

High Grade Lymphomas in Extranodal Sites

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Extranodal Lymphomas

Risk Factors

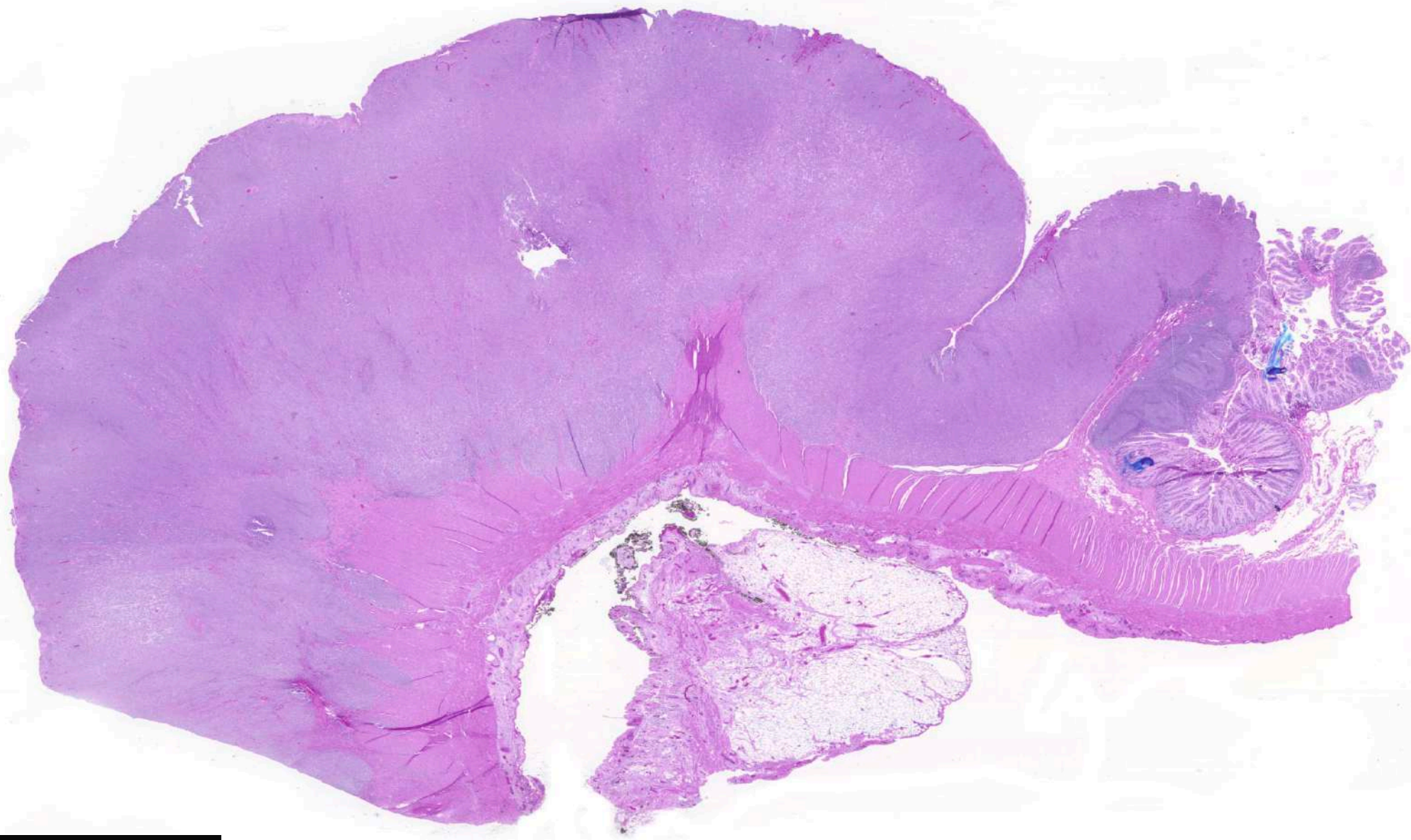
- **Helicobacter pylori (gastric marginal zone lymphoma (MZL))**
- **Campylobacter jejuni (IPSID)**
- **Chlamydia psittaci (some orbital MZL)**
- **Autoimmune disease**
- **Celiac disease (EATL)**
- **HIV/AIDS**
- **Organ transplant (PTLD)**
- **Hepatitis C virus**
- **IgG4-related disease (?)**
- **Longstanding chronic inflammation**
- **Breast implants (?)**

High Grade Extranodal Lymphomas

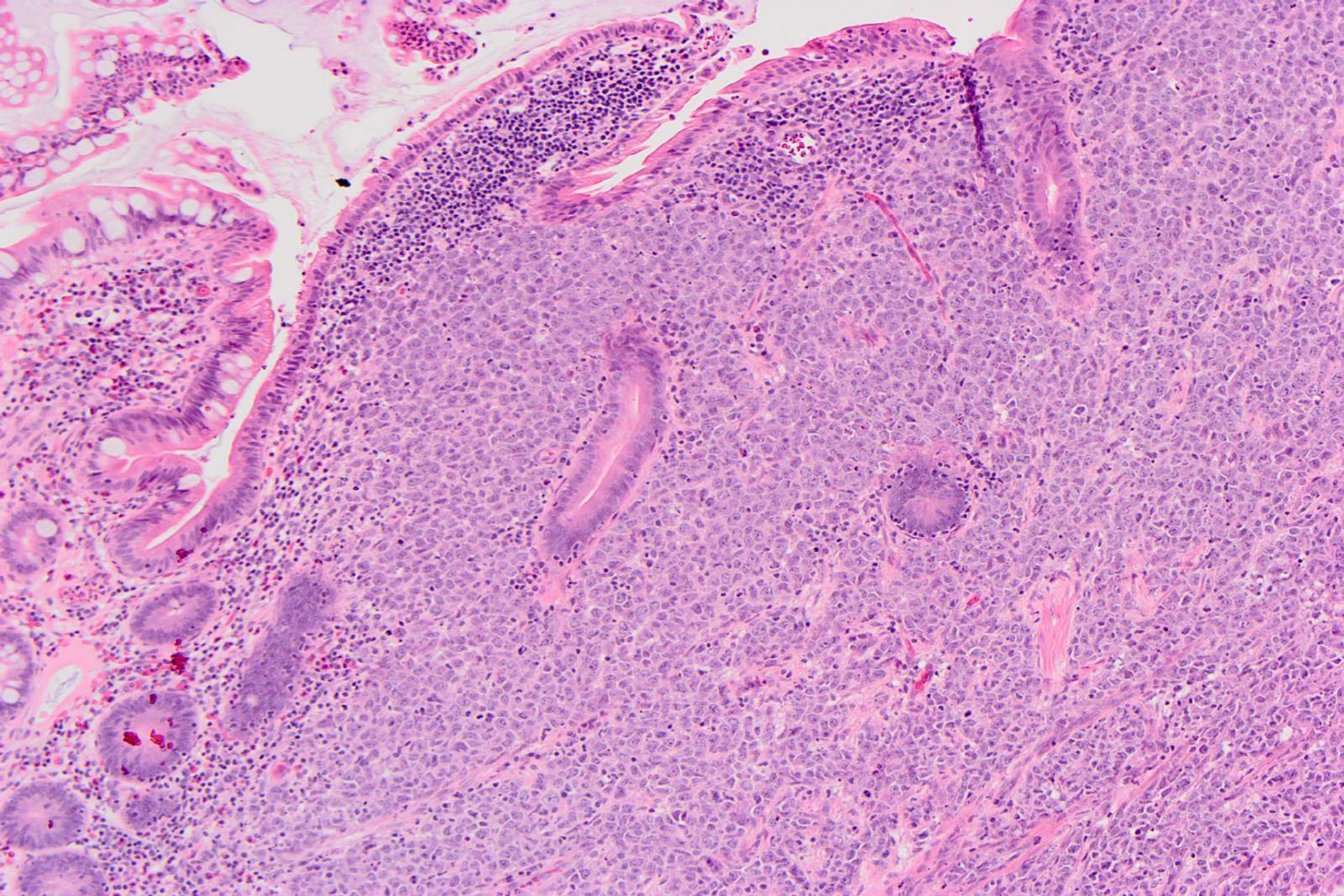
- **B-, T-, and NK-lineage**
- **Focus on lymphomas:**
 - **Recent updates**
 - **Causing problems in differential diagnosis**

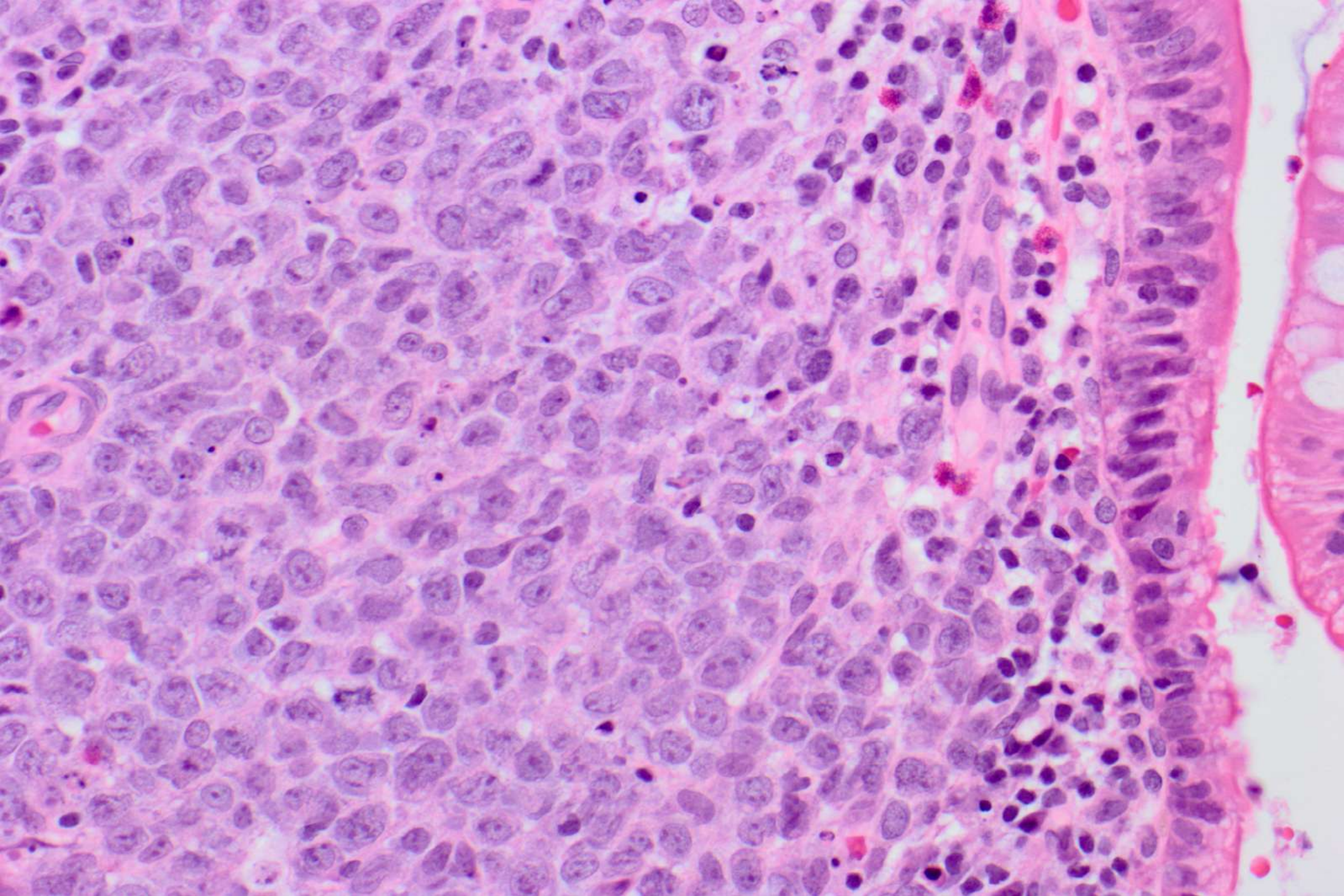
DIFFUSE LARGE B-CELL LYMPHOMA

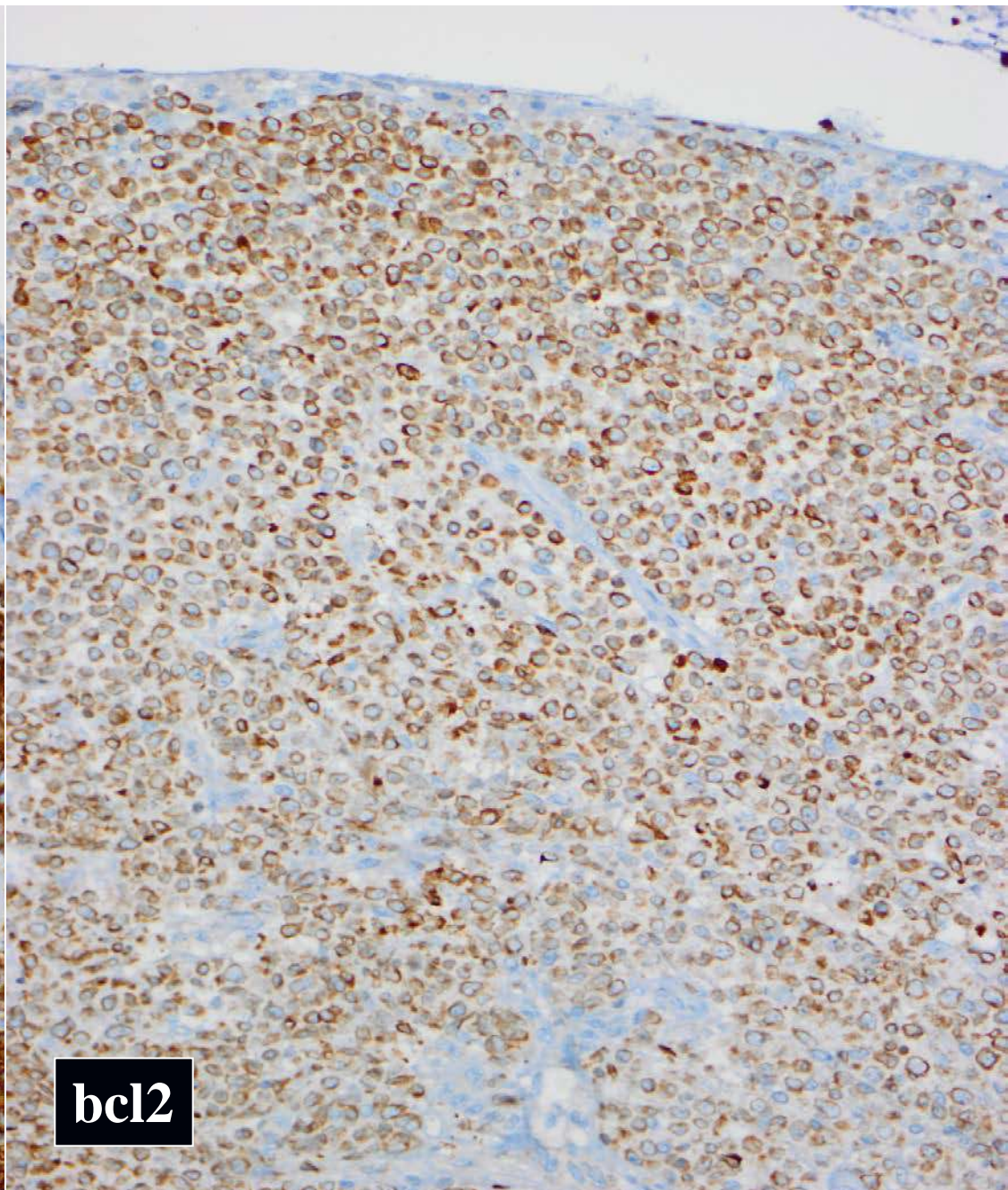
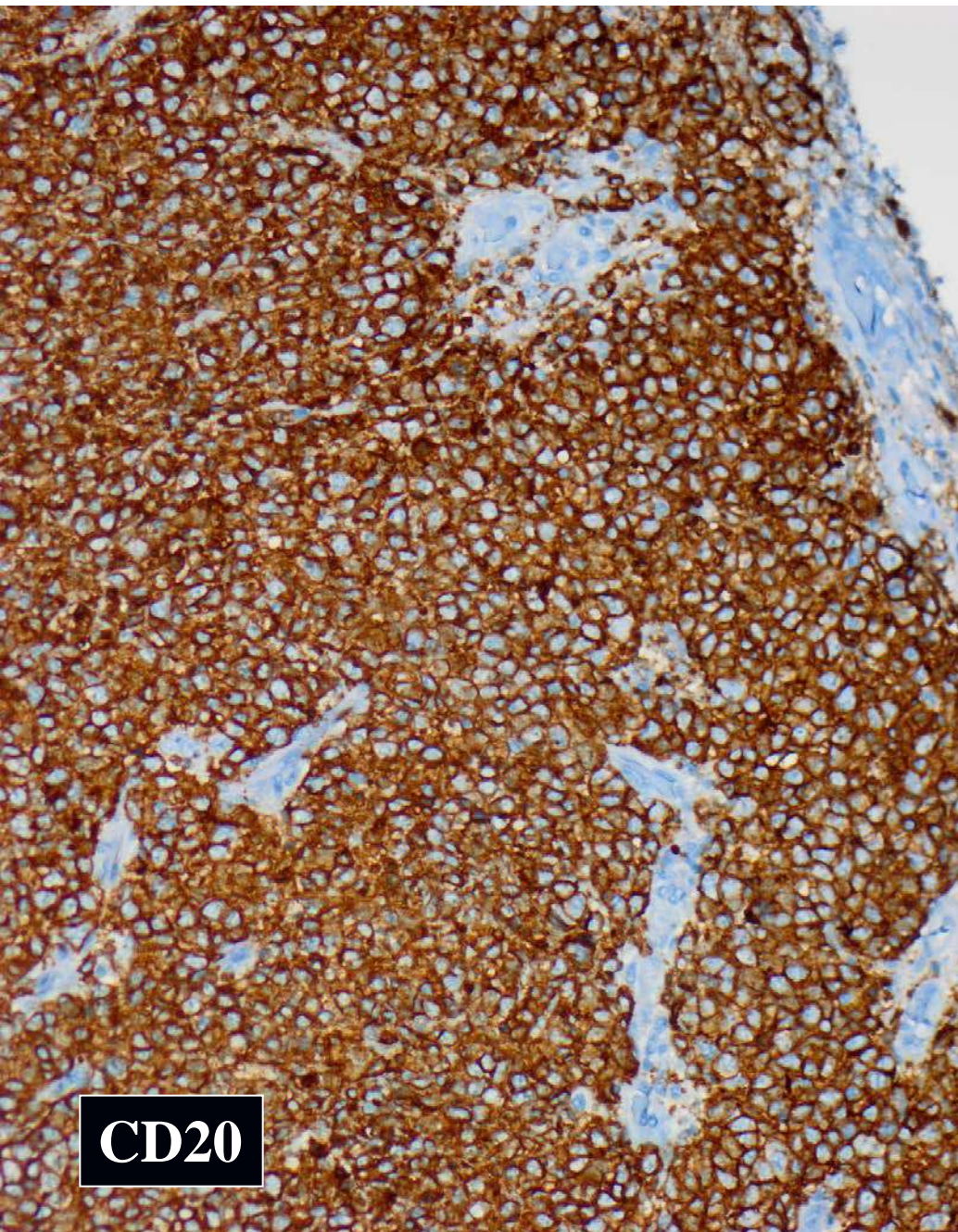
- **Most common extranodal lymphoma overall**
- **Almost all lymphomas are DLBCL in CNS, testis, bone, paranasal sinuses**
- **DLBCL is common among lymphomas of GI tract, Waldeyer's ring, breast, skin...**
- **Older adults most often, children & young adults also**
- **Most common HIV-associated lymphoma**
- **Stage I/II in most cases**
- **Centroblasts, immunoblasts, large bizarre cells**
- **sIg+ (or Ig-), pan B+, bcl-6+/-, bcl-2+/-, CD10-/+**
- **Outcome: overall better than 1° nodal DLBCL (better for GI, bone, others; worse for CNS, testicular primaries)**



DLBCL, nos





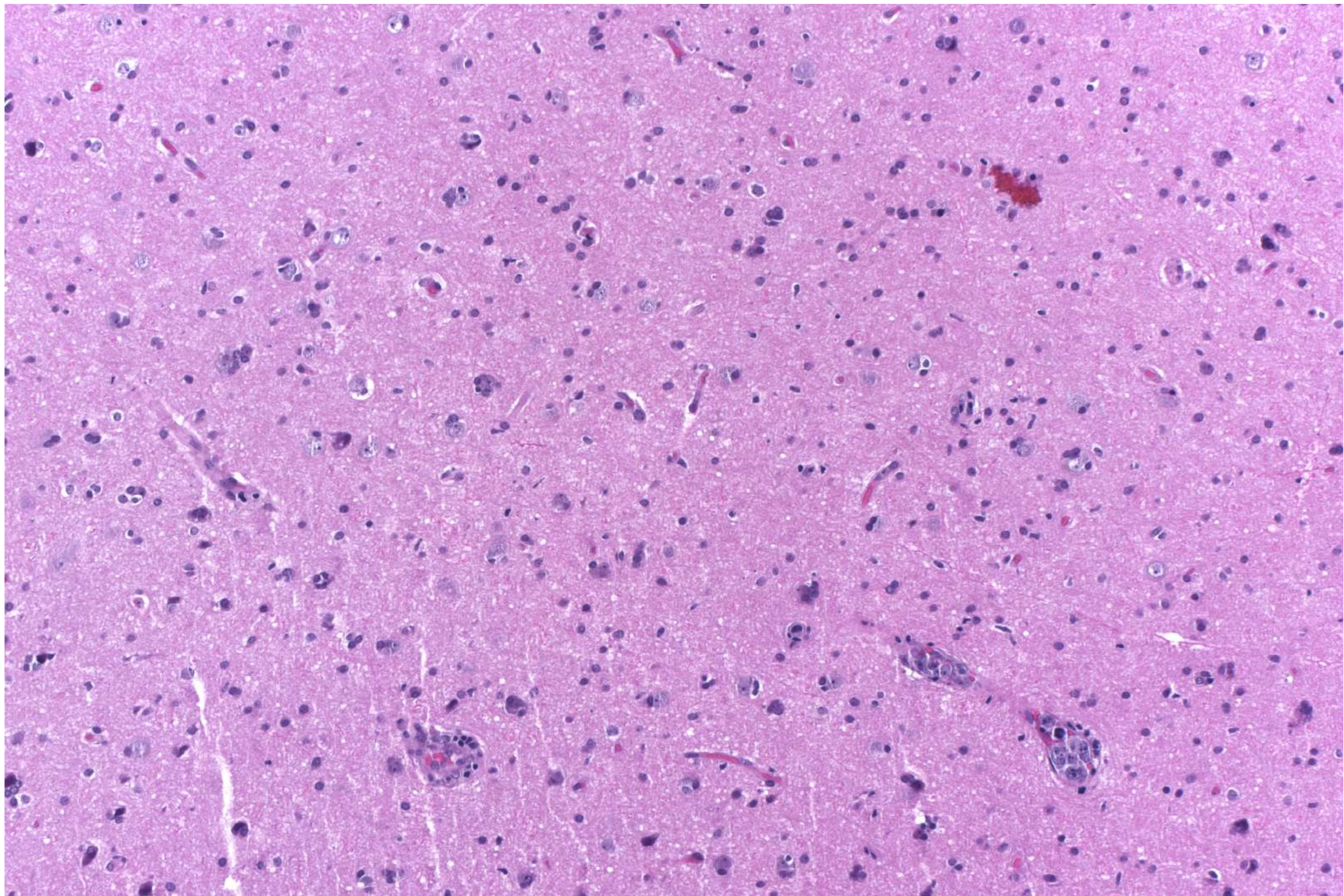


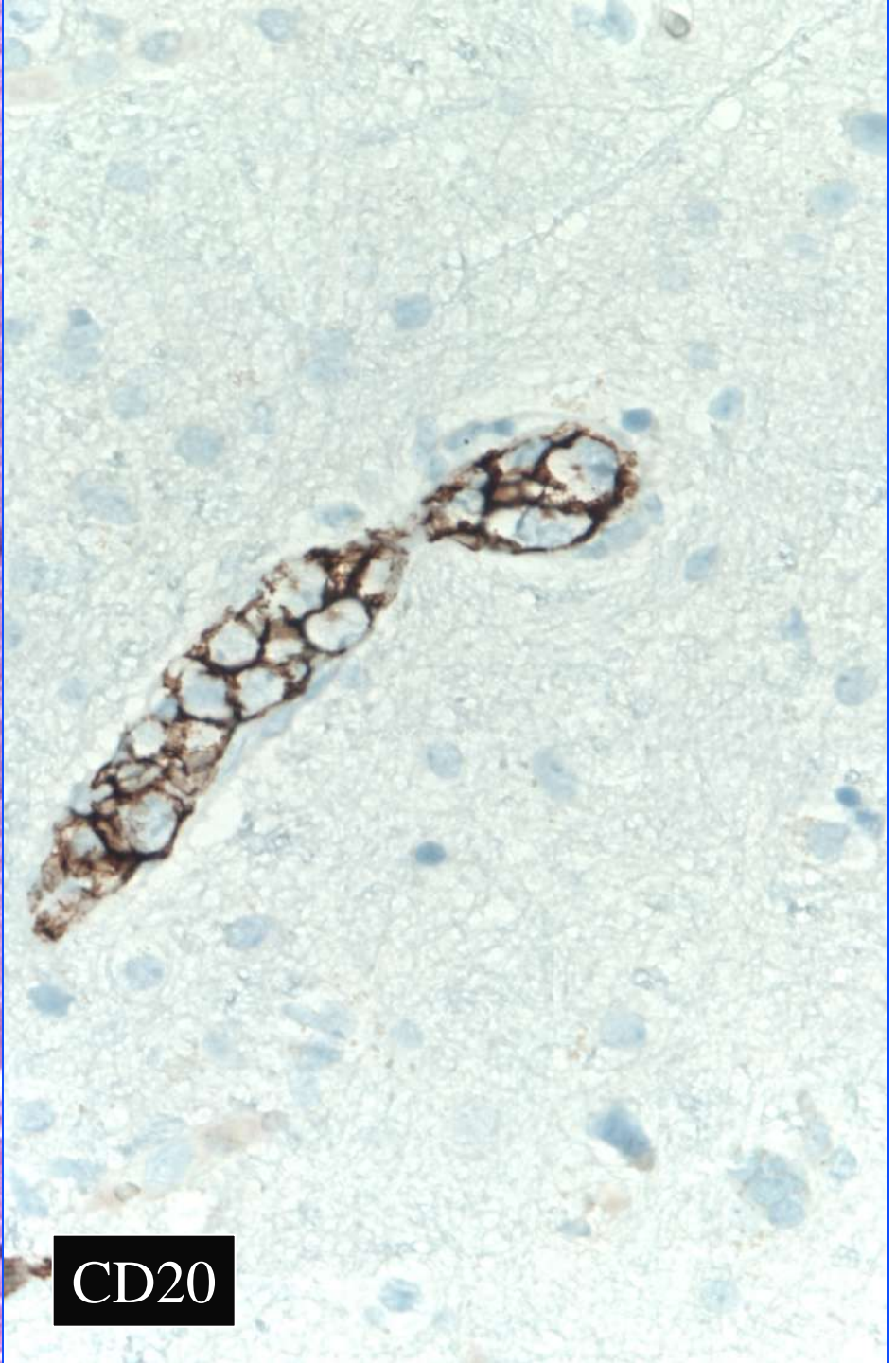
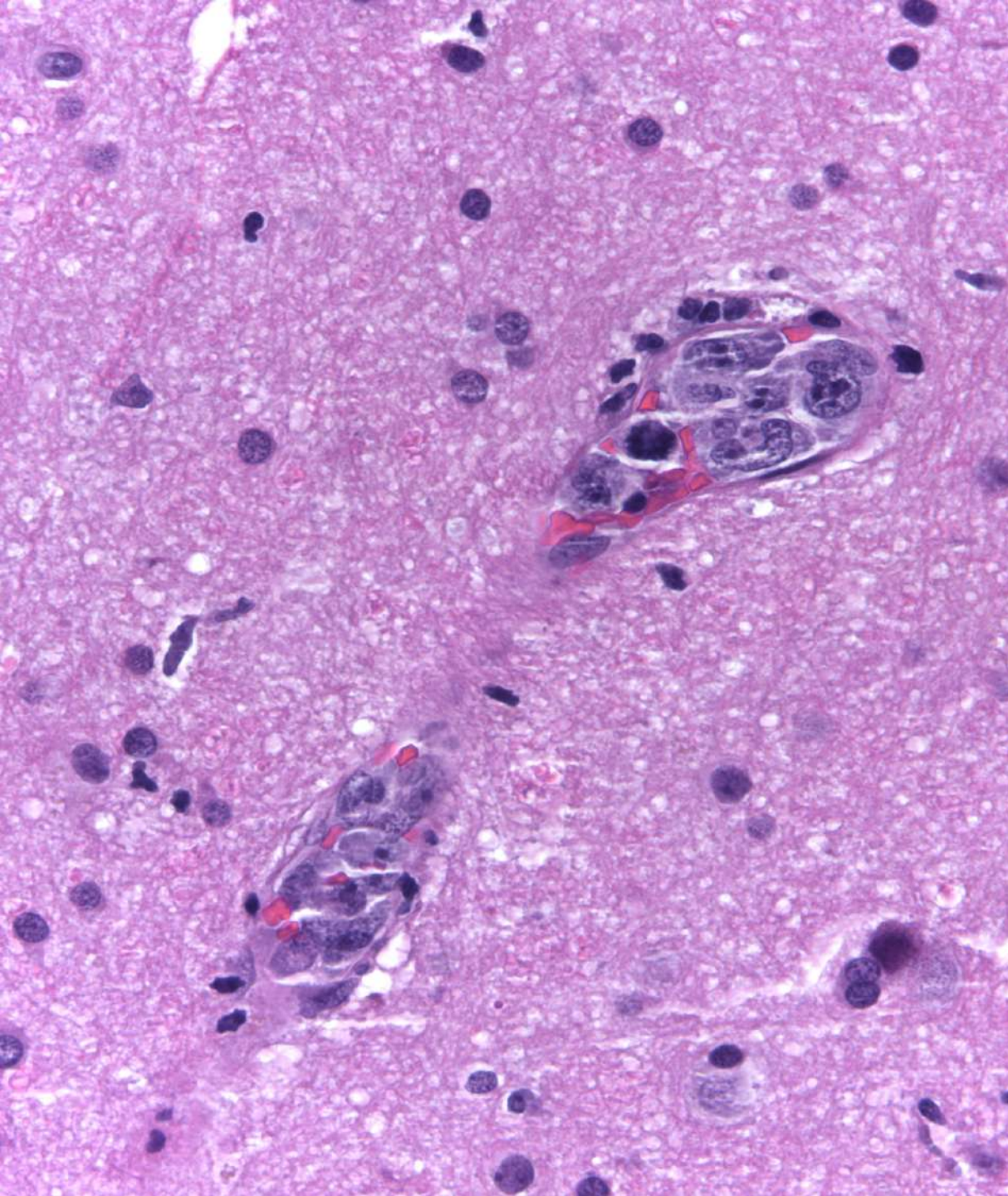
INTRAVASCULAR LARGE B-CELL LYMPHOMA

- **aka: malignant angioendotheliomatosis, angiotropic lymphoma**
- **Middle-aged to older adults**
- **Only rarely associated with immunodeficiency**
- **Symptoms are protean, related to vascular obstruction in a wide variety of extranodal sites: CNS, kidneys, adrenals, lungs, skin**
- **Usually no mass, delayed diagnosis common**
- **High mortality; better prognosis with prompt therapy for lymphoma**
- **Pathogenesis: homing receptor defect?**

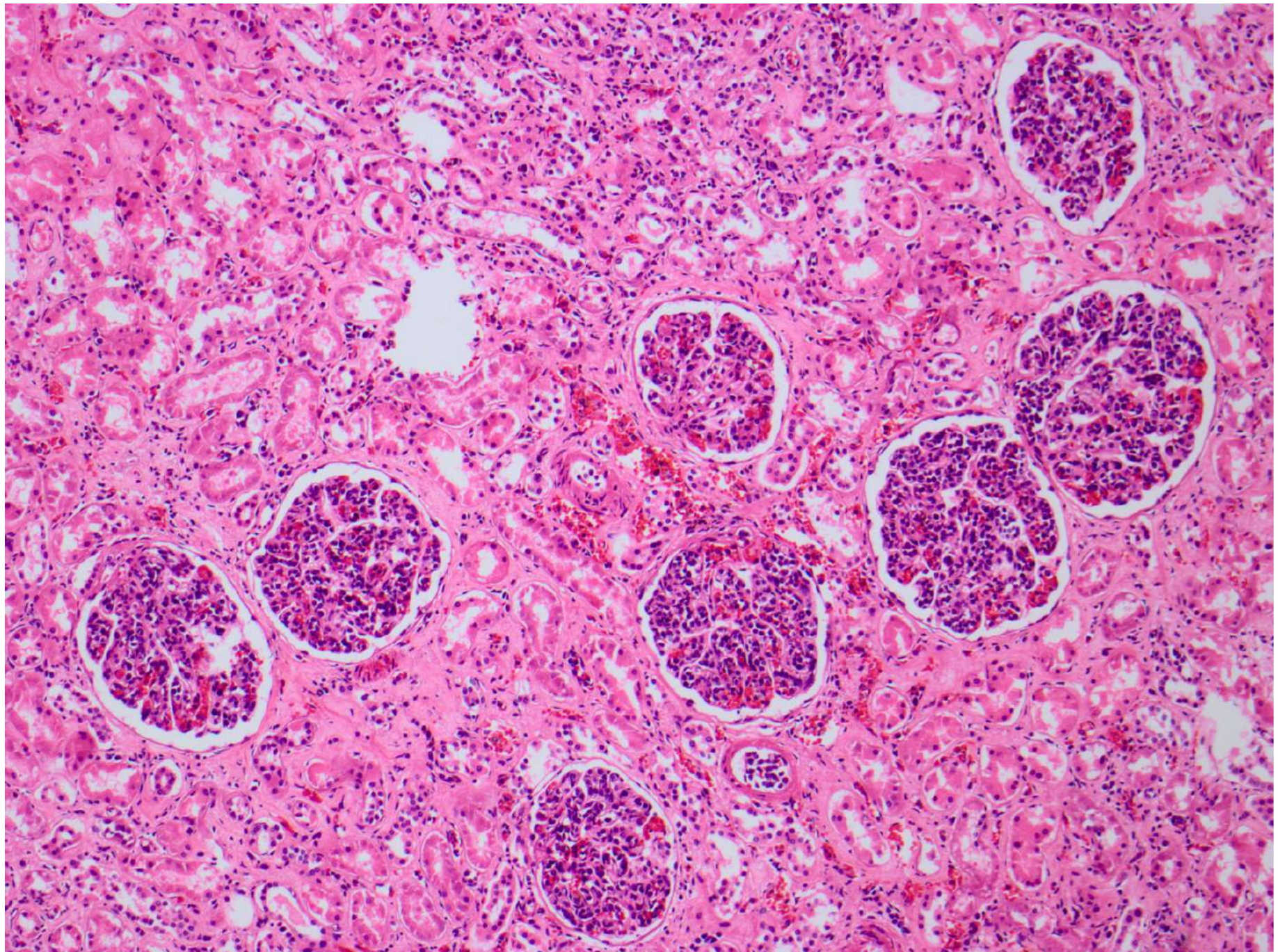
INTRAVASCULAR LARGE B-CELL LYMPHOMA: VARIANTS

- **Asian variant (in contrast to classical form or Western variant):**
 - **Nearly all patients are Asian**
 - **Presentation with hepatosplenomegaly**
 - **Sites involved: liver, spleen, bone marrow, lung, adrenals...**
 - **Uncommonly involved: CNS, skin**
- **Cutaneous variant:**
 - **Confined to dermis and subcutis at presentation**
 - **Better prognosis**

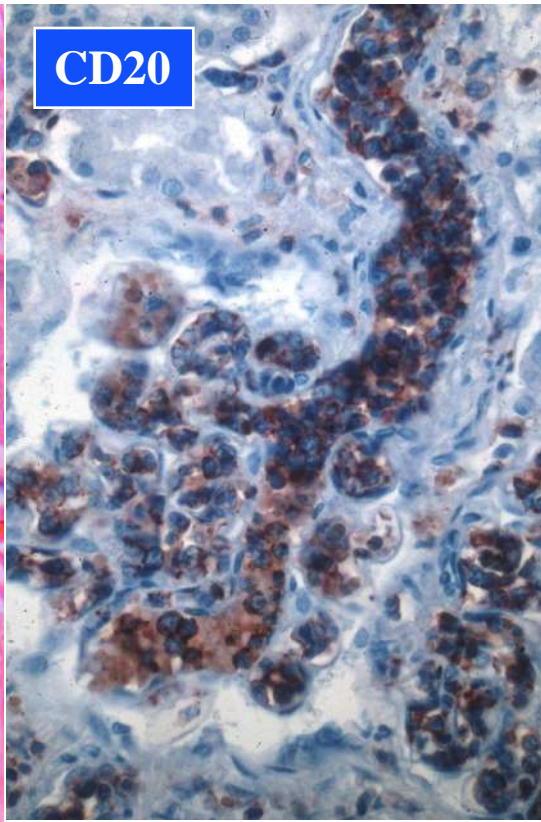
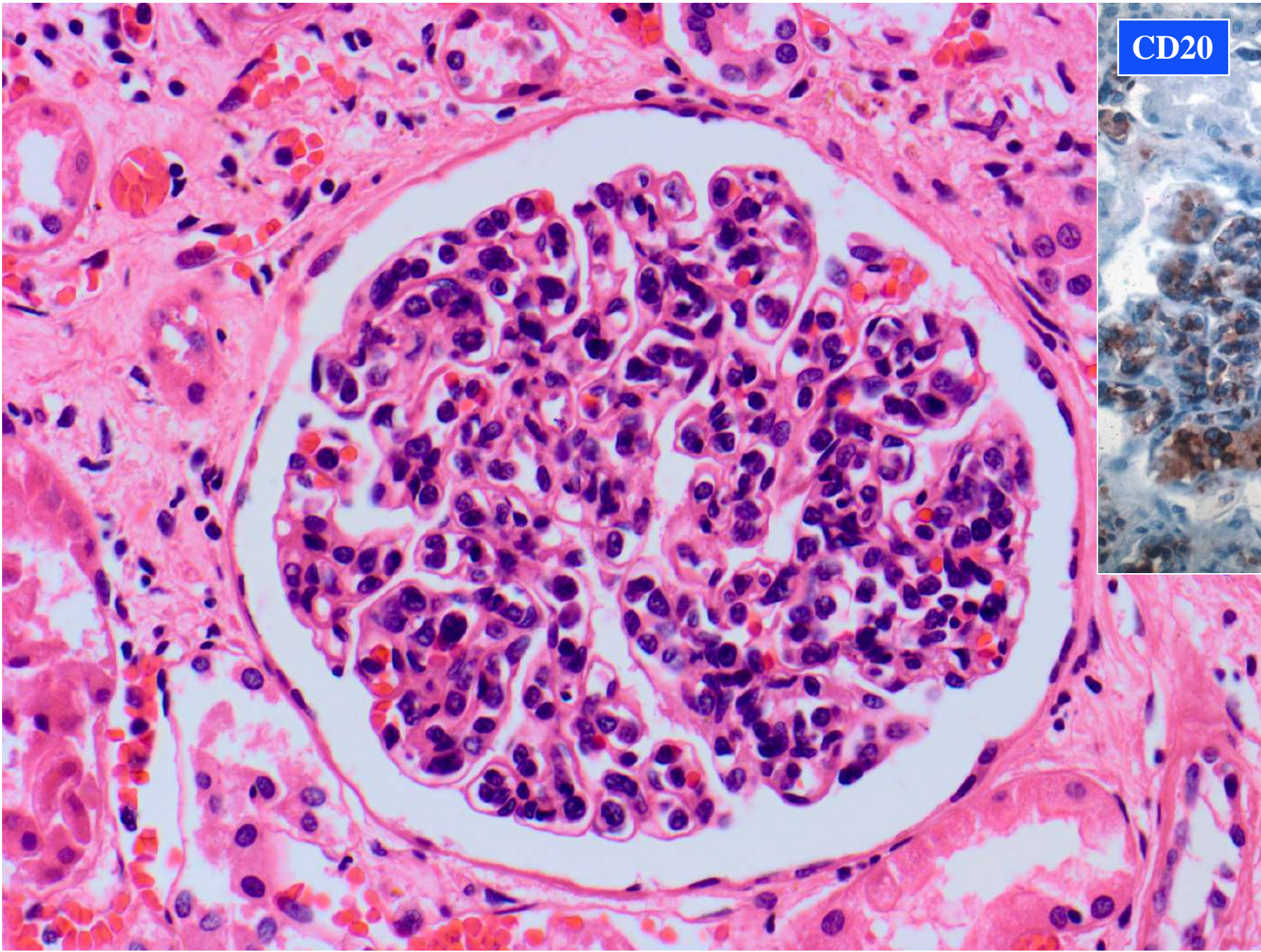


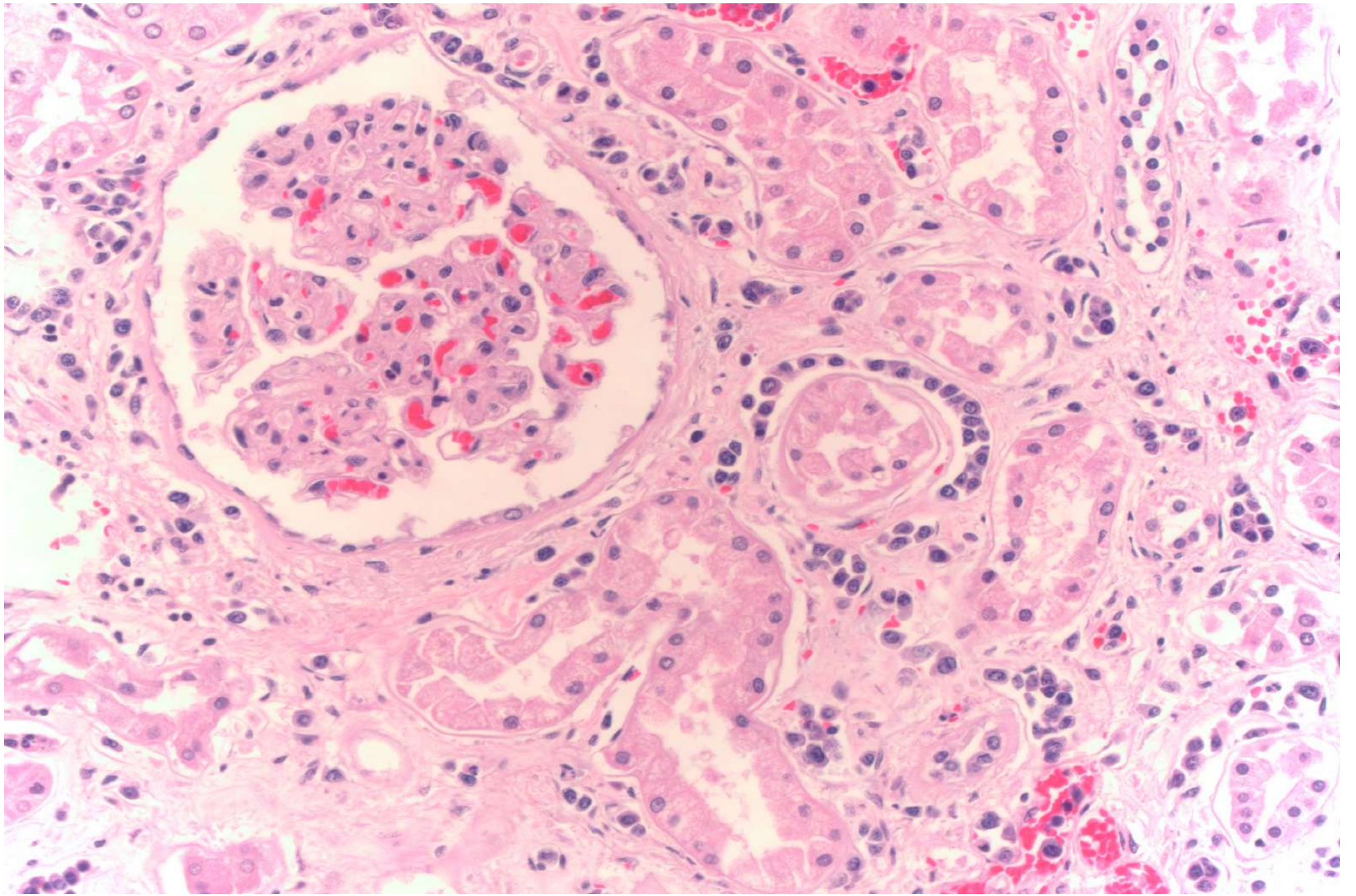


CD20



CD20

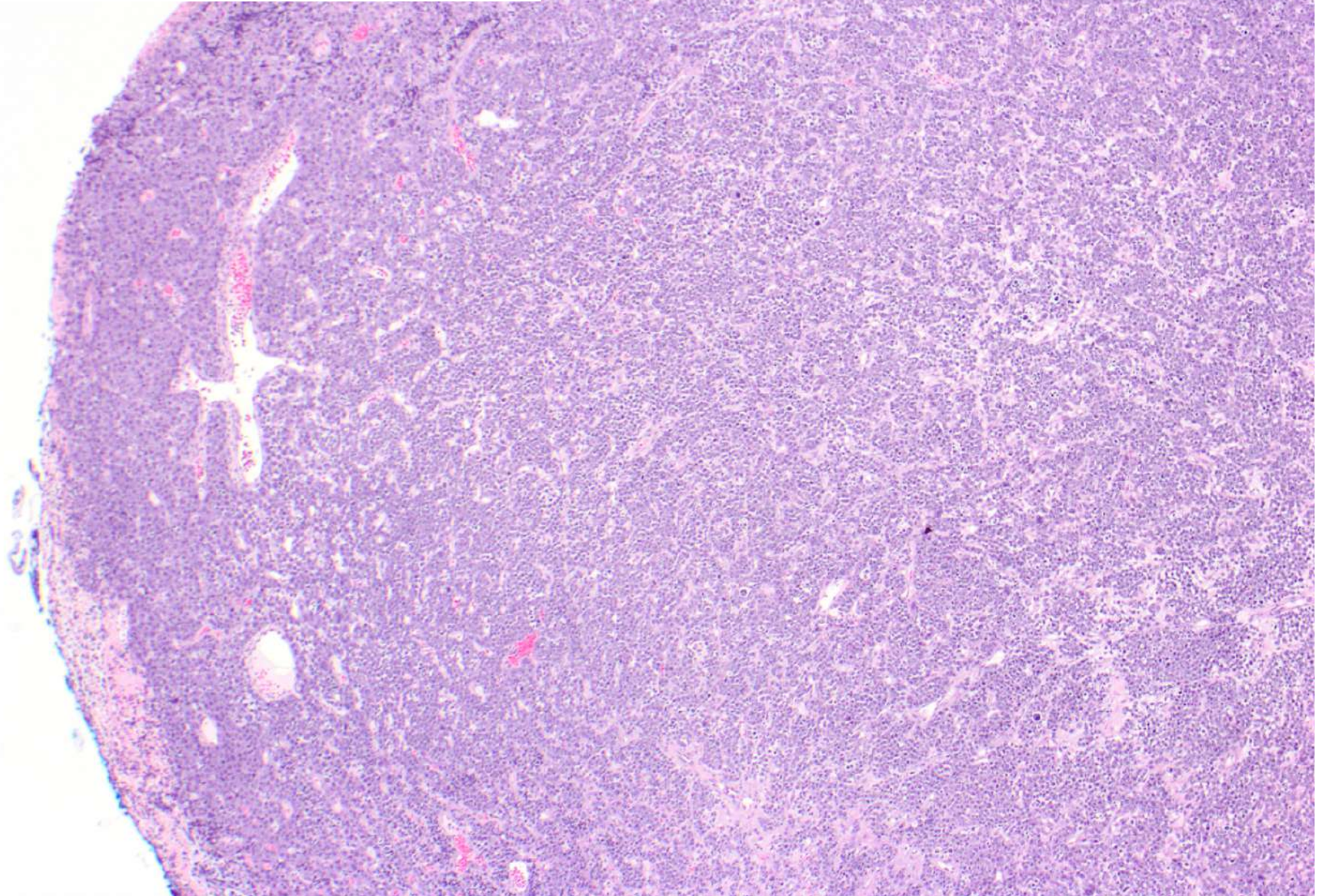


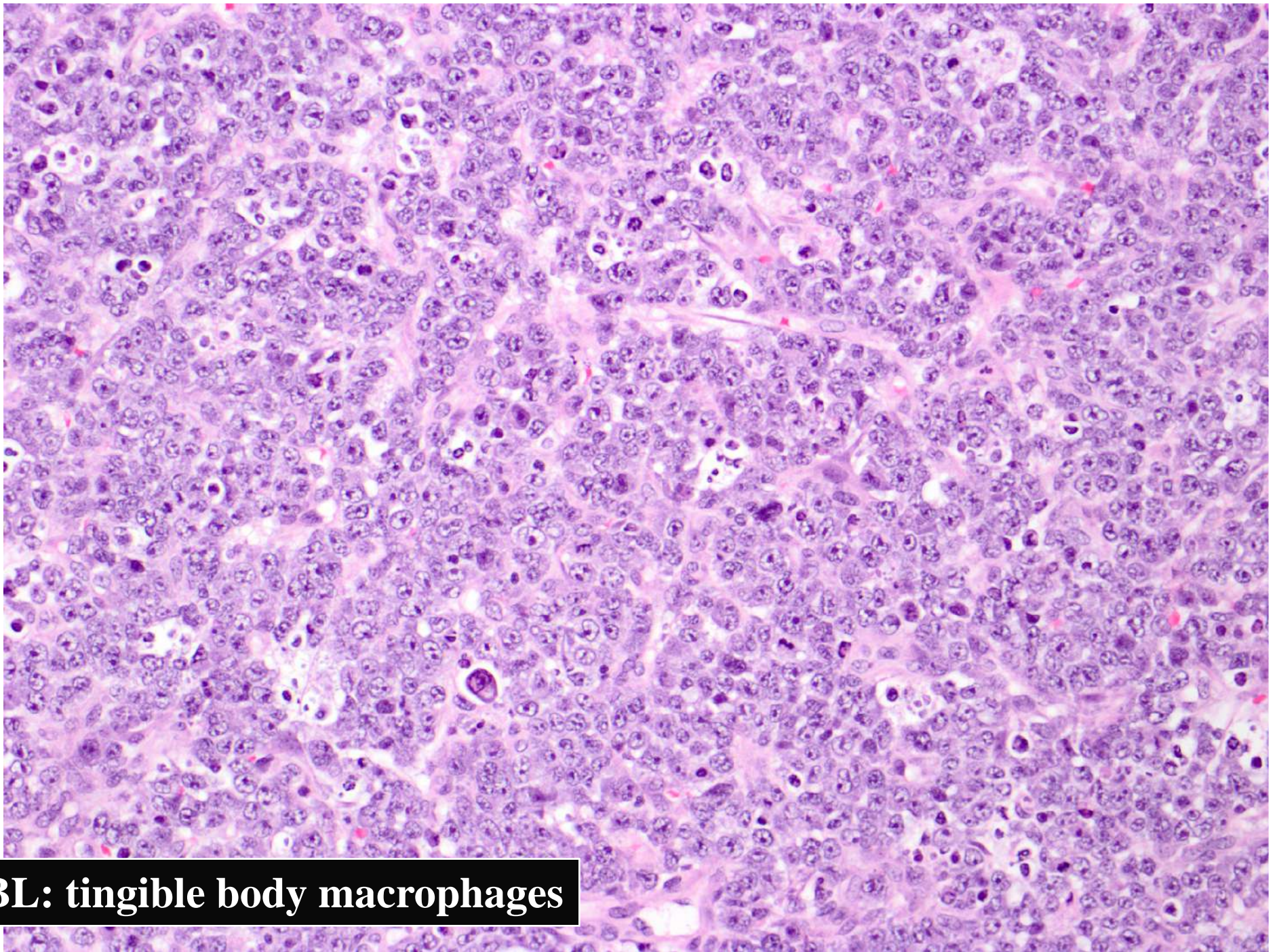


PLASMABLASTIC LYMPHOMA

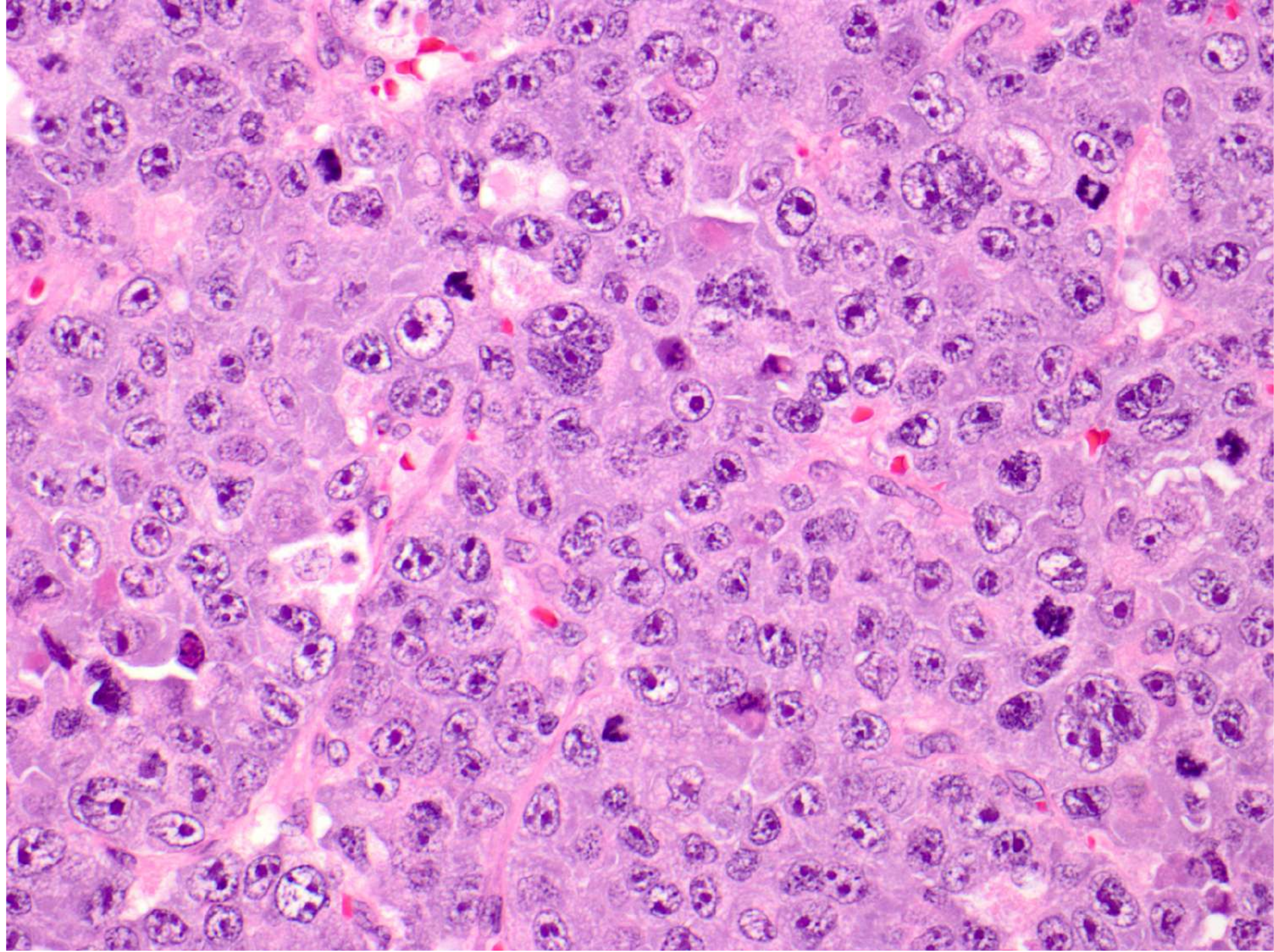
- Most patients immunosuppressed (most HIV+)
- Oral cavity, GI tract, other extranodal sites, lymph nodes
- Plasmacytoid immunoblasts, some monomorphic, some with more obvious plasmacytic differentiation
- Plasma cell phenotype: CD45-/+ , CD20- , CD138+ , MUM1/IRF4+ , high Ki67 , cIg+/- (κ or λ)
- EBV+ : Majority ; HHV8- ; *MYC* rearrangement common
- Poor prognosis
- Differential: DLBCL nos, plasma cell neoplasm, non-hematologic neoplasm

**Adult male with colonic polyps:
Plasmablastic lymphoma**

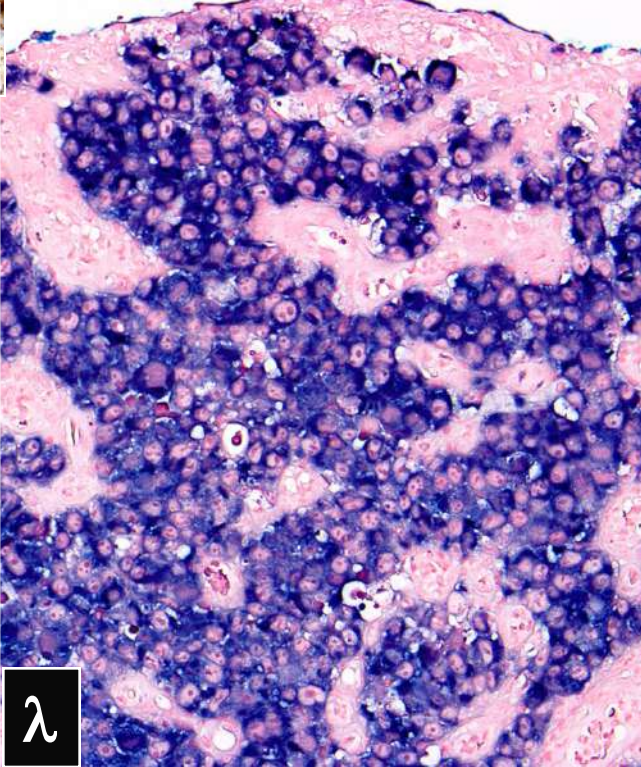
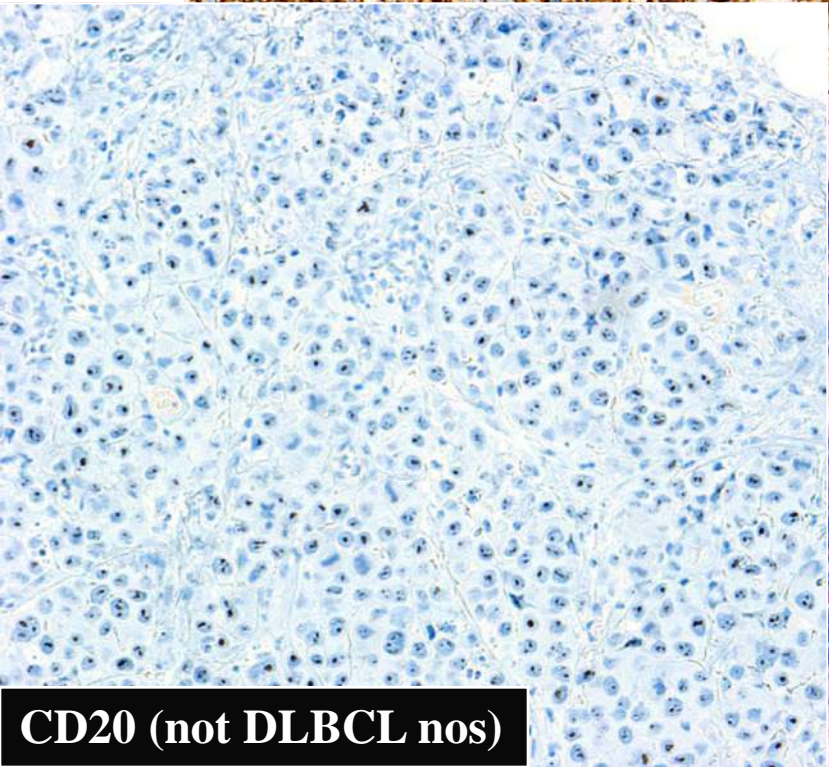
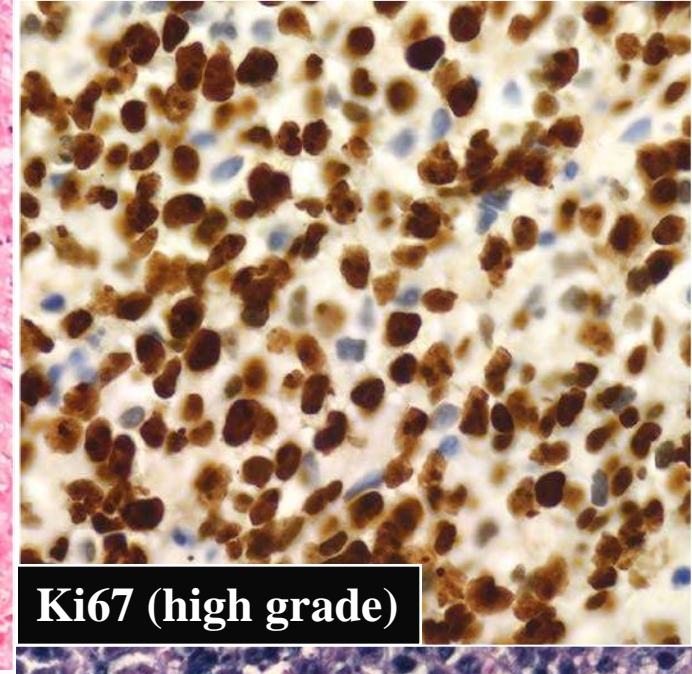
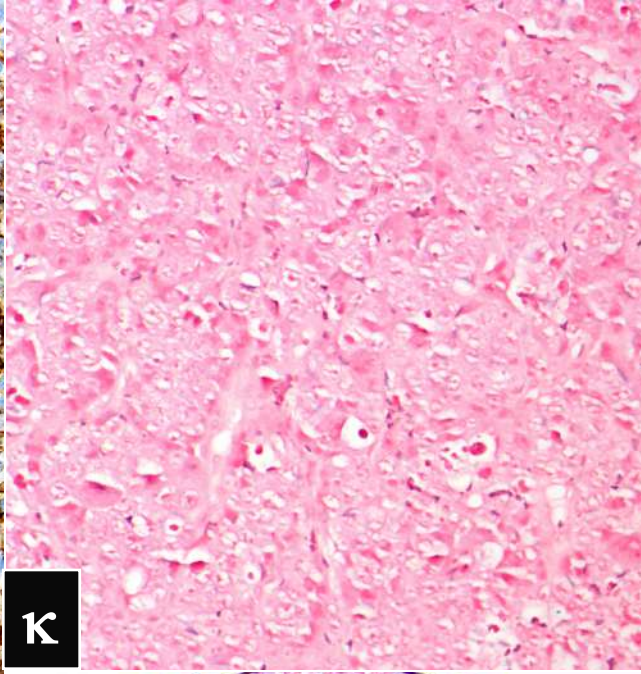
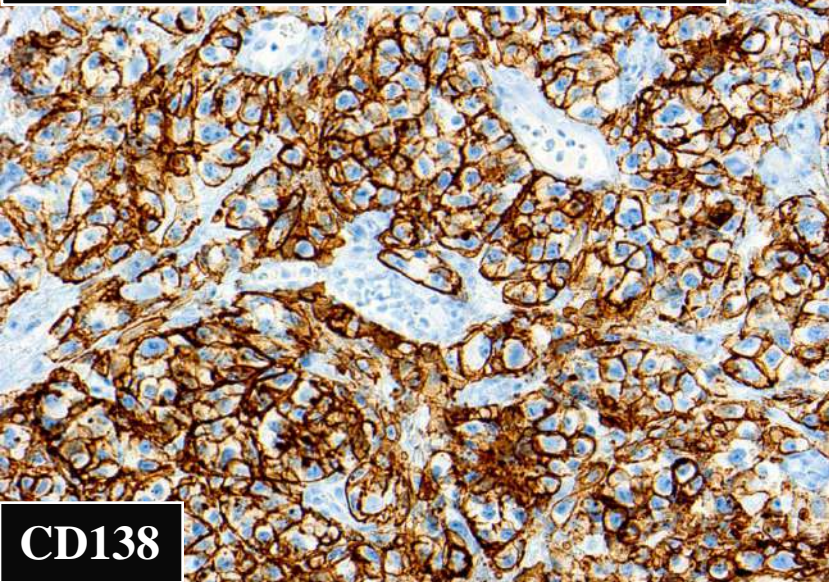




PBL: tingible body macrophages



Plasmablastic lymphoma



DLBCL with Chronic Inflammation

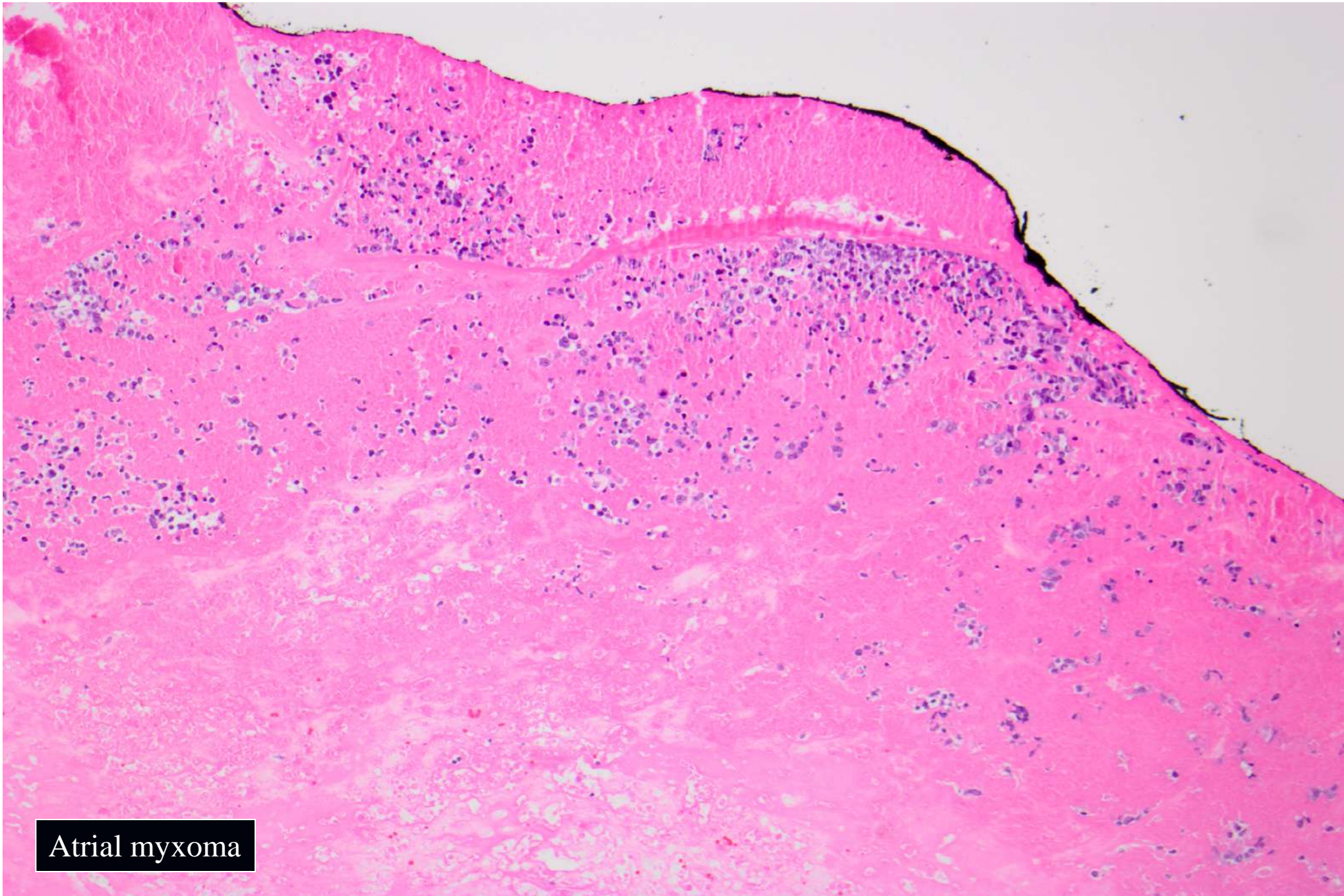
- **Long-standing, severe CI (> 10 years) in variety of extranodal sites:**
 - **Tend to occur in closed spaces**
 - **Local immune dysregulation, decreased immune surveillance**
 - **Promotes EBV+ B-cell proliferation**
- **Accepted associations:**
 - **Iatrogenic pneumothorax for TB with pyothorax**
 - **Osteomyelitis**
 - **Metal implant**
 - **Venous stasis ulcer**
- **Suggested associations**
 - **Cardiac replacement valves**
 - **Atrial myxoma**
 - **Splenic pseudocyst**
 - **Long-standing hydrocele**

EBV+ DLBCL with CI

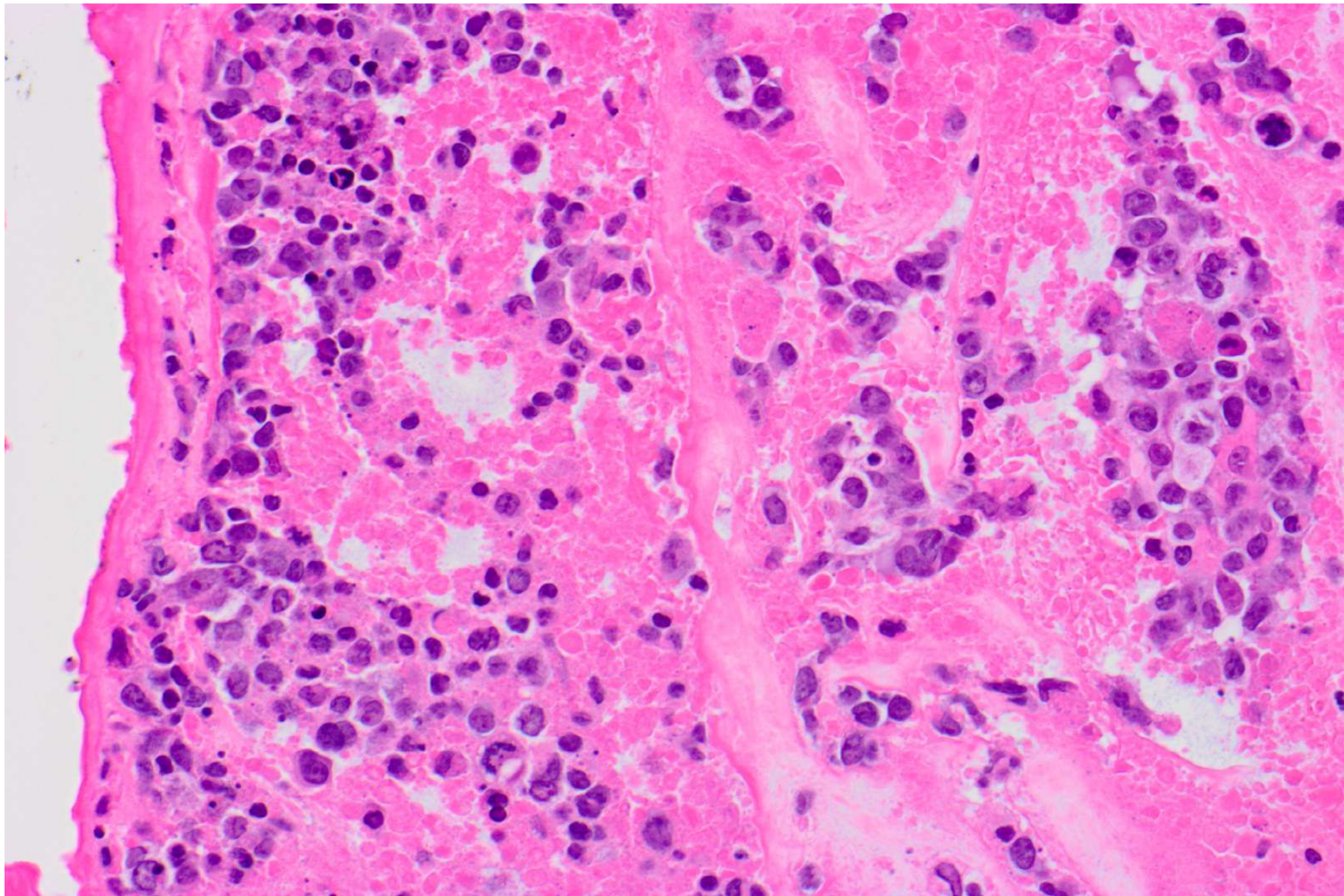
- **Centroblastic, immunoblastic, some plasmacytoid**
- **Necrosis, angiocentric growth may occur**
- **CD20 usually+, CD10-, bcl6-/+ , MUM1/IRF4+, CD30+/-, EBER+**
- **Non-germinal center phenotype**
- **Localized disease**
- **Poor prognosis (better for cardiac cases?)**

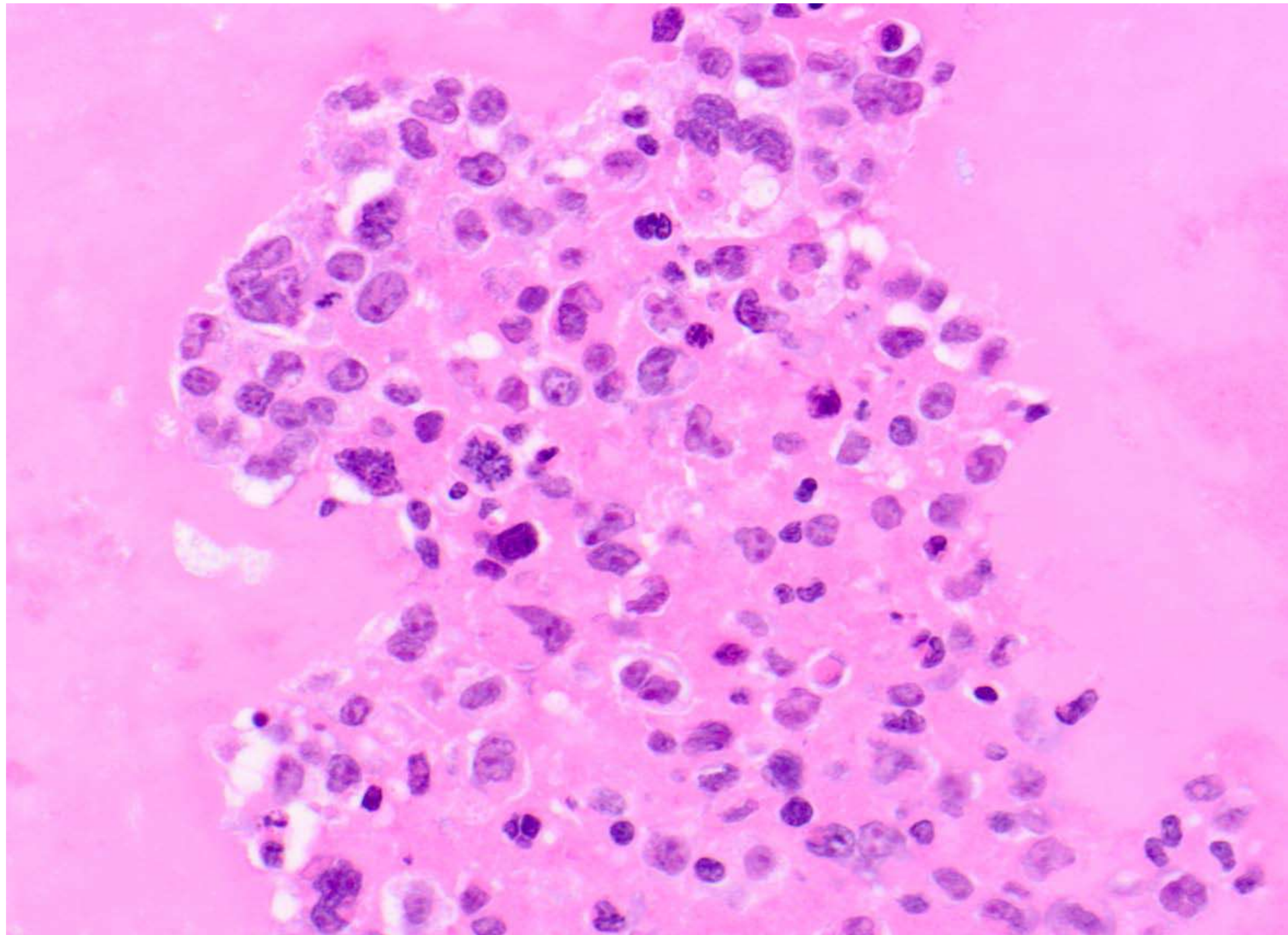
55-year-old female with atrial myxoma

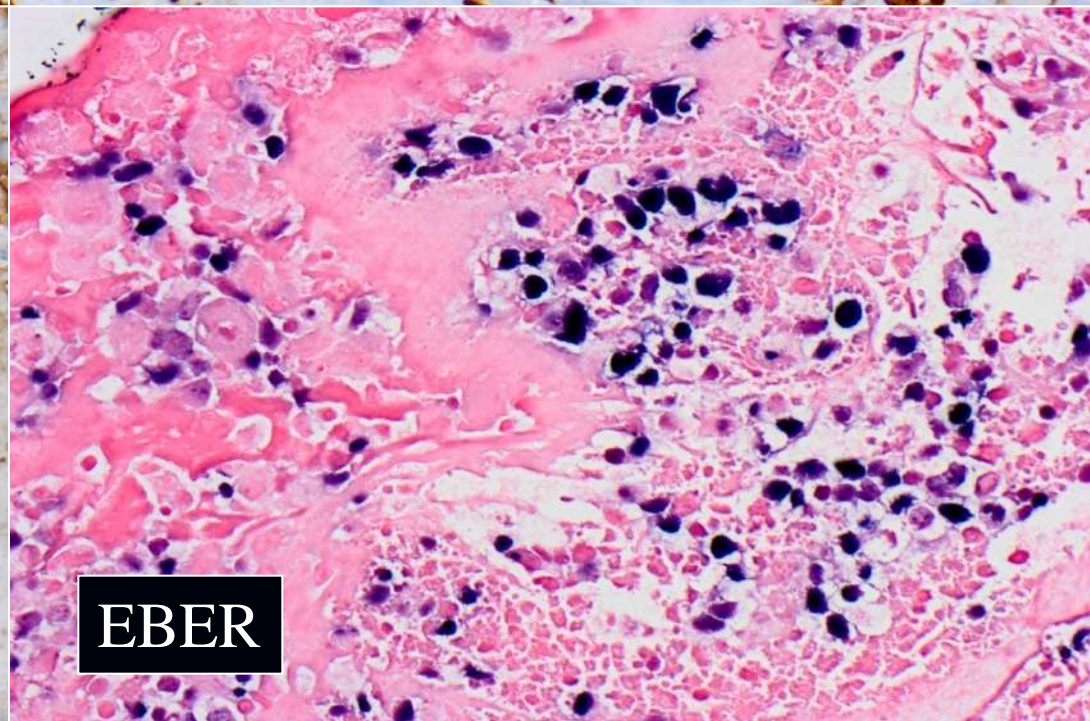
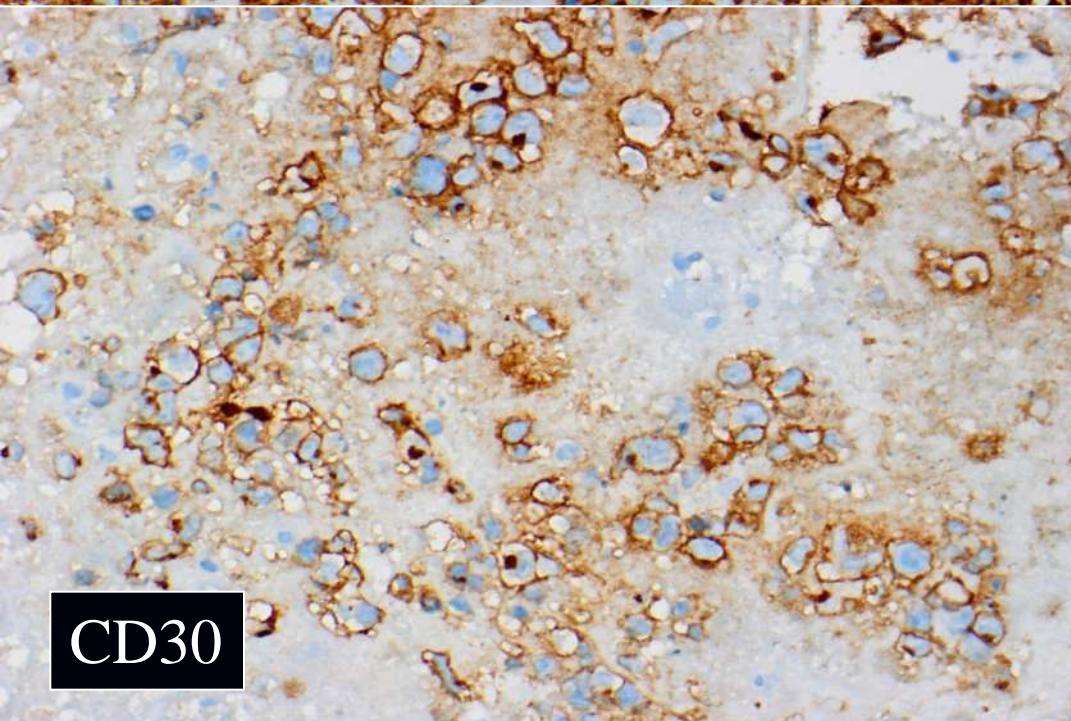
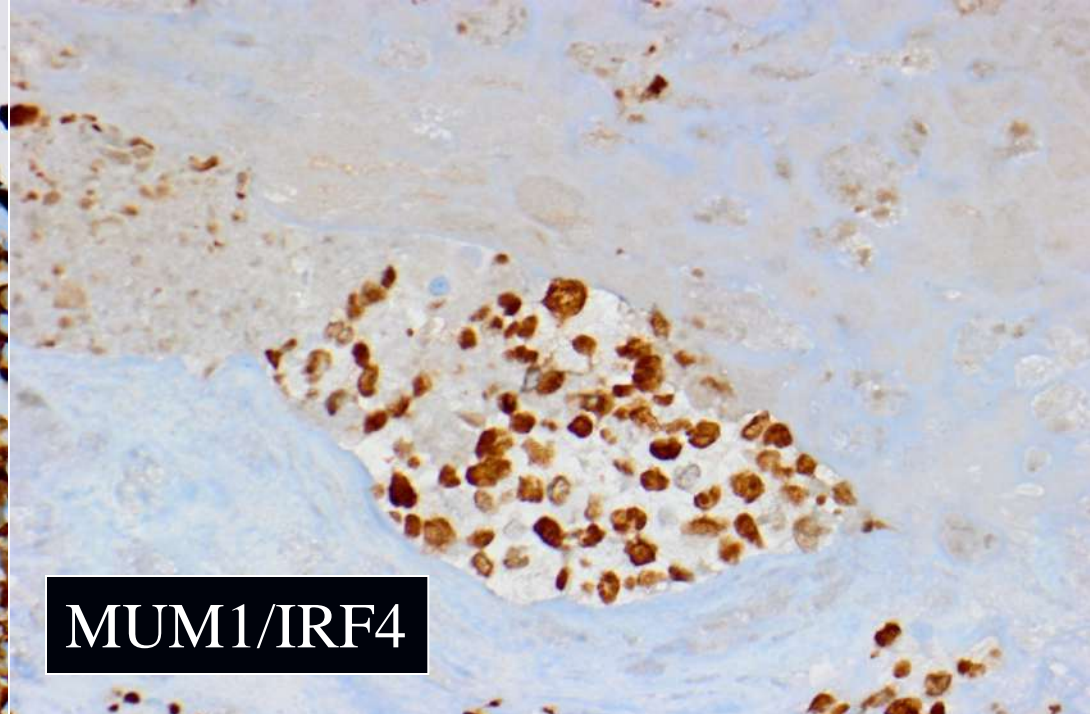
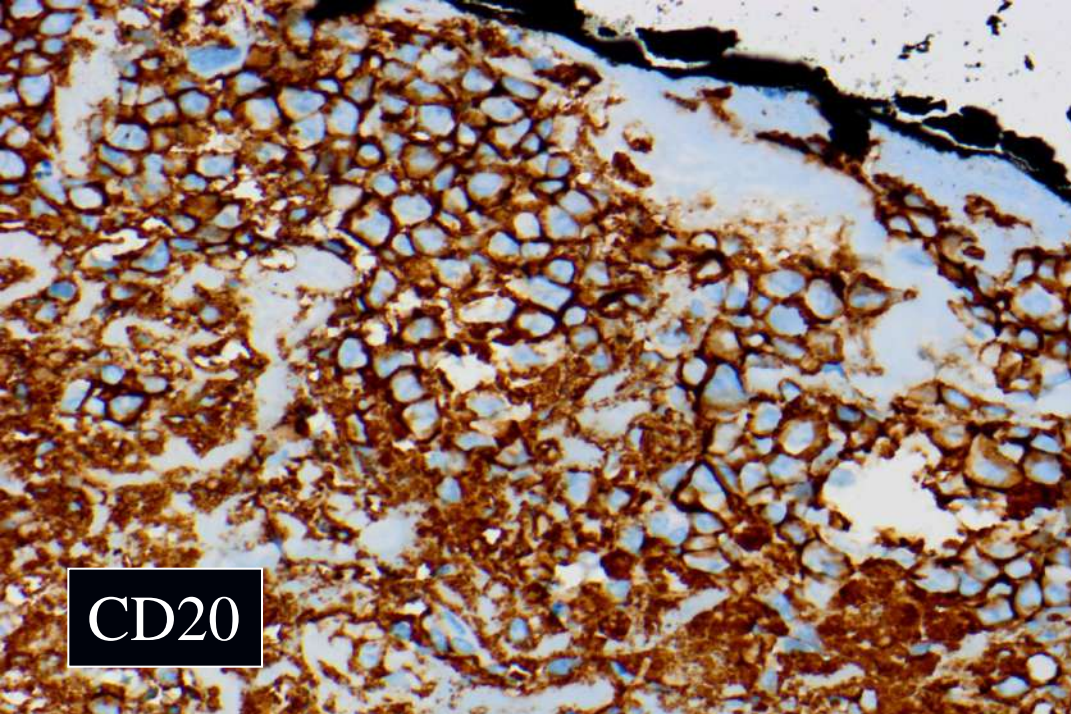




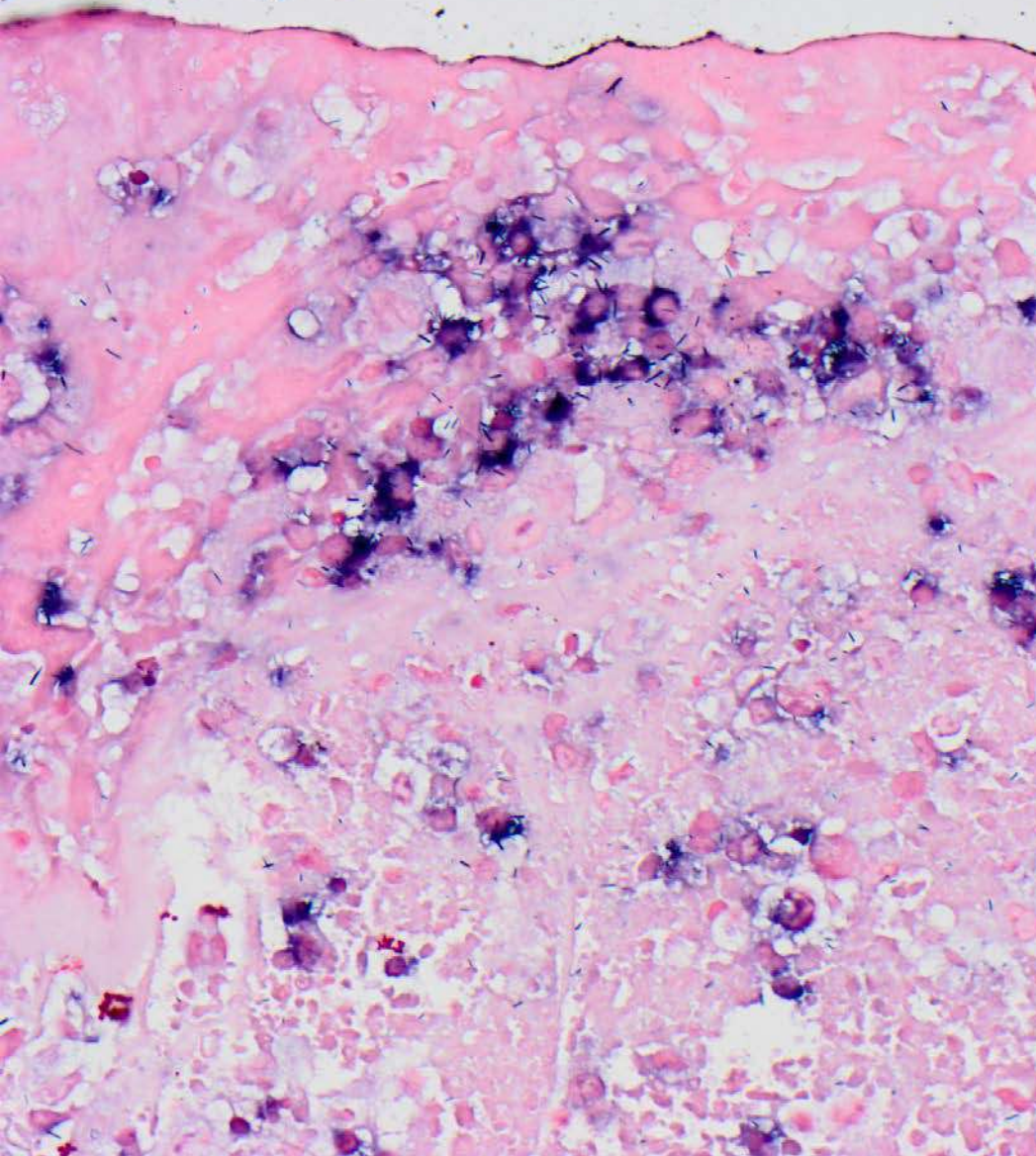
Atrial myxoma



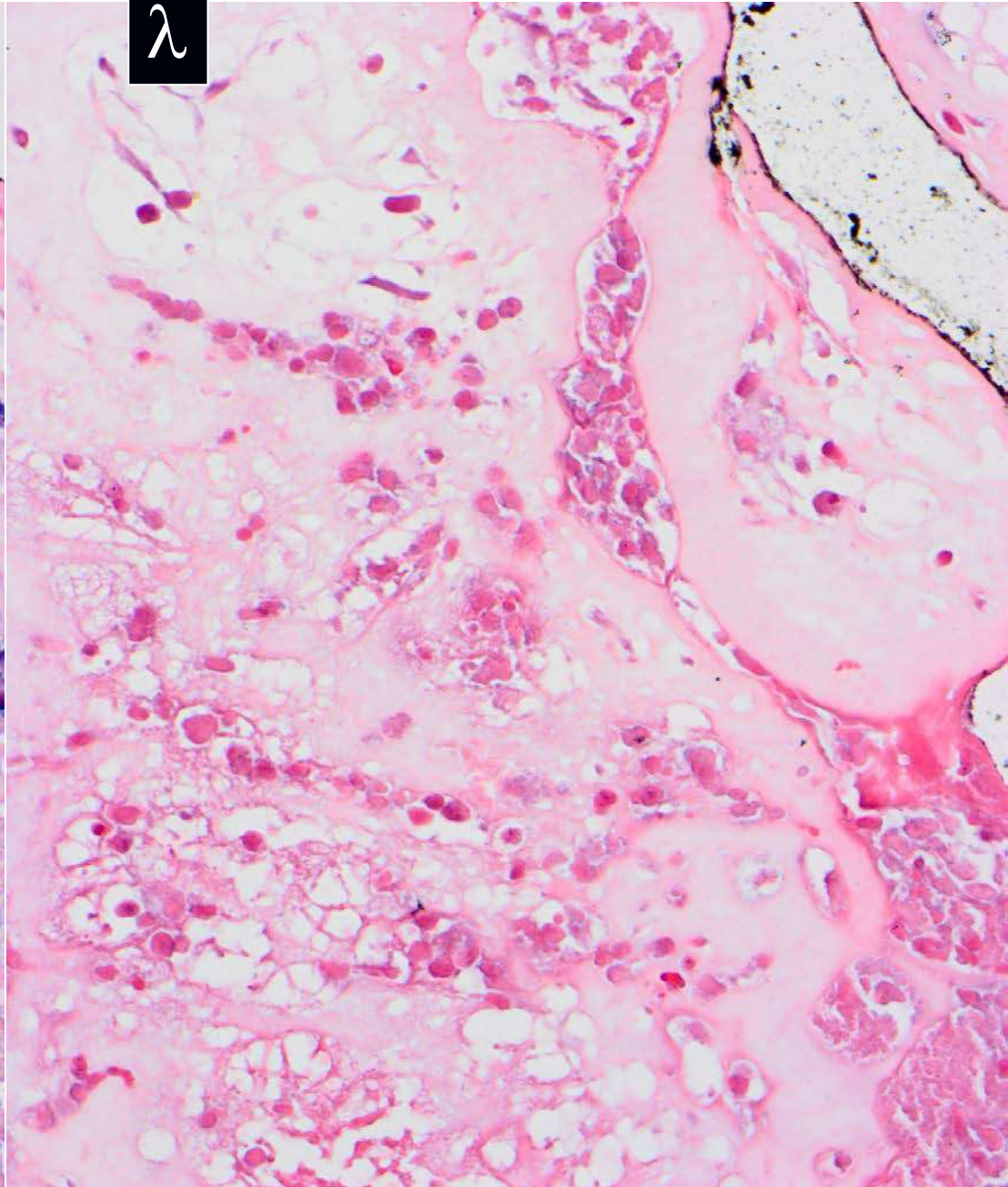




κ



λ

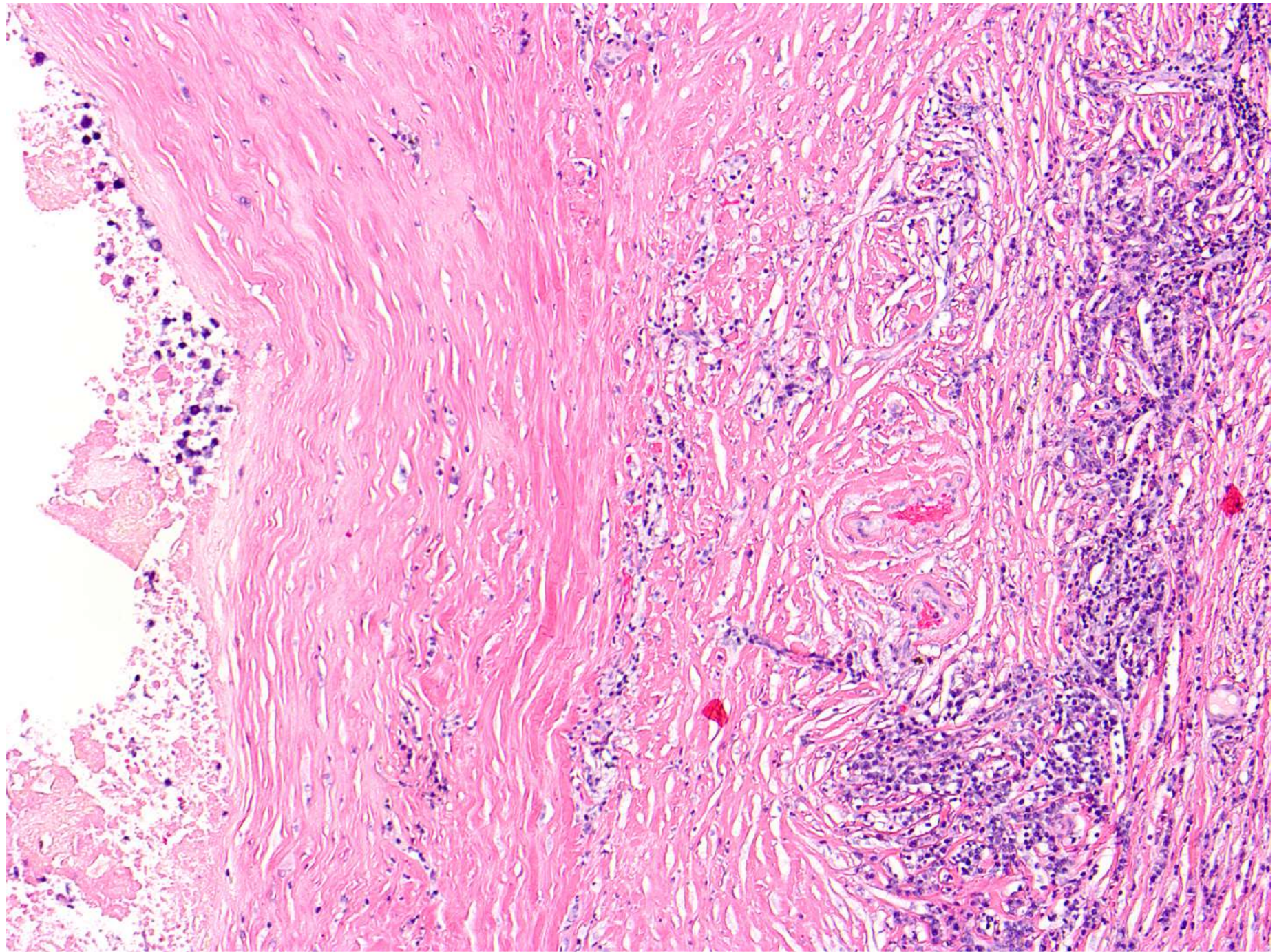


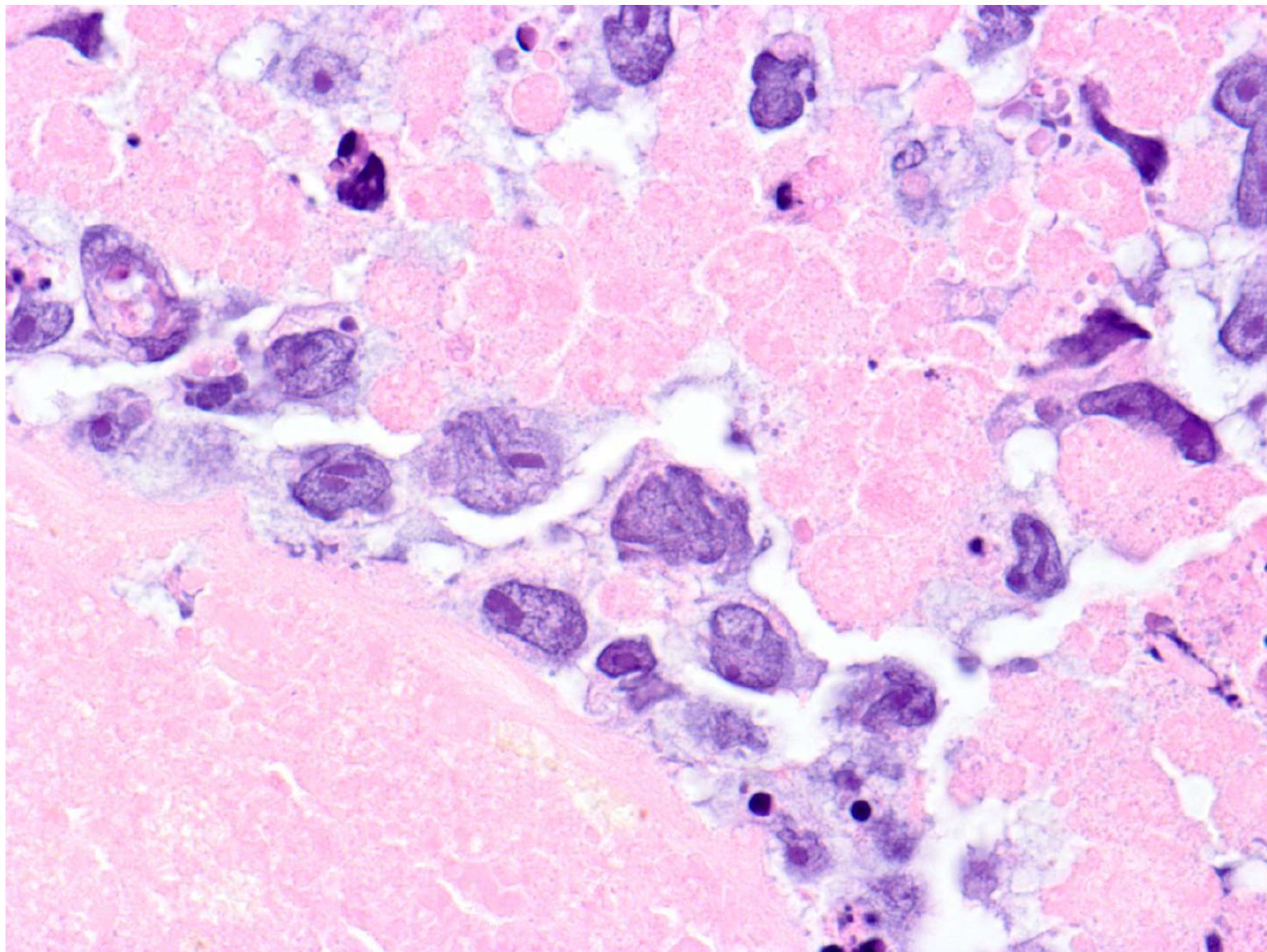
Follow-up:

- **The patient died 6 weeks post-op (not treated)**
- **Complete postmortem examination**
- **Cardiomegaly, 4-chamber dilatation, small infarcts**
- **No evidence of lymphoma**
- **Thus, confirms EBV+ lymphoma arising in myxoma**

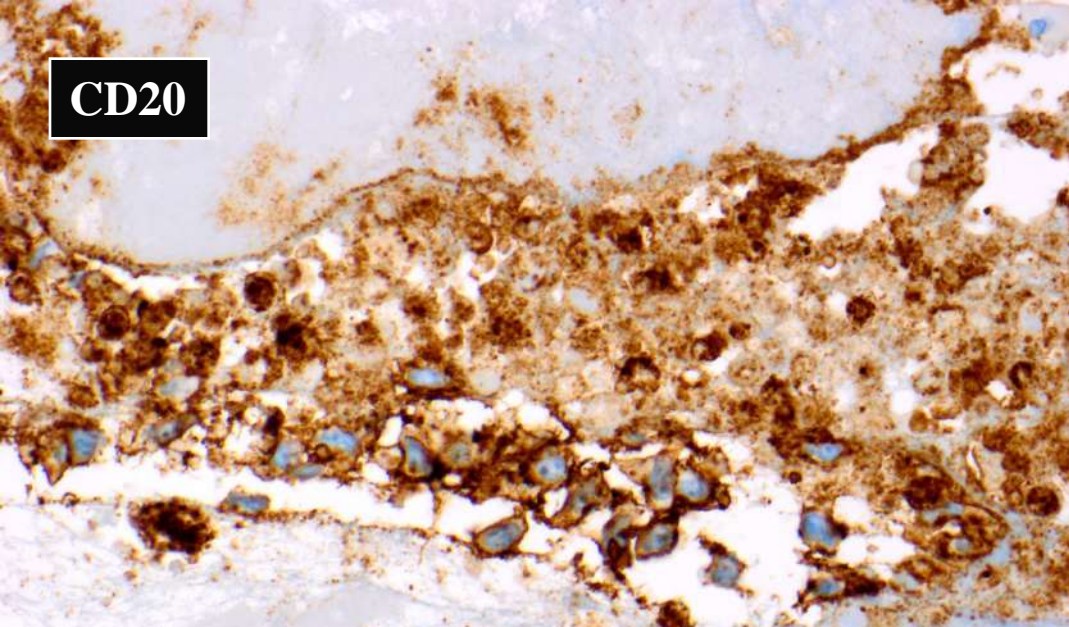
75 yo male with 9cm retroperitoneal cyst



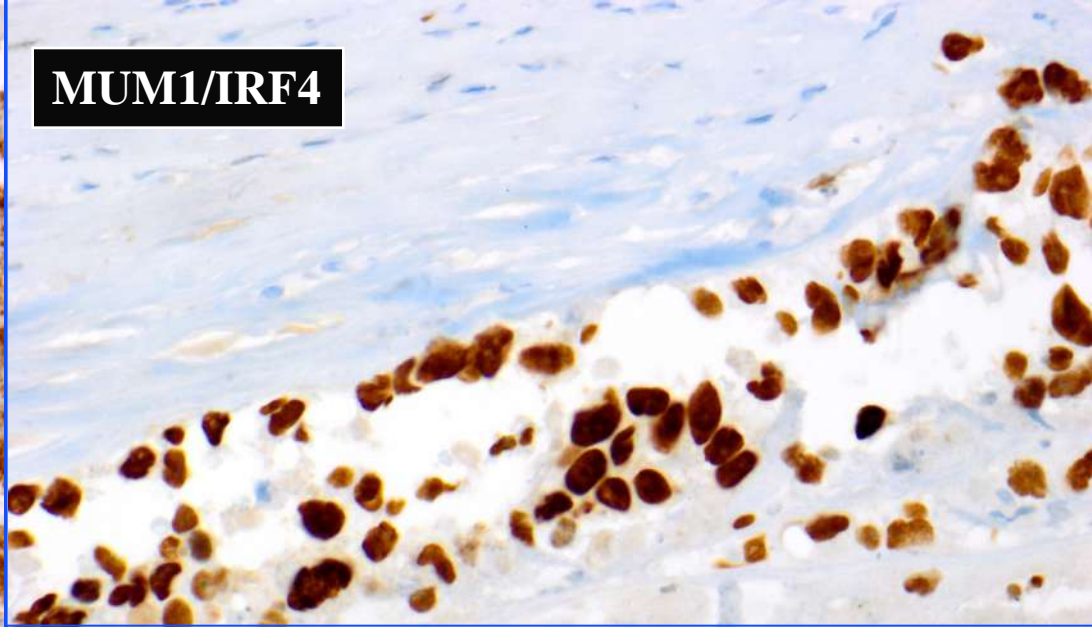




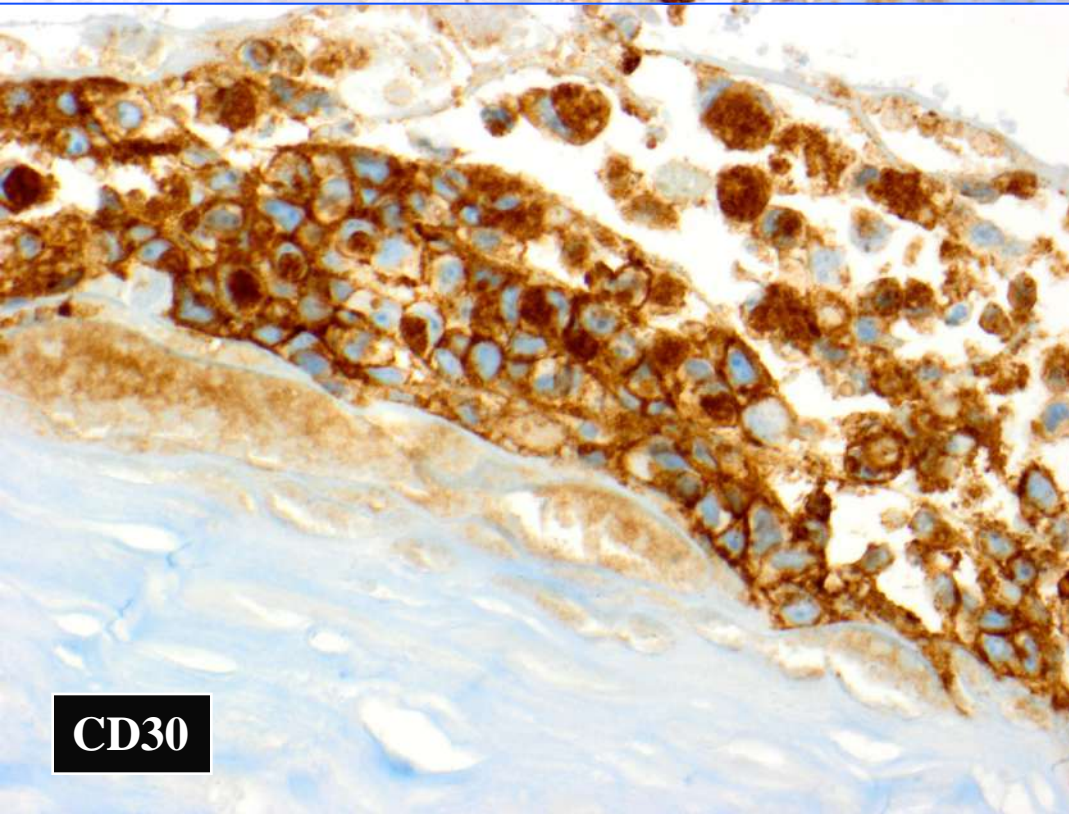
CD20



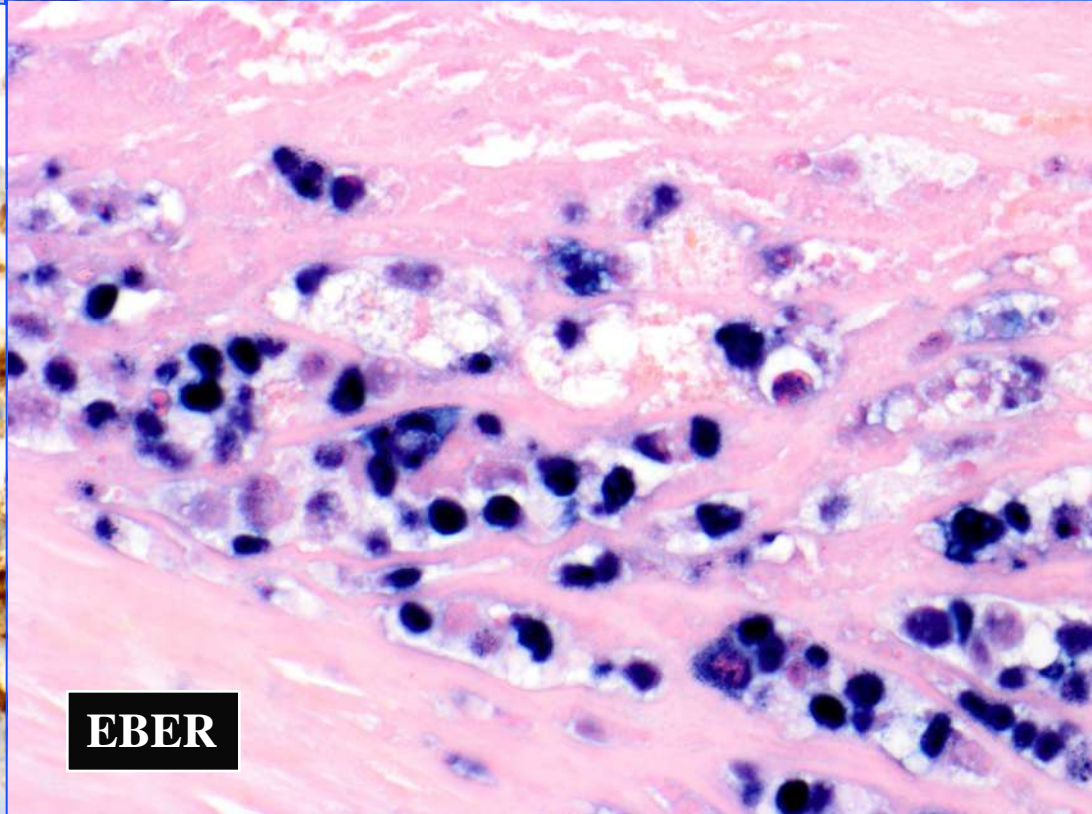
MUM1/IRF4



CD30



EBER

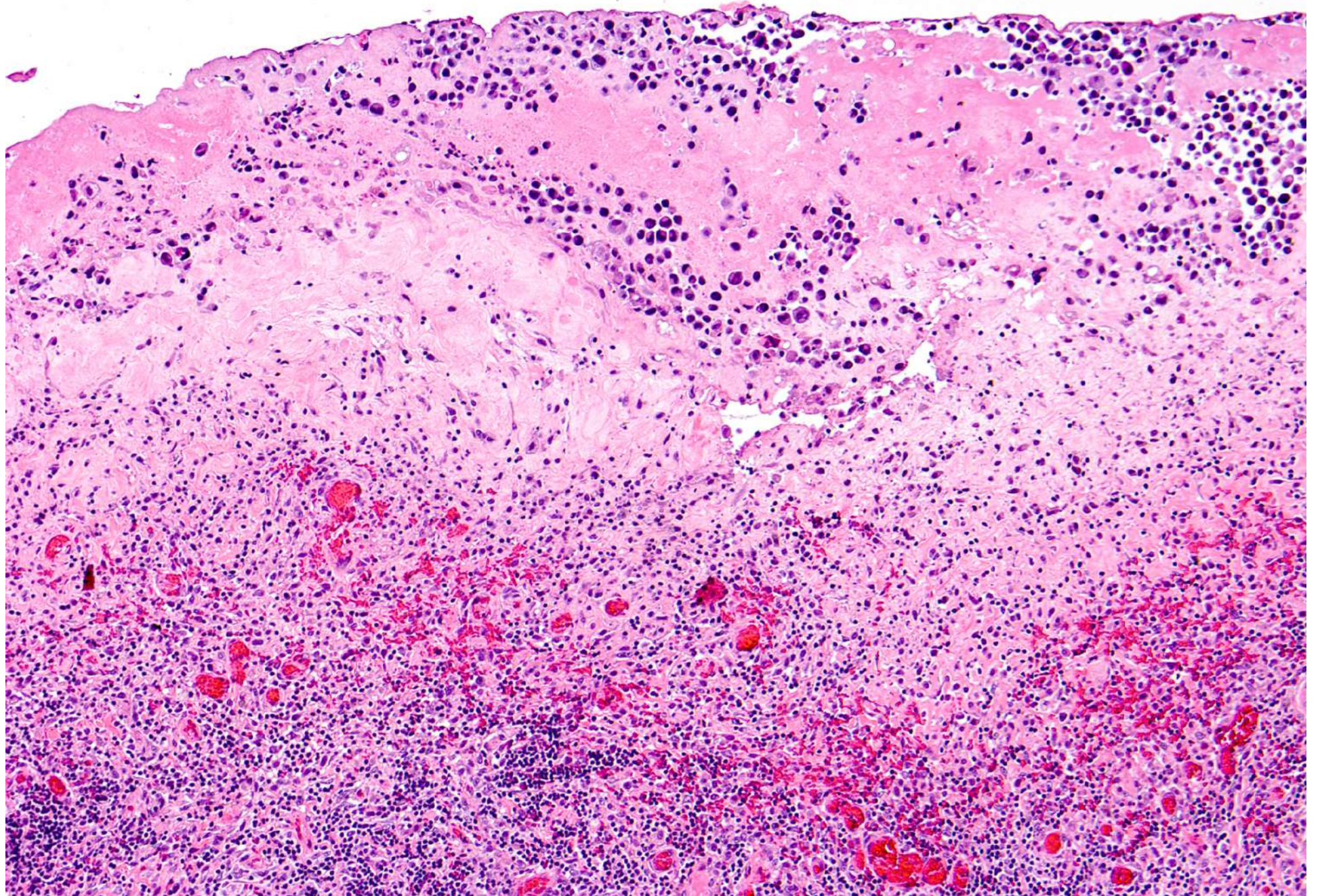


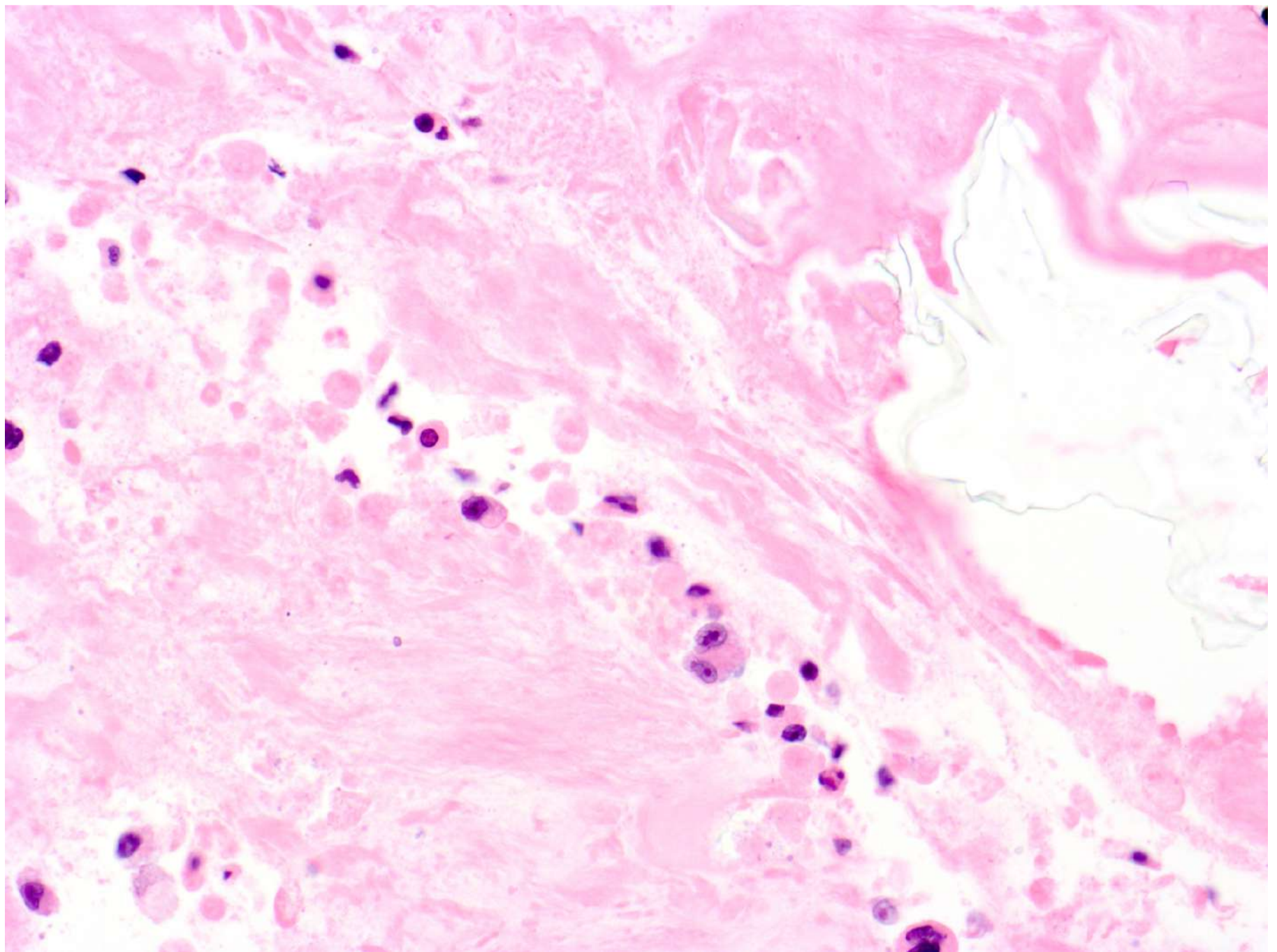
Breast Implants and Lymphoma

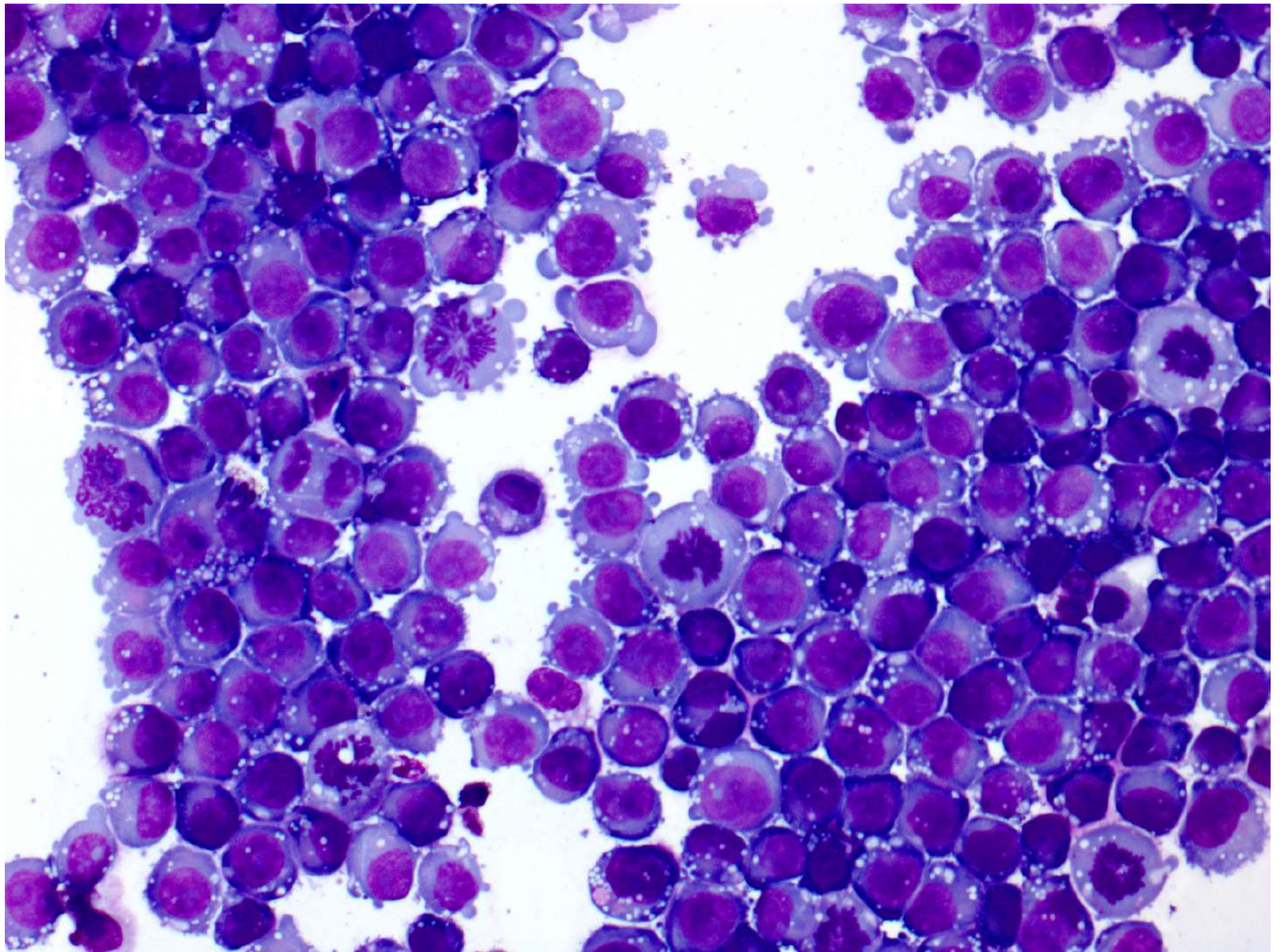
- Most breast lymphomas are B-cell lymphomas
- Most implant-associated lymphomas are anaplastic large cell lymphomas, ALK- (T lineage)
 - Cosmetic or reconstruction after cancer
 - Saline or silicone implants
 - Unilateral, almost always; usually localized
 - Seroma, not mass lesion, in most
 - CD30+, Alk1-, often CD43+, CD4+, EMA+ with loss of one or more pan T-cell antigens
 - Clonal TCR genes
 - Localized disease, good prognosis in most
 - Poor prognosis: discrete mass, spread beyond breast, ?systemic symptoms

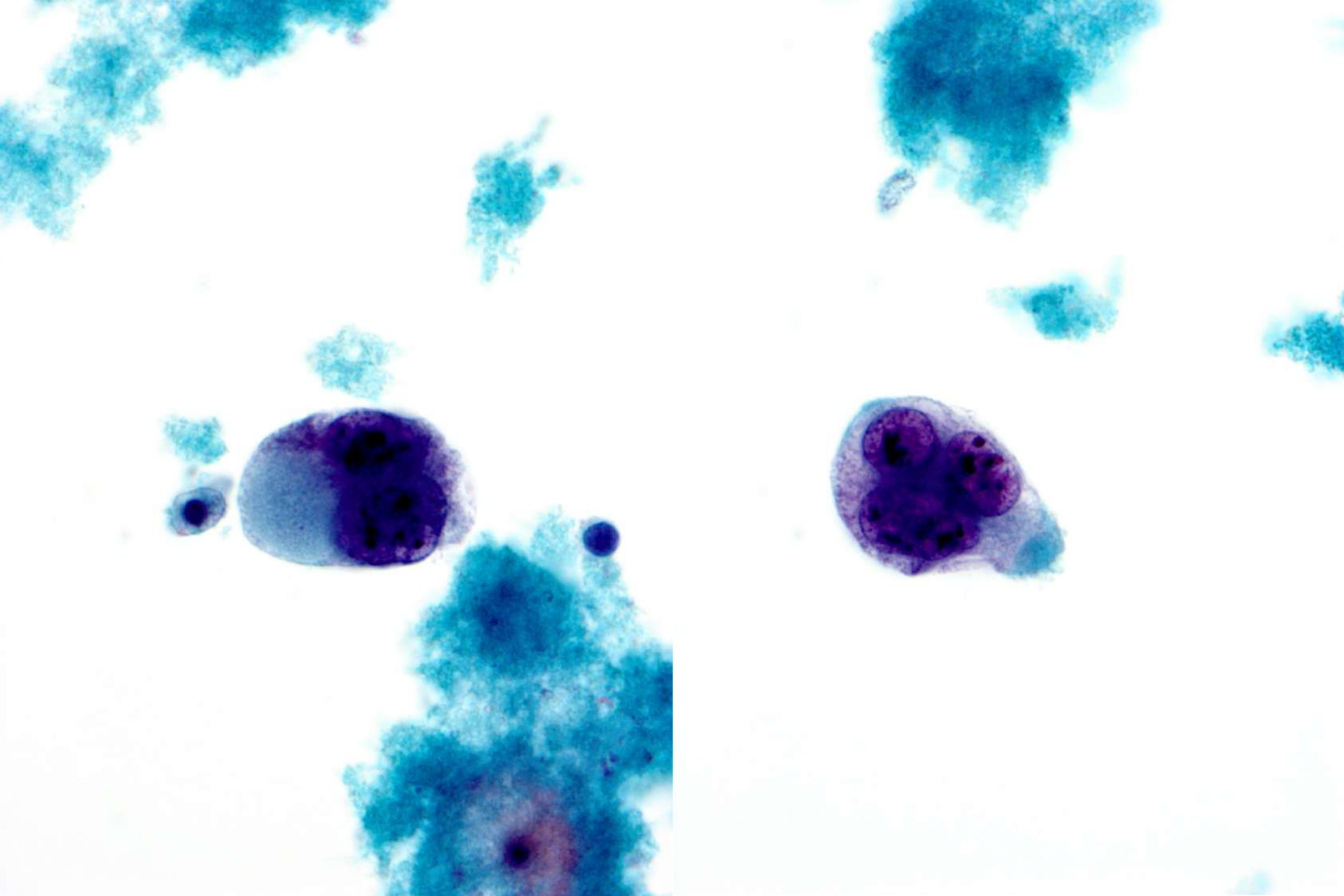


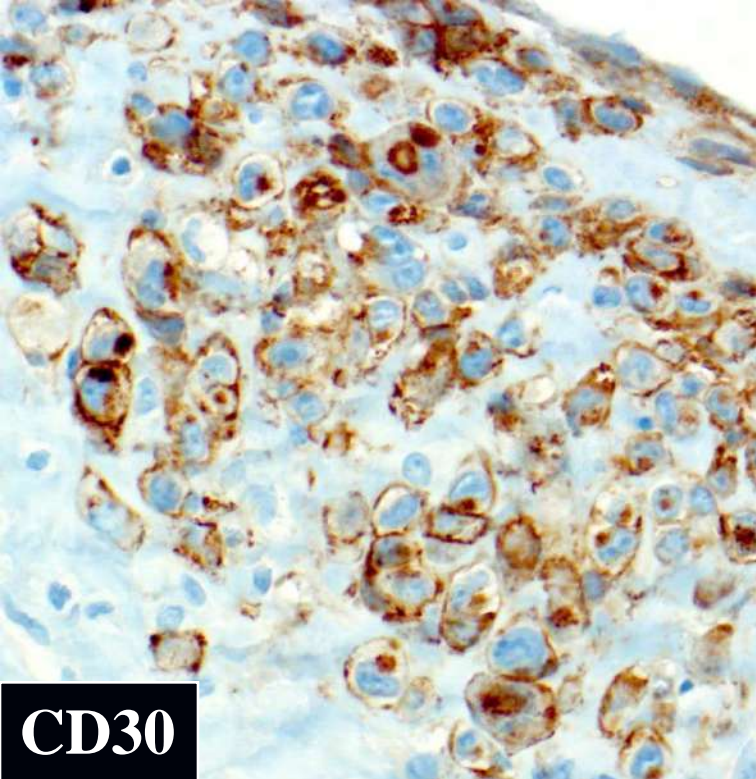
Capsulectomy; image courtesy of Dr. Syed Hoda, Cornell



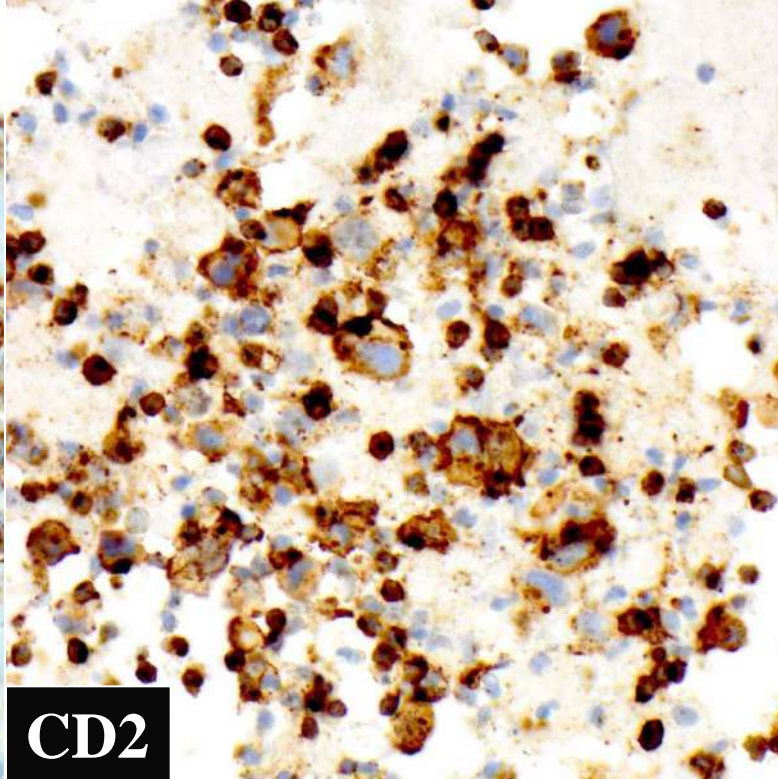




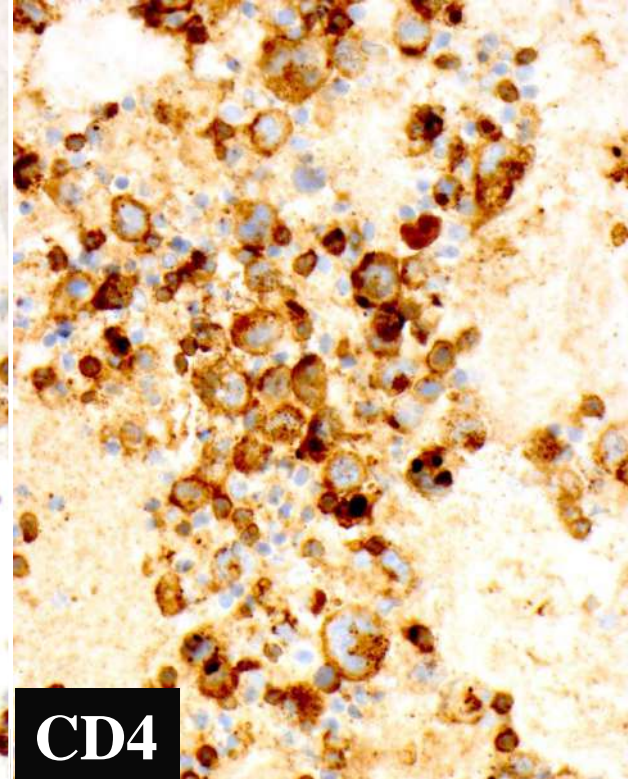




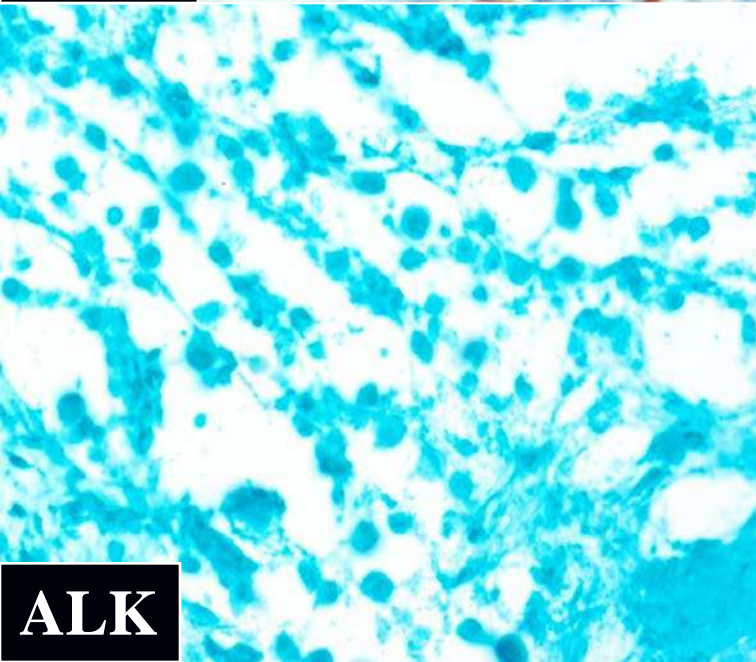
CD30



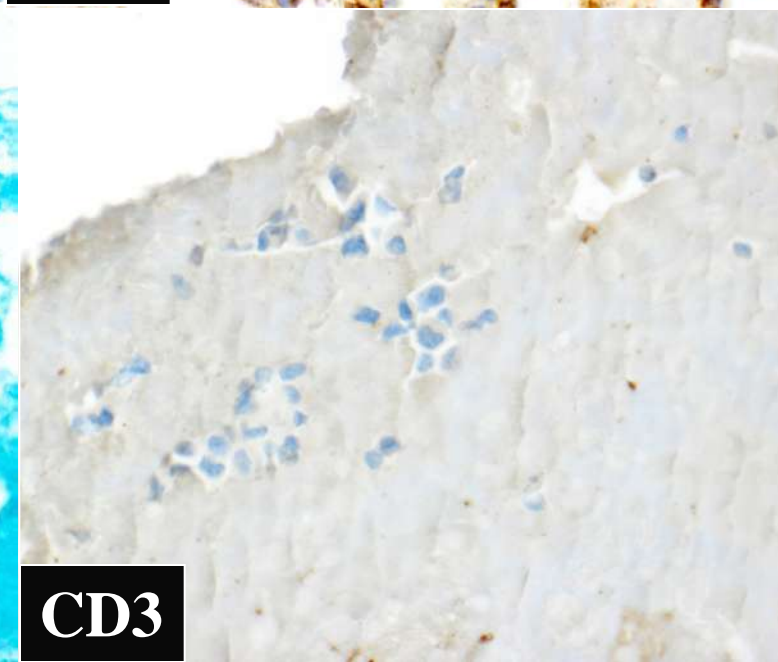
CD2



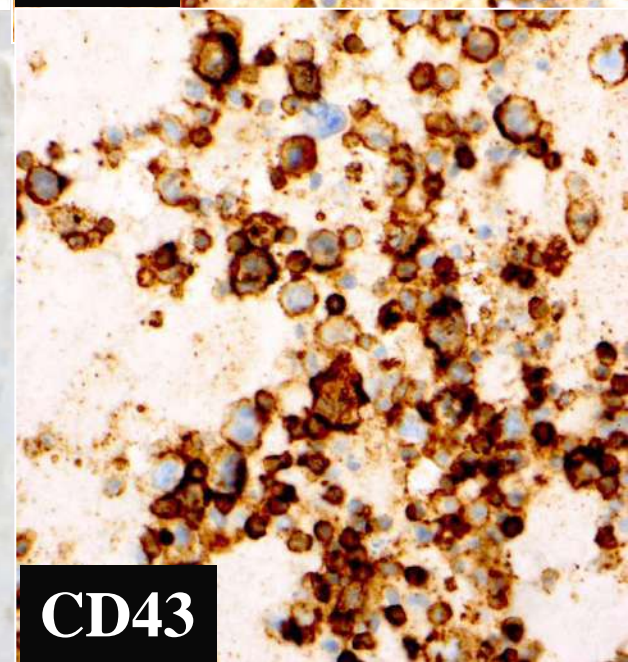
CD4



ALK



CD3



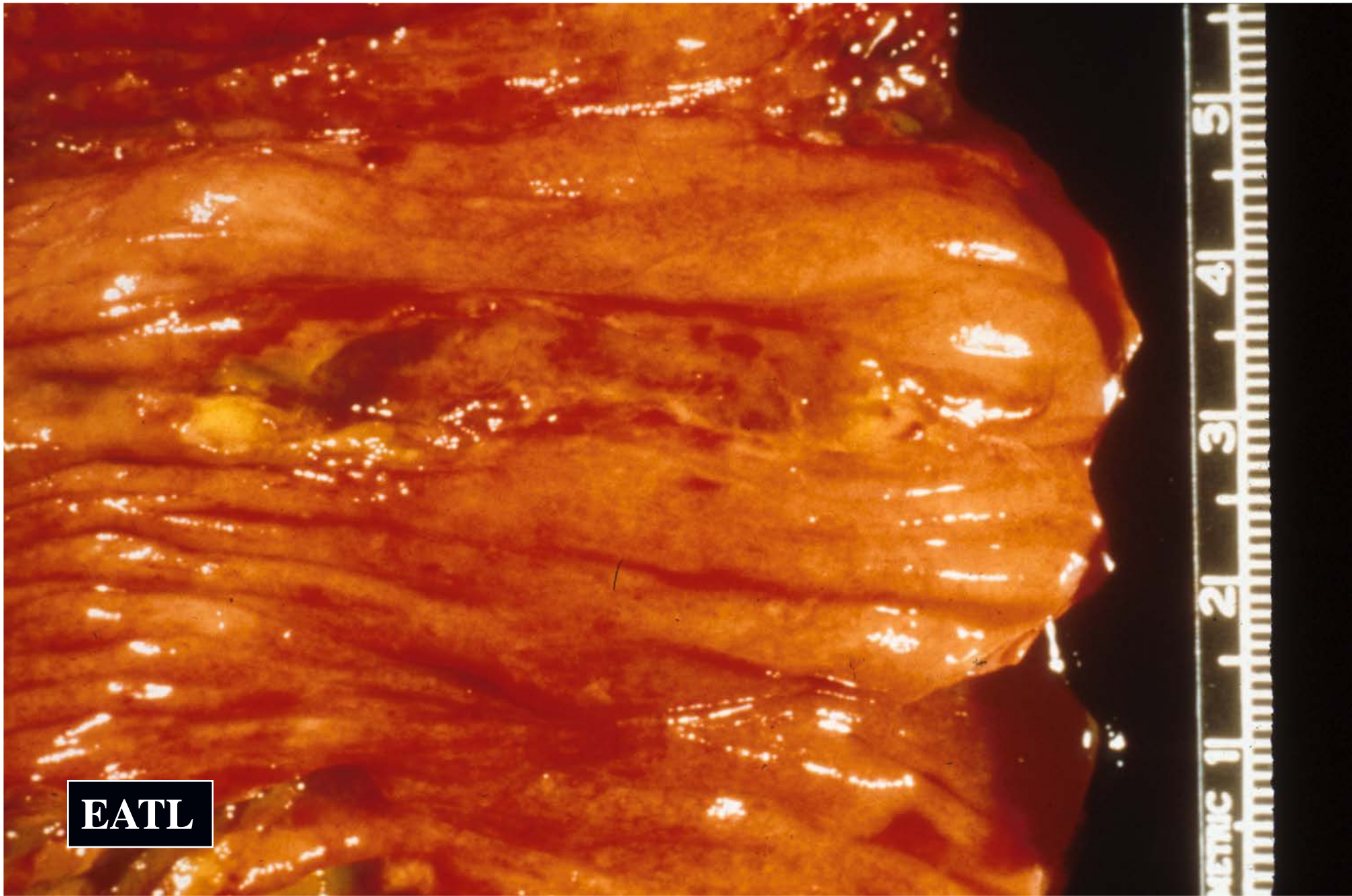
CD43

ENTEROPATHY-ASSOCIATED T-CELL LYMPHOMA

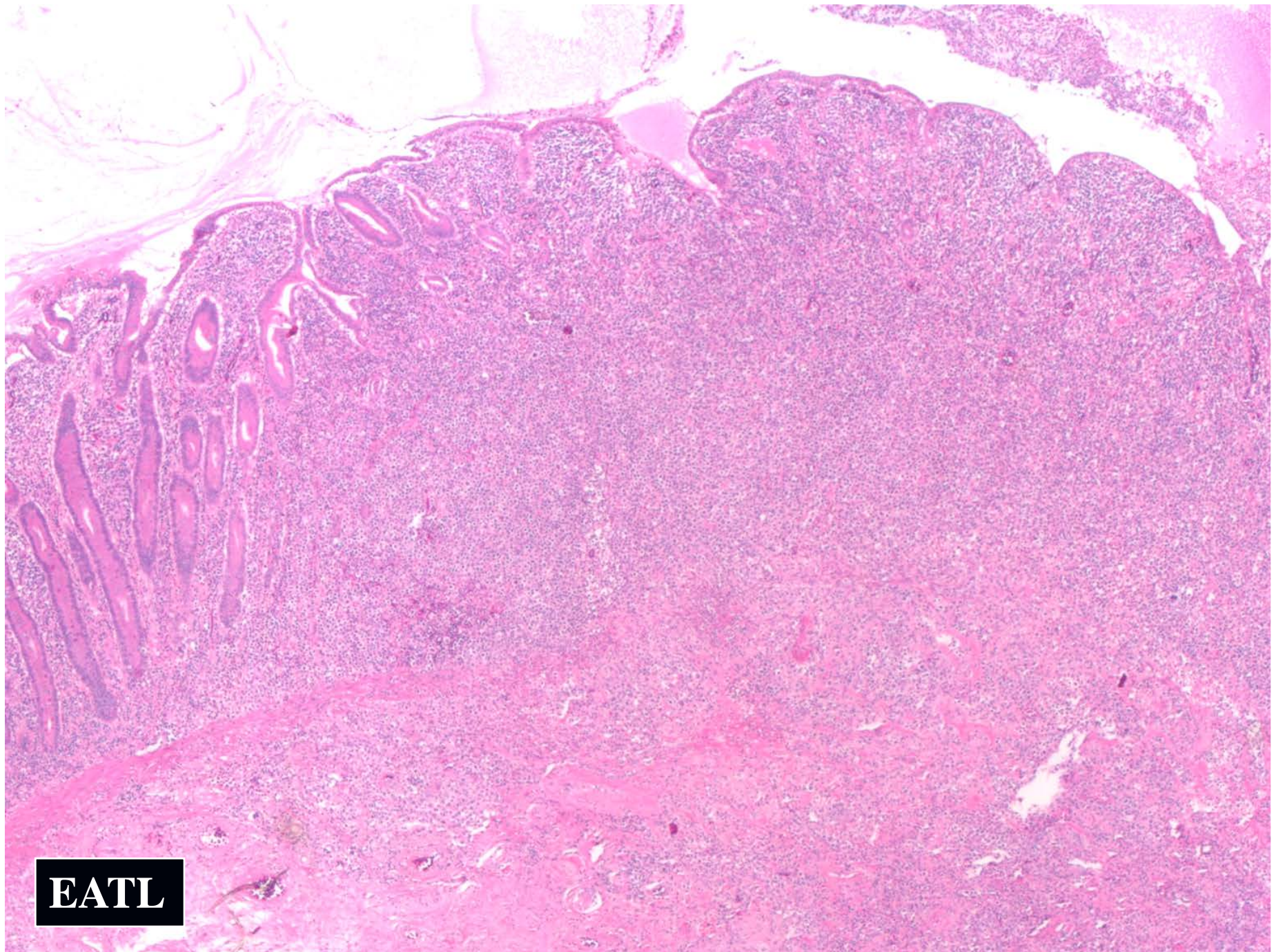
- Adults, with evidence of celiac disease and/or histologic evidence of enteropathy
- Symptoms: abdominal pain, sometimes acute
- Small bowel (jejunum): multifocal ulceration +/- perforation +/- mass
- Cell of origin: intraepithelial T lymphocyte
- Very poor prognosis
- Malnourished patients cannot tolerate chemo
- Death due to perforation, extranodal spread
- Many cases could be prevented with gluten-free diet

ENTEROPATHY-ASSOCIATED T-CELL LYMPHOMA

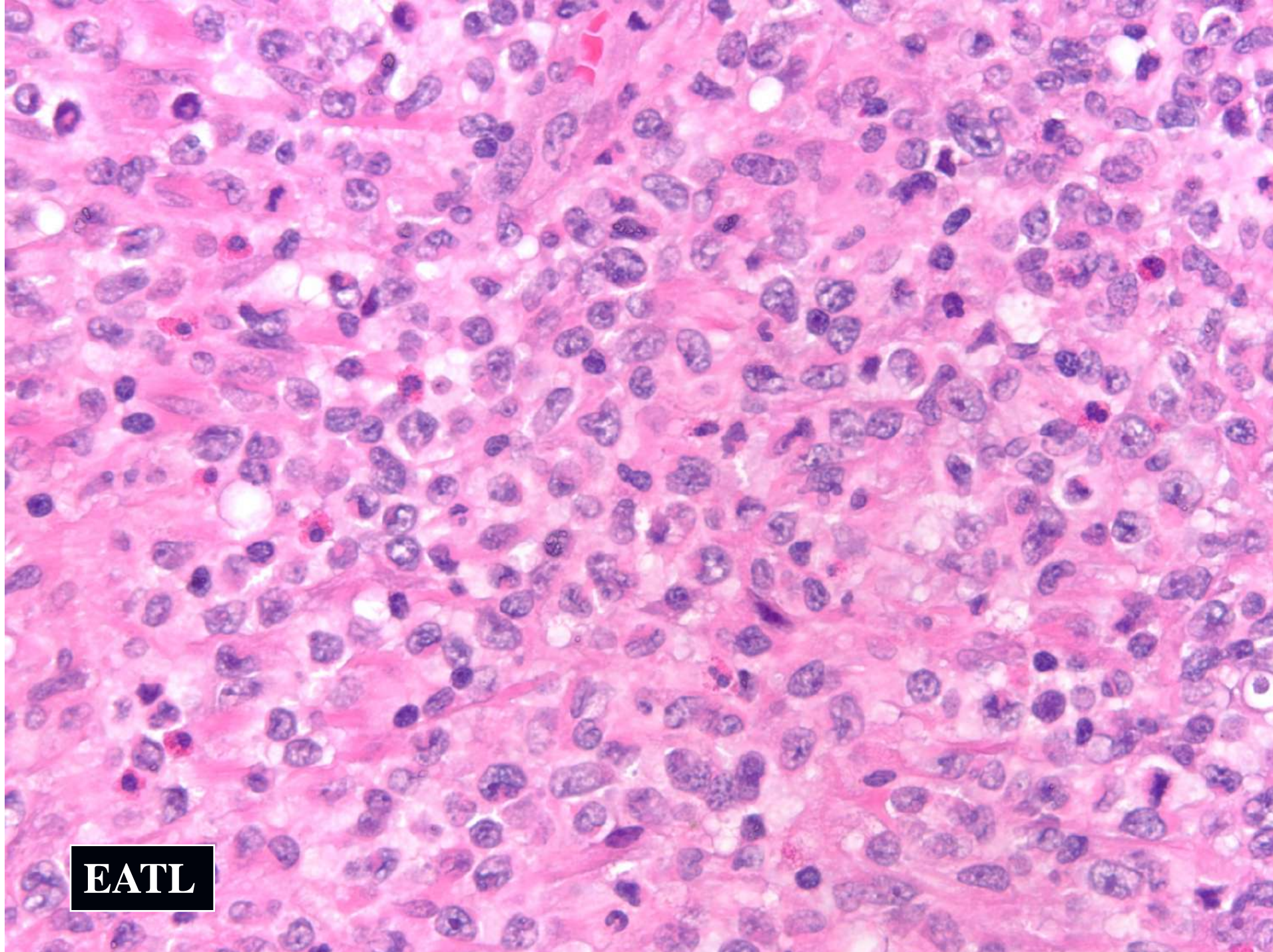
- EATL type I, classic EATL:
 - 80-90% of EATL in Western countries
 - Large cells, more fibrosis and admixed inflammatory cells (histiocytes, eosinophils...), necrosis; CD3+; CD4-, CD8->CD8+>CD4+, CD30+/-
 - Gains of 9q (*NOTCH1*, *ABL1*) or loss of 16q; gains of 5q (*APC*); others
 - Adjacent mucosa: villous atrophy, increased intraepithelial lymphocytes; rarely normal
- EATL type II:
 - Small or medium-sized, pleomorphic or uniform cells, CD3+; CD8+, CD56+/-; often lack evidence of celiac disease
 - Gains of 9q or loss of 16q; gains of 8q (*MYC*); others
- EBV typically absent
- Cytotoxic phenotype (granzyme B, perforin, TIA-1+)
- Differential: BCLs, other TCLs, non-neoplastic ulceration



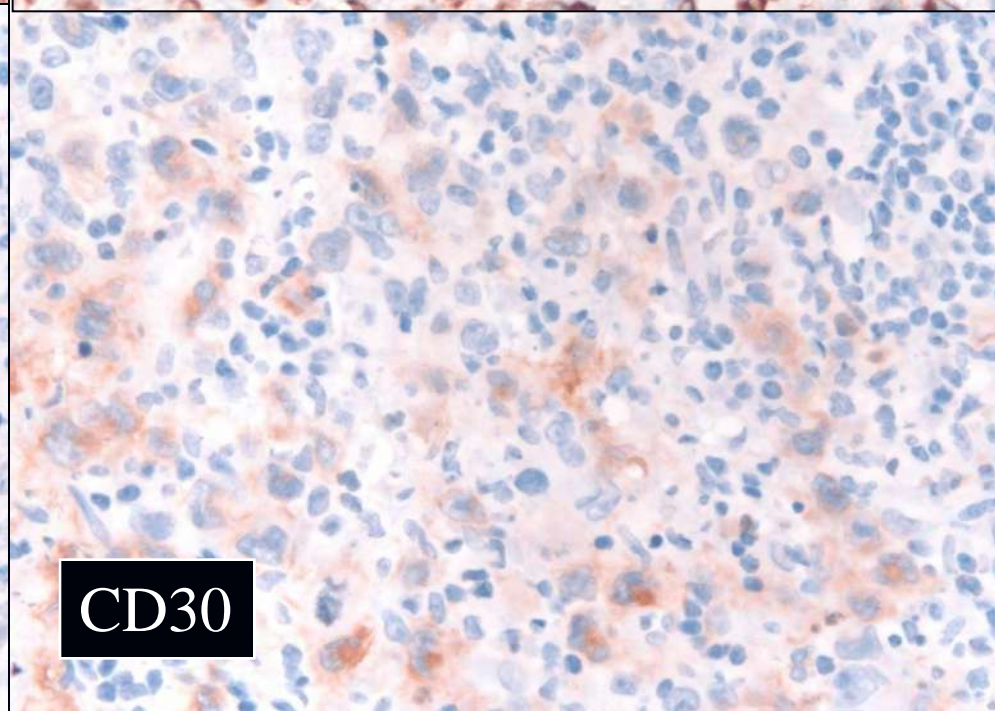
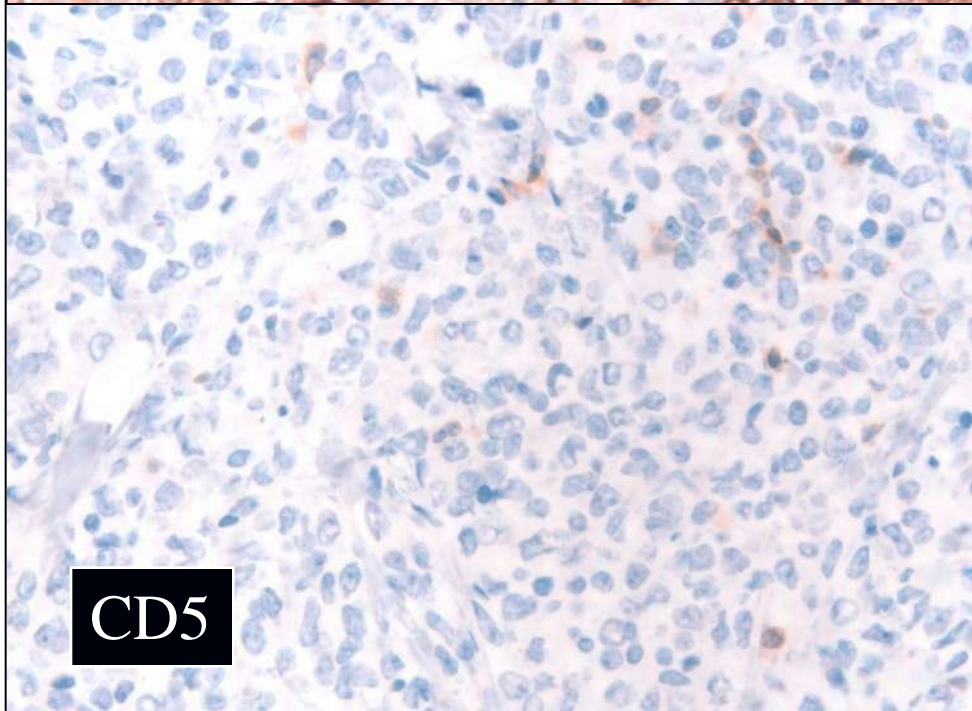
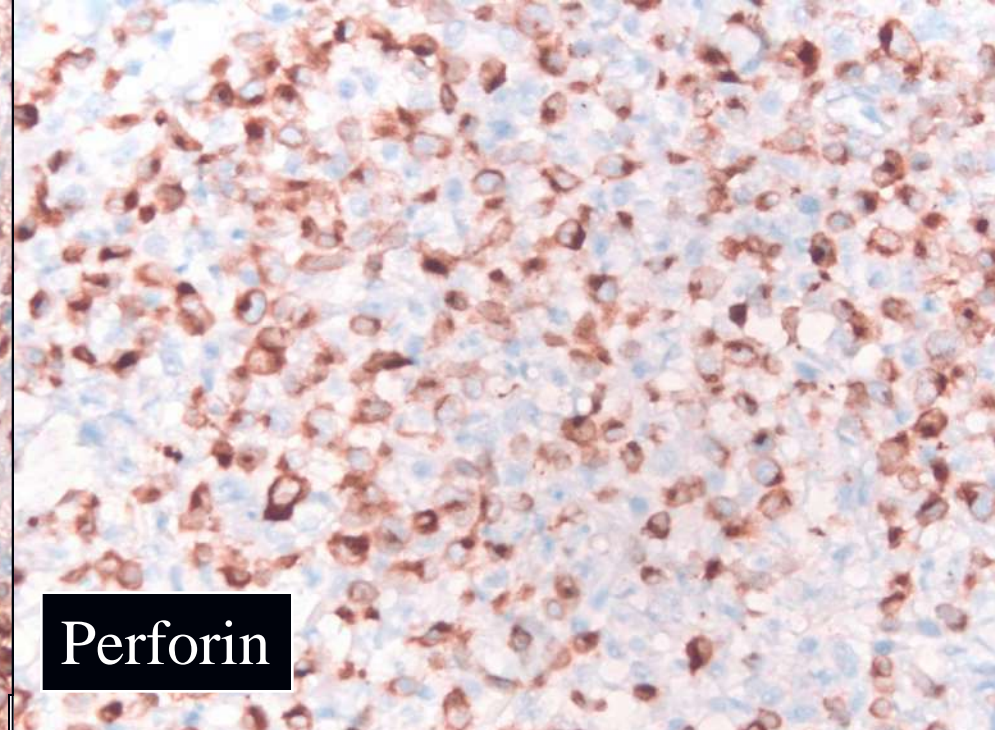
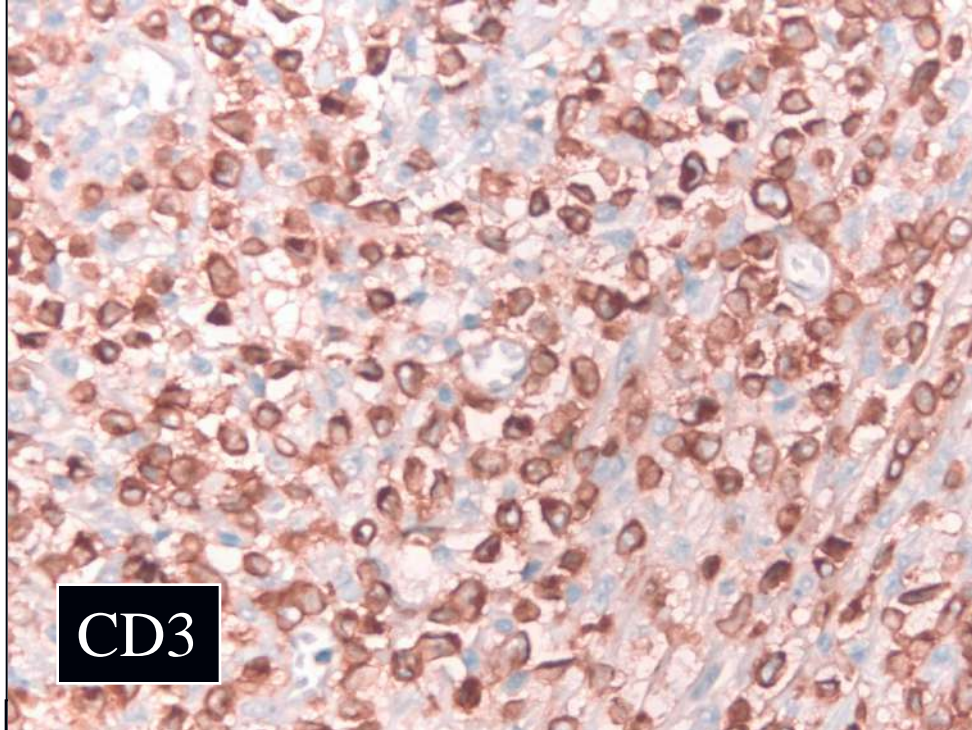
EATL

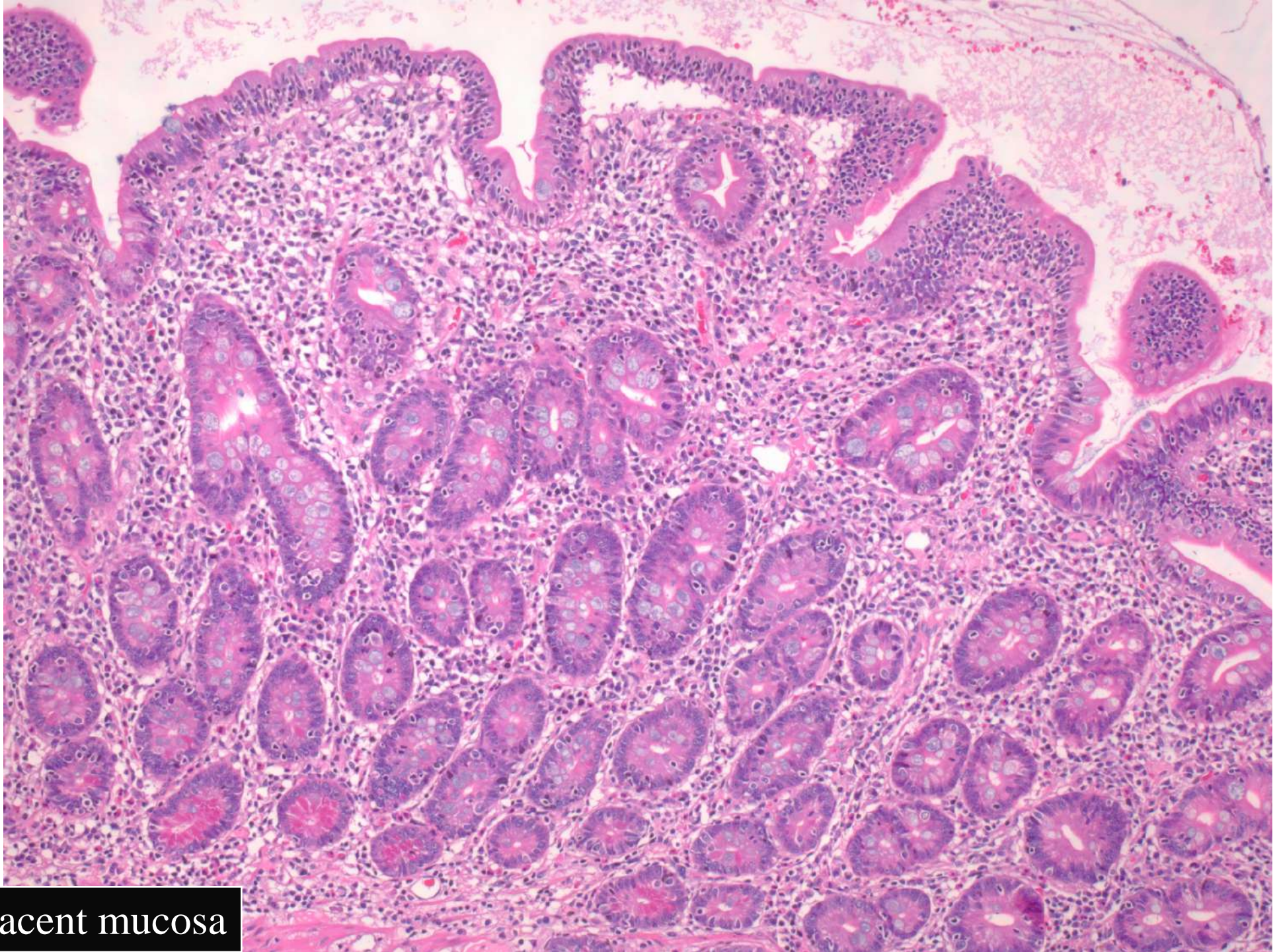


EATL

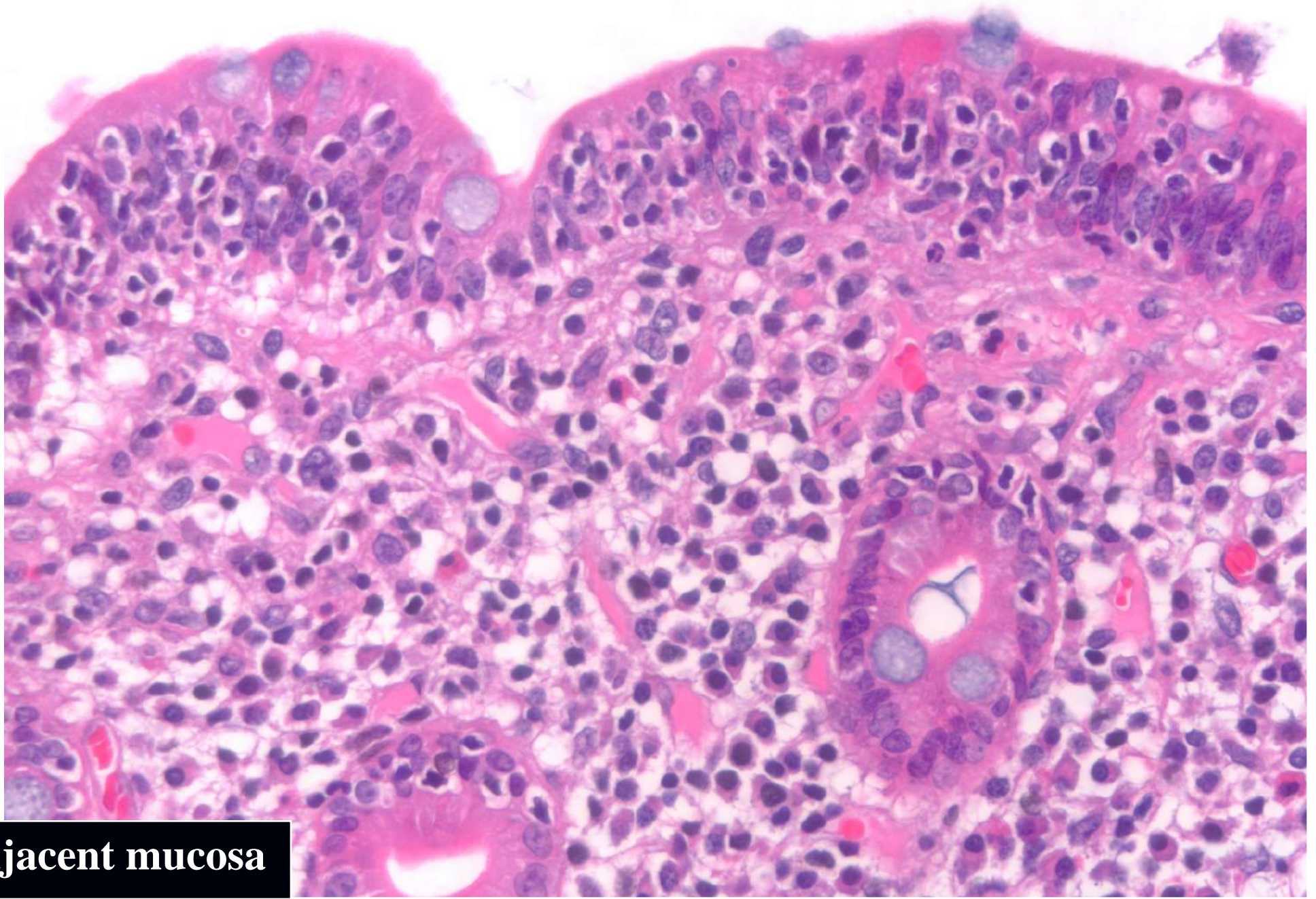


EATL



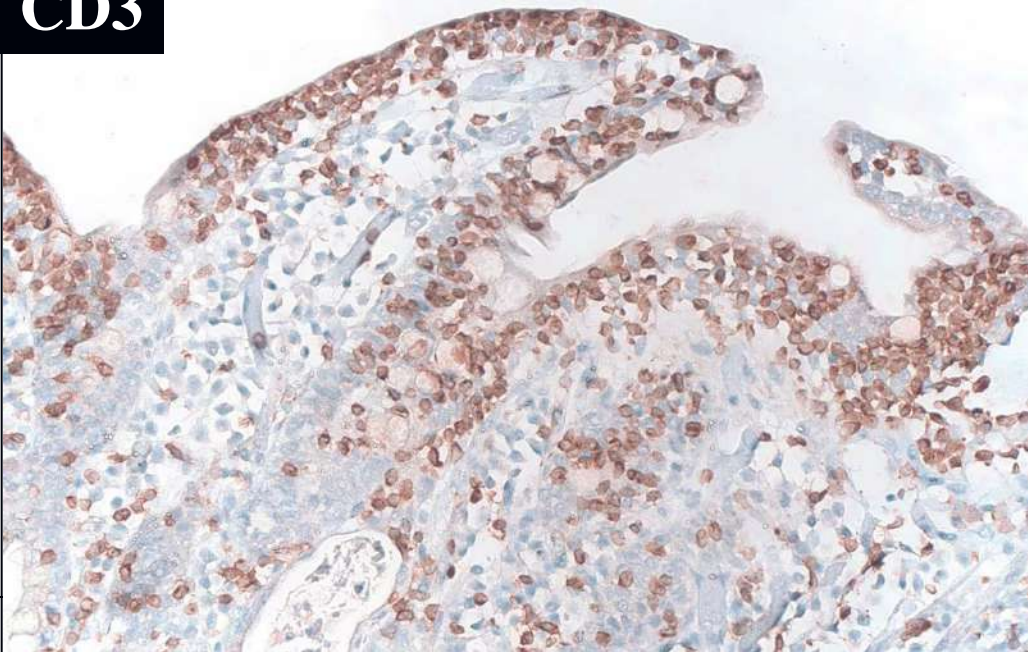


Adjacent mucosa

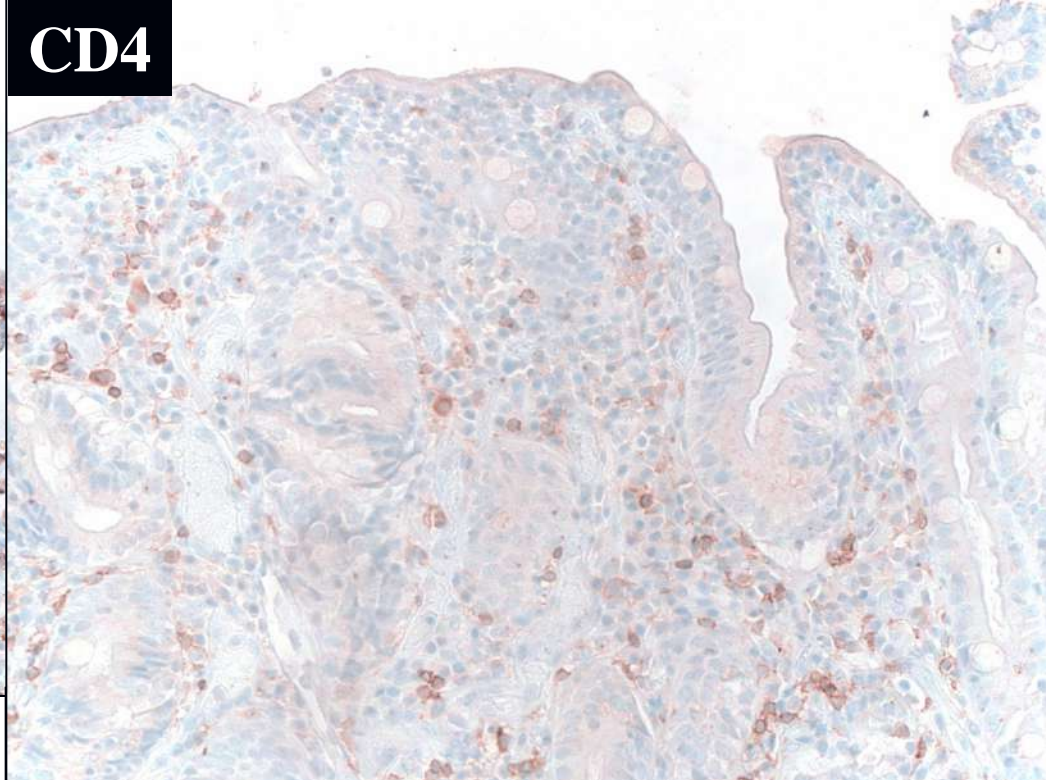


Adjacent mucosa

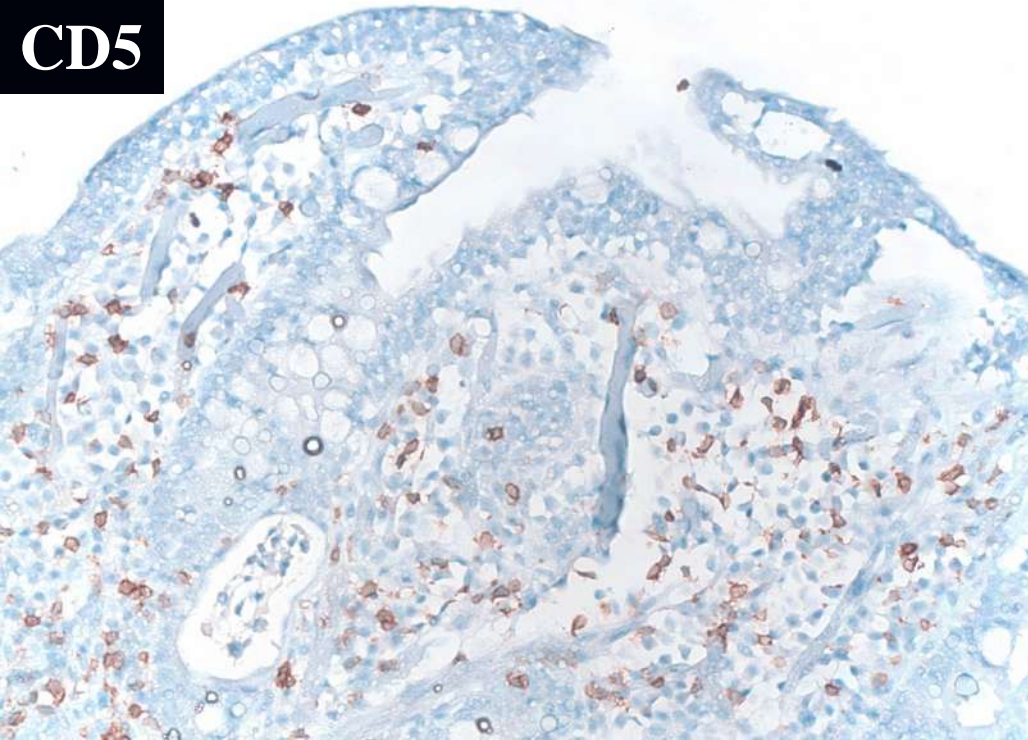
CD3



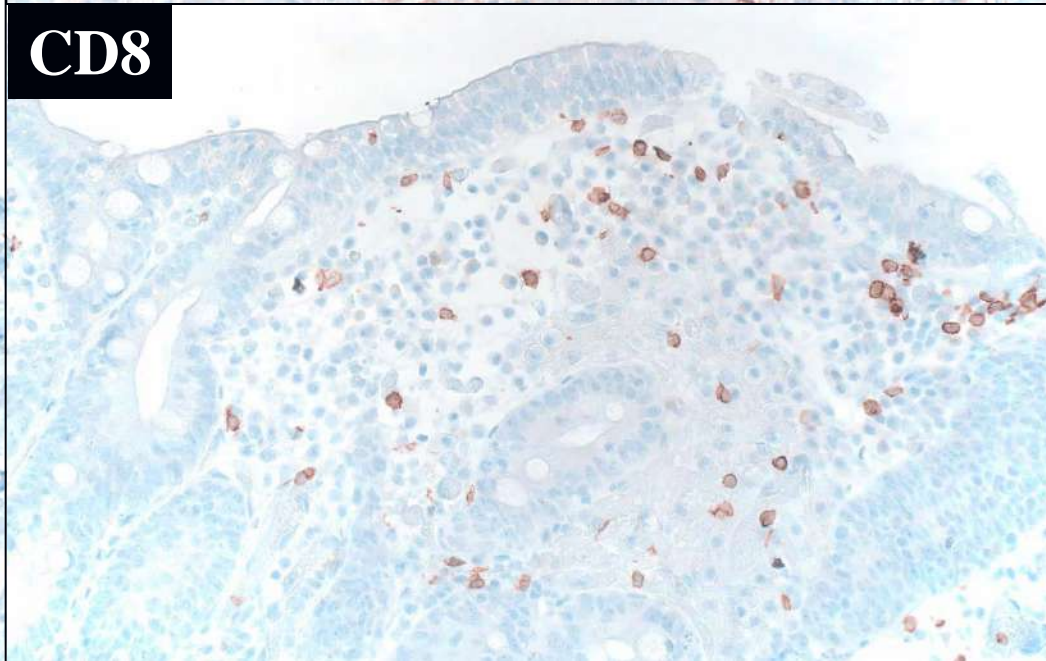
CD4



CD5



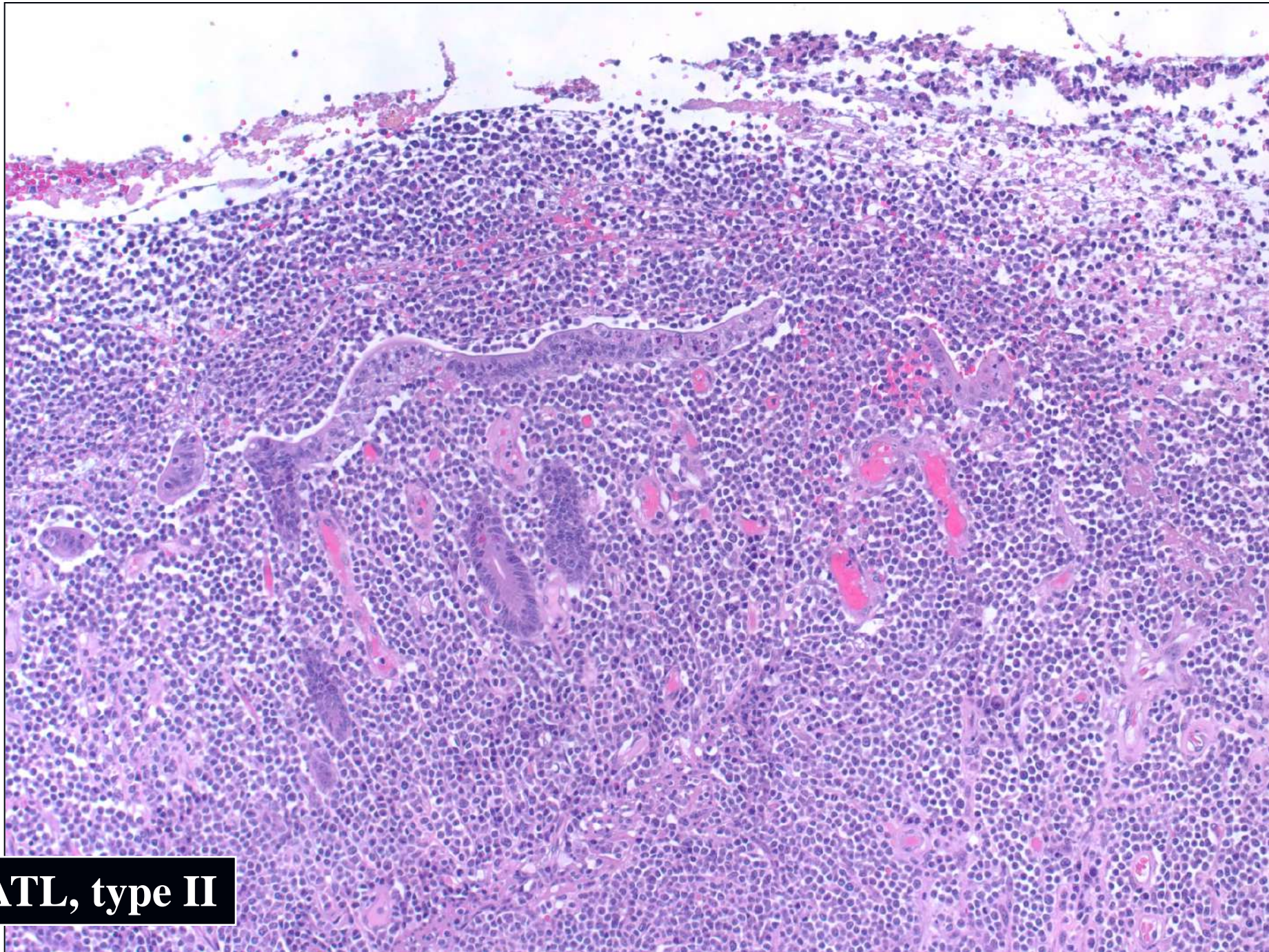
CD8



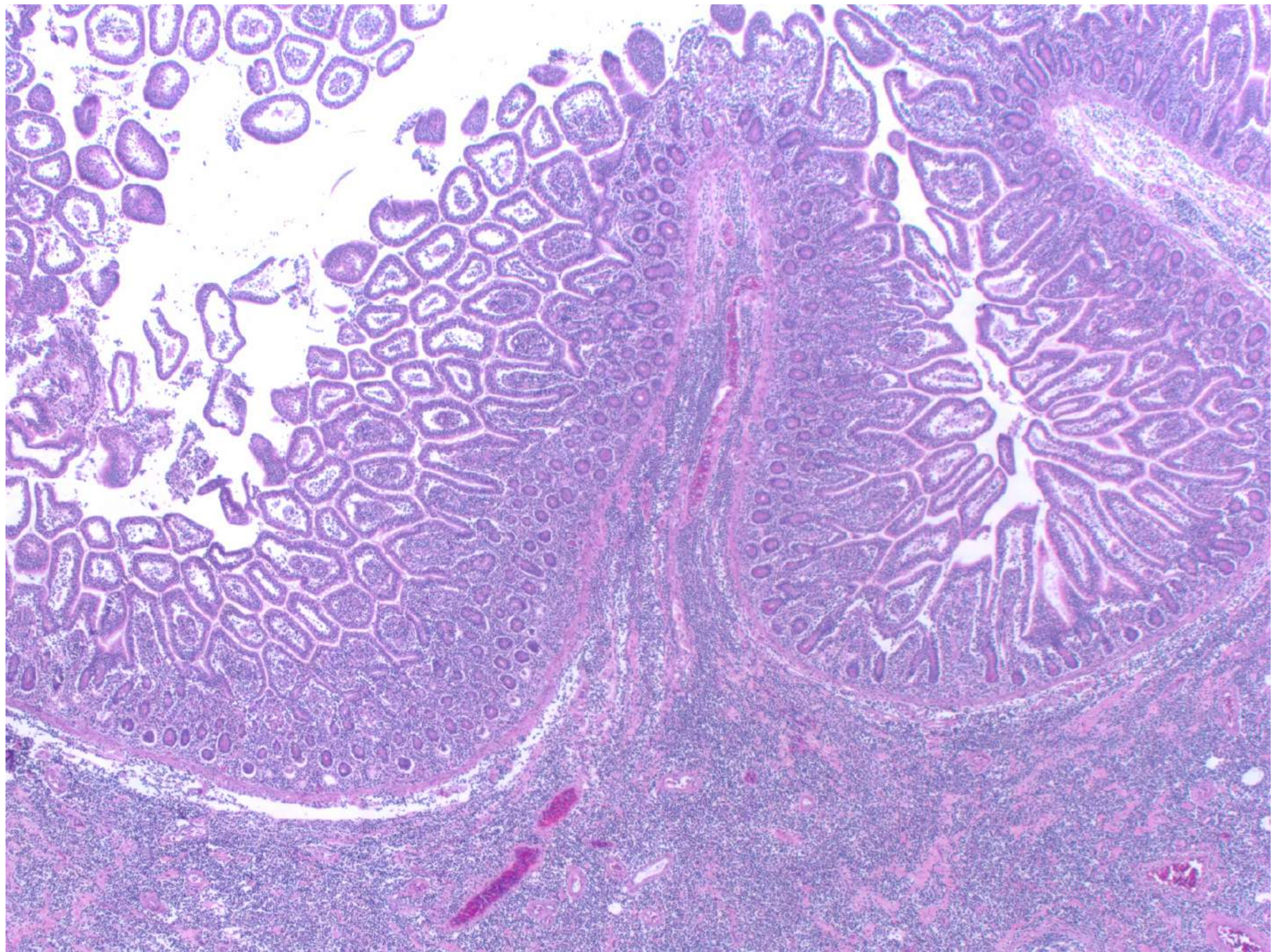
EATL, Type II

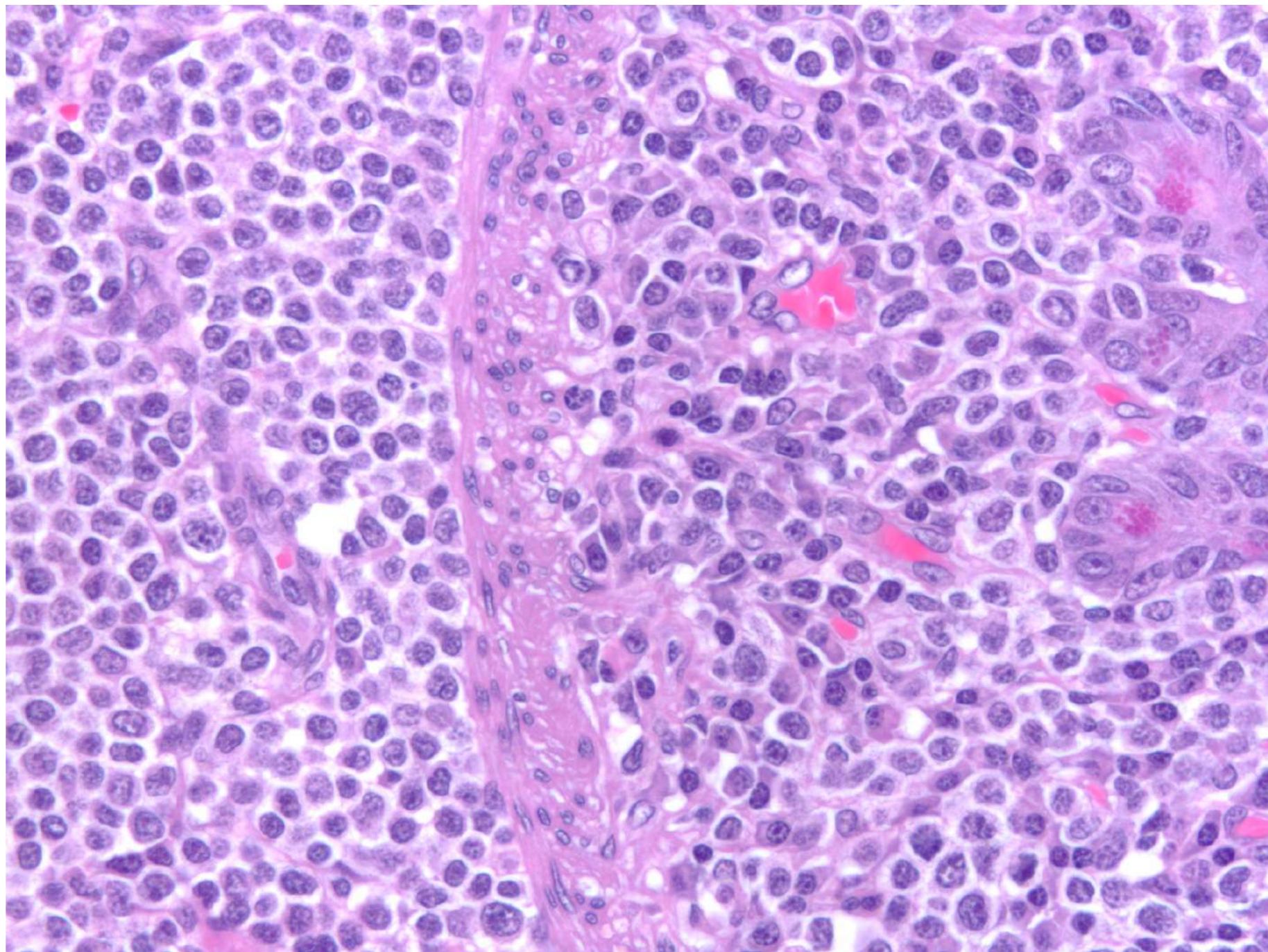
In contrast to EATL type I (classic EATL), type II:

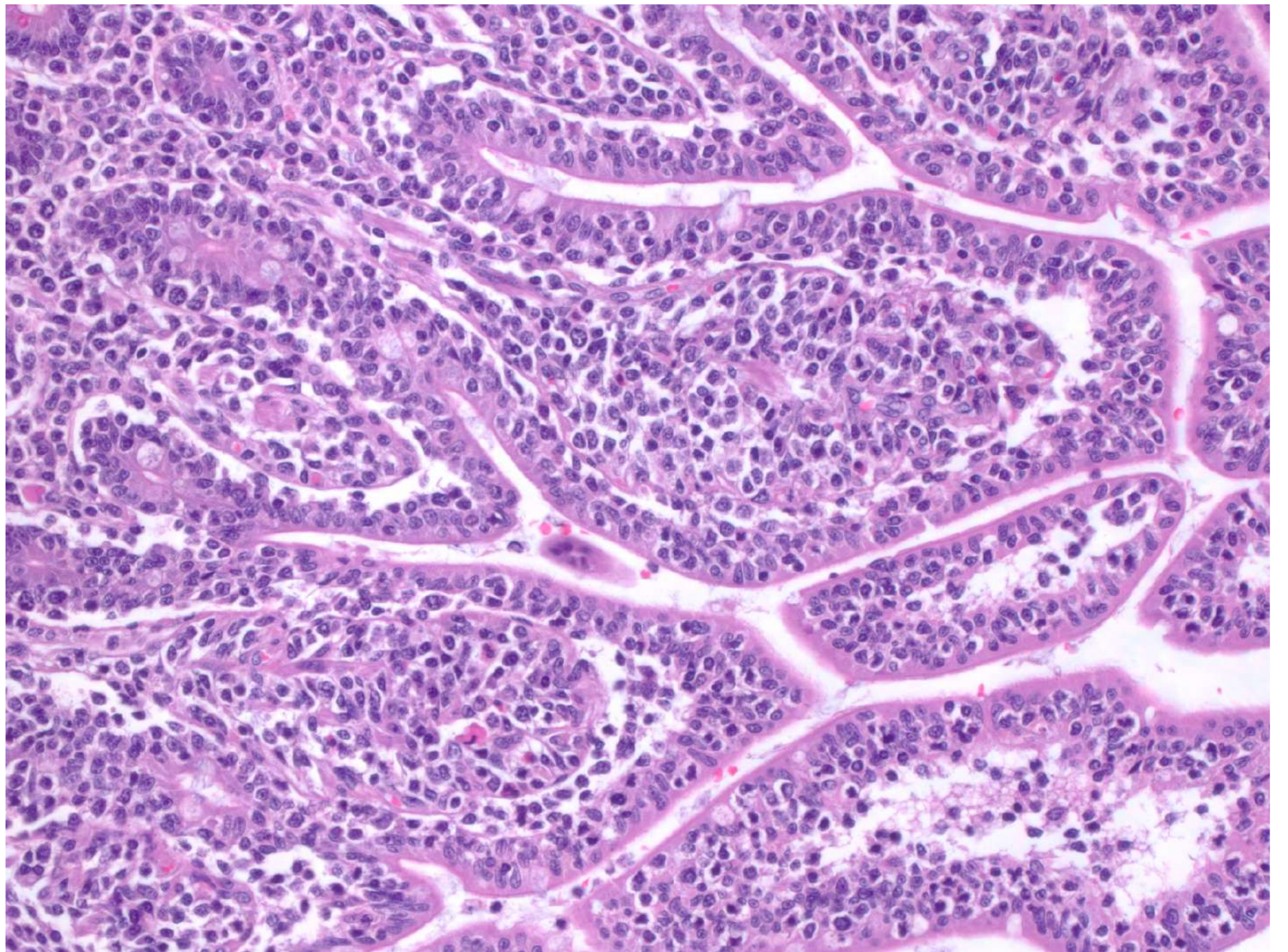
- Lack of association with celiac disease
- Occurs in any race, but accounts for ~all cases of EATL in Asians
- Monotonous infiltrate of small and/or medium-sized neoplastic lymphoid cells
- Few admixed reactive cells
- Absence of necrosis except in ulcer bed
- Immuno: CD3+, CD5-, CD8+, CD56+/-, often TCR $\gamma\delta$ +
- Adjacent or distant mucosa: Abnormal, increased IELs without other features of celiac disease
- Differing cytogenetic abnormalities from EATL, type I
- Suggested name: Monomorphic intestinal T-cell lymphoma

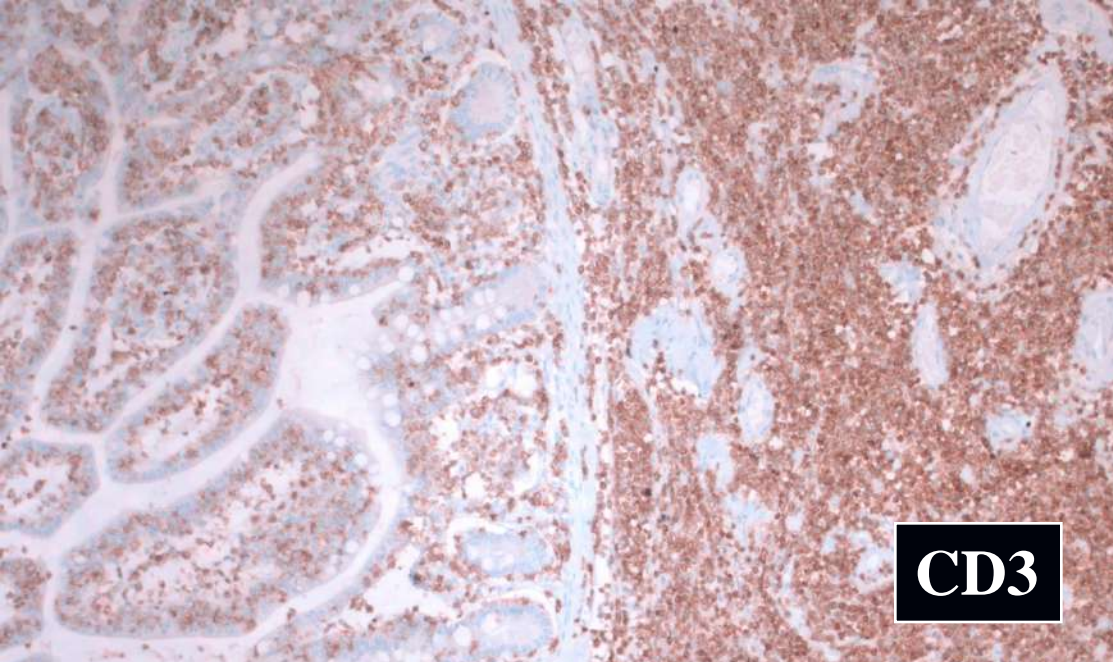


EATL, type II

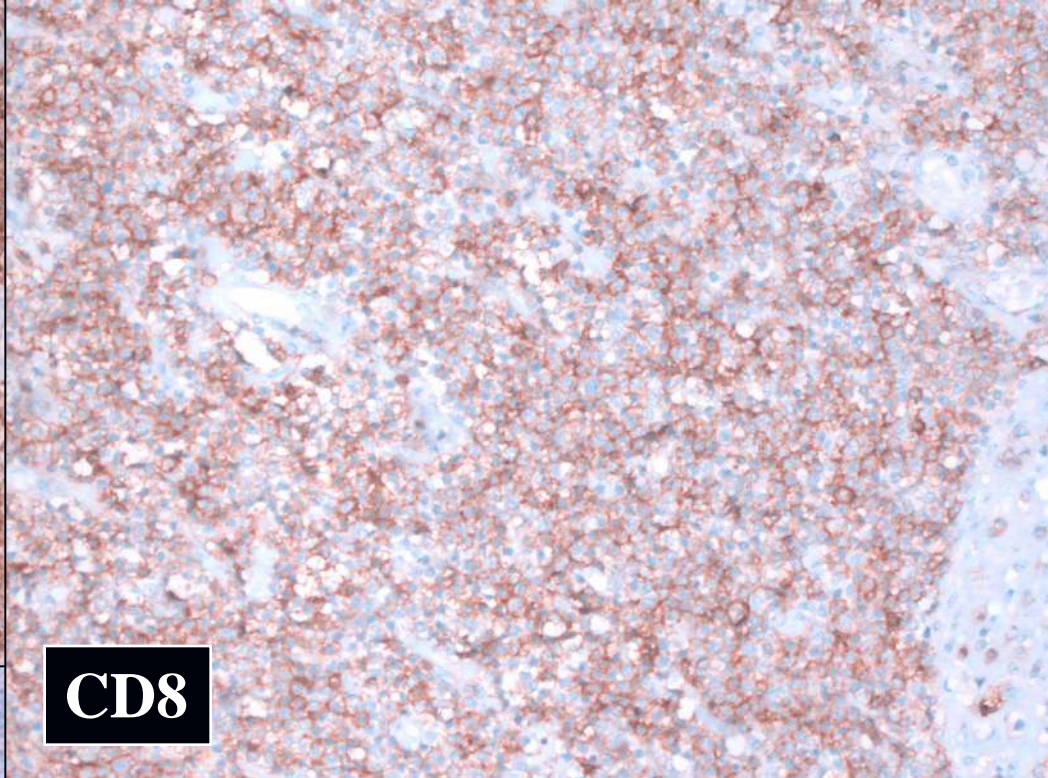




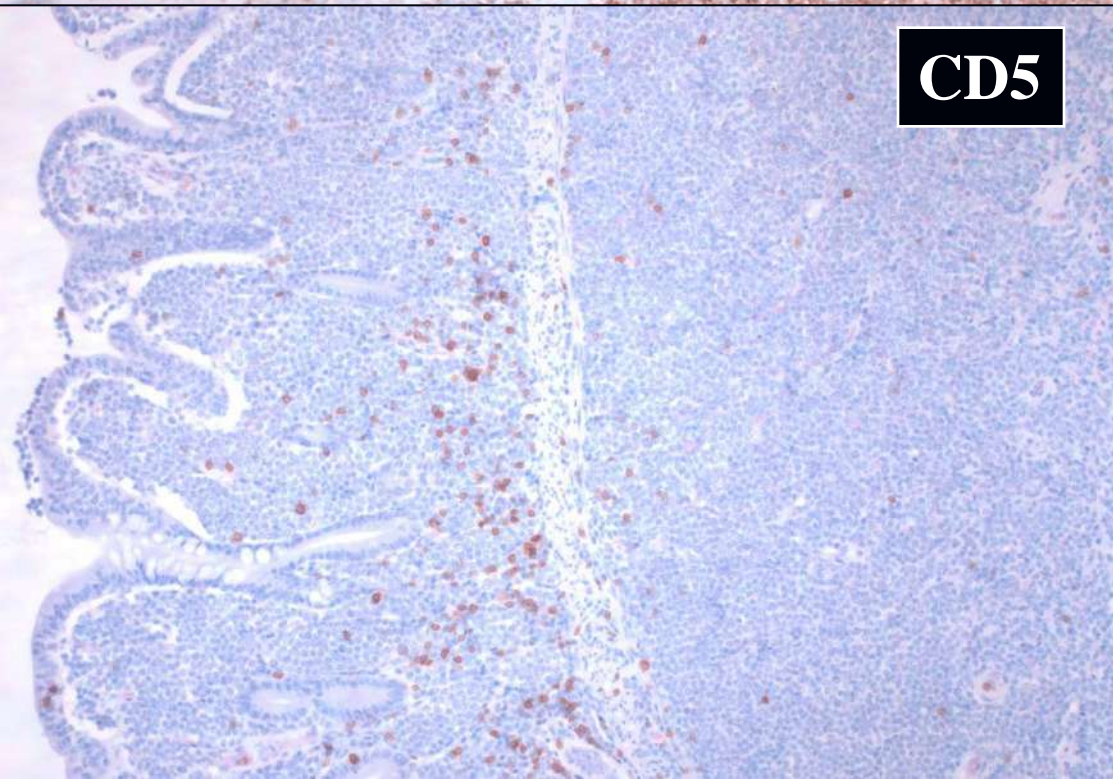




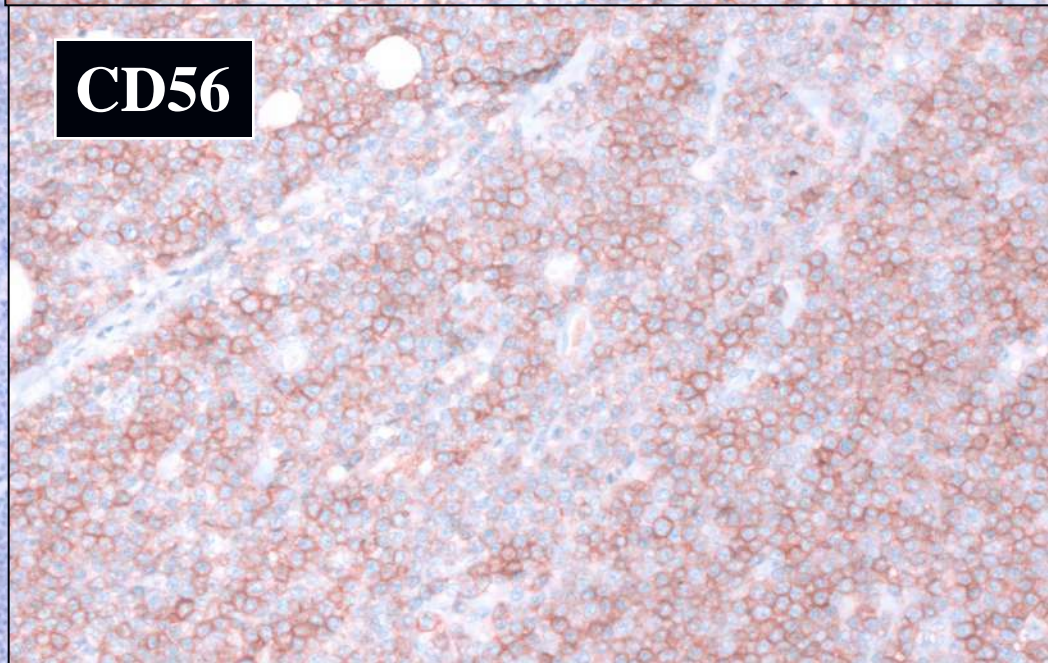
CD3



CD8



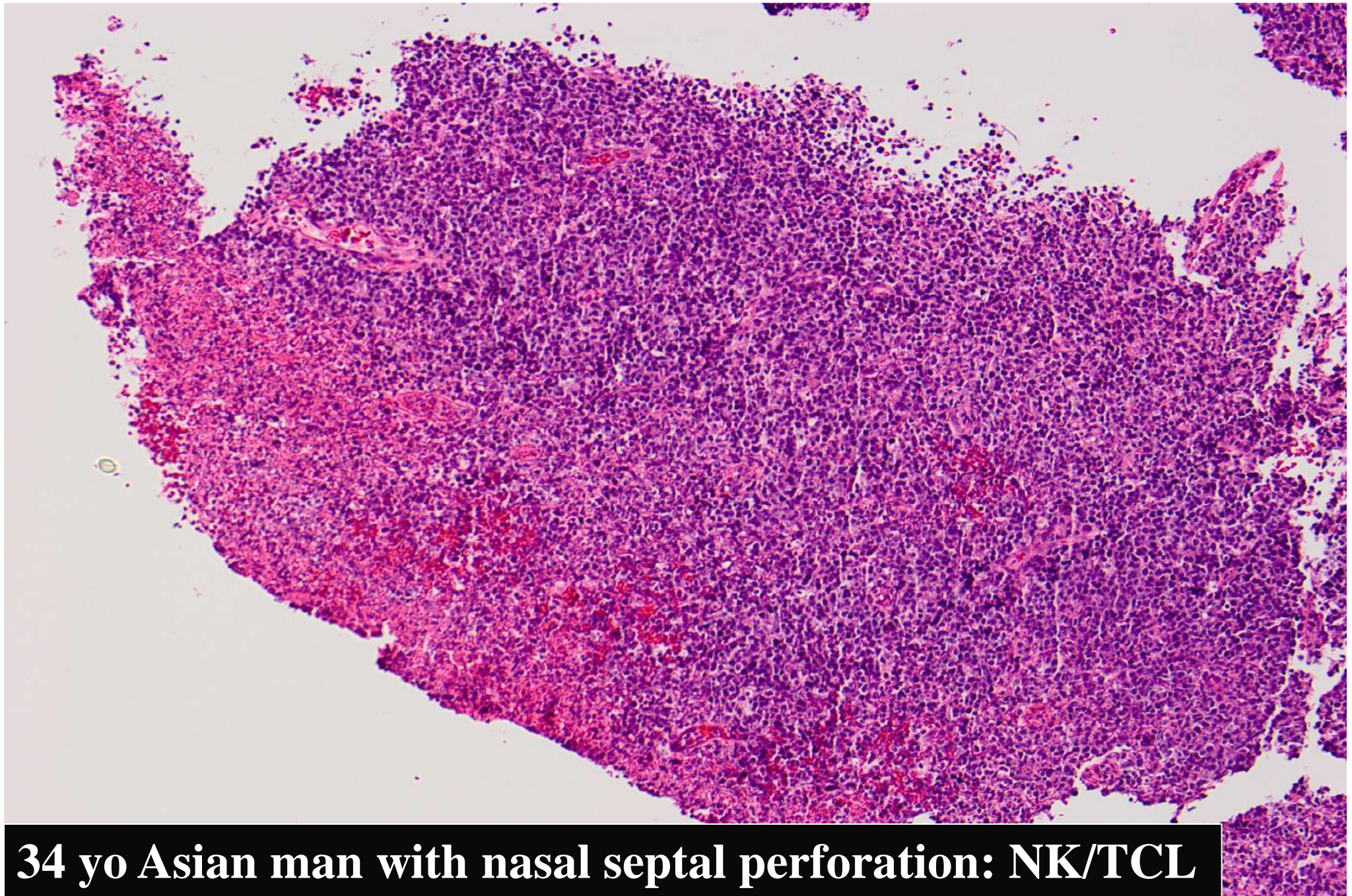
CD5



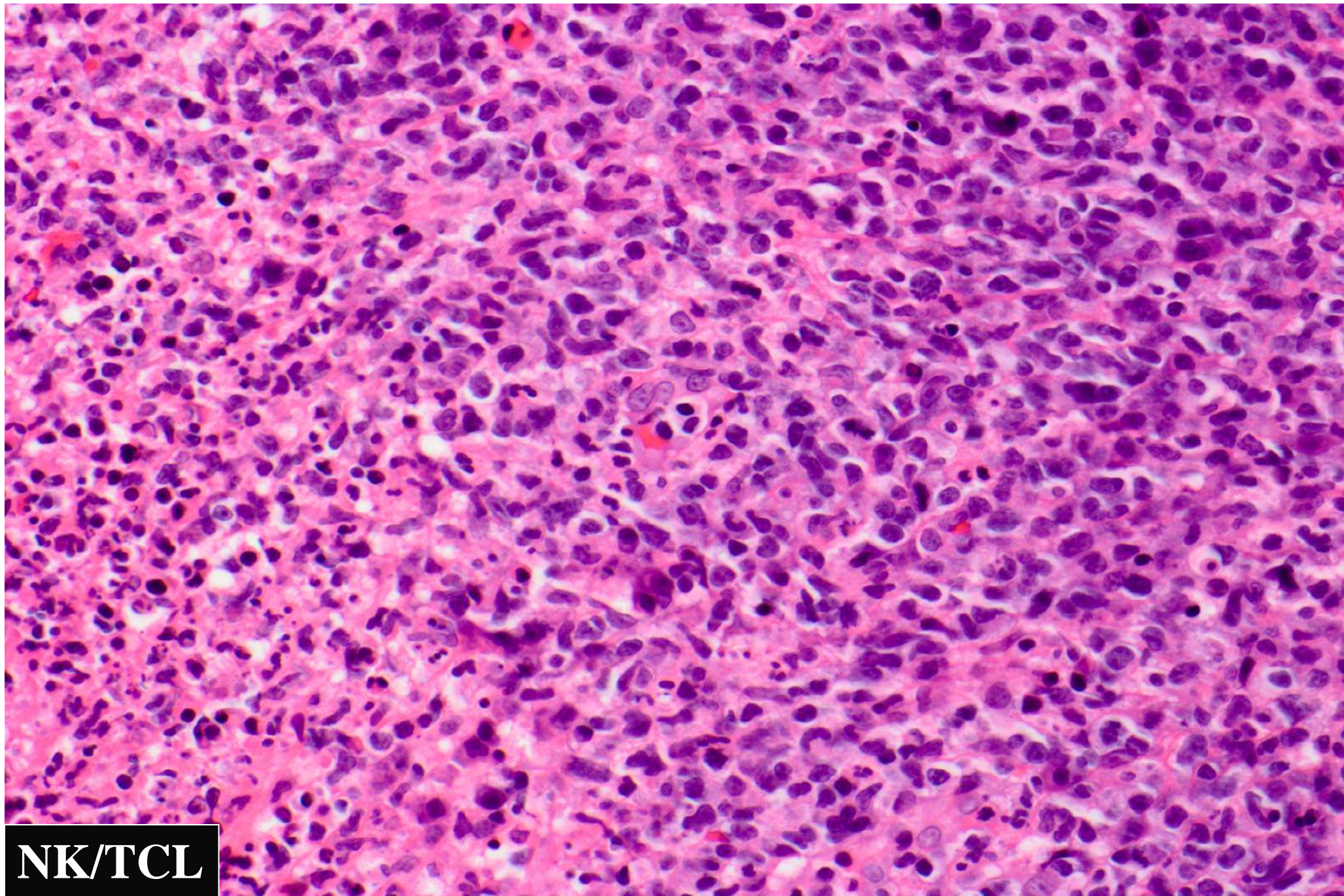
CD56

Extranodal NK/T-Cell Lymphoma, Nasal-Type

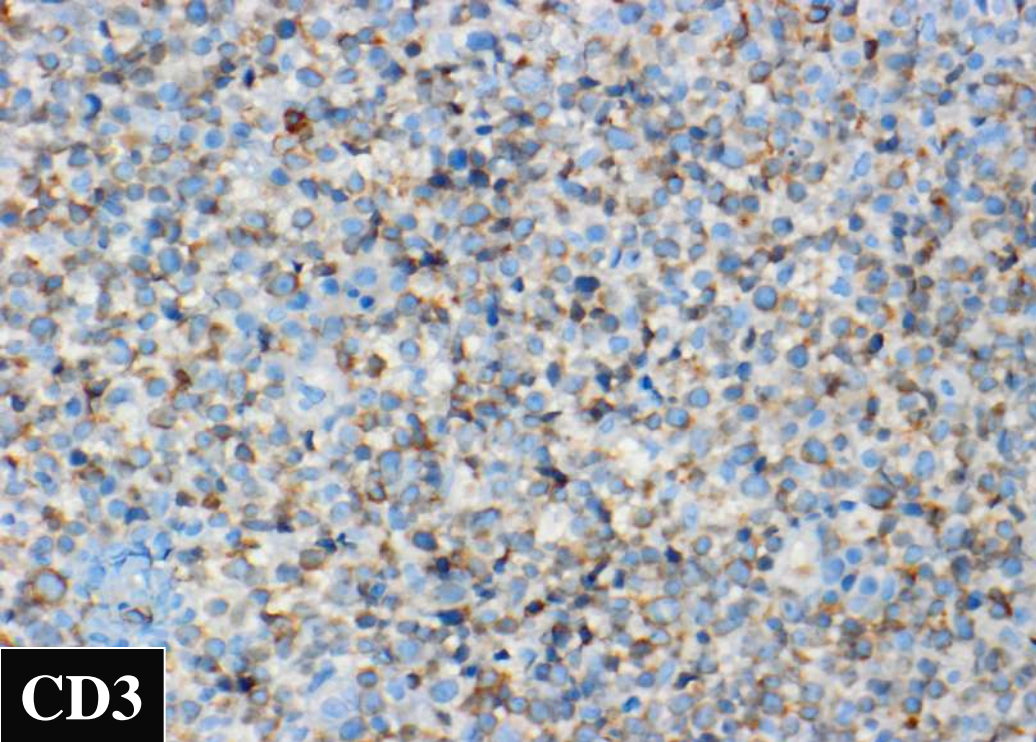
- **Adults, rarely children; Asians, native Americans > Caucasians**
- **Destructive nasal or midfacial tumor**
- **Other sites: non-nasal URT sites (such as larynx), skin, GI tract, testis**
- **Usually stage I**
- **Cytology: cells may be small, medium-sized, irregular, uniform or pleomorphic or large & bizarre**
- **Most: NK cell origin; minority: T cell origin**
- **sCD3-, cCD3+, CD56+, perforin+, TIA-1+, granzyme B+ (cytotoxic phenotype)**
- **TCR usually germline (NK cell), occasionally rearranged (T cell)**
- **EBV+**
- **Poor prognosis historically; good prognosis with low stage and RT**
- **Hemophagocytic syndrome, some cases**



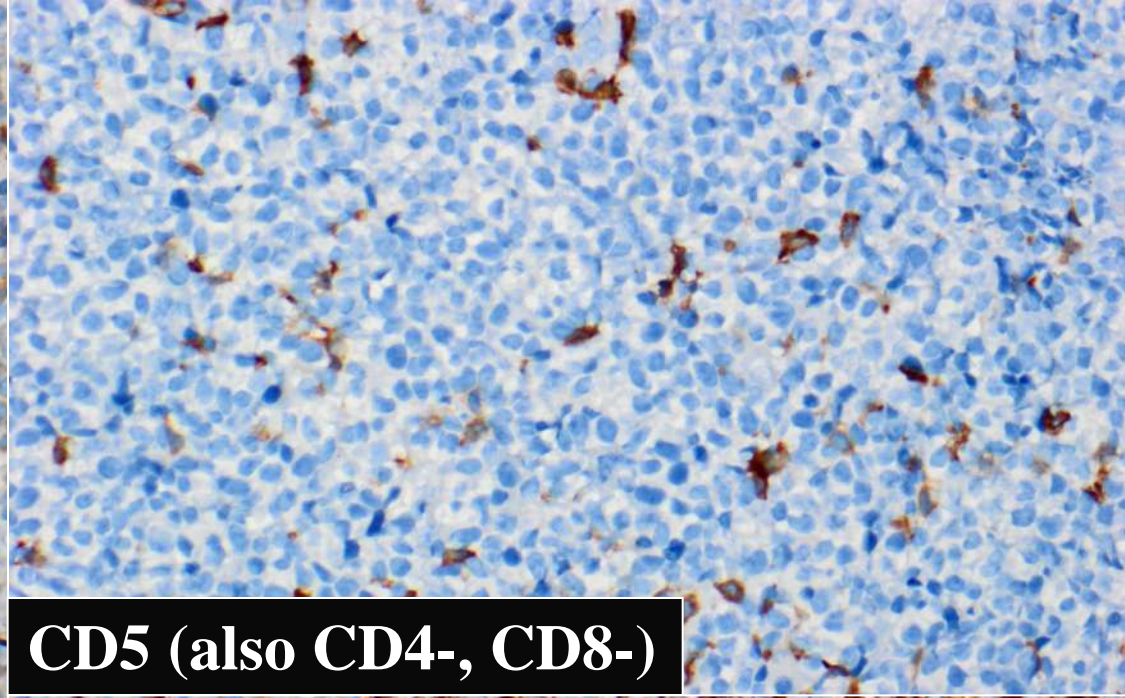
34 yo Asian man with nasal septal perforation: NK/TCL



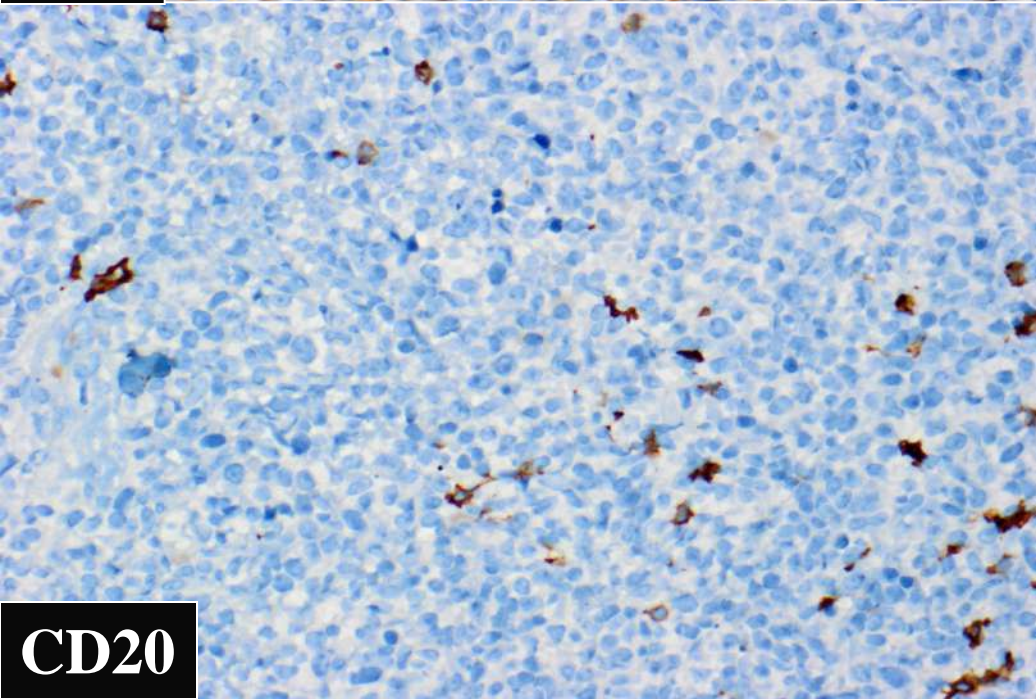
NK/TCL



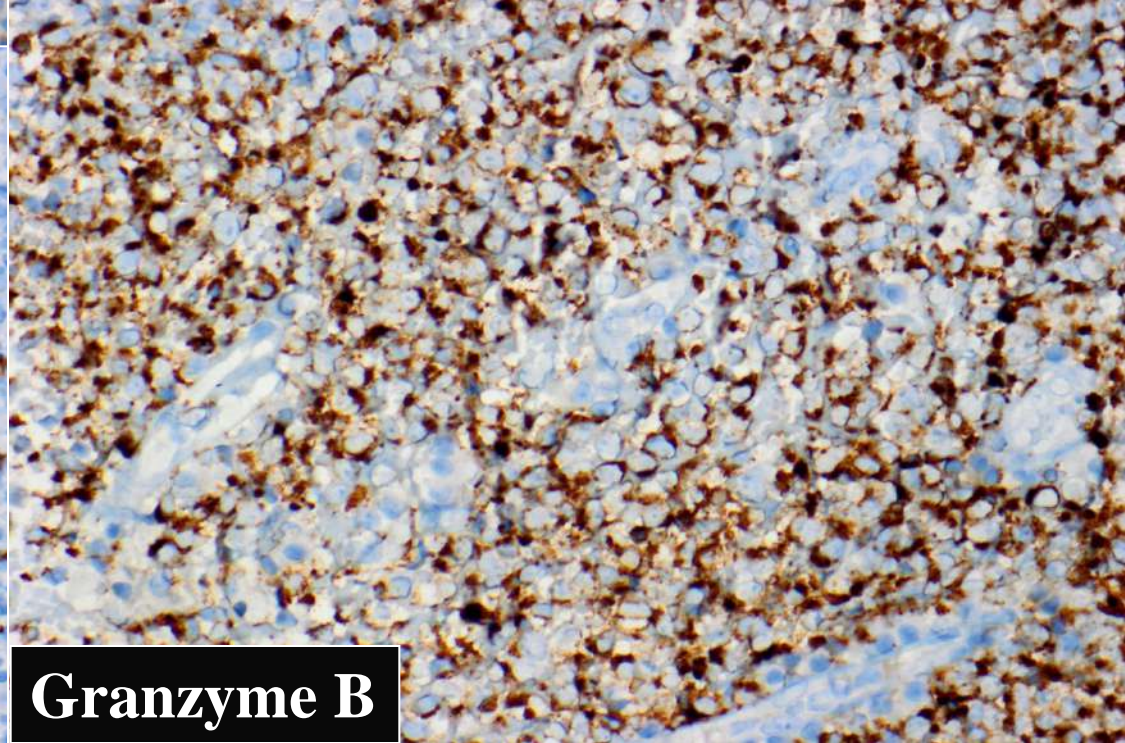
CD3



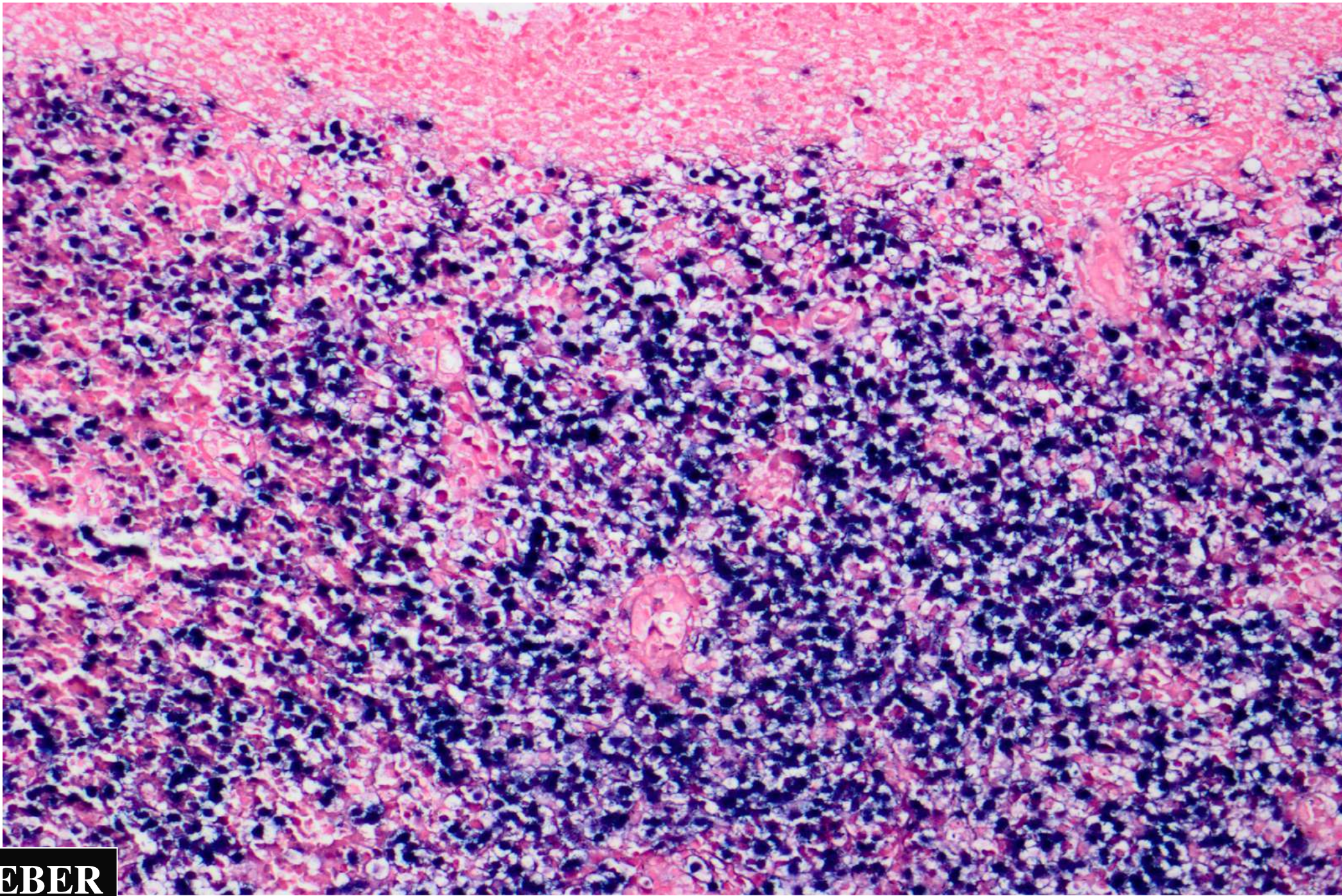
CD5 (also CD4-, CD8-)



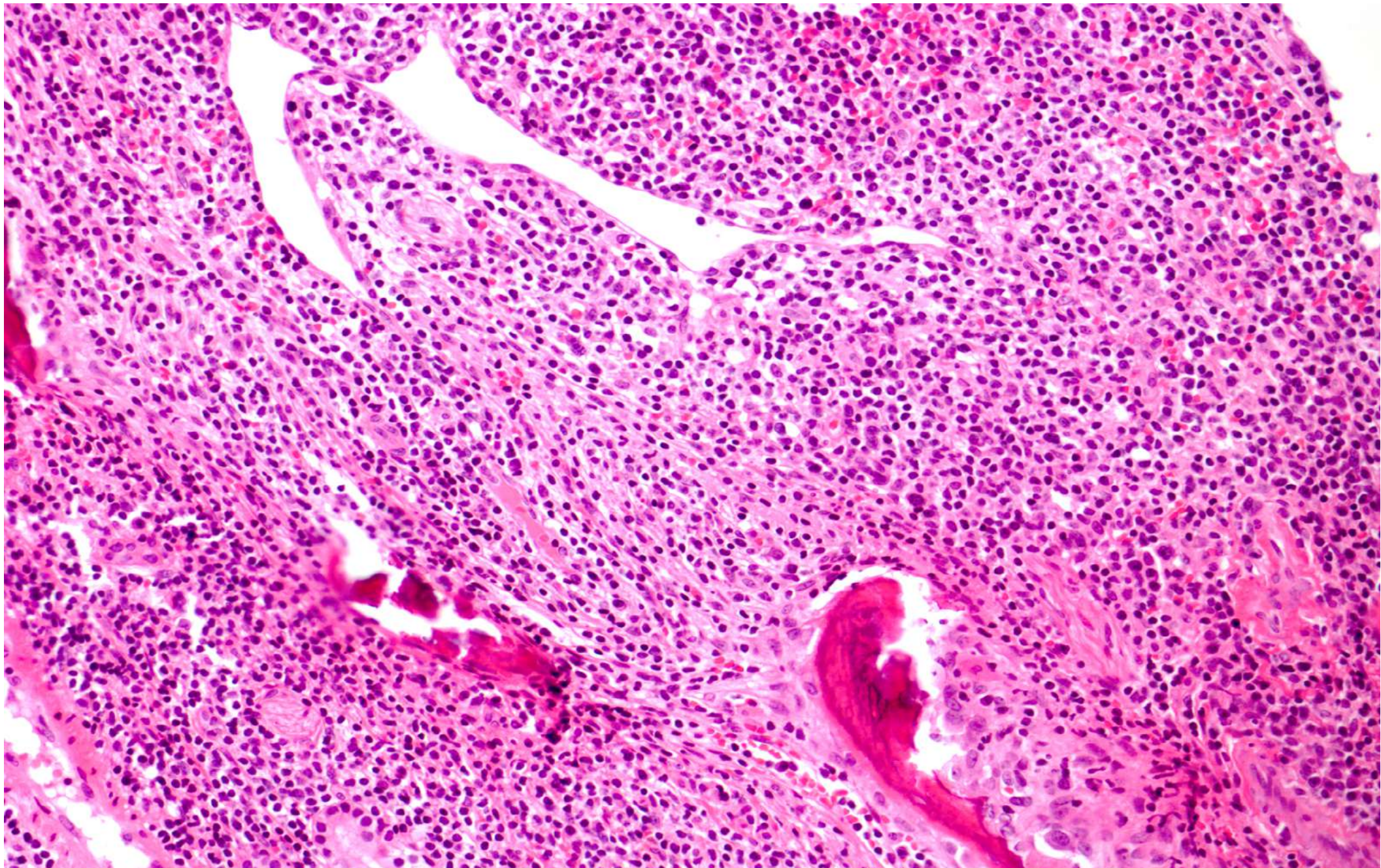
CD20



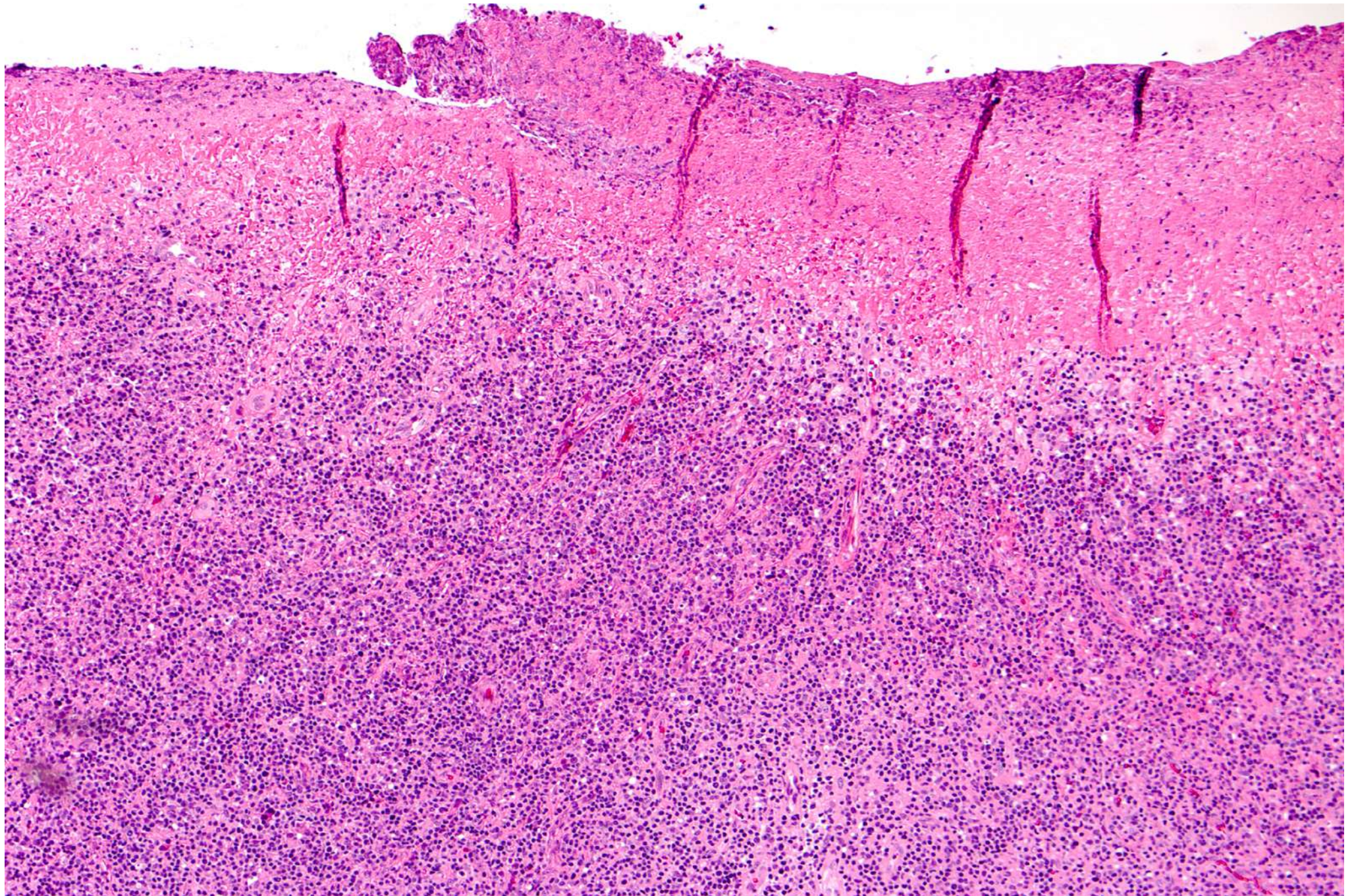
Granzyme B

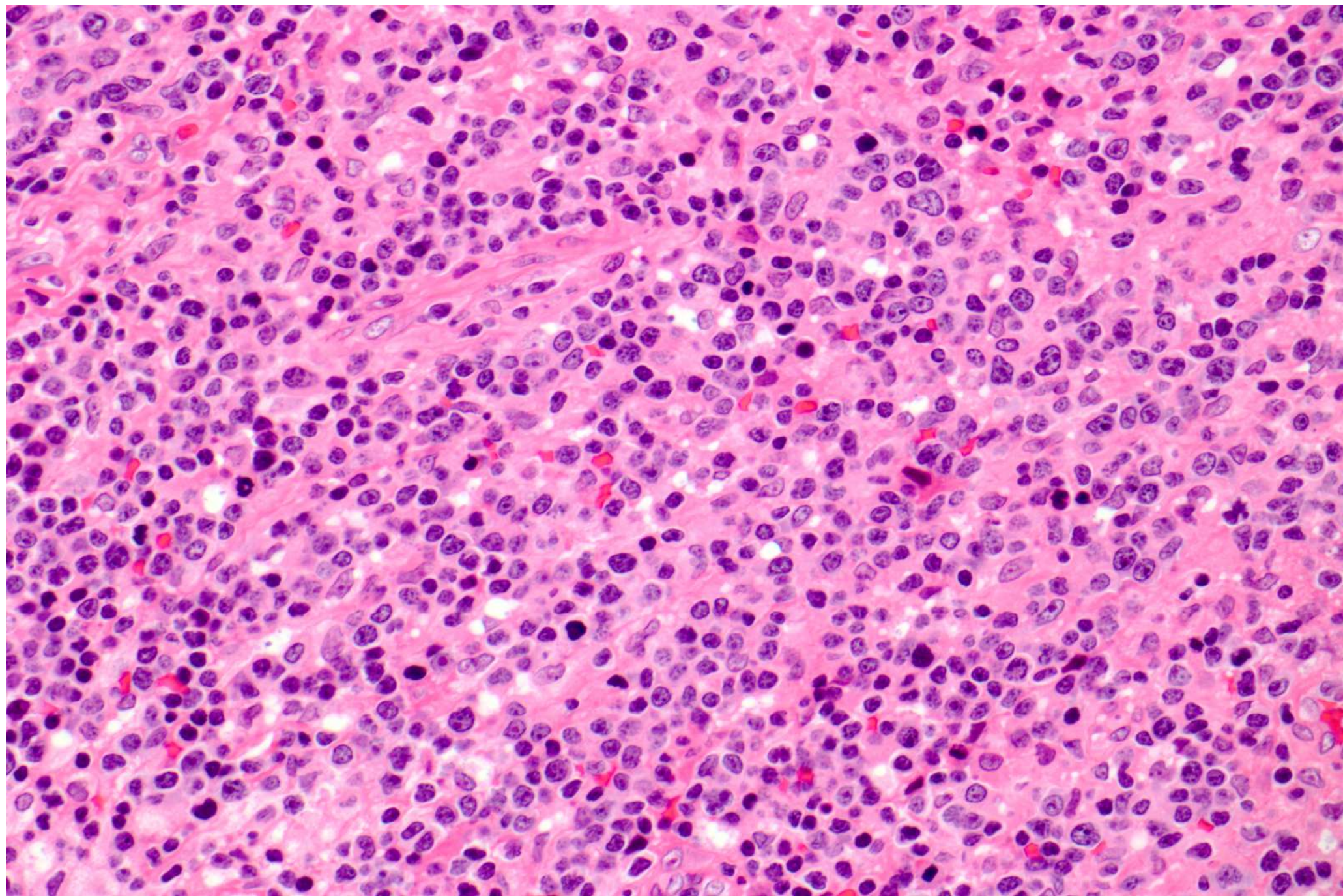


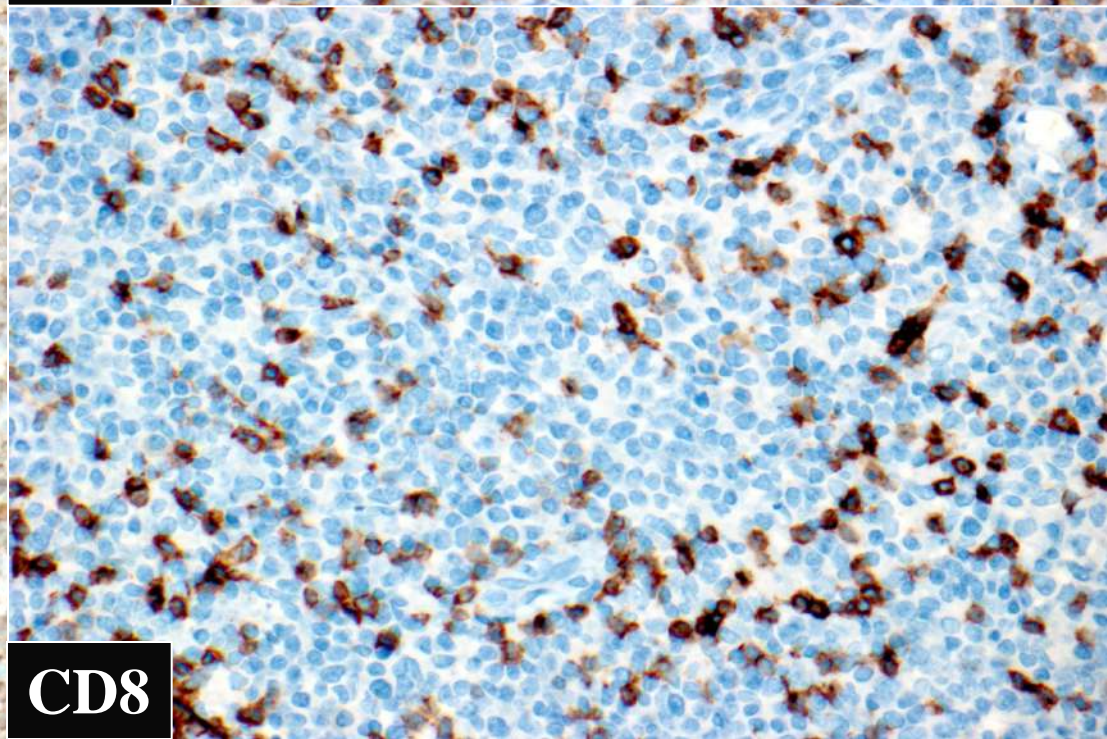
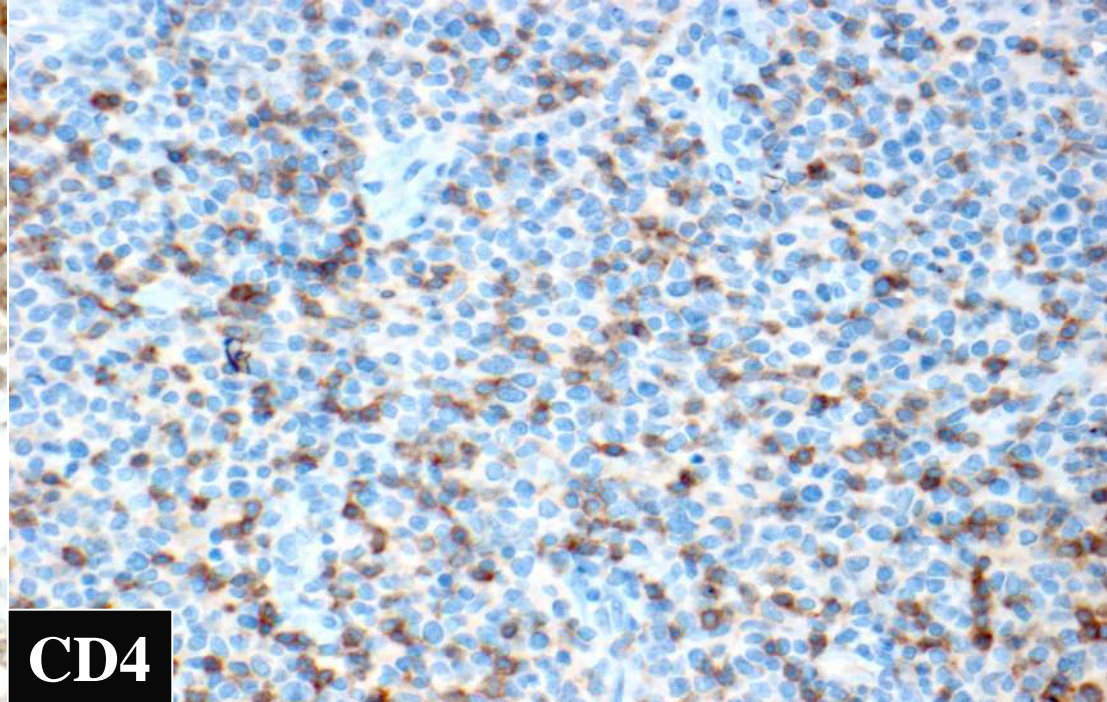
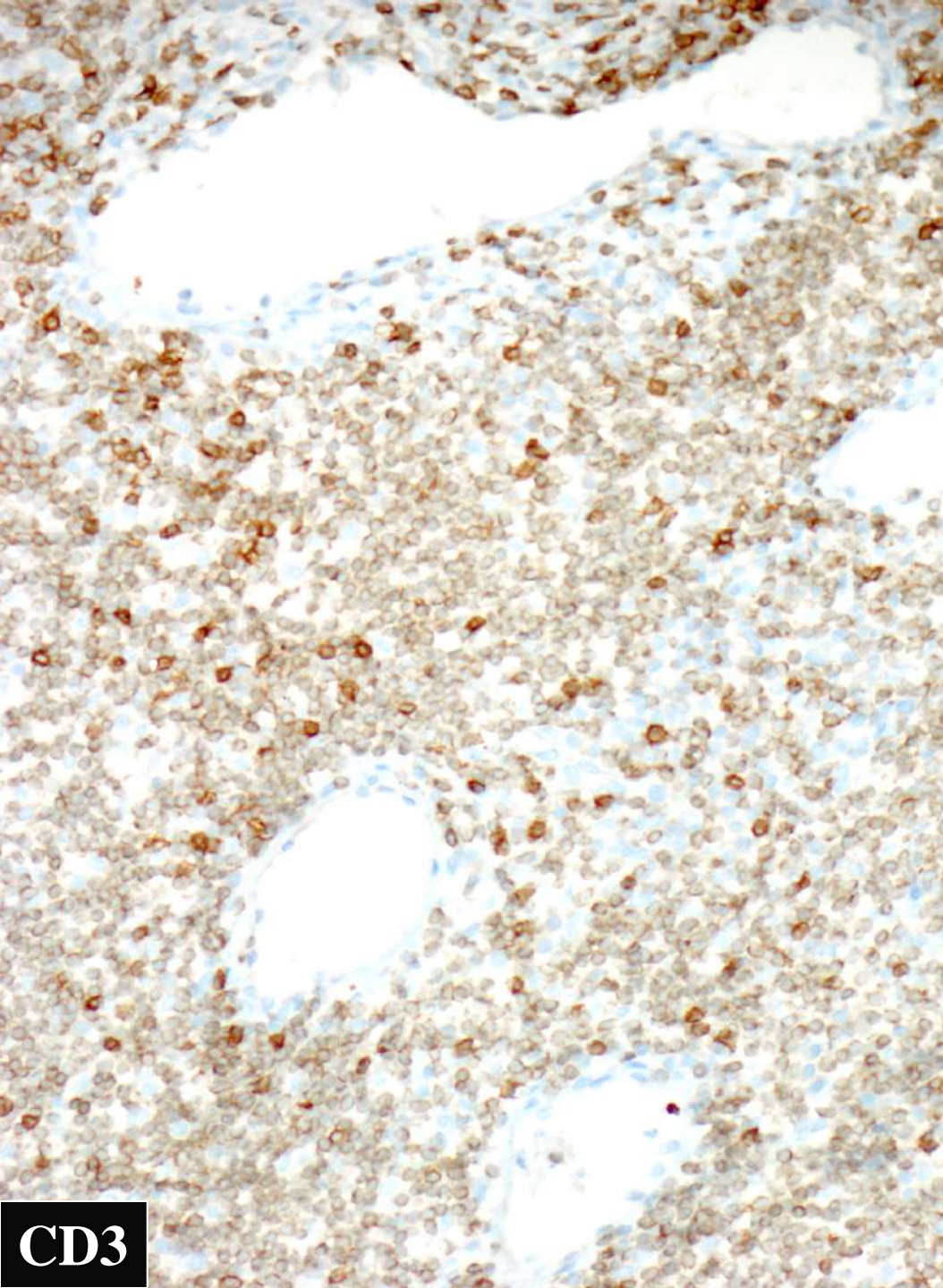
EBER

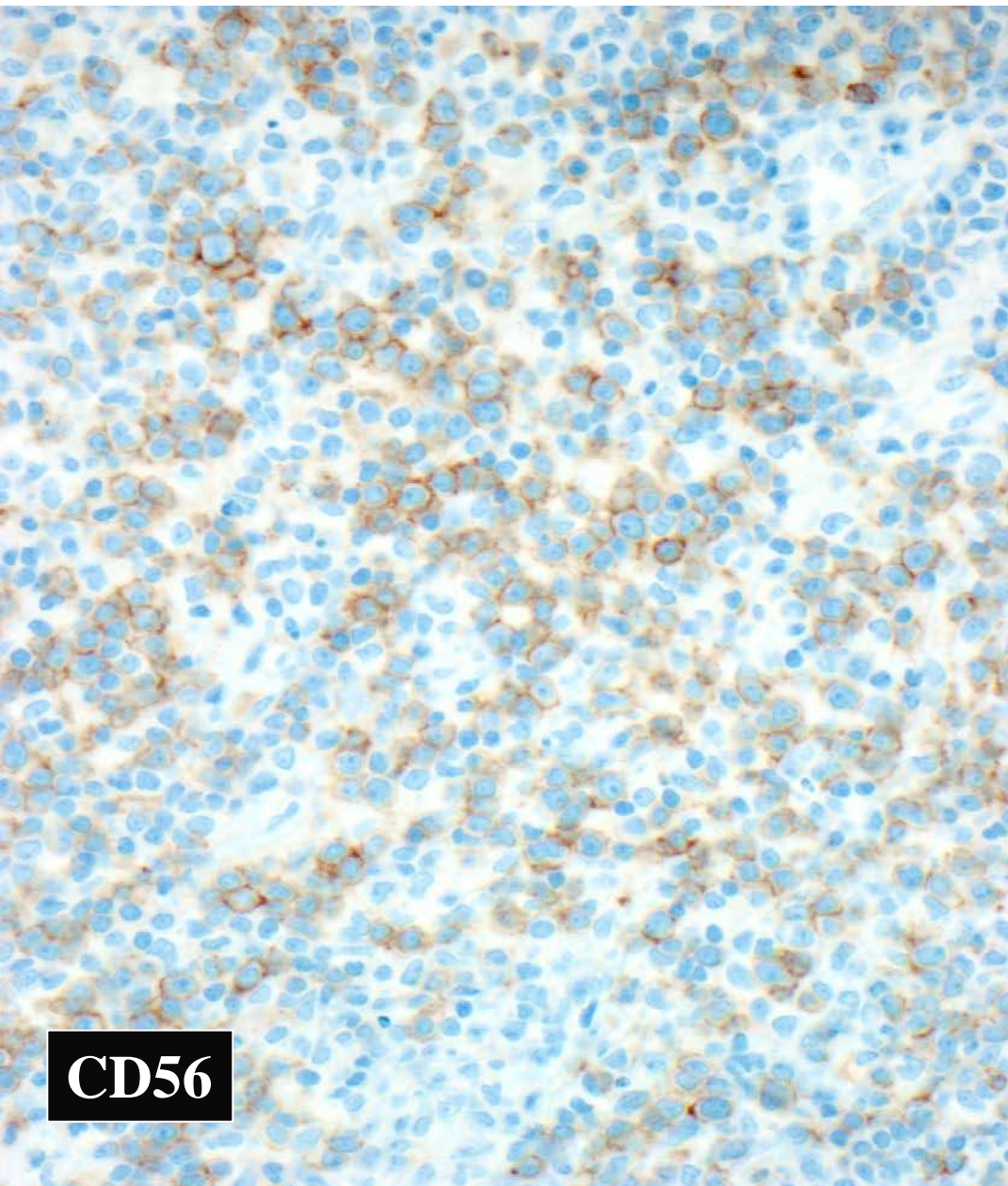


31 yo Hispanic female with severe chronic rhinosinusitis, loss of smell

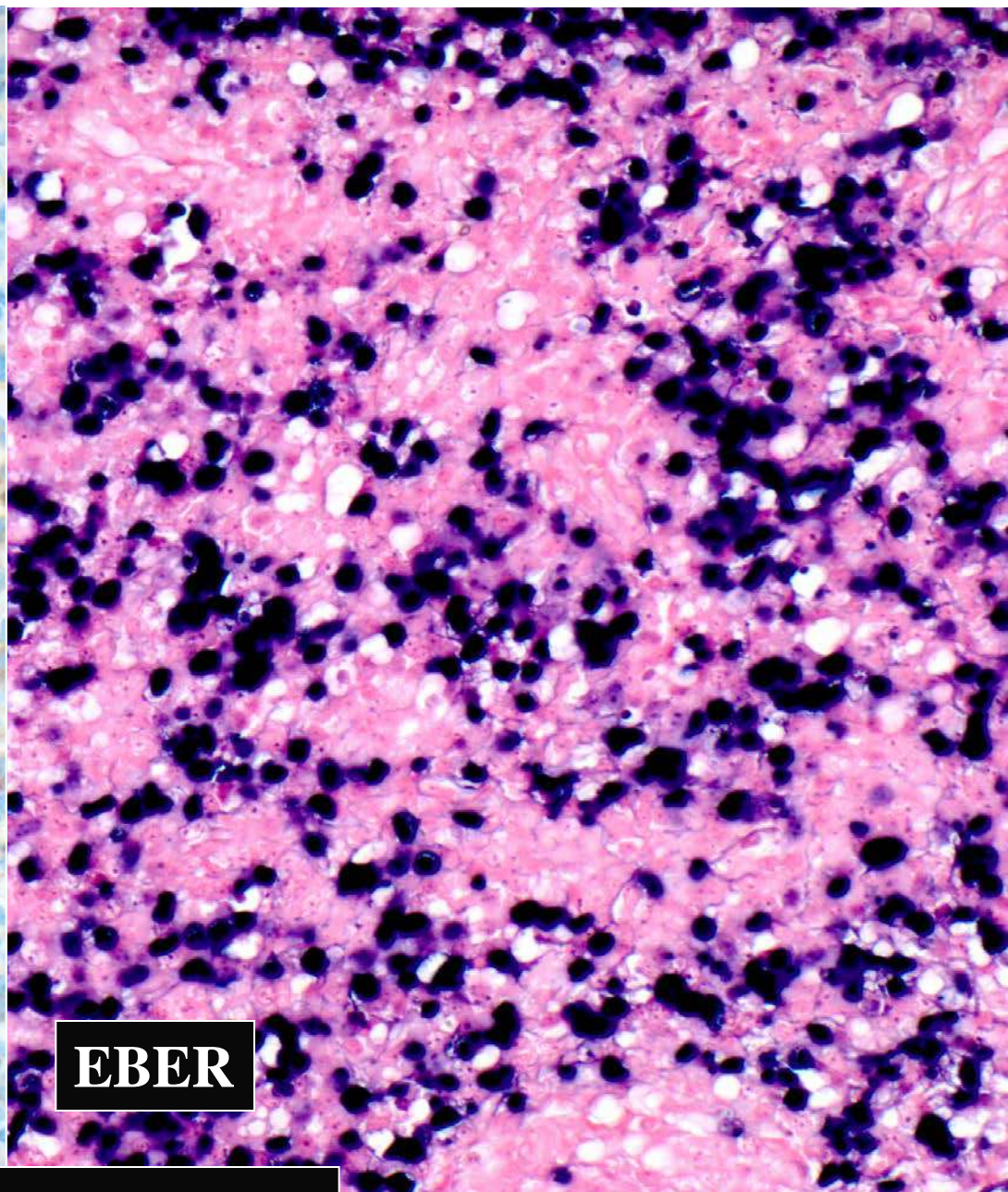








CD56



EBER

Diagnosis: extranodal (nasal) NK/T-cell lymphoma

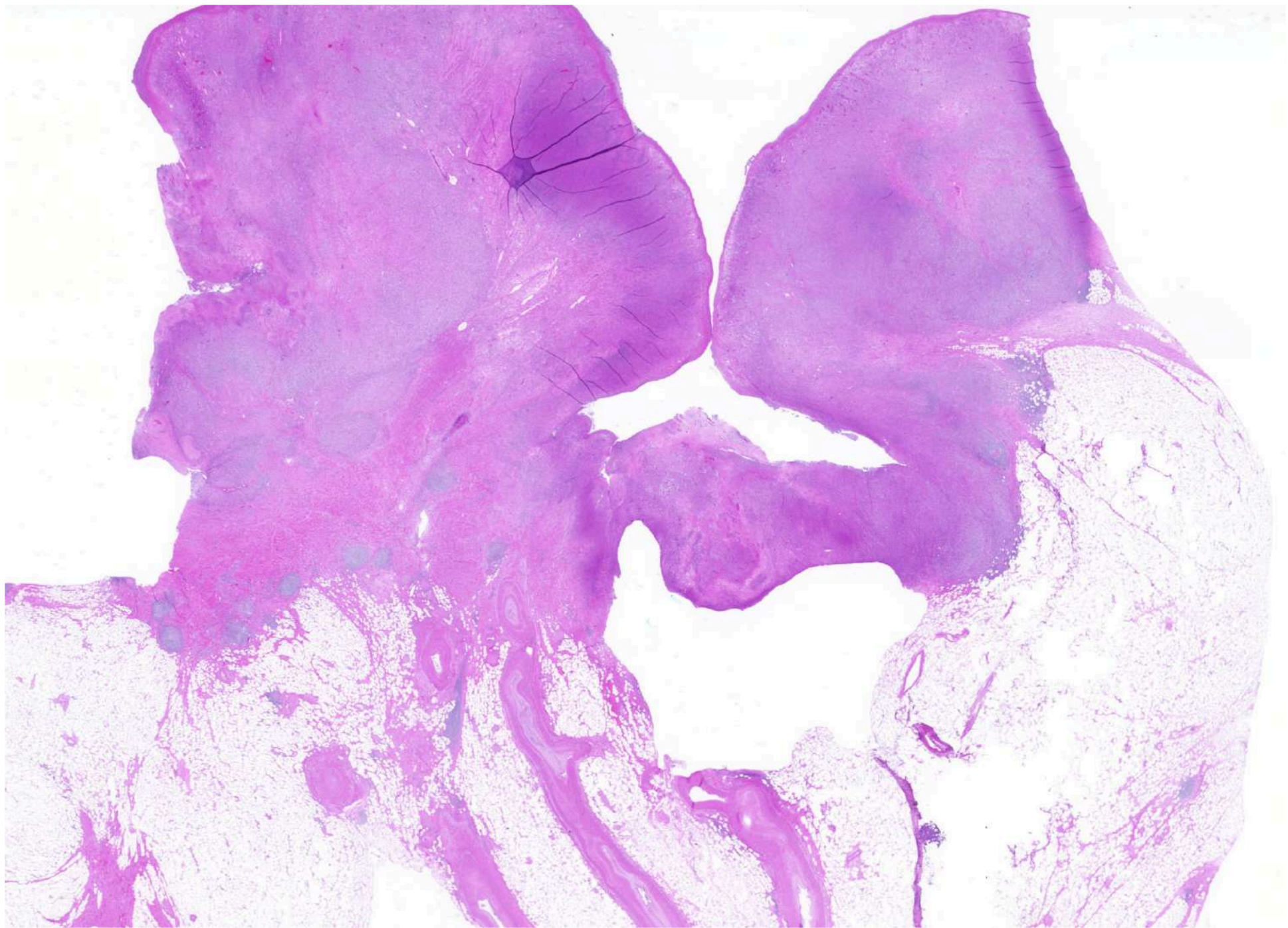
Hodgkin's Lymphoma in Extranodal Sites

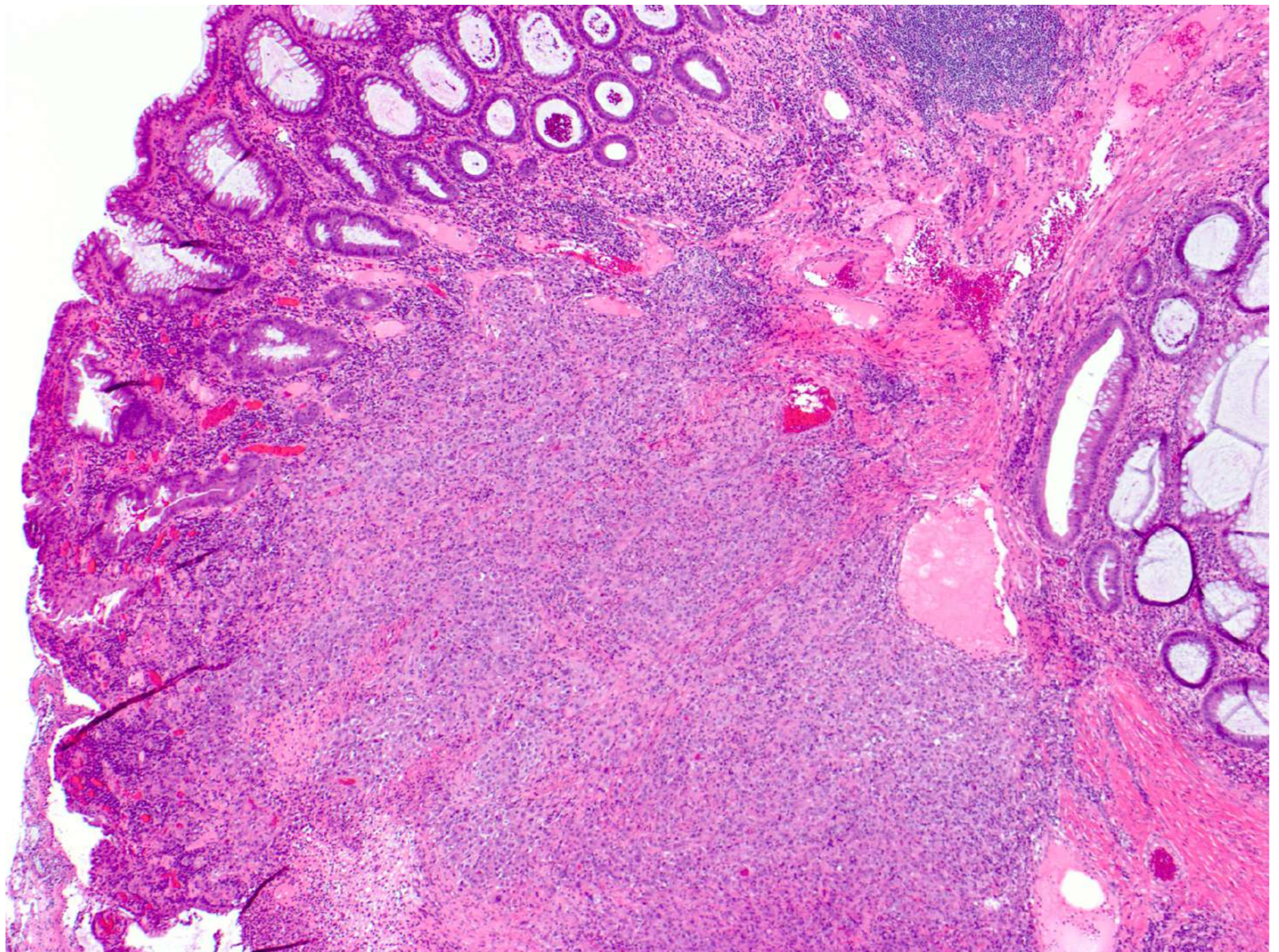
- Primary extranodal Hodgkin's lymphoma is rare
- Primary GI Hodgkin's lymphoma is a distinct entity
- <0.5% of all Hodgkin's arises in GI tract
- Broad age range, males > females
- Underlying IBD common (Crohn's >> UC)
- Hodgkin's arises in areas with IBD
- Symptoms mimic exacerbation of IBD
- Other immunologic abnormality in some cases
- ~Always classical Hodgkin's lymphoma
- ~Always EBV+
- Differential: NHL, carcinoma, benign ulcer, Hodgkin's-like lesions related to immunosuppression
- Diagnose Hodgkin's in extranodal sites with caution

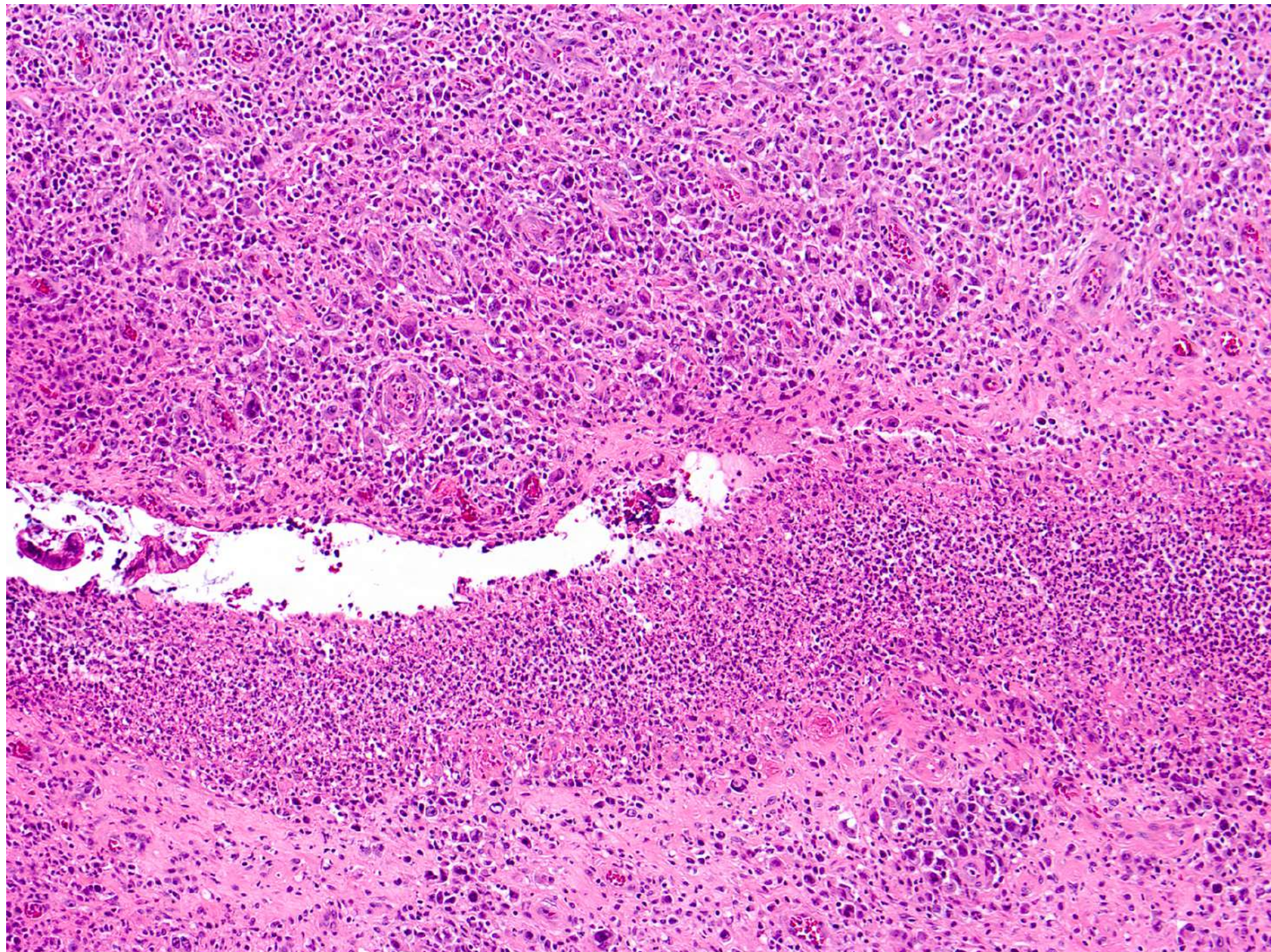
Mass General Hospital Pathology Department
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

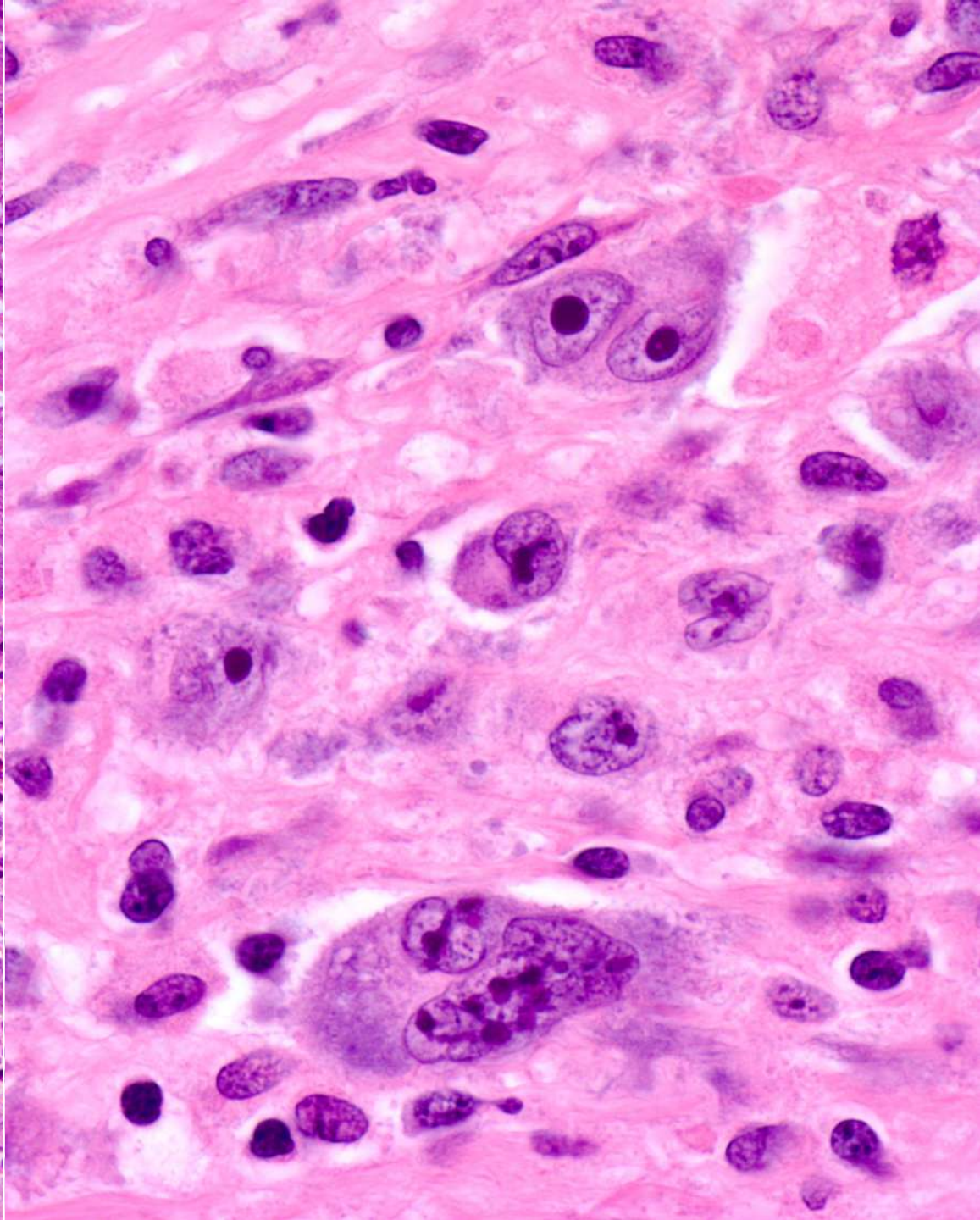
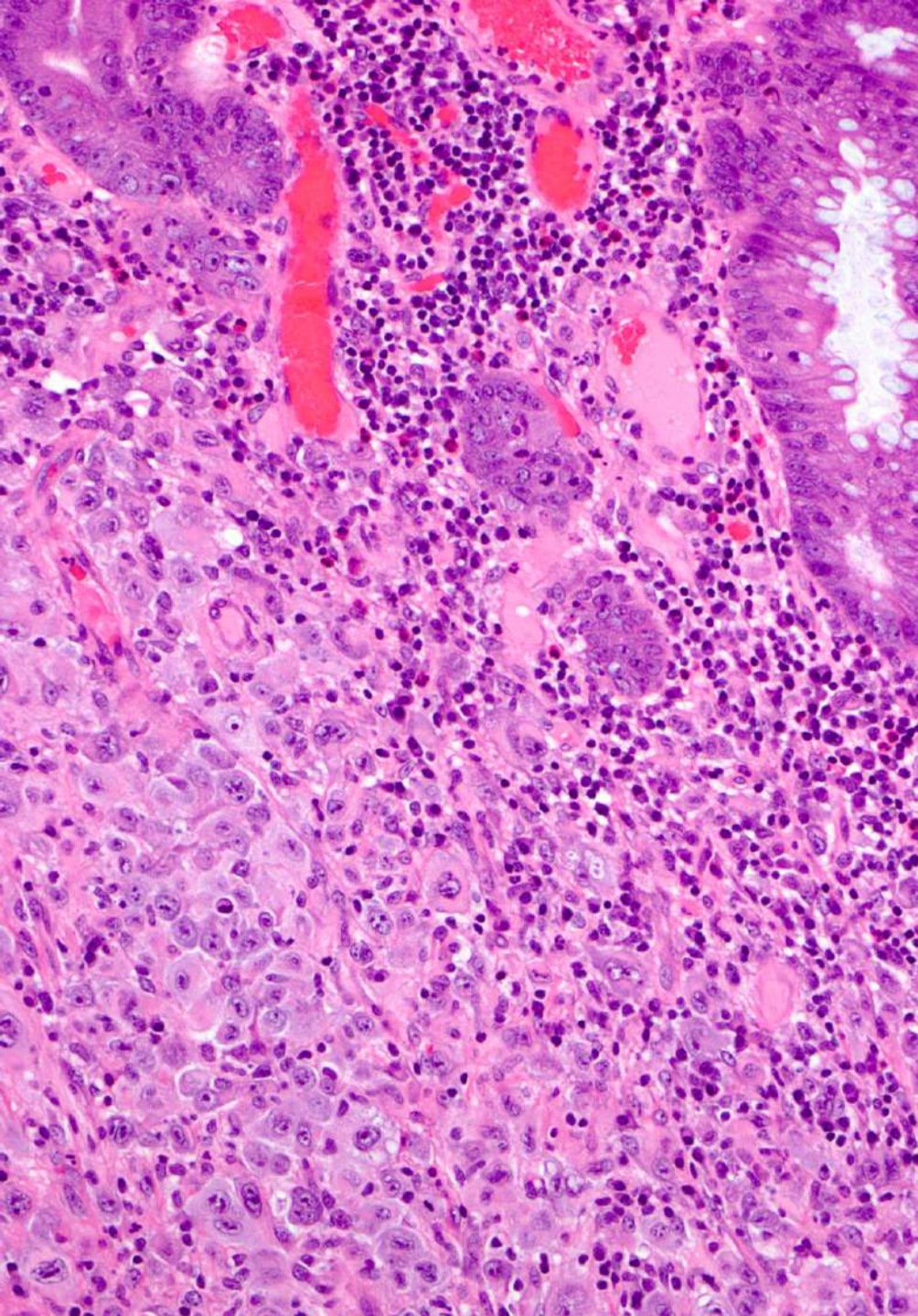


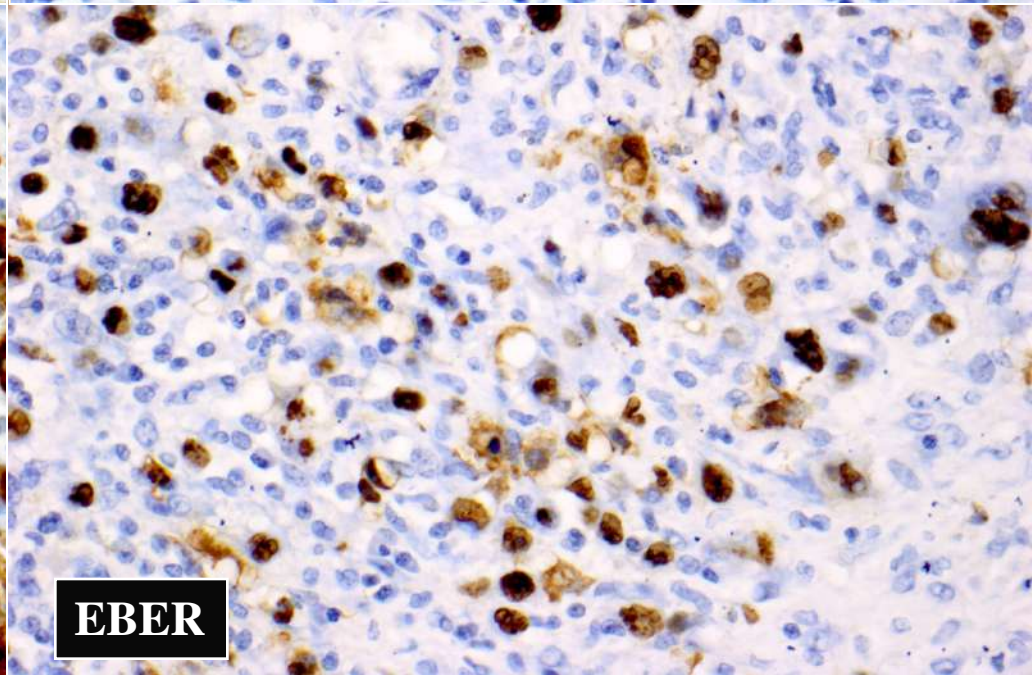
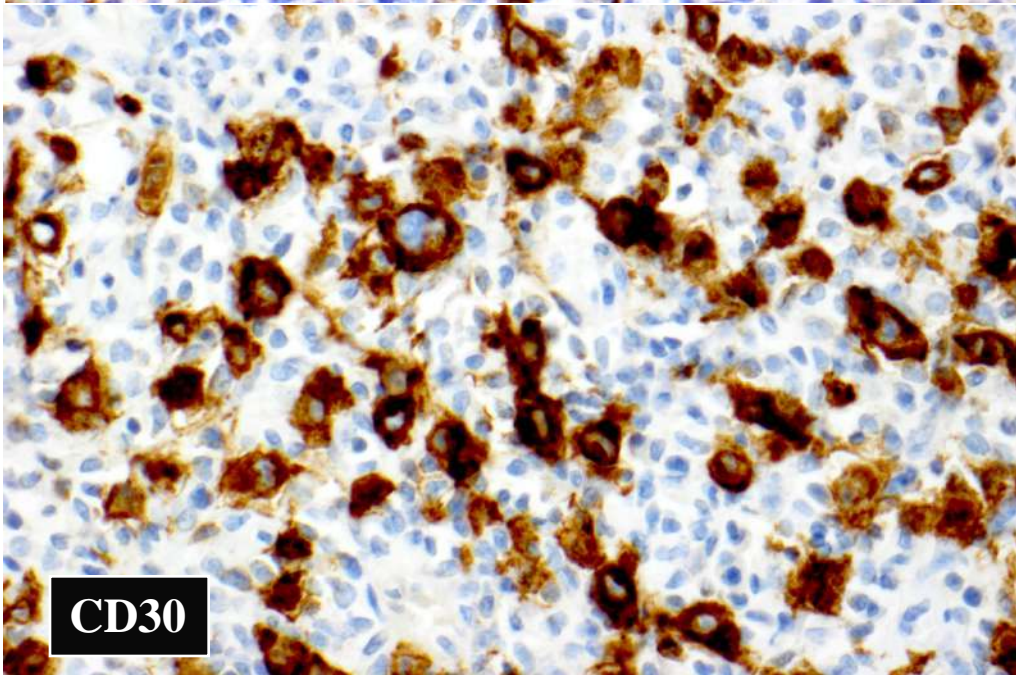
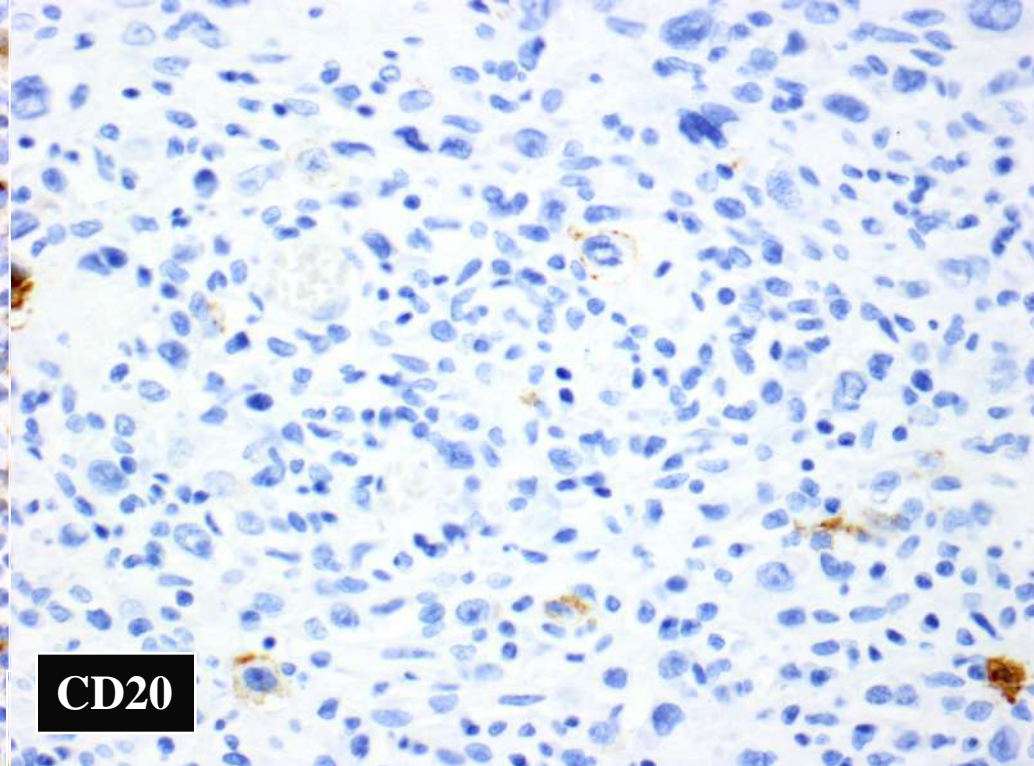
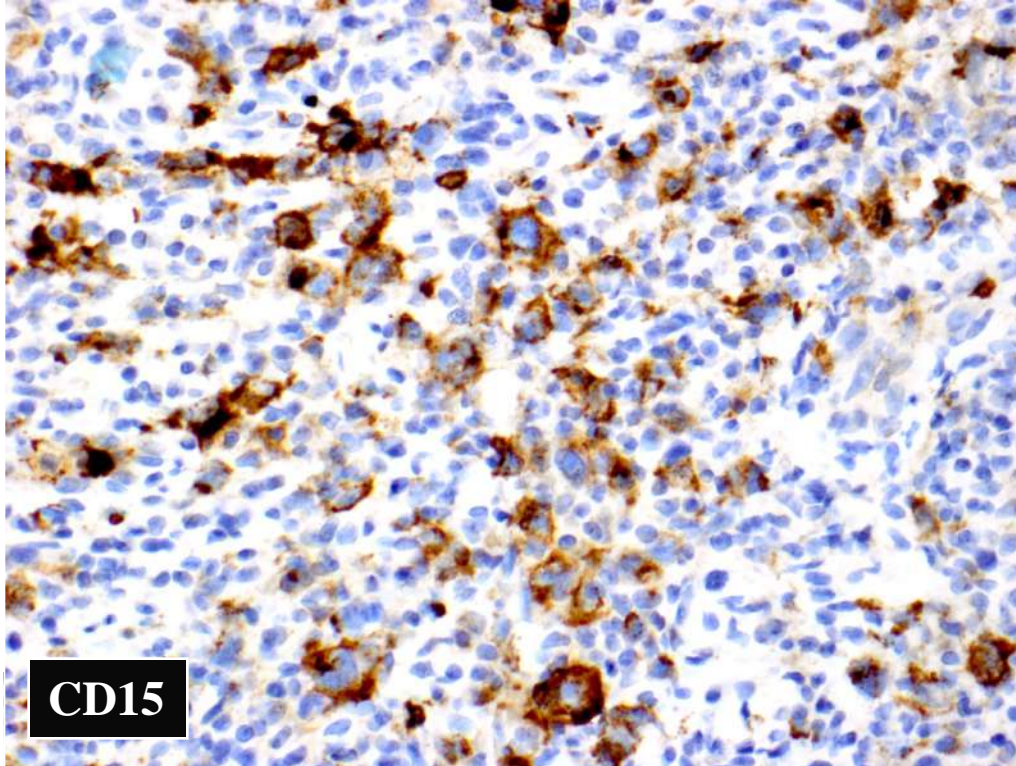
**67-year-old male, h/o Crohn's:
classical Hodgkin's lymphoma**





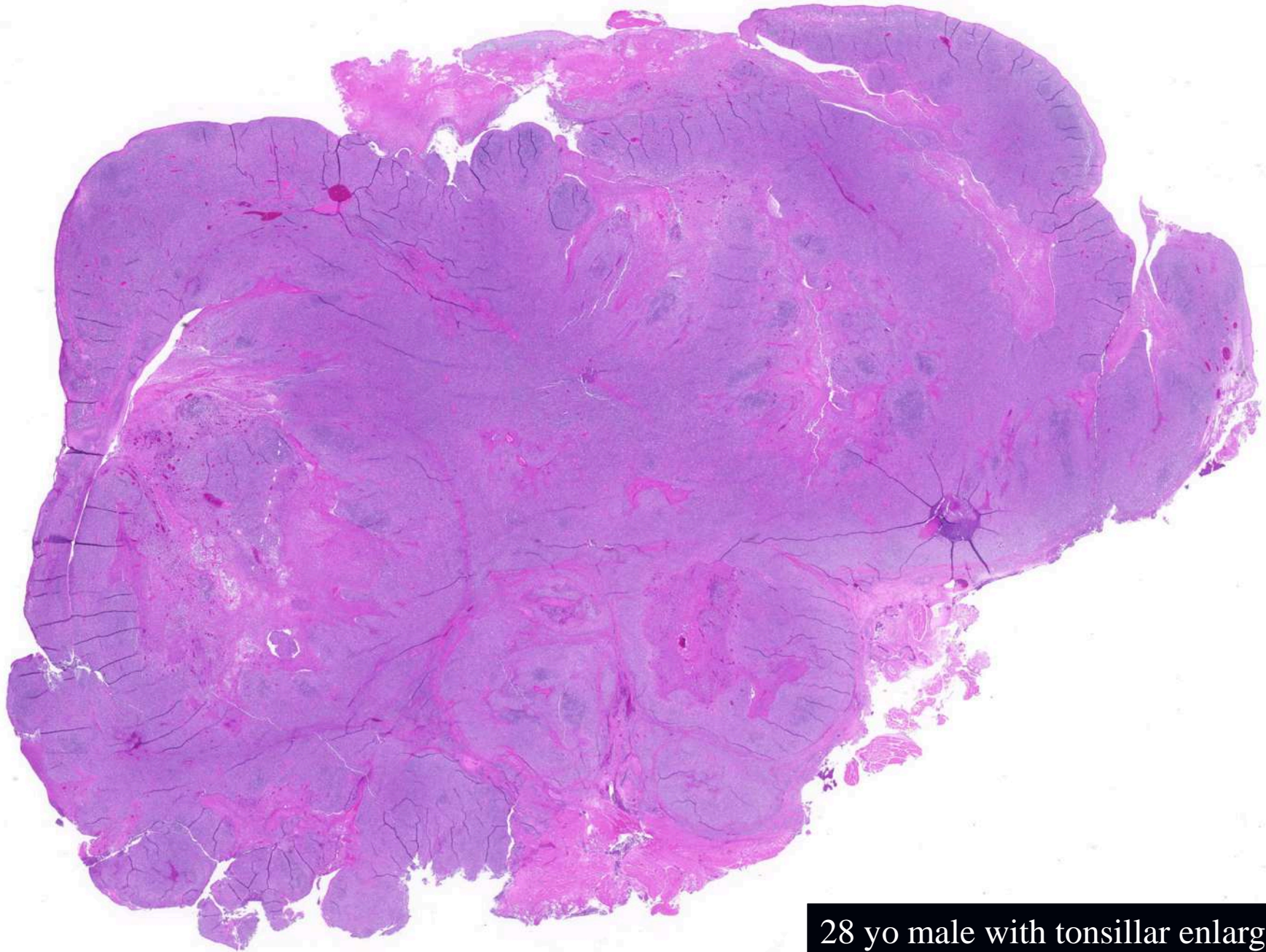




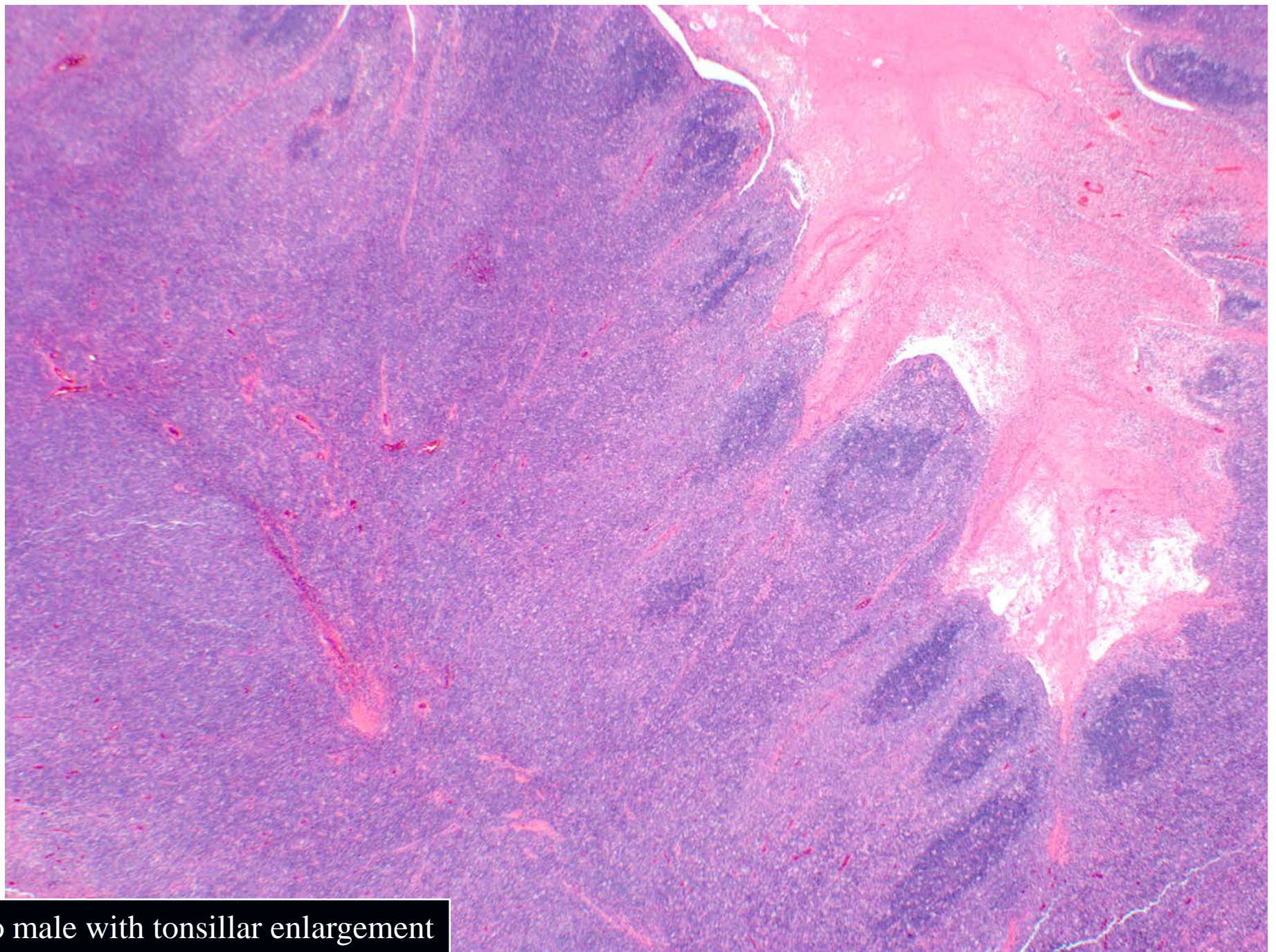


One last case...

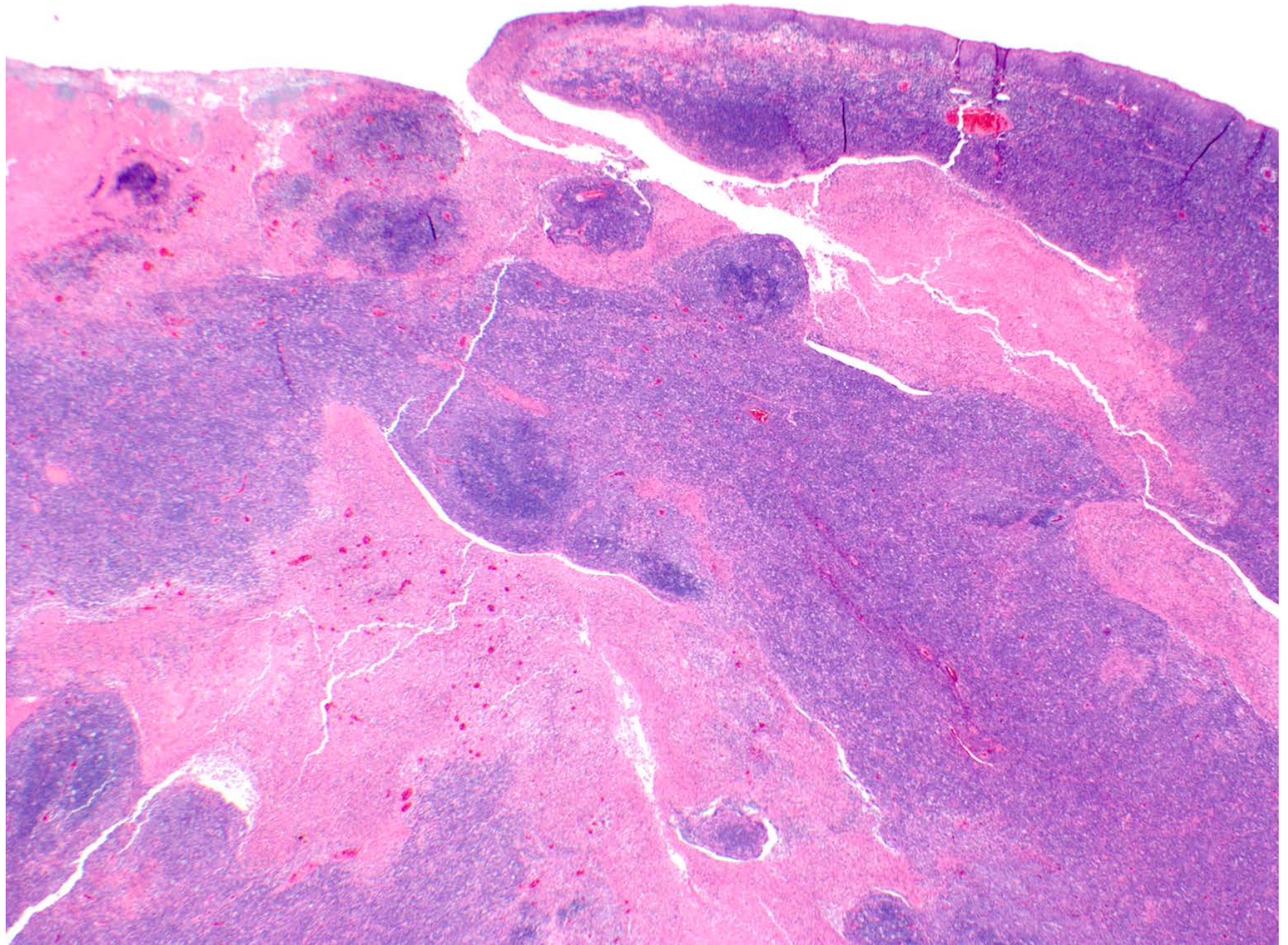


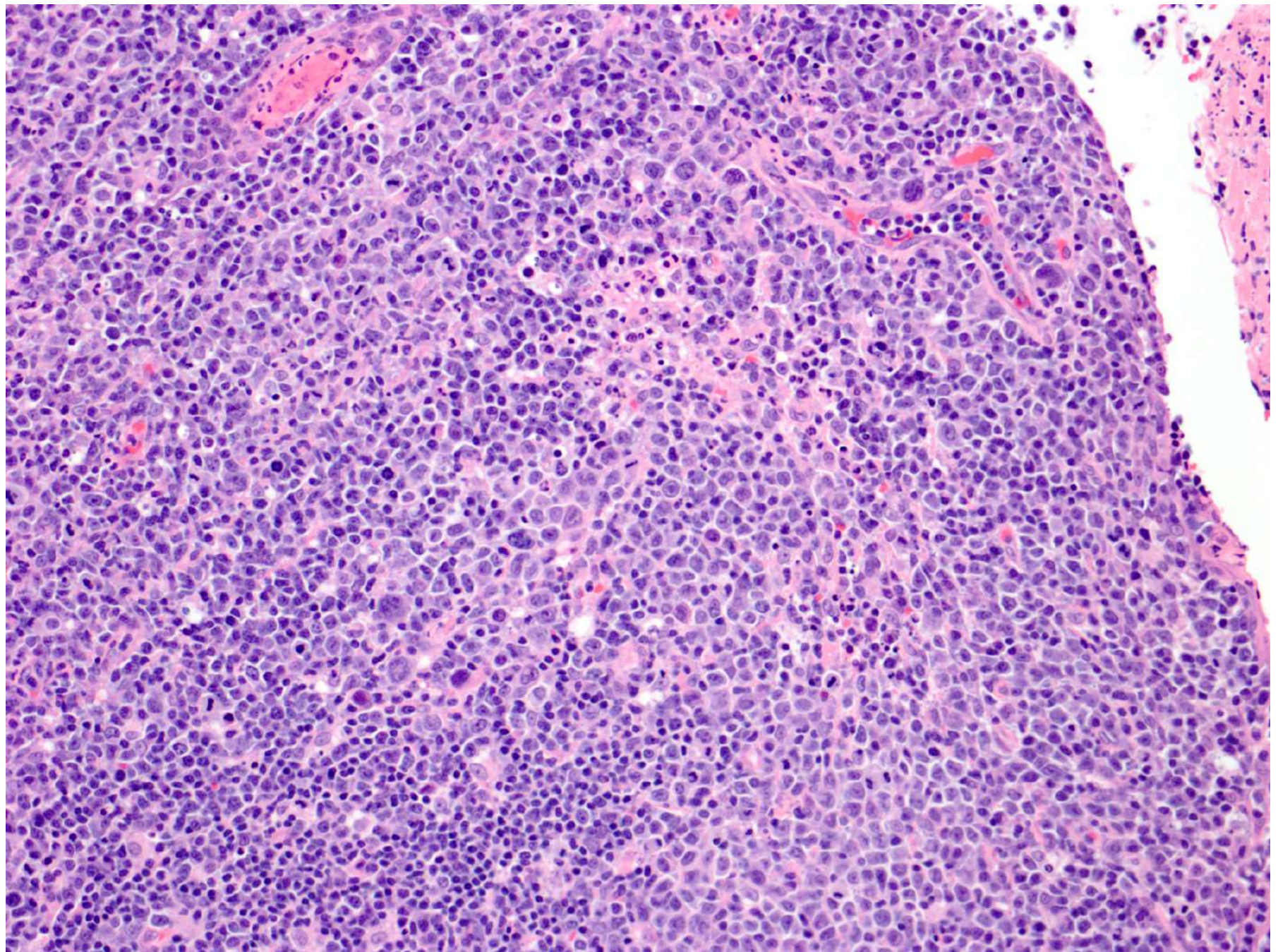


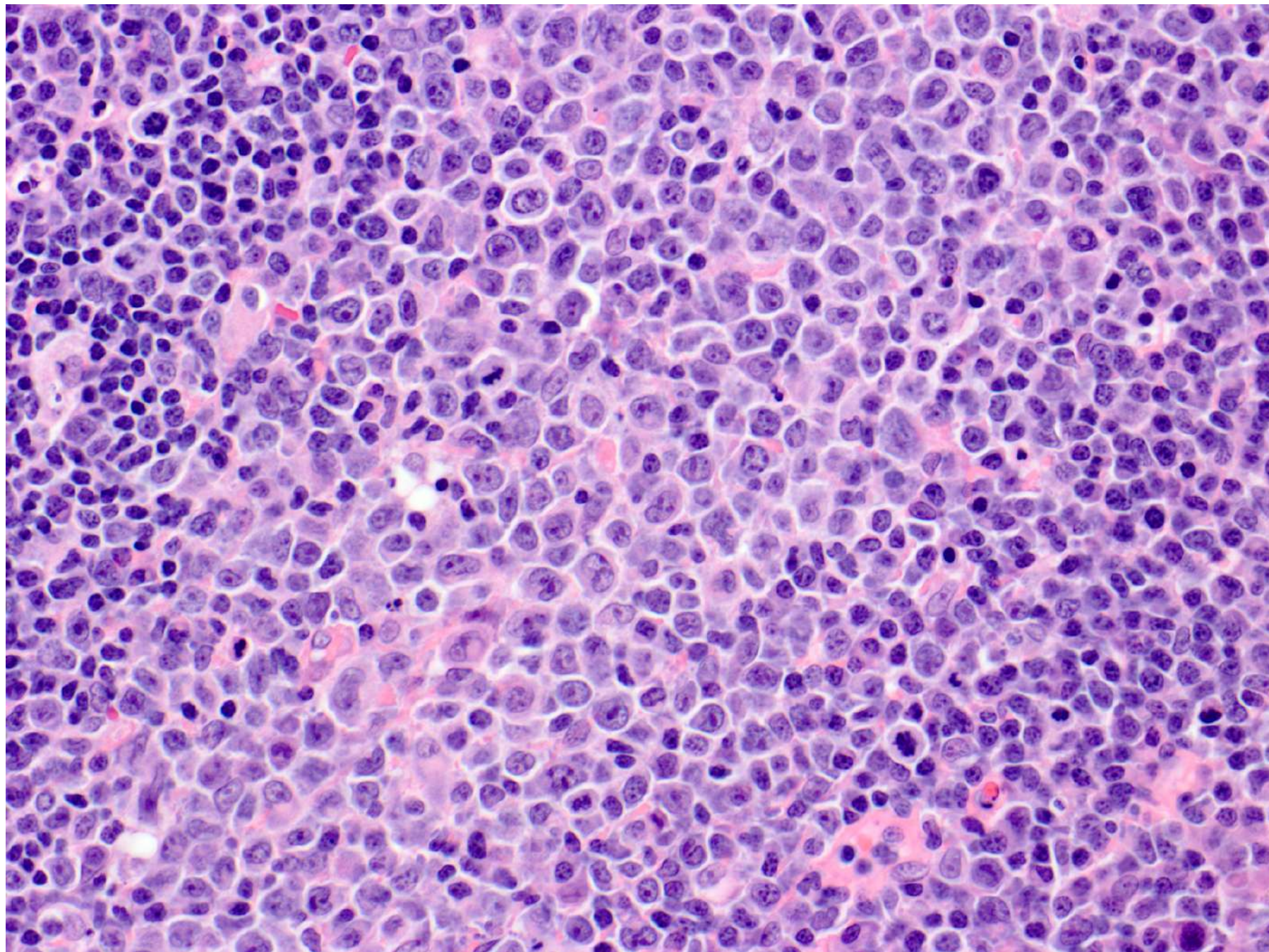
28 yo male with tonsillar enlargement

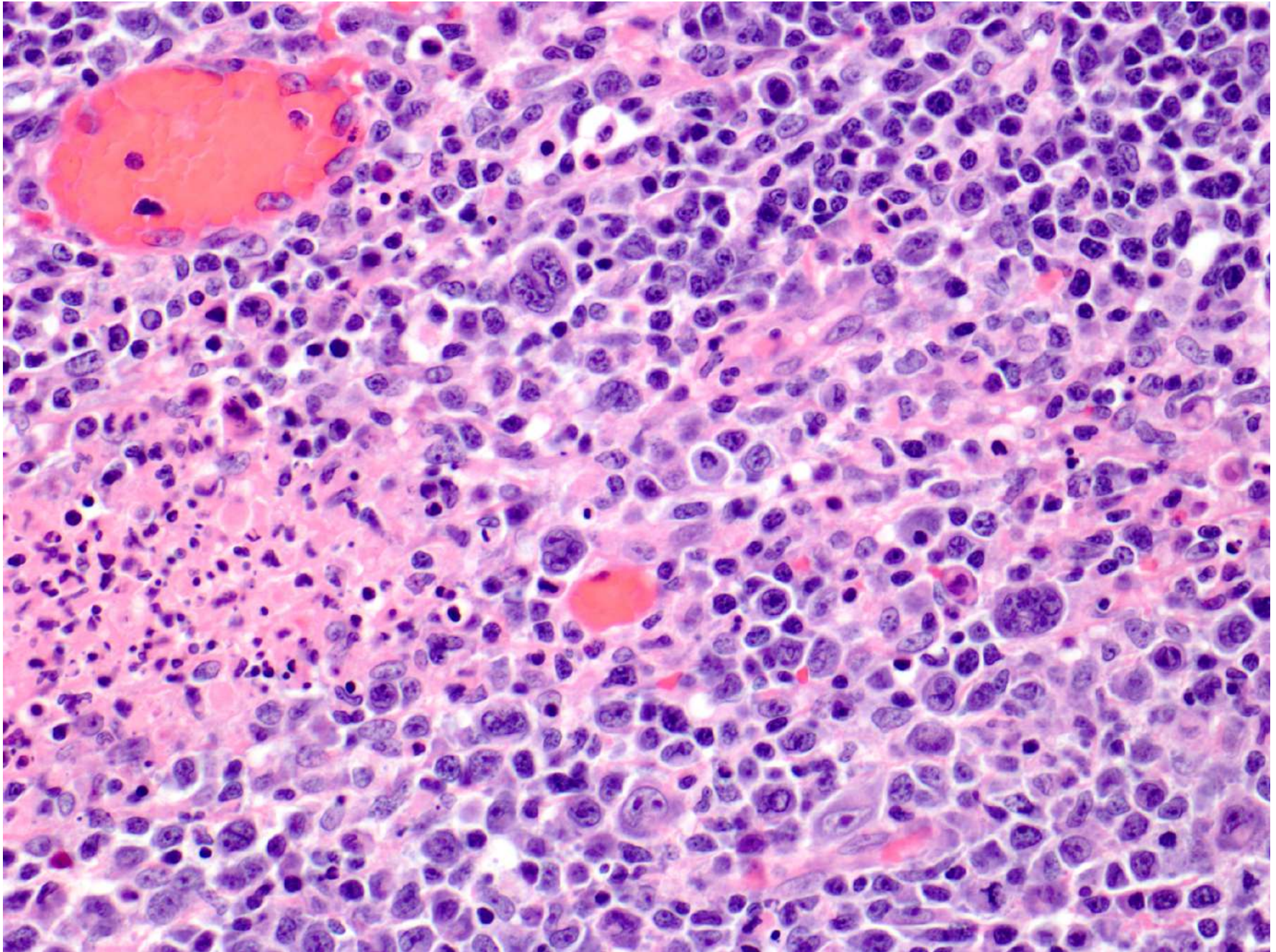


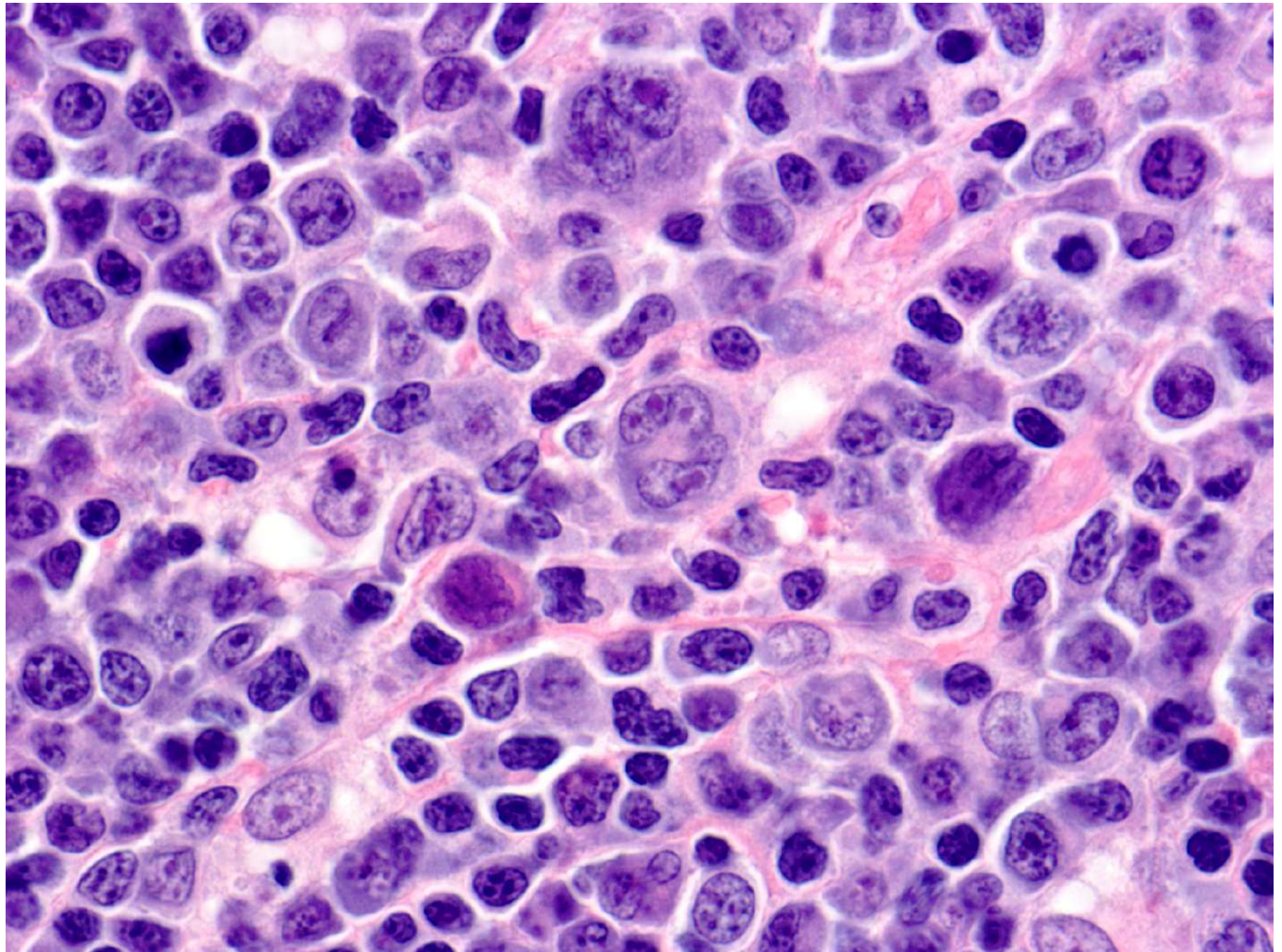
28 yo male with tonsillar enlargement

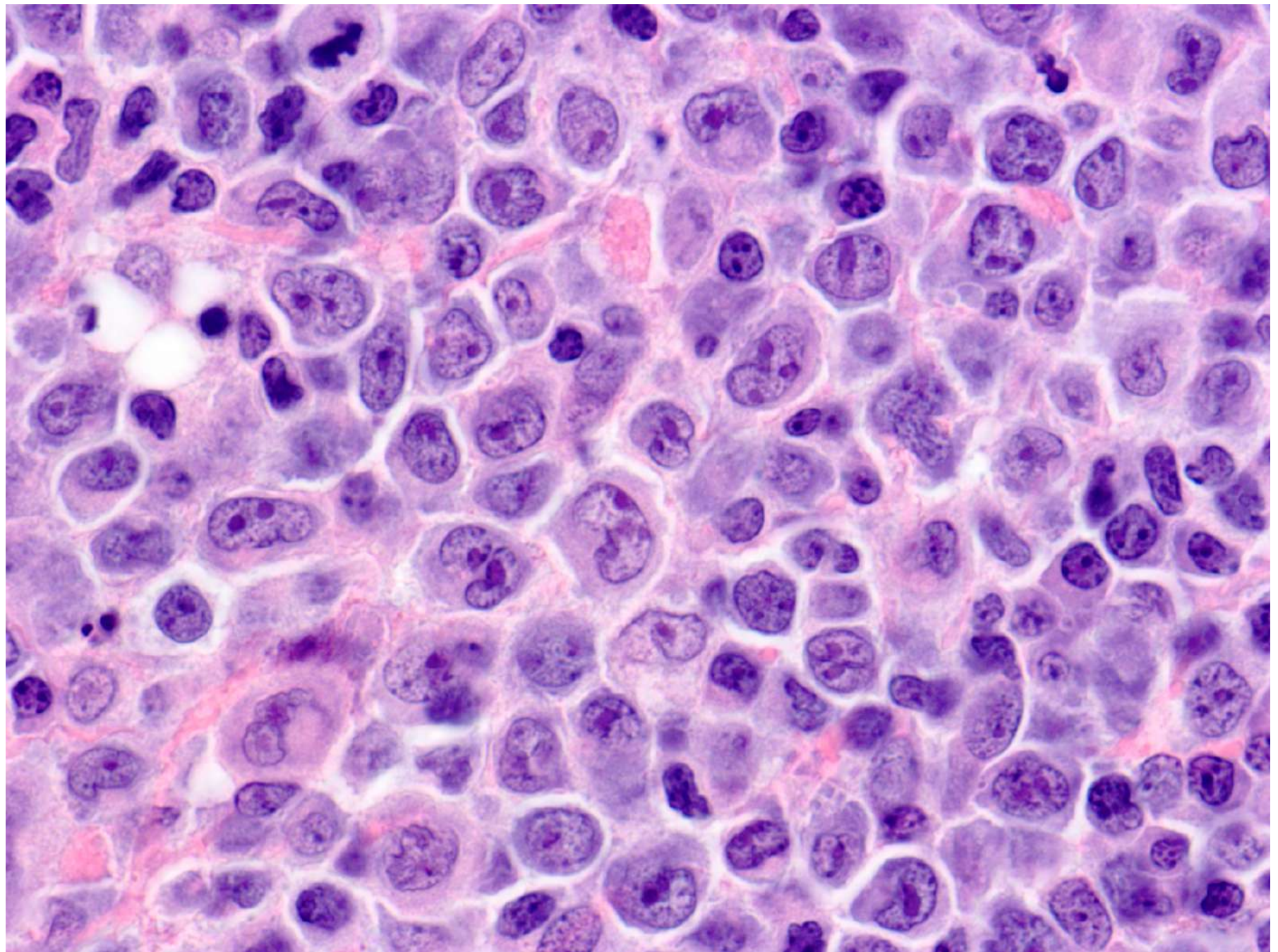






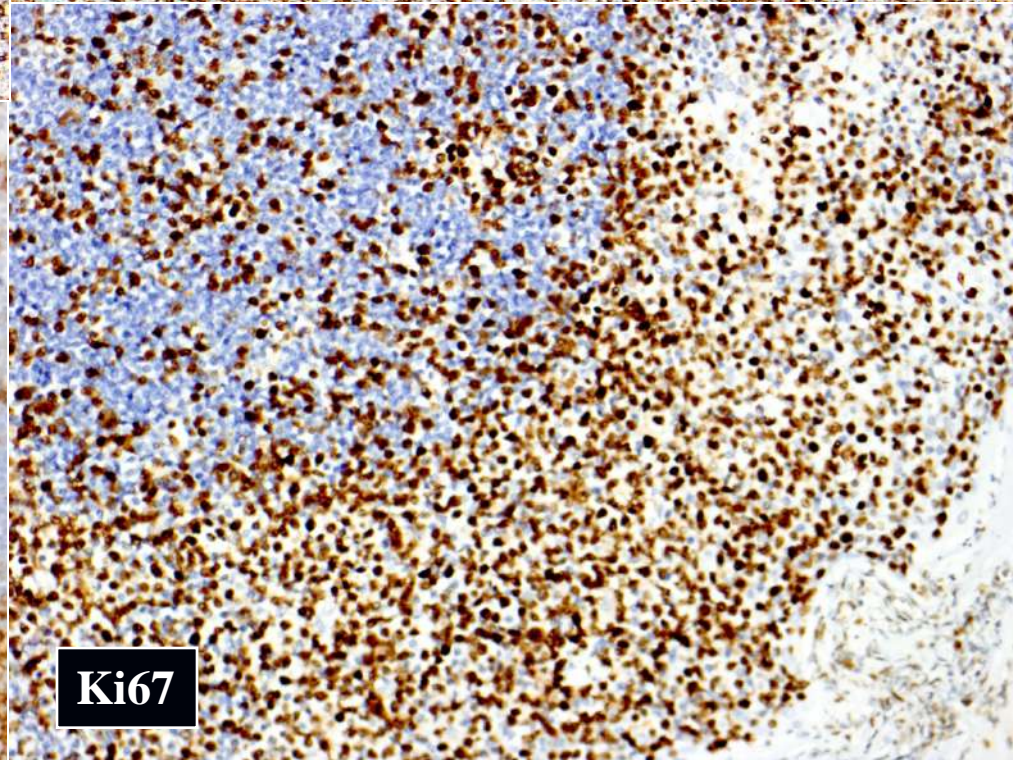
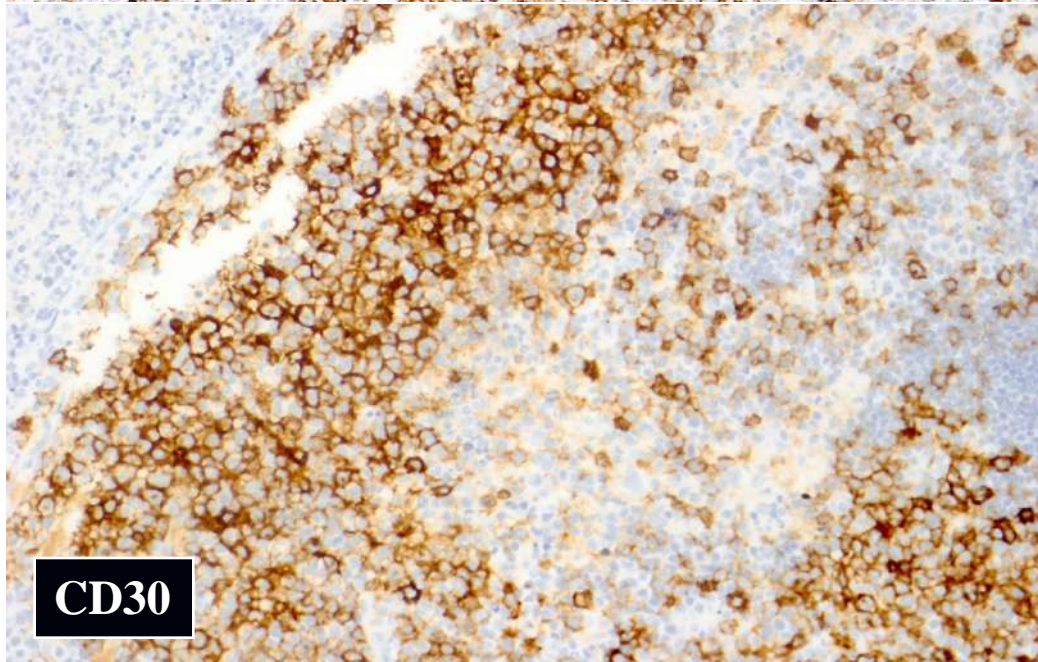
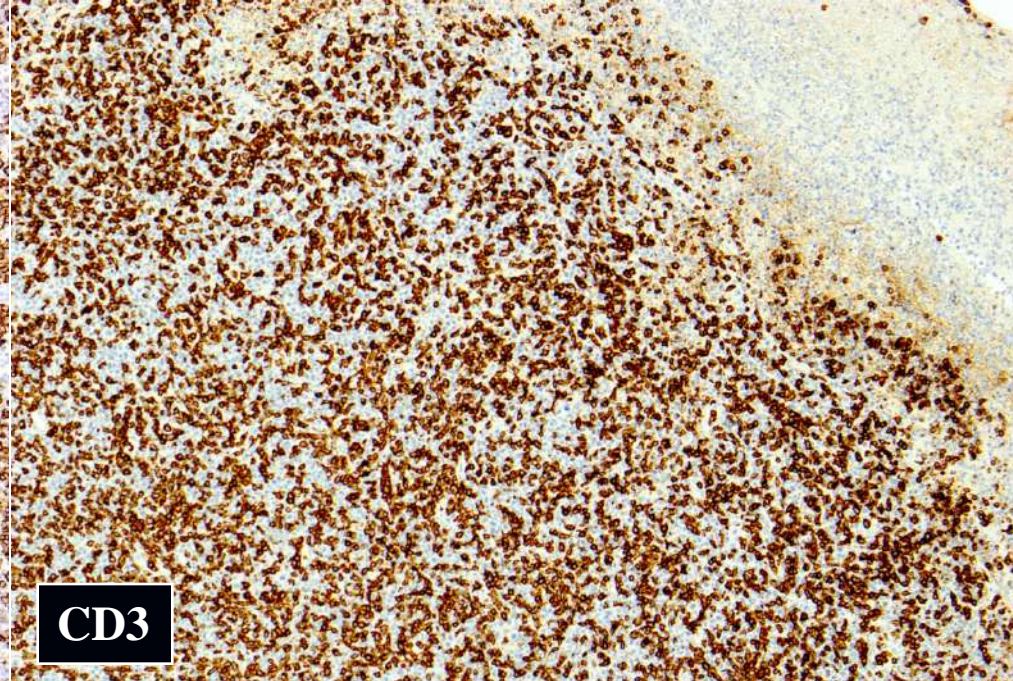
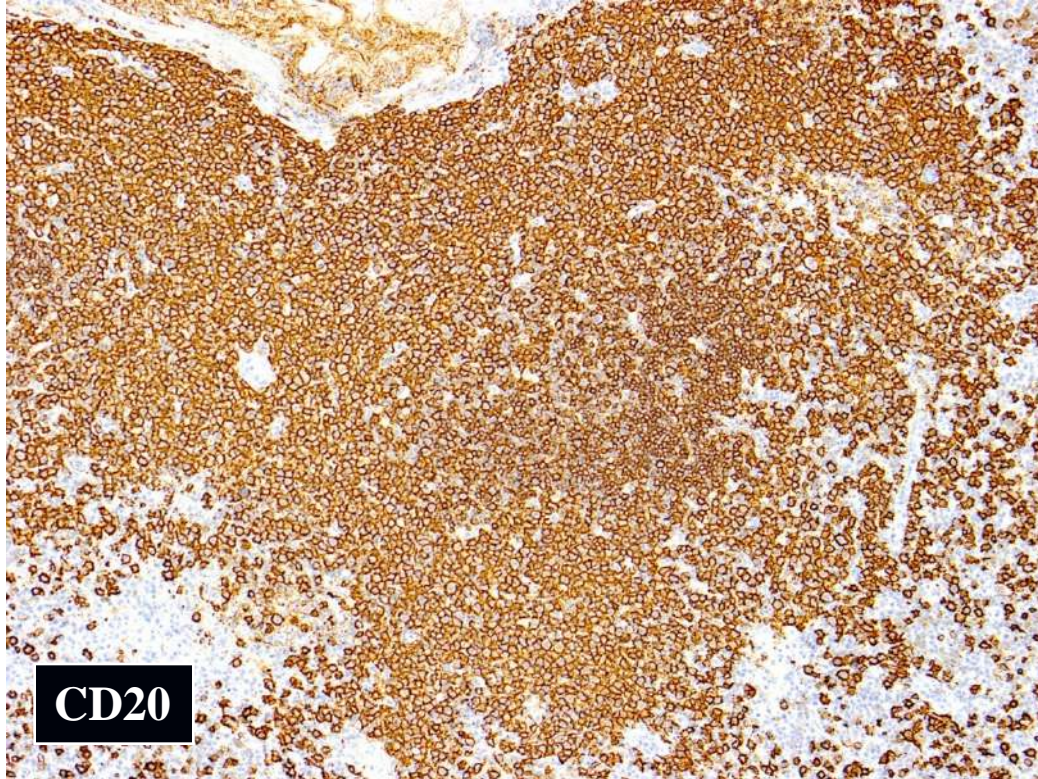




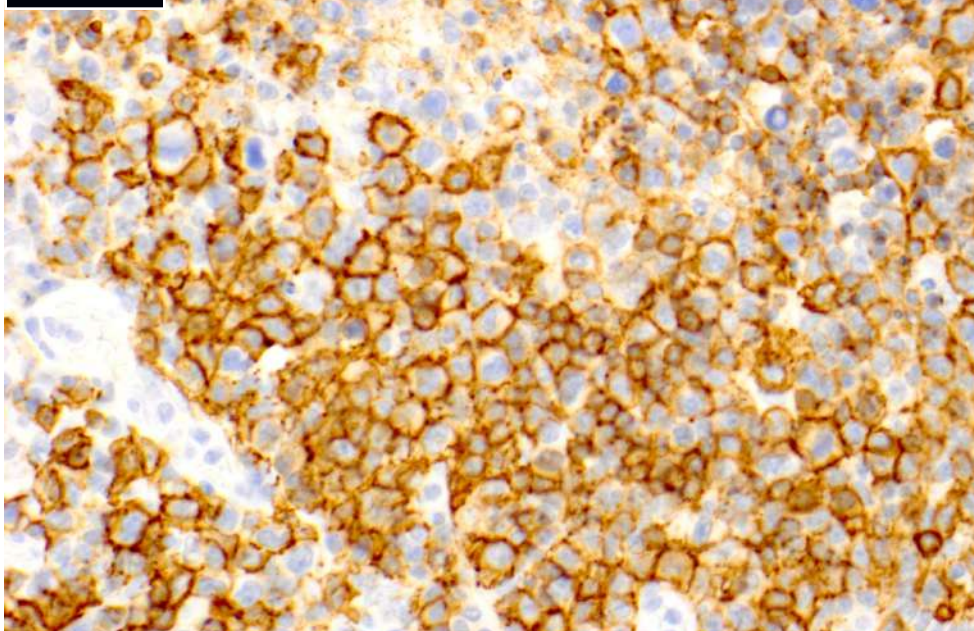


Diagnosis:

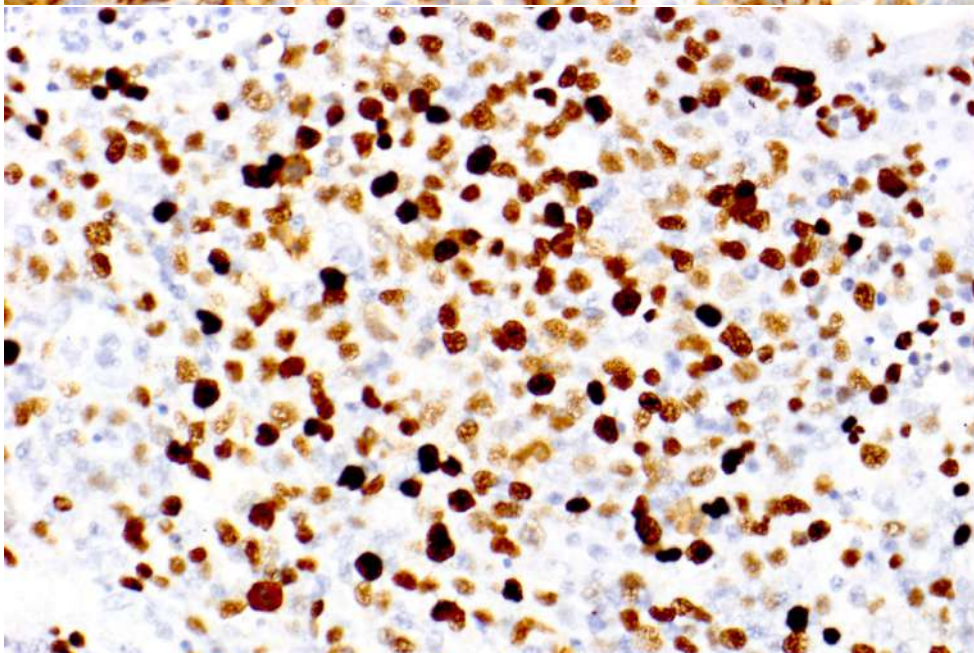
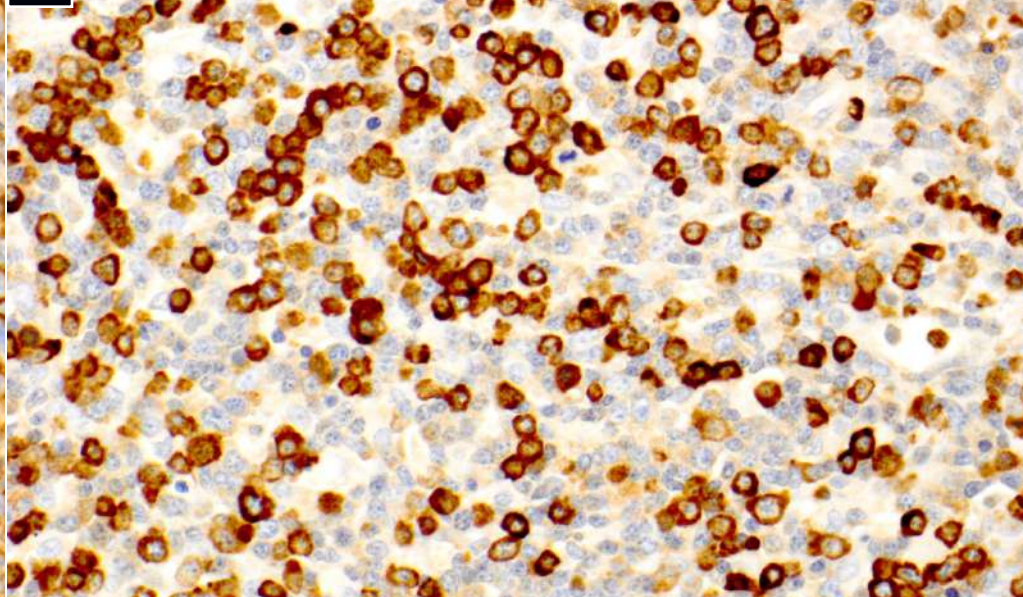
- A. DLBCL with anaplastic features**
- B. Classical Hodgkin's lymphoma**
- C. Anaplastic large cell lymphoma**
- D. Reactive process**



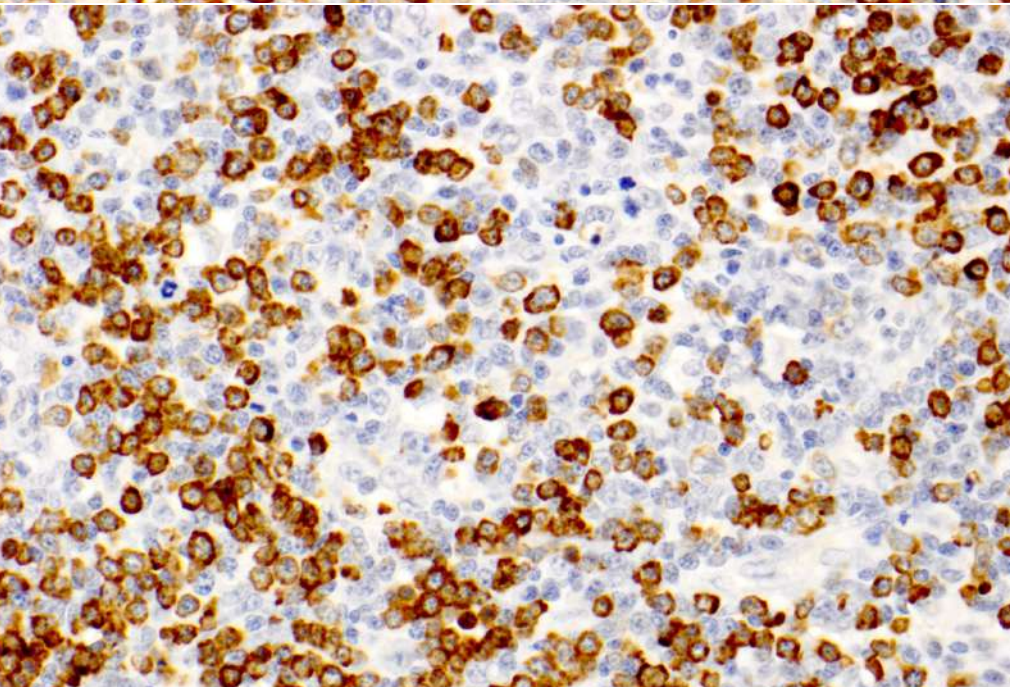
CD20



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Diagnosis

A. DLBCL

B. Classical Hodgkin's lymphoma

C. Anaplastic large cell lymphoma

D. Reactive process:

Infectious mononucleosis

