Primary Sclerosing Cholangitis: New Ways to Think About an Old Disease

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Primary Sclerosing Cholangitis

- A chronic, progressive inflammatory disease of the liver and biliary tree
- Etiology unknown but strongly associated with IBD
  - Almost always associated with colonic inflammation
- Can progress over time to:
  - ESLD
  - Portal hypertension
  - Jaundice
  - Pruritis
  - Cholangiocarcinoma

Feurer, Hilden, Adler Clin Gastroenterol Hepatol 2012
ERCP Risks & Stricture Management

Old CW
- Stenting controversial
- Dilation favored
  - Balloons
  - Catheter dilators
- Role of antibiotics unclear

New CW
- Stenting safe
- Balloon dilation may be associated with worse outcome
- Antibiotics of great value
- Operator experience associated with better outcomes
- Beware comorbidities


Table 2  Outcomes of multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>0.701</td>
</tr>
<tr>
<td>Endoscopist</td>
<td>0.012</td>
</tr>
<tr>
<td>Stenting during procedure</td>
<td>0.163</td>
</tr>
<tr>
<td>Dilation during procedure</td>
<td>0.021</td>
</tr>
<tr>
<td>Presence of dominant stricture</td>
<td>0.069</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>0.587</td>
</tr>
<tr>
<td>Sphincterotomy during procedure</td>
<td>0.031</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>0.049</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Alkhatib and Adler Dig Dis Sci 2011
PSC and Malignancy

- PSC strongly associated with cholangiocarcinoma
  - Often diagnosed at an advanced stage
  - Resection or OLTx only curative options
- PSC also associated with:
  - Gallbladder cancer 3-14%
  - Hepatocellular carcinoma (due to underlying cirrhosis)

Razumilava et al Hepatology 2011

What is a “dominant stricture?”

- All PSC patients have, by definition, biliary strictures
- The “Dominant Stricture”
  - A nonspecific term
  - Can refer to intra or extrahepatic strictures
  - Often associated with clinical biliary obstruction
- Definition of a “Dominant Stricture”
  - A stricture less than 1.5mm in diameter of the CBD
  - A stricture of less than 1mm in diameter in the intrahepatic ducts
  - Technical definitions may lose the forest for the trees ...

Bjornsson E AJG 2004
Adler’s Definition

- “A dominant stricture is the cholangiographic finding of a stricture that stands out amongst all others in a patient with primary sclerosing cholangitis.”
- Pro: Immediately intuitive, universally applicable
- Con: Subjective
Cholangiocarcinoma
Benign for 5 years

Tissue Acquisition in PSC

- Brushings
  - Routine Cytology
  - FISH
- Forceps biopsy
- EUS guided FNA
Routine Brushings

- Three possible results:
  - Positive for malignancy
  - Negative for malignancy
  - Atypical cells (AARGHHH!!!)
- Brush cytology
  - Sensitivity 30-60%
  - Specificity 90-96%
- Pro - Cheap, easy, fast
- Con - May be less than helpful

Atypical Cells...

- A common result on biliary brush cytology in PSC
- Inflammation can influence cellular appearance
- Malignancy sometimes difficult to detect
- May warrant re-sampling or evaluation of stricture in full clinical context
ABBS Score

Score ≥ 4 statistically associated with malignancy

<table>
<thead>
<tr>
<th>Atypical Biliary Brushing Score (ABBS)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 60</td>
<td>+1</td>
</tr>
<tr>
<td>Endoscopic impression malignant</td>
<td>+2</td>
</tr>
<tr>
<td>Procedure indication pancreatic mass</td>
<td>+1</td>
</tr>
<tr>
<td>Stricture in Common Hepatic Duct</td>
<td>+2</td>
</tr>
<tr>
<td>Stricture in Distal Common Bile Duct</td>
<td>+1</td>
</tr>
<tr>
<td>Presence of PSC</td>
<td>+2</td>
</tr>
<tr>
<td>CA 19-9 above 300 U/mL</td>
<td>+1</td>
</tr>
</tbody>
</table>

Witt, Adler et al Diagnostic Cytopathology In Press

FISH

- Originally developed to test for urothelial cancer
- Malignant PB cancers: 80% show aneuploidy
- Targets the pericentromeric regions of the chromosomes 3 (CEP 3), 7 (CEP 7), and 17 (CEP 17) as well as the chromosomal band 9p21 (LSI 9p21).
- Four or more morphologically abnormal cells with two or more chromosomes with polysomy constitutes a positive test.
- Fourteen or more nuclei with a single gain constitutes a positive test
- Isolated trisomy 7 is equivocal

Huddleston, Lamb, Gopez, Adler, Collins Diagnostic Cytopathology 2012
Negative Biliary FISH Study

Positive Biliary FISH Study
FISH

- FISH can detect polysomic cells before other tests
- In one study, 69% of FISH-Positive patients with PSC ultimately had CCA
- FISH Polysomy
  - Sensitivity: Specificity 46%:88%
- FISH Trisomy/Tetrasomy
  - Sensitivity : Specificity 25%: 67%
- Should FISH be used universally along with routine brushings in patients with PSC?
  - Perhaps best used as part of institutional clinical or research protocol

Barr Fritcher AJG 2011, Bangarulingam Hepatology 2011

Cholangioscopy

- Mother-Baby ERCP scope system
- Allows direct visualization of biliary tree
- Allows more targeted brushings and biopsies
- Once rarely performed
  - Practice now widespread
Cholangioscopy

**Pro**
- Can be very helpful
- Allows targeted biopsies
- Allows targeted brushings
- May reveal concerning areas unsuspected on cholangiogram
- Relatively fast: 15-20 mins
- CPT code available
- Biopsies up to 82% accurate

**Con**
- Additional hardware
- Learning curve
- Images not always ideal
- Appearance of concerning lesions not always classic
- Small forceps biopsies may be too small to be diagnostic

Hartman CGH 2012, Ramchandani GIE 2011

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**Biopsy diagnosis**

<table>
<thead>
<tr>
<th>Visual diagnosis</th>
<th>Benign</th>
<th>Malignant</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>10</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Malignant</td>
<td>5</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>5</td>
<td>20</td>
</tr>
</tbody>
</table>

Preliminary concordance between visual and biopsy diagnosis = 75% (15/20)

Chen Y and Pleskow DK, GIE 2007
EUS For Cholangiocarcinoma

**Pro**  
- May allow diagnosis by FNA  
- Allows for sampling of lymph nodes  
- May provide additional data regarding relationship of ducts to tumor

**Con**  
- May be technically difficult  
- FNA of primary tumor may predispose to tumor seeding and iatrogenic upstaging  
- May eliminate ability to undergo liver transplant

Conclusions

- PSC stricture management continues to evolve
- Threshold for suspicion of cancer should be low
- Consider FISH for any concerning lesion
- Take FISH results seriously
- Cholangioscopy provides meaningful information
  - Even in the absence of a tissue diagnosis
- EUS helpful, but FNA may not be for everyone