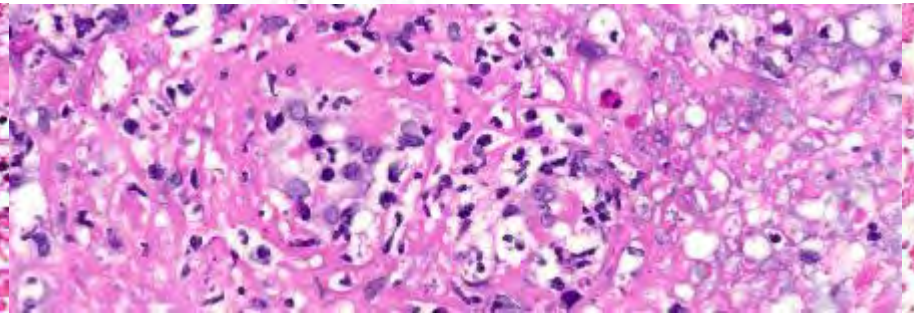
Sepsis, septic vasculitis

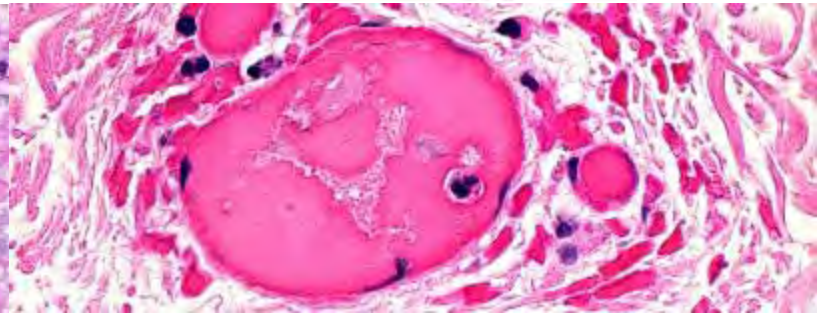
Sepsis, purpura fulminans



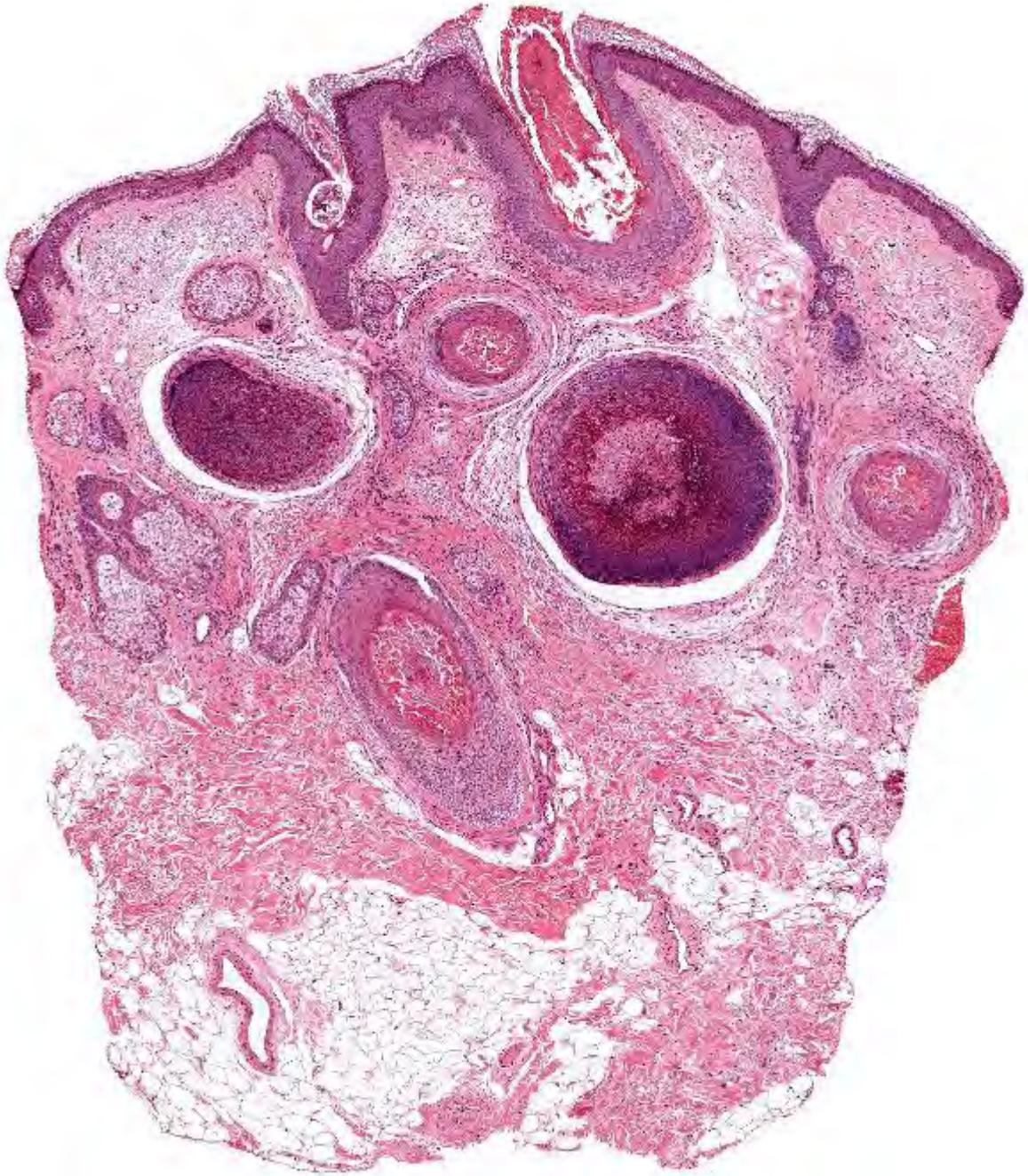


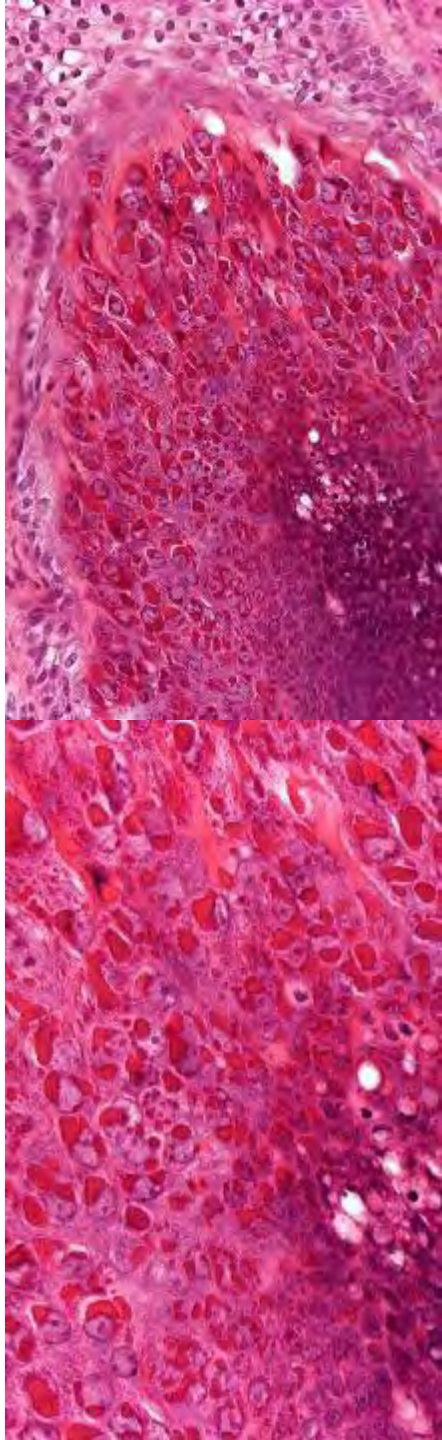






Aspergillus sepsis

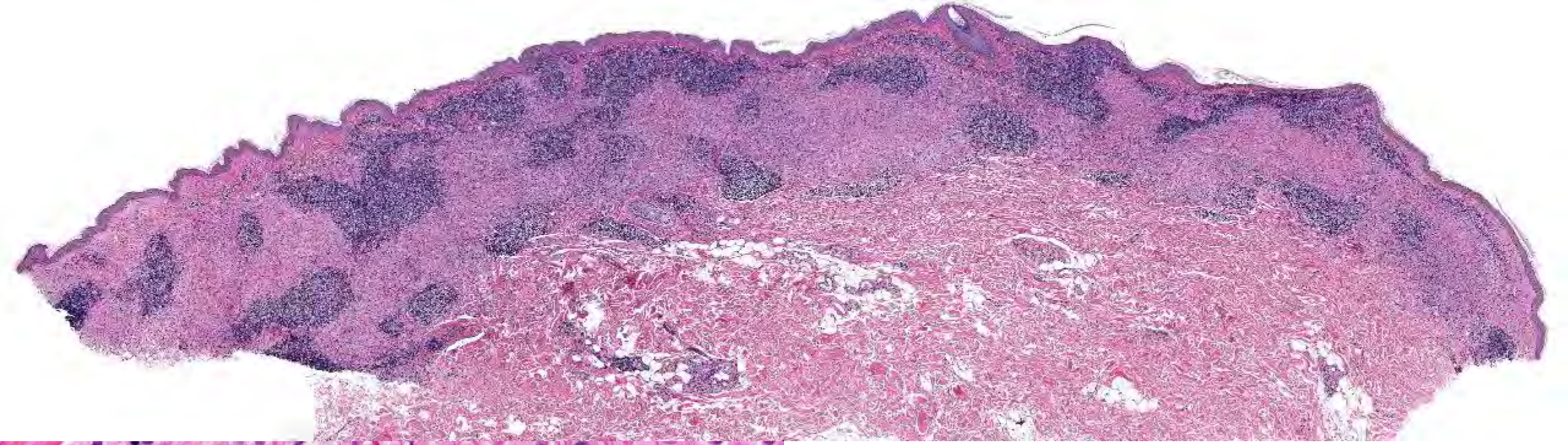


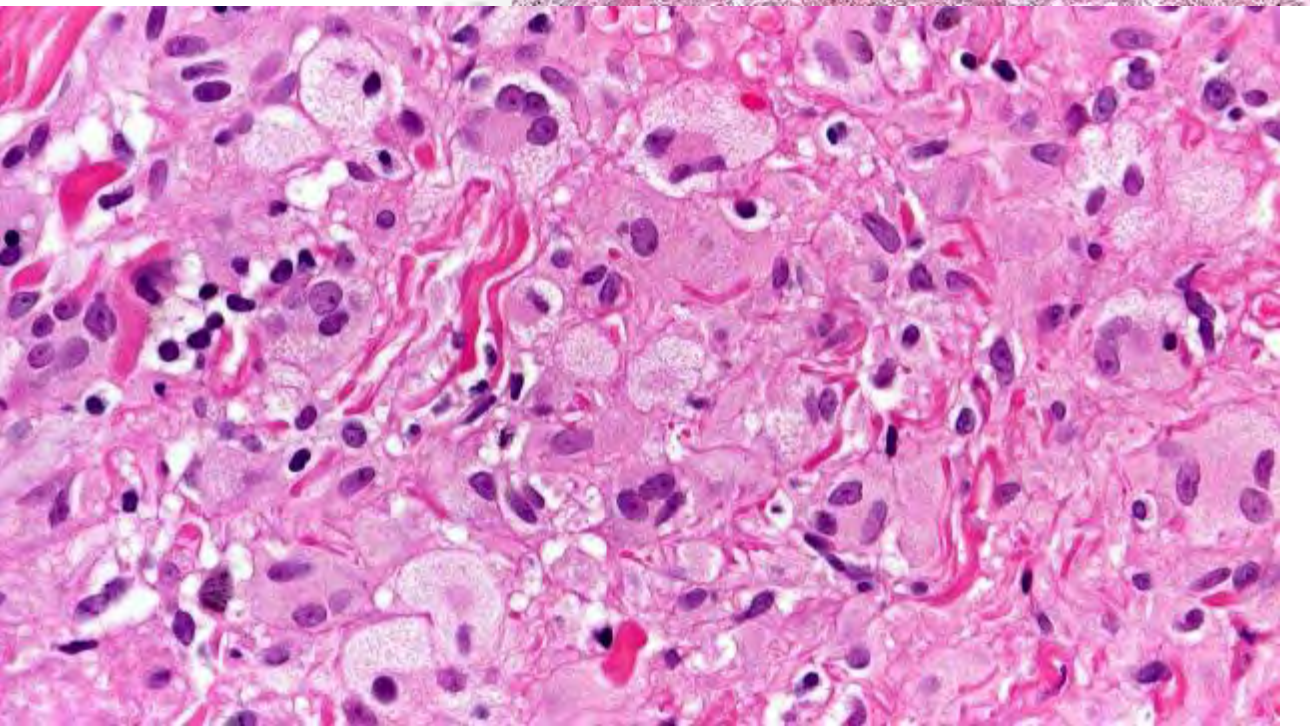


Trichodysplasia spinulosa

Skin conditions sometimes associated with hematological malignancies

- *Exaggerated insect bite-like reactions:* Observed mostly in patients with B-CLL; the term "eosinophilic dermatosis of hematological malignancy" (EDHM) to my eyes too vague (e.g., a drug eruption in a leukemic patient may be diagnosed as EDHM), and not reflecting the "exaggerated" clinical and histopathological features of this condition
- *Trichodysplasia spinulosa:* infection by a polyoma virus (TSPyV), related to severely impaired immune system (observed in different settings besides hematological malignancies, e.g. organ Tx, AIDS)
- *Scleredema adultorum Buschke:* sometimes related to paraproteinemia
- *Others:* A large number of cutaneous conditions may be observed in patients with hematological malignancies due to the leukemia/lymphoma, the treatment-associated immune suppression, infections, or a combination of these factors

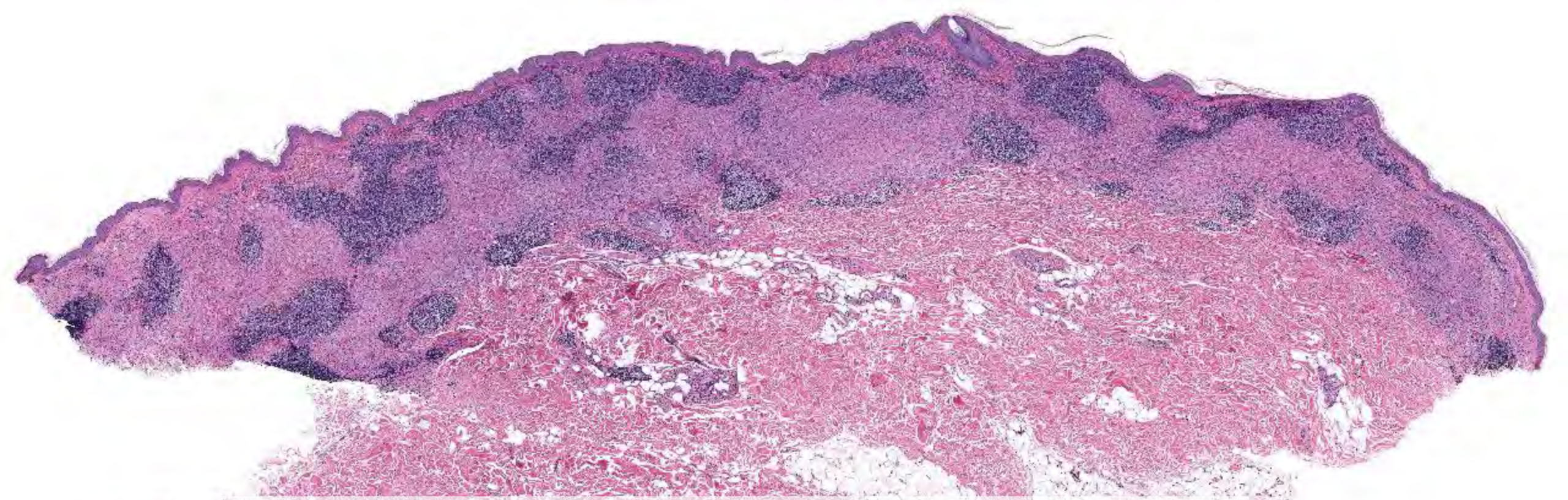




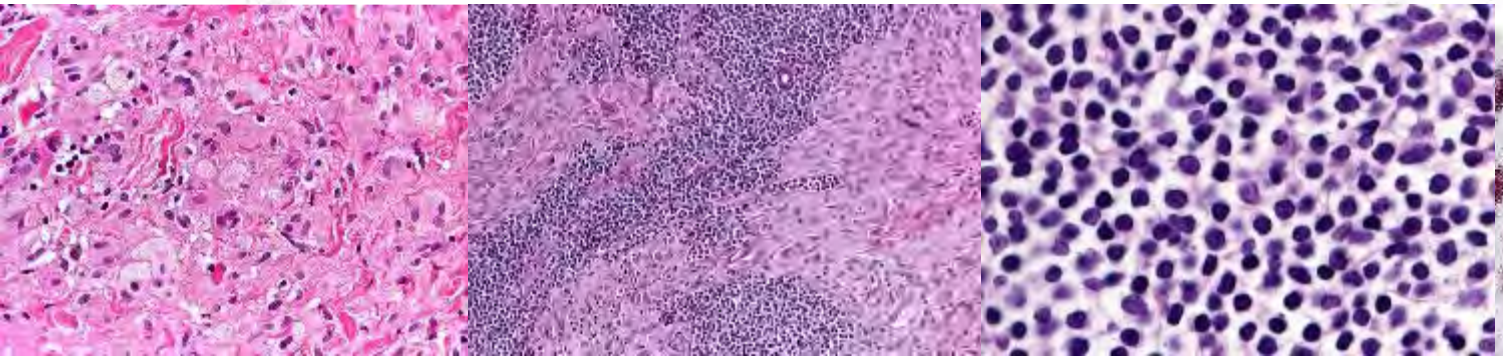
F, 71

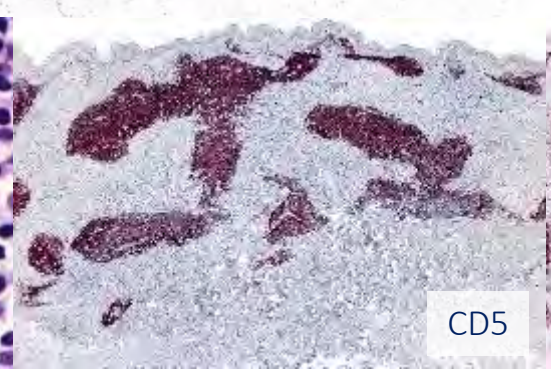
History of B-CLL (1st diagnosis 16 years previously, managed intermittently with chlorambucil). History of *herpes zoster* of the left flank two months before presentation.

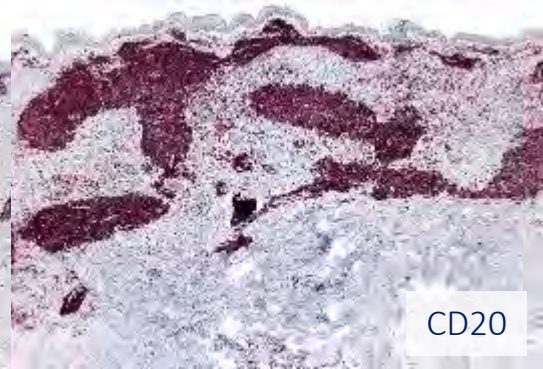
Onset of generalized papules (starting on the area of the previous *h. zoster*) one month before presentation. No hyperlipidemia / hypercholesterolemia.



Generalized normolipemic plane xanthomas with specific infiltrate of B-CLL







Clinical and Experimental Dermatology 1993; 18: 259–260

Plane xanthomatosis with chronic lymphatic leukaemia

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Accepted for Publication 4 June 1992

Summary

A case of plane xanthomatosis in a 67-year-old woman, suffering from chronic lymphatic leukaemia, who developed asymptomatic yellow plaques on the neck, upper arms and chest is reported. Histology was suggestive of xanthelasma. Development of plane xanthomata has been reported in association with various haematological malignancies and with benign monoclonal gammopathies, but not previously with chronic lymphatic leukaemia.

Case report

At routine cardiological follow up a 67-year-old woman was noted to have yellow plaques on her neck, upper arms and chest. These were asymptomatic apart from the cosmetic appearance. She was referred to the dermatology clinic and a diagnosis of plane xanthomatosis was made. A biopsy showed collections of foam cells in the dermis, but no giant cells or granulomata (Fig. 1).

Three years previously she had suffered a myocardial infarction and was treated with thrombolytic therapy. At that time a full blood count revealed a white cell count of $28{\cdot}6 \times 10^9$ (80% lymphocytes). Lymphocyte surface markers were investigated and a diagnosis of chronic lymphatic leukaemia (CLL) was made. At this time her immunoglobulins were normal apart from a low IgA—a depression found commonly in CLL. As she had no systemic symptoms and no hepatosplenomegaly or lymphadenopathy, no specific therapy was instituted.

Present investigations confirm a high white cell count of $38{\cdot}9 \times 10^9$. An immunophoretic strip shows a band in the γ-region, although the overall level of protein is not raised. Fasting lipid levels are normal apart from a minimally raised cholesterol. This slight elevation of cholesterol was also noted at the time of the patient's myocardial infarction and has persisted subsequently (Table 1). There is no family history of hyperlipidaemia, nor any evidence of biliary cirrhosis or myxoedema.

Figure 1. Sparse numbers of foam cells around dermal vessels.

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Discussion

Plane xanthomata (PX) commonly occur around the eyes—xanthelasma palpebrum, but are uncommon elsewhere (usually involving the neck, shoulders and upper trunk). Generalized plane xanthomatosis occurs, with other xanthomatous processes, in the primary hereditary hyperlipidaemias and the secondary hyperlipidaemias associated with liver disease, nephrotic syndrome and myxoedema. Normolipaemic plane xanthomatosis also occurs.[1] This can be essential, associated with reticuloendothelial disease, or associated with miscellaneous, probably coincidental, disorders. The commonest reticuloendothelial disease is multiple myeloma, which seems to run a more benign course when associated with PX.[1] Cases of PX have also been reported in association with chronic granulocytic leukaemia, Waldenstrom's macroglobulinaemia, cryoglobulinaemia, lymphoma and benign monoclonal gammopathy.[2,3]

The mechanism for the deposition of lipid in PX has been studied in various reports.[2–10] In cases with an associated gammopathy it is postulated that lipoprotein forms a complex with the abnormal paraprotein. This complex may be cryoprecipitable.[4] It is likely that the immune complex is then deposited in the skin, and studies have shown evidence of complement consumption, supporting this theory.[3] A low density lipoprotein

Dermatology

Report

Dermatology 2002;204:251–254

Diffuse Plane Normolipaemic Xanthomatosis in a Patient with Chronic Lymphatic Leukaemia and Monoclonal Gammopathy

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Key Words

Diffuse plane normolipaemic xanthomatosis · Lymphocytic leukaemia · Monoclonal gammopathy

Abstract

Diffuse plane normolipaemic xanthomatosis is a well-defined uncommon cutaneous manifestation of yellowish-orange papules involving the eyelids, neck, upper trunk, and flexural folds. Some [illegible] of the reported cases are associated with [illegible] proliferative disorders. The papules may arise as a result of permeation of lipoprotein-immunoglobulin complexes. We present a female patient with clear clinical features of diffuse plane xanthomatosis associated with chronic lymphatic leukaemia and monoclonal gammopathy. In the patient, we found evidence of lipoprotein consumption supporting the hypothesis that deposition of lipoprotein-paraprotein complexes is involved. Lipid electrophoresis of lesional skin revealed the presence of a band precipitating in the apolipoprotein E area, indicative of the presence of apolipoprotein E.

Introduction

Diffuse plane normolipaemic xanthomatosis (DPNX) was first described by Altman et al. [1] in 1969. DPNX is a [illegible] disease in which yellowish-orange to yellow-brown soft plaques gradually appear. The papules are 3 to 4 mm in diameter and are localized on the eyelids, neck, upper trunk, and flexural folds. In 1988, Lynch and Winkelmann [2] recognized the relationship of DPNX's incidence of the reticulo-endothelial system. Since then, several cases of DPNX associated with [illegible] myeloma, monoclonal gammopathy, chronic granulocytic or lymphocytic leukaemia, Waldenström's macroglobulinaemia and lymphoma were reported. Davis and Price [3] described the first patient with DPNX and chronic lymphatic leukaemia in 1993. However, Marsoval et al. [4] performed a clinicopathological study to determine the incidence of association. Among [illegible] patients with DPNX, they found an association in only 3 cases. They concluded that the incidence of underlying disease [illegible] might be due to the fact that authors tend to report only those patients with significant associations.

Case Report

A 72-year-old woman was referred to our clinic in April 2001 for further investigation of [illegible] plane xanthomas. The first papule had appeared 10 years before on the chest. Further papules had appeared on the chest, the face, the [illegible] in the following regions (fig. 1). Her medical history revealed a chronic lymphatic leukaemia, known since 1994 that had been treated with [illegible] (Leukeran) and methylprednisolone (Medrol) in various [illegible] cycles until 1997. Since then, the leukaemia [illegible] and [illegible] remained stable. The patient also suffered [illegible] hypothyroidism, hypercholesterolaemia and hypertension. In 1977, she was also diagnosed as having diabetes mellitus. Her therapy consisted of Leopard (sotalol 80 mg), Efexor (isosorbid mononitrate), Zoloft (fluoxetine), Lasilix (furosemide), Lipanthyl (fenofibrate), Lantus (insulin glargine), Lexomil (bromazepam), Dafalgan (paracetamol), Lorazepam, Cipralex (escitalopram) and Zestril (lisinopril).

Physical examination revealed flat, slightly infiltrated yellow-orange and yellow-brown plaques covering the forehead, the eyelids, the periorbital folds, the neck, but mostly upper trunk and inframammary area. Identical plaques were located in the axillary folds and groins and almost confluent [illegible].

Histological examination of a skin biopsy revealed an infiltrate of foamy macrophages in the upper and mid-dermis associated with an [illegible] plasmocytic infiltrate. The tissue specimen was [illegible] to Congo red dye, the [illegible] immunohistochemical staining pattern was as follows: CD68+, PNH1+, S100−, CD1a−, M ACT387−

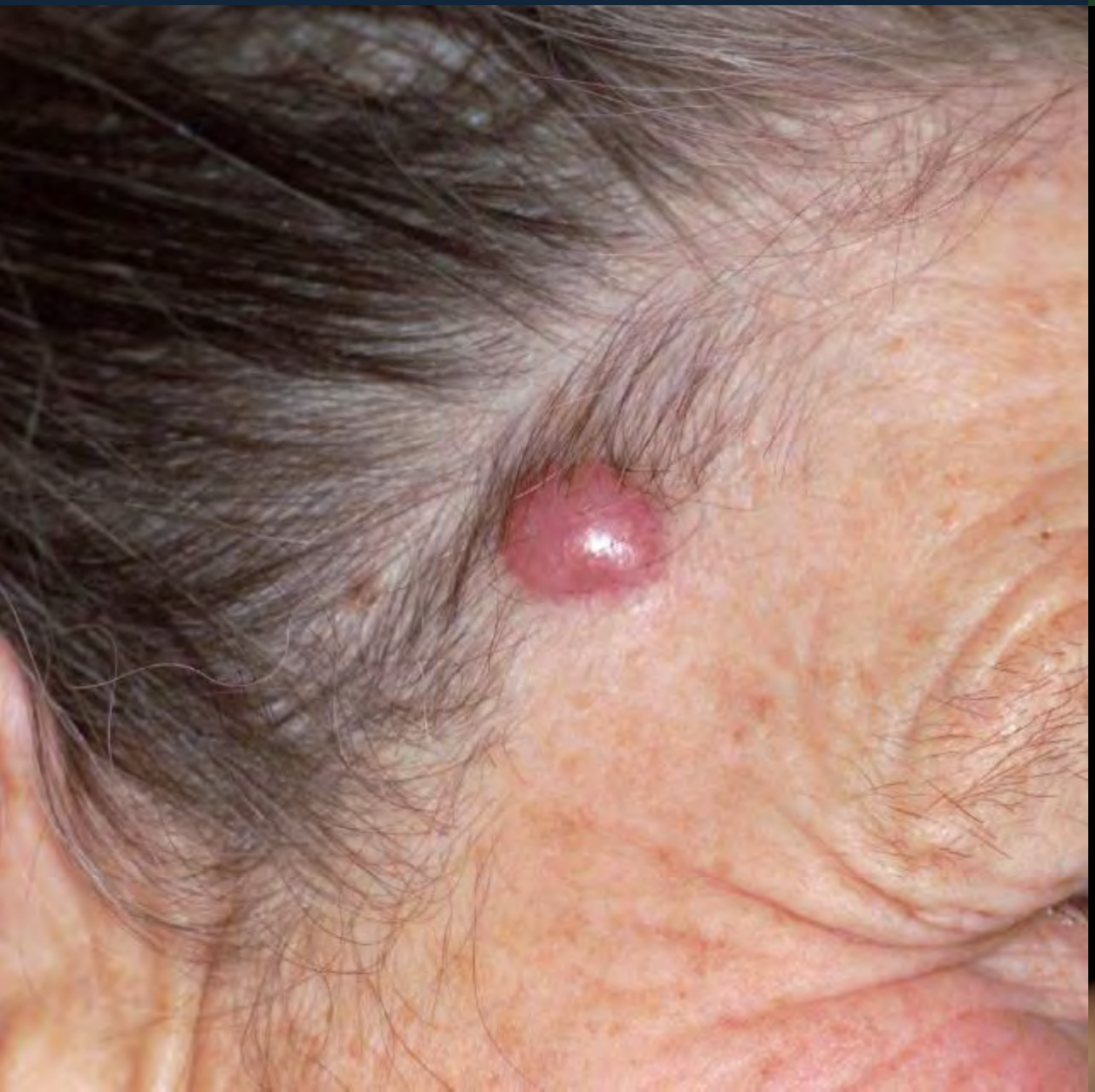
KARGER

[illegible]

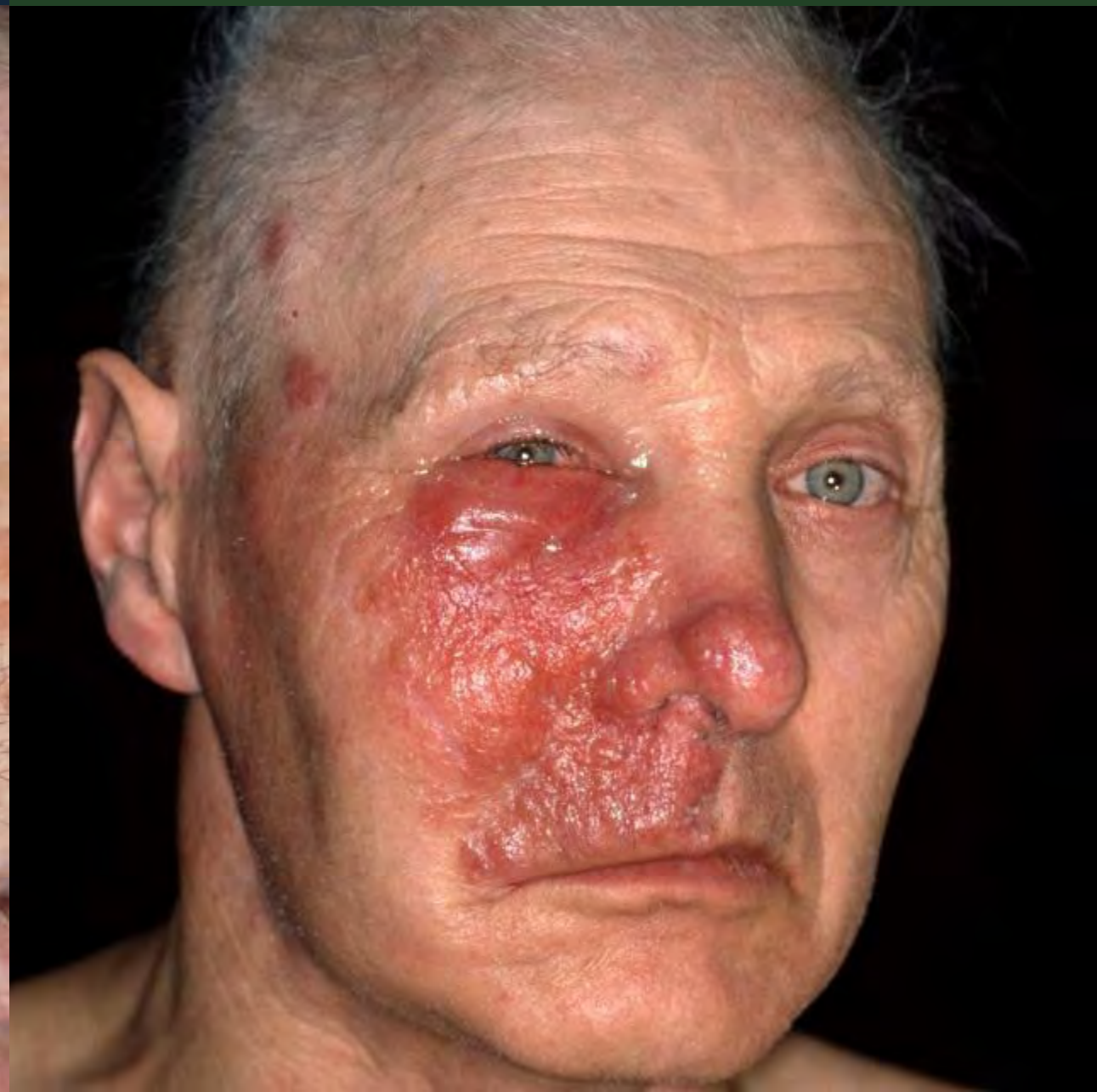
Non-specific and specific skin involvement in hematological malignancies

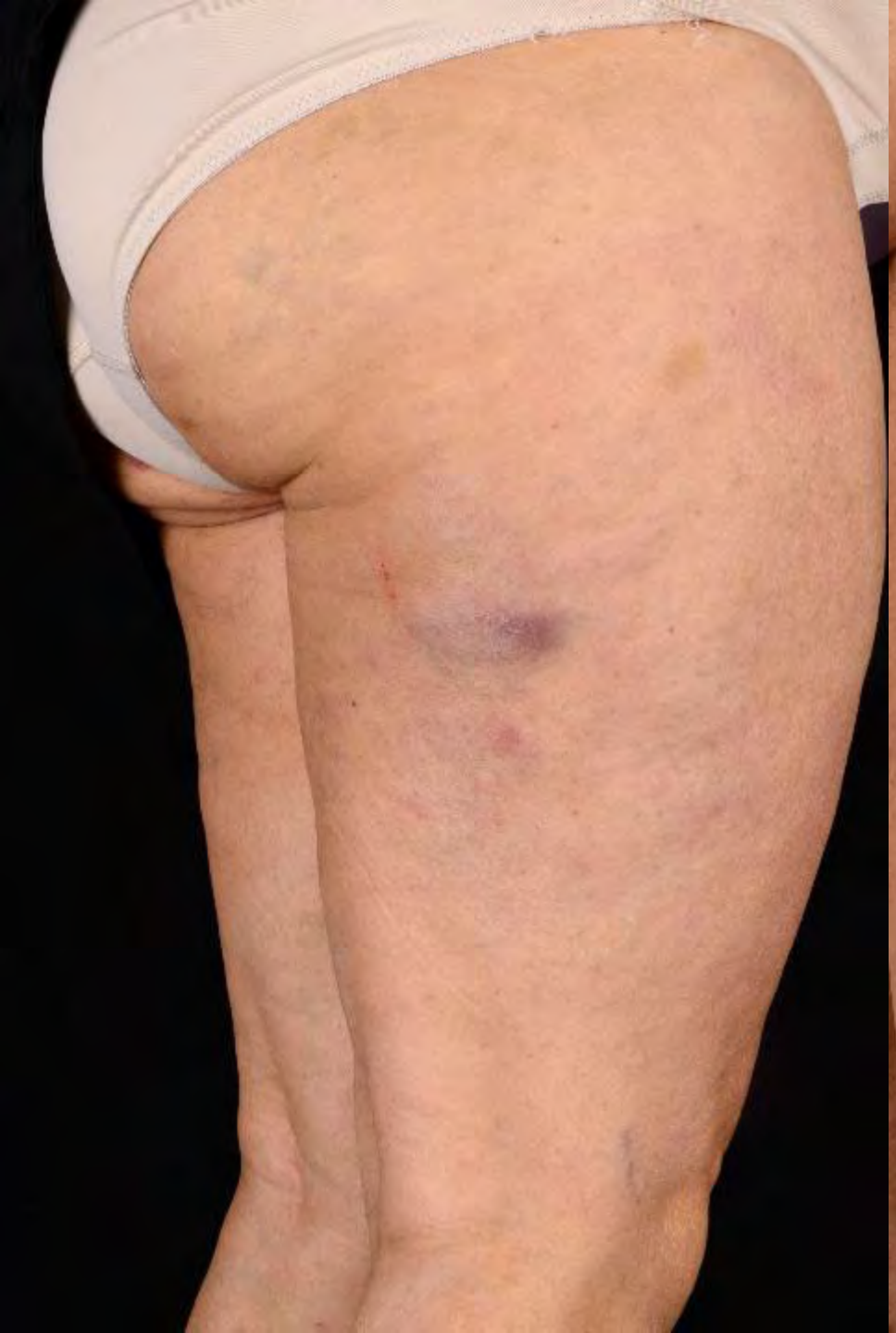
- Cutaneous involvement usually either "non-specific" (e.g., necrobiotic xanthogranuloma, scleromyxedema, opportunistic infections) or specific (e.g., accumulation of malignant cells in the skin, cutaneous deposition of paraproteins)
- Particularly in B-CLL (but sometimes in myeloid disorders as well), a specific infiltrate of malignant cells may be observed at the site of a non-specific cutaneous manifestation (e.g., neoplastic lymphocytes of B-CLL at the site of normolipemic plane xanthomas)
- The malignant hematological disorder may still be undiagnosed (particularly in myeloid malignancies), thus a high degree of suspicion and complete phenotypic analyses are necessary in these cases

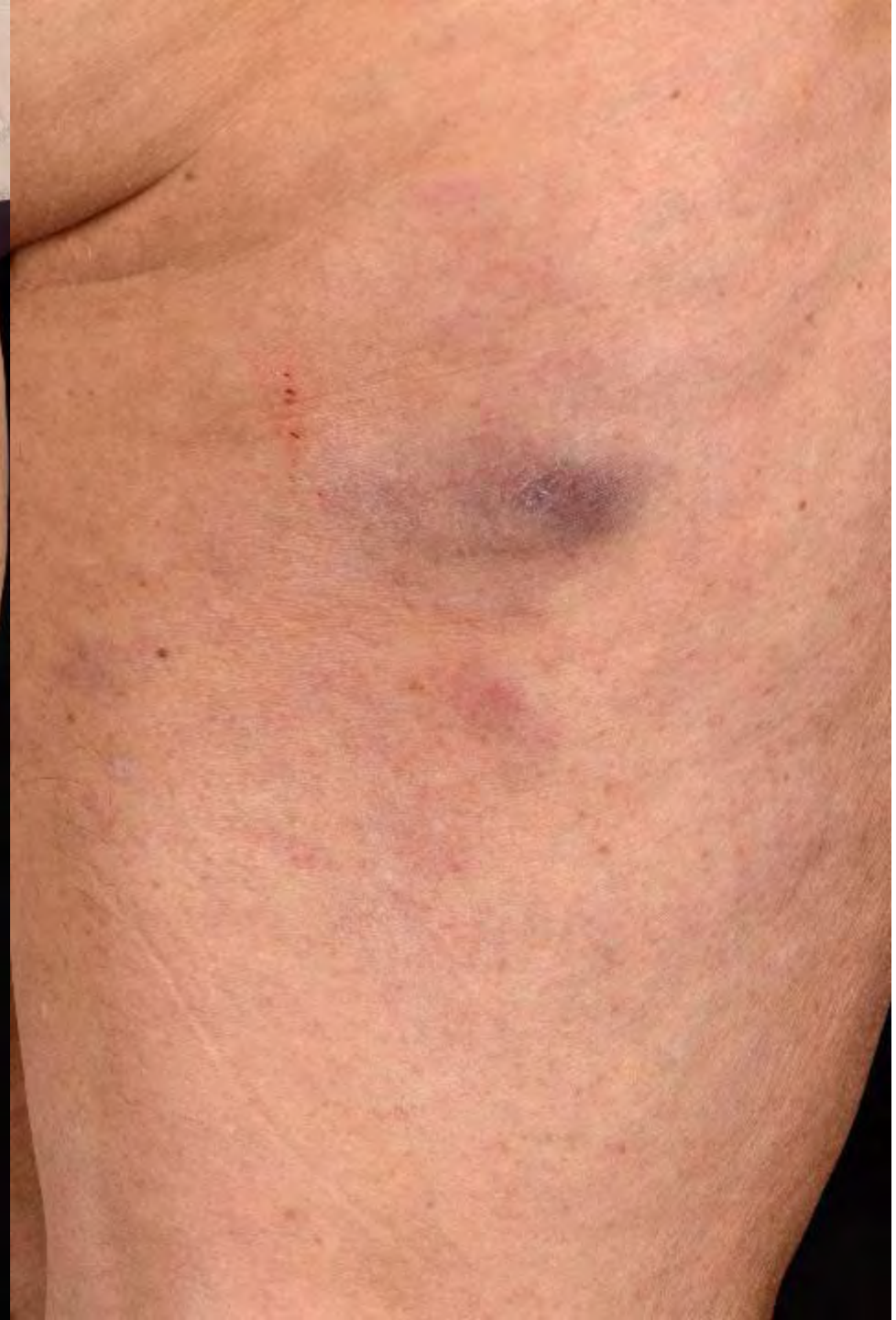
Cutaneous manifestations of B-CLL unrelated to a skin disorder (uncommon)



Cutaneous manifestations of B-CLL related to a skin disorder (inflammatory or neoplastic) (common)





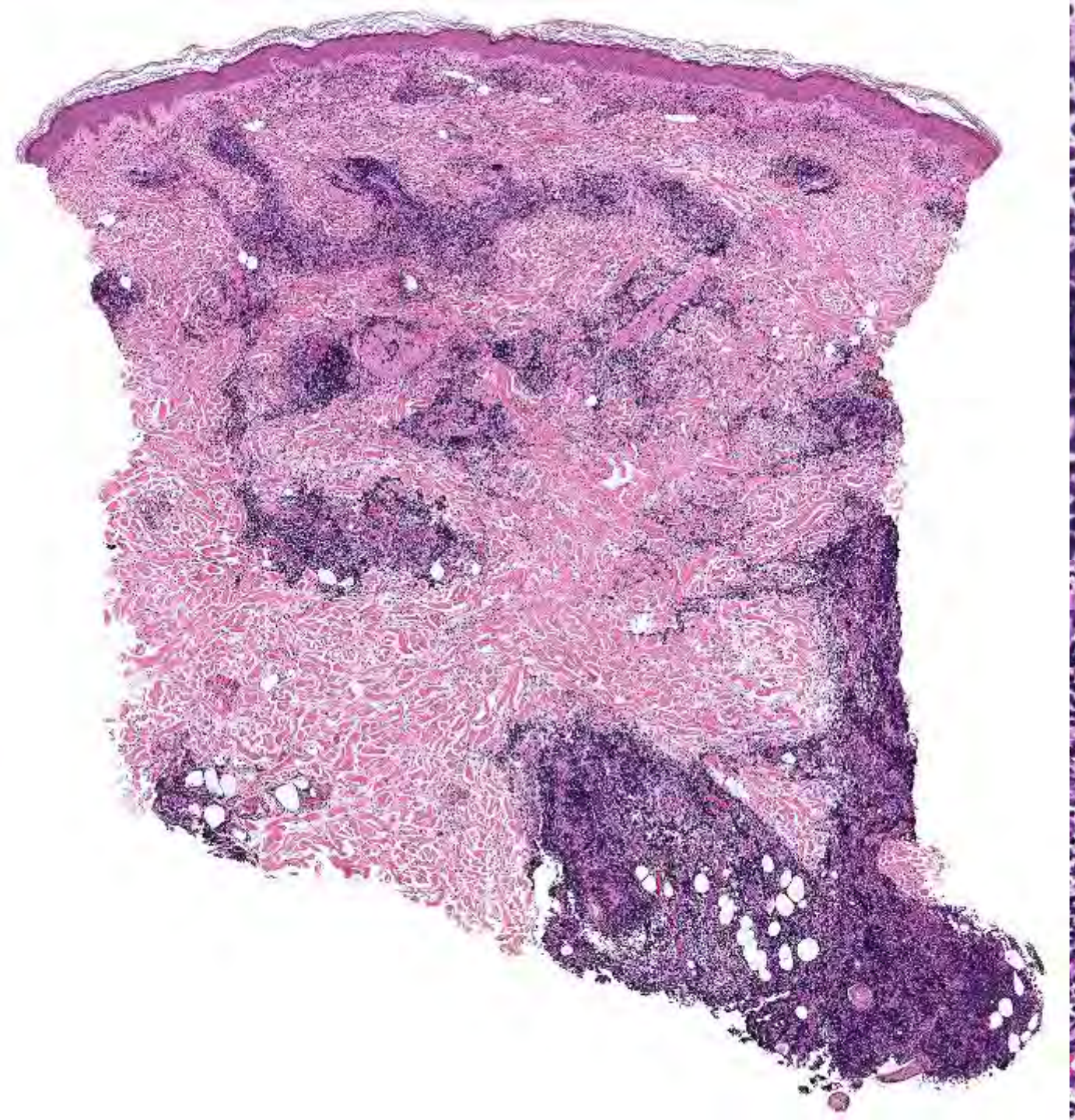


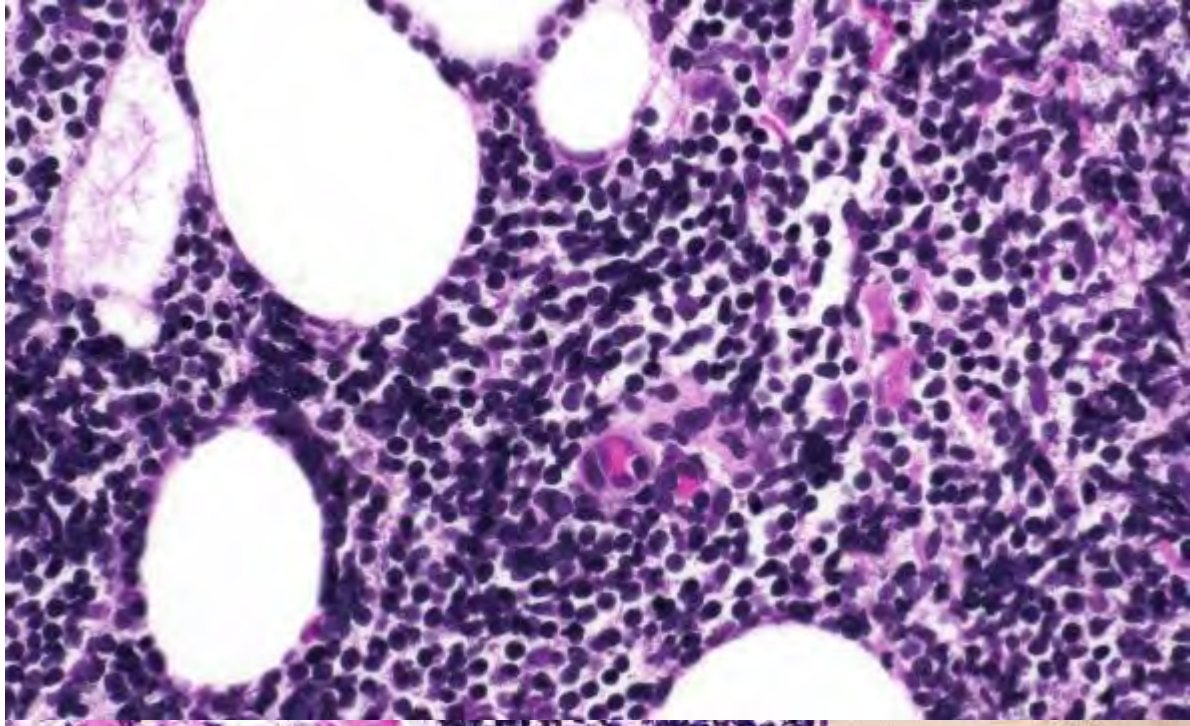
F, 62

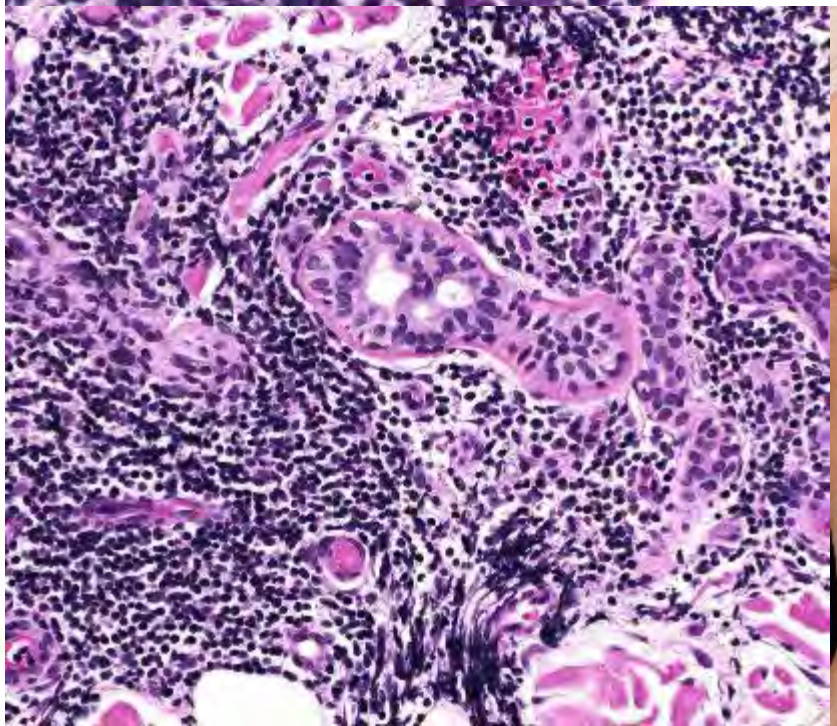
A private dermatologist made a biopsy under the clinical diagnosis of "infiltration on the right thigh", reported externally as atypical lymphoid proliferation, consistent with specific manifestation of B-CLL.

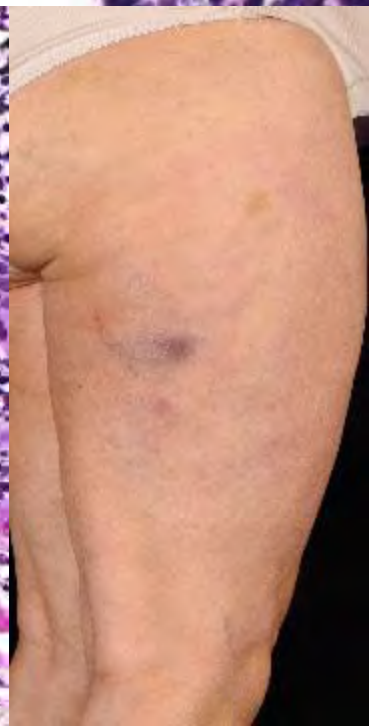
History of B-CLL (1st diagnosis 4 years before presentation, stage Binet A / Rai 1, del 13q14, IgHV mutated (no treatment needed).

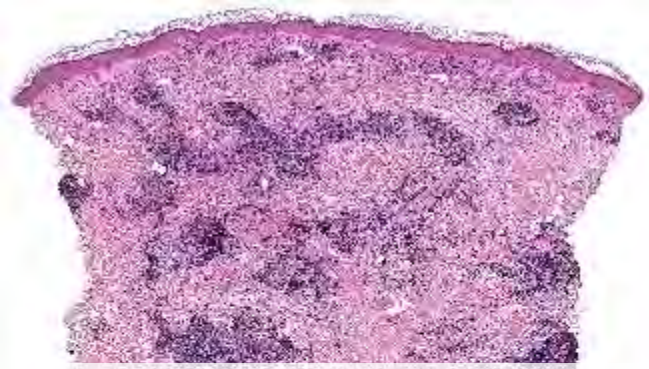
A new biopsy is taken.

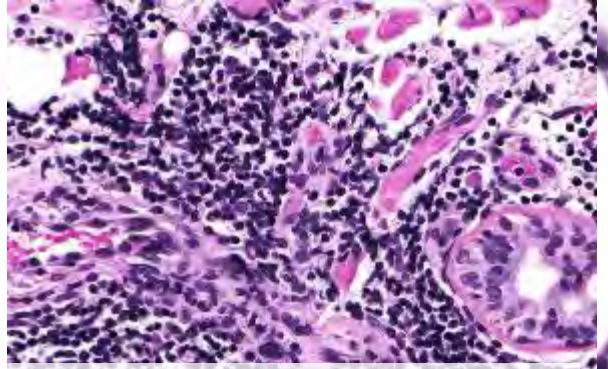


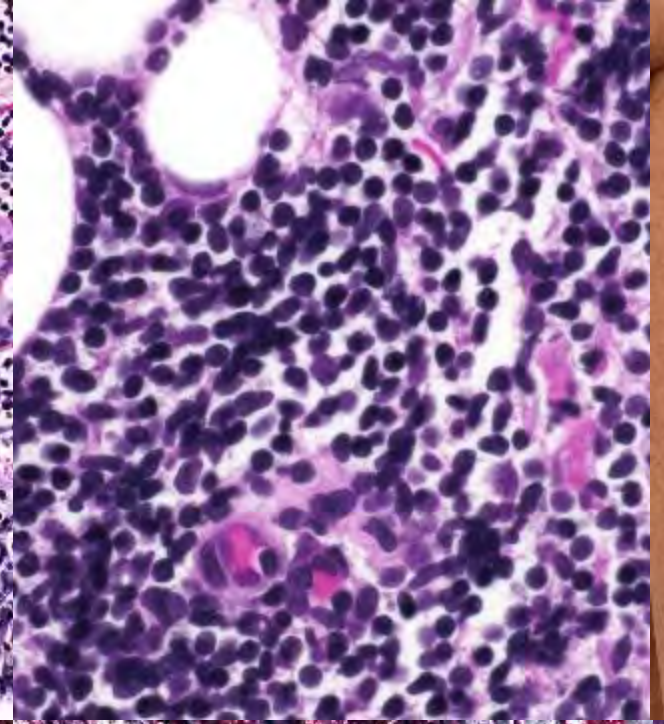


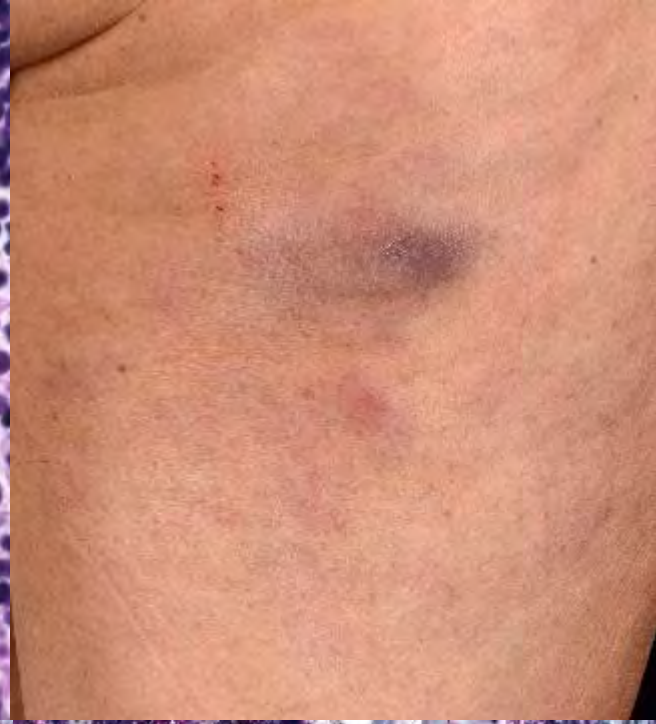








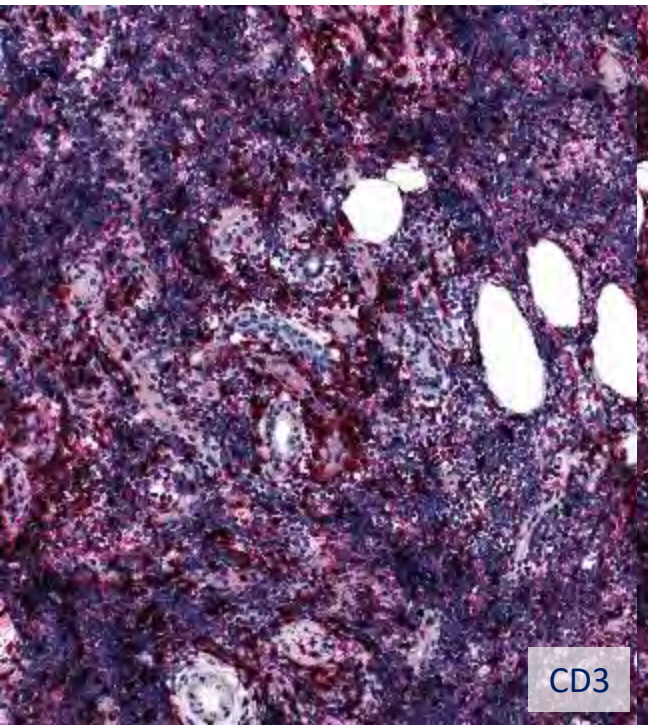


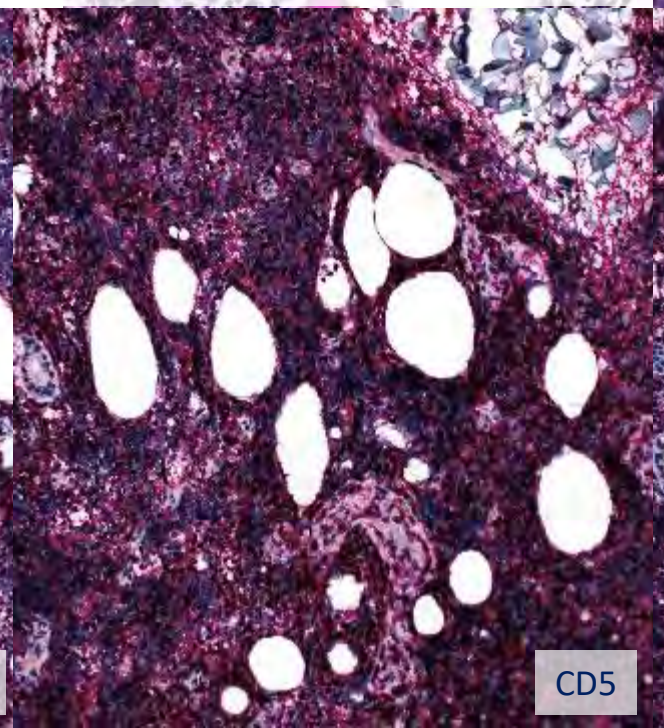


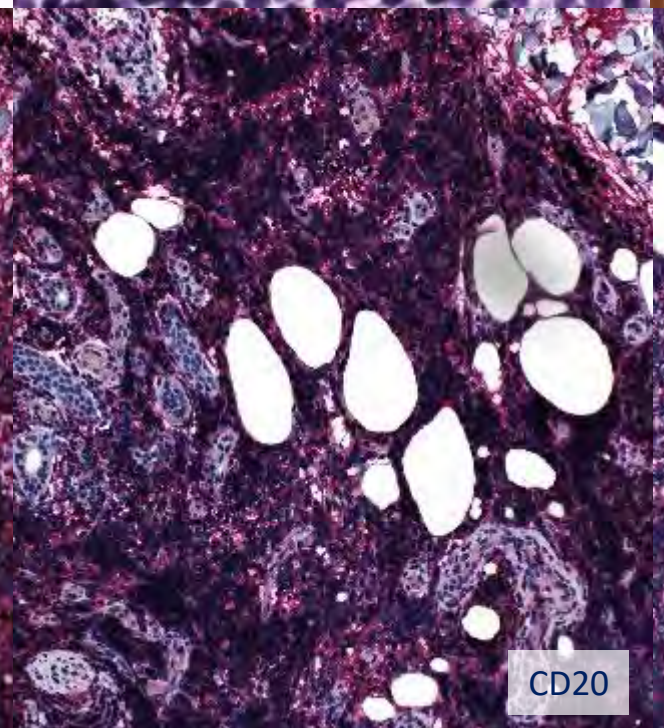
Erythema migrans

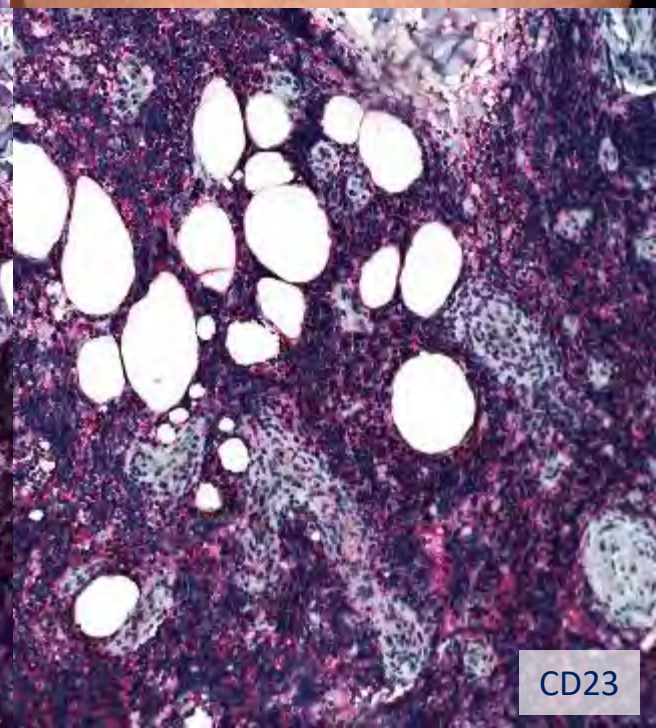
with specific infiltrate of B-CLL

PCR on lesional tissue positive for *Borrelia*









Journal of
Cutaneous Pathology

Specific cutaneous infiltrates of B-cell chronic lymphocytic leukemia (B-CLL) at sites typical for *Borrelia burgdorferi* infection

Lorenzo Cerroni, Gerald Höfler,[1] Barbara Bäck, Peter Wolf, Gerlinde Maier and Helmut Kerl

From the Departments of Dermatology and [1]Pathology, University of Graz, Austria

Background: Cutaneous manifestations of B-cell chronic lymphocytic leukemia (B-CLL) comprise a wide spectrum of clinicopathologic presentations. In some cases, onset of skin lesions is triggered by antigenic stimulation, and specific skin infiltrates at sites of previous herpes simplex or herpes zoster infection have been well documented. Specific skin manifestations of B-CLL can also be observed at sites typical for lymphadenosis benigna cutis (e.g. nipple, scrotum, earlobe), a *Borrelia burgdorferi*-associated cutaneous B-cell pseudolymphoma.

Methods: We studied specific skin manifestations of B-CLL arising at sites typical for *B. burgdorferi*-induced lymphocytoma benigna cutis, analyzing tissues for presence of *B. burgdorferi* DNA using the polymerase chain reaction (PCR) technique. Six patients with B-CLL, (M:F = 1:2, mean age 67.8) presented with specific skin lesions located on the nipple (four cases) and scrotum (two cases).

Results: Clinically there were solitary erythematous plaques or nodules. Histology revealed in all cases a dense, monomorphous infiltrate of small lymphocytes showing an aberrant $CD20^+/CD43^+$ phenotype. In all cases monoclonality was demonstrated by PCR analysis of the J_H gene rearrangement. PCR analysis showed in four of the six cases the presence of DNA sequences specific for *B.burgdorferi*.

Conclusions: Our study demonstrates that infection with *B. burgdorferi* can trigger the development of specific cutaneous infiltrates in patients with B-CLL.

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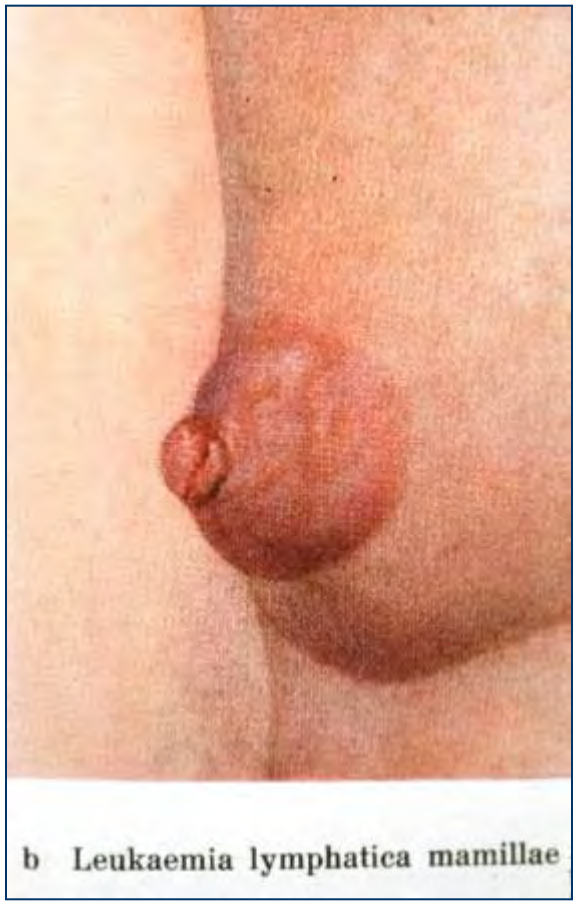
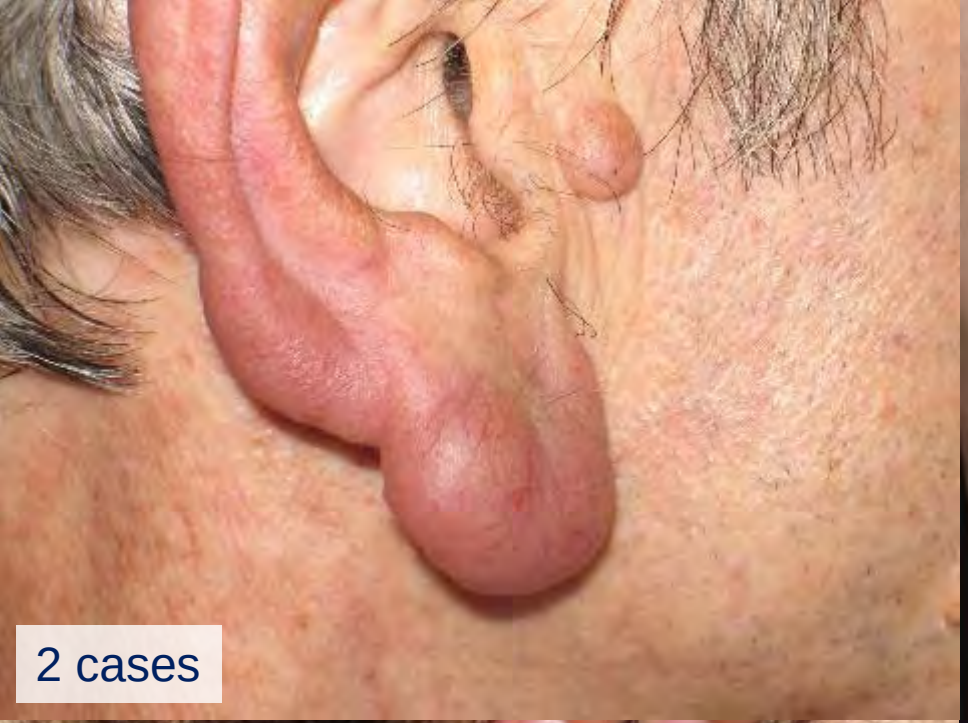
Cutaneous manifestations of B-cell chronic lymphocytic leukemia (B-CLL) comprise a wide spectrum of clinicopathologic presentations.[1,2] In some cases skin lesions are induced by antigenic stimulation; in this context, specific skin infiltrates of B-CLL at sites of previous herpes simplex or herpes zoster infection have been well documented.[3] In some patients, specific skin manifestations of B-CLL arise at sites typical for *Borrelia burgdorferi*-associated diseases such as lymphadenosis benigna cutis (lymphocytoma cutis). The association between these lesions and *B. burgdorferi* infection has not been investigated thus far.

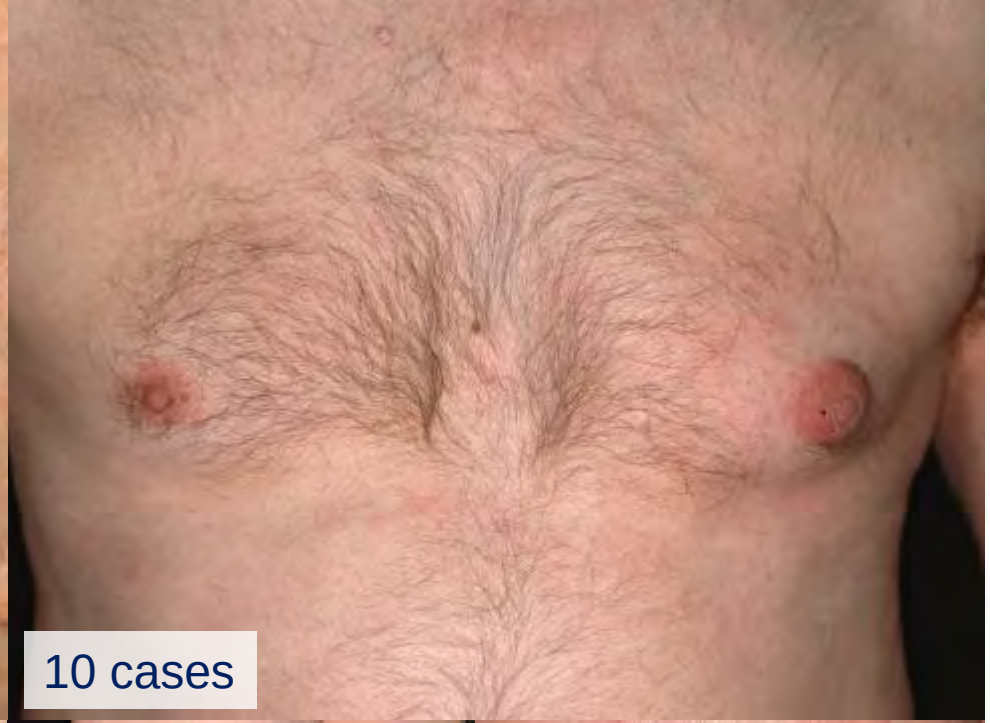
Nipple: 4 cases
Scrotum: 2 cases

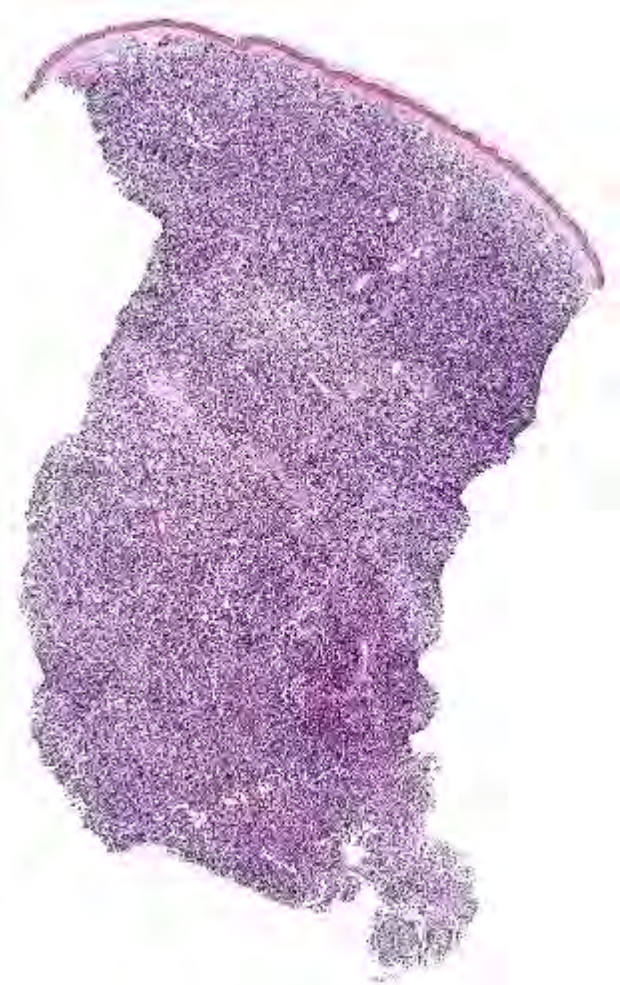
(at present: 18 cases)



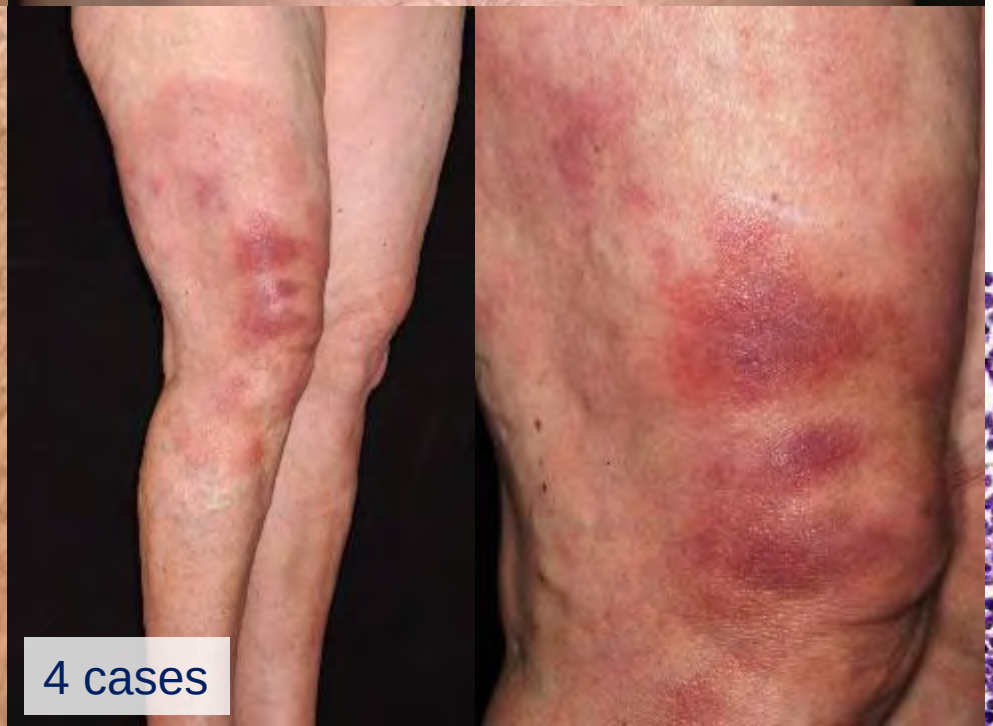
b Leukaemia lymphatica mamillae

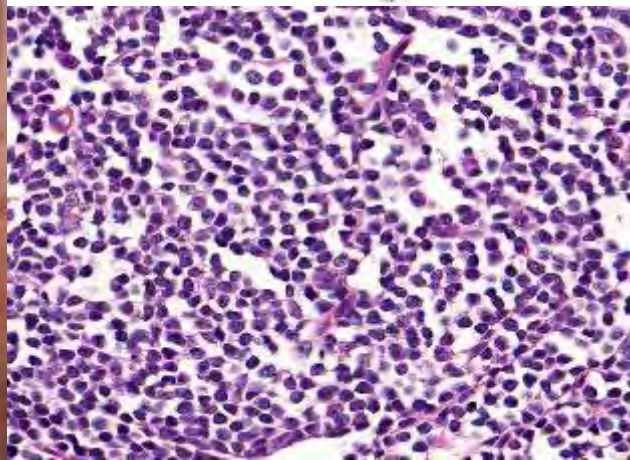

2 cases

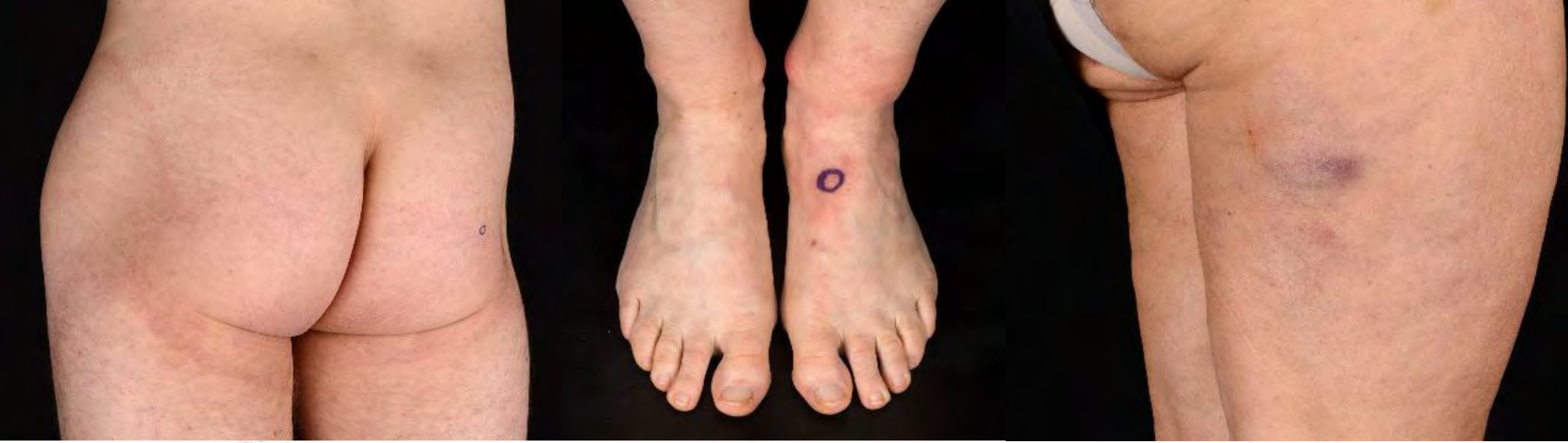

10 cases

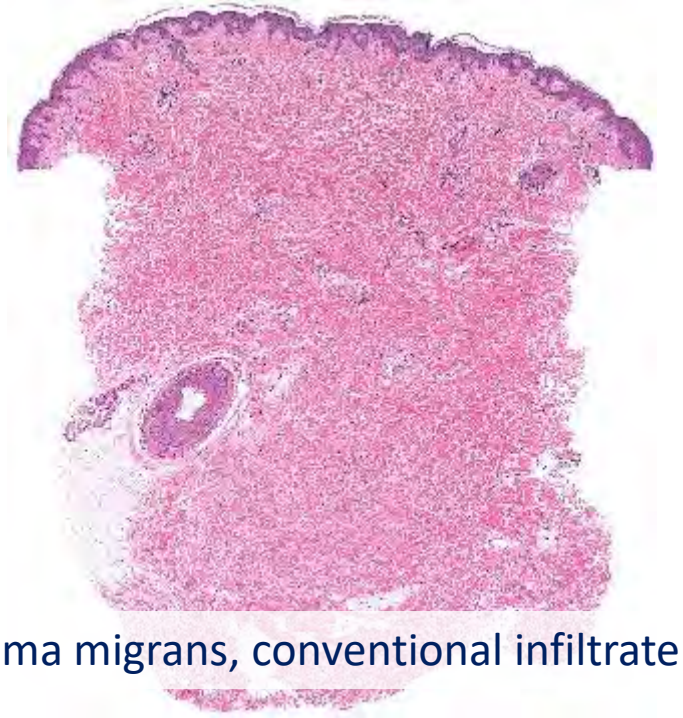



2 cases

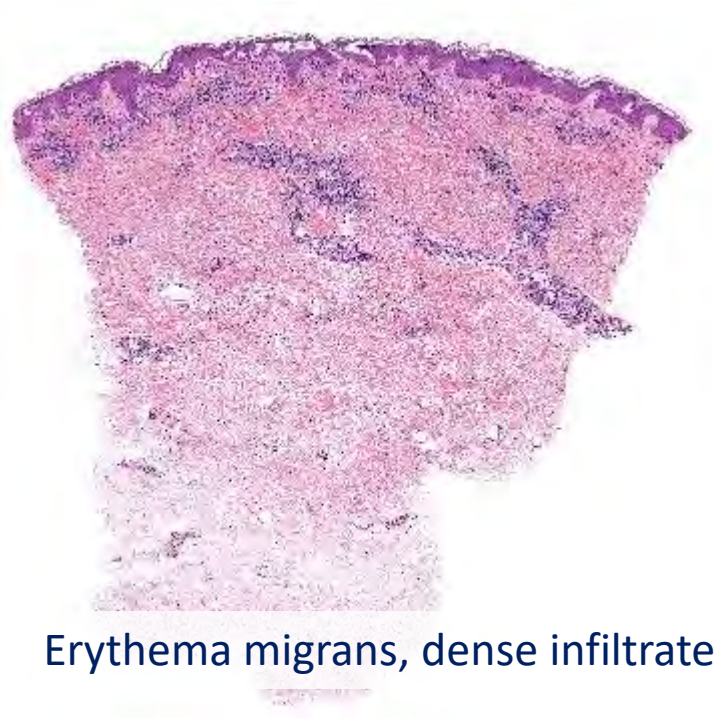

4 cases



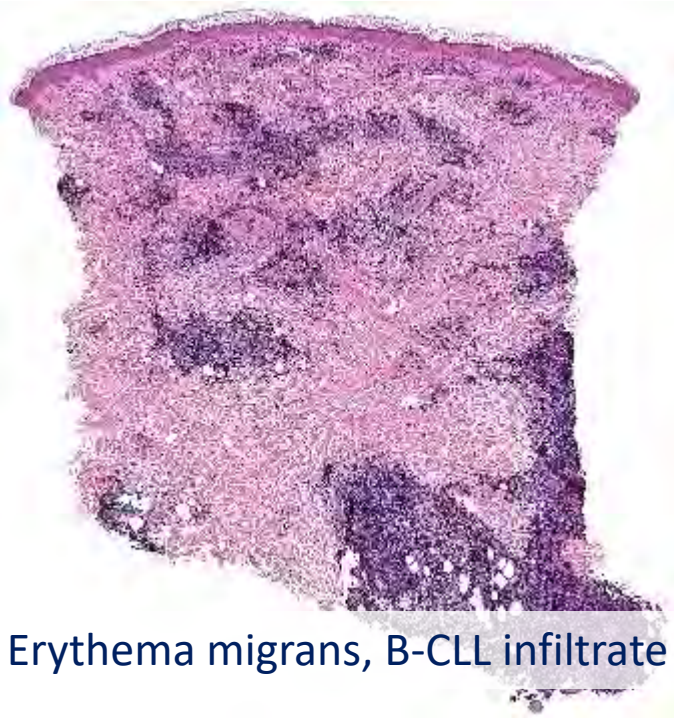




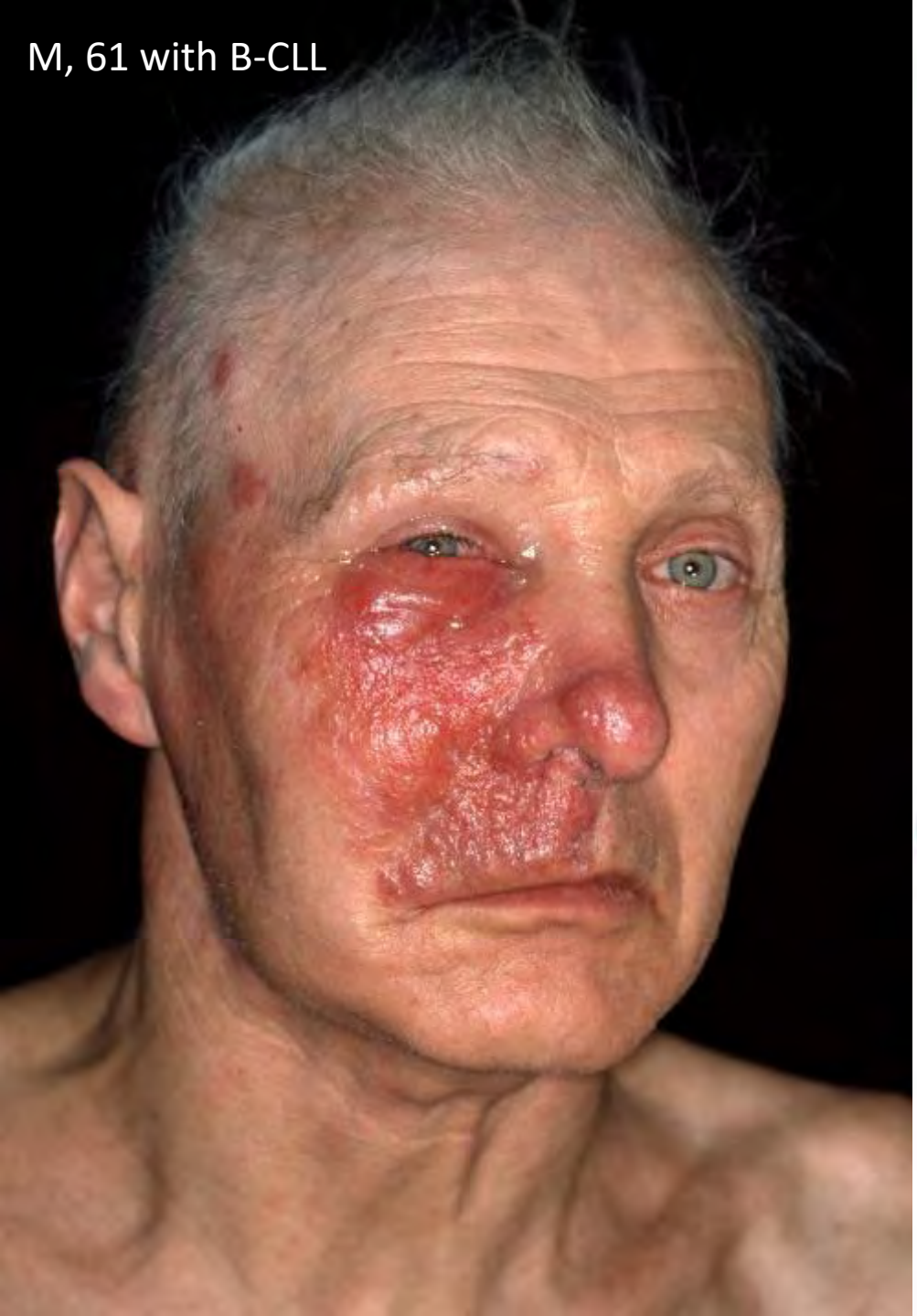
Erythema migrans, conventional infiltrate

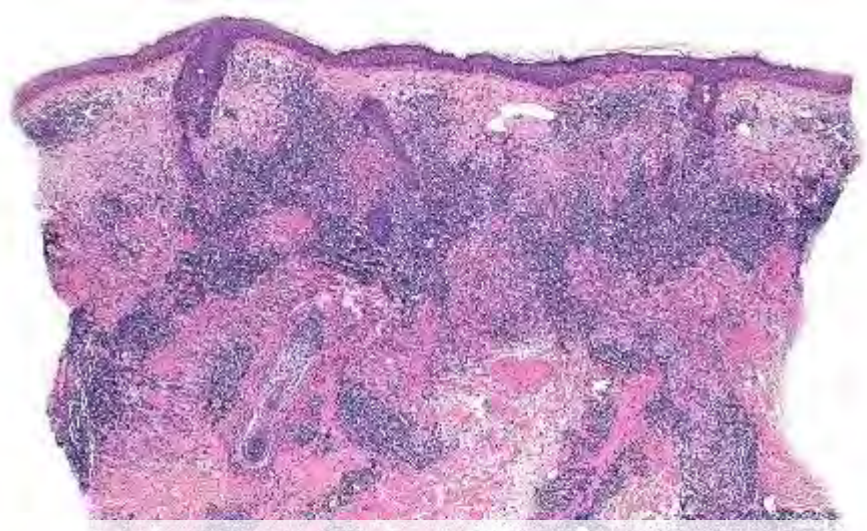


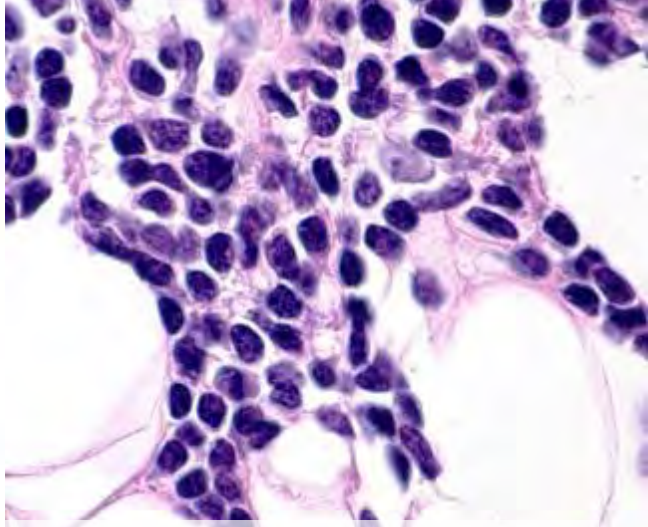
Erythema migrans, dense infiltrate



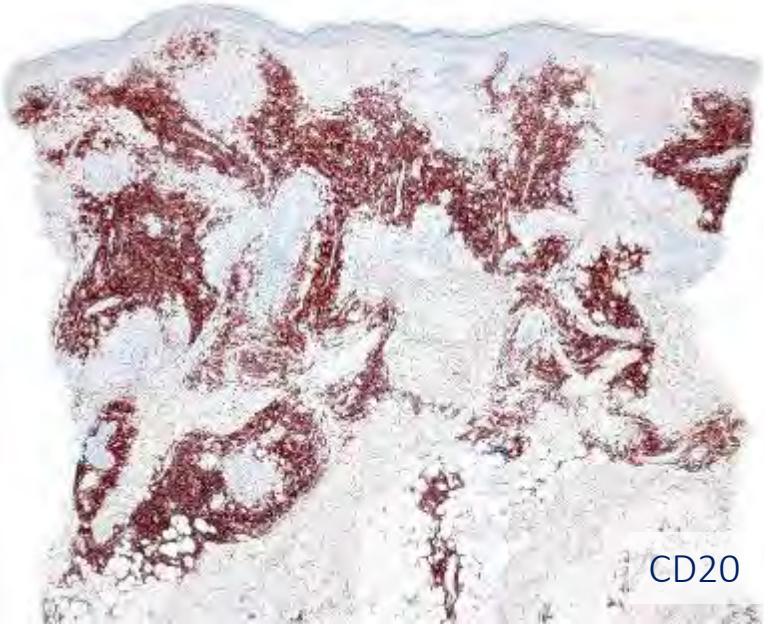
Erythema migrans, B-CLL infiltrate

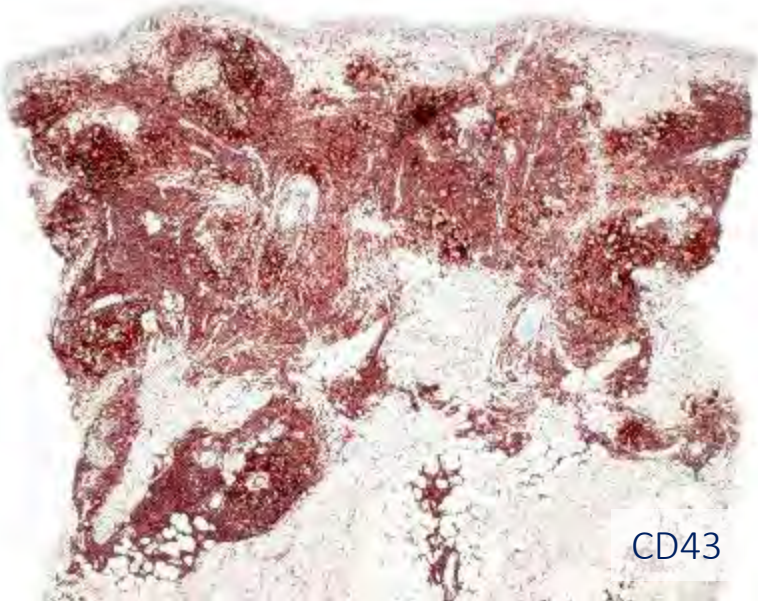






Specific cutaneous infiltrate of B-CLL at the site of *H. zoster* infection





Specific Cutaneous Infiltrates of B-Cell Chronic Lymphocytic Leukemia Arising at the Site of Herpes Zoster and Herpes Simplex Scars

Lorenzo Cerroni, M.D., Paul Zenahlik, M.D., and Helmut Kerl, M.D.

Background. **Cutaneous lymphoid infiltrates at sites of herpes zoster scars in patients with B-cell chronic lymphocytic leukemia (B-CLL) often are diagnosed as benign lymphoid hyperplasia ("pseudolymphomas"). The histologic and immunophenotypic features of these lesions are not well characterized. Appearance of skin lesions in B-CLL patients is considered a poor prognostic sign.**

Method. **Eight punch biopsies from five patients (three males, two females; mean age, 66.7 years) affected by B-CLL and presenting with lesions at sites of previous herpes simplex (upper lip, one patient) or herpes zoster (trunk, four patients; forehead, one patient) infections were included in the study. Histologic examination was performed on routine sections stained with hematoxylin and eosin and Giemsa. Immunohistologic stainings were performed with a standard three-step immunoperoxidase technique on formalin fixed, paraffin embedded tissue sections.**

Results. **Specific cutaneous infiltrates of B-CLL were diagnosed histopathologically and immunophenotypically in eight biopsies from all five patients. Clinically, patients presented with erythematous papules or plaques confined to the area of previous herpes virus eruptions. Histopathologic features in most cases were characterized by a variably dense perivascular and periadnexal infiltrate of small hyperchromatic lymphocytes throughout the entire dermis, reaching the subcutaneous fat. In one case, a dense, diffuse infiltrate involving the entire dermis was observed. A granulomatous reaction with presence of epithelioid and multinucleated giant cells was a prominent feature in four biopsies from three patients. Light areas containing large lymphoid cells with features of prolymphocytes and paraimmunoblasts (so-called "proliferation centers") could be observed only in the case characterized by a diffuse infiltrate. Immunohistology revealed an aberrant $CD20^+/CD43^+$ phenotype of neoplastic B cells, which is not found in normal B lymphocytes ($CD20^+/CD43^-$). Reactive T lymphocytes were present in all lesions and had a normal $CD20^-/CD43^+/CD45Ro^+$ phenotype. At the time of this writing, four patients were alive without signs of skin disease after a mean follow-up of 58.5 months, and one patient died of B-CLL 24 months after the cutaneous eruption.**

Conclusions. **Specific cutaneous infiltrates of B-CLL are not uncommon at sites of herpes virus scars. The diagnosis can be confirmed by histopathologic and immunophenotypic criteria. The prognosis is better than previously reported. *Cancer* 1995;76:26–31.**

Key words: skin, B-cell chronic lymphocytic leukemia, Herpes simplex, Herpes zoster, specific cutaneous infiltrate, immunophenotype.

Cutaneous lesions induced by herpes virus infection (both herpes simplex and herpes zoster) are not uncommon in patients affected by malignant lymphomas and in particular by B-cell chronic lymphocytic leukemia (B-CLL).[1] They are considered to be one of the nonspecific skin manifestations associated with the malignant disease, possibly related to the immunodeficiency typically found in these patients. Complete resolution usually can be achieved with standard antiviral therapy. In some patients, however, lesions persist or recur after a short time. In these cases, skin biopsies reveal a dense lymphocytic infiltrate extending throughout the entire dermis to the subcutaneous tissues. Interpretation of these histopathologic features may be difficult, and lesions variously have been classified as "benign lymphoid hyperplasia" ("pseudolymphoma")[2,3] or "specific infiltrate of B-CLL"[4–6] in different reports. At present, there is no comprehensive histopathologic and immunohistochemical study addressing the question of the characteristics of lymphoid infiltrates at sites of herpes scars in patient with B-CLL. In this paper, we report on the occurrence of specific cutaneous infiltrates at the

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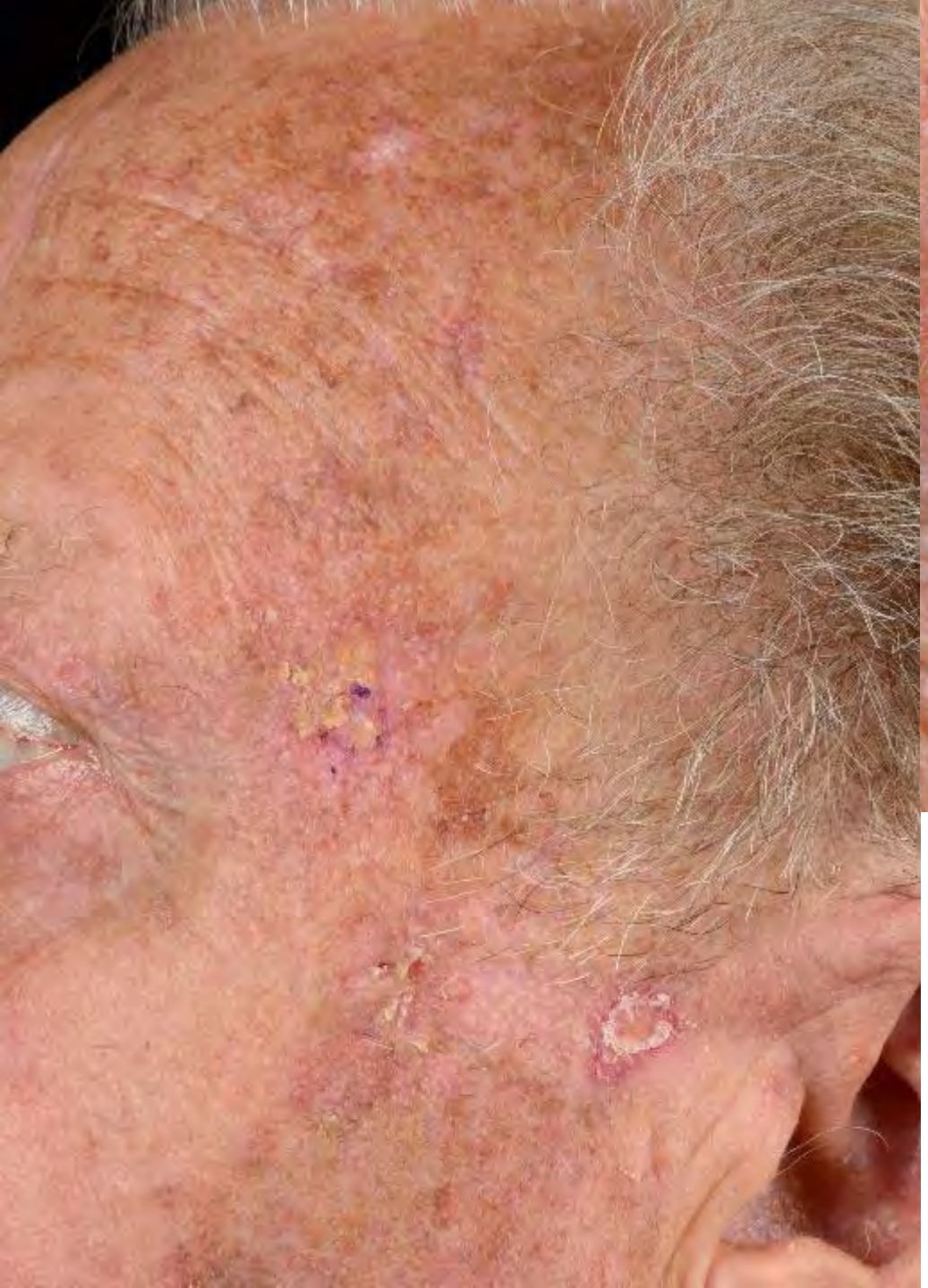
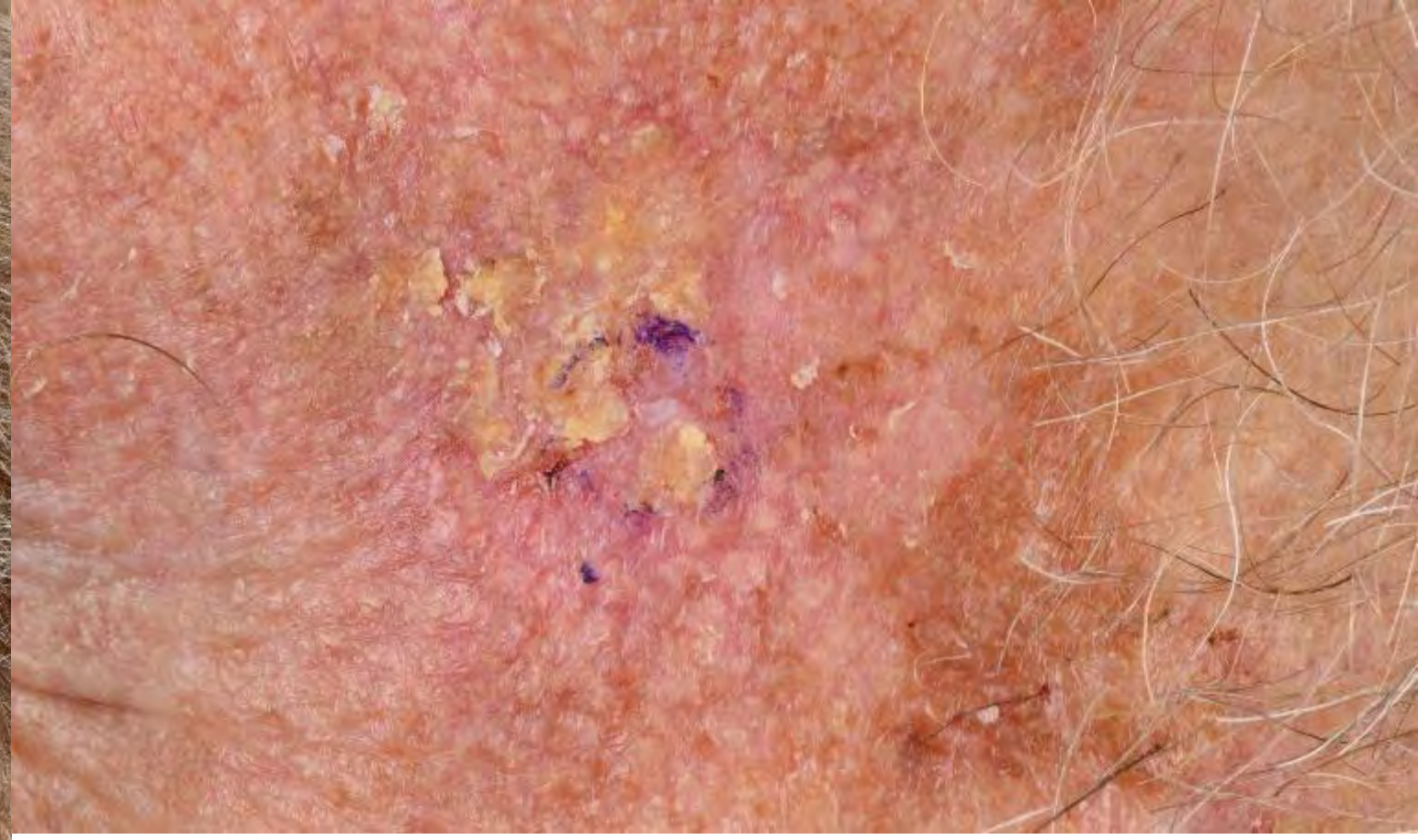
H. simplex: 1 case
H. zoster: 4 cases

(at present: 25 cases)





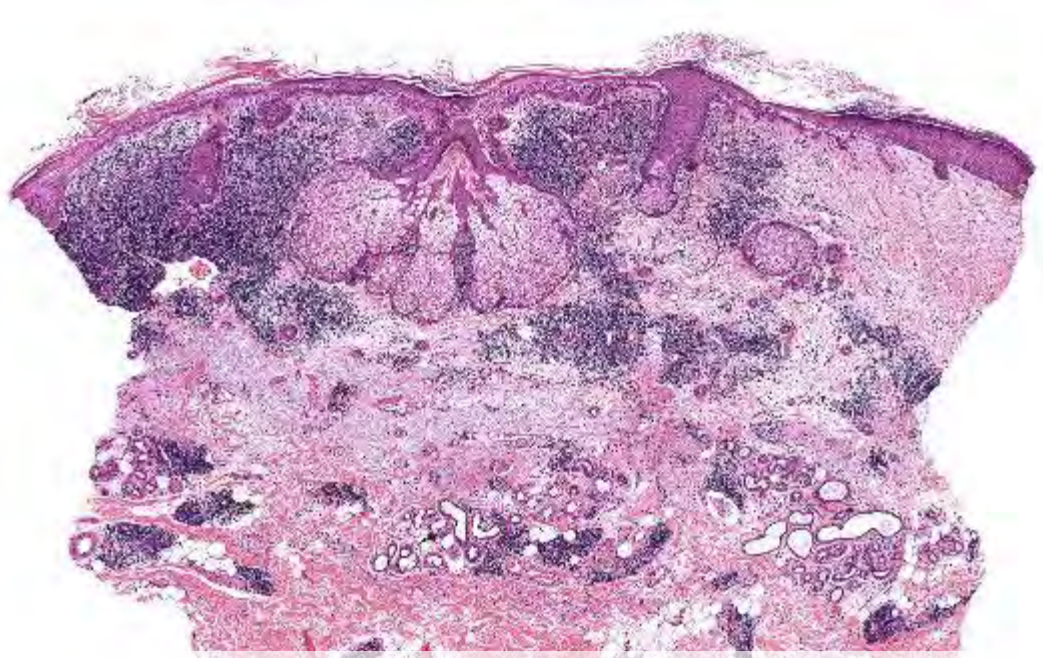
M, 73

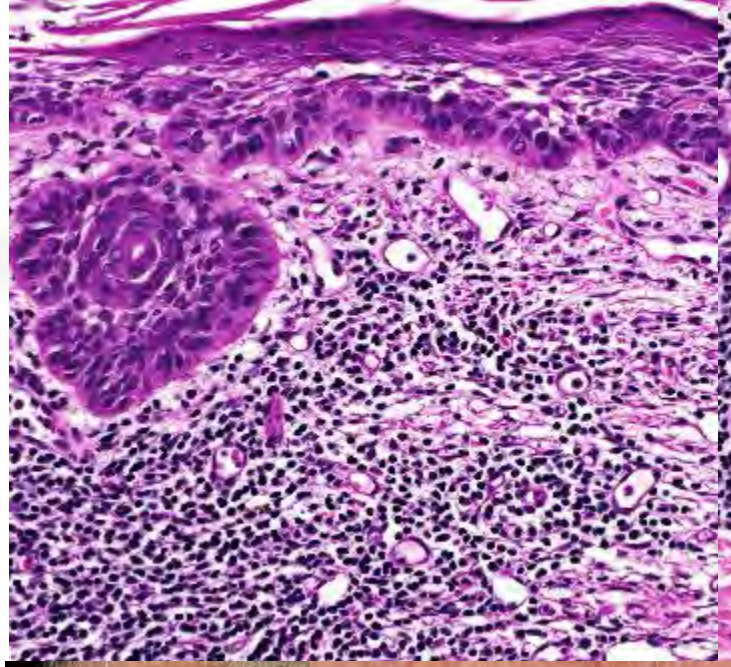
History of B-CLL (1st diagnosis 24 years before actual presentation, at present best supportive care).

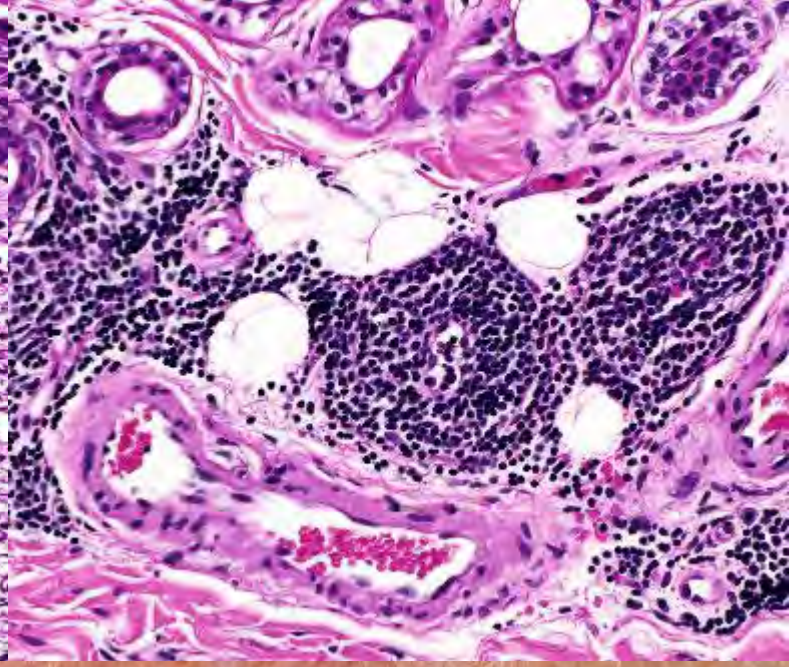
History of several cutaneous BCCs, SCCs and AKs.

Clinical diagnosis of "BCC vs. inflammation" on the left temple.

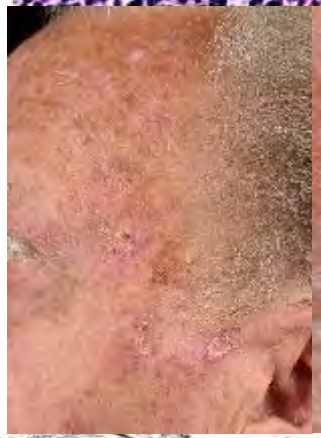
A biopsy is taken.

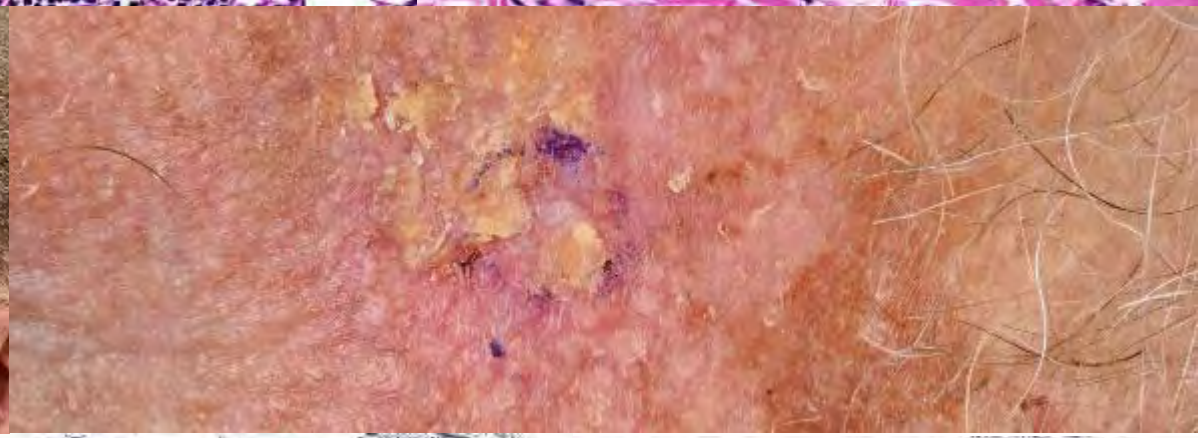


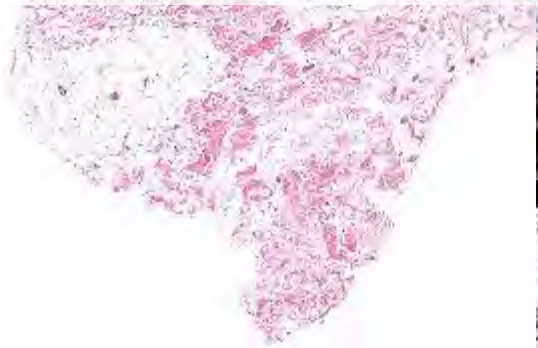


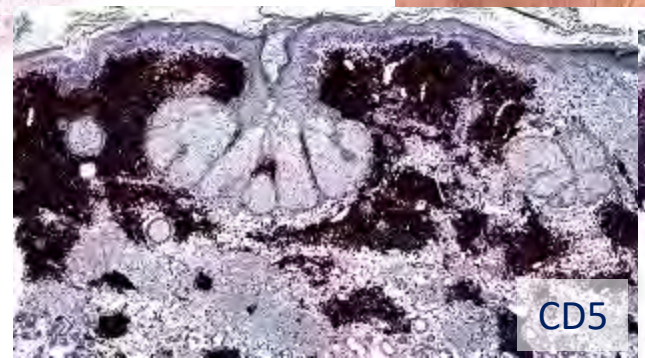


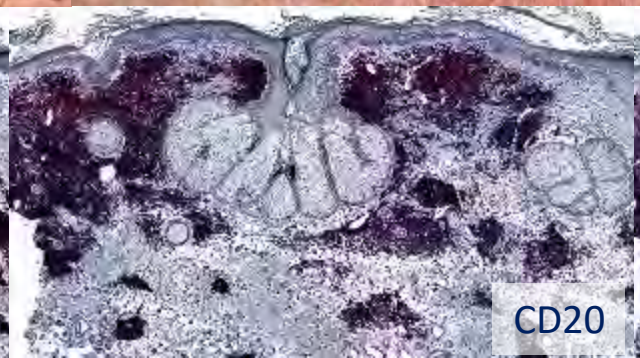
Specific infiltrate of B-CLL at the site of actinic keratosis

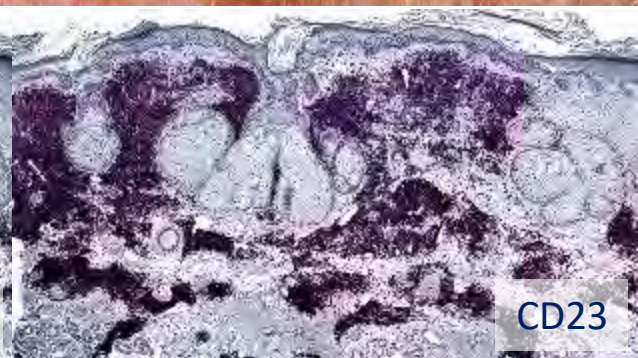


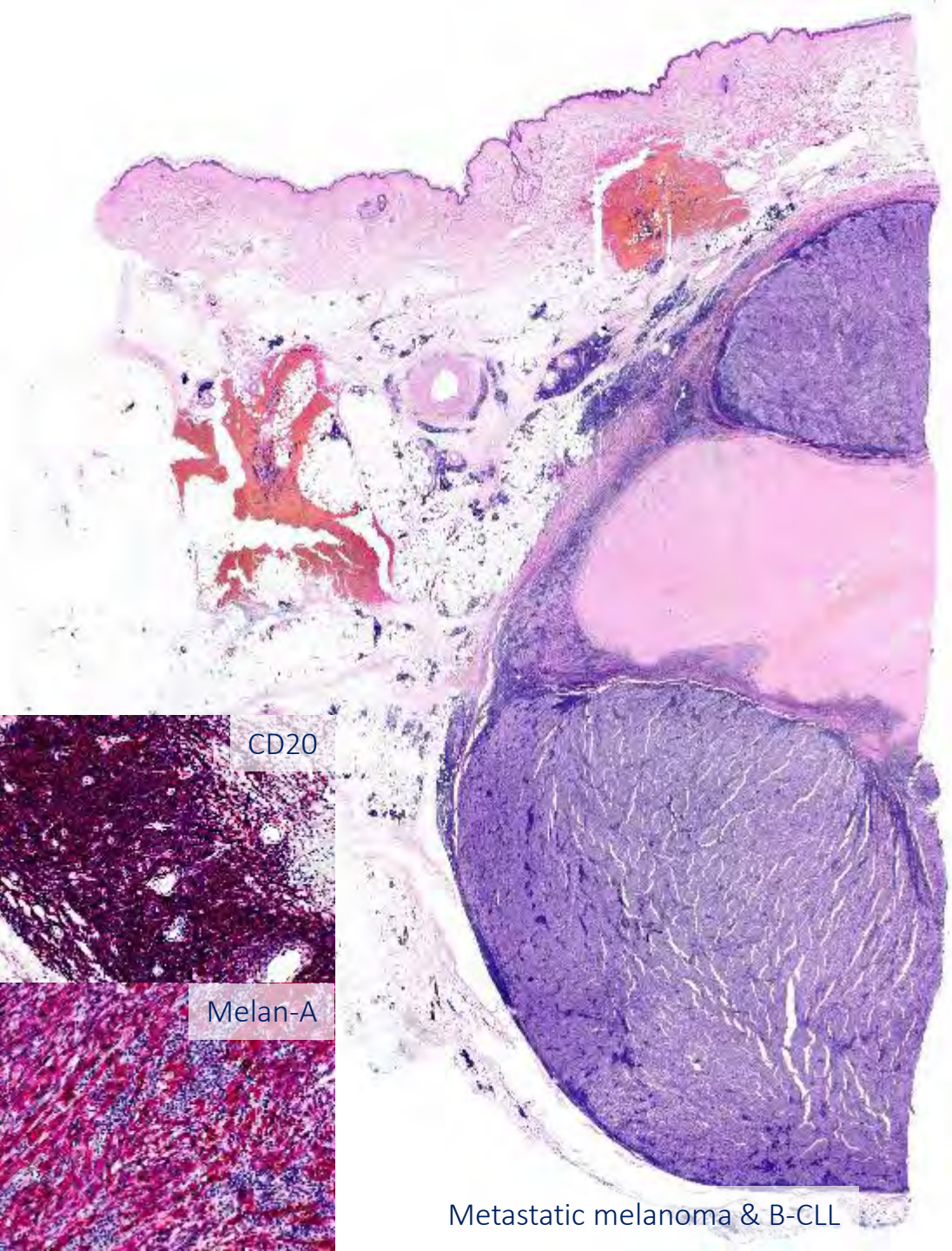








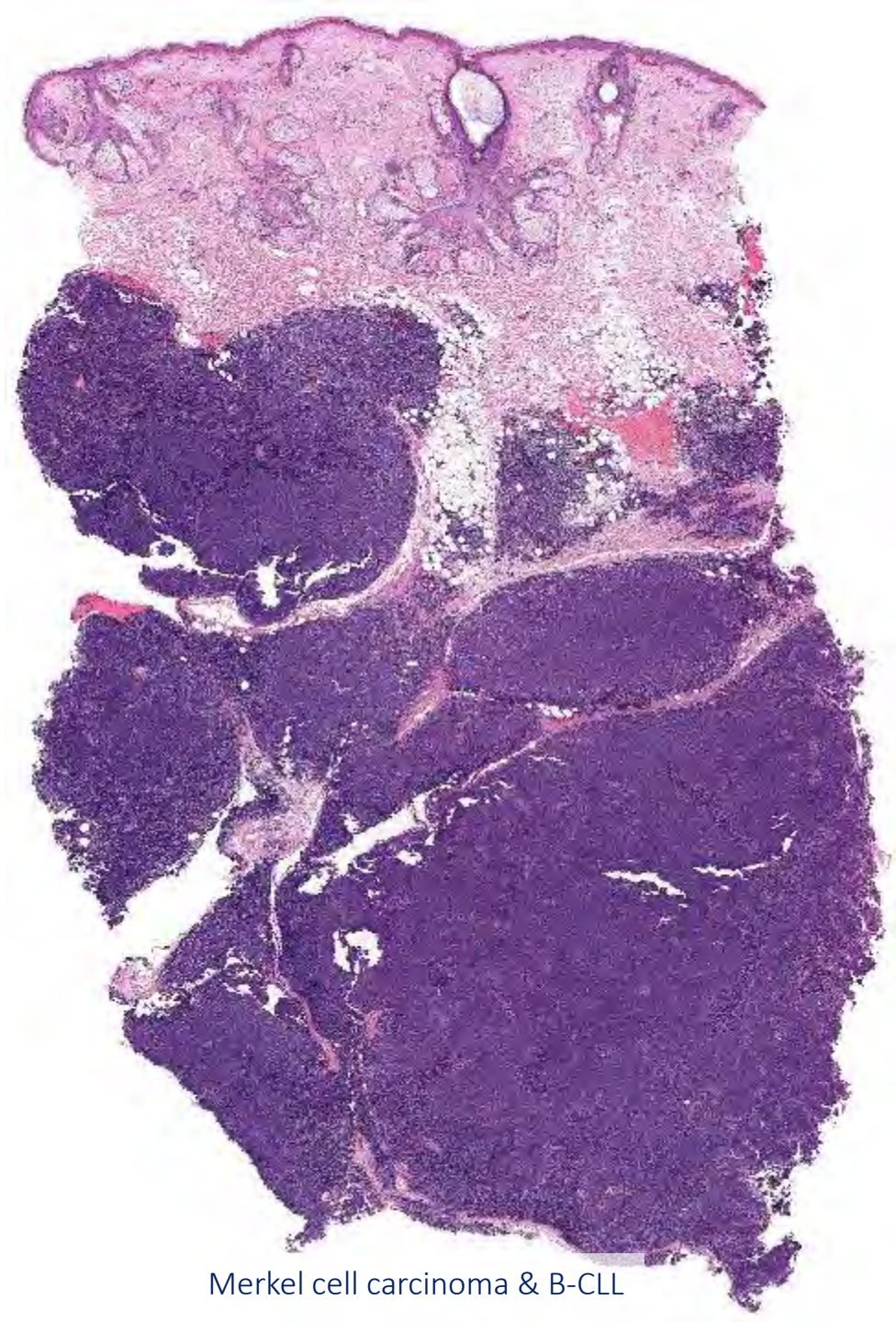




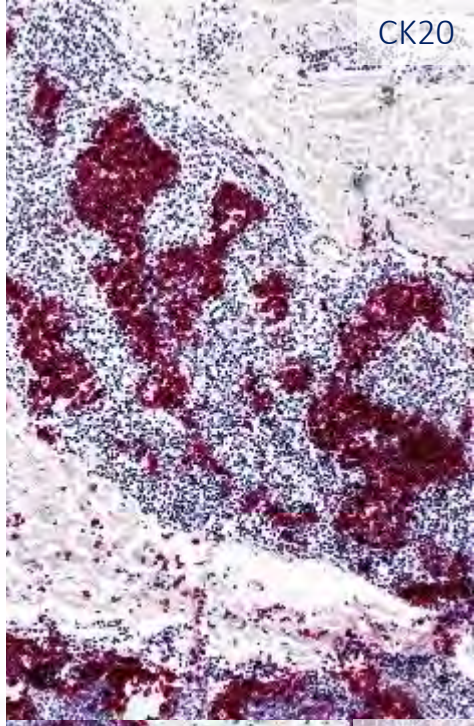
CD20

Melan-A

Metastatic melanoma & B-CLL



Merkel cell carcinoma & B-CLL



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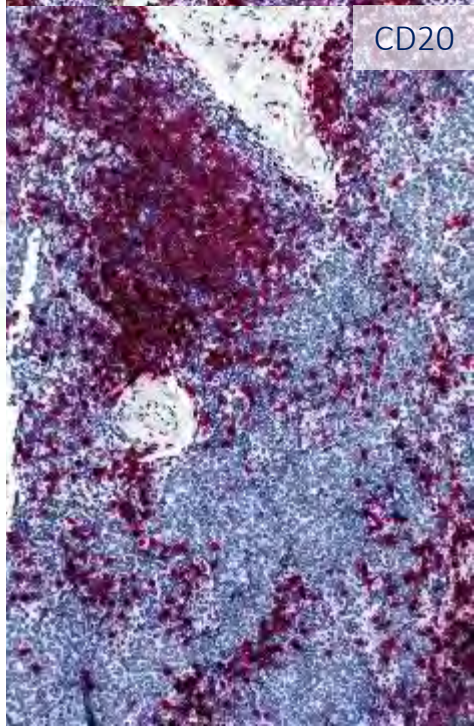
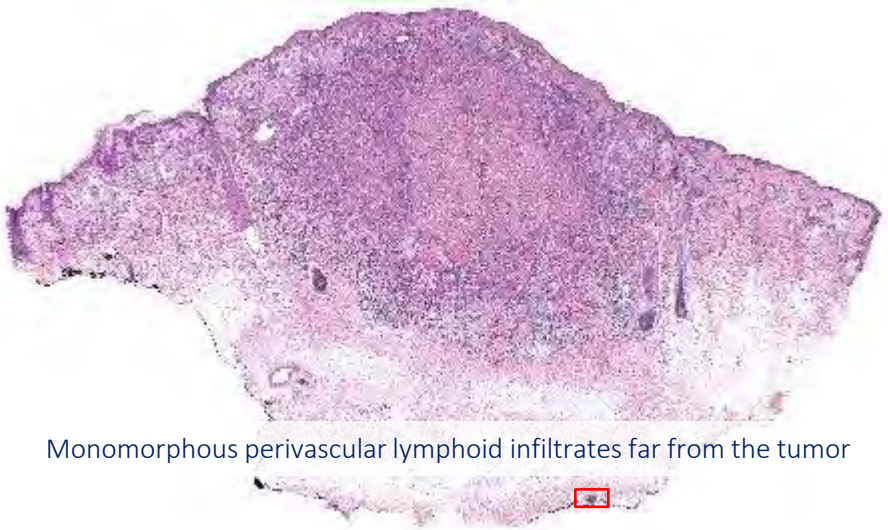


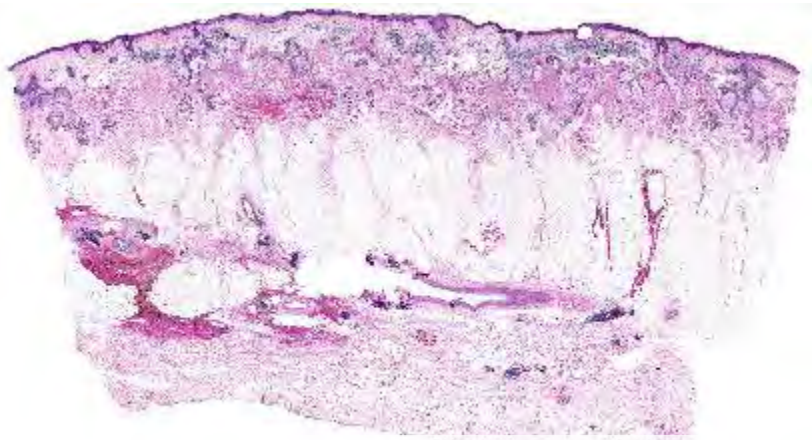
CD20

Clues to the presence of lymphocytes of B-CLL in skin biopsies

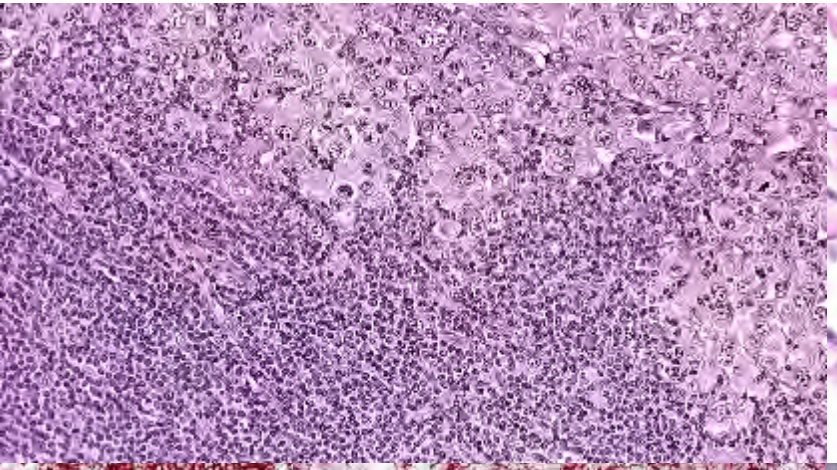
Monomorphous lymphoid infiltrates in the proximity of the tumor

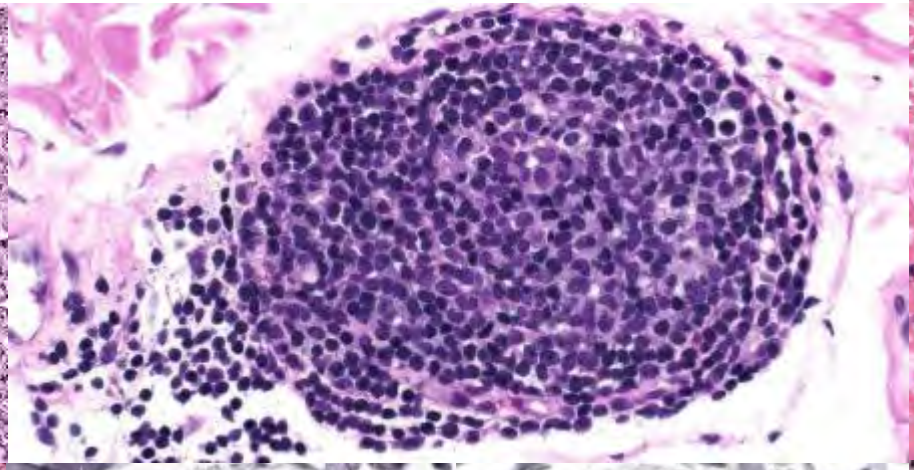


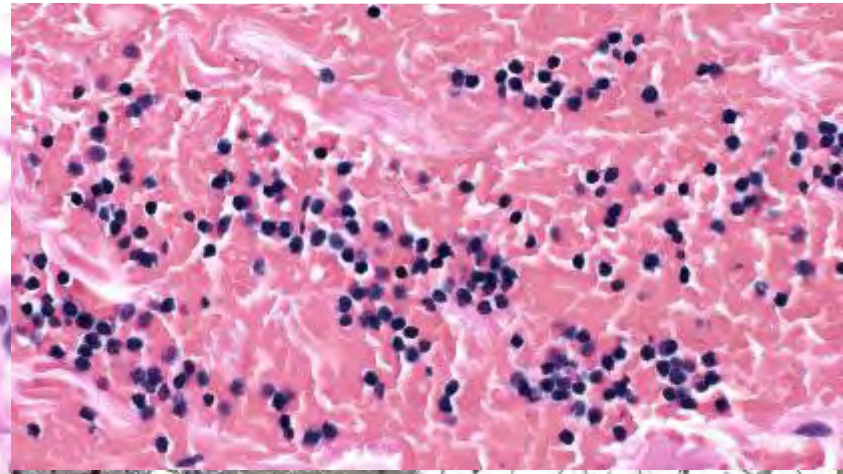
Monomorphous perivascular lymphoid infiltrates far from the tumor

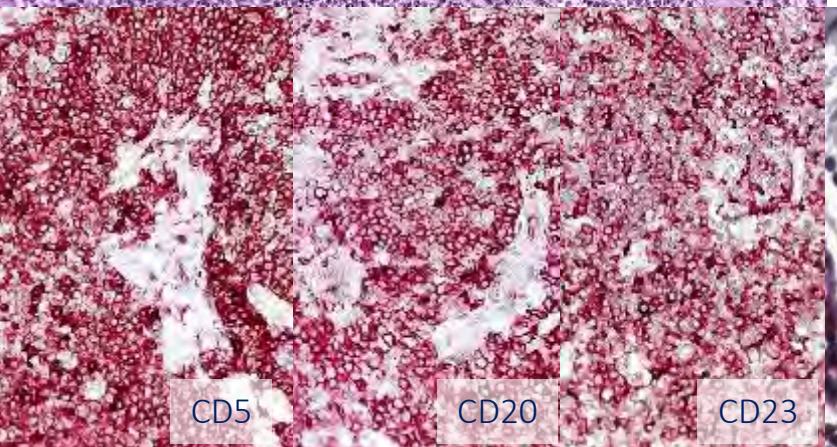


Lymphocytes within the surgery-related hemorrhage









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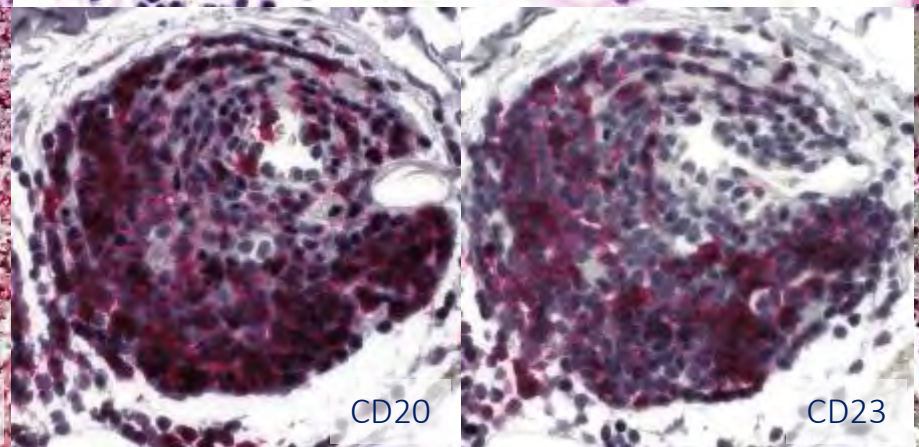

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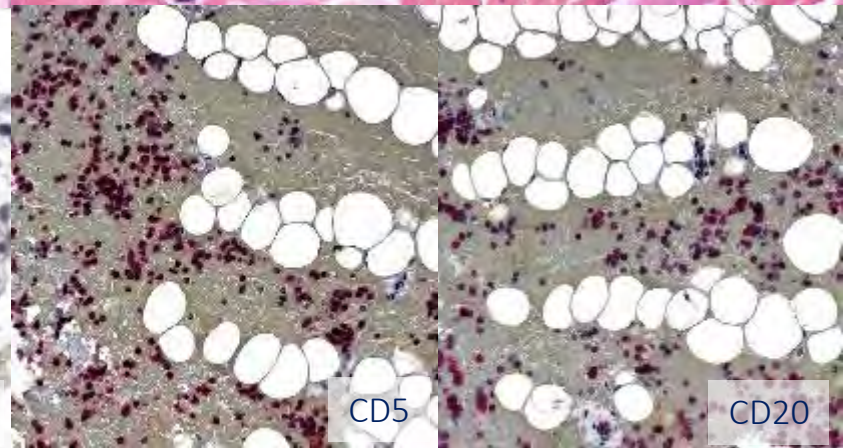

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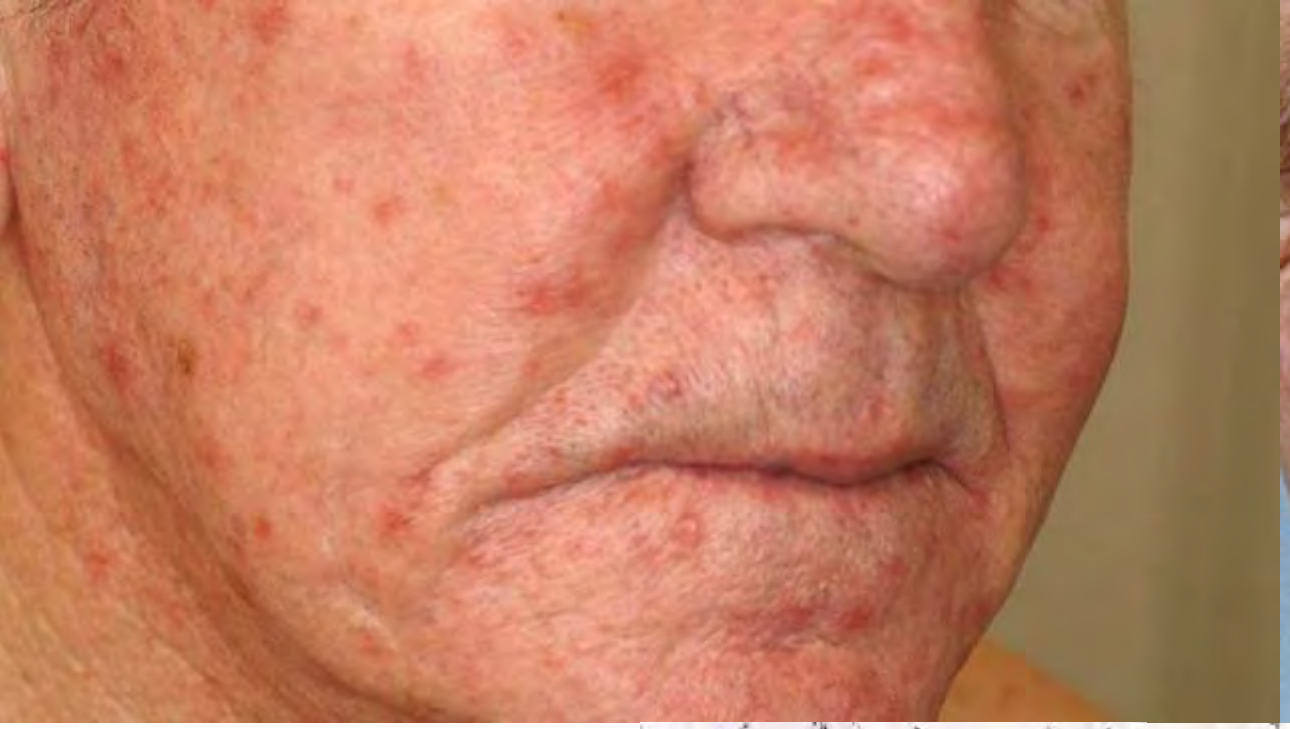
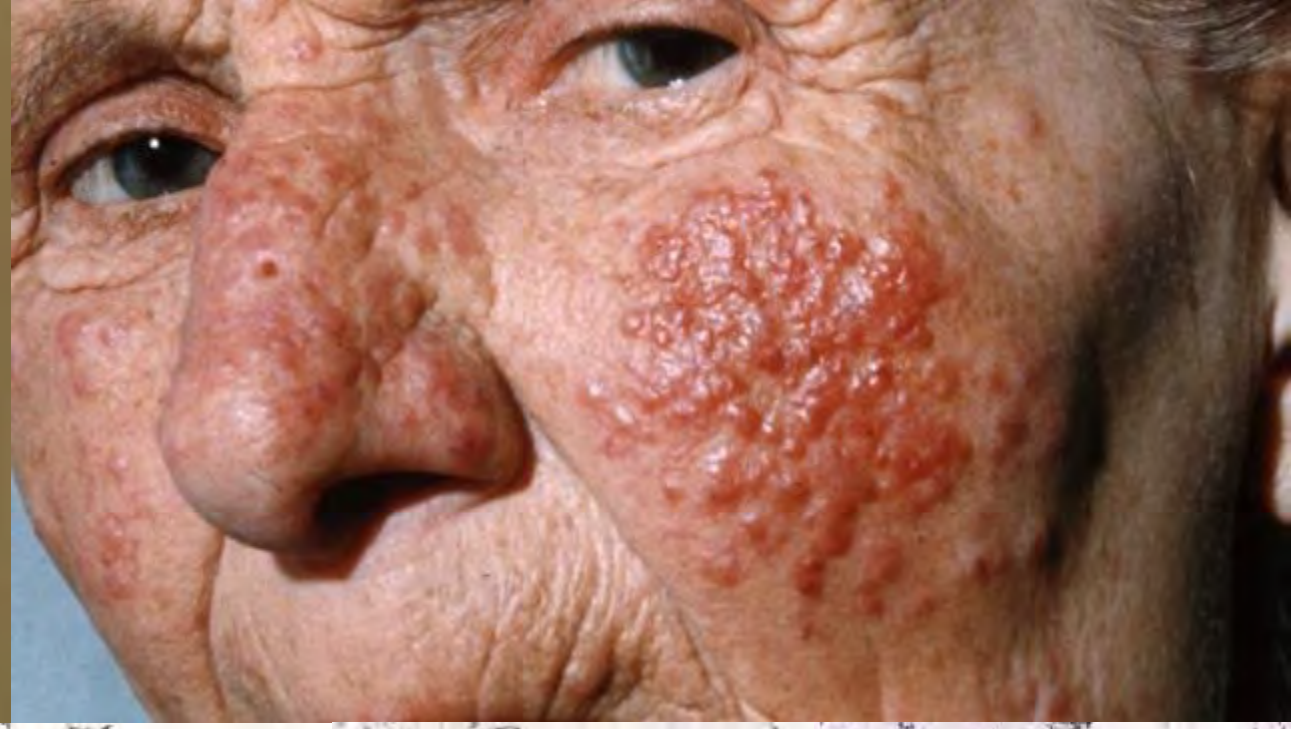
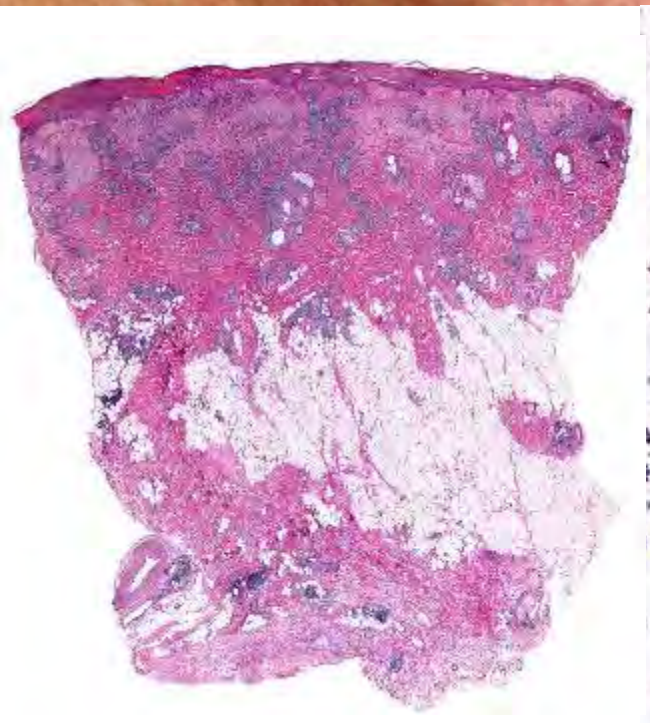
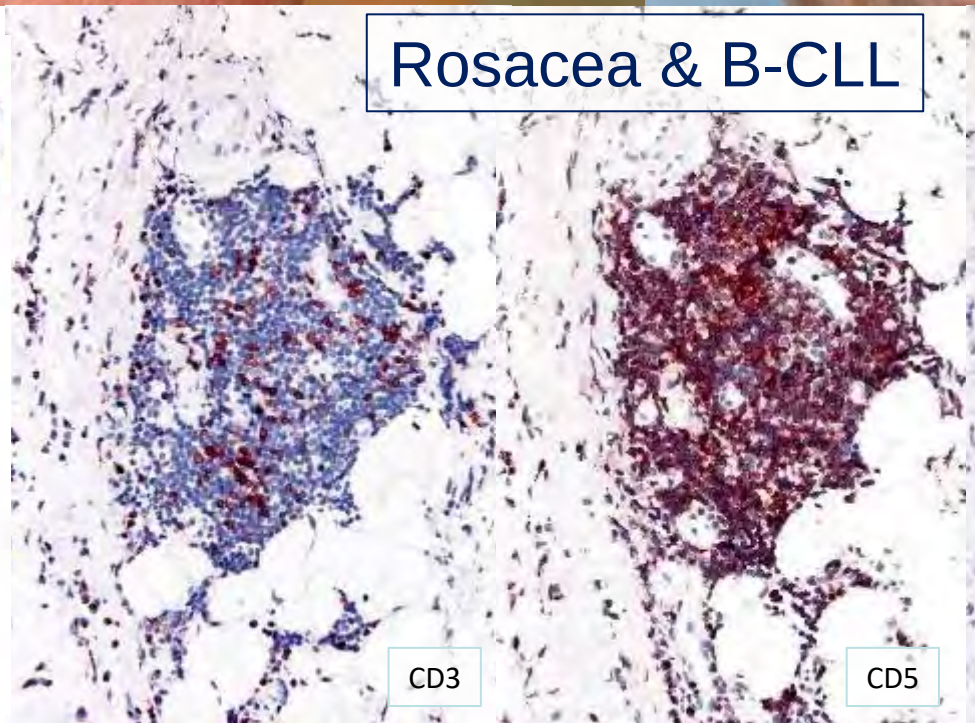
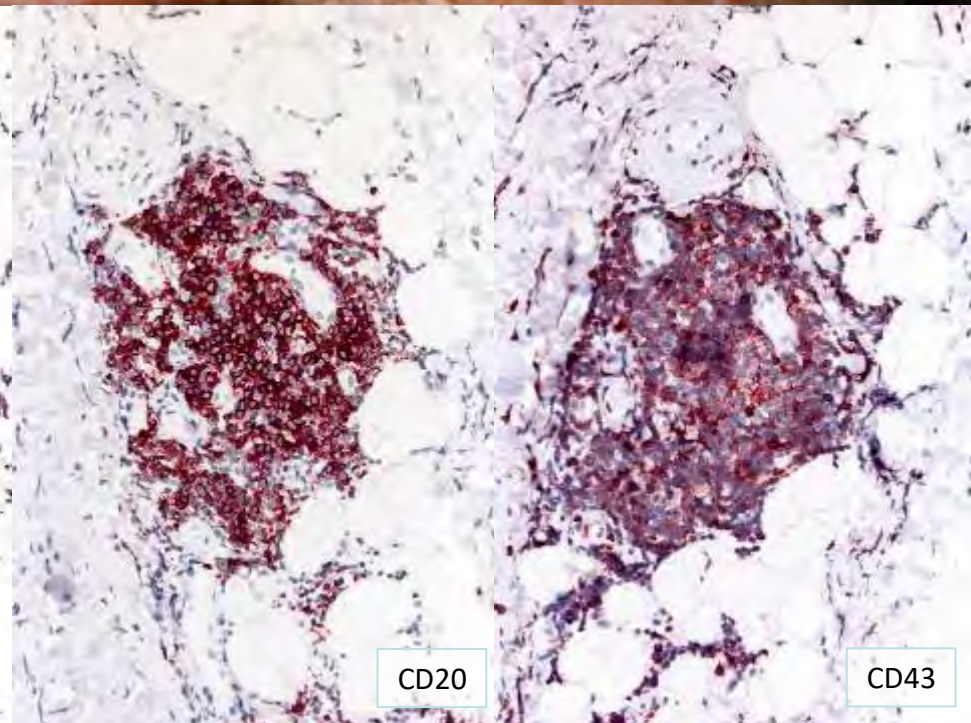


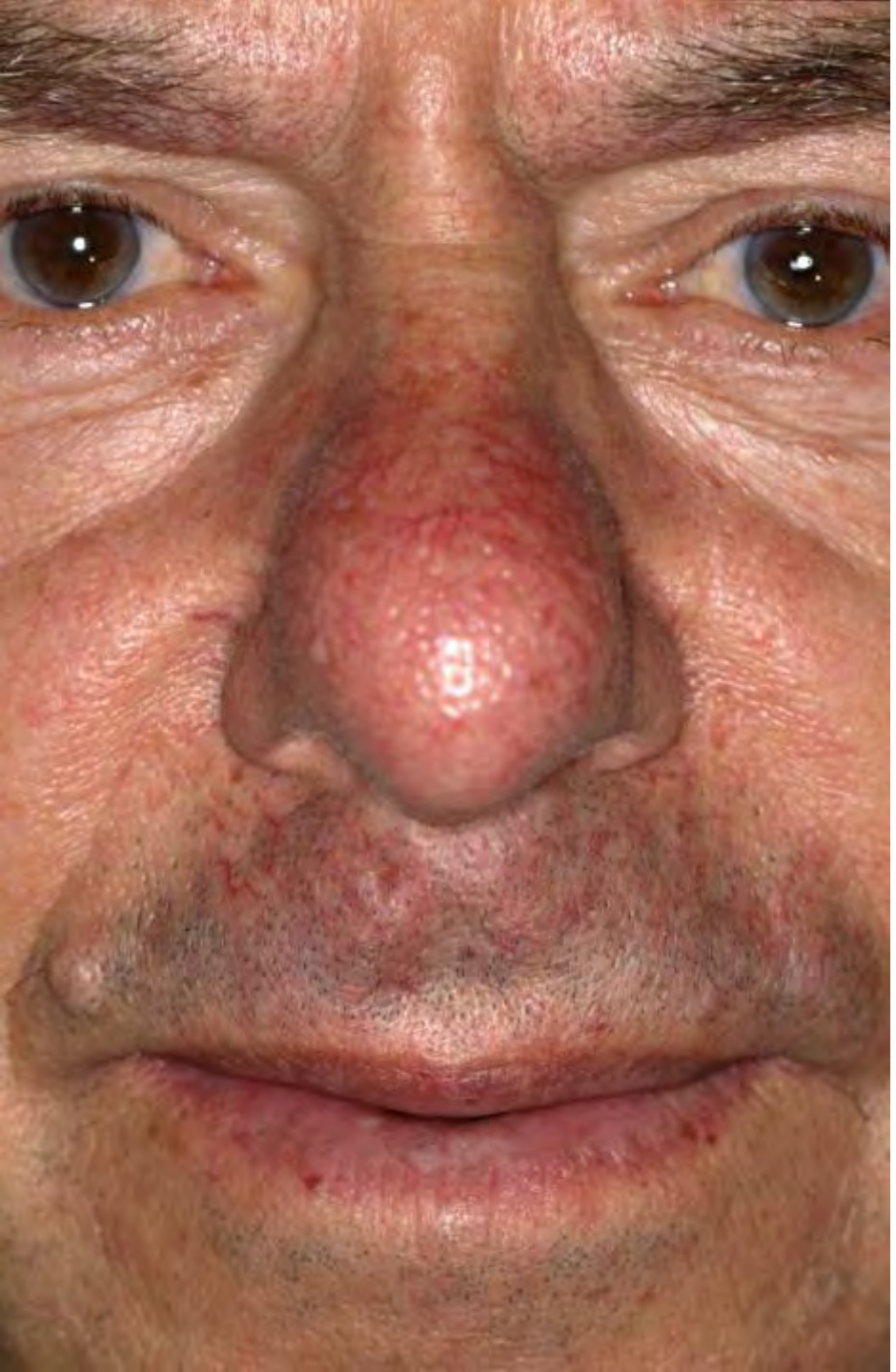


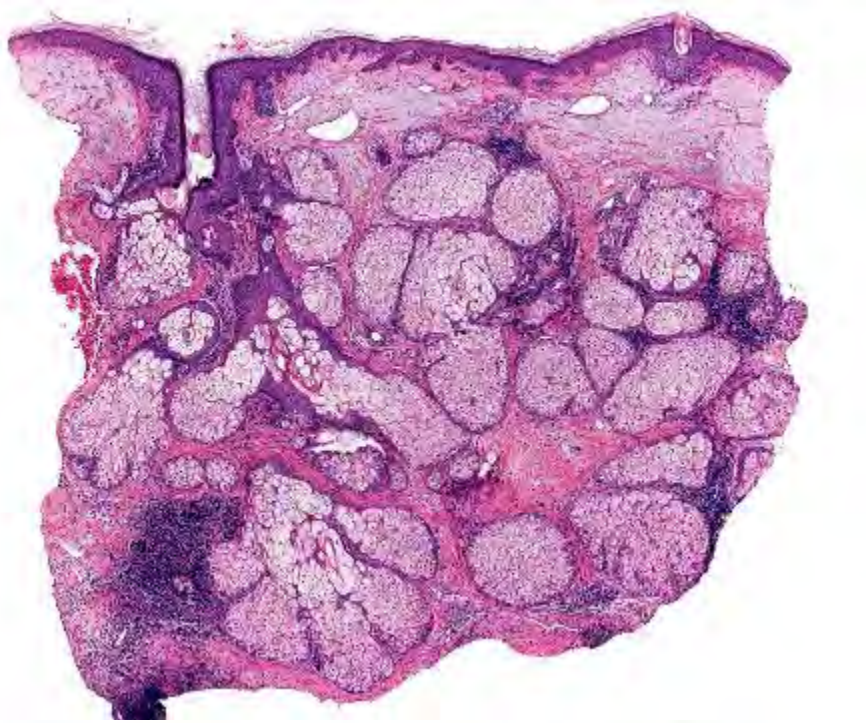


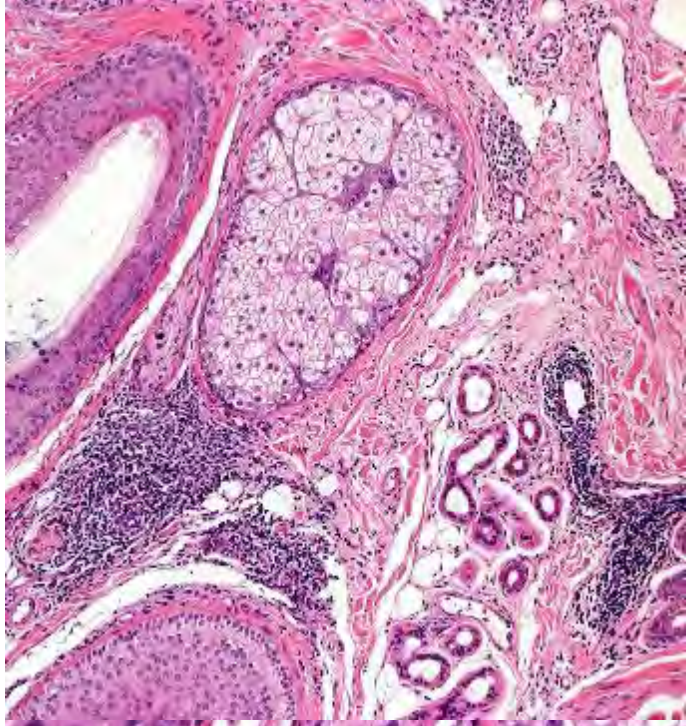
Rosacea & B-CLL

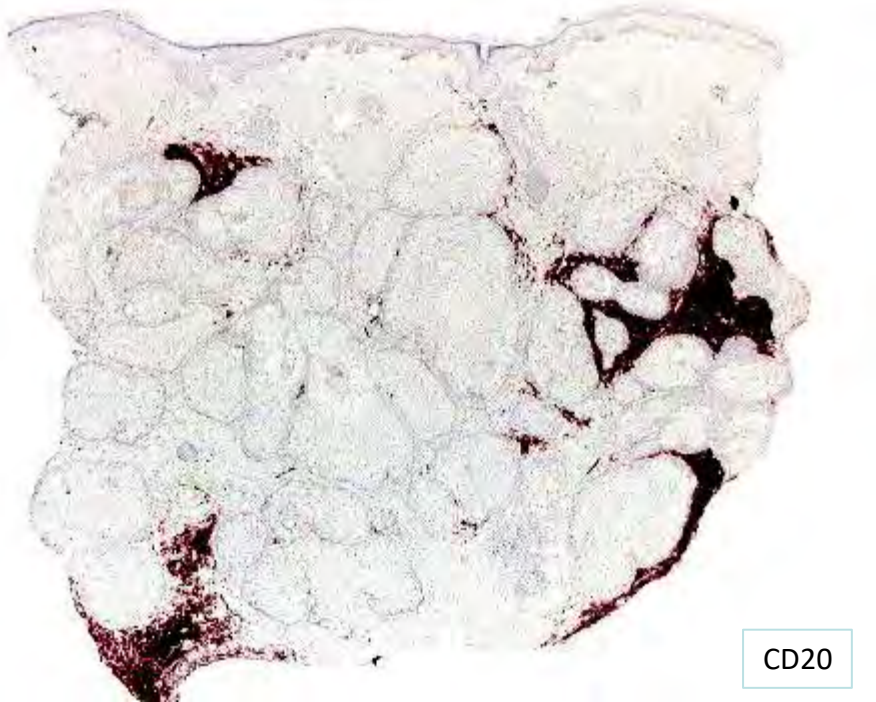












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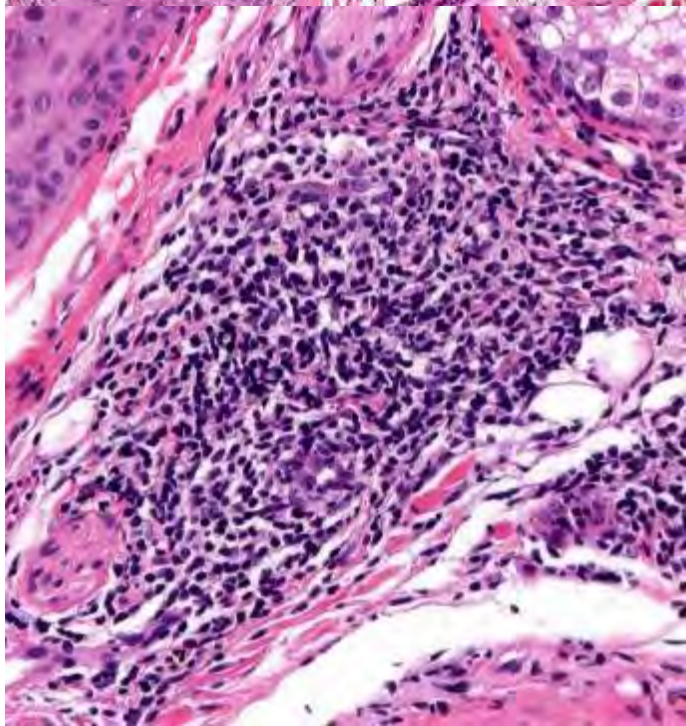

B-CLL & other skin disorders

- Besides "colonizing" cutaneous tumors, B-CLL cells may be found in the skin at the site of several inflammatory disorders
- Most common: *herpes simplex / zoster* or *Borrelia* infection
- B-CLL cells at the site of other inflammatory disorders (e.g., rosacea) probably more common than previously realized
- In elderly patients, monomorphous infiltrates of small hyperchromatic cells in the proximity of or far away from the tumor as well as lymphocytes within the surgical-related hemorrhage represent histopathological clues

The American Journal of Surgical Pathology 20(8): 1000–1010, 1996

Hematopathology Section:
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Specific Cutaneous Infiltrates of B-cell Chronic Lymphocytic Leukemia

A Clinicopathologic and Prognostic Study of 42 Patients

Lorenzo Cerroni, M.D., Paul Zenahlik, M.D., Gerald Höfler, M.D., Steven Kaddu, M.D., Josef Smolle, M.D., and Helmut Kerl, M.D.

The clinical and histopathologic features of specific skin infiltrates in patients with B-cell chronic lymphocytic leukemia (B-CLL) have rarely been reported in detail. In this study we analyzed the clinical, histopathologic, immunophenotypic, and molecular features of 84 skin lesions from 42 patients (M:F = 1.3:1; mean age, 66.0 years; range, 42–83 years) with specific cutaneous manifestations of B-CLL. The duration of B-CLL before skin manifestations varied from 0 to 142 months (mean, 39 months). In seven patients (16.7%), skin lesions represented the first sign of disease. Clinical presentations included localized or generalized erythematous papules, plaques, nodules, and large tumors. Ulceration was uncommon. In six patients lesions were confined at the sites of scars from previous herpes zoster (four patients) or herpes simplex (two patients) eruptions. Histologically, three main patterns were recognized: (a) patchy perivascular and periadnexal, (b) nodular-diffuse, and (c) band-like. Cytomorphologically, small monomorphous lymphocytes predominated. Proliferation centers were observed in only four specimens. In two patients presenting with tumors, a high content of large cells with features of centroblasts and immunoblasts was found (Richter's syndrome). Immunohistologic analyses were performed on paraffin-embedded specimens in 40 biopsies from 20 patients and on cryostat sections in 17 biopsies from 11 patients. Neoplastic B lymphocytes in all cases showed an aberrant phenotype (paraffin sections: $CD20^+/CD5^+/CD43^+$; cryostat sections: $CD19^+/CD5^+$; immunoglobulin light-chain restriction). Proliferation markers (Ki67, PCNA, MIB1) stained 5 to 80% of cells (mean, 25%; median, 20%). Polymerase chain reaction performed in nine cases on paraffin-embedded tissues using consensus primers for immunoglobulin heavy-chain genes showed a monoclonal population of B lymphocytes in all cases. Several discrete bands in addition to the prominent ones were noted in five cases, indicating the additional presence of B lymphocytes whose immunoglobulin genes were not monoclonally but oligoclonally rearranged. Follow-up data could be obtained from 31 patients. The two patients with Richter's syndrome died after 5 and 8 months, respectively. The 5-year survival of patients with small-cell cutaneous B-CLL was 66.6%. Our study indicates that cutaneous specific manifestations of B-CLL present with characteristic histologic, immunophenotypic, and molecular patterns. Prognosis in these patients is probably not affected by skin involvement.

Key Words: B-cell chronic lymphocytic leukemia—Skin—Prognosis—Immunohistochemistry—Histology—Gene rearrangement.

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Cutaneous lesions in patients affected by B-cell chronic lymphocytic leukemia (B-CLL) are not rare. In most instances they represent nonspecific manifestations related to the impaired immune competence of these patients or to the ingestion of drugs (12,31). In some cases, however, neoplastic B lymphocytes are found within the skin. Such lesions are referred to as specific cutaneous manifestations of the disease, or *leukemia cutis* (5,12,13,29). The clinical and histopathologic features of specific cutaneous infiltrates of B-CLL have seldom been studied in detail. Moreover, immunohistological and molecular genetic analyses helpful for the diagnosis were reported in only a few instances. The importance of correctly identifying specific cutaneous manifestations of B-CLL is stressed by some studies and reports pointing out a poor prognosis for these patients (1,29,32).

In this study we analyzed the clinical, histopathologic, immunophenotypic, molecular genetic, and prognostic features of specific cutaneous manifestations in 42 patients with B-CLL.

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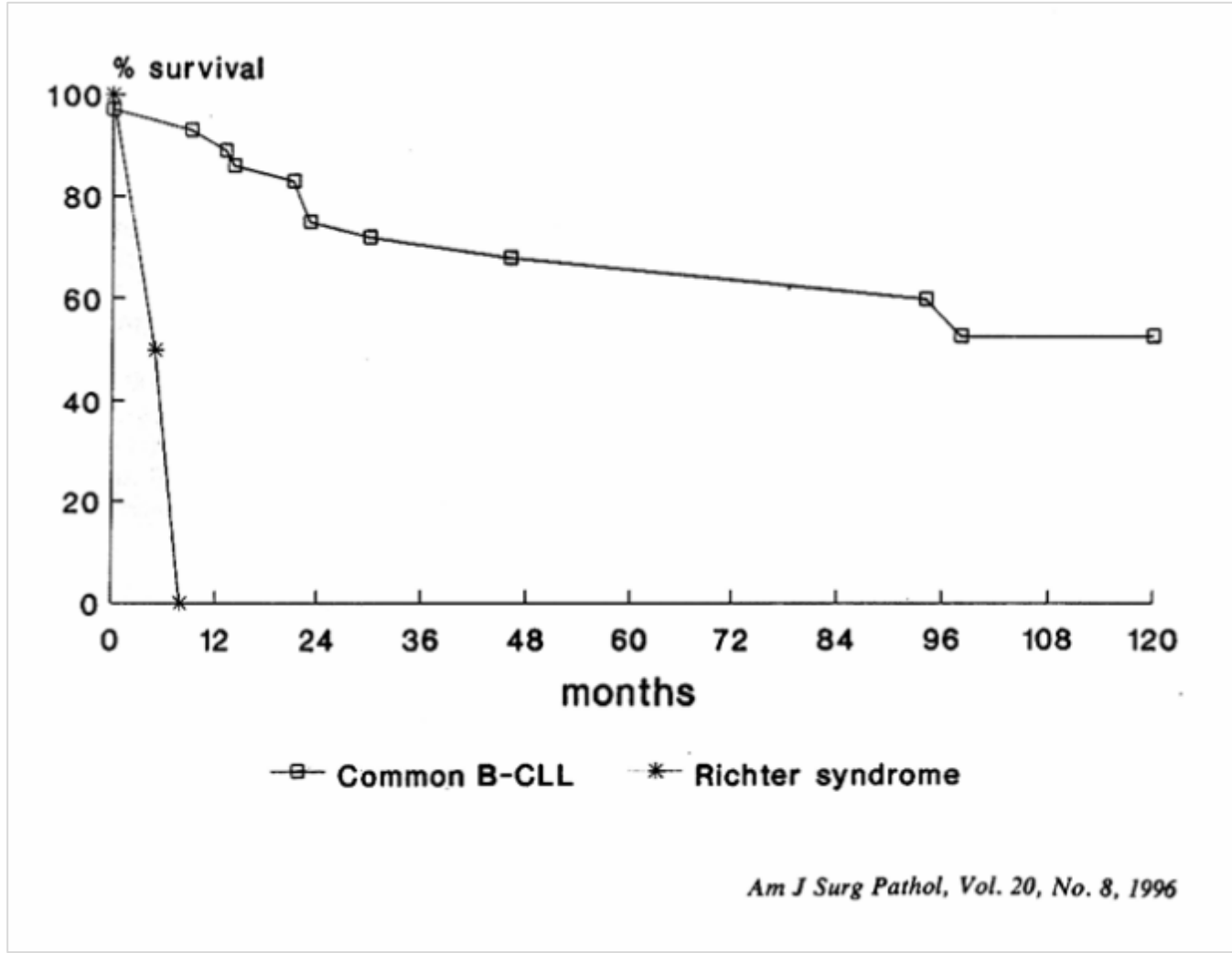

Skin involvement by chronic lymphocytic leukaemia is frequently associated with unrelated neoplastic or inflammatory cutaneous disease and is not indicative of general disease progression

DOI: 10.1111/bjd.17138

Chronic lymphocytic leukaemia (CLL) is the most frequent mature B-cell leukaemia in adults and follows a variable disease course ranging from indolent to aggressive. Histological features of CLL within the skin have been described.[1] The present study adds knowledge about the clinical and histological features associated with dermatopathic CLL.

There was skin involvement in 70 (3%) of 2174 histologically proven cases of CLL diagnosed between 2000 and 2015 in the Lymph Node Registry Kiel. We reconfirmed the diagnosis by reviewing the histological, clinical and immunophenotyping according to World Health Organization criteria.[2] We documented the histopathological features and any additional cutaneous pathology in the same specimen. Clinical features of all cases were provided retrospectively by the treating dermatologist and/or haematologist.

We also assessed several universal risk factors. DNA extracted from the formalin-fixed skin biopsy specimens was used to analyse the status of somatic hypermutation within the rearranged immunoglobulin heavy chain variable (IGHV) locus and assignment to major B-cell receptor stereotyped subsets according to established guidelines and bioinformatic methods.[3,4] In selected cases, all available specimens by fluorescence in situ hybridization (FISH) on paraffin slides for 17p13 deletion (TP53 gene) using commercially available probes (Abbott Vysis, Downers Grove, IL, U.S.A.).[5] The study was performed according to the recommendations of the ethics board of the Medical Faculty of the University of Kiel (D 554/07).

Histopathology revealed an indistinct CLL type small B-cell dominated infiltration in 45 of 70 patients, in line with previous cohorts of cutaneous CLL.[1] Two fulfilled the criteria of a Richter transformation. Beyond suspicion in 17% (12 of 70) the CLL in blasts were observed in close proximity to a different second disease. The most frequent simultaneous diseases were epithelial neoplasms (14 of 44, 32%) specifically squamous cell carcinoma (7 of 38, 18%), basal cell carcinoma (3 of 38, 8%) and Merkel cell carcinoma (4 of 44, 9%). We also observed one Merkel cell carcinoma and primary cutaneous anaplastic large cell lymphoma and several cases with cutaneous (12 of 38, 32%). In some dermatological skin disorders unrelated to the CLL infiltration.

In most patients the CLL was already known and had manifested in low clinical stages[6] with localized skin involvement.

Table 1 Clinical features of patients with chronic lymphocytic leukaemia (CLL) involving the skin (n = 70)

	Total evaluated	CLL without concomitant skin disease[a]	CLL with concomitant skin disease[a]	P-value
Sex	70	37	33	0·02
Men	50	16	29	
Women	20	11	4	
Age at first skin manifestation (years), median ± SD	75 ± 10·4	70·8 ± 12·2	76·6 ± 7·2	0·06
Awareness of the CLL at the time of skin manifestations	60	25	28	0·57
CLL previously unknown	17 (28)	8 (32)	7 (25)	
CLL already known	43 (72)	17 (68)	21 (75)	
Distribution of skin lesions	48	21	19	0·09
Solitary lesion	26 (54)	9 (43)	14 (74)	
Multiple in one skin area	18 (38)	9 (43)	4 (21)	
Disseminated	4 (8)	3 (14)	1 (5)	
Binet stage	37	15	17	0·99
A	22 (59)	10 (67)	10 (59)	
B	12 (32)	3 (20)	6 (35)	
C	3 (8)	2 (13)	1 (6)	

Values are n or n (%) unless otherwise indicated. [a]Patients in whom a concomitant second disease was suspected but who lacked definite histological criteria for a second diagnosis were excluded from the comparison of the two groups (n = 10).

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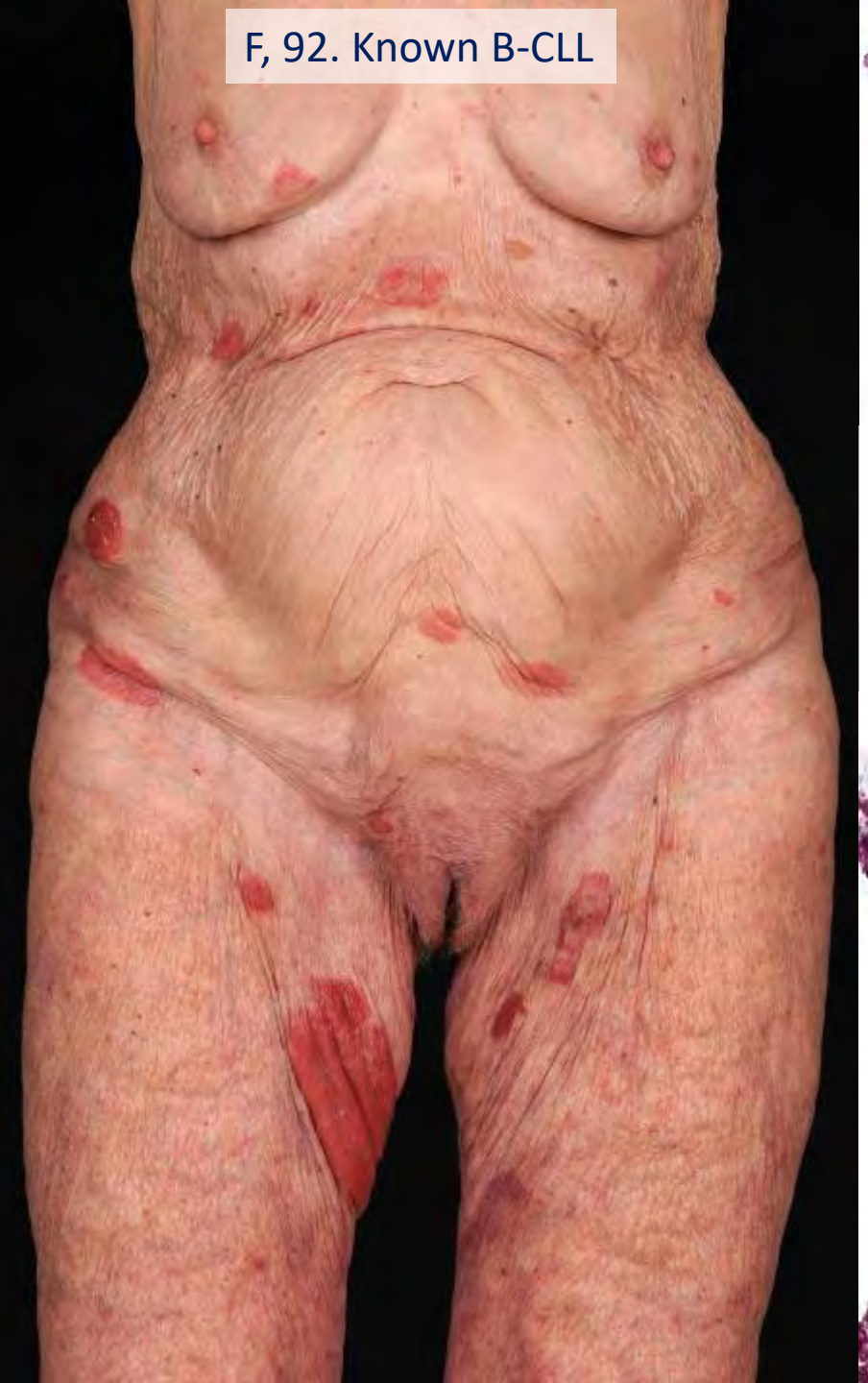
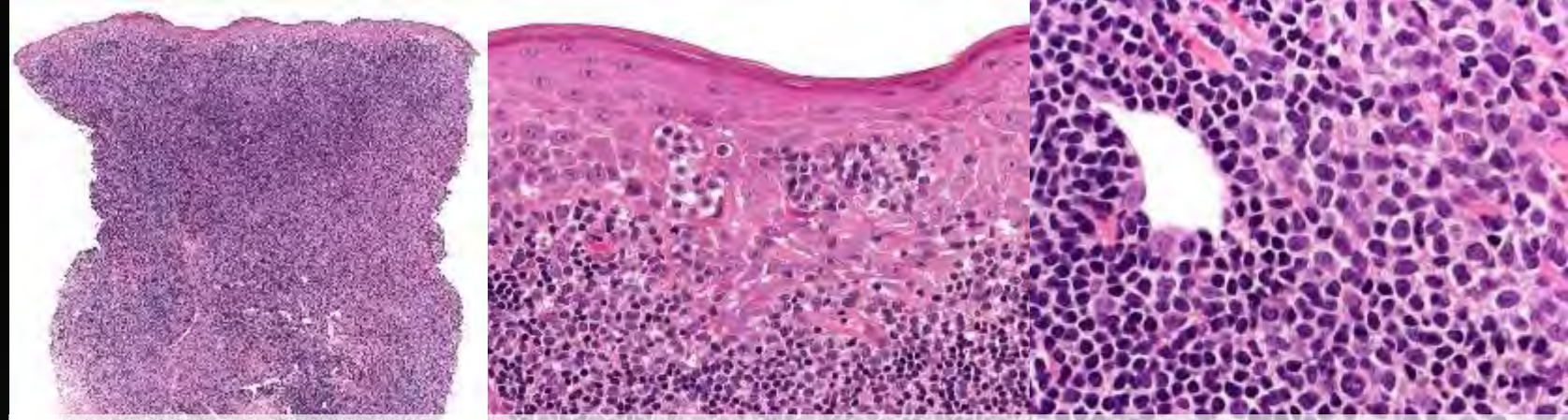
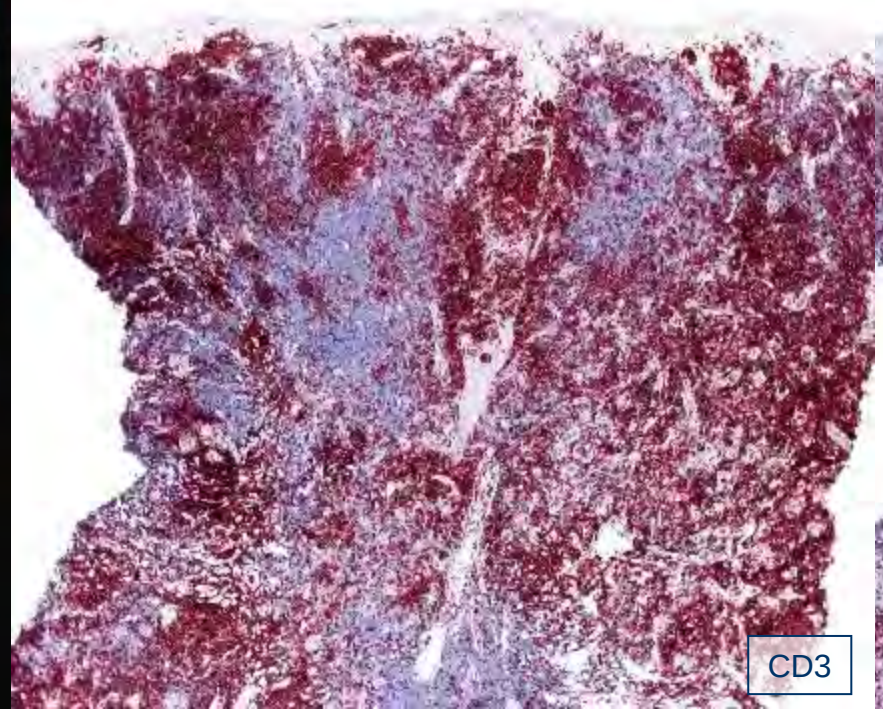
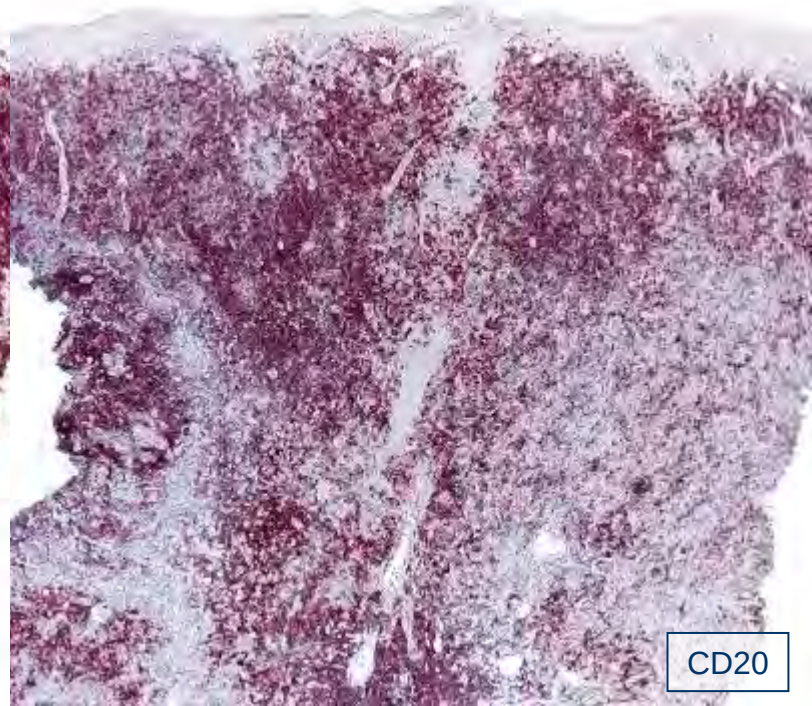




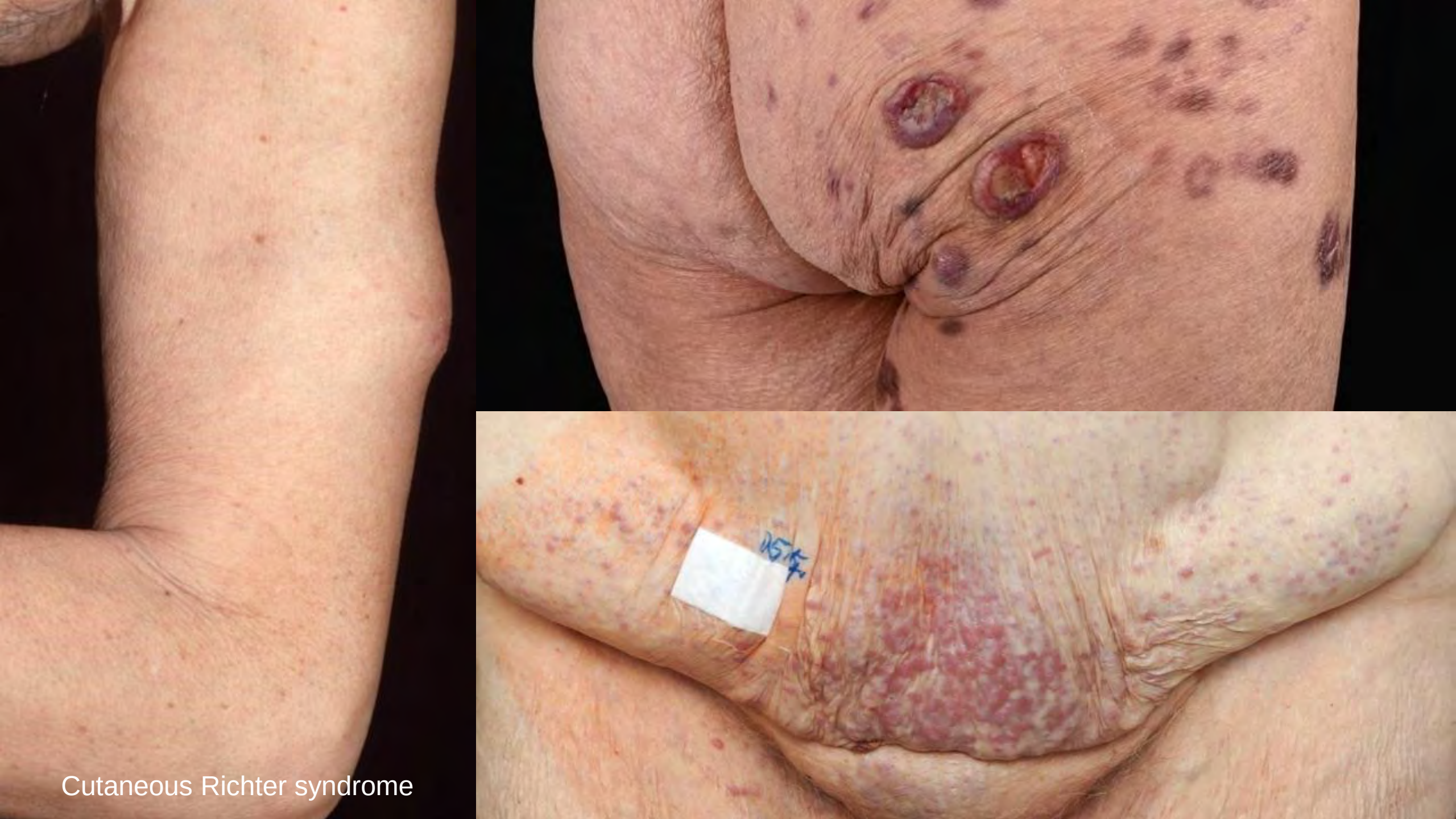
Specific infiltrate of B-CLL at the site of MF with large cell transformation





Cutaneous composite lymphomas

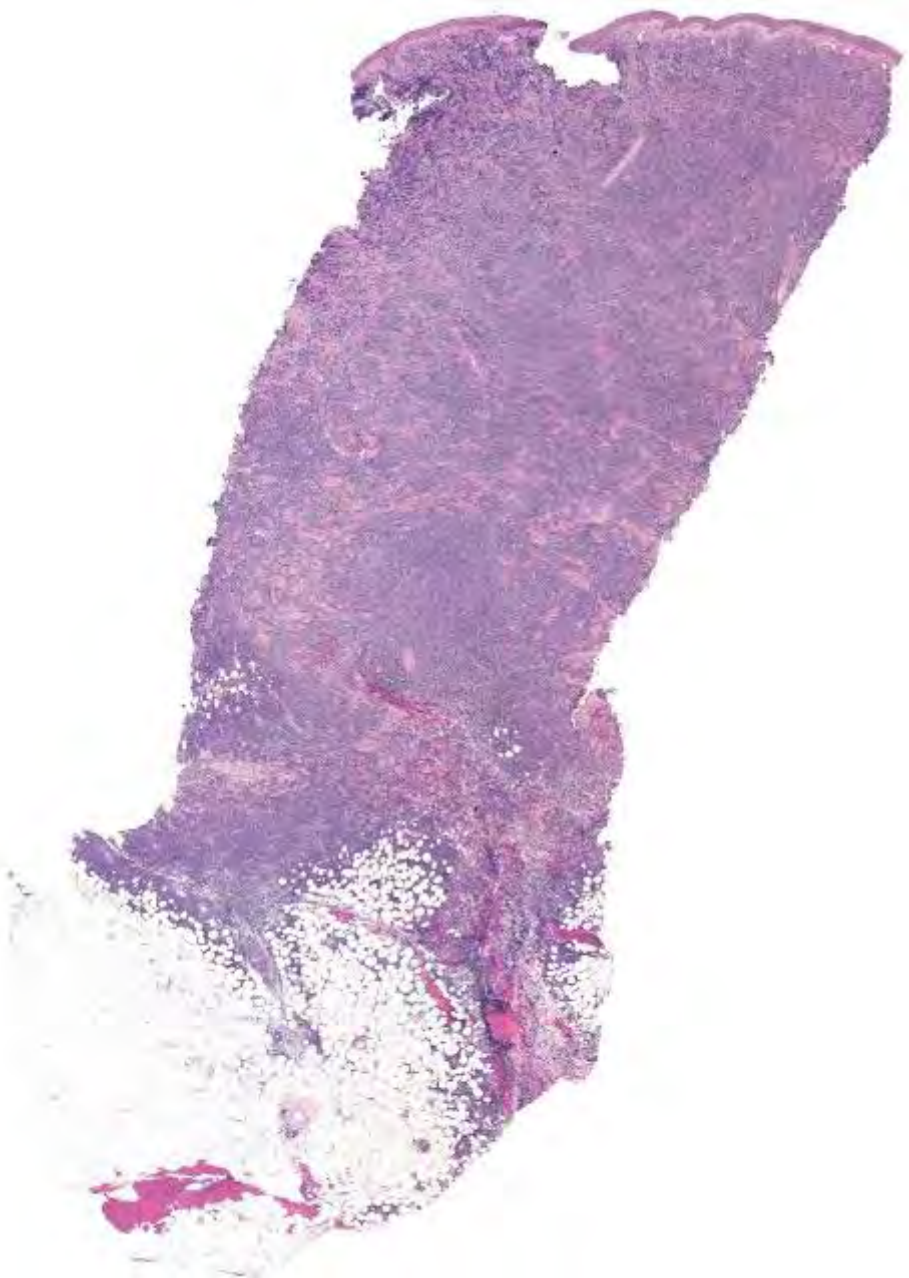
- Composite lymphoma is defined as the presence of two different lymphomas within one and the same lesion ("concomitant" lymphomas are different from composite lymphomas)
- The most frequent type of cutaneous composite lymphoma is characterized by the presence of neoplastic T lymphocytes of MF and neoplastic B lymphocytes of B-CLL within one and the same specimen
- Treatment of composite lymphomas usually tailored on the most aggressive of the two lymphomas

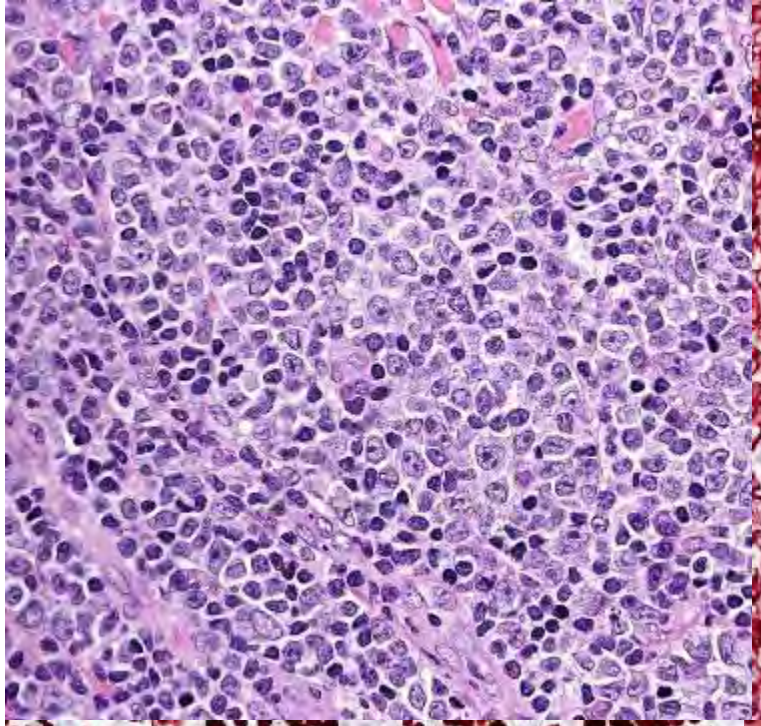


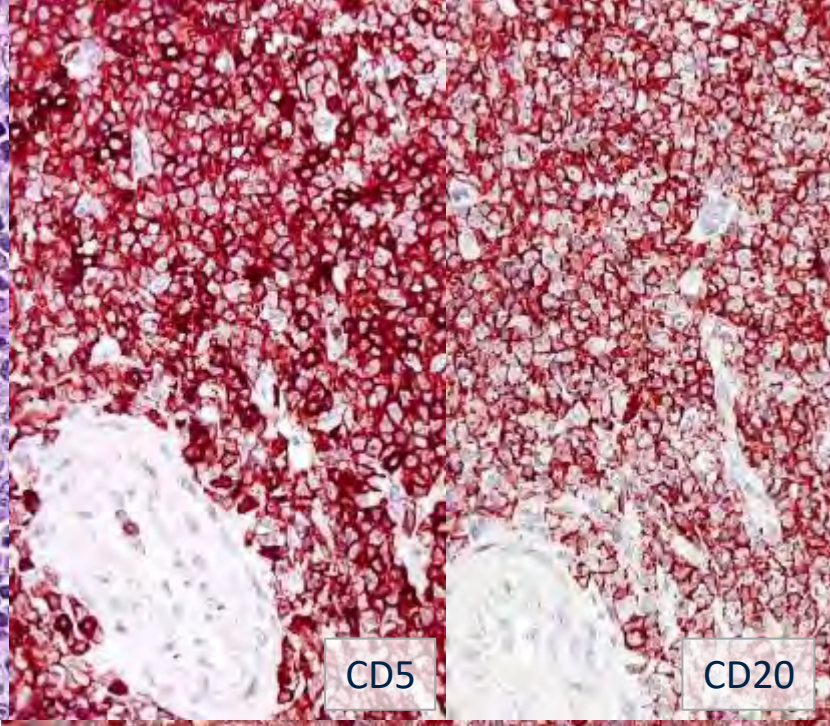
Cutaneous Richter syndrome

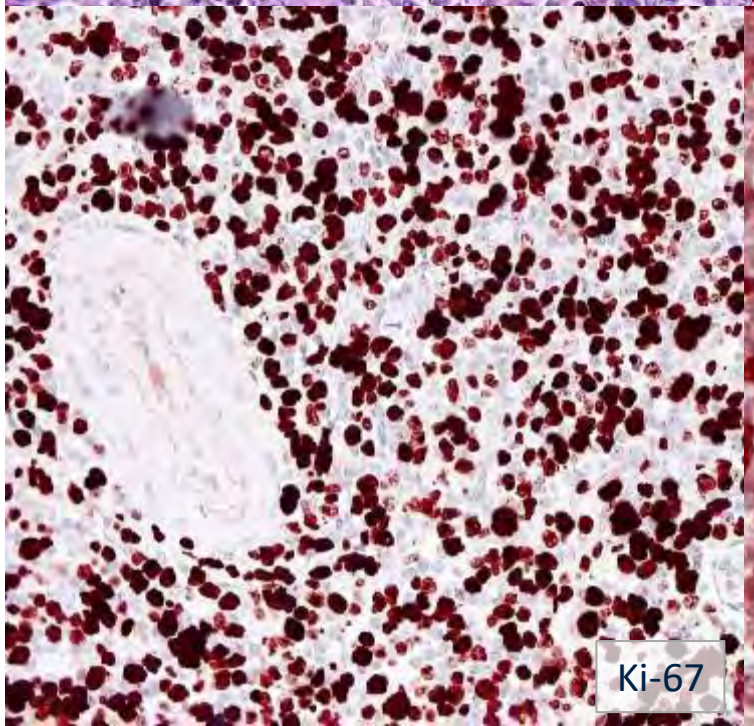
F, 65

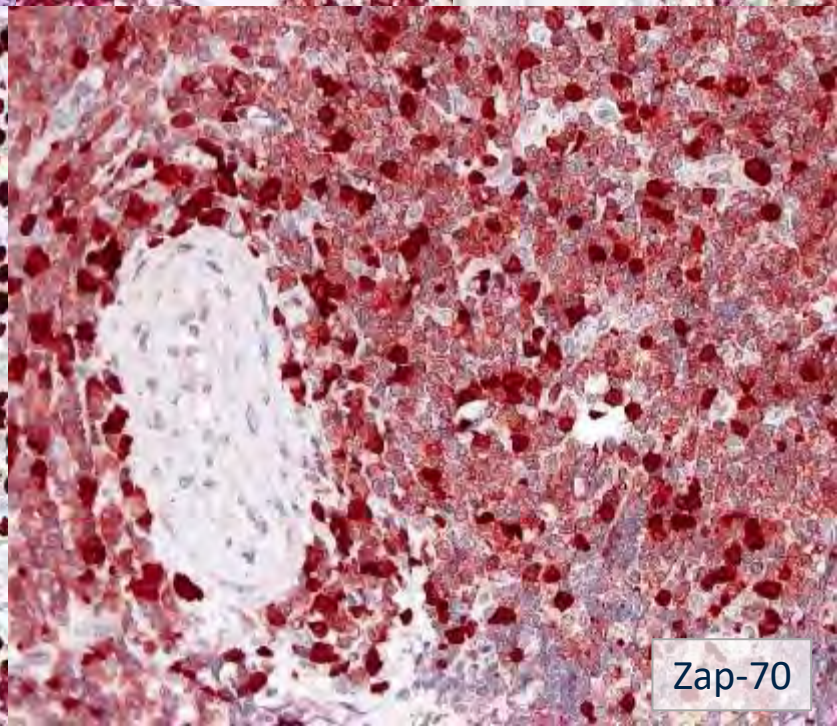
History of B-CLL for 7 years. Tumor on the thigh.

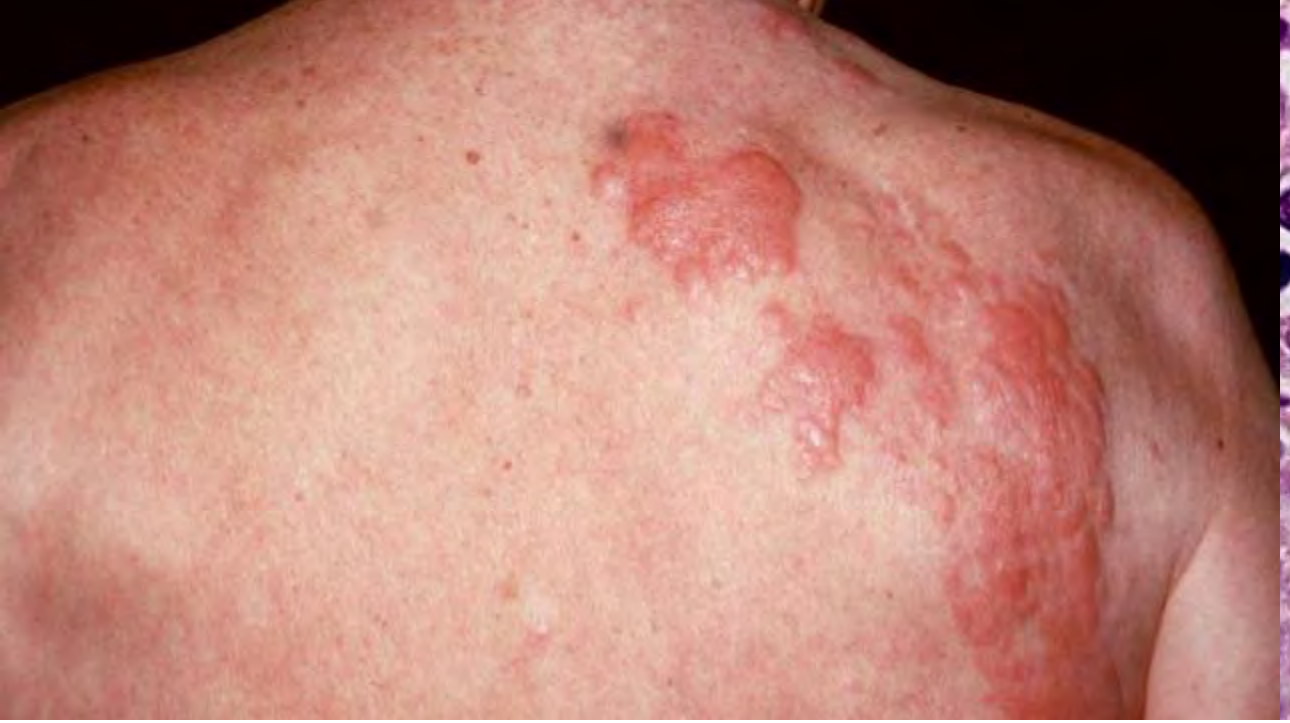


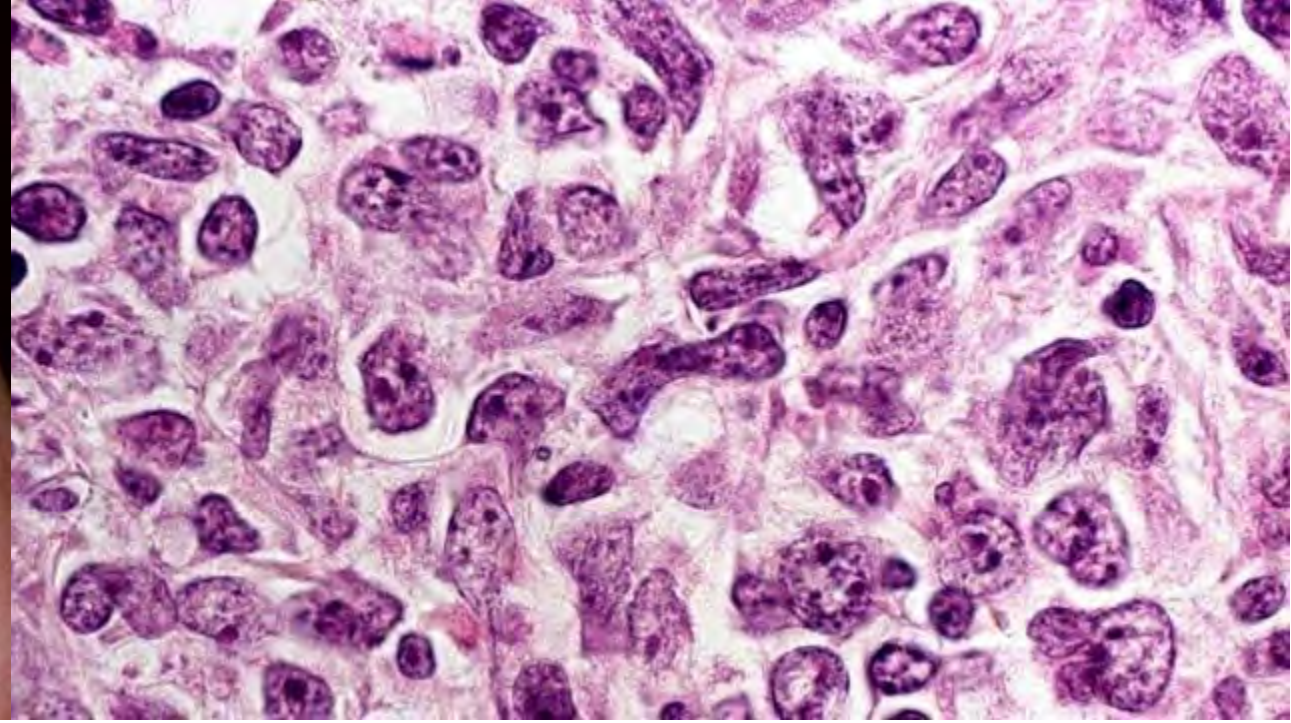




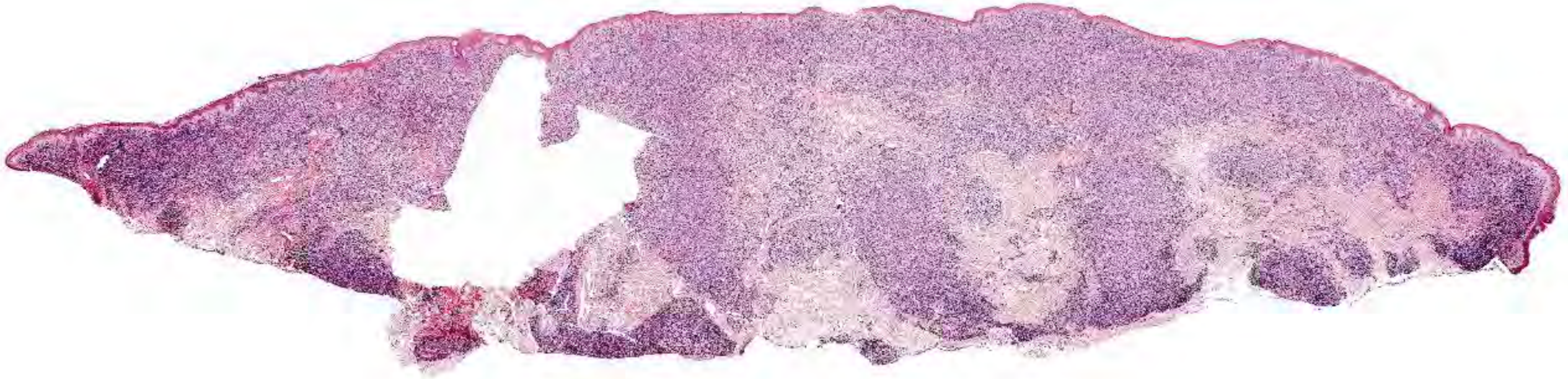








Richter syndrome at the site of previous *Herpes zoster*



Richter syndrome

- Large cell transformation of B-CLL
- May represent progression of the original B-CLL clone or onset of a second lymphoma *(in unmutated B-CLL usually progression, in mutated B-CLL usually second lymphoma)*
- Like other skin infiltrates of B-CLL it may be observed at the site of cutaneous inflammation (e.g., *H. zoster*)
- In the skin it should be distinguished from other types of diffuse large B-cell lymphoma (including leg-type)

Cutaneous Richter syndrome: Report of 3 cases from one institution

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Ann Arbor, Michigan, and Los Angeles, California

Background: Richter syndrome (RS) is large-cell transformation of chronic lymphocytic leukaemia (CLL). It commonly involves lymph nodes and bone marrow, but may rarely manifest in skin. Certain triggering factors, such as Epstein-Barr virus infection and p53 overexpression, have been implicated in the pathogenesis of RS. Here, we present 3 cases of cutaneous RS from our institution with a follow up period of up to 8 years.

Objective: We present a series of cutaneous RS from a single institution with the longest follow-up period (up to 8 years) to date.

Methods: Clinical characteristics were collected and histopathological findings of skin biopsy specimens were analyzed.

Results: All 3 patients had prior CLL and later developed cutaneous RS lesions. The mean age at the diagnosis of cutaneous RS was 67 years old. The time intervals between CLL and cutaneous RS were 3 to 8 years. Skin biopsy specimens demonstrated dermal nodular or perivascular infiltrates of large B cells, showing similar immunophenotypes to the lesional cells in the original CLL. Overexpression of p53 and positive stain for Epstein-Barr virus–encoded small RNA was found in one patient. One patient remained alive 8 years after the diagnosis whereas the other two died of the disease at 5 years and 3 weeks, respectively, after the onset of cutaneous RS.

Limitations: Three patients with RS were followed up for up to 8 years.

Conclusions: Our findings suggested that, in contrast to extracutaneous RS, cutaneous RS generally has a less aggressive course with longer survival unless other worse prognostic factors are present. (J Am Acad Dermatol 2012;67:e187-93.)

Key words: chronic lymphocytic leukemia; cutaneous Richter syndrome; prognosis.

The development of high-grade non-Hodgkin lymphoma in patients with chronic lymphocytic leukemia (CLL) is known as Richter syndrome (RS). The syndrome was first described in 1928 by Maurice N. Richter who reported a patient with rapidly generalized lymphadenopathy and hepatosplenomegaly associated with CLL.[1] Later on, more cases were documented and the condition was named as "histiocytic lymphoma" in association with CLL.[2] In 1961, Lortholary et al[3] described 4 similar cases and suggested the terminology of "Richter syndrome" to replace "histiocytic lymphoma." RS is estimated to occur in 3% to 10% of patients with CLL.

Abbreviations used:

CLL:	chronic lymphocytic leukemia
EBER:	Epstein-Barr virus–encoded RNA
EBV:	Epstein-Barr virus
RS:	Richter syndrome

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Cutaneous Richter syndrome: a better place to transform?

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Summary

The development of high-grade lymphoma in patients with chronic lymphocytic leukaemia is known as Richter syndrome (RS) and is associated with a grave prognosis, with a mean survival of 8 months despite treatment. Cutaneous RS has been described in a handful of cases and may be associated with a better outcome than the more common extracutaneous variants. We review the literature with particular emphasis on pathogenesis, treatment and survival of RS. We postulate that the absence of B symptoms and a normal lactate dehydrogenase level, presumably reflecting localized or limited disease, and a lower tumour burden, may explain the apparently better survival in some patients with cutaneous RS than with extracutaneous variants.

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Conflicts of interest
None declared.

Some of the data contained within Tables 1 and 2 were extracted from a table published in Yamazaki et al.[11] Primary cutaneous Richter syndrome: prognostic implications and review of the literature. J Am Acad Dermatol 2009; 60:157–61. The tables presented herein have been significantly expanded to include cases of cutaneous Richter syndrome reported subsequently and to examine further variables.

DOI: 10.1111/bjd.13193

What's already known about this topic?

- Richter syndrome (RS) denotes the development of high-grade lymphoma in patients with chronic lymphocytic leukaemia and is associated with a grave prognosis.
- Skin involvement is exceptionally rare with <20 cases reported in the literature.

What does this study add?

- We review the literature and present two further examples of RS arising in the skin.
- Cutaneous RS may have a more favourable prognosis than more common extracutaneous variants.

First described in 1928 by Maurice Richter, Richter syndrome (RS) denotes the development of high-grade lymphoma in patients with chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL), and typically heralds an abrupt clinical deterioration and rapid demise, despite aggressive treatment.

Although RS arises in the lymph nodes or bone marrow in most cases, extranodal RS is recognized and may involve the gastrointestinal (GI) tract, central nervous system (CNS), eyes, lungs, kidneys or testes. Skin involvement is exceptionally rare, with < 20 cases reported in the literature. Although some authors have observed a more favourable clinical course with greater survival times in individuals with cutaneous RS compared with extracutaneous RS, firm conclusions cannot be drawn from the small number of cases reported. We present two patients with cutaneous RS seen in our institutions and highlight this entity to the dermatology readership.

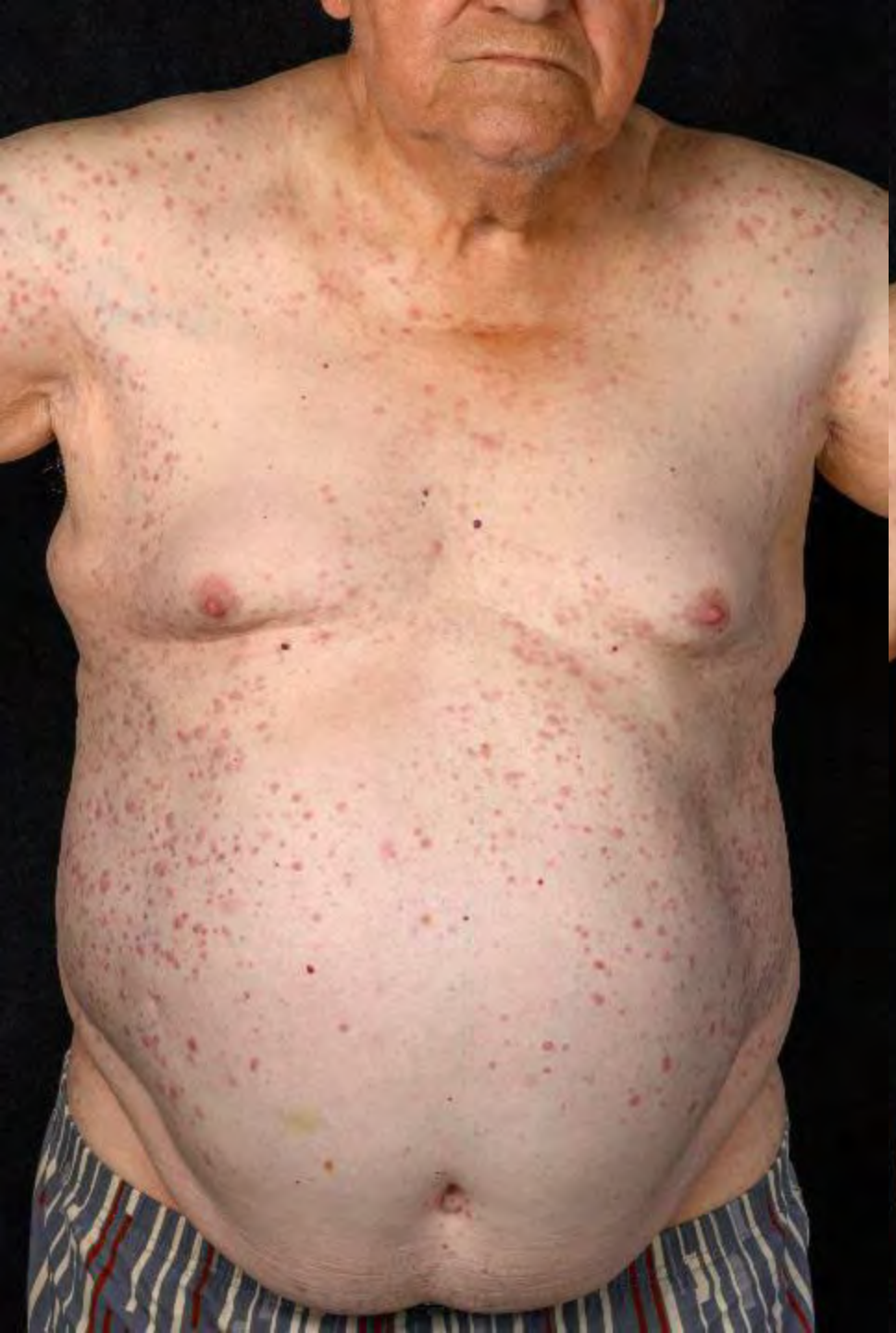
Case report

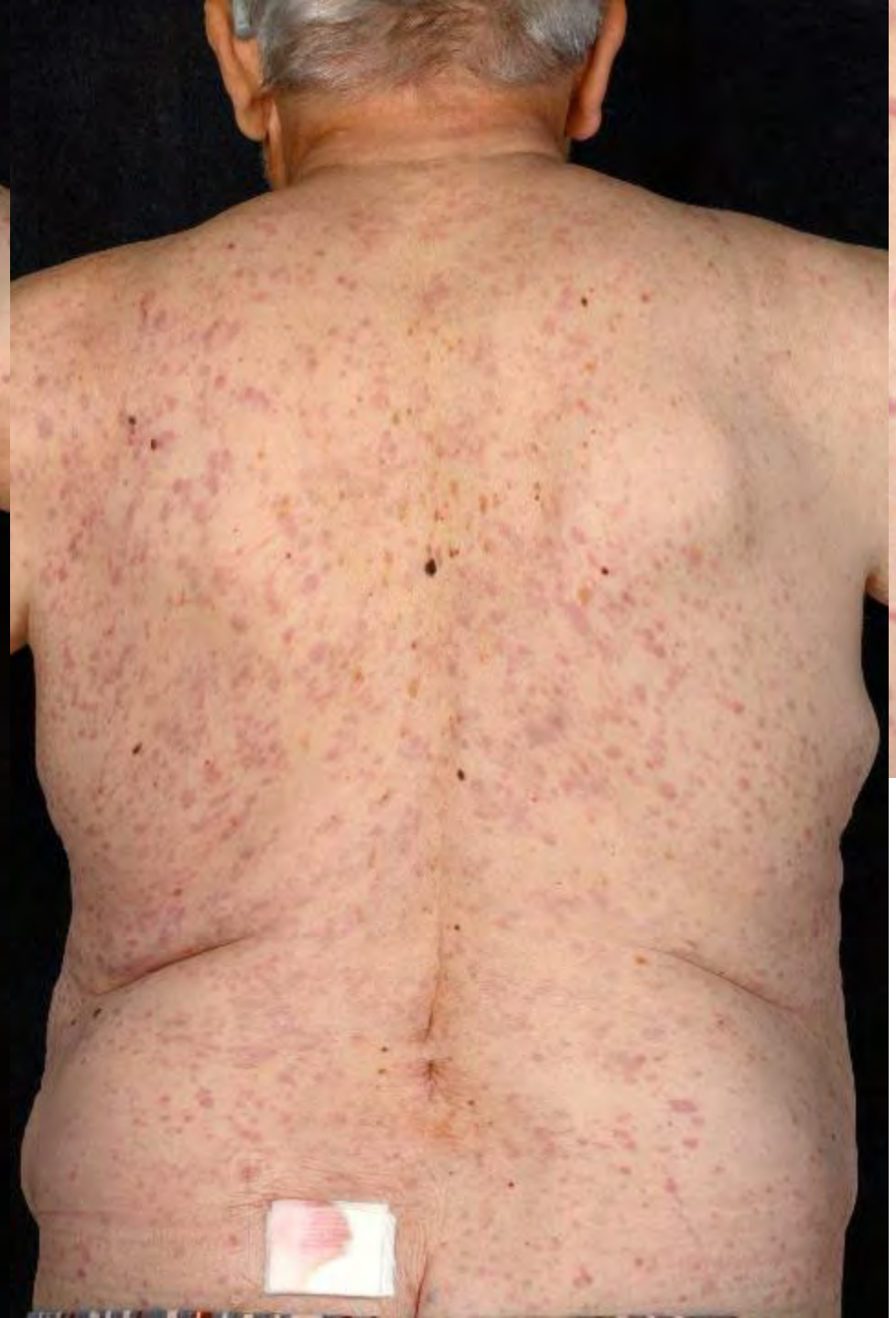
Patient 1

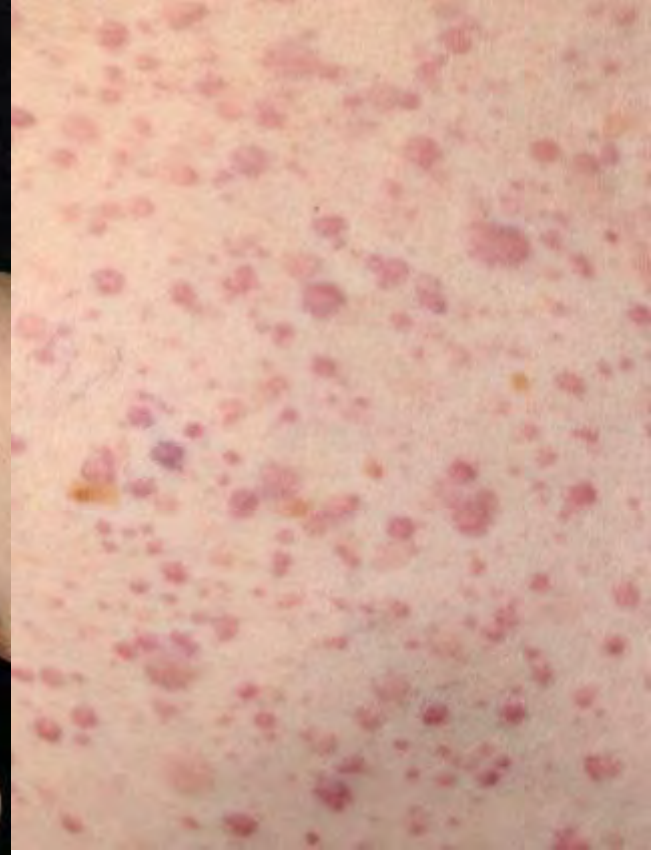
A 79-year-old woman with a 10-year history of CLL (Binet stage A) was referred to the cutaneous lymphoma clinic with

B-cell chronic lymphocytic leukemia (B-CLL)

- Skin rarely primary site of diagnosis (never of onset)
- Oft found in the context of other cutaneous neoplastic or inflammatory disorders *(i.e., incidental histopathological finding)*; seldom as a "conventional" ("metastatic") secondary spread
- Some clinicopathological presentations are typical *(e.g., specific manifestations at sites of herpes simplex / zoster or of Borrelia infection)*
- Should be distinguished from skin infiltration of other systemic lymphomas *(esp. mantle cell lymphoma)*
- Rarely in the skin large cell transformation *(Richter's syndrome – clonally related or unrelated to the underlying B-CLL)*
- With the exception of Richter syndrome, the finding of neoplastic cells within the skin is not associated with a worse prognosis



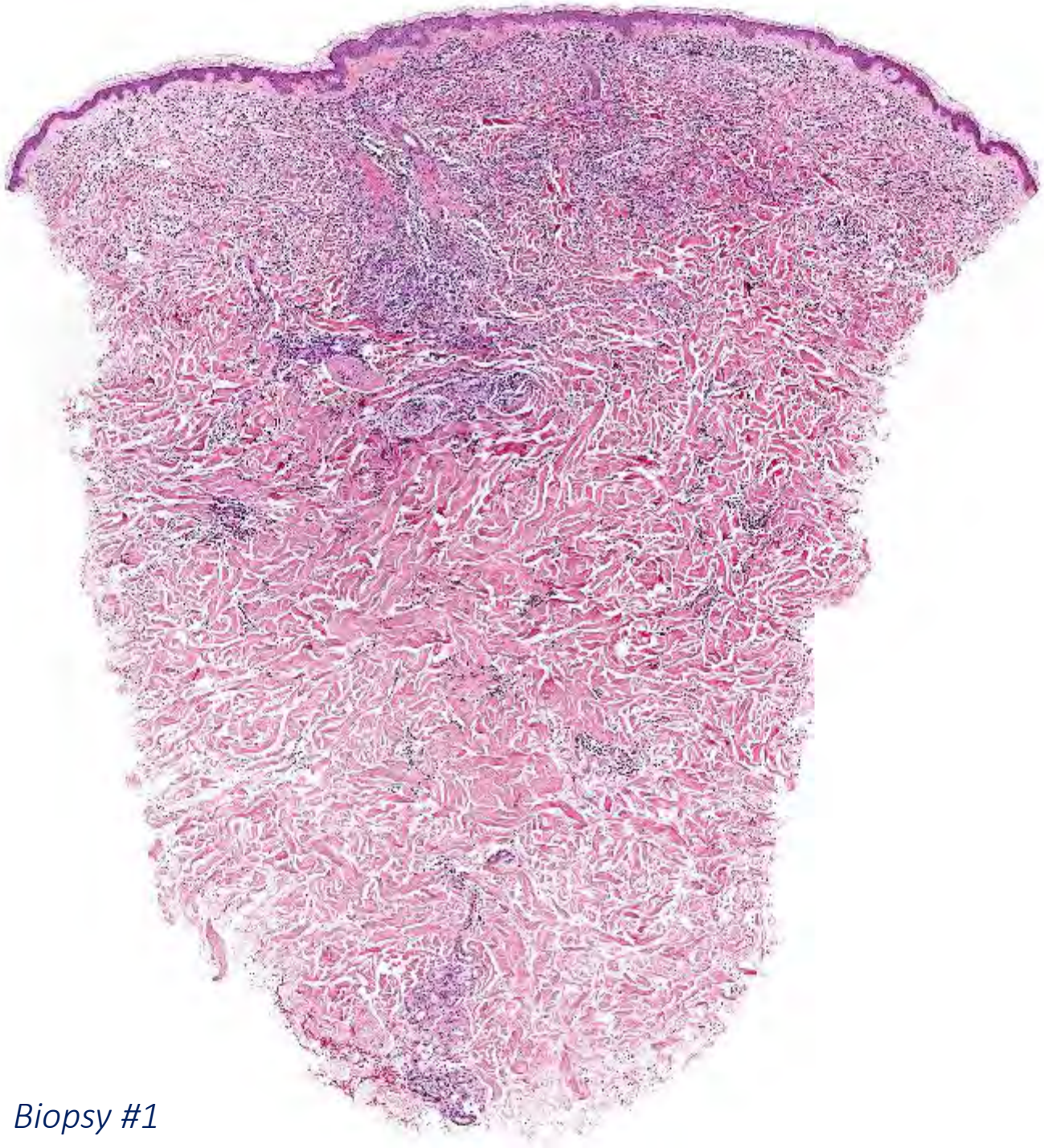




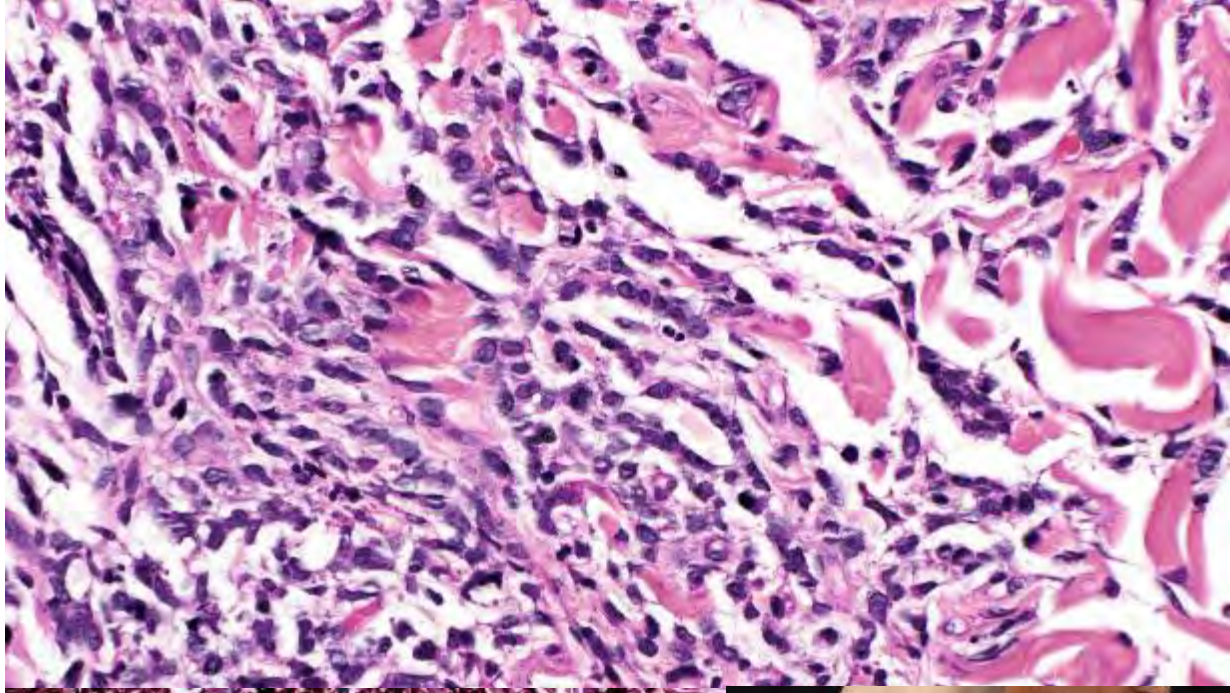
M, 82

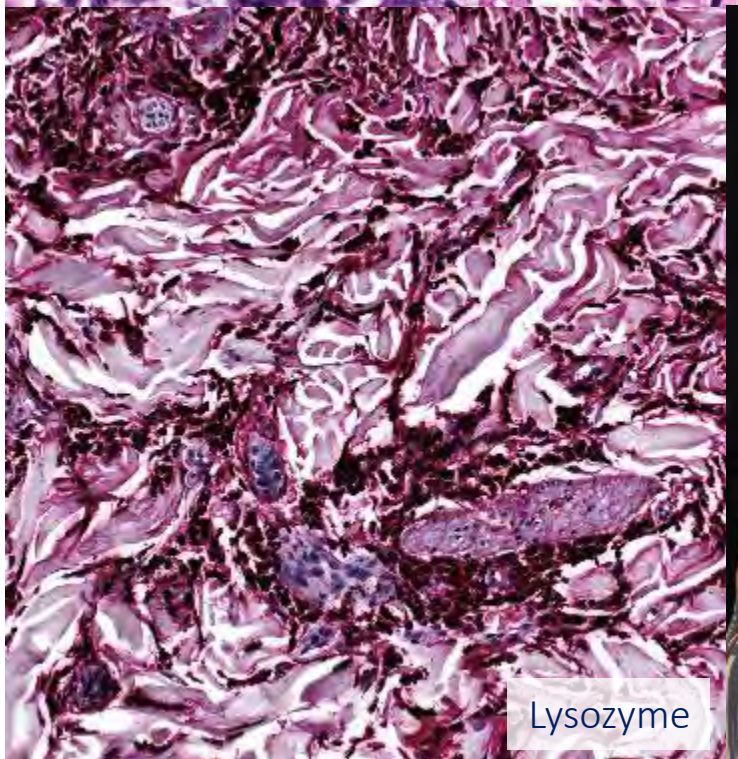
According to the patient generalized, asymptomatic lesions for 3-4 weeks. An external biopsy was reported as "suspicious for cutaneous infiltration of myelomonocytic leukemia".

Two new biopsies are taken.

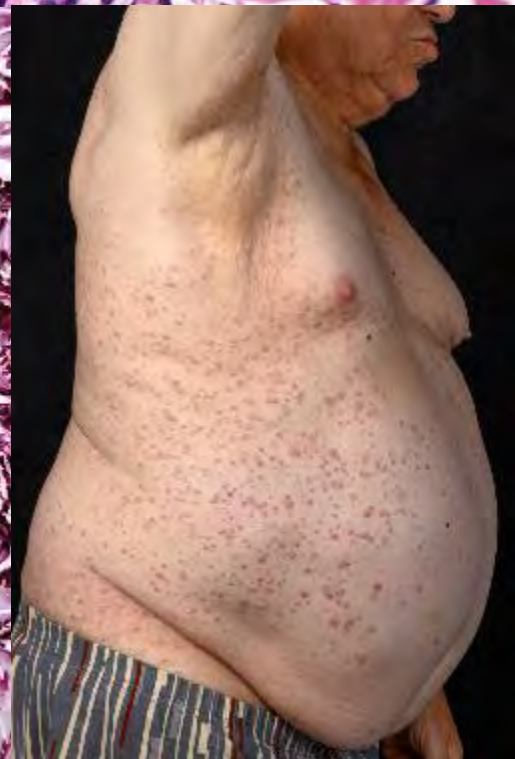


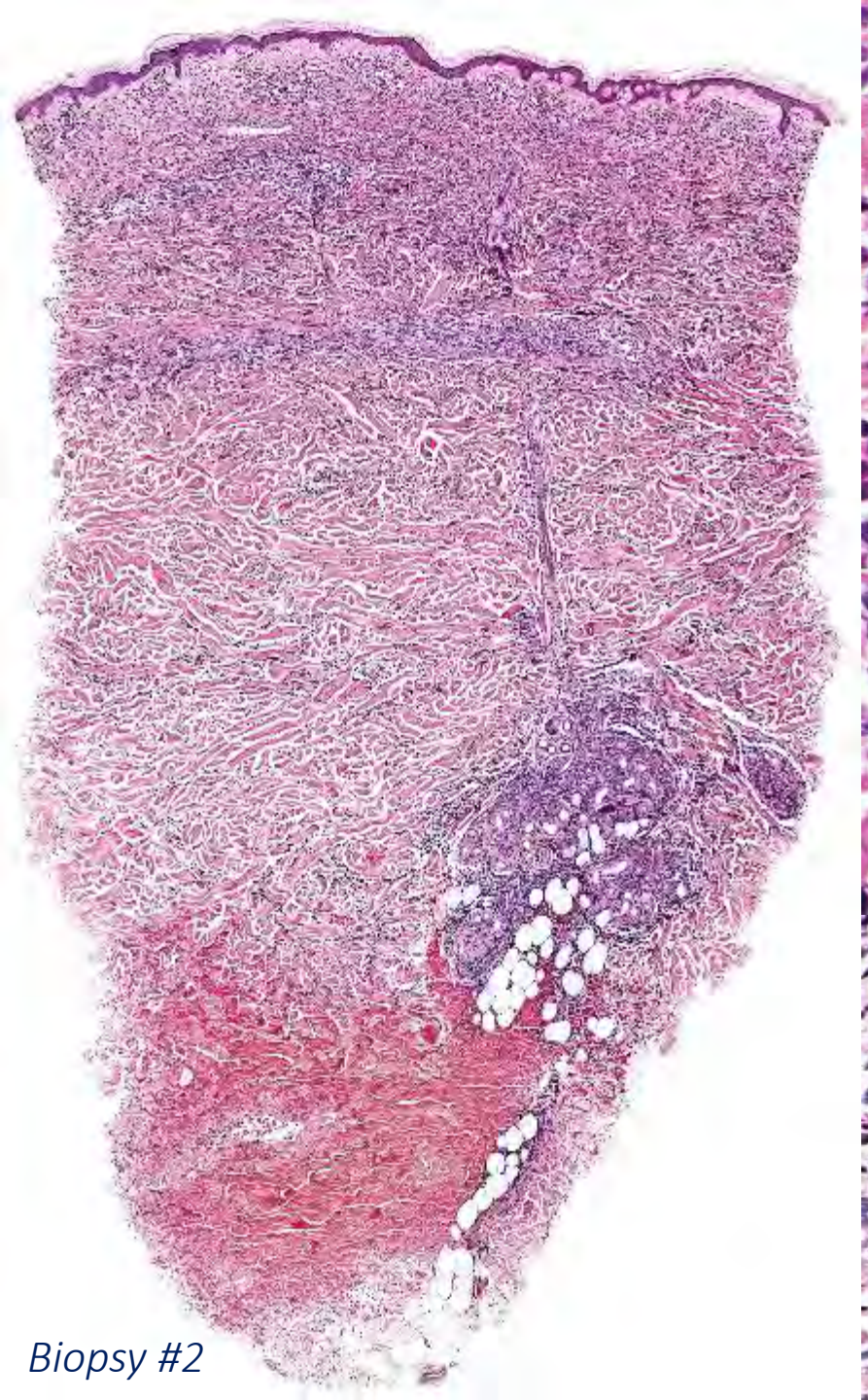
Biopsy #1



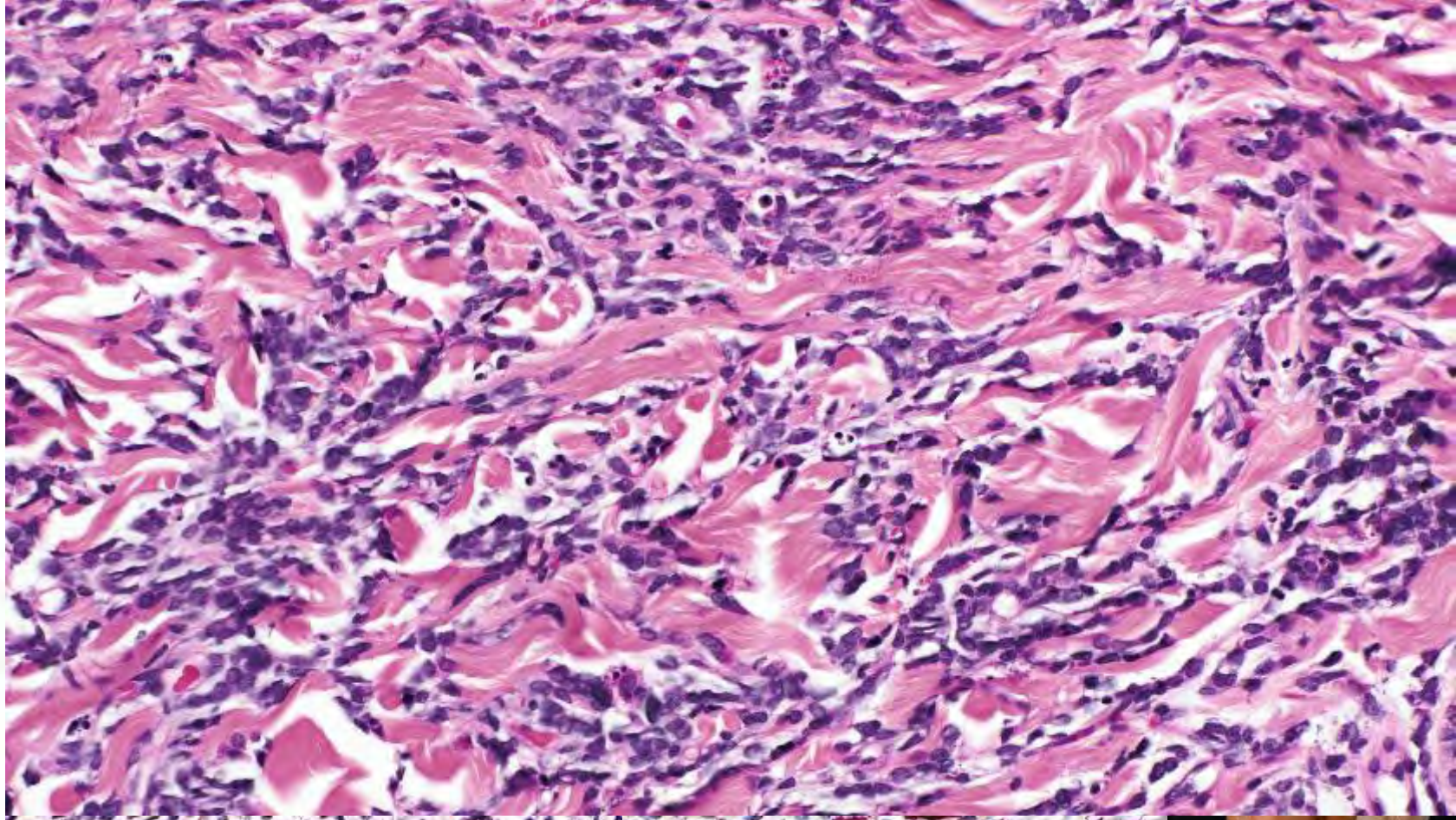


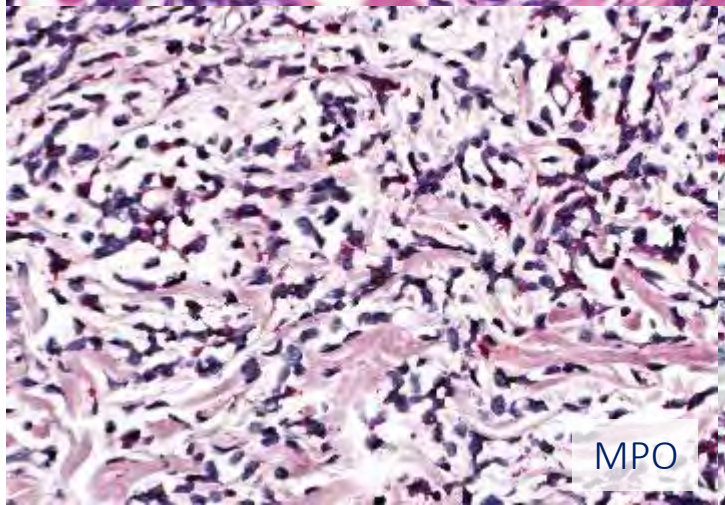
Lysozyme



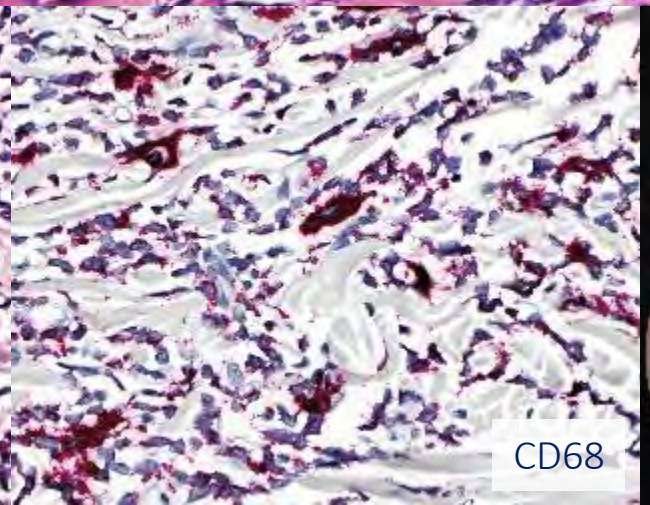


Biopsy #2

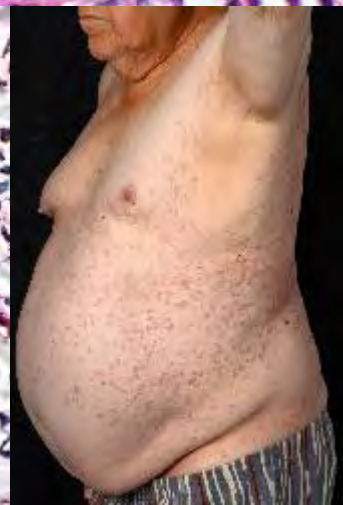


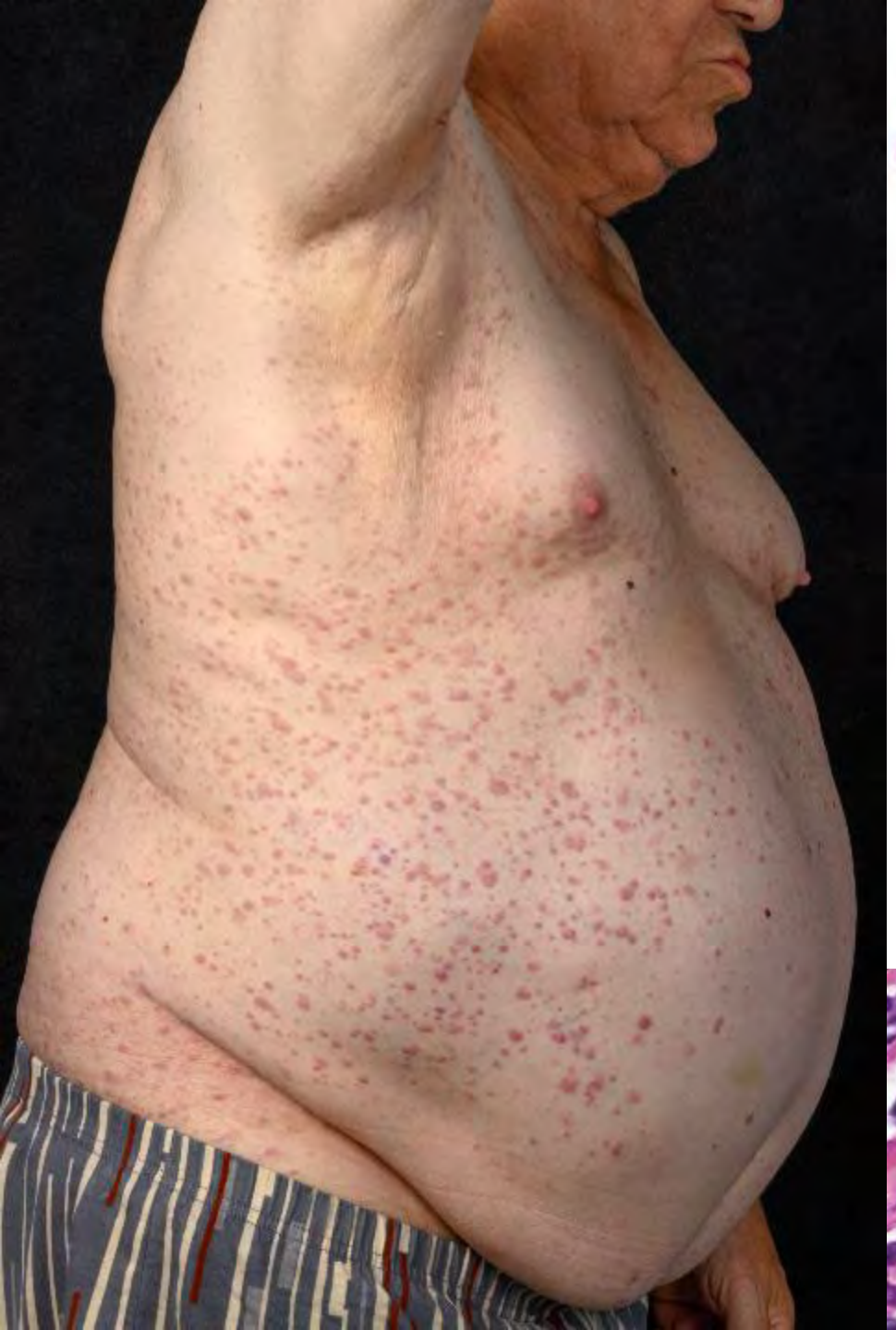


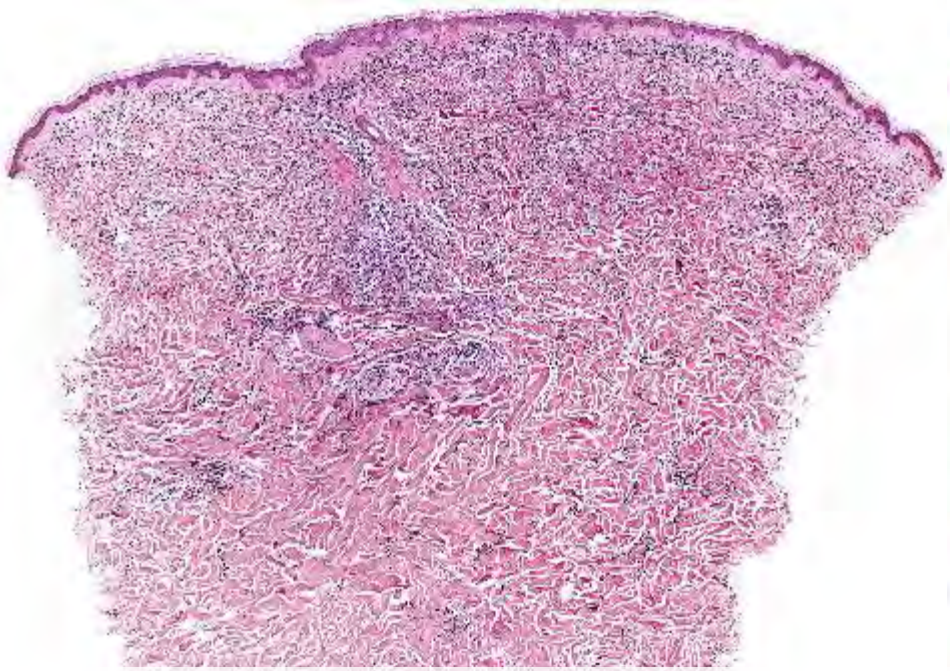
MPO

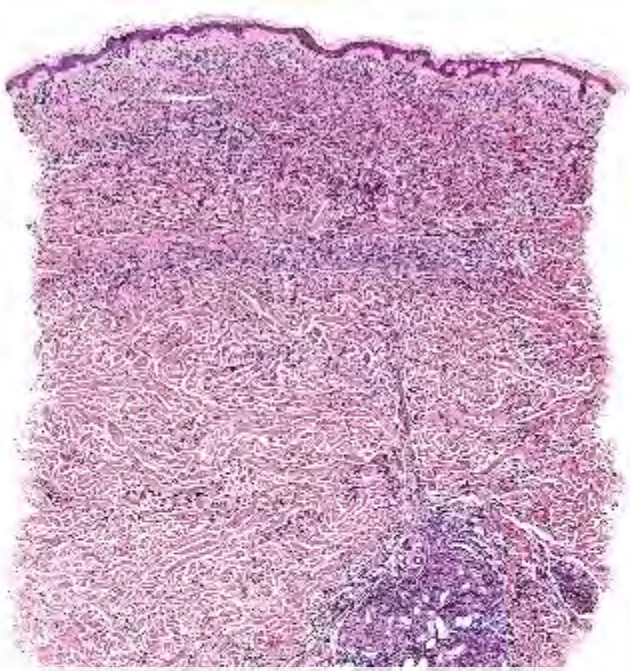


CD68



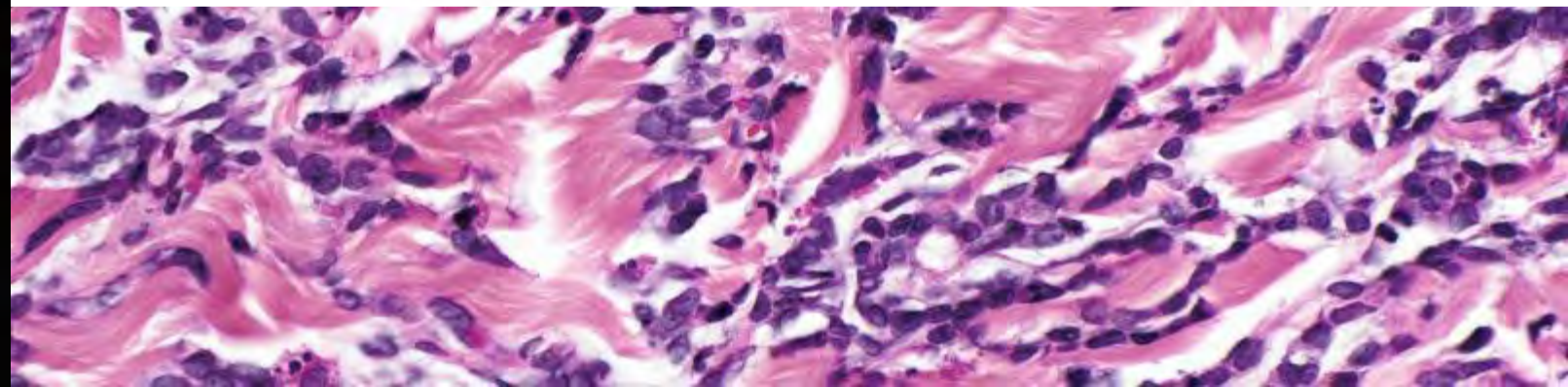




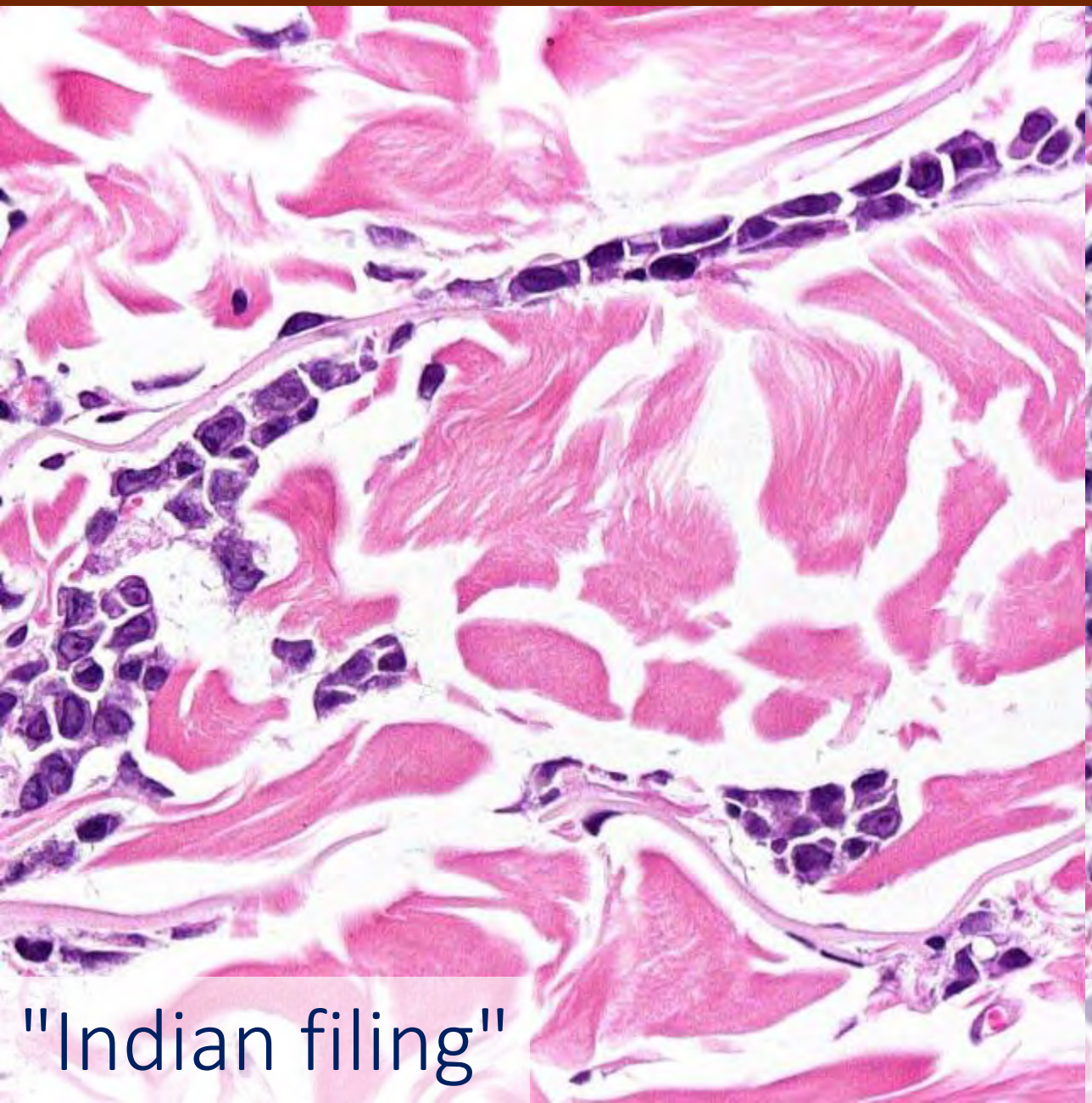


Specific cutaneous infiltrate of myeloid leukemia

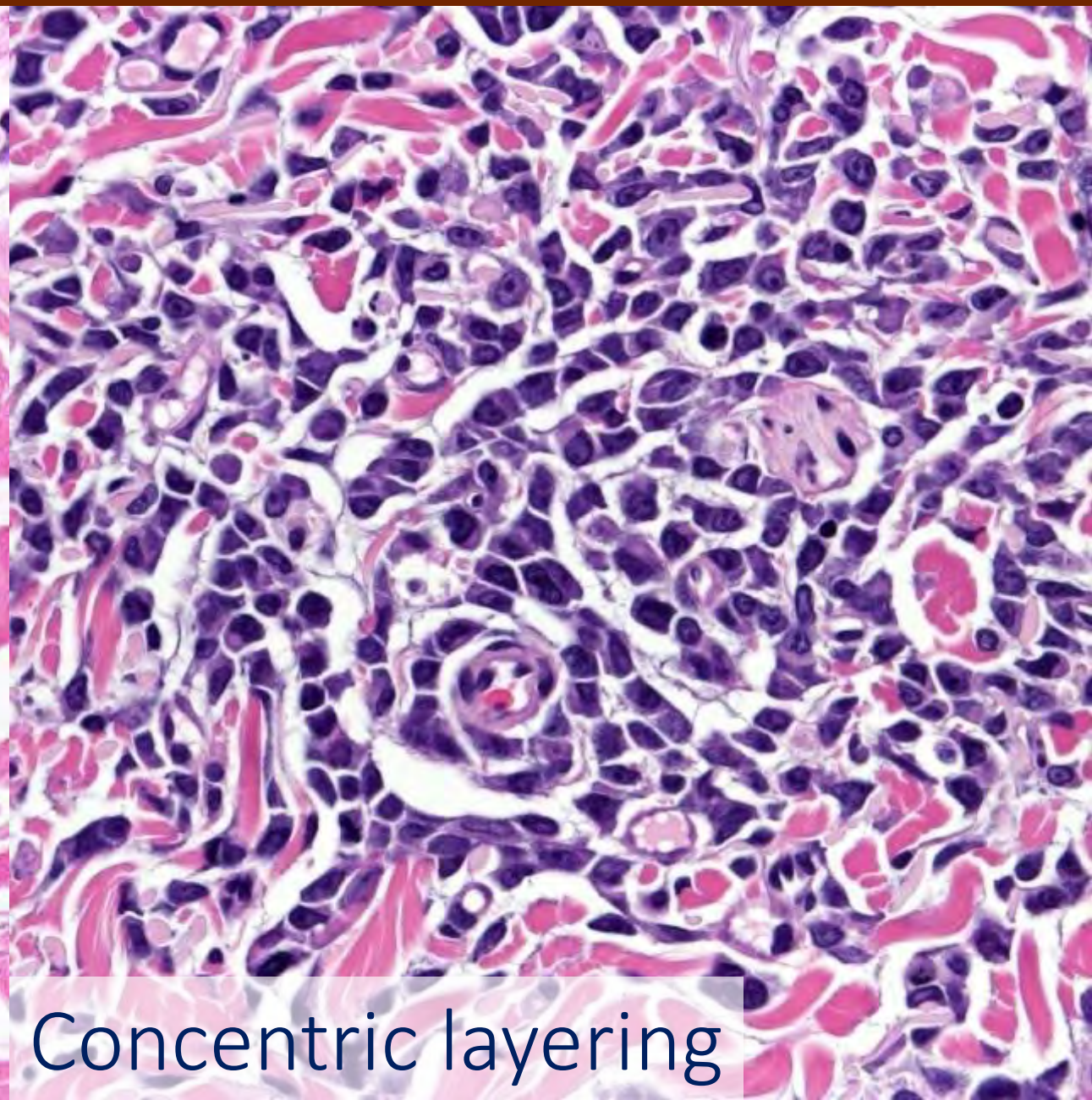
IDH2 and SRSF2 mutations found in peripheral blood



Clues by histological pattern



"Indian filing"



Concentric layering

"Indian filing"

Aggressive

Myelogeneous leukemia

Distinction of BPDCN from cAML may be difficult in cases of BPDCN with abnormal phenotype, but indian filing not encountered in BPDCN.

Cutaneous metastases of carcinoma

An "indian filing" arrangement of neoplastic cells is a typical morphologic presentation of carcinoma metastatic to the skin, particularly breast carcinoma.

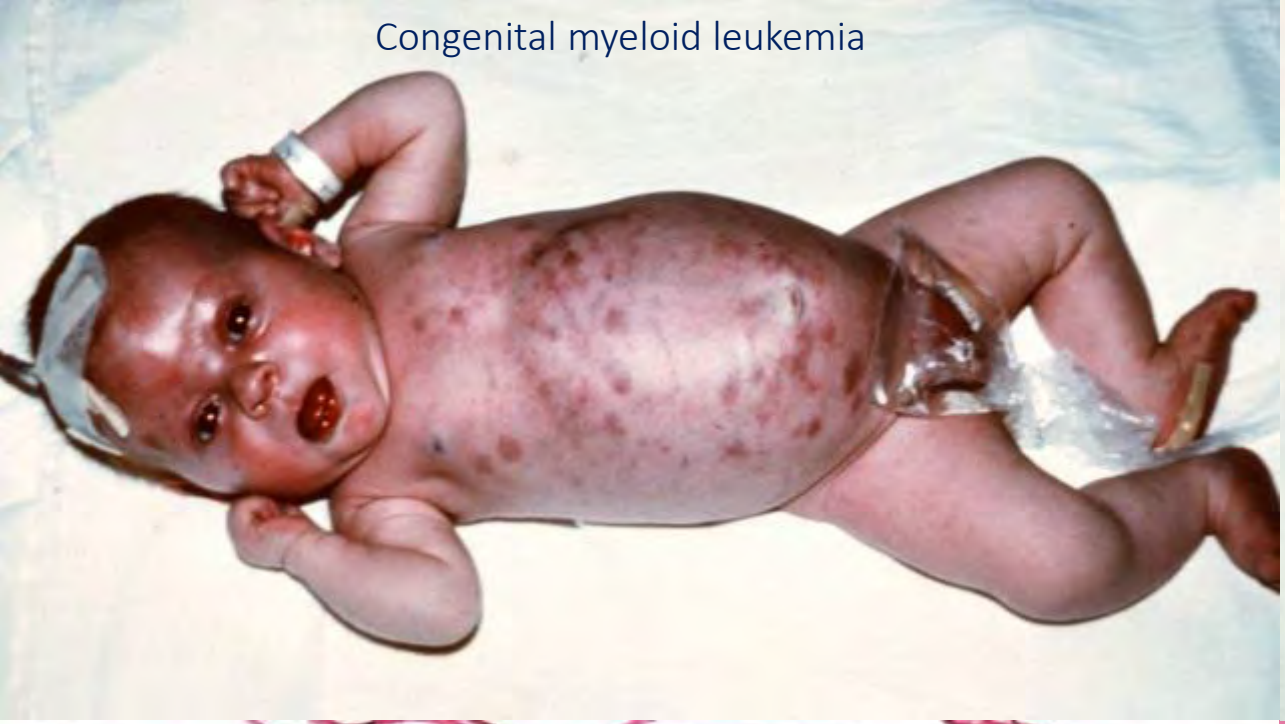
Interstitial mycosis fungoides

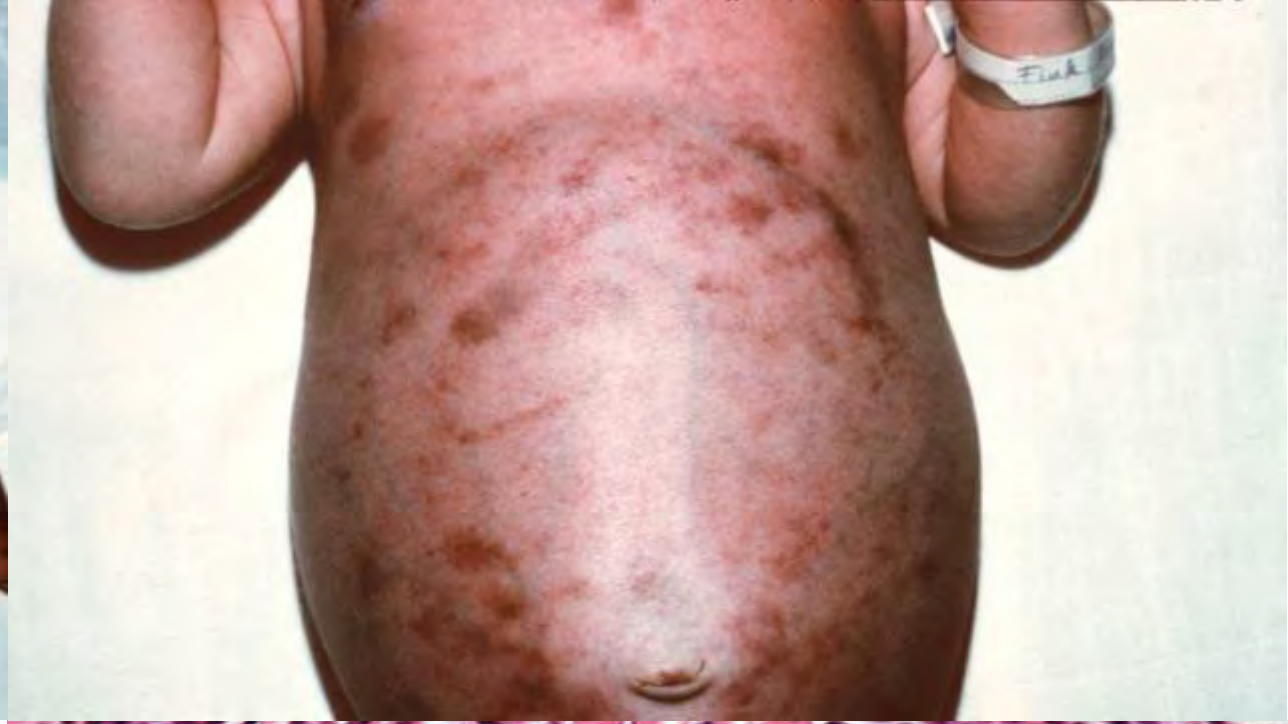
Not a true "indian filing" arrangement, but interstitial neoplastic cells may resemble it.

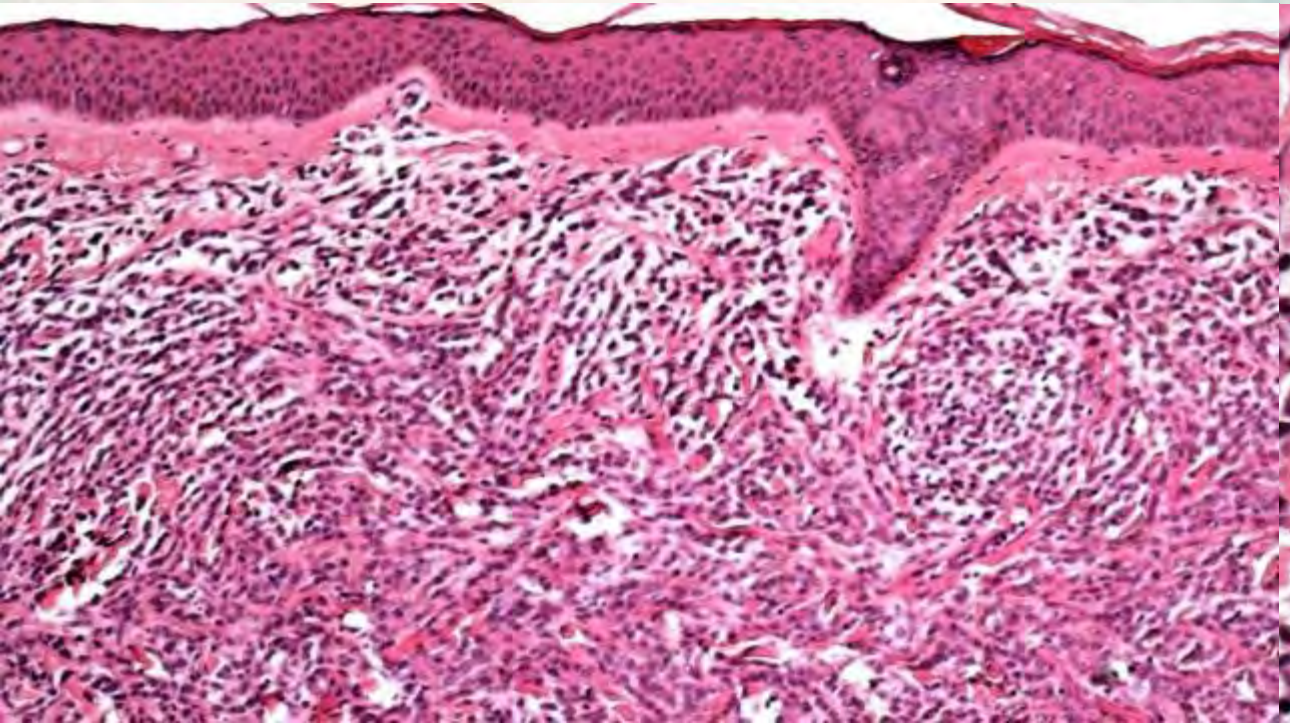
Indolent

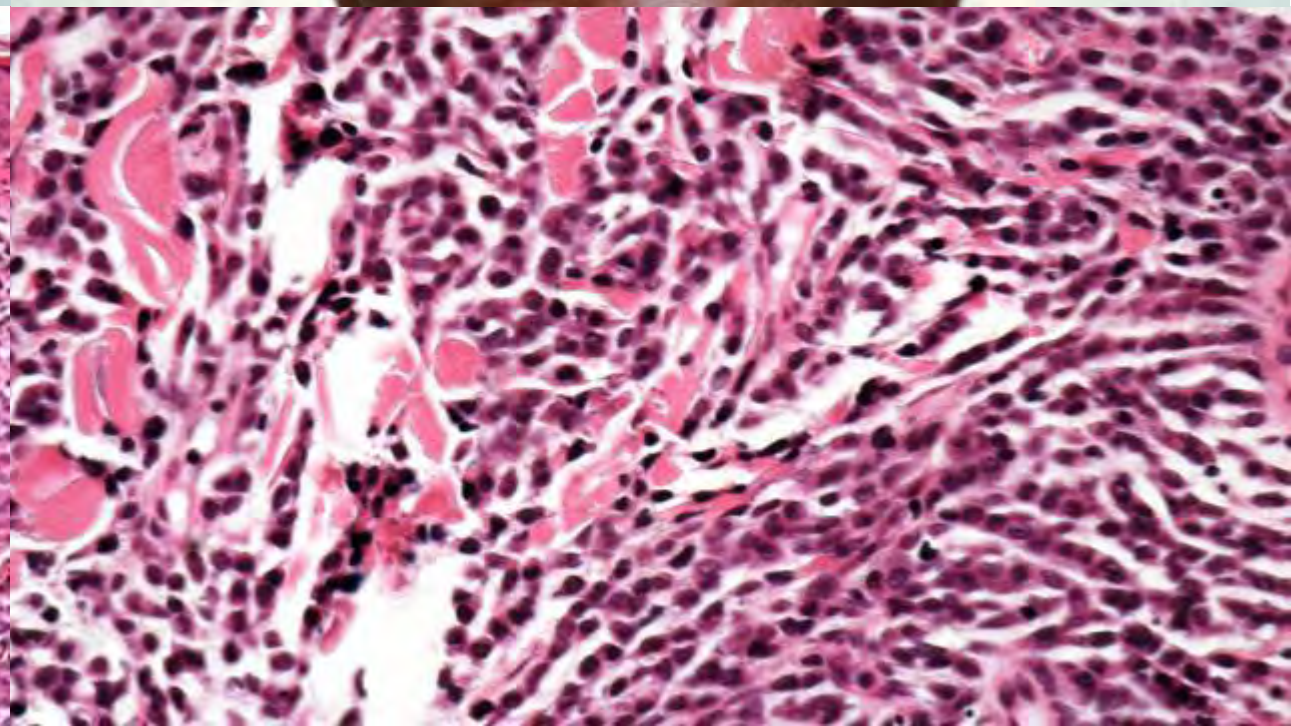
A pattern observed in lesser amount in some reactive conditions (e.g., interstitial granulomatous dermatitis); true "indian filing", however, not observed in benign inflammatory dermatoses

Congenital myeloid leukemia









Aleukaemic Congenital Leukaemia Cutis: A Critical Primary Sign of Systemic Disease

Eleni Sotiriou, Antonia Manousari, Zoi Apalla, Ioannis Papageriallou and Demetris Ioannides
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Accepted August 20, 2010.

Leukaemia is considered the most common malignancy in childhood. However, congenital leukaemia (CL) is extremely rare, accounting for only 0.5–1% of all recorded cases of childhood leukaemia (1–3). CL is defined as leukaemia that is present at birth or develops within the first month of life (1, 4, 5). Leukaemia cutis (LC), which is characterised by infiltration of the skin by immature malignant haematopoietic cells, is a common feature in CL, occurring in up to 25–30% of cases (1, 4, 6). CL and congenital LC (CLC) have similar sex distributions, with a 2:1 male-to-female ratio (1, 3).

Aleukaemic LC is a term applied to describe a form of leukaemia in which infiltration of the skin by leukaemic cells occurs before the appearance of the disease in the peripheral blood or bone marrow (6). Aleukaemic CLC is rarely reported in the literature.

CASE REPORT

A 15-day-old boy, born by vaginal delivery at 40 weeks gestation after an uneventful pregnancy, was referred to us for evaluation of a widespread eruption over his trunk and extremities. The exanthema consisted of numerous firm red-to-violaceous subcutaneous papules and nodules, primarily affecting the posterior and anterior parts of the trunk, as well as the proximal regions of legs. The lesions ranged from 1 to 4 cm in diameter. Symmetrically distributed moist scaly erythematous plaques were also observed over the inguinal creases, mimicking napkin dermatitis (Fig. 1). The results of a systematic physical examination were otherwise unremarkable. According to the patient's medical history, most of the lesions were present at birth and had gradually deteriorated since. Differential diagnosis included nodular mastocytosis, histiocytosis and LC.

The results of laboratory investigations, including haematology, chemistry, an immunoglobulin assay, a Coombs test, serology for hepatitis A, B, C and TORCH (toxoplasma, other infections, Rubella, cytomegalovirus, HSV), and urinalysis, were normal. Ultrasonography and X-rays also revealed nothing unusual. Bone marrow in two subsequent aspiration biopsy samples did not demonstrate leukaemic infiltration.

Histological examination of a suspicious skin nodule demonstrated diffuse infiltration of the dermis by atypical medium-sized cells with round or folded nuclei and indistinct nucleoli. Immunohistochemical analysis revealed diffuse staining of neoplastic cells for MPO, lysozyme, CD68 and CD43. Staining for CD34, c-kit/CD117, mast cell tryptase, S-100, CD1α, LCA, CD20/L26, CD79α, CD45RO/UCHL1, CD3, CD4, CD8, CD56, CD30/Ki-1 and CD15/LeuM1 was negative. Collectively, these observations provide evidence of cutaneous infiltration by immature myeloid tumour cell blasts. Therefore skin involvement as the primary clinical manifestation of acute myeloid leukaemia (AML) was diagnosed.

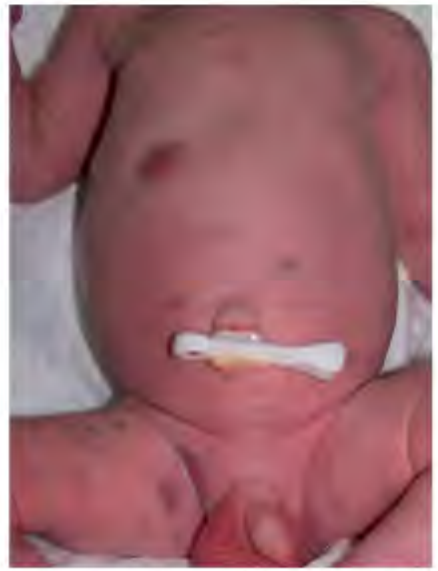

Fig. 1. Firm violaceous subcutaneous nodules on the trunk and legs.

The patient's disease progressed rapidly and he died within 7 days of diagnosis. The ultimate cause of death was established during an autopsy as AML, based on a bone marrow blast population of greater than 20%.

DISCUSSION

Factors associated with CL include inherited genetic traits, environmental factors and factors related to gestation.

Diagnostic criteria for CL include: presentation at birth or within the first four weeks of life; proliferation of immature myeloid, lymphoid or erythroid cells; infiltration of these cells into extra-haematopoietic tissues; and absence of diseases that provoke leukaemoid reactions mimicking CL (1, 4, 5).

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Spontaneous Regression of Aleukemia Congenital Leukemia Cutis

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Abstract: **A full-term 2-week-old boy was referred to the pediatric dermatology clinic with numerous blue to violaceous nodules present since birth. TORCH titers (against toxoplasmosis, cytomegalovirus, herpes simplex virus, rubella, and syphilis) were negative. Complete blood count and peripheral smear were normal. A skin biopsy specimen showed an atypical cellular infiltrate suspicious for leukemia or lymphoma. A bone marrow biopsy specimen demonstrated acute myelogenous leukemia (M4 subtype). Following consultation with pediatric oncology and the recognition of the potential for spontaneous regression, chemotherapy for the infant's condition was not recommended. He remained otherwise healthy and was followed-up with biweekly to monthly complete blood counts and physical examinations, which were repeatedly normal. By 3 months of age, the nodules had completely resolved and there was no evidence of recurrence at 8 months of follow-up. We report this instance of aleukemic congenital leukemia with spontaneous regression of leukemia cutis without therapeutic intervention.**

Leukemia cutis presents as firm erythematous to violaceous to blue macules, papules, and nodules as a result of infiltrating leukemic cells in the skin. Often, leukemia cutis in the newborn population can be the only manifestation of congenital leukemia, or antedate the onset of systemic leukemia (1,2). We report an infant with congenital acute myelogenous leukemia whose cutaneous disease regressed spontaneously without therapy.

CASE REPORT

A 3391-g boy (blood type A positive) was born at term to a healthy 34-year-old mother [gravida 4, para 1, blood type O positive, hepatitis B surface antigen negative, group B *Streptococcus* (GBS) negative, rubella immune, venereal disease research laboratory (VDRL) test negative]. The pregnancy was complicated by mild pre-eclampsia during pregnancy and ABO incompatibility. The infant had mild jaundice, which resolved without treatment. There was no family history of malignancy.

Physical examination revealed a healthy, vigorous, phenotypically normal boy with multiple nonblanchable, blue-violaceous dermal nodules (0.5–2 cm in diameter) on his scalp, face, neck, chest, abdomen, back, buttocks, and extremities, present at birth (Fig. 1). No petechiae or ecchymoses were seen. The nodules spared the mucous

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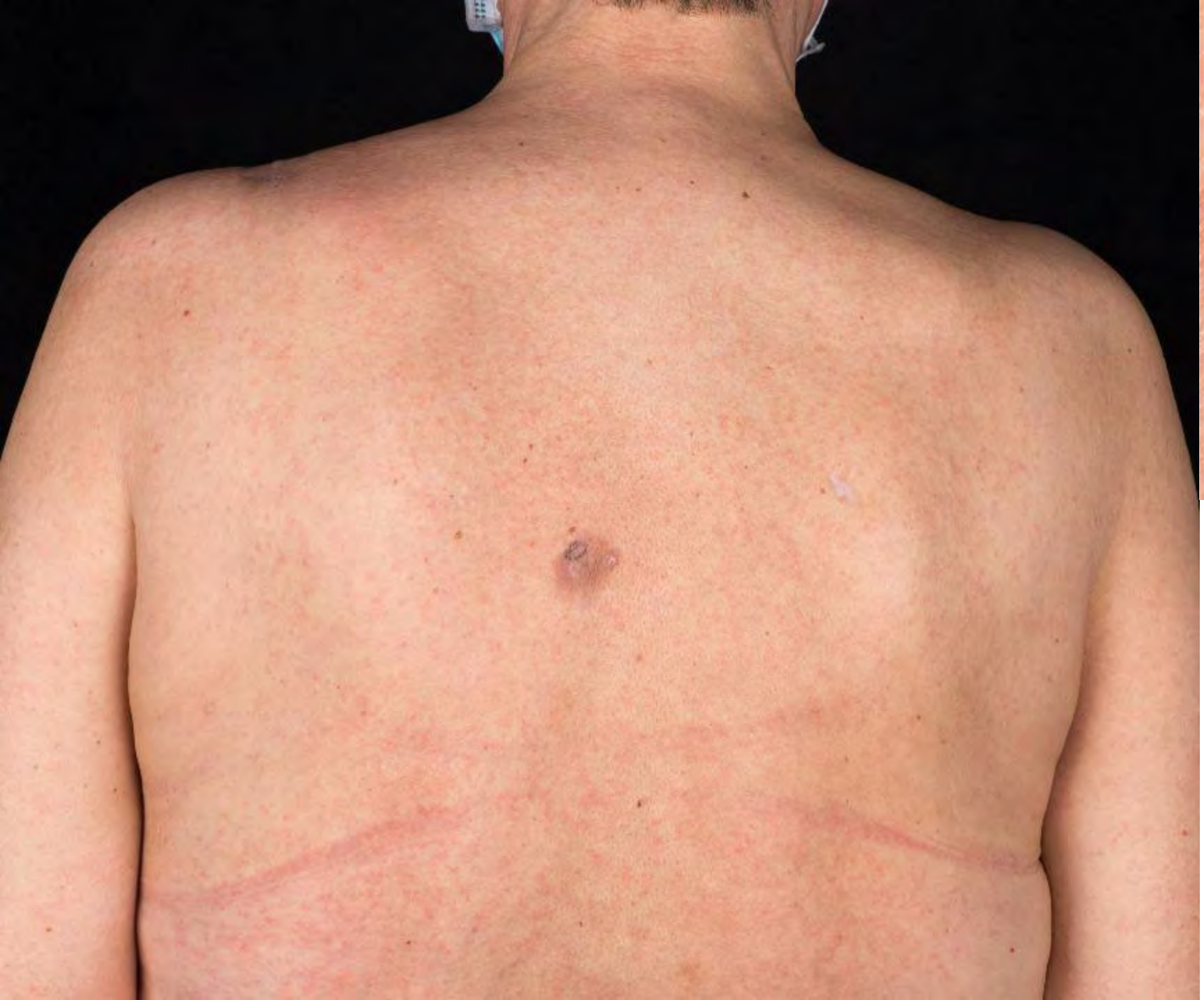
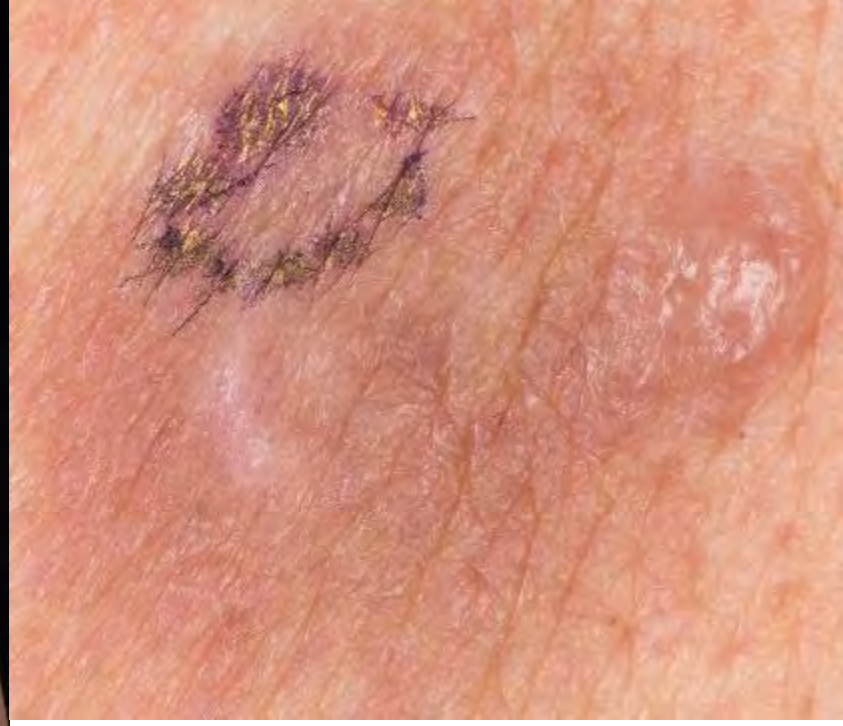
Pediatric myelogenous leukemia

- May be observed in neonates (congenital myelogeneous leukemia; rarely spontaneous complete remission without treatment)
- May be observed in the setting of "secondary" leukemia (after chemotherapeutic treatments for solid tumors or for other lymphomas or leukemias)
- Skin manifestations may be the first sign of the disease (aleukemic cutaneous myeloid leukemia)
- Poor prognosis; aggressive treatment





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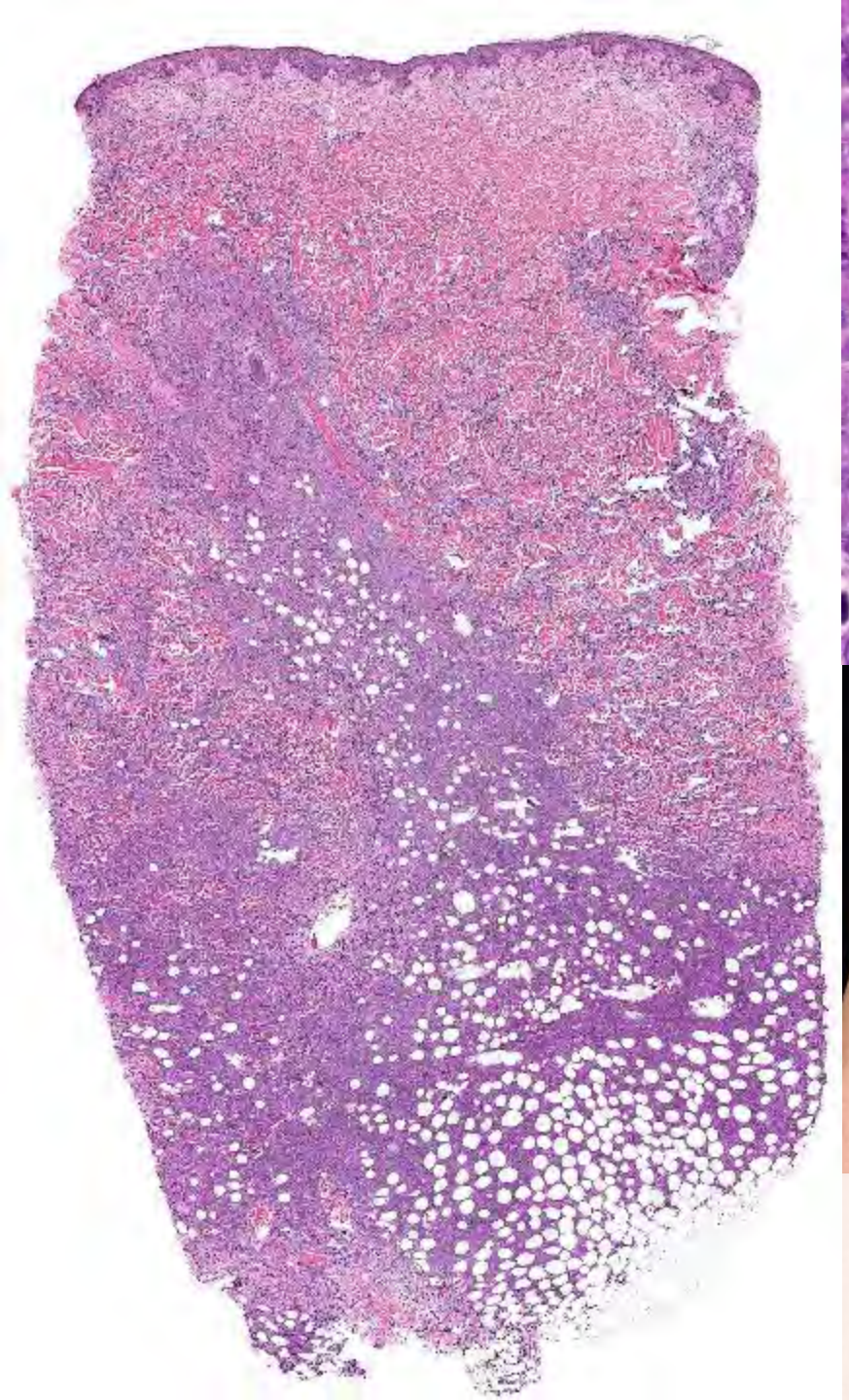
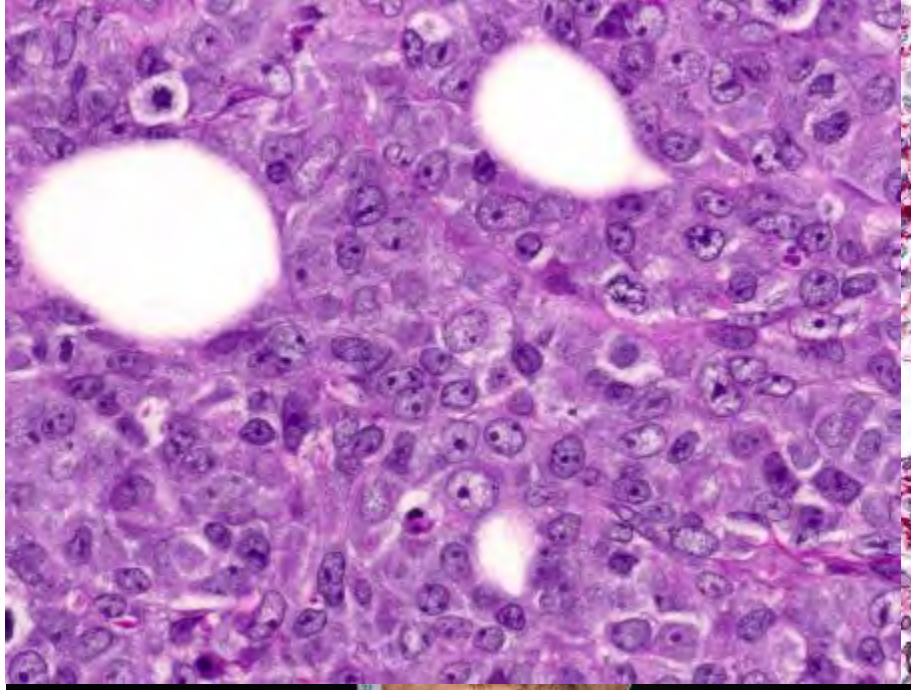
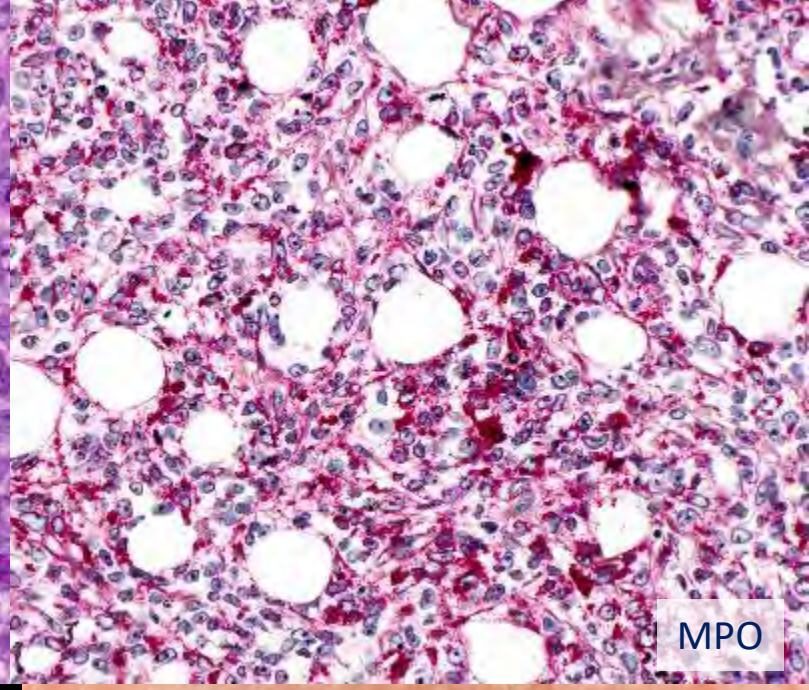
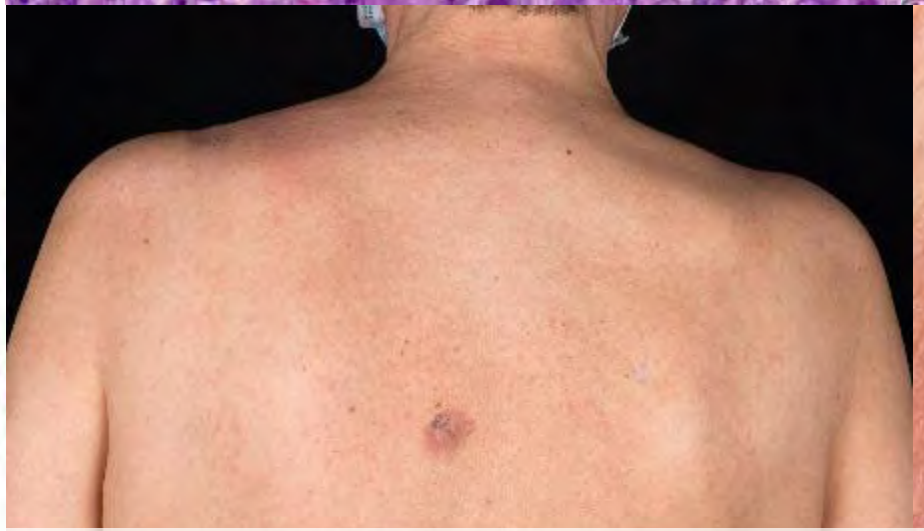
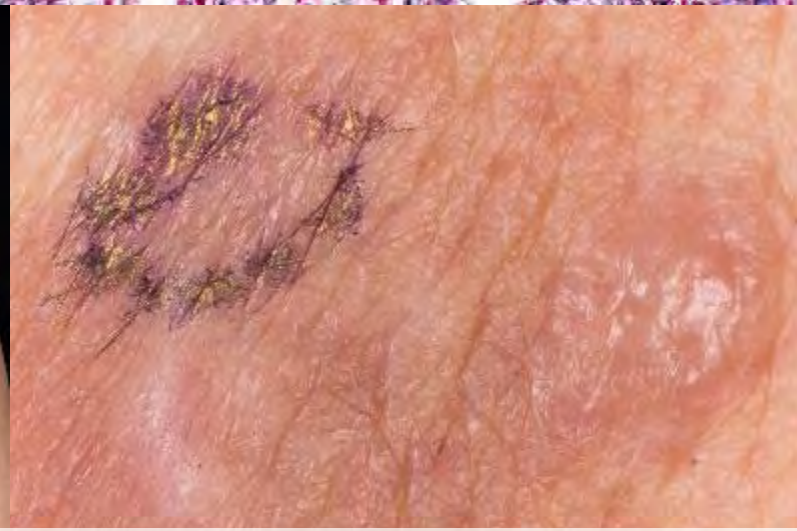
History of breast carcinoma in 2010 treated with chemotherapy and radiotherapy.
Therapy- associated cutaneous myelosarcoma 6 months before presentation (in remission after allogeneic stem cell Tx).
New lesion at the site of the previous myelosarcoma.





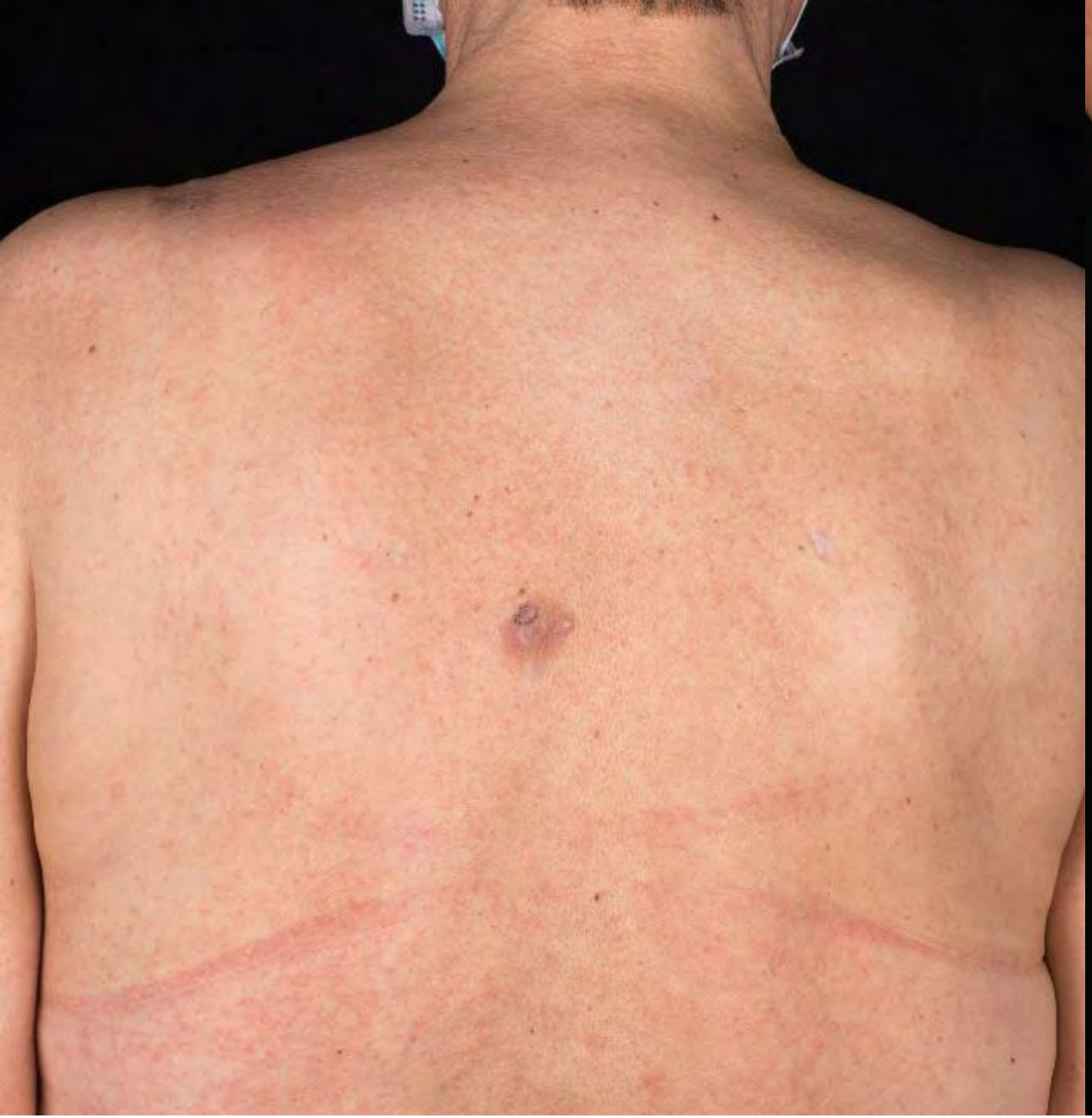




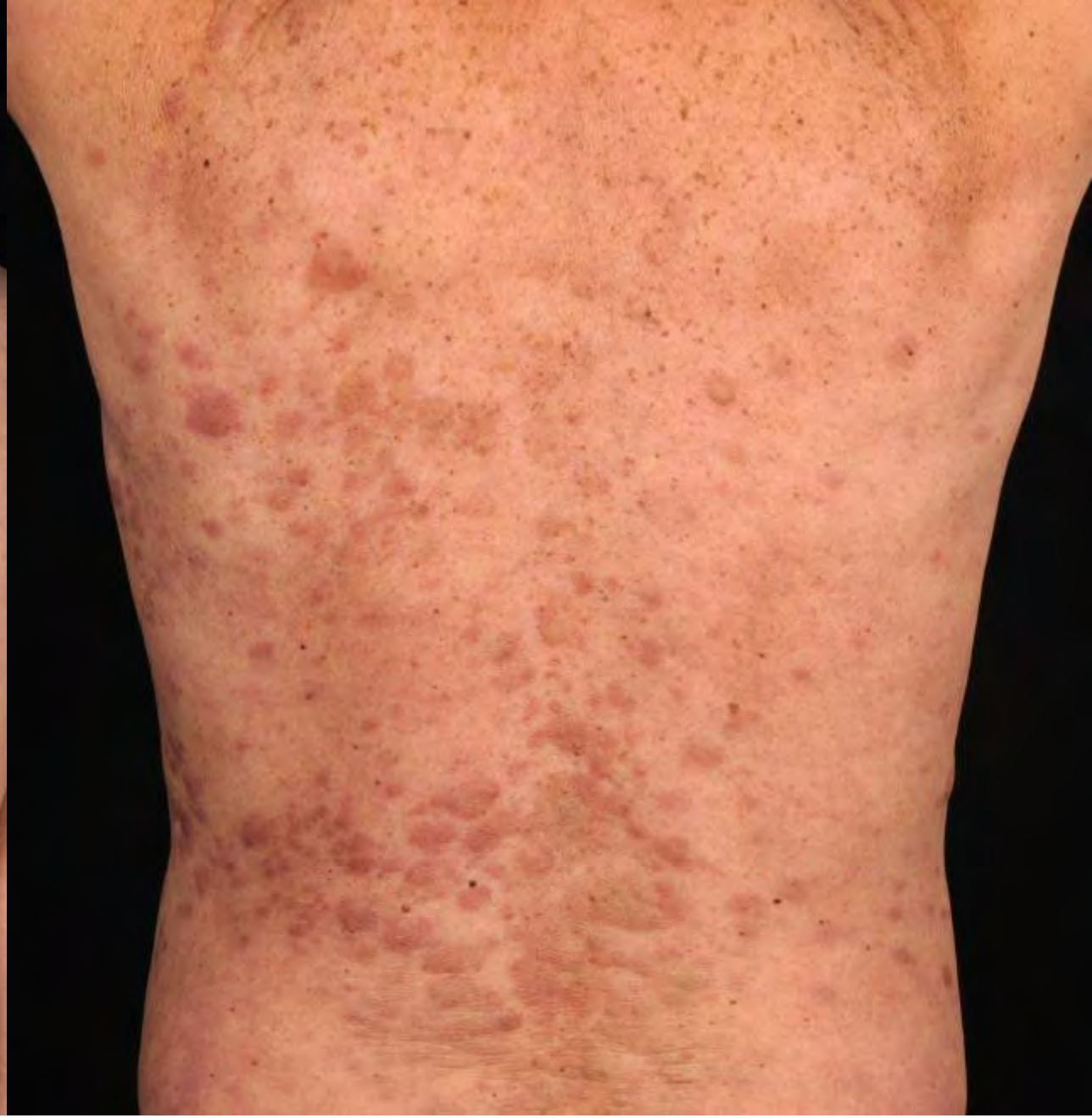


Recurrent cutaneous myelosarcoma

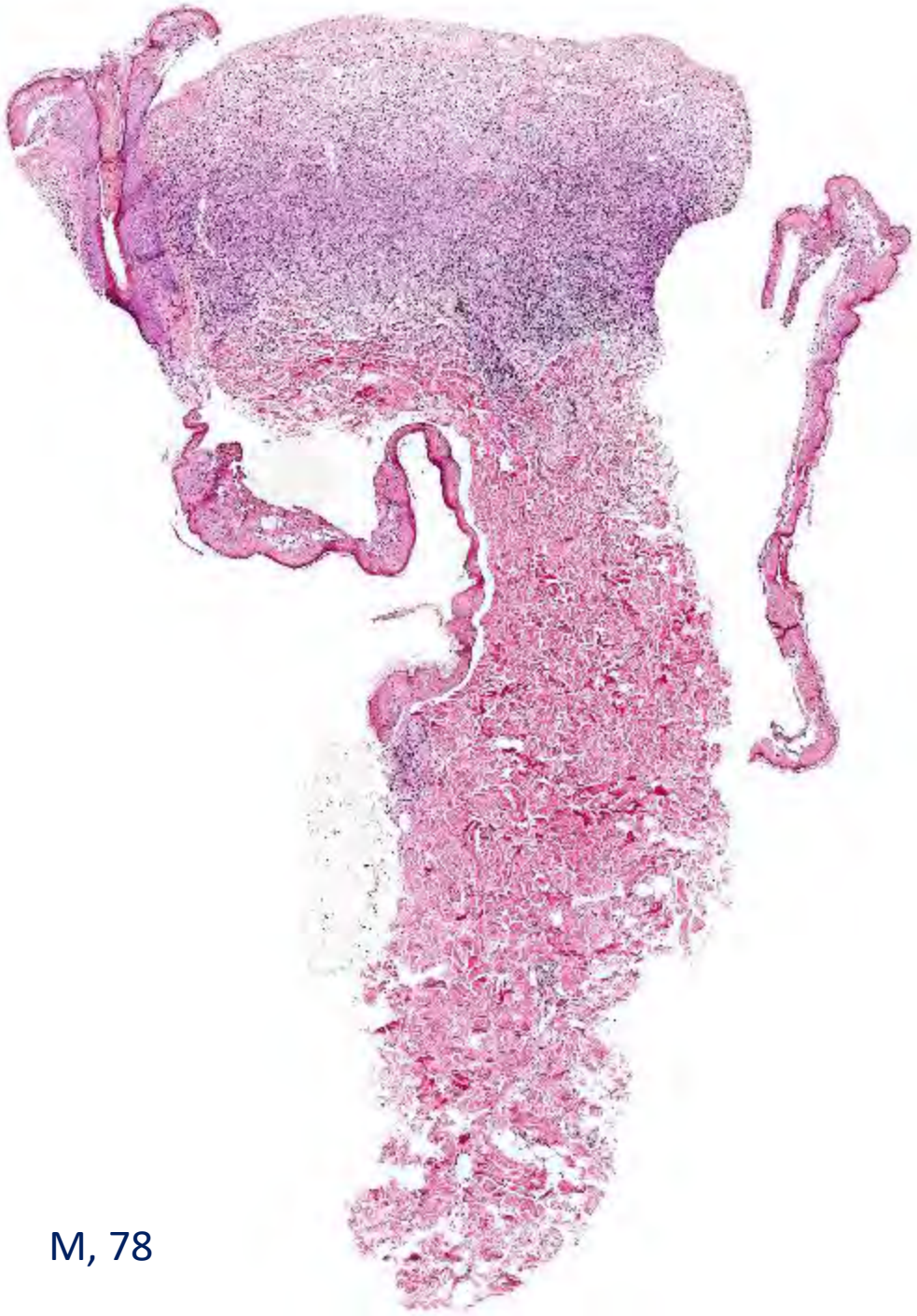
Died of complications 2 months after presentation



Myelosarcoma



Myeloid leukemia



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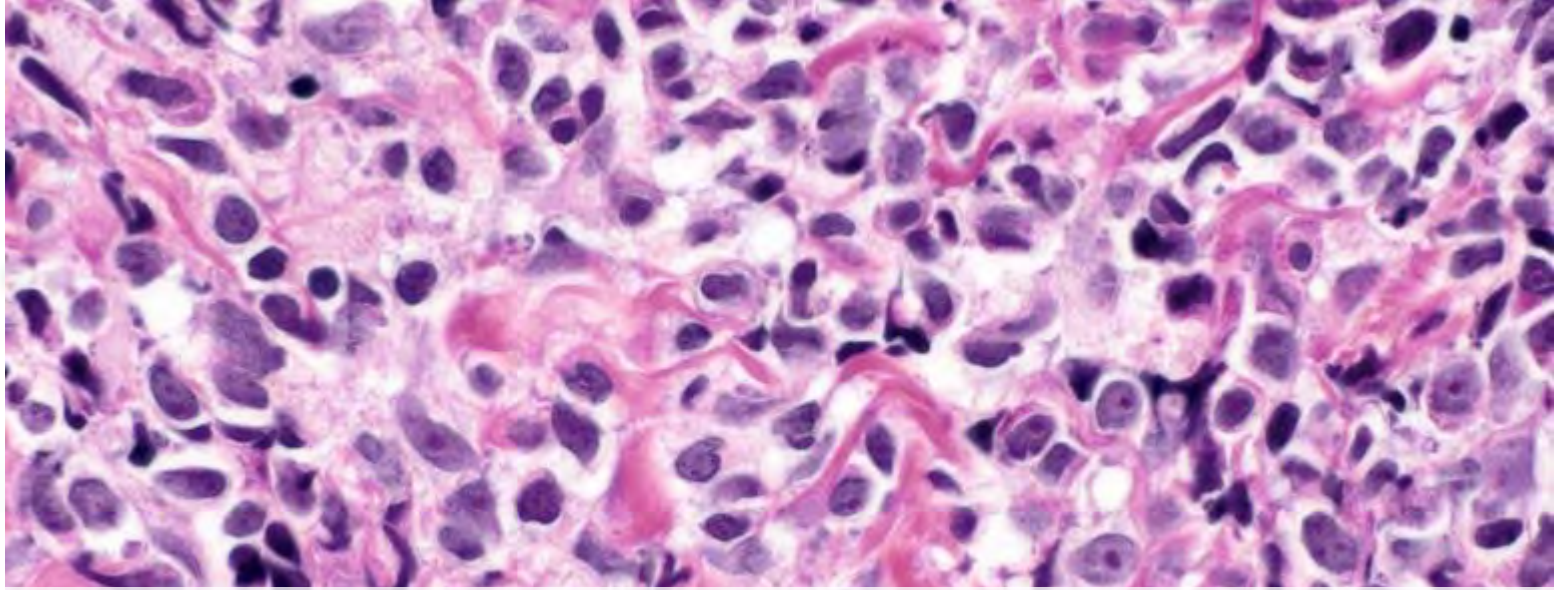
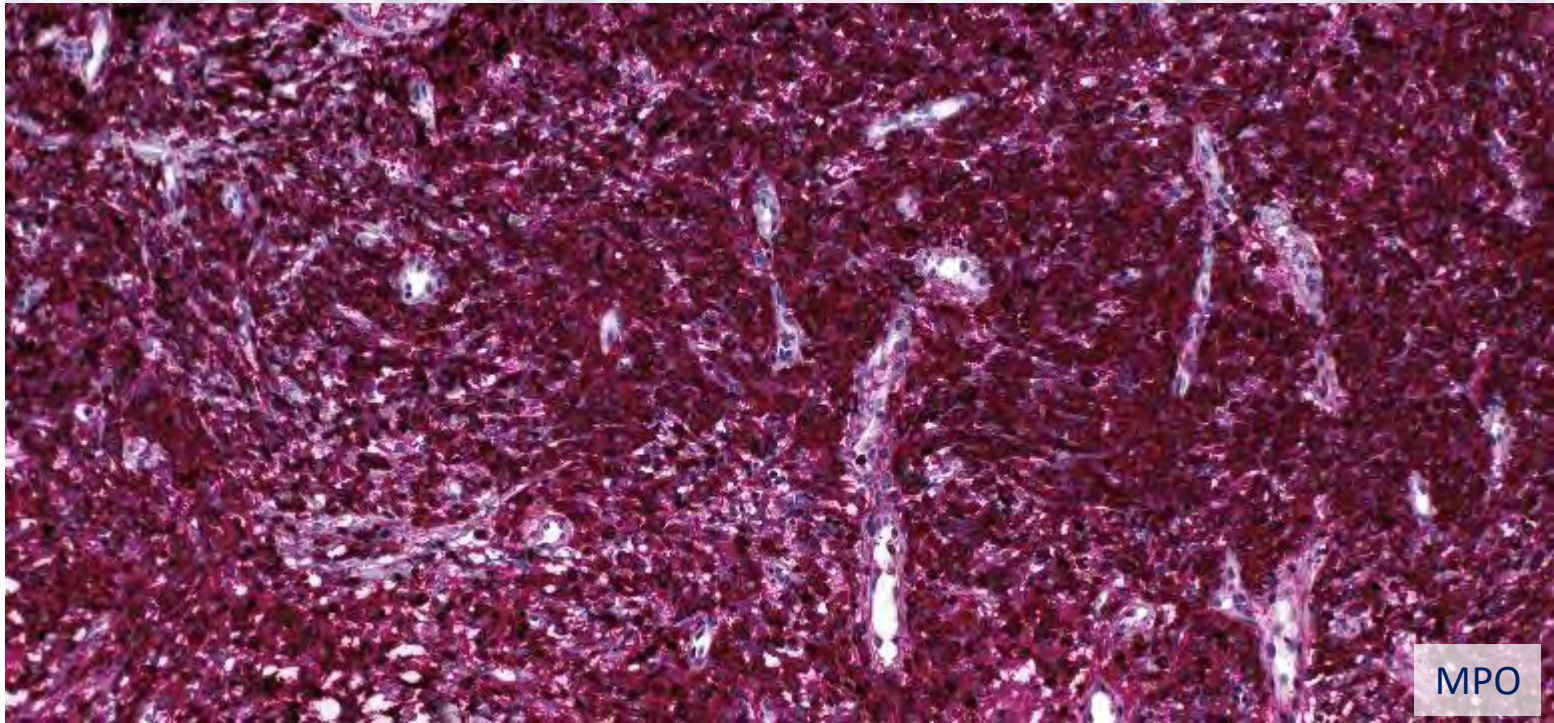
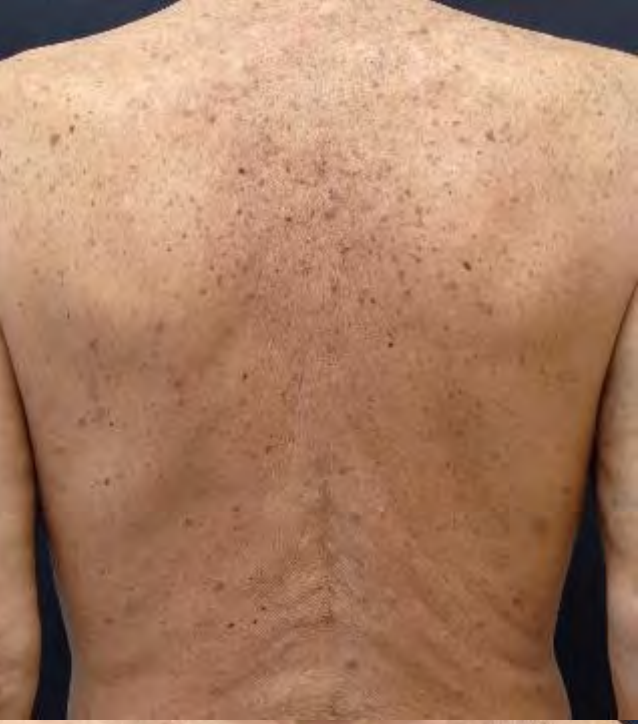
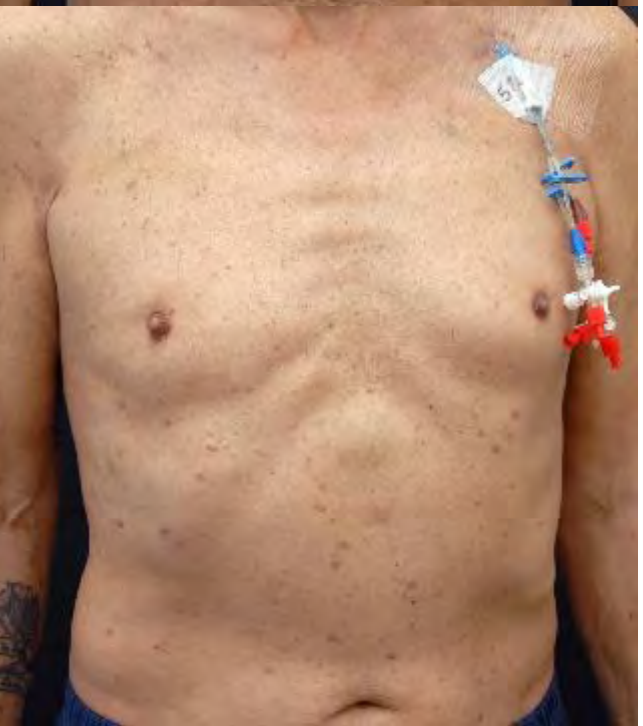


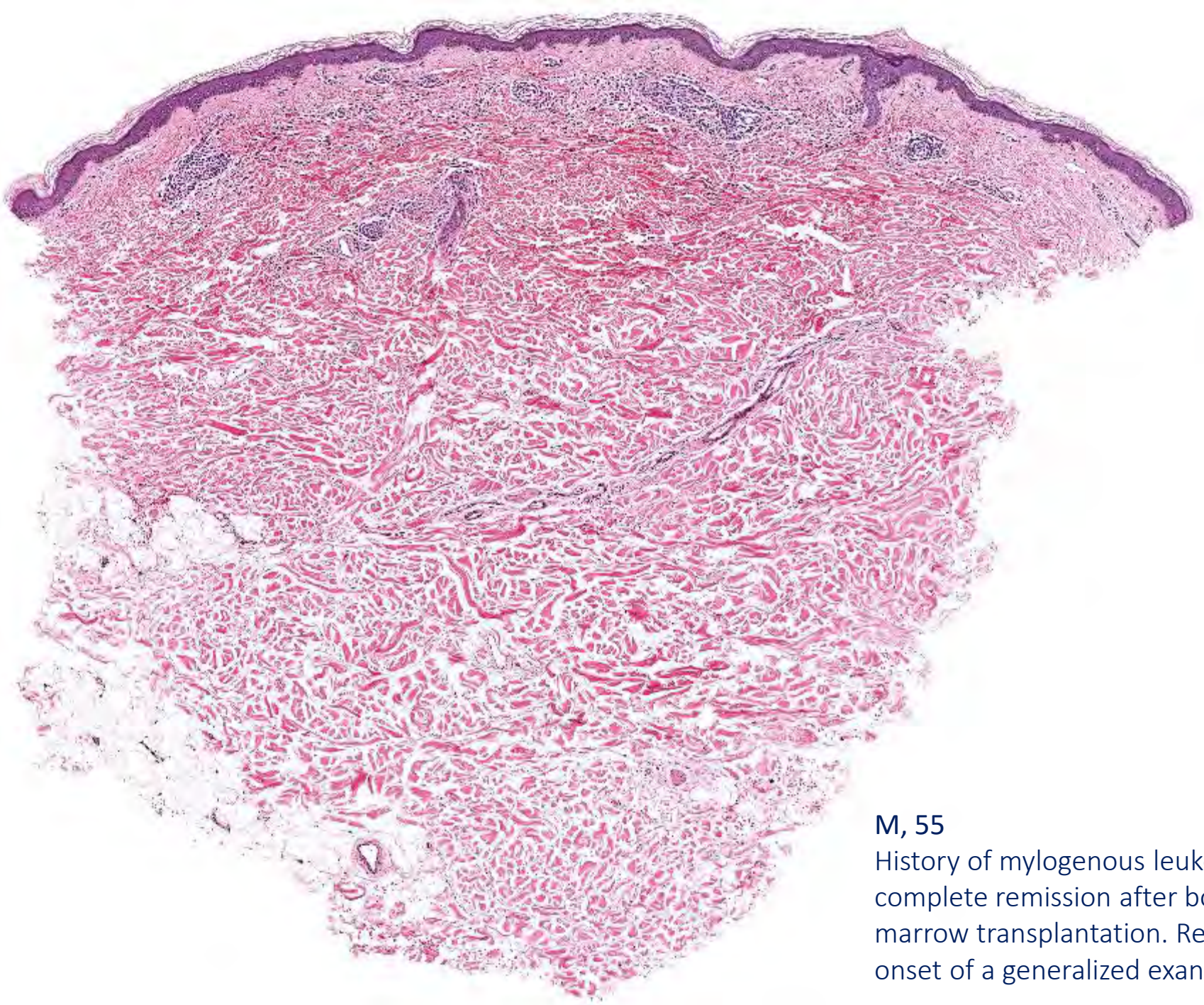
Band-like, necrotizing myeloid leukemia



MPO

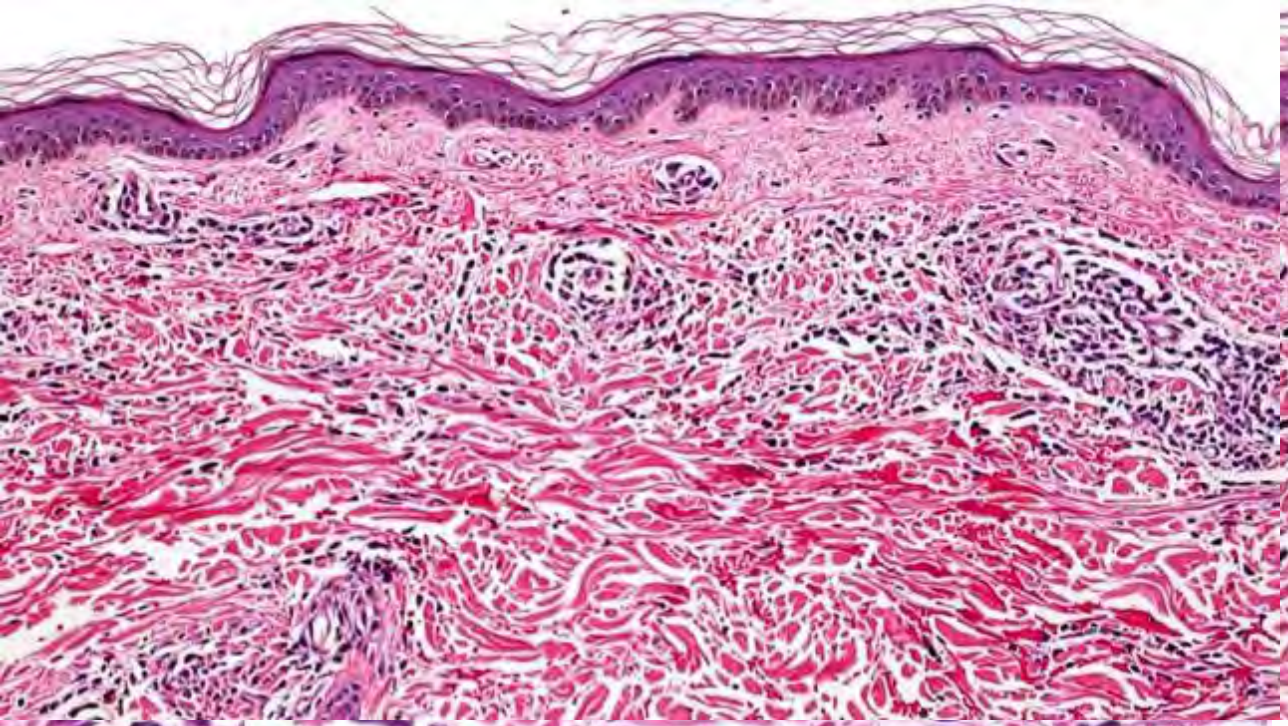


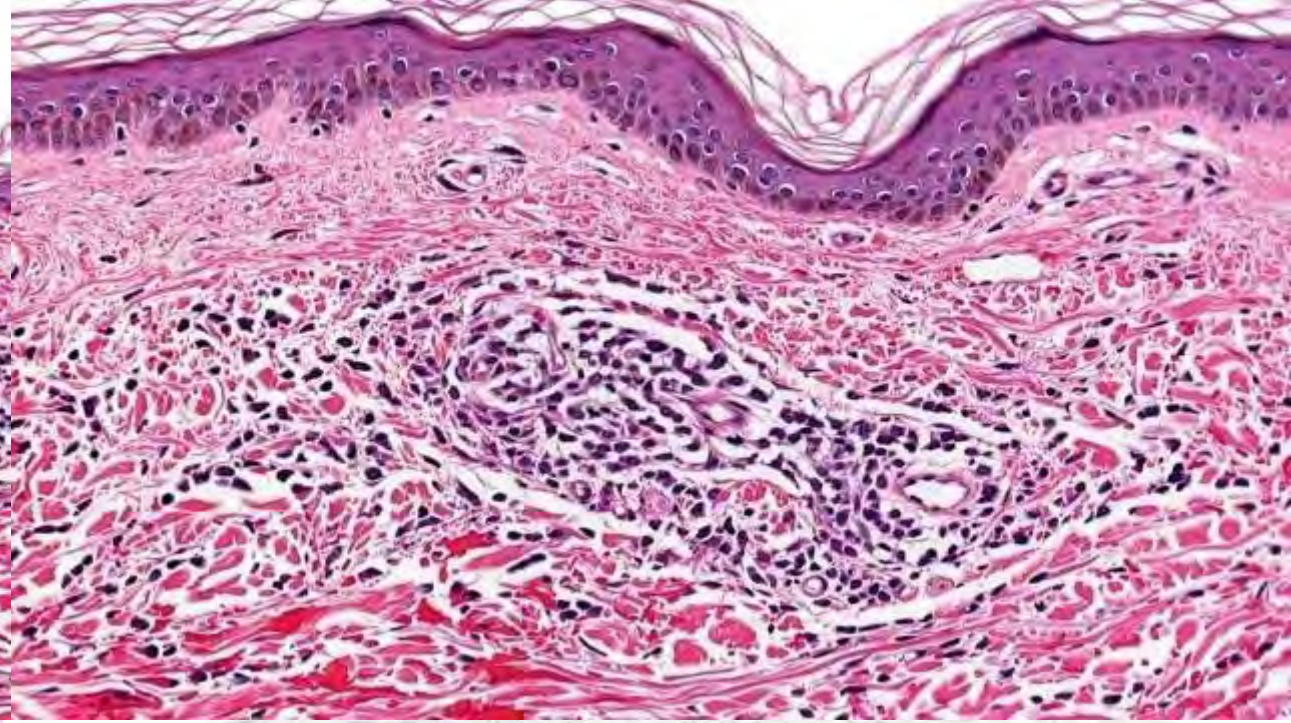


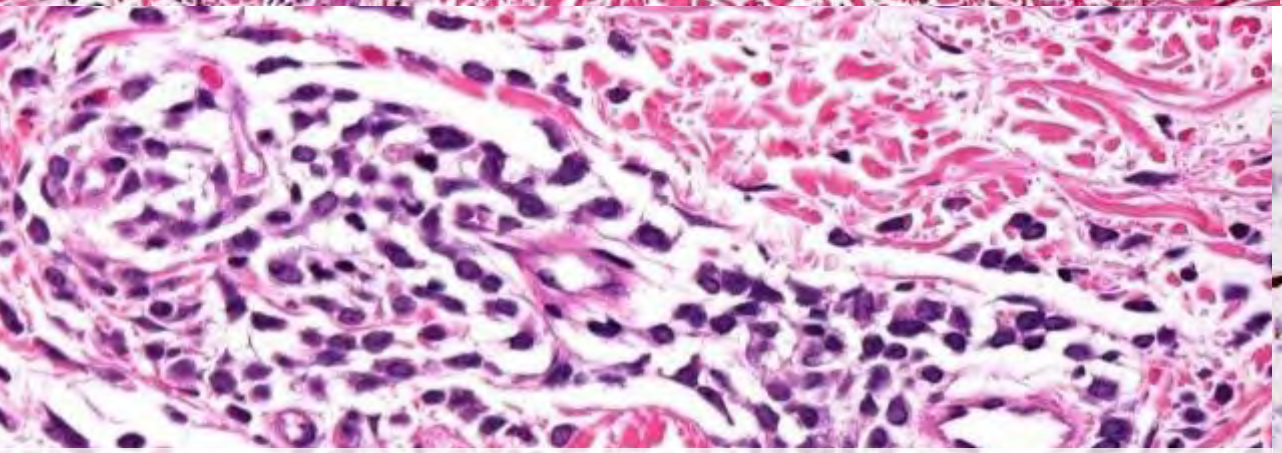


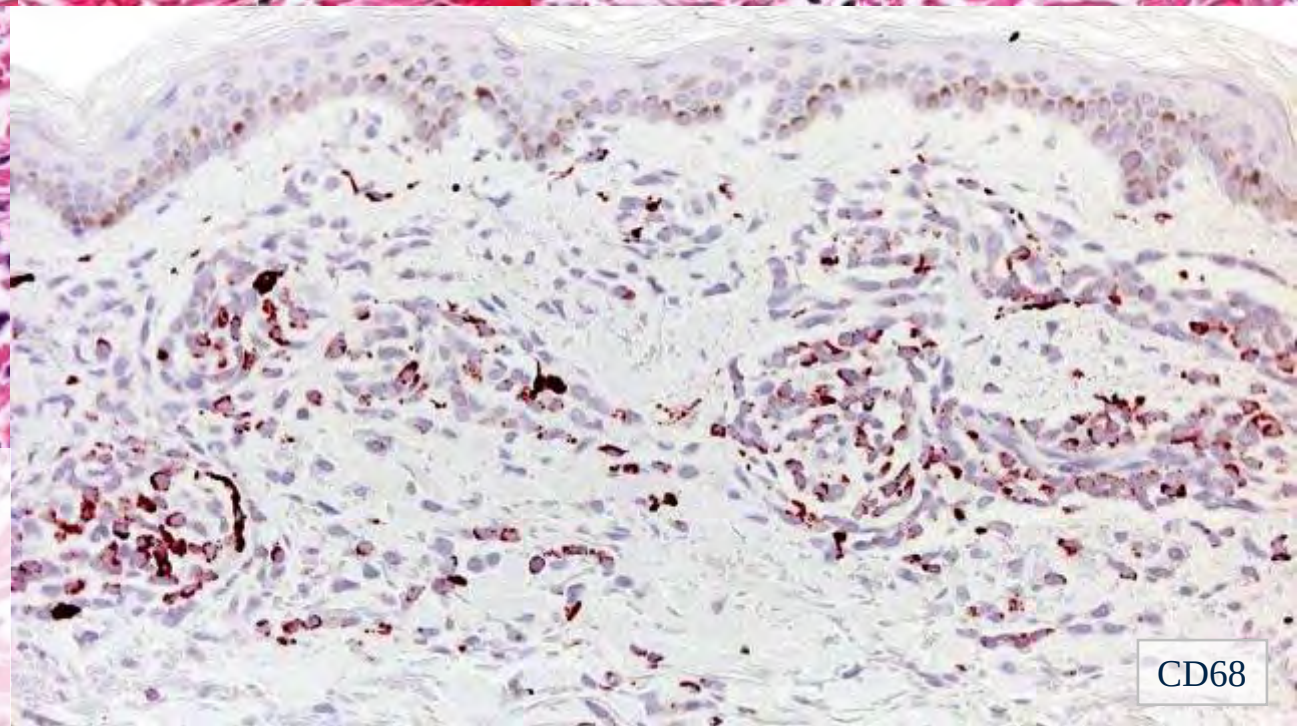
M, 55

History of mylogenous leukemia in complete remission after bone marrow transplantation. Recent onset of a generalized exanthema

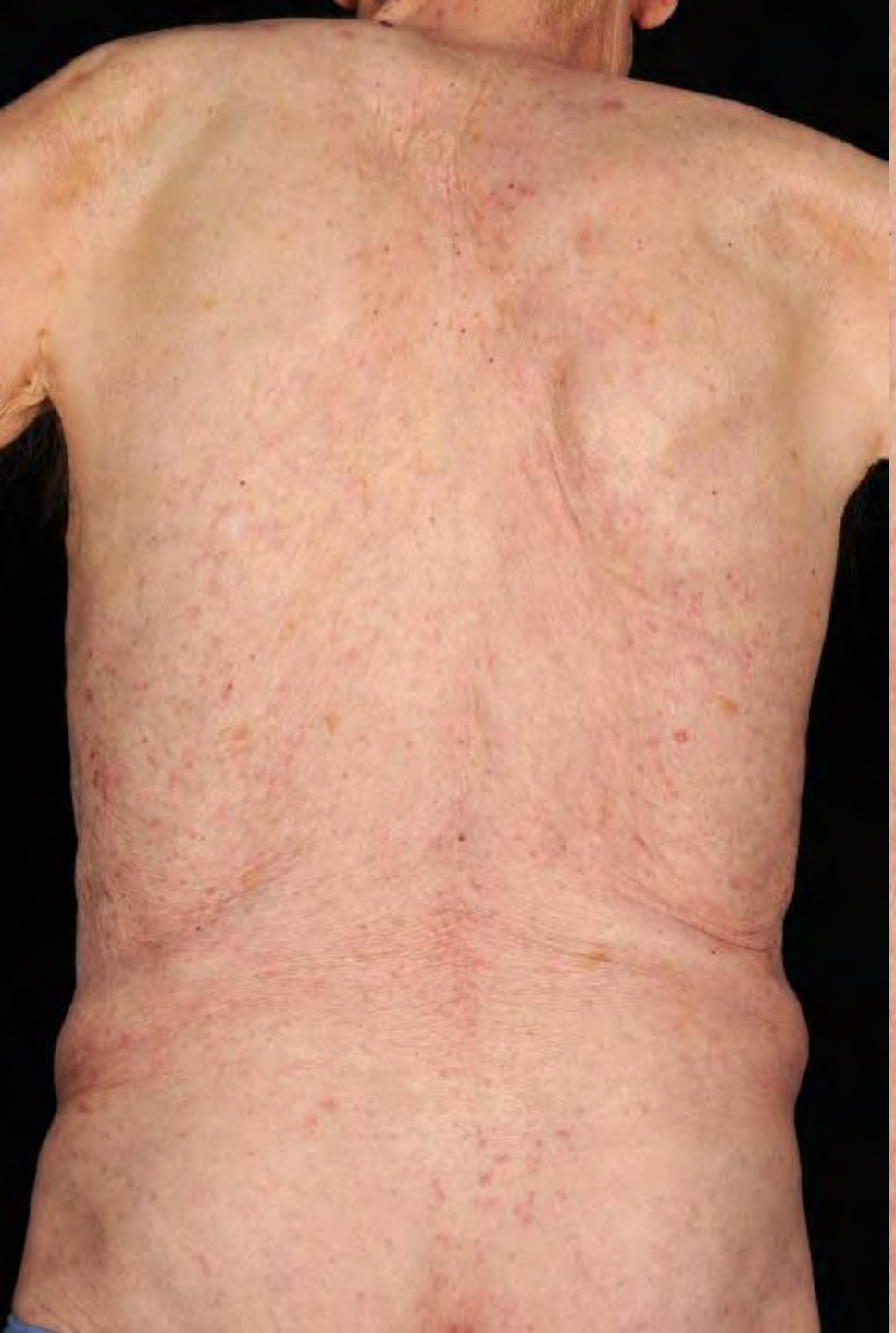


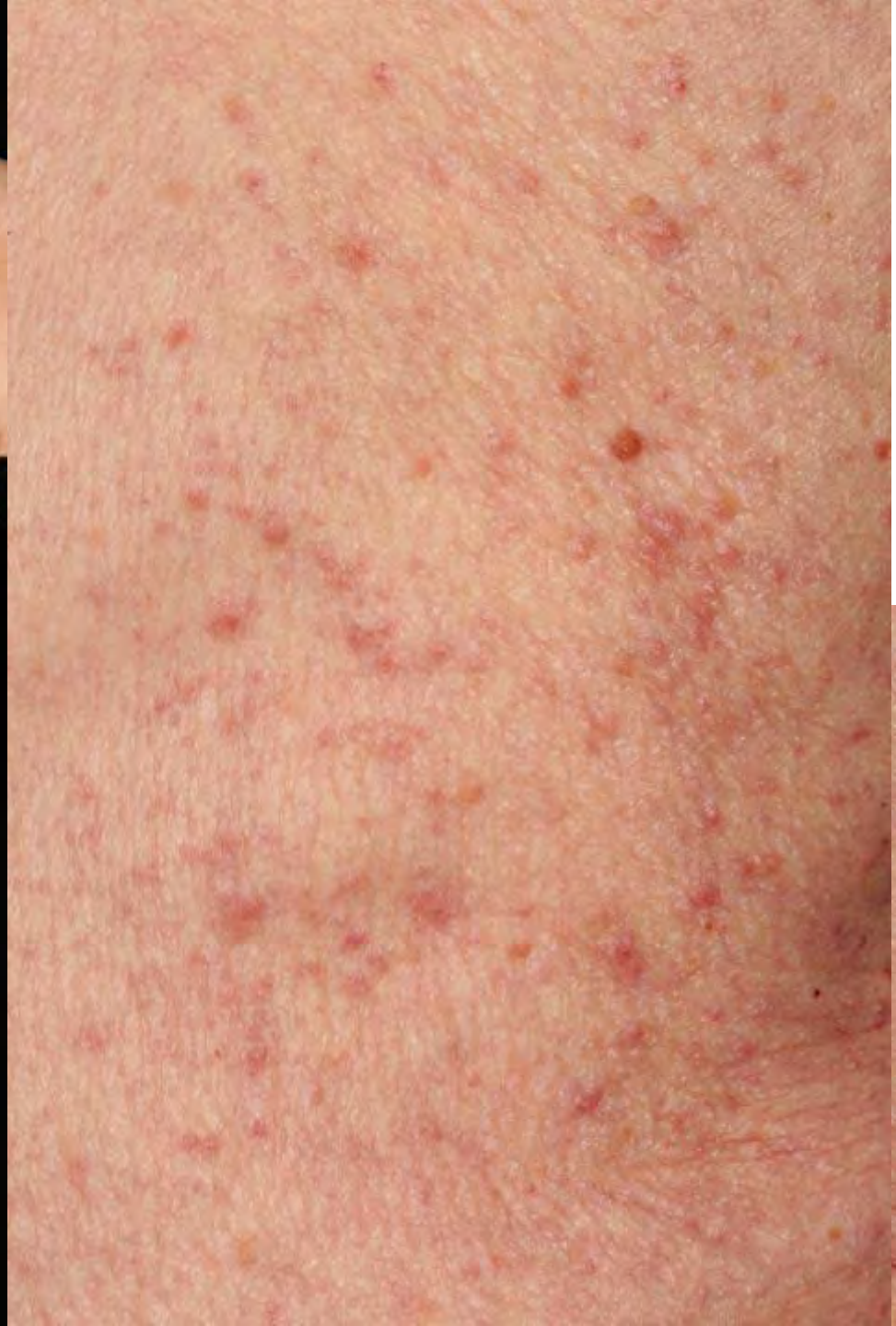






Specific cutaneous infiltrate of myeloid leukemia



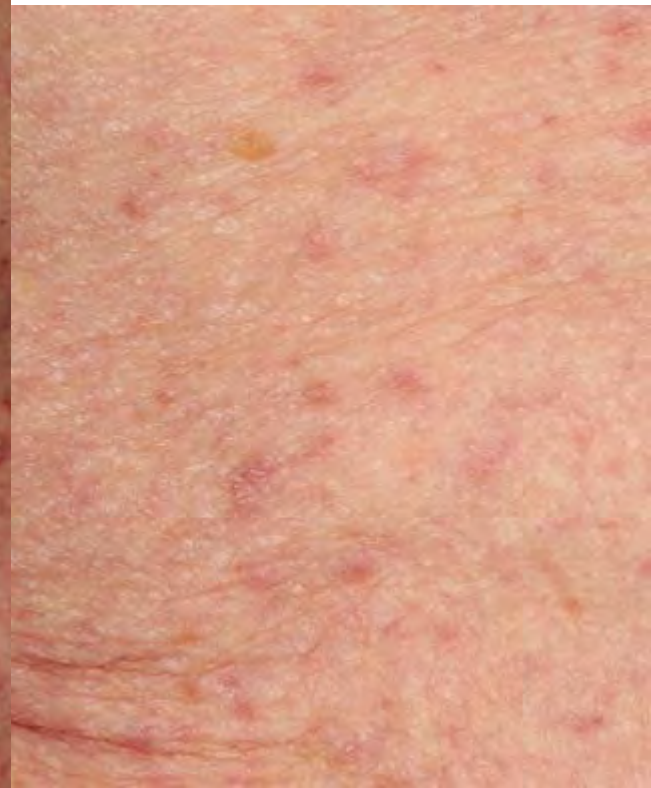


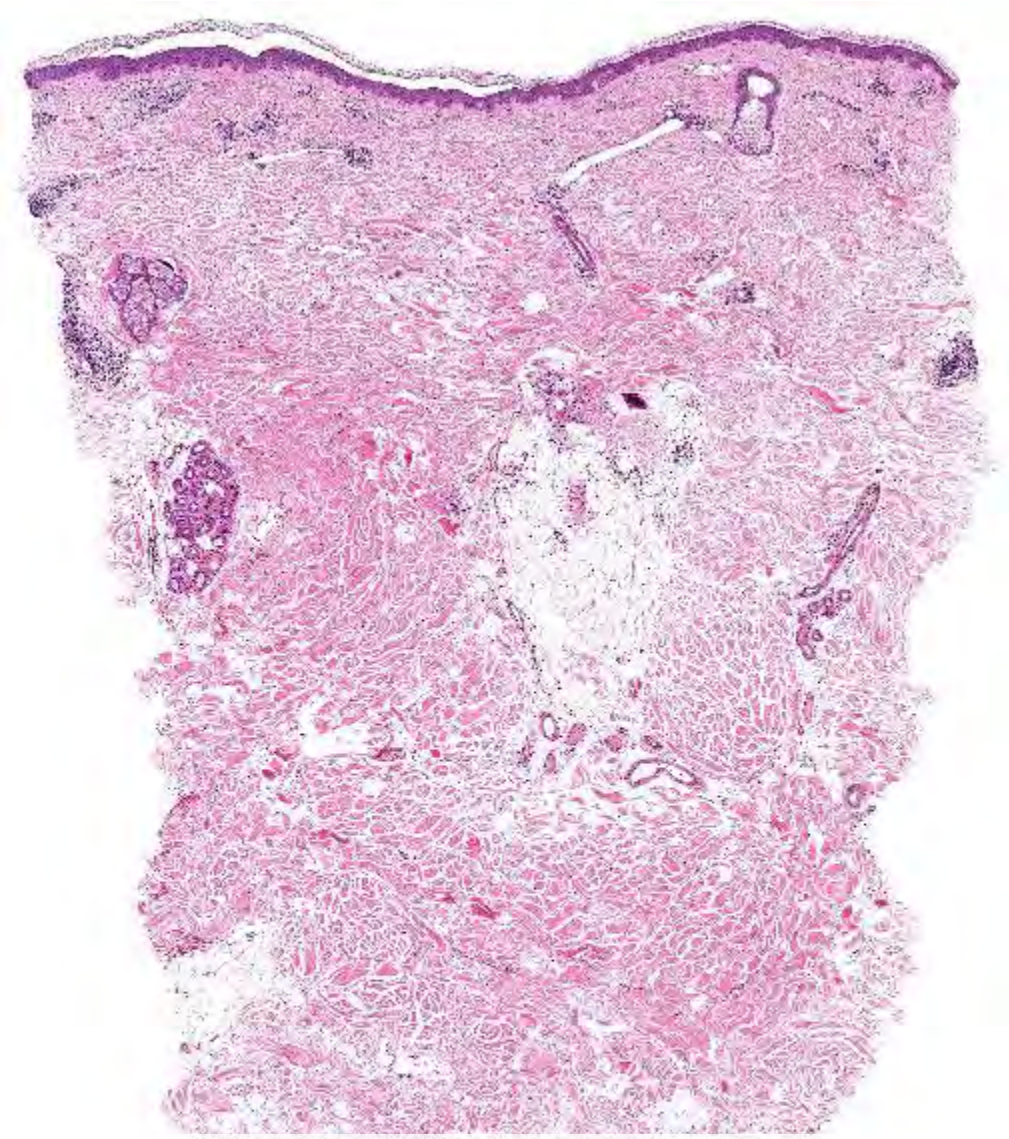
M, 71

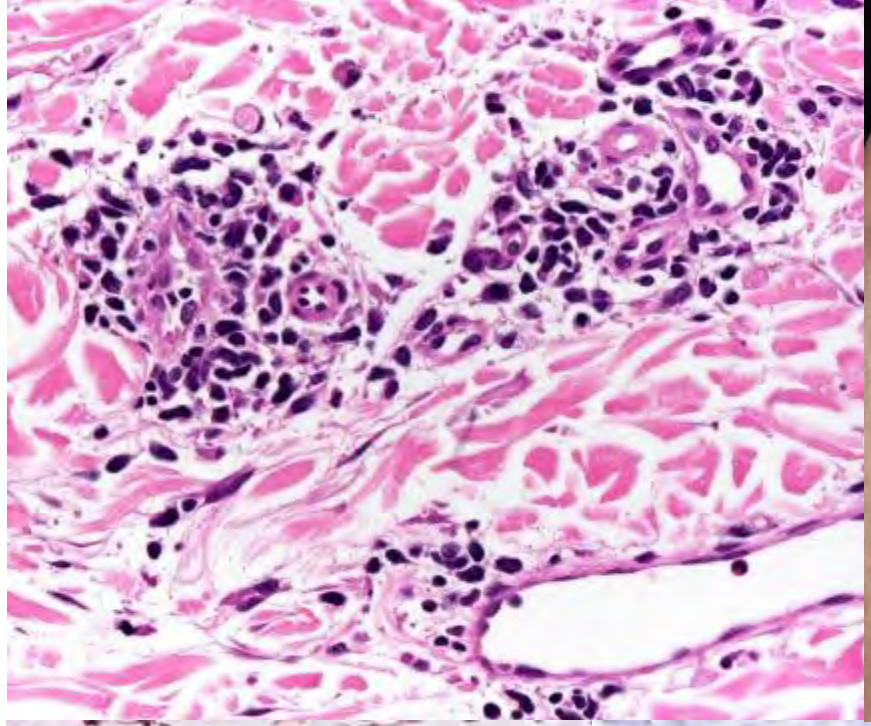
History of acute myeloid leukemia in partial remission after blinded therapy in the context of a study; further palliative treatment.

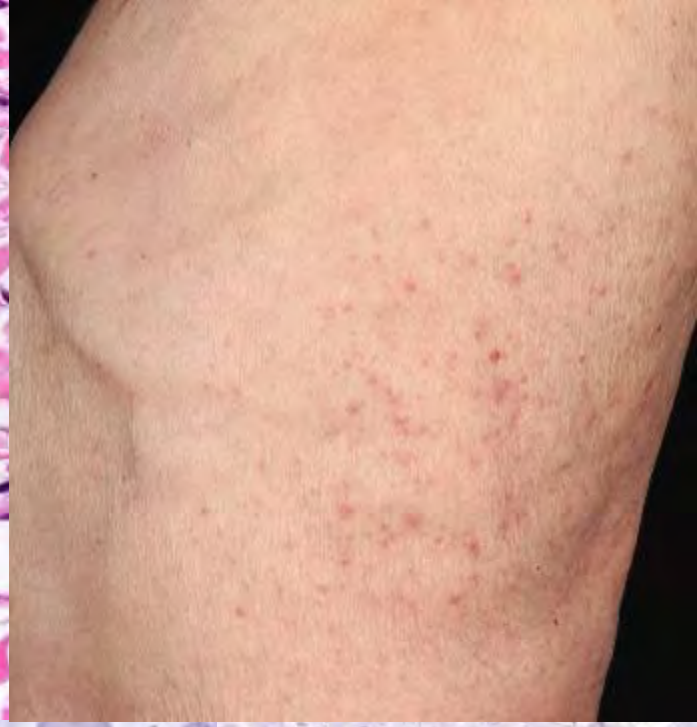
According to the patient generalized, asymptomatic tiny papules for one day.

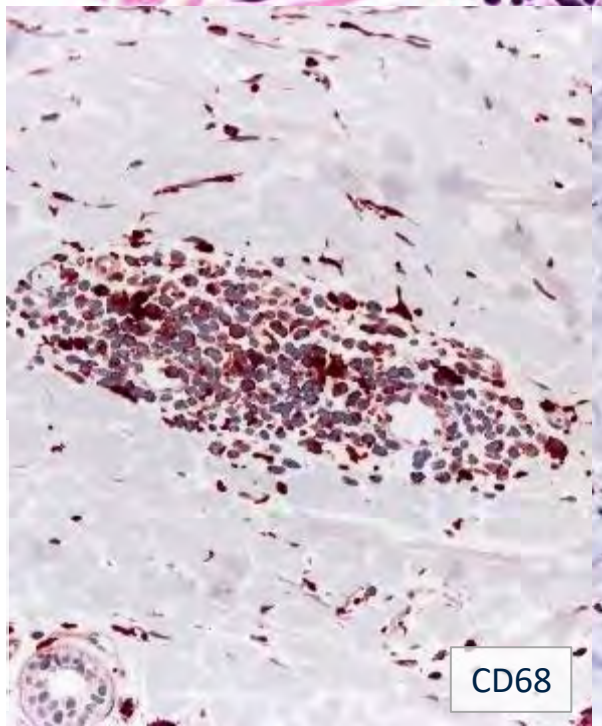
A biopsy is taken.

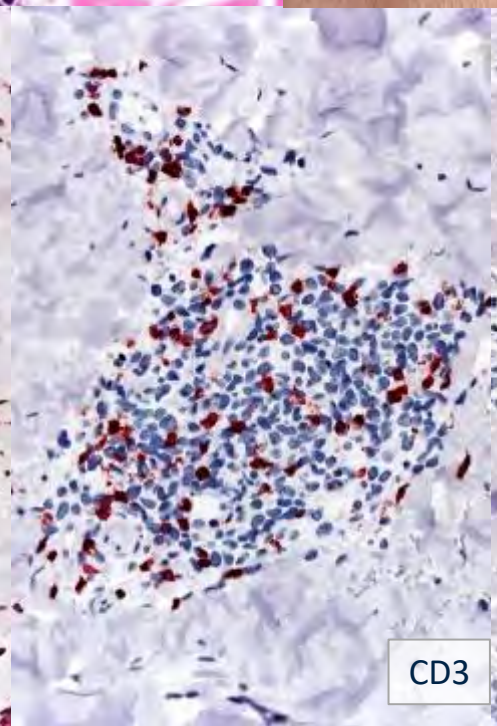


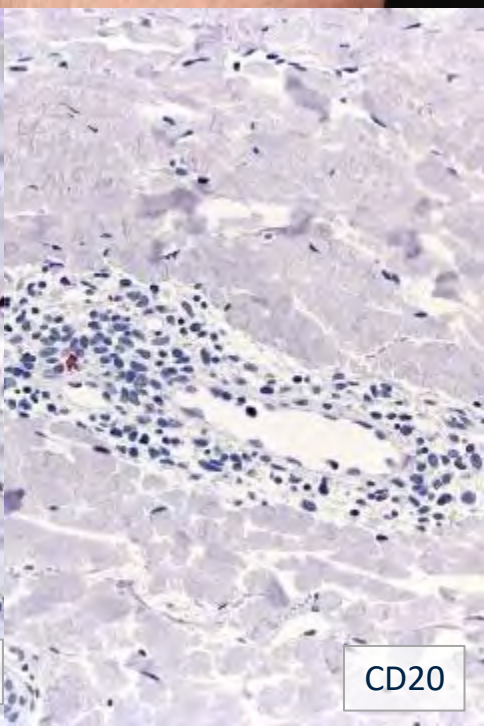








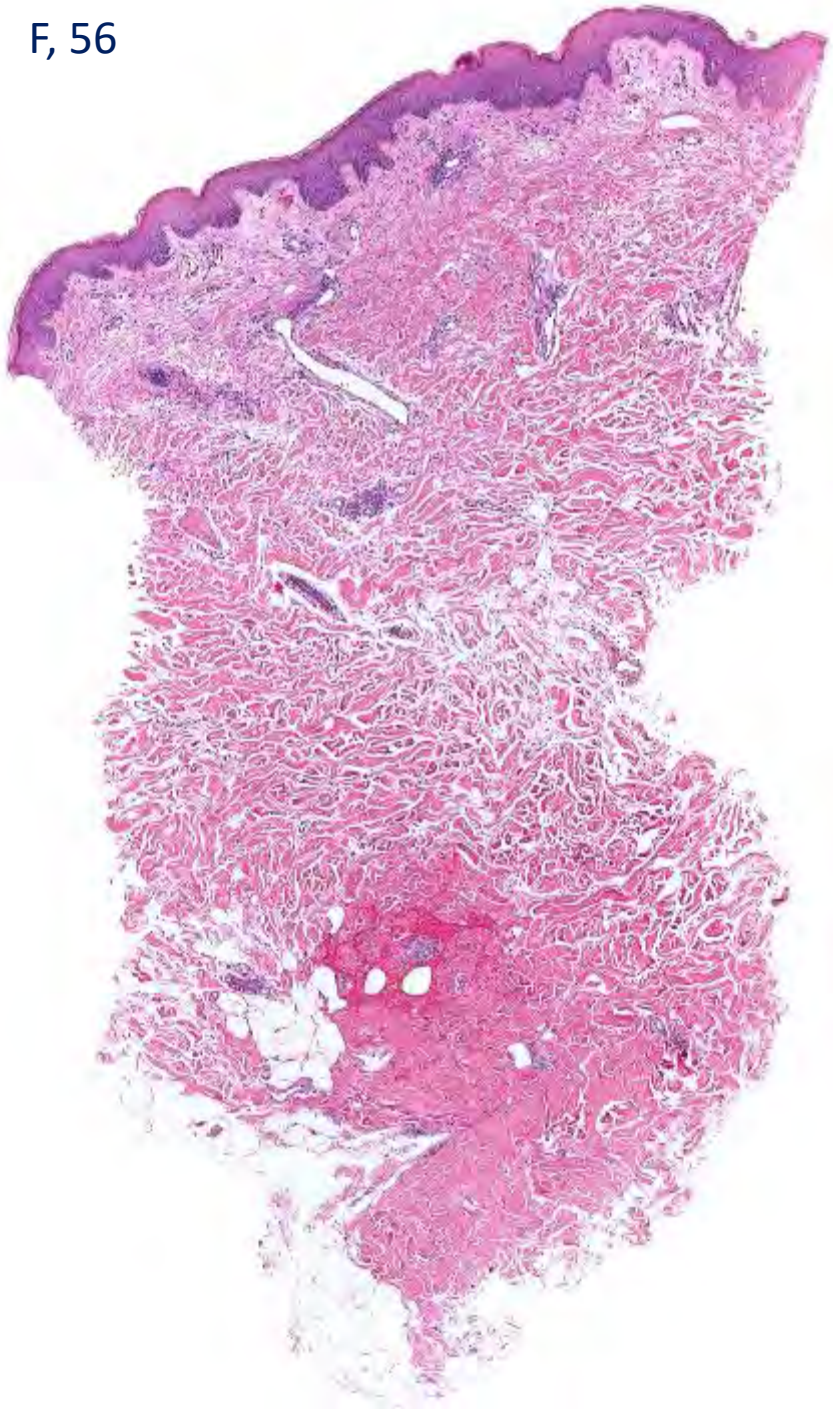


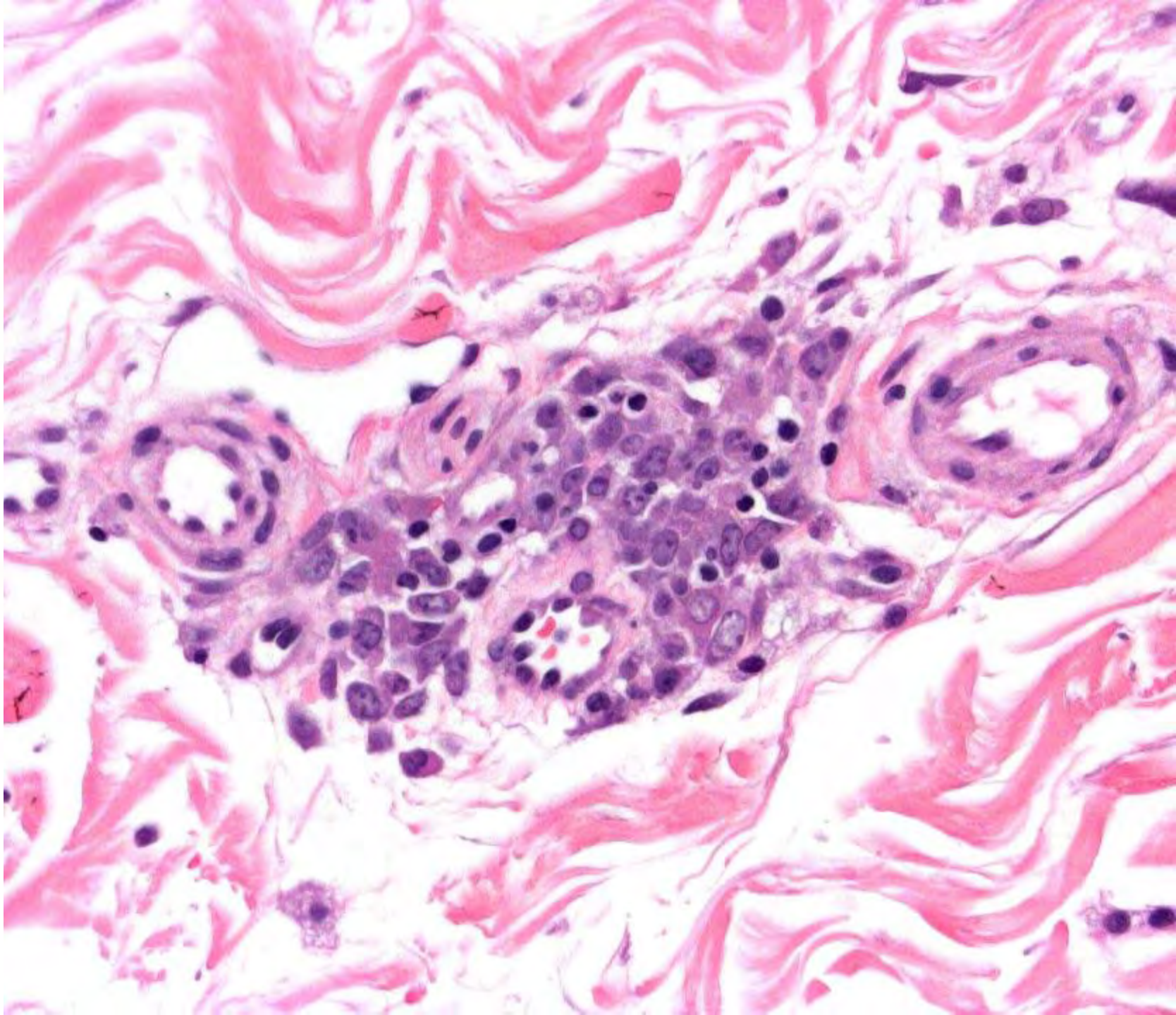


Specific cutaneous infiltrate of myeloid leukemia

Bone marrow: 80% infiltration

F, 56





Cutaneous Infiltrates of Acute Myelogenous Leukemia Simulating Inflammatory Dermatoses

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

Abstract: Some cases of specific cutaneous manifestations of acute myelogenous leukemia (AML) may mimic inflammatory dermatoses both clinically and histopathologically, presenting with an inconspicuous maculopapular eruption and with only sparse dermal infiltrates. The authors studied the histopathological and immunohistochemical features of 17 biopsies from 16 patients (11 men and 5 women, age range 15–85 years) presenting with minimal skin infiltrates as the first manifestation of AML or as first sign of recurrence after complete remission of the disease. In all cases, the diagnosis of leukemia has been confirmed by bone marrow examination. Two of these cases had been sent to one of us for second expert consultation. Patients presented with generalized, exanthematic maculopapular eruptions, sometimes with a hemorrhagic note, that were mostly interpreted clinically as drug reactions. Histopathologically, the lesions showed sparse, superficial, and mid-dermal infiltrates with minimal perivascular and periadnexal accentuation. Infiltrating cells consisted mostly of neoplastic monocytoid elements with only few reactive lymphocytes and histiocytes. Immunohistochemical stainings revealed in the majority of cases positivity for CD68 (14 of 16 patients), naphthol chloroacetate esterase (NaSDCl) (7 of 10 patients), and myeloperoxidase (6 of 9 patients). Other markers tested were positive only in a minority of cases. These cases represent a pitfall both in the clinical and in the histopathological diagnosis of cutaneous AML. Accurate morphologic and phenotypic correlation together with a high index of suspicion allows a precise diagnosis in these unconventional cases.

Key Words: acute myelogenous leukemia, CD68, inflammatory dermatoses

(*Am J Dermatopathol* 2013;35:419–424)

INTRODUCTION

Specific cutaneous infiltrates in patients with acute myelogenous leukemia (AML) show variable clinical and histopathological features,[1–4] sometimes deviating from the conventional presentation characterized by generalized papules, plaques, and nodules with histopathologically nodular/diffuse infiltrates.[5,6] Relatively mild dermal infiltrates of myelogenous cells have been observed in 11.6% of cases in a recent study.[7] Accurate identification of these cases is important for planning management, especially when skin lesions precede the onset of leukemia or when they represent the first sign of relapse after complete remission (CR).[4,8] Cases with minimal infiltrates may be mistaken for inflammatory dermatoses and represent a pitfall in the histopathological diagnosis of cutaneous manifestations of AML.

We studied histopathological and immunohistochemical features of specific cutaneous manifestations of AML with inconspicuous infiltrates, to identify diagnostic criteria in these difficult cases.

MATERIALS AND METHODS

The study has been conducted at the Research Unit Dermatopathology, Department of Dermatology, Medical University of Graz, Austria, and has been approved by the Ethic Committee of the University. Files were searched for skin specimens with diagnosis of cutaneous manifestations of AML from 1972 to June 2011. Cases presenting with histopathological features characterized by sparse infiltrates resembling inflammatory dermatoses were included in the study. In all cases, the diagnosis of leukemia had been confirmed by bone marrow examination. Cases characterized histopathologically by "conventional" nodular/diffuse infiltrates were excluded from the study. From a total of 108 cases of specific cutaneous manifestations of AML, 16 met the criteria and were included in the study. Two of these cases (cases 5 and 13) had been sent to L.C. for second expert consultation. Details of another case (case 8) have been published previously.[10]

Histopathological and Immunohistochemical Studies

A total of 17 biopsy specimens from the 16 patients were available for examination. Specimens were stained with hematoxylin and eosin and naphthol AS-D chloroacetate esterase (NaSDCl). All specimens were examined independently by 3 dermatopathologists (M.M.E., D.Z., and L.C.).

In cases with sufficient material, immunohistochemical studies using a panel of antibodies for myelogenous and lymphatic cells were performed (Table 1). A previously described standard 3-step immunoperoxidase technique with microwave enhancement was applied according to the manufacturer's protocol.[11] Tonsil tissue and normal skin structures served as external and internal controls, respectively. For

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The authors declare no conflicts of interest.

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TABLE 1. Clinical Data and Immunohistochemical Results

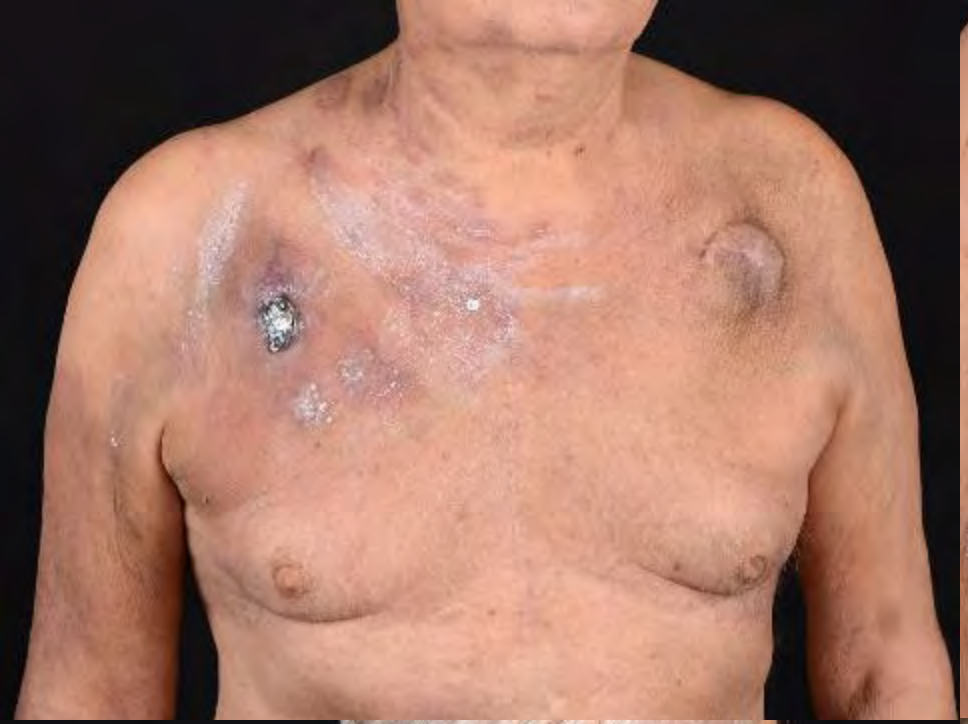
Case no.	Gender/Age	Provided Clinical Diagnosis	History of ML	Interval, Months	Follow-Up (Months)
1	M/81	Leukocytoclastic vasculitis	Yes (CR)	0	D+ (1)
2	M/62	Hemorrhagic drug reaction		18	D+ (32)
3	F/56	Sweet syndrome		1	A+ (19)
4	M/59	Drug reaction		0	A+ (25)
5	M/89	Granuloma faciale		0	A+ (1)
6	F/24	Eczema		3	A+ (14)
7	M/55	Extramedullary hematopoiesis	Yes (CR)	0	D+ (2)
8	M/81	Psoriasis		0	A+ (3)
9	F/31	No clinical diagnosis		2	A+ (6)
10	M/63	Drug reaction vs. specific manifestations of AML	Yes (CR)	0	D+ (26)
11	M/70	Rule out specific manifestations of AML	Yes (CR)	0	D+ (5)
12	M/72	Drug reaction	Yes (CR)	0	A+ (2)
13	F/15	Drug reaction		0	A+ (1)
14	F/27	Drug reaction vs. specific manifestations of AML	Yes (CR)	0	D+ (15)
15	M/55	No clinical diagnosis		1	A+ (5)
16	M/71	Drug reaction		0	A+ (1)

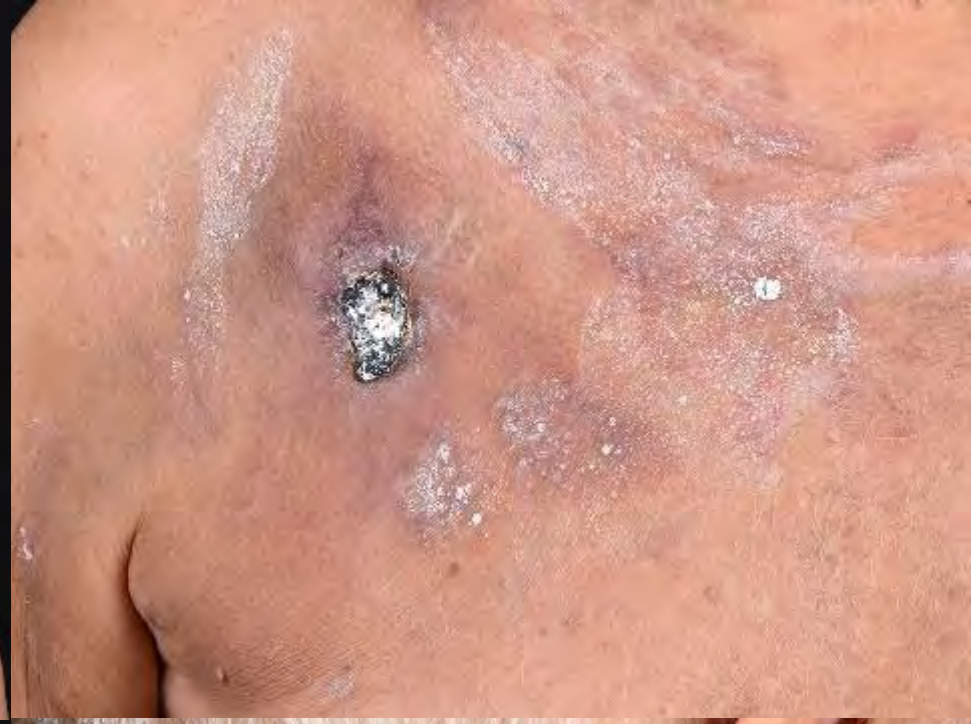
Case no.	CD13	CD15	CD33	CD34	CD68	CD117	MPO	NaSDCl	CD56	CD123
1	–	–	+	+	+	–	ND	–	+	–
2	–	–	–	ND	+	–	ND	ND	ND	ND
3	–	–	–	–	+	–	ND	+	–	–
4	+	ND	ND	ND	–	ND	–	ND	–	+
5	ND	ND	ND	ND	+	ND	+	ND	ND	ND
6	–	–	+	–	+	–	ND	+	–	–
7	–	–	+	–	+	ND	+	+	+	–
8	–	–	–	–	+	–	+	ND	–	–
	–	–	–	–	+	–	ND	+	–	–
9	–	–	+	–	–	–	ND	+	+	–
10	–	–	–	+	+	–	+	+	+	–
11	–	–	–	–	+	+	–	–	–	–
12	ND	ND	ND	ND	+	ND	ND	ND	ND	ND
13	ND	ND	ND	ND	ND	ND	+	ND	ND	ND
14	–	–	–	–	+	–	ND	ND	–	–
15	–	–	+	+	+	–	+	+	–	–
16	–	ND	–	ND	+	ND	–	–	ND	ND

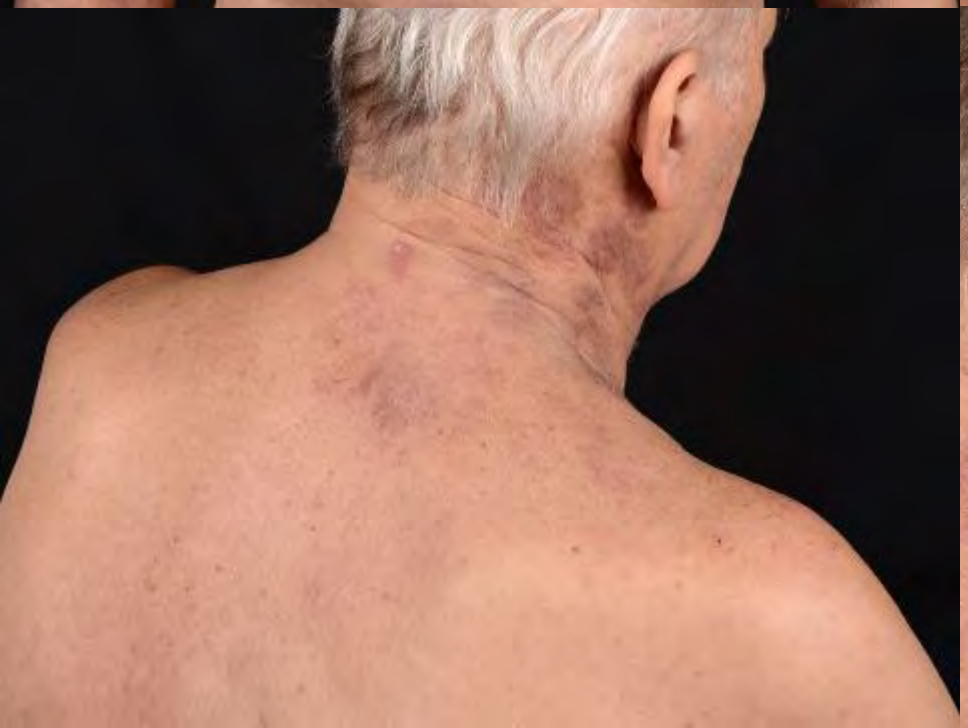
A+, alive with systemic leukemia; D+, dead of leukemia; F, female; interval, interval between skin biopsy and diagnosis of systemic leukemia; M, male; ML, myelogenous leukemia; MPO, myeloperoxidase; NaSDCl, naphthol chloroacetate esterase; ND, not done.

Inflammatory dermatitis-like specific skin infiltrates of myelogenous leukemia

- Represent oft the first manifestation of recurrent disease in patients with AML in complete remission
- Generalized rash mimicking clinically a drug or viral eruption
- Sparse perivascular infiltrate of mononuclear cells with morphological atypia; focal layering, splaying of collagen bundles ("Indian filing")
- The phenotype may be different from that of the original leukemia; sometimes "CD68+ only" perivascular and interstitial "dermatitis" (nuclear atypia and lack of "rosetting" allows distinction from interstitial granulomatous dermatitis)
- Rapidly progressive disease







M, 67

History of nodal FCL 6 years before presentation; (1999); 4 years later progression, treated with R-CHOP.

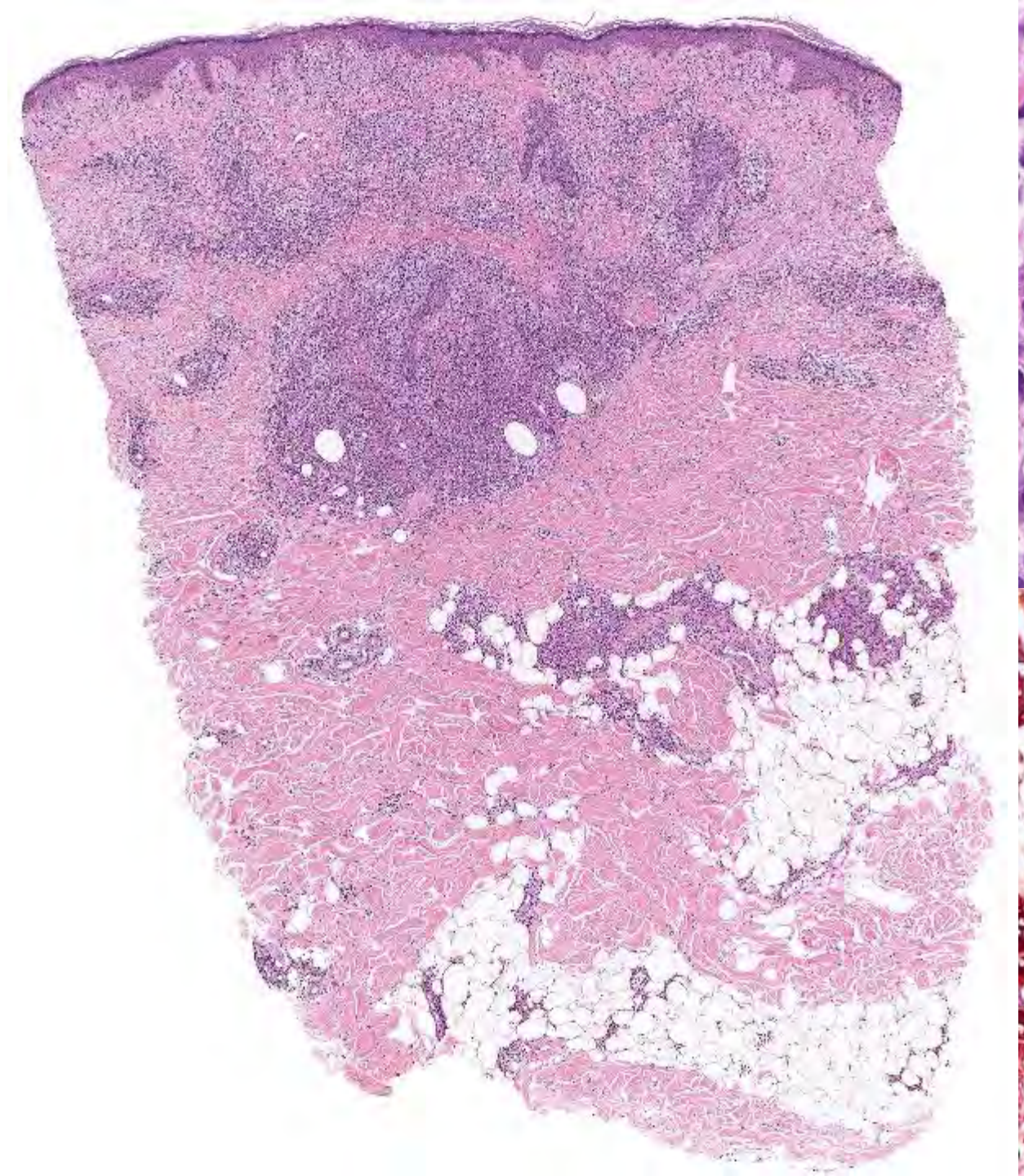
MDS discovered after treatment; one year later evolution into AML.

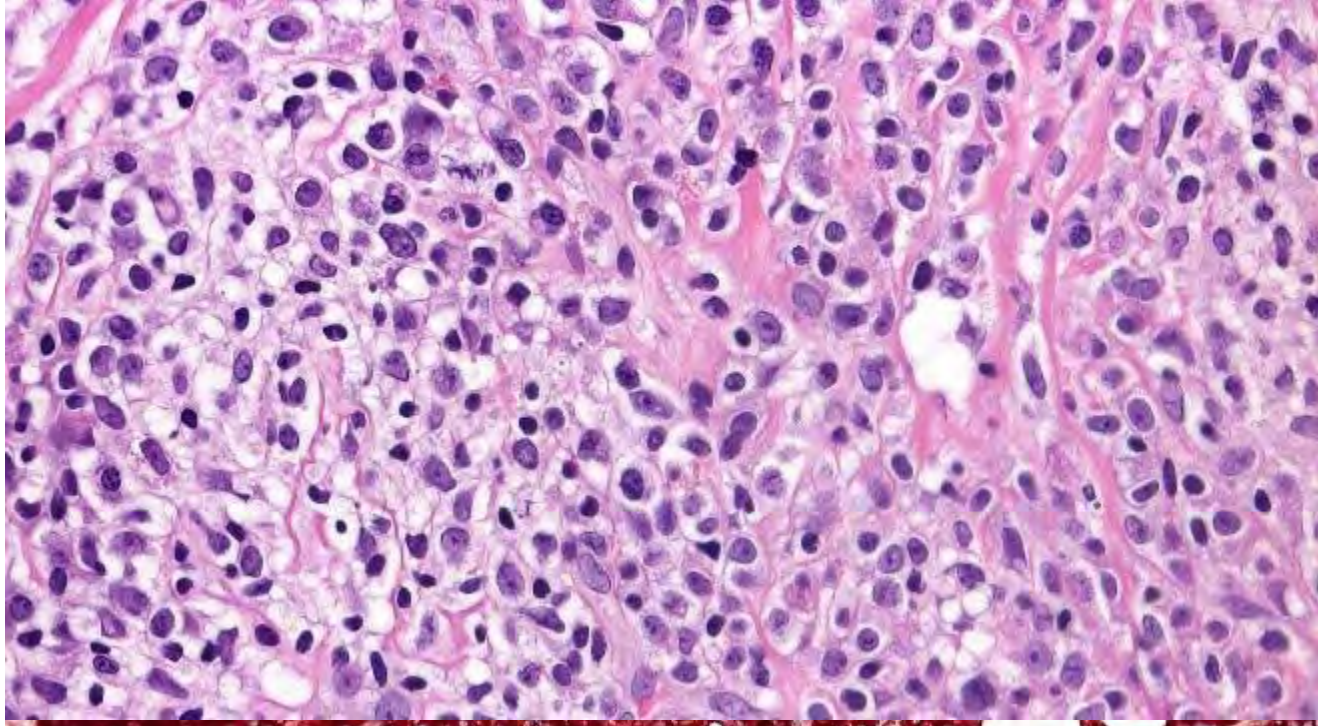
Best supportive care.

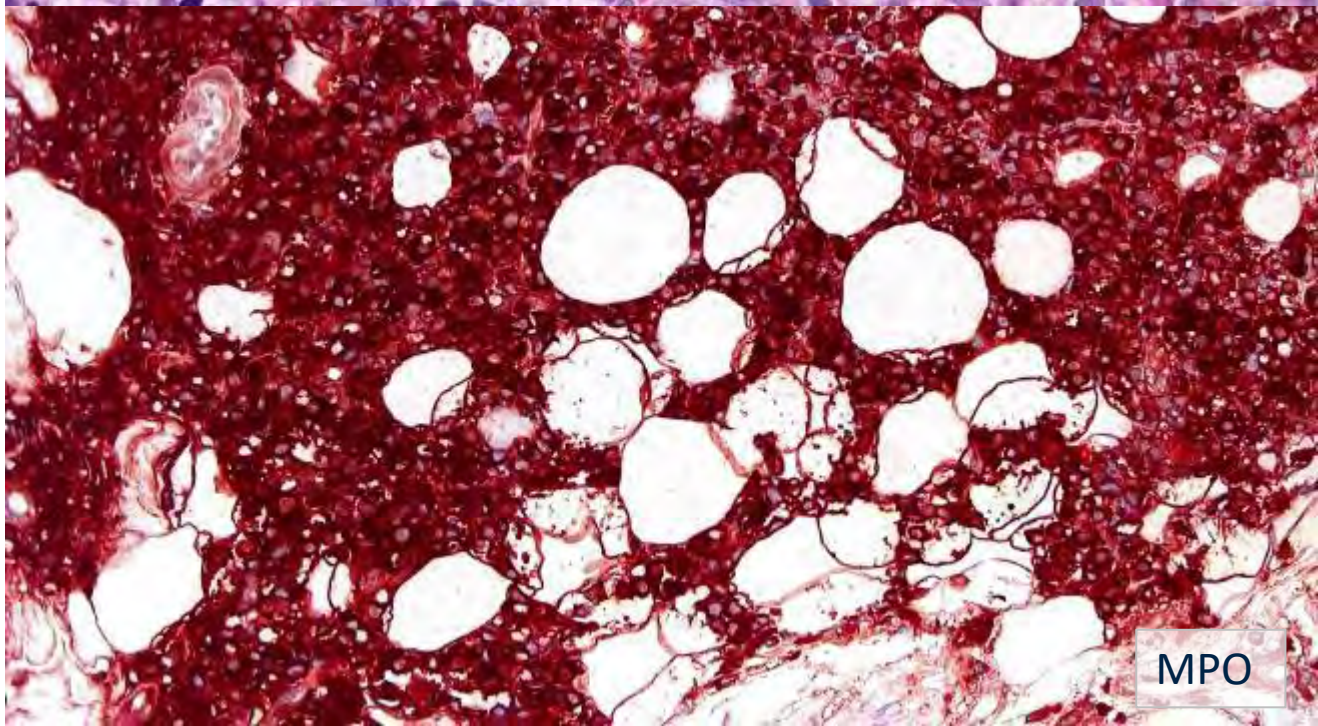
Herpes zoster cervico-thoracal dx.

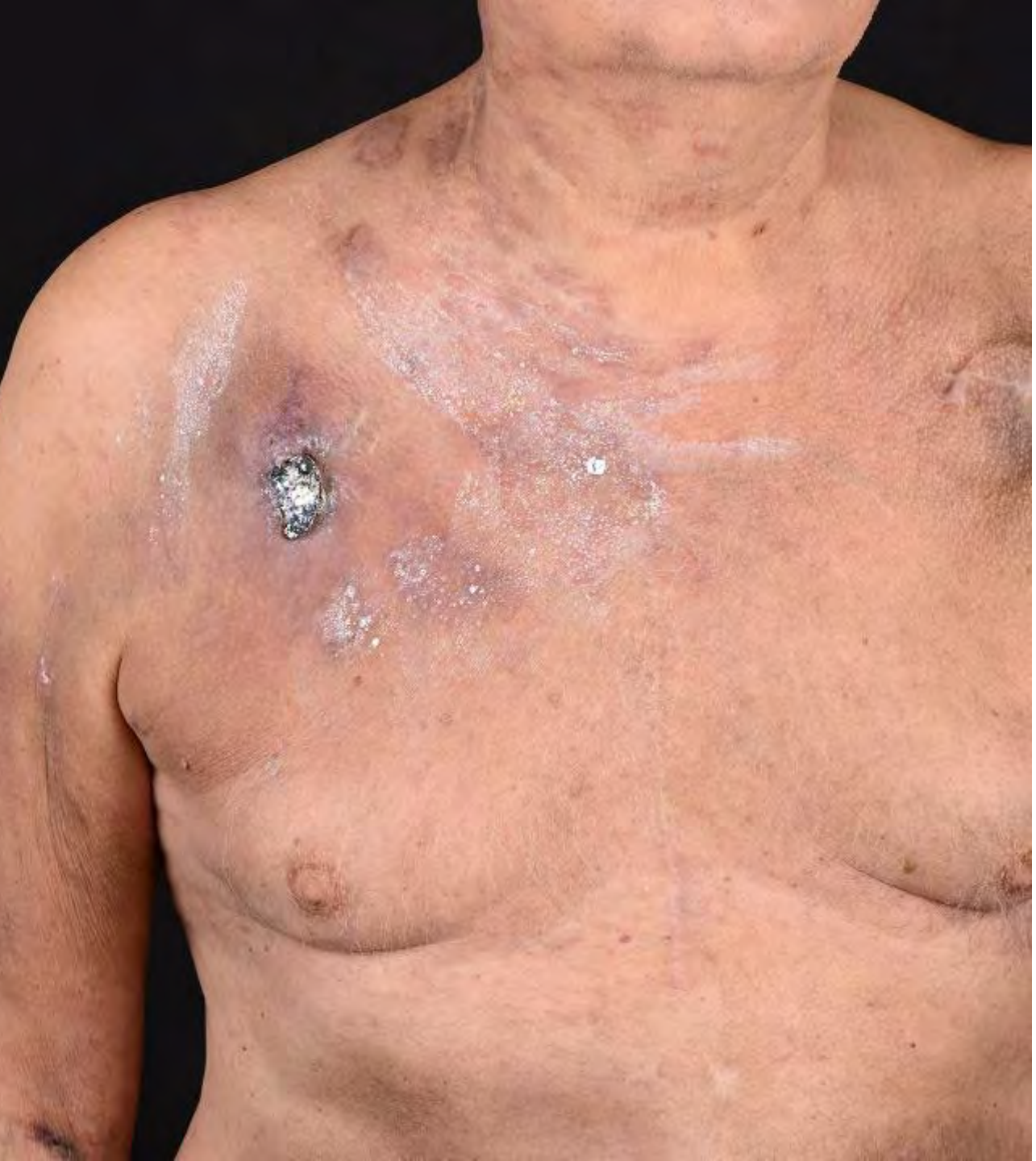
No improvement under anti-viral treatment (lesions become more infiltrated).

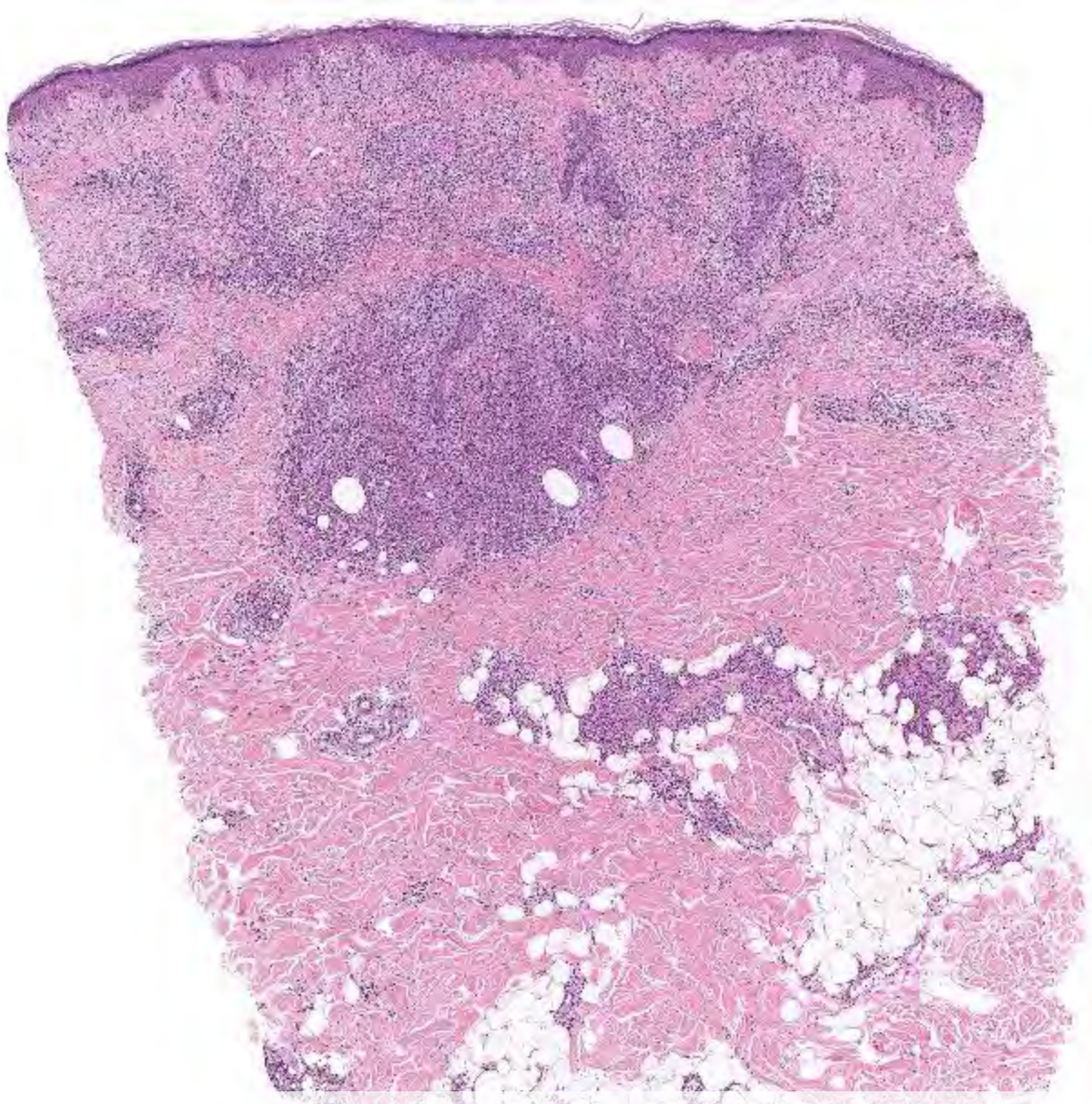
A biopsy is taken.






MPO

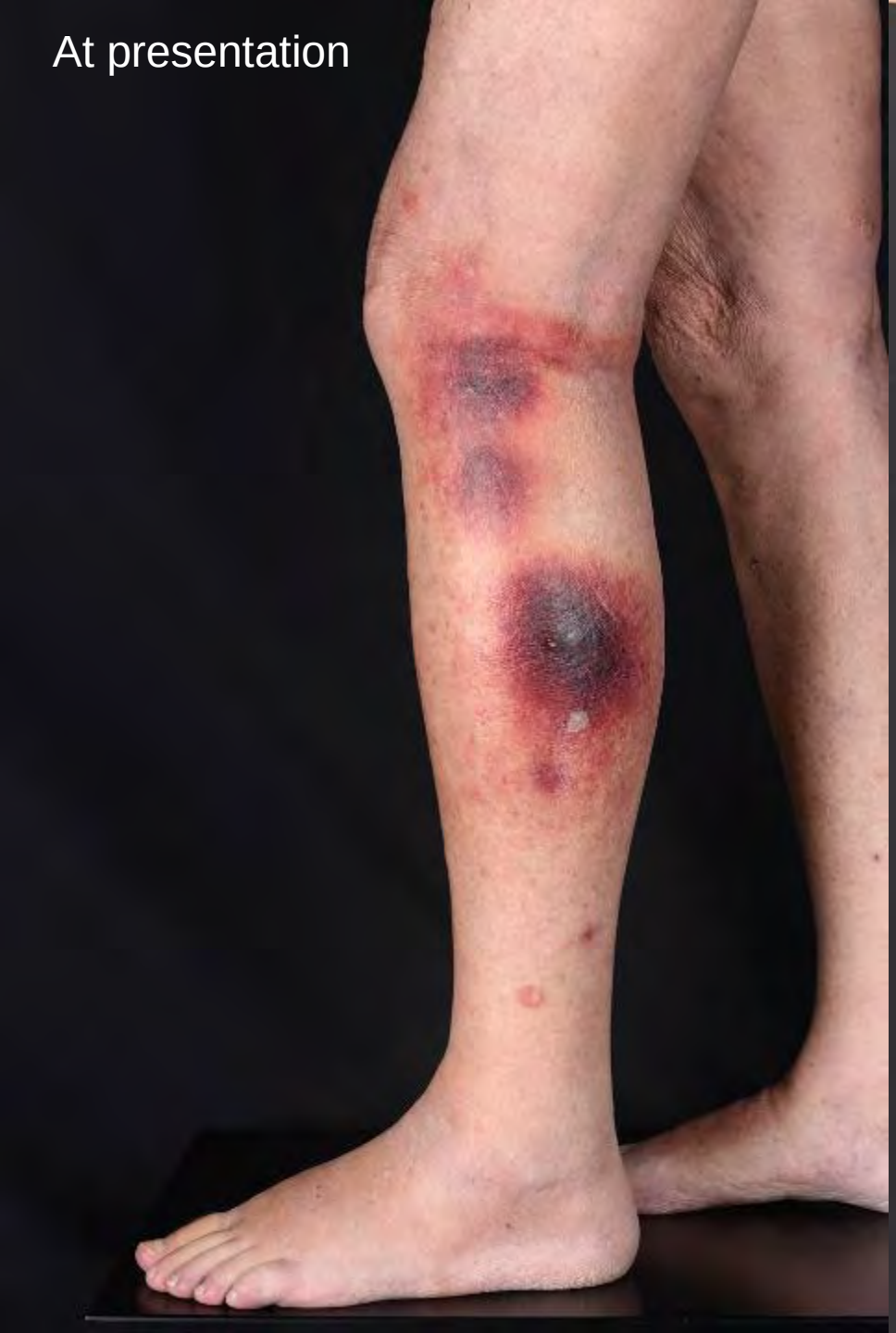


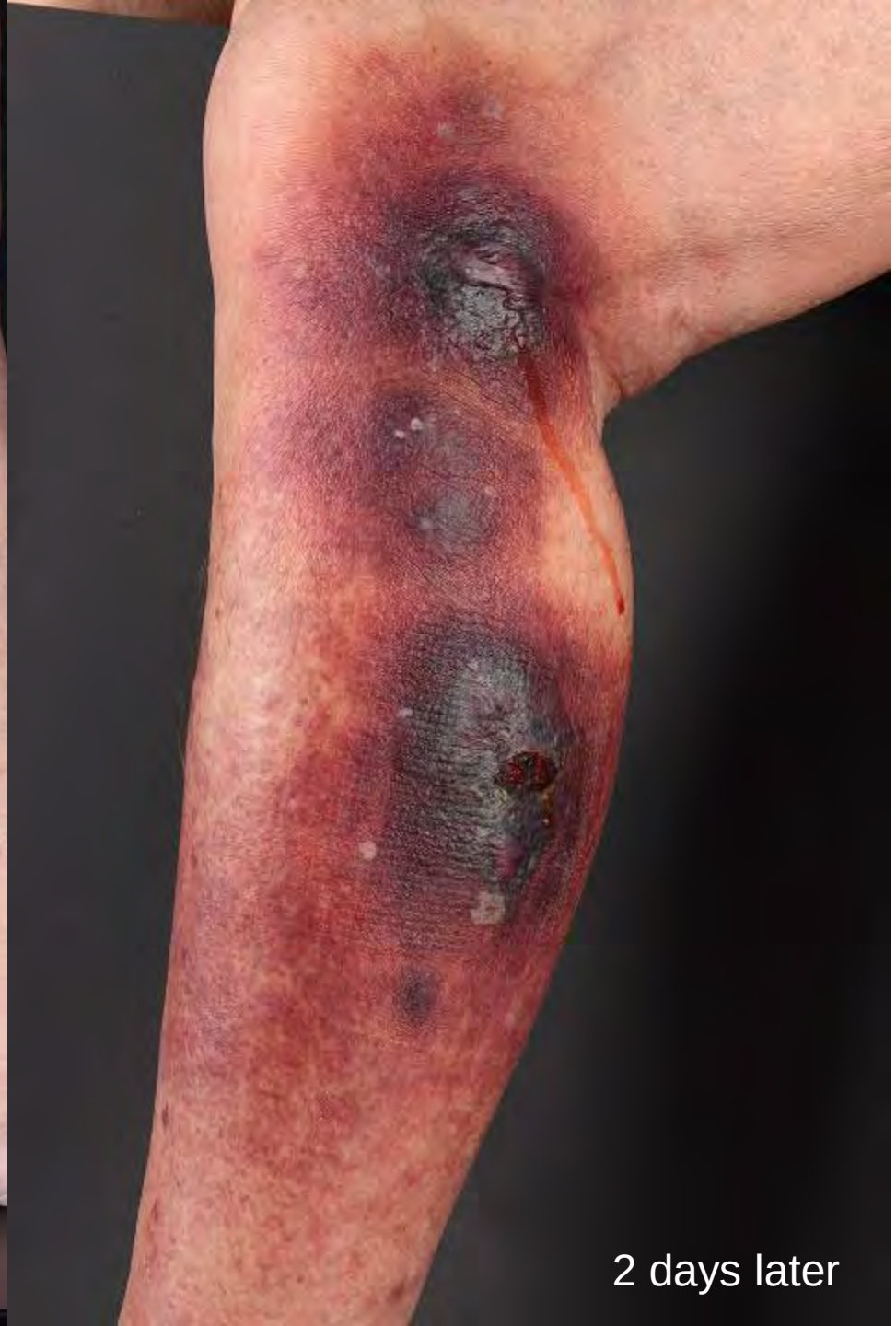


Specific infiltrate of myelogeneous leukemia at the site of *herpes zoster*

Post-zoster infiltrates

- Granulomatous infiltrates (different types)
- Pseudolymphomatous infiltrates
- Specific manifestations of B-CLL
- Specific manifestations of other haematological malignancies
- Cutaneous metastases of solid tumors *(in some cases "zosteriform" arrangement without previous history of H. zoster)*
- Rarely Koebner phenomenon at the site of previous *H. Zoster (e.g., psoriasis)*





SA 2025

M, 88

According to the patient sudden onset of purpuric lesions on the left leg.

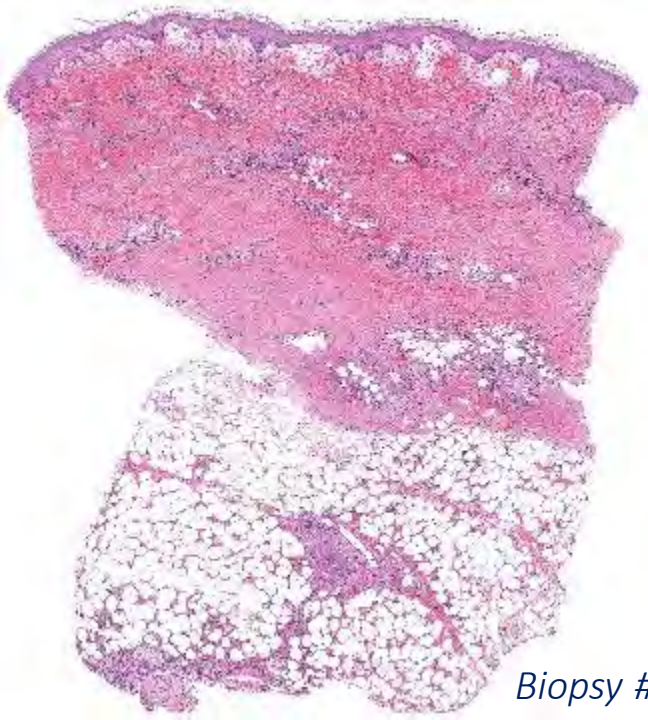
Fever, malaise.

Pancytopenia, LDH 420 (120-240), CRP 16,1 (0-5).

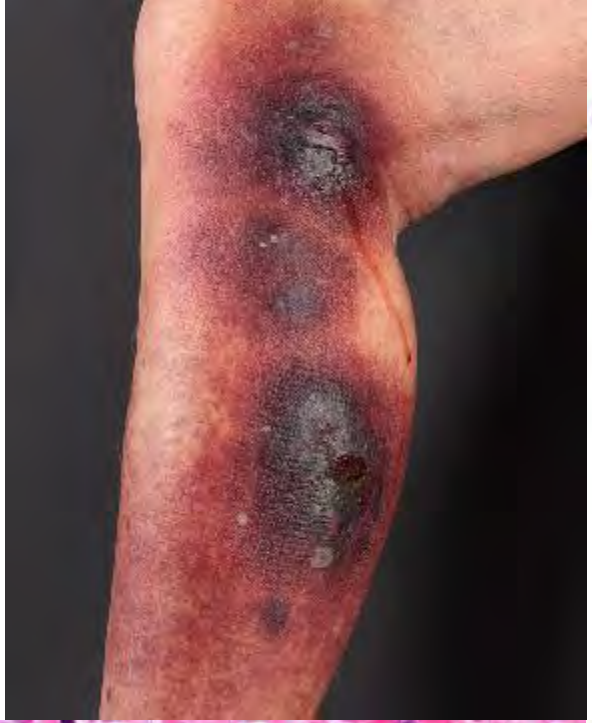
Platelets: 19 g/l (140-400).

Bacterial smear: *St. aureus.*

Two biopsies are taken.



Biopsy #1



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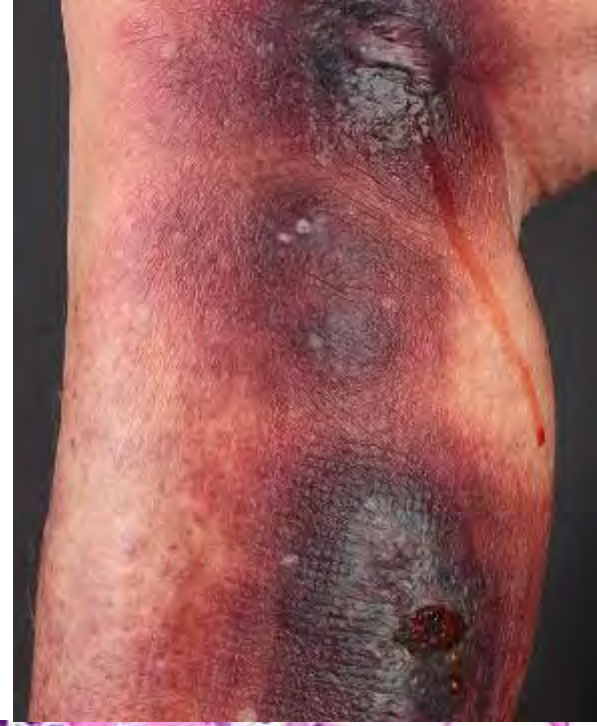
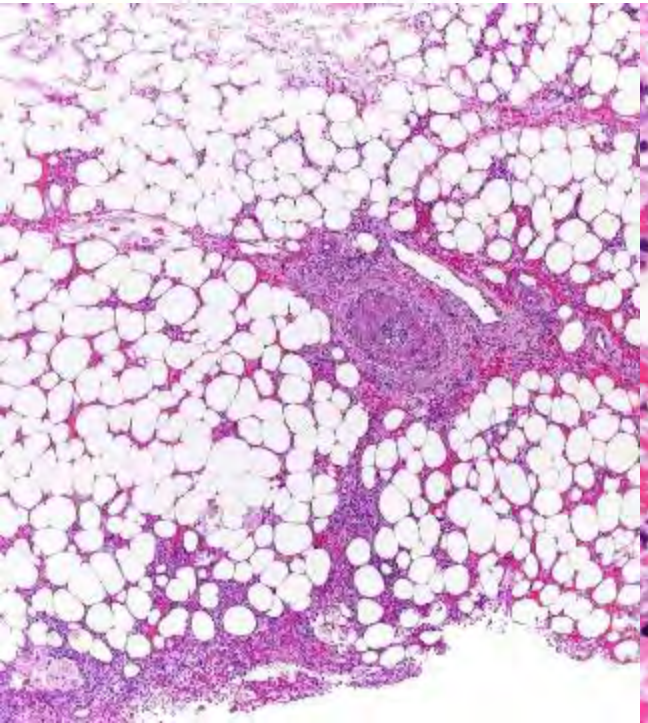
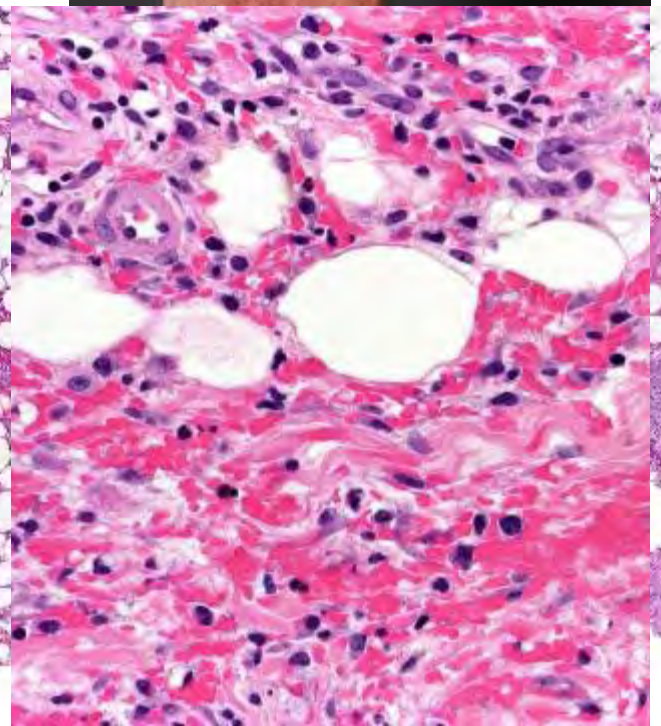
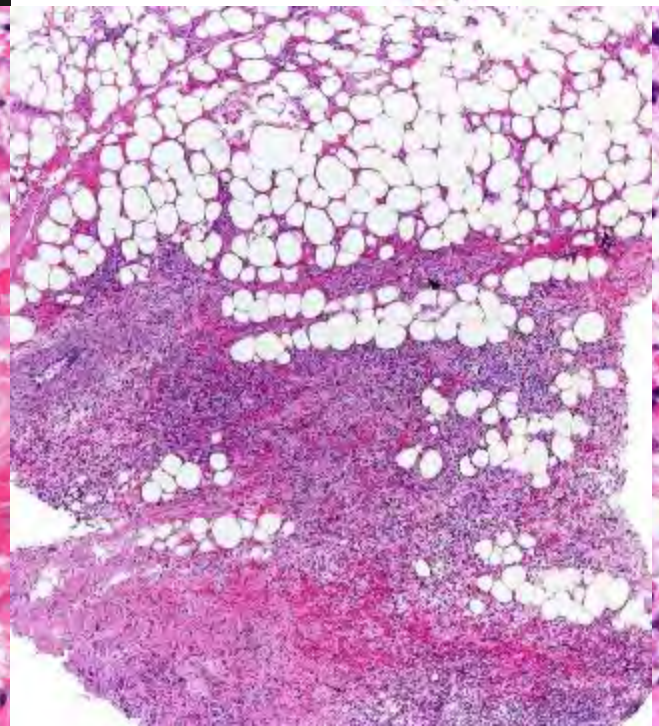
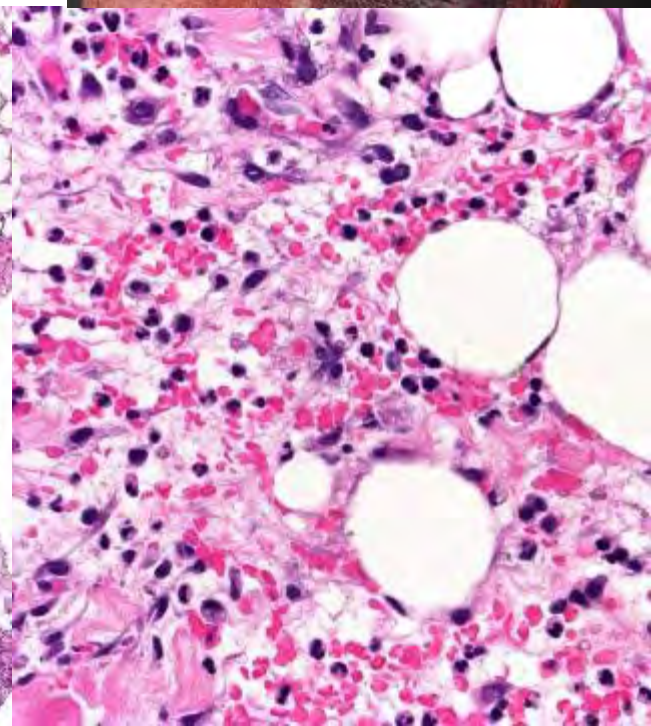
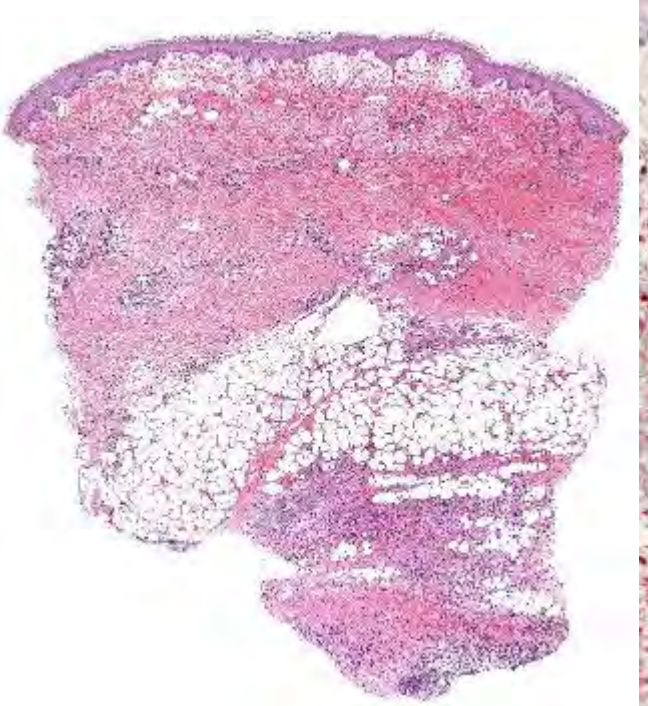


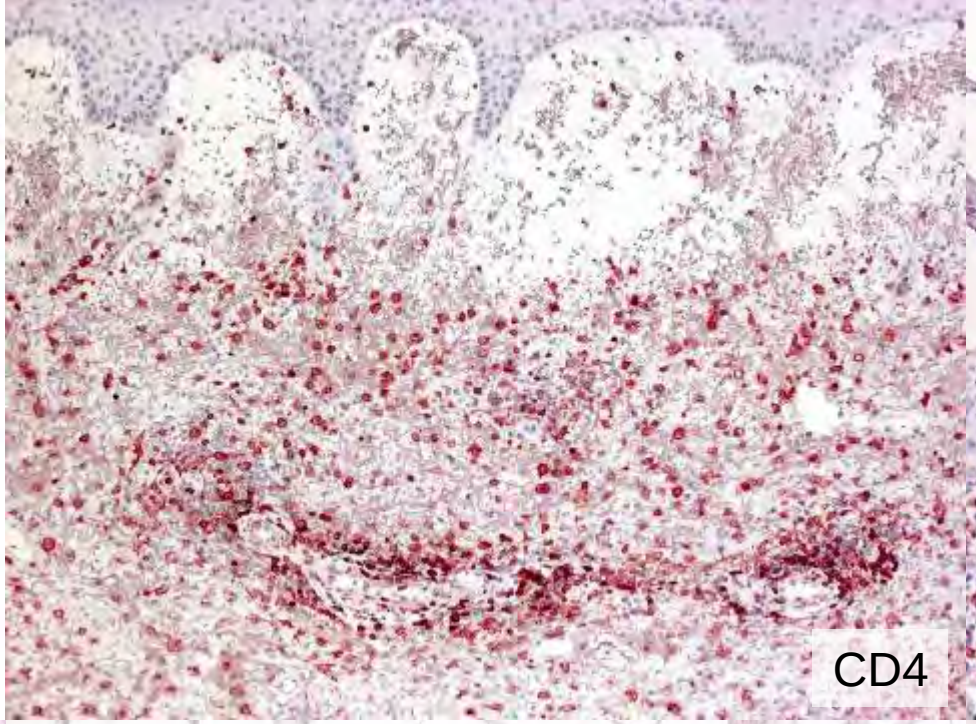


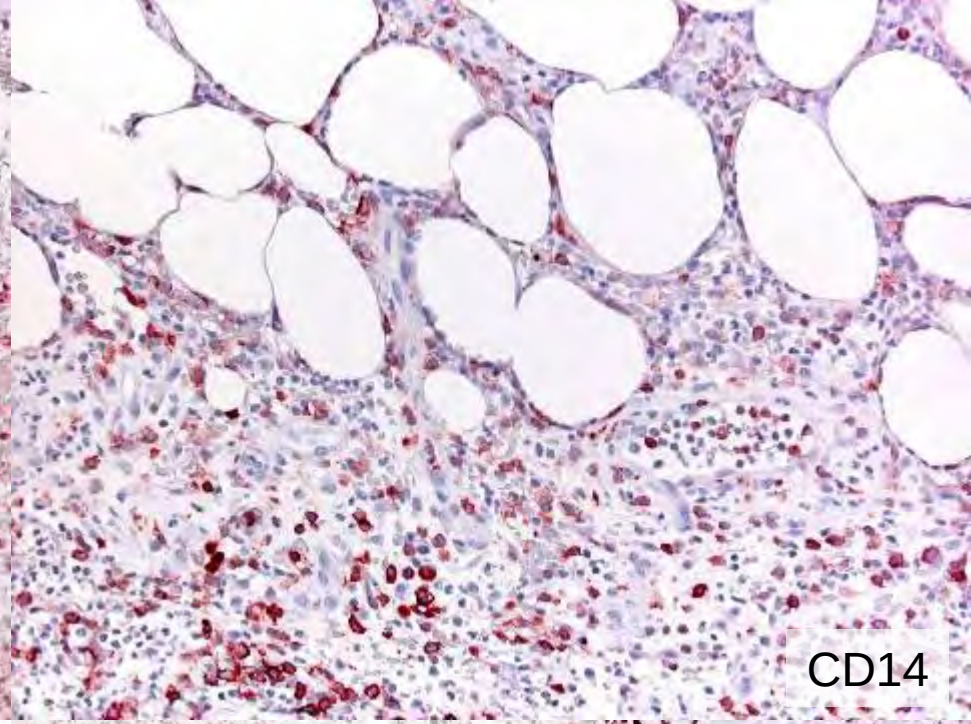




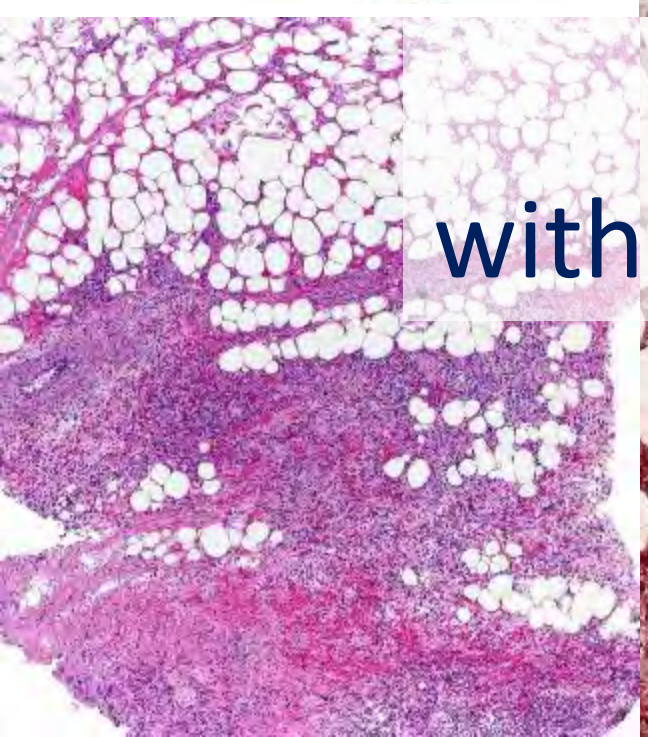


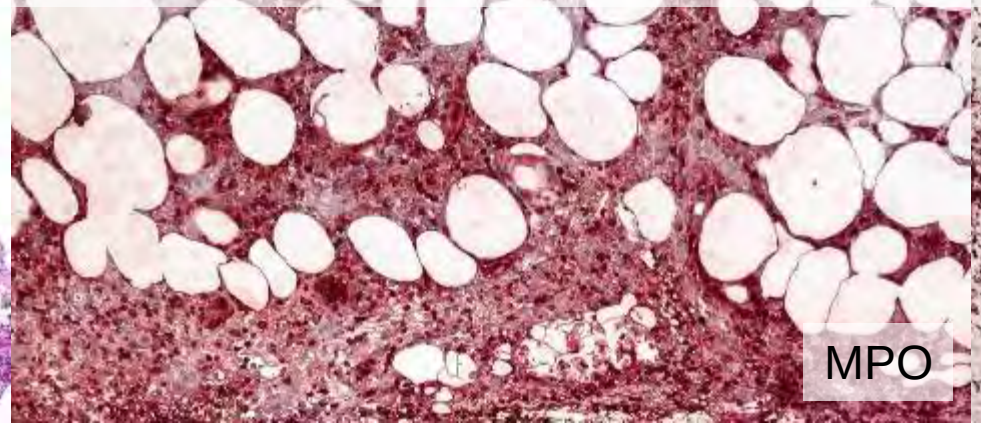


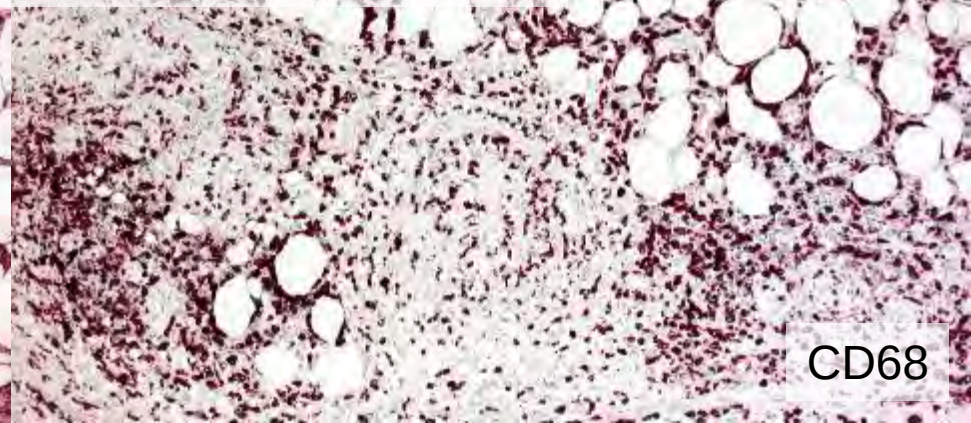


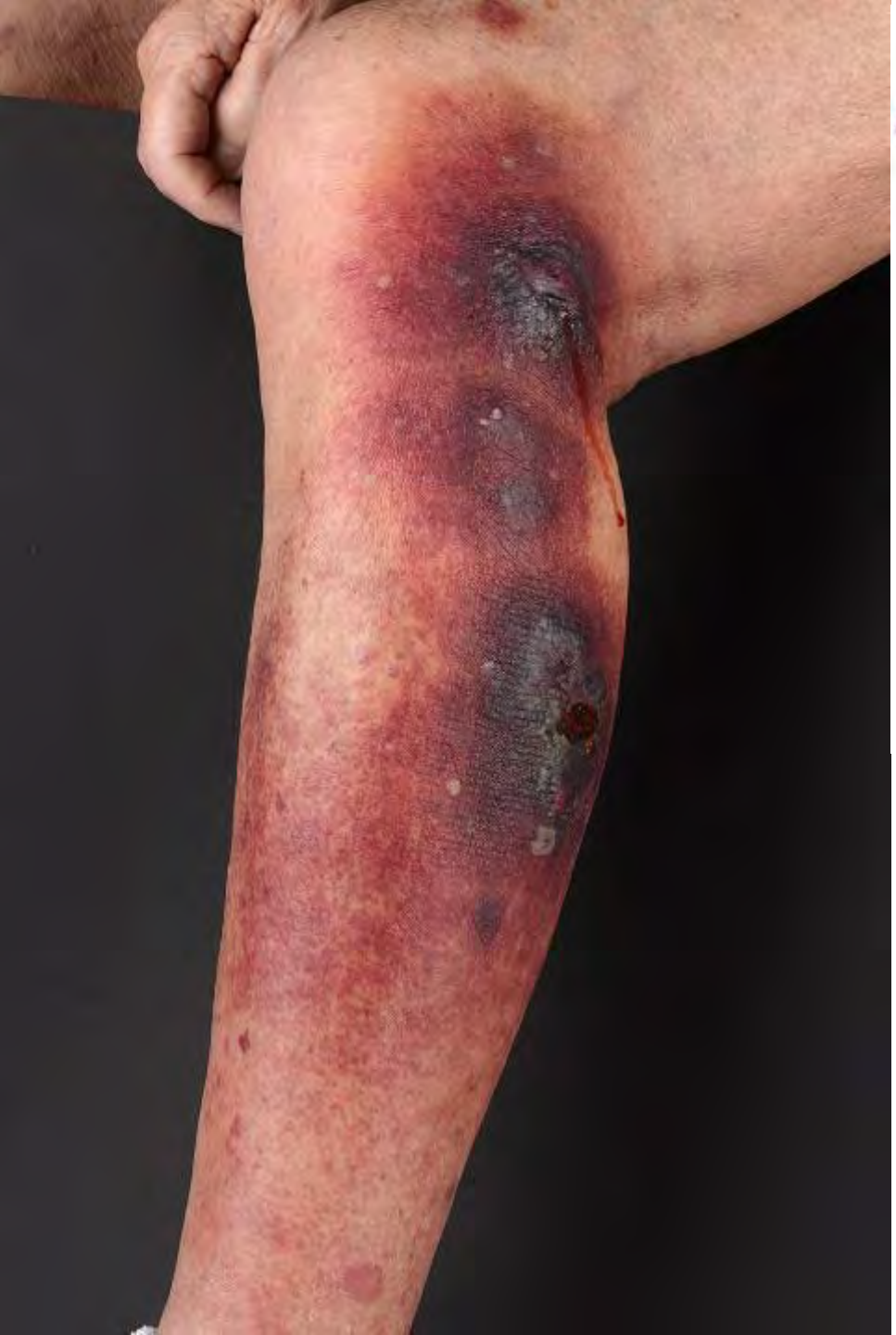


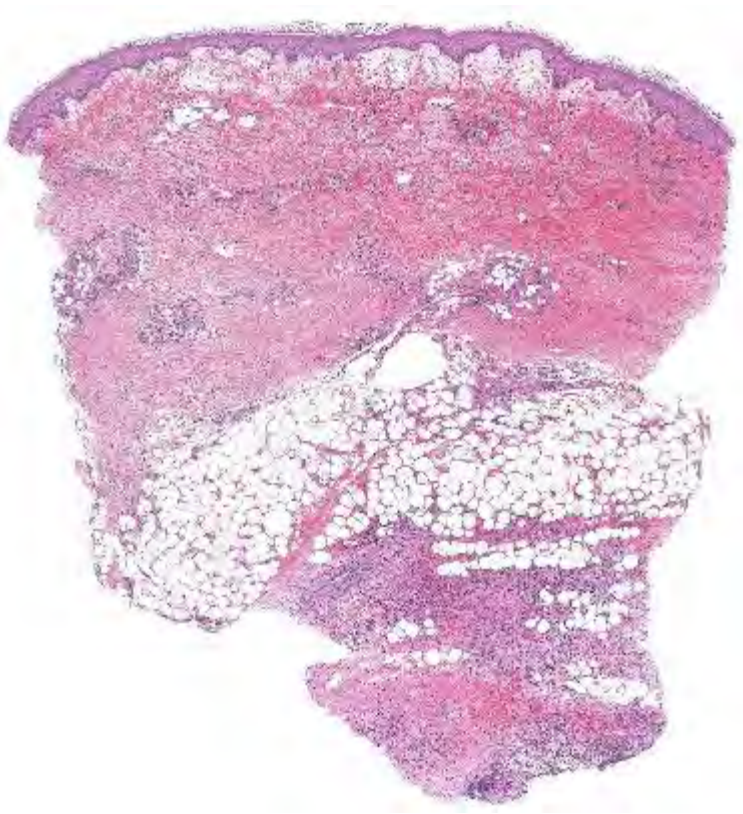
Hemorrhagic erysipelas with atypical myelo-monocytic cells

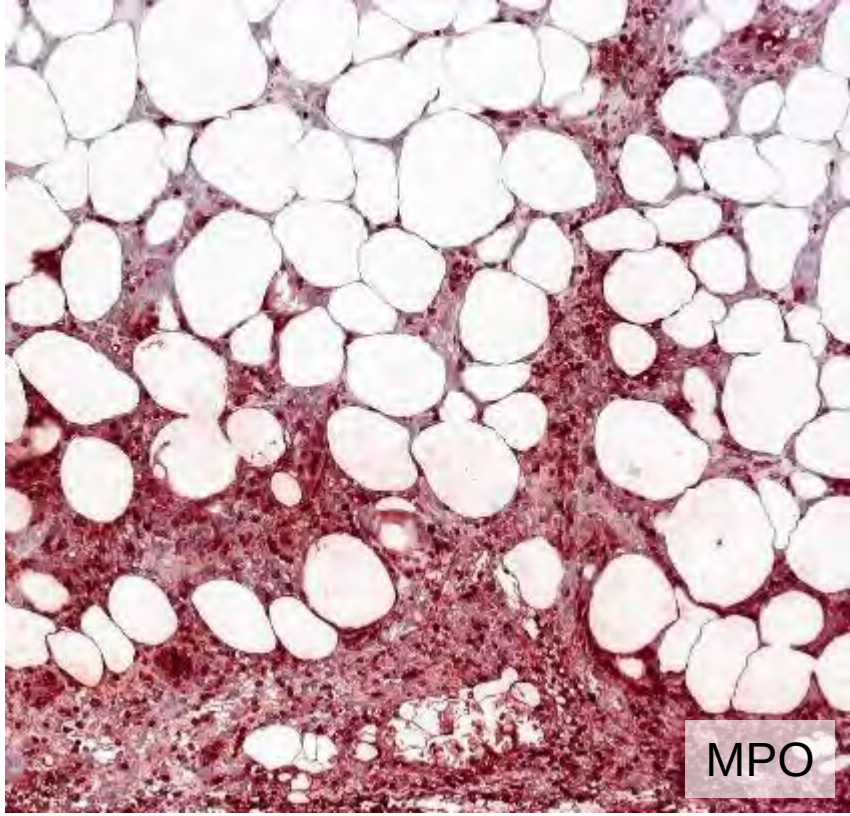










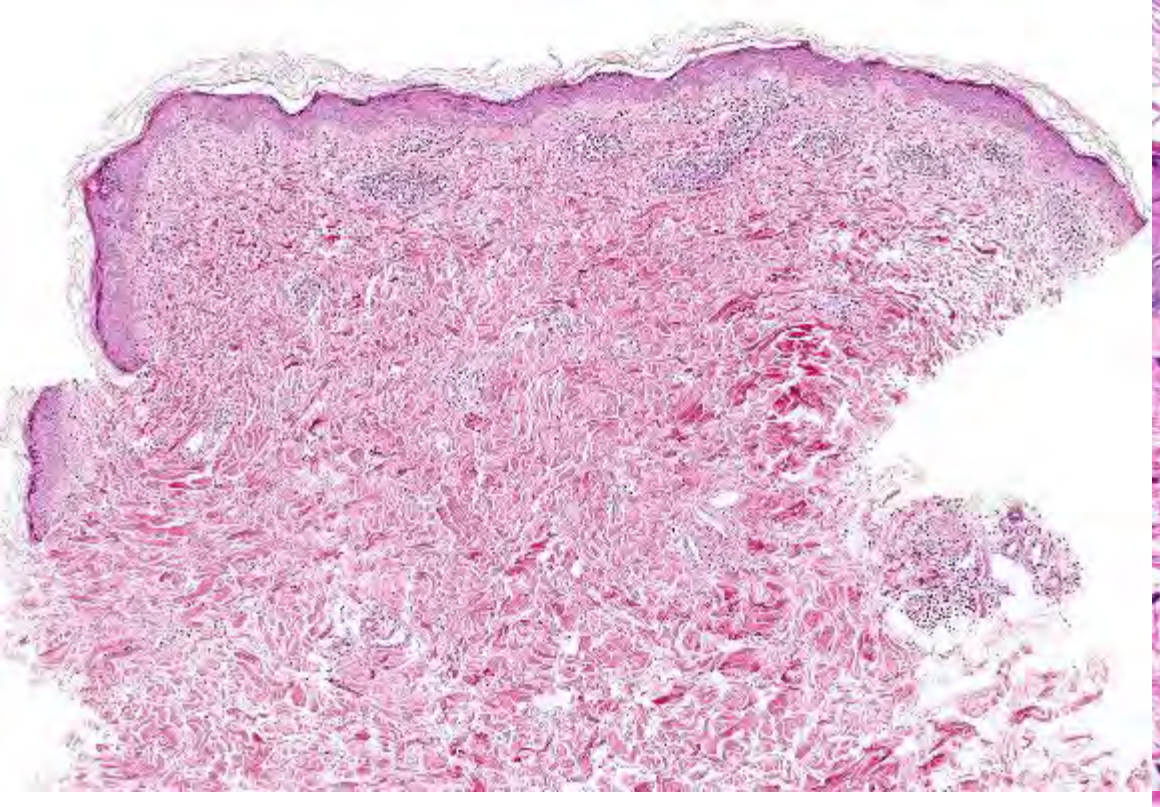


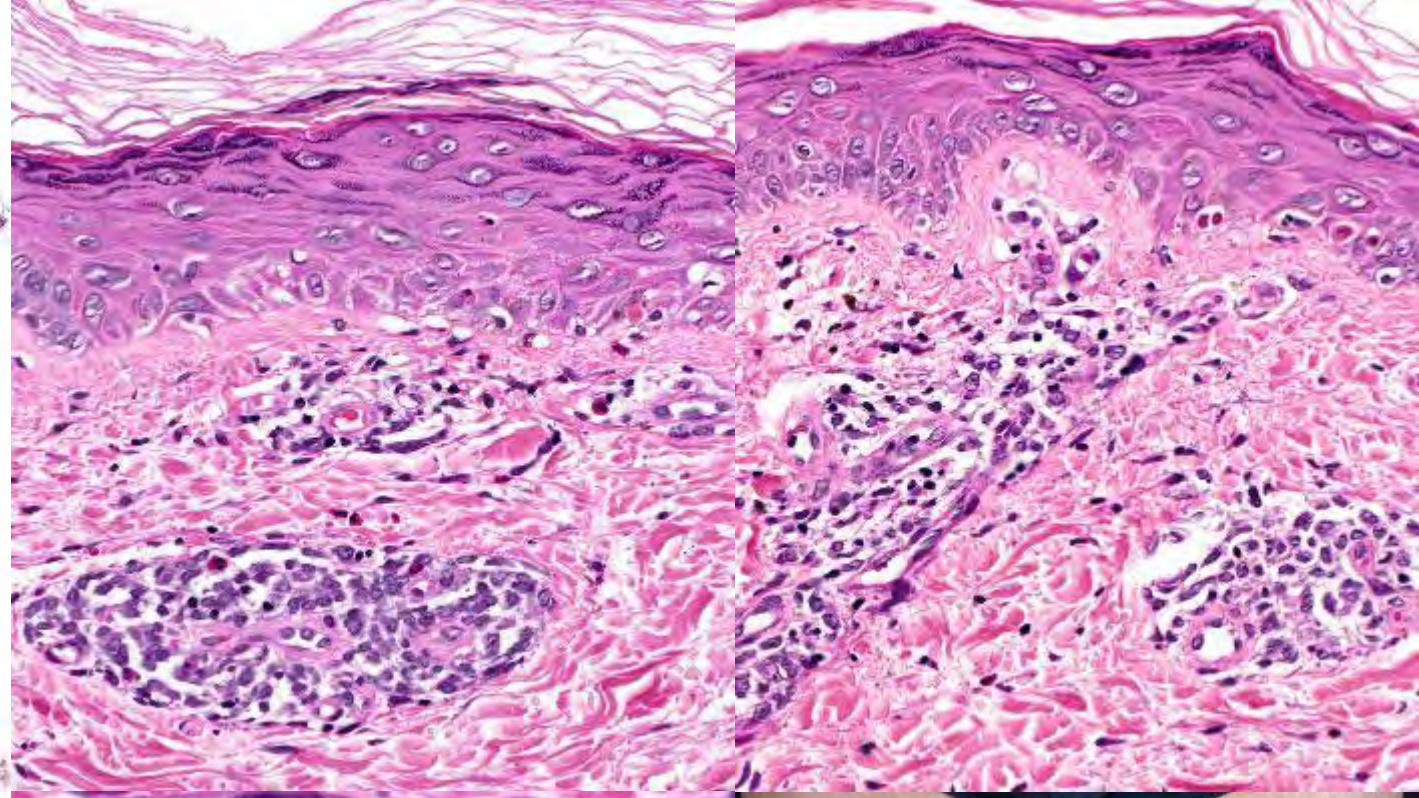
5 months later:

Myelodysplastic syndrome with evolution in acute myeloid leukemia.

Death 5 months after first presentation.

Heavy mononuclear infiltrates are not typical of erysipelas, and a reason for concern; investigation for an associated myeloid disorder is mandatory.





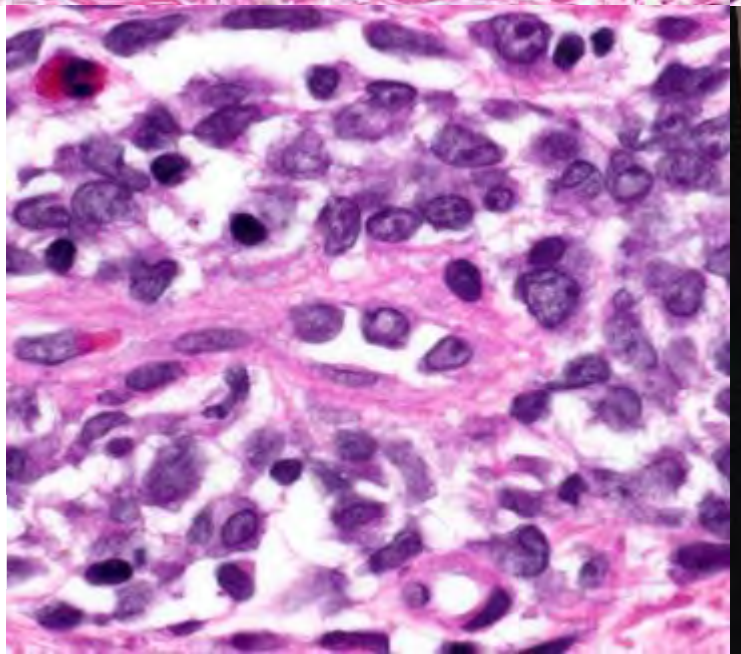
(Summer Academy 2025, SA case #9)

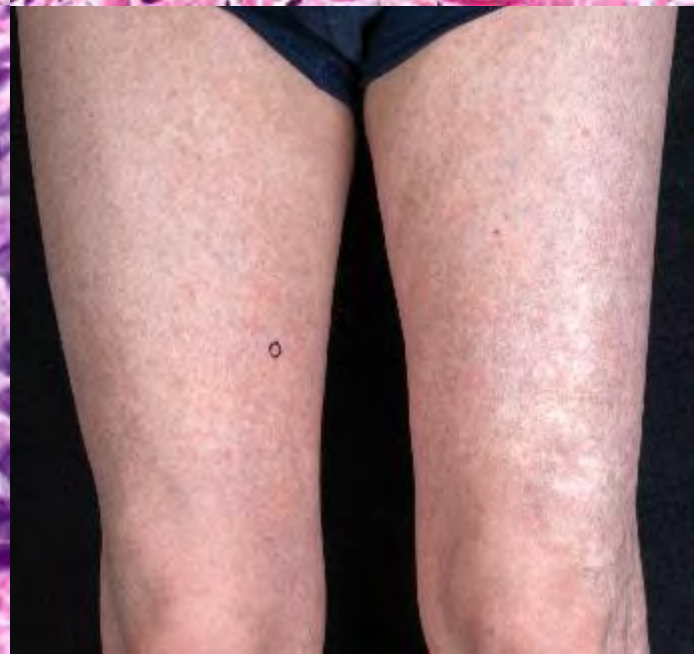
M, 48

History of AML (myelodysplasia-associated; 1st diagnosis 6 months previously). Allogeneic stem cell Tx (day +53).

Itchy skin lesions for 7 days.

Specific infiltrate of AML at the site of GVHD





J Cutan Pathol 1997: 24: 445–448
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Journal of
Cutaneous Pathology
ISSN 0303-6987

Leukemic cells within skin lesions of psoriasis in a patient with acute myelogenous leukemia

Gisela Metzler[1], Lorenzo Cerroni[2], Helmut Schmidt[3], H. Peter Soyer[2], Heinz Sill[3] and Helmut Kerl[2]

[1]Department of Dermatology, University of Tübingen, Germany, and Departments of [2]Dermatology and [3]Internal Medicine, University of Graz, Austria

We report on an 81-year-old man with acute myelo-monocytic leukemia (FAB M4) and a long-standing history of psoriasis. Biopsy of psoriatic plaques revealed the coexistence of characteristic histopathologic aspects of psoriasis together with an infiltrate of blasts with features of myelo-monocytes, suggestive of a specific leukemic infiltrate within plaques of psoriasis. Immunohistologic stainings showed positivity of blasts for LN2 (CD74), MT1 (CD43), and lysozyme, consistent with a myeloid lineage of these cells. To the best of our knowledge, this is the first report on the association of psoriasis with myelogenous leukemia. The presence of leukemic cells within psoriatic skin plaques may be explained by non-specific recruitment of recirculating malignant cells to the skin. Alternatively, as psoriasis is an inflammatory disease involving granulocytes among other cell types, it may be hypothesized that leukemic cells retain to some extent their capability to respond to physiologic stimuli and enter the skin in response to specific chemotactic factors.

Metzler G, Cerroni L, Schmidt H, Soyer HP, Sill H, Kerl H. Leukemic cells within skin lesions of psoriasis in a patient with acute myelogenous leukemia
J Cutan Pathol 1997: 24: 445–448. © Munksgaard 1997.

Lorenzo Cerroni, M. D., Department of Dermatology, University of Graz, Auenbruggerplatz 8, A-8036 Graz, Austria

Accepted February 21, 1997

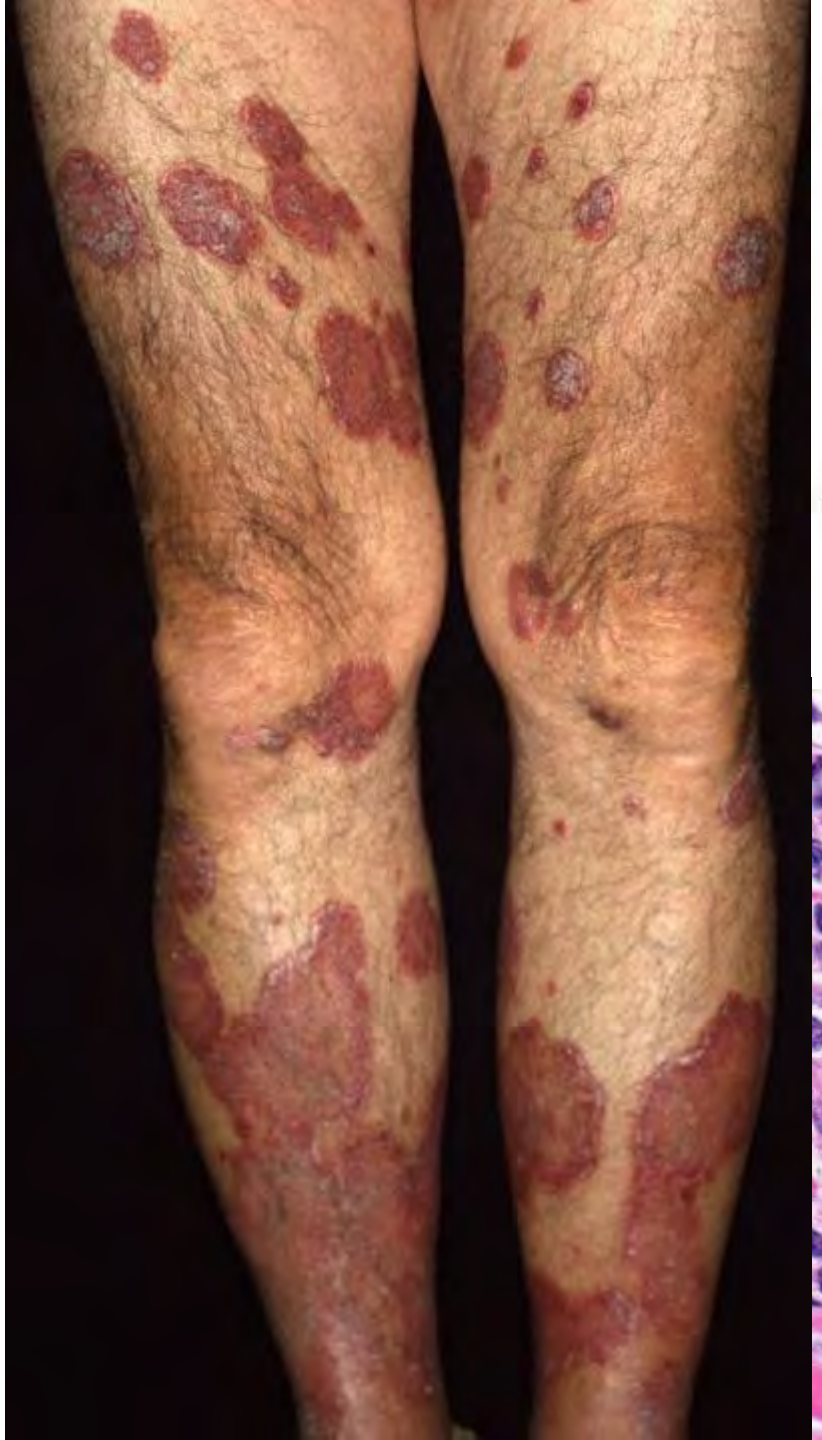
Specific skin involvement can be observed in more than 10% of patients with acute myelogenous leukemia (AML) (1). Clinical manifestations are usually characterized by generalized erythematous papules, plaques or nodules. Skin infiltrates may precede, be concomitant with or arise after leukemic blood involvement. We describe a patient with acute myelo-monocytic leukemia presenting with infiltrates of leukemic cells within skin lesions of psoriasis.

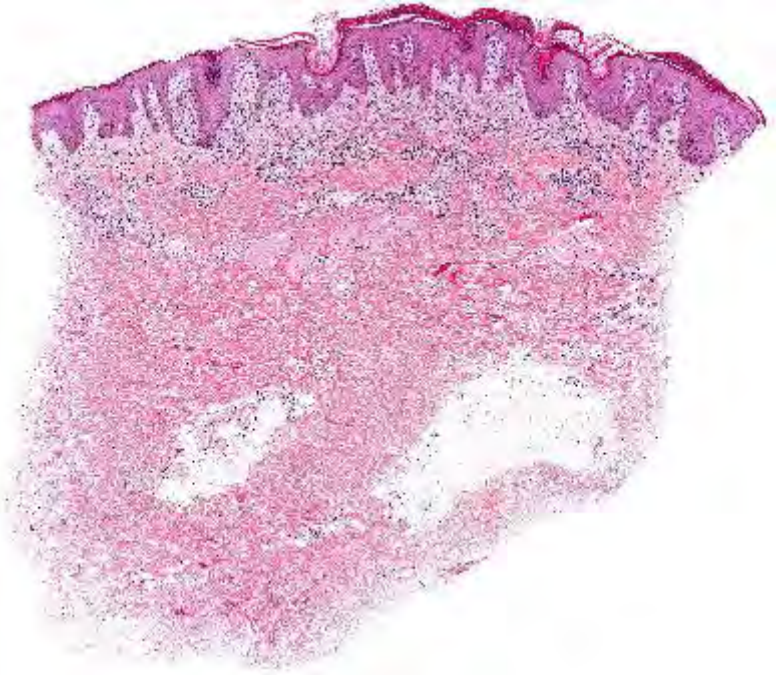
Case report

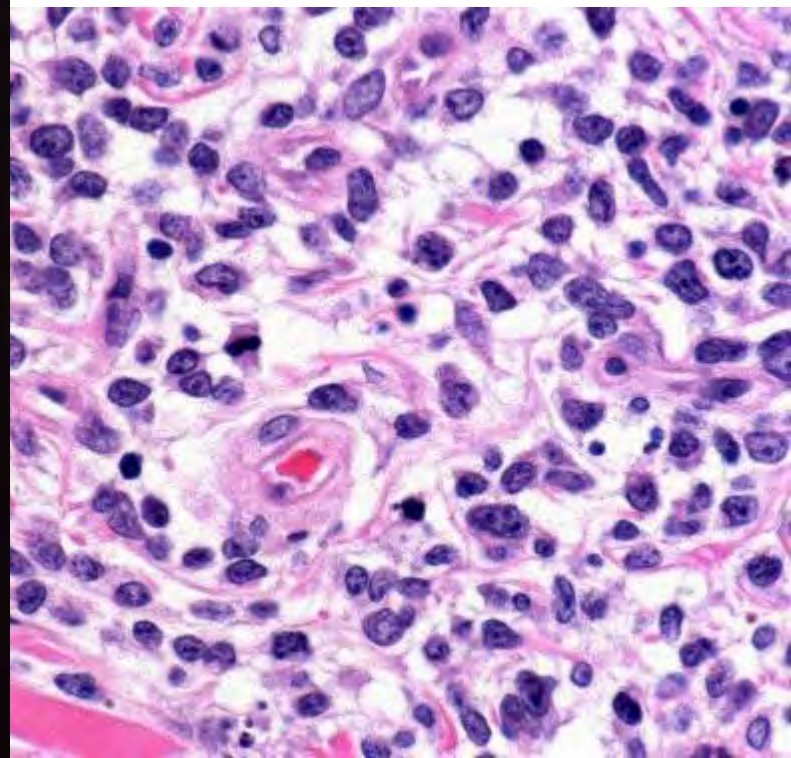
An 81-year-old man with a long-standing history of psoriasis localized to the elbows presented with increasing fatigue, anemia and leucocytopenia. Bone marrow examination showed diffuse infiltration of myelomonocytic blast cells positive for CD13, CD14, CD15 and CD33. According to these findings, a diagnosis of AML (FAB-M4) was made. Due to the advanced age no chemotherapy was administered, and the patient was followed-up at short intervals.

At the same time, the patient experienced a sudden generalization of psoriasis with manifestations on previously uninvolved skin such as the trunk and both lower extremities (Fig. 1). In order to rule out uncommon skin infiltrates of myelo-monocytic leukemia, three 4-mm punch biopsies were obtained from lesions on both lower legs. Specimens were fixed in 4% buffered formalin and embedded in paraffin for routine histopathologic and immunohistochemical studies.

Histopathology. All three skin biopsies revealed similar histopathologic features. The epidermis showed a marked psoriasiform acanthosis (Fig. 2). Neutrophils could be observed within both the epidermis and a parakeratotic horny layer. Dermal papillae were elongated and characterized by the presence of dilated, tortuous blood vessels (Fig. 2). In the upper dermis there was a relatively dense infiltrate composed of lymphocytes and histiocytes mingled with numerous medium-sized and large atypical mononuclear cells (Fig. 3). Cytomorphology of atypical cells was characterized by irregular nuclei with prominent nucleoli and







Stasis dermatitis-like leukaemic infiltration in a patient with myelodysplastic syndrome

CLINICAL REPORT

Myeloid Sarcoma Developing in Pre-existing Pyoderma Gangrenosum

LETTER TO THE EDITOR

Leukemia cutis is an early sign of blast transformation that may mimic a common skin disease: Sycosis-like eruptions in chronic myelomonocytic leukemia

LETTER TO THE EDITOR

Leukemia cutis limited to the needle puncture sites

Chilblain-like Leukemia Cutis

CASE REPORT

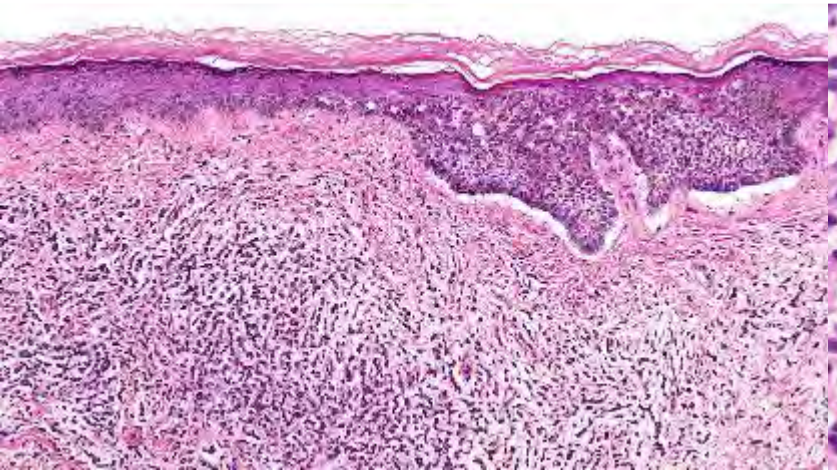
Leukemia cutis originating in the extravasation site of i.v. gabexate mesilate infusion

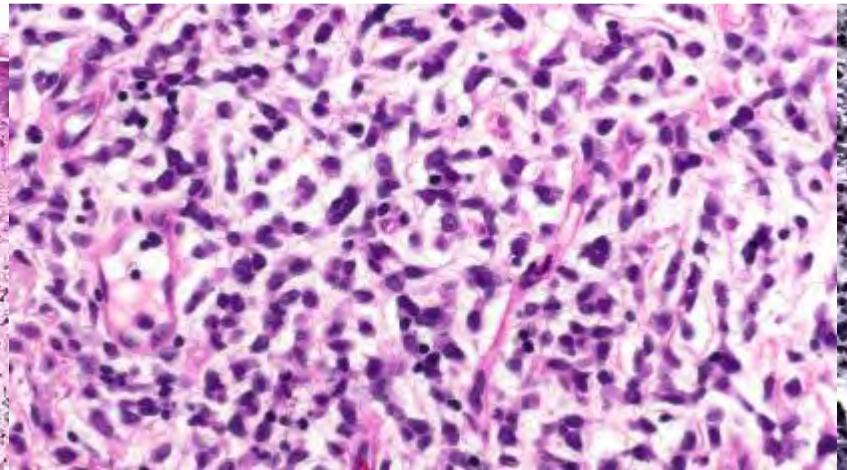
Takashi MIYAKURA, Toshiyuki YAMAMOTO, Yuta KURASHIGE, Ayako NAGAI, Tomotaka IGUCHI, Yasuo AOTA, Ryoji TSUBOI

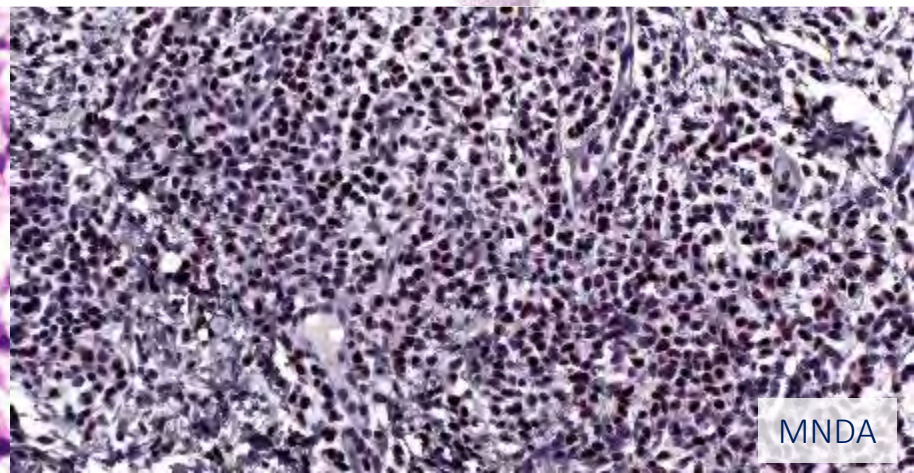
F, 67
BCC on the back

Specific infiltrate of AML at the site of BCC

*AML not known at the time of biopsy; bone marrow punction: 60-70 % blasts: NPM1, p.W288Cfs*12: 46.95%; DNMT3A, p.V636M: 53.44%*







AML & other skin disorders

- In contrast to B-CLL, specific skin infiltrates of myelogeneous leukemia are mostly unrelated to inflammatory or neoplastic skin disorders
- In some cases, specific infiltrates at the site of neutrophil-rich dermatoses (e.g., erysipelas, psoriasis) or of other inflammatory skin disorders
- Unlike B-CLL, specific infiltrates of myelogeneous leukemia are only exceptionally observed at the site of skin tumors
- Unlike B-CLL, specific infiltrates of myelogeneous leukemia portend a bad prognosis

JAMA Dermatology | Original Investigation

Association of Leukemia Cutis With Survival in Acute Myeloid Leukemia

Cynthia X. Ning, MPH; Ilona A. Joe, MD; Mirna J. Acevedo, MD

IMPORTANCE Leukemia cutis (LC) is an important yet uncommon extramedullary manifestation of leukemia. Previous reports have suggested poor prognosis for patients with LC, but these reports have largely consisted of descriptive studies with a limited number of patients.

OBJECTIVE To identify patient factors associated with LC and characterize the association of LC with the course of acute myeloid leukemia (AML).

DESIGN, SETTING, AND PARTICIPANTS This retrospective, nested case-control study included 1568 patients with AML diagnosed from January 1, 2005, to April 1, 2017, with and without biopsy-proven LC seen at a single-center, tertiary care hospital in St Louis, Missouri. To specifically evaluate differences in survival, propensity scoring was used to match patients with AML with LC to patients with AML without LC on the basis of a propensity score based on age, leukemia subtype, sex, and leukemic type. Kaplan-Meier methods were used to compare cumulative probability survived. Matched survival analysis was performed with extended Cox regression to determine factors associated with leukemia-specific and overall survival.

MAIN OUTCOMES AND MEASURES Leukemia-specific survival and overall survival.

RESULTS A total of 1682 patients were reviewed, including 68 patients with biopsy-proven LC of the AML type and 1605 patients with AML without LC. A total of 62 of the patients with AML and LC (mean [SD] age, 58.7 [11.7] years; 35 [56.5%] male) were matched in a 1:3 ratio to 186 patients with AML without LC (mean [SD] age, 58.2 [13.5] years; 103 [55.4%] male). The 5-year survival among the 62 patients with AML with LC was 8.6%, shorter than the 28.3% among the 186 matched patients with AML without LC. Matched survival analysis revealed that patients with AML and LC compared with those without LC had hazard ratios of 2.06 (95% CI, 1.25-3.38; $P = .004$) for leukemia-specific death and of 1.66 (95% CI, 1.06-2.60; $P = .03$) for all-cause death. In addition, matched patients with LC had greater odds of extramedullary organ involvement (odds ratio, 3.48; 95% CI, 1.77-7.05; $P < .001$).

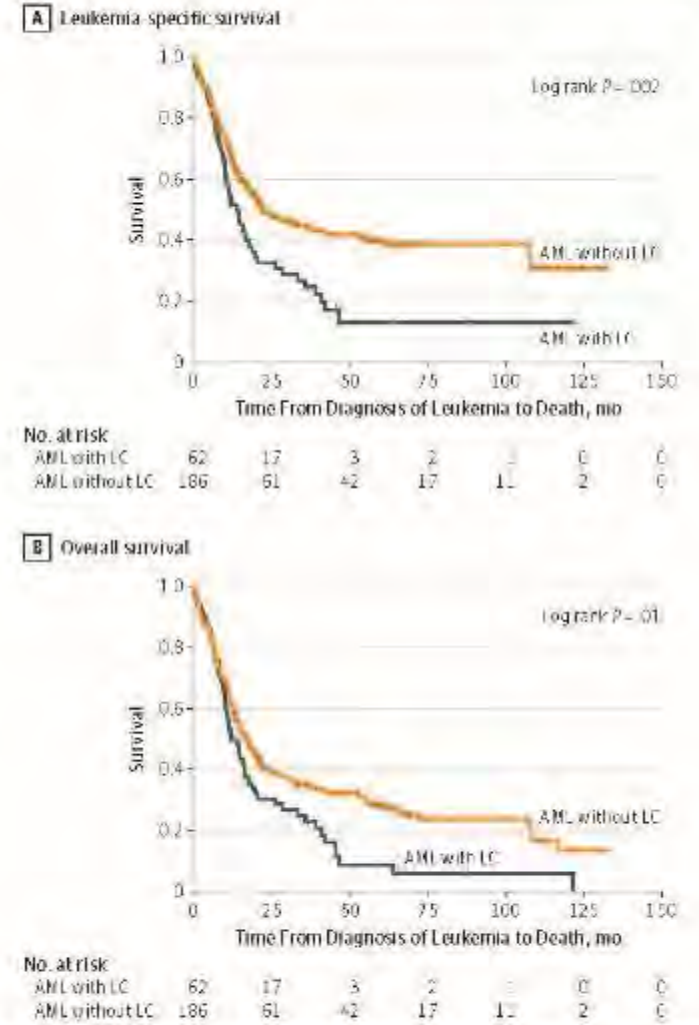
CONCLUSIONS AND RELEVANCE These results suggest that the presentation of LC in patients with AML is associated with decreased overall survival and leukemia-specific survival. Patients with AML presenting with LC may require more intensive treatment and monitoring of their leukemic disease.

Author Affiliations: Department of Medicine, Washington University School of Medicine in St Louis, St Louis, Missouri (Ning); Department of Oncologic Analysis, Division of Oncology, Washington University School of Medicine in St Louis, St Louis, Missouri (Joe); Division of Dermatology, Washington University School of Medicine in St Louis, St Louis, Missouri (Acevedo).

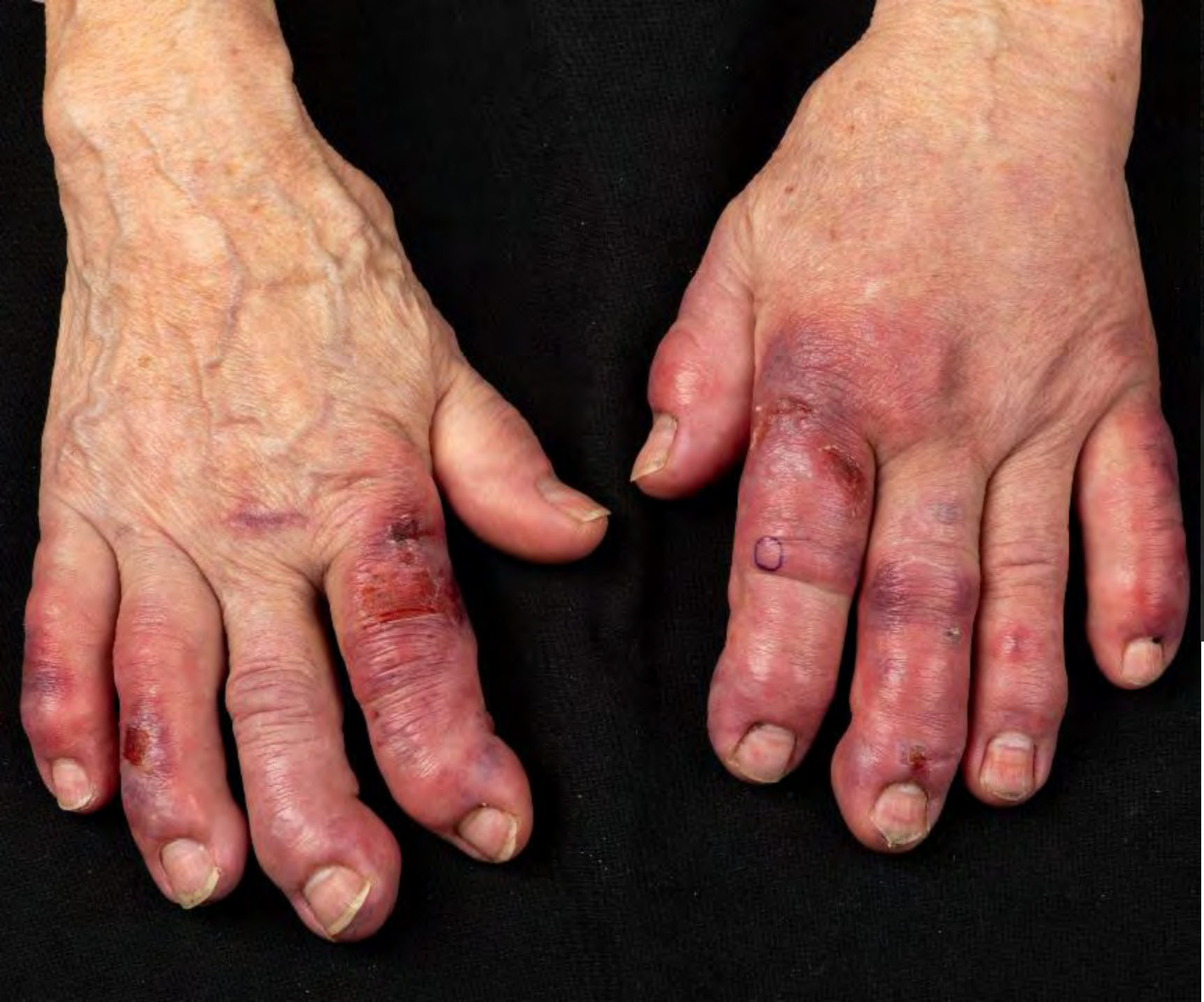
Corresponding Author: Mirna J. Acevedo, MD (Dermatology, Washington University School of Medicine in St Louis, 660 S Euclid Ave, Campus Box 8123, St Louis, MO 63110) (macevedo@dermatology.wustl.edu).

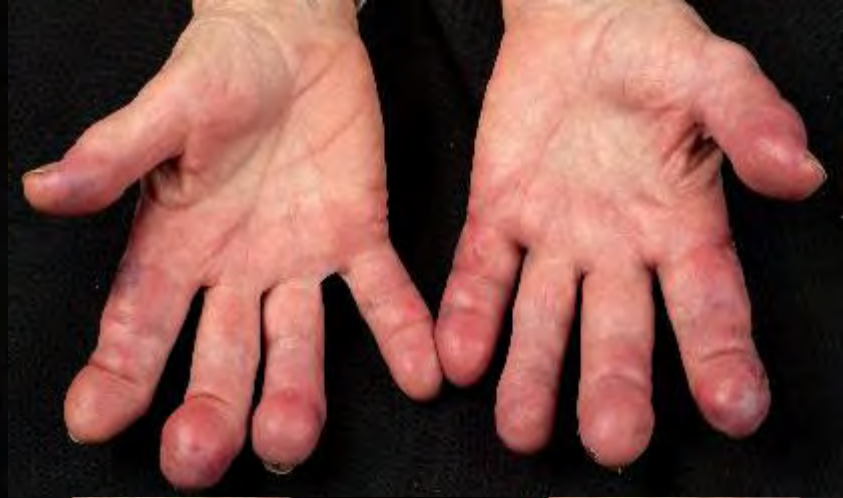
JAMA Dermatol. 2019;155(7):826-832. doi:10.1001/jamadermatol.2019.0663
Published online April 10, 2019.

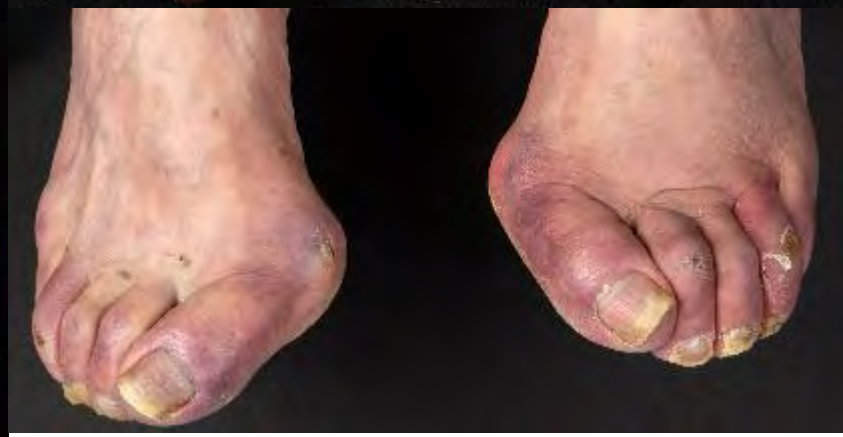
Figure 2. Kaplan-Meier Survival Curves Comparing Survival for Patients With Acute Myeloid Leukemia (AML) With Leukemia Cutis (LC) and Without LC



A, Patients with LC had a median leukemia-specific survival of 13.86 months compared with 22.21 months for patients without LC. B, Patients with LC had a median overall survival of 13.03 months (95% CI, 10.02-16.62 months) compared with 17.21 months (95% CI, 13.53-21.25 months) for patients without LC. The overall 5-year survival among the patients with LC was 8.6%, shorter than the 28.3% survival among the patients without LC.



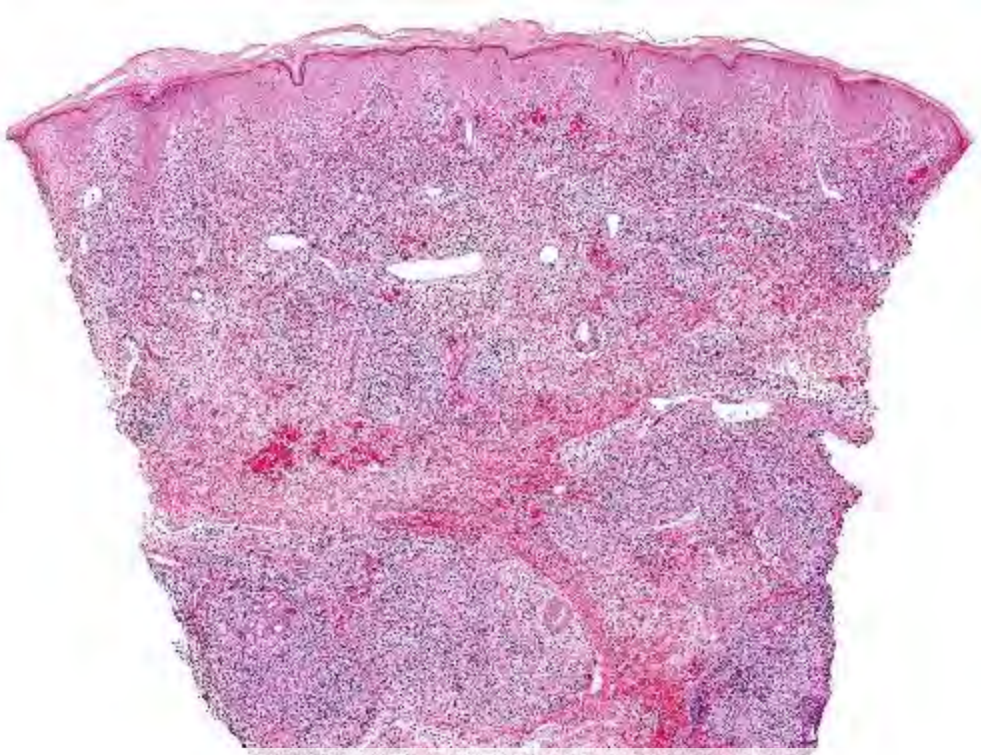




F, 83

History of CMML (1st diagnosis 3 months before observation). According to the patient painful, partly erosive lesions on the fingers and toes for approximately 3 years.

A biopsy is taken.



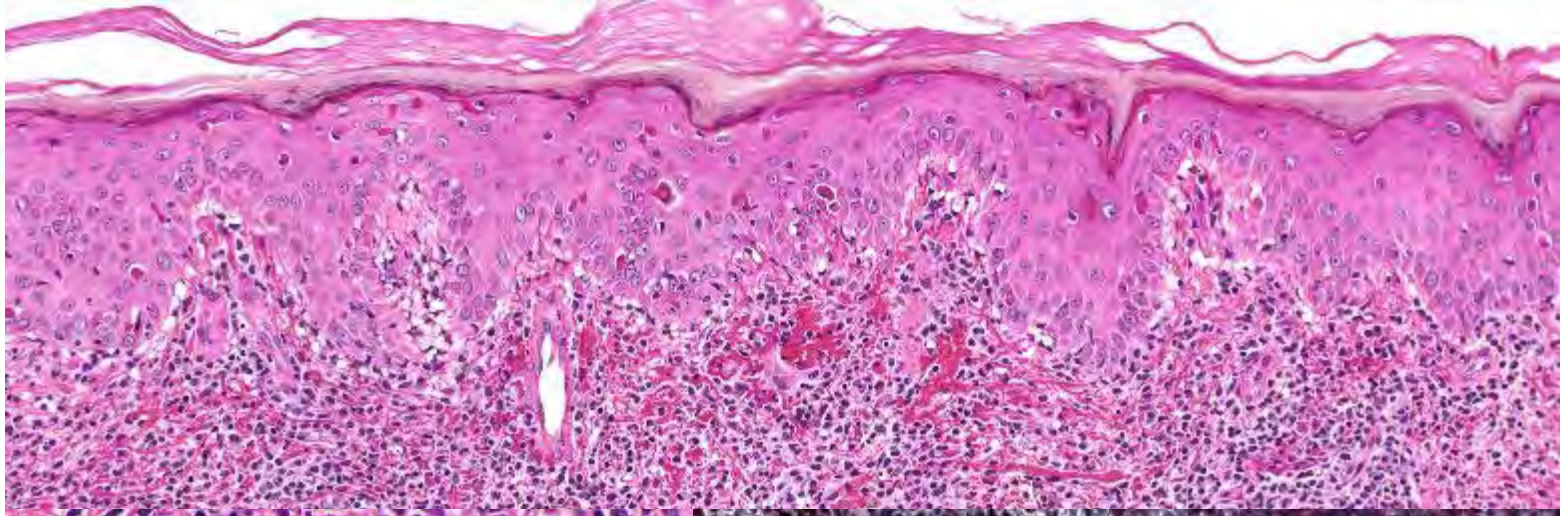
Chilblain & antiphospholipid syndrome

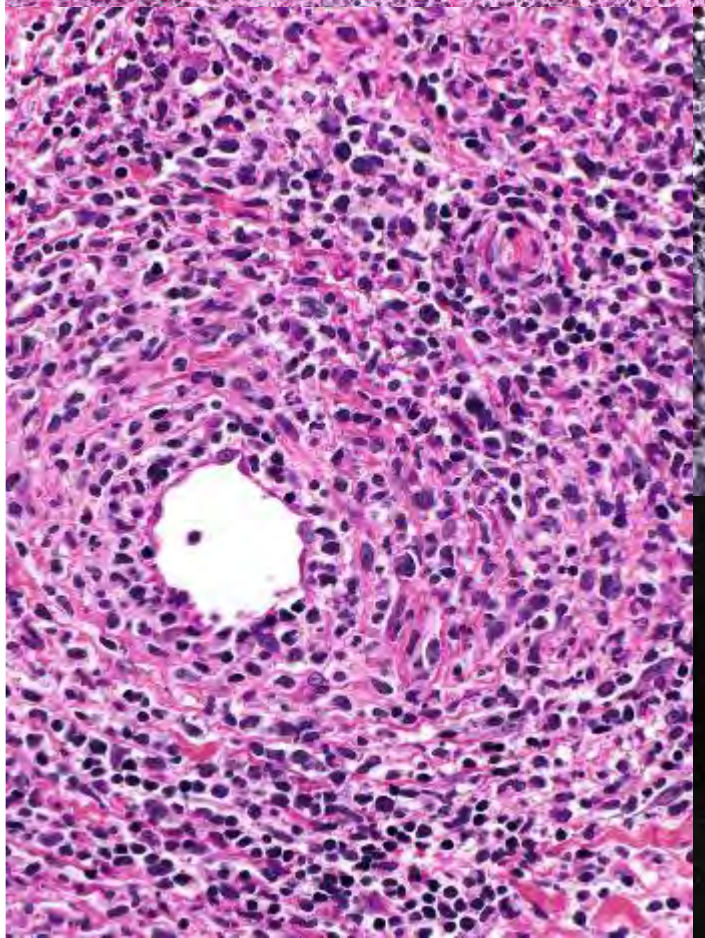
with mature plasmacytoid dendritic cell proliferation associated with CMML

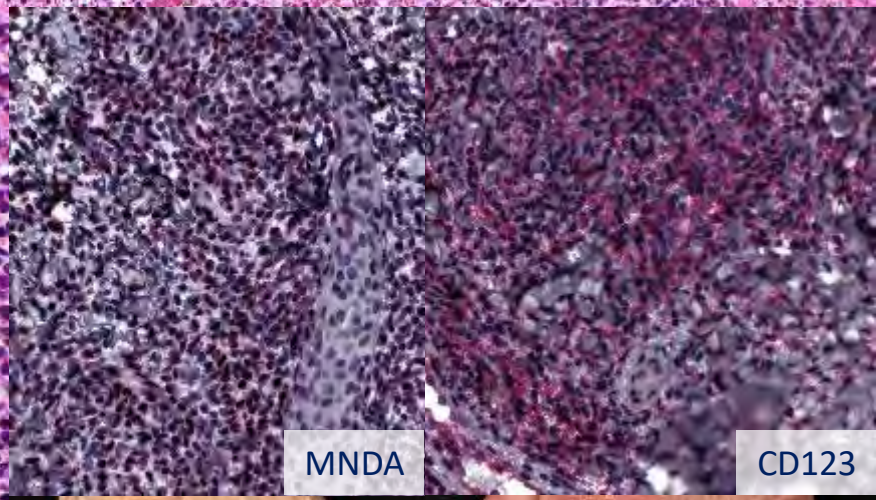
ANA: 1:80

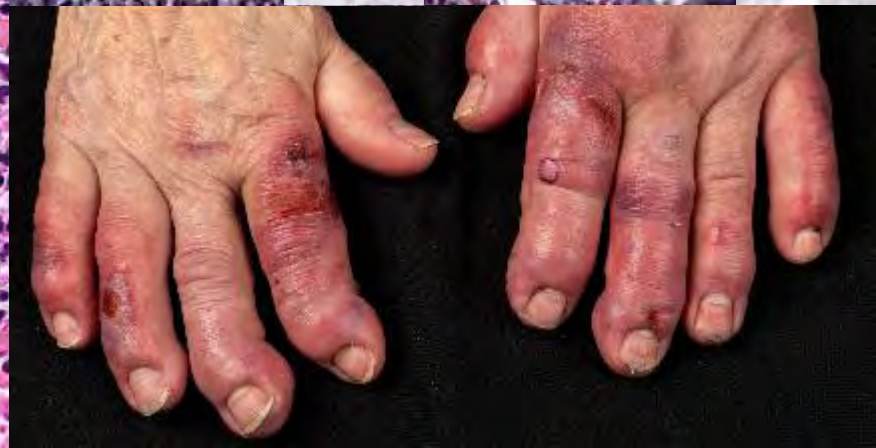
cardiolipin abs: >90+

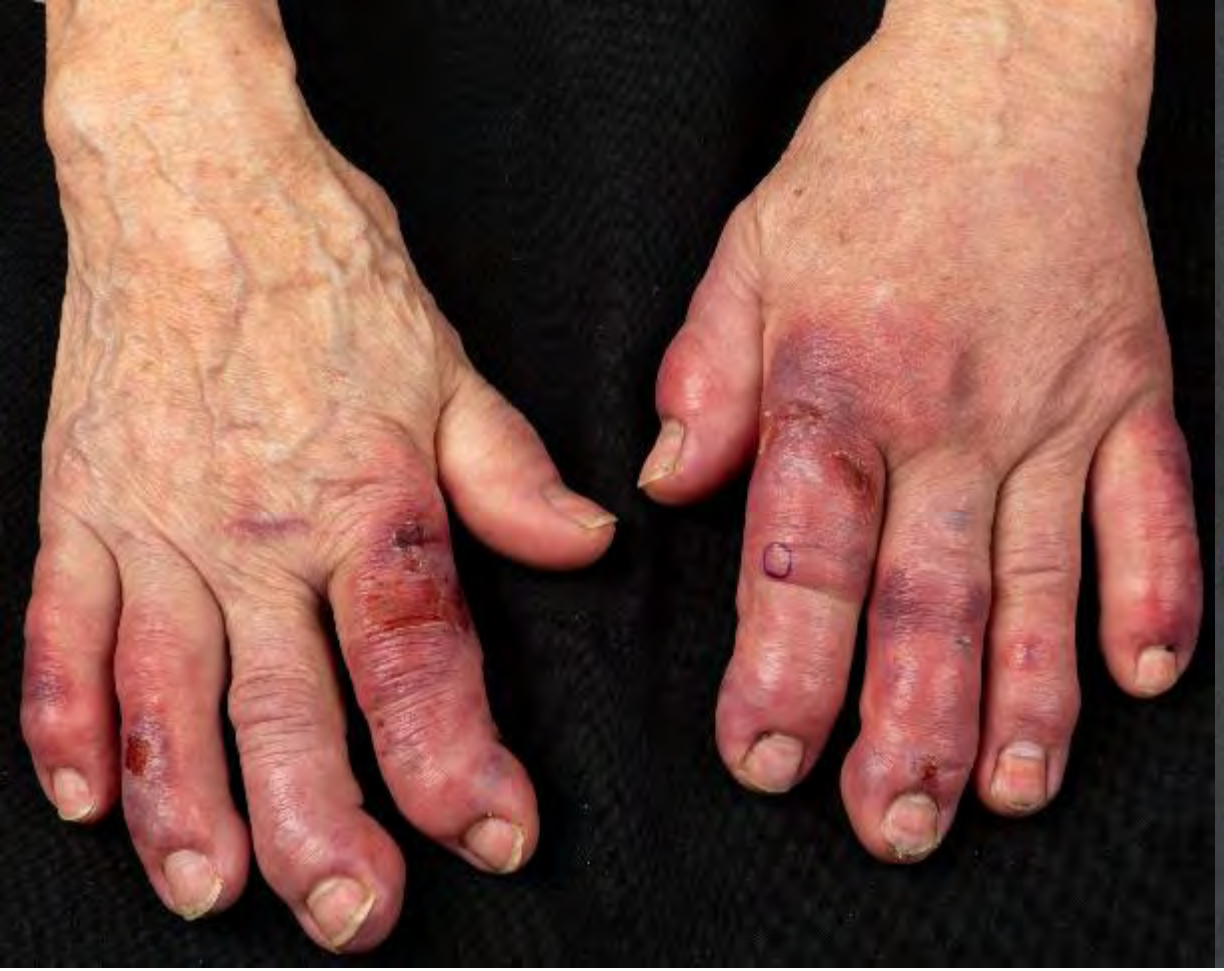
ß2 glycoprotein abs: 9,5+

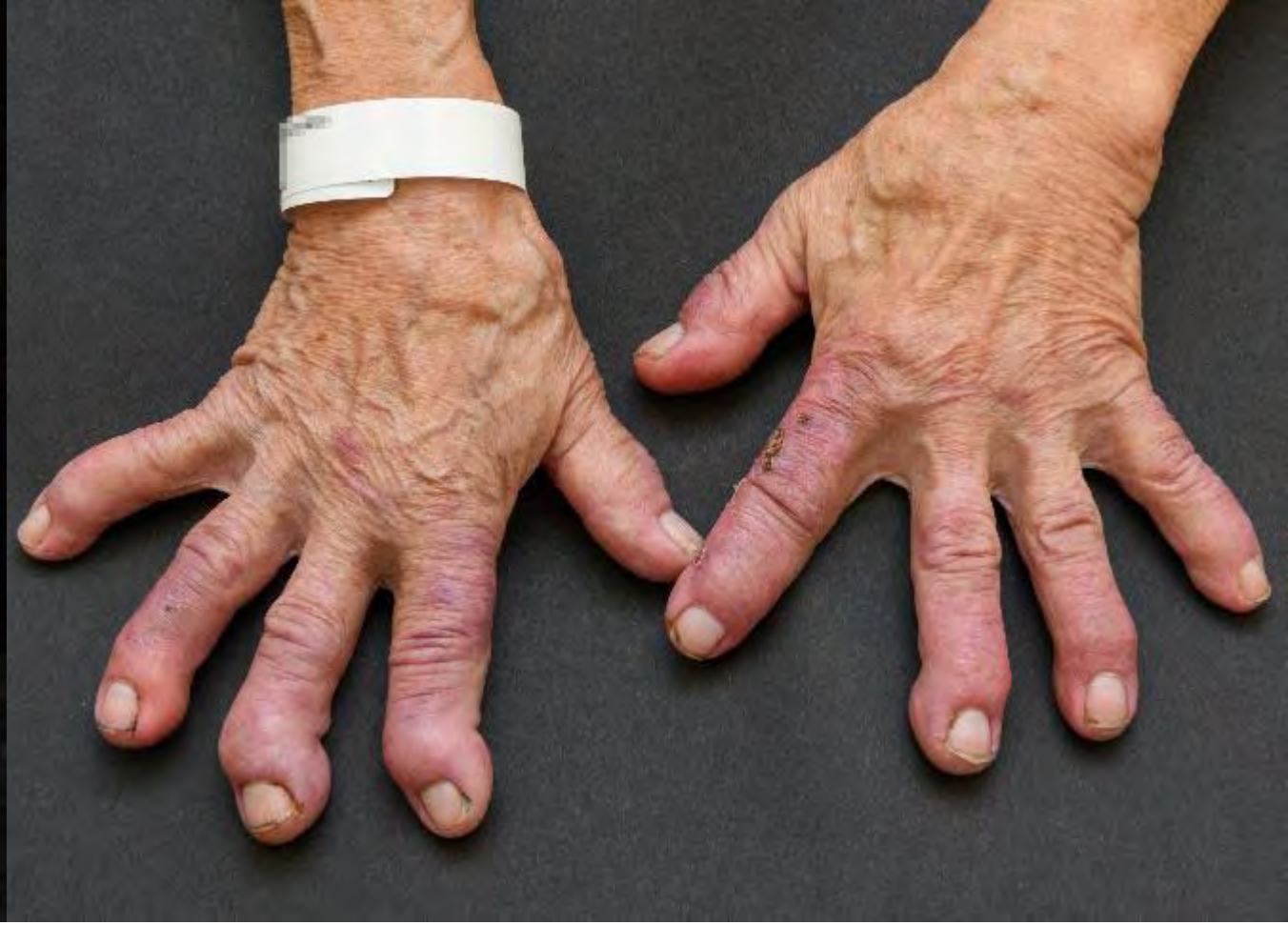








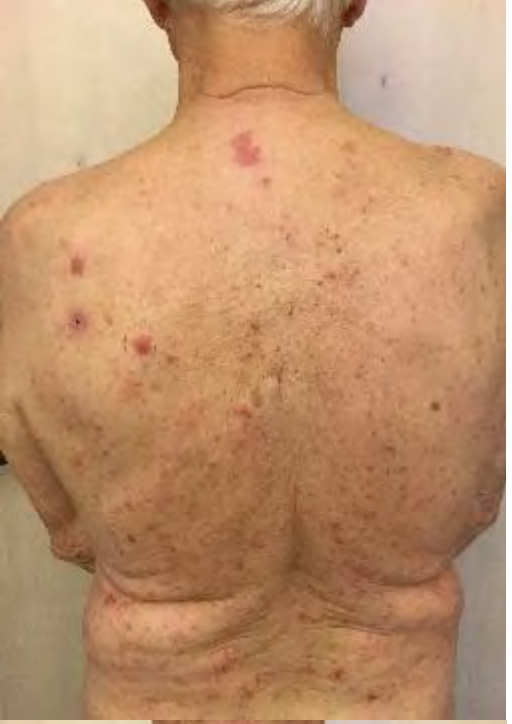


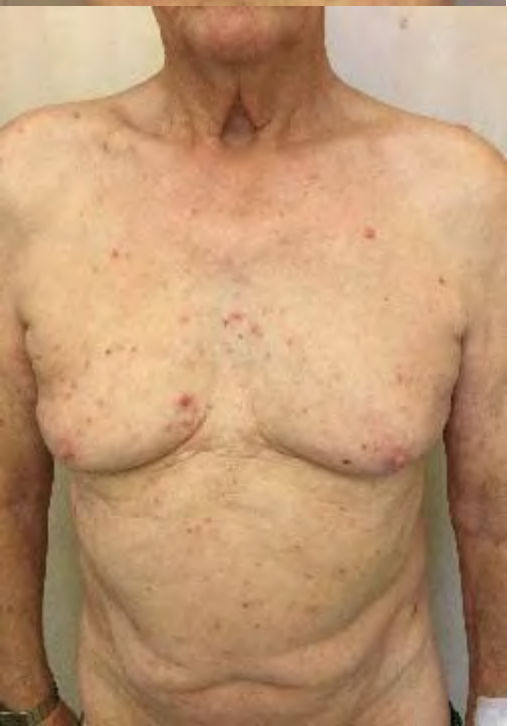


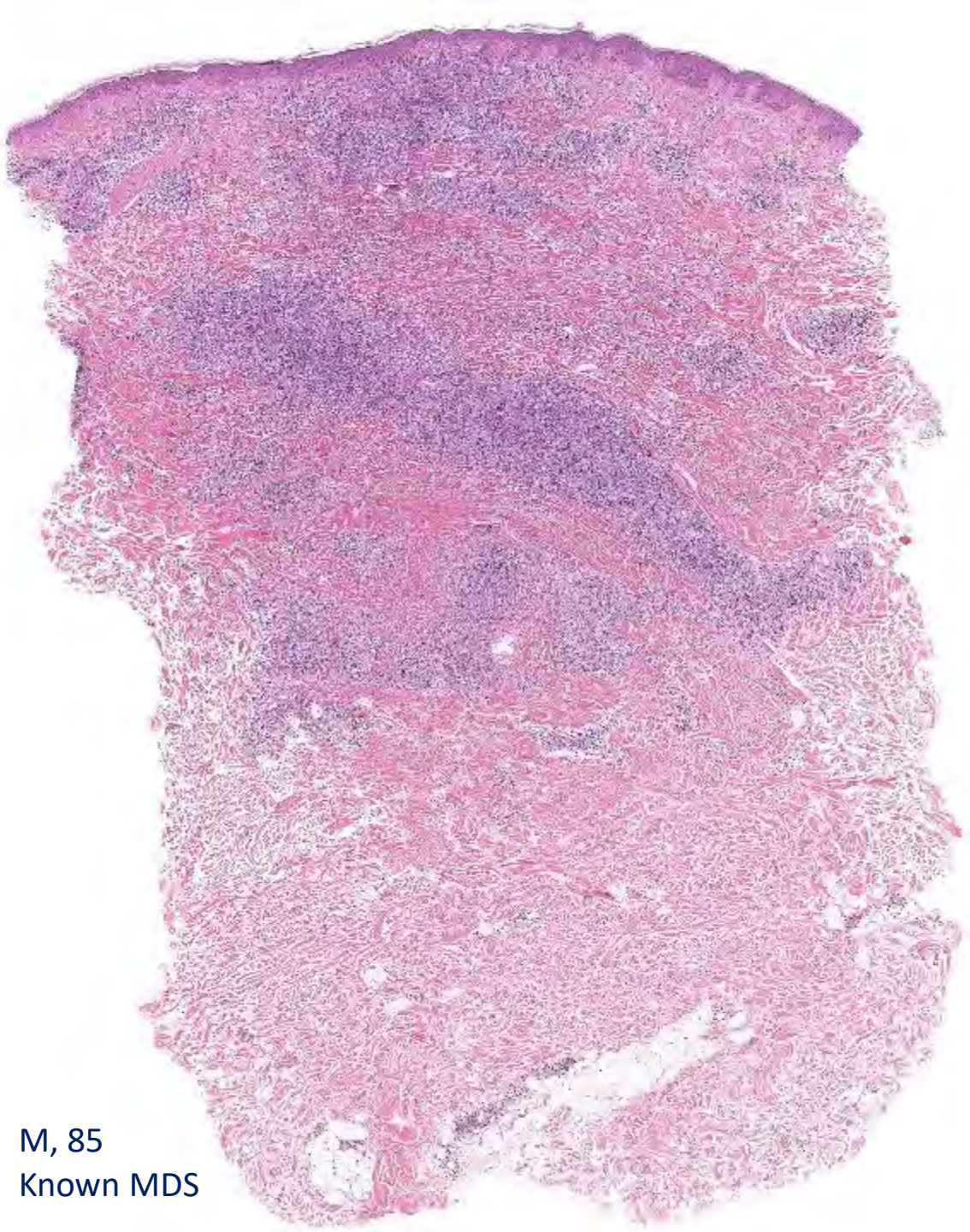
1st presentation

10 months later

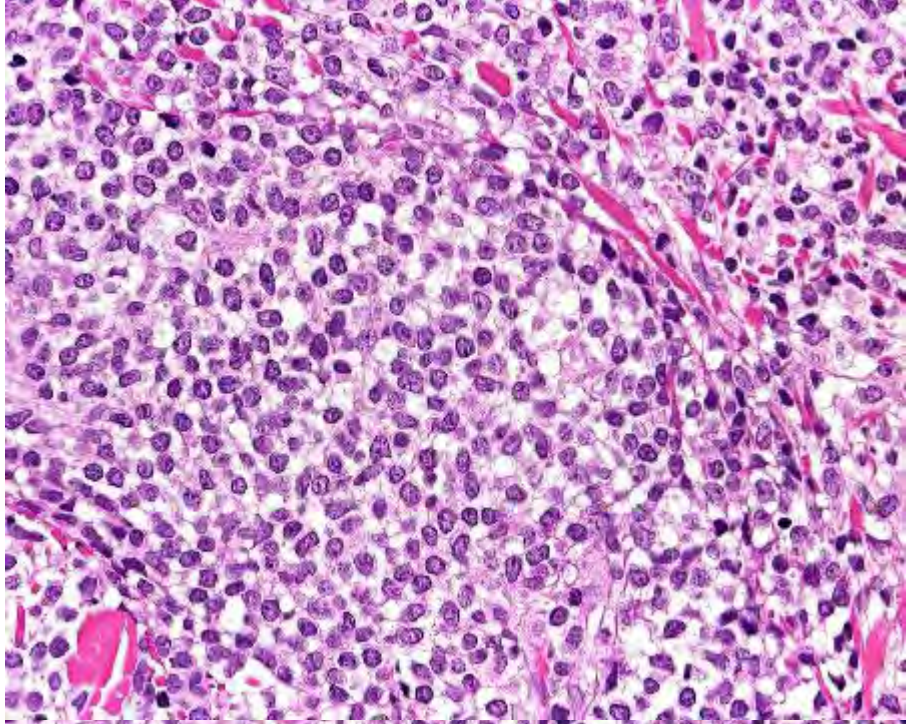
Stable hematological disease
Persisting antiphospholipid antibodies
Hypergammaglobulinemia

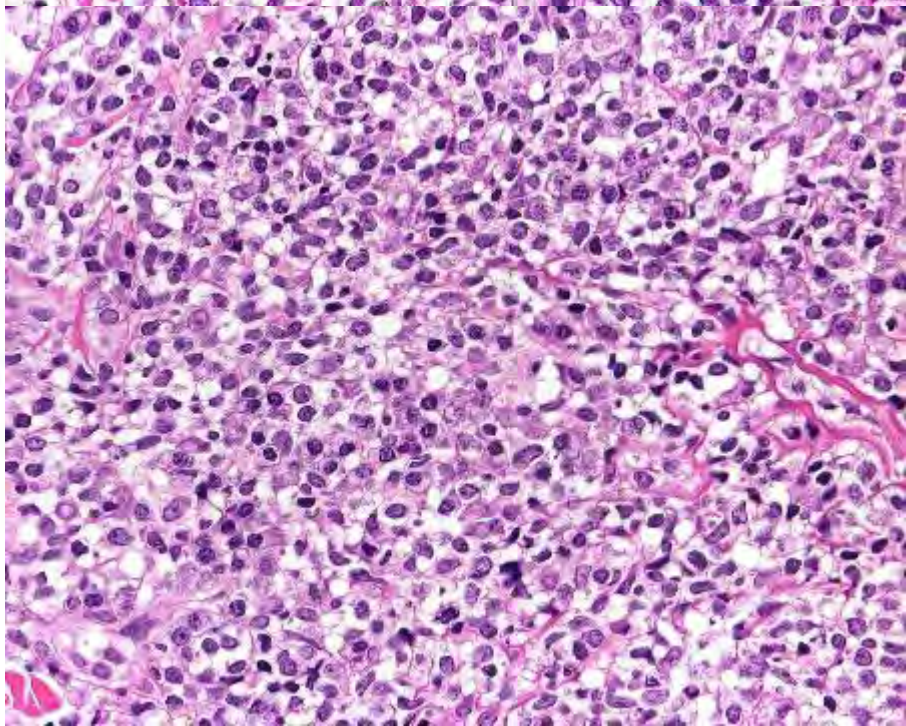


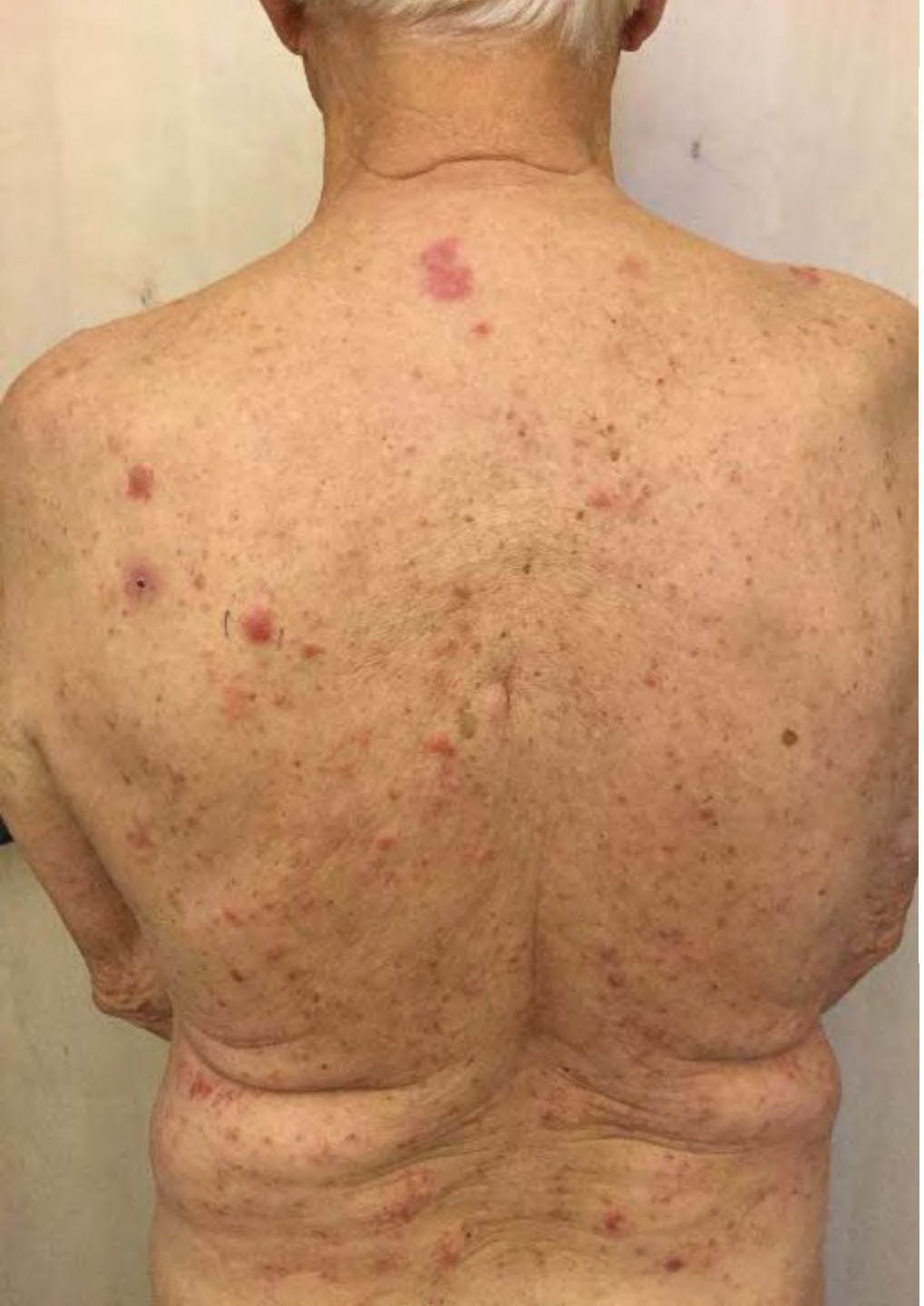


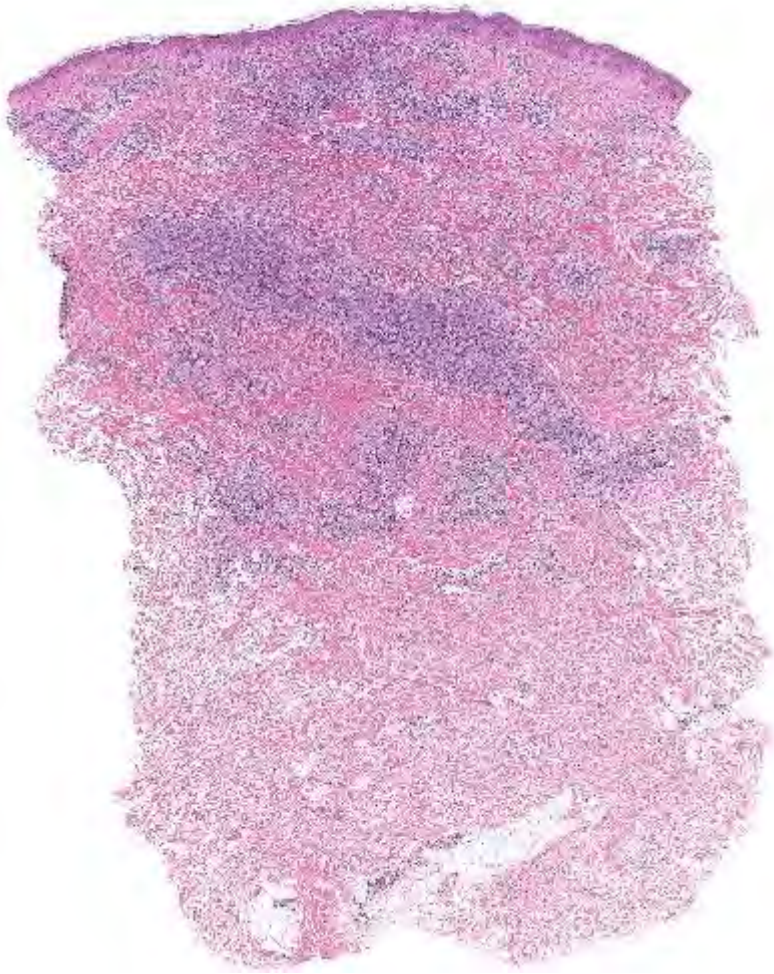


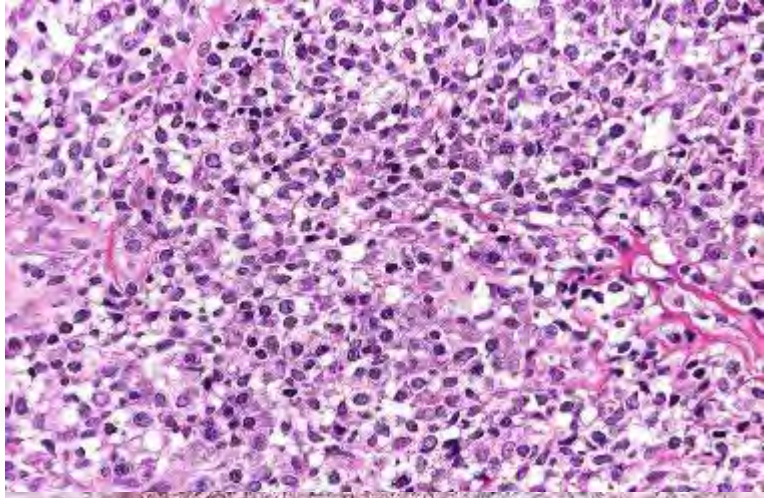
M, 85
Known MDS

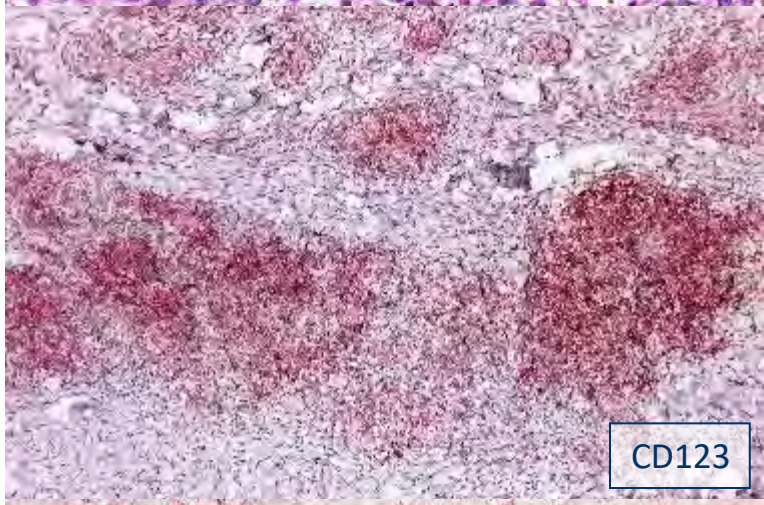


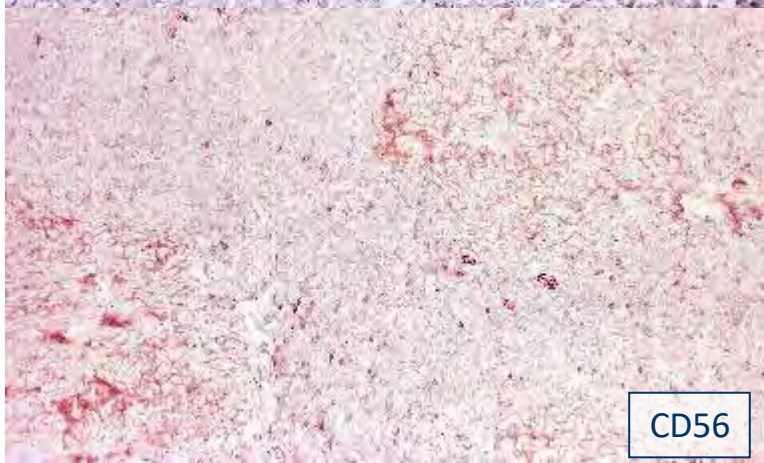




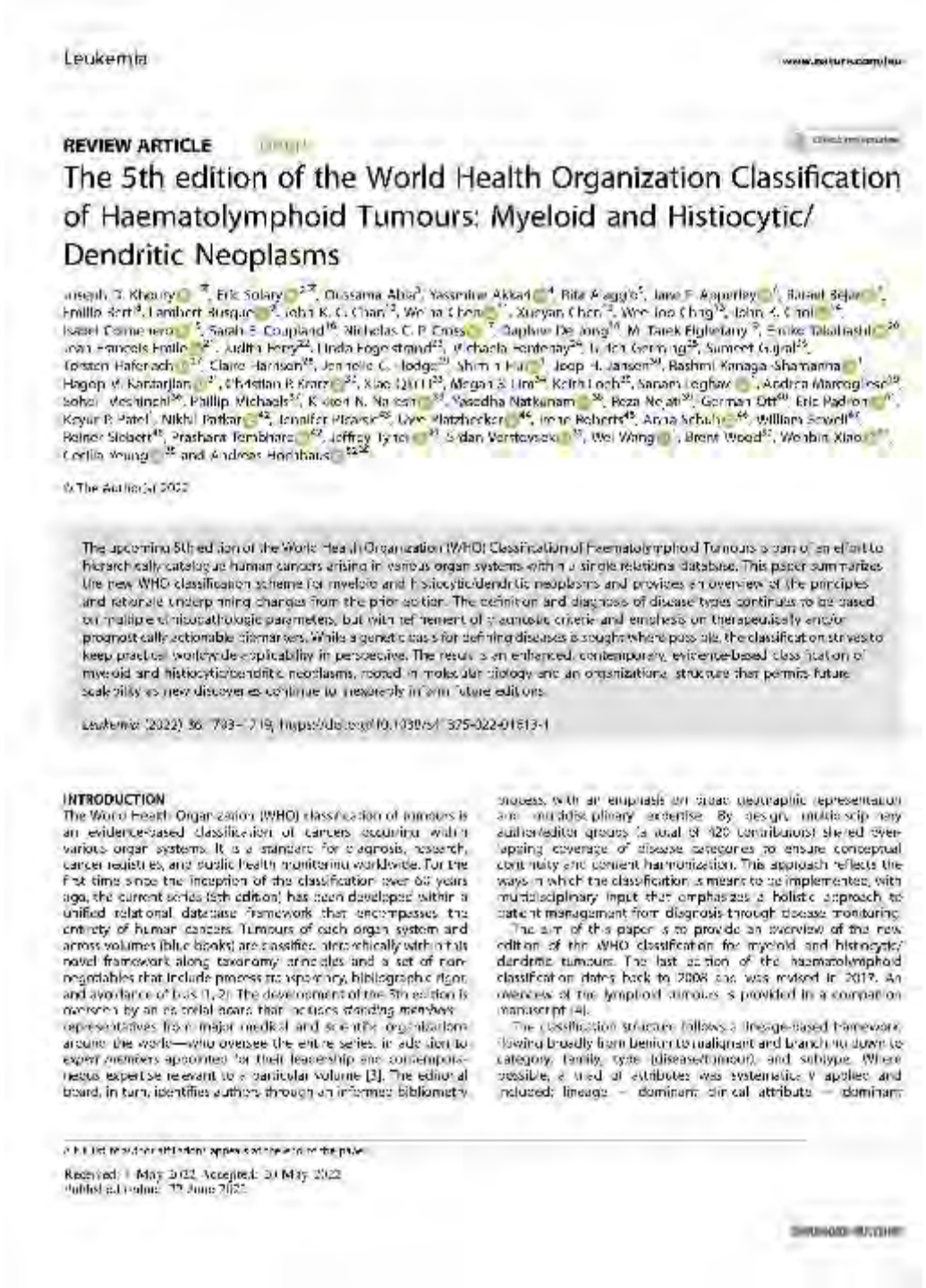








Mature plasmacytoid dendritic cell proliferation associated with MDS



Leukemia

REVIEW ARTICLE

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms

Joseph D. Khoury[1] ✉, Eric Solary[2,3] ✉, Ossama Abla[4], Yasmine Akkari[5], Rita Alaggio[6], Jane F. Apperley[7], Rafael Bejar[8], Emilio Bertti[9], Lambert Busque[10], John K. C. Chan[11], Wee Joo Chng[12], Xueyan Chen[13], Wee Joo Chng[14], John K. Choi[15], Isabel Colmenero[16], Sarah E. Coupland[17], Nicholas C. P. Cross[18], Daphne De Jong[19], M. Tarek Elghetany[20], Eneko Elorza[21], Jean-Francois Emile[22], Judith Ferry[23], Linda Fogelstrand[24], Michaela Fontenay[25], Lukas Frenzel[26], Sumeet Gujral[27], Torsten Haferlach[28], Claire Harrison[29], Jennifer C. Hodge[30], Shim Y. Hu[31], Joop H. Jansen[32], Rashmi Kanagal-Shamanna[33], Hagop M. Kantarjian[34], Christian P. Kratz[35], Xiao Qi Li[36], Megan S. Lim[37], Keith Loch[38], Sanam Loghavi[39], Andrea Marcogliese[40], Sohail Meshinchi[41], Phillip Michaels[42], Kikkeri N. Naresh[43], Vasudha Natkunam[44], Reza Nejati[45], German Ott[46], Eric Padron[47], Keyur P. Patel[48], Nikhil Patkar[49], Jennifer Pittaluga[50], Uwe Platzbecker[51], Irene Roberts[52], Anna Schuh[53], William Scott[54], Reiner Siebert[55], Prashant Tembhare[56], Jeffrey Tyner[57], Sidan Verstovsek[58], Wei Wang[59], Brent Wood[60], Wenbin Xiao[61], Cecilia Yeung[62] and Andreas Hochhaus[63,64]

The upcoming 5th edition of the World Health Organization (WHO) Classification of Haematolymphoid Tumours is part of an effort to hierarchically catalog all human cancers arising in various organ systems with a single relational database. This paper summarizes the new WHO classification scheme for myeloid and histiocytic/dendritic neoplasms and provides an overview of the principles and rationale underpinning changes from the prior edition. The definition and diagnosis of disease types continues to be based on multiple clinicopathologic parameters, but with refinement of genomic criteria and emphasis on therapeutically and/or prognostically actionable biomarkers. While a genetic basis for defining diseases is sought where possible, the classification strives to keep practical worldwide applicability in perspective. The result is an enhanced, contemporary, evidence-based classification of myeloid and histiocytic/dendritic neoplasms, rooted in molecular biology and an organizational structure that permits future scalability as new discoveries continue to reverberate in forthcoming future editions.

Leukemia (2022) 36:1703–1719 https://doi.org/10.1038/s41375-022-01613-1

INTRODUCTION

The World Health Organization (WHO) classification of tumours is an evidence-based classification of cancers occurring within various organ systems. It is a standard for diagnosis, research, cancer registries, and public health monitoring worldwide. For the first time since the inception of the classification over 60 years ago, the current series (5th edition) has been developed within a unified relational database framework that encompasses the entirety of human cancers. Tumours of each organ system and across volumes (blue books) are classified according to this novel framework along taxonomic principles and a set of non-negotiables that include consensus, transparency, bibliographic rigor, and avoidance of bias [1, 2]. The development of the 5th edition is overseen by an international team of scientists standing members representatives from major medical and scientific organizations around the world—who oversee the entire series, in addition to expert members appointed for their leadership and contemporaneous expertise relevant to a particular volume [3]. The editorial board, in turn, identifies authors through an informed bibliometric process, with an emphasis on broad geographic representation and multidisciplinary expertise. By design, multiple lead author/editor groups (a total of 429 contributors) shaped overlapping coverage of disease categories to ensure conceptual continuity and content harmonization. This approach reflects the ways in which the classification is meant to be implemented, with multidisciplinary input that emphasizes a holistic approach to patient management from diagnosis through disease monitoring.

The aim of this paper is to provide an overview of the new edition of the WHO classification for myeloid and histiocytic/dendritic tumours. The last edition of the haematolymphoid classification dates back to 2008 and was revised in 2017. An overview of the lymphoid tumours is provided in a companion manuscript [4].

The classification structure follows a lineage-based framework, flowing broadly from benign to malignant and branching down to category, family, type (disease/tumour), and subtype. Where possible, a triad of attributes was systematically applied and ordered: lineage – dominant clinical attribute – dominant

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"Mature plasmacytoid dendritic cell proliferation (MPDCP) associated with myeloid neoplasm reflects recent data showing that these represent clonal proliferation of pDCs with low grade morphology identified in the context of a defined myeloid neoplasm. Clonal MPDCP cells accumulate in the bone marrow of patients with myeloproliferative CMML harbouring activating RAS pathway mutations. Patients with AML can have clonally expanded pDCs (pDC-AML), which share the same mutational landscape as CD34+ blasts, and frequently arise in association with *RUNX1* mutations. It is unknown whether the pathogenetic mechanisms leading to MPDCP in association with MDS or MDS/MPN and with AML are the same."

International Agency for Research on Cancer

World Health Organization

WHO Classification of Tumours online

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3. Histiocytic/Dendritic cell neoplasms

- Introduction
- **Plasmacytoid dendritic cell neoplasms**
  - *Plasmacytoid dendritic cell neoplasms*
    - Mature plasmacytoid dendritic cell proliferation associated with myeloid neoplasm
    - Blastic plasmacytoid dendritic cell neoplasm
- **Langerhans cell and other dendritic cell neoplasms**
  - *Langerhans cells neoplasms*
    - Langerhans cell histiocytosis
    - Langerhans cell sarcoma
  - *Other dendritic cell neoplasms*
    - Indeterminate dendritic cell tumour
    - Interdigitating dendritic cell sarcoma
- **Histiocyte/macrophage neoplasms**
  - *Histiocytic neoplasms*
    - Juvenile xanthogranuloma
    - Erdheim-Chester disease
    - Rosai-Dorfman Disease
    - ALK-positive histiocytosis
    - Histiocytic sarcoma

Localization

Most cases have been described in the skin and bone marrow, and very rarely, in lymph nodes.

Essential and desirable diagnostic criteria

Essential:

Accumulation of mature cells with plasmacytoid morphology and expression of CD123 and/or other pDC markers in the context of a defined myeloid neoplasm.

Desirable:

Aberrant pDC immunophenotype

Absence or low/partial expression of CD56.

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REVIEW

Plasmacytoid dendritic cells in the setting of myeloid neoplasms: Diagnostic guide to challenging pathologic presentations

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Summary

In this article, we describe three broad pathologic presentations of plasmacytoid dendritic cells (pDCs) that may be encountered in clinical practice, in which an association between pDCs and myeloid neoplasms is identified: (1) myeloid neoplasms with maturely appearing pDC expansion, most commonly seen in chronic myelomonocytic leukaemia (CMML); (2) myeloid neoplasms with pDC differentiation, in which pDCs show a spectrum of maturation from early immature pDCs to mature forms, most commonly seen in acute myeloid leukaemia (AML); (3) myeloid neoplasms associated with blastic plasmacytoid dendritic cell neoplasm (BPDCN), either stemming from the same precursor or representing an independent clonal process. Additionally, we also discuss AML with pDC-like phenotype, in which myeloblasts show immunophenotypic features that may mimic those seen in pDCs. Using these presentations, we provide a diagnostic algorithm for appropriate pathologic classification, while attempting to clarify and homogenize nomenclatures pertaining to different biologic states of pDCs.

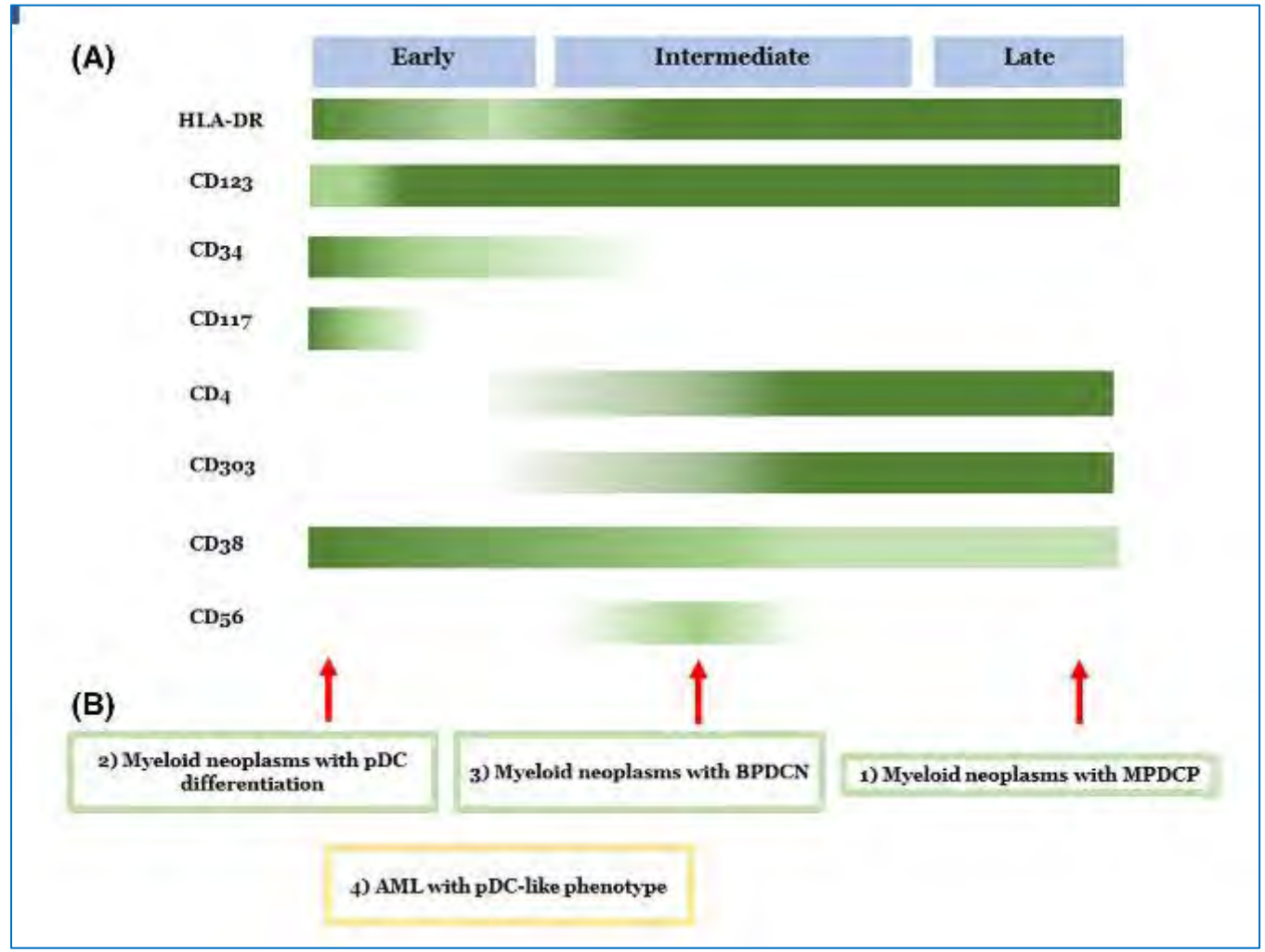
KEYWORDS

differentiation, immunophenotype, myeloid neoplasms, pDCs, plasmacytoid dendritic cells

INTRODUCTION

Plasmacytoid dendritic cells (pDCs) are the major natural type I interferon producing dendritic cells and key players in immune response.[1,2] In normal bone marrow and peripheral blood, pDCs represent less than 1% of total nucleated cells.[3–5] pDCs are proposed to derive from a common haematopoietic progenitor shared with myeloid DCs and monocytes.[6] The development of pDCs depends on FMS-like tyrosine kinase 3 ligand (FLT3L),[7] and master transcription factor 4 (TCF4).[8] Prior studies suggested physiologic stages of pDC maturation in the bone marrow have been described based on the expression status of stem cell markers, such as CD34, CD117, and pDCs markers including CD4, CD123, HLA-DR, CD303 and CD304.[9] Figure 1A illustrates the expression pattern of key markers during pDC maturation. Briefly, the earliest pDCs express CD34 and CD117, with negativity for CD4 and CD303 expression. As pDCs mature, they quickly lose CD117 expression and at the intermediate stage, pDCs show negative CD117 and partial CD34 expression, and gain of CD4 and CD303 expression. Mature pDCs at late stages are negative for CD34, with positive CD4, CD303 and CD304 expression. CD45 level gradually increases as pDCs mature. CD38 is bright at early stages and its expression gradually decreases, but stays positive as cell is mature. Of note, a small subset of normal pDCs expresses CD56,[10,11] a marker commonly used for the diagnosis of blastic plasmacytoid dendritic cell neoplasm (BPDCN).

Non-neoplastic accumulations of pDCs have been observed in reactive lymph nodes and skin in Kikuchi's lymphadenitis,[12] hyaline vascular Castleman disease,[13] lupus erythematosus,[14] and Drug Reaction With Eosinophilia and Systemic Symptoms Syndrome (DRESS) mimicking lymphadenopathy.[15] In this review, we focus on neoplastic pDCs which historically have been thought to manifest as two distinctly and pathologically distinct forms: (1) BPDCN, and (2) mature plasmacytoid dendritic cell proliferation (MPDCP) associated with myeloid neoplasms. BPDCN is proposed to derive from CD34+ CD56+ pDC precursors and is characterized by cutaneous and bone marrow tropism. MPDCP manifests as nodules/aggregates of clonally expanded mature pDCs in lymph nodes, skin, and bone marrow, and has been associated predominantly with chronic myelomonocytic



Received: 22 September 2022 | Accepted: 5 December 2022

REVIEW

Plasmacytoid dendritic cells in the setting of myeloid neoplasms: Diagnostic guide to challenging pathologic presentations

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Summary

In this article, we describe three broad pathologic presentations of plasmacytoid dendritic cells (pDCs) that may be encountered in clinical practice, in which an association between pDCs and myeloid neoplasms is identified: (1) myeloid neoplasms with monocytic differentiation, most commonly seen in chronic myelomonocytic leukaemia (CMML); (2) myeloid neoplasms with pDC differentiation, in which pDCs show a spectrum of maturation from early immature pDCs to mature forms, most commonly seen in acute myeloid leukaemia (AML); (3) myeloid neoplasms associated with blastic plasmacytoid dendritic cell neoplasm (BPDCN), either stemming from the same precursor or representing an independent clonal process. Additionally, we also discuss AML with pDC-like phenotype, in which myeloblasts show immunophenotypic features that may mimic those seen in pDCs. Using these presentations, we provide a diagnostic algorithm for appropriate pathologic classification, while attempting to clarify and homogenize nomenclatures pertaining to different biologic states of pDCs.

KEYWORDS
dendritic cell neoplasm, myeloid neoplasms, pDCs, plasmacytoid dendritic cells

INTRODUCTION

Plasmacytoid dendritic cells (pDCs) are the major natural type I interferon producing dendritic cells and key players in immune response.[1,2] In normal bone marrow and peripheral blood, pDCs represent less than 1% of total nucleated cells.[3–5] pDCs are proposed to derive from a common haematopoietic progenitor shared with myeloid DCs and monocytes.[6] The development of pDCs depends on FMS-like tyrosine kinase 3 ligand (FLT3L),[7] and master transcription factor E2-2 (TCF4).[8] Flow cytometry confirms physiologic stages of pDC maturation in the bone marrow and have been described based on the expression status of stem cell markers, such as CD34, CD117, and pDCs markers including CD4, CD123, HLA-DR, CD303 and CD304.[9] Figure 1A illustrates the expression pattern of key markers during pDC maturation. Briefly, the earliest pDCs express CD34 and CD117, with negativity for CD4 and CD303 expression. As pDCs mature, they quickly lose CD117 expression and at the intermediate stage, pDCs show negative CD117 and partial CD34 expression, and gain of CD4 and CD303 expression. Mature pDCs at late stages are negative for CD34, with positive CD4, CD303 and CD304 expression. CD45 level gradually increases as pDCs mature. CD38 is bright at early stages and its expression gradually decreases, but stays positive as cells mature. Of note, a small subset of normal pDCs expresses CD56,[10,11] a marker commonly used for the diagnosis of blastic plasmacytoid dendritic cell neoplasm (BPDCN).

Non-neoplastic accumulations of pDCs have been observed in reactive lymph nodes and skin in Kikuchi's lymphadenitis,[12] hyaline vascular Castleman disease,[13] lupus erythematosus,[14] and Drug Reaction With Eosinophilia and Systemic Symptoms Syndrome (DRESS) mimicking lymphadenitis.[15] In this review, we focus on neoplastic pDCs which historically have been thought to manifest as two distinctly and pathologically distinct forms: (1) BPDCN, and (2) mature plasmacytoid dendritic cell proliferation (MPDCP) associated with myeloid neoplasms. BPDCN is proposed to derive from CD34+ CD56+ pDC precursors and is characterized by cutaneous and bone marrow tropism. MPDCP manifests as nodules/aggregates of clonally expanded mature pDCs in lymph nodes, skin and bone marrow, and has been associated predominantly with chronic myelomonocytic

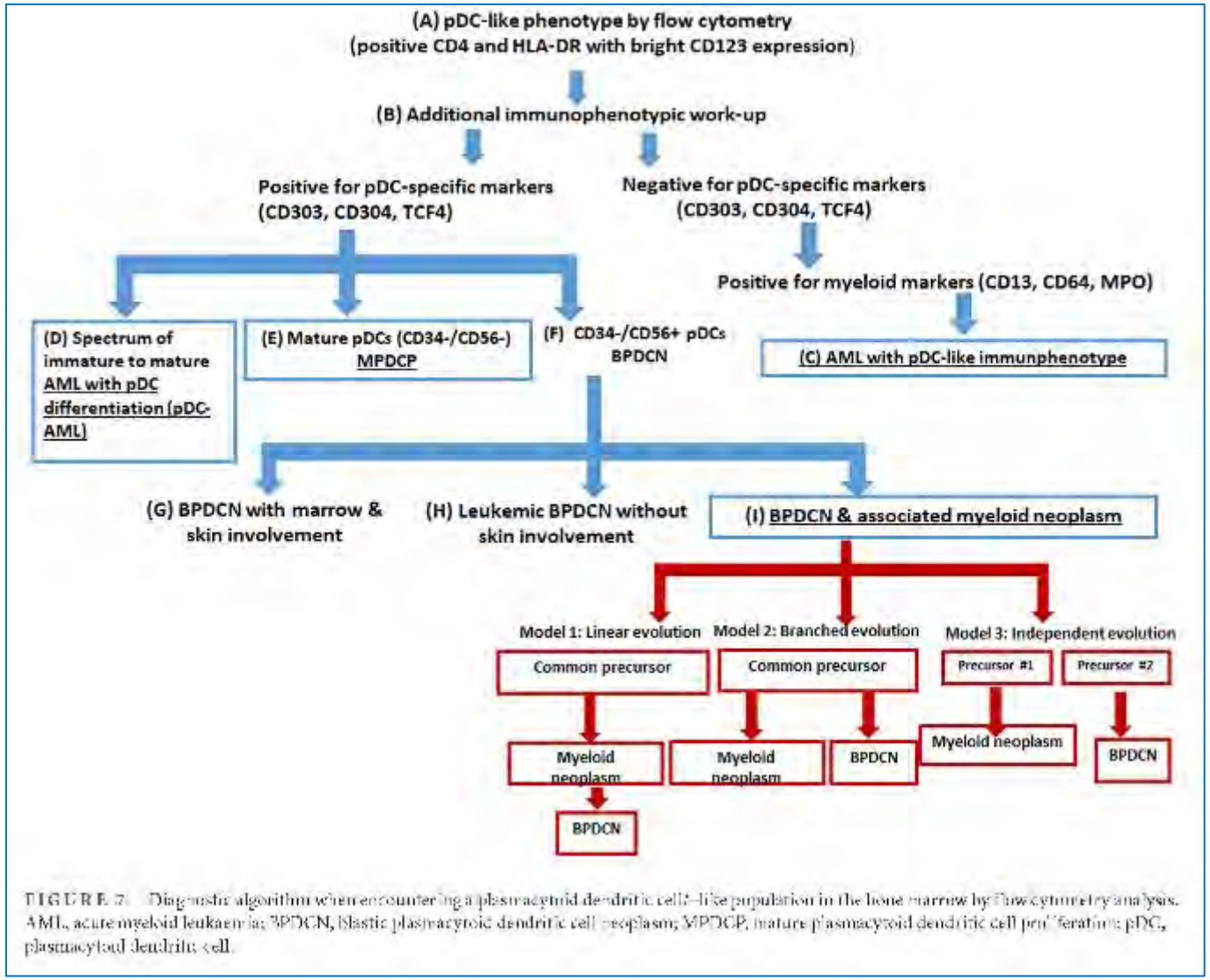

FIGURE 2 Diagnostic algorithm when encountering a plasmacytoid dendritic cell?-like population in the bone marrow by flow cytometry analysis. AML, acute myeloid leukaemia; BPDCN, blastic plasmacytoic dendritic cell neoplasm; MPDCP, mature plasmacytoid dendritic cell proliferation; pDC, plasmacytoid dendritic cell

Plasmacytoid Dendritic Cell Dermatosis Associated to Myeloproliferative/Myelodysplastic Neoplasms

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Abstract: Cutaneous lesions in the setting of myeloproliferative neoplasms and myelodysplastic syndromes are poorly understood. We report 6 patients with pruritic papular eruptions composed of mature T-lymphocytes and large clusters of CD123-positive cells. Double immunohistochemical studies demonstrated a lack of myeloid cell nuclear differentiation antigen in the CD123-positive cells, which expressed SPIB, confirming that they were mature plasmacytoid dendritic cells. Four patients were diagnosed with chronic myelomonocytic leukemia and 2 with myelodysplastic syndromes (ARTE3 I and myelodysplastic syndromes with 5q deletion, respectively). All patients had a long history of hematological alterations, mainly thrombocytopenia, preceding the cutaneous disorder. Nevertheless, the skin lesions developed in all cases coincidentally with either progression or full establishment of their hematological disease. Most cutaneous lesions disappeared spontaneously or after corticosteroid treatment. Methotrexate administered to both bone marrow and cutaneous lesions in 2 patients demonstrated the same antitumoral profile, confirming the specific neoplastic nature of these mature plasmacytoid dendritic cell-composed cutaneous lesions.

Key Words: PDC, CD123, myelodysplastic/myeloproliferative neoplasm, skin

(*Am J Surg Pathol* 2022;46:1623–1631)

Dermatologic manifestations in the setting of either myelodysplastic or myeloproliferative neoplasms (MDS/MPN) are more frequent and diverse than generally acknowledged. They are classically divided into specific and nonspecific, depending on whether neoplastic cells can be identified in the cutaneous lesions; the latter may appear before, during, or after the diagnosis of the hematologic disease. The most frequent and best recognized specific cutaneous manifestation is the involvement of the skin by acute myeloid leukemia cells, which is known as leukemia cutis. The prognosis of these lesions is usually poor, and the patients require intense chemotherapy regimes, even in the absence of bone marrow involvement. Moreover, systemic inflammatory and autoimmune diseases have been reported in 10 to 30% of patients diagnosed with MDS or MPNs. Interestingly, more than half of these patients show in turn evidence of cutaneous involvement, consisting in neutrophilic dermatoses, vasculitis, or cutaneous granulomatosis.[1]

After acute myeloid leukemia, chronic myelomonocytic leukemia (CMML) is the main myeloid disorder prone to develop cutaneous manifestations.[2] CMML, a clonal hematopoietic malignancy with features of both an MPN and an MDS, has persistent blood monocytosis ($\geq 1 \times 10^9$/L) as one of its diagnostic criteria, with monocytes accounting for $\geq 10\%$ of the leukocytes. According to the percentage of blasts and promonocytes in either peripheral blood or bone marrow, CMML patients are currently subdivided into 3 groups: CMML-0, CMML-1, and CMML-2. In most instances, the cells found in cutaneous lesions are cells, mature or immature myeloid cells or, histiocytes.

From the *Dermatology Department, Pharmacology Department, Pathology Department, ‡ENT and §Plastic Surgery Department, Hospital Universitario Puerta de Hierro - Majadahonda, Madrid, Spain; and ‖Comité de Ética de la Investigación de la Fundación Jiménez Díaz, CEIm-FJD approved the study "Estudios de nuevos marcadores clínicos y moleculares para una medicina de precisión (PIC178/IBMTS-2375_LINFOMAS CM_CT_PIC178-19)" in which this study is included.

SM, and J.M.A.D. contributed equally to this paper.

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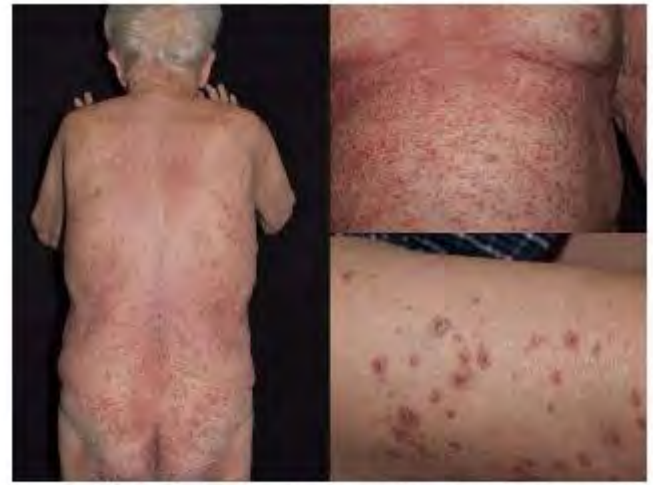


FIGURE 1. Clinical picture of case number 2. Disseminated erythematous macules and papules in the same stage of development with occasional pale halos. Vasculitis, toxicoderma among other diseases were suspected.

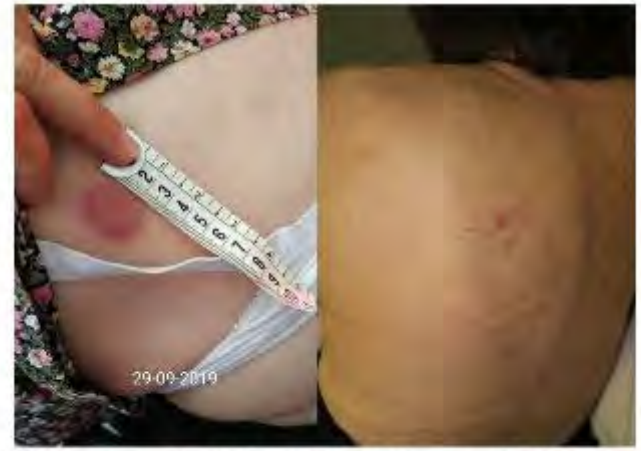


FIGURE 2. Clinical picture of case number 4. Isolated nodules on left flank and breast covered by erythematous skin. Lymphoma was clinically suspected.

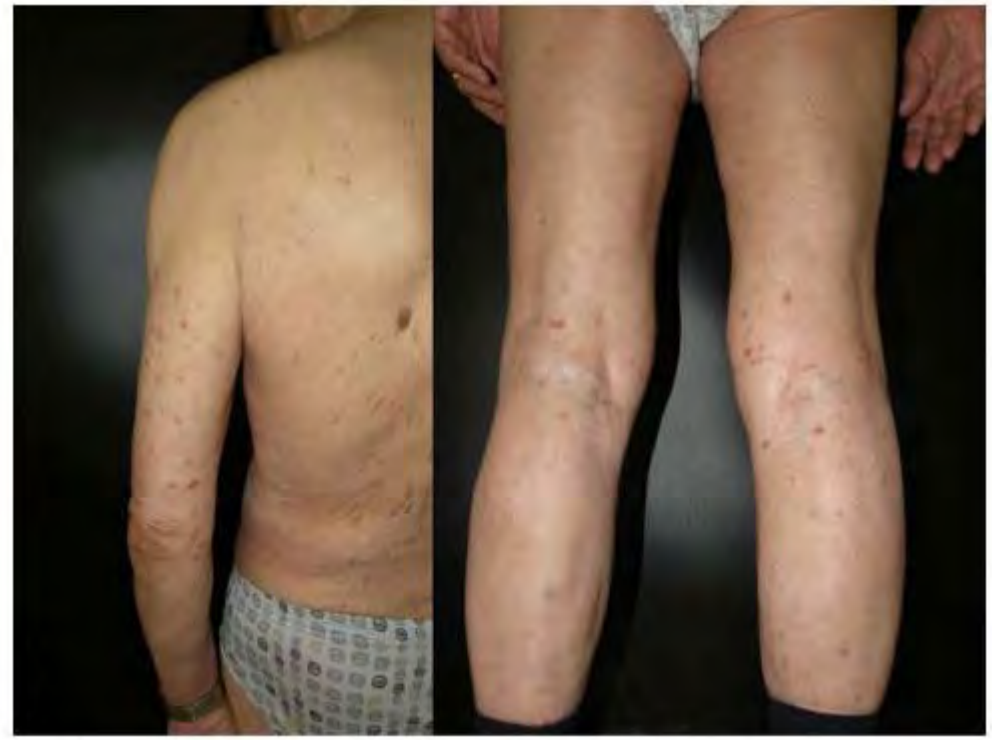
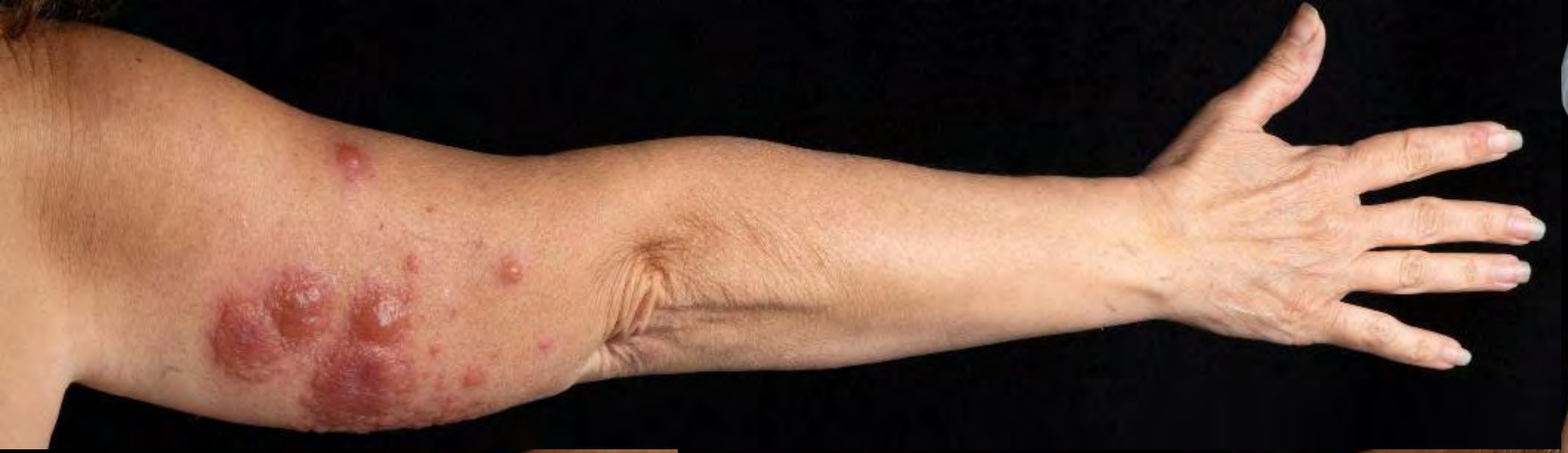
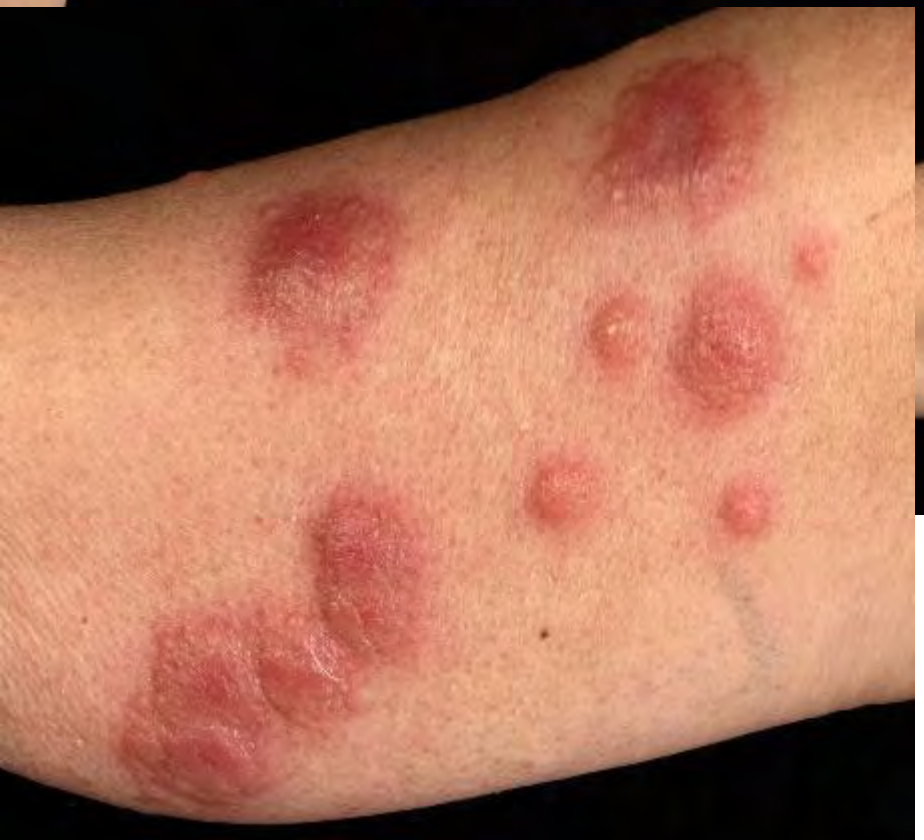
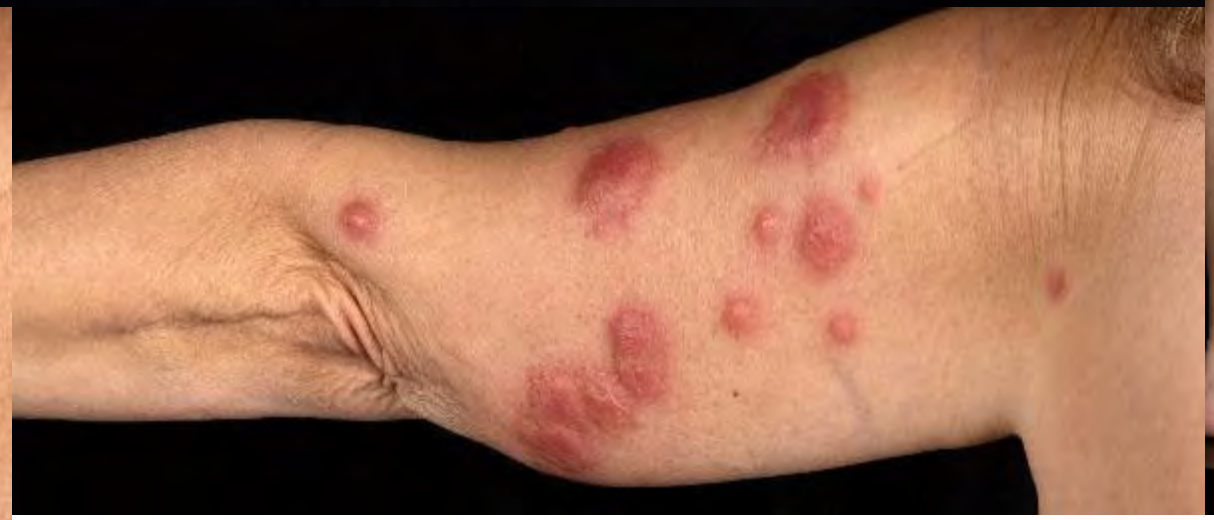
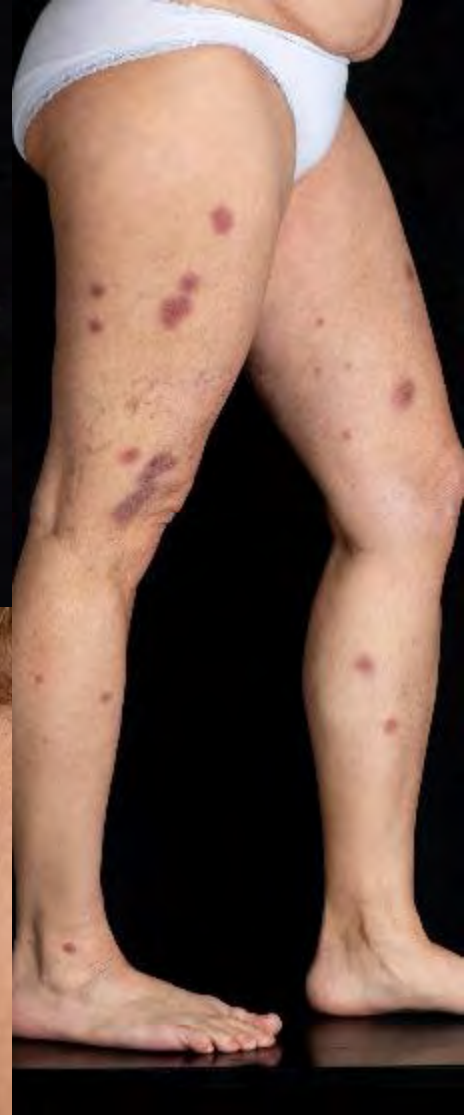


FIGURE 3. Clinical picture of case number 5. Erythematous papules on arms and legs mimicking insect bites.





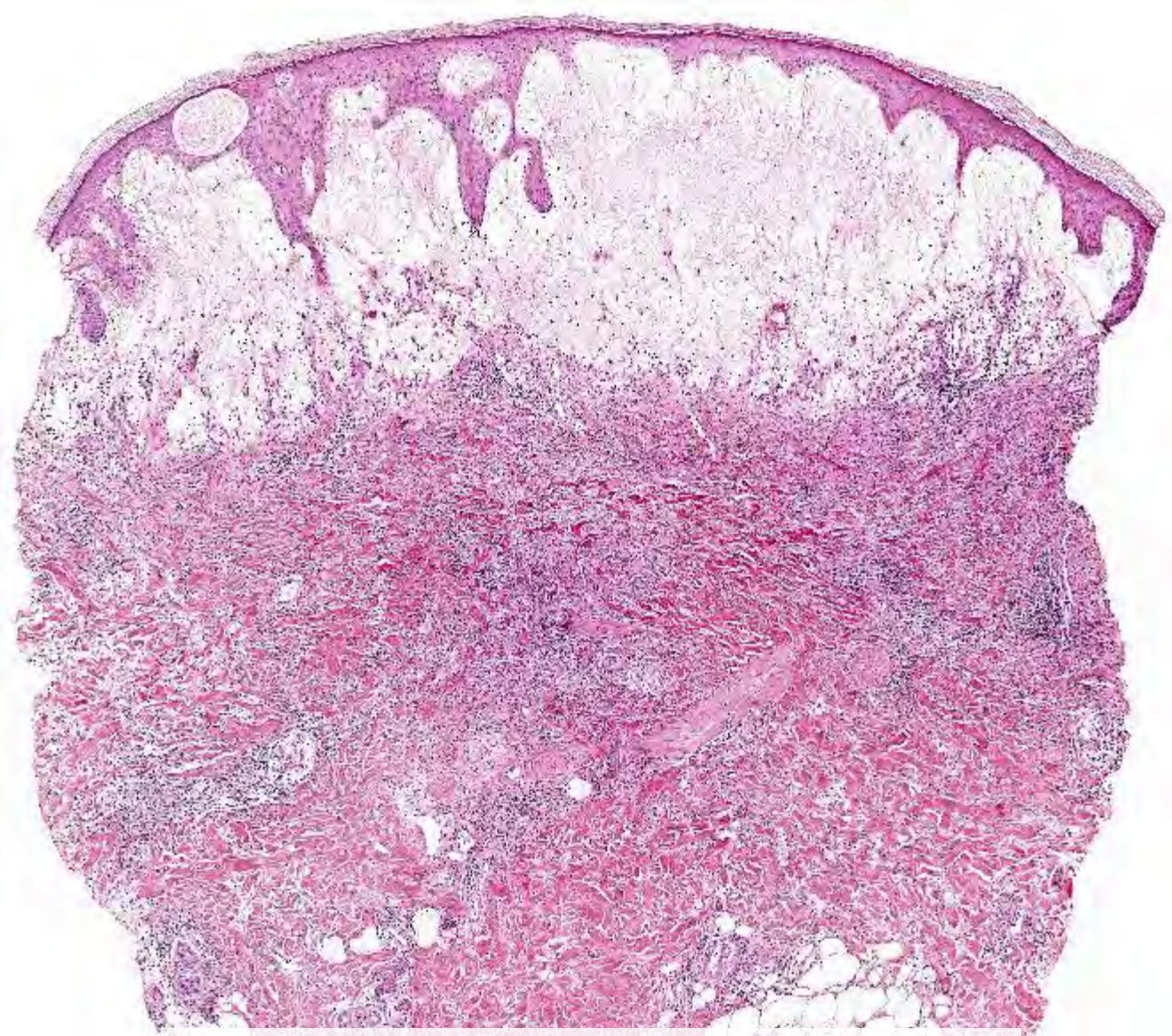




F, 59

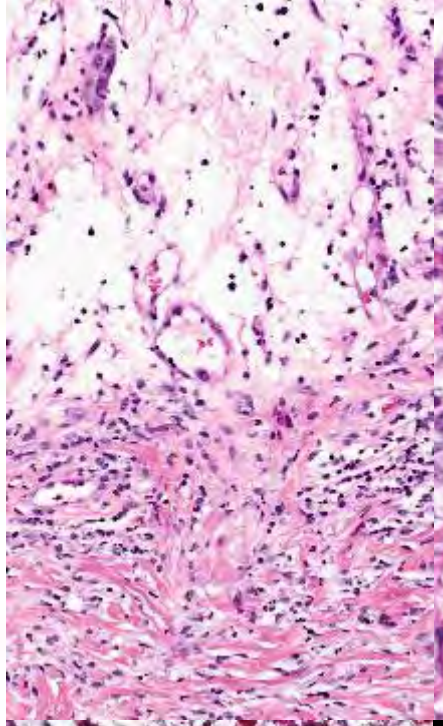
According to the patient skin lesions for 8 days, first on the lower extremities and later on the upper extremities. Infection 2 weeks before. Neutrophils 19.0 ↑.

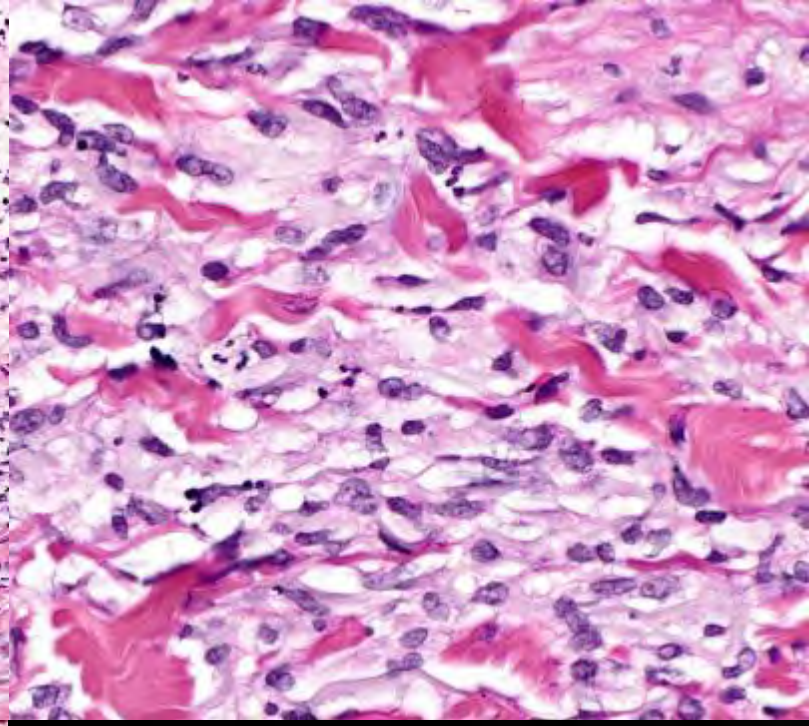
A biopsy is taken.

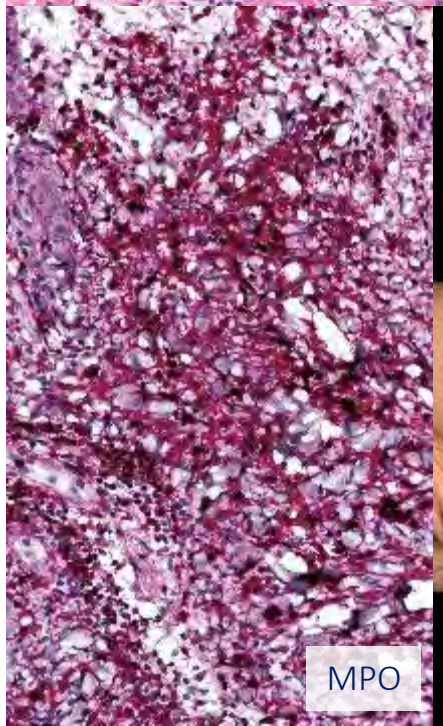


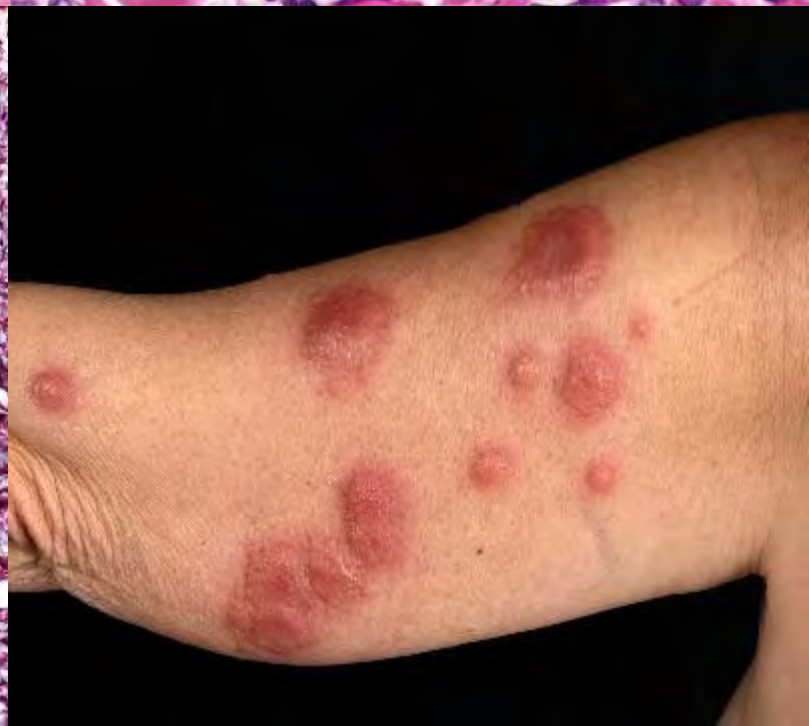
Sweet syndrome

histiocytoid









STUDY

Histiocytoid Sweet Syndrome

A Dermal Infiltration of Immature Neutrophilic Granulocytes

Luis Requena, MD; Boris Kutzner, MD; Gabriele Kiszewski, PhD; Marcia Mazereeuw, MD; Jesús Fernández-Herrera, MD; Javier Fraga, MD; Amparo García-Díez, MD; Francisco Sánchez Yus, MD

Objective: To describe a series of 41 patients with fresh lesions of Sweet syndrome in which the histopathologic study demonstrated an inflammatory infiltrate mostly composed of histiocytoid mononuclear cells.

Design: Histomorphologic, immunohistochemical, and ultrastructural studies on the inflammatory infiltrate in a case series of histiocytoid Sweet syndrome.

Setting: University departments of dermatology and a private laboratory of dermatopathology.

Methods: Conventional histopathologic study as well as immunohistochemical investigations were performed using the alkaline phosphatase antialkaline phosphatase technique with a large panel of antibodies. In some cases, fluorescent in situ hybridization studies were performed to investigate the presence of the *bcr/abl* gene fusion.

Results: Immunohistochemical studies demonstrated that most cells of the infiltrate showed immunoreactivity for CD15, CD43, CD45, CD68, KP1, MAC 386, HAM56, and lysozyme, which is consistent with a monocytic-histiocytic immunophenotype. However, nonspecific esterase reactivity was detected in most of the cells with histiocytic appearance, which raised the possibility of specific differentiation toward myelogenous leukemia. Nevertheless, cytologic peripheral blood examinations, bone marrow biopsy, and cytogenetic studies to investigate the *bcr/abl* gene fusion, and follow-up of the patients, taken all together, ruled out this possibility.

Conclusions: This case series demonstrates that some fresh cutaneous lesions of Sweet syndrome are histopathologically characterized by an infiltrate mostly composed of cells that may be misdiagnosed as histiocytes when in fact they are immature myeloid cells. We named this clinicopathologic variant *histiocytoid Sweet syndrome*, which should not be confused with leukemia cutis or other inflammatory dermatoses that are histopathologically characterized by histiocytes interstitially arranged between collagen bundles of the dermis.

Arch Dermatol. 2005;141:834-842

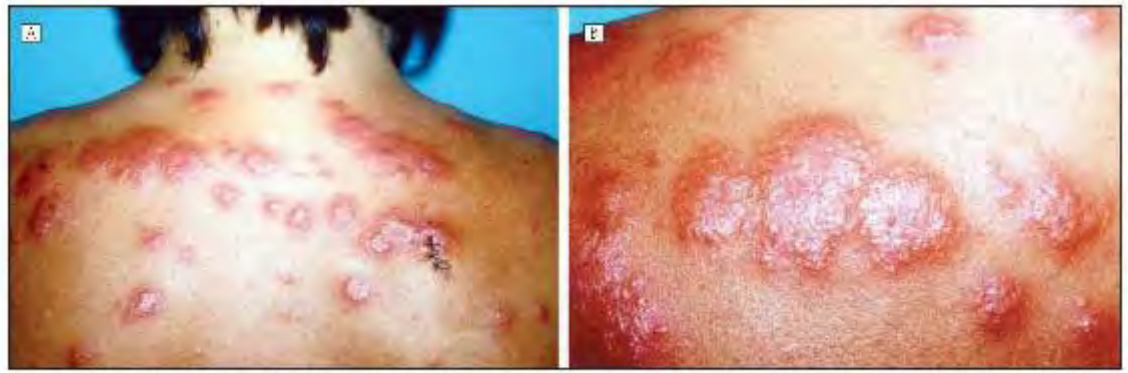


Figure 1. Clinical features of a patient (case 13) with histiocytoid Sweet syndrome. A, The patient showed numerous edematous erythematous plaques involving the upper back. B, Close-up view of the lesions.

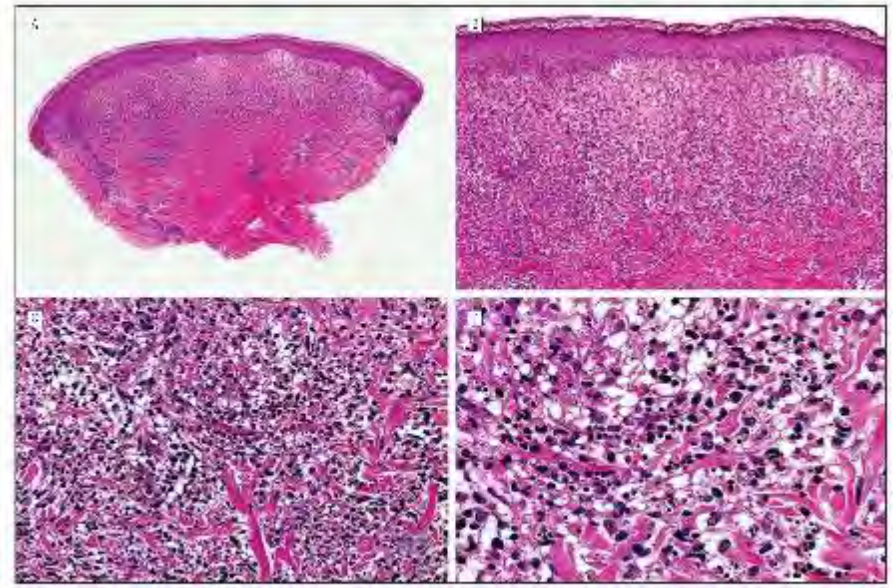


Figure 2. Histopathologic features of histiocytoid Sweet syndrome (case 13). A, Staining proved edematous dermis and a dense, inflammatory infiltrate involving the superficial and mid-dermis. B, The inflammatory infiltrate spared the epidermis. C, In some areas, the collagen bundles of the dermis (in pink) were separated by aggregates of inflammatory cells showing a histiocytoid appearance. D, Most of the cells of the infiltrate showed a histiocytic appearance, with folded eccentric nuclei, inconspicuous nucleoli, and scarce cytoplasm (hematoxylin-eosin, original magnifications ×10 [A], ×40 [B], ×200 [C], ×400 [D]).

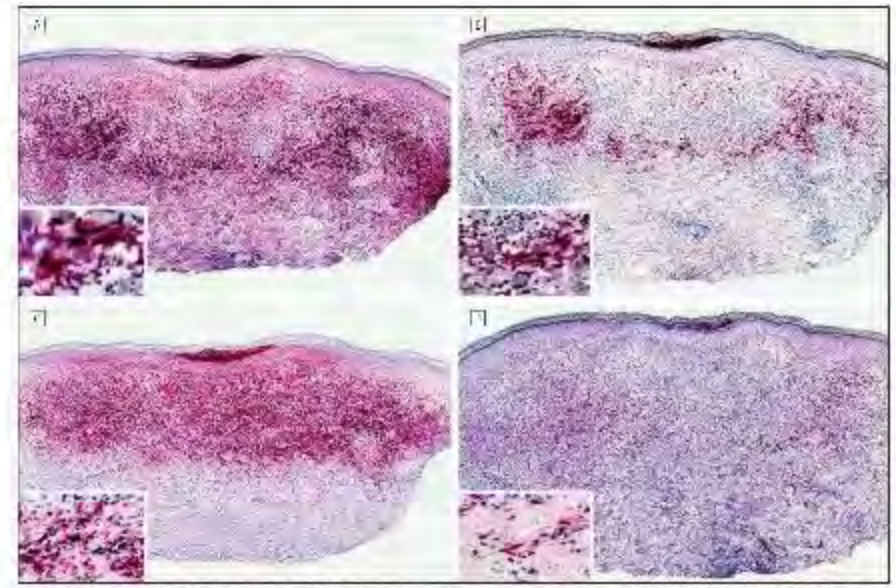
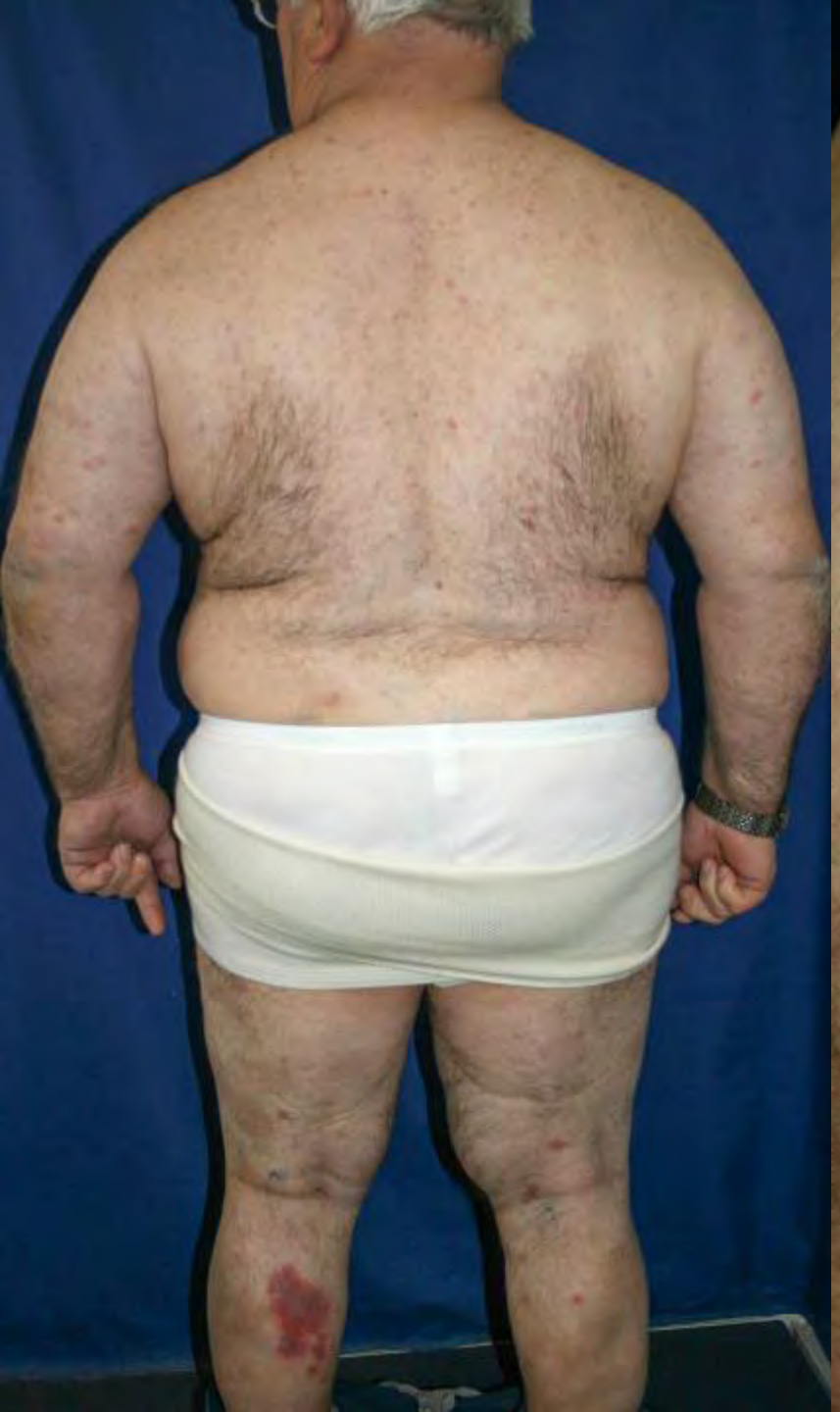
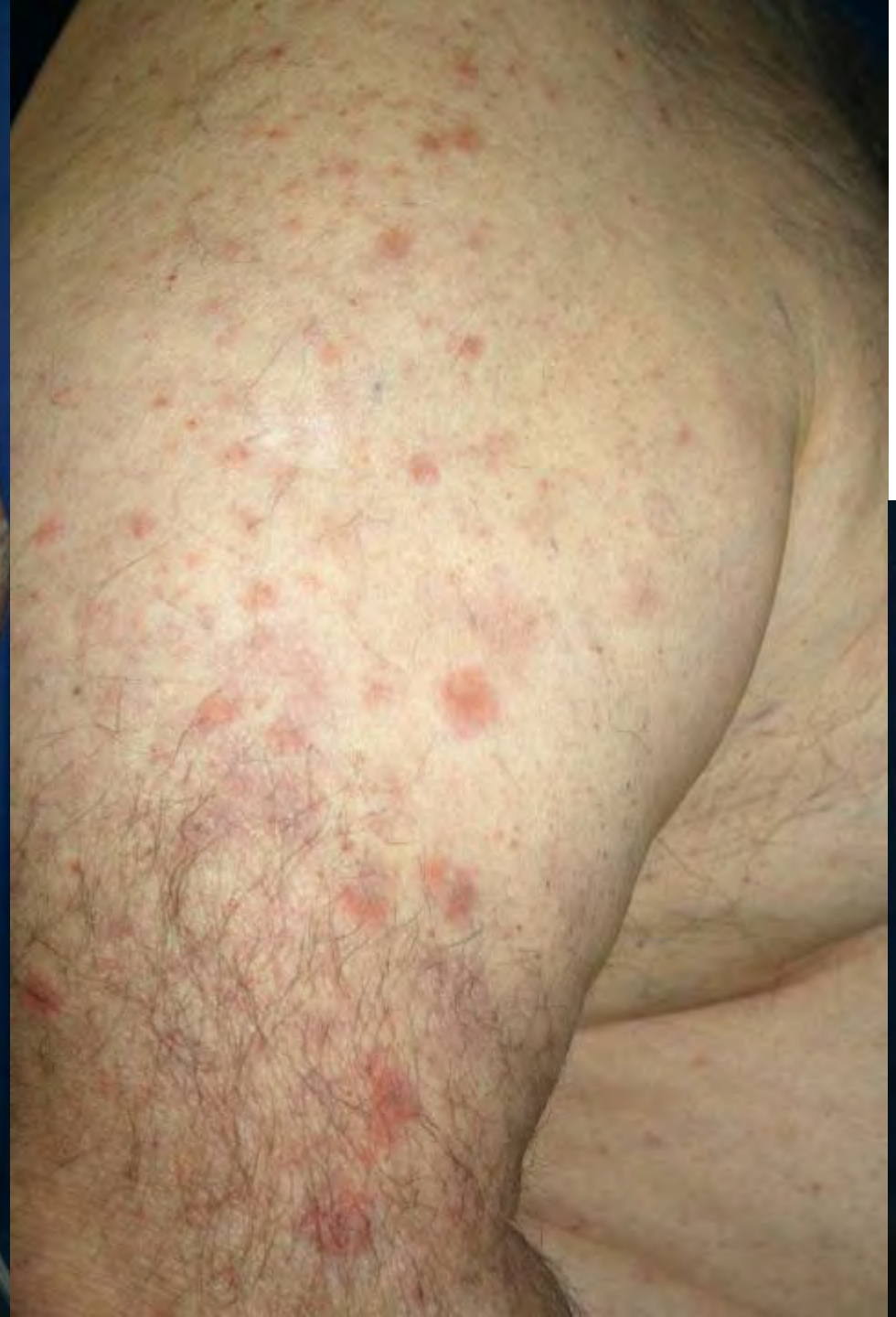


Figure 4. Immunohistochemical findings of histiocytoid Sweet syndrome (case 13). A, Strong immunoreactivity for myeloperoxidase in most of the cells of the dermal infiltrate. B, Only a few cells expressed immunoreactivity for neutrophil elastase. C, Many of the cells of the infiltrate expressed CD68 (clone KP1). D, Similar pattern of reactivity for L1 (anti-histiocyte antigen). Counterstaining with hematoxylin was used for all panels. Original magnifications ×10 (inset: high-power magnification [original magnification ×200] of each immunostaining result).



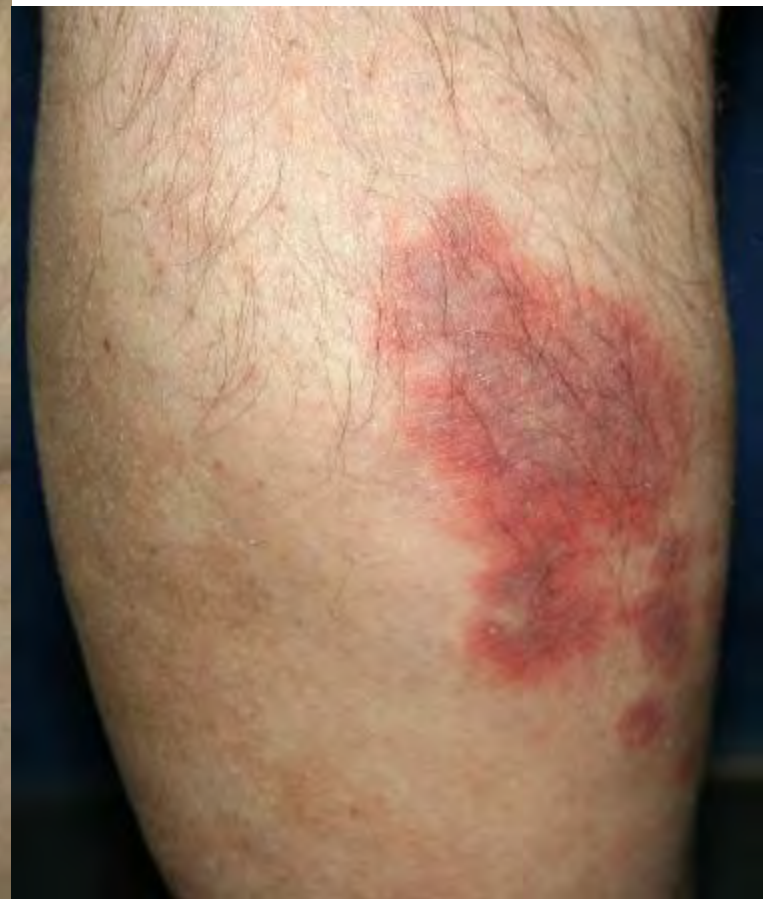


M, 69

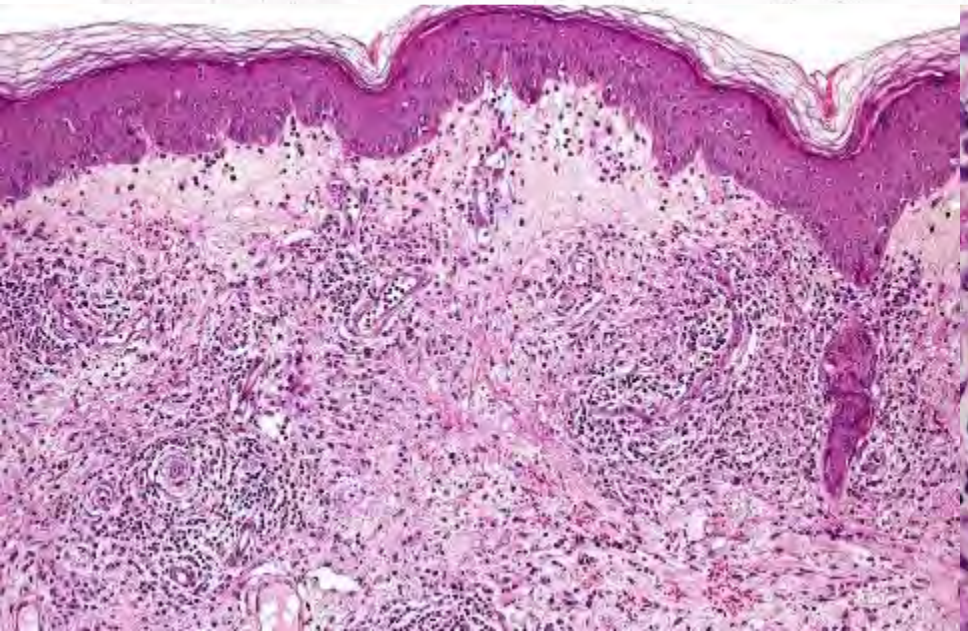
History of myelodysplastic syndrome. Partly purpuric, generalized lesions.

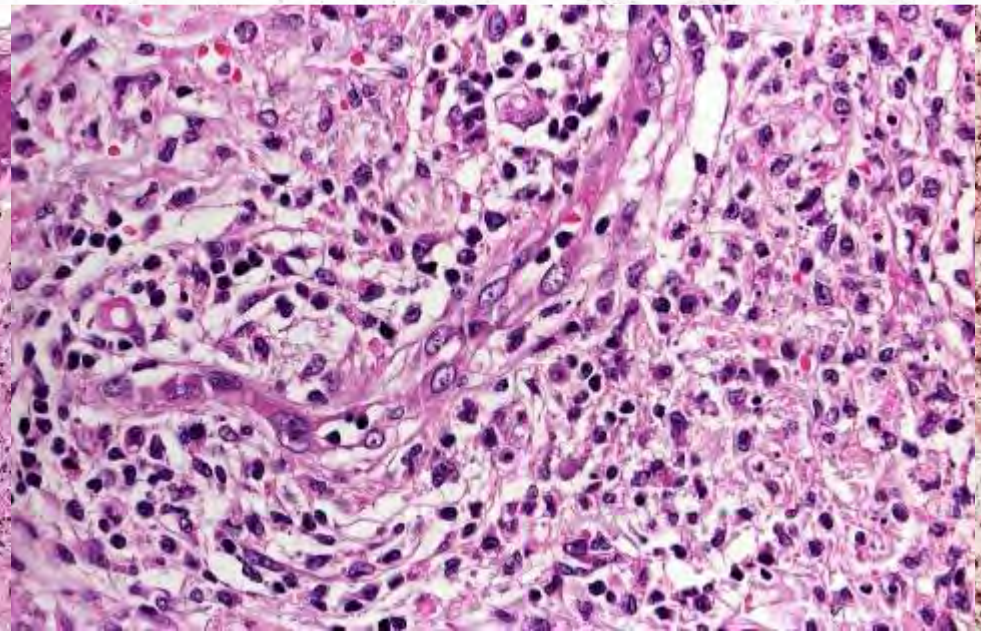
A biopsy is taken.

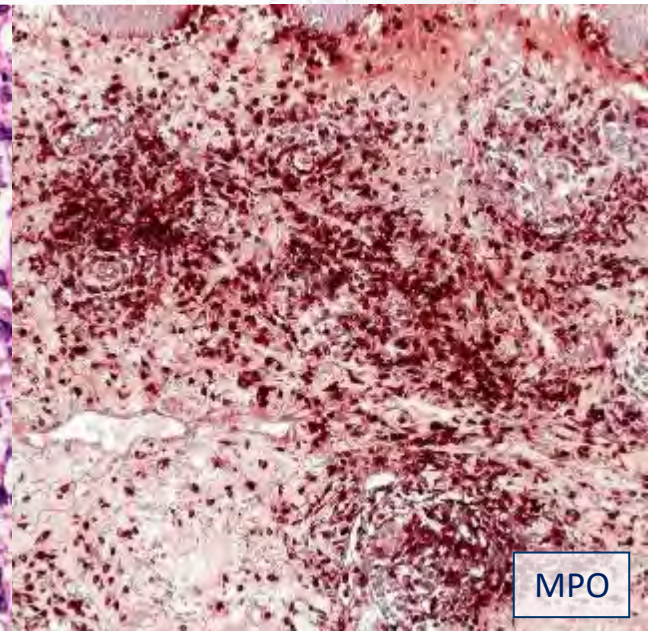
(Consultation Dr. Gentile, Bari)



Histiocytoid Sweet syndrome in MDS







Histiocytoid Sweet syndrome may indicate leukemia cutis: A novel application of fluorescence in situ hybridization

Rahul N. Chavan, MD, PhD,[a] Mark A. Cappel, MD,[b] Rhett P. Ketterling, MD,[b,c] David A. Wada, MD,[b] Nicole M. Rochet, MD,[a] Ryan Knudson, BA, MBA,[b] and Lawrence E. Gibson, MD[a,d]
Rochester, Minnesota; Jacksonville, Florida; and Salt Lake City, Utah

Background: In patients with malignancy-associated Sweet syndrome, a thorough evaluation for leukemia cutis should be considered.

Objective: We sought to describe the clinicopathologic characteristics of histiocytoid Sweet syndrome.

Methods: We retrospectively identified patients with histiocytoid Sweet syndrome at our institution from January 1992 through December 2010. We evaluated the underlying cutaneous infiltrate using immunohistochemistry and fluorescence in situ hybridization.

Results: We re-evaluated all 22 patients with hematologic malignancy–associated Sweet syndrome. Six patients had a monocytoid infiltrate that was consistent with histiocytoid Sweet syndrome; subsequent evaluation of these patients demonstrated cytogenetic abnormalities on prior bone-marrow biopsy specimens. Fluorescence in situ hybridization analysis was feasible in cutaneous specimens from 5 of the 6 patients and demonstrated the same cytogenetic abnormalities that were identified on prior bone-marrow biopsy specimens in 4 patients. Therefore, these 4 patients may have had a form of leukemia cutis.

Limitations: This was a retrospective study.

Conclusion: For patients with histiocytoid Sweet syndrome, an underlying hematologic malignancy, and a monocytoid infiltrate on biopsy specimen, fluorescence in situ hybridization of the cutaneous infiltrate may be beneficial to identify cytogenetic abnormalities that may indicate leukemia cutis. J Am Acad Dermatol 2014;70:1021-7.)

Key words: cytogenetic abnormalities; fluorescence in situ hybridization analysis; histiocytoid Sweet syndrome; leukemia cutis; malignancy-associated Sweet syndrome; Sweet syndrome.

In 1964, Sweet syndrome, also known as acute febrile neutrophilic dermatosis, was initially described by Robert Douglas Sweet.[1] Since then, Sweet syndrome has become part of a larger group of dermatologic diseases with an underlying neutrophilic infiltrate.[2] The diagnostic criteria of Sweet syndrome were delineated by Su and Liu,[3] and one of the major criteria required for diagnosis is histopathologic evidence of a neutrophilic infiltrate, typically in the absence of leukocytoclastic vasculitis.[2,4,5] Sweet syndrome can be associated with an underlying hematologic (myeloid disorder, solid tumor malignancies, inflammatory bowel disease, and gastrointestinal tract and upper respiratory tract infections.[6–11] A number of medications are also known to cause Sweet syndrome.[12,13]

Abbreviations used:

FISH: fluorescence in situ hybridization
MLL: mixed lineage leukemia gene

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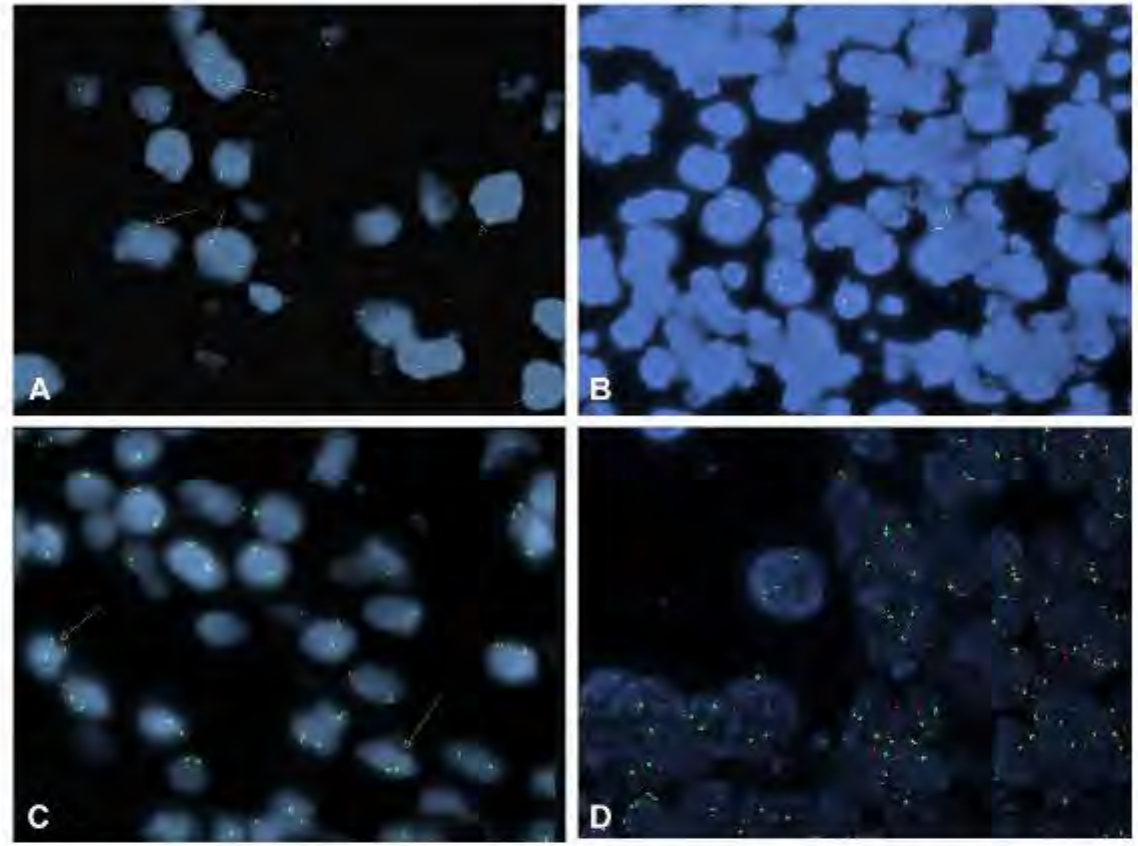
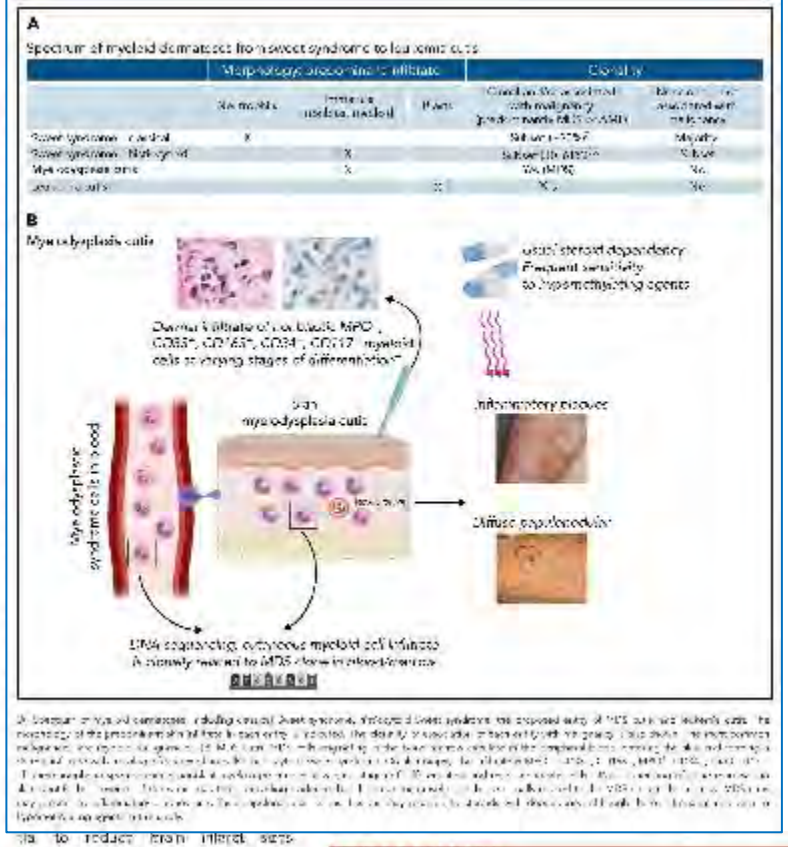


Fig 3. Evaluation of initial cutaneous biopsy specimens with fluorescence in situ hybridization to identify chromosomal abnormalities, which confirmed leukemia cutis in 4 patients. **A**, *Arrows* indicate fusion of DEK/CAN cells expressing the 6;9 translocation (DEK 6p23, *red*; CAN 9q34, *green*) in patient 1, consistent with leukemia cutis. **B**, Cells express the 9;22 translocation resulting in BCR/ABL fusion (ABL 9q34, *red*; BCR 22q11.2, *green*) in patient 2, indicative of leukemia cutis. **C**, Cells express the 7q deletion (7q32, *red*; centromere 7, *green*) in patient 8. *Arrows* indicate nuclei with deletion of D7S486, indicative of leukemia cutis in this patient. **D**, Approximately 10% of the cells in patient 12 demonstrated trisomy 8, consistent with leukemia cutis (centromere 8, *green*; cMYC 8q24.1, *red*).



is to reduce brain injury, restore cerebral blood flow, and preserve neurocognitive function following stroke.

As is typically the case with studies highlighting novel mechanisms, new questions emerge. First, although the investigators provide compelling evidence that neutrophil-derived PKM2 is mediating the observed effects, it is possible that PKM2 expression in other cell types is contributing to stroke pathogenesis. In particular, additional studies should focus on other immune cell types such as macrophages and T cells, which express PKM2 and have been linked to the pathogenesis of stroke and cerebral ischemia-reperfusion injury. Future studies should also clarify the precise PKM2-related mechanisms that exacerbate immune cell function in stroke. The investigators argue that nuclear PKM2 protein kinase activity is responsible for driving myeloid cell

MYELOID NEOPLASIA

Comment on Delaleu et al, page 1251

Skin in the game: the emergence of myelodysplasia cutis

Katherine R. Calvo | National Institutes of Health Clinical Center

In this issue of *Blood*, Delaleu et al[1] provide compelling evidence for formal recognition of an entity termed "myelodysplasia cutis" (MDS cutis) with histologic features of histiocytoid Sweet syndrome in the skin and a clonal relationship to myelodysplastic cells in the bone marrow.

In 1964, Robert Sweet first reported 8 patients with an acute febrile neutrophilic dermatosis, later termed Sweet syndrome.[2] Classical Sweet syndrome is histologically characterized by an inflammatory dermal infiltrate composed primarily of mature neutrophils. Sweet syndrome is associated with many etiologies, including infection, inflammatory disease, pregnancy, drug-related (commonly

TO THE EDITOR:

Clinical, pathological, and molecular features of myelodysplasia cutis

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A wide array of cutaneous manifestations can be observed in myelodysplastic syndromes (MDS), ranging from nonspecific, MDS-associated vasculitis, Sweet syndrome (SS) (sterile neutrophilic dermal infiltrate), and leukemia cutis (blast cell skin infiltration) corresponding to AML progression in the skin concomitant with or heralding MDS bone marrow (BM) progression.

Histiocytoid SS is a variant of SS composed of immature myeloid cells at various different maturation stages that is strongly associated with MDS.[1,3] One group introduced the term "myelodysplasia cutis" (MDS cutis) to describe specific myelodysplastic cell infiltration within the skin of MDS patients previously diagnosed as histiocytoid SS.[1,3] The relevance of this entity has been a matter of debate because the clinical origin of sterile-looking myeloid cells was rarely demonstrated.[4,5] Recently, however, we found that patients with MDS cutis harbor a clonal origin of myeloid cells present in the BM and infiltrating the skin, supporting MDS cutis as a true entity.[1]

Here, we report 5 cases of concomitant MDS cutis cases, related to the MDS clone, in 7 MDS patients. In the corresponding series

We retrieved MDS patients with cutaneous specific skin infiltrate followed at Hôpital Saint-Louis, Paris, between January 2007 and April 2021. Patients fulfilling the following criteria: "(1) diagnosis of MDS according to the World Health Organization 2016 criteria," (2) cutaneous histology consistent with "histiocytoid" immature myeloid cells, and (3) identical mutations of at least 1 same recurrently mutated in MDS in the BM and skin were considered to have MDS cutis. This definition ruled out leukemia cutis and neutrophilic MDS-associated SS.

Targeted next-generation sequencing (NGS) of 80 genes frequently mutated in MDS (and U2AF1 gene by Sanger sequencing) were performed on DNA extracted from BM and from formalin-fixed paraffin-embedded tissue sections of skin biopsy samples. Patients were classified according to the International Prognostic Scoring System (IPSS), considering IPSS low or intermediate-1 as lower risk and IPSS intermediate-2 and high as higher risk.[6]

Characteristics of the 7 patients (6 males, 1 female) are summarized in supplemental Table 1. Median age was 68 years (range, 40-79) at MDS diagnosis and 68 years (range, 42-80) at MDS cutis diagnosis. Median interval from MDS diagnosis to MDS cutis occurrence was 1 months (range, 1-233).

At diagnosis of MDS cutis, 6 patients had higher risk and 1 had low risk MDS. MDS features worsened at the time of MDS cutis diagnosis in 2 patients (acquisition of del(12p) in patient number 4 and of trisomy 8 in patient number 7) and 6 months after MDS cutis diagnosis in patient number 2 (progression from low risk to higher risk).

Clinically, 7 patients presented with erythematous, edematous (inflammatory) plaque pattern of the limbs and/or face (SS like) (Figure 1A-B) and 3 patients presented with a diffuse papulonodular cutaneous leukemia infiltrate (Figure 1C-D). Histology showed in all patients a dense infiltrate of immature myeloid cells at various differentiation stages, some of them presenting pseudo-Pelger-Huet abnormality (Figure 1E). A perivascular lymphocytic infiltrate was found in all cases, without any significant features of vasculitis, and a perivascular perineural distribution.

These neoplastic cells expressed CD68+, CD163+, CD117+, CD43+, PGM1+, and myeloperoxidase (MPO+) (Figure 1F) but did not express CD34-, CD56-, or CD1a-. Dermal edema and a correlation of CD3+ T cells were associated with the myeloid infiltrate in all cases.

NGS analysis (supplemental Table 1) identified 1 to 5 genes mutated both in the BM (with a median variant allele frequency [VAF] of 40%) and the skin paired sample (with a median VAF of 11%). Same mutations were detected in 1 sample and not the other, supporting clonal evolution in 1 of the tissues.

One patient had *DDX41* mutation in the blood and the skin whereas the 6 other patients tested were *DDX41* wild-type in both tissues. The patient with *DDX41* mutation had a 12 months history of vasculitis, arterial and leg venous thrombosis, hepatic liver, and cytoplasmic neutrophilic inclusions in myeloid and erythroid precursors in BM aspirate. The histologic profile of his cutaneous lesions did not differ from those of the other patients.

Six of the 7 patients received corticosteroids, and 4 (number 1 to 4) became steroid dependent. Azacytidine (75 mg/m² per day, in 5 day cycles) was introduced in those last 4 patients yielding complete resolution (CR) of MDS cutis in all cases with hematological improvement in 3 of them. Patient number 5 received low-dose cytarabine also with CR of MDS cutis. Three patients (number 2, number 3, and number 5) died of MDS progression within 9 months, 2 had more prolonged survival (>20 and >30 months, respectively), and the remaining 2 had short follow up (<4 and <12 months).

Myelodysplasia Cutis Versus Leukemia Cutis

Journal of Investigative Dermatology (2015) 135, 2321–2322; doi:10.1038/jid.2015.146; published online 14 May 2015

TO THE EDITOR

Skin lesions in myelodysplastic syndrome (MDS) include neutrophilic dermatoses (Vignon-Pennamen *et al.*, 2006), leukocytoclastic vasculitis, infections, drug reactions, and leukemia cutis (Aviv *et al.*, 1999). In MDS patients, leukemia cutis, a blastic myeloid cell infiltration of the skin (Oso-Vega *et al.*, 2008), has a poor prognosis (Aractingi *et al.*, 1996; Kaddu *et al.*, 1999), with a rapid development of acute myeloid leukemia (AML) and death (Longacre *et al.*, 1993). The prognostic value of skin lesions infiltrated only by non-blastic MDS tumor cells has not yet been characterized.

We studied 24 MDS patients with non-blastic skin infiltrate and compared them with 20 leukemia cutis patients. This study adheres to the declaration of Helsinki principles, and patient consent for experimentals was not required because the French laws consider human tissue left over from surgery as discarded material. Detailed patient data are given in Supplementary Table S1 online.

Between 1995 and 2012, 800 patients were diagnosed with MDS in Hôpital-Saint-Louis, Paris. One hundred and fifty patients underwent skin biopsy, and we identified 24 skin involvements by non-blastic tumor cells, defined as medium-sized immature myeloid cells (Figure 1) with (i) abundant cosmophilic cytoplasm and (ii) twisted nuclei or pseudo-Pelger-Huet anomaly, a specific myelodysplasia marker on blood smears (Shetty *et al.*, 2001). The tumor cells had a combined myeloid and monocytic phenotype, expressing both myeloperoxydase (100% of cases) and CD163 (100%) or CD68 (96%). They did not express CD34, CD117, or CD56. The proliferative index with Mib-1 was low (<10% positive cells) in 56% of cases, or intermediate (10 to 66% positive cells) in 44% of cases, but never high (≥66% positive cells). Mature neutrophils and normal CD3+ lymphocytes were numerous (46% and 100% of cases, respectively) and edema was frequent (67%).

Abbreviations: AML, acute myeloid leukemia; CGH, fluorescent in situ hybridization; IPSS, international Prognostic Scoring System; MDS, myelodysplastic syndromes; OS, overall survival

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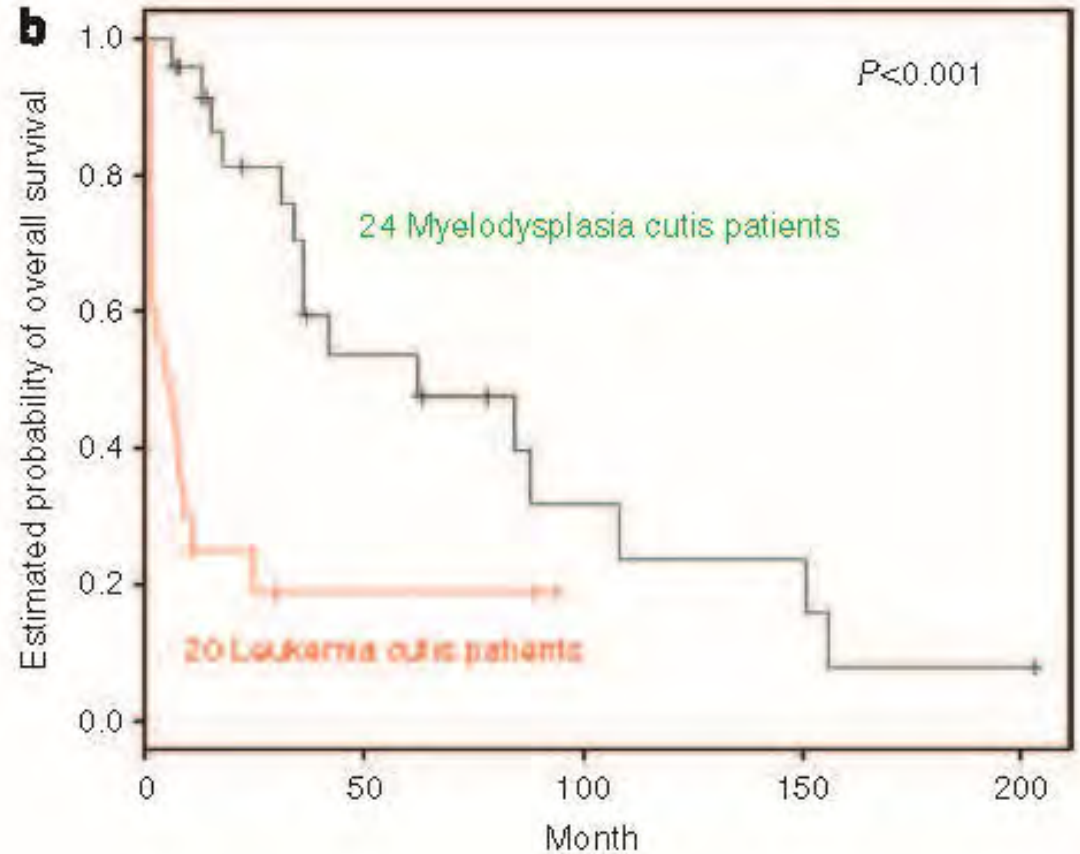
Osio A., et al.



Clinical report

Cynthia M. MAGRO
Shahrzad MOMTAHEN
Giang H. NGUYEN
Xuan WANG

Histiocytoid Sweet's Syndrome: A localized cutaneous proliferation of macrophages frequently associated with chronic myeloproliferative disease

Background: Histiocytoid Sweet's syndrome was originally described as cutaneous lesions of Sweet's syndrome where the infiltrate is mostly composed of histiocytoid mononuclear cells. The putative cell has been interpreted as an immature neutrophil based on the intense expression of myeloperoxidase. *Methods:* To better understand the nature of the infiltrate and potential mechanisms leading to this distinct form of cutaneous inflammatory cell influx, thirteen cases of histiocytoid Sweet's syndrome, encountered in the routine and consult practice of one of the authors, were studied. The clinical features and microscopic findings are summarized. *Results:* The study comprised eight men and five women aged from 23 to 80. There was a significant association with underlying myeloproliferative disease. In particular, five patients had underlying myelodysplastic syndrome. One patient had unspecified chronic myeloproliferative disorder and another had AML. Two cases were triggered by drug therapy (Cox-2 inhibitors). One patient had familial Mediterranean fever. The eruption was asymptomatic and an aggressive clinical course was not observed in most cases. Skin biopsies were composed of striking angiocentric and interstitial mononuclear cell infiltrates, often accentuated in the deeper dermis and subcutaneous fat. There was marked leukocytoclasia. Neutrophils were sparse or absent. These cells were strongly positive for CD163 and other expressed CD16 or myeloperoxidase. Variable positivity for myeloid dendritic cell markers including CD11c, BDCA-3, TCL1 oncogene, MXA and CD123 was observed. *Conclusions:* The histiocytoid cells of histiocytoid Sweet's syndrome define a novel subset of activated monocytes. This variant of Sweet's syndrome has a significant association with underlying myeloproliferative disease.

Key words: histiocytoid Sweet's syndrome, Sweet's syndrome, clonal cutaneous monocytosis

13 cases
5 patients had MDS
1 patient had AML
1 patient had unspecific chronic myeloproliferative disorder

Materials and methods

Thirteen cases of histiocytoid Sweet's syndrome were retrieved from the consultative files of one of the authors during the time frame of 2008 to 2014. These cases were presented in an abstract form at the United States

JAMA Dermatology | Original Investigation

Clinicopathologic, Immunohistochemical, and Molecular Features of Histiocytoid Sweet Syndrome

Victoria Aegerter-Wilmsen, MD; Socorro María Rodríguez-Peralto, MD; Ángel Santos-Briz, MD; Beatriz Rodríguez-Peralto, MD; Victoria Alegre, MD; Ismael Cerroni, MD; Ilaria Guitera, MD; Luis Requena, MD

IMPORTANCE Histiocytoid Sweet syndrome is a rare histopathologic variant of Sweet syndrome. The nature of the histiocytoid infiltrate has generated considerable controversy in the literature.

OBJECTIVE The main goal of this study was to conduct a comprehensive overview of the immunohistochemical phenotype of the infiltrate in histiocytoid Sweet syndrome. We also analyze whether this variant of Sweet syndrome is more frequently associated with hematologic malignancies than classic Sweet syndrome.

DESIGN This is a retrospective case series study of the clinicopathologic, immunohistochemical, and molecular features of 33 patients with a clinicopathologic diagnosis of histiocytoid Sweet syndrome was conducted in the dermatology departments of 3 university hospitals and a private laboratory of dermatopathology.

MAIN OUTCOMES AND MEASURES Theclinical, histopathological, immunohistochemical, and follow-up features of 33 patients with histiocytoid Sweet syndrome were analyzed. In some cases, cytogenetic studies of the dermal infiltrate were also performed. We compare our findings with those of the literature.

RESULTS There was infiltration in the 33 study patients (20 female, median age, 49 years; age range, 5-98 years; and 13 male, median age, 42 years; age range, 4-76 years) was mainly composed of myeloperoxidase-positive human leukocyte antigen–negative cells with histiocytoid morphology. No cytogenetic abnormalities were found in the infiltrate except in 1 case in which neoplastic cells of chronic myelogenous leukemia were intermingled with the cells of histiocytoid Sweet syndrome. Aberrant histologic features were also found in most cases of the classic immunoprofile, but they appeared to be a minor component of the infiltrate. Histiocytoid Sweet syndrome was not more frequently related with hematologic malignancies than classic neutrophilic Sweet syndrome.

CONCLUSIONS AND RELEVANCE The dermal infiltrate of cutaneous lesions of histiocytoid Sweet syndrome is composed mostly of mature cells of myeloid lineage. This infiltrate should not be interpreted as cutaneous

33 cases
1 patient had CML

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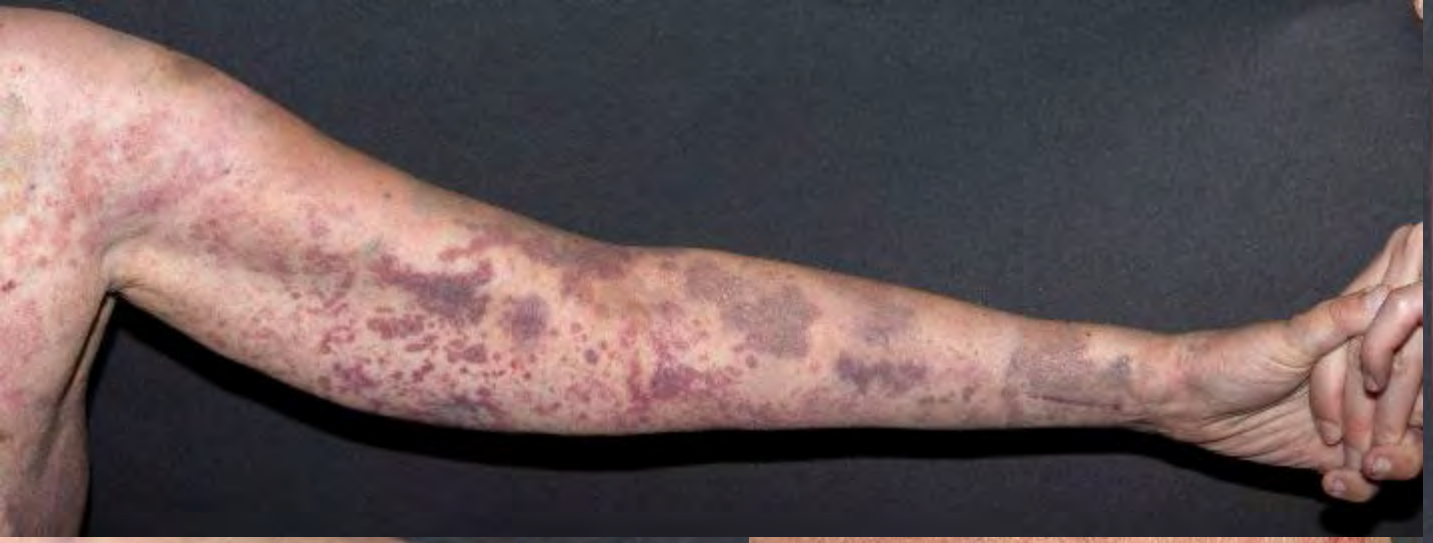
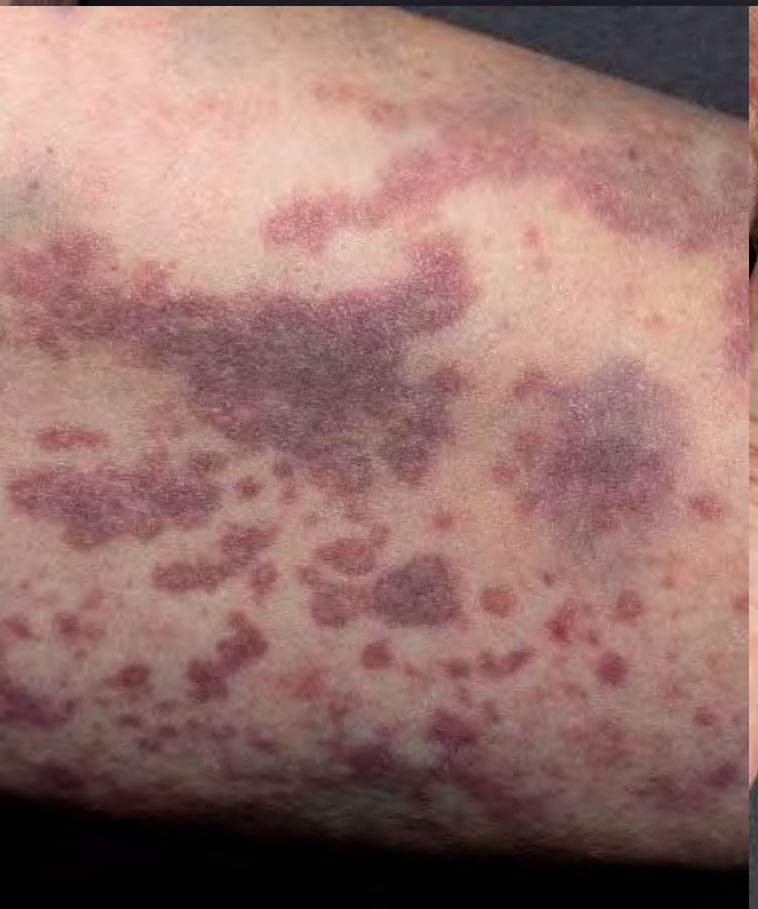
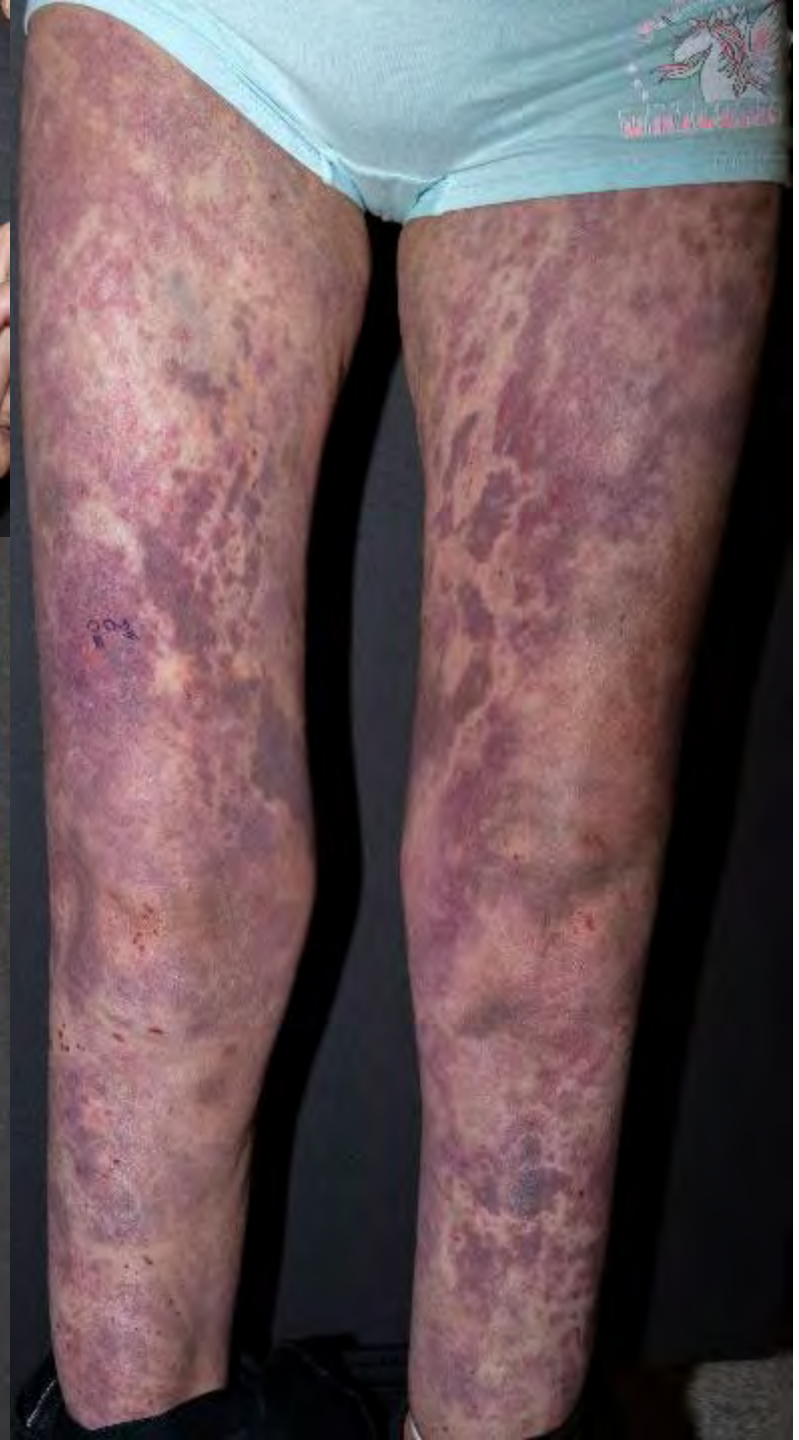
Cutaneous lesions in myelodysplastic syndrome

- Patients with myelodysplastic syndromes may present with skin manifestations related or unrelated to the underlying disease
- Specific manifestations may precede bone marrow signs of MDS; in some cases represent a sign of progression to overt leukemia
- The term "myelodysplasia cutis" has been proposed for so-called histiocytoid Sweet syndrome, as the same clone can be found in skin lesions and in the bone marrow (yet histiocytoid Sweet syndrome can be observed also in AML *and in patients without hematological diseases*)







F, 41

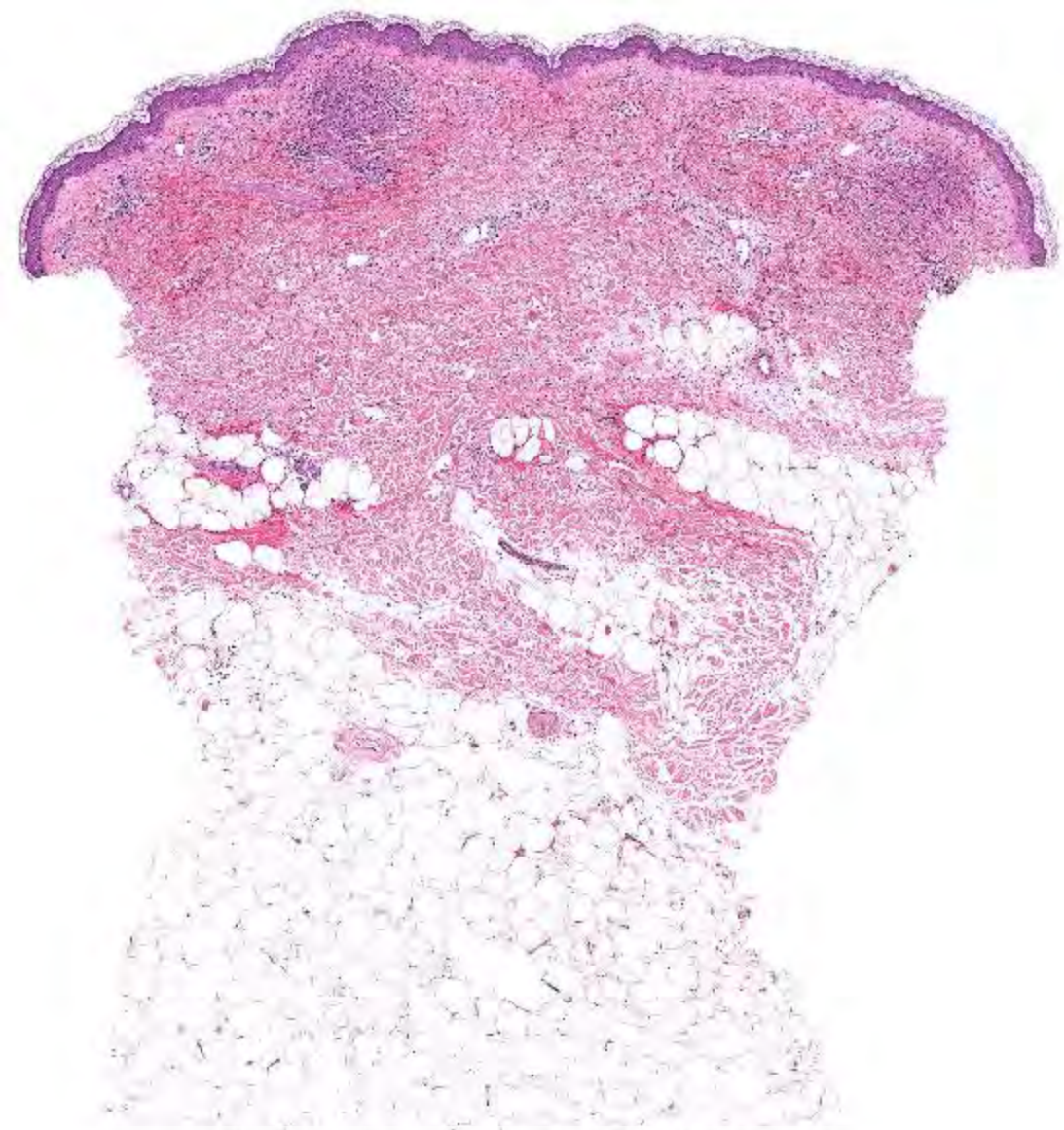
History of mental retardation since early childhood.

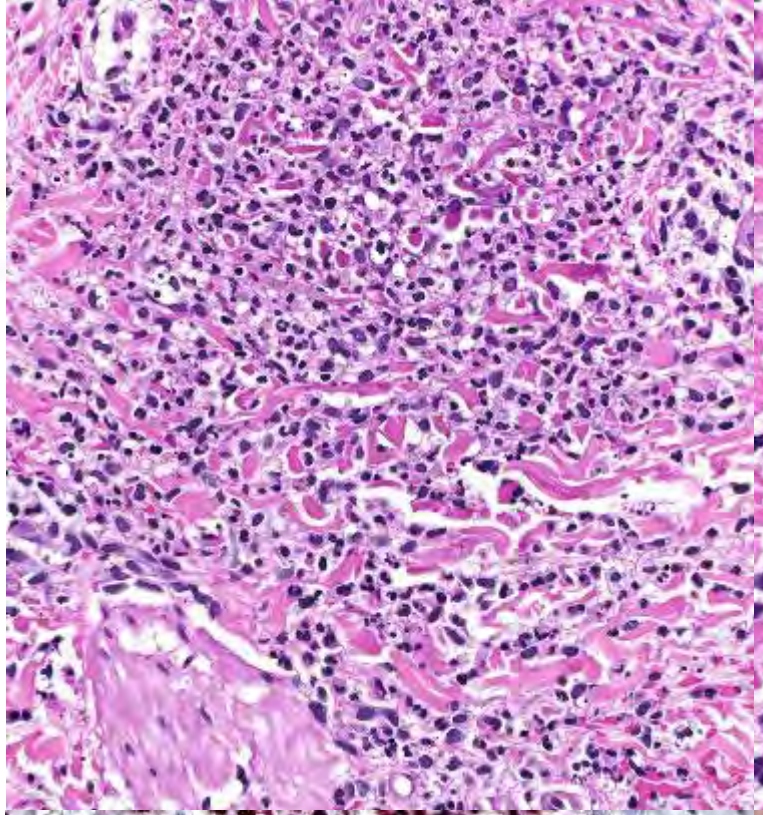
Almost complete bone marrow aplasia for the last 3 months.

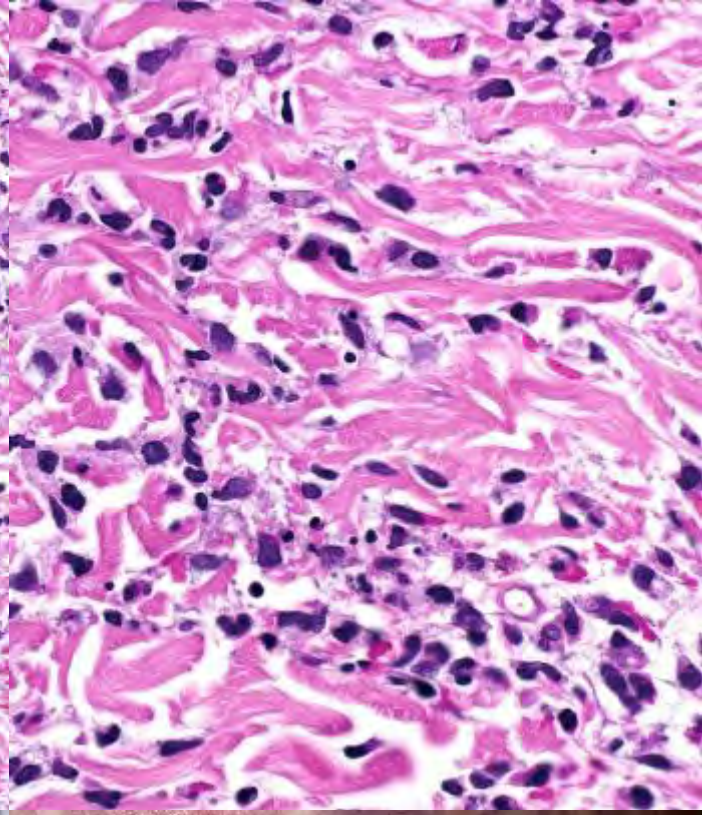
Thrombopenia (12.700).

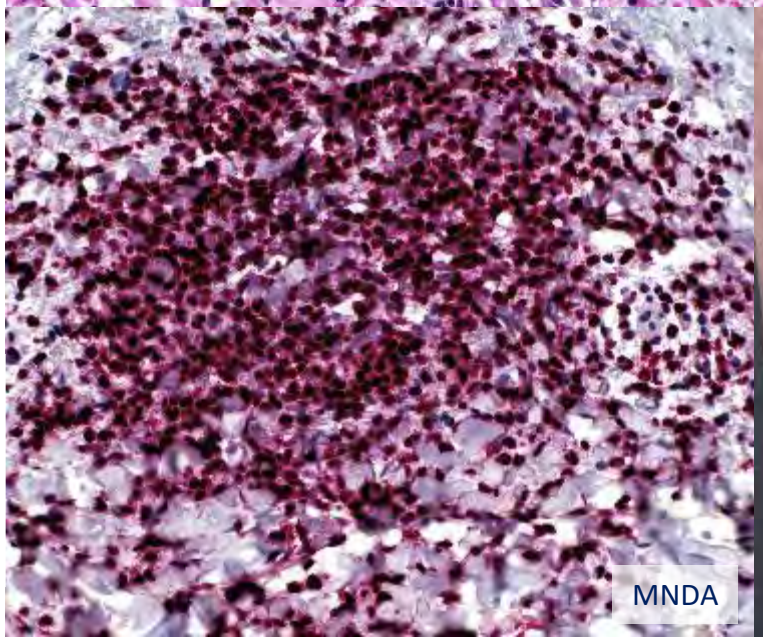
Treatment with filgrastim and paracetamol for 3 weeks. Approx. 30 minutes after the 9th injection of filgrastim and intake of paracetamol onset of "exanthema".

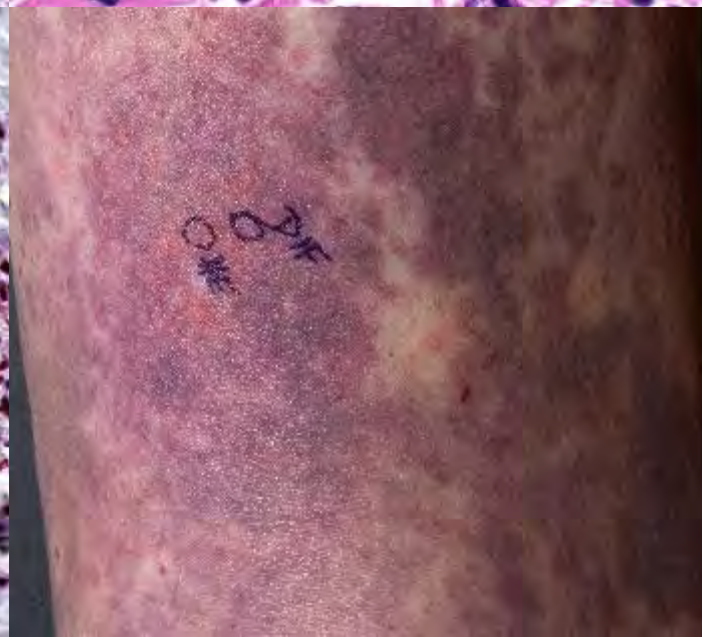
A biopsy is taken.





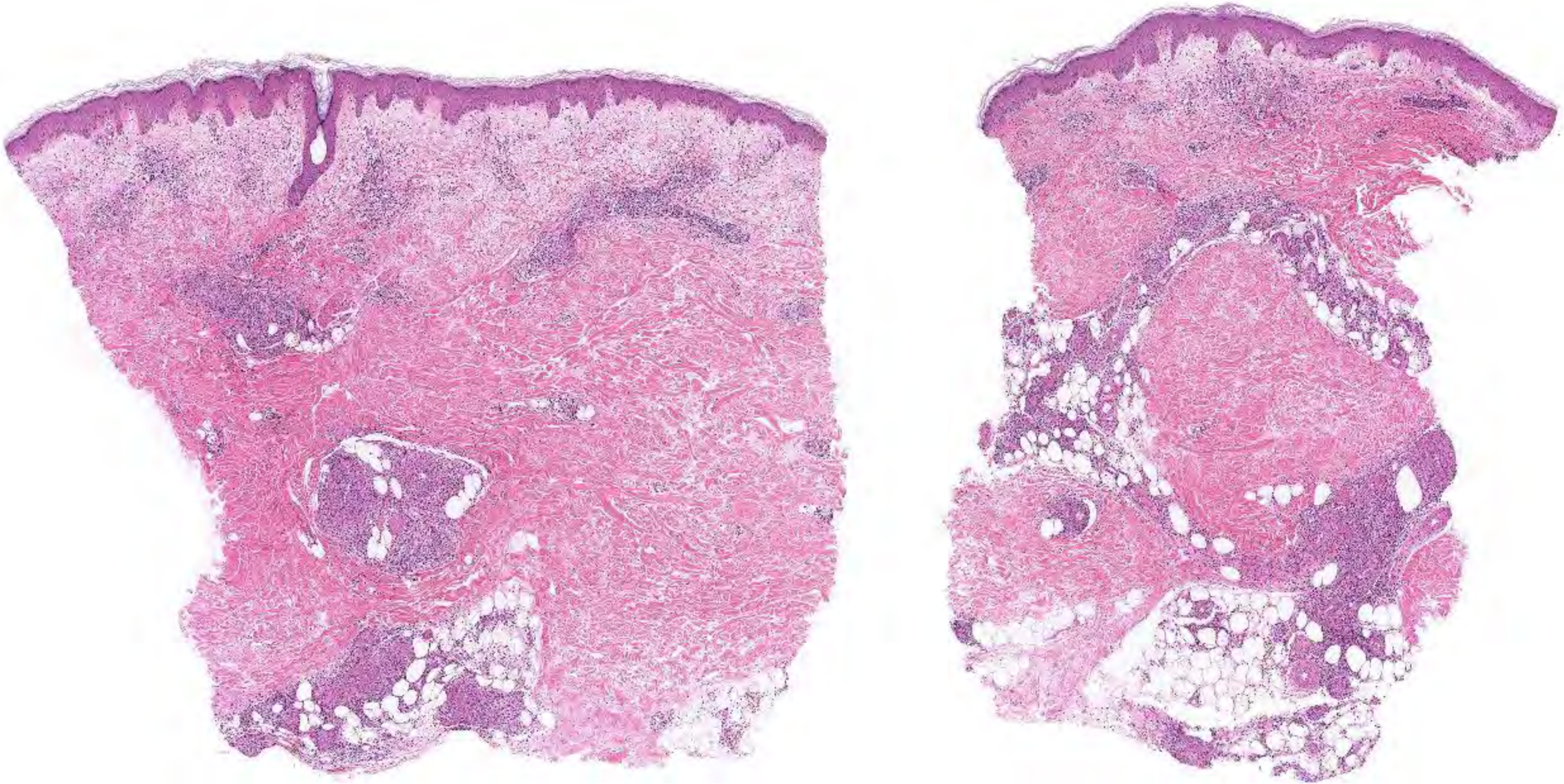






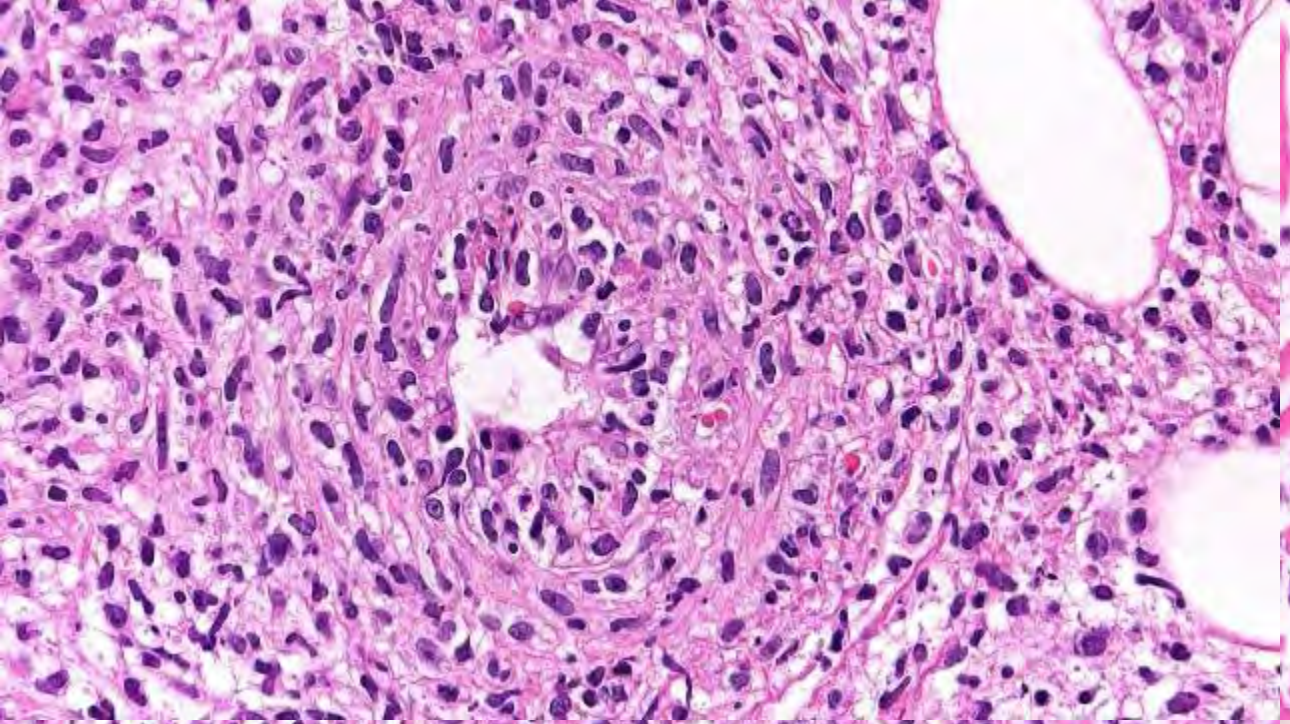
Leucocytoclastic vasculitis

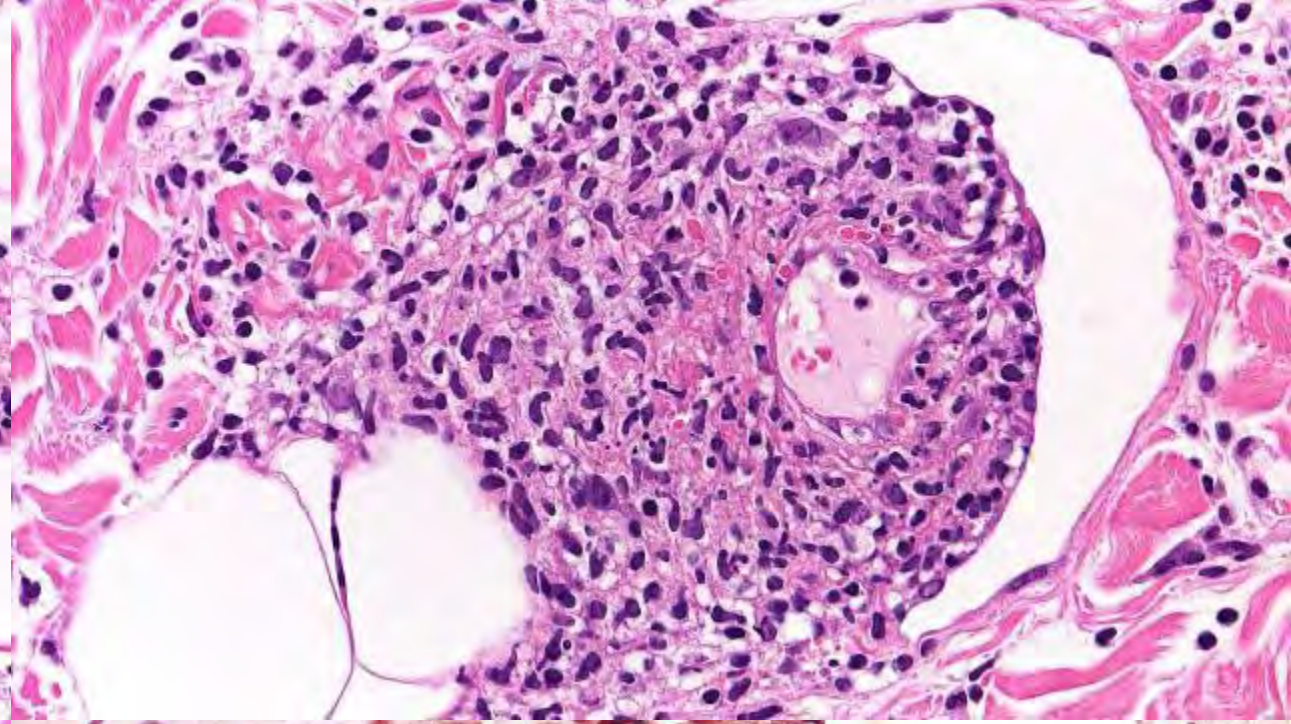
with "histiocytoid" cells

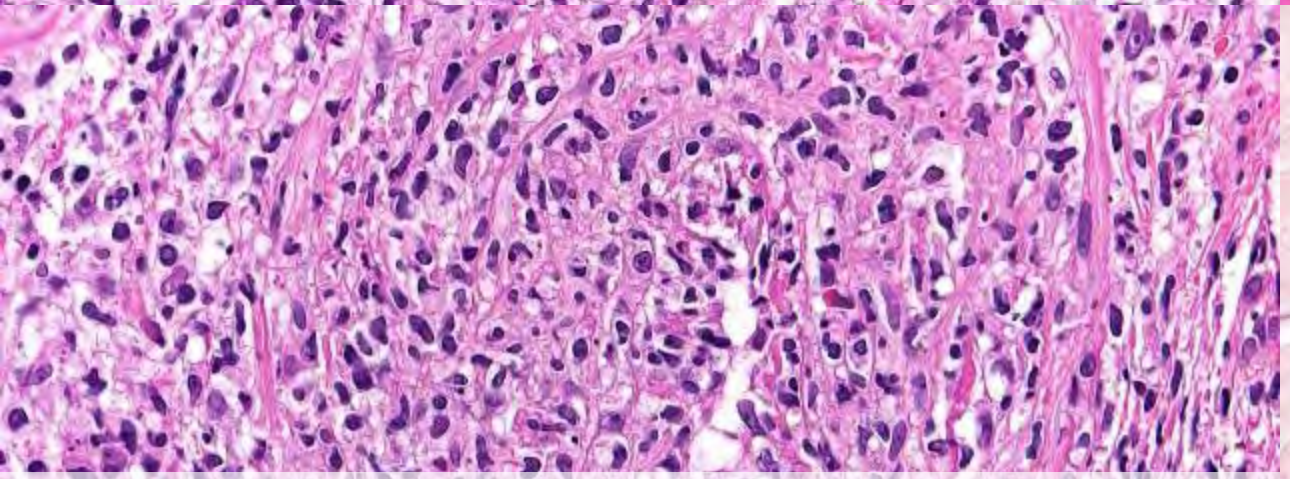


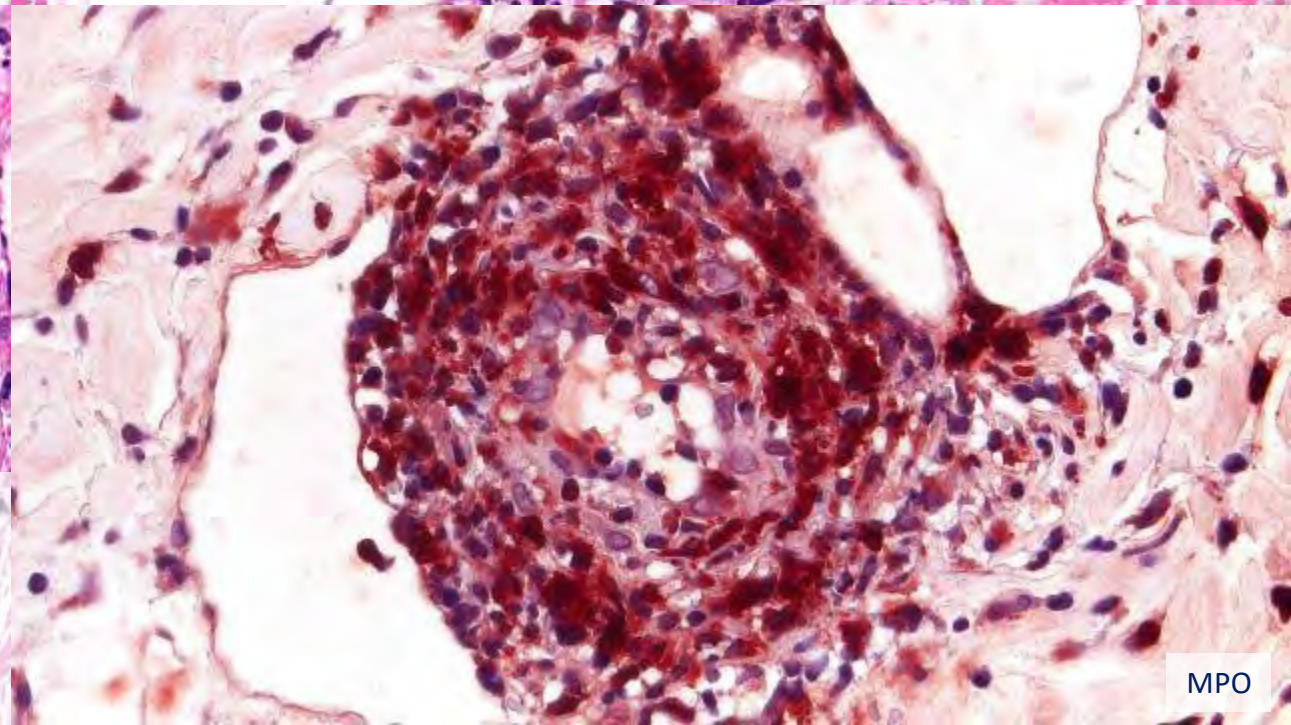
M, 76

History of chronic myelomonocytic leukemia (1st diagnosis 5 years before this biopsy). Recurrent erythema nodosum-like lesions on the legs for 1 year.







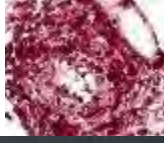


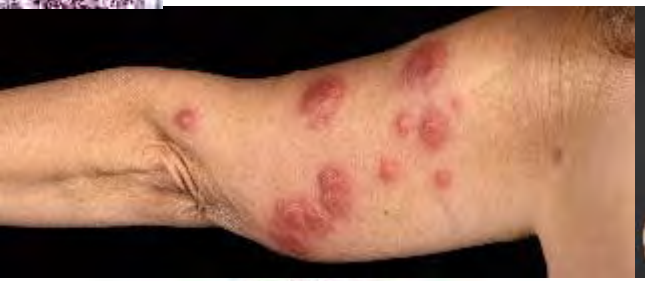
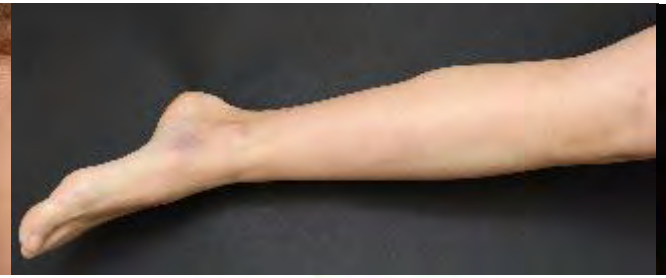
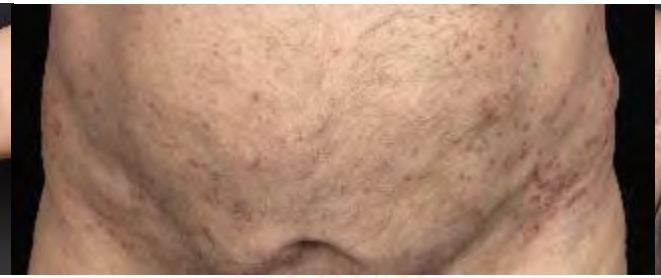
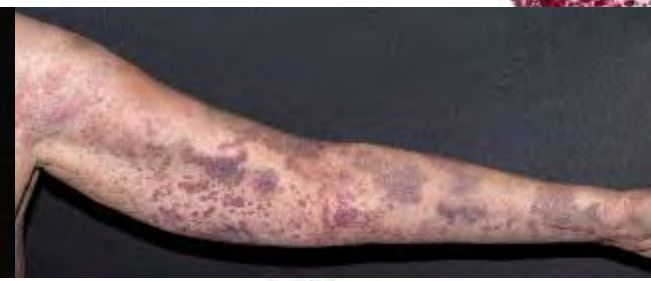
Leucocytoclastic vasculitis

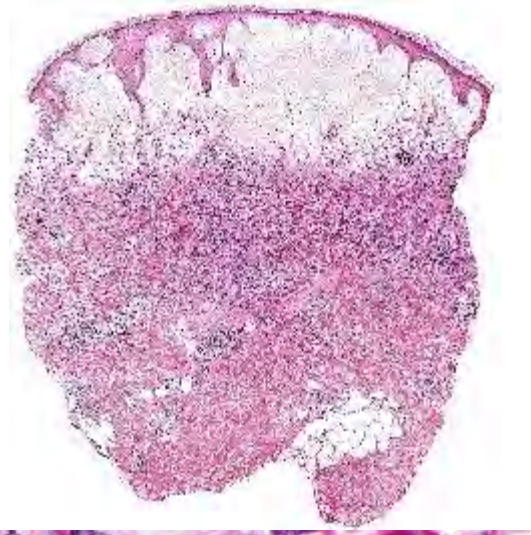
with "histiocytoid" cells

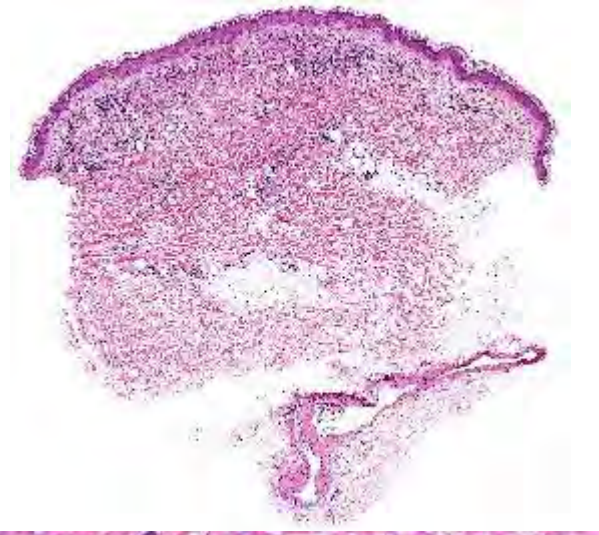
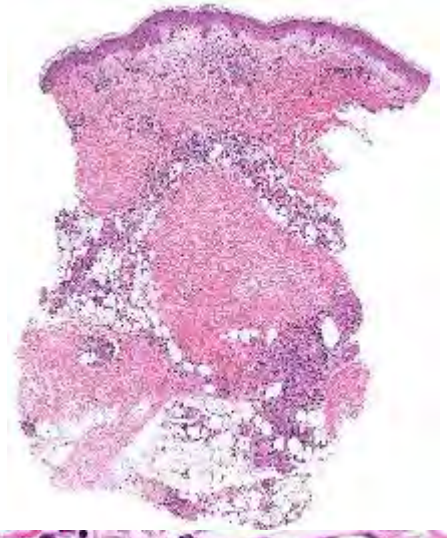
"Histiocytoid" cells in cutaneous infiltrates

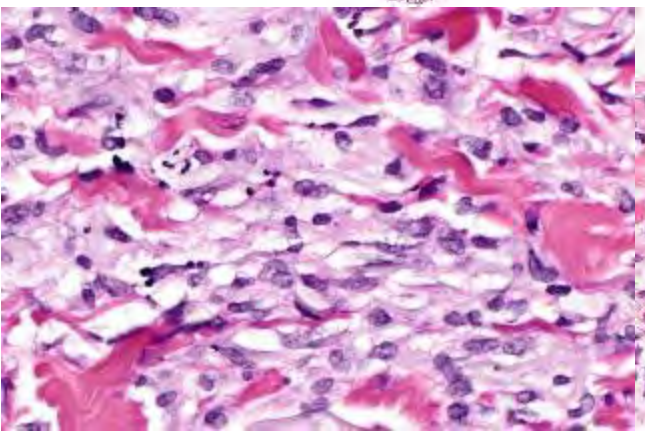

MNDA

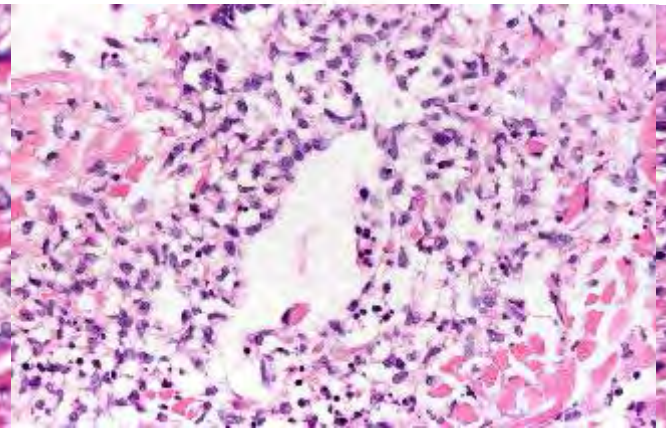

MPO

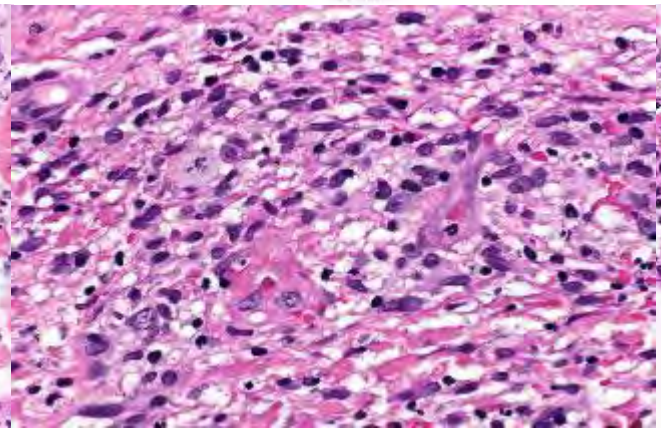





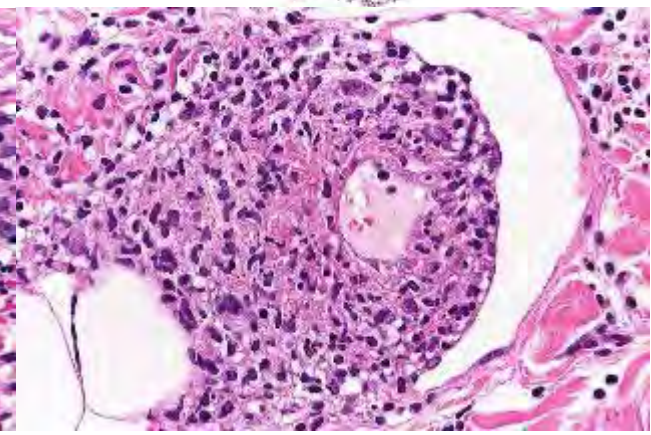



Sweet syndrome


Erythema nodosum


Drug reaction


Leukocytoclastic vasculitis

Cutaneous myelogenous leukemia

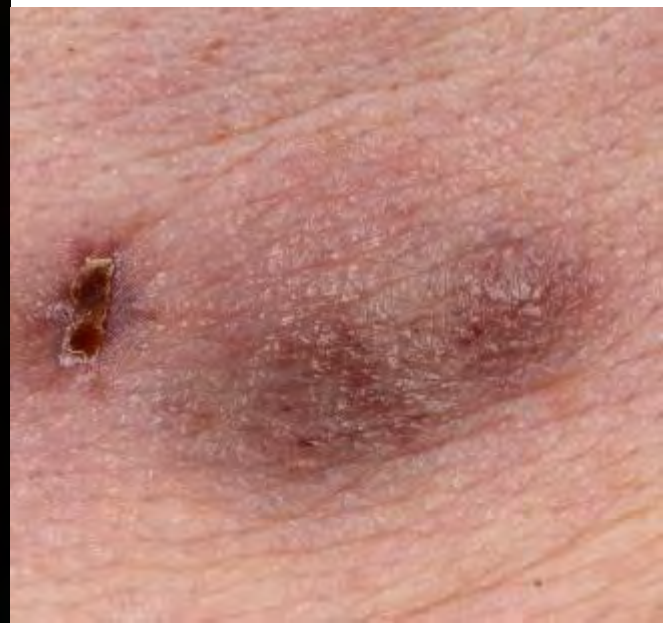
- Skin often involved; may be the site of first diagnosis, rarely without overt leukemia *("aleukemic leukemia cutis"),* or of relapse after successful treatment
- Skin involvement observed in various types of AML as well as in CMML (usually as a sign of progression); Skin lesions in MDS are rare and not always associated with progression to overt leukemia
- In several cases of AML "inflammatory-like" pattern of dermal infiltration, representing a pitfall in the histopathological diagnosis
- Rare patients may present with a cutaneous infiltrate of mature plasmacytoid dendritic cells (CD123+ / CD56-); the exact nature and prognostic relevance (if any) of these infiltrates is still unclear

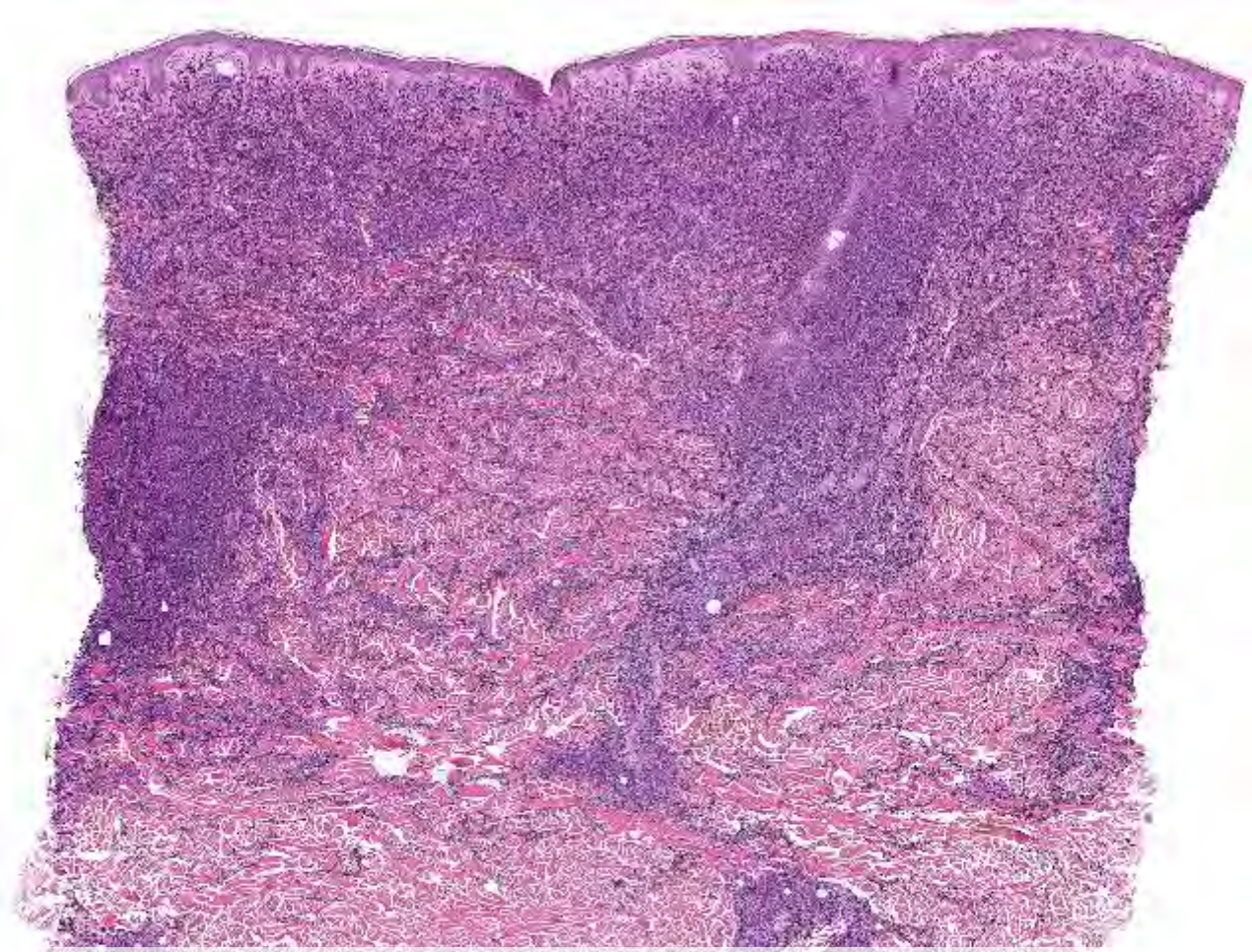
M, 71

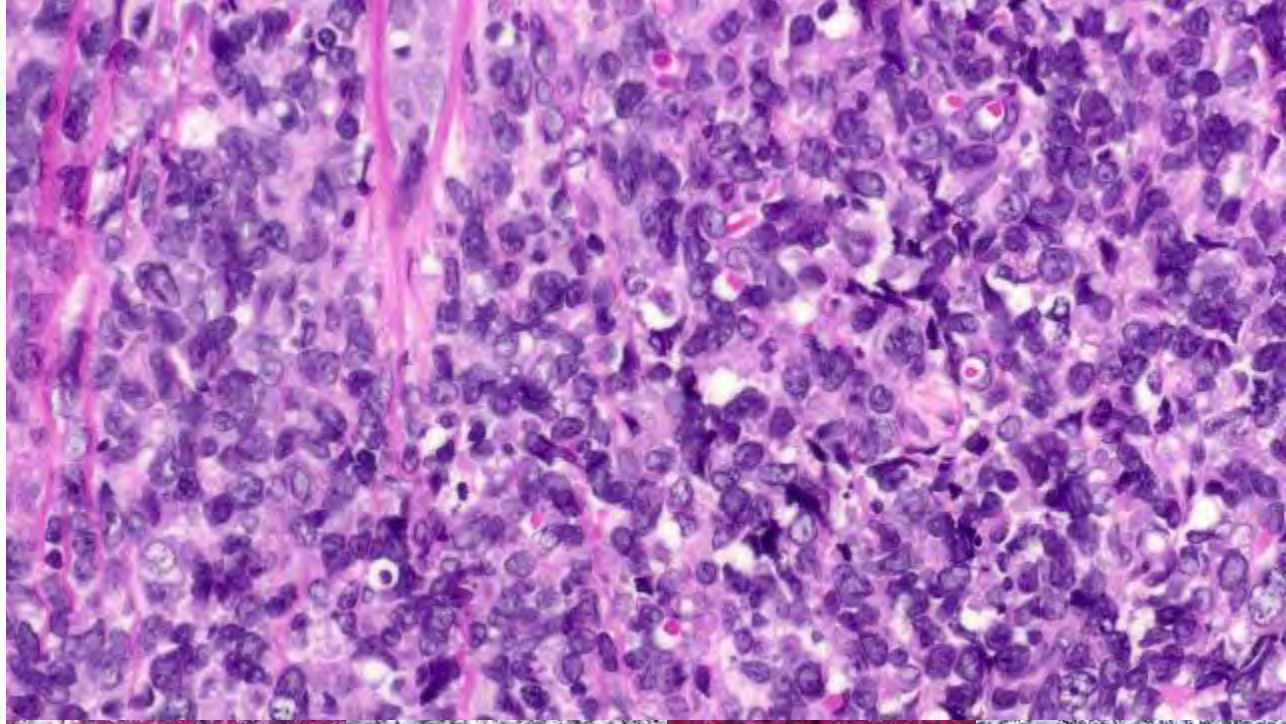
Asymptomatic, infiltrated, red-brownish skin lesions on the left flank since 3 weeks.

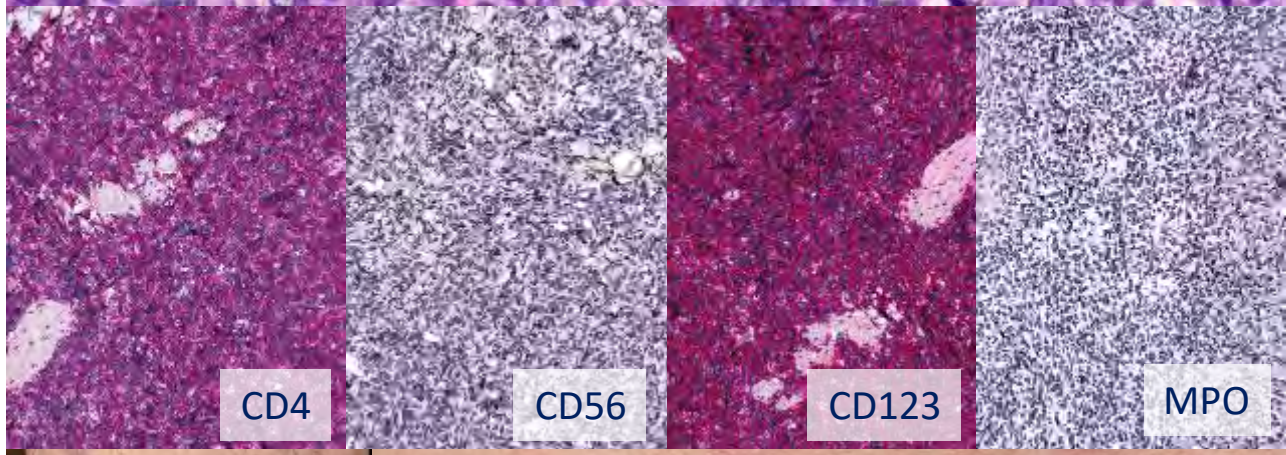
Good general condition.

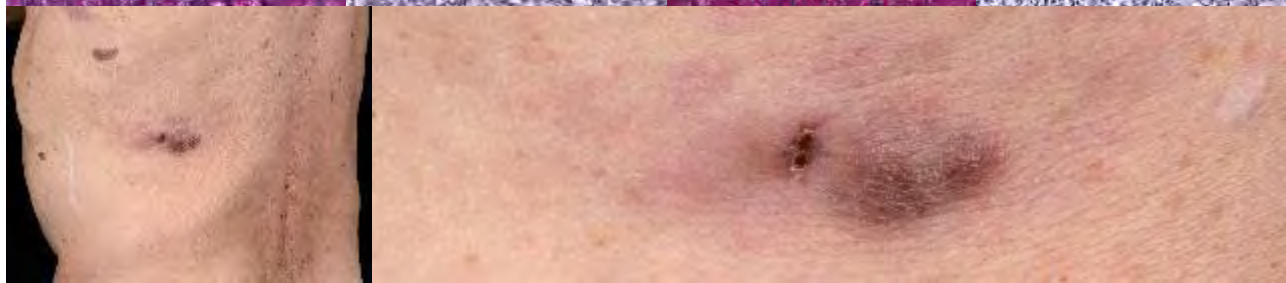
Clinical picture taken after a punch biopsy.











Blastic plasmacytoid dendritic cell neoplasm

Positive liquor & bone marrow

CD4+/CD56+ Hematodermic Tumor

The Features of an Evolving Entity and Its Relationship to Dendritic Cells

Marco Herling, MD, and Dan Jones, MD, PhD

Key Words: CD4+/CD56+ hematodermic tumor; Blastic NK-cell lymphoma; DC2; Dendritic cells; TCL1

DOI: 10.1309/FV6PK426NBK0RYD4

Am J Clin Pathol 2007;127:687-700

Table 1

An Evolving Entity: Past and Current Nomenclature of Tumor Types That Overlap With the CD4+/CD56+ Hematodermic Tumor

Tumor Type	References
Histiocyte-associated hematologic malignancy	Gattei et al[1]
CD4+/CD56+ acute monoblastic leukemia	Tauchi et al[2]
Acute agranular CD4+ NK-cell leukemia	Brody et al[3]
Cutaneous agranular CD2–/CD4+/CD56+ lymphoma	Kameoka et al[4]
Myelomonocytic precursor cell–related lymphoma	Bagot et al[5]
Primary cutaneous CD4+/CD56+ hematolymphoid neoplasm	Petrella et al[6]
Agranular CD4+/CD56+ blastic NK leukemia/lymphoma	Kimura et al[7]
Blastic NK-cell lymphoma (WHO)	Chan et al,[8] DiGiuseppe et al,[9] Bayerl et al,[10] and Falcao et al[11]
(Lympho)blastoid NK-leukemia/lymphoma	Estalilla et al,[12] Ginarte et al,[13] and Knudsen et al[14]
DC2 precursor acute leukemia	Chaperot et al[15] and Anargyrou et al[16]
CD56+TdT+ blastic NK-cell tumor of skin	Khoury et al[17]
CD4+/CD56+ acute leukemia	Feuillard et al[18]
Agranular CD4+/CD56+ hematodermic tumor	Petrella et al[19] and Kato et al[20]
Early plasmacytoid dendritic cell leukemia/lymphoma	Jacob et al[21] and Giagounidis et al[22]
DC2-related CD4+/CD56+ blastic tumor of skin	Herling et al[23]
Closely related tumors with unclear single-entity status	
Plasmacytoid T-cell lymphoma	Prasthofer et al[24]
Plasmacytoid monocytes associated with myeloid disorders	Vermi et al[25]

DC2, a subset of dendritic cells; NK, natural killer; TdT, terminal deoxynucleotidyl transferase; WHO, World Health Organization.

International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data

collaboration was primarily based on input from a clinical advisory committees (CACs) composed of pathologists, hematologists, oncologists, geneticists, and bioinformaticians from around the world. The recent advances in our understanding of the biology of hematologic malignancies, the experience with the use of the 2016 WHO classification in clinical practice, and the results of clinical trials have indicated the need for further revising and updating the classification. As a multiparameter approach, the main objective of the consensus process was the definition of real disease entities, including the introduction of new entities and refined criteria for existing diagnostic categories, based on accumulated data. The ICC is aimed at facilitating diagnosis and prognostication of these neoplasms, improving treatment of affected patients, and allowing the design of innovative clinical trials.

Leukemia

REVIEW ARTICLE

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/ Dendritic Neoplasms

Joseph D. Khoury, Eric Solary, Oussama Abla, Yassmine Akkari, Rita Alaggio, Jane F. Apperley, Rafael Bejar, Emilia Bell, Lambert Busque, John K. C. Chan, Wee Joo Chng, Xueyan Chen, Wee Joo Chng, John K. Choi, Isabel Colmenero, Sarah E. Coupland, Nicholas C. P. Cross, Daphne De Jong, M. Tarek Elghetany, Emike Takahashi, Jean-Francois Emile, Judith Ferry, Linda Fogelstand, Michaela Fontenay, Lukas Frenzel, Sumeet Gujral, Torsten Haferlach, Claire Harrison, Jennifer L. Hodge, Shih-Sung Hu, Joop H. Jansen, Rashmi Kanagal-Shamanna, Hagop M. Kantarjian, Christian P. Kratz, Xiao Qin Li, Megan S. Lim, Keith Loch, Sanam Loghavi, Andrea Marcogliese, Sohail Meshinchi, Phillip Michaels, K. Joseph N. Naresh, Vasudha Natkunam, Reza Nejati, German Ott, Eric Padron, Keyur P. Patel, Nikhil Patkar, Jennifer Piccaluga, Uwe Platzbecker, Irene Roberts, Anna Schuh, William Sewell, Reiner Siebert, Prashant Tembhare, Jeffrey Tyner, Sidan Verstovsek, Wei Wang, Brent Wood, Wenbin Xiao, Cecilia Yeung and Andreas Hochhaus

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ICC 2022/2025 & WHO 2023/2024:

Blastic plasmacytoid dendritic cell neoplasm

Diagnostic criteria similar in both classifications

Special Report

North American Blastic Plasmacytoid Dendritic Cell Neoplasm Consortium: position on standards of care and areas of need

Nayoon Pemmaraju,[1] Hagop Kantarjian,[2] Kendra Sweet,[3] Eunice Wang,[4] Jayesh Sanapar,[5] Nemanja P. Wilson,[6] Marina Konopleva,[2] Ayalew Tefferi,[7] Mike Deeg,[8] Ruben Mesa,[9] Matthew J. Kelly,[10] Edward Gladu,[11] Ankur Bhatia,[12] Tulin Kaskar Aydogan,[13] Jonas Mauro,[14] Maria Teresa Garcia Rodriguez,[15] Nancy Jones Santiago,[16] Gabriela Guzman Mejia,[16] Daniel Vaughan,[17] Sangeeta Lee,[18] Vijaya Raj Bhatt,[19] William Blum,[20] Richard B. Walter,[21] Jane Beckey,[22] Ilana Gojo,[23] Madeleine Duvic,[24] Isaac K. Rampal,[25] Marcos de Lima,[26] James Foran,[27] Amir T. Fathi,[28] Ann Cameron Haley,[29] Meagan A. Jacoby,[30] Jeffrey Lancet,[31] Gabriel Morris,[32] Anthony S. Stein,[33] Alice Mims,[34] David Rizzieri,[35] Rebecca Olin,[36] Alexander Perl,[37] Gary Schiller,[38] Paul Shaw,[39] Richard M. Stone,[40] Shannon Stockerl-Goldstein,[41] Matthew J. Wieduwilt,[42] Navid Davani,[43] Farrukh Awan,[44] Marina Konopleva,[2] Sanjay Mukherji,[45] Joseph Khoury,[46] Maria Dela Cruz,[47] Priya Kishtagari,[48] Jianke Zeng,[49] Yosry Madanat,[50] Mohamed A. Kharfan-Dabaja,[51] Anna Pawlowska,[52] Justin Taylor,[53] Marc Tallman,[54] Pawel Muchel,[55] and Andrew A. Lane[56]

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[47]Division of Hematology, Department of Medicine, Stanford University, Stanford, CA; [48]Division of Hematology, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; [49]Division of Hematology, Department of Medicine, Mayo Clinic, Jacksonville, FL; [50]Harvard Medical School, Boston, MA; [51]Division of Hematology, Mayo Clinic, Rochester, MN; [52]Division of Hematology, Department of Medicine, Stanford University, Stanford, CA; [53]Division of Hematology, Department of Medicine, University of Washington School of Medicine, Seattle, WA; [54]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; [55]Department of Hematology, Poznan University of Medical Sciences, Poznan, Poland; [56]Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematologic malignancy with historically poor outcomes and no worldwide consensus treatment approach. Unique among most hematologic malignancies for its frequent cutaneous involvement, BPDCN can also invade other extramedullary compartments, including the central nervous system. Generally affecting older adults, many patients are unfit to receive intensive chemotherapy, and although hematopoietic stem cell transplantation is preferred for younger, fit individuals, not all are eligible. One recent therapeutic breakthrough is that all BPDCNs express CD123 (IL3Rα) and that this accessible surface marker can be pharmacologically targeted. The first-in-class agent for BPDCN, tagraxofusp, which targets CD123, was approved in December 2018 in the United States for patients with BPDCN aged ≥2 years. Despite favorable response rates in the frontline setting, many patients still relapse in the setting of monotherapy, and

Incidence: 0,04 cases / 100.000 (US)

~ 0,5% of hematological malignancies

~ 0,7 % of cutaneous lymphomas/leukemias

M:F = 3:1 – 5:1

Age

0-19: 27%

20-39: 16%

40-59: 16%

≥60: 41%

Pathogenesis

Inactivation of tumor suppressor genes (*TP53, RB1, CDKN1B, CDKN2A*)

Activation of oncogenes (*NRAS, KRAS, FLT3, RUNX2, HES6*)

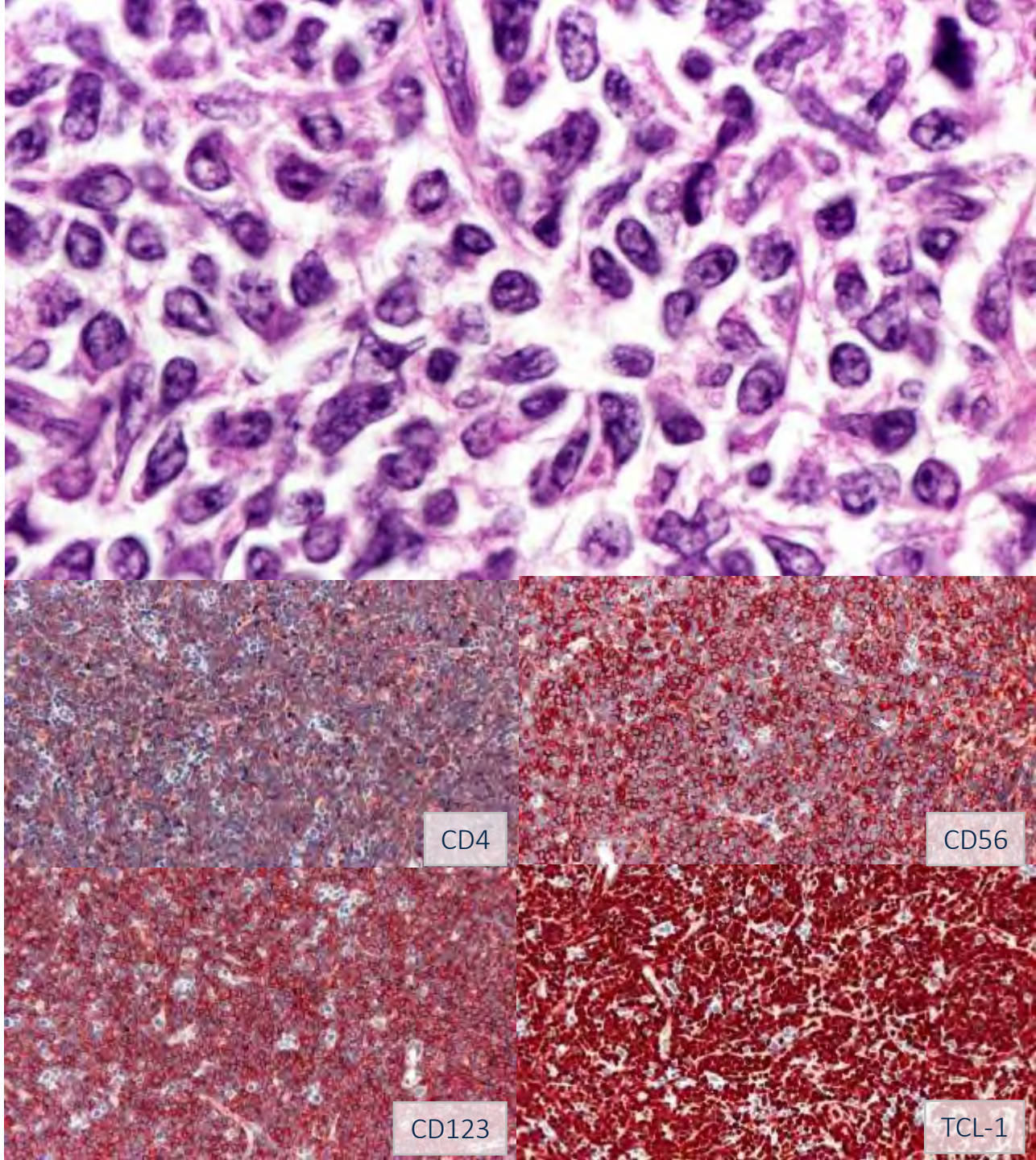
Activated NF-κB pathway

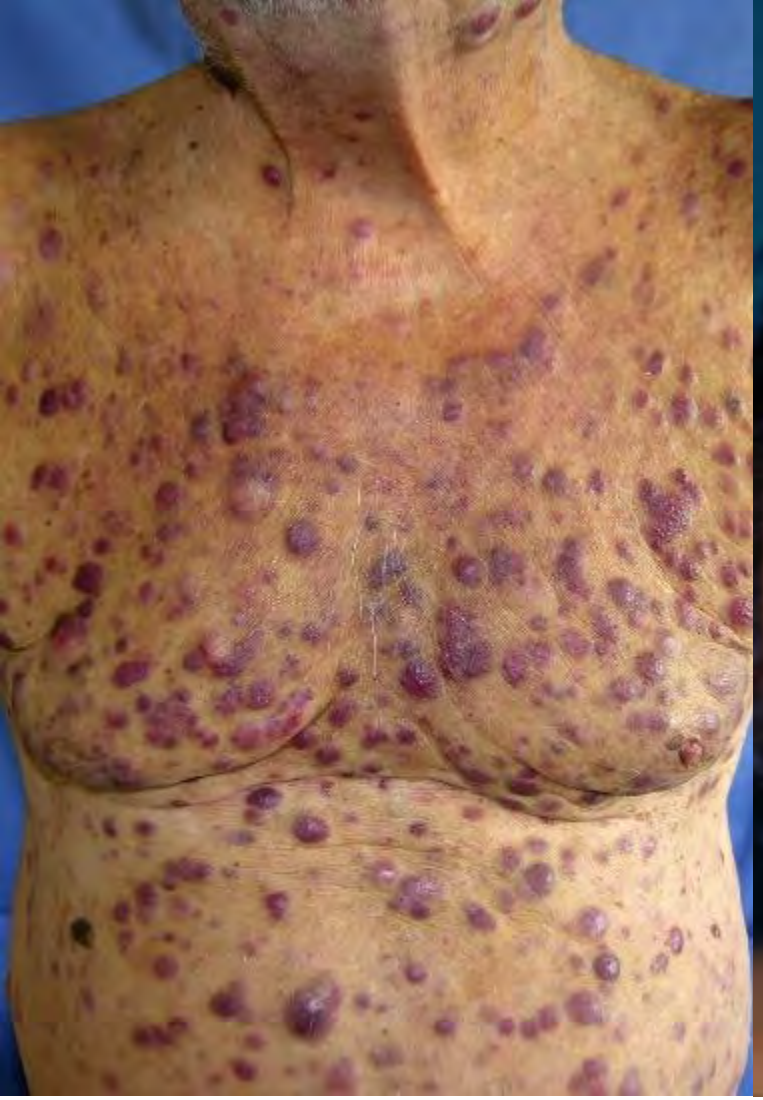
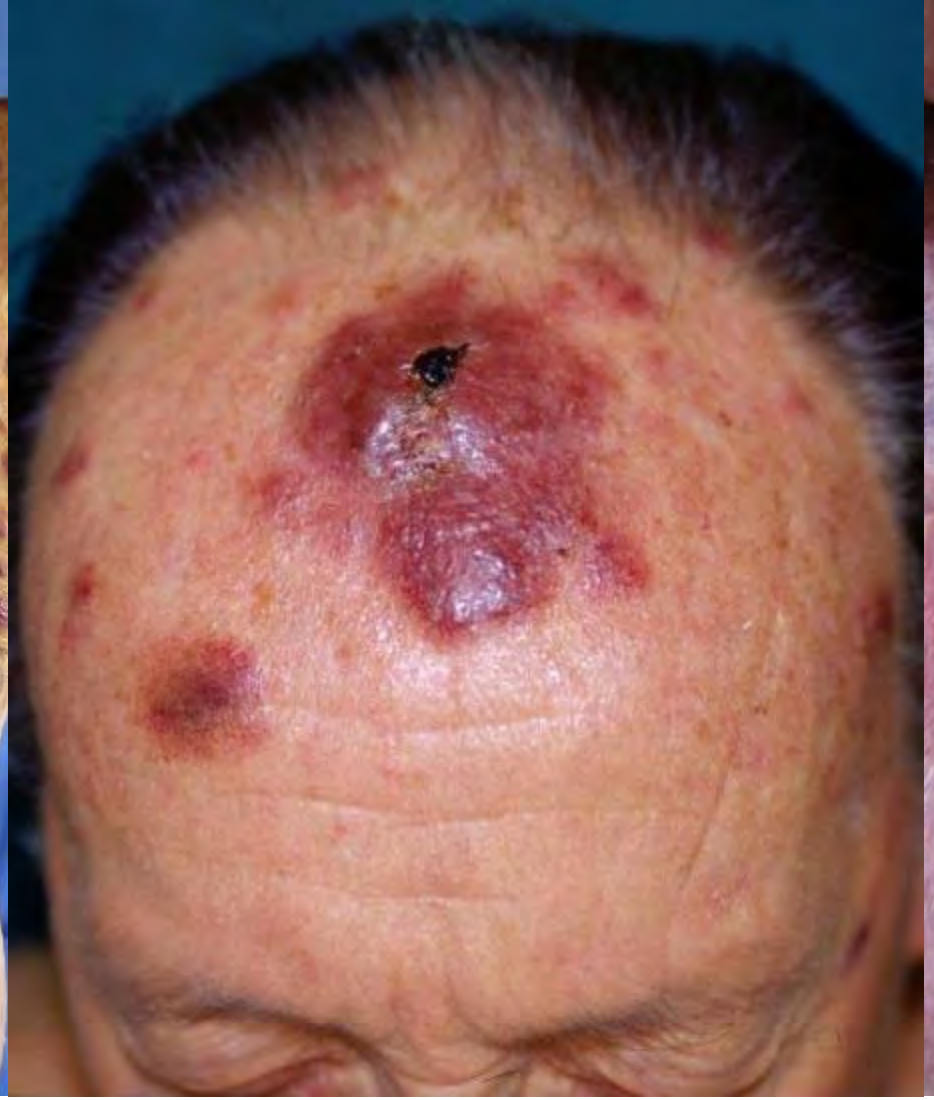
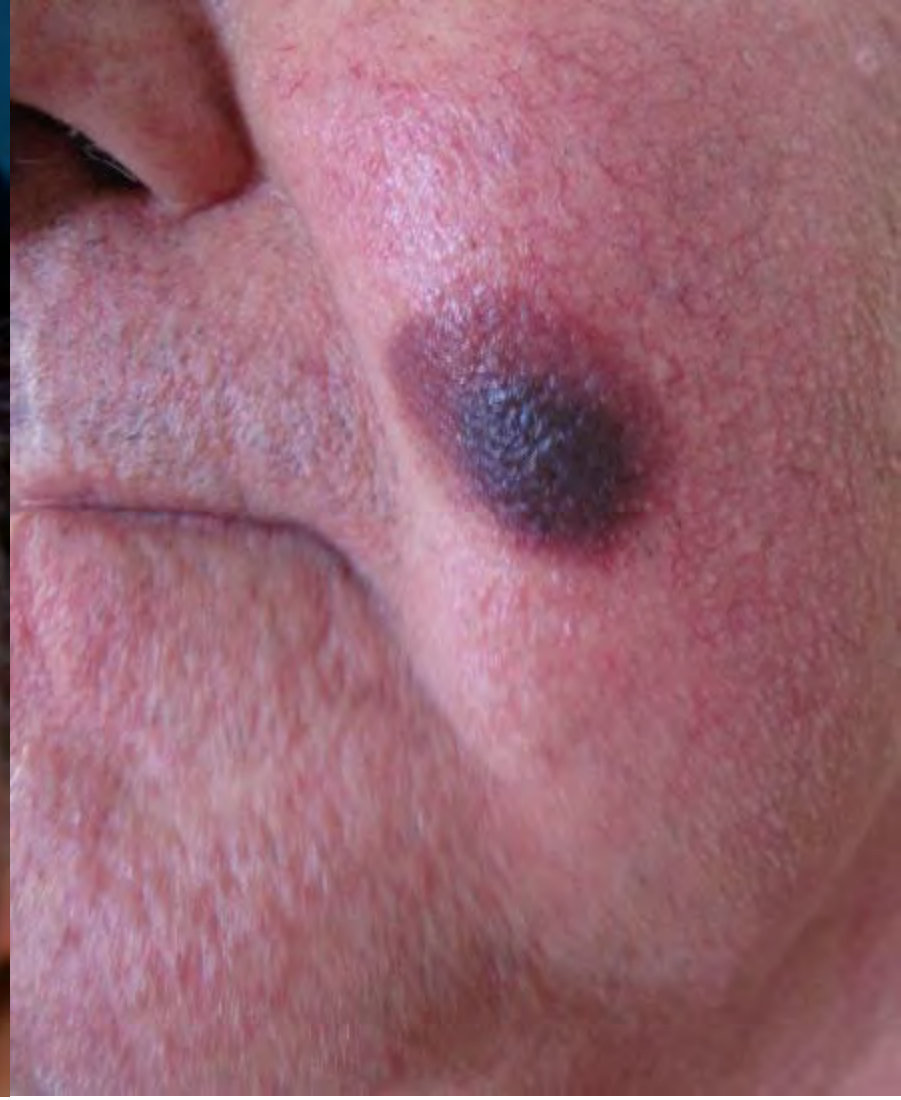
Mutated RNA spliceosomes (*ZRSR2* and others)

Immune response gene dysregulation (*IFNGR, TGFB, CLEC4C, IFNA* cluster)

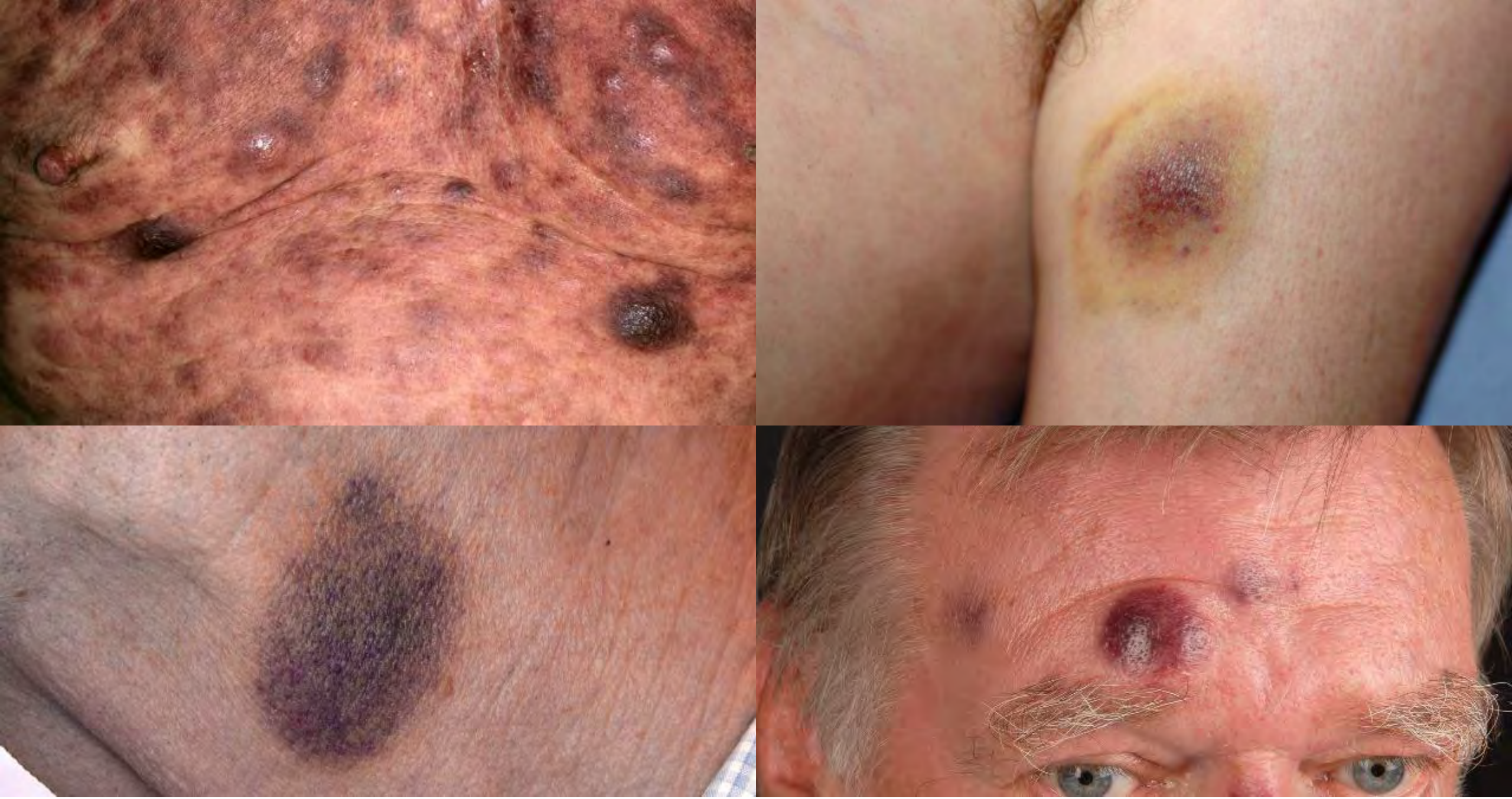
Epigenetic dysregulation (*IDH1, IDH2, TET1, TET2, ASXL1*)

Skin: >80%
Skin w/o extracutaneous involvement: ~50%



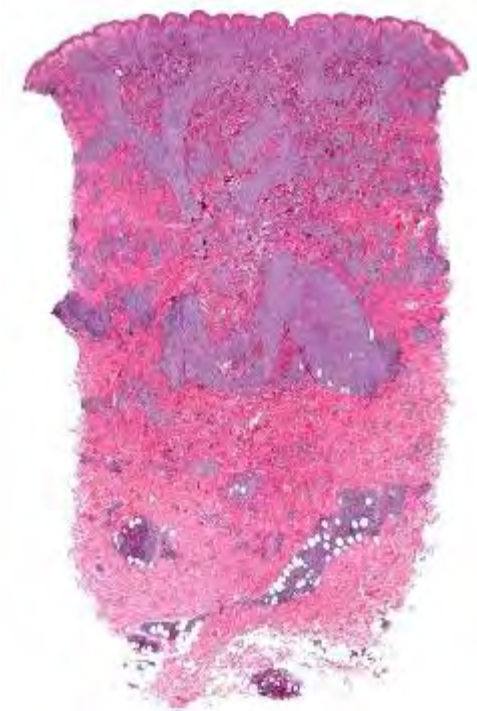
Lesions may be generalized, localized to one area of the body, or (rarely) solitary

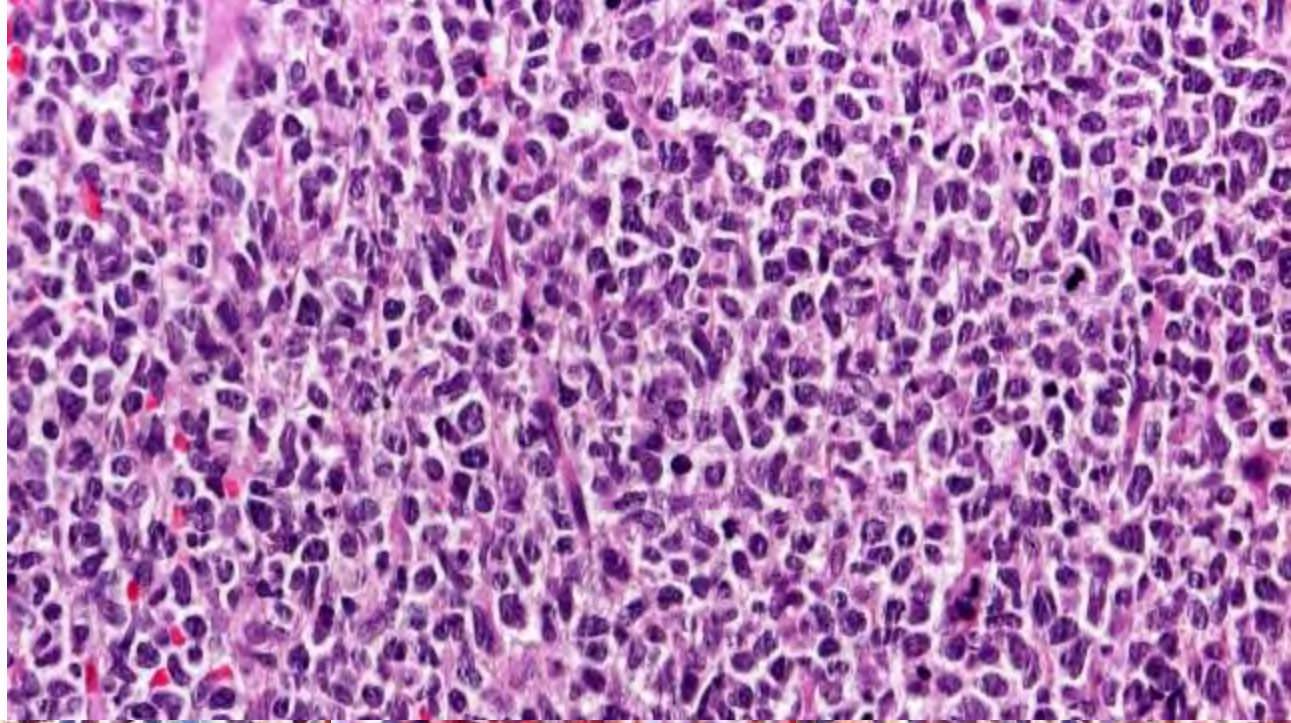


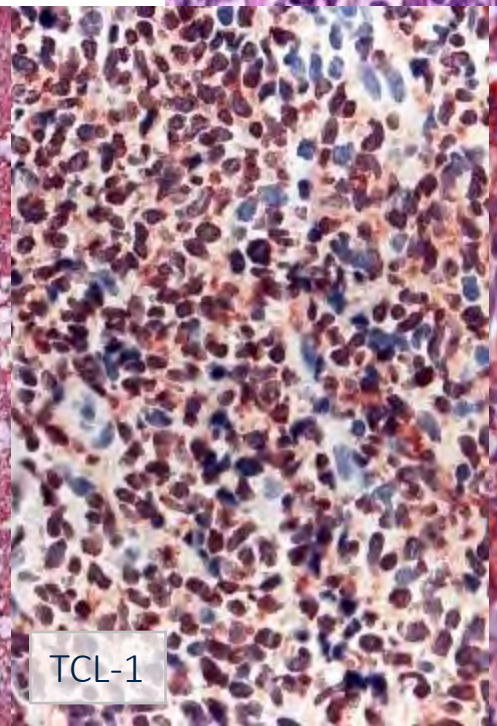
Common "bruise-like" aspect

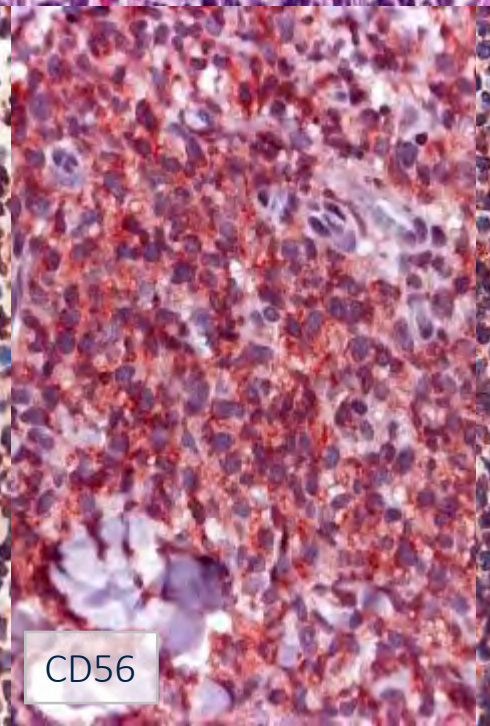
14-year-old boy

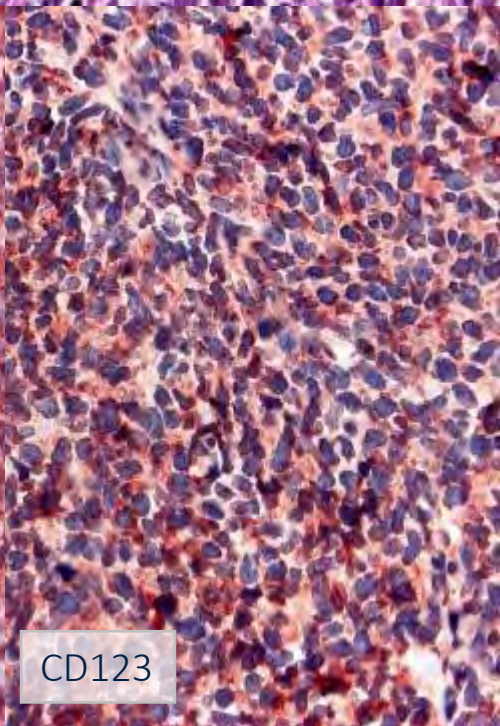
(Consultation Dr. C. Cota, Roma)

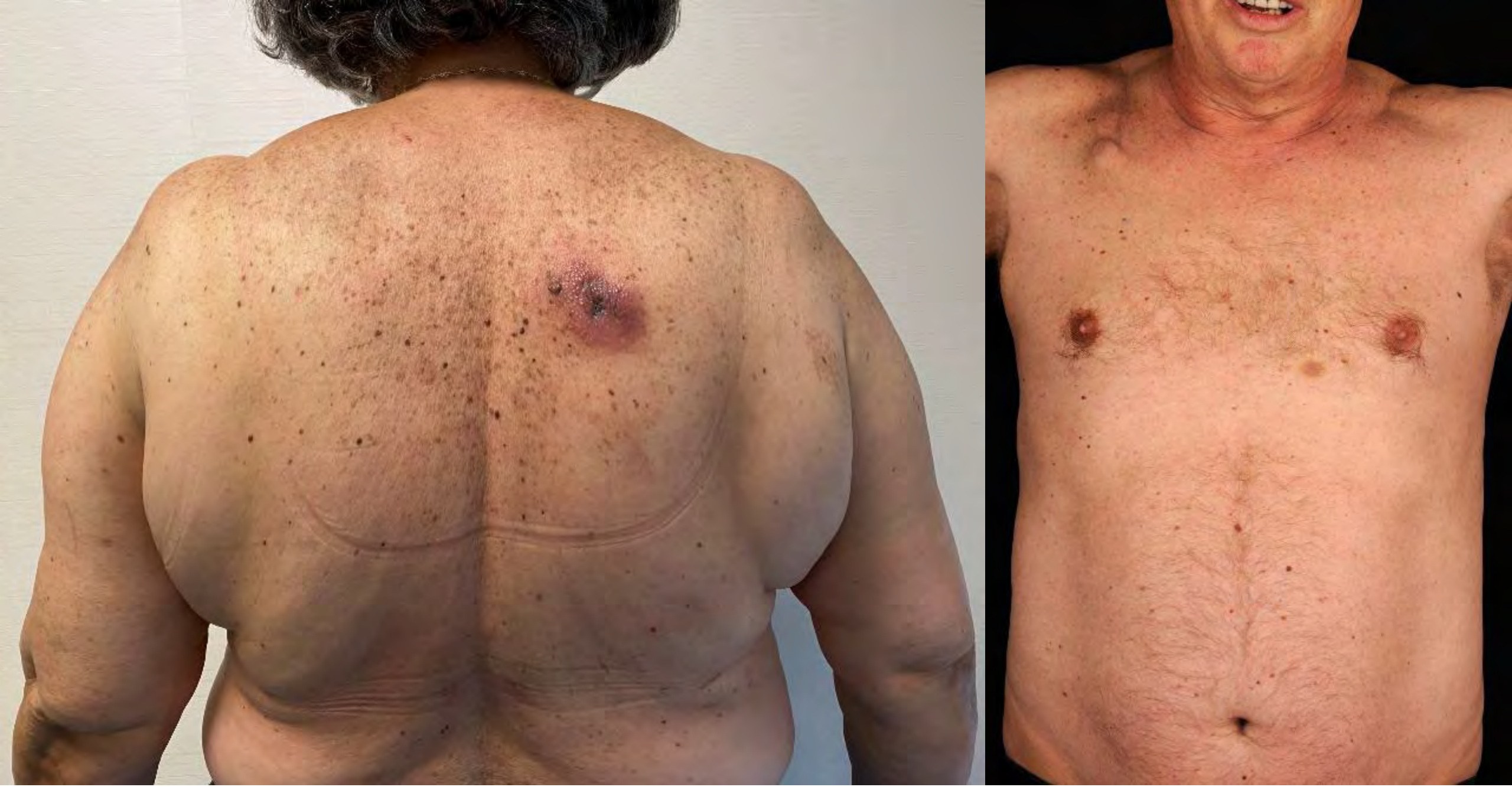




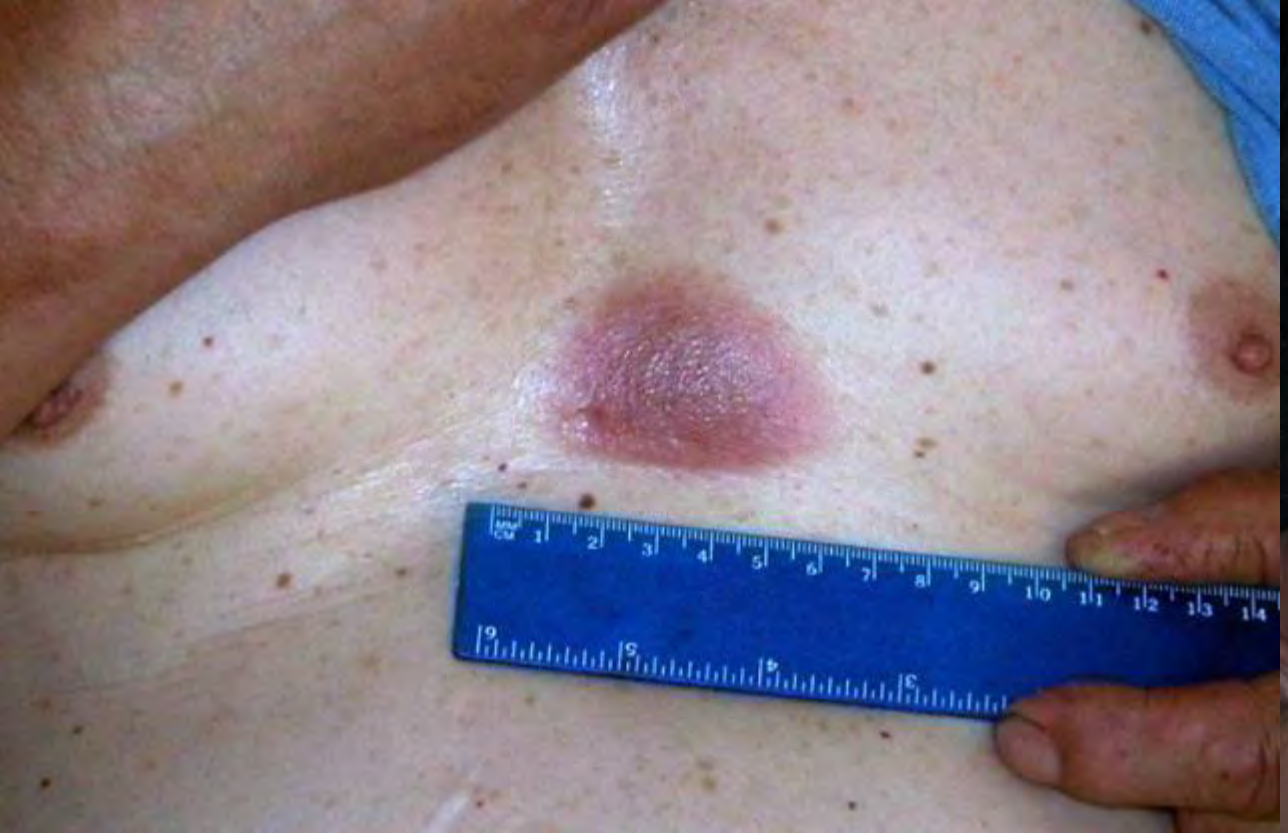


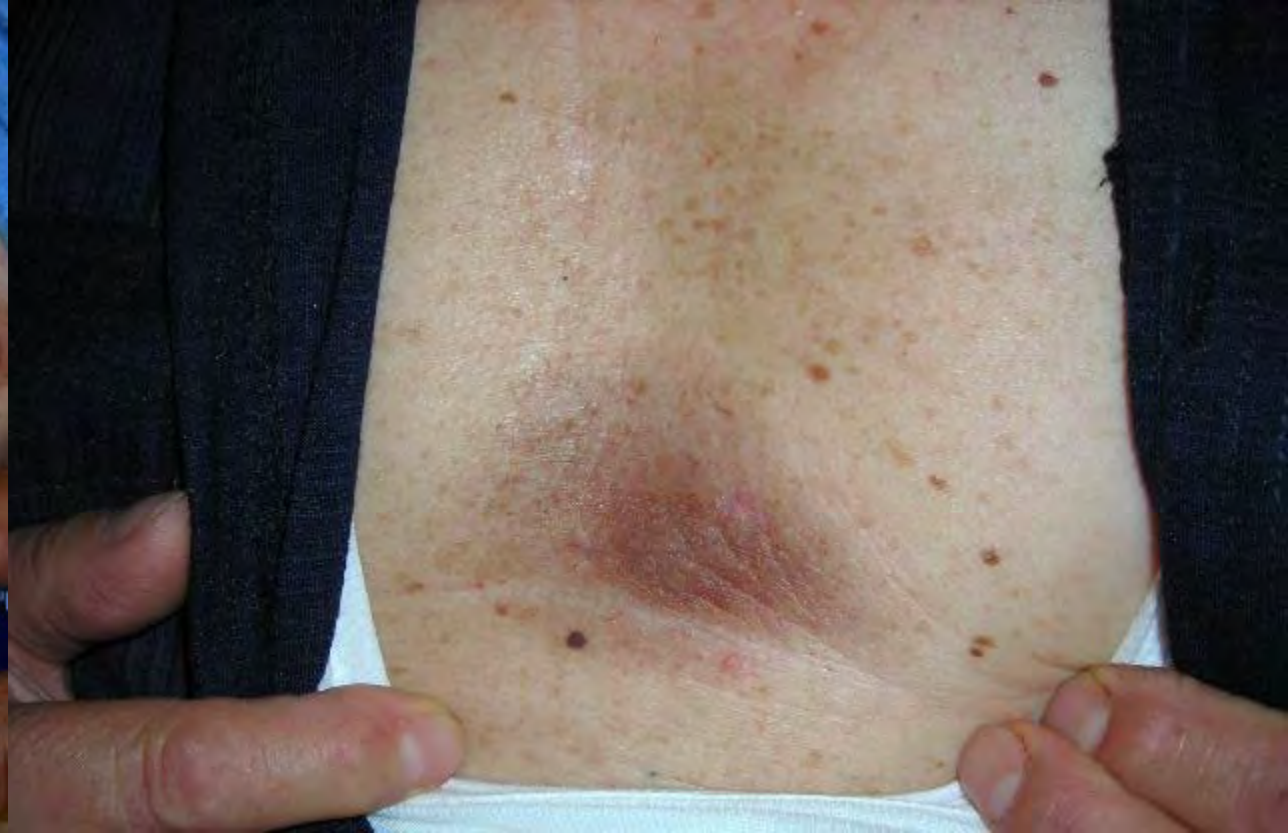






Common denominator: most patients are in a seemingly good shape at first presentation

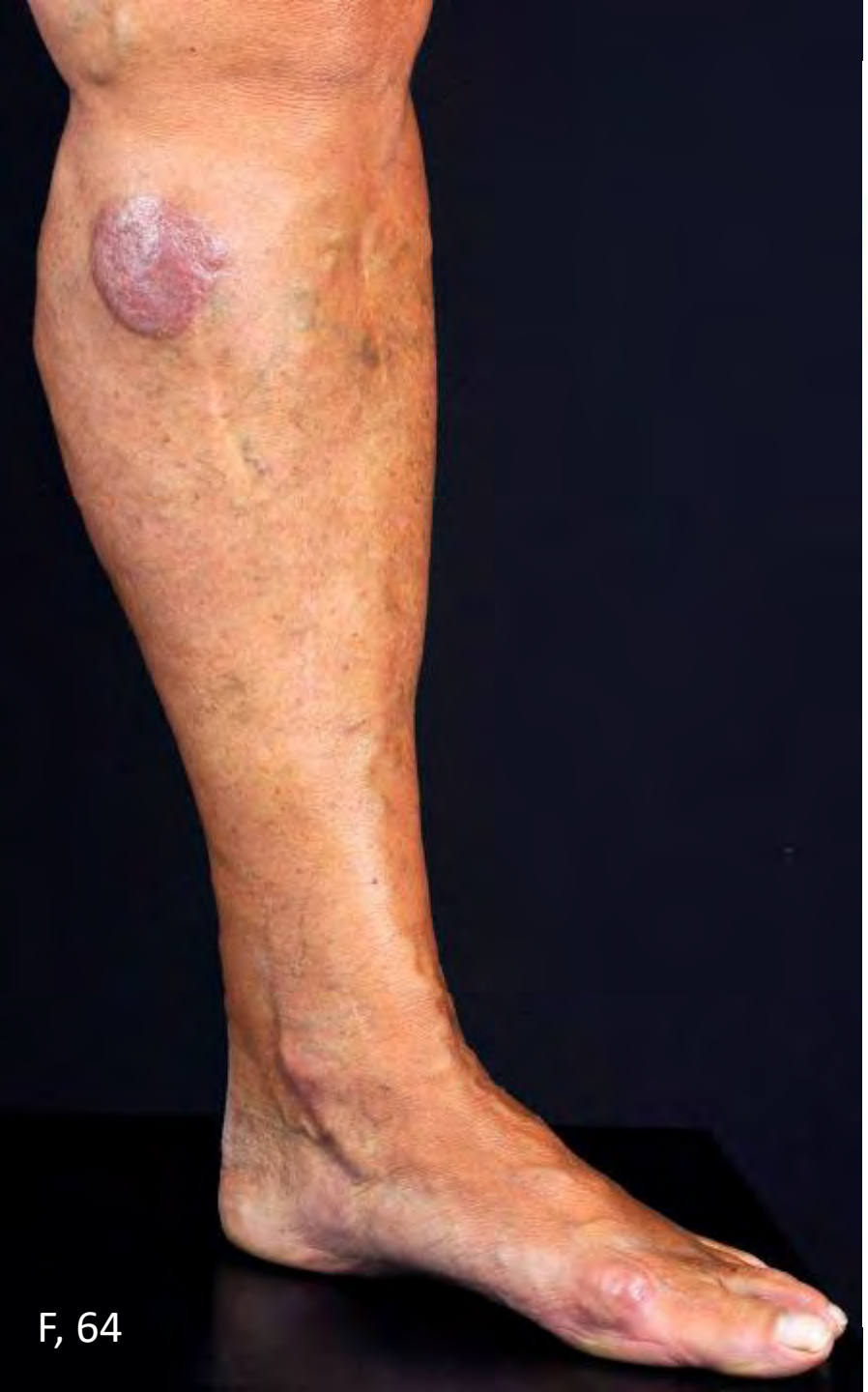


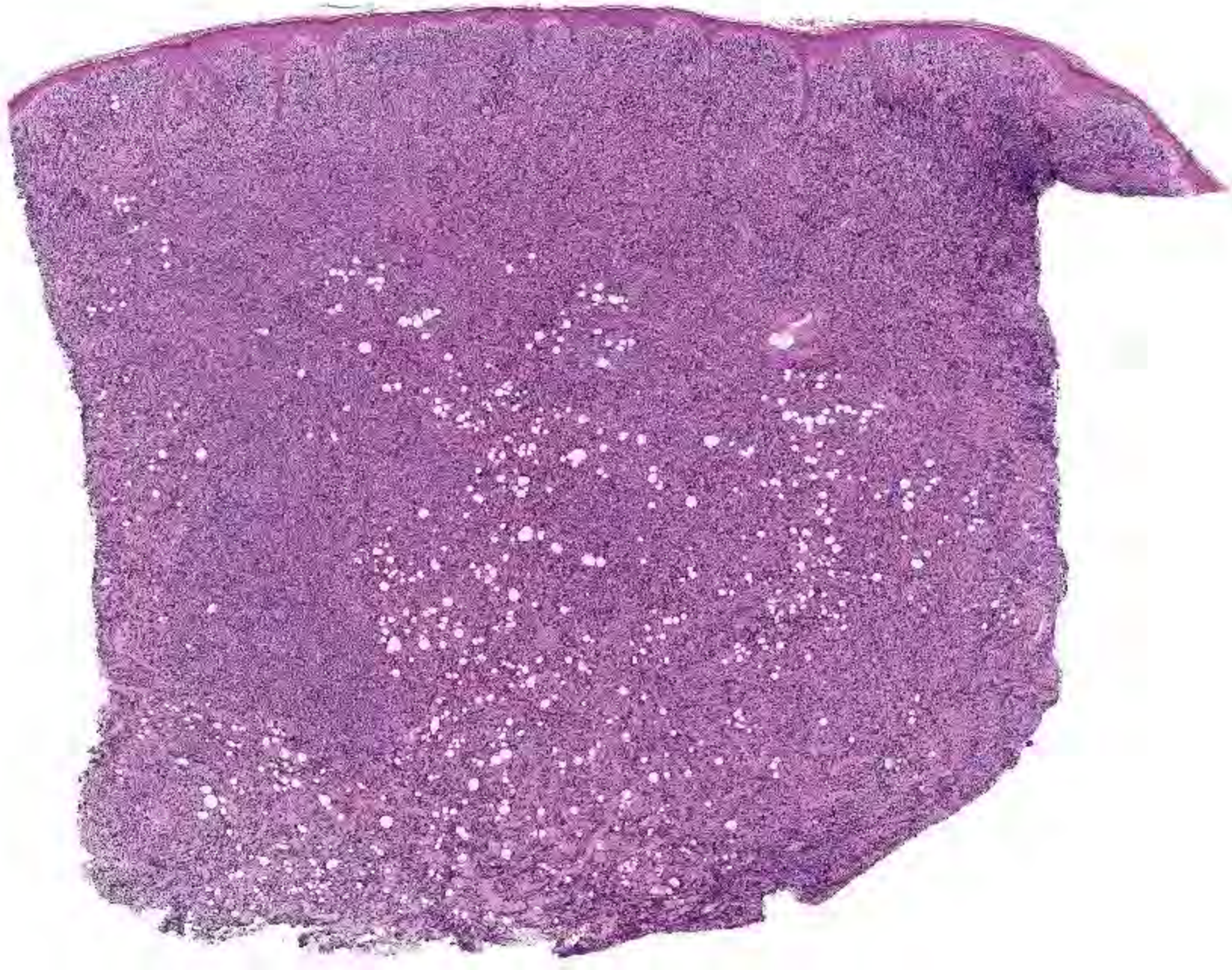


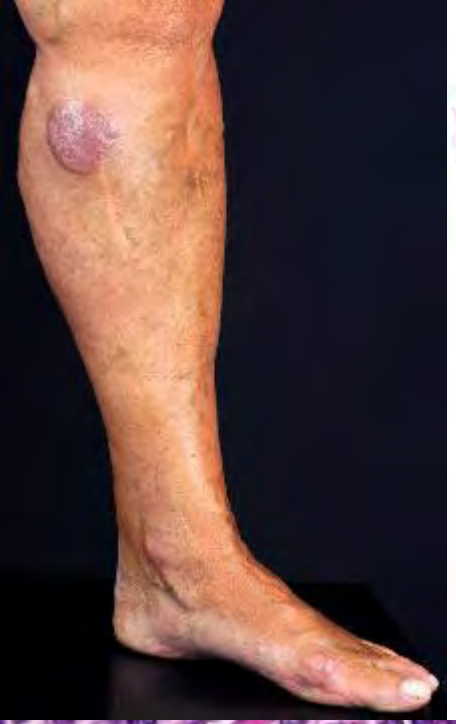
M, 66

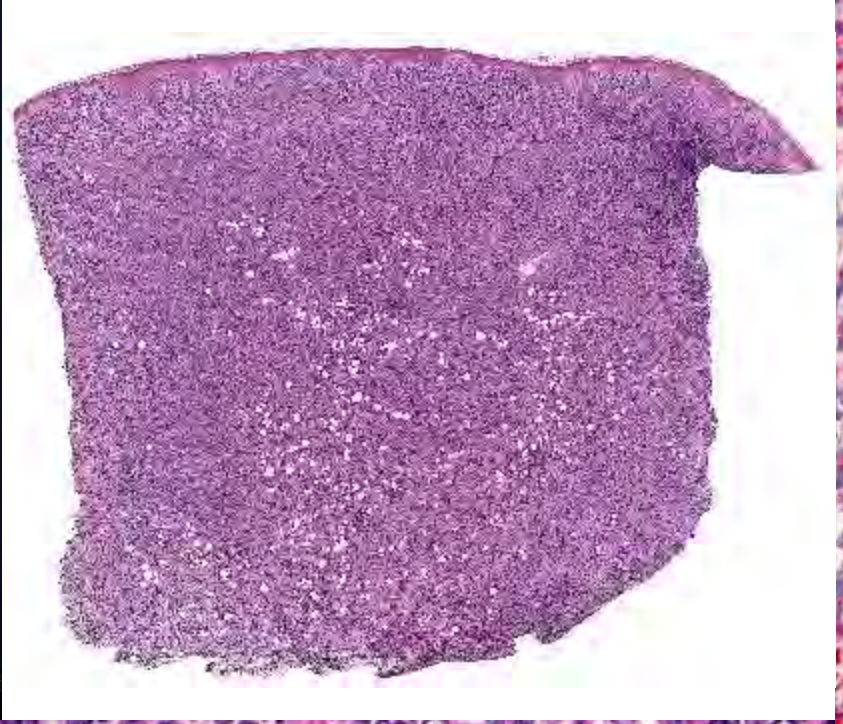
Solitary, flat tumor on the chest of rapid onset.
Staging negative.
CR after local radiotherapy (patient refused chemotherapy and SCTx).

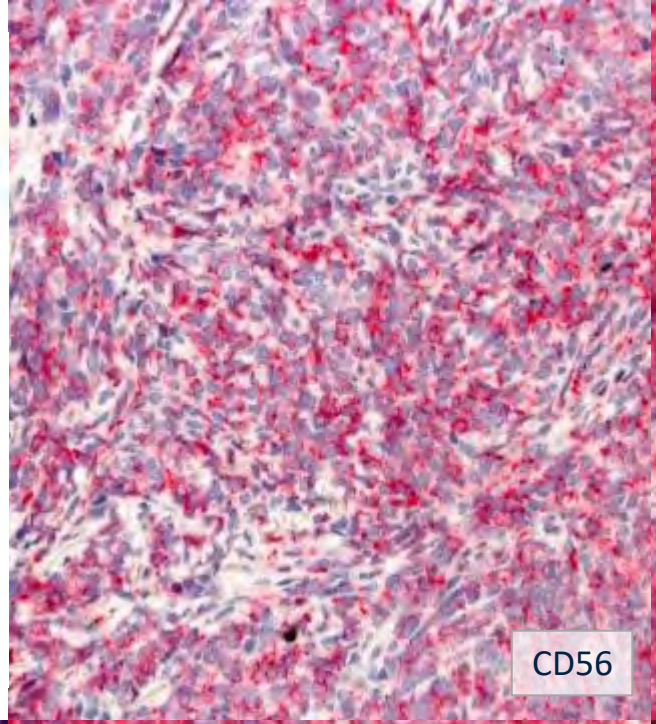
Local recurrence after 25 months as well as a new lesion on the left arm.
Chemotherapy (2 cycles); died of rapid progression 6 months later *(31-month survival from first diagnosis).*

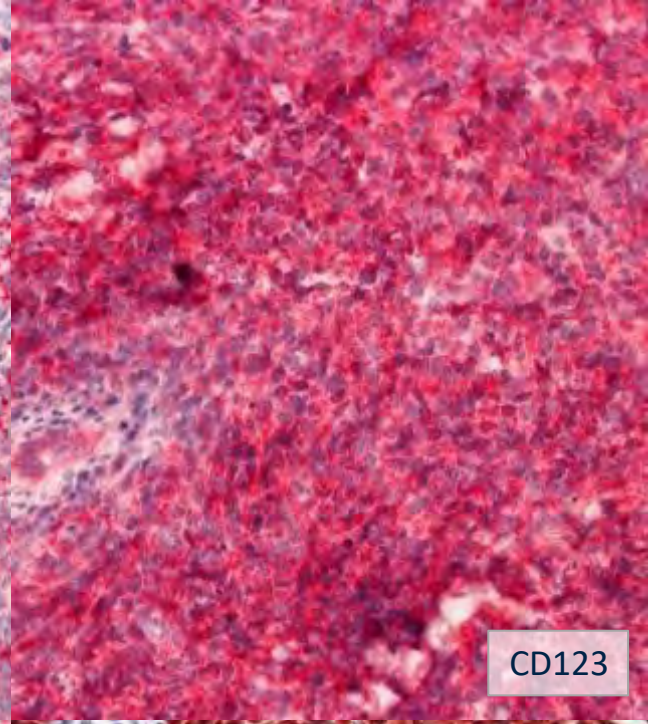

F, 64

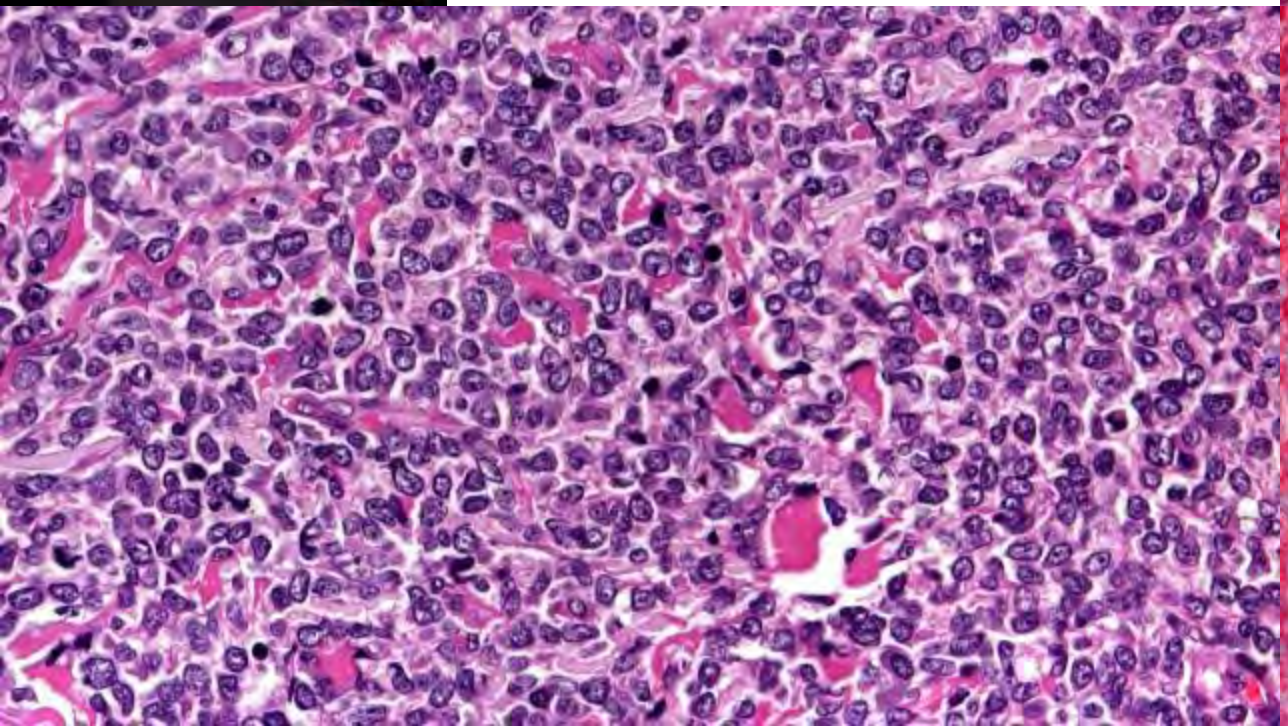


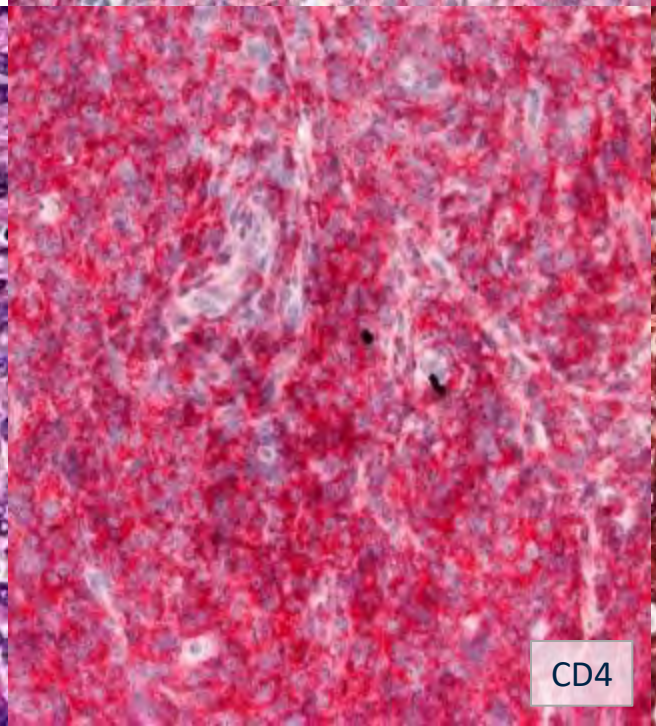


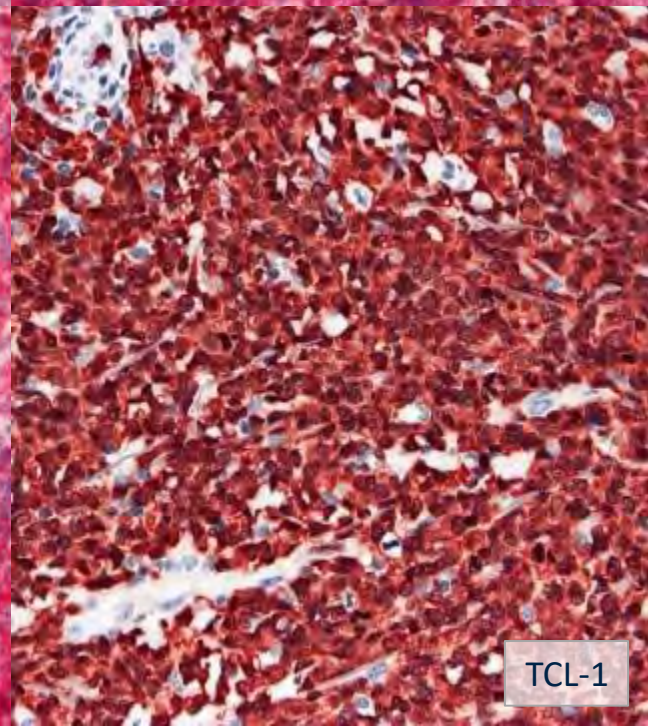


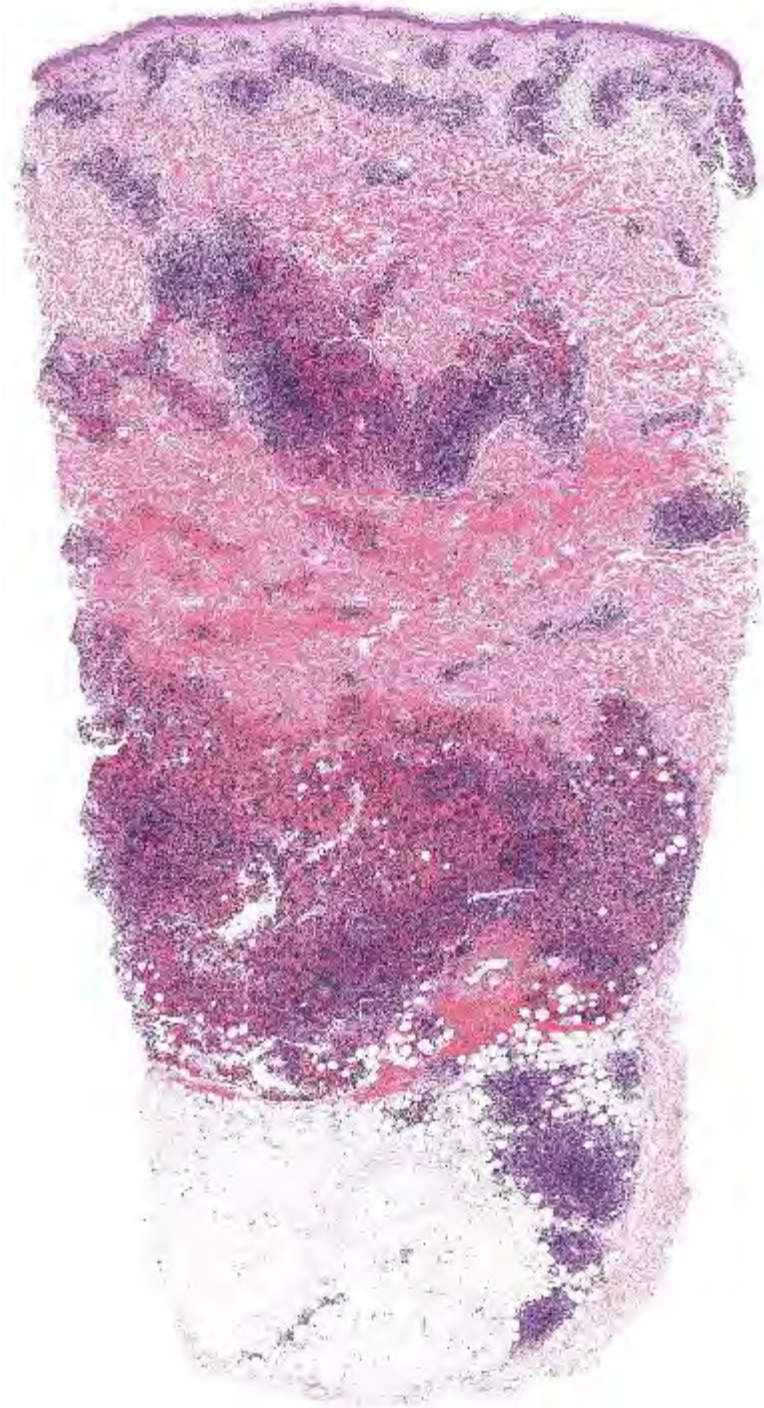

CD56

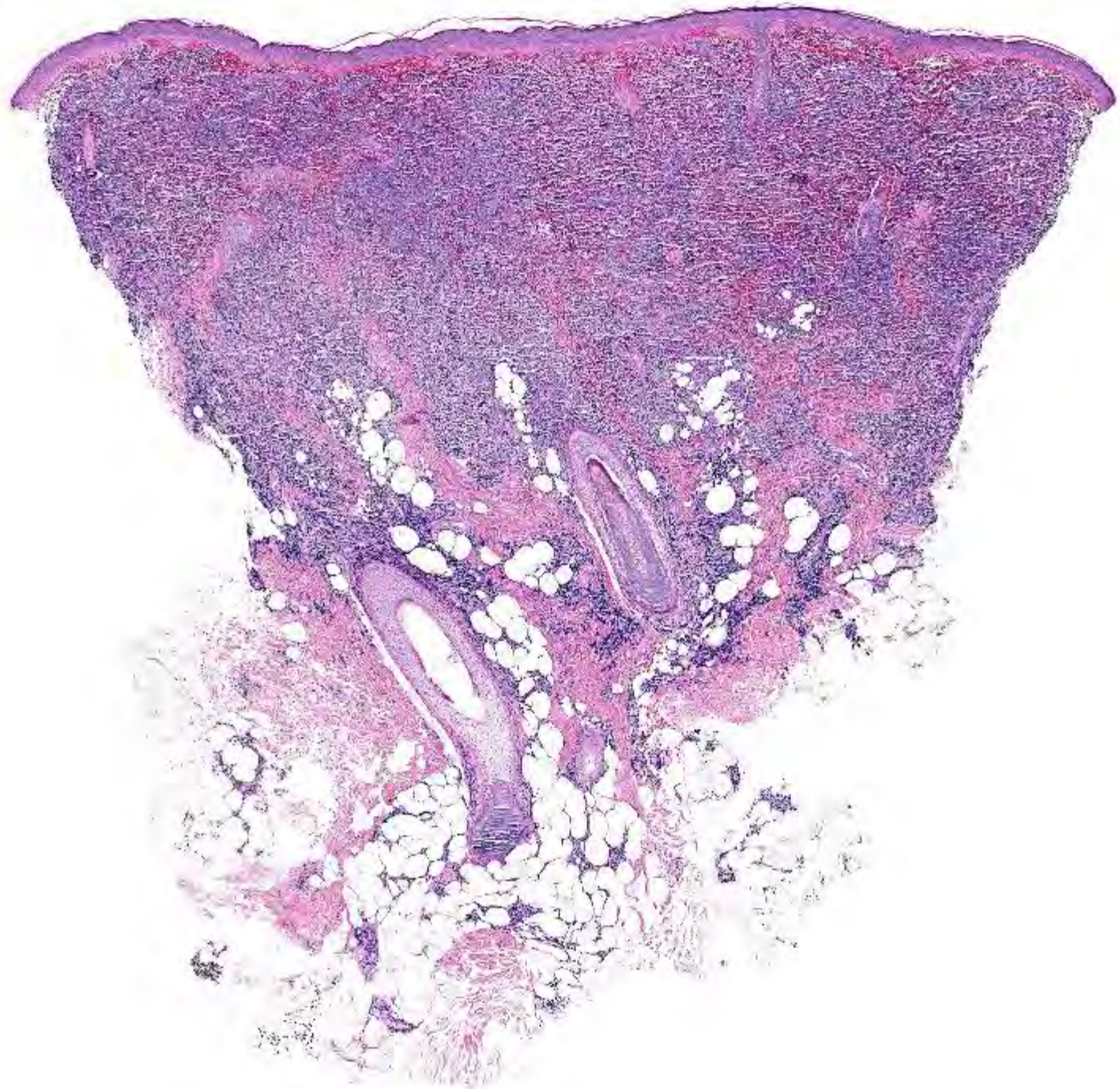

CD123

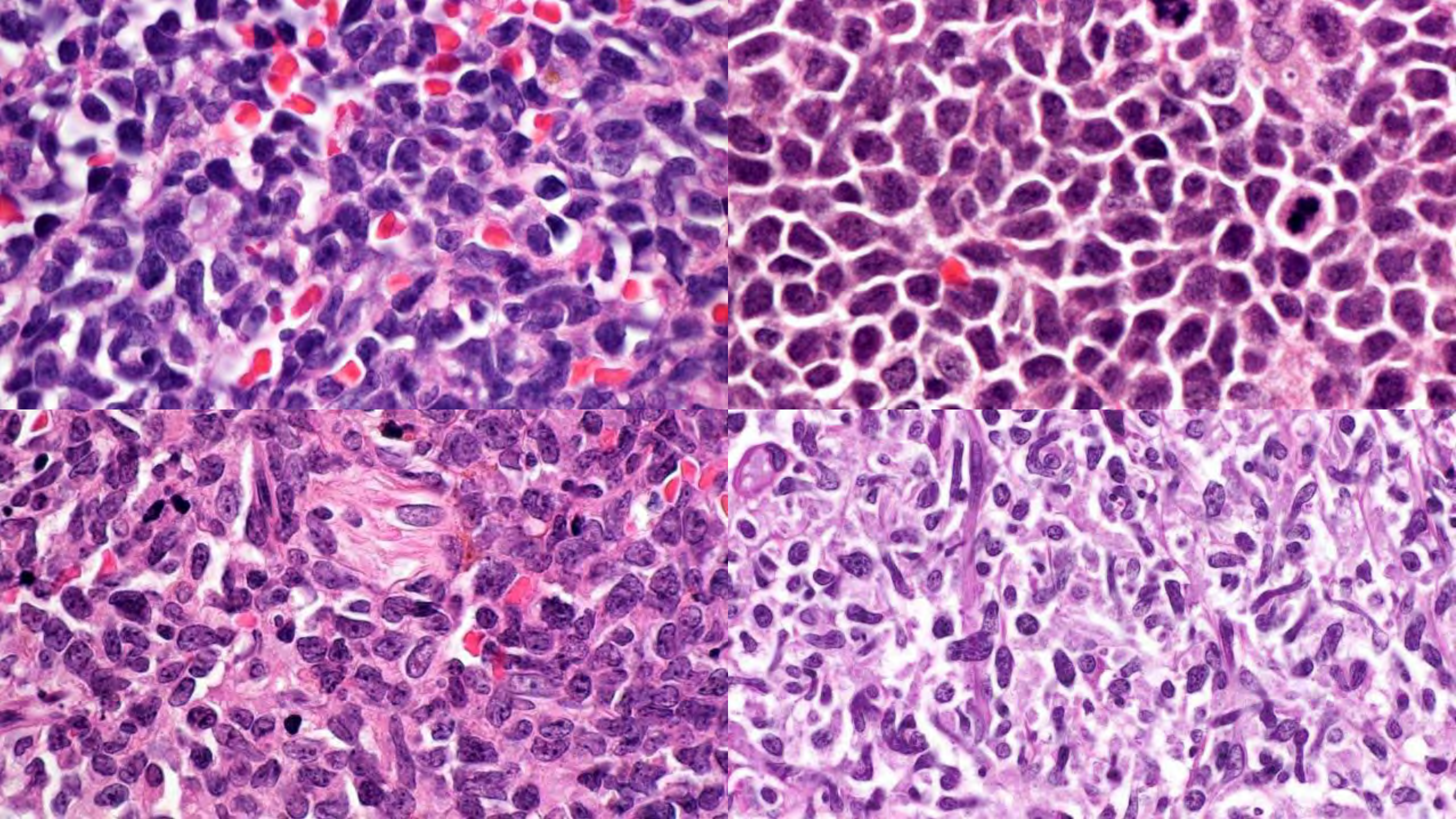


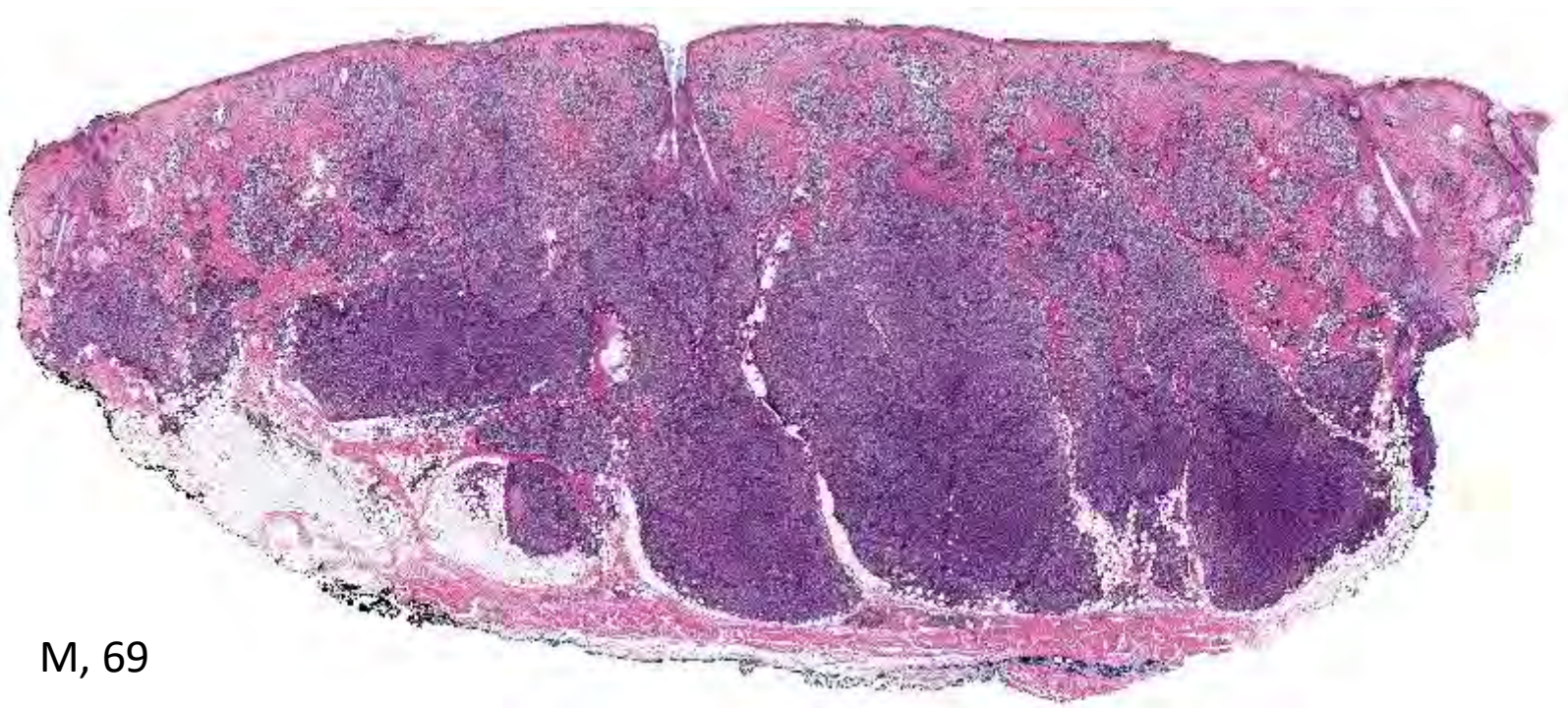

CD4


TCL-1

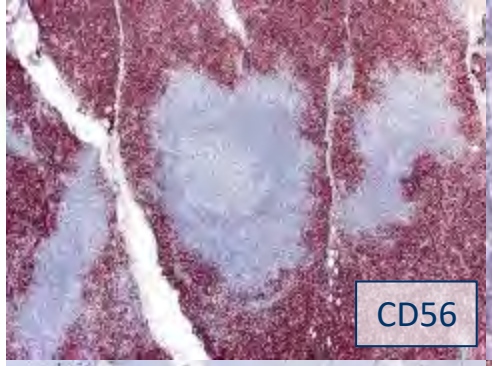






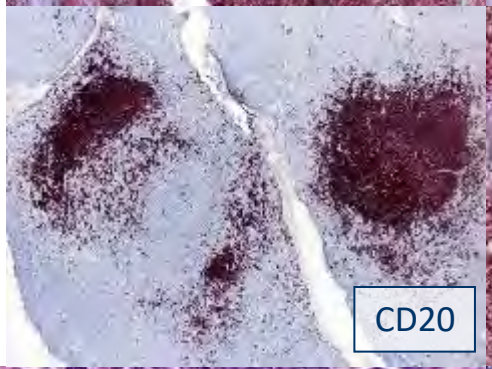


M, 69

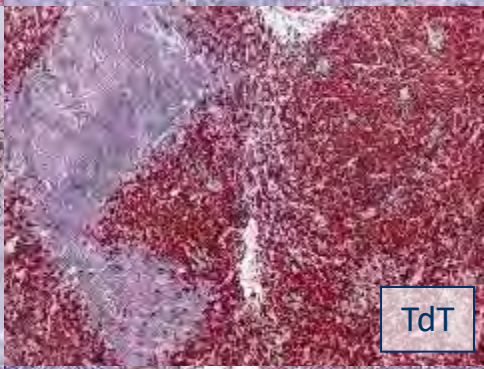


CD56

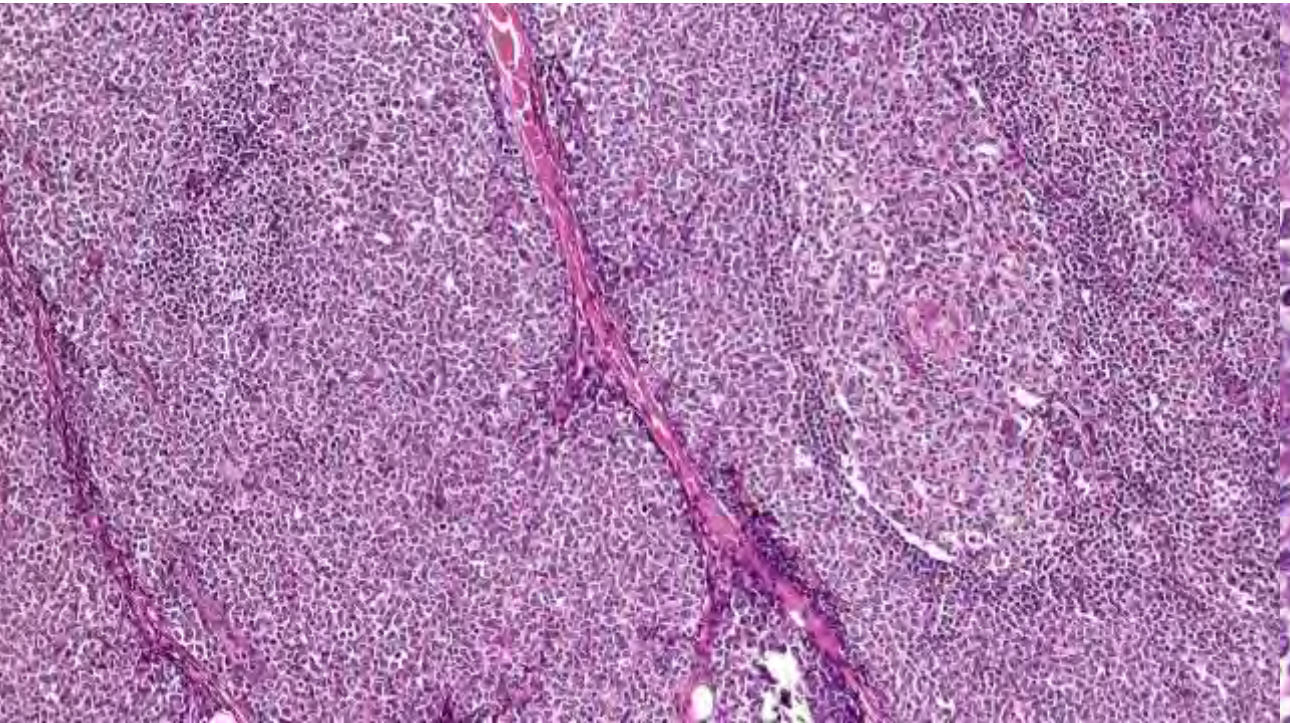
CD4

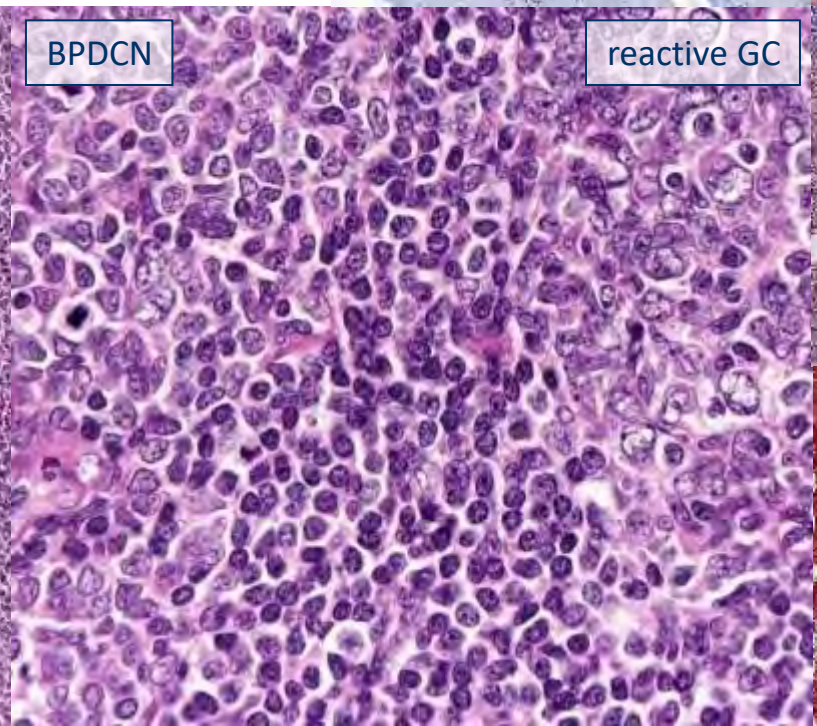


CD20



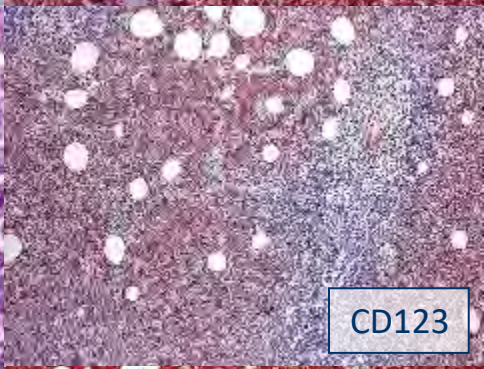
TdT



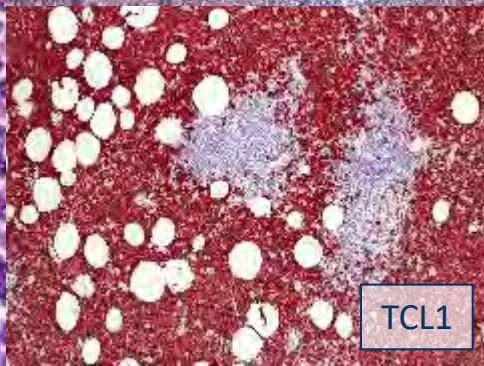


BPDCN

reactive GC



CD123



TCL1

Leukemia

REVIEW ARTICLE

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms

Joseph D. Khoury[1], Eric Solary[2,3], Ossamu Abla[4], Yasmine Akkari[5], Rita Alaggio[6], Jane F. Apperley[7], Rafael Bejar[8], Emilio Berti[9], Lambert Busque[10], John K. C. Chan[11], Wee Joo Chng[12], Xueyan Chen[13], Wee Joo Chng[12], John K. C. Chan[14], Isabel Colmenero[15], Sarah E. Coupland[16], Nicholas C. P. Cross[17], Daphne De Jong[18], M. Tarek Elghetany[19], Emilie Faisalli[20], Jean-Francois Emile[21], Judith Ferry[22], Linda Fogelstand[23], Michaela Fontenay[24], Lukas Frenzel[25], Sumeet Gujral[26], Torsten Haferlach[27], Claire Harrison[28], Jennifer C. Hodge[29], Shim Y. Hu[30], Joop H. Jansen[31], Rashmi Kanagal-Shamanna[32], Hagop M. Kantarjian[33], Christian P. Kratz[34], Xiao Qi Li[35], Megan S. Lim[36], Keith Loch[37], Sanam Loghavi[38], Andrea Matolcsy[39], Sohei Meshinchi[40], Phillip Michaels[41], Kikuo N. Nakamura[42], Vasudha Natkunam[43], Reza Nejati[44], German Ott[45], Eric Padron[46], Keyur P. Patel[47], Nikhil Patkar[48], Jennifer Picarsic[49], Uwe Platzbecker[50], Imre Plesa[51], Anna Schuh[52], William Stock[53], Reiner Siebert[54], Prashant Tembhare[55], Jeffrey Tyner[56], Sidan Vardiman[57], Wei Wang[58], Brent Wood[59], Wenbin Xiao[60], Cecilia Yeung[61] and Andreas Hochhaus[62,63]

The upcoming 5th edition of the World Health Organization (WHO) Classification of Haematolymphoid Tumours is part of an effort to hierarchically catalogue human cancers arising in various organ systems within a single relational database. This paper summarizes the new WHO classification scheme for myeloid and histiocytic/dendritic neoplasms and provides an overview of the principles and rationale underpinning changes from the prior edition. The definition and diagnosis of disease types continues to be based on multiple clinicopathologic parameters, but with refinement of genomic criteria and emphasis on therapeutically and/or prognostically actionable biomarkers. While a genetic basis for defining diseases is sought where possible, the classification strives to keep practical worldwide applicability in perspective. The result is an enhanced, contemporary, evidence-based classification of myeloid and histiocytic/dendritic neoplasms, rooted in molecular biology and an organizational structure that permits future scalability as new discoveries continue to inexorably inform future editions.

Leukemia (2022) 36:1703–1719; https://doi.org/10.1038/s41375-022-01613-1

INTRODUCTION

The World Health Organization (WHO) classification of tumours is an evidence-based classification of cancers occurring within various organ systems. It is a standard for diagnosis, research, cancer registries, and public health monitoring worldwide. For the first time since the inception of the classification over 60 years ago, the current series (5th edition) has been developed within a unified relational database framework that encompasses the entirety of human cancers. Tumours of each organ system and across volumes (blue books) are classified, ontologically within this novel framework along taxonomy, principles and a set of non-negotiables that include process transparency, bibliographic rigor, and avoidance of bias [1, 2]. The development of the 5th edition is overseen by an international panel that includes standing members—representatives from major medical and scientific organizations around the world—who oversee the entire series. In addition to expert members appointed for their leadership and contemporaneous expertise relevant to a particular volume [3]. The editorial board, in turn, identifies authors through an informed bibliometry process, with an emphasis on global geographic representation and multidisciplinary expertise. By design, multidisciplinary author/editor groups (a total of 420 contributors) shepherd overlapping coverage of disease categories to ensure conceptual continuity and content harmonization. This approach reflects the ways in which the classification is meant to be implemented, with multidisciplinary input that emphasizes a holistic approach to patient management from diagnosis through disease monitoring.

The aim of this paper is to provide an overview of the new edition of the WHO classification for myeloid and histiocytic/dendritic tumours. The last edition of the haematolymphoid classification dates back to 2008 and was revised in 2017. An overview of the lymphoid tumours is provided in a companion manuscript [4].

The classification structure follows a lineage-based framework, flowing broadly from benign to malignant and branching down to category, family, type (disease/tumour), and subtype. Where possible, a triad of attributes was systematically applied and reduced: lineage – dominant clinical attribute – dominant

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Table 15. Immunophenotypic diagnostic criteria of blastic plasmacytoid dendritic cell neoplasm.

Expected positive expression:
CD123*
TCF4*
TCL1*
CD303 *
CD304*
CD4
CD56
Expected negative markers:
CD3
CD14
CD19
CD34
Lysozyme
Myeloperoxidase
Immunophenotypic diagnostic criteria:
-Expression of CD123 and one other pDC marker(*) in addition to CD4 and/or CD56.
or,
-Expression of any three pDC markers and absent expression of all expected negative markers.

Cutaneous Manifestations of Blastic Plasmacytoid Dendritic Cell Neoplasm—Morphologic and Phenotypic Variability in a Series of 33 Patients

Carlo Cota, MD,† Esmeralda Vale, MD,‡ Isabel Viana, MD,‡ Luis Requena, MD,§ Gerardo Ferrara, MD,‖ Lucia Anemona, MD,¶ Dieter Metze, MD,# Regina Fink-Puches, MD,* Thomas Wiesner, MD,* and Lorenzo Cerroni, MD**

Abstract: Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a neoplasm derived from precursors of plasmacytoid dendritic cells. Cutaneous involvement represents often the first manifestation of the disease. We studied 45 skin biopsies from 33 patients (M:F = 2.25:1; median age: 71 y; age range: 41 to 89) with BPDCN to delineate histopathologic and immunophenotypic features of this disease. Patients presented with generalized (n = 18), localized (n = 6), or solitary (n = 9) macules, plaques, and/or tumors. Staging investigations at presentation were negative in 20 patients. Unusual histologic features included a perivascular/periadnexal pattern (6 biopsies from 4 patients) and the presence of pleomorphism of neoplastic cells with blastoid cells admixed with elongated, twisted, or hyperchromatic cells (observed in 21 specimens). Negativity of 1 among the 4 markers CD4, CD56, CD123, and TCL-1 was seen in 11 biopsies, and of 2 markers in 4 biopsies. Staining for CD68 revealed positivity of the majority of cells in 1 and of scattered cells in 21/37 stained cases. Terminal deoxynucleotidyl transferase was observed in 22/37 stained cases. Staining for Bcl-6, MUM-1 and FOX-P1 revealed positivity of a variable proportion of neoplastic cells in 16/30, 19/29, and 21/23 cases, respectively. Our study shows that cutaneous lesions of BPDCN display a greater variability of morphologic and phenotypic features than recognized earlier. Discrete perivascular infiltrates, plasmorphic morphology of neoplastic cells, and unusual phenotypic profiles may be the source of diagnostic pitfalls. These atypical variants should be recognized to make an early diagnosis and to manage properly patients with this aggressive hematological disorder.

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Key Words: Blastic plasmacytoid dendritic cell neoplasm, CD4+/CD56- hematodermic neoplasm, phenotype

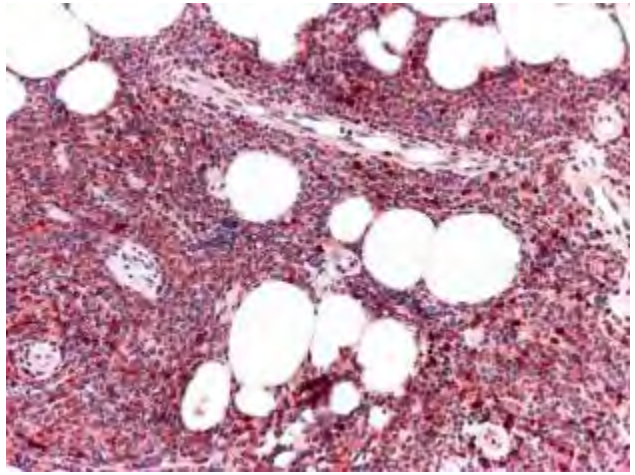
(*Am J Surg Pathol* 2010;34:75–87)

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) as defined in the new 2008 World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissue is a rare neoplasm derived from precursors of plasmacytoid dendritic cells, a specialized subset of dendritic cells that are also known as professional type-1 interferon producing cells.[1] BPDCN is characterized by a high incidence of cutaneous involvement, common leukemic dissemination, and aggressive course with poor prognosis.[1] Solitary or multiple skin plaques and tumors are often the first clinical manifestation of the disease; thus, cutaneous biopsies are crucial to correctly classify the cases. This rare and aggressive hematopoietic neoplasm has been renamed several times in previous years (reviewed in [1]) and was listed as CD4+/CD56- hematodermic neoplasm in the 2005 WHO-European Organization for the Research and Treatment of Cancer classification of cutaneous lymphomas.[2,3] Although initially thought to be of natural killer cell lineage,[3] there is now general agreement that the tumor differentiates toward pDC precursors.[4–11,27] Histopathologically, it is characterized by dense monomorphous infiltrates of medium-sized blastoid cells positive for CD4, CD56, CD123, and TCL-1.[1]

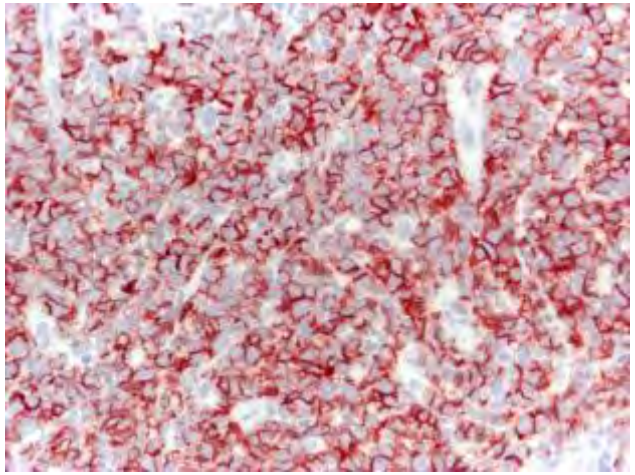
A few series of BPDCN have been reported in the literature, but diagnostic criteria have changed with changing nomenclature and classification; thus, older series are probably quite heterogeneous.[4,5,13,16,21,25,26,30,34,36] In this study, we analyzed the clinical, pathological, and phenotypic features of a large series of patients with skin manifestations of BPDCN to better delineate unusual morphologic and phenotypic variants of the disease.

PATIENTS AND METHODS

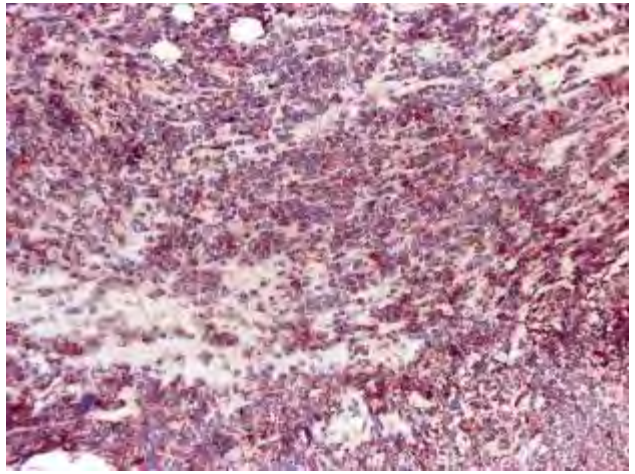
Thirty-three patients with a proven diagnosis of BPDCN were included in the study. All cases were retrieved from the files of the Research Unit Dermatopathology,



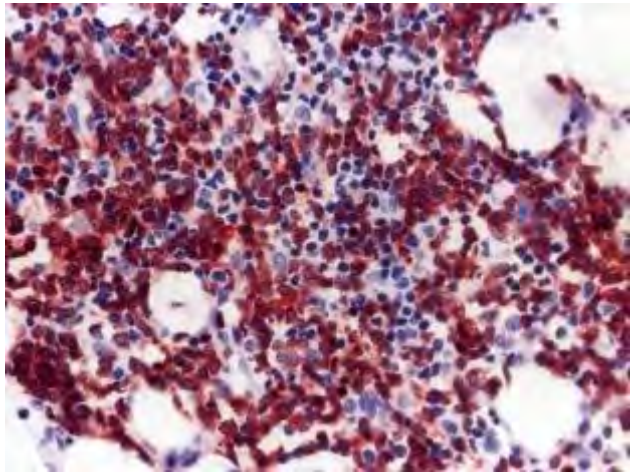
CD4
(negative in 20% of cases)



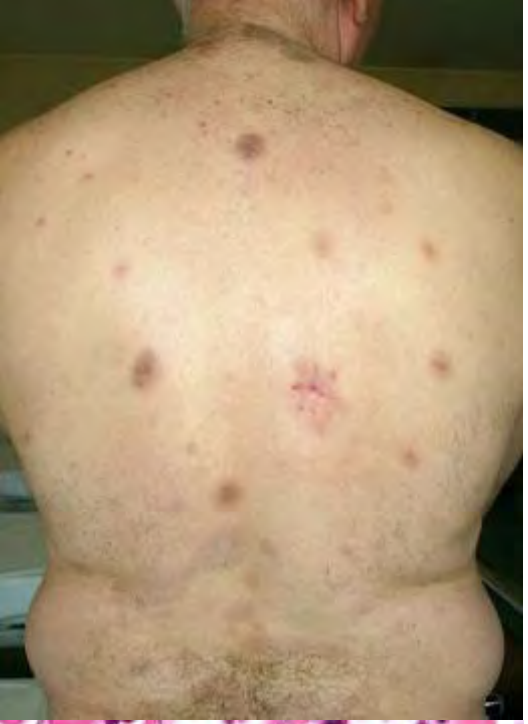
CD56
(negative in 8,9% of cases)

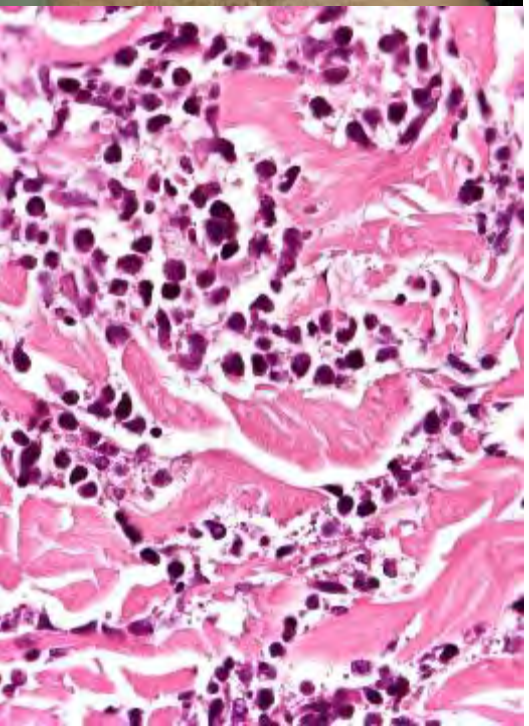


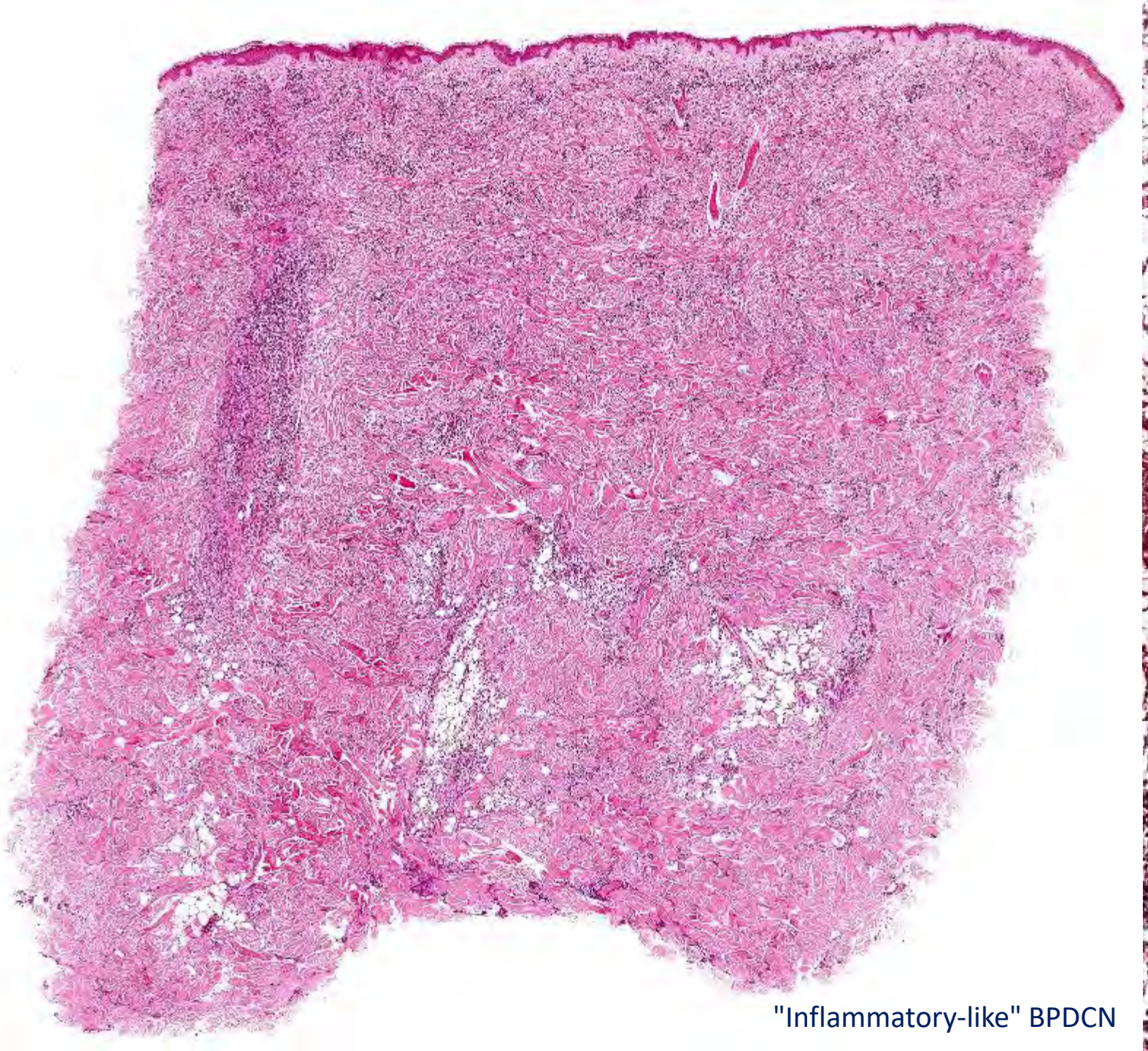
CD123
(negative in 4,4% of cases)



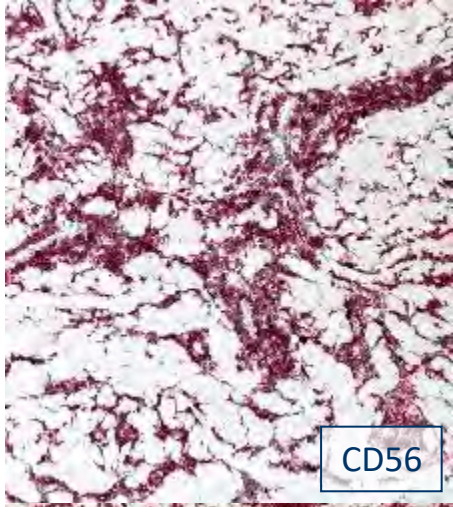
TCL-1
(negative in 10,2% of cases)

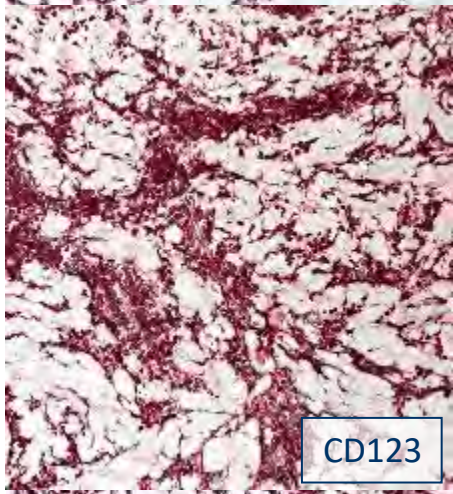


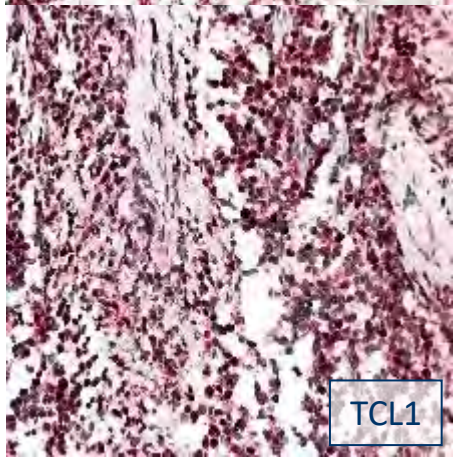




"Inflammatory-like" BPDCN

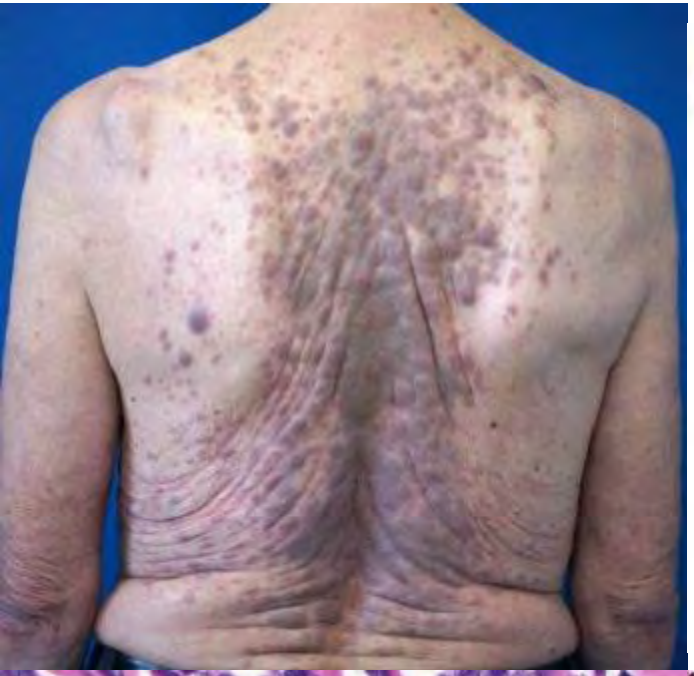


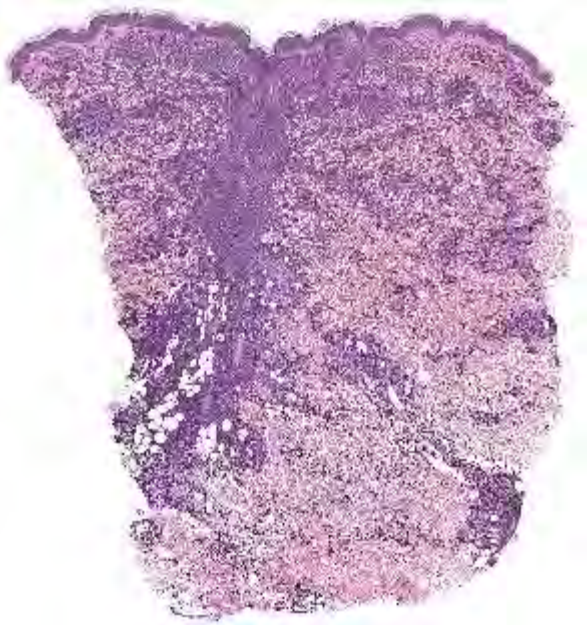


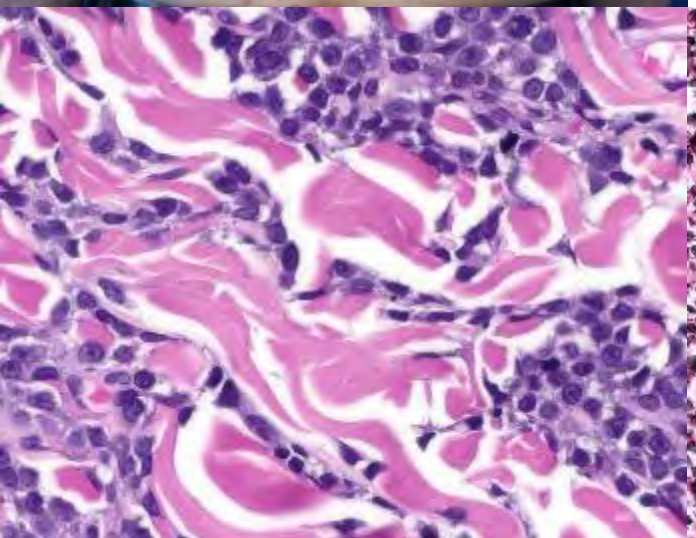


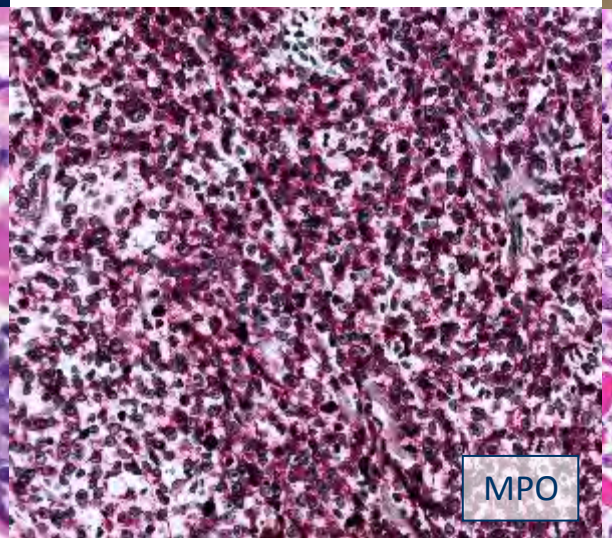
Clinicopathological differential diagnosis

Myelogeneous leukemia

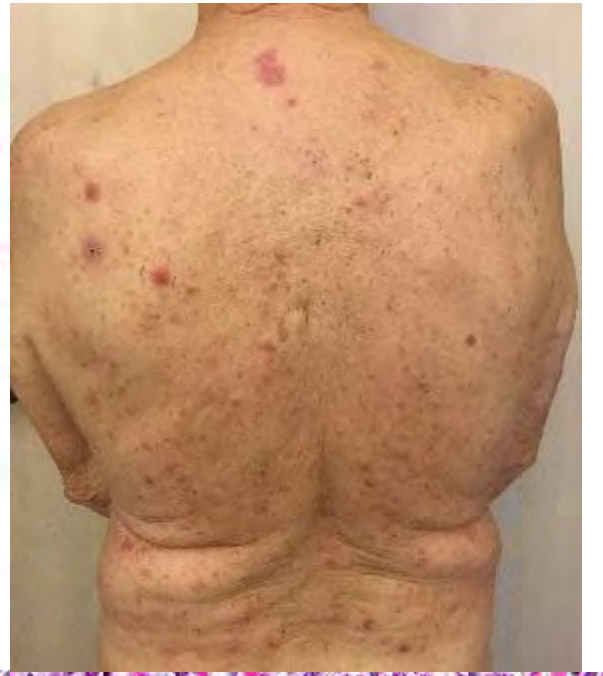


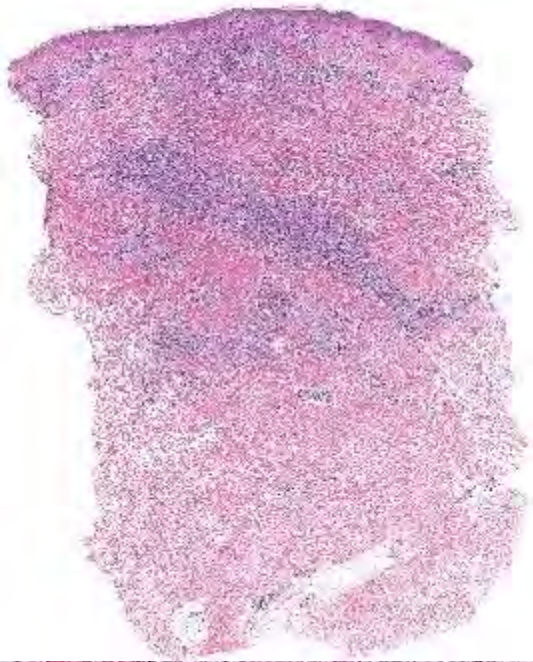


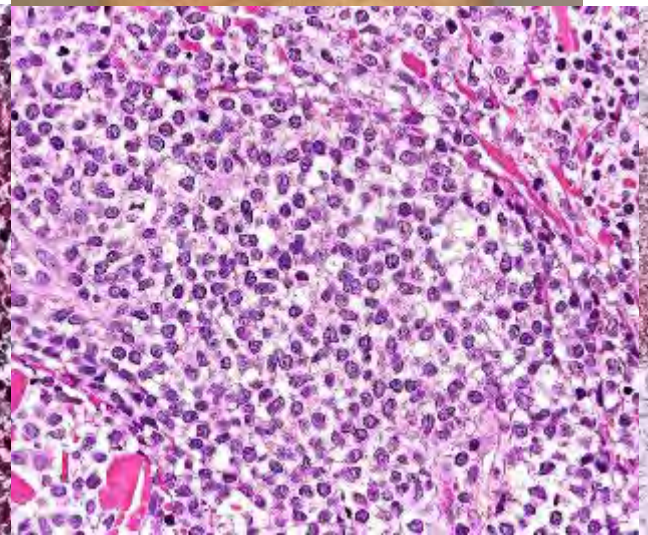


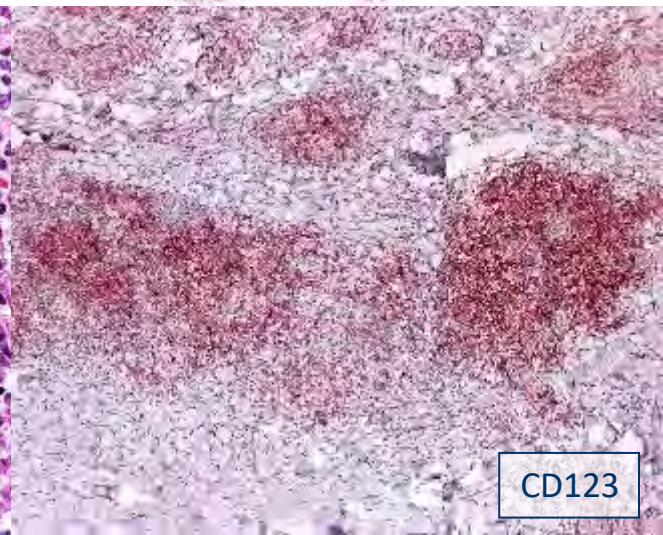


Mature plasmacytoid dendritic cell proliferation associated with myeloid neoplasms



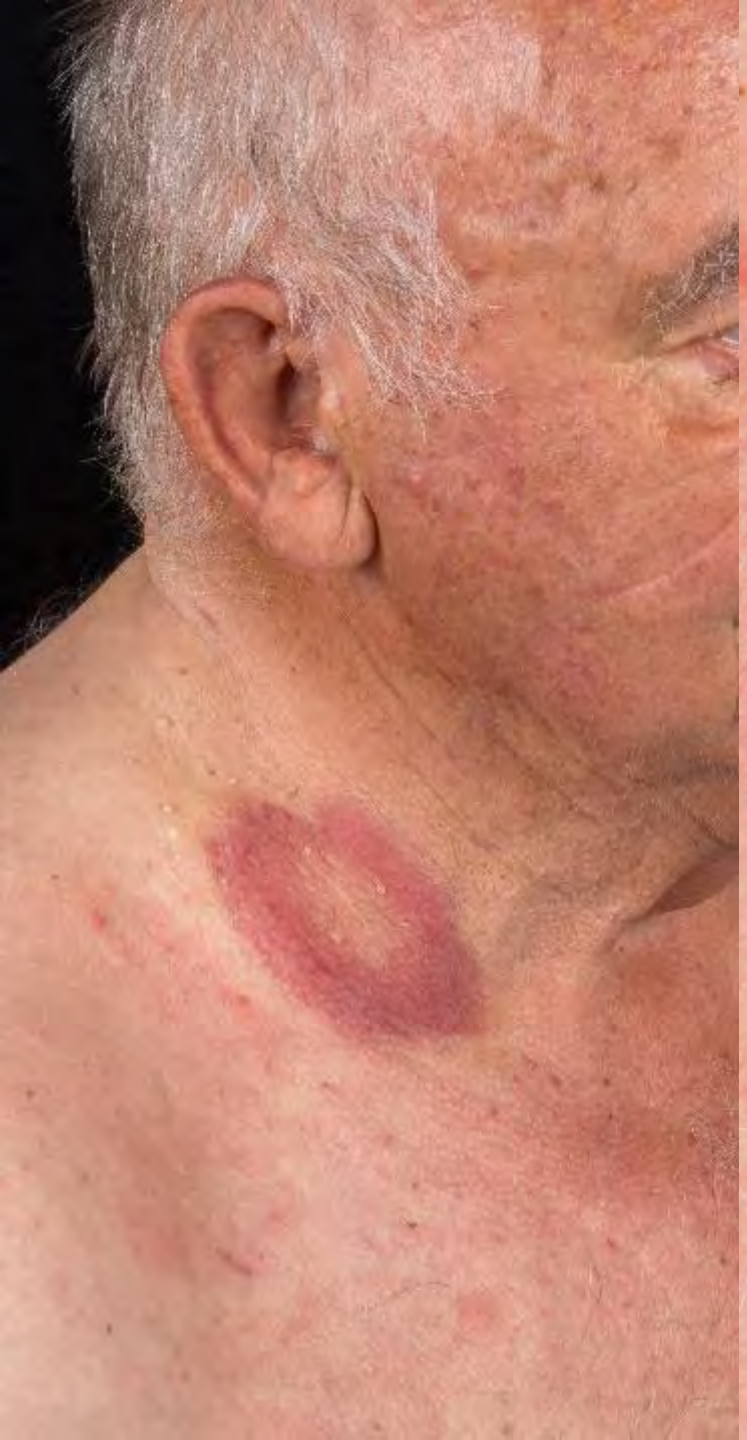


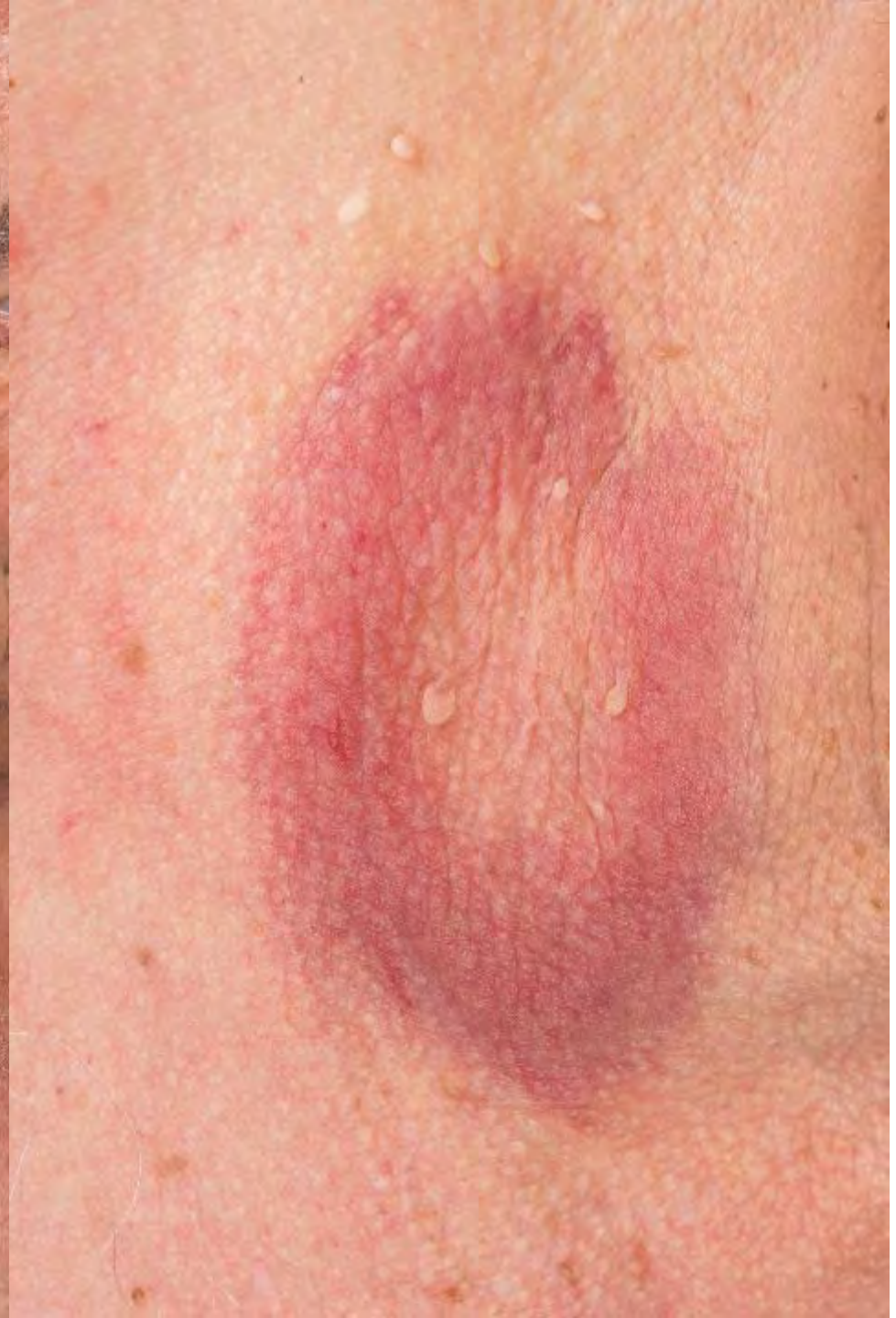




Blastic plasmacytoid dendritic cell neoplasm

- Adults; children/adolescents may be affected (15-30% of cases)
- Skin frequently primary site of onset; staging negative in approximately 50% of cases *("primary cutaneous" cases are conceptually similar to aleukemic leukemia cutis – aggressive treatment mandatory irrespective of staging results !)*
- Localized / generalized cutaneous plaques, nodules and tumors, oft with "bruise-like" aspect
- Aggressive clinical course with leukemic manifestations and common CNS involvement; may remain confined to the skin for some months (max. 1-2 years)
- Histopathological diagnosis not difficult in typical cases; may be suspected morphologically (blastoid infiltrates, subepidermal grenze zone, hemorrhage); confirmed by immunohistochemical stainings (CD4+, CD56+, CD123+, CD303+, TCF4+, TCL1+, MPO-, CD14-, CD34-, lysozyme-)
- Should be distinguished mainly from myelogeneous leukemia and from mature plasmacytoid dendritic cell proliferations in patients with MDS / CMML
- CD123 represents a therapeutic target but may be negative in a small proportion of cases





M, 80

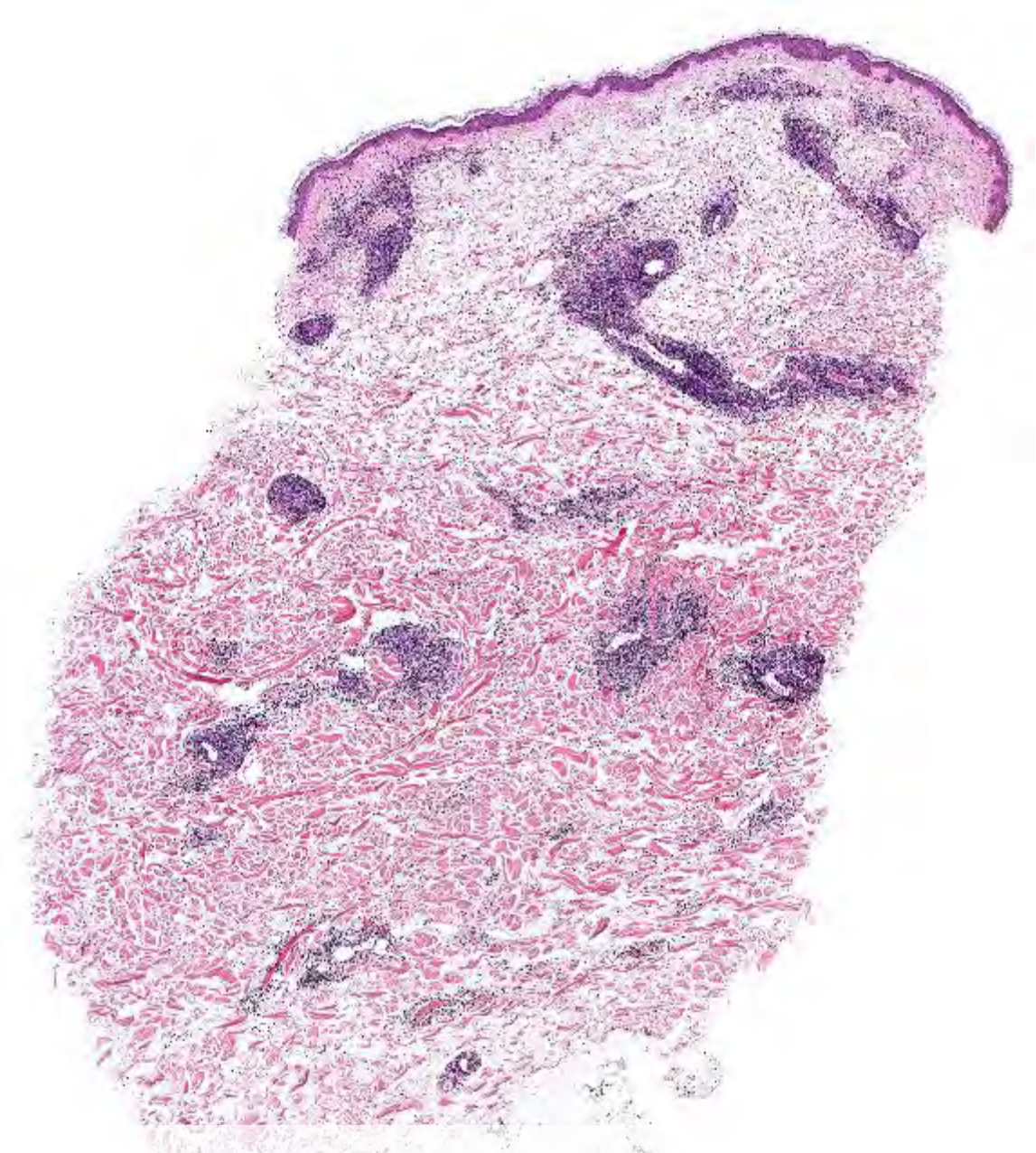
History of T-cell population of unclear dignity in the blood (41 months previously) and of T-PLL (10 months previously). No treatment at time of observation.

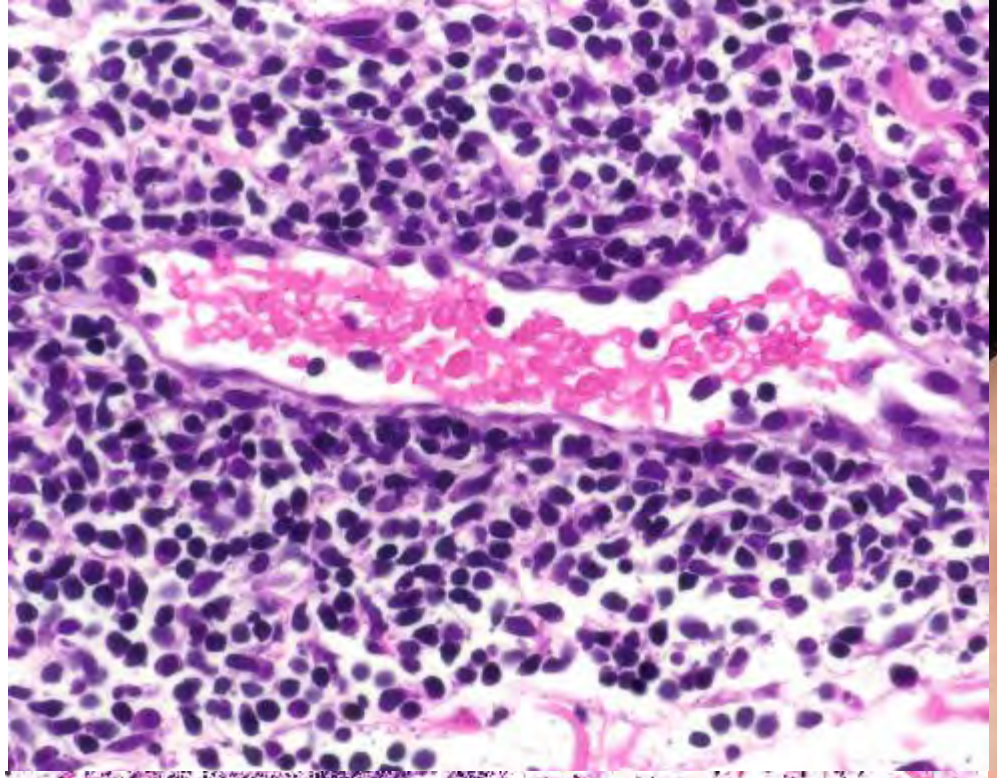
According to the patient asymptomatic skin lesion present for approximately 2 months.

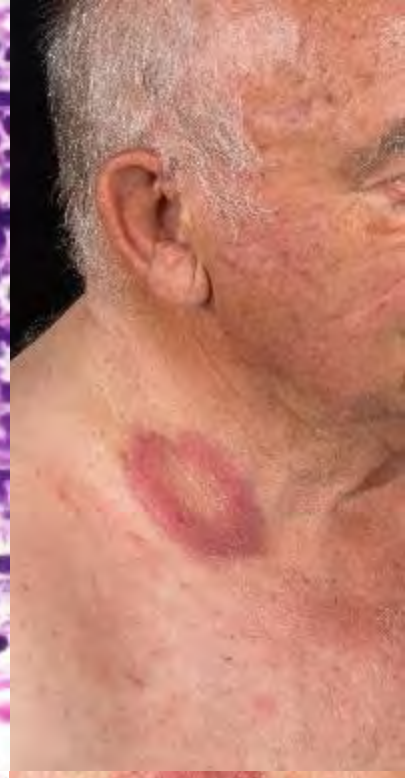
Leucocytes: 75.01/L
ANA & subsets: negative

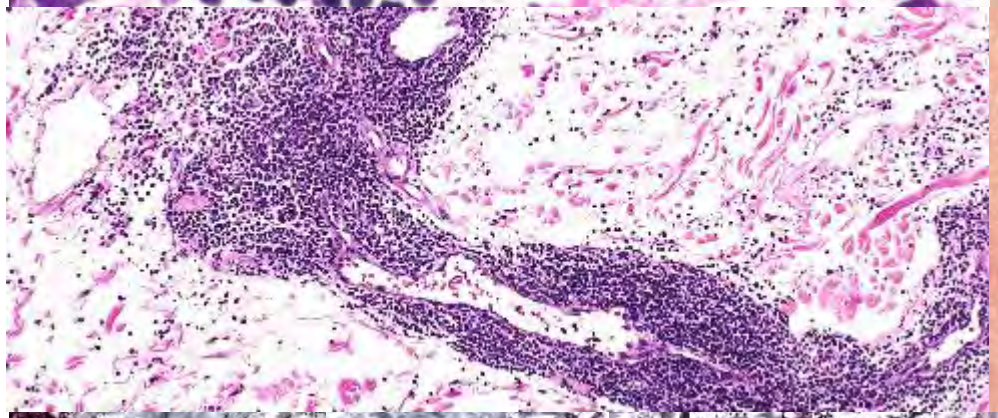
A previous biopsy performed by a private dermatologist was reported as lupus erythematosus tumidus, DDx erythema migrans (biopsy not available for review).

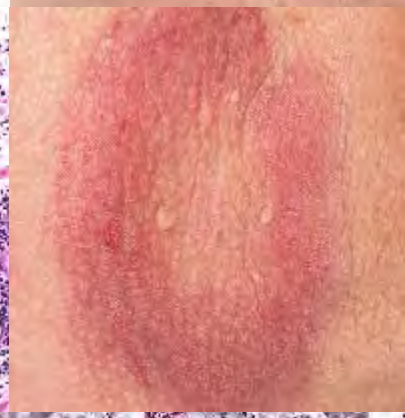
A new biopsy is taken.

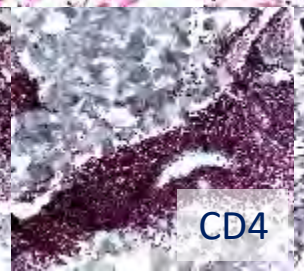


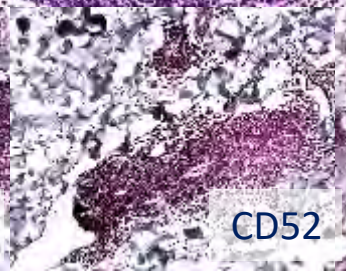


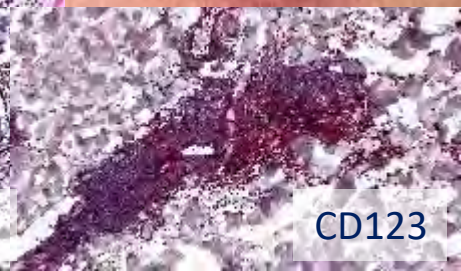






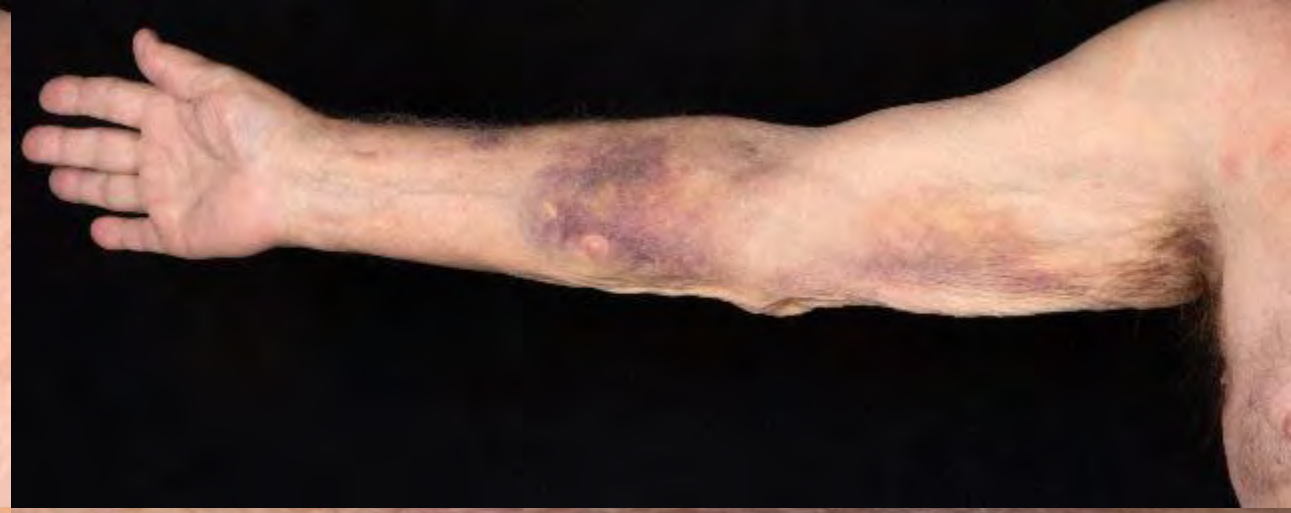


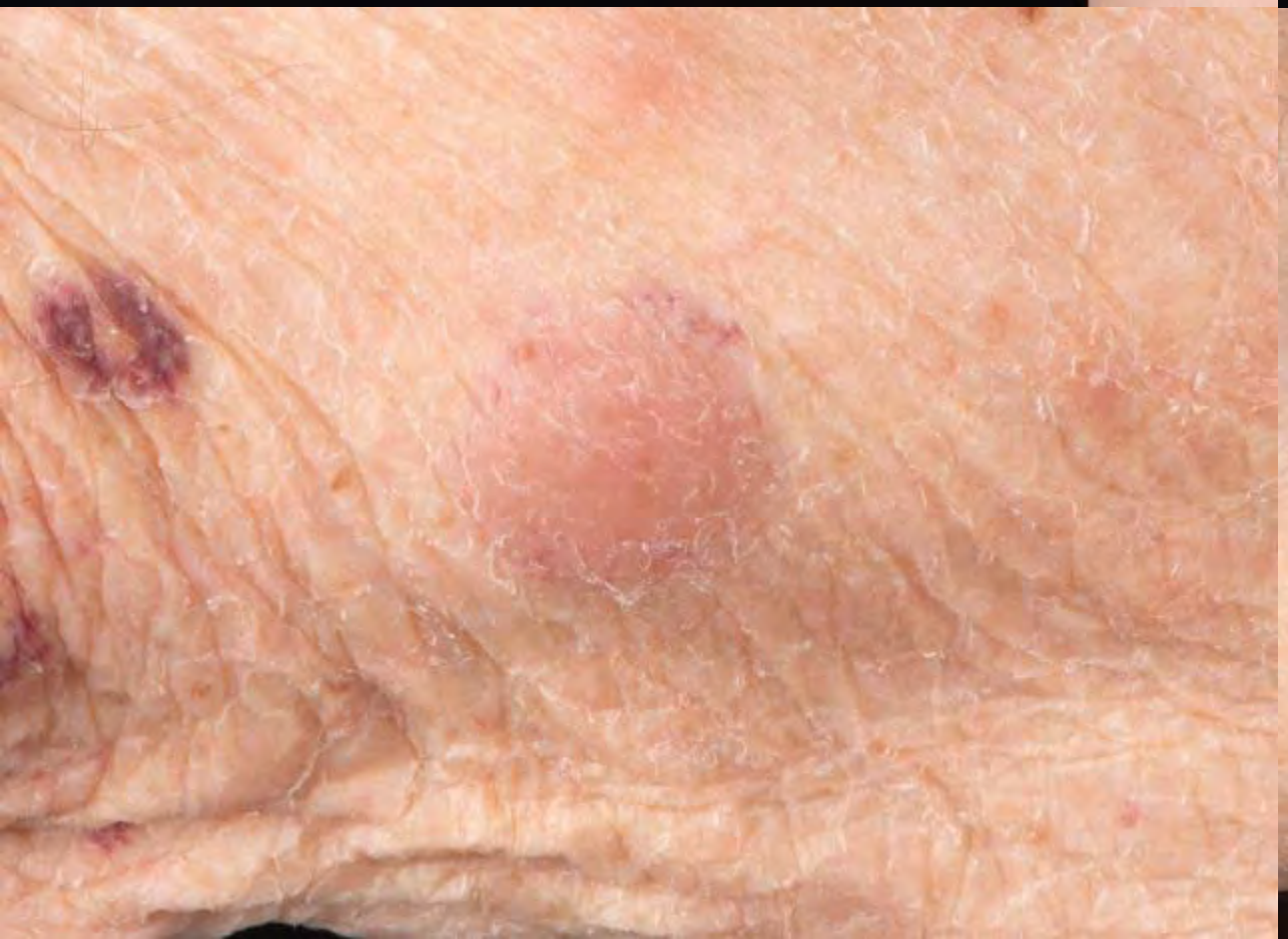


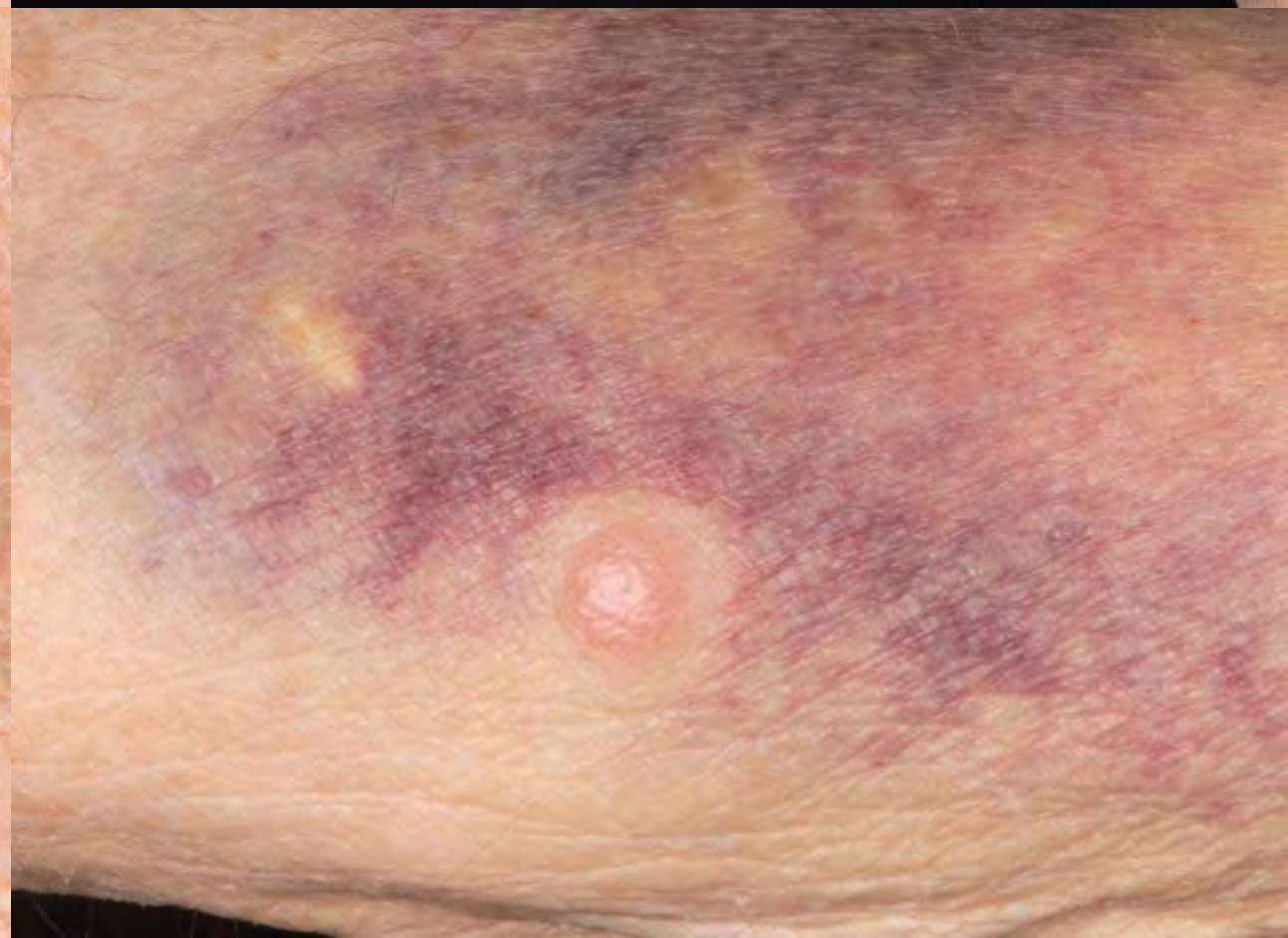


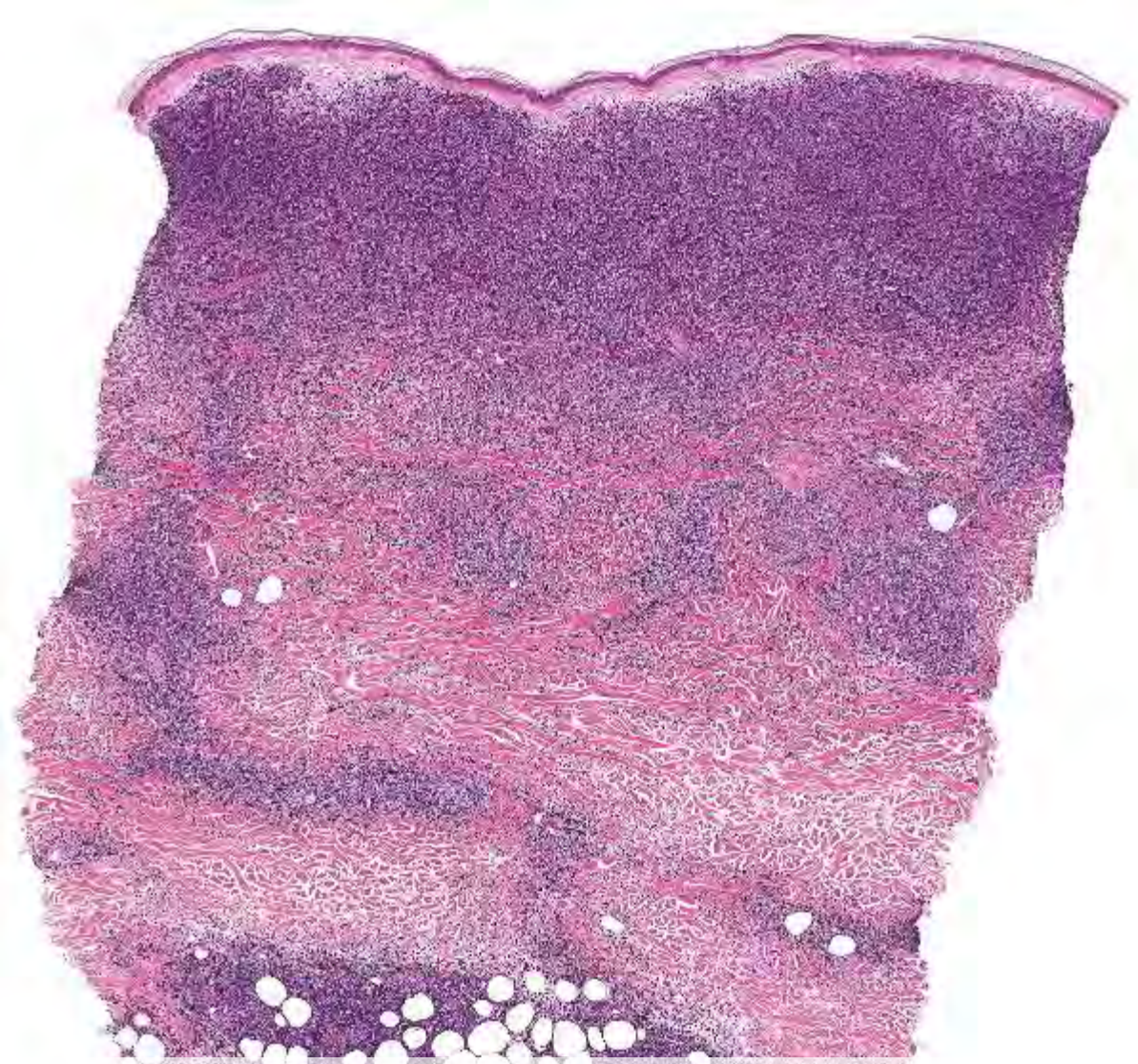
Specific infiltrate of T-PLL

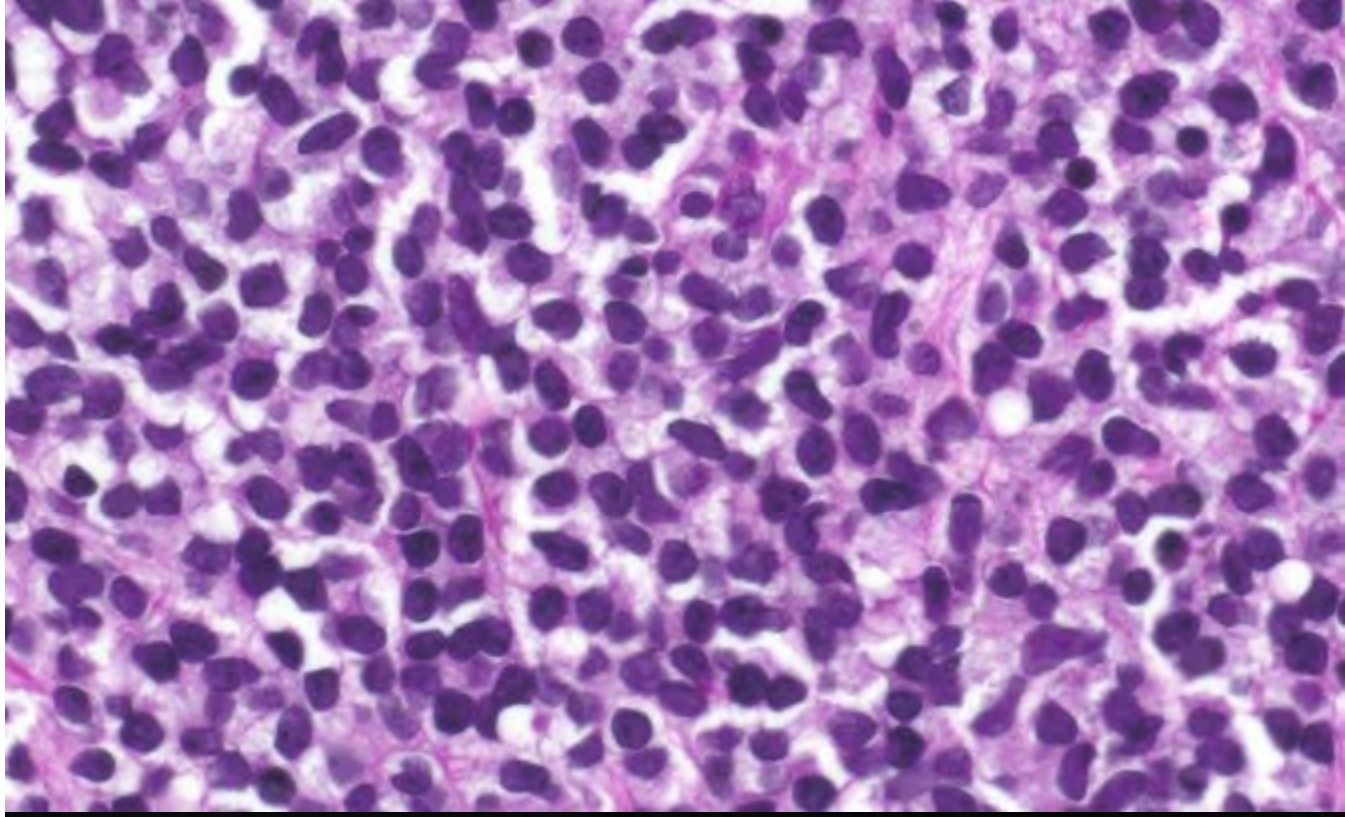
19 months later. Hematological CR (alemtuzumab).
Small nodules on the arms for 2-3 weeks.
A new biopsy is taken.

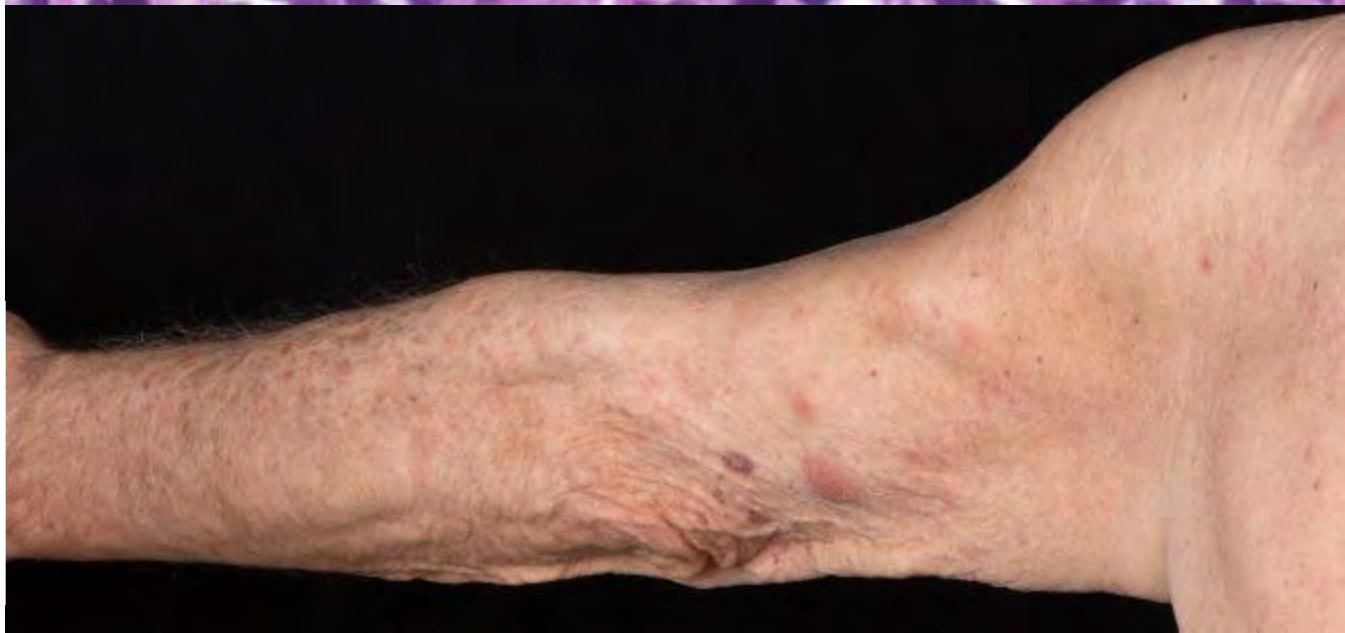






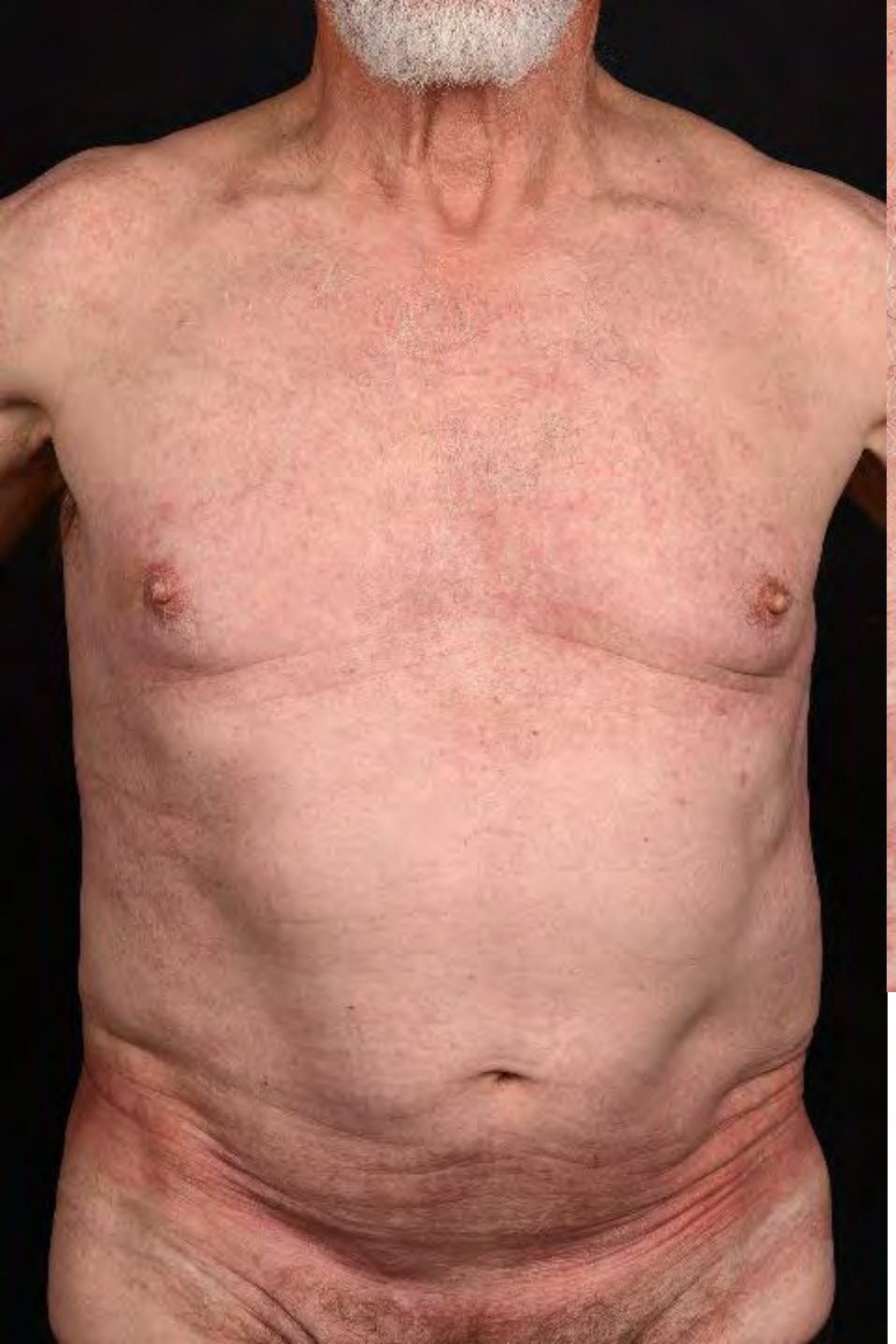


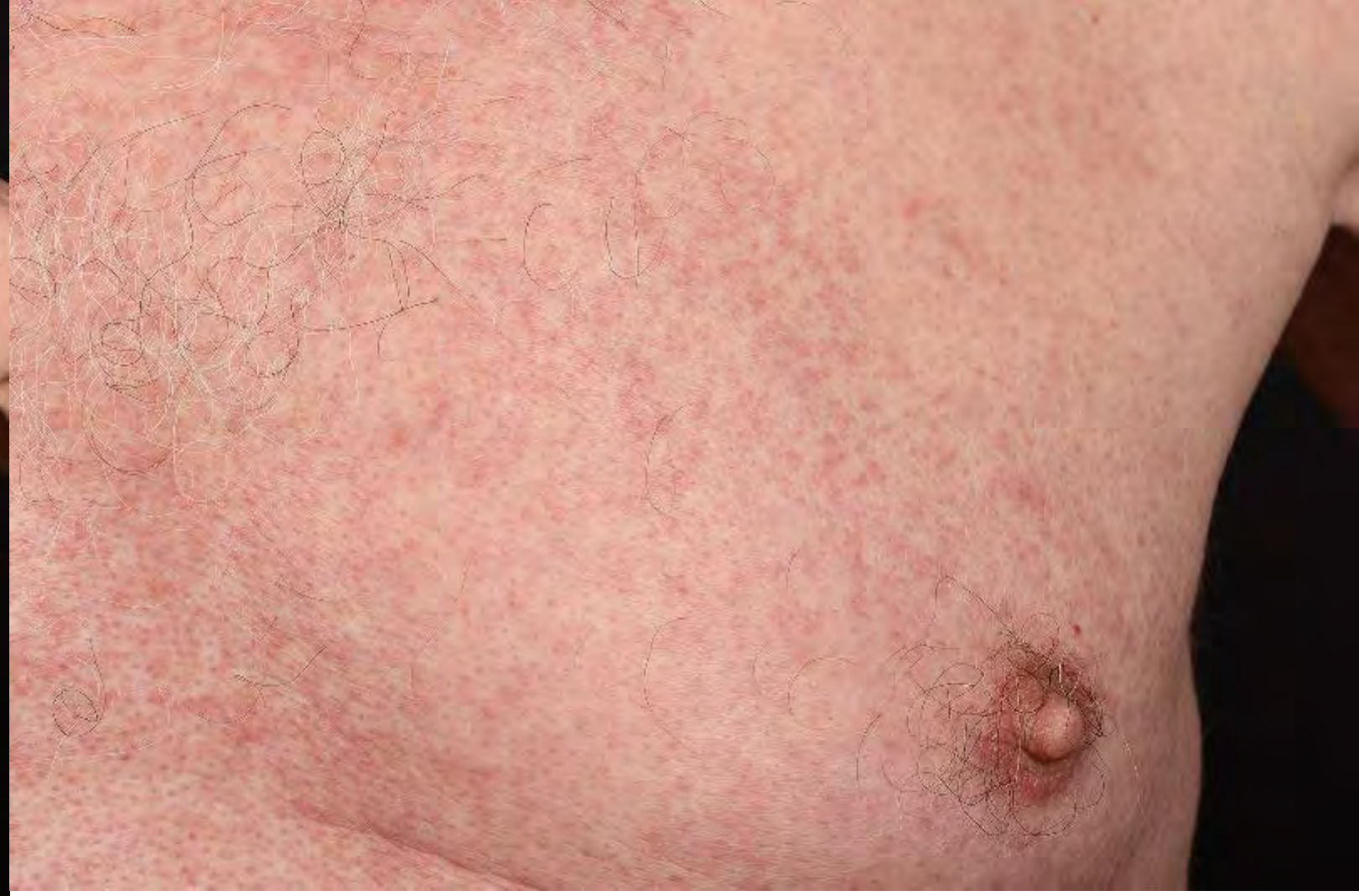




Specific infiltrate of T-PLL

(leukocytosis, loss of CD52 expression, therapy changed to pentostatin, progressive disease)



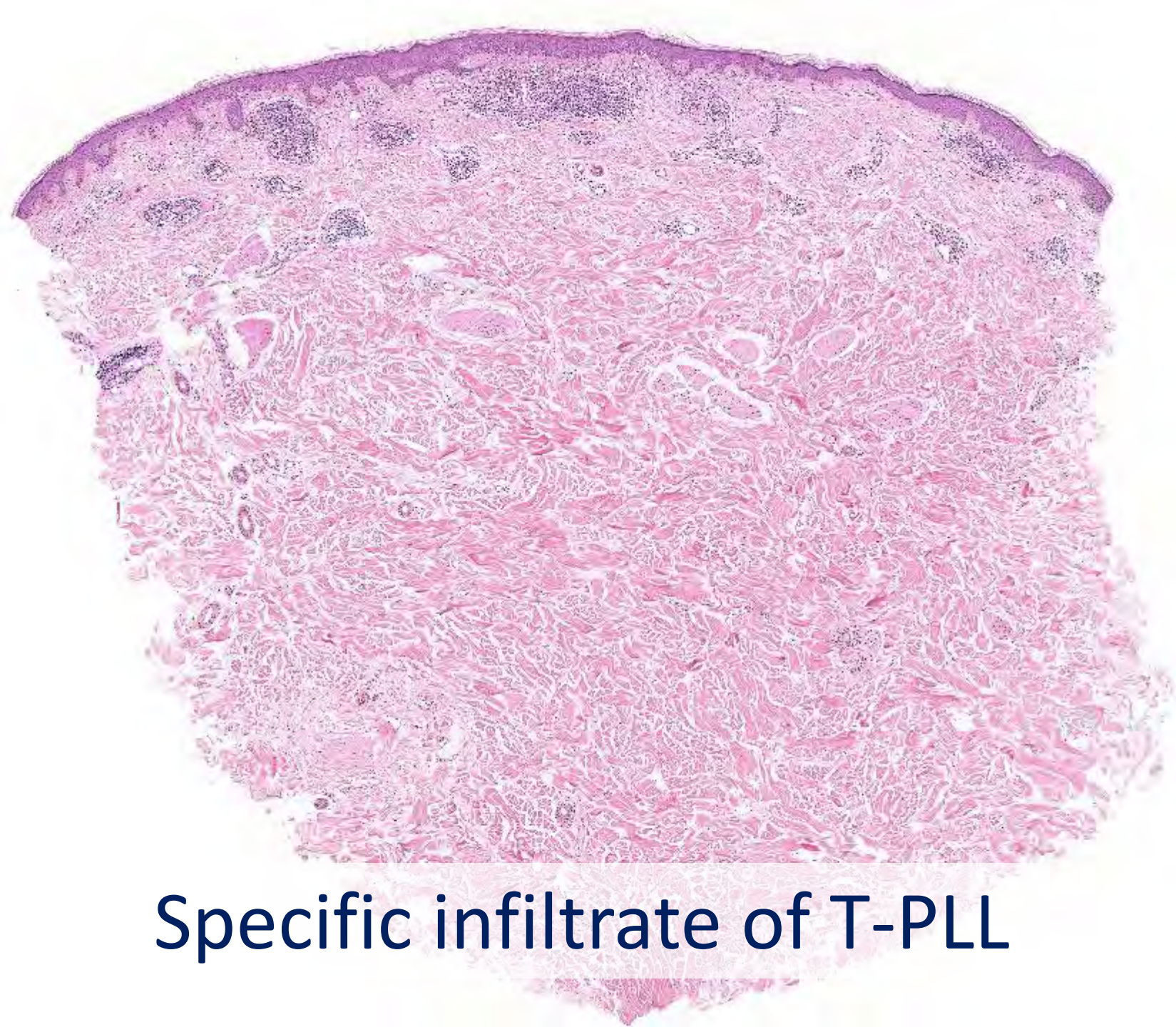


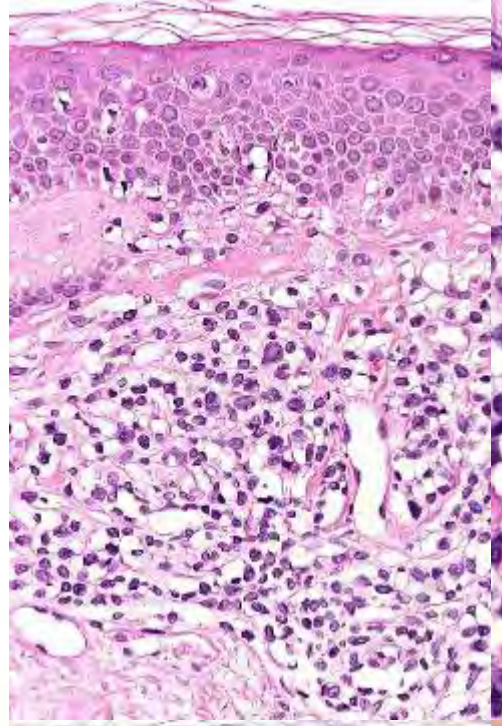
M, 69

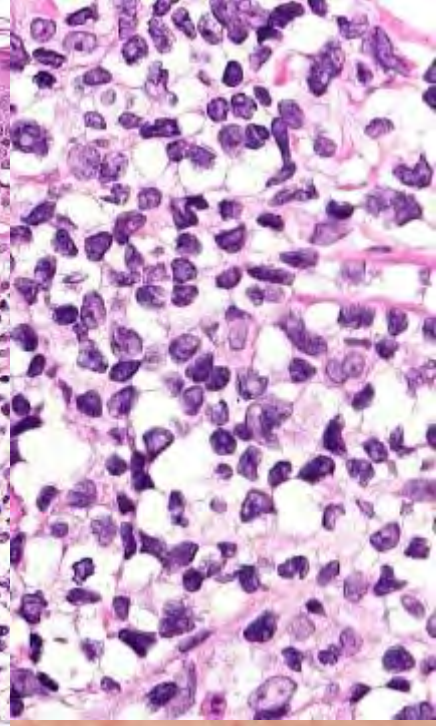
History of T-PLL (1st diagnosis 5 years before presentation; at present no treatment).

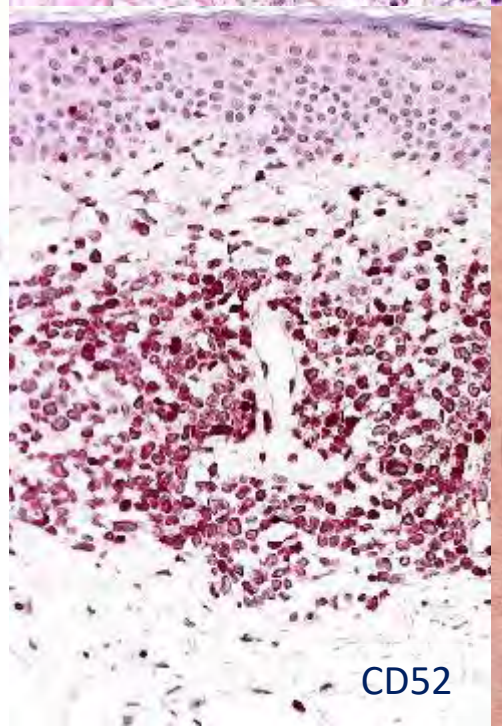
Generalized, itchy skin lesions present for 3-4 years, managed by hematologists with intermittent courses of local steroids (improvement with recurrence upon discontinuation).

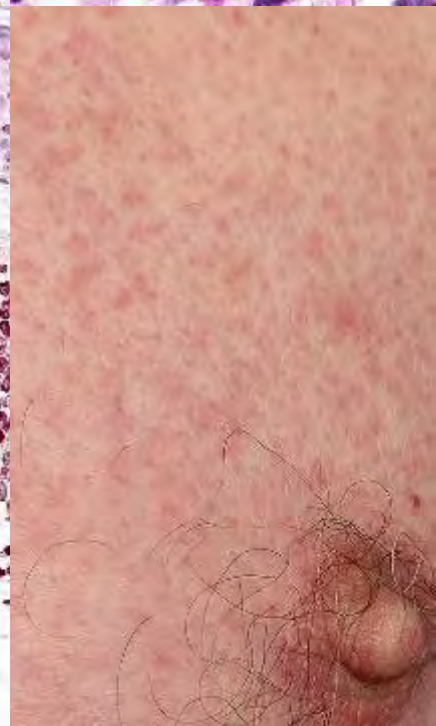
A biopsy is taken.









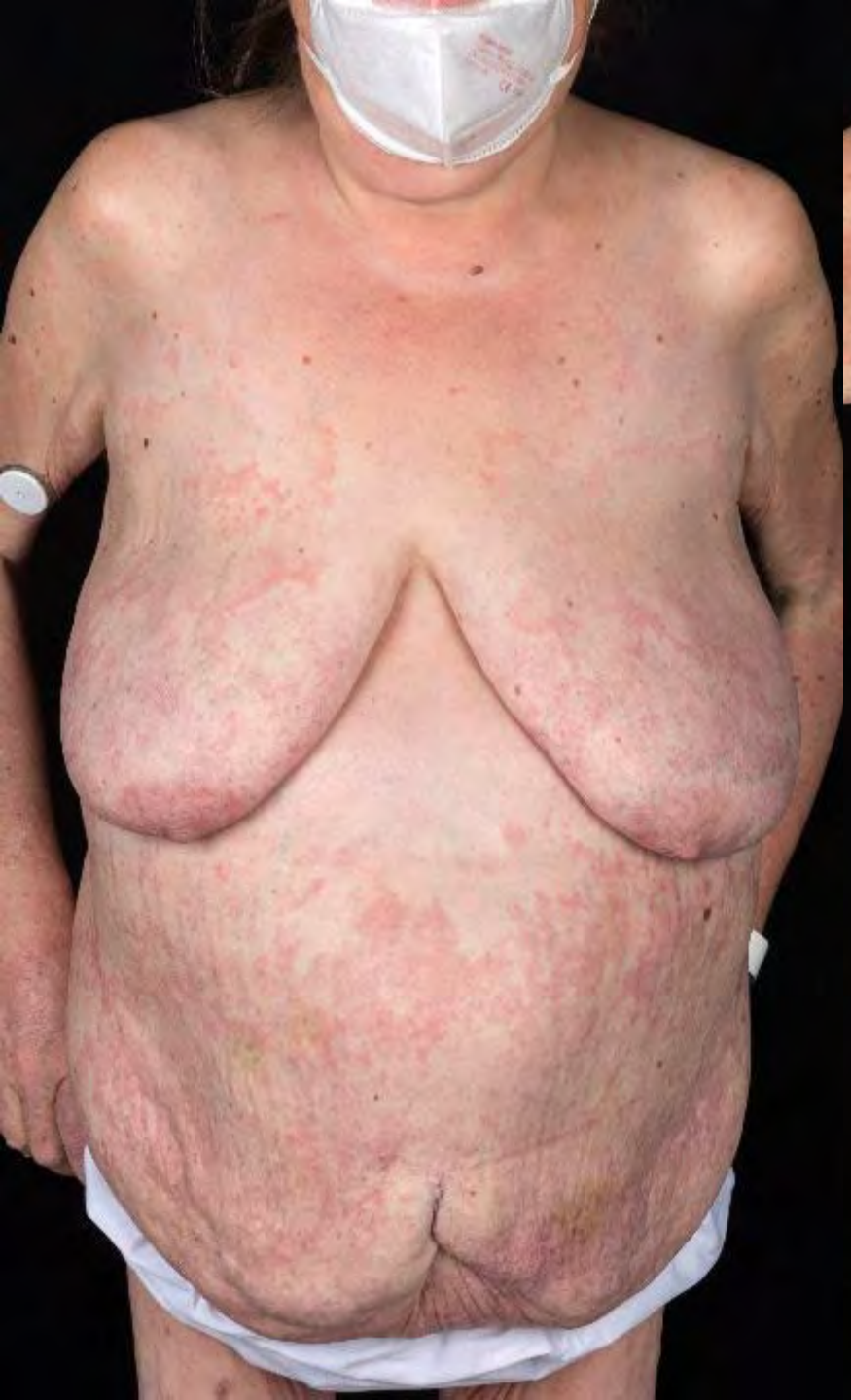


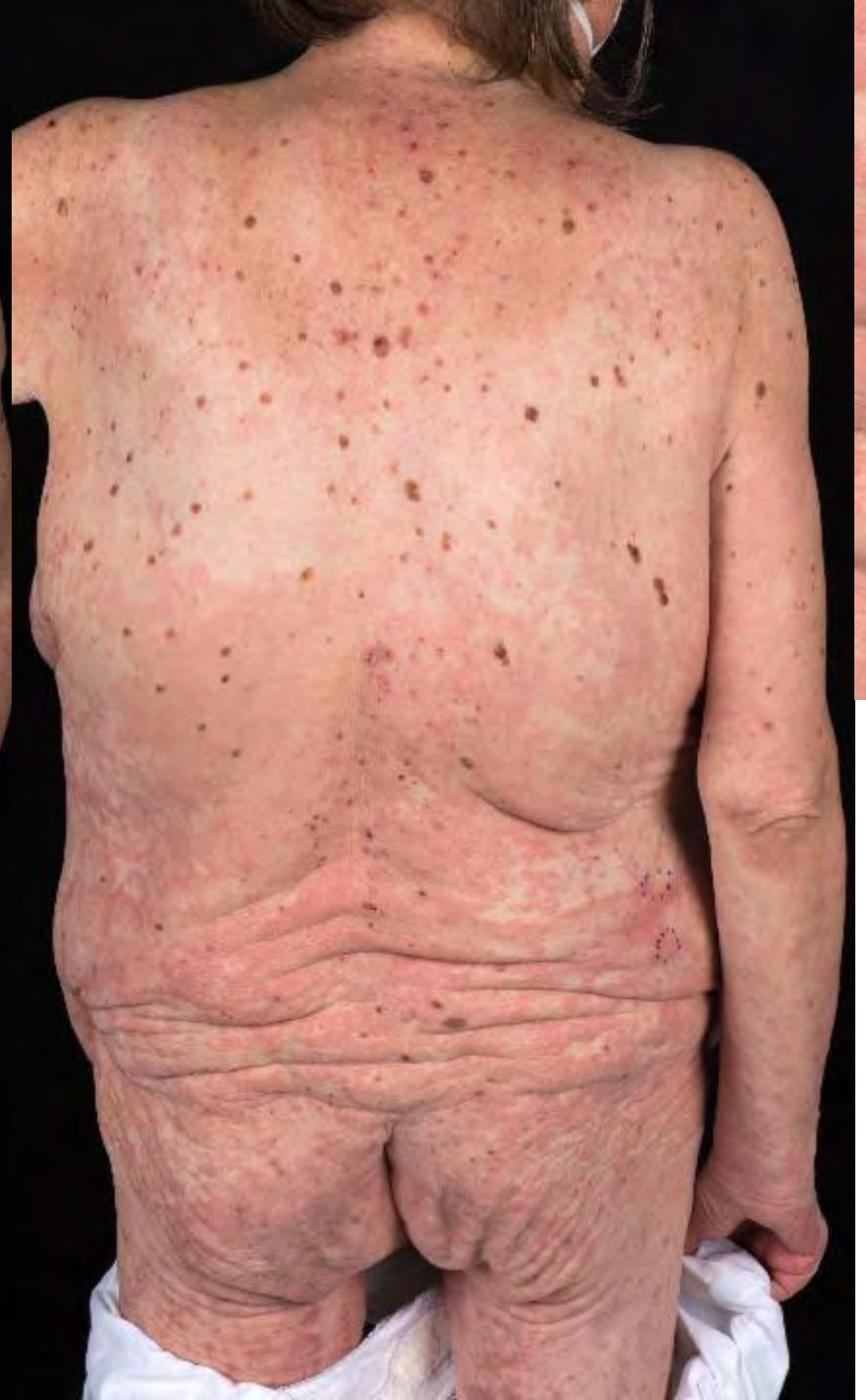
Specific infiltrate of T-PLL

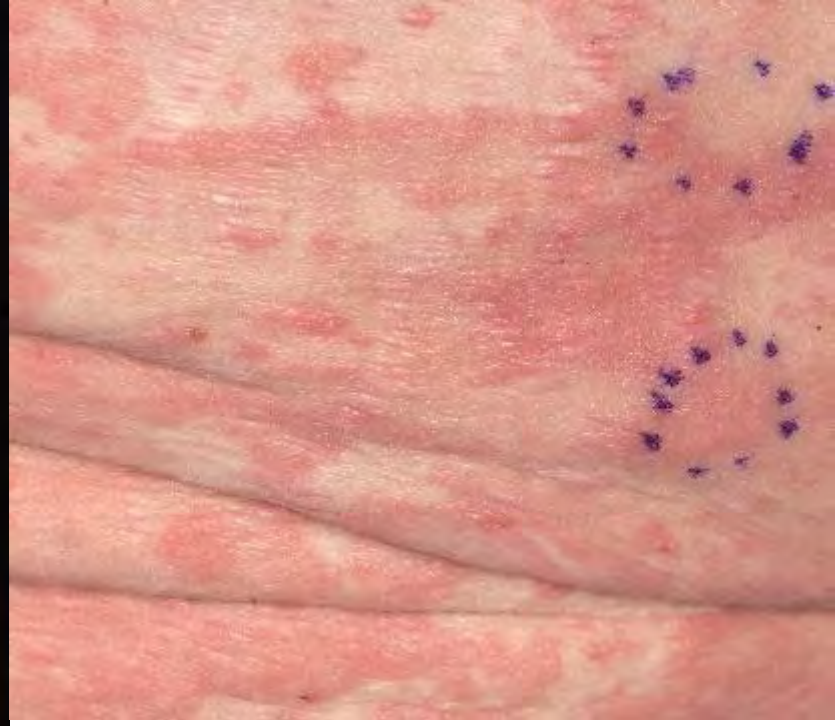
CD52

T-cell prolymphocytic leukemia

- Mostly in elderly patients; cutaneous involvement in 20-30% of cases and may be the first sign of the disease
- Erythroderma may develop and is indistinguishable from Sézary syndrome
- Histology reveals a monomorphous, superficial infiltrate of small lymphocytes, sometimes with epidermotropism, usually indistinguishable from mycosis fungoides or Sézary syndrome
- α/β T-helper phenotype (TCRβ+, TCRδ-, CD2+, CD3+, CD4+, CD5+, CD7+, CD8-, CD52+, TCL1+; S100+ in 1/3 of cases)
- Rearrangements involving TCL1 genes (*TCL1A, MTCP1*) and the TRA/TRD loci
- Aggressive course; poor prognosis





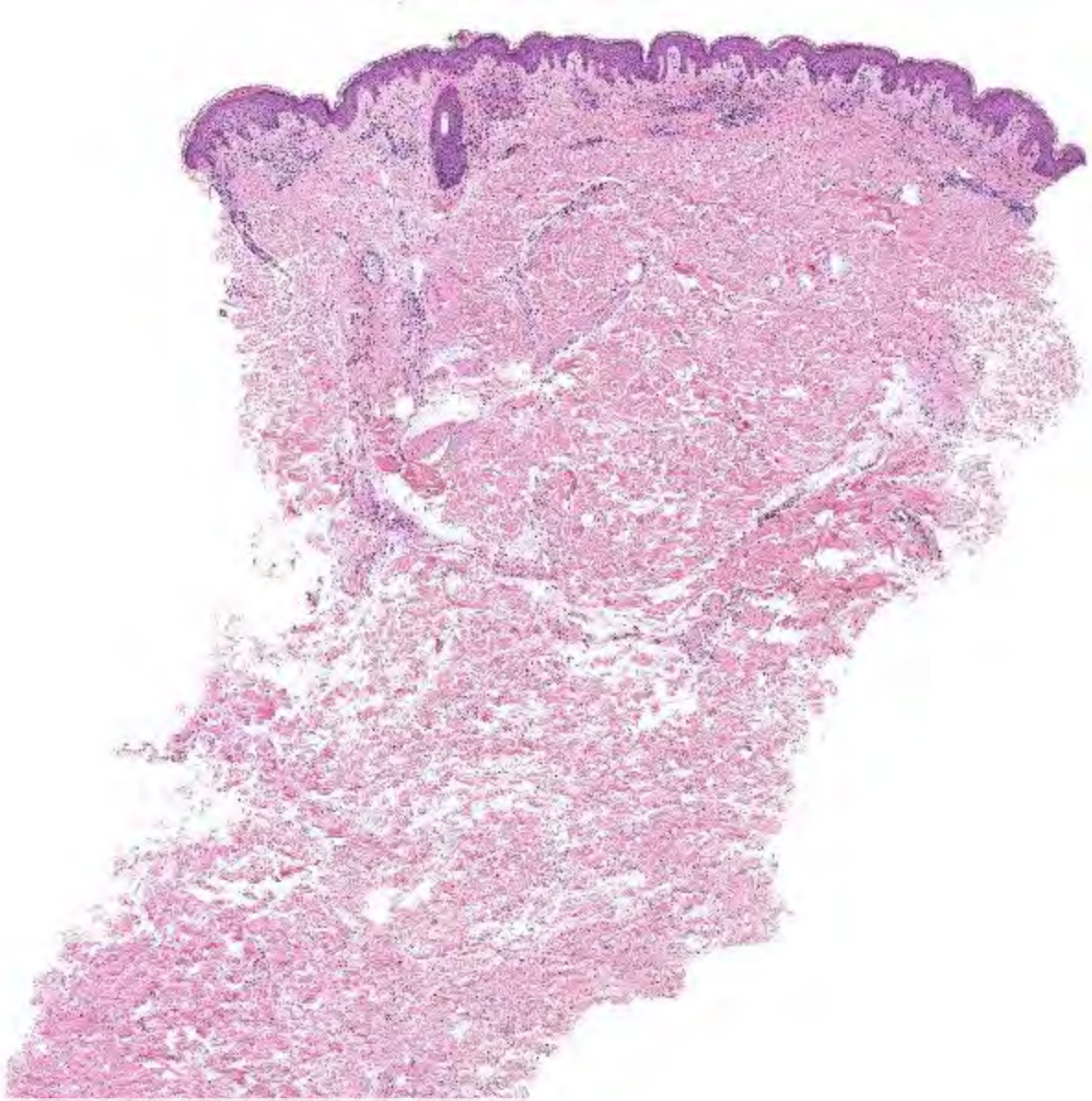


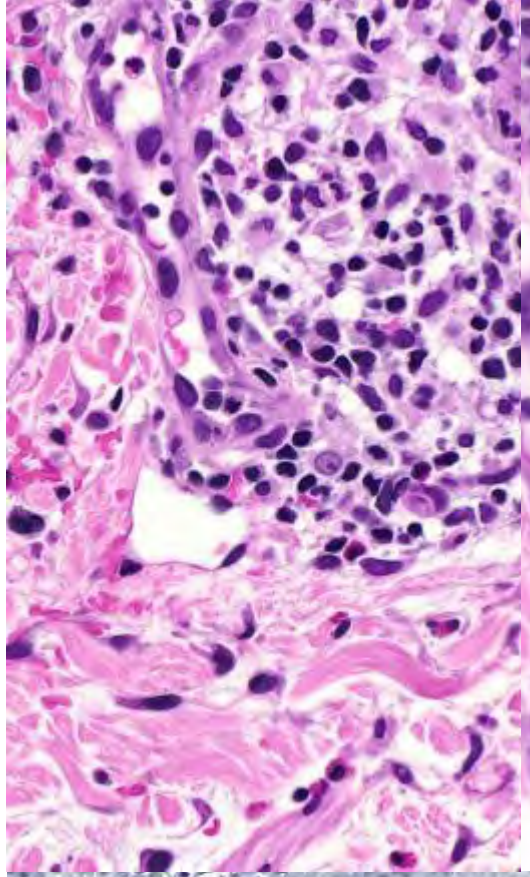
F, 50

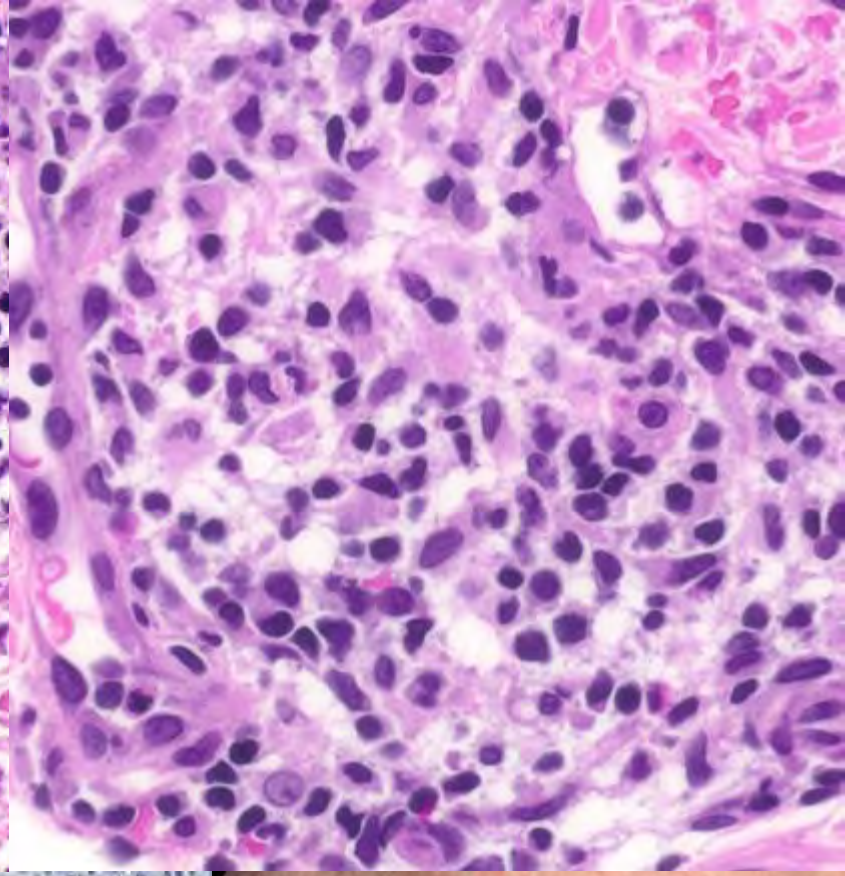
History of T-LGL (1st diagnosis 8 year before presentation; at present managed with methotrexate and steroids).

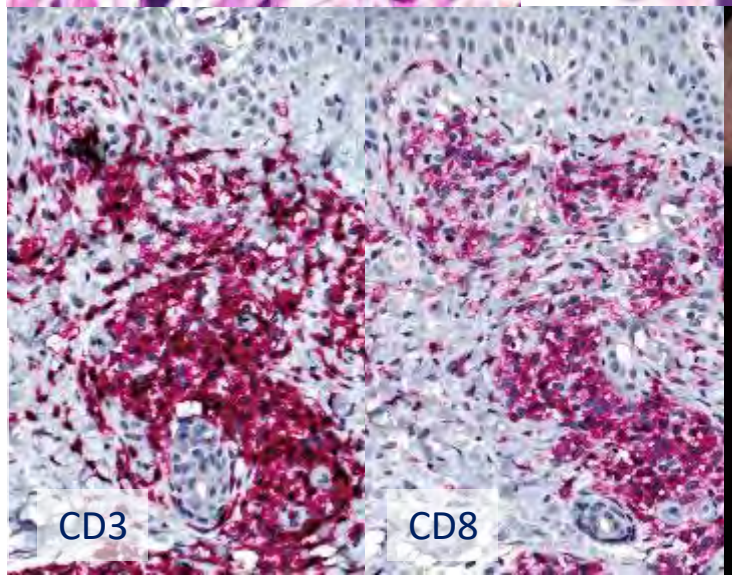
Generalized skin lesions present for "some months".

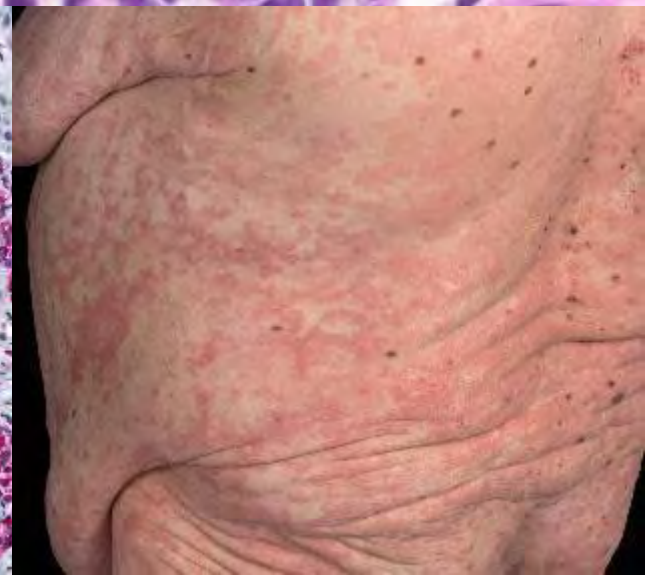
A biopsy is taken.





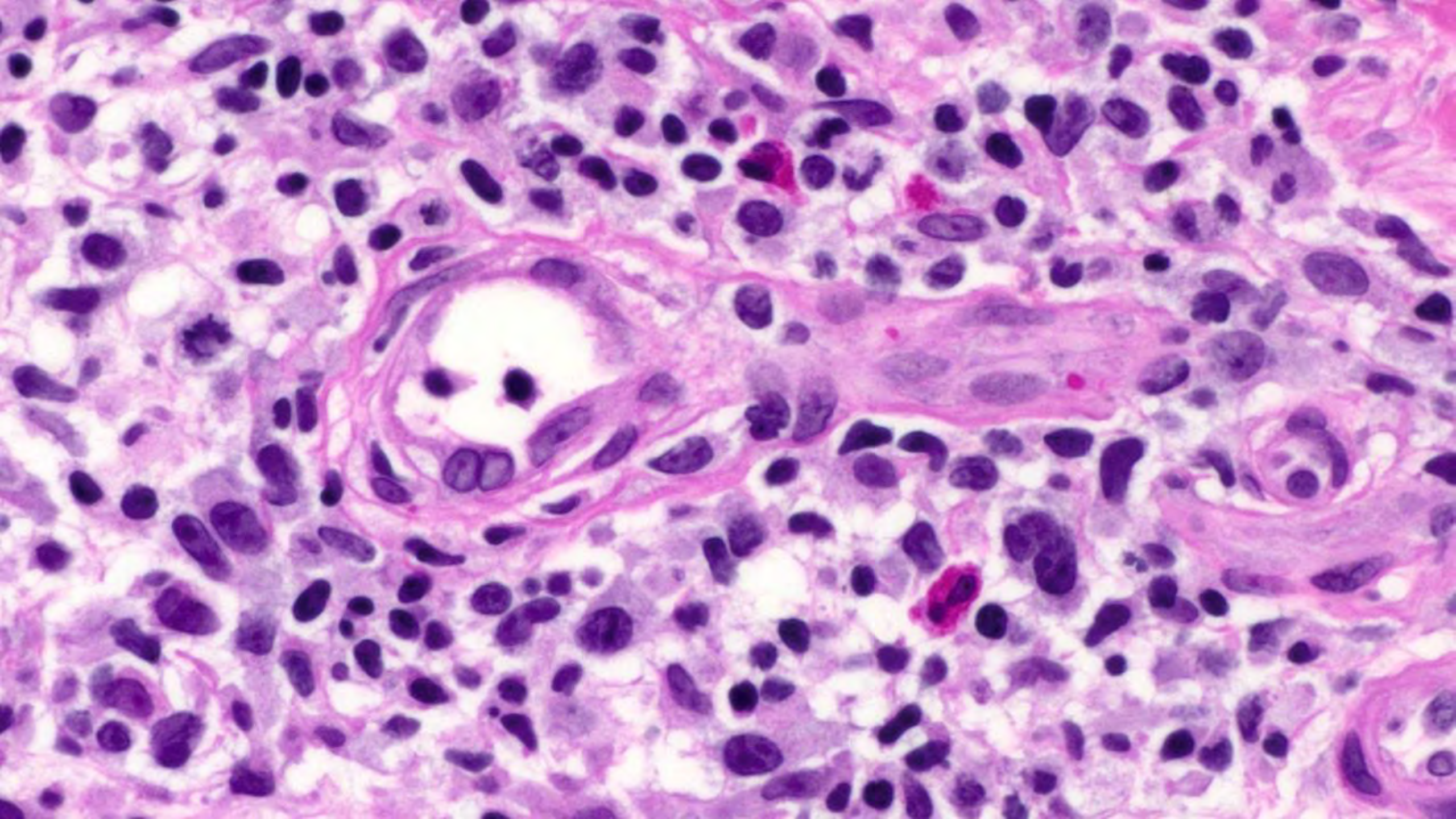






Specific infiltrate of T-LGL

Possibly triggered by a drug reaction



T-large granular lymphocytic leukemia

- Usually elderly patients; often asymptomatic or symptoms due to disease-associated cytopenias
- Rheumatoid arthritis is present in 20% of cases; other autoimmune diseases may be observed (LE, Sjögren)
- Cutaneous involvement infrequent; non-specific clinical presentation
- Small to medium-sized lymphocytes with abundant cytoplasm containing azurophilic granules (blood)
- Most cases are characterized by an α/β T-cytotoxic phenotype (CD3+, CD4-, CD8+, TIA-1+, Granzyme B+, TCRβ+, TCRδ-, CD57+; CD5 often negative)
- *STAT3* and *STAT5B* mutations are the most common molecular alterations
- Indolent course (*STAT3* mutations associated with a worse prognosis)

Aggressive NK-cell leukemia

Frequent (~90%) association with EBV.

Acute presentation, highly aggressive course.

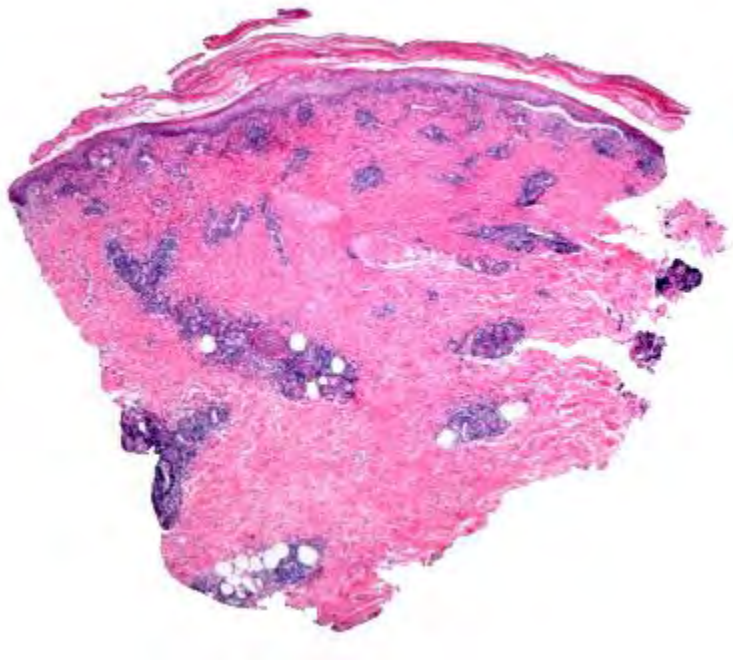
Skin lesions uncommon.

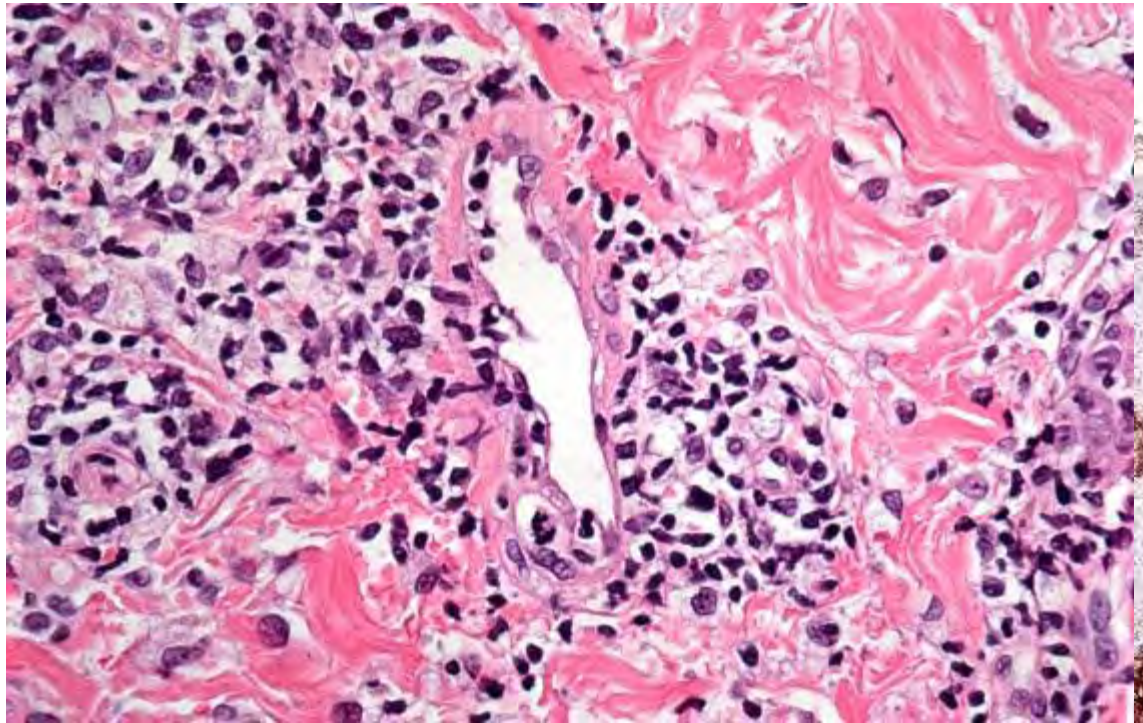
Round or irregularly folded nuclei, condensed chromatin, and small nucleoli; significant nuclear pleomorphism can be present.

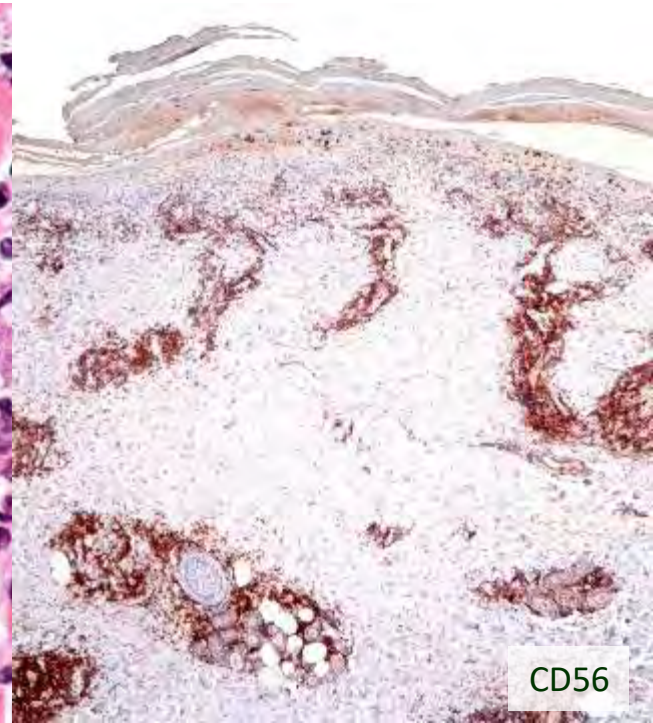
CD2+, CD3ε+, CD5-, CD7+, CD56+, TIA1+, granzyme B+, perforin+, CD8-/+.

Intravascular NK/T-cell lymphoma provisionally included in this group in the WHO classification (a very, very odd decision to my humble eyes…)

Case courtesy Philip LeBoit, San Francisco







Skin manifestations of leukemias

- Mostly in the setting of B-CLL and AML and related disorders; BPDCN is oft diagnosed in a dermatological setting, yet leukemic spread common
- Specific cutaneous manifestations of B-CLL are common, yet oft devoid of prognostic implications and not requiring specific treatment (antibiotic treatment should be used for cases related to *Borrelia*); histopathologically, neoplastic cells are often found as an incidental finding at sites of cutaneous inflammation / neoplasms
- Specific cutaneous manifestations of myelogeneous leukemia may occur in the absence of overt leukemia and may simulate an inflammatory dermatosis both clinically and histopathologically
- Other leukemias may present with specific skin infiltrates, sometimes triggered by inflammatory skin diseases (e.g., drug reactions)