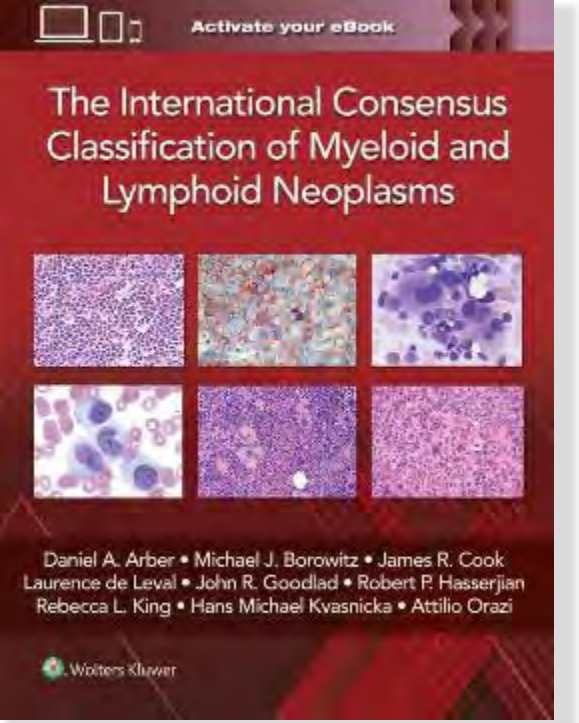
Aggressive cutaneous lymphomas

Lorenzo Cerroni



2025

2024

Cutaneous lymphomas discussed in specific chapters (includes the same entities as the WHO but for "primary cutaneous peripheral T-cell lymphoma NOS")

Three specific chapters for primary cutaneous B-cell lymphoproliferative disorders and lymphomas; different nomenclature for "primary cutaneous marginal zone lymphoproliferative disorder"

Does not include "intravascular NK/T-cell lymphoma"

Specific section on "primary cutaneous T-cell lymphoid proliferations and lymphomas" (includes "primary cutaneous peripheral T-cell lymphoma NOS"; Sézary syndrome included in a section on "mature T-cell and NK-cell leukemias")

Three specific chapters for primary cutaneous B-cell lymphoproliferative disorders and lymphomas; different nomenclature for "primary cutaneous marginal zone lymphoma"

Does not include "intravascular NK/T-cell lymphoma"

Comparison of the 2025 *International Consensus Classification of Myeloid and Lymphoid Neoplasms* and the 2024 *WHO Classification of Haematolymphoid Tumours* for entities relevant to the skin, and corresponding entities in the 2018 *WHO-EORTC Classification of Cutaneous Lymphomas*

WHO 5ed	International Consensus Classification	2018 WHO-EORTC Classification of Cutaneous Lymphomas
Mycosis fungoides & variants Folliculotropic mycosis fungoides Pagetoid reticulosis Granulomatous slack skin	Mycosis fungoides & variants Folliculotropic mycosis fungoides Pagetoid reticulosis Granulomatous slack skin	Mycosis fungoides & variants Folliculotropic mycosis fungoides Pagetoid reticulosis Granulomatous slack skin
Sézary syndrome	Sézary syndrome	Sézary syndrome
Adult T-cell leukemia/lymphoma	Adult T-cell leukemia/lymphoma	Adult T-cell leukemia/lymphoma
Cutaneous CD30+ lymphoproliferative disorders Cutaneous anaplastic large cell lymphoma Lymphomatoid papulosis	Cutaneous CD30+ lymphoproliferative disorders Cutaneous anaplastic large cell lymphoma Lymphomatoid papulosis	Cutaneous CD30+ lymphoproliferative disorders Cutaneous anaplastic large cell lymphoma Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma
Extranodal NK/T-lymphoma, nasal-type	Extranodal NK/T-lymphoma, nasal-type	Extranodal NK/T-lymphoma, nasal-type
Cutaneous gamma/delta T-cell lymphoma	Cutaneous gamma/delta T-cell lymphoma	Cutaneous gamma/delta T-cell lymphoma
Cutaneous aggressive epidermotropic CD8+ CTCL	Cutaneous aggressive epidermotropic CD8+ CTCL	Cutaneous aggressive epidermotropic CD8+ CTCL *(provisional)*
pCSMPCD4+T-cell lymphoproliferative disorder	pCSMPCD4+T-cell lymphoproliferative disorder	pCSMPCD4+T-cell lymphoproliferative disorder *(provisional)*
Acral CD8+ T-cell lymphoproliferative disorder	Acral CD8+ T-cell lymphoproliferative disorder	Acral CD8+ T-cell lymphoma *(provisional)*
EBV+ T/NK-cell LDs and lymphomas of childhood	EBV+ T/NK-cell lymphoproliferative disorders of childhood	Chronic active EBV infection
Cutaneous peripheral T-cell lymphoma, NOS	Peripheral T-cell lymphoma, NOS	Cutaneous peripheral T-cell lymphoma, NOS
Cutaneous marginal zone lymphoma	Cutaneous marginal zone lymphoproliferative disorder	Cutaneous marginal zone lymphoma
Cutaneous follicle center lymphoma	Cutaneous follicle center lymphoma	Cutaneous follicle center lymphoma
Cutaneous diffuse large B-cell lymphoma, leg-type	Cutaneous diffuse large B-cell lymphoma, leg-type	Cutaneous diffuse large B-cell lymphoma, leg-type
Intravascular large B-cell lymphoma	Intravascular large B-cell lymphoma	Intravascular large B-cell lymphoma
EBV+ mucocutaneous ulcer	EBV+ mucocutaneous ulcer	EBV+ mucocutaneous ulcer *(provisional)*

Aggressive cutaneous lymphomas

- Cutaneous T-, NK- or B-cell lymphoma entities with aggressive behavior and poor prognosis
- Distinction between primary cutaneous cases and secondary spread of extracutaneous lymphomas may be difficult (and often does not influence management and prognosis)
- Some differences between cutaneous and extracutaneous cases yet exist (e.g., primary cutaneous peripheral T-cell lymphoma, NOS may have an indolent behavior)
- Aggressive *primary* cutaneous lymphomas are lymphomas limited to the skin after adequate staging investigations

Aggressive types of cutaneous lymphoma

Sézary syndrome

Cutaneous adult T-cell leukemia/lymphoma

Cutaneous extranodal NK/T-lymphoma, nasal-type

Cutaneous gamma/delta T-cell lymphoma

Cutaneous aggressive epidermotropic CD8+ T-cell lymphoma

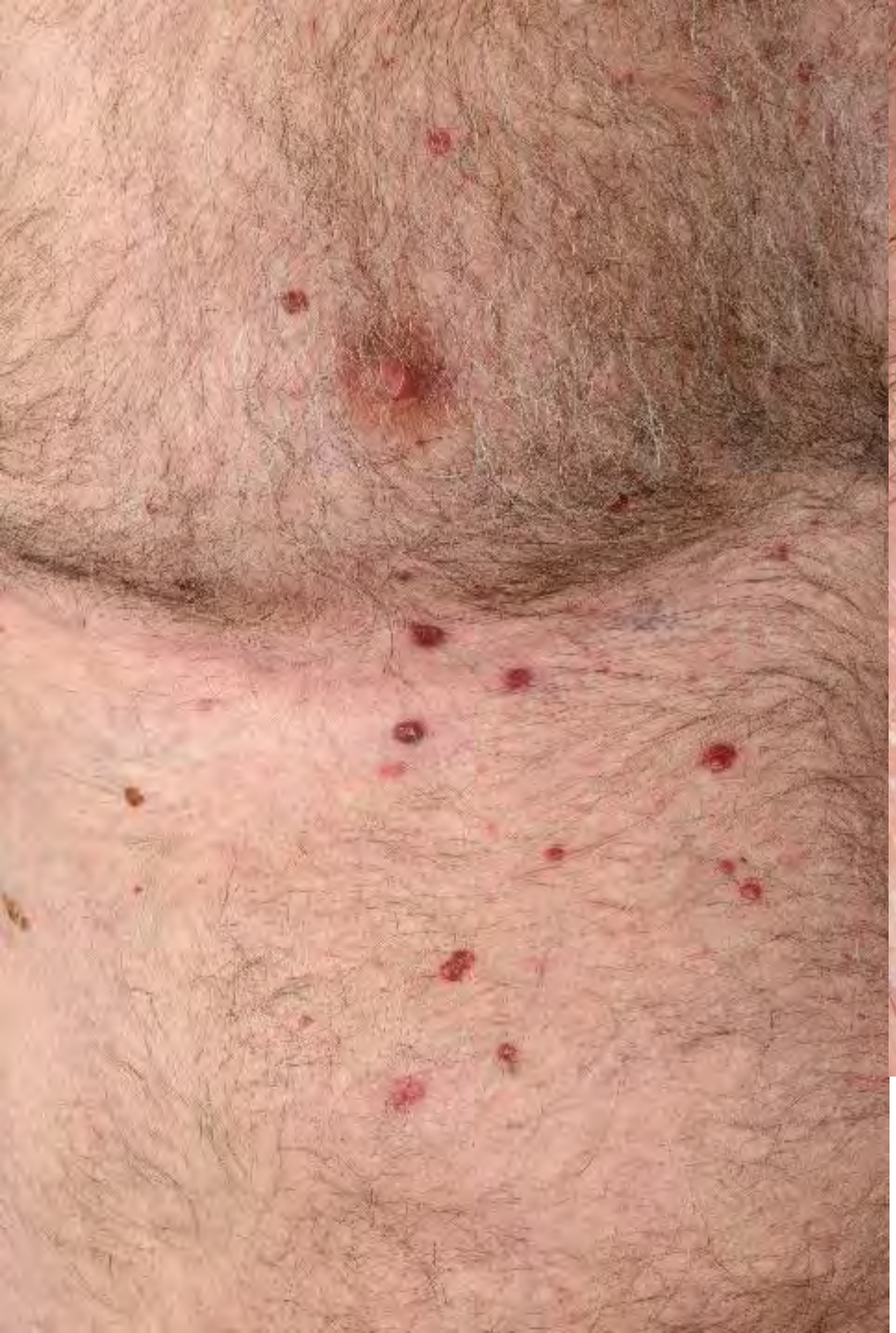
Cutaneous (peripheral) T-cell lymphoma, NOS

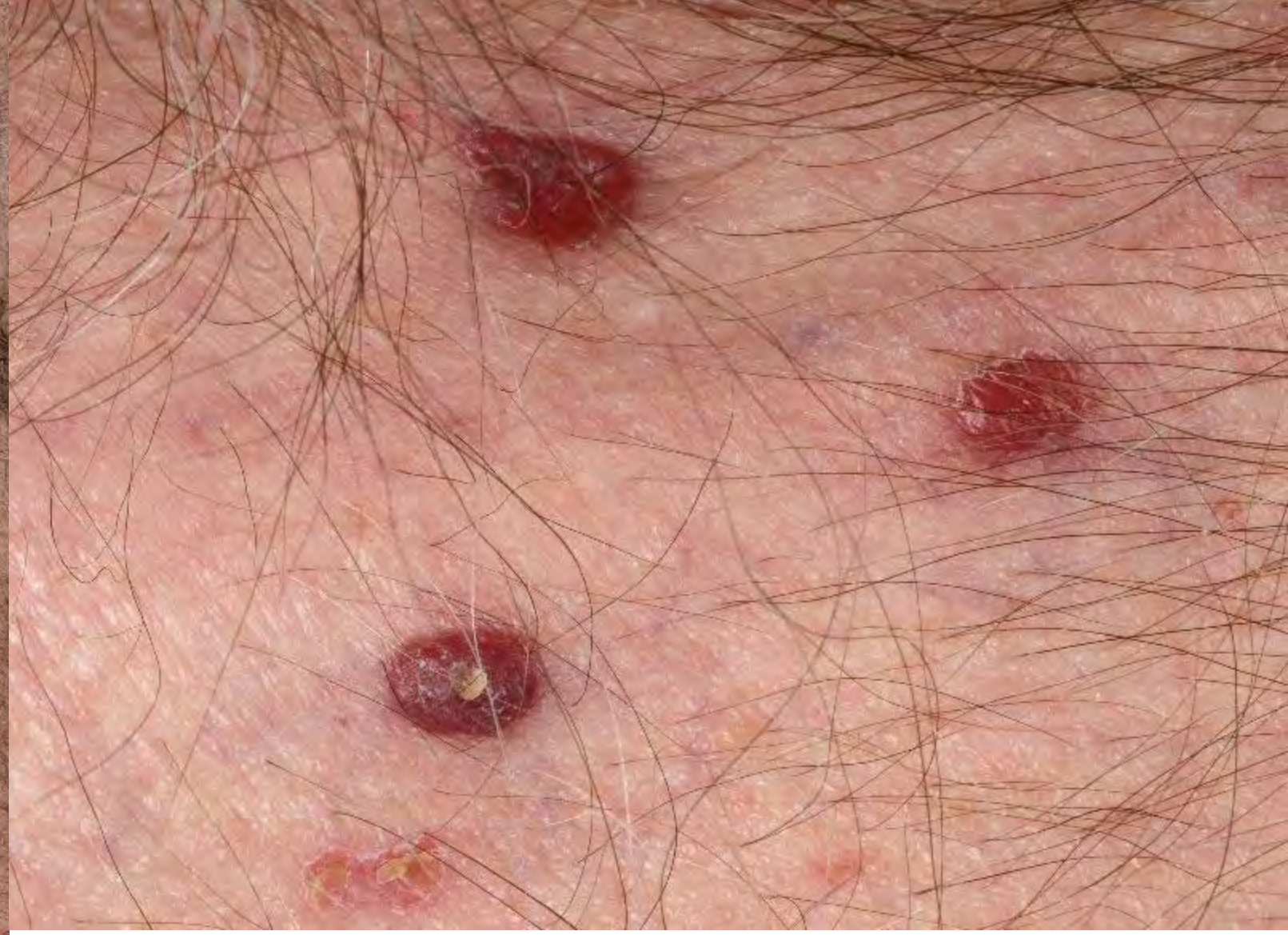
EBV+ T/NK-cell lymphoproliferative disorder of childhood

Cutaneous diffuse large B-cell lymphoma, leg-type

Intravascular large B-cell (or NK/T-cell) lymphoma

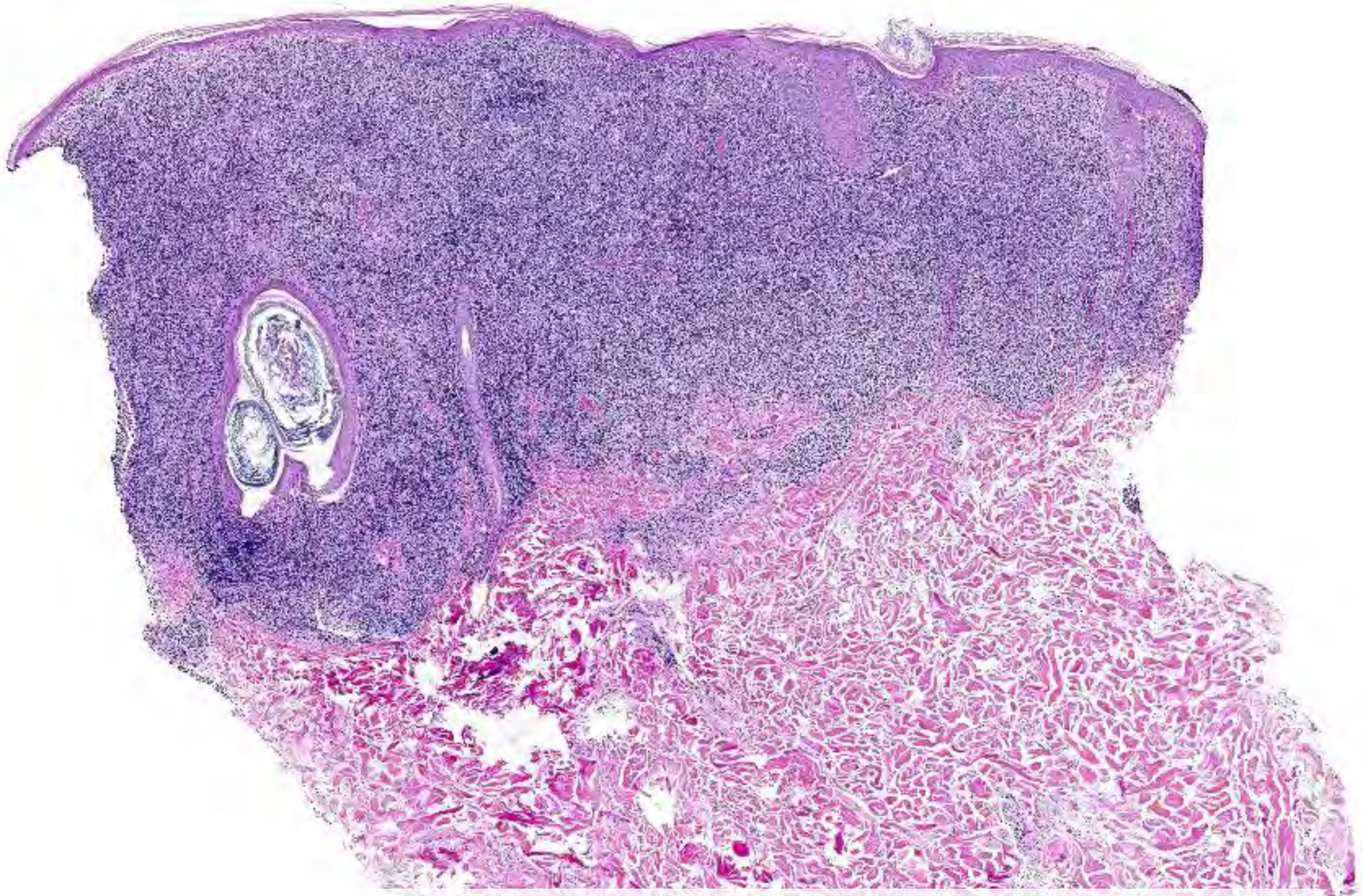
Other rare cases arising primary in the skin or involving it secondarily

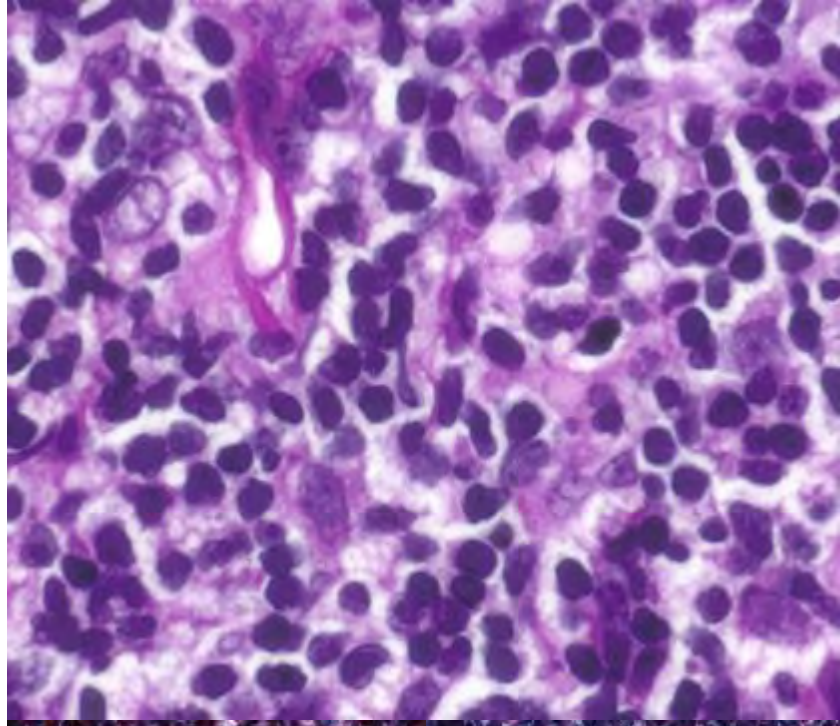


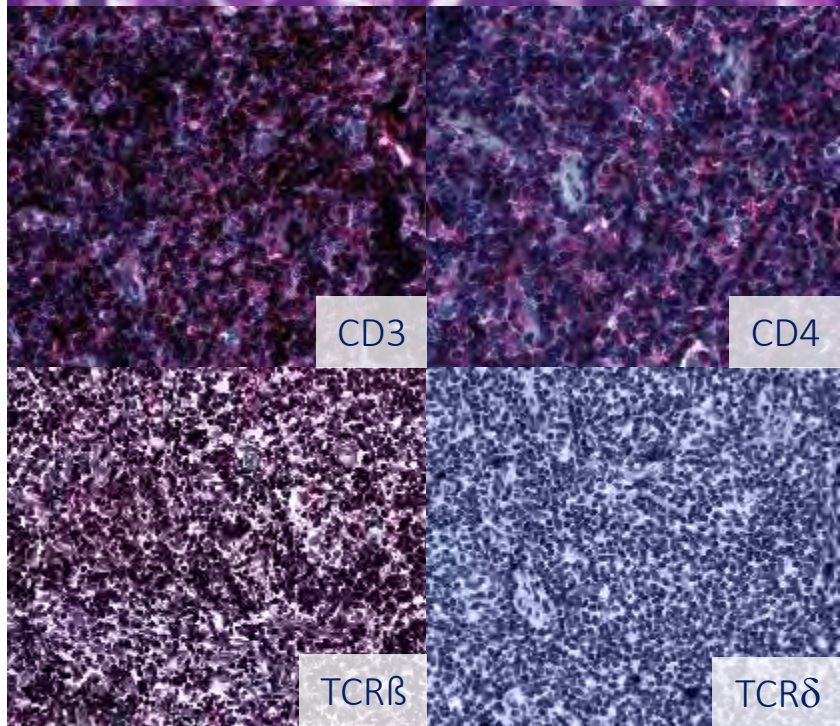


M, 61

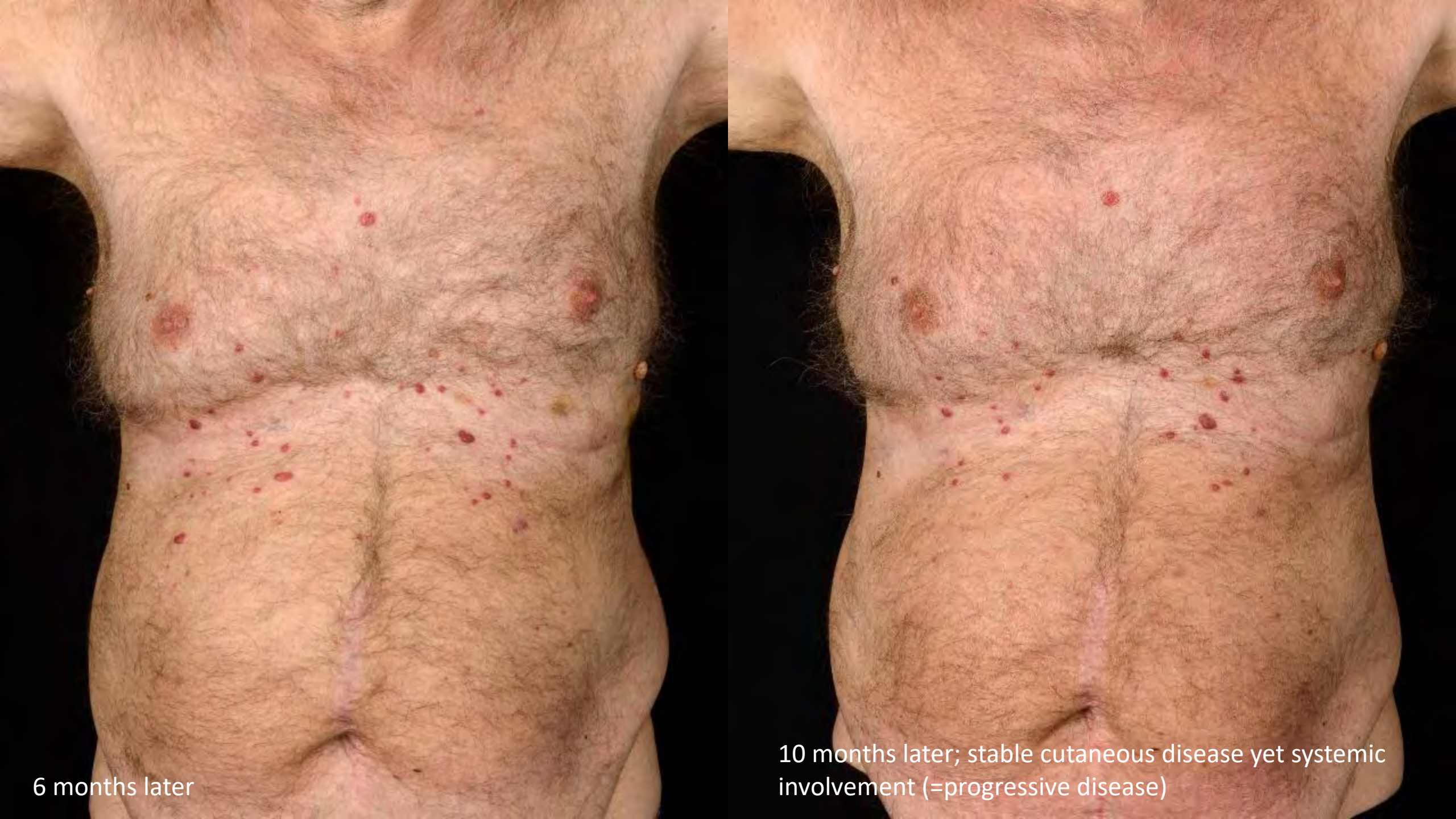
Recent onset of a multiple red papules on the abdomen and chest.

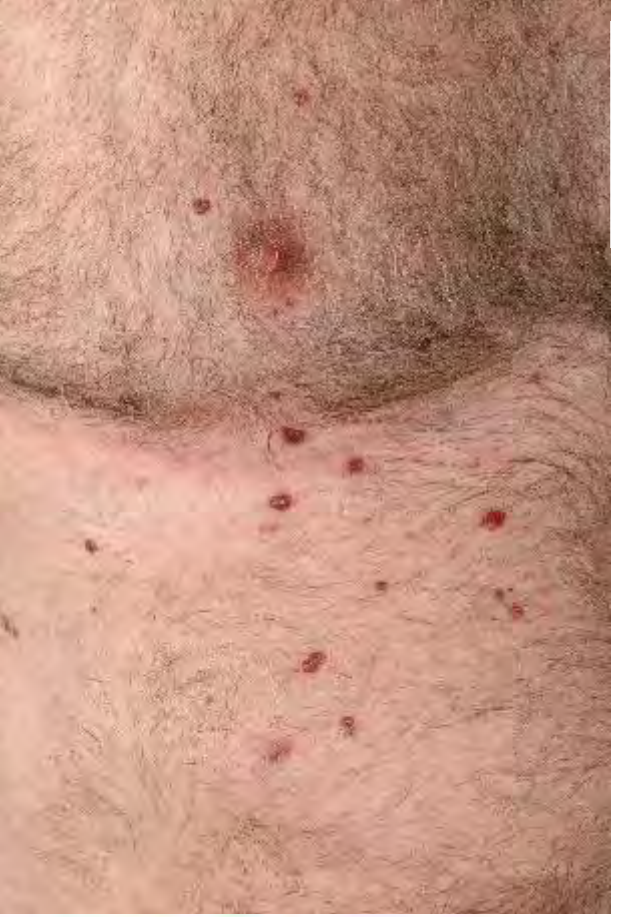


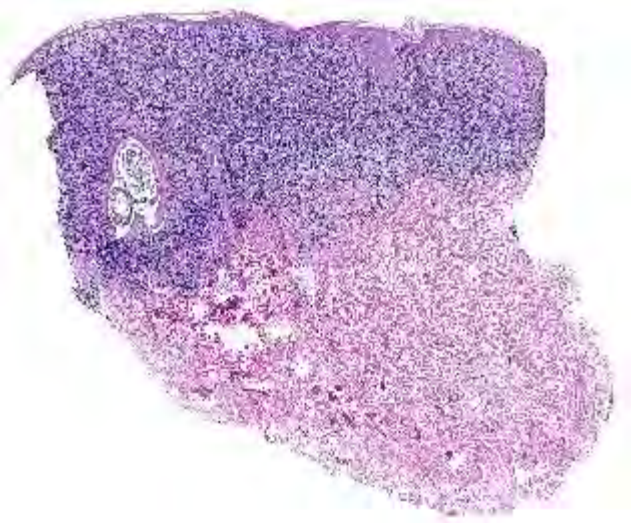




Primary cutaneous (peripheral) T-cell lymphoma, NOS


6 months later
10 months later; stable cutaneous disease yet systemic involvement (=progressive disease)





Primary cutaneous (peripheral) T-cell lymphoma, NOS

A diagnosis of exclusion

Rule out

Mycosis fungoides
history, clinical features

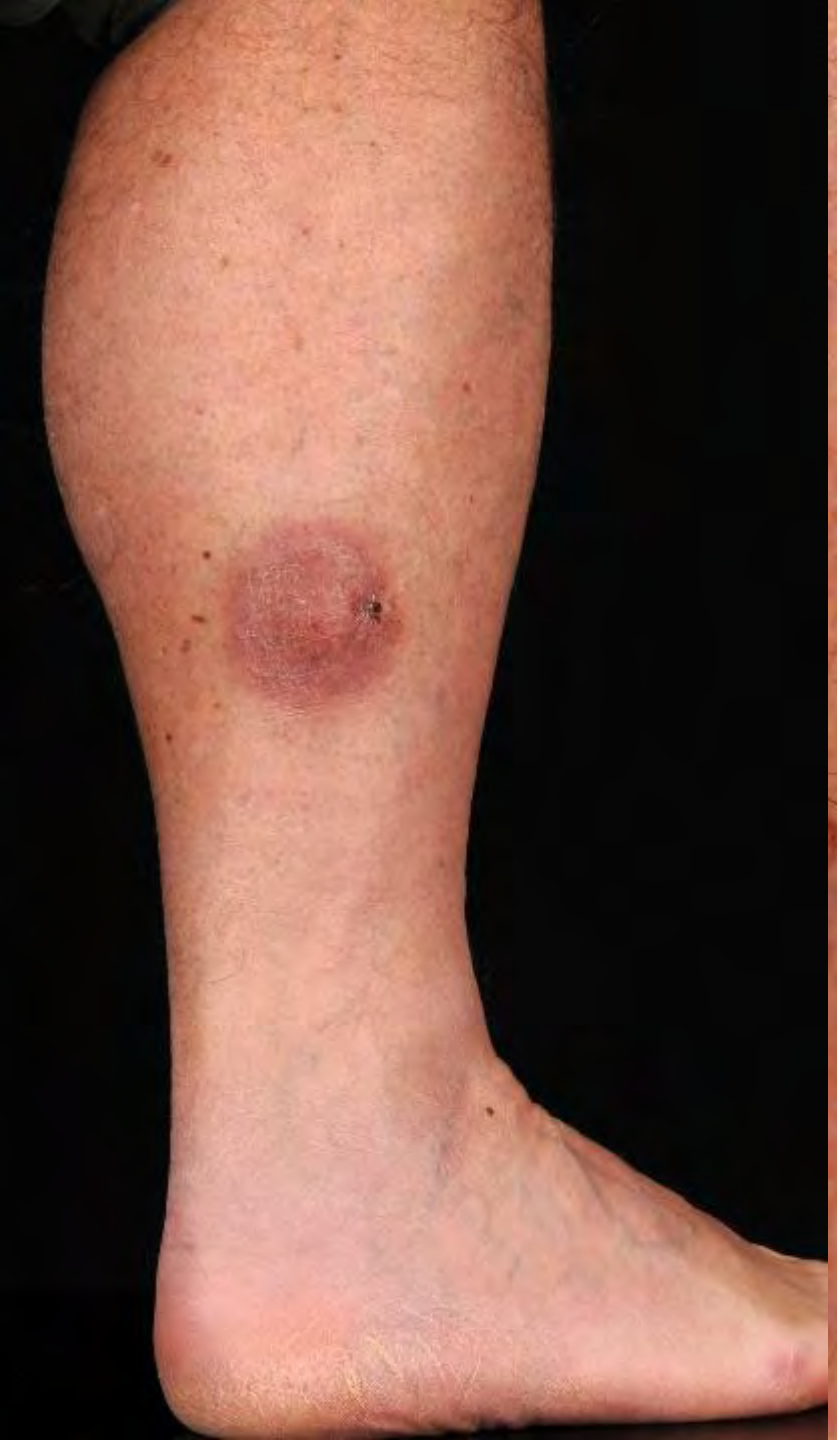
Cutaneous extranodal NK/T-cell lymphoma, nasal-type
EBER-1+

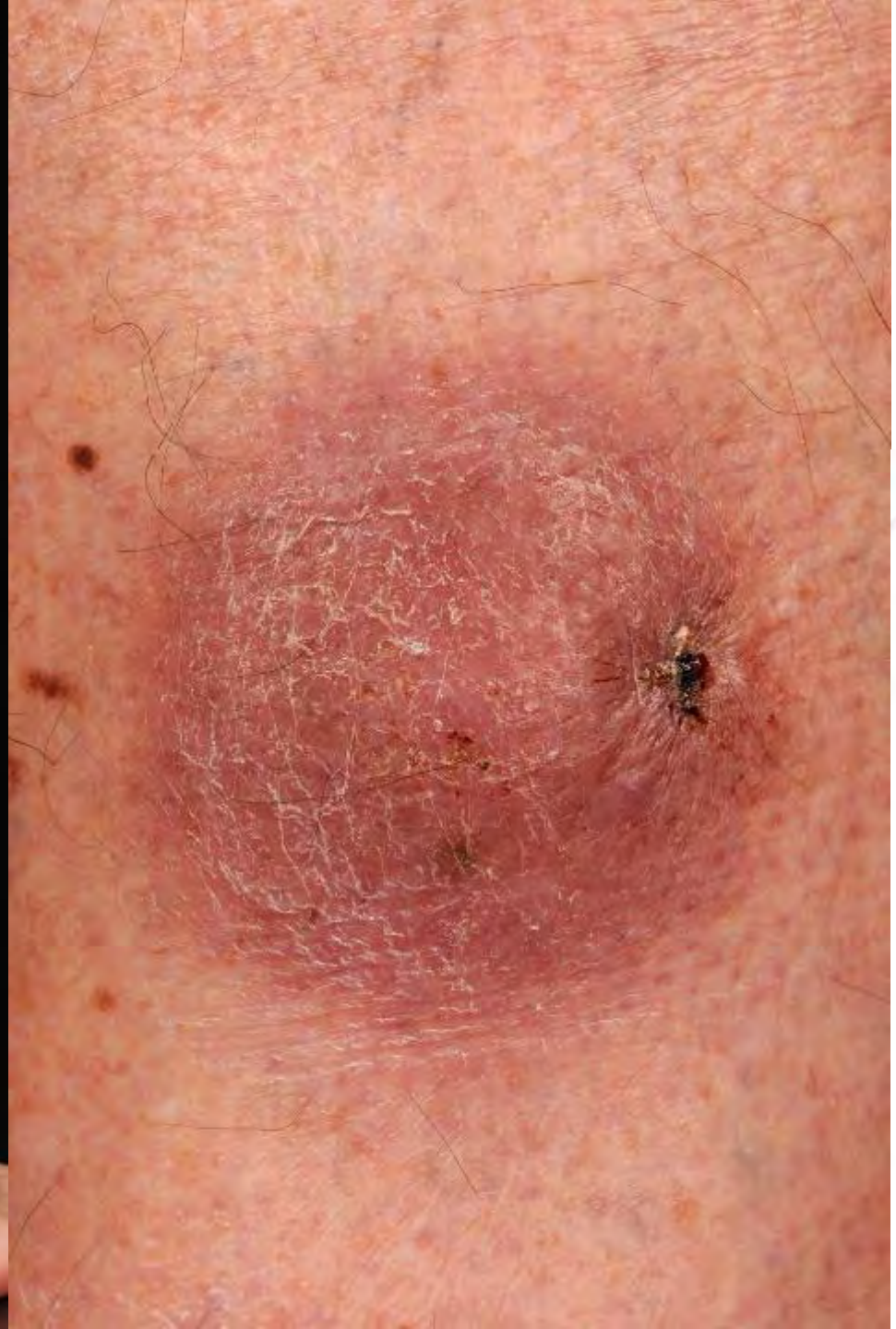
Cutaneous gamma/delta T-cell lymphoma
TCR-delta+

Cutaneous aggressive epidermotropic CD8+ T-cell lymphoma
epidermotropism of CD8+ cells

Cutaneous CD30+ lymphoproliferative disorders
ALCL: CD30+ (>75%); LyP: mixed cell infiltrate, wedge-shape

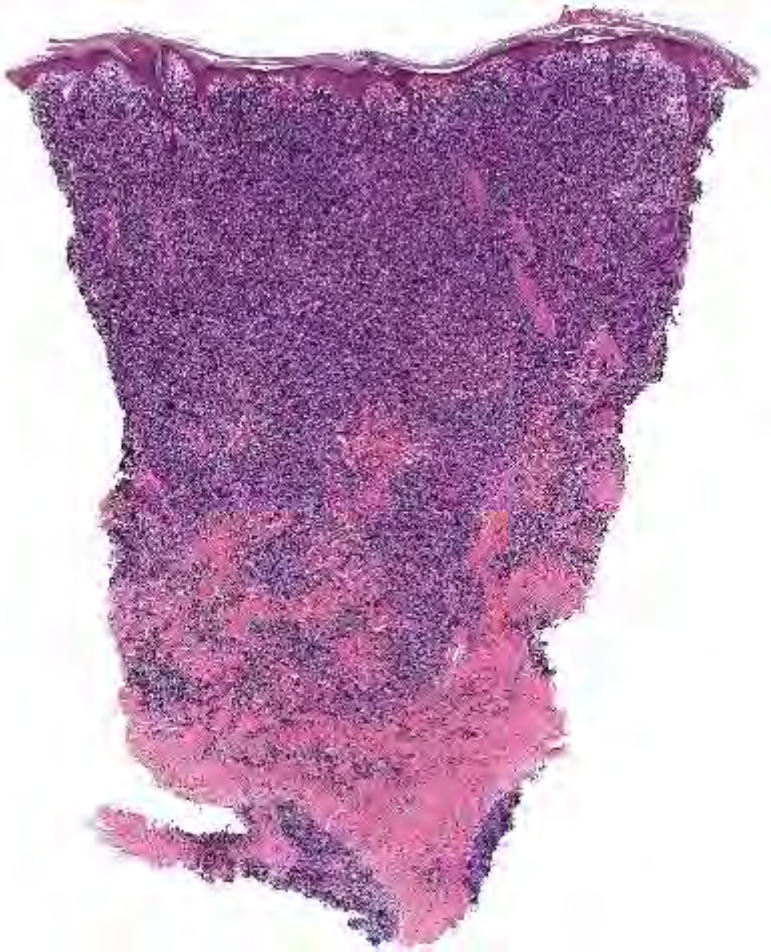
Cutaneous small/medium pleomorphic CD4+ T-cell LD
low Ki-67; mostly solitary lesions on the face

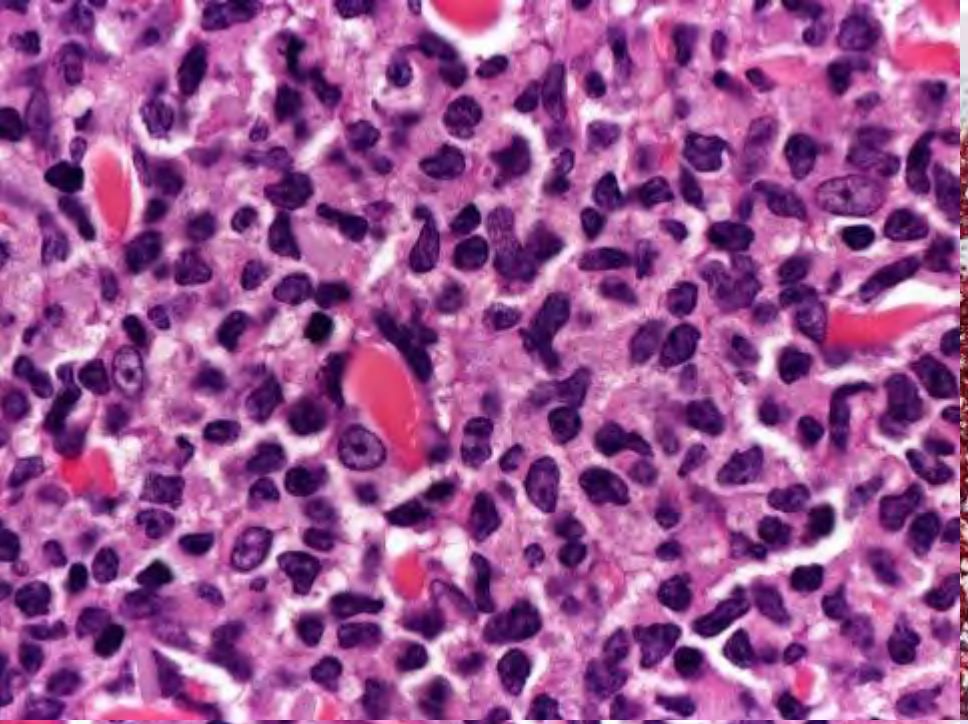


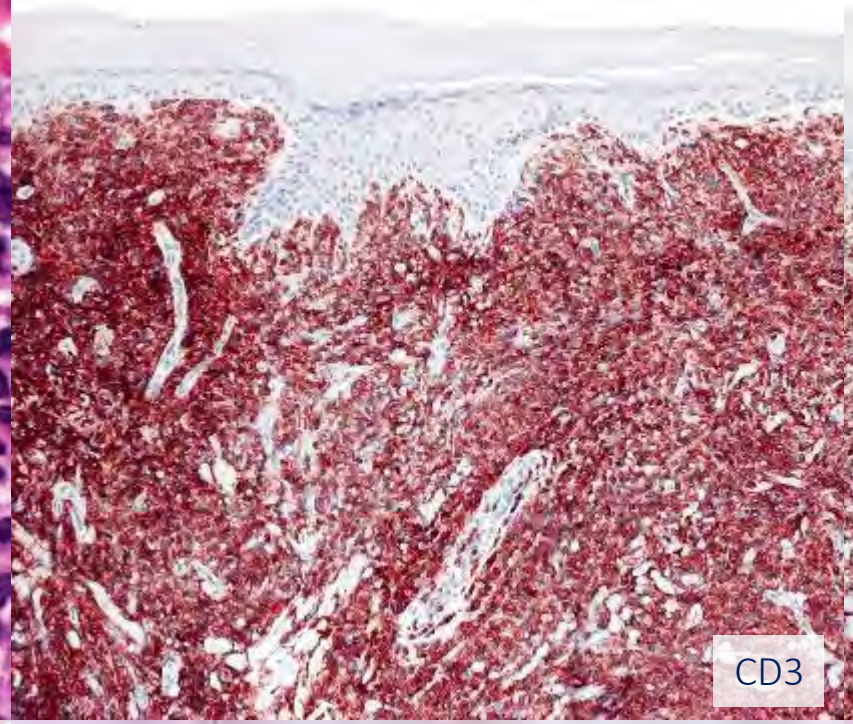


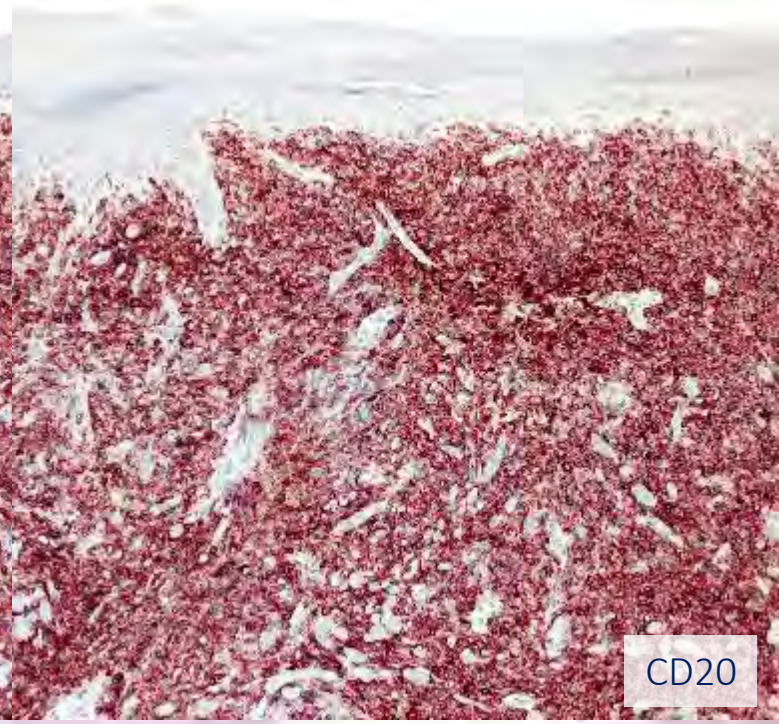
M, 72

Recent onset of a solitary tumor on the right lower leg (picture taken after a punch biopsy).






CD3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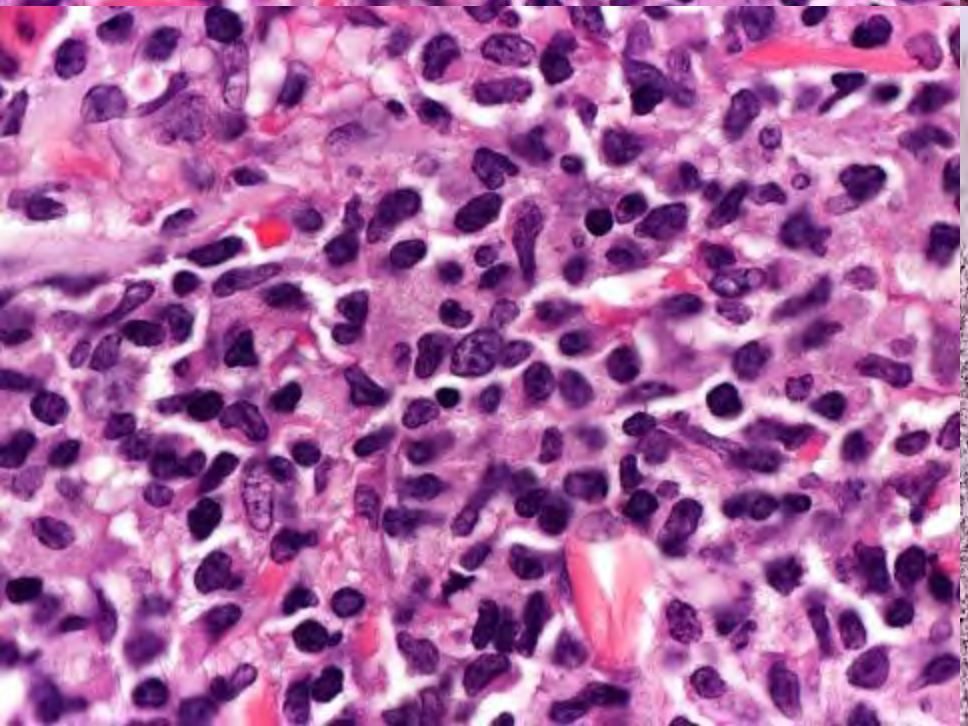

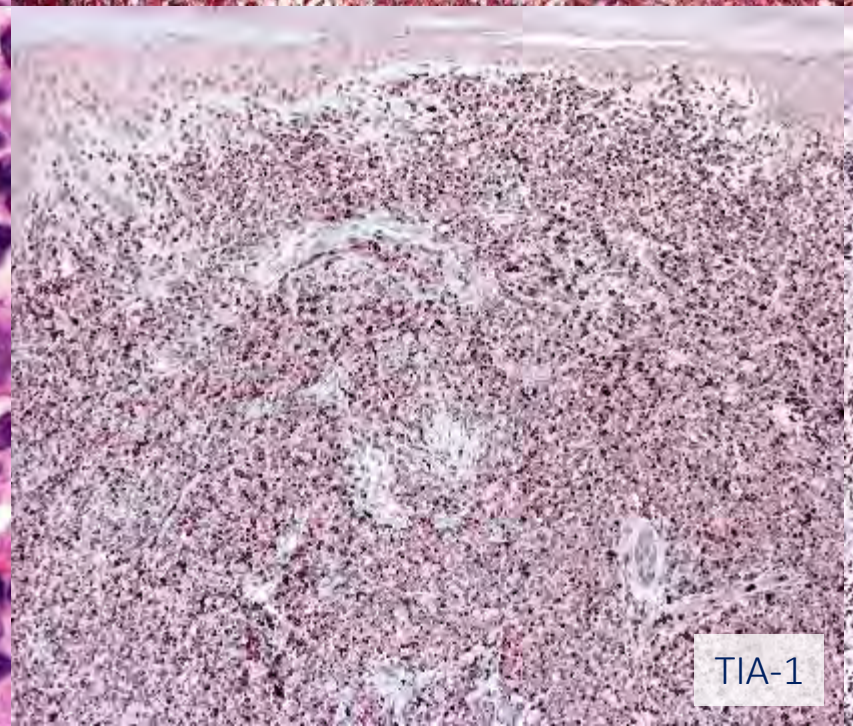
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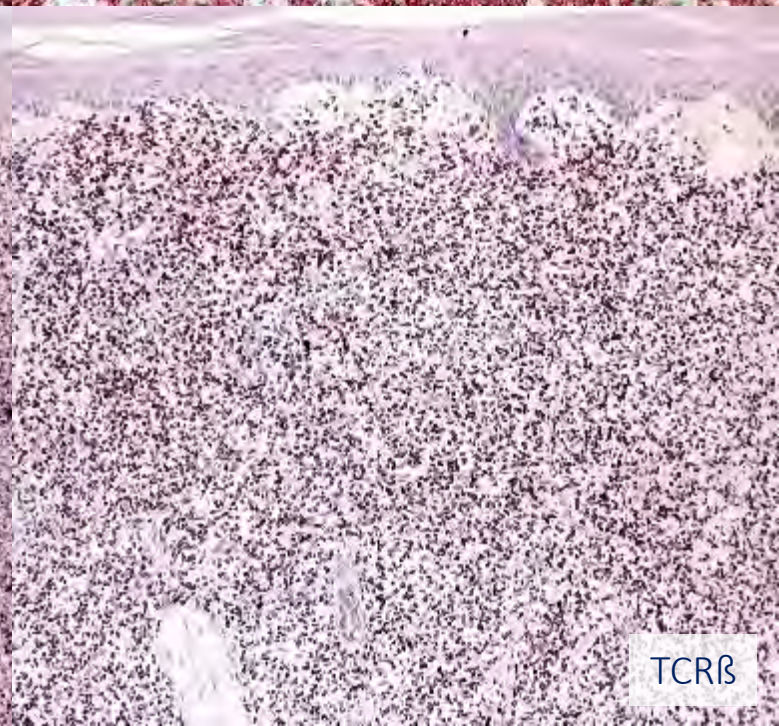
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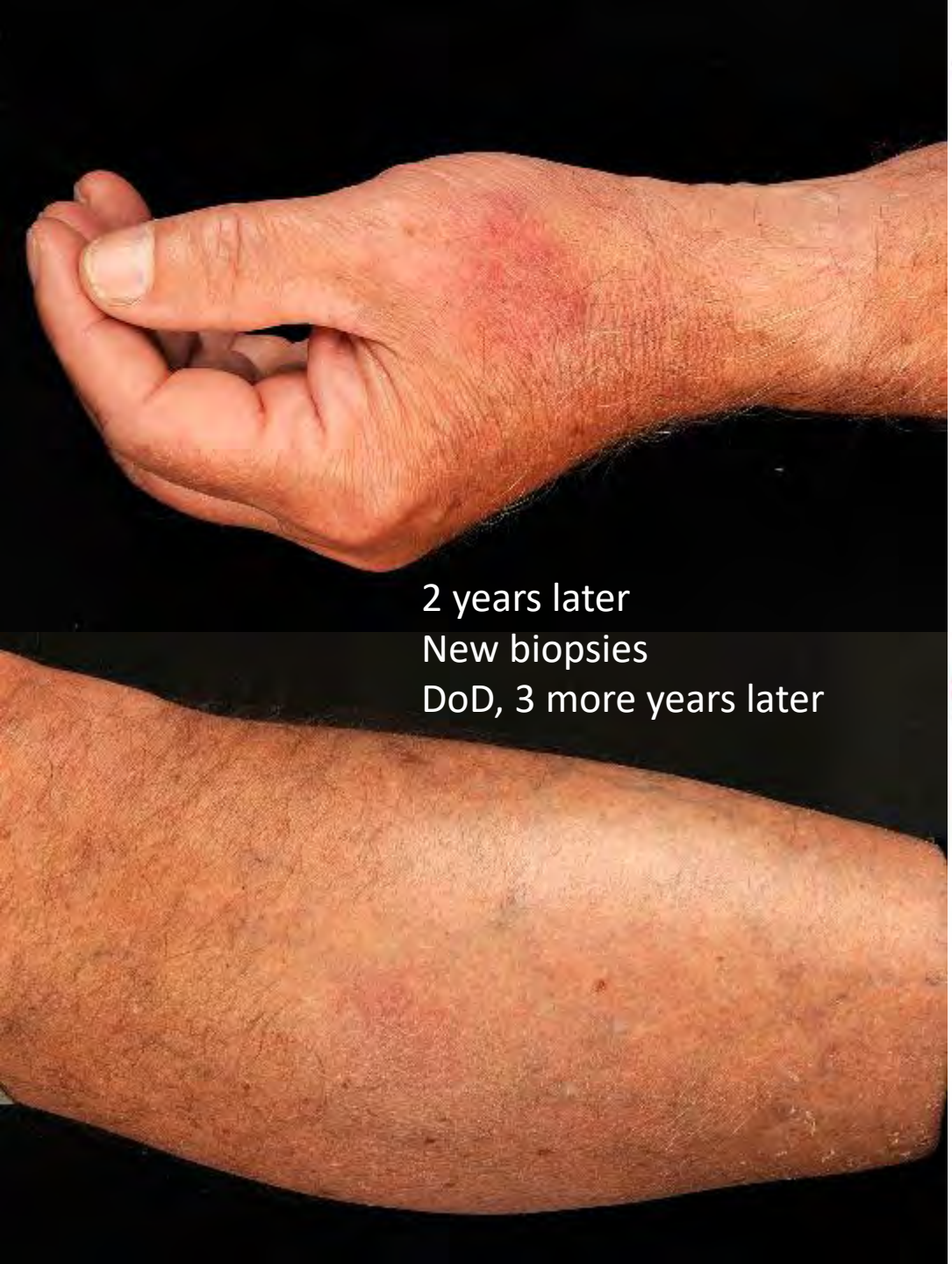
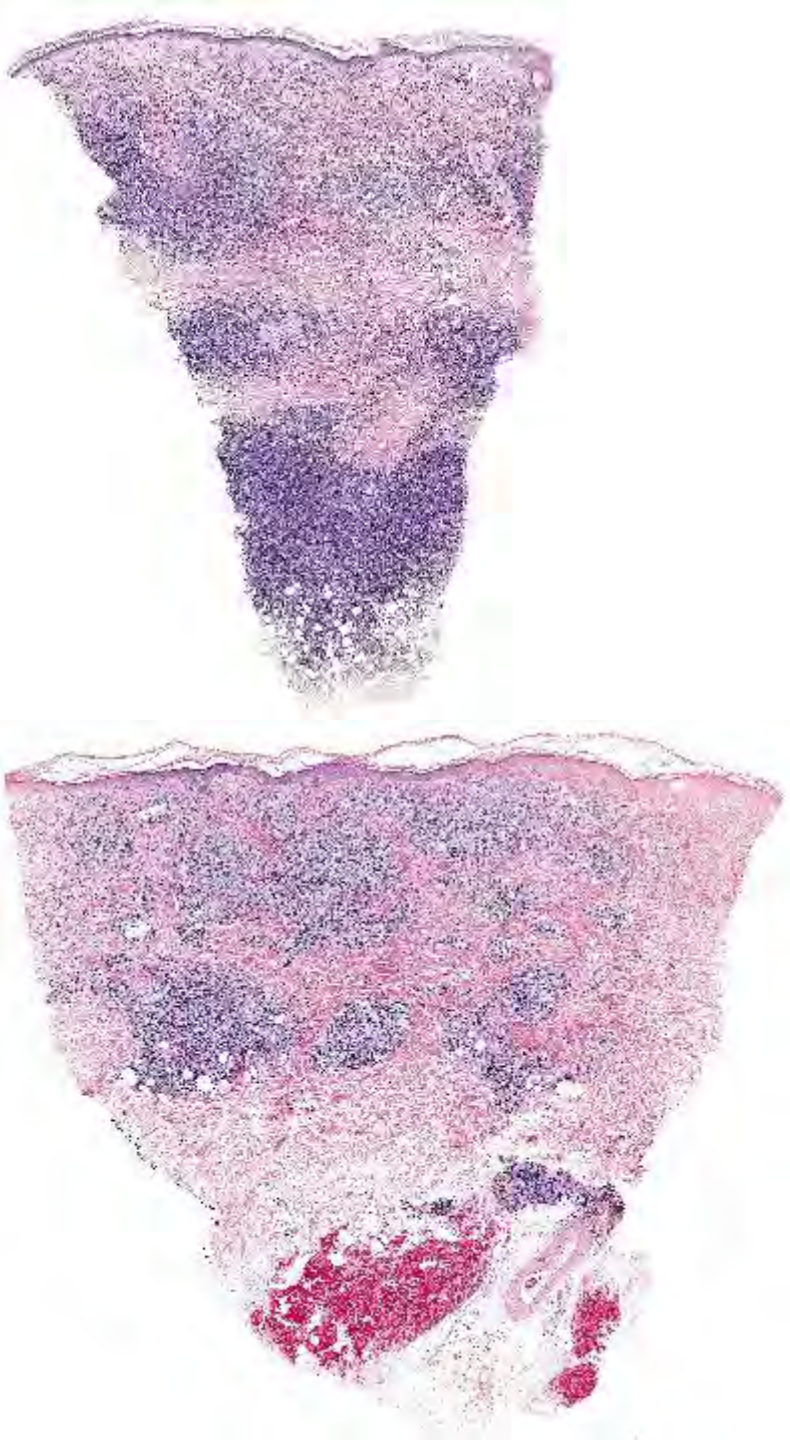
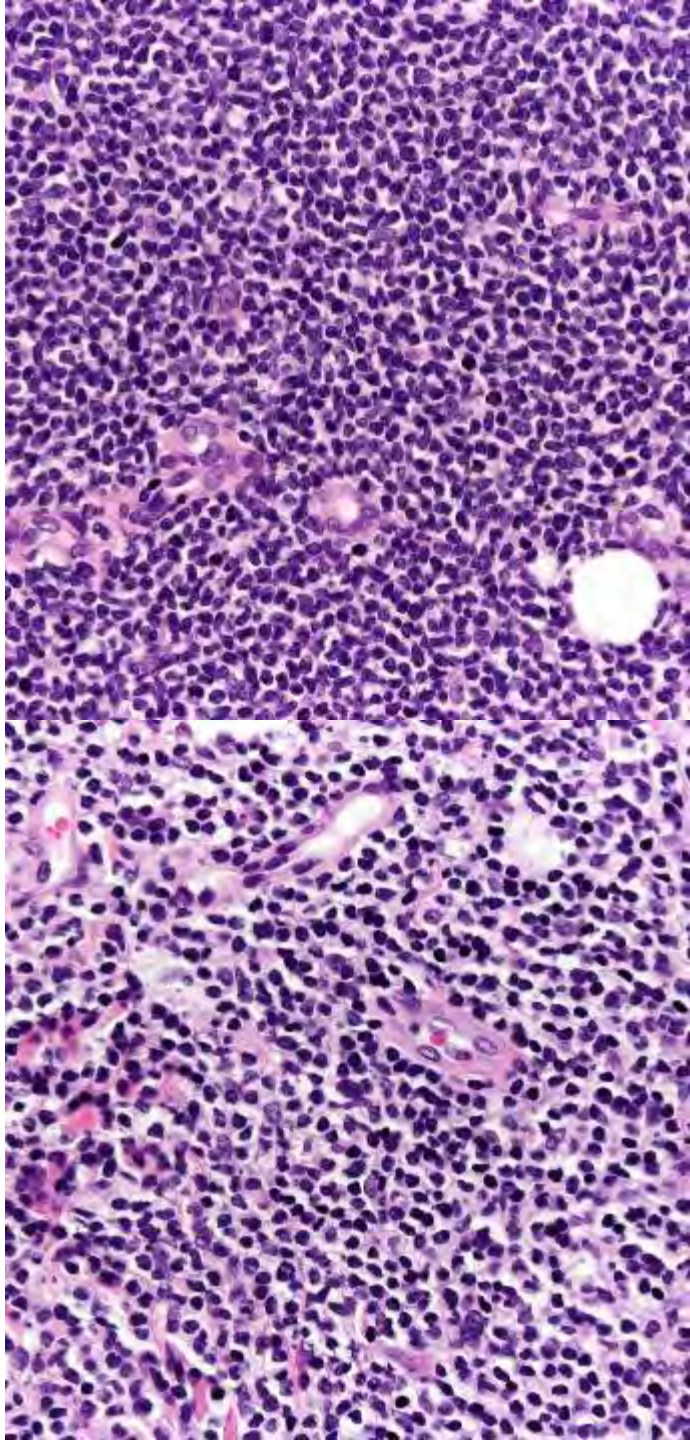
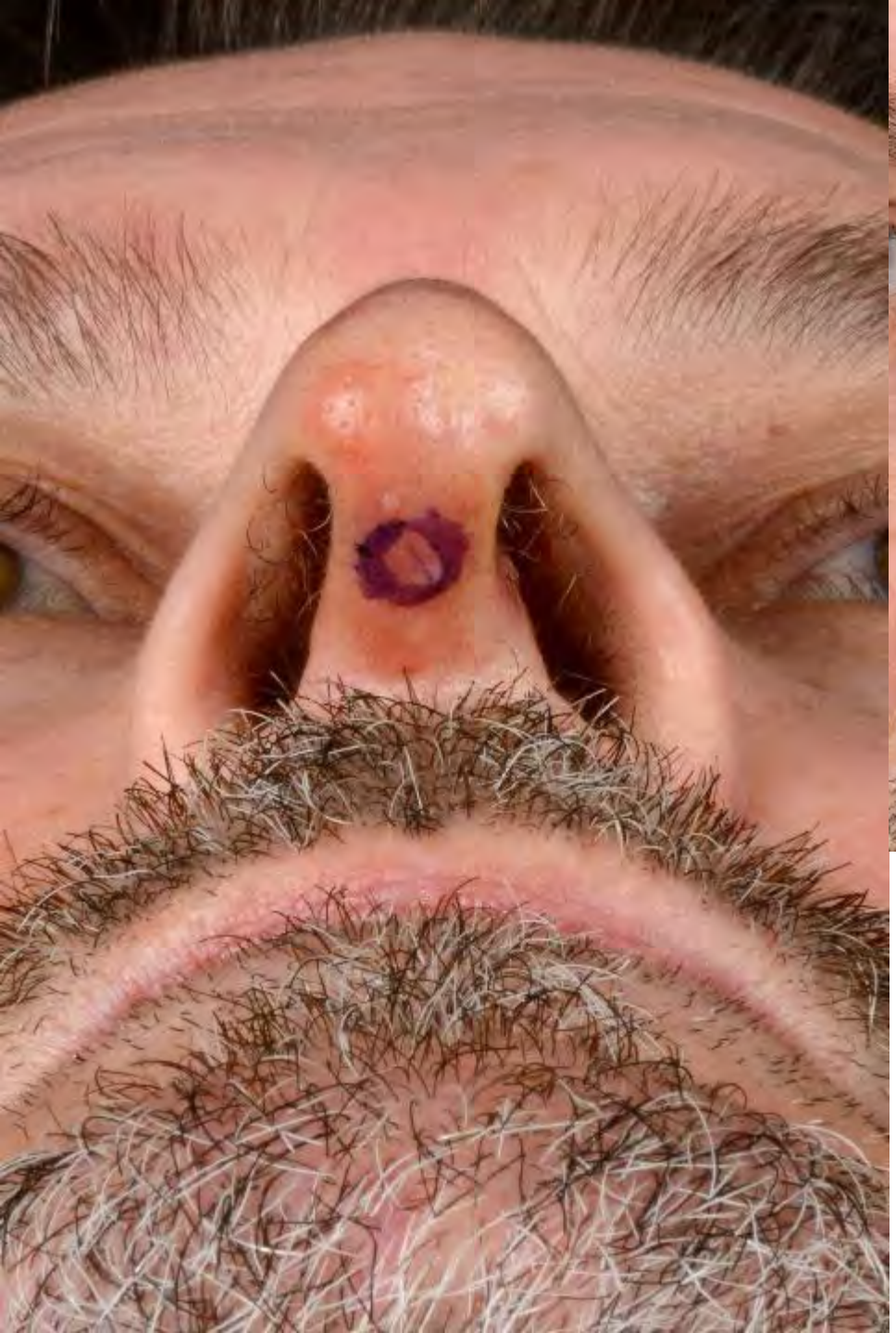
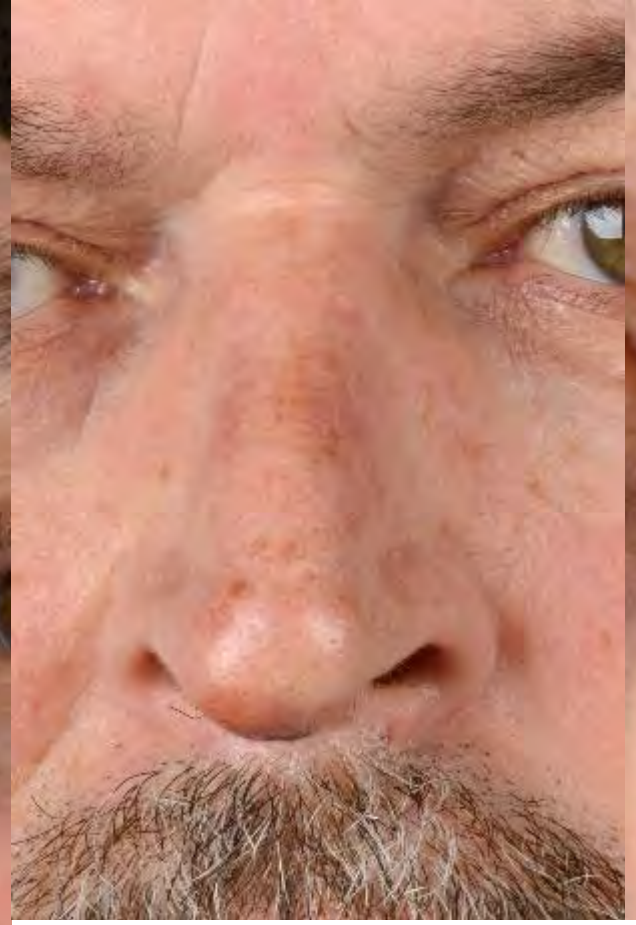
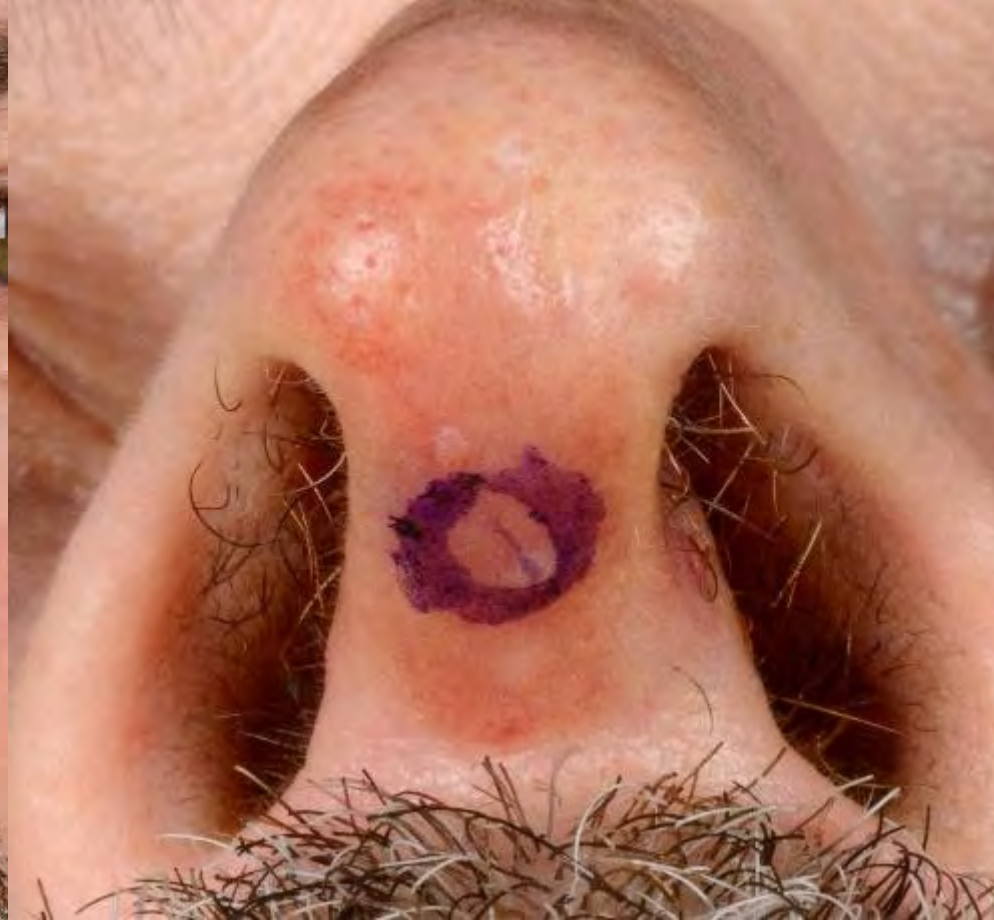

2 years later
New biopsies
DoD, 3 more years later

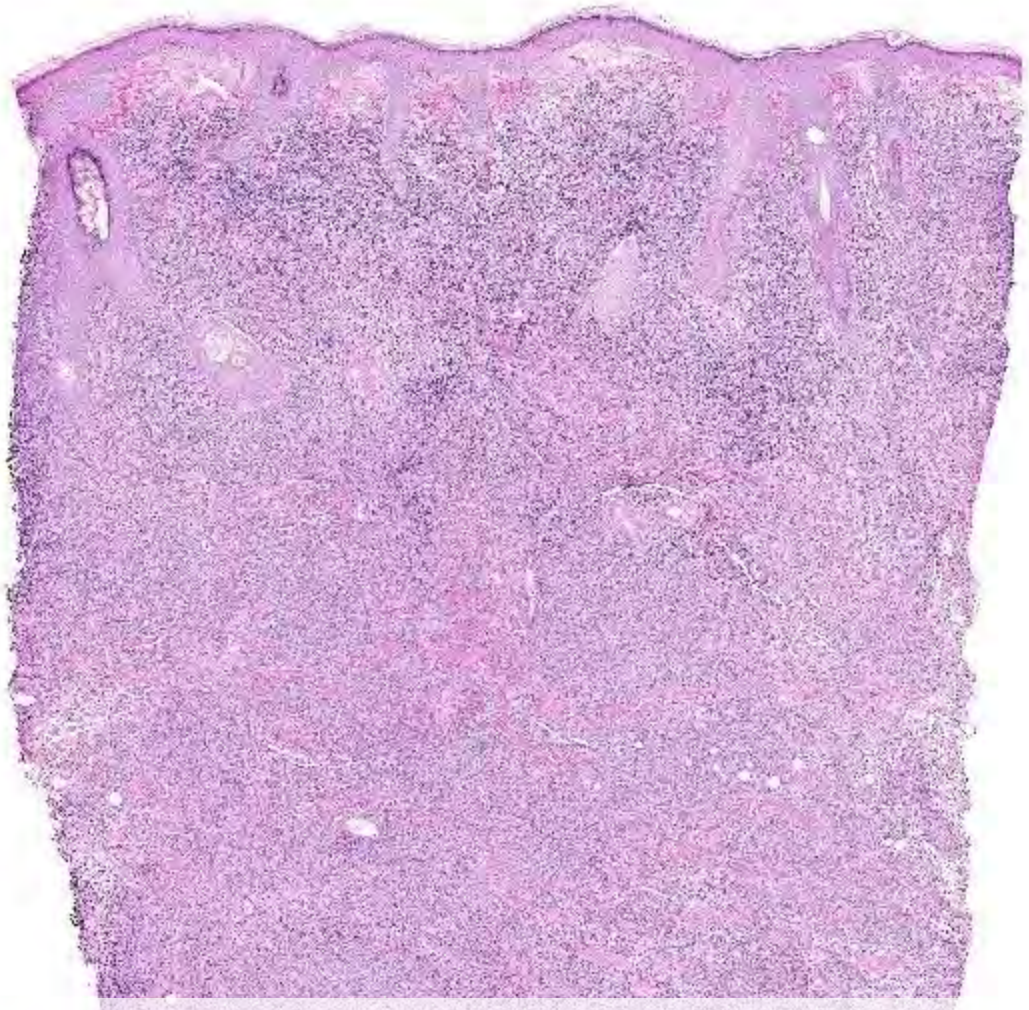


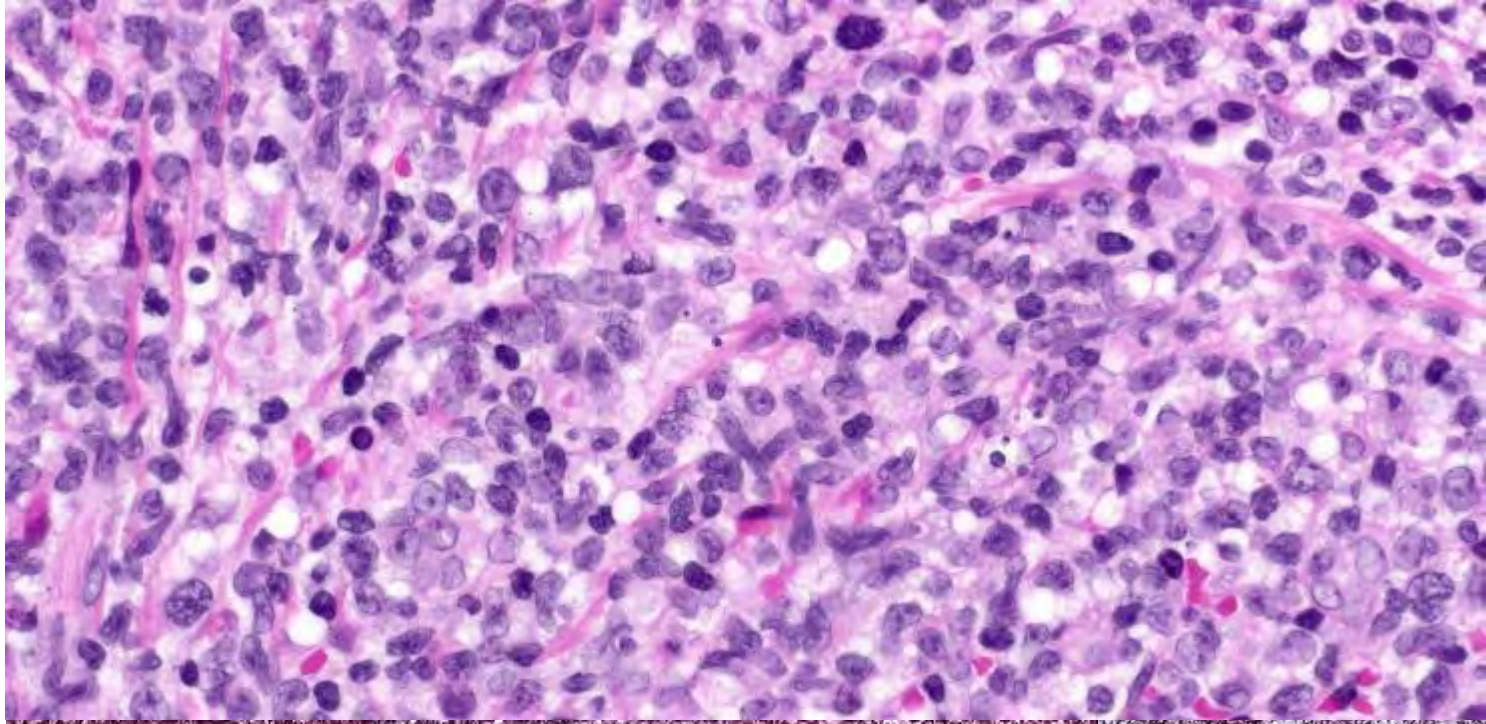


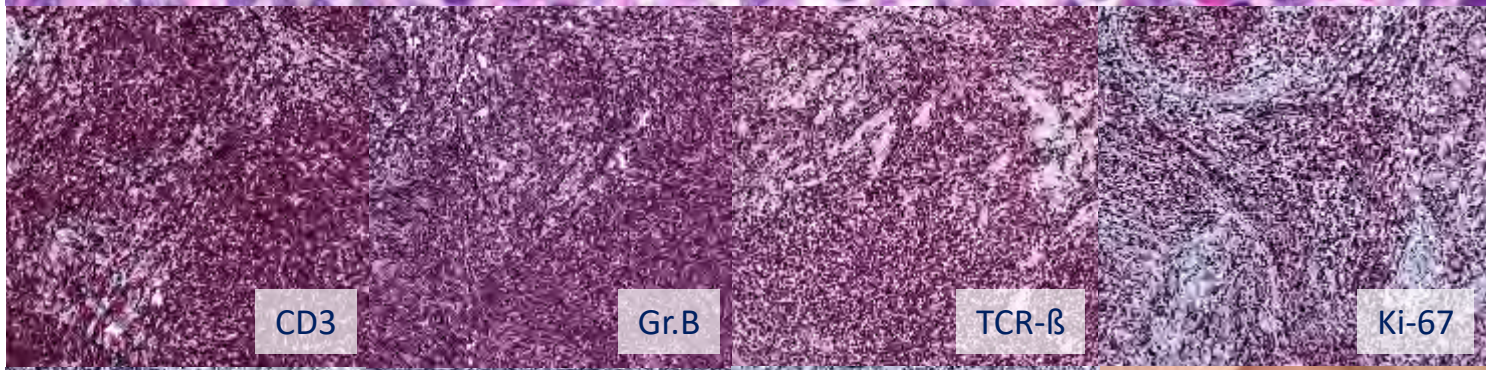




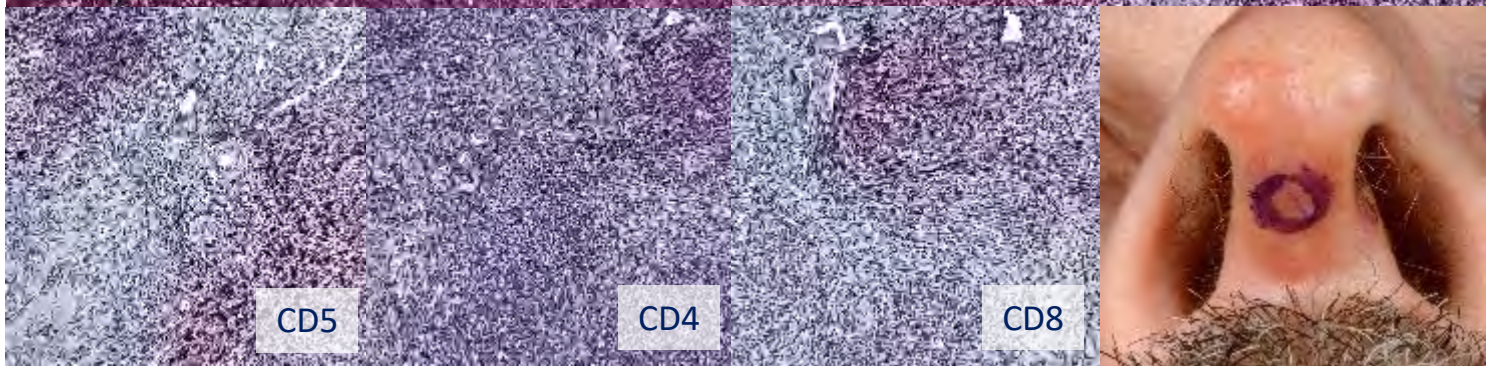
M, 59

History of primary cutaneous peripheral T-cell lymphoma, NOS, located on the right arm and on the right thumb (1st diagnosis 2 years before presentation).
Managed with CHOEP; autologous stem-cell transplantation 15 months before presentation; complete remission.
According to the patient 7 days before presentation sudden onset of a reddish lesion on the nose.
A biopsy is taken.



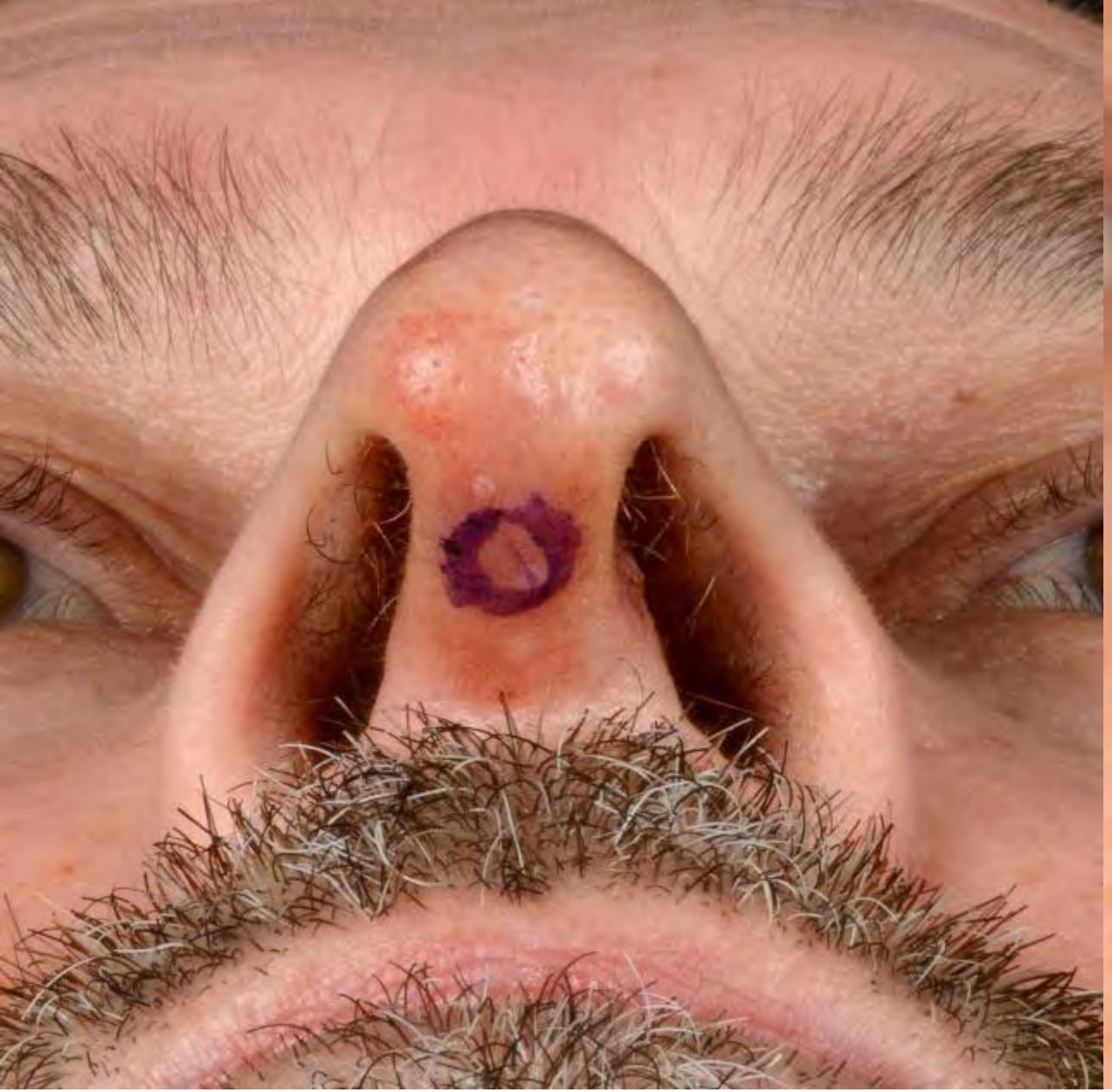




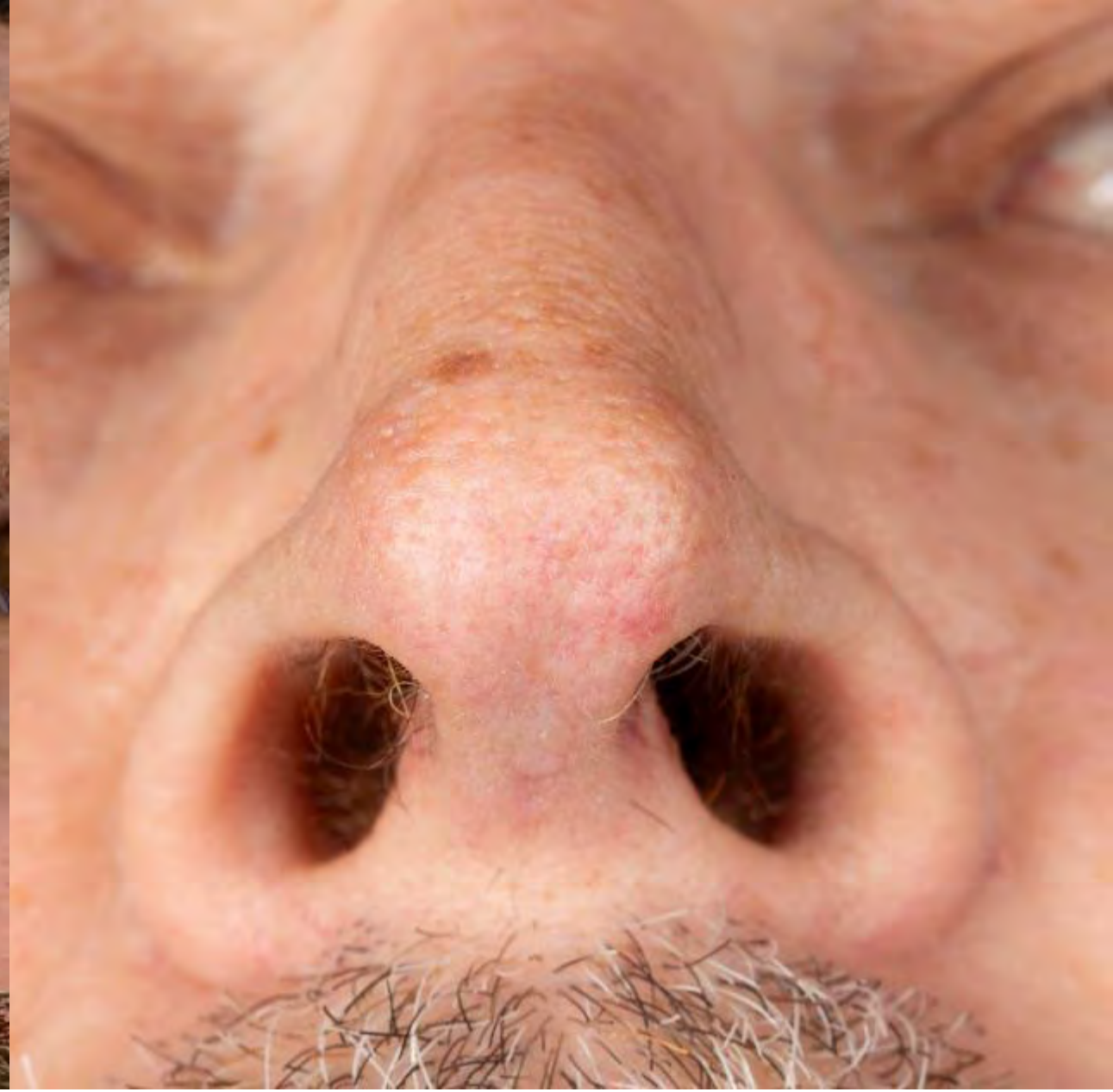


Recurrent cutaneous (peripheral) T-cell lymphoma, NOS with cytotoxic phenotype

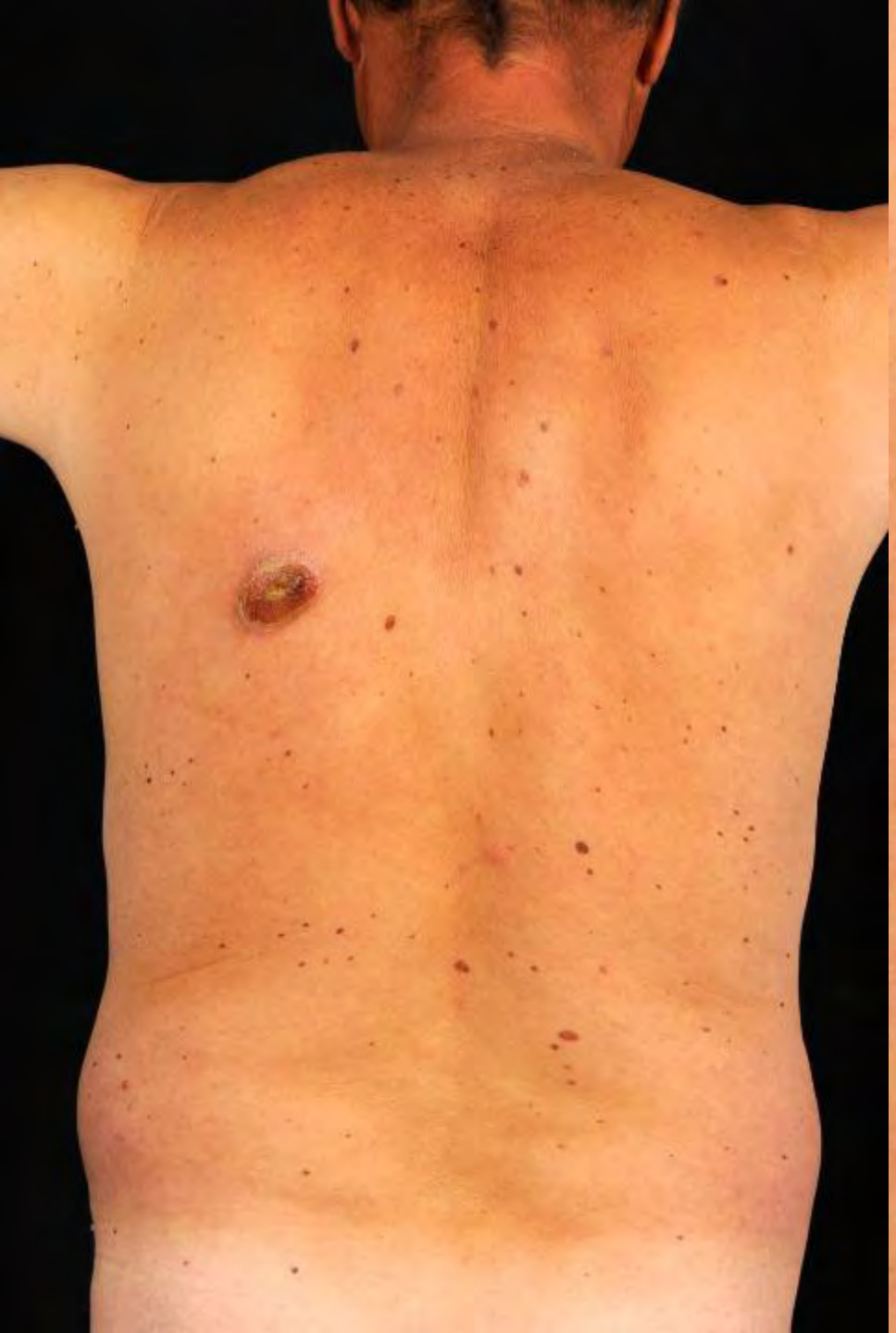
Staging negative

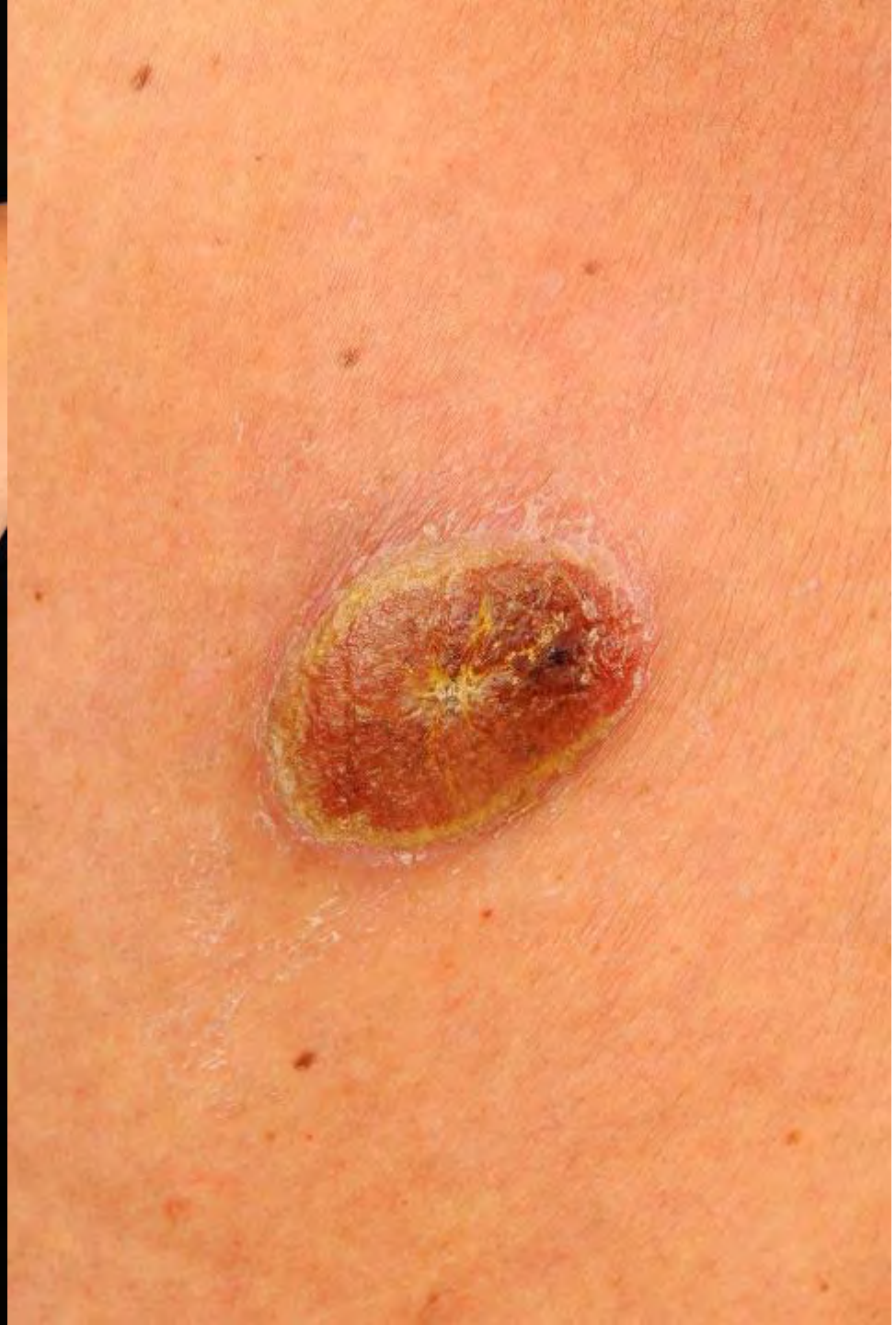


First presentation



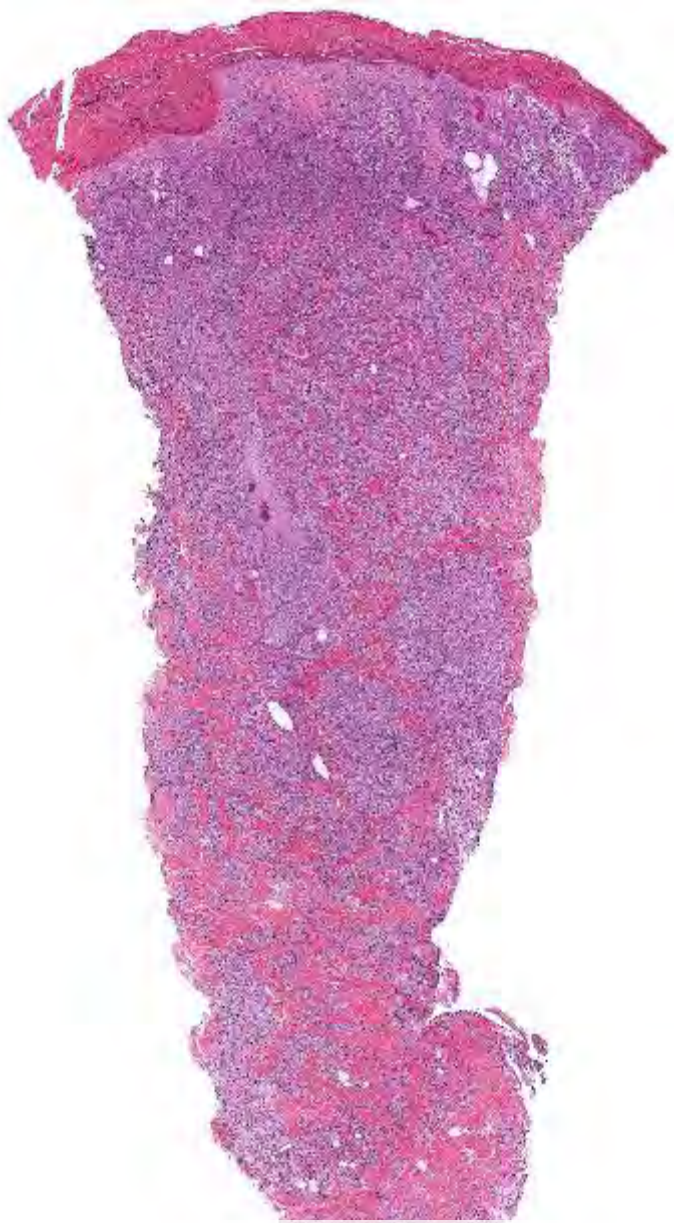
One year later
(18x Rx until 6 months before picture)

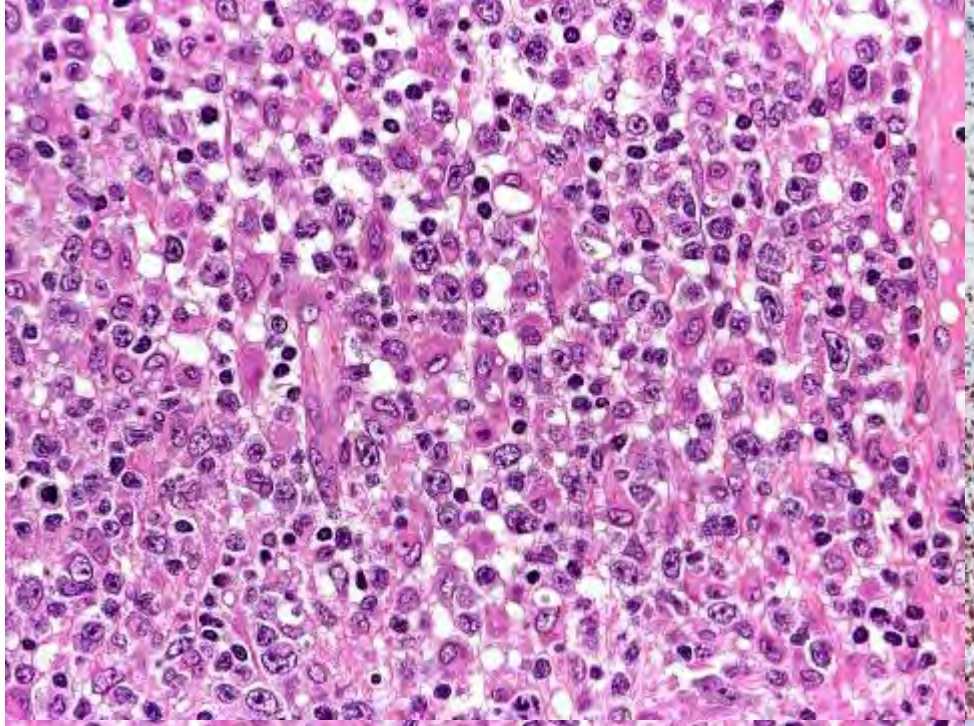


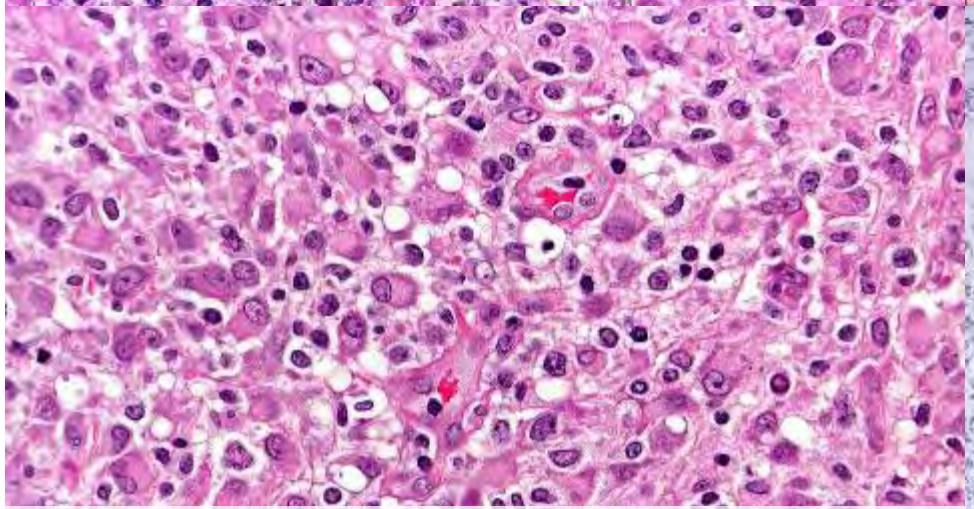


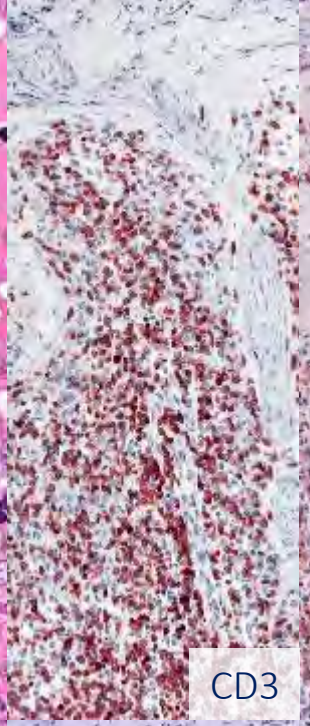
M, 47

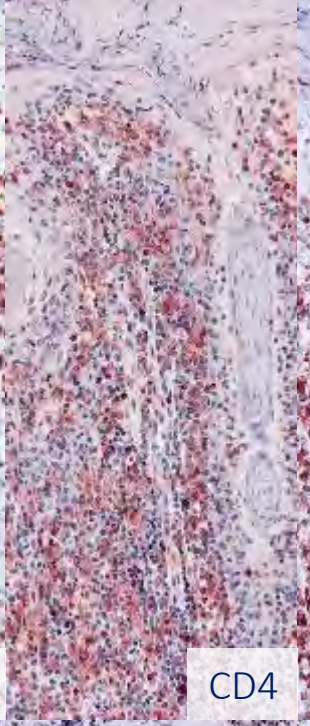
Recent onset of a solitary, ulcerated tumor on the left upper back.

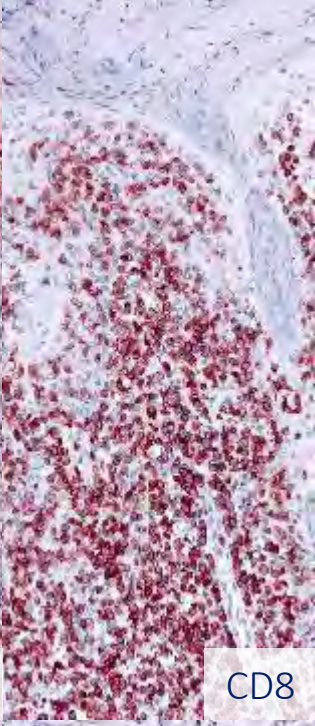


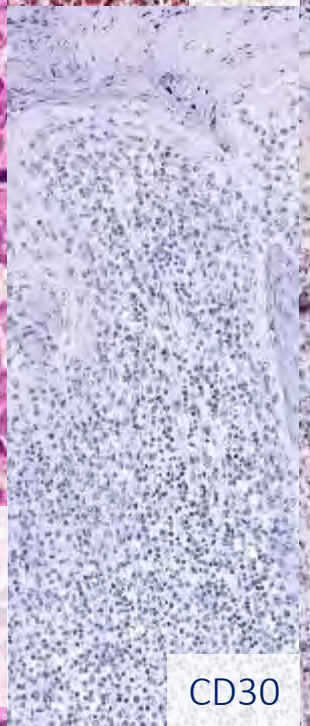


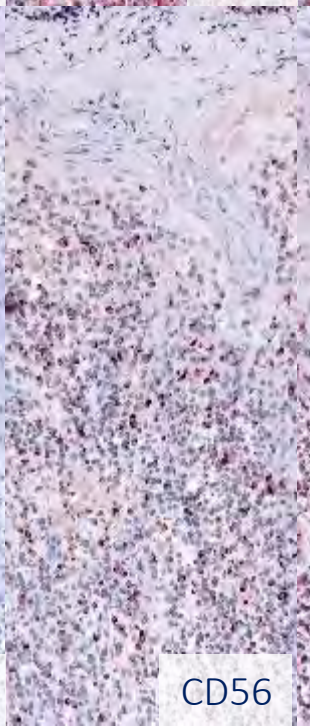


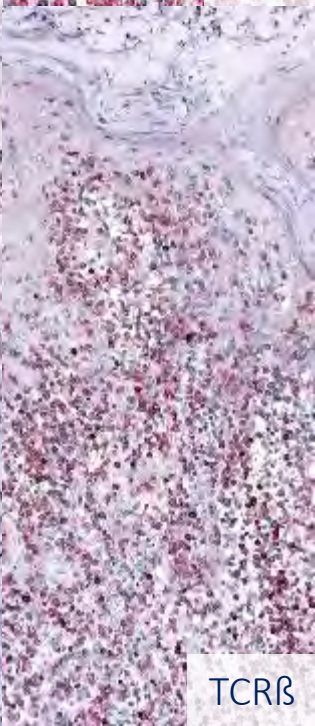






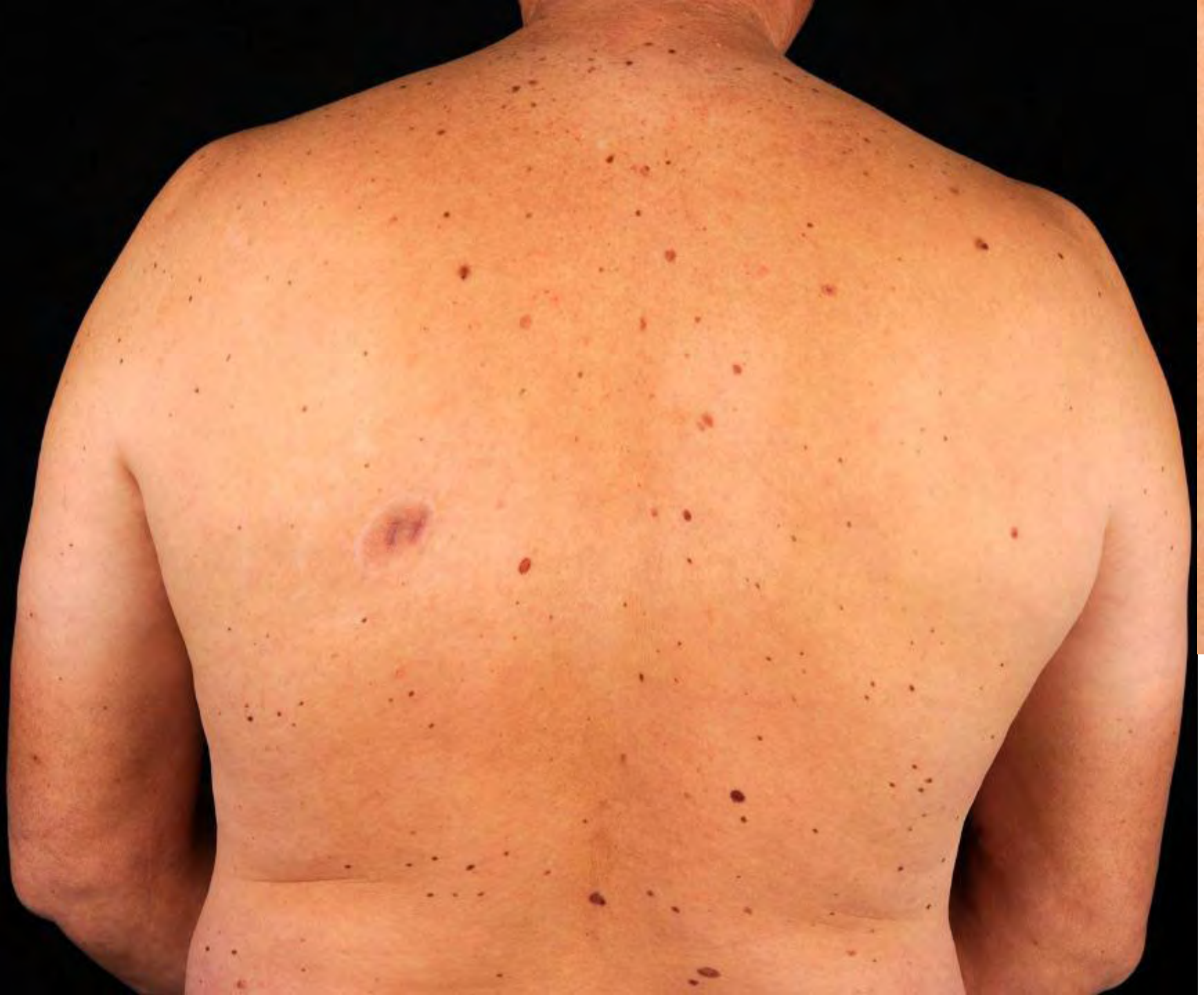


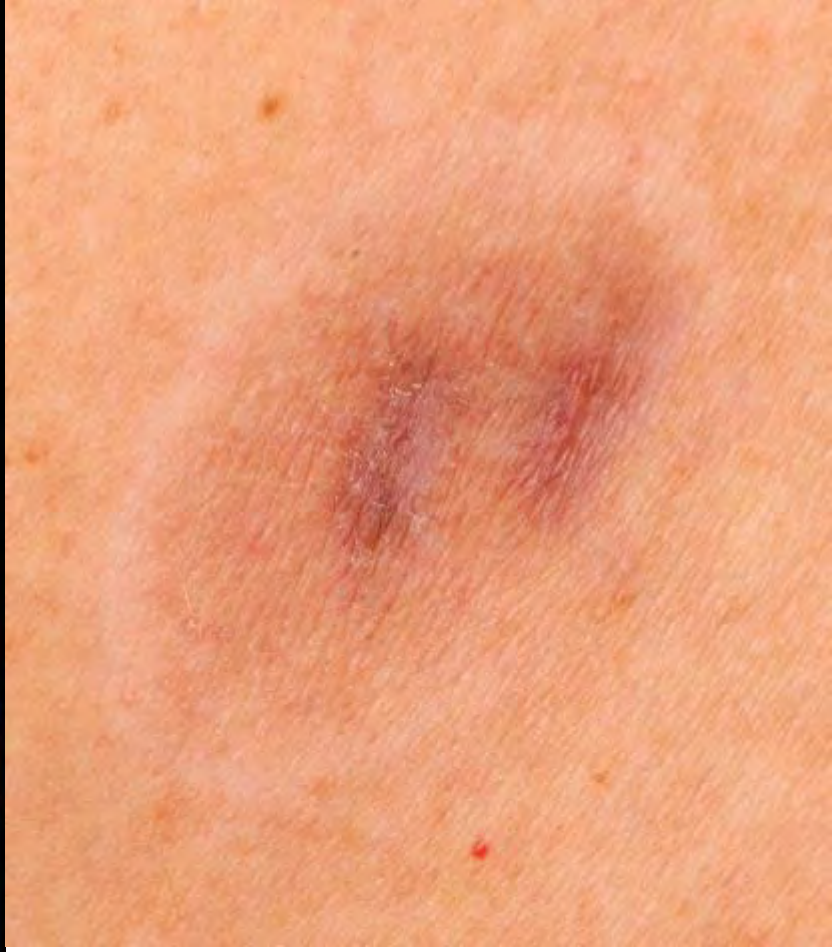




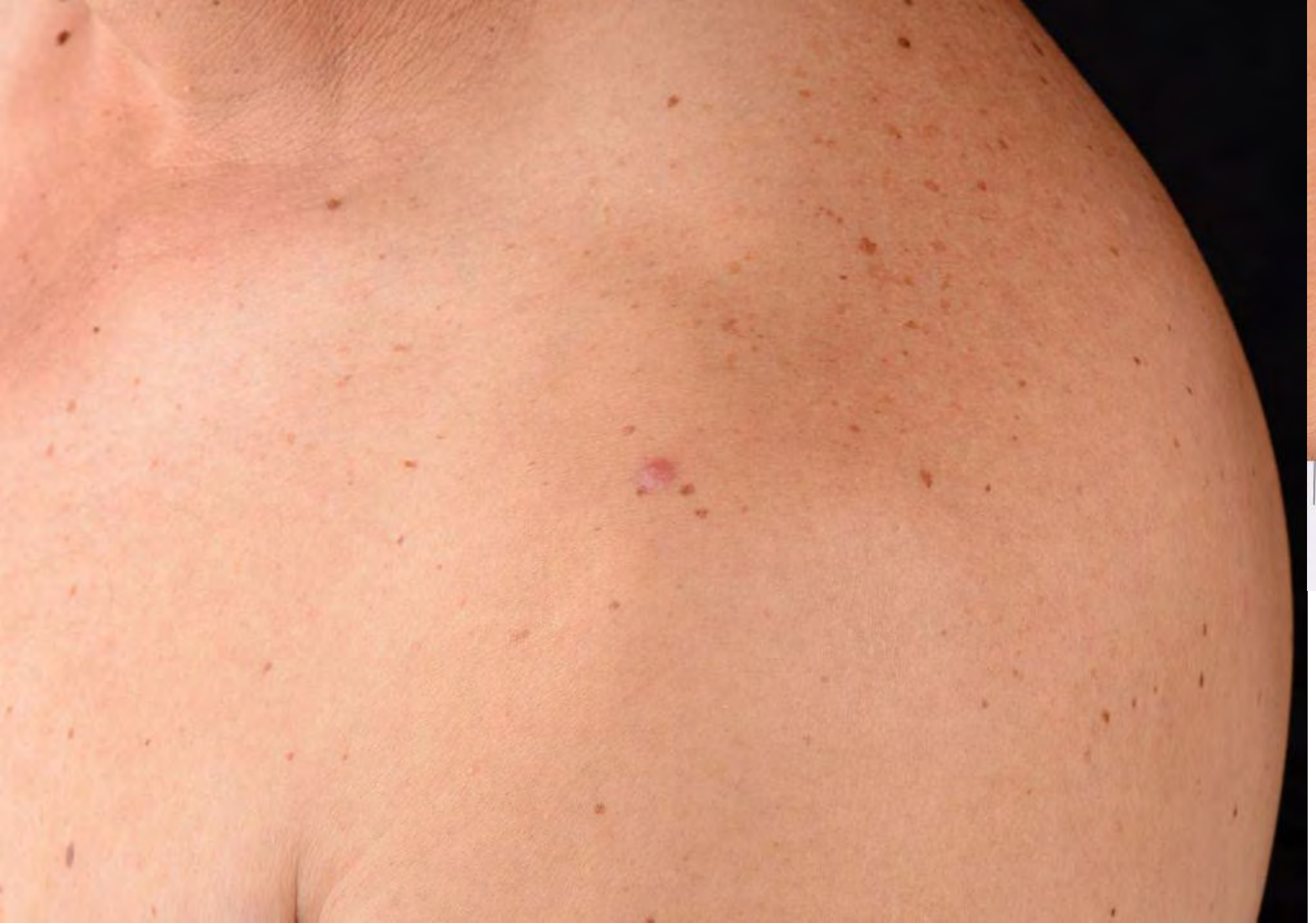
Cutaneous (peripheral) T-cell lymphoma, NOS

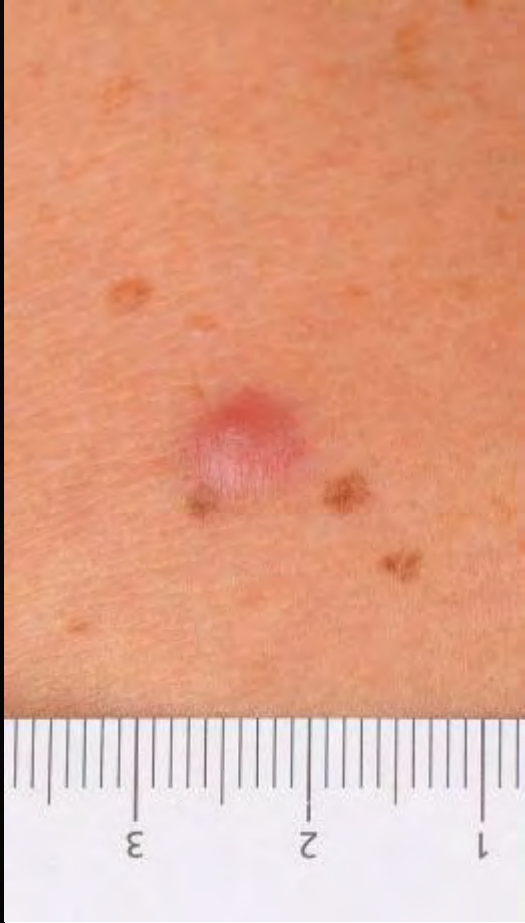
with cytotoxic phenotype



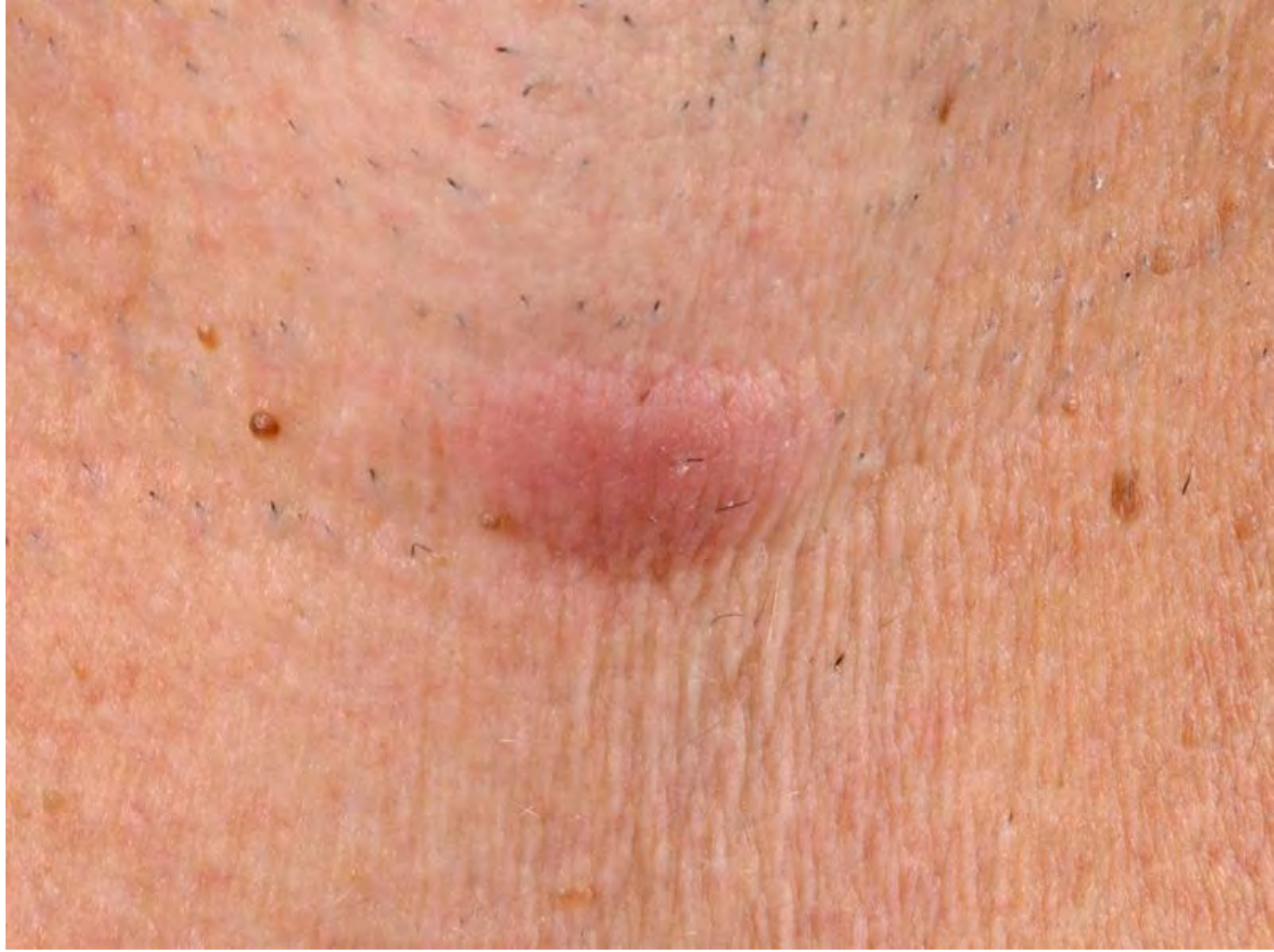


3 months later
Regression after biopsy, without further treatment

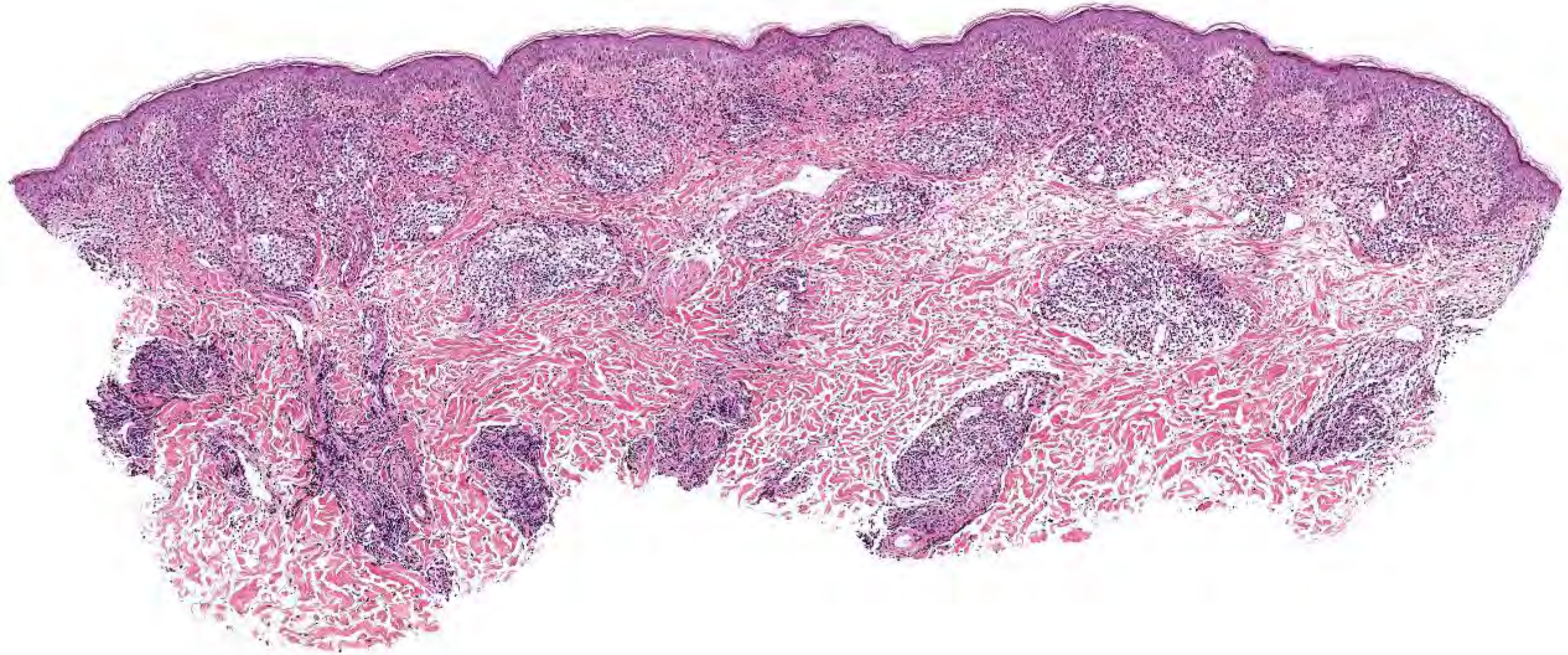


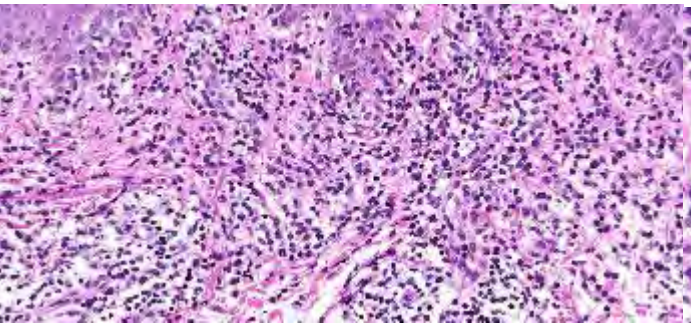


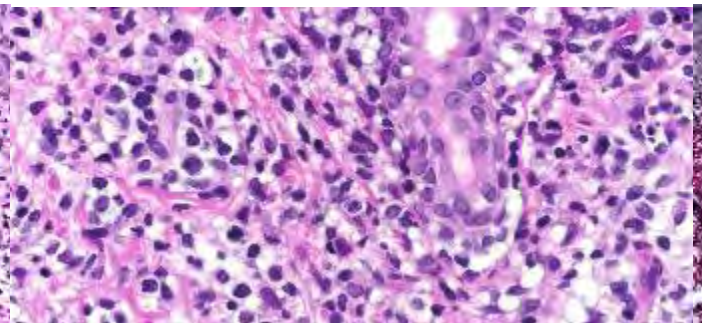
2 years after 1st presentation

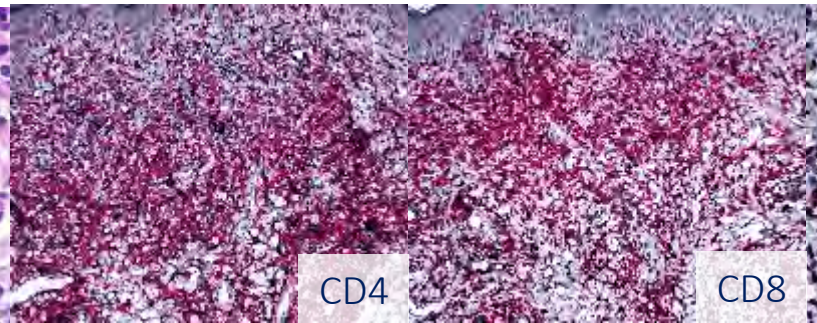


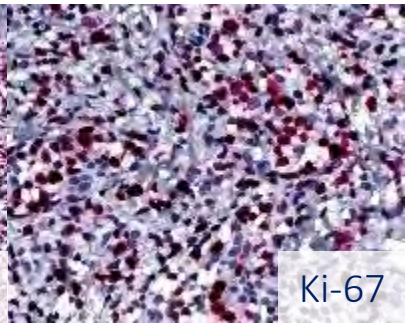
7,5 years after 1st presentation
New biopsy

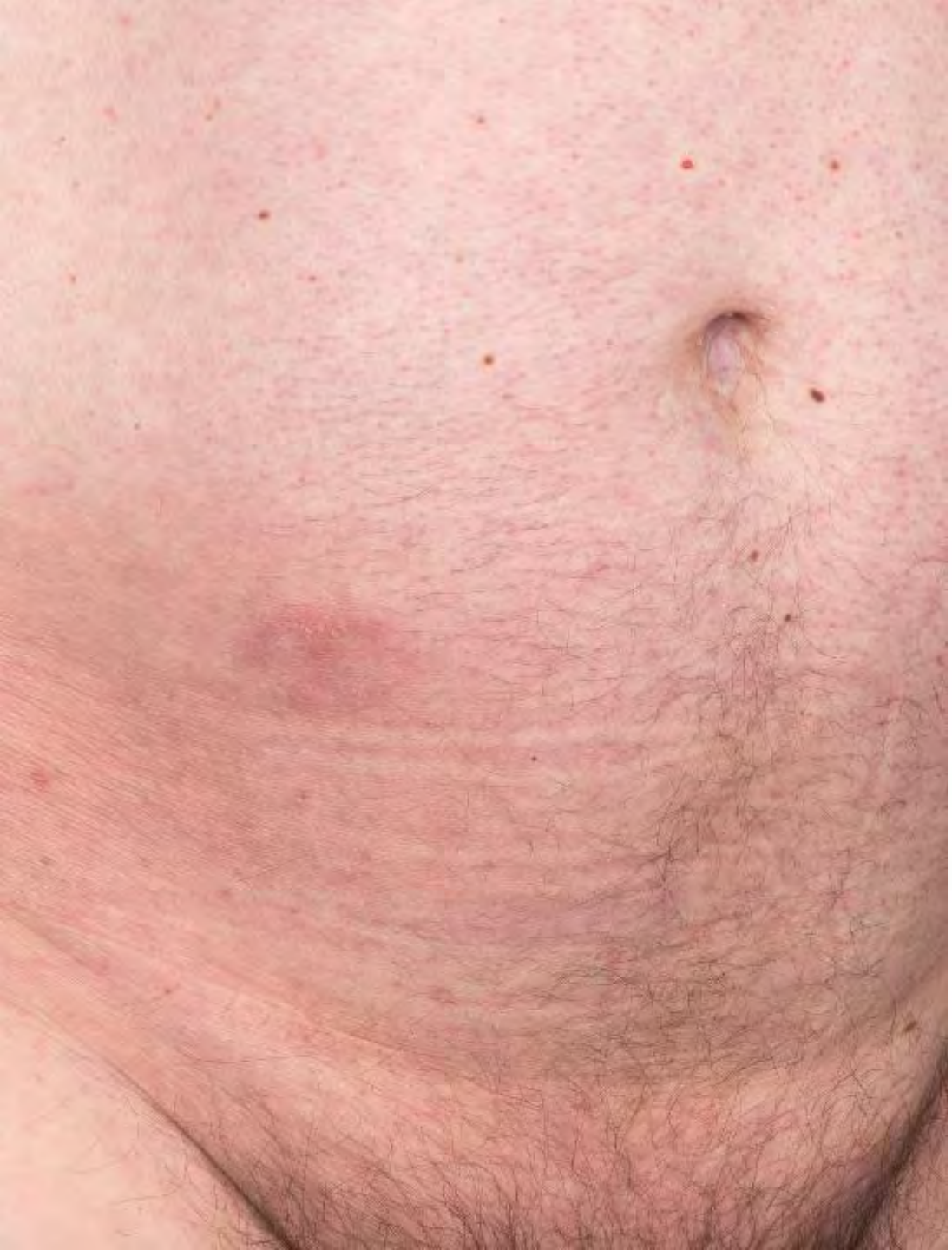


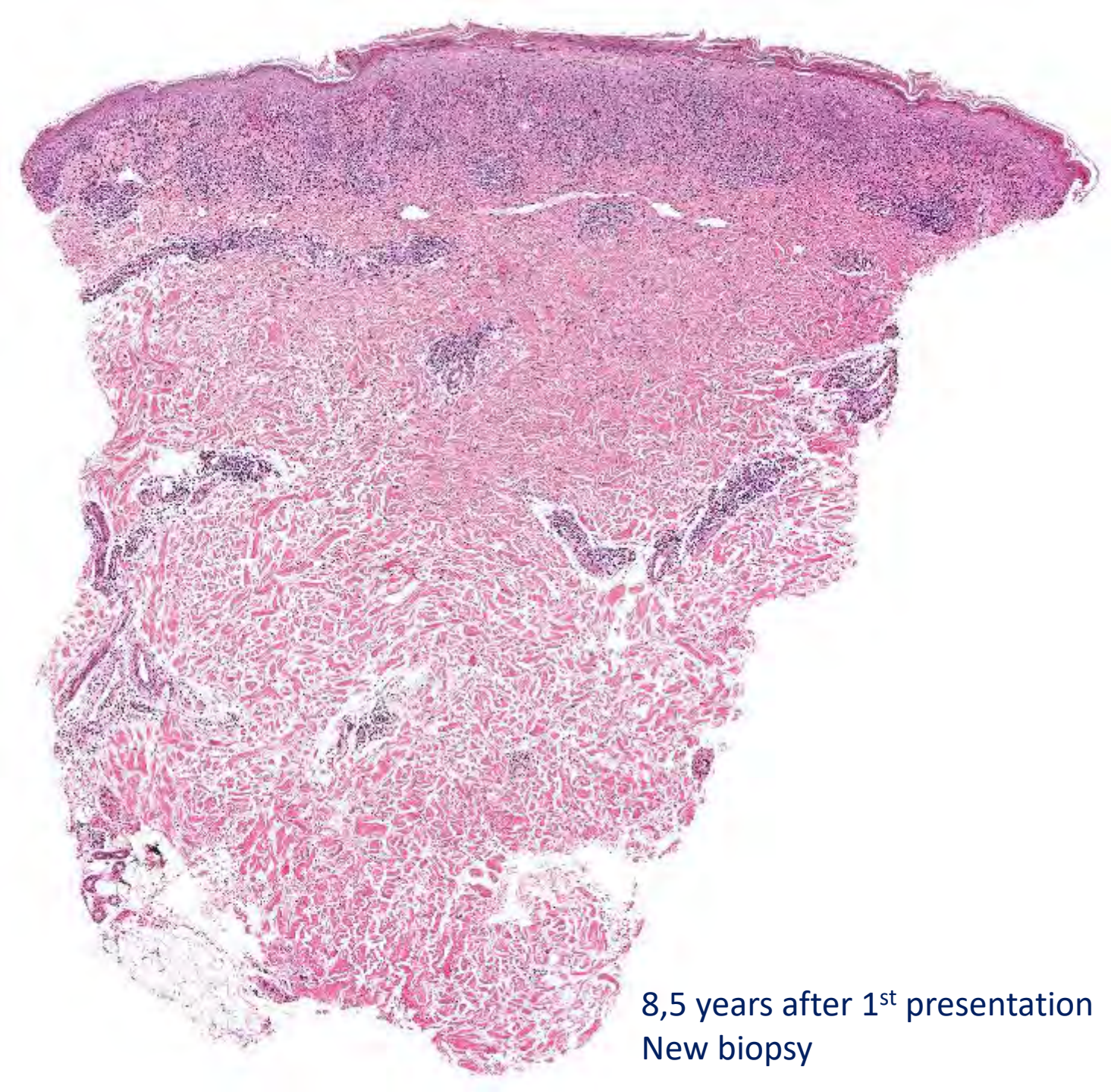




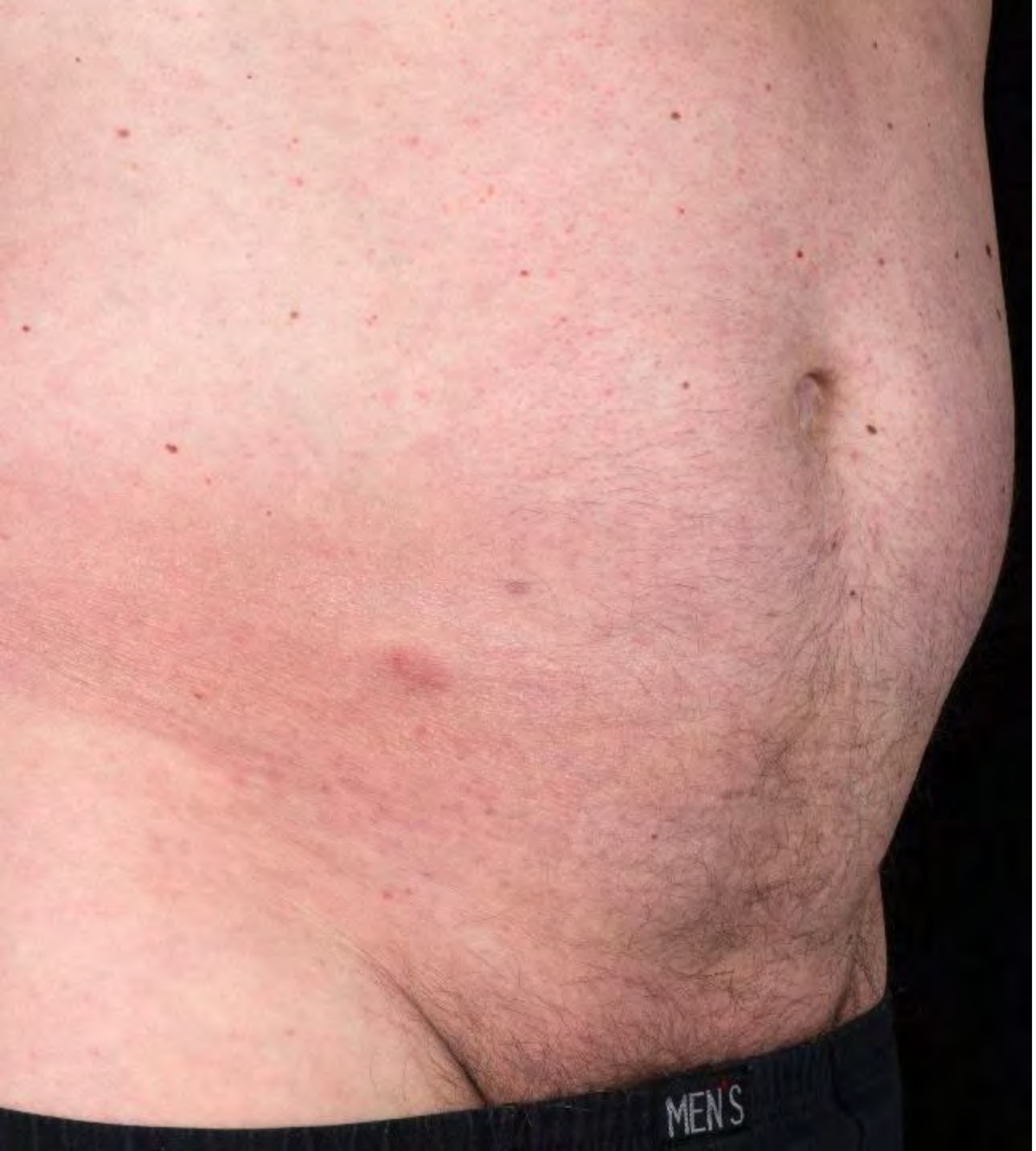

CD4
CD8

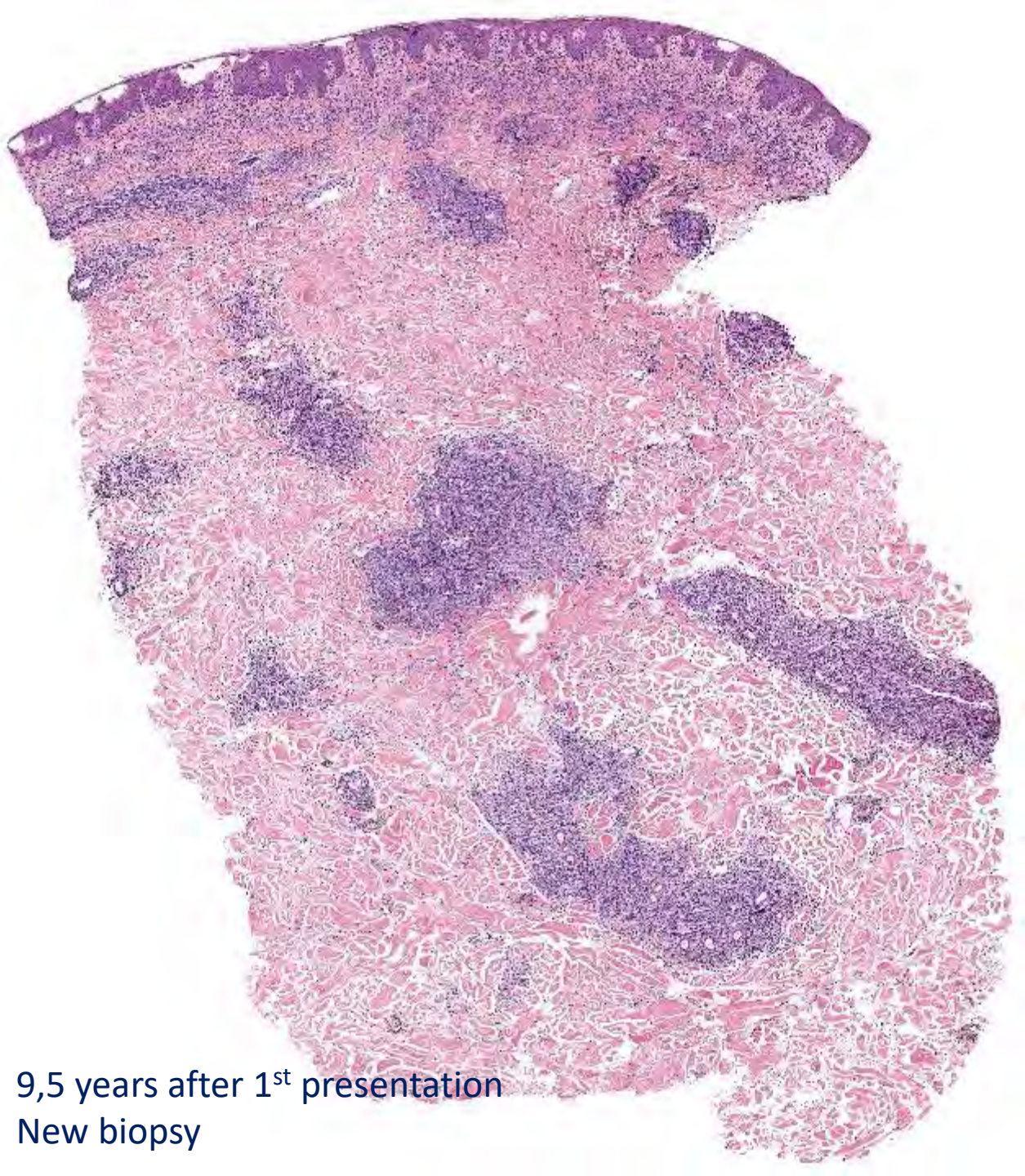

Ki-67





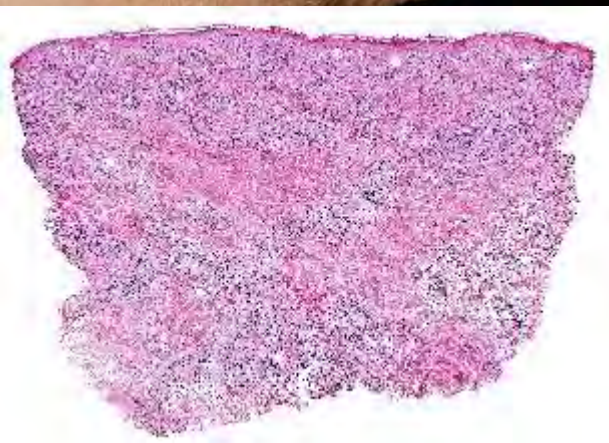
8,5 years after 1st presentation
New biopsy

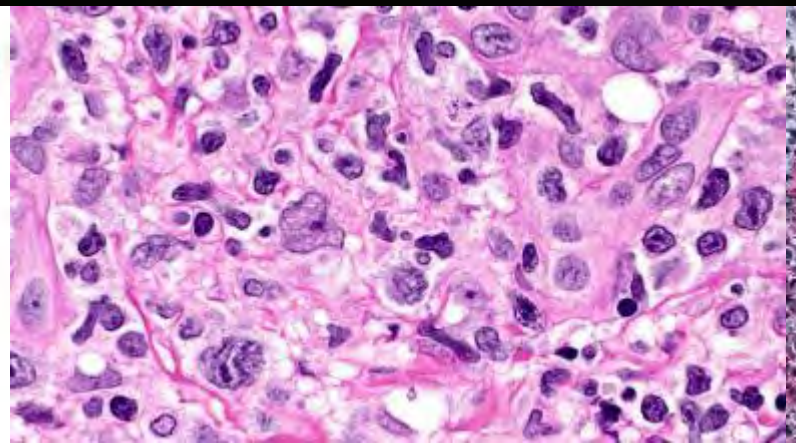


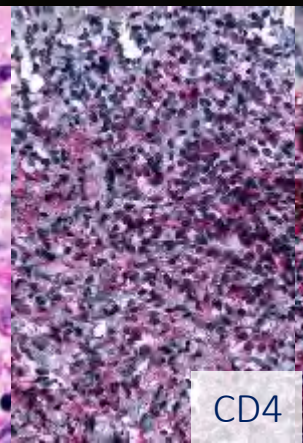


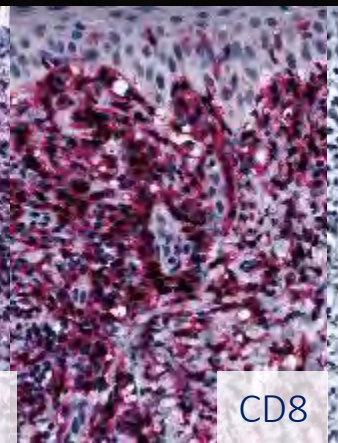
9,5 years after 1st presentation
New biopsy

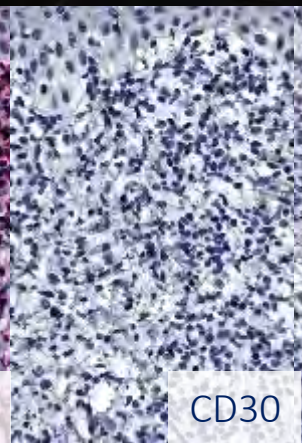
11,5 years after 1st presentation
New biopsy

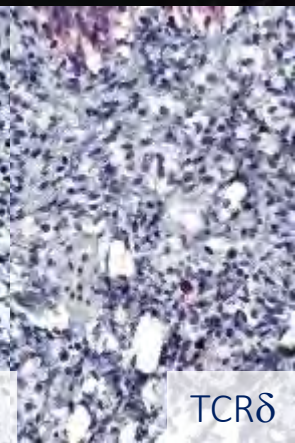




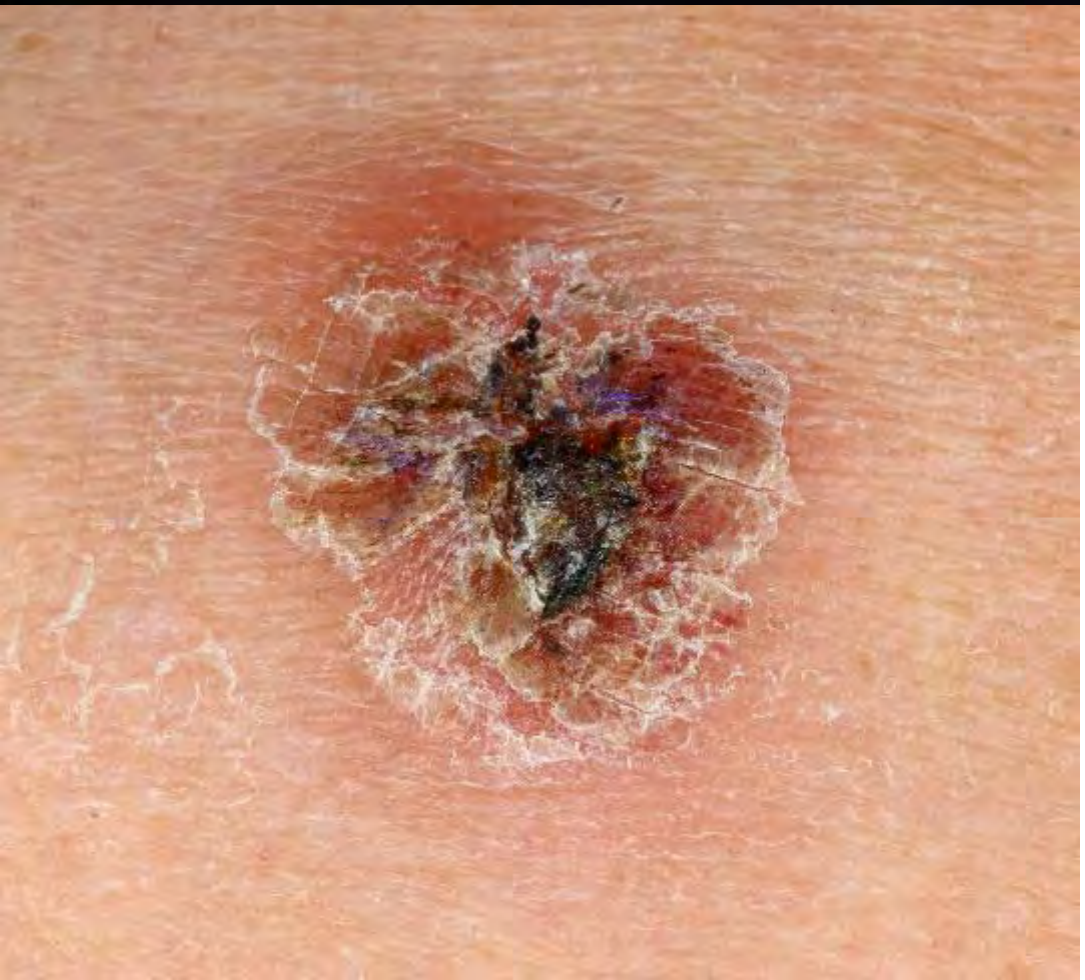


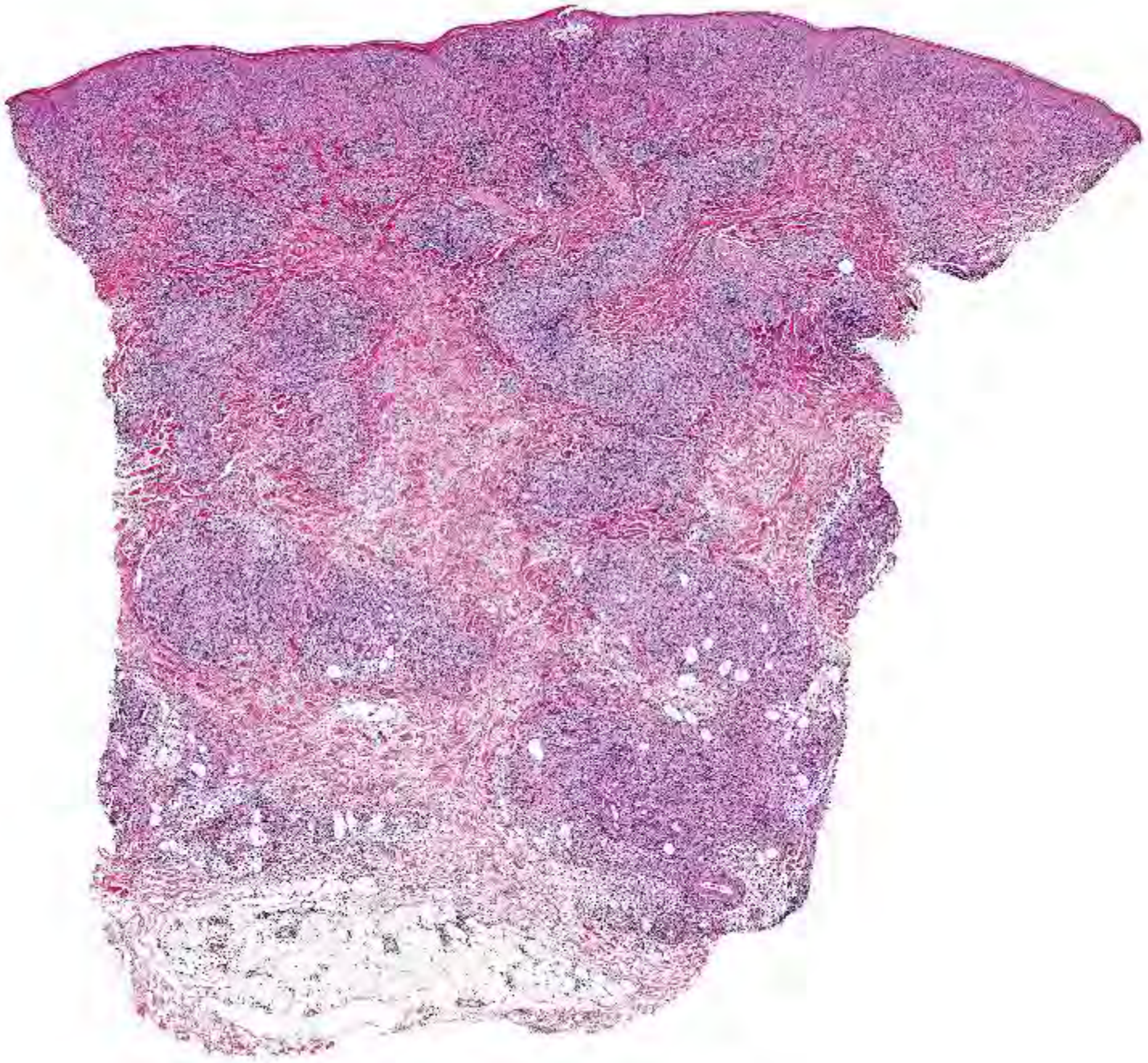


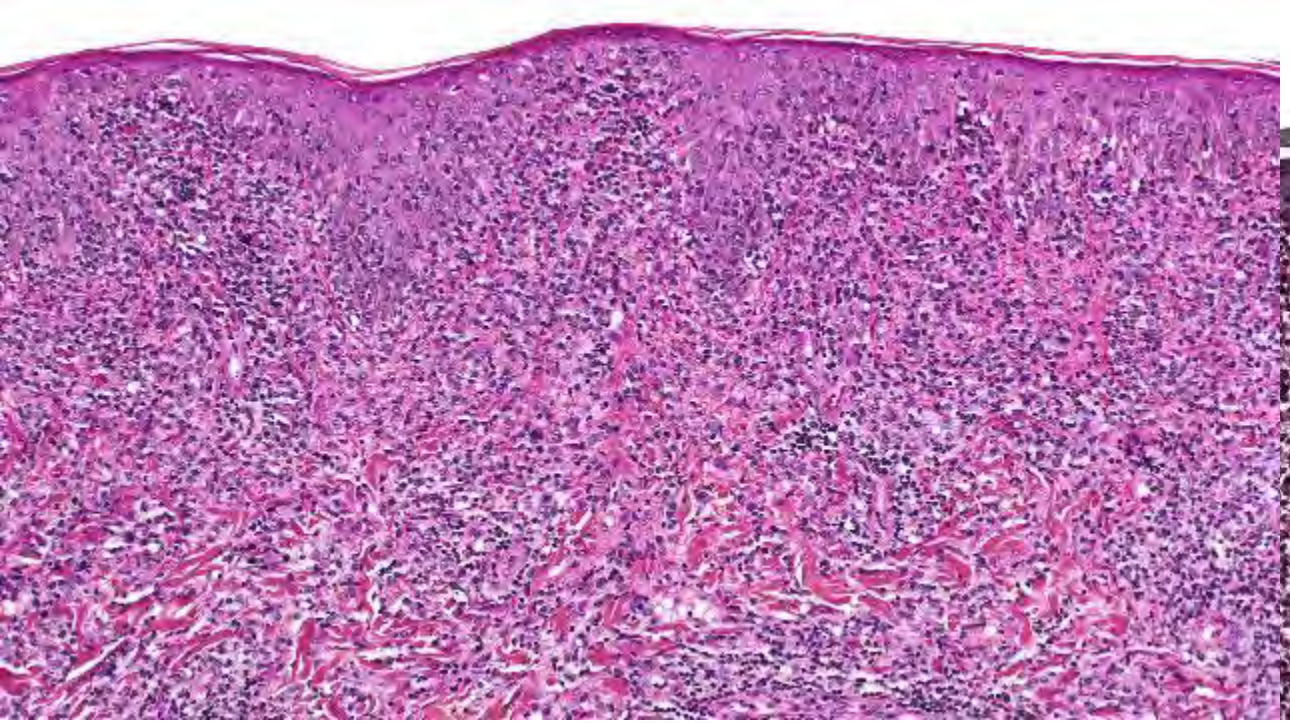


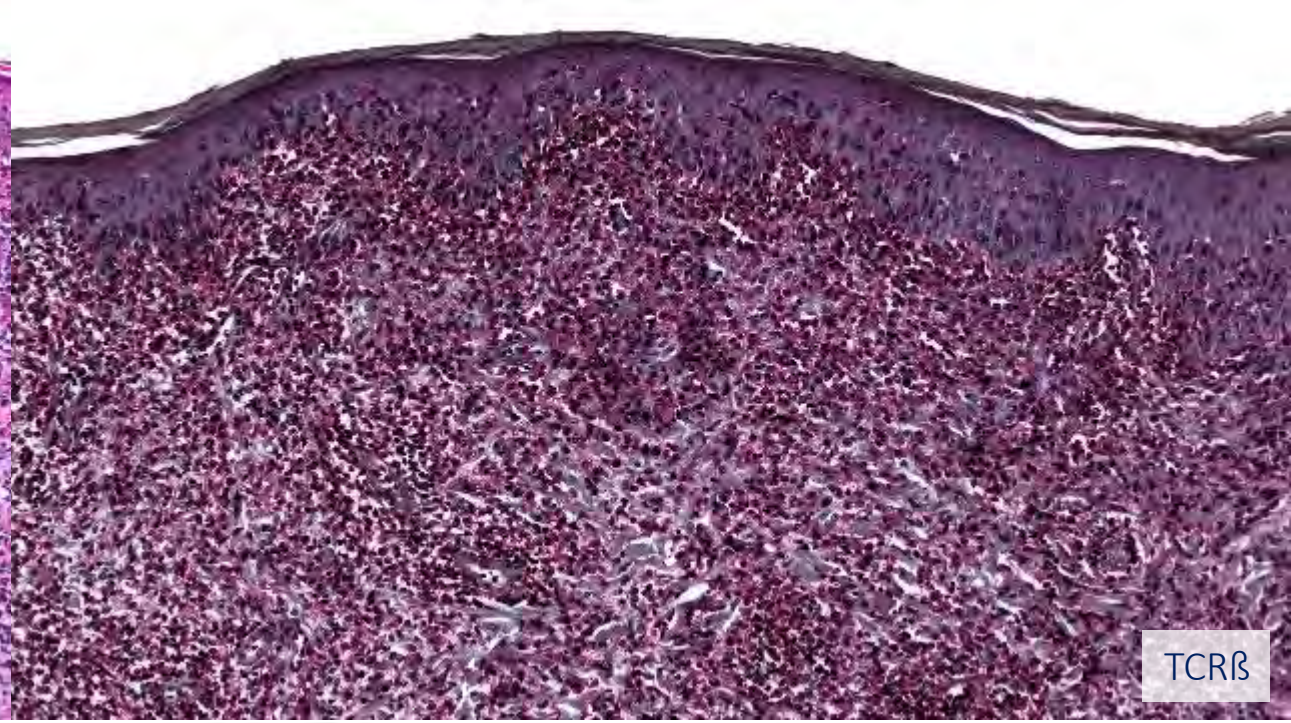


12,5 years after 1st presentation
New biopsy





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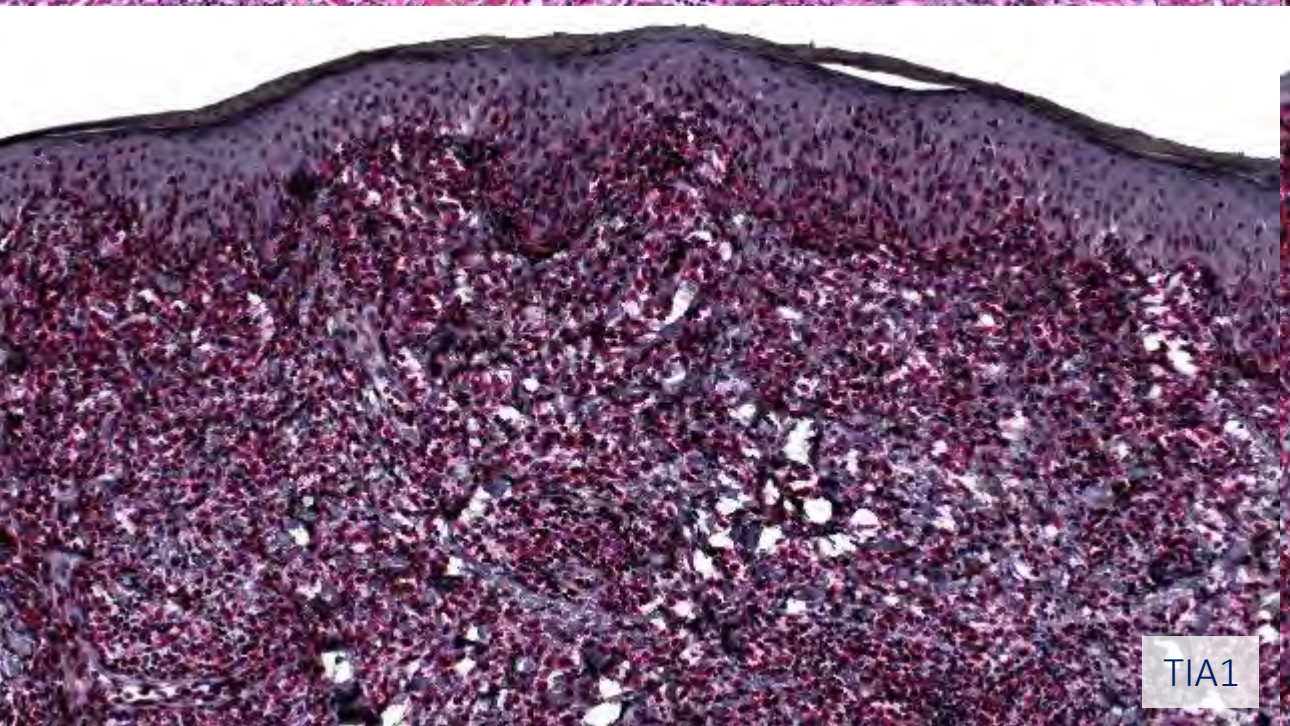
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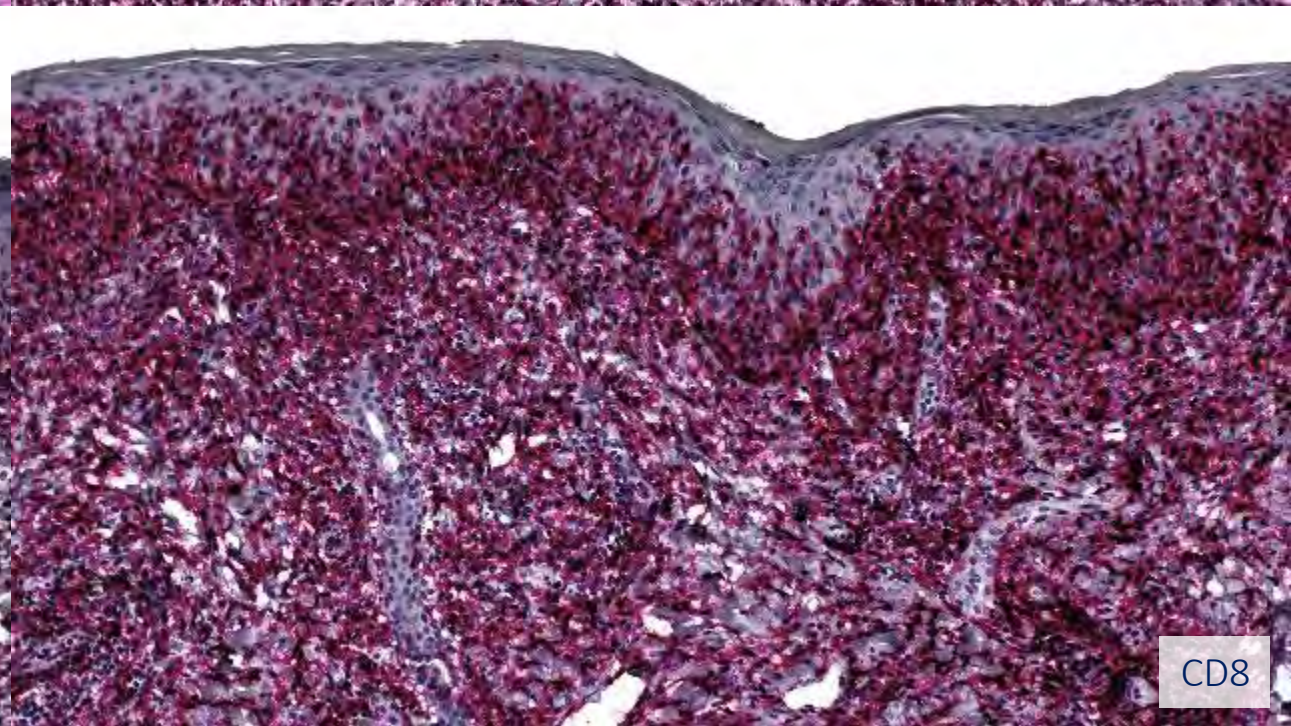
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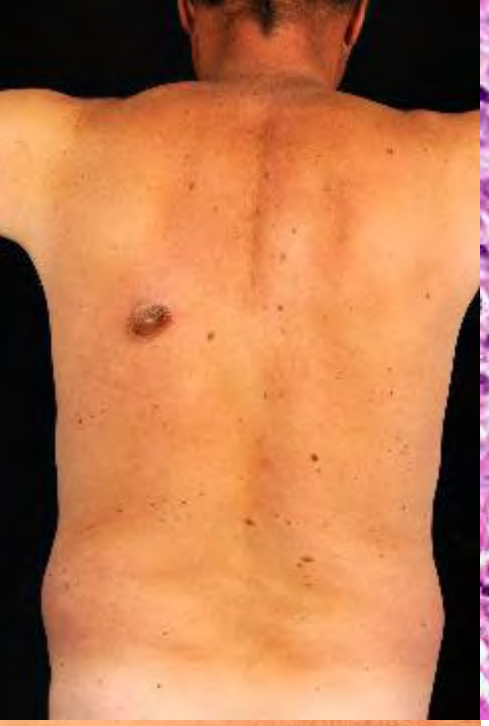
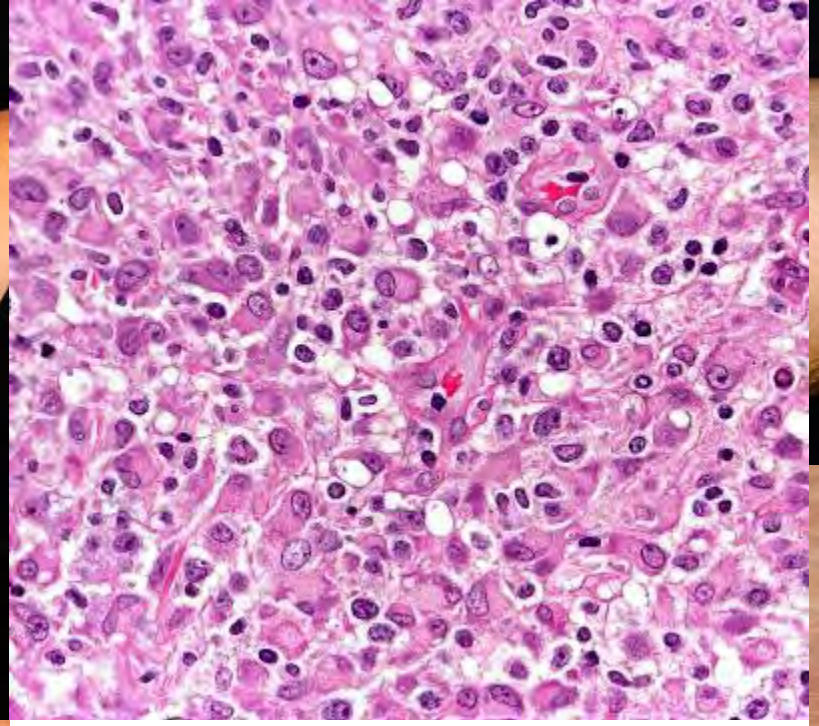
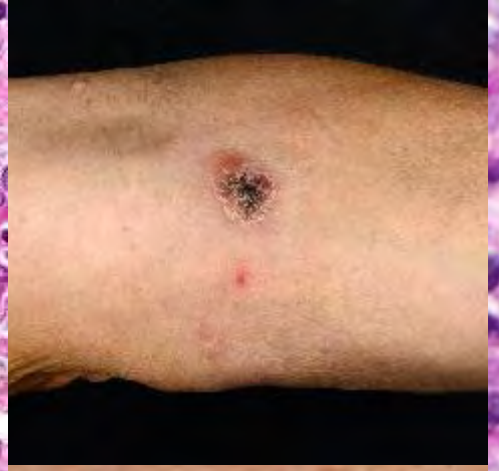
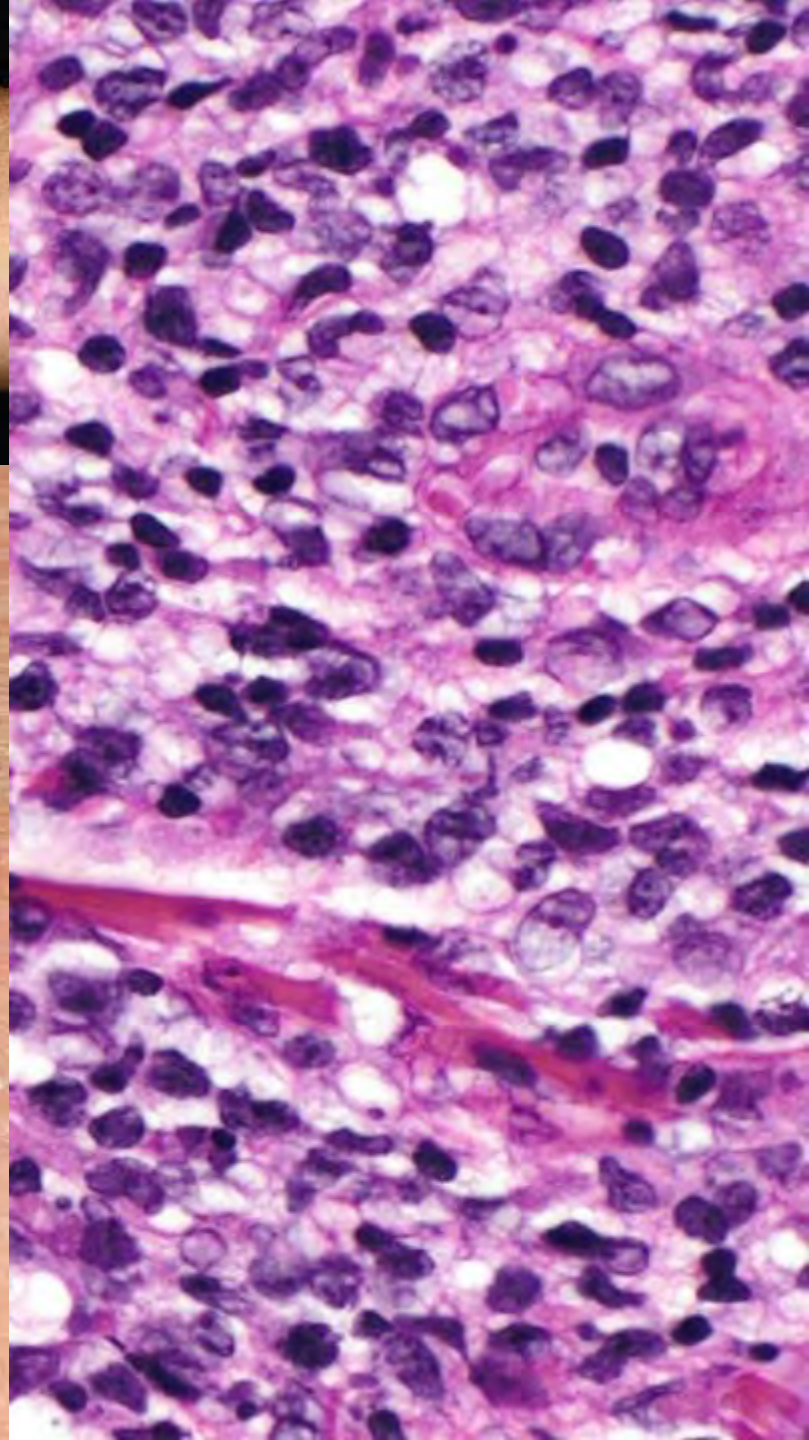
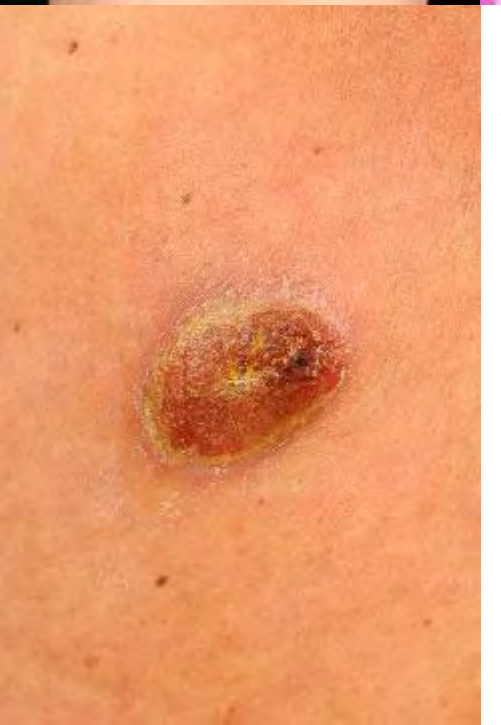










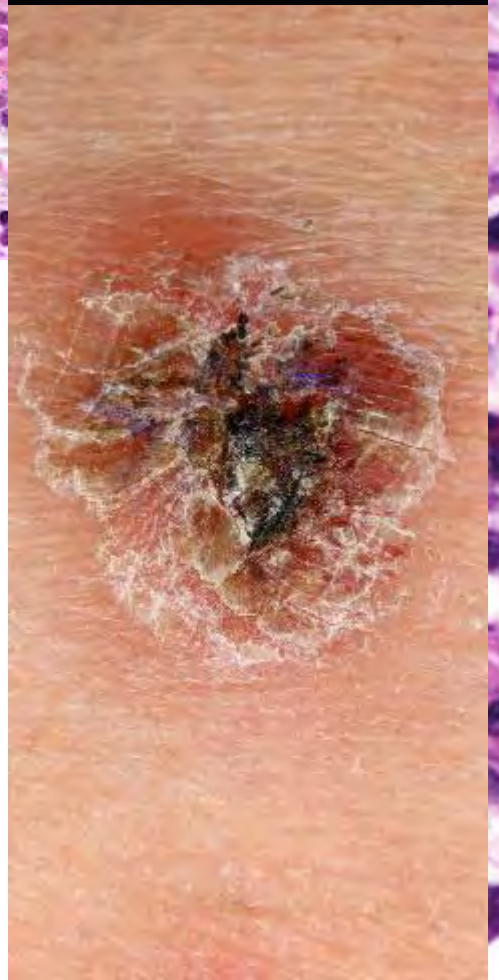
>12 years of skin disease without systemic involvement

Large cell morphology from the beginning

CD30 consistently negative in 7 biopsies; TCRδ negative

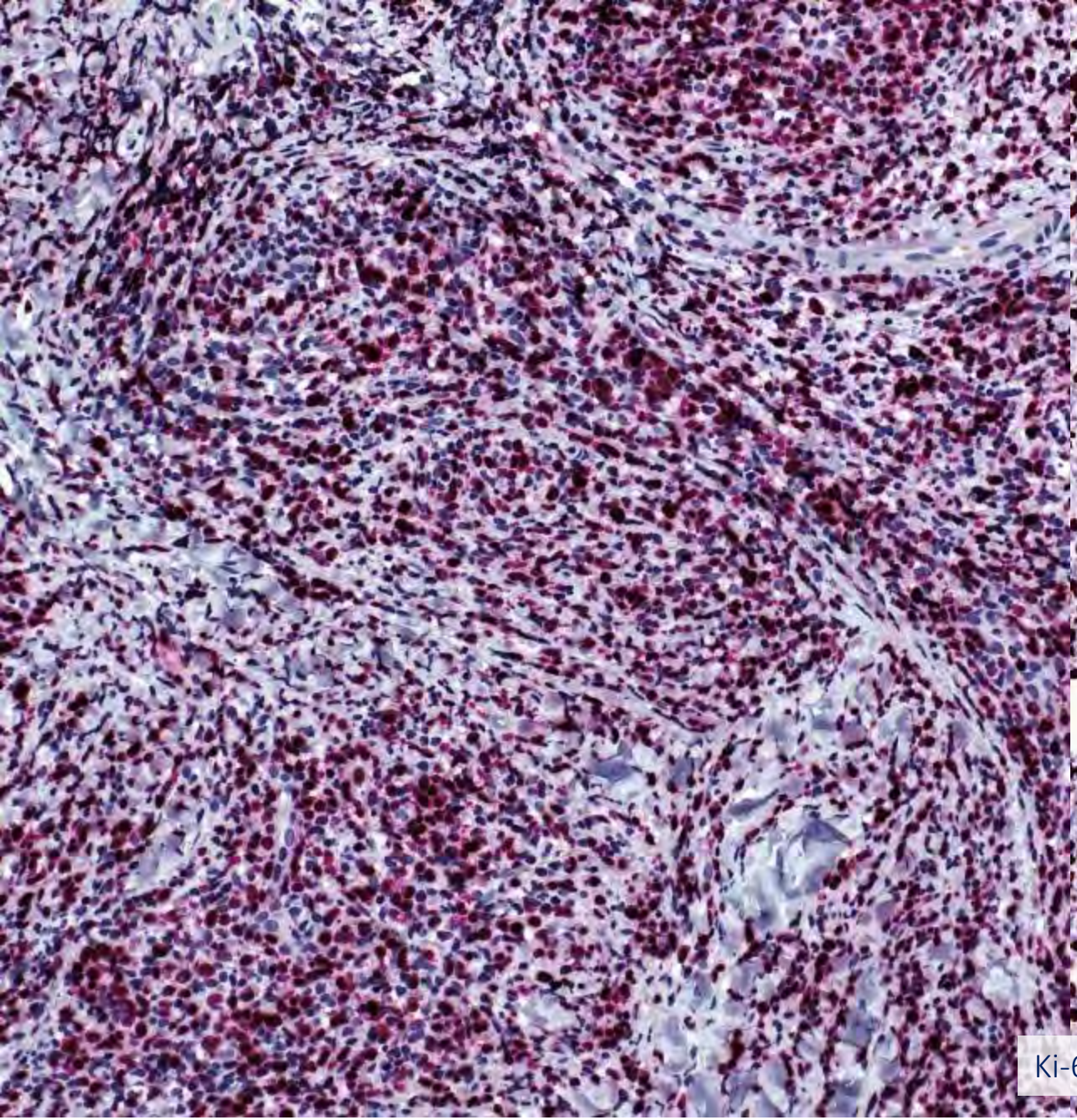
CD4+/CD8+ cytotoxic phenotype

Does not fit in any specific category of CTCL → (peripheral) CTCL, NOS

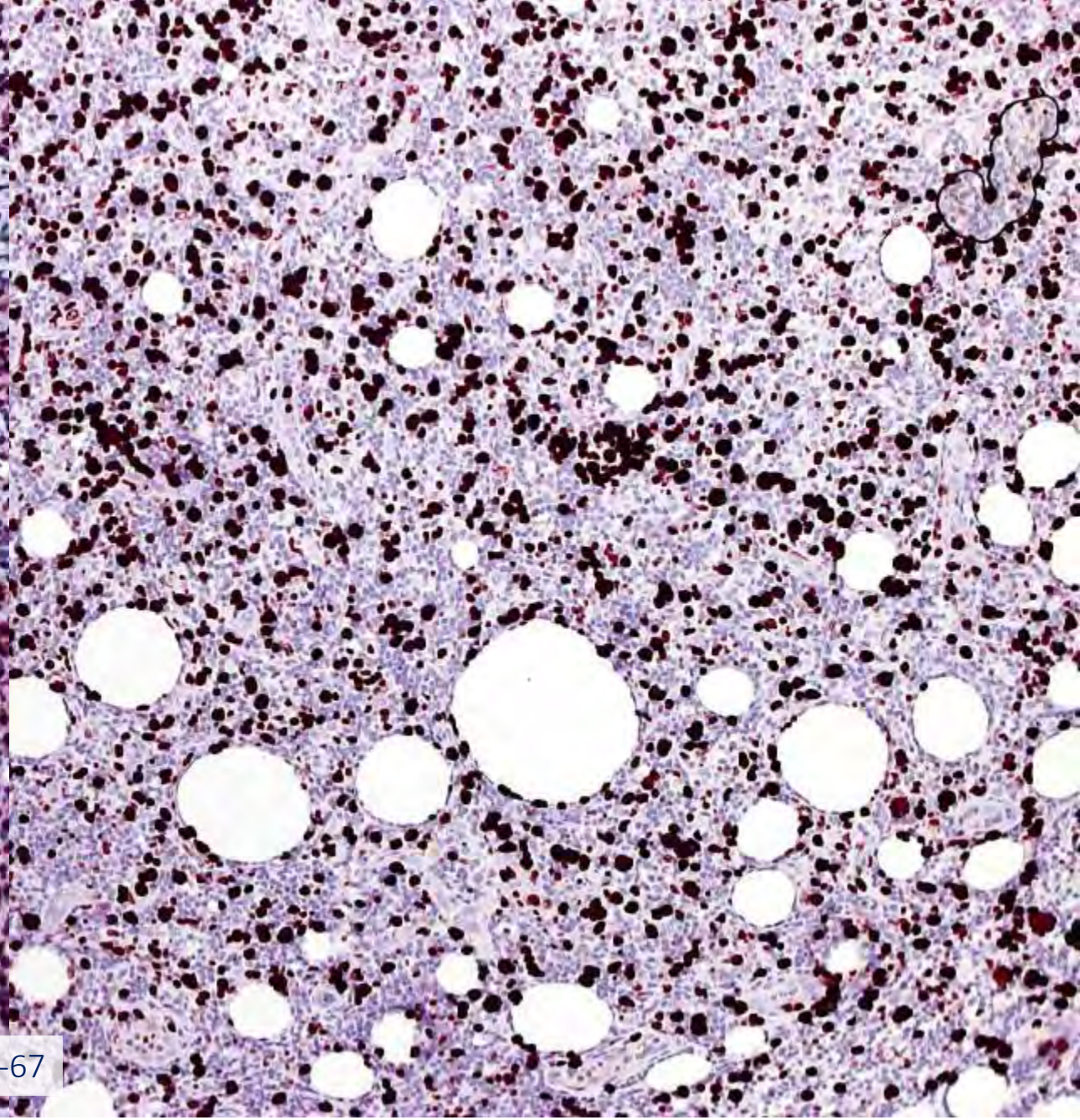


Primary cutaneous (peripheral) T-cell lymphoma, NOS

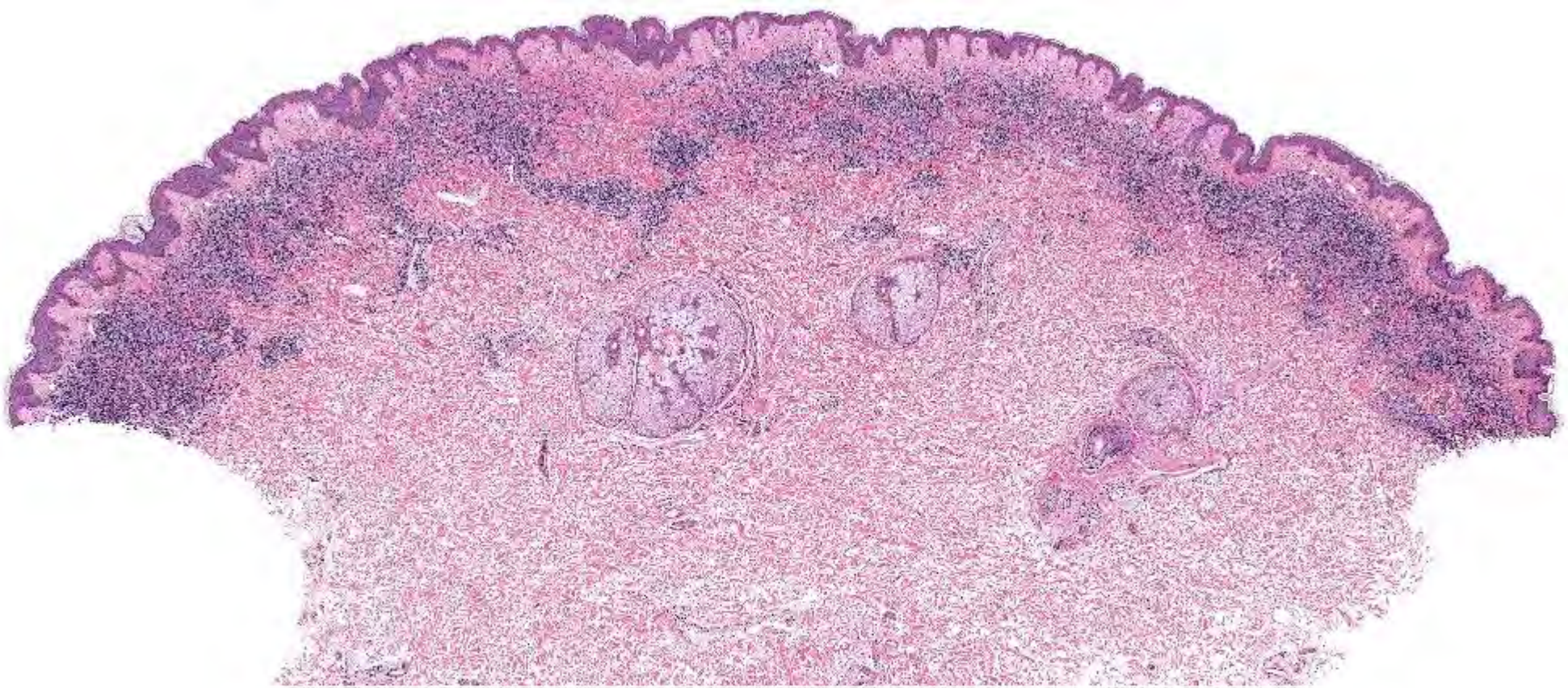
- Included as a distinct entity in the 5th edition of the WHO Classification of Haematolymphoid Tumours, but not in the International Consensus Classification (ICC) of Myeloid and Lymphoid Neoplasms
- *Essential diagnostic criteria:* A diagnosis of exclusion; defined as "a heterogeneous category of nodal and extranodal mature T-cell lymphomas that cannot be assigned to a specific peripheral T-cell lymphoma entity"
- *Main differential diagnoses:* Small-medium pleomorphic CD4+ T-cell lymphoproliferative disorder; Cutaneous lymphomas with T_{FH} phenotype; If cytotoxic phenotype: other cutaneous cytotoxic lymphomas
- Some cutaneous cases are characterized by an indolent behavior with cutaneous recurrences but without systemic spread – management ?
- *Questions still debated:* Classification (separate primary cutaneous category ?); Include cases with T_{FH} phenotype ? Nomenclature (pcPTCL, NOS ? CTCL, NOS ?); Management (how to recognize and approach indolent cases ?)

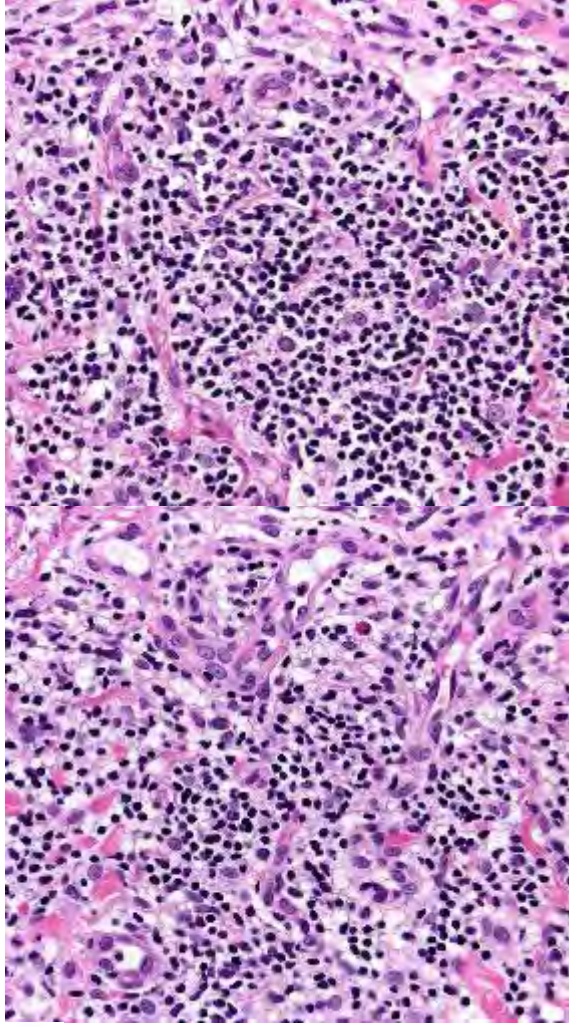


Cutaneous (peripheral) T-cell lymphoma, NOS

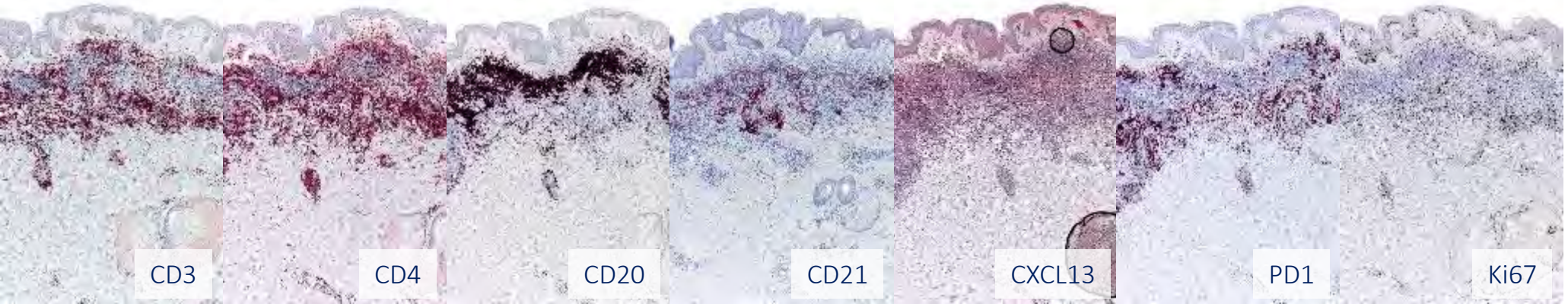


Cutaneous small-medium pleomorphic CD4+ T-cell lymphoproliferative disorder





Cutaneous T_{FH}-cell lymphoma



M, 22

Generalized, confluent papular lesions for some weeks.

A biopsy is taken.

Consultation Dr. G. Ferrara (Benevento)

Cutaneous T-follicular helper (T_{FH})-cell lymphoma

- In the International Consensus Classification (ICC) of Myeloid and Lymphoid Neoplasms and the 5th edition of the WHO Classification of Haematolymphoid Tumours, nodal T_{FH}-cell lymphoma, angioimmunoblastic type has been included in a group of nodal T_{FH}-cell lymphoma(including also nodal T_{FH}-cell lymphoma, follicular type and nodal T_{FH}-cell lymphoma, NOS); Cutaneous cases not considered as a distinct entity
- *Essential diagnostic criteria:* A T_{FH} phenotype is defined as positivity of neoplastic cells for two T_{FH} markers (including PD-1, CD10, CXCL13, BCL6, ICOS, and CXCR5) *and* for CD4
- *Main differential diagnoses:* Peripheral T-cell lymphoma, NOS with T_{FH} phenotype; Small-medium pleomorphic CD4+ T-cell lymphoproliferative disorder; Other cutaneous lymphomas with T_{FH} phenotype (including MF)
- *Question still debated:* Is primary cutaneous TFH cell lymphoma, NOS a separate entity (distinct from pcPTCL, NOS)?

Primary cutaneous peripheral T-cell lymphomas with a T-follicular helper phenotype: an integrative clinical, pathological and molecular case series study*

Luojun Wang, Delphine Rocas, Stéphane Dalle, Nouhoum Sako, Laura Pelletier, Nadine Martin, Aurélie Dupuy, Nadia Tazi, Brigitte Balme, Béatrice Vergier, Marie Beylot-Barry, Agnès Carlotti, Martine Bagot, Maxime Battistella, Guillaume Chaby, Saskia Ingen-Housz-Oro, Philippe Gaulard and Nicolas Ortonne

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Accepted for publication
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L.W., D.R., P.G. and N.O. contributed equally.

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Summary

Background Primary cutaneous peripheral T-cell lymphomas with a T-follicular helper phenotype (pcTFH-PTCL) are poorly characterized, and often compared to lesions corresponding with mycosis fungoides (MF), Sézary syndrome, primary cutaneous $CD4^+$ lymphoproliferative disorder, and skin manifestations of angioimmunoblastic T-cell lymphomas (AITL).

Objectives We describe the clinicopathological features of pcTFH-PTCL in this original series of 23 patients, and also characterize these cases molecularly.

Methods Clinical and histopathological data of the selected patients were reviewed. Patient biopsy samples were also analysed by targeted next-generation sequencing.

Results All patients (15 men, eight women; median age 66 years) presented with skin lesions without systemic disease. Most were stage T3b, with nodular (n = 18), papular (n = 4) or plaque (atypical for MF, n = 1) lesions. Three (13%) developed systemic disease and died of lymphoma. Nine (39%) patients received more than one line of chemotherapy. Histologically, the lymphomas were $CD4^+$ T-cell proliferations, usually dense and located in the deep dermis (n = 14, 61%), with the expression of at least two TFH markers (CD10, CXCL13, PD1, ICOS, BCL6), including three markers in 16 cases (70%). They were associated with a variable proportion of B cells. Eight patients were diagnosed with an associated B-cell lymphoproliferative disorder (LPD) on biopsy, including Epstein–Barr virus (EBV)-positive diffuse large B-cell lymphomas (n = 3), EBV^- LPD (n = 1) and monotypic plasma cell LPD (n = 4). Targeted sequencing showed four patients to have a combined TET2/DNMT3A association (as frequently seen in AITL) and another a TET2/DNMT3A/PLCG1/SETD2 mutational profile. The latter patient, one with a TET2/RHOA association and one with no detected mutations, developed systemic disease and died. Five other patients showed isolated mutations in TET2 (n = 1), PLCG1 (n = 2), SETD2 (n = 1) or STAT5B (n = 1).

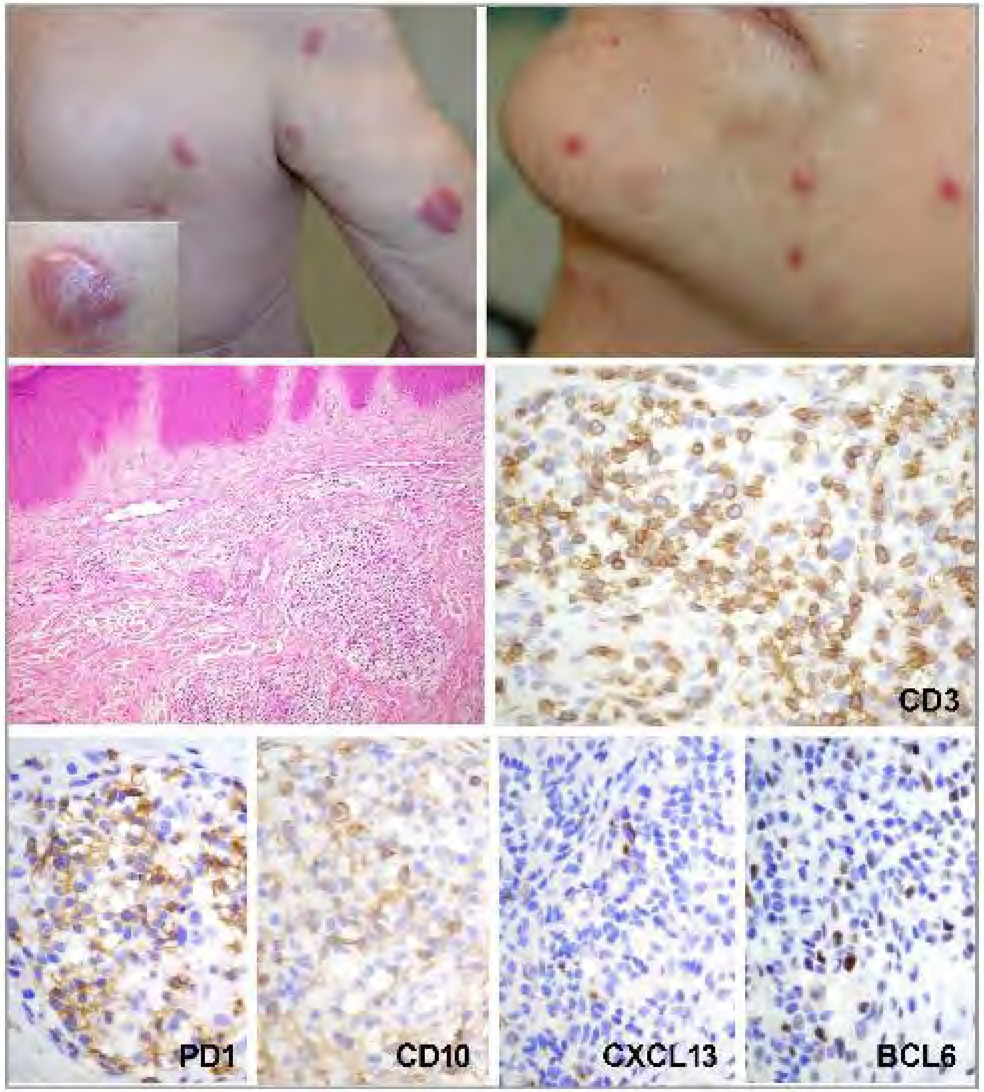
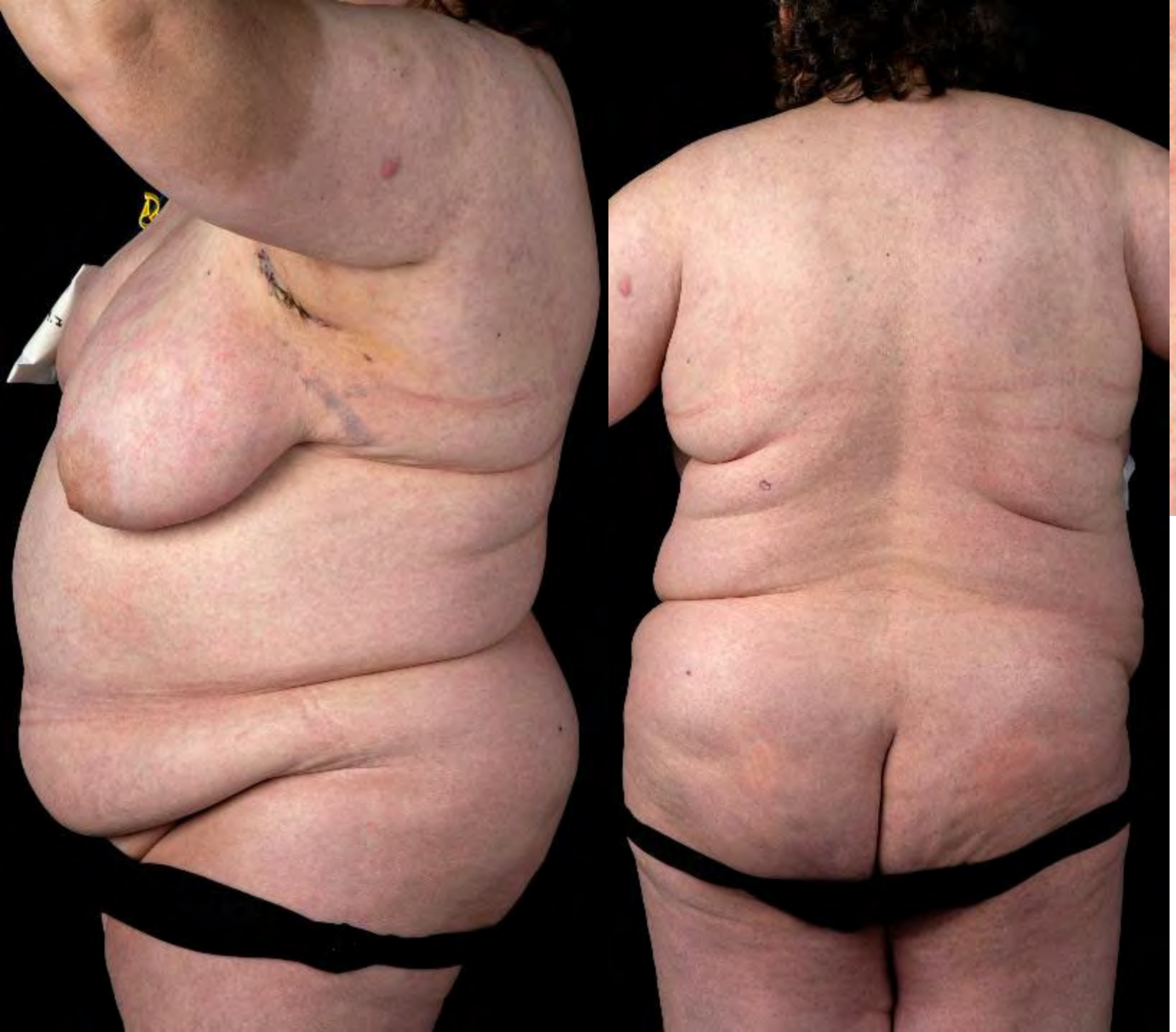
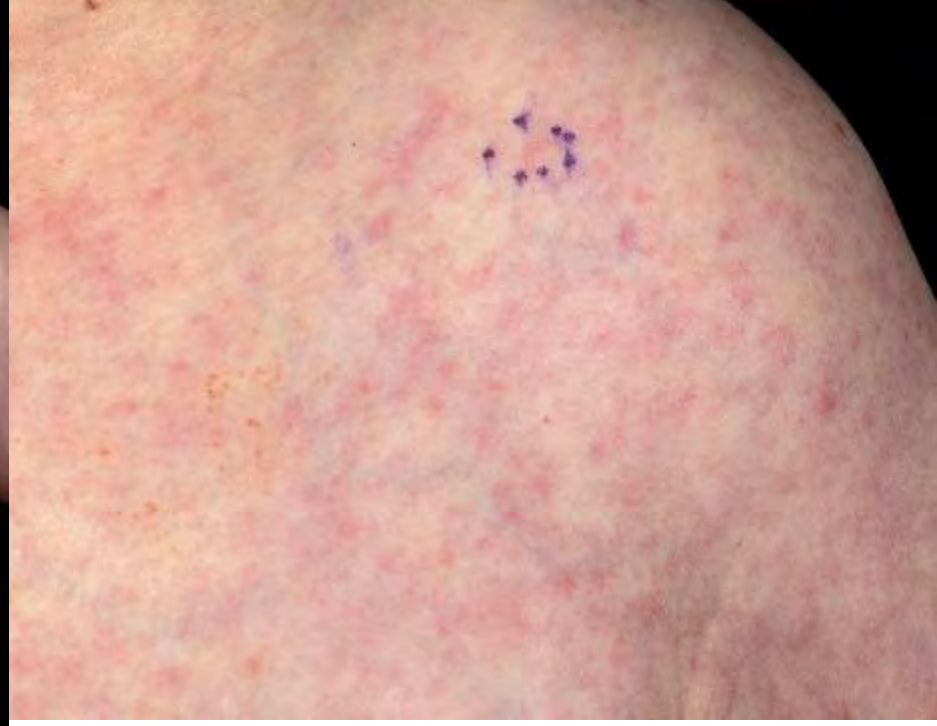


Figure 2 Representative clinical and histopathological aspects of pcTFH-PTCL. Clinical photographs show multiple erythematous nodules on the trunk and the right arm in patient 5, with a 'dome-shaped' erythematous and slightly squamous nodule, strongly resembling a pcSMLPD (inset). Erythematous papules on the cheek and chin were the manifestation of disease in patient 17. In patient 11's biopsy, there is a dermal infiltrate, made of small/medium-sized atypical lymphocytes. The neoplastic T cells show a full TFH phenotype, with positivity for CD3, PD1, CD10, CXCL13 and BCL6. pcTFH-PTCL, primary cutaneous peripheral T-cell lymphomas with a TFH phenotype; pcSMLPD, primary cutaneous $CD4^+$ small-/medium-sized cell lymphoproliferative disorder; TFH, T-follicular helper.



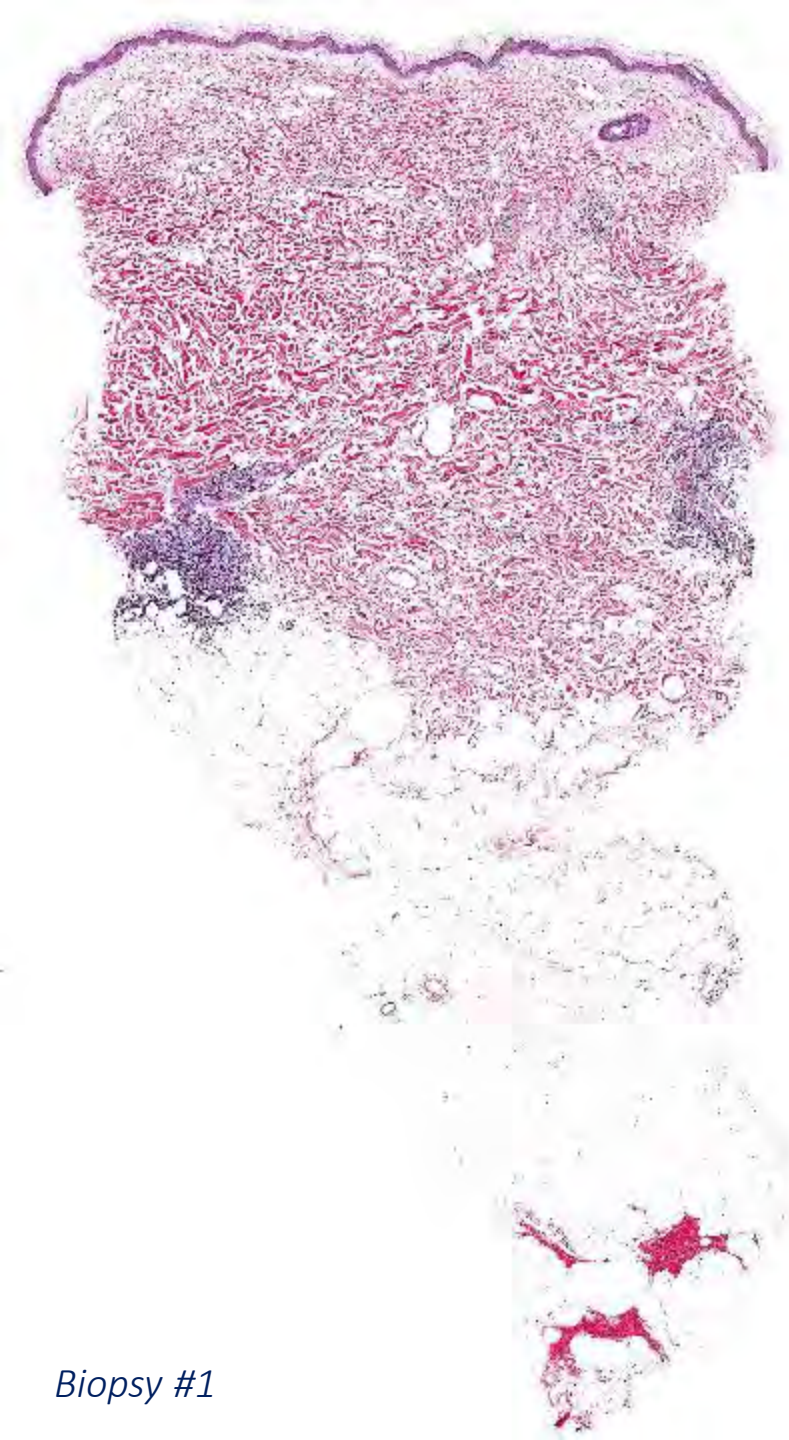


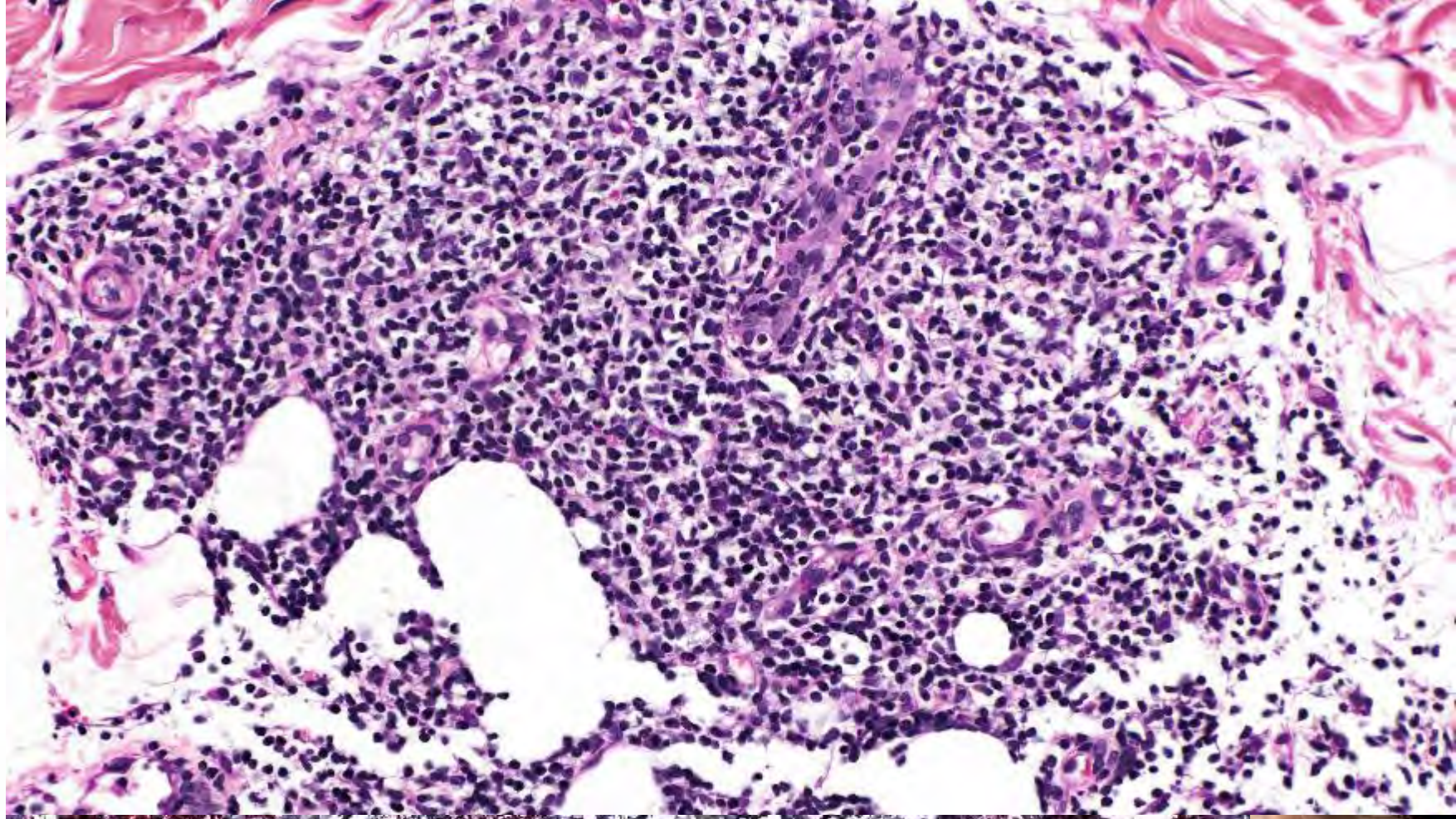
F, 54

History of nodal angioimmunoblastic T-cell lymphoma (1st diagnosis 2 years before presentation) managed with autologous stem cell transplantation 15 months before presentation.

Exanthema for the last 7 weeks.

Two biopsies are taken.





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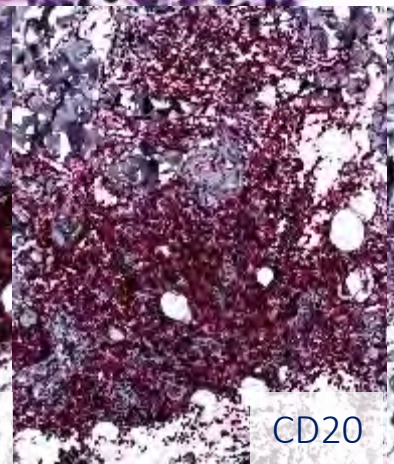

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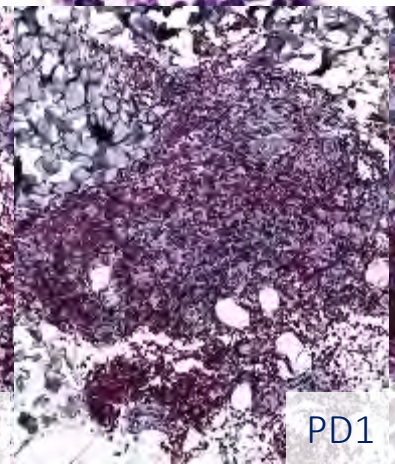
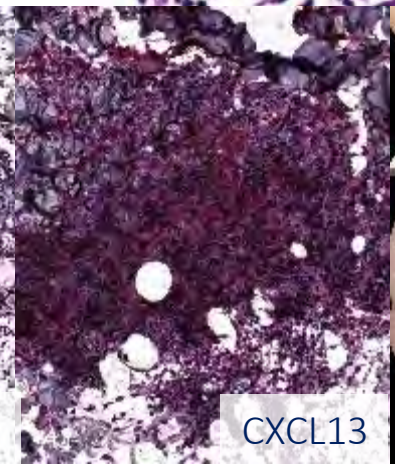
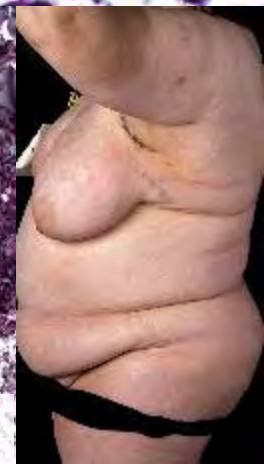


PD1



CXCL13



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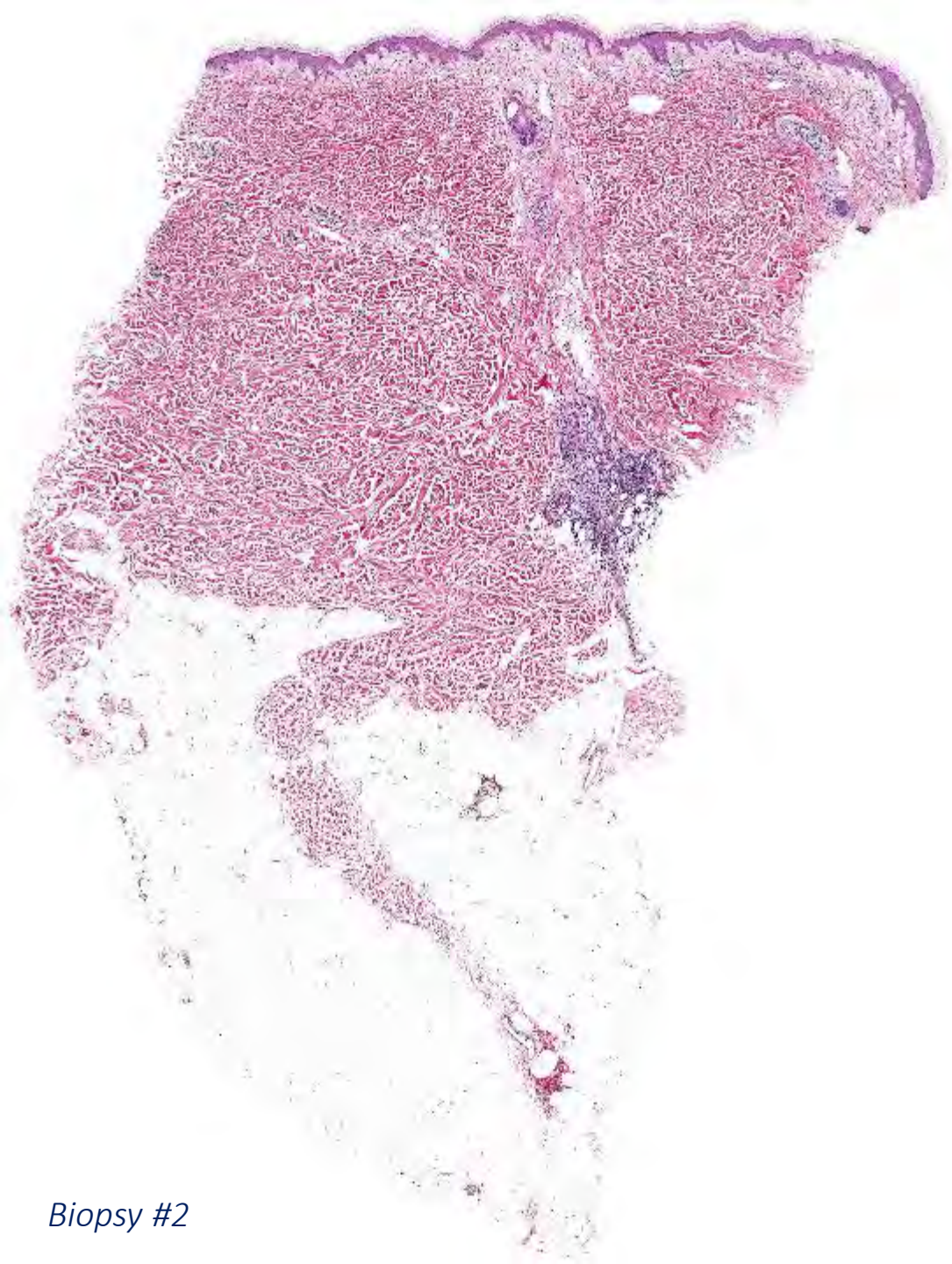

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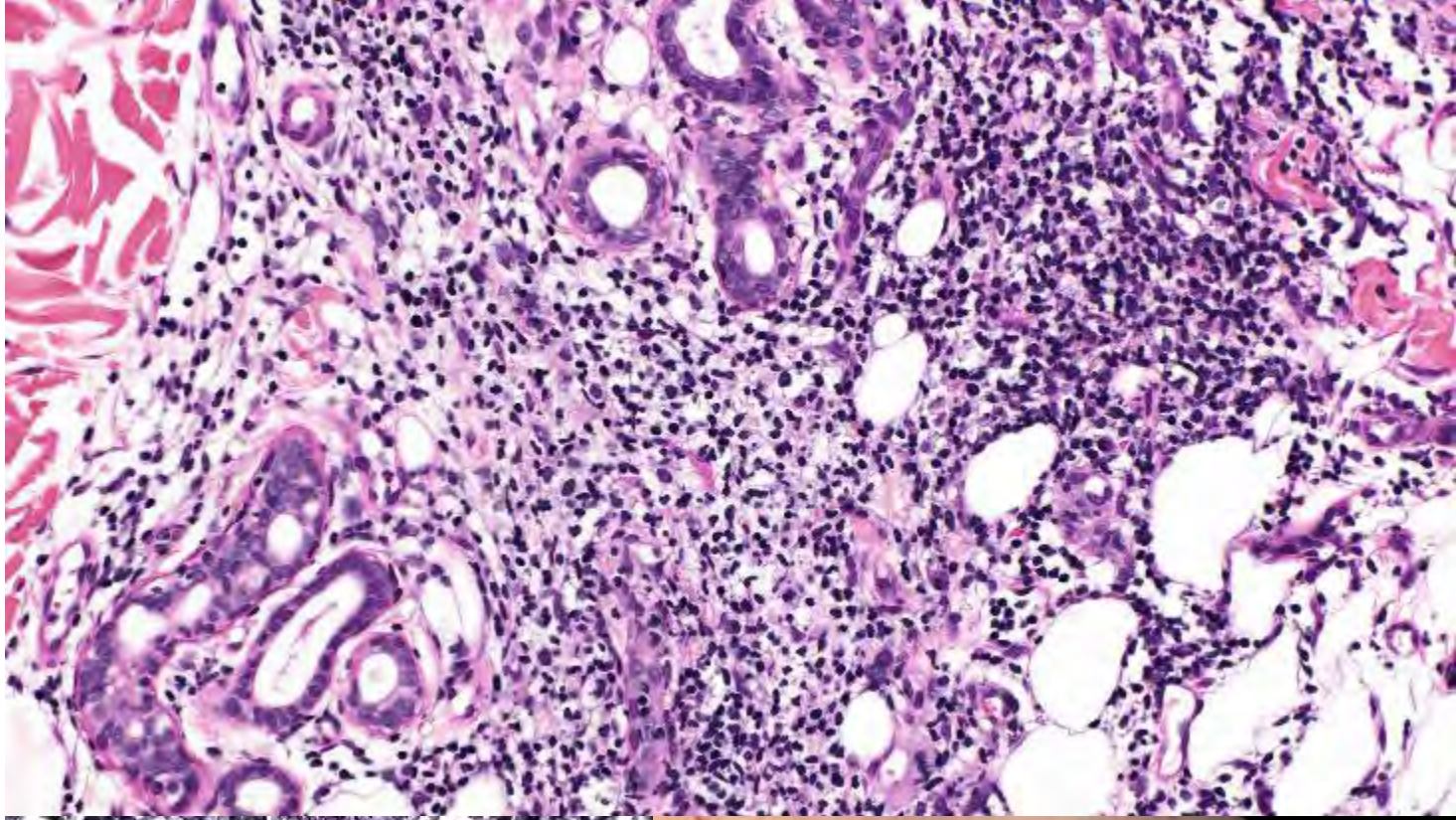
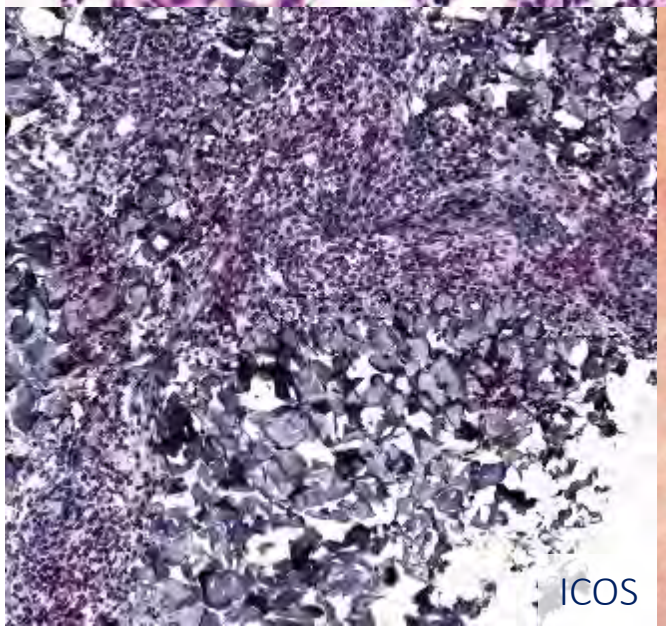
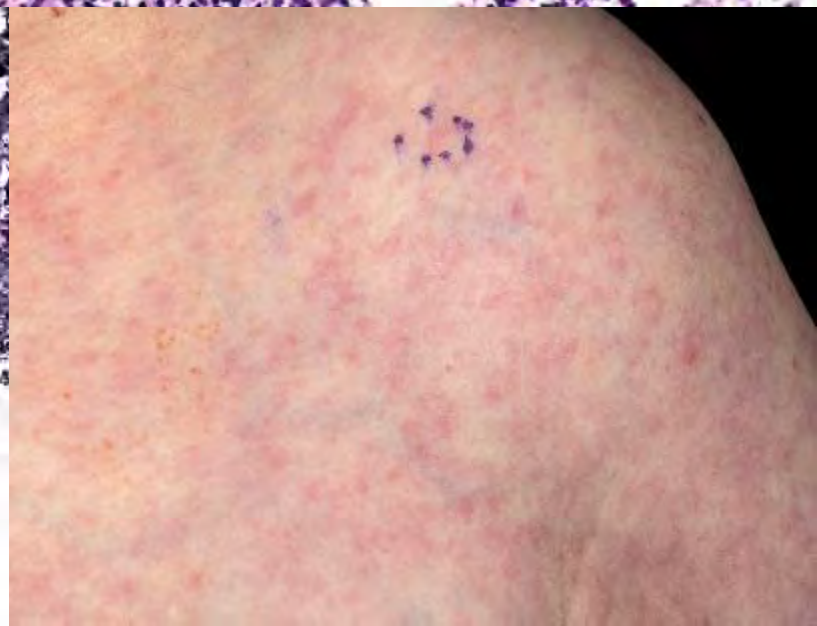
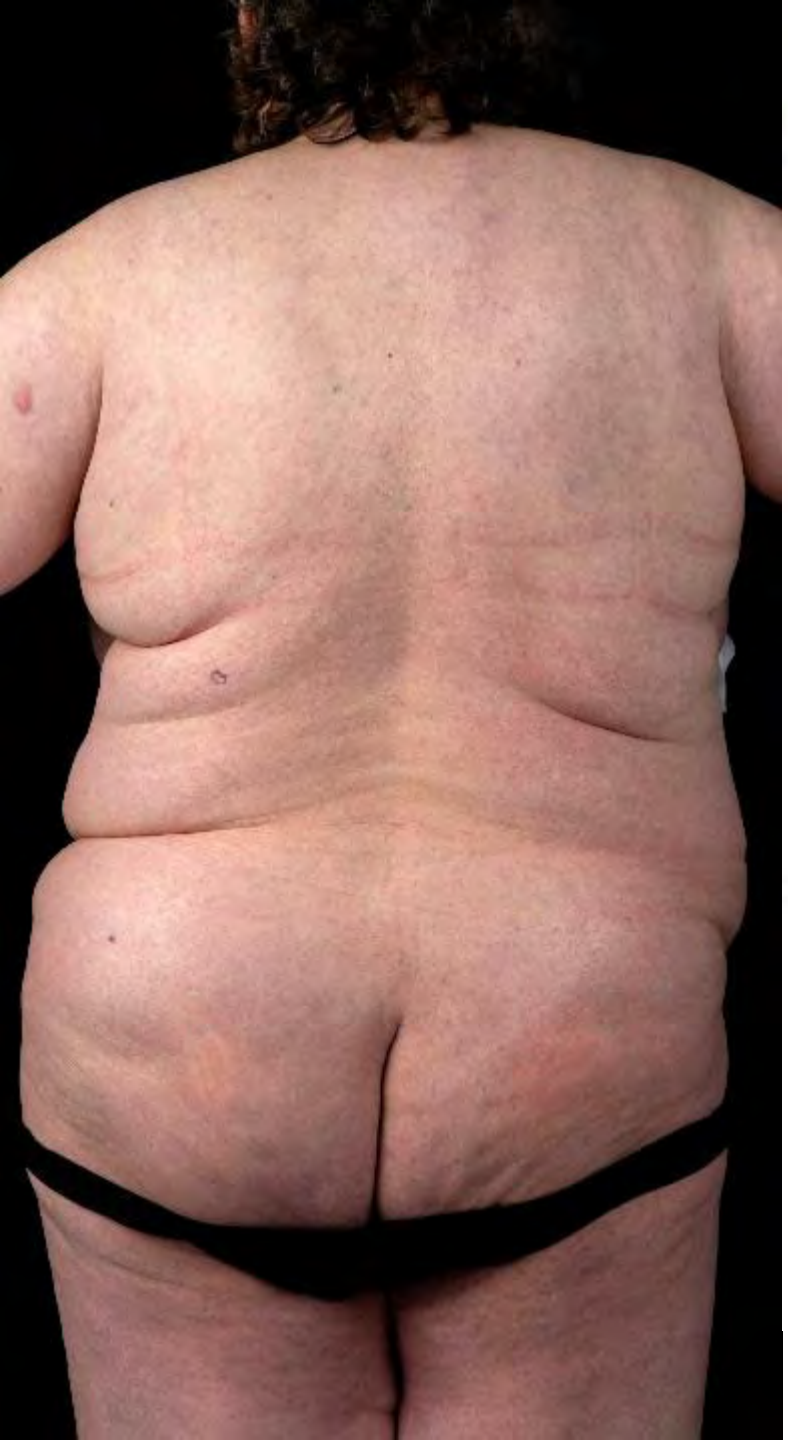
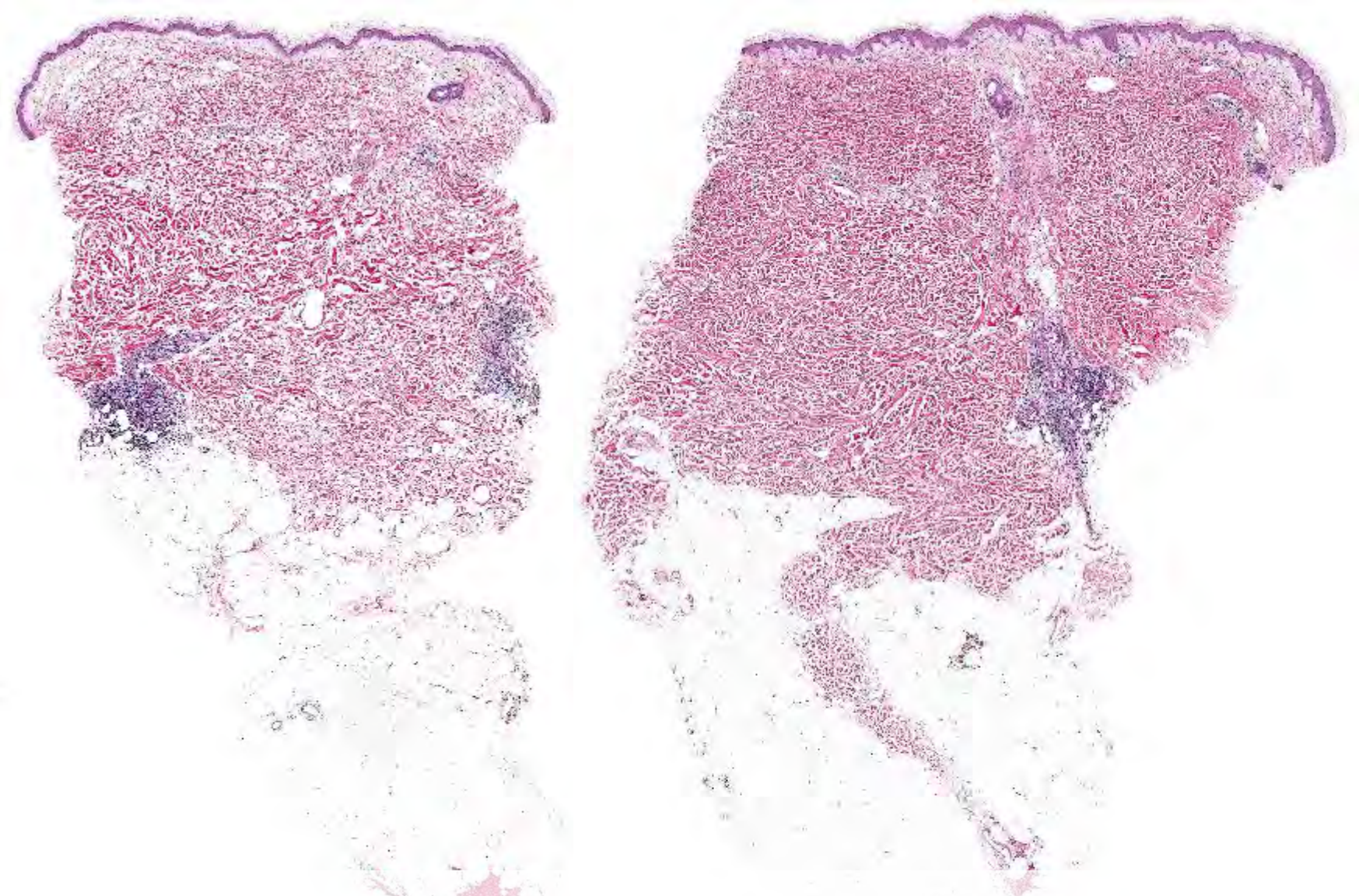




ICOS



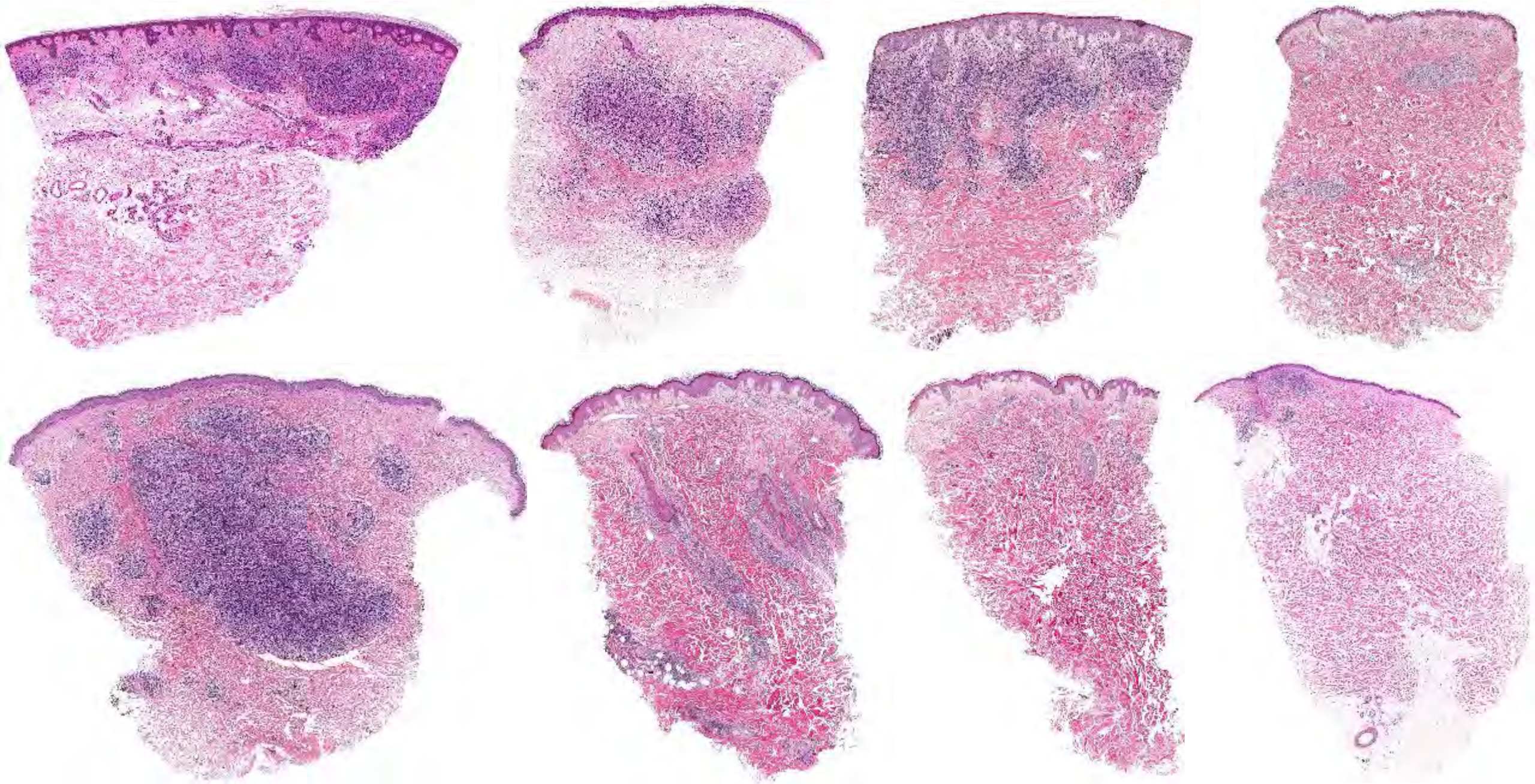




Specific cutaneous manifestation of AITL

with concomitant involvement of axillary lymph nodes
and presence of same clone of T lymphocytes in skin and LNs

Most cases of T_{FH}-cell lymphoma in the skin are secondary, and show a great variability in pattern of infiltration



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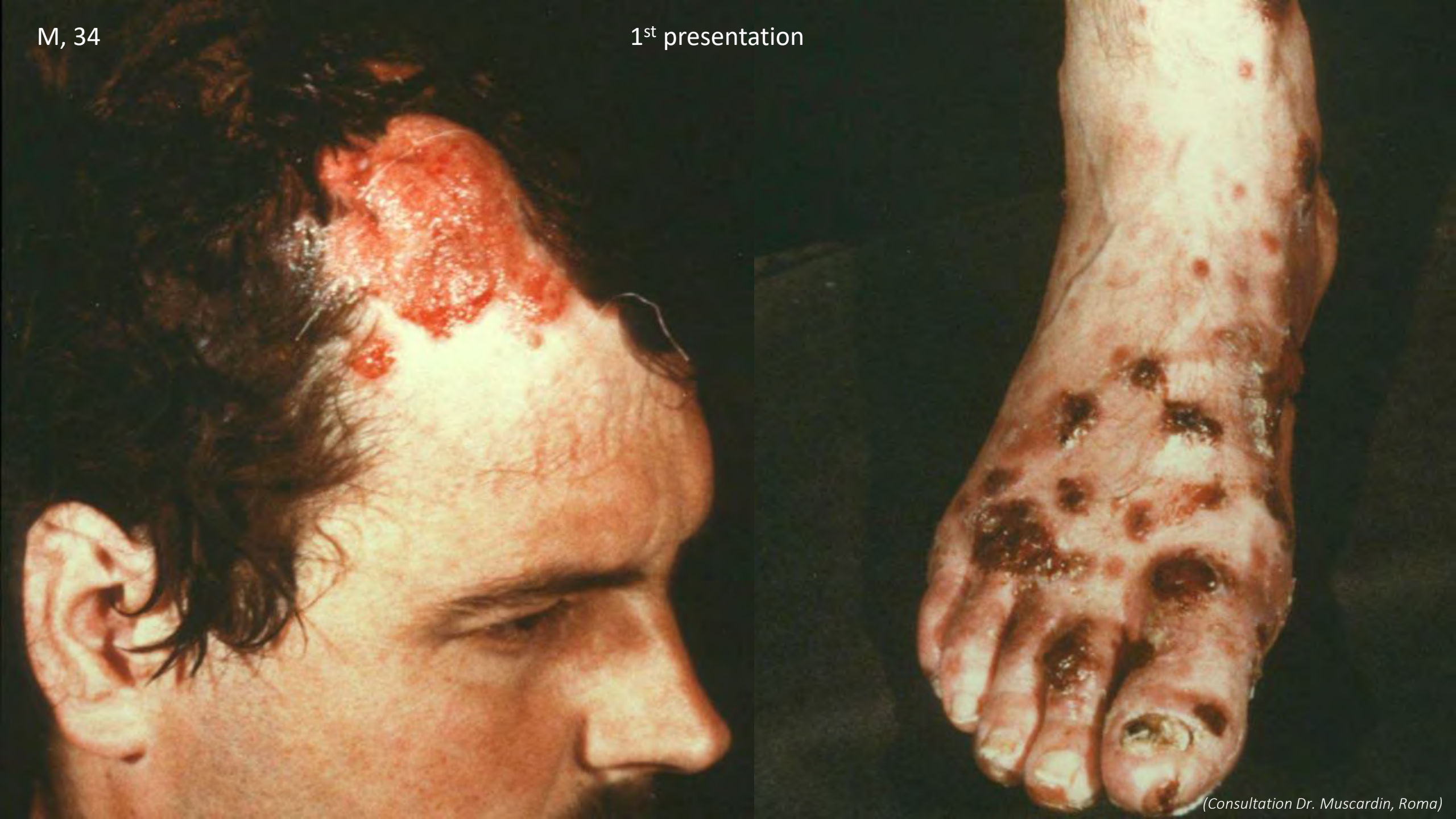
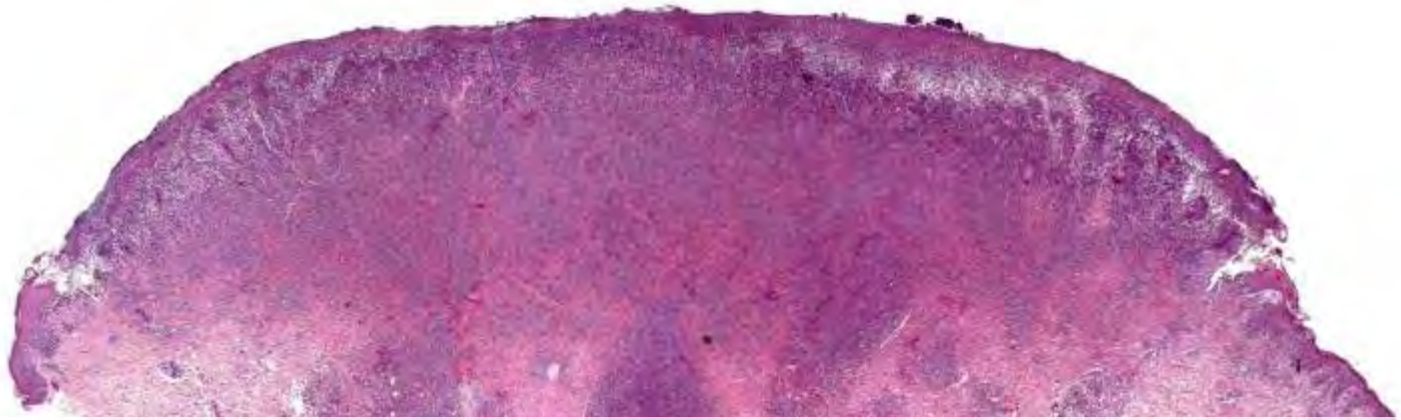
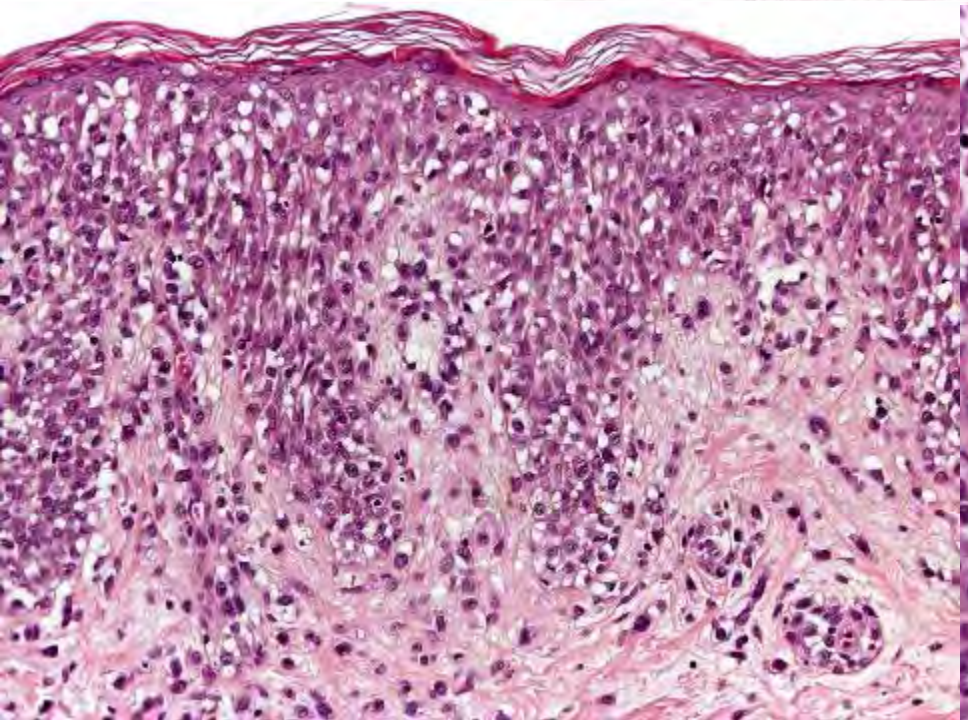
1st presentation

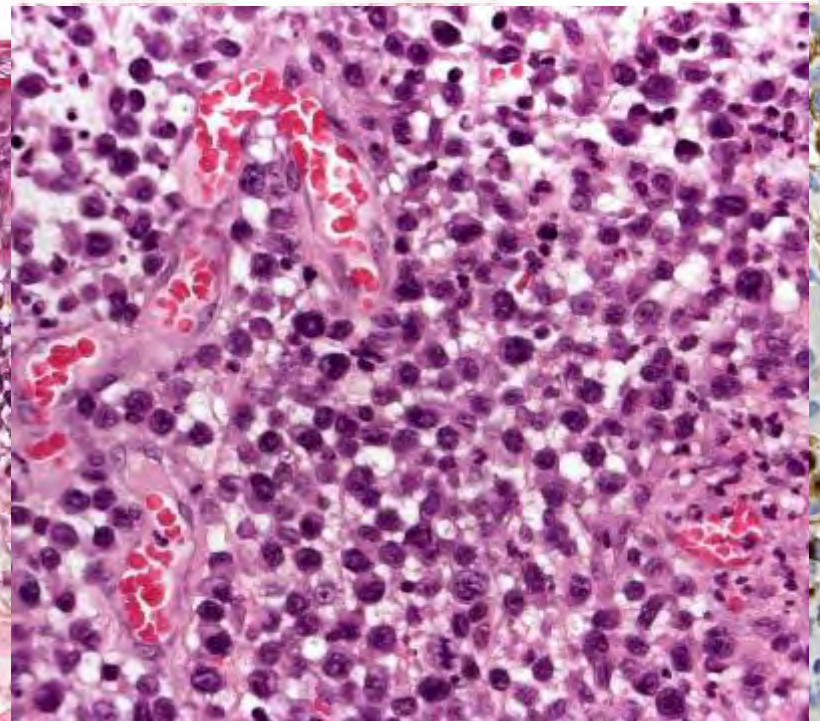


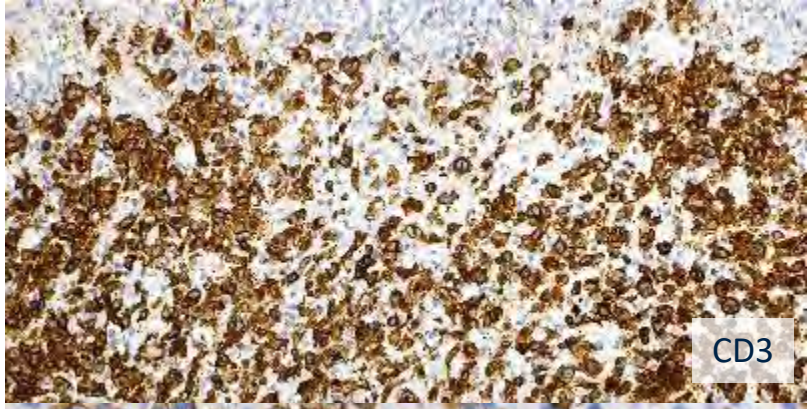
(Consultation Dr. Muscardin, Roma)

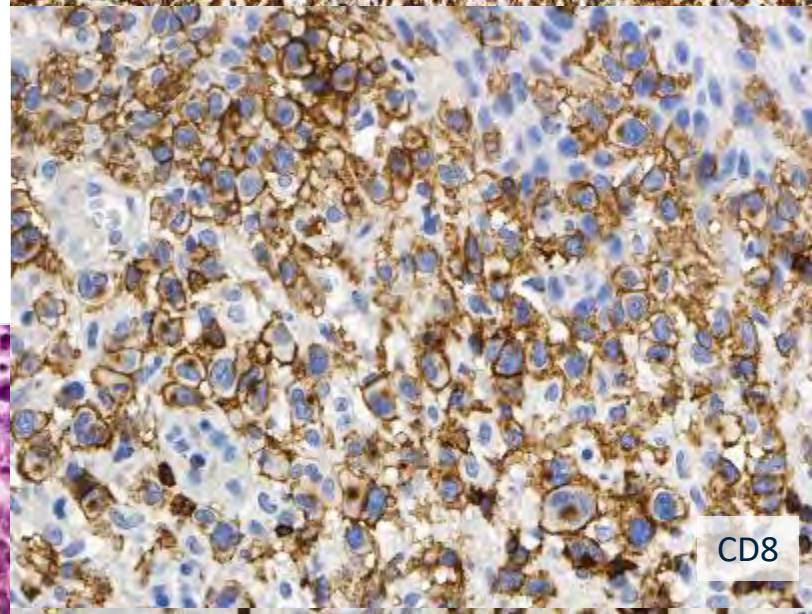


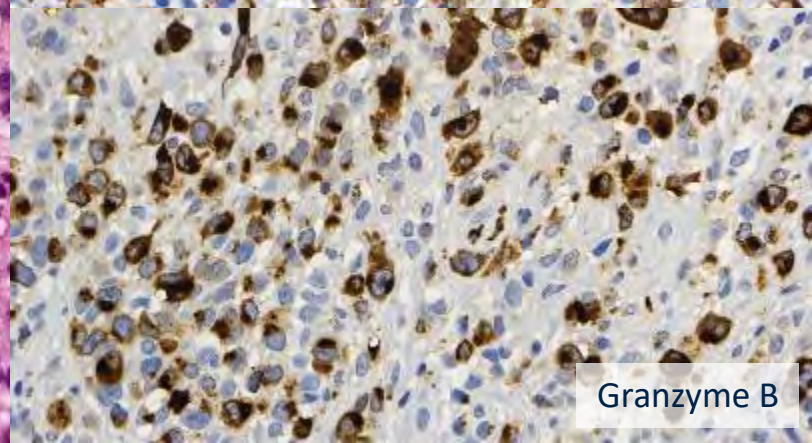
Cutaneous aggressive epidermotropic CD8+ T-cell lymphoma

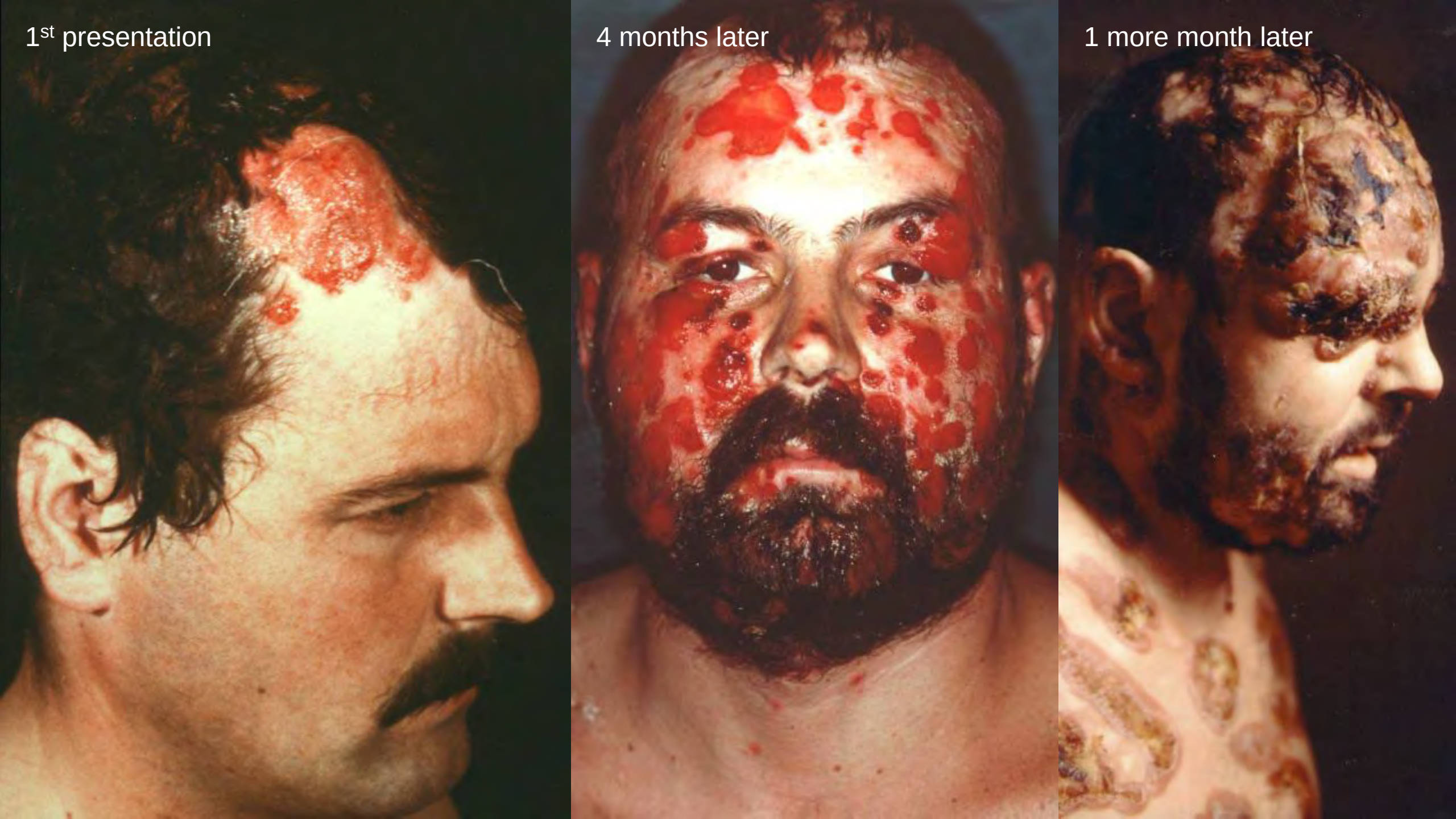











1st presentation
4 months later
1 more month later

Aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma

- Included as a distinct entity in the International Consensus Classification (ICC) of Myeloid and Lymphoid Neoplasms, the 2019 and 2024 updates of classification of cutaneous lymphomas by the EORTC, and the 5th edition of the WHO Classification of Haematolymphoid Tumours
- *Essential diagnostic criteria:* Positivity of neoplastic cells for CD8; negativity for TCR gamma/delta; no history of mycosis fungoides
- *Main differential diagnoses:* Cytotoxic mycosis fungoides; Lymphomatoid papulosis, type D; Cutaneous gamma/delta T-cell lymphoma; Cutaneous (peripheral) T-cell lymphoma, NOS with cytotoxic phenotype; Hydroa vacciniforme-like lymphoproliferative disorder; Acral CD8+ T-cell lymphoproliferative disorder; Subcutaneous panniculitis-like T-cell lymphoma

American Journal of Pathology, Vol. 155, No. 2, August 1999

Primary Cutaneous CD8-Positive Epidermotropic Cytotoxic T Cell Lymphomas

A Distinct Clinicopathological Entity with an Aggressive Clinical Behavior

Emilio Berti,* Dario Tomasini,†
Maarten H Vermeer,‡ Chris JLM Meijer,‡
Elvio Alessi,* and Rein Willemze‡

From the Institute of Dermatologic Science and IRCCS Ospedale Maggiore, Milan, Italy, the Department of Dermatology,† Ospedale Busto Arsizio, Italy; and the Departments of Dermatology and Pathology,‡ Free University Hospital, Amsterdam, The Netherlands*

Cutaneous T cell lymphomas (CTCL) generally have the phenotype of CD3+, CD4+, CD45RO+ memory T cells. CTCL expressing a CD8+ T cell phenotype are extremely rare and ill-defined. To elucidate whether these CD8+ CTCL represent a distinct disease entity, the clinical, histological, and immunophenotypical features of 17 CD8+ CTCL were reviewed. None of the 17 cases expressed markers characteristic of natural killer cells or γ/δ T cells. Nine of 17 cases showed the characteristic clinical and histological features as well as clinical behavior of well defined types of CTCL, such as mycosis fungoides (2 cases), pagetoid reticulosis (2 cases), lymphomatoid papulosis (2 cases), and CD30+ large T cell lymphoma (2 cases), all of which usually express a CD4+ T cell phenotype, and 1 case of subcutaneous panniculitis-like T cell lymphoma. The other 8 cases formed a homogeneous group showing a distinctive set of clinicopathological and immunophenotypical features, not consistent with that of other well defined types of CTCL. Clinical characteristics included presentation with generalized patches, plaques, papulonodules, and tumors mimicking disseminated pagetoid reticulosis; metastatic spread to unusual sites, such as the lung, testis, central nervous system, and oral cavity, but not to the lymph nodes; and an aggressive course (median survival, 32 months). Histologically, these lymphomas were characterized by band-like infiltrates consisting of pleomorphic T cells or immunoblasts, showing a diffuse infiltration of an acanthotic epidermis with variable degrees of spongiosis, intraepidermal blistering, and necrosis. The neoplastic cells showed a high Ki-67 proliferation index and expression of CD3, CD8, CD7, CD45RA, βF1, and TIA-1 markers, whereas CD2 and CD5 were frequently lost. Expression of TIA-1 pointed out that these lymphomas are derived from a cytotoxic T cell subset. The results of this and other studies reviewed herein suggest that these strongly epidermotropic primary cutaneous CD8+ cytotoxic T cell lymphomas represent a distinct type of CTCL with an aggressive clinical behavior. (Am J Pathol 1999, 155:483–492)

Recently, the European Organization for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Group proposed a new classification for primary cutaneous T (CTCL) and B (CBCL) cell lymphomas.[1] This classification is based on a combination of clinical, histological, immunohistochemical, and genetic criteria and contains a number of well defined entities as well as some provisional forms. Well defined entities within the CTCL group include classical mycosis fungoides (MF), follicular MF, pagetoid reticulosis, Sézary's syndrome (SS), CD30+ primary cutaneous large T cell lymphomas (PC-LCL) and CD30− PC-LCL. Together they constitute about the 96% of CTCL in the Dutch registry.[1] In the overwhelming majority the neoplastic T cells have the phenotype of resting or activated CD4+ memory T cells (CD45RO+, CD29+). However, rare cases of CD8+ CTCL, with the clinicopathological features of MF or pagetoid reticulosis,[2–6] were also reported. In 1980, Jensen[10] described a fulminant MF-like case in which the neoplastic T lymphocytes were CD8+. Since that initial report, other aggressive cases have been reported.[11–16] However, because of the small number and the heterogeneity in clinical presentation and course of the cases published so far, CD8+ CTCL were not included as a separate group in the EORTC classification for primary cutaneous lymphomas.

In the present study we discuss the clinical, histological, immunohistochemical, and molecular features of 17

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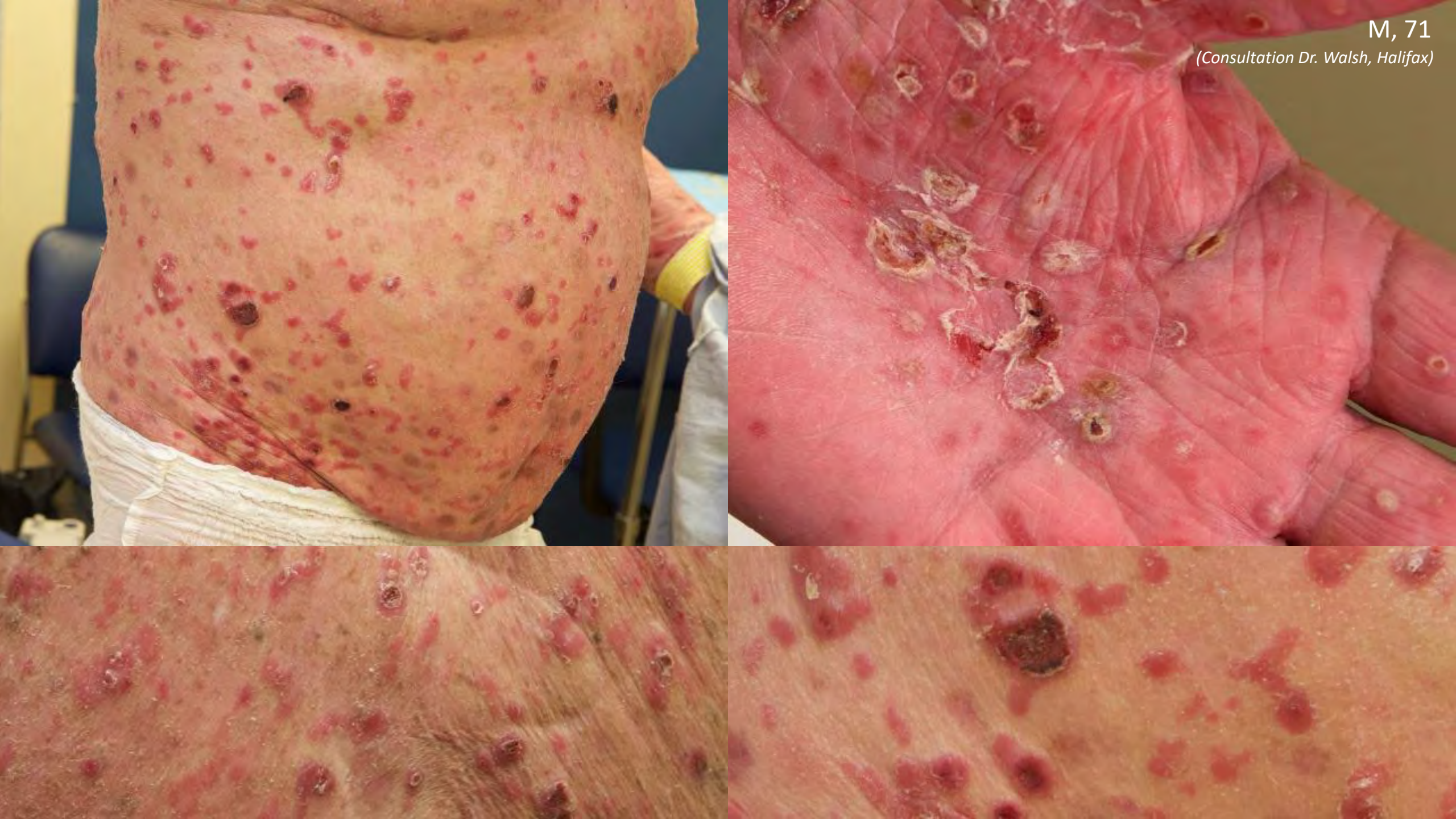
17 cases of CD8+ CTCL	
MF	2
Pagetoid reticulosis	2
Lymphomatoid papulosis	2
cALCL	2
SPTCL	1
Aggressive CD8+ CTCL:	8

CD2	2/7
CD3	8/8
CD4	0/7
CD5	2/7
CD7	6/7
CD8	8/8
CD30	0/7
CD45Ro	0/8
CD45Ra	7/8
TCRß	8/8
TIA-1	8/8
Granzyme B	2/8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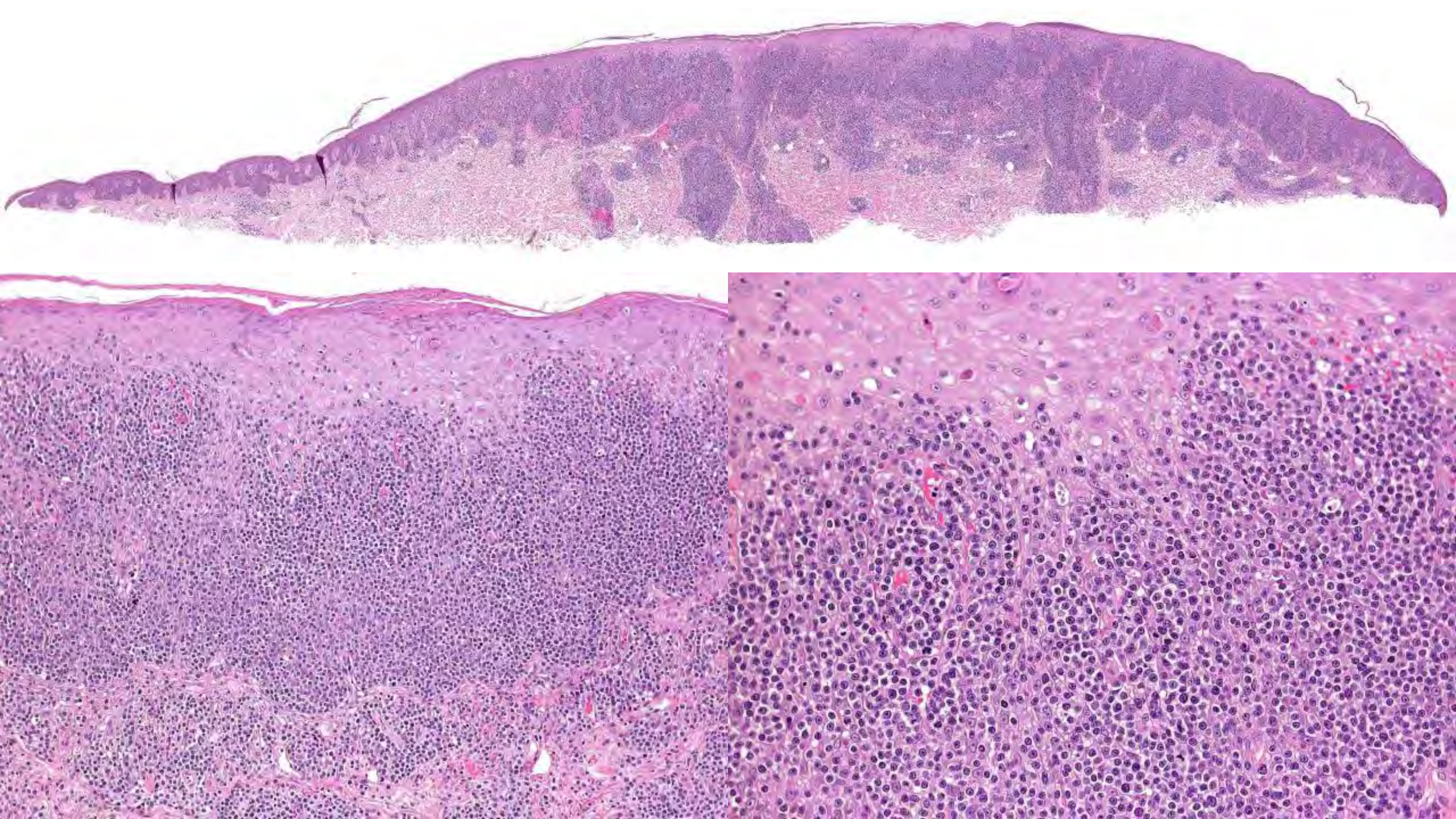
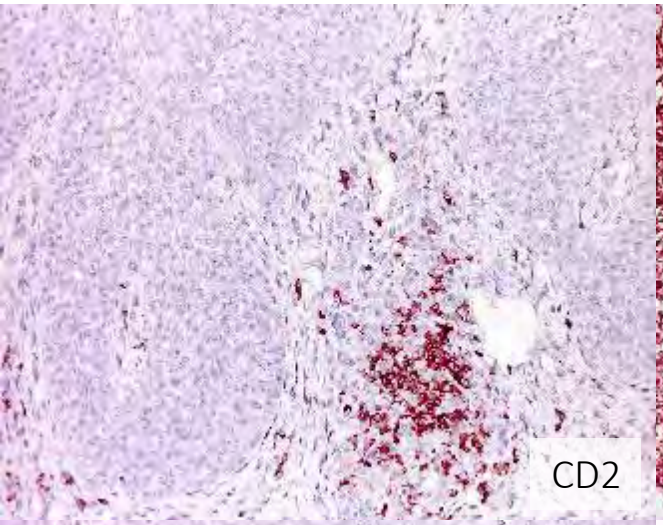
(Consultation Dr. Walsh, Halifax)




CD8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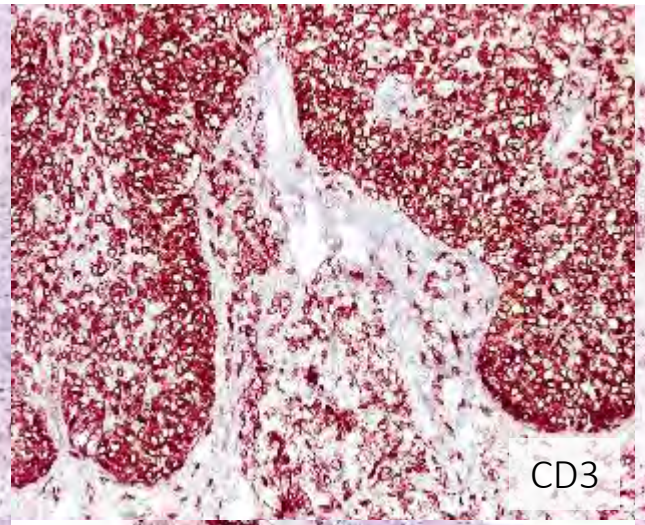
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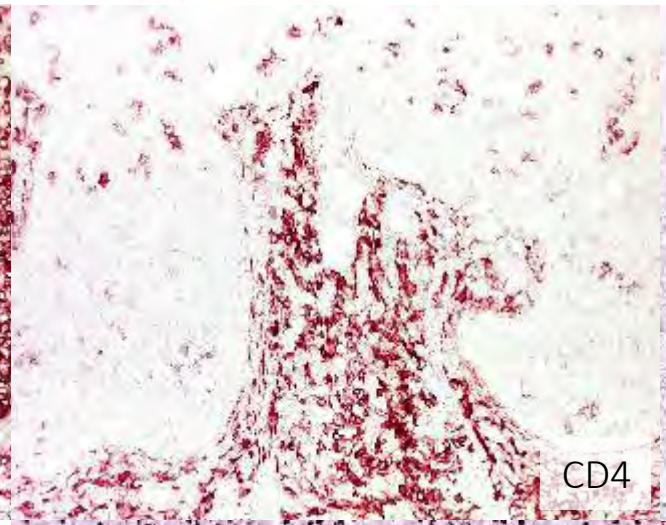
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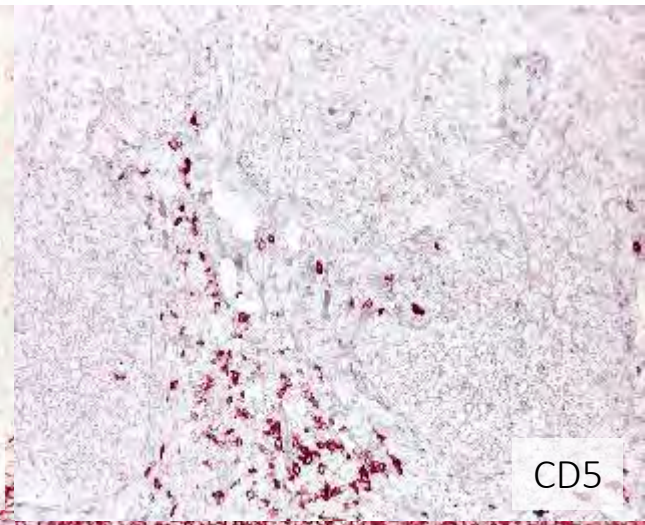
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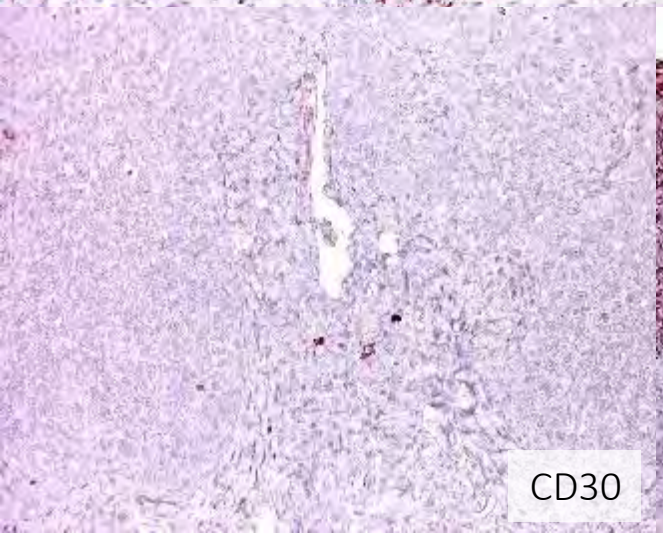
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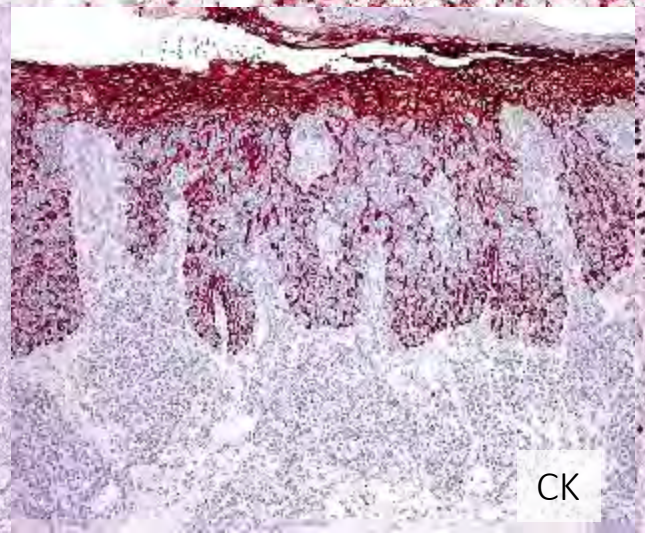
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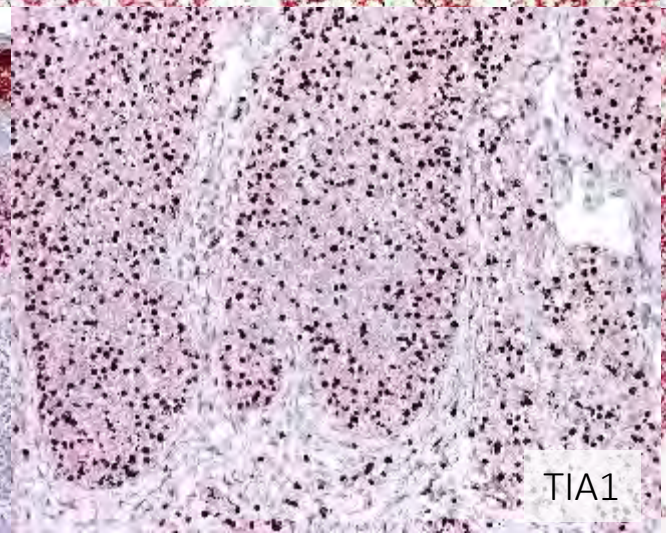
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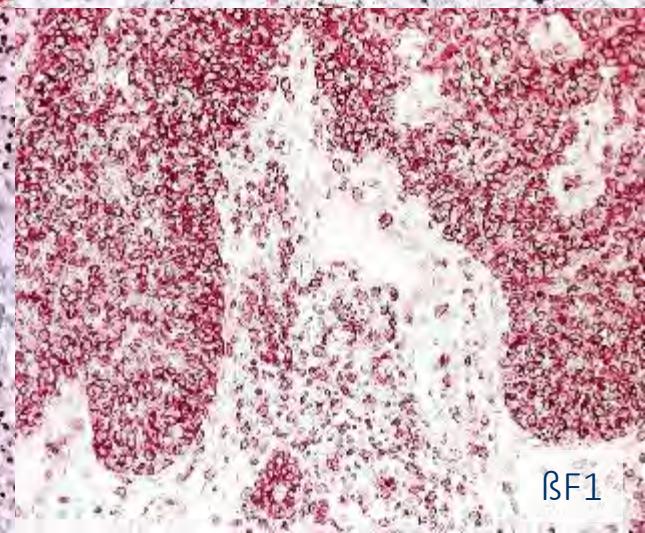
ßF1

Histopathology

SPECIAL TOPIC

Aggressive epidermotropic cutaneous CD8+ lymphoma: a cutaneous lymphoma with distinct clinical and pathological features. Report of an EORTC Cutaneous Lymphoma Task Force Workshop

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Aggressive epidermotropic cutaneous CD8+ lymphoma: a cutaneous lymphoma with distinct clinical and pathological features. Report of an EORTC Cutaneous Lymphoma Task Force Workshop

Abstract: Aggressive epidermotropic cutaneous CD8+ lymphoma is currently afforded provisional status in the WHO classification of lymphomas. An EORTC Workshop was convened to describe in detail the features of this putative neoplasm and evaluate its nosological status with respect to other cutaneous CD8+ lymphomas. *Methods and results:* Sixty-two CD8+ cases were analysed at the workshop; clinical details, often with photo-

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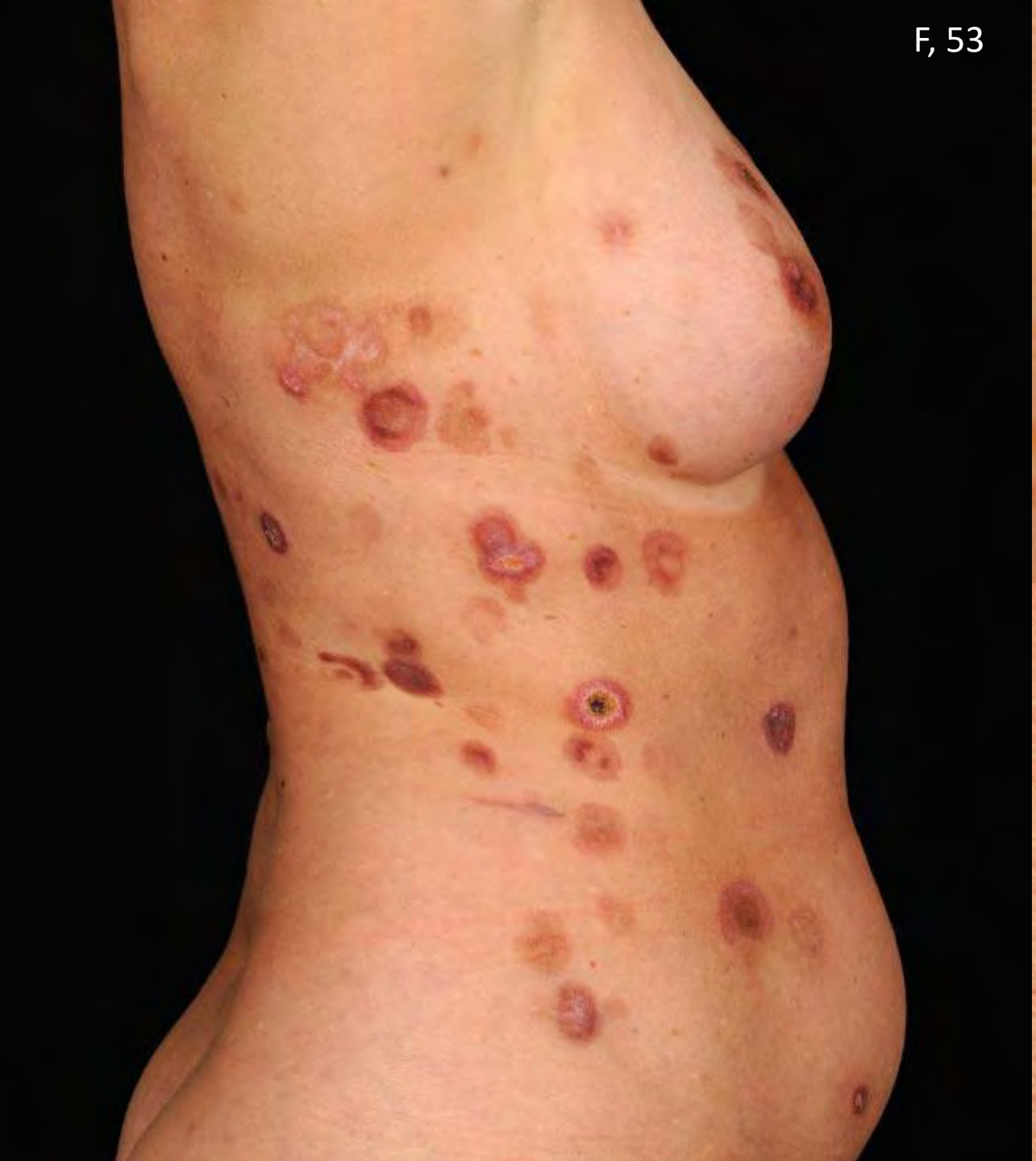
Eighteen cases had distinct features and conformed to the diagnosis of aggressive epidermotropic cutaneous CD8+ lymphoma.

The patients typically present with widespread plaques and tumors, often ulcerated and hemorrhagic, and have striking pagetoid epidermotropism histologically.

A CD8+ CD45RA+ CD45RO- CD2- CD5- CD56- phenotype, with 1 or more cytotoxic markers was found in 7/18 cases, with a very similar phenotype in the remainder.

The tumors seldom involve lymph nodes but mucosae and central nervous system involvement is not uncommon.

The prognosis is poor, with a median survival of 12 months.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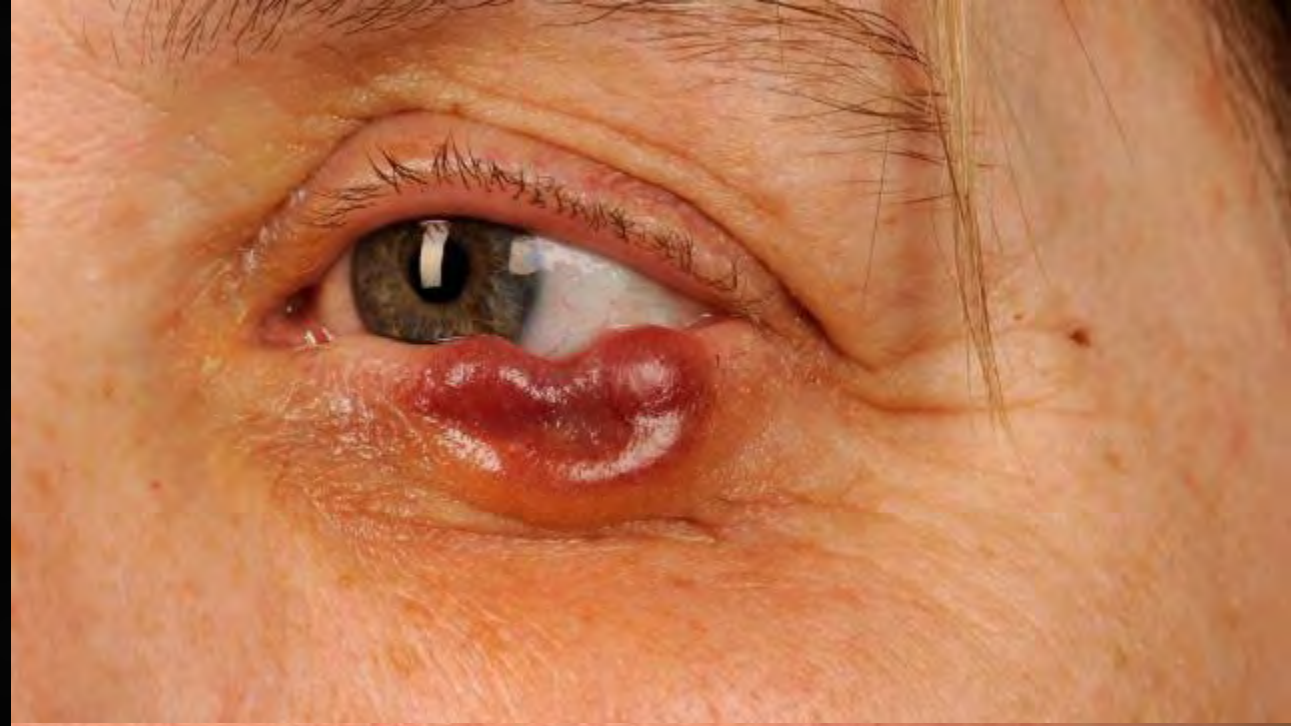
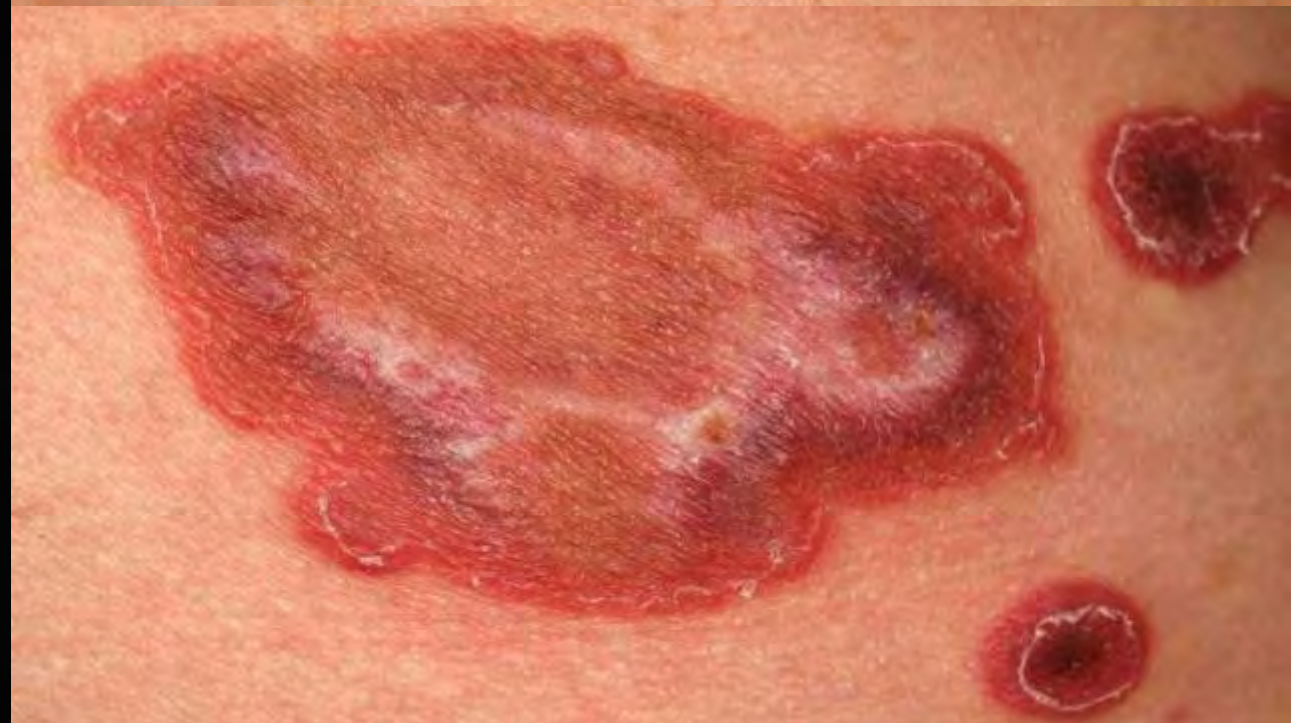

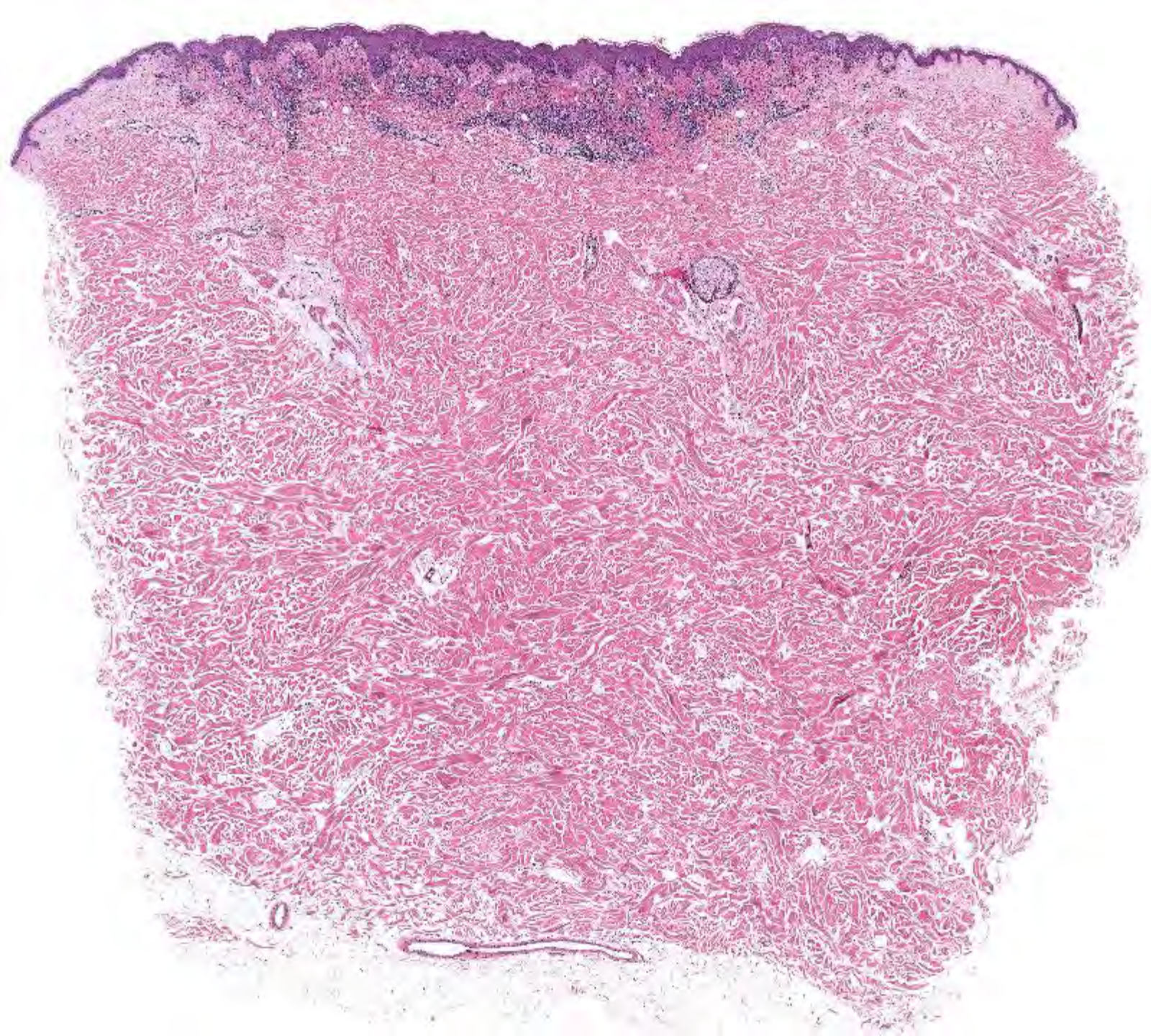

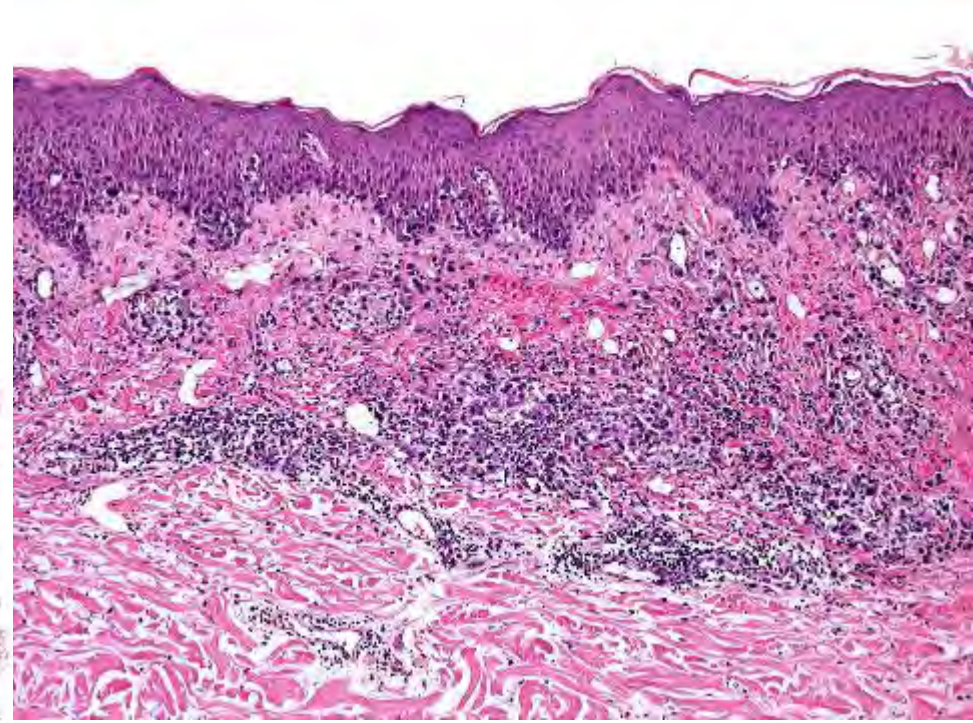

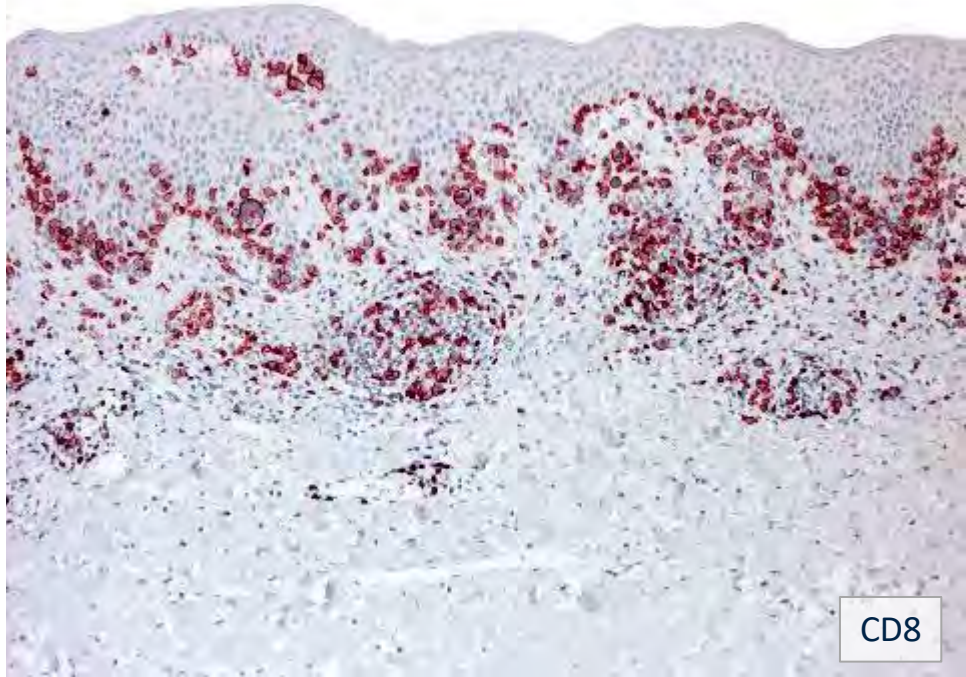
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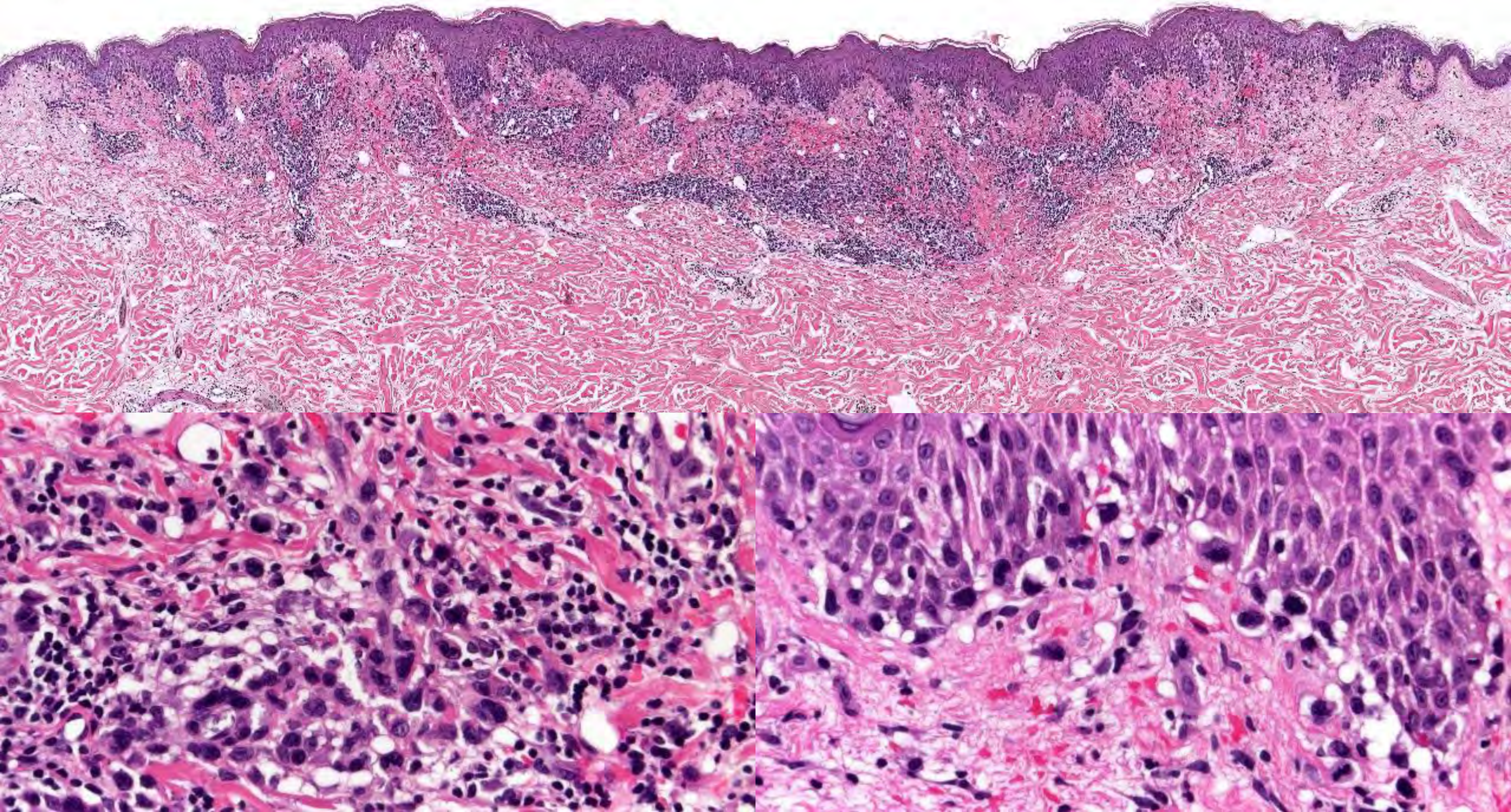

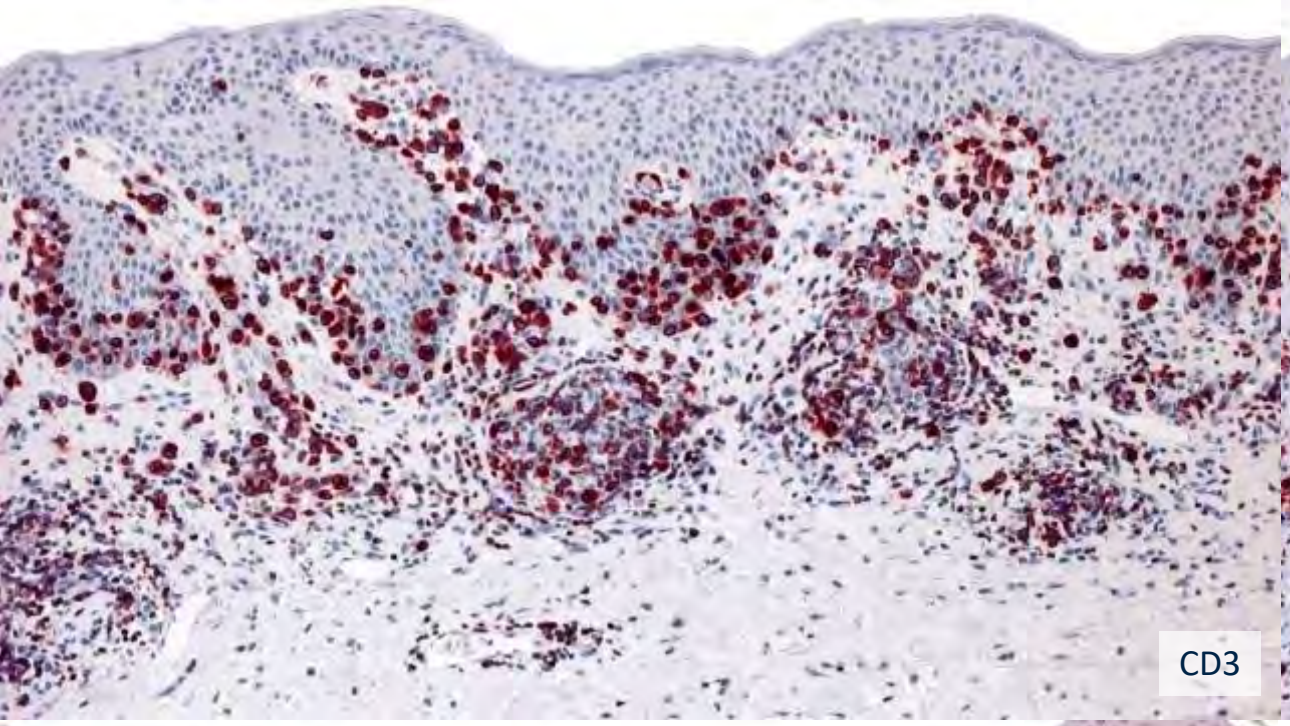
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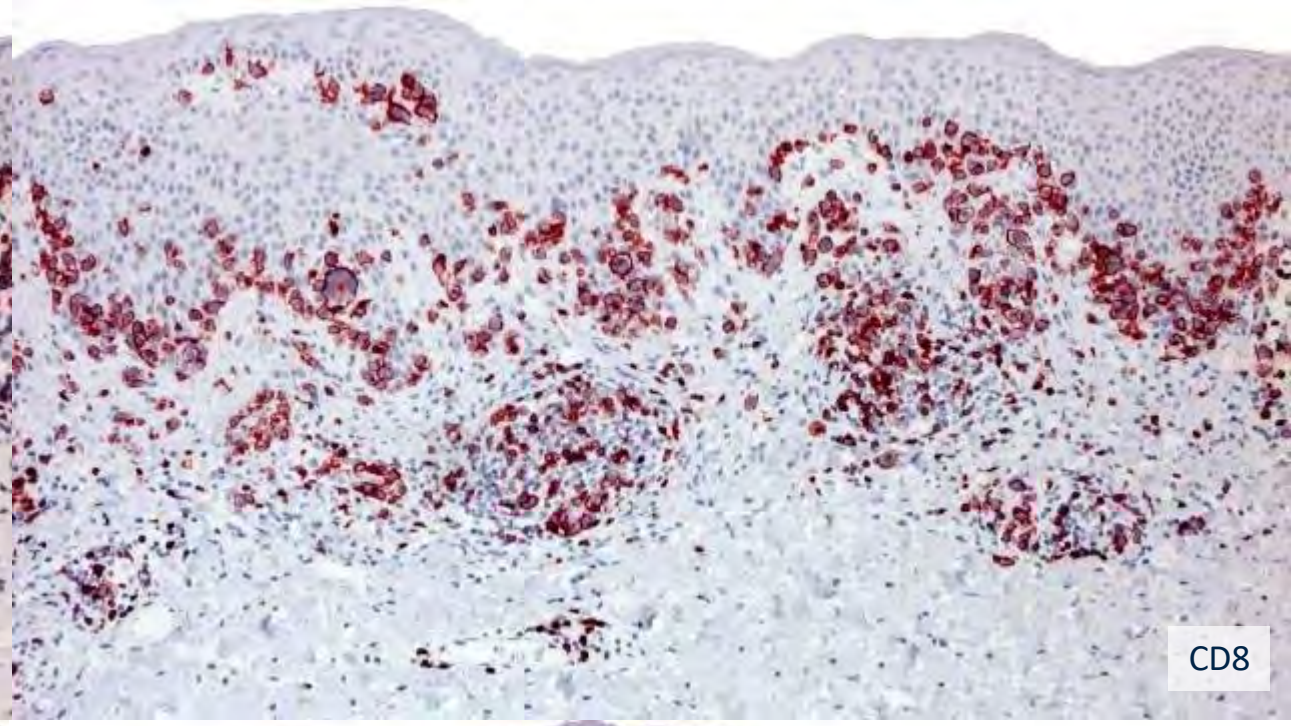
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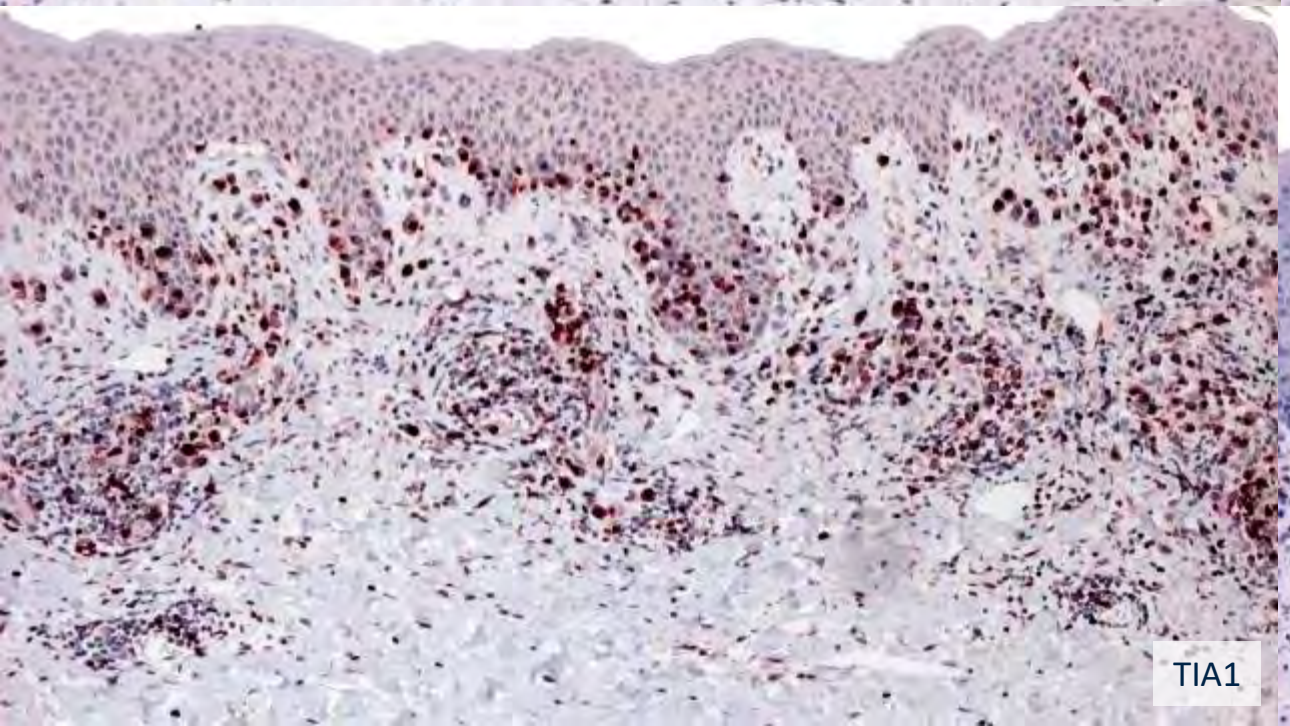
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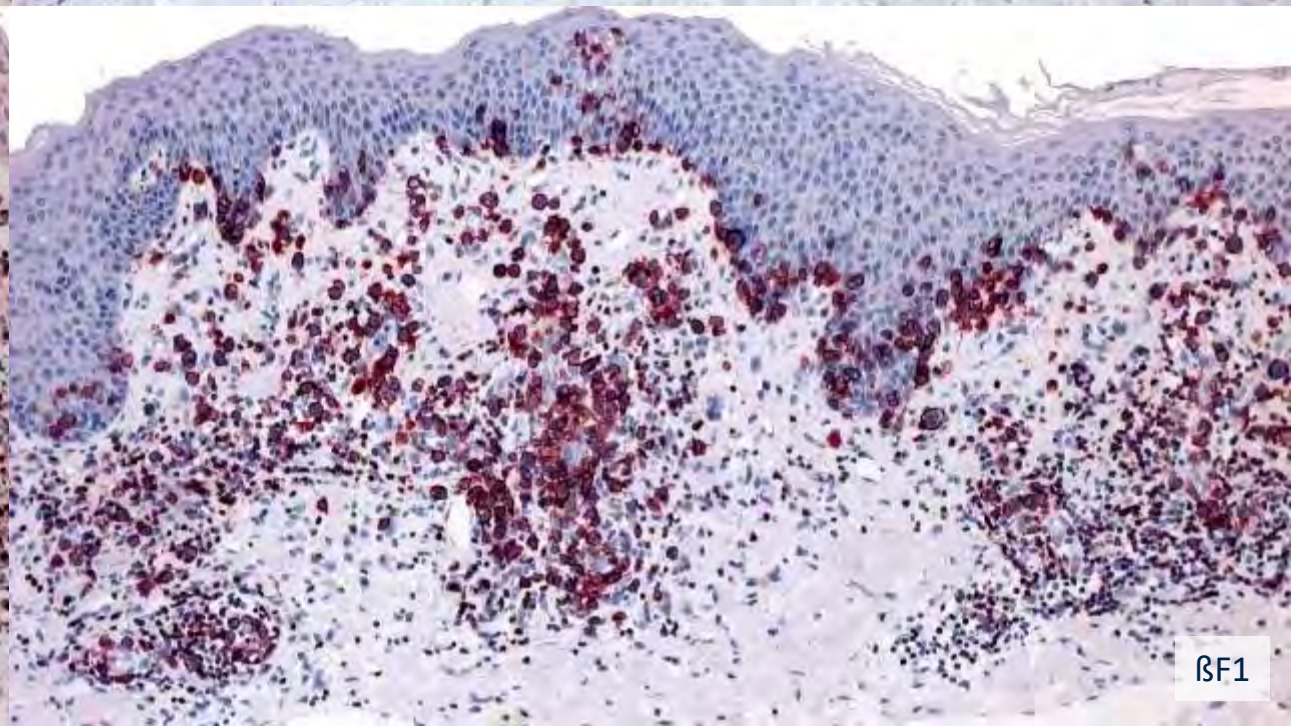
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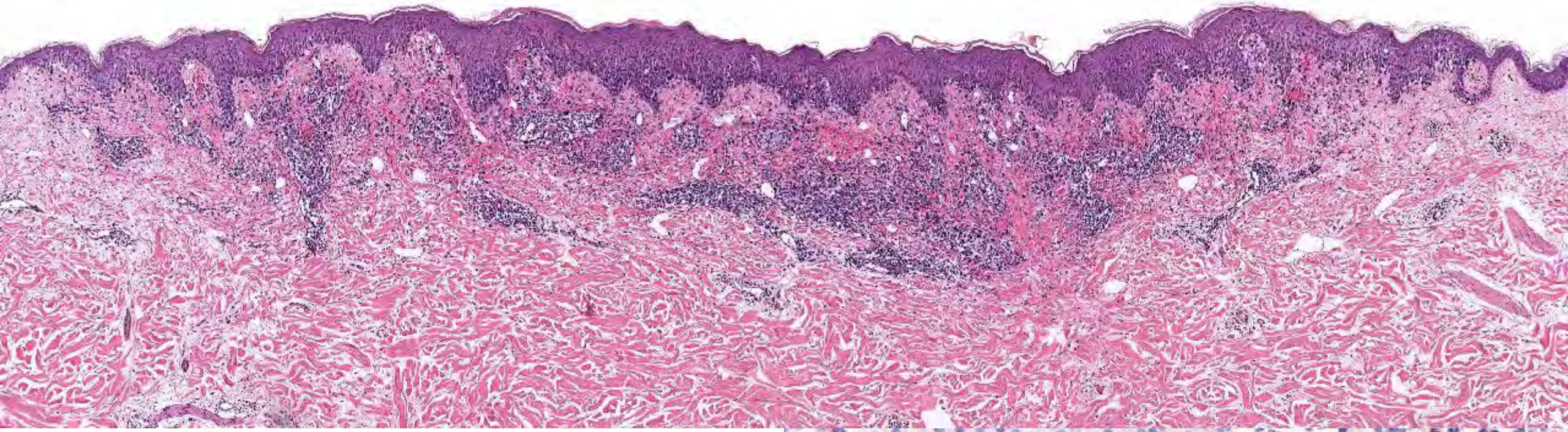

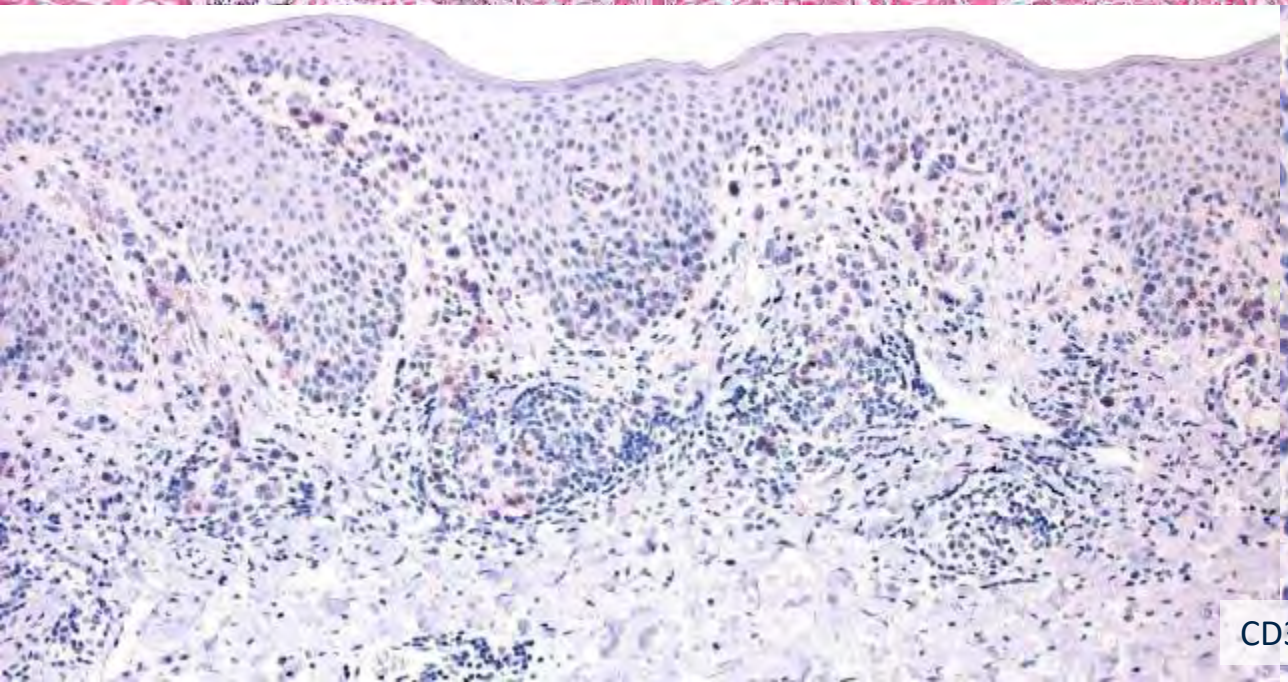

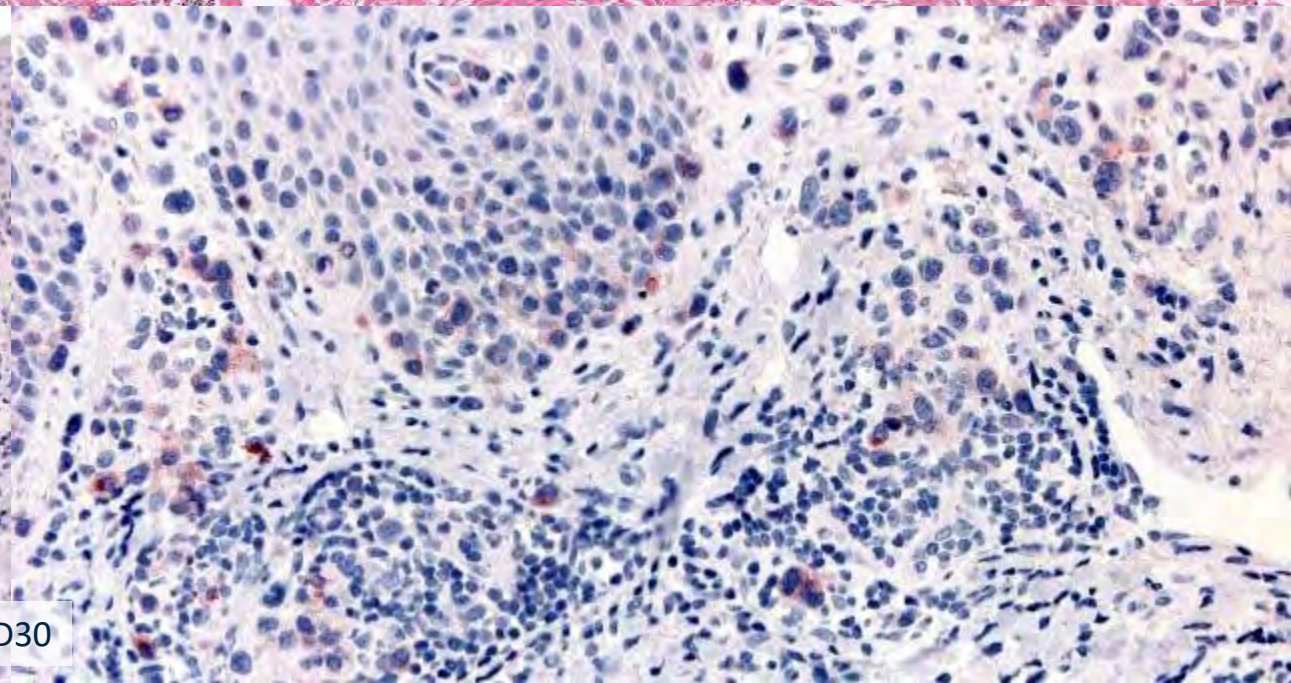

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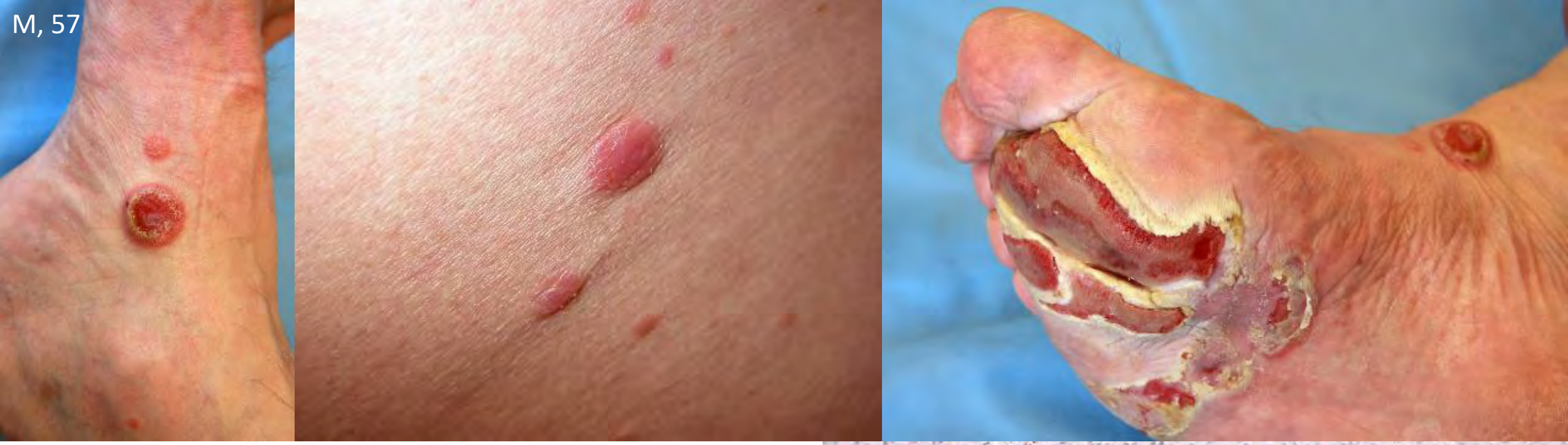
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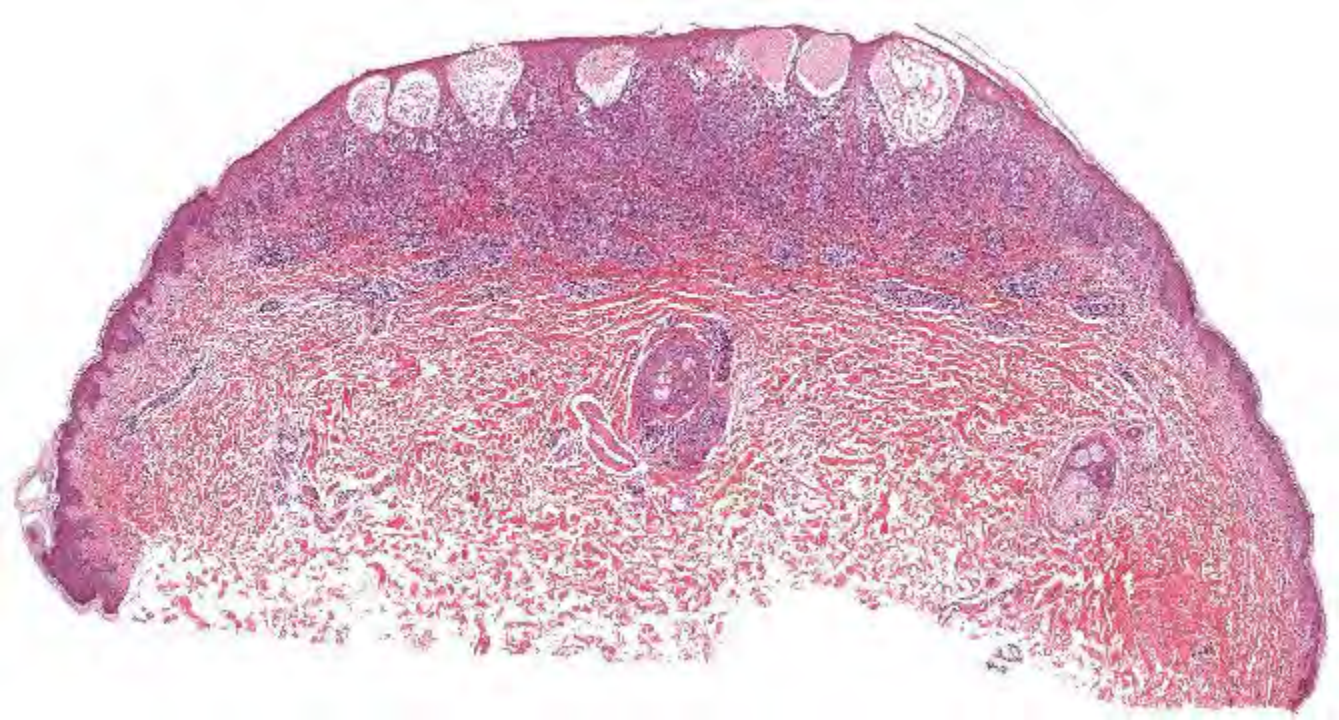
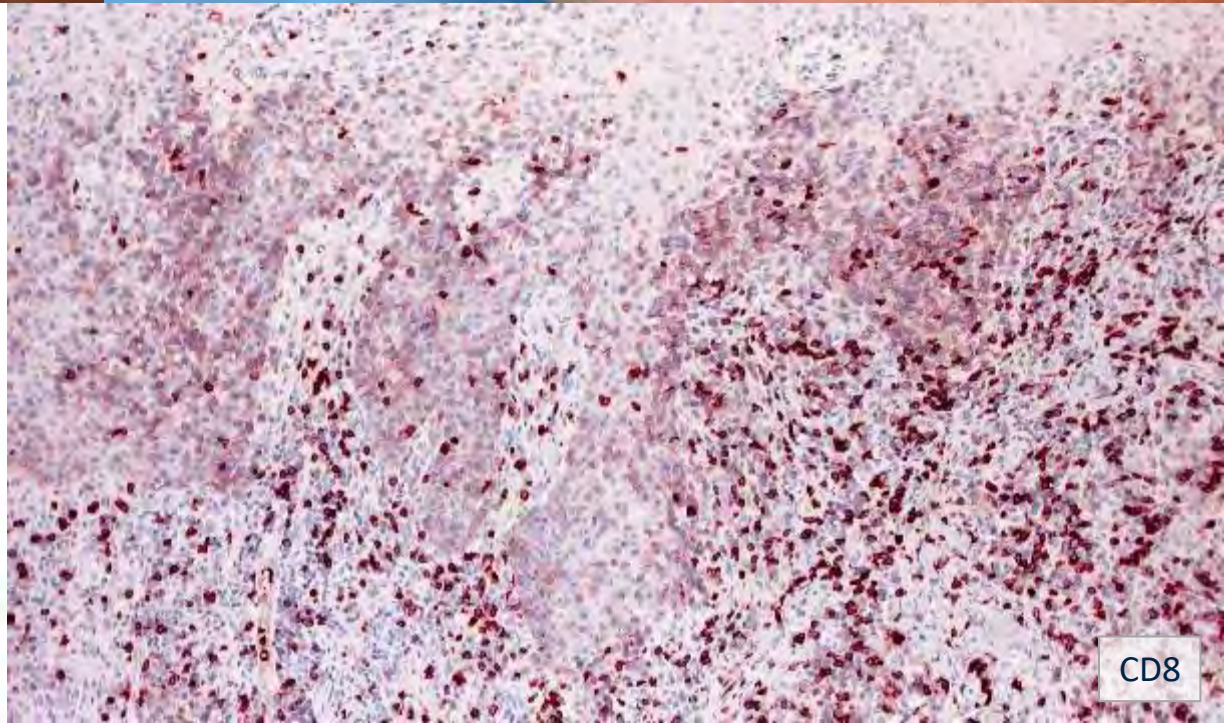
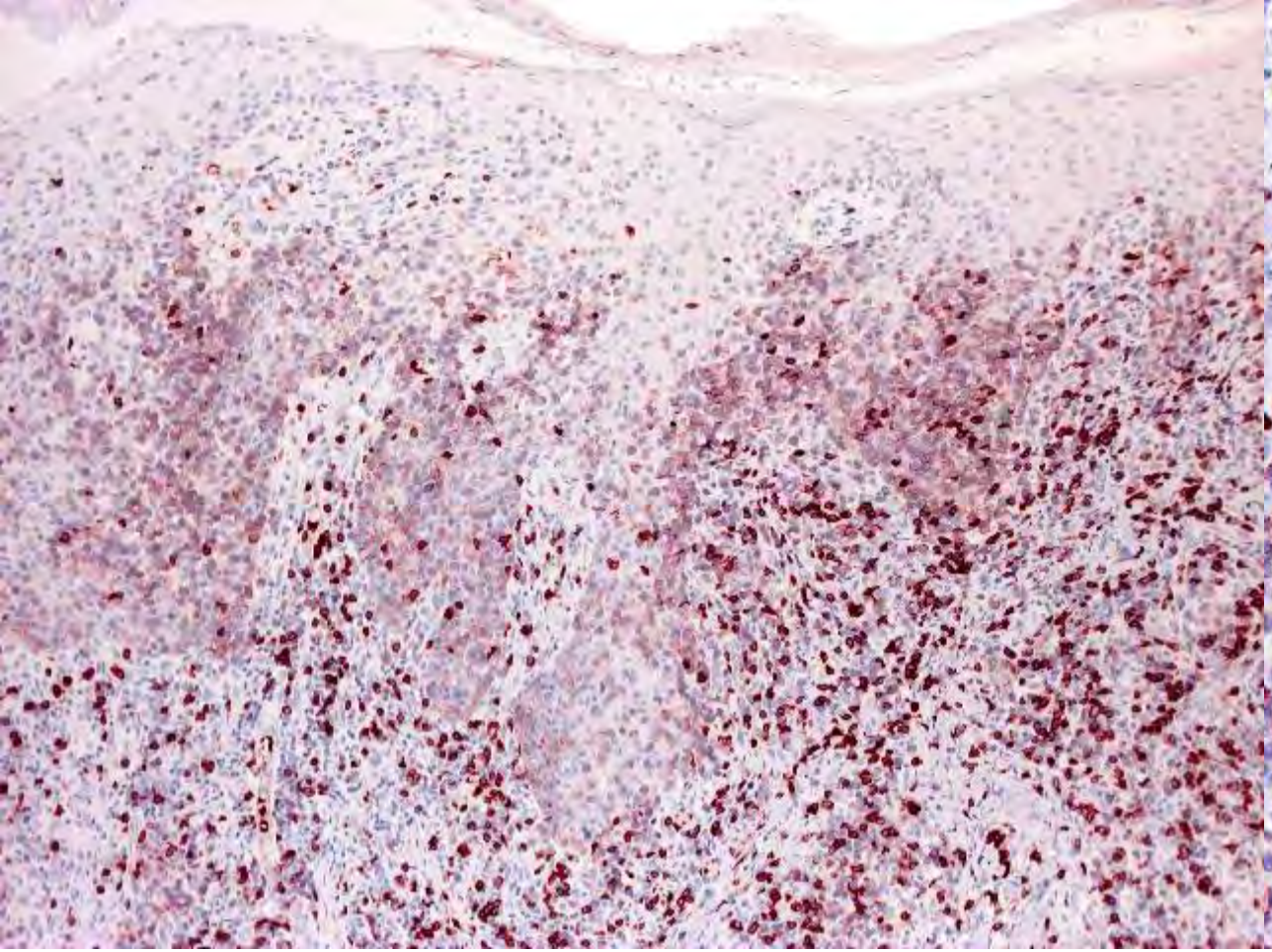
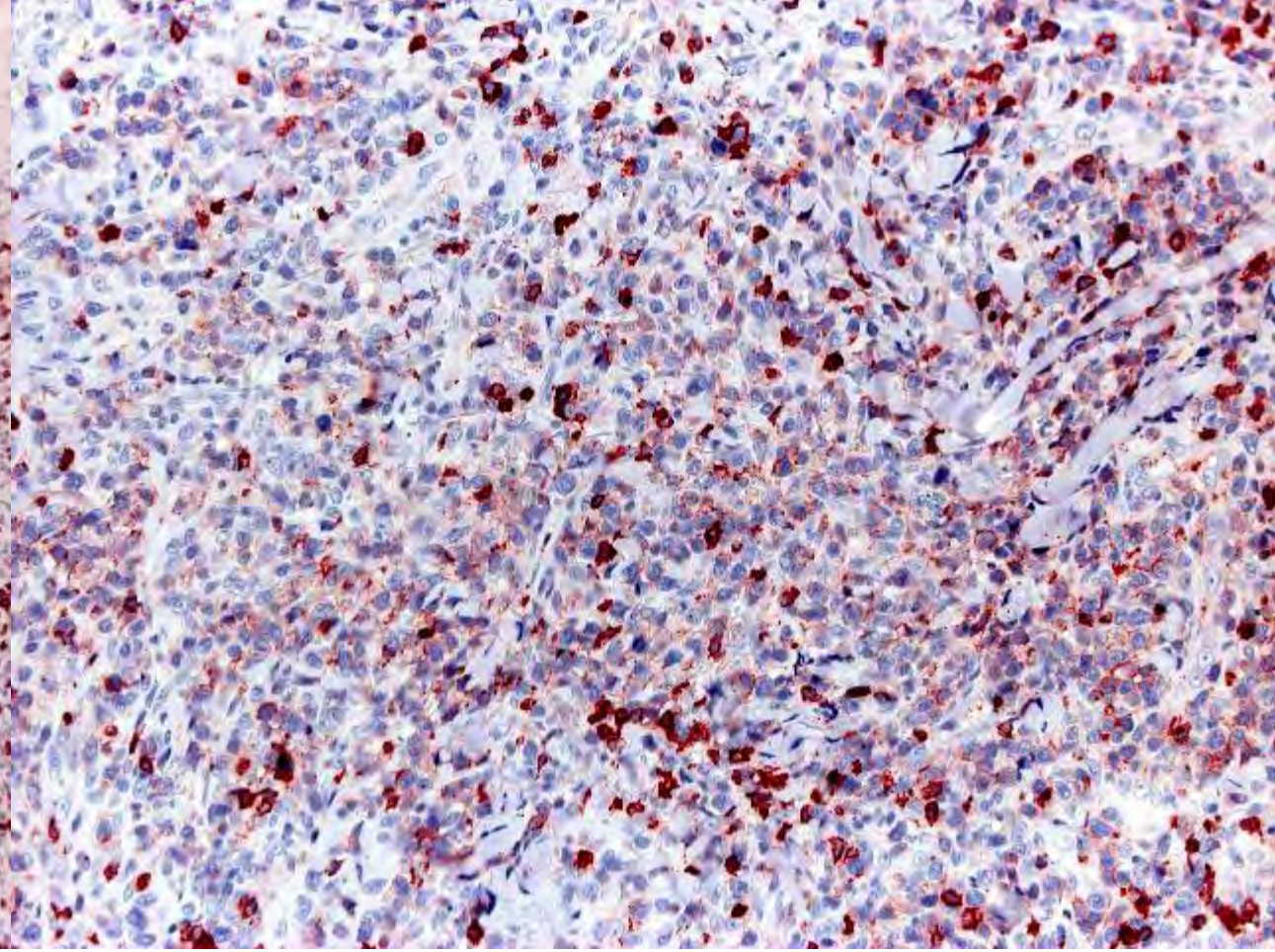



CD8





Pitfall: "dim" CD8 expression on neoplastic cells

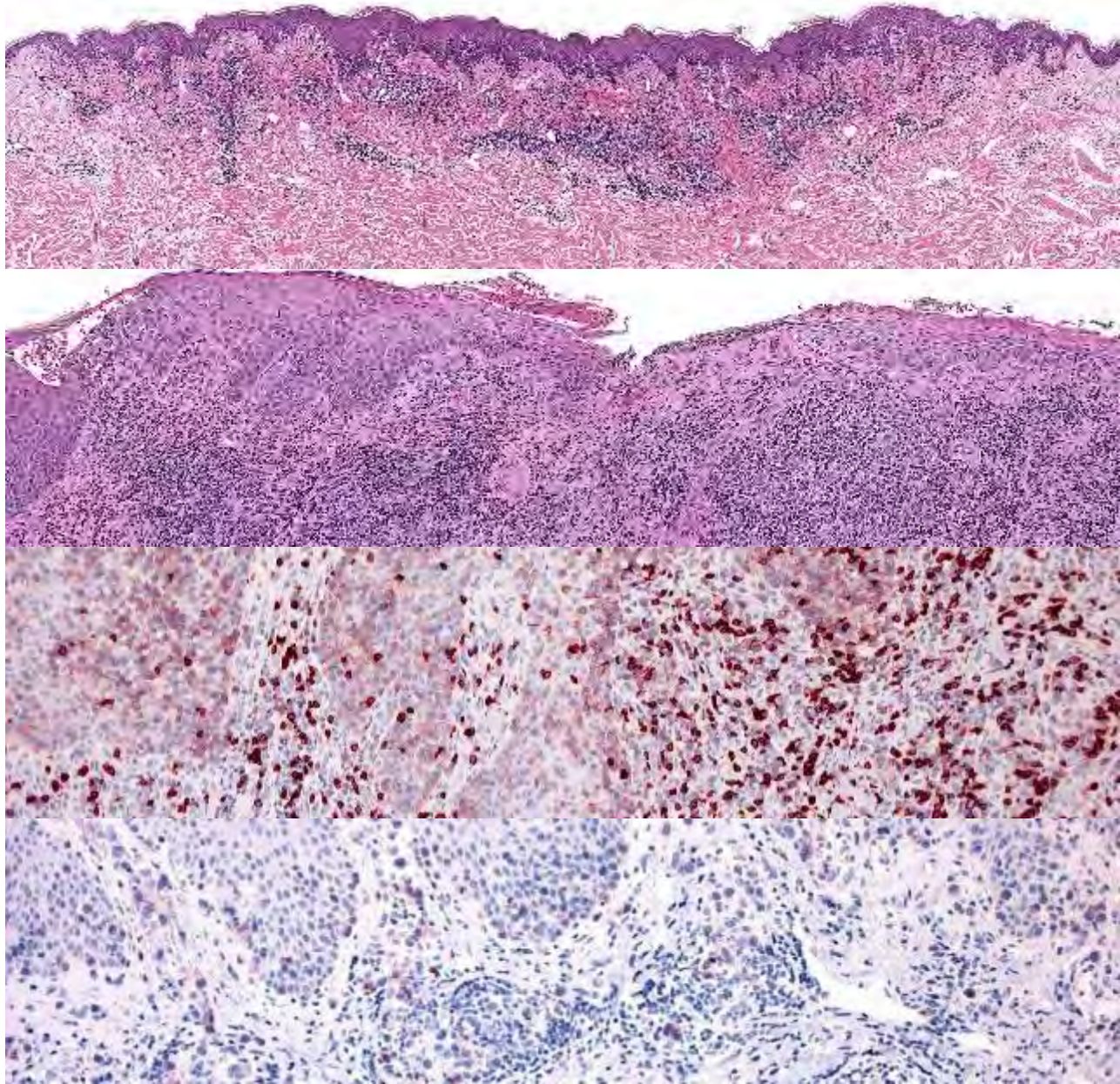
Main histopathological pitfalls

Infiltrate often flat, resembling mycosis fungoides

Lack of or minimal/focal epidermotropism in a given biopsy

Dim expression of CD8 – may seem negative if not properly fixed / stained

Low CD30 expression in some cases may suggest a lymphomatoid papulosis



Epidermotropic Precursor T-cell Lymphoma With Highly Aggressive Clinical Behavior Simulating Localized Pagetoid Reticulosis

Bernd Leinweber, MD,* Andreas Chott, MD,† Helmut Kerl, MD,* and Lorenzo Cerroni, MD*

Abstract: We describe a 43-year-old patient with a solitary, eczematous plaque on his right nipple that had developed during the previous 6 weeks. Histopathology revealed a superficial band-like infiltrate of medium to large sized pleomorphic lymphocytes with striking epidermotropism. The tumor cells expressed a T-phenotype (CD3+, CD29+) and were CD30+, CD4−, and CD8-negative. A diagnosis of localized pagetoid reticulosis (Woringer-Kolopp disease) with possible large cell transformation was proposed. A cervical lymph node excised 2 months later showed features of a highly aggressive blastoid precursor T-cell lymphoma. Reevaluation of the skin lesion and of a tonsil specimen previously interpreted as benign hyperplasia showed features consistent with those observed in the lymph node. The disease was rapidly progressive, and the patient died 15 months after the first skin biopsy. [illegible]

Key Words: pagetoid reticulosis, Woringer-Kolopp, precursor T-cell lymphoma, cutaneous T-cell lymphoma

(Am J Dermatopathol 2007;29:392–394)

INTRODUCTION

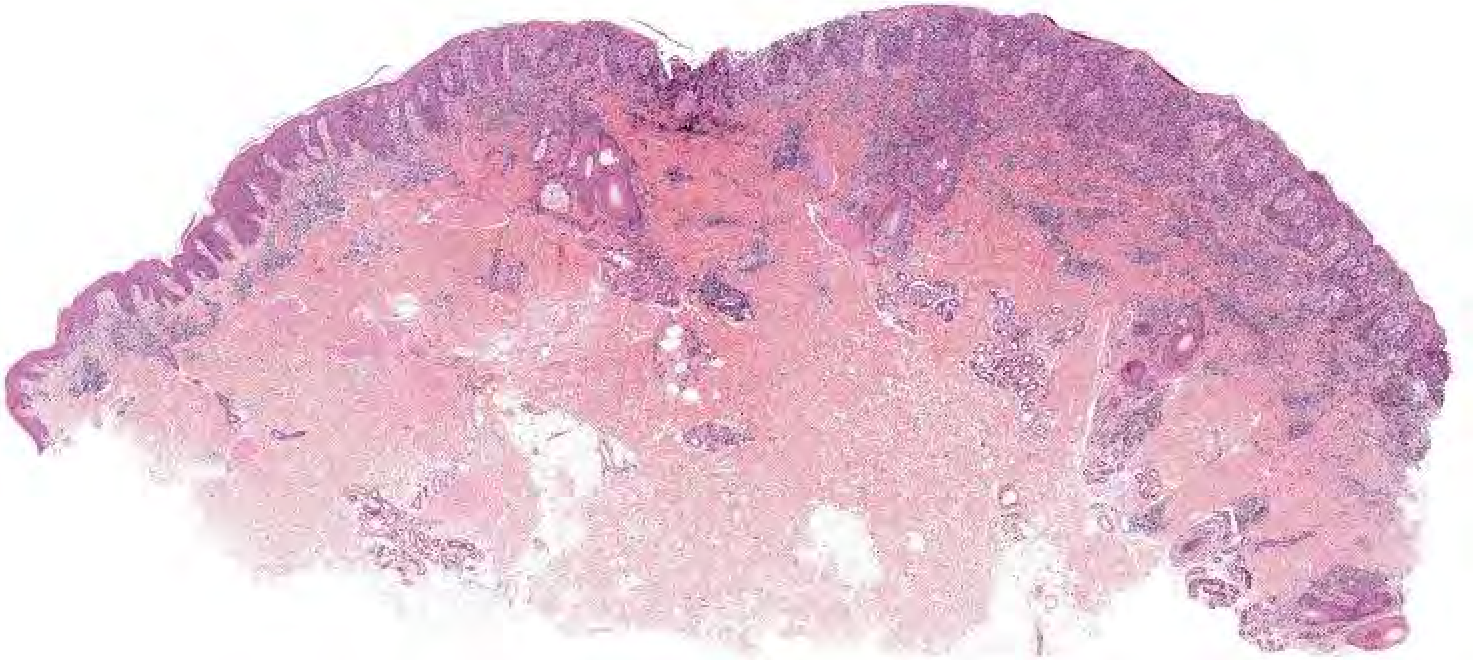
Localized pagetoid reticulosis (Woringer-Kolopp disease) [illegible]

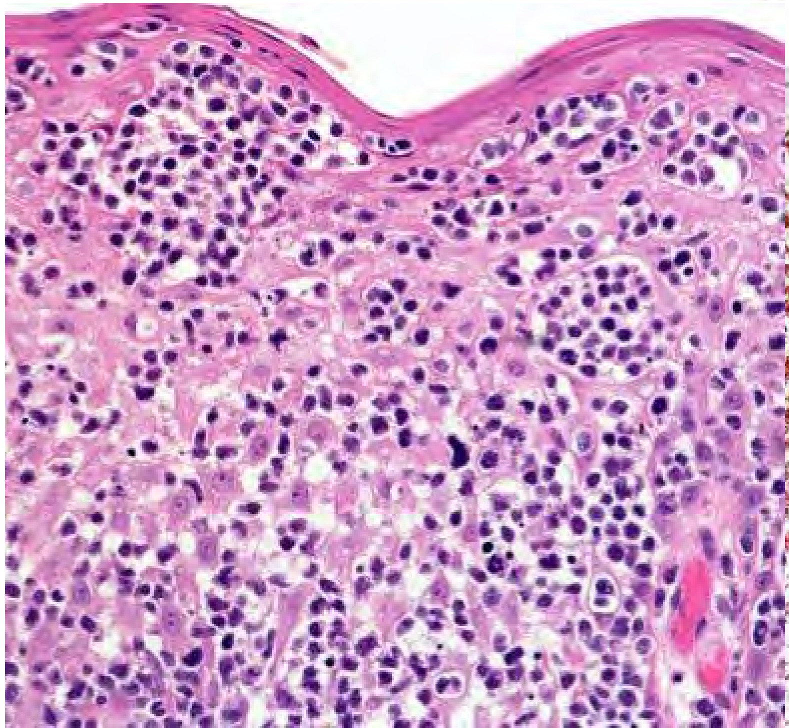
CASE REPORT

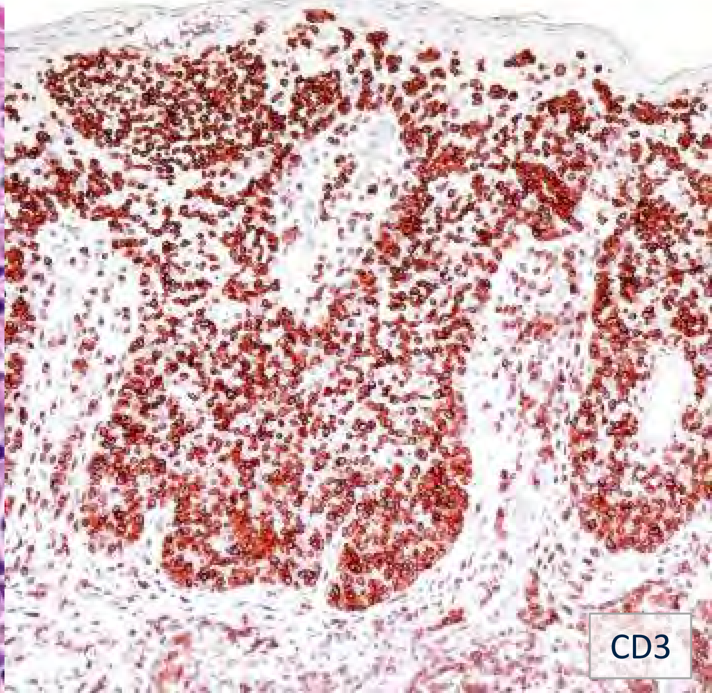
[illegible]

The patient's medical history was remarkable for an excision of his right pharyngeal tonsil 4 months earlier that was reported histopathologically as benign lymphoid hyperplasia. After the excision of the tonsil and before the appearance of the lesion on the nipple, the patient suffered from recurring infections and fatigue. Peripheral blood was checked several times without pathological findings, and no suspicious lymph nodes could be detected.

[illegible]







T-Lymphoblastic Leukemia/Lymphoma With Annular Skin Rash and Epidermotropism

Parisa Mansoori, MD, Arash Taheri, MD,† Stacey S. O'Neill, MD, PhD,* and Omar P. Sangueza, MD*‡*

Abstract: Leukemia cutis is uncommon in patients with acute lymphoblastic leukemia. It typically presents with dermal papules or subcutaneous nodules, with no epidermal or upper papillary dermal involvement on histopathology. We present an unusual clinical presentation of leukemia cutis, with annular plaques and epidermotropism.

Key Words: leukemia cutis, acute lymphoblastic leukemia, epidermotropism, annular

Am J Dermatopathol 2018;40:676–678

INTRODUCTION

Leukemia cutis is unusual in patients with acute lymphoblastic leukemia (ALL). It occurs in less than 1% of patients.[1–3] Dermal papules and nodules and subcutaneous nodules are the most common presentation of skin involvement. The frequency of leukemia cutis is higher among children than adults.[1] B-ALL has a predilection for cutaneous involvement in comparison to T-ALL.[4,5] The head and neck are the most common sites for skin involvement in ALL.[4,5] Histologically, it

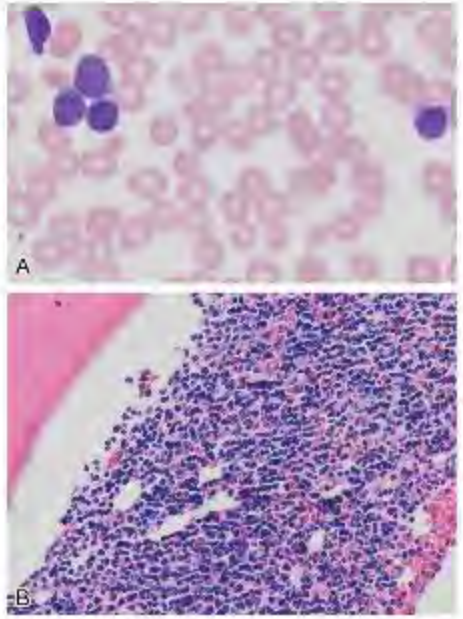


FIGURE 1. A, Circulating blasts in the peripheral blood (hematoxylin and eosin, ×400). B, Bone marrow core biopsy involved by T-ALL (hematoxylin and eosin, ×200).

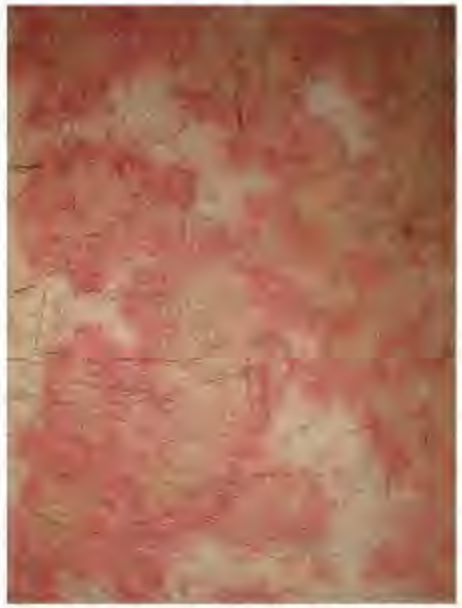


FIGURE 2. Annular erythematous plaques with petechia on the abdomen.

From the Departments of *Pathology, †Internal Medicine, and ‡Dermatology, Wake Forest School of Medicine, Winston-Salem, NC

The authors declare no conflicts of interest.

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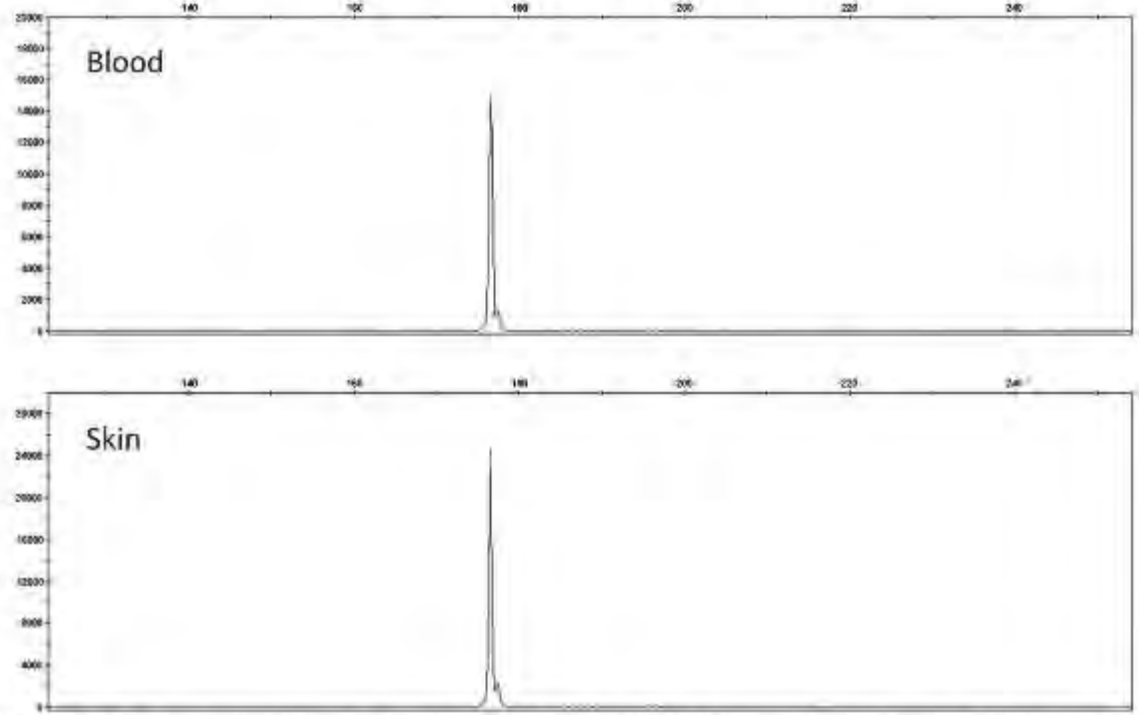


FIGURE 4. T-cell gene rearrangement in the patient's peripheral blood and skin biopsy showed the same T-cell clone in both.

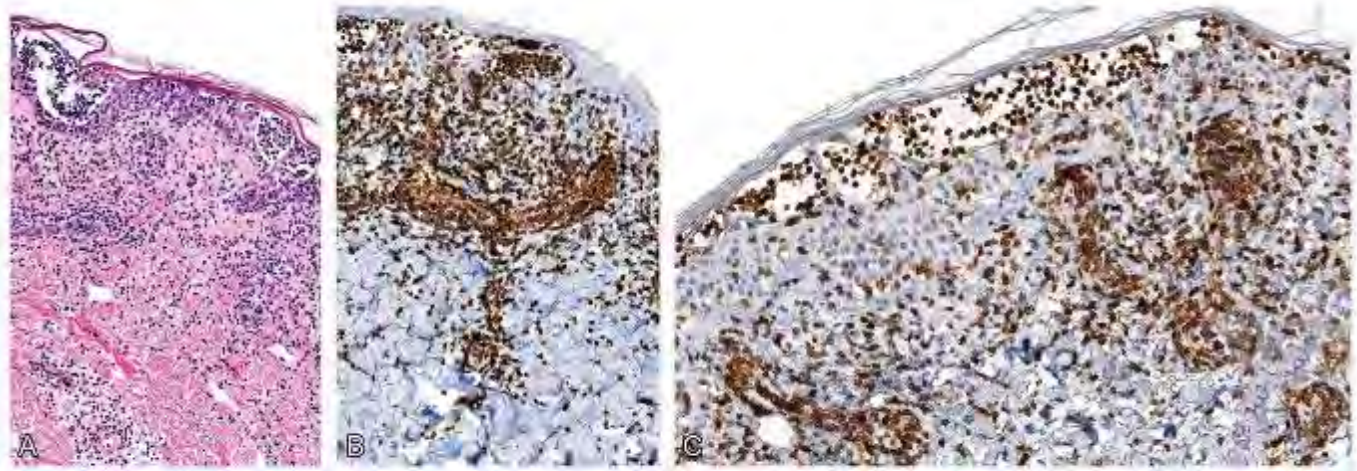
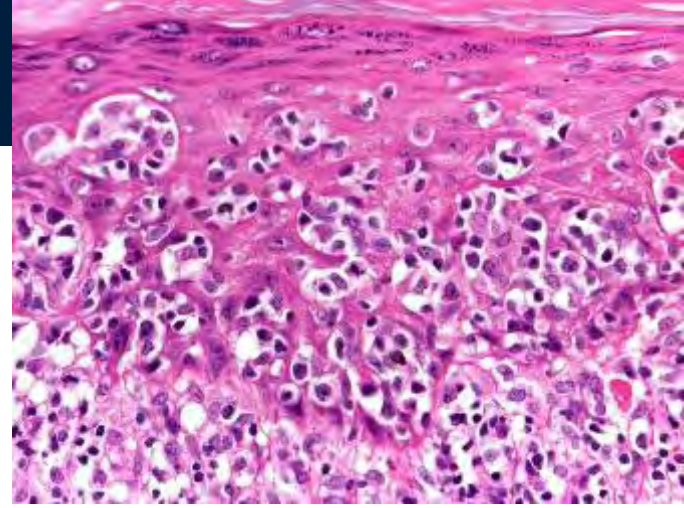


FIGURE 3. A, Skin biopsy with superficial perivascular and interstitial lymphoid infiltration and epidermotropism (hematoxylin and eosin, ×100), B, CD3 immunohistochemistry (×100) and C, CD7 immunohistochemistry (×100).

"Pagetoid" epidermotropism



Aggressive cutaneous lymphomas

Aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma

CD8+ by definition; CD30 usually negative (DDx from LyP type D); TCRß+ / TCRγ/δ–

Cutaneous γ/δ T-cell lymphoma

TCRγ/δ cytotoxic phenotype pre-requisite for diagnosis; TCRß may be coexpressed

Other NK/T-cell lymphomas and precursor T-cell (T-lymphoblastic) lymphomas

EBER-1+ in cutaneous extranodal NK/T-cell lymphoma, nasal-type

Indolent cutaneous lymphomas

Mycosis fungoides

Pagetoid epidermotropism mostly in cases with cytotoxic phenotype

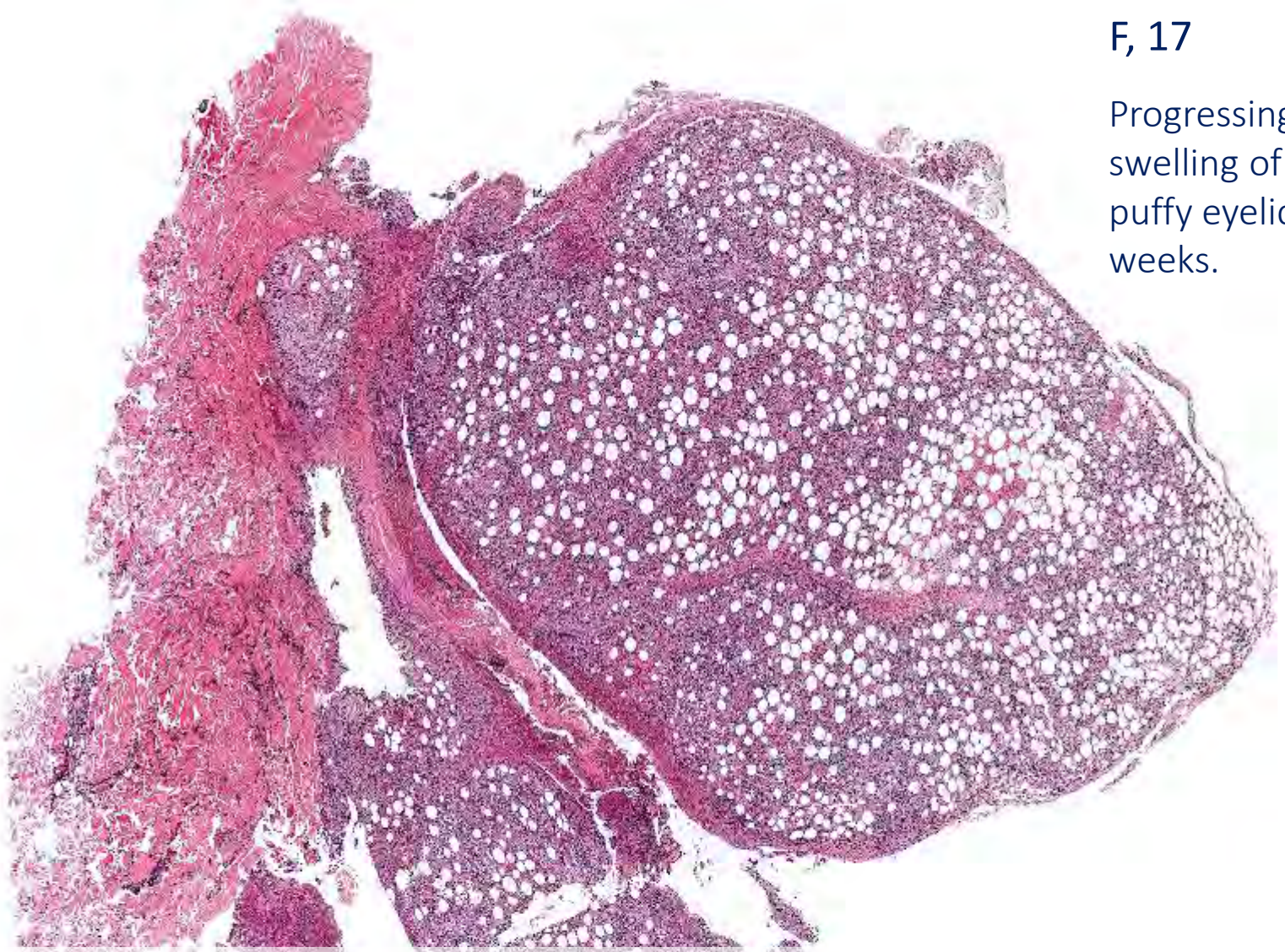
Lymphomatoid papulosis, type B or D

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

Cutaneous anaplastic large cell lymphoma with DUSP22-IRF4 (6p25) translocation

Pagetoid epidermotropism of CD30+ lymphocytes which are smaller than those of the dermal component

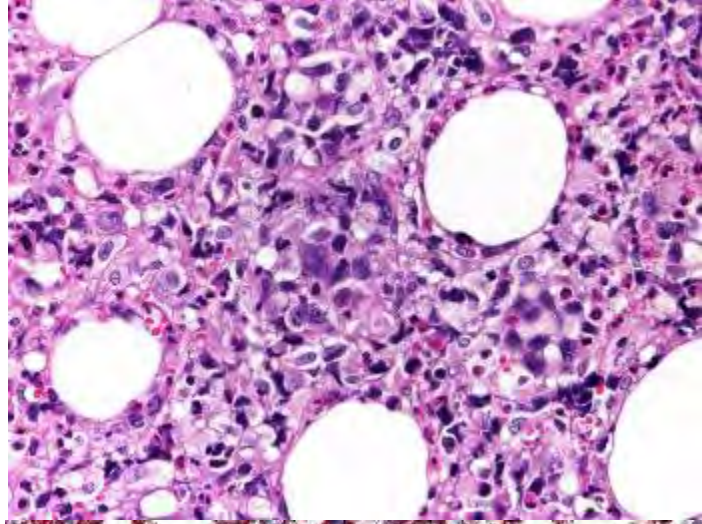
Exceedingly rare in benign conditions (e.g., vitiligo)

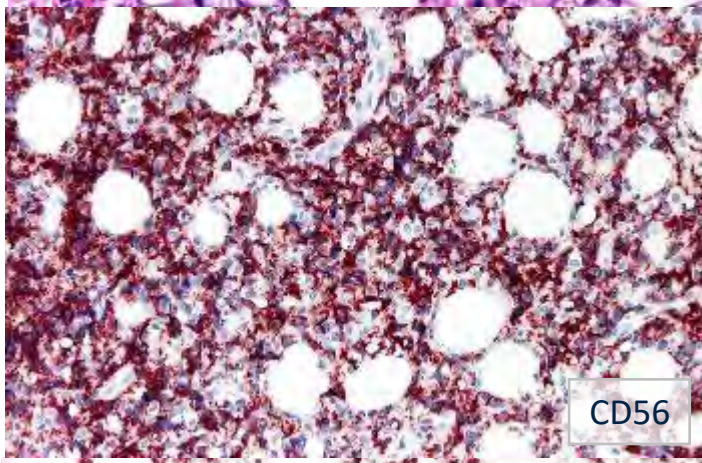


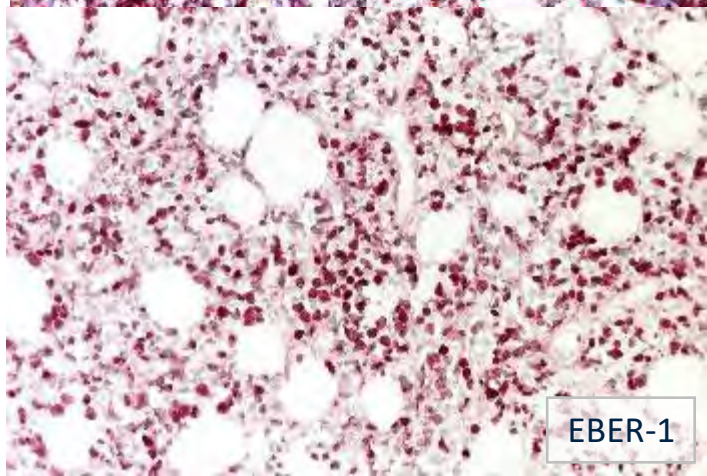
F, 17

Progressing, persistent swelling of the face and puffy eyelids for some weeks.

Extranodal NK/T-cell lymphoma, nasal-type







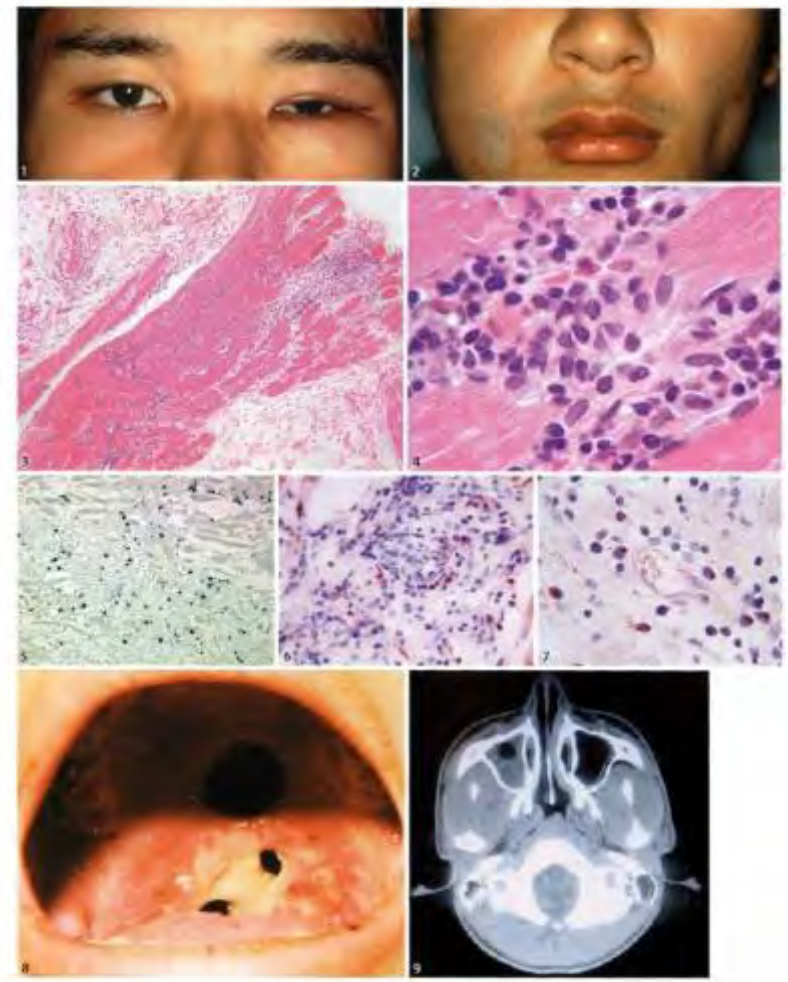
Cutaneous Extranodal NK/T-Cell Lymphoma, Nasal Type

- Cutaneous cases are not considered as a specific entity in current lymphoma classifications (yet primary cutaneous cases exist)
- *Essential diagnostic criteria:* Positivity of neoplastic cells for EBV (EBER-1-positivity mandatory for diagnosis); absence of an immune deficiency
- *Main differential diagnoses:* Cutaneous (peripheral) T-cell lymphoma, NOS with cytotoxic phenotype; Systemic hydroa vacciniforme lymphoproliferative disorder; Cutaneous gamma/delta T-cell lymphoma; Subcutaneous panniculitis-like T-cell lymphoma; MF, tumor stage with cytotoxic phenotype

1.5 Extranodal NK/T-cell Lymphoma

Nasal NK-cell lymphoma preceded by a puffy eyelid and swollen cheek due to intramuscular infiltration of Epstein-Barr virus-infected cells

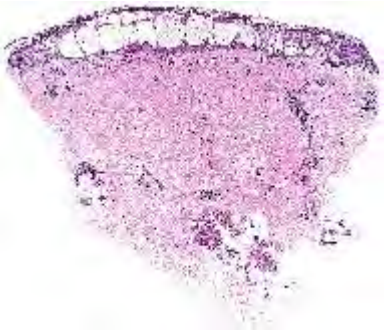
K. Iwatsuki and M. Ohtsuka



Main conditions behind facial swelling

Angioedema; Contact dermatitis; Erysipelas; After facial surgery (including subcutaneous facial emphysema); Burn; Tooth abscess; Some drug reactions.

Contact dermatitis

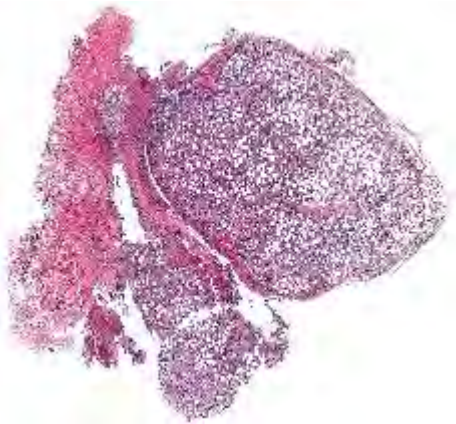


Morbihan disease

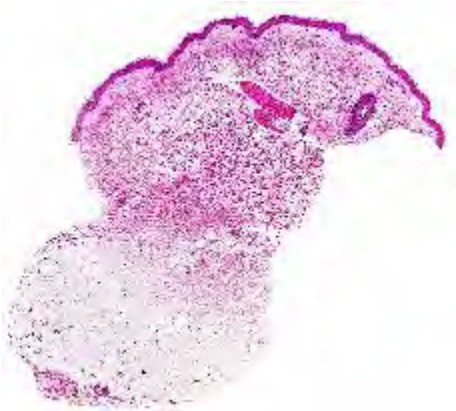
Emphysema

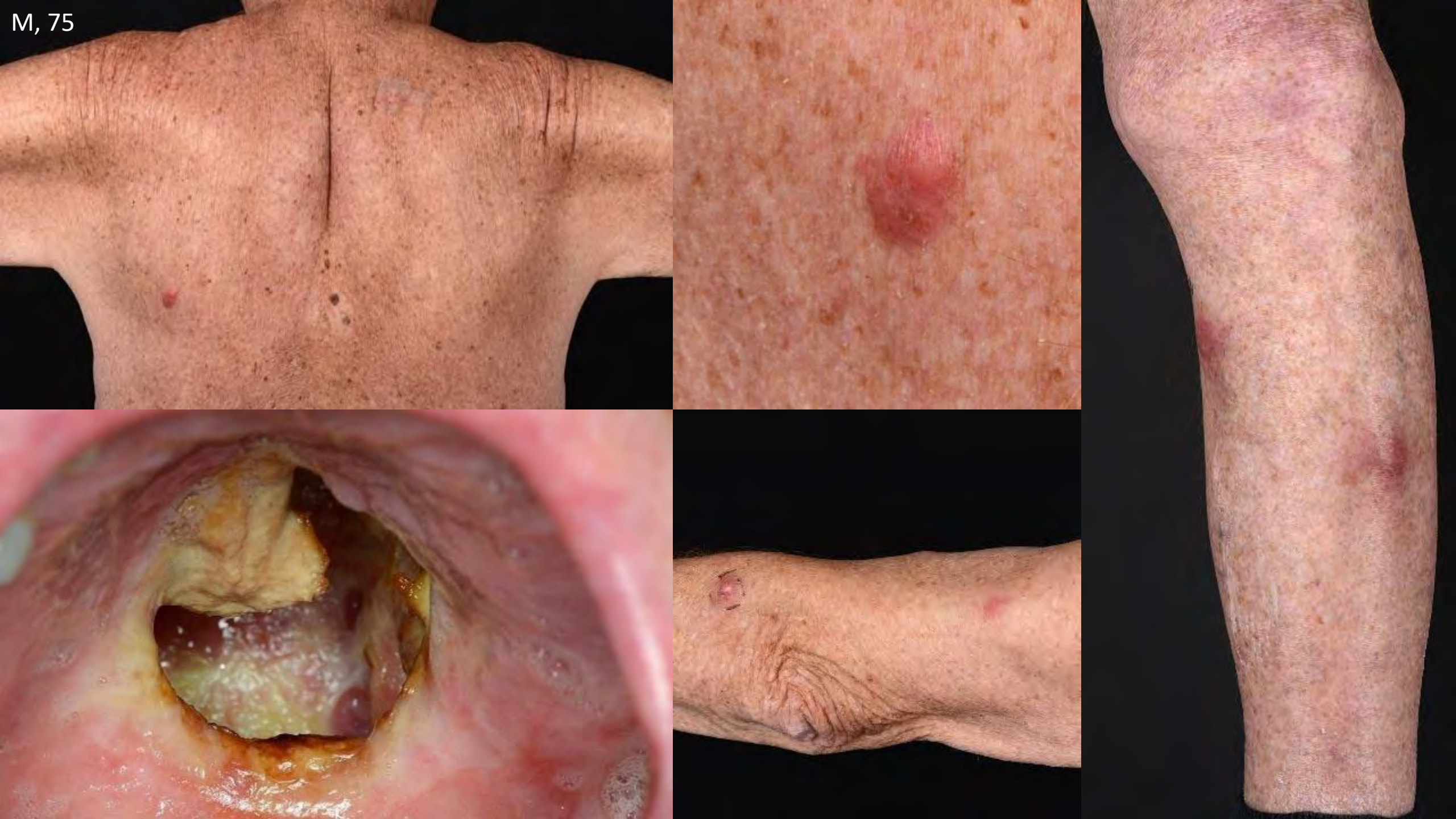
Filler reaction

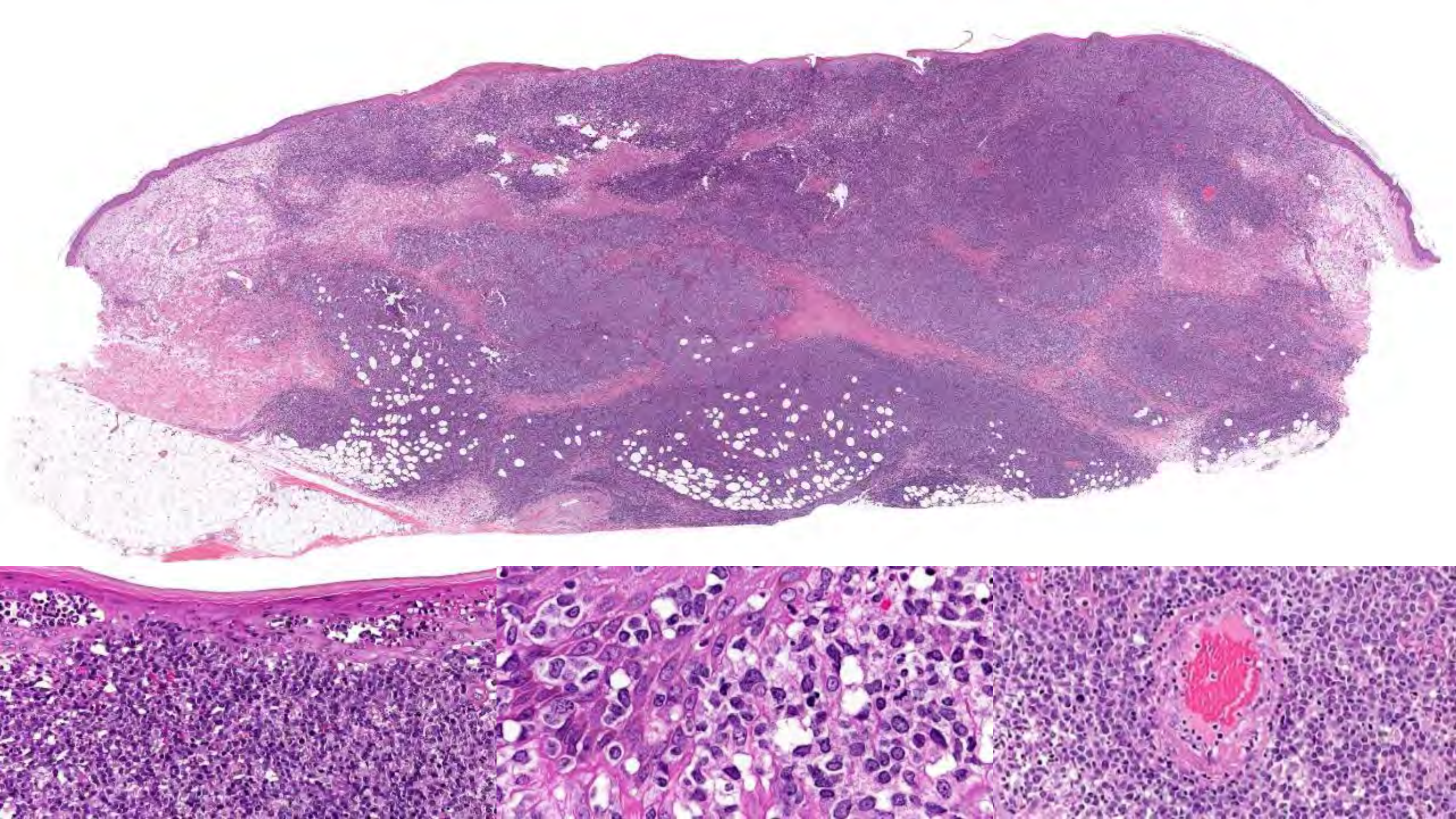
NK/T-cell lymphoma

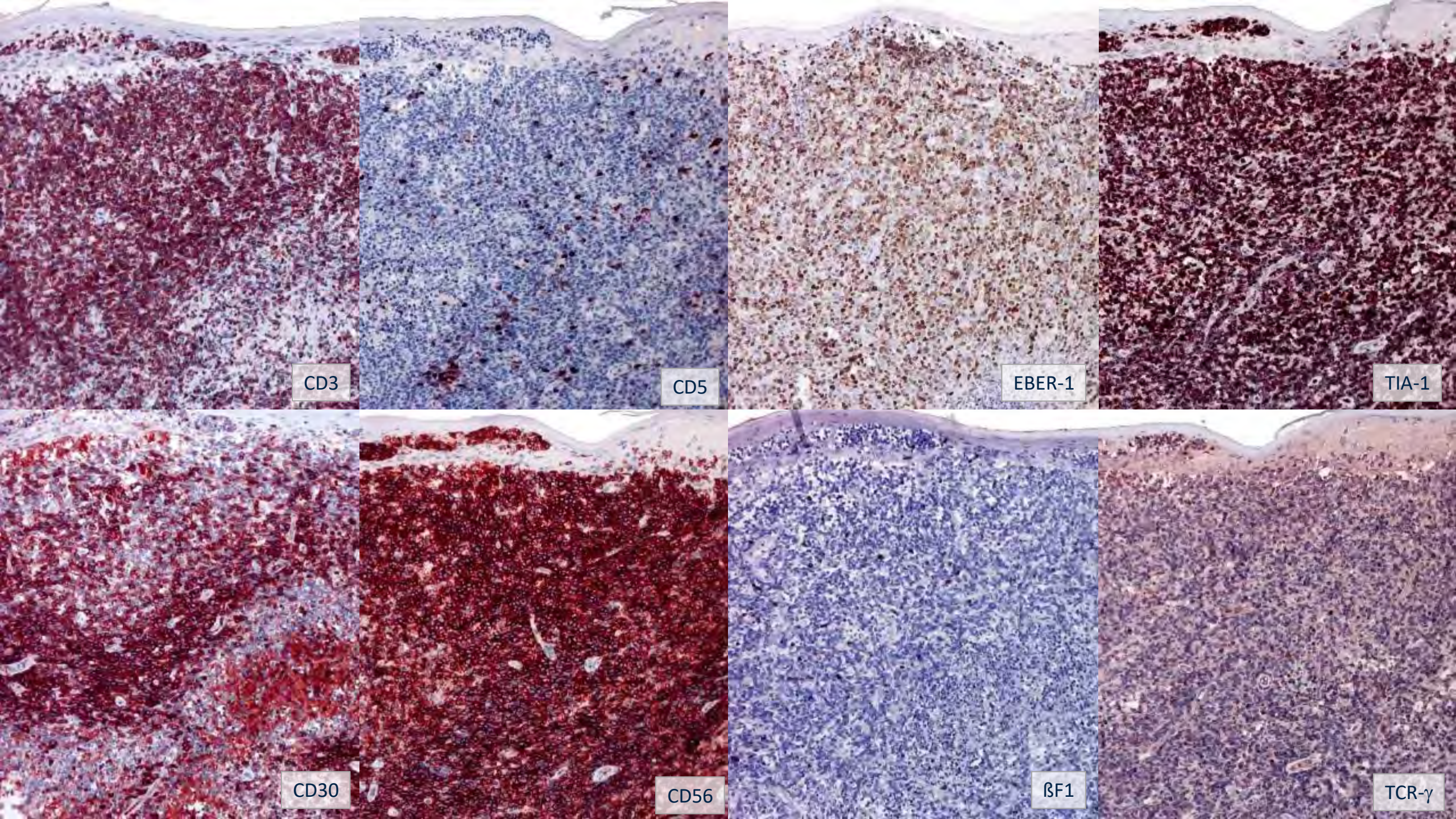


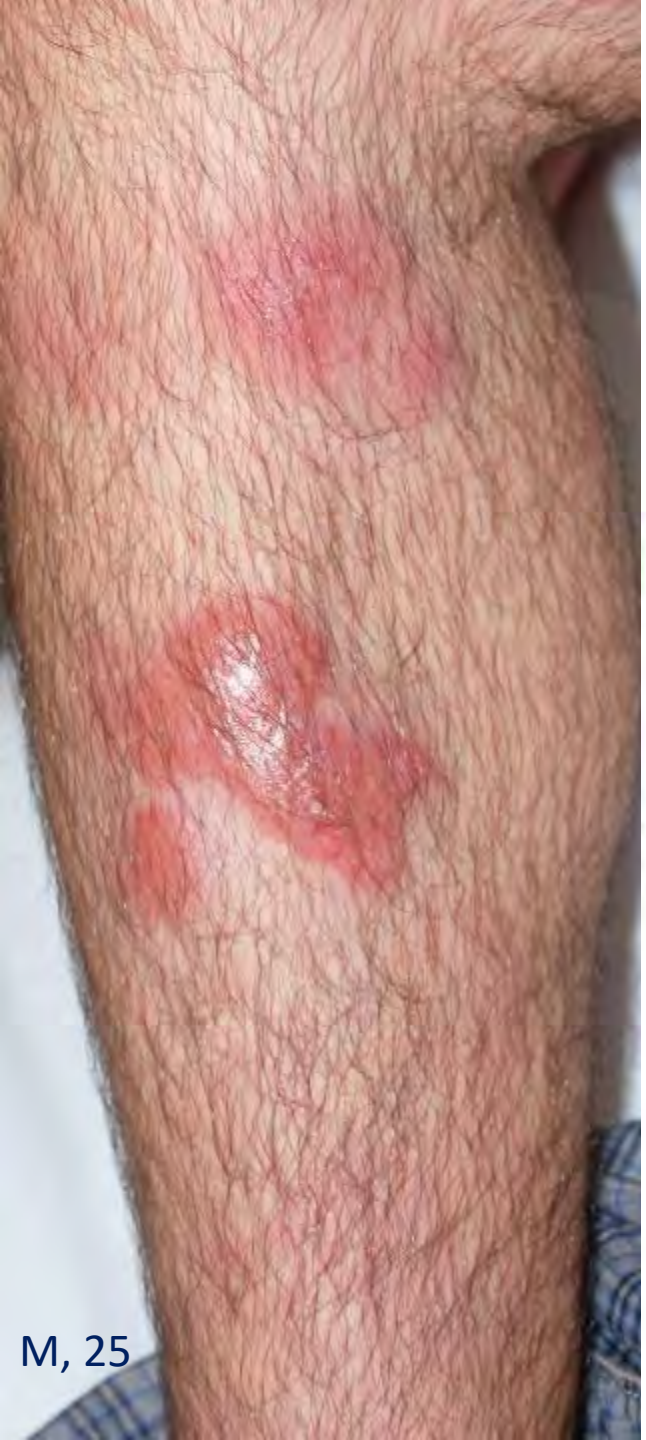
Erysipelas




M, 75




CD3
CD5
EBER-1
TIA-1
CD30
CD56
ßF1
TCR-γ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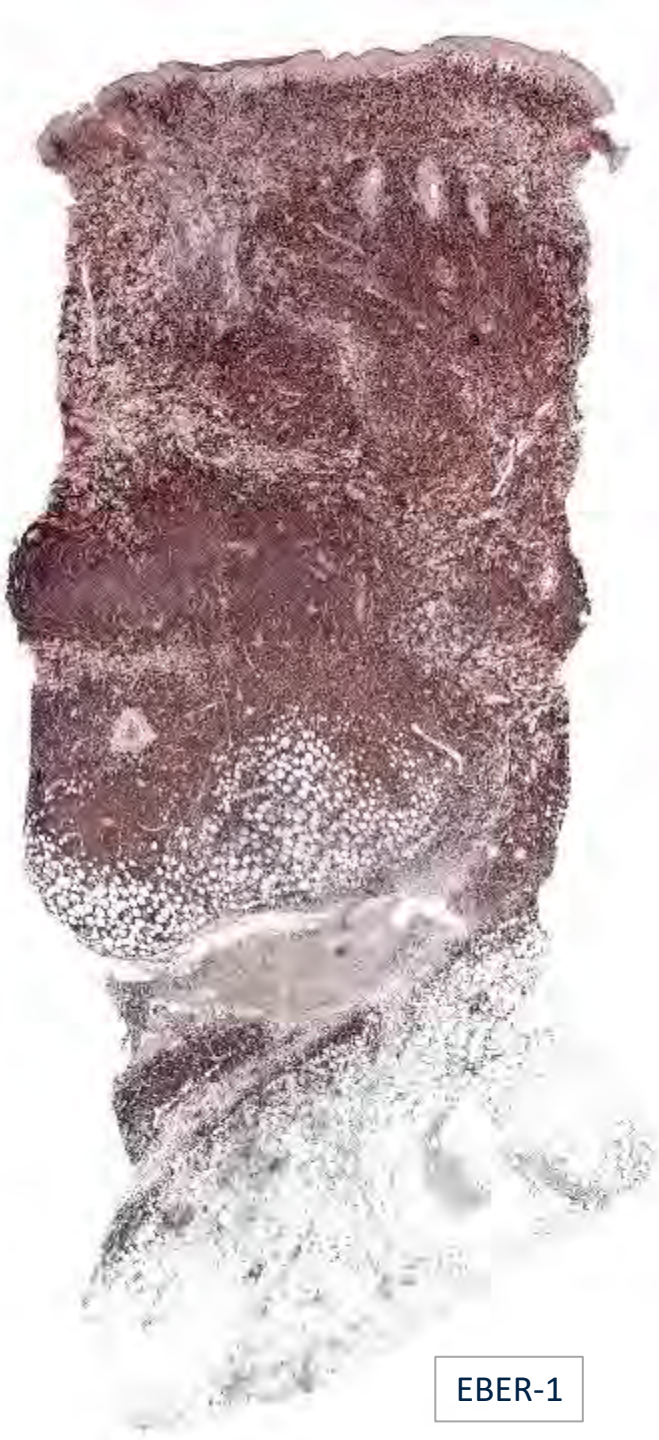
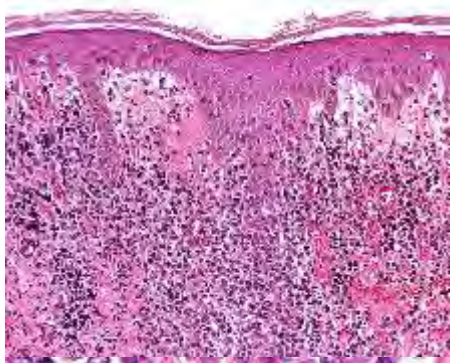
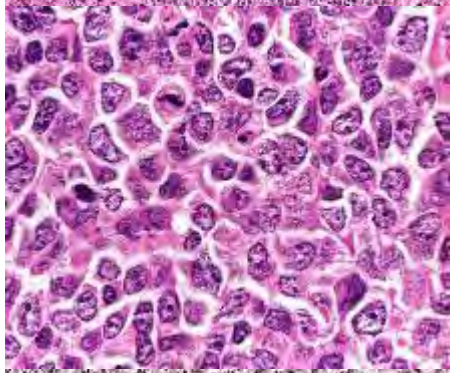
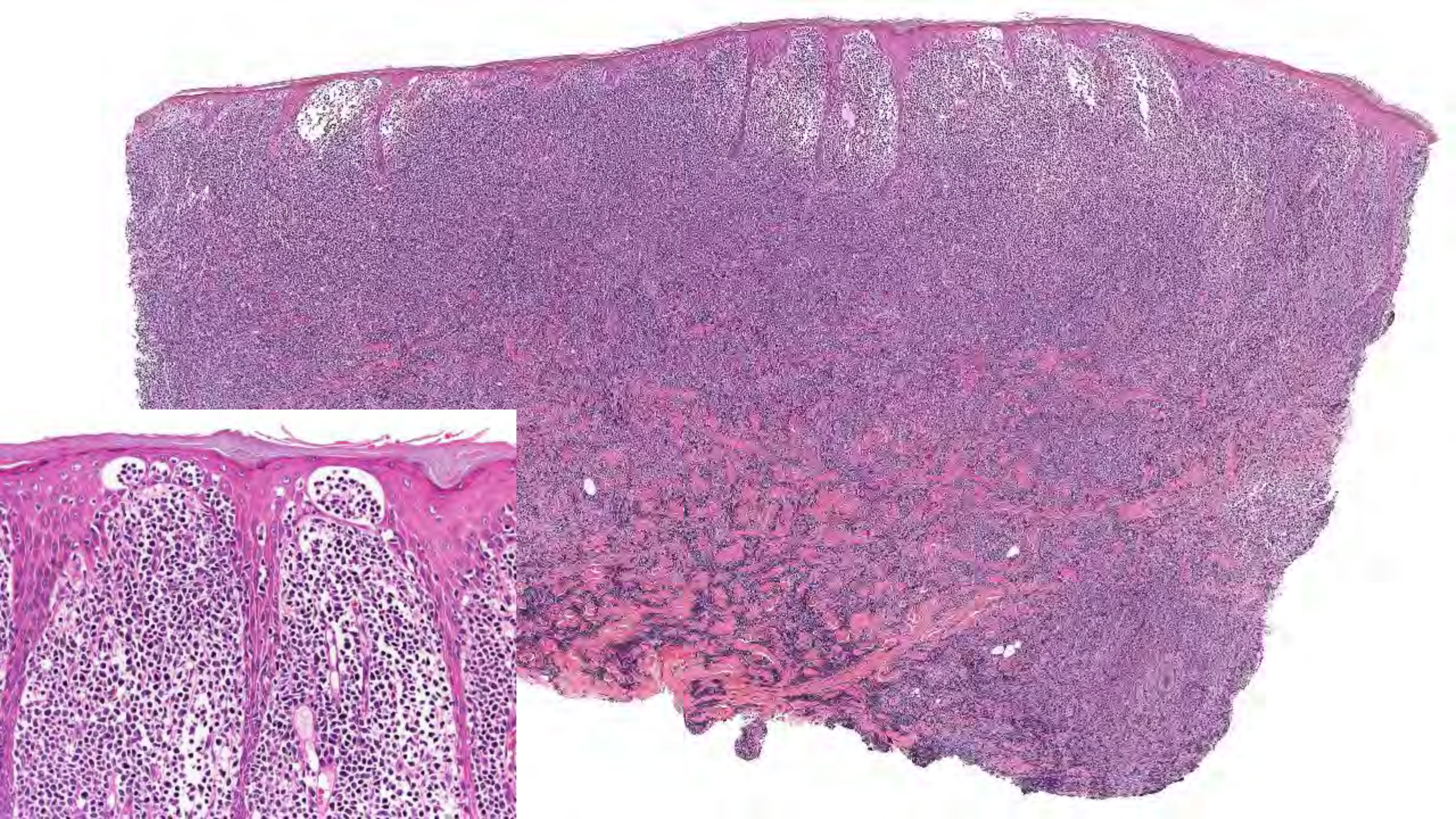

EBER-1

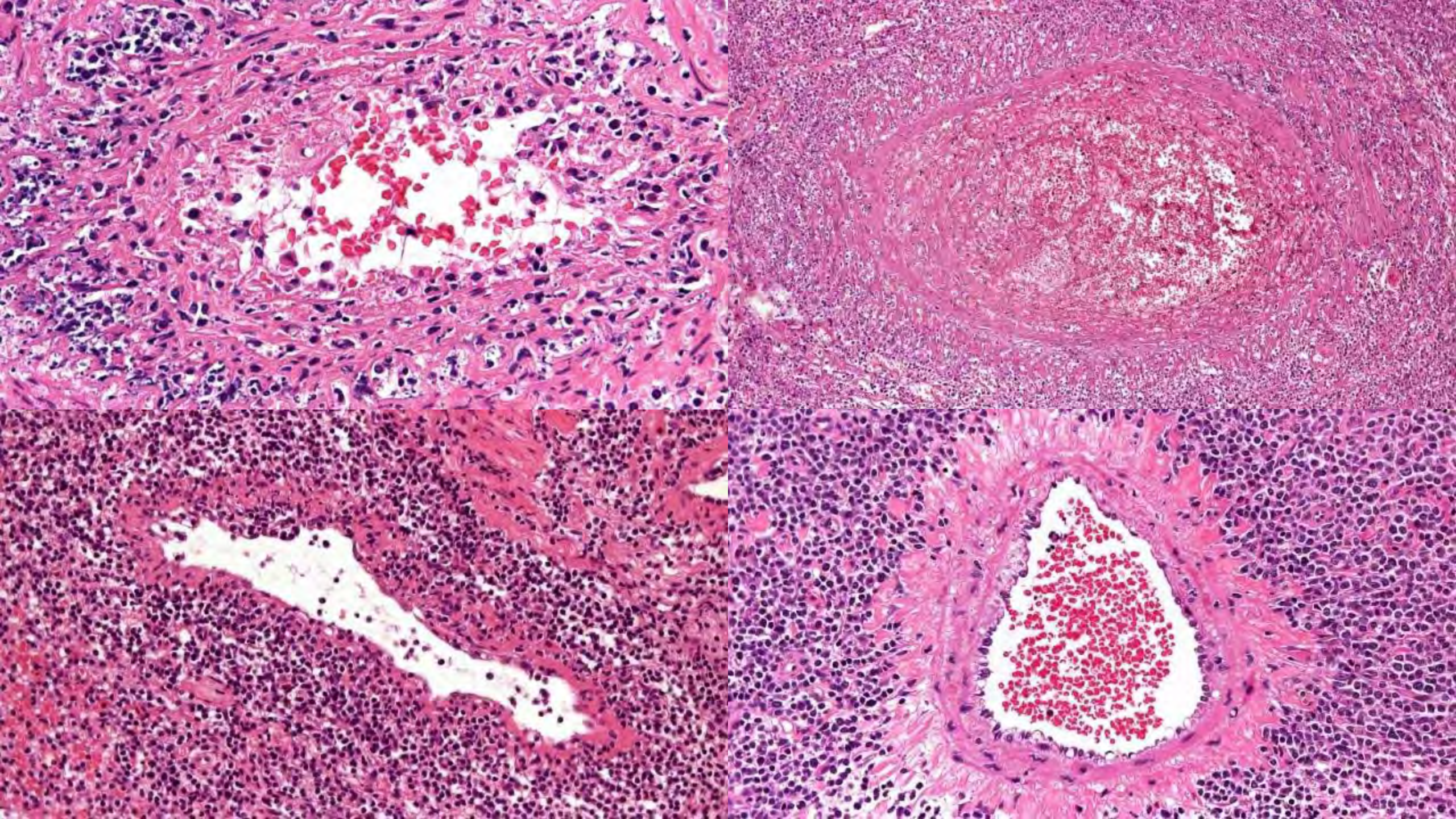





TIA1


CD56





Extranodal NK/T-cell Lymphoma, Nasal Type

A Report of 73 Cases at MD Anderson Cancer Center

Shaoying Li, MD, Xiaoli Feng, MD,* Ting Li, MD,† Shuang Zhang, MD,† Zhuang Zuo, MD, PhD,* Pei Lin, MD,* Sergej Konoplev, MD, PhD,* Carlos E. Bueso-Ramos, MD, PhD,* Francisco Vega, MD, PhD,* L. Jeffrey Medeiros, MD,* and C. Cameron Yin, MD, PhD**

Abstract: Extranodal NK/T-cell lymphoma, nasal type (ENKTL) is uncommon in the United States. We report 73 patients with ENKTL, including 49 men and 24 women (median age, 46 y). Sixty-three patients had nasal/upper aerodigestive tract disease, 10 had extranasal disease involving skin, nasal, intestine, epiglottis, testis, adrenal glands, kidney, and breast. Complete staging data were available for 58 patients: 44 stage I/II and 24 stage IV. Fifteen of 69 (22%) had lymphadenopathy and 10/63 had bone marrow involvement. Histologically, 67/73 (92%) showed necrosis, and 48/70 (69%) had an angiocentric/angiodestructive growth pattern. The neoplastic cells showed a wide spectrum: medium sized (n = 34), mixed small and large (n = 21), large (n = 13), and small (n = 5). In situ hybridization for Epstein-Barr virus–encoded small RNA was positive in every case. Immunohistochemical studies showed expression of cytotoxic markers (100%), T-bet (96%), CD2 (98%), CD3 (92%), CD56 (90%), and ETS-1 (64%). Ki-67 was ≥60% in 46% cases. Therapy was known for 64 patients: 14 received only chemotherapy, 8 radiation alone, and 42 received combined radiation and chemotherapy. Median survival was 4.2 years, and 5-year overall survival was 46% (median follow-up, 3.8 y). Extranasal disease, high International Prognostic Index score, and high proliferation rate correlated with poorer prognosis. We conclude that ENKTL cases in the United States are similar to those reported in Asia and other countries. Absence of the angiocentric/angiodestructive pattern and presence of lymphadenopathy, features underemphasized in the literature, occurred in appreciable subsets of patients. The International Prognostic Index score, anatomic site of disease, and proliferation rate had prognostic value in this patient cohort.

Key Words: extranodal NK/T-cell lymphoma, nasal type, southern United States

(*Am J Surg Pathol* 2013;37:14–23)

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Extranodal NK/T-cell lymphoma, nasal type (ENKTL) is a rare type of lymphoma that is endemic to East Asia and parts of Central and South America. Most (80% to 90%) patients present with nasal obstruction, sinusitis, ulcer, and epistaxis due to a destructive mass involving the midline facial tissues. ENKTL most often presents as a localized disease, clinical stage I-II; however, widespread dissemination can occur in a subset of patients. Occasionally, patients with ENKTL present with only extranasal sites of disease, most often skin, lung, and gastrointestinal tract, but a variety of other extranasal sites have been reported.[1–9]

Accurate diagnosis of ENKTL can be challenging, especially in small biopsy specimens or in frozen sections, as the neoplastic cells are often admixed with inflammatory cells and necrosis. An angiocentric and angiodestructive growth pattern is common and has been emphasized in the literature, but this pattern is not invariable.[1] Most cases of ENKTL are thought to be of NK-cell lineage or derived from an NK/T-cell precursor cell, but a subset of cases meets the criteria for T-cell lineage.[1] In the 2008 World Health Organization classification, presence of Epstein-Barr virus (EBV), usually shown by assessment for EBV-encoded small RNA (EBER), was included in the disease definition, and EBV has been implicated in disease pathogenesis.[1,10–13]

Although the clinicopathologic features of ENKTL are well recognized, most current data are derived from patient populations in endemic regions, particularly East Asia.[3,6,7] Data on patients with ENKTL in developed countries are limited.[2] In this study, we report the clinicopathologic and immunophenotypic features of a large series of patients with ENKTL at our institution in the United States.

MATERIALS AND METHODS

Case Selection

We searched the database of the Department of Hematopathology at The University of Texas MD Anderson Cancer Center from January 1, 1985 to March 31, 2012 for cases of ENKTL. The diagnosis was based on morphologic and immunophenotypic criteria as specified in the World Health Organization classification.[1] Clinical information was obtained by review of medical records.

73 cases

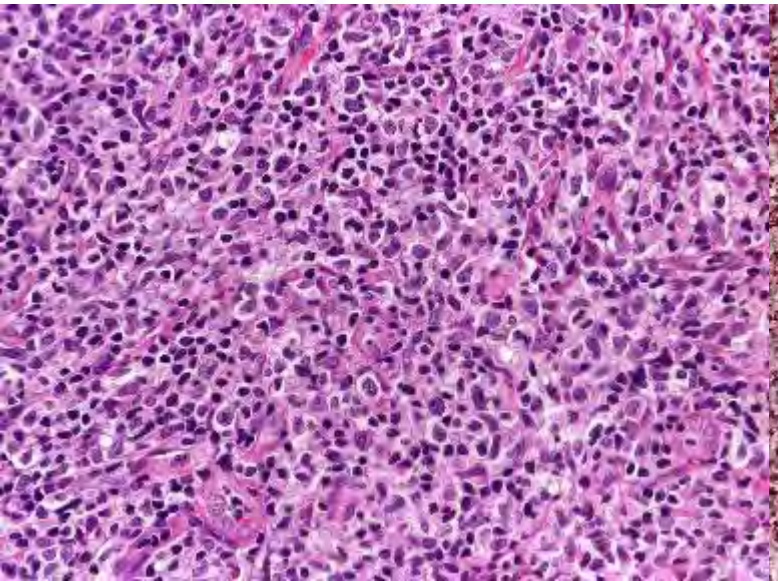
(63 nasal / upper aereodigestive tract, 10 extranasal including skin)

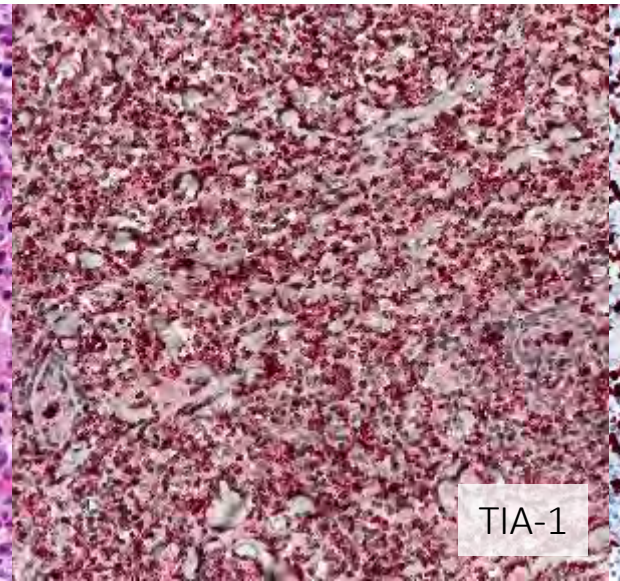
32 cases with incomplete data, lineage could not be assigned

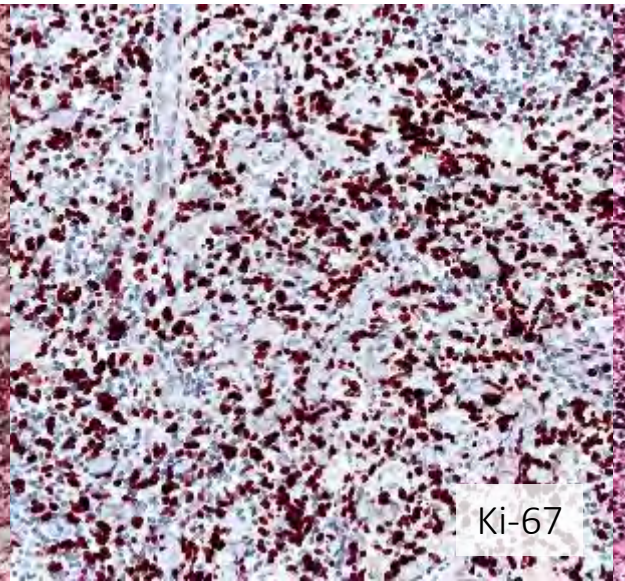
24 cases (59%) of NK-cell lineage
17 cases (41%) of T-cell lineage

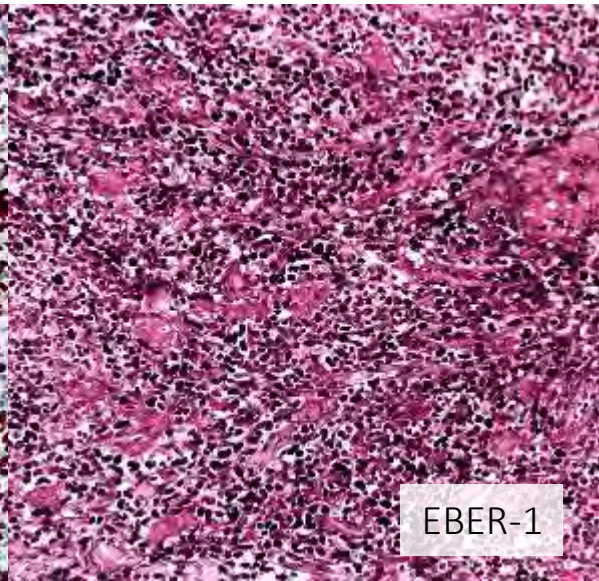
All cases positive for EBV (EBER-1)

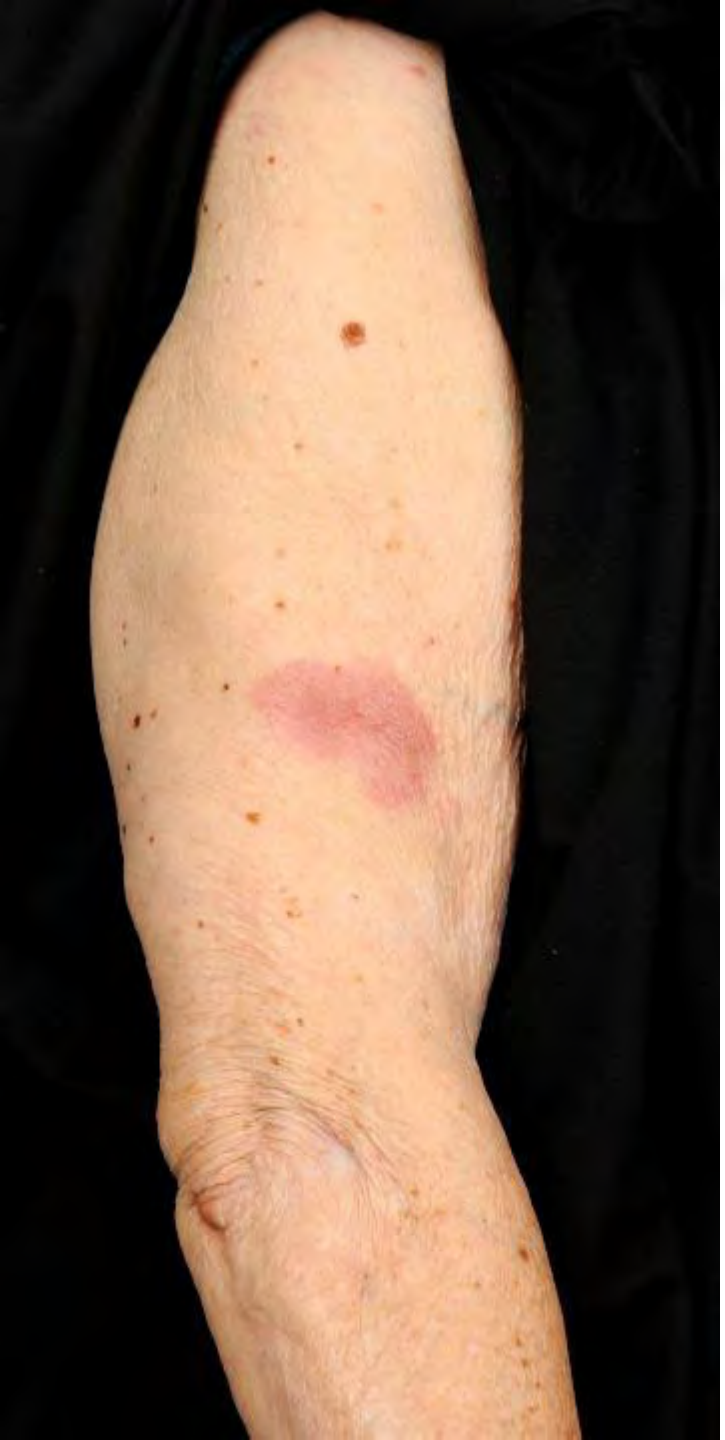
F, 55 Solitary, infiltrated plaque on the right upper arm for some weeks.

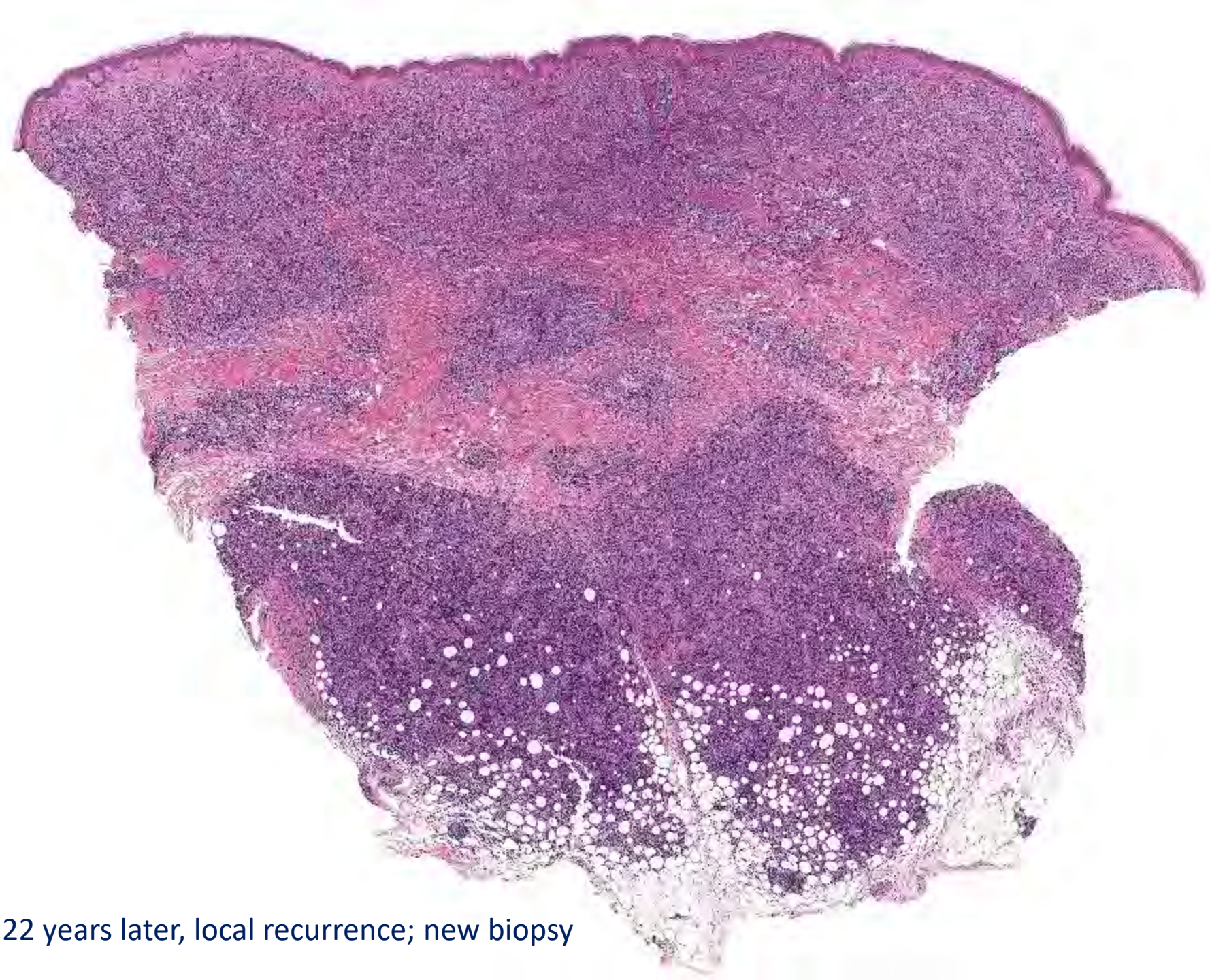




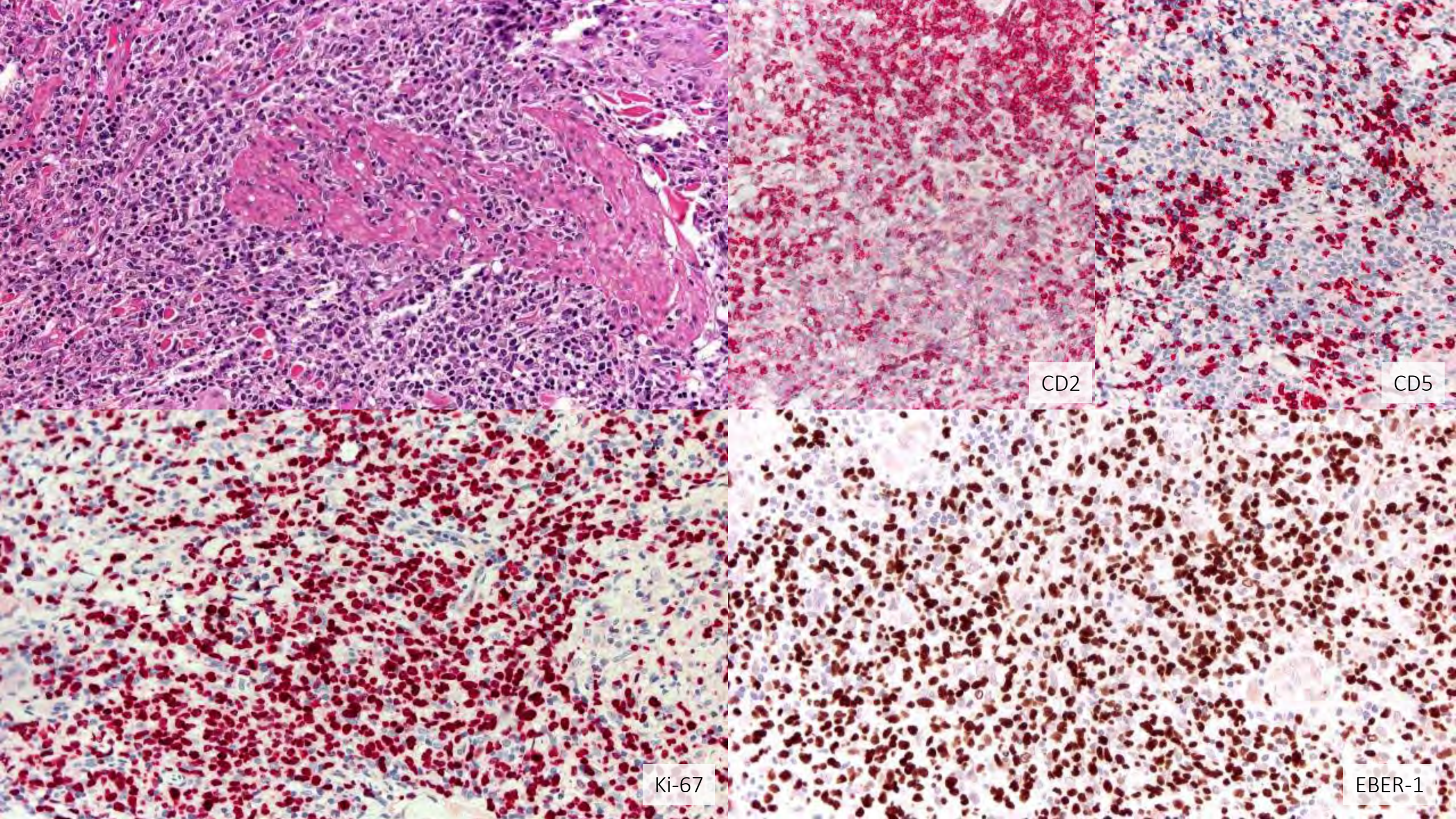


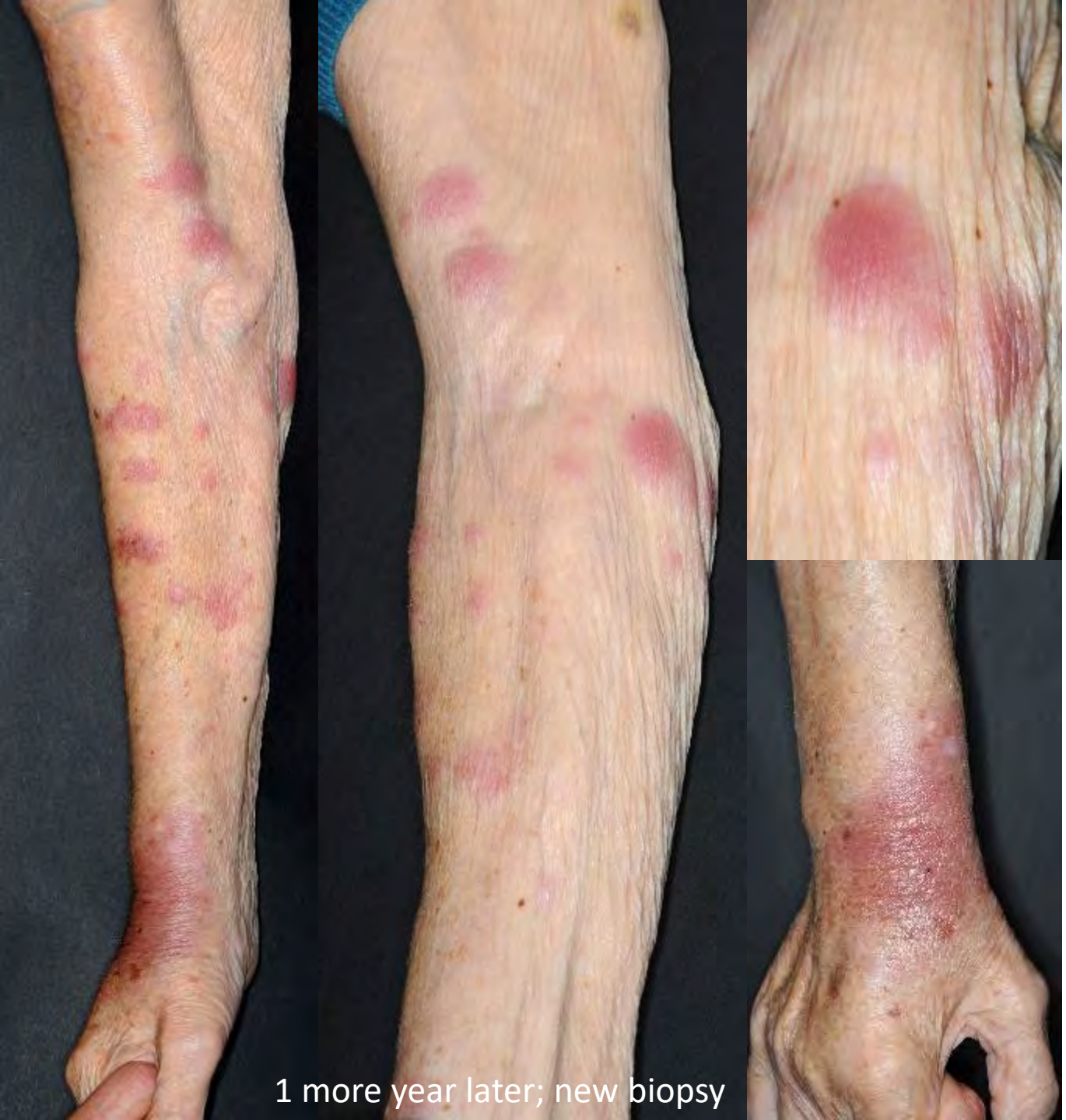


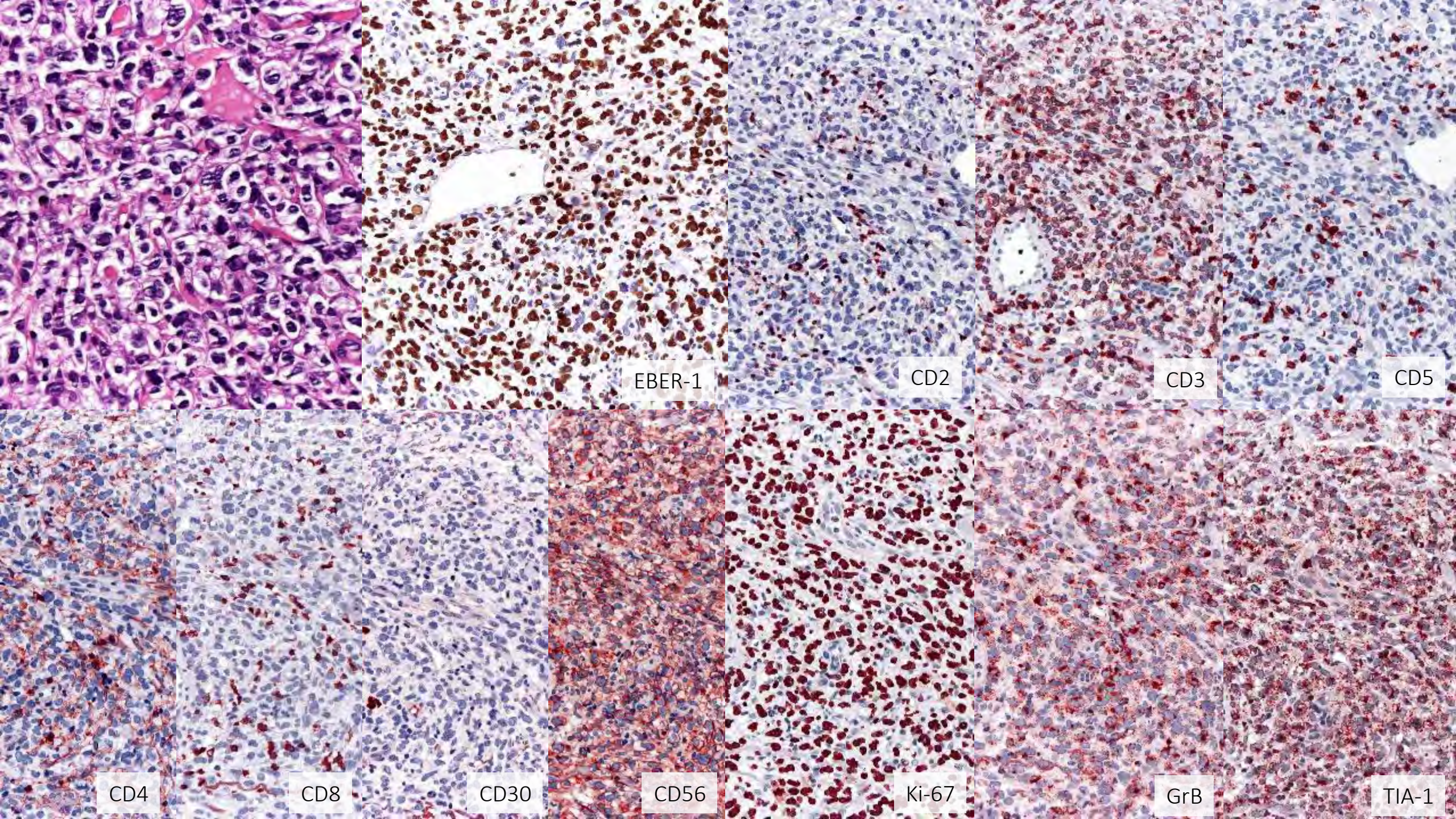




22 years later, local recurrence; new biopsy

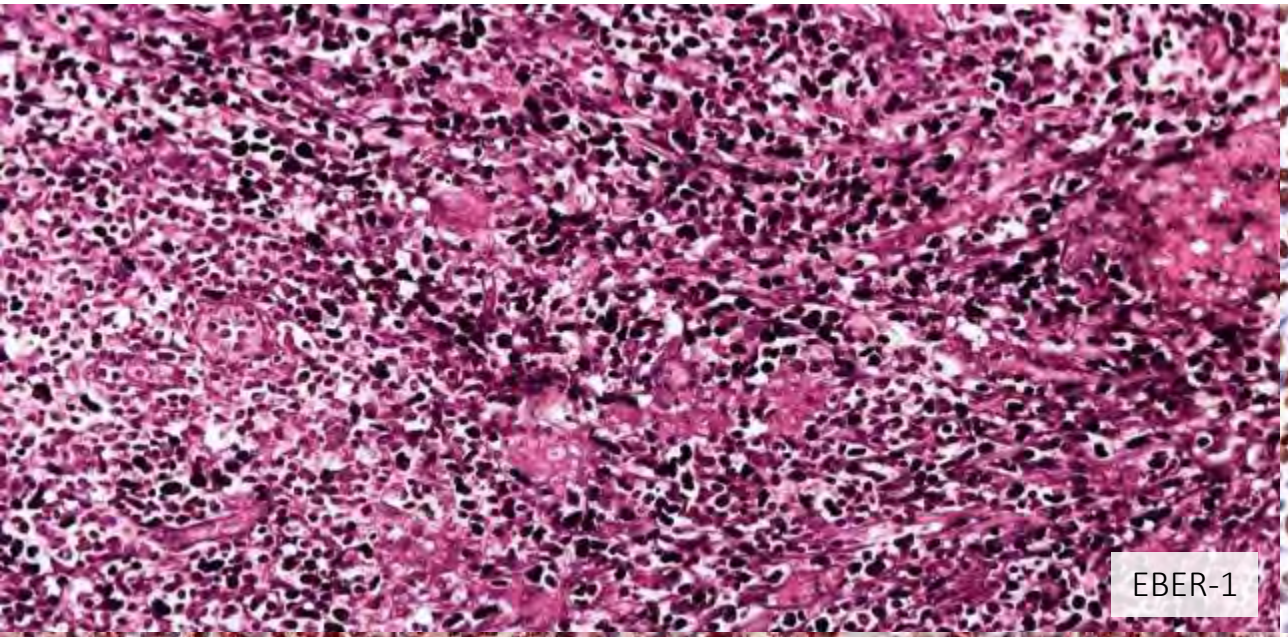

CD2
CD5
Ki-67
EBER-1

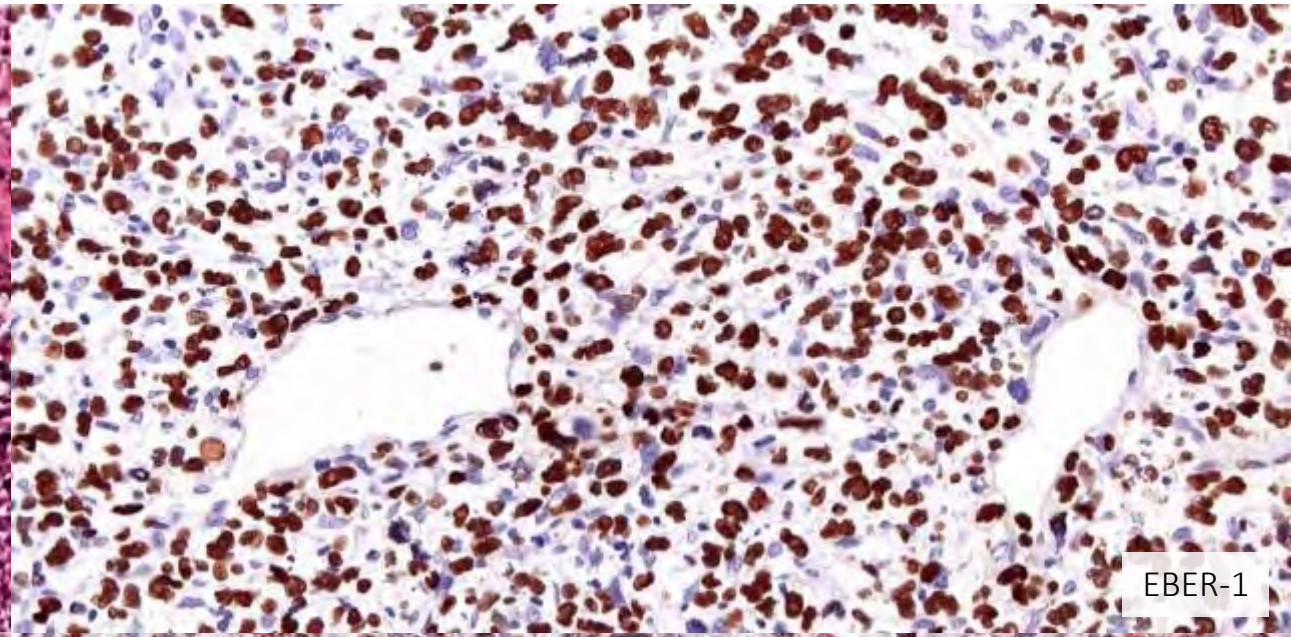

1 more year later; new biopsy

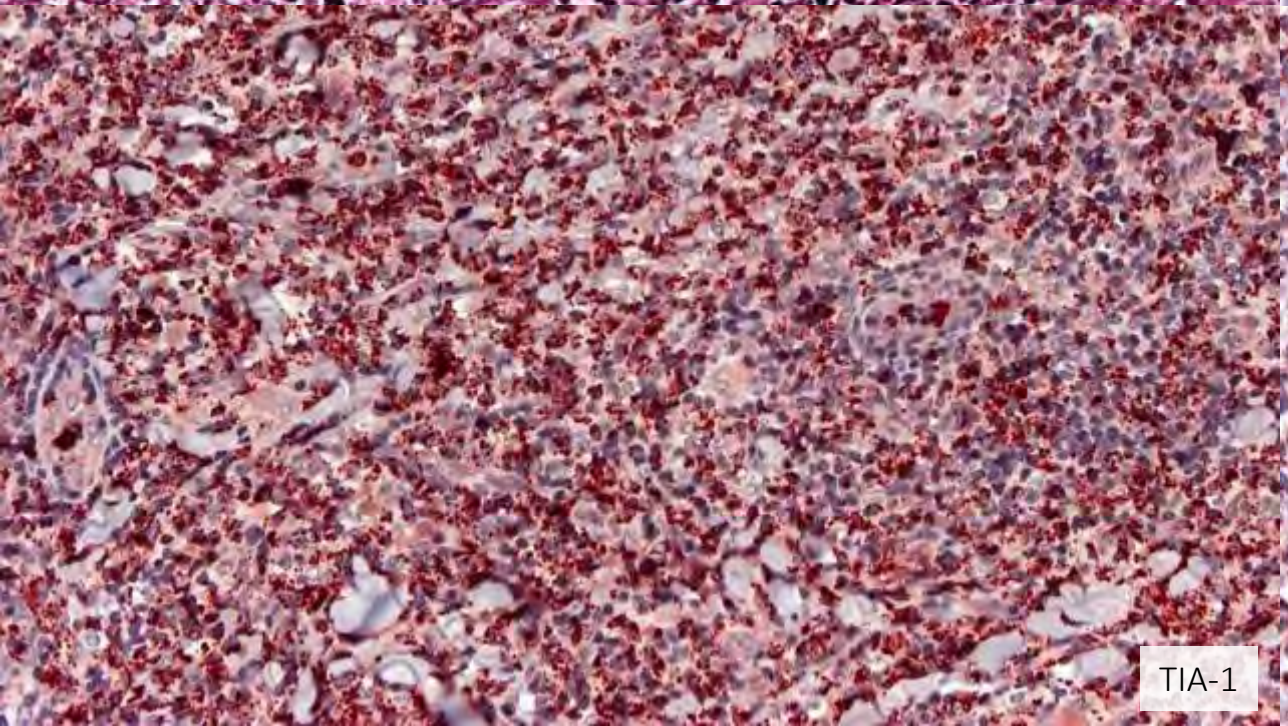

EBER-1
CD2
CD3
CD5
CD4
CD8
CD30
CD56
Ki-67
GrB
TIA-1

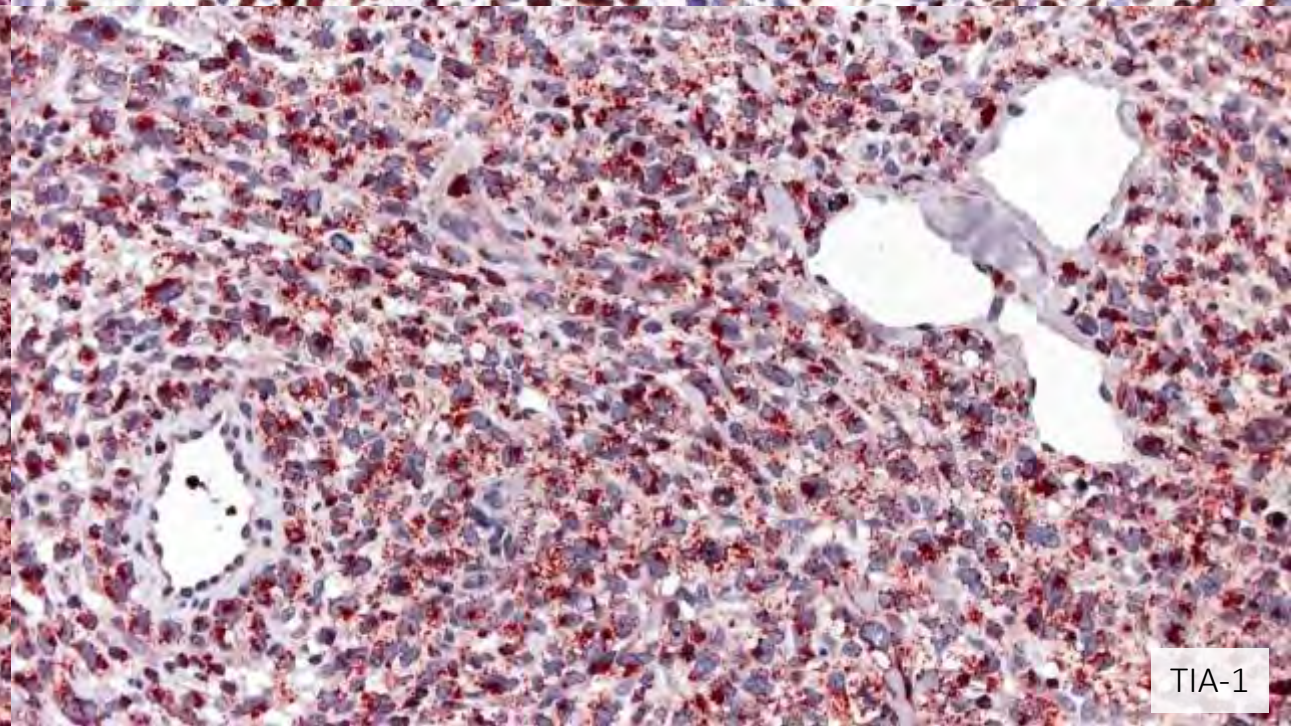
1st presentation

23 years later

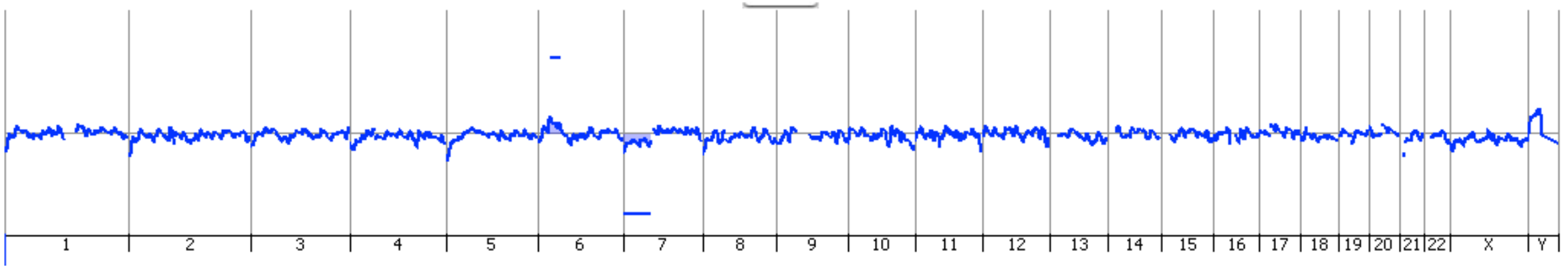




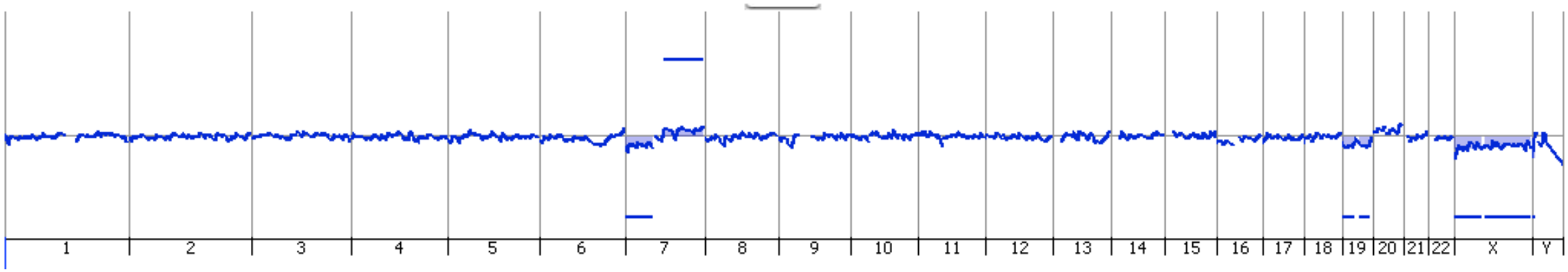




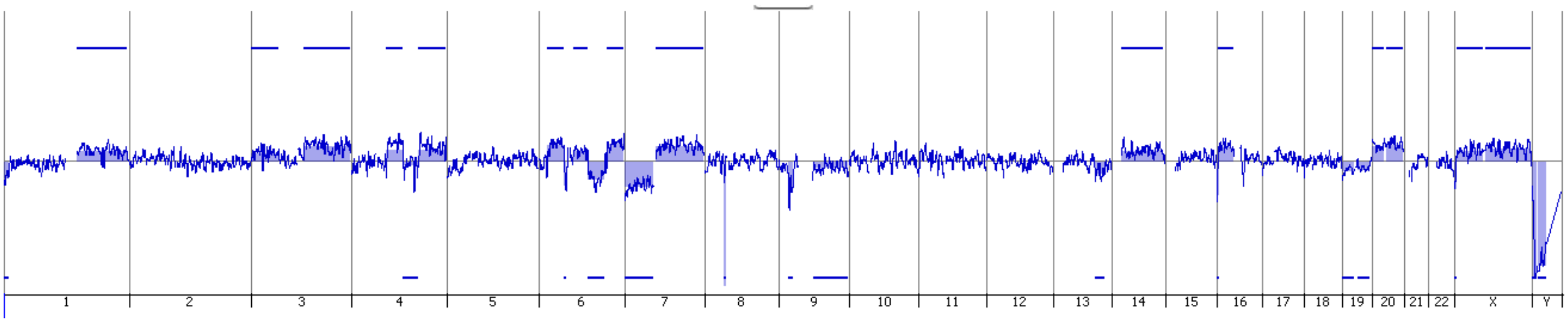
Day 0



+22 years



+23 years



condition, notoriously difficult to treat, in which a dense infiltrate of T lymphocytes and neutrophils plays a significant pathophysiological role. It is, therefore, not surprising that TNF-α inhibitors are effective in downregulating this process to achieve disease remission.

Our three patients had a dramatic and sustained response to adalimumab. Two of the three had failed previous treatment with other biologic therapies, showing that adalimumab can be effective in ACH where other biologics have failed. Adalimumab was well tolerated. One patient developed metastatic lung cancer but it is unclear what role, if any, the drug played. Although it is possible that 5 years of anti-TNF-α treatment with infliximab, etanercept and adalimumab and a multitude of prior immunosuppressive agents contributed to the development of lung cancer, she was an 80-year-old lifelong smoker. This report confirms adalimumab to be an effective agent for ACH.

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C. Ryan
P. Collins
B. Kirby
S. Rogers

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Key words: acrodermatitis continua of Hallopeau, adalimumab

Conflicts of interest: S.R. has acted as a consultant and advisor for Wyeth, Schering Plough and Abbott Pharmaceuticals; B.K. has acted as a consultant and advisor for Wyeth, Merck-Serono Ltd and Abbott Pharmaceuticals.

A case of primary cutaneous natural killer/T-cell lymphoma, nasal type, with indolent clinical course: monoclonal expansion of Epstein–Barr virus genome correlating with the terminal aggressive behaviour

DOI: 10.1111/j.1365-2133.2008.08892.x

Sir, Extranodal natural killer/T-cell lymphoma, nasal-type (NKTL-NT), is nearly always an Epstein–Barr virus (EBV)-positive lymphoma usually with a natural killer-cell or more rarely a T-cell phenotype,[1] and shows poor prognosis in general.[2,3] Skin is the second most common site of involvement after the nasal cavity and nasopharynx,[4] and skin involvement can be a primary manifestation of the disease. We report a case of primary cutaneous NKTL-NT that showed an indolent course and a finally aggressive clinical behaviour 10 years after the onset.

A 39-year-old Japanese woman presented in December 1997 with an 8-month history of subcutaneous nodules on both legs. Skin biopsy was performed and the diagnosis of EBV-related cutaneous T-cell lymphoma was made. There was no evidence of extracutaneous involvement. After oral administration of etoposide and topical radiotherapy, the skin lesions disappeared. However, during the next year, subcutaneous indurations recurred four times on her extremities, and regressed following topical radiotherapy on each occasion. Skin biopsy of the second relapse was performed in October 1998 (early lesion). After the last radiotherapy was completed in August 1999, the development and subsequent spontaneous regression of subcutaneous nodules was observed several times until 2003. In November 2006, a skin tumour developed on the right abdominal wall, and rapidly increased in size. Skin biopsy was performed and the diagnosis of primary cutaneous NKTL-NT (WHO–EORTC)[2] was highly suspected. In April 2007 a further biopsy was performed (late lesion), and EBV-related antibody titres were: antiviral capsid antigens 1280× (IgG) and < 10× (IgM); and anti-early antigens 40× (IgG). She exhibited intermittent fever and bone marrow aspiration showed a slightly hypercellular marrow with infiltration of CD56+ CD3+ atypical lymphoid cells and haemophagocytosis. Antineoplastic chemotherapy and radiotherapy were not effective and she died in July 2007. A post mortem was not performed.

Microscopically, the late skin lesion exhibited diffuse proliferation of atypical cells throughout the dermis into subcutaneous adipose tissue (Fig. 1e). In the deep dermis, the small arterial wall structure was almost intact (Fig. 1f). By immunohistochemistry (IHC), most of these tumour cells were positive for CD56 (Fig. 1g), CD3ε and granzyme B, and negative for perforin, CD4, CD8, CD20 and CD30. On review of the early skin lesion, the histopathological findings in the tumour tissue were almost the same as those in

39-year-old Japanese woman. Many skin recurrences.
10-year survival.

A Case of Primary Cutaneous Extranodal Natural Killer/T-Cell Lymphoma, Nasal Type, With a 22-Year Indolent Clinical Course

Daniel Zuriel, MD,† Regina Fink-Puches, MD,* and Lorenzo Cerroni, MD**

Abstract: Extranodal natural killer (NK)/T-cell lymphoma, nasal type, is a rare type of cytotoxic lymphoma involving mainly the upper aerodigestive tract and associated with Epstein–Barr virus. The disease has usually a poor prognosis related to several factors. The skin is the second most common affected organ, and cases may be localized to the skin only without any other extracutaneous manifestations. Although primary cutaneous cases may have a better prognosis, survival usually is still poor. We report a case of primary cutaneous extranodal NK/T-cell lymphoma, nasal type, in a 77-year-old woman with an indolent course for more than 22 years and still limited to the skin.

Key Words: primary cutaneous extranodal NK/T-cell lymphoma, nasal type, Epstein–Barr virus, prognosis

(*Am J Dermatopathol* 2012;34:194–197)

INTRODUCTION

Extranodal natural killer (NK)/T-cell lymphoma, nasal type, is a rare type of cytotoxic lymphoma associated with Epstein–Barr virus (EBV) and involving mainly the upper aerodigestive tract.[1] The disease has a poor prognosis related to factors such as extranasal location, stage, performance status, and the number of extranodal involvement, as well as to the type of treatment.[2–5] The skin is the second most common affected organ, and cases may be localized to the skin only without any other extracutaneous manifestations.[6] We report a case of primary cutaneous extranodal NK/T-cell lymphoma, nasal type, with a remarkably indolent course over a period of 22 years.

CASE REPORT

A white woman first presented to the Department of Dermatology of the University of Graz in January 1989 at the age of 55 years with a large, red-violaceous, infiltrated plaque on the right upper arm. A biopsy was diagnosed at that time as a reactive lymphoid infiltrate ("nonfollicular pseudolymphoma"). Sonography of the lymph nodes and of the abdomen and routine blood investigations were normal. A final diagnosis of pseudolymphoma was made, and the patient underwent local radiotherapy with complete resolution of the lesion. She was disease free for the next 16 years. In 2005, she presented at another institution with a recurrent plaque in the same location. Histologic examination disclosed a cytotoxic infiltrate with features of NK/T extranodal cytotoxic lymphoma, nasal type (slides not available for review). Complete staging investigations (including total body computed tomography, lymph node sonography, and bone marrow biopsy) were negative. Examination of the upper respiratory tract was negative. The patient underwent 6 cycles of chemotherapy

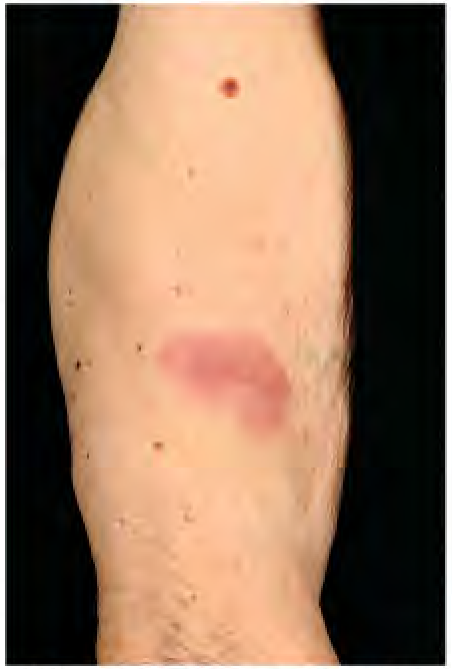

FIGURE 1. Infiltrated plaque on the right upper arm as observed in February 2011.

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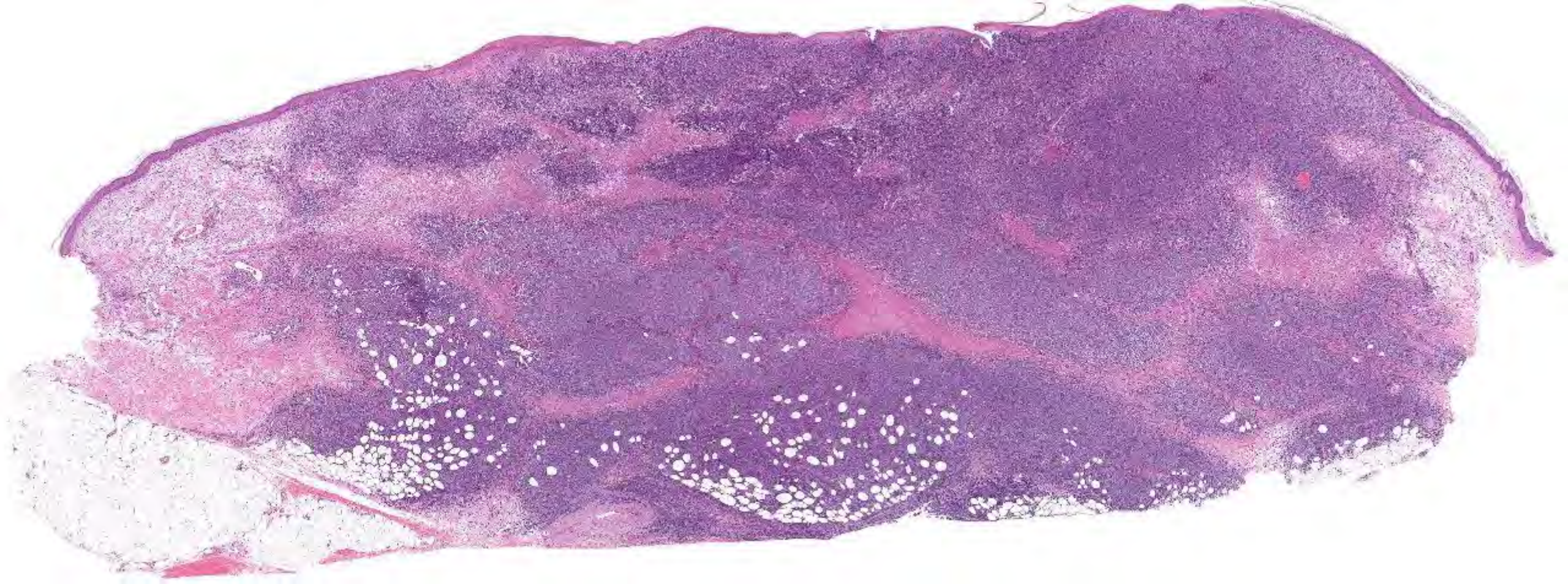
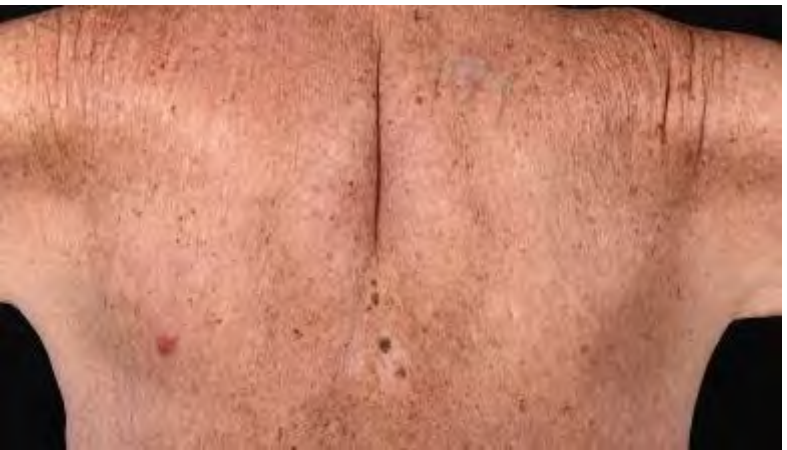
55-year-old Austrian woman.
23-year survival.





Cutaneous extranodal NK/T-cell lymphoma, nasal type

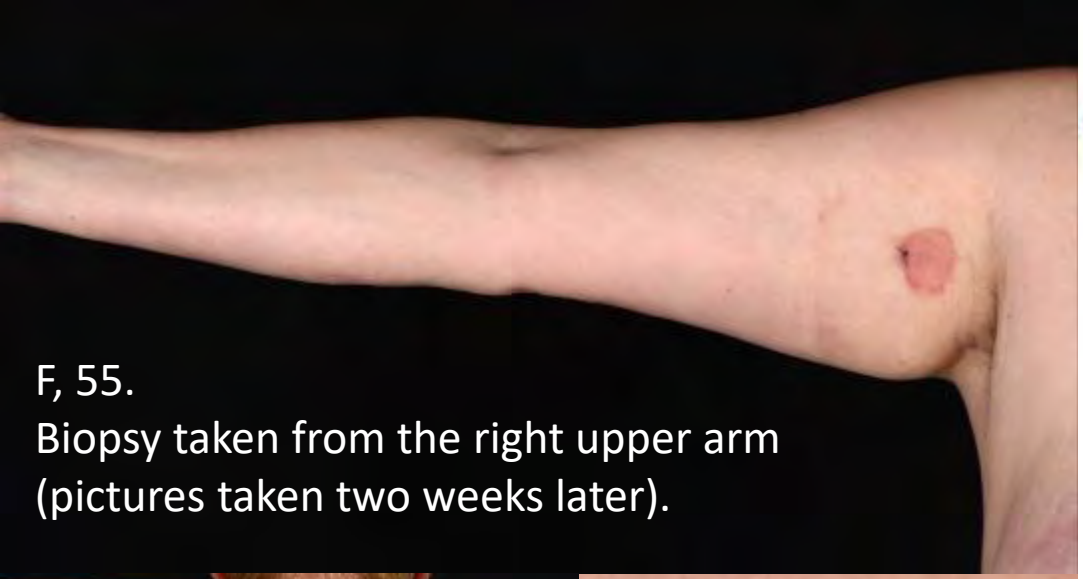
Nasal/perinasal erythematous, partly necrotic plaques ("lethal midline granuloma") and/or palatal ulcers; Persistent facial swelling is another typical presentation; non-descript patches, plaques and tumors on any region of the body.

Cell morphology variable (small, medium, large).

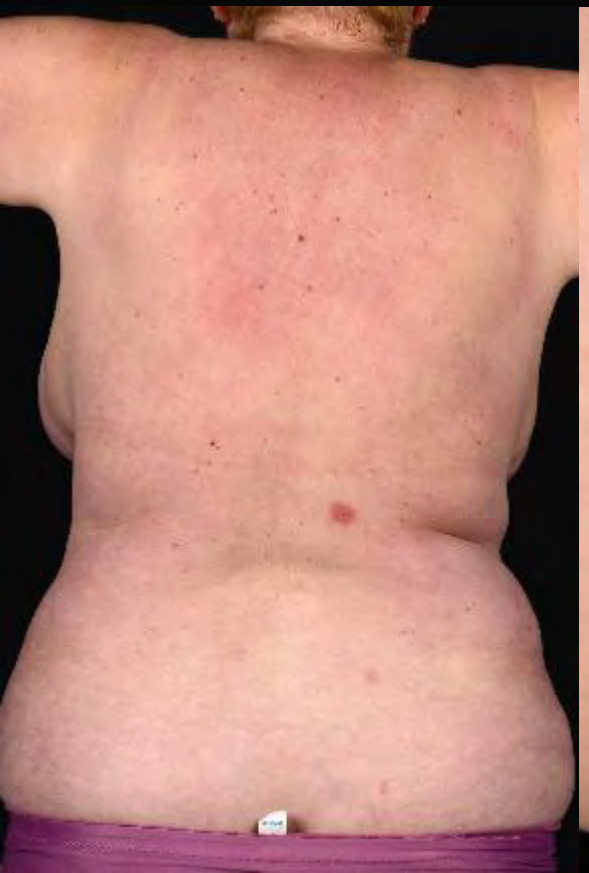
Phenotype: CD2+, CD3+, CD5-, CD4-, CD8-, ßF1-, TCRγ/δ-, CD56+, TIA-1+, Skin often CD2-, CD56-; CD30+ in approx. 30% of cases.

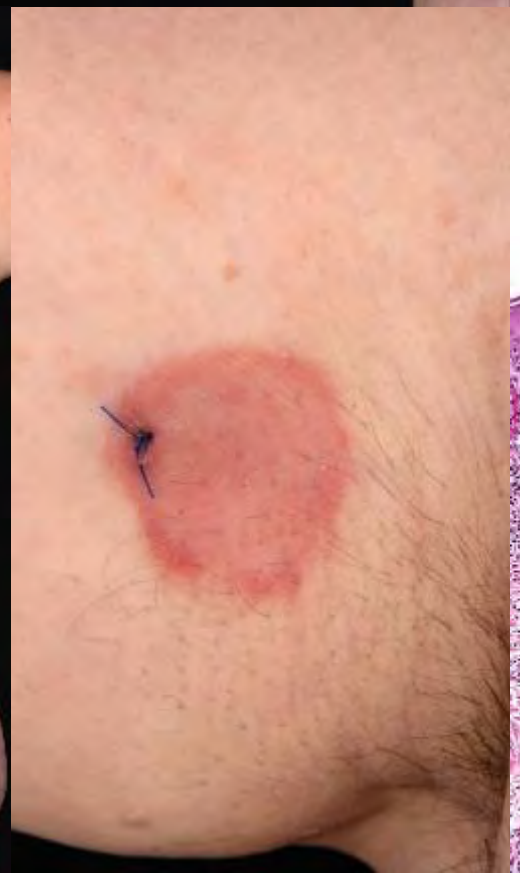
EBV-positivity (EBER-1) and expression of cytotoxic proteins pre-requisites for diagnosis!

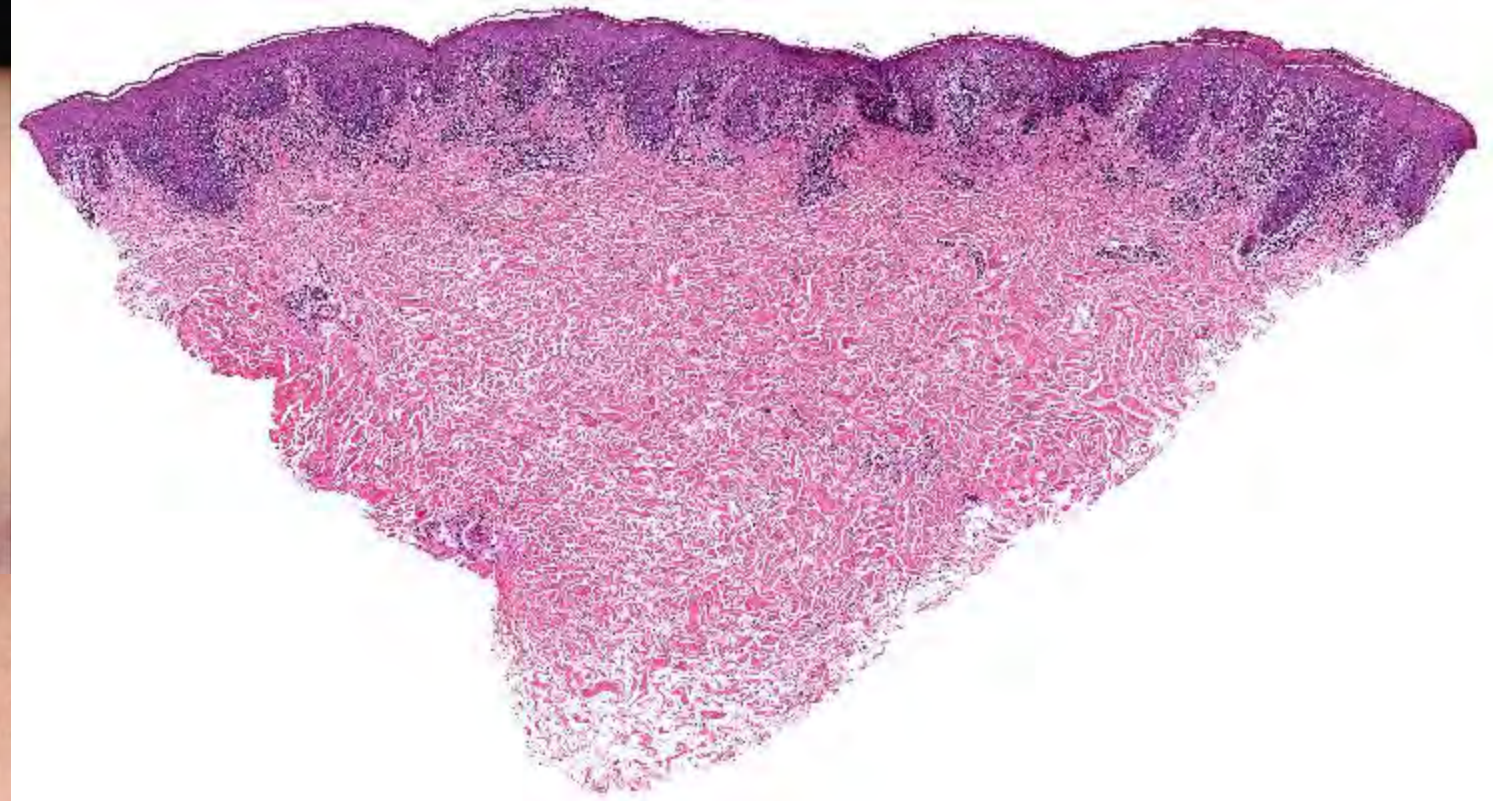
Aggressive behavior; rare cases with indolent course reported.

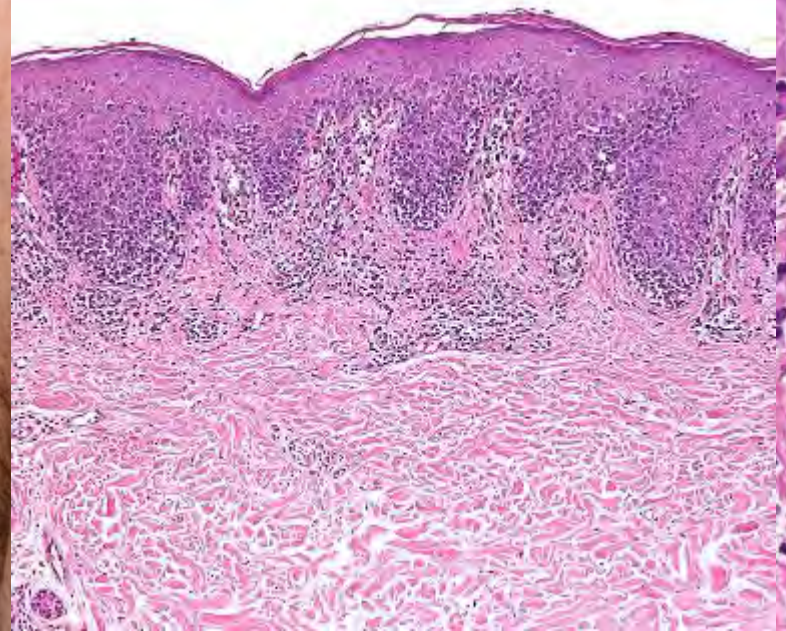


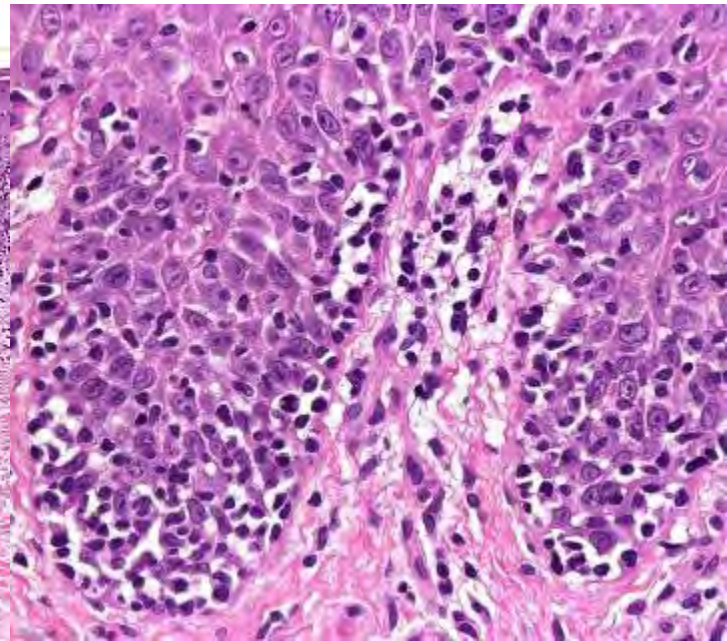
F, 55.
Biopsy taken from the right upper arm
(pictures taken two weeks later).

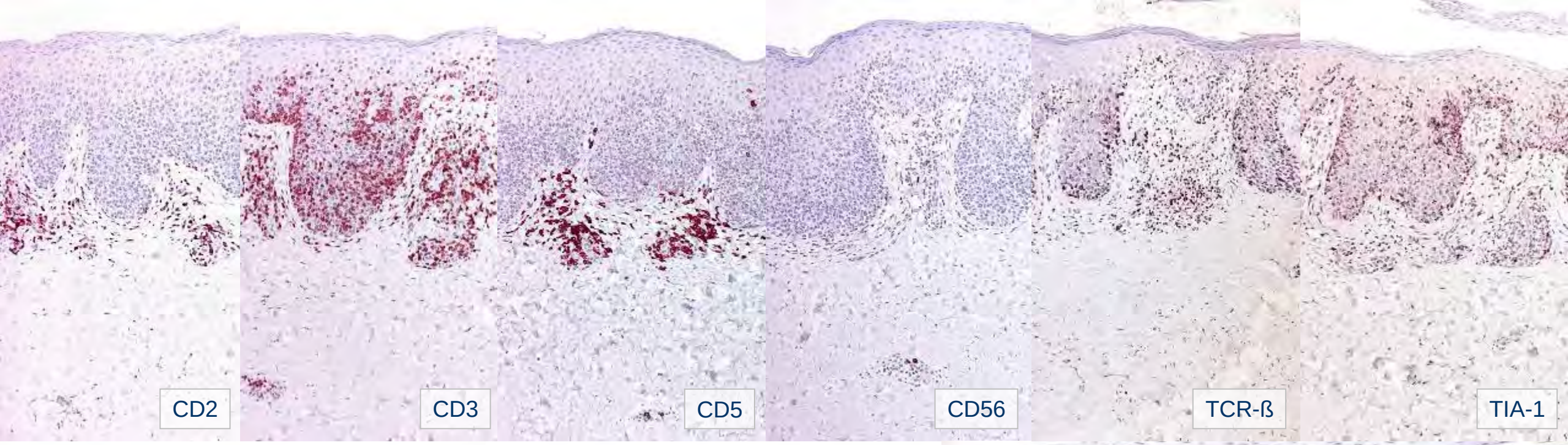


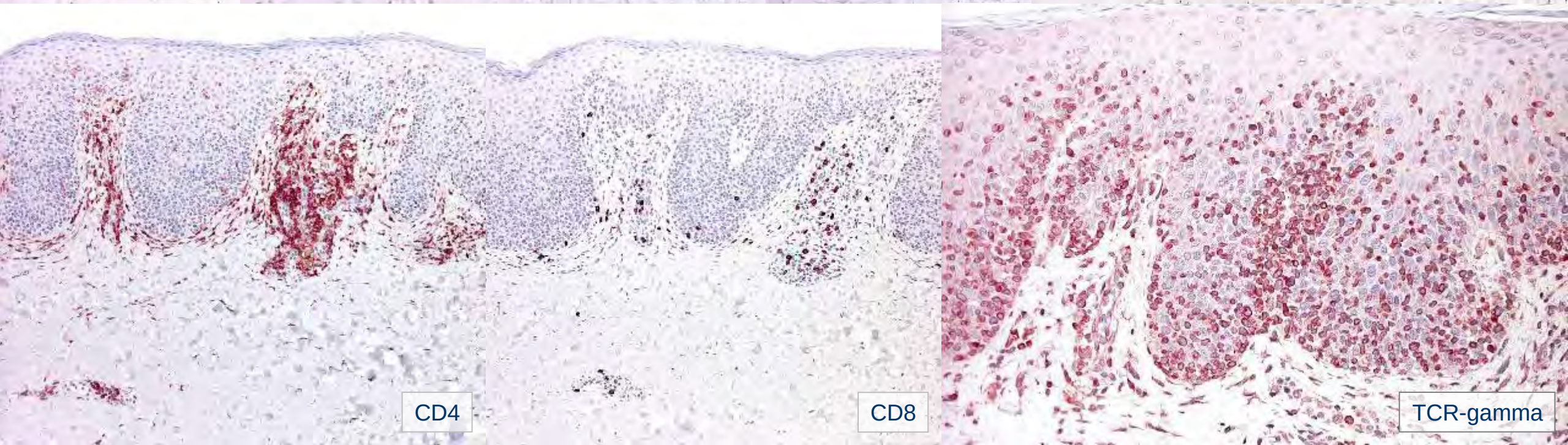




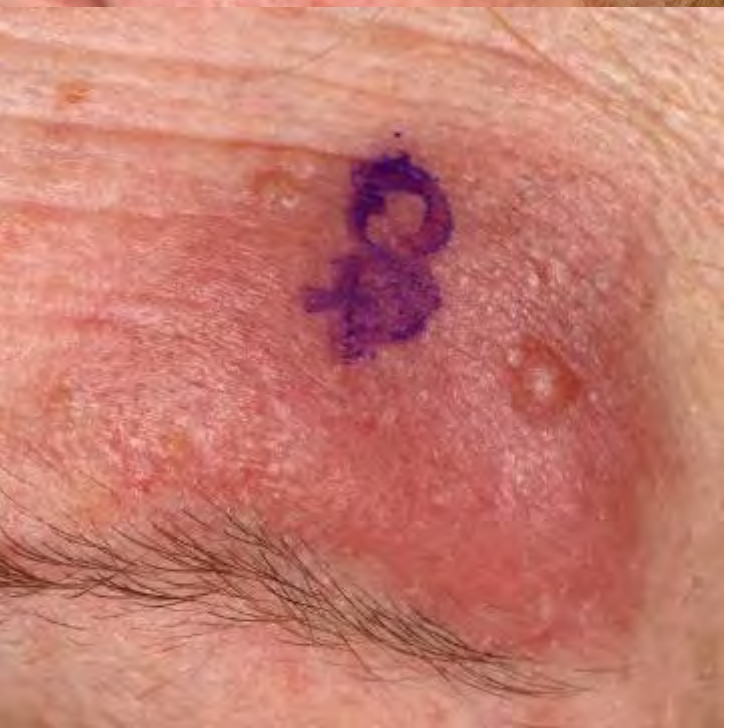


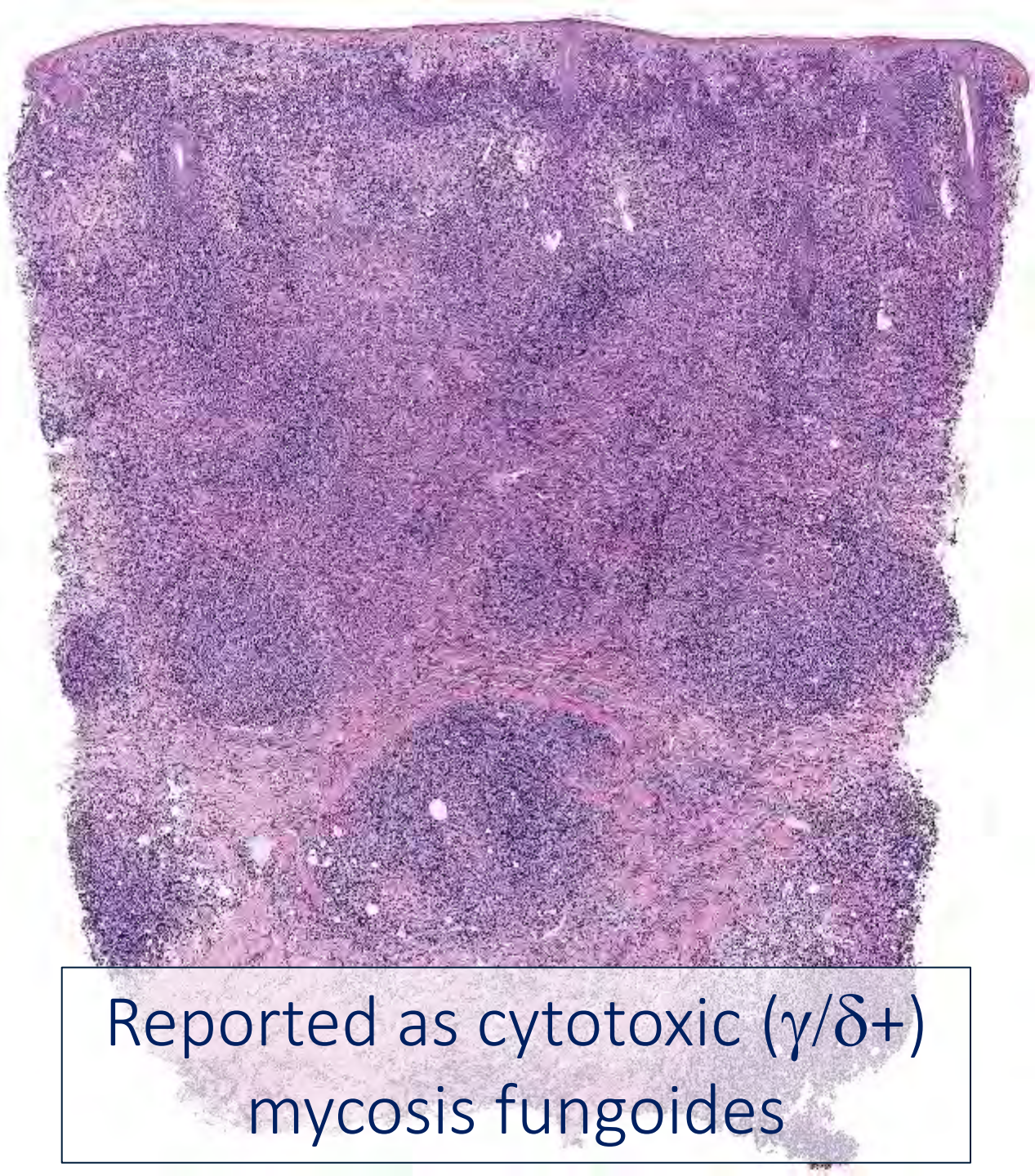



CD2
CD3
CD5
CD56
TCR-ß
TIA-1

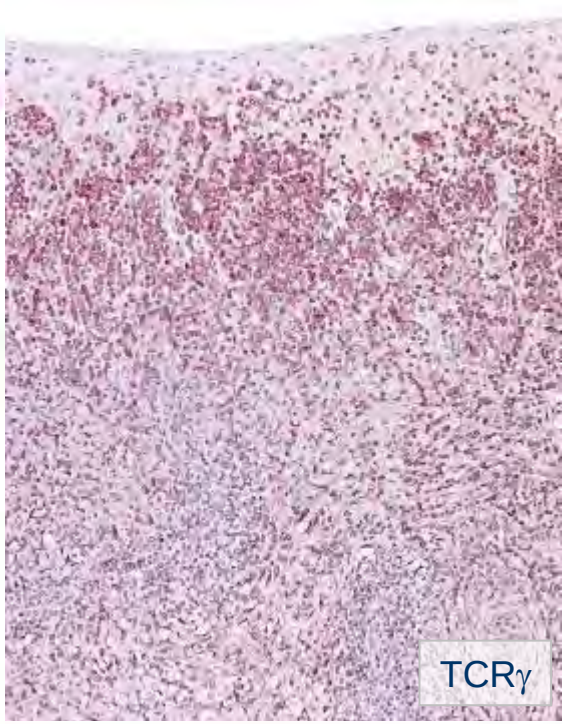

CD4
CD8
TCR-gamma

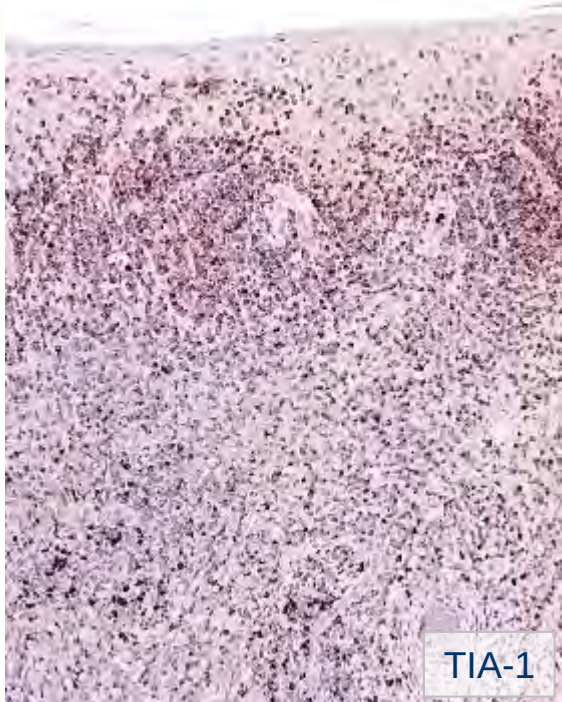
Two weeks later one more biopsy is taken from the left eyebrow.

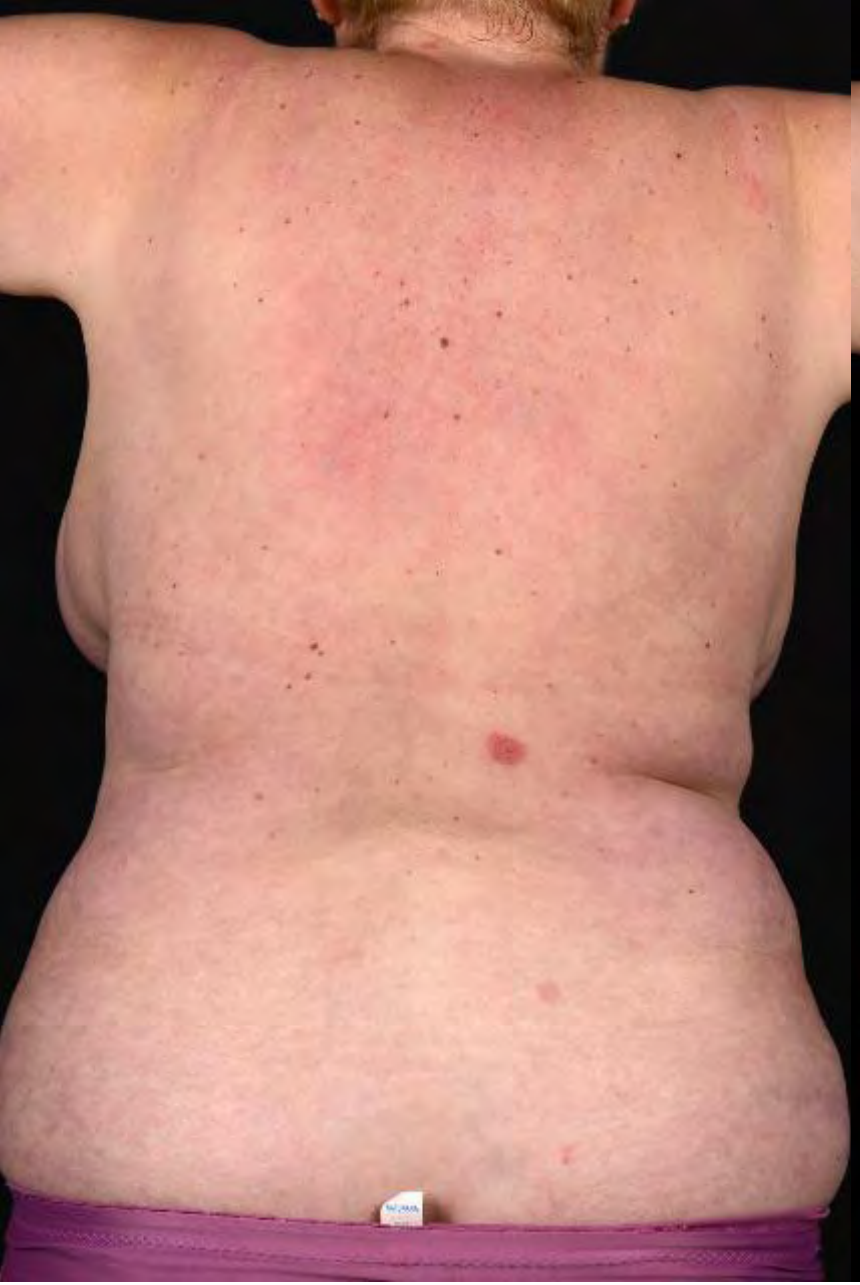




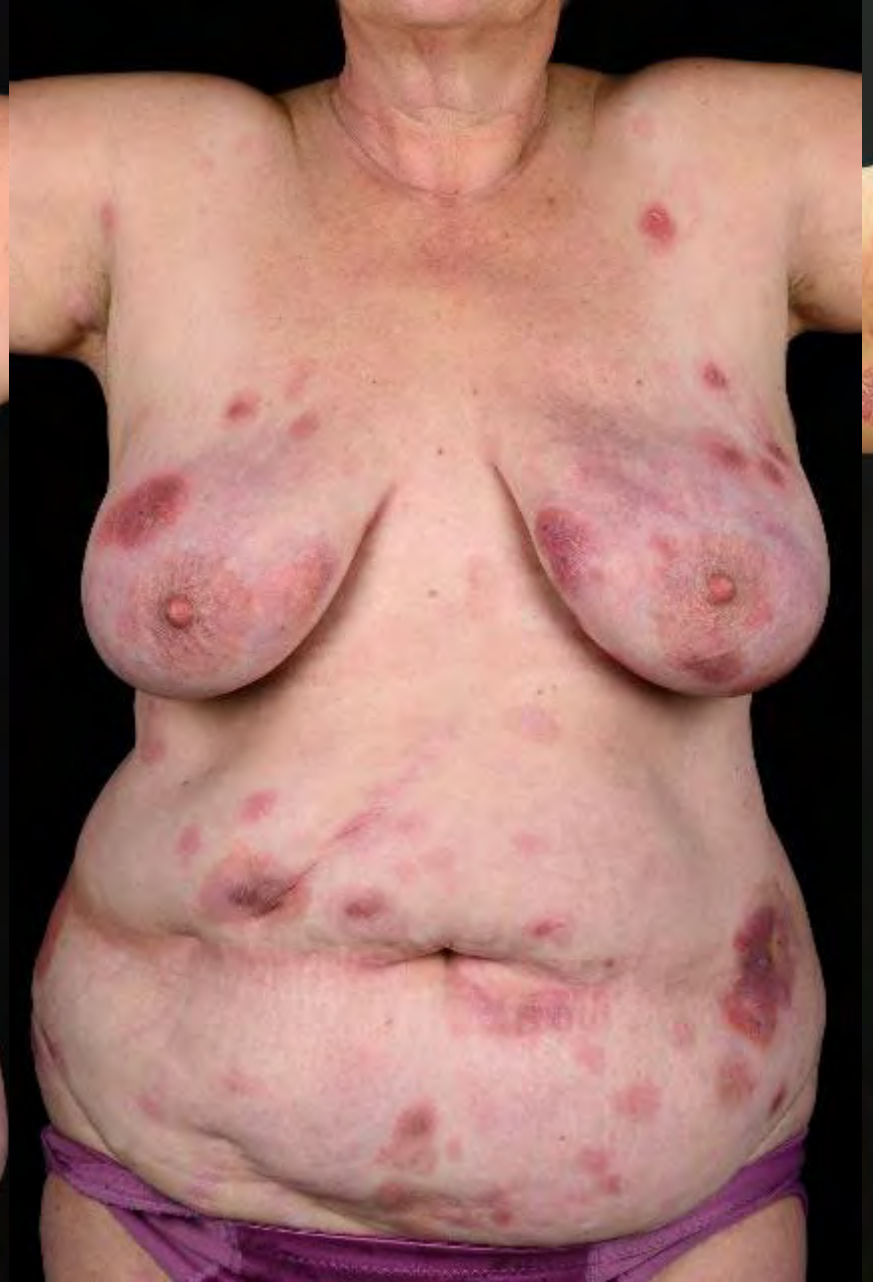
Reported as cytotoxic (γ/δ+) mycosis fungoides



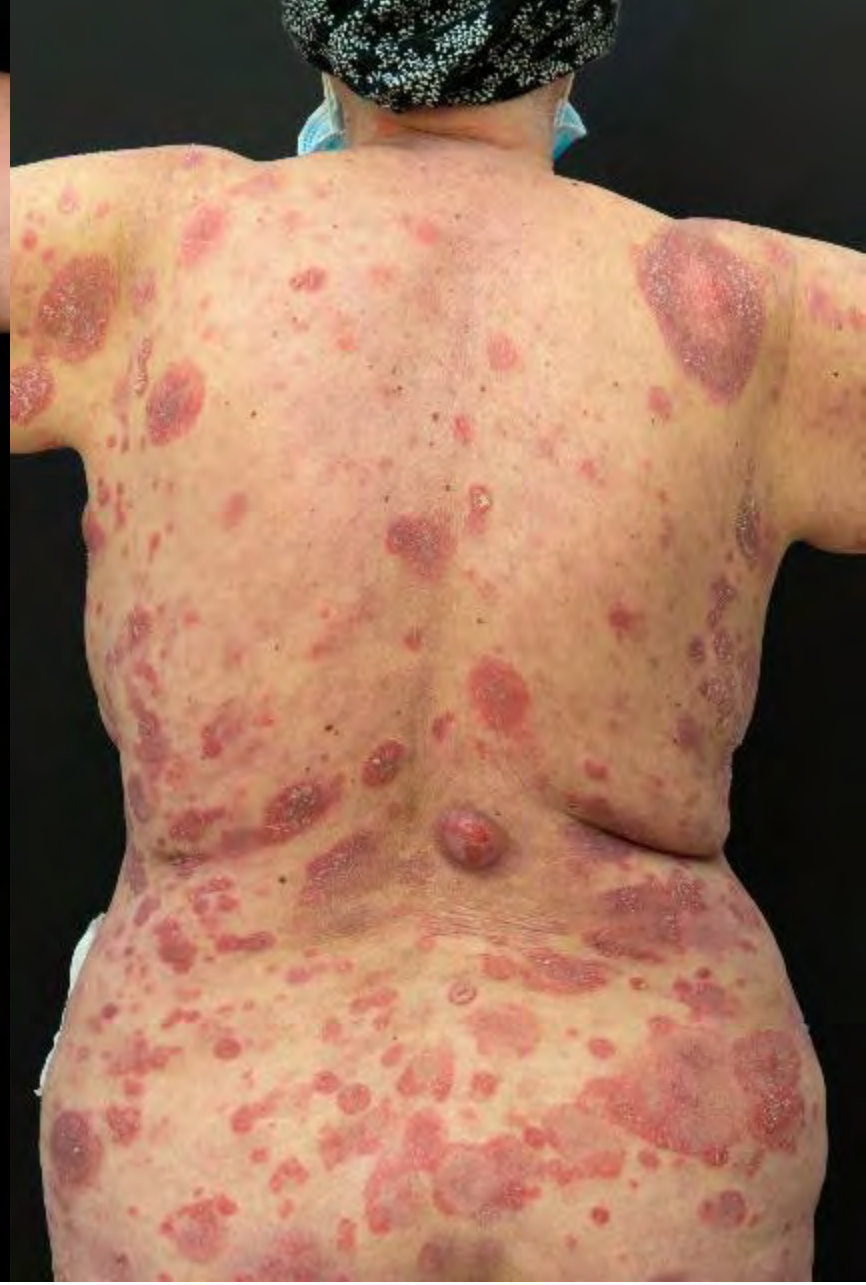




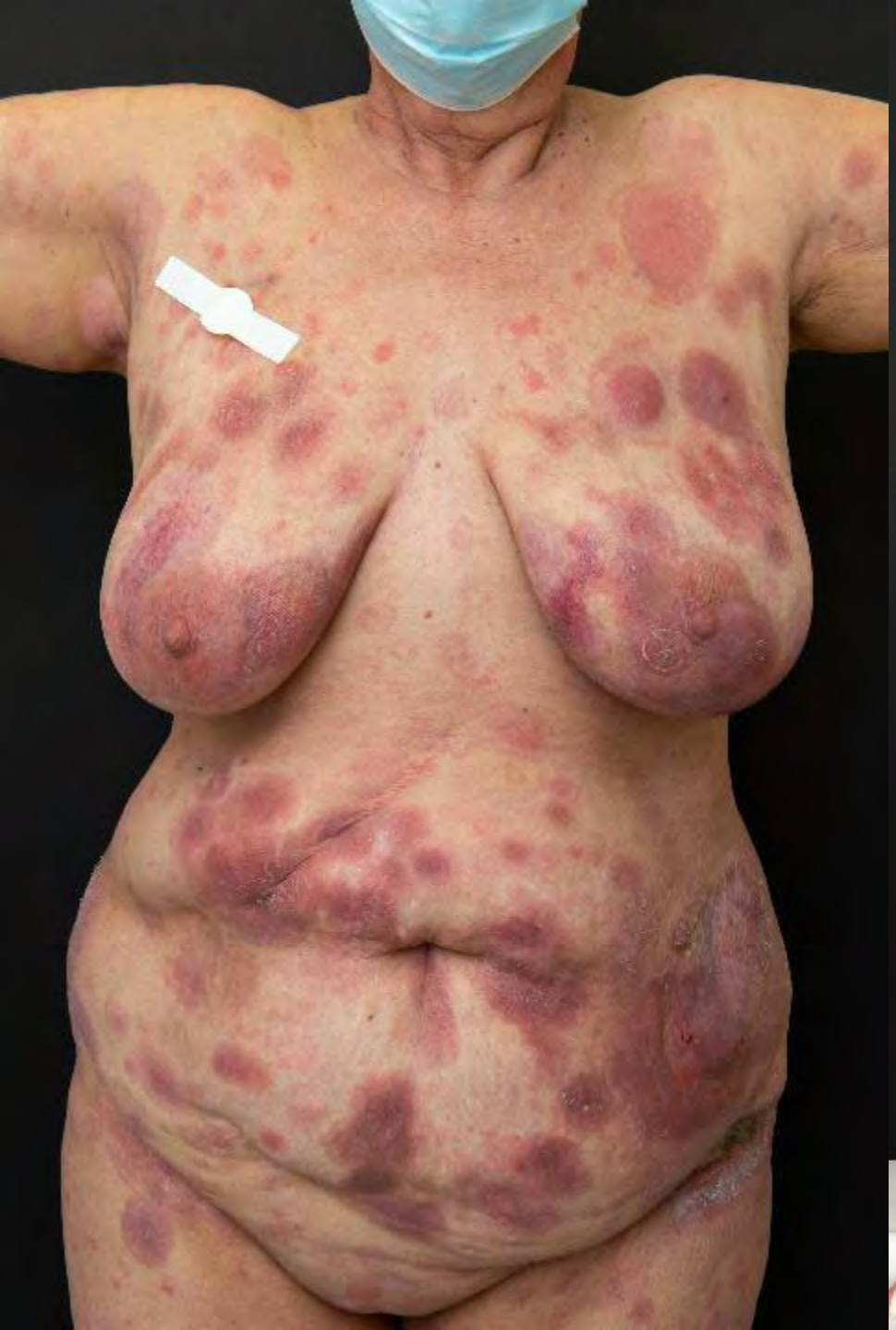
1st presentation

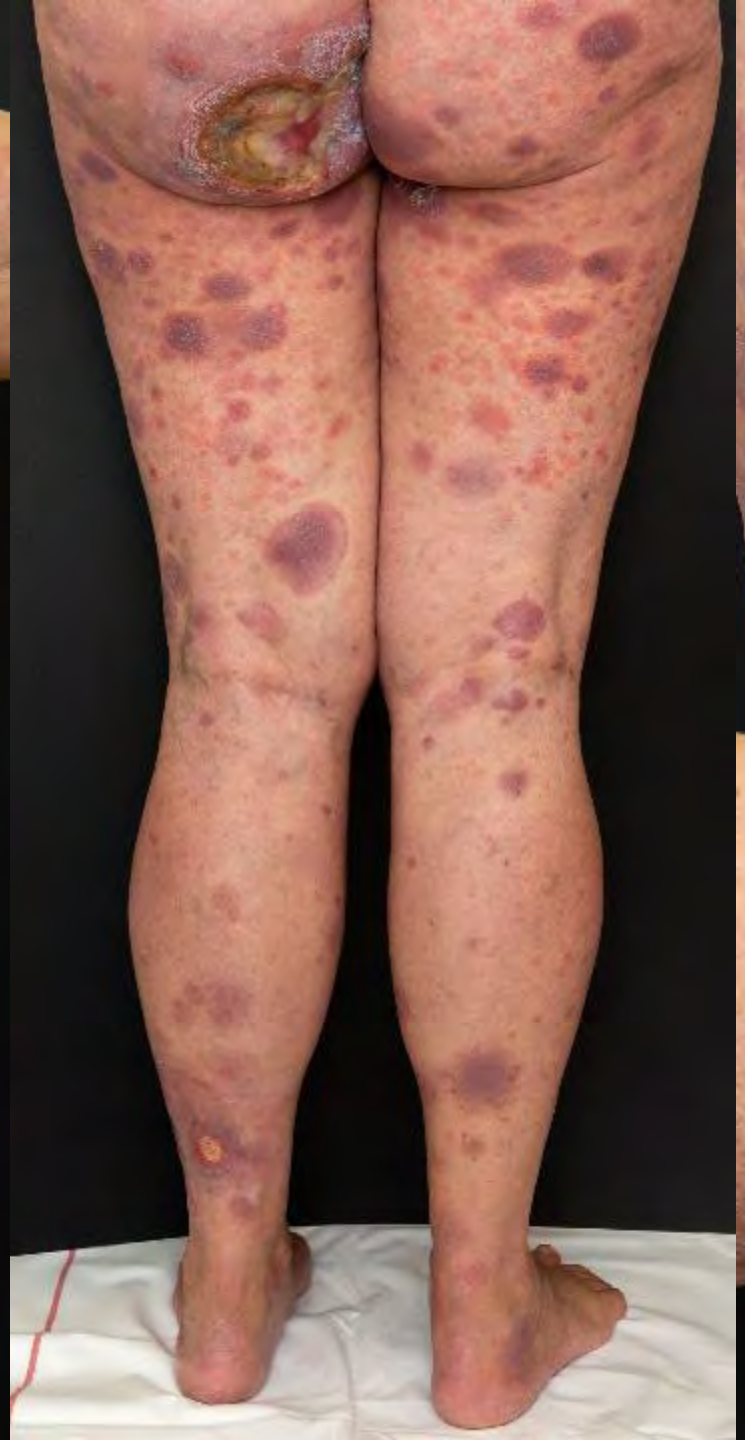


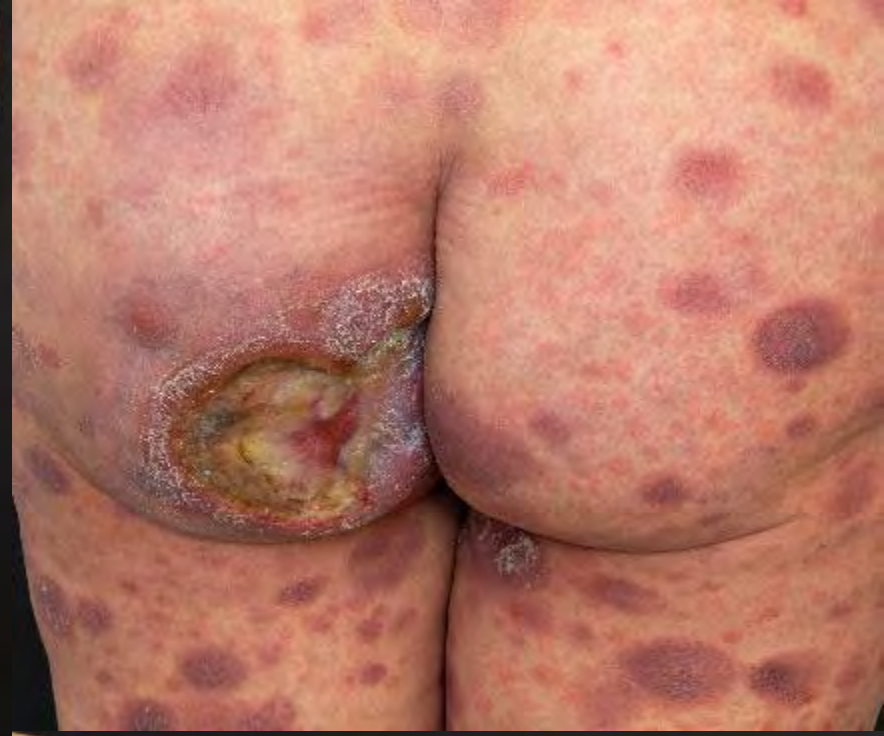
3 years later

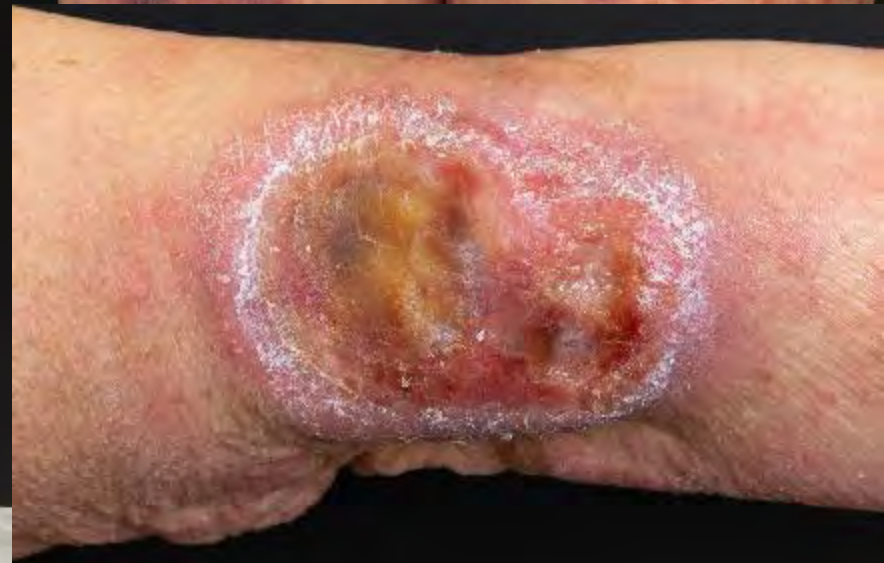


4 years later

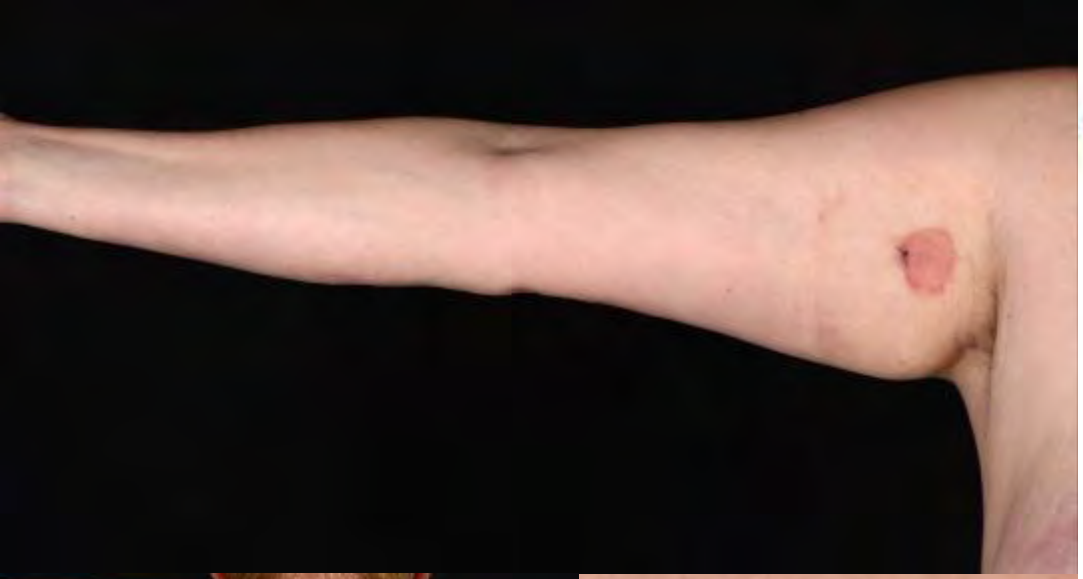


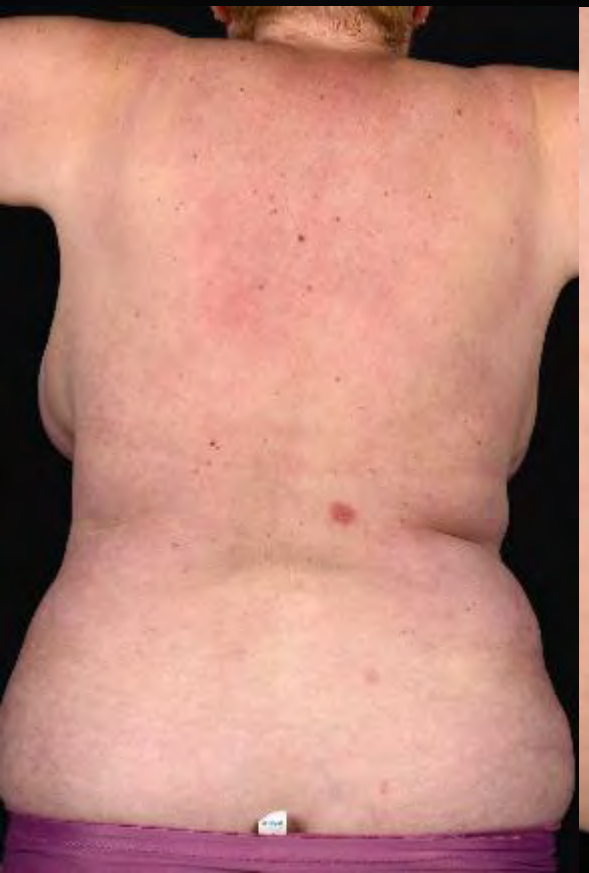


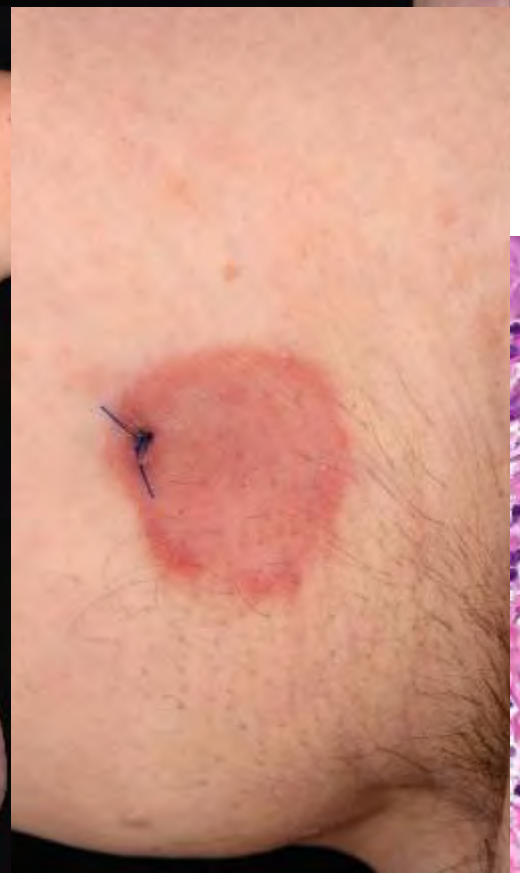


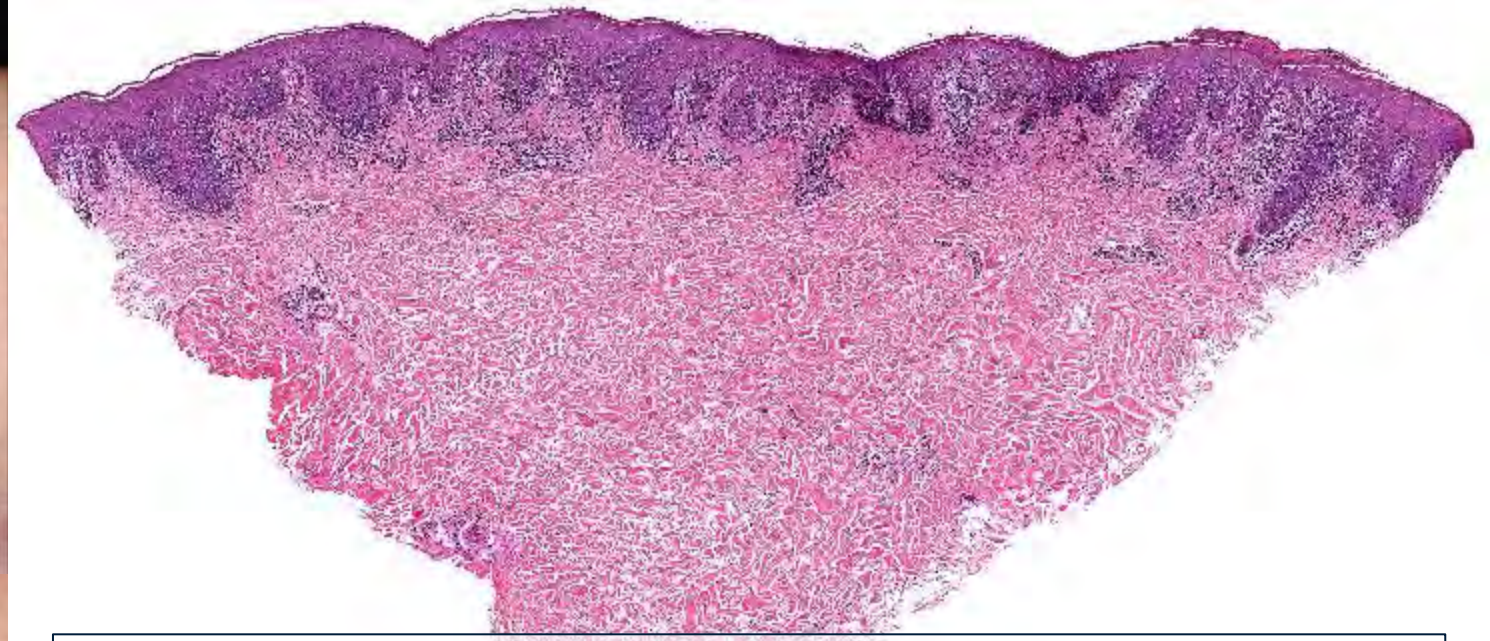


Died of progressive disease 5 years after 1st presentation

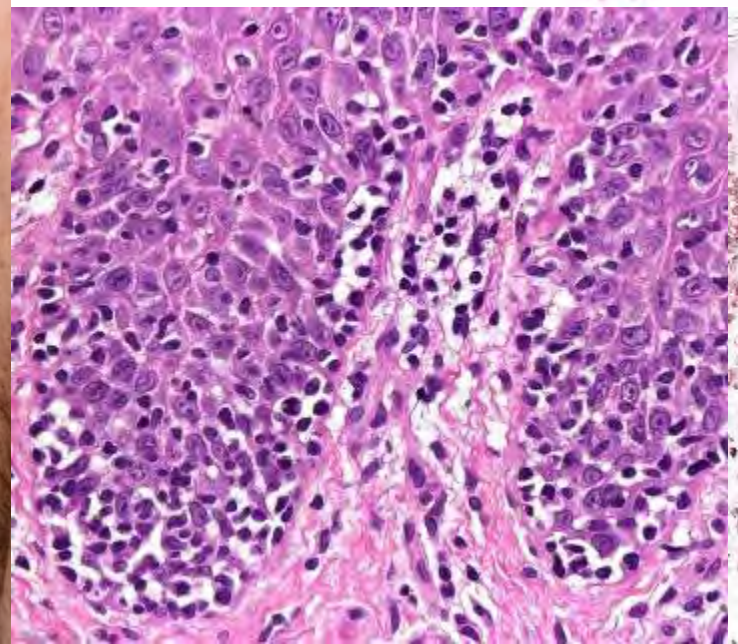


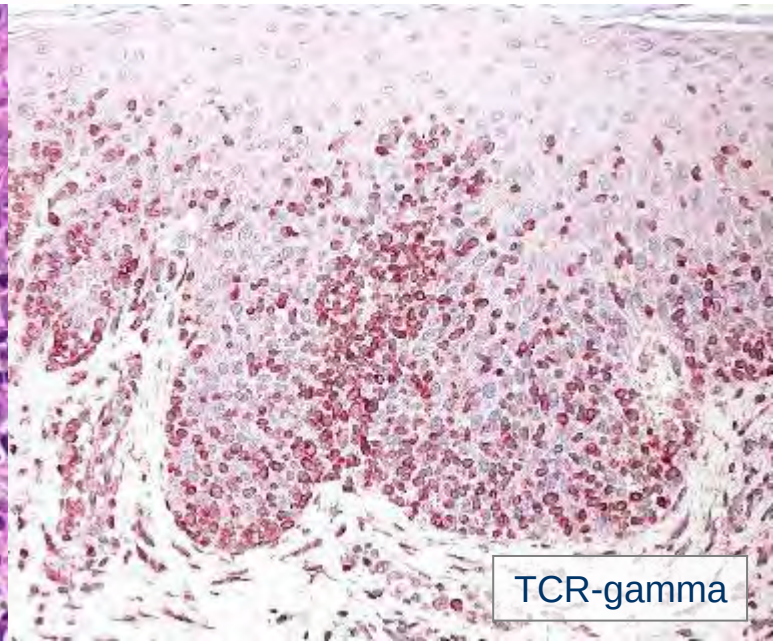






Cutaneous γ/δ T-cell lymphoma





Primary cutaneous gamma/delta T-cell lymphoma

- Included as a distinct entity in the International Consensus Classification (ICC) of Myeloid and Lymphoid Neoplasms, the 2019 and 2024 updates of classification of cutaneous lymphomas by the EORTC, and the 5th edition of the WHO Classification of Haematolymphoid Tumours
- *Essential diagnostic criteria:* Positivity of neoplastic cells for TCR gamma/delta; no history of mycosis fungoides
- *Main differential diagnoses:* Cytotoxic mycosis fungoides; Lymphomatoid papulosis with gamma/delta phenotype; Subcutaneous panniculitis-like T-cell lymphoma; Other cutaneous cytotoxic lymphomas; Lupus erythematosus
- *Question still debated:* Distinction between early stages of primary cutaneous gamma/delta T-cell lymphoma and gamma/delta+ mycosis fungoides?

Diagnosis of gamma/delta mycosis fungoides requires longitudinal clinical observation

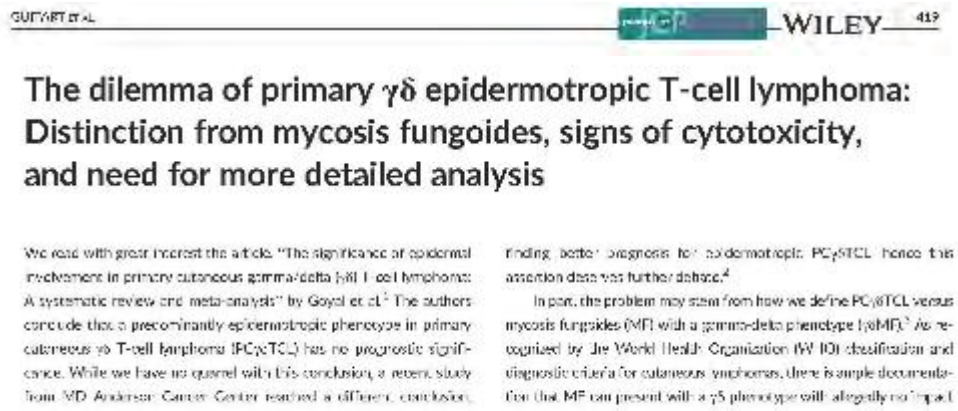
To the Editor: It is unclear whether epidermotropic cutaneous T cell lymphomas (CTCLs) exhibiting a T-cell receptor gamma delta (TCR$\gamma\delta$) phenotype initially presenting with patches and plaques should be considered a variant of mycosis fungoides ($\gamma\delta$-MF) or as primary cutaneous $\gamma\delta$ T cell lymphomas (PC$\gamma\delta$TCL).[1] Because PC$\gamma\delta$TCL is considered an aggressive lymphoma,[1] the misclassification of epidermotropic PC$\gamma\delta$TCL as MF may delay the decision to use systemic treatments. Our objective was to identify unique features that differentiate $\gamma\delta$-MF from epidermotropic PC$\gamma\delta$TCL.

We reviewed 4 patients (2 women and 2 men 39-71 years of age) from our cutaneous lymphoma clinic who presented with features resembling early-stage MF (stages IA-IB) and who had the TCR$\gamma\delta$ phenotype. The clinical courses and histopathologic and immunophenotypic profiles of each patient are described in detail (Supplemental Tables I and II available via Mendeley at https://doi.org/10.17632/fhvvw2xtpy6.2). Cutaneous signs preceded the first diagnostic biopsy specimen by a median of 20 months (range 6-48 months), with a median follow-up of 64 months. Stage progression was noted in 3 patients, and 1 patient died. Besides case 1, all patients presented with patches and plaques on the distal extremities or the face rather than on sun-protected areas typical for MF. When disease progressed to tumors, the localization was atypical for classic MF (ie, the face and plantar aspects of the feet; Fig 1 and Supplemental Fig S1).

Histologically, the infiltrate was indistinguishable from classic early-stage MF (Supplemental Figs S2 and S3). Immunophenotypically, cases demonstrated cytotoxic markers (granzyme B or T-cell intracellular antigen 1), a double-negative phenotype (CD4−/CD8−), an absence of TCR-βF1, positivity for TCR$\gamma\delta$, and monoclonal rearrangements

In conclusion, CTCLs clinically and histologically presenting as early-stage MF with a cytotoxic and $\gamma\delta$ phenotype seem to have a more aggressive disease course compared with classic MF. We suggest reserving the diagnosis of $\gamma\delta$-MF only after an indolent clinical course is established.

Andrew Ferrier, Laura Soong, Abdulrahim Alabdulsalam, Brenden Kunimoto, Xiao Zhu, Jean Deschenes, Robert Gniadecki.



GUITART ET AL WILEY 419

The dilemma of primary γδ epidermotropic T-cell lymphoma: Distinction from mycosis fungoides, signs of cytotoxicity, and need for more detailed analysis

We read with great interest the article, "The significance of epidermal involvement in primary cutaneous gamma/delta (γδ) T cell lymphoma: A systematic review and meta-analysis" by Goyal et al.[1] The authors conclude that a predominantly epidermotropic phenotype in primary cutaneous γδ T-cell lymphoma (PCγδTCL) has no prognostic significance. While we have no quarrel with this conclusion, a recent study from MD Anderson Cancer Center reached a different conclusion, finding better prognosis for epidermotropic PCγδTCL; hence this assertion does not further debate.[2]

In part, the problem may stem from how we define PCγδTCL versus mycosis fungoides (MF) with a gamma-delta phenotype (γδMF).[3] As recognized by the World Health Organization (WHO) classification and diagnostic criteria for cutaneous lymphomas, there is ample documentation that MF can present with a γδ phenotype with allegedly no impact

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Christopher Chung
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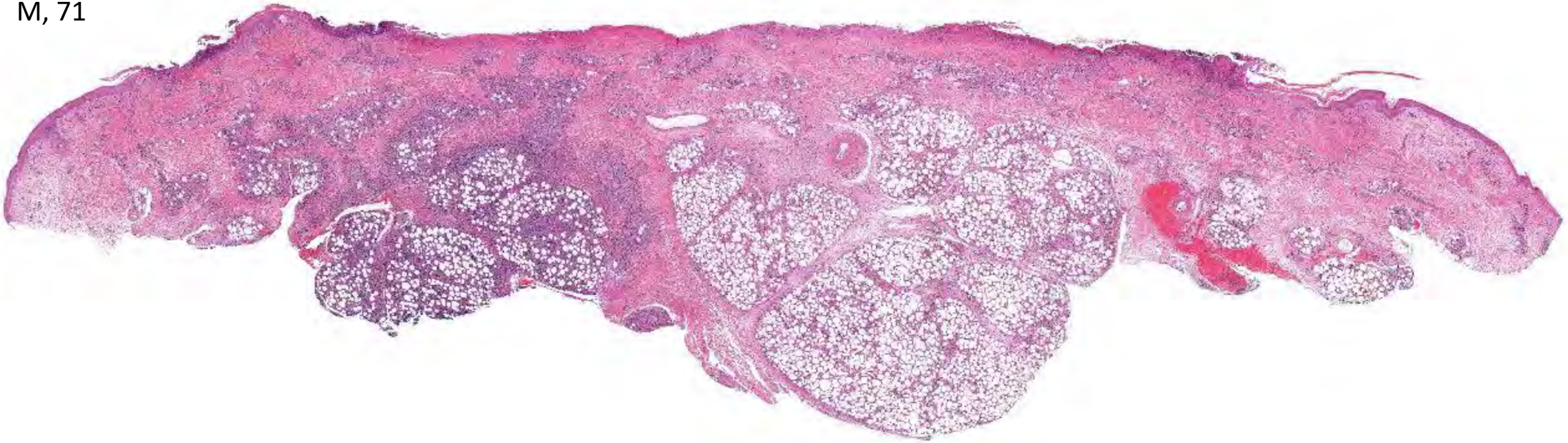
J Cut Pathol, 2022

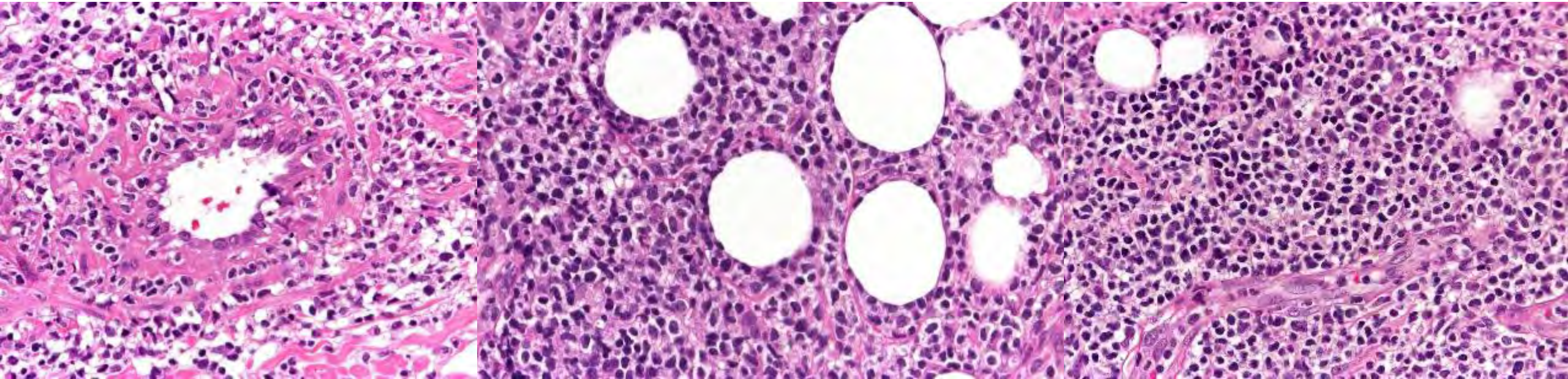
However, in our experience, epidermotropic-γδ MF can present similarly to αβ MF, especially with CD8+ or CD4/CD8 cases typically beginning with an indolent course, but eventually evolving into aggressive cytotoxic lymphomas. (...)

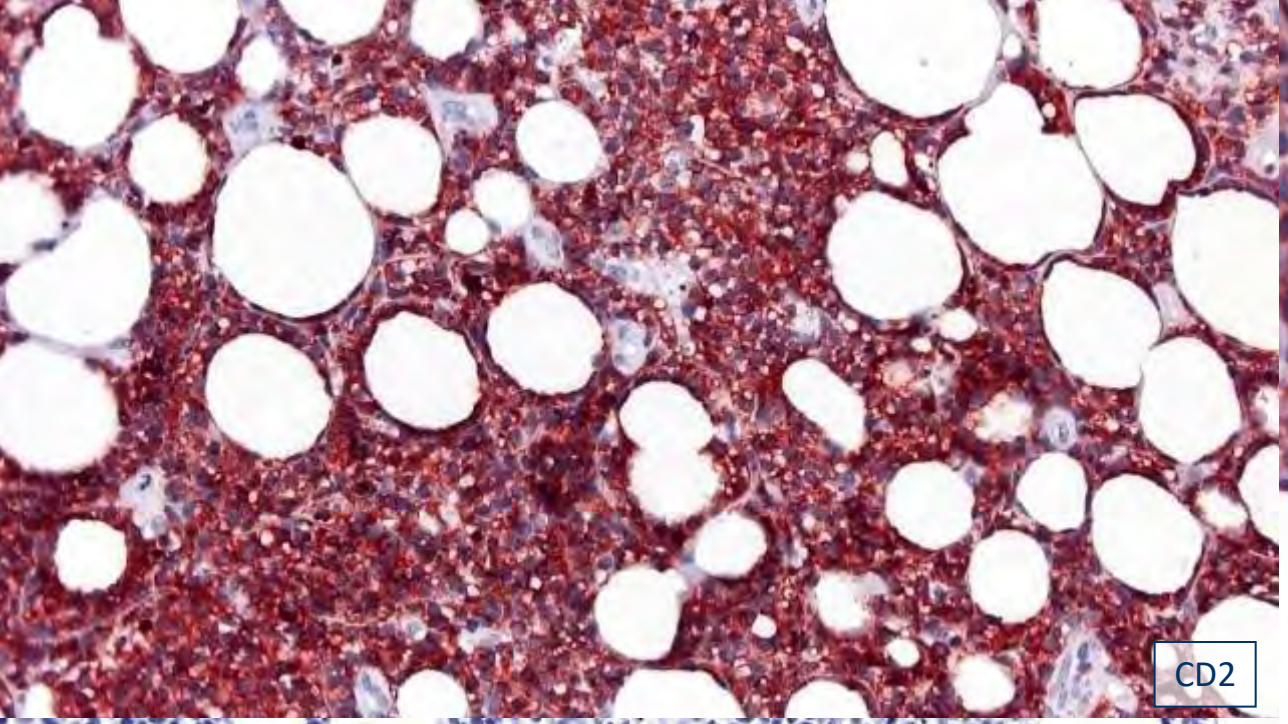
In our experience, there are clues to help identify epidermotropic γδ T-cell infiltrates at risk of progression to an aggressive course. Clinically, the presence of erosive or ulcerative features even when confined to limited patches, as well as tumoral evolution, should raise the possibility of γδ T-cell lymphoma rather than MF. Histopathologically, the same suspicions should be raised by the identification of conspicuous or confluent necrotic keratinocytes, ulceration, adnexotropism, hemorrhage, and obviously the tumoral involvement of dermis and subcutaneous tissue.

M, 71



(Consultation Dr. Walsh, Halifax)

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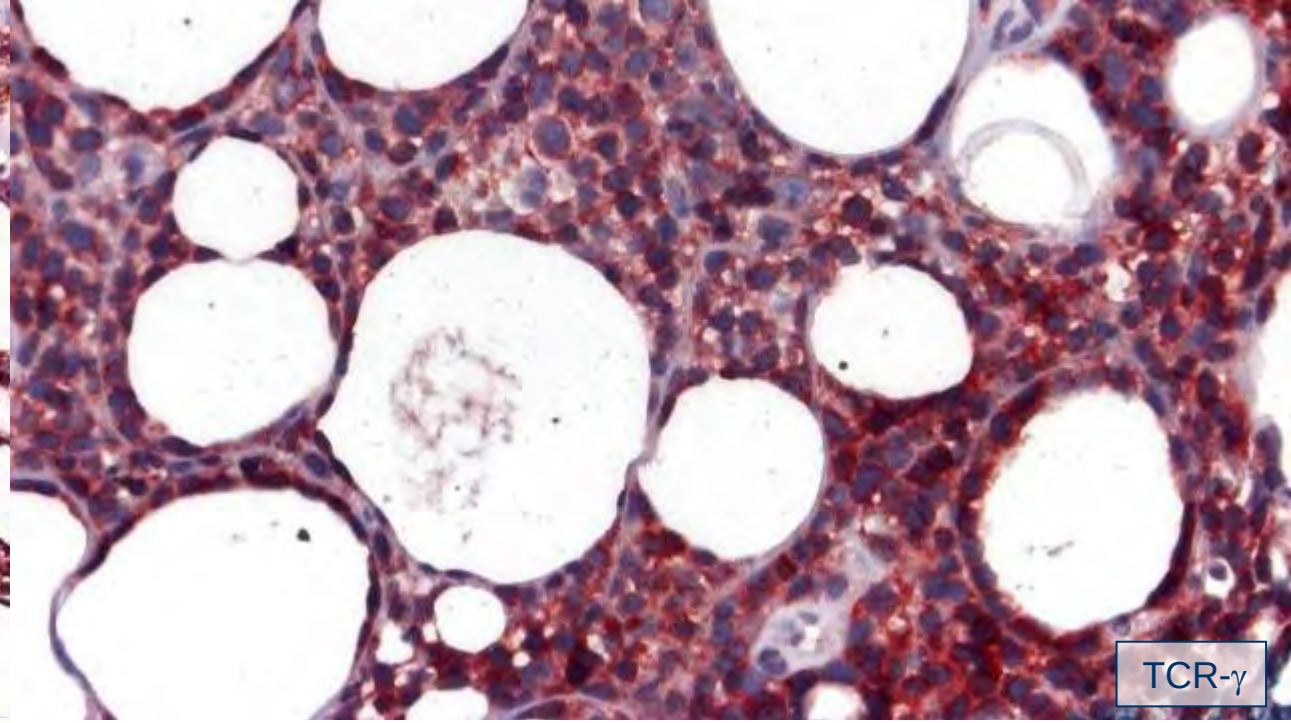
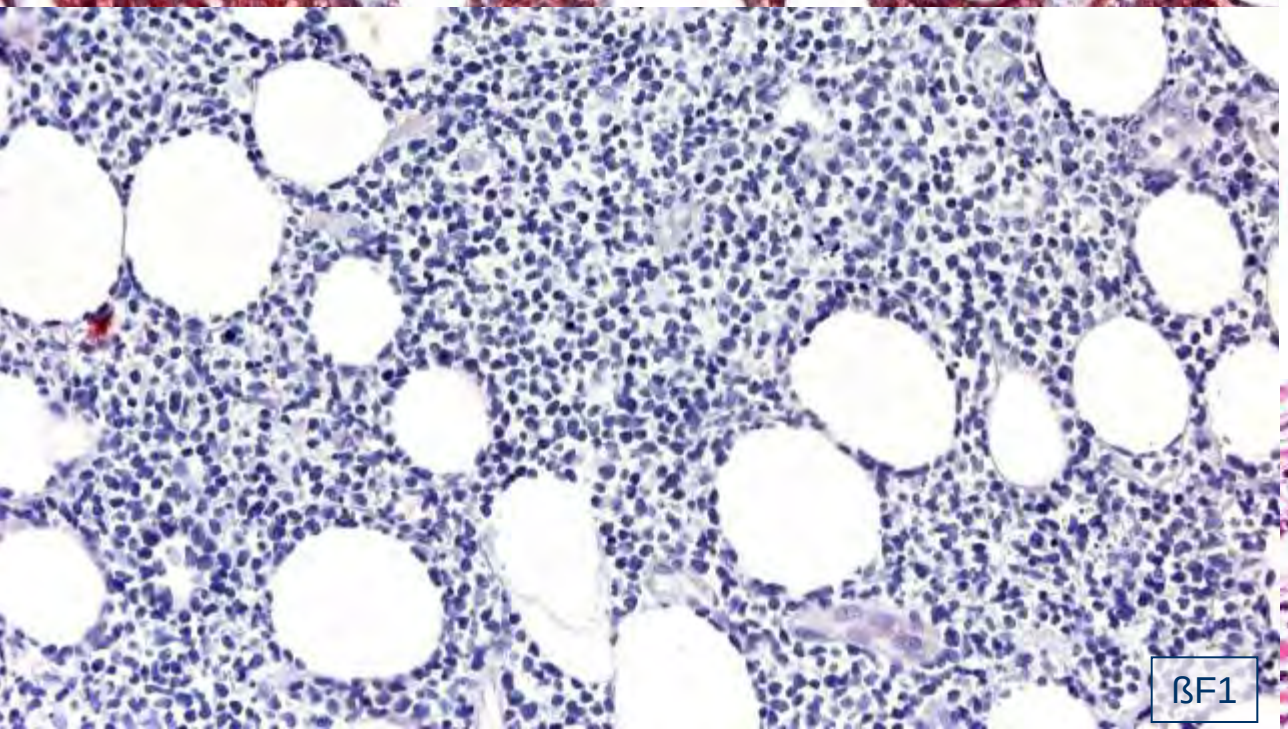

TCR-γ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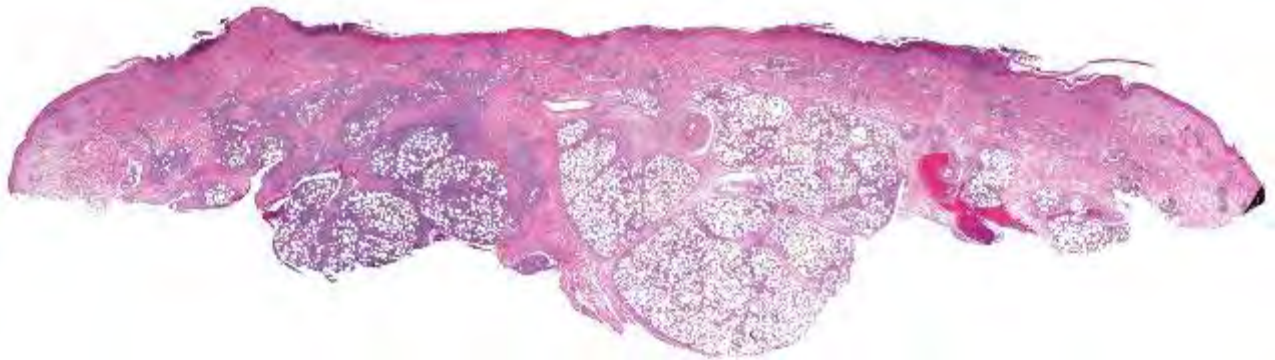

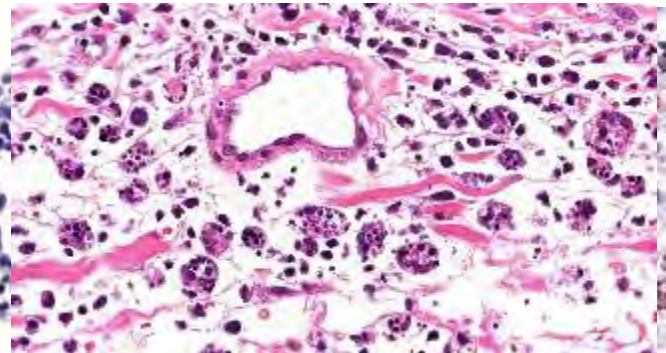

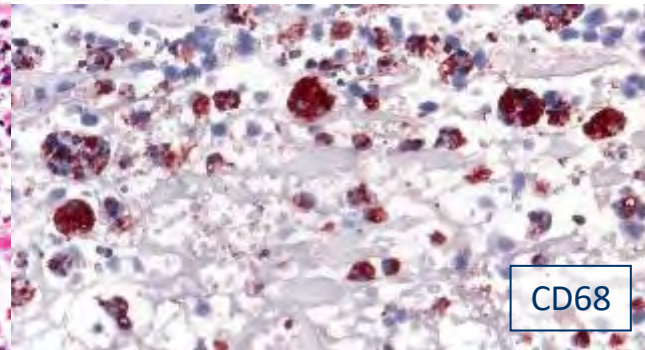
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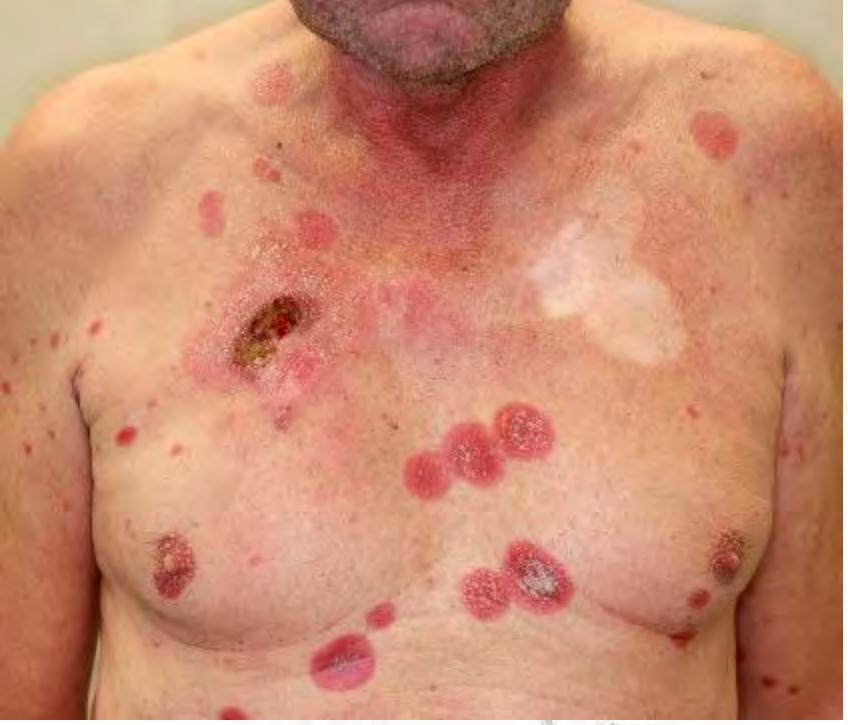
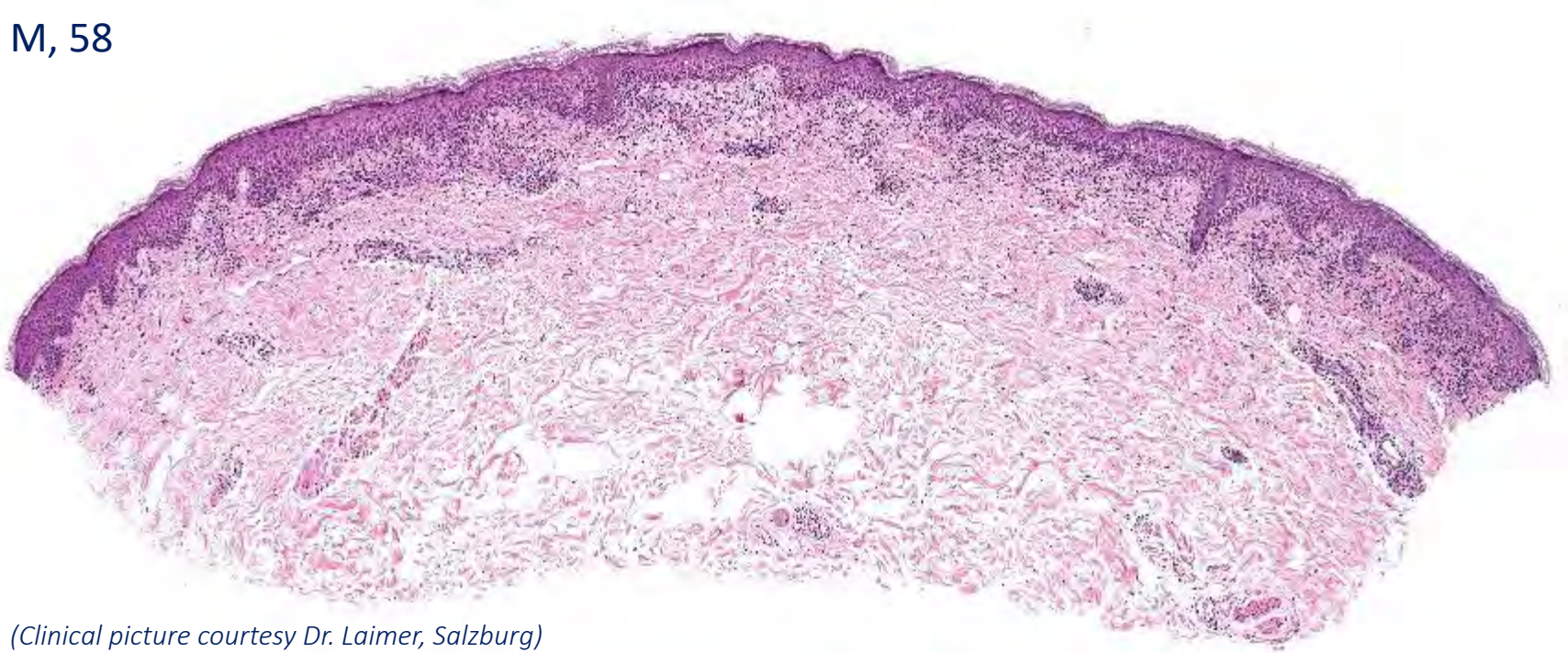
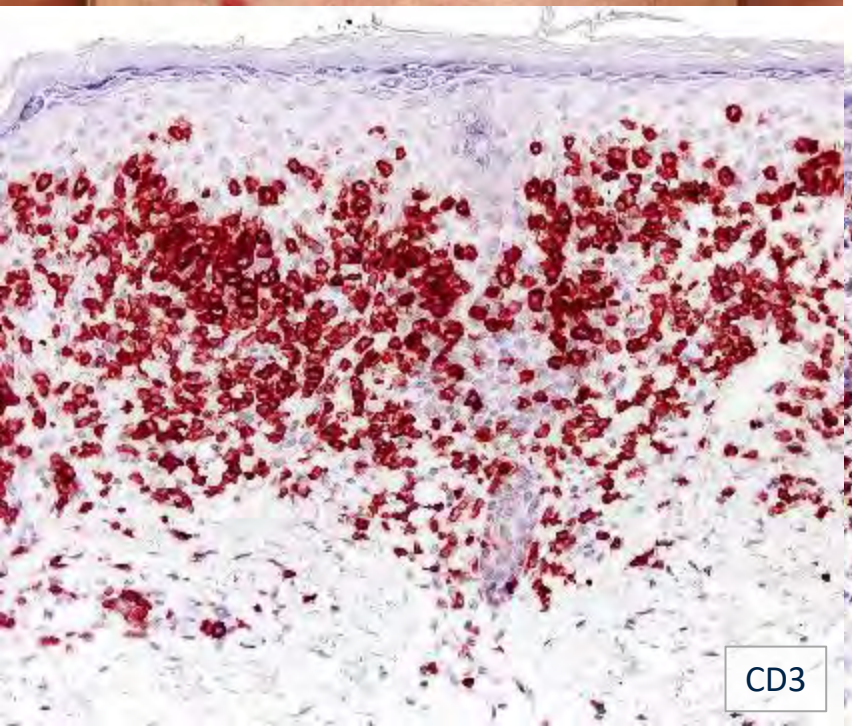
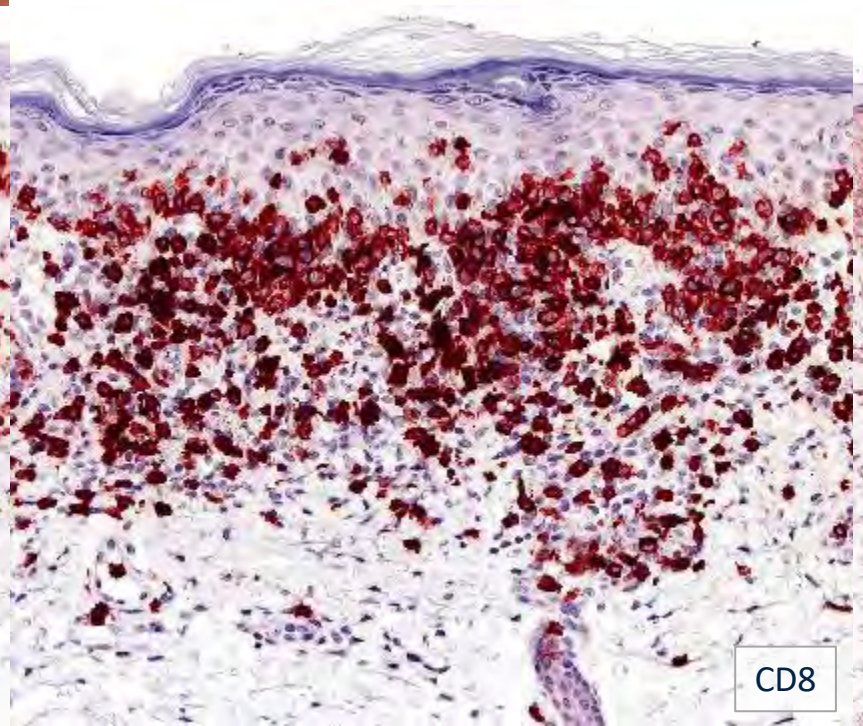


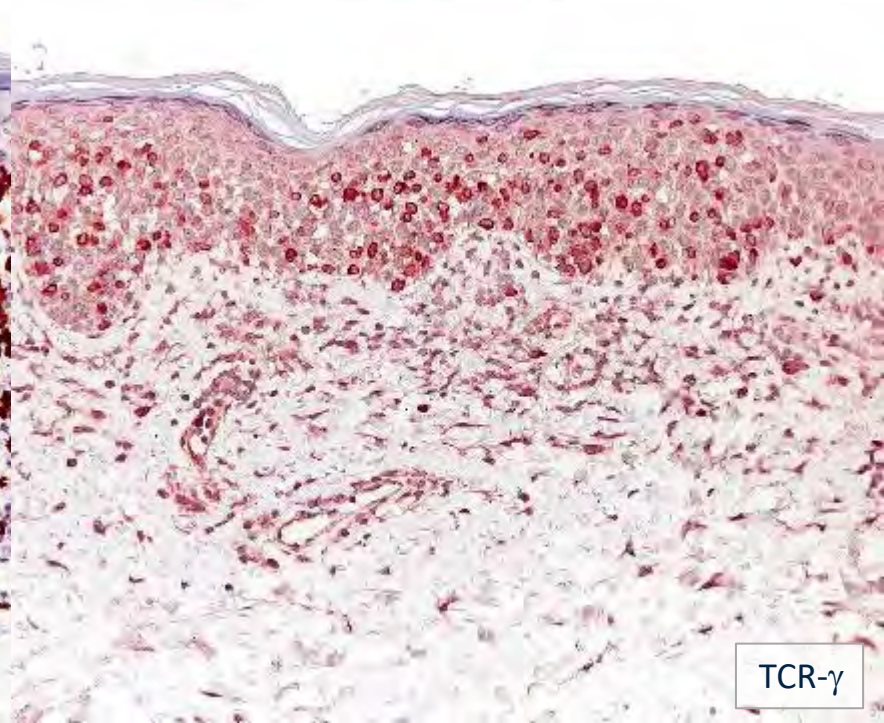
M, 58

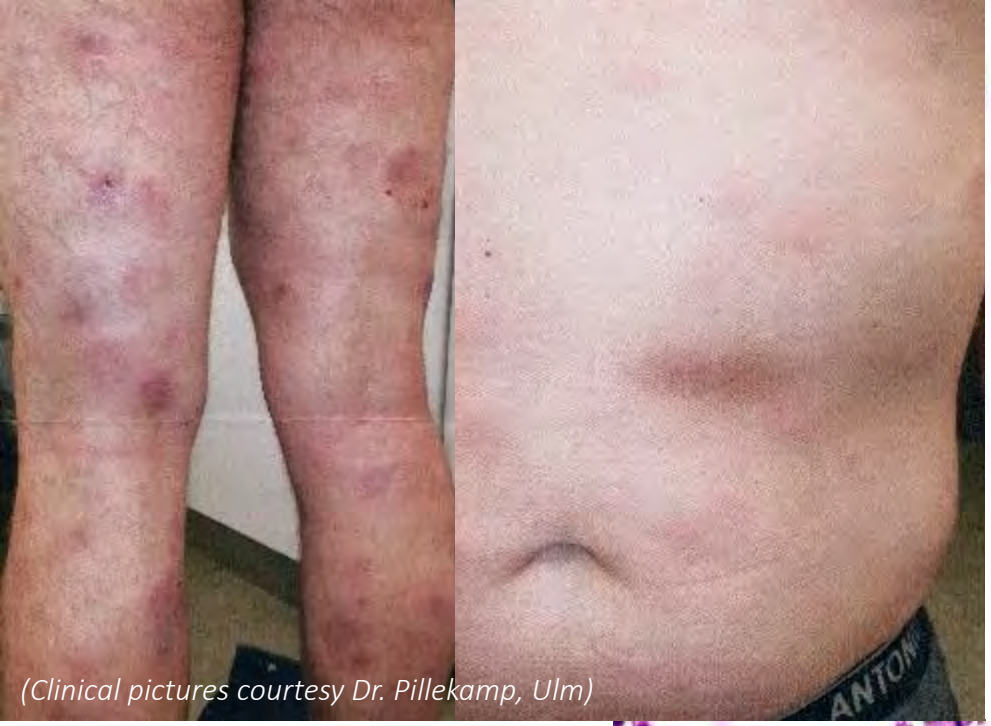


(Clinical picture courtesy Dr. Laimer, Salzburg)

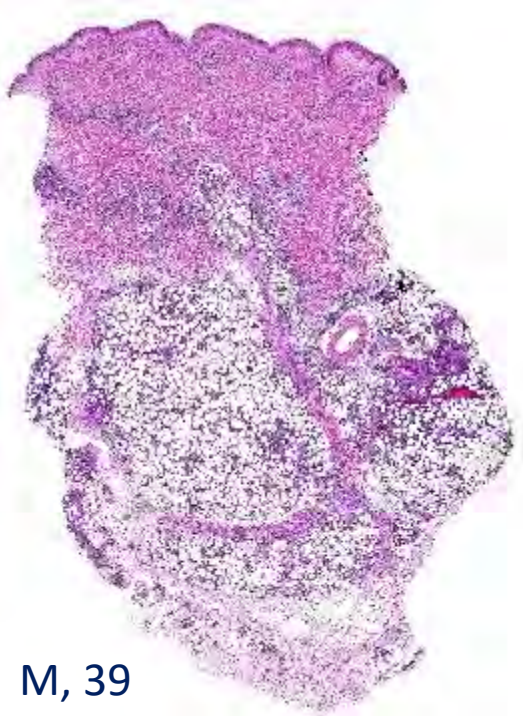




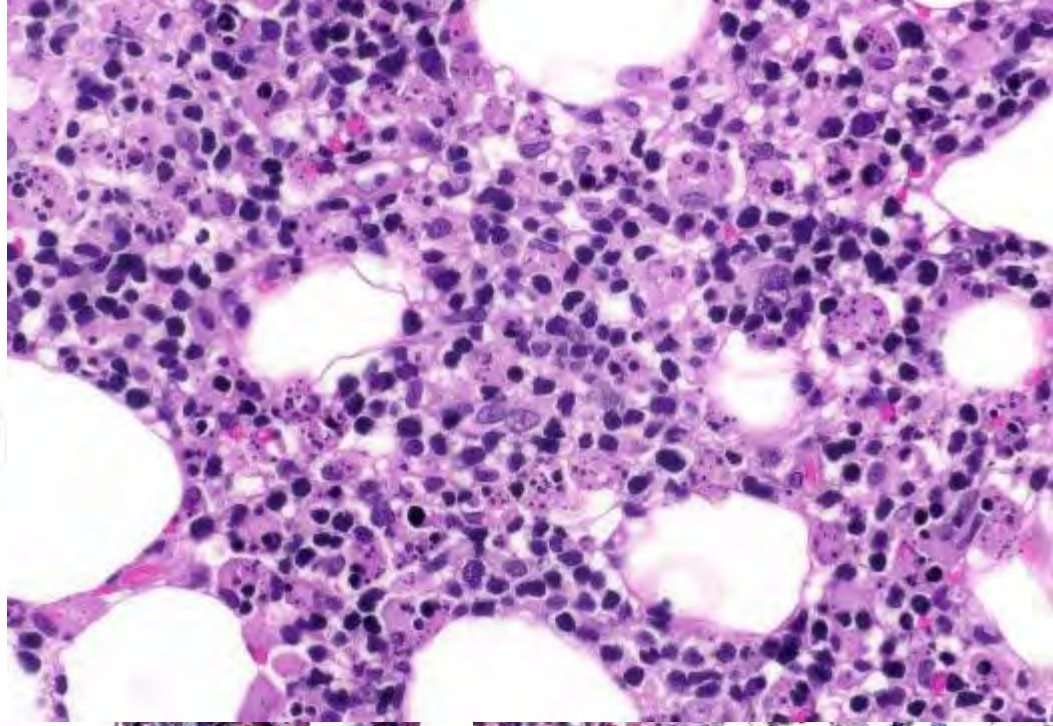


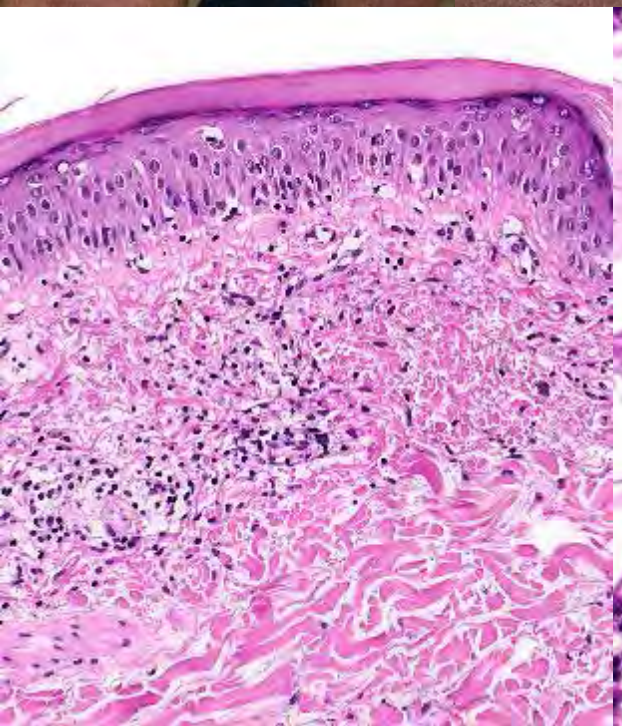


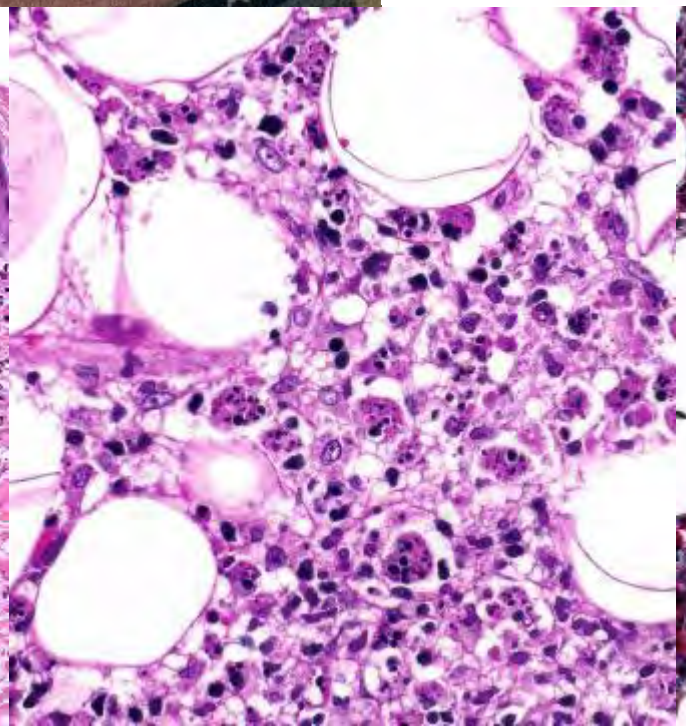
(Clinical pictures courtesy Dr. Pillekamp, Ulm)

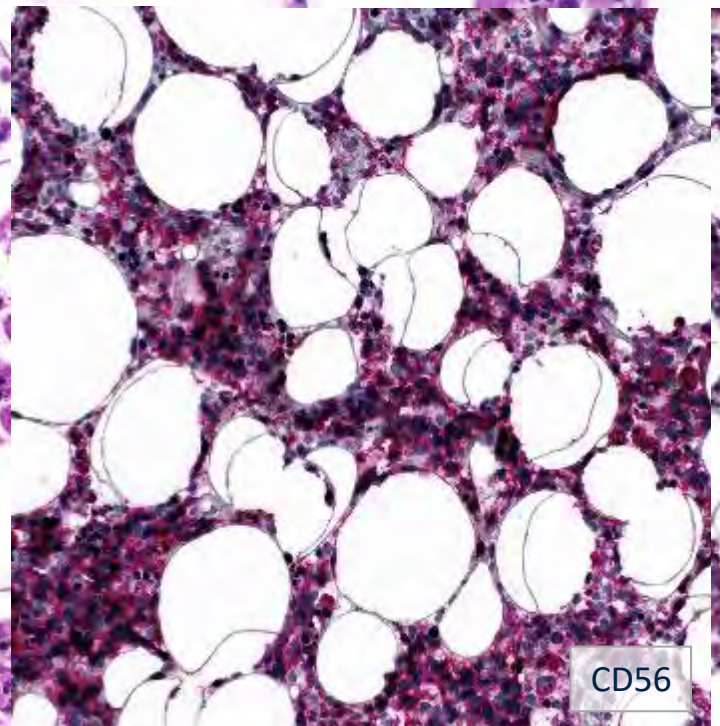


M, 39

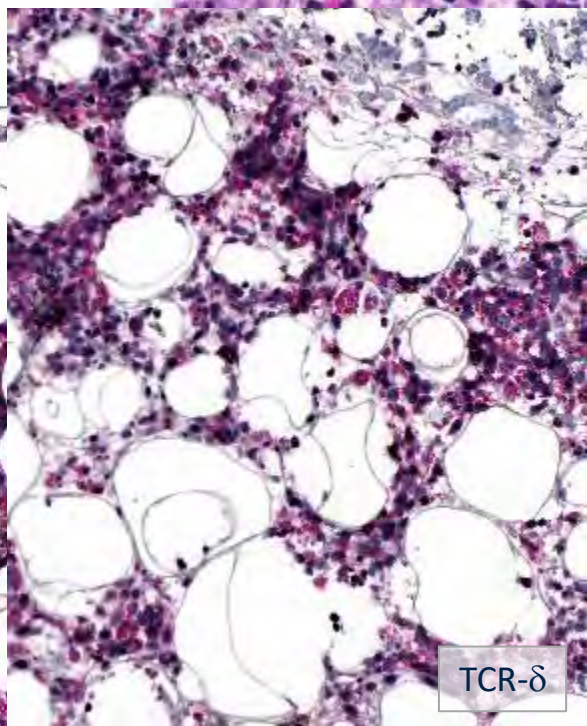






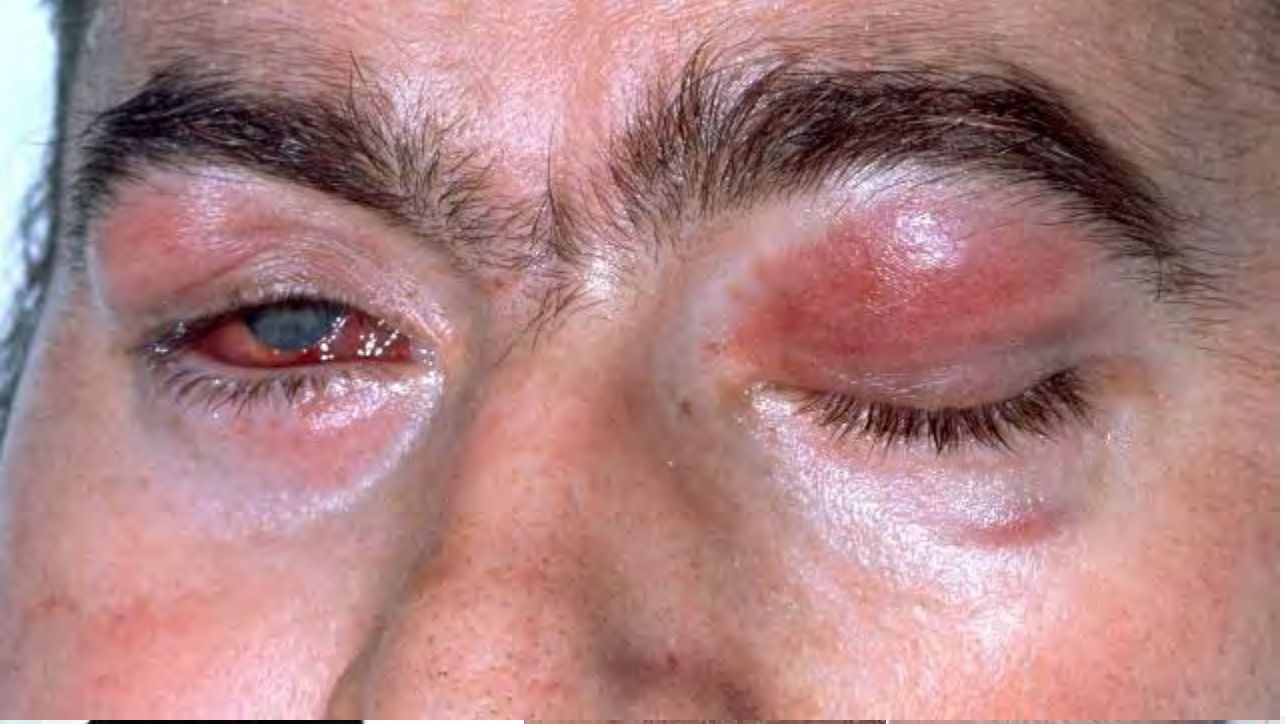


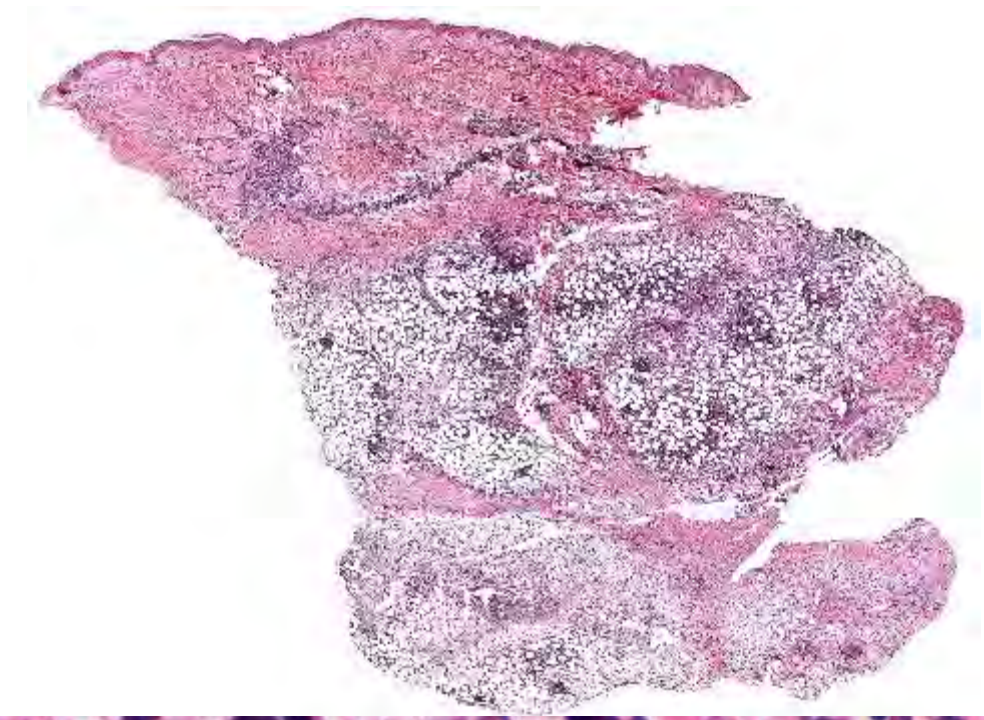
CD56

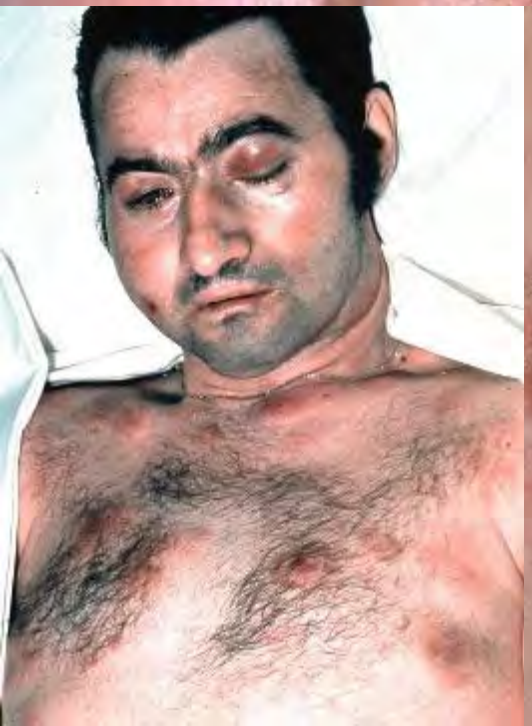


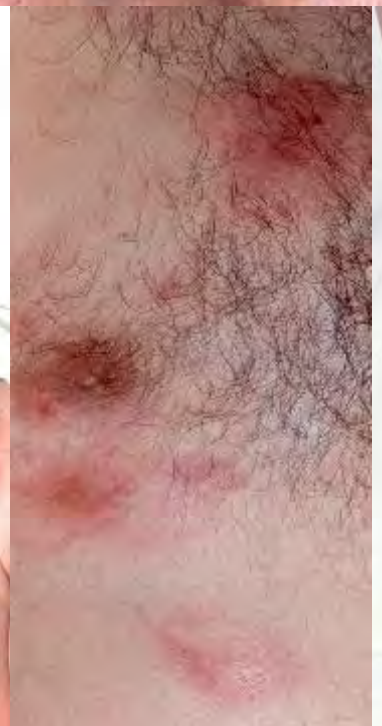
TCR-δ

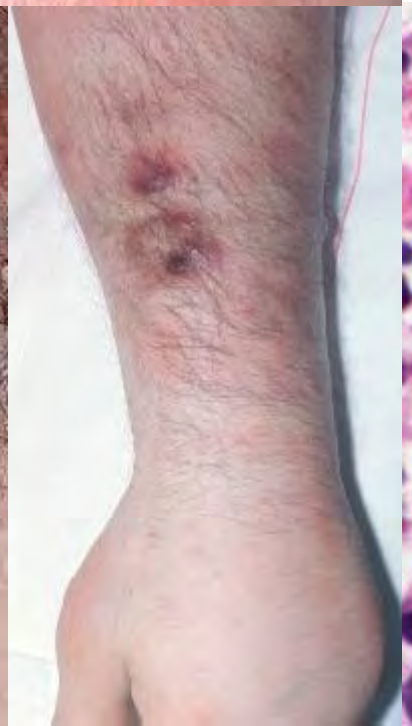
M, 34

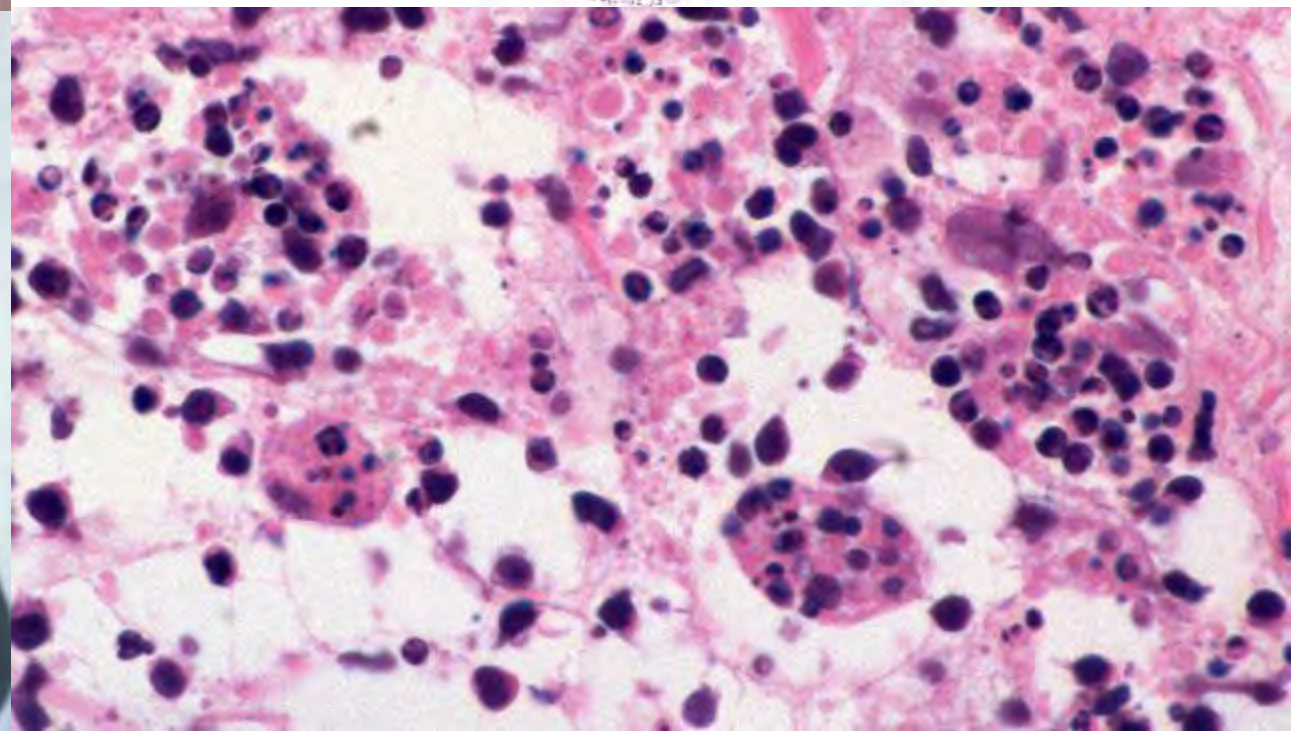


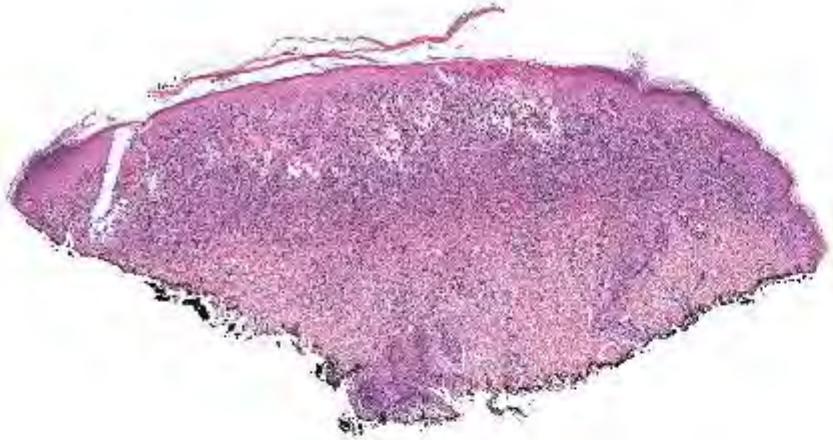


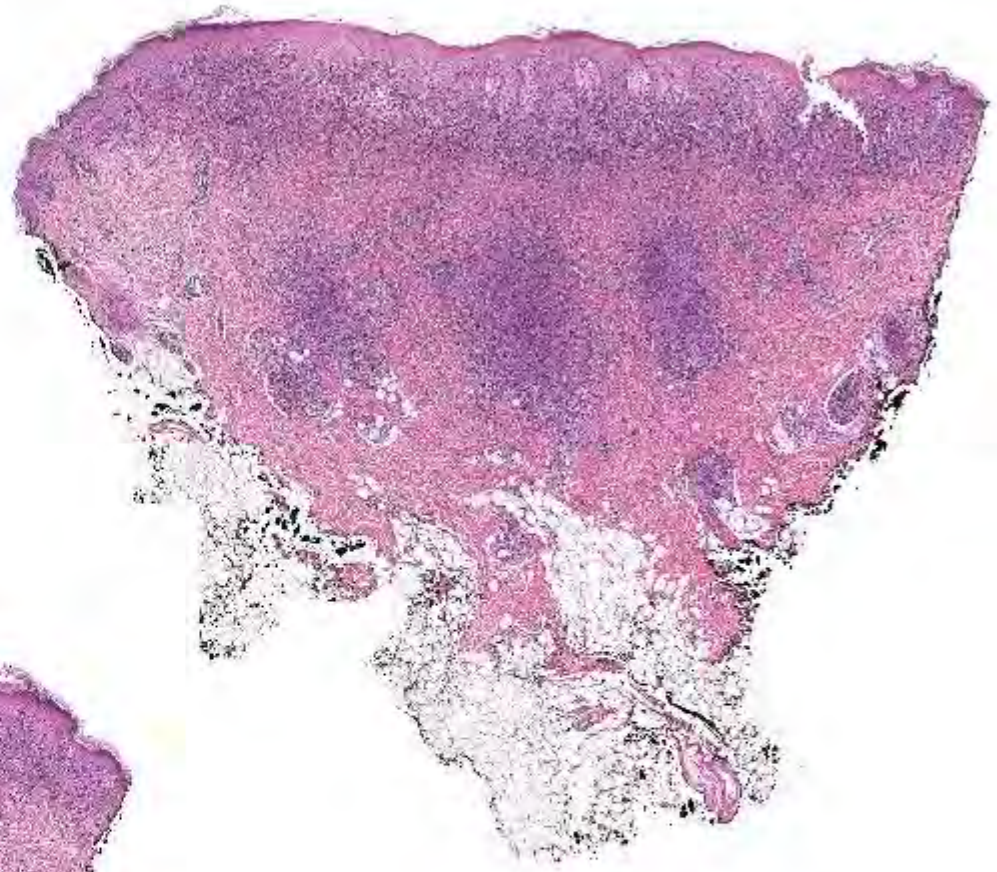


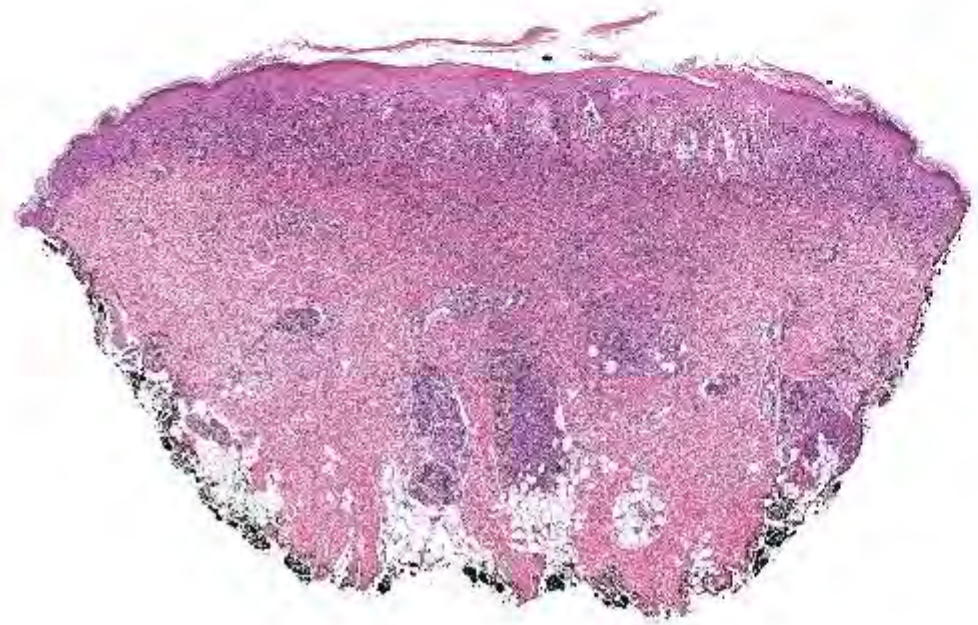


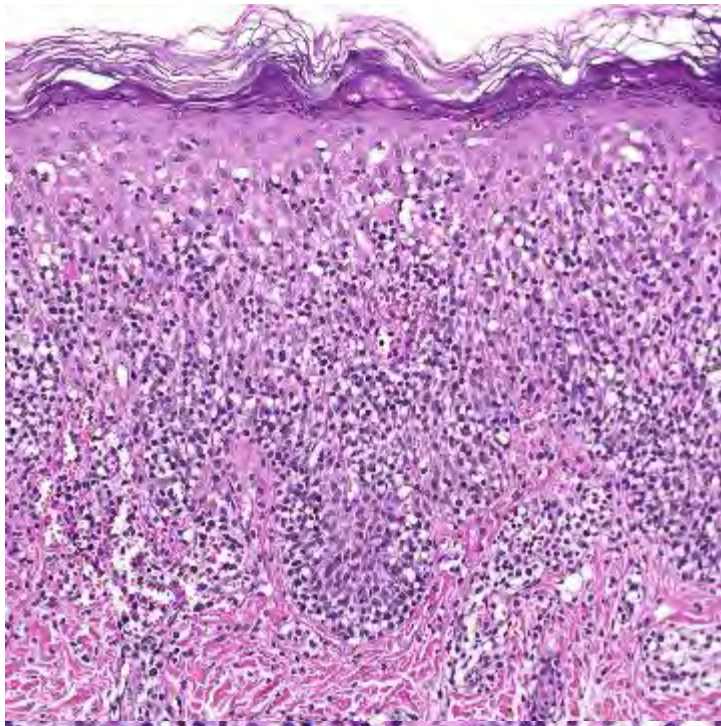


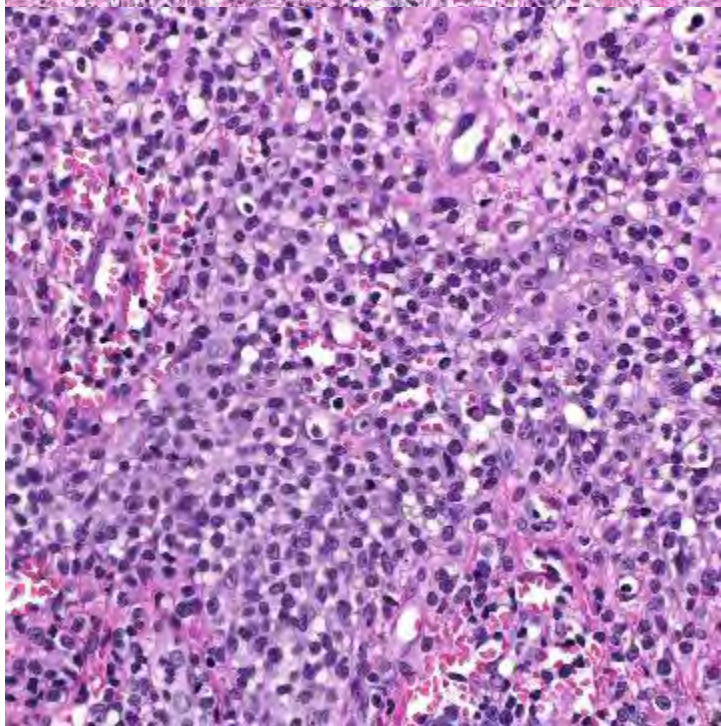








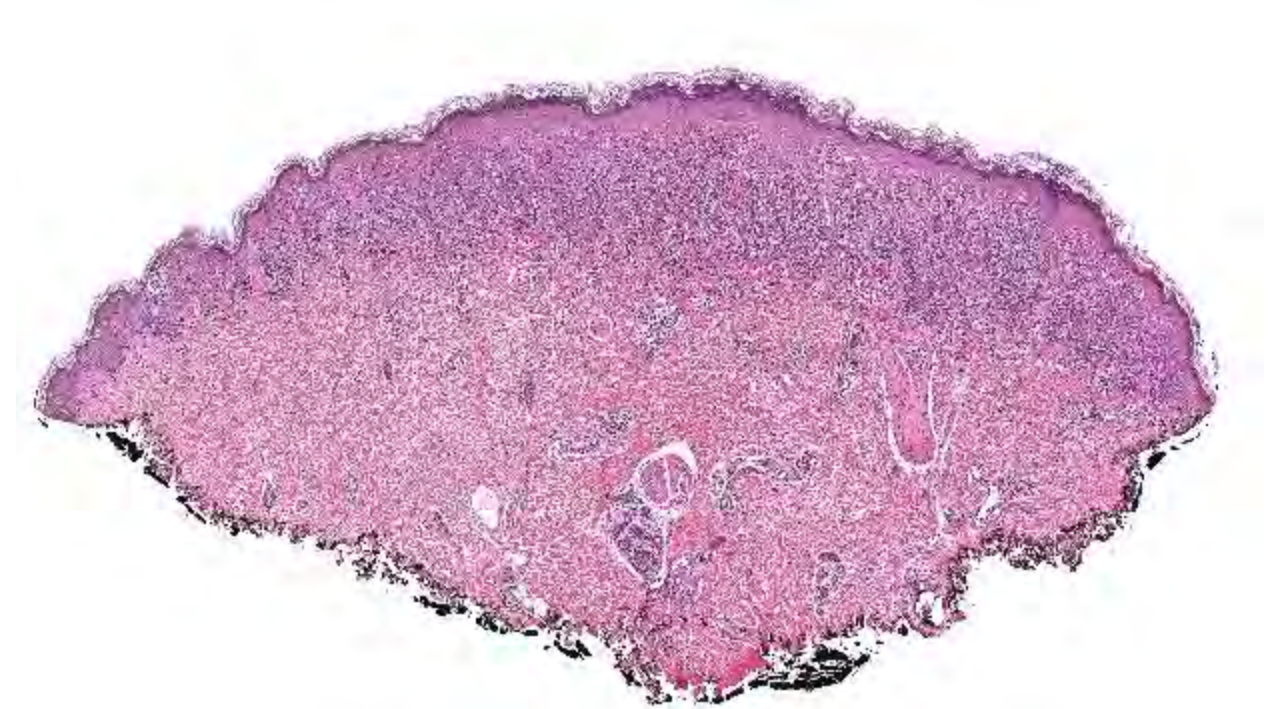


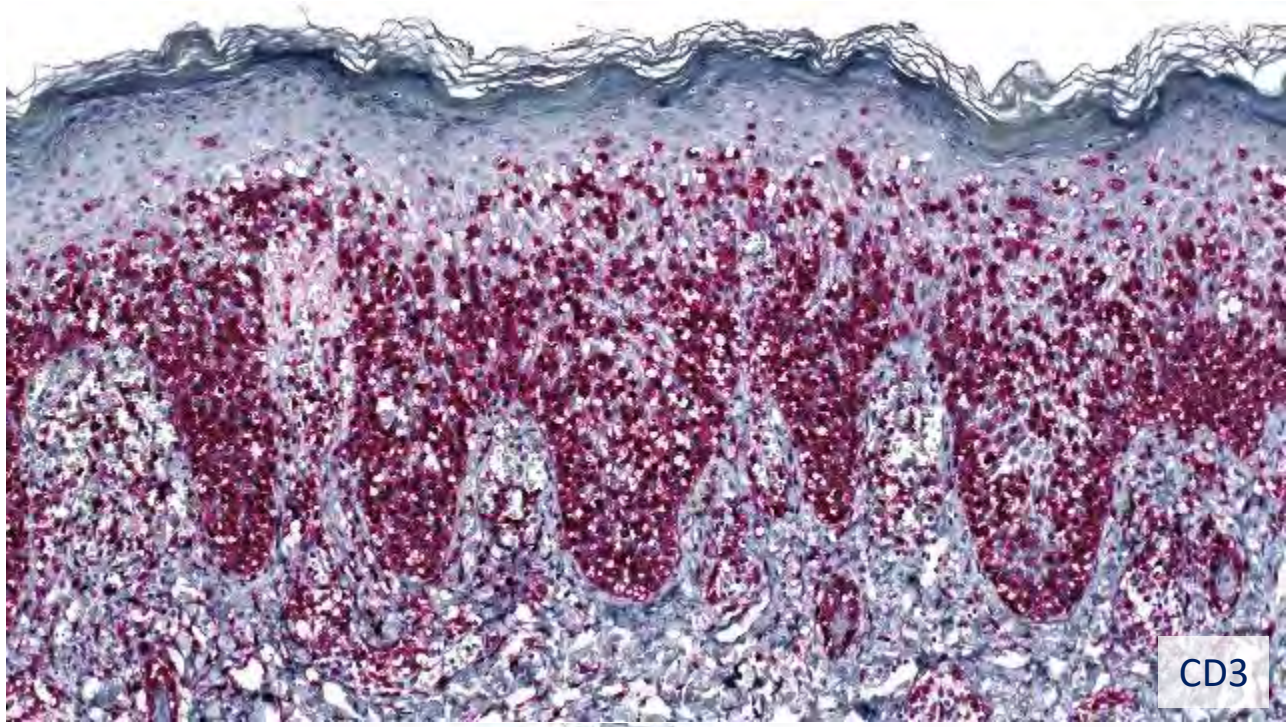


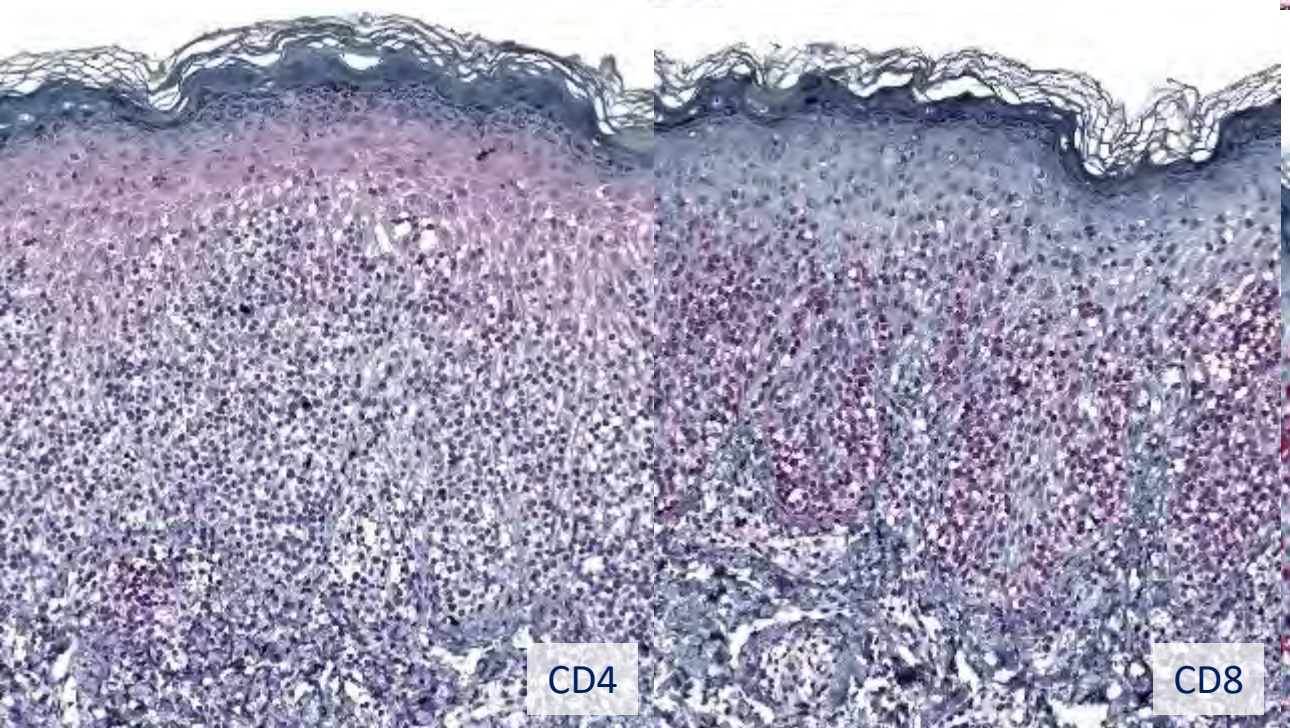
M, 1

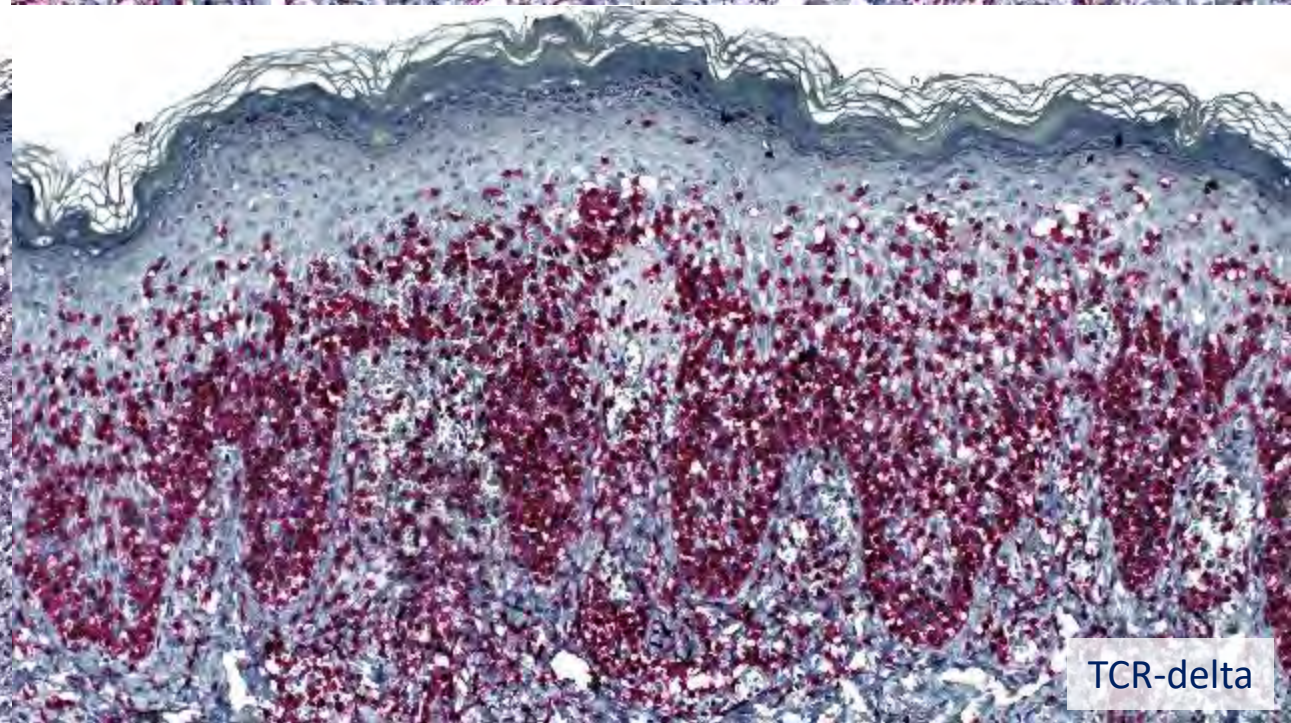
At the age of 10 months onset of a pink papule on the left thigh, rapidly becaming larger and ulcerating.

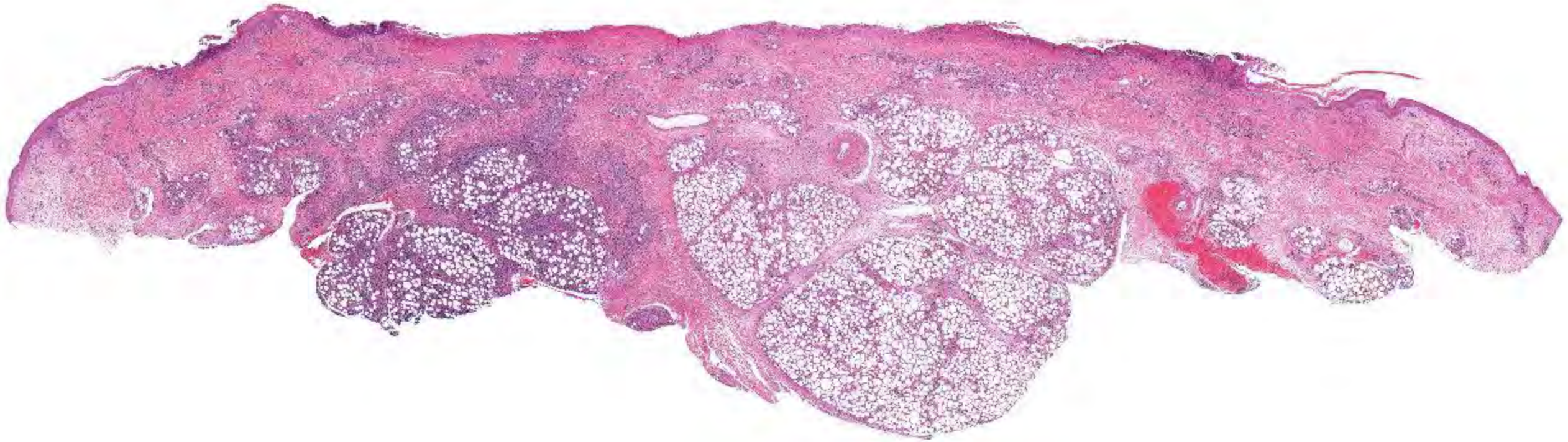
Consultation from Dr. Betina Werner (Curitiba, Brazil)

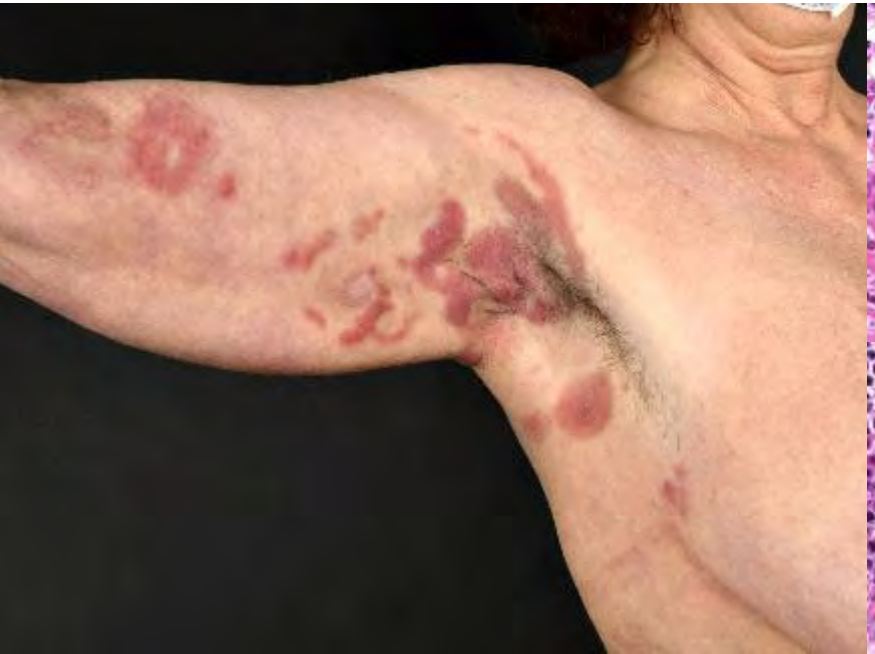


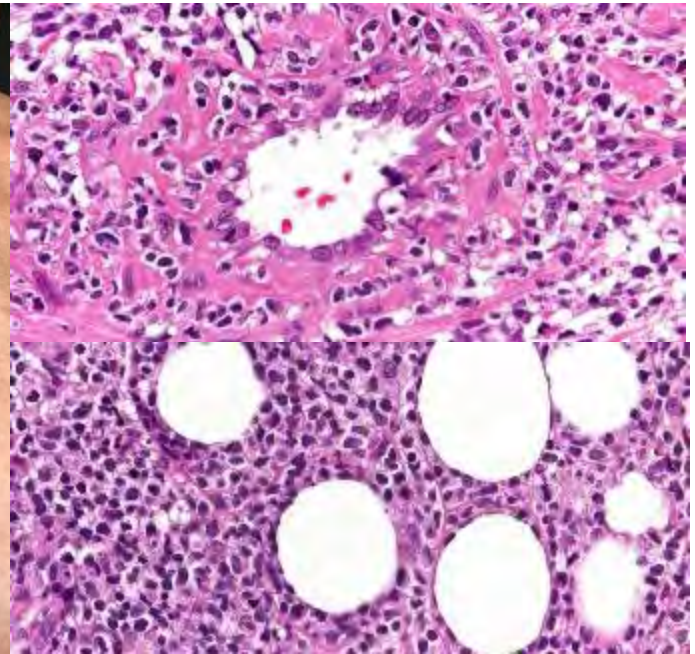

CD3


CD4
CD8


TCR-delta







Cutaneous γ/δ T-cell lymphoma

Cases lumped in the past together with MF and SPTCL.

A γ/δ phenotype is not unique to cutaneous γ/δ T-cell lymphoma (MF, LyP, ALCL), but is never observed in reactive conditions (clusters of γ/δ+ T-cells may be observed in LE panniculitis).

Oft involvement of both epidermis and subcutaneous fat; angiocentricity / angiotropism.

Hemophagocytic syndrome (particularly in tumors involving the subcutaneous fat).

Diffuse large B-cell lymphoma, leg-type

- Included as a distinct entity in the International Consensus Classification (ICC) of Myeloid and Lymphoid Neoplasms, the 2019 and 2024 updates of classification of cutaneous lymphomas by the EORTC, and the 5th edition of the WHO Classification of Haematolymphoid Tumours
- *Essential diagnostic criteria:* Cutaneous infiltrate of large cells (immunoblasts, centroblasts) positive for B-cell markers
- *Main differential diagnoses:* Cutaneous follicular lymphoma with diffuse pattern of growth
- *Question still debated:* classified separately or included in an umbrella category of "immune-privileged DLBCL"?

Diffuse large B-cell lymphoma, leg-type – Important points

- The main differential diagnosis is represented by cutaneous follicular lymphoma, diffuse type; in the lymph nodes these 2 entities considered as a spectrum of diffuse large B-cell lymphoma – in the skin completely different behavior and management of patients
- Criteria used in the lymph nodes to distinguish between the 2 entities do not work in the skin – i.e., follicular lymphoma, diffuse type has a good prognosis irrespective of phenotypic aspects identified by the so-called Hans algorithm
- Mutational landscape combining highly recurrent hotspot mutations in genes involved in NF-kB and B-cell signaling pathways, akin to the category of C5/MCD DLBCL and closely resembling diffuse large B-cell lymphomas arising in immune privileged sites such as primary DLBCL of the CNS and testis

ORIGINAL ARTICLE

Cell-of-origin classification using the Hans and Lymph2Cx algorithms in primary cutaneous large B-cell lymphomas

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Abstract

Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT) and primary cutaneous follicle center lymphoma with a diffuse population of large cells (PCFCL-LC) are both primary cutaneous B-cell lymphomas with large cell morphology (CLBCL) but with different clinical characteristics and behavior. In systemic diffuse large B-cell lymphoma, not otherwise specified (DLBCL-NOS), gene-expression profiling (GEP) revealed two molecular subgroups based on their cell of origin (COO) with prognostic significance: the germinal center B-cell like (GCB) subtype and the activated B-cell like (ABC) subtype. This study investigated whether COO classification is a useful tool for classification of CLBCL. For this retrospective study, 51 patients with PCDLBCL-LT and 15 patients with PCFCL-LC were analyzed for their COO according to the immunohistochemistry-based Hans algorithm and the NanoString GEP-based Lymph2Cx algorithm. In PCFCL-LC, all cases (100%) classified as GCB by both Hans and Lymph2Cx. In contrast, COO classification in PCDLBCL-LT was heterogeneous. Using Hans, 75% of the PCDLBCL-LT patients classified as non-GCB and 25% as GCB, while Lymph2Cx classified only 18% as ABC, 45% as unclassified/intermediate, and 39% as GCB. These COO subgroups did not differ in the expression of BCL2 and IgM, mutations in *MYD88* and/or *CD79B*, loss of *CDKN2A*, or survival. In conclusion, PCFCL-LC uniformly classified as GCB, while PCDLBCL-LT classified along the COO spectrum of DLBCL-NOS using the Hans and Lymph2Cx algorithms. In contrast to DLBCL-NOS, the clinical relevance of COO classification in CLBCL using these algorithms has limitations and cannot be used as an alternative for the current multiparameter approach in differentiation of PCDLBCL-LT and PCFCL-LC.

Keywords Primary cutaneous diffuse large B-cell lymphoma · Leg type · Primary cutaneous follicle center lymphoma · Cell-of-origin · Hans algorithm · Lymph2Cx algorithm

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Introduction

Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT) and primary cutaneous follicle center lymphoma with a diffuse population of large cells (PCFCL-LC) are both primary cutaneous B-cell lymphomas with large-cell morphology (CLBCL), but with different clinical characteristics and behavior [1]. PCDLBCL-LT is an aggressive lymphoma with a 5-year disease-specific survival (DSS) of 56% despite standard immunochemotherapy (R-CHOP). PCFCL-LC usually has an indolent behavior with a 5-year DSS of 95% and is preferably treated with local radiotherapy [2, 3]. PCDLBCL-LT was historically recognized as a subgroup of PCFCL-LC with a somewhat different morphology, typical presentation with skin lesions on the leg(s), and a more

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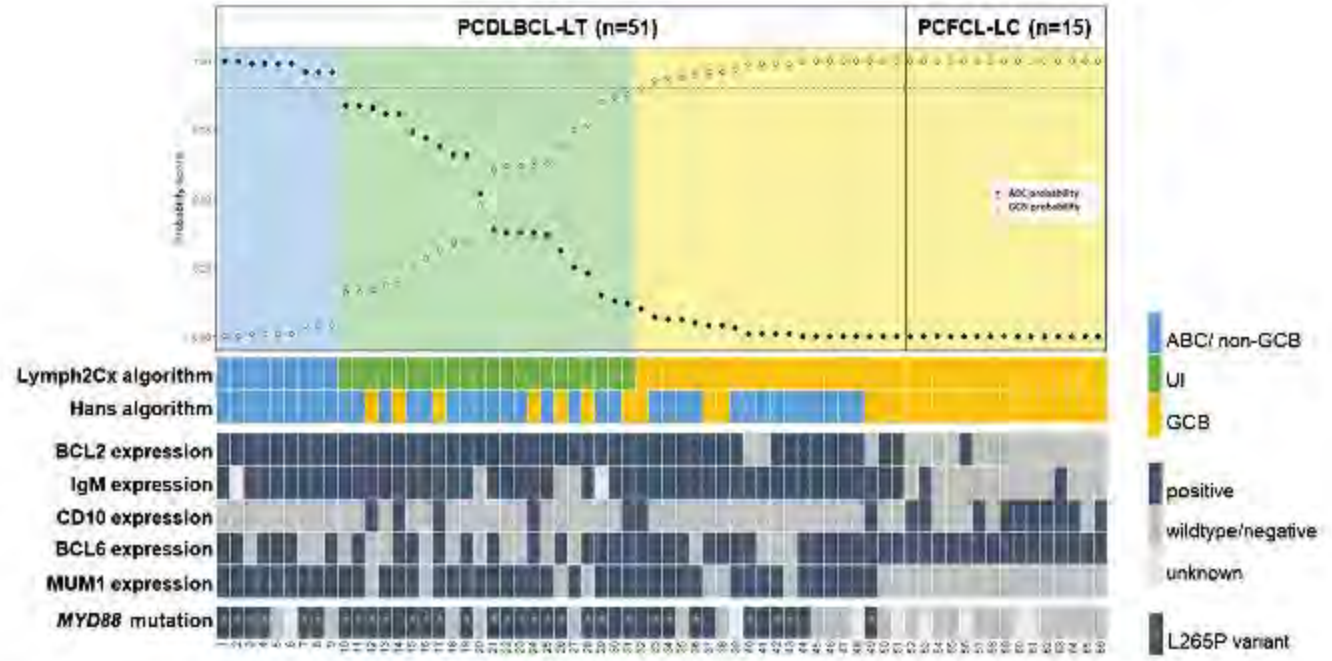
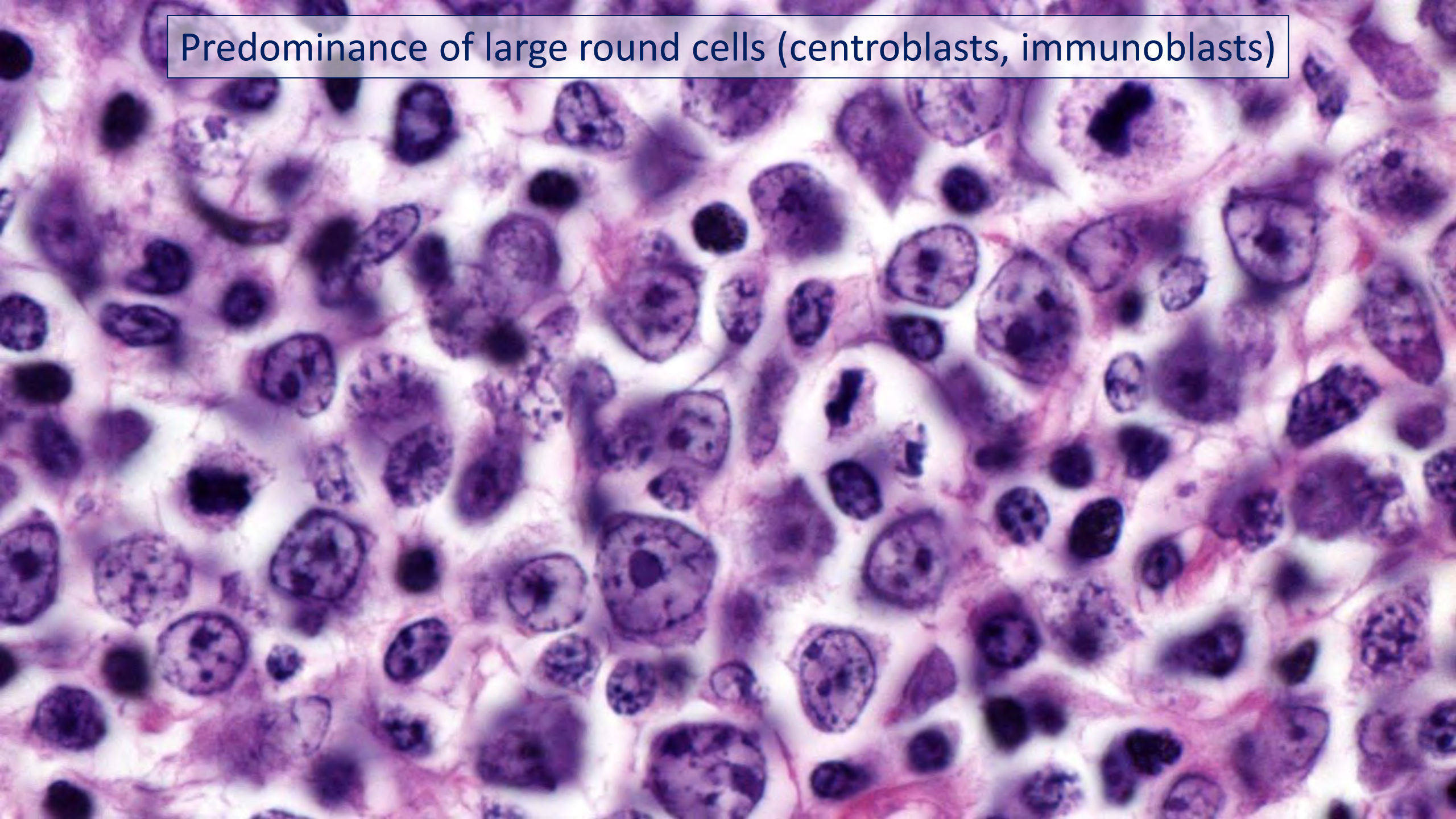
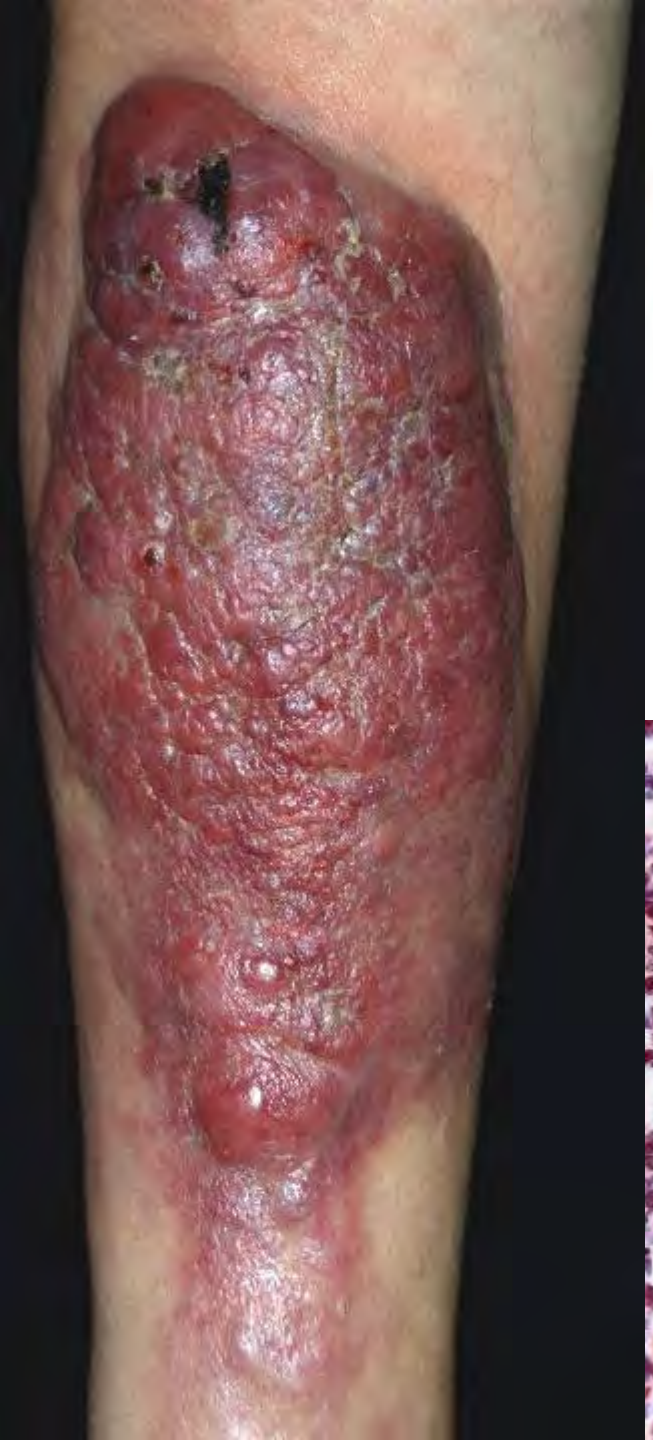
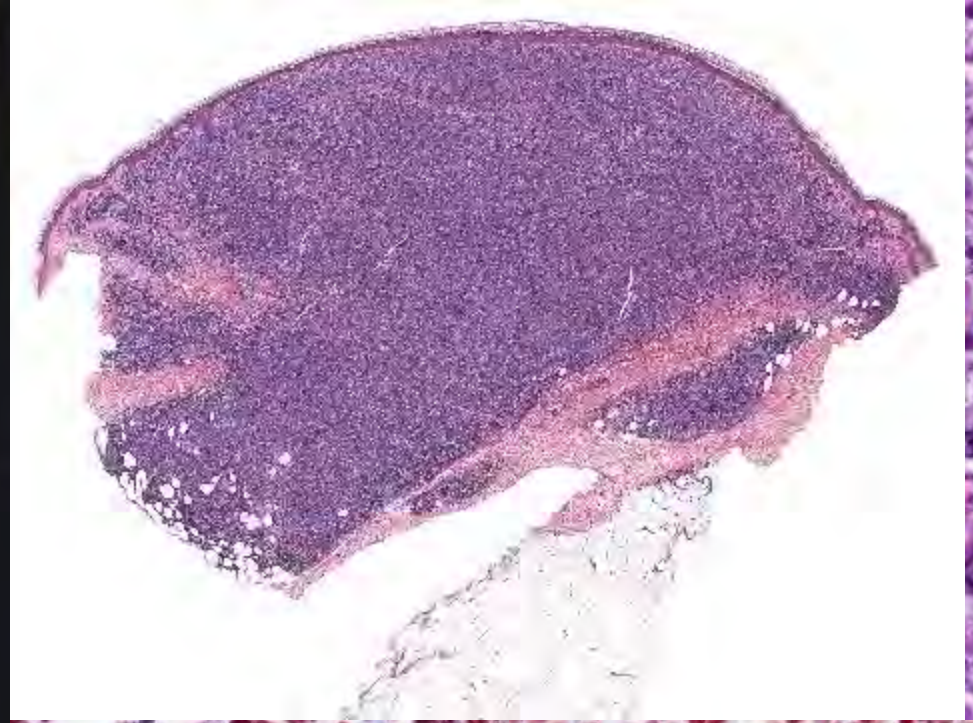


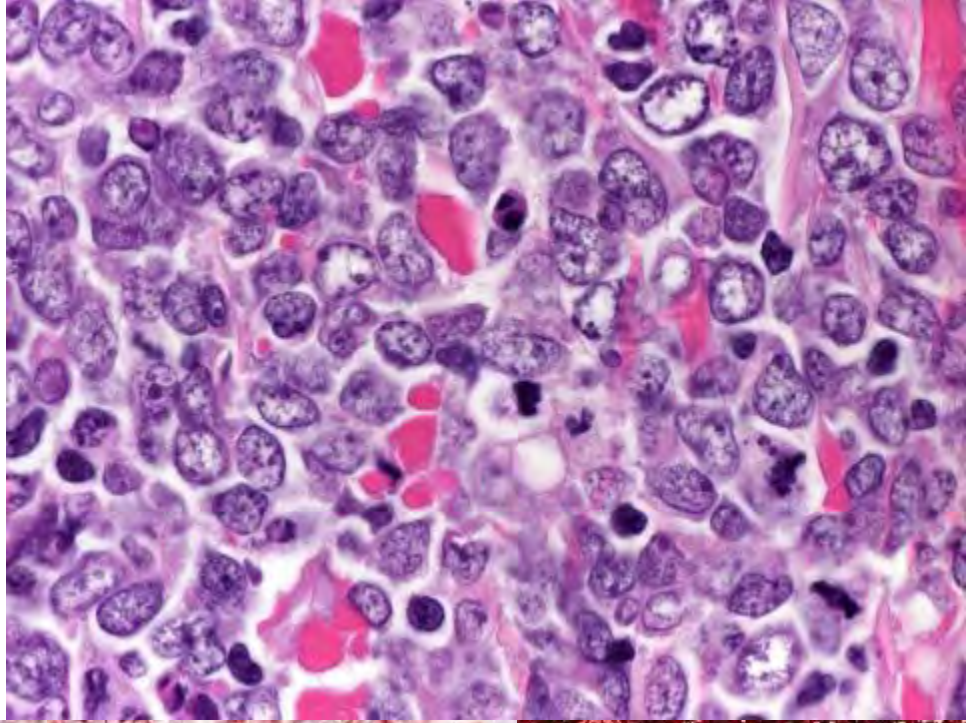
Fig. 1 Overview of cell of origin (COO) classification. Immunohistochemistry, and *MYD88* status in 51 cases with primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT) and 15 cases of primary cutaneous follicle center lymphoma with a diffuse population of large cells (PCFCL-LC). The Hans and Lymph2Cx algorithms were fully concordant in the PCFCL-LC cases (15/15; 100%) but were discordant in the majority (36/51, 71%) of the cases with PCDLBCL-LT. The majority of PCDLBCL-LT cases expressed BCL2 (94%), IgM (94%), and MUM1 (82%), while expression of BCL2 (7%), IgM (7%), and MUM1 (0%) was absent or only rarely present in PCFCL-LC. Mutations in *MYD88* were detected in 36 of 47 (77%) of PCDLBCL-LT but in none of 11 (0%) PCFCL-LC cases. There was no statistically significant difference for the frequency of BCL2 or IgM expression and *MYD88* mutations between the COO subgroups as defined by Hans or Lymph2Cx in PCDLBCL-LT. Remark: A probability score ≤0.1 indicated classification as GCB, 0.11 to 0.89 as unclassified, and ≥0.90 as ABC [15]. Abbreviations: PCDLBCL-LT, primary cutaneous diffuse large B-cell lymphoma, leg type; PCFCL-LC, primary cutaneous follicle center lymphoma with a diffuse population of large cells; ABC, activated B-cell-like subtype; GCB, germinal center B-cell-like subtype; UI, unclassified/intermediate. *MYD88 non L265P mutations consisted of S234N (n=4), Y240S (n=1), and M232T (n=1)

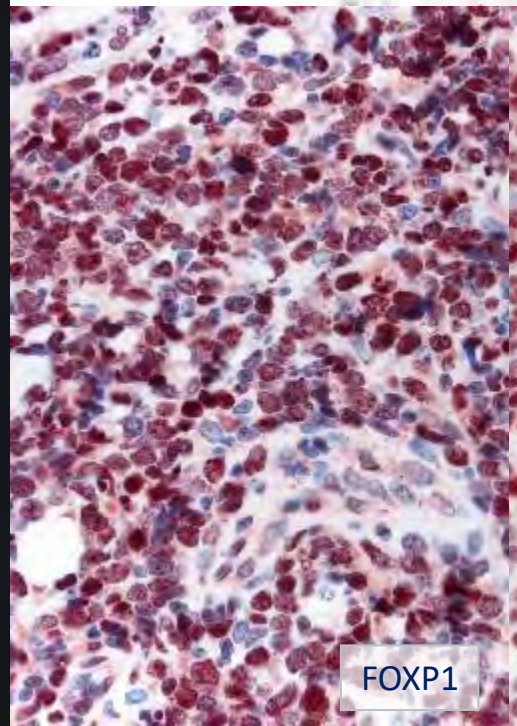
The (Hans algorithm) cannot be used as an alternative for the current multiparameter approach in differentiation of PCDLBCL-LT from PCFCL-LC.


Predominance of large round cells (centroblasts, immunoblasts)





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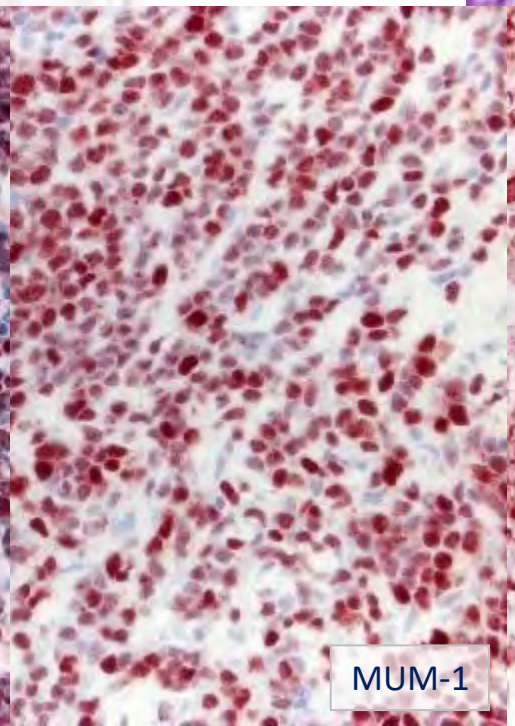
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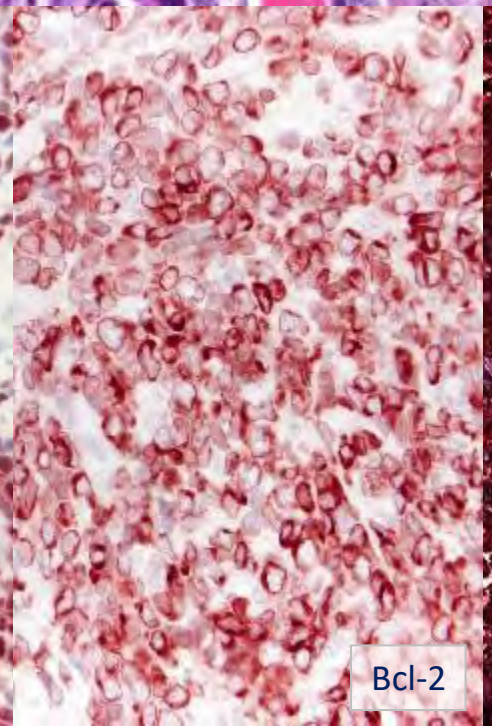
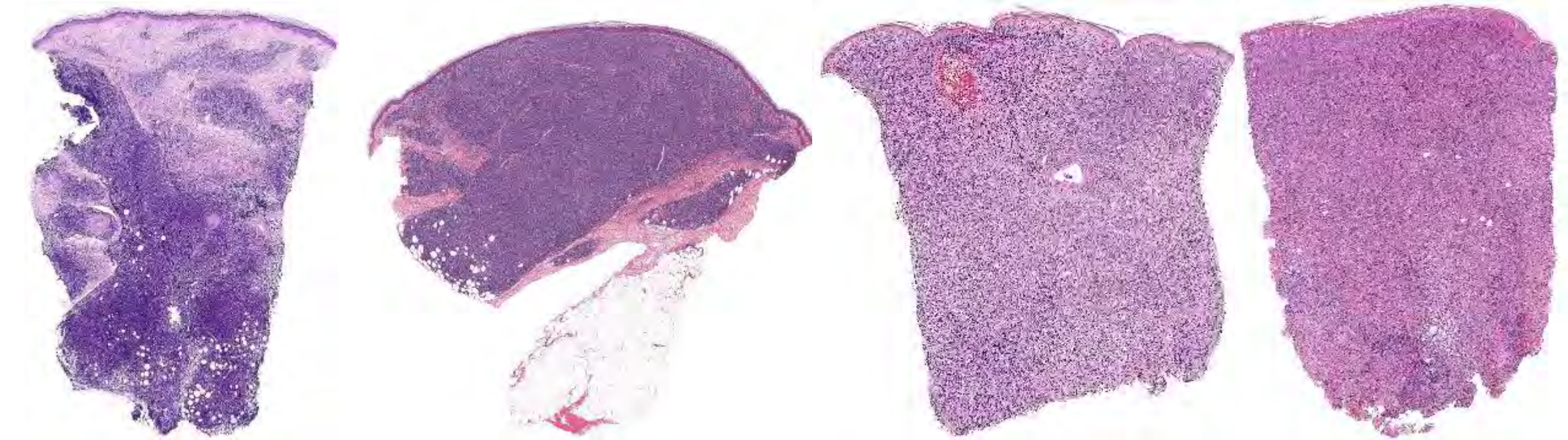
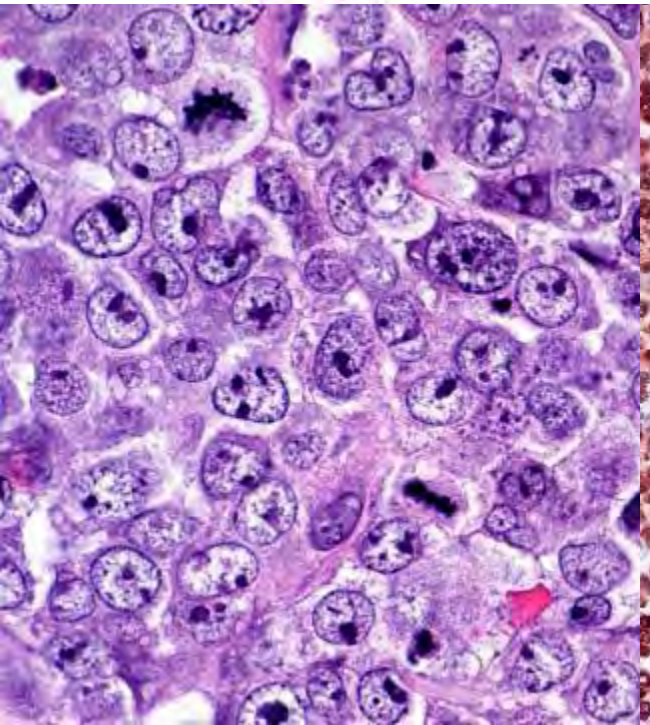
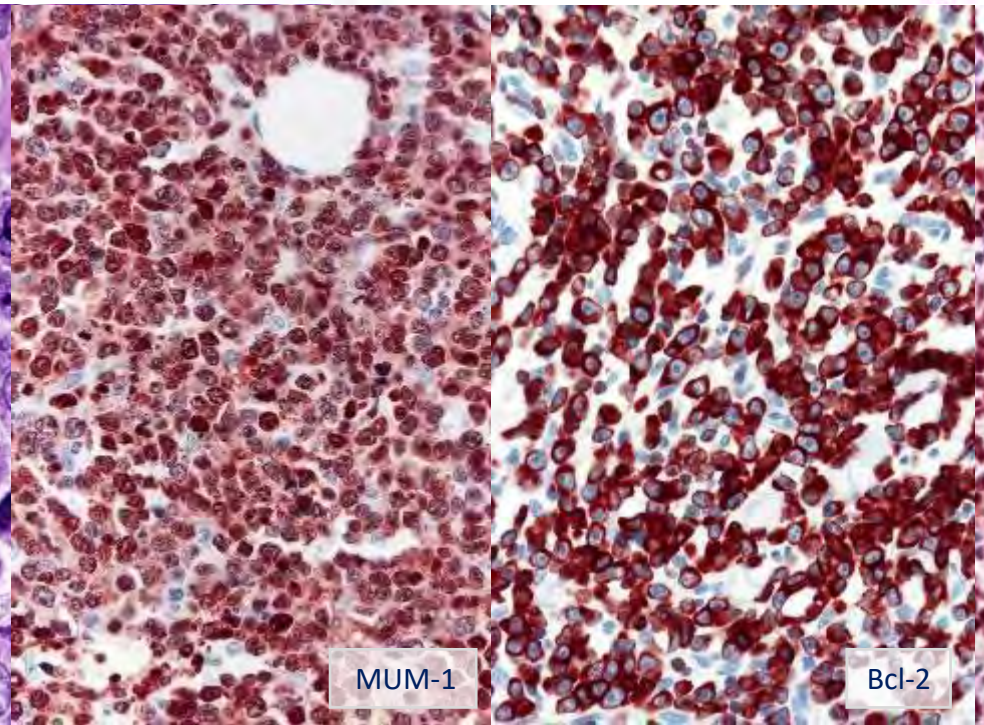
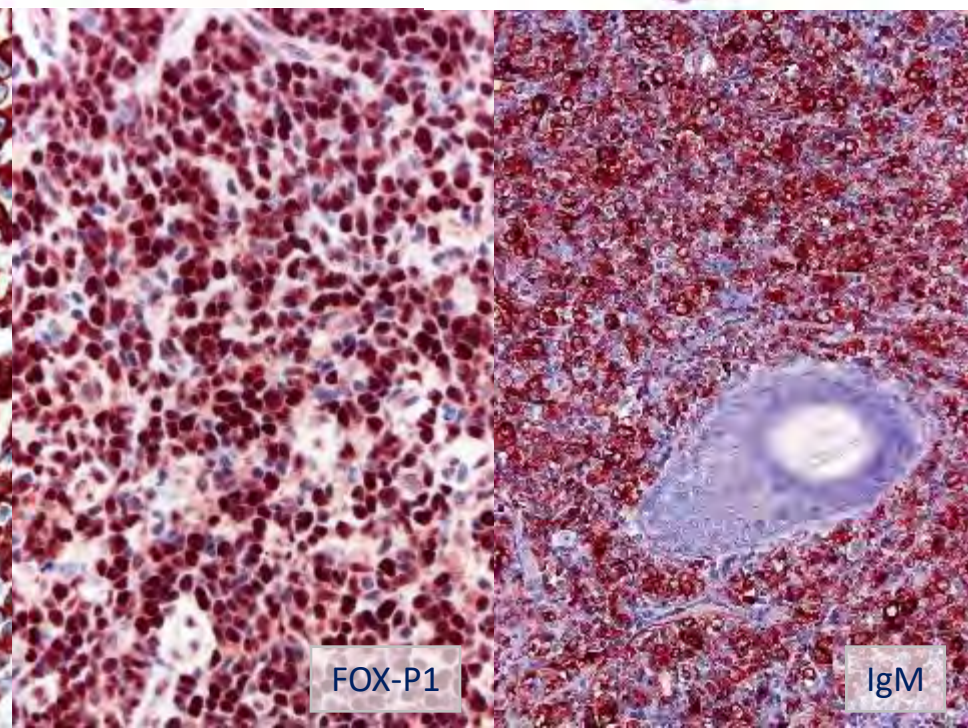

Bcl-2


IgM






MUM-1
Bcl-2


FOX-P1
IgM

Primary cutaneous large B-cell lymphomas: clinicopathologic features, classification, and prognostic factors in a large series of patients

Kazuo Kodama, Cesare Massone, Andreas Chott, Dieter Metze, Helmut Kerl, and Lorenzo Cerroni

In the new World Health Organization/ European Organization for Research and Treatment of Cancer (WHO/EORTC) classification of cutaneous lymphomas, large B-cell lymphomas (LBCLs) are divided into 3 groups: LBCL, leg-type (LBCLLT); follicle center lymphoma, diffuse type (FCLDT); and LBCL, others (LBCLO). We studied a large number of primary cutaneous LBCLs to test the validity of the classification and to identify prognostic factors for these patients. Ninety-three cases of primary cutaneous LBCL were analyzed for clinicopathologic features, expression of several markers including Bcl-2, Bcl-6, MUM-1, and FOX-P1, in situ hybridization for Epstein-Barr virus, and molecular analyses of *IGH* gene rearrangement and of *Borrelia burgdorferi* and human herpesvirus 8 DNA. Patients were classified into the following categories: FCLDT, 44 cases; LBCLLT, 40 cases; and LBCLO, 9 cases. Statistical analyses showed that the LBCLLT and FCLDT groups were clearly distinct in terms of clinicopathologic features and survival. The LBCLO group had features in between those of LBCLLT and FCLDT. Our study shows that accurate morphologic and phenotypic analyses allow us to stratify most patients into the prognostically different categories of LBCLLT and FCLDT. The definition of a third category of LBCLO requires further studies to clarify whether these cases indeed show distinct clinicopathologic features. (Blood, 2005;106:2491-2497)

Introduction

In the new World Health Organization/European Organization for Research and Treatment of Cancer (WHO/EORTC) classification of cutaneous lymphomas, large B-cell lymphomas (LBCLs) are divided into 3 groups. Large B-cell lymphoma, leg-type (LBCLLT) is defined as a cutaneous B-cell lymphoma with a predominance of large round cells (centroblasts, immunoblasts) that are positive for Bcl-2.[1] Cases of LBCL with a predominant cleaved cell morphology (large centrocytes) are included within the follicle center lymphomas, diffuse type (FCLDT). These cases would be included in the categories of diffuse LBCL in the WHO classification of tumors of hematopoietic and lymphoid tissues[2] and of cutaneous follicle center cell lymphomas in the first EORTC classification of primary cutaneous lymphomas, respectively.[3] Rare other cases not fitting within these 2 categories are included in a group of large B-cell lymphoma, other (LBCLO). Although the new WHO/EORTC classification is the result of a consensus among representatives of the WHO and EORTC groups, at present there are no clinicopathologic data supporting the inclusions of primary cutaneous LBCLs into the 3 groups. In addition, prognostic factors for these patients are largely unknown.

Recently, we could confirm the clinical value of the classification of cutaneous lymphomas proposed in 1997 by the EORTC.[4] In the present study, we analyzed data on a large group of patients with primary cutaneous LBCL, classifying patients according to the new WHO/EORTC classification, and evaluating the prognostic value of several factors including classification, age of patients, anatomic site of onset, number of lesions at presentation, cell morphology, and expression of Bcl-2, multiple myeloma-1 (MUM-1), and Forkhead box-P1 (FOX-P1) proteins.

Patients, materials, and methods

Biopsy specimens from 93 cases of primary cutaneous LBCL were retrieved from the database files of the Division of Dermatopathology, Department of Dermatology, Medical University of Graz. The cases had been registered between 1960 and 2004. Primary cutaneous LBCL was defined as large cells constituting more than 80% of the infiltrate[3] and absence of extracutaneous dissemination after staging investigations.[1,4] Staging procedures were performed with standard methods available at time of first diagnosis including, when applicable, physical examination, blood-cell count, chest radiograph, computed tomographic scan, abdominal ultrasound sonography, sonography of superficial lymph nodes, and bone marrow biopsy. Unfortunately, we do not have exact data on therapy for all patients. First-line treatment strategies, however, were similar, with radiotherapy generally preferred to chemotherapy, with the exception of cases presenting with disseminated skin involvement.

The histopathologic features were reviewed by at least 3 independent investigators (K.K., C.M., and L.C.). We only included cases characterized by diffuse infiltrates of large cells with morphologic features of large centrocytes, centroblasts, or immunoblasts. Cases with a follicular growth pattern were excluded, as well as cases with the presence of remnants of lymphoid follicles as detected by immunohistologic staining for follicular dendritic cells (CD21). Cases arising in immunosuppressed individuals were excluded as well.

All cases were classified according to the new WHO/EORTC classification of cutaneous lymphomas.[1] FCLDT was defined as a tumor with predominance of large cleaved cells, irrespective of Bcl-2 expression.

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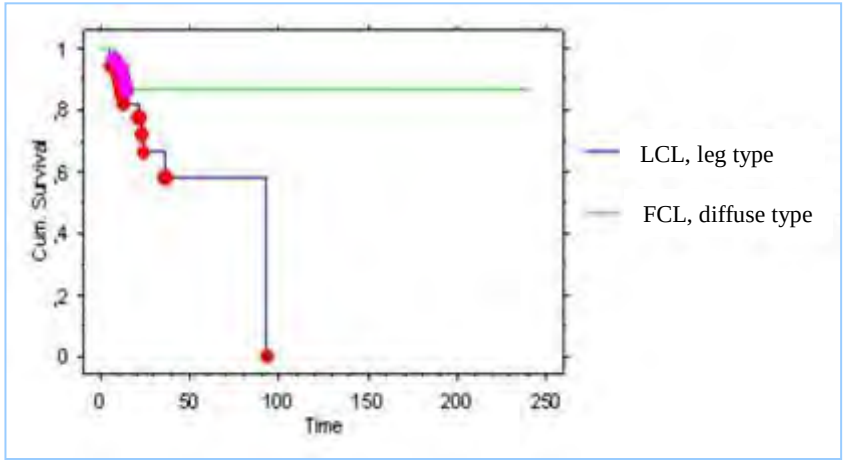
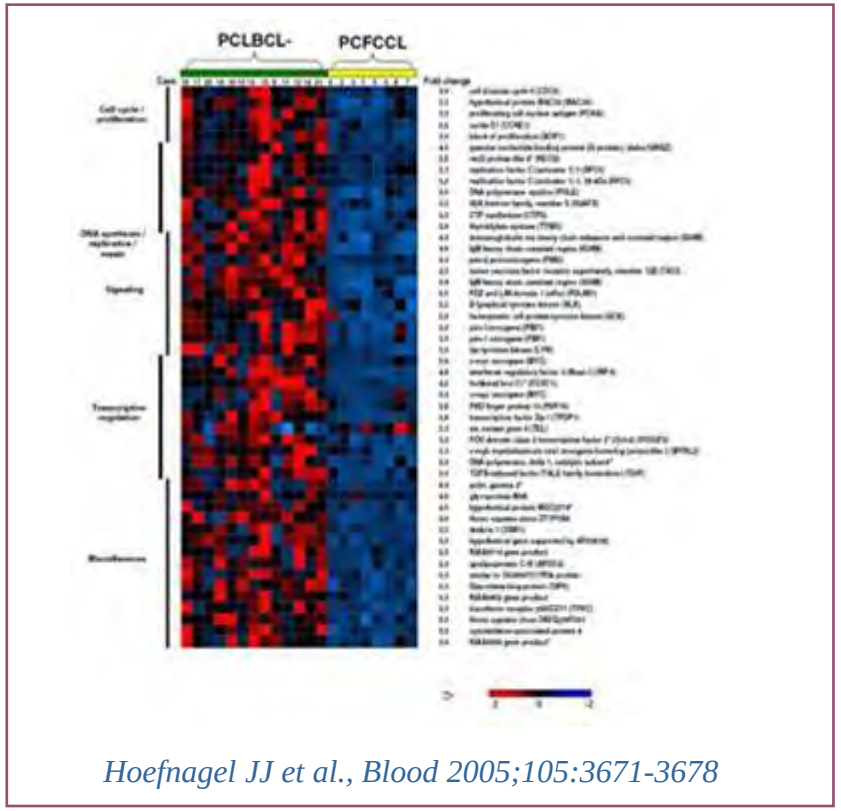
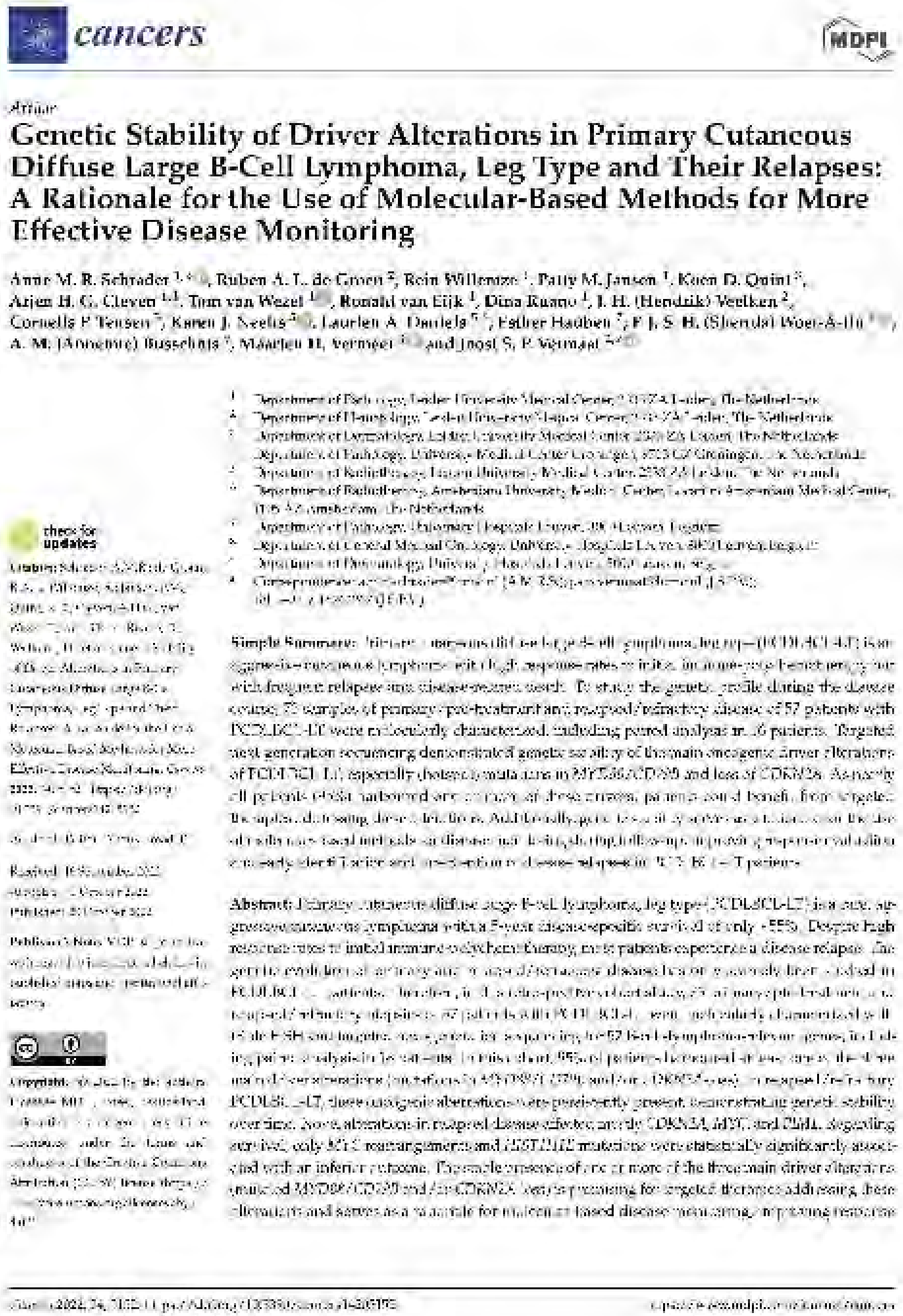




Hoefnagel JJ et al., Blood 2005;105:3671-3678


cancers
MDPI
Article
Genetic Stability of Driver Alterations in Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type and Their Relapses: A Rationale for the Use of Molecular-Based Methods for More Effective Disease Monitoring
Anne M. R. Schrader, Ruben A. L. de Groen, Rein Willemze, Patty M. Jansen, Koen D. Quint, Arjen H. G. Cleven, Tom van Wezel, Ronald van Eijk, Dina Ruano, J. H. (Hendrik) Veelken, Cornelis P. Tensen, Karen J. Neelis, Laurien A. Daniels, Esther Hauben, F. J. S. H. (Sherida) Woei-A-Jin, A. M. (Annemie) Busschots, Maarten H. Vermeer and Joost S. P. Vermaat

Gene expression profiling: ABC-type of DLBCL
Translocations: *BCL6* (30%), *MYC* (30%), *IgH* (50%)
Deletion 6q (*BLIMP1:* 60%); deletion 9p21.3 (*CDKN2A:* 67%)
NF-kB pathway mutations (*MYD88:* 70%; *CD79b:* 20%, other)

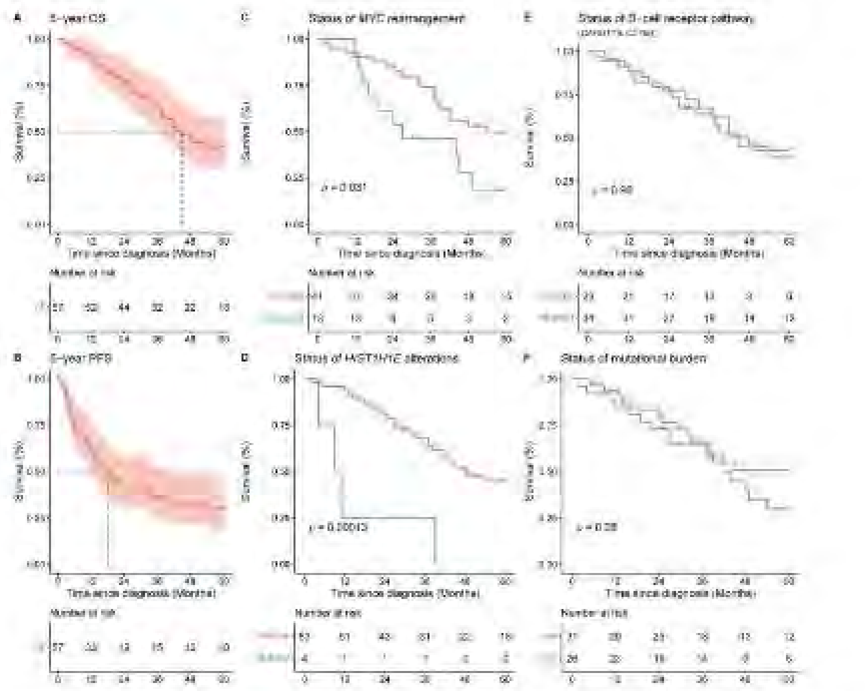
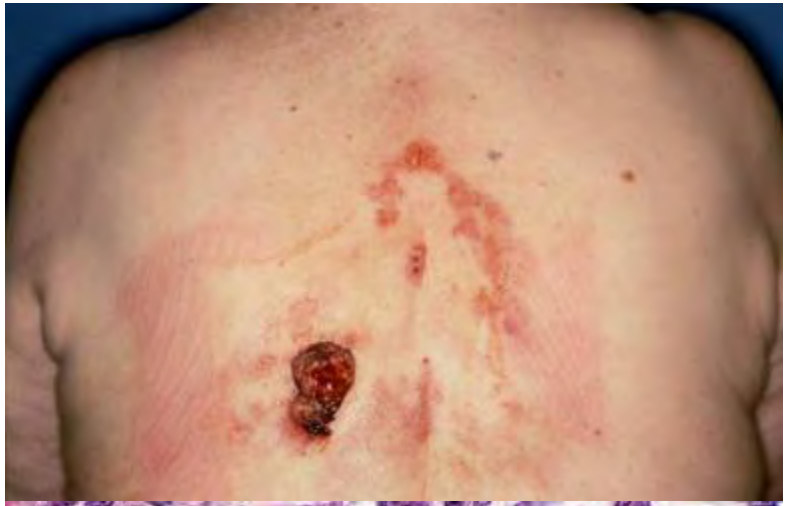
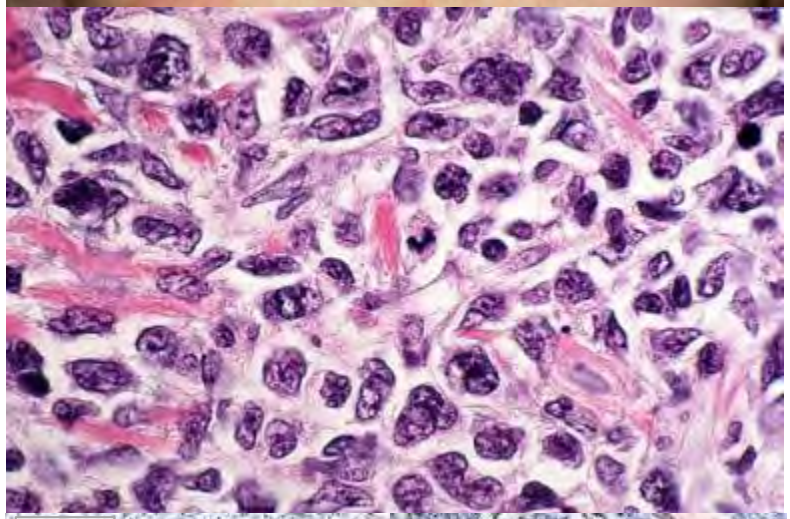
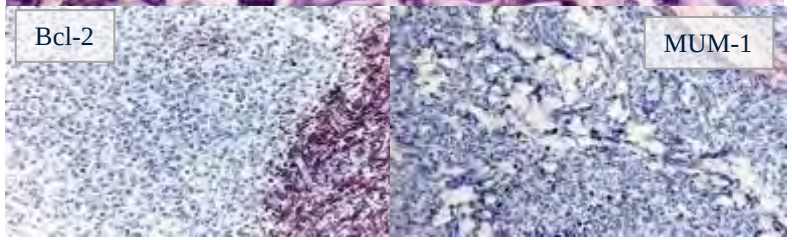


Figure 4. Overall survival (OS) and progression-free survival (PFS) of 57 patients with PCDLBCL-LT. The median OS of the cohort was 44 months. (**A**) The median PFS of the cohort was 17 months. (**B**) Rearrangements of *MYC* (**C**) and mutations in *HIST1H1E* (**D**) were associated with an inferior survival (Log rank; $p = 0.001$ and $p = 0.00013$, respectively). There were no statistically significant differences in OS for (**E**) patients with or without mutations in the B-cell receptor pathway (*CD79A/B* or *CARD11*) and (**F**) patients with a high (>6 mutations) or low (≤6 mutations) mutational burden.

Follicle center lymphoma, diffuse type

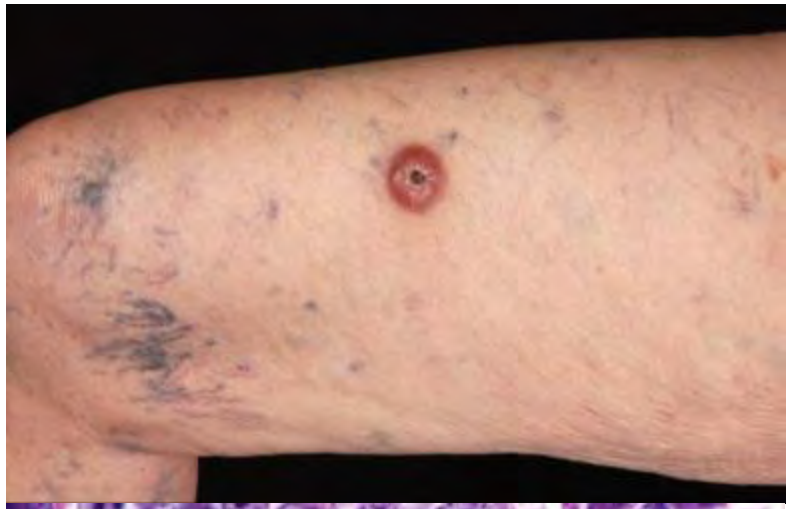


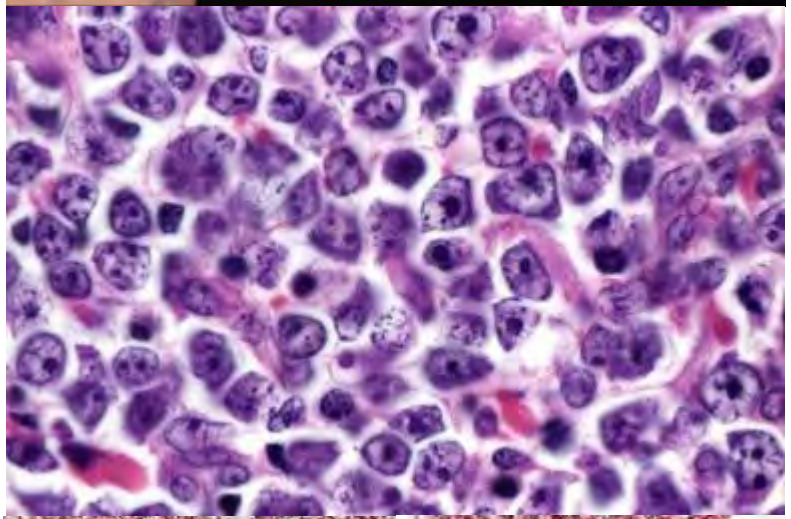


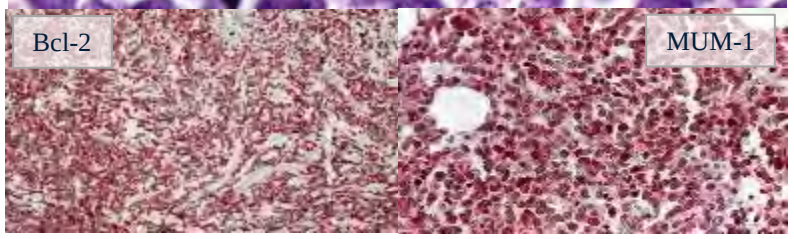


Non-aggressive treatment

Diffuse large B-cell lymphoma, leg type

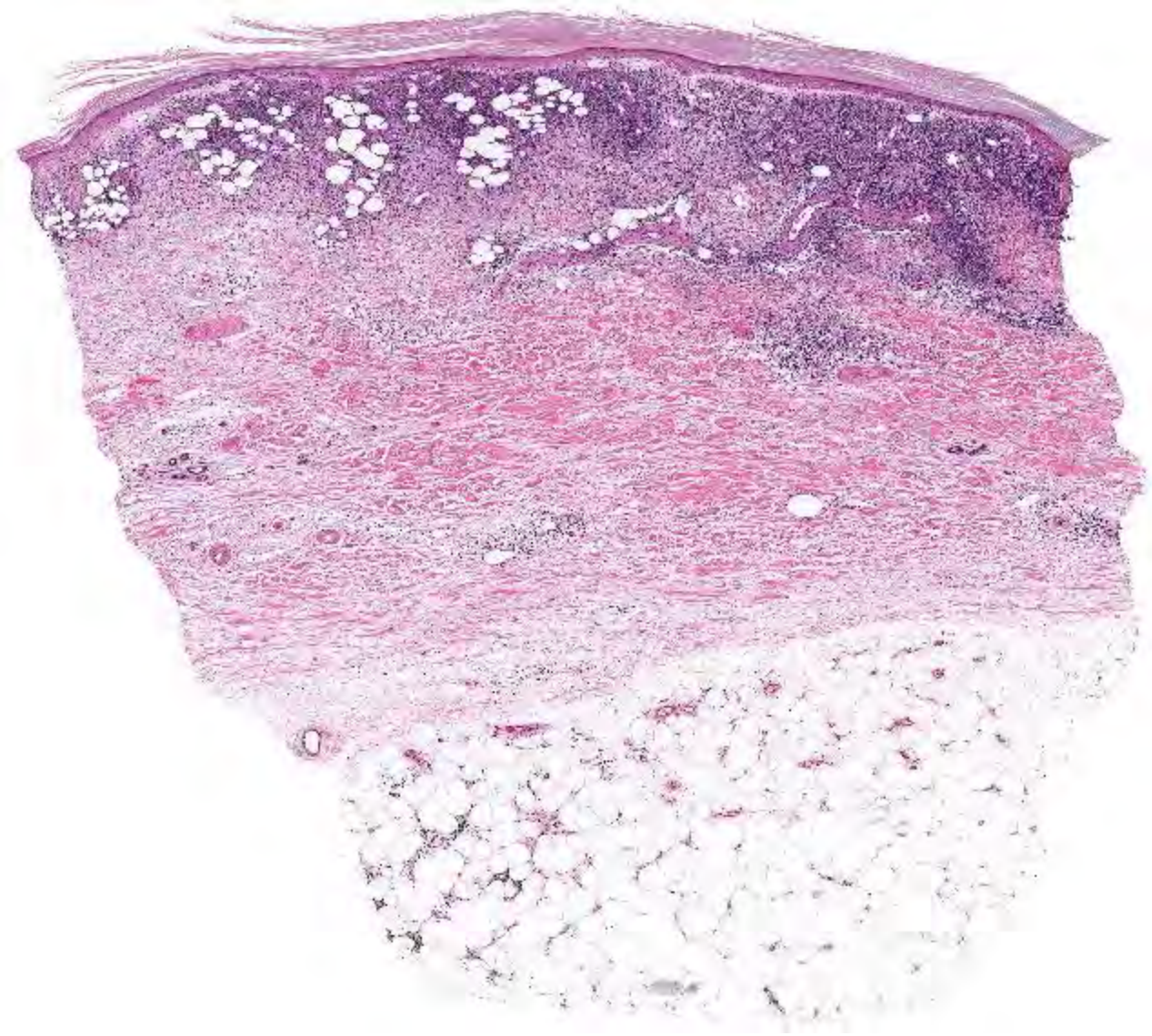


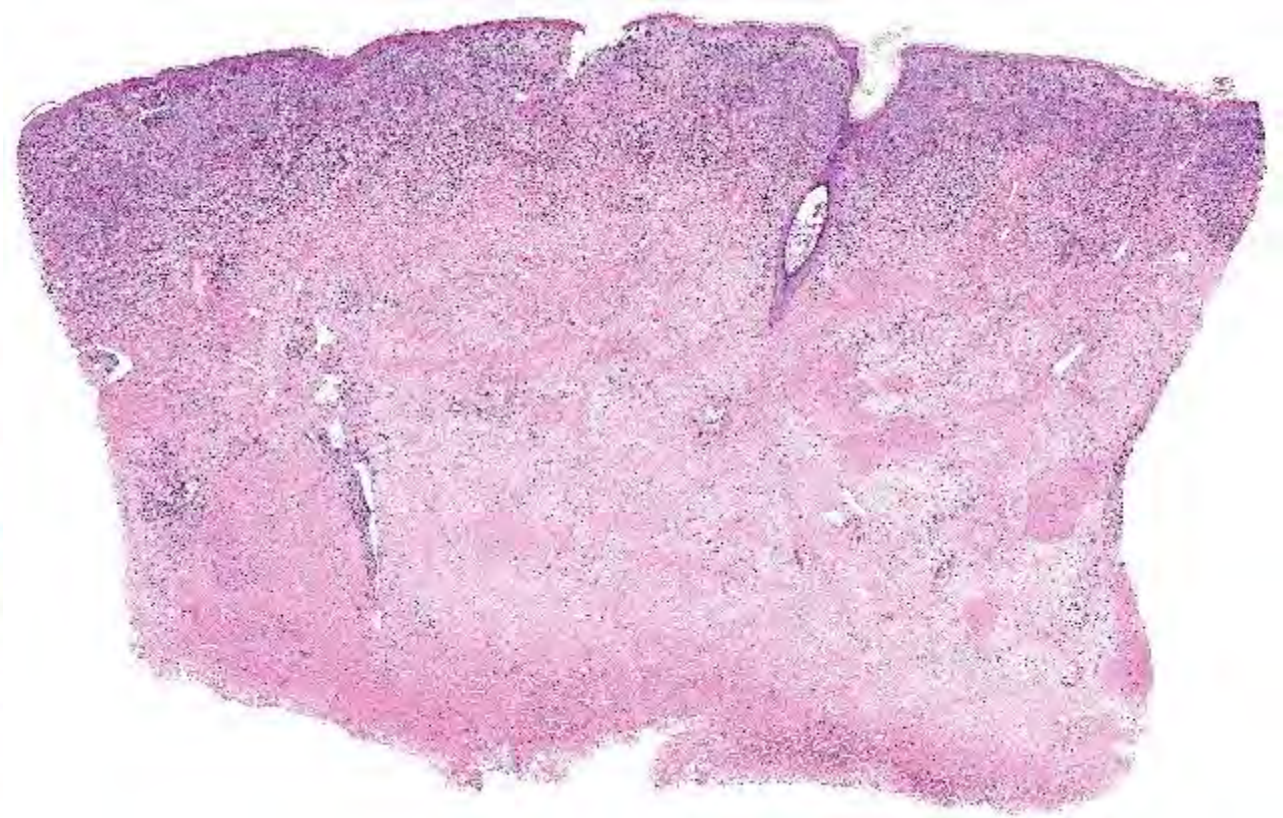


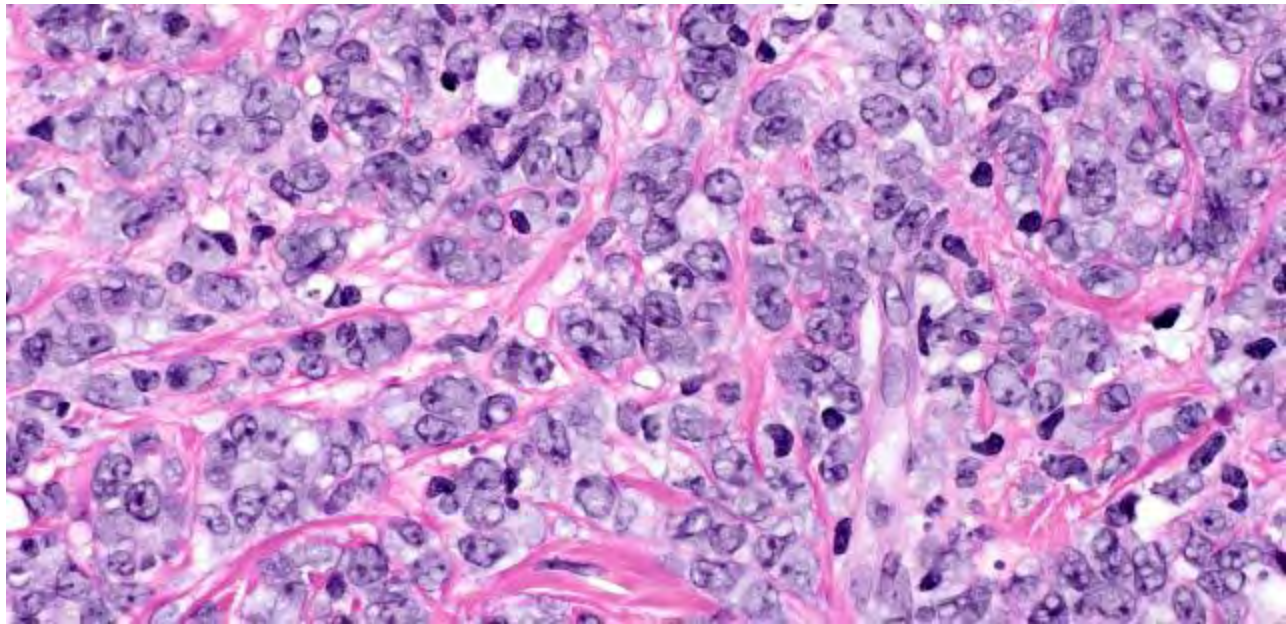


Aggressive treatment

	DLBCL-LT	FCL
Bcl-2	+	-
MUM-1	+	-
IgM	+	-
FOX-P1	+	-
MYC	(+)	-

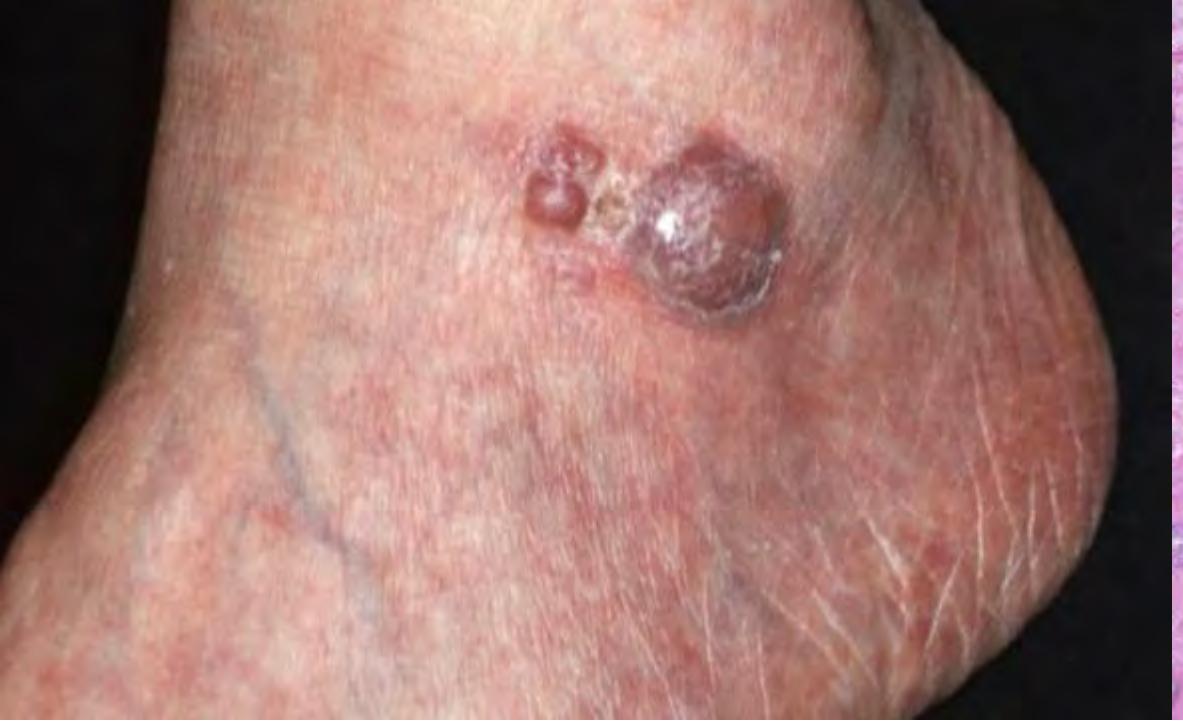


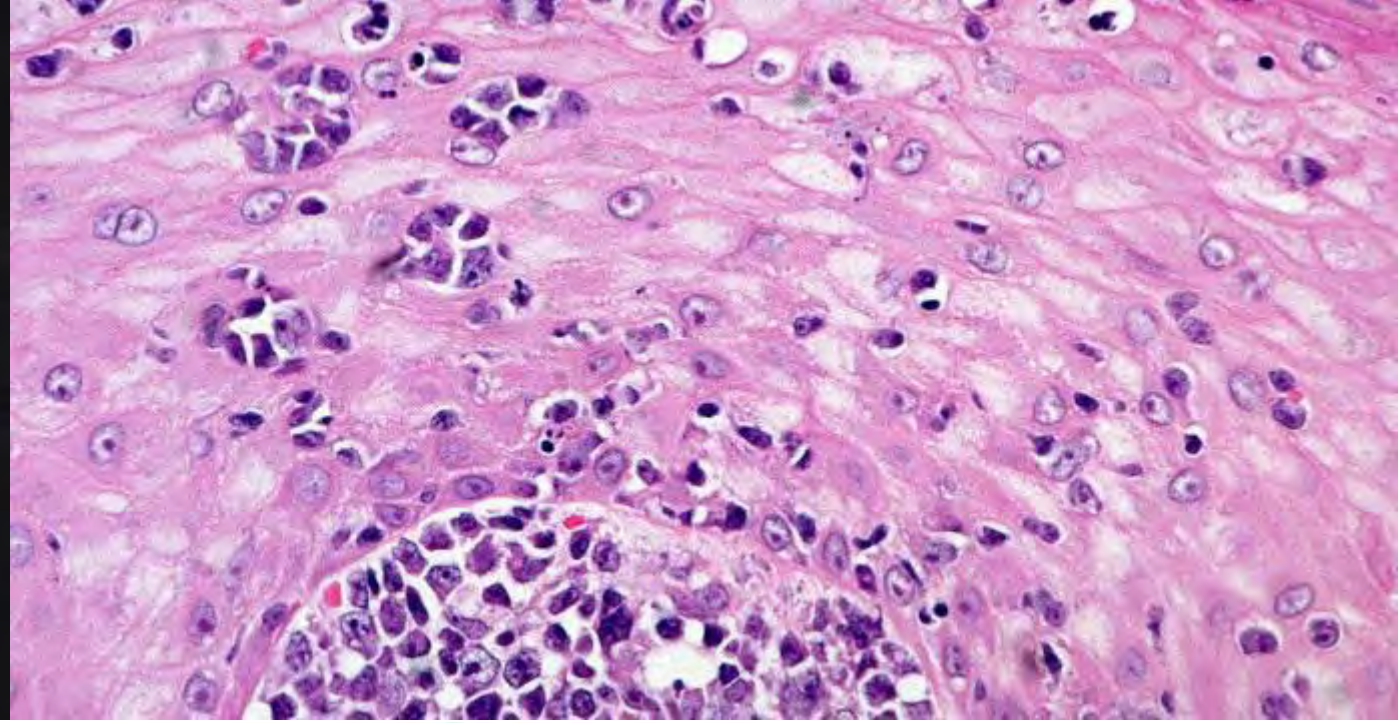


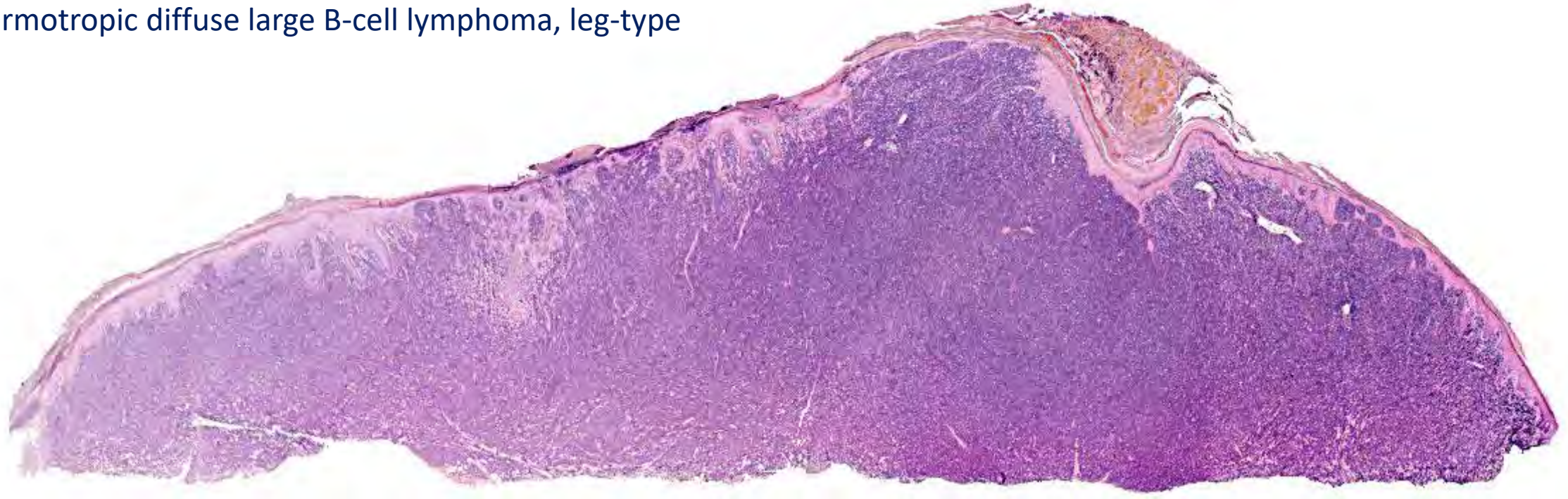


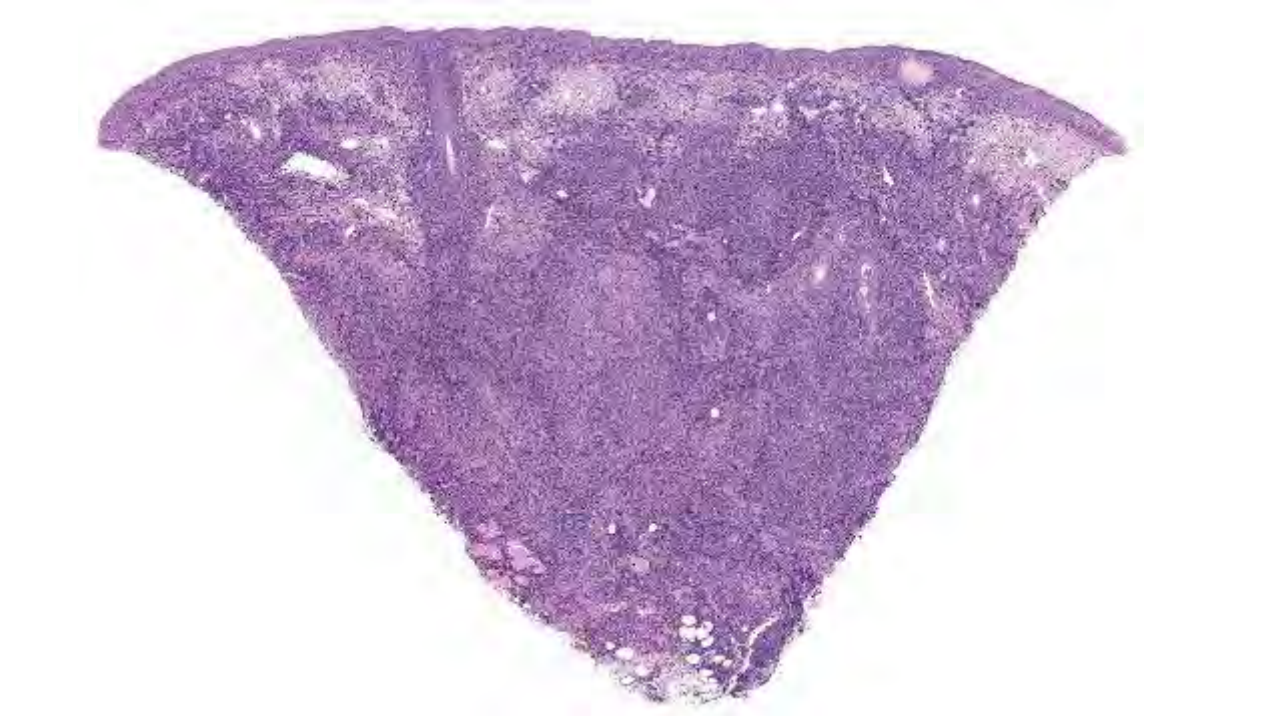
Diffuse large B-cell lymphoma with band-like infiltrate (a pattern that can be observed in both primary and secondary cutaneous diffuse large B-cell lymphomas)

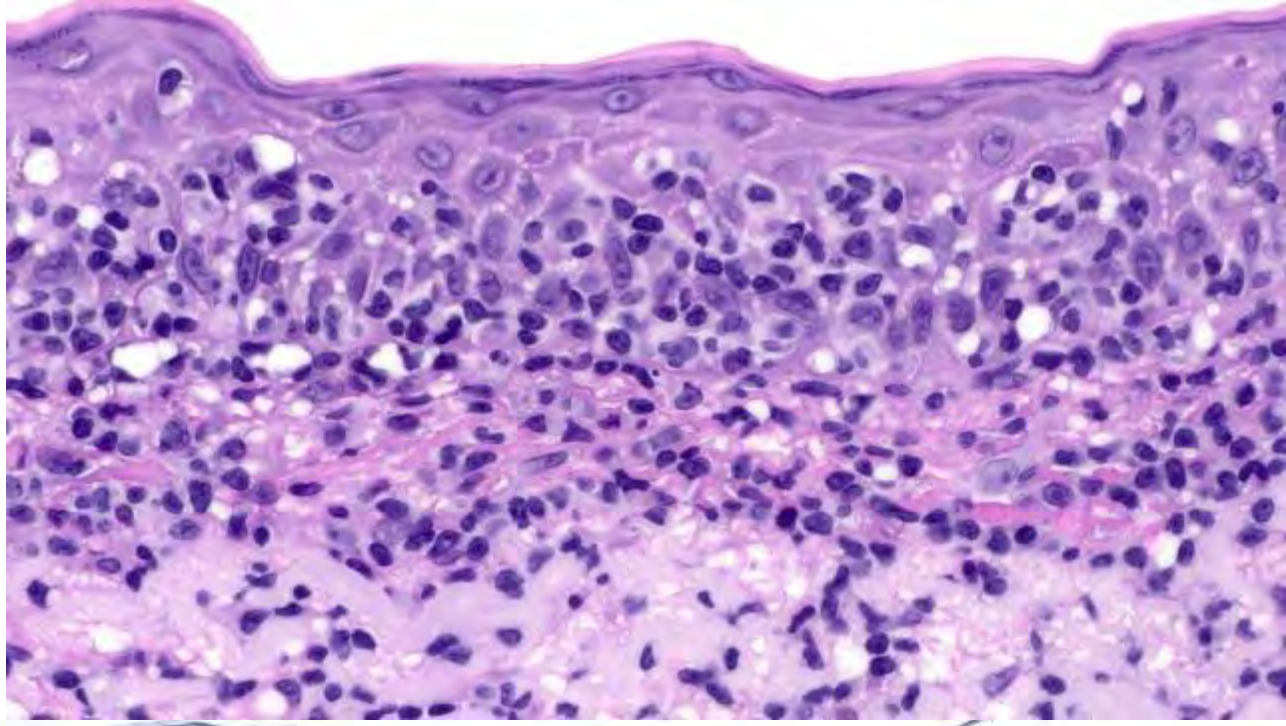
Epidermotropic diffuse large B-cell lymphoma, leg-type

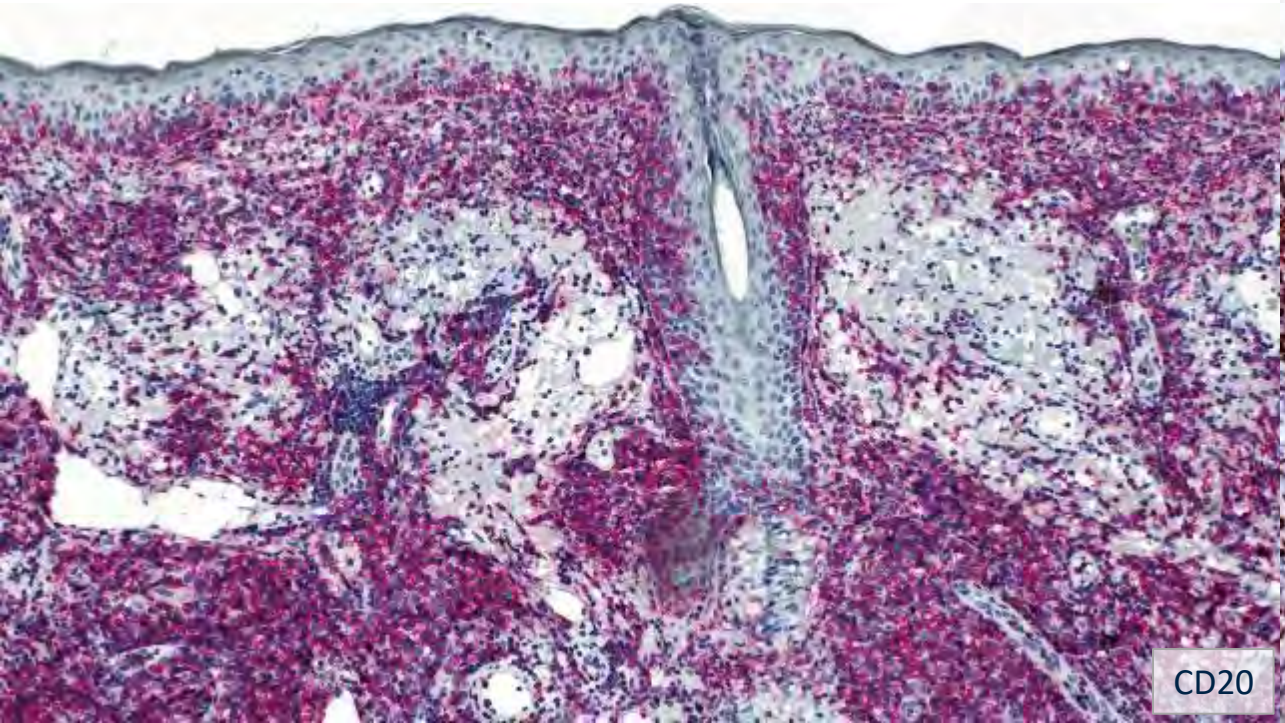








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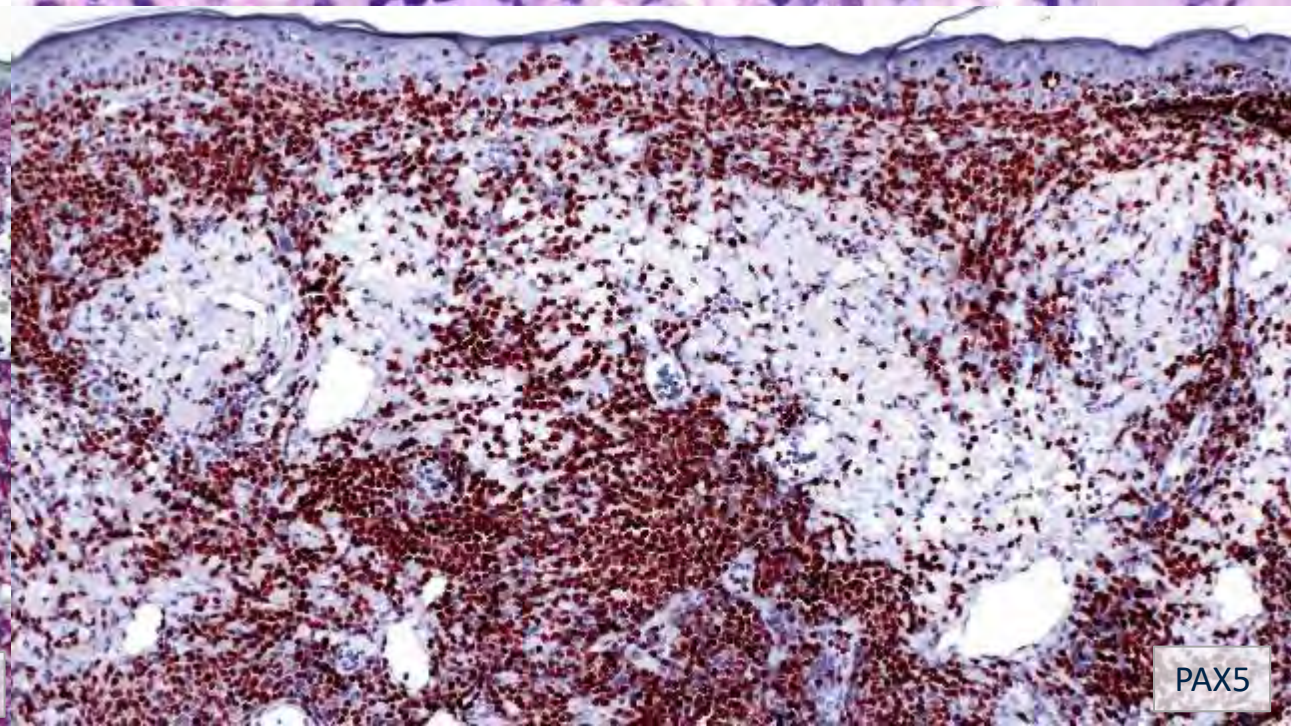
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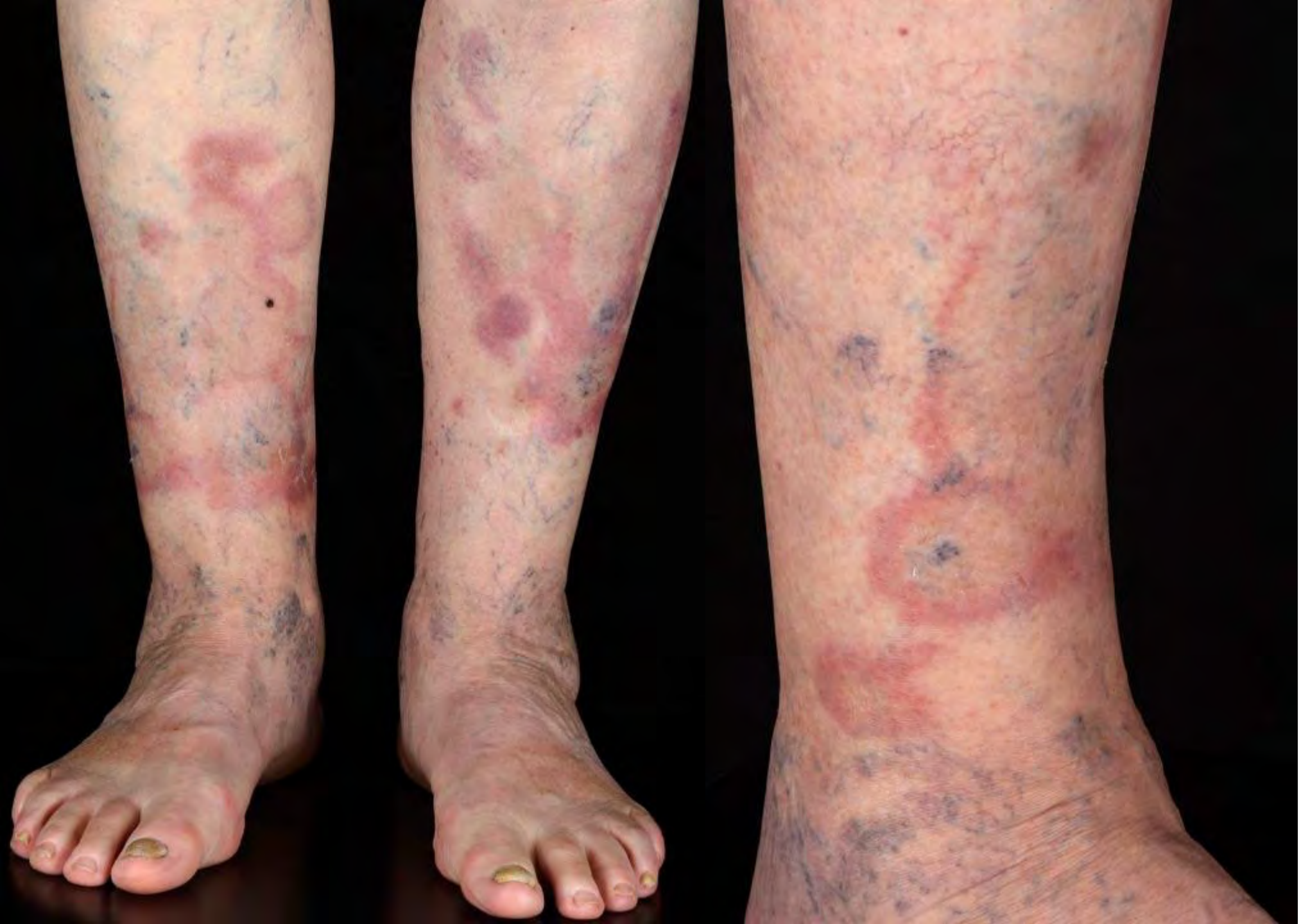
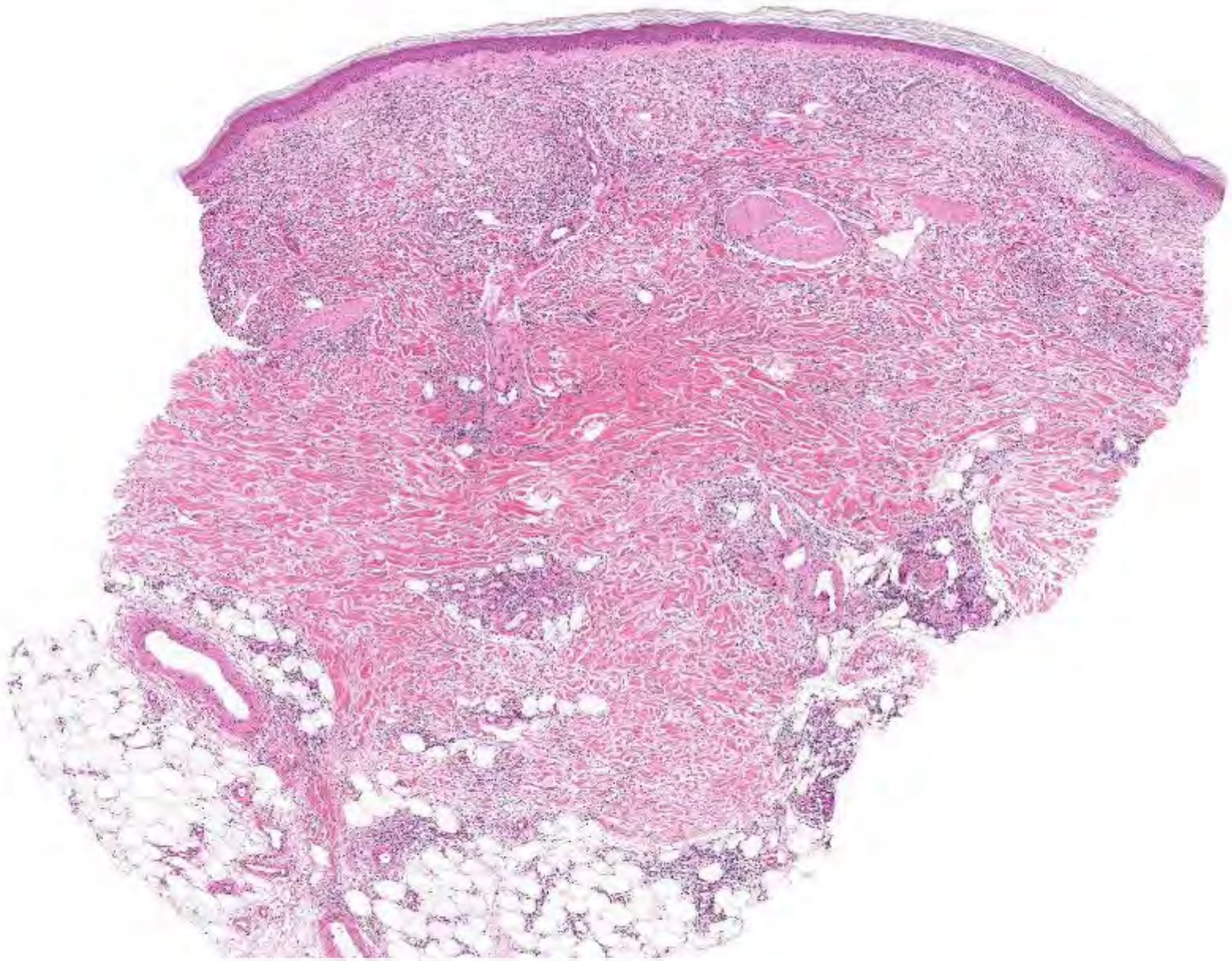
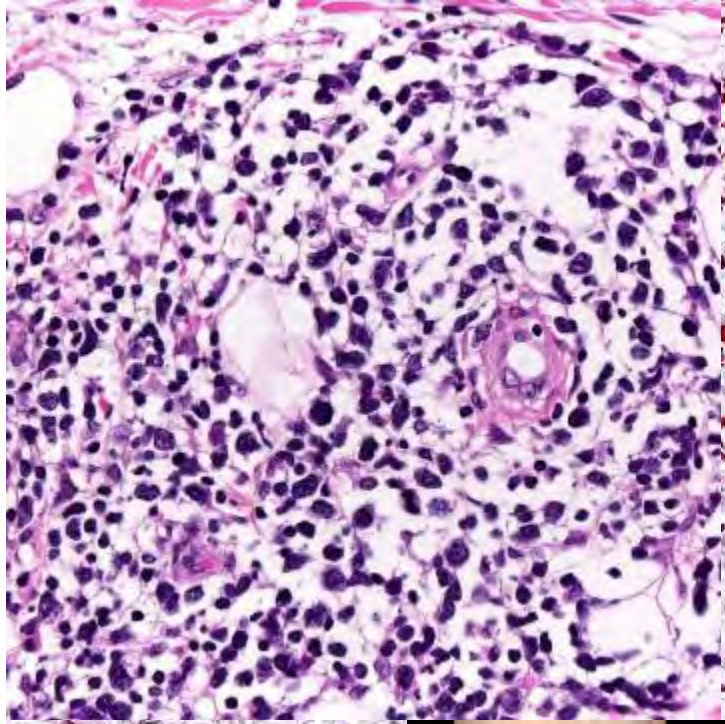


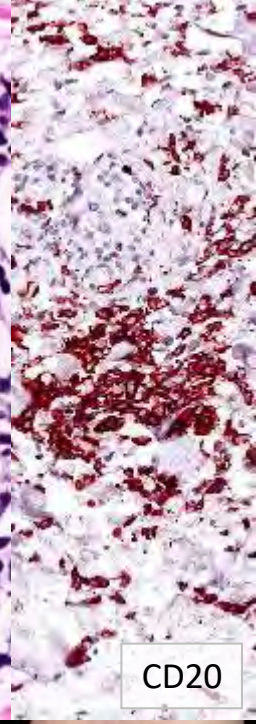
F, 72

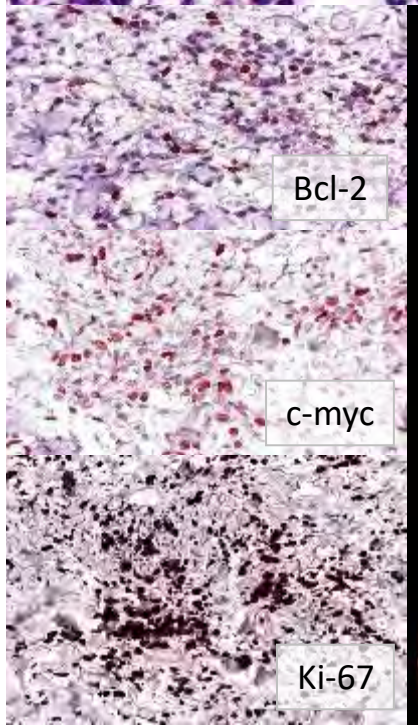
Annular, infiltrated lesions on both lower legs for some months.

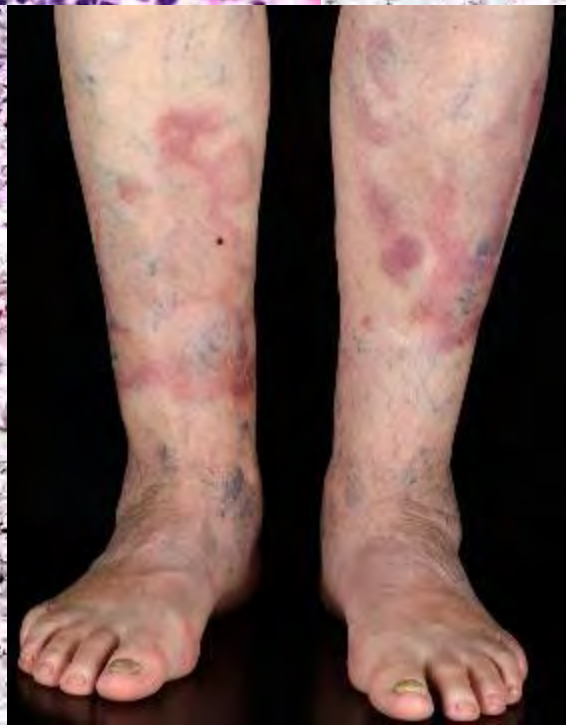
A biopsy is taken.



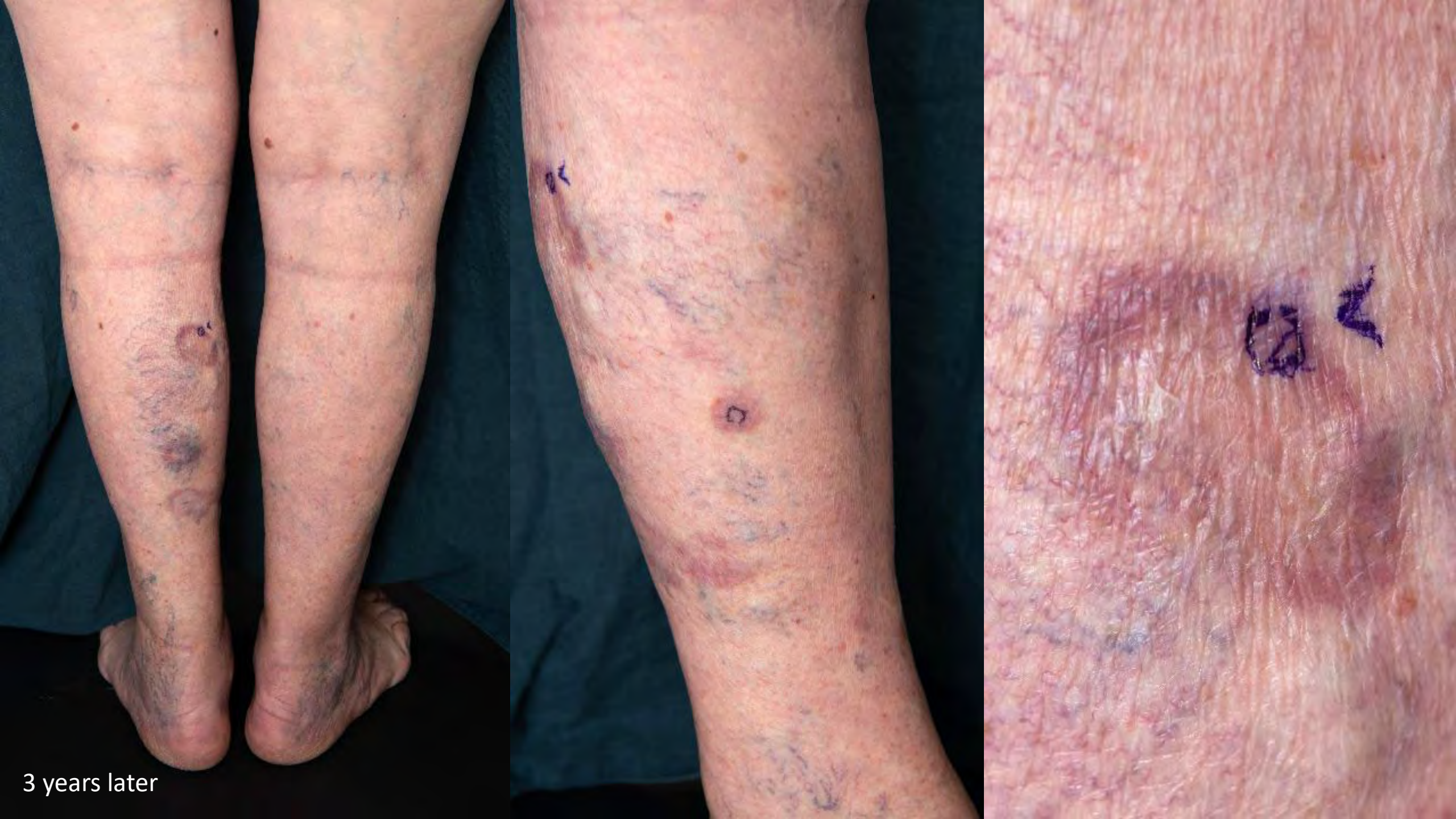








Diffuse large B-cell lymphoma, leg-type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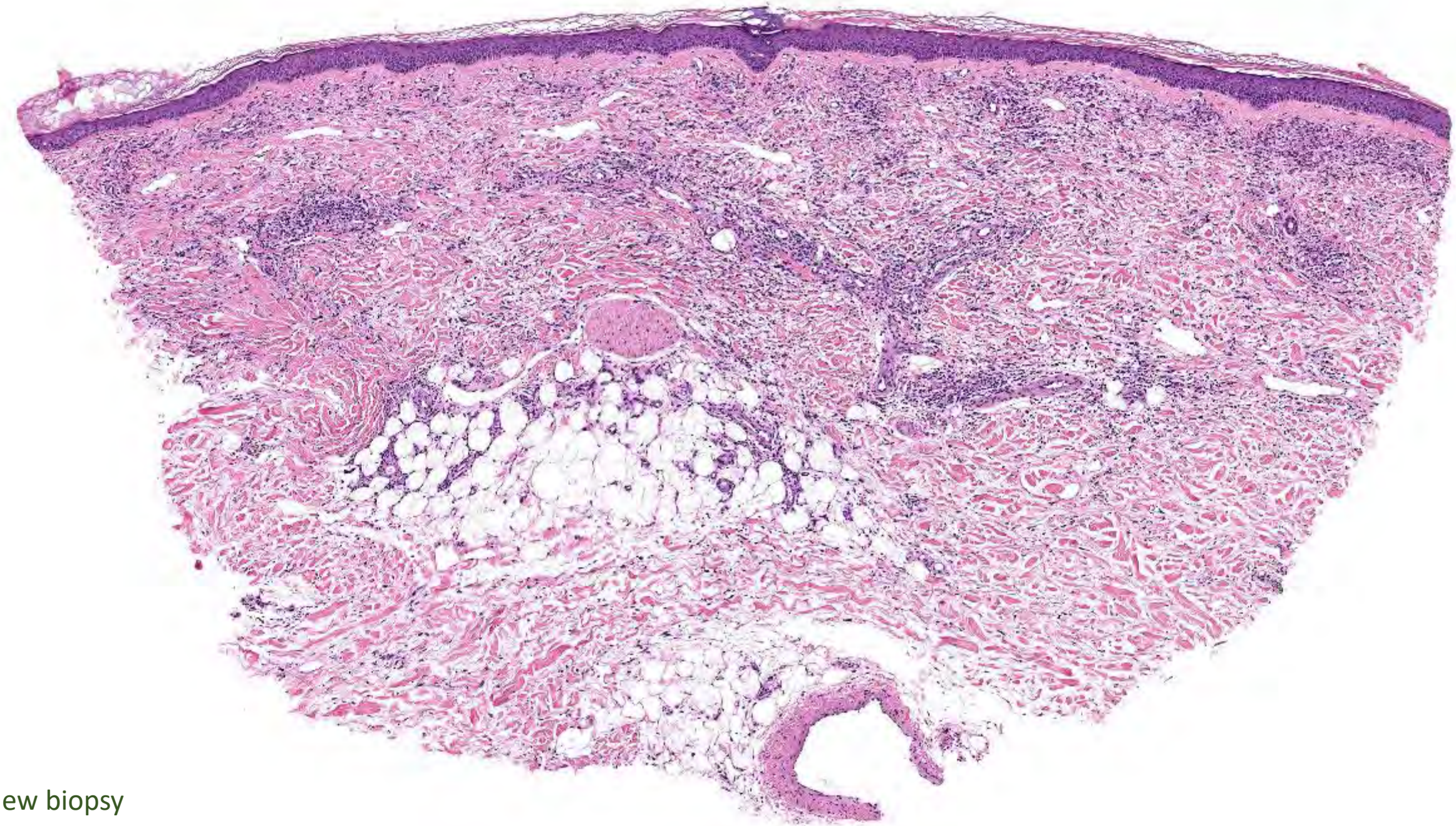
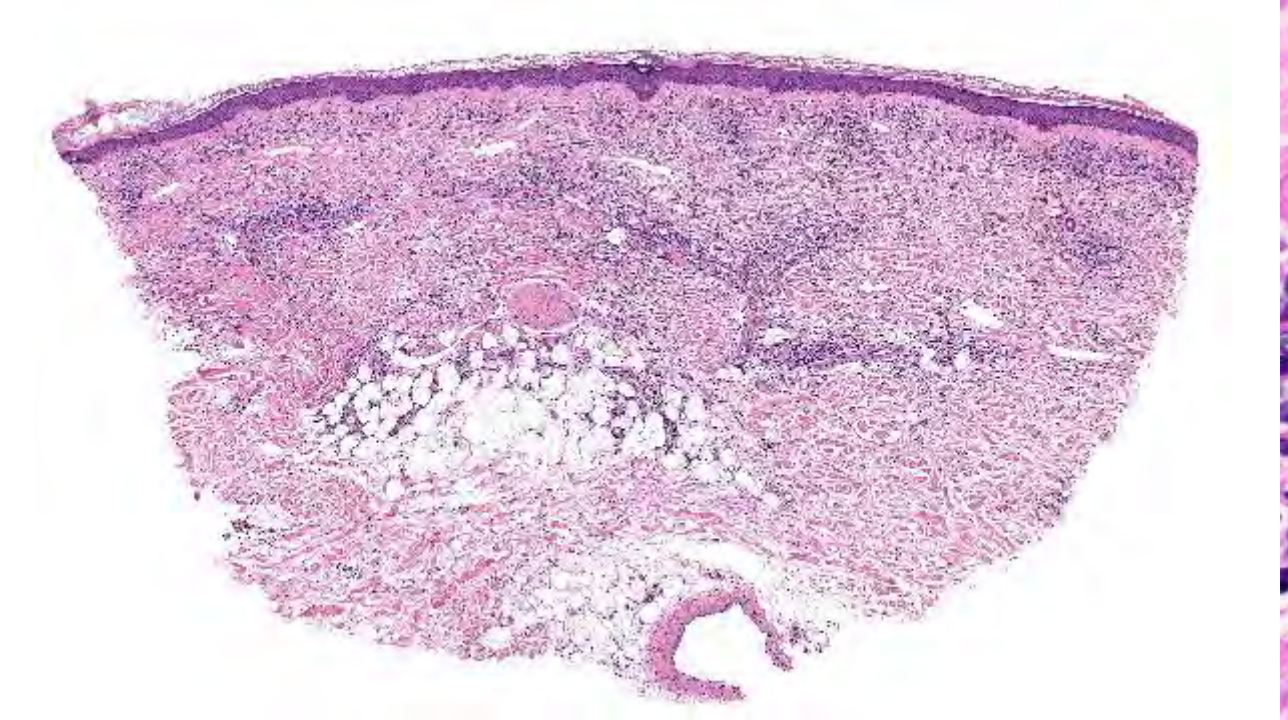
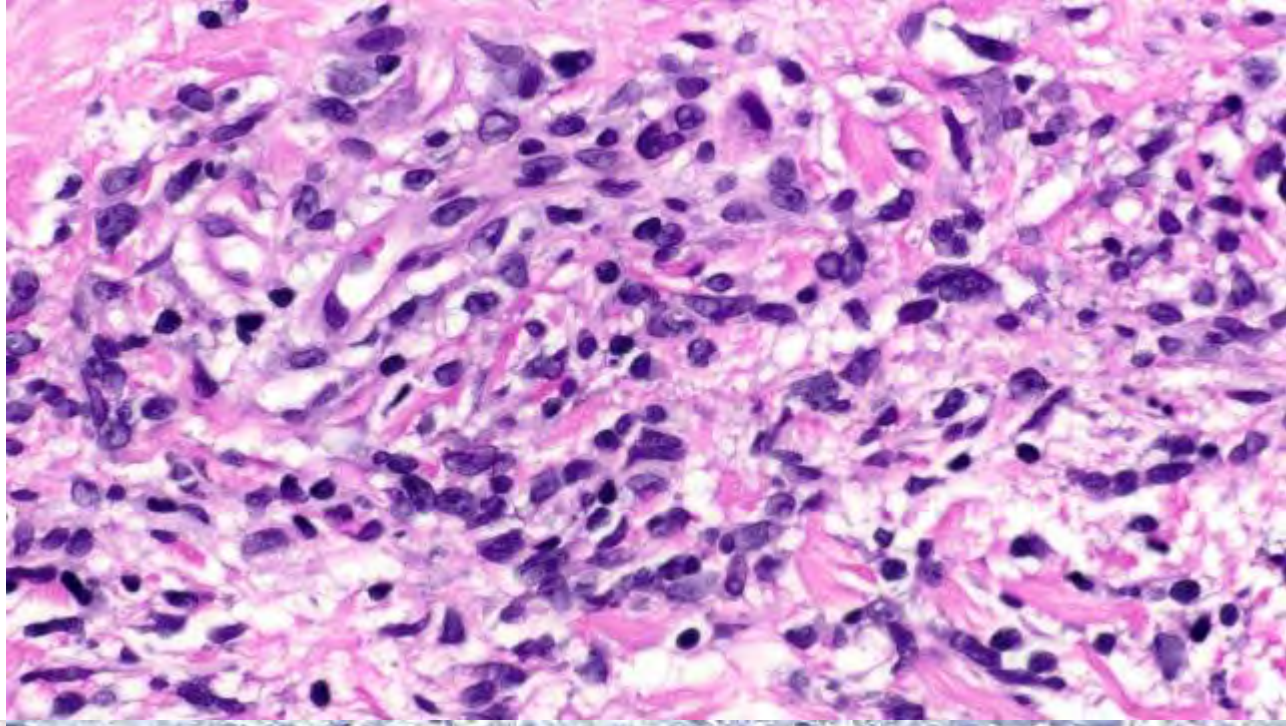
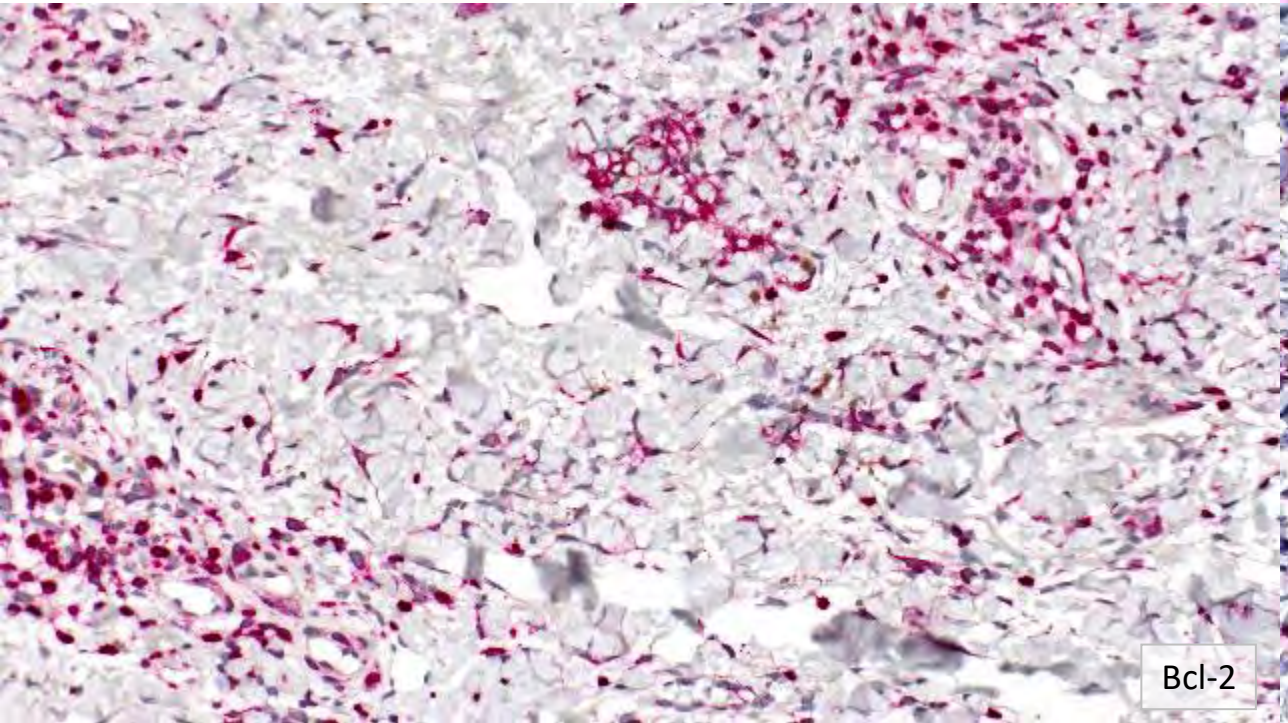
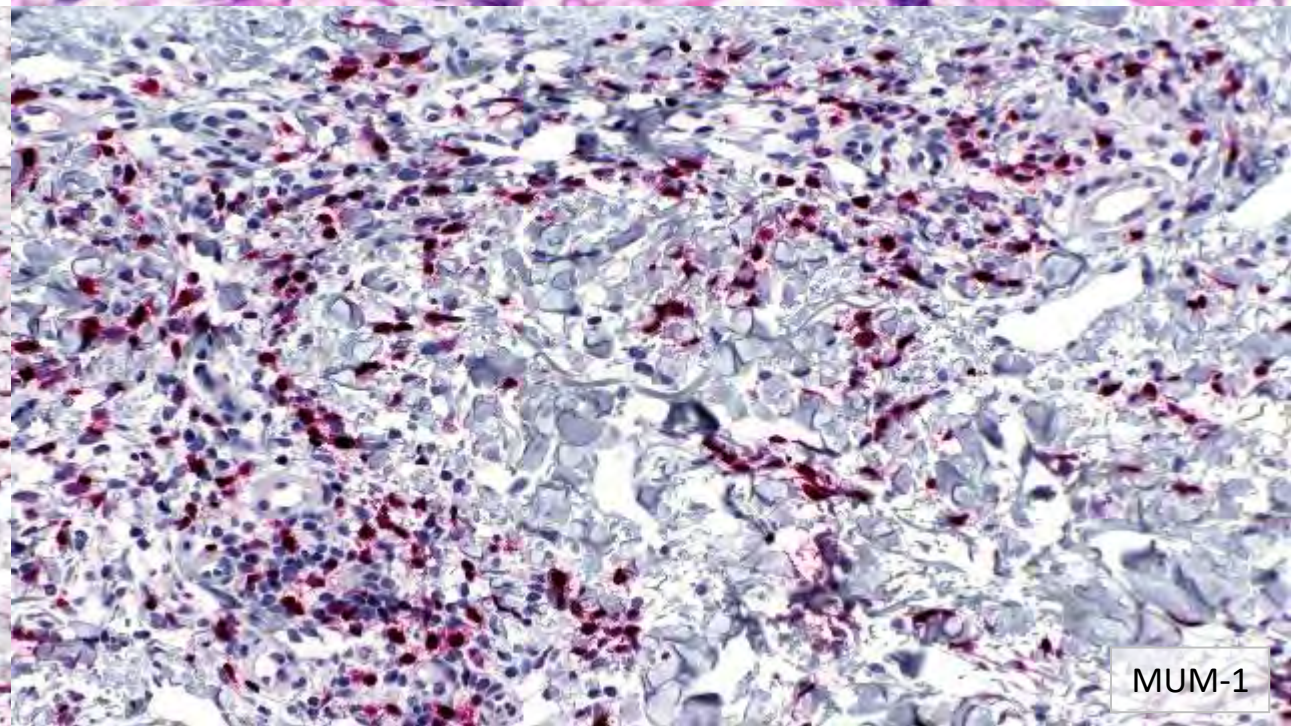


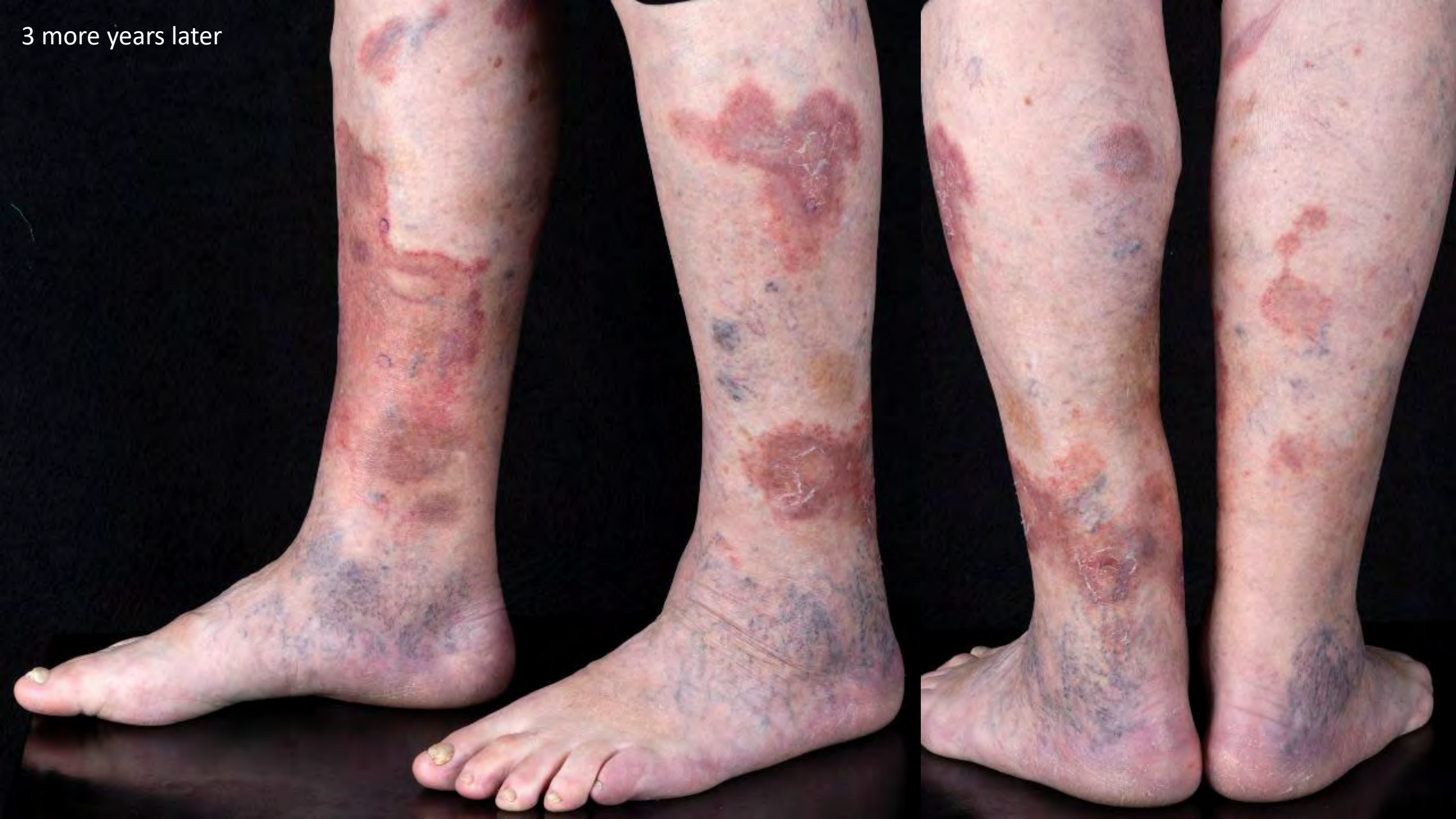
New biopsy






Bcl-2


MUM-1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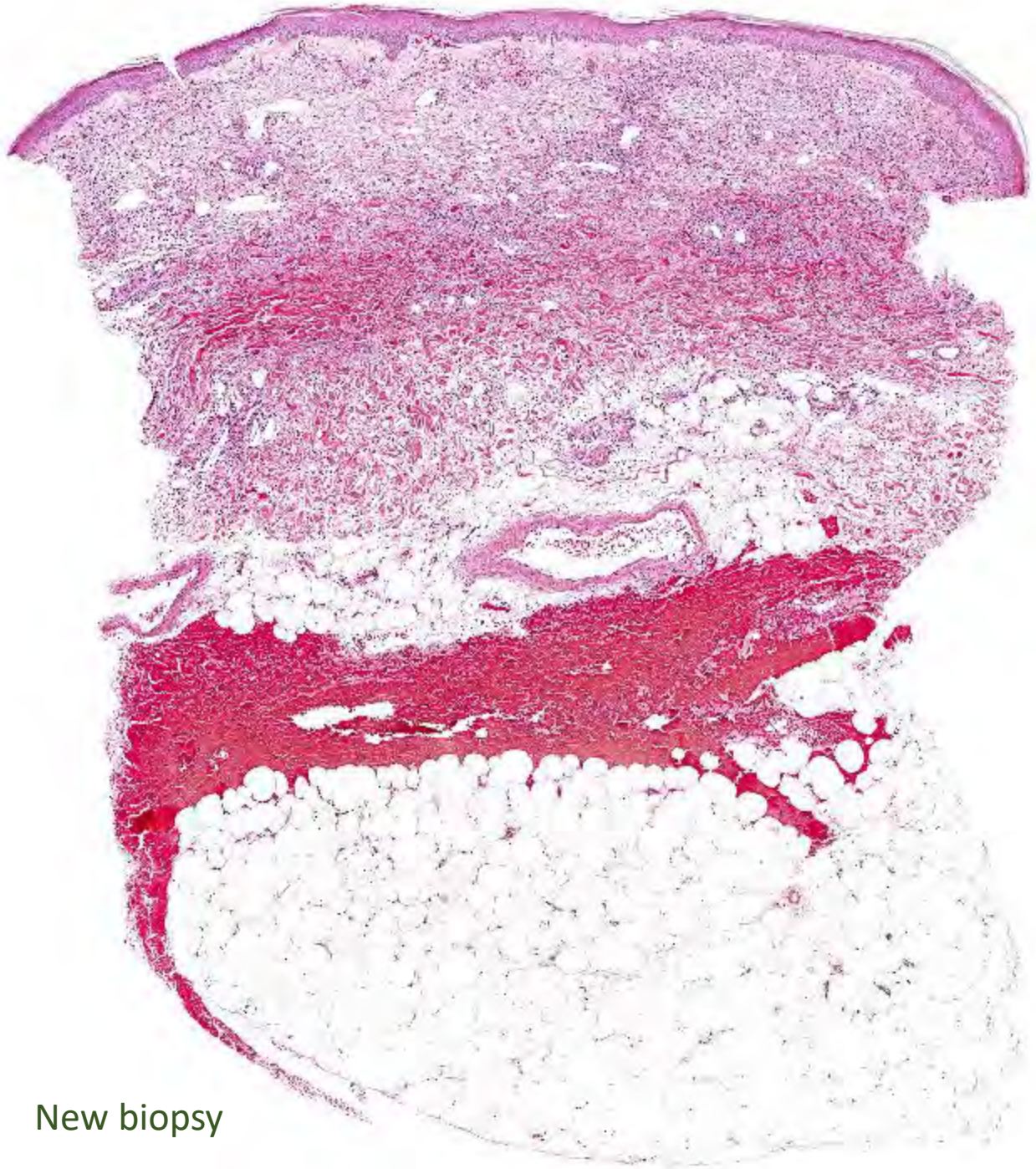

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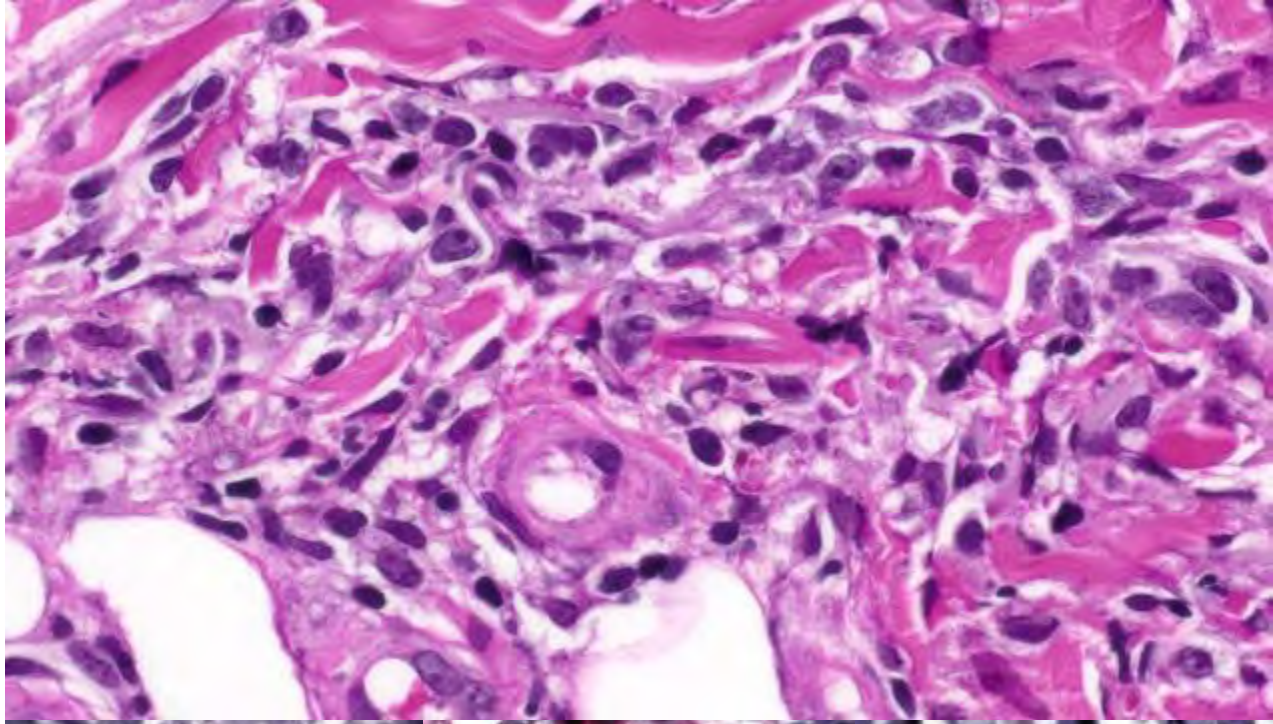
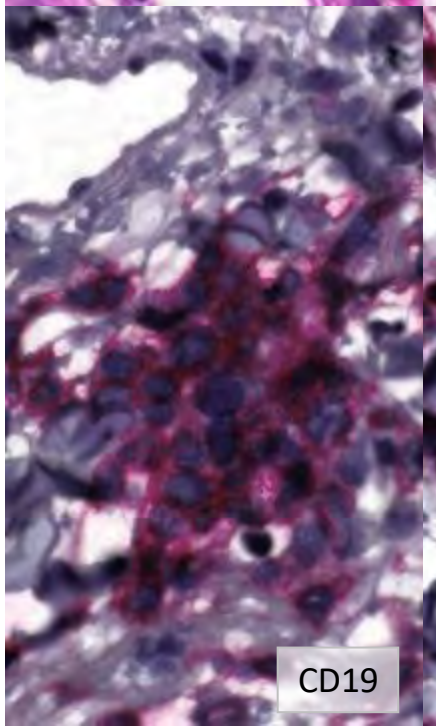
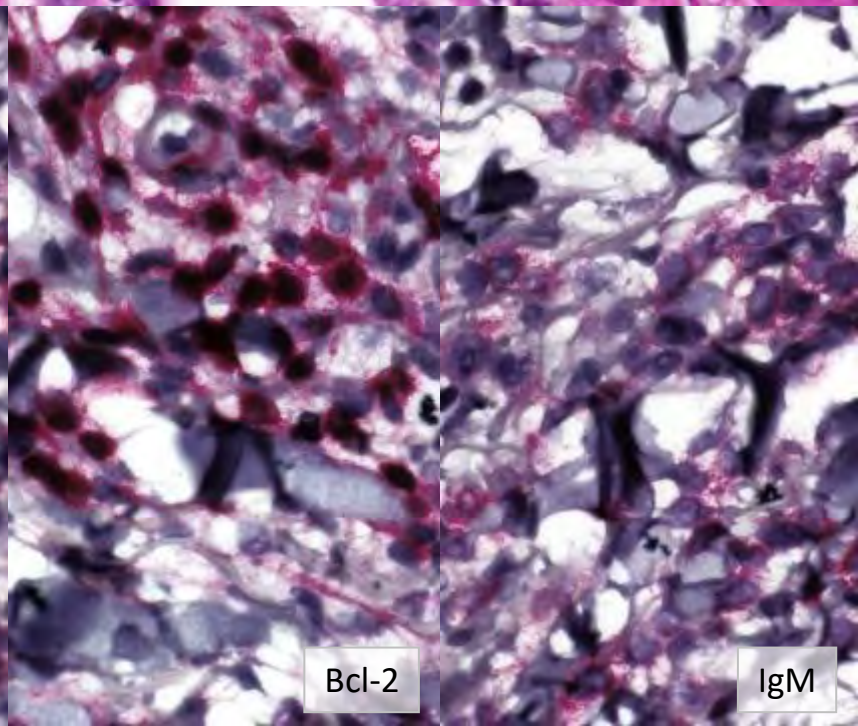


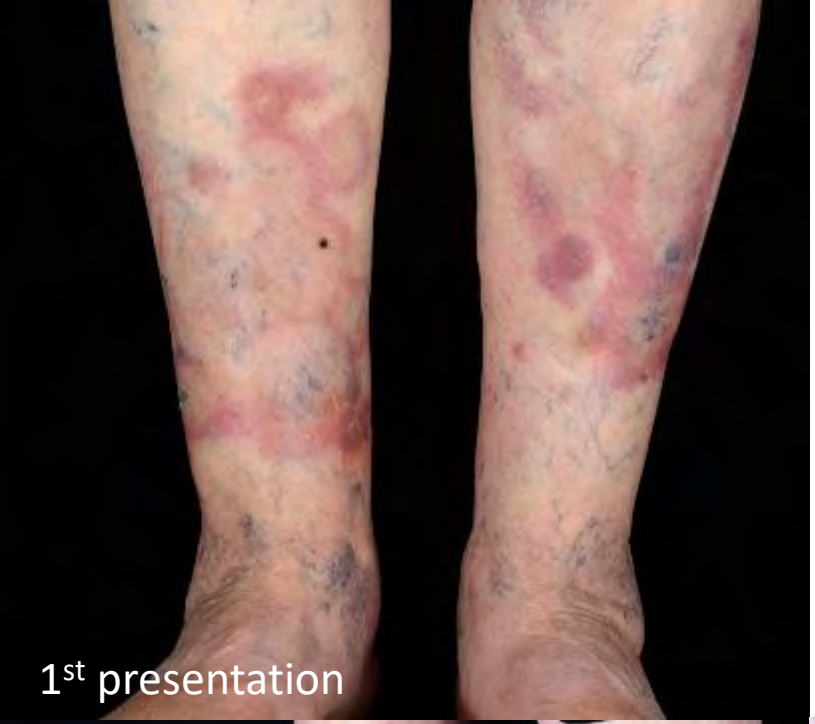


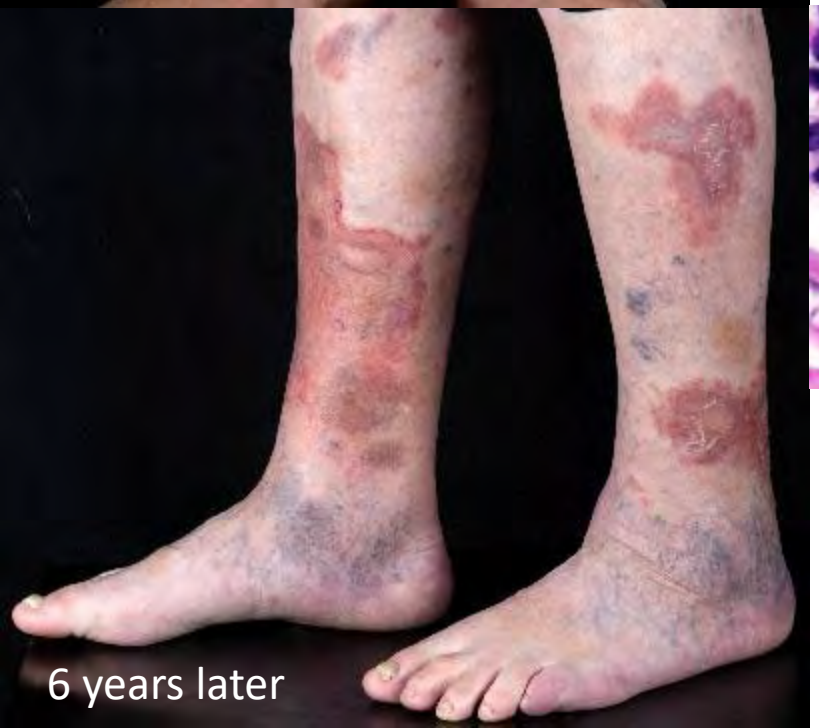
CD19

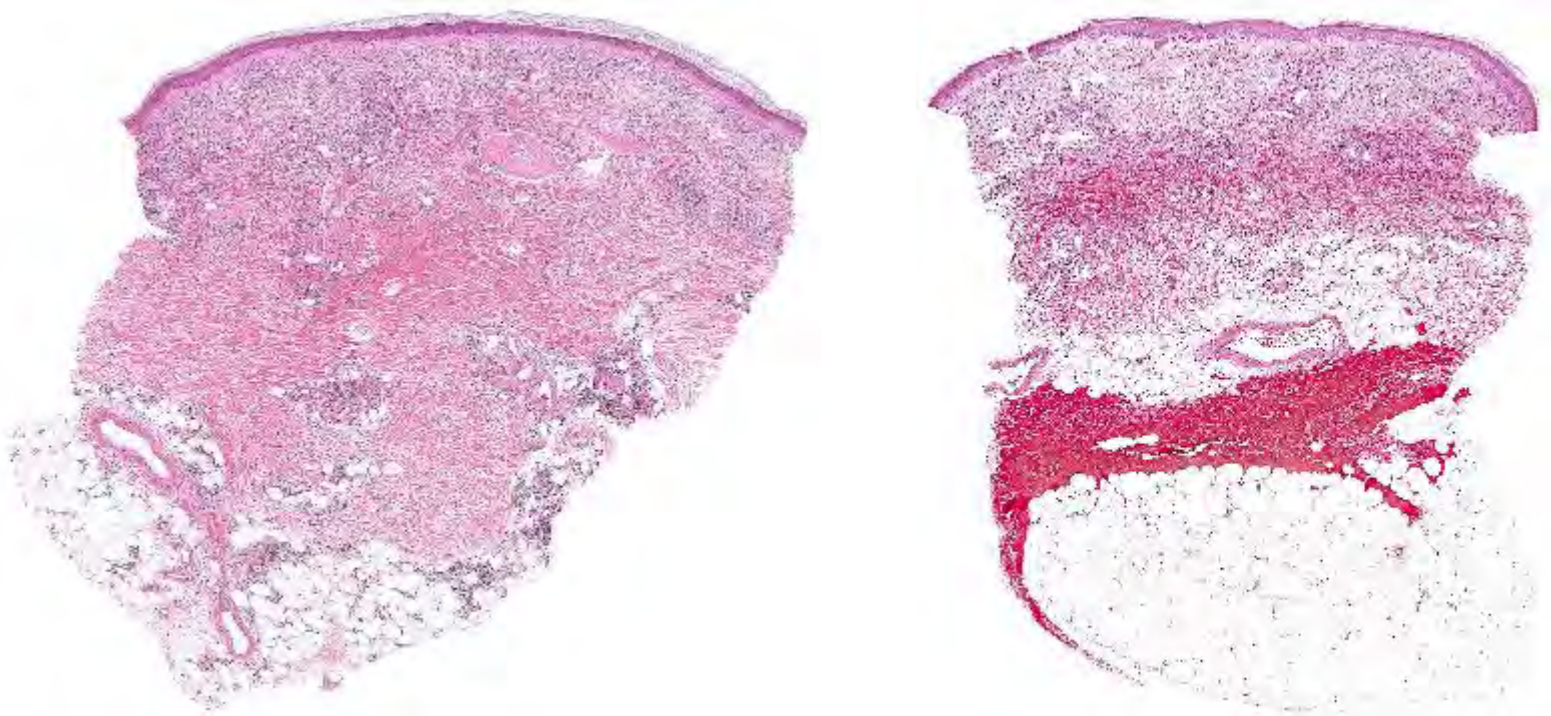


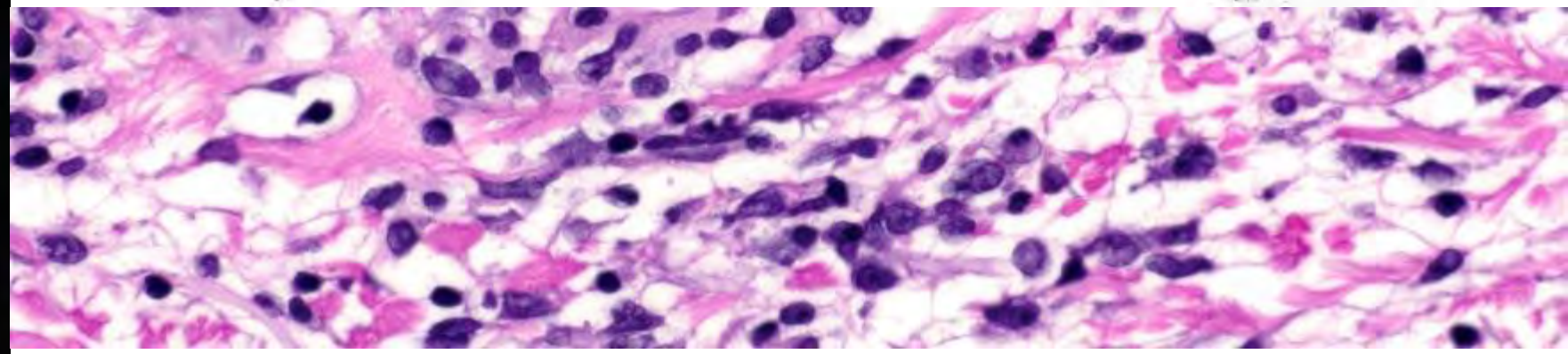
Bcl-2

IgM









Diffuse large B-cell lymphoma, leg-type with figurate lesions and "inflammatory-like" histopathological features.
Recurrent lesions after 6x R-CHOP (managed with local radiotherapy).

Atypical clinicopathologic presentation of primary cutaneous diffuse large B-cell lymphoma, leg type

Cesare Massone, MD, Regina Fink-Puches, MD, Ingrid Wolf, MD, Iris Zalaudek, MD, and Lorenzo Cerroni, MD
Graz, Austria

Background: Primary cutaneous diffuse large B-cell lymphoma, leg type (cDLBCL-LT) is a well-defined entity of cutaneous B-cell lymphoma affecting predominantly elderly patients, mostly women. The typical clinical presentation is characterized by solitary or multiple, rapidly growing plaques or tumors on 1 leg (rarely both legs).

Objective: We sought to describe a new clinical variant of cDLBCL-LT that deviates from the conventional one.

Methods: Clinical, histopathologic, phenotypical, and molecular features of 3 cases of cDLBCL-LT presenting with patches or thin plaques were reviewed (all were women, aged 60, 62, and 87 years; lesions were located on the leg in all patients).

Results: These patients presented with patches or thin plaques that represented the first manifestation of cDLBCL-LT. All 3 patients reported a history of long-standing lesions (present for 6, 9, and 18 months, respectively). Histology revealed moderately dense, perivascular infiltrates of small lymphocytes admixed with variable numbers of large cells that were $CD20^+$, $Bcl\text{-}2^+$, and $MUM\text{-}1^+$.

Limitations: There were only a small number of cases.

Conclusions: We reported an unusual clinical presentation of cDLBCL-LT that deviates from the conventional one and that represents a formidable diagnostic challenge. Biopsy specimens of unusual patches/thin plaques or annular lesions should be obtained from the legs of adult patients if the lesions do not respond to conventional treatment. (J Am Acad Dermatol 2015;72:1016-20.)

Key words: annular erythema; clinical presentation; cutaneous B-cell lymphoma; primary cutaneous diffuse large B-cell lymphoma; leg type.

Primary cutaneous diffuse large B-cell lymphoma, leg type (cDLBCL-LT) is a well-defined entity of cutaneous B-cell lymphoma (CBCL) affecting predominantly elderly patients, mostly women.[1-3] In most cases, the clinical presentation is characterized by solitary or localized, sometimes ulcerated plaques or tumors located on 1 or both legs. In rare cases, large, ulcerated lesions may be clinically difficult to differentiate from venous leg ulcers.[3-5] Another rare clinical presentation with a migratory lesion has been described in 1 patient.[6]

Abbreviations used:

CBCL:	cutaneous B-cell lymphoma
cDLBCL-LT:	cutaneous diffuse large B-cell lymphoma, leg type
PCR:	polymerase chain reaction

We have recently observed 3 patients with cDLBCL-LT with an atypical presentation characterized by variably large erythematous, infiltrated

From the Dermatopathology Research Unit, Department of Dermatology, Medical University of Graz.
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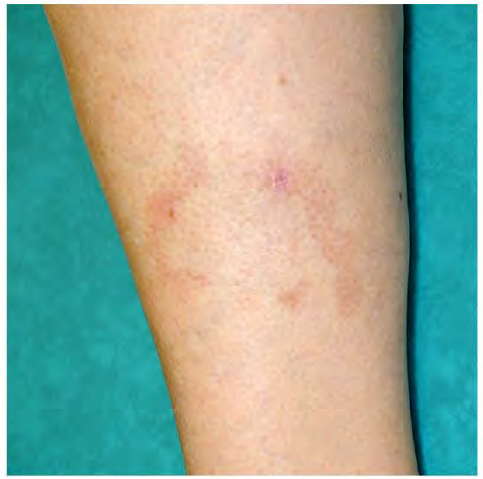


Fig 1. Primary cutaneous diffuse large B-cell lymphoma, leg type. Patient 1. Annular lesion on the leg. A small scar represents the site from which the biopsy specimen was obtained.

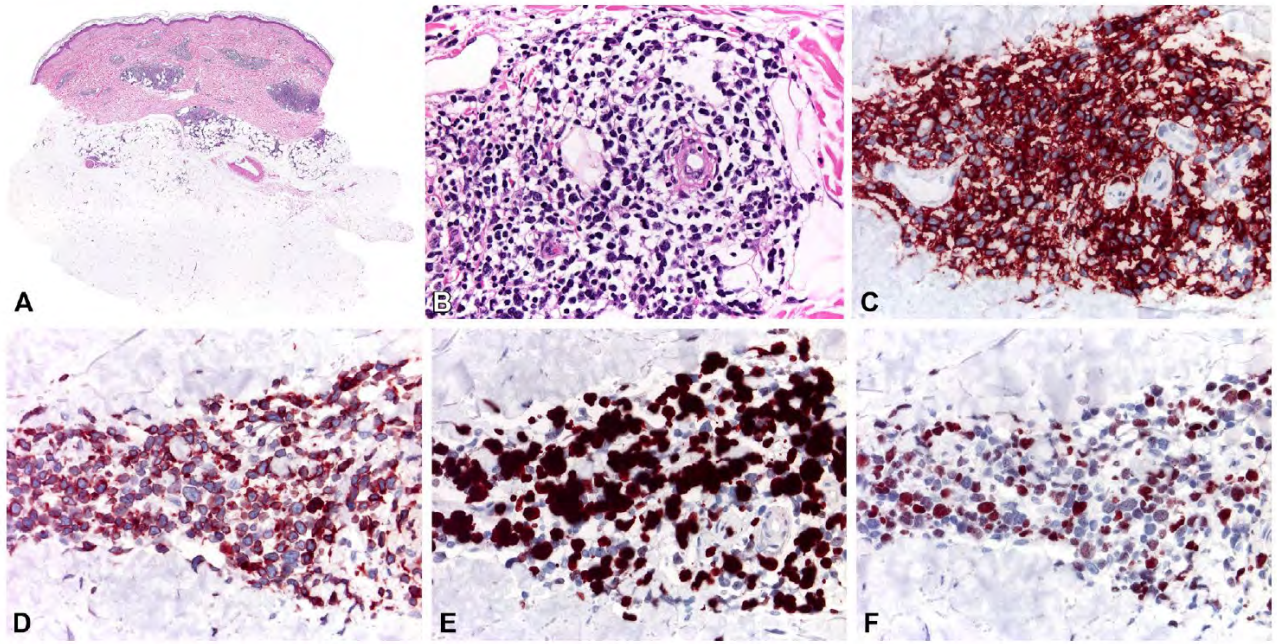
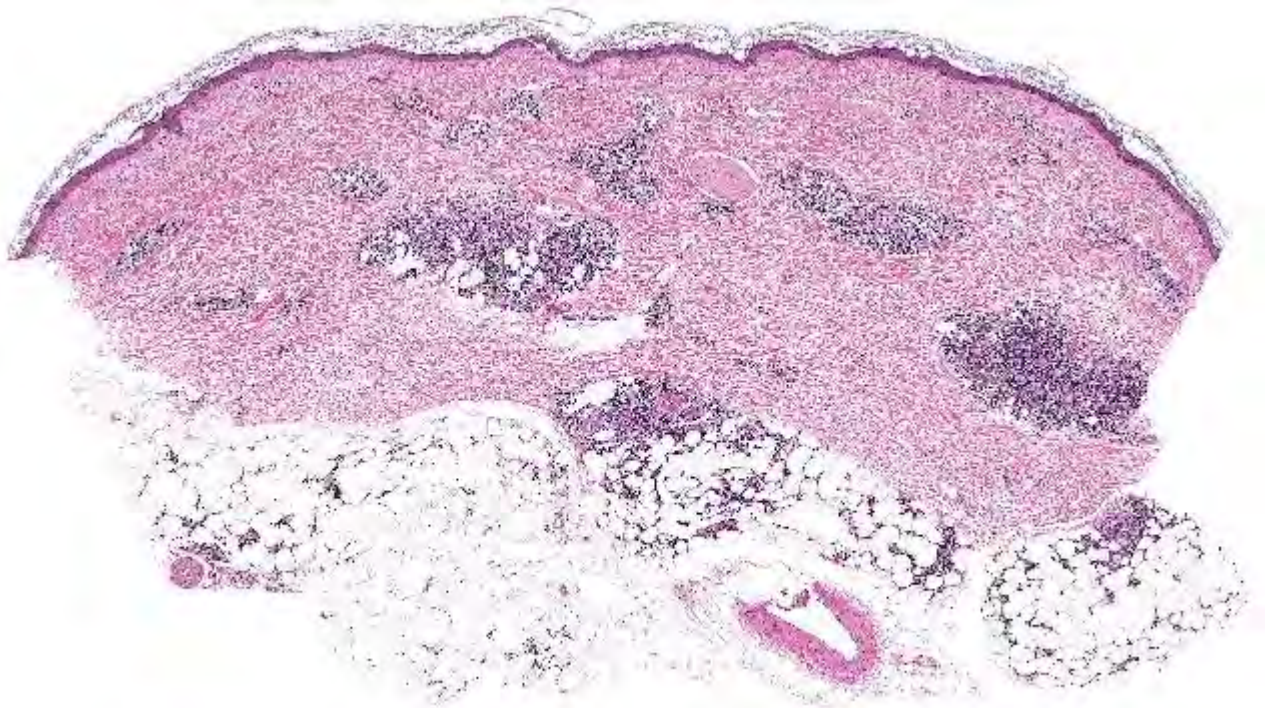
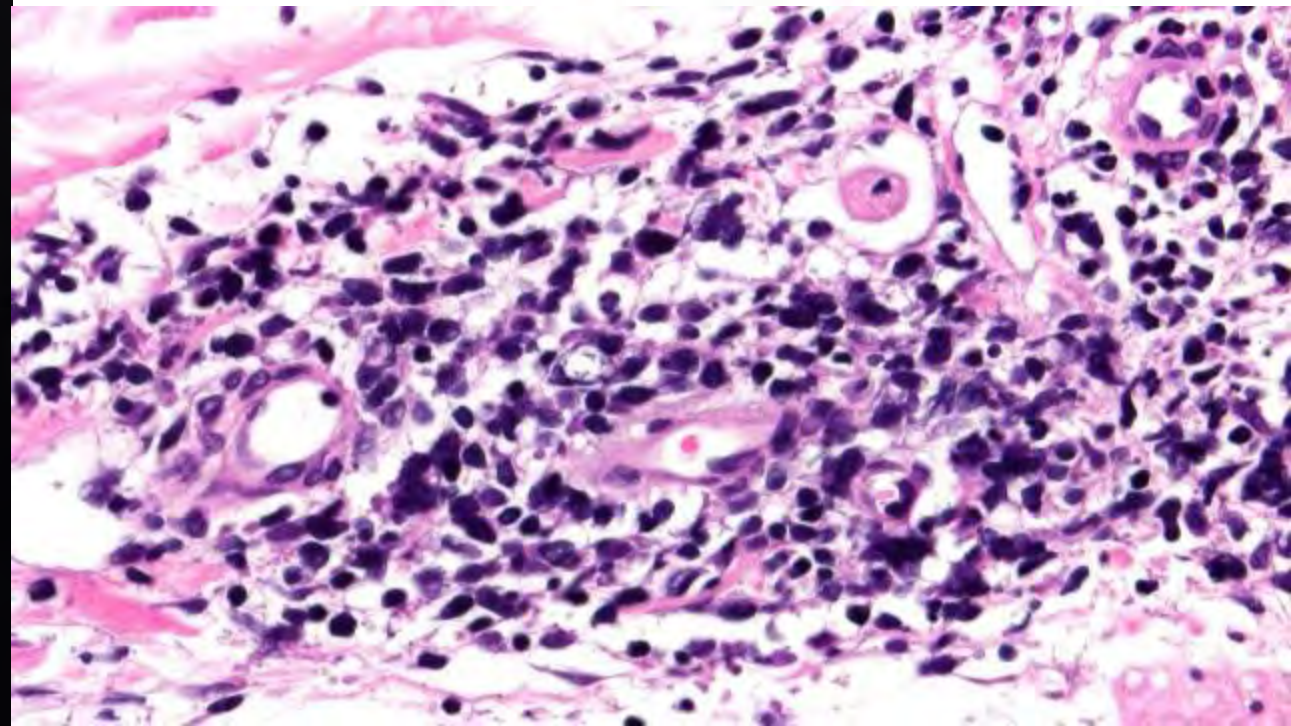
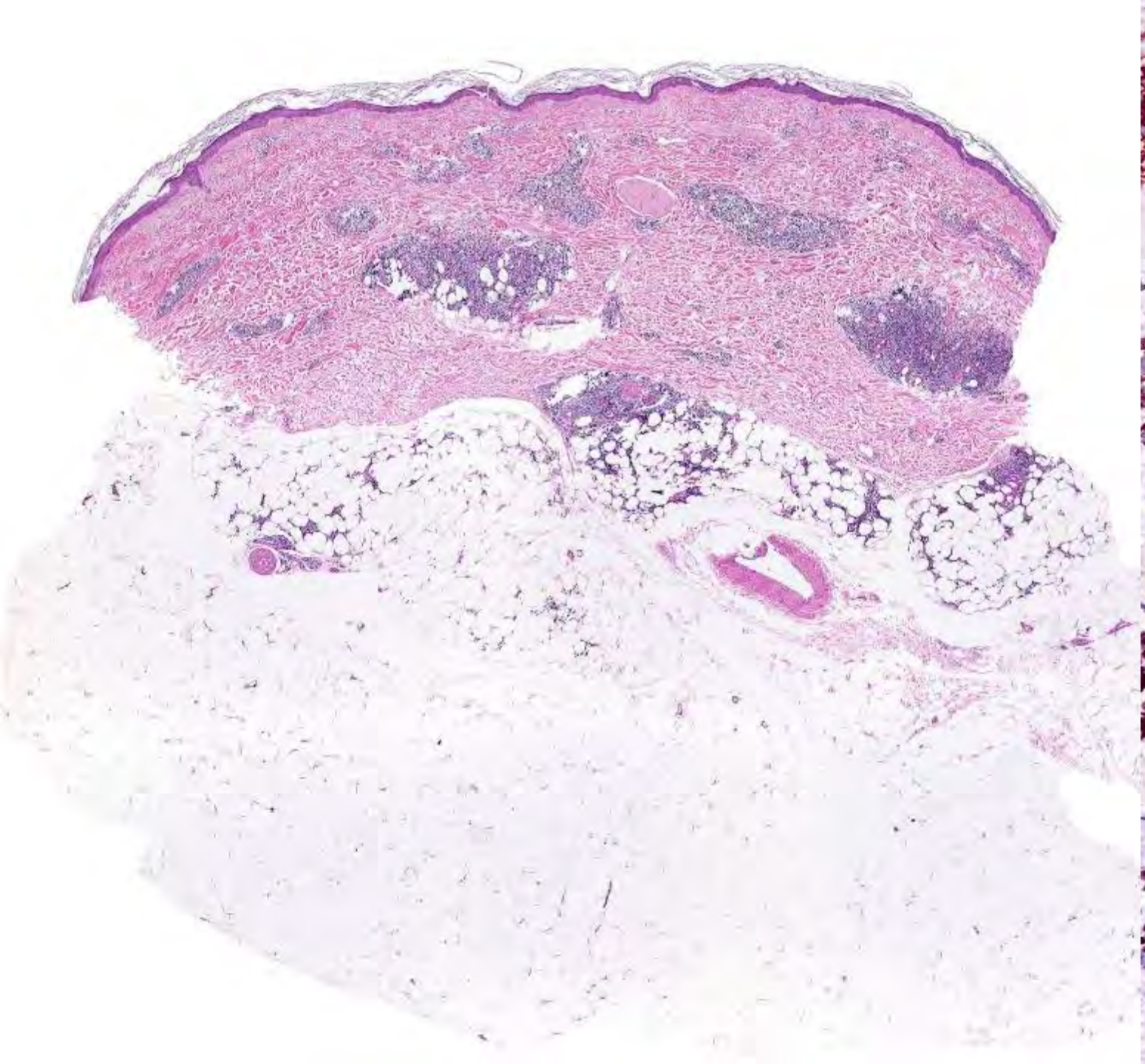


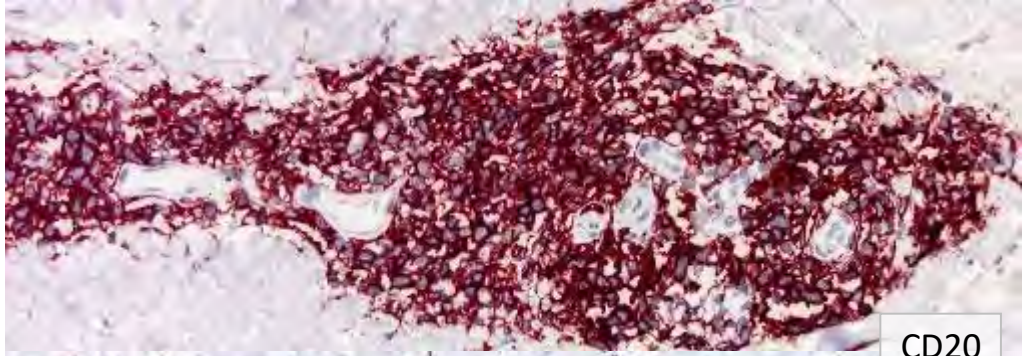
Fig 2. Primary cutaneous diffuse large B-cell lymphoma, leg type. Patient 1. Histopathologic and phenotypical studies reveal (**A**) a moderately dense, perivascular infiltrate (**B**) characterized by small lymphocytes admixed with several large cells. The cells are positive for (**C**) CD20, (**D**) Bcl-2, and (**E**) MUM-1 and (**F**) show a high proliferation as detected by the antibody Ki-67.

F, 60

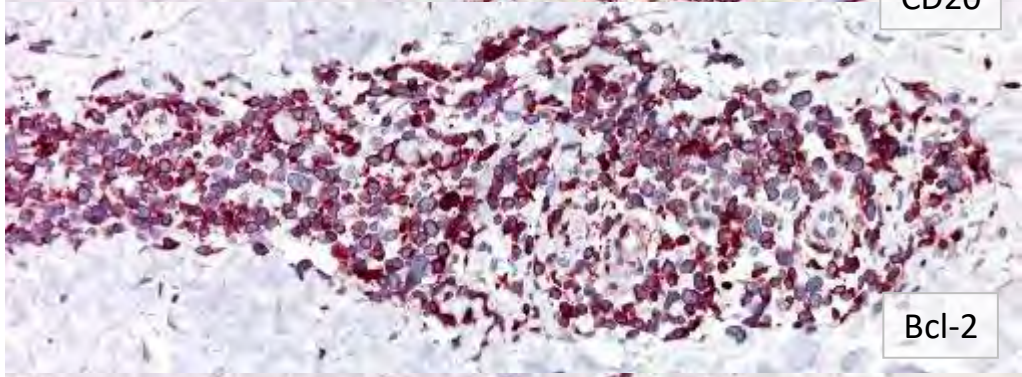




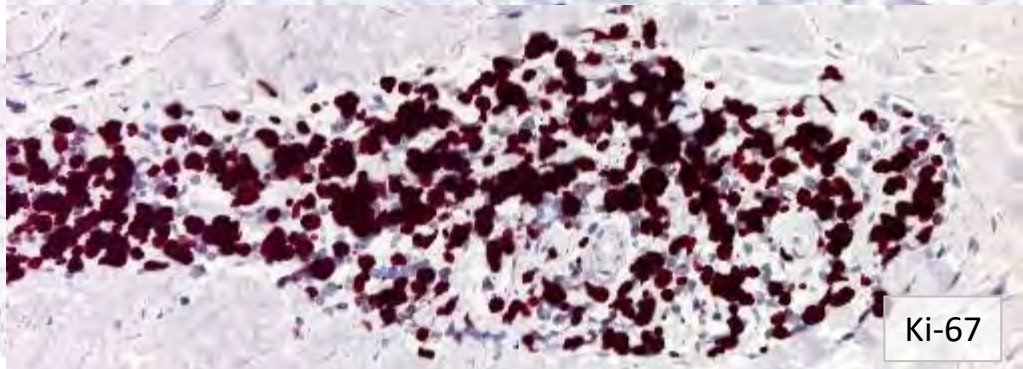




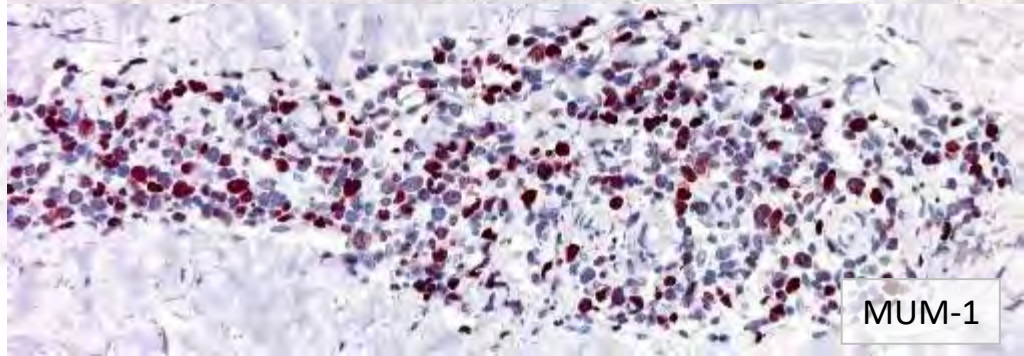
CD20



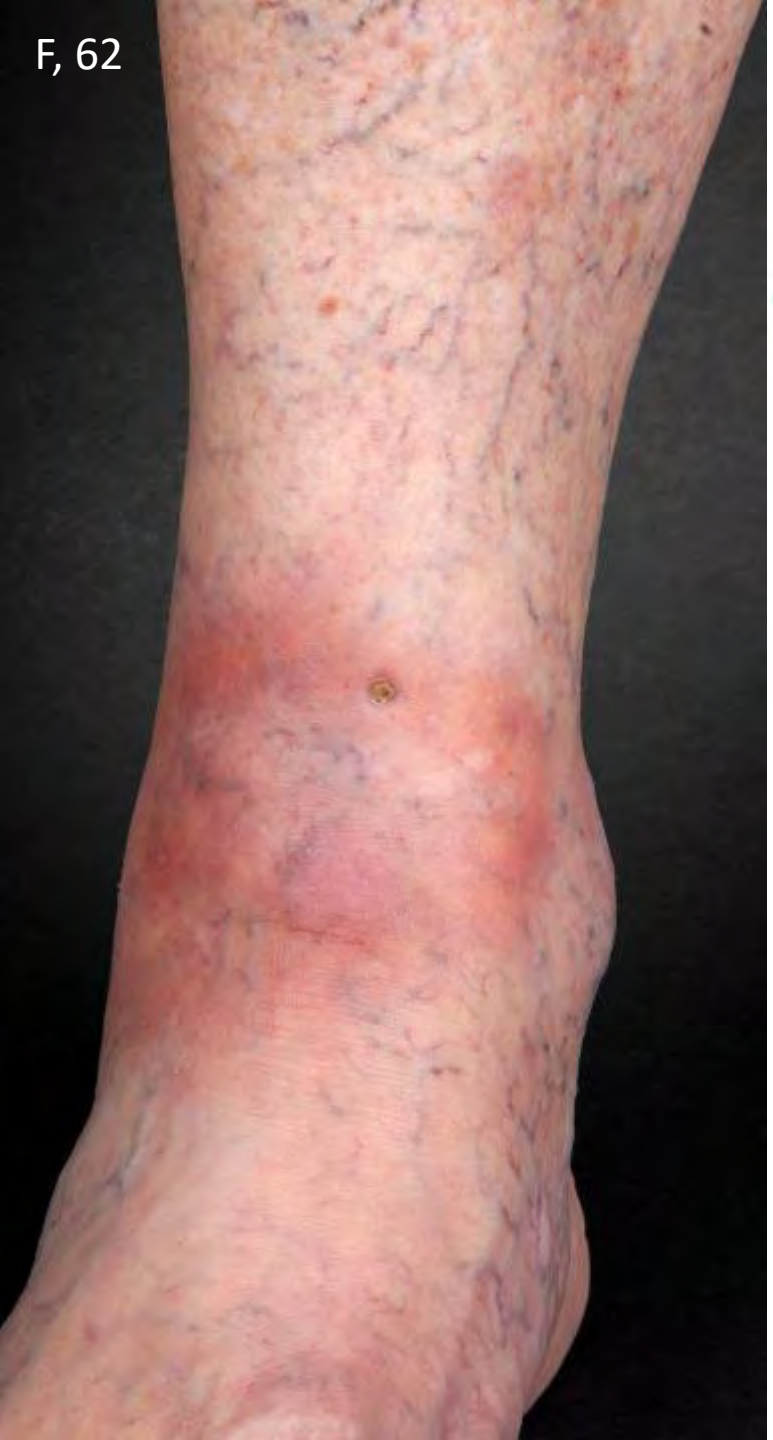
Bcl-2



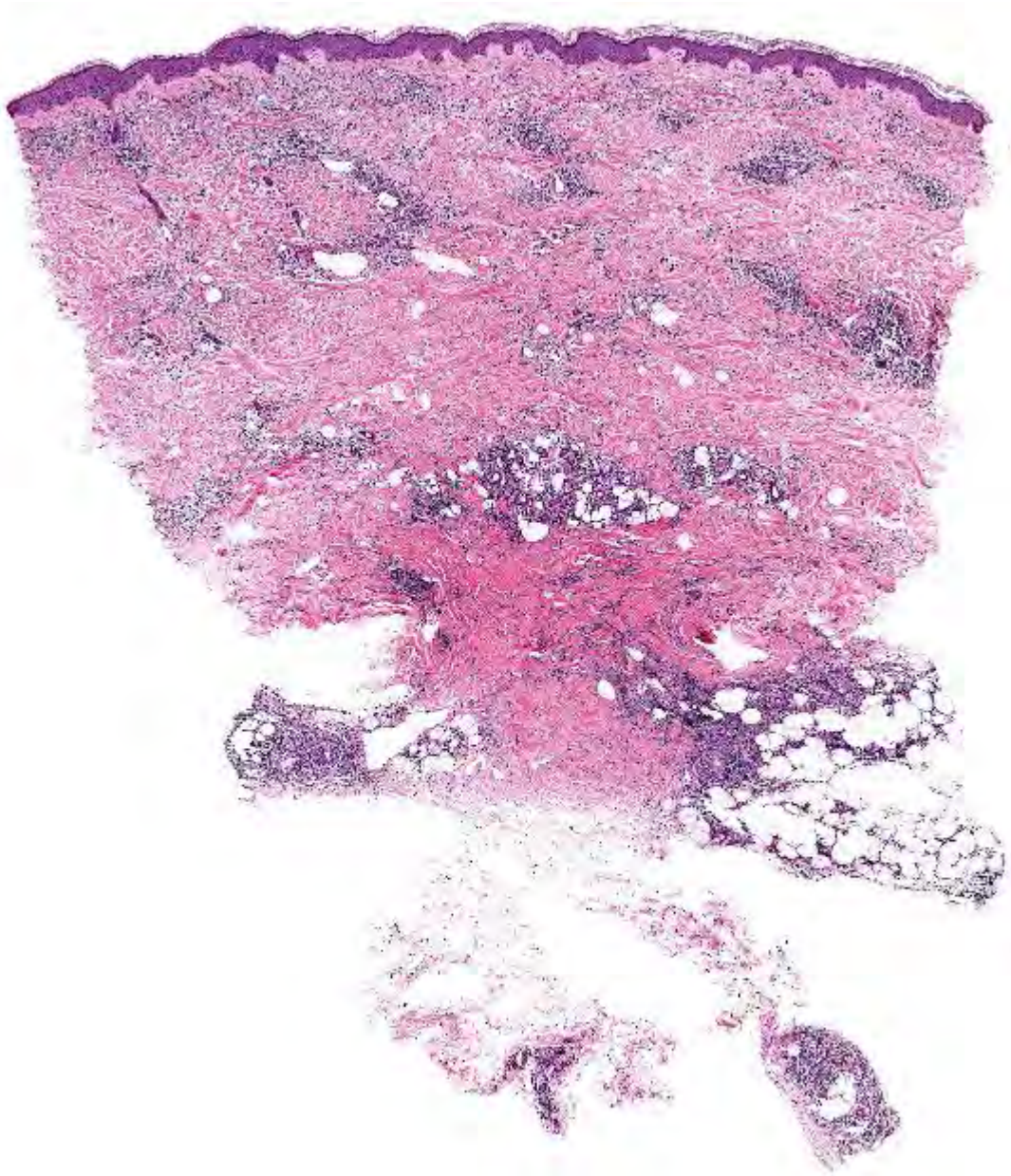
Ki-67

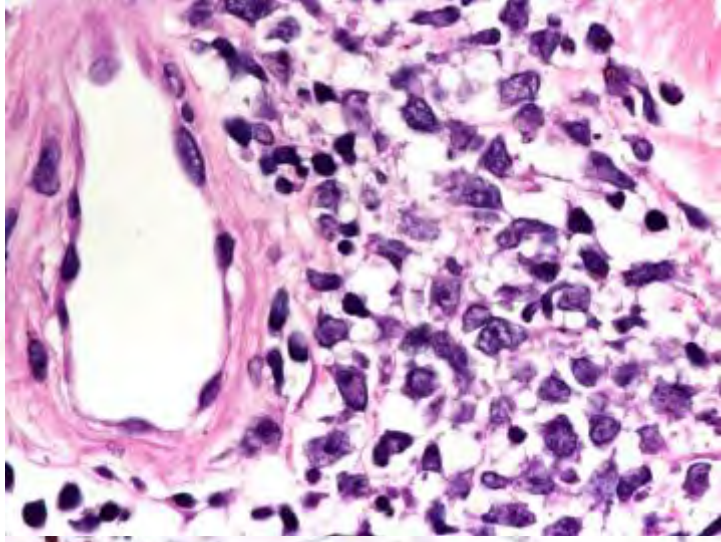


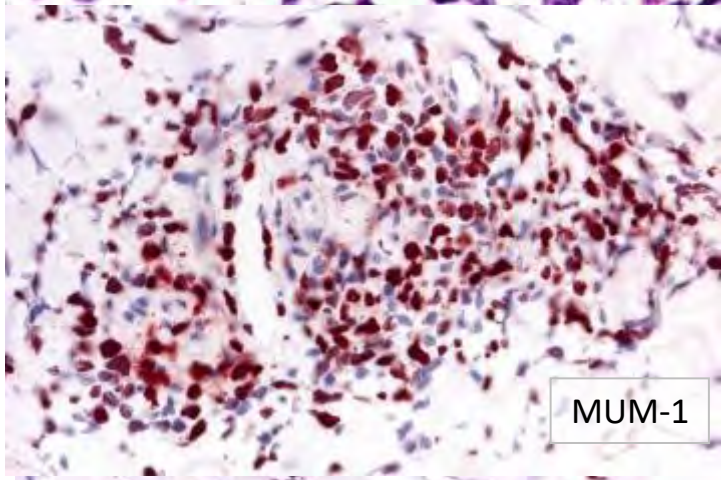
MUM-1

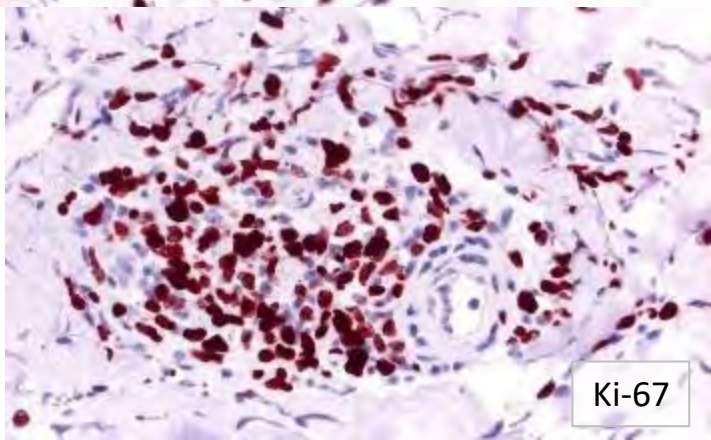


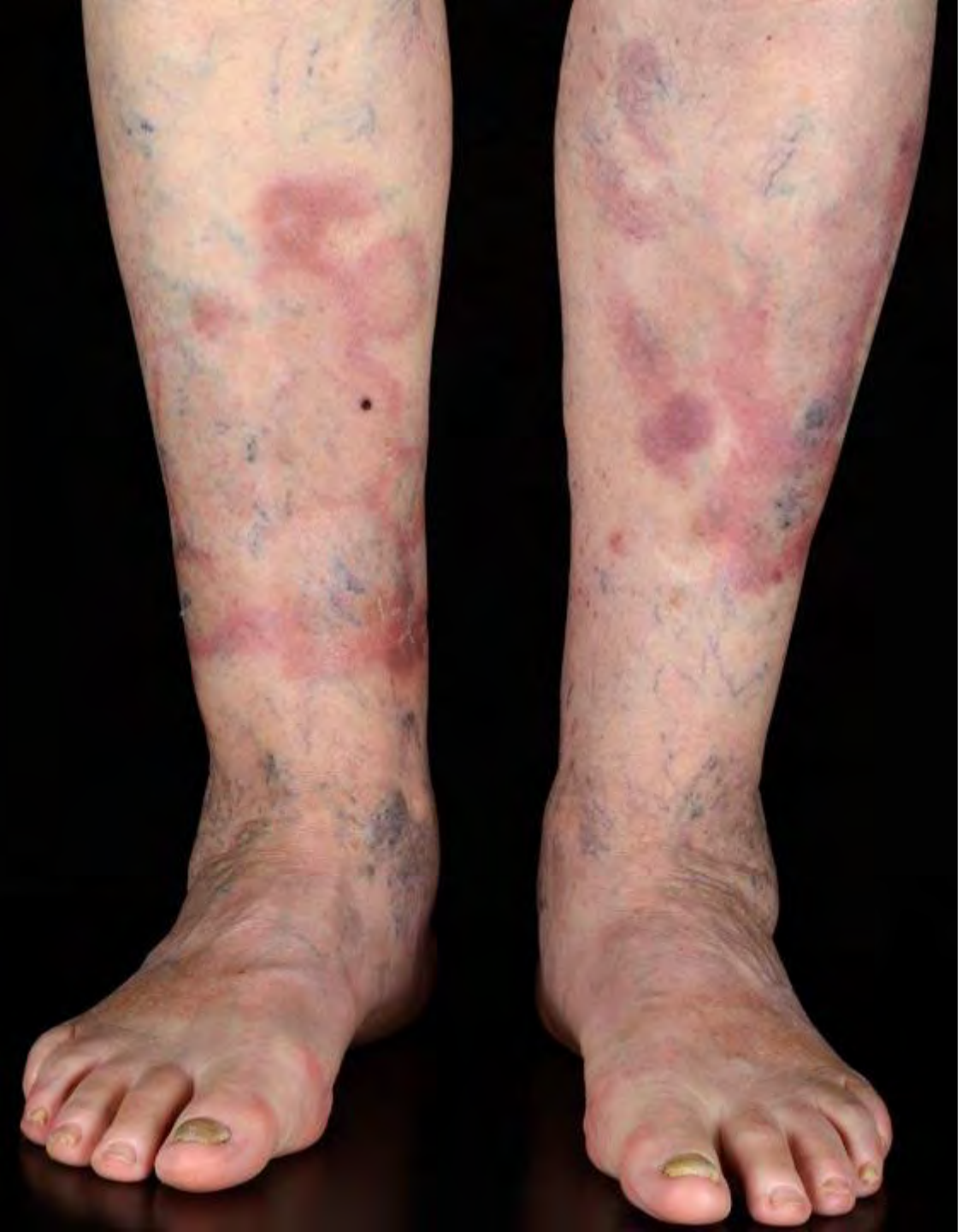
Recurrence after chemotherapy; died 22 months after presentation











"Figurate" primary cutaneous diffuse large B-cell lymphoma, leg-type

A rare presentation of primary cutaneous diffuse large B-cell lymphoma, leg-type, mimicking clinically a figurate erythema (including *Borrelia*-associated erythema migrans), and histopathologically an inflammatory disorder.

Represents approximately 10% of cases of DLBCL-LT seen in the lymphoma out-patient service in Graz; Probably a true clinicopathological variant (recurrences present with the same pattern).

Not described in current classifications (WHO: *"Patients with PCLBCL-LT present with red or bluish-red, often rapidly growing and ulcerating, localized or multiple skin tumours most frequently affecting one or both (lower) legs"*; ICC: *"Disease usually presents as multiple, or less frequently solitary, red or reddish-blue nodules and tumors."*).

Histopathological clue represented by the presence of clusters of large B-cells with a CD20+/MUM1+/IgM+/Bcl2+ phenotype; high proliferation.

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CONCISE COMMUNICATION

Spontaneous regression of primary cutaneous diffuse large B-cell lymphoma, leg type: A case series and review of the literature

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Abstract

Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL, LT) is a subtype of cutaneous B-cell lymphoma with unfavorable prognosis usually requiring aggressive polychemotherapy for disease control. Only single cases of spontaneous regression of PCDLBCL, LT are reported in the literature, peaking 3 months post-biopsy following a clinical history of no longer than 1 year. Here, we report the first case of a spontaneously relapsing and remitting PCDLBCL, LT with complete regression after a clinical history of more than 9 years and thus an atypically indolent clinical course. The female patient presented with recurrent erythematous, non-ulcerated, non-raised plaques of the right lower leg for 6 years. Pathological workup and exclusion of a systemic disease confirmed the diagnosis of PCDLBCL, LT. Due to the history of repeated spontaneous remission, no therapy was initiated. Nine years after first occurrence the patient presented with complete clinical remission lasting for 64 months. We retrospectively identified four additional PCDLBCL, LT patients with spontaneous remission lasting up to 63 months. Our

Manuel Winkler and [illegible] contributed equally to this work and share first authorship.
Cyrill Géraud and Jan Peter Nicolay contributed equally as senior authors.

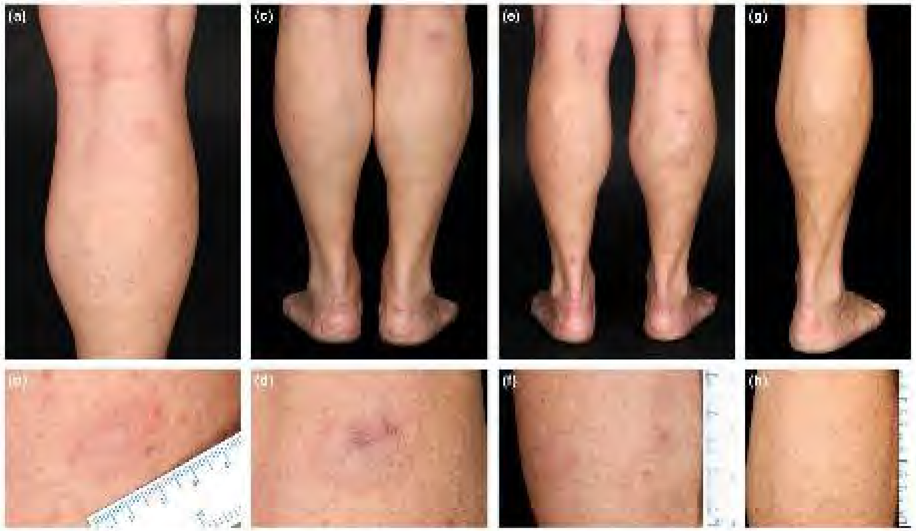


FIGURE 1 Clinical presentation. Annular erythematous plaque at the right calf (a, b) on initial presentation and (c, d) 2 months after biopsy. (e, f) Spontaneous regression and recurrence elsewhere at the right calf 1 year after initial presentation. (g, h) Spontaneous complete regression 9 years after initial presentation.

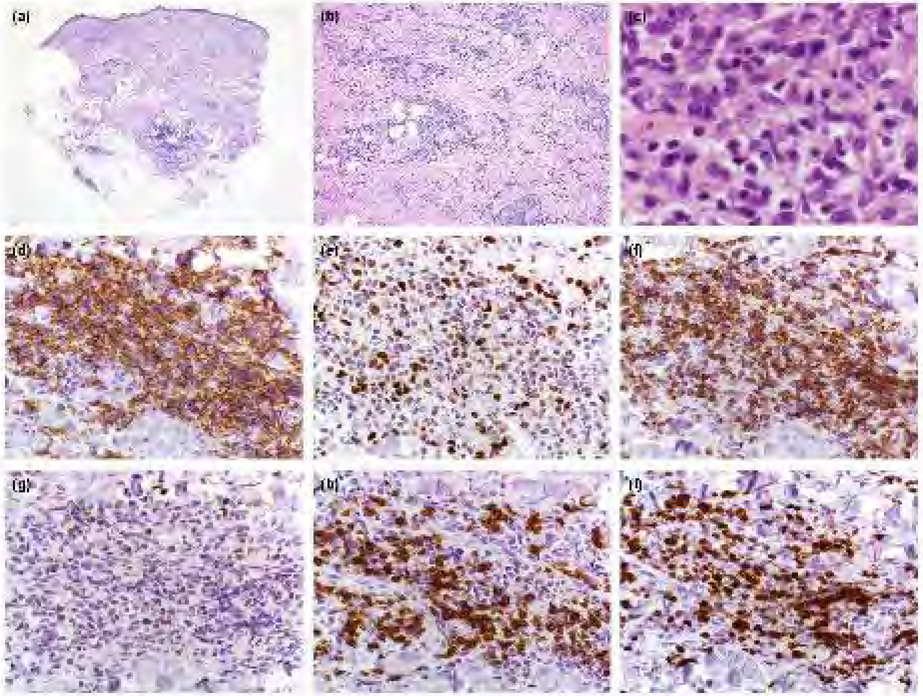
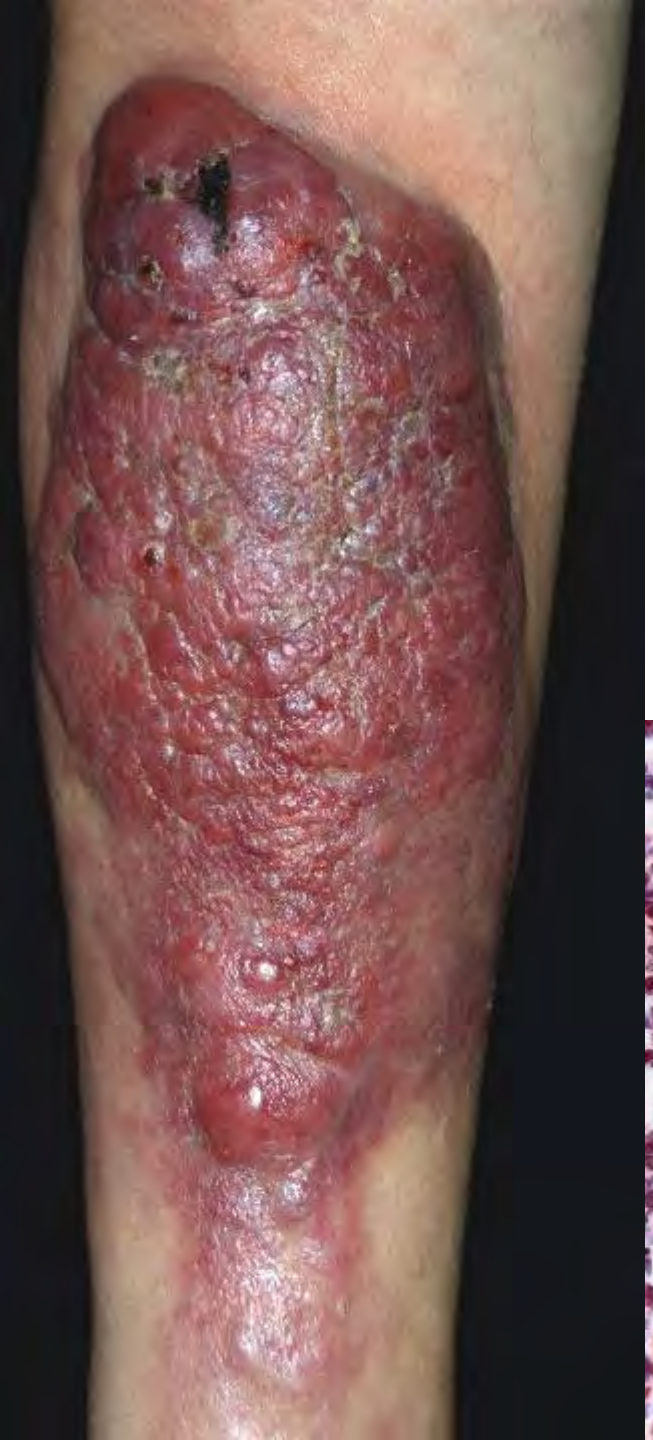


FIGURE 2 Histopathology of a punch biopsy. Nodular and interstitial infiltrate occupying the entire dermis and subcutis without epidermal involvement but with formation of a narrow grenz zone in the H&E stain (a–c). The infiltrate consisted of large B cells, positive for (d) CD20, (e) MUM1 and (f) BCL2 and partly positive for (g) BCL6 in immunohistochemistry as well as small nests of (h) CD3-positive T cells. High proliferative activity was detected by (i) Ki67 in the atypical lymphoid cells. Magnification: (a) ×10, (b) ×100, (c) ×1000, (d–i) ×400.

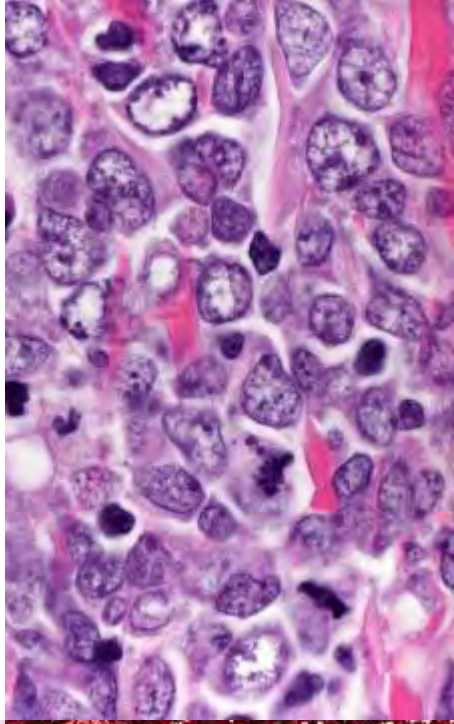


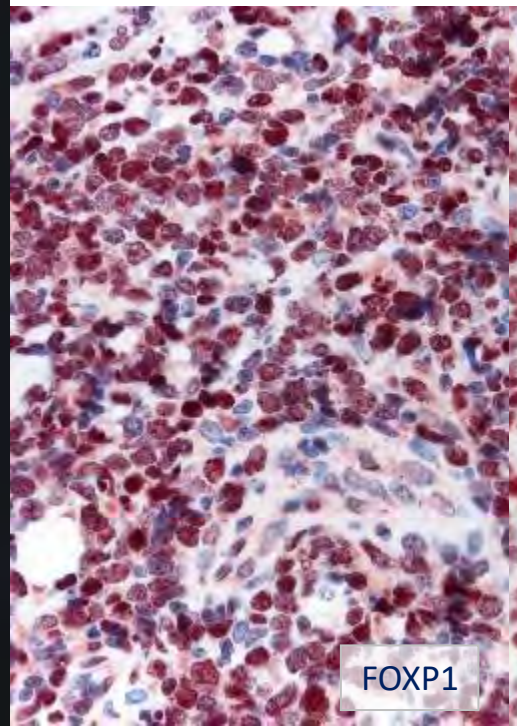
Primary cutaneous diffuse large B-cell lymphoma, leg-type

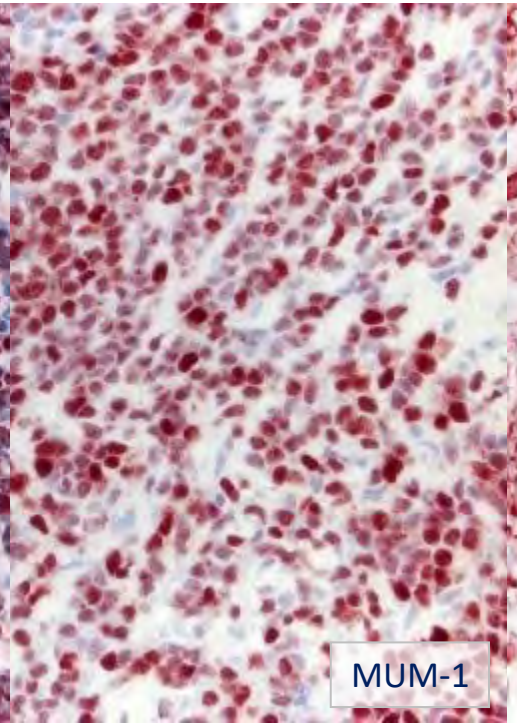
Edlerly patients; in >80% of cases located on the leg(s). Sheets of centroblasts and/or immunoblasts. Bcl2+, MUM1+, Bcl6+/-, FOXP1+, IgM+, MYC+/-, CD10-(+); rare cases may express TdT.

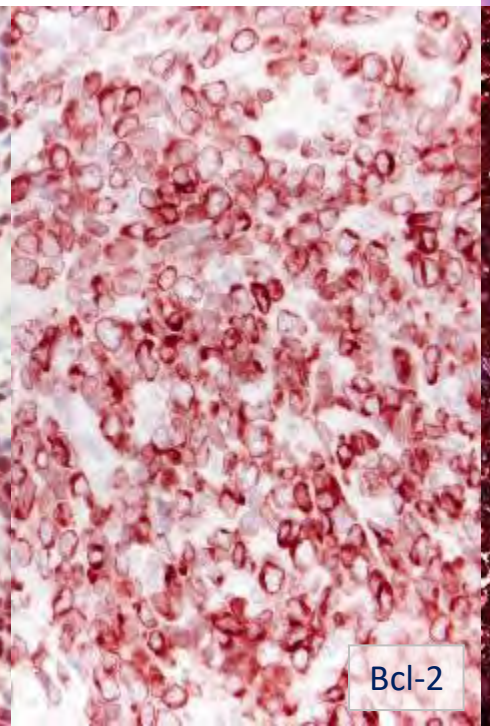
Main differential diagnosis represented by cutaneous follicular lymphoma, diffuse type; in the lymph nodes these 2 entities considered as a spectrum of diffuse large B-cell lymphoma – in the skin completely different behavior and management of patients

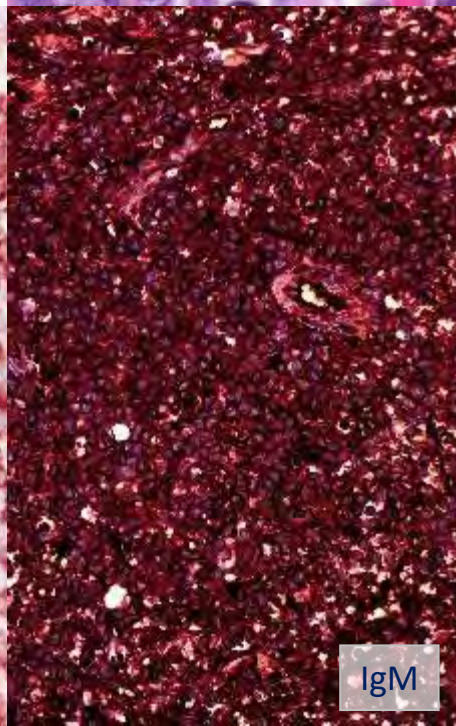
Mutational landscape combining highly recurrent hotspot mutations in genes involved in NF-kB and B-cell signaling pathways, akin to the category of C5/MCD DLBCL of the CNS and testis.







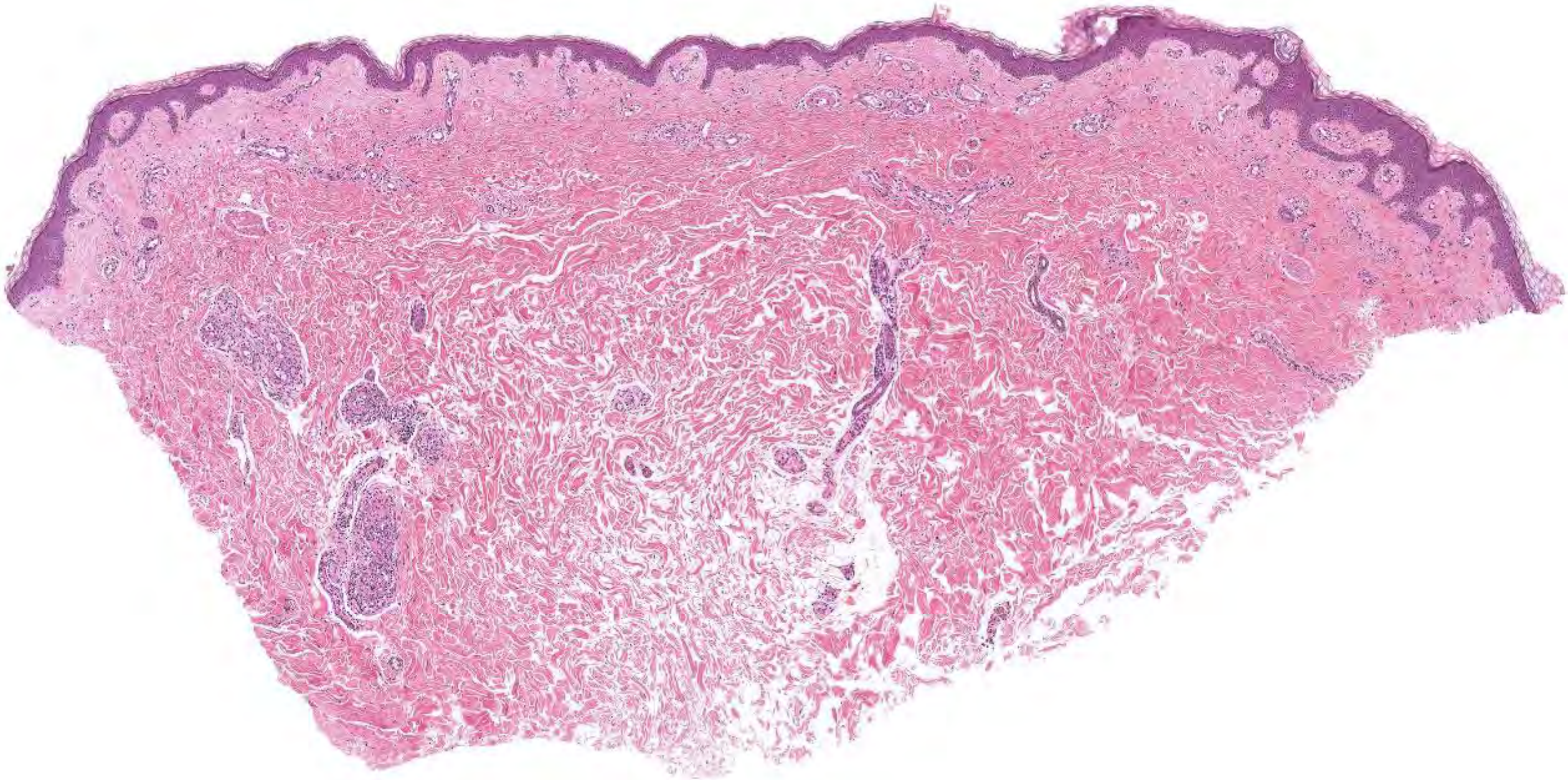


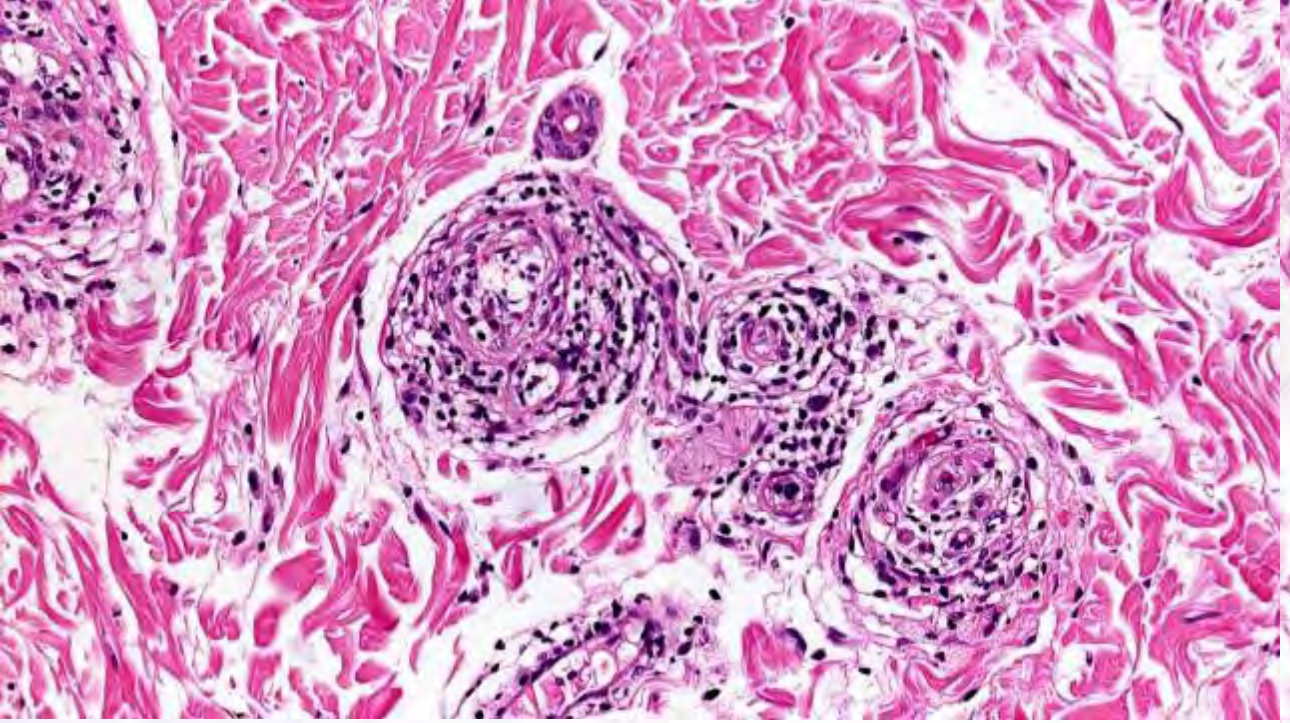


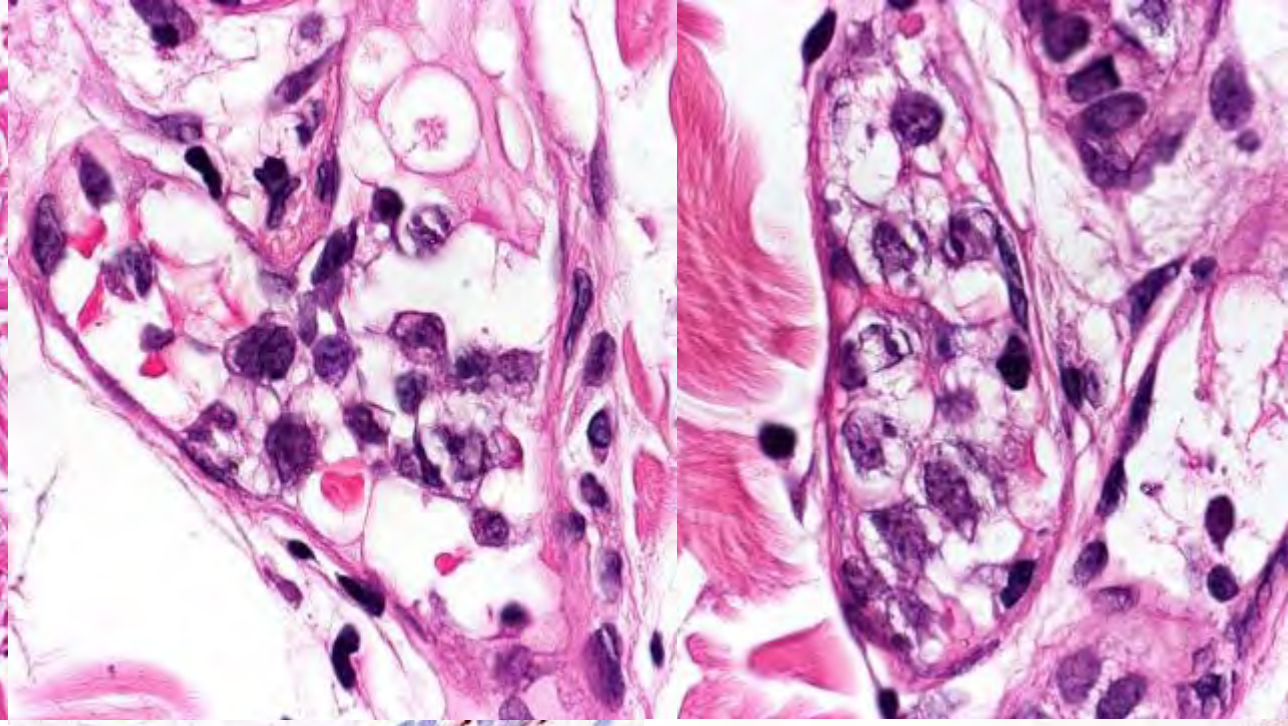
Intravascular large cell lymphomas

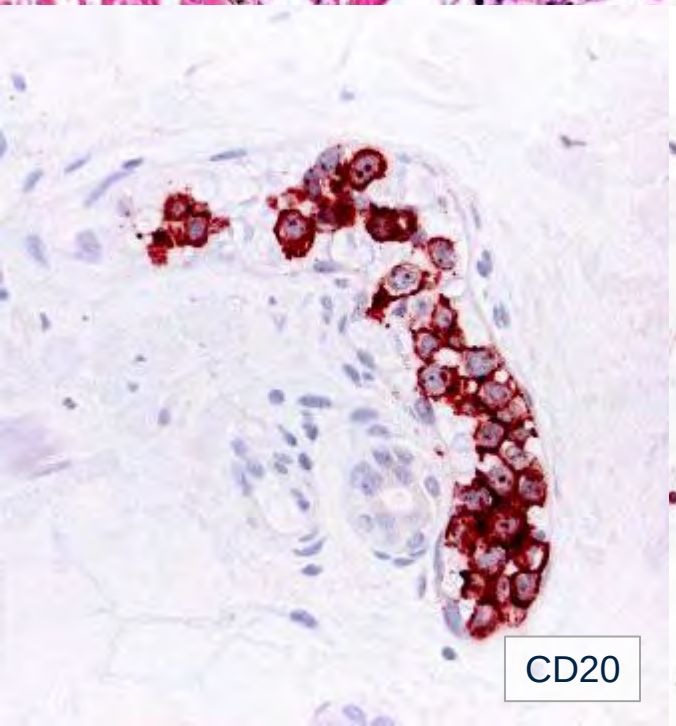
- The B-cell variant is included as a distinct entity in the International Consensus Classification (ICC) of Myeloid and Lymphoid Neoplasms and the 5th edition of the WHO Classification of Haematolymphoid Tumours; The T-cell variant is not covered specifically in any lymphoma classification (WHO 5ed: mentioned in the paragraph on aggressive NK-cell leukemia)
- *Essential diagnostic criteria (B-cell variant):* Positivity for B-cell markers; neoplastic cells confined to dilated blood vessels
- *Essential diagnostic criteria (T-cell variant):* Positivity for T-cell markers; neoplastic cells confined to dilated blood vessels
- *Main differential diagnoses:* Intralymphatic anaplastic large cell lymphoma; Intralymphatic / intravascular histiocytosis; Benign intralymphatic proliferation of T-cell blasts; Diffuse large B-cell lymphoma with intravascular cells

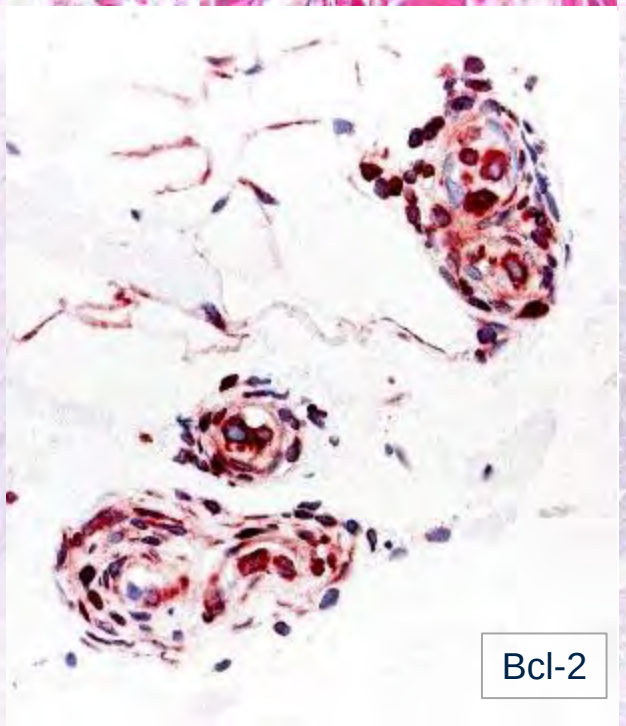
M, 72

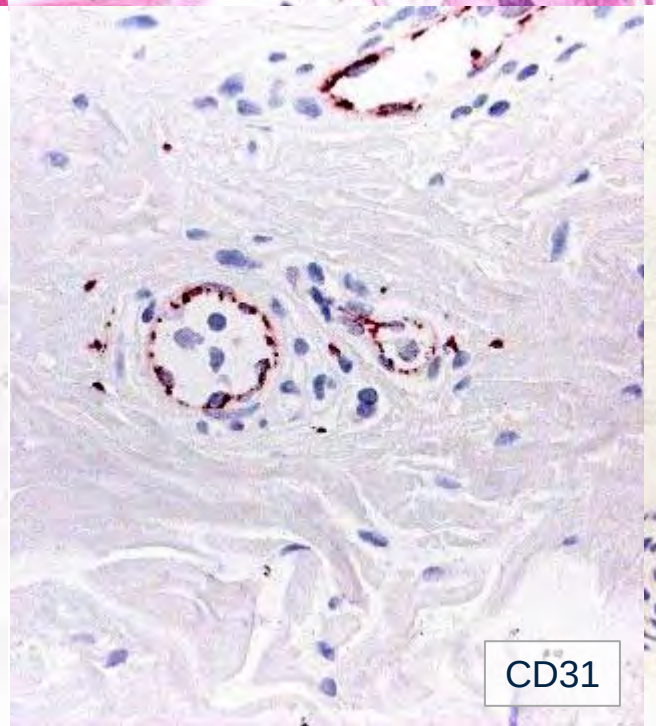


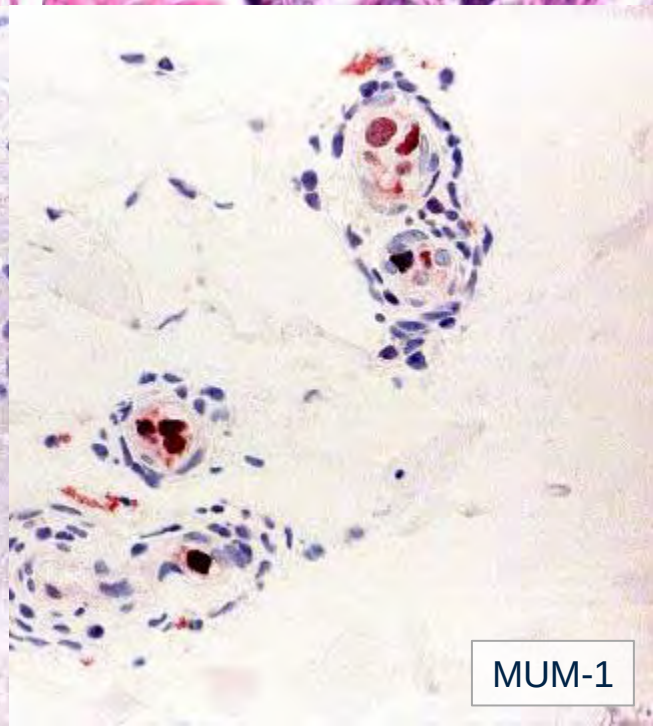





CD20


Bcl-2


CD31


MUM-1

blood®
Prepublished online March 7, 2018;
doi:10.1182/blood-2017-12-822817

High prevalence of *MYD88* and *CD79B* mutations in intravascular large B-cell lymphoma

Anne M.R. Schrader, Patty M. Jansen, Rein Willemze, Maarten H. Vermeer, Anne-Marie Cleton-Jansen, Sebastiaan F. Somers, J.H. (Hendrik) Veelken, Ronald van Eijk, Willem Kraan, Marie José Kersten, Michiel van den Brand, Wendy B.C. Stevens, Daphne de Jong, Myrurgia Abdul Hamid, Bea C. Tanis, Eduardus F.M. Posthuma, Marcel Nijland, Arjan Diepstra, Steven T. Pals, Arjen H.G. Cleven and Joost S.P. Vermaat

25 patients; skin 12 (6 skin only).
Other affected organs: bone marrow 8, brain 7, lung 7, spleen 5, liver 4, lymph nodes 4, kidney 3, other 5 (thyroid, testis, soft tissue, cardiac muscle)

From a therapeutic perspective, our results suggest that a substantial number of IVLBCL patients may be amenable to treatments targeting NFκβ-signalling. Recent studies showed that DLBCL patients with *MYD88* and/or *CD79B* mutations are more sensitive to treatment with ibrutinib, a Bruton Tyrosine Kinase inhibitor that blocks the NFκβ-pathway.[23-25] Further studies are required to assess whether IVLBCL patients may also benefit from these therapeutic approaches.

ORIGINAL RESEARCH

Cancer Medicine WILEY

PD-L1 (SP142) expression in neoplastic cells predicts a poor prognosis for patients with intravascular large B-cell lymphoma treated with rituximab-based multi-agent chemotherapy

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Abstract

Background: Intravascular large B-cell lymphoma (IVLBCL) is a rare form of diffuse large B-cell lymphoma (DLBCL) arising in extranodal sites. PD-L1 expression of tumor cells has been reported in IVLBCL cells, but its clinicopathological significance remains to be elucidated.

Aims: This study was aimed to reveal the characteristics of PD-L1$^+$ IVLBCL.

Methods and results: Neoplastic PD-L1 expression was examined in 34 cases of IVLBCL and clinicopathological characteristics between patients with PD-L1$^+$ and PD-L1$^-$ IVLBCL were compared. We assessed PD-L1 expression with SP142 antibody. Twelve (35%) of 34 cases showed positivity for PD-L1. The PD-L1$^+$ group had significantly lower survival rates compared to the PD-L1$^-$ group. The PD-L1$^+$ IVLBCL group also had a significantly lower age distribution and a lower frequency of patients older than 60 years compared to the PD-L1$^-$ group. Very recently, we speculated that there is possible link between PD-L1$^+$ IVLBCL and PD-L1$^+$ extranodal DLBCL, NOS (eDLBCL) because features of the two groups showed clear sparing. Therefore, we compared the clinicopathological characteristics of the PD-L1$^+$ IVLBCL and PD-L1$^+$ eDLBCL. There were no significant differences in clinicopathological parameters and prognosis.

Conclusions: The worse prognosis of the PD-L1$^+$ group might be caused by immune evasion mechanisms, which are linked to PD-L1 expression. Therefore, PD-L1$^+$ IVLBCL cases might be regarded as good candidates for targeted immunotherapy. We also highlighted the overlapping features of PD-L1$^+$ IVLBCL and PD-L1$^+$ eDLBCL. This result suggests that they should be regarded as one entity, known as extranodal and extranodal large B-cell lymphoma.

KEYWORDS

TABLE 2 Clinical and phenotypic characteristics of patients with PD-L1$^-$ IVLBCL and PD-L1$^+$ eDLBCL

Variables	PD-L1$^-$ IVLBCL (n = 12)	PD-L1$^+$ eDLBCL (n = 7)	*P*
Sex (male/female)	5/7	4/3	.65
Age, median (range)	74 (51-81)	72 (59-84)	.68
Age > 60 y	9/12 (75%)	6/7 (86%)	1.0
Performance status > 1	8/12 (75%)	6/7 (86%)	.60
IPI (HI/H)	10/11 (91%)	5/7 (71%)	.53
Stage III/IV	11/12 (92%)	4/7 (57%)	.12
plt < 14 × 10^4/μL	9/11 (82%)	5/6 (83%)	1.0
WBC < 3.5 × 10^3/μL	4/11 (36%)	3/7 (43%)	1.0
Alb < 3.0 g/dL	8/11 (73%)	3/6 (50%)	.59
CRP > 1.0 mg/dL	11/11 (100%)	3/5 (60%)	.083
sIL-2R > normal	11/12 (92%)	7/7 (100%)	1.0
LDH > normal	11/11 (100%)	6/7 (94%)	.39
B symptoms	8/12 (67%)	5/7 (71%)	1.0
Hepatomegaly	2/12 (8.3%)	1/7 (14%)	1.0
Splenomegaly	7/12 (58%)	2/7 (29%)	.35
CD5 positivity	2/7 (29%)	2/7 (29%)	1.0
COO (GCB/non-GCB subtype)	1/6	0/7	1.0

Abbreviations: Alb, albumin; CNS, central nervous system; COO, cell of origin; CRP, C reactive protein; GCB, germinal center B cell; H, high; Hb, hemoglobin; HI, high-intermediate; HPS, hemophagocytic syndrome; IPI, international prognostic index; LDH, lactate dehydrogenase; plt, platelet; sIL-2R, soluble interleukin-2 receptor; WBC, white blood cell.

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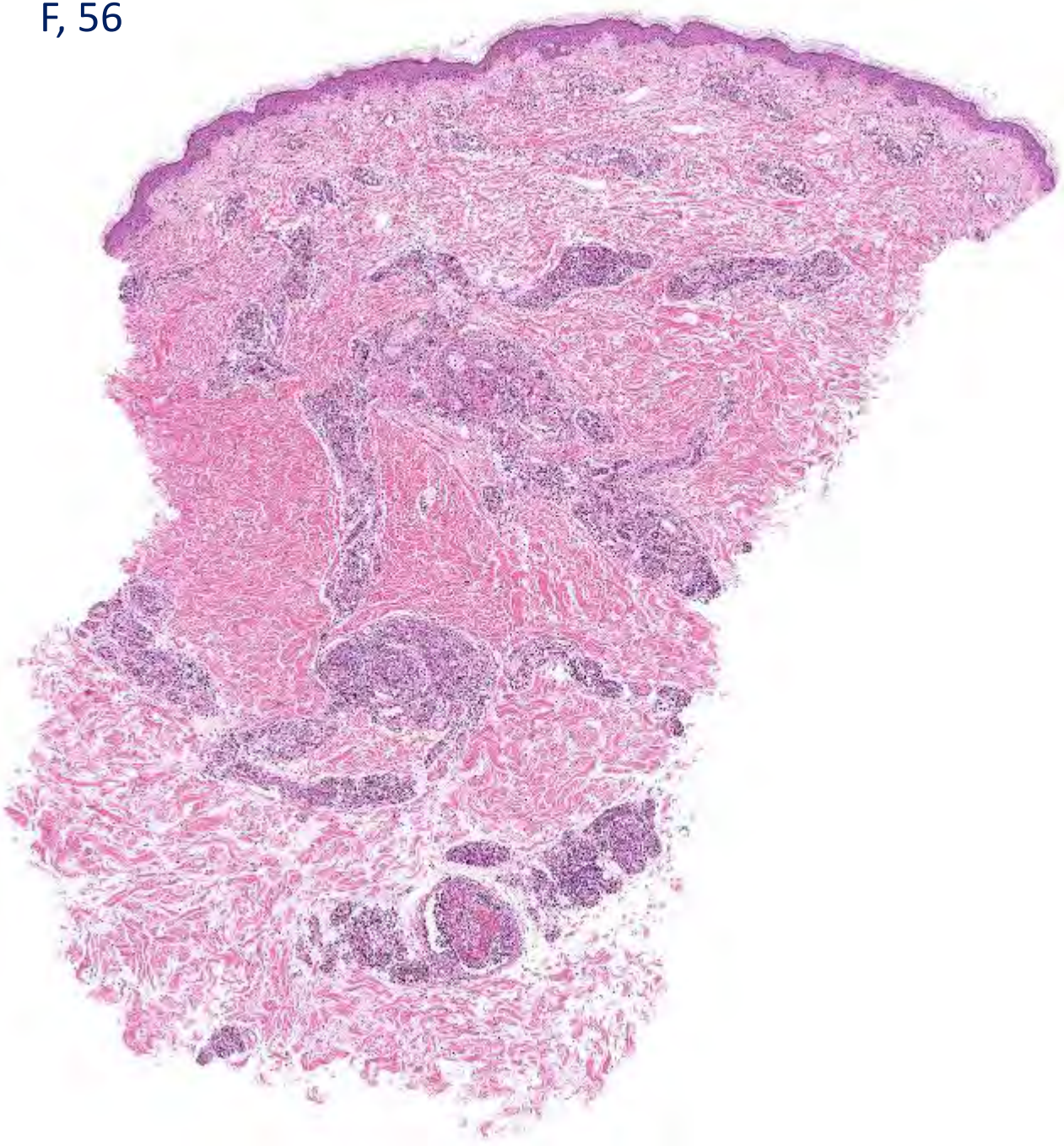

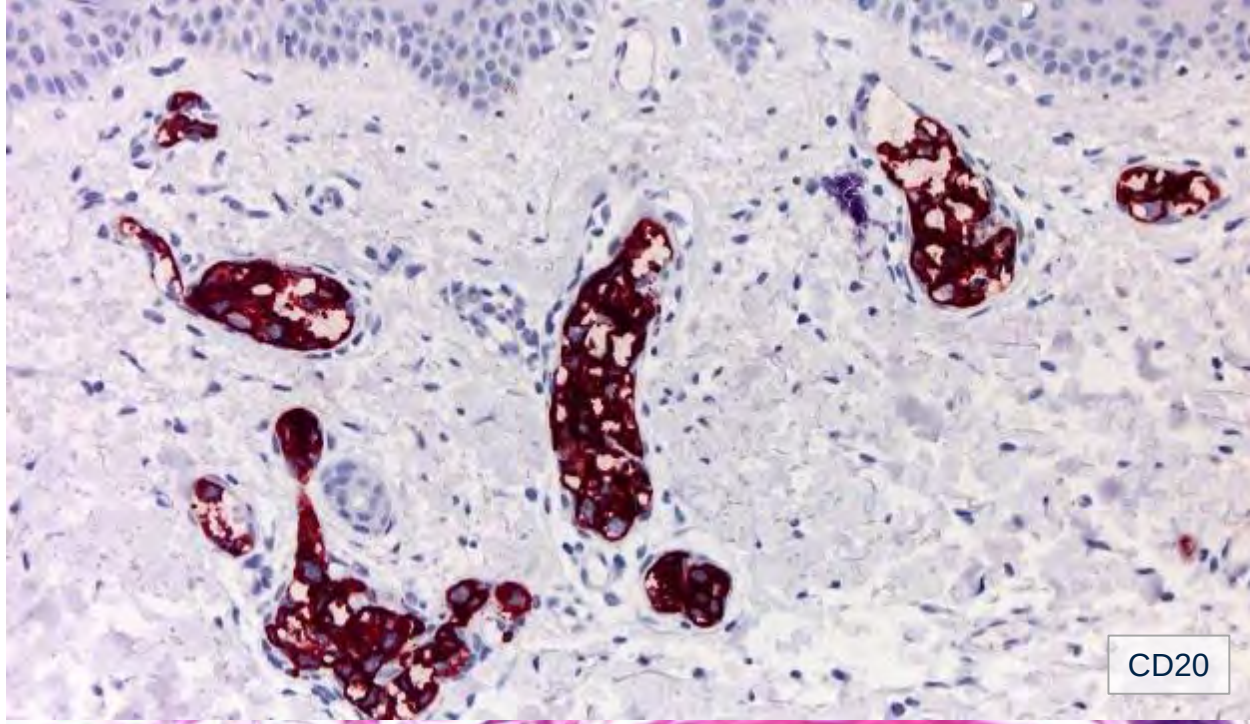

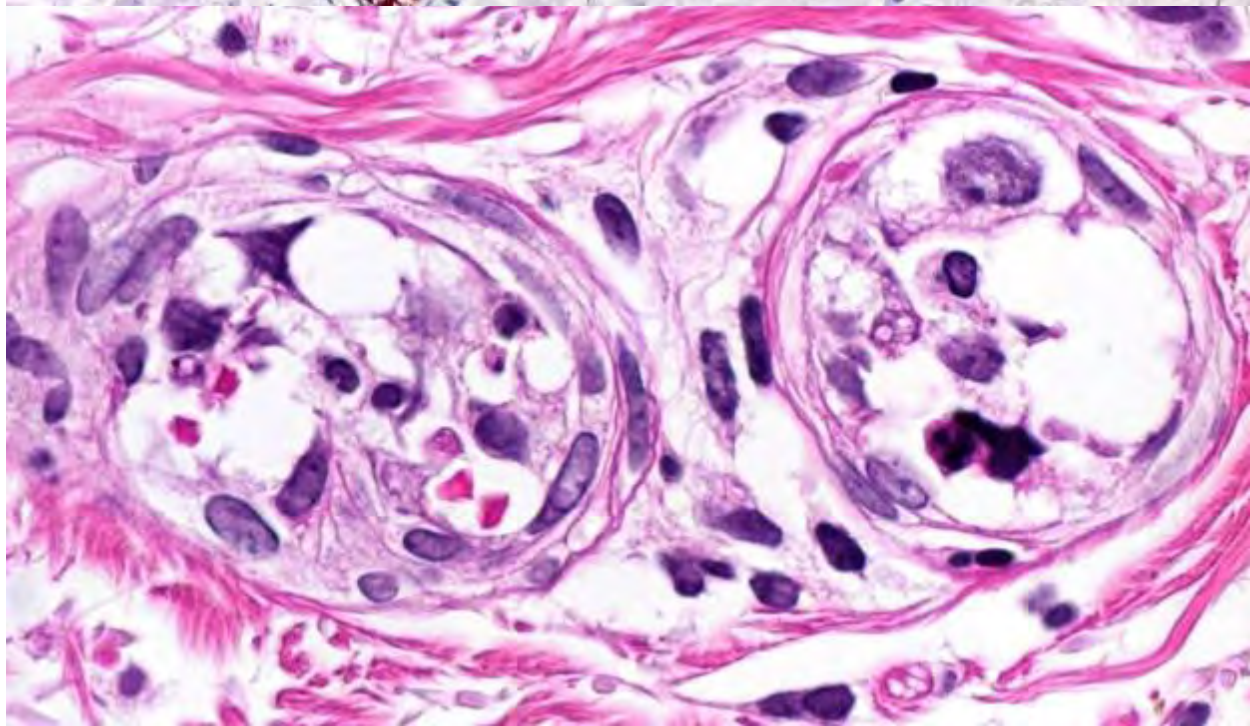

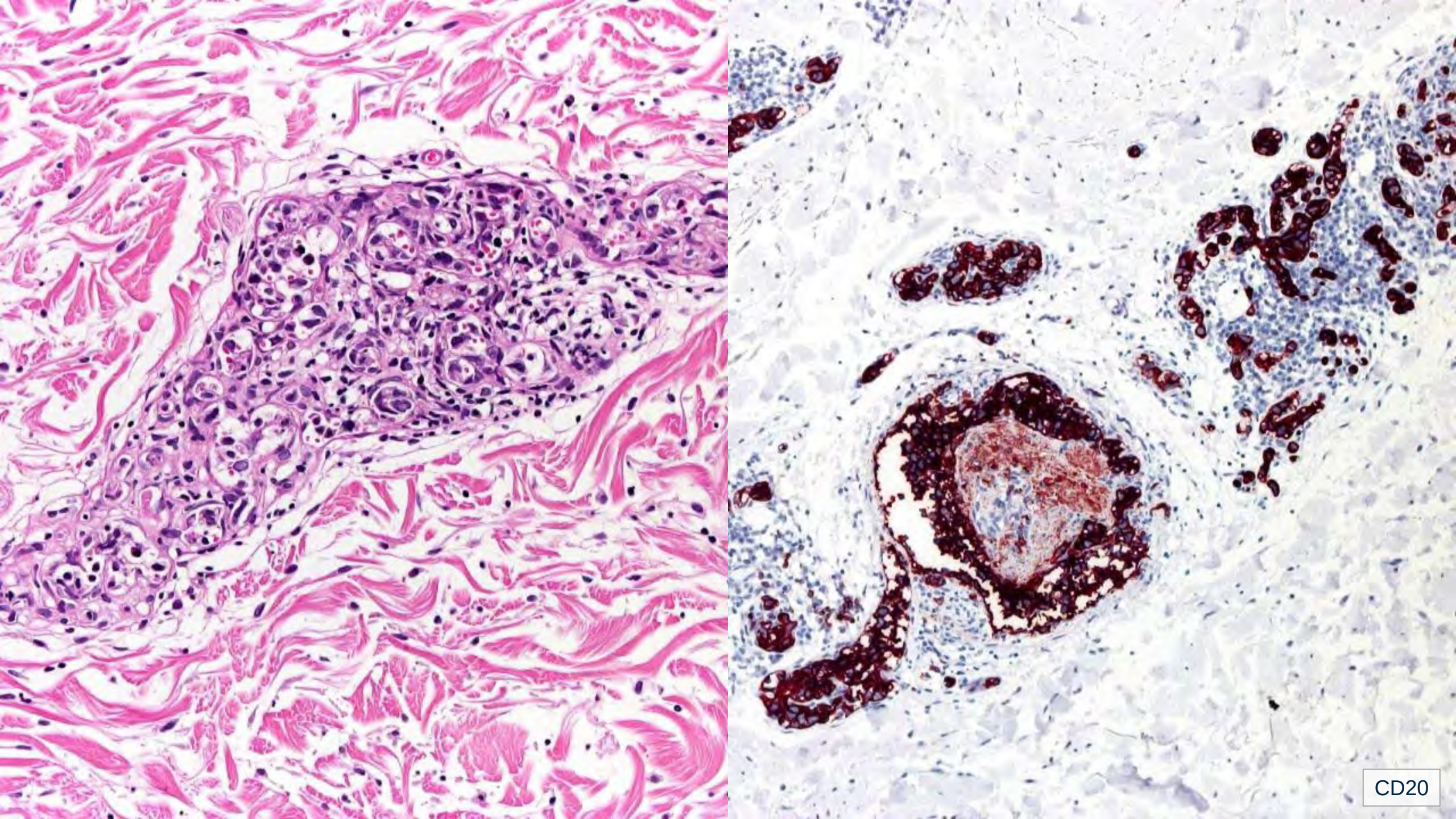
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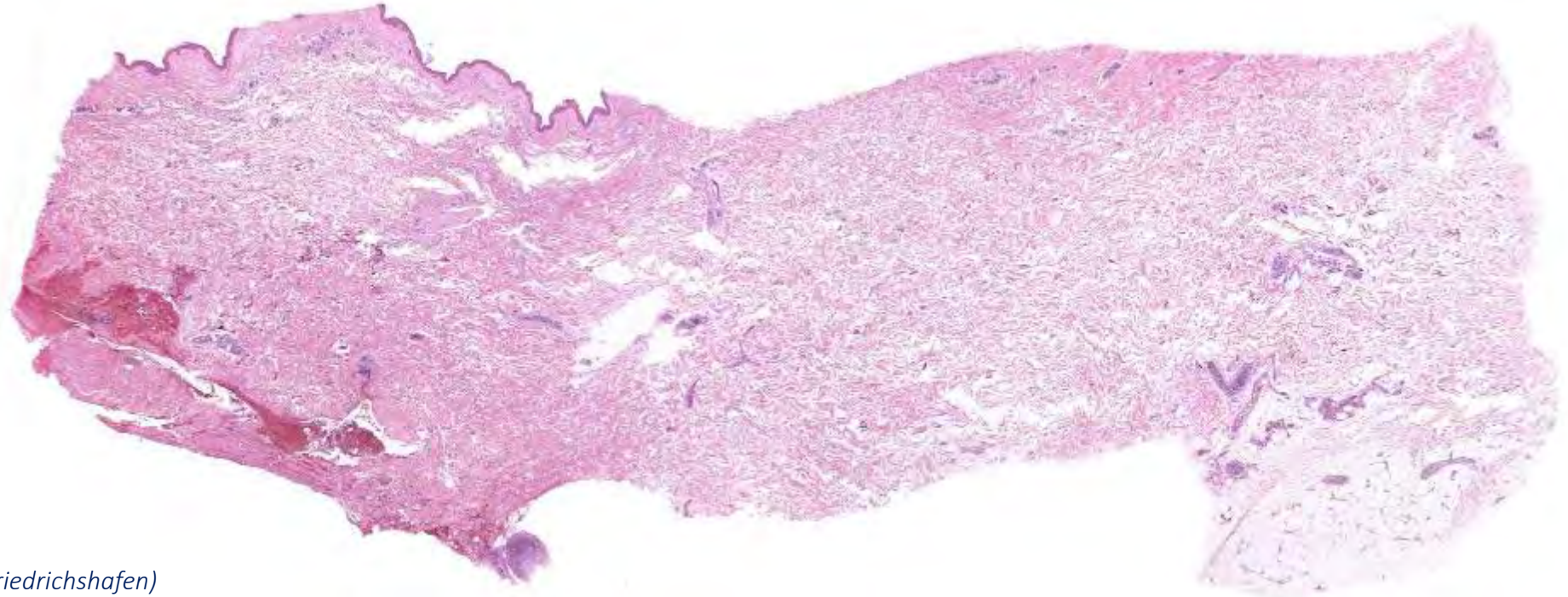
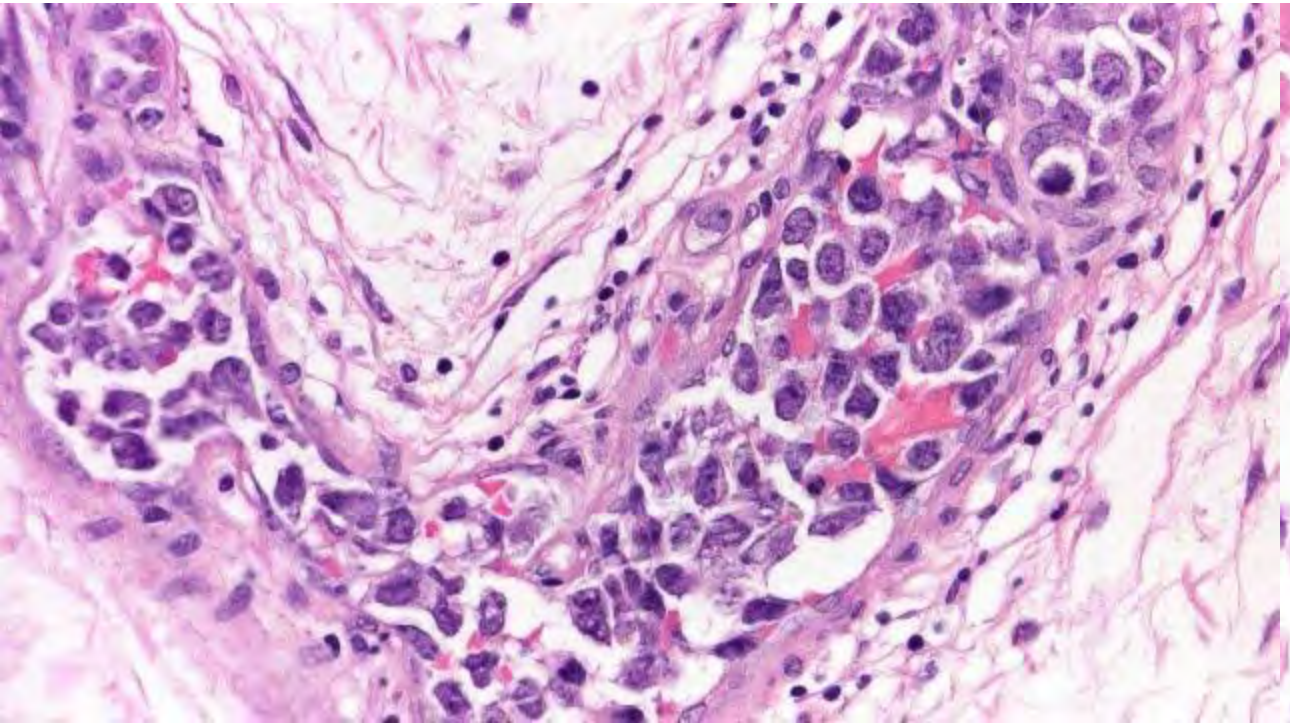
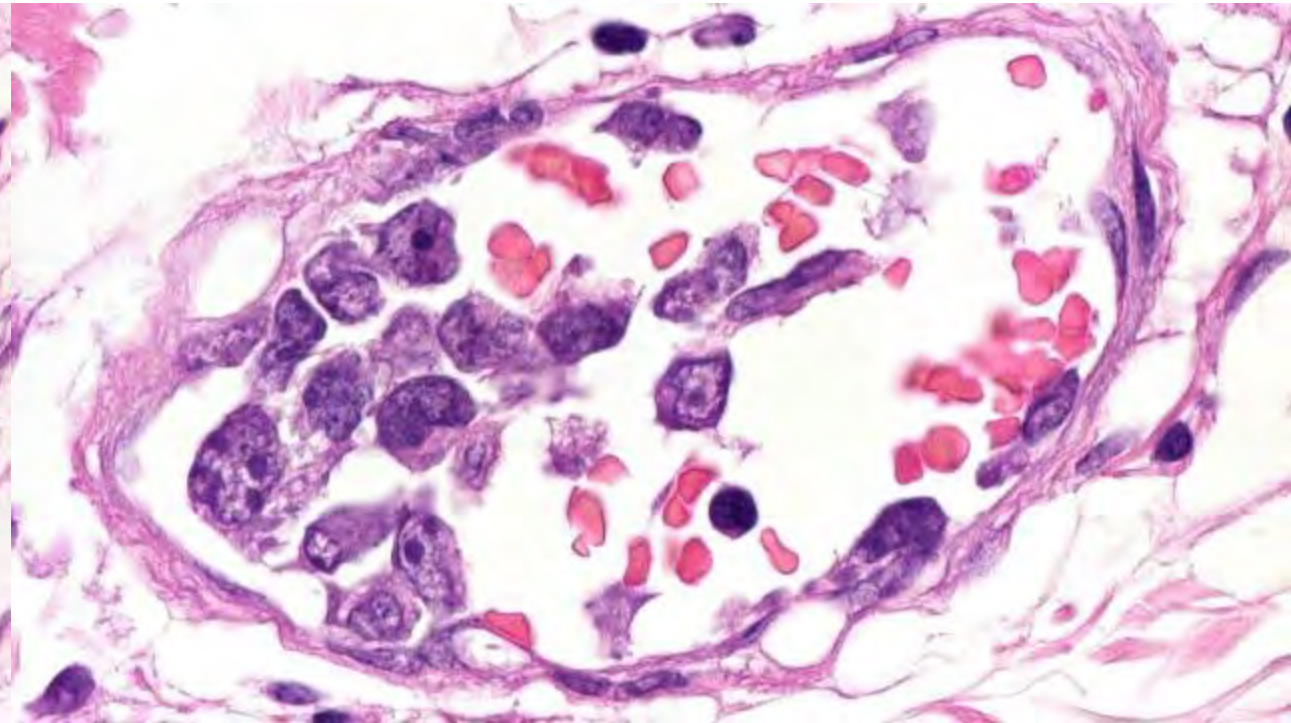
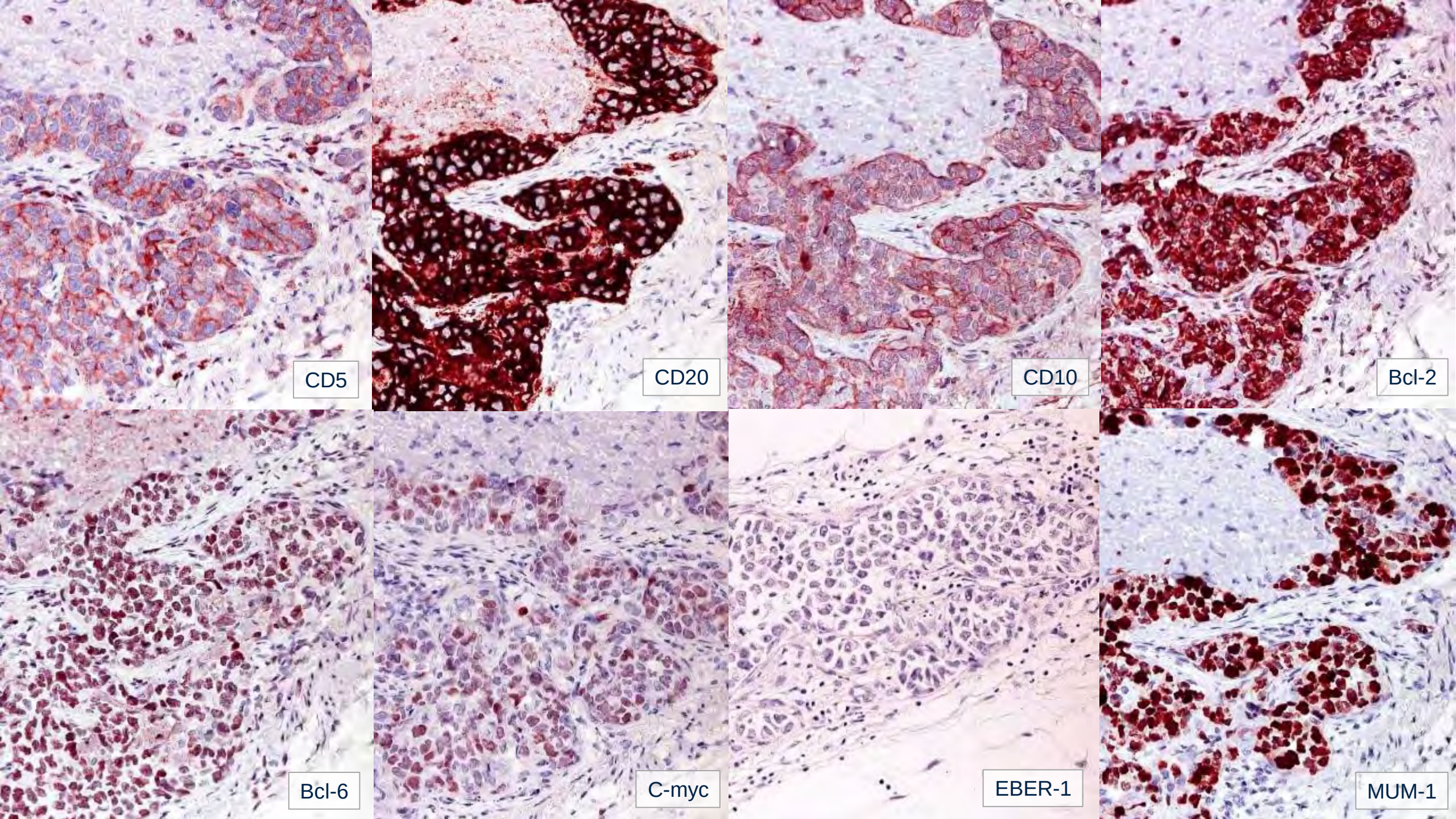


(Courtesy Dr. H. Kutzner, Friedrichshafen)






CD5
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EBER-1
MUM-1

Editorial

Dermatology

Dermatology 2004;209:79–80
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Hemangiomas with a (Bad) Surprise

Lorenzo Cerroni

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Few lesions are less eye-catching for dermatologists and dermatopathologists than senile (cherry) hemangiomas. For one, they are among the most common benign neoplasms in the adult and elderly population, and two, they are devoid of any particular clinicopathologic or therapeutic problem: they are straightforward clinically, a glance diagnosis histopathologically, and treatment, if desired, is easy as well. In short, they are hardly the source of particular interest. And yet, in this issue of *Dermatology* 2 cases of cherry hemangioma or hemangioma-like skin changes draw the attention to these unremarkable neoplasms, showing that behind their innocent appearance sometimes the devil can hide. Our case [1] and that reported by Motegi et al. [2] show two different faces of the 'hemangiomas with a surprise': one characterized by colonization of preexisting cherry hemangiomas by neoplastic cells of an intravascular large B-cell lymphoma and the second showing an eruption of hemangioma-like skin lesions representing in truth skin involvement of angiotropic lymphoma. In both cases, the diagnosis was completely unexpected and represented a surprise, unfortunately a bad one, for the clinicians, the dermatopathologists and the patients.

Intravascular large B-cell lymphoma (also termed angiotropic lymphoma) is a malignant proliferation of large B lymphocytes within blood vessels. It was first described by Pfleger and Tappeiner in 1959 [3] and was formerly classified as a vascular neoplasm (malignant angioendotheliomatosis) [4]. It is considered as a subtype of extranodal diffuse large B-cell lymphoma [5]. This peculiar disease may arise de novo or in patients with preexisting cutaneous or, more often, nodal large B-cell lymphoma, in the latter instance probably representing a recurrence of the original malignancy rather than a second lymphoma [6, 7]. Neoplastic cells are positive for B-cell-associated markers, but a very rare T-cell variant of the disease has been reported [8]. Prognosis is usually very poor, with a median survival of about 12 months. The prognosis of cases limited to the skin may be better than that of the generalized (multisystem) disease, but only a very limited number of patients has been followed up to date.

The most common clinical presentation of intravascular large B-cell lymphoma is characterized by indurated, erythematous or violaceous patches and plaques, preferentially located on the trunk and thighs. The clinical appearance is not typical of lymphoma and may suggest a diagnosis of panniculitis or of purpura [9–13]. In rare cases, the skin may be the only affected site (primary cutaneous intravascular large B-cell lymphoma), though more often the lymphoma is disseminated, and neurologic symptoms as a sign of involvement of the central nervous system are commonly present [14]. Other organs that are frequently involved are the liver, lungs and kidneys. Systemic symptoms due to specific manifestations at extracutaneous sites are more likely to be caused by clots within the blood vessels and subsequent infarction of tissue than by destructive neoplastic growth.

Colonization of preexistent cutaneous hemangiomas, similar to that observed in our patient, has been described in 2 other cases [15–17]. Although this is an exceptional

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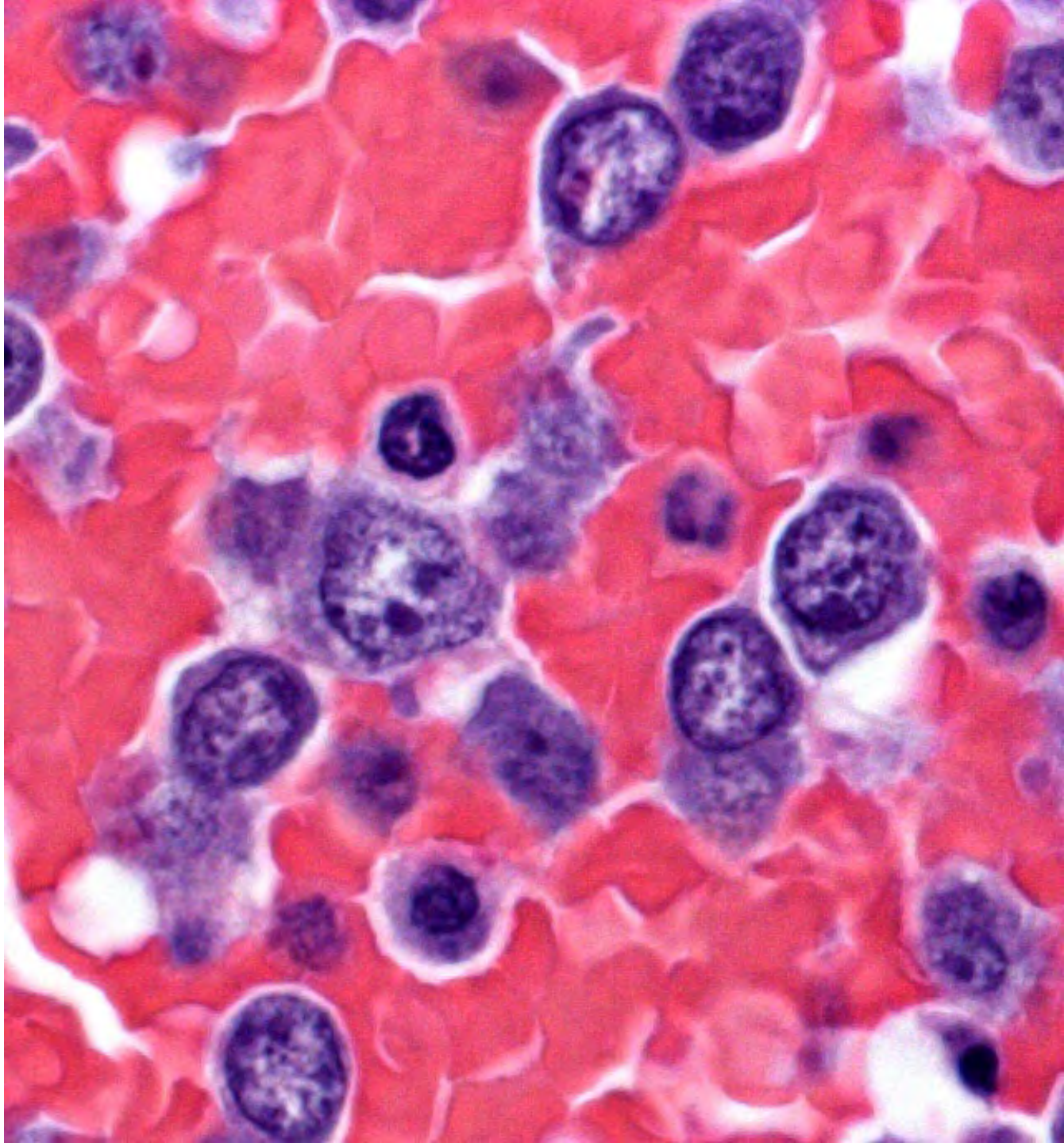
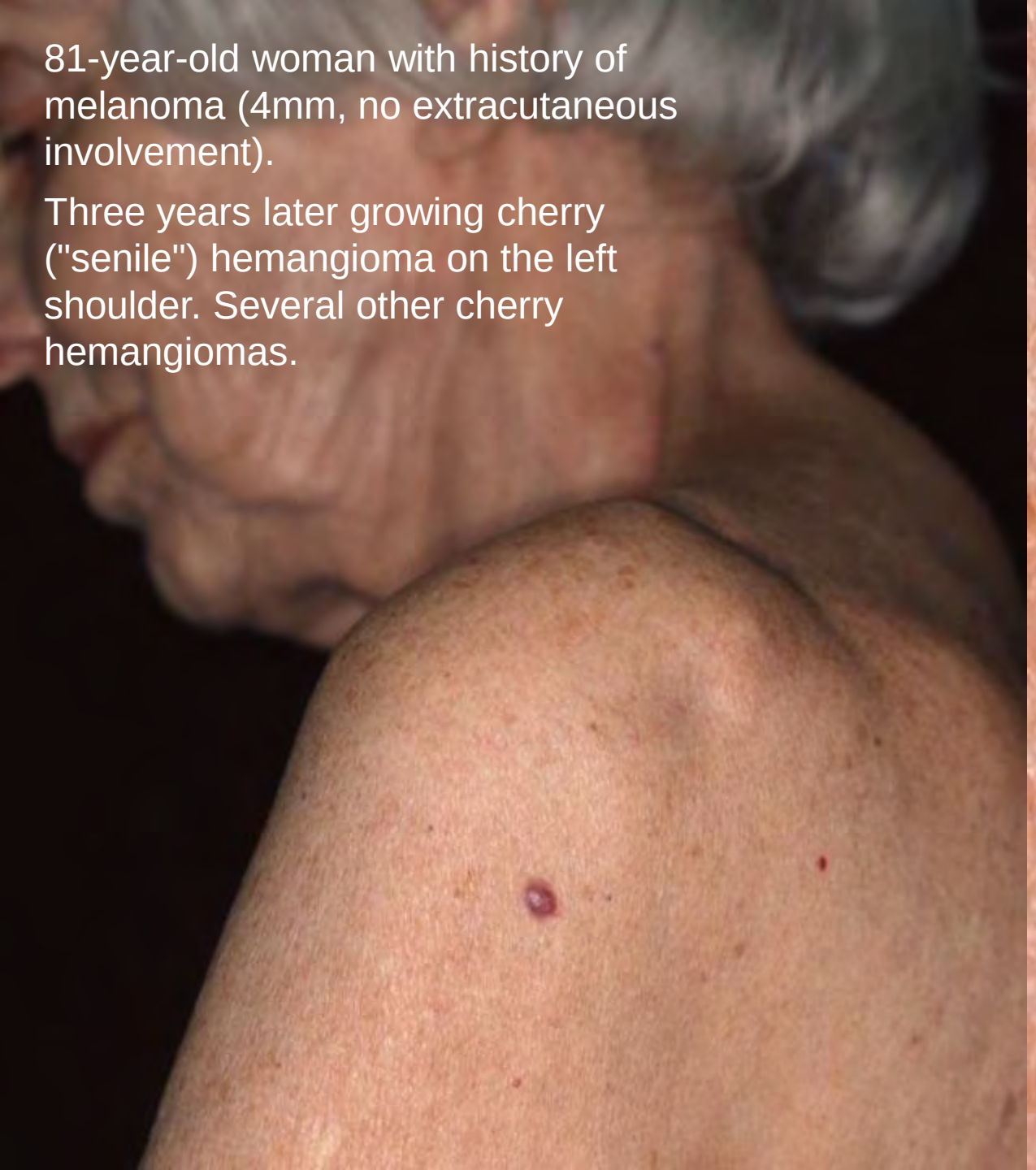
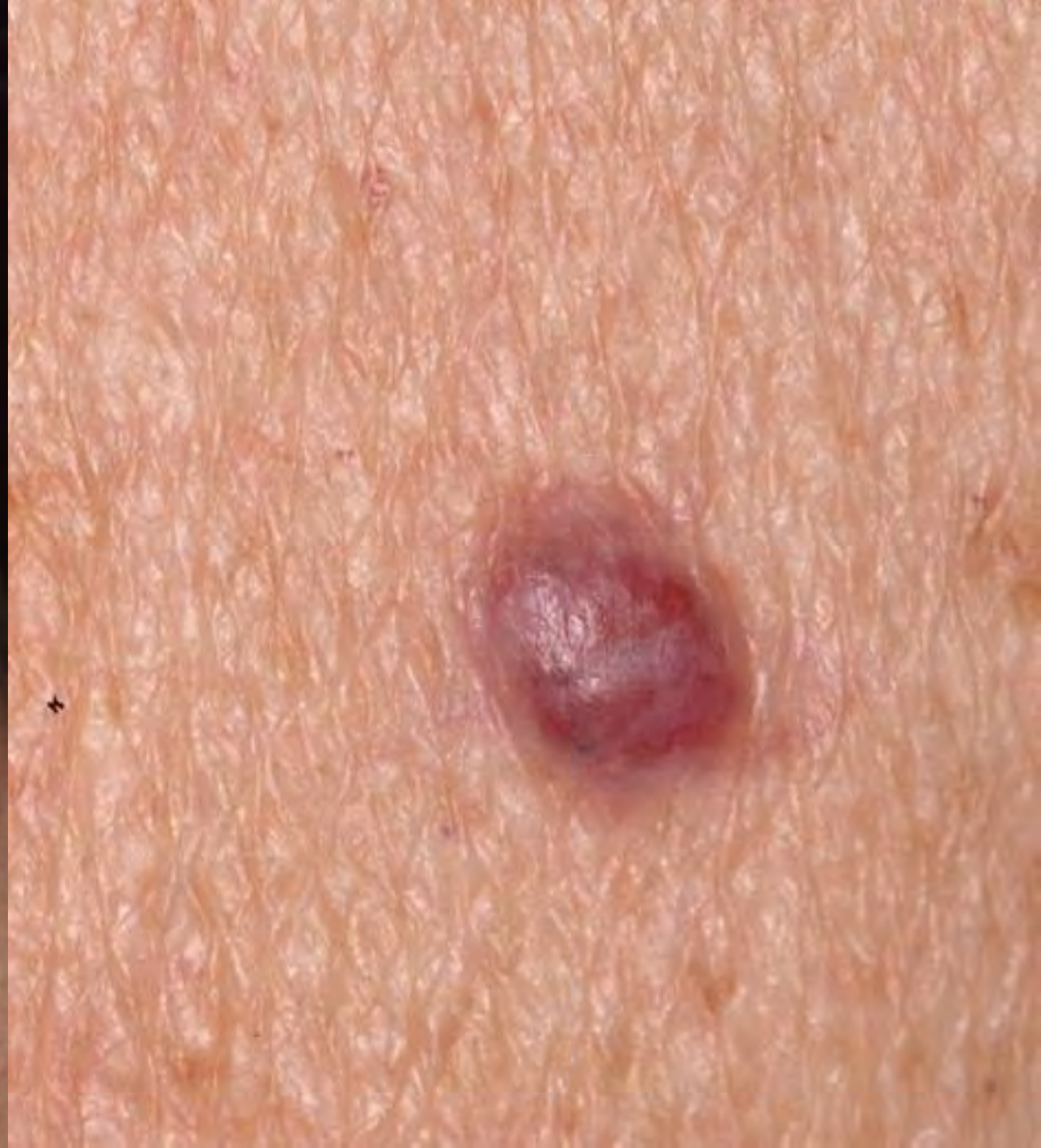
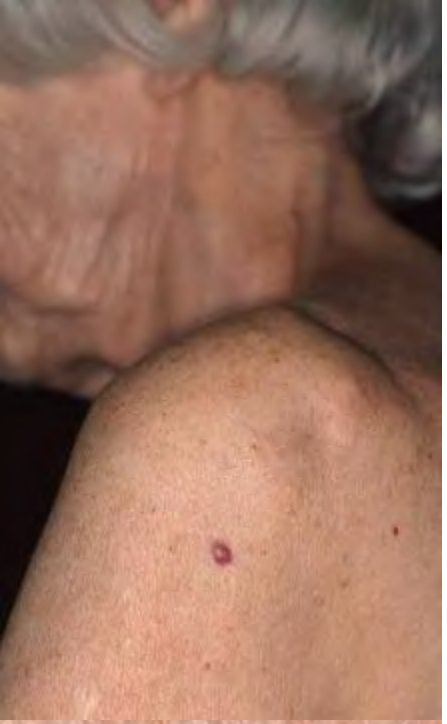


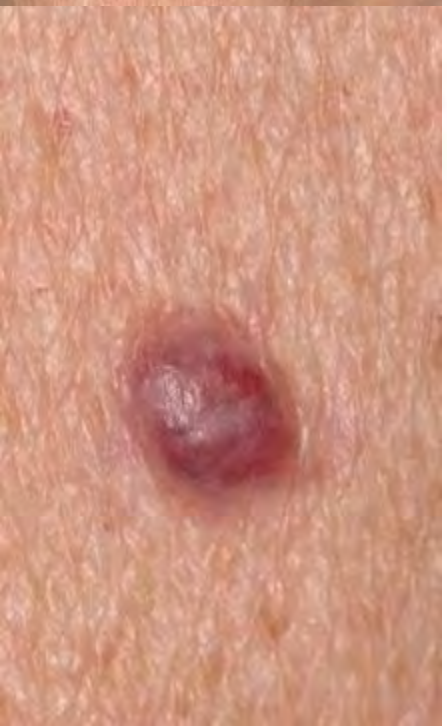
81-year-old woman with history of melanoma (4mm, no extracutaneous involvement).

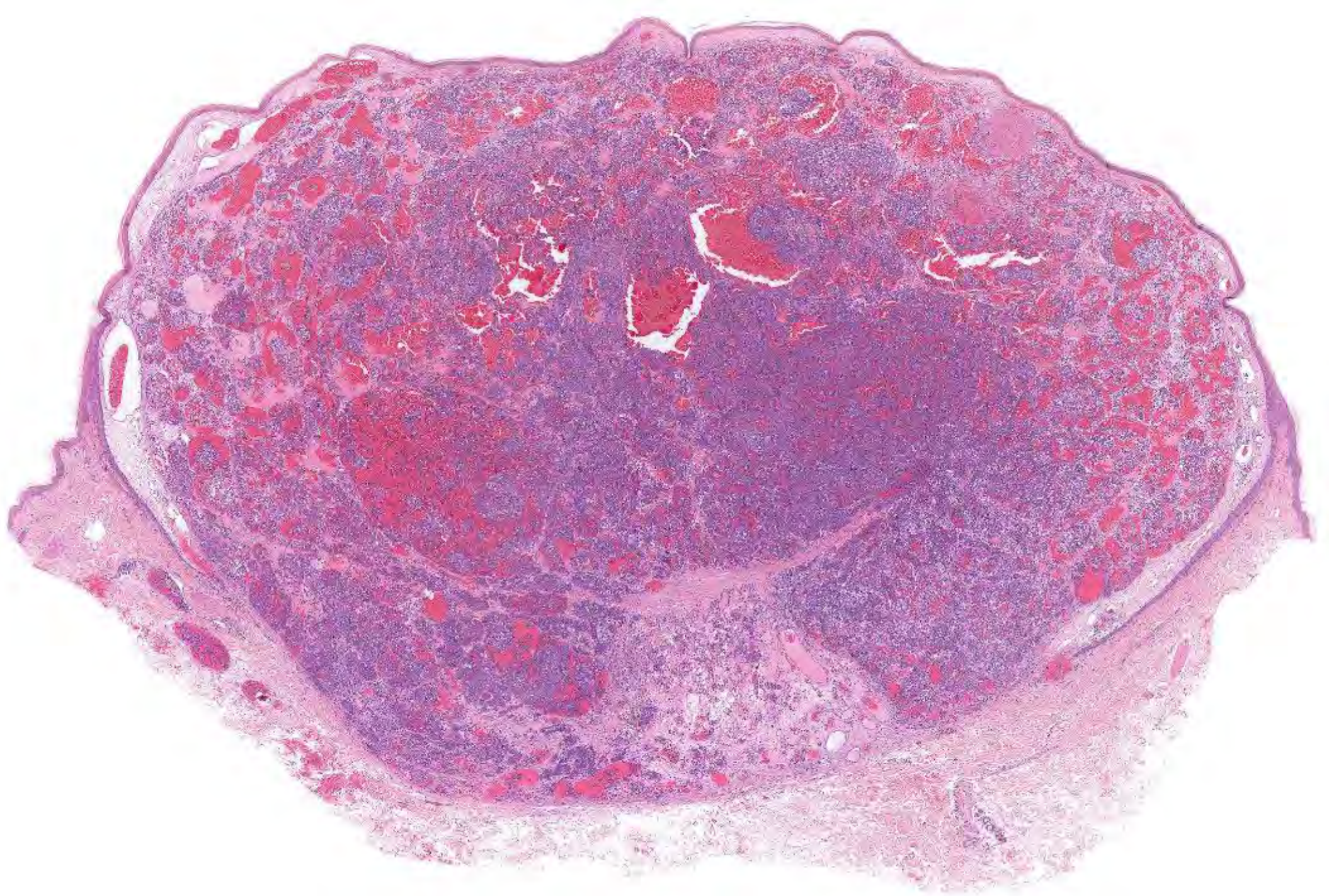
Three years later growing cherry ("senile") hemangioma on the left shoulder. Several other cherry hemangiomas.

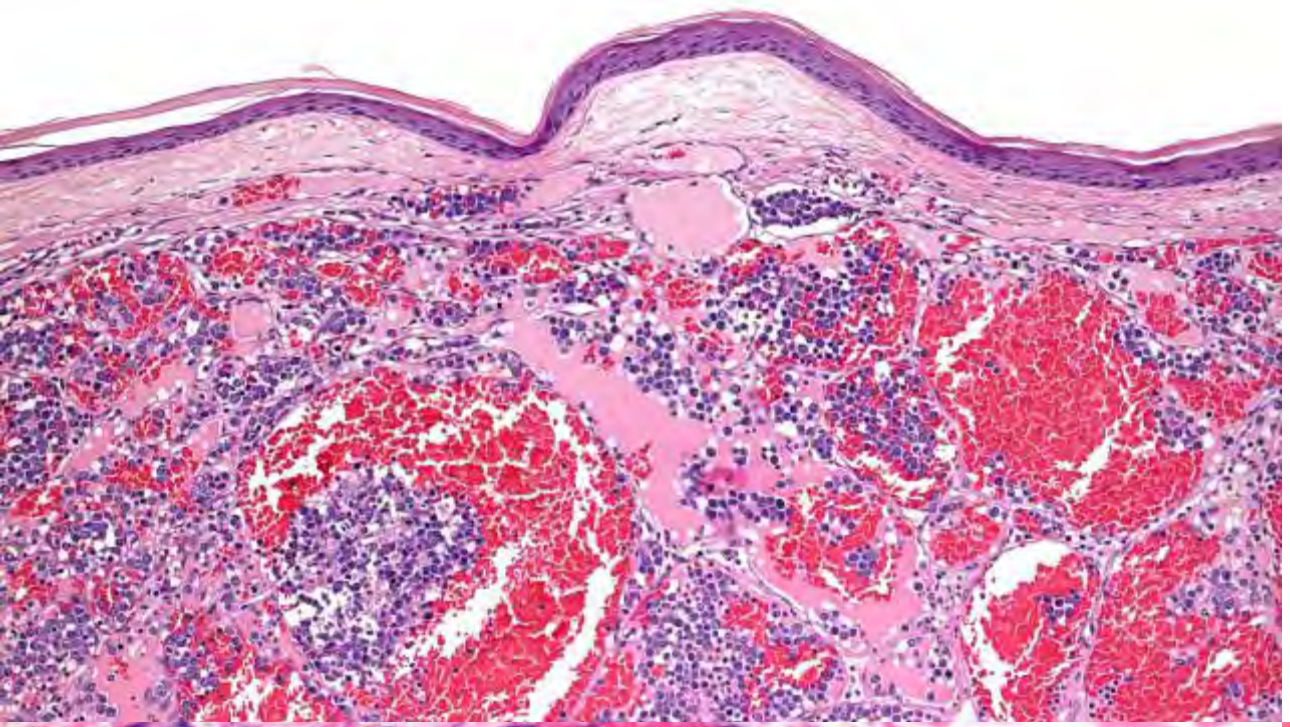


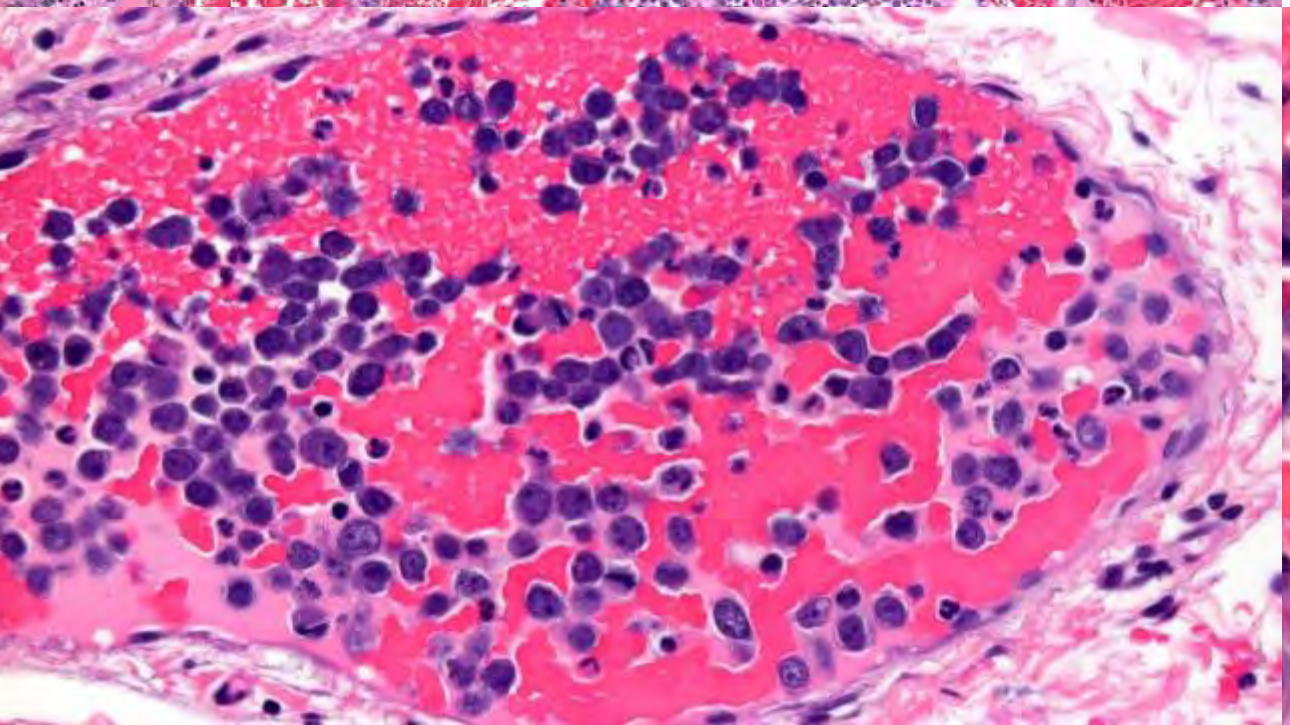


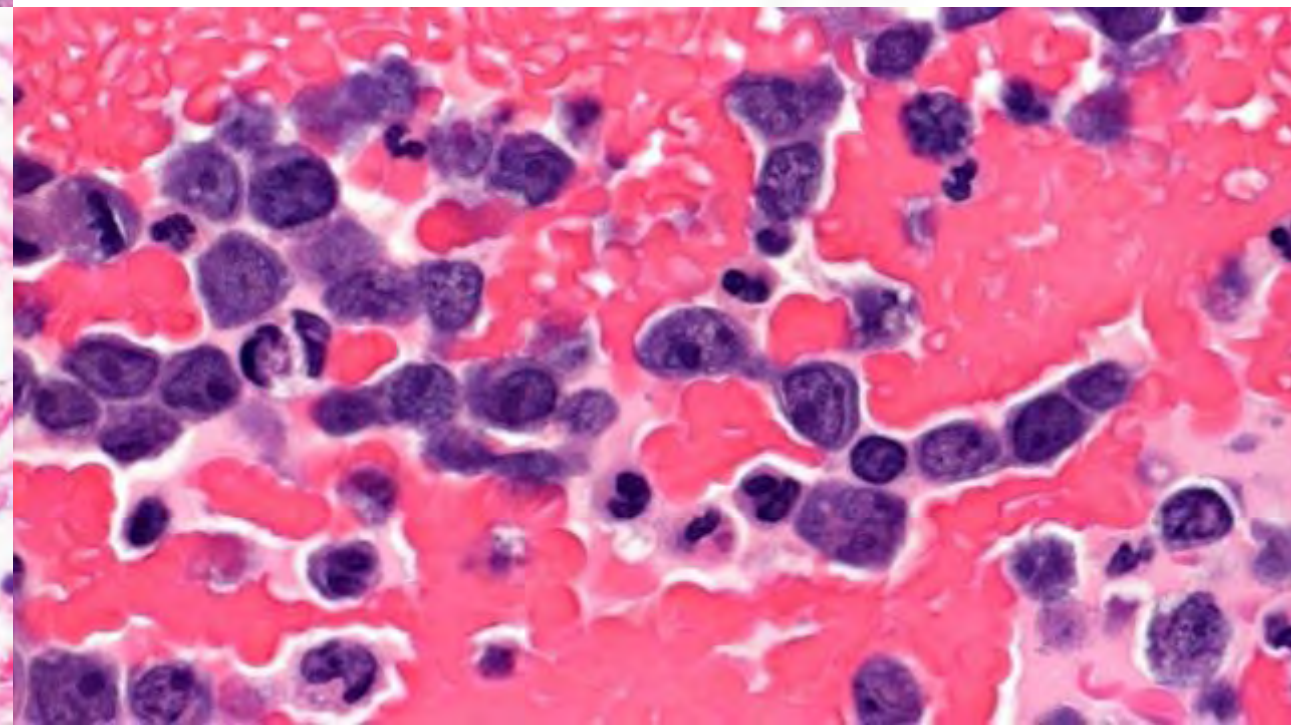


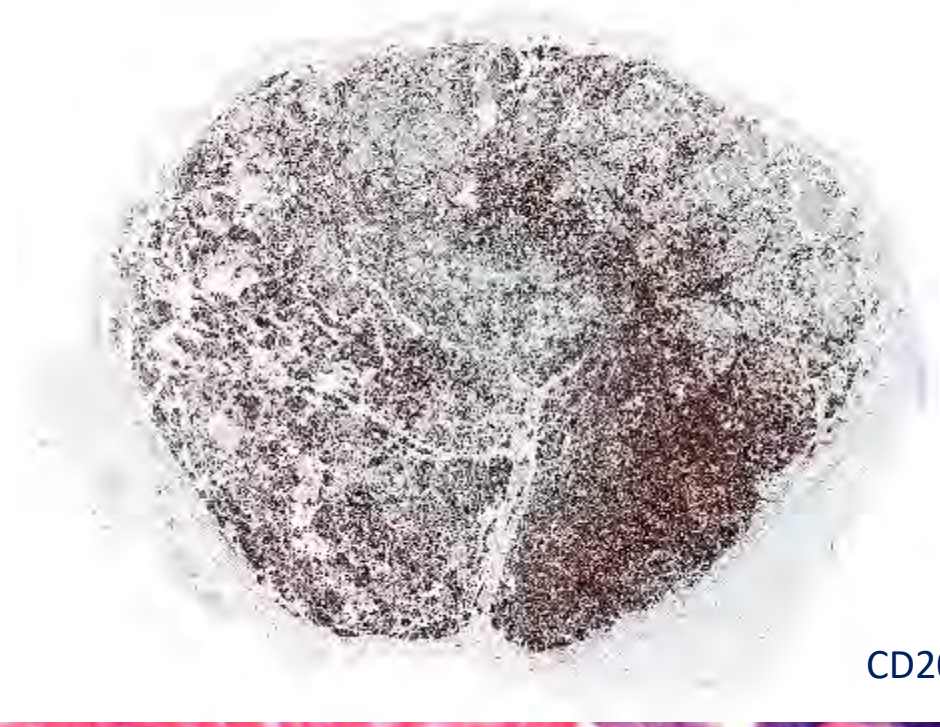












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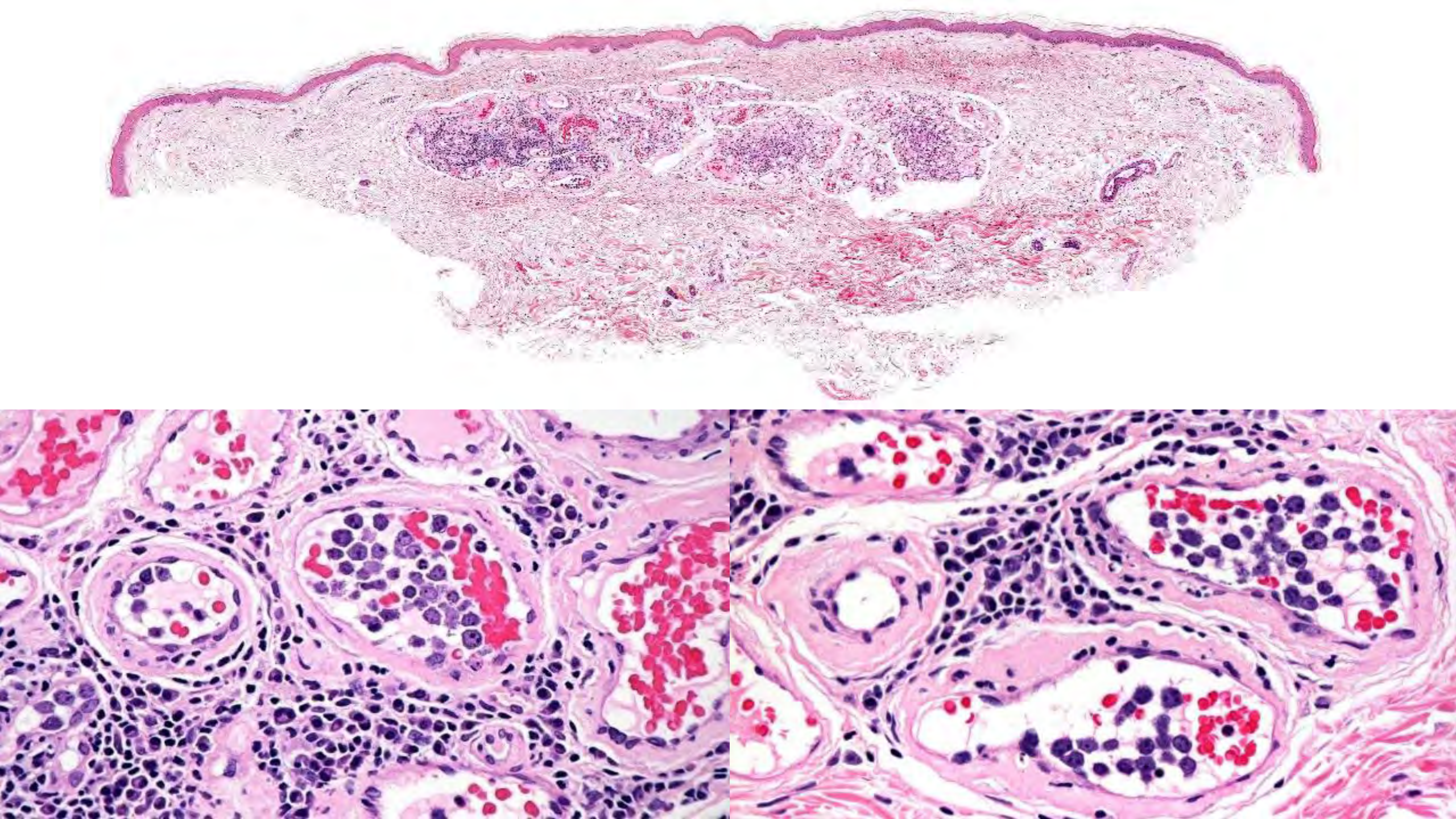

Case Report

Dermatology

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Intravascular Large B-Cell Lymphoma Colonizing Cutaneous Hemangiomas

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Key Words
Intravascular large B cell lymphoma · Cherry hemangioma

Abstract
Intravascular large B-cell lymphoma is a malignant neoplasm characterized by the proliferation of large B cells (rarely of T lymphocytes) confined within the blood vessels. Although the disease can be limited to the skin, involvement of other organs is common. We report a case of intravascular large B-cell lymphoma colonizing the vessels of preexisting cutaneous cherry hemangiomas.

Intravascular large B-cell lymphoma (formerly malignant angioendotheliomatosis, angiotropic lymphoma) is a malignant neoplasm characterized by the proliferation of large B cells (rarely of T lymphocytes) confined within the blood vessels. Although the disease can be limited to the skin, involvement of other organs, especially the central nervous system, is common. We report a case of intravascular large B-cell lymphoma colonizing the vessels of preexisting cutaneous cherry hemangiomas.

Report of a Case

An 81-year-old woman with a history of malignant melanoma in 1999 (tumor thickness 4 mm; no extracutaneous involvement) presented to our department in April 2002 for a routine follow-up examination. Physical examination did not show any sign of recurrence of melanoma. She had several small senile (cherry) hemangiomas which had been present for many years. However, she had noticed that one of them located on the left upper arm had been slightly enlarging in the last few months and asked to have it removed for cosmetic reasons (fig. 1). The hemangioma was surgically removed, fixed in formalin and embedded in paraffin for routine histopathologic examination. Histology revealed the overall architecture of a capillary hemangioma. However, the vessels were filled with large atypical cells with cytomorphologic features of centroblasts and immunoblasts (fig. 2). Immunohistology showed that these cells were positive for CD45, CD20 and CD79a, and negative for CD3, CD5 and CD30. They were also negative for melanocytic markers (S-100, HMB-45, Melan-A) and for cytokeratin. Based on clinicopathologic features, a diagnosis of intravascular large B-cell lymphoma colonizing a preexistent hemangioma was made.

The patient was submitted to staging investigations that failed to reveal any extracutaneous involvement. Five more cutaneous hemangiomas were surgically removed (all of them located on the trunk). Histopathologic evidence of intravascular large B-cell lymphoma could be found in 2 of them (fig. 3). In contrast to the first lesion, colonization of the blood vessels in these 2 was only partial and limited to a part of the hemangioma. Surgical excision of 5 lesions clinically diagnosed as lipoma revealed the histopathologic features of angiolipoma, without any malignant lymphoid cells within or outside the vessels.

The patient declined any treatment, but was attending regular follow-up controls. At the last follow-up examination 9 months after the first diagnosis she complained of increasing fatigue, but did not show any central nervous system or systemic symptoms. She died at home 12 months after presentation, and the relatives denied authorization for autopsy.

Discussion

Intravascular large B-cell lymphoma is a very rare variant of large B-cell lymphoma frequently involving the skin, first described by Pfleger and Tappeiner in 1959 [1]. Clinically, lesions are often inconspicuous purpuric macules and plaques, and may be misdiagnosed as 'purpura' or 'panniculitis'. Colonization of preexistent hemangiomas has been described rarely in these patients and seems to be a peculiar clinicopathologic manifestation of this unusual lymphoma [2, 3].

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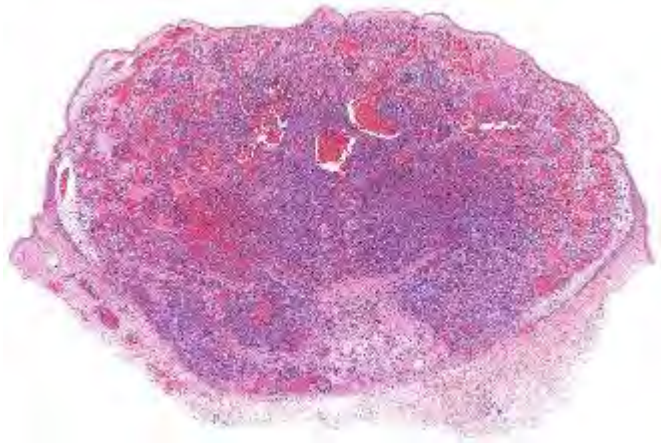
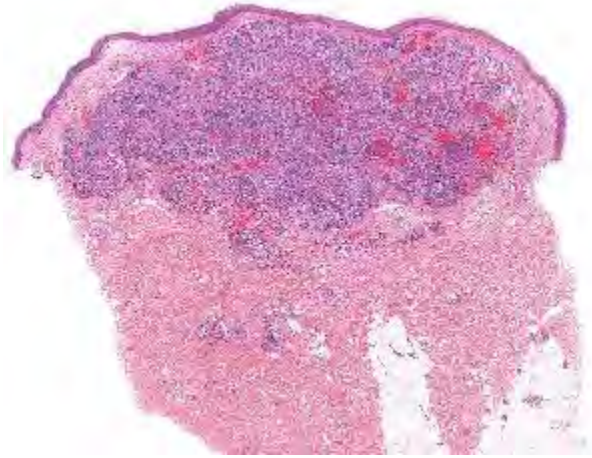
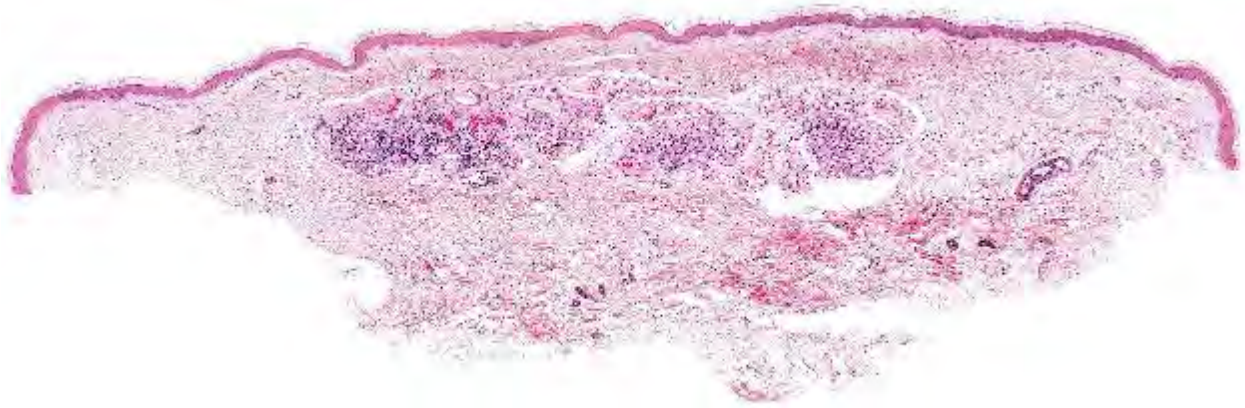
IVLBCL in 3/6 angiomas.
5/5 angiolipomas negative.
Normal skin at the side of involved angiomas did not show histopathological signs of intravascular lymphoma.







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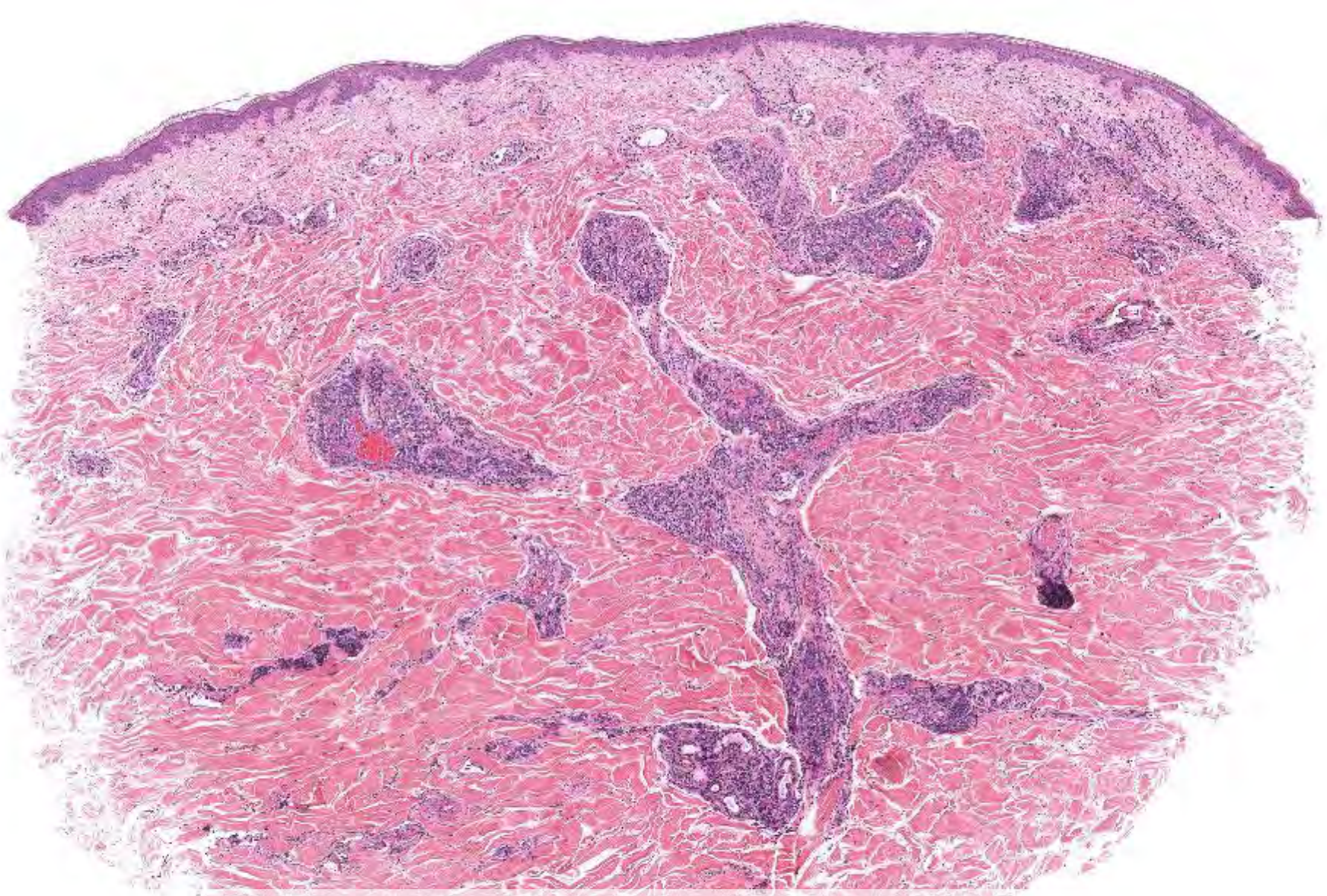
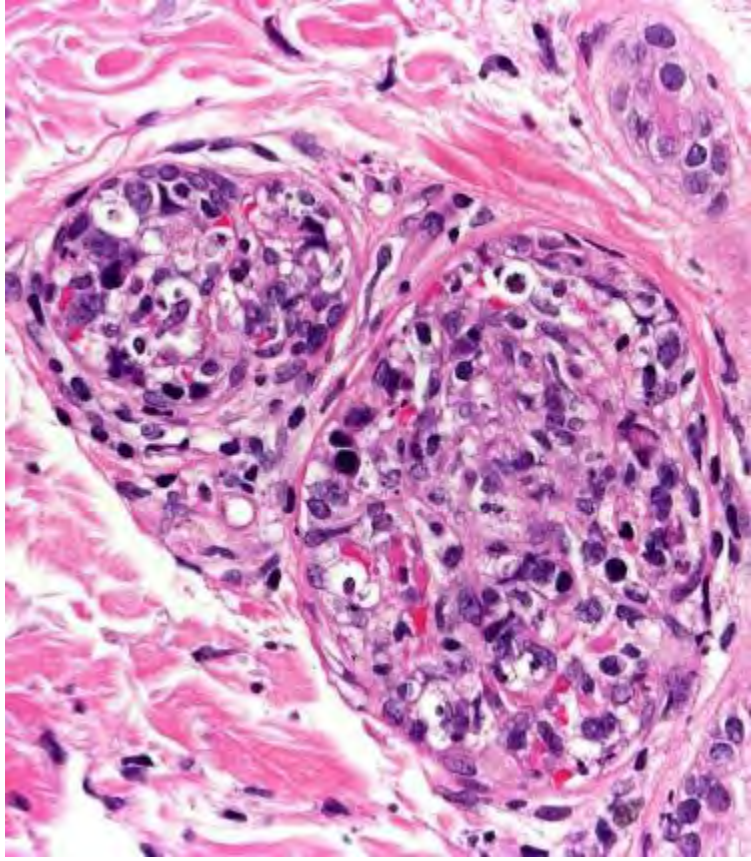




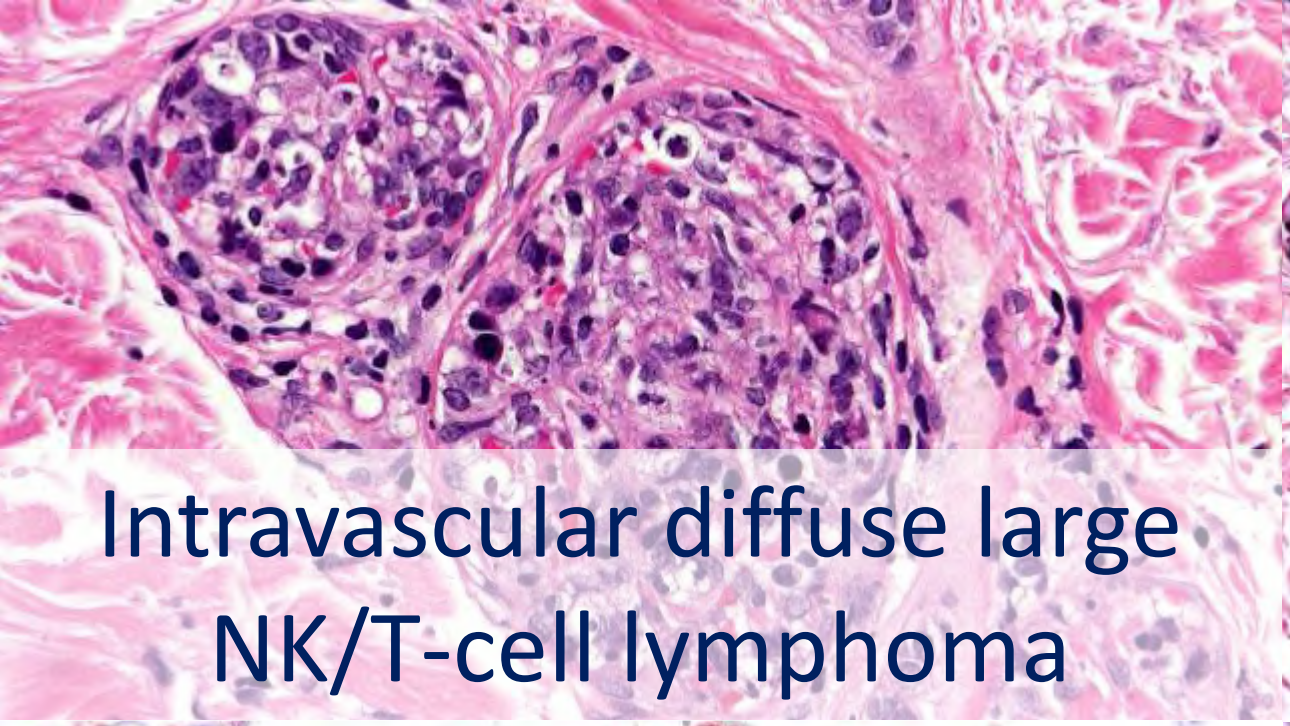
Intravascular diffuse large-cell lymphoma

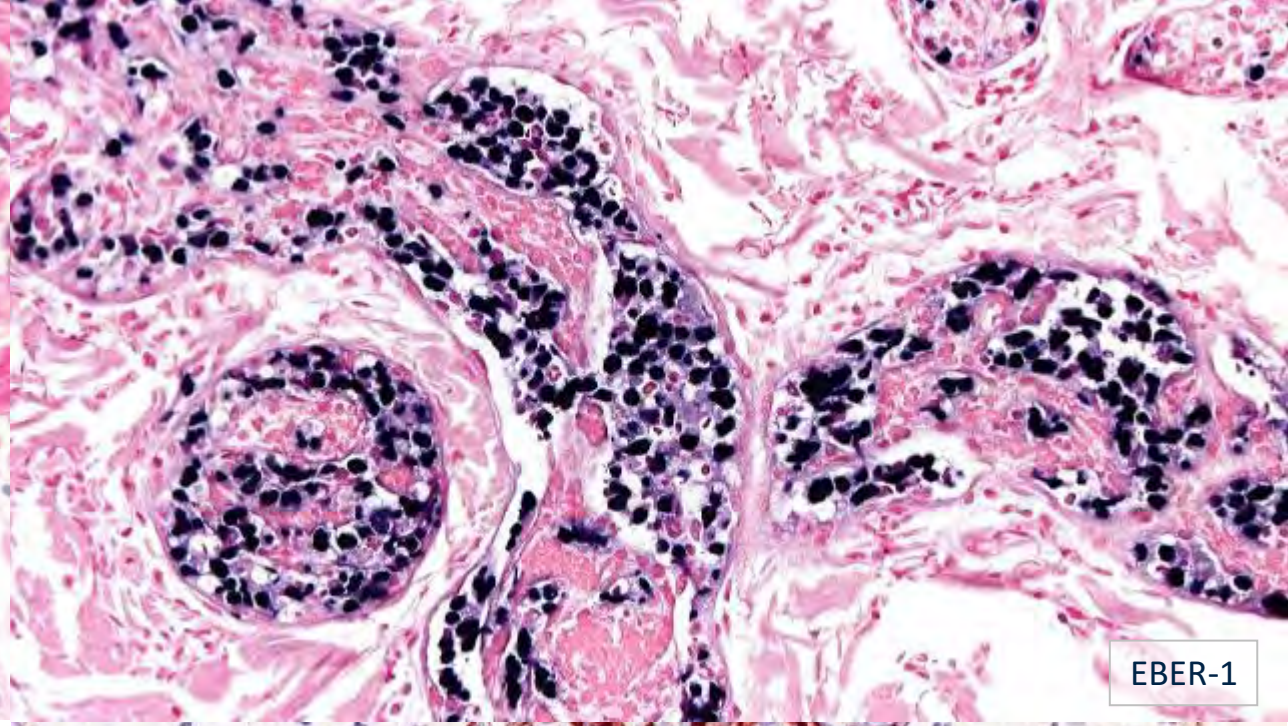
Phenotype ?

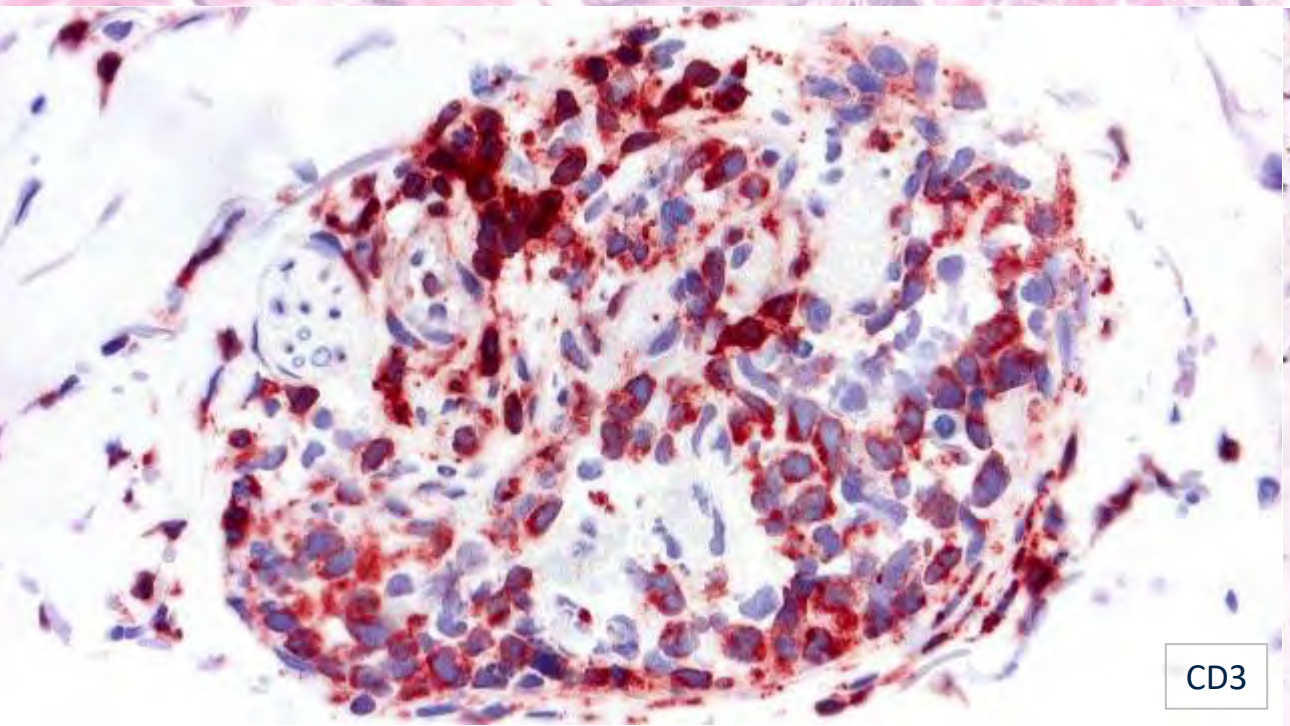
M, 87

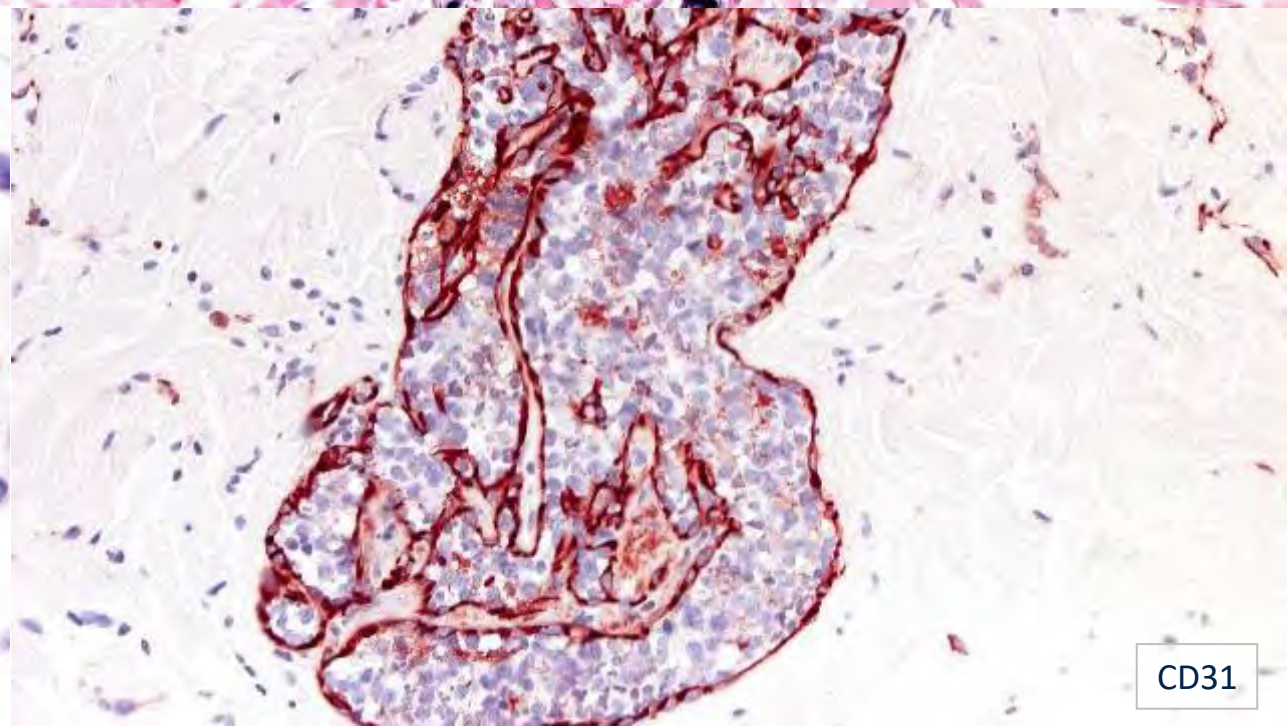
Recent onset of localized indurated lesions on the trunk.

Intravascular diffuse large NK/T-cell lymphoma









Intravascular Large T-cell or NK-cell Lymphoma

A Rare Variant of Intravascular Large Cell Lymphoma With Frequent Cytotoxic Phenotype and Association With Epstein-Barr Virus Infection

Lorenzo Cerroni, MD, Cesare Massone, MD,* Heinz Kutzner, MD,† Thomas Mentzel, MD,† Pablo Umbert, MD,‡ and Helmut Kerl, MD**

Abstract: Most cases of intravascular large cell lymphoma have a B-cell phenotype, but rare T-cell and natural killer (NK)-cell variants have been reported. We describe the clinicopathologic features of 4 patients (M:F = 3:1, age range: 63 to 87, median age: 65) with intravascular large NK/T-cell lymphoma. The skin was the site of presentation in all patients (leg: 1 case; trunk: 1 case; trunk and extremities: 2 cases). Two patients had lesions confined to the skin; in 1 case concomitant involvement of the brain was detected and in 1 case no further studies were carried out. Immunohistology showed positivity for cytotoxic markers in 3/4 cases. One case had an NK phenotype similar to NK/T-cell lymphoma, nasal-type, whereas the other cases could not be precisely classified into specific categories (peripheral T-cell lymphoma, NOS). One of these cases was negative for cytotoxic markers and was positive only for CD2 and CD3ε. Association with Epstein-Barr virus (EBV) was demonstrated in 2 cases by in situ hybridization, whereas 1 case was negative. All our patients had aggressive disease and died between 2 weeks and 7 months from presentation. Analysis of our cases and of those published in the literature shows that intravascular large NK/T-cell lymphoma is a rare, aggressive lymphoma with variable phenotypic features, frequent expression of cytotoxic proteins, true NK-cell phenotype and association with Epstein-Barr virus infection, and common presentation in the skin. Homogeneous studies on larger number of patients and reevaluation of cases published with incomplete phenotypic data would be necessary to gather more information on this extremely rare type of lymphoma.

Key Words: intravascular large T-cell lymphoma, angiotropic lymphoma, phenotype, Epstein-Barr virus

(*Am J Surg Pathol* 2008;32:891–898)

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Intravascular large cell lymphoma (IVLCL) (formerly malignant angioendotheliomatosis, angiotropic lymphoma) is a rare variant of non-Hodgkin lymphoma (NHL) with peculiar arrangement of neoplastic cells within the lumina of blood vessels,[4] described first by Pfleger and Tappeiner[20] in 1959. Most cases have a B-cell phenotype, but rare T-cell and natural killer (NK)-cell variants have been described in occasional patients.[5] In a large series of 38 cases of IVLCL published recently, only 1 (2.6%) had a T-cell phenotype.[7] Precise lineage determination in non–B-cell cases requires accurate phenotypic analyses to differentiate cases with T cell from those with NK-cell phenotype. Differentiation may be particularly difficult, as NK cells can be positive for markers expressed also by T lymphocytes, such as CD3ε, CD2, CD7, CD8, CD56, and cytotoxic antigens. NK cells are always negative for CD5 and α/β (βF1 antibody) and γ/δ markers (no antibodies available for paraffin sections); the T-cell receptor (TCR) genes are not rearranged in true NK-cell proliferations.

We present the clinicopathologic features of 4 patients with intravascular large NK/T-cell lymphoma (IVLTCL), and review the literature for similar cases.

PATIENTS AND METHODS

Four patients with IVLTCL have been included in the study (Table 1). Diagnoses were based on typical histologic appearance and demonstration of a T-cell or NK-cell phenotype. Partial details of two of these cases have been published previously.[11,17]

Histology

Biopsy specimens were fixed in 10% buffered formalin and subsequently embedded in paraffin. Sections were stained with hematoxylin and eosin for routine histopathologic evaluation.

Immunohistochemical Analyses

Detailed immunophenotypic analyses were performed on routinely fixed, paraffin-embedded tissue sections according to a previously described 3-step immunoperoxidase technique.[3] Microwave enhancement was used for all of the antibodies. Details on primary antibodies are listed in Table 2. Second and third

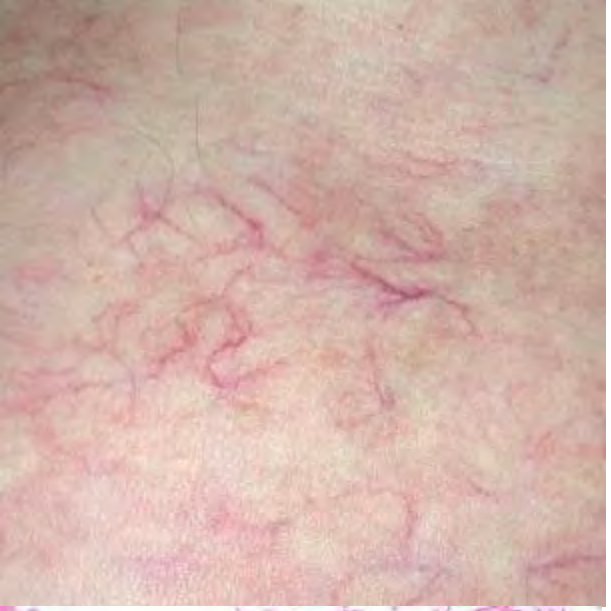
A few cases reported (possibly the rarest type of NHL)

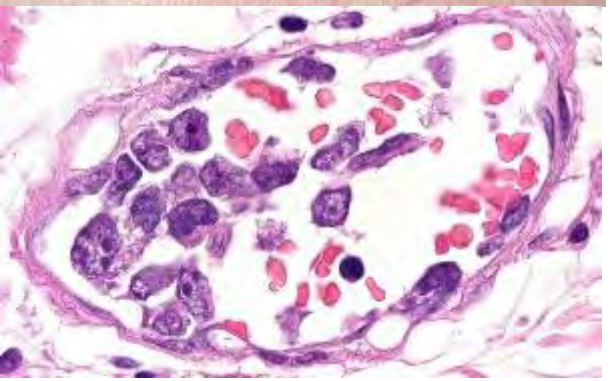
Association with EBV in ~70% of tested cases

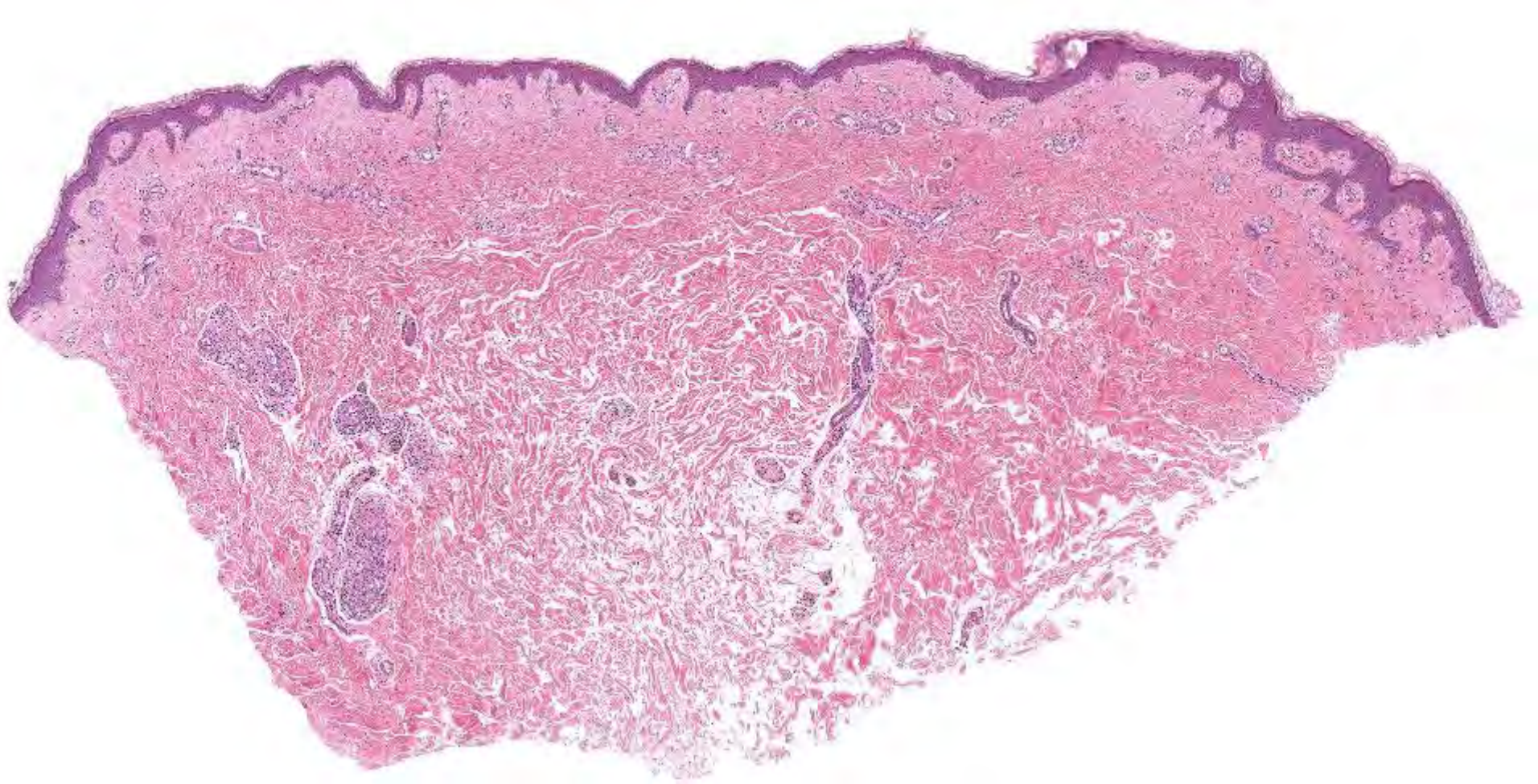
Cytotoxic phenotype in the vast majority of tested cases

Common presentation in the skin

Clinical, morphologic features and prognosis similar to the B-cell variant (possibly the only type of lymphoma where morphologic features, namely intravascular location, are more important than phenotype for classification and treatment)







Intravascular diffuse large B-cell lymphoma

Rare variant of large B-cell lymphoma confined to the lumina of small blood vessels. Common involvement of skin and CNS ("Western variant "); multiorgan failure, haemophagocytic syndrome ("Asian variant"); a purely cutaneous variant, observed only in Western women, has a better prognosis. Sometimes diagnosed by "random" skin biopsy; located within haemangiomas in more cases than mere chance would explain. *MYD88 and CD79B* hot spot mutations are reported in 50% and almost 70% of cases, respectively. Morphologically indistinguishable from IV-NK/T-cell ly.

Main "intravascular" proliferation of cells

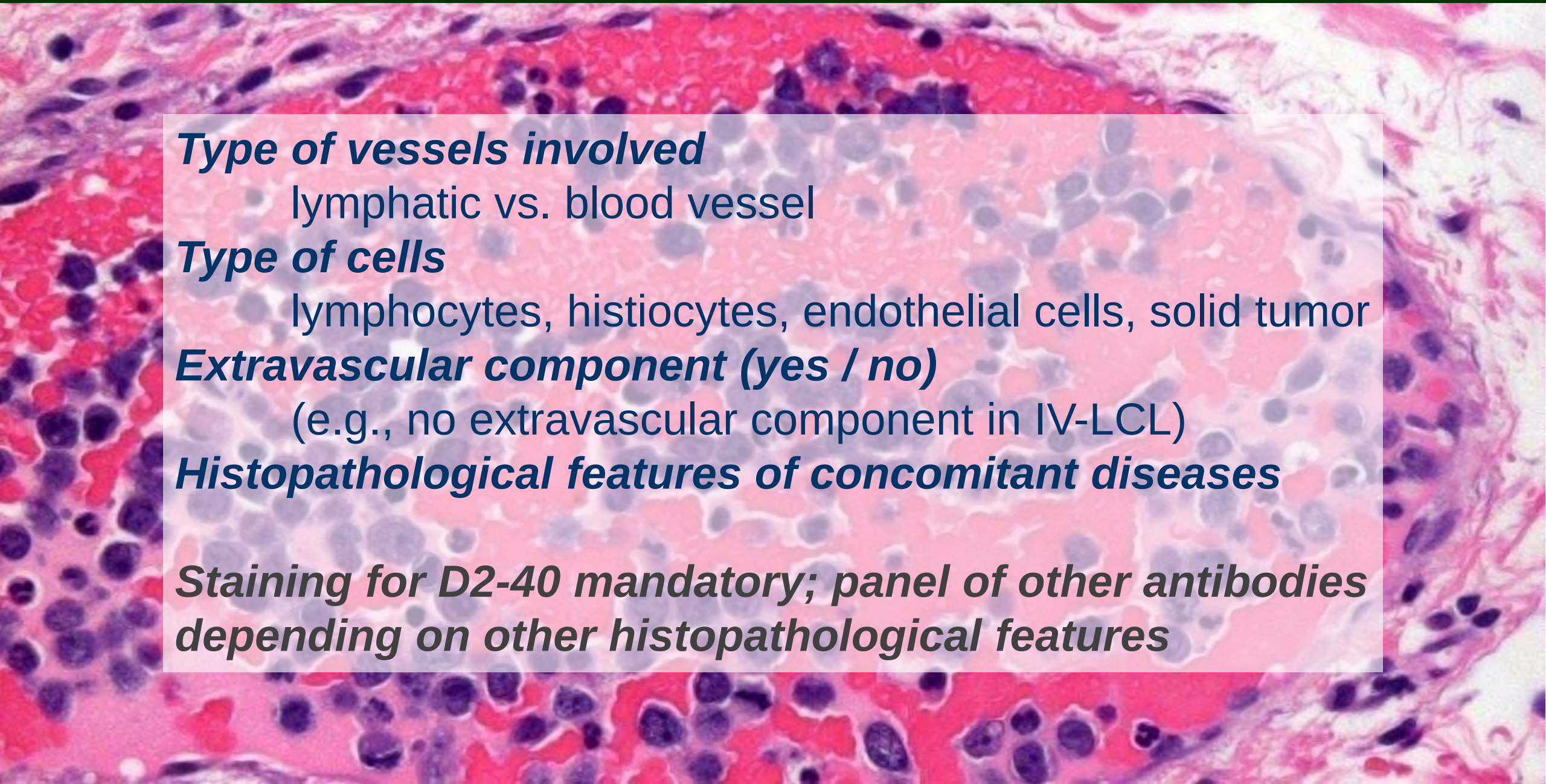
Within blood vessels

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

Within lymphatic vessels

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

Approach to diagnosis of intraluminal cells



Type of vessels involved

lymphatic vs. blood vessel

Type of cells

lymphocytes, histiocytes, endothelial cells, solid tumor

Extravascular component (yes / no)

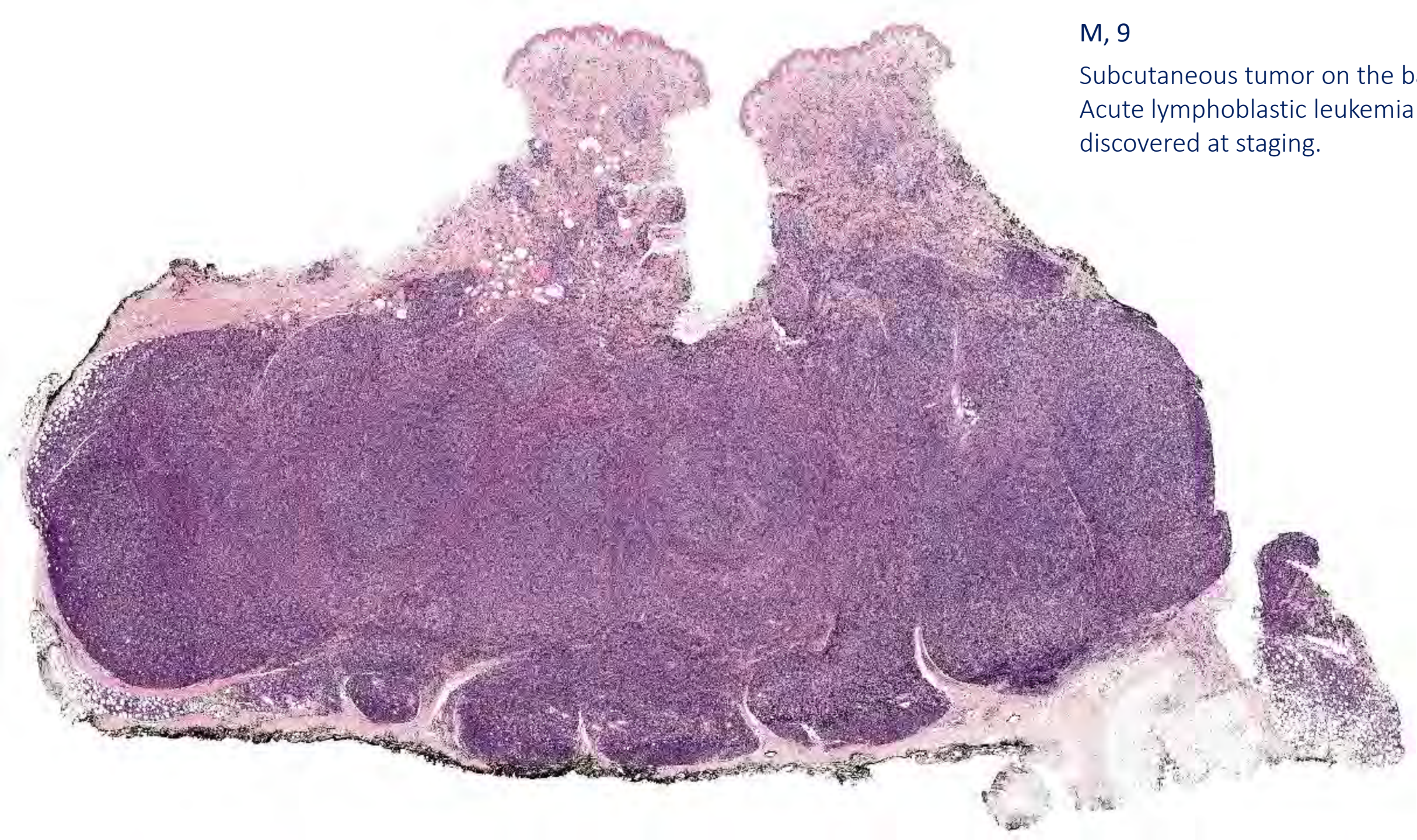
(e.g., no extravascular component in IV-LCL)

Histopathological features of concomitant diseases

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

Cutaneous lymphoblastic lymphoma

- Cutaneous manifestations may be observed both in the B- and T-cell variants
- Some cases of "primary cutaneous" B-lymphoblastic lymphoma have been reported; prognosis probably better (but overall survival in childhood B-LBL >80% irrespective of site of onset)
- Morphology of T-LBL and B-LBL considered indistinguishable; in the skin T-LBL may show a more "pleomorphic" appearance
- CD19+, CD79a+, CD10+, PAX5+, TdT+ (B-LBL)
  CD3+, CD7+, CD1a+, TdT+ (T-LBL) (may be CD79a+)
  Common phenotypic variations
- The new WHO and ICC classifications recognize several molecular entities of B- and T-LB lymphoma; molecular profile of primary cutaneous cases not well characterized



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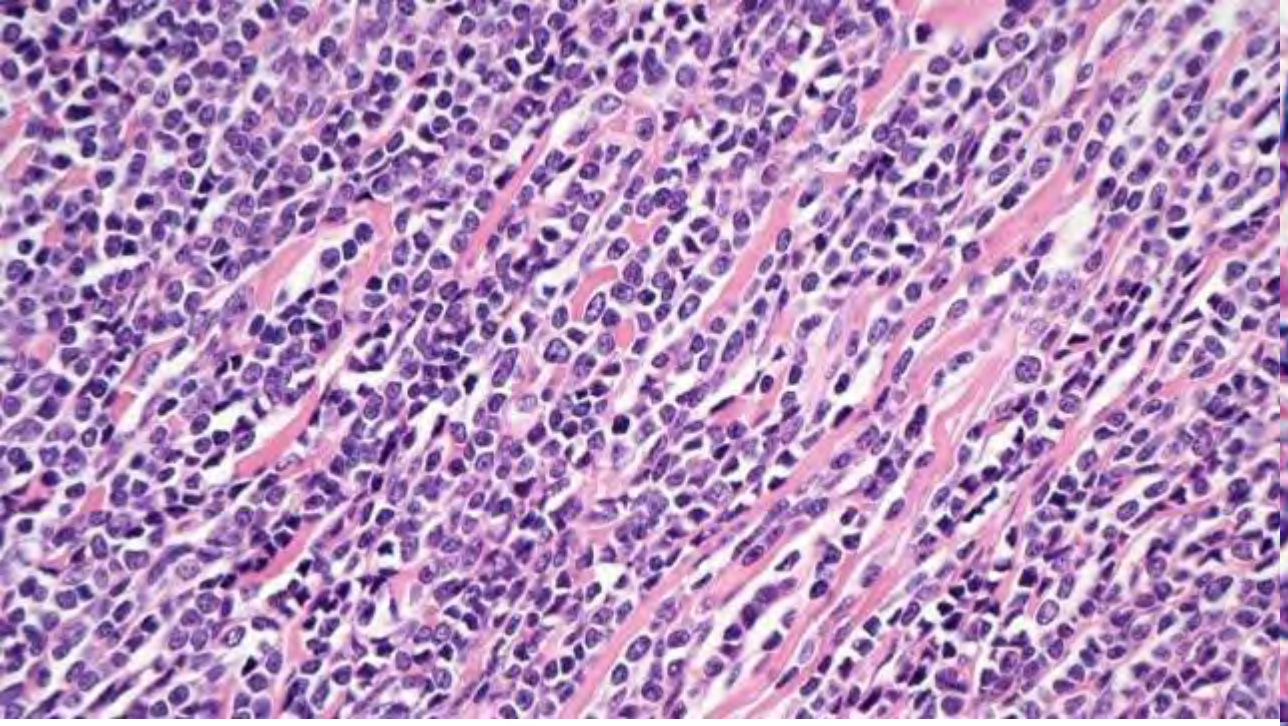
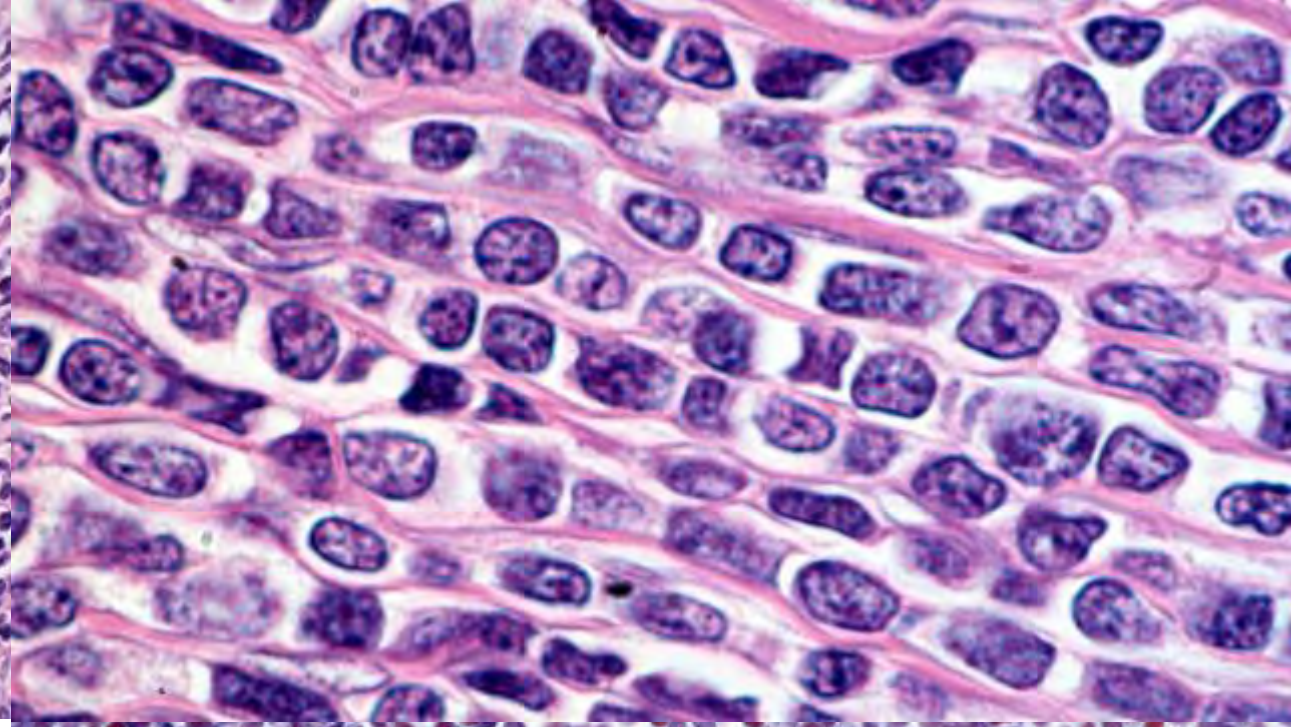
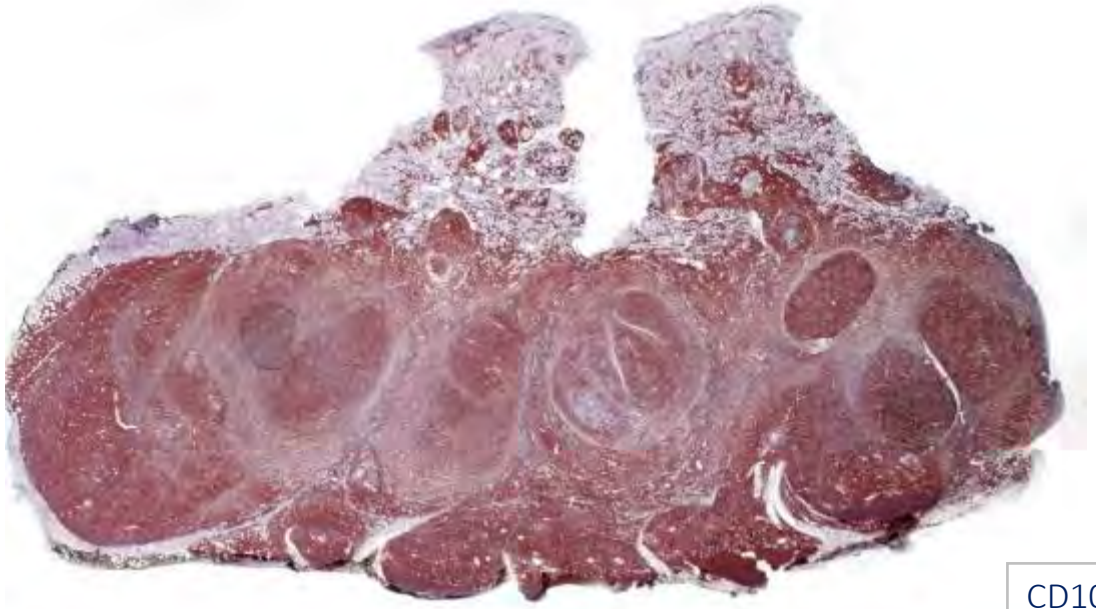
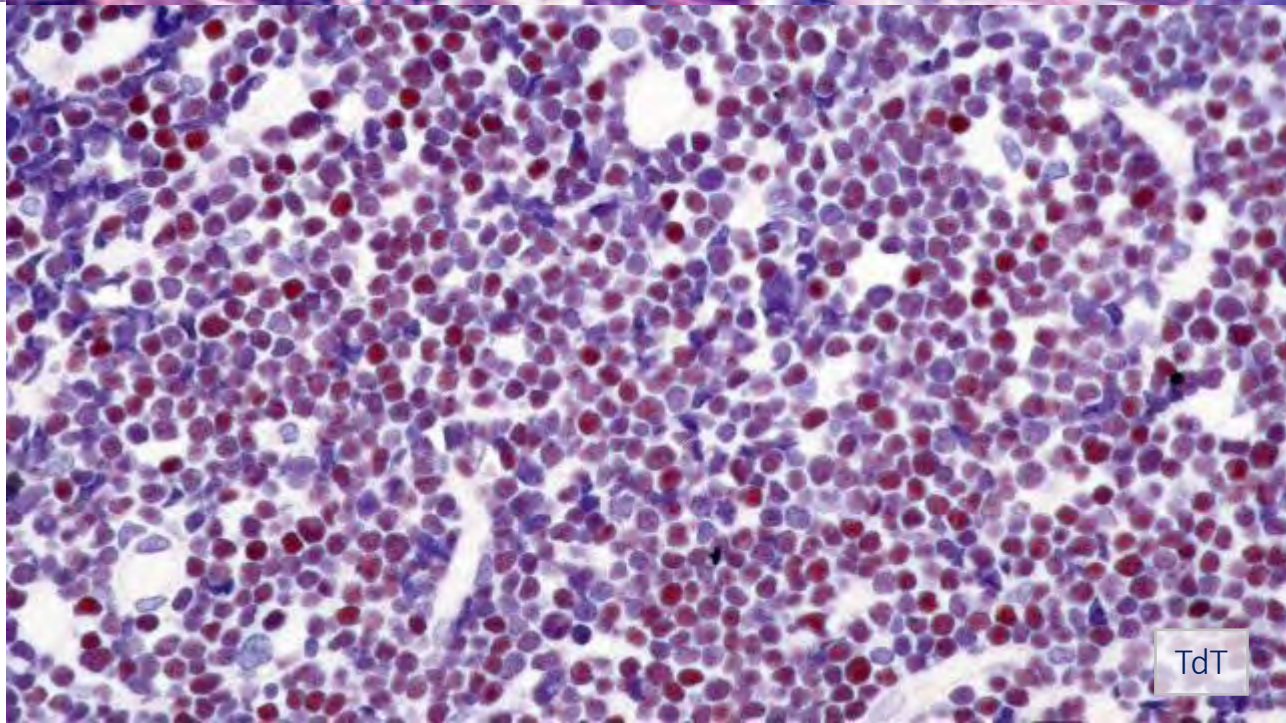
Subcutaneous tumor on the back.
Acute lymphoblastic leukemia
discovered at staging.





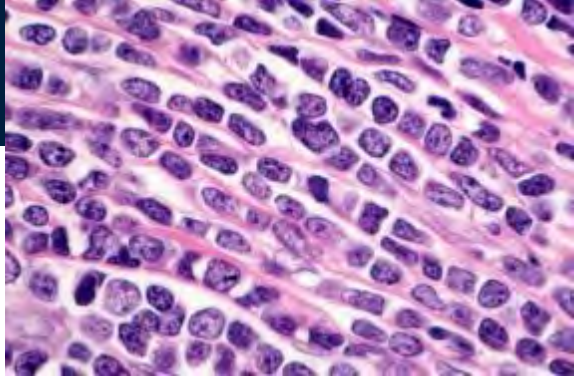


CD10



TdT

Mosaic stone-like pattern



Aggressive

Lymphoblastic lymphoma

Distinction from Burkitt lymphoma and DBLCL made mostly on phenotype (morphological features may be overlapping)

Burkitt lymphoma

(i) endemic (arising mostly in equatorial African and Papua New Guinea children and always associated with EBV), (ii) sporadic (arising mostly in children and young adults without racial predilection and associated with EBV in 20–30% of cases), and (iii) immunodeficiency-associated (arising mostly in immunocompromised HIV+ patients and associated with EBV in 25–40% of cases)

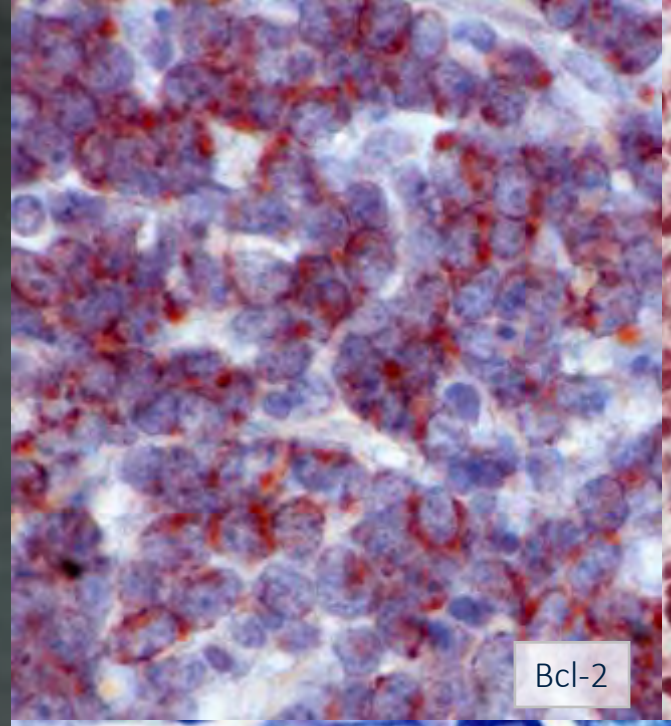
Diffuse large B-cell lymphoma, leg-type

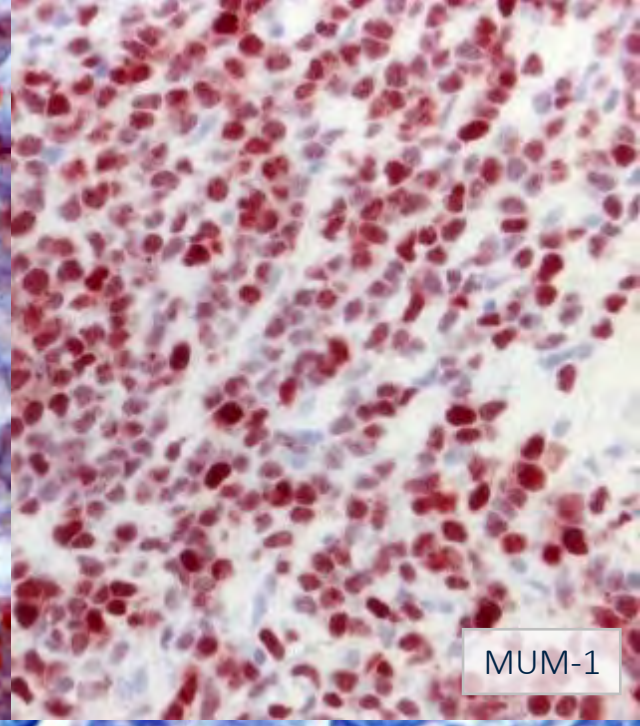
Very rare cases with a "mosaic stone"-like pattern should be distinguished from cutaneous involvement in Burkitt lymphoma or lymphoblastic lymphoma

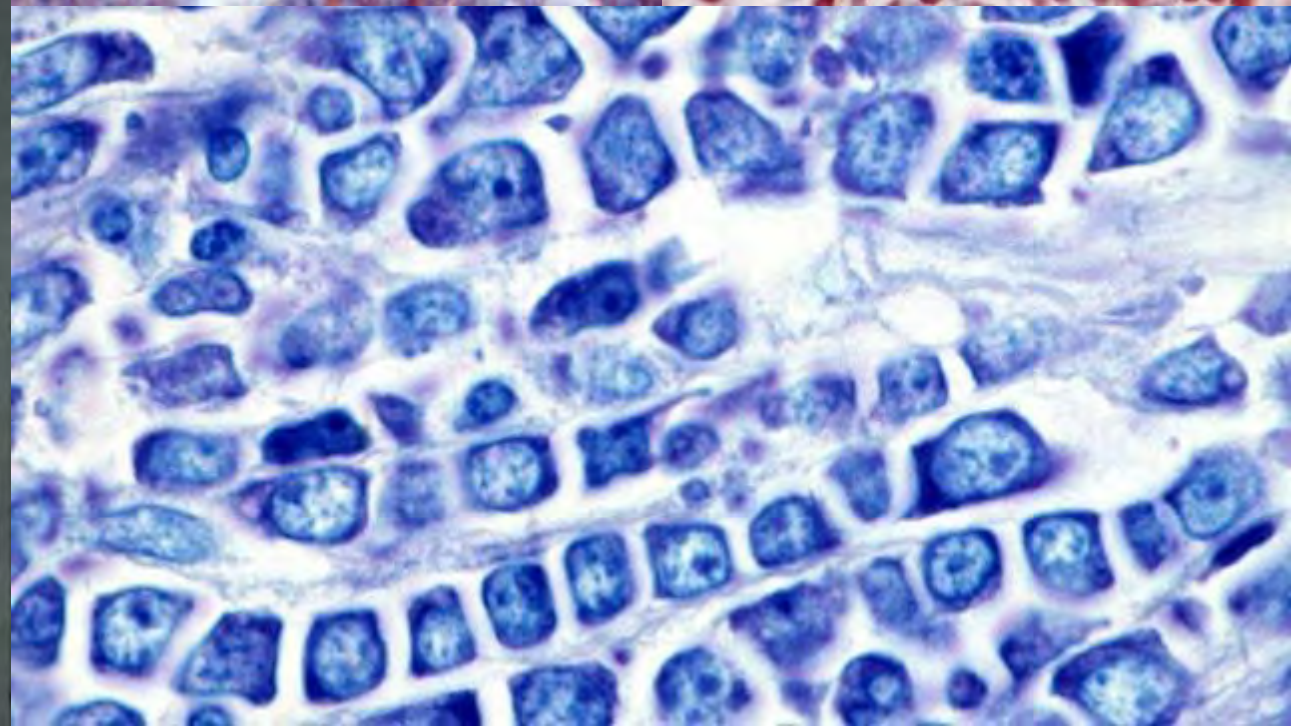
Indolent

A pattern not observed in indolent cutaneous lymphomas

Diffuse large B-cell lymphoma, leg-type







Precursor B- or T-lymphoblastic lymphoma presenting with cutaneous involvement: A series of 13 cases including 7 cases of cutaneous T-lymphoblastic lymphoma

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Seoul, Korea

Background: Lymphoblastic lymphoma (LBL) is a rare neoplasm of precursor lymphocytes, and cutaneous involvement is present in less than 20% of cases.

Objective: We sought to describe the clinical and histopathological features of cutaneous LBL.

Methods: We retrospectively examined the clinical and histologic features of 13 patients with cutaneous LBL, 6 with B-LBL and 7 with T-LBL.

Results: Five of 6 patients with B-LBL had lesions in the head and neck area, whereas 4 of 7 patients with T-LBL developed skin lesions on sites other than the head and neck. Seven patients (1 case of B-LBL, and 6 of 7 cases of T-LBL) developed multiple skin lesions, and the T-LBL cases frequently developed multiple skin lesions in the head, neck, and throughout the torso. Complete remission was achieved in 9 patients (3 patients with T-LBL and all patients with B-LBL).

Limitations: This study used a retrospective design and included a small sample size.

Conclusion: This study compared the clinical features of T-LBL and B-LBL, in particular the affected sites and number of skin lesions. Cutaneous T-LBL is likely to be accompanied by disseminated disease and has a relatively poor prognosis compared with B-LBL. (J Am Acad Dermatol 2014;70:318-25.)

Key words: lymphoblast; lymphoblastic lymphoma; lymphoma; precursor B lymphocytes; precursor T lymphocytes; skin.

Lymphoblastic lymphoma (LBL) is defined by neoplasms that arise from precursor B- or T-cell lymphocytes and its cytologic features are morphologically identical to those of acute lymphoblastic leukemia (ALL). Among lymphoblastic disorders, ALL accounts for 90% of all cases, and LBL accounts for approximately 10%.[1] LBL also accounts for roughly one third of childhood and less than 5% of adult non-Hodgkin lymphoma cases.[2,3] Of all the malignant lymphomas that affect the skin, approximately 3.5% to 7% are lymphoblastic.[4] Cutaneous LBL is a rare disease that has been defined in the literature as a cutaneous involvement along with existing systemic LBL, but also as a primary cutaneous disease.[4-6]

Abbreviations used:

ALL: acute lymphoblastic leukemia
LBL: lymphoblastic lymphoma
TdT: terminal deoxynucleotidyl transferase

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http://dx.doi.org/10.1016/j.jaad.2013.10.020

B-LB lymphoma: 6 (3 primary cutaneous)
6/6 pediatric age (1-13)

T-LB lymphoma: 7 (0 primary cutaneous)
2/7 pediatric age (16-17)

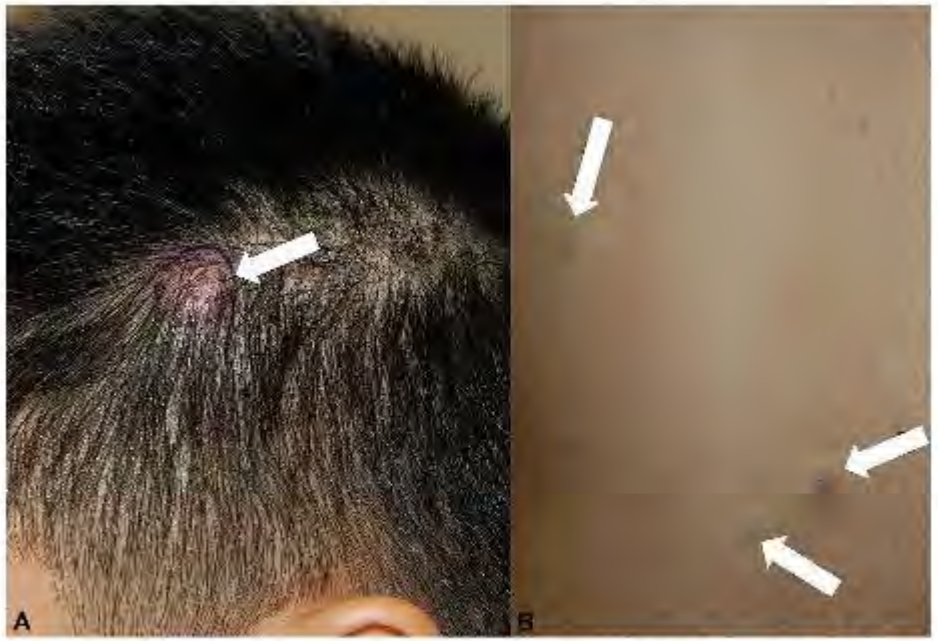

Fig 1. Clinical features of cutaneous lymphoblastic lymphoma (LBL). **A**, A solitary subcutaneous nodule on the scalp of a patient with B-LBL. **B**, Multiple subcutaneous nodules on the back of a patient with T-LBL.

Outcome and clinicophenotypical features of acute lymphoblastic leukemia/lymphoblastic lymphoma with cutaneous involvement: A multicenter case series

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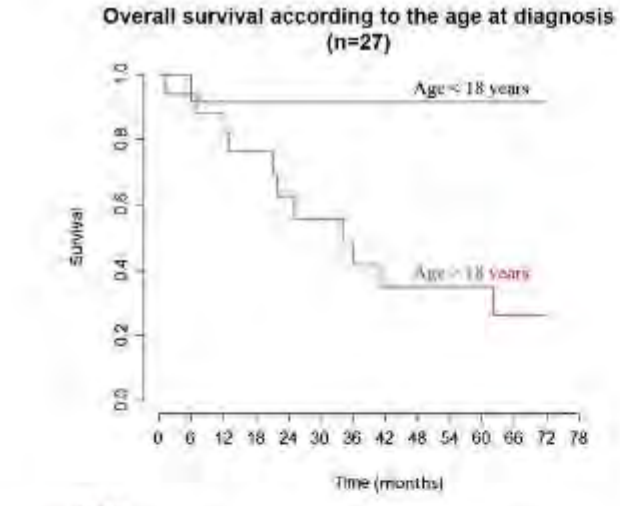
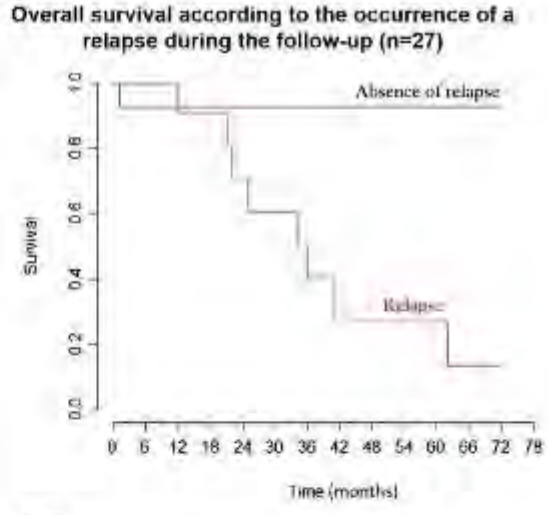
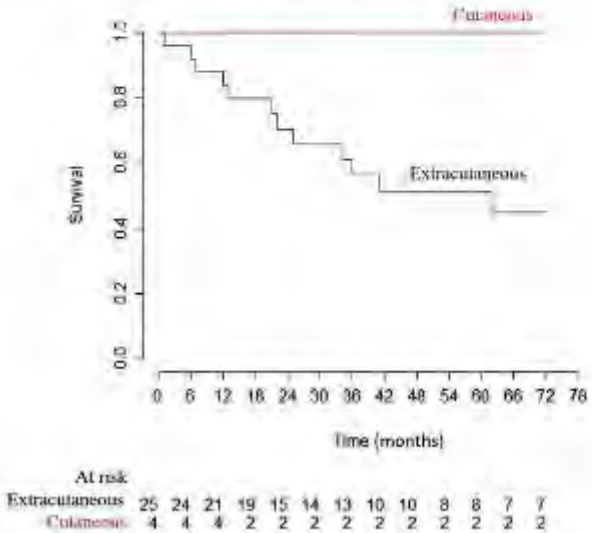
To the Editor: Cutaneous involvement by acute lymphoblastic leukemia/lymphoblastic lymphoma (ALL/LBL) is very uncommon. Current knowledge of this situation remains limited, based on small retrospective case series without data regarding overall survival (OS) and associated prognostic factors nor molecular features.[1-3] Besides, no data about differential antigen expression of tumoral cells in skin vs bone marrow are available.

Our objective was to describe outcome, prognostic factors, and clinicophenotyping specificities of ALL/LBL with skin involvement. We collected retrospective data from a multicenter cohort of patients with ALL/LBL with cutaneous involvement from 13 hospitals from 1997 to 2018.

Patients' characteristics are listed in Table I. Among 38 patients with ALL/LBL (12 females, 26 males),



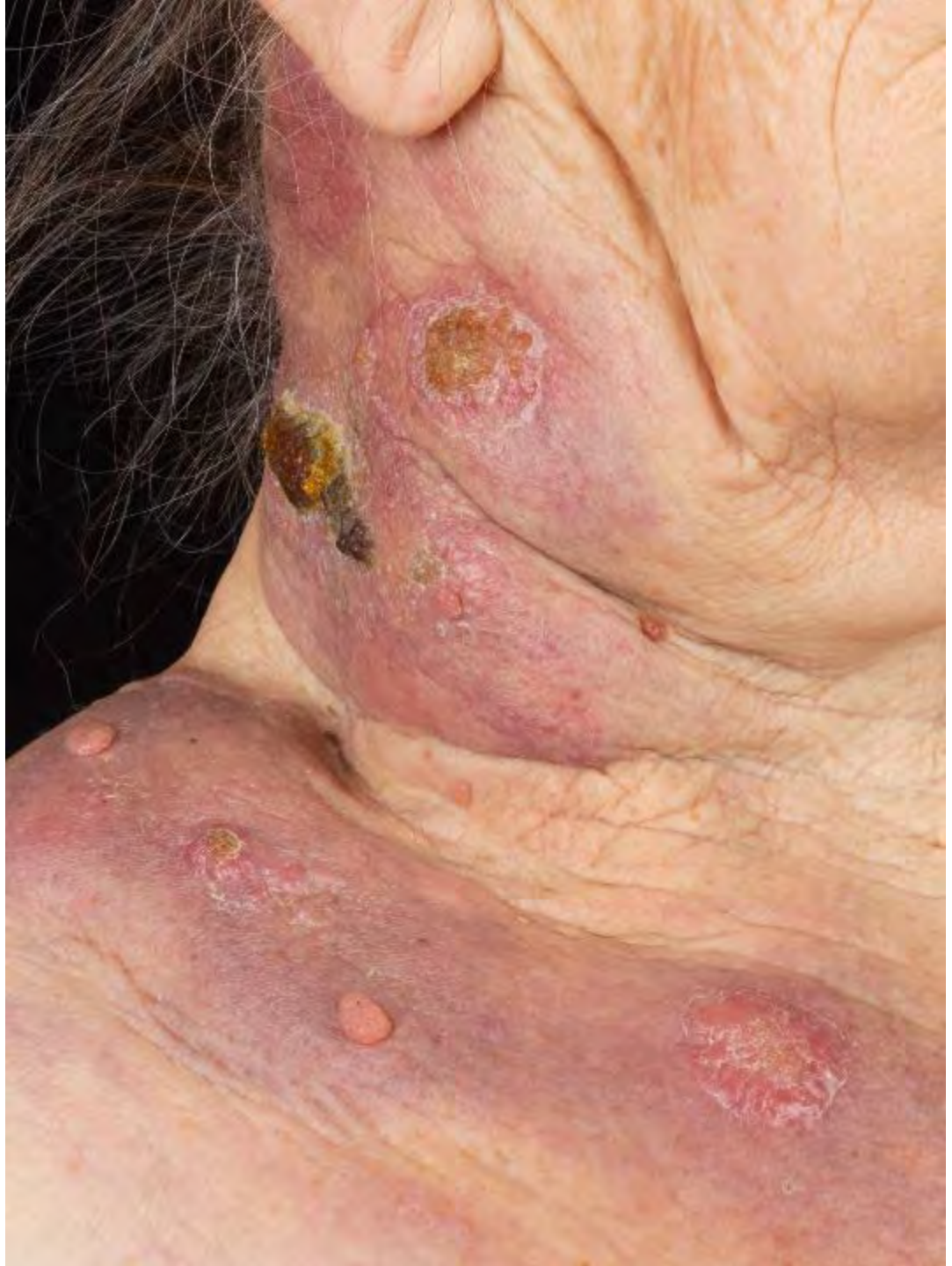




Univariable Cox analysis on survival

Variable	HR (95% CI)	p
B-cell LBL (versus T-cell LBL)	0,6 (0.2-1.8)	0.33
Cutaneous (versus extracutaneous)	10^9 (0-∞)	0.99
Relapse	19 (2.3-159)	*0.006*
Multiple lesions	3.1 (0.7-14)	0.14
Age > 18 years	11 (1.5-88)	*0.02*
High molecular risk	1.3 (0.4-4.1)	0.7

Fig 1. Kaplan-Meier probabilities and univariate Cox analysis on prognostic factors of overall survival for patients with acute lymphoblastic leukemia/lymphoblastic lymphoma (*LBL*) and skin involvement (n = 27). *CI*, Confidence interval; *HR*, hazard ratio.

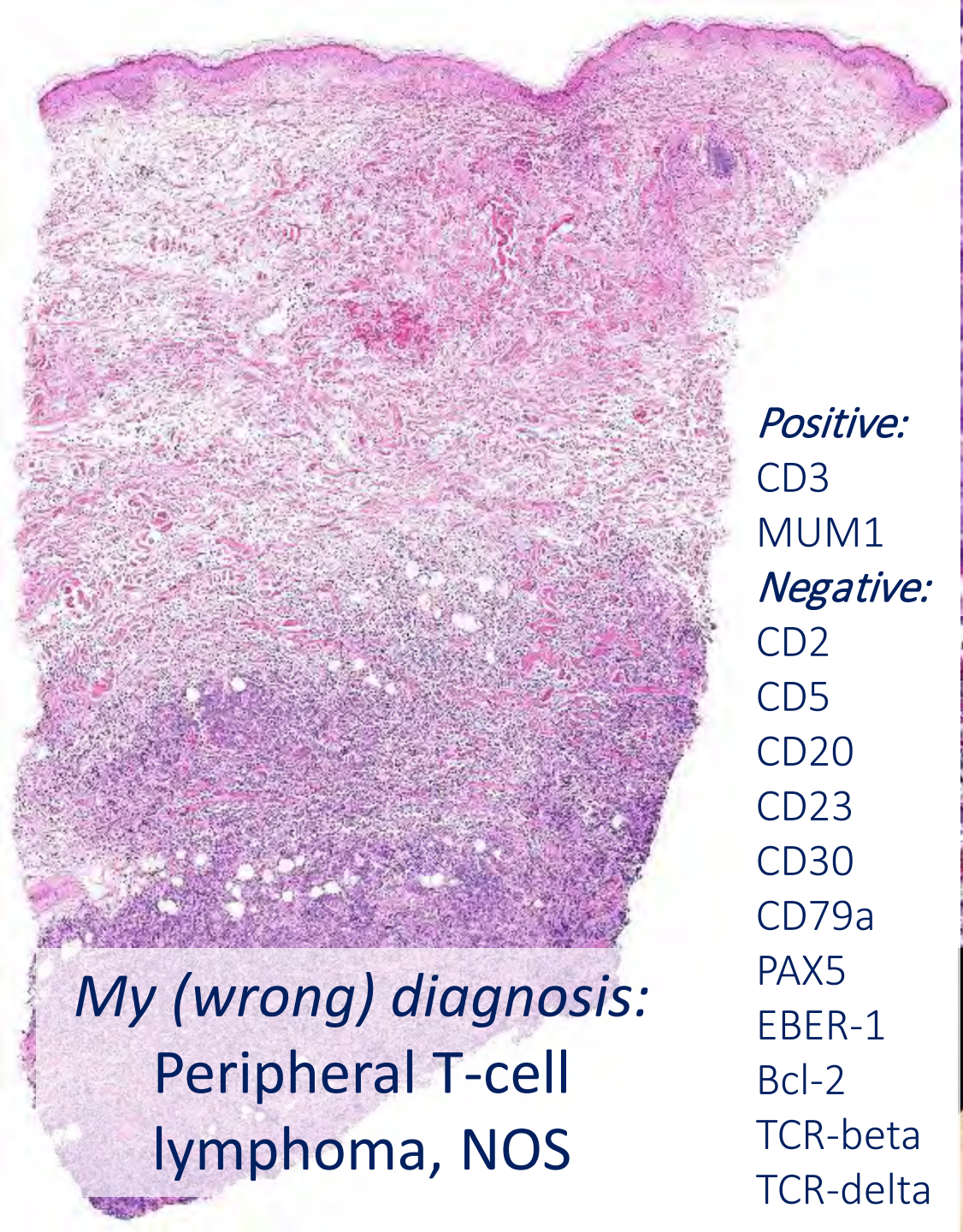


F, 72

History of B-CLL (1st diagnosis 19 years before presentation). One year before presentation systemic Richter syndrome managed with chemotherapy (CR 3 months before presentation).

Progressive swelling and ulcerations on the right side of the neck for one month.

A biopsy is taken.



My (wrong) diagnosis:

Peripheral T-cell lymphoma, NOS

Positive:

CD3

MUM1

Negative:

CD2

CD5

CD20

CD23

CD30

CD79a

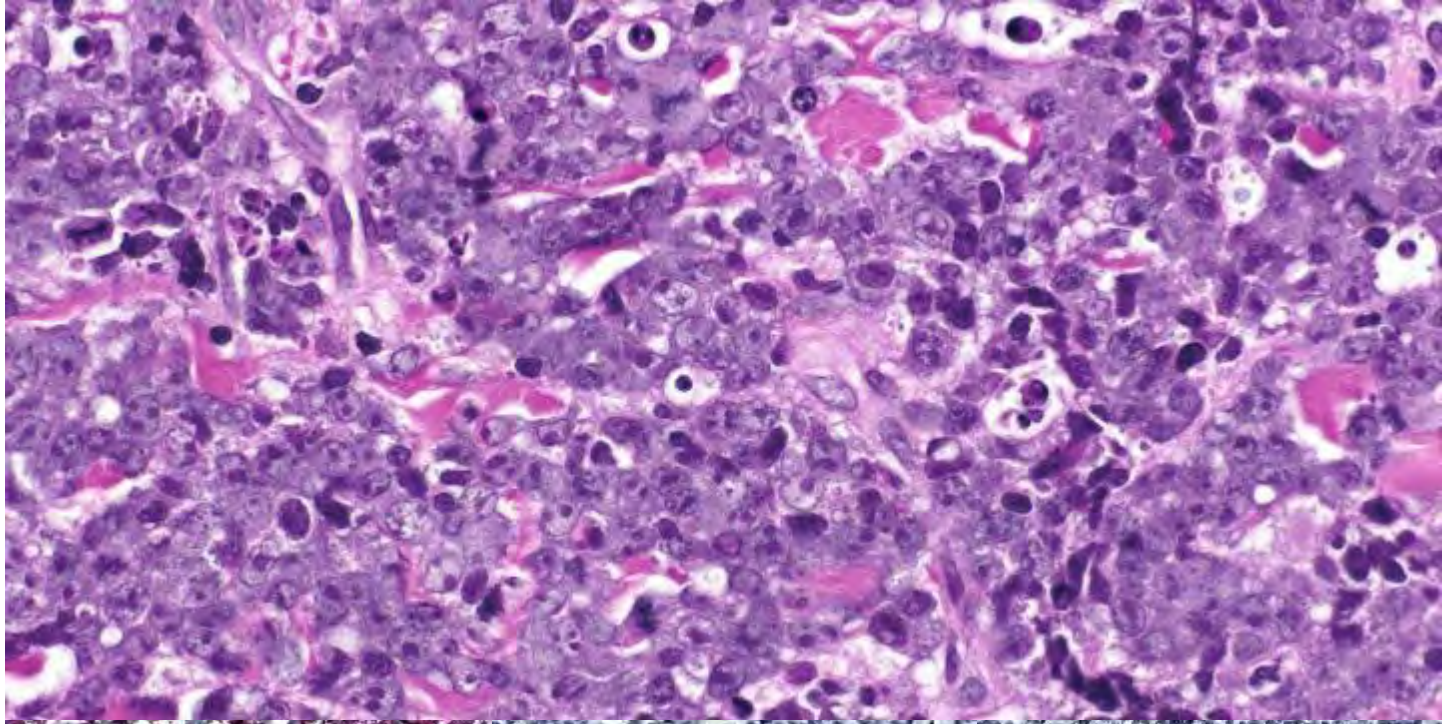
PAX5

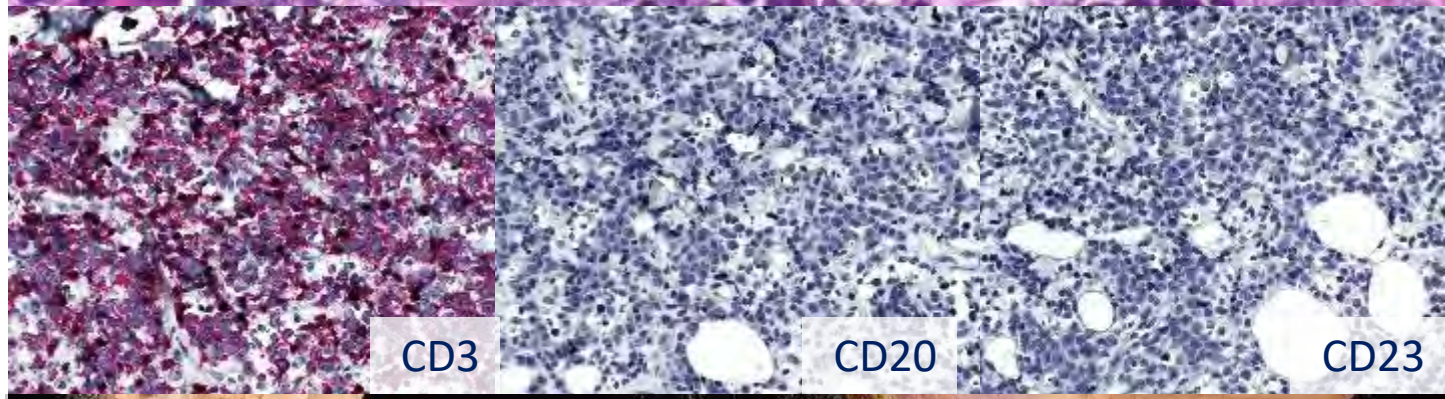
EBER-1

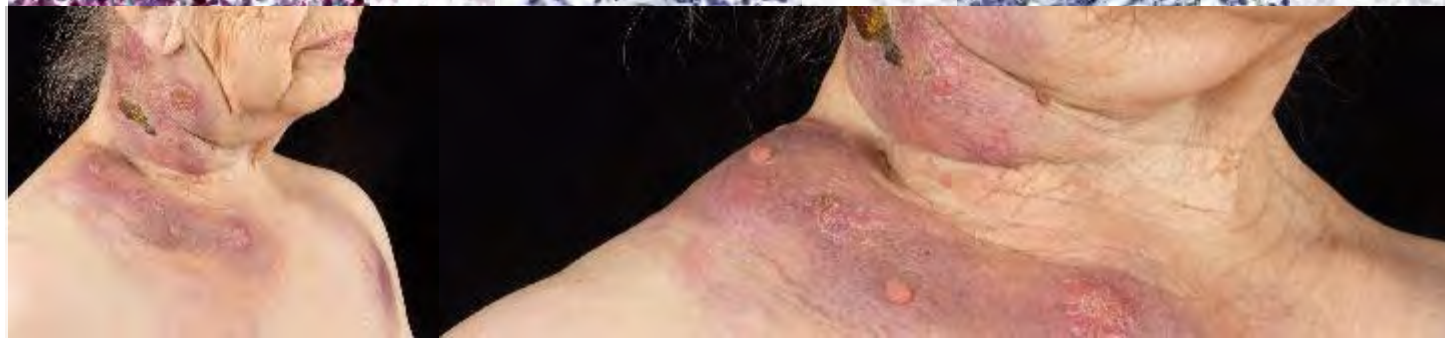
Bcl-2

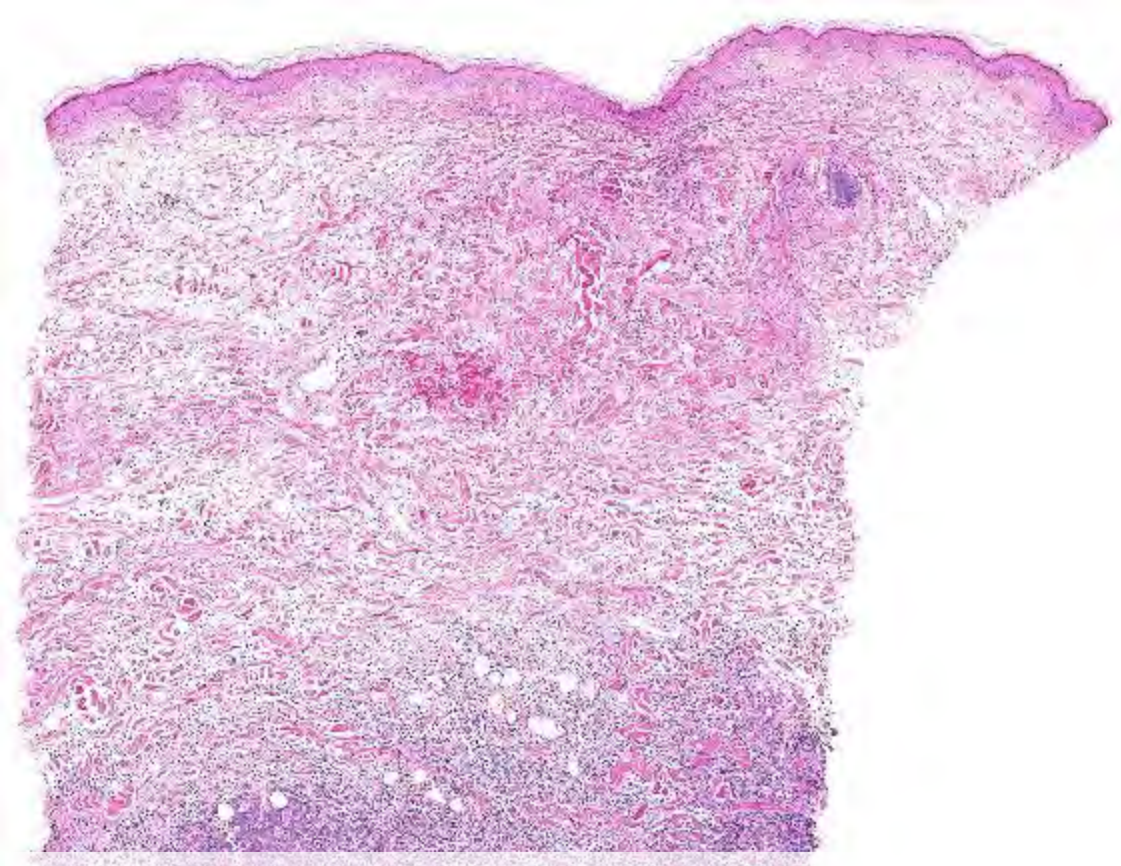
TCR-beta

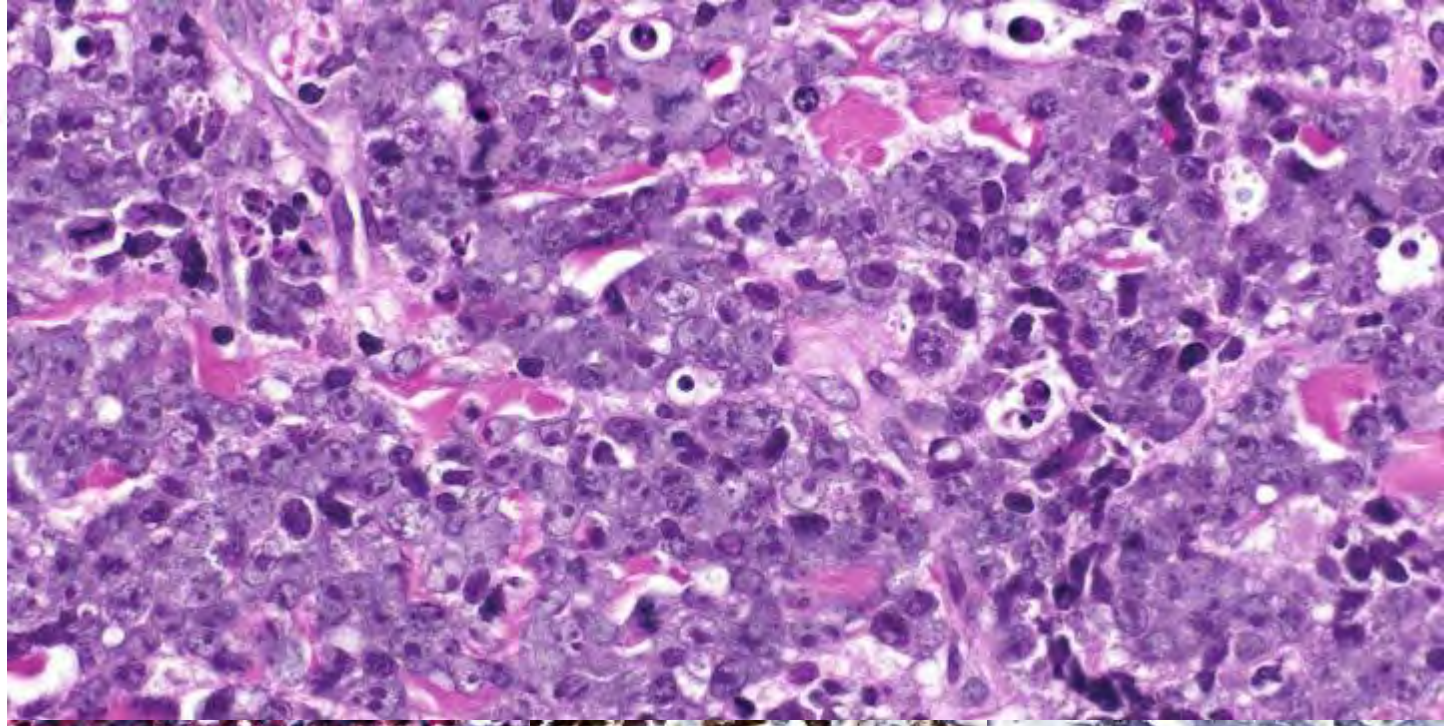
TCR-delta

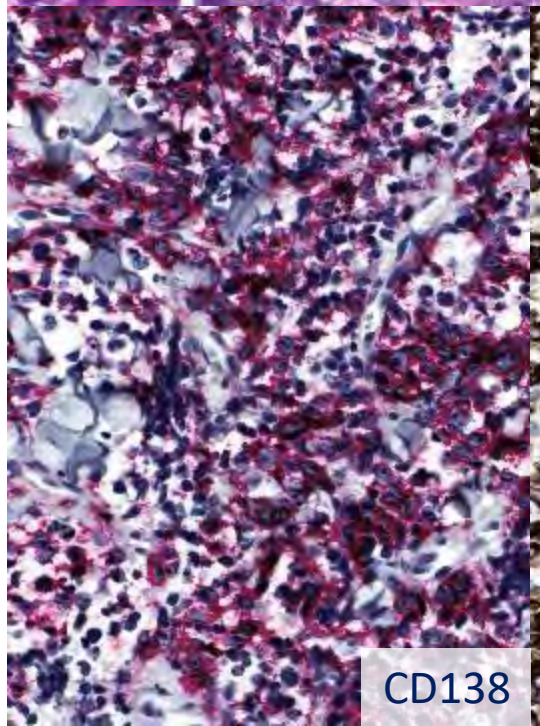


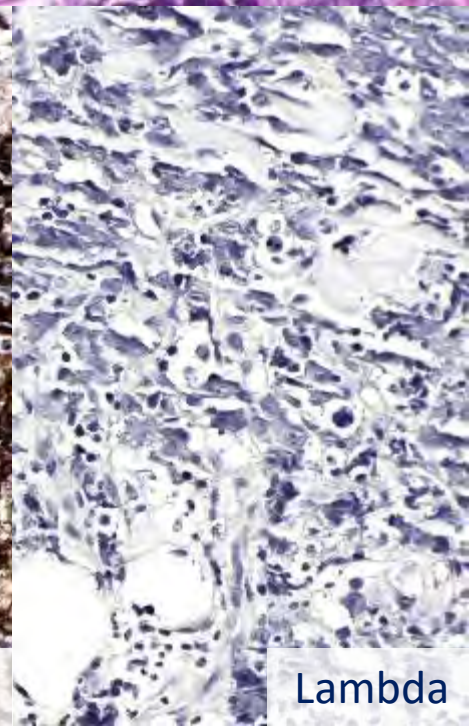






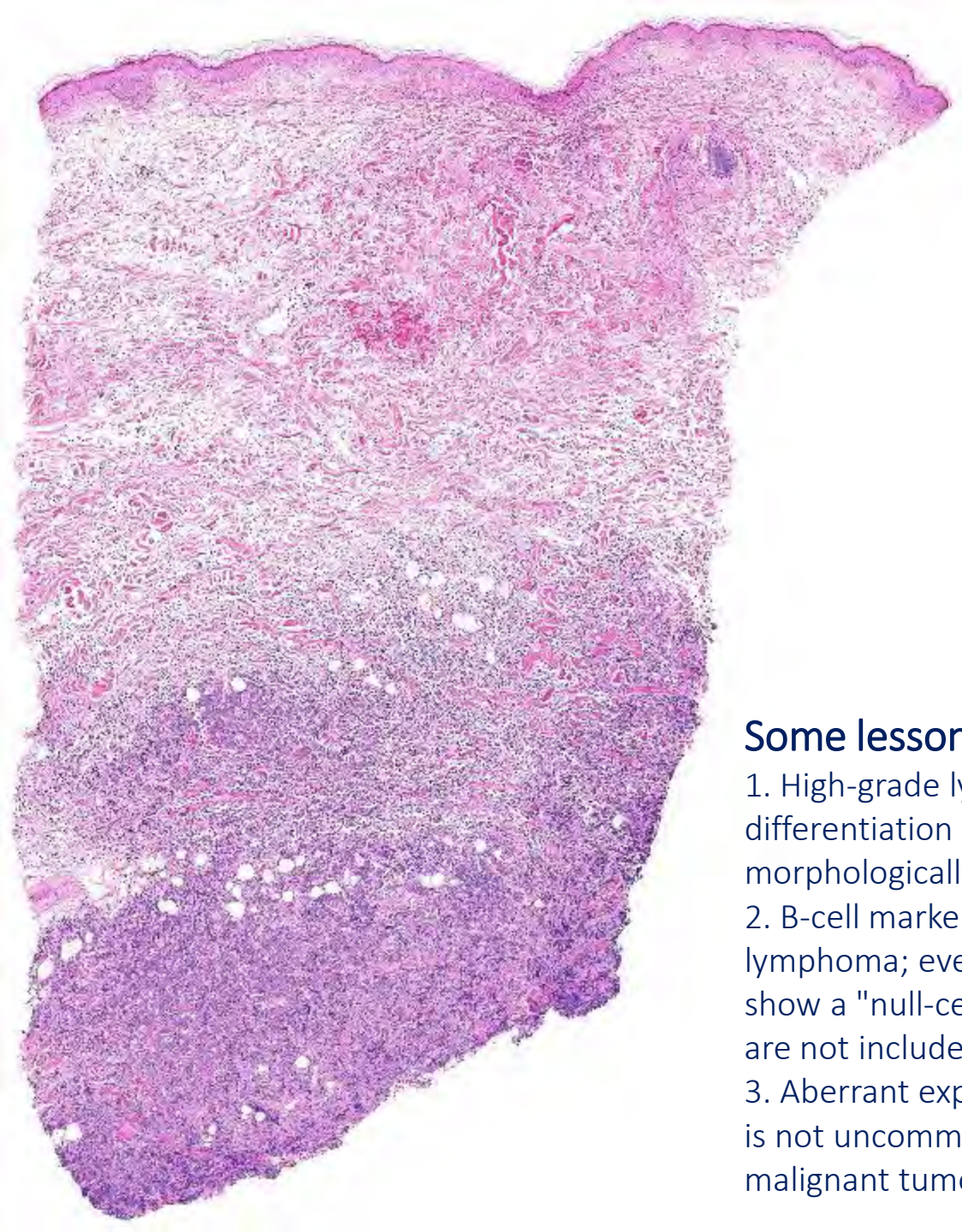


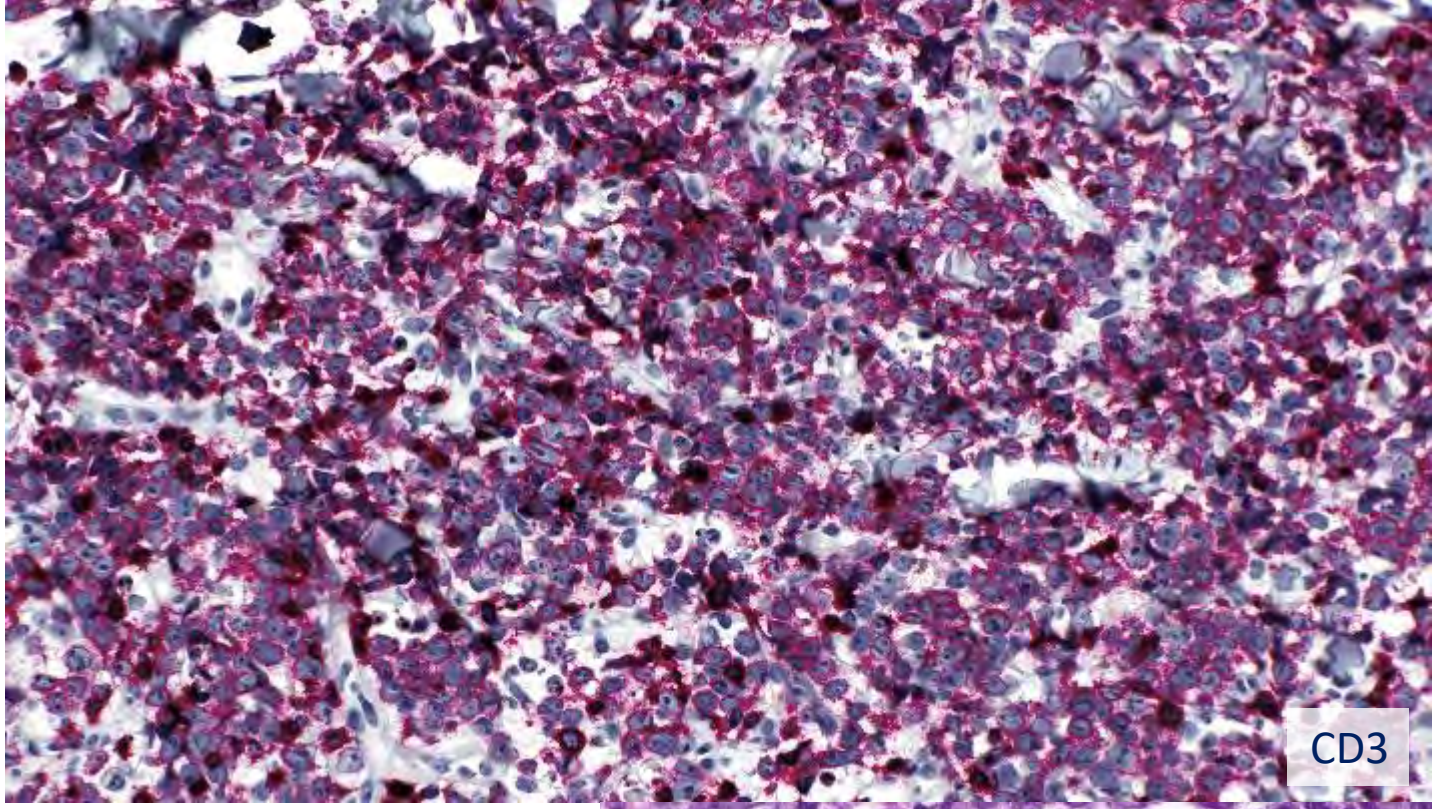




Revised diagnosis:

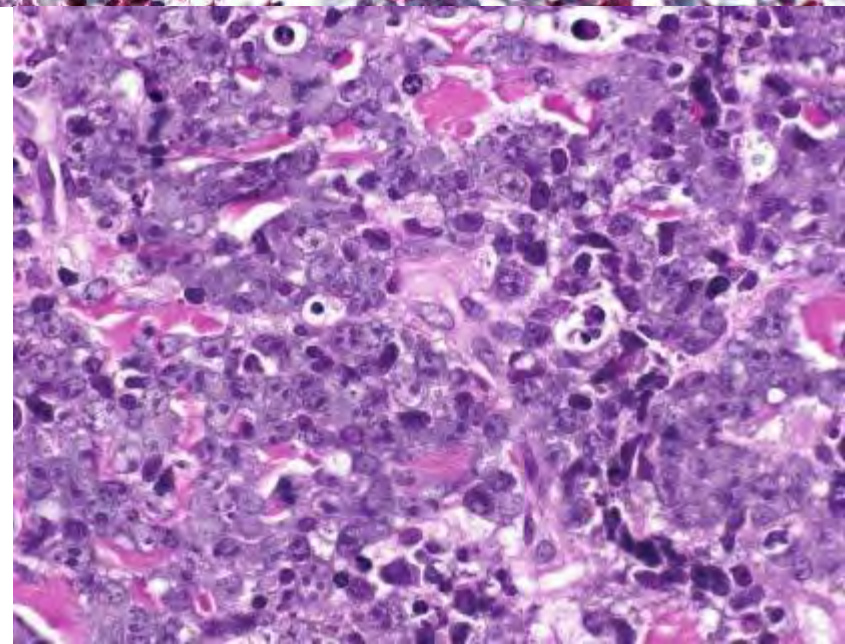
Plasmablastic lymphoma as skin manifestation of Richter syndrome





Some lessons (that I may never learn…)

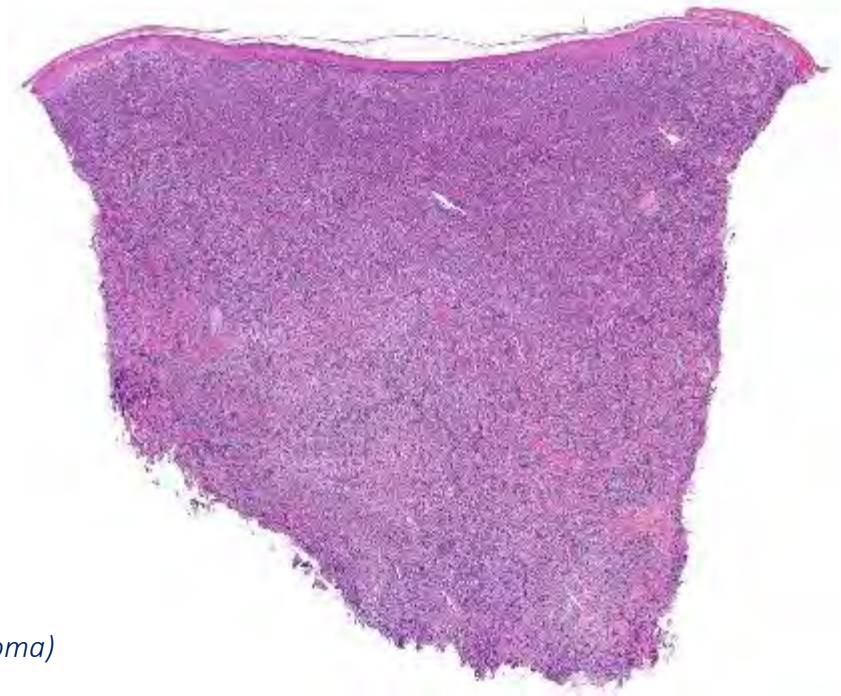
1. High-grade lymphomas with plasma cell differentiation do not resemble plasma cells morphologically
2. B-cell markers are negative in plasmablastic lymphoma; even a wide panel of antibodies may show a "null-cell" phenotype if specific markers are not included
3. Aberrant expression of one or more antigens is not uncommon in lymphomas (and other malignant tumors as well)

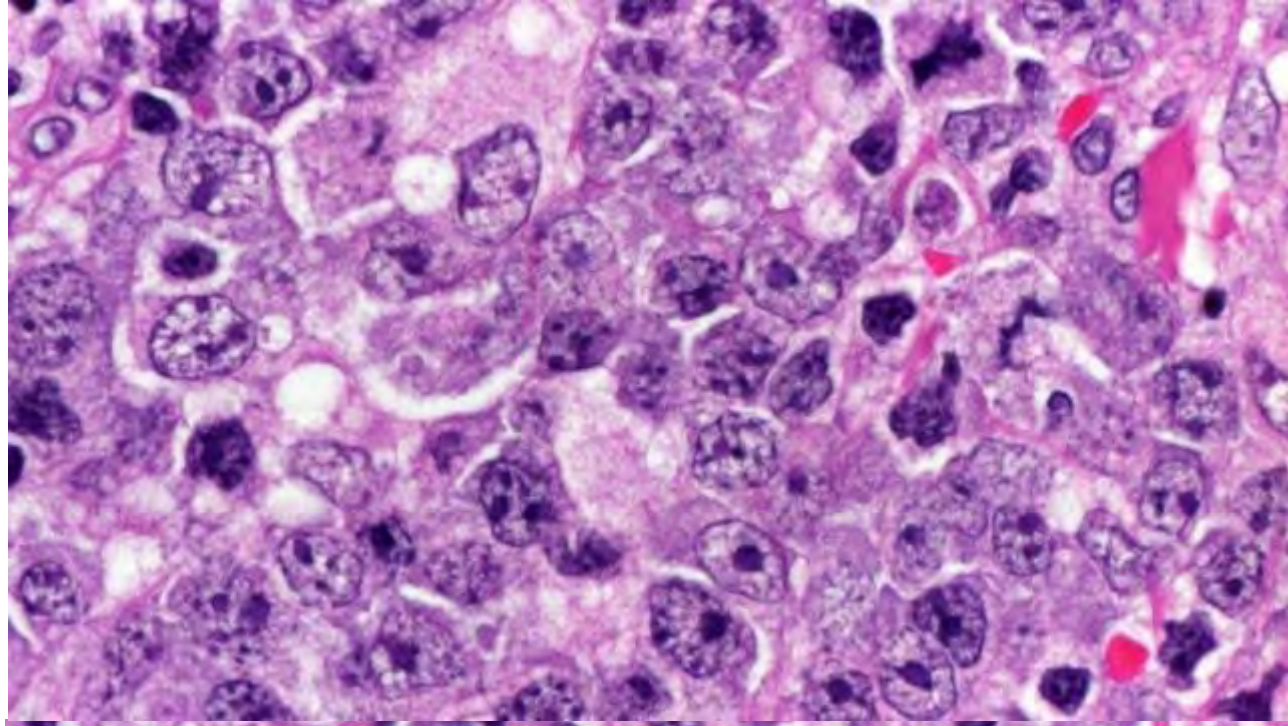


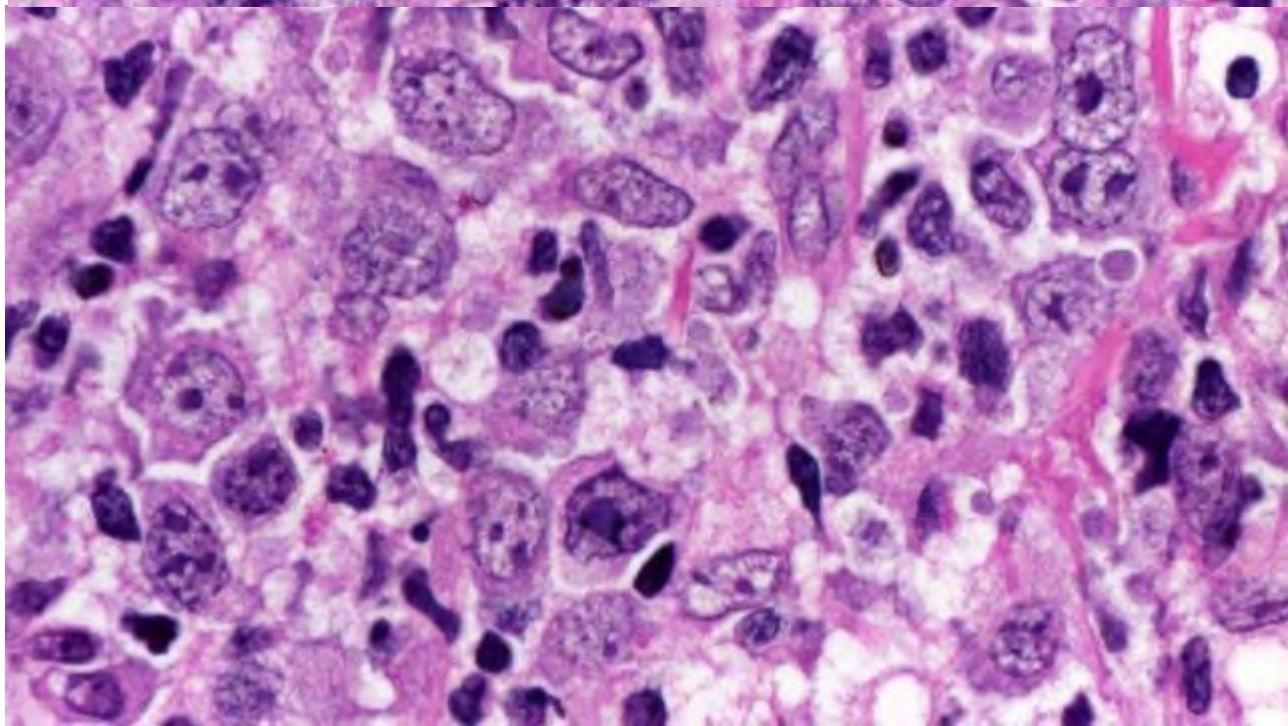
Cutaneous plasmablastic lymphoma

- Cutaneous lesions represent usually a manifestation of extracutaneous lymphoma; observed mainly (but not exclusively) in HIV patients (particularly in the oral cavity); overlapping (indistinguishable) features with plasmablastic multiple myeloma
- *Essential diagnostic criteria:* Positivity of neoplastic cells for CD38 or CD138; monoclonal restriction of the immunoglobulin light chains
- *Main differential diagnoses:* Primary cutaneous diffuse large B-cell lymphoma, leg-type
- May be observed in different settings of immune suppression, and rarely also in immunocompetent patients; most cases are EBV-associated; may be observed as high-grade transformation of a low-grade B-cell lymphoma/leukemia
- CD20-, CD38+, CD138+, Ig+, EBV+(-), Ig light chain restriction

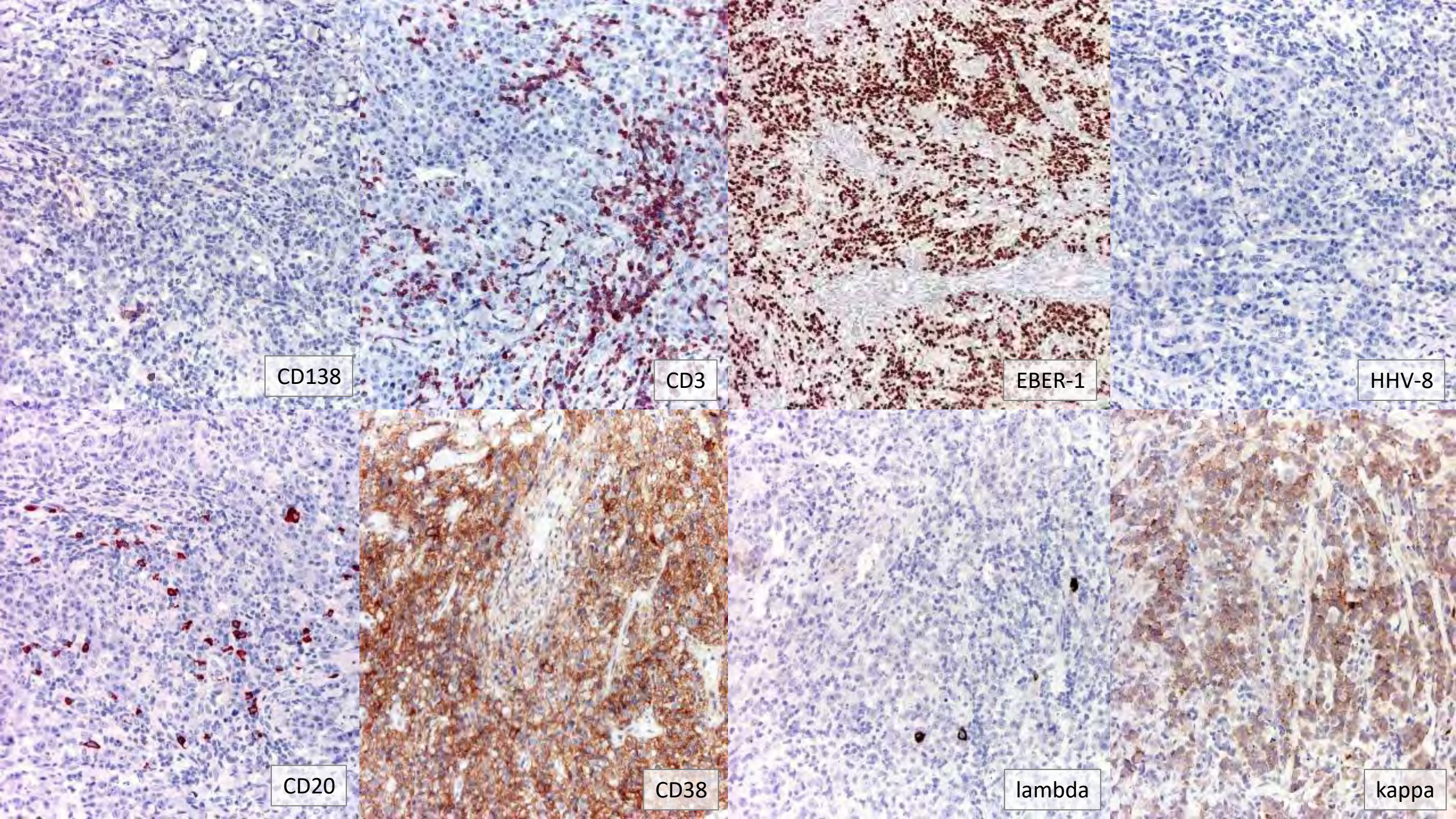
M, 49, HIV+

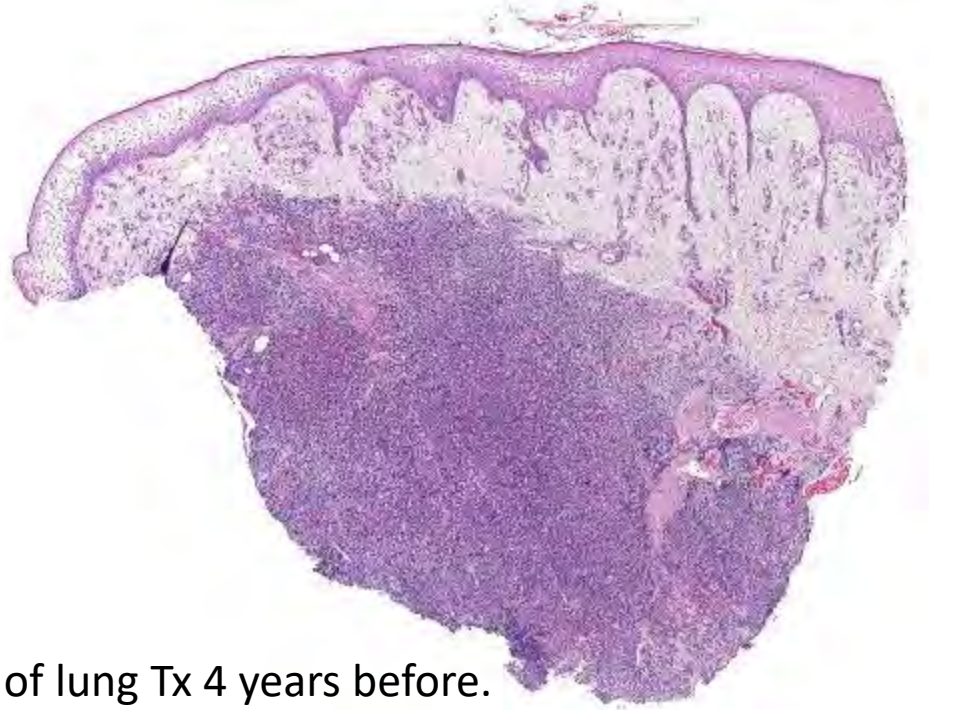




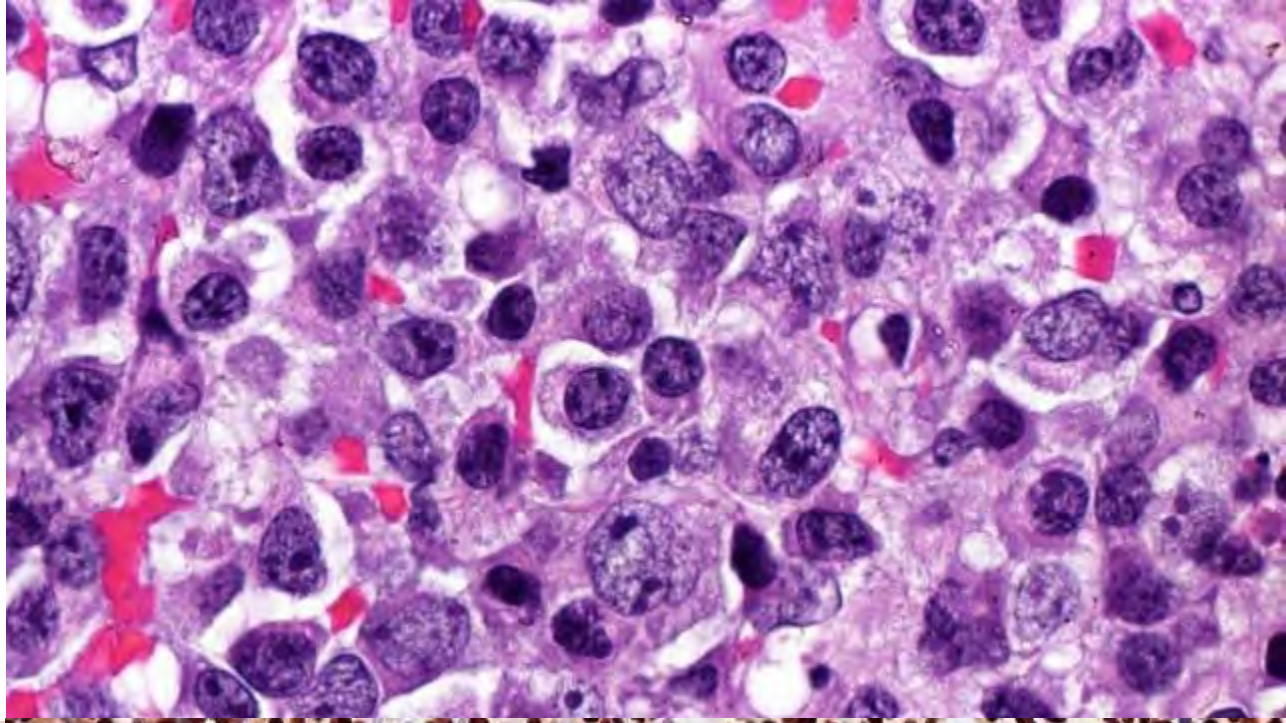


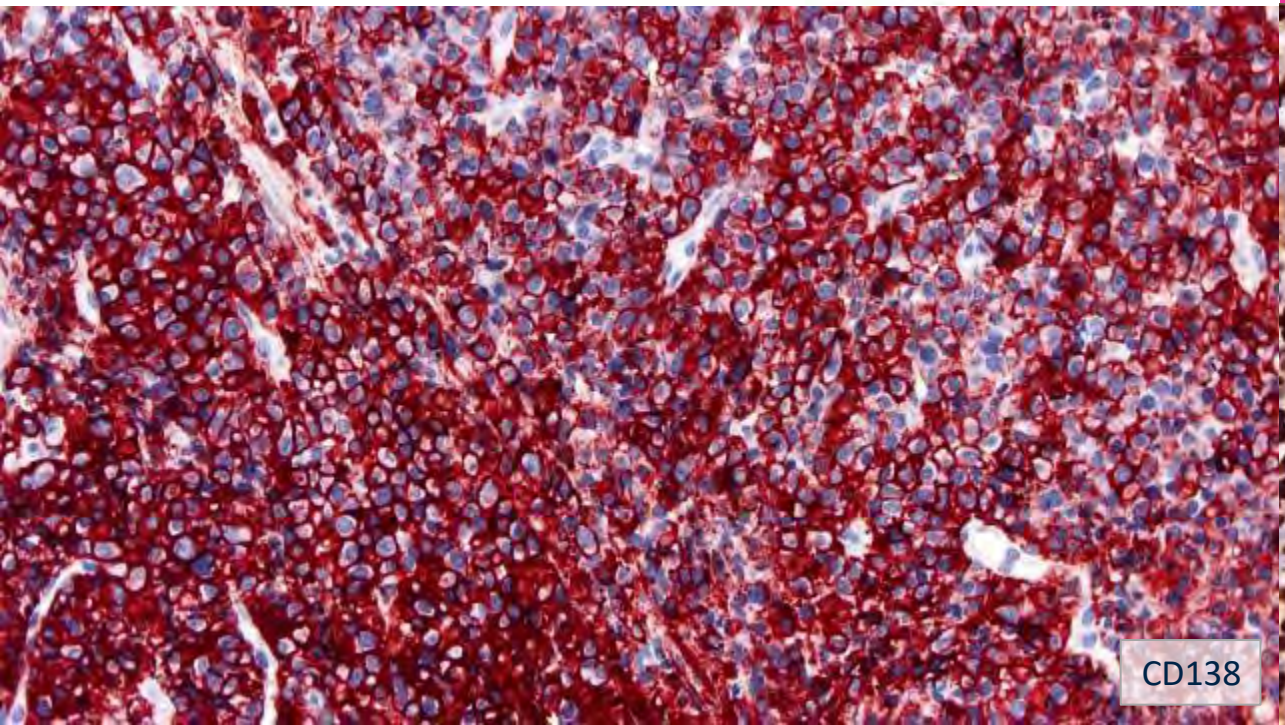
(Consultation Dr. Cota, Roma)

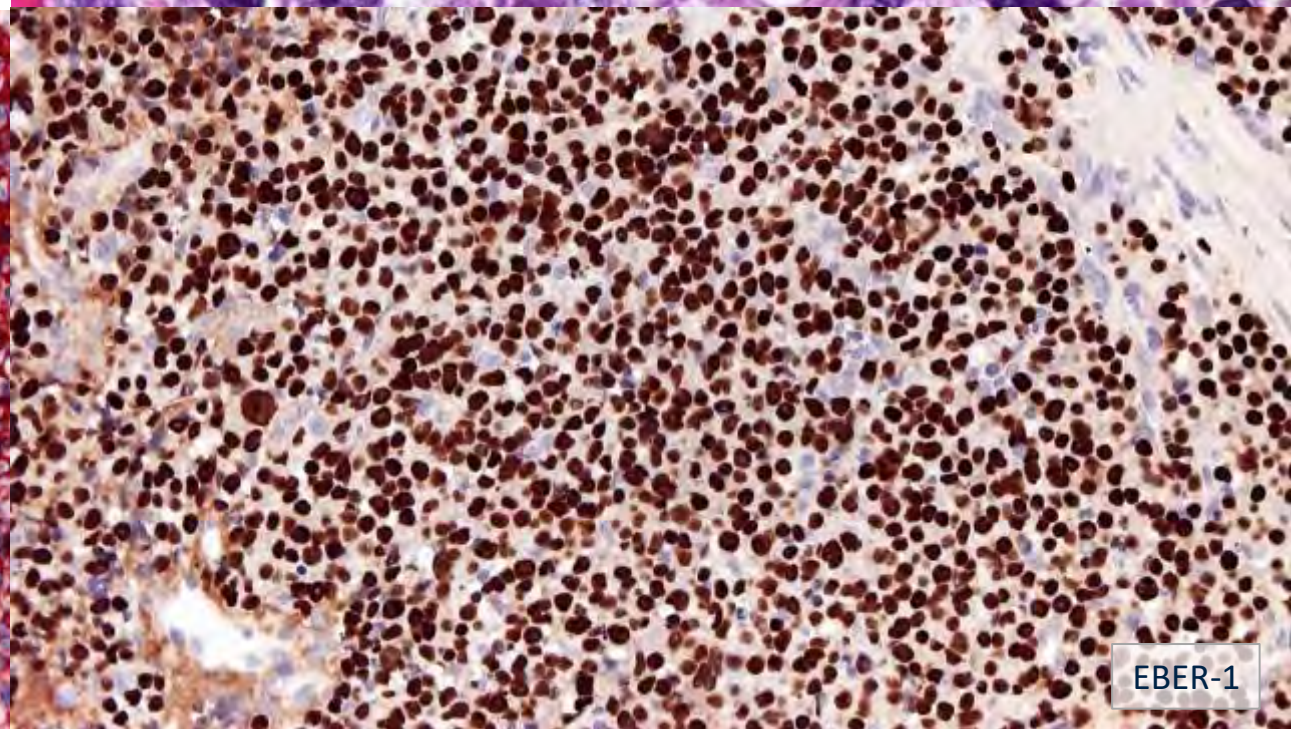

CD138
CD3
EBER-1
HHV-8
CD20
CD38
lambda
kappa

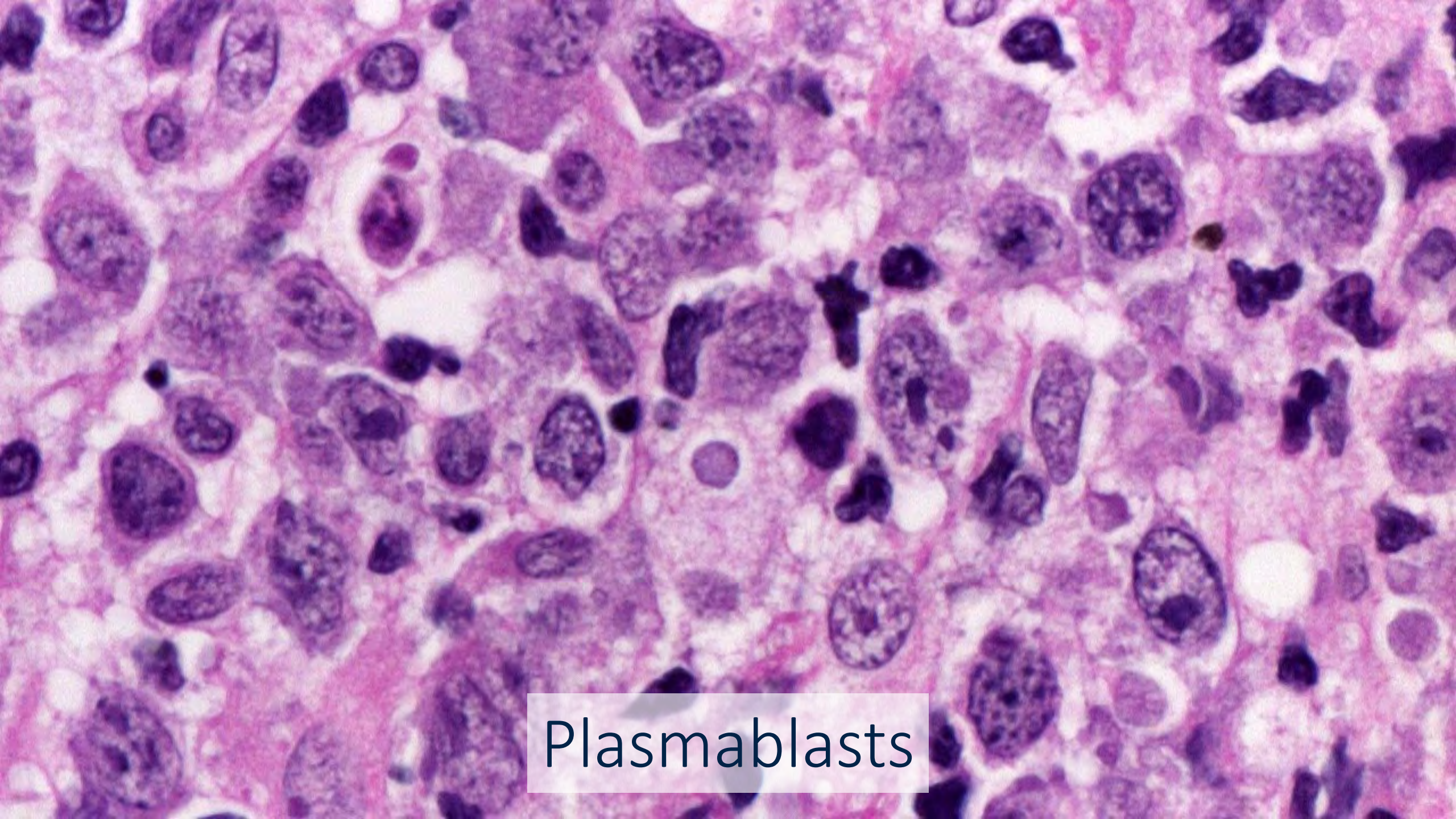


M, 60. History of lung Tx 4 years before.



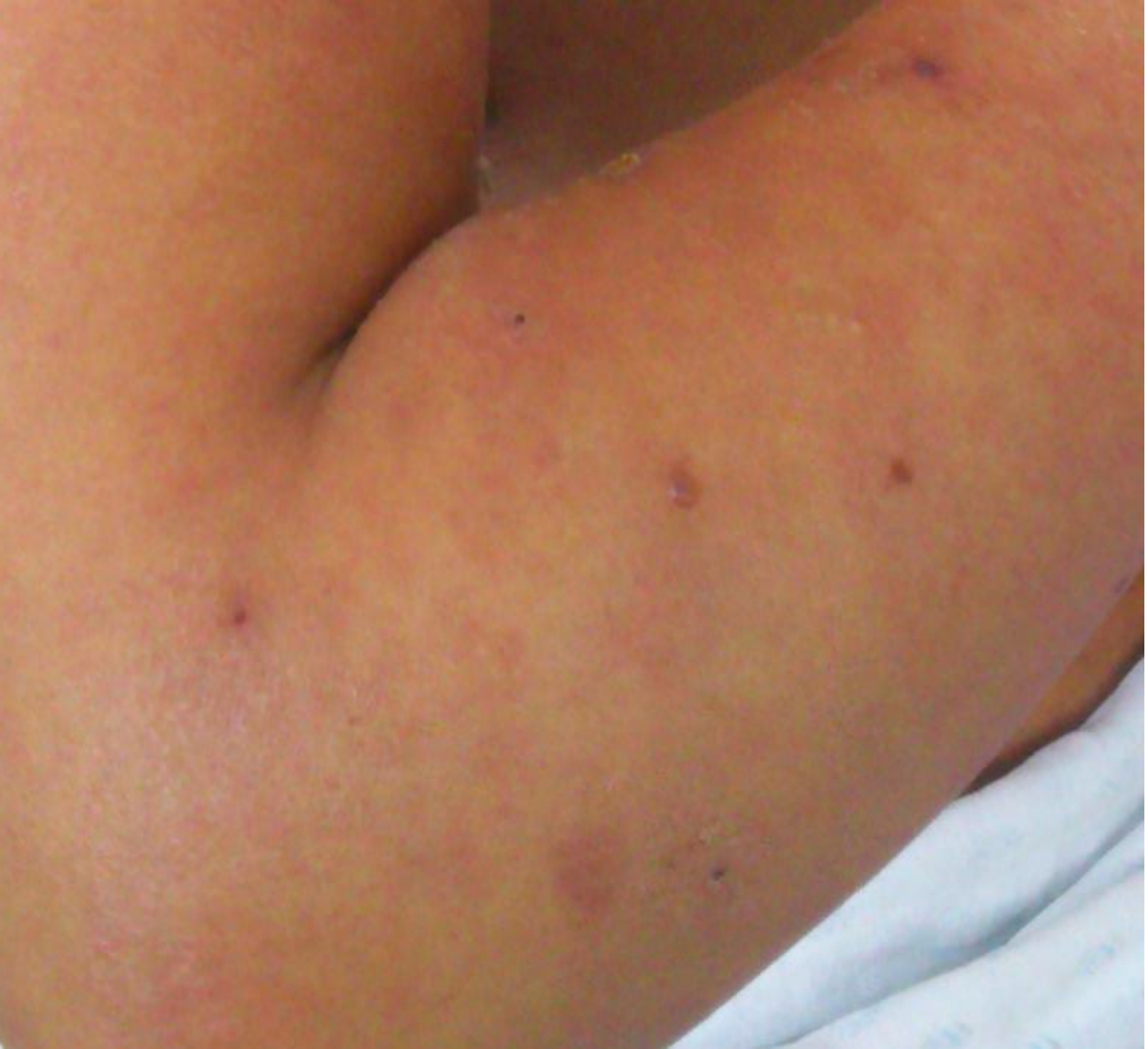





Plasmablasts

Systemic hydroa vacciniforme lymphoproliferative disorder

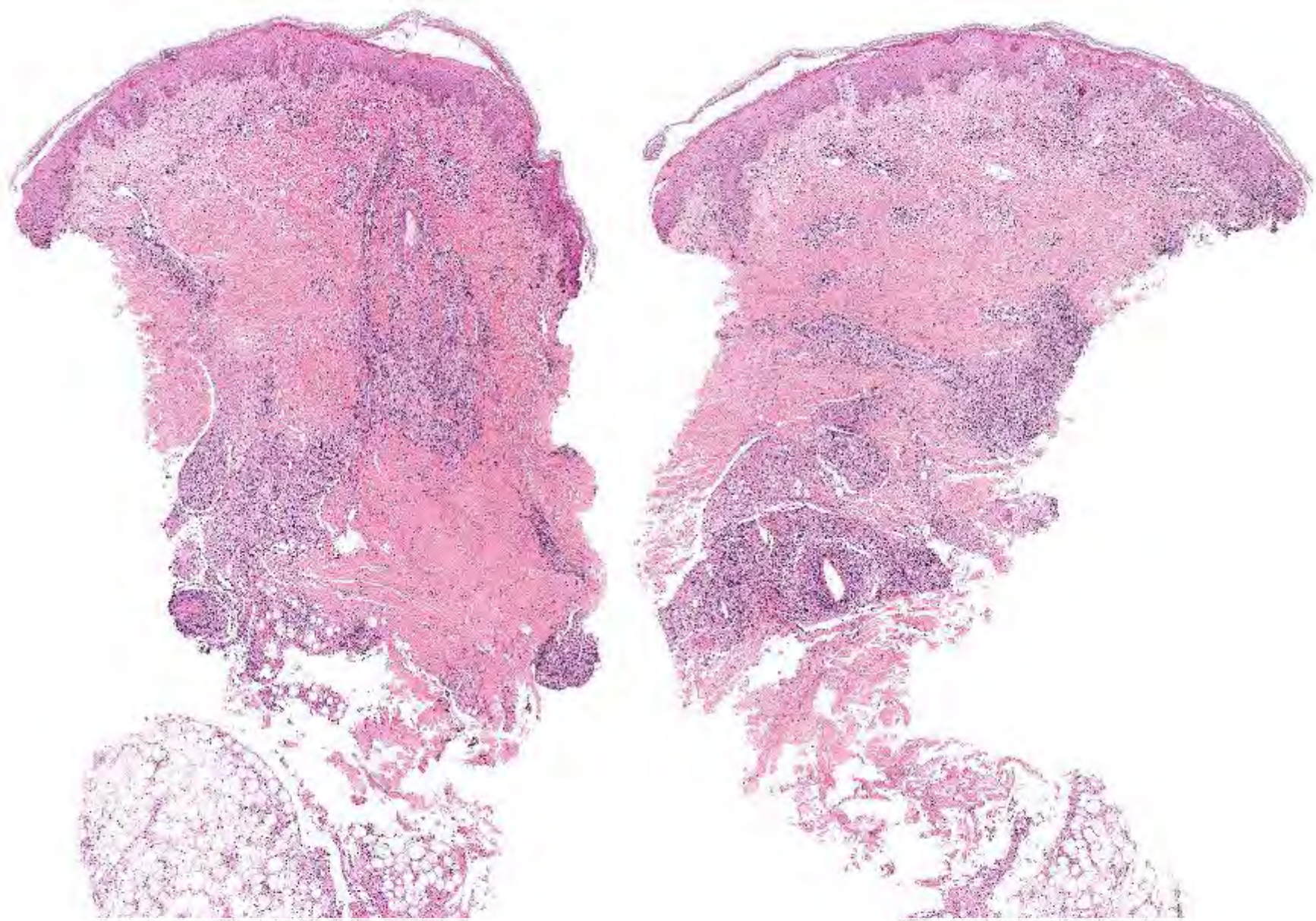
- Included among the *cutaneous manifestations in Epstein-Barr virus-positive T-cell and NK-cell lymphoid proliferations and lymphomas of childhood* in the International Consensus Classification (ICC) of Myeloid and Lymphoid Neoplasms and the 5th edition of the WHO Classification of Haematolymphoid Tumours; classic hydroa vacciniforme considered as part of the same spectrum, which includes also severe mosquito bite allergy
- *Essential diagnostic criteria:* Neoplastic T-cells positive for EBV
- *Main differential diagnoses:* Extranodal NK/T-cell lymphoma, nasal-type; other cutaneous cytotoxic lymphomas
- Consider this diagnosis only in the proper ethnical background (East Asia - Japan, Taiwan, China, and South Korea, Mexico, some other Central American and South American countries)
- Relationship to classic hydroa vacciniforme unclear *(my opinion)*

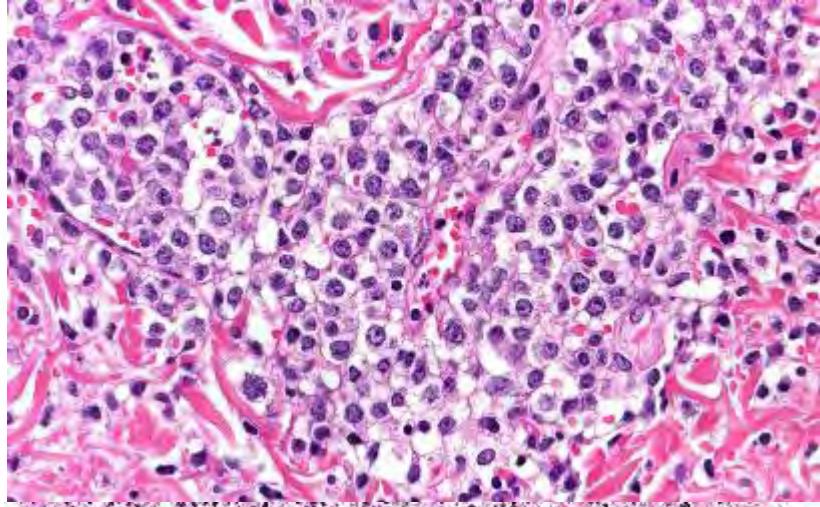


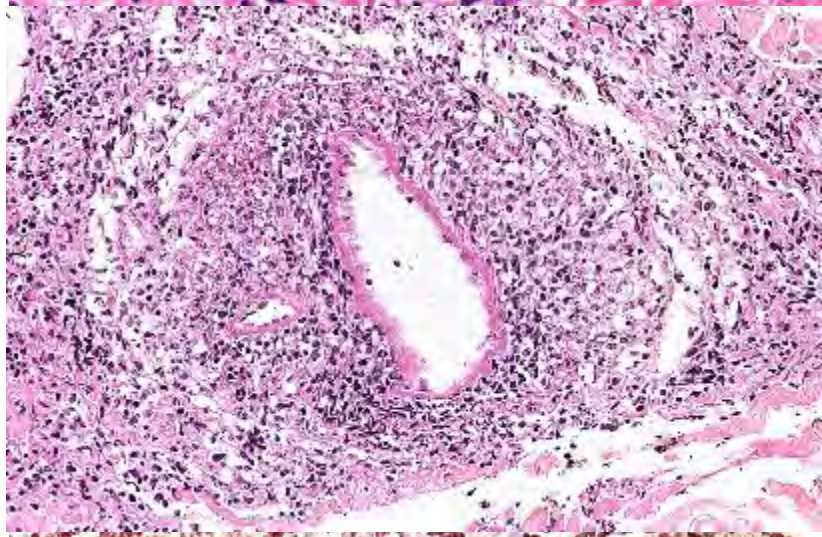
M, 12

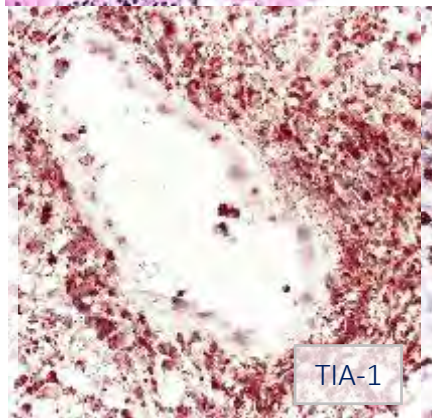
Long history of partly ulcerated lesions located mostly on sun-exposed areas.

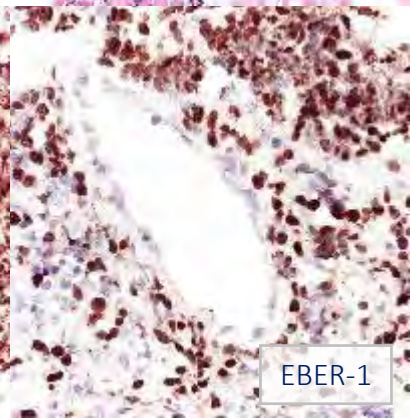
A biopsy is taken.





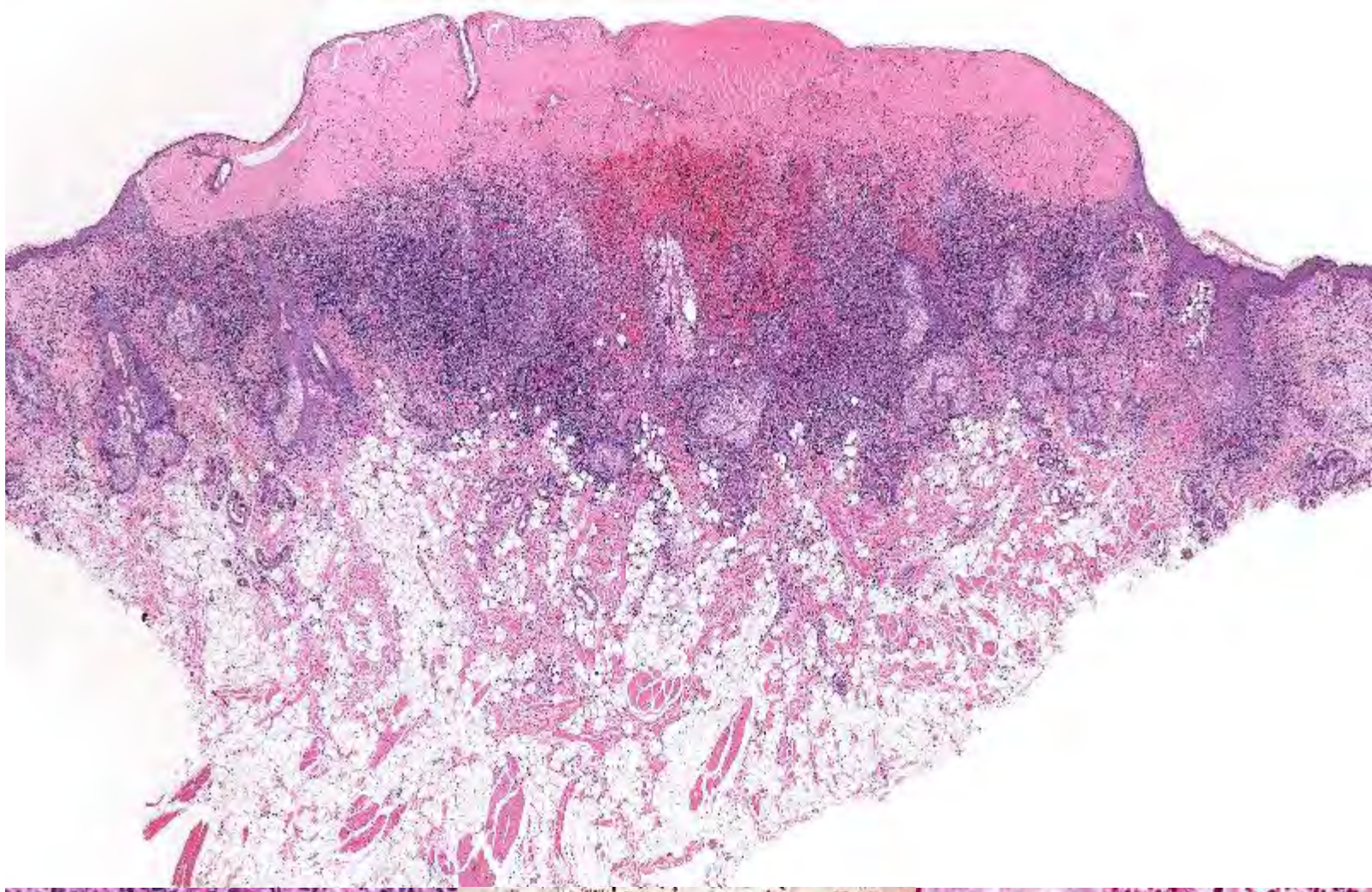


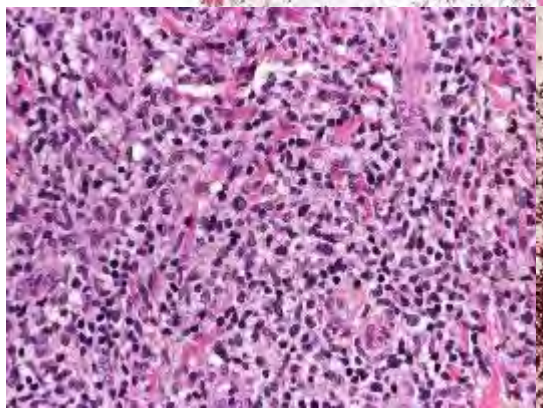


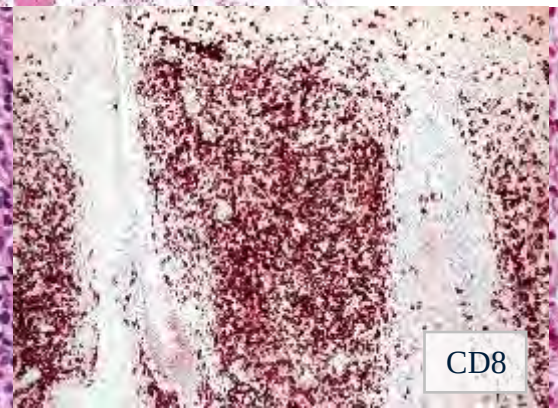


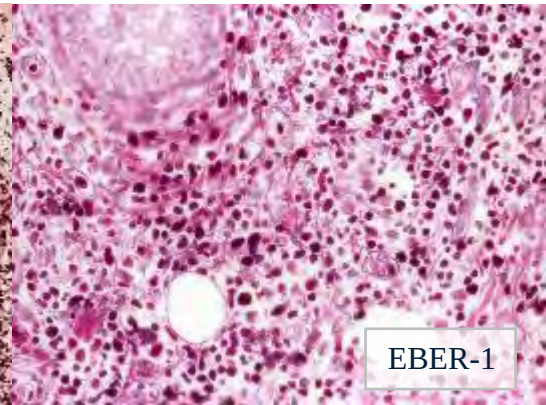
Systemic hydroa vacciniforme lymphoproliferative disorder (hydroa-like lymphoma)

F, 23

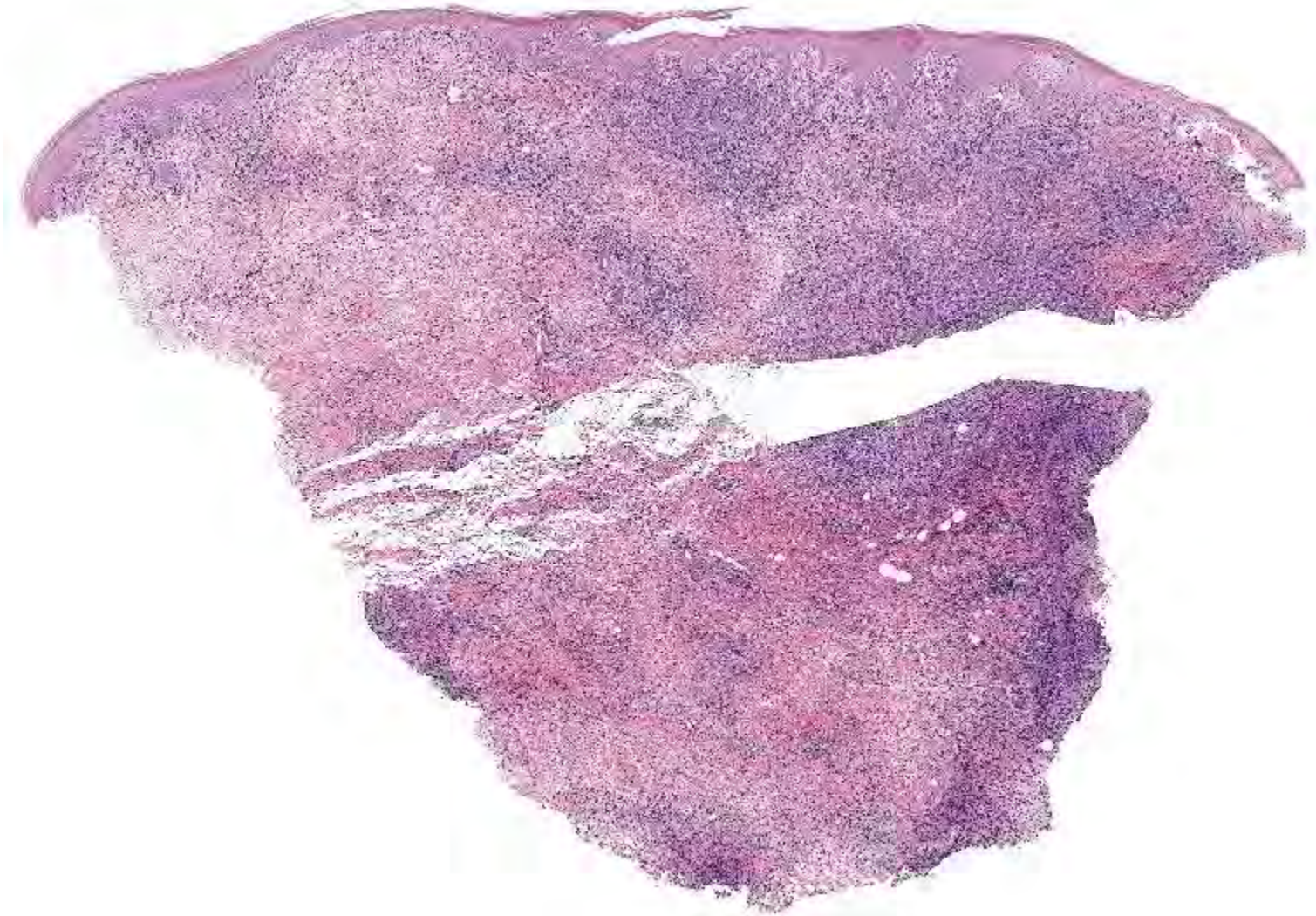


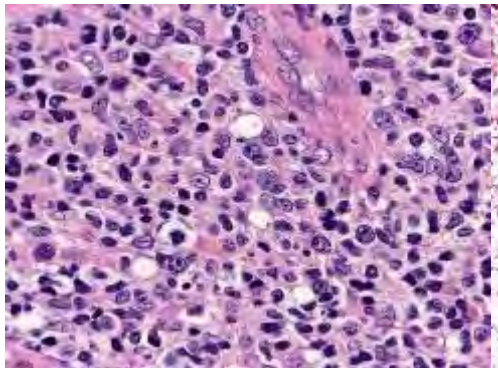


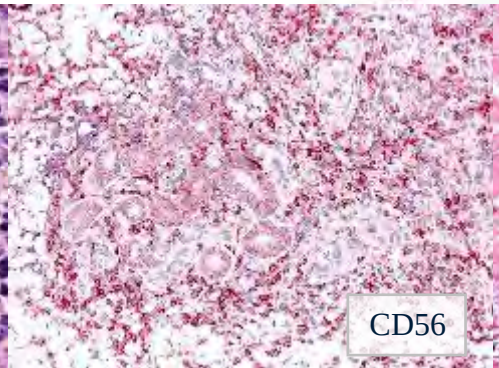


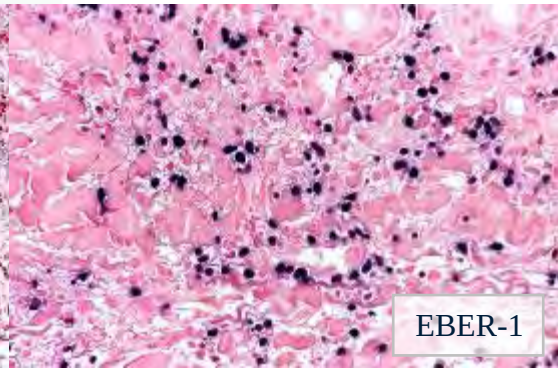


F, 16









Clinicopathologic Features of Hydroa Vacciniforme–Like Lymphoma: A Series of 9 Patients

Mario Magaña, MD, Cesare Massone, MD,†*
Pablo Magaña, MD, and Lorenzo Cerroni, MD†*

Abstract: Hydroa vacciniforme–like lymphoma is a recently recognized cutaneous T-cell lymphoma associated with Epstein–Barr virus. The disease is observed in children of Latin American or Asian ethnicity. The authors report the clinical, histopathological, and immunophenotypical features of 9 new Mexican patients (M:F = 2:1; mean age, 14.5 years; median age, 13.3 years; age range, 4–27 years), expanding on previous observations of this elusive disease. The most common clinical aspects were persistent facial edema with necroses and pitted scars. Histopathological analyses revealed variably dense lymphoid infiltrates with common angiodestructive features. Neoplastic cells expressed CD3 and cytotoxic markers in all cases and were constantly positive for Epstein–Barr virus (EBER-1). Expression of other markers was variable. Follow-up data revealed that all patients died within 6 months or less, thus showing a very aggressive course with poor prognosis.

Key Words: hydroa-like lymphoma, hydroa vacciniforme–like cutaneous T-cell lymphoma, angiocentric cutaneous T-cell lymphoma of childhood, Epstein–Barr virus, hydroa vacciniformis, cutaneous T-cell lymphoma

(*Am J Dermatopathol* 2016;38:20–25)

INTRODUCTION

Hydroa vacciniforme–like lymphoma (HVLL), originally described in 1998 as "angiocentric cutaneous T-cell lymphoma (CTCL) of childhood,"[1] is an Epstein–Barr virus (EBV)–driven lymphoproliferative disease that involves children and young adults of Latin American and Asian descent.[1–5] In the World Health Organization (WHO)–European Organization for Research and Treatment of Cancer (EORTC) classification of primary cutaneous lymphomas, HVLL was considered as a variant of the extranodal NK/T-cell lymphoma nasal type.[6] In the 2008 WHO classification of hematological neoplasms, HVLL is recognized as a distinctive clinicopathologic type of cutaneous lymphoma, included in the group of EBV+ T-cell lymphoproliferative disorders of childhood.[7] Several studies on clinicopathologic, phenotypic, and molecular features of HVLL have been published.[8–14]

HVLL was initially interpreted as an association of hydroa vacciniforme (HV) and non-Hodgkin lymphoma[15,16] or as an inflammatory disorder.[2] Nowadays, it is clear that it represents a primary CTCL with a prolonged but usually fatal course.[6,7,17] In this article, we studied the clinicopathologic and phenotypic features of 9 additional patients with HVLL, reporting interesting features that expand on the knowledge about this rare and peculiar disease.

MATERIALS AND METHODS

We searched the electronic database of the Centre for Dermatology & Dermatopathology in Mexico City, and found 11 cases of HLL that were received as consultation by one of us (M.M.) from 2000 to 2014. Two additional cases were seen at the Hospital General de México "Eduardo Liceaga," Mexico City. Among these 13 cases, only those with available clinical record, one or more skin specimens with sufficient tissue for ancillary studies, and available clinical pictures were included in the study. Nine cases fulfilled these criteria. The other 4 cases were excluded because of lack of appropriate clinical and/or follow-up data or tissue available for study. A total of 11 biopsy specimens from these 9 patients were available. All skin specimens were fixed in 10% buffered formalin, routinely processed and embedded in paraffin. Hematoxylin and eosin (H&E)–stained sections with a thickness of 4 μm were studied for standard histopathologic analysis. In all cases, the diagnosis of HVLL was made according to criteria listed in the WHO classification.[7] In every case, the original histopathological sections were reviewed by at least 2 authors (M.M., L.C.). Immunohistochemical and molecular analyses and in situ hybridization for EBV were performed at the Research Unit Dermatopathology, Department of Dermatology, Medical University of Graz, Austria.

For immunohistochemical studies, sections were stained with monoclonal antibodies against CD2, CD3, CD4, CD5, CD56 (Novocastra), CD8, CD20, CD30, KI67 (Dako), TIA-1 (Immunotech), Granzyme-B (Monosan), BetaF1 (Endogen), T-cell receptor gamma (Thermo Scientific), and PD-1 (Abcam). Positive controls were done on tonsil tissue; for negative controls, the primary antibody was omitted.

Polymerase chain reaction analysis to evaluate TCR gene rearrangement was performed on 7 biopsies according to the BIOMED-2 protocol. EBV in situ hybridization (EBER-1)

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The authors declare no conflicts of interest.

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9 Mexican patients
M:F = 2:1
Mean age, 14.5 years; median age, 13.3 years; age range, 4–27 years

Facial edema in all cases
No case with mosquito bite hypersensitivity
All cases with extracutaneous involvement at first diagnosis and survival <6 months

Always cytotoxic phenotype (TIA1+)
3 cases CD8+; 4 cases CD4-/CD8-; 2 cases CD8- with some CD4+ neoplastic cells

BJD
British Journal of Dermatology

Survival rates and prognostic factors of Epstein–Barr virus-associated hydroa vacciniforme and hypersensitivity to mosquito bites

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Summary

Background Epstein-Barr virus (EBV)-associated T/natural-killer lymphoproliferative disorders form a group of diseases that includes classical and systemic hydroa vacciniforme (HV) and hypersensitivity to mosquito bites (HMB). Patients with systemic HV (sHV) and HMB often have a poor prognosis, although little is known about the prognostic factors.
Objectives To elucidate the prognostic factors of HV and HMB.
Methods We studied clinicopathological manifestations, routine laboratory findings, anti-EBV titres, EBV DNA load and EBV-encoded gene expression, including expression of BZLF1, in 50 patients with classical HV (cHV), sHV, HMB only and HMB with HV (HMB + HV), and further analysed 30 patients who were available for follow-up.
Results The median age of disease onset was 5 years (range 1–74). A follow-up study indicated that fatal outcomes were observed in three of eight patients with sHV, two of six patients with HMB only, and two of five patients with HMB + HV. The main causes of death were complications from haematopoietic stem-cell transplantation and multiorgan failure. There were no fatalities among the 11 patients with cHV. Univariate analysis revealed two poor prognostic indicators: (i) onset age > 9 years and (ii) the expression of an EBV-encoded immediate–early gene transcript, BZLF1 mRNA, in the skin lesions ($P < 0{\cdot}001$ and $P = 0{\cdot}003$, respectively).
Conclusions No prognostic correlation was observed in EBV-infected lymphocyte subsets, anti-EBV antibody titres or EBV DNA load. Late onset and EBV reactivation are both related to more severe phenotypes of the disease, and thus may predict a poor prognosis.

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Conflicts of interest
None declared.

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What's already known about this topic?

- Epstein–Barr virus-associated T/natural-killer lymphoproliferative disorders form a group of diseases that includes classical and systemic hydroa vacciniforme (HV), and hypersensitivity to mosquito bites (HMB).
- Patients with systemic HV and HMB usually present with fever, liver damage and haematological abnormalities, and often have a fatal outcome.

What does this study add?

- Our patients with classical HV showed a favourable prognosis, while approximately one-third of the patients with systemic HV or HMB died during the 10-year follow-up.
- Late onset (over 9 years of age) and an EBV reactivation signal (BZLF1 mRNA expression) were both related to more severe phenotypes of the disease, and a poor prognosis.

A follow-up study indicated that fatal outcomes were observed in three of eight patients with systemic hydroa vacciniforme, two of six patients with hypersensitivity to mosquito bites only, and two of five patients with hypersensitivity to mosquito bites + hydroa vacciniforme.

Hydroa Vacciniforme–Like Lymphoma With Primarily Periorbital Swelling: 7 Cases of an Atypical Clinical Manifestation of this Rare Cutaneous T-Cell Lymphoma

Jose A. Plaza, MD and Martin Sangueza, MD†*

Abstract: Hydroa vacciniforme–like lymphoma (HVL) is a rare cutaneous T-cell lymphoma that is usually seen in children of Hispanic or Asian origin. Association between chronic latent Epstein–Barr virus infection in both hydroa vacciniforme (HV) and HVL has been demonstrated and has recently been categorized by the World Health Organization as one of the Epstein Barr virus–positive lymphoproliferative disorders of childhood. Patients with HVL present with a cutaneous rash characterized by edema, blisters, ulcers, and scars mainly seen on the face and extremities that mimic HV; however, unlike in HV, the lesions tend to be extensive and deeper and are associated with severe scarring, necrosis, and systemic manifestations. We are reporting 7 cases of an unusual clinical variant of HVL with primarily periorbital edema. All of our patients in this series presented with progressive periorbital edema that was accompanied with systemic symptoms including fever, malaise, and lymphadenopathy. Most cases were initially misinterpreted as inflammatory processes including cellulitis, arthropod bite reactions, and periorbital lupus erythematosus. The biopsy of these lesions revealed an atypical lymphocytic infiltrate predominantly distributed in the deep dermis and in subcutaneous fat. Immunohistochemistry studies revealed a cytotoxic T-cell ($CD8^+$) profile. All cases were associated with Epstein–Barr virus infection. Our study presents a rare clinical variant of HVL with predominant periorbital edema. This variant could potentially be overlooked and misdiagnosed as an inflammatory condition; thus, it needs to be included in the differential diagnosis of periorbital edema in young patients.

Key Words: cutaneous T-cell lymphoma, cytotoxic lymphomas, Epstein–Barr virus, Epstein–Barr virus–associated lymphoma, hydroa vacciniforme, hydroa vacciniforme–like lymphoma

(*Am J Dermatopathol* 2015;37:20–25)

INTRODUCTION

Hydroa vacciniforme–like lymphoma (HVL) is an Epstein–Barr virus (EBV)-driven cutaneous cytotoxic T-cell lymphoma occurring in children and adolescents from Asia, Central, and South America.[1] In the updated World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues (2008), HVL has been recognized as one of the EBV-positive lymphoproliferative disorders of childhood.[2] Since the inclusion of HVL in the WHO lymphoma classification, several interesting points have been raised, including whether HVL represents a true lymphoma from its initial clinical manifestation, a preneoplastic disorder with the risk of developing into a systemic lymphoma, or an aggressive lymphoma that develops in patients with long-standing hydroa vacciniforme (HV).[1,3–6] The severity and the clinical presentation of the skin lesions in HVL vary among patients.[1,7] Clinically, classic examples of HVL usually present with vesicles, blisters, erythema, ulcerations, crusts, vacciniforme scars, and edema mainly involving the face and upper extremities.[4,8] Patients often presented with severe, deep skin lesions with disfiguring scars in both nonexposed and sun-exposed areas. Systemic symptoms such as fever, hepatosplenomegaly, and lymphadenopathy are common.

Here, we report 7 cases of HVL with unusual clinical presentation predominantly involving the periorbital area, highlighting their salient and distinctive clinical, histological, and immunohistological features. To the best of our knowledge, this is the first series of HVL-affected patients reported with such an unusual clinical presentation.

MATERIALS AND METHODS

Seven cases of HVL with primarily periorbital involvement formed the basis of our study. All cases were collected at the Department of Dermatology and Pathology at Hospital Obrero, La Paz, Bolivia, and were seen in consultation at the Medical College of Wisconsin. The study included 2 females and 5 males, aged 9–17 years. Clinical data and follow-up information were obtained from the hospital and private office records. The study was approved by the Medical College of Wisconsin Institutional Review Board Committee.

All tissues were fixed in neutral buffered formalin and embedded in paraffin for histologic processing. Tissue sections were stained with hematoxylin and eosin (H&E) for conventional histology. From 1 to 5 histologic sections stained with H&E were analyzed in each case. Immunohistochemical staining was performed in a DAKO autostainer using a standard ABC method (avidin–biotin peroxidase complex technique). Heat-induced epitope retrieval was applied as pretreatment for selected markers. The chromogen, diaminobenzidine, was used for antigen localization. The antibodies

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The authors declare no conflicts of interest.

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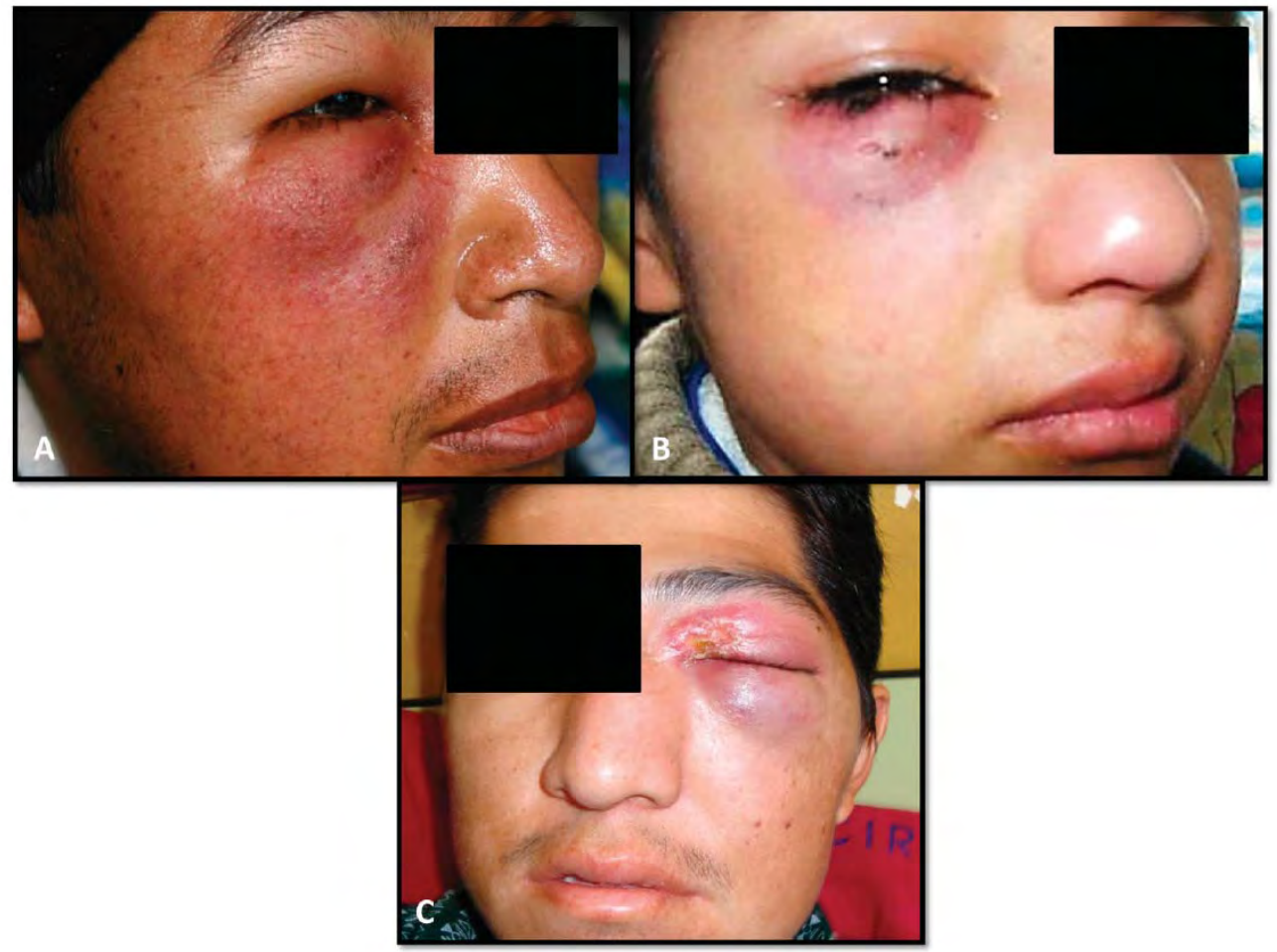
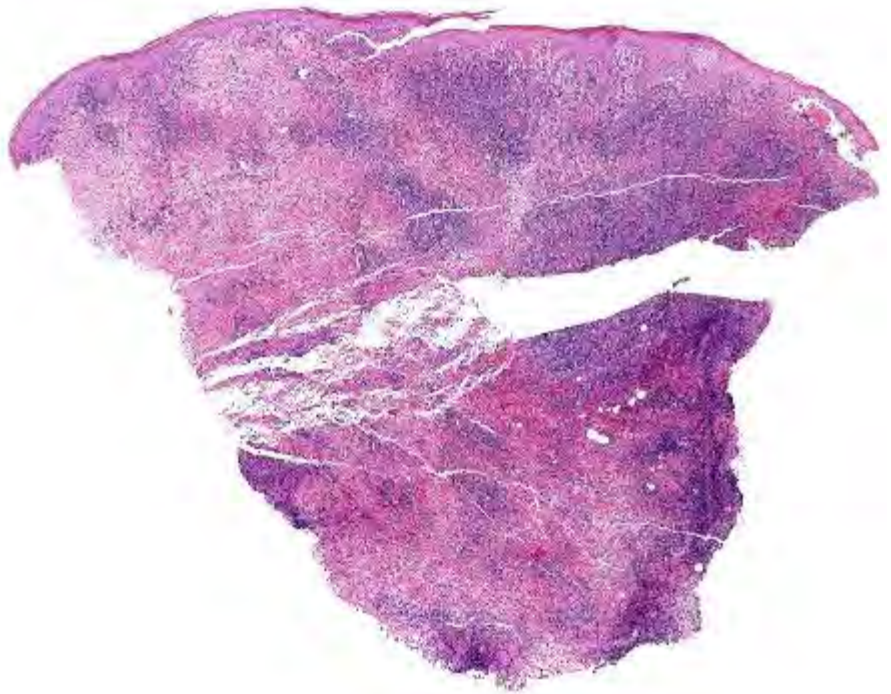
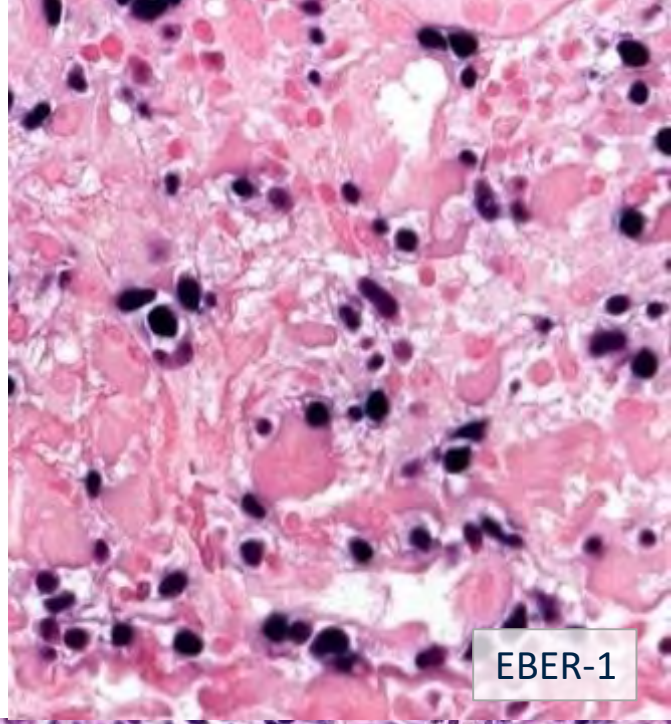
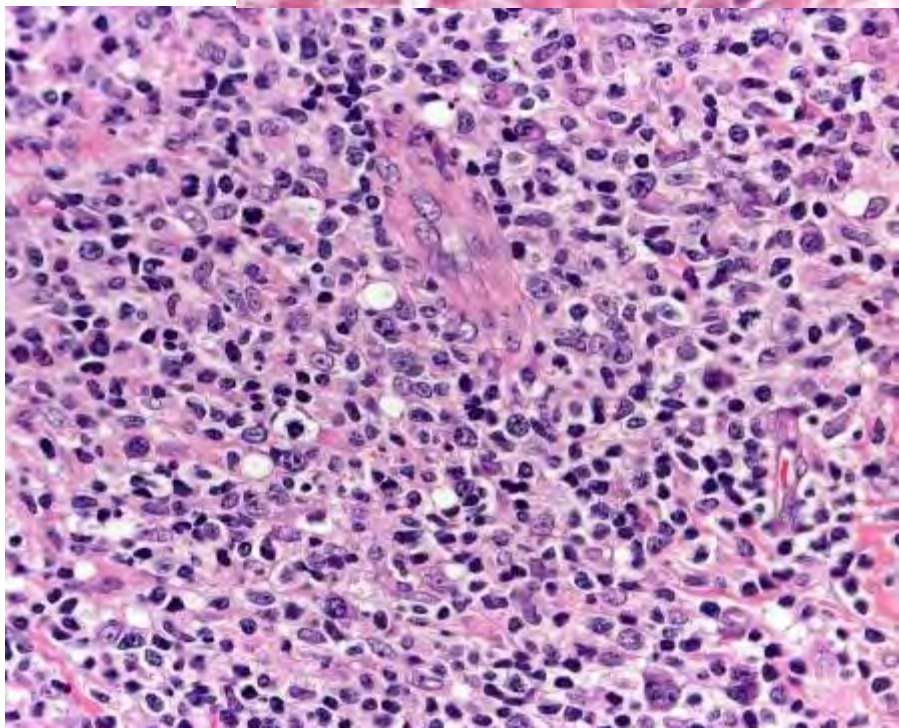






Systemic hydroa vacciniforme lymphoproliferative disorder

- WHO 2024: included in the group of EBV+ T/NK-cell lymphoid proliferations and lymphomas of childhood
- Spectrum of clinicopathologic presentations from classic hydroa vacciniforme to severe hydroa vacciniforme and to hydroa vacciniforme-like T-cell lymphoma; ethnical background plays a major role
- Hypersensitivity to sun and to mosquito bites
- Observed mainly in Asia, Mexico, Central- and South-America
- Primary cutaneous; variable clinical course but in HV-like T-cell lymphoma fatal outcome within 10-15 years



Aggressive cutaneous lymphomas

- A protean group of T-, NK- and B-cell lymphomas
- Some entities yet to be defined precisely (e.g., cutaneous peripheral T-cell lymphoma, NOS – may be termed CTCL, NOS in future classifications)
- Must be distinguished mostly from advanced stages of mycosis fungoides; in some case distinction difficult and/or arbitrary (e.g., cutaneous gamma/delta T-cell lymphoma)
- Distinction from secondary cutaneous lymphomas important, yet less relevant for management of the patients than in indolent cases
- Some entities related to immune deficiency (e.g., plasmablastic lymphoma)
- Systemic hydroa vacciniforme lymphoproliferative disorder (hydroa-like lymphoma) observed only in particular ethnicities