**Practical Gastrointestinal (and Liver) Pathology**

*Noon Slide Session*

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**Disclosures**

*I have nothing to disclose*

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**Summary**

- Colonic Adenomas
- Hepatocellular Adenomas

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**Colonic Adenomas – Diagnostic Issues**

- “Intramucosal adenocarcinoma” confusion
- Epithelial misplacement/pseudoinvasion vs pT1
- Lymphovascular invasion
- Risk stratification
- Unusual cell clusters
- IBD dysplasia
“intramucosal adenocarcinoma”

- Tumor cells extend through BM into lamina propria, but not through muscularis mucosa
- Single cells, abortive gland formation, marked sheet like growth
- No metastatic risk

Pseudoinvasion

- Misplaced (herniated) epithelium in submucoa
- Most often in pedunculated polyps in sigmoid (~ 86%)
- Usually > 1 cm
- Well circumscribed crypts, lobular architecture
- Surrounding rim of lamina propria
- No desmoplasia
- Hemorrhage/hemosiderin deposition in stroma

Differential diagnosis – Invasive adenocarcinoma, mucinous adenocarcinoma, localized colitis cystica profunda/prolapse

2012 Recommendations for Screening

- No polyps                                          10 years
- Small (<10 mm) HPs in rectum or sigmoid           10 years
- 1–2 small (<10 mm) tubular adenomas              5–10 years
- 3–10 tubular adenomas                            3 years
- >10 adenomas                                      <3 years
- One or more tubular adenomas ≥10 mm              3 years
- One or more villous adenomas                     3 years
- Adenoma with HGD                                 3 years

- Invasion in a pedunculated adenoma               0.5-1 year
- Inadequately removed or large sessile adenoma    2-6 months
**Colectomy?**

Traditional pT1 treatment decisions:
- Colectomy for unfavorable histology (pedunculated), invasion in sessile polyp, invasion beyond stalk into bowel wall
- Unfavorable histology (poorly differentiated, LVI, <1-2 mm from margin), 20-43% recurrence +/- LN mets

**Risk for pT1 tumors**

- Residual local disease (20% in R1 cases)
- Lymph node metastasis (10-15% in high risk cases)
- Distant metastasis (? Increased risk in poorly differentiated tumors)
- Risk is balanced against operative morbidity (age, site, comorbidities) and mortality

**Risk Parameter Table (adapted, USCAP 2013, Prof Kieran Sheahan)**

<table>
<thead>
<tr>
<th>Risk Parameter</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depth of tumor invasion from muscularis mucosa = 0.8 mm</td>
<td>Low</td>
</tr>
<tr>
<td>Tumor width = 2.8 mm</td>
<td>Low</td>
</tr>
<tr>
<td>Kikuchi level = Sm2</td>
<td>Low</td>
</tr>
<tr>
<td>Radial margins = uninvolved</td>
<td>Low</td>
</tr>
<tr>
<td>Deep margin = negative, &gt;1 mm</td>
<td>Low</td>
</tr>
<tr>
<td>Tumor budding level is low</td>
<td>Low</td>
</tr>
<tr>
<td>Lymphovascular invasion present (1 vein only by elastic stain)</td>
<td>High</td>
</tr>
<tr>
<td>Site = rectum</td>
<td>High ?</td>
</tr>
<tr>
<td>Morphology = Sessile Lesion</td>
<td>High ?</td>
</tr>
</tbody>
</table>

**IBD associated dysplasia**

<table>
<thead>
<tr>
<th>Risk</th>
<th>CRC Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic Adenoma/ Adenoma-like DALM</td>
<td>Low</td>
</tr>
<tr>
<td>Non-adenoma DALM</td>
<td>&gt;40%</td>
</tr>
<tr>
<td>Low grade flat dysplasia</td>
<td>20%*</td>
</tr>
<tr>
<td>High grade flat dysplasia</td>
<td>20-50%</td>
</tr>
<tr>
<td>Indefinite for dysplasia</td>
<td>9% (in 5 yrs)</td>
</tr>
</tbody>
</table>

**PRELIMINARY DATA**

<table>
<thead>
<tr>
<th>Risk</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSA-like changes (n=29)</td>
<td>0%</td>
</tr>
<tr>
<td>TSA-like changes (n=30)</td>
<td>77%</td>
</tr>
<tr>
<td>“Hyperplastic polyp with cytologic atypia” (n=19)</td>
<td>53%</td>
</tr>
</tbody>
</table>
Low grade dysplasia in Crohns

Hepatic Adenomas – Diagnostic Issues
- HCA vs FNH
- Subtyping of HCA
- Risk of HCC

Adenoma (HCA) Variants
- **Variant 1**: HNF1α-inactivated HCA
  - **Hallmark**: Fatty change
- **Variant 2**: β-catenin mutated HCA
  - **Hallmark**: Increased risk for HCC
- **Variant 3**: Inflammatory adenoma
  - **Hallmark**: Obesity/metabolic syndrome association
- **Others** (Variant 4 + ?)
  - **Hallmark**: No specific trait

Well Differentiated Lesion Algorithm
- History of a mass -> 1 H&E, 1 reticulin, and 8 unstained on first cut
- Portal tracts?
  - **Yes**
    - Atypia/reticulin abnormalities
      - Yes → early HCC vs partial sampling of HCA → GS, SAA, BC, LFABP, CD34, GPC3
      - No → Mass not sampled or FNH-like lesion → GS
  - **No**
    - Well differentiated hepatocellular lesion
      - FNH features present, no atypia/reticulin abnormalities
        - Yes – FNH vs Inflammatory variant HCA → GS, SAA, BC
        - No – HCA, requires stains for further subclassification → GS, SAA, BC, LFABP
        - If atypia/reticulin abnormalities, w/u early HCC as above
Hepatocellular Adenoma diagnosis

- Cases:
  - HCA, inflammatory variant
  - Focal nodular hyperplasia
  - HCA, HNF1 alpha inactivated variant
  - HCA, beta catenin mutated variant
  - HCC arising in HCA
**Current Risk Stratification**

- Low risk (no resection needed) – 40% of cases
  - No LVI
  - Moderately to well differentiated
  - No tumor budding

- "High risk"/"unfavorable histology" (... it depends) – 60% of cases
  - LVI present, poorly differentiated, and tumor budding present warrants immediate surgery if possible
  - One or two risk factors present = uncertainty!
  - In high risk cases that go to surgery ~80% of patients will have no residual tumor or metastasis

**Risk Factor Quantitation**

- Semi-quantitative
  - Haggitt level (0-4) - pedunculated
  - Kikuchi level (sm1-3) – non-polypoid

- Quantitative
  - Depth of tumor invasion
  - Tumor width
  - Distance from resection margin

**Pseudoinvasion**
Pseudoinvasion?

Colonic Adenoma
- Cases
  - Tubular adenoma with pseudoinvasion
  - Localized Colitis Cystica Profunda/prolapse
  - Tubular adenoma with invasive adenocarcinoma
  - Colorectal dysplasia (IBD associated)

Sinusoidal Infiltrates
- Case
  - Primary DLBCL, sinusoidal predominant
Primary Hepatic Lymphoma

- Rare diagnosis (0.06% of NHL)
- Wide age range, M:F (2:1)
- Hepatomegaly is common
- Mild transaminitis may be present, jaundice rare
- Solitary mass, multinodular, or diffuse
- DLBCL, Burkitt lymphoma, MALT lymphoma, LPL, Follicular lymphoma, and PTCL most common

Primary Hepatic Lymphoma

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- Mild transaminitis may be present, jaundice rare
- Solitary mass, multinodular, or diffuse
- DLBCL, Burkitt lymphoma, MALT lymphoma, LPL, Follicular lymphoma, and PTCL most common

Differential Diagnosis

<table>
<thead>
<tr>
<th>Lymphoid neoplasms</th>
<th>Reactive infiltrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinusoidal distention/cells pile up</td>
<td>Single mature lymphoid cells</td>
</tr>
<tr>
<td>Cytologic atypia</td>
<td>Mixed acute and chronic inflammation</td>
</tr>
<tr>
<td>Aberrant T-cell antigen loss</td>
<td>Viral type injury</td>
</tr>
<tr>
<td>Hemophagocytosis</td>
<td>EBER in rare B-cells</td>
</tr>
<tr>
<td>EBER positive tumor cells</td>
<td>Other liver disease findings</td>
</tr>
<tr>
<td>Geographic necrosis</td>
<td>TCR PCR negative</td>
</tr>
</tbody>
</table>

Sinusoidal Infiltrate

- Diffuse large B-cell lymphoma
- Follicular lymphoma
- EBV positive LPD of childhood
- Mantle cell lymphoma
- Peripheral T-cell lymphoma, NOS
- PTLD
- T-cell LGL leukemia

Sinusoidal Involvement

<table>
<thead>
<tr>
<th>Mature B-cell neoplasms</th>
<th>Mature T- and NK-cell neoplasms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkitt lymphoma</td>
<td>Adult T-cell leukemia/lymphoma</td>
</tr>
<tr>
<td>B-cell prolymphocytic leukemia</td>
<td>Aggressive NK cell leukemia</td>
</tr>
<tr>
<td>CLL/SLL</td>
<td>Anaplastic large cell lymphoma</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>Angioimmunoblastic T-cell lymphoma</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>EBV positive LPD of childhood</td>
</tr>
<tr>
<td>Hairy cell leukemia</td>
<td>Hepatosplenic T-cell lymphoma</td>
</tr>
<tr>
<td>Lymphomatoid granulomatosis</td>
<td>Other γδ T-cell lymphomas</td>
</tr>
<tr>
<td>Lymphoplasmacytic lymphoma</td>
<td>Mycosis fungoides/Sezary syndrome</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>Peripheral T-cell lymphoma, NOS</td>
</tr>
<tr>
<td>Marginal zone lymphoma (MALT)</td>
<td>PTLD</td>
</tr>
<tr>
<td>PTLD</td>
<td>T-cell LGL leukemia</td>
</tr>
</tbody>
</table>
Atypical Sinusoidal Infiltrate

Pitfalls

- Ductopenia due to lymphoma
- EBV hepatitis
- Atypical lymphoid infiltrates in a hepatocellular lesion
Hepatocellular Adenoma
Inflammatory Variant

Key Points
- Reactive infiltrates are common in the liver, most are benign
- Correlate with background GI and liver disease findings
- Cytologic atypia an important clue
- Immunohistochemical evaluation
- Molecular testing as needed
Duodenum Benign MALT

CD20

CD3
Small Intestine Follicular lymphoma

CD20

CD3

CD10
BCL6

CD21

CD43

BCL2
Low grade (grade 2, scale 1-3)
Approach to Sinusoidal Infiltrates

- Sinusoidal infiltrate cell type?
- Out of proportion to primary liver disease?
- Cytologic atypia?
- Immunophenotype?
- Molecular testing if still uncertain.

Sinusoidal Infiltrate – Cell Type

- Granulocytes/ immature myeloid
- Macrophages
- Blasts
- Mature lymphoid cells

Sinusoidal Infiltrate – Cell Type

- Granulocytes/ immature myeloid
  - MPN
  - Leukemoid reaction
  - Surgical effect
- Macrophages
- Blasts
- Mature lymphoid cells
Myeloid Proliferation related to Down Syndrome
Transient Abnormal Myelopoiesis

Extramedullary Hematopoiesis in Polycythemia Vera

Extramedullary Hematopoiesis in Polycythemia Vera

MPN/MDS
Sinusoidal Infiltrate – Cell Type

- Granulocytes/myeloid
- Macrophages
- Immunologic (HLH)
- Infectious (Histoplasmosis, Cryptococcus, visceral leishmaniasis)
- Storage disorders (Gaucher disease, Niemann-Pick disease, etc)
- Blasts
- Mature lymphoid cells

Niemann-Pick Disease

Organisms

Gill RM et al. Macrophage Infiltrate, Ch 18 Liver Pathology, eds Linda Ferrell and Sanjay Kakar, Demos 2011
**Amastigotes of Visceral Leishmaniasis**

*Gill RM et al. Macrophage Infiltrate, Ch 18 Liver Pathology, eds Linda Ferrell and Sanjay Kakar, Demos 2011*

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**Sinusoidal Infiltrate – Cell Type**

- Granulocytes/myeloid
- Macrophages
- Blasts
  - ALL
  - AML
  - CML blast crisis
- Mature lymphoid cells

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**Suspicious Sinusoidal Infiltrate**

**Lymphoblasts**
**Sinusoidal Infiltrate – Cell Type**

- Granulocytes/myeloid
- Macrophages
- Blasts
- Mature lymphoid cells
  - Reactive infiltrate
  - B-cell neoplasms
  - T-cells/NK cell neoplasms

**Mature T and NK cell Neoplasms**

- Hepatosplenic T-cell lymphoma
- Aggressive NK cell leukemia
- EBV positive T cell lymphoproliferative disorder of childhood
- Peripheral T cell lymphoma, NOS
**Hepatosplenic T-cell lymphoma**

- Rare, <5% of PTCL, median age 35, male>female
- Medium sized lymphoid cells
- Marked sinusoidal infiltration/expansion of liver, spleen and bone marrow
- 20% arise in setting of chronic immune suppression or in patients treated with azathioprine and infliximab for Crohn's disease

**Atypical Sinusoidal T-cells**

- CD3+, CD2+, TIA-1+, CD7+/−, CD56+/−
- CD4−/CD8− (or CD4−/CD8+)
- CD5−, TCRβF1−, granzyme B−, CD25−, CD30−
- Typically a large TCRγ clone by PCR and EBER is negative
- Recurrent cytogenetic abnormality (i7q)
- Aggressive disease with early relapse
**Aggressive NK Cell Leukemia**

- Similar presentation to HSTL and fulminant course
- NK cell neoplasm with a leukemic component
- CD2+, cCD3+, CD56+, TIA-1+. Granzyme B +
- T-cell markers negative (sCD3, CD5, CD4, CD8, TCRβF1, CD7)
- EBER positive, TCR genes germline
- Hemophagocytosis

**Atypical Sinusoidal Infiltrate**

- Clonal EBV infected T-cell proliferation, often in children and young adults
- Geographic predisposition (most prevalent in Asia and Latin America)
- Aggressive clinical course with hemophagocytic syndrome, multiple organ failure, and sepsis
- Liver and spleen usually involved
- Rare form presents in “elderly” with generalized lymphadenopathy and usually HBV or HCV infection
**EBV positive T-cell LPD of childhood**

- Sinusoidal and portal infiltration by medium sized cells
- Erythrophagocytosis, necrosis, steatosis, and cholestasis
- CD3+, CD2+, CD5+, TCRβF1+, TIA-1+, granzyme B+, CD8+/-, CD4+/-, CD56-
- EBER ISH is positive
- TCRγ clone can be demonstrated by PCR

**Peripheral T-cell lymphoma, NOS**

- Monomorphous lymphocytes with dark smudgy chromatin and cleared out cytoplasm
- Portal based with focal extension into liver parenchyma along sinusoids
- Histiocytes and other inflammatory cells may be present.
- Usually CD3+, CD4+, TCRβF1+, CD8-, CD56-, CD30-
- Aberrant immunophenotype: CD7/CD5/ and/or CD2 loss
- Typically a large TCR clone by PCR and EBER is negative by ISH
Portal and Sinusoidal Infiltrate

Large Atypical Lymphoid Cells

Summary

Colonic Adenomas
Extranodal B-cell lymphoma
Hepatocellular adenomas
Primary hepatic lymphoma

Part 1
GI

Part 2
Liver
References


Ferrell, LD, Kakar S, eds. Liver Pathology, Consultant Pathology Series. Demos Medical, New York, 2011


Purtilo DR et al. EBV associated lymphoproliferative disorder. Lab Invest 1992;66:5-23

Swerdlow SH, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC, Lyon 2008


Differential Diagnosis

T-cell Large Granular Lymphocytic Leukemia

- Indolent/assymptomatic, cytopenia, autoimmune disease
- LGL increased in peripheral blood
- CD2+, CD3+, CD5w+, CD7+, CD8+CD4-, CD56+/- TCRβ F1+, granzyme B+
- TCRγ rearranged
Large Atypical Lymphoid Cells