Hepatic Lymphoma Diagnosis
An Algorithmic Approach
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Why the Hepatopathologist?
- When to initiate work-up for a lymphoproliferative disorder
- Hepatic lymphoma may mimic a liver tumor
- Hepatic lymphoma may mimic medical liver disease

Challenges for the Hepatopathologist
- Hematopathology is rapidly evolving and diagnosis integrates morphologic, immunophenotypic, and cytogenetic/molecular data.
- The classification scheme allows for significant immunophenotypic variability
- Limited tissue may be available in a liver biopsy once a lymphoproliferative disorder is detected
Outline

1. What is an atypical lymphoid infiltrate in the liver?
2. How to diagnose EBV hepatitis.
3. Approach to the significant sinusoidal infiltrate.
4. Primary hepatic lymphoma.

Atypical Hepatic Lymphoid Infiltrate

- Normal
- Portal Effacing/Destructive
- Sinusoidal

Effacing/Destructive

CD20

Large Cells in the Sinusoids

CD20
Which is lymphoma?

Primary Hepatic MALT lymphoma

Atypical Cytologic Features

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<th>Feature</th>
<th>Description</th>
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<td>Large cells</td>
<td>Hemophagocytosis</td>
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<td>Piling up in sinusoids</td>
<td>Ductopenia</td>
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<td>Increased mitotic figures</td>
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<td>Atypical mitotic figures</td>
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<td>Prominent nucleoli</td>
<td>Granulomas</td>
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Atypical Cytologic Features

Mitotic Activity

Nuclear Atypia/ Nucleoli

Hemophagocytosis

Atypical Cytologic Features

Piling up in Sinusoids

Fibrin Ring Granuloma

Extramedullary Hematopoiesis in Polycythemia Vera

Megakaryocyte

Erythroid Precursors
Geographic Necrosis

EBV Hepatitis

- EBV typically infects B-cells
- Usually only a mild sinusoidal lymphohistiocytic infiltrate without necrosis or atypia
- Non-necrotizing granulomas (and rarely, fibrin ring granulomas) may be present
- Lineage markers important in establishing the diagnosis

EBV Case #1

- 17 year old obese male with a persistent mild elevation in LFTs. Abdominal ultrasound demonstrates an enlarged liver, no lesions identified. HCV PCR is negative. ANA negative. SMA negative. IgG normal.
- Recent labs:
  - AST 33 U/L
  - ALT 49 U/L
  - ALK 67 U/L
  - T bili 1.4 mg/dL
EBV Case #2

- 21 year old female with splenomegaly, hepatomegaly, and thrombocytopenia and elevated liver enzymes. No history of immune suppression. Underwent liver biopsy and received a diagnosis of EBV hepatitis.
- Treated with 4 cycles of rituximab, due to clinical concern for hemophagocytic syndrome, and returns with similar symptoms after 1 year (AST and ALT ~200 U/L with thrombocytopenia, but still a normal ferritin, hemoglobin, and neutrophil count), undergoes a second liver biopsy. Clonality testing negative.
The Significant Sinusoidal Infiltrate
What next?

Blast Morphology

Caution in TdT Interpretation

Pax5 TdT

Sinusoidal: Large Cells
- Differential diagnosis
  - DLBCL
  - ALCL
  - PTLD
- CD20, PAX5, CD3, CD30, and EBER, then stain for ALCL (e.g. CD4, EMA, ALK) or DLBCL (e.g. CD10, BCL6, MUM1)

Sinusoidal: Small/Intermediate cells
- Differential diagnosis
  - HCL
  - PTLD
  - ANK
  - CAEBV
  - HSTCL
  - Other cytotoxic T cell lymphoma
  - T-LGL
- CD20, PAX5, CD3, CD5, CD56, and EBER
What if it is not Sinusoidal?

- Broad differential diagnosis
- Assess for a predominant lineage
- EBER ISH
- Additional immunohistochemical stains may be needed
- Clonality testing (Kappa/lambda ISH, BCR PCR, TCR PCR)
- Consider bone marrow/peripheral blood evaluation

Primary Hepatic Lymphoma

- Rare
- DLBCL and PTLD are most common diagnoses
- Older men, solitary mass, longer survival than systemic lymphoma with hepatic involvement
- May present as hepatomegaly and no discrete mass (predominant sinusoidal infiltrate)
- No clear association with viral infection

Algorithm?

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