176 Liver Biopsy Evaluation: A Novel Approach To Arriving at Differential Diagnosis

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Liver biopsies show various histologic features that most often involve both the portal tracts and parenchyma. The pathologist, for instance, may see a liver biopsy demonstrating portal lymphocytic infiltrates, atypical bile ducts, mild lobular inflammation, and mild fatty change. Many liver diseases can show these individual features, yet only a few show most or all of the features together. This session will discuss the most common liver histology in table format and how the information acquired from these tables can be used in arriving at differential diagnoses. The session will also show the attendees how pertinent clinical and laboratory correlation can help arrive at the most probable diagnosis. A general review of liver pathology highlighting these pertinent histologic features will be presented.

- Identify the various morphologic features in the portal tracts and parenchyma seen in liver biopsy material
- Arrive at likely diagnoses and differential possibilities using access to specific tables that list the various liver diseases that show these individual features
- Assess the pertinent clinical and laboratory data to arrive at a most probable clinical-pathologic diagnosis

FACULTY:

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Practicing Pathologists
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Surgical Pathology (GI, GU, Etc.)
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Liver Biopsy Evaluation: A Novel Approach to Arriving at Differential Diagnoses

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Disclosure

In compliance with the ACCME and ASCP expectations of CME that is independent from commercial influence or bias, I disclose my relevant financial relationships below:

Lead author of Atlas of Liver Pathology 3e
Elsevier publisher, 2011

Objective and goals of this session

• This session addresses the use of tables at arriving at differential diagnoses in liver biopsy interpretation.
• Use of tables is a useful adjunct in helping solve diagnostic problems. For example, if a Mallory body is present on liver biopsy, it is quite useful to refer to a table listing all of the liver diseases associated with Mallory bodies.
• We often signal out, however, only one morphologic feature and don’t give others much importance. Are other features significant as well?
  – For example, in this same biopsy, is a portal or lobular lymphocytic infiltrate important in diagnoses, or are those features rather insignificant?
  – Does the presence of a granuloma as well entirely change the diagnostic possibilities, or not?
Objective and goals of this session

- Why not note and list all of the morphology seen on biopsy, whether we initially feel those features are important or not?
- After all of the features are listed, not giving any significance of one over the other, the pathologist can refer to specific tables addressing each of these features, these tables listing the various diseases associated with that particular histology.
- By reviewing all of the tables, the pathologist can then arrive at a possible diagnosis with differentials by noting the diseases listed more than once.
- A final diagnosis can then be made after pertinent clinical and laboratory information is integrated.

Objective and goals of this session

- This session addresses this approach, with the use of tables in a more objective rather than subjective way.
- The session will be presented as follows:
  - Review of the anatomy and histology of the normal liver
  - Review of the numerous tables, with histologic examples, that list liver diseases that frequently (in italics) as well as less commonly show specific histological features
  - Show four examples demonstrating how the tables work together in arriving at diagnoses and differential possibilities
  - Briefly discuss the corresponding liver disorders for each of these examples

Gross Anatomy of Normal Liver
Three-Dimensional Architecture

Lobule with terminal hepatic (central) venules

Hepatic lobule

Terminal hepatic (central) venules

Portal tract

Normal Liver

- Portal Tracts
  - Bile ducts
  - Hepatic arteriole
  - Portal venule
  - Fibroconnective tissue framework
Normal Liver

- Parenchyma
  - Hepatic cords
  - Sinusoids
  - Kupffer/Endothelial cells
  - Terminal (central) hepatic venules

Histological features
(Table format*)

<table>
<thead>
<tr>
<th>Portal Tracts</th>
<th>Parenchyma and Vessels</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Portal Lymphocytes</td>
<td>10. Lobular Necrosis with Inflammation</td>
</tr>
<tr>
<td>2. Portal Neutrophils</td>
<td>11. Lobular Necrosis with Minimal to Absent Inflammation</td>
</tr>
<tr>
<td>8. Bile Ducts: Periductal Fibrosis</td>
<td>17. Pigments</td>
</tr>
<tr>
<td>21. Vessels (Excluding Sinusoids): Thrombosis, Occlusion</td>
<td></td>
</tr>
</tbody>
</table>


Portal Lymphocytes

- Acute viral hepatitis, HCV
- Chronic viral hepatitis, HCV
  Periportal interface activity ("piecemeal" necrosis)
Table 1 - Portal Lymphocytes

- Allograft, acute (cellular) rejection
- Alcoholic cirrhosis
- Autoimmune hepatitis
- Biliary atresia, extrahepatic
- Brucellosis
- Caroli disease
- Chronic granulomatous disease of childhood
- Cytomegalovirus
- Epstein-Barr virus
- Extrahepatic bile duct obstruction, late stage
- Graft versus host disease
- Idiopathic adulthood ductopenia
- Indian childhood cirrhosis
- Inflammatory bowel disease
- Lassa fever
- Leukemic, lymphocytic
- Lymphoma, Hodgkin’s (non-tumor liver) and non-Hodgkin’s
- Non-alcoholic steatohepatitis
- Non-specific reactive hepatitis
- Polycythemia vera
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Q fever
- Rheumatoid arthritis
- Rocky Mountain spotted fever
- Sarcoidosis
- Sepsis
- Specific reactive hepatitis
- Wilson disease
- Yellow fever

1 Periportal interface inflammation in active stage of disease

Table 2 - Portal Neutrophils

- Alcoholic hepatitis
- Allograft, acute (cellular) rejection
- Autoimmune hepatitis
- Biliary atresia, extrahepatic
- Caroli disease
- Choleodochal cyst (associated bile duct obstruction)
- Churg-Strauss syndrome
- Cystic fibrosis
- Extrahepatic bile duct obstruction, early and mid stages
- Hepatic vein phlebitis
- Hyperalimentation (TPN), infants
- Impaired bile syndrome
- Polycythemia rubra
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Pulmonary embolism
- Reactive changes, bacterial infections
- Recurrent pyogenic cholangiohepatitis
- Sepsis, secondary
- Toxic shock syndrome
- Tuberculosis (severe)
Autoimmune hepatitis

Table 3 - Portal Plasma Cells

- Acute viral hepatitis, HAV
- Allograft, acute (cellular) rejection
- Autoimmune hepatitis
- Chronic granulomatous disease of childhood
- Chronic viral hepatitis, HBV
- Chronic viral hepatitis (other than HBV)
- Echinococcosis (hydatid cyst)
- Epstein-Barr virus
- Hodgkin’s lymphoma (non-tumor liver)
- Leishmaniasis
- Multiple myeloma
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Q fever
- Visceral larva migrans
- Waldenström’s macroglobulinemia
- Wilson disease

Portal Eosinophils

Allograft, acute (cellular) rejection
Table 4 - Portal Eosinophils

- Parasitic infestations
  - Ascariasis
  - Capillariasis
  - Clonorchiasis
  - Echinococcosis (hydatid cyst)
  - Enterobiasis
  - Fascioliasis
  - Schistosomiasis (early)
  - Strongyloides
  - Visceral larva migrans
- Acute fatty liver of pregnancy
- Allograft, acute (cellular) rejection
- Churg-Strauss syndrome
- Eosinophilic gastroenteritis
- Epstein-Barr virus
- Hodgkin's lymphoma (non-tumor liver)
- Hypereosinophilic syndrome
- Polyarteritis nodosa
- Primary sclerosing cholangitis
- Primary biliary cirrhosis
- Recurrent pyogenic cholangiohepatitis

Table 5 - Portal Fibrosis, Cirrhosis

- Alcoholic cirrhosis
- Alcoholic hepatitis
- Alpha-1-antitrypsin deficiency
- Autoimmune hepatitis (cholangitis)*
- Autoimmune hepatitis
- Biliary atresia, extrahepatic *
- Cystic fibrosis *
- Extrahepatic bile duct obstruction, late stage *
- Erythrohepatioprotoporphyria
- Hereditary hemochromatosis
- Idiopathic adulthood ductopenia *
- Hepatic venous outflow obstruction (Budd-Chiari syndrome), chronic *
- Hyperalimentation (TPN)
- Indian childhood cirrhosis
- Inflammatory bowel disease: Ulcerative colitis
- Metabolic diseases (e.g., Glycogen storage disease III, Gaucher disease)
- Non-alcoholic steatohepatitis
- Pseudocyst of ducts syndrome, non-syndromic*
- Primary biliary cirrhosis *
- Primary sclerosing cholangitis *
- Progressive familial intrahepatic cholestasis (Byler syndrome)*
- Sarcoidosis
- Syphilis, tertiary (hepat lobatum)
- Venous-occlusive disease (VOD), chronic *
- Venous congestion secondary to right-sided heart failure, chronic *
- Viral hepatitis, chronic
- Wilson disease

(* Biliary type  † Cardiac type)
**Bile Ducts: Inflammation by Neutrophils (Acute Cholangitis)**

- Allograft, acute (cellular) rejection
- Biliary atresia, extrahepatic
- Caroli disease
- Choledochal cyst
- Cystic fibrosis
- Echinococcosis (hydatid cyst) (cyst rupture)
- Extrahepatic bile duct obstruction
- Hepatic artery thrombosis
- Parasitic infestations
- Primary sclerosing cholangitis (large ducts only)
- Pyogenic abscess
- Reactive changes, bacterial infections
- Recurrent pyogenic cholangiohepatitis
- Salmonellosis
- Syphilis, secondary
- Toxic shock syndrome
- Tuberculosis

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**Table 6 - Bile Ducts: Inflammation by Neutrophils (Acute Cholangitis)**

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**Bile Ducts: Inflammation by Lymphocytes (Nonsuppurative Cholangitis)**

- Primary biliary cirrhosis

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*Primary biliary cirrhosis*
Table 7 - Bile Ducts: Inflammation by Lymphocytes
(Non supp purative Cholangitis)

- Acute viral hepatitis, HCV, HEV
- Allograft, acute (cellular) rejection
- Autoimmune hepatitis (cholangitis)
- Caroli disease (biliary cyst walls)
- Chronic viral hepatitis, HCV
- Cryptosporidiosis
- Cytomegalovirus
- Epstein-Barr virus
- Graft versus host disease
- Hodgkin's lymphoma (non-tumor liver)
- Human immunodeficiency virus (HIV) associated cholangiopathy
- Idiopathic adulthood ductopenia
- Paucity of ducts syndrome, syndromic (Alagille’s)
- Primary biliary cirrhosis
- Primary sclerosing cholangitis (also large ducts)
- Recurrent pyogenic cholangiohepatitis (large ducts only)
- Sarcoidosis

Table 8 - Bile Ducts: Periductal Fibrosis

- Caroli disease
- Choledochal cyst
- Cryptosporidiosis
- Echinococcosis (hydatid cyst)
- Eosinophilic gastroenteritis
- Extrahepatic bile duct obstruction, early stage
- Extrahepatic bile duct obstruction, early-to-mid stage
- Extrahepatic bile duct obstruction, late stage
- Human immunodeficiency virus (HIV) associated cholangiopathy
- Idiopathic adulthood ductopenia
- Microsporidiosis
- Primary sclerosing cholangitis
- Recurrent pyogenic cholangiohepatitis
Bile Ducts: Cytologic Atypia, Duct Loss (Ductopenia)

- Allograft, early chronic rejection
- Primary sclerosing cholangitis
- Duct atypia
- Allograft, hepatic artery thrombosis
- Cystic fibrosis
- Cytomegalovirus, adult
- Extrahepatic bile duct obstruction, late stage (small ducts)
- Graft versus host disease
- Hodgkin's lymphoma (non-tumor liver)
- Human immunodeficiency virus (HIV) associated cholangiopathy
- Idiopathic adulthood ductopenia
- Pauci of ducts syndrome, non-syndromatic
- Pauci of ducts syndrome, syndromatic (Alagille's)
- Polycystic disease, perinatal (infantile) form
- Primary biliary cirrhosis
- Primary sclerosing cholangitis (small ducts)
- Progressive familial intrahepatic cholestasis (Byler syndrome)
- Sarcoidosis

Lobular Necrosis with Inflammation

- Acute viral hepatitis, HCV
- Lymphocytic infiltrates
- Alcoholic hepatitis
- Neutrophilic infiltrates
Table 10 - Lobular Necrosis with Inflammation

- Alcoholic hepatitis PMN *
- Alcoholic foamy degeneration PMN, L *
- Allograft, acute (cellular) rejection PMN, L *
- Alpha-1-antitrypsin deficiency L
- Autoimmune hepatitis L, PC *
- Benign recurrent intrahepatic cholestasis L **
- Biliary atresia, extrahepatic PMN, L **
- Caroli disease PMN, L **
- Cholangiocarcinoma (with bile duct obstruction) PMN **
- Cystic fibrosis PMN *
- Extrahepatic bile duct obstruction PMN **
- Graft versus host disease L
- Hemochromatosis L
- Indian childhood cirrhosis PMN, L

*Cholestasis in active disease
**Cholestasis as a primary factor in the disease
L – lymphocytes PMN – Neutrophils PC – Plasma cells EO – Eosinophils

Table 10 - Lobular Necrosis with Inflammation

- Infections, non-viral
  - Bacterial (pyogenic abscess) PMN *
  - Bacterial (e.g., salmonellosis) PMN
  - Fungal (e.g., cryptococcosis) L
  - Parasitic (e.g., Amebiasis) L, ED
- Inflammatory bowel disease L
- Neonatal hepatitis PMN, L *
- Non-alcoholic steatohepatitis PMN, L *
- Primary biliary cirrhosis L, PC *
- Primary sclerosing cholangitis L *
- Recurrent pyogenic cholangitis PMN **
- Sarcoidosis L *
- Viral hepatitis, acute and chronic
  - Hepatotropic viruses L *
  - EBV/CMV hepatitis L *
- Wilson disease L

*Cholestasis in active disease
**Cholestasis as a primary factor in the disease
L – lymphocytes PMN – Neutrophils PC – Plasma cells EO – Eosinophils

Lobular Necrosis with Minimal to Absent Inflammation

Coagulative ischemic necrosis
Table 11 - Lobular Necrosis with Minimal to Absent Inflammation

- Acute hepatic venous outflow obstruction (Budd-Chiari syndrome)
- Allograft, hepatic artery thrombosis
- Amebiasis
- Aspergillosis
- Babesiosis
- Churg-Strauss syndrome
- Dengue fever
- Hyperpyrexia and heat stroke
- Hypoxic injury secondary to hypotension
- Malaria
- Pneumocystis carinii infection
- Polyarteritis nodosa
- Viruses, non-A-G (e.g., Ebola, Marburg, Adenovirus, Echovirus, Lassa fever, HSV)
- Rheumatoid arthritis
- Sickle cell anemia
- Spontaneous rupture in pregnancy
- Systemic lupus erythematosus (secondary to arthritis)
- Toxemia of pregnancy
- Veno-occlusive disease (VOD)

Table 12 - Cholestasis, Simple

- Acute fatty liver of pregnancy
- Amyloidosis
- Criglar-Najjar syndrome
- Cystic fibrosis
- Fibrolamellar hepatocellular carcinoma
- Hepatic venous outflow obstruction (Budd-Chiari syndrome), acute and chronic
- Hepatocellular carcinoma, common patterns
- Hyperalimentation (TPN)
- Hypoxic injury secondary to hypotension
- Infection-associated (reactive) hemophagocytic syndrome
- Inspissated bile syndrome
- Intrahepatic cholestasis of pregnancy
- Liver cell adenoma
- Nodular regenerative hyperplasia
- Paucity of ducts syndrome, syndromic (Alagille’s) and non-syndromic
- Progressive familial intrahepatic cholestasis (Byler syndrome)
- Sickle cell anemia
- Veno-occlusive disease (VOD), acute and chronic
- Venous congestion secondary to right-sided heart failure, acute and chronic
### Fatty Change

**Alcoholic fatty liver**

**Table 13 - Fatty Change (>50% liver cells involved)**

<table>
<thead>
<tr>
<th>Macrovesicular</th>
<th>Microvesicular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abetalipoproteinemia</td>
<td>Acute fatty liver of pregnancy</td>
</tr>
<tr>
<td>Acute alcoholic fatty liver with or without cholestasis</td>
<td>Alcoholic foamy degeneration</td>
</tr>
<tr>
<td>Alcoholic fatty liver</td>
<td>Alper's disease</td>
</tr>
<tr>
<td>Alcoholic hepatitis</td>
<td>Cholesterol ester storage disease</td>
</tr>
<tr>
<td>Galactosemia</td>
<td>Reye syndrome</td>
</tr>
<tr>
<td>Hereditary fructose intolerance</td>
<td>Wolman's disease</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td></td>
</tr>
<tr>
<td>Kwashiorkor (later stage)</td>
<td></td>
</tr>
<tr>
<td>Long chain acyl-CoA dehydrogenase deficiency</td>
<td></td>
</tr>
<tr>
<td>Non-alcoholic fatty liver</td>
<td></td>
</tr>
<tr>
<td>Non-alcoholic steatohepatitis</td>
<td></td>
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<tr>
<td>Perivenular alcoholic fibrosis</td>
<td></td>
</tr>
<tr>
<td>Systemic carnitine deficiency</td>
<td></td>
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<tr>
<td>Weber-Christian disease</td>
<td></td>
</tr>
</tbody>
</table>

**Table 13 - Fatty Change (<50% cells involved, macrovesicular)**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Allograft, recurrent hepatitis, HCV</td>
<td>Malaria</td>
</tr>
<tr>
<td>Alpha-1-antitrypsin deficiency</td>
<td>Mannosidosis</td>
</tr>
<tr>
<td>Amebiasis</td>
<td>Marasmus</td>
</tr>
<tr>
<td>Chronic viral hepatitis, HCV</td>
<td>Porphyria cutanea tarda</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Primary sclerosing cholangitis</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Q fever</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>Reactive changes, non-specific and bacterial infections</td>
</tr>
<tr>
<td>Gilbert syndrome</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Glycogen storage disease I, II, VI</td>
<td>Rocky Mountain spotted fever</td>
</tr>
<tr>
<td>Hereditary hemochromatosis</td>
<td>Sickle cell anemia</td>
</tr>
<tr>
<td>Hereditary tyrosinemia</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Human immunodeficiency virus (HSV)</td>
<td>Toxoplasmosis</td>
</tr>
<tr>
<td>Hyperalimentation (TPN), adult</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Inflammatory bowel diseases</td>
<td>Wilson disease</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td></td>
</tr>
</tbody>
</table>
### Table 13 - Fatty Change
(<50% cells involved, microvesicular)

- Acute and chronic viral hepatitis, HBV and delta
- Hyperpyrexia and heat stroke
- Lyme disease
- Salmonellosis
- Toxic shock syndrome
- Yellow fever

### Granulomas

- Acute alcoholic fatty liver with/without cholestasis
- Alcoholic fatty liver
- Alcoholic hepatitis
- Chronic granulomatous disease of childhood
- Eosinophilic gastroenteritis
- Foreign body giant cell reaction
- Idiopathic granulomatous hepatitis
- Infections:
  - Viral (e.g., acute HCV, CMV, EBV)
  - Fungal (e.g., Cryptococcus, Histoplasma)
  - Bacterial (e.g., Salmonella, Brucella)
  - Mycobacterium
  - Parasitic (e.g., Schistosoma, visceral larva migrans)
- Inflammatory bowel disease: Crohn's disease

### Table 14 - Granulomas

- Nonplasmacytoma, tumor-like lesions:
  - Hepatosplenic carinoma
  - Hodgkin's lymphoma (non-tumor liver)
  - Inflammatory pseudotumor
  - Langerhans cell histiocytosis
  - Liver cell adenoma
- Non-alcoholic steatohepatitis
- Nonspecific reactive hepatitis
- Polyarteritis nodosa
- Polymyositis rheumatica
- Primary biliary cirrhosis
- Rheumatoid arthritis
- Sarcoidosis
- Systemic lupus erythematosus
Mallory Bodies

Alcoholic hepatitis

Table 15 - Mallory Bodies

- Abetalipoproteinemia
- Alcoholic hepatitis
- Alpha-1-antitrypsin deficiency
- Biliary atresia, extrahepatic
- Extrahepatic bile duct obstruction, mid/late stage
- Focal nodular hyperplasia
- Glycogen storage disease Ia
- Hepatocellular carcinoma, common patterns
- Hyperalimentation (TPN), adults
- Indian childhood cirrhosis
- Kwashiorkor
- Liver cell adenoma
- Non-alcoholic steatohepatitis
- Perivenular alcoholic fibrosis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Weber-Christian disease
- Wilson disease

Inclusions: Hepatocytes

Chronic viral hepatitis, HBV
"Ground-glass" cells (HBsAg)

Non-alcoholic steatosis
Glycogenated nuclei
### Table 16 – Inclusions: Hepatocytes
#### Nuclear
- **Viral inclusions**
  - Adenovirus
  - Cytomegalovirus (immunocompromised, allograft)
  - Herpes simplex virus (Cowdry A, B)
  - Herpes zoster
  - Parvovirus (B19 virus)
  - Rubeola
  - Yellow fever
- **Glycogenated nuclei**
  - Alpha-1-antitrypsin deficiency
  - Glycogen storage diseases I, III, VI
  - Hereditary hemochromatosis
  - Non-alcoholic fatty liver
  - Non-alcoholic steatohepatitis
  - Porphyria cutanea tarda
  - *Wilson disease*

#### Cytoplasmic
- Acute fatty liver of pregnancy
- Alcoholic liver disease
  - Fatty liver, foamy degeneration, alcoholic hepatitis
- Alpha-1-antitrypsin deficiency
- Chronic viral hepatitis, HBV
- Cytomegalovirus (immunocompromised, allograft)
- Fibrinogen storage disease
- Glycogen storage disease IV
- Hepatic injury from hypotension
- Non-alcoholic steatohepatitis
- Porphyria cutanea tarda
- Raye syndrome
- Rubeola
- Venous congestion secondary to right sided heart failure

- Megamitochondria
- Periportal eosinophilic DIFAS + globule (A-1-AT)
- Ground glass cells
- Cytoplasmic inclusions
- Eosinophilic globules (fibrinogen)
- Eosinophilic globules (amylopectin)
- Megamitochondria
- Needle-shaped, birefringent
- Distorted mitochondria
- Eosinophilic globules (zone 3 liver cells)
- Eosinophilic globules (zone 3 liver cells)

### Pigments
- Hereditary hemochromatosis
- Hemosiderin with iron stain
Table 17 - Pigments: Hemosiderin

<table>
<thead>
<tr>
<th>Pigments</th>
<th>Hepatocytes</th>
<th>Portal macrophages, Kupffer cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemosiderosis (secondary iron overload)</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Hereditary hemochromatosis</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Hereditary tyrosinemia</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Hyperalimentation (TPN), adults</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Infection-associated (reactive) hemophagocytic syndrome</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Inspissated bile syndrome</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Malaria</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Neonatal hepatitis</td>
<td>+/++</td>
<td></td>
</tr>
<tr>
<td>Non-alcoholic steatohepatitis</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td>+/++</td>
<td></td>
</tr>
<tr>
<td>Wilson disease</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Table 17 - Pigments: Copper

<table>
<thead>
<tr>
<th>Often abundant</th>
<th>Occasionally increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Biliary atresia, extrahepatic</td>
<td>• Alpha-1-antitrypsin deficiency (neonate)</td>
</tr>
<tr>
<td>• Idiopathic adulthood ductopenia</td>
<td>• Congenital hepatic fibrosis</td>
</tr>
<tr>
<td>• Indian childhood cirrhosis</td>
<td>• Cystic fibrosis</td>
</tr>
<tr>
<td>• Paucity of ducts syndrome, non-syndromatic</td>
<td>• Extrahepatic bile duct obstruction, late stage</td>
</tr>
<tr>
<td>• Paucity of ducts syndrome, syndromatic (Alagille's)</td>
<td>• Fibrolamellar hepatocellular carcinoma</td>
</tr>
<tr>
<td>• Primary biliary cirrhosis (late stage)</td>
<td>• Focal nodular hyperplasia</td>
</tr>
<tr>
<td>• Primary sclerosing cholangitis (late stage)</td>
<td>• Galactosemia</td>
</tr>
<tr>
<td>• Progressive familial intrahepatic cholestasis</td>
<td>• Graft versus host disease</td>
</tr>
<tr>
<td>(Byler syndrome)</td>
<td>• Hereditary fructose intolerance</td>
</tr>
<tr>
<td>• Wilson disease</td>
<td>• Hyperalimentation (TPN, adults)</td>
</tr>
</tbody>
</table>

Table 17 - Pigments: Other

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>• Angiosarcoma</td>
<td>Thorotrast (in non-tumor)</td>
</tr>
<tr>
<td>• Chronic granulomatous disease of childhood</td>
<td>Lipochrome</td>
</tr>
<tr>
<td>• Chronic viral hepatitis</td>
<td>IV particulate injectant (IV drug users)</td>
</tr>
<tr>
<td>• Cystinosis</td>
<td>Cystine</td>
</tr>
<tr>
<td>• Dubin-Johnson syndrome</td>
<td>Lipochrome-like</td>
</tr>
<tr>
<td>• Erythropoietic protoporphyria</td>
<td>Protoporphyrin</td>
</tr>
<tr>
<td>• Focal nodular hyperplasia</td>
<td>Lipochrome</td>
</tr>
<tr>
<td>• Gilbert syndrome</td>
<td>Lipochrome</td>
</tr>
<tr>
<td>• Hepatoblastoma</td>
<td>Melanin</td>
</tr>
<tr>
<td>• Liver cell adenoma</td>
<td>Lipochrome</td>
</tr>
<tr>
<td>• Melanin</td>
<td>Hemozoin</td>
</tr>
<tr>
<td>• Niemann-Pick disease</td>
<td>Lipochrome-like</td>
</tr>
<tr>
<td>• Porphyria cutanea tarda</td>
<td>Lipochrome</td>
</tr>
<tr>
<td>• Schistosomiasis</td>
<td>Lipochrome-like</td>
</tr>
<tr>
<td>• Wilson disease</td>
<td>Lipochrome</td>
</tr>
</tbody>
</table>

Sinusoids: Fibrosis

Alcoholic hepatitis
Perivenular fibrosis (trichrome)
### Table 18 - Sinusoids: Fibrosis

- Alcoholic foamy degeneration
- Alcoholic hepatitis
- Allograft, fibrosing cholestatic hepatitis
- Allograft, chronic (ductopenic) rejection
- Chronic viral hepatitis, HCV
- Cystic fibrosis
- Erythropoietic protoporphyria
- Hyperalimentation (TPN), adults
- Hyperalimentation (TPN), infants
- Indian childhood cirrhosis
- Leishmaniasis (long term infection)
- Metabolic (e.g., cholesterol ester storage disease, gangliosidosis, GM2, Gaucher disease)
- Neonatal hepatitis
- Non-alcoholic steatohepatitis
- Non-cirrhotic portal fibrosis
- Pausity of ducts syndrome, non-syndromatic
- Perivenular alcoholic fibrosis
- Schistosomiasis
- Sickle cell anemia
- Syphilis, congenital
- Wilson disease

### Sinusoids: Circulating Cells

![T-cell lymphoma/CLL](image)

### Table 19 - Sinusoids: Circulating Cells

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute viral hepatitis, HCV</td>
<td>L, PMN</td>
</tr>
<tr>
<td>Alcoholic hepatitis</td>
<td>PMN</td>
</tr>
<tr>
<td>Allograft, acute (cellular) rejection (severe)</td>
<td>L</td>
</tr>
<tr>
<td>Chronic viral hepatitis, HCV</td>
<td>L</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>L</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>L</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>L</td>
</tr>
<tr>
<td>Leukemia, CCL</td>
<td>PMN</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>L, PMN</td>
</tr>
<tr>
<td>Malaria (tropical splenomegaly syndrome)</td>
<td>L</td>
</tr>
<tr>
<td>Pyogenic abscess</td>
<td>PMN</td>
</tr>
<tr>
<td>Reactive changes, bacterial infections</td>
<td>PMN</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>L</td>
</tr>
<tr>
<td>Rocky Mountain</td>
<td>L</td>
</tr>
<tr>
<td>Salmonellosis</td>
<td>L</td>
</tr>
<tr>
<td>&quot;Surgical&quot; hepatitis</td>
<td>PMN</td>
</tr>
</tbody>
</table>

L – Lymphocytes  PMN - Neutrophils
Vessels (Excluding Sinusoids): Inflammation, Thrombosis/Occlusion

Table 20 - Vessels (Excluding Sinusoids): Inflammation

<table>
<thead>
<tr>
<th>Arteries, arterioles</th>
<th>Veins, venules</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Allograft, acute (cellular) rejection</td>
<td>• Acute viral hepatitis</td>
</tr>
<tr>
<td>• Allograft, hyperacute (humoral) rejection</td>
<td>• Allograft, acute (cellular) rejection</td>
</tr>
<tr>
<td>• Churg-Strauss syndrome</td>
<td>• Autoimmune hepatitis</td>
</tr>
<tr>
<td>• Hereditary hemorrhagic telangiectasia (OWR)</td>
<td>• Epstein-Barr virus</td>
</tr>
<tr>
<td>• Polyarteritis nodosa</td>
<td>• Graft versus host disease</td>
</tr>
<tr>
<td>• Rheumatoid arthritis</td>
<td>• Hepatic vein phlebitis</td>
</tr>
<tr>
<td>• Rocky Mountain spotted fever</td>
<td>• Non-alcoholic steatohepatitis</td>
</tr>
<tr>
<td>• Syphilis, secondary</td>
<td>• Perivenular alcoholic fibrosis</td>
</tr>
<tr>
<td>• Syphilis, tertiary</td>
<td>• Polyphlebitis</td>
</tr>
<tr>
<td>• Systemic lupus erythematosus</td>
<td>• Recurrent pyogenic cholangiohepatitis</td>
</tr>
<tr>
<td>• Toxic shock syndrome</td>
<td>• Salmonellosis</td>
</tr>
<tr>
<td></td>
<td>• Sarcoidosis</td>
</tr>
<tr>
<td></td>
<td>• Schistosomiasis</td>
</tr>
<tr>
<td></td>
<td>• Syphilis, secondary</td>
</tr>
<tr>
<td></td>
<td>• Toxic shock syndrome</td>
</tr>
</tbody>
</table>

Table 21 - Vessels (Excluding Sinusoids): Thrombosis, Occlusion

<table>
<thead>
<tr>
<th>Thrombosis, fibrous thickening/occlusion</th>
<th>Veno-occlusive disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Alcoholic hepatitis</td>
<td>• Malignant/interstitial disorders (secondary hepatic vein thrombosis)</td>
</tr>
<tr>
<td>• Alcoholic cirrhosis</td>
<td>• Non-cirrhotic portal fibrosis</td>
</tr>
<tr>
<td>• Allograft, chronic (ductopenic) rejection</td>
<td>• Polyarteritis nodosa</td>
</tr>
<tr>
<td>• Allograft, hepatic artery thrombosis</td>
<td>• Polyphlebitis</td>
</tr>
<tr>
<td>• Churg-Strauss syndrome</td>
<td>• Scleroderma</td>
</tr>
<tr>
<td>• Congenital hepatic fibrosis</td>
<td>• Sickle cell anemia</td>
</tr>
<tr>
<td>• Hepatic vein phlebitis</td>
<td>• Venous congestion secondary to right-sided heart failure, chronic</td>
</tr>
<tr>
<td>• Hepatic venous outflow obstruction (Budd-Chiari syndrome), acute and chronic</td>
<td></td>
</tr>
</tbody>
</table>

Veno-occlusive changes

- Alcoholic cirrhosis
- Alcoholic hepatitis
- Graft versus host disease
- Non-alcoholic steatohepatitis
- Perivenular alcoholic fibrosis
- Veno-occlusive disease (VOD), acute and chronic
Case Examples

Case #1

• 56 year old woman with pruritus
• Liver tests:
  – AST 56
  – ALT 87
  – Alkaline phosphatase 456
  – Total bilirubin 0.8
  – Normal albumin, globulin
• Biopsy performed and showed the following features

Portal fibrosis with bridging
Case #1

Prominent portal plasma cell infiltrates

Case #1

Interlobular bile ducts with cytologic atypia and focal infiltration by lymphocytes ("Nonsuppurative cholangitis")

Case #1

Interlobular bile duct with cytologic atypia and surrounding lymphocytes, histiocytes and plasma cells
Case #1

Interlobular bile duct with focal infiltration by lymphocytes
("Nonsuppurative cholangitis")
Prominent surrounding plasma cells

Case #1

Interlobular bile duct with focal infiltration by lymphocytes
("Nonsuppurative cholangitis")

Case #1

Mallory bodies
Case #1

Summary of liver pathology:
- Portal fibrosis with bridging
  - Table 5: "Portal Fibrosis, Cirrhosis"
- Portal lymphocytes with increased numbers of plasma cells
  - Table 2: "Portal Plasma Cells"
- Lymphocytes surrounding and invading interlobular bile ducts (nonsuppurative cholangitis)
  - Table 7: "Bile Ducts: Inflammation by Lymphocytes"
- Mallory bodies in periportal hepatocytes
  - Table 15: "Mallory Bodies"
- Portal and lobular granuloma formation
  - Table 14: "Granulomas"

Briefly review all five tables, with the diseases in *italics* the more frequent diseases showing that feature.
- Highlight the diseases (>underline) that appear to recur more often within the tables (in this example the diseases listed three or more times are underlined).
- List these diseases in order of frequency for differential diagnoses.
### Table 5 - Portal Fibrosis, Cirrhosis

- Alcoholic cirrhosis
- Alcoholic hepatitis
- Alpha-1-antitrypsin deficiency
- Autoimmune hepatitis (cholangitis) *
- Autoimmune hepatitis
- Biliary atresia, extrahepatic *
- Cystic fibrosis *
- Extrahepatic bile duct obstruction, late stage *
- Erythropoietic protoporphyria
- Hereditary hemochromatosis
- Idiopathic adulthood ductopenia *
- Hepatic venous outflow obstruction (Budd-Chiari syndrome), chronic *
- Hyperalimentation (TPN)
- Indian childhood cirrhosis
- Inflammatory bowel disease: Ulcerative colitis

(* Biliary type  † Cardiac type)

### Table 3 - Portal Plasma Cells

- Acute viral hepatitis, HAV
- Allograft, acute (cellular) rejection
- Autoimmune hepatitis
- Chronic granulomatous disease of childhood
- Chronic viral hepatitis, HBV
- Chronic viral hepatitis (other than HBV)
- Echinococcosis (hydatid cyst)
- Epstein-Barr virus

- Hodgkin’s lymphoma (non-tumor liver)
- Leishmaniasis
- Multiple myeloma
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Q fever
- Visceral larva migrans
- Waldenstrom’s macroglobulinemia
- Wilson disease
### Table 3 - Portal Plasma Cells

- Acute viral hepatitis, HAV
- Allograft, acute (cellular) rejection
- Autoimmune hepatitis (cholangitis)
- Chronic granulomatous disease of childhood
- Chronic viral hepatitis, HBV
- Chronic viral hepatitis (other than HBV)
- Echinococcosis (hydatid cyst)
- Epstein-Barr virus
- Hodgkin's lymphoma (non-tumor liver)
- Leishmaniasis
- Multiple myeloma
- Primary biliary cirrhosis
- Primary biliary cirrhosis (cholangitis)
- Q fever
- Visceral larva migrans
- Waldenström's macroglobulinemia
- Wilson disease

### Table 7 - Bile Ducts: Inflammation by Lymphocytes (Nonsuppurative Cholangitis)

- Acute viral hepatitis, HCV, HEV
- Allograft, acute (cellular) rejection
- Autoimmune hepatitis (cholangitis)
- Caroli disease (biliary cyst walls)
- Chronic viral hepatitis, HCV
- Cryptosporidiosis
- Cytomegalovirus
- Epstein-Barr virus
- Graft versus host disease
- Hodgkin's lymphoma (non-tumor liver)
- Human immunodeficiency virus (HIV) associated cholangiopathy
- Idiopathic adulthood ductopenia
- Paucity of ducts syndrome, syndromic (Alagille's)
- Primary biliary cirrhosis
- Primary sclerosing cholangitis (also large ducts)
- Recurrent pyogenic cholangiohepatitis (large ducts only)
- Sarcoidosis

- Acute viral hepatitis, HCV, HEV
- Allograft, acute (cellular) rejection
- Autoimmune hepatitis (cholangitis)
- Caroli disease (biliary cyst walls)
- Chronic viral hepatitis, HCV
- Cryptosporidiosis
- Cytomegalovirus
- Epstein-Barr virus
- Graft versus host disease
- Hodgkin's lymphoma (non-tumor liver)
- Human immunodeficiency virus (HIV) associated cholangiopathy
- Idiopathic adulthood ductopenia
- Paucity of ducts syndrome, syndromic (Alagille’s)
- Primary biliary cirrhosis
- Primary sclerosing cholangitis (also large ducts)
- Recurrent pyogenic cholangiohepatitis (large ducts only)
- Sarcoidosis
### Table 15 - Mallory Bodies

- Abetalipoproteinemia
- Alcoholic hepatitis
- Alpha-1-antitrypsin deficiency
- Biliary atresia, extrahepatic
- Extrahepatic bile duct obstruction, mid/late stage
- Focal nodular hyperplasia
- Glycogen storage disease Ia
- Hepatocellular carcinoma, common patterns
- Hyperalimentation (TPN), adults

- Indian childhood cirrhosis
- Kwaishiodor
- Liver cell adenoma
- Non-alcoholic steatohepatitis
- Perivenular alcoholic fibrosis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Weber-Christian disease
- Wilson disease

### Table 14 - Granulomas

- Acute alcoholic fatty liver with/without cholestasis
- Alcoholic fatty liver
- Alcoholic hepatitis
- Chronic granulomatous disease of childhood
- Eosinophilic gastroenteritis
- Foreign body giant cell reaction
- Idiopathic granulomatous hepatitis
  - Infections:
    - Viral (e.g., acute HCV, CMV, EBV)
    - Fungal (e.g., Cryptococcus, Histoplasmosis)
    - Bacterial (e.g., Salmonella, Brucella)
    - Mycobacteria
    - Parasitic (e.g., Schistosoma, visceral larva migrans)
- Inflammatory bowel disease: Crohn's disease

- Neoplasms, tumor-like lesions:
  - Hepatosplenic carcinoma
  - Hodgkin's lymphoma (non-tumor liver)
  - Inflammatory pseudotumor
  - Langerhans cell histiocytosis
  - Liver cell adenoma
  - Non-alcoholic steatohepatitis
  - Nonspecific reactive hepatitis
  - Polyarteritis nodosa
  - Polymyositis rheumatica
  - Primary biliary cirrhosis
  - Rheumatoid arthritis
  - Sarcoidosis
  - Systemic lupus erythematosus
Table 14 - Granulomas

- Acute alcoholic fatty liver with/without cholestasis
- Alcoholic fatty liver
- Alcoholic hepatitis
- Chronic granulomatous disease of childhood
- Eosinophilic gastroenteritis
- Foreign body giant cell reaction
- Idiopathic granulomatous hepatitis
- Infectious granulomas
  - Viral (e.g., acute HCV, CMV, EBV)
  - Fungal (e.g., Cryptococcus, Histoplasma)
  - Bacterial (e.g., Salmonella, Brucella)
  - Mycobacterium
- Inflammatory bowel disease: Crohn’s disease
- Neoplasms, tumor-like lesions:
  - Hepatosclerotic carcinoma
  - Hodgkin’s lymphoma (non-tumor liver)
  - Inflammatory pseudotumor
  - Langerhans cell histiocytosis
  - Liver cell adenoma
- Non-alcoholic steatohepatitis
- Nonspecific reactive hepatitis
- Primary biliary cirrhosis
- Polyarteritis nodosa
- Polymyalgia rheumatica
- >Primary sclerosing cholangitis
- Rheumatoid arthritis
- >Sarcoidosis
- Systemic lupus erythematosus

Case #1
Differential Diagnoses

- Five of five parameters
  - Primary biliary cirrhosis
- Four of five parameters
  - Primary sclerosing cholangitis
- Three of five parameters
  - Autoimmune hepatitis
  - Epstein Barr virus
  - Non-alcoholic steatohepatitis
  - Sarcoidosis
  - Wilson disease
- Two of five parameters
  - Acute (cellular) rejection
  - Acute viral hepatitis, HCV
  - Alpha-1-antitrypsin deficiency
  - Biliary atresia, extrahepatic
  - Cytomegalovirus
  - Extrahepatic biliary obstruction
  - Hyperalimentation
  - Idiopathic adult ductopenia
  - Indian childhood cirrhosis
  - Paucity of ducts

Case #1
Differential Diagnoses
(if no granulomas were present)

- Four of four parameters
  - Primary biliary cirrhosis
  - Primary sclerosing cholangitis
- Three of four parameters
  - Autoimmune hepatitis
  - Wilson disease
- Two of four parameters
  - Acute (cellular) rejection
  - Alpha-1-antitrypsin deficiency
  - Biliary atresia, extrahepatic
  - Epstein Barr virus
  - Extrahepatic biliary duct obstruction
  - Hyperalimentation
  - Idiopathic adult ductopenia
  - Indian childhood cirrhosis
  - Non-alcoholic steatohepatitis
  - Paucity of ducts
  - Sarcoidosis
Case #1
Additional Information and Final Diagnosis

- Serologies for viral hepatitis A, B, C: non-reactive
- Autoimmune serologies
  - ANA: weak positive
  - SMA: non-reactive
  - AMA M2: positive
- ERCP: normal
- Final diagnosis
  - Primary biliary cirrhosis, stage 3 of 4

What about the differential diagnoses in the list that do not fit?

- For example, in this case we see Mallory bodies, and Epstein Barr Virus (EBV) induced hepatitis, listed under 3 of 5, does not include Mallory bodies.
- Why is EBV hepatitis still on the list of differentials? Because of the presence of Mallory bodies, cannot EBV infection automatically be excluded?
- When a liver biopsy represents only ONE specific disease, then EBV could certainly be excluded.
- However, we do not know that, and in fact co-existing liver diseases (e.g., EBV in a patient on a medication that can include Mallory bodies such as amiodarone, or EBV in a patient with a chronic biliary tract stricture that can also show Mallory bodies) may be present in this case, hence these other disorders MUST be included and remain on the list of differentials UNTIL clinical and laboratory correlation is provided.
- It is important to note that it is not infrequent for co-existing liver diseases to be present. An example of co-existing diseases will be addressed in this session in Case #4.

Case #2

- 32 year old man with non-specific clinical features
- Liver tests:
  - AST 67
  - ALT 82
  - Other liver tests normal
- Hepatitis serologies:
  - HAV IgM, HBsAg, HCV Ab: non-reactive
- Biopsy performed and showed the following features
Case #2

Portal lymphocytic infiltrates

Case #2

Lobular necroinflammatory change with infiltration by lymphocytes

Case #2

Sinusoidal lymphocytosis
Case #2

Summary of liver pathology:
- Portal lymphocytic infiltrates
  - Table 1: “Portal Lymphocytes”
- Diffuse necroinflammatory change
  - Table 10: “Lobular Necrosis with Inflammation”
- Sinusoidal lymphocytosis
  - Table 19: “Sinusoids: Circulating Cells”
- Granuloma formation
  - Table 14: “Granulomas”

Table 1: Portal Lymphocytes
- Allograft, acute (cellular) rejection
- Alcoholic cirrhosis
- Autoimmune hepatitis
- Biliary atresia, extrahepatic
- Bacterial
- Caroli disease
- Chronic granulomatous disease of childhood
- Cytomegalovirus
- Epstein-Barr virus
- Erythropoietic protoporphyria
- Extrahepatic bile duct obstruction, late stage
- Graft versus host disease
- Idiopathic adulthood ductopenia
- Indian childhood cirrhosis
- Inflammatory bowel disease
- Lassa fever
- Leukemia, lymphocytic
- Lymphoma, Hodgkin’s (non-tumor liver) and non-Hodgkin’s
- Malignant hepatoblastoma
- Non-alcoholic steatohepatitis
- Noninfectious reactive hepatitis
- Pneumoconiosis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Q fever
- Rheumatoid arthritis
- Rocky Mountain spotted fever
- Salmonellosis
- Sarcoidosis
- Tuberculosis
- Viral hepatitis, acute and chronic
- Wilson disease
- Yellow fever

† Periportal interface inflammation in active stage of disease
**Table 10 - Lobular Necrosis with Inflammation**

- Alcoholic hepatitis
- Alcoholic fatty degeneration
- Allograft, acute (cellular) rejection
- Alpha-1-antitrypsin deficiency
- Autoimmune hepatitis
- Benign recurrent intrahepatic cholestasis
- Biliary atresia, extrahepatic
- Caroli disease
- Cholangiohepatitis (with bile duct obstruction)
- Cystic fibrosis
- Extrahepatic bile duct obstruction
- Graft versus host disease
- Hemochromatosis
- Indian childhood cirrhosis
- Infections, non-viral
  - Bacterial (pyogenic abscess)
  - Fungal (e.g., cryptococcosis)
  - Parasitic (e.g., Amoebiasis)
- Inflammatory bowel disease
- Recurrent hepatitis
  - Non-alcoholic steatohepatitis
  - Primary sclerosing cholangitis
- Recurrent pyogenic cholangitis
- Sarcoidosis
- Viral hepatitis, acute and chronic
  - Hepatitis A
  - Hepatitis B
  - Hepatitis C
  - Epstein-Barr virus
  - Hepatitis E
  - HDV/HEV hepatitis
  - HIV infection
  - Hepadnavirus
  - CMV/HHV-8
- Wilson disease

*Cholestasis in active disease
**Cholestasis as a primary factor in the disease

- L - Lymphocytes
- PMN - Neutrophils
- PC - Plasma cells
- EO - Eosinophils

---

**Table 19 - Sinusoids: Circulating Cells**

- Acute viral hepatitis, HCV
- Alcoholic hepatitis
- Allograft, acute (cellular) rejection (severe)
- Chronic viral hepatitis, HCV
- Cryoglobulinemia
- Hepatitis B virus
- Leishmaniasis
- Leukemia, CML
- Lyme disease
- Malaria (tropical splenomegaly syndrome)
- Nonalcoholic fatty liver disease
- Pyogenic abscess
- Reactive changes
- Rocky Mountain spotted fever
- Salmonellosis
- “Surgical” hepatitis

- L - Lymphocytes
- PMN - Neutrophils

---
Table 14 - Granulomas

- Acute alcoholic fatty liver with/without cholestasis
- Alcoholic fatty liver
- Alcoholic hepatitis
- Chronic granulomatous disease of childhood
- Eosinophilic gastroenteritis
- Foreign body giant cell reaction
- Idiopathic granulomatous hepatitis
- Neoplasms, tumor-like lesions:
  - Hepato cellular carcinoma
  - Hodgkin's lymphoma (non-tumor liver)
  - Inflammatory pseudotumor
  - Langerhans cell histiocytosis
  - Liver cell adenoma
- Neutrophilic granulomatous hepatitis
- Infectious:
  - Viral (e.g., acute HCV, CMV, EBV)
  - Fungal (e.g., Cryptococcus, Histoplasma)
  - Bacterial (e.g., Salmonella, Brucella)
  - Mycobacterium
  - Parasitic (e.g., Schistosoma, visceral larva migrans)
- Inflammatory bowel disease: Crohn's disease
- Non-alcoholic steatohepatitis
- Nonspecific reactive hepatitis
- Idiopathic granulomatous hepatitis
- Infectious:
  - Viral (e.g., acute HCV, CMV, EBV)
  - Fungal (e.g., Cryptococcus, Histoplasma)
  - Bacterial (e.g., Salmonella, Brucella)
  - Mycobacterium
  - Parasitic (e.g., Schistosoma, visceral larva migrans)
- Inflammatory bowel disease: Crohn's disease
- Nonspecific reactive hepatitis
- Polyarteritis nodosa
- Polymyalgia rheumatica
- Primary biliary cirrhosis
- Rheumatoid arthritis
- Sarcoidosis
- Systemic lupus erythematosus

Case #2
Differential Diagnoses

- Four of four parameters
  - Cytomegalovirus
  - Epstein-Barr virus infection

- Three of four parameters
  - Acute and chronic hepatitis (HCV)
  - Inflammatory bowel disease: Crohn's disease
  - Non-alcoholic steatohepatitis
  - Non-specific reactive hepatitis
  - Primary biliary cirrhosis
  - Rheumatoid arthritis
  - Sarcoidosis

Case #2
Additional Information and Final Diagnosis

- Monospot test: negative
- EBV-specific IgM, EBV-associated nuclear Ag (EBNA): negative
- CMV IgM, CMV-DNA (PCR): positive
- Serologies for viral hepatitis A, B, C: non-reactive

- Final diagnosis
  - CMV induced acute hepatitis
Case #3

- 39 year old woman with splenomegaly
- Liver tests:
  - AST 587
  - ALT 955
  - Alkaline phosphatase 665
  - Total bilirubin/direct 3.2/2.9
  - Total protein/albumin 8.6/3.5
- Biopsy performed and showed the following features

Portal fibrosis with bridging

Portal lymphocytes with periportal interface inflammatory activity
Case #3

Portal plasma cell infiltrates

Case #3

Portal tract with interlobular bile duct loss (ductopenia)

Case #3

Lobular necroinflammatory change with infiltration by lymphocytes and some plasma cells
Case #3

Summary of liver pathology:

- Portal fibrosis with bridging
- Portal lymphocytes with periporal interface inflammation
- Portal plasma cells
- Duct loss (ductopenia)
- Portal lymphocytes with periportal interface inflammation
- Diffuse lymphocytic necroinflammatory change
- Endothelialitis of terminal hepatic venules

Table 5: “Portal Fibrosis, Cirrhosis”

- Alcoholic cirrhosis
- Alcoholic hepatitis
- Alpha-1-antitrypsin deficiency
- Autoimmune hepatitis
- Biliary atresia, extrahepatic *
- Cystic fibrosis *
- Extrahepatic bile duct obstruction, late stage *
- Erythropoietic protoporphyria
- Hematologic hemochromatosis
- Idiopathic adulthood ductopenia *
- Hepatic venous outflow obstruction (Budd-Chiari syndrome), chronic *
- Hyperalimentation (TPN)
- Indian childhood cirrhosis
- Inflammatory bowel disease: Ulcerative colitis
- Metabolic diseases (e.g., Glycogen storage disease III, Gaucher disease)
- Non-alcoholic steatohepatitis
- PauciIty of ducts syndrome, non-syndromic *
- Primary biliary cirrhosis *
- Primary sclerosing cholangitis *
- Progressive familial intrahepatic cholestasis (Byler syndrome) *
- Sarcoidosis
- Syphilis, tertiary (hepar lobatum)
- Venous-occlusive disease (VOD), chronic *
- Venous congestion secondary to right-sided heart failure, chronic *
- Shunt hepatitis, chronic
- Wilson disease

(*) Biliary type
(†) Cardiac type
### Table 1 - Portal Lymphocytes
- Allograft, acute (cellular) rejection
- Alcoholic cirrhosis
- Autoimmune hepatitis
- Biliary atresia, extrahepatic
- Brucellosis
- Caroli disease
- Chronic granulomatous disease of childhood
- Cytomegalovirus
- Epstein-Barr virus
- Extrhepatic portal hypertension
- Extrahepatic bile duct obstruction, late stage
- Graft versus host disease
- Idiopathic adulthood ductopenia
- Indian childhood cirrhosis
- Inflammatory bowel disease
- Lassa fever
- Periportal interface inflammation in active stage of disease

### Table 2 - Portal Plasma Cells
- Acute viral hepatitis, HAV
- Allograft, acute (cellular) rejection
- Autoimmune hepatitis
- Chronic granulomatous disease of childhood
- Chronic viral hepatitis, HBV
- Chronic viral hepatitis (other than HBV)
- Echinococcosis (hydatid cyst)
- Epstein-Barr virus
- Hodgkin's lymphoma (non-tumor liver)
- Leishmaniasis
- Multiple myeloma
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Q fever
- Visceral larva migrans
- Waldenstrom’s macroglobulinemia
- Wilson disease

### Table 3 - Bile Ducts: Cytologic Atypia, Duct Loss (Ductopenia)
- Allograft liver, hepatic artery thrombosis
- Allograft liver, chronic rejection
- Autoimmune hepatitis (cholangitis)
- Cystic fibrosis
- Cytomegalovirus, adult
- Extrhepatic bile duct obstruction, late stage (small ducts)
- Graft versus host disease
- Hodgkin's lymphoma (non-tumor liver)
- Human immunodeficiency virus (HIV) associated cholangiopathy
- Idiopathic adulthood ductopenia
- Paucity of ducts syndrome, non-syndromic
- Paucity of ducts syndrome, syndromic (Alagille’s)
- Polycystic disease, perinatal (infantile) form
- Primary biliary cirrhosis
- Primary sclerosing cholangitis (small ducts)
- Progressive familial intrahepatic cholestasis (Byler syndrome)
- Sarcoidosis
### Table 10 - Lobular Necrosis with Inflammation

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cells</th>
</tr>
</thead>
<tbody>
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<td>Parasitic (e.g., Amoebiasis)</td>
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<td>L, PC</td>
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<tr>
<td>Recurrent pyogenic cholangiohepatitis</td>
<td>PMN</td>
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<td>Sarcoidosis</td>
<td>L</td>
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<td>Wilson disease</td>
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<td>Infectious diseases</td>
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<td>Epstein-Barr virus</td>
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<td>Hepatic vein phlebitis</td>
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<td>Chronic biliary obstruction</td>
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<td>Polyarteritis nodosa</td>
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<td>Rheumatoid arthritis</td>
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<tr>
<td>Rocky Mountain spotted fever</td>
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<td>Syphilis, secondary</td>
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<tr>
<td>Syphilis, tertiary</td>
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<tr>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>Toxic shock syndrome</td>
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</tbody>
</table>

*Cholestasis in active disease
**Cholestasis as a primary factor in the disease
L - Lymphocytes PMN – Neutrophils PC – Plasma cells EO – Eosinophils

### Table 20 - Vessels (Excluding Sinusoids): Inflammation

#### Arteries, arterioles
- Allograft, acute (cellular) rejection
- Allograft, hyperacute (humoral) rejection
- Churg-Strauss syndrome
- Hereditary hemorrhagic telangiectasia (DHN)
- Polyarteritis nodosa
- Rheumatoid arthritis
- Rocky Mountain spotted fever
- Syphilis, secondary
- Syphilis, tertiary
- Systemic lupus erythematosus
- Toxic shock syndrome

#### Veins, venules
- Acute viral hepatitis
- Allograft, acute (cellular) rejection
- >Autoimmune hepatitis
- Epstein-Barr virus
- Graft versus host disease
- Hepatic vein phlebitis
- Non-alcoholic steatohepatitis
- Perivenular alcoholic fibrosis
- Polyphlebitis
- Recurrent pyogenic cholangiohepatitis
- Salmonellosis
- >Sarcoidosis
- Schistosomiasis
- Syphilis, secondary
- Toxic shock syndrome
Case #3
Differential Diagnoses

- **Six of six parameters**
  - Autoimmune hepatitis (including cholangitis variant)

- **Five of six parameters**
  - Primary biliary cirrhosis
  - Primary sclerosing cholangitis
  - Sarcoidosis

- **Four of six parameters**
  - Chronic viral hepatitis (HBV)
  - Wilson disease

- **Three of six parameters**
  - Acute (cellular) rejection
  - Chronic viral hepatitis (other than HBV)
  - Epstein Barr virus
  - Graft vs host
  - Non-alcoholic steatohepatitis

Case #3
Additional Information and Final Diagnosis

- Autoimmune serologic markers
  - ANA 1:1280, SMA 1:640
  - Negative AMA M2
  - Negative atypical anti-neutrophilic cytoplasmic Ab (ANCA)

- Serologies for viral hepatitis A, B, C: non-reactive

- Normal ERCP

- No pulmonary manifestations

- Final diagnosis
  - Autoimmune hepatitis with ductopenia ("autoimmune cholangitis")

Case #4

- 56 year old diabetic woman

- Liver tests:
  - AST 145
  - ALT 189
  - Alkaline phosphatase 289

- Biopsy performed and showed the following features
Case # 4

Portal and periportal sinusoidal fibrosis (trichrome)

Case # 4

Perivenular (pericentral) sinusoidal fibrosis (trichrome)

Case # 4

Portal lymphocytic infiltrates with periportal interface activity
Case # 4

Moderate (2+ to 3+) macrovesicular fatty change
Rare glycogenated nuclei of hepatocytes (arrows, left)

Case # 4

Fatty change with mild predominantly lymphocytic infiltrates
Focal liver cell ballooning (arrow, right)

Case # 4

• Summary of liver pathology
  – Portal fibrosis
    • Table 5: “Portal Fibrosis, Cirrhosis”
  – Sinusoidal collagen deposition
    • Table 18: “Sinusoids: Fibrosis”
  – Portal lymphocytes with periportal activity
    • Table 1: “Portal Lymphocytes with Periportal Inflammation”
  – Fatty change (>50% hepatocytes involved), macrovesicular
    • Table 13: “Fatty Change”
  – Lobular necrosis and lymphocytic inflammation
    • Table 10: “Lobular Necrosis with Inflammation”
### Table 5 - Portal Fibrosis, Cirrhosis

- Alcoholic cirrhosis
- Alcoholic hepatitis
- Alpha-1-antitrypsin deficiency
- Autoimmune hepatitis (cholangitis)
- Autoimmune hepatitis
- Biliary atresia, extrahepatic
- Cystic fibrosis
- Extrahepatic bile duct obstruction, late stage
- Erythropoietic protoporphyria
- Idiopathic adulthood ductopenia
- Hepatic venous outflow obstruction (Budd-Chiari syndrome), chronic
- Hyperalimentation (TPN)
- Indian childhood cirrhosis
- Inflammatory bowel disease: Ulcerative colitis
- Metabolic diseases (e.g., Glycogen storage disease III, Gaucher disease)
- Non-alcoholic steatohepatitis
- Pauci-ducts syndrome, non-syndromic
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Progressive familial intrahepatic cholestasis (Byler syndrome)
- Sarcoïdosis
- Venous congestion secondary to right-sided heart failure, chronic
- Viral hepatitis (chronic)
- Wilson disease

(*Biliary type †Cardiac type)

### Table 18 - Sinusoids: Fibrosis

- Alcoholic foamy degeneration
- Alcoholic hepatitis
- Allograft, fibrosing cholestatic hepatitis
- Allograft, chronic (ductopenic) rejection
- Chronic viral hepatitis, HCV
- Cystic fibrosis
- Erythropoietic protoporphyria
- Hyperalimentation (TPN), adults
- Hyperalimentation (TPN), infants
- Indian childhood cirrhosis
- Leishmaniasis (long term infection)
- Metabolic (e.g., cholesterol ester storage disease, gangliosidosis, GM2, Gaucher disease)
- Neonatal hepatitis
- Non-alcoholic steatohepatitis
- Non-cirrhotic portal fibrosis
- Pauci-ducts syndrome, non-syndromic
- Perivenular alcoholic fibrosis
- Schistosomiasis
- Sickle cell anemia
- Syphilis, congenital
- Wilson disease

### Table 1 - Portal Lymphocytes

- Allograft, acute (cellular) rejection
- Alcoholic cirrhosis
- Autoimmune hepatitis
- Biliary atresia, extrahepatic
- Brucellosis
- Caroli disease
- Chronic granulomatous disease of childhood
- Cytomegalovirus
- Epstein-Barr virus
- Erythropoietic protoporphyria
- Extrahepatic bile duct obstruction, late stage
- Graft versus host disease
- Idiopathic adulthood ductopenia
- Indian childhood cirrhosis
- Inflammatory bowel disease
- Lassa fever
- Lepomem, lymphocytic
- Lymphoma, Hodgkin's (non-tumor liver) and non-Hodgkin's
- Neonatal hepatitis
- Non-alcoholic steatohepatitis
- Non-specific reactive hepatitis
- Porphyrnia cutanea tarda
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Q fever
- Rheumatoid arthritis
- Rocky Mountain spotted fever
- Salmonellosis
- Sarcoidosis
- Tuberculosis
- Wilson disease
- Yellow fever

*Periportal interface inflammation in active stage of disease
### Table 13 - Fatty Change (>50% liver cells involved)

<table>
<thead>
<tr>
<th>Macrovesicular</th>
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</thead>
<tbody>
<tr>
<td>Abetalipoproteinemia</td>
</tr>
<tr>
<td>Acute alcoholic fatty liver with or without cholestasis</td>
</tr>
<tr>
<td>Alcoholic fatty liver</td>
</tr>
<tr>
<td>Alcoholic hepatitis</td>
</tr>
<tr>
<td>Galectosemia</td>
</tr>
<tr>
<td>Hereditary fructose intolerance</td>
</tr>
<tr>
<td>Homocystinuria</td>
</tr>
<tr>
<td>Kawasaki [later stage]</td>
</tr>
<tr>
<td>Long chain acyl-CoA dehydrogenase deficiency</td>
</tr>
<tr>
<td>Non-alcoholic fatty liver</td>
</tr>
<tr>
<td>Non-alcoholic steatohepatitis</td>
</tr>
<tr>
<td>Systemic carnitine deficiency</td>
</tr>
<tr>
<td>Weber-Christian disease</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Microvesicular</th>
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</thead>
<tbody>
<tr>
<td>Acute fatty liver of pregnancy</td>
</tr>
<tr>
<td>Alcoholic foamy degeneration</td>
</tr>
<tr>
<td>Alper’s disease</td>
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<tr>
<td>Cholesterol ester storage disease</td>
</tr>
<tr>
<td>Medium chain acyl-CoA dehydrogenase deficiency</td>
</tr>
<tr>
<td>Reye syndrome</td>
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<tr>
<td>Wolman’s disease</td>
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</table>

### Table 10 - Lobular Necrosis with Inflammation

<table>
<thead>
<tr>
<th>PMN</th>
<th>PMN, L</th>
<th>L</th>
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<tbody>
<tr>
<td>Alcoholic hepatitis</td>
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<tr>
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<td>Caroli disease</td>
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<td>Cholestatic cyst (with bile duct obstruction)</td>
<td>PMN</td>
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</tr>
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<tr>
<td>Extrahepatic bile duct obstruction</td>
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<td>Graft versus host disease</td>
<td>L</td>
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<td>Hemochromatosis</td>
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*Cholestasis in active disease
**Cholestasis as a primary factor in the disease

PMN – Neutrophils  PC – Plasma cells  EO – Eosinophils

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<tr>
<td>Mycobacterium</td>
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<tr>
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<tr>
<td>Sarcoidosis</td>
<td>L</td>
<td>*</td>
</tr>
<tr>
<td>Viral hepatitis, acute and chronic</td>
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</tr>
</tbody>
</table>
| Hepatitis A virus | L | *
| Hepatitis B virus | L | *
| Hepatitis C virus | L | *
| Hepatitis E virus | L | *
| Wilson disease | L | *

*Cholestasis in active disease
**Cholestasis as a primary factor in the disease

PMN – Neutrophils  PC – Plasma cells  EO – Eosinophils
Case # 4
Differential Diagnoses

• 4 of 5
  – Chronic viral hepatitis, HCV
  – Non-alcoholic steatohepatitis
  – Wilson disease

• 3 of 5
  – Alcoholic hepatitis
  – Autoimmune hepatitis
  – Erythropoietic protoporphyria
  – Indian childhood cirrhosis
  – Primary biliary cirrhosis
  – Primary sclerosing cholangitis
  – Sarcoidosis
  – Viral hepatitis, chronic (other than HCV)

Case # 4
Additional Information and Final Diagnosis

• No history of alcohol use
• Serologies for viral hepatitis A, B: non-reactive
• Serologies for viral hepatitis C:
  – HCV Ab: reactive
  – HCV-RNA: positive
• Autoimmune serologies
  – ANA, SMA: non-reactive

• Final diagnosis:
  – Non-alcoholic steatohepatitis and chronic hepatitis (HCV)

General References

• Kanel GC, Korula J. Atlas of Liver Pathology, 3e. Elsevier, 2011
• Lefkowitch JH. Scheuer’s Liver Biopsy Interpretation, 8e. Elsevier, 2010