

# **The Many Faces of MALT Lymphoma**

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# **Extranodal Marginal Zone Lymphomas of Mucosa-Associated Lymphoid Tissue (MALT Lymphomas) Risk Factors**

- **Helicobacter pylori (gastric marginal zone lymphoma (MZL))**
- **Campylobacter jejuni (IPSID)**
- **Chlamydia psittaci (some orbital MZL)**
- **Borrelia burgdorferi (some cutaneous MZLs in Europe)**
- **Autoimmune disease**
  - **Sjögren's syndrome**
  - **Hashimoto's thyroiditis**
- **Hepatitis C virus**
- **IgG4-related disease (?)**

# MALT Lymphomas

- Adults, usually middle-aged or older
- Stomach, salivary glands, intestine, orbit, thyroid, lung, skin, dura, kidney...
- M:F ratio varies by site
- Usually localized (stage I or II)
- Indolent; may be treated with local therapy (antibiotics, RT, surgery)
- Prognosis: very good
- May undergo large cell transformation

# MALT Lymphomas

## *Histology*

- Diffuse, vaguely nodular
- Marginal zone cells +/- monocytoid B cells
- Plasma cells (+/- Dutcher bodies)
- Reactive follicles (+/- follicular colonization)
- Lymphoepithelial lesions
- Few large cells (<5%)

## *Immunophenotype*

- sIg(usually M)+, cIg+/-, pan B+, CD5-, CD10-, CD43+/-

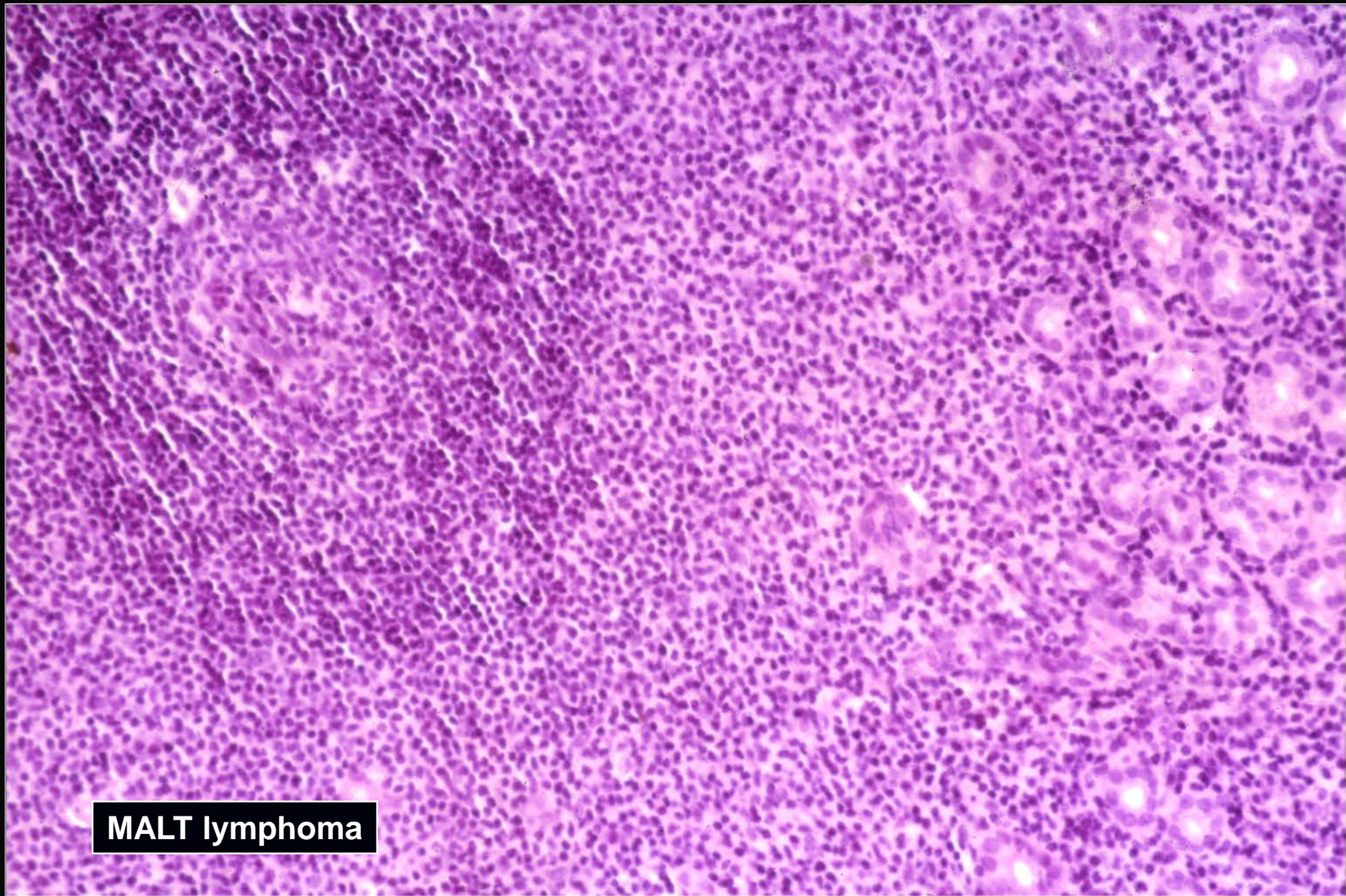
# MALT Lymphomas

## *Genetic features*

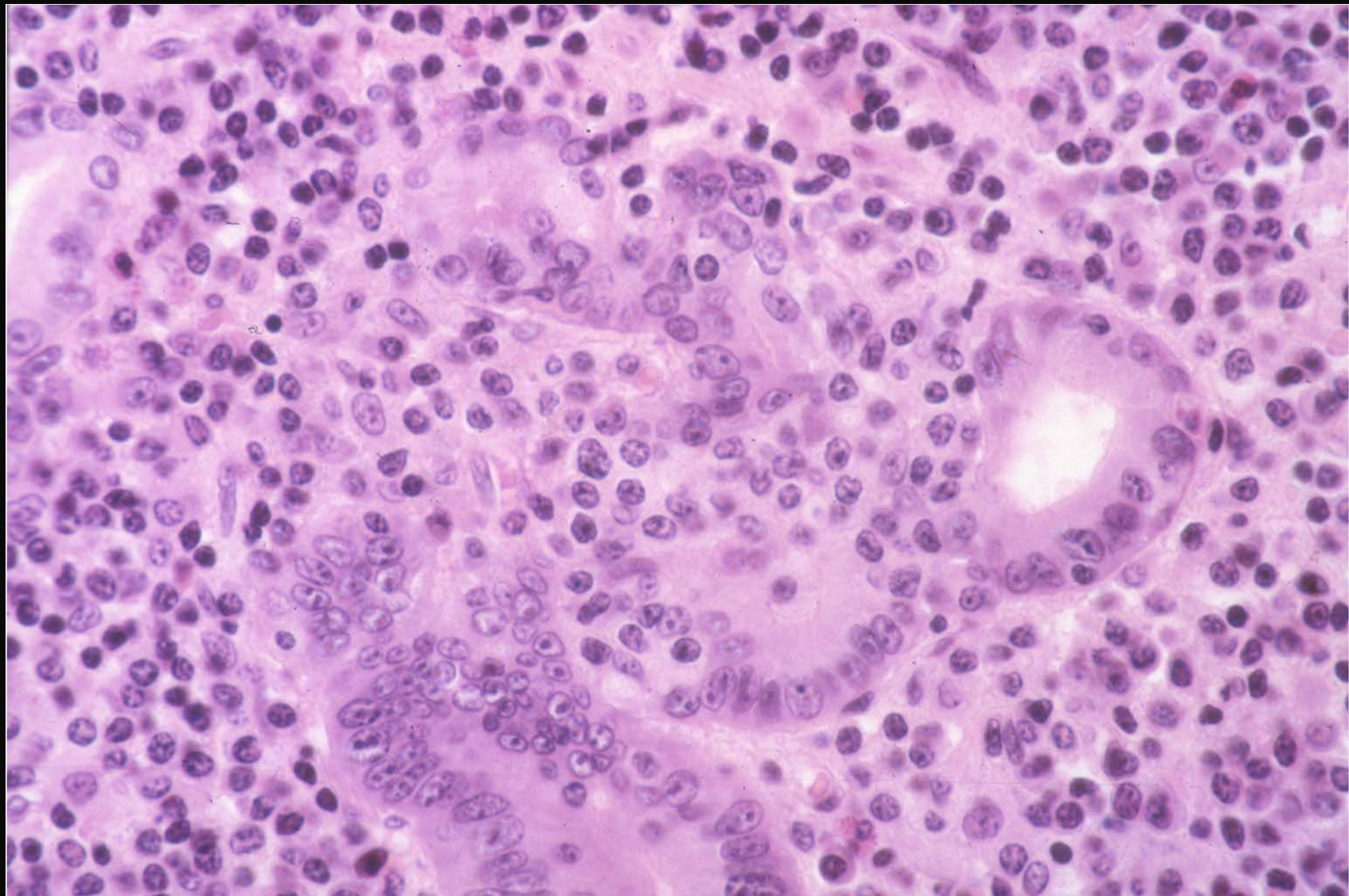
Mutually exclusive translocations in some cases

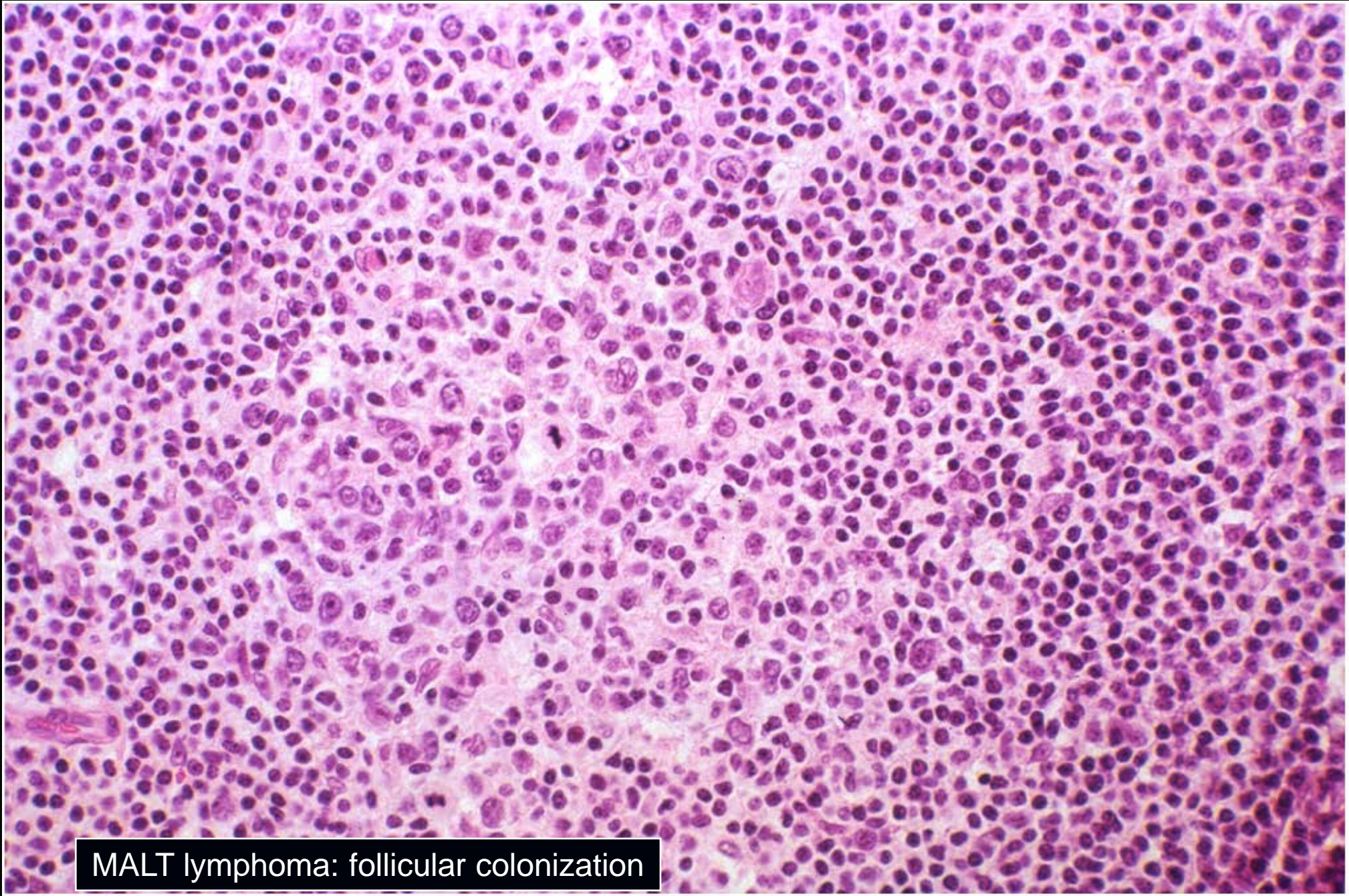
Type of translocation varies by site

- $t(11;18)(q21;q21)$  (*API2-MALT1*),
- $t(14;18)(q32;q21)$  (*IGH/MALT1*),
- $t(1;14)(p22;q32)$  (*BCL10/IGH*) or
- $t(3;14)(p14.1;q32)$  (*FOXP1/IGH*)
- Trisomy 18 or trisomy 3 in some cases



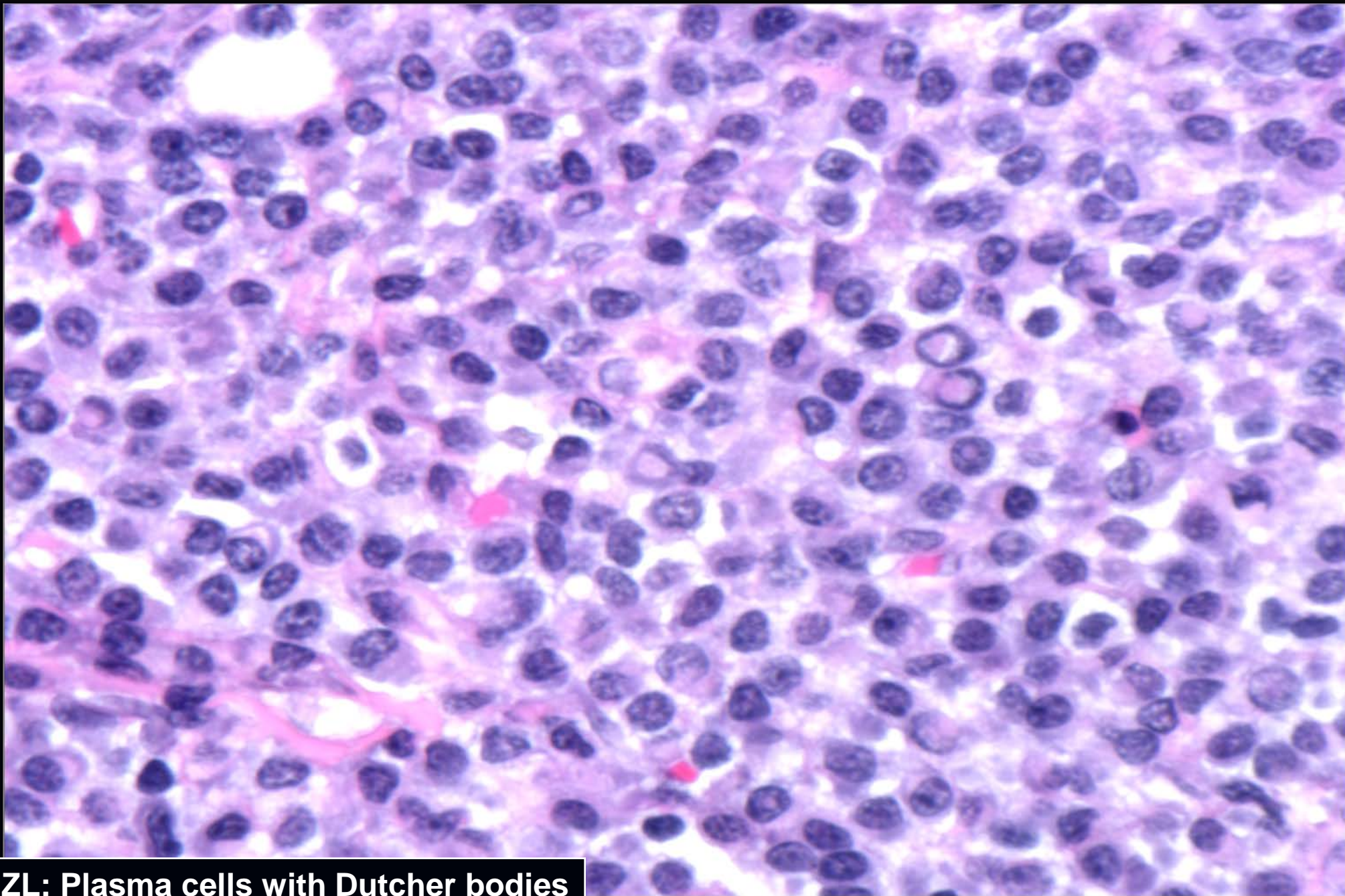
**MALT lymphoma**





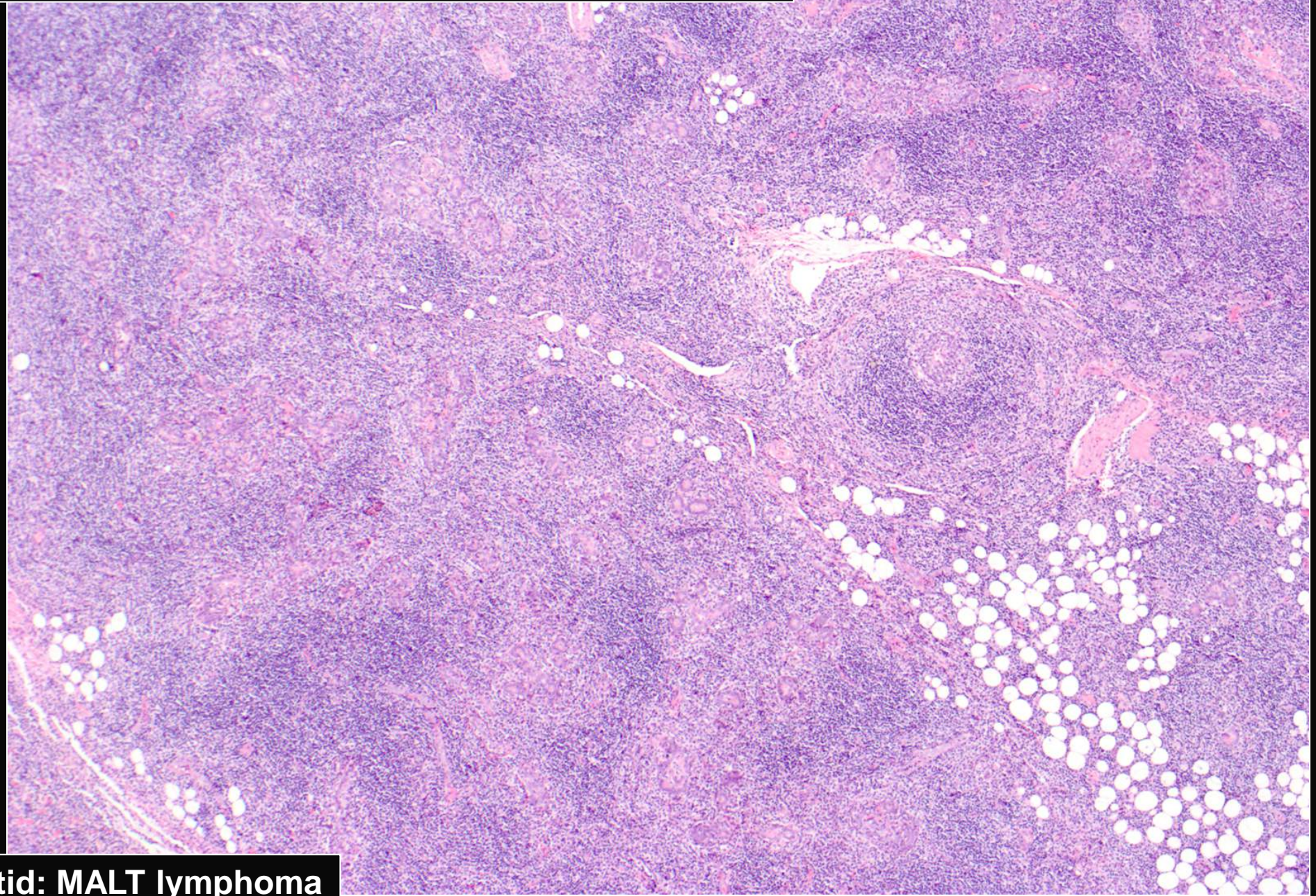
MALT lymphoma: follicular colonization



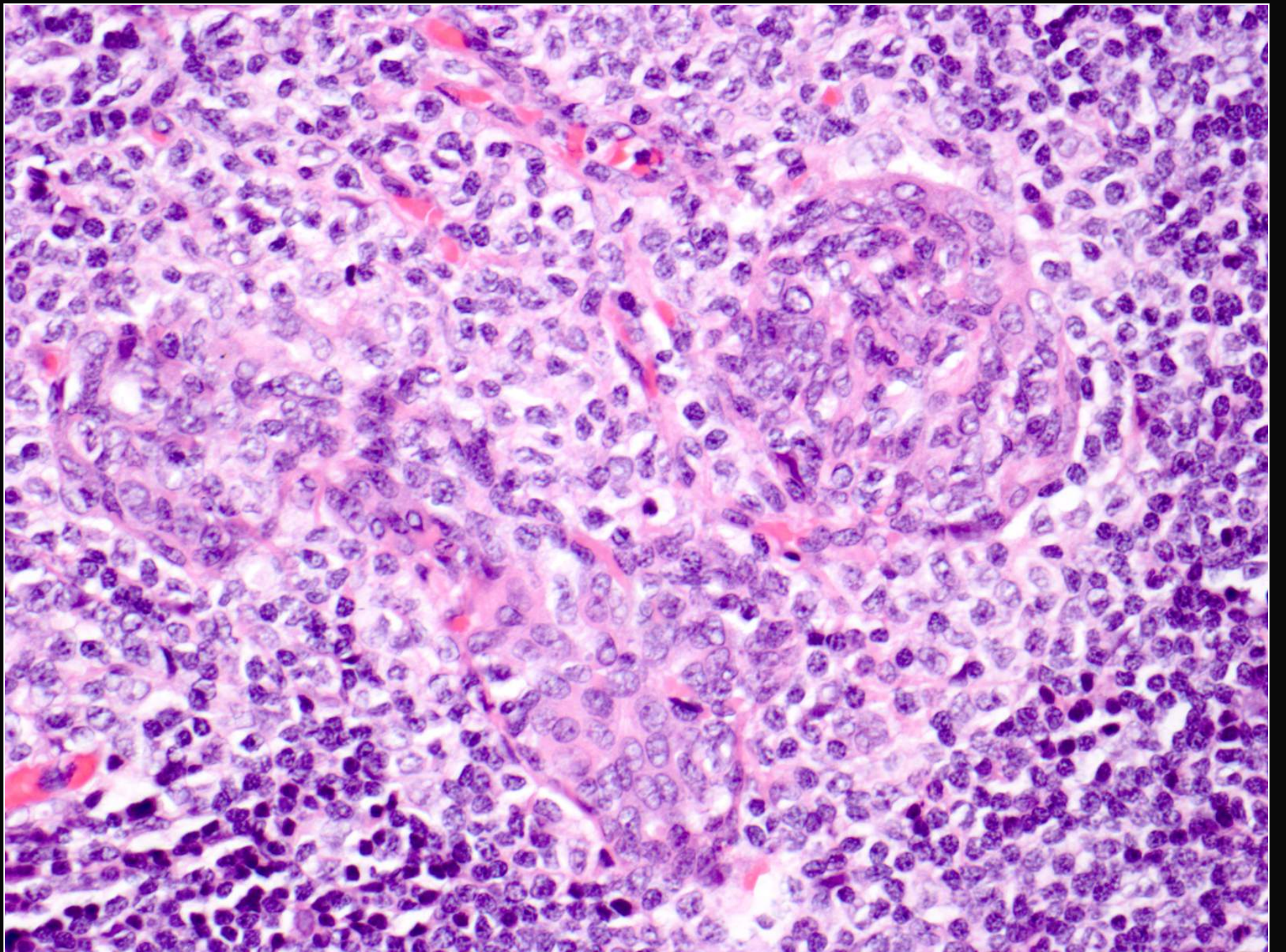


**MZL: Plasma cells with Dutcher bodies**

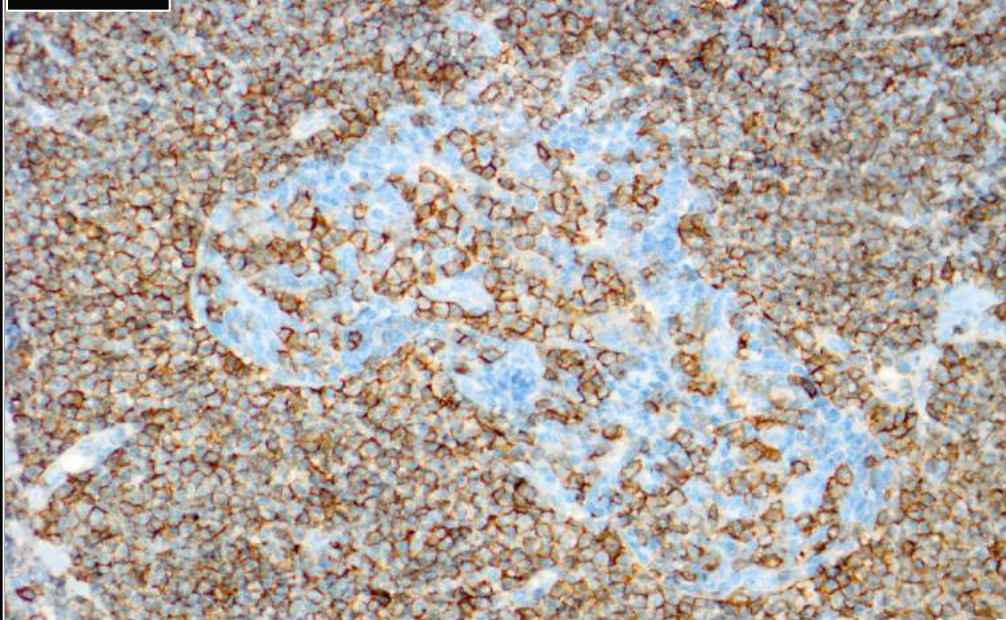
**Morphological and immunophenotypic heterogeneity among MALT lymphoma in different sites**



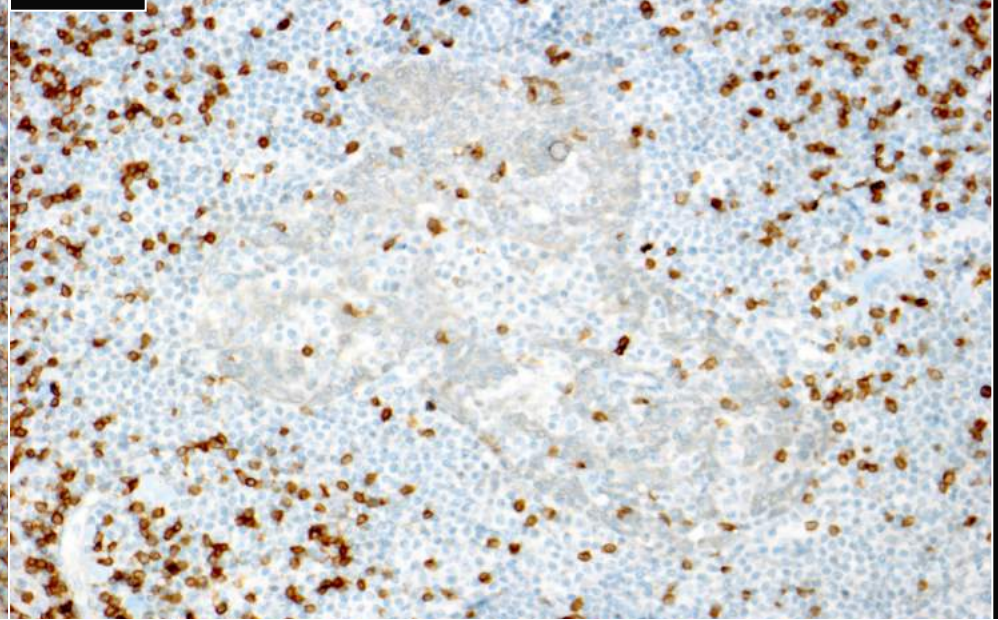
**Parotid: MALT lymphoma**



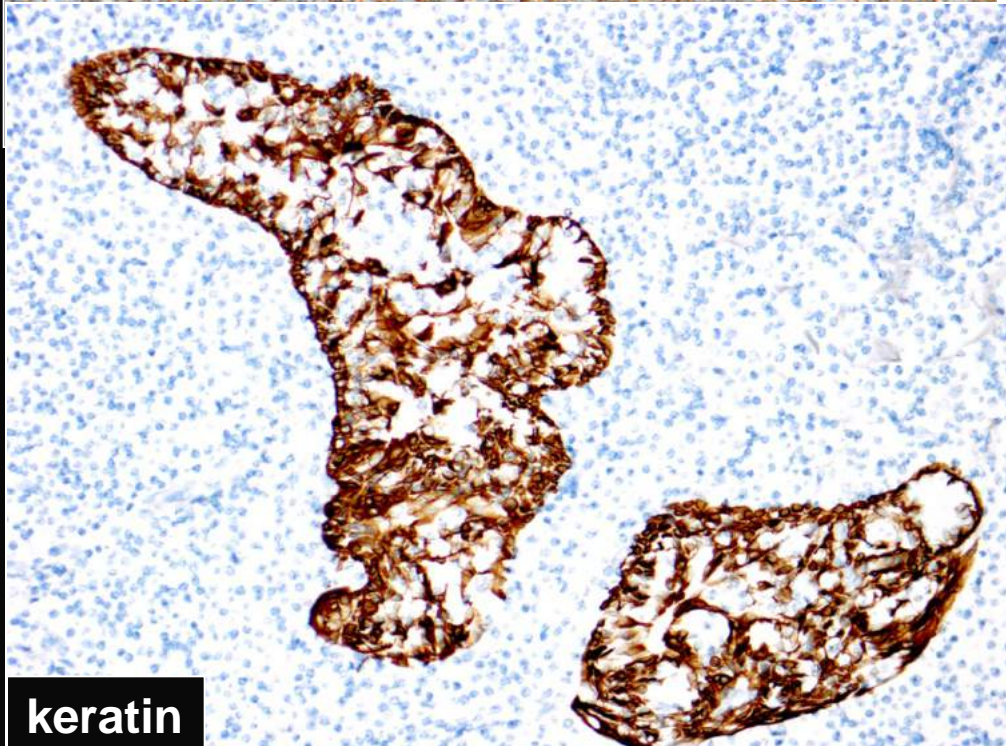
**CD20**



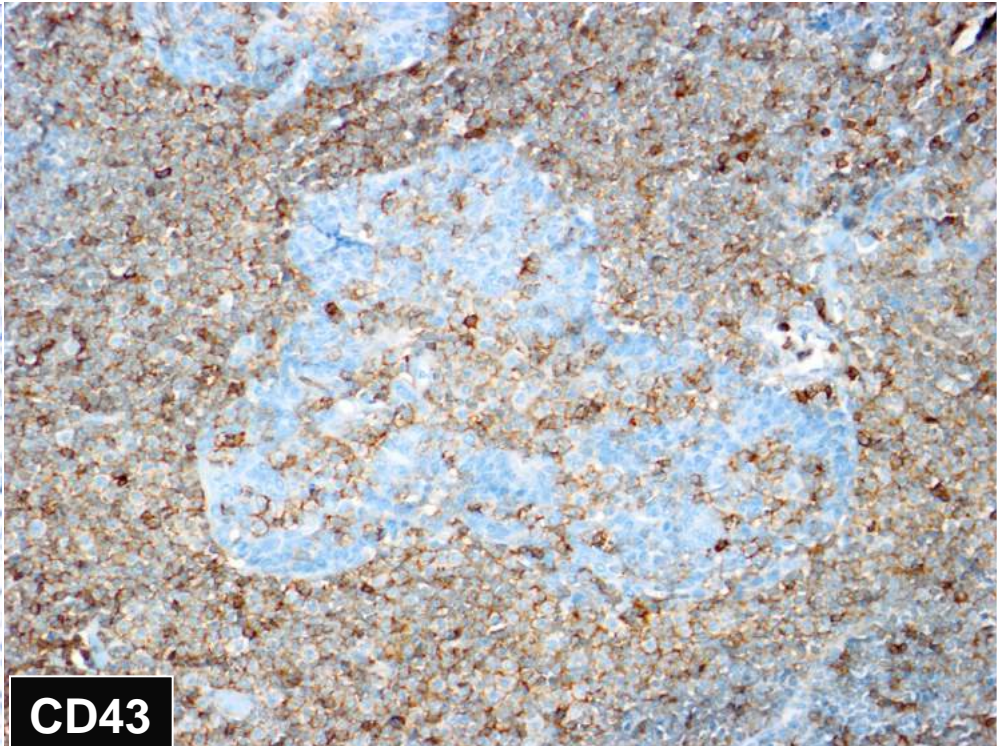
**CD3**



**keratin**



**CD43**

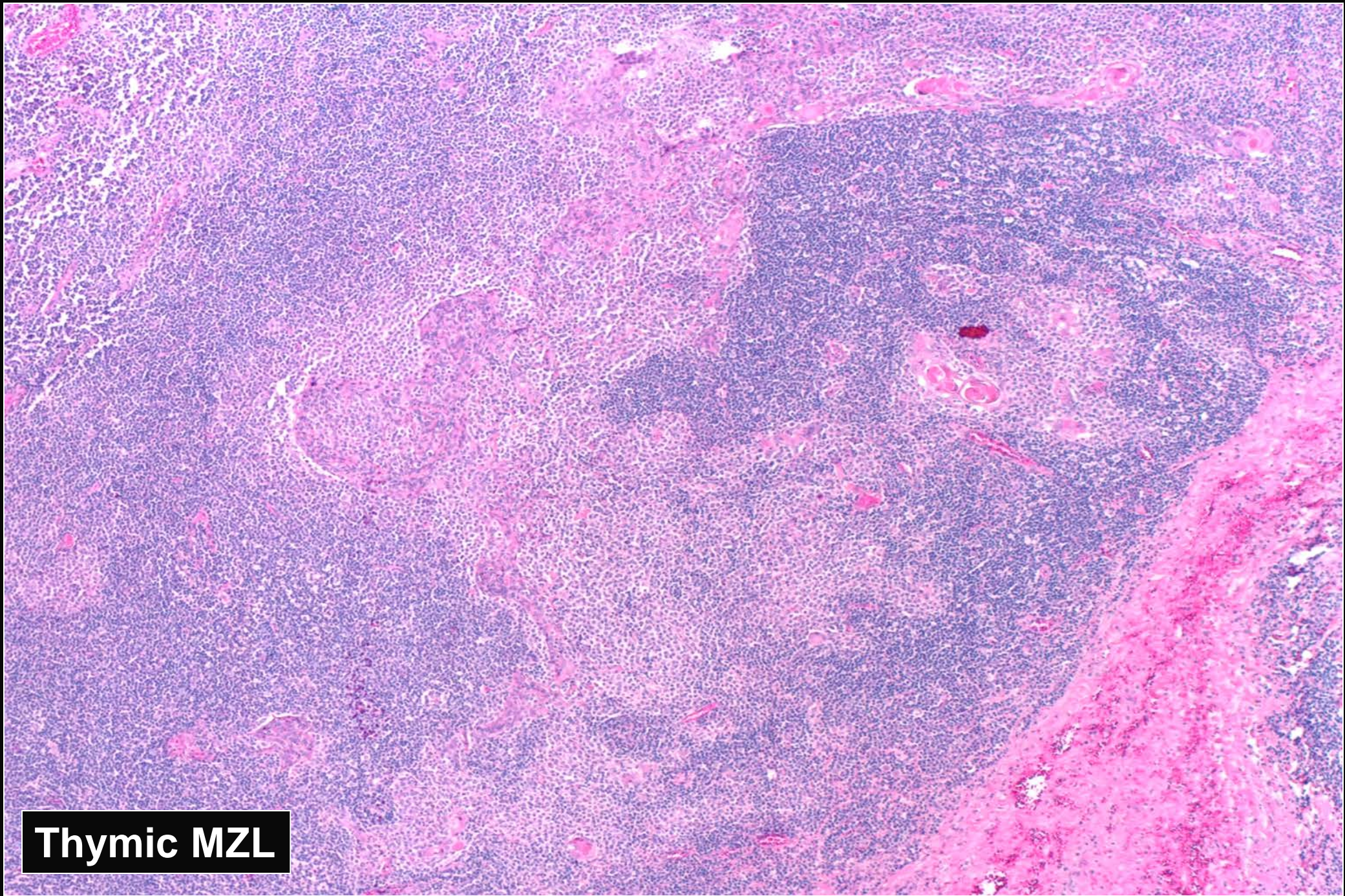


# Thymic Marginal Zone Lymphoma

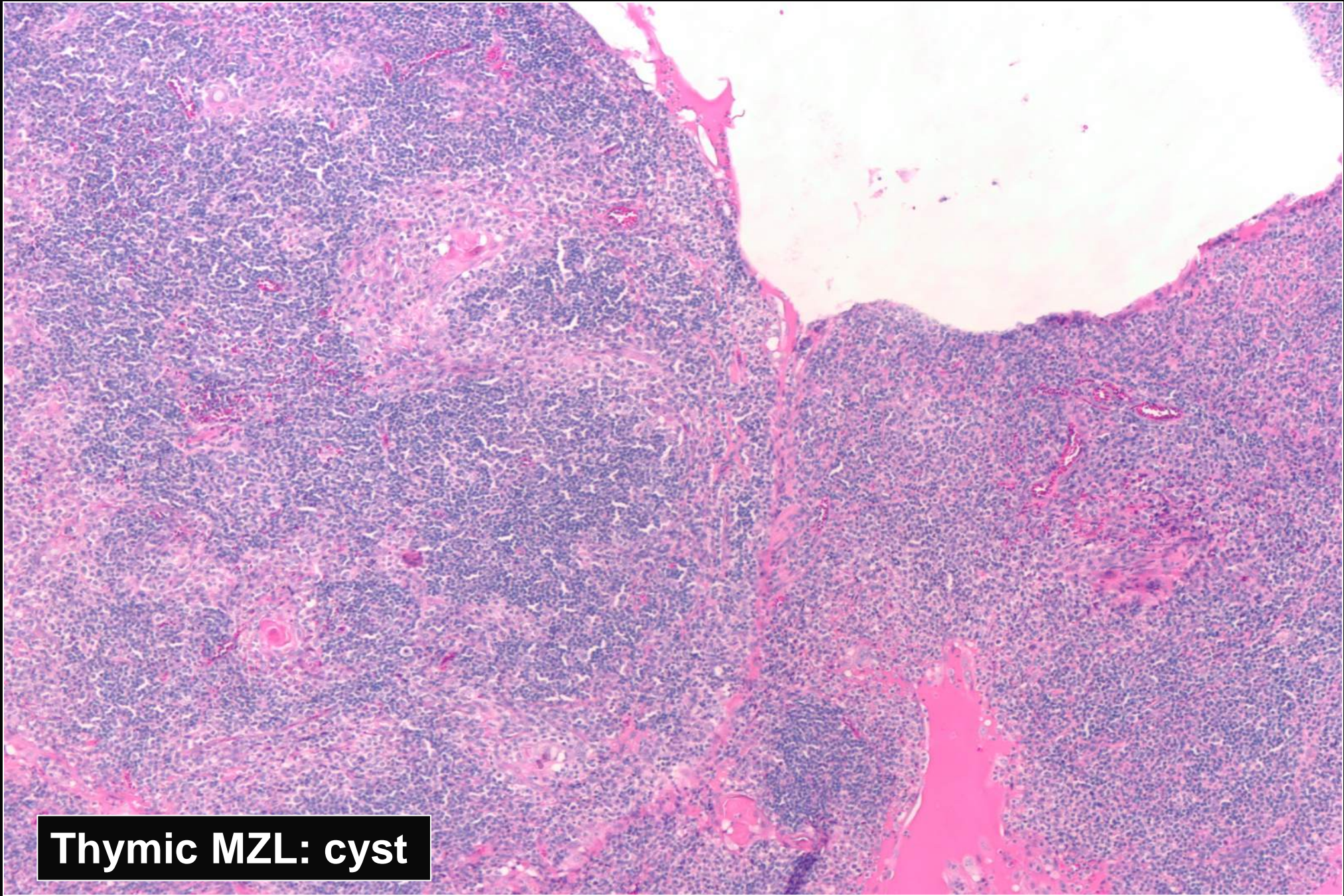
- Rare but distinctive form of marginal zone lymphoma
- Adults, M:F ~ 1:3
- Asians most often affected
- Autoimmune disease in most, especially Sjögren's
- M component (IgA) or polyclonal hypergammaglobulinemia
- Usually incidental findings

# Thymic Marginal Zone Lymphoma

- Usually solid and cystic
- Lymphoma begins in the medulla of the thymus
- Lymphoepithelial lesions: Hassall's corpuscles
- Plasmacytoid differentiation
- IgA+, almost always
- Behavior: similar to MZL arising elsewhere
- *Not* the precursor of mediastinal large BCL
- Differential: thymic lymphoid hyperplasia

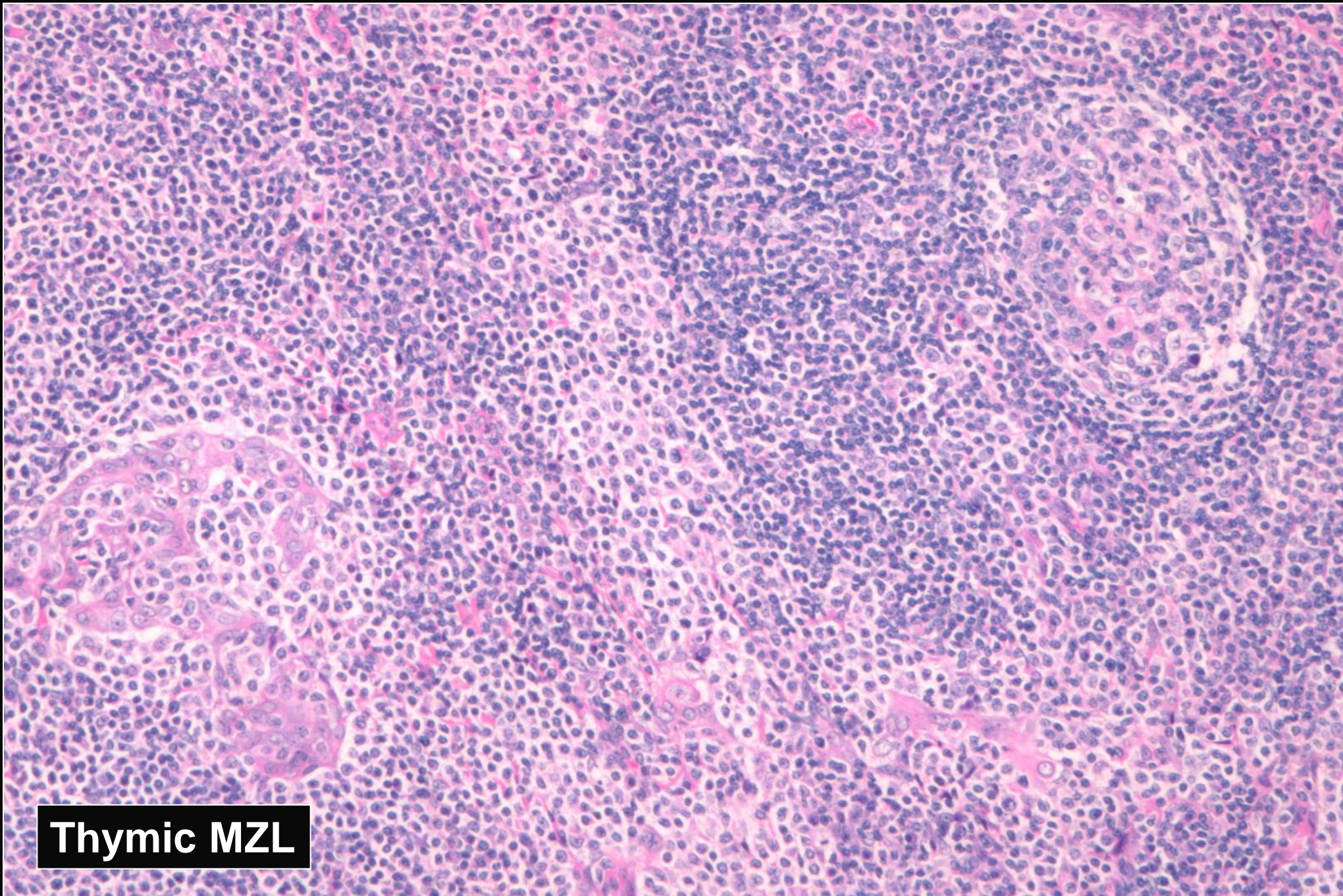


**Thymic MZL**

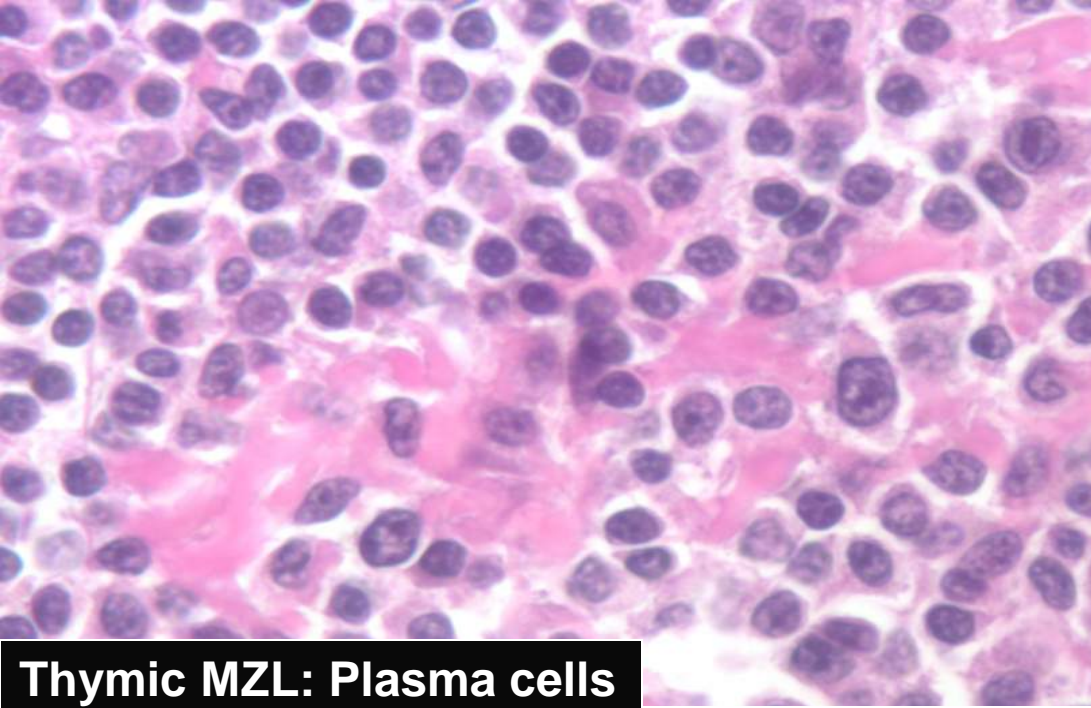


**Thymic MZL: cyst**

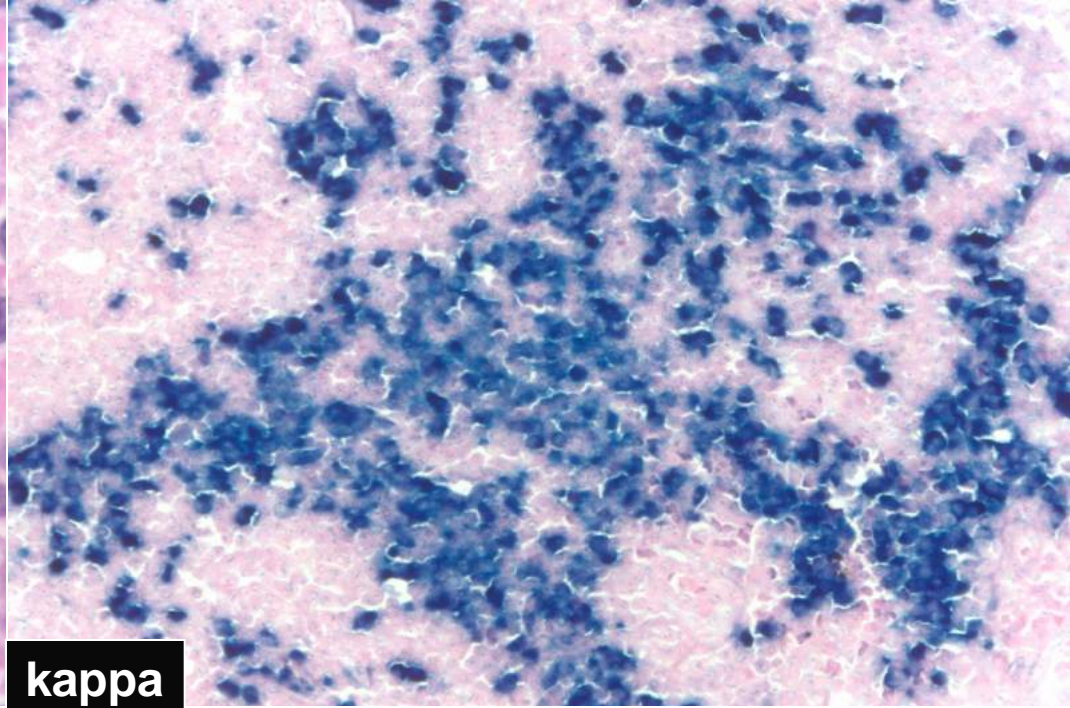




**Thymic MZL**



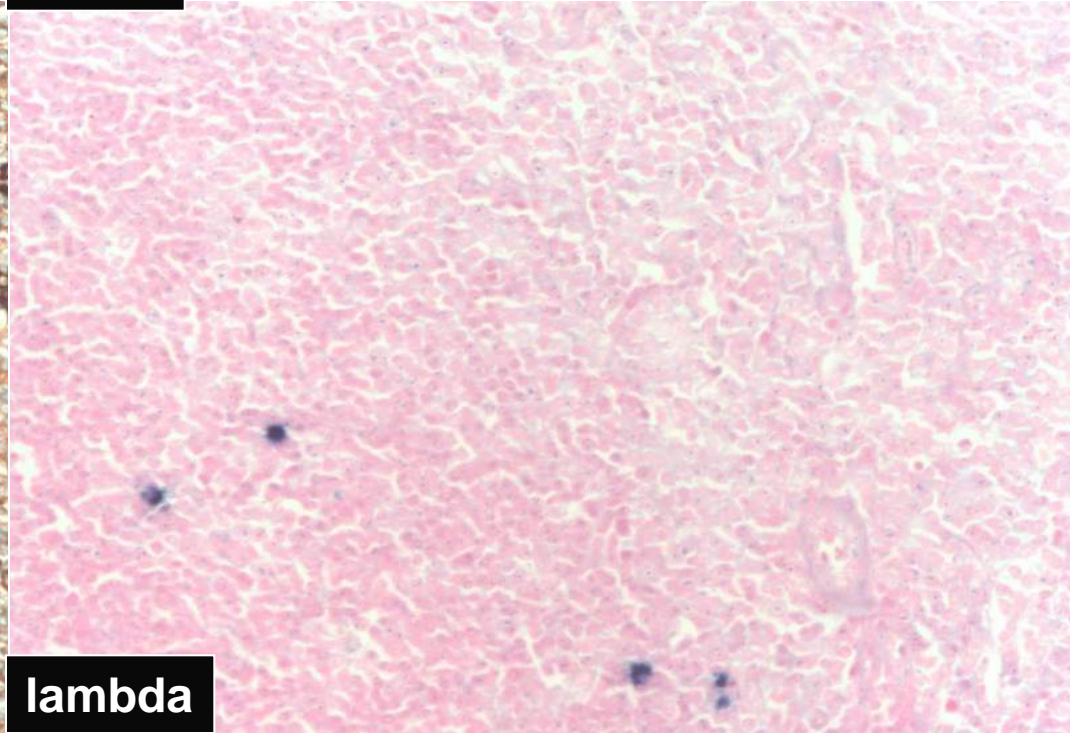
**Thymic MZL: Plasma cells**



**kappa**



**IgA**



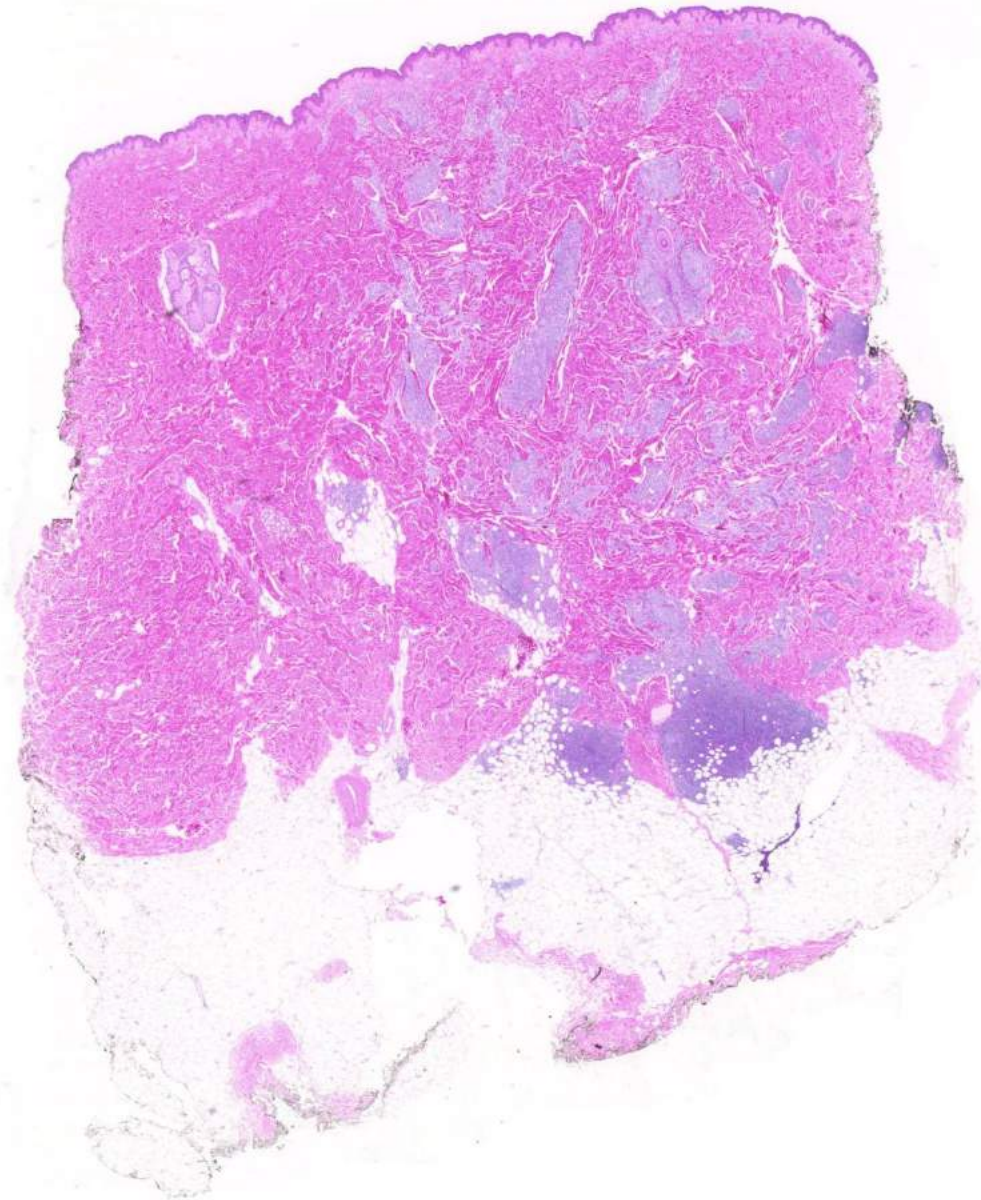
**lambda**

# Cutaneous MALT Lymphoma

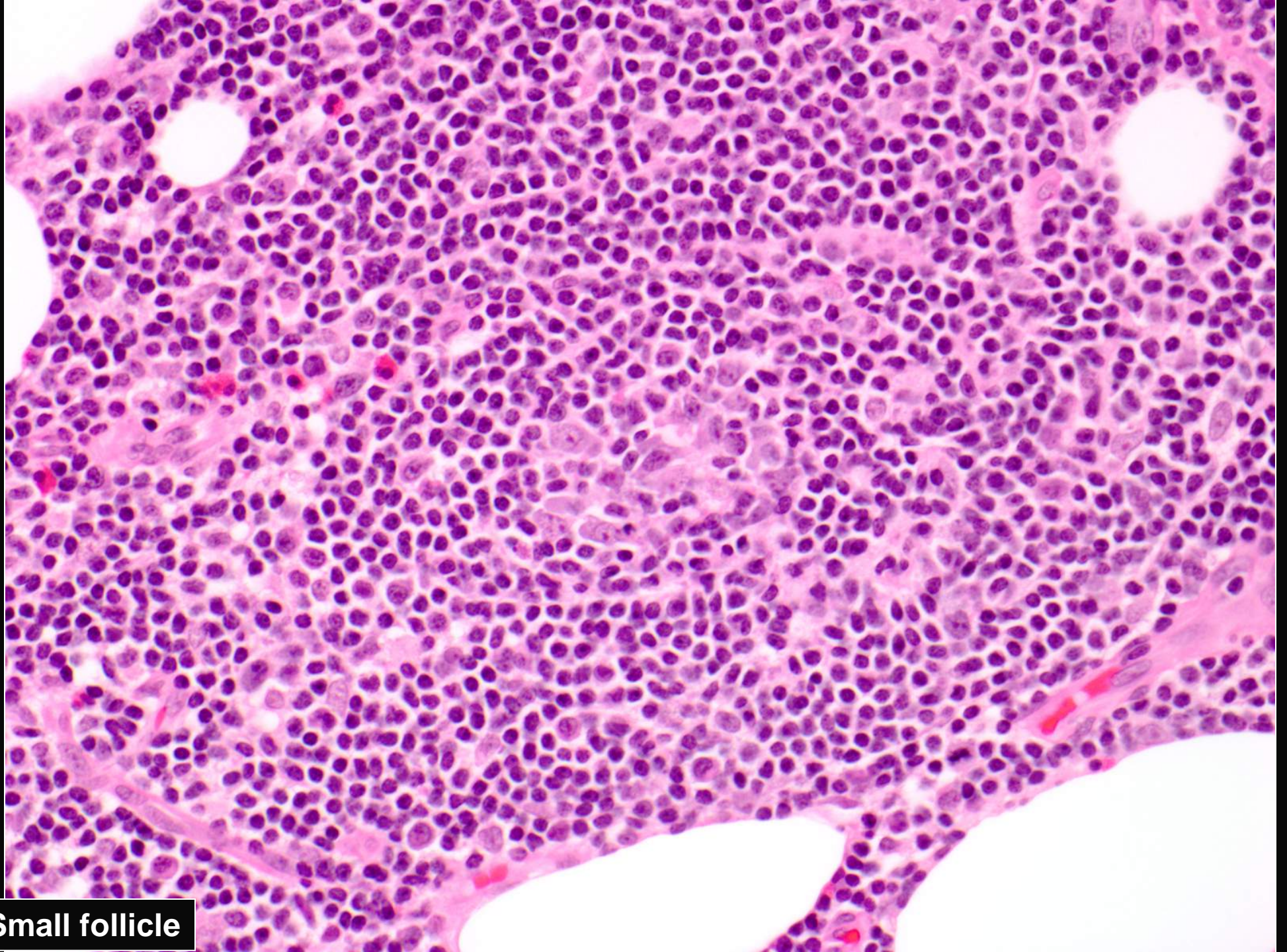
## *Study of cases with plasmacytic differentiation\**

- **Class-switched cases (~76%)**
  - **IgG+ (almost all)**
  - **Discontinuous lymphoid infiltrate**
  - **T-cell predominant**
  - **Localized to skin**
  
- **IgM+ cases (21%)**
  - **Confluent infiltrate**
  - **B-cell predominant**
  - **Extracutaneous involvement (50%)**

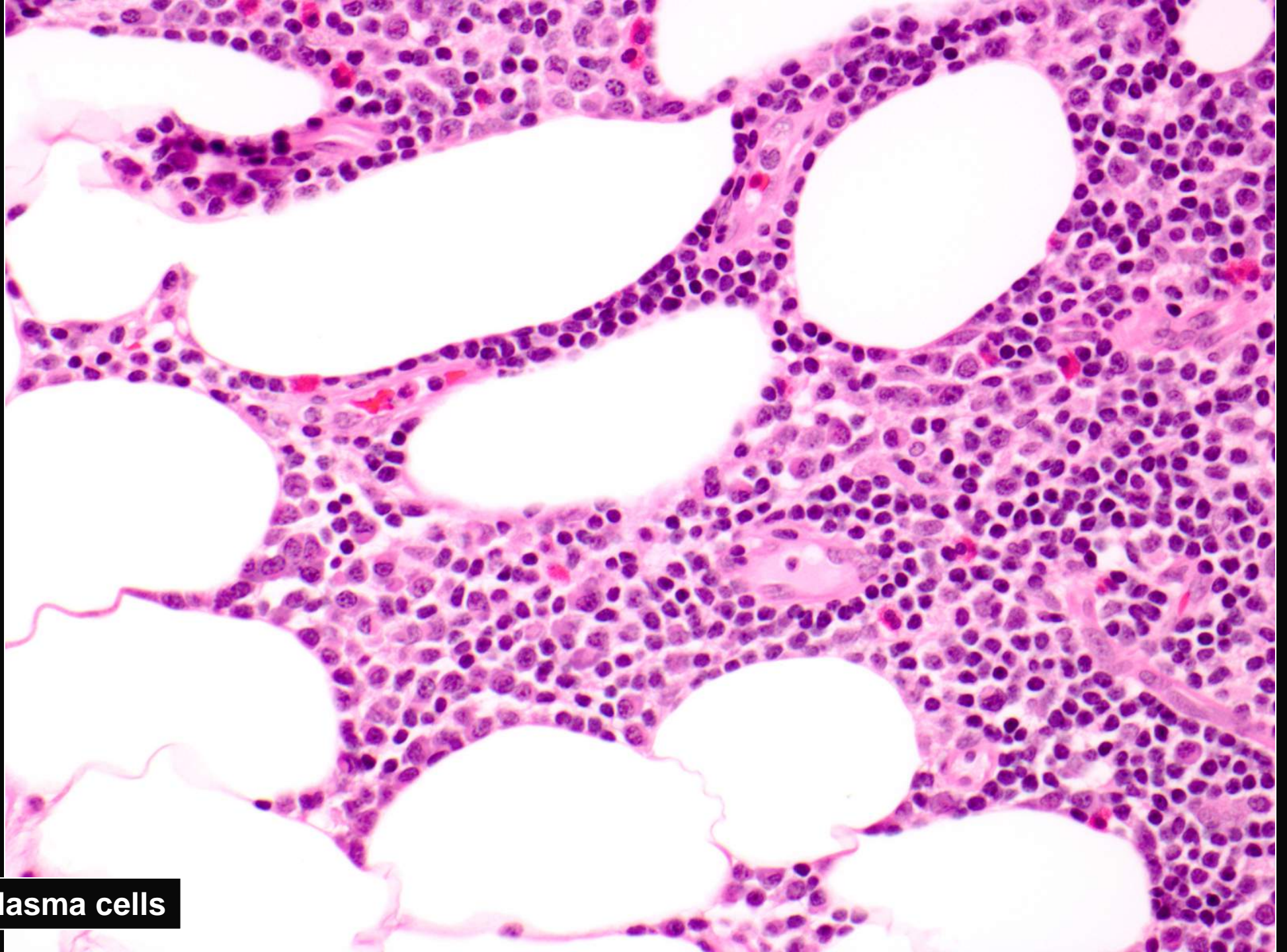
\*Edinger JT, Kant JA, Swerdlow SH. Am J Surg Pathol 2010;34:1830-41.



Cutaneous MALT lymphoma

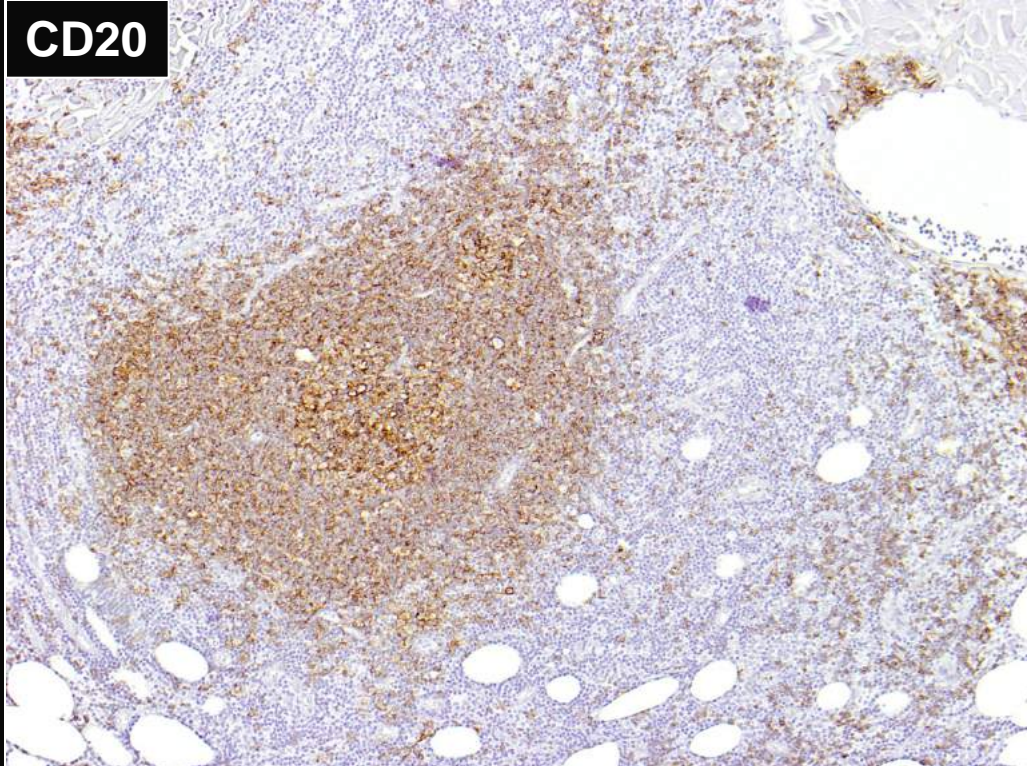


**Small follicle**

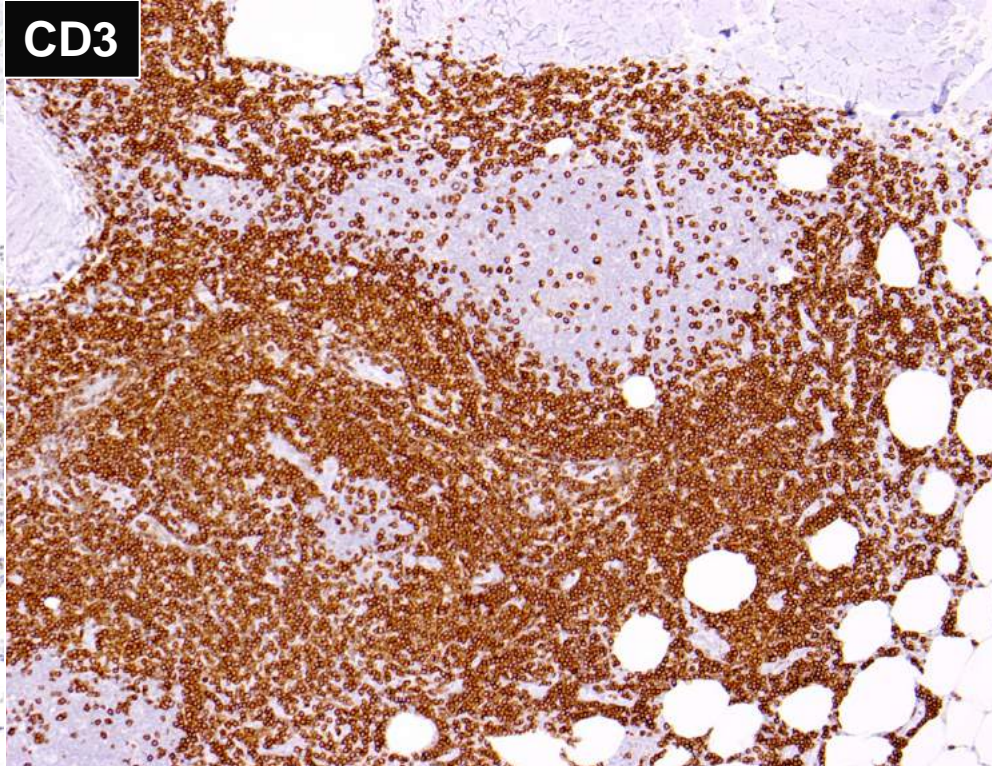


**Plasma cells**

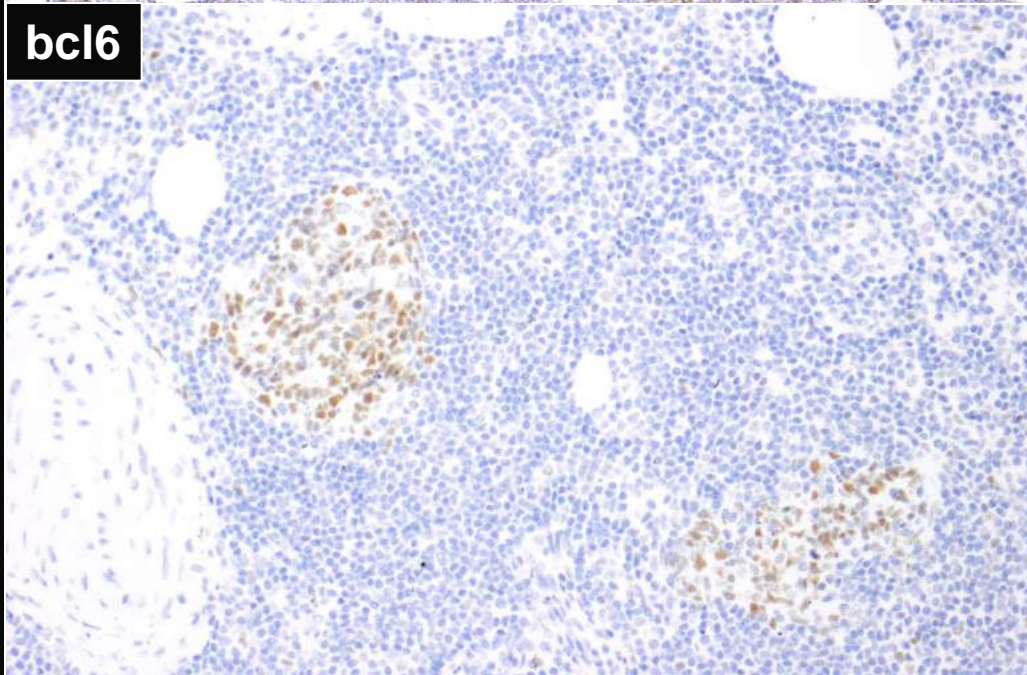
**CD20**



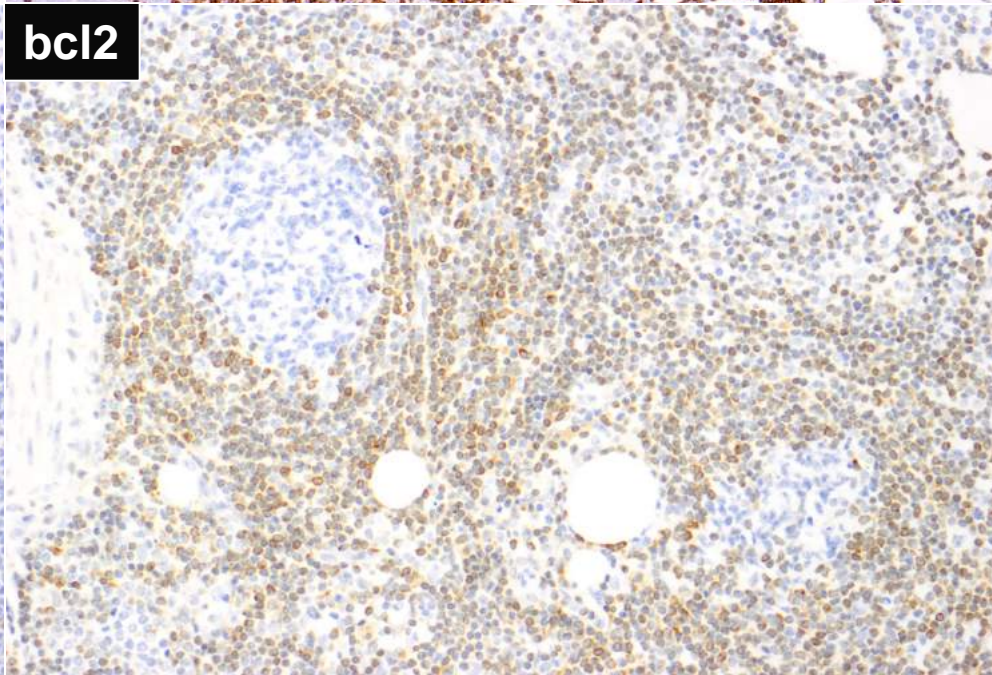
**CD3**



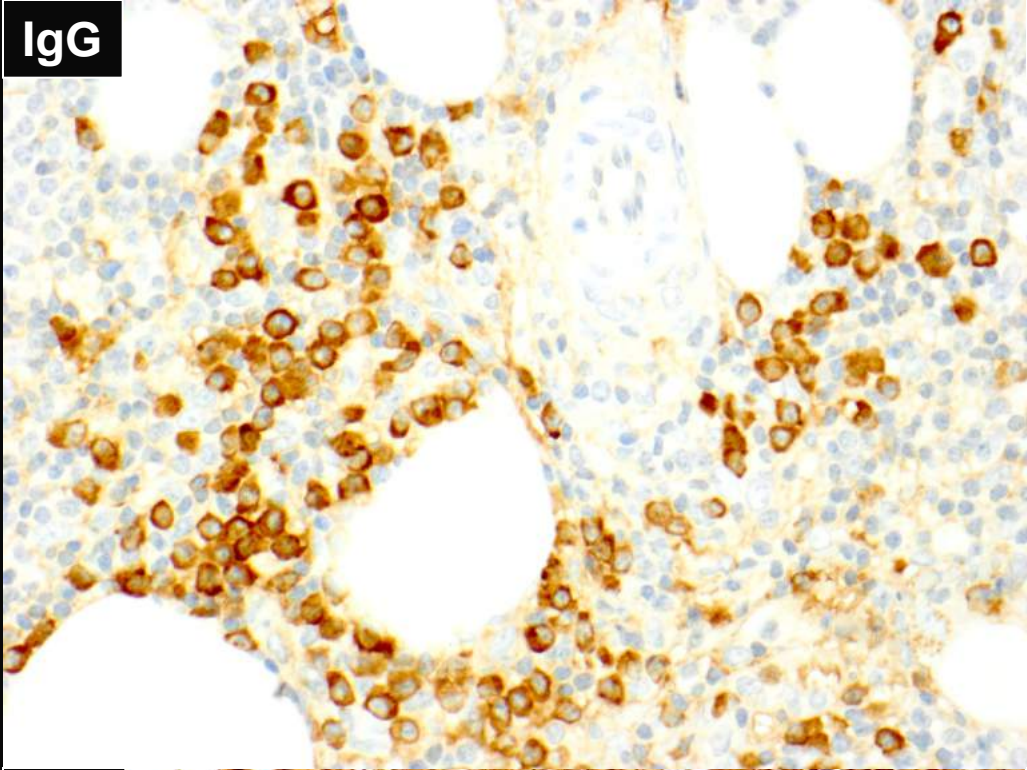
**bcl6**



**bcl2**



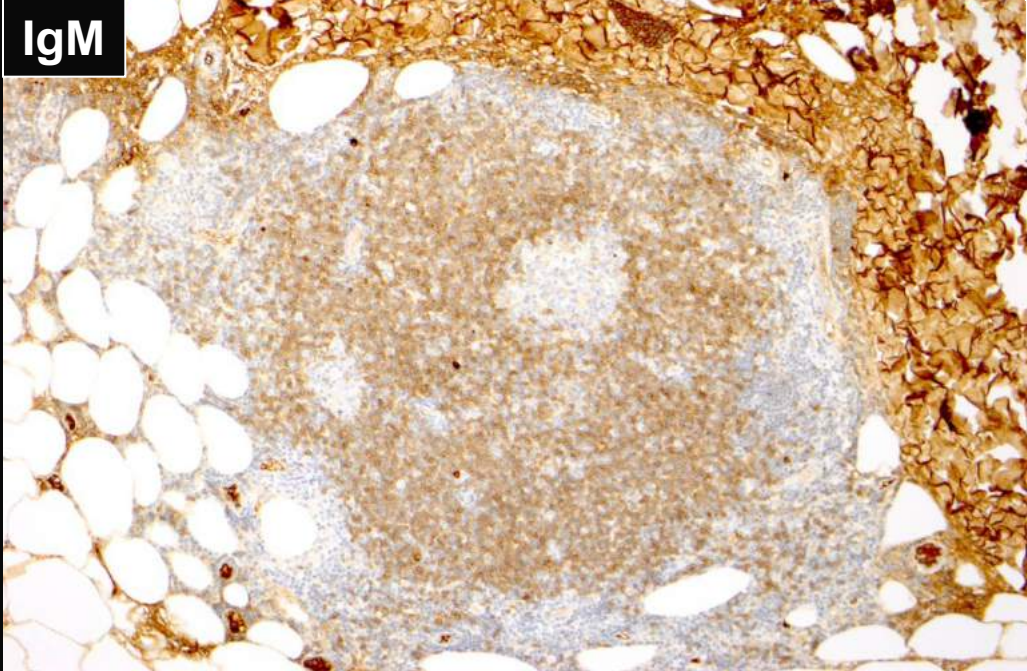
IgG



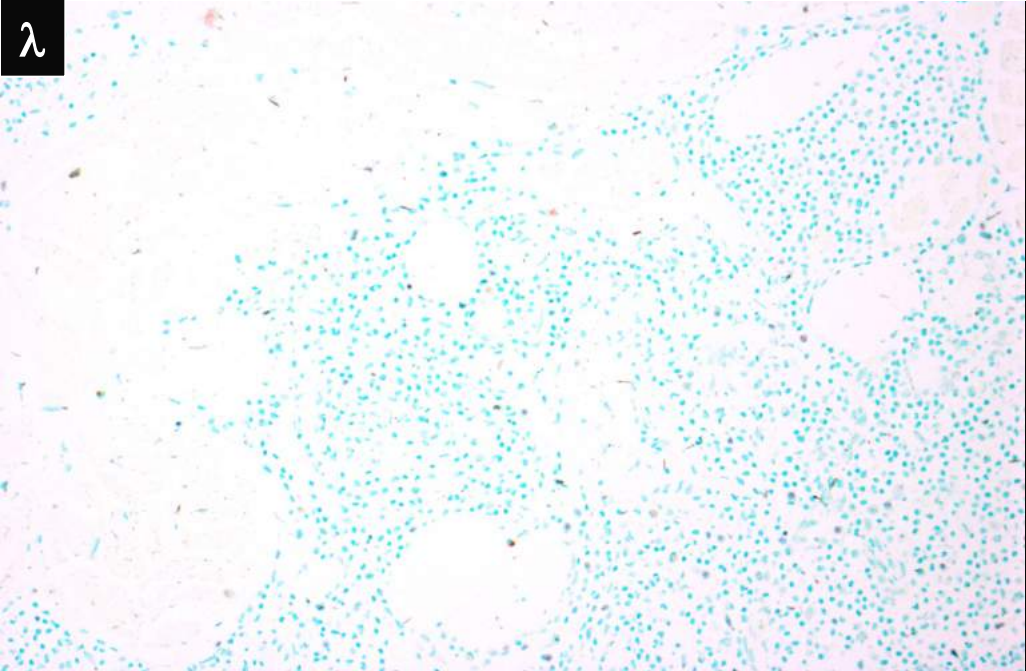
$\kappa$



IgM



$\lambda$





# **MALT Lymphomas**

## **Differential Diagnosis**

**Chronic inflammatory process**

**Other small B-cell lymphomas**

**Mantle cell lymphoma**

**Follicular lymphoma**

**Lymphoplasmacytic lymphoma**

**Significant overlap of path features**

**In favor of LPL:**

**Lymphoma NOT confined to MALT site**

**Prominent marrow involvement**

**Large IgM M-component**

**MYD88 L265P mutation**

# **MALT LYMPHOMA vs INFLAMMATION**

## **Lymphoma:**

**Expansile, destructive infiltrate with loss  
of normal architecture**

**Cytologic atypia**

**Many lymphoepithelial lesions**

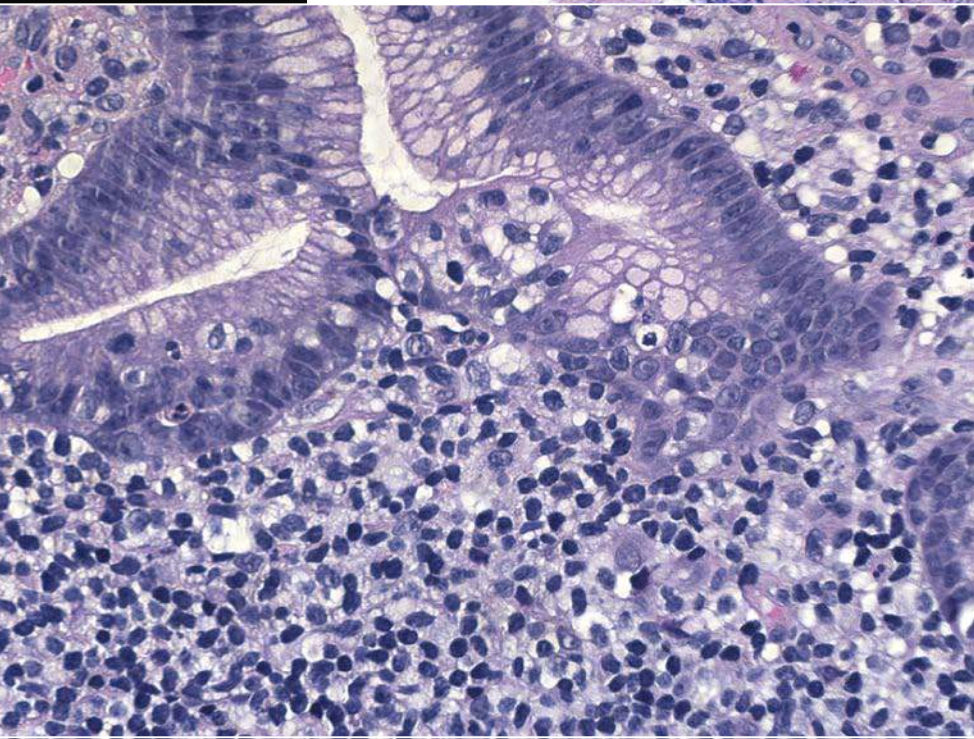
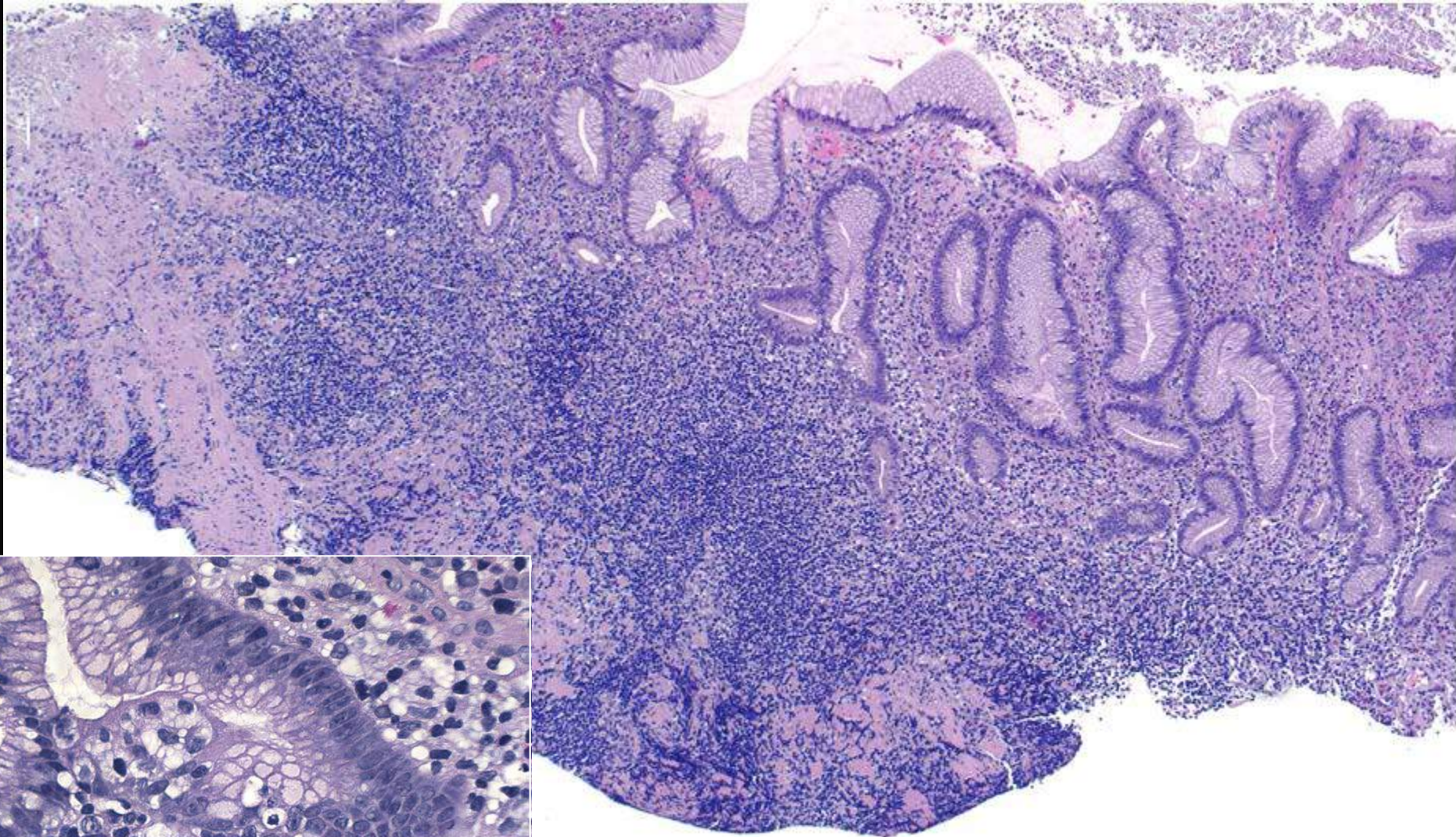
**Dutcher bodies**

**Dense, diffuse infiltrate of B cells**

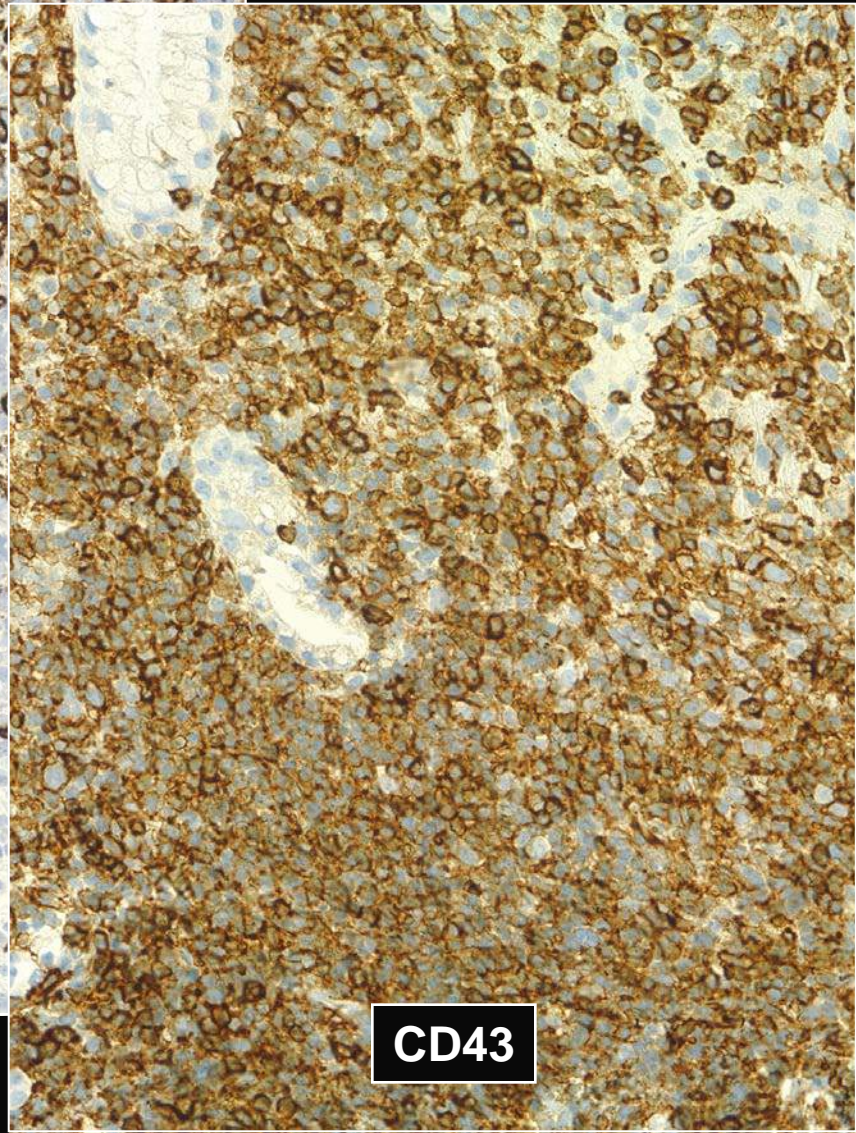
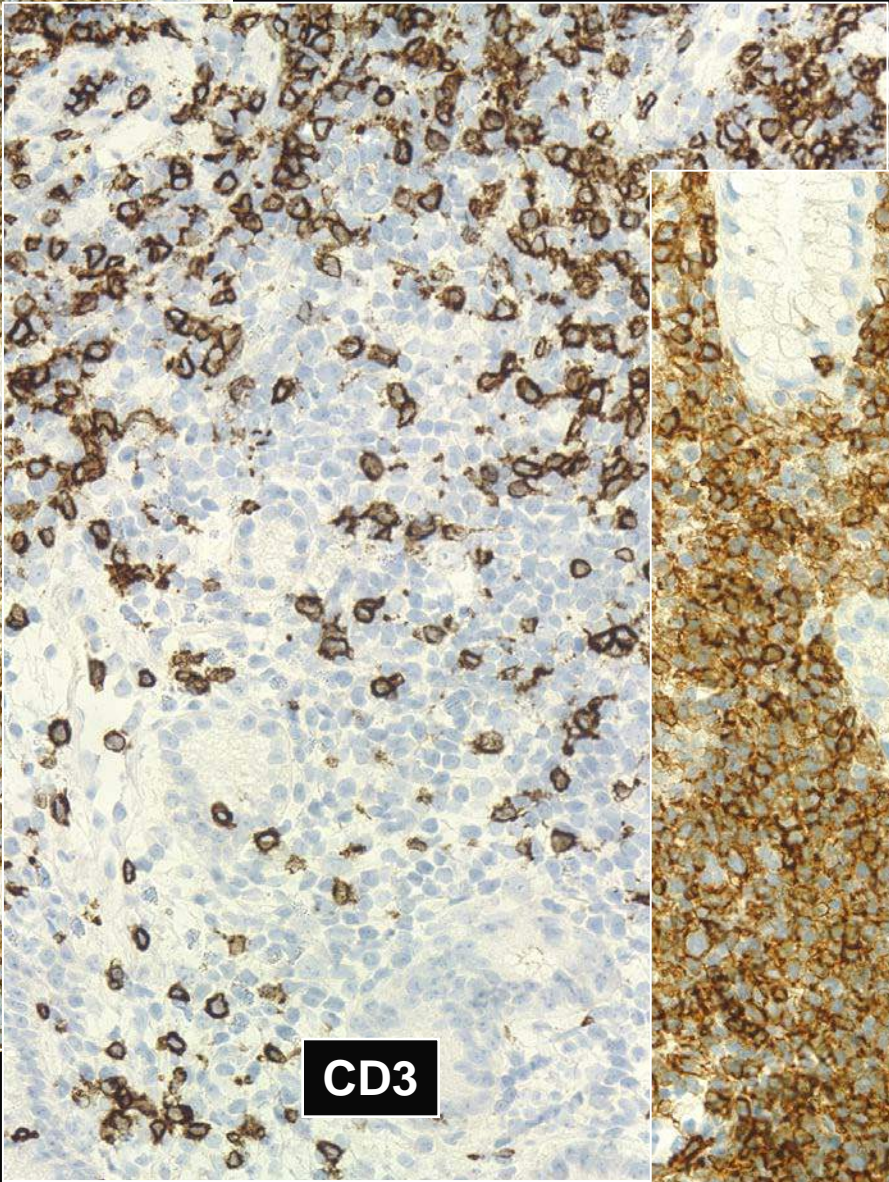
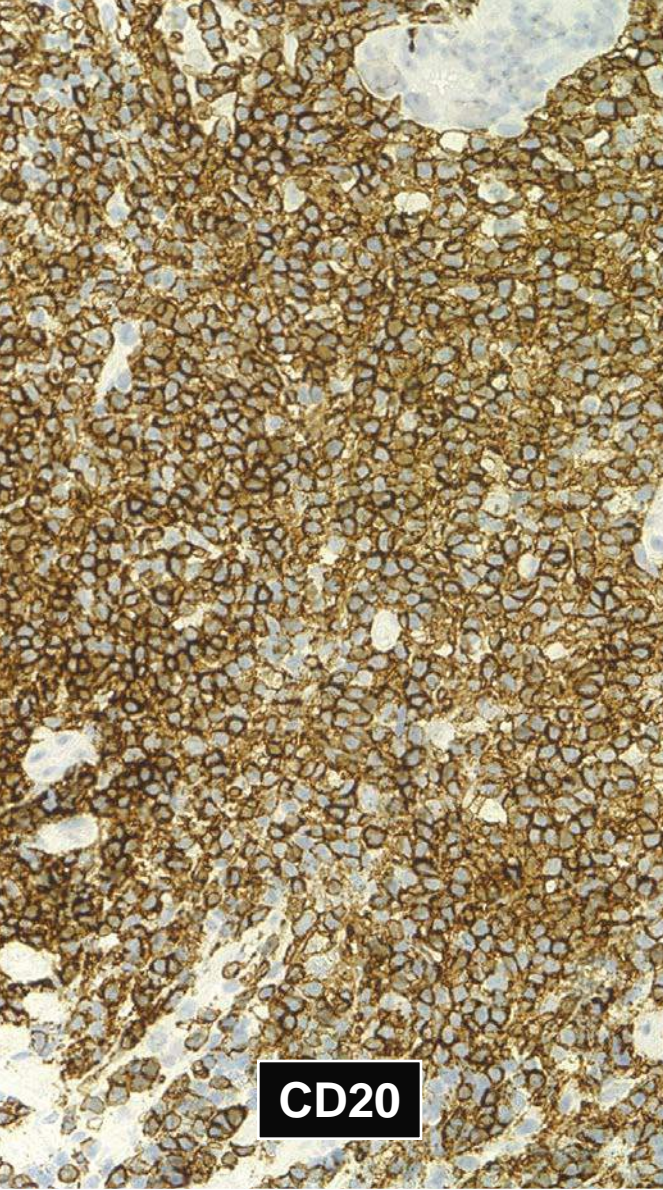
**Clonal light chains**

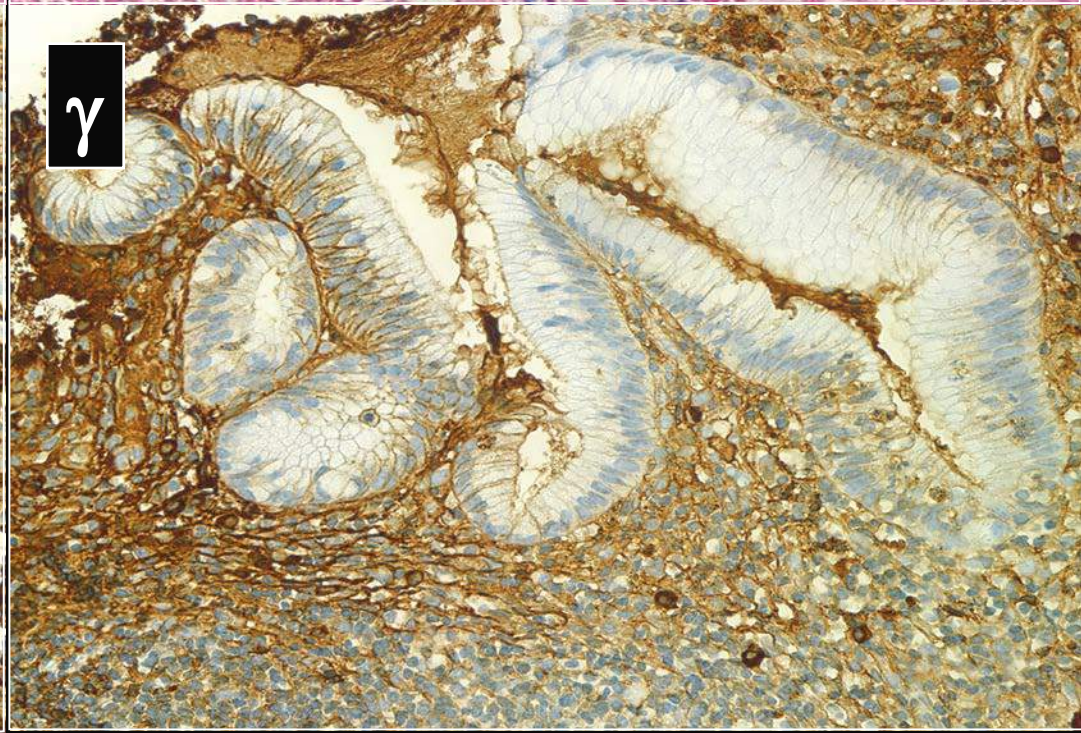
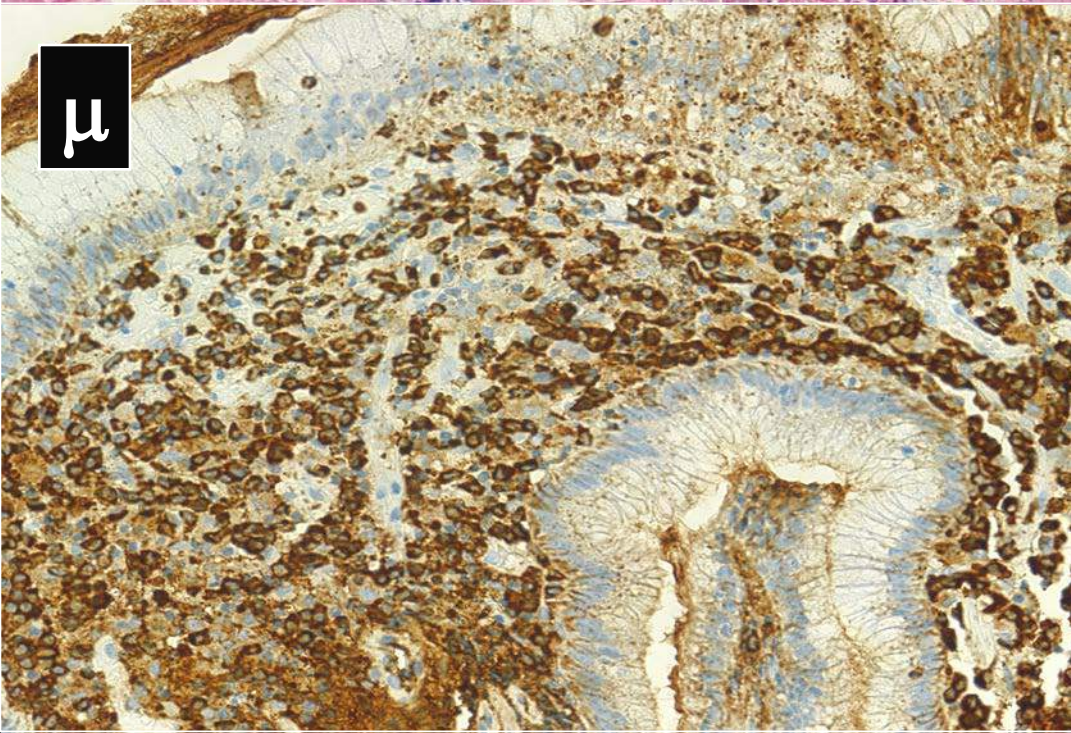
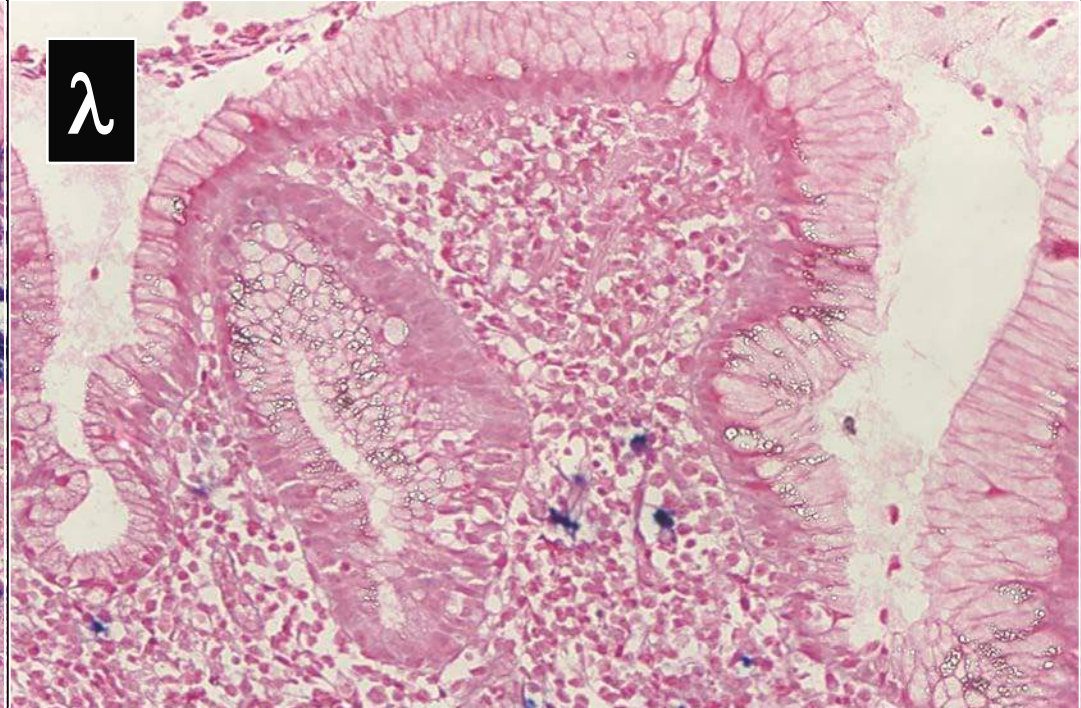
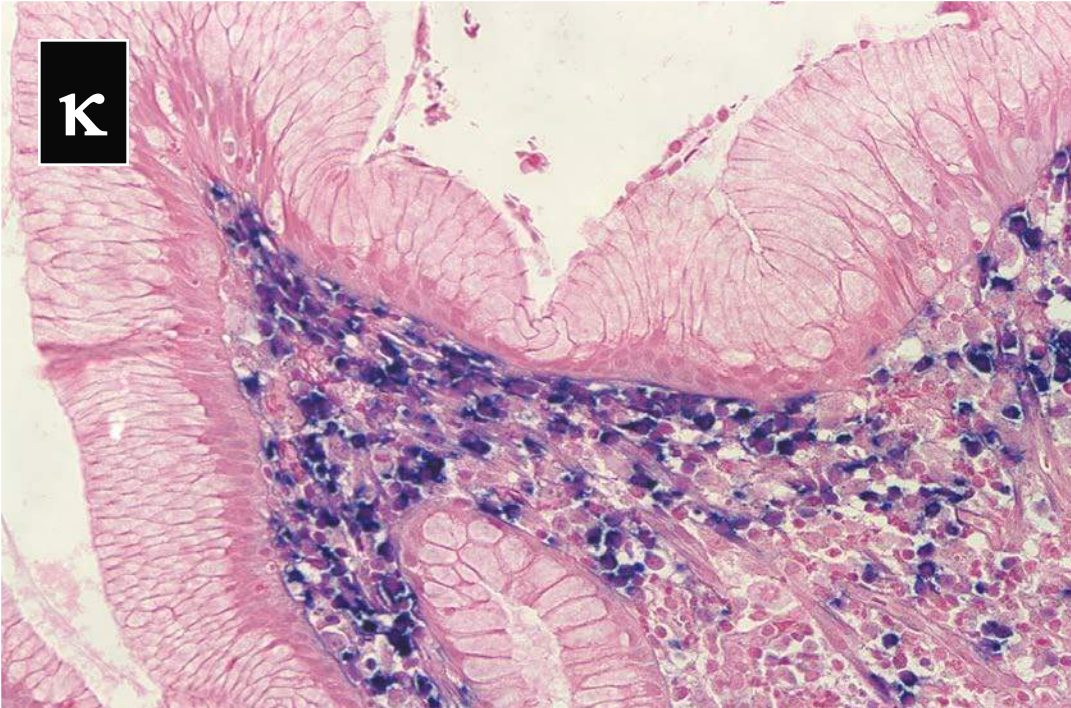
**Ig heavy chain  $\mu$**

**Co-expression of CD43 on lymphocytes**



**Stomach: MALT lymphoma?**





# MANTLE CELL LYMPHOMA

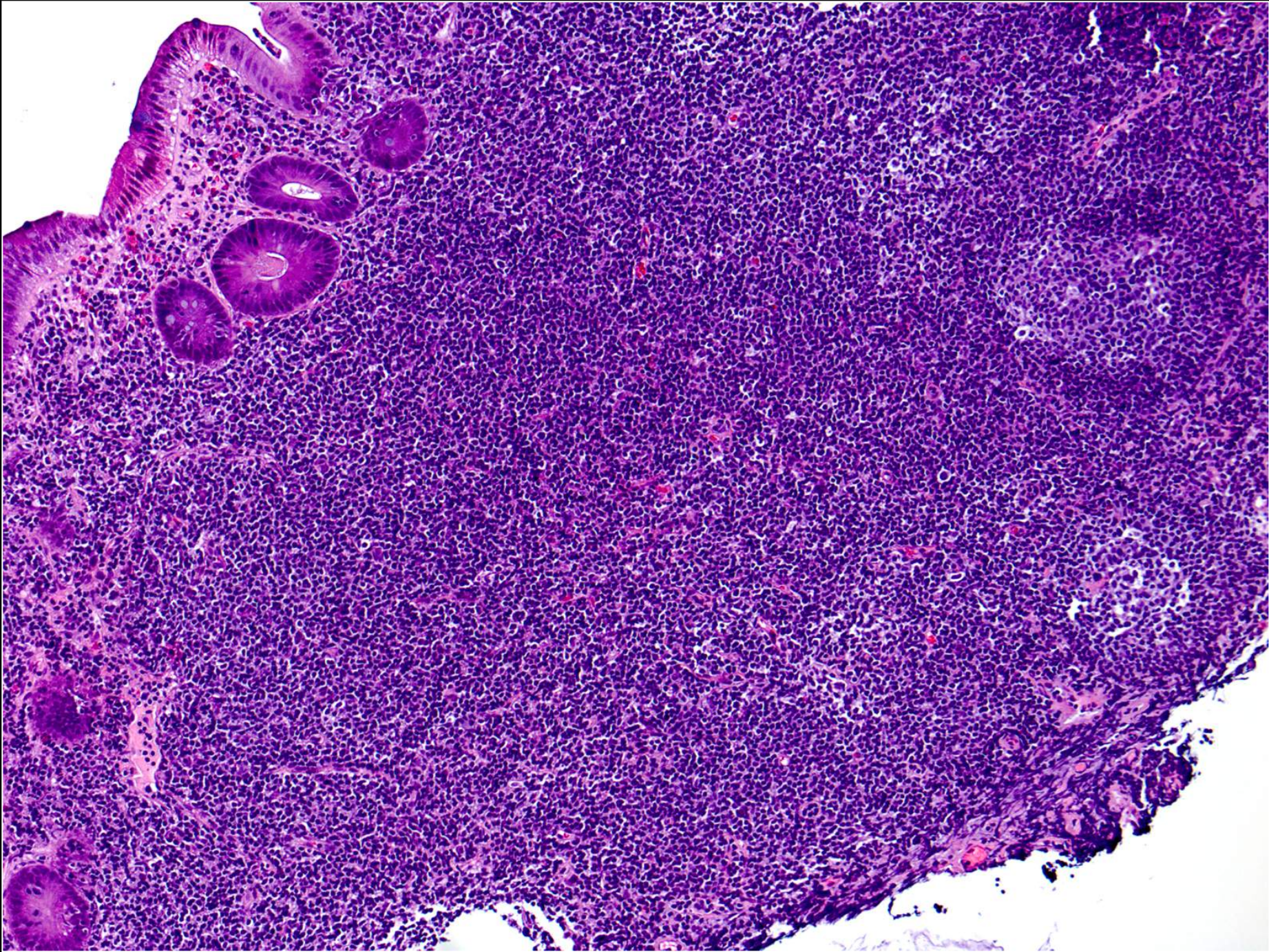
- **Older adults, male preponderance**
- **Widespread disease usual, lymph nodes and extranodal sites**
- **Usually takes the form of multiple lymphomatous polyposis (MLP) in GI tract**
- **Other: Waldeyer's ring, orbit, skin**
- **Staging: more extensive disease usually present**
- **Immuno: CD20+, CD5+, CD10-, CD23-, cyclin D1+, SOX11+, IgM/IgD+,  $\lambda > \kappa$**

# Mantle Cell Lymphoma: Lymphomatous Polyposis

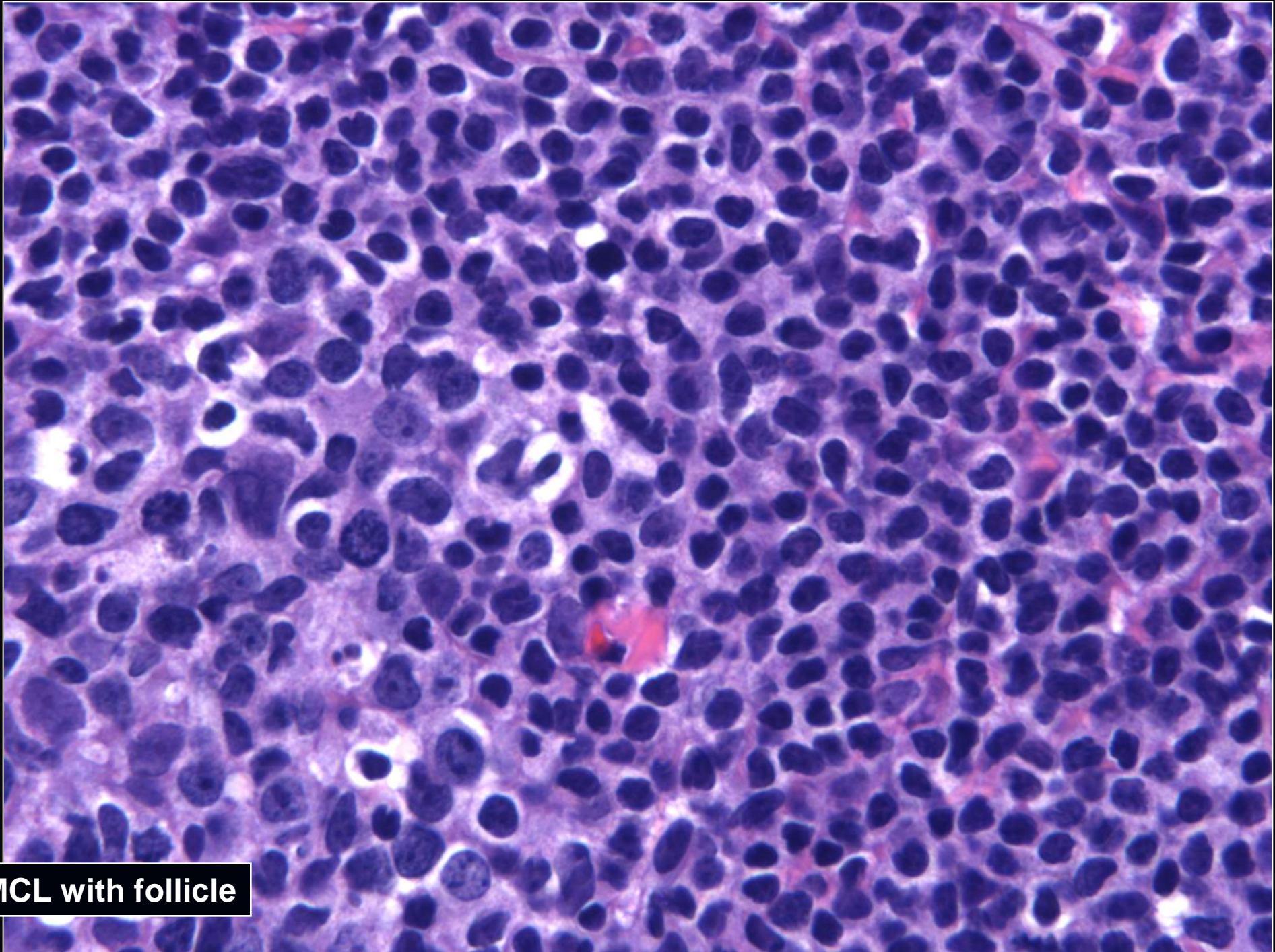


Mass General Hospital Pathology Department

Multiple polyps of varying size; can involve entire GI tract (stomach, small and large bowel)

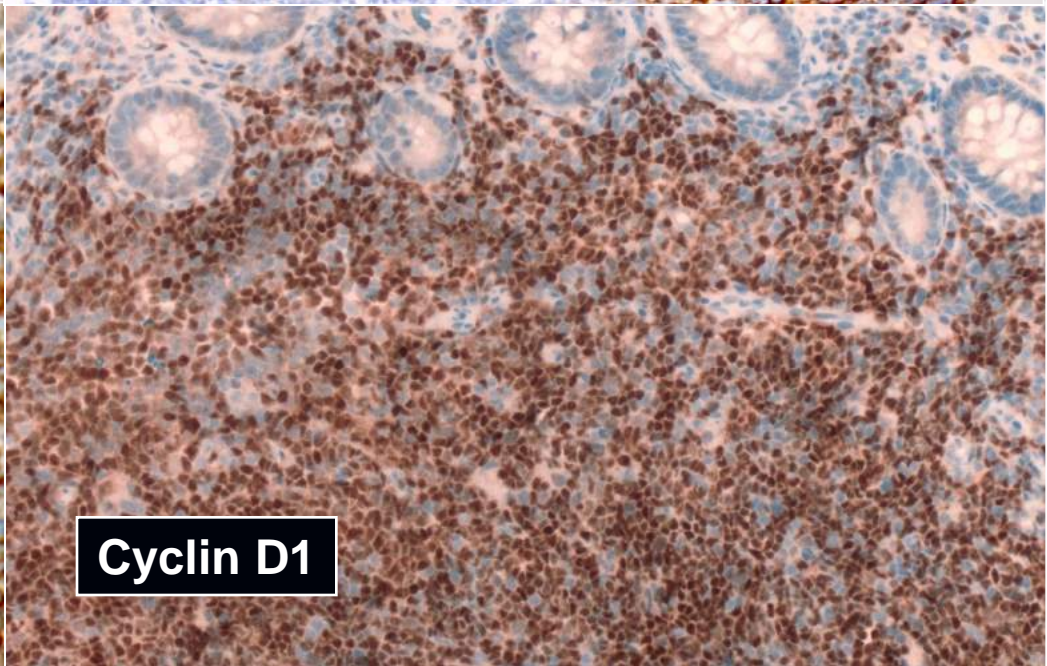
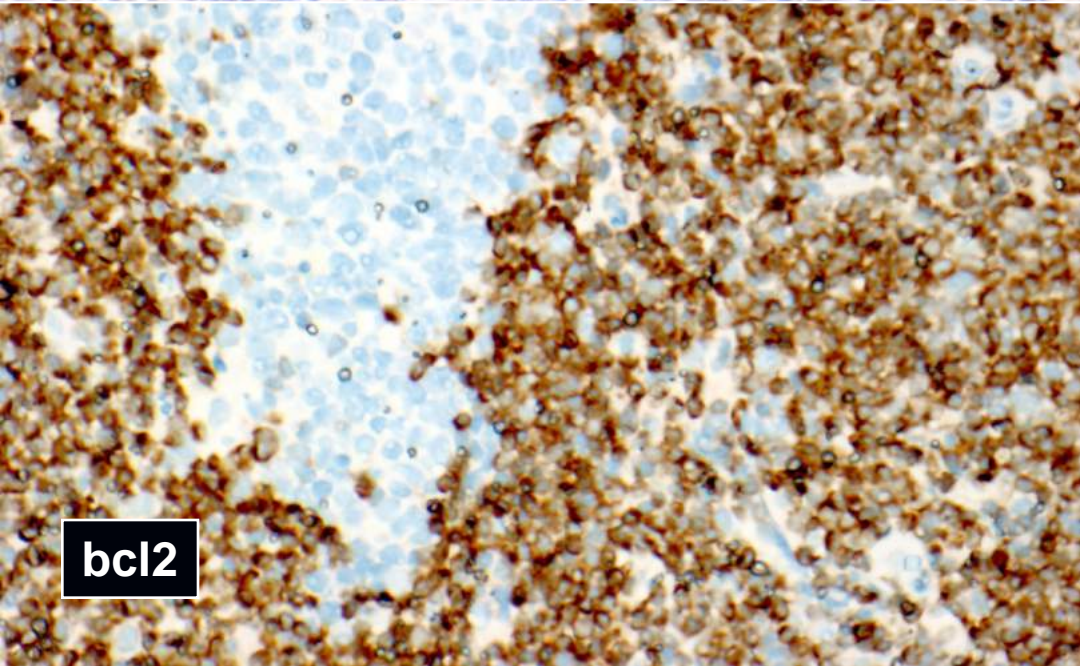
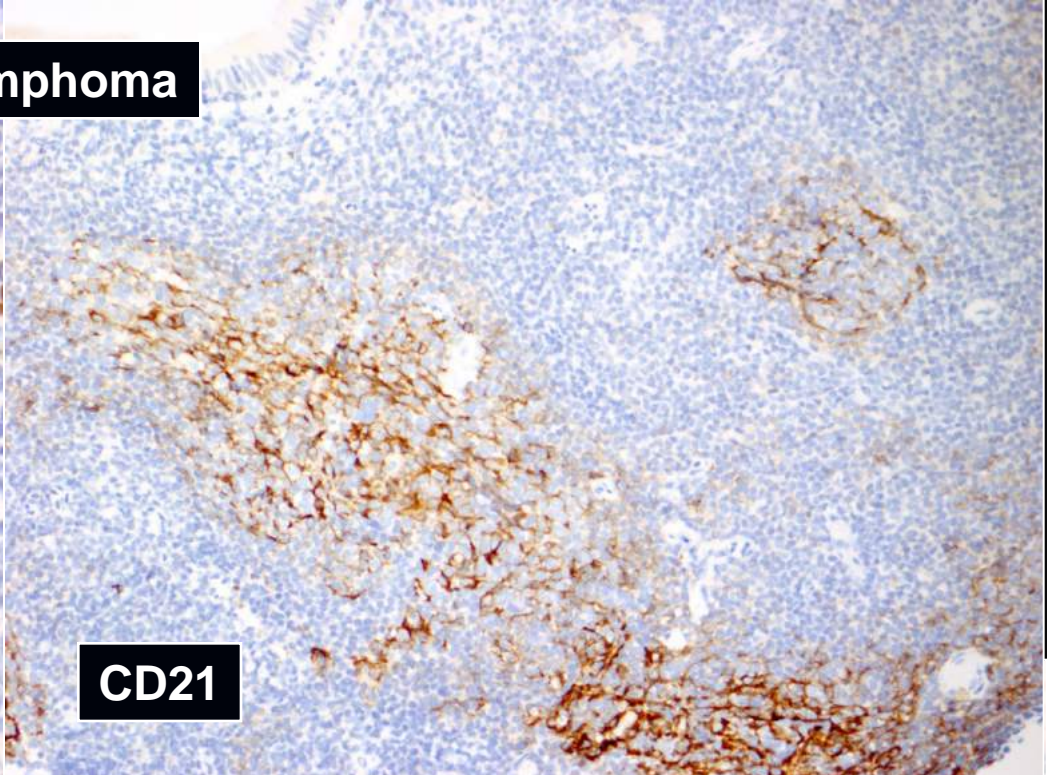
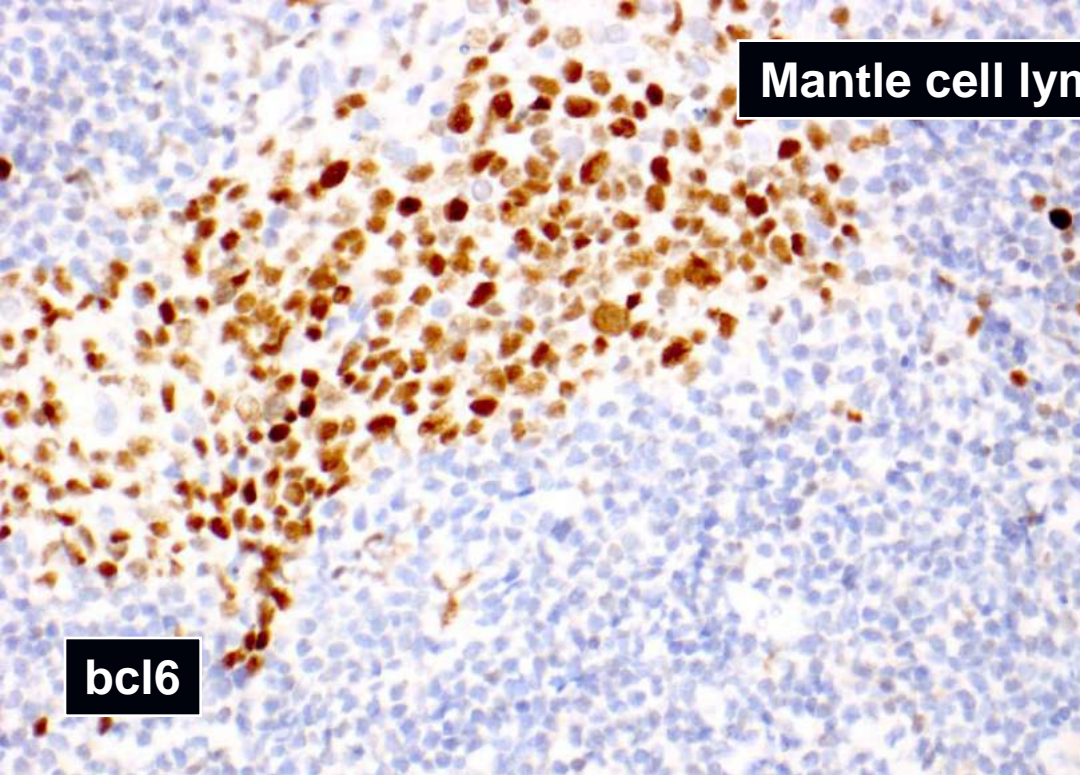






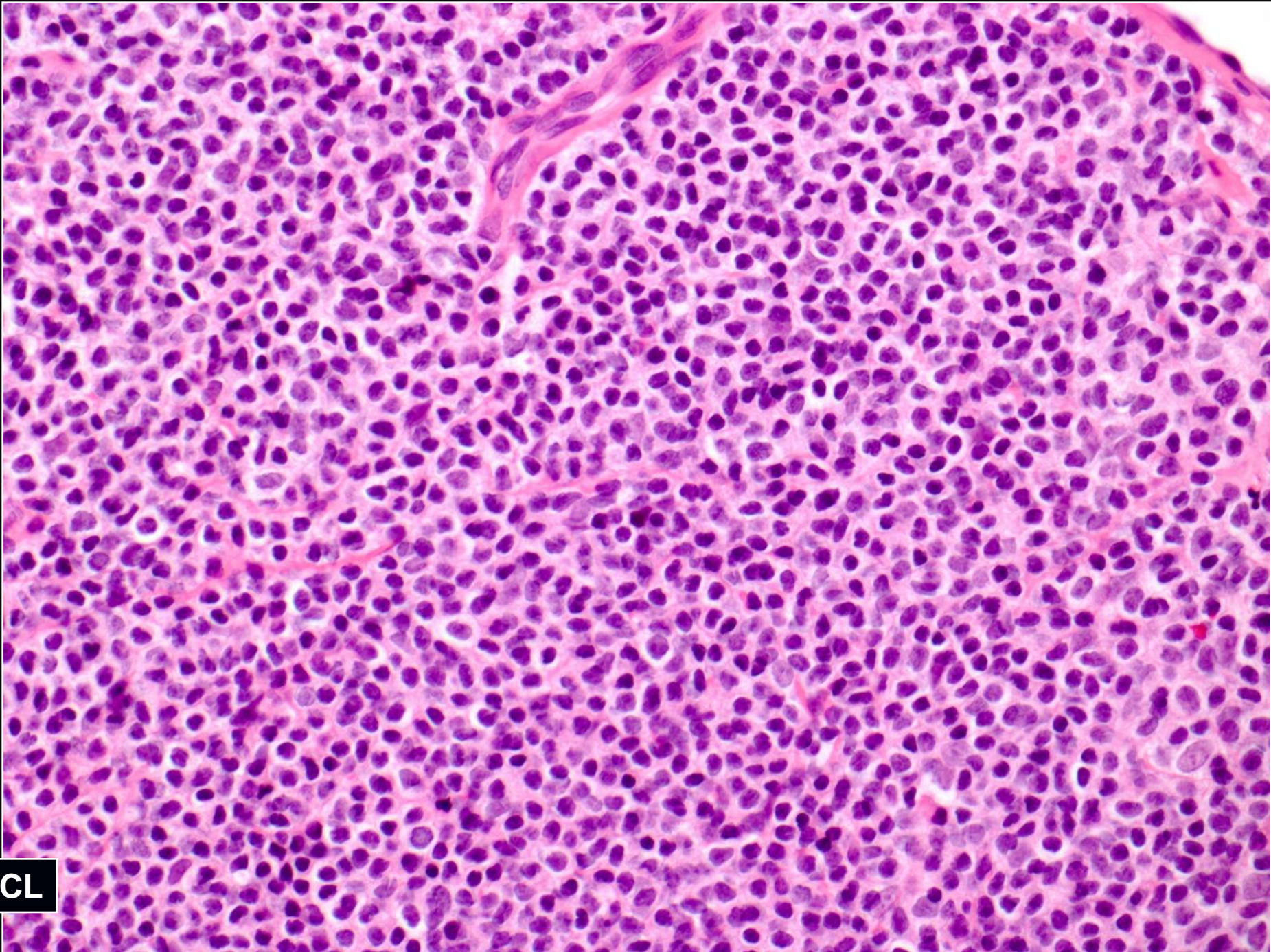
**MCL with follicle**

**Mantle cell lymphoma**



# Mantle Cell Lymphoma

- **Cytology**
  - **Typical**
  - **Aggressive variants**
    - » **Blastoid variant**
    - » **Pleomorphic variant**
  - **Other variants**
    - » **Small cell**
    - » **Marginal zone-like**

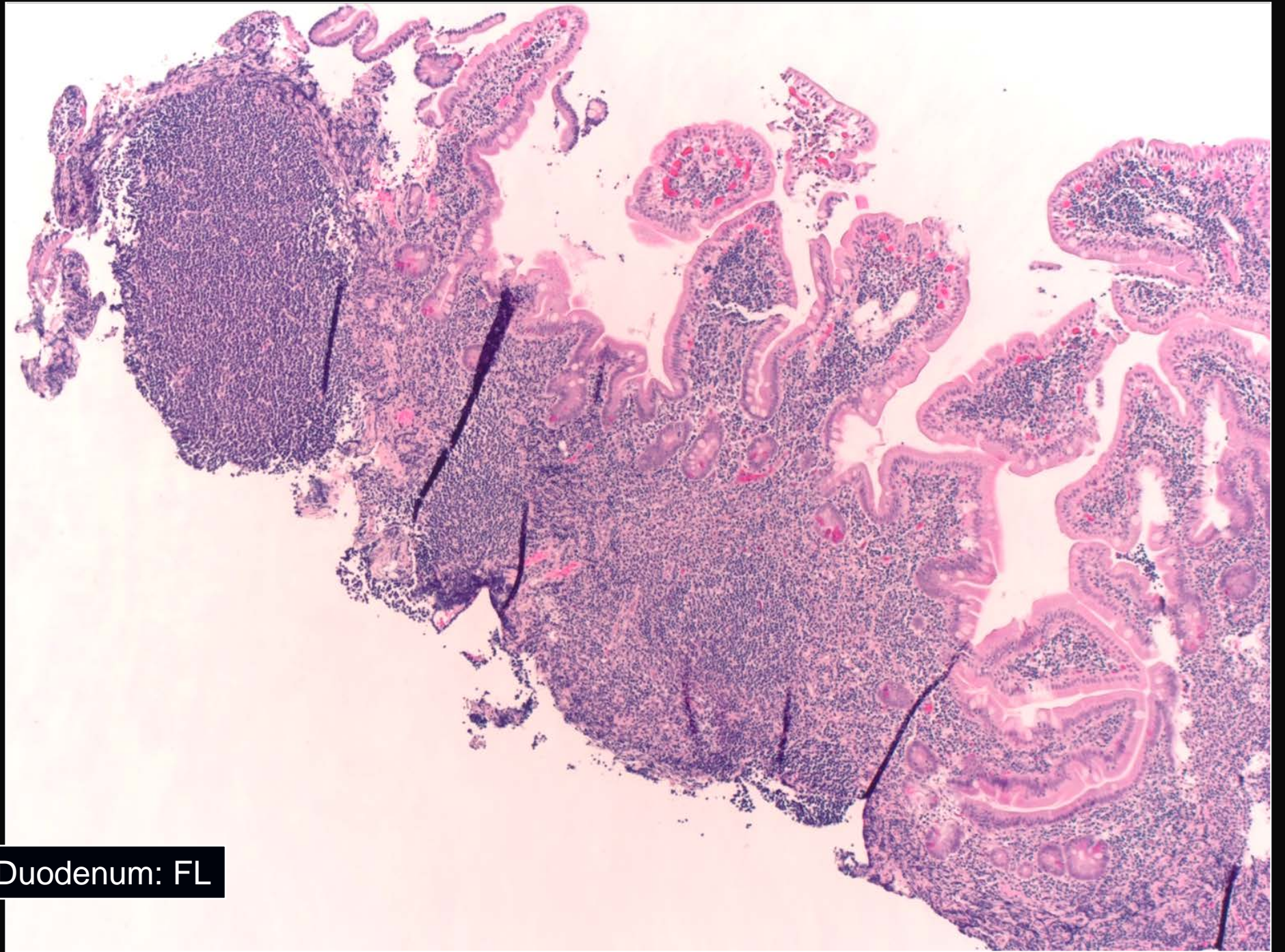


MCL

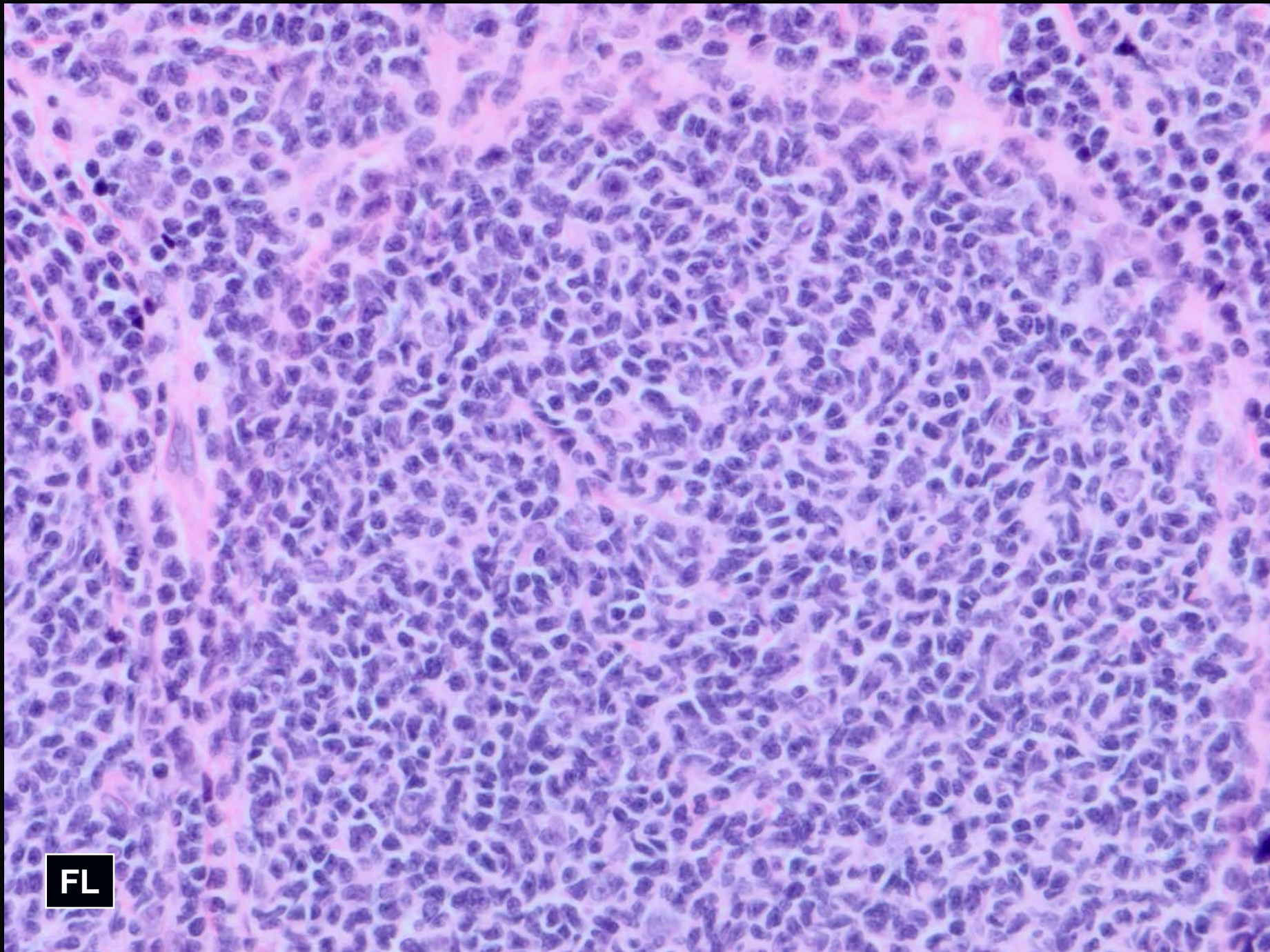
# **EXTRANODAL FOLLICULAR LYMPHOMA**

## *GI follicular lymphoma*

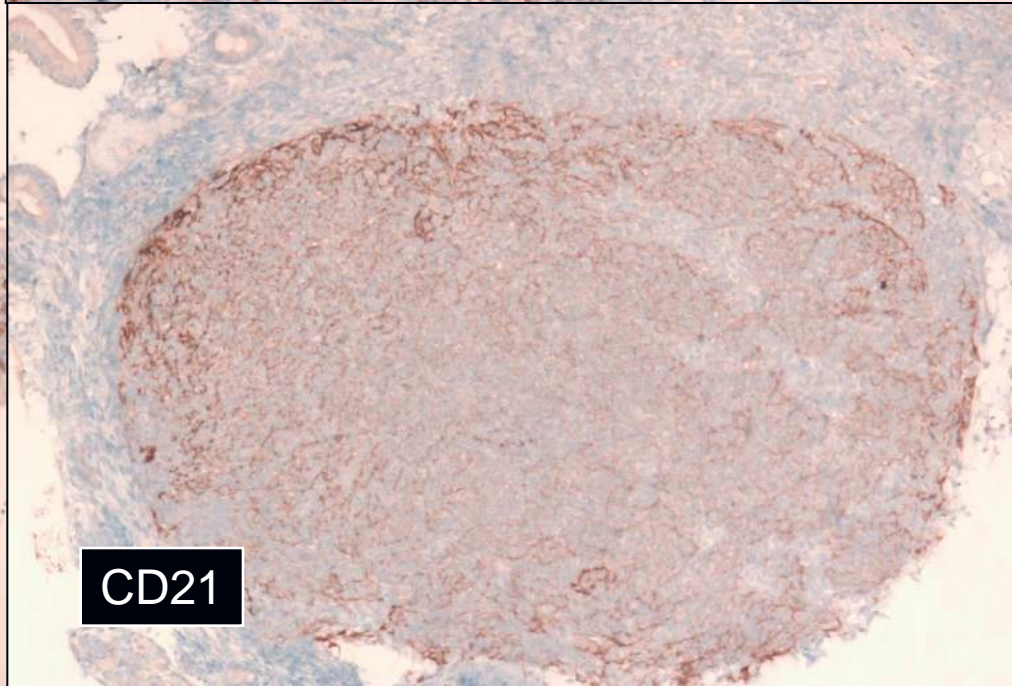
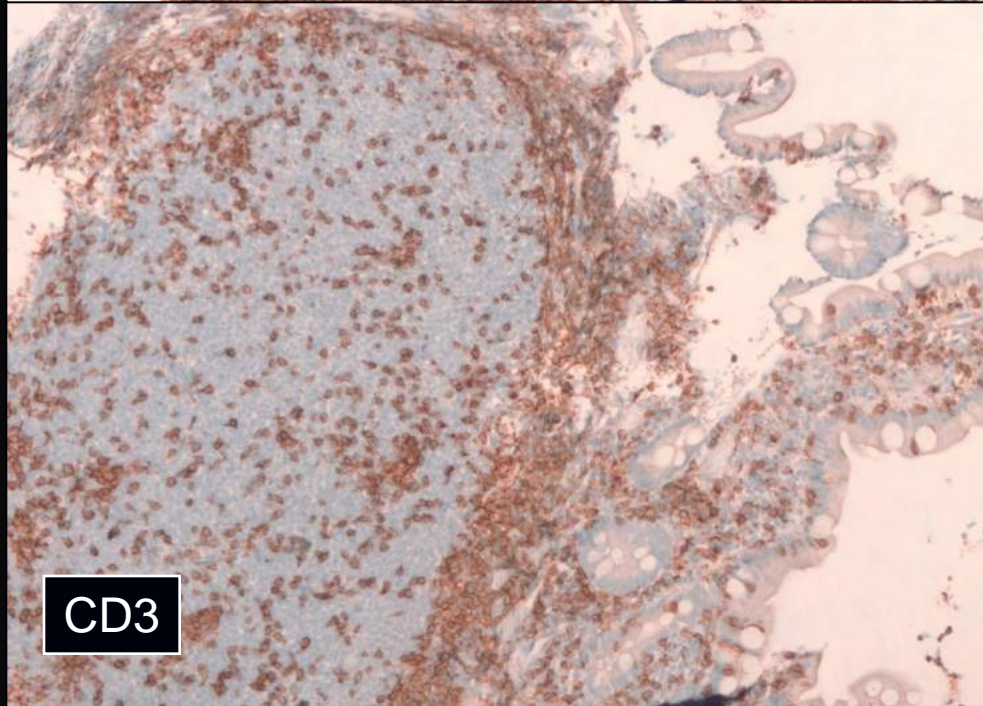
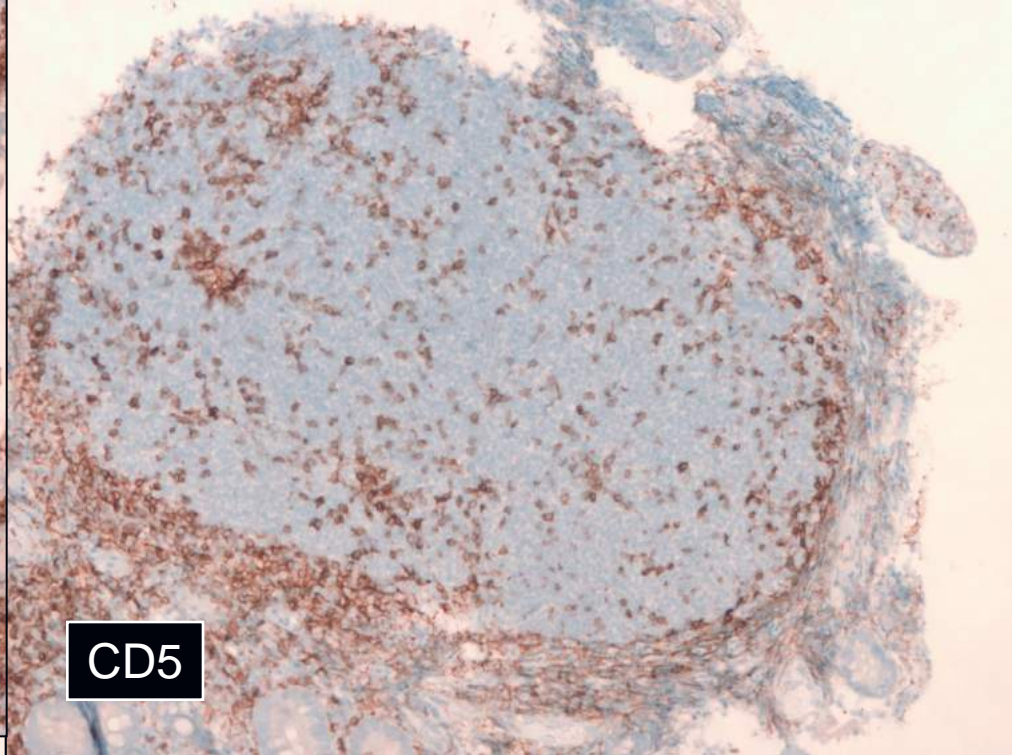
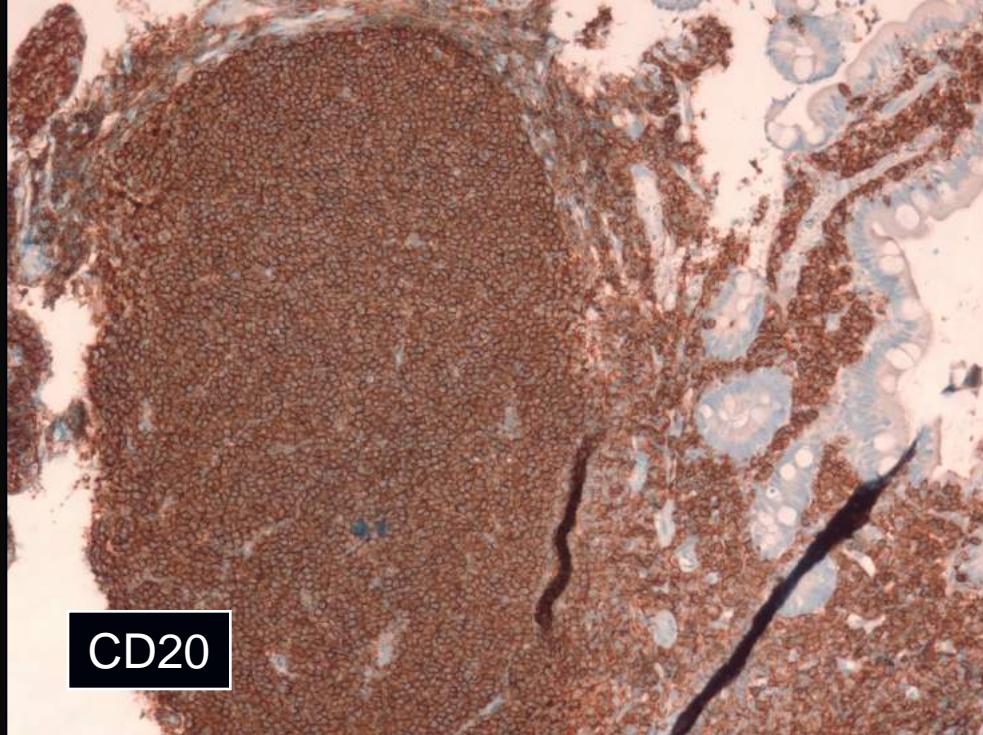
- **FL is rare in GI tract, but most cases involve duodenum, esp. its 2nd portion**
- **Adults, F > M**
- **Mucosal nodularity, small polyps or large tumors**
- **Often localized, has good prognosis**
- **Immuno: CD20+, CD10+, CD5-, bcl-6+, bcl-2+**
- ***BCL2* gene rearranged: t(14;18)**
- **Immuno and genetic features are similar to nodal FL**



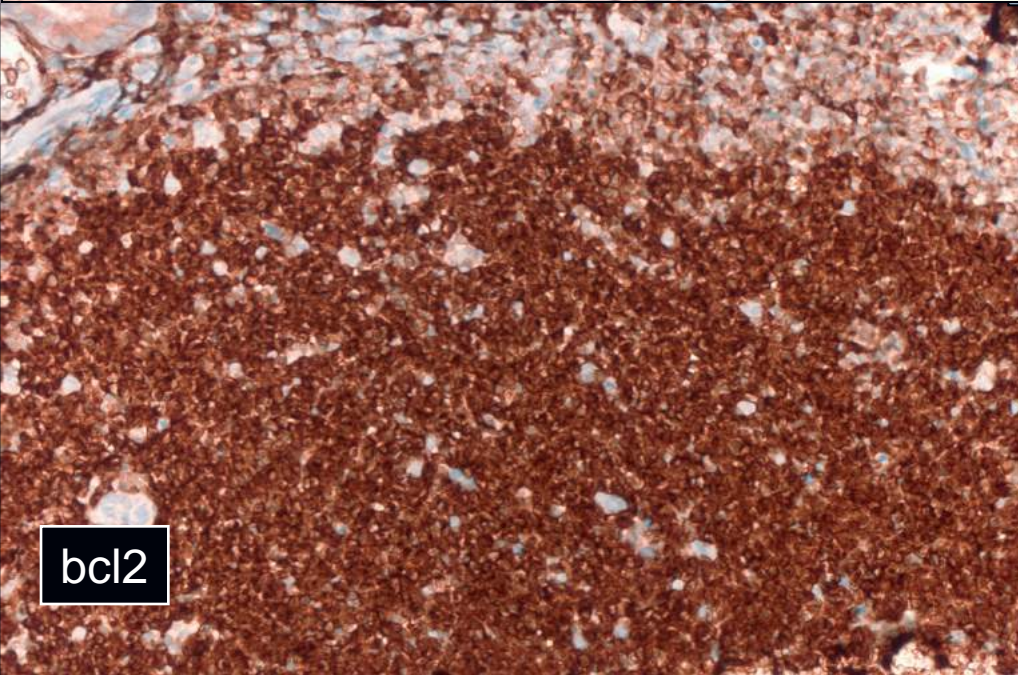
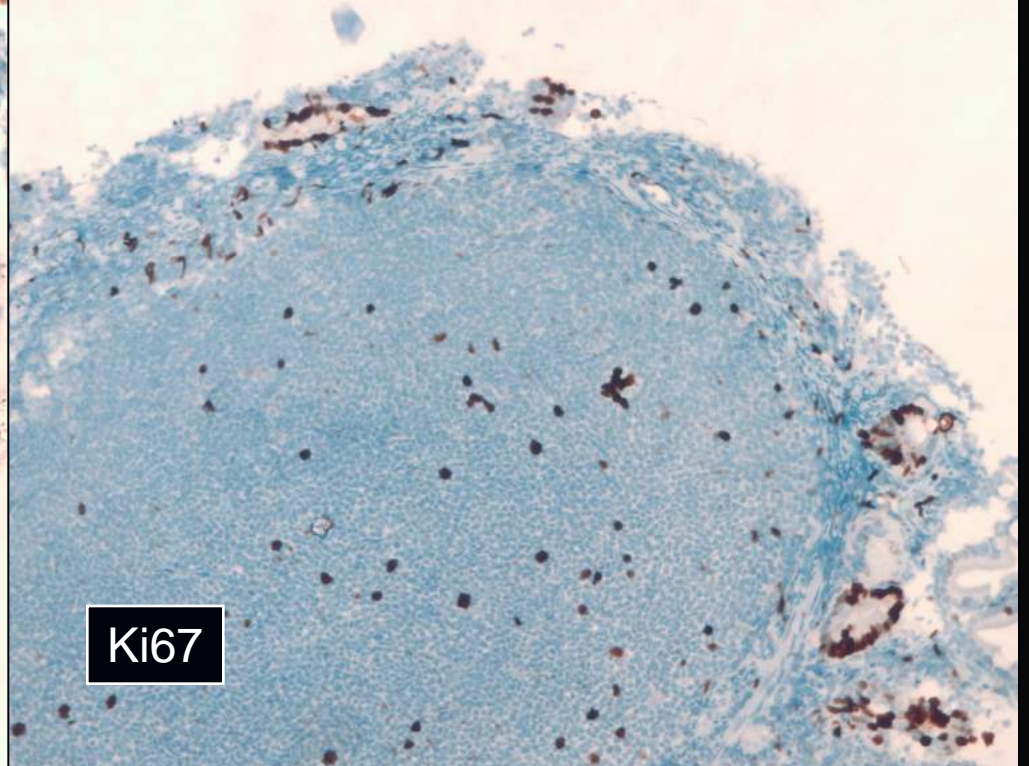
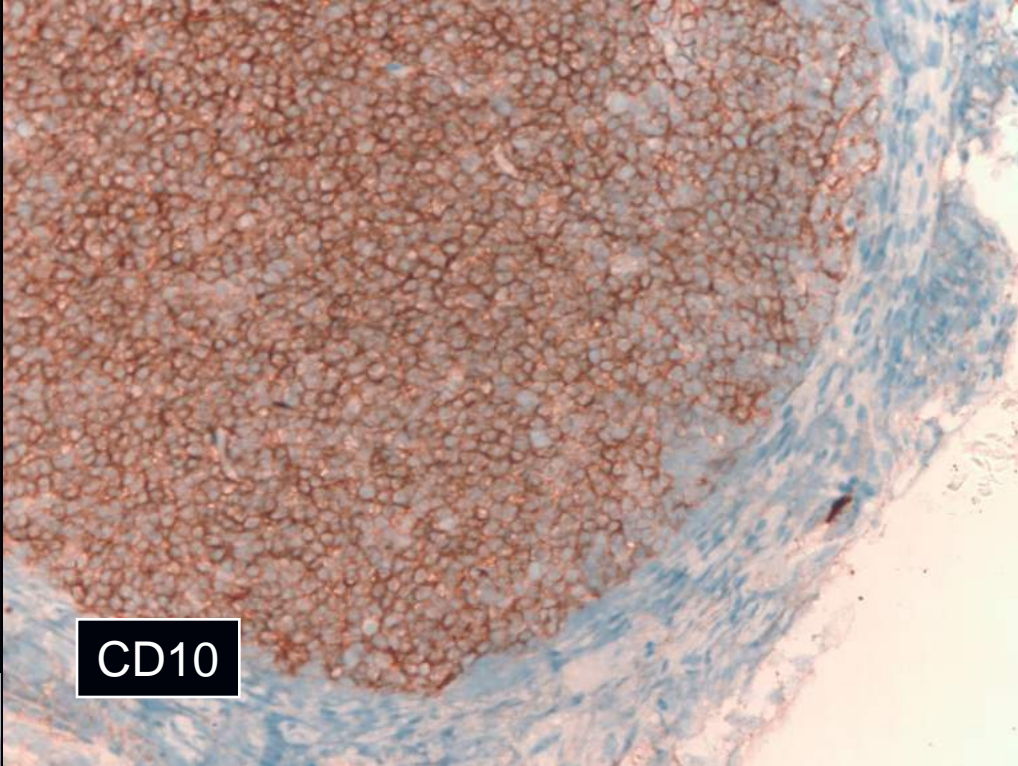
Duodenum: FL



FL





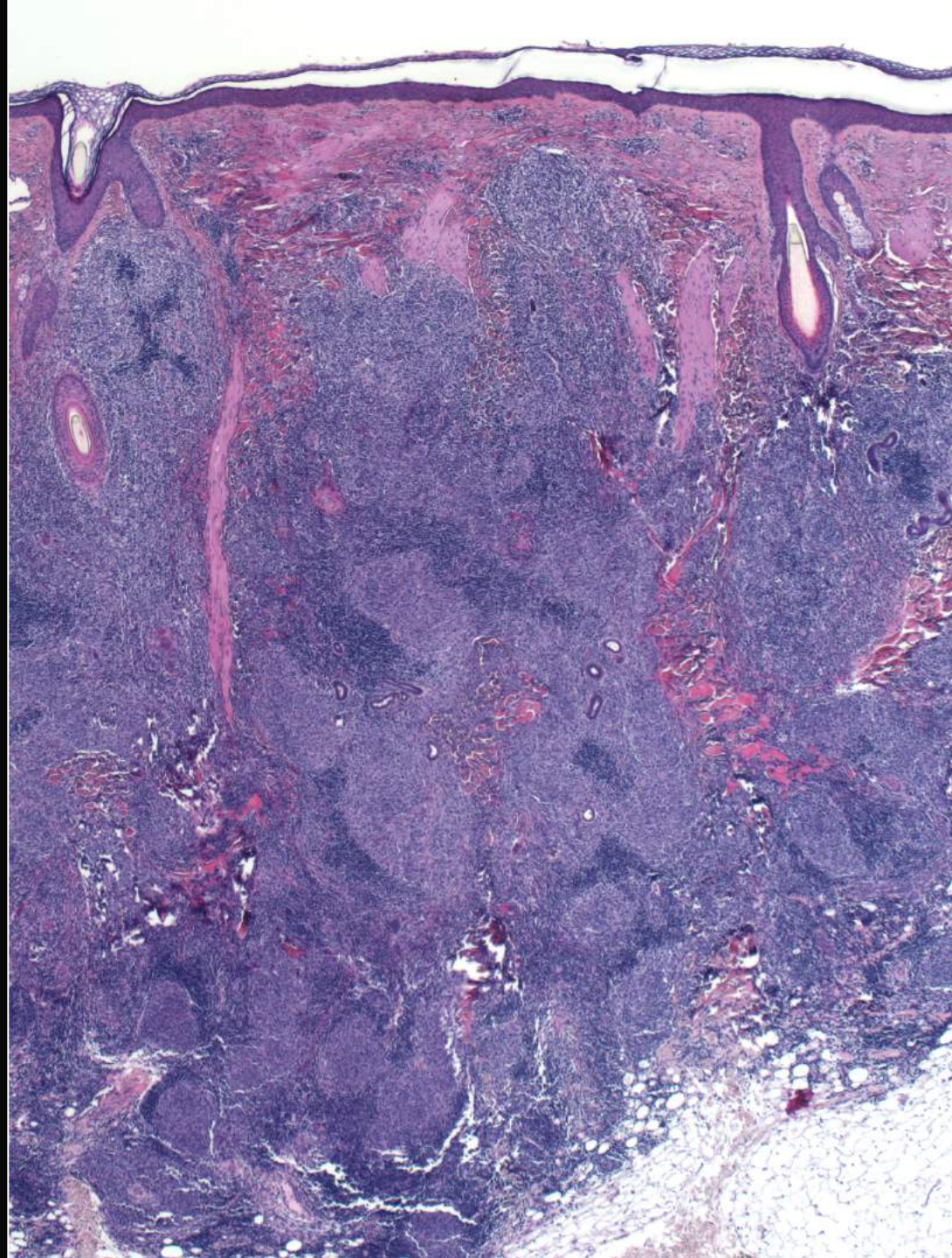


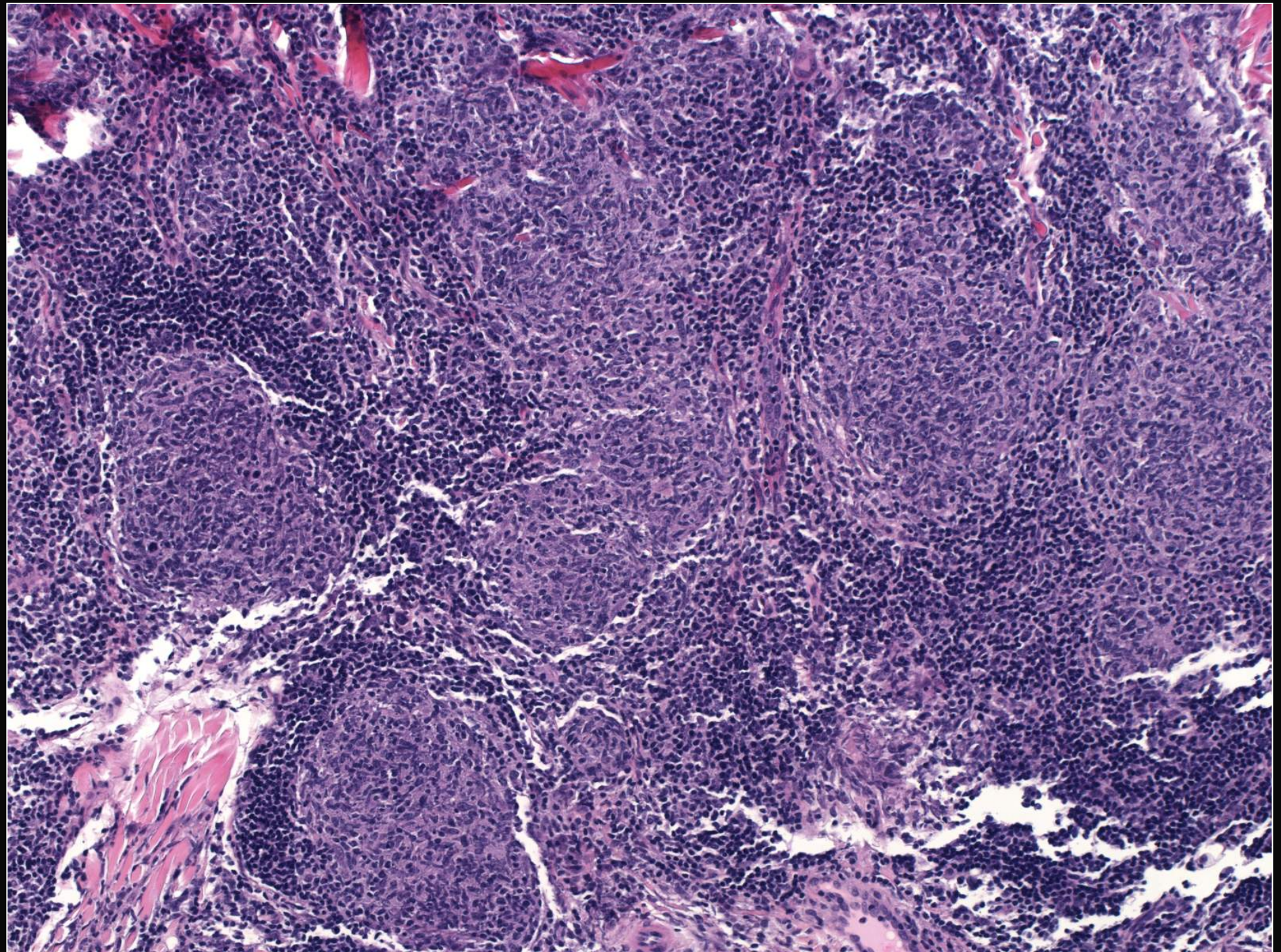
***Diagnosis***

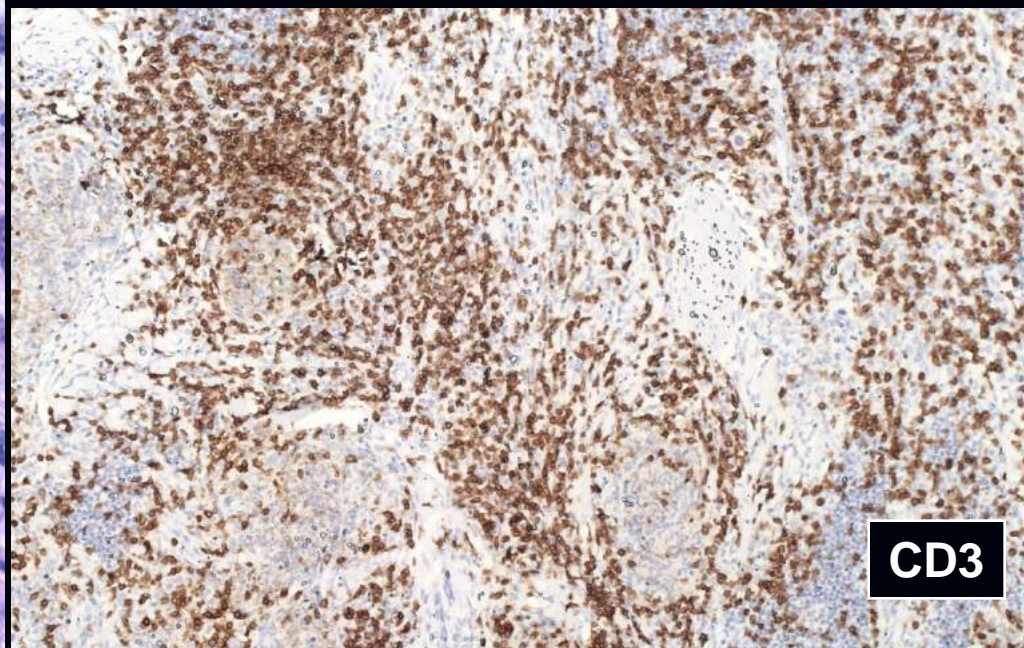
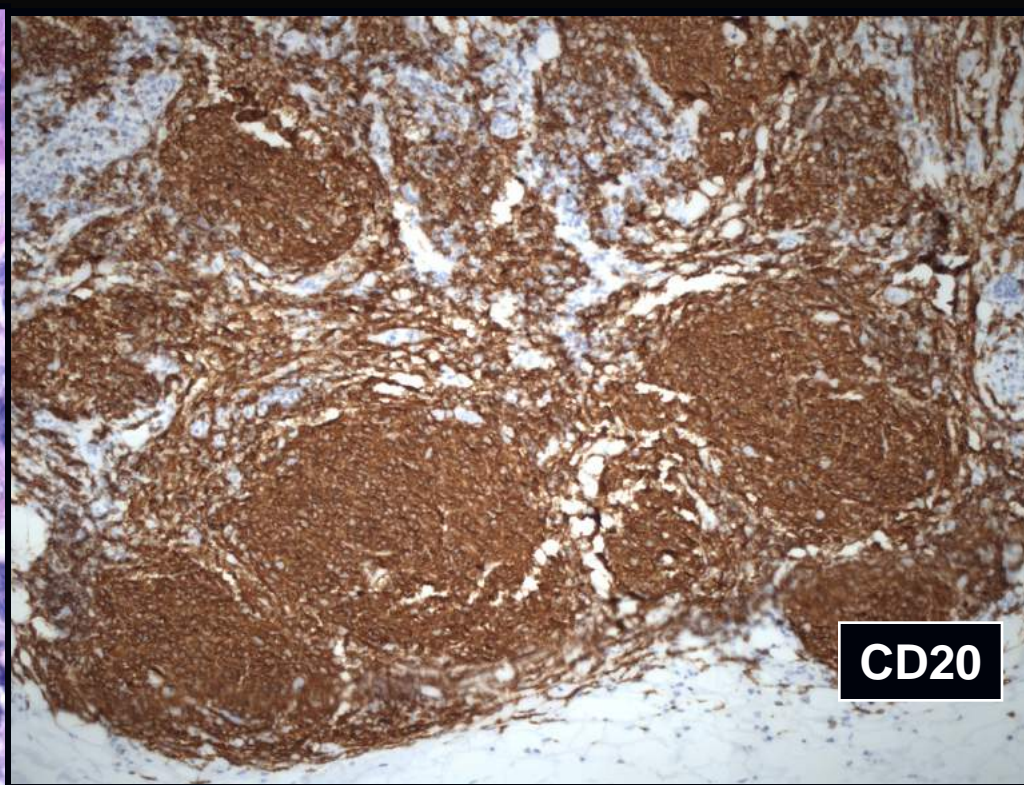
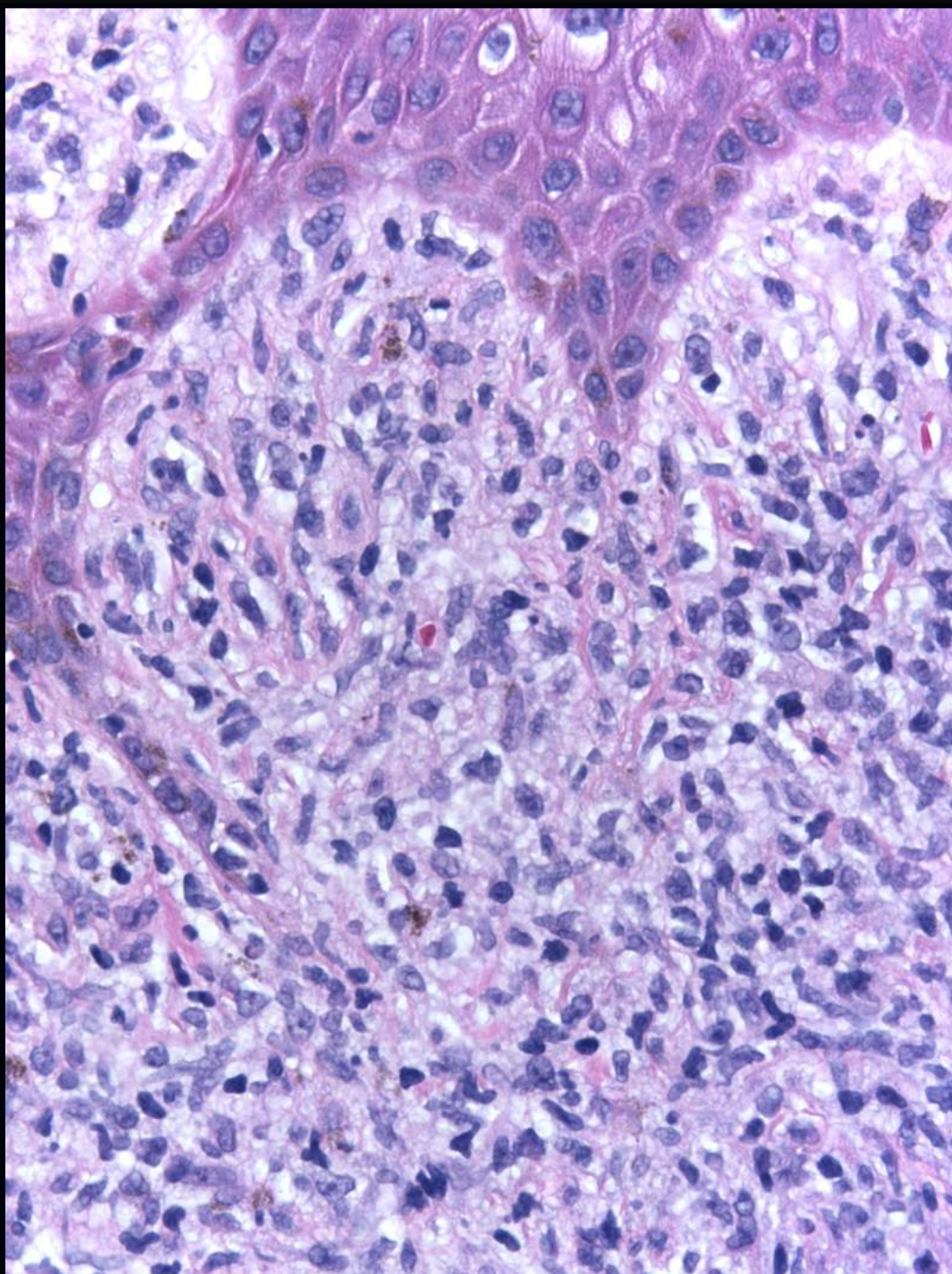
**Follicular lymphoma, grade 1 of 3**

# Primary Cutaneous Follicle Center Lymphoma

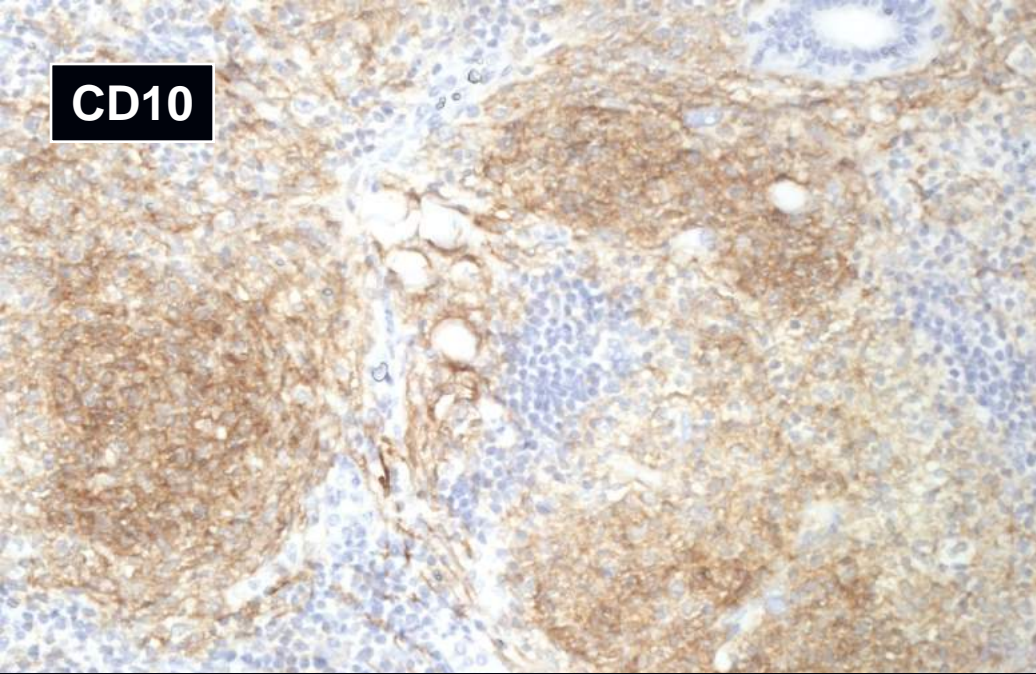
- Middle-aged adults
- Red or violaceous plaques, nodules, tumors on head, neck, trunk
- Composed of small and large centrocytes +/- centroblasts
- Pattern: follicular, follicular and diffuse or diffuse
- No need to grade!
- B cells: CD20+, bcl6+, CD10+/-, bcl2-/+
- Admixed T cells may be abundant
- Prognosis: excellent



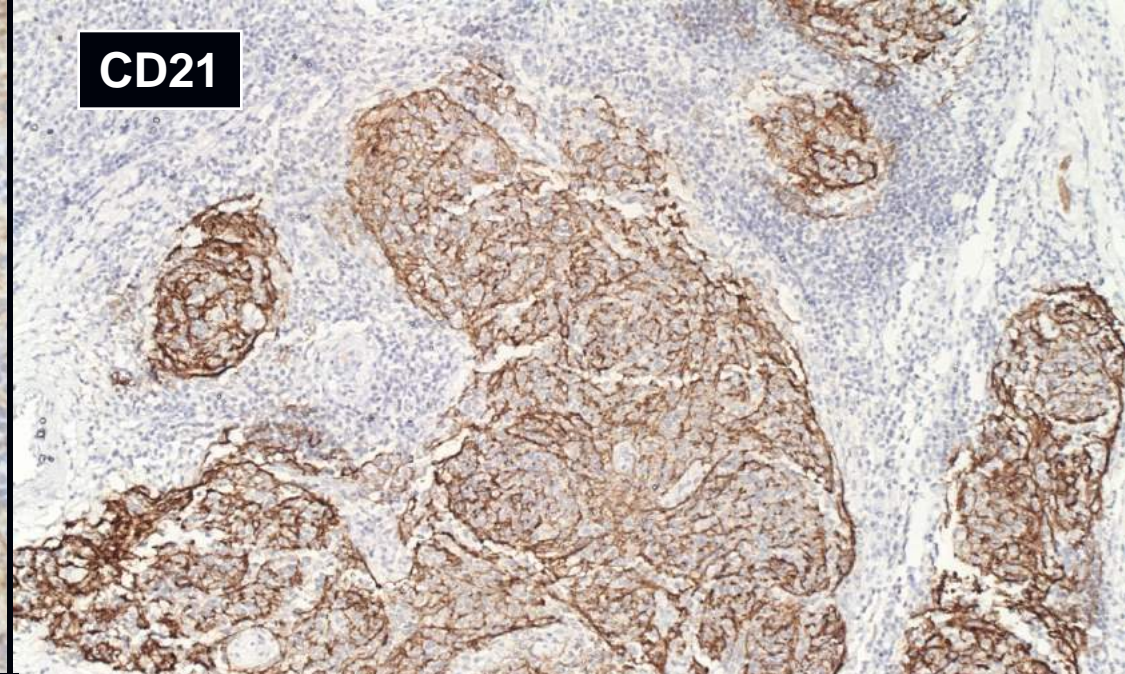




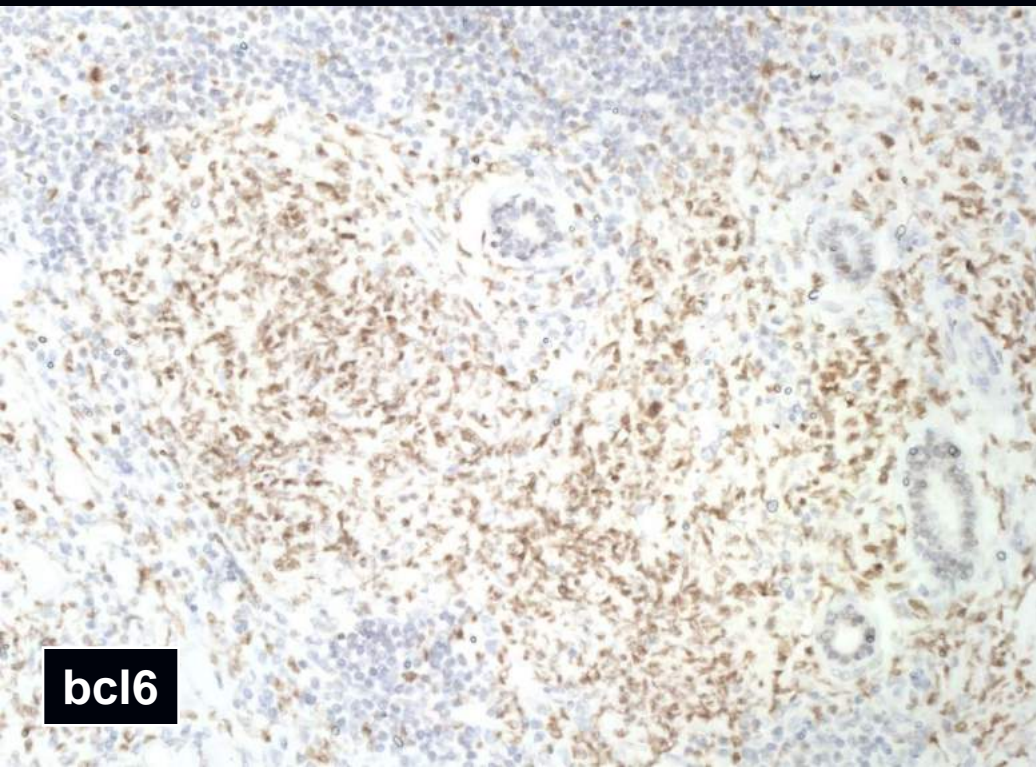
**CD10**



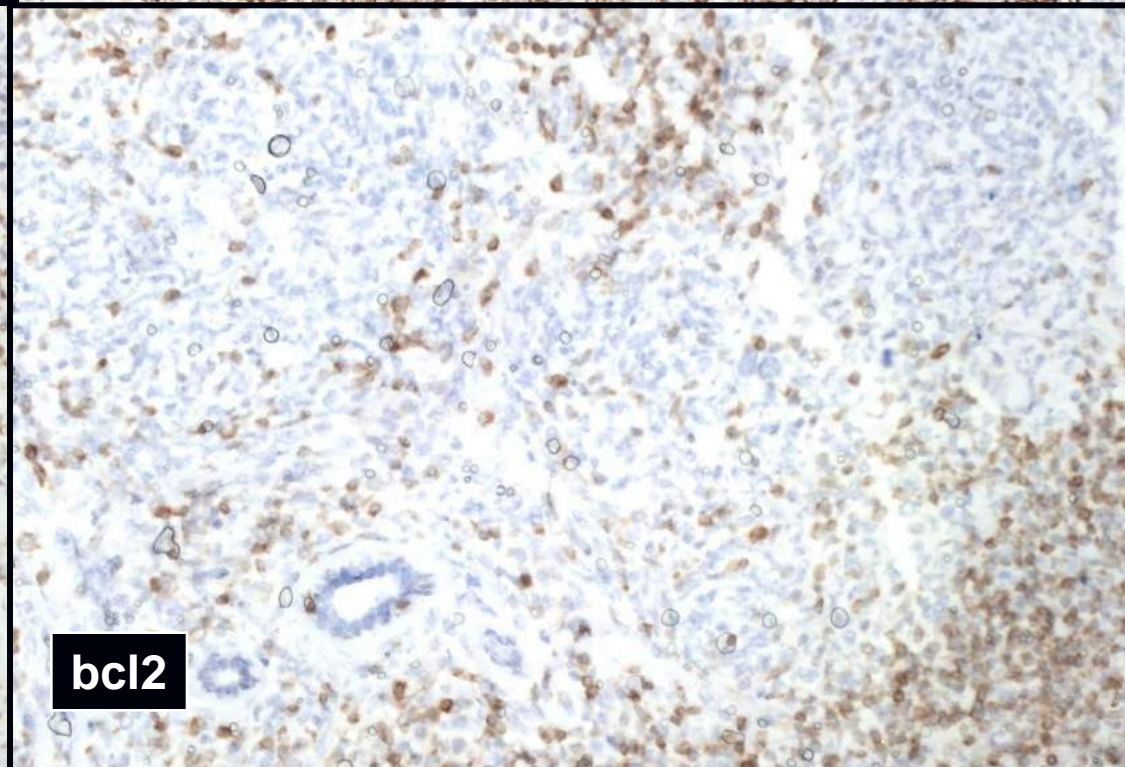
**CD21**



**bcl6**



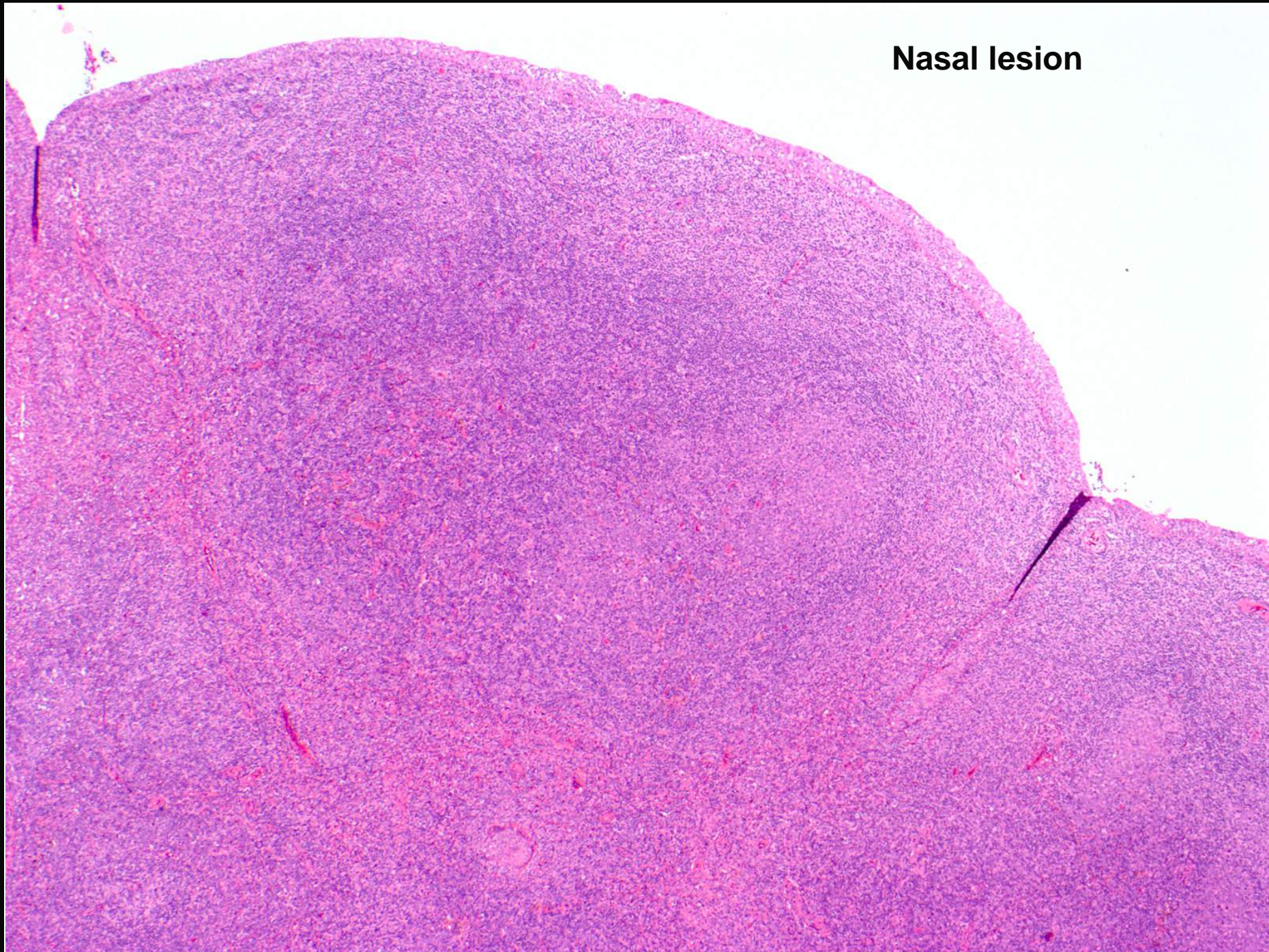
**bcl2**



# Follicular Lymphoma in Extranodal Sites

- Some extranodal follicular lymphomas resemble nodal follicular lymphomas
- Others are *bcl2* protein-negative, lack *BCL2* rearrangement, may have a different pathogenesis
- Primary extranodal *bcl2* negative follicular lymphomas may be a distinct entity with localized disease and a good prognosis
- Diagnosis may be difficult
  - If *bcl2*-negative
  - If no tissue sent for flow cytometry
- Differential dx with MALT lymphoma
  - With prominent reactive follicles

**Nasal lesion**





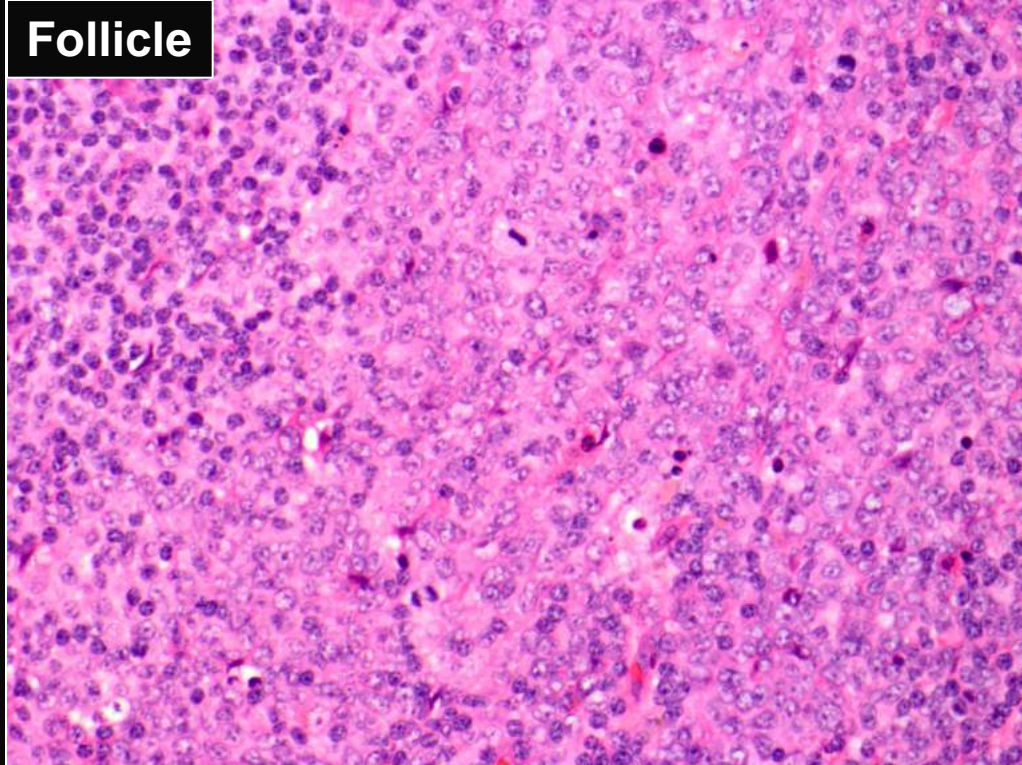


This histological image shows a dense population of small, dark-staining lymphocytes. A prominent feature is a lymphoepithelial lesion, where a cluster of these lymphocytes is seen infiltrating and surrounding an epithelial structure. The overall architecture is characteristic of a lymphoid organ, with various cellular components and structural elements visible throughout the field.

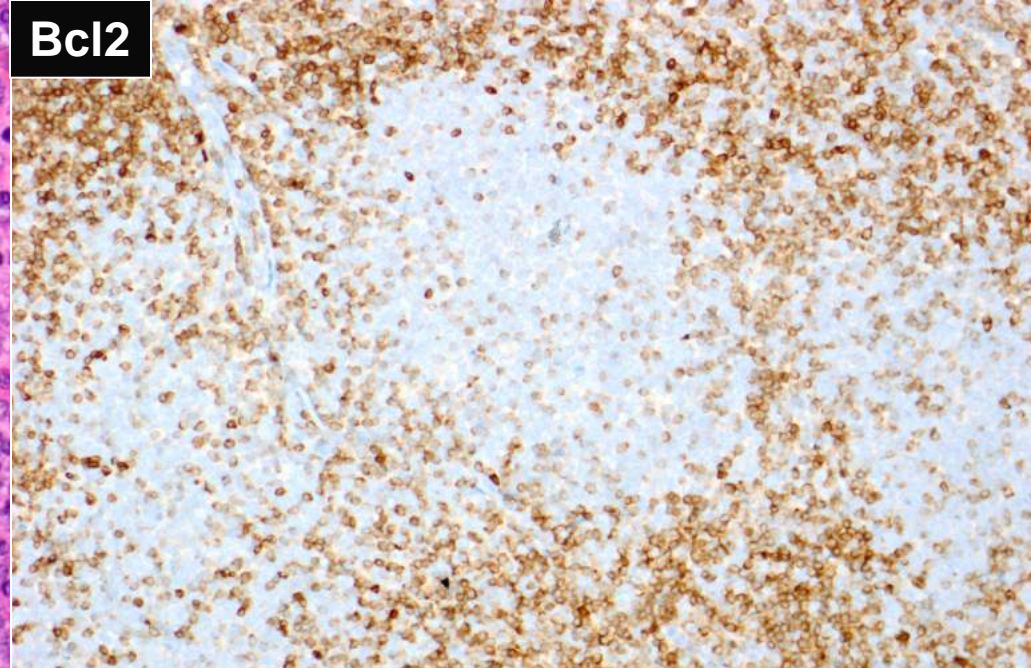
**Lymphoepithelial lesion**

**Follicle**

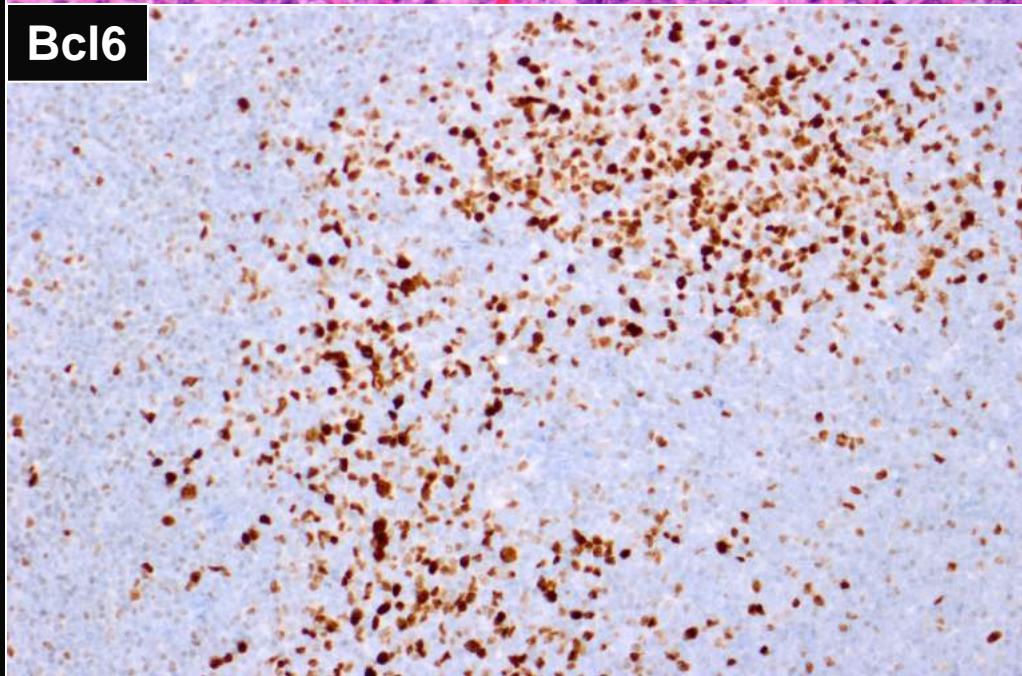
**Follicle**



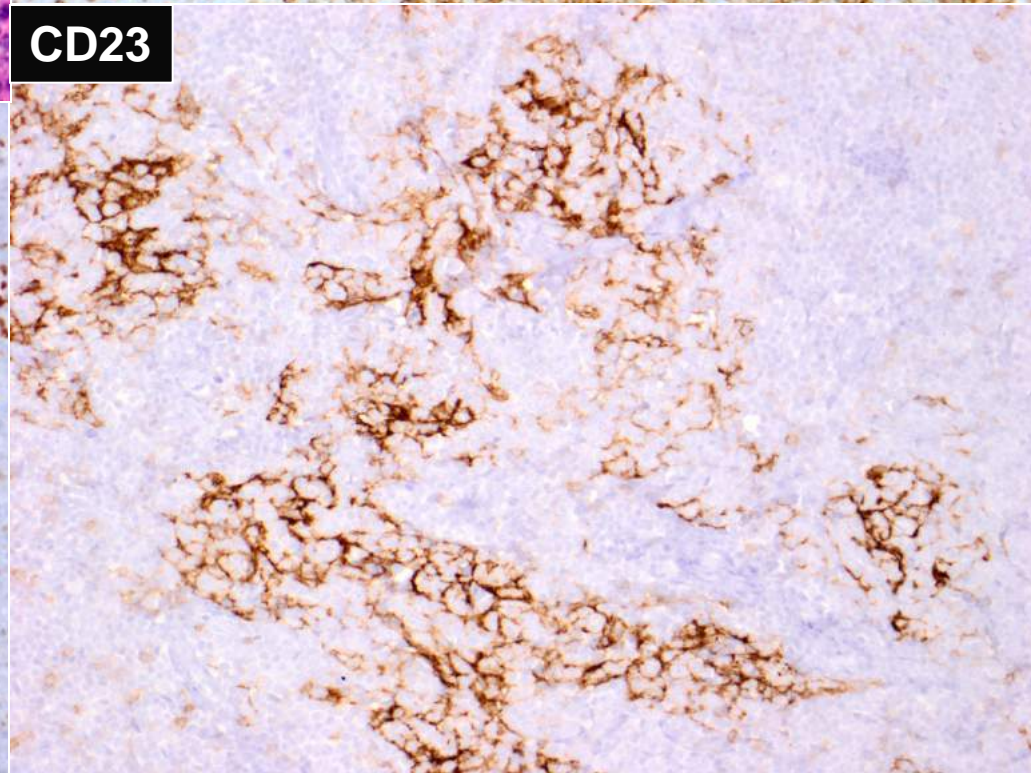
**Bcl2**

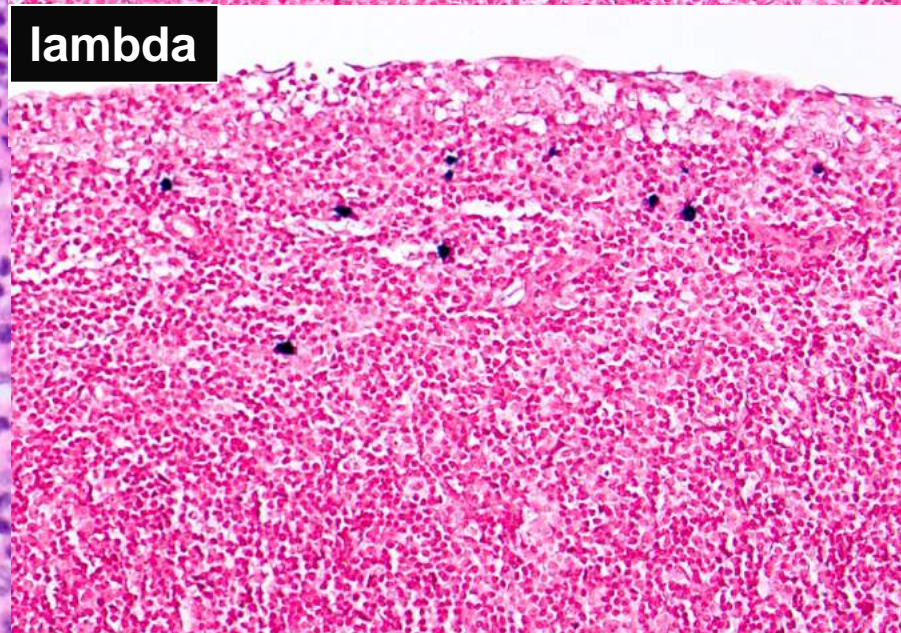
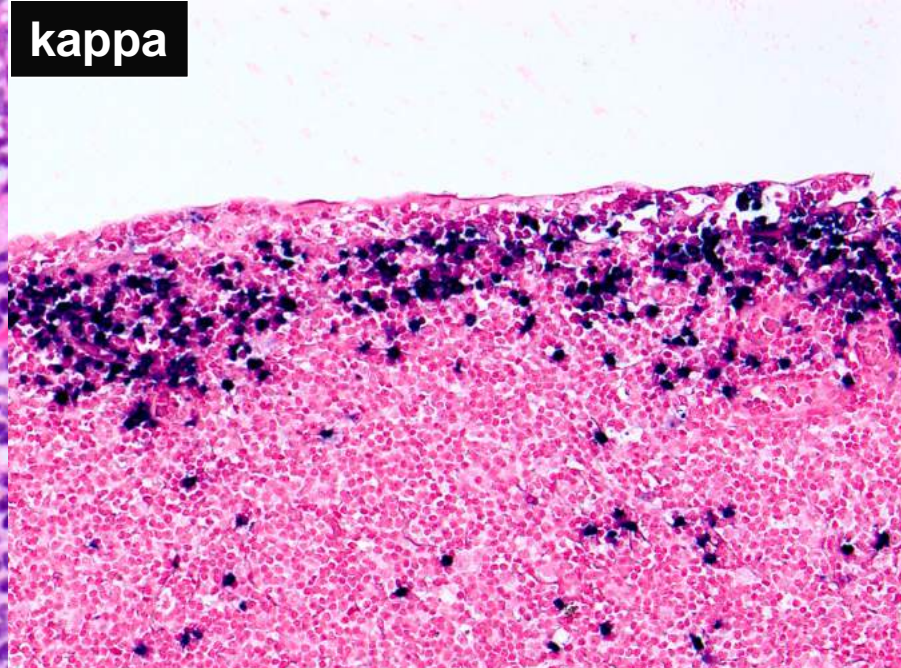
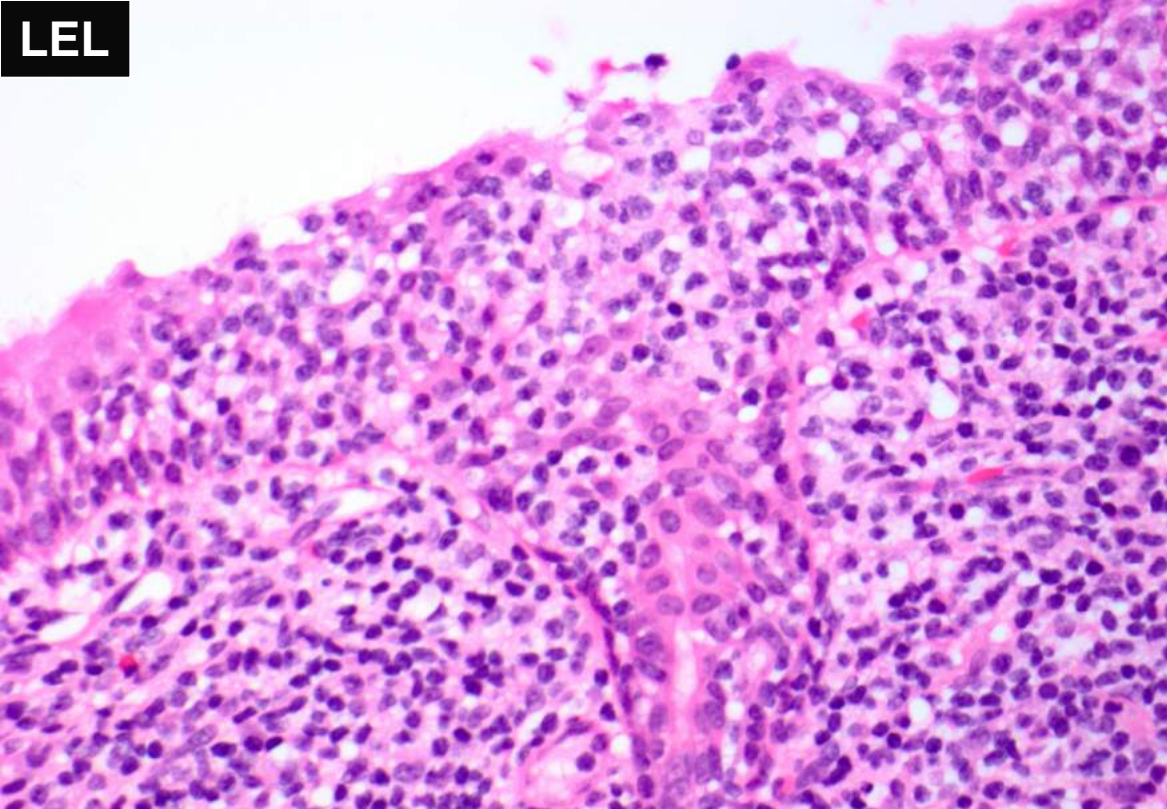


**Bcl6**



**CD23**





**Diagnosis: MALT lymphoma  
(with plasmacytic differentiation)**

# **IgG4**

**Least abundant IgG subclass**

**< 5% of total serum IgG**

**Amino acid differences in second constant domain: weak binding to C1q and Fcγ receptor**

**Weak/no activation of classical complement**

**Limited role in immune activation**

**Disulfide bonds between heavy chains: weak, unstable**

**Subset of IgG4 molecules are:**

**Bispecific/functionally monovalent antibodies**

**Unable to crosslink antigens**

**Unable to form immune complexes**

**IgG4 molecules may have RF-like activity in certain settings**

# **Lymphoma in Setting of IgG4-Related Disease**

- **Adults, aged 48 – 90 years**
- **Nearly all > 55**
- **Mostly men (M:F ~ 3:1)**
- **IgG4-related disease:**
  - **Orbital by far most common**
  - **Pancreatitis**
  - **Sclerosing cholangitis**
  - **Sialadenitis**
  - **Sclerosing inflammation of soft tissue**
  - **Lymphadenopathy concurrent with extranodal IgG4-related disease**

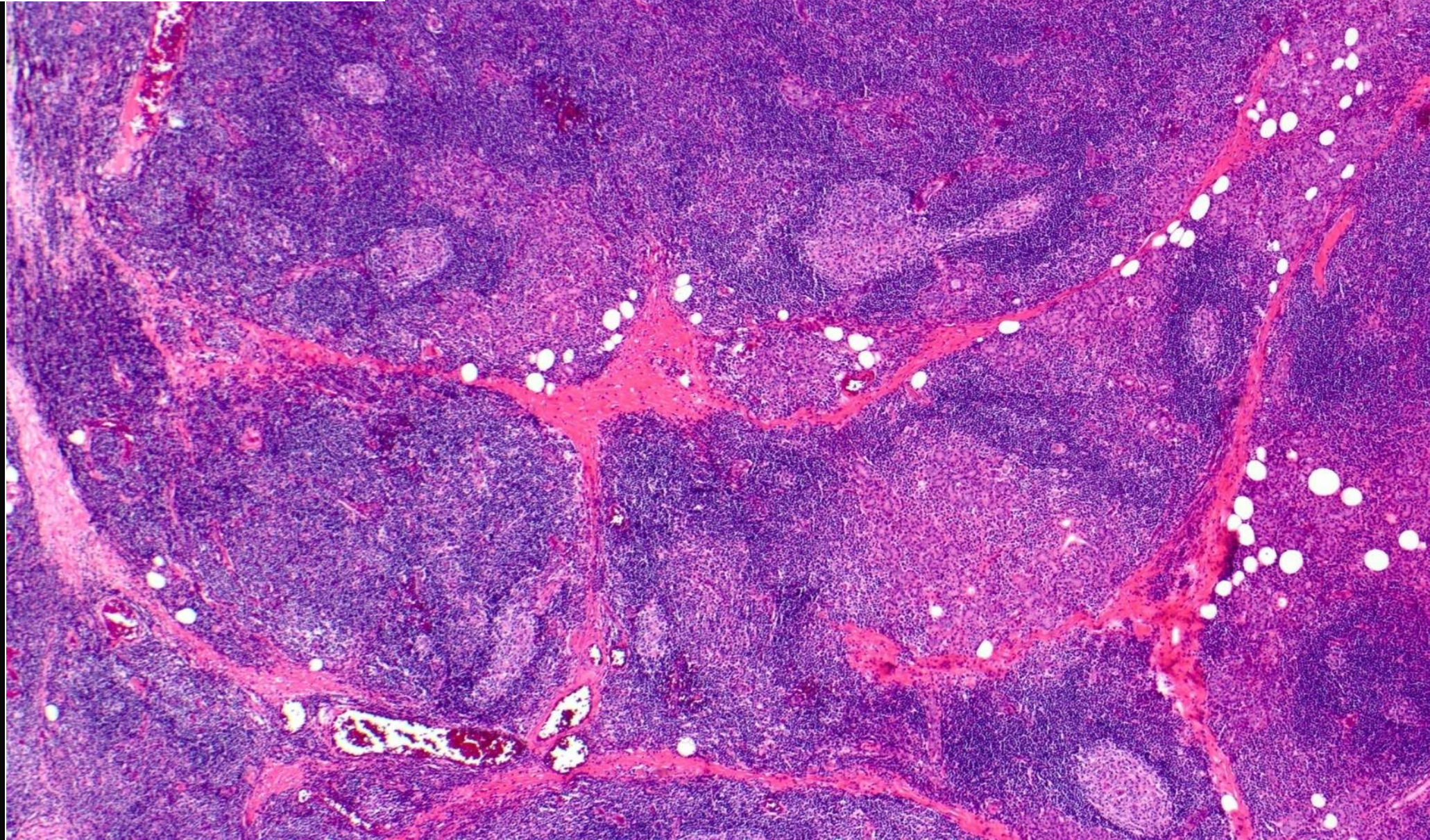
# **Lymphoma in Setting of IgG4RD**

- **Lymphomas:**
  - **Almost always extranodal (orbit most common)**
  - **Usually in a site involved by IgG4-RD**
- **MALT lymphoma most common by far**
- **Follicular lymphoma**
- **Diffuse large B-cell lymphoma**
- **Peripheral T-cell lymphoma**
- **CLL**

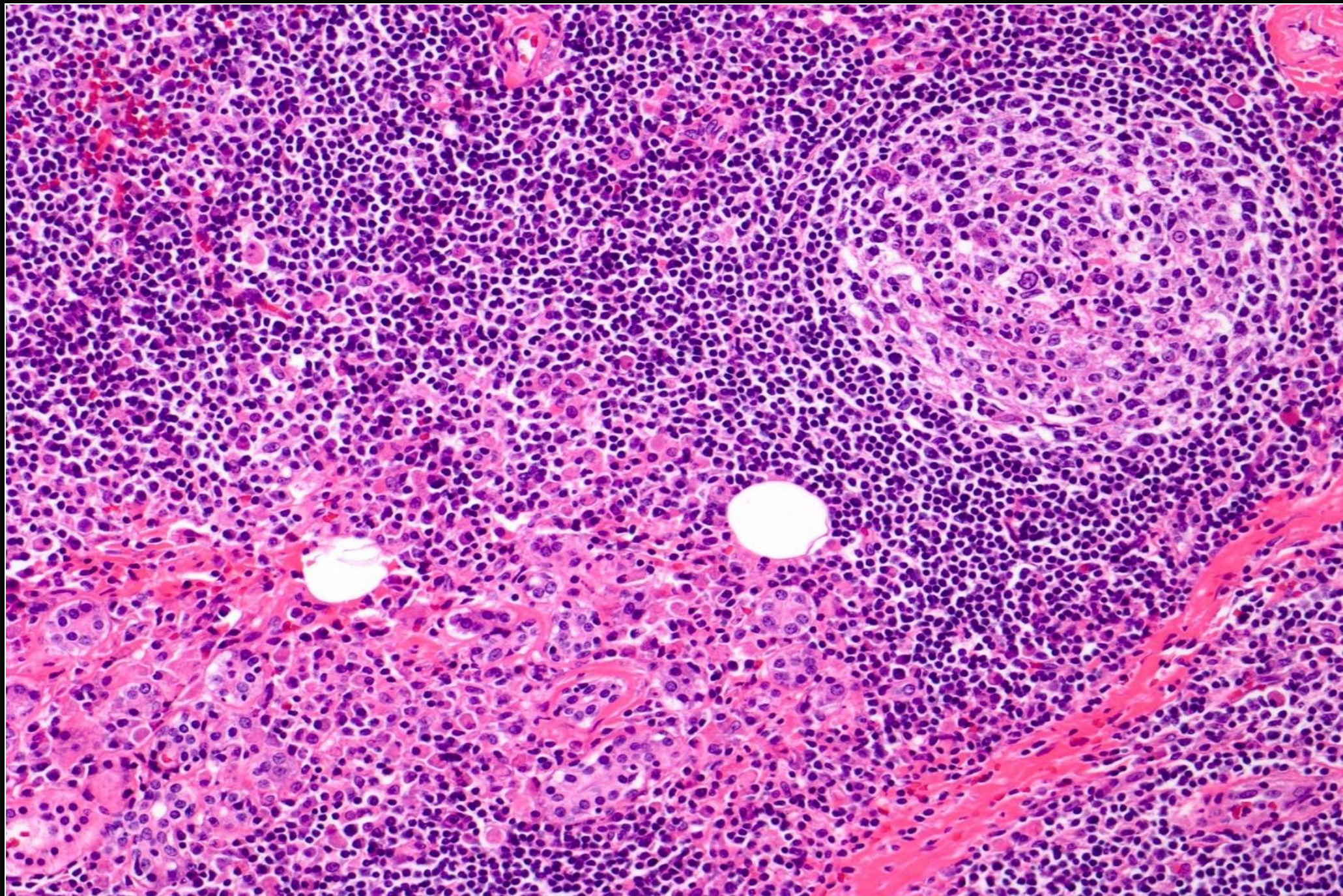
# **Lymphoma in Setting of IgG4RD**

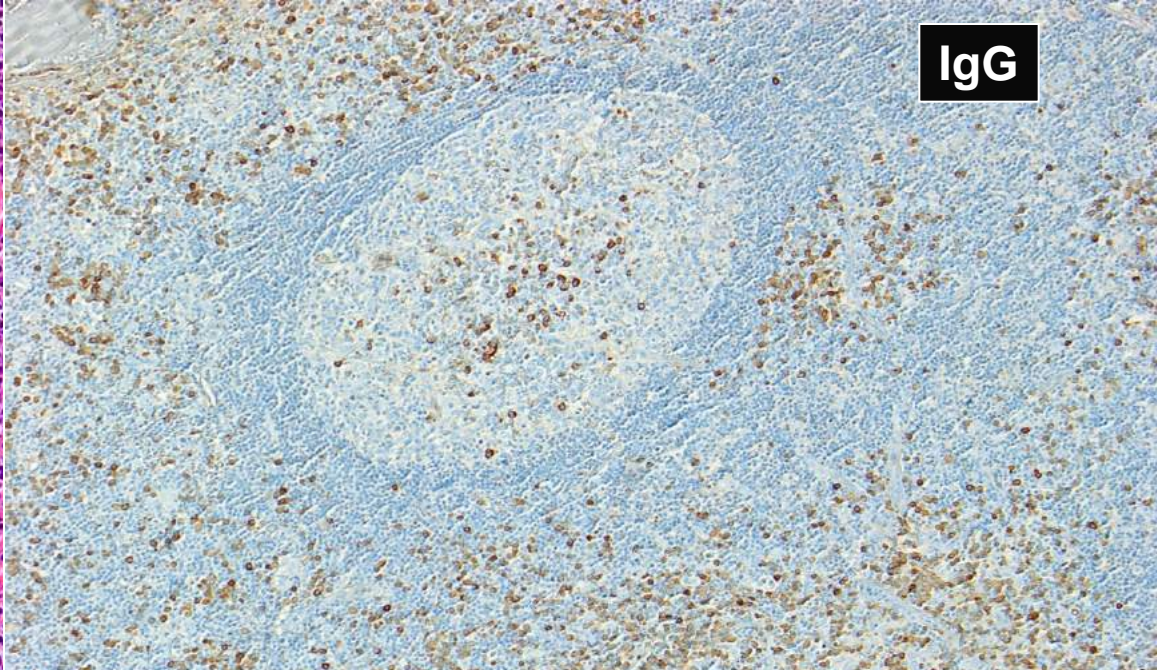
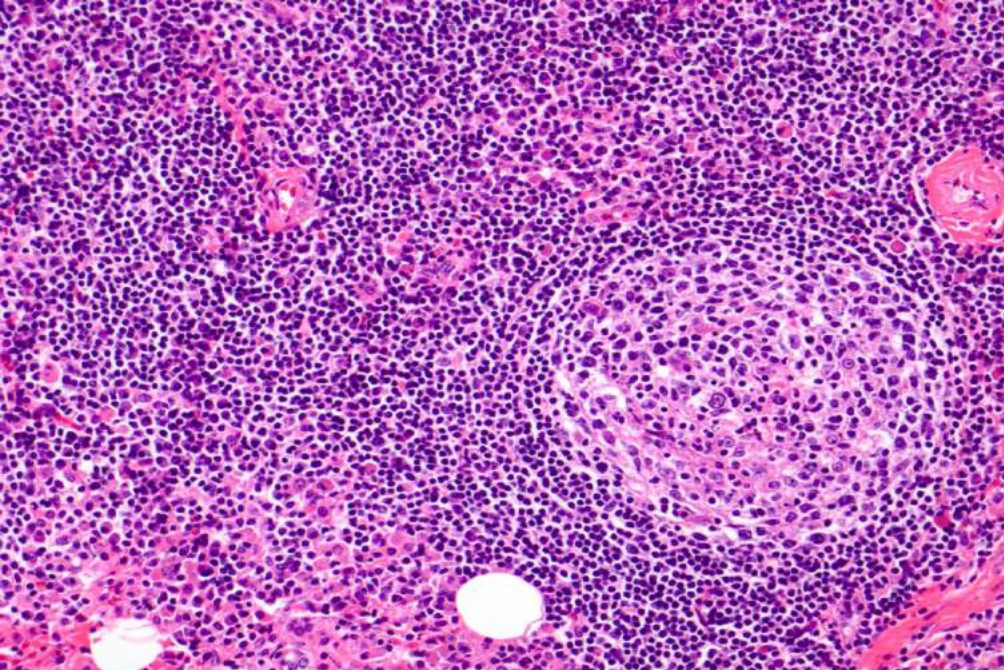
- **Several patients have had 2 lymphomas**
- **Synchronous or metachronous**
- **2 patients: each with 2 MALT lymphomas, clonally unrelated by PCR**
- **1 patient: MALT lymphoma in one site, Hodgkin's lymphoma in another**

**Submandibular gland:  
IgG4-related sialadenitis  
(Kuttner tumor)**

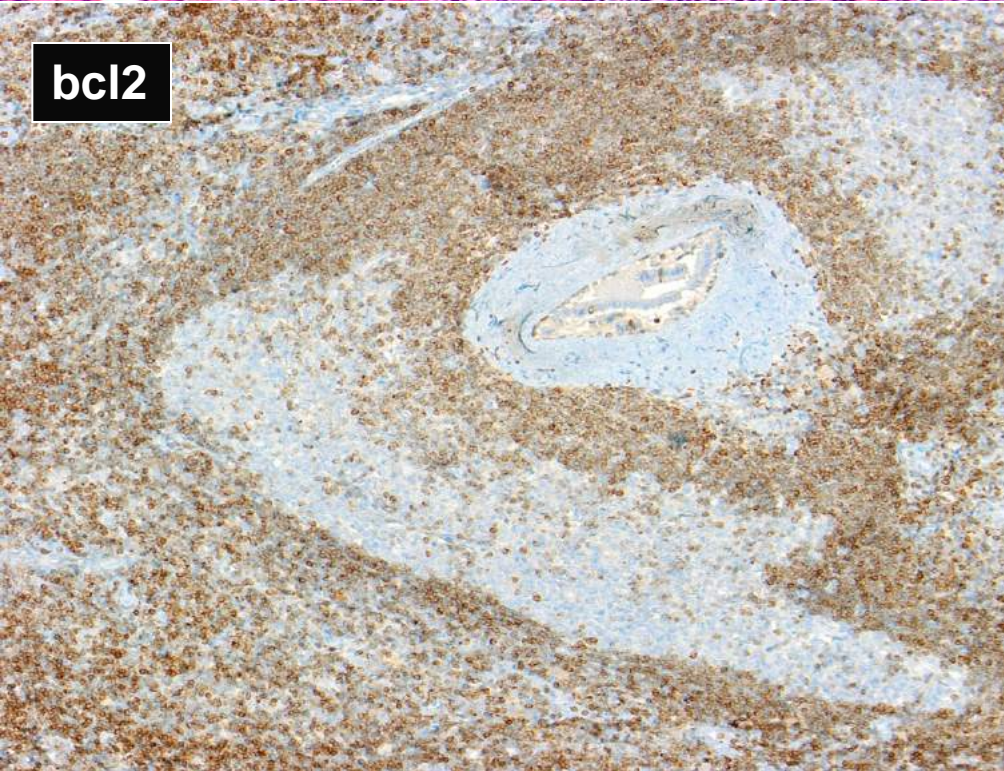




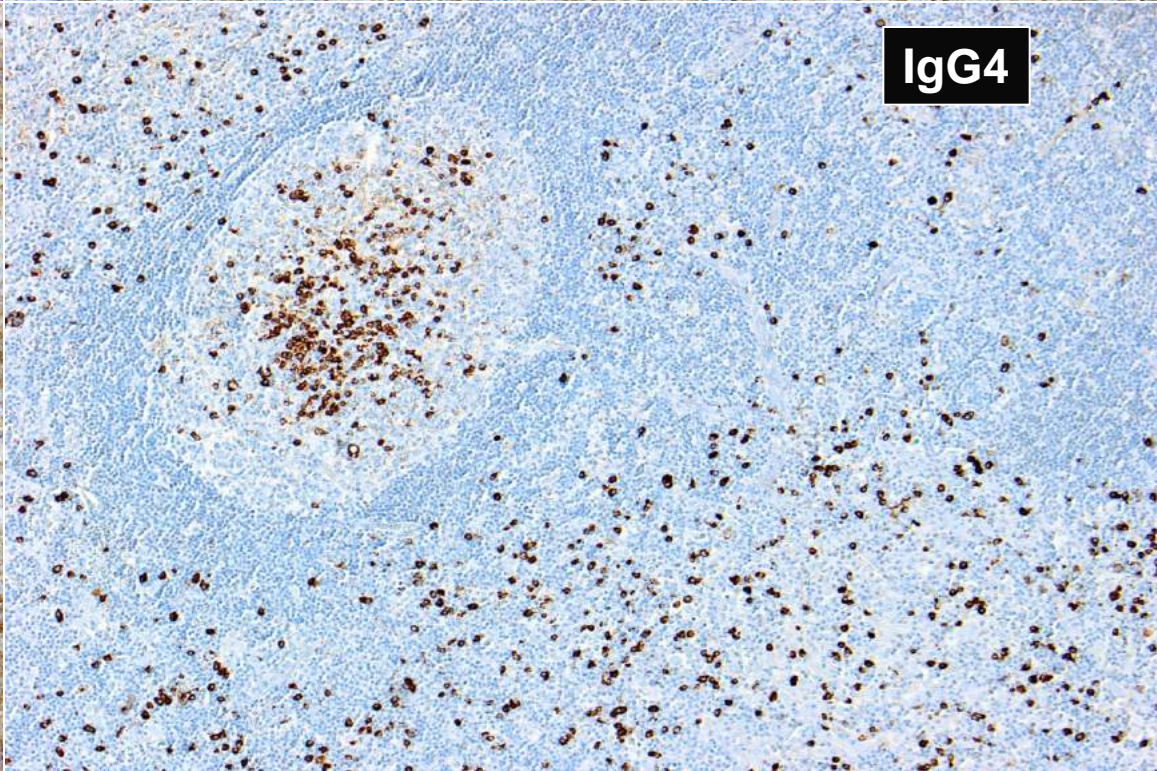




**IgG**

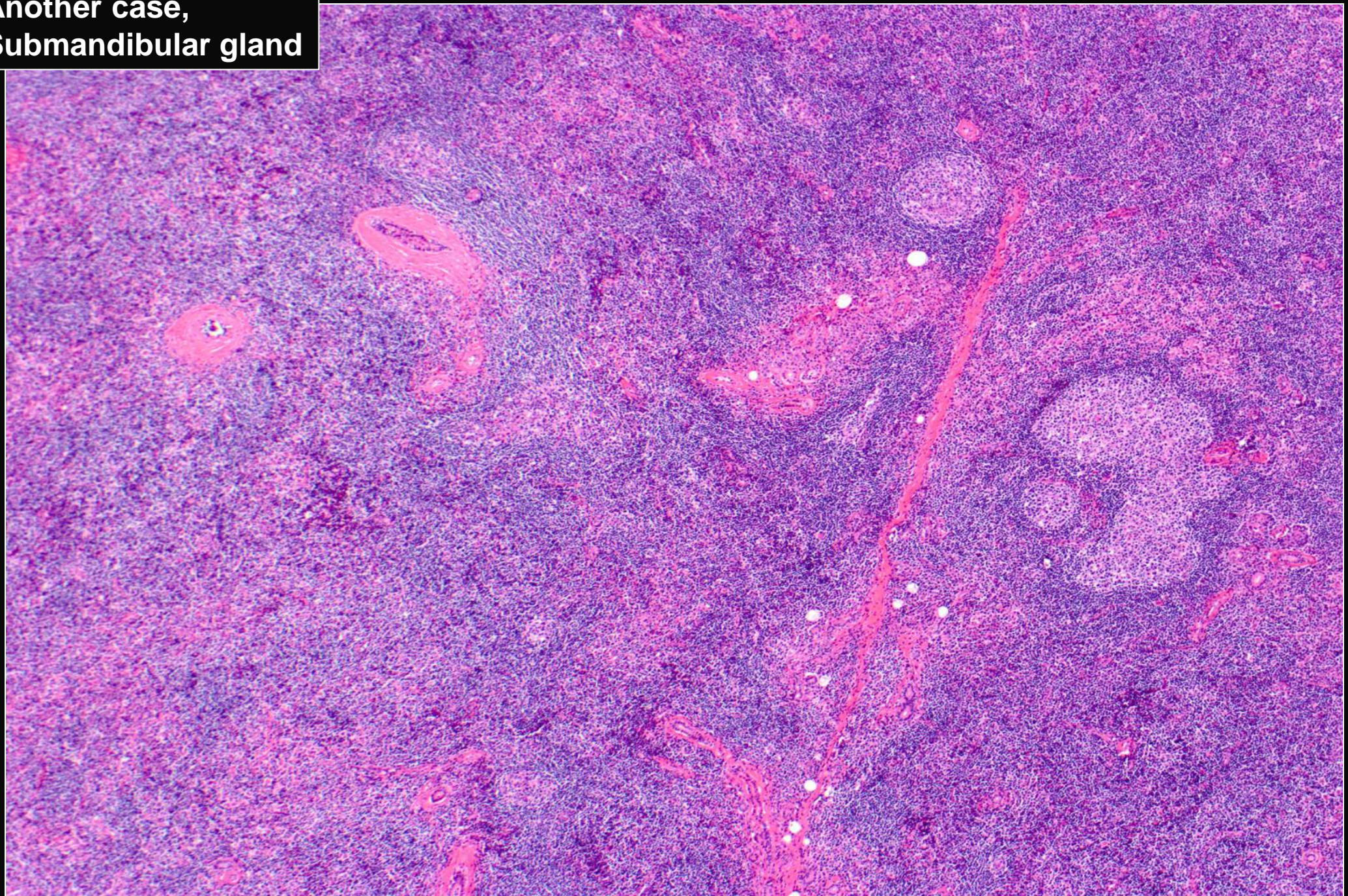


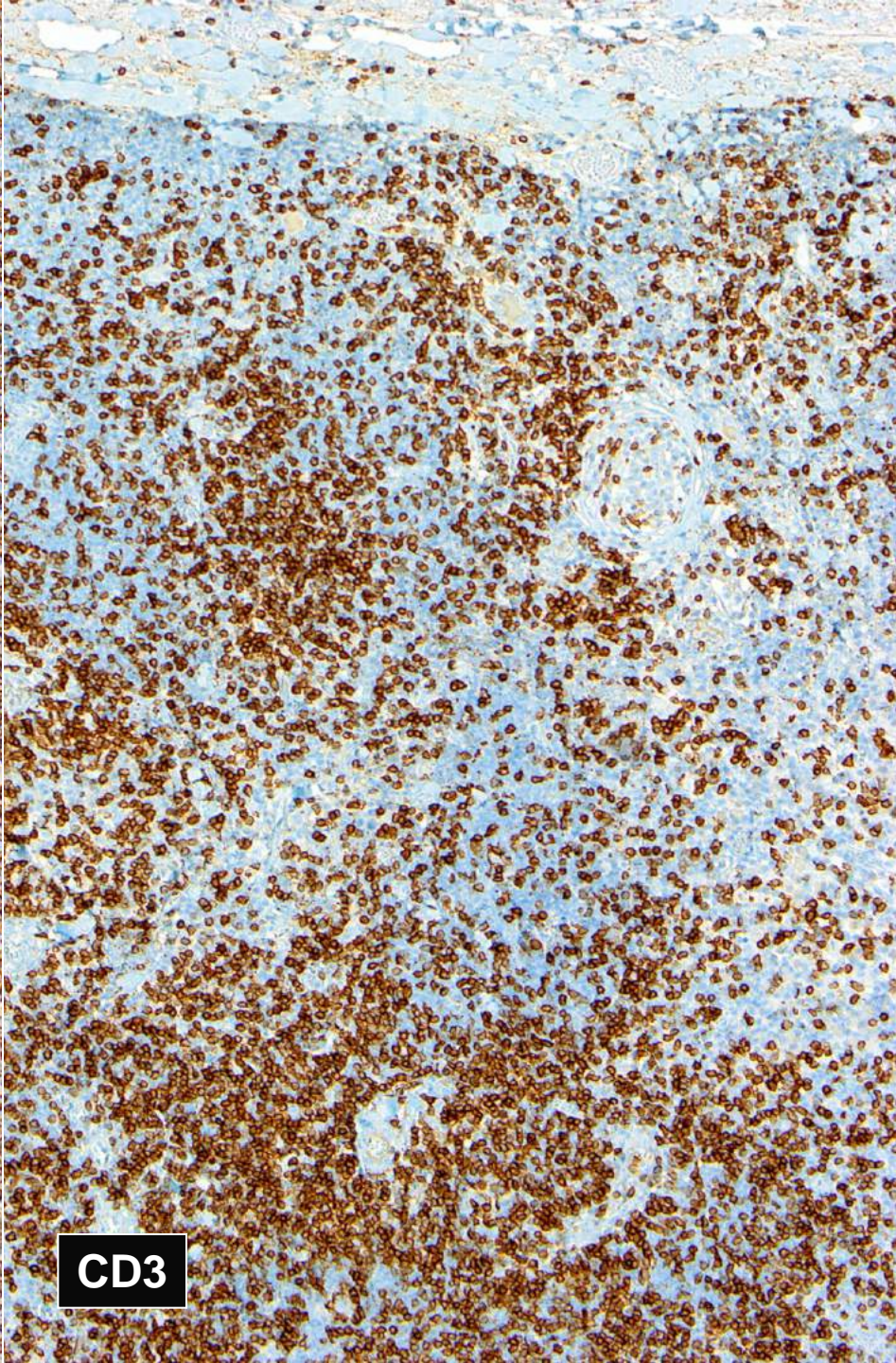
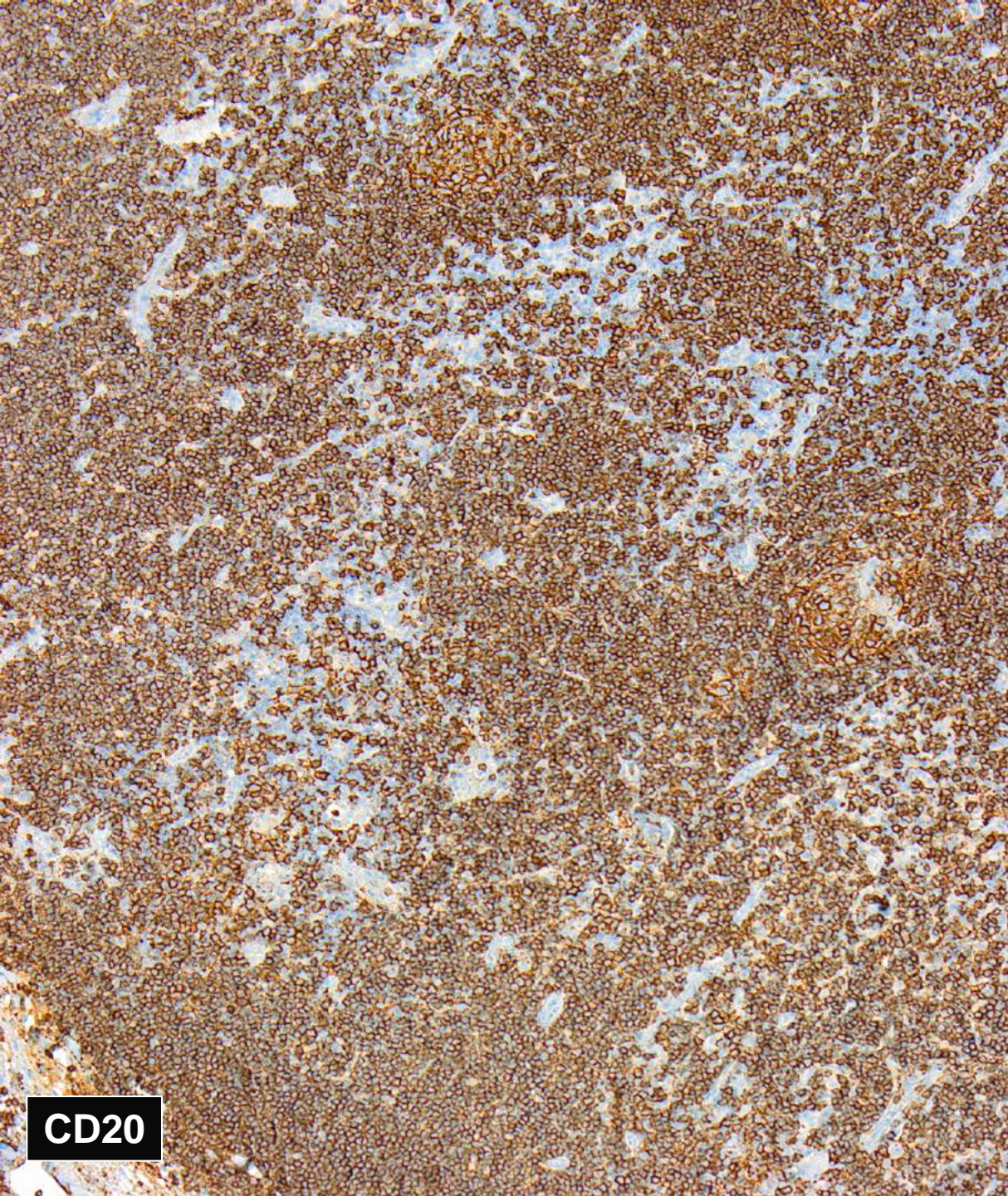
**bcl2**



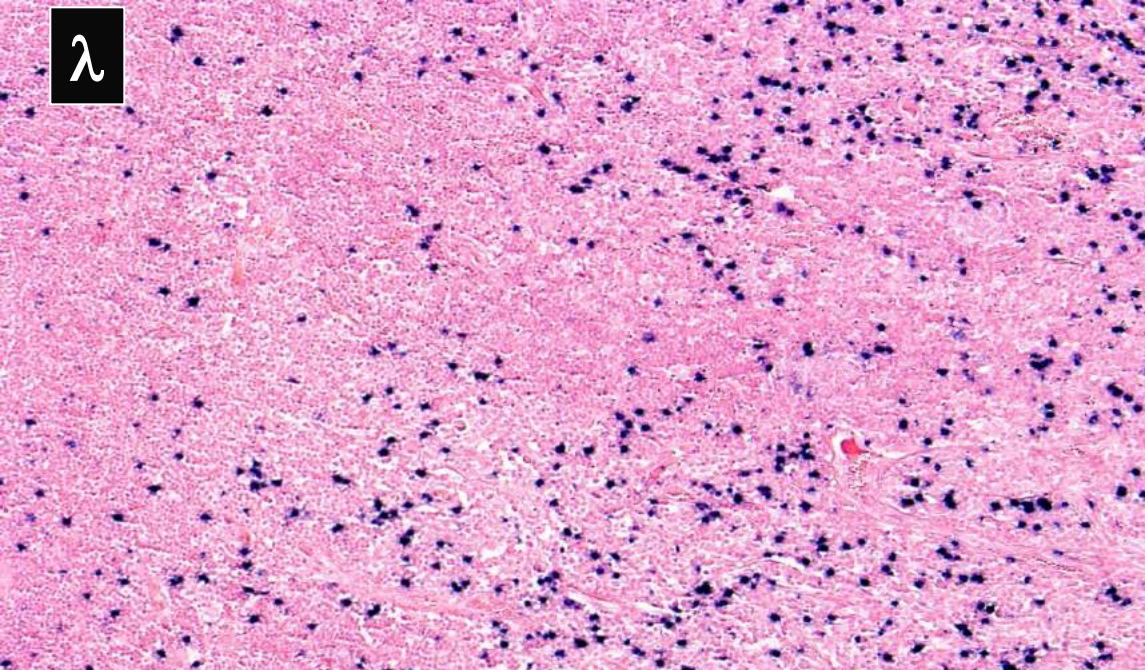
**IgG4**

Another case,  
Submandibular gland

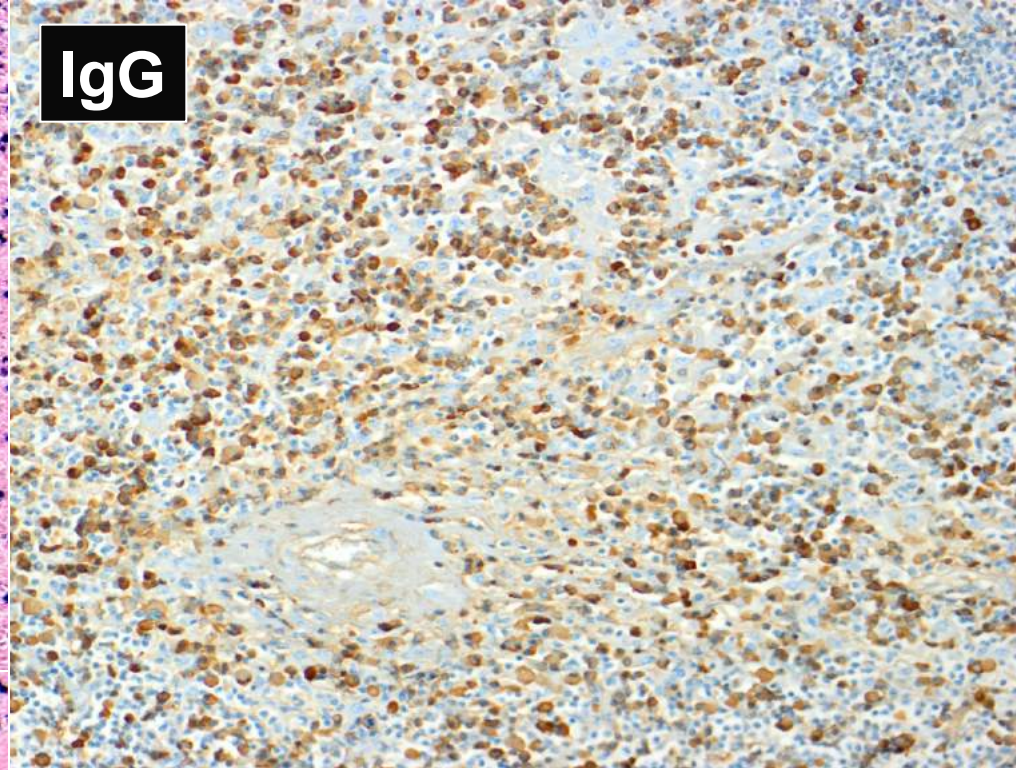




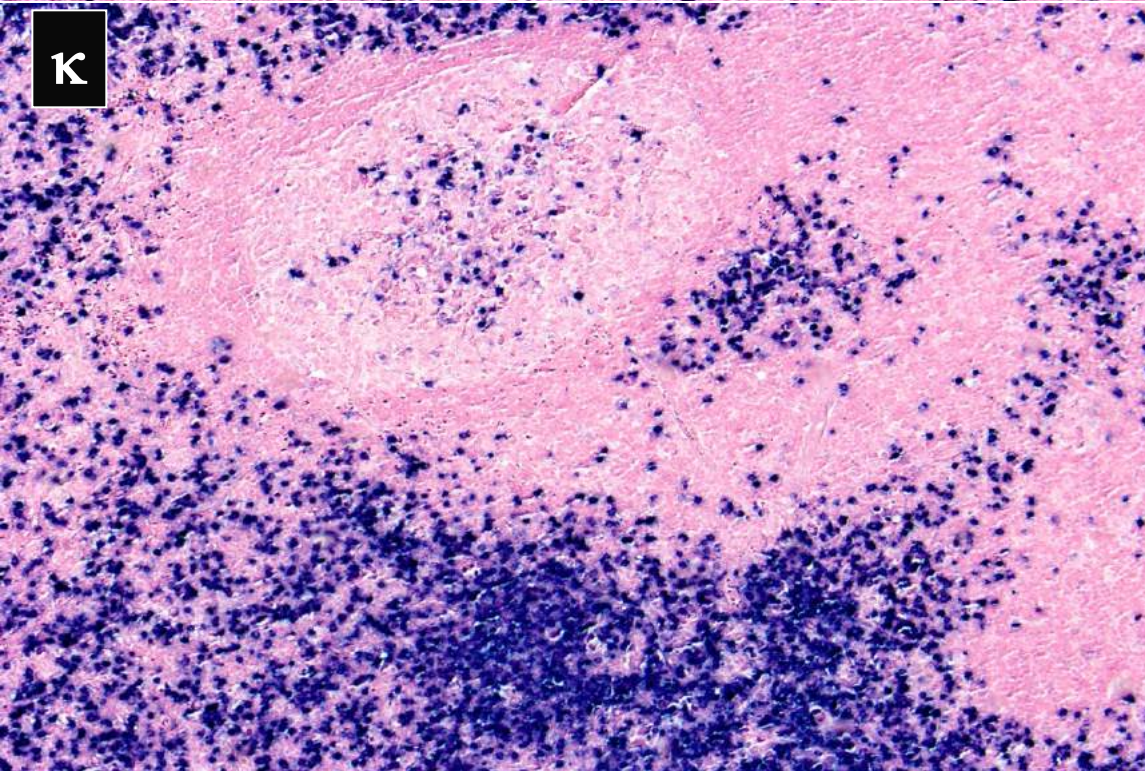
$\lambda$



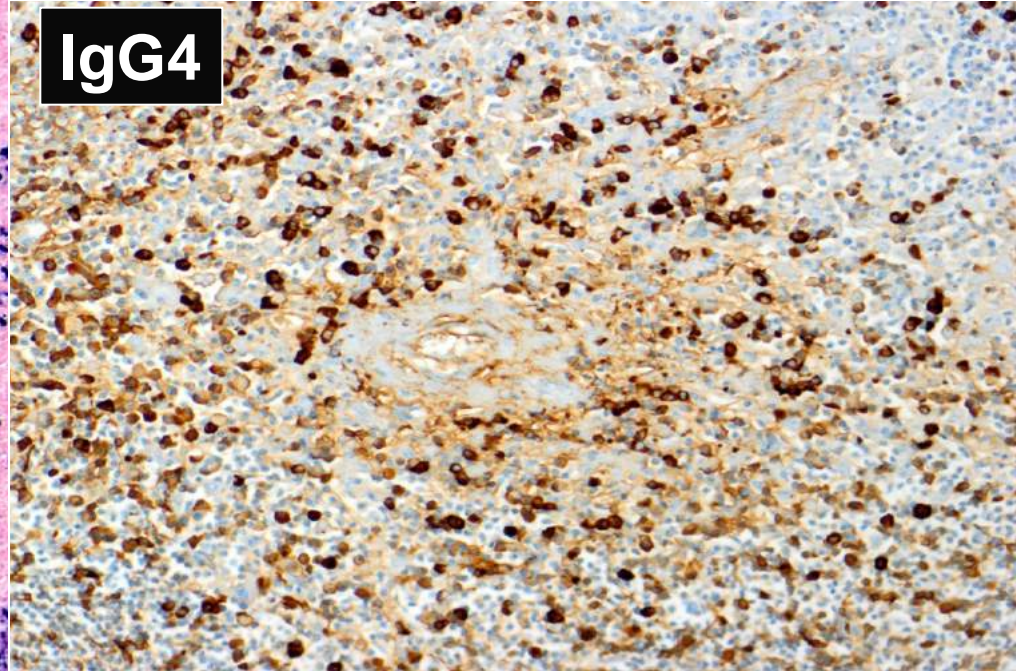
IgG



$\kappa$



IgG4



## **Diagnosis:**

- **MALT lymphoma (with marked plasmacytic differentiation) arising in association with IgG4-related chronic sclerosing sialadenitis**

## **Recommendation:**

- **Sclerosis and plasma cells:**
  - **Consider IgG/IgG4 stains**
  - **Examine lymphoid tissue for evidence of lymphoma**
  - **Stain for  $\kappa$  and  $\lambda$  if plasma cells are abundant**

# **Lymphoma in Setting of IgG4RD**

- **Magnitude of risk**
  - **Several series show ~ 10% of IgG4-RD complicated by lymphoma, or clonal IGH@**
- **More than one lymphoma per patient?!**
- **Is IgG4-RD a major factor in development of lymphoma?**



# **Lymphoma in Setting of IgG4RD**

## **Questions:**

- **Almost all cases have been from Far East; are Western patients different?**
- **Large series of Western ocular adnexal lymphomas show predominance of MALT lymphoma, but mostly IgM+, and lacking sclerosis: are IgG4-RD-associated lymphomas being missed?**
- **Is orbit the most common site with concurrent IgG4-RD and lymphoma because it is superficial and both components more likely to be sampled?**

# **IgG4+ Lymphomas**

- **A small number of lymphomas with marked plasmacytic differentiation are IgG4+, without associated IgG4-RD**
- **Almost all: MALT lymphomas**
- **Site-restricted**
  - **Cranial dura**
  - **Skin**
  - **Orbit**

# Dural IgG4+ Lymphomas

- **Dural lymphomas**
  - MALT lymphoma is most common dural lymphoma, mainly occurring in women
  - Of 18 cases of dural MALT lymphoma, 6 were IgG4+, 5 of 6 in women, 5 of 6 younger than 55 years of age
  - IgG4+ dural MALT lymphomas have clinical and pathological features like those of other dural MALT lymphomas but IgG4+ cases are unexpectedly common
  - Their clinical features differ from those of patients with IgG4-RD (age, gender)

## Reference:

Venkataraman G, Rizzo KA, Chavez JJ, et al. Marginal zone lymphomas involving meningeal dura: possible link to IgG4-related diseases. *Mod Pathol* 2011;24:355-66.

# Cutaneous IgG4+ Lymphomas

- **Cutaneous MALT lymphomas are mostly Ig class-switched (IgG+ >> IgM+) in contrast to MALT lymphomas in most other sites**
- **Study of MALT lymphomas with plasmacytic differentiation in many different anatomic sites**
  - 1 of 120 non-cutaneous cases was IgG4+ (ocular adnexal)
  - 19 of 49 (39%) primary cutaneous MALT lymphomas were IgG4+
  - In skin, IgG4+ cases had features similar to those not expressing IgG4
  - Patients with IgG4+ lymphomas were not known to have IgG4-RD
- **What is the role of IgG4 in lymphomagenesis in these disparate sites?**

## References

Edinger JT, Kant JA, Swerdlow SH. Cutaneous marginal zone lymphomas have distinctive features and include 2 subsets. *Am J Surg Pathol* 2010;34:1830-41.

Brenner I, Roth S, Puppe B, Wobser M, Rosenwald A, Geissinger E. Primary cutaneous marginal zone lymphomas with plasmacytic differentiation show frequent IgG4 expression. *Mod Pathol* 2013

