# Gastrointestinal Lymphomas

## EATL, MALT, and beyond

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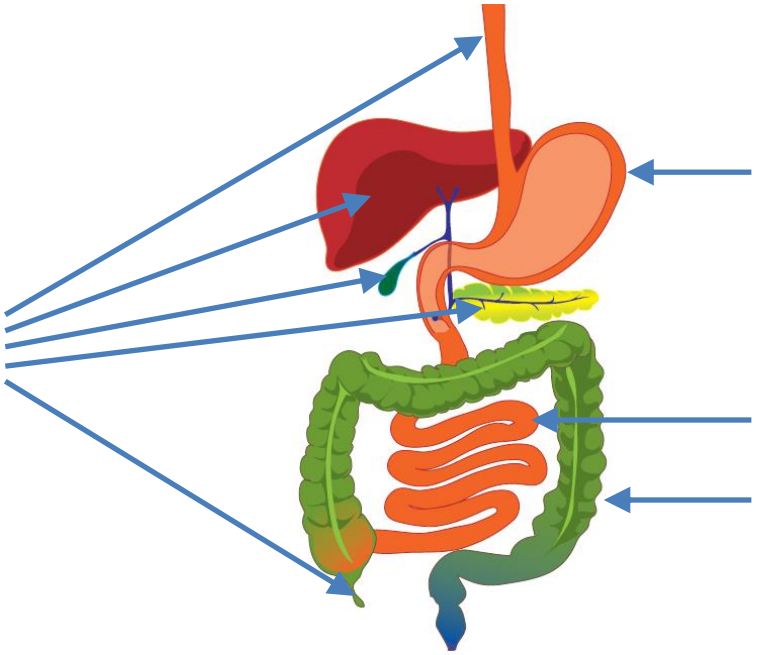
# Lymphoma in GI tract

- Uncommon compared to GI epithelial neoplasms
- 20% of all lymphomas occur in the GI tract
- B-cell lymphomas are far more common than T-cell lymphomas
- Most common lymphoma in GI tract is diffuse large B-cell lymphoma

# GI Lymphoma Distribution



**RARE**

55-65%; 5-10% of all gastric malignancies

20-35%; 25% of all small intestinal malignancies

7-20%; 0.5% of colonic malignancies

# Classic Sites of GI Lymphomas

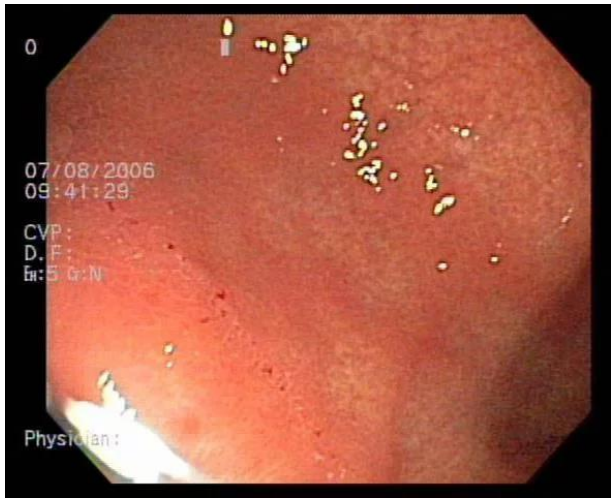
| Site | Lymphoma |
|---|---|
| Stomach | MALT Lymphoma |
| 2nd portion of duodenum | Primary intestinal follicular lymphoma |
| Small intestine | EATL |
| Terminal ileum | Burkitt lymphoma |
| Colonic polyps | Mantle cell lymphoma (lymphomatous polyposis) |

# How to approach lymphoid processes?

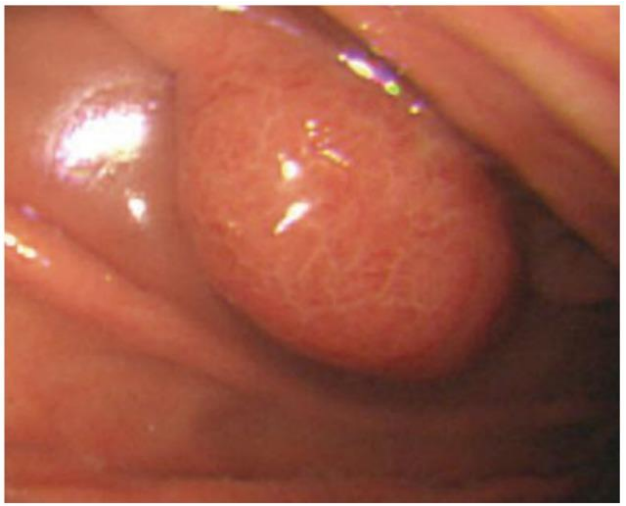
- "SurgPath" / GI view
  - What disease could this be:
    - Inflammatory conditions
    - Lymphoma
    - Another malignancy (epithelial, myeloid, mesenchymal)
    - Normal ??
  - Immunostains
    - Some "CDs", other immunos (Keratins, etc.)
- "Hemepath" view
  - Morphology – lymphoid collections are fun!
  - Immunostains (lots more of "CDs")
  - Molecular studies ??
  - Conclusions: Lymphoma / Reactive / Atypical
- Consult the other side at least once

# Thoughts to consider

- Small amount of tissue (usually), but
- The endoscopist's description can provide important clues



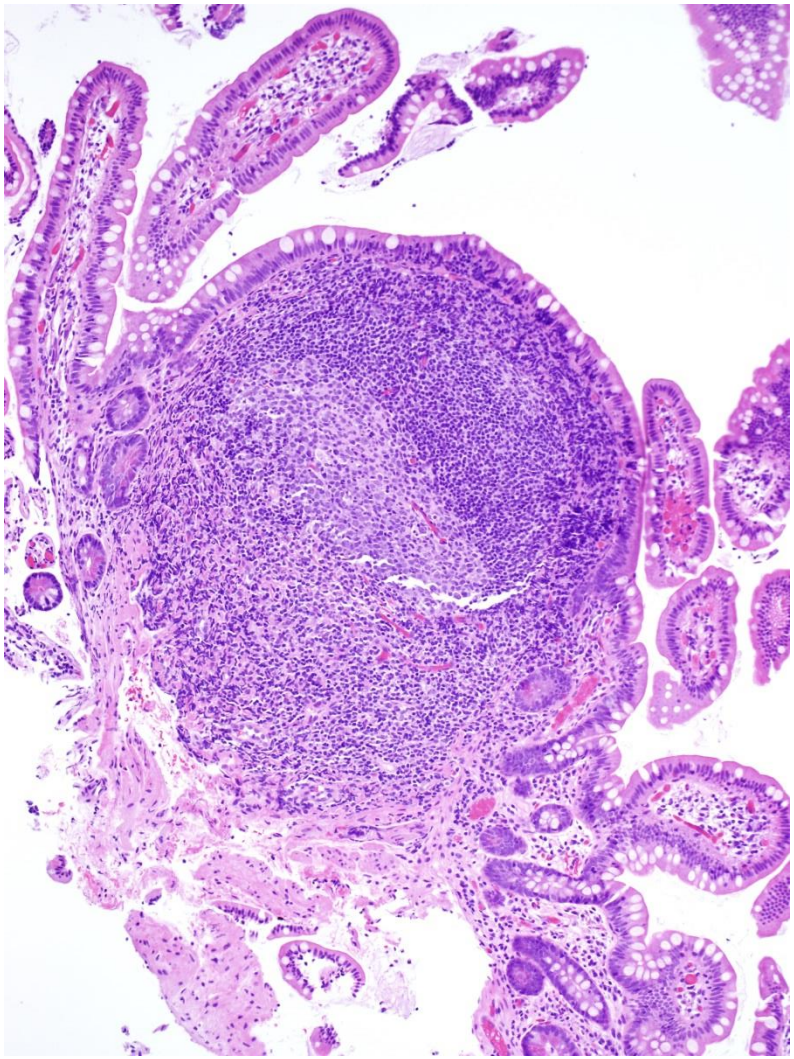

https://emedicine.medscape.com/article/175909-overview



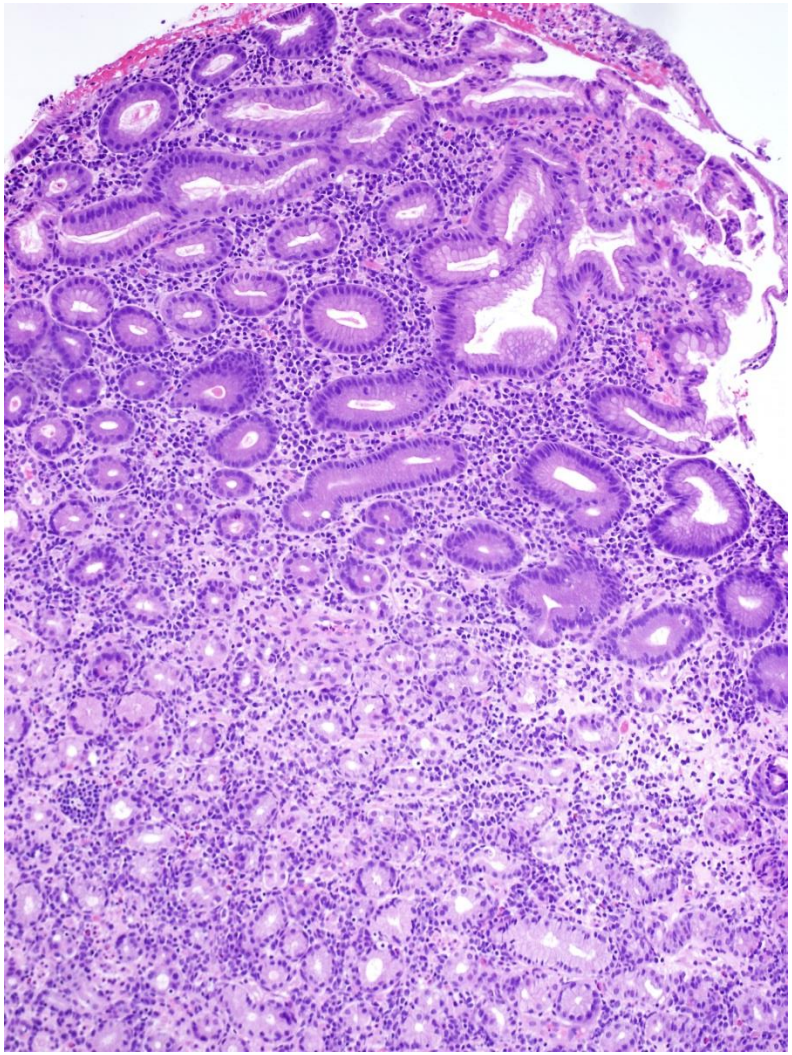
SY Min, et al. Clin Endosc. 2013;46(6):647-650.

- However, the GI tract has normal populations of lymphoid tissues and can have lots of inflammatory conditions – both can give rise/result in lymphoproliferative disorders *and* confound our diagnosis of them

# Native mucosa-associated lymphoid tissue (MALT) vs acquired MALT



Peyer's patch



*H. pylori* gastritis

# Tough Decisions

- Does a “label” of lymphoma lead to appropriate management?
- Toughest when the process is small and/or early
  - Is it really lymphoma?
    - Or inflammatory process?
    - Or normal MALT?
  - Endoscopic impression?
  - How can it be followed?
  - Should it be treated and how?

# Additional complexities:

- Balance between pragmatic approach and keen eye for subtle findings
- Unusual variants and mimics present conundrums and pitfalls
- 2016 Update to the WHO Classification of Tumors of Haematopoietic and Lymphoid Tissue

# Some Practical Examples

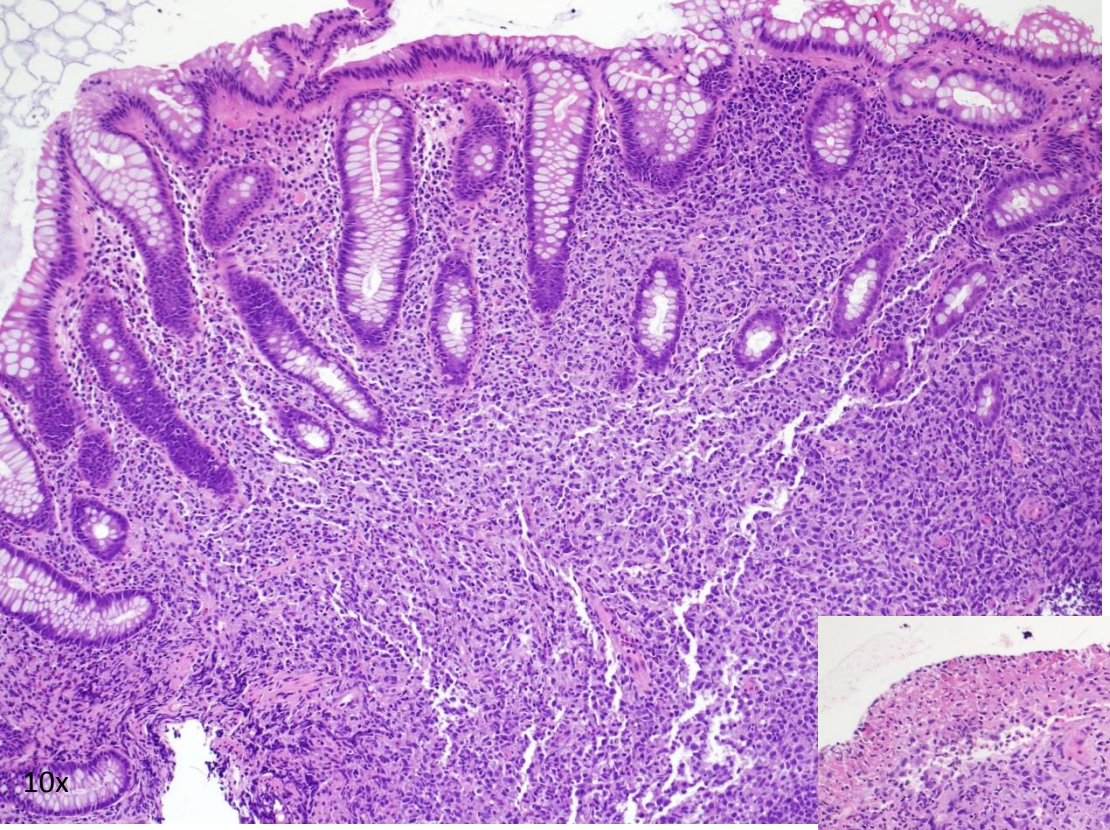
- Diffuse Large B-cell Lymphoma
- Extranodal Marginal Zone Lymphoma of Mucosa-associated Lymphoid Tissue
- Follicular Lymphoma
- Mantle Cell Lymphoma
- Burkitt Lymphoma
- Enteropathy-Associated T-cell Lymphoma
- Monomorphic Epitheliotropic Intestinal T-cell Lymphoma
- NK/T Lymphoma, nasal type
- Hepatosplenic T-cell lymphoma

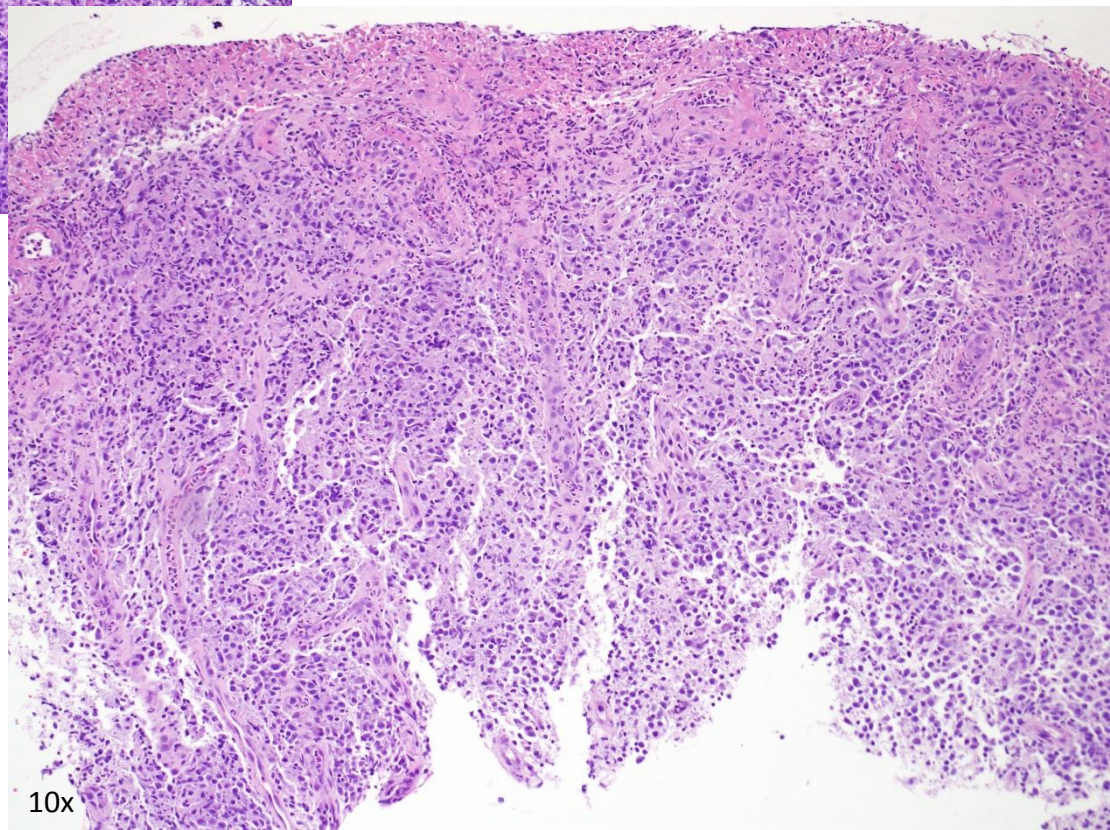
# Diffuse Large B-cell Lymphoma (DLBCL)

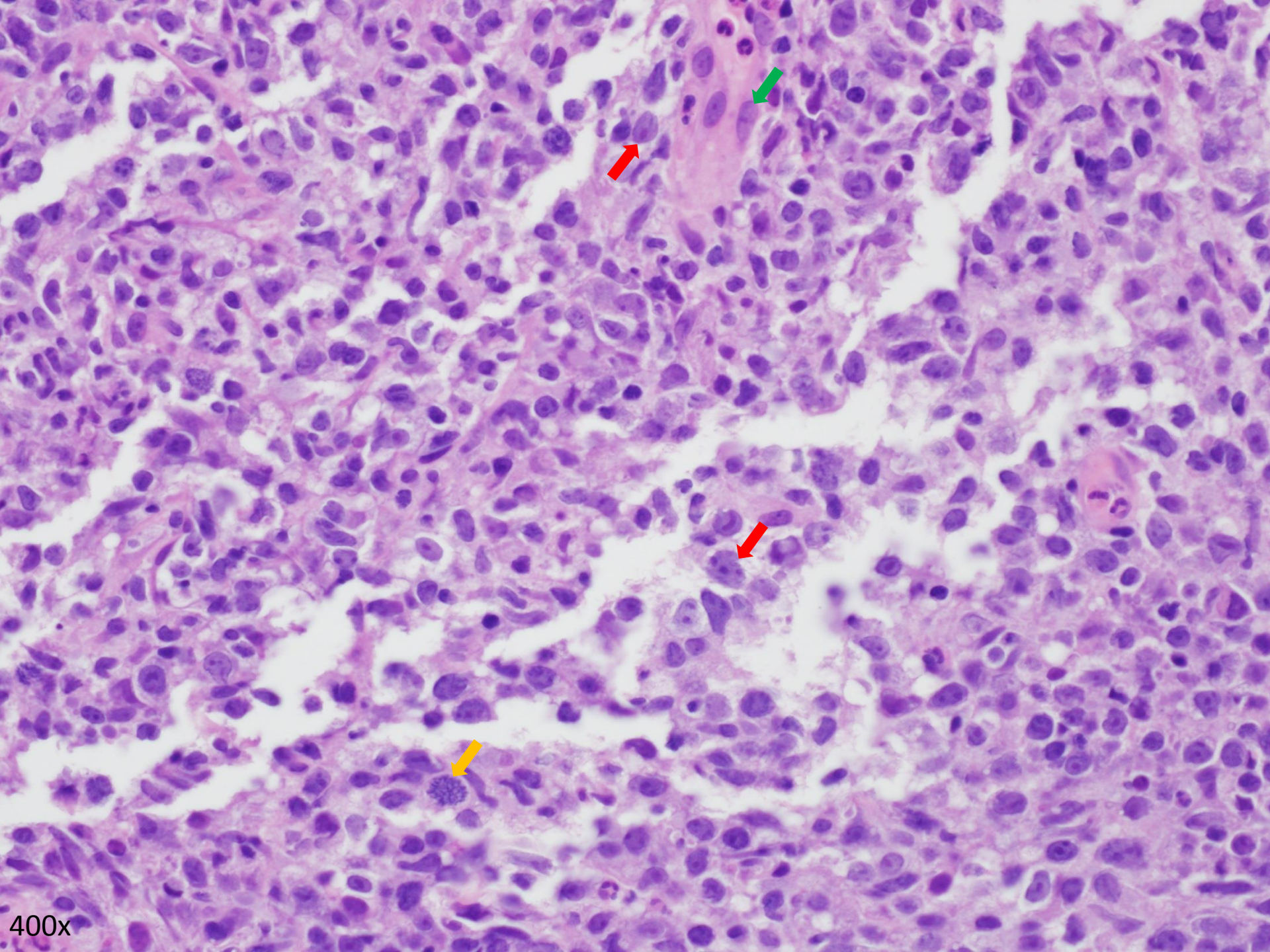
# DLBCL

- Most common type of lymphoma in GI tract
- Mature large B-cell lymphoma that can occur anywhere in GI tract
- May arise de novo or evolve from underlying low-grade B-cell lymphoma
- Subtypes related to Epstein-Barr infection
  - Predilection for elderly and immunosuppressed
  - If arises in iatrogenically immunocompromised following transplant, then classified as monomorphic post-transplant lymphoproliferative disorder (PTLD)
- Clinically aggressive
  - Potentially curable with chemotherapy and immunotherapy
  - low-grade B-cell component may be refractory and persist

# DLBCL: Morphology

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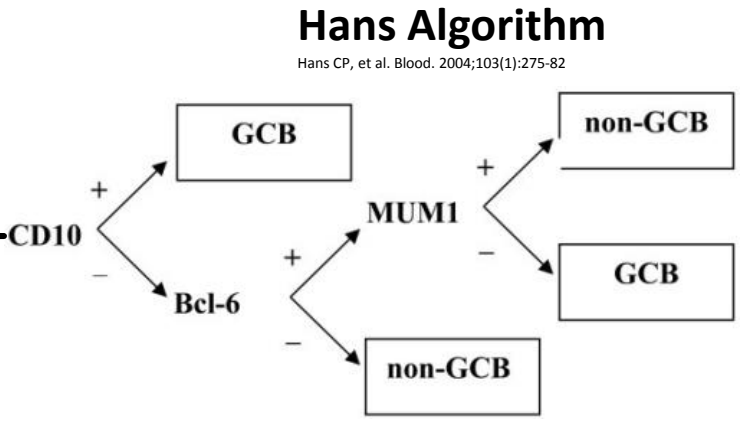
# DLBCL: Immunophenotype

- Pan-B cell marker expression
  - CD20, CD79a, Pax-5
- Aberrant Bcl-2 expression (most)
- Germinal center B-cell phenotype
  - CD10, Bcl-6 expression
- Activated B-cell type
  - MUM1/IRF4 expression
- No expression of T-cell markers
  - except CD5 (~10%)



# DLBCL: Other Immunophenotypic and Molecular/Cytogenetic Features

- MYC alterations and expression
  - *MYC* rearranged in 5-15% of DLBCL, NOS
    - Frequently associated with *BCL2* or *BCL6* translocation = “double hit” or “triple hit” lymphomas
    - new formal category in WHO2016: High-grade B-cell lymphoma (HGBL) with rearrangements of MYC and BCL2 and/or BCL6
  - MYC protein expression in 30-50% of DLBCL, associated with concomitant BCL2 expression in 20-35%
    - BUT do not carry MYC/BCL2 chromosomal alteration, thus named “double expressor lymphoma”
    - Positive expression: at least 40% for c-myc and 50% for Bcl-2 by IHC
    - Prognostic indicator: double-expressor lymphomas have worse outcome than other DLBCL, NOS but are not as aggressive as HGBL with rearrangements of MYC and BCL2 and/or BCL6

# DLBCL: Other Immunophenotypic and Molecular/Cytogenetic Features

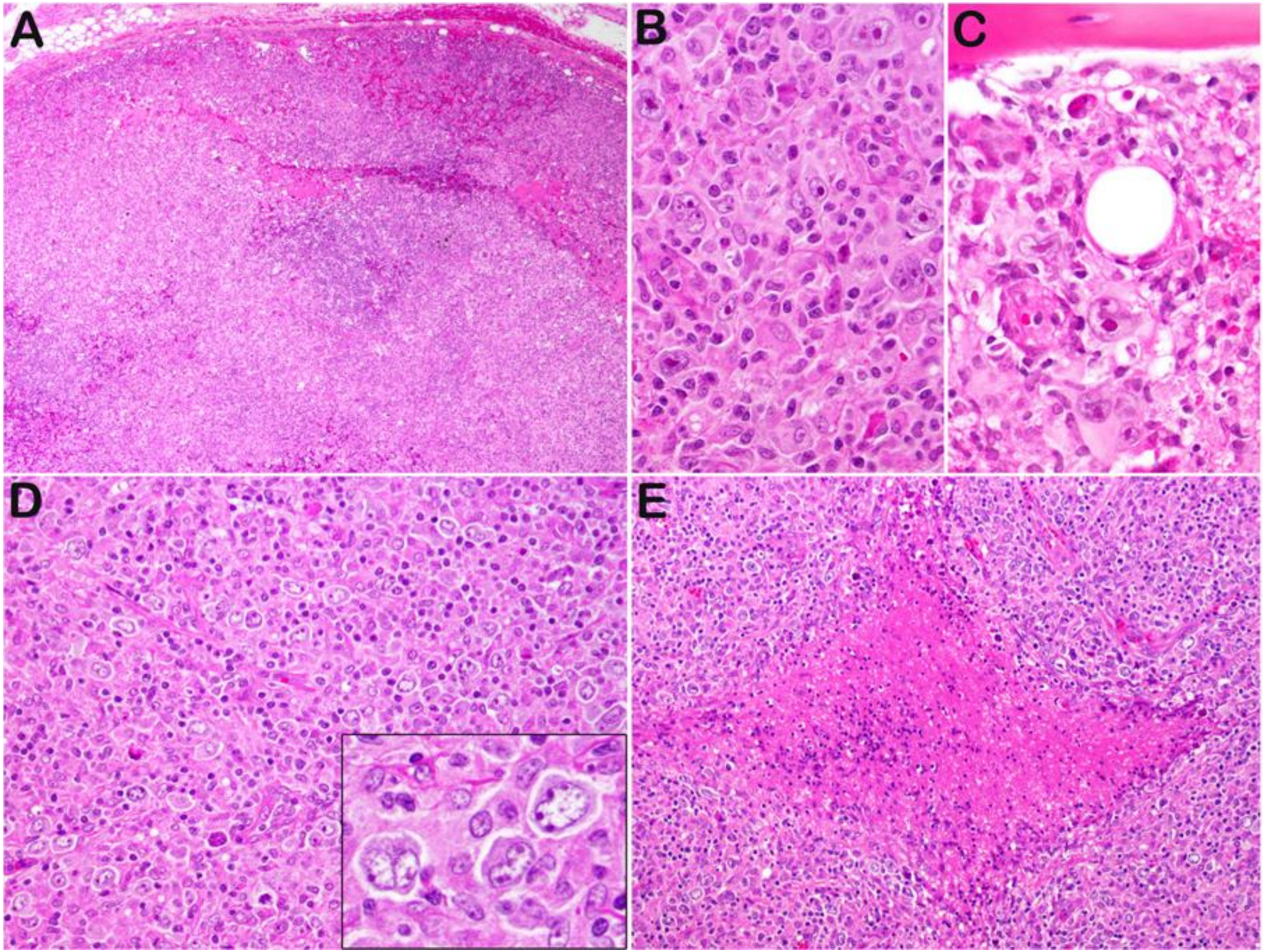
- CD30 expression
  - Target for brentuximab vedotin immunotherapy
- NGS studies
  - GCB-DLBCL: frequent alteration of histone methyl transferase EZH2, BCL2 translocations, and cell motility regulator GNA13 mutations
  - ABC-DLBCL: mutations in genes activating BCR/TLR and NFkB pathways (MYD88, CD79a, CARD11, TNFAIP3)
  - Both: inactivating mutation of TP52, immunosurveillance-related genes, alterations in epigenetic regulators, and oncogenic activation of BCL6

# Subtype: EBV+ DLBCL, NOS

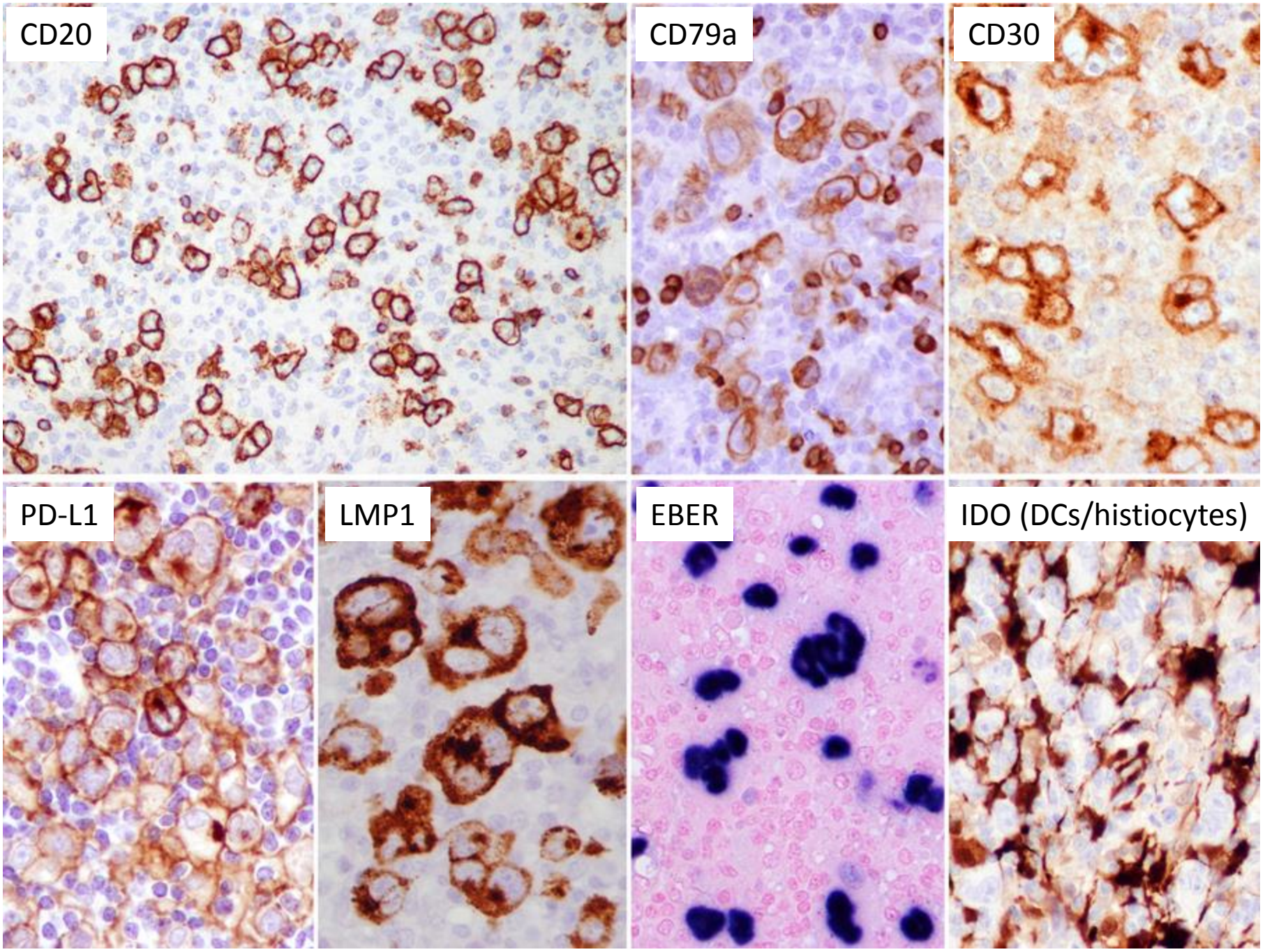
- Previously known as EBV+ DLBCL of the elderly
- In the “elderly” (>50 y): presumed immune senescence leads to development of lymphoma
  - 70% present with extranodal disease (skin, lung, tonsil, stomach)
  - Aggressive (median survival 2 y)
- Nicolae et al described a series of EBV+ DLBCL in young patients (median age 23 y) without known immunodeficiency
  - Predominantly nodal disease, 3 of 46 with liver involvement
  - Good outcome with treatment

# Subtype: EBV+ DLBCL, NOS

- Morphology:
  - some resemble T-cell/Histiocyte-rich large B-cell lymphoma with scattered large B cells mimicking HRS cells and variants
  - some more DLBCL-like
  - geographic necrosis common
- Usually non-GCB phenotype (CD10-, MUM1+), EBV+




Nicolae A, et al. Blood. 2015;126(7):863-72.




Nicolae A, et al. Blood. 2015;126(7):863-72.

# Subtype: EBV+ DLBCL, NOS

- NOS designation excludes specific EBV-associated lymphoma subtypes (Burkitt lymphoma, classical Hodgkin lymphoma, lymphomatoid granulomatosis, primary effusion lymphoma, plasmablastic lymphoma)
- Implied suggestion to screen cases with above morphologies for EBV without regard for age

# WHO2016 update summary:

| | |
|---|---|
| Diffuse large B-cell lymphoma, NOS | • Distinction of GCB vs ABC/non-GC type required with use of immunohistochemical algorithm acceptable, may affect therapy.<br>• Coexpression of MYC and BCL2 considered new prognostic marker (double-expressor lymphoma).<br>• Mutational landscape better understood but clinical impact remains to be determined. |
| $EBV^+$ DLBCL, NOS | • This term replaces $EBV^+$ DLBCL of the elderly because it may occur in younger patients.<br>• Does not include $EBV^+$ B-cell lymphomas that can be given a more specific diagnosis. |
| $EBV^+$ mucocutaneous ulcer | • Newly recognized entity associated with iatrogenic immunosuppression or age-related immunosenescence. |
| High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* translocations | • New category for all "double-/triple-hit" lymphomas other than FL or lymphoblastic lymphomas. |
| High-grade B-cell lymphoma, NOS | • Together with the new category for the "double-/triple-hit" lymphomas, replaces the 2008 category of B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma (BCLU).<br>• Includes blastoid-appearing large B-cell lymphomas and cases lacking *MYC* and *BCL2* or *BCL6* translocations that would formerly have been called BCLU. |

Swerdlow SH, et al. Blood. 2016;127(20):2375-90.

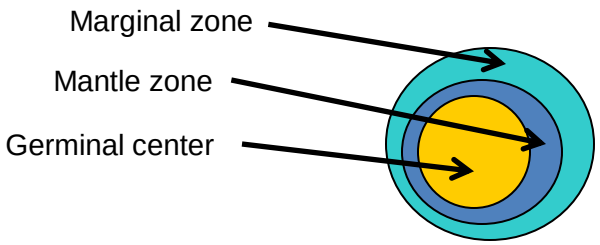
# Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

# MALT lymphoma

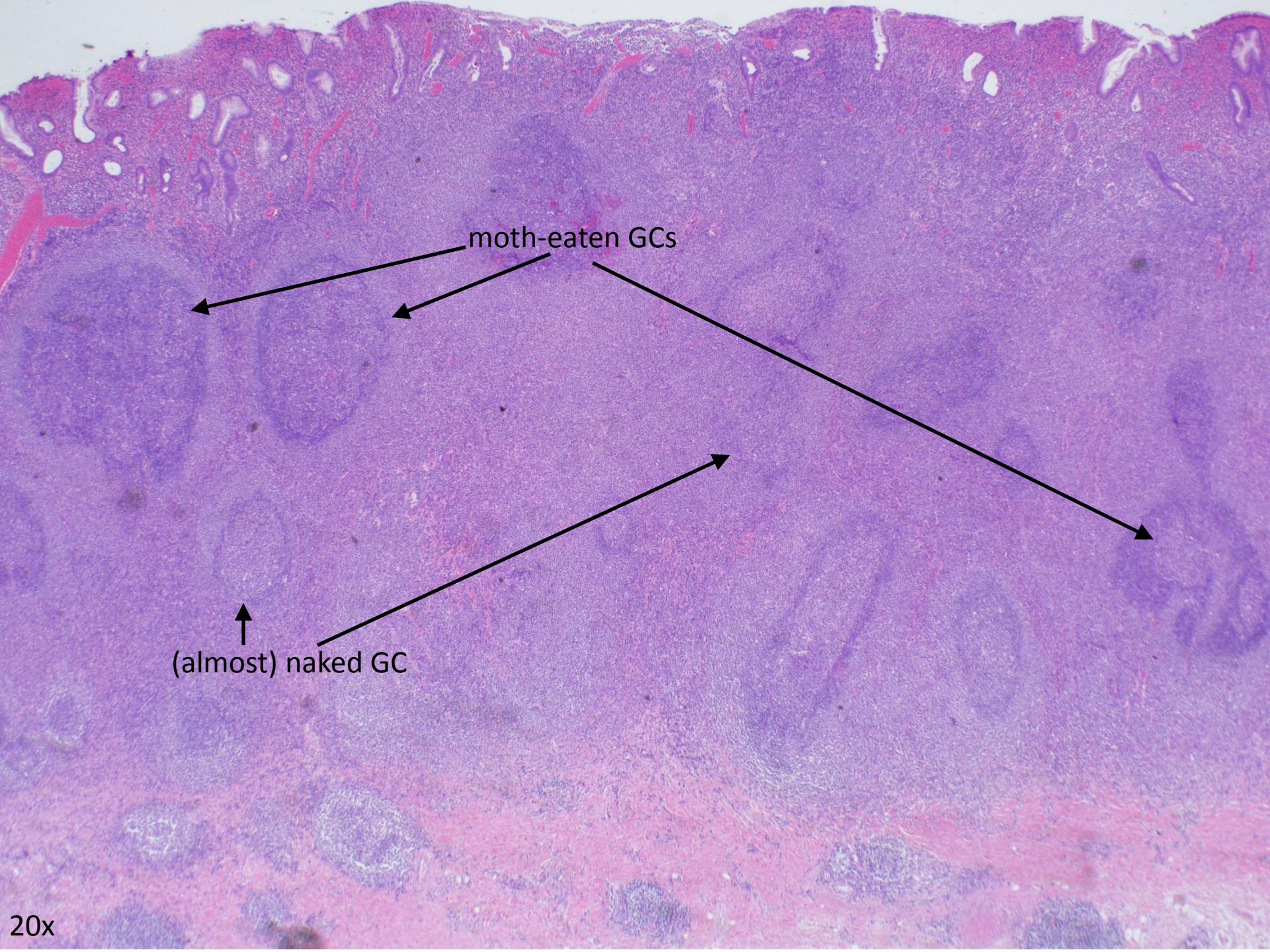
- Mature B-cell lymphoma that can occur anywhere in GI tract
  - 85% in stomach, often in association with *H pylori*-associated gastritis
- Lymphoma of small mature B lymphocytes that has a destructive growth pattern (ulcer or thickened mucosal folds)
- Majority present with low-stage disease
- Bone marrow often uninvolved in GI cases
- M-proteins are rare, despite relatively frequent plasmacytic differentiation
  - In immunoproliferative small intestinal disease (IPSID), a subtype of MALTL associated with *Campylobacter jejuni*, a paraprotein is <u>usually</u> found (alpha heavy chain)

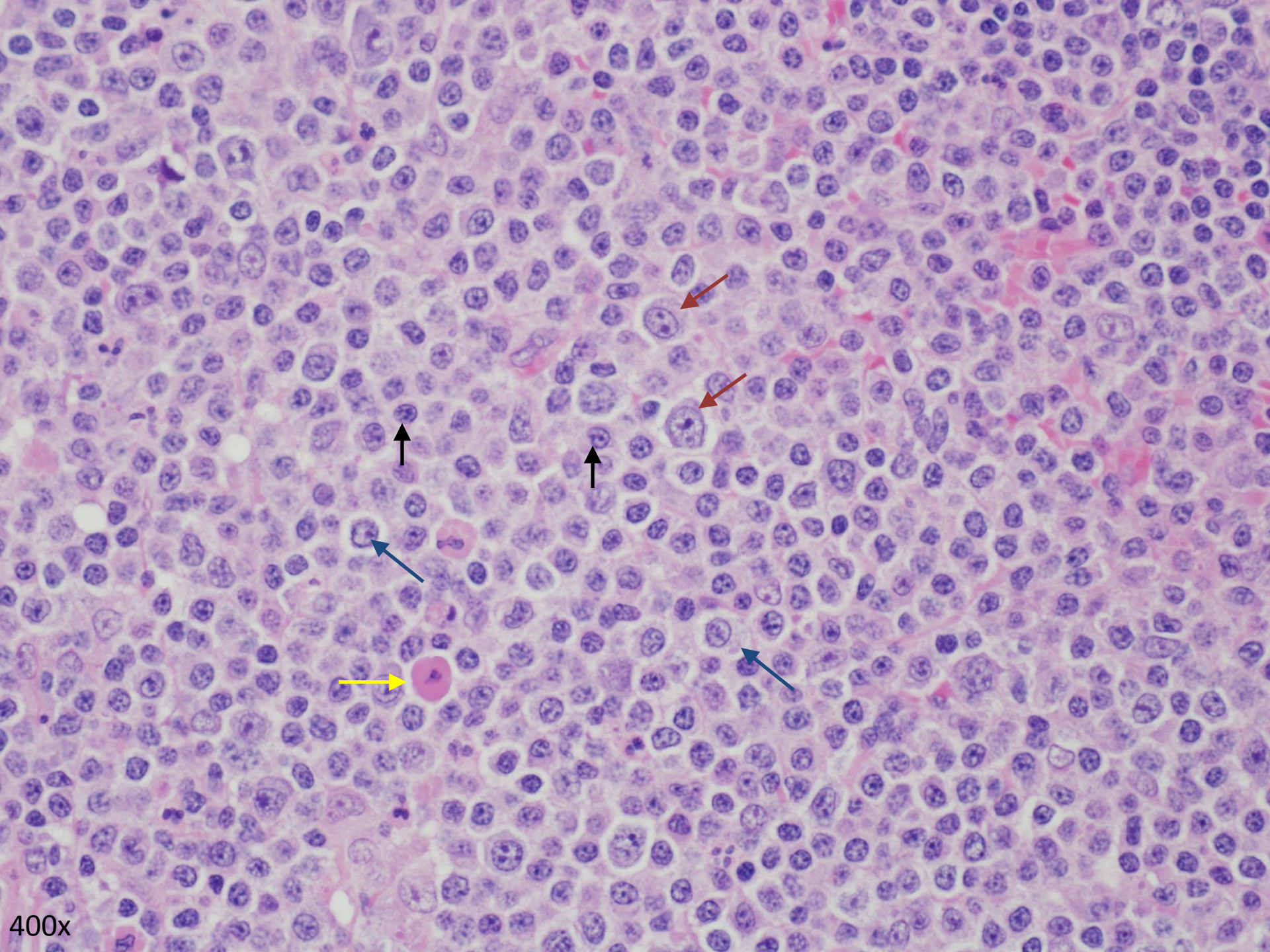
# MALT Lymphoma: Morphology

- Reactive germinal centers commonly accompany lymphoma
  - May be invaded or disrupted, leading to “naked” or “moth-eaten” appearance




- Heterogeneous, predominantly small B-lymphocytes
  - centrocyte-like cells (indistinguishable from small cells of normal germinal center
  - monocytoid cells (slightly larger cells with more ample cytoplasm and slightly indented nuclei)
  - few scattered large cells (immunoblast- and/or centroblast-like, recapitulate centroblasts of germinal center)


moth-eaten GCs
(almost) naked GC
20x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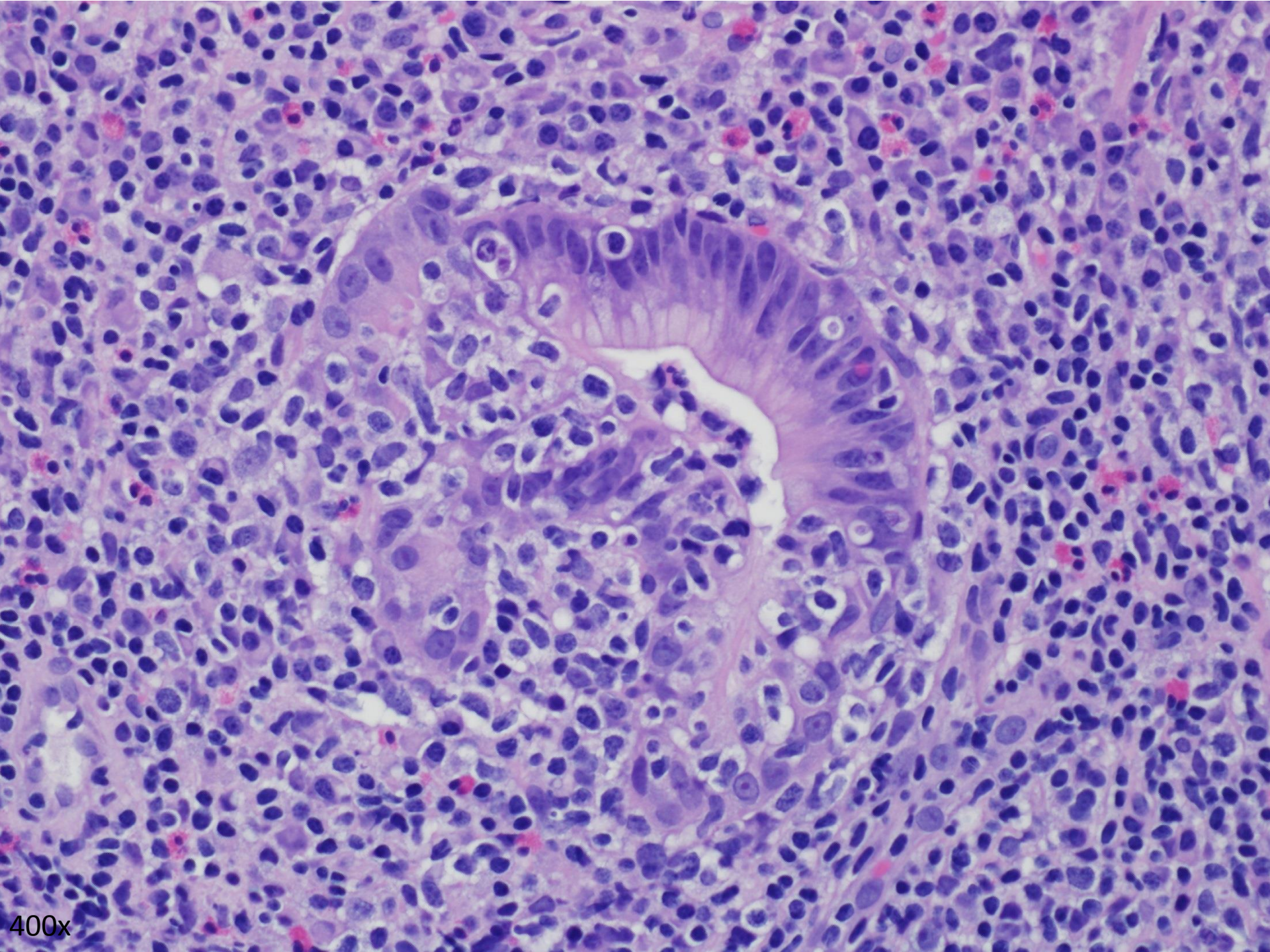
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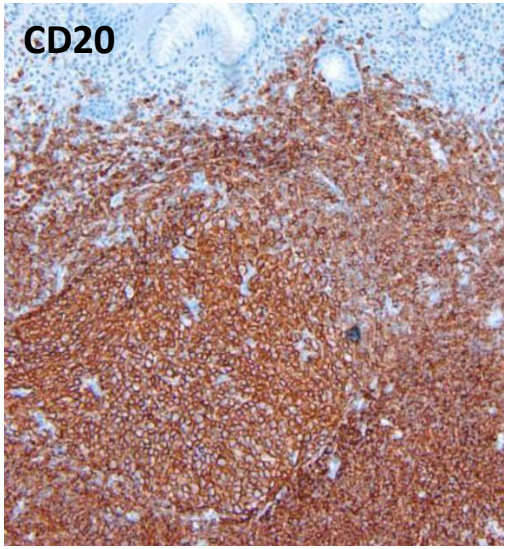
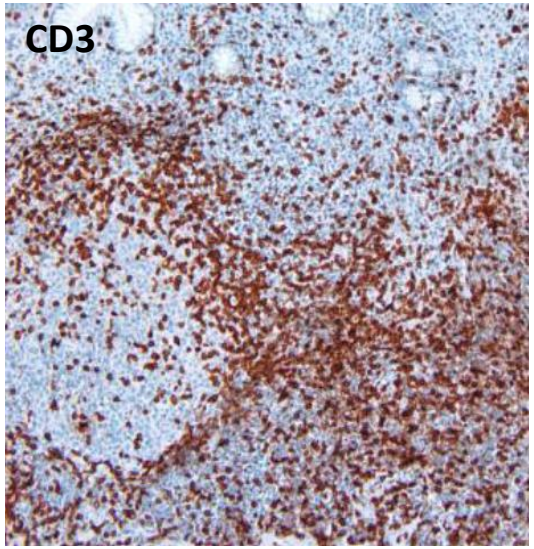
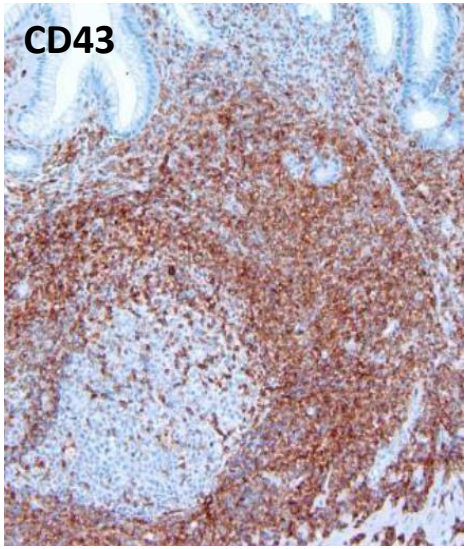
# MALT Lymphoma: Morphology + IHC

- Some cases have plasma cell differentiation
  - Kappa & lambda light chain IHC may be helpful in establishing clonality
- No distinctive immunophenotype
  - Aberrant CD43 expression in only 40-50% of cases




- Lymphoepithelial lesion (LEL) is histologic hallmark
  - Destructive epithelial infiltration by lymphoma cells
  - Characteristic but not absolutely specific

# MALT Lymphoma vs *H pylori* gastritis

| MALT lymphoma | *H pylori* gastritis |
|---|---|
| Mucosal destruction present | Intact architecture with inflammatory infiltrate among pits/ glands |
| Lymphoepithelial lesions (with B cells) | Epithelial structures intact |
| B cells predominate | Mixture of B and T cells |
| Deep follicles with colonization | Intact follicles in deep mucosa |
| Light chain restriction (if plasmacytic differentiation) | Polytypic plasma cells (kappa/lambda ~2:1) |

Owens SR. Surg Pathol Clin. 2017;10(4):1021-1037

# MALT Lymphoma: Clinical Aspects

- 80% are responsive to conservative therapy aimed at eradication of inciting entity
  - Evidence suggests that antibiotic therapy can be effective in *H. pylori*-negative cases of MALT, *and in some cases outside the stomach*
  - Gastric MALT lymphomas with t(11;18)(q21;q21) translocation resulting in API2-MALT1 fusion occur independent of *H pylori* stimulus and are resistant to conservative therapy
- Resolution of atypical lymphoid infiltrate can take months (typically 4-10 months) to more than a year
  - Reporting of residual (regressing) disease on serial biopsies should include comparison statement
  - Progression is worrisome and requires another treatment modality

# MALT Lymphoma: Gray zone cases

- What to do with borderline or minimal cases??
  - “Intense H. pylori gastritis with atypical lymphoid infiltrate”
  - In the comment address the possibility of early MALTL and offer a statement about typical response to conservative therapy

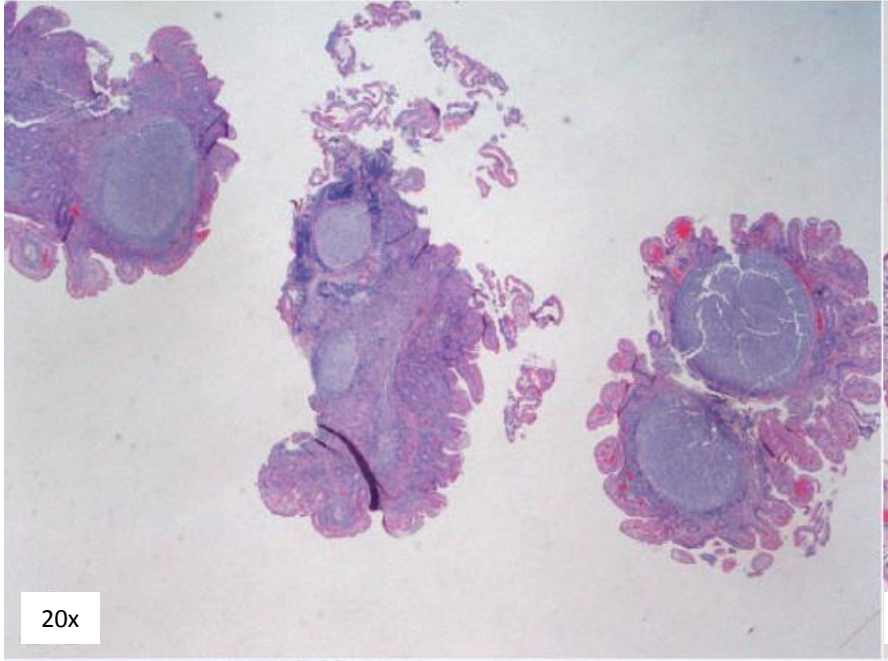
# Follicular Lymphoma

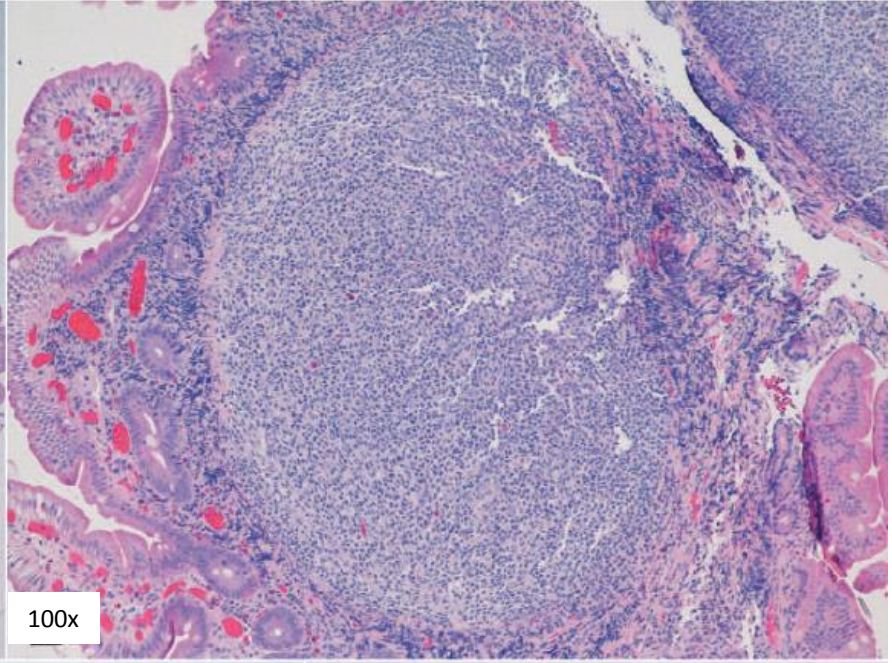
# Follicular Lymphoma

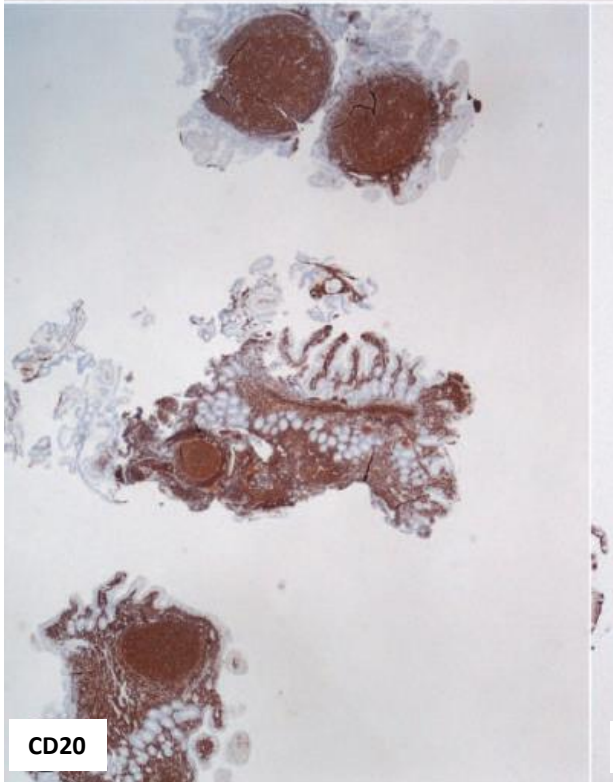
- Mature B-cell lymphoma that may involve the GI tract secondarily or occasionally primarily
  - Duodenal-type FL presents as multiple small polyps
  - Formal clinical staging work-up must be performed
    - CANNOT diagnose primary GI/duodenal-type FL on histology alone
- Nodular infiltrate of small mature lymphocytes that recapitulate follicle center B-cells (centrocytes and centroblasts)
  - Proportions of each population determine grade
- Typically indolent
  - Frequently involve bone marrow and can be difficult to cure
  - Duodenal-type FL very indolent, may not need additional therapy beyond local excision

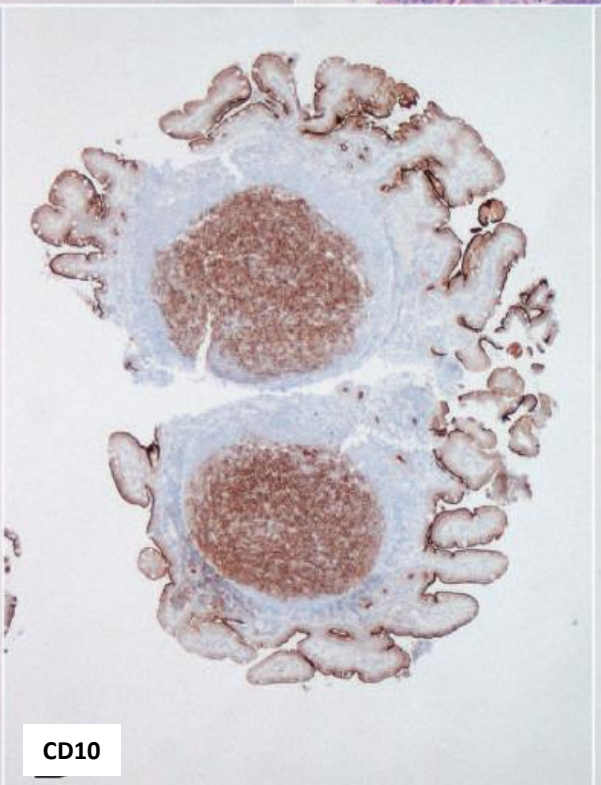
# Follicular Lymphoma: Morphology

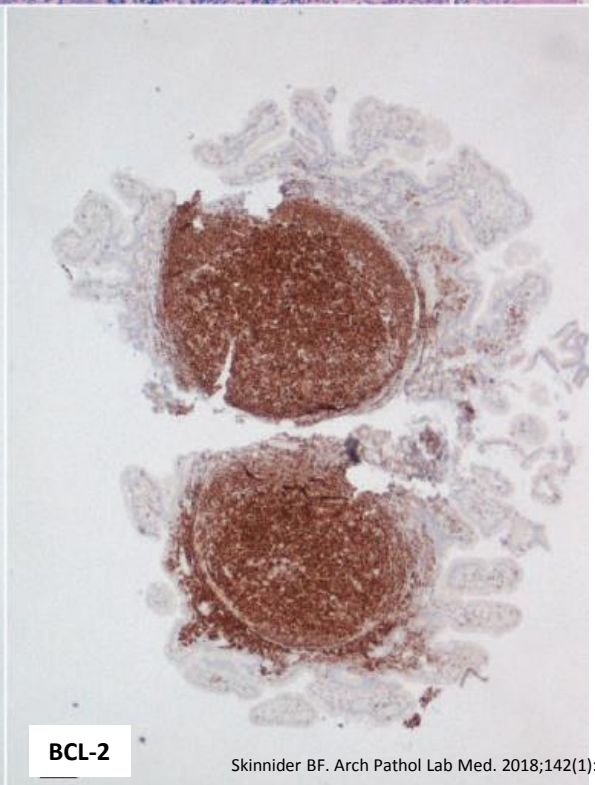
- Nodular infiltrate with closely-packed follicles with attenuated or absent mantle zones
- Neoplastic follicles have randomly distributed centrocytes and centroblasts without tingible-body macrophages
  - In contrast, reactive germinal centers of normal follicles demonstrate polarization due to centrocytes and centroblasts occupation of different zones and have tingible-body macrophages




Skinnider BF. Arch Pathol Lab Med. 2018;142(1):44-52.

# Follicular Lymphoma: Immunophenotype & Cytogenetics

- Pan-B cell marker expression (CD20, Pax5)
- Follicle center cell differentiation (CD10, Bcl-6)
- Dendritic cell meshwork present in neoplastic follicles (highlighted with CD21 and CD23)
- Aberrant expression of BCL-2
  - Also positive in many other lymphomas and normal T-cells and plasma cells
  - Negative in germinal centers of reactive follicles
- All forms associated with t(14;18)(q32;q21) translocation involving *IGH* and *BCL2*

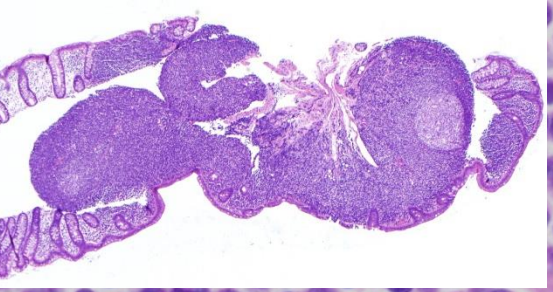
# Mantle Cell Lymphoma

# Mantle Cell Lymphoma

- Systemic small mature B-cell lymphoma
  - Involves GI tract in one-third of cases
  - Hepatosplenomegaly, lymphadenopathy, PB involvement common
- Classically presents as lymphomatous polyposis
  - Multiple (sometimes hundreds) of polyps throughout GI tract
- Aggressive, with overall survival of 3-5 years

# Mantle Cell Lymphoma: Morphology

- Monomorphic lymphoid proliferation
  - Pattern can be diffuse, nodular, “mantle zone”
    - Mantle zone pattern has central follicle surrounded by neoplastic cells
- small to medium-sized neoplastic lymphoid cells with dark angulated nuclei
- interspersed hyalinized small vessels (thick-walled capillaries) and epithelioid eosinophilic histiocytes (mimicking “starry sky” appearance)
- Blastoid and pleomorphic variants may mimic ALL and DLBCL
  - Important to recognize as the latter two are potentially curable, whereas MCL is not



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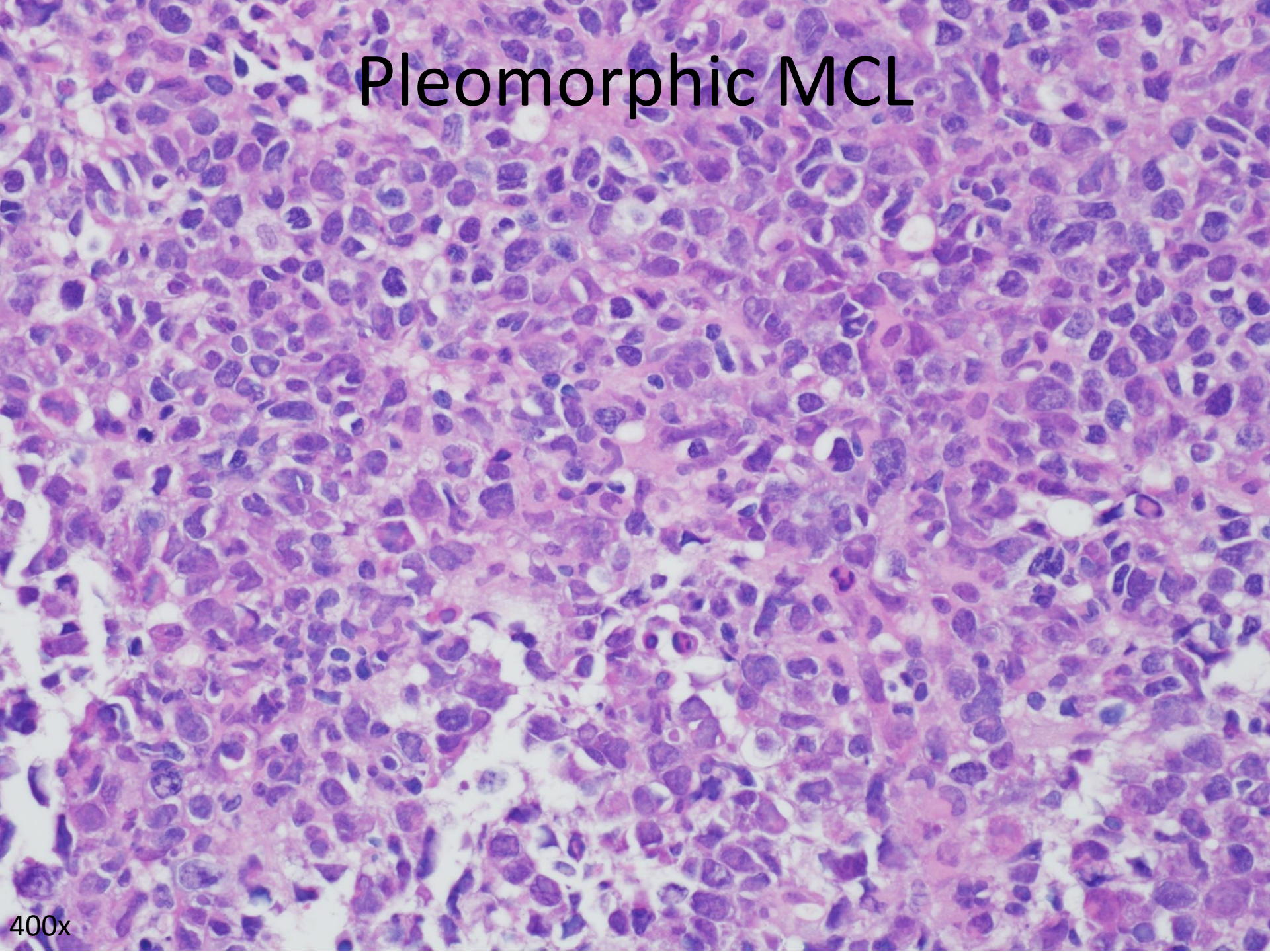

Pleomorphic MCL
400x

# Classical Mantle Cell Lymphoma: Immunophenotype

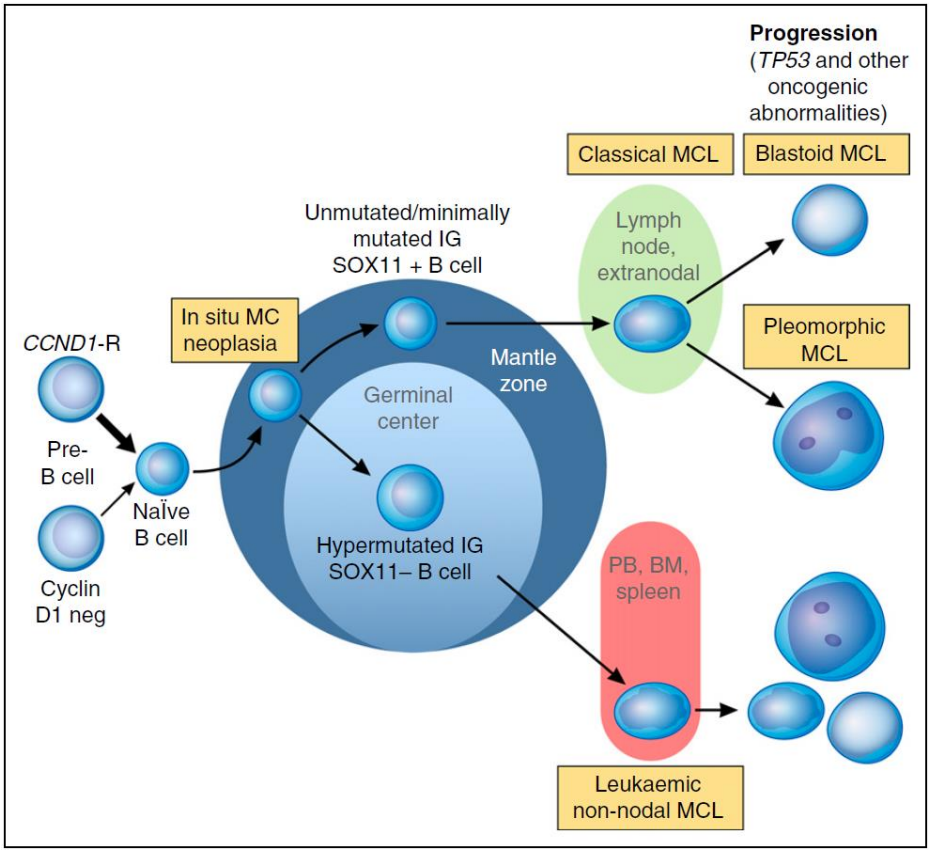
- Pan-B cell marker expression (CD20, Pax5)
- Aberrant expression of CD5 (rarely negative), CD43 (usually), BCL-2, nuclear CyclinD-1 (very rare negative cases express cyclin D2 or cyclin D3)
- Surface IgM and/or IgD expression
- Sox11 expression
- Negative for CD10, BCL-6, CD23

# Classical Mantle Cell Lymphoma: Cytogenetics

- Ig genes
  - IgH rearranged
  - IgH Variable regions unmutated or minimally mutated
- t(11;14)(q13;q32) rearrangement
  - Involves IgH and CyclinD1 genes (PRAD1, BCL1)
  - Classical cytogenetics detects 70-95%
  - FISH detects ~100%
- Other
  - p53, p16, p18 (especially in blastoid variant)
  - 13q14 deletion
  - Total or partial trisomy 12

# MCL: WHO2016 Update

- Two MCL subtypes recognized with different clinicopathological manifestations and molecular pathogenetic pathways: one largely with unmutated/minimally mutated IGHV and mostly SOX11$^{+}$ and the other largely with mutated IGHV and mostly SOX11$^{-}$ (indolent leukemic nonnodal MCL with PB, bone marrow (BM), ±splenic involvement, may become more aggressive).
- Mutations of potential clinical importance, such as *TP53*, *NOTCH 1/2*, recognized in small proportion of cases.
- *CCND2* rearrangements in approximately half of cyclin D1$^{-}$ MCL.




Swerdlow SH, et al. Blood. 2016;127(20):2375-90.

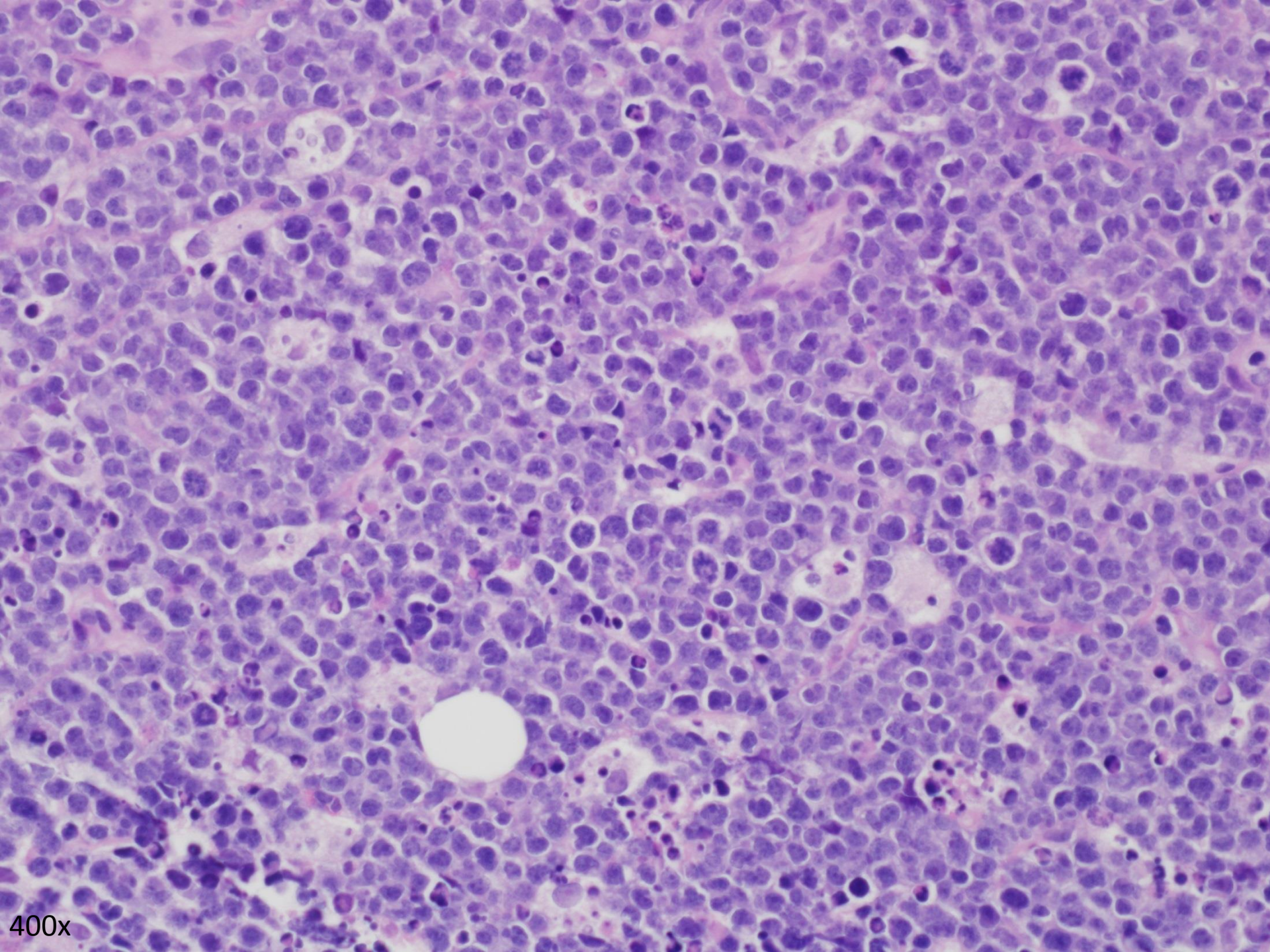
# Burkitt Lymphoma

# Burkitt Lymphoma

- Mature B-cell lymphoma of children and young adults
- Has very short doubling time
- Presents often in extranodal sites or as acute leukemia
  - Classic lesion is large and destructive mass in distal ileum and/or cecum
  - Can involve any portion of GI tract
- Variable global distribution
  - Endemic: equatorial Africa and Papua New Guinea
  - Sporadic: around globe
- Epstein-Bar virus association
  - Endemic: majority of neoplastic cells in all patients
  - Sporadic: 30% of cases
  - Immunodeficiency-associated (HIV): 25-40% of cases
- Good prognosis (up to 90% survival) with appropriate therapy

# Burkitt Lymphoma: Morphology

- Low magnification: “starry sky”
  - Sheets of lymphoma cells are punctuated by tingible-body macrophages with cellular debris
- Lymphoma cells are monotonous, medium-sized, with round nuclei, dispersed chromatin, inconspicuous nucleoli, scant basophilic cytoplasm
- Nearly 100% proliferative fraction, numerous mitotic figures, lots of apoptotic debris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# Burkitt Lymphoma: Immunoprofile & Cytogenetics

- B-cell marker expression (CD20, CD19, CD79a)
- Germinal center cell differentiation (CD10, Bcl-6)
- High Ki-67 proliferative index (nearly 100%)
- Negative for Bcl-2 (weakly positive in 20%), TdT, CD5

- MYC translocation is characteristic (but not specific)
  - t(8;14)(q24;q32): c-MYC and IgH (75%)
  - t(2;8)(p12;q24): Ig kappa and c-MYC (15%)
  - t(8;22)(q24;q11): c-MYC and Ig lambda (10%)

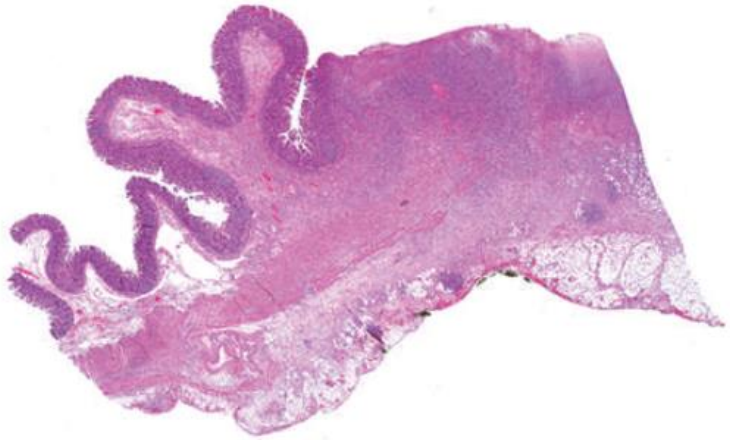
# Enteropathy-Associated T-cell Lymphoma (EATL)

# EATL

- Aggressive T-cell lymphoma that produces large, destructive masses, often in jejunum
- Arises in patients with celiac disease
  - In setting of refractory sprue
  - As sentinel event in patients with undiagnosed celiac disease
- Associated with HLA haplotypes DQ2 and DQ8
  - Northern European descent
- Poor prognosis due to aggressive nature and debilitated state of patients with malabsorption
  - Common presentation is ulcerated mass +/- perforation
  - Median survival of months

# EATL: Morphology

- Diffuse, destructive infiltrate of intermediate-sized or large cells with angulated or pleomorphic nuclei (resembling those of DLBCL) with prominent nucleoli
- Tumor infiltration by inflammatory cells including histiocytes and eosinophils
- Neoplastic cells infiltrate individual crypts
- Areas of necrosis may be present
- Adjacent intestinal mucosa demonstrates variable degree of enteropathy (villous atrophy, crypt hyperplasia, intraepithelial lymphocytosis)



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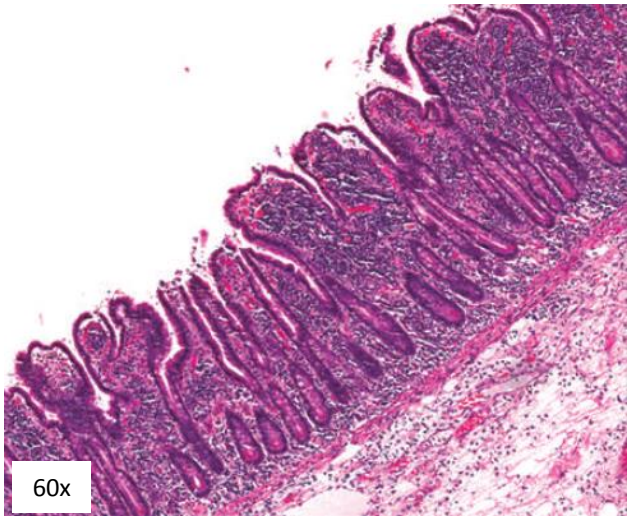

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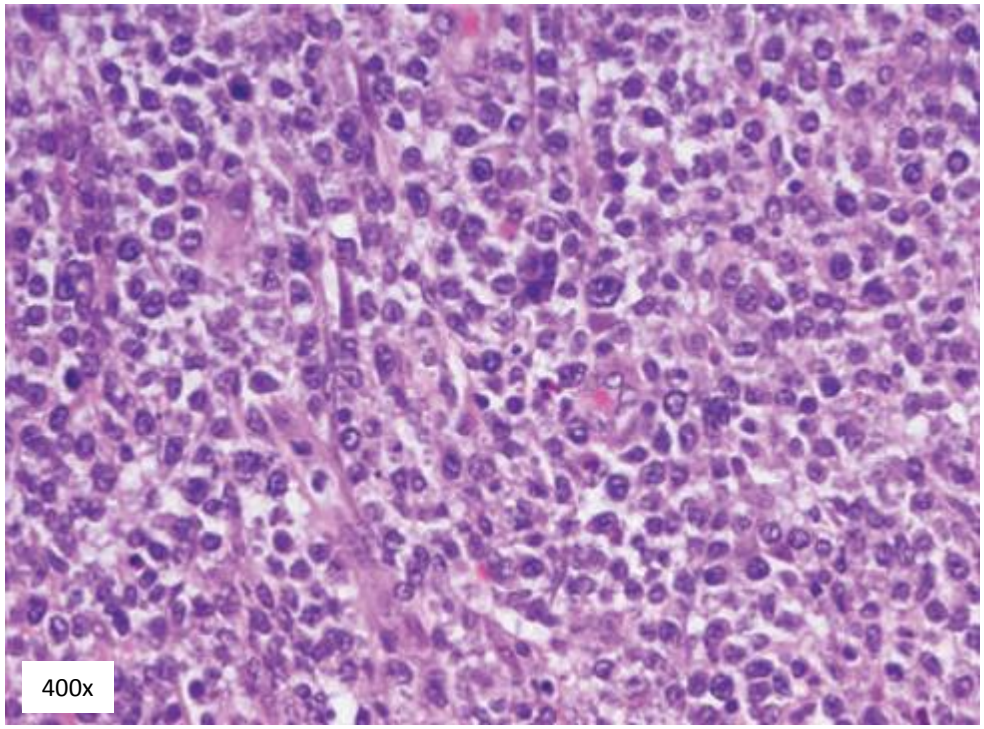

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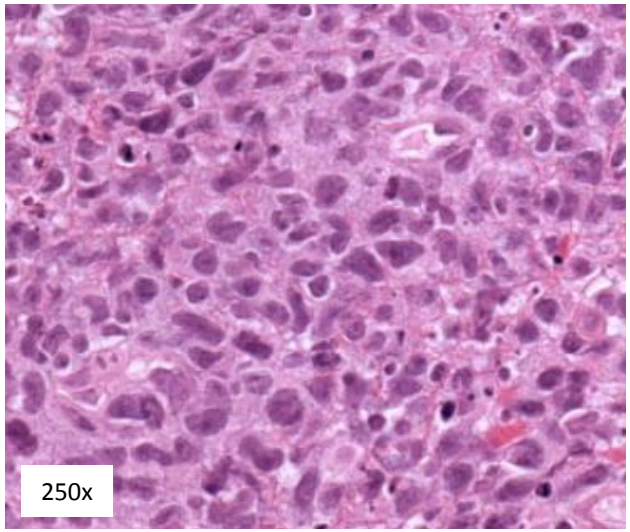


250x

Arps DP, Smith LB. Arch Pathol Lab Med. 2013;137(9):1227-31.
Delabie J, et al. Blood. 2011;118(1):148-55.

# EATL: Immunophenotype

- Cytotoxic phenotype (granzyme B, TIA-1)
- TCR alpha/beta in most cases
- Typically positive for CD3, CD7, occasional cases CD8+, variable CD30
- Usually negative for CD4, CD8, CD5, CD56, MATK

- Intraepithelial lymphocytes in the adjacent enteropathic mucosa have a similar phenotype

# Monomorphic Epitheliotropic Intestinal T-cell Lymphoma (MEITL)

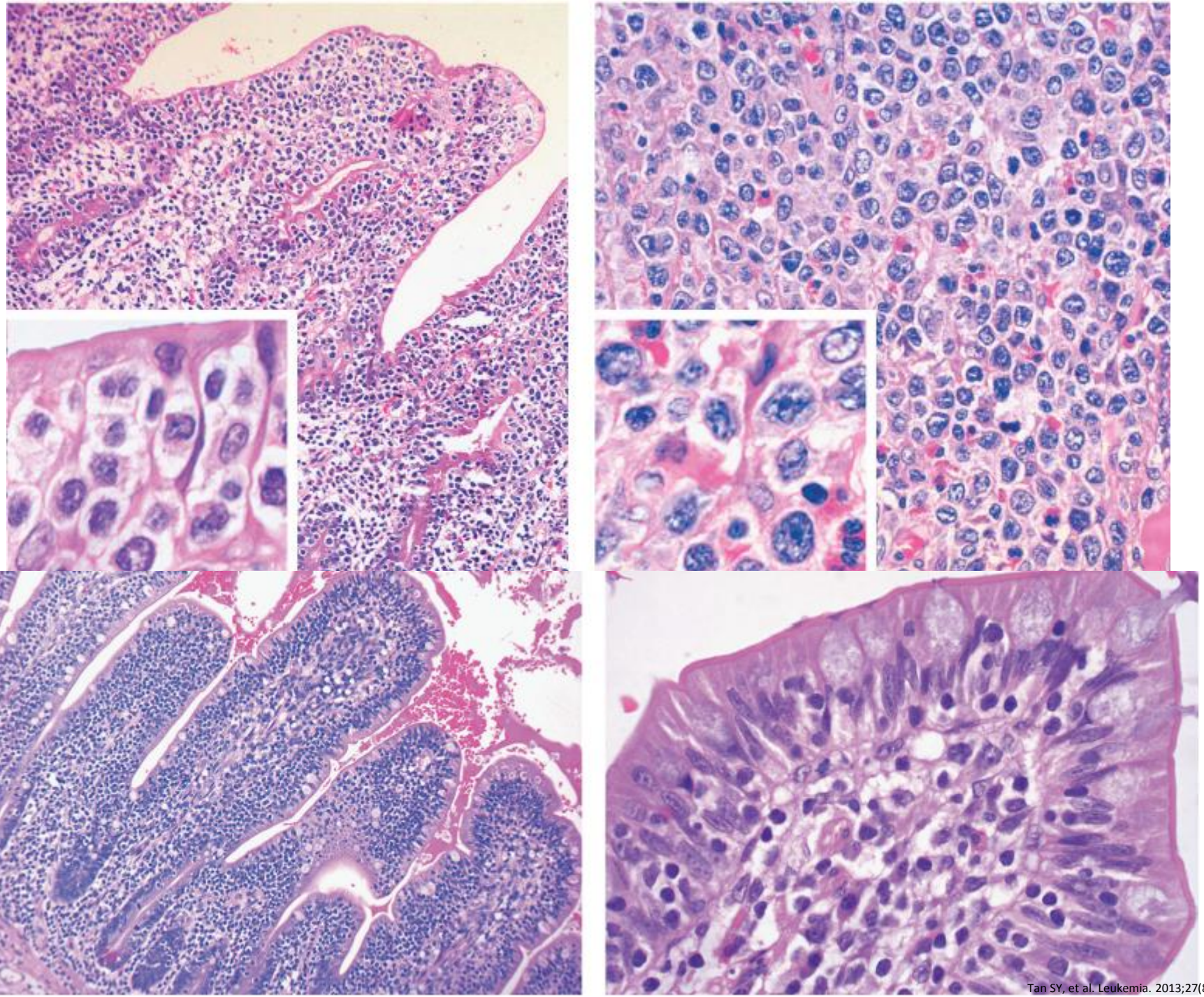
Formerly known as EATL II or EATL, monomorphic form

# MEITL

- Aggressive T-cell lymphoma
- NO association with celiac disease
- Apparent increased frequency in patients of Asian and Hispanic descent
- Poor prognosis due to aggressive nature and debilitated state of patients
  - Common presentation is ulcerated mass +/- perforation
  - Median survival of months

# MEITL: Morphology

- Diffuse, destructive, often ulcerated infiltrate of monotonous medium-sized lymphoid cells with dispersed chromatin, inconspicuous nucleoli, and ample clear cytoplasm (monocytoid appearance)
- Prominent epitheliotropism of tumor cells in adjacent mucosa with little involvement of submucosa/muscularis propria (lateral spread)
- Distant mucosa without enteropathy
- Paucity of reactive inflammatory cells within tumor
- Tumor perforation frequent



Tan SY, et al. Leukemia. 2013;27(8):1688-96.

# MEITL: Immunophenotype

- Cytotoxic phenotype (TIA-1, granzyme B)
- Typically express CD2, CD3, CD7, CD8, CD56, nuclear MATK
- TCR gamma/delta in most cases
  - Some TCR silent
  - Some TCR alpha/beta
- Typically negative for CD5, CD4

| | |
|---|---|
| Enteropathy-associated T-cell lymphoma (EATL) | • Diagnosis only to be used for cases formerly known as type I EATL, typically associated with celiac disease. |
| Monomorphic epitheliotropic intestinal T-cell lymphoma | • Formerly type II EATL; segregated from type I EATL and given a new name due to its distinctive nature and lack of association with celiac disease. |

| | EATL | MEITL |
|---|---|---|
| Frequency | 80-90% | 10-20% |
| Epidemiology | Complication of GSE | Occurs sporadically |
| | associated with HLA-DQ2/DQ8 | |
| | refractory GSE patients at high risk | |
| | Northern Europeans descent | Asian and Hispanic descent |
| | | |
| Morphology | Variable, pleomorphic, intermediate to large cells | Monotonous small to intermediate-sized cells |
| | Angulated nuclei | Round nuclei |
| | Prominent nucleoli | Inconspicuous nucleoli |
| | Areas of necrosis | Rare necrosis |
| | Variable to heavy background mixed inflammatory infiltrate | Minimal background inflammatory infiltrate |
| | | |
| Immunophenotype | CD3+, CD5-, CD7+ | CD3+, CD5-, CD7+ |
| | CD8- (80%) | CD8+ (80%) |
| | CD56- (>90%) | CD56+ (>90%) |
| | nuclear MATK- | nuclear MATK+ |
| | | |
| Cytogenetics | | |
| +9q31.3 or -16q12.1 | 86% | 83% |
| +1q32.2-q41 | 73% | 27% |
| +5q34-q35.2 | 80% | 20% |
| +8q24 (MYC) | 27% | 73% |

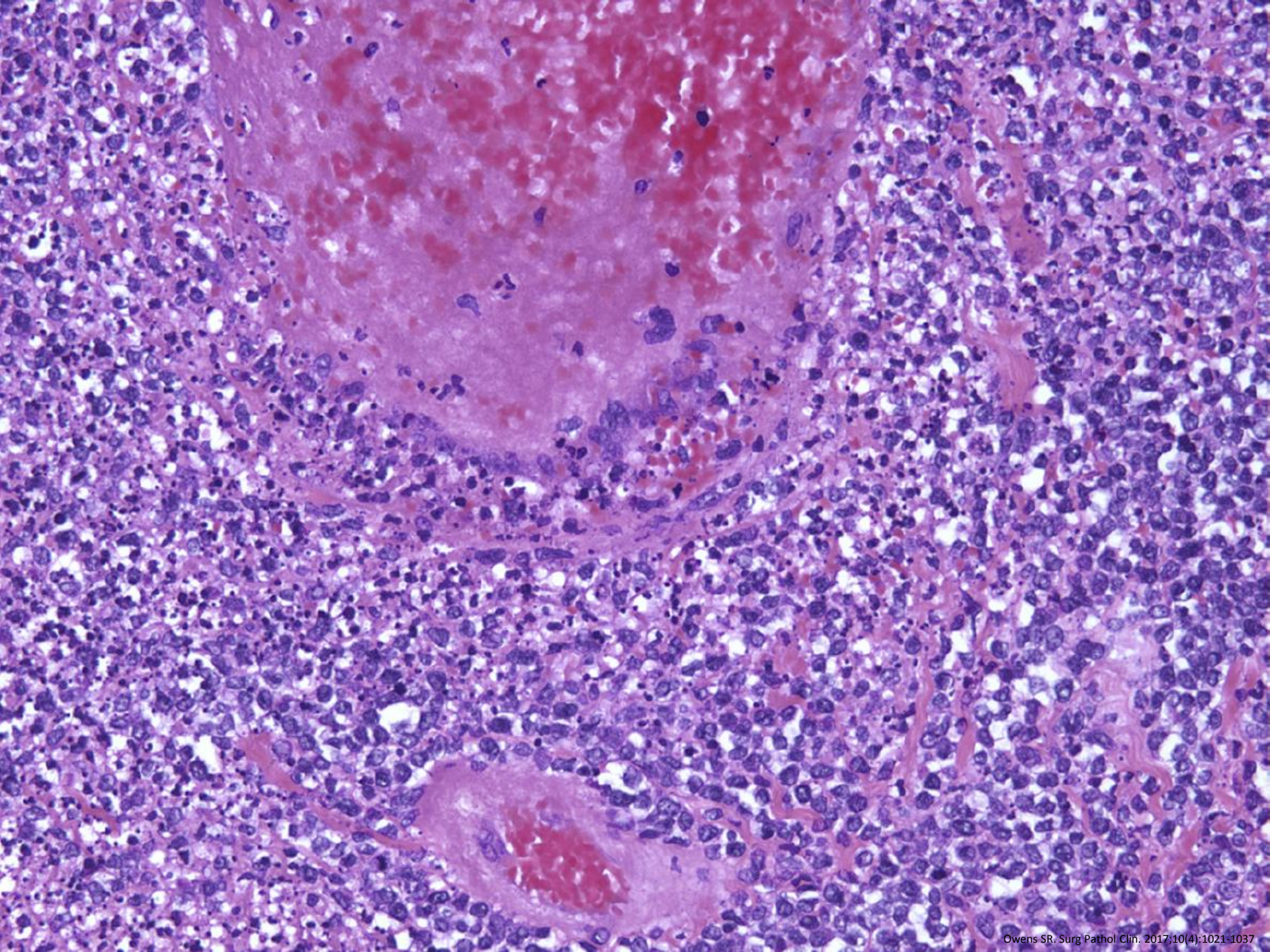
# Extranodal Natural Killer/T-cell Lymphoma, Nasal Type (ENKTL)

# ENKTL

- Rare, very aggressive lymphoma most commonly involving upper aerodigestive tract
  - Propensity to involve the GI tract
- Frequent tumor ulceration due to angiocentric and angiodestructive growth
- Associated with Epstein-Barr virus
- Higher prevalence in Asian and Native American populations
- Variable prognosis for nasal ENKTL, but extranasal ENKTL has short survival times and poor response to therapy

# ENKTL: Morphology

- Variably-sized neoplastic cells
  - Small, medium-sized, large, or anaplastic
  - Irregularly folded nuclei with granular or vesicular chromatin
  - Inconspicuous nucleoli
  - Moderate pale cytoplasm
- Mitotic figures easily seen
- Angiocentric and angiodestructive growth with fibrinoid changes in vessels
- Coagulative necrosis and many apoptotic bodies



Owens SR. Surg Pathol Clin. 2017;10(4):1021-1037

# ENKTL: Immunophenotype

- Typically express CD2, CD56, CD3epsilon (cytoplasmic), cytotoxic molecules (granzyme B, TIA1, perforin), CD43, CD25
- EBV+ (by IHC or ISH)
- Typically negative for surface CD3, CD4, CD8, CD5, CD16, CD57
- TCR in germline configuration

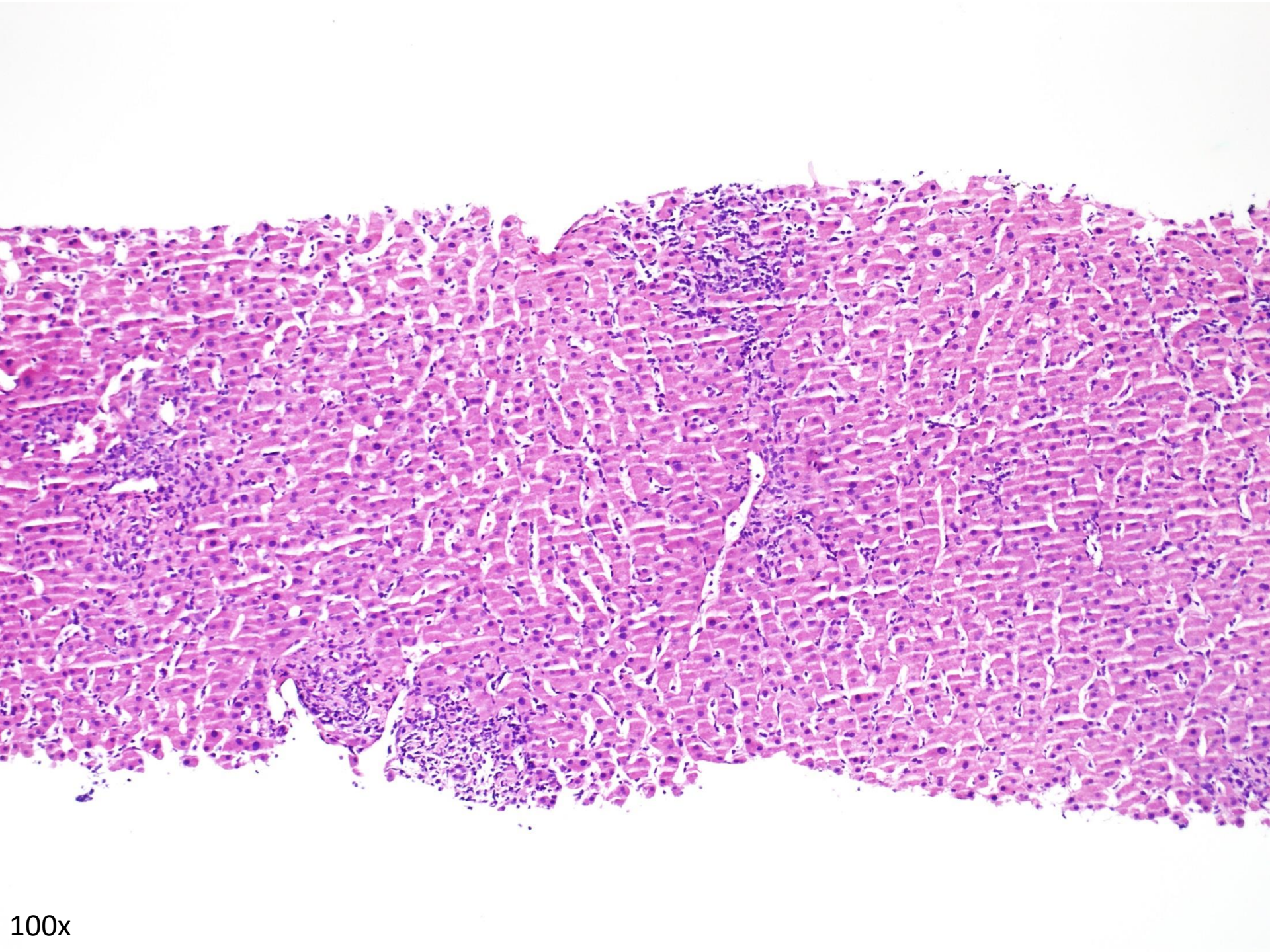
# Hepatosplenic T-cell Lymphoma (HSTL)

# HSTL

- Rare extranodal, systemic cytotoxic gamma/delta T-cell lymphoma of young adults
- 20% arise in setting of chronic immune suppression
  - After solid-organ transplant; considered PTLD
  - Immunosuppression for IBD
- Presents with marked splenomegaly, (usually) hepatomegaly, without lymphadenopathy, but with BM involvement
  - Marked thrombocytopenia
  - Often anemia, leukopenia
- Aggressive, with relapses after treatment is most cases
  - Median survival <2 years

# HSTL: Morphology

- Spleen: diffuse involvement of cords and sinuses of red pulp, white pulp atrophy
- Liver: diffuse infiltration of sinusoids
- Neoplastic cells are monotonous medium-sized cells with pale cytoplasm



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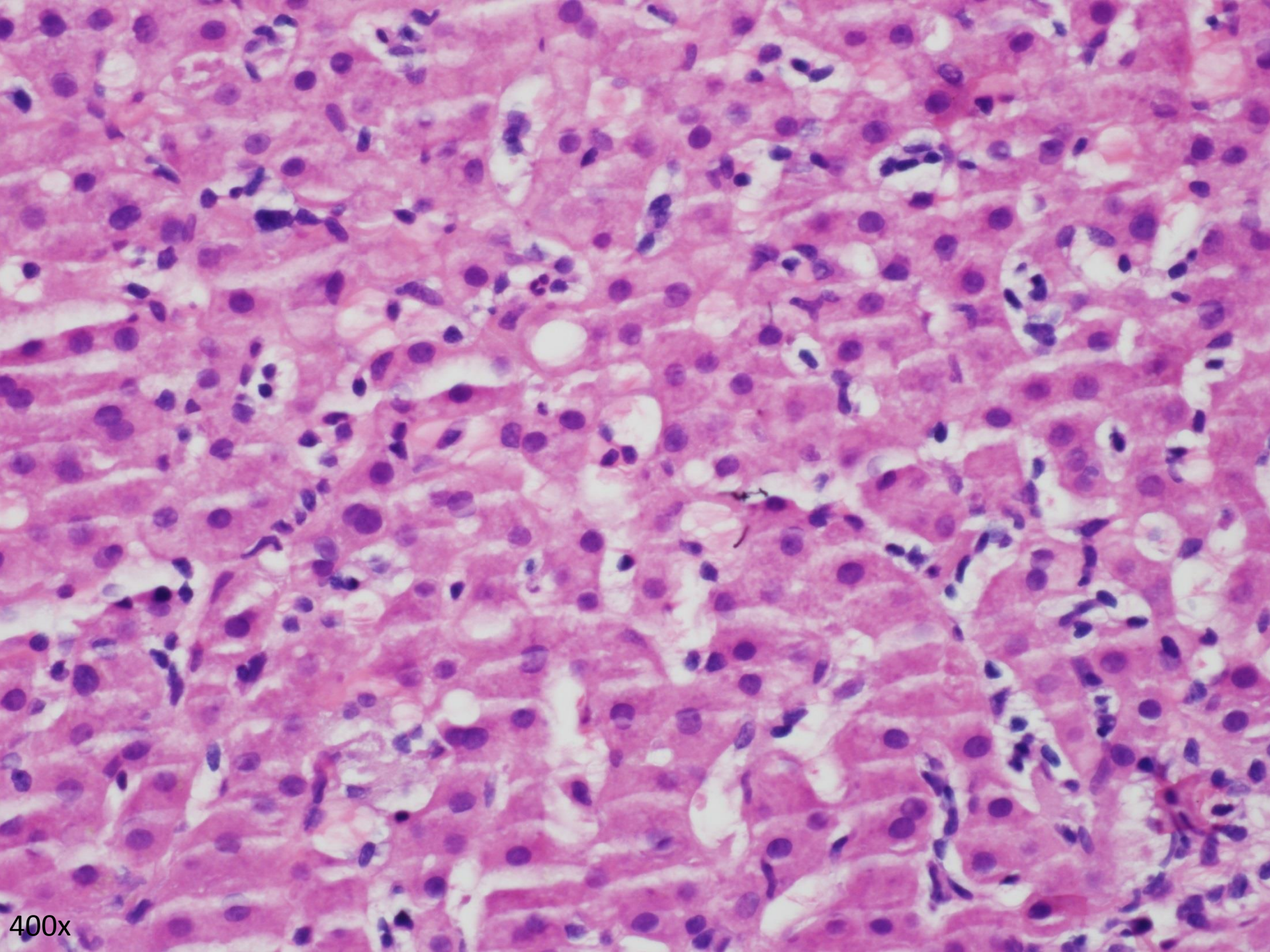
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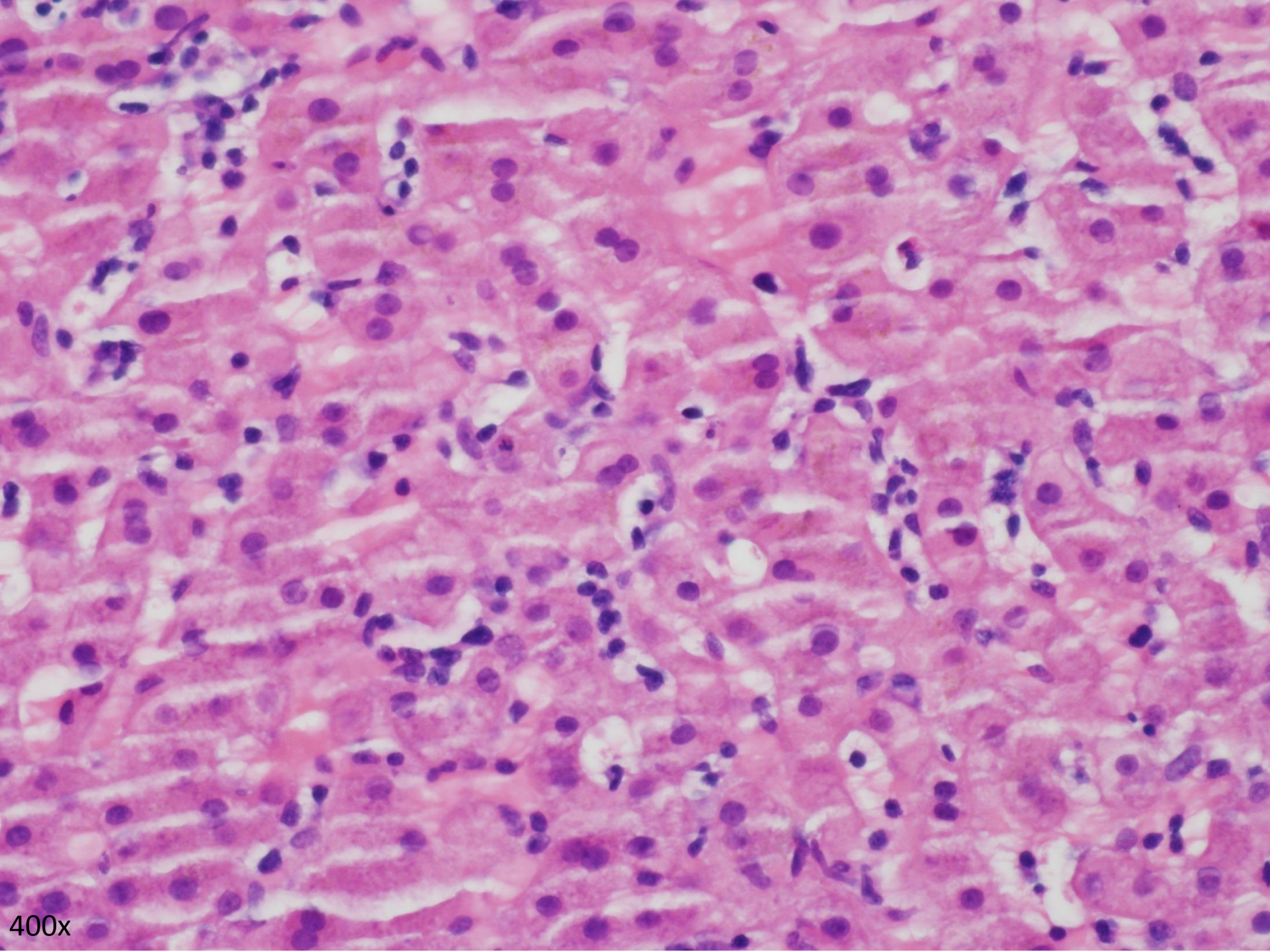
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# HSTL: Immunophenotype

- Typically express CD3, CD2, CD56 (frequent), TCR gamma/delta (alpha/beta in a minority), and cytotoxic granule-associated proteins (TIA1 and granzyme M)
- Typically negative for CD4, CD8 (minority +), CD5 & CD7 (frequent loss), granzyme B, perforin, CD57, CD30

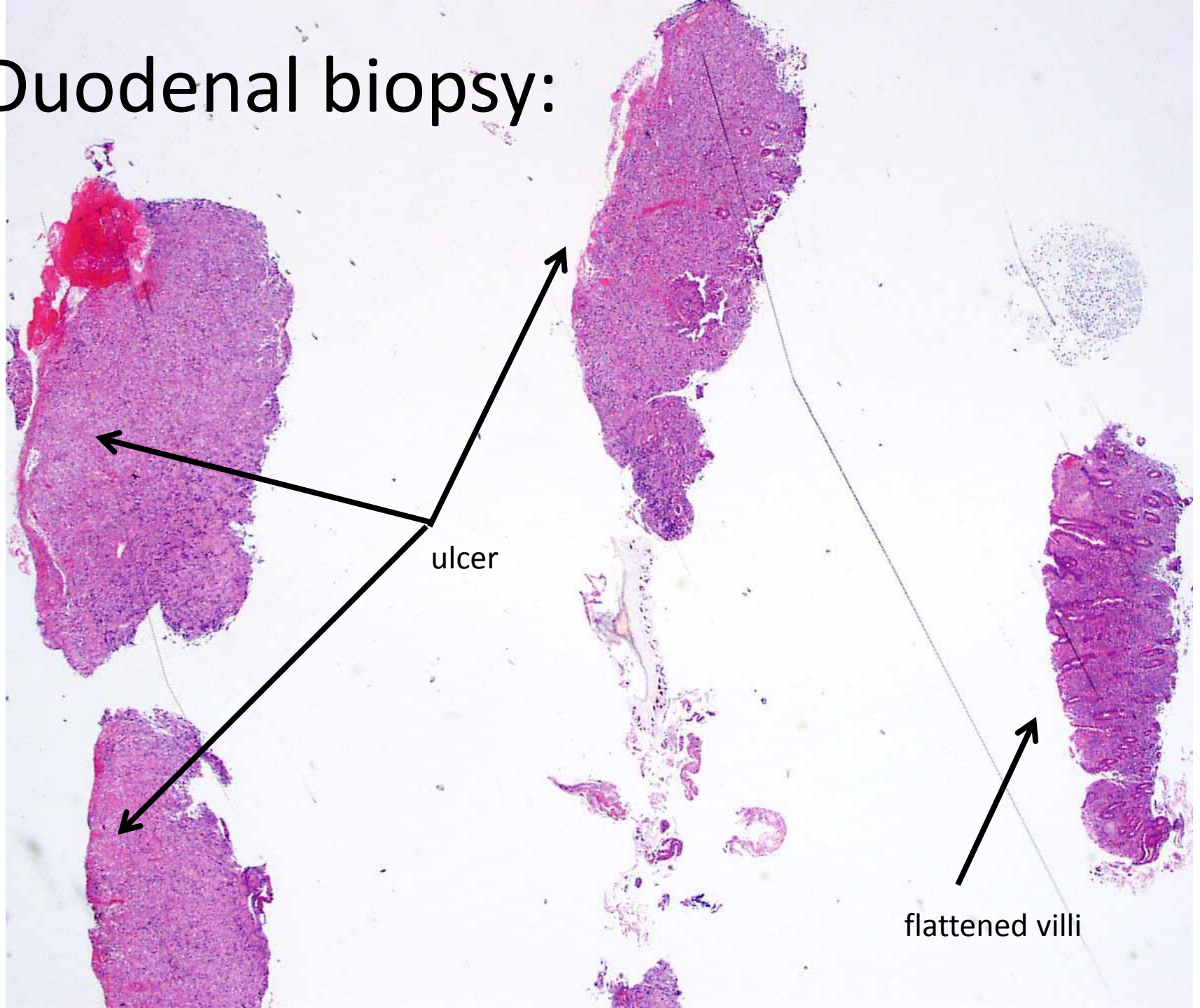
# Approach to Evaluation

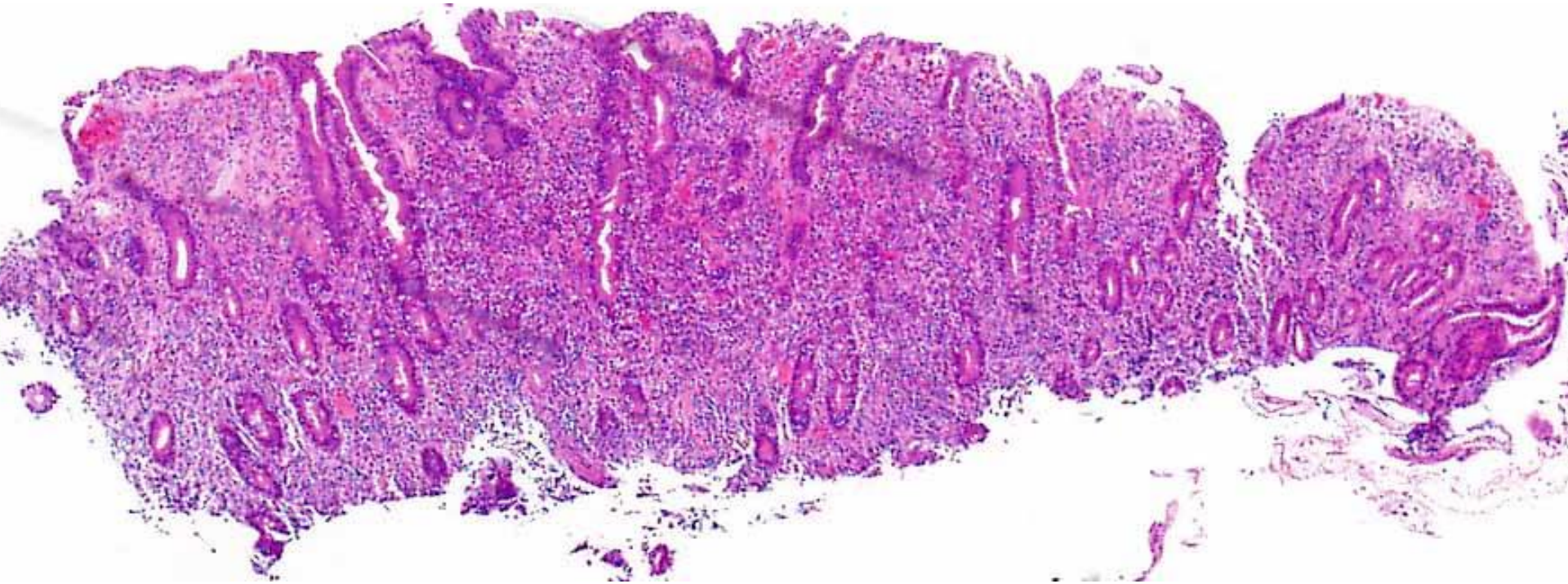
- Careful morphologic evaluation
  - Inflammatory conditions vs Lymphoma vs Another malignancy vs Normal
- Tiered immunostain panels
  - CD20, CD3, CD43
    - Reactive: T-cell predominant, but mixed
    - Aberrant CD43 expression on CD20-positive B-cells: MCL, CLL/SLL, subset of MALTL
    - CD43 expression without CD20 or CD3: possibility of myeloid neoplasm
  - Targeted additional immunos as needed to complete characterization of an entity or exclude others
  - Targeted additional immunos as needed for prognosis or treatment
- Molecular studies for specific gene alterations if needed for diagnostic refinement
- Clonality studies may not be useful
  - Benign reactive populations can have small clones that may amplify erroneously leading to lymphoma diagnosis

# Quick Case Study

- Elderly Caucasian man
- Celiac sprue x 7 years
- Presented with abdominal pain, nausea, and vomiting
- Imaging revealed partially obstructing duodenal mass

# Duodenal biopsy:





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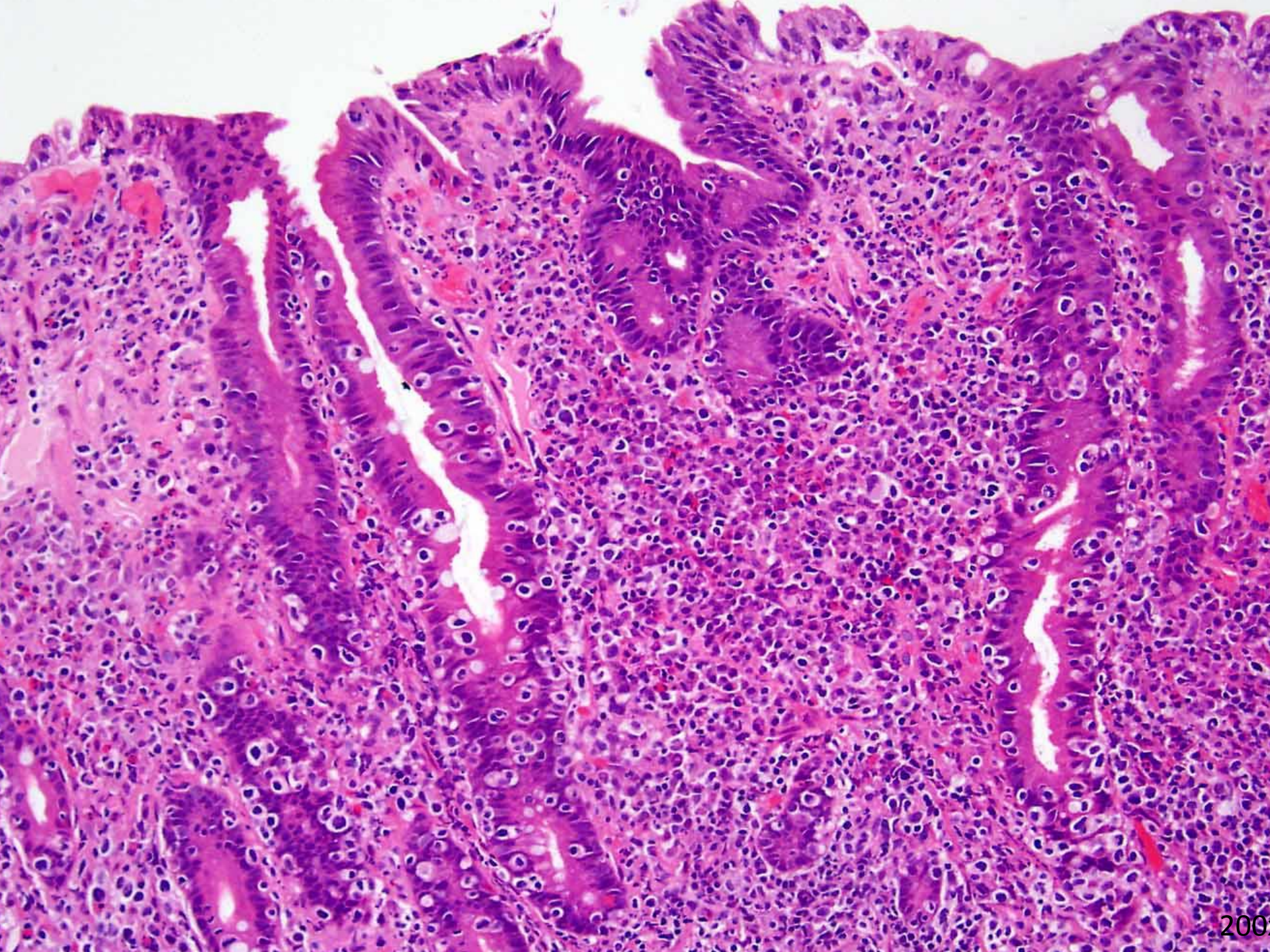
# Low Power DDx

- Gluten-sensitive enteropathy / celiac disease
  - Refractory GSE
  - Collagenous sprue
- Tropical sprue
    - Totally flat mucosa rare in tropical sprue
- Autoimmune enteropathy
- Medication effect
  - NSAIDs
  - Olmesartan
  - Colchicine
  - Mycophenolate mofetil
  - Ipilimumab (anti-CTLA4)
  - Chemotherapy agents
- Inflammatory bowel disease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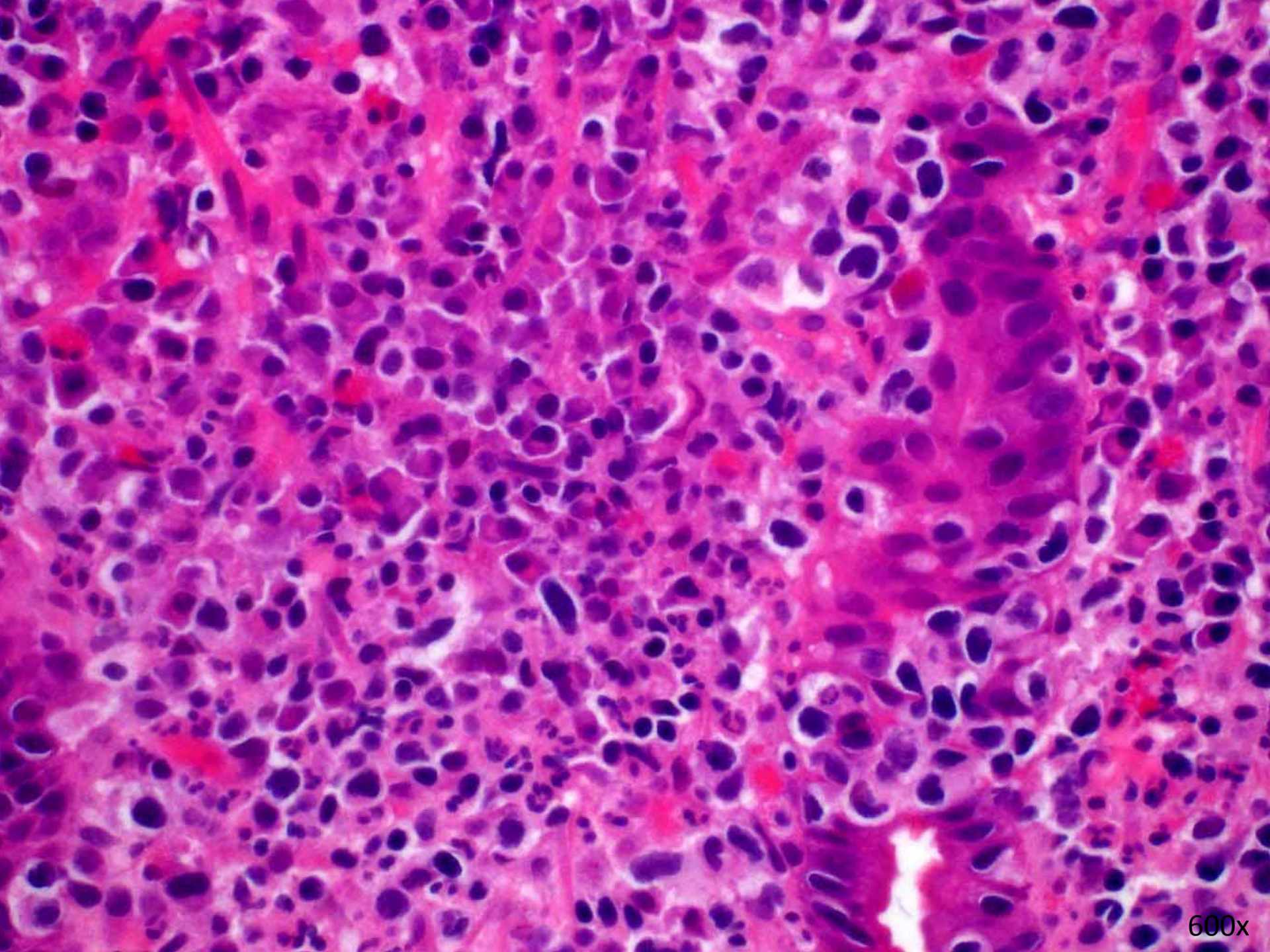
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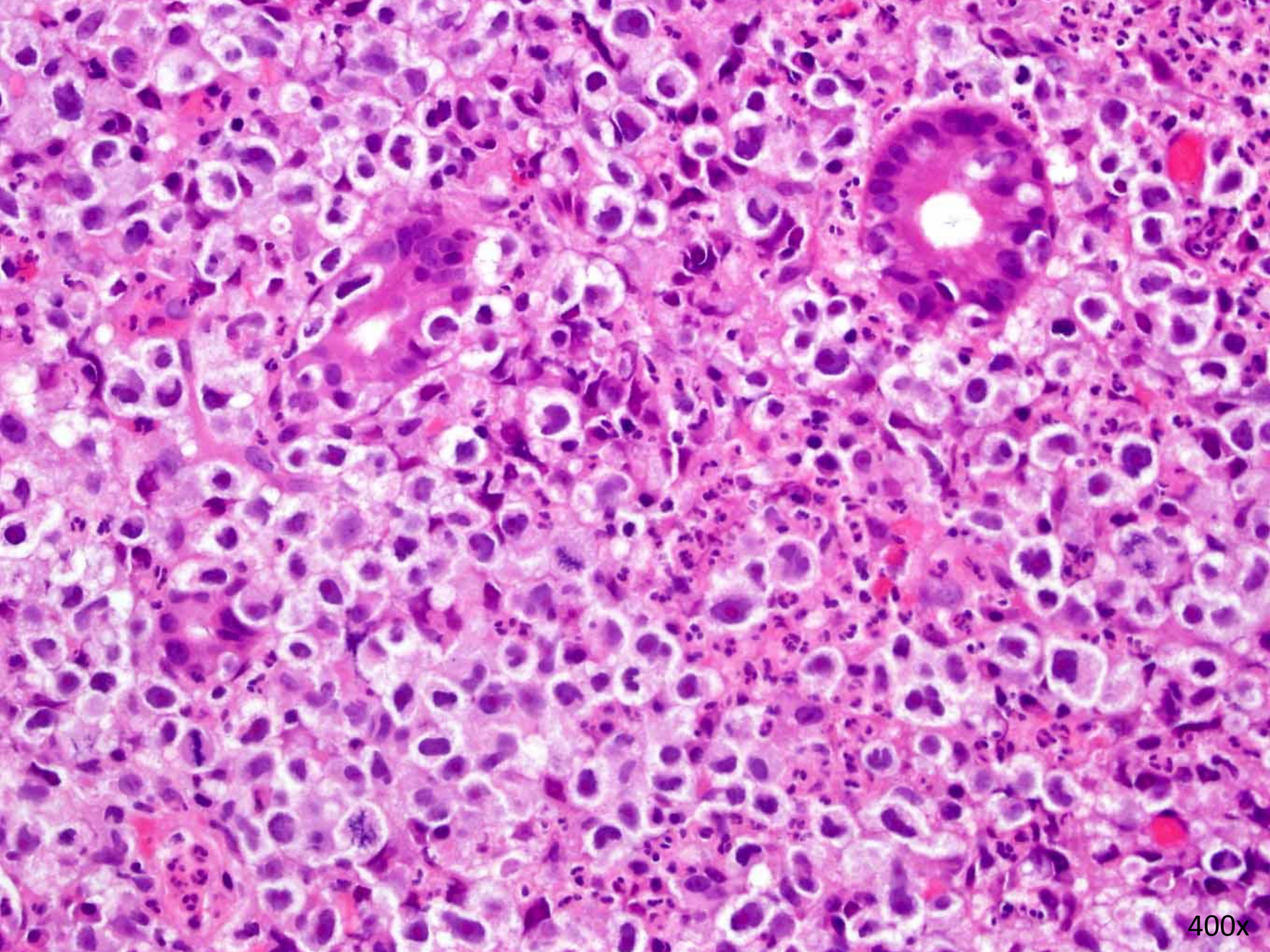
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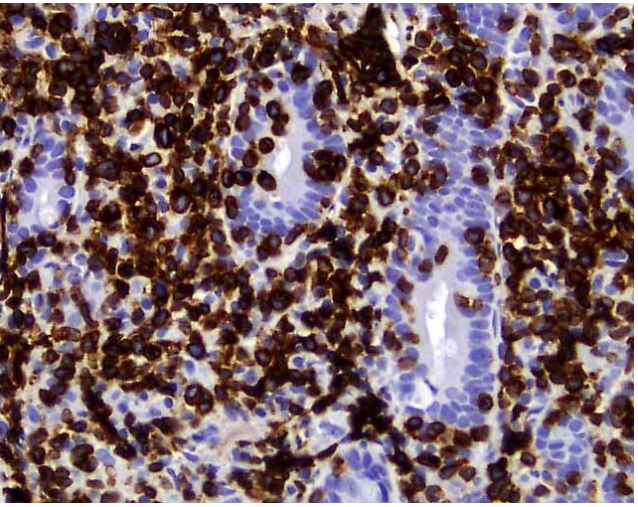
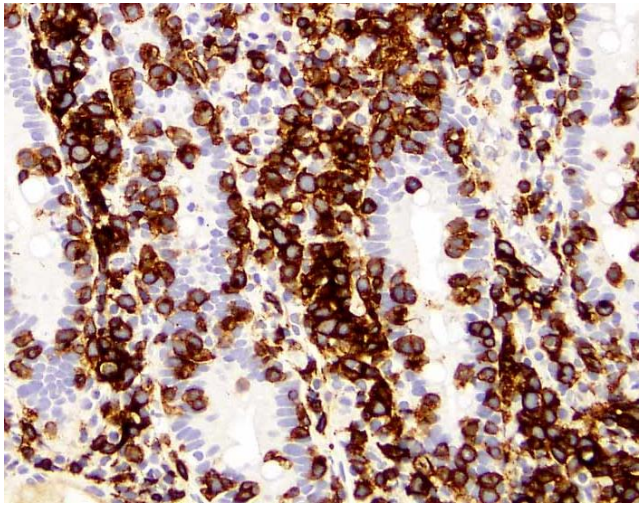
# Immunophenotype

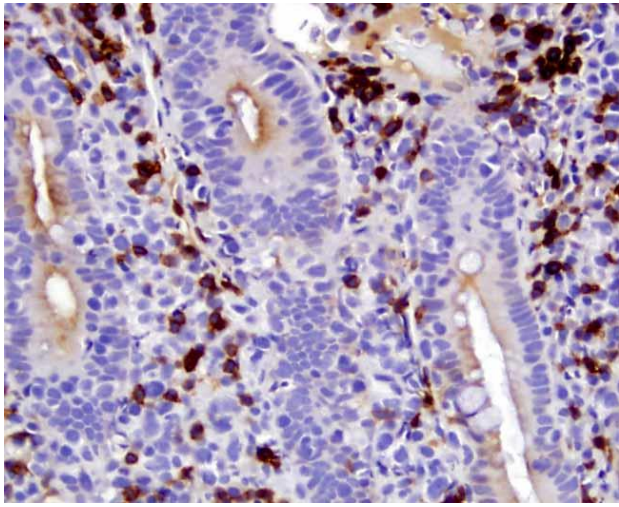
CD3



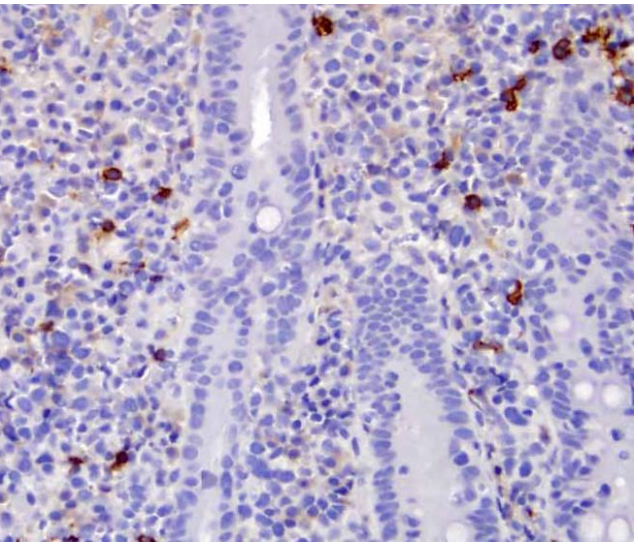
CD8



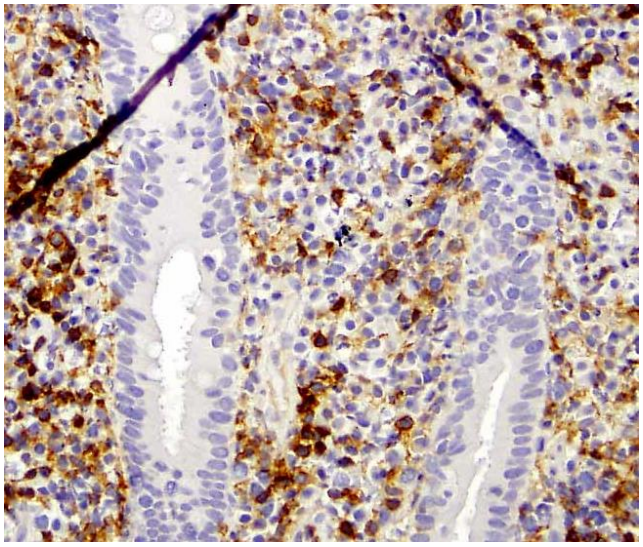
CD5



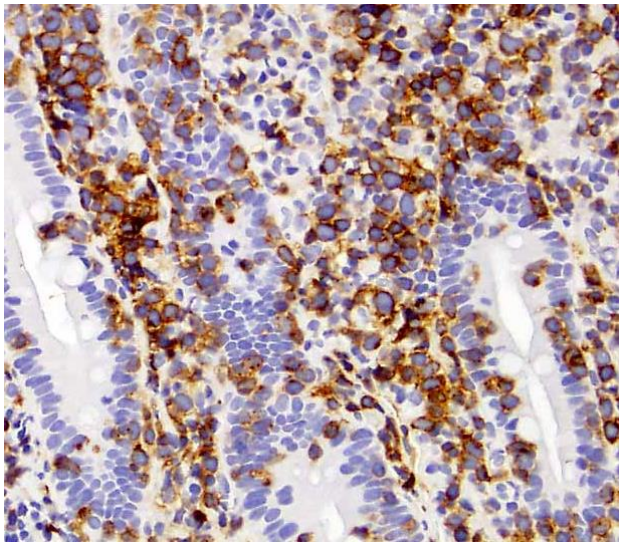
CD56



CD4



CD7



# Diagnosis: EATL

| | **EATL** | **MEITL** |
|---|---|---|
| Frequency | 80-90% | 10-20% |
| Morphology | Variable | Monomorphic small to medium |
| Immunophenotype | | |
| CD8 | Mostly negative (20%+) | Mostly positive (80%+) |
| CD56 | Negative (>90%) | Positive (>90%) |
| HLA-OQ2/-0Q8 | Positive (>90%) | Positive (30-40%) |
| antecedent GSE | present | absent |
| GSE changes in adjacent mucosa | Villous atrophy, crypt hyperplasia, lamina propria lymph- & plasmacytosis, IELs | Villous atrophy, crypt hyperplasia, lamina propria w/o inflammatory background, IELs |

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Questions?