



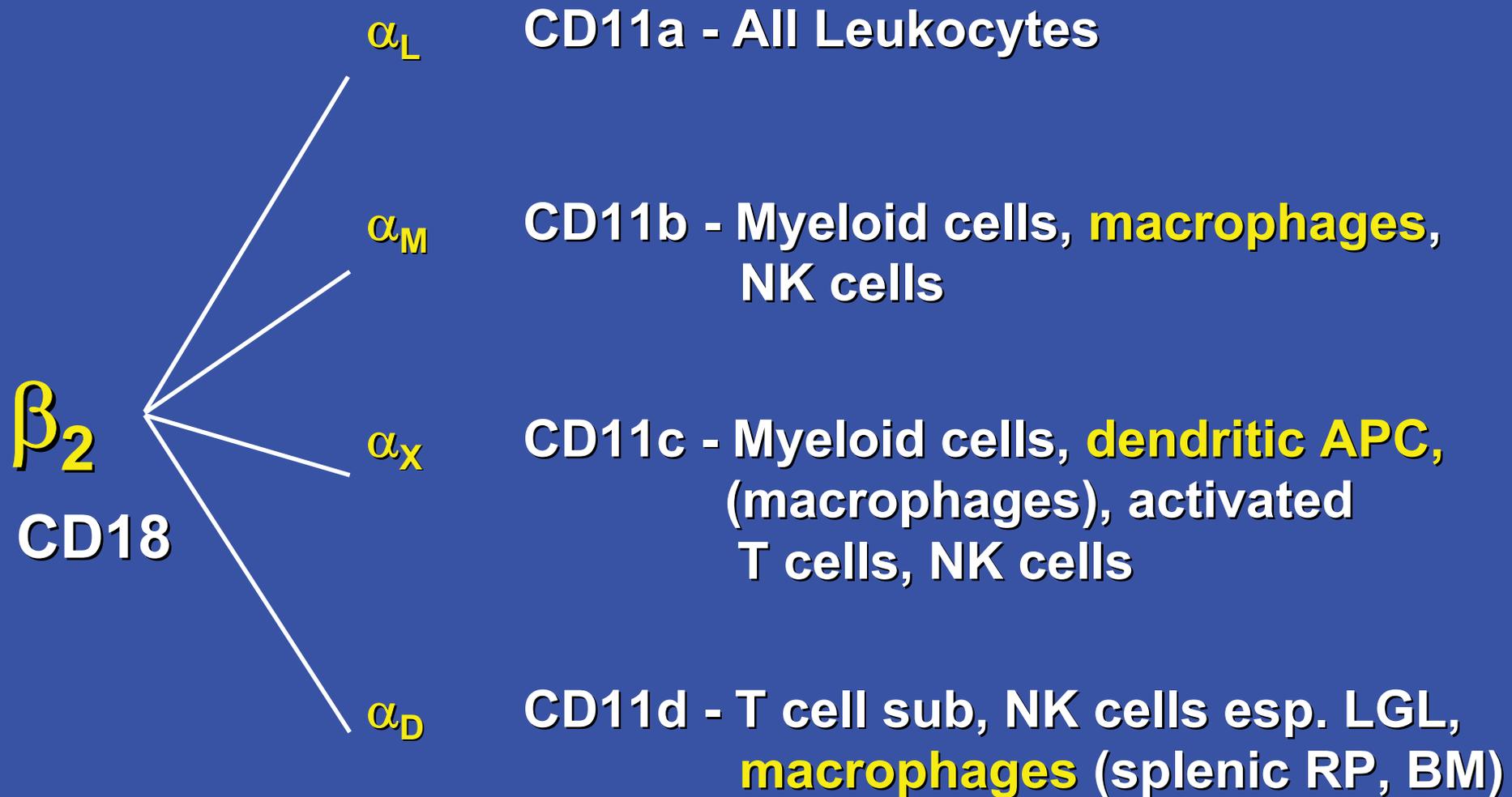
**Let's
move on**

Canine Histiocytic Diseases



- Cutaneous Histiocytoma
- Langerhans Cell Histiocytosis
- Histiocytic Sarcoma
- Periarticular Histiocytic Sarcoma
- Hemophagocytic Histiocytic Sarcoma
- **(Malignant Histiocytosis)**
- Cutaneous (reactive) Histiocytosis
- Systemic (reactive) Histiocytosis
- CD18+, CD45+, CD3-, CD79a-

β_2 Integrins - Cellular Expression



Histiocyte expression of $\beta 2$ integrins is highly regulated



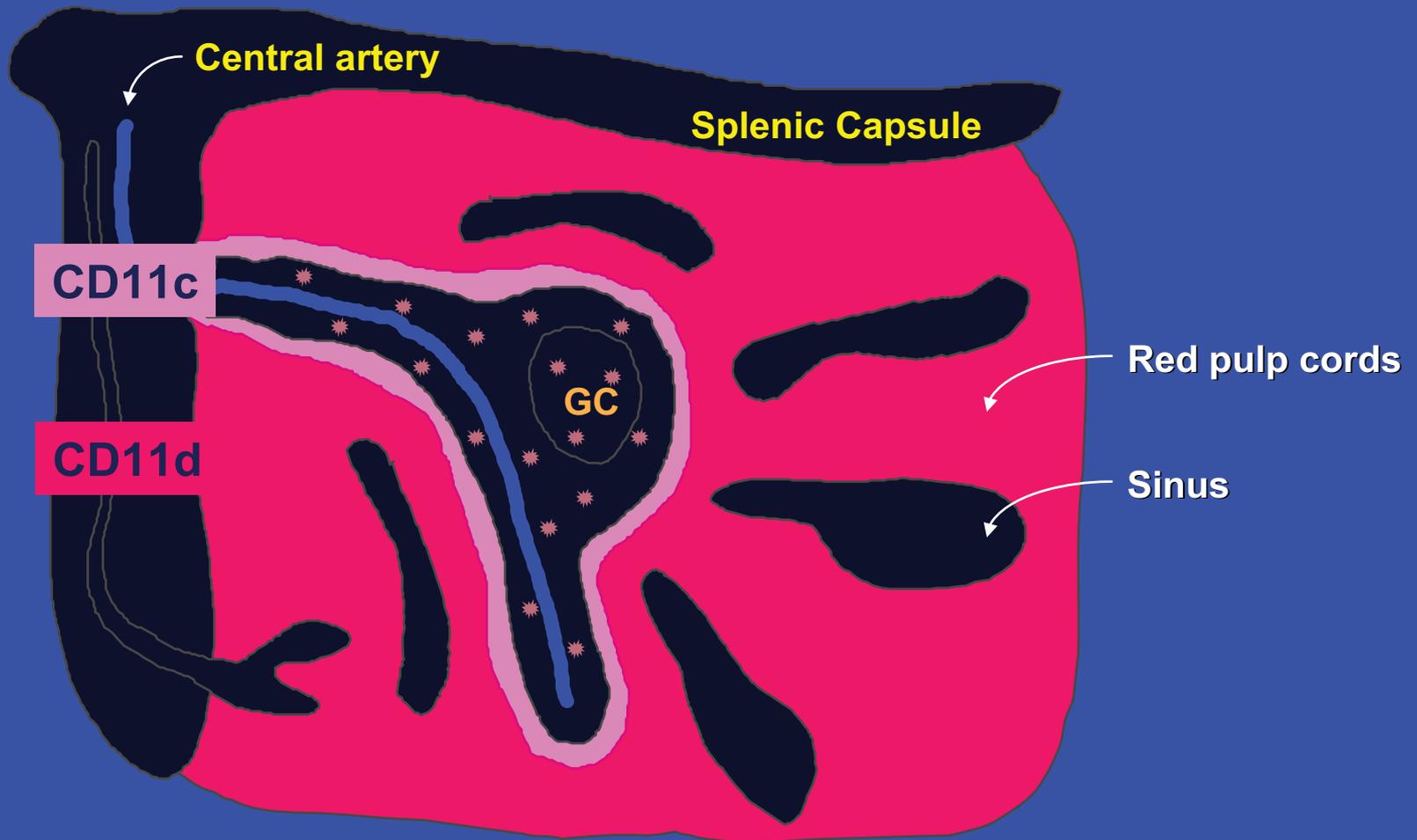
CD11c

Splenic marginal zone DC
Splenic PALS DC
Interstitial DC
Epithelial DC (LC)
Pulmonary alveolar M ϕ

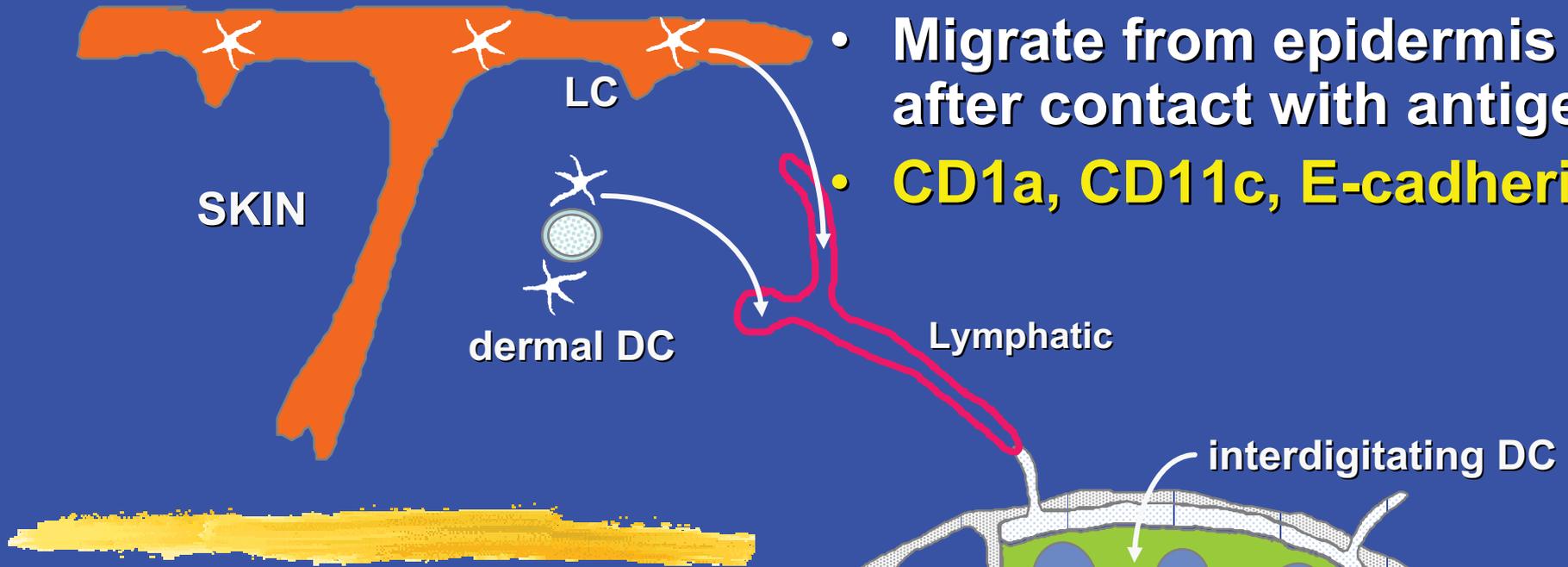
CD11d

Splenic red pulp M ϕ
Bone marrow M ϕ
Lymph node sinus
M ϕ
Perivascular
microglia
Deep dermal DC

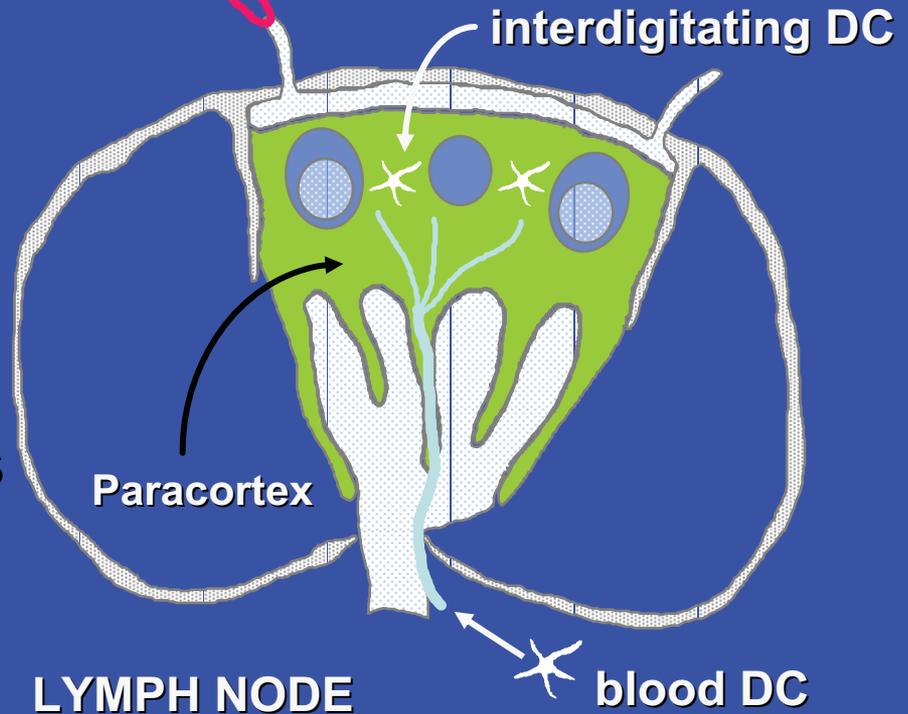
β_2 Integrin Expression in Spleen



- Epithelial dendritic APC
- Migrate from epidermis after contact with antigen
- **CD1a, CD11c, E-cadherin**

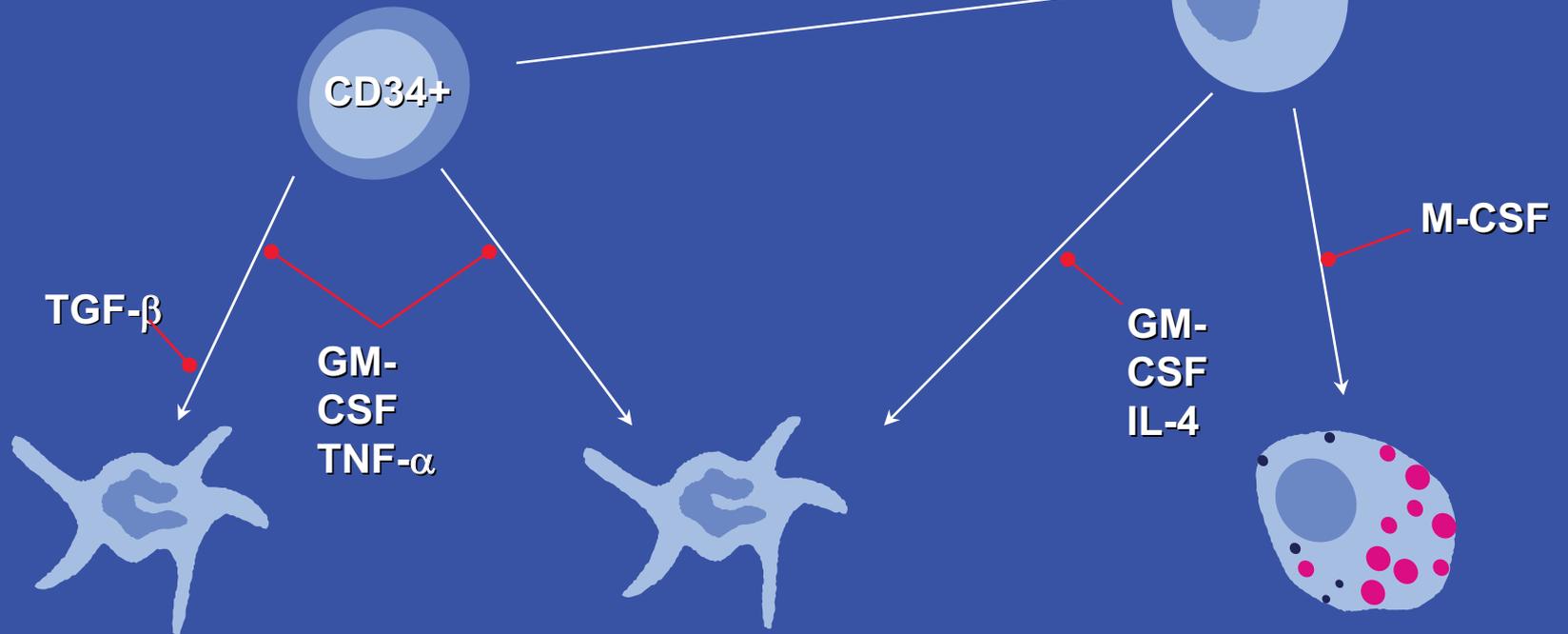


- Interstitial dendritic APC
- Early, rapid expansion in antigen driven responses
- **CD1a, CD1b±, CD1c**
- **MHC class I, II**
- **CD11b±, CD11c, Thy-1**



Blood Monocyte

BM Stem Cell



Langerhans DC

CD11c+ CD18+
MHC II+ CD11d-
E-cad+ Thy-1-

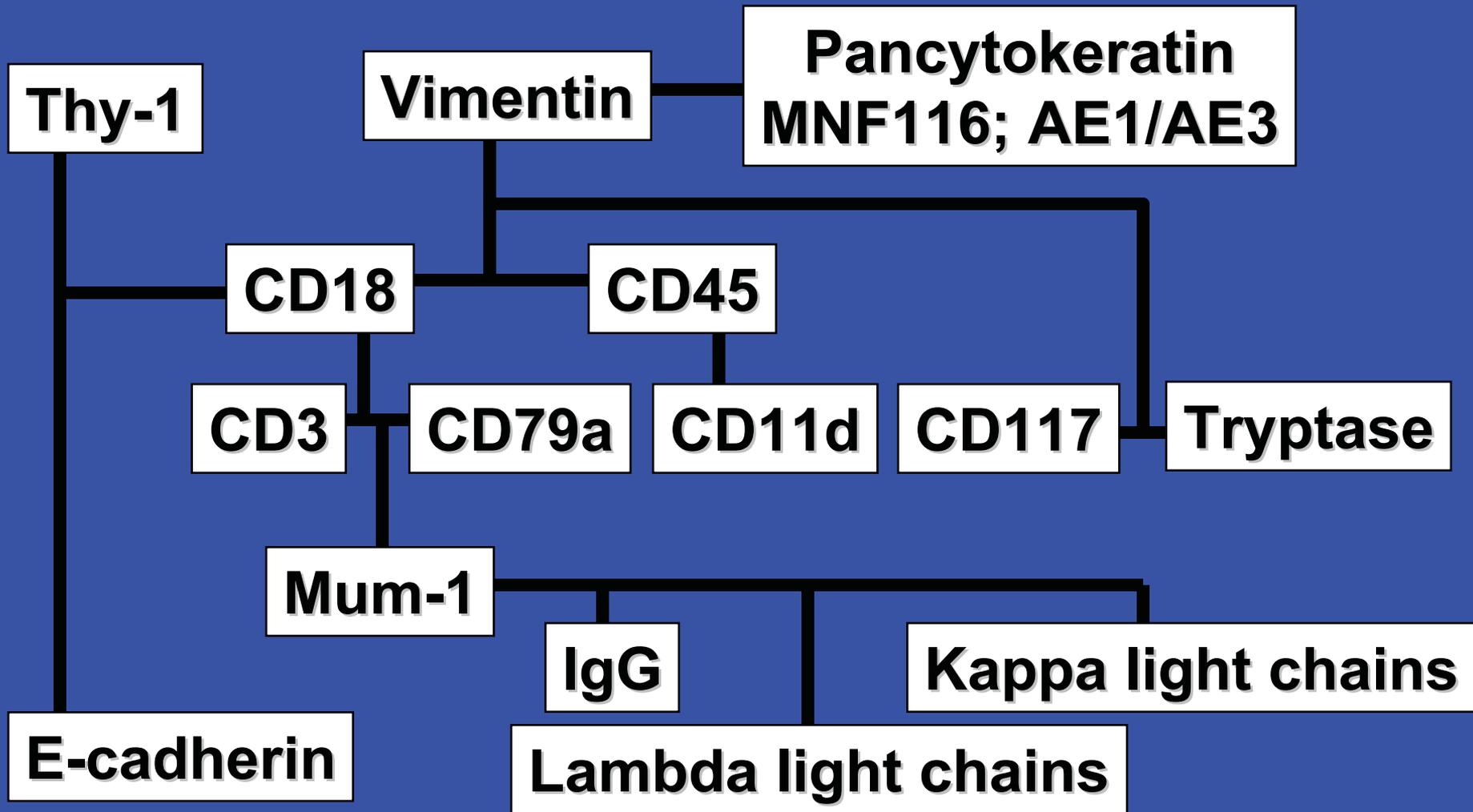
Interstitial DC

CD11c+ CD18+
MHC II+ CD11d-
E-cad- Thy-1+

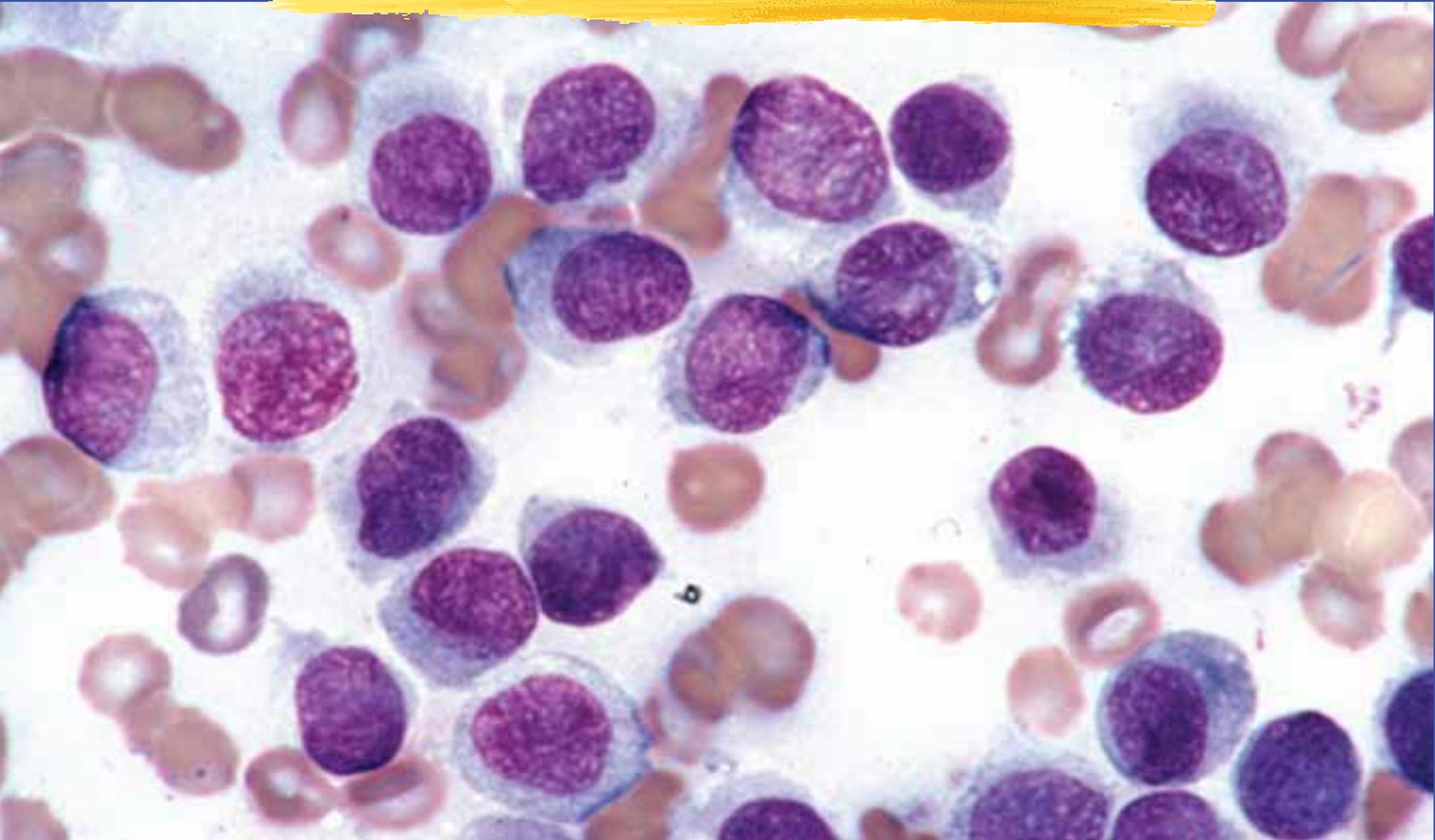
Macrophage

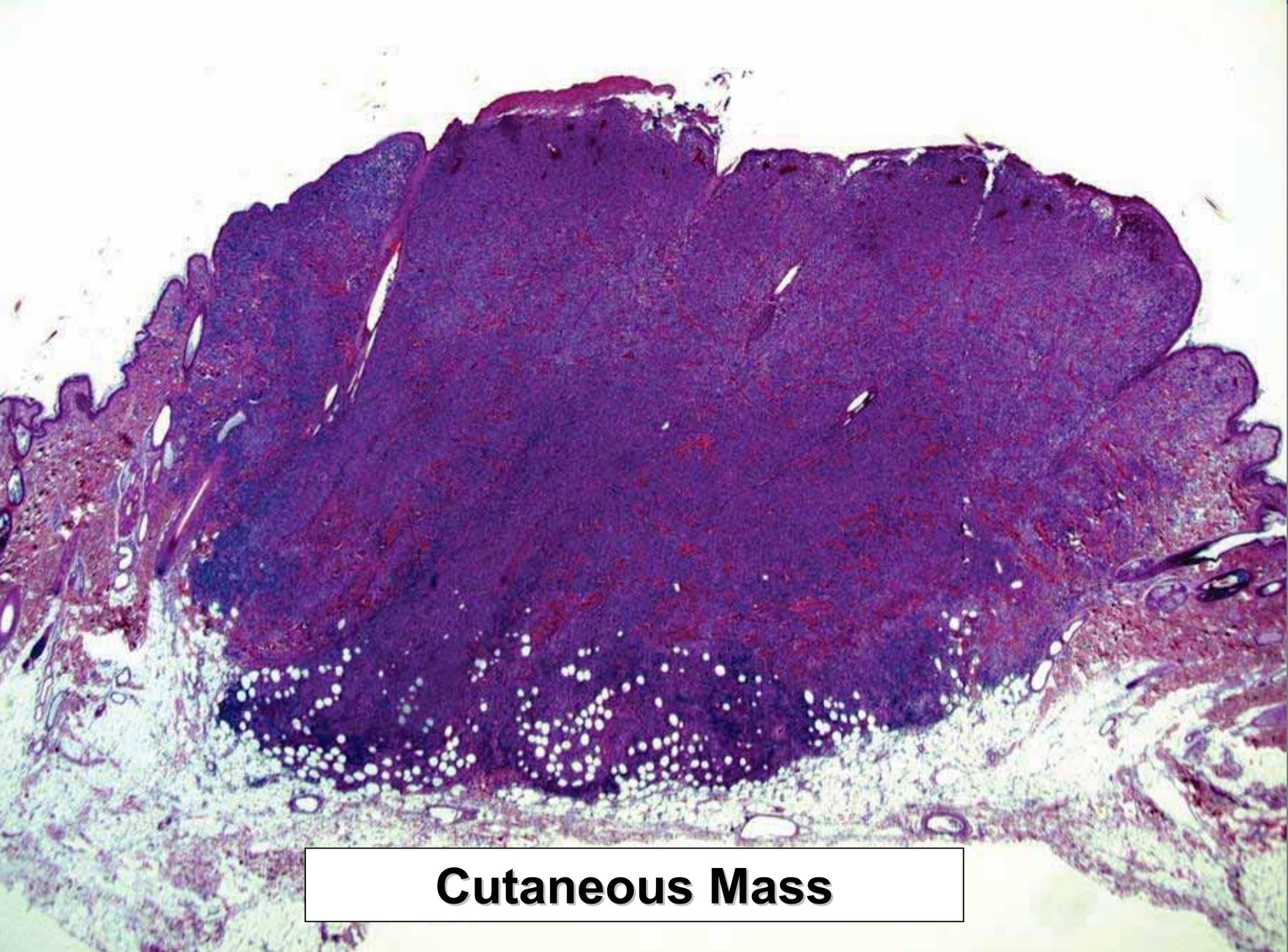
CD11c- CD18+
MHC II \pm CD11d+
E-cad- Thy-1-

Cutaneous Round Cell Tumors

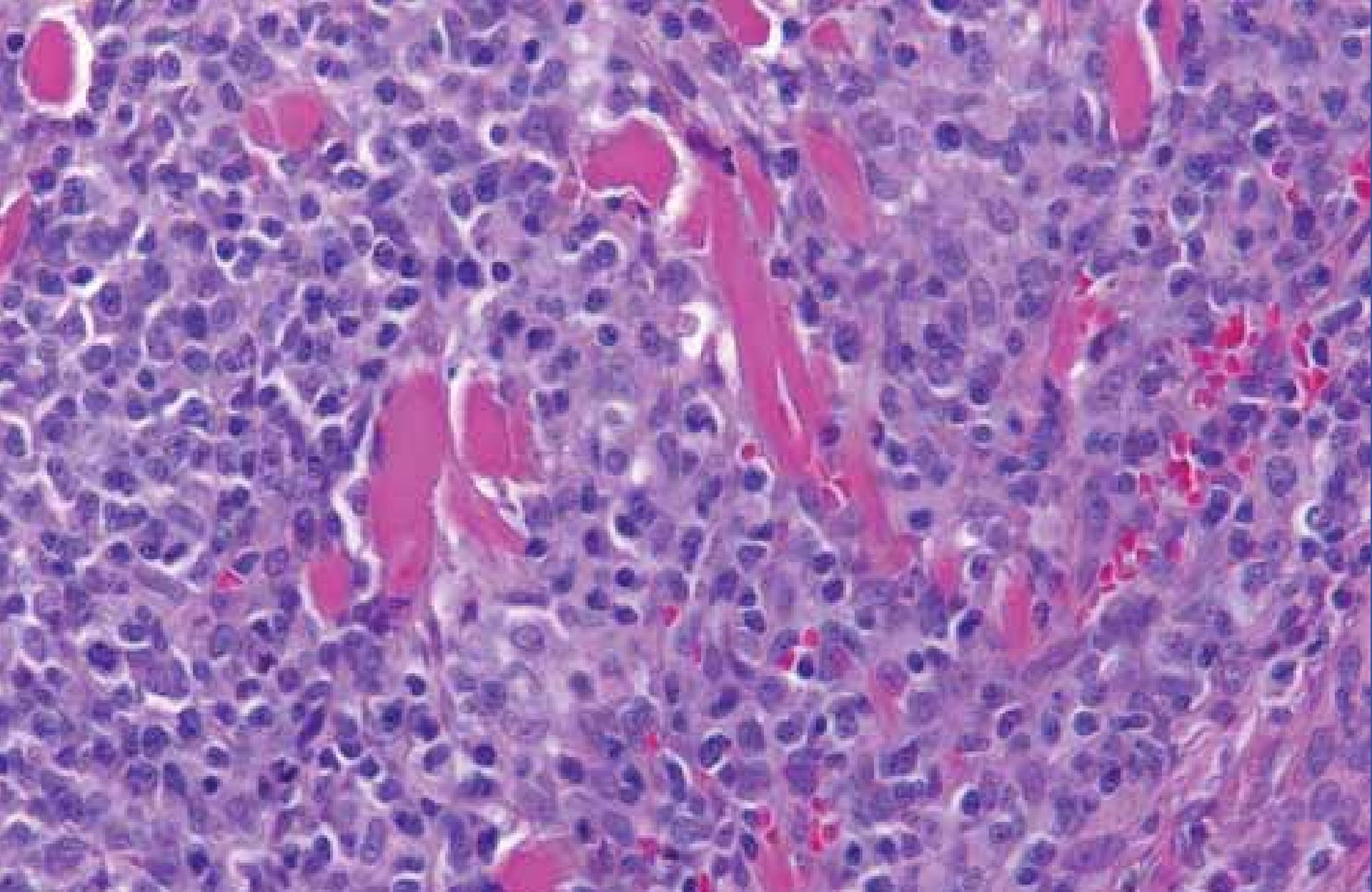


Cutaneous Mass

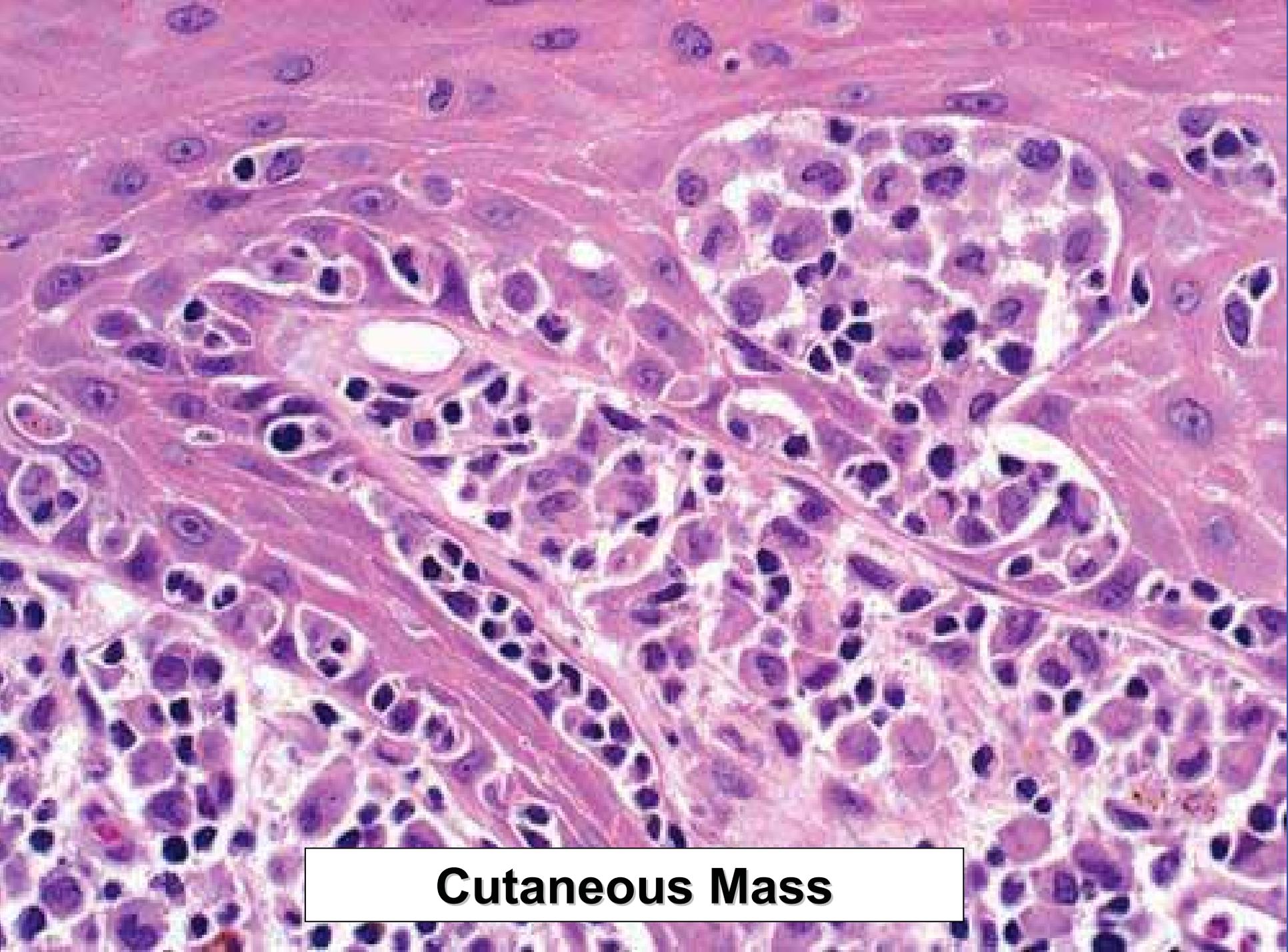




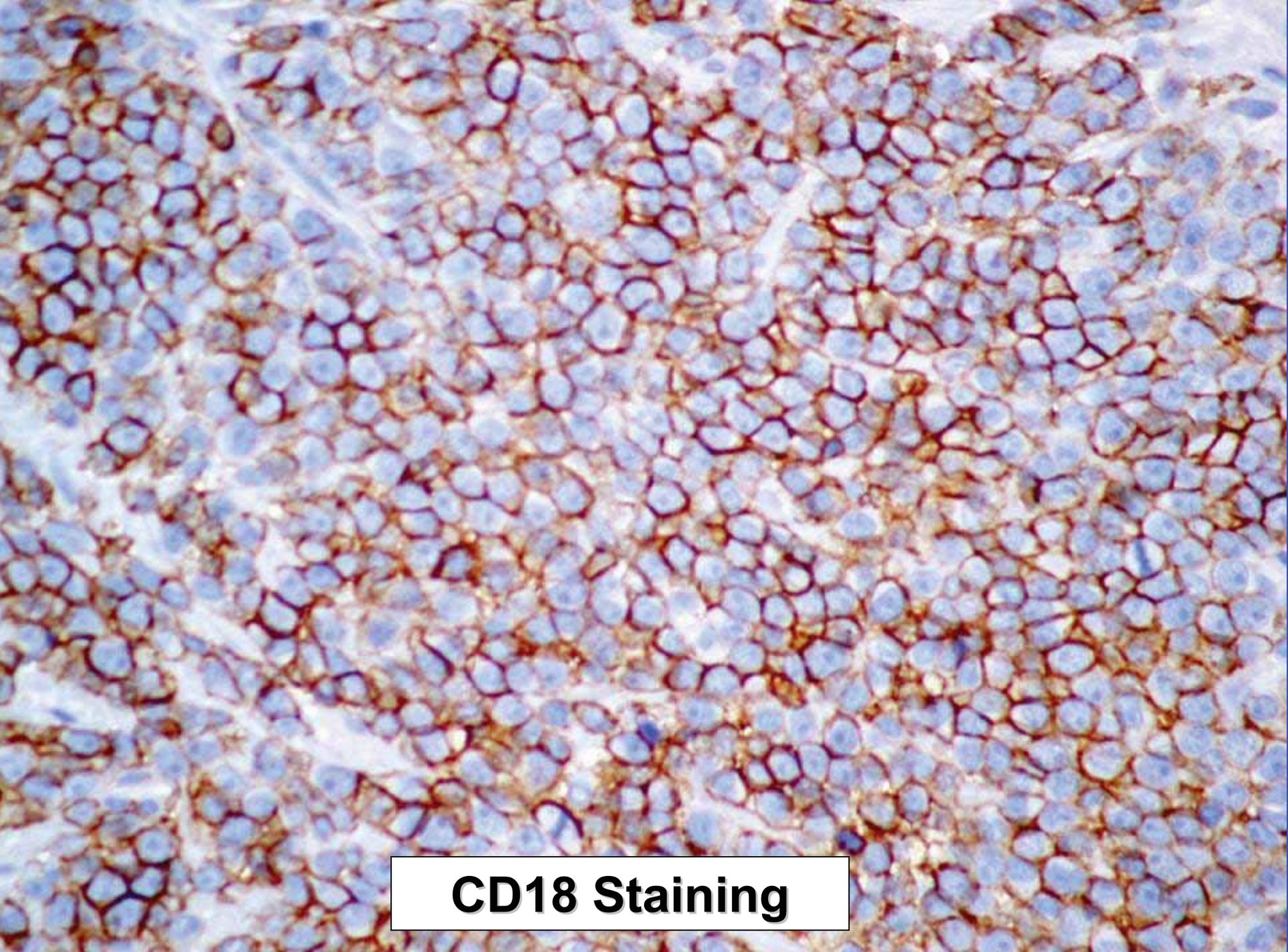
Cutaneous Mass



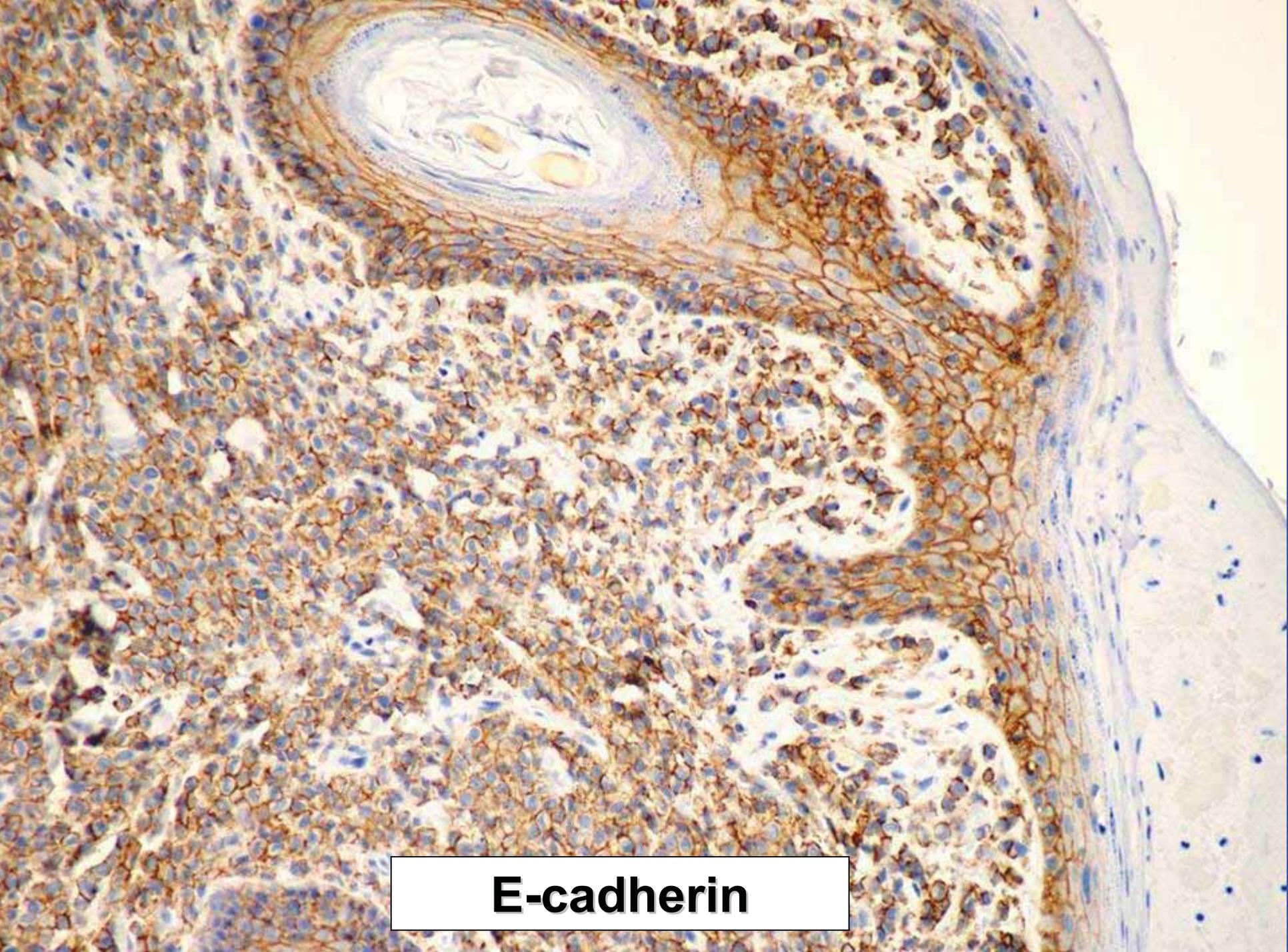
Cutaneous Mass



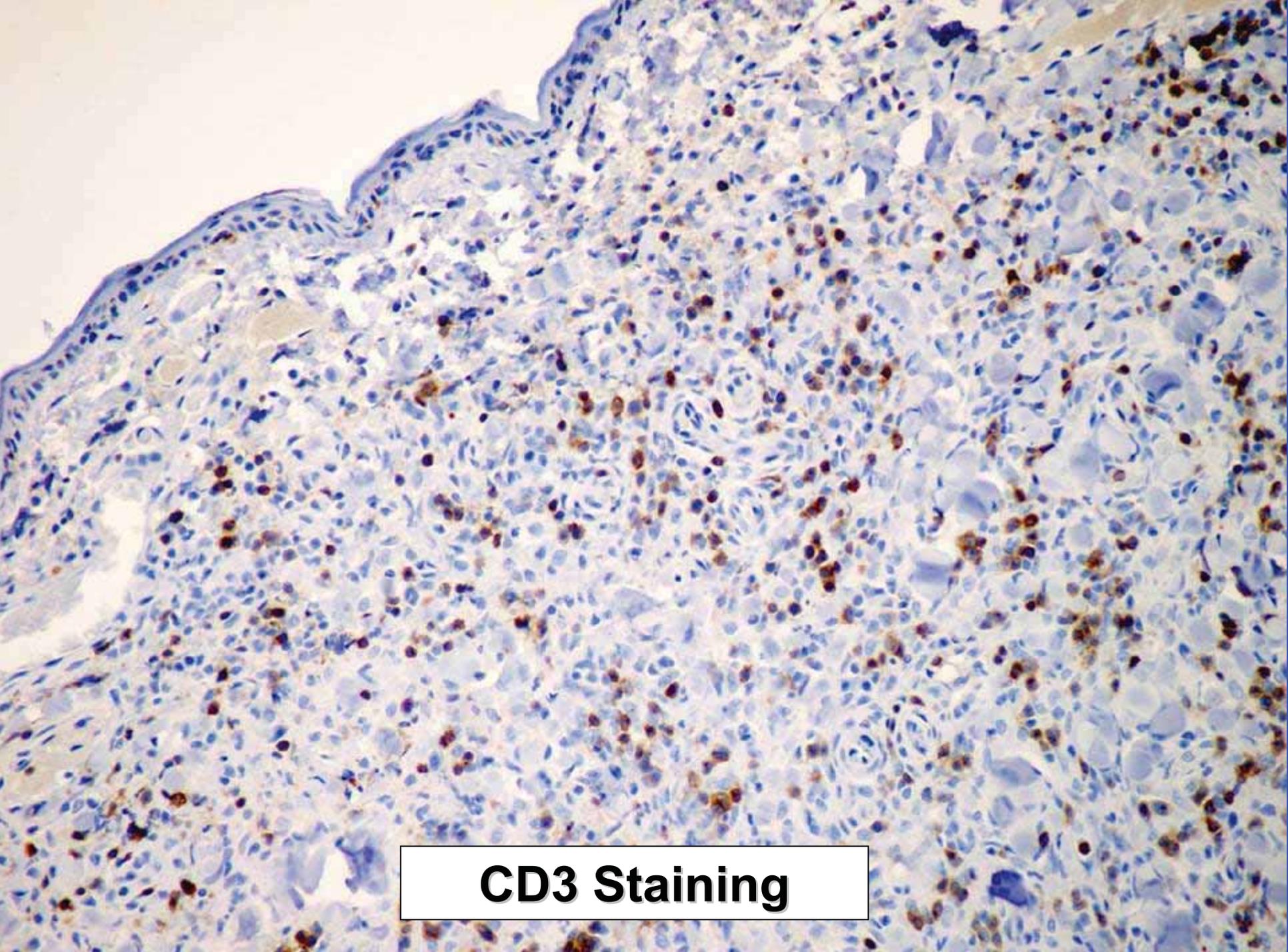
Cutaneous Mass



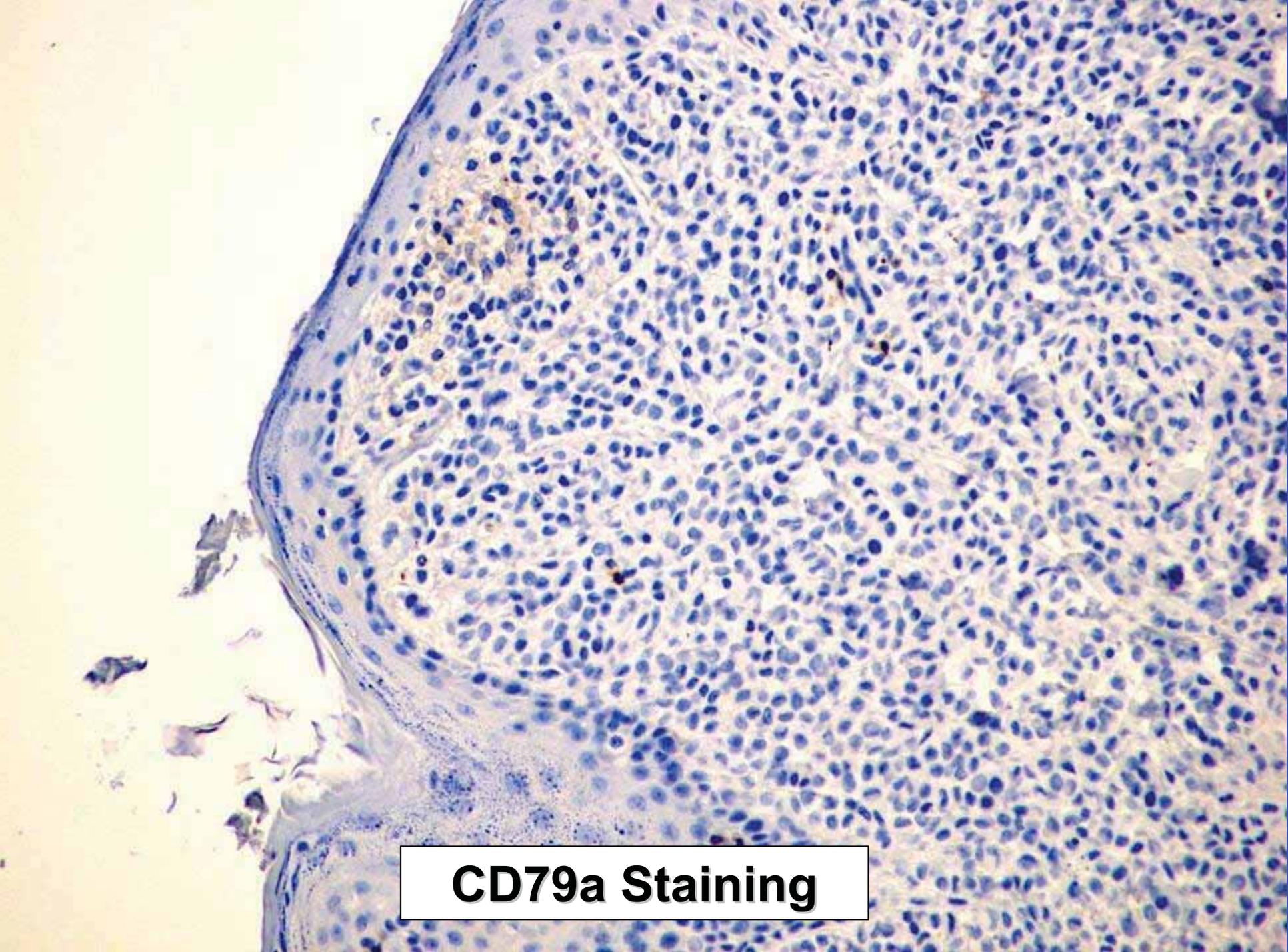
CD18 Staining



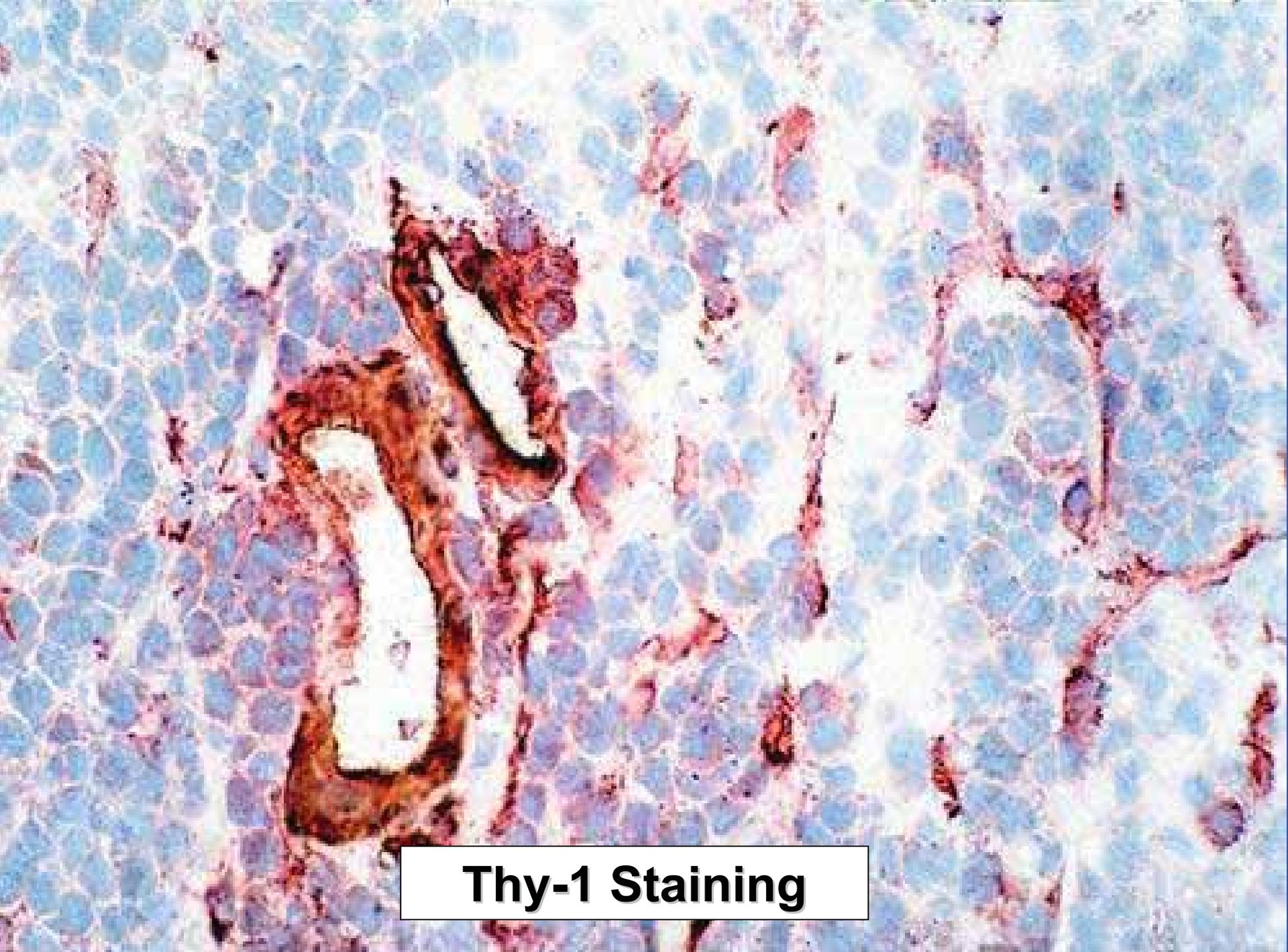
E-cadherin



CD3 Staining



CD79a Staining



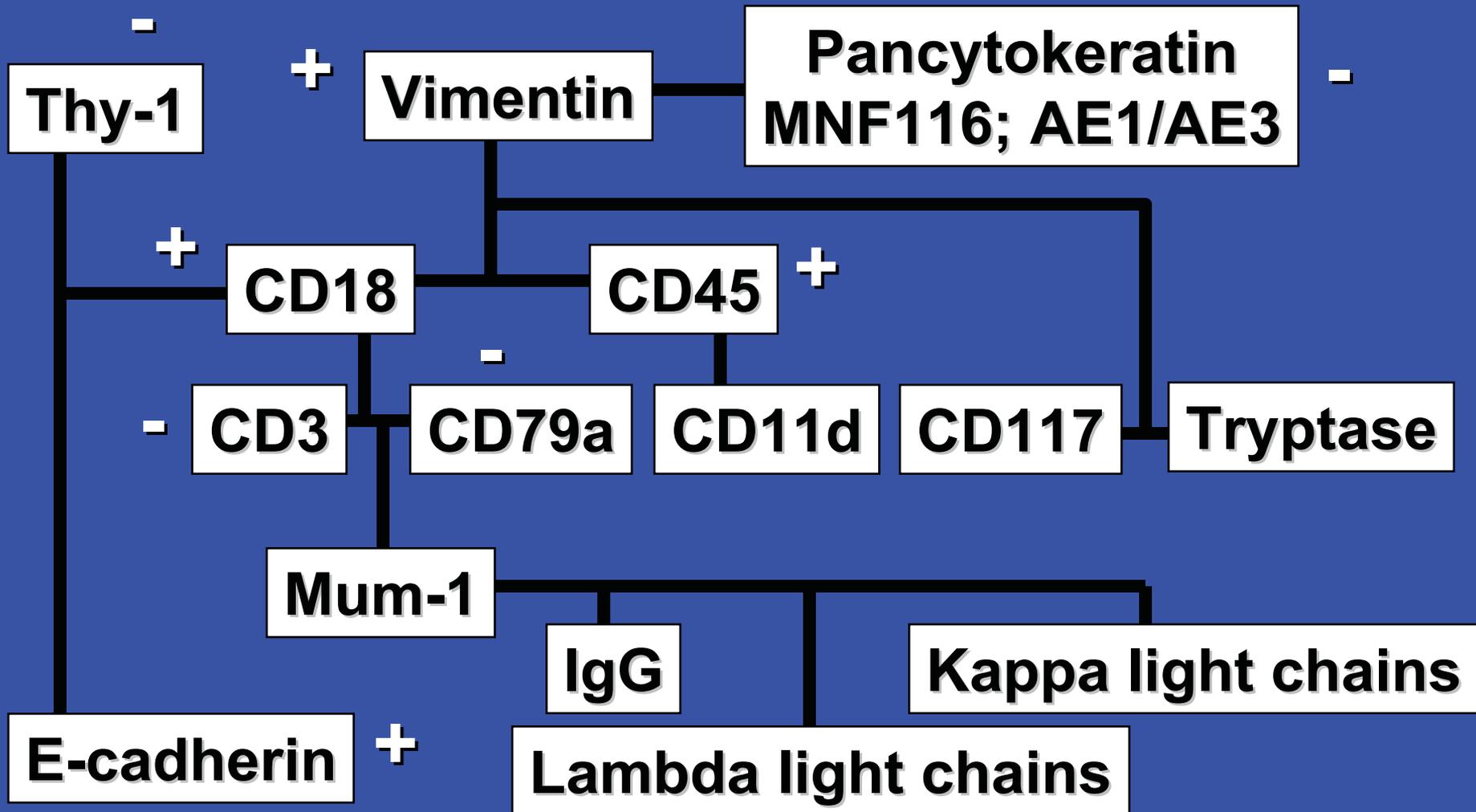
Thy-1 Staining



**What's
your
Diagnosis**

Hot Dogs
\$1.00

Cutaneous Histiocytoma

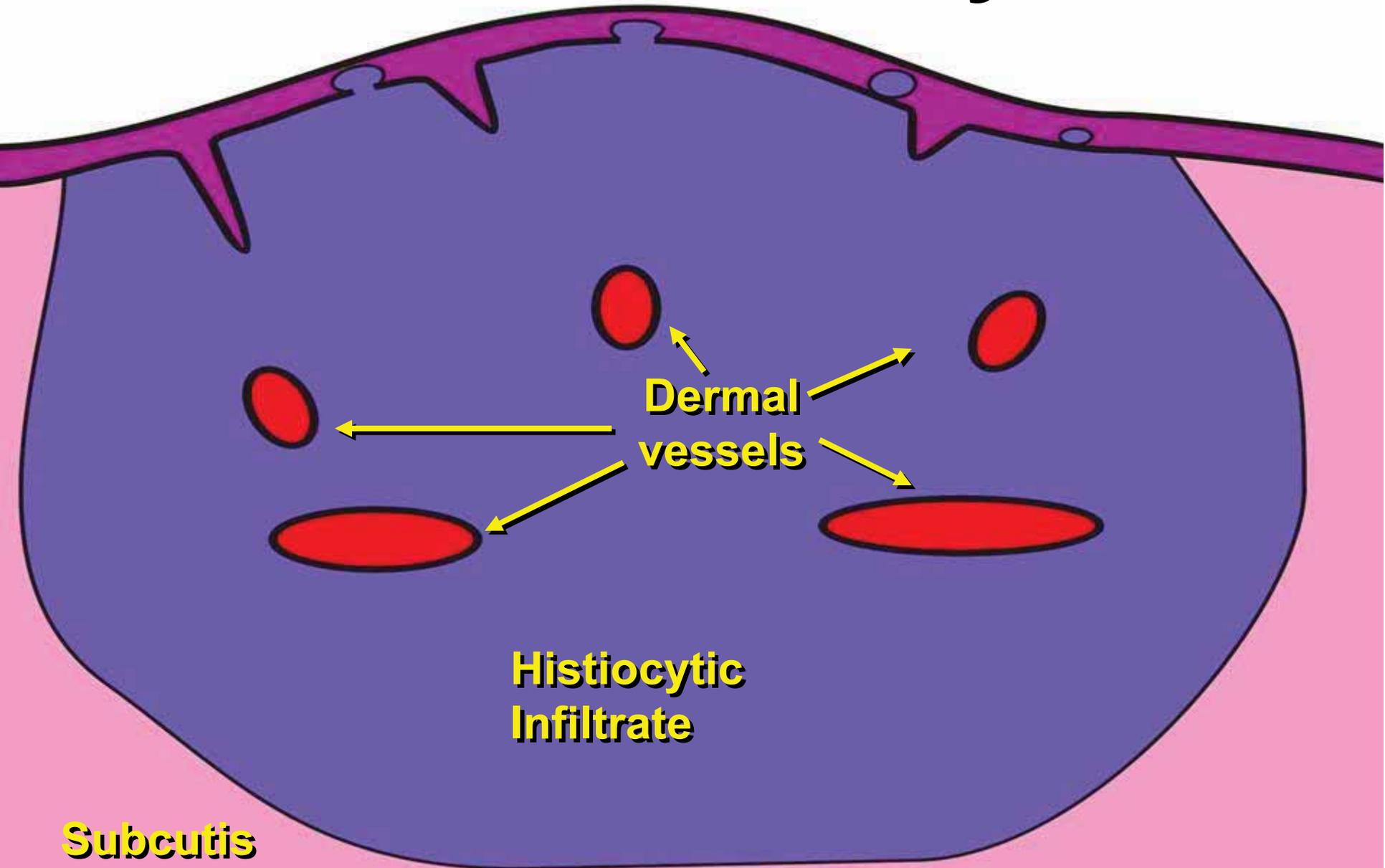


Cutaneous Histiocytoma

- Age specific incidence highest in 1-3 year age group
- All breeds affected
- Multiple tumors and recurrence of tumors unusual
- **Spontaneous regression**
- Epidermotropic histiocytic dermal nodular mass
- Intense T cell infiltrates are associated with tumor regression
- Plasma cell infiltrates are seen in lesions with delayed regression



Cutaneous Histiocytoma



Cutaneous Histiocytoma



- Langerhans dendritic cells
- CD11d-, MHC II+, Thy1-, E-cadherin+
- Frozen sections:
- CD1+, CD4-, CD11b+, CD11c+

Aberrant Syndromes

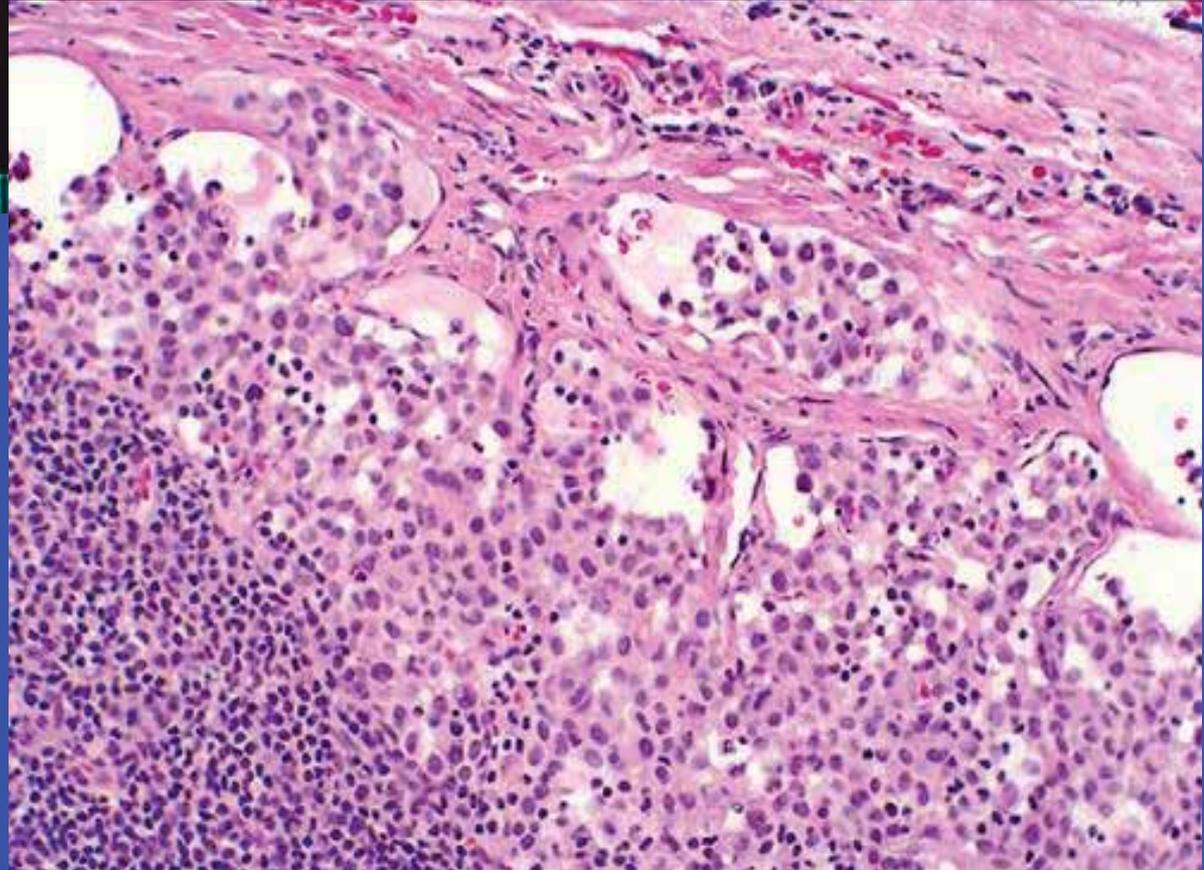


- Recognition of diverse biological behavior more like **Langerhans Cell Histiocytosis** (human)
- **Multiple histiocytomas** (up to 100+) - delayed regression - new lesions (up to 10 months)
- **Migration/Metastasis** to lymph node with obliteration - spontaneous regression possible
- **Systemic Migration/Metastasis** - euthanasia

Metastatic Histiocytoma



lymph node

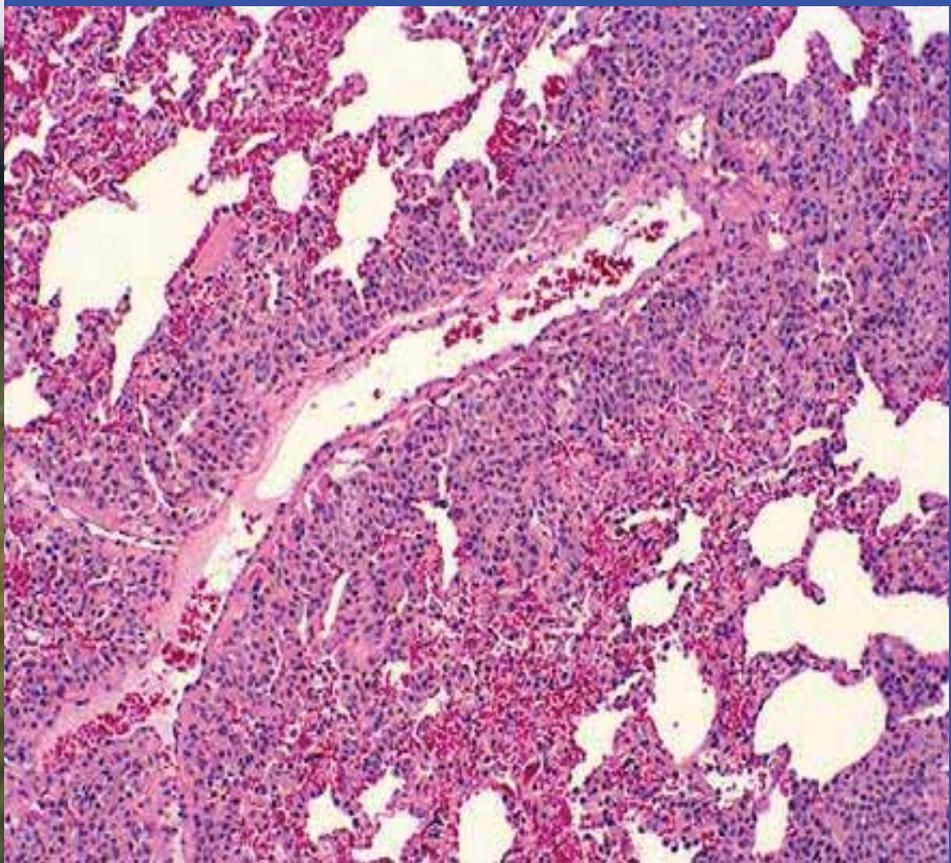


Subcapsular sinus

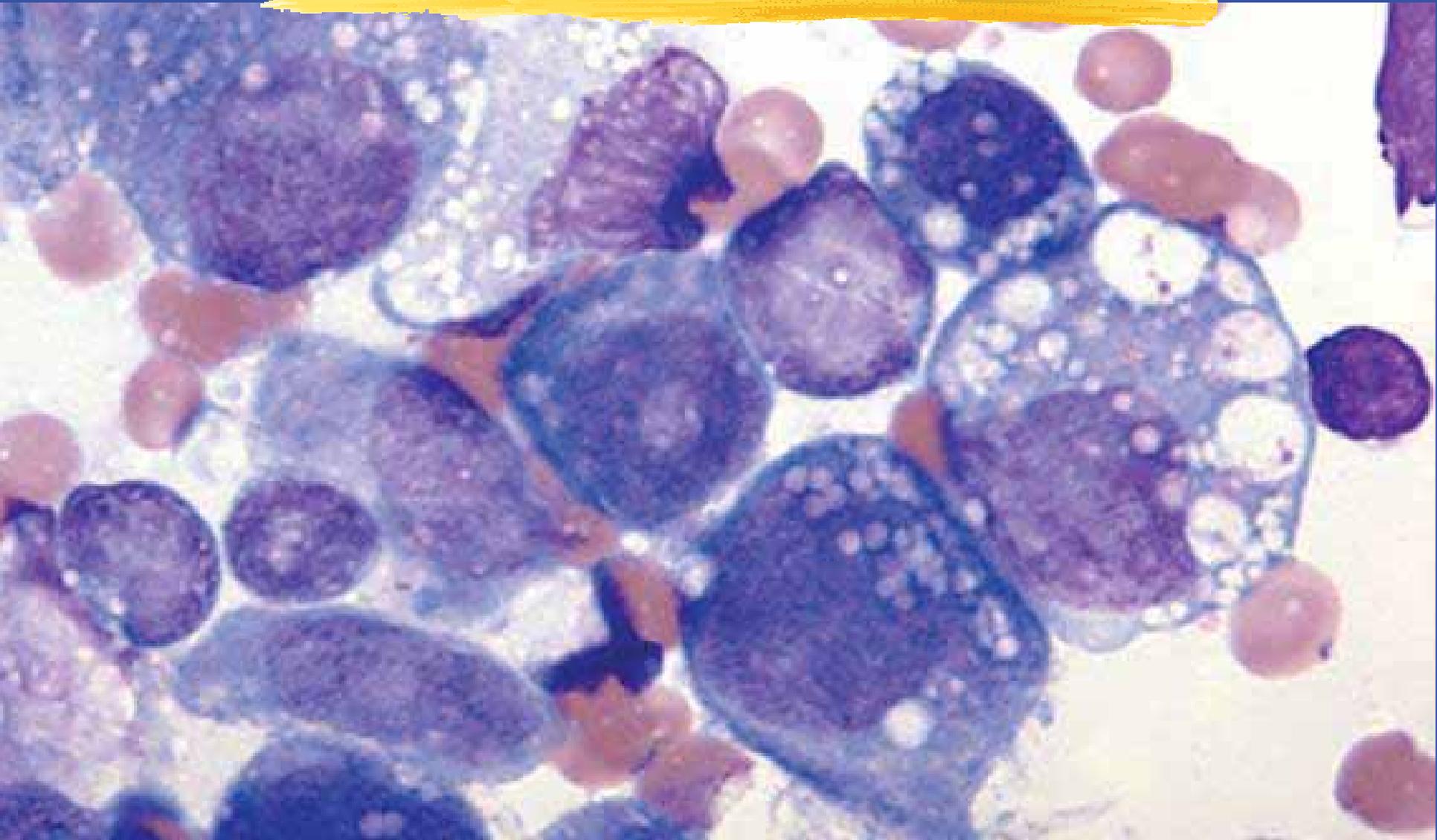


Langerhans Cell Histiocytosis

lung

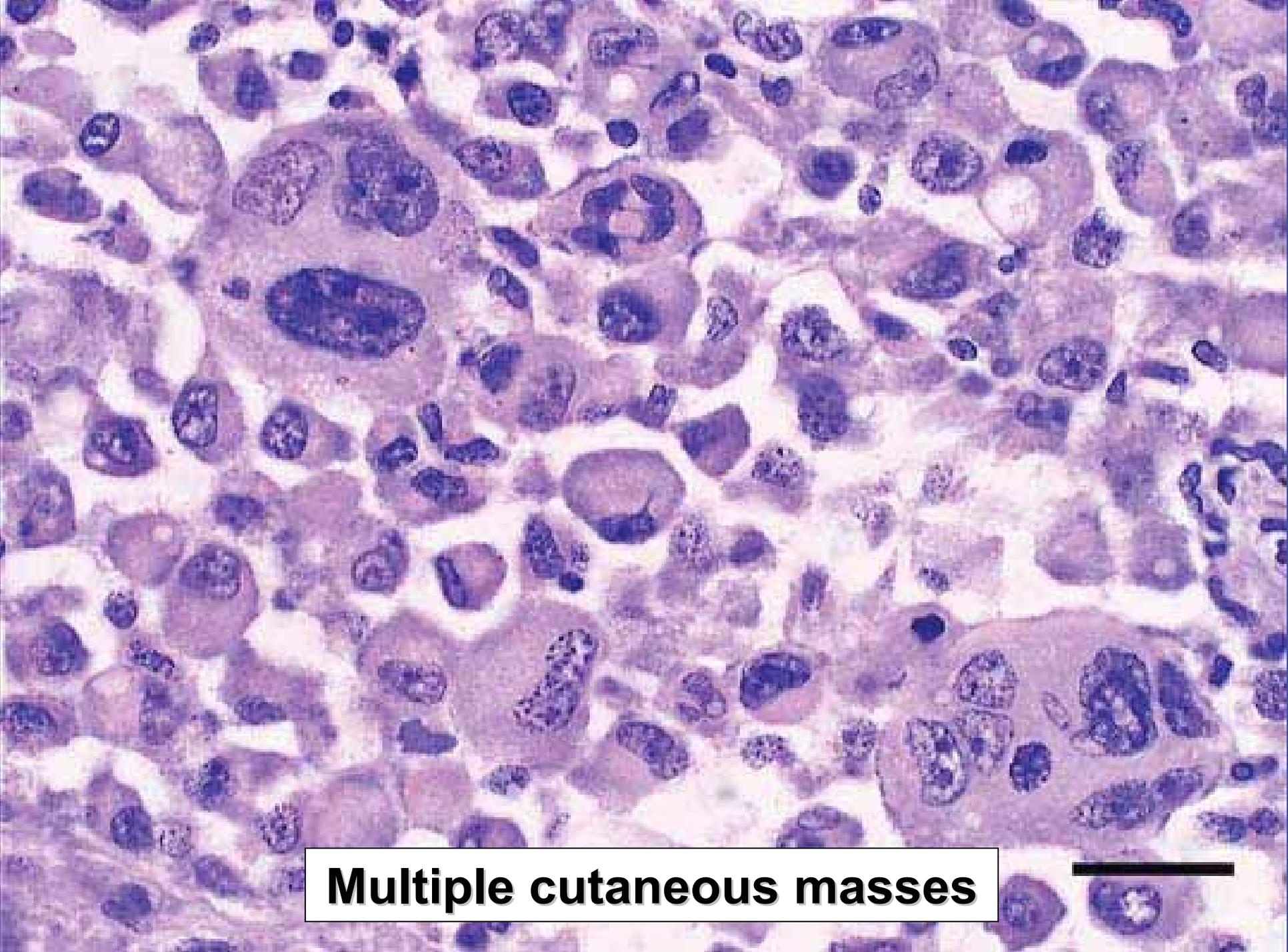


Cutaneous Mass

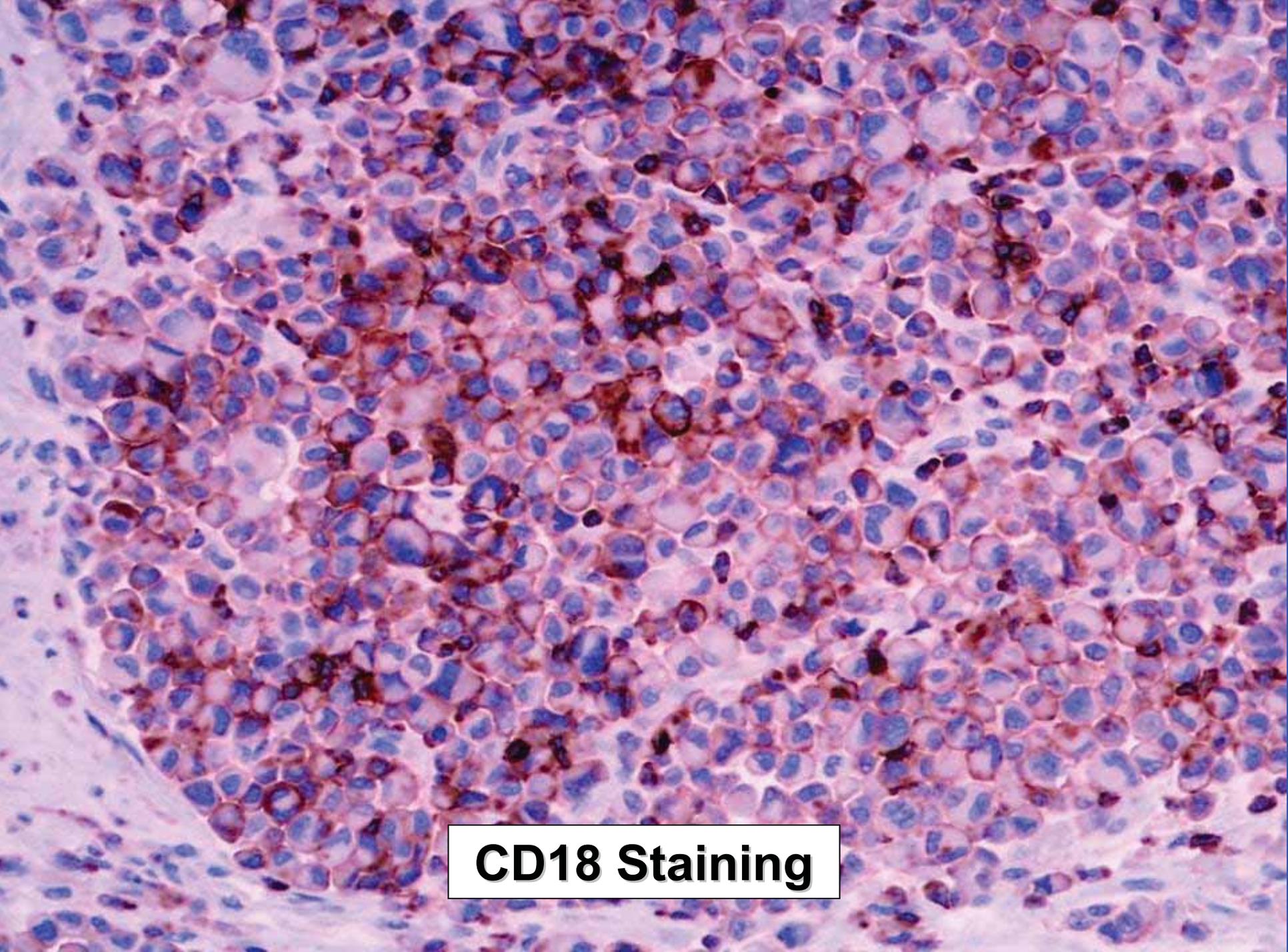




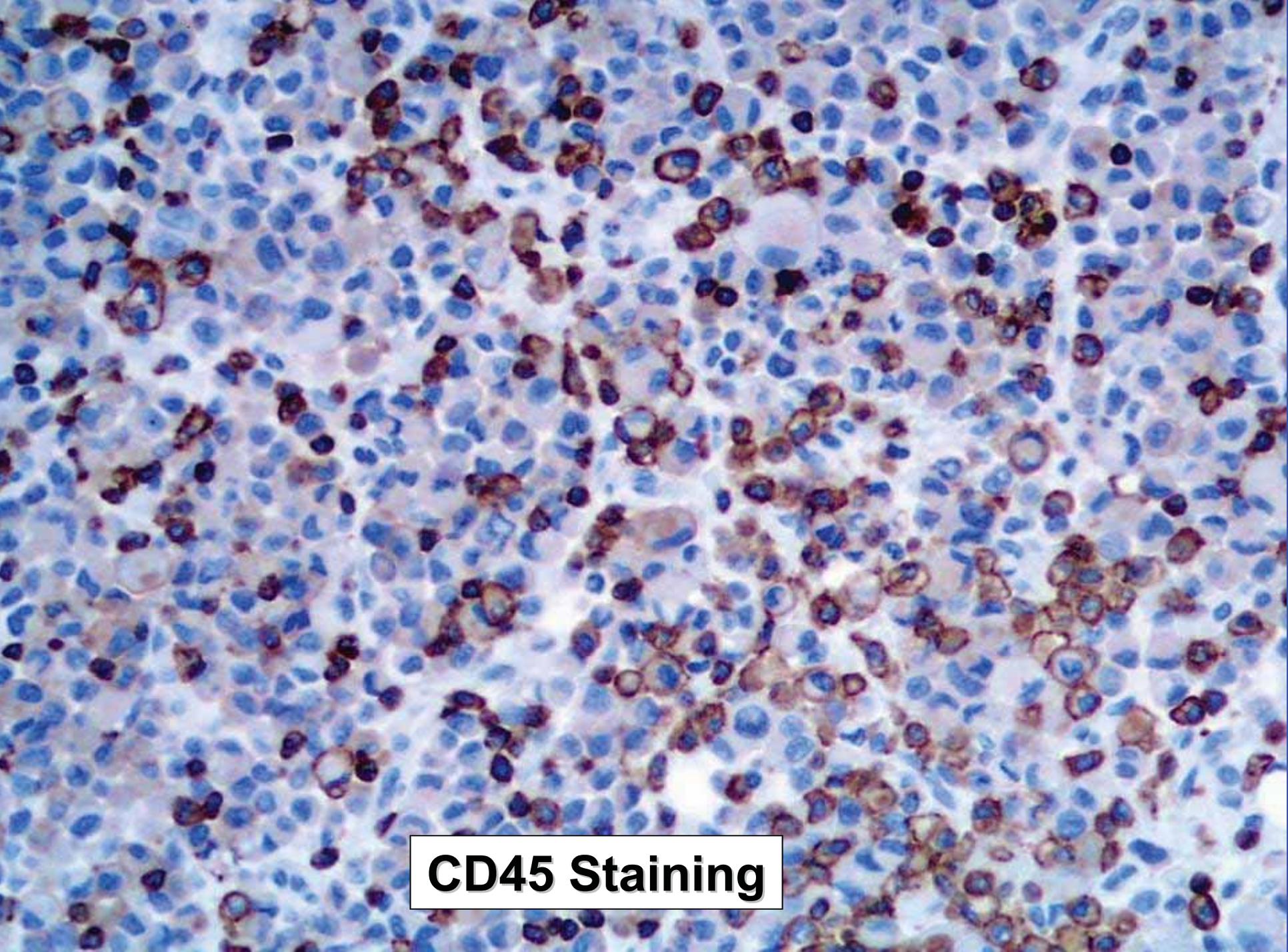
Multiple cutaneous masses



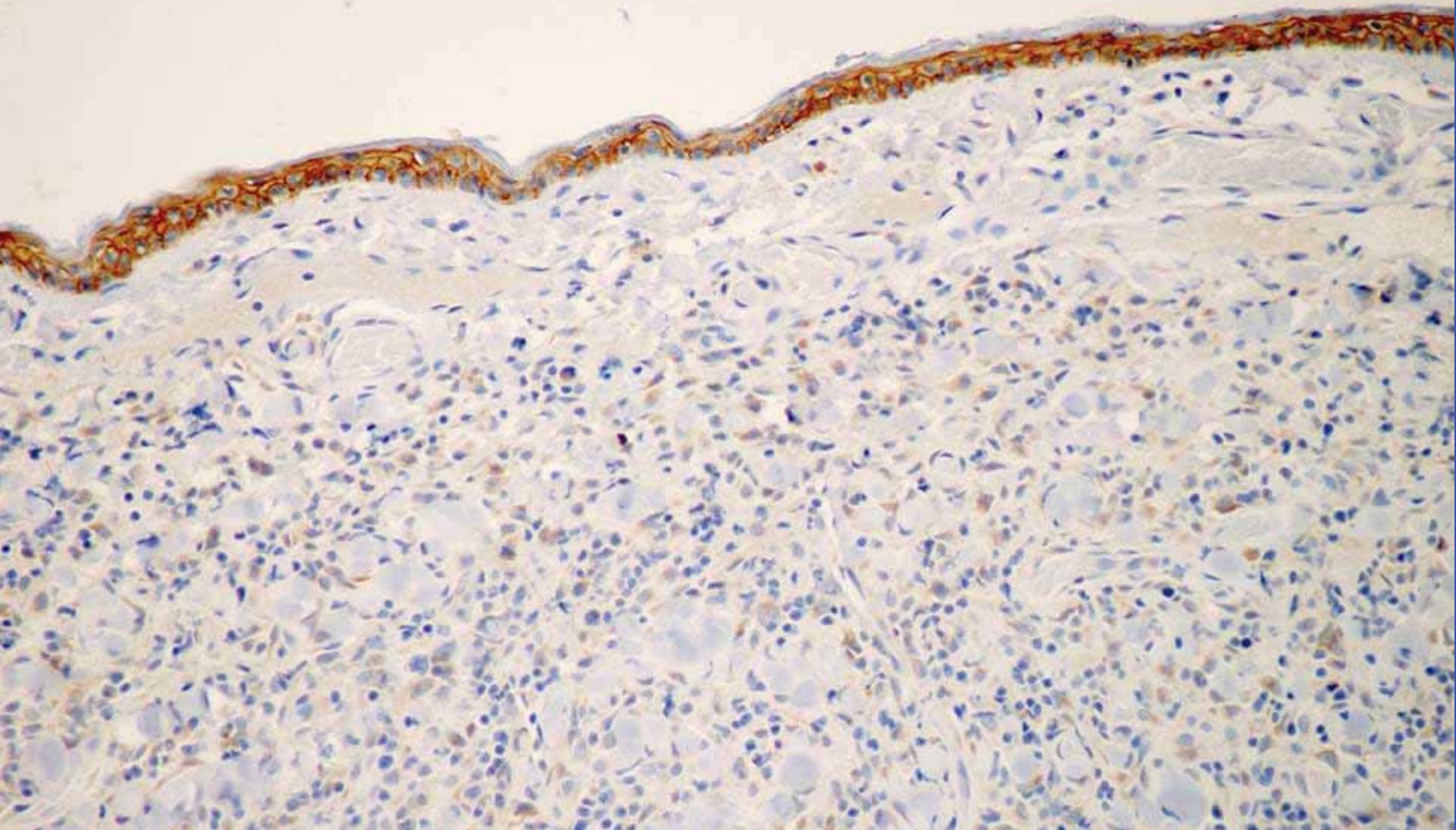
Multiple cutaneous masses



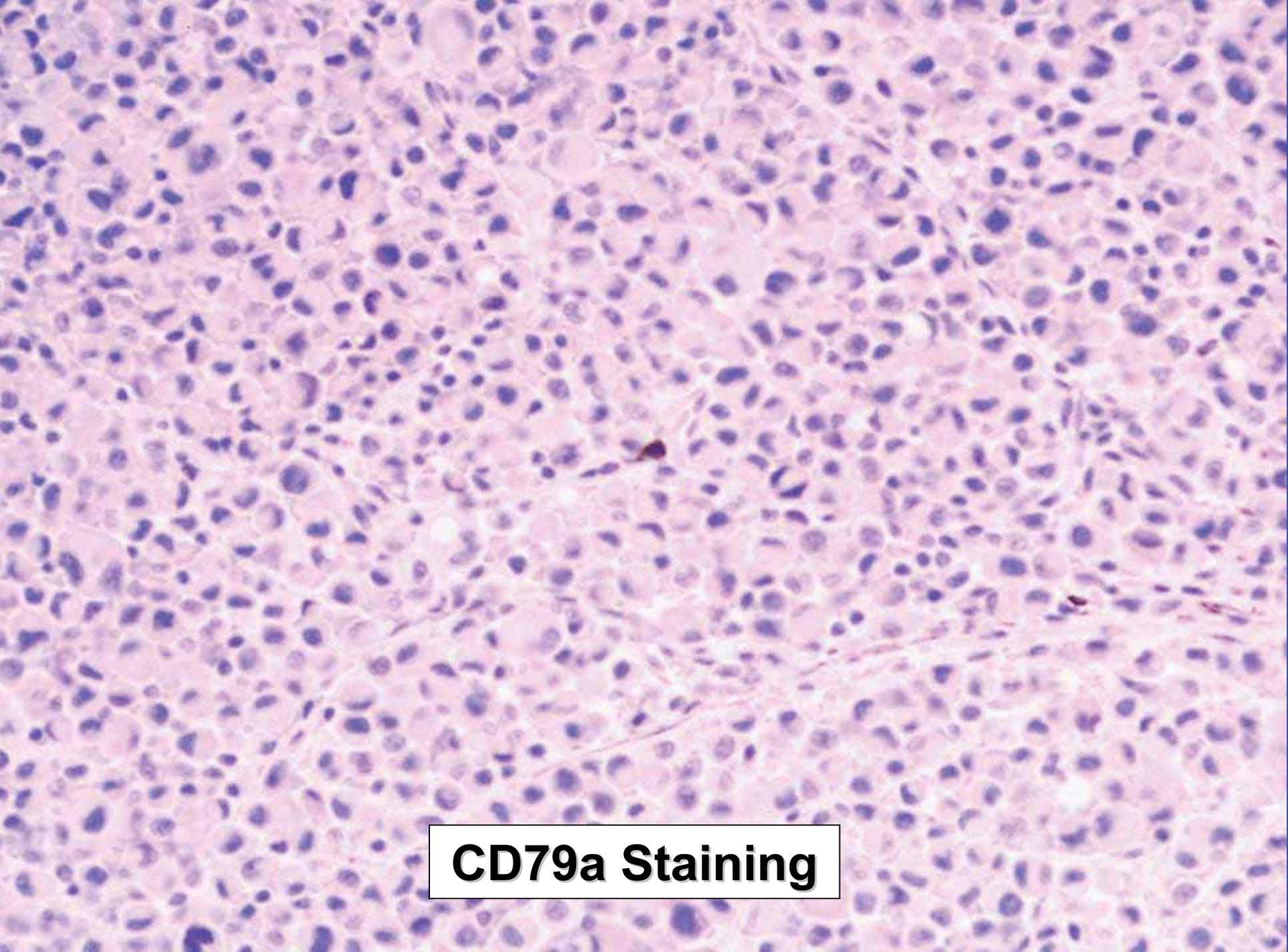
CD18 Staining



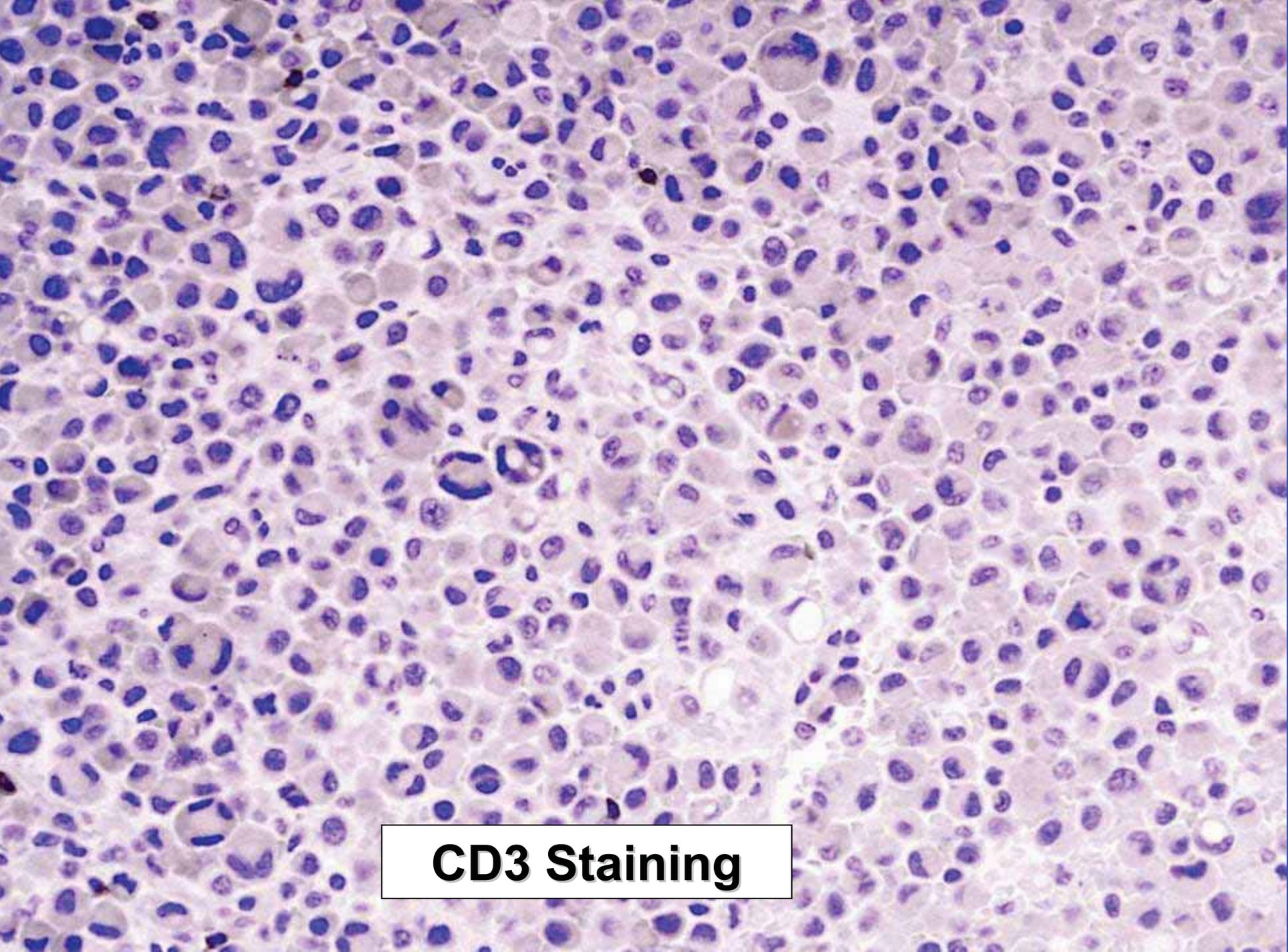
CD45 Staining



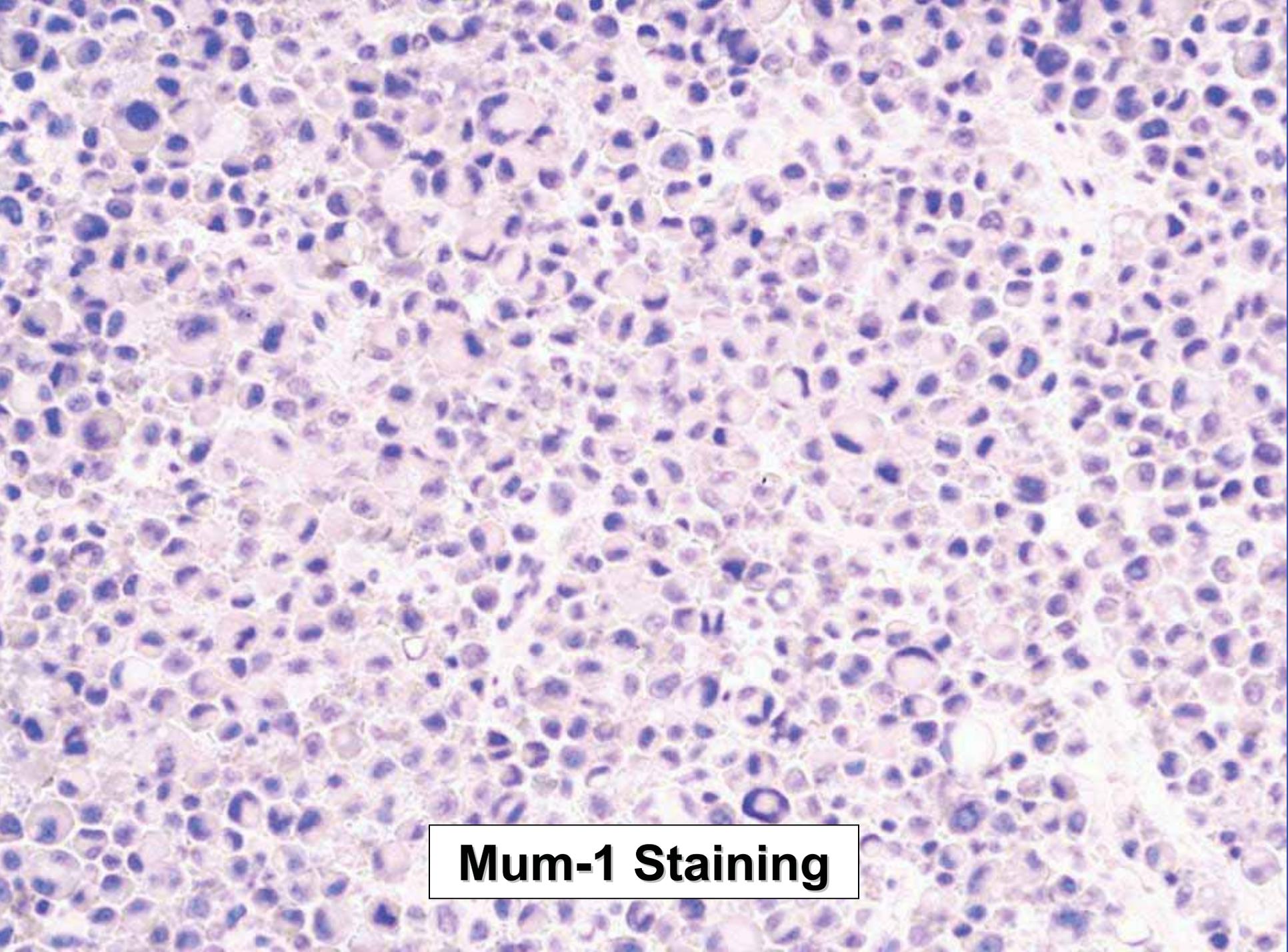
E-cadherin Staining



CD79a Staining



CD3 Staining

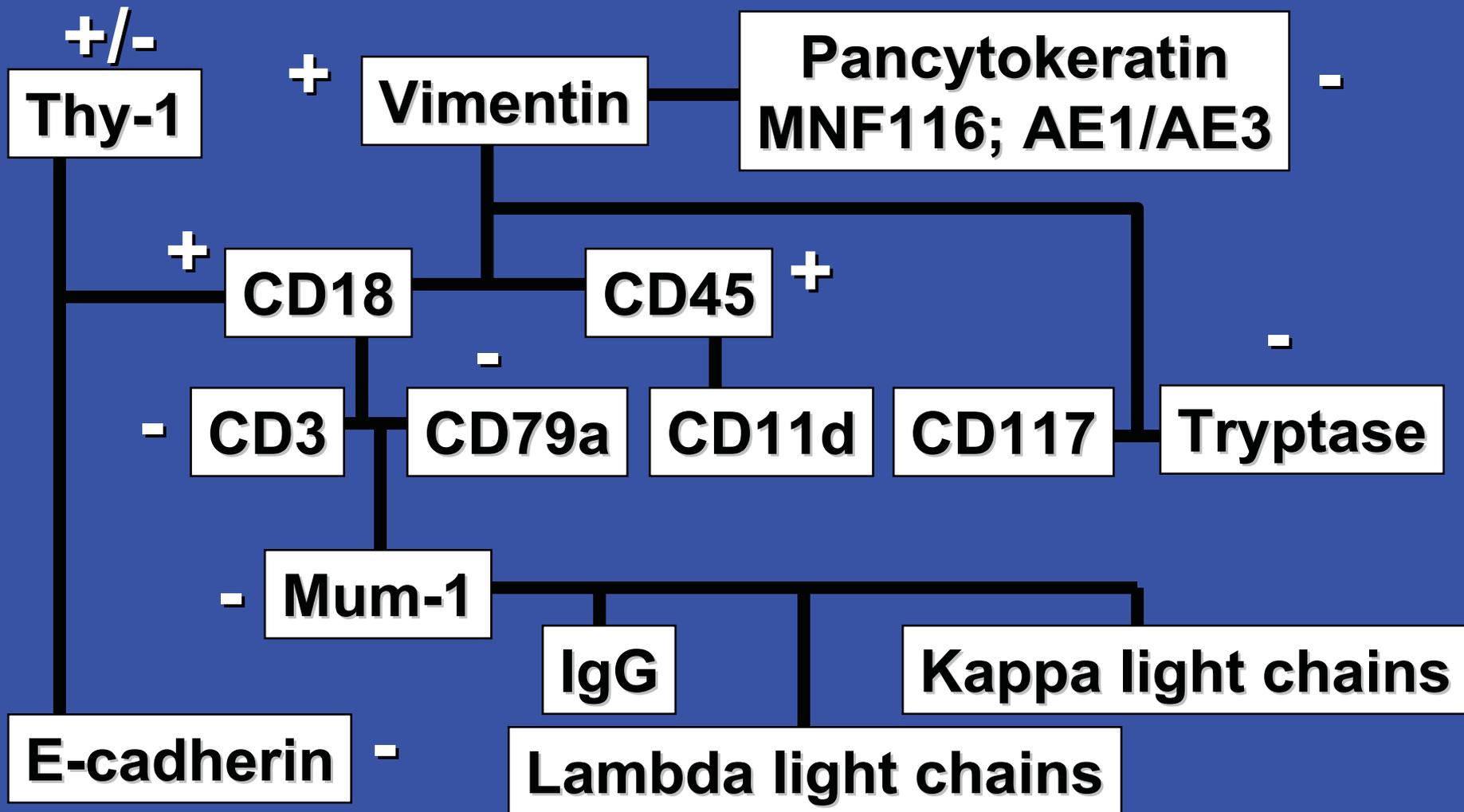


Mum-1 Staining

**What's
your
Diagnosis**



Histiocytic Sarcoma



Histiocytic Sarcoma



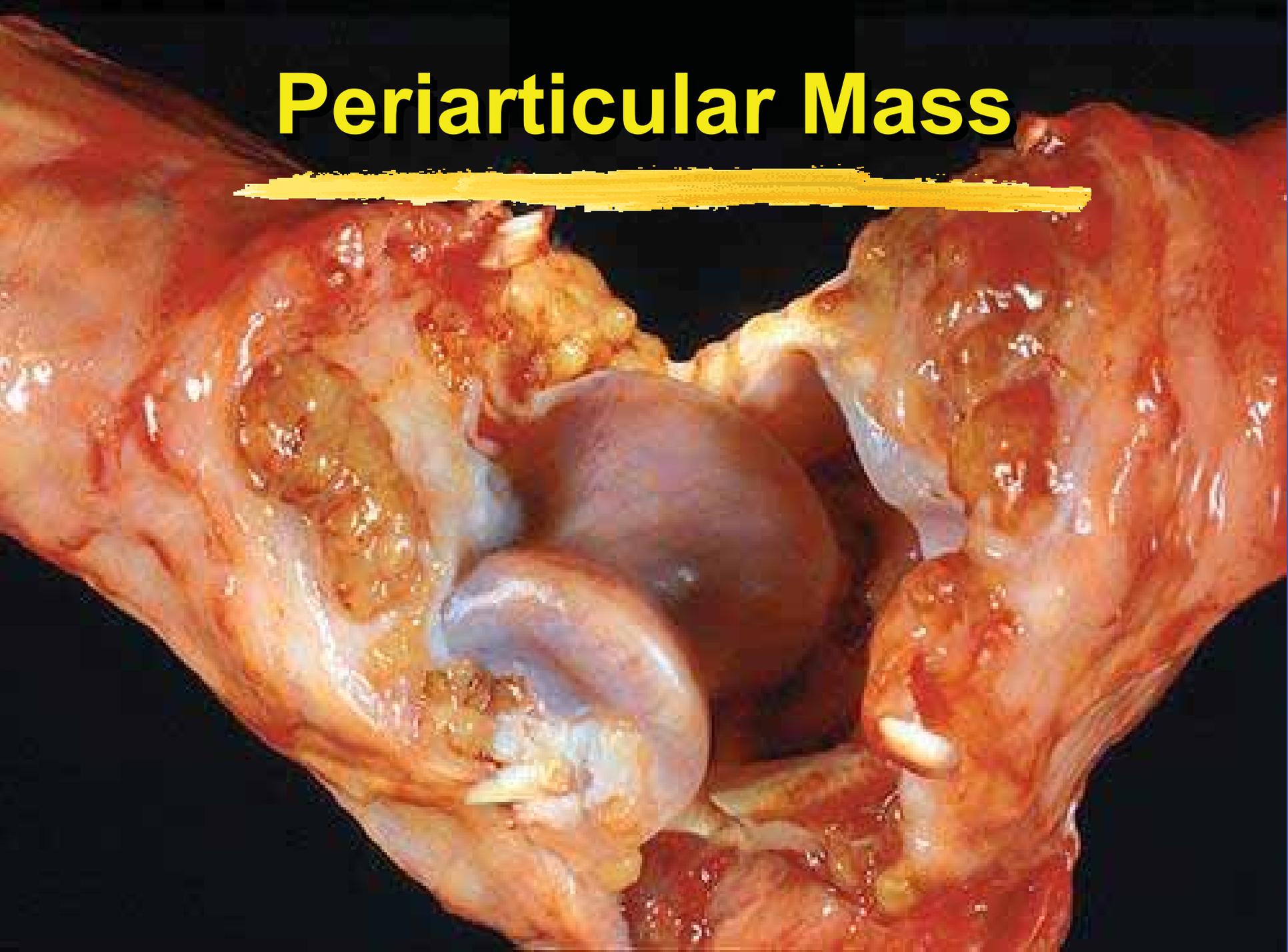
- **Malignant Histiocytosis** – familial, multicentric
- **Histiocytic sarcoma** - solitary and disseminated
- Interstitial DC phenotype predominates
- Spleen & lymph node interdigitating DC origin (PALS/marginal zone OR paracortex)
- Lung, skin, periarticular tissues - interstitial DC origin likely; CNS primary lesions??
- **Primary sites** - Spleen, lung, dermis/subcutis, lymph node, bone marrow, peri-articular tissues, and CNS
- **Breeds** - Bernese Mountain Dog (**familial**), Rottweiler, Golden Retriever and Flat-coated Retriever

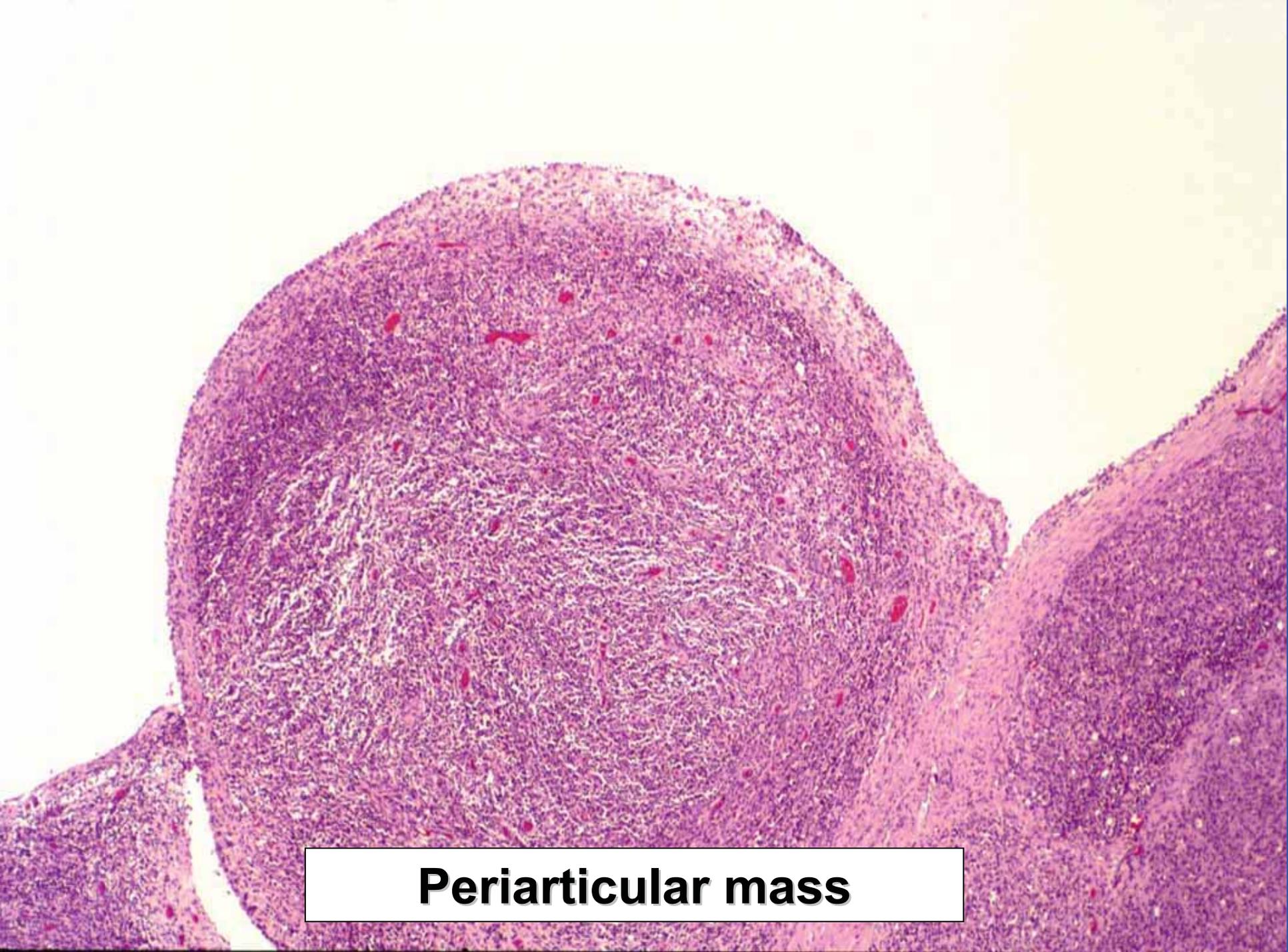
Histiocytic Sarcoma



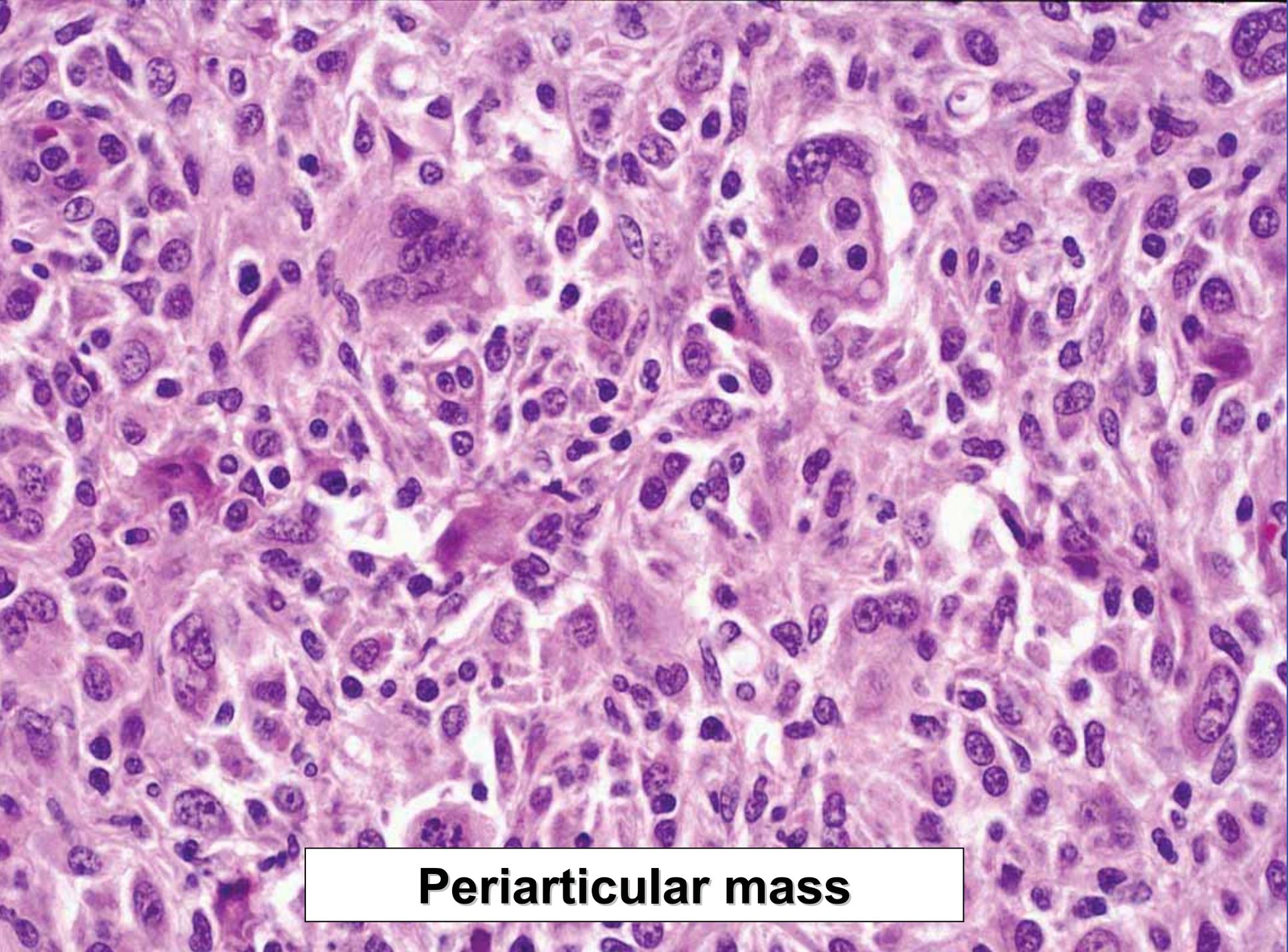
- Interstitial dendritic cell phenotype
- Formalin fixed sections:
 - **CD11d-**, **MHC II+**, **Thy1±**, **E-cadherin-**
- Frozen sections:
 - **CD1+**, **CD4-**, **CD11b±**, **CD11c+**

Periarticular Mass



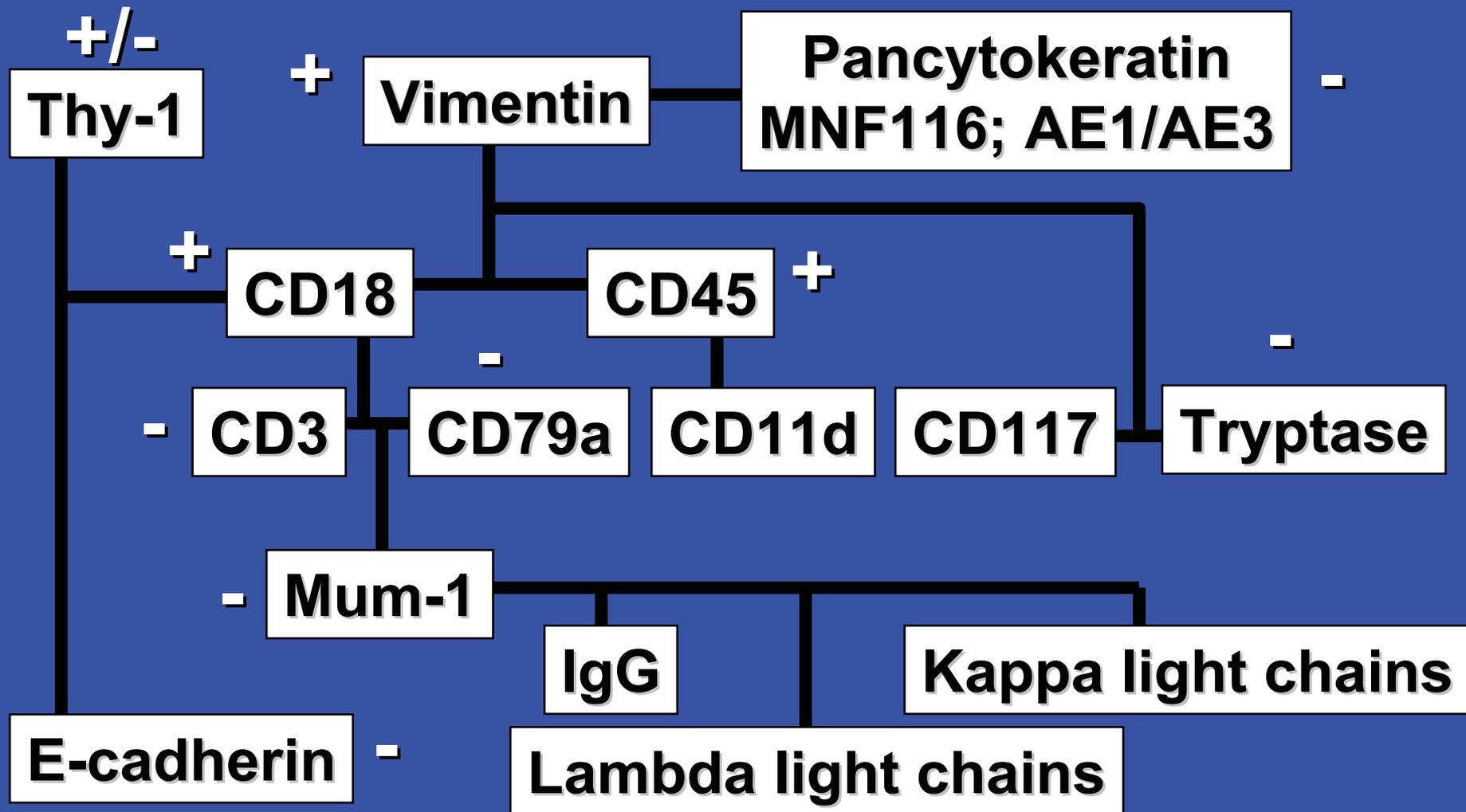


Periarticular mass



Periarticular mass

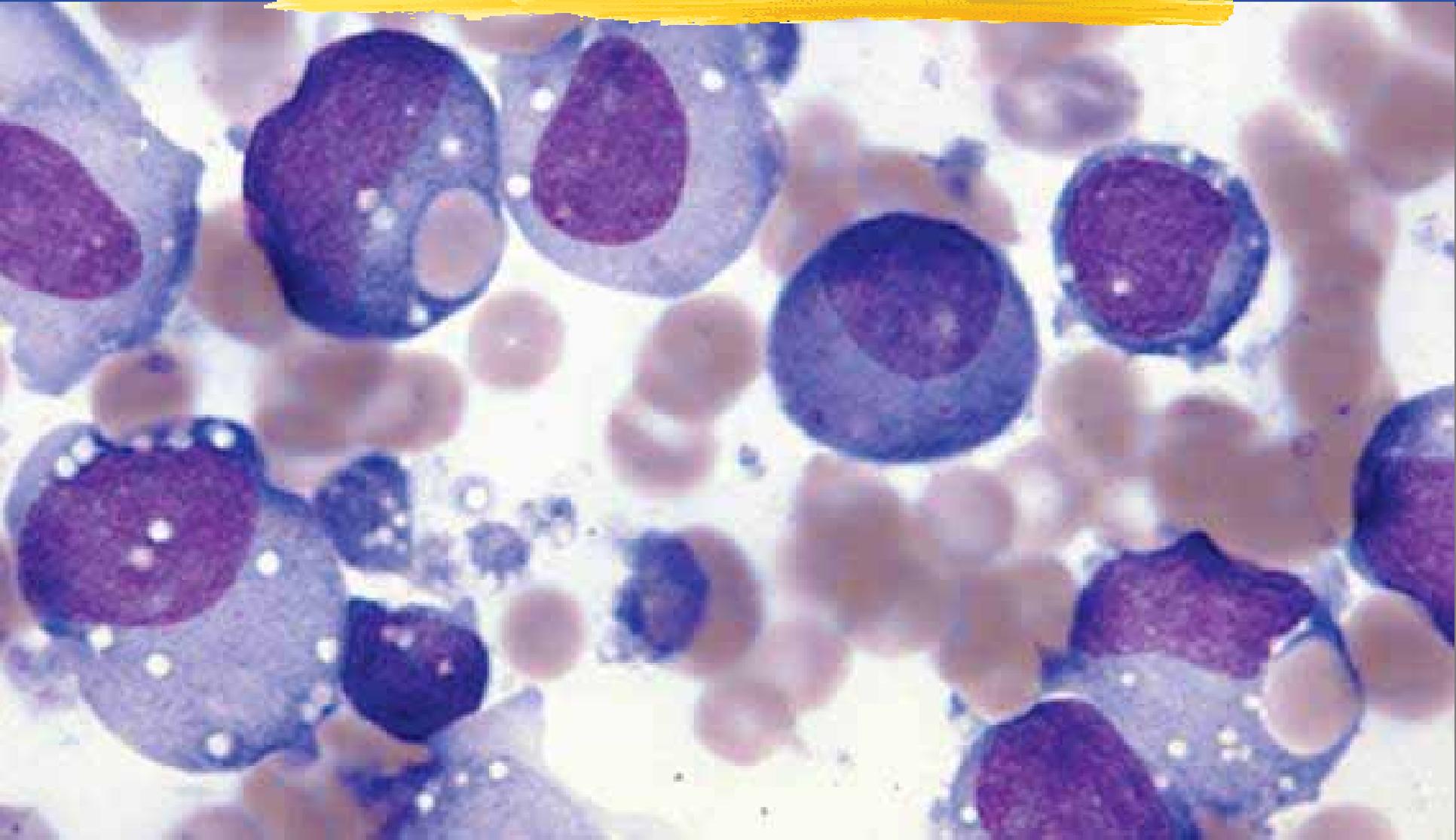
Periarticular Histiocytic Sarcoma

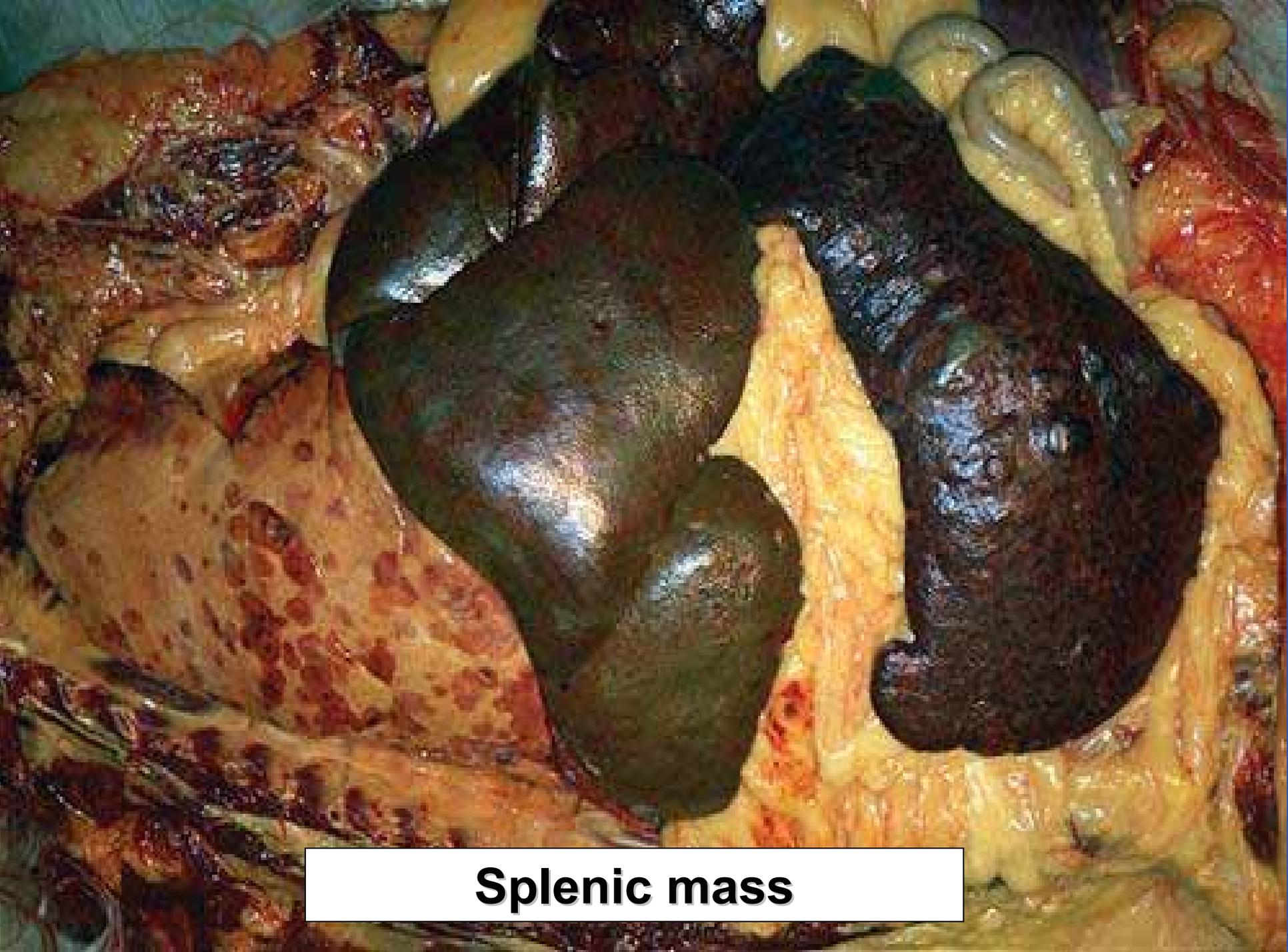


Periarticular Histiocytic Sarcoma

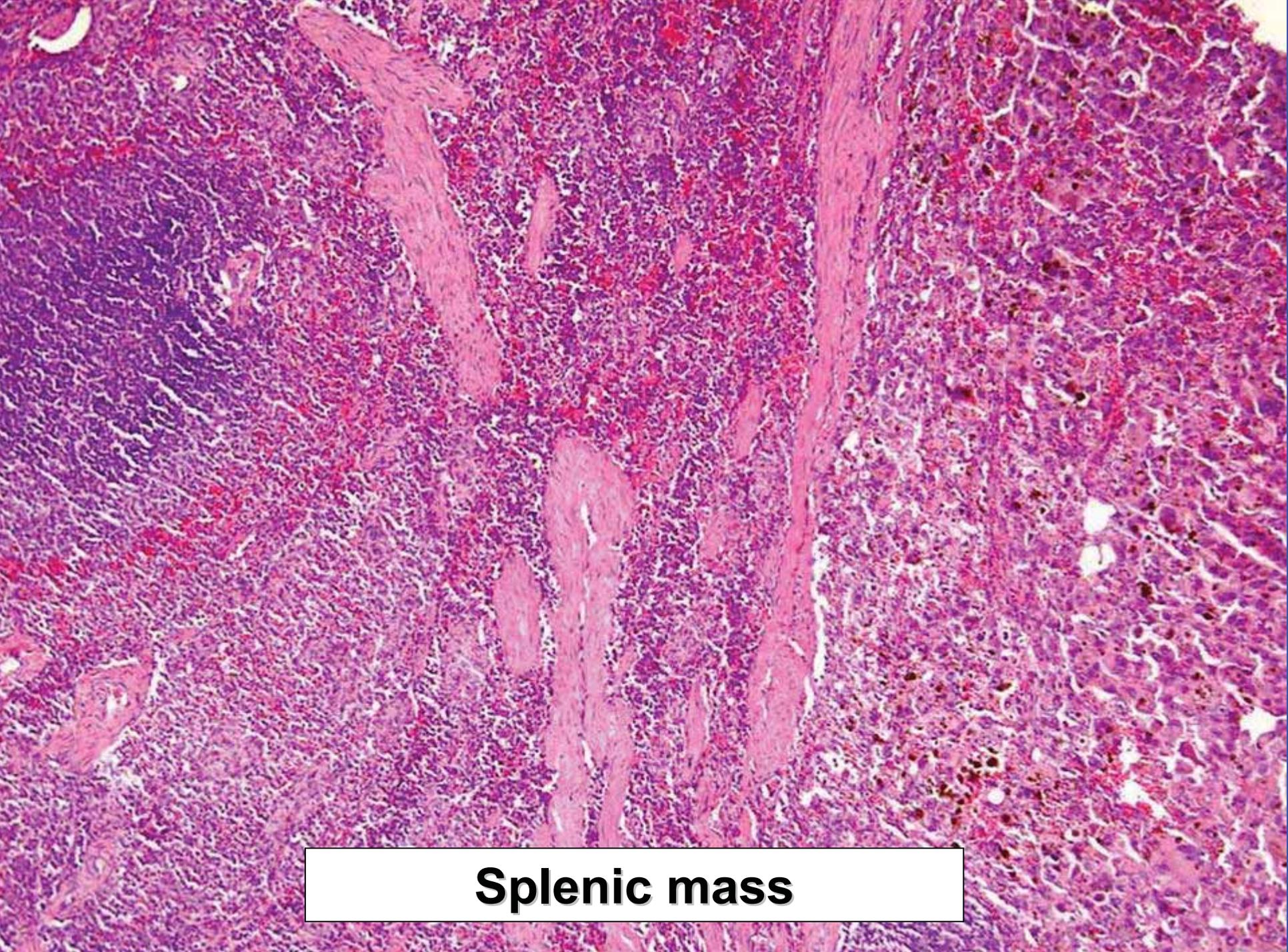
- **Multinodular masses encircling affected joints**
Stifle, hock, shoulder, elbow and digits
- **Localized lesions with distant metastatic potential**
- **Inconsistent history of preceding synovitis**
- **Likely origin from subsynovial perivascular DC, not synovial type A cells (macrophages)**
CD1+, CD4-, CD11b±, CD11c+, CD11d-, MHC-II+, Thy-1±

Splenic Mass

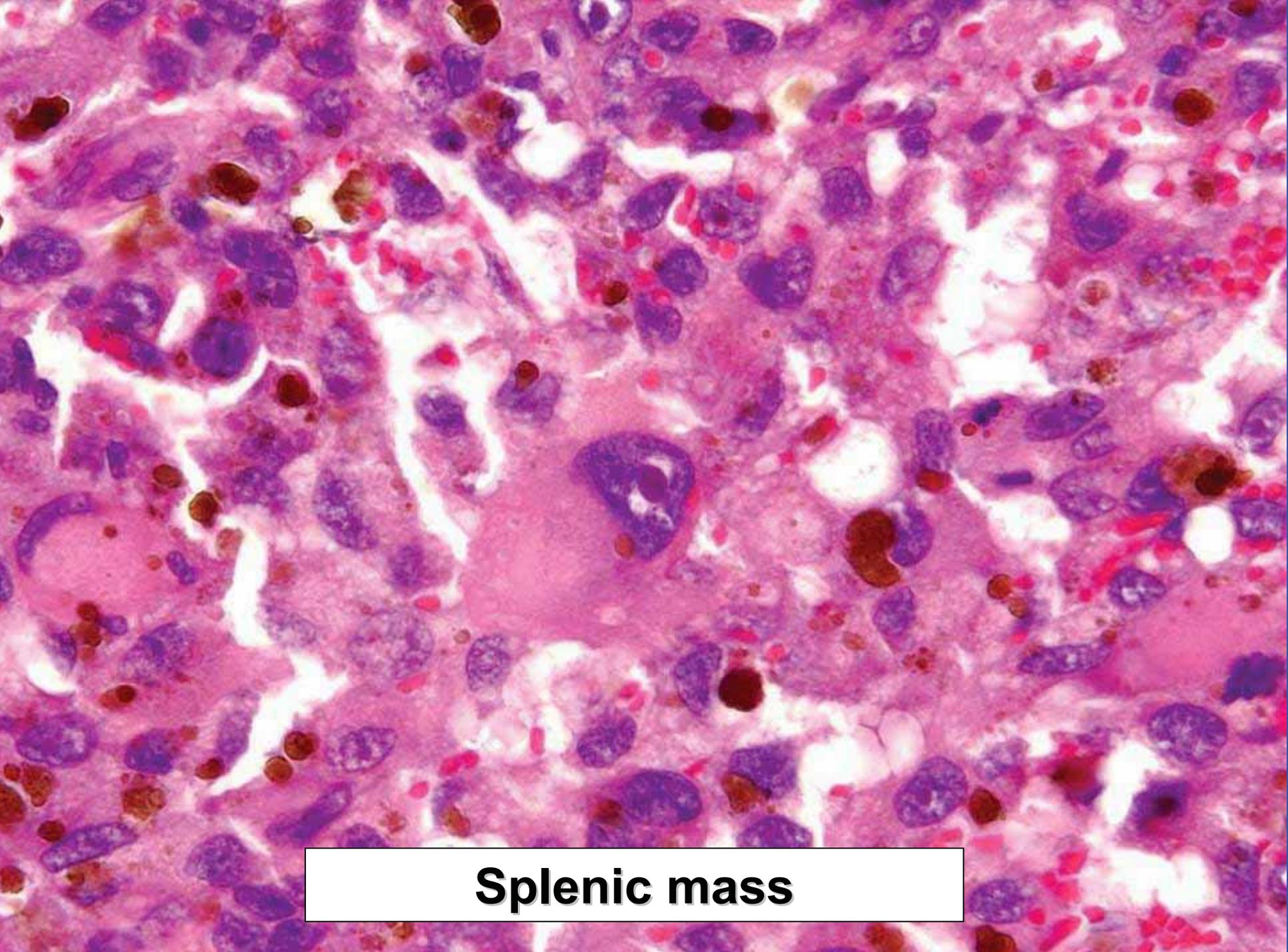




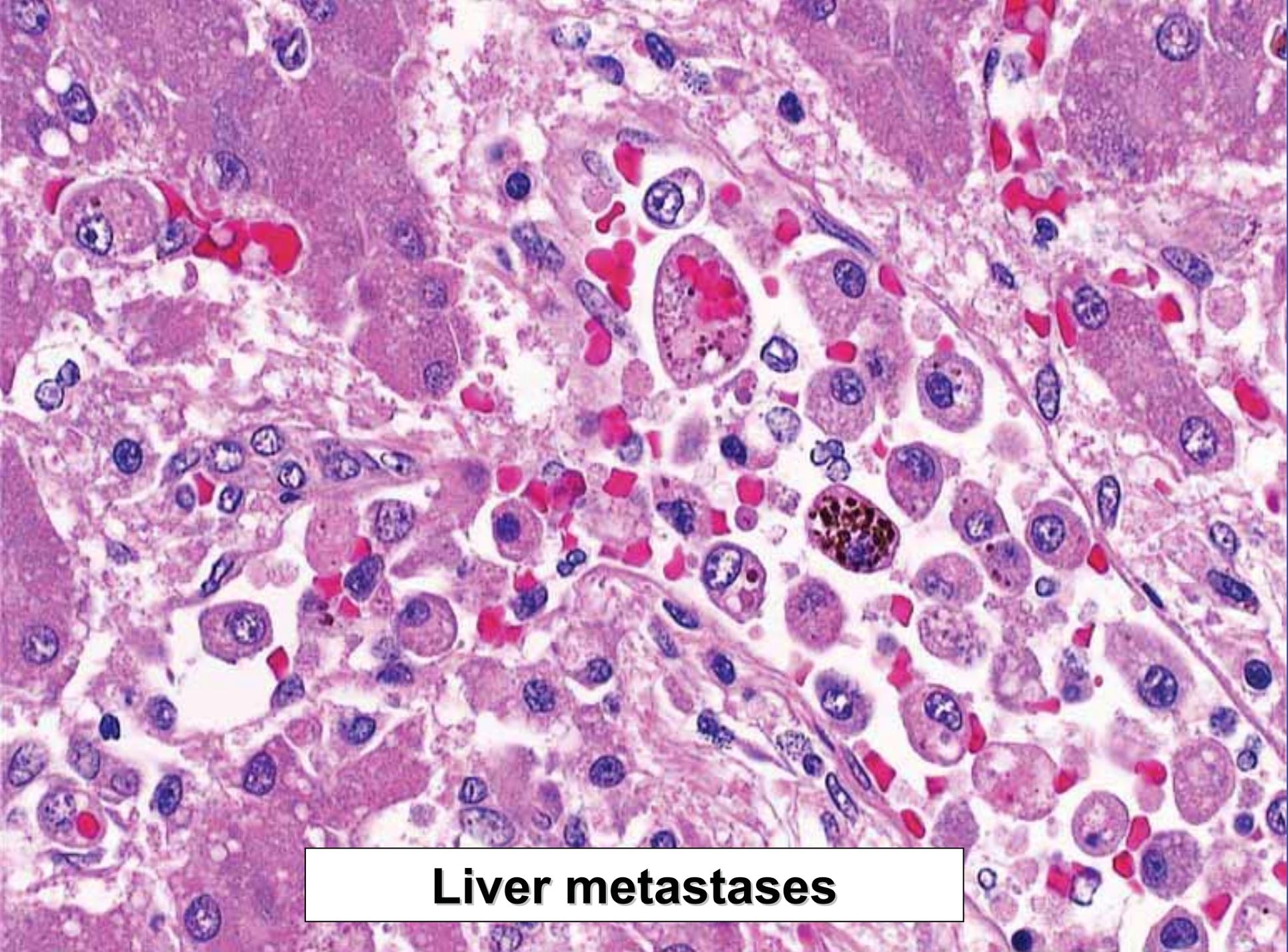
Splenic mass



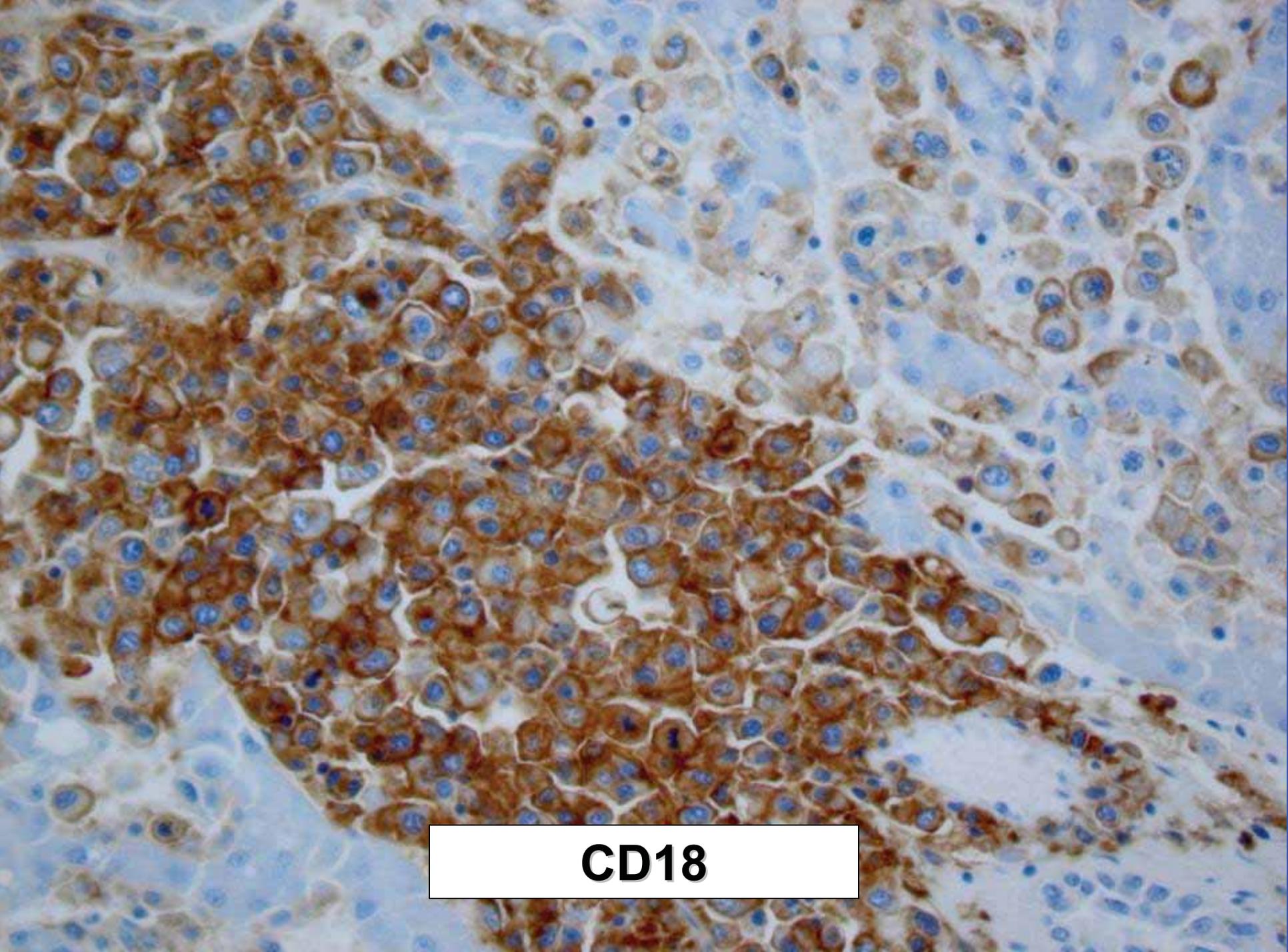
Splenic mass



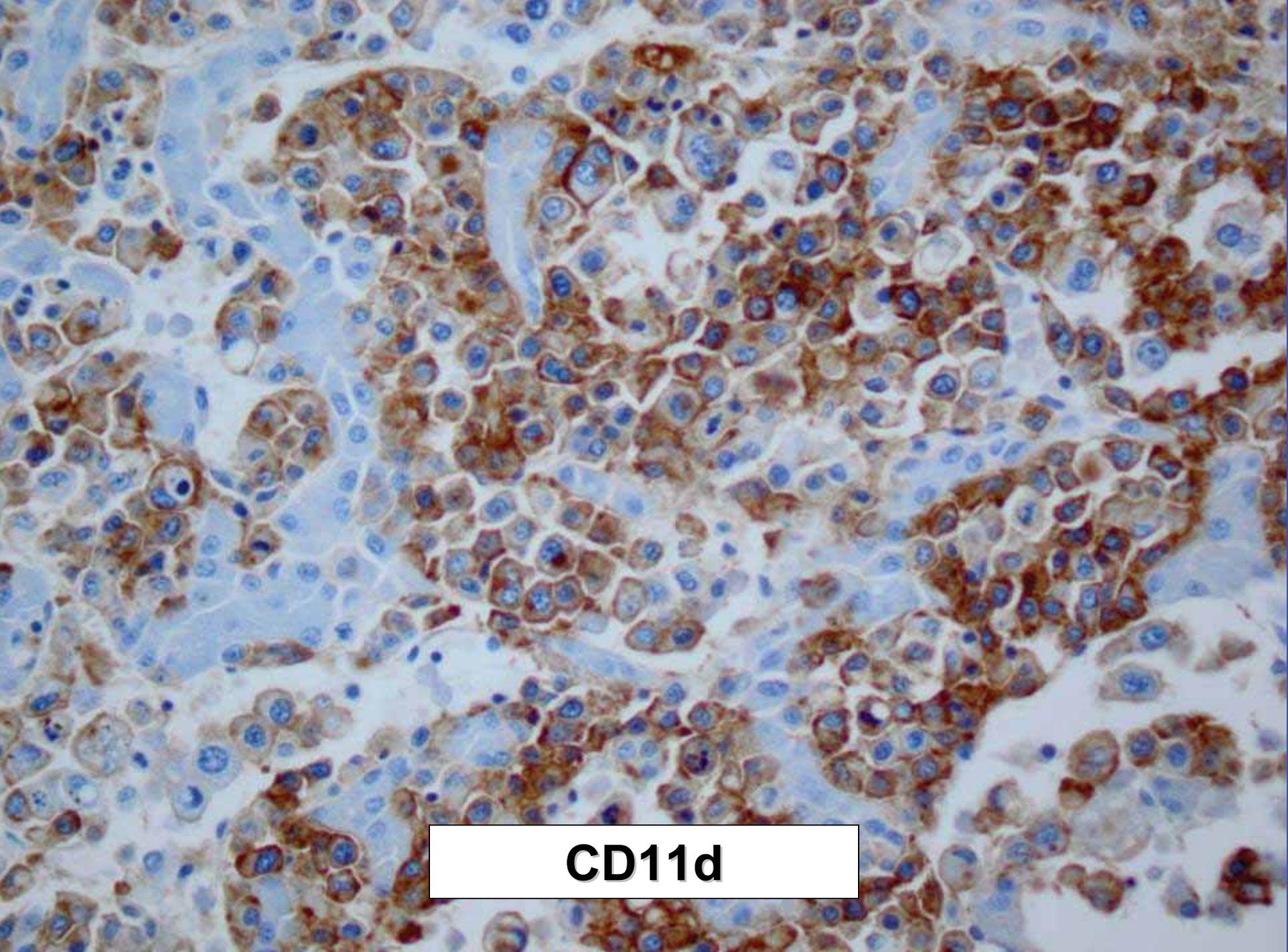
Splenic mass



Liver metastases



CD18



CD11d



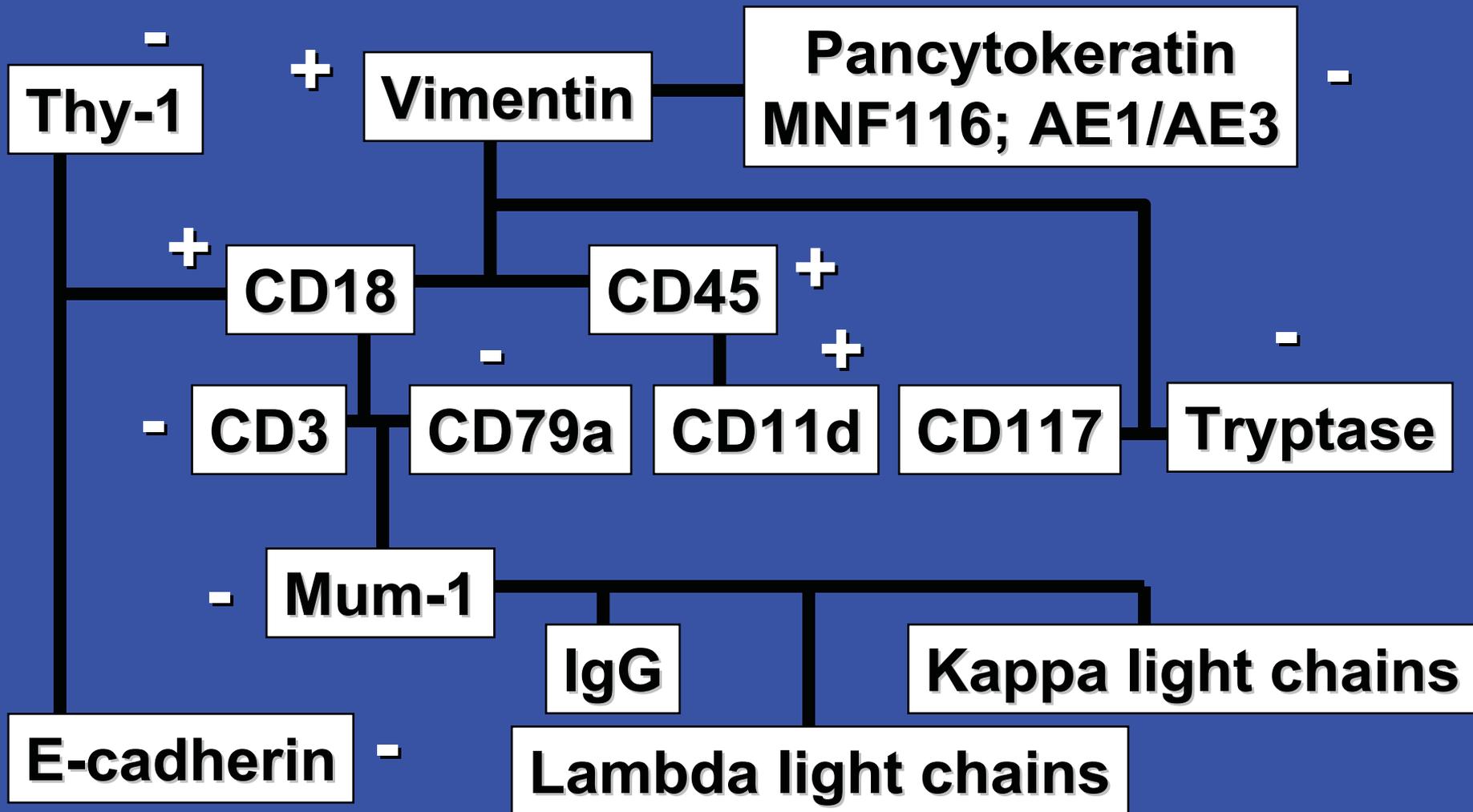
Blonde
Secretary

Boss

Workaholic

**What's
your
Diagnosis**

Hemophagocytic Histiocytic Sarcoma

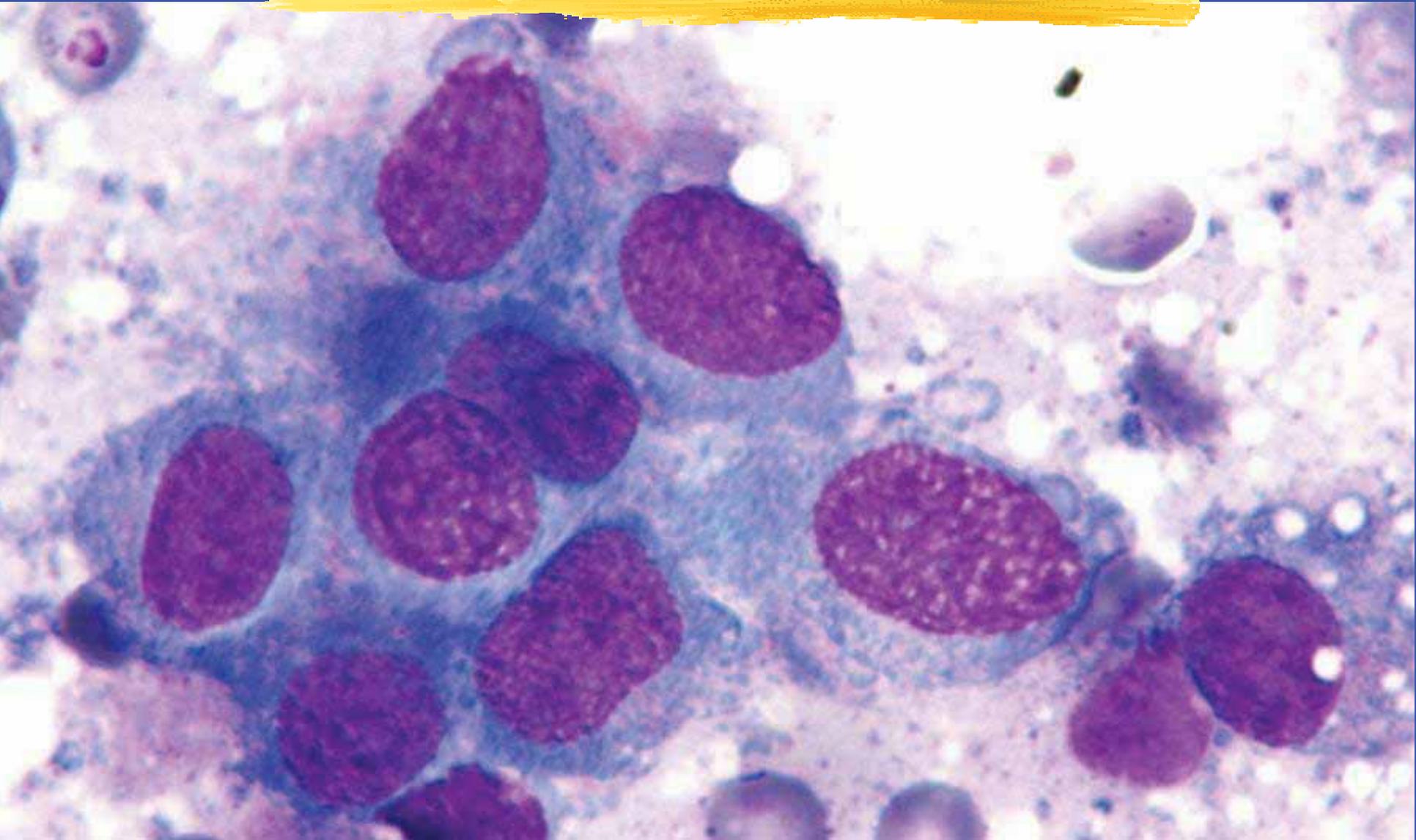


Hemophagocytic Histiocytic Sarcoma



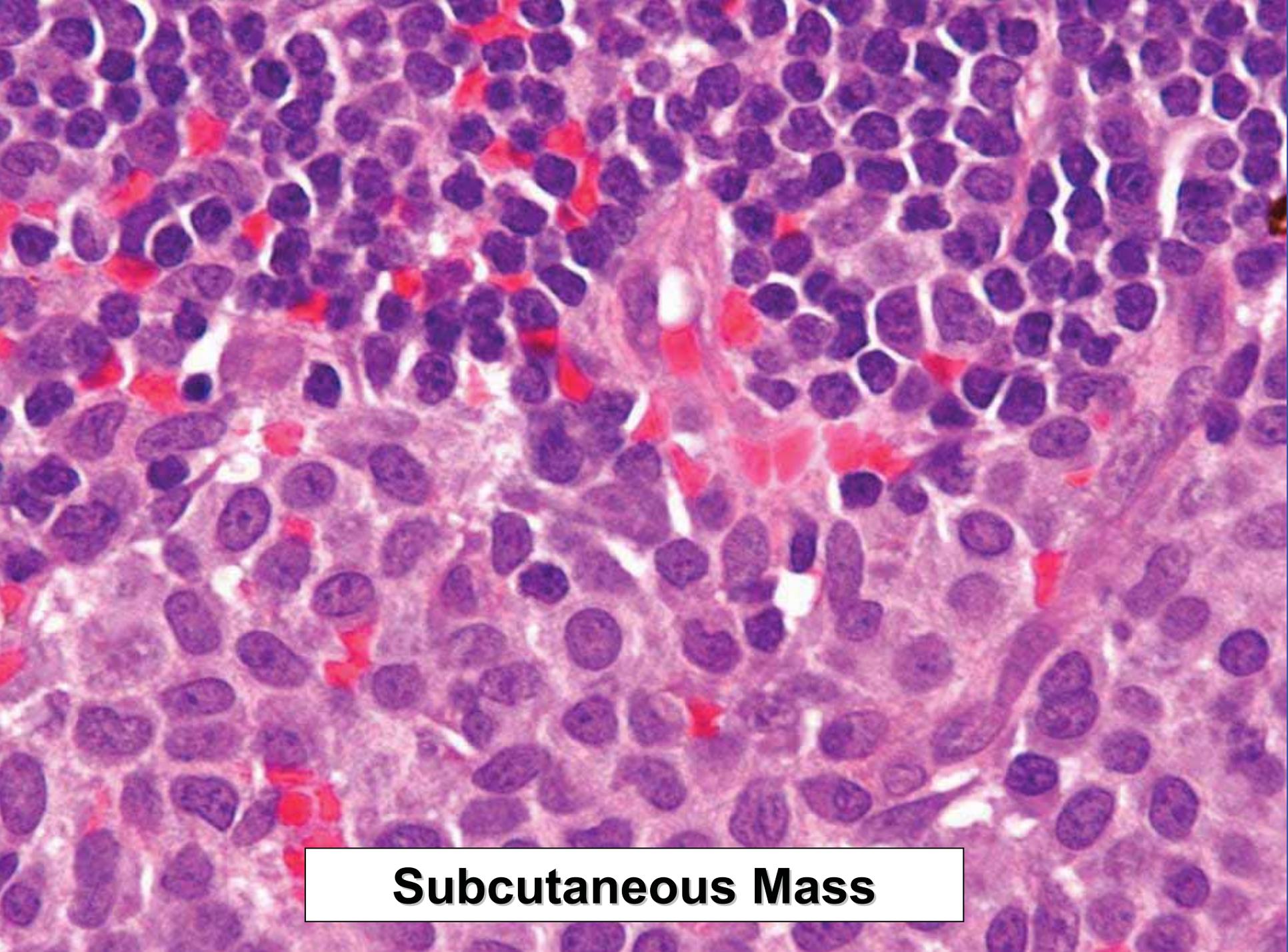
- Splenic red pulp (\pm bone marrow) macrophage origin
 - **CD1 \pm , CD4-, CD11b \pm , CD11c \pm , CD11d+, MHC-II+, Thy-1-**
- Insidious intravascular invasion - liver, lung – in early metastatic lesions
- Profound anemia - often poorly responsive
- Paradoxically - histiocytic infiltrates accompanied by marked EMH

Cutaneous Mass

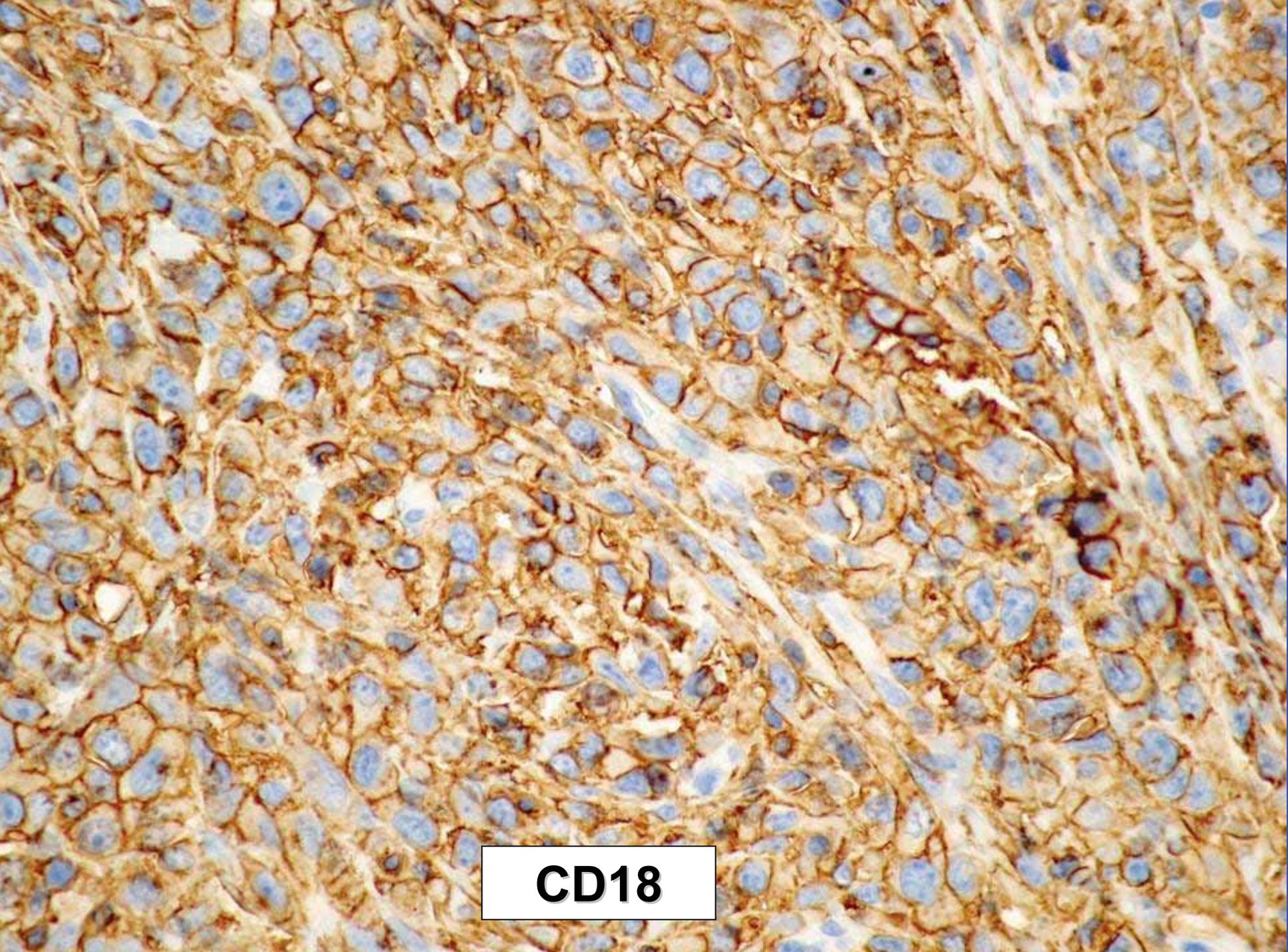




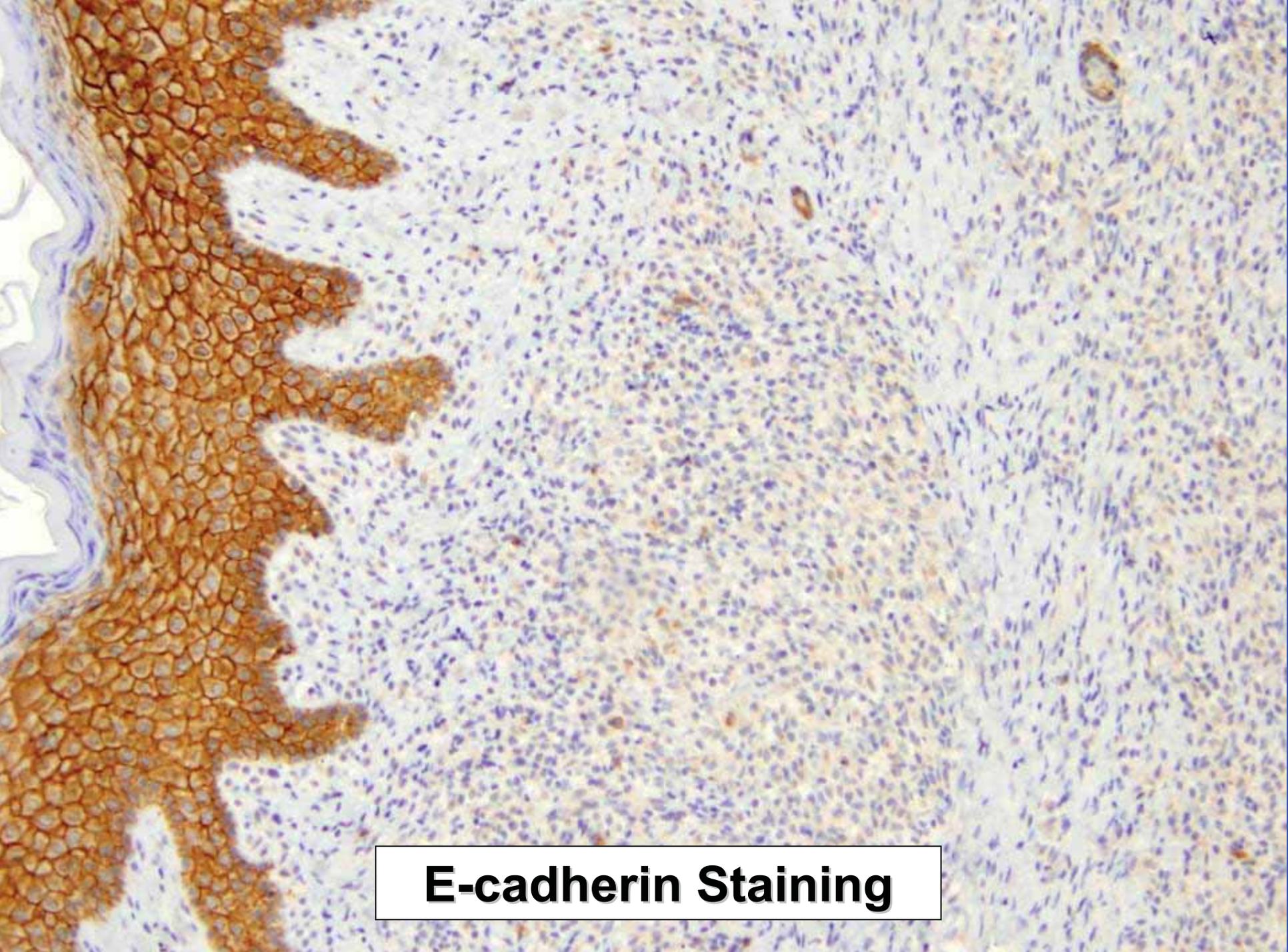
Cutaneous Mass



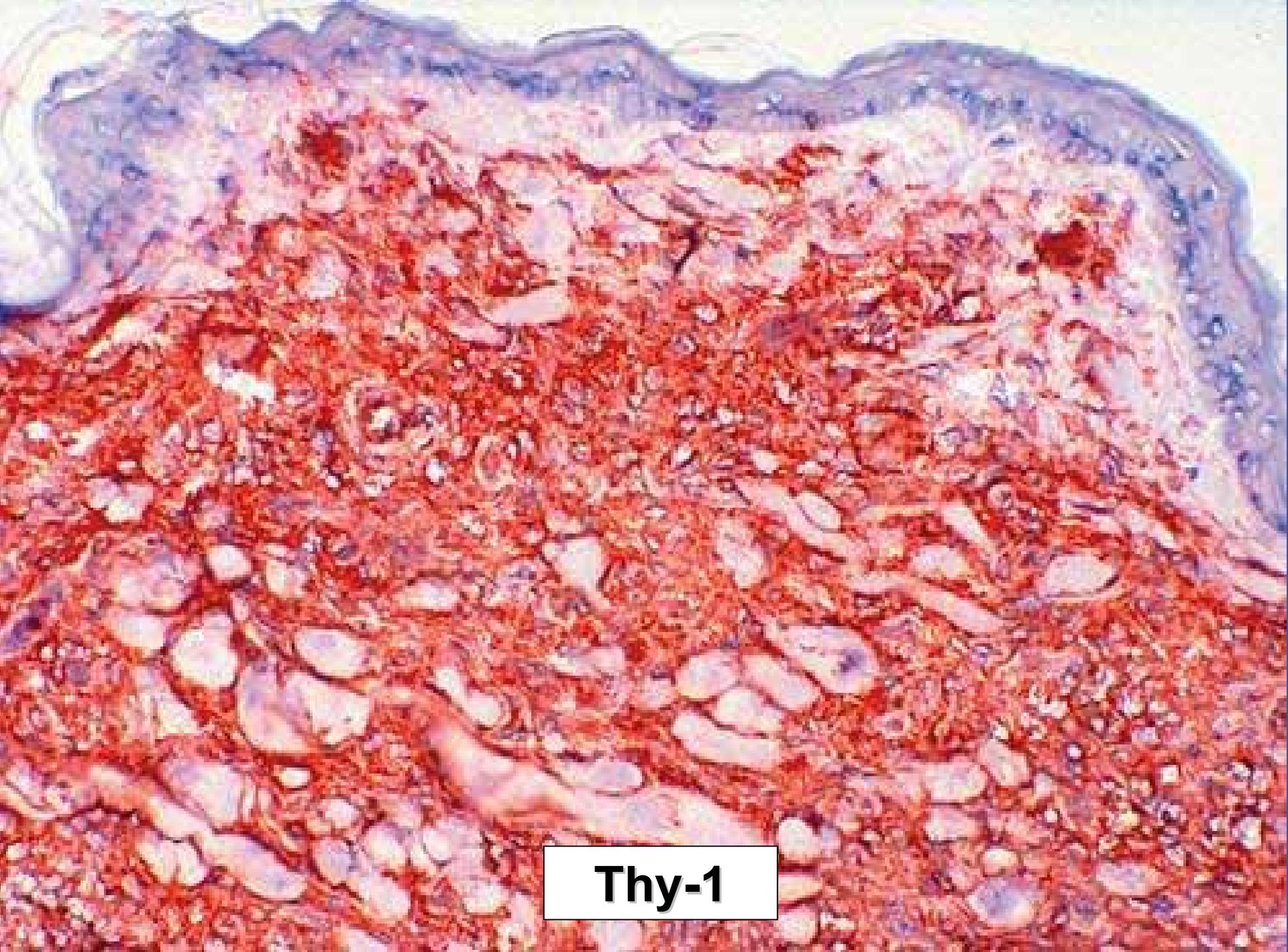
Subcutaneous Mass



CD18

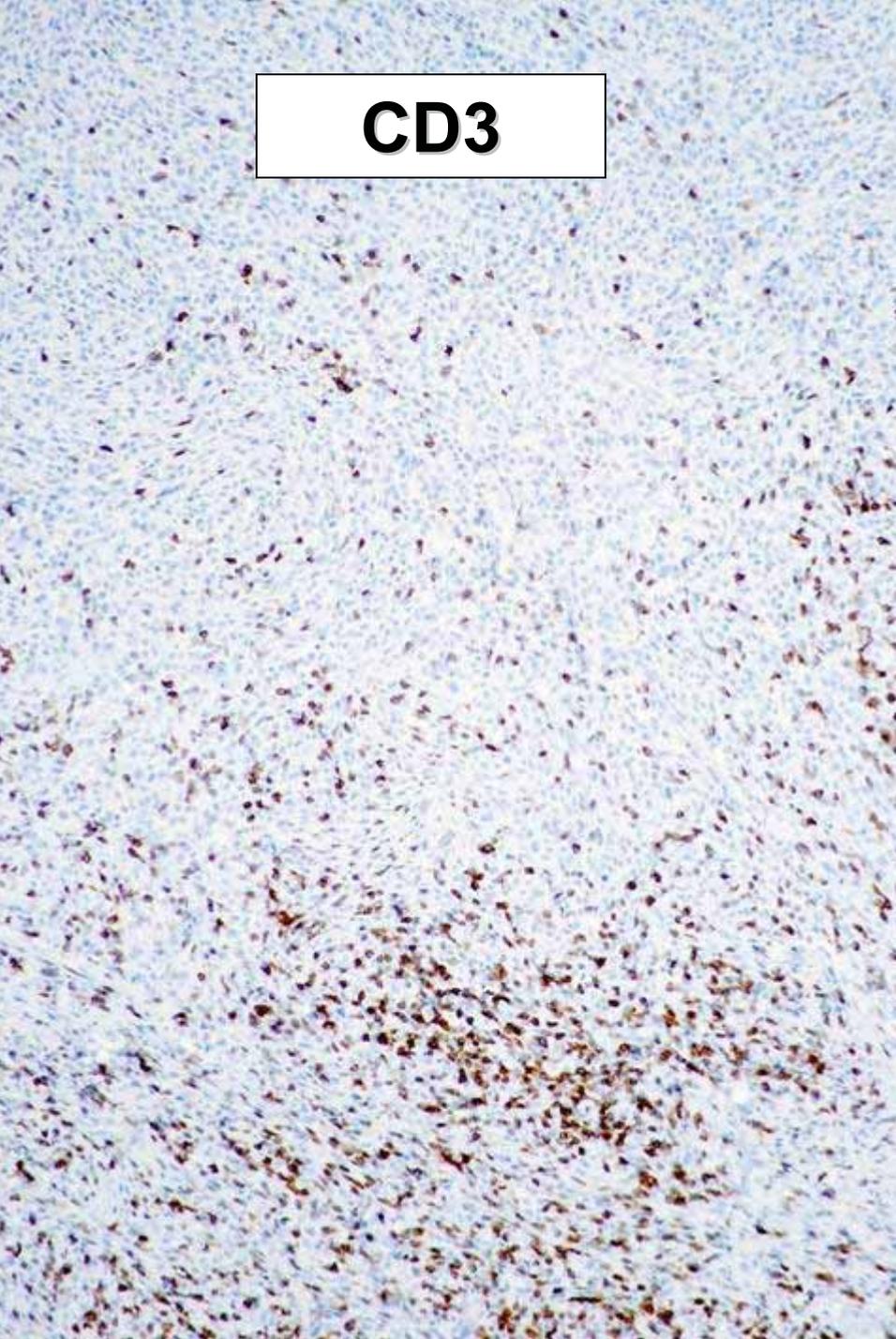


E-cadherin Staining

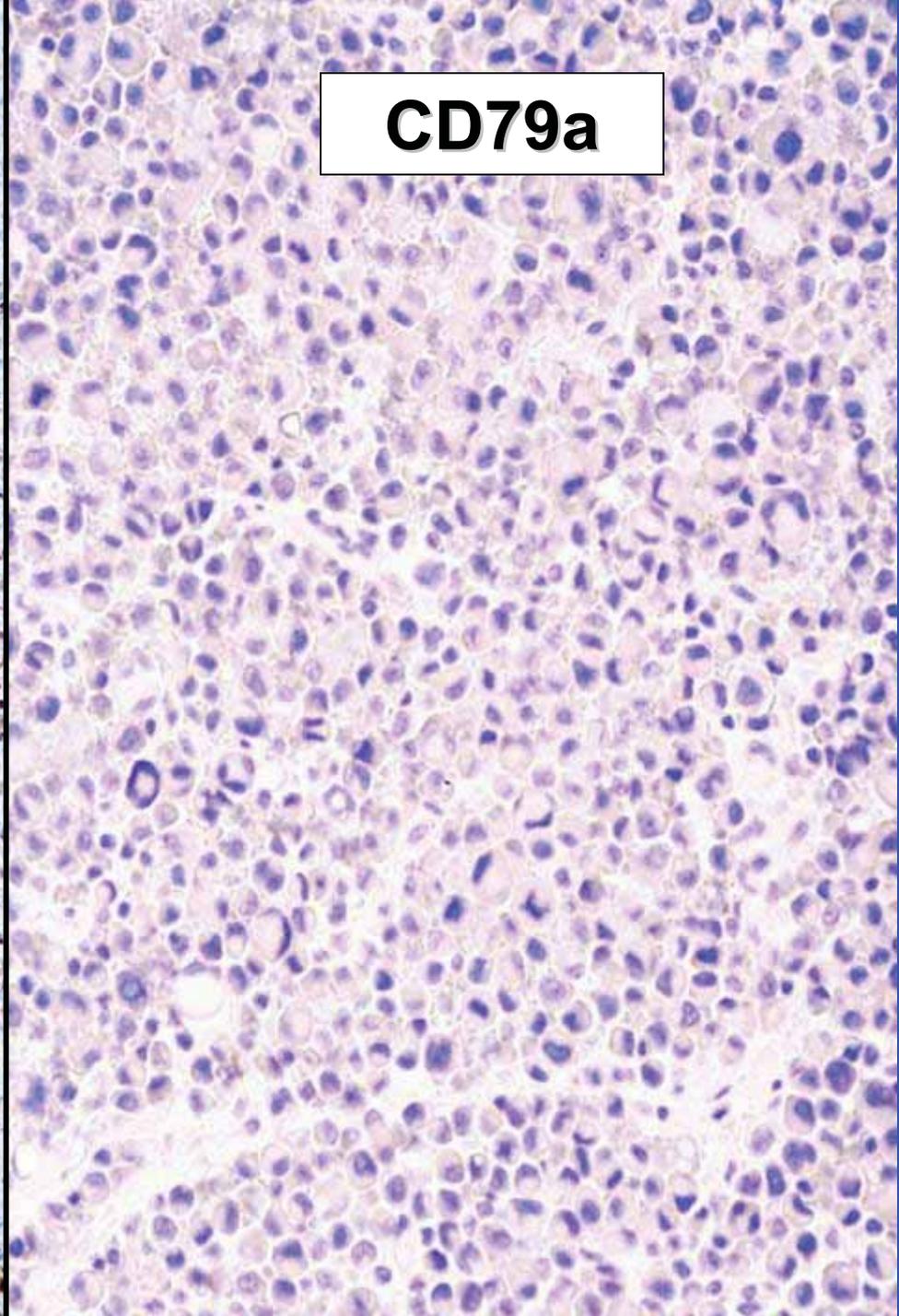


Thy-1

CD3



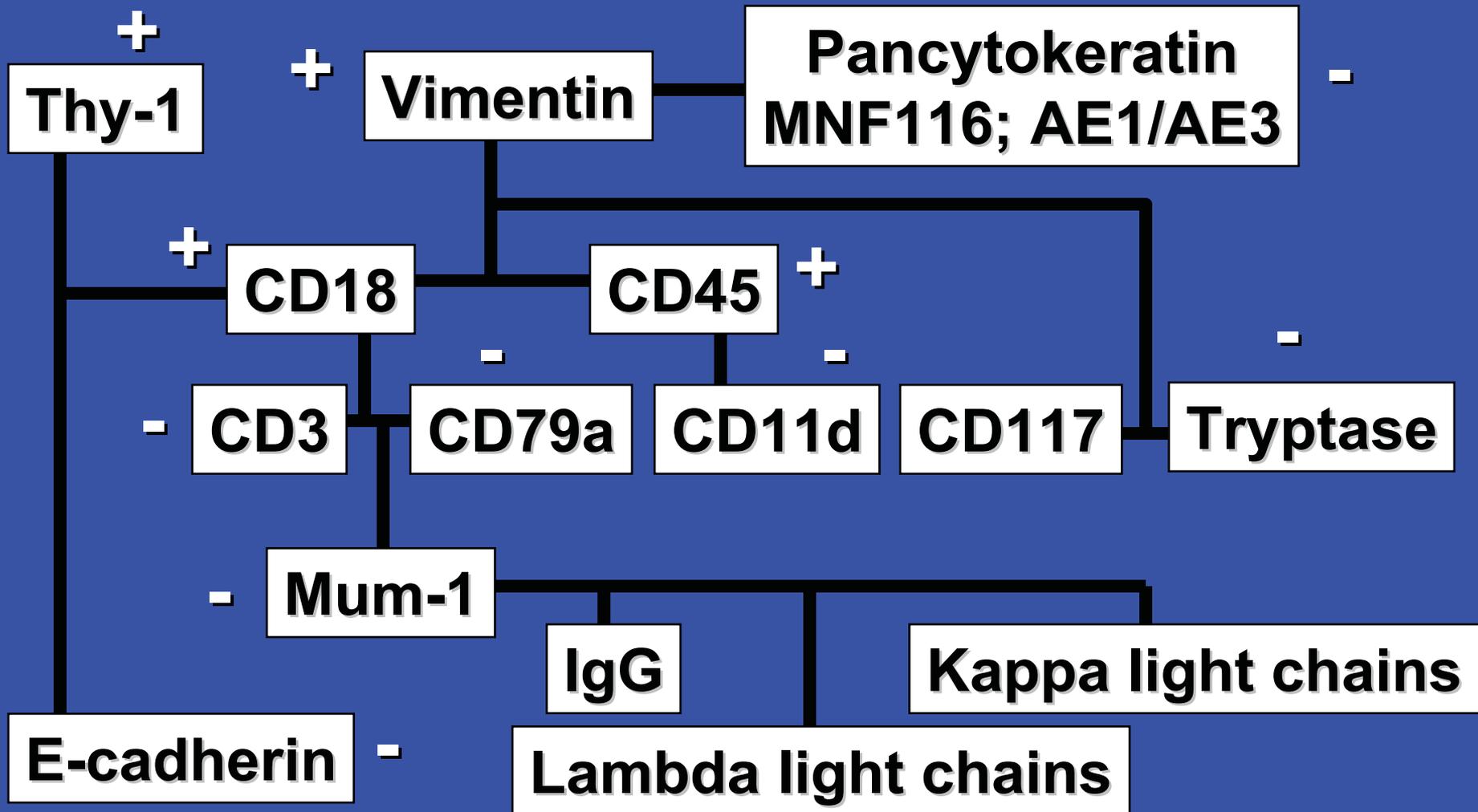
CD79a





What's your Diagnosis

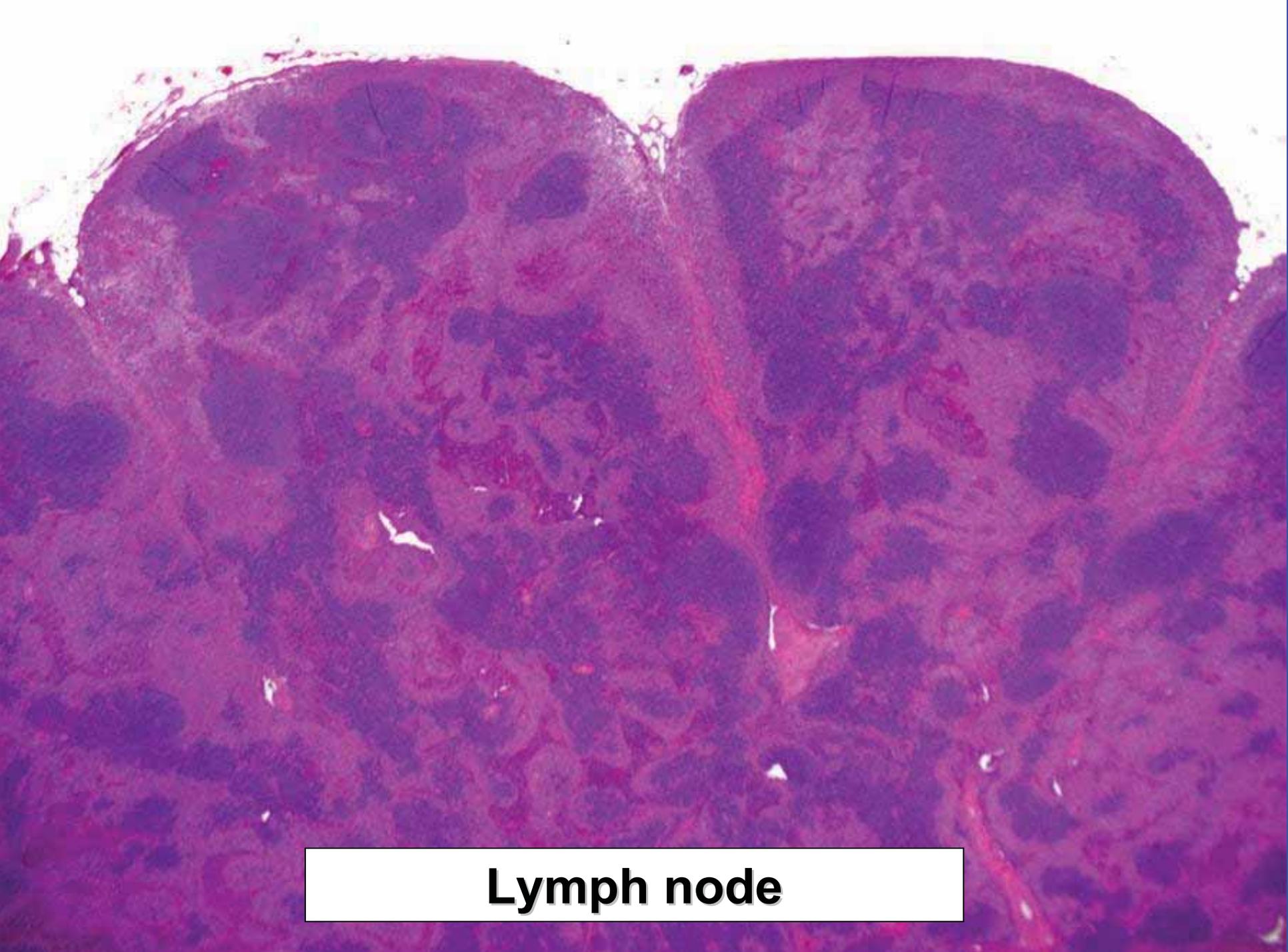
Cutaneous Reactive Histiocytosis



Cutaneous Histiocytosis

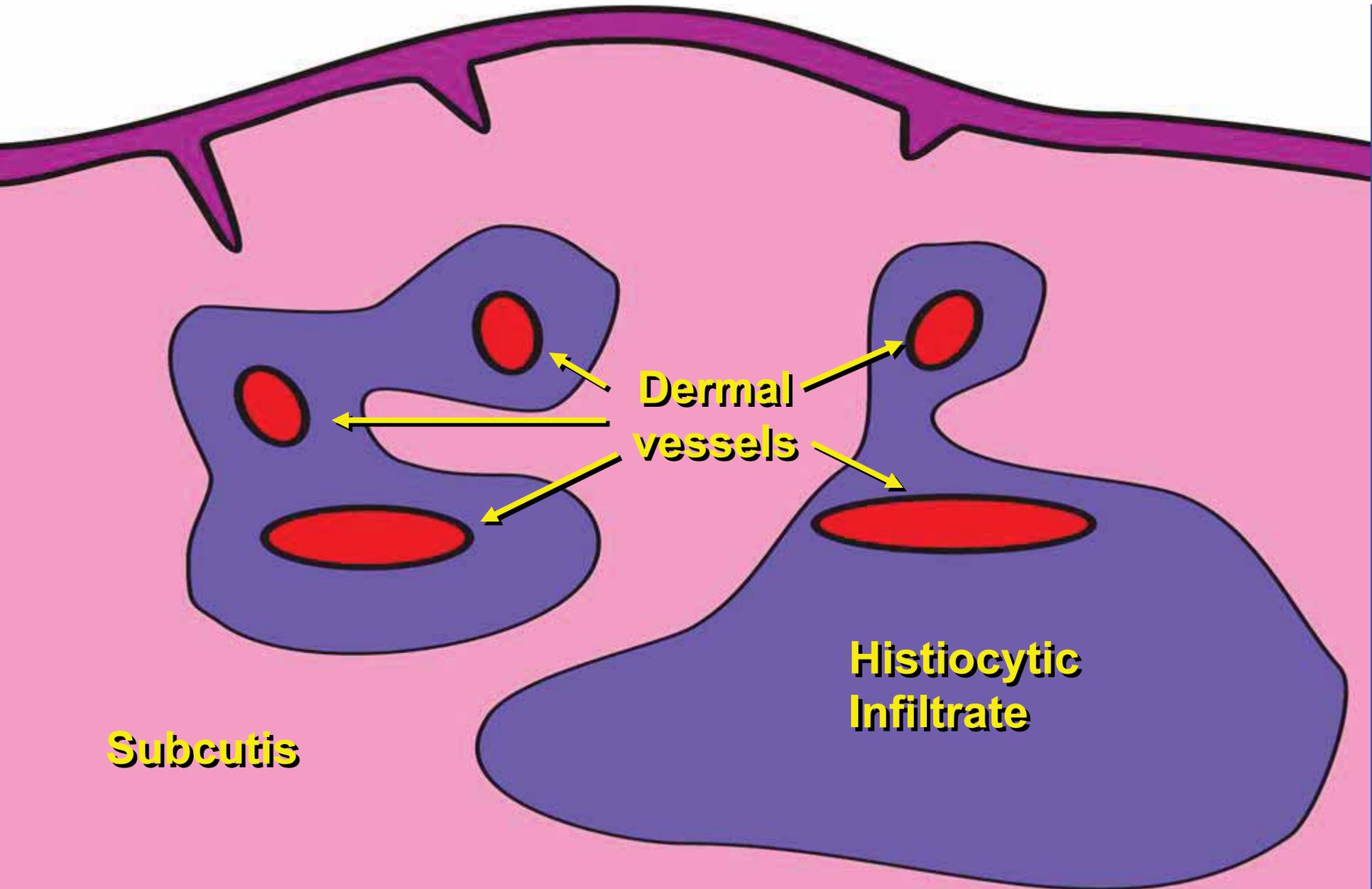


Systemic Histiocytosis



Lymph node

Cutaneous Reactive Histiocytosis





CD4

Canine Reactive Histiocytosis



- **Cutaneous histiocytosis (CH) and Systemic histiocytosis (SH):** CH is **skin-limited reactive histiocytosis**, and SH is **systemic reactive histiocytosis** - a more aggressive disease
- Reactive diseases, rare neoplastic progression
- Prevalent in Bernese Mountain dog (familial)
- Widespread cutaneous lesions with **spread beyond the skin in SH** (lymph nodes, lung, ocular and nasal mucosa, spleen, BM etc)
- Spontaneous remissions possible

Reactive Histiocytosis

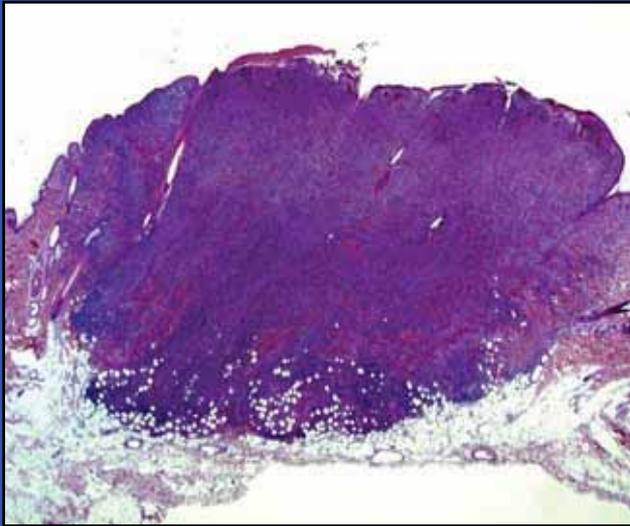


- **Perivascular/vaso-invasive infiltrates** of histiocytes with variable lymphocytic infiltration
- Skin - lesions are centered on vessels of the dermis and subcutis; lesions coalesce in subcutis
- Lymph nodes - complex lesions
- Histiocytes in CH and SH lesions consist of **reactive, activated dermal DC**
- Formalin fixed section: **CD11d-, MHC II+, Thy1+, E-cad-**
- Frozen sections: **CD1+, CD4+, CD11b+, CD11c+**
- Adhesion molecule upregulation involved in migratory capability and enhanced ability to present antigen to T cells: **(CD11b+), CD44+, VLA-4+, ICAM-1+, ICAM-3+**

Histiocytic Diseases

- **Histiocytoma/Langerhans Histiocytosis** - epidermal LHC proliferation with diverse biological behavior
- **Histiocytic Sarcoma/Malignant Histiocytosis** - aggressive neoplasia of DC
- **Hemophagocytic Histiocytic Sarcoma** - aggressive neoplasia of macrophages
- **Systemic (cutaneous) reactive Histiocytosis** - immuno-regulatory disorder of reactive proliferation of T cells and activated dermal interstitial DC

Cutaneous Histiocytoma

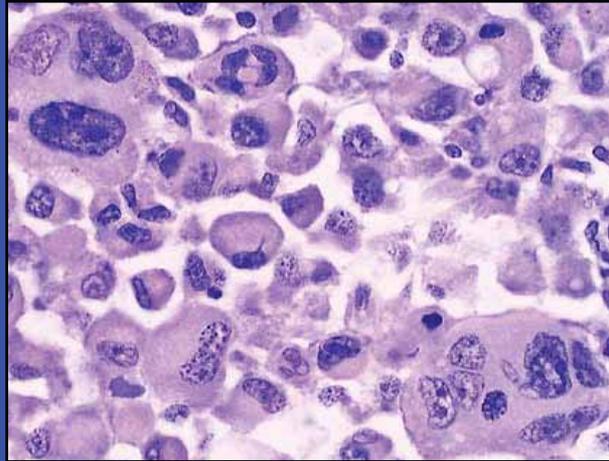


Langerhans Histiocytosis

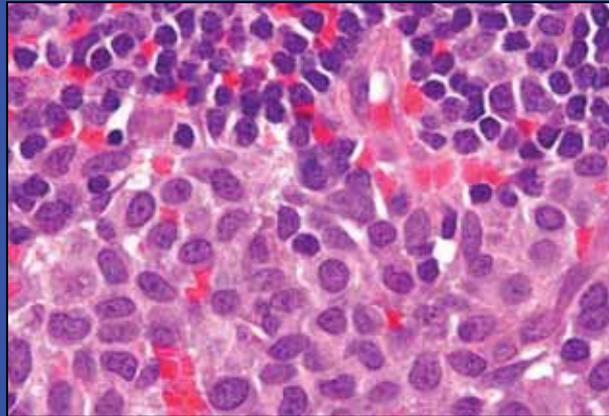
Langerhans DC

CD11c+ CD18+
MHC II+ CD11d-
E-cad+ Thy-1-

Histiocytic Sarcoma



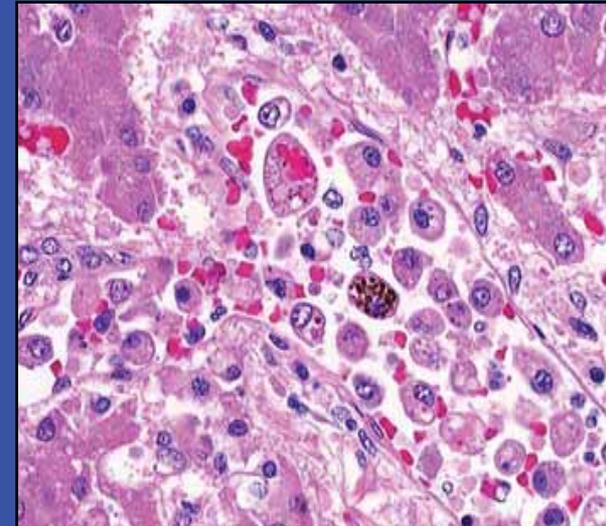
Reactive Histiocytosis



Interstitial DC

CD11c+ CD18+
MHC II+ CD11d-
E-cad-
Thy-1+, CD4+ (CH+SH)

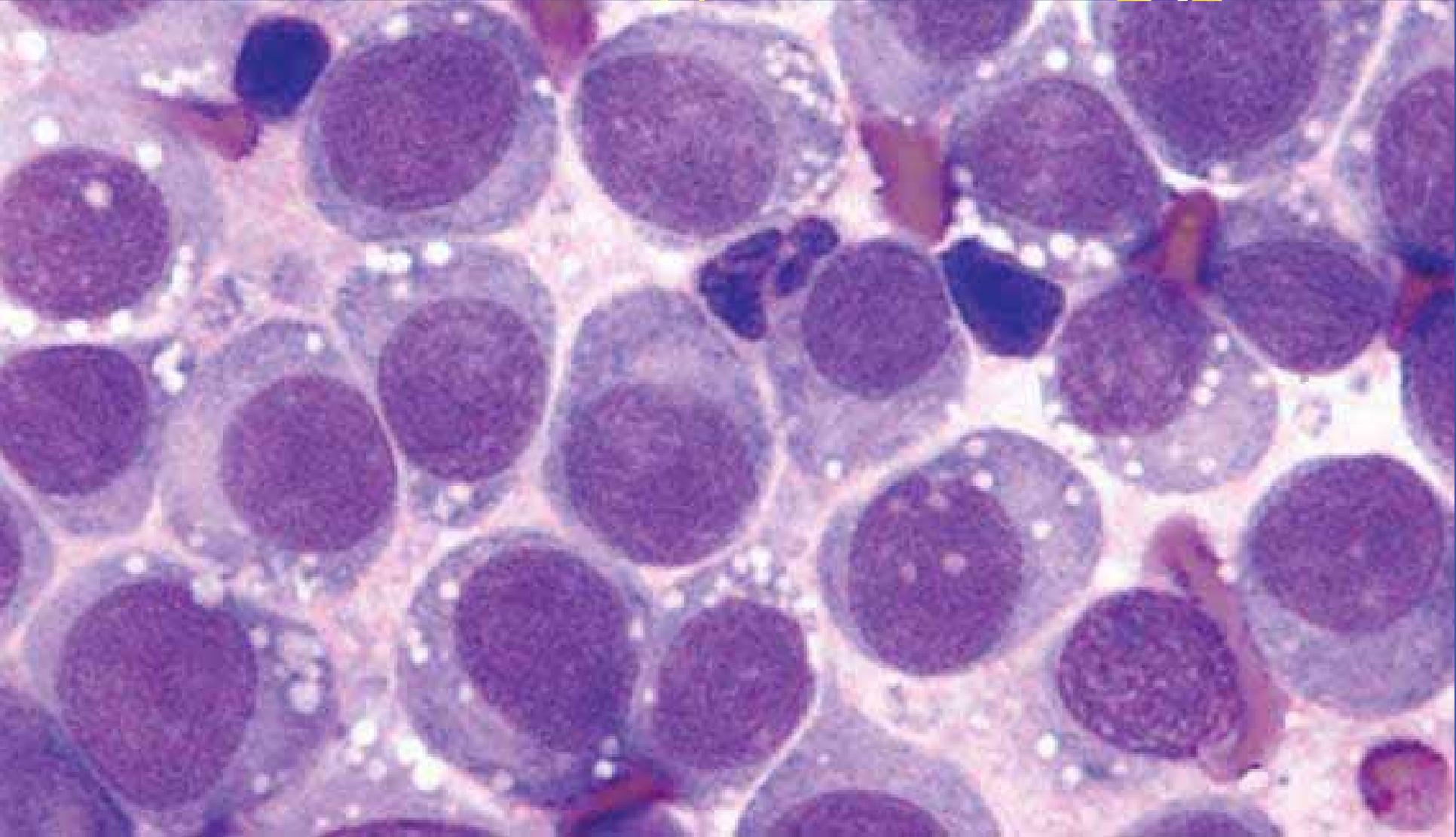
Hemophagocytic Histiocytic Sarcoma

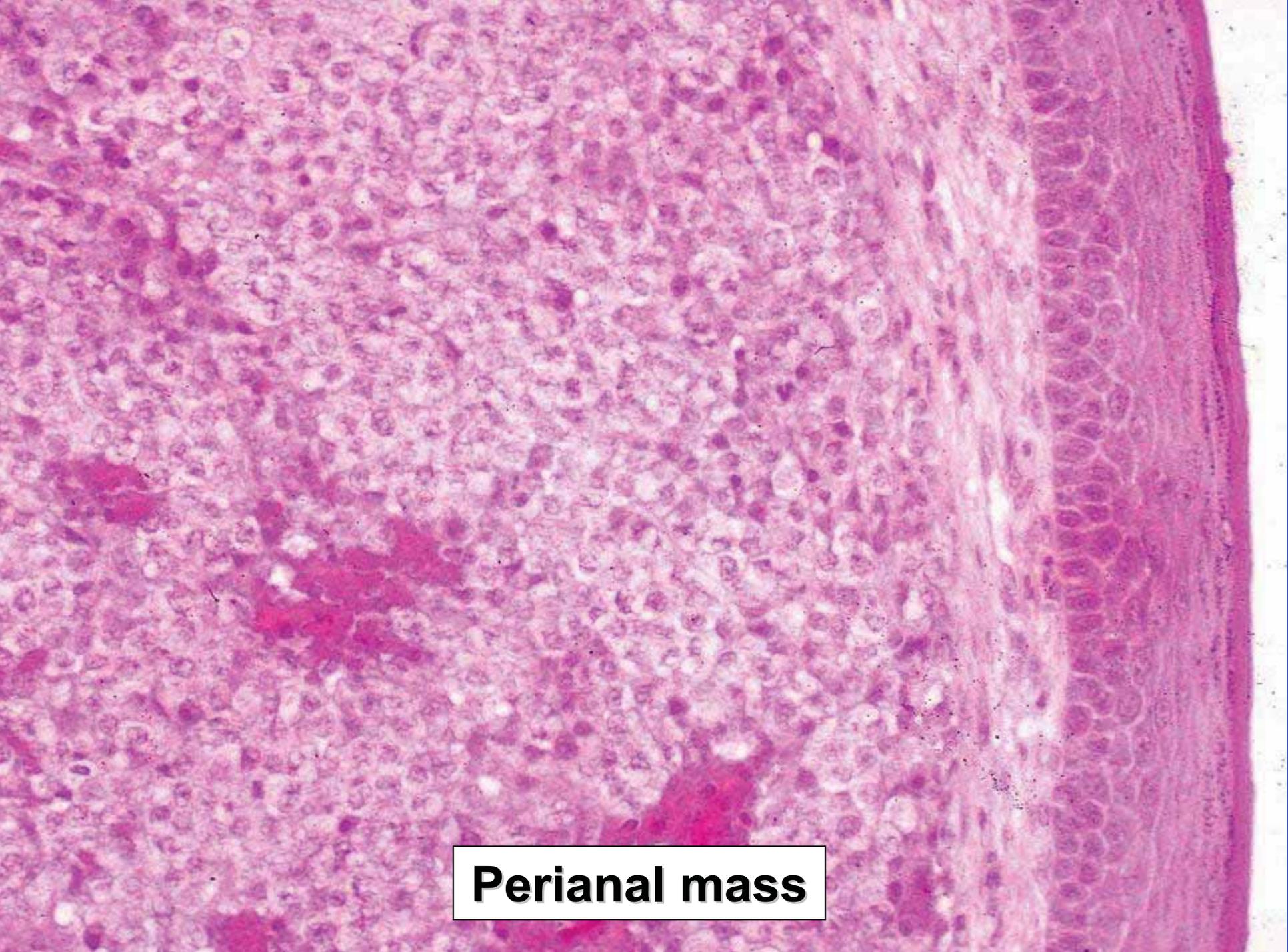


Macrophage

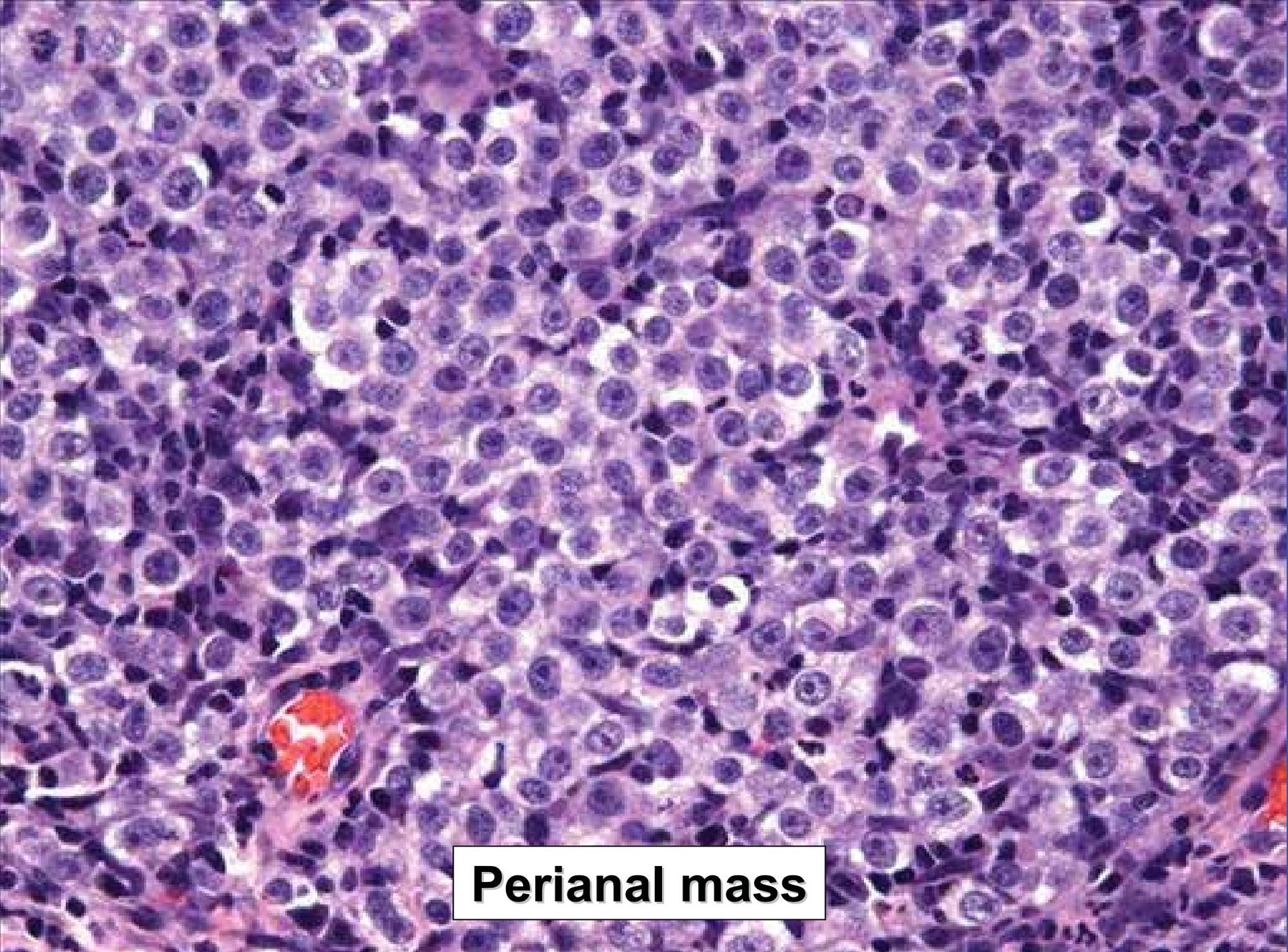
CD11c- CD18+
MHC II± CD11d+
E-cad- Thy-1-

Cutaneous Mass

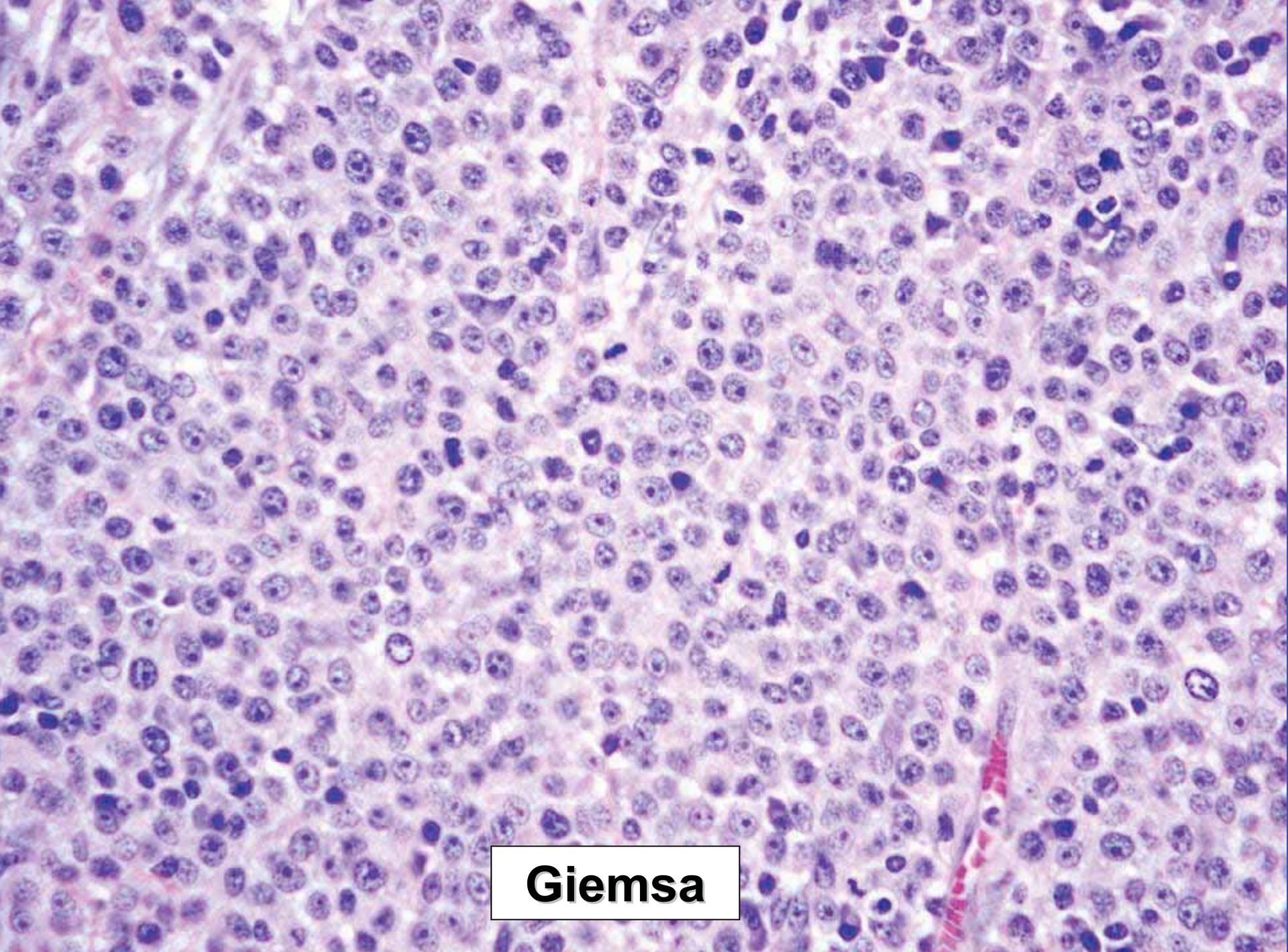




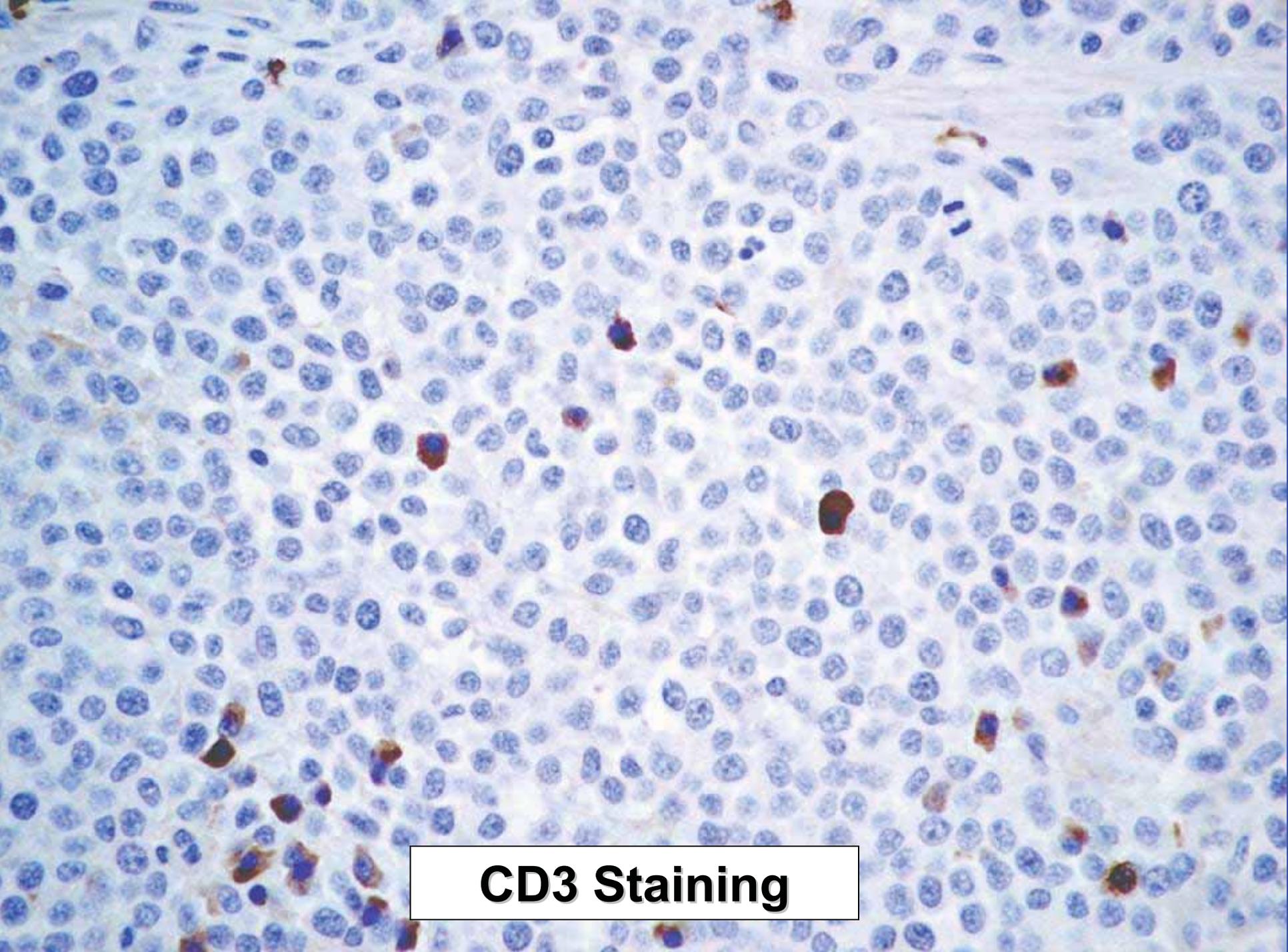
Perianal mass



Perianal mass



Giemsa



CD3 Staining