Colons, Cholangio’s and Controversies

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CMJAH and WDGMC
Overview

• Epidemiology
• Pathogenesis
• Natural History
• Diagnosis
• Treatment
• PSC and IBD
Primary Sclerosing Cholangitis

- Chronic Progressive Cholestatic Inflammatory
- Extra and Intra Hepatic Ducts
- Variable Rate of Progression
- Unclear Pathogenesis
- Poor Long term outcomes
Epidemiology

- Incidence 1-3/100 000
- Prevalence of 16/100 000
- 60-70% Male
- Mean Age of Diagnosis 30-40 years
- Strongly associated with IBD
  - Conversely 4-5% of IBD associated with PSC
Natural History

Population–based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis
Pathogenesis

- Genetics
- Microbiome
- Toxic Bile Theory
- Macrophage changes and Leucocyte Trafficking
Diagnosis

- **Cholestasis**
  - Elevated Alk Phos
  - Auto Antibodies
  - AMA
  - IgG/IgM
  - IgG₄

- **Cholangiogram**
  - ERCP vs MRCP
    - Beading and Stricturesing

- **Liver Biopsy**
  - Not Recommended
  - Small Duct PSC
  - Overlap Syndromes
### Differential Diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Choledocholithiasis</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
</tr>
<tr>
<td>HIV assoc. Cholangiopathy</td>
</tr>
<tr>
<td>IgG$_4$ Related Cholangitis</td>
</tr>
<tr>
<td>Portal Hypertensive Bilopathy</td>
</tr>
<tr>
<td>Diffuse Intrahepatic SOL</td>
</tr>
<tr>
<td>Surgical Biliary Trauma</td>
</tr>
<tr>
<td>Recurrent Pyogenic Cholangitis</td>
</tr>
<tr>
<td>Recurrent Pancreatitis</td>
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<tr>
<td>Sclerosing cholangitis in the critically ill</td>
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<tr>
<td>Intra-arterial chemotherapy</td>
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</tbody>
</table>
# PSC vs IgG<sub>4</sub> Disease

<table>
<thead>
<tr>
<th></th>
<th>PSC</th>
<th>IgG&lt;sub&gt;4&lt;/sub&gt; Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>65%</td>
<td>80%</td>
</tr>
<tr>
<td>Age</td>
<td>25-45yrs</td>
<td>65yrs</td>
</tr>
<tr>
<td>IBD</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Jaundice</td>
<td>End Stage</td>
<td>Presenting Sympt 75%</td>
</tr>
<tr>
<td>Other Organs</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>IgG&lt;sub&gt;4&lt;/sub&gt;</td>
<td>9%</td>
<td>70%</td>
</tr>
<tr>
<td>Steroid</td>
<td>No Response</td>
<td>Dramatic Response</td>
</tr>
<tr>
<td>CCA</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
Medical Management

There is No Established Medical Therapy!
Role of UDCA

- **Low Dose**: 13-15mg/kg/day
  - Improves Biochem
  - No Survival Benefit

- **Medium Dose**: 17-23mg/kg/day
  - Improves Biochem
  - Trend towards Survival Benefit
  - Study underpowered

- **High Dose**: 25-30mg/kg/day
  - Increased rates of Treatment failure

Prospective evaluation of ursodeoxycholic acid withdrawal in patients with primary sclerosing cholangitis - Wunsch et al
“More recently, several studies have shown that patients with PSC, who normalize liver biochemistries, whether this occurs spontaneously or more often with UDCA therapy, have a better prognosis. This has led some to revisit the issue of UDCA treatment for PSC; many practitioners are using a dose of ~20 mg/kg/day, although data from well-controlled clinical trials are lacking (47–49).”
General Measures

- Pruritus: Step up approach
  - Bile Acid Resins/Rifampin/Naltrexone/Sertraline

- Monitor for Varices/Osteoporosis

- Fat Soluble Vitamin Deficiencies

- Refer for Liver Transplant
  - Decompensated Liver Disease
  - PSC Mayo Risk Score >2
Complications

- Dominant Strictures
- Cholangitis
- Malignancy
Screening Cholangiocarcinoma

- Cross sectional imaging every 6-12 months
  - US/CT/MRI
  - Ca 19-9

- MRI + Ca19-9 Sens 100% Spec 38%

- US + Ca 19-9 Sens 91% Spec 62%

- Cytology + FISH

- Cholangioscopy
Screening
Gall bladder CA

- Polyps > 8mm in the gall bladder should result in Cholecystectomy

Lindor KD et al, AJG 2015
Screening Colon

- Colonoscopy at Diagnosis
- Annual Colonoscopy if Concurrent IBD
- Every 3-5 years if no IBD
- Chromoendoscopy
PSC and IBD
Non PSC Liver Disease in IBD

<table>
<thead>
<tr>
<th>NAFLD</th>
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<tbody>
<tr>
<td>DILI</td>
</tr>
<tr>
<td>Portal Vein Thrombosis</td>
</tr>
<tr>
<td>Hepatic Amyloidosis</td>
</tr>
<tr>
<td>Granulomatous Hepatitis</td>
</tr>
<tr>
<td>Hepatic Abscess</td>
</tr>
</tbody>
</table>
PSC IBD and CRC

- 4-5 x Greater risk than IBD alone
- Carcinomas are Right Sided
- Low Dose UDCA has possible benefit
### Ursodiol and Colorectal Cancer or Dysplasia Risk in Primary Sclerosing Cholangitis and Inflammatory Bowel Disease: A Meta-Analysis

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tung</td>
<td>0.44 (0.26, 0.75)</td>
<td>20.22</td>
</tr>
<tr>
<td>2</td>
<td>Pardi</td>
<td>0.30 (0.09, 1.00)</td>
<td>11.12</td>
</tr>
<tr>
<td>3</td>
<td>Wolf</td>
<td>0.97 (0.50, 1.89)</td>
<td>18.20</td>
</tr>
<tr>
<td>4</td>
<td>Lindstrom</td>
<td>0.78 (0.29, 2.08)</td>
<td>13.73</td>
</tr>
<tr>
<td>5</td>
<td>Braden</td>
<td>2.22 (0.29, 17.14)</td>
<td>5.45</td>
</tr>
<tr>
<td>Subtotal (I-squared = 40.3%, p = 0.152)</td>
<td></td>
<td>0.64 (0.38, 1.07)</td>
<td>68.72</td>
</tr>
<tr>
<td>Subtotal (I-squared = .%, p = .)</td>
<td></td>
<td>3.72 (1.13, 12.30)</td>
<td>11.26</td>
</tr>
<tr>
<td>Navaneethan</td>
<td></td>
<td>1.06 (0.61, 1.83)</td>
<td>20.02</td>
</tr>
<tr>
<td>Subtotal (I-squared = .%, p = .)</td>
<td></td>
<td>1.06 (0.61, 1.83)</td>
<td>20.02</td>
</tr>
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**Overall (I-squared = 63.9%, p = 0.011)**

0.87 (0.51, 1.50) 100.00

**NOTE:** Weights are from random effects analysis.
Vedolizumab

- Monoclonal Antibody directed against $\alpha_4\beta_7$
- Decrease Leucocyte trafficking
- Other Novel Treatments include FXR agonists
In Conclusion

- **At Diagnosis**
  - Measure IgG4
  - Colonoscopy
  - Consider UDCA

- **Follow up**
  - Quarterly labs
  - 6-12 monthly Cross sectional imaging and Ca19-9
In Conclusion

- Dominant Strictures
  - ERCP with Brush Cytology and FISH
  - Dilatation

- Refer Liver Transplant
  - Clinical Decompensation
  - Suspicion of CCA
Slide 3

PSC - Chronic Progressive Cholangitis Distal Cholestasis
- Intra & Extrahepatic Bile Ducts
- Variable Rate of Progression
- Uncommon Pancreatitis
- Poor long Term Outcome

Slide 4

Epidemiology:
- Frequency 1-3/100,000 / Prevalence 16-170,000
- Male Prevalence 60-70%. Age 50-40 yrs.
- Strongly Associated = IBD. - Predominantly Ulcerative Colitis
- Approximately 4-5% of IBD associated w/ PSC.

Slide 5

Nominales:
Barriger et al published a large study from the US.
North Carolina & Duke University + Canopy Children's Hospital.
Median age death in 15 yrs.

Slide 6

Pathogenesis:
Not fully understood.
- Humoral, T cells, Genetic Factors, & Molecular Models
- Humoral factors
- T cell mediated. Multiple Studies have show 16 loci in our analysis. 7 loci specifically.
- In PSC: 4 loci assoc with IBD

Slide 7

CellCept
- T 
- Tumour Necrosis Factor - Liposomal Aldosteron in the Kid & Liver
Slide 03 - 2013 Trial by Wooden et al for HCC. Carcinogen therapy was used. By reviewed RCT who had discussed VDC-70 RCT in presence of enzymes and symptoms. AFP level and no symptoms 8/10 vs 8/10 vs better outcome.

Slide 04 - 2015 ACC guideline led to this summary version statement.

Slide 05 - General principles:
- Use HCC/Prostate/ovary/renal 1 vs 20-year/55RTE 3 times
- Median: For patients > 40 years 2 vs 10
- Adv disease: Look for high risk features.
- Tumor for liver Tx: Delineate on CT/PET scans.
- PCNS may occur > 30/30: MCD 14.

Slide 06 - Dominant Surgical: Sonar alone in 39% or alone + Hepatocellular.
- 20 vs. live donor surgery 0% vs 1%.
- 18-26% complication.
- Major survival: Surgery: CCA? A HCC?
- Endoscopic MPD = Dilatation and Stent removal.
- Exposed Mayo bowl Scanner.
- Choledochitis = Sural Decompression.
- E-F Dominant Sphincterotomy/
- Choledochotomy + + Decompression.
- Metastatic 400 vs 500 Risk for CCA vs even age 15%.
- 8% vs. 10% in 1st year.
- Endoscopy + FSGH + Polype.
- Cholangioscopy + Polype: Better yields.
Slide 17
Screening CCA: Core Several 12-18 Gy in 6-12.Inst 1
To Check with Ca 19-9

Slide 20
Cell Block or Pap:
- 78 mm: Cholangiocarcinoma
- Colonic: Colonoscopy
- Dr. Baker: Annual if >50 or 3+ yearly
- Hepatic: Biopsy
- Vague by CEA or CA 125

Slide 20
Thank you for indulging me.
- Yes I wanted it not CT in December.
- So here's a little about CEA
- CEA: Pharynx:
- 1st choice: often baseline, good base of screening
- 2nd Dr: Boost early lesions and local biopsy
- PSC: Biliary:胆道 Bile ducts and internal biliary

Slide 21
Non-PSC Liver Dr.

Slide 22
A-Sy Spectrum Flow E2D alone.
- CD 25 KIR-1: soccer
- CD 25 KIR-2: soccer

Slide 23
Monocytosis by R: KIR-1: low Dose Trend to Imuran
- High Dose 25 mg Trend to "March!"

Slide 24
Vascular:
- Massive LV KIR
- Systolic: Block
- CVP: Low
- Swelling: Fluid: Venous flow: ALP
- 20/12/17: Study Lymphoedema
glioblastoma

CellCept®
mycophenolate mofetil
Slide 8 
**Diagnosis**
- Cholestasis - ACRP - May be incident in autoimmune 
  - Liver Function Test: ANA, Anti-Mitochondrial Antibody (AMA)
  - ACRP = 90% Cautious = PRC
  - Glutathione S-transferase - MAgEP = 10X

Slide 19
- Cholestasis: More Cautious = ACRP / Sputum Culture
  - ACRP: No Evidence of Sub-Duodenal Disease
  - Alcohol for Transformation

- Liver Biopsy: Not recommended to make the diagnosis

Slide 23
- RBC is still a diagnosis of Gastroenterology

Slide 26
- Differentiation between PSC and Fibro-Disorder
  - Invariance seen in the Distal Pyloric 
    - Aleatory: Regurgitation
  - IRSAGT - History: Recovery / Course again: Return to work

Slide 31
- No official medical treatment
  - Esophageal Ultrasound: Hypertension Intolerance
  - No Survival: Restana, 
  - PSC - Colic Disease - No Survival: Restana

Slide 40
- Dyspnea, Headache - ED Survival: Restana
  - ESPO: Emergency surgery - works in ACRP Study 2012
  - Emergency medication, Sub-Treatment (R) is found to improved outcomes.