LYMPHOID, HISTIOCYTIC & DENDRITIC CELL PROLIFERATIONS IN SUPERFICIAL SOFT TISSUES

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LYMPHOID PROLIFERATIONS

Reactive

- Various types of lymphoid hyperplasia (pseudolymphomas, including IgG4-related sclerosing disease)
- Kimura disease
- Panniculitis
- Castleman disease

Lymphomatous

- Hodgkin lymphoma (very rare)
- T-cell and NK-cell lymphomas
- B-cell lymphomas

Commoner lymphomas of superficial soft tissues (WHO-EORTC, 2005)

Mycosis fungoides	44%
Lymphomatoid papulosis	12%
Primary cutaneous follicle center lymphoma	11%
Primary cutaneous anaplastic large cell lymphoma	8%
Primary cutaneous marginal zone lymphoma	7%
Primary cutaneous diffuse large B-cell lymphoma, leg-type	4%

Less common but distinctive lymphoma types of superficial soft tissues

- Intravascular large B-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Extranodal NK/T-cell lymphoma
- Cutaneous gamma-delta T-cell lymphoma
- CD8+ lymphoproliferative disorder of the ear
- CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
- CD4+ small/medium T-cell lymphoma
- B-lymphoblastic lymphoma

HISTIOCYTIC-DENDRITIC CELL PROLIFERATIONS

Reactive

- Various histiocytic infiltrates
- Mycobacterial spindle cell pseudotumor
- Xanthoma
- Rosai-Dorfman disease

Neoplastic

- Juvenile xanthogranuloma
- Reticulohistiocytoma
- Histiocytic sarcoma
- Langerhans cell histiocytosis/ sarcoma
- Indeterminate cell histiocytosis
- Follicular/ interdigitating dendritic cell tumor (rare)

NON-EPIDERMOTROPIC SMALL OR MIXED LYMPHOID INFILTRATES

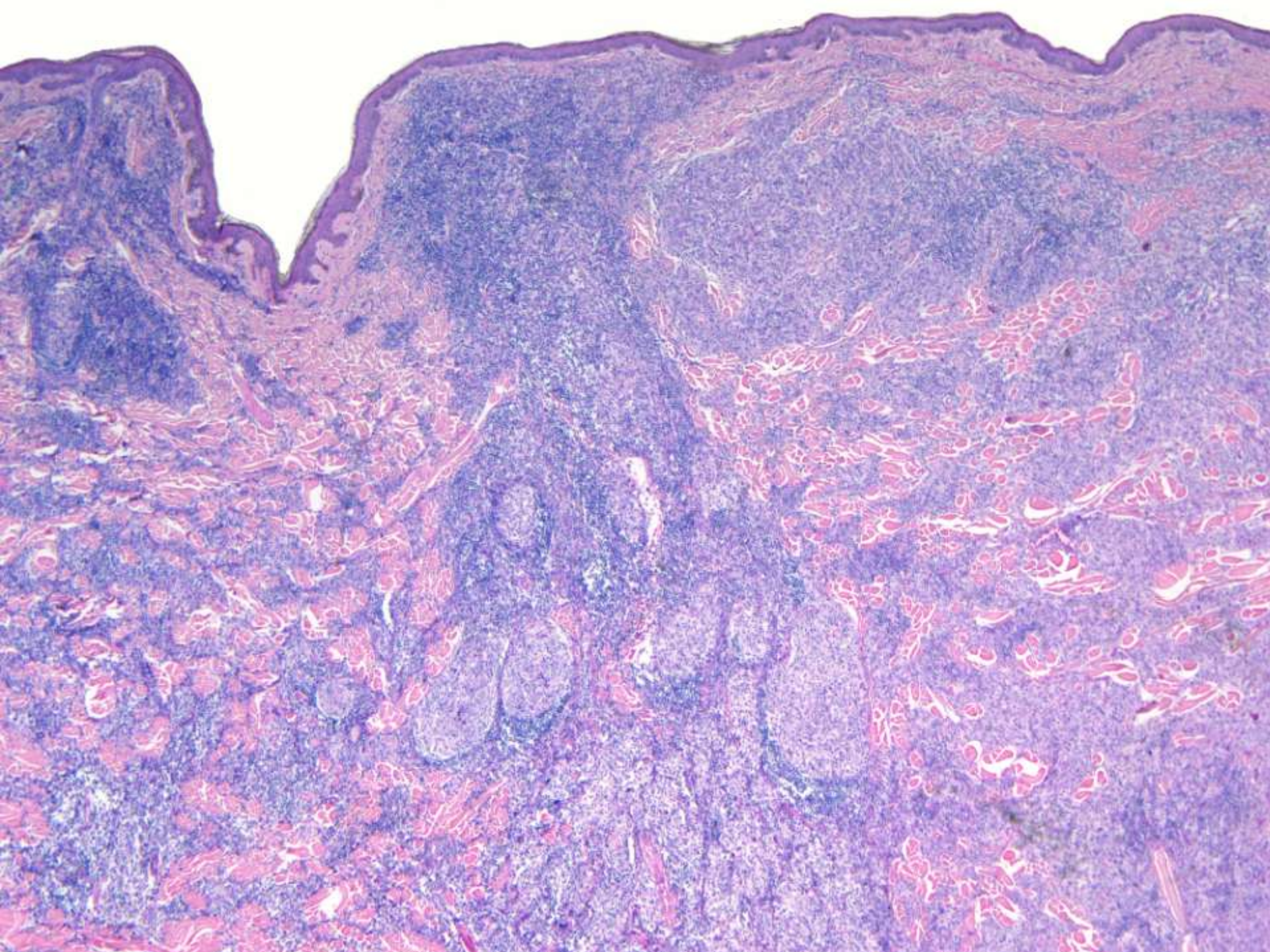
- Primary cutaneous follicle center lymphoma
- Primary cutaneous marginal zone lymphoma
- Lymphomatoid papulosis
- Various T-cell lymphomas, e.g. CD4+ small/medium T-cell lymphoma
- Various reactive lymphoid hyperplasias

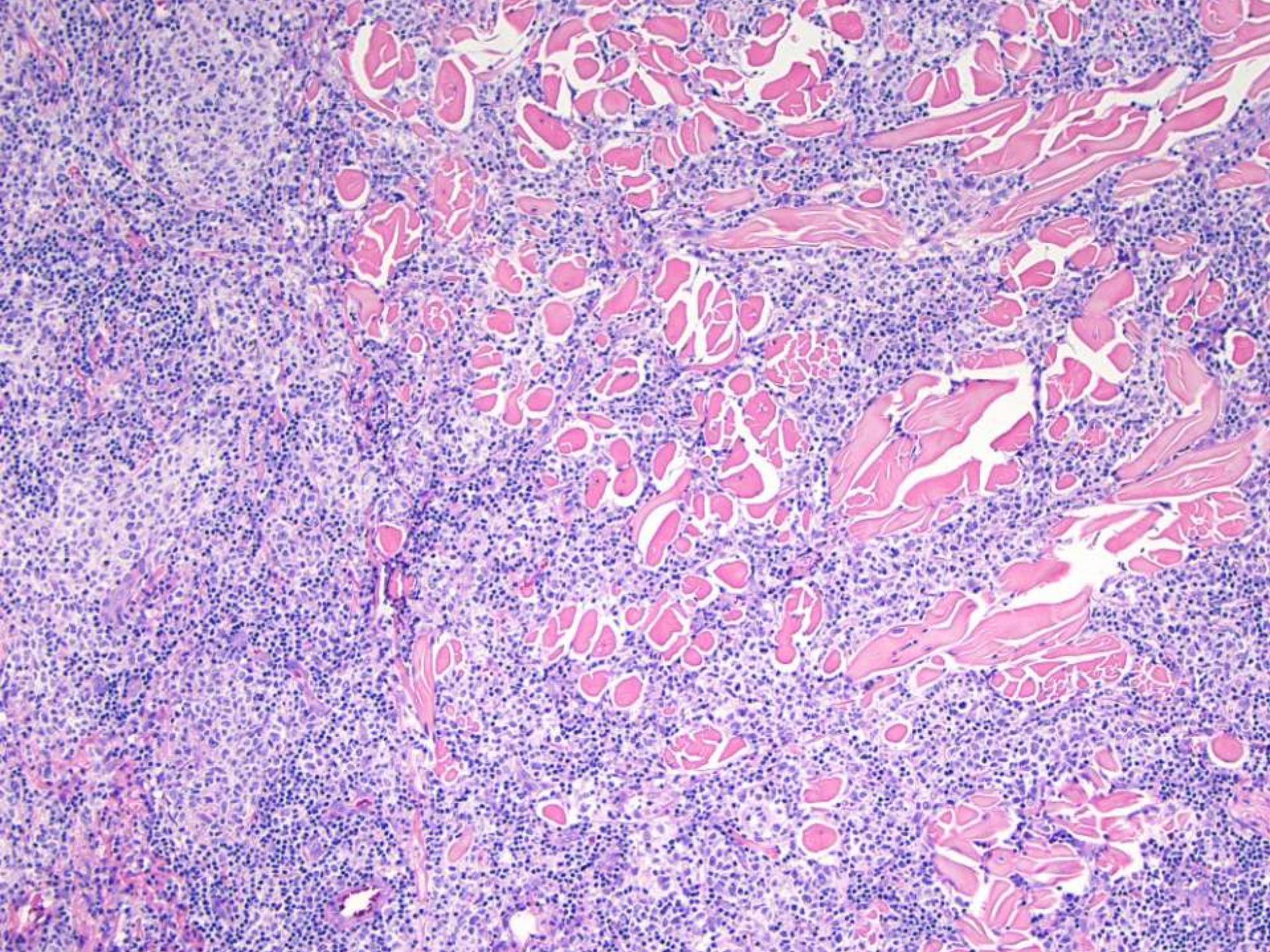
Primary cutaneous follicle center lymphoma

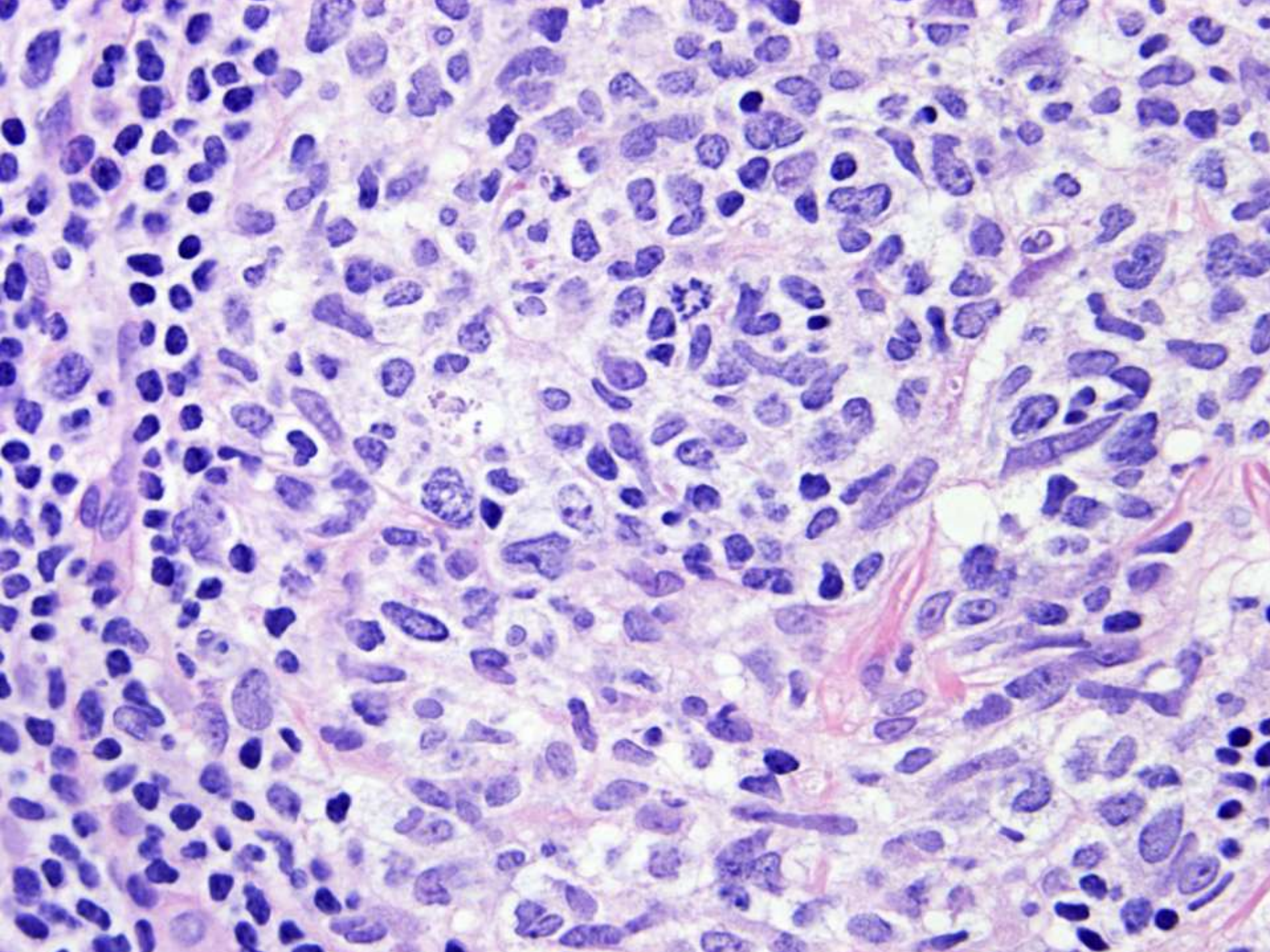
- Tumor of follicular center cells, comprising centrocytes (small or large) and variable numbers of centroblasts
- Presentation: Solitary or grouped plaques and tumors, preferentially on scalp, forehead or trunk
- Natural history: Gradual increase in size, but systemic dissemination rare
- Excellent prognosis. 5-yr survival ~95% (irrespective of number of large cells and growth pattern)

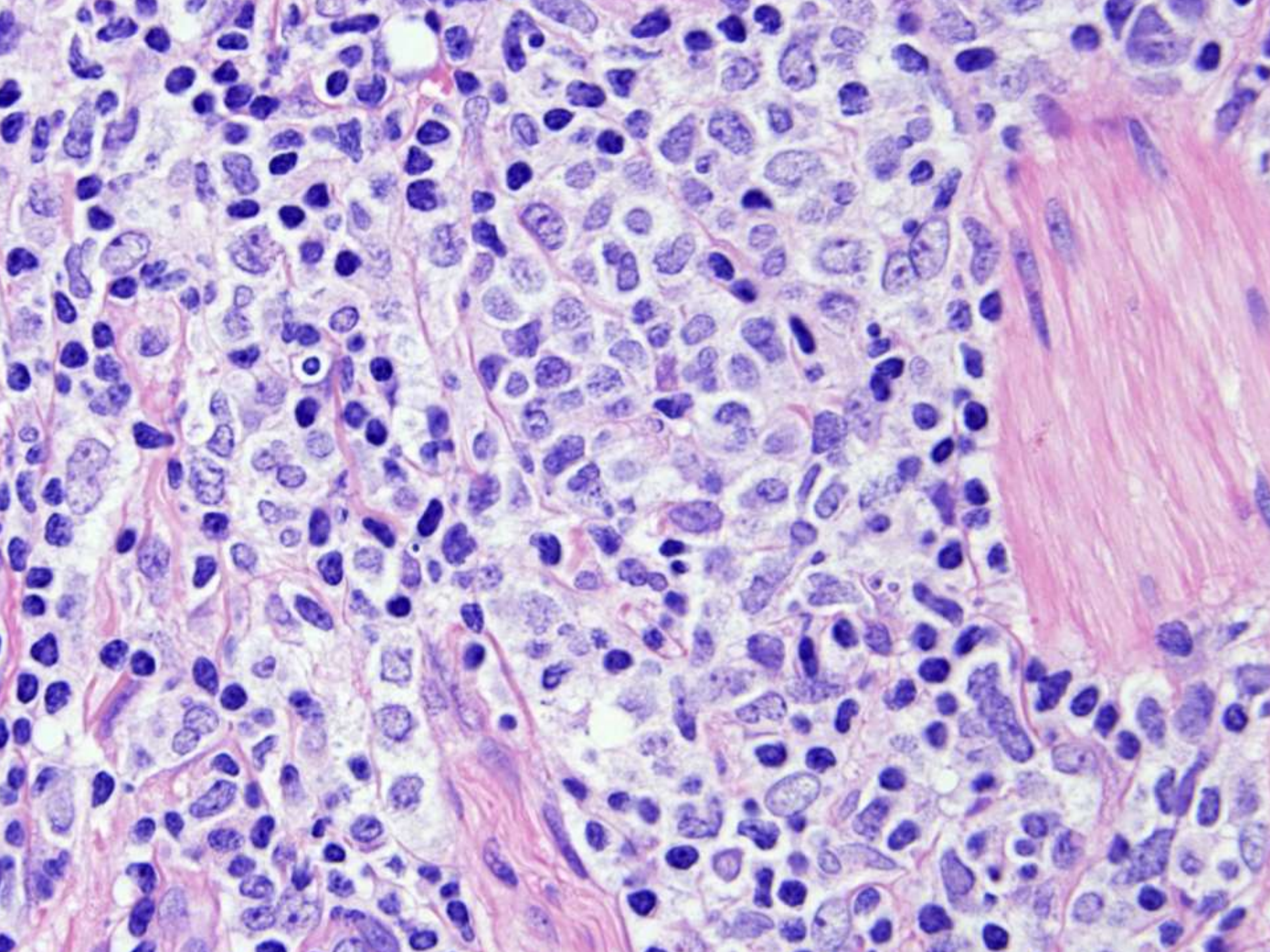
Primary cutaneous follicle center cell lymphoma: Pathology

- Follicular, follicular and diffuse, or diffuse non-epidermotropic growth
- Centrocytes, large centrocytes, centroblasts
- BCL6+, CD10+/-, BCL2-/weak
- *BLC2* gene rearrangement: variable (more commonly negative)

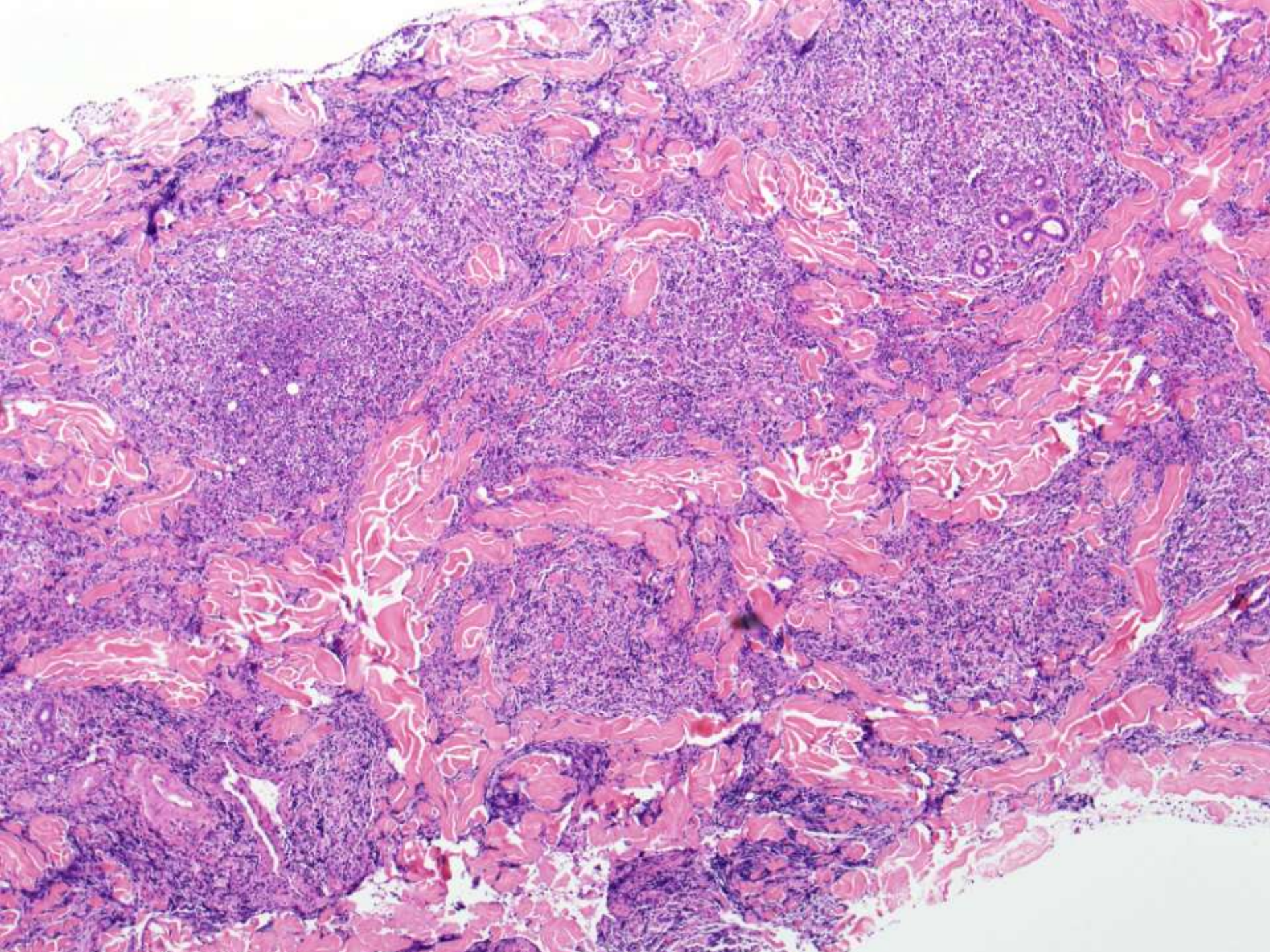


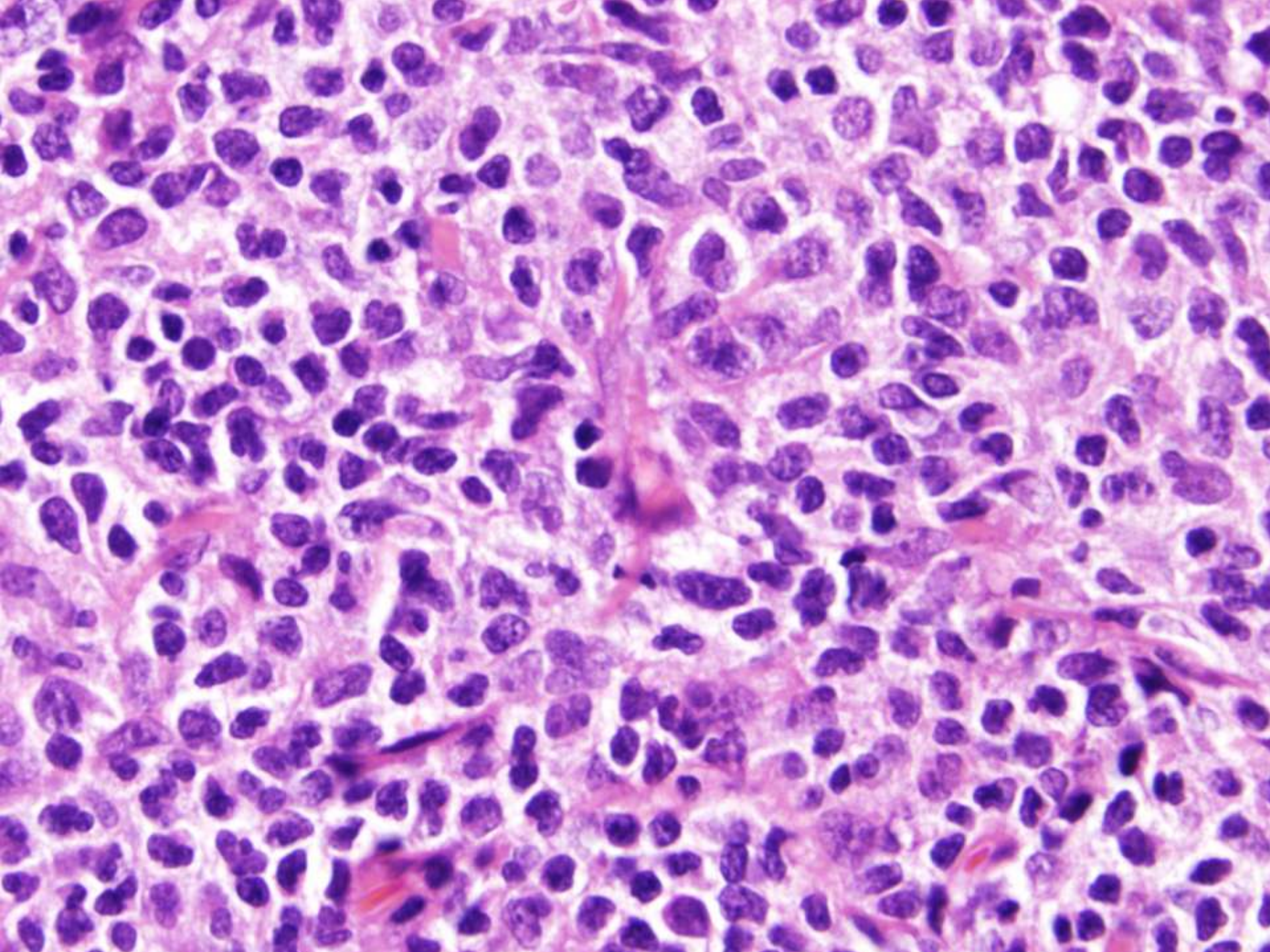


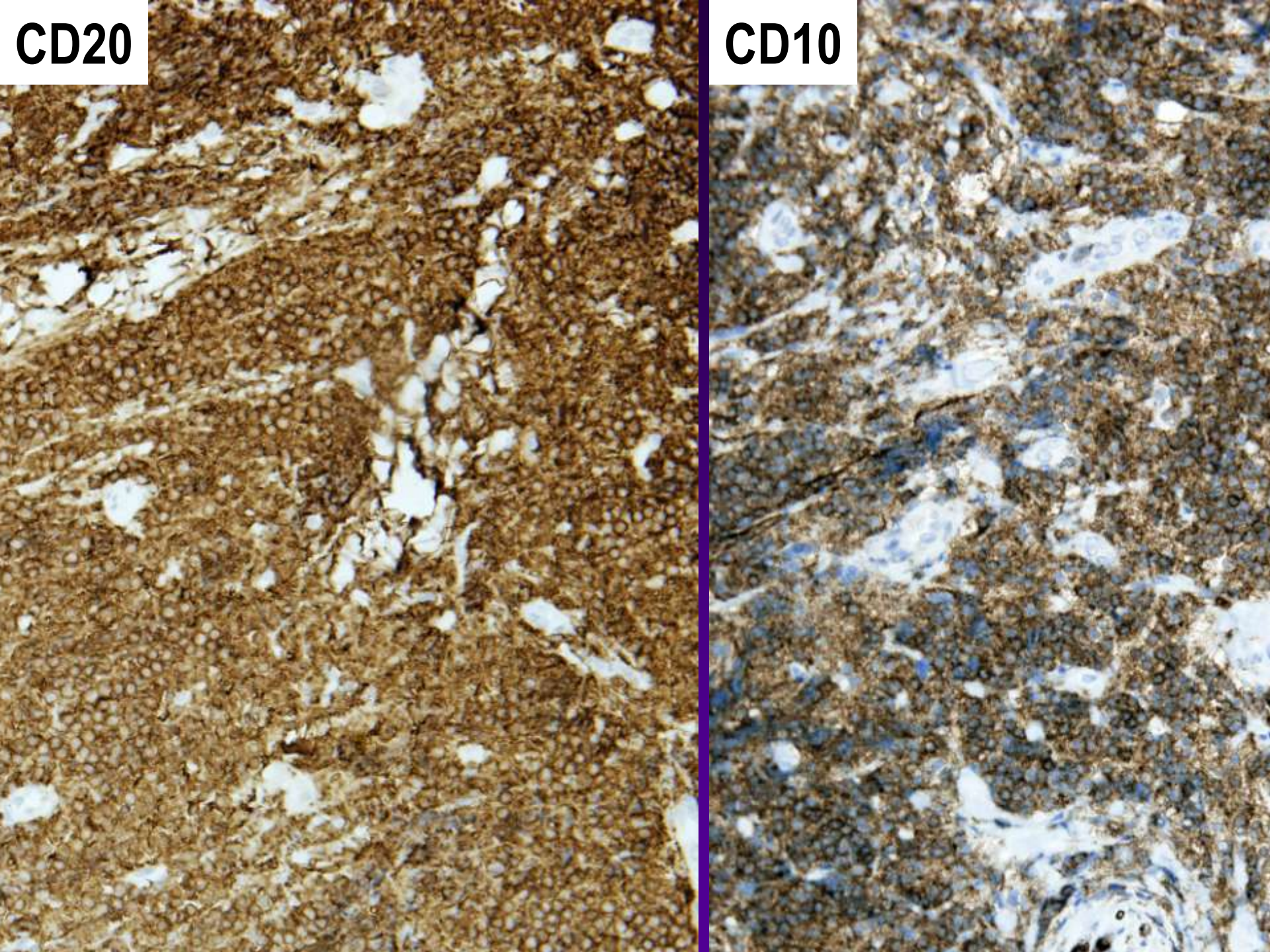


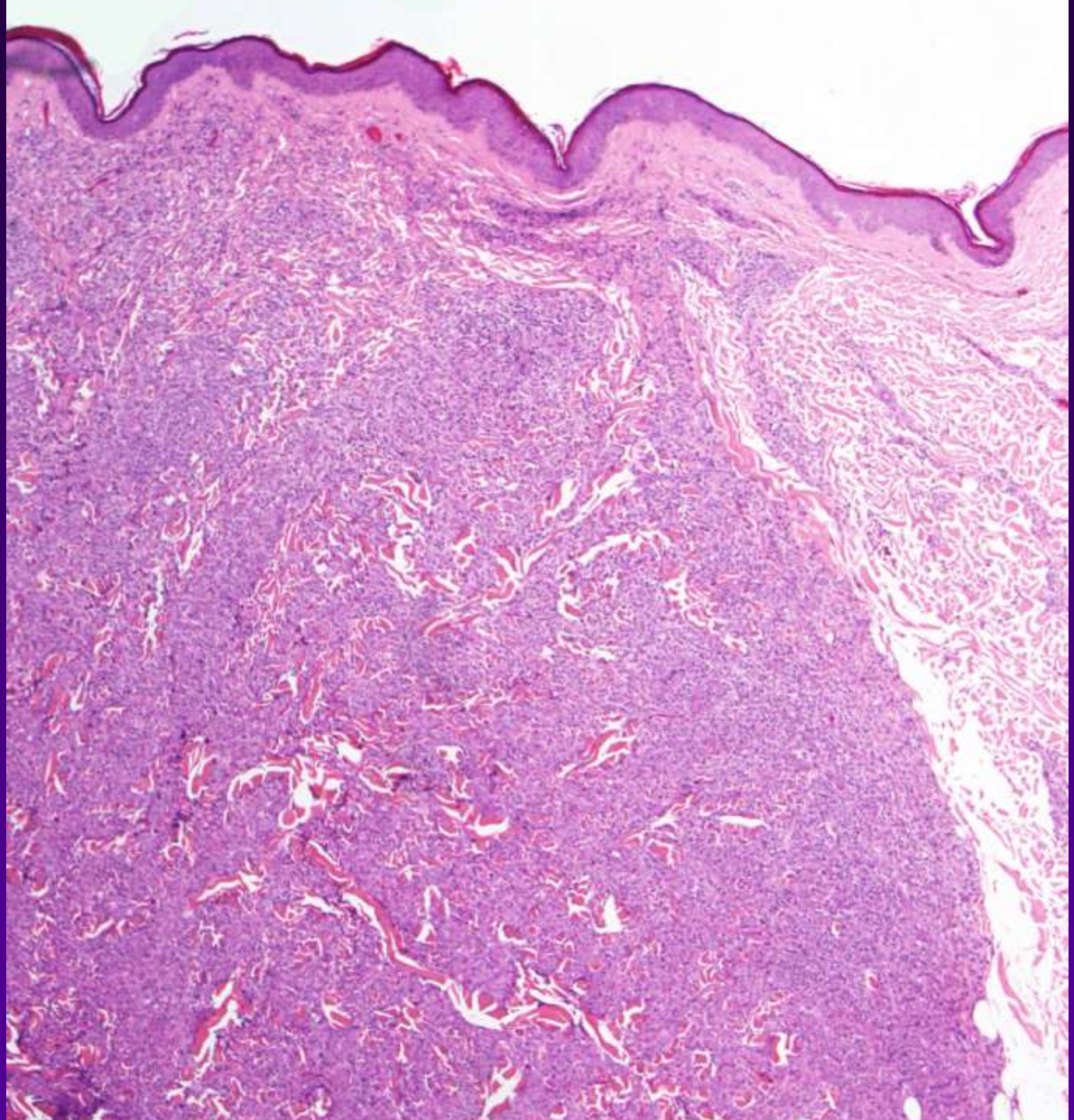


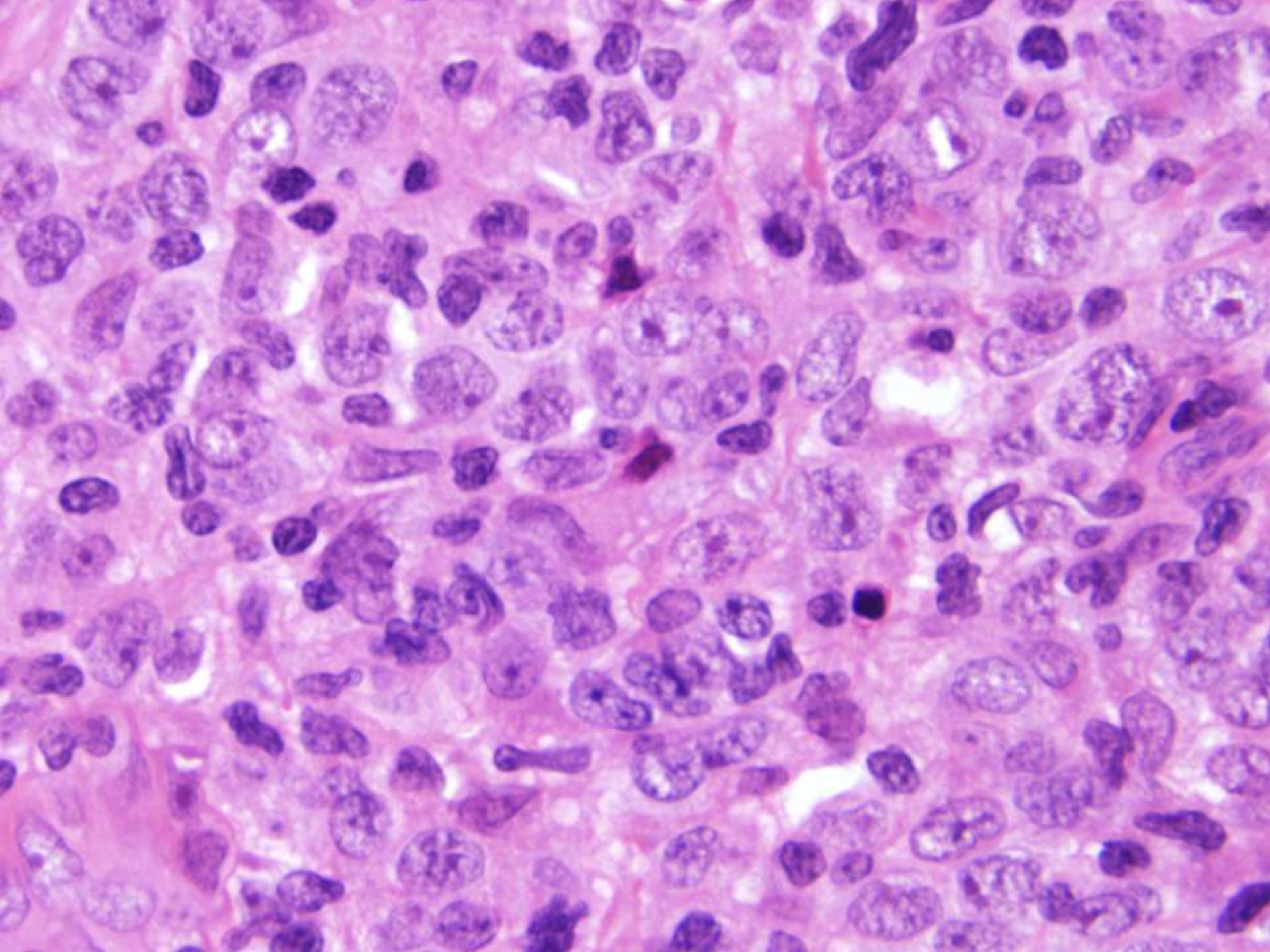

CD20






CD20
CD10





Primary cutaneous follicle center lymphoma

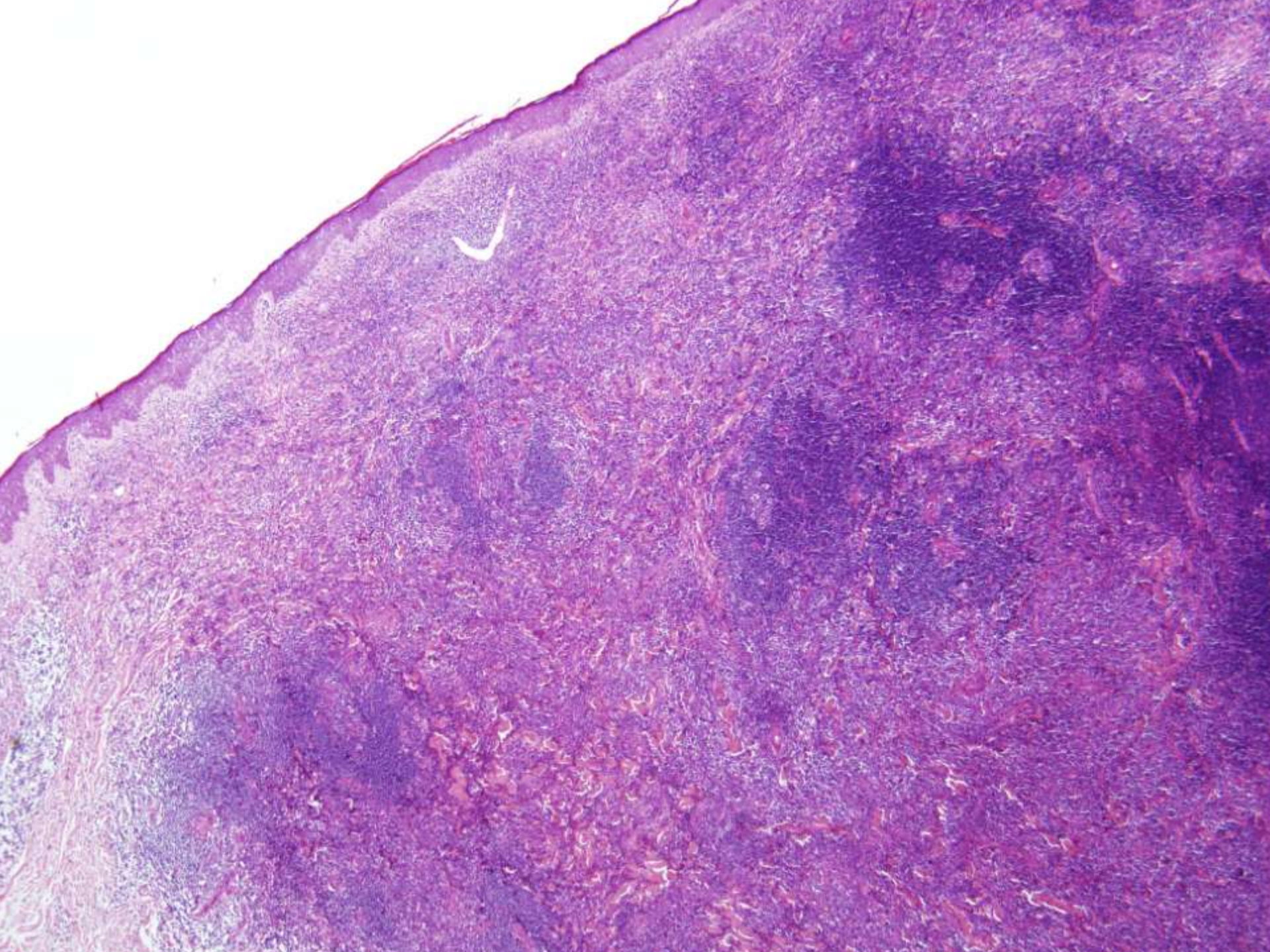
- Differences from conventional follicular lymphoma
  - Localized rather than disseminated disease in majority of cases
  - Presence of many centroblasts acceptable, as long as there are admixed centrocytes (such cases would have otherwise been considered large B-cell lymphoma)
  - *BCL2* gene uncommonly rearranged

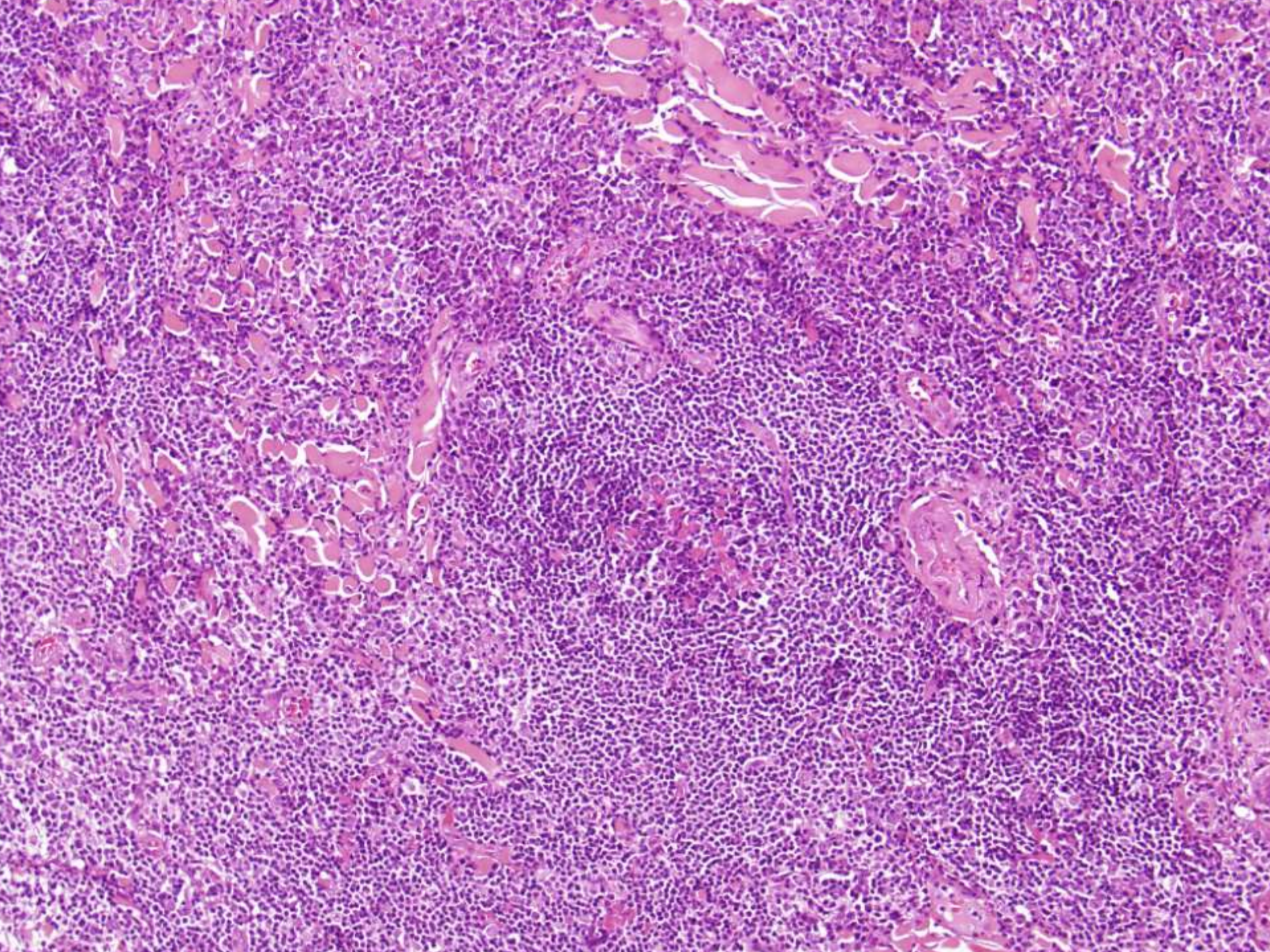
Primary cutaneous marginal zone B-cell lymphoma

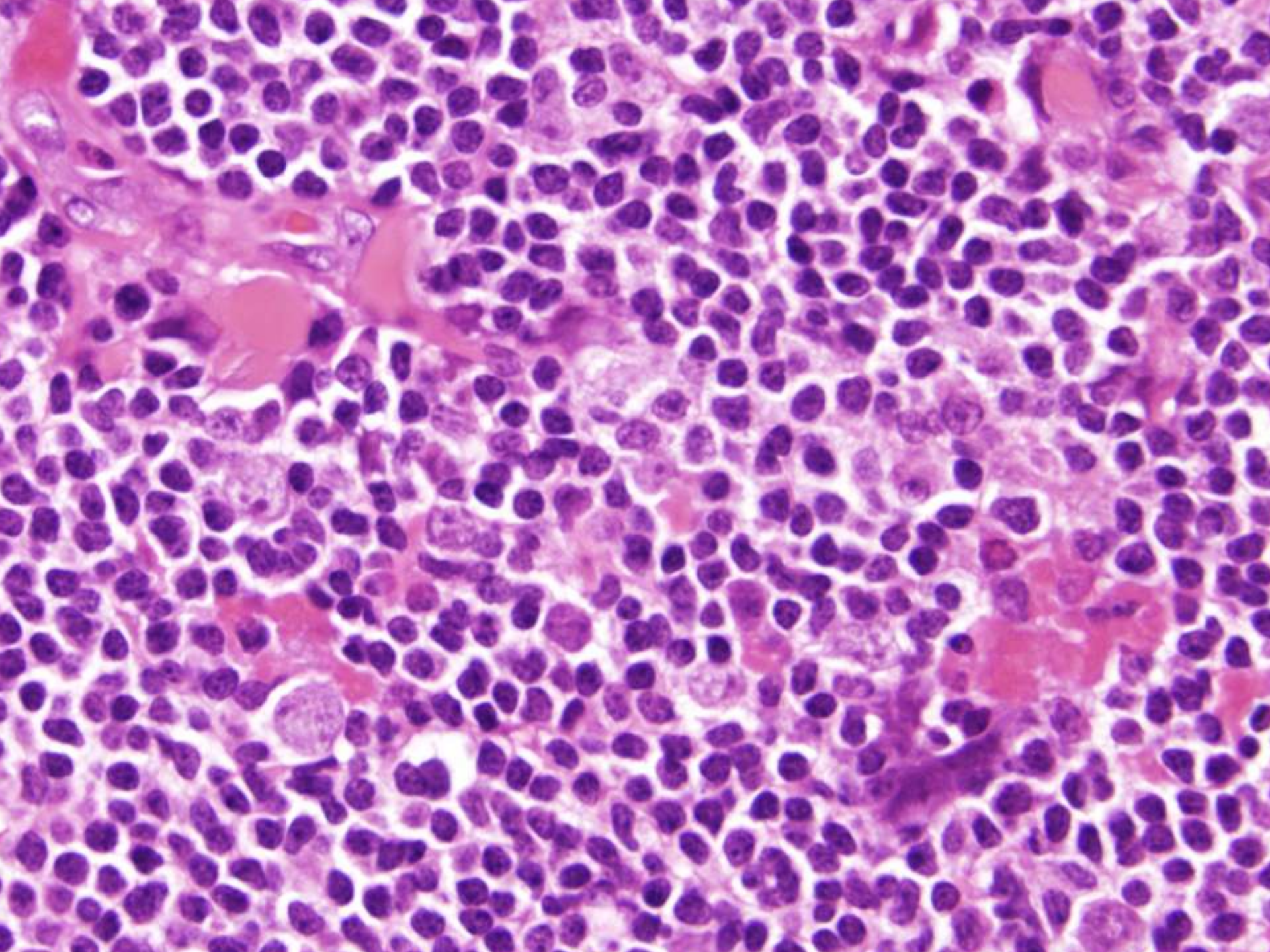
- Presentation: red to violaceous papules, plaques, or nodules
- Site: Most commonly trunk or extremities (esp. arm)
- Not uncommonly multifocal
- Natural history: Tendency to recur, but systemic dissemination rare
- Excellent prognosis. 5-yr survival ~100%

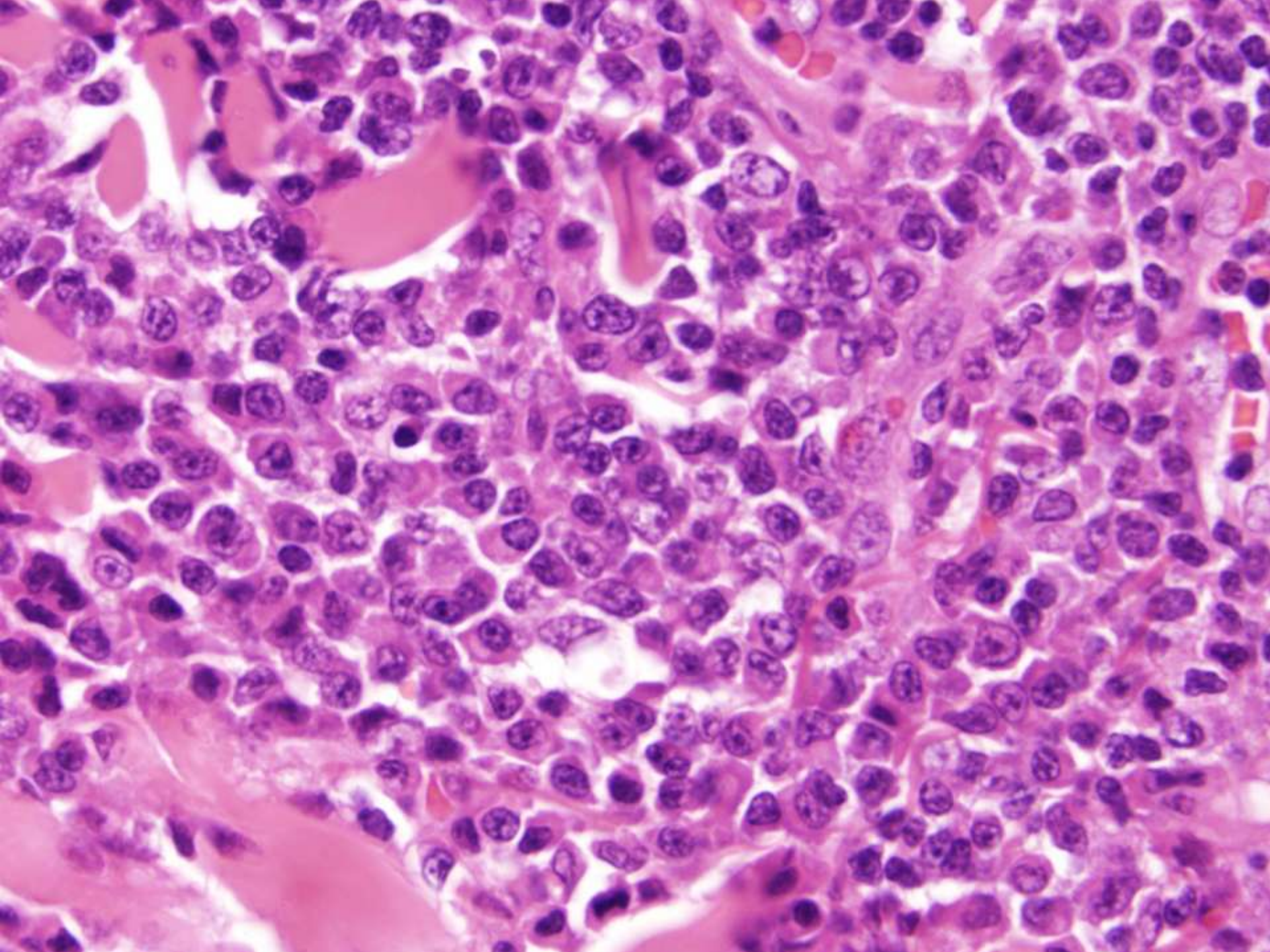
Primary cutaneous marginal zone B-cell lymphoma: Pathology

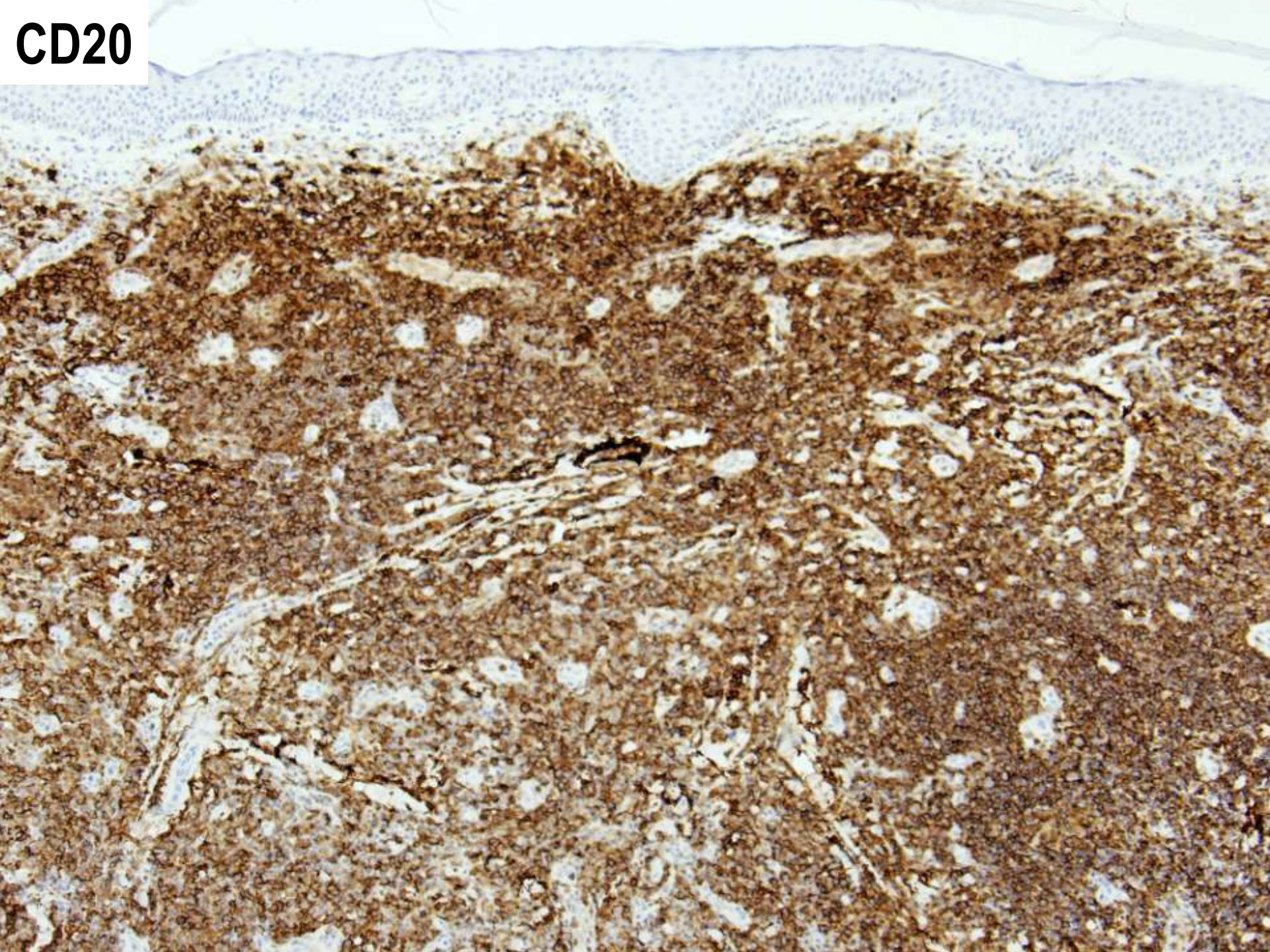
- Non-epidermotropic nodular or diffuse infiltrate
- Scattered reactive follicles
- Lymphoma cells: small, centrocyte-like, monocytoid, lymphoplasmacytoid, plasmacytic, occasional large cells
- CD10-, BCL6-
- Some cases show *IGH-MALT1* or *IGH-FOXP1* fusion

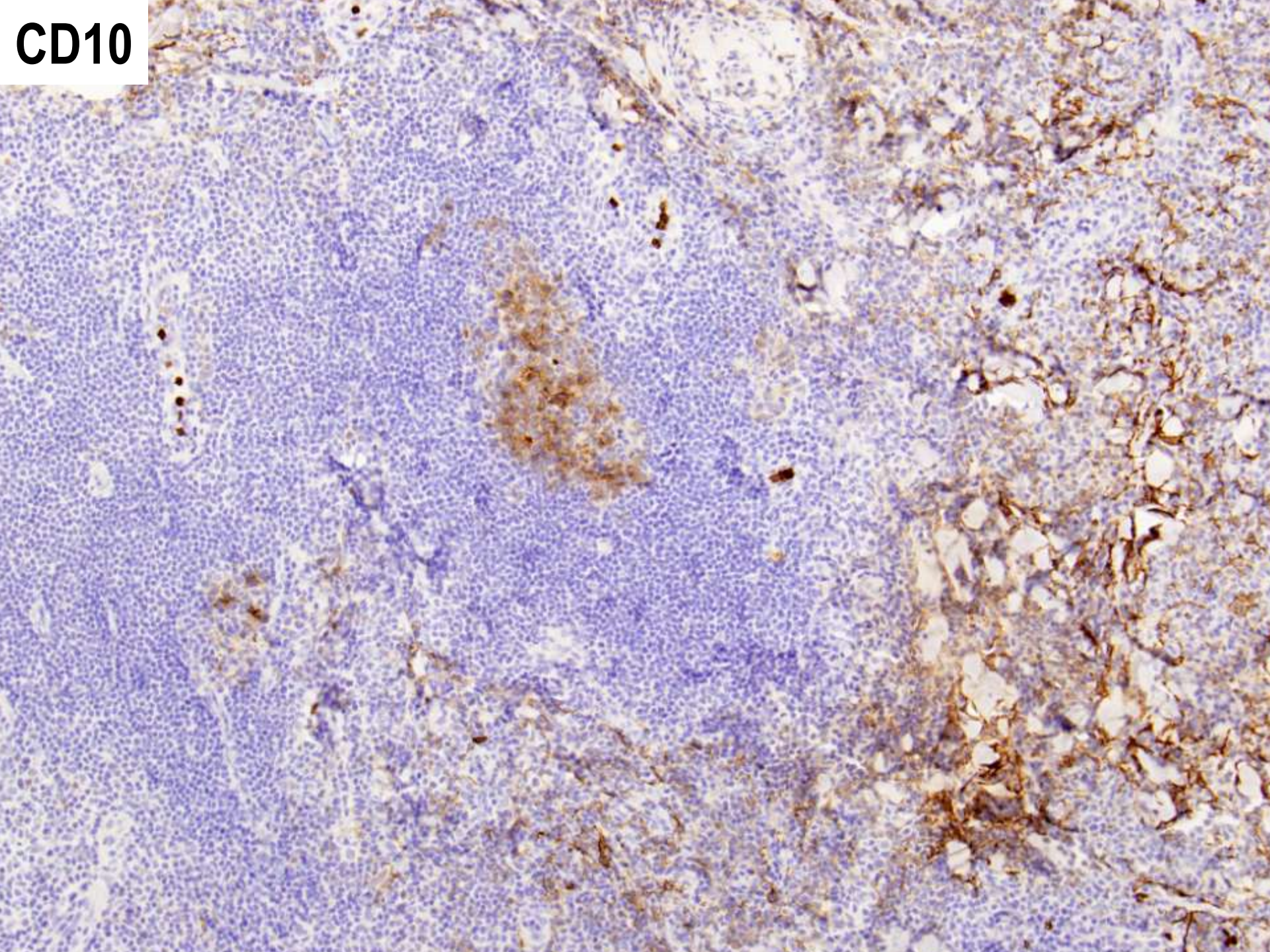









CD20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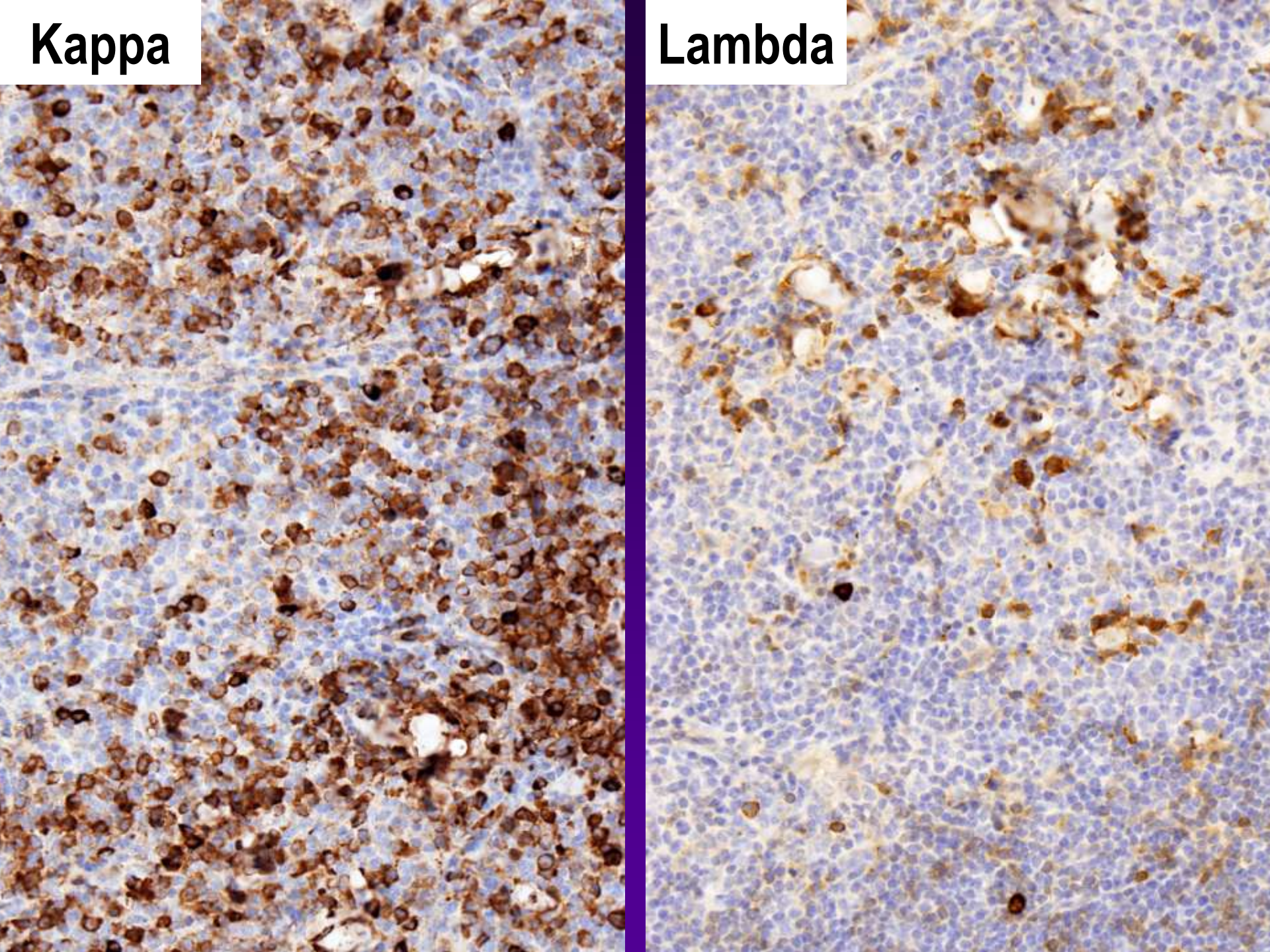

Kappa
Lambda

IgG4-related disease

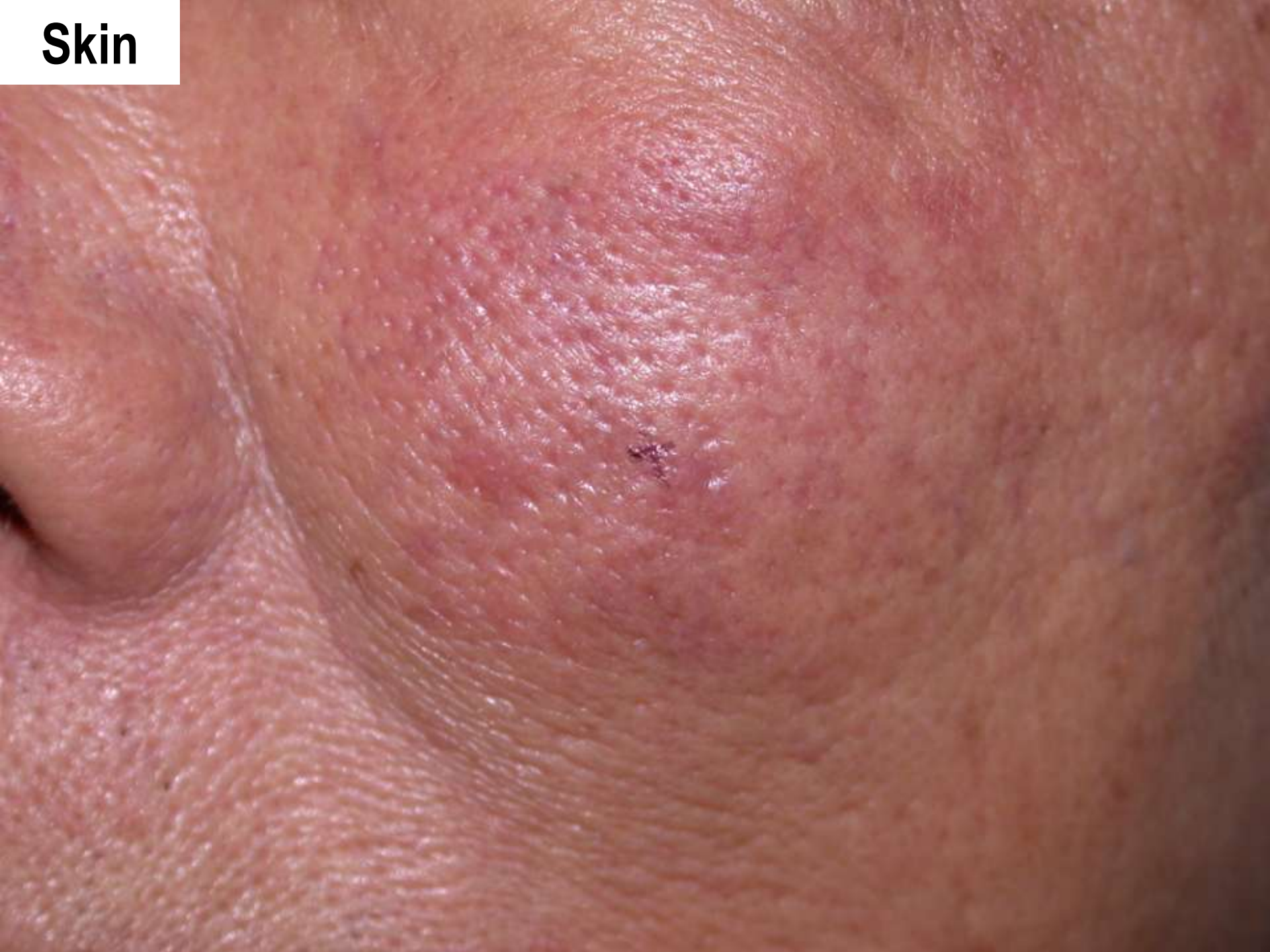
- A recently recognized clinicopathologic syndrome characterized by
  - Tumor-like enlargement of one or more exocrine glands or extranodal sites
  - Raised serum IgG4 level
  - Lymphoplasmacytic infiltration, sclerosis, phlebitis, increased IgG4-secreting plasma cells

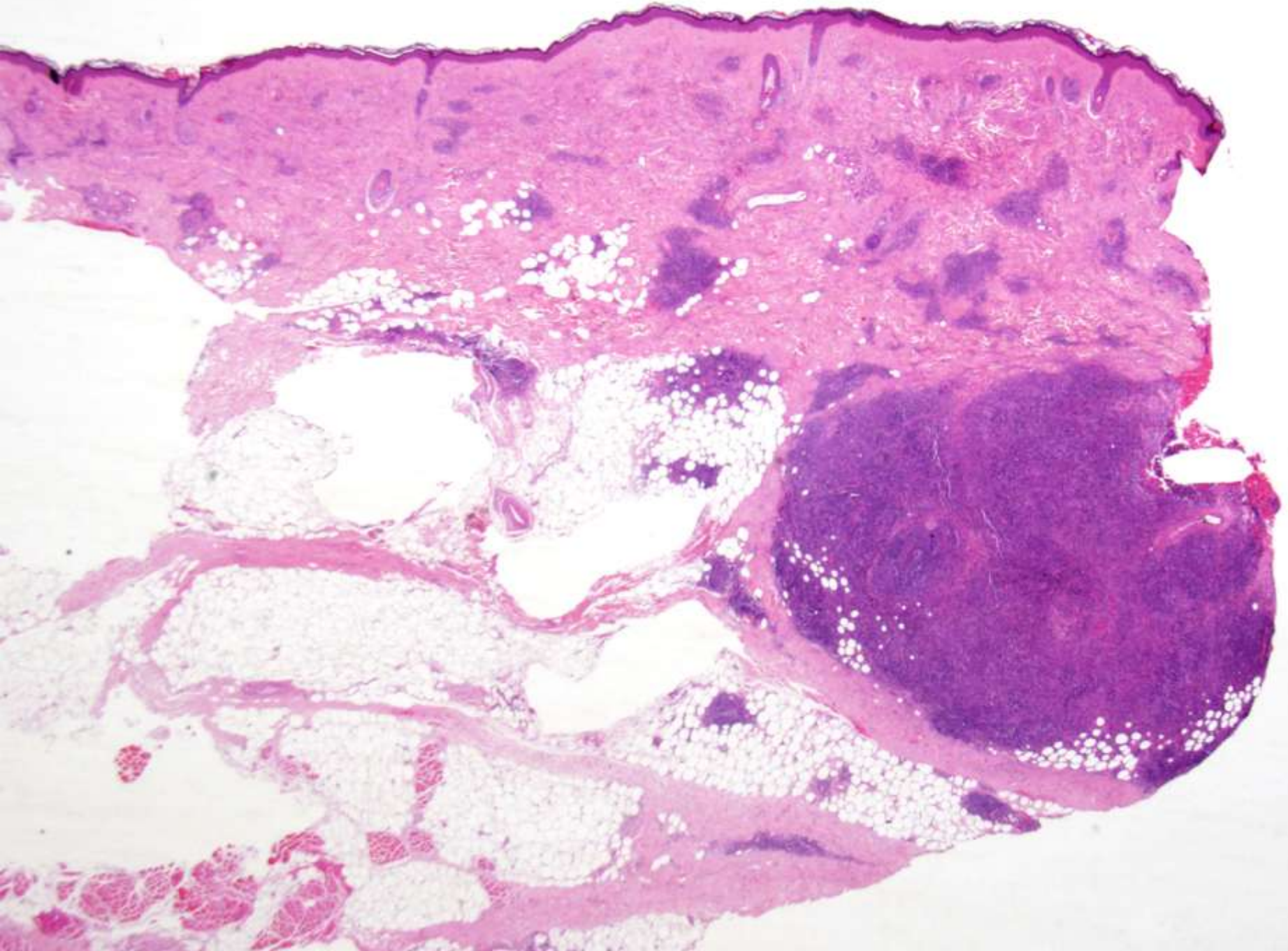
Prototype: Autoimmune pancreatitis (IgG4-related sclerosing pancreatitis)

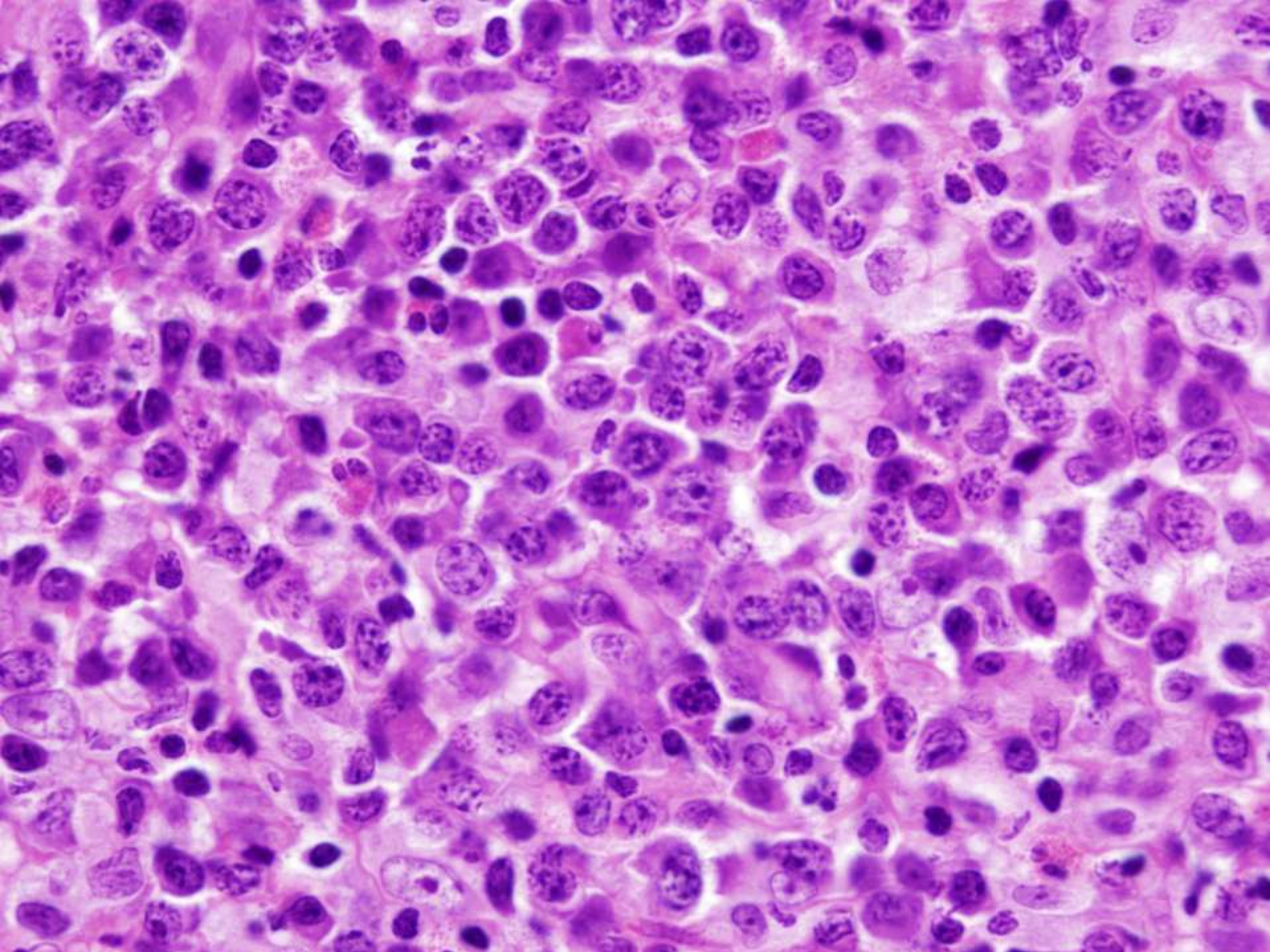
IgG4-related disease

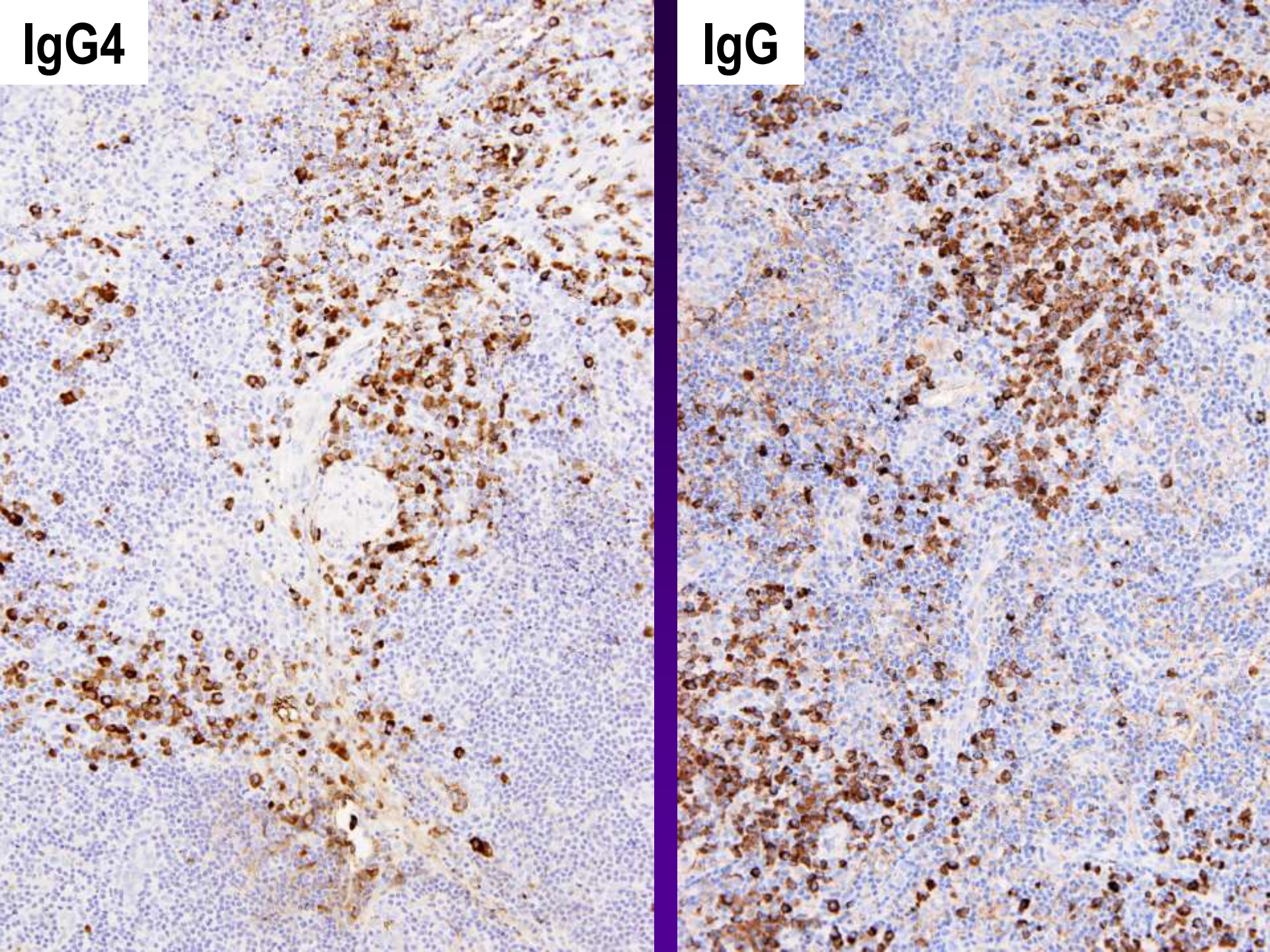
- Extrapancreatic lesions are common, especially hepatobiliary tract, eye, salivary gland and lymph nodes
- Disease usually occurs in more than one site, i.e. systemic disorder
- These may co-exist, precede or develop subsequent to diagnosis of IgG4-related sclerosing pancreatitis
- Occasionally skin involvement can occur

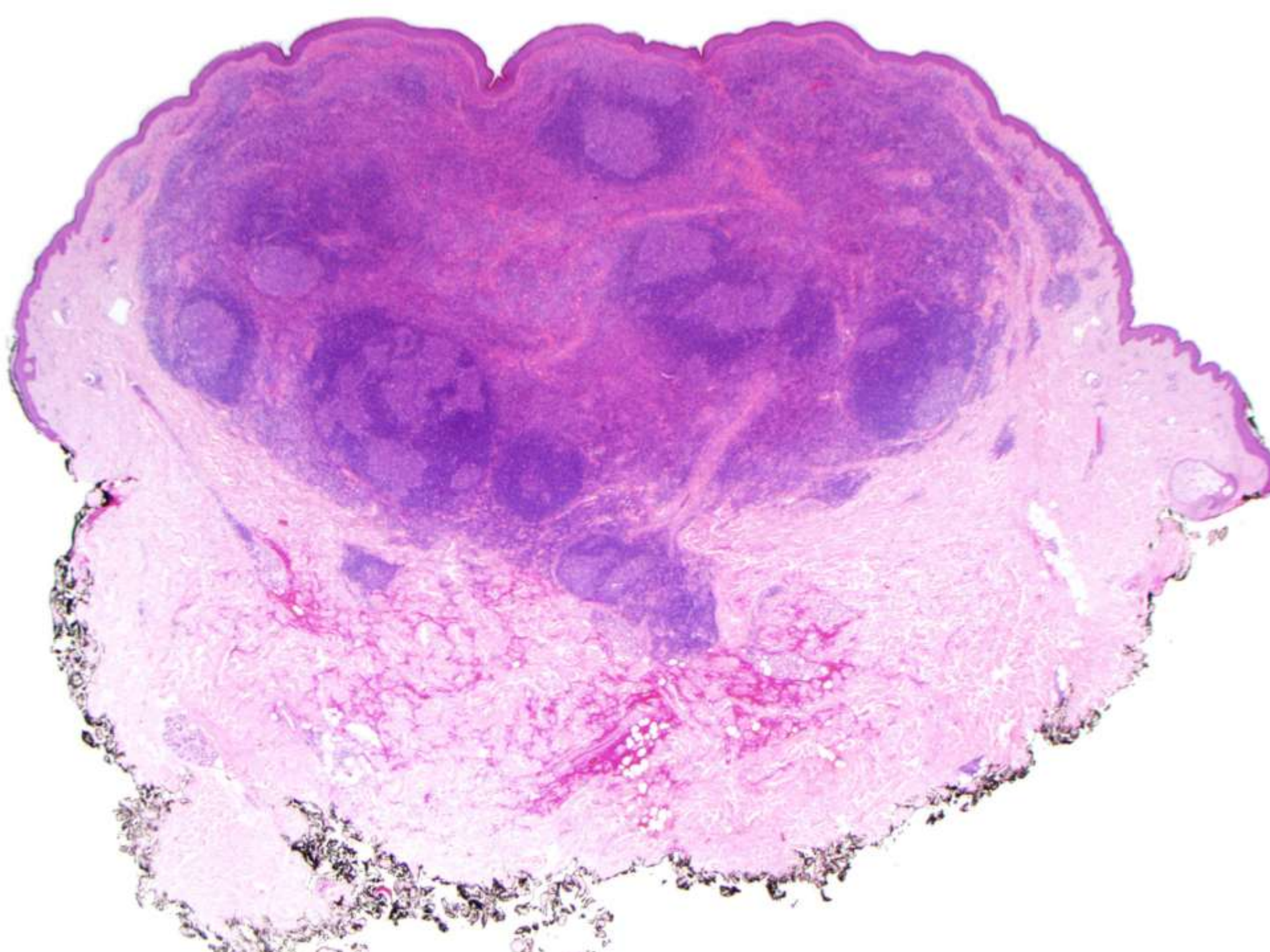
Skin

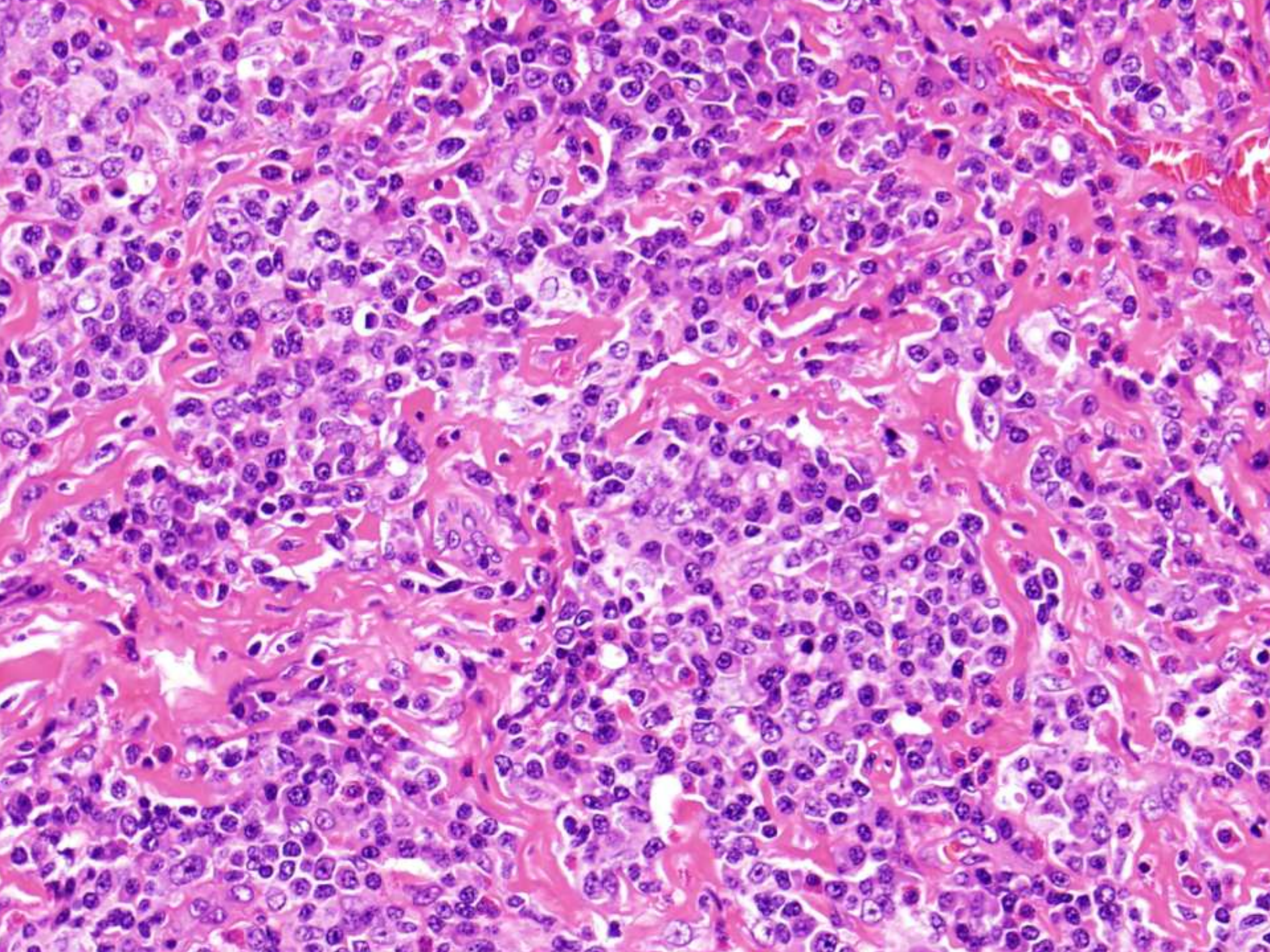






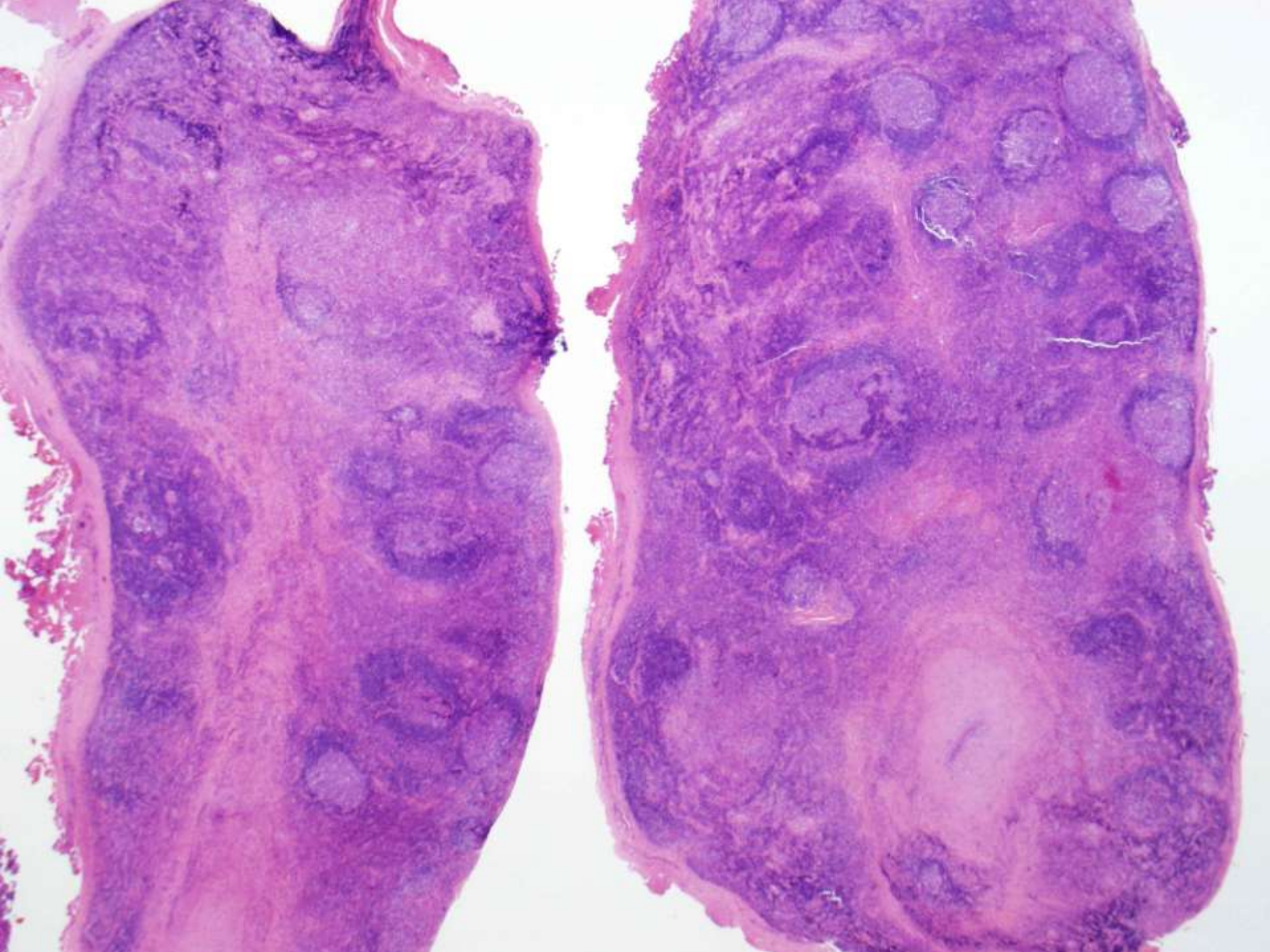

IgG4
IgG

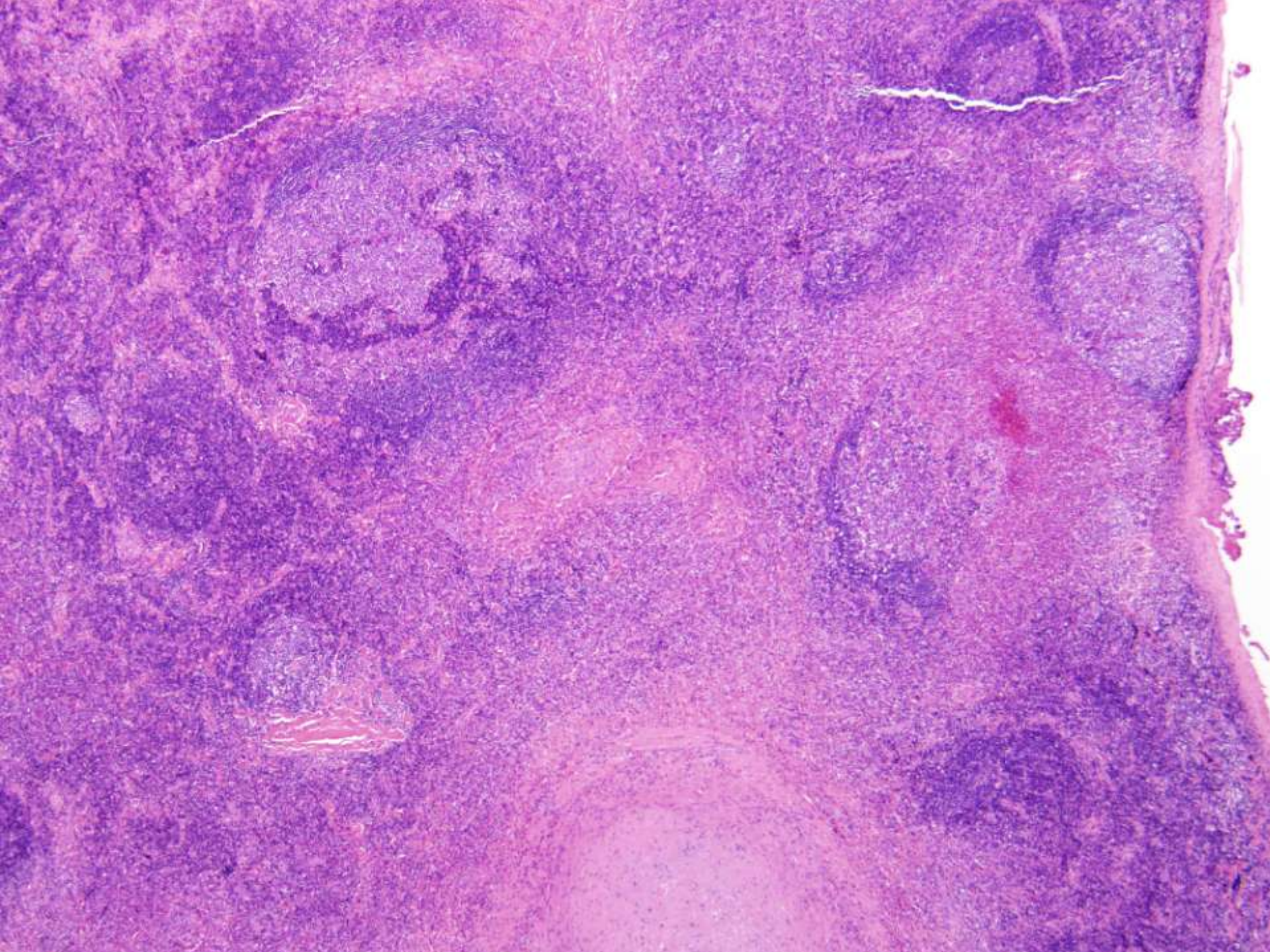


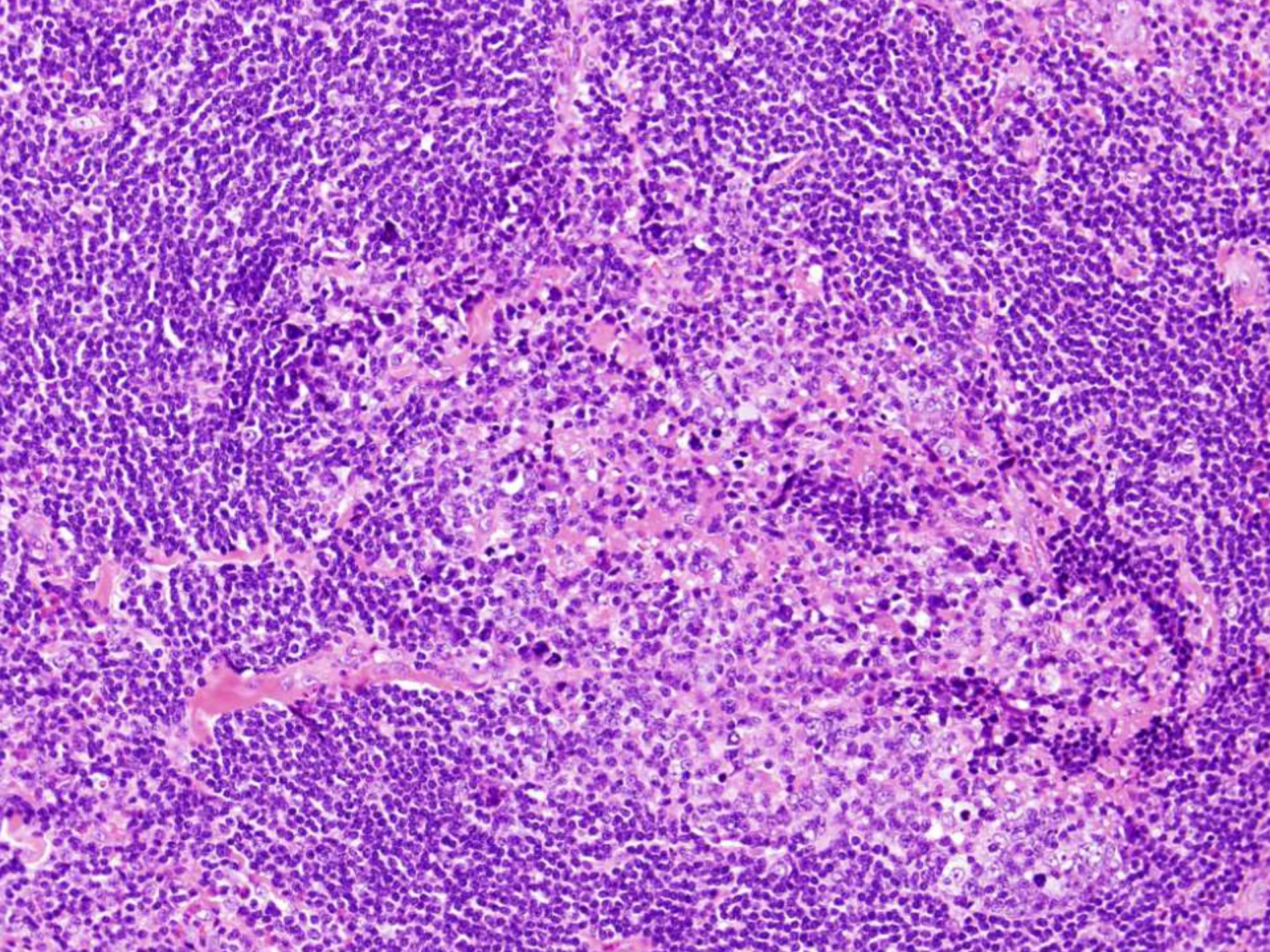


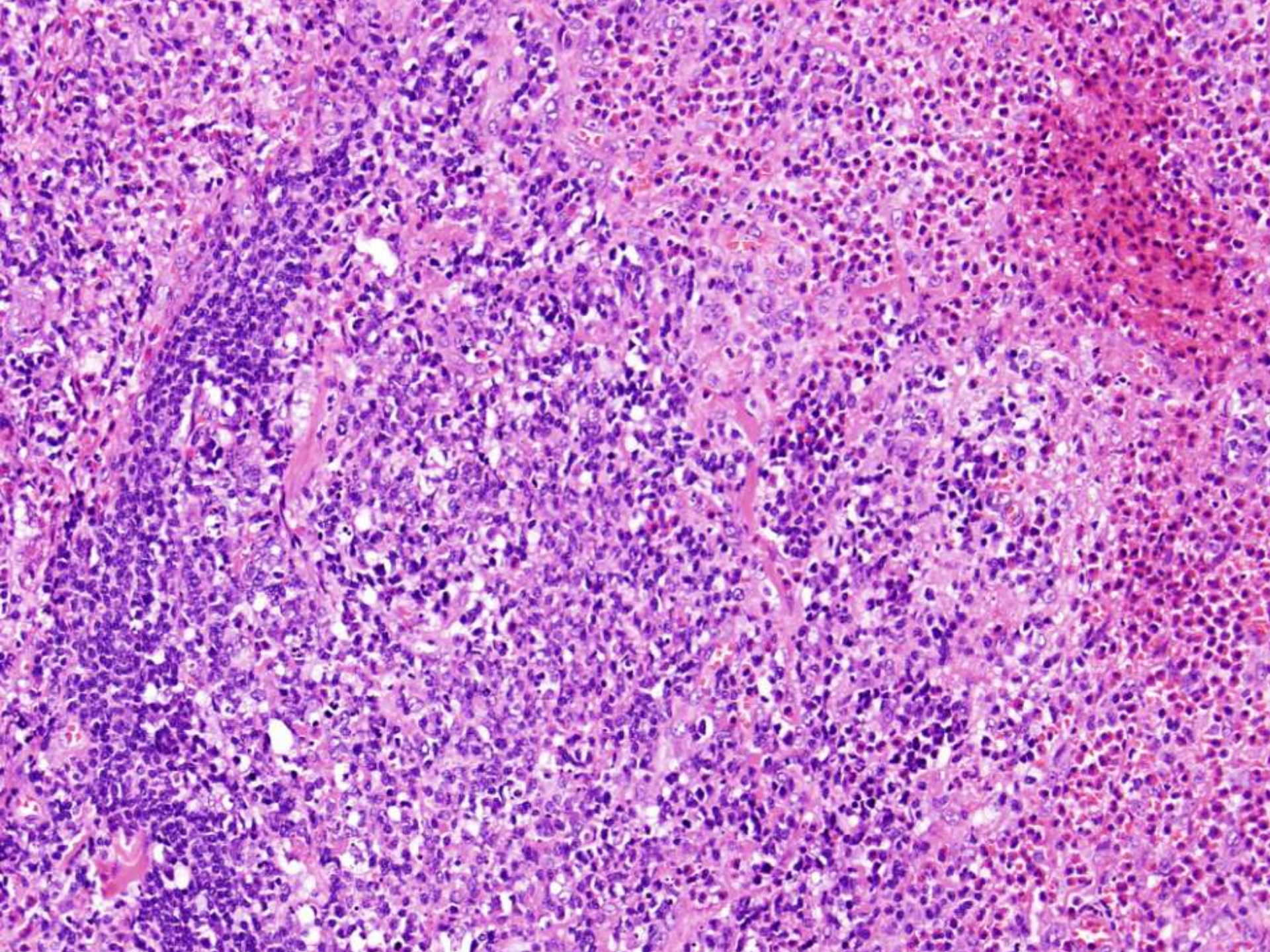
Kimura disease

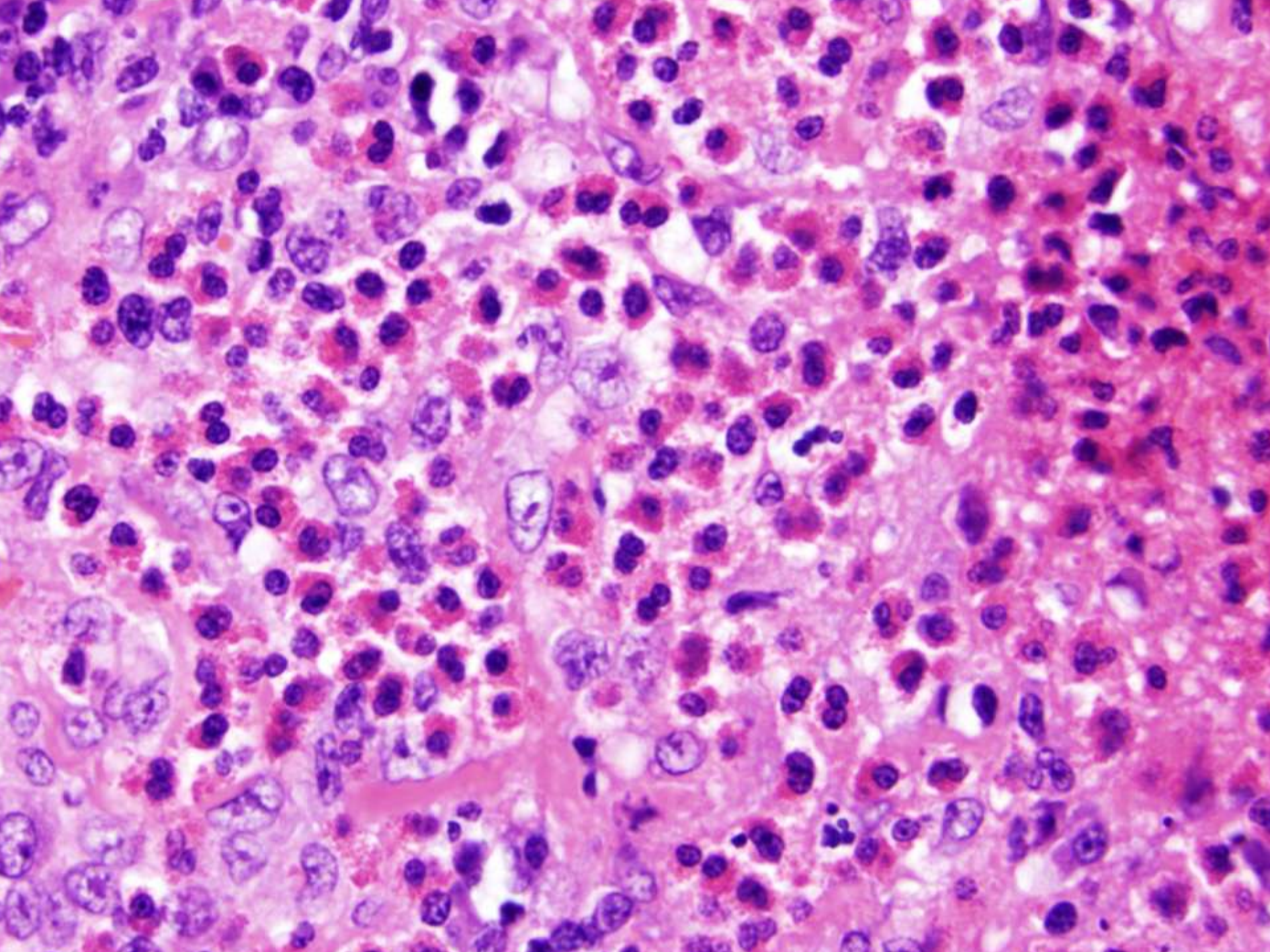
- Idiopathic, chronic, allergic-inflammatory condition
- Age: young to middle-aged subjects
- Sex: striking male predominance
- More prevalent in (but not limited to) Orientals
- Presenting with slowly enlarging mass lesions in head and neck
- Involvement of soft tissues (esp. subcutis), major salivary glands and lymph nodes











A mere increase in eosinophils is insufficient for a diagnosis of Kimura disease, because this can be seen in allergy, parasitic infestation, etc.

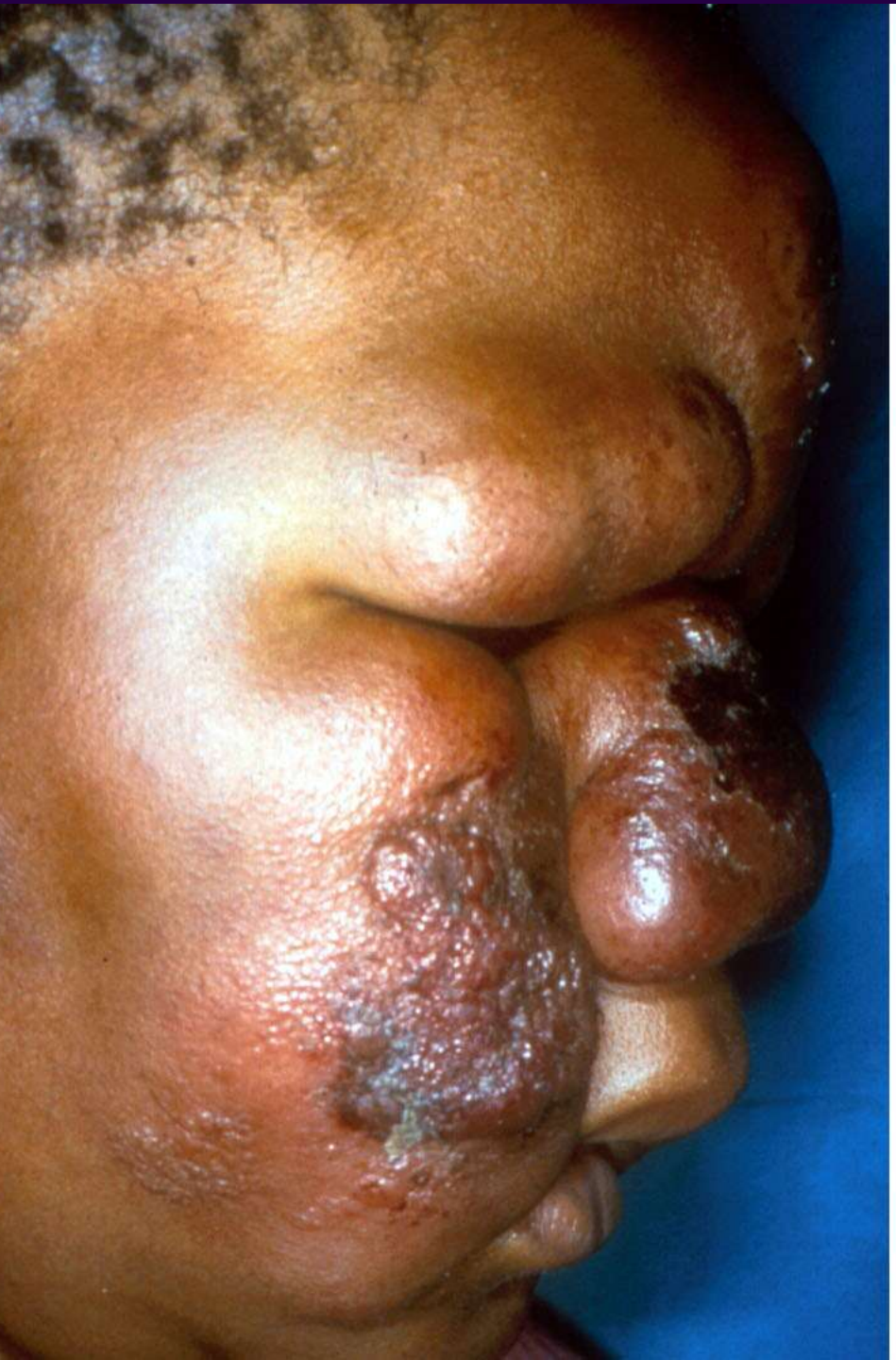
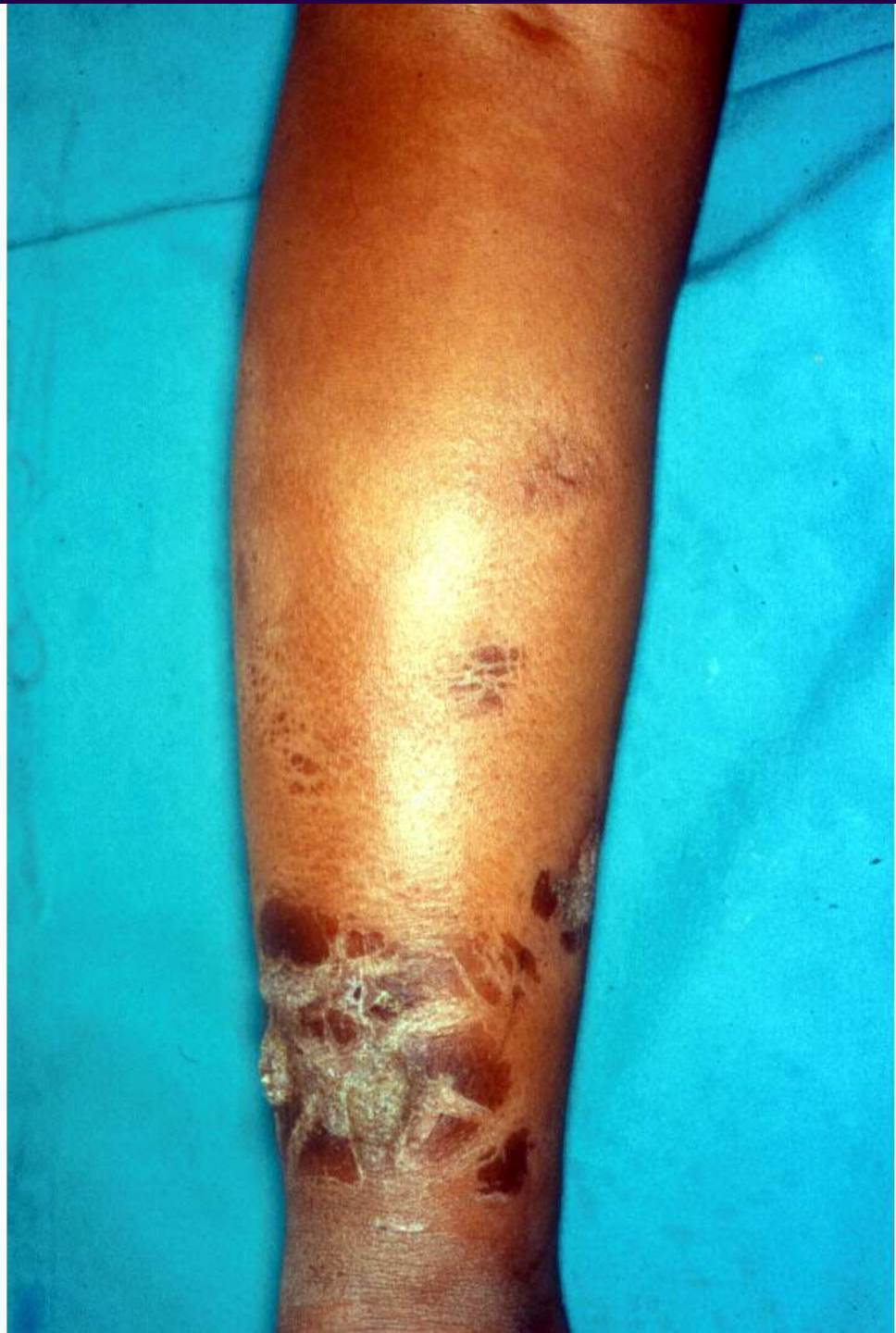
The characteristic changes in the lymphoid follicles have to be found

BLASTIC MEDIUM-SIZED CELLULAR PROLIFERATIONS

- Blastic plasmacytoid dendritic cell neoplasm
- Acute myeloid leukemia
- Lymphoblastic lymphoma/ leukemia
- Blastoid variant of mantle cell lymphoma

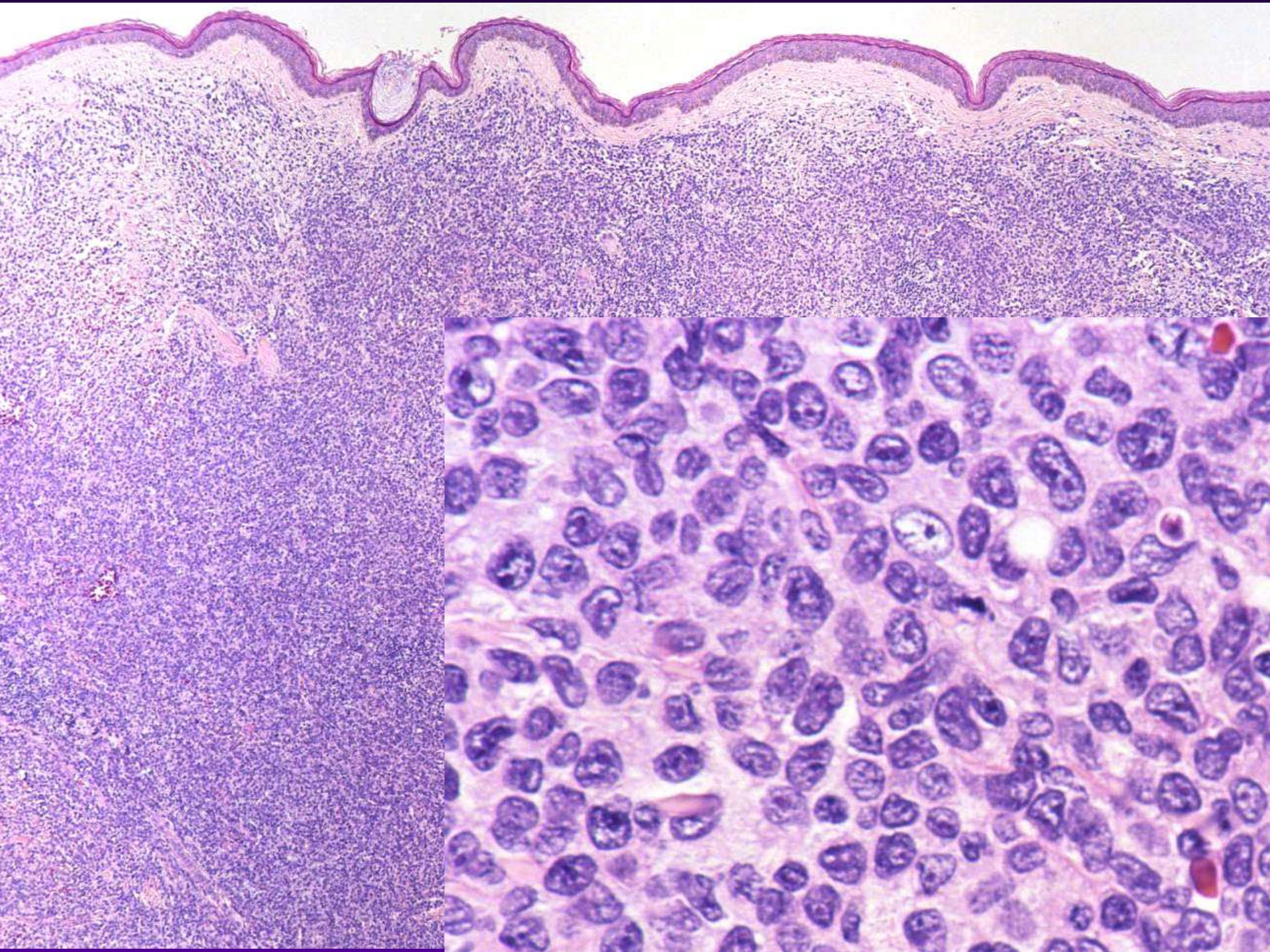
Blastic plasmacytoid dendritic cell neoplasm

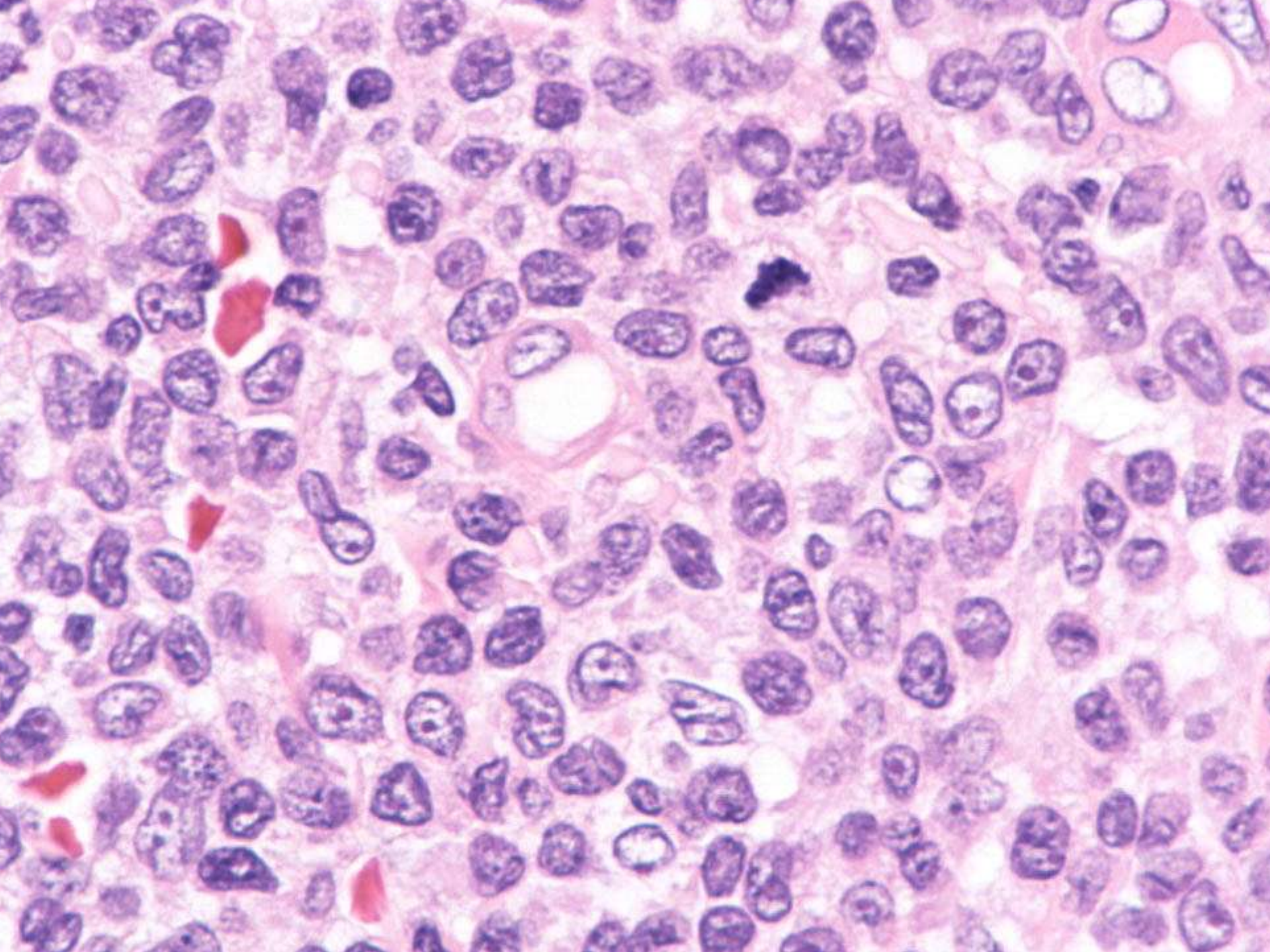
- Formerly known as “blastic NK cell lymphoma” or “CD4+ CD56+ hematodermic malignancy”
- Presents with skin lesions
- May have simultaneous lymph node, bone marrow or peripheral blood involvement
- Relentless course, with frequent relapses despite initial response to chemotherapy (survival only 12-14 months)

Blastic plasmacytoid dendritic cell neoplasm: Histology

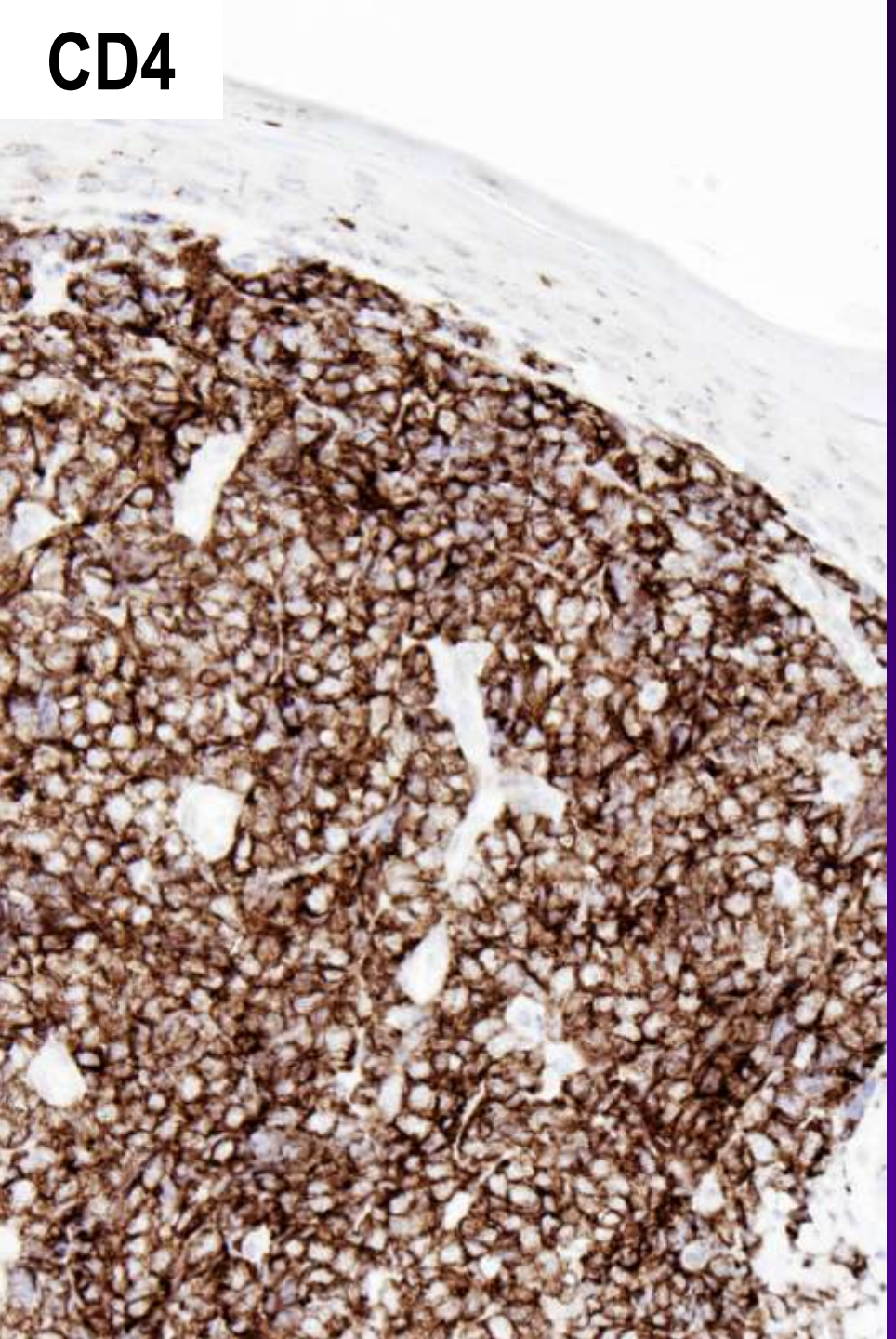
- Monotonous diffuse dermal infiltrate, often with single-file pattern in areas
- No epidermal invasion
- Medium-sized cells with fine chromatin, resembling acute myeloid or lymphoblastic leukemia
- Frequent mitoses
- Usually no necrosis and angioinvasion

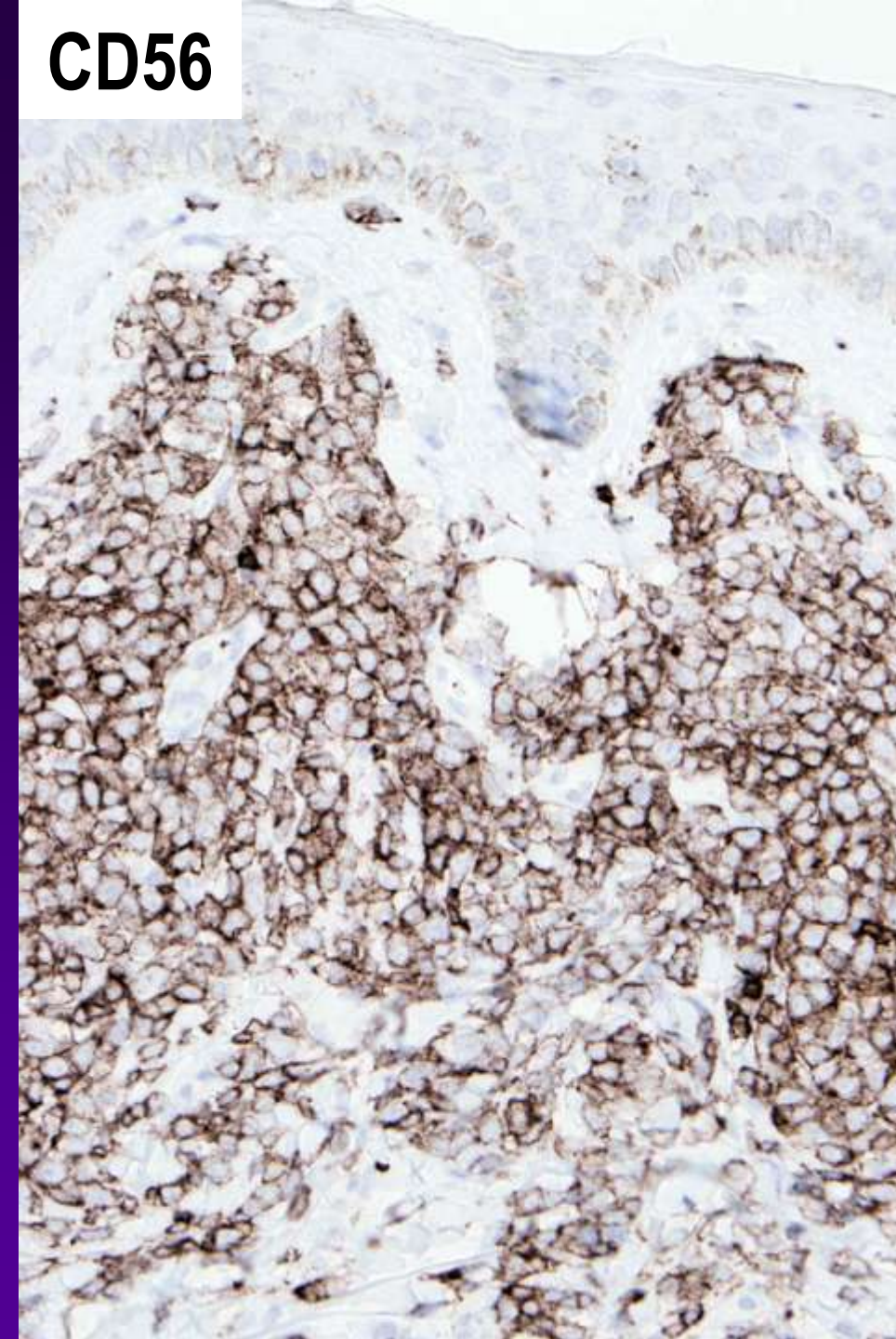




Immunophenotype

- Surface CD3 - Cytoplasmic CD3ε -/+
- CD56 +
- CD4 +
- CD123 +
- Myeloid markers -
- TdT + in 60%
- Cytotoxic markers -
- BDCA-2/CD303 +, TCL1 +, CLA +


CD4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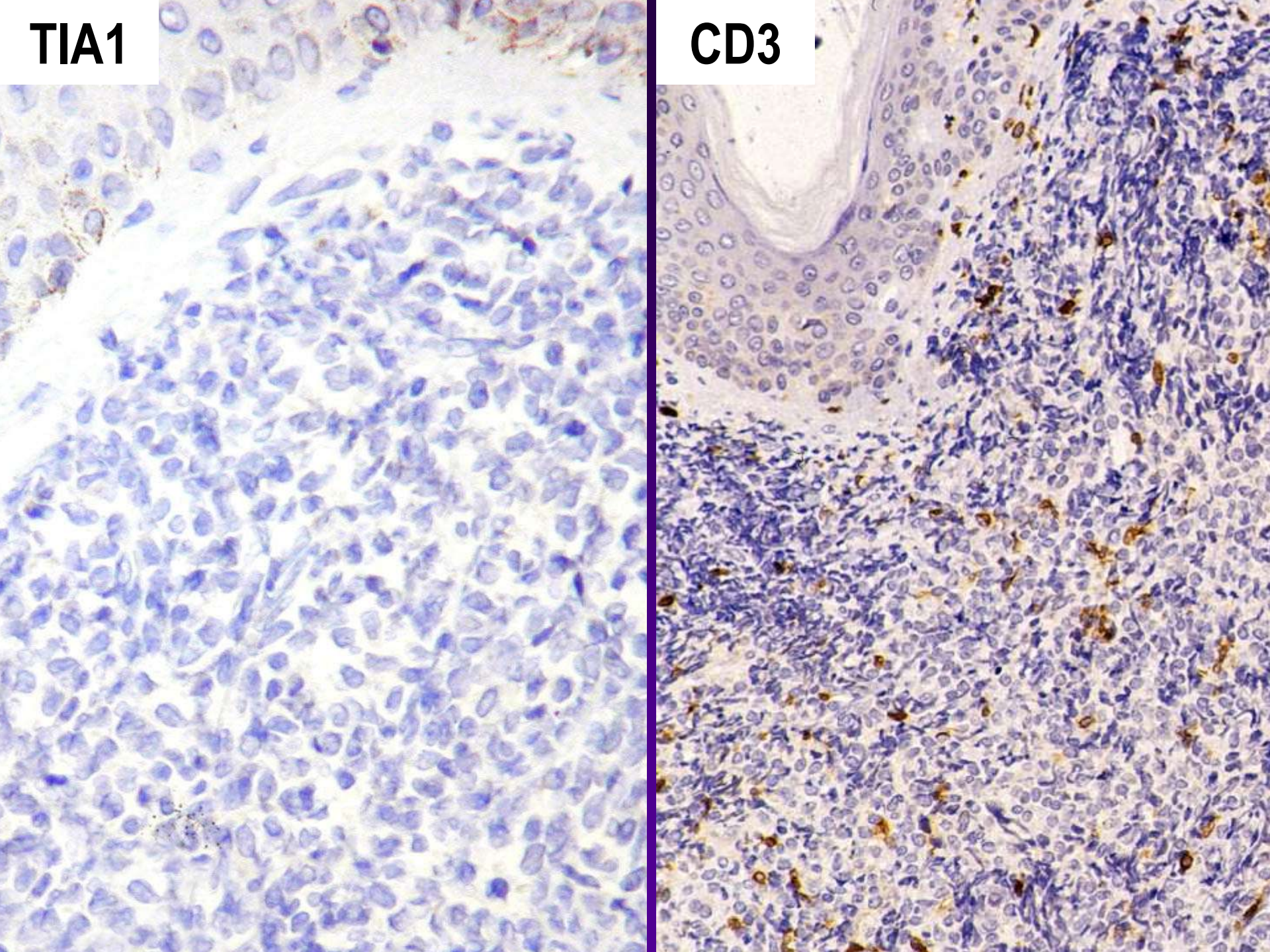
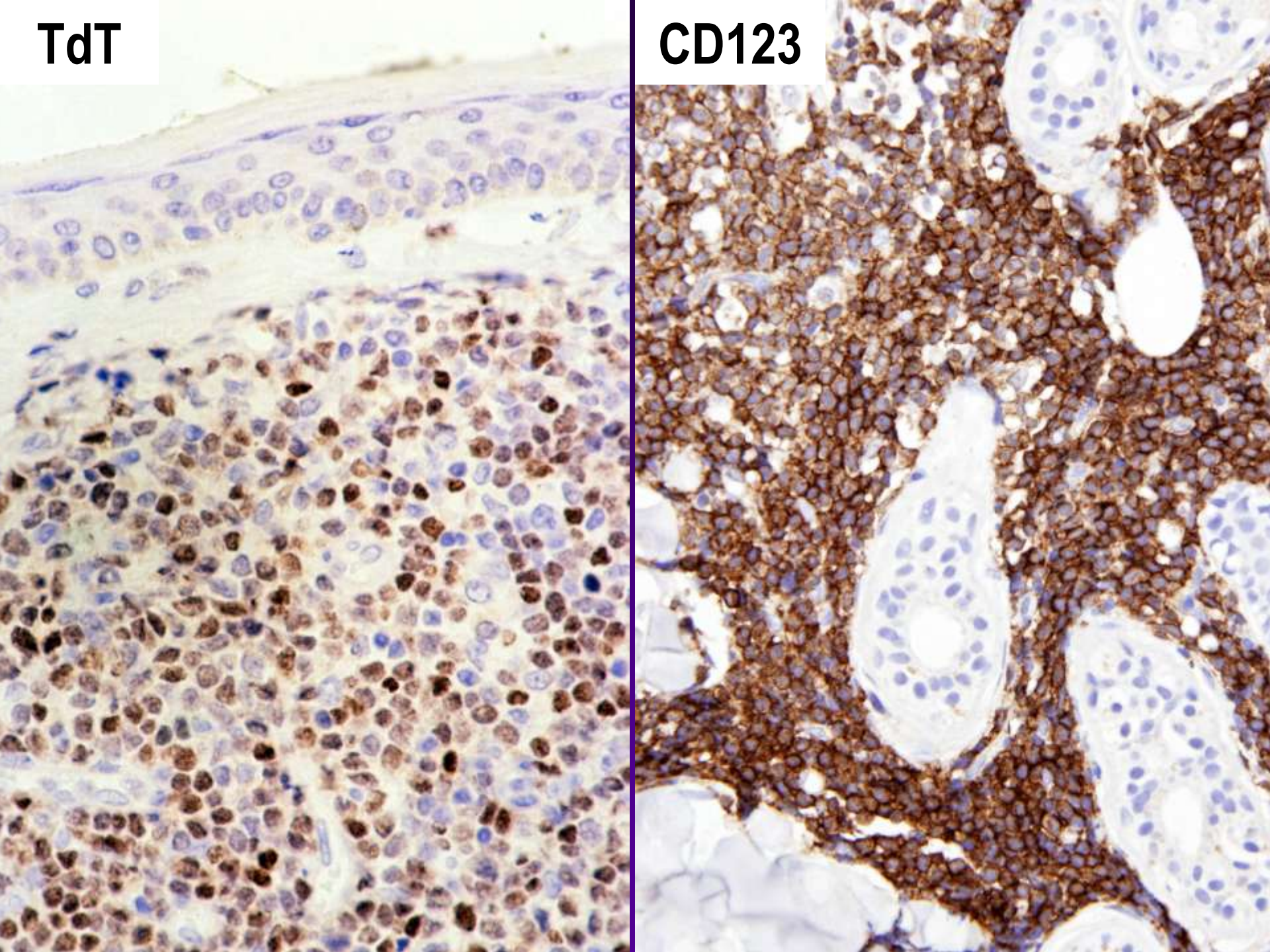
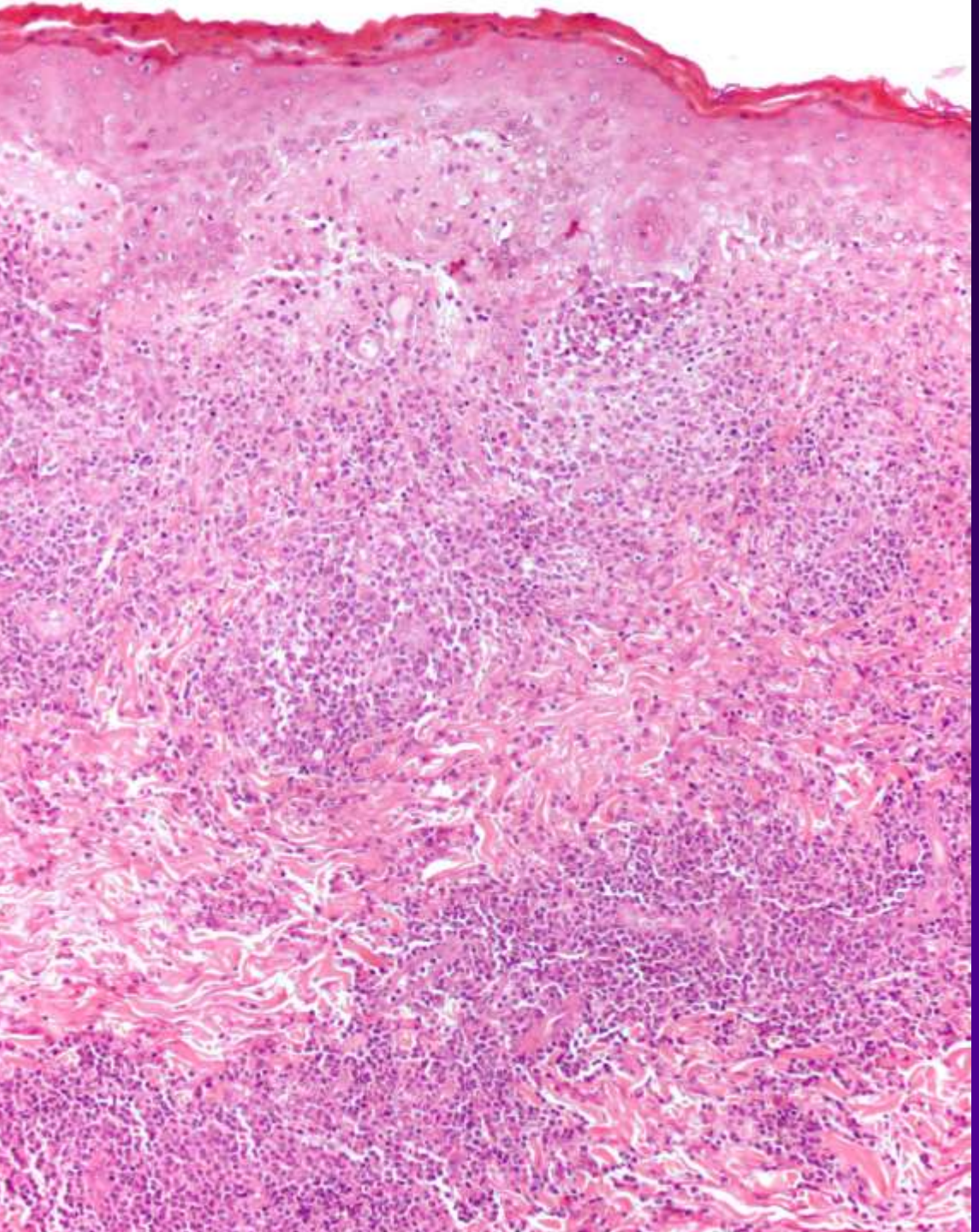
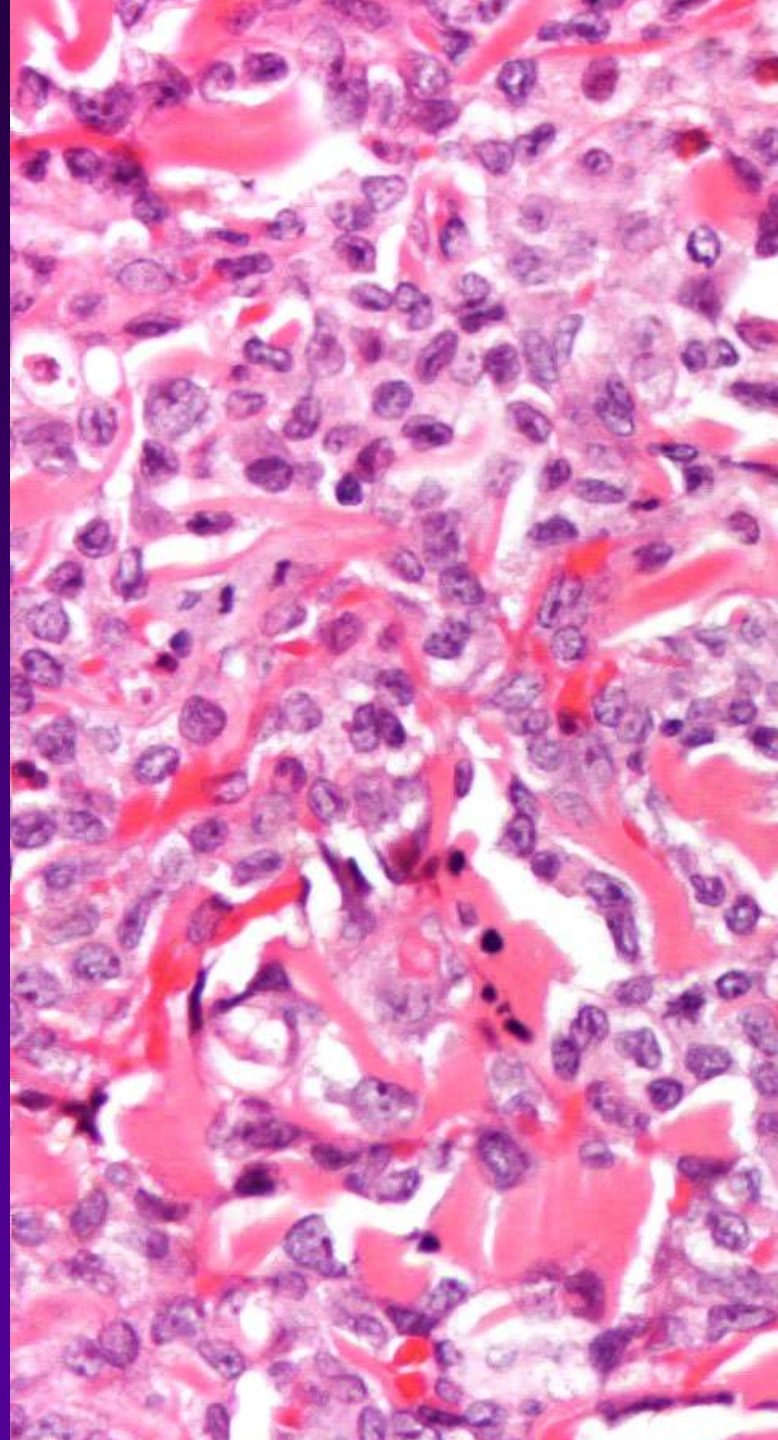

TIA1
CD3


TdT
CD123

Extramedullary myeloid sarcoma (granulocytic sarcoma)

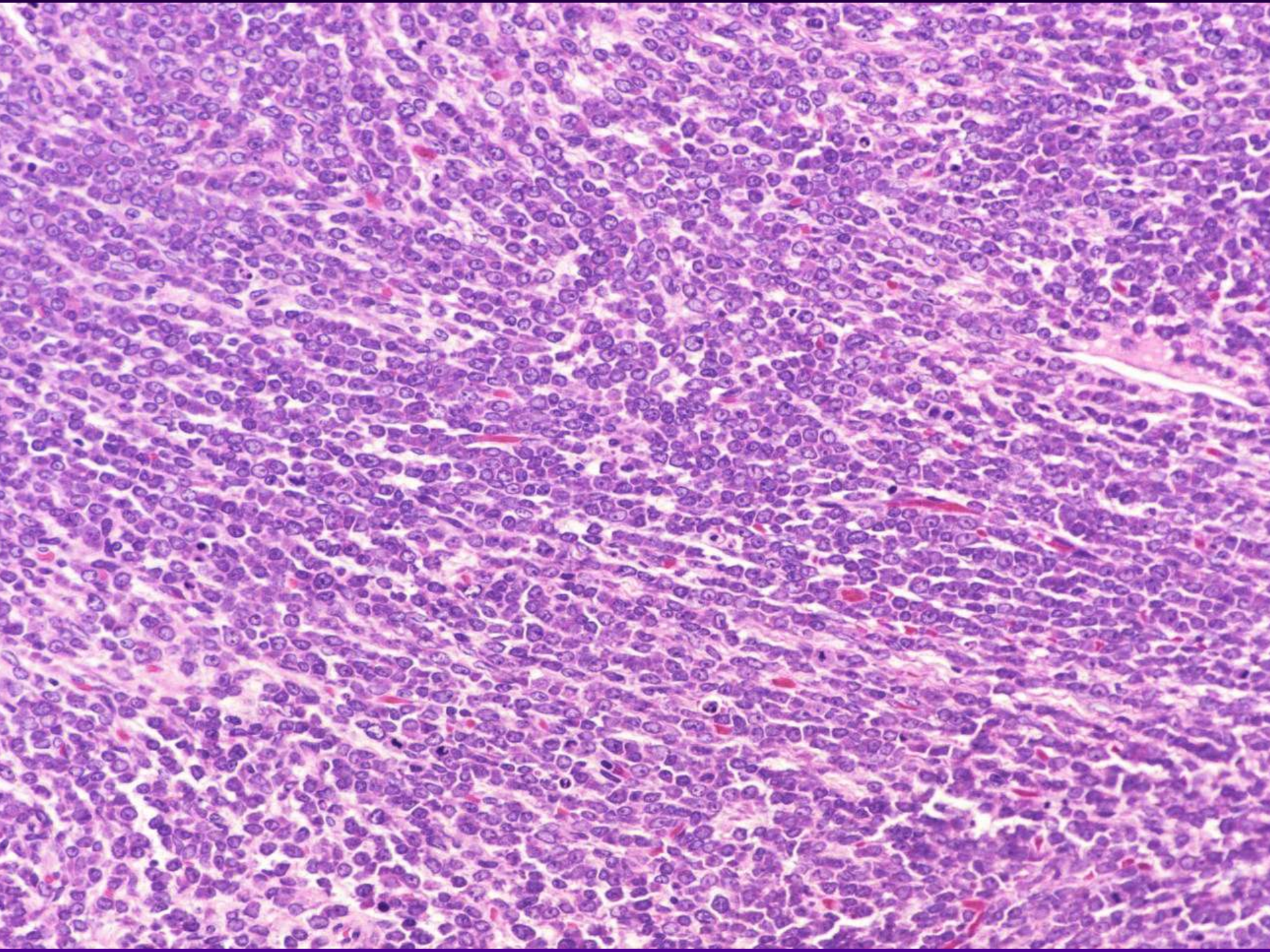
- Localized tumor of primitive myeloid cells
- Site: practically any site in the body, especially skin
- Can develop before, simultaneous with, or after the diagnosis of acute myeloid leukemia. Can complicate MDS or chronic myeloproliferative disorder
- For apparently localized cases, leukemia almost always ensues in weeks to months if systemic treatment is not given

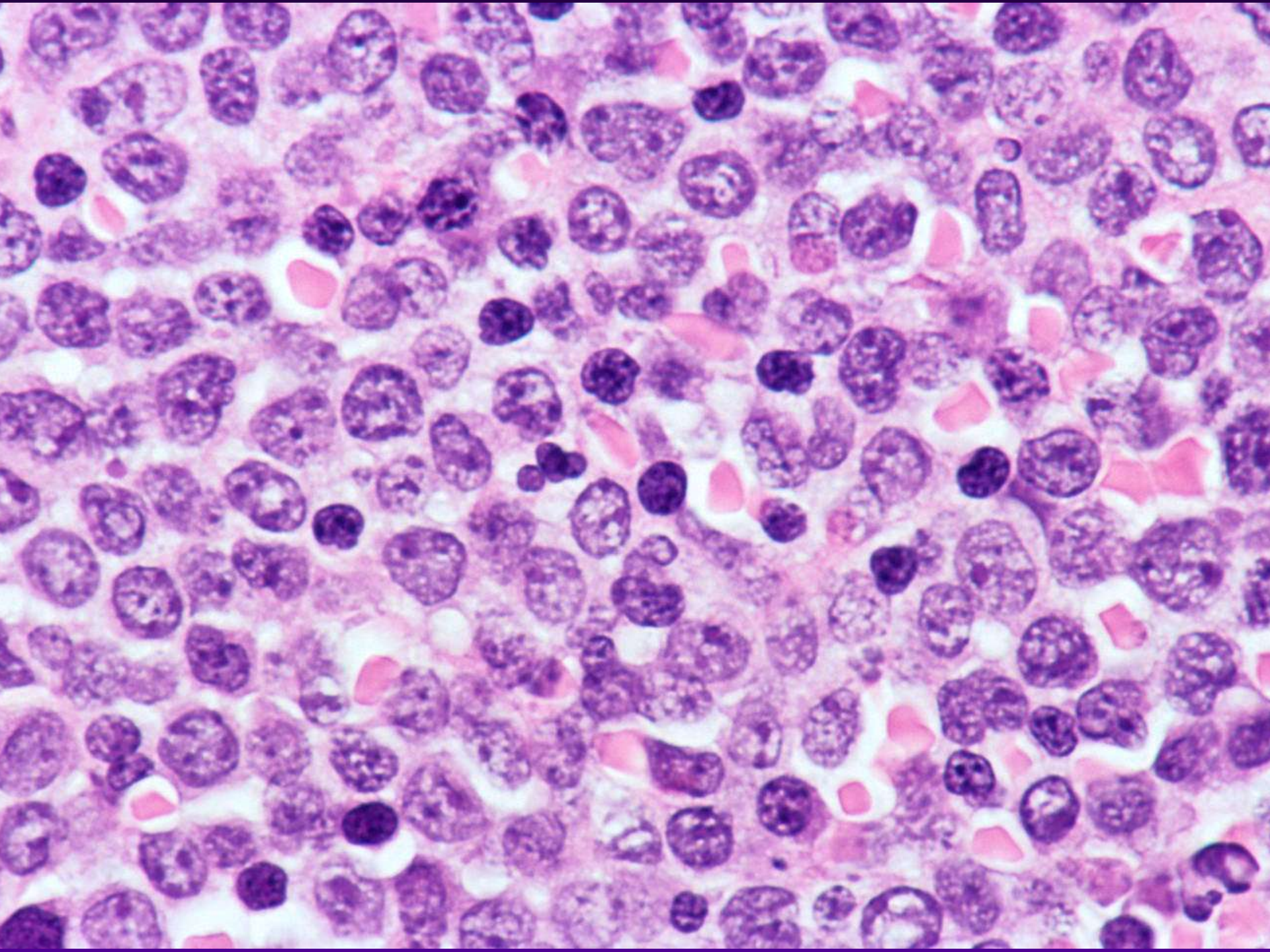


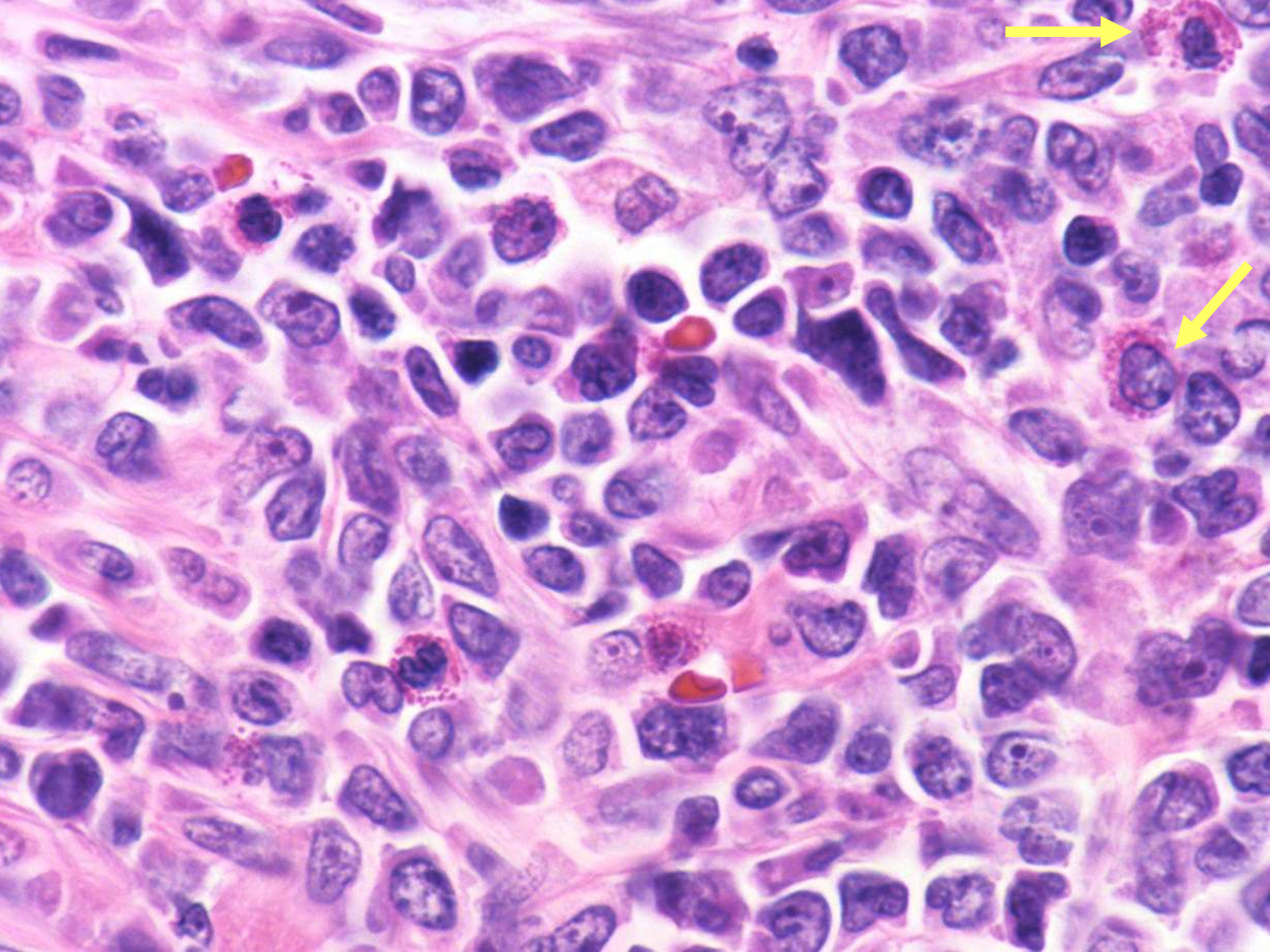


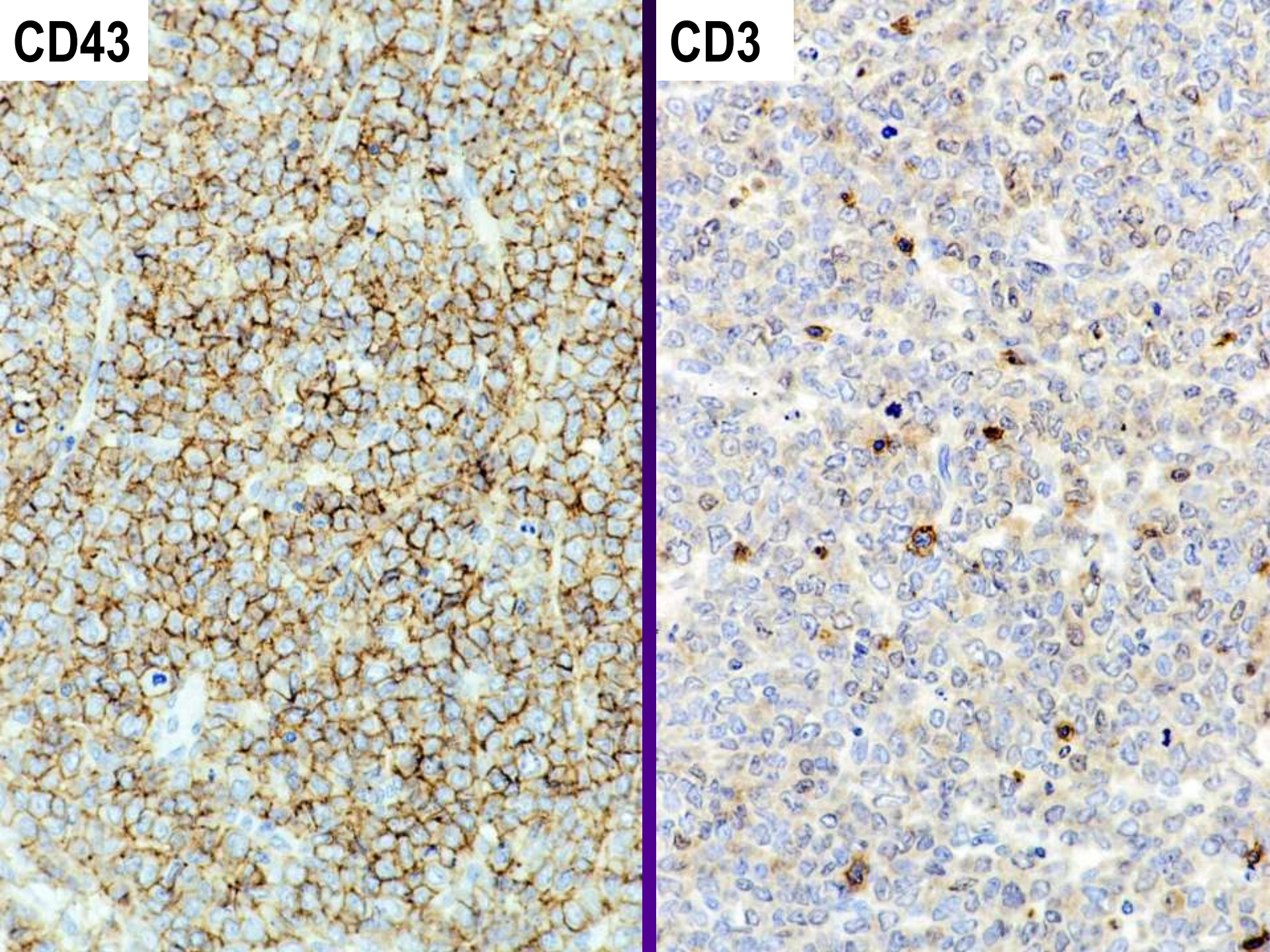
Clues for diagnosis of myeloid sarcoma

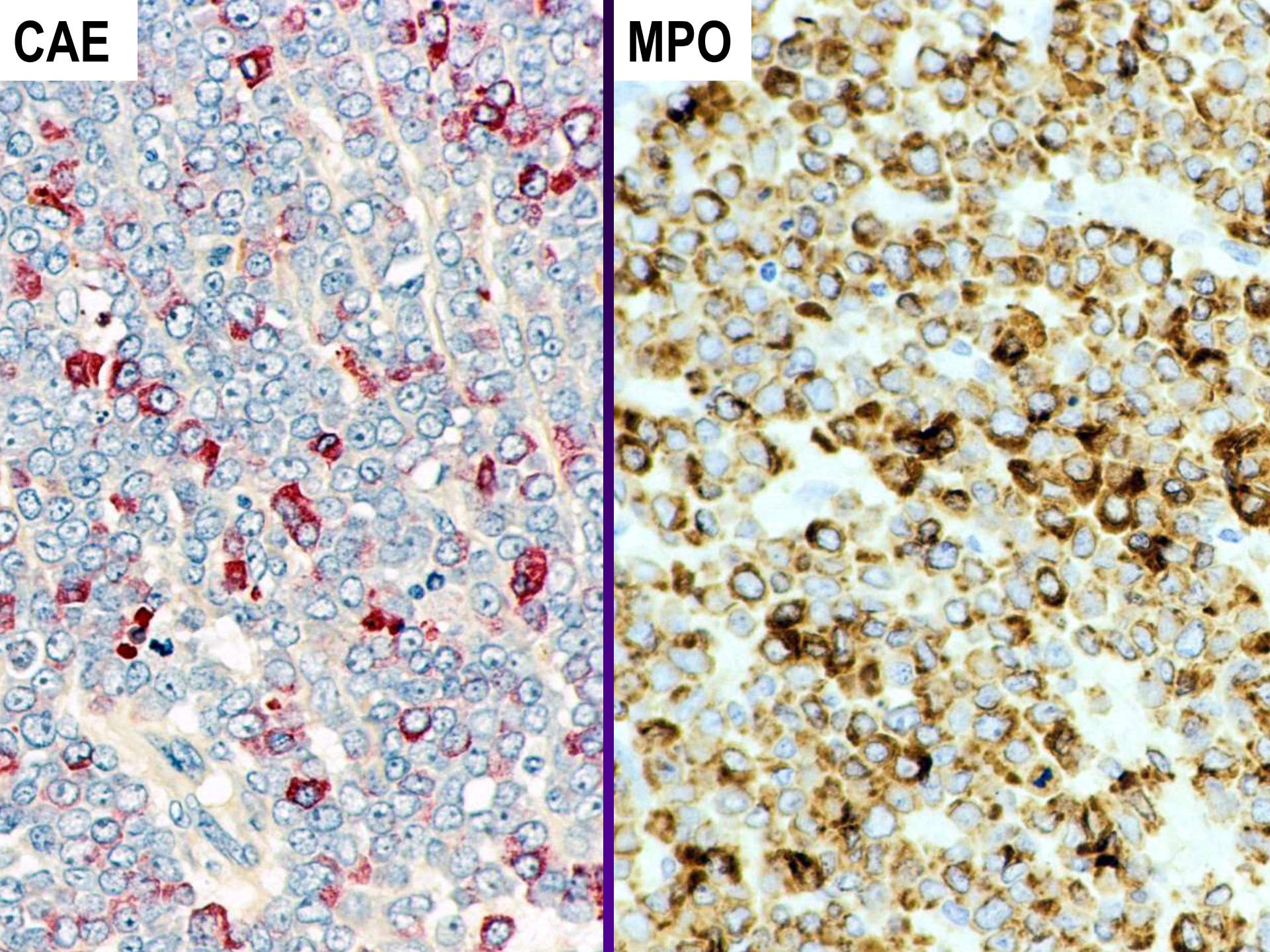
- Any unusual, odd-looking or difficult to classify "lymphoma"
- Eosinophilic rather than amphophilic/basophilic cytoplasm
- Fine granularity in cytoplasm
- Interspersed eosinophilic myelocytes
- Prominent Indian-file pattern of infiltration
- "CD43+ only" phenotype (CD20- CD3-)

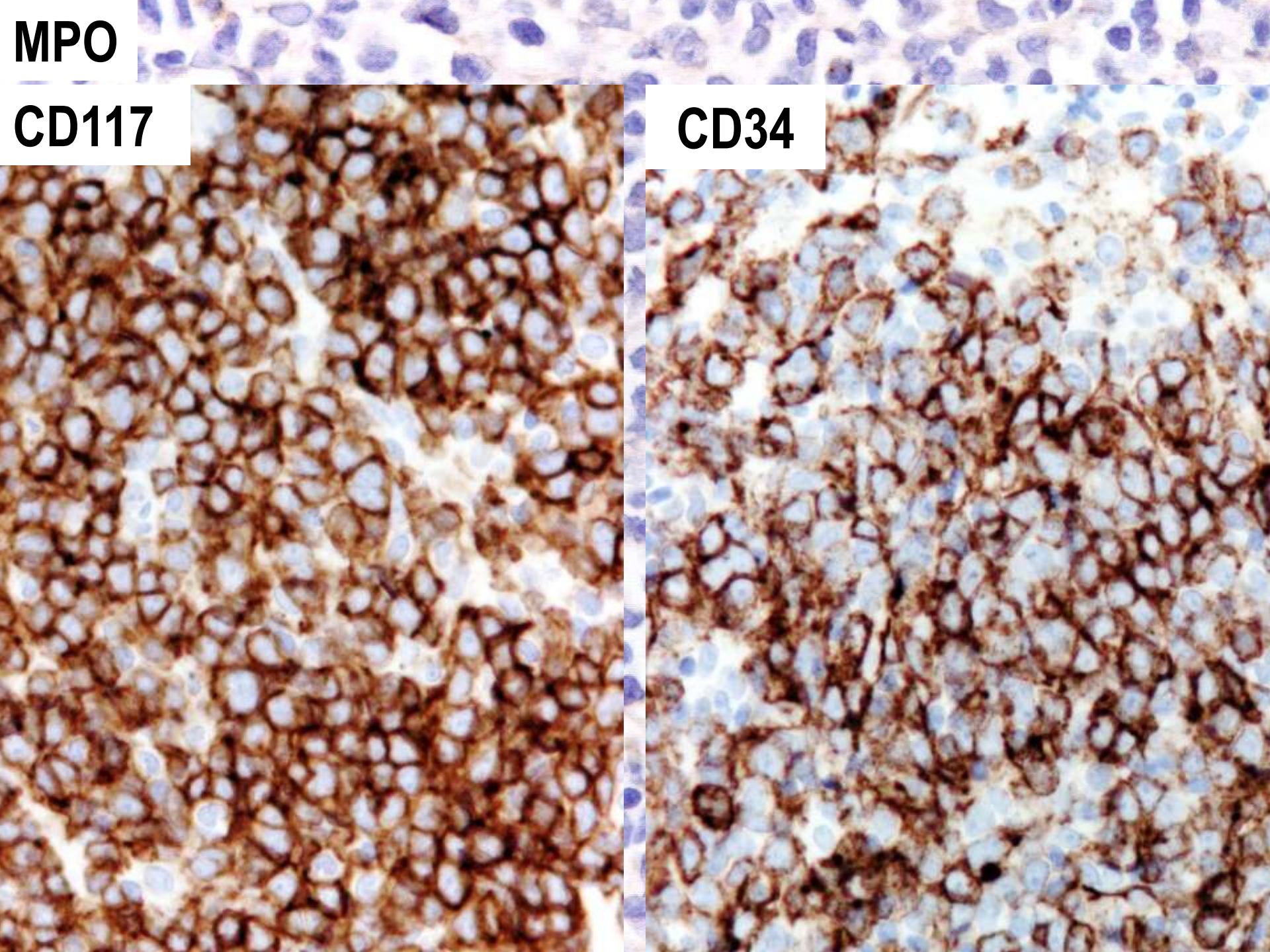




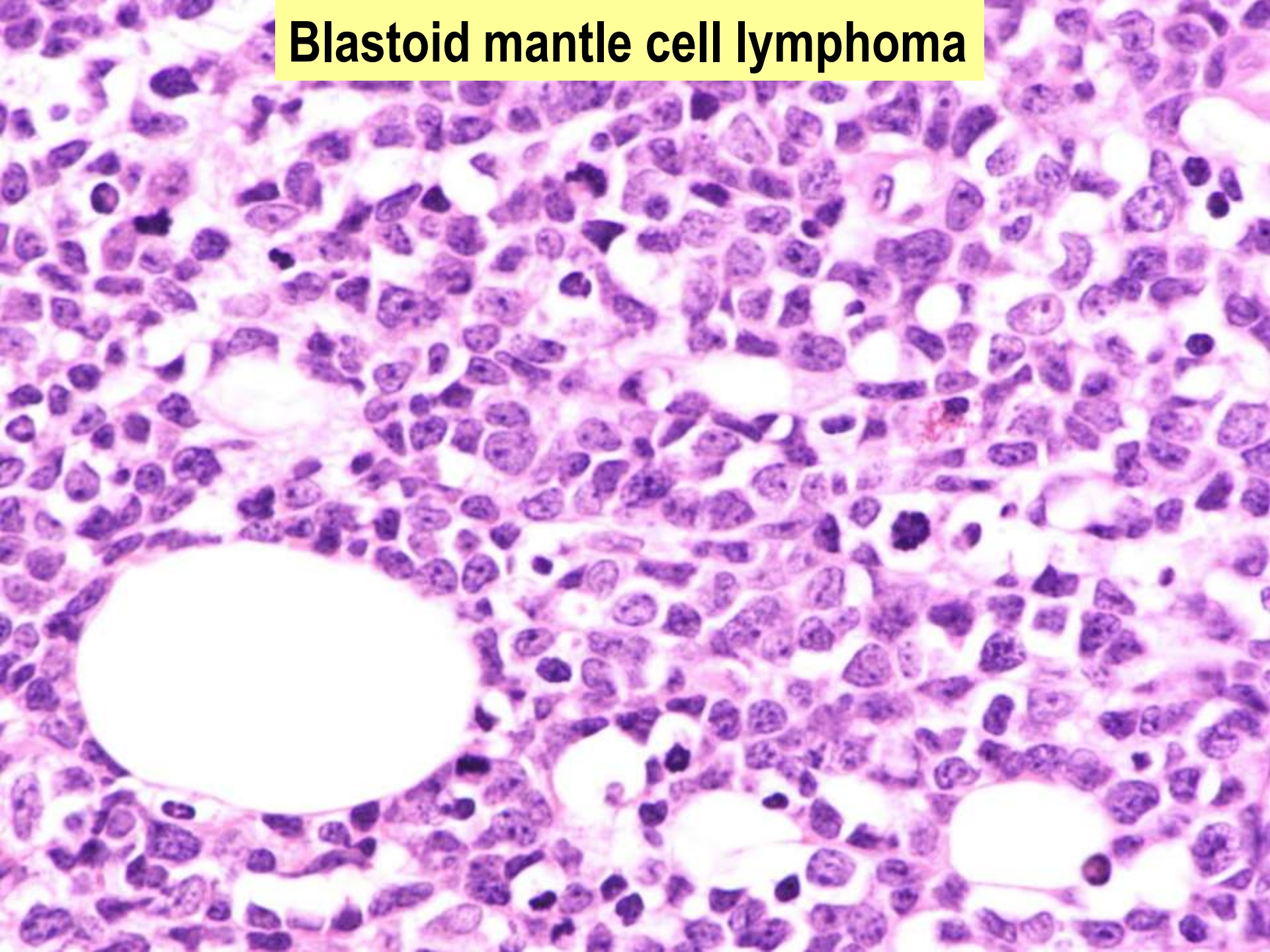


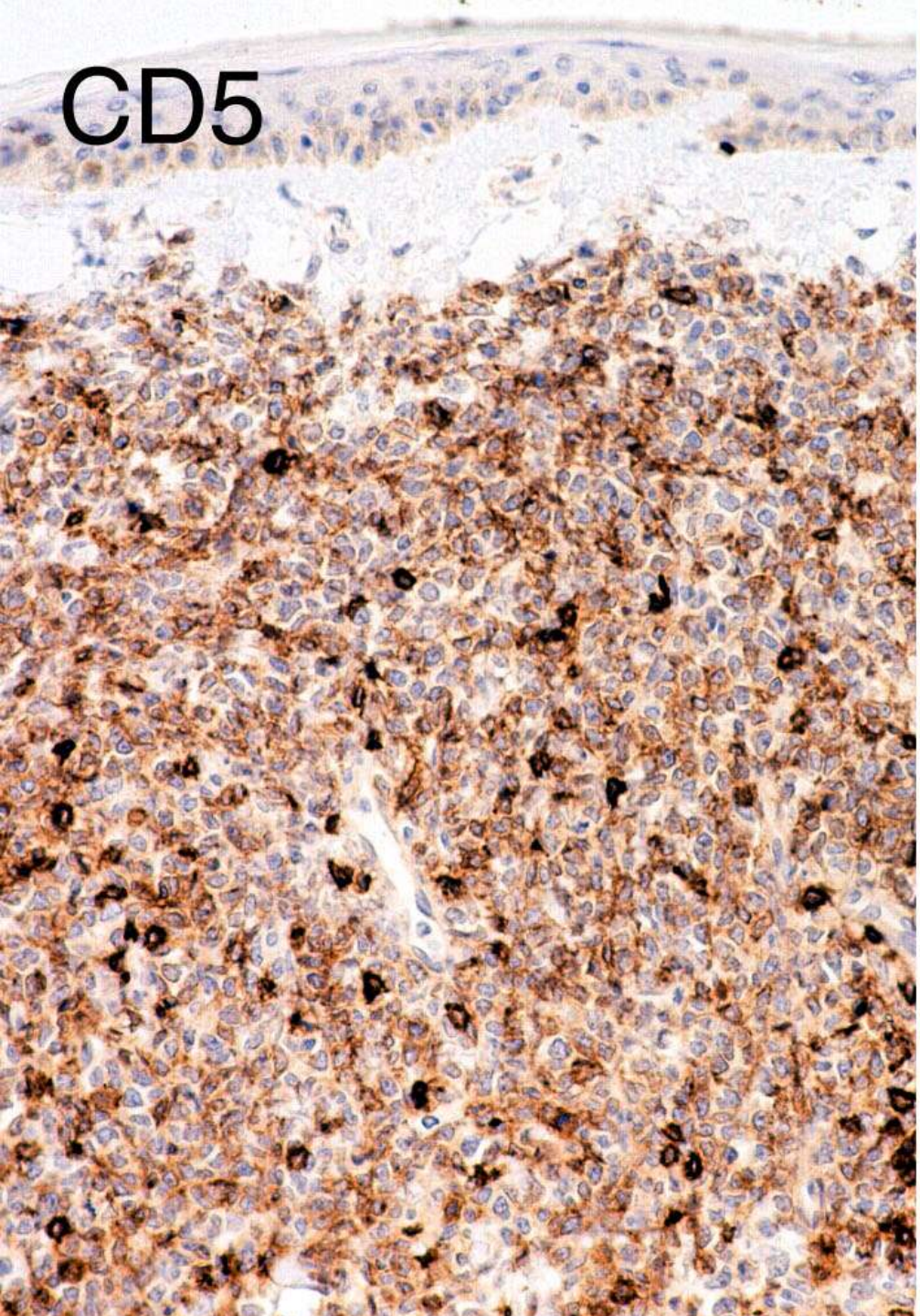

CD43
CD3

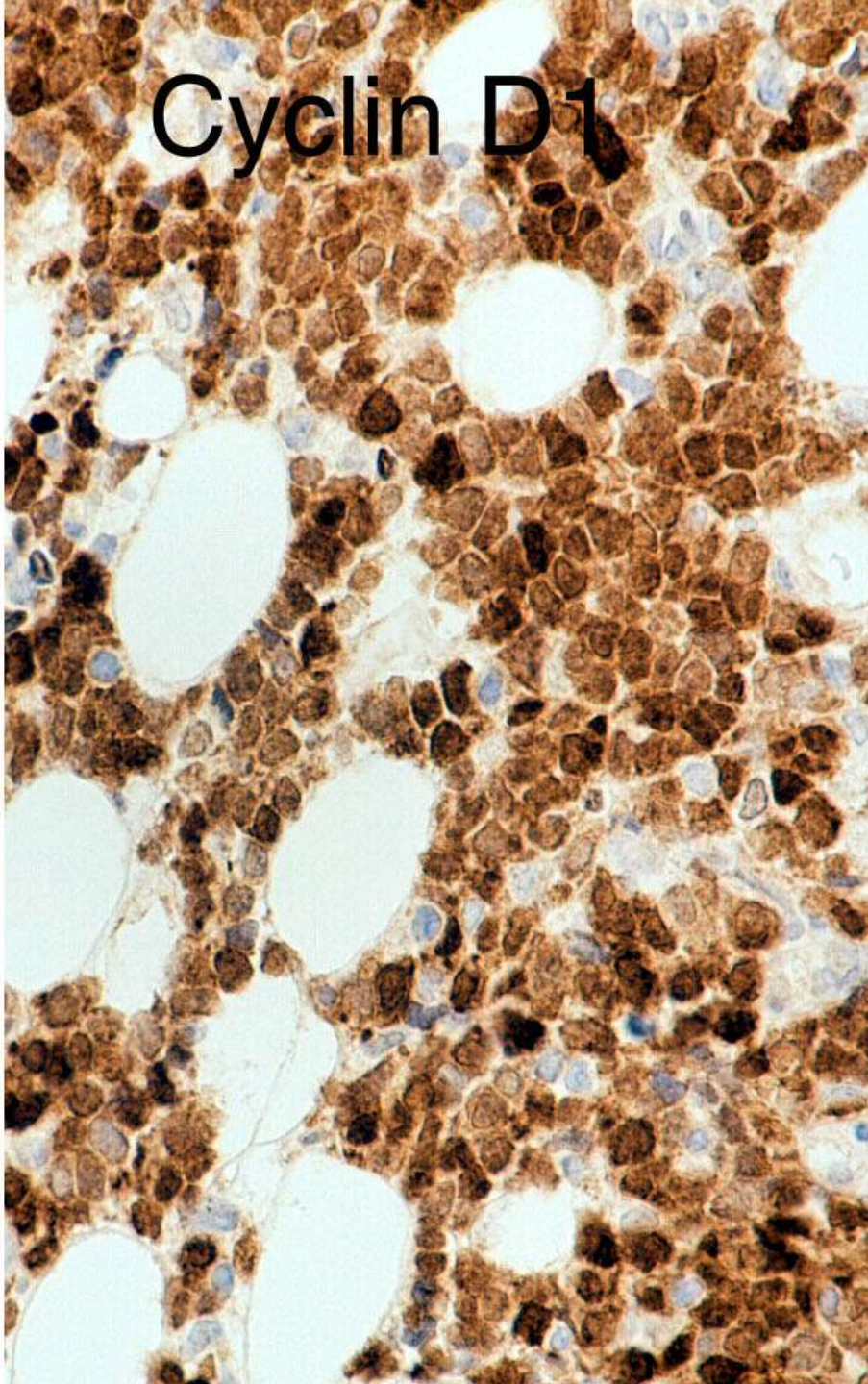

CAE
MPO


MPO
CD117
CD34

Blastoid mantle cell lymphoma




CD5


Cyclin D1

PANNICULITIS PATTERN

- Panniculitis (various types)
- Subcutaneous panniculitis-like T-cell lymphoma
- Extranodal NK/T-cell lymphoma (some cases)
- Primary cutaneous γδ T-cell lymphoma (some cases)

Subcutaneous panniculitis-like T-cell lymphoma

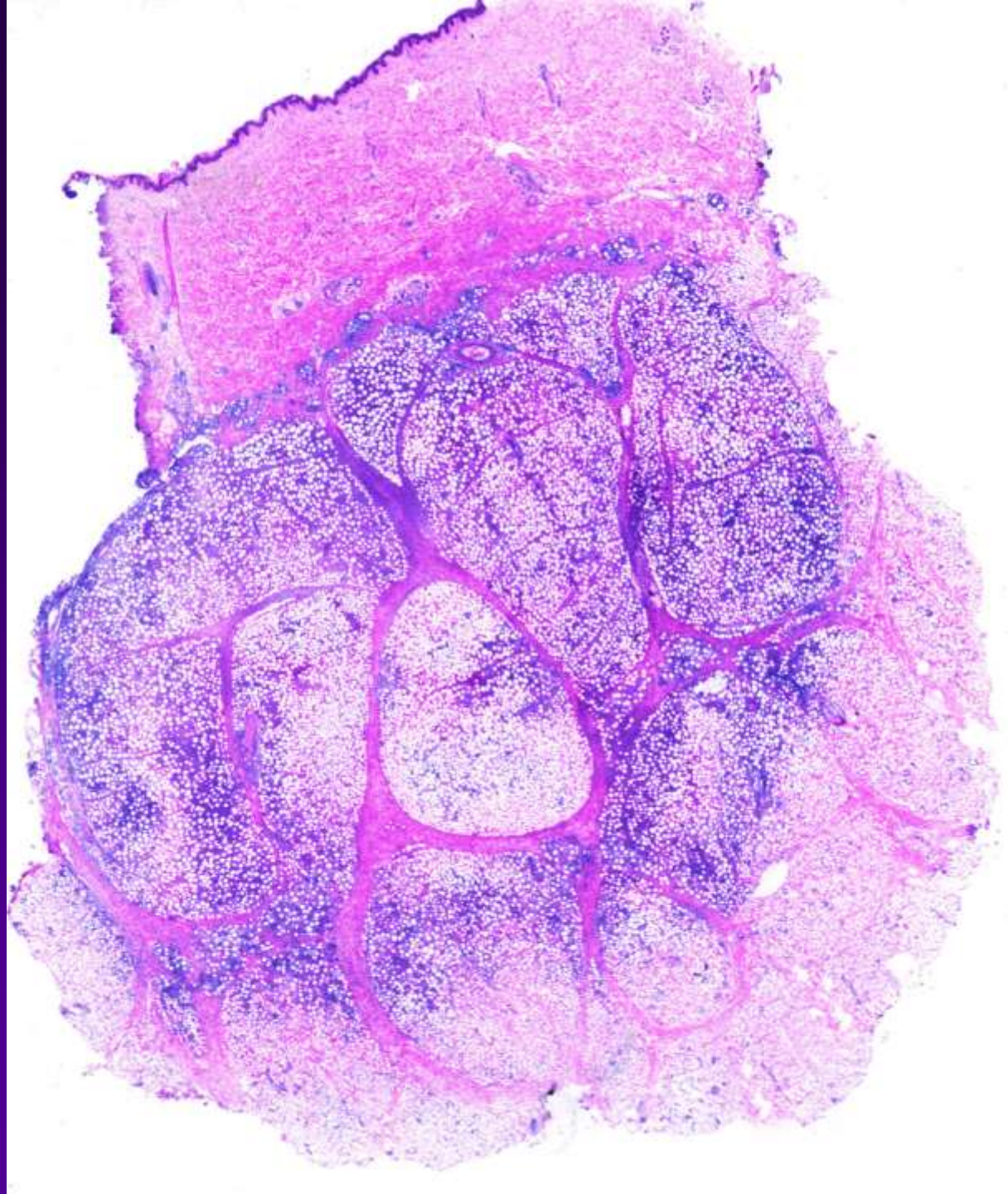
- Definition: A cytotoxic T-cell lymphoma which preferentially infiltrates subcutaneous tissue
- WHO 2001: “Most cases are derived from αβ cells, although 25% may be γδ positive”
- WHO 2008: Cases expressing γδ T-cell receptor are excluded, and classified as “cutaneous gamma-delta T-cell lymphoma” (aggressive)

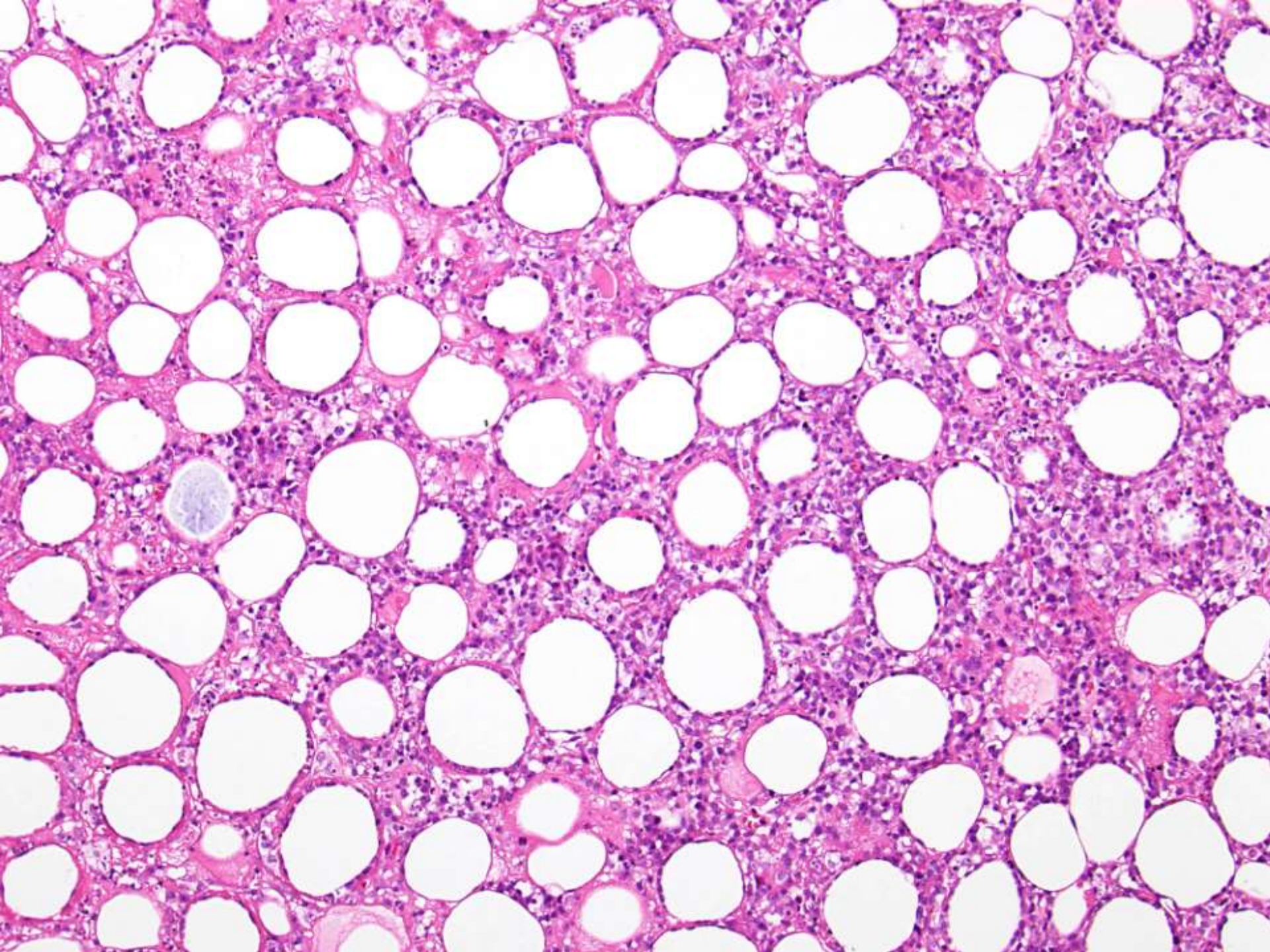
Subcutaneous panniculitis-like T-cell lymphoma: Clinical features

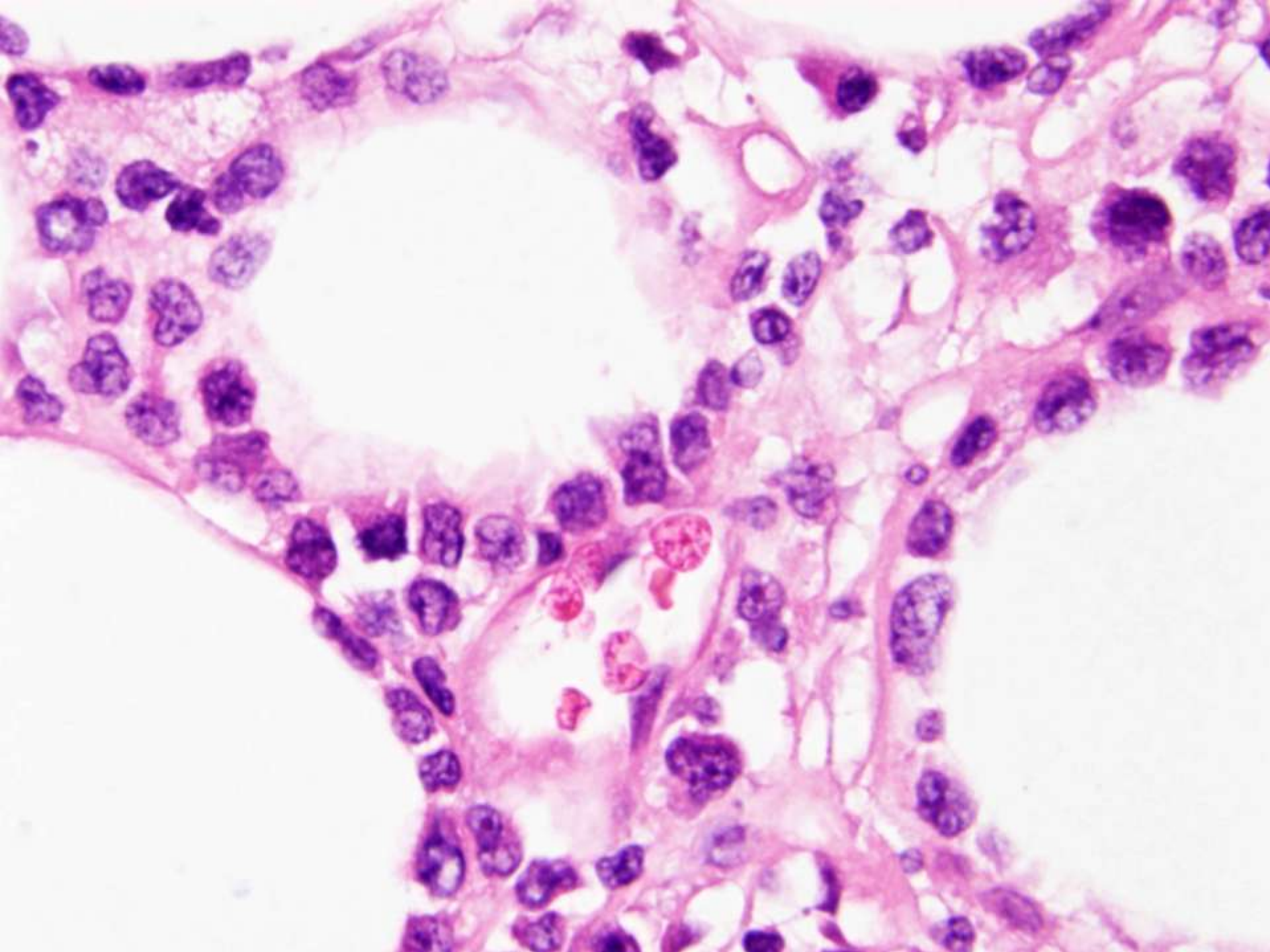
- Median age: 30 years
- Presentation: solitary or multiple subcutaneous nodules (limbs > trunk)
- Dissemination to LN and other organs uncommon and often late
- 59% have B symptoms
- Prognosis favorable, with 5-yr overall survival 82%
  - 91% for cases without hemophagocytic syndrome
  - 46% for cases with hemophagocytic syndrome

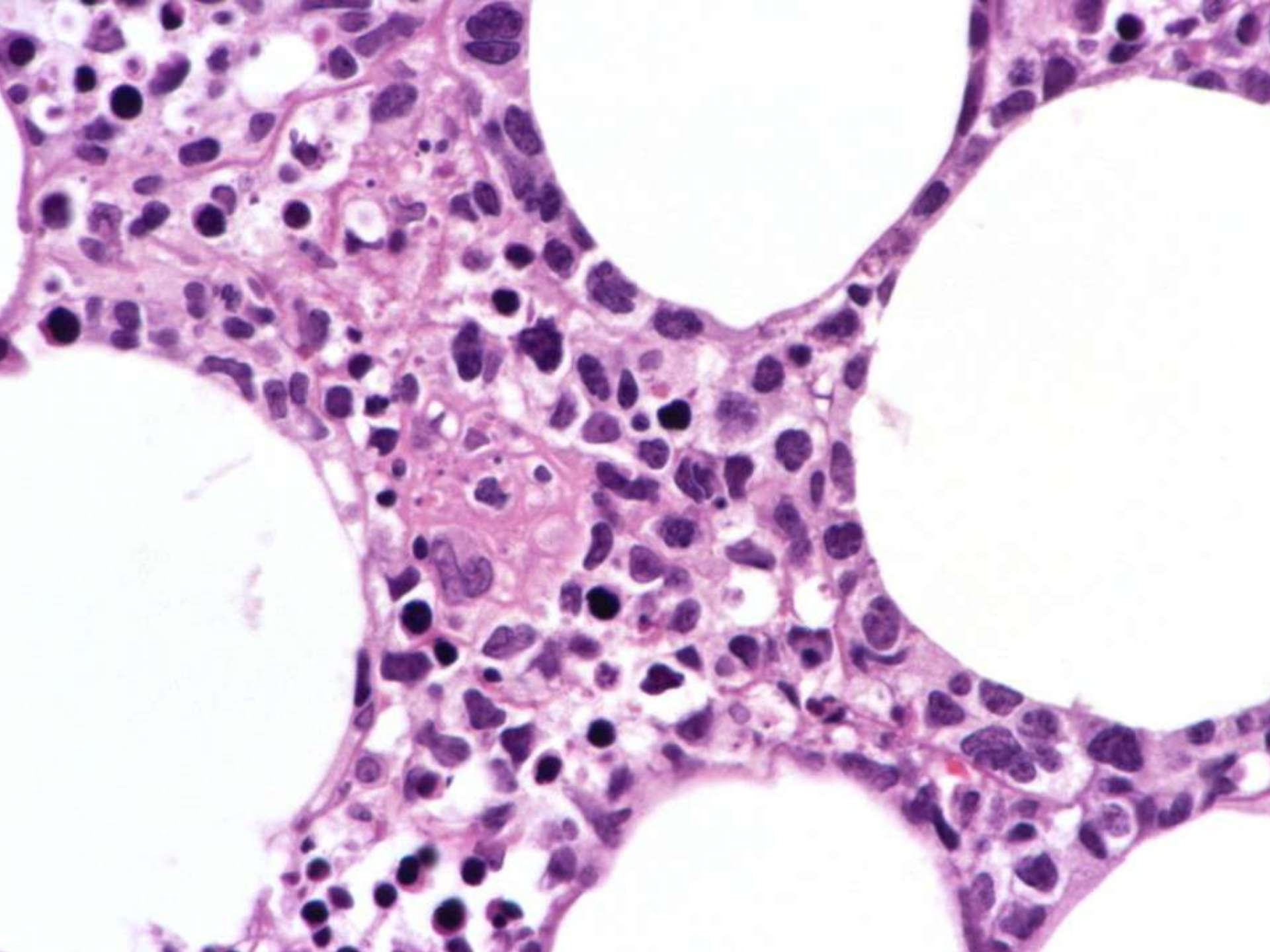
Subcutaneous panniculitis-like T-cell lymphoma: Pathology

- Usually confined to subcutis (at most minimal extension to lower dermis)
- Lace-like pattern of interstitial infiltrate
- Rimming of fat spaces (characteristic but not specific)
- Necrosis and apoptosis common
- Lymphoma cells: minimally atypical small cells to medium-sized or large cells
- Interspersed phagocytic histiocytes common



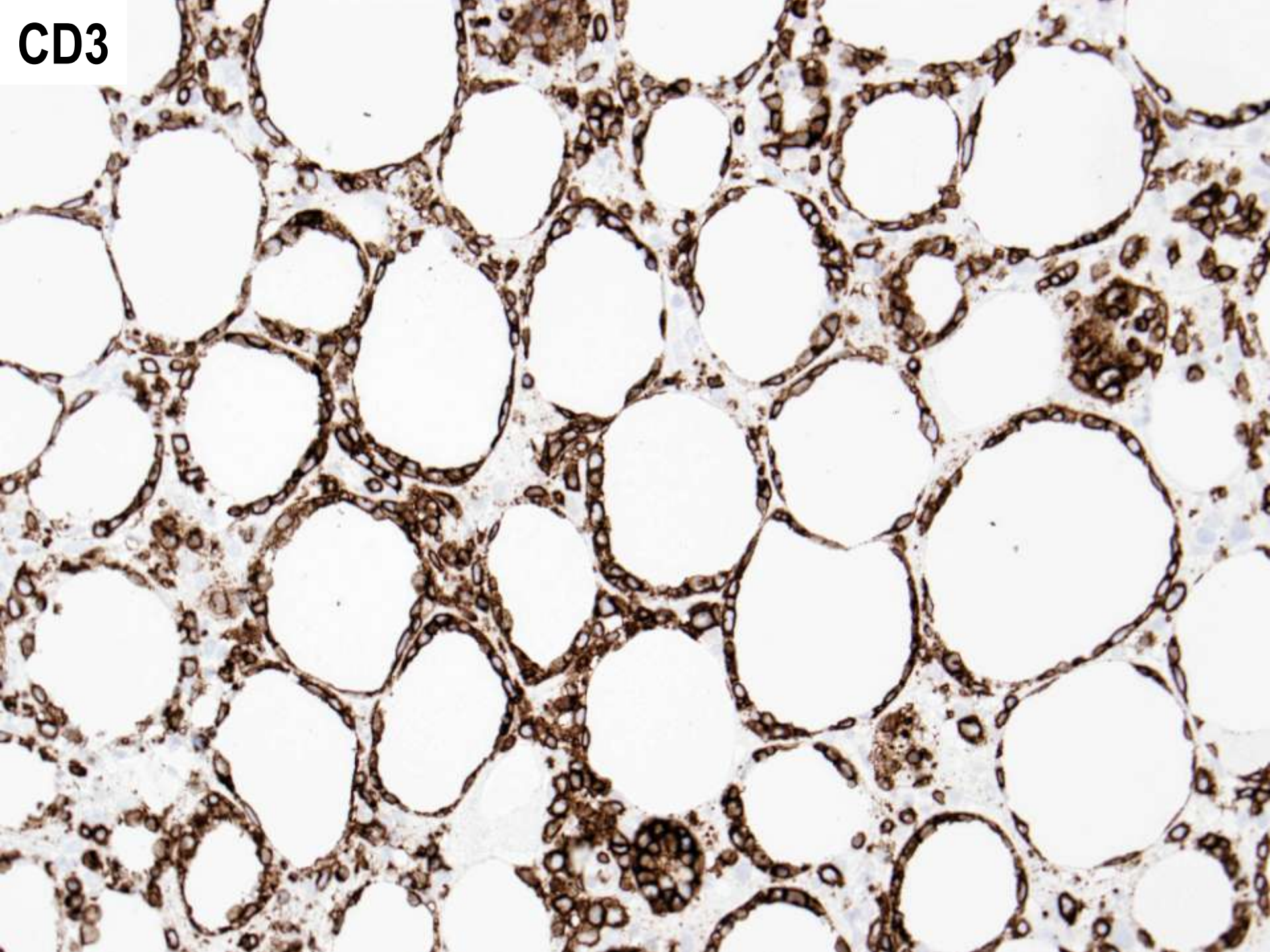






Subcutaneous panniculitis-like T-cell lymphoma: Biologic features

- Pan T+
- Most cases CD4-, CD8+
- Cytotoxic makers+ (e.g. TIA-1)
- CD56-
- TCR genes: rearranged
- EBV: negative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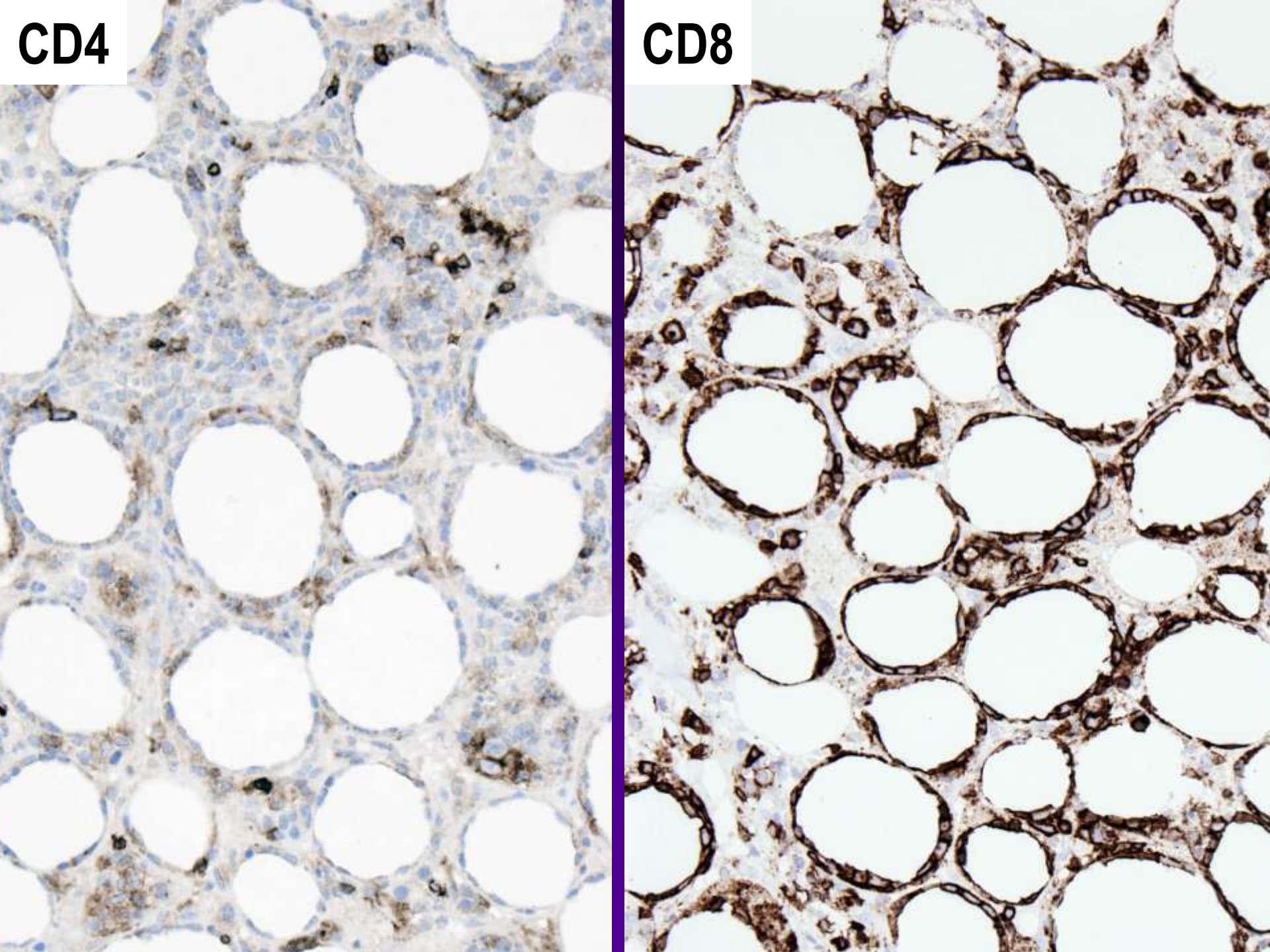
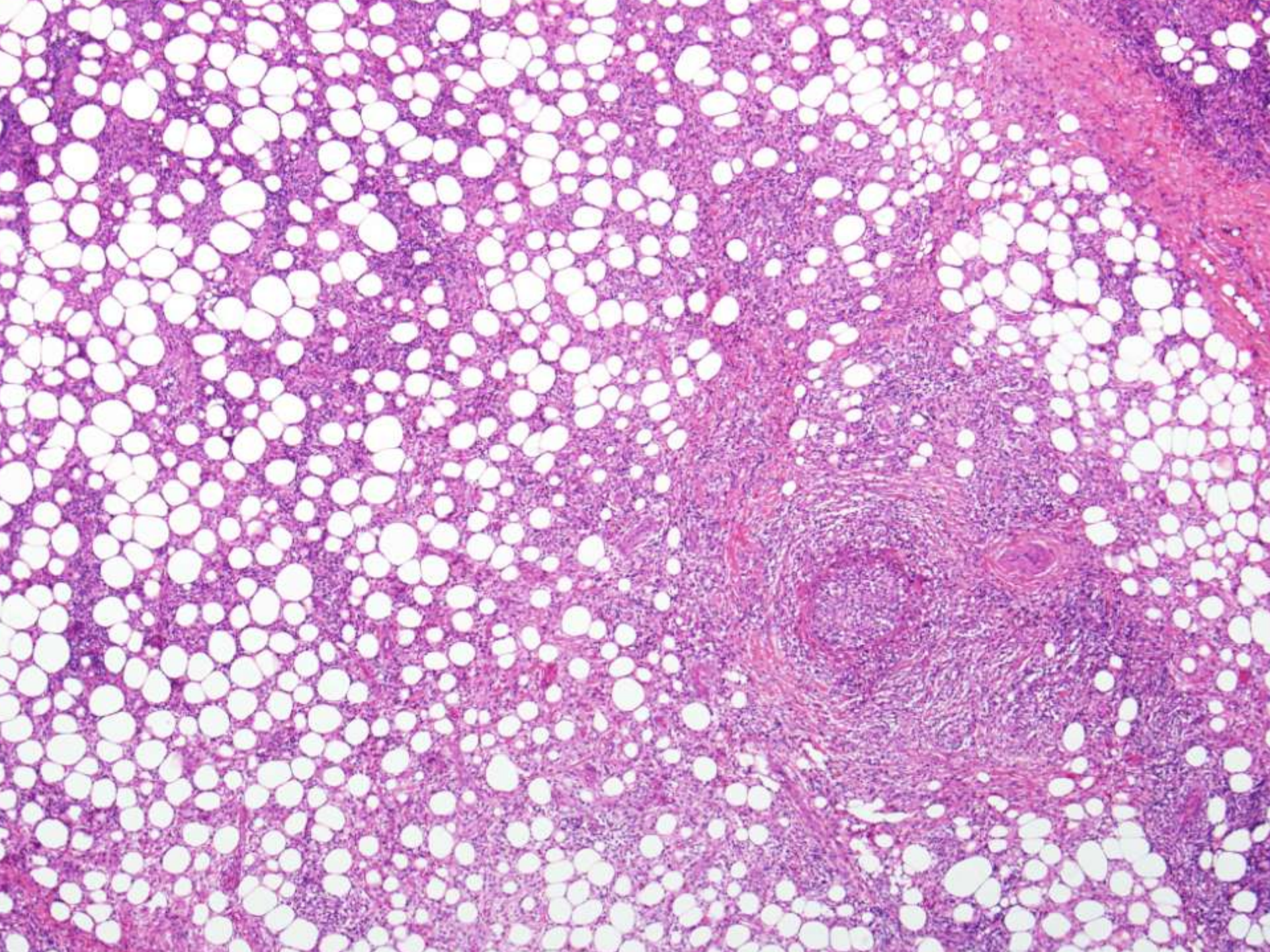
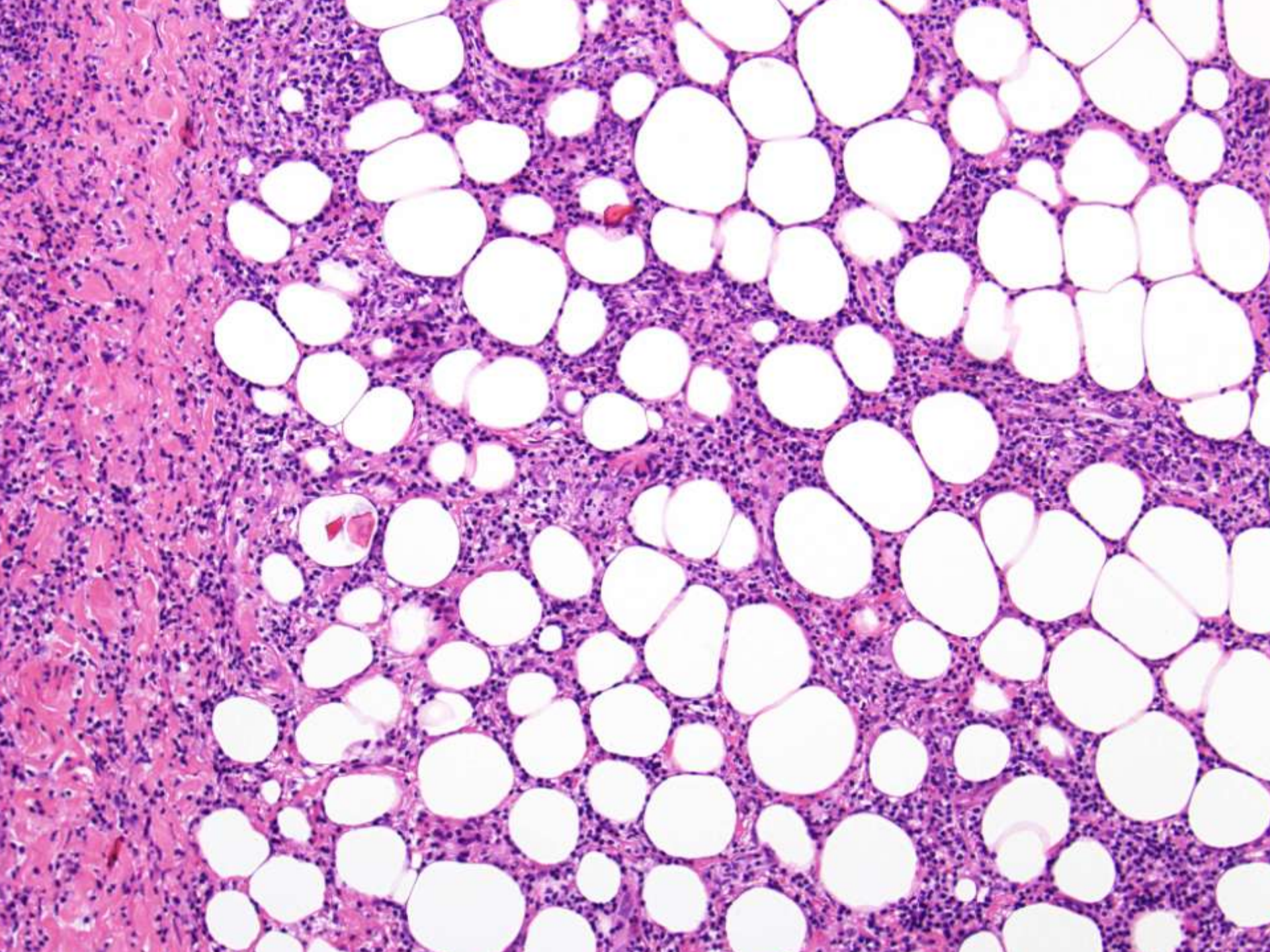
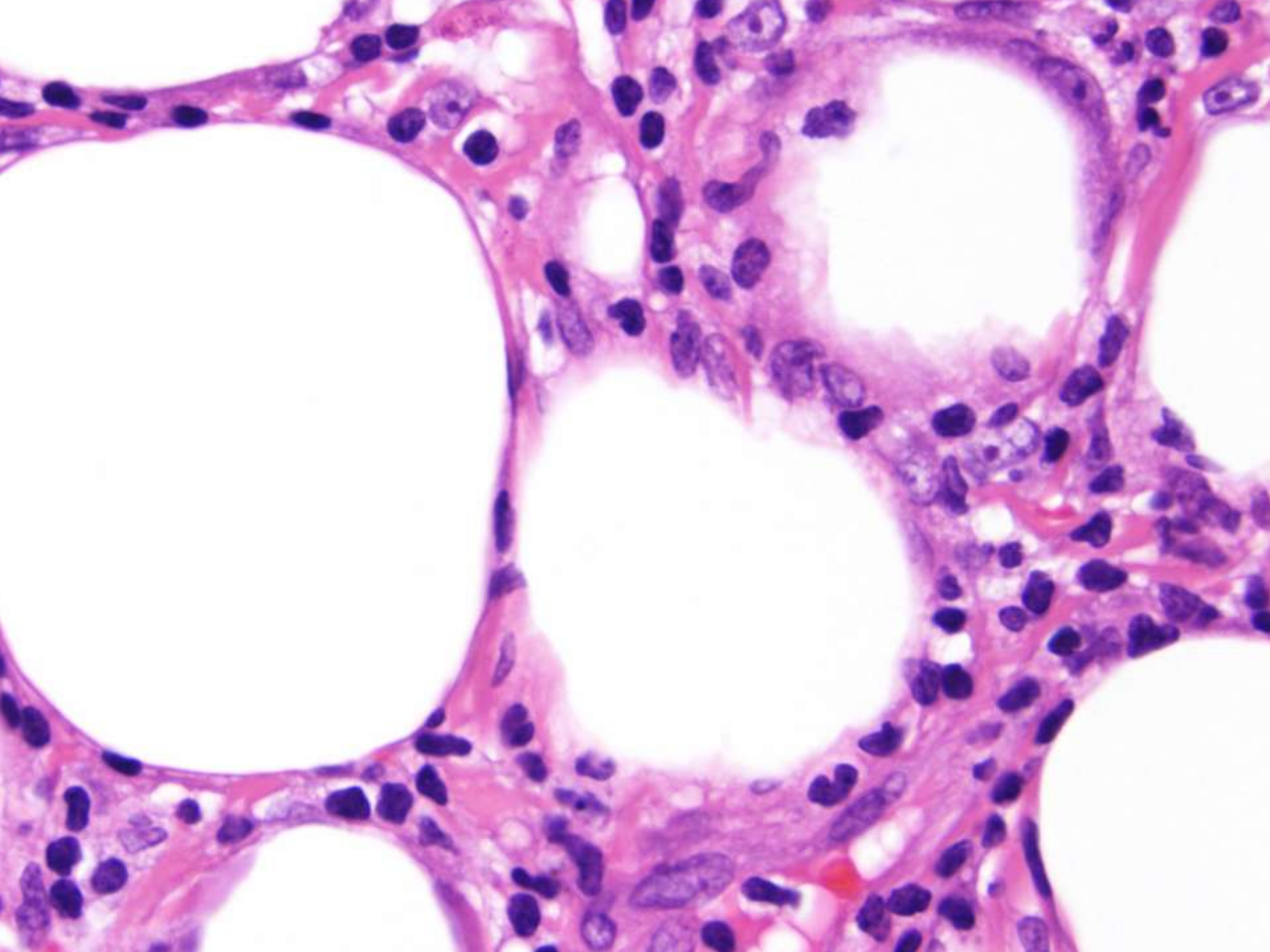
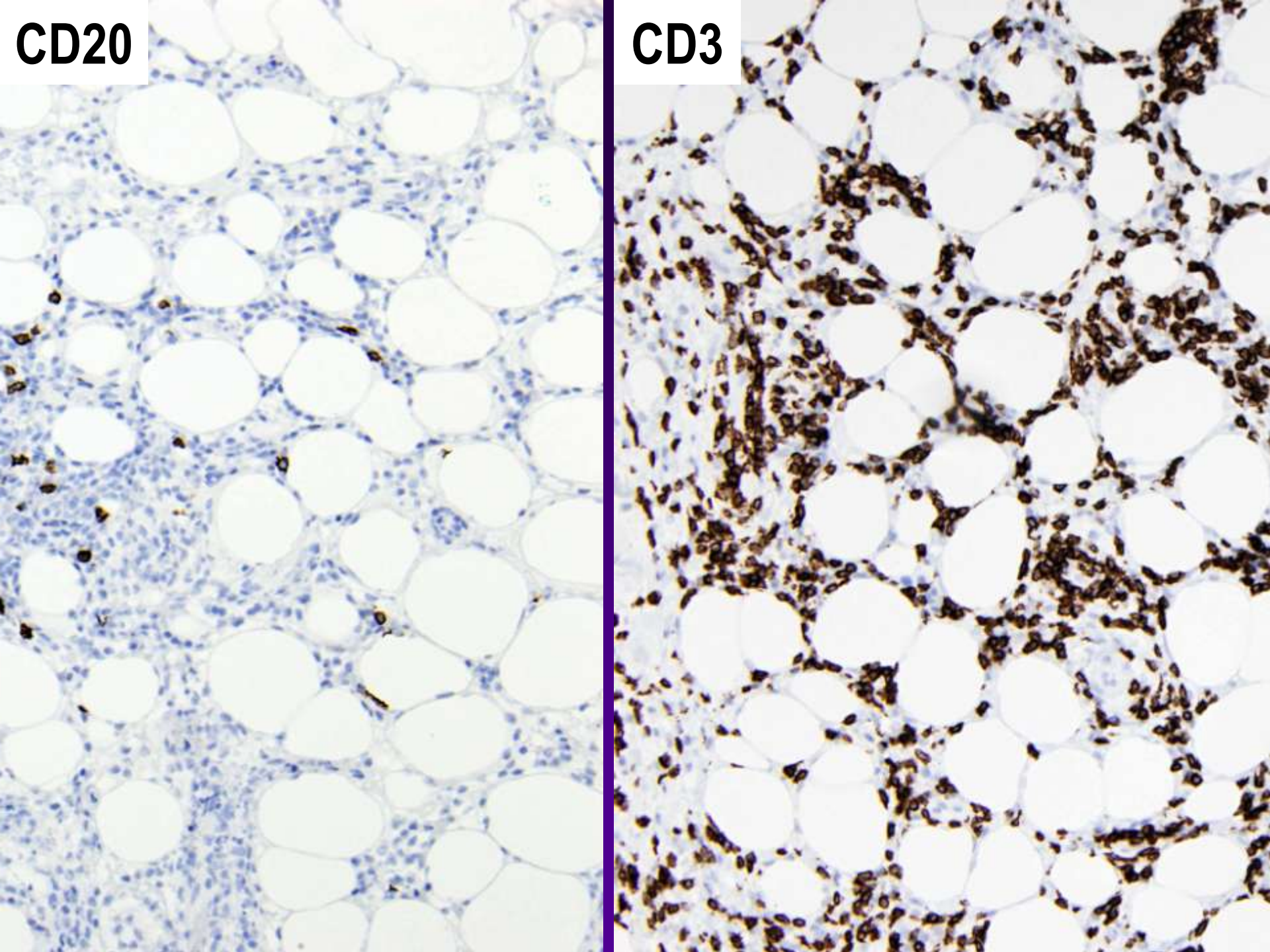

CD4
CD8

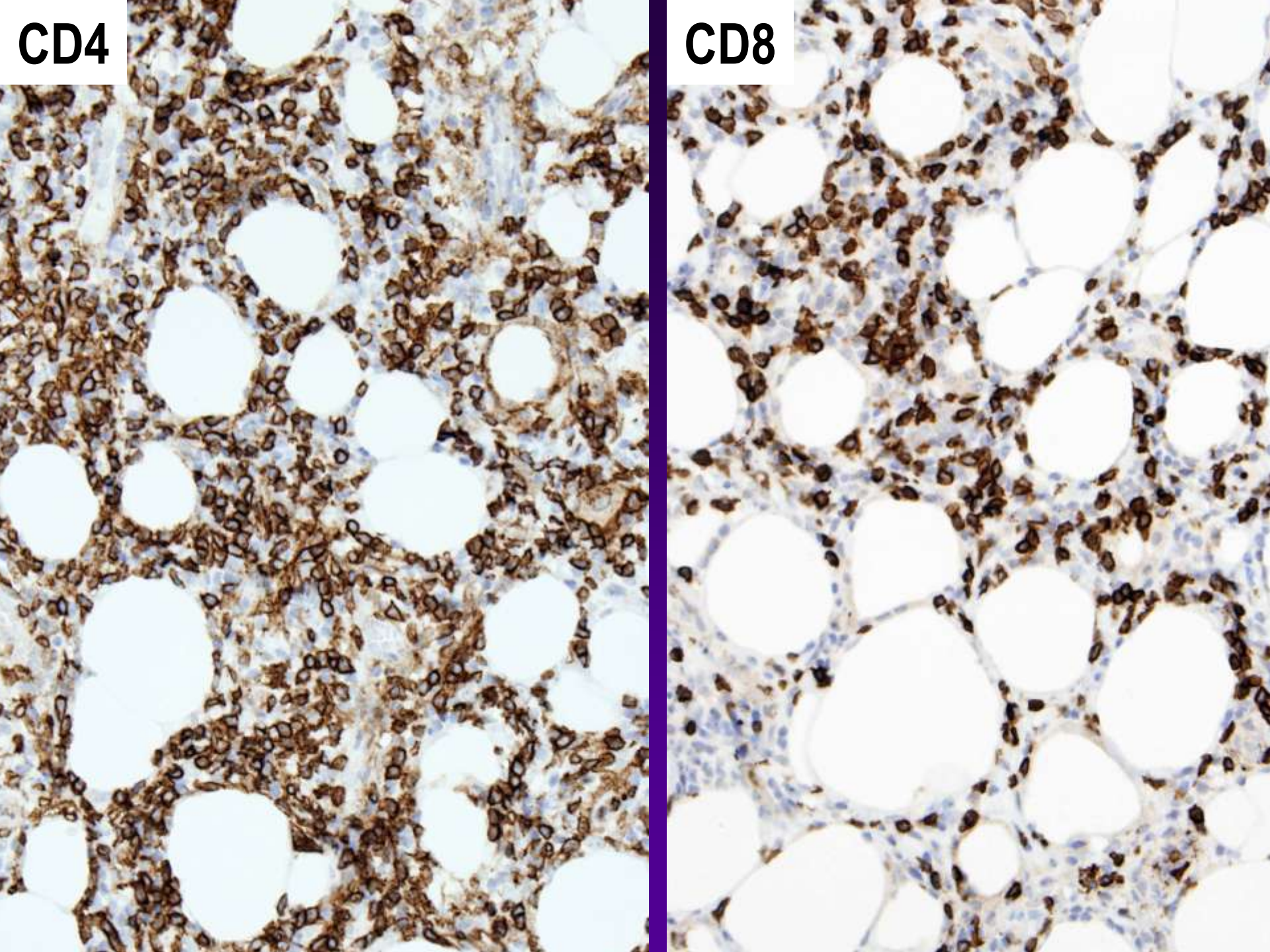
	Subcutaneous panniculitis-like T cell lymphoma	Panniculitis, e.g. erythema nodosum, lupus profundus
Lobular septa	Often obliterated	Usually preserved septa
Lymphoid follicles	Very rare	Common
Rimming of fat spaces	Common	Uncommon
Cell types	Cytologic atypia minimal to definite; CD8+ T cells	No cytologic atypia; mixture of T cell (CD4 and CD8), B cells, plasma cells





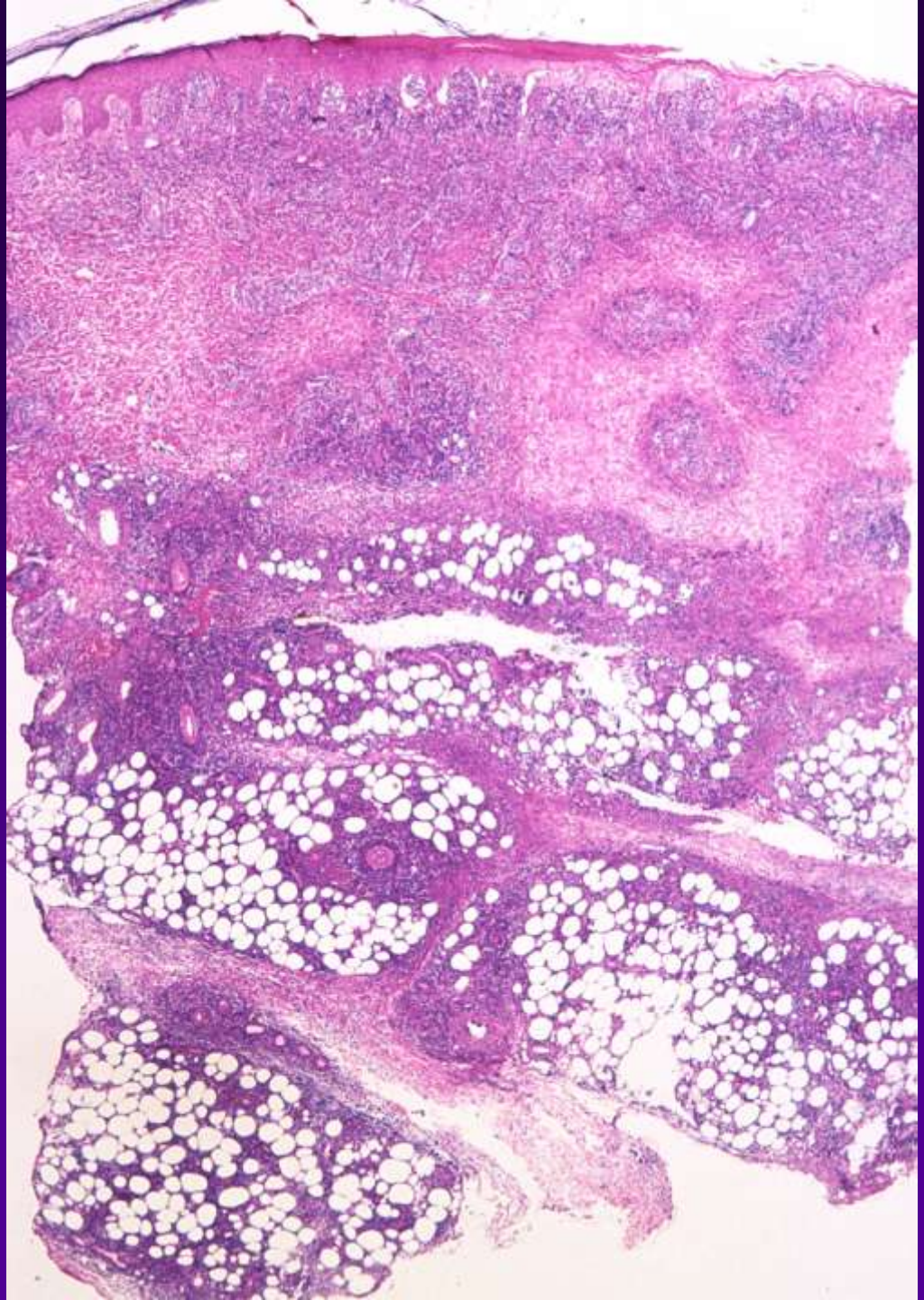


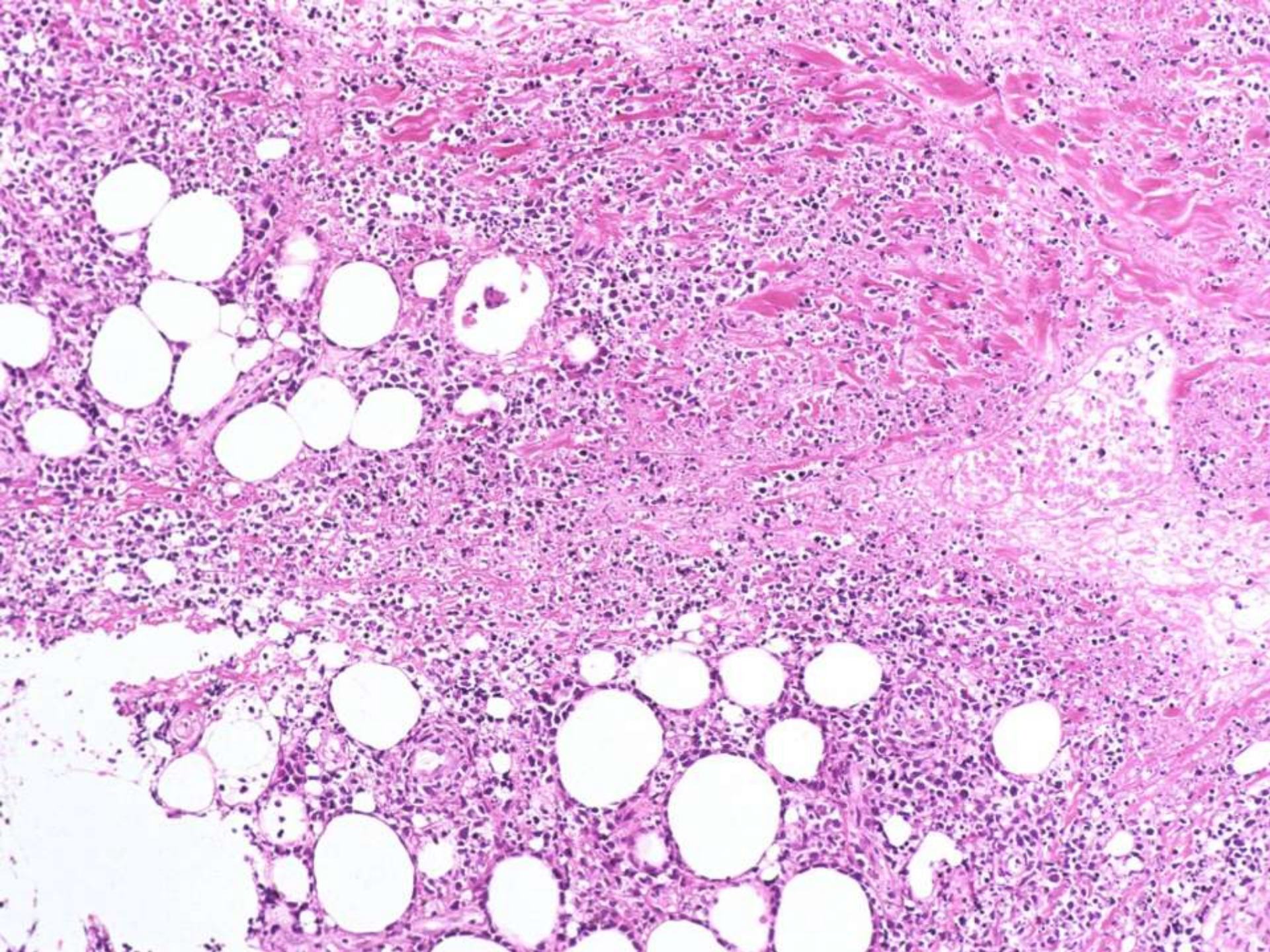

CD20
CD3

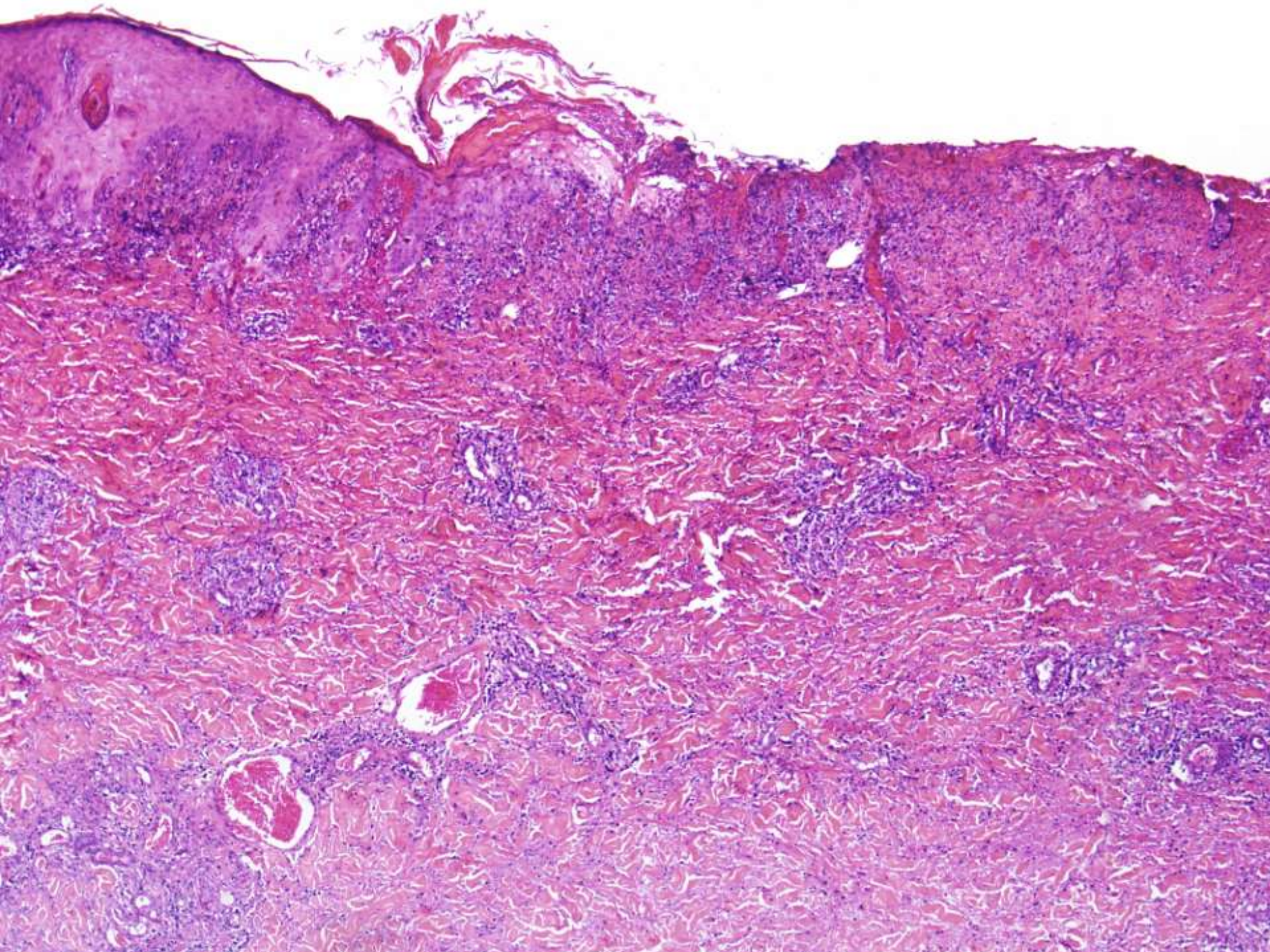

CD4
CD8

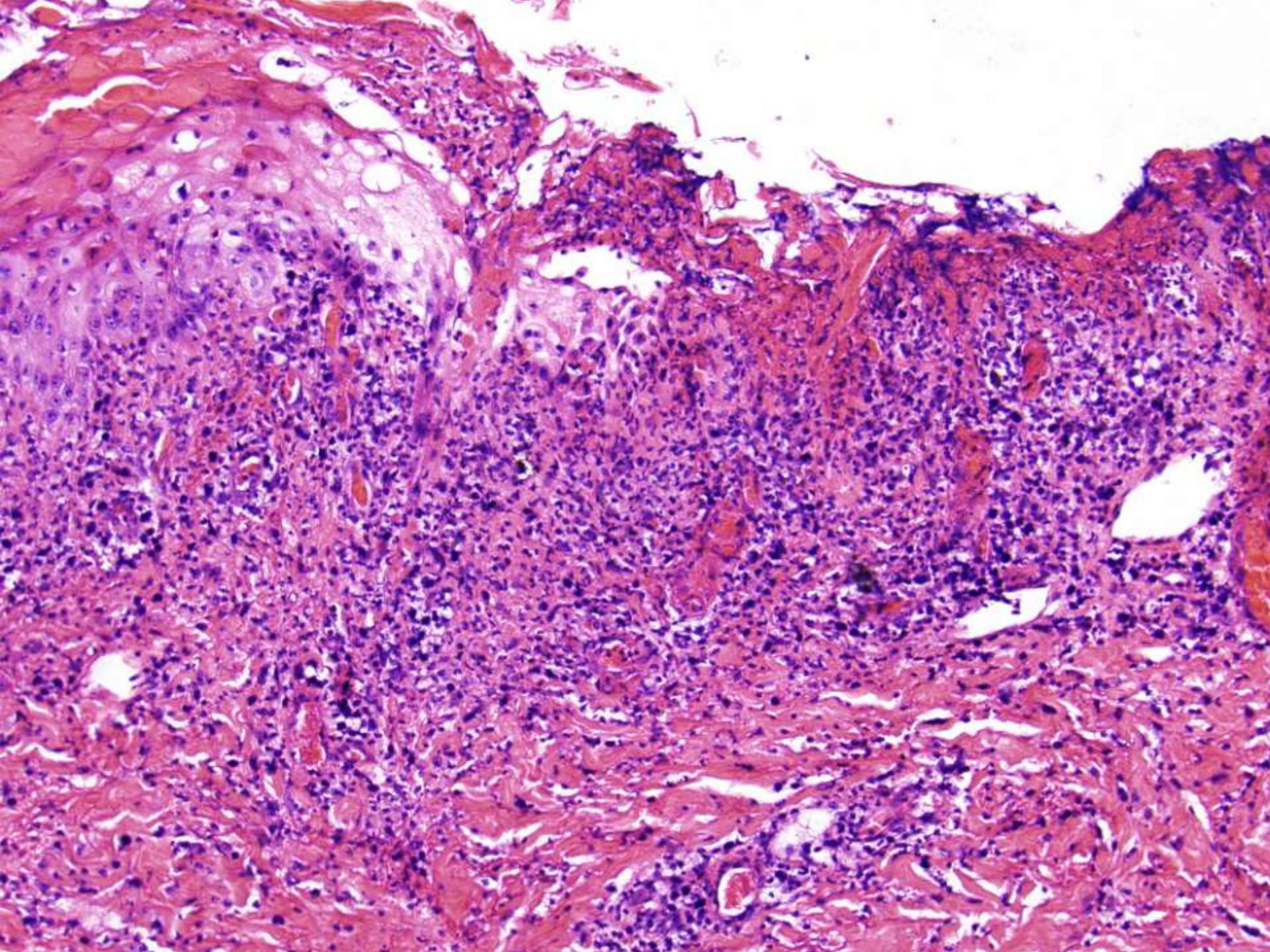
Extranodal NK/T-cell lymphoma

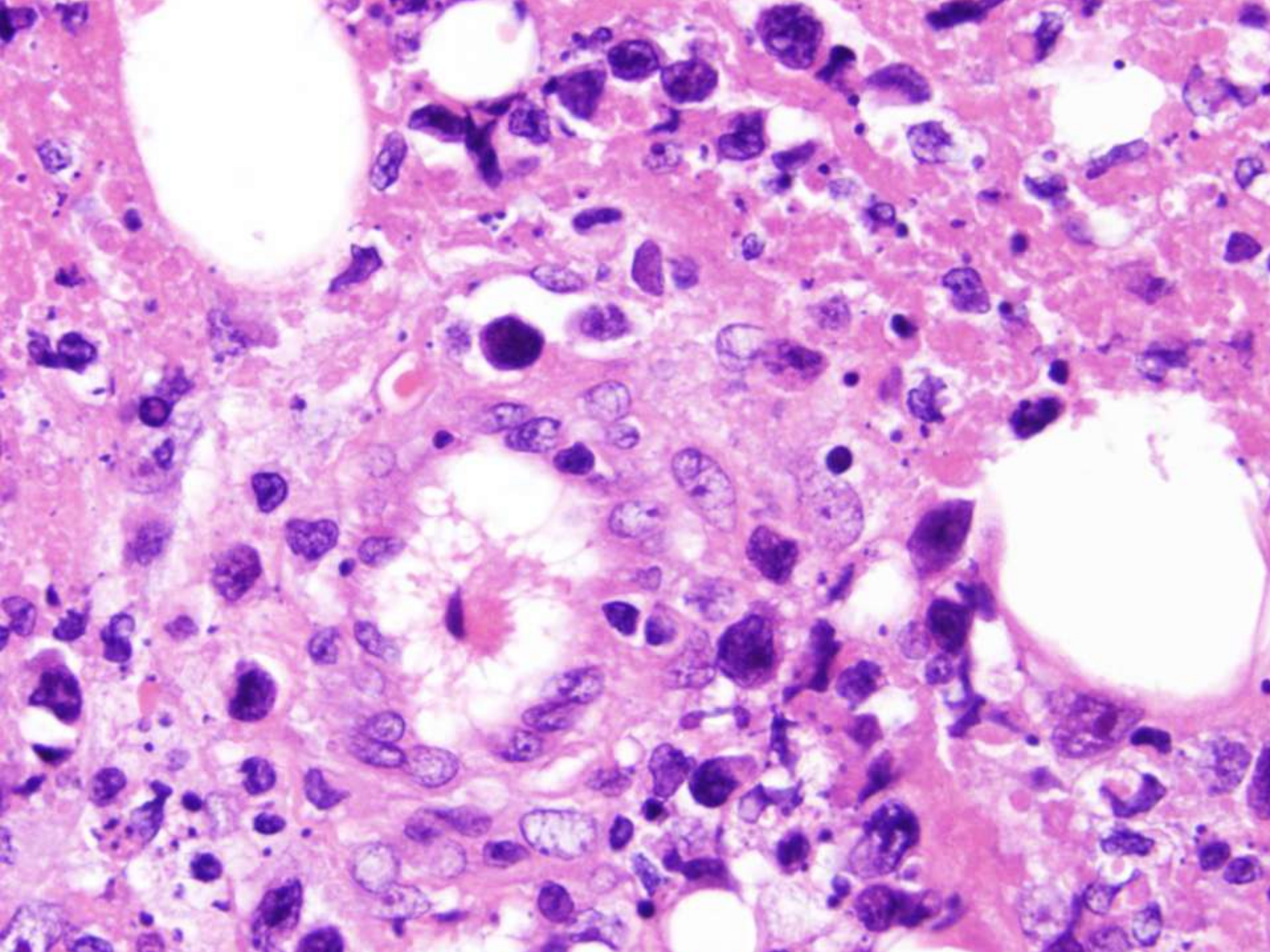
- More prevalent among Asians, Mexicans and South Americans than Caucasians
- The prototype involves nasal cavity, but various extranodal sites can be affected, especially skin
- Skin lesions often occur in multiple anatomic sites
- Skin nodules often show ulceration and necrosis
- Systemic symptoms are common
- Highly aggressive, with poor response to treatment, with most patients die within 6 months





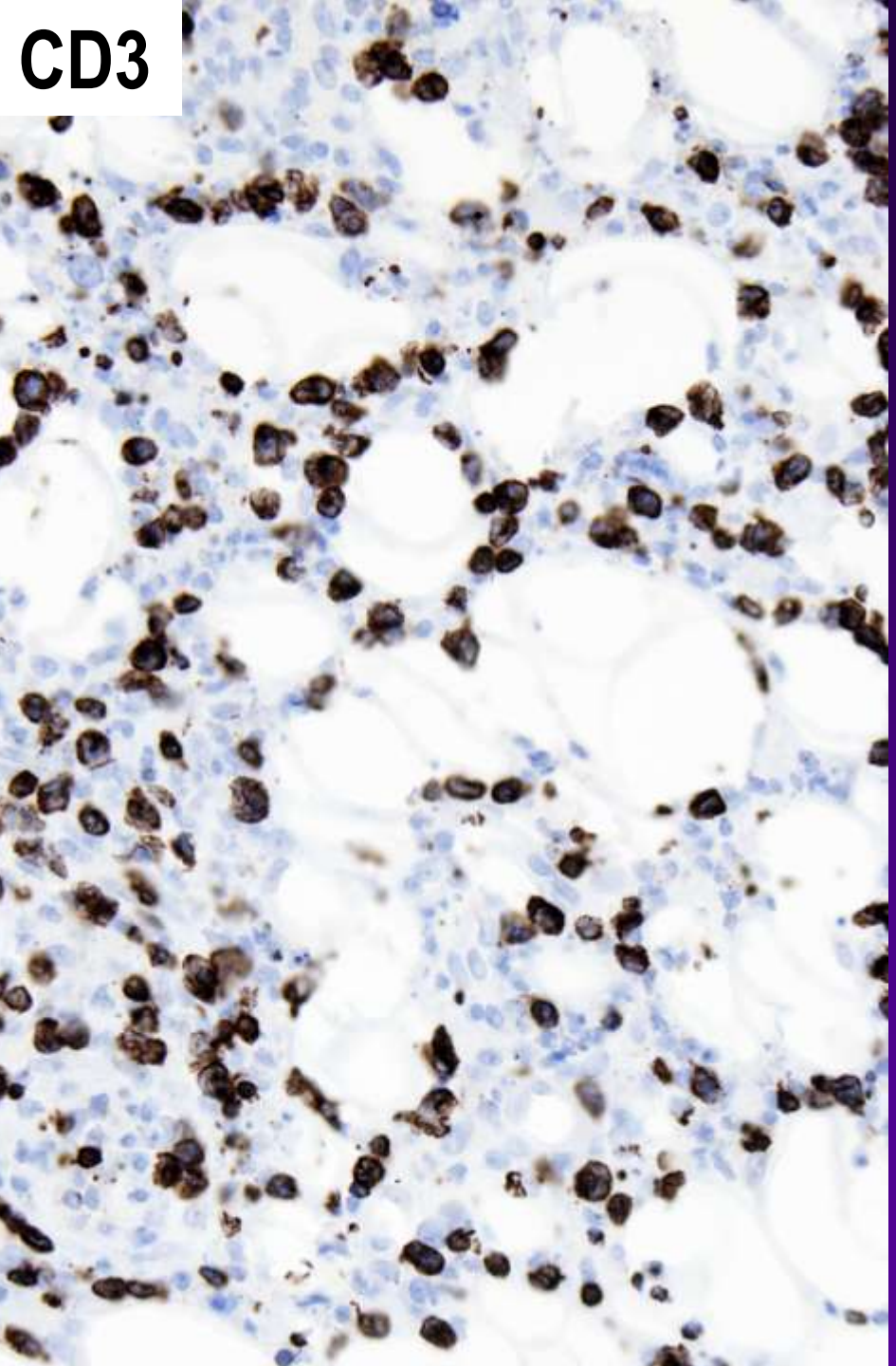


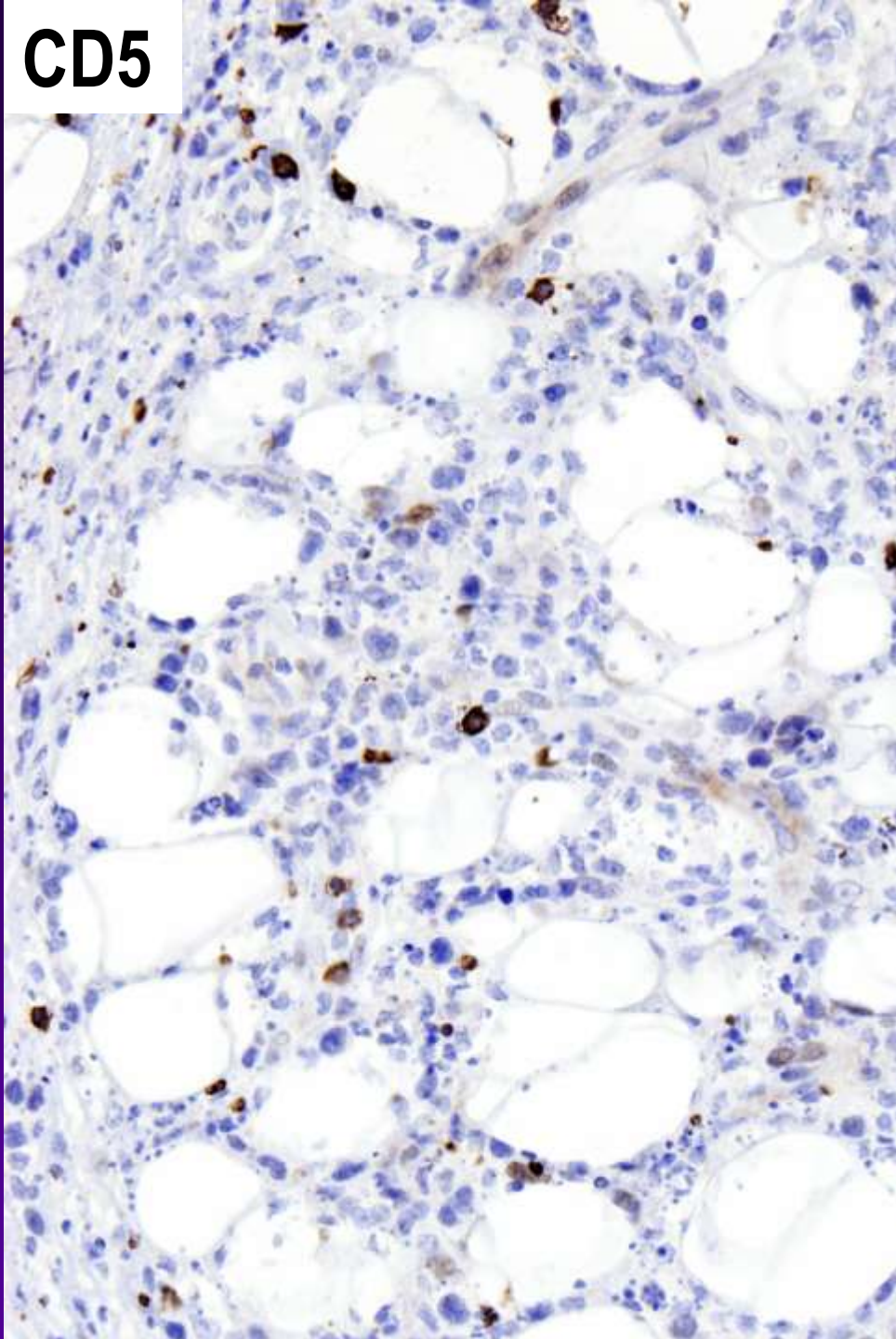


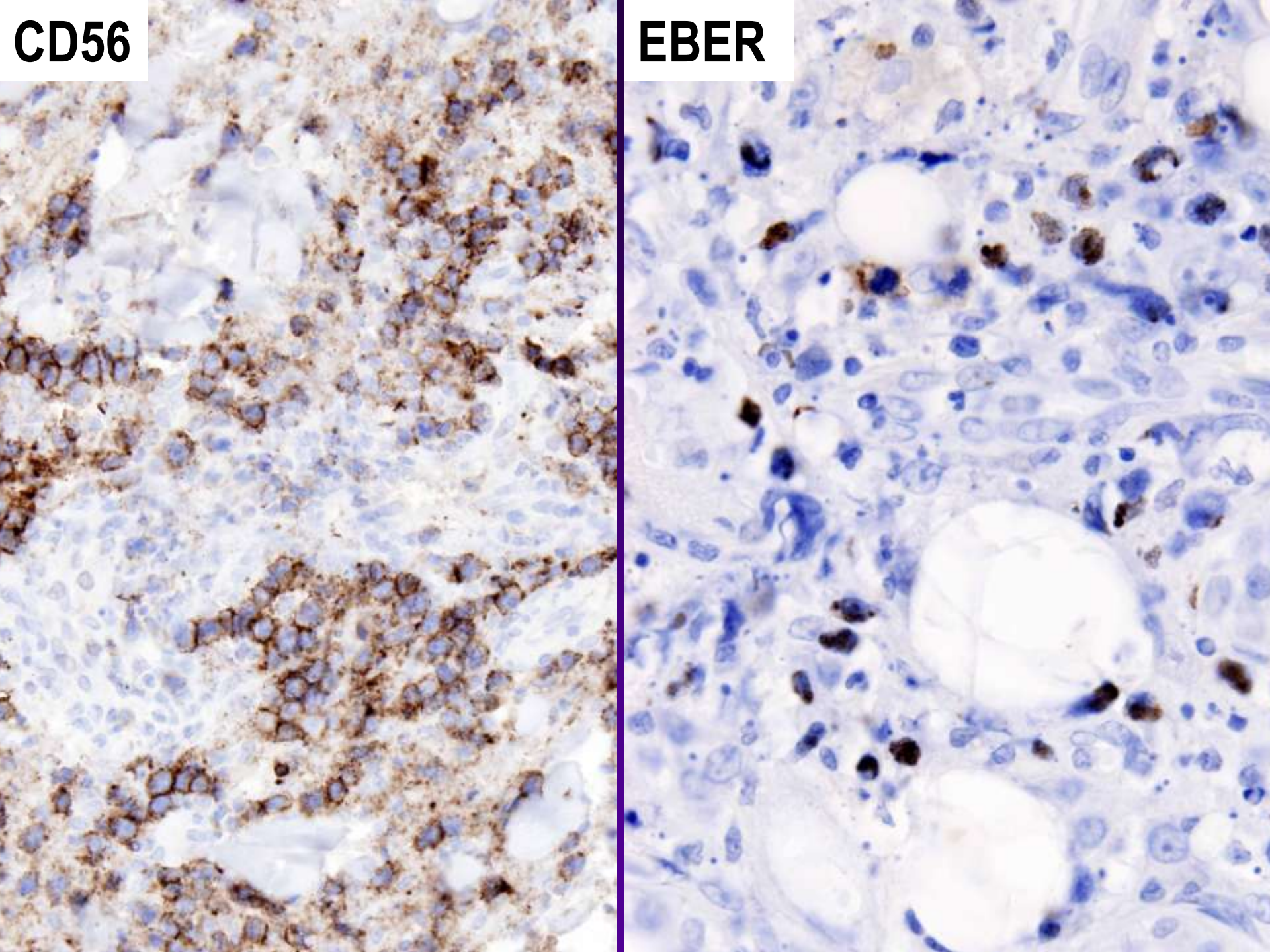


Extranodal NK/T-cell lymphoma: Immunophenotype and genotype

- CD2 +
- Surface CD3-; TCR-; Cytoplasmic CD3ε+
- CD56+
- CD4, CD5, CD7, CD8: often negative
- Cytotoxic molecules+ (perforin, granzyme B, TIA1)
- Occasionally positive for CD30
- EBER-


CD3


CD5


CD56
EBER

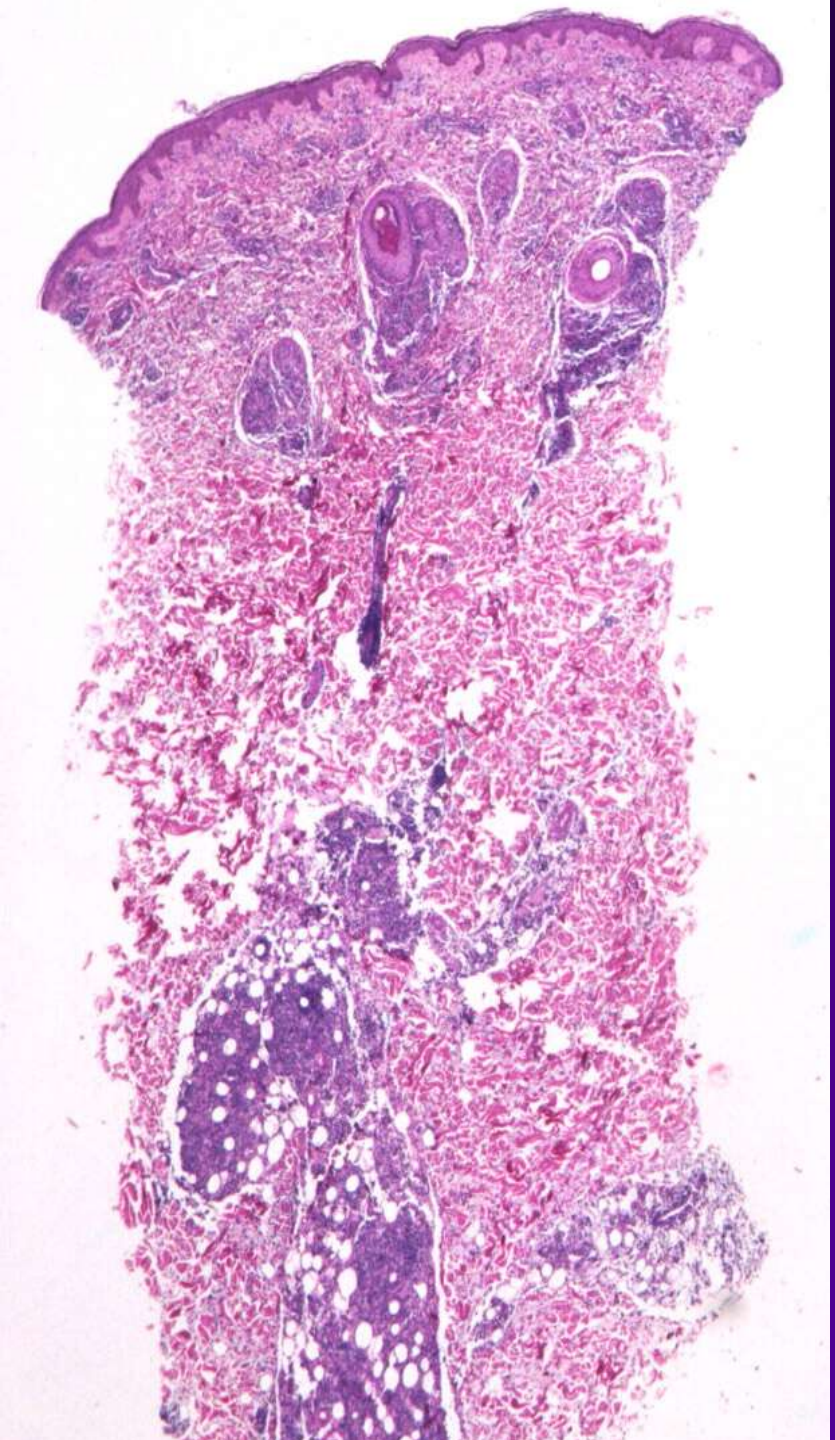
	Subcutaneous panniculitis-like T cell lymphoma	Extranodal NK/T cell lymphoma involving skin
Age	Younger (median 30)	Older (median 53)
Extracutaneous disease	Uncommon	Common
Dermal involvement	Absent	Common
Nature of tumor	T cell neoplasm, with TCR rearrangement	Mostly NK neoplasms, with germline TCR
EBV	Negative	Positive

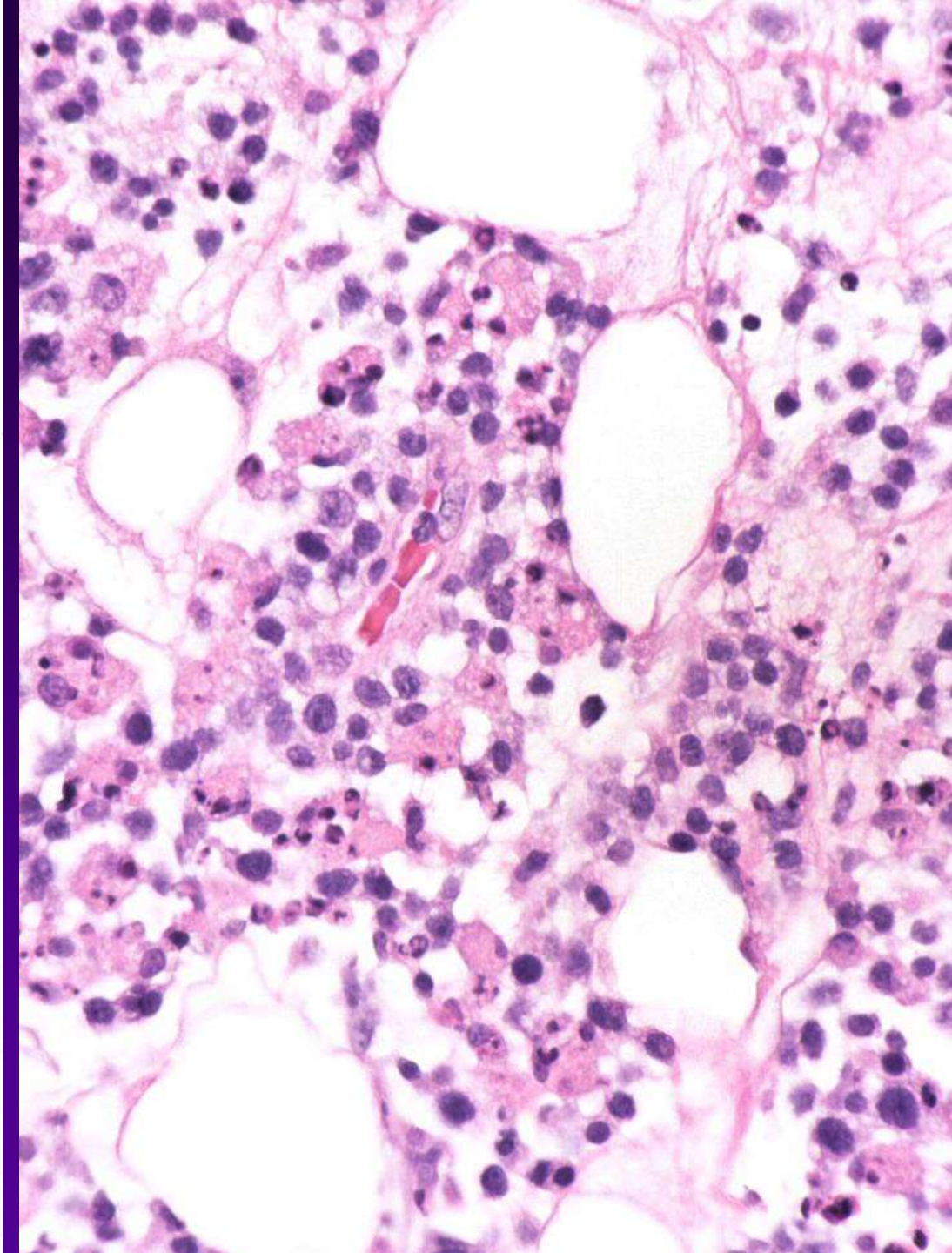
Primary cutaneous γδ T-cell lymphoma

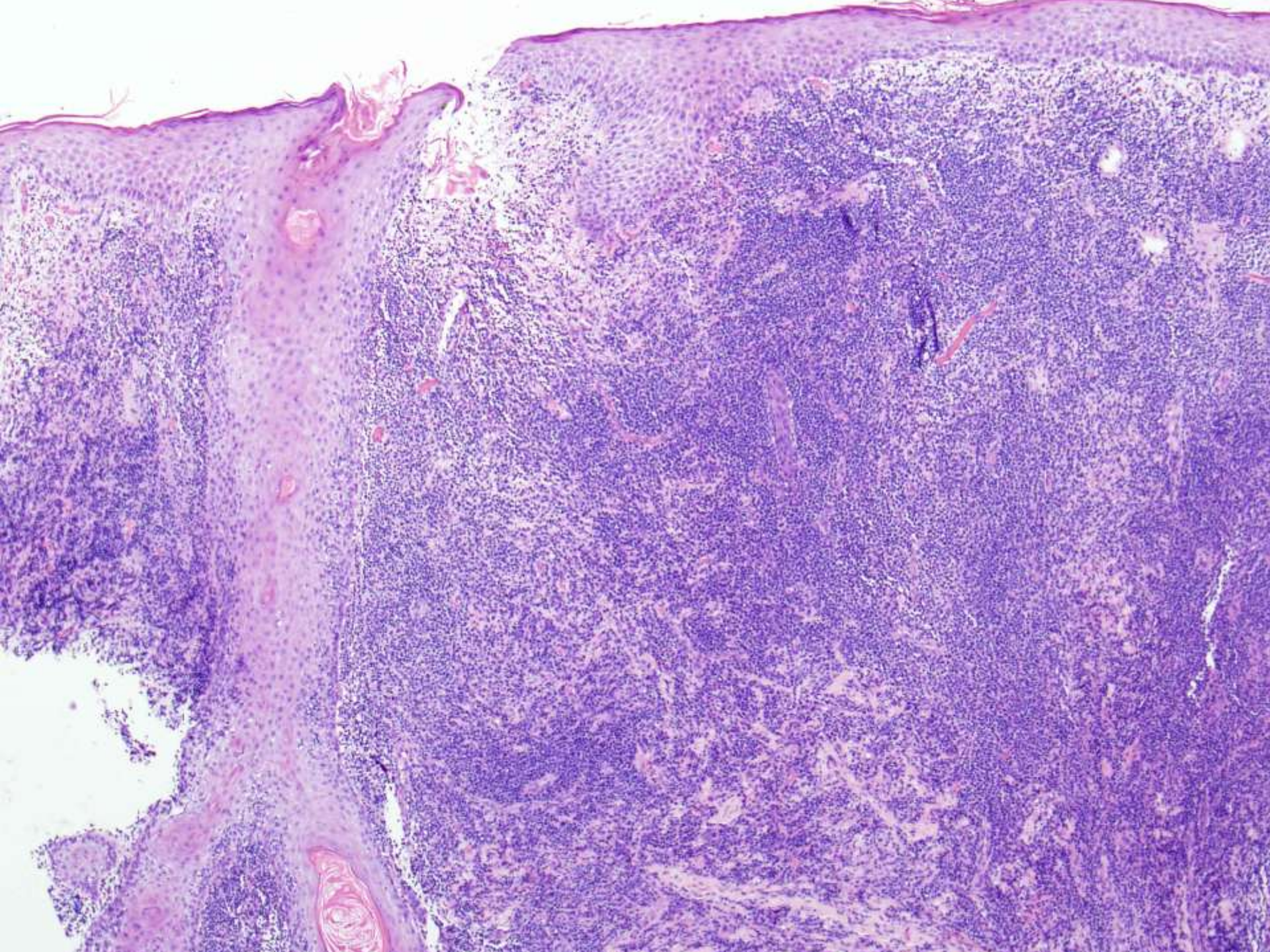
- Primary T-cell lymphoma of skin expressing γδ TCR
- Age: Adults
- Skin lesions: Often generalized, especially limbs. Patches, plaques, nodules +/- ulceration, necrosis
- B symptoms are common
- May be complicated by hemophagocytic syndrome
- Aggressive lymphoma with poor response to treatment (median survival 15 months)

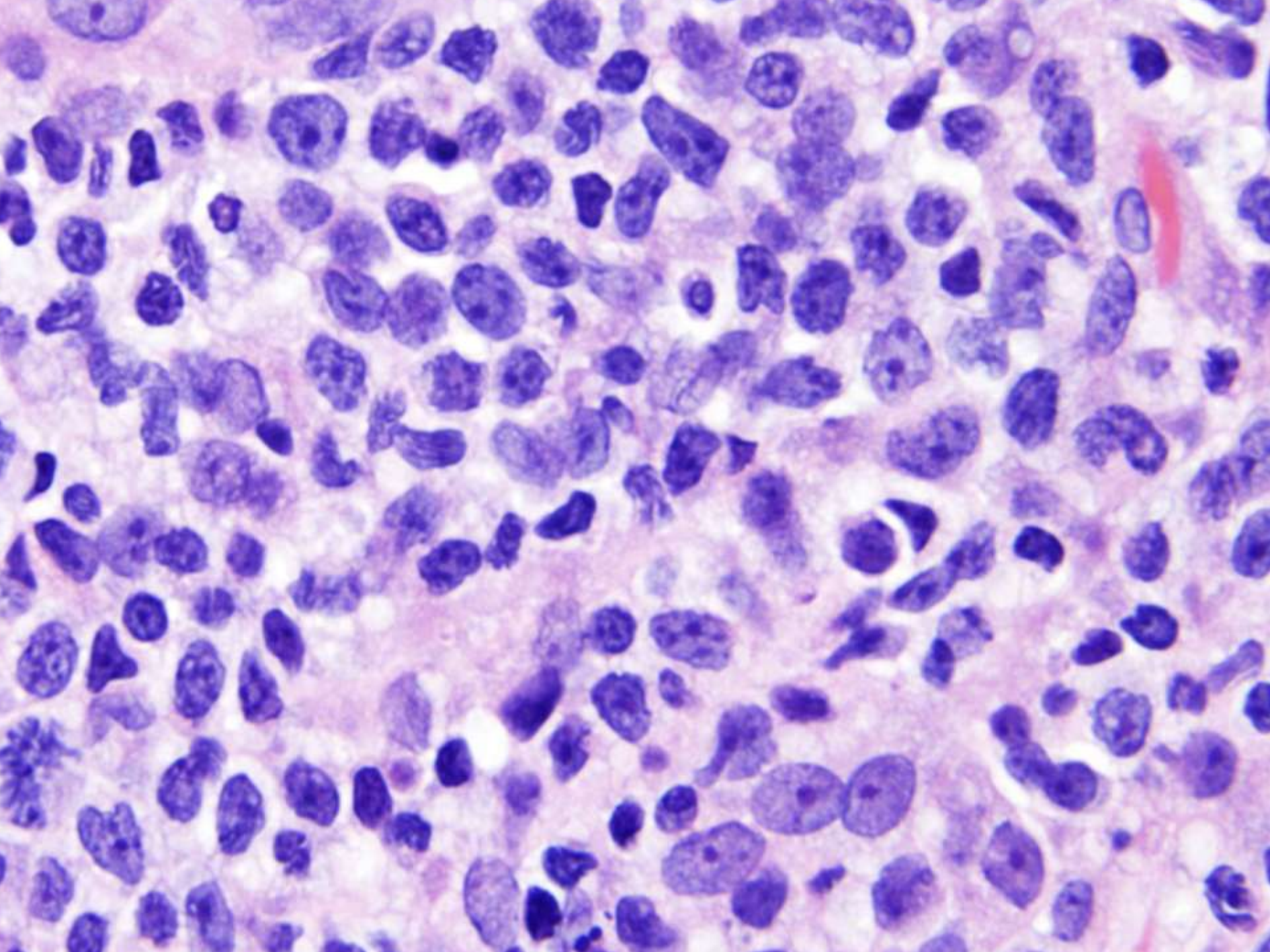
Primary cutaneous γδ T-cell lymphoma: Pathology

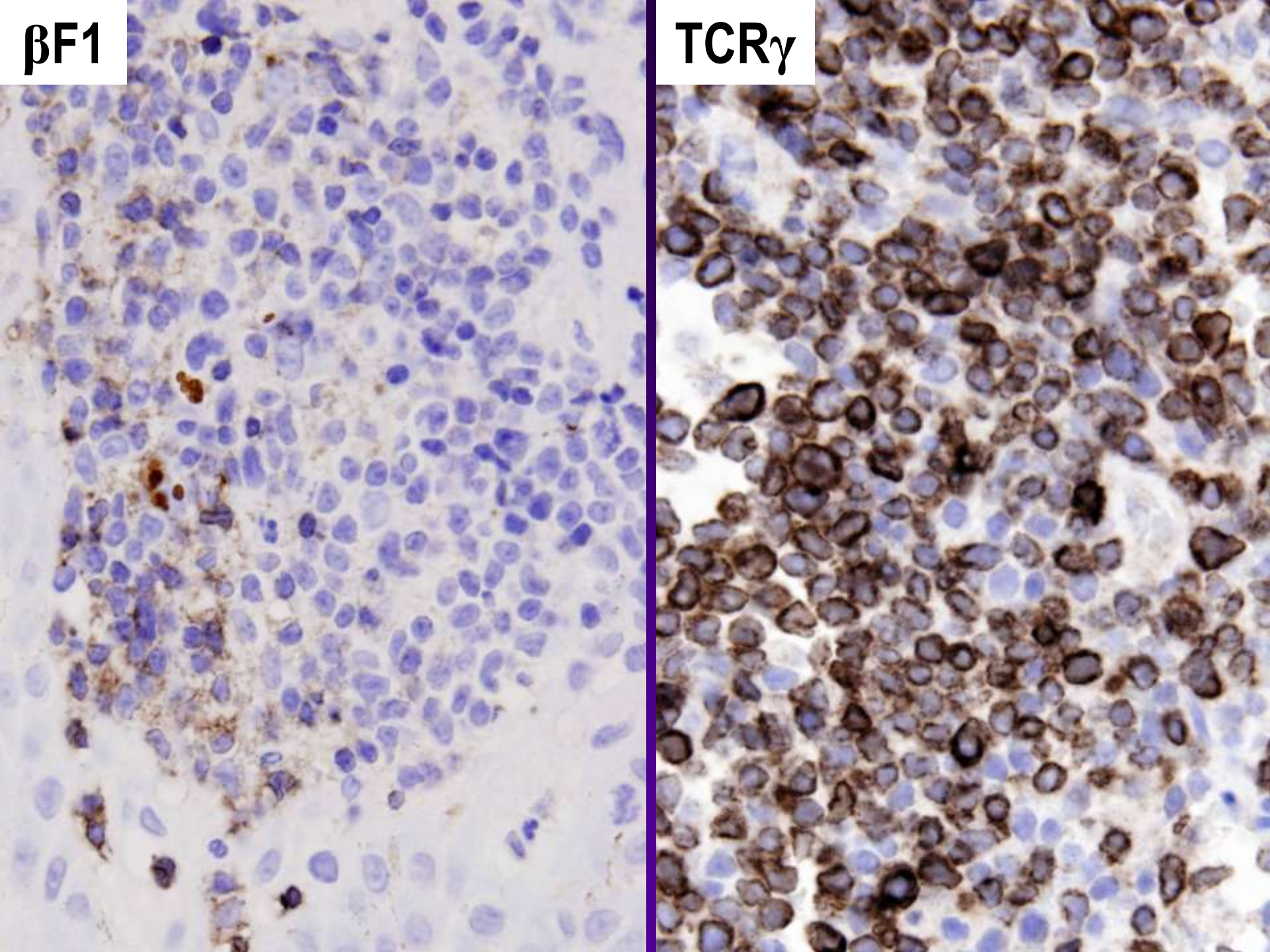
- Possible patterns: epidermotropic, dermal, subcutaneous
- Usually medium-sized or large lymphoma cells with clumped chromatin
- Apoptosis common
- Usually CD3+, CD5-, CD4-, CD8-, CD56+/-, TCRγ+
- EBER-










βF1
TCRγ

	Subcutaneous panniculitis-like T-cell lymphoma	Cutaneous γδ T-cell lymphoma
T-cell receptor	αβ	γδ
Hemophagocytic syndrome	17%	50%
Morphology	No or minimal dermal involvement	Dermal and epidermal involvement common
Usual immunophenotype	CD4-, CD8+, CD56-	CD4-, CD8-, CD56+/-
5-yr overall survival	82%	11%

Lymphoma with panniculitis pattern: Summary

- Subcutaneous panniculitis-like T-cell lymphoma: CD56-, CD8+, EBER-
- Extranodal NK/T-cell lymphoma: CD56+, EBER+, βF1-, TCRγ –
- Cutaneous γδT-cell lymphoma: CD56+, EBER-βF1-, TCRγ+

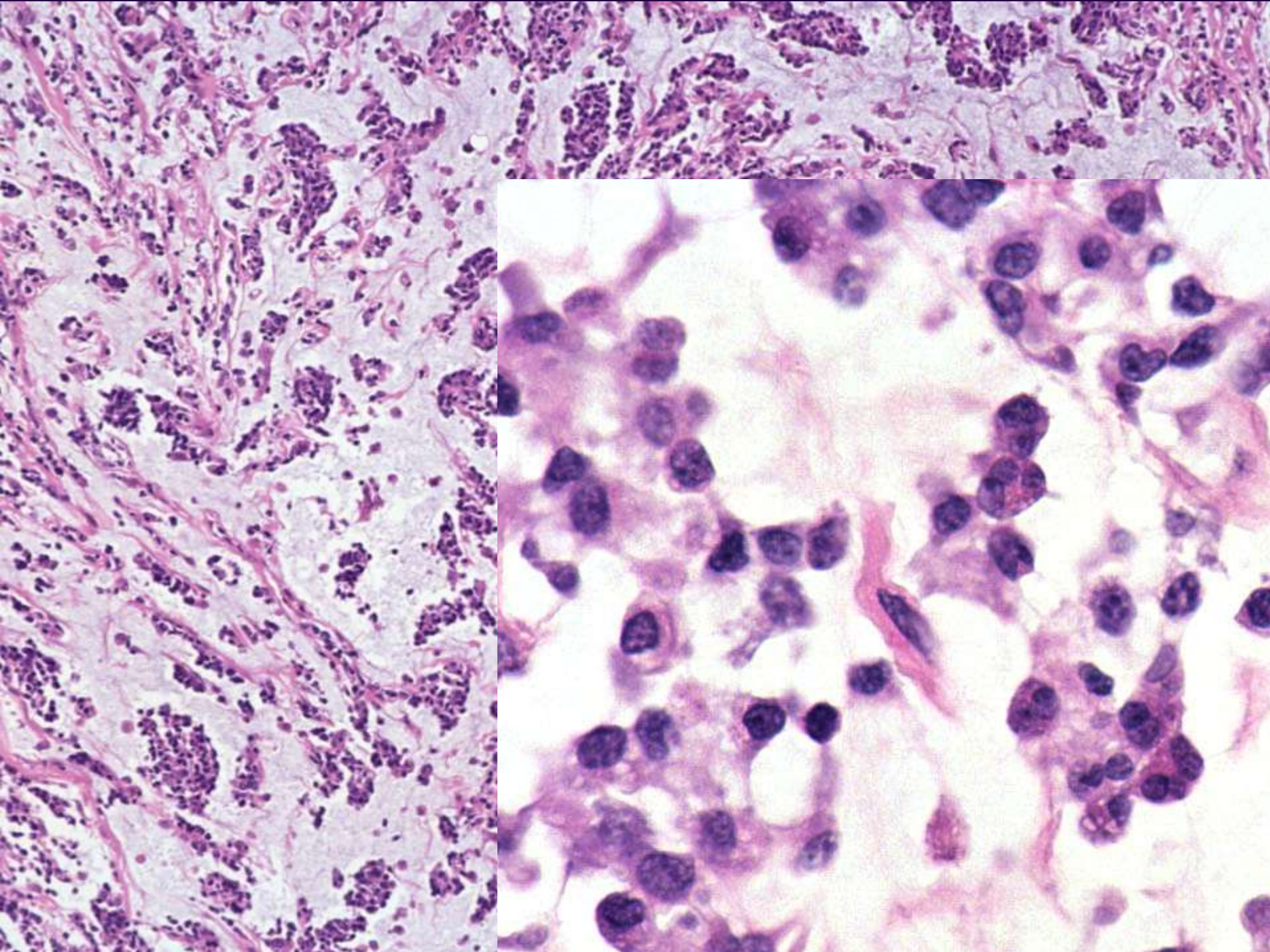
LARGE CELL PROLIFERATIONS

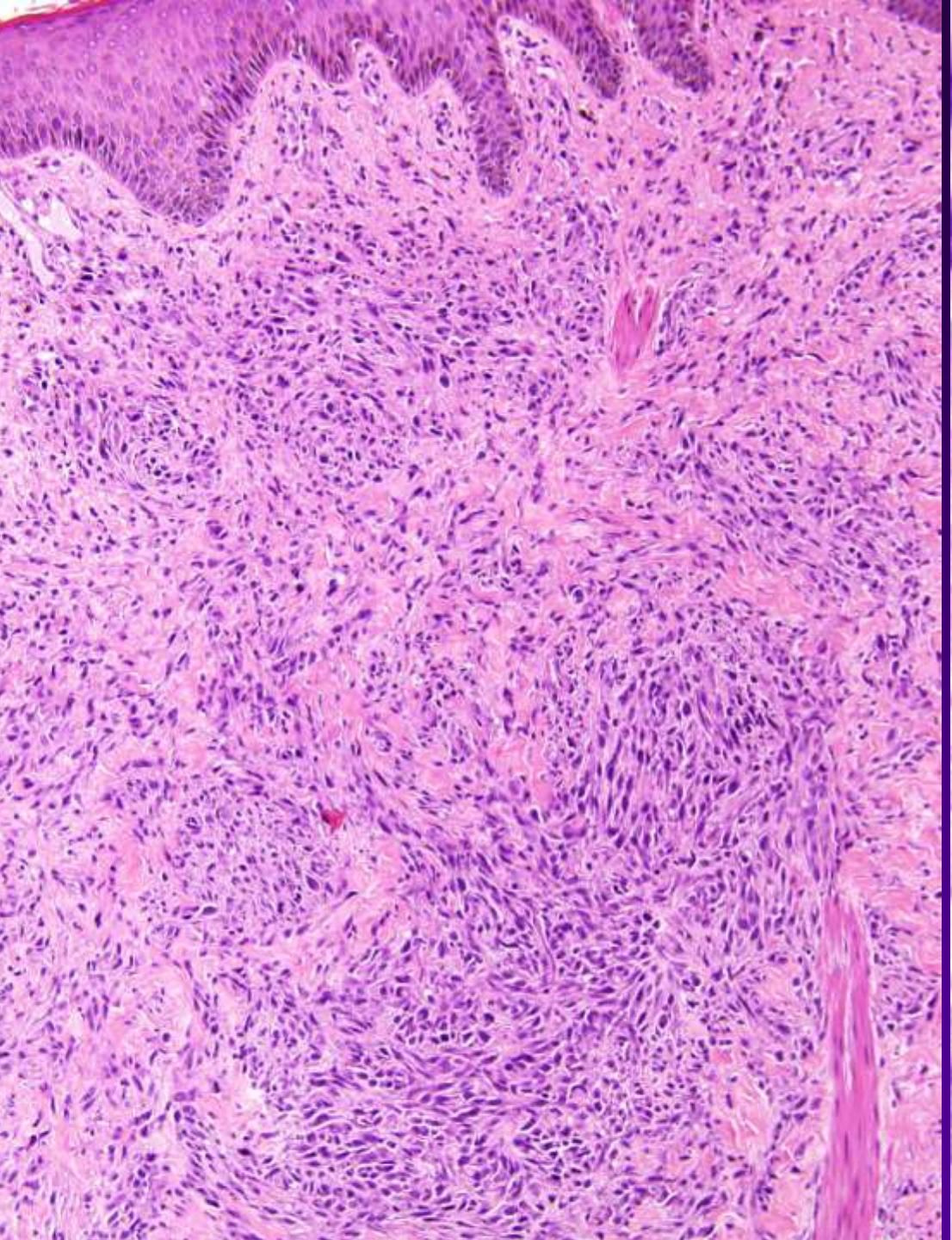
- Lymphoma (various types)
- Primary cutaneous CD30+ T-cell lymphoproliferative disorder
- Histiocytic and dendritic cell neoplasms

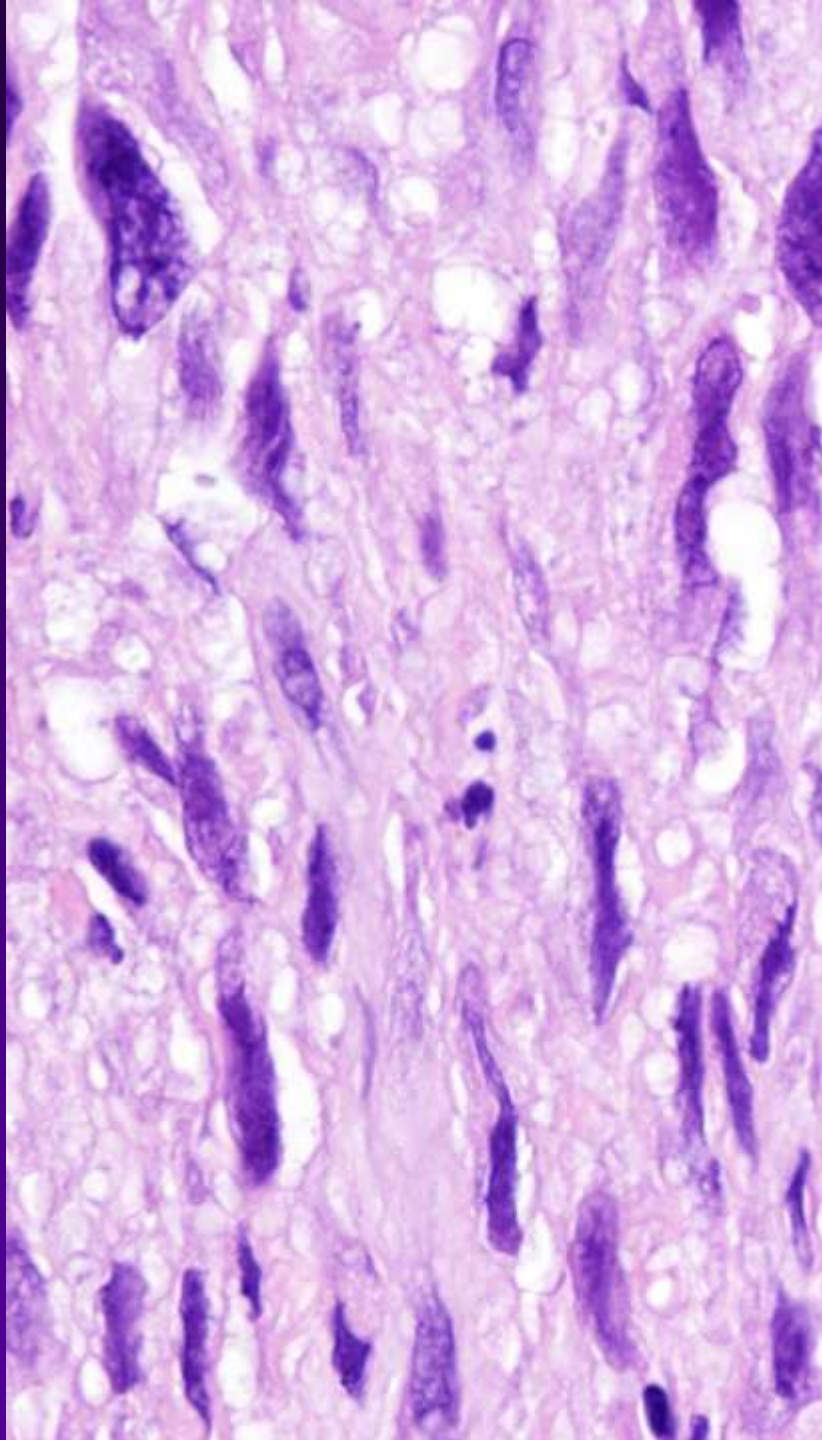
- Carcinoma
- Melanoma
- Sarcoma

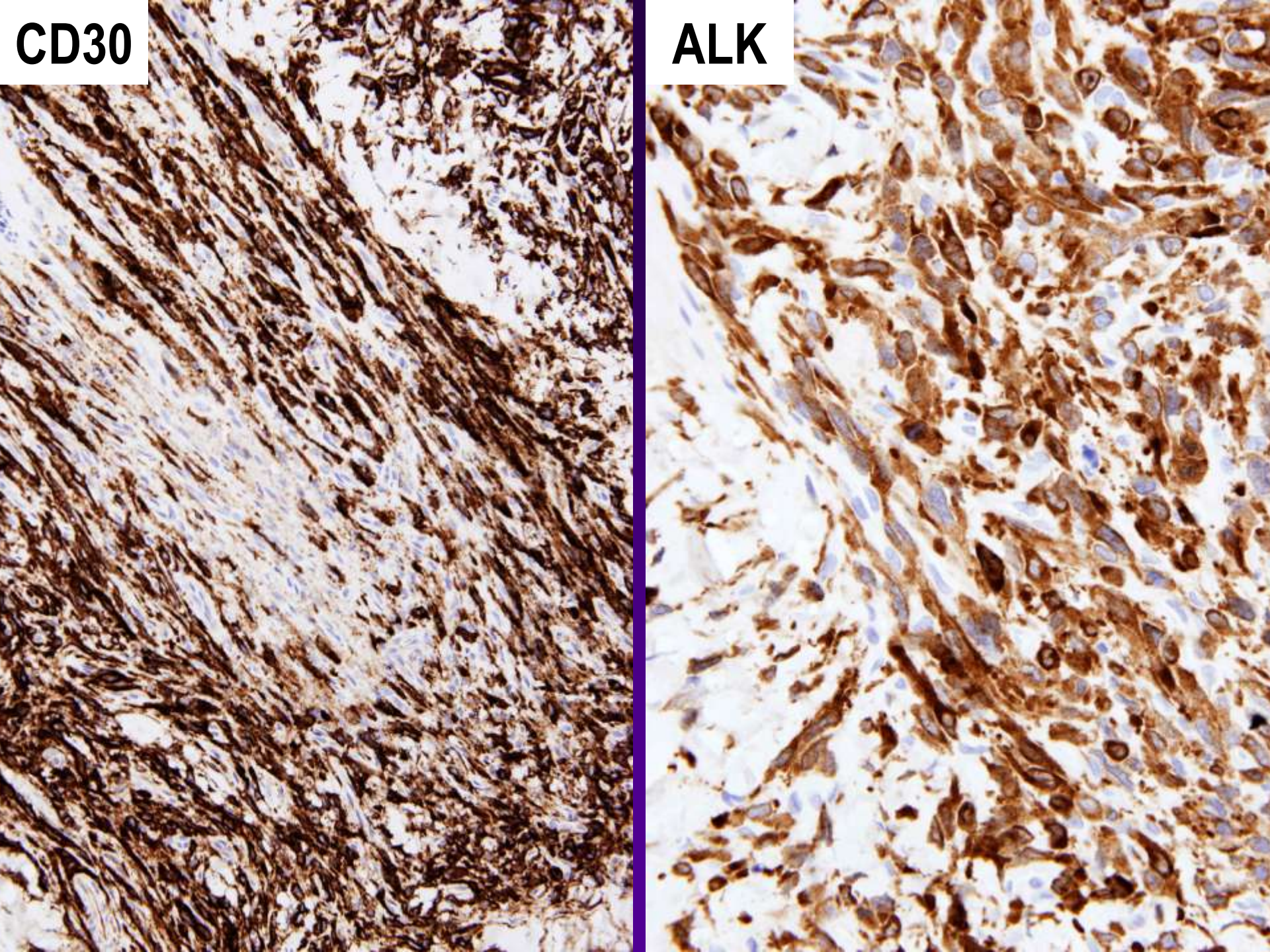
Large cell proliferations: Problem 1

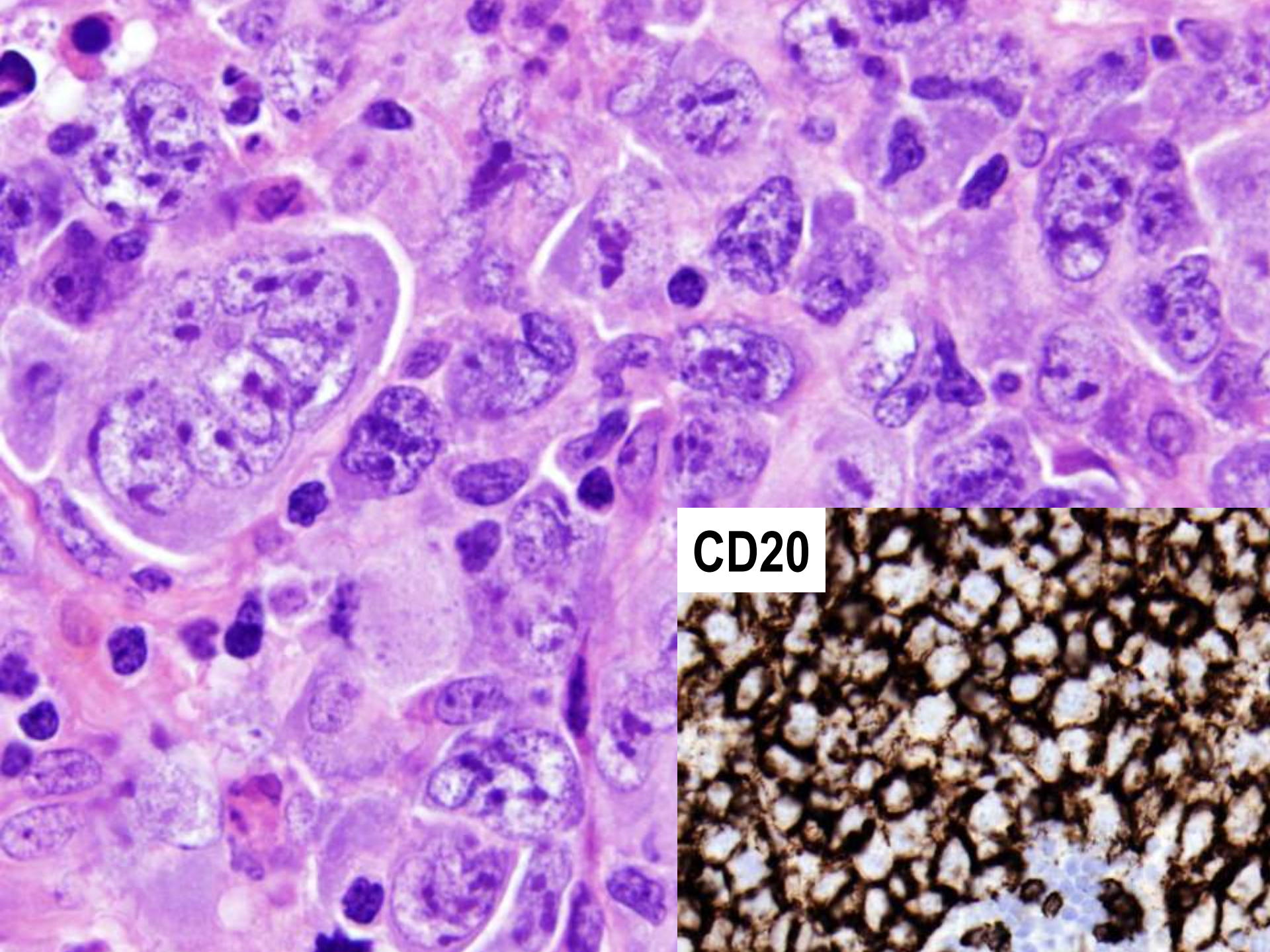
- Lymphomas mimicking non-hematolymphoid tumors
  - Myxoid stroma
  - Spindly cells
  - Extreme anaplasia mistakenly thought to be incompatible with lymphoma
  - Signet ring cells
  - Fibrillary matrix and rosettes
  - Deceptively cohesive, mimicking carcinoma
  - Angiosarcoma-like due to intravascular growth or presence of irregular cleft-like spaces

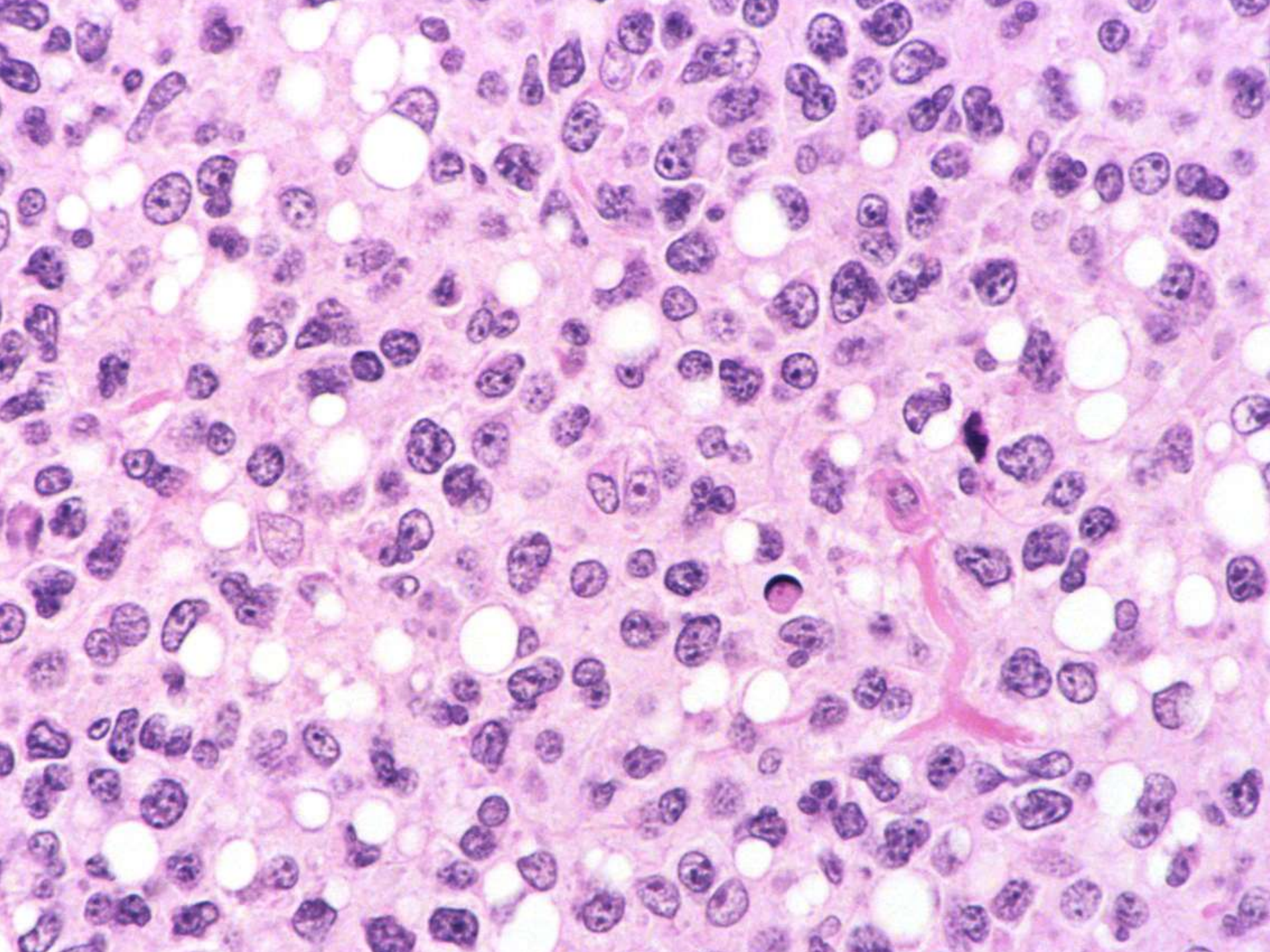


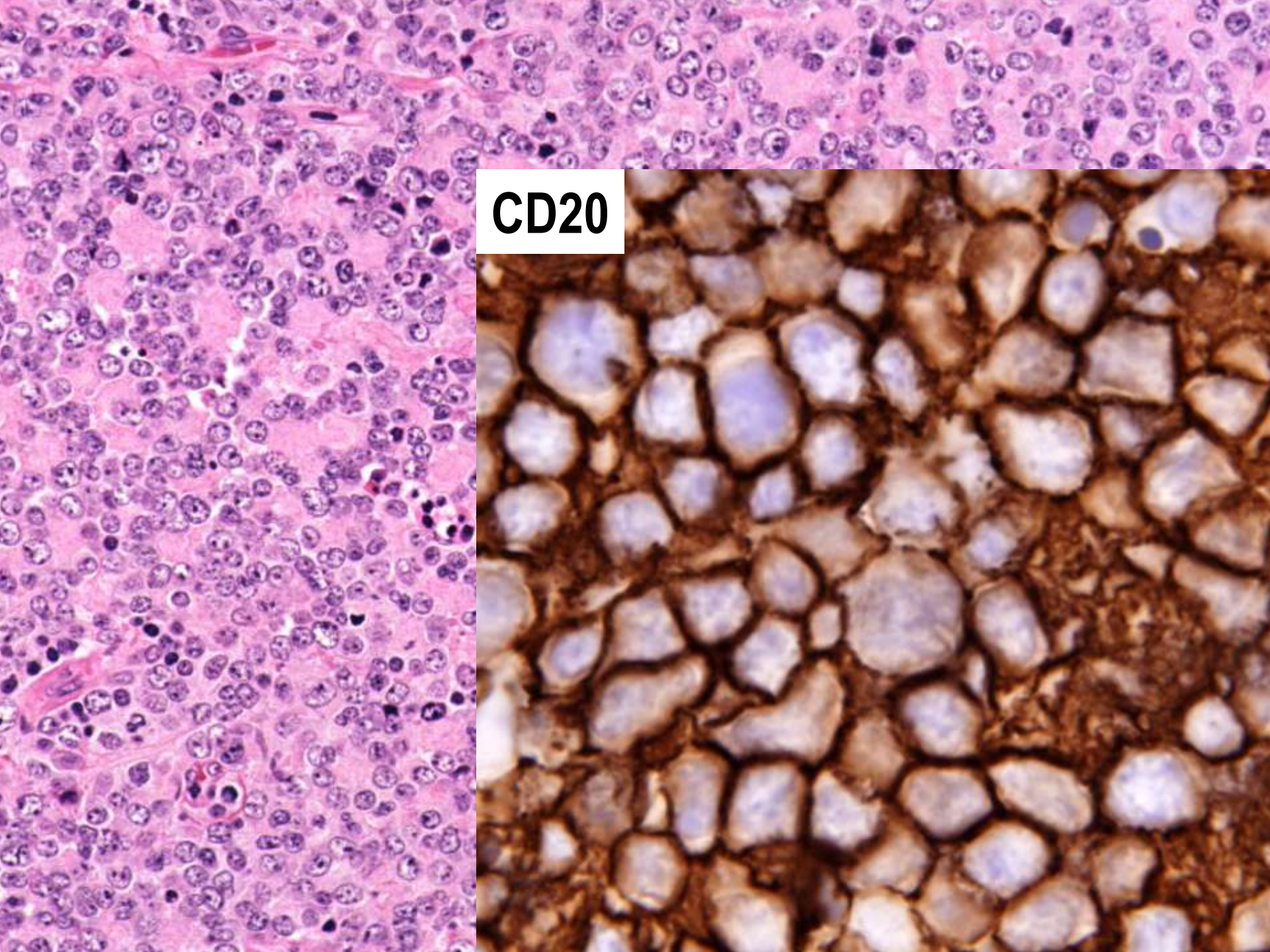





CD30
ALK


CD20

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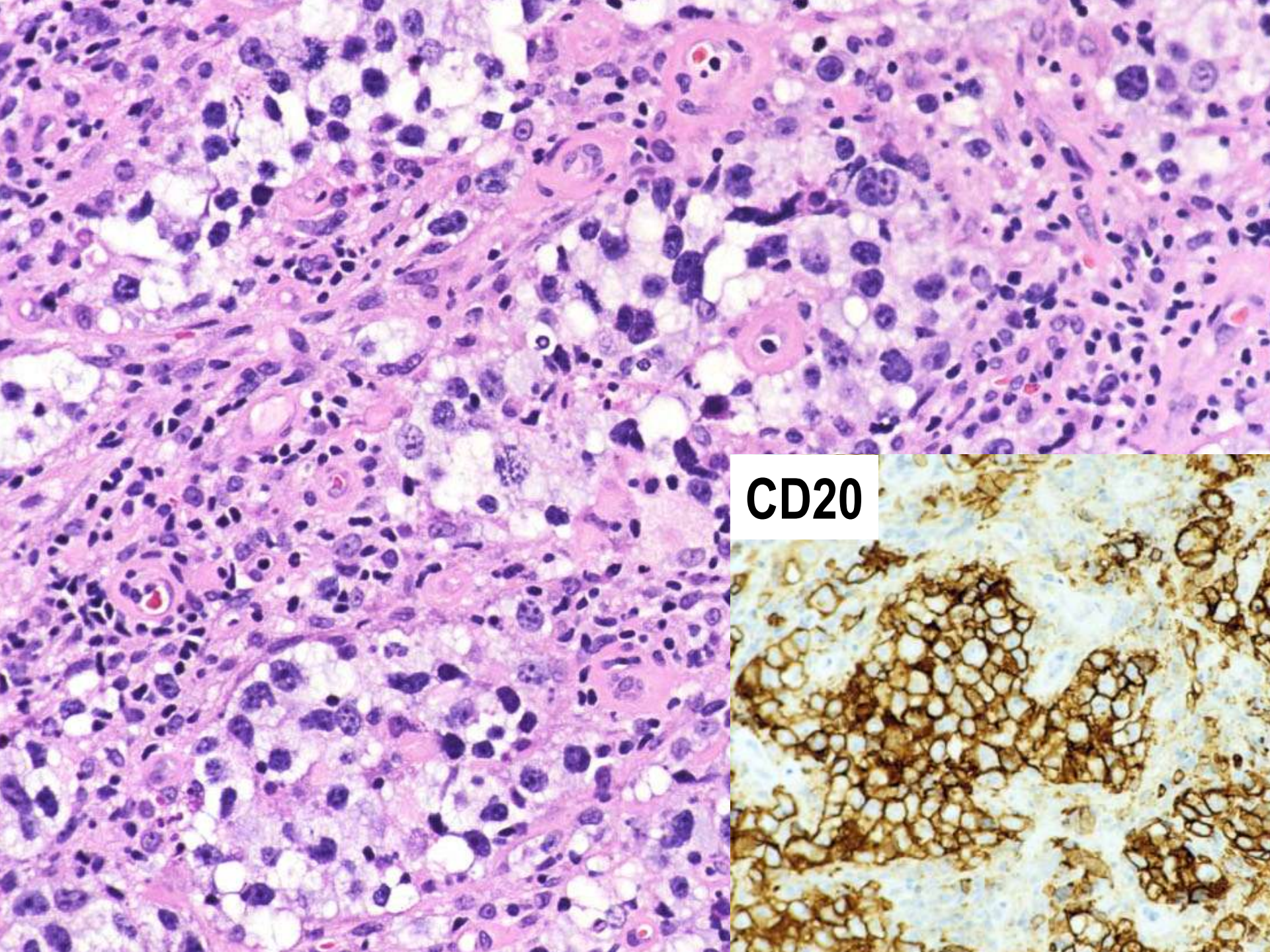
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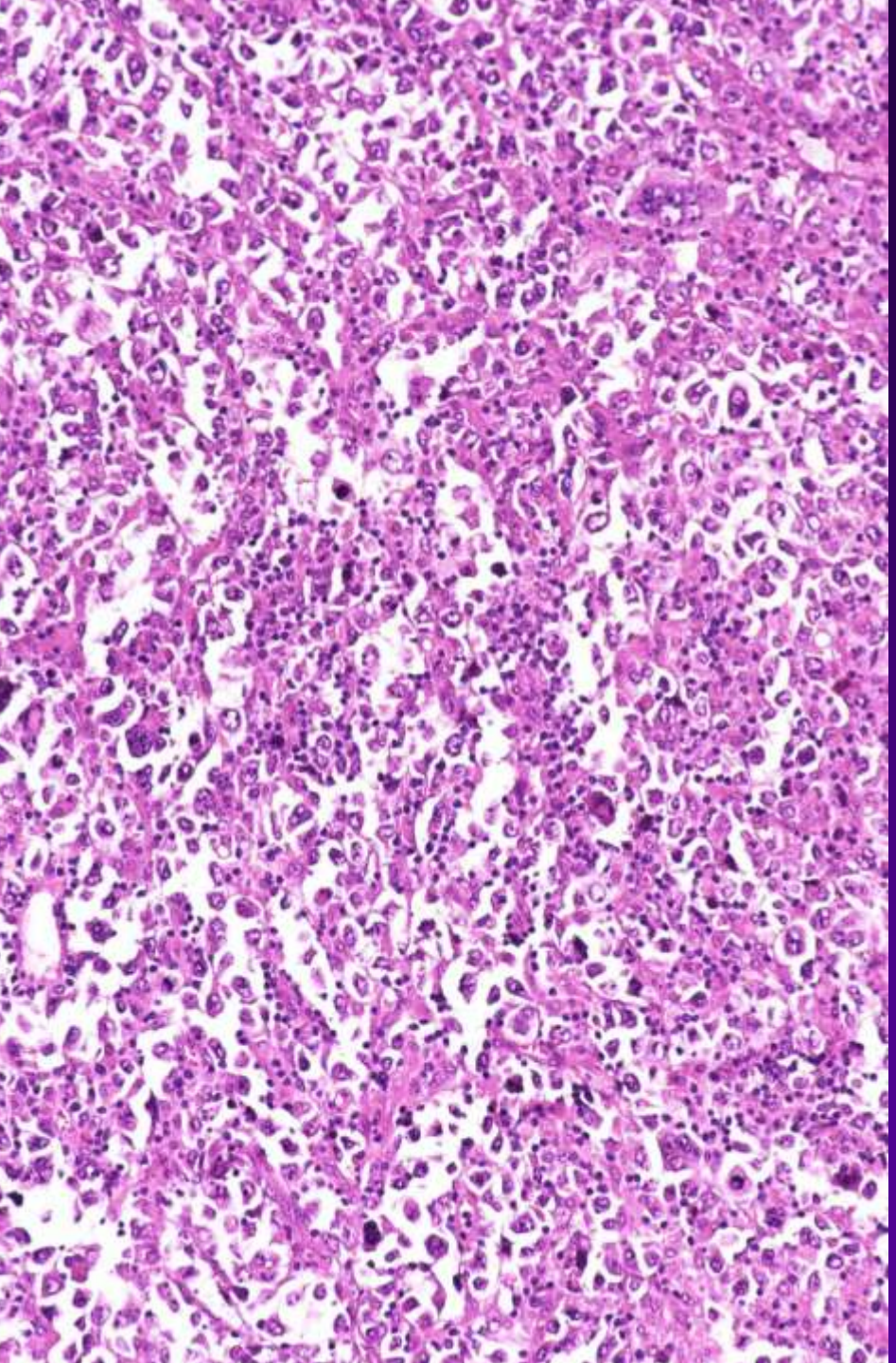
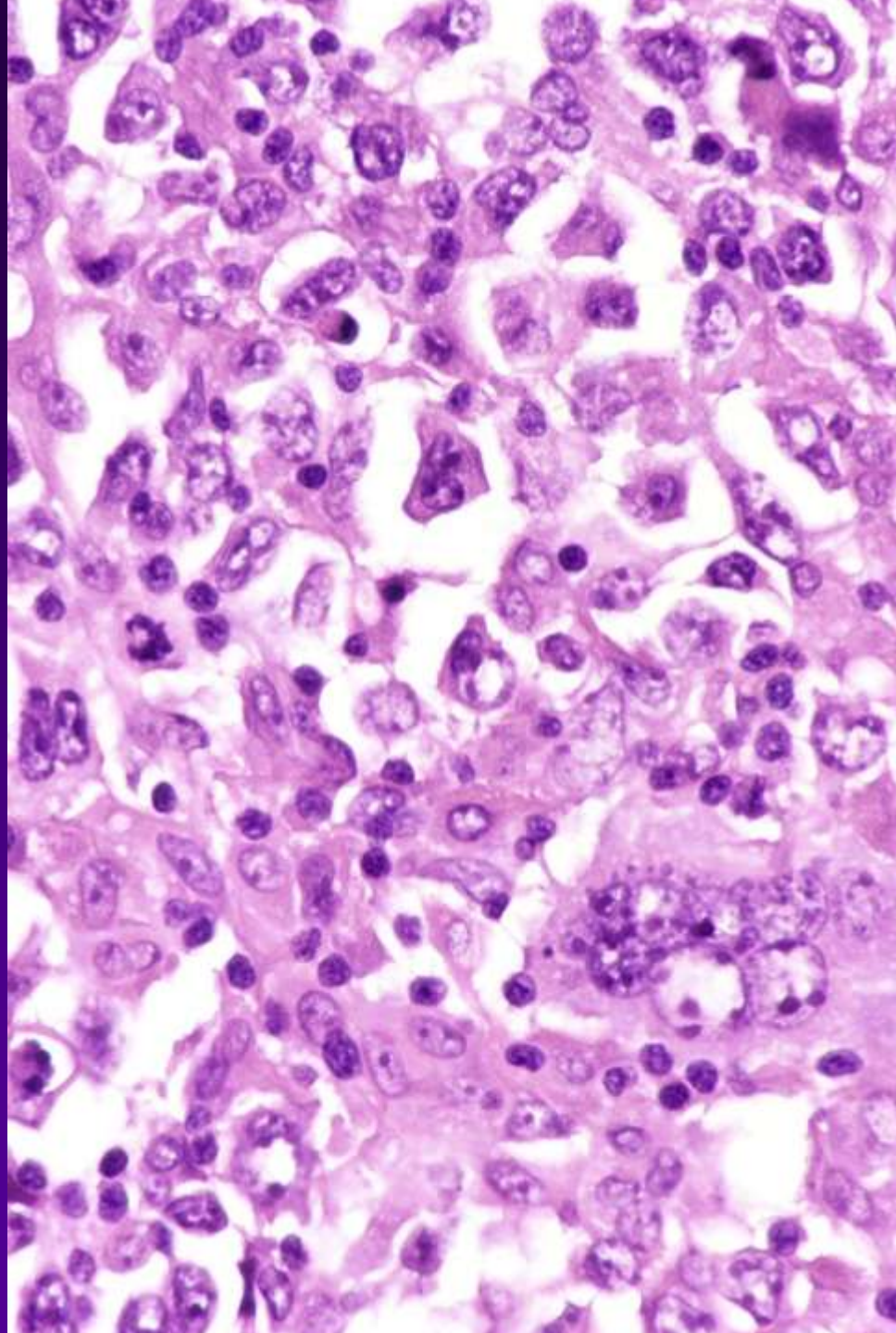
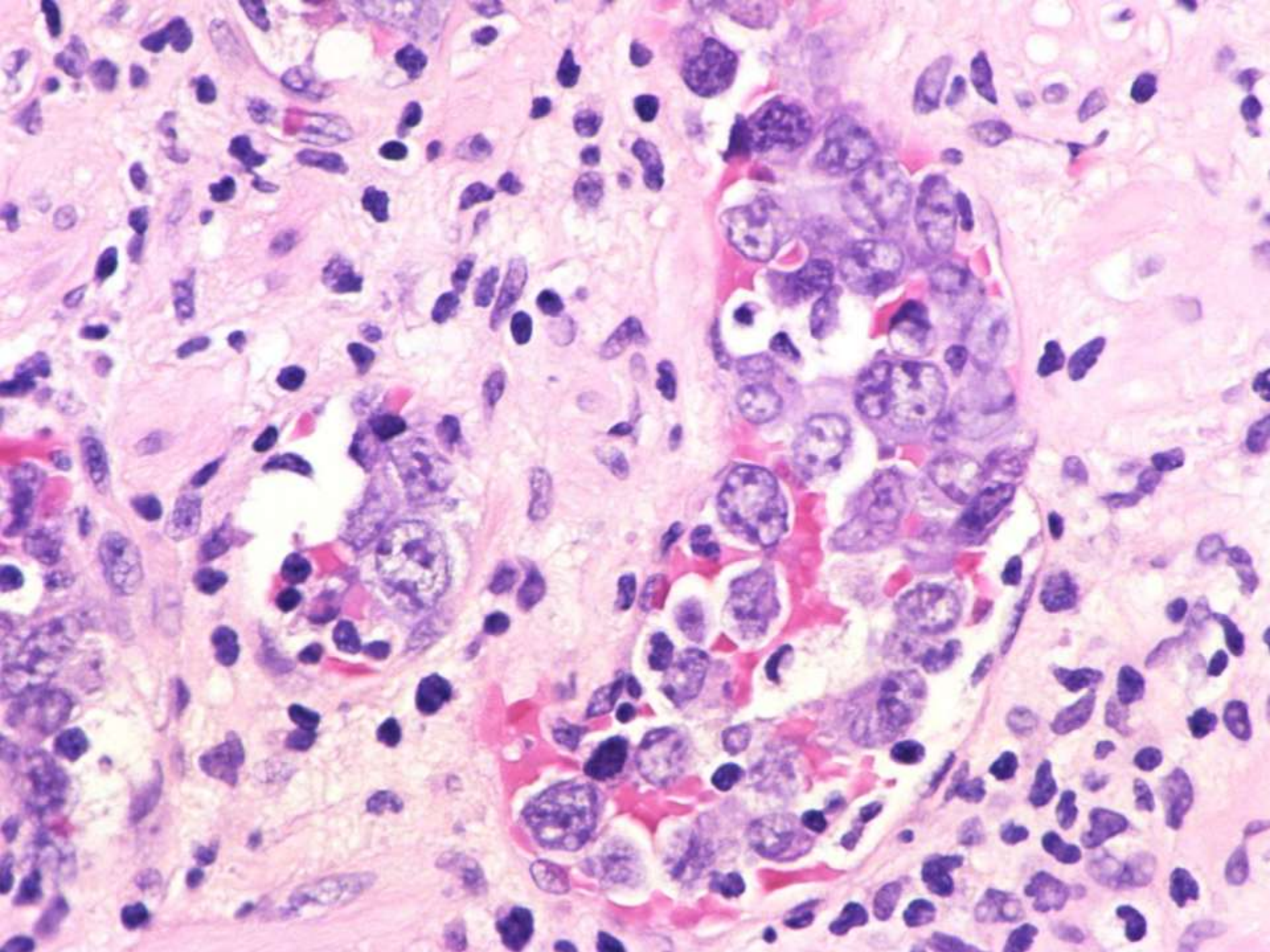
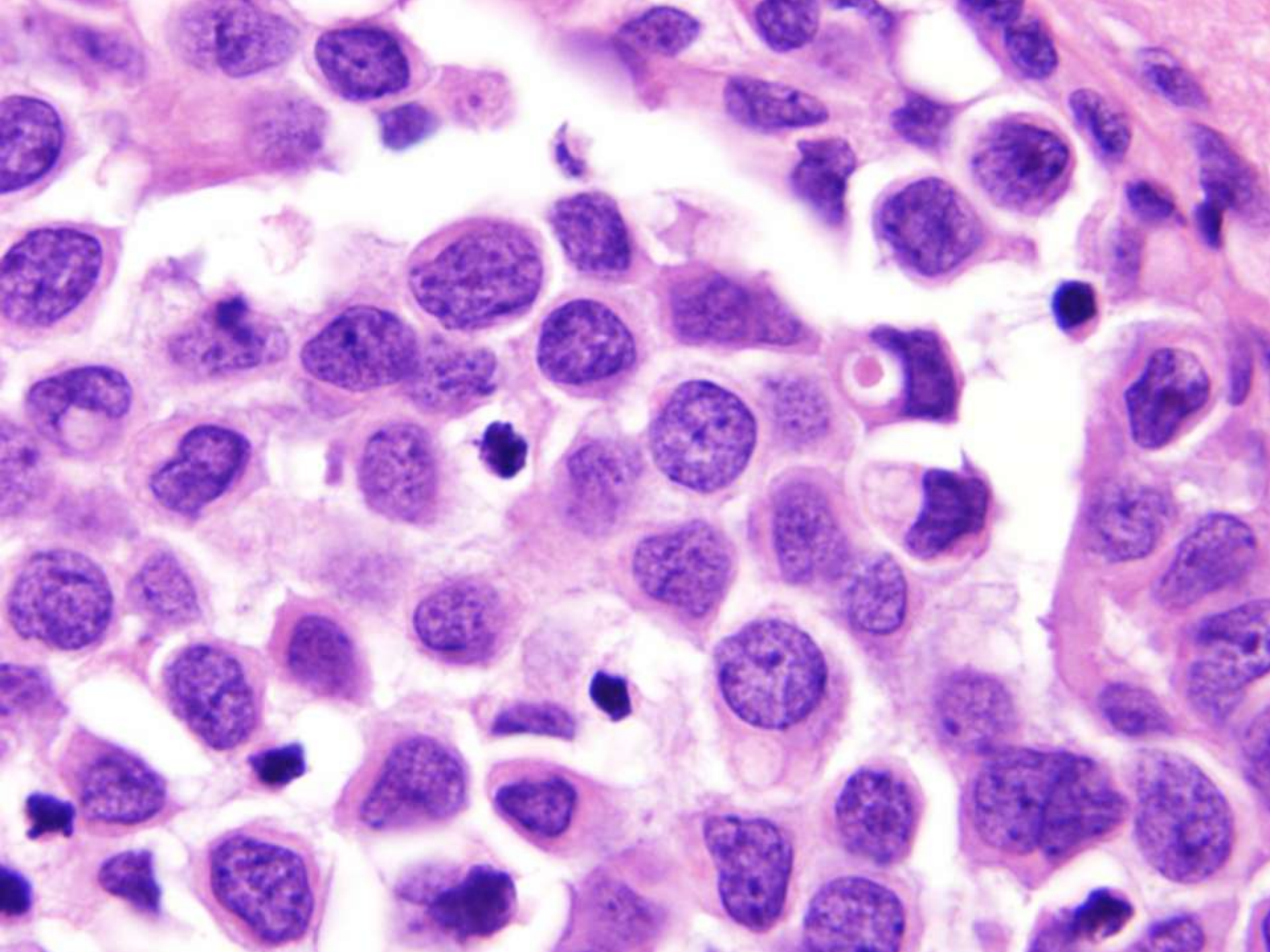





Nothing is impossible in terms of the morphologic spectrum of lymphomas!!

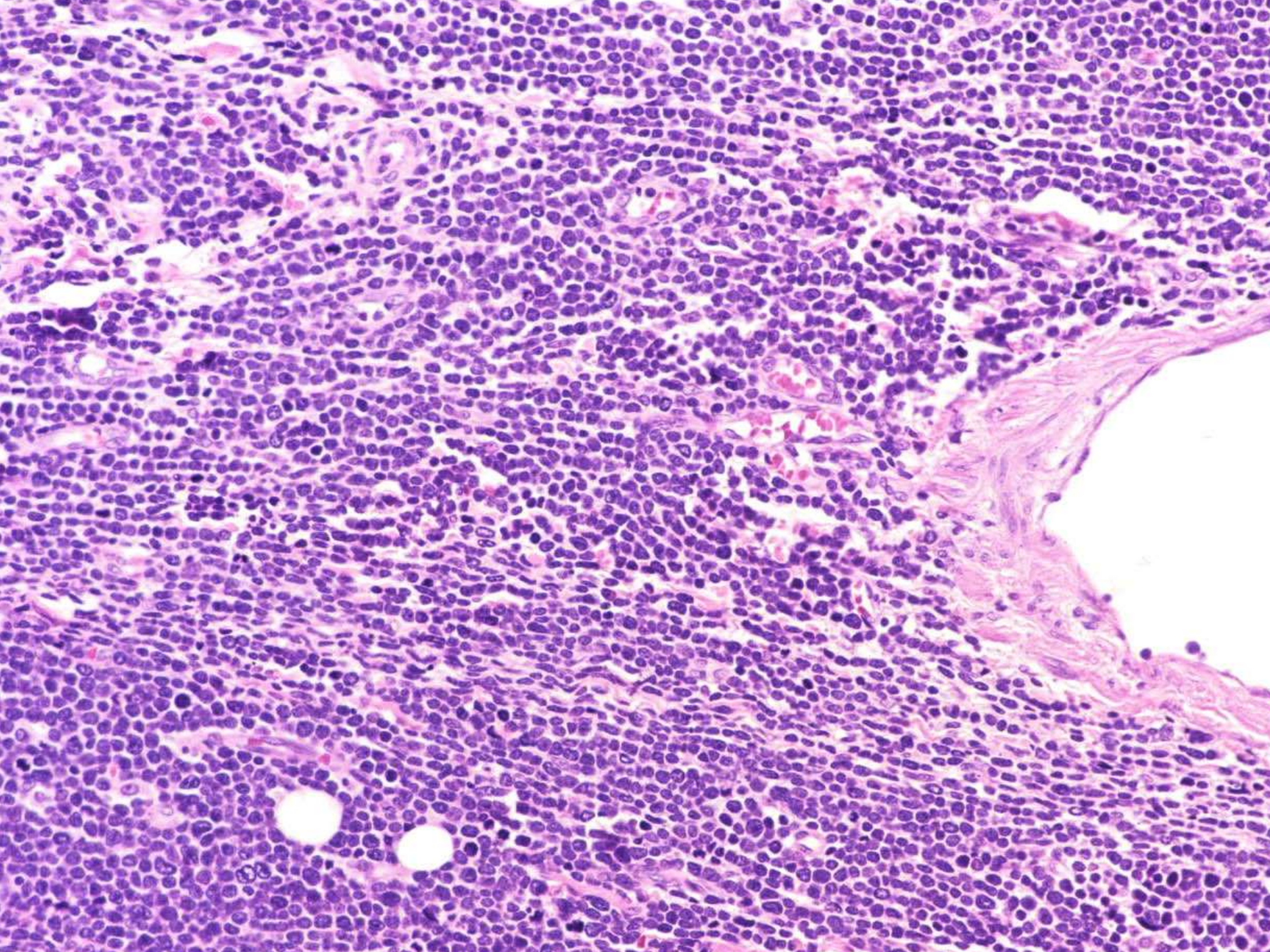
Large cell proliferations: Problem 2

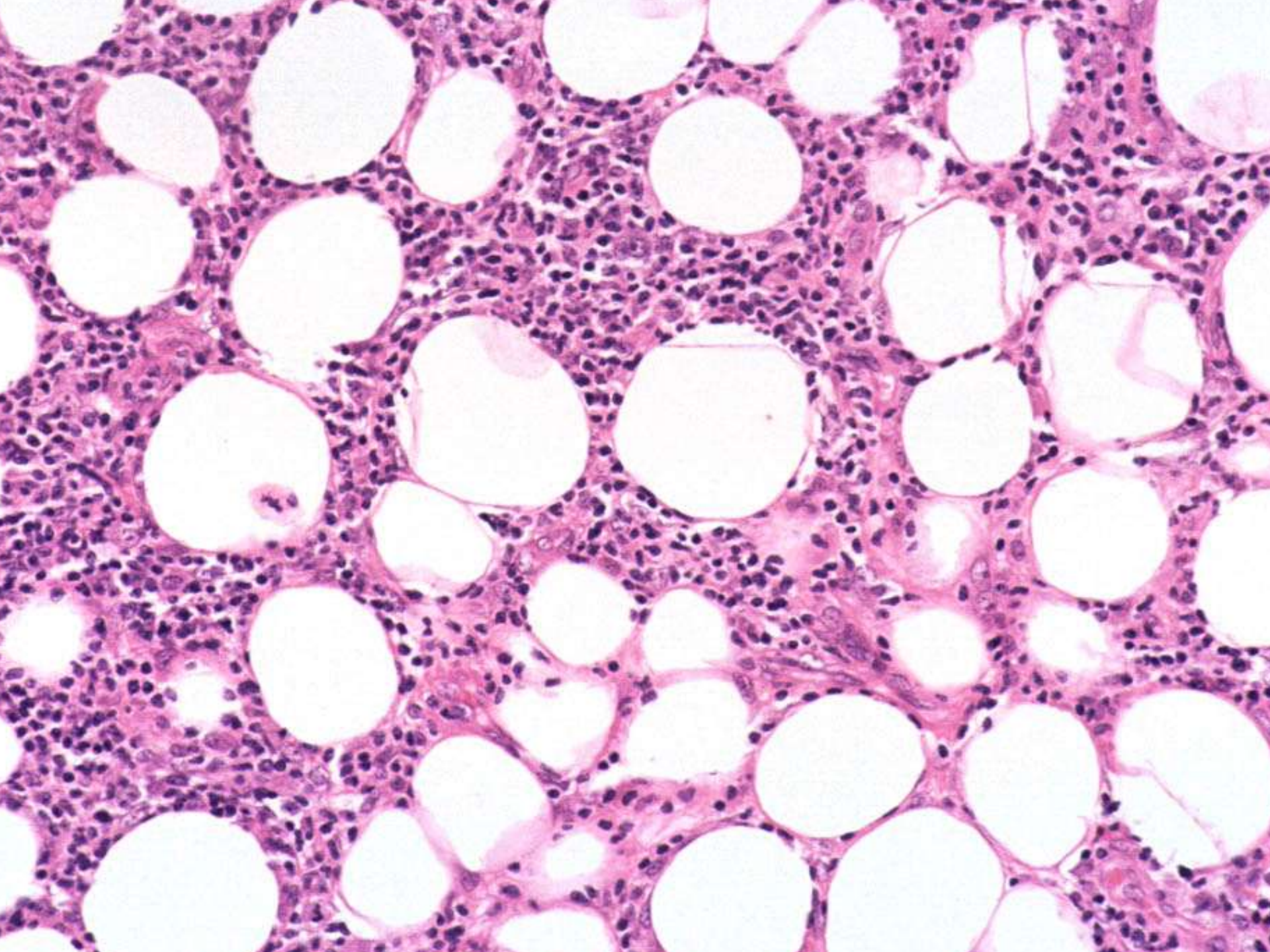
- Non-hematolymphoid neoplasms mimicking hematolymphoid tumors
  - Carcinoma with non-cohesive growth, e.g. lobular carcinoma
  - Malignant melanoma
  - Myxoinflammatory fibroblastic sarcoma (mimicking Hodgkin lymphoma)

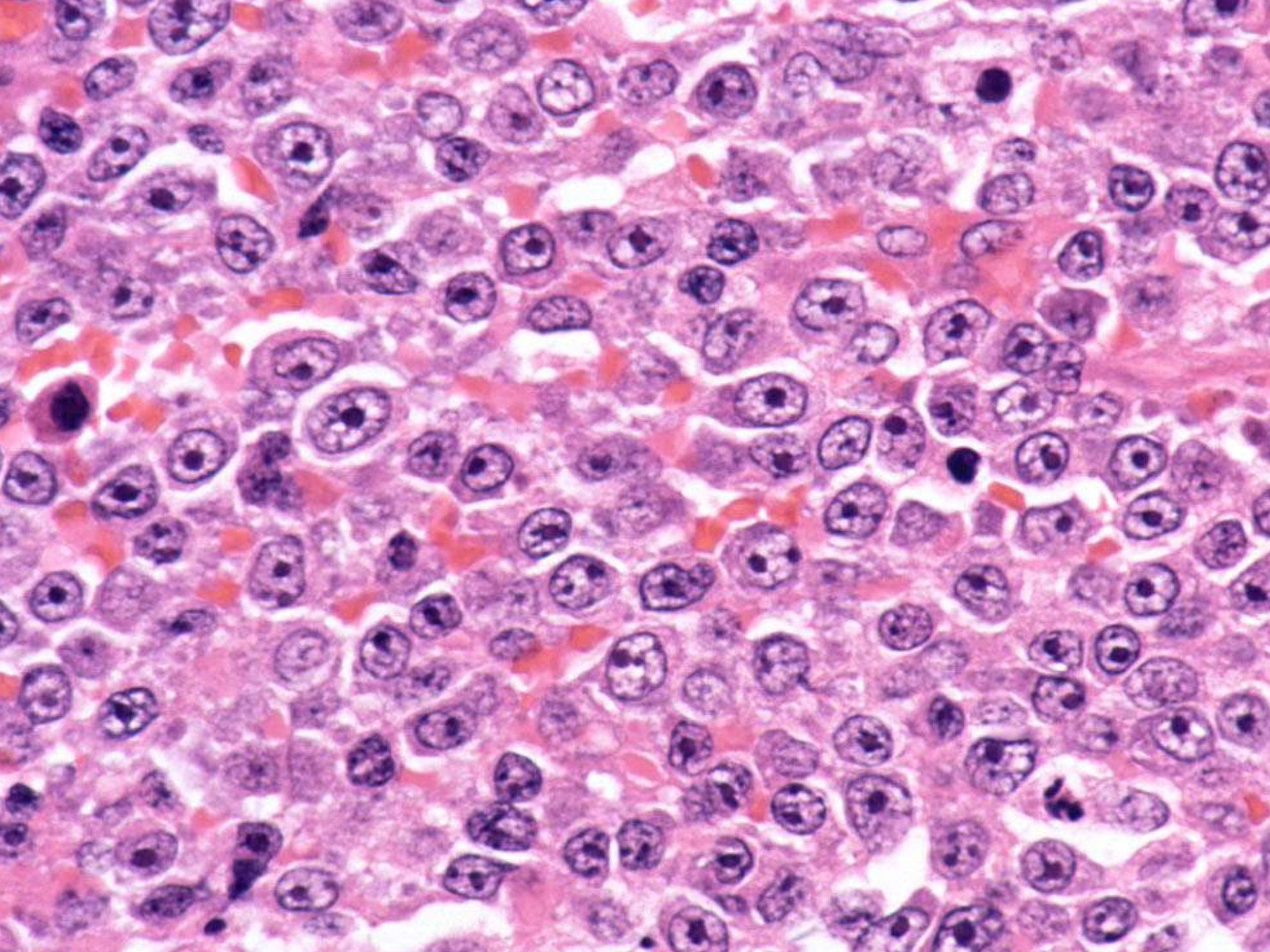


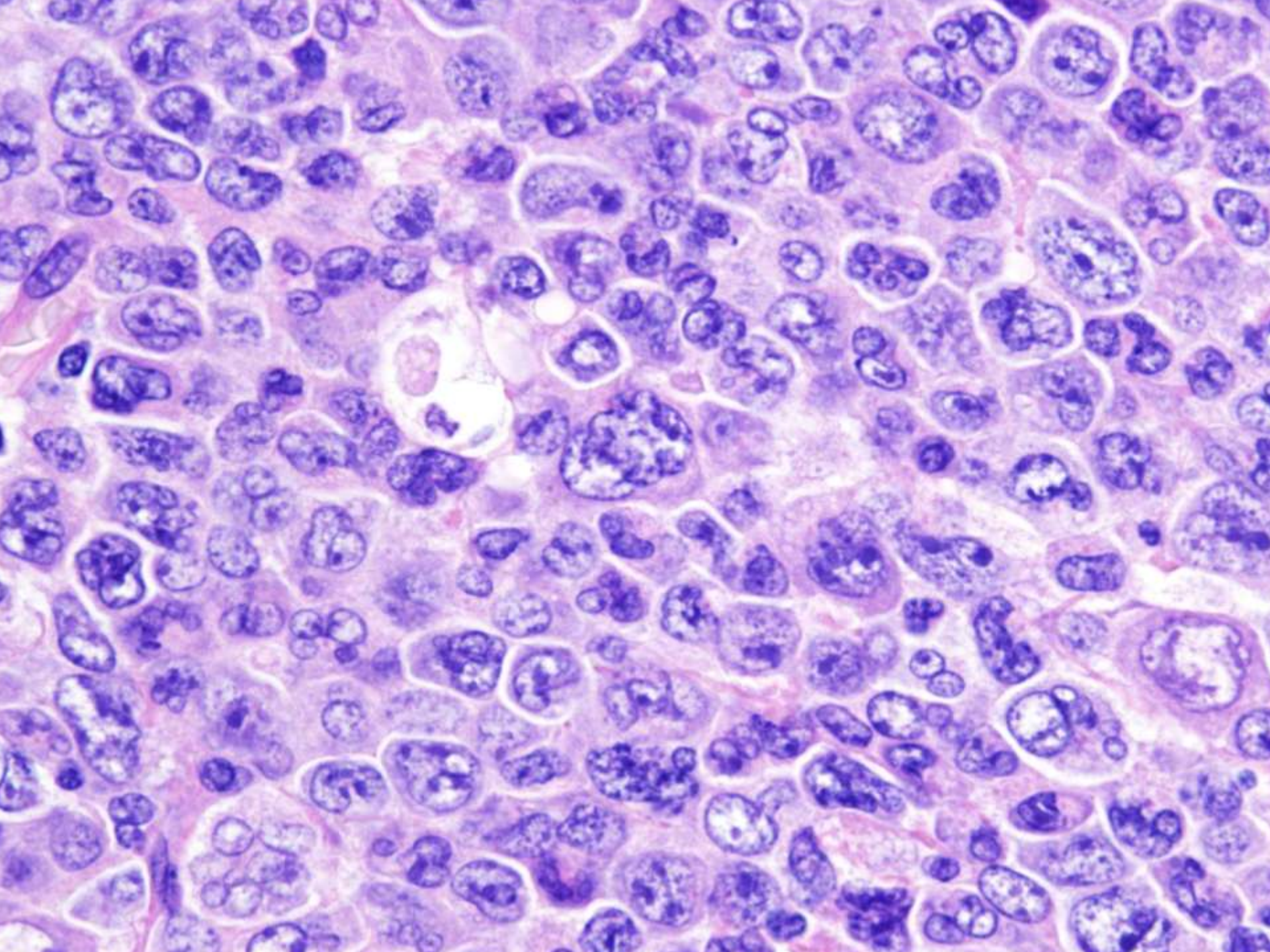
Morphologic assessment

- Assess growth pattern and cytology
- Morphologic features suggestive of lymphoma (hematolymphoid neoplasm):
  - Highly permeative growth
  - Basophilic or amphophilic cytoplasm
  - Multilobated nuclei



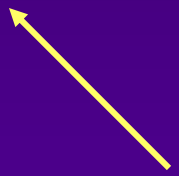






Large cell hematolymphoid neoplasms: Main considerations

- ✓ Large B-cell lymphoma
- ✓ Anaplastic large cell lymphoma (CD30+ T-cell LPD)
- ✓ T or NK cell lymphoma predominated by large cells
- ✓ Histiocytic / dendritic cell neoplasms

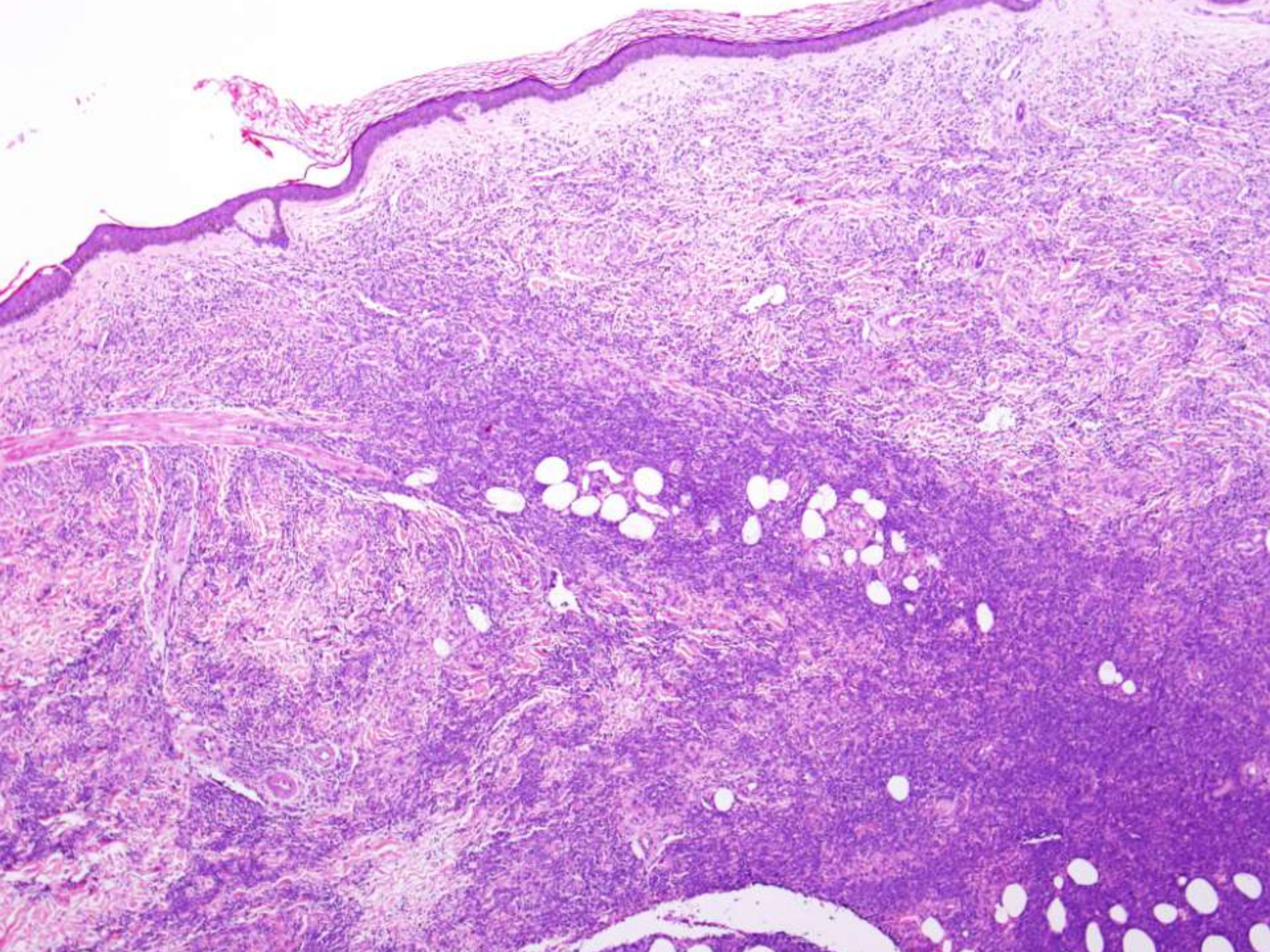


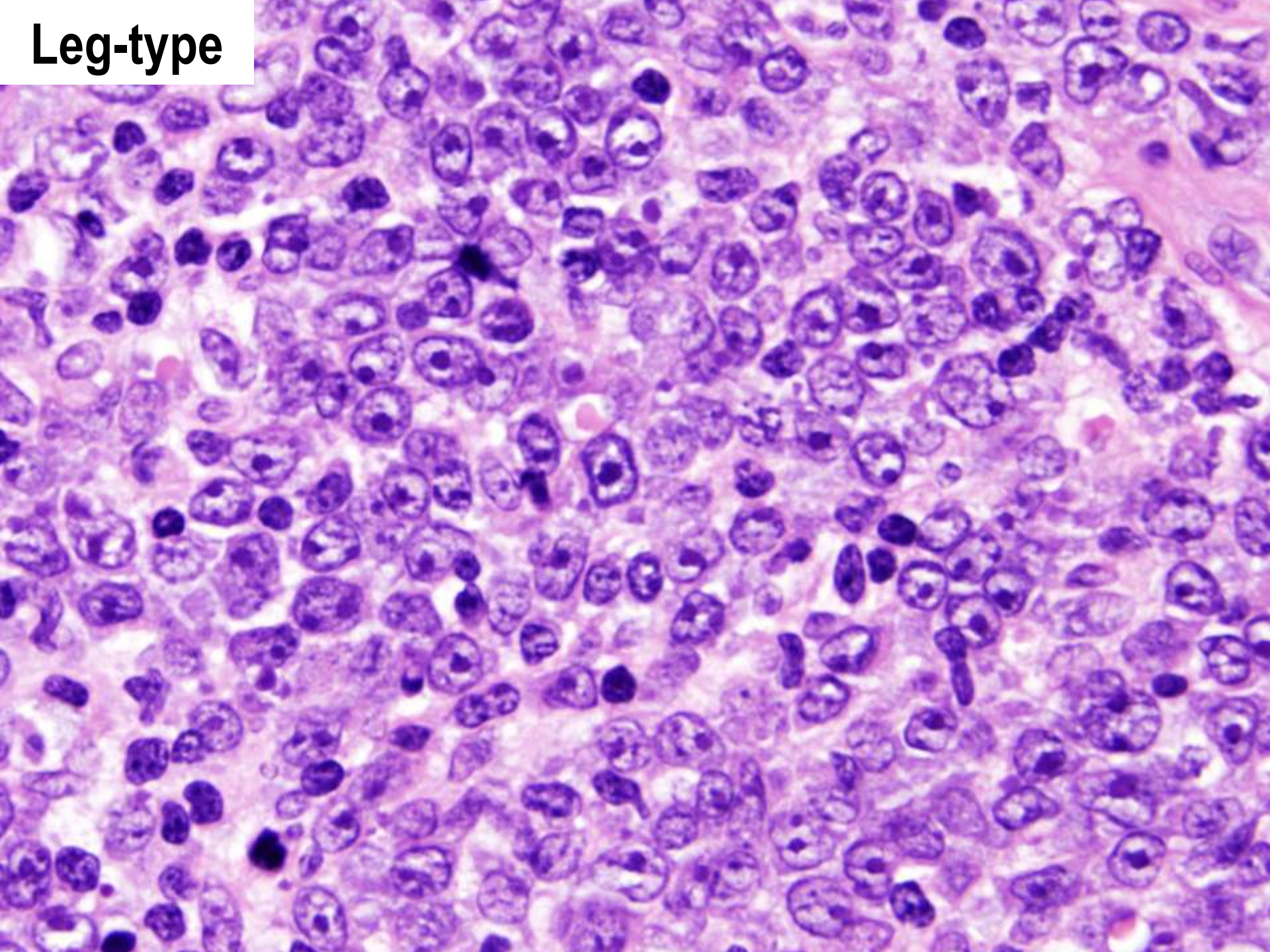
Often have eosinophilic rather than amphophilic cytoplasm; dendritic cell neoplasms favored if cell borders are indistinct

“Large B-cell lymphoma” of superficial soft tissues: Possibilities

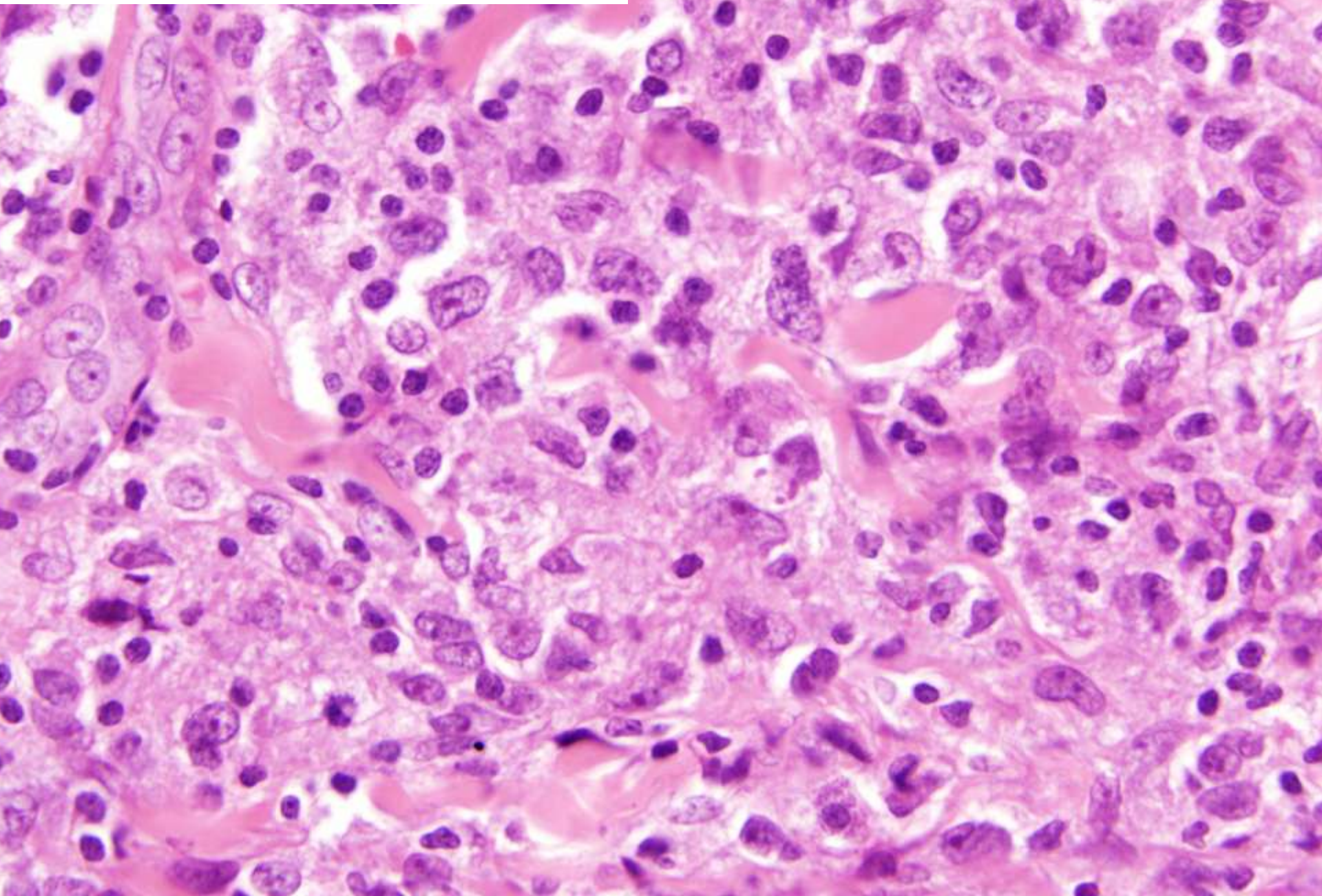
- Cutaneous or subcutaneous involvement by systemic diffuse large B-cell lymphoma
- Primary cutaneous diffuse large B-cell lymphoma, leg type
- Primary cutaneous follicle center lymphoma (rich in large cells)

Highly favorable prognosis



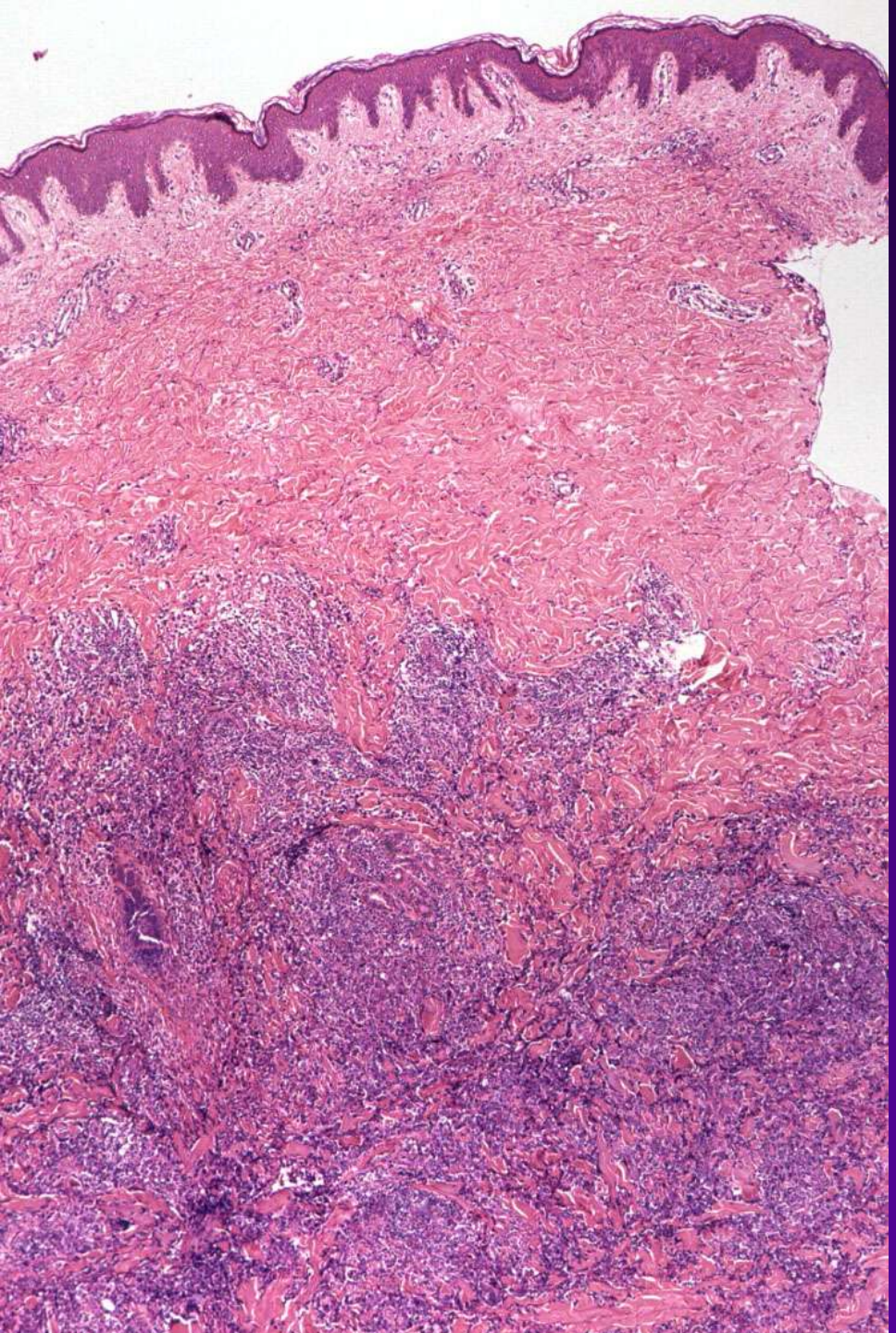

Leg-type

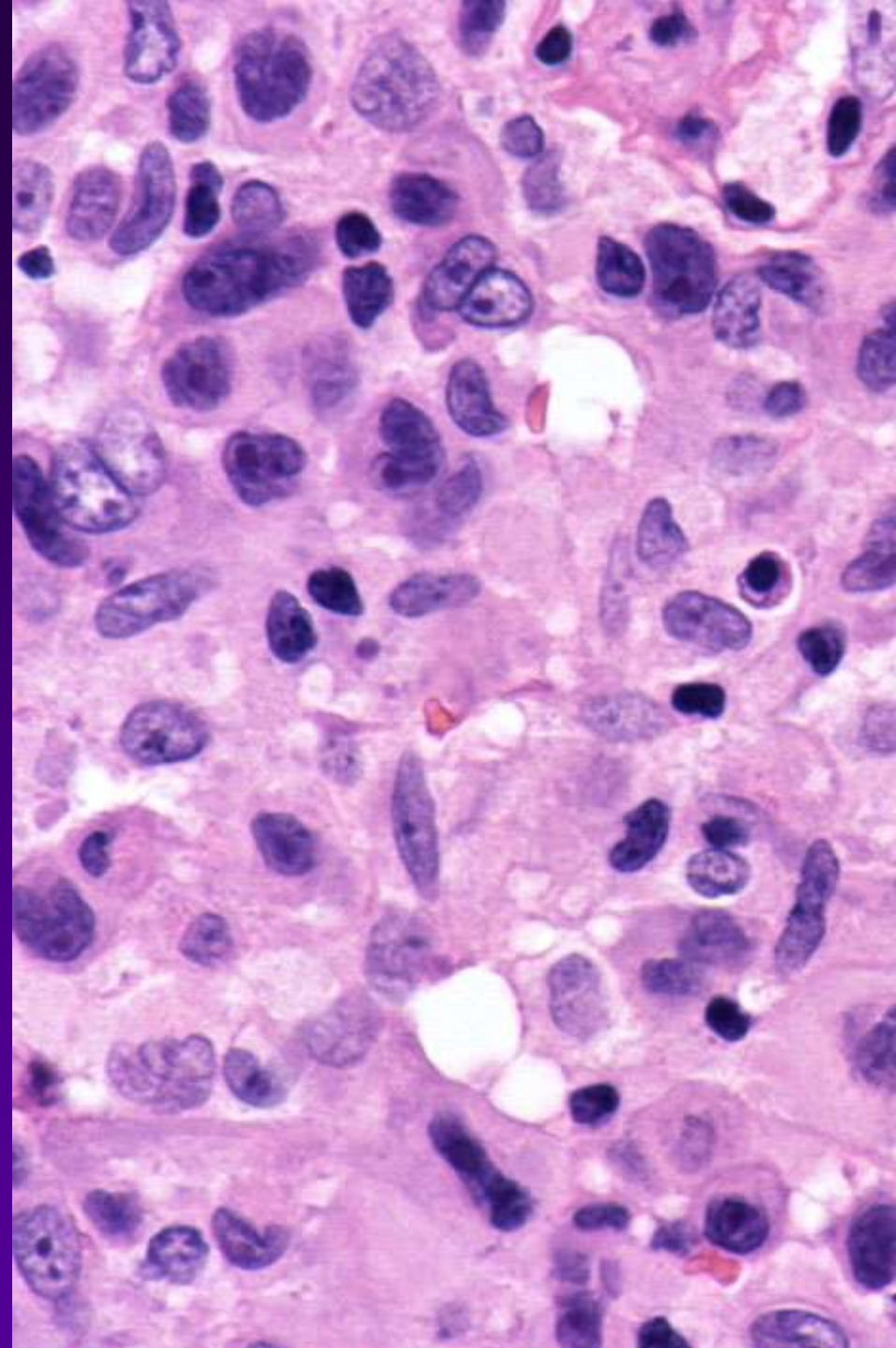
Follicle center lymphoma



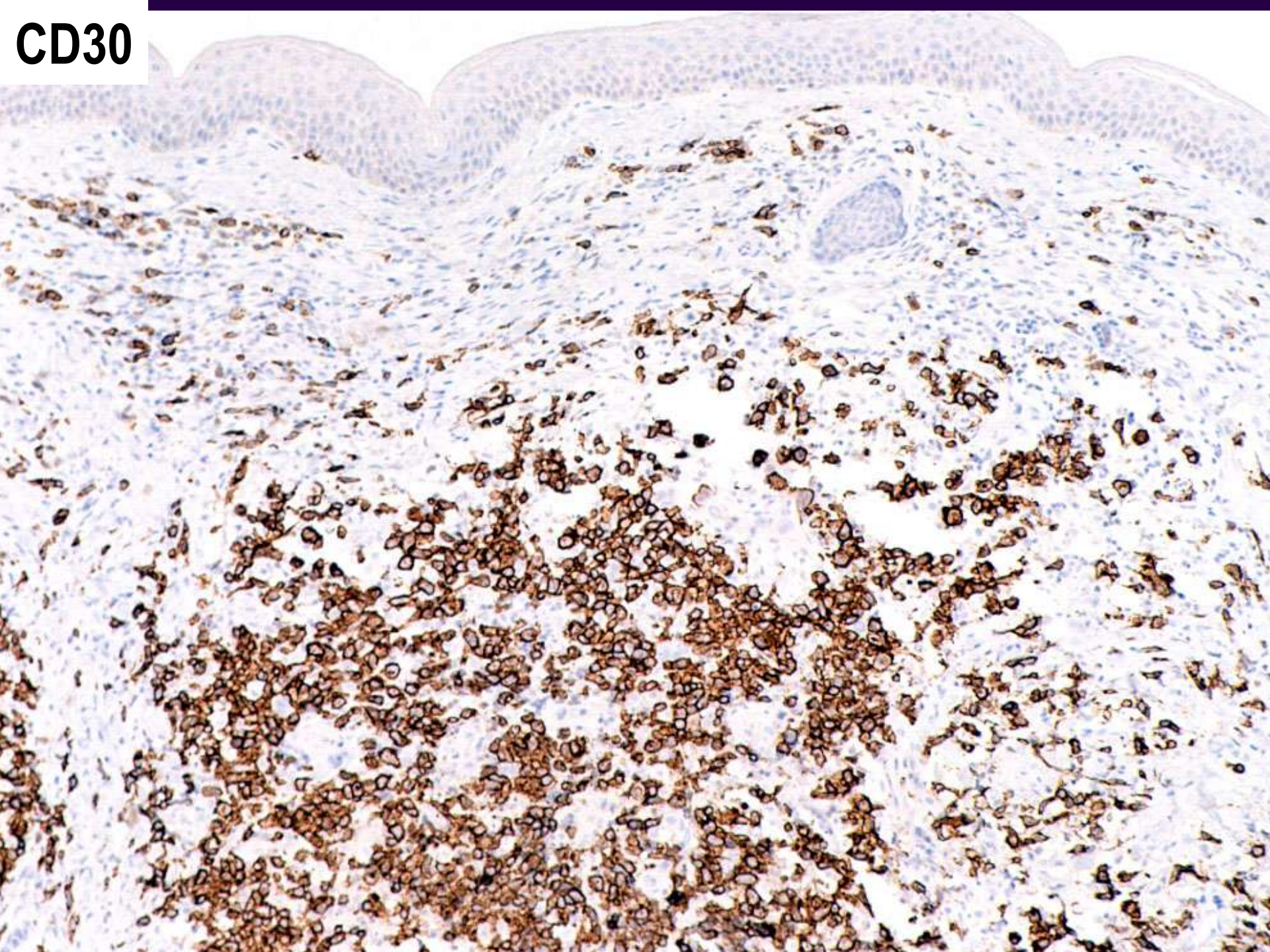
Primary cutaneous anaplastic large cell lymphoma

- More often presents as solitary tumor nodule, with or without ulceration
- Highly favorable prognosis; may show spontaneous regression
- Histology:
  - Numerous anaplastic large cells (sometimes non-anaplastic)
  - Inflammatory background variable





CD30



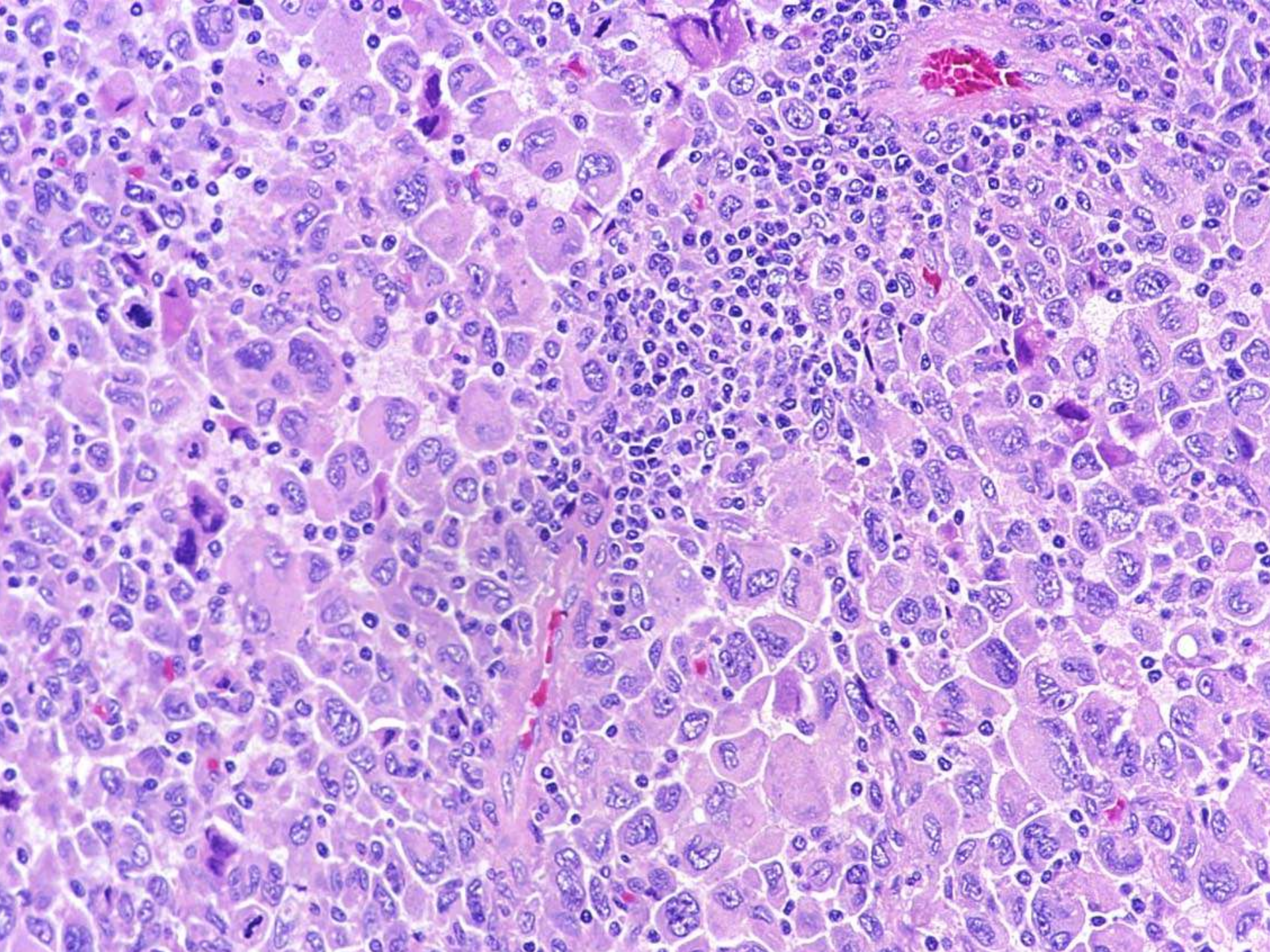
Histiocytic sarcoma

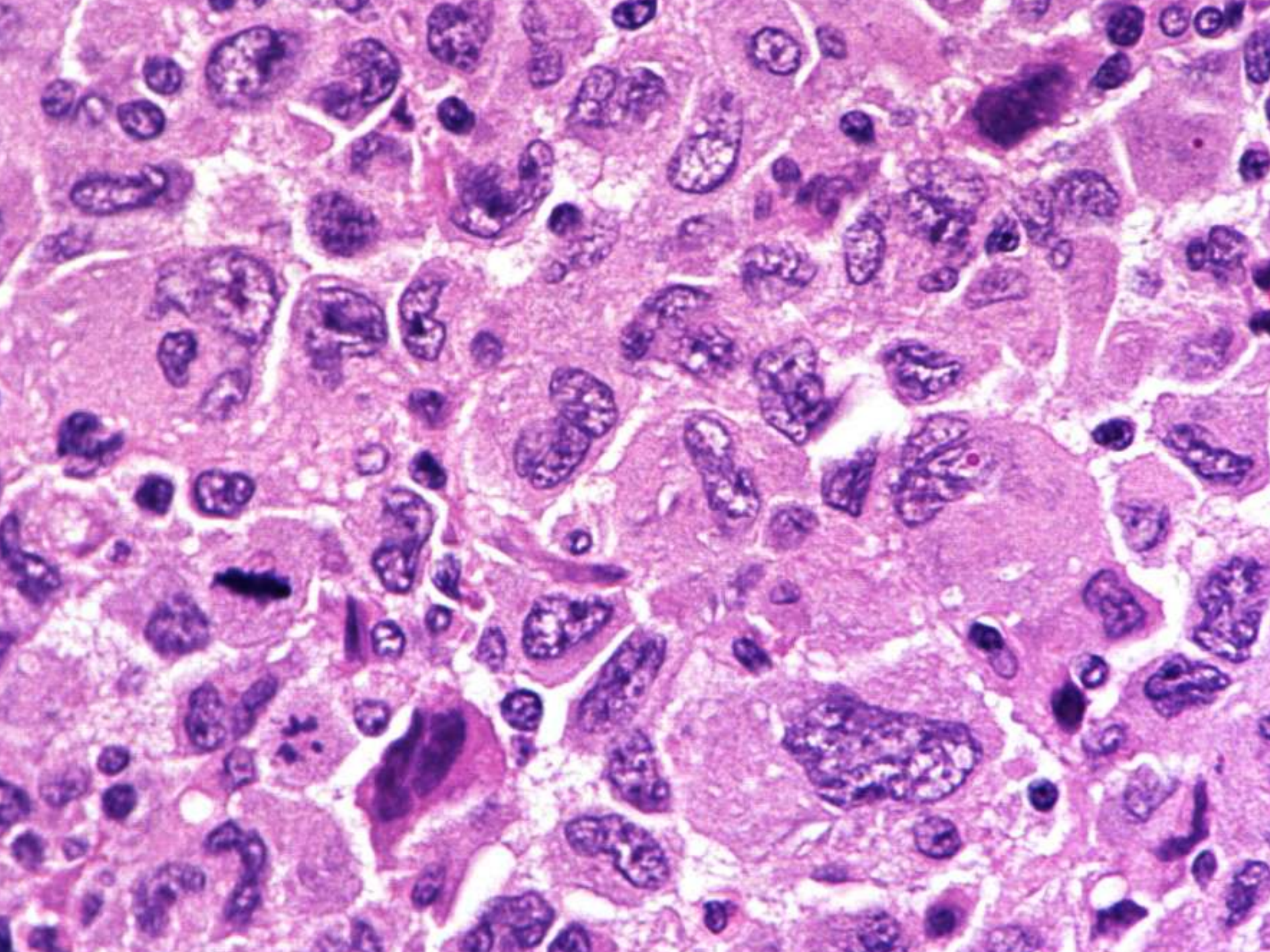
- A tumor-forming neoplasm showing monocytic-phagocytic differentiation. No relation to malignant fibrous histiocytoma.
- Age: Wide age range, mean 44 years
- Extranodal presentation common, especially in skin
- Often high stage (~70% Stage III/IV)
- Most die from disseminated disease within 2 years, although there are some survivors

Histiocytic sarcoma: Pathology

- Diffuse infiltrate
- Very large cells with abundant *eosinophilic* cytoplasm (which can be finely vacuolated)
- Eccentric nuclei: round, oval, irregular or grooved, with delicate or coarse chromatin
- Nucleoli often small
- Cellular pleomorphism moderate to marked

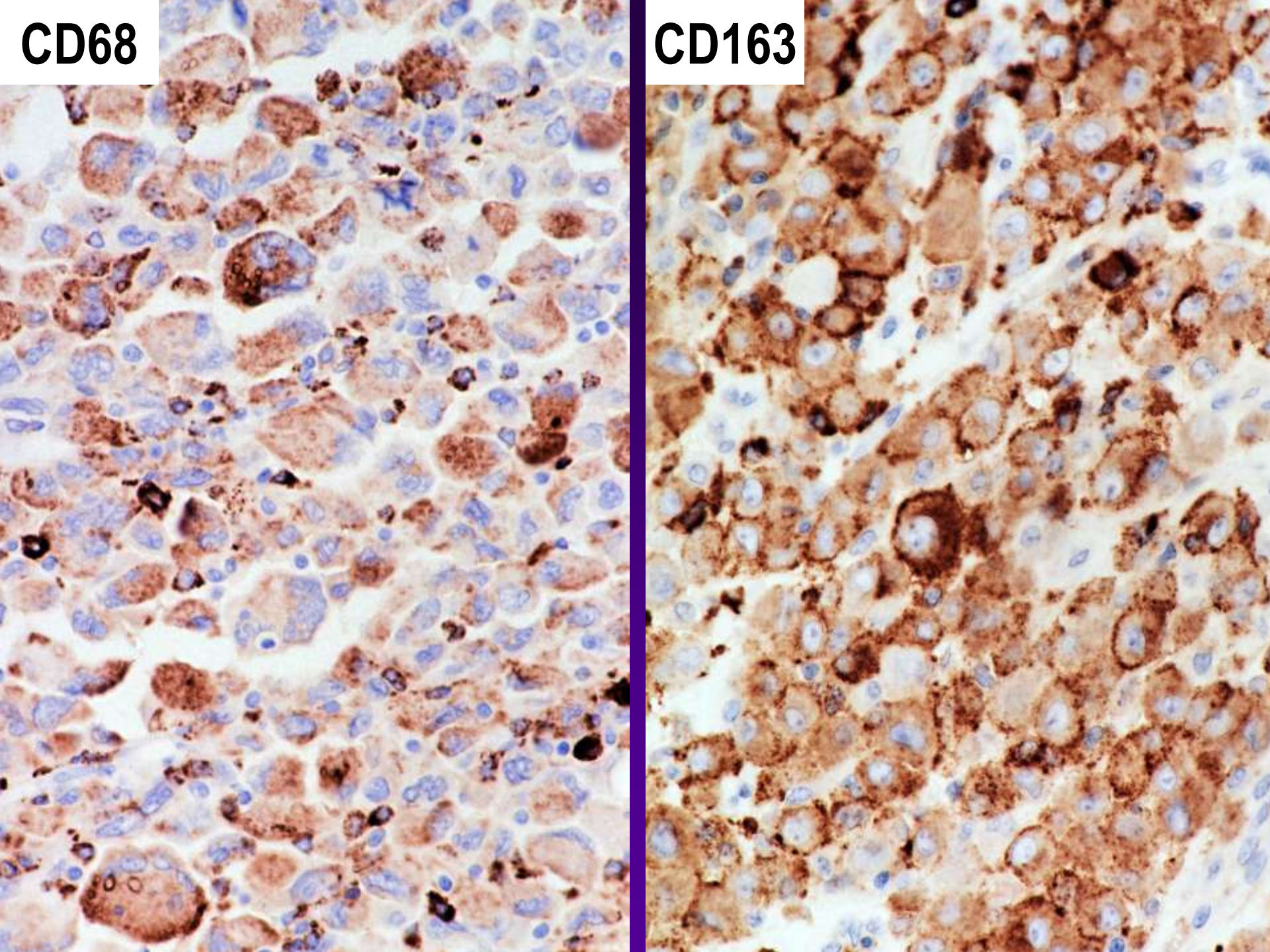
Can be difficult to distinguish from T or B-large cell lymphoma!





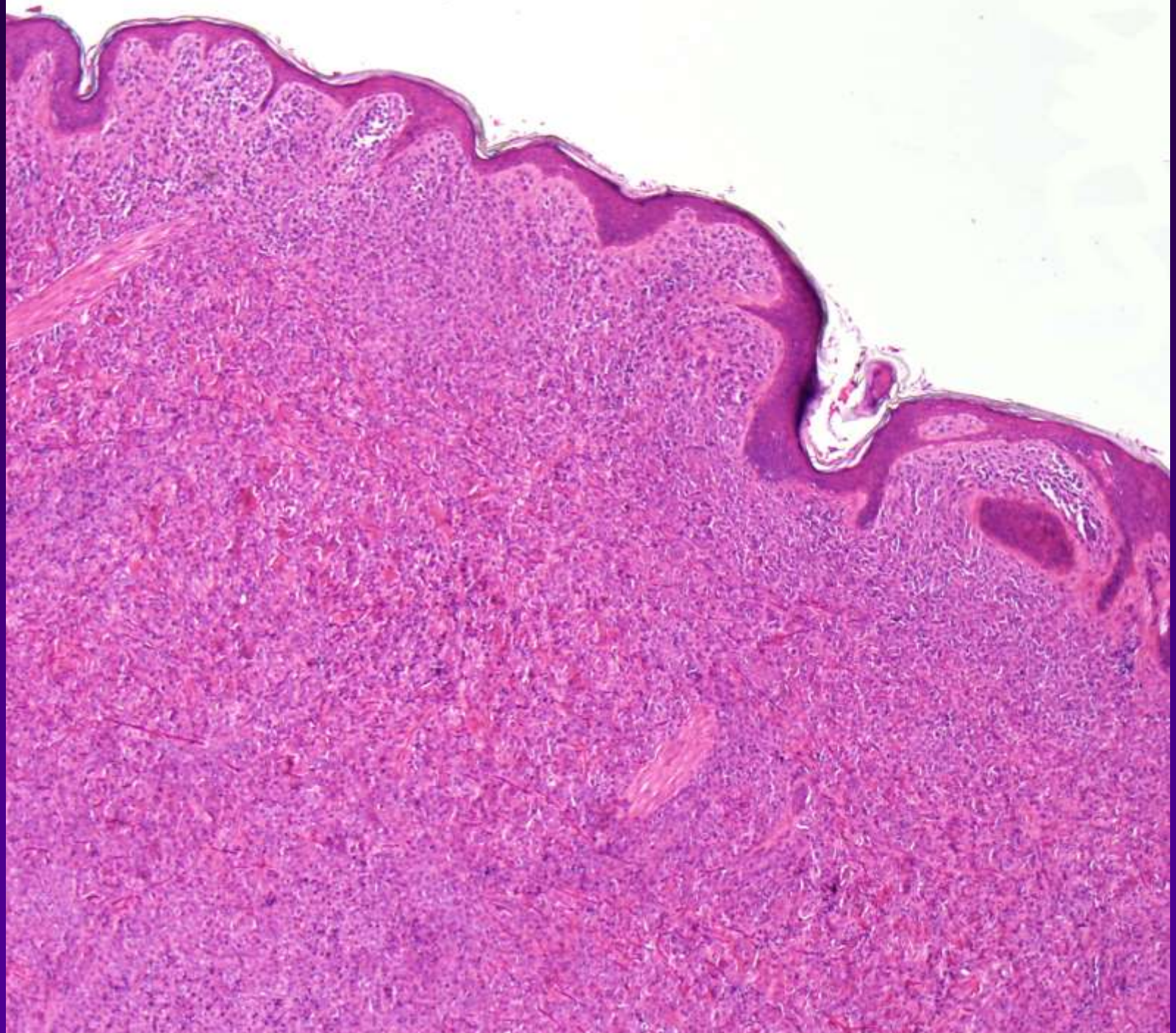
Histiocytic sarcoma: Immunophenotype

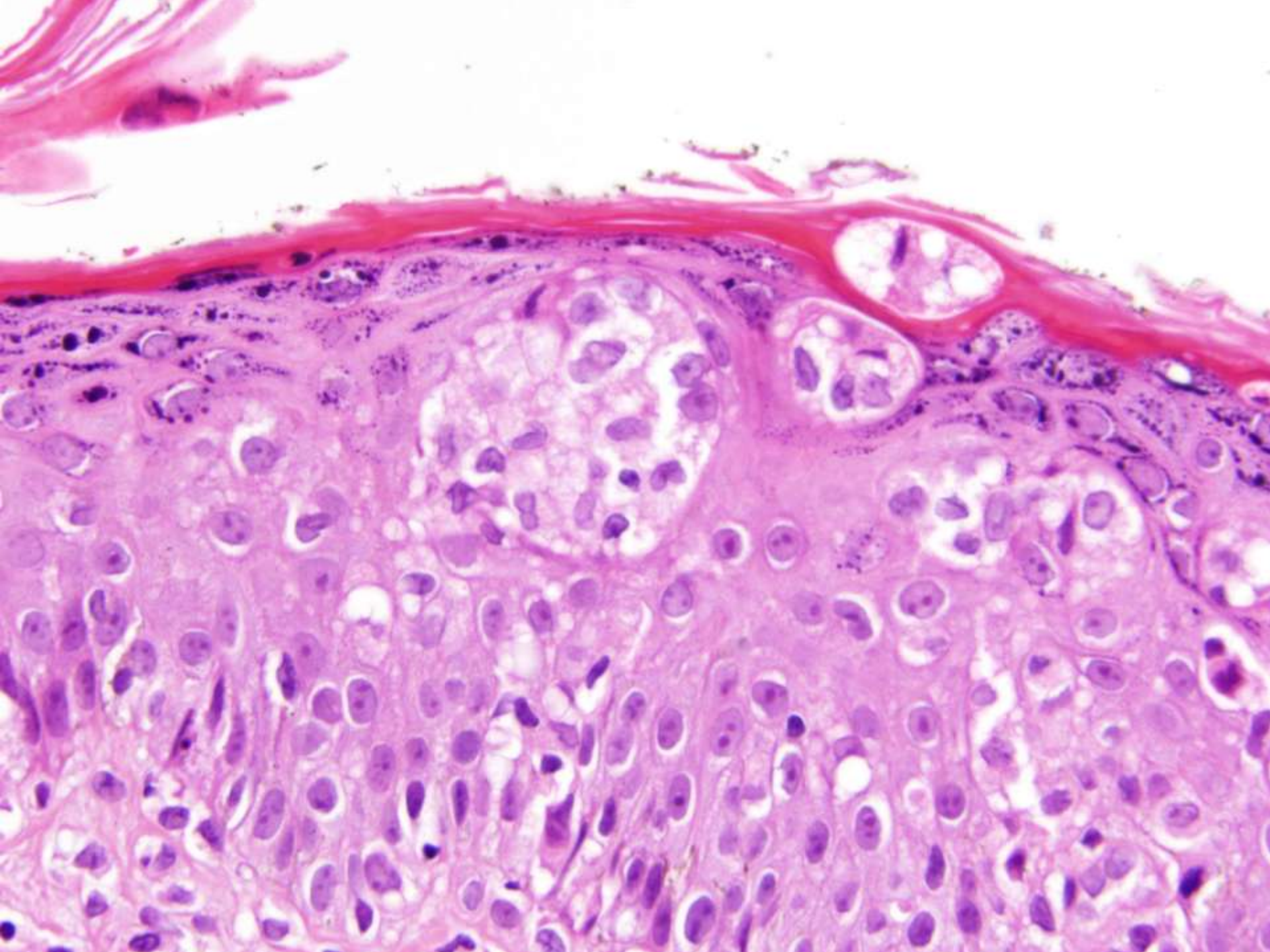
- *CD68*+, *Lysozyme (granular)*+, *CD163*+
- CD4 usually +
- S100 protein -/+ (often heterogeneous), CD1a -
- LCA +/-
- Negative for B, T, myeloid and FDC markers (although CD43 and CD45RO are often +)
- Negative for CD30

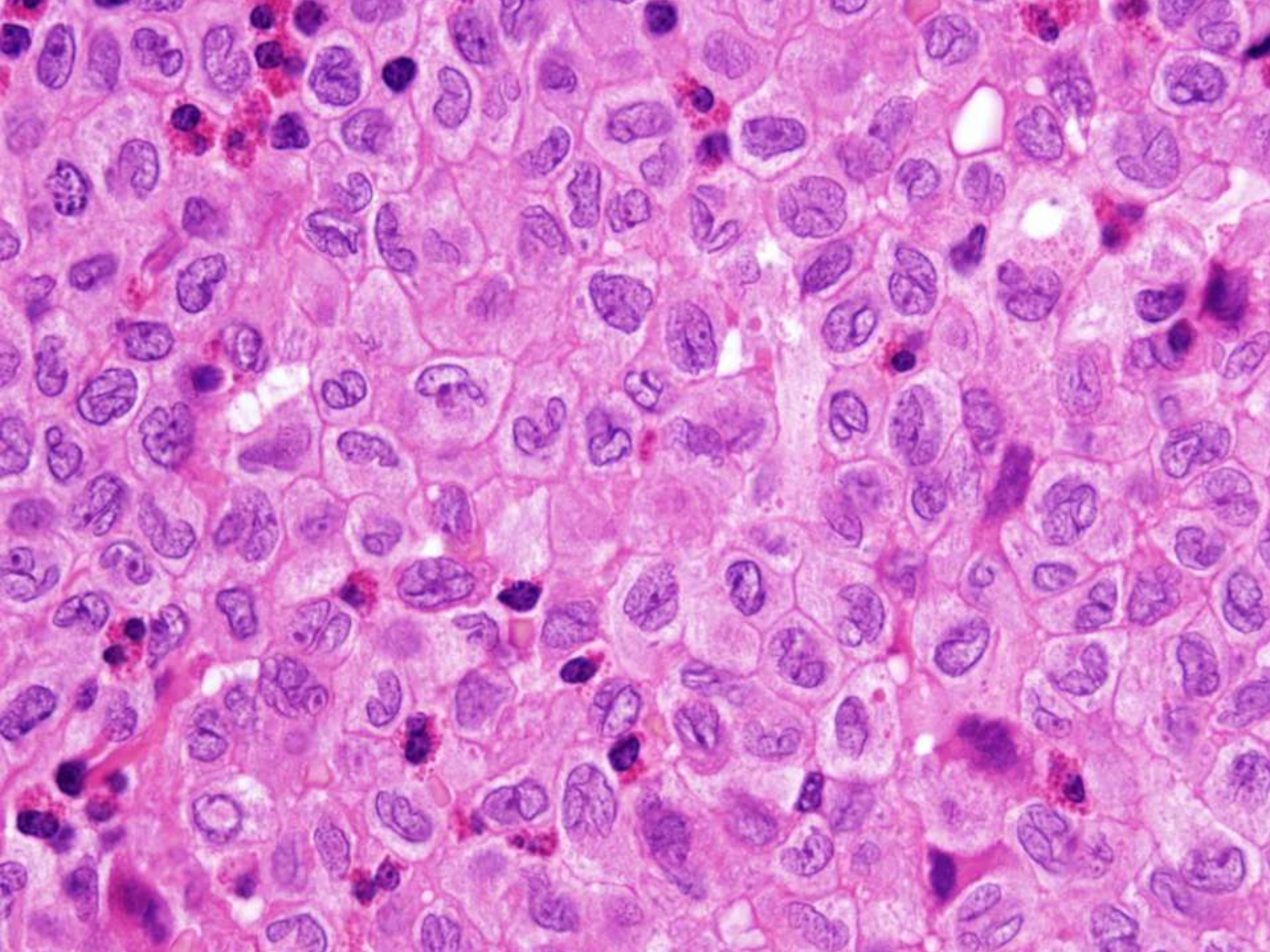

CD68
CD163

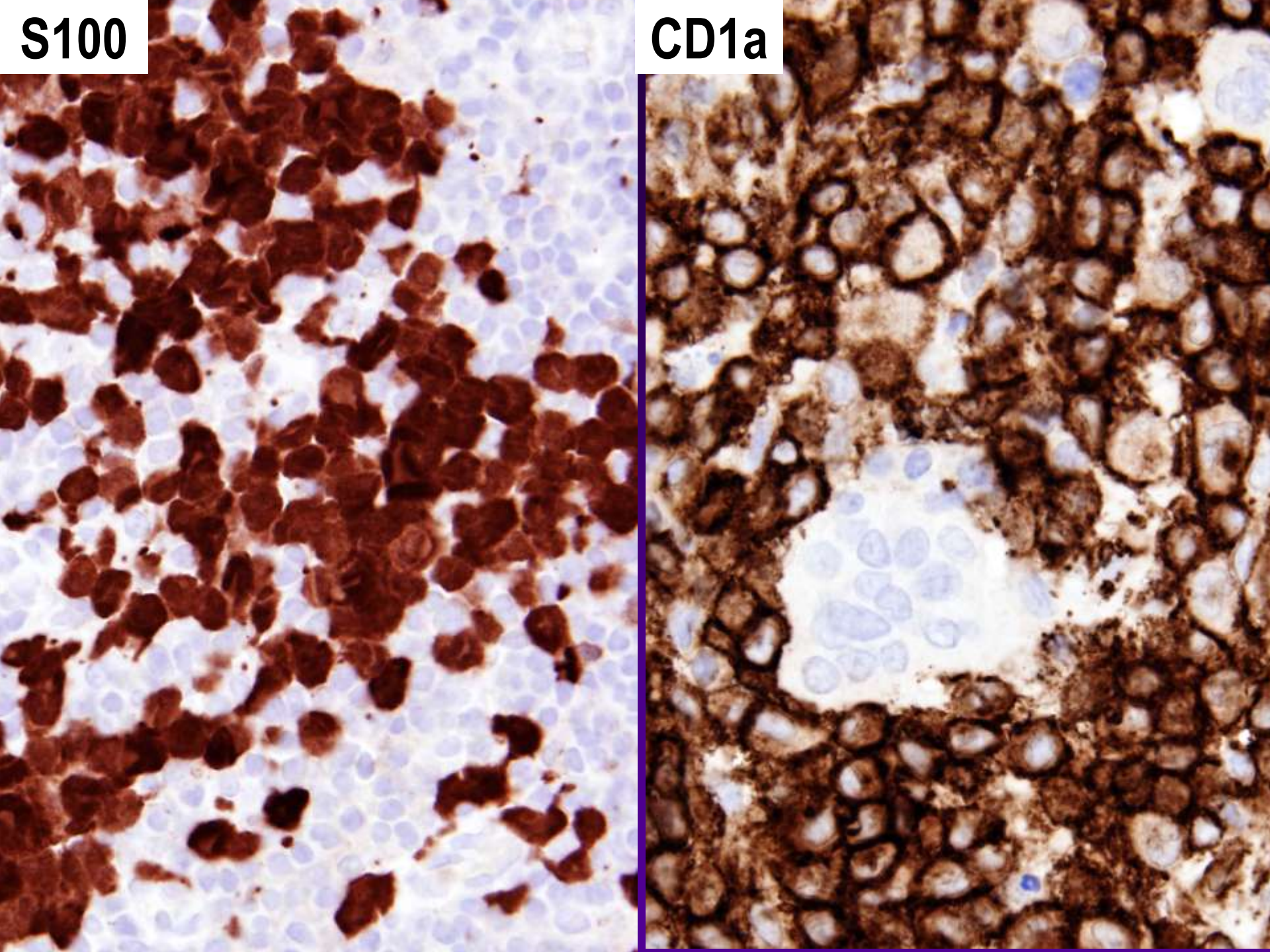
Langerhans cell histiocytosis (LCH)

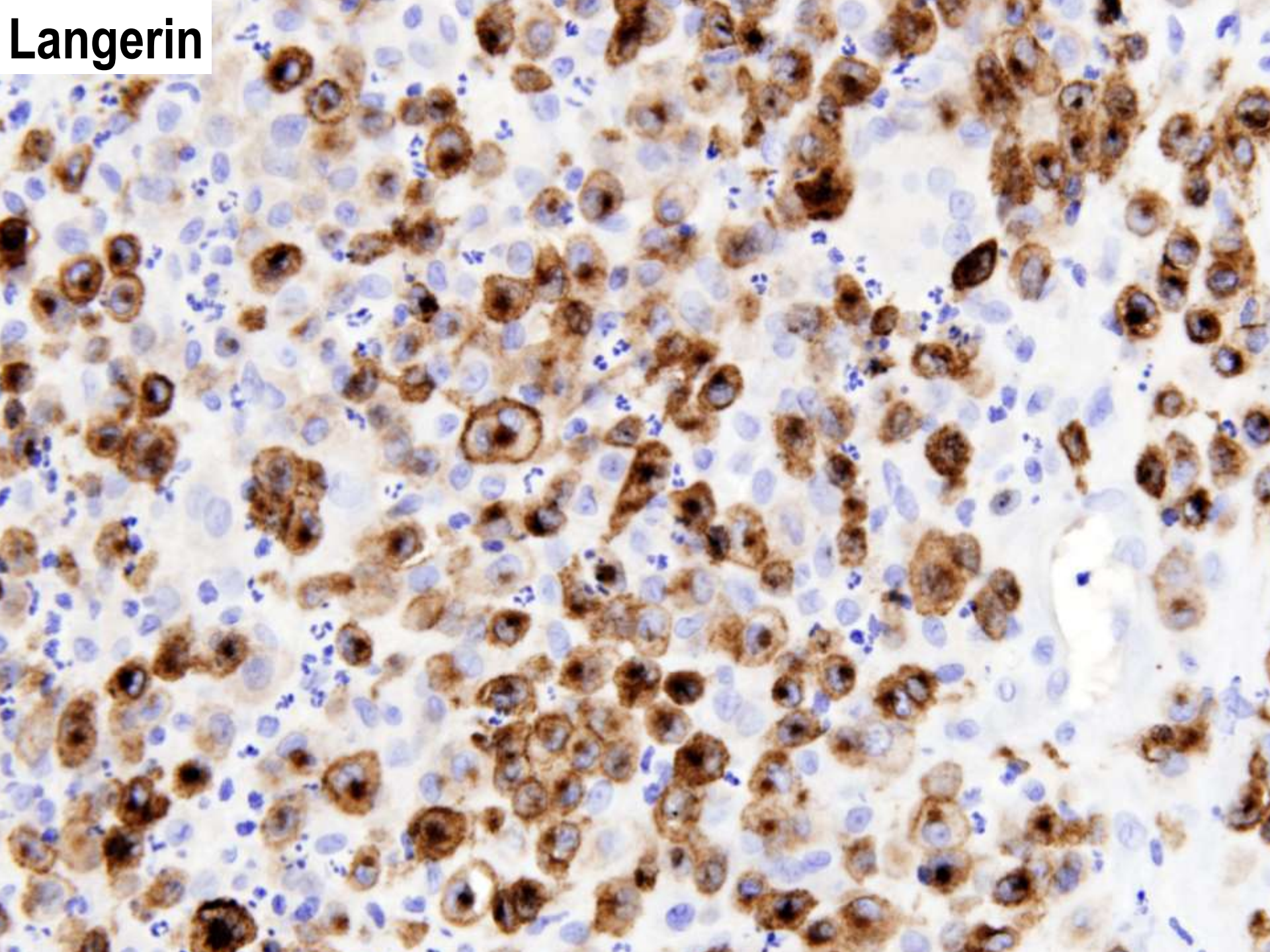
- A localized or systemic proliferative disorder of Langerhans cells.
- Molecular analysis has shown it to be a *clonal disorder, i.e. neoplasm.*
- Usually children
- Skin involvement common





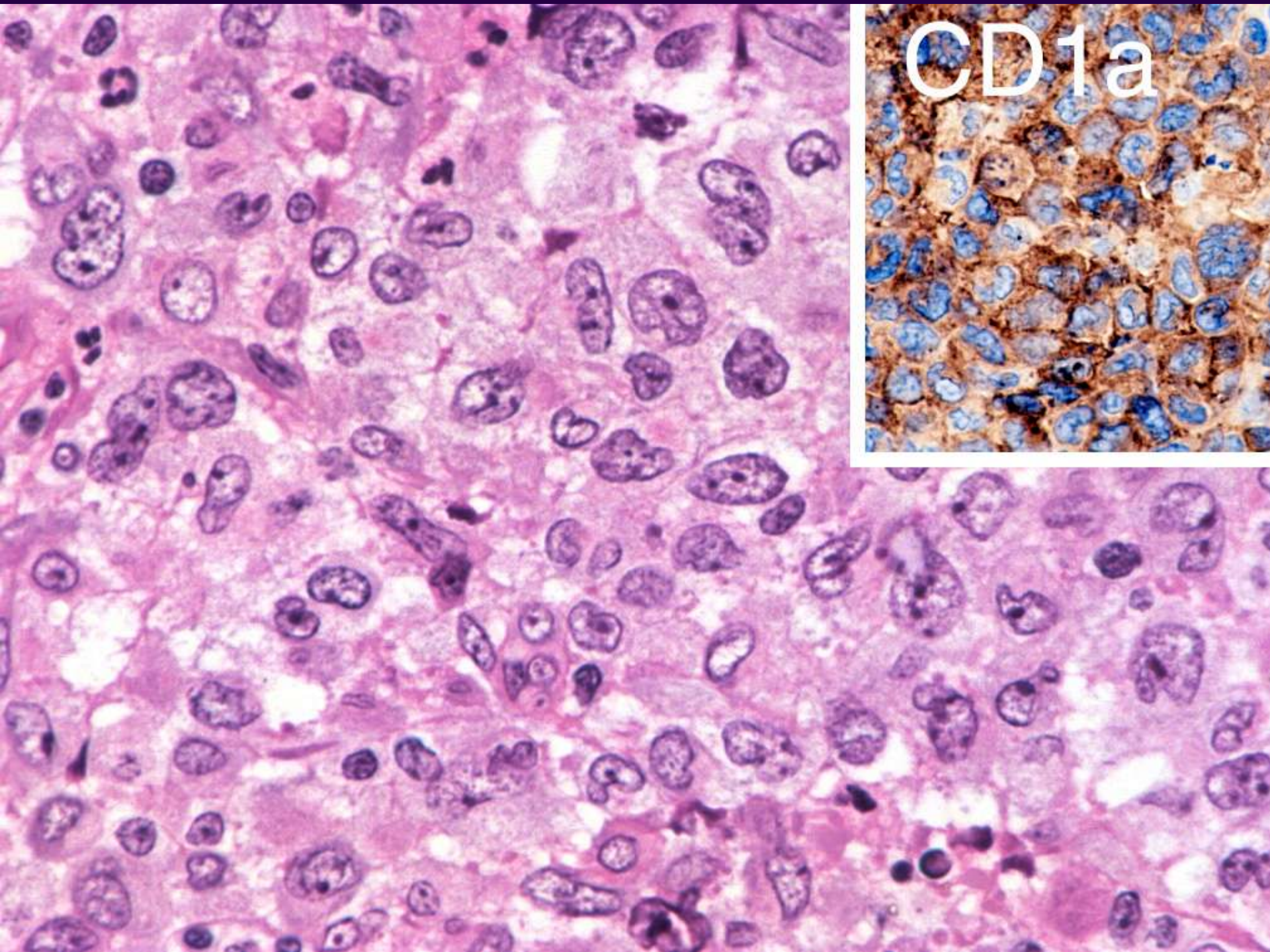



S100
CD1a


Langerin

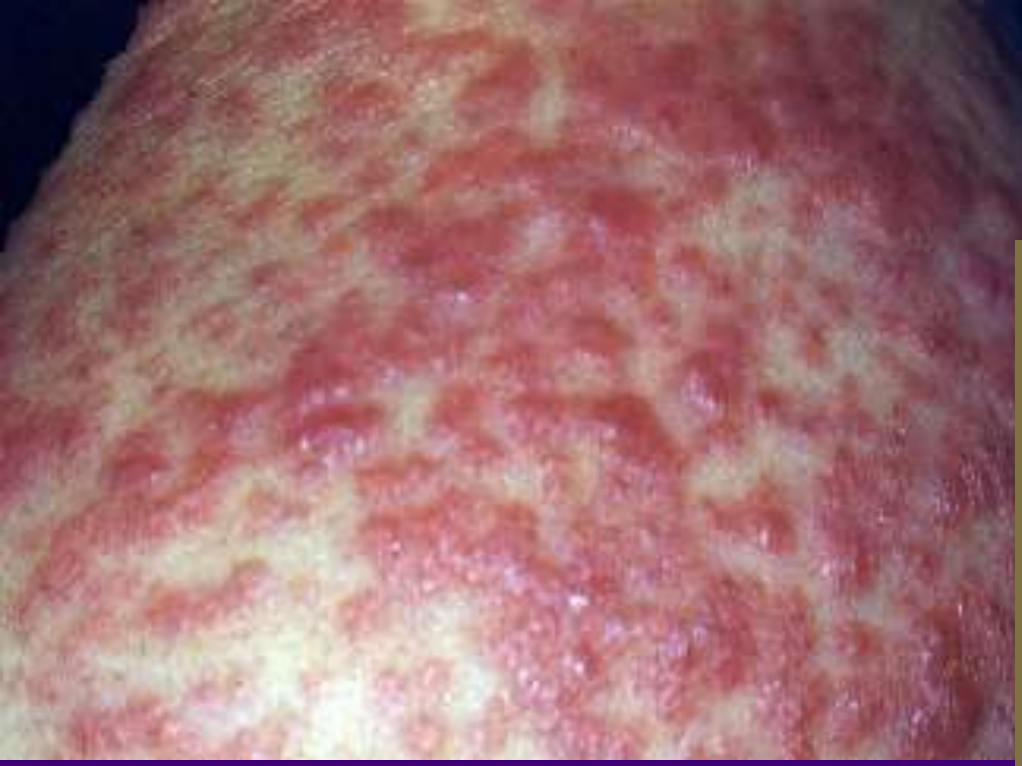
Langerhans cell sarcoma

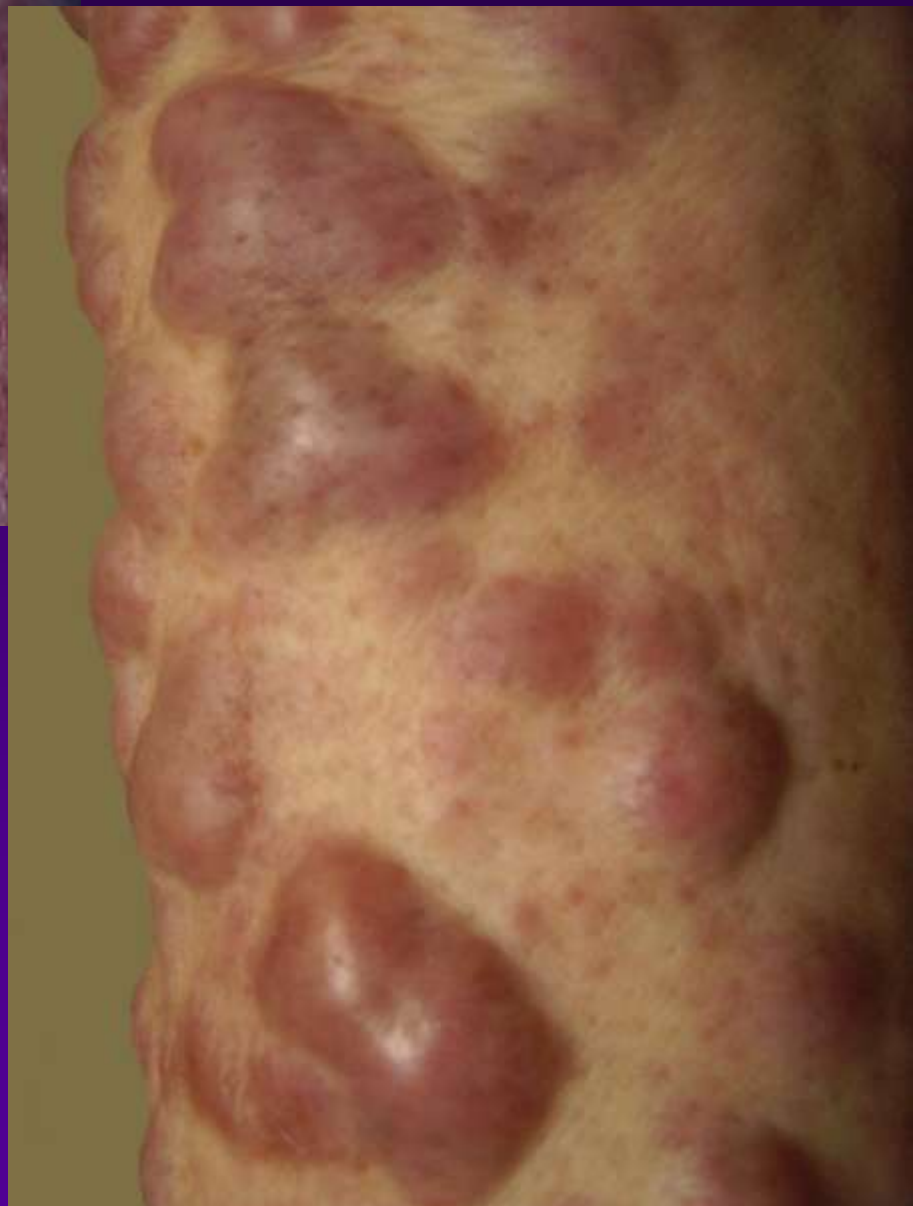
- Variant of LCH with frankly malignant cytologic features and mitotic activity, and showing the typical S100+ CD1a+ phenotype
- Occurs in older age group (mean 40 yr)
- More aggressive than conventional LCH:
  - 4/8 died of disease
  - 1/8 alive with disease

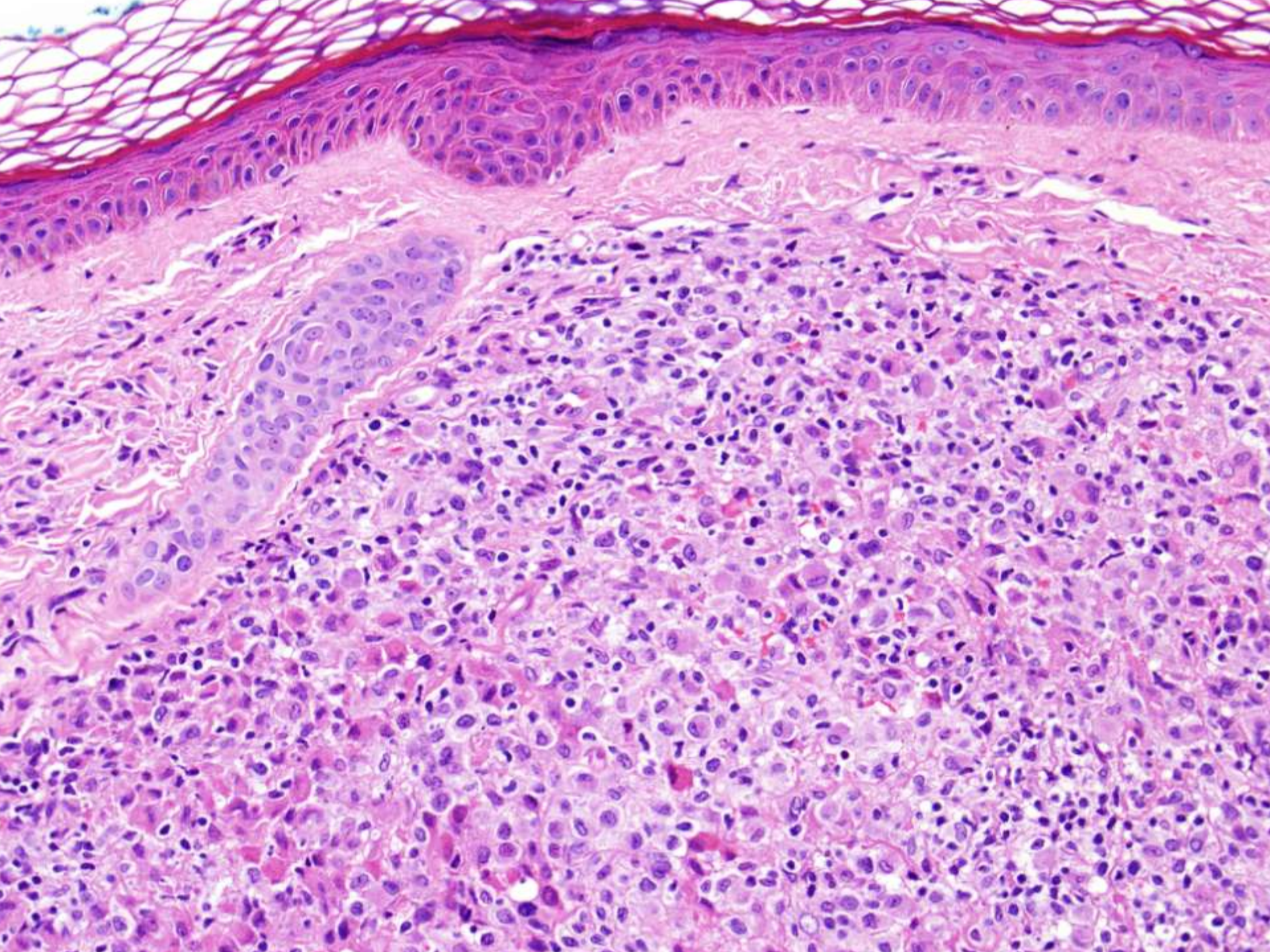

CD1a

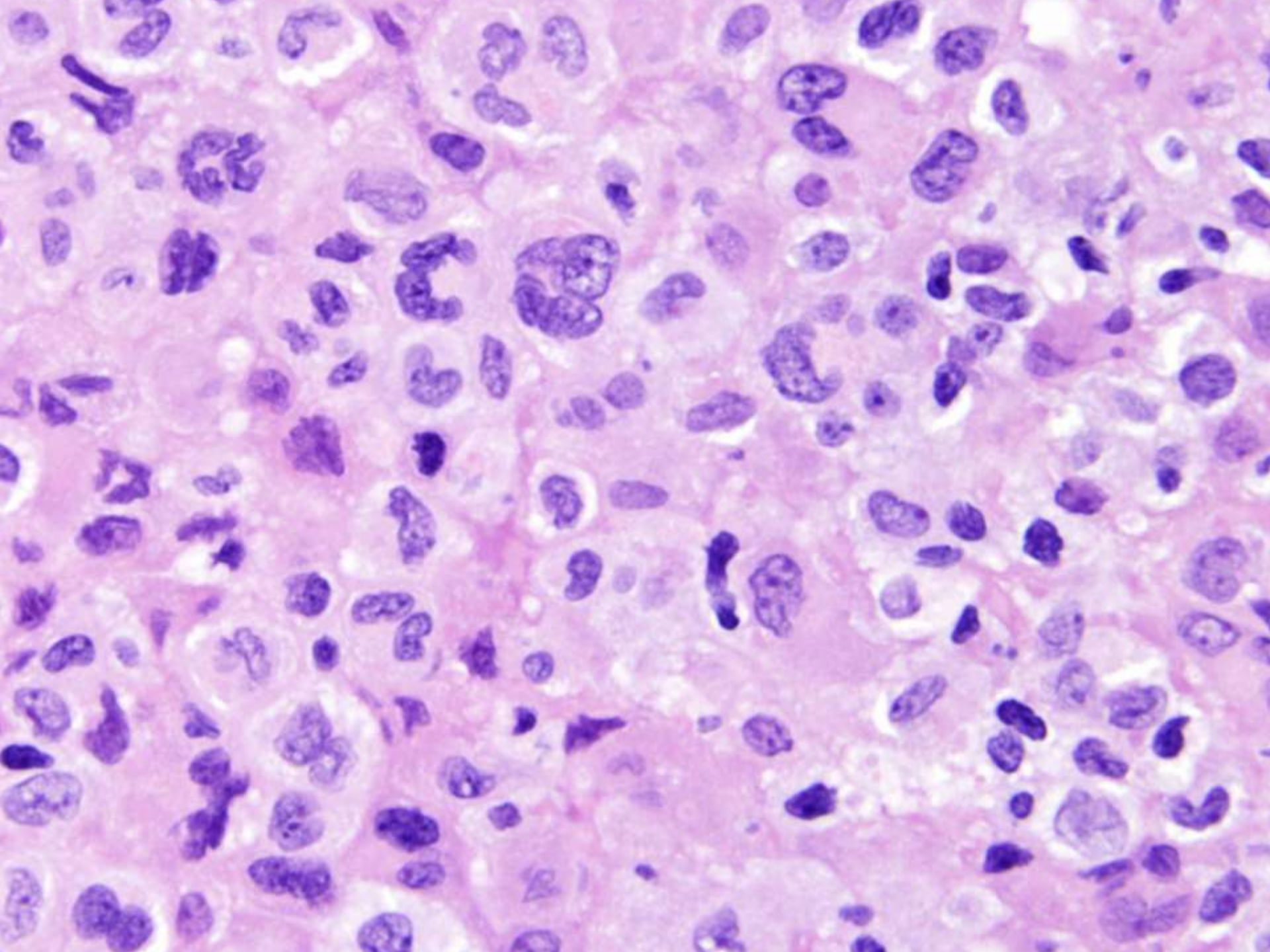
Indeterminate dendritic cell tumor

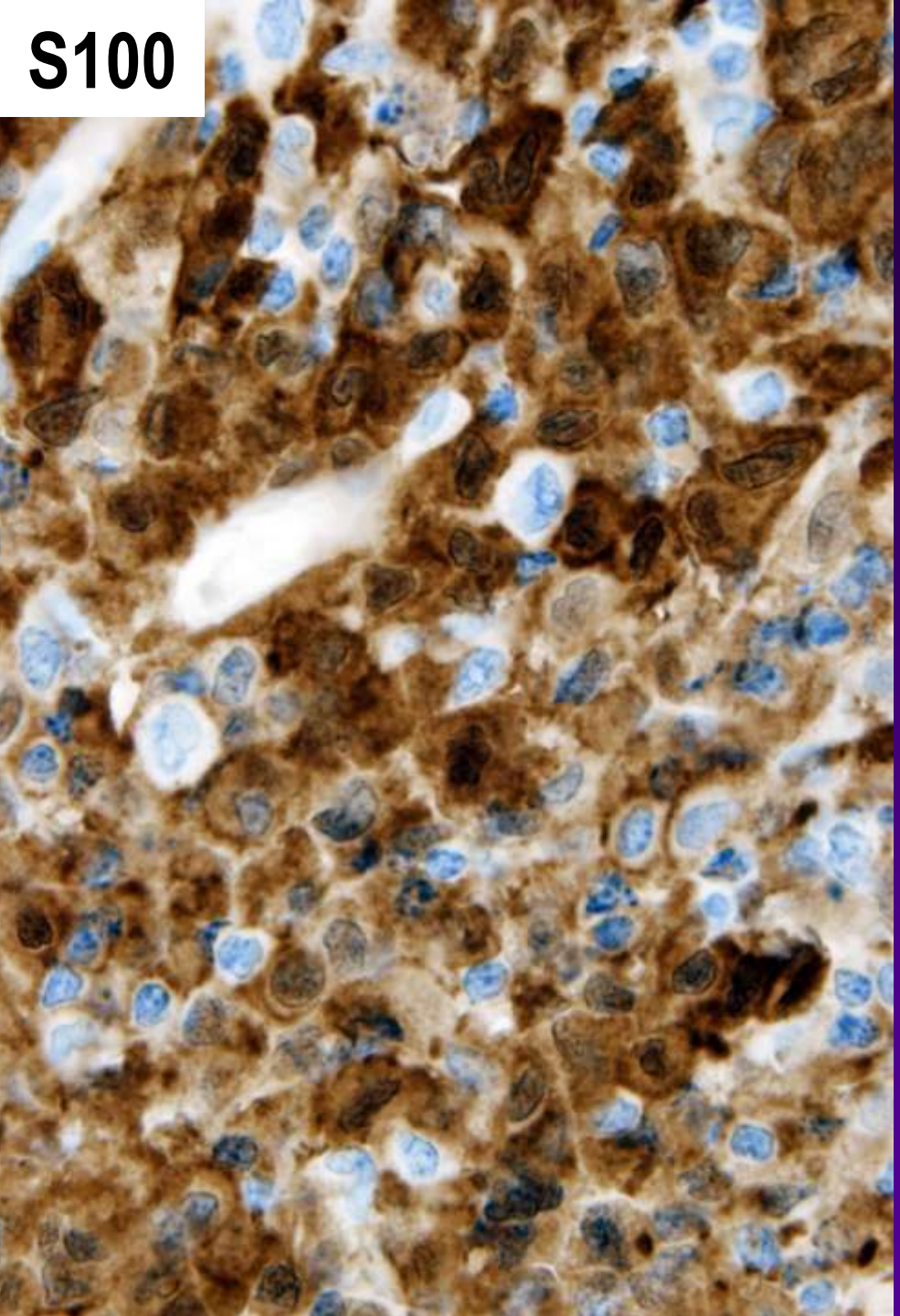
- Also known as “indeterminate cell histiocytosis”
- Sites of disease:
  - Skin (commonest)
  - Lymph node or other sites
- Morphology similar to Langerhans cell sarcoma
- While S100 and CD1a are positive, Langerin is negative
- Highly variable clinical course, while cutaneous cases tend to be indolent

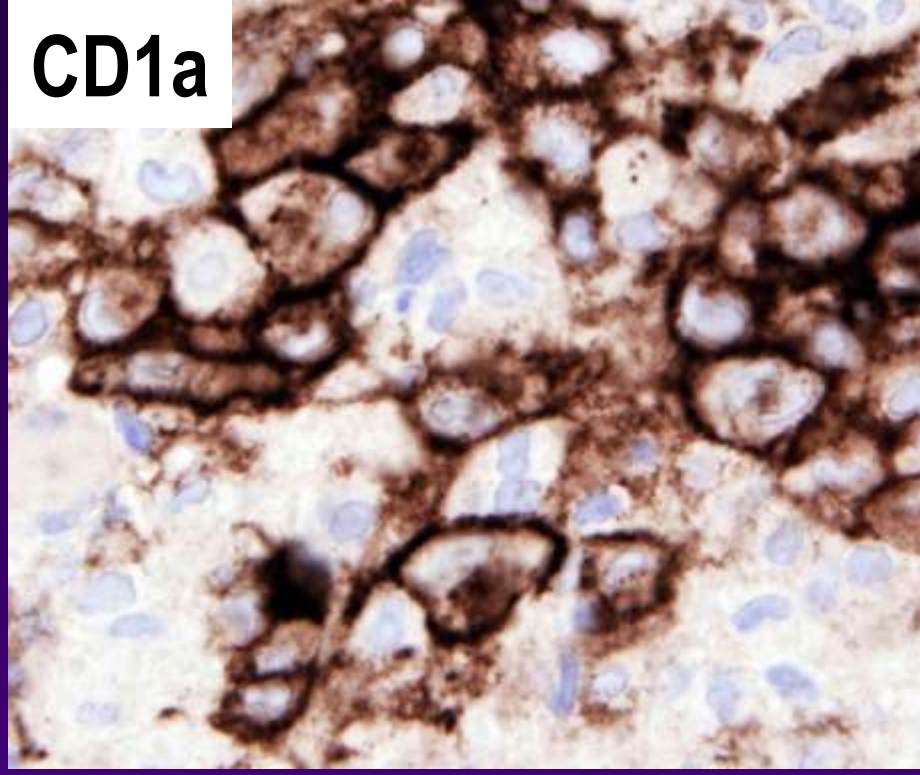


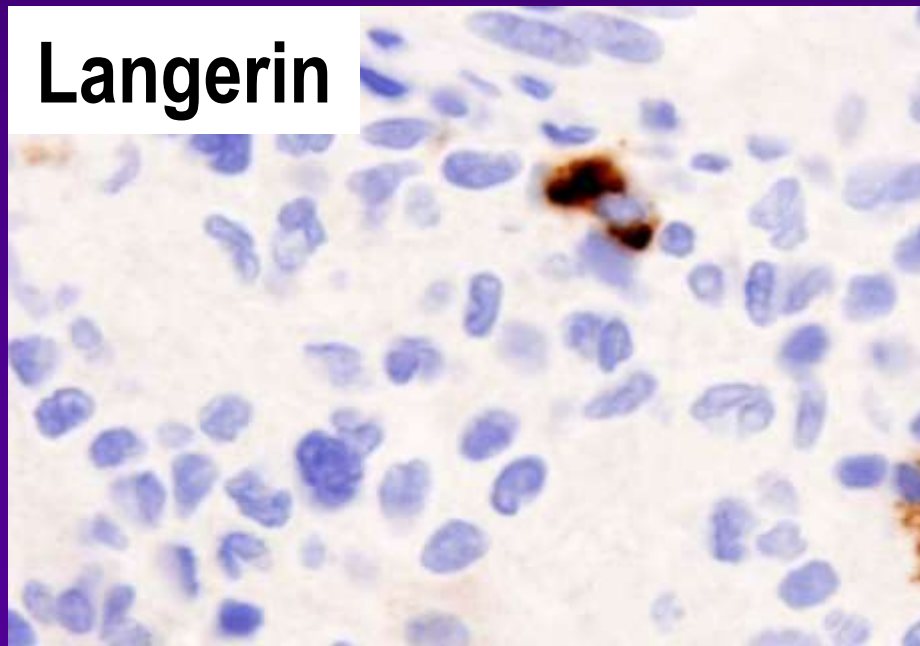







S100


CD1a

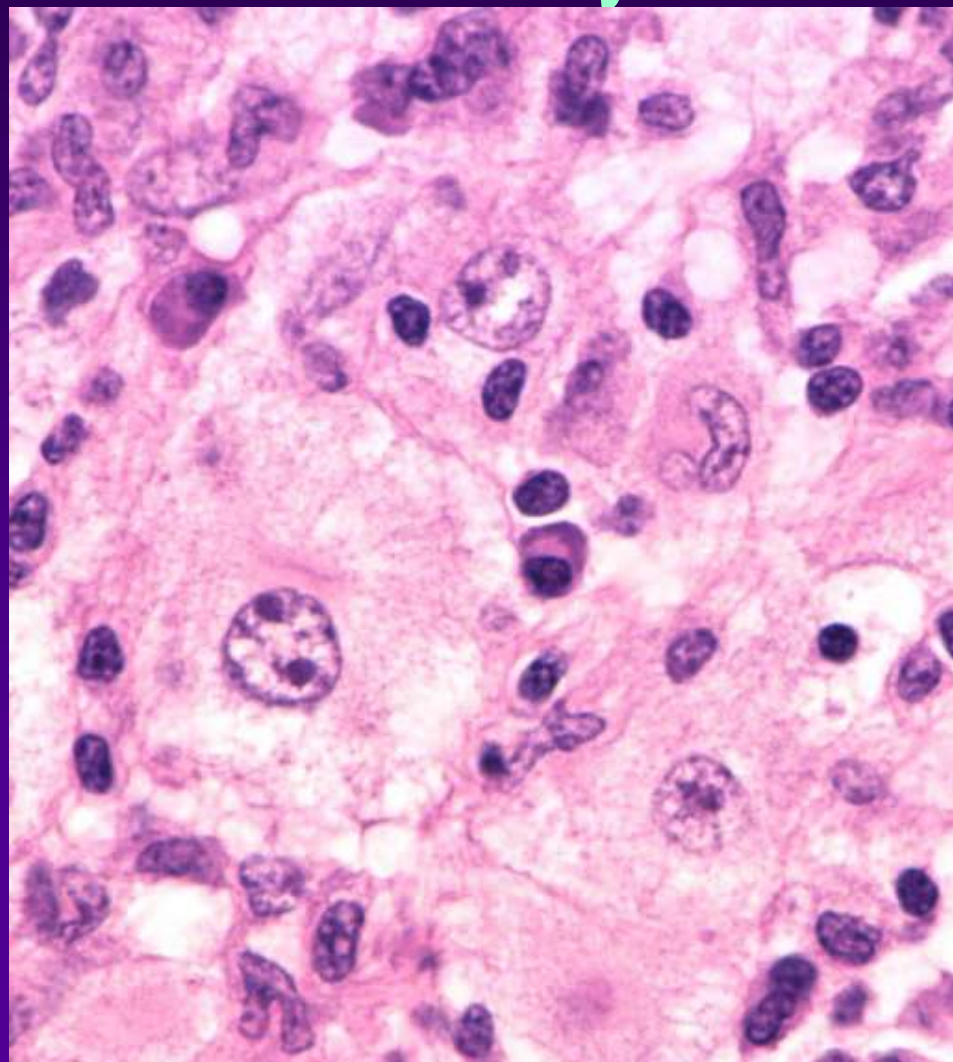

Langerin

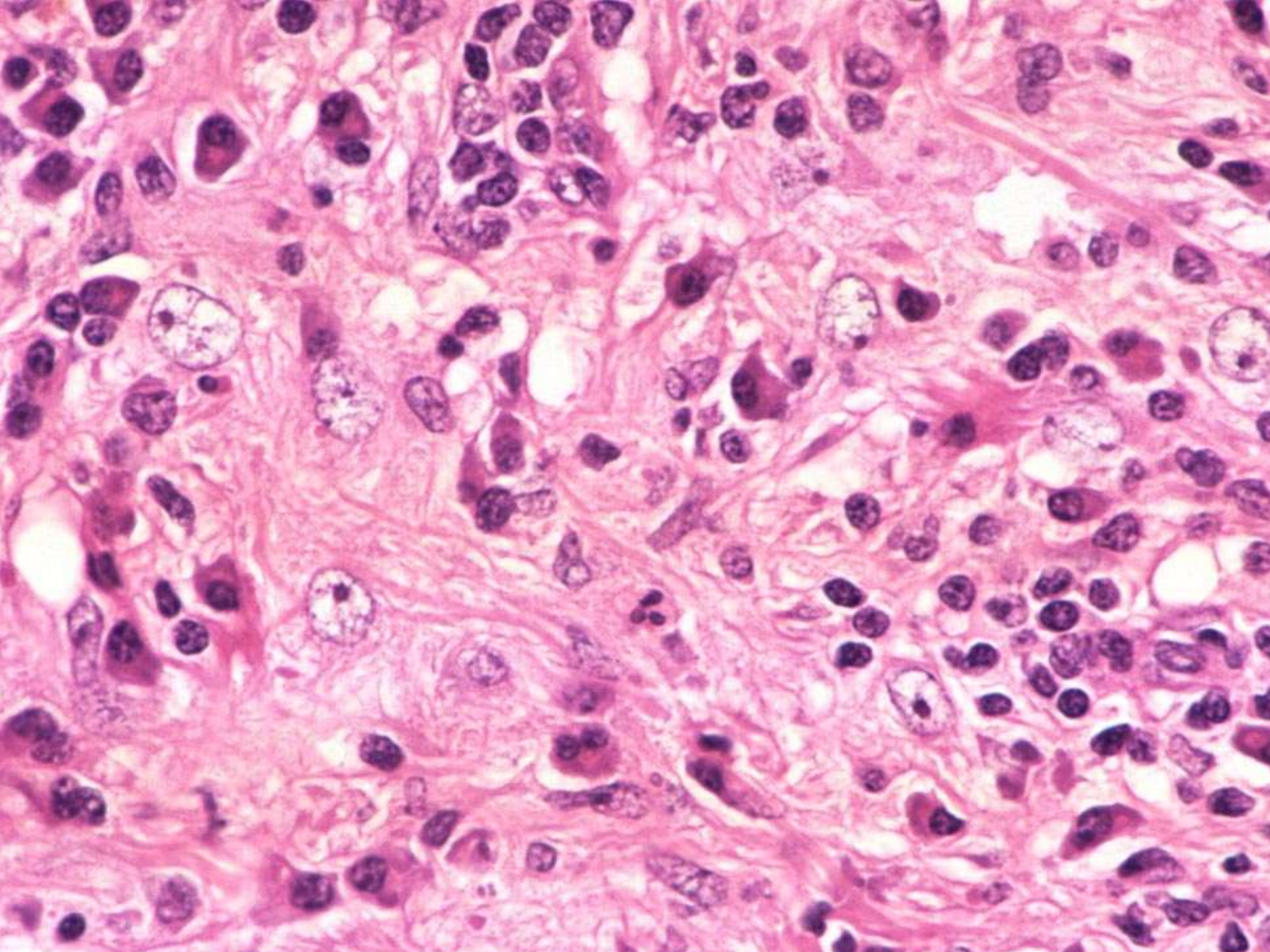
Rosai-Dorfman disease

- A reactive, idiopathic, proliferative disorder of histiocytes
- Young age
- Extranodal involvement common (43%)
  - With or without simultaneous LN involvement
  - Commonest sites: skin, upper respiratory tract, bone

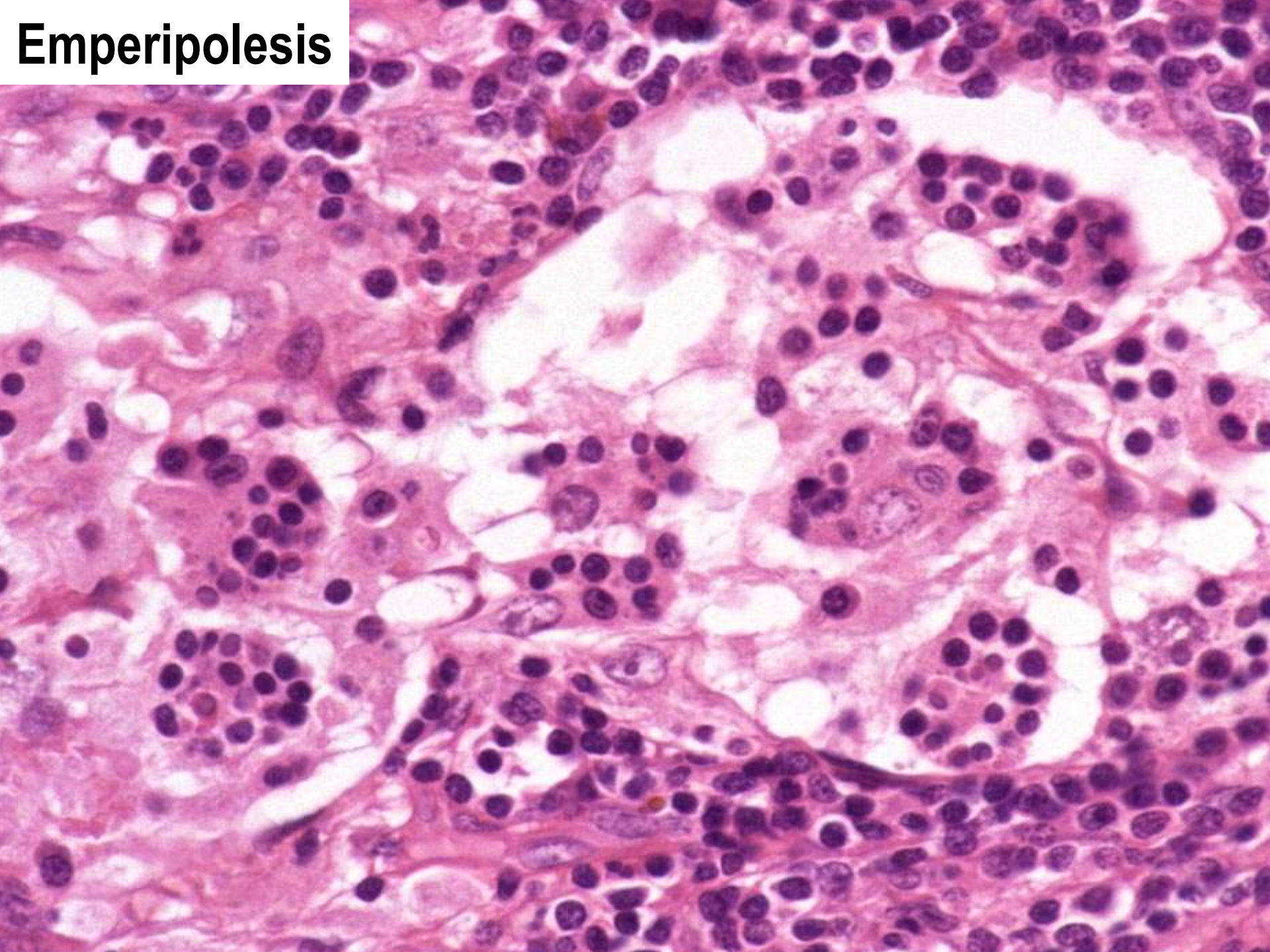
Rosai-Dorfman disease: Distinctive appearance of histiocytes

- Very large size, with voluminous cytoplasm (typically pale to clear, sometimes eosinophilic)
- Nucleus often round, with vesicular chromatin
- Distinct nucleolus



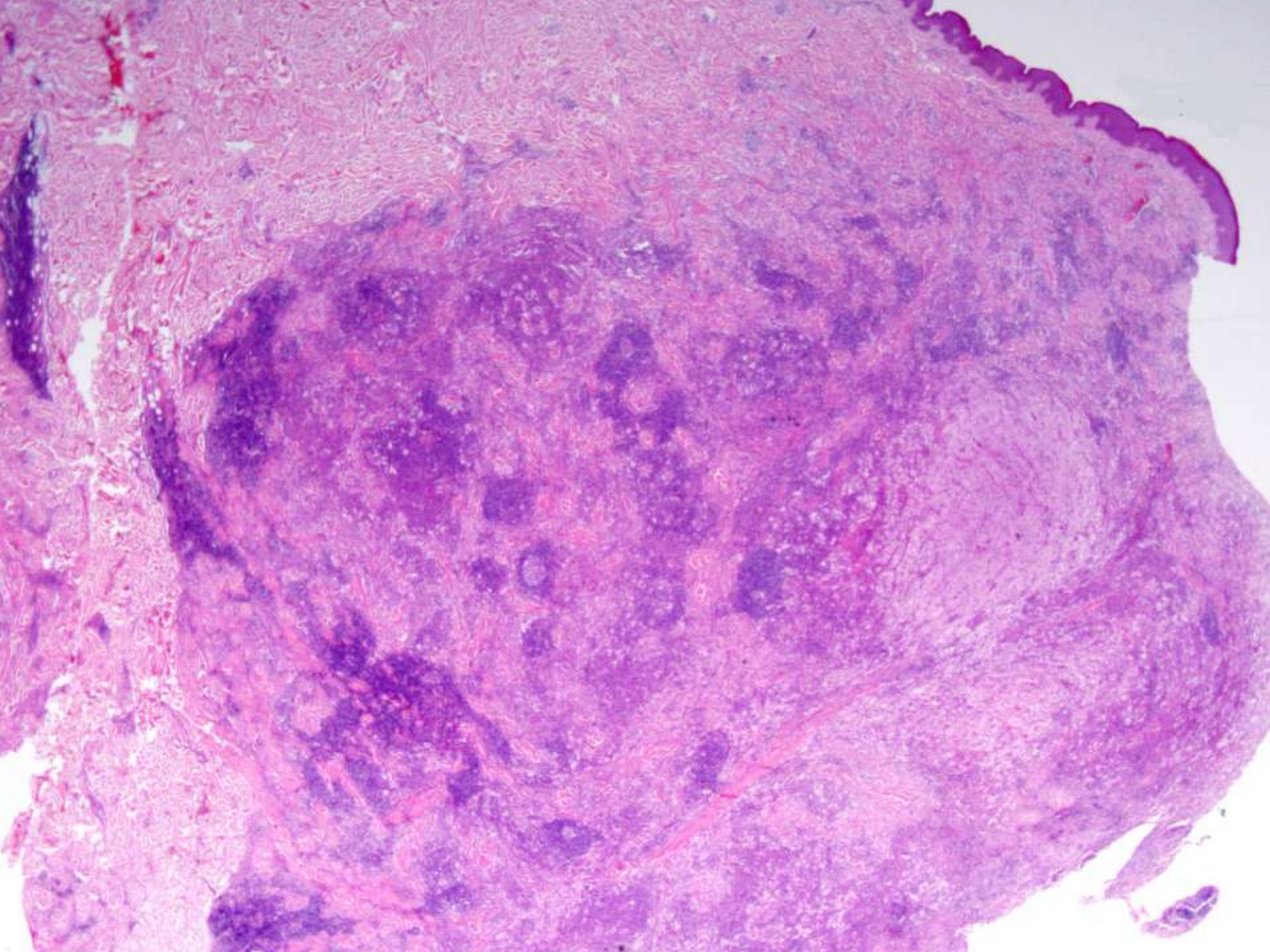


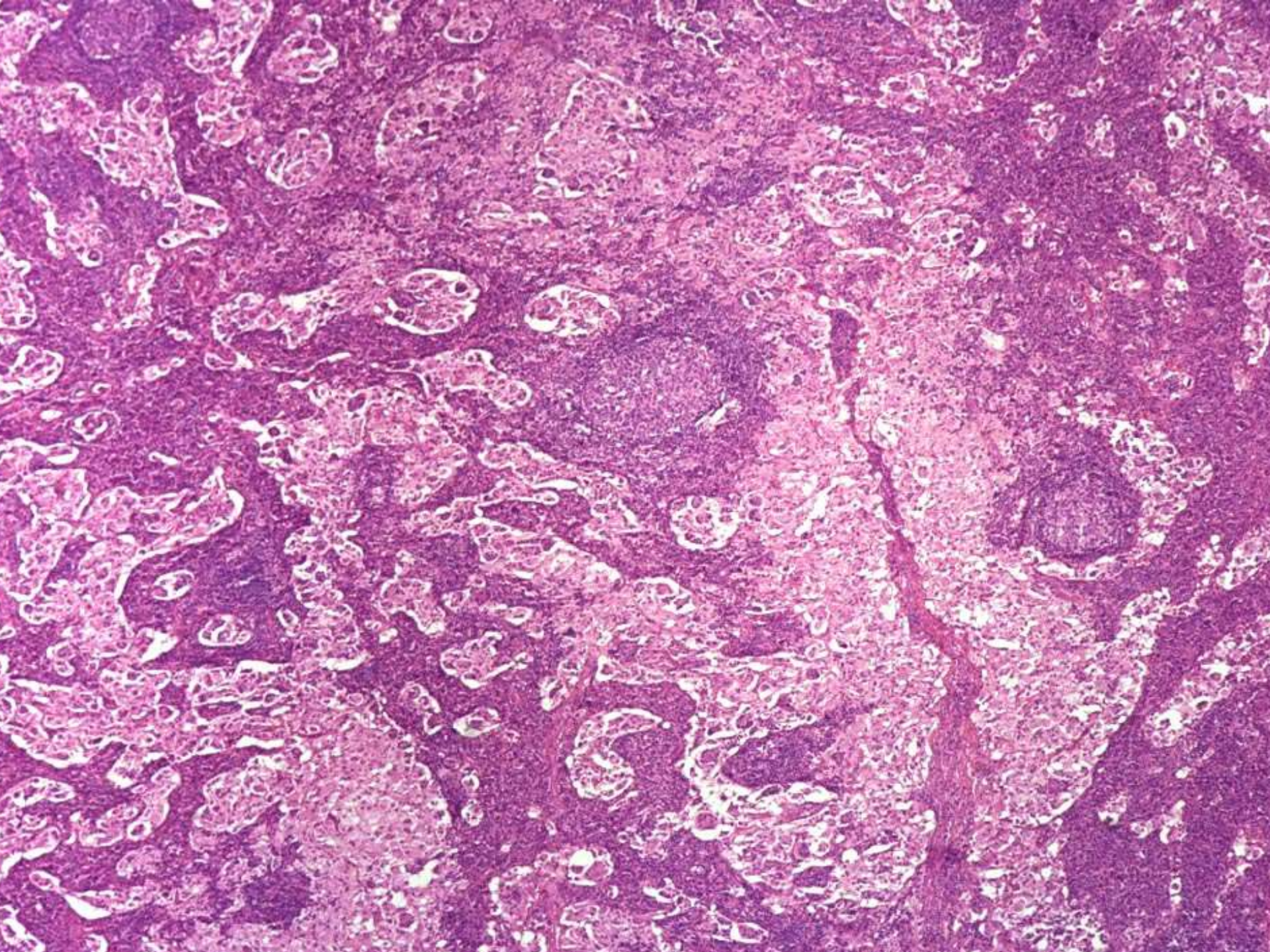
Emperipolesis

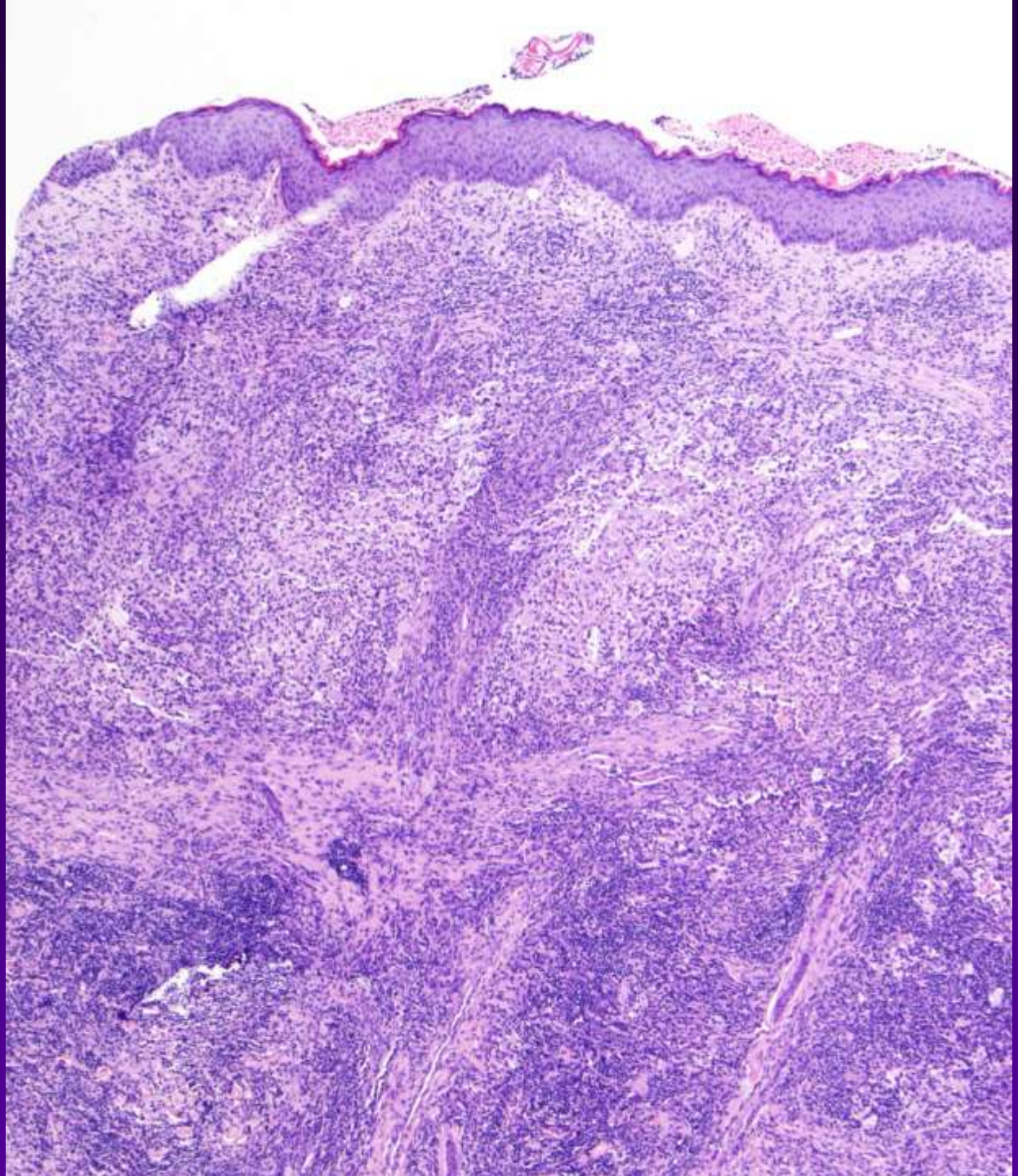


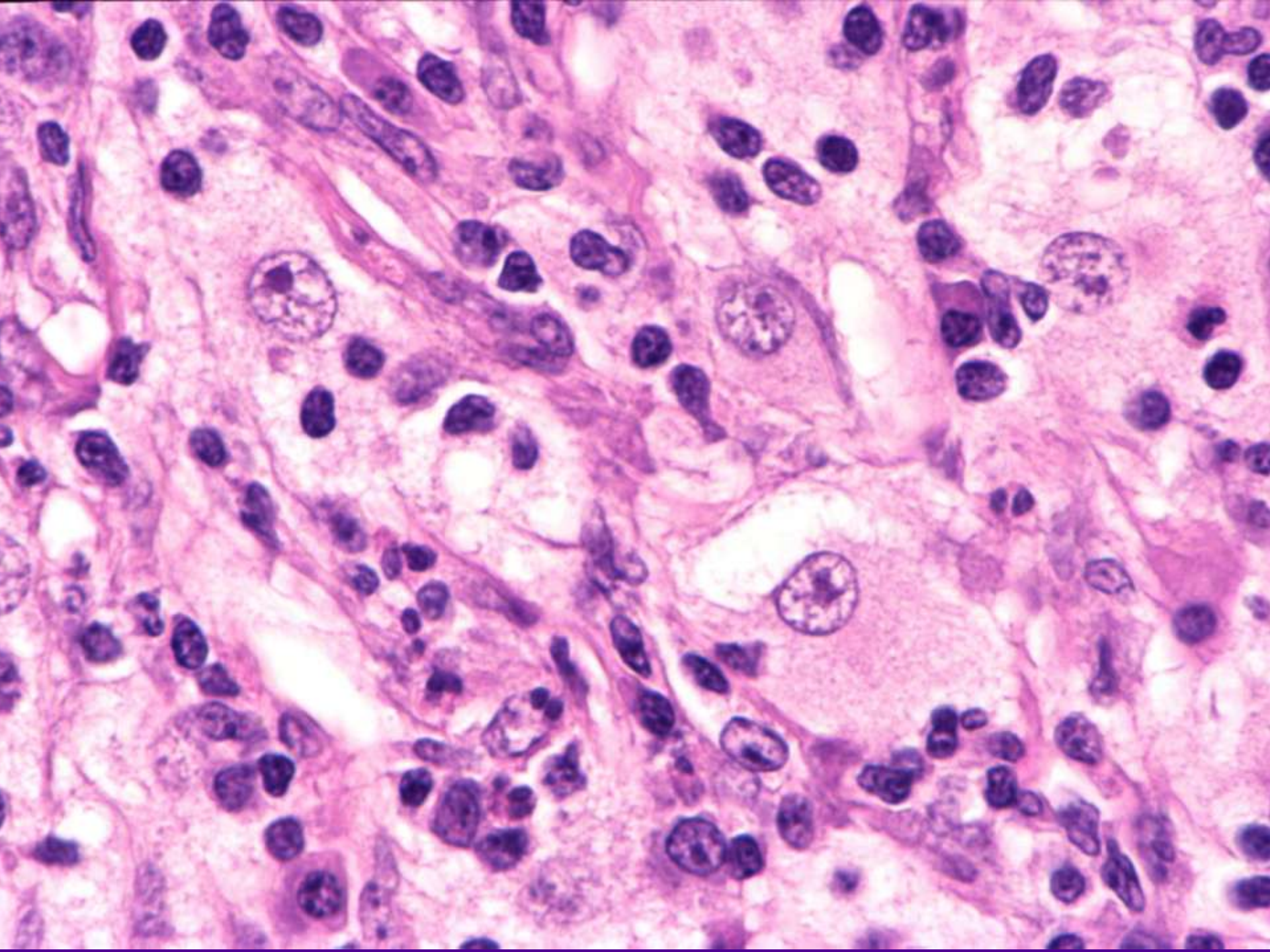
Rosai-Dorfman disease: Clues to diagnosis

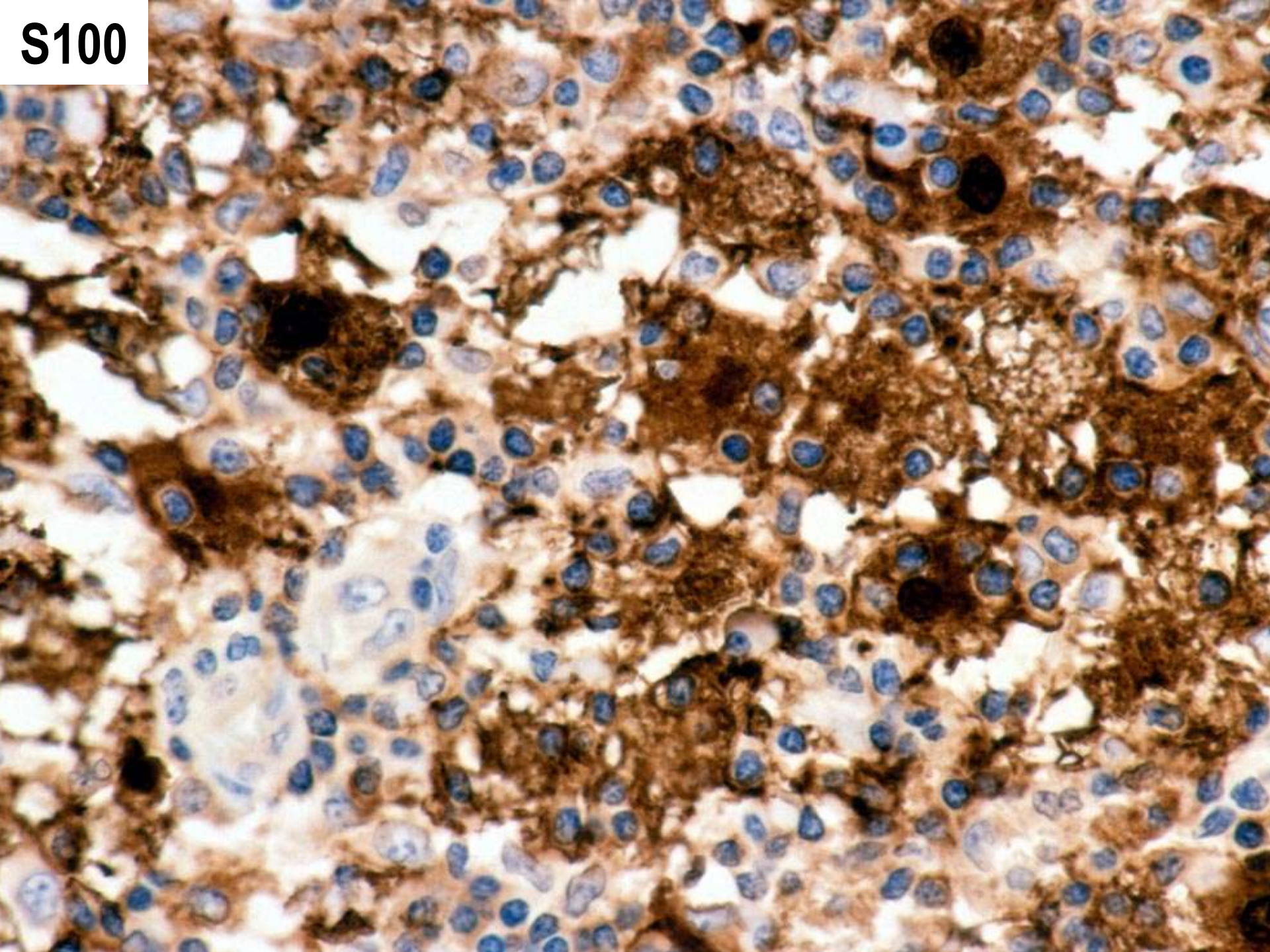
Pale-staining bands of cells (Rosai-Dorfman histiocytes) alternating with dark-staining areas (plasma cells), in a sinuous-like pattern, irrespective of site










S100