NEXT GENERATION LEARNING

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USCAP
Creating a Better Pathologist
PBC and PSC Revisited

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• No conflict of interest to disclose
Aims

• Review histologic features of PBC and PSC
• Update on PBC nomenclature
• Discuss uncommon variants of both entities
• Cover important differential diagnosis
“Name change initiative for PBC”

As of 2015, new proposed nomenclature by national and international experts from EASL, AASLD, APASL, UEG and AGA, together with PBC patient groups:

Primary biliary cholangitis

Primary Biliary Cholangitis

- Autoimmune chronic cholestatic disease
- Middle-aged females
- Fatigue, pruritus, elevated AlkP
- AMA positive (95% patients); elevated IgM
- UDCA therapy slows disease progression in 2/3 of patients (Lammers WJ et al. Gastroenterology 2014)
PBC Pathogenesis

• T-cell mediated immune attack of bile duct epithelial cells
  – Anti-mitochondrial autoantibodies to PDC-E2
  – Break of B/T cell tolerance to biliary epithelial cells

• **Multifactorial disease**
  – Genetic predisposition
    • Cordell HJ et al. Nat Communications 2015
  – Chemical environmental factors
    • Prince MI et al. Hepatology. 2001
    • Ala A et al. Hepatology. 2006
  – Infections: molecular mimicry to bacterial PDC-E2, ?retroviral
    • Mao TK et al. Hepatology. 2005
PBC Diagnosis

Two of the following 3 criteria (AASLD Recommendation)

- Elevated AlkP
- AMA +, >90% pts
- Histologic evidence of *nonsuppurative destructive cholangitis affecting interlobular bile ducts*
Lymphocytic cholangitis of **small to medium bile ducts** ("non-suppurative destructive cholangiopathy")

- Hallmark of PBS: **granulomatous cholangitis** (florid duct lesion)
- **Ductopenia**, chronic cholestasis and fibrosis
Lymphocytic cholangitis
Florid duct lesion
Ductular proliferation and interface hepatitis
Ductular proliferation and bile duct atrophy
Lobular granuloma
Portal-based fibrosis
Ductopenia, CBP accumulation
Cirrhosis, “halo” effect
Cholate stasis
PBC Grading and Staging

- Scheuer/Batts-Ludwig: widely used in the US
  - Stage 1: florid duct lesion
  - Stage 2: ductular proliferation and more inflammation with interface hepatitis and lymphoid aggregates
  - Stage 3: fibrosis and mild duct loss
  - Stage 4: cirrhosis and ductopenia

- Other systems have been proposed:
  - Kakuda Y et al. Hum Pathol. 2013
    - Grading: hepatitis and cholangitis
    - Staging: fibrosis, CBP accumulation and duct loss
Differential diagnosis of PBC

Duct damage and ductopenia
- PSC and SSC
- Infantile or childhood disease (Alagille, NSBDP, PFIC, BA)
- DILI
- Hodgkin’s lymphoma (post-treatment)
- CR or GVHD
- Idiopathic adulthood ductopenia

Granulomas
- sarcoidosis
- infections

Chronic hepatitic features
- HCV, HBV
PBC vs. PSC

- **Cholestasis** occurs earlier in PSC than PBC
- Periductal fibrosis and fibro-obliterative lesions favor PSC
- Granulomas favor PBC
Drug-induced bile duct injury

- Portal edema and ductular reaction/cholestasis/resolution OR ductopenia and cirrhosis
- Cholestasis occurs early in course
Idiopathic adult ductopenia

• Diagnosis of exclusion
• Young males (too young for AMA-negative PBC)
• May represent small-duct PSC without IBD OR late-onset of infantile NSPBD, PFIC
• ABCB4 mutation recently reported in family with cholestatic disorder manifesting in adult age
But this is not all...

- Sampling error
- Less common variants:
  - “Overlap” syndrome (PBC/AIH)
  - AMA-negative PBC
  - Premature ductopenic variant (Vleggaar, F et al. Gut 2001)
- Isolated AMA positivity
Overlap syndrome (PBC-AIH)

- ~4% pts of PBC pts
- AMA+, PBC features on biopsy and disproportionately elevated transaminases/IgG
- No formal definition
- Paris Criteria: at least 2 of 3 accepted criteria for each condition
- IAIHC Position Paper:
  - Diagnostic criteria are “arbitrary”
  - “Dominant clinical feature should be treated first”

- Majority evolve into either PBC or AIH
- Therapy should be individually tailored, corticosteroids should be considered

Kuiper EM et al. Clin Gastroenterol Hepatol. 2010
AMA-negative PBC

- 5-10% pts (by IF), previously regarded as “autoimmune cholangitis”
- AMA-M2 may be identified by EIA or Western blot
- Anti-nuclear antibodies +, 30-50% pts
  - subtypes specific to PBC:

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>Anti-gp210</td>
<td>22.2–26.2%</td>
</tr>
<tr>
<td>Anti-centromere</td>
<td>12.6–26.1%</td>
</tr>
<tr>
<td>Anti-sp100</td>
<td>8.7–21.6%</td>
</tr>
<tr>
<td>Anti-chromatin</td>
<td>5.4–25%</td>
</tr>
<tr>
<td>MIT3</td>
<td>82.2%</td>
</tr>
<tr>
<td>Anti-kelch-like 12</td>
<td>16–40%</td>
</tr>
<tr>
<td>Anti-hexokinase 1</td>
<td>16–45%</td>
</tr>
</tbody>
</table>

Sclair S et al. Clin Transl Gastroenterol. 2015
Anti-gp210 and anti-centromere antibodies are different risk factors for the progression of primary biliary cirrhosis.
Primary Sclerosing Cholangitis

Inflammation and fibrosis of intra- and/or extrahepatic bile ducts and:
• EHBT involvement no longer a pre-requisite
• Absence of choledocholithiasis
• Absence of previous surgery

Martin JA. Am J Gastroenterol 102 (2007)
Primary sclerosing cholangitis

- Bile duct fibrosis and obliteration caused by long standing inflammation, ischemia and/or obstructive injury
- Multifactorial disease (genetic and environmental)
- <50 yrs; M>F
- 75% IBD (UC>Crohn); 5% of UC pts have PSC
- Complications:
  - **Cholangiocarcinoma** – 20% over 30 yrs, also GBC, CRC
  - **Recurrence** post OLT in approx. 20% cases over 5 years
  - Biliary tract infections (bacterial and Candida)
Labs are non-specific

- p-ANCA positive (80%)

- **Cholangiography is diagnostic:** **MRCP** recommended as first-line imaging (also ERCP, PTC): short, annular strictures alternating with dilated segments (**beaded appearance**).

- Liver biopsy: staging, small duct PSC, exclusion of other entities (overlap PSC-AIH)
Concentric periductal fibrosis

Classic histopathology of PSC
Concentric periductal fibrosis and epithelial atrophy
Early periductal collagen accumulation
Fibrous obliteration of bile duct
Fibrous obliteration of small bile duct
Distinctive histologic features of PSC

- Comparison of PSC and control (PBC and HCV) explants by SAM (Carrasco-Avino G et al. AJCP 2015):
  - Bile duct scars
  - Onion-skin fibrosis of *terminal* and medium-size BDs
  - Medium-size BD loss
  - *Arterial fibrointimal hyperplasia (75% of cases)*
  - Less inflammatory activity

Periductal fibrosis of terminal BD
Arterial fibrointimal hyperplasia and periductal fibrosis
Arterial fibrointimal hyperplasia
• Scoring depends on adequacy (Guido et al. >22 mm, >11 portal tracts)
• No specific scoring system for PSC
• Ludwig and Nakanuma systems (developed to assess PBC)
  – **Degree of fibrosis** is of important prognostic value
  – Nakanuma system shows strongest predictive power: fibrosis and **orcein deposition** predicted Tx-free survival and time to LTx (De Vries EDM, et al. J Hepatol 2015)
Differential diagnosis

Obstructive:
- Tumors,
- Choledocholithiasis
- Past surgeries

Inflammatory:
- IgG4-associated cholangitis
- AIDS-related cholangiopathy
- PBC

Ischemic cholangiopathy/SSC in critically ill
IgG4-associated cholangitis
Storiform fibrosis
Obliterative phlebitis
Dense lymphoplasmacytic infiltrates with increased IgG4+ PC
<table>
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<tr>
<th></th>
<th>PSC</th>
<th>IgG4-assoc cholangitis</th>
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<tbody>
<tr>
<td>Age</td>
<td>&lt;40</td>
<td>60-80</td>
</tr>
<tr>
<td>Elevated serum IgG4</td>
<td>10-25%</td>
<td>100%</td>
</tr>
<tr>
<td>IgG4/IgG1 ratio</td>
<td>&lt;0.24</td>
<td>&gt;0.24</td>
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<tr>
<td>Cholangiography</td>
<td>Segmental strictures,</td>
<td>One or more strictures,</td>
</tr>
<tr>
<td></td>
<td>beaded appearance</td>
<td>migrating strictures</td>
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<tr>
<td>IBD and CCa</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Response to steroids</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Progression to cirrhosis</td>
<td>Yes</td>
<td>No</td>
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Challenges: can changes be identified on random liver biopsy?

New approaches:
- HISORt criteria
- IgG4+ B cell clones ny NGS (highly specific)
- Blood IgG4 mRNA

Mailette de Buy Wenniger and Beuers. Curr Opin Gastroenterol 2015
Beuers et al. Dig Dis 2015
Ischemic cholangiopathy

Risk Factors
- Thrombotic disorders
- Systemic vasculitis
- Liver transplantation (ABO incompatible)
- Hepatic intra-arterial chemotherapy
- Severely ill patients
• Limited biopsies
• PSC variants:
  – Small duct PSC and
  – “Overlap” syndrome (PSC-AIH)
• Posttransplantation biopsies
• Risk of malignancy

But this is not all...
Small duct PSC

- 6-16% of PSC cases
- Clinical and laboratorial features of PSC with normal cholangiography
- Slower progression, better survival rates and less Cca
- 20% progress to large duct PSC in median 7.4 yrs
Overlap syndrome (PSC-AIH)

• Children and young adults, more frequent than in PBC
• Serology is characteristic of AIH; may begin as AIH and progress to PSC
• Small-duct PSC may be more prevalent in overlap (27%, Olsson R et al 2009)
• Consider corticosteroids/immunosuppression
Cancer surveillance in PSC

• **72% 5-year disease-free survival in patients with early stage perihilar Cca treated with neoadjuvant chemotherapy and transplant** (Murad SD et al. Gastroenterology 2012)

• ERCP for dominant strictures
  – Brushing cytology/biopsy – low sensitivity
  – FISH

• Most sensitive: high-grade dysplasia (73%) and positive FISH (82%) (Boberg KM et al. J Hepatol 2006)
PBC and PSC are chronic, progressive, cholestatic liver diseases that share some clinical and histologic manifestations.

**PBC:**
- Nomenclature change from “cirrhosis” to “cholangitis”
- Early biopsies may show nonspecific/reactive hepatitis
- Must remember DDx (infections, sarcoidosis, DILI) and variants (overlap, AMA-negative PBC)

**PSC:**
- Liver biopsy often not diagnostic: used for staging and to rule out small duct PSC and overlap syndromes
- No known etiology nor therapy is available
- Clinical information is key to rule out important ddx (eg. IgG4-RD and ischemic cholangitis)
- Pre-malignant condition