Gastrointestinal Lymphomas

a practical approach to work-up

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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

- **STOMACH**: 50-60%; 5-10% of all gastric malignancies
- **SMALL BOWEL**: 30%; 25% of all small intestinal malignancies
- **COLON**: 10%; 0.5% of colonic malignancies
  - **ESOPHAGUS, APPENDIX, LIVER, GALLBLADDER, PANCREAS**: RARE
# Classic Sites of GI Lymphomas

<table>
<thead>
<tr>
<th>Site</th>
<th>Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>MALT Lymphoma</td>
</tr>
<tr>
<td>2nd portion of duodenum</td>
<td>Primary intestinal follicular lymphoma</td>
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<tr>
<td>Small intestine</td>
<td>EATL</td>
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<tr>
<td>Terminal ileum</td>
<td>Burkitt lymphoma</td>
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<tr>
<td>Colonic polyps</td>
<td>Mantle cell lymphoma (lymphomatous polyposis)</td>
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<tr>
<td>Entire GI tract</td>
<td>DLBCL</td>
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</table>
Evaluation: Clinical clues

• Patient’s age and immune status
  – Young patients have more normal mucosa-associated lymphoid tissue (MALT)
  – Immune system undergoes senescence with age
  – Immunosuppression leads to decreased efficiency of immune surveillance against malignancy
  – Chronic inflammatory conditions (eg. IBD)

• Infection +/- treatment status
Evaluation: Endoscopic clues

• Native and acquired MALT populations
  – Terminal ileum Peyer patches may appear as visible mucosal nodularity or small polyps
  – H. pylori-associated gastritis may appear as normal mucosa or as erythema +/- ulcers
  – Rectal lymphoid hyperplasia (rectal tonsil / rectal lymphoid polyp) may be polypoid and span up to 1cm

• Lymphomas
  – Tend to form mass lesions +/- ulcers +/- perforations, but not always
Evaluation: Histologic clues

- Peyer patch (native MALT)
- Germinal center
- Mantle zone
- Marginal zone
- H. pylori gastritis (acquired MALT)
Evaluation: Ancillary studies

• Immunohistochemical stains
  – Comprehensive panel vs Select stains
    • CD3, CD20 (or Pax5), CD43
  – Important prognostic markers

• Molecular/cytogenetic studies
  – Diagnostic gene rearrangements, specific translocations
  – Immunoglobulin or T-cell receptor gene rearrangements

• Flow cytometry
Evaluation: Additional Complexities

• 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?
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 virus 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
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%)

Expression by at least 30% cells is required for “positivity”
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 WHO2017: 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 conventional DLBCL-like
  - geographic necrosis common

- Usually non-GCB phenotype (CD10-, MUM1+), EBV+
Subtype: EBV+ DLBCL, NOS

• NOS designation excludes specific EBV-associated lymphoma subtypes (Burkitt lymphoma, classical Hodgkin lymphoma, lymphomatoid granulomatosis, primary effusion lymphoma, plasmablastic lymphoma)

• No longer “of the elderly” - Implied suggestion to screen cases with above morphologies for EBV without regard for age
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 MALT associated with *Campylobacter jejuni*, a paraprotein is usually 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)
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

<table>
<thead>
<tr>
<th>MALT lymphoma</th>
<th><em>H pylori</em> gastritis</th>
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<tbody>
<tr>
<td>Mucosal destruction present</td>
<td>Intact architecture with inflammatory infiltrate among pits/glands</td>
</tr>
<tr>
<td>Lymphoepithelial lesions (with B cells)</td>
<td>Epithelial structures intact</td>
</tr>
<tr>
<td>B cells predominate</td>
<td>Mixture of B and T cells</td>
</tr>
<tr>
<td>Deep follicles with colonization</td>
<td>Intact follicles in deep mucosa</td>
</tr>
<tr>
<td>Light chain restriction (if plasmacytic differentiation)</td>
<td>Polytypic plasma cells (kappa/lambda ~ 2:1)</td>
</tr>
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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 MALTL, *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 MALT L 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
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 \textit{IGH} and \textit{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 / distinctively 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
Pleomorphic MCL
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
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
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)
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
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
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<tr>
<th></th>
<th><strong>EATL</strong></th>
<th><strong>MEITL</strong></th>
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<tbody>
<tr>
<td><strong>Frequency</strong></td>
<td>80-90%</td>
<td>10-20%</td>
</tr>
<tr>
<td><strong>Epidemiology</strong></td>
<td>Complication of GSE</td>
<td>Occurs sporadically</td>
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<tr>
<td></td>
<td>associated with HLA-DQ2/DQ8</td>
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<tr>
<td></td>
<td>refractory GSE patients at high risk</td>
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<tr>
<td></td>
<td>Northern Europeans descent</td>
<td>Asian and Hispanic descent</td>
</tr>
<tr>
<td><strong>Morphology</strong></td>
<td>Variable, pleomorphic, intermediate to large cells</td>
<td>Monotonous small to intermediate-sized cells</td>
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<tr>
<td></td>
<td>Angulated nuclei</td>
<td>Round nuclei</td>
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<tr>
<td></td>
<td>Prominent nucleoli</td>
<td>Inconspicuous nucleoli</td>
</tr>
<tr>
<td></td>
<td>Areas of necrosis</td>
<td>Rare necrosis</td>
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<tr>
<td></td>
<td>Variable to heavy background mixed inflammatory infiltrate</td>
<td>Minimal background inflammatory infiltrate</td>
</tr>
<tr>
<td><strong>Immunophenotype</strong></td>
<td>CD3+, CD5-, CD7+</td>
<td>CD3+, CD5-, CD7+</td>
</tr>
<tr>
<td></td>
<td>CD8- (80%)</td>
<td>CD8+ (80%)</td>
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<tr>
<td></td>
<td>CD56- (&gt;90%)</td>
<td>CD56+ (&gt;90%)</td>
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<tr>
<td></td>
<td>nuclear MATK-</td>
<td>nuclear MATK+</td>
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<tr>
<td><strong>Cytogenetics</strong></td>
<td>+9q31.3 or -16q12.1</td>
<td>86%</td>
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<td>83%</td>
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<tr>
<td></td>
<td>+1q32.2-q41</td>
<td>73%</td>
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<td>27%</td>
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<tr>
<td></td>
<td>+5q34-q35.2</td>
<td>80%</td>
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<td>20%</td>
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<tr>
<td></td>
<td>+8q24 (MYC)</td>
<td>27%</td>
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<td></td>
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<td>73%</td>
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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
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
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 Summary

• Careful morphologic evaluation within context of clinical and endoscopic data
  – 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
A parting case

• 42 year old man with HIV and painless anal masses that progressed in size over 3 months
• On sigmoidoscopy, “a field of a mix of large and small nodules”
References: