Sinusoidal Infiltrates in the Liver

Ryan M. Gill, M.D., Ph.D.
Assistant Professor
Department of Pathology

Diagnostic Issues

- Reactive infiltrates are common and may raise concern for lymphoma
- Lymphoid neoplasms with sinusoidal involvement are rare and are often confused with hepatitis or missed
- Liver biopsy may allow for primary diagnosis of an infection or myeloid lesion if the sinusoidal infiltrate is carefully evaluated

Disclosures

I have nothing to disclose
**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**

- Erythroid Precursors
- Megakaryocyte
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

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

Amastigotes of Visceral Leishmaniasis

Sinusoidal Infiltrate – Cell Type

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

Suspicious Sinusoidal Infiltrate
**Sinusoidal Infiltrate – Cell Type**

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

**Reactive T cell Infiltrate**

- Reactive infiltrates consist of small mature T-cells
- PTCL may have piling up in sinusoids
- Viral hepatitis may cause hepatocellular damage (e.g. spotty necrosis (e.g. HCV) or neutrophil microabscesses (e.g. CMV))
- A normal immunophenotype does not exclude T-cell lymphoma
- Gene rearrangement studies can be helpful in confirming a diagnosis of lymphoma
Sinusoidal Infiltrate

Hepatic Lymphomas

<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>
**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 γ/δ 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>

**Primary Hepatic Lymphoma**

- Rare diagnosis (0.06% of NHL)
- Wide age range, M:F (2:1), B-symptoms, RUQ pain, or asymptomatic
- Hepatomegaly is common
- Mild transaminitis may be present, jaundice rare
- Immune dysfunction or chronic infection (e.g. HCV)
- Solitary mass, multinodular, or diffuse
- DLBCL, Burkitt lymphoma, MALT lymphoma, LPL, Follicular lymphoma, and PTCL most common

**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**

**EBV positive T-cell LPD of childhood**

- 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

EBV+ T-cell Lymphoproliferative Disorder of Childhood

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**

**Differential Diagnosis**

<table>
<thead>
<tr>
<th>T and NK cell 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>

**Pitfalls**

- Ductopenia due to lymphoma
- EBV hepatitis
- Atypical lymphoid infiltrates in a hepatocellular lesion
Artery

No Interlobular Bile Duct!

Cholestasis & Atypical Sinusoidal Infiltrate

CD3
Prolonged Transaminitis Following Acute Viral Illness

T-cell Lymphoma Associated Vanishing Bile Duct Syndrome
EBER ISH +

EBV Hepatitis

Atypical Sinusoidal Infiltrate?

Hepatocellular Adenoma
Inflammatory Variant

Key Points
- Sinusoidal infiltrates are common, most are benign
- Correlate with background liver disease findings
- Cytologic atypia
- Immunohistochemical evaluation
- Molecular testing
References


Differential Diagnosis

T-cell Large Granular Lymphocytic Leukemia
- Indolent/asymptomatic, cytopenia, autoimmune disease
- LGL increased in peripheral blood
- CD2+, CD3+, CD5w+, CD7+, CD8+, CD56+/-, TCRβF1+, granzyme B+
- TCRγ rearranged
Portal Involvement

Large Atypical Lymphoid Cells