Liver Disease in IBD

2 cases

6 ½ yo F bloody stools → Crohn colitis

Other labs:
- ANA NEG
- α-SMA + (4+)
- pANCA ++

Liver Bx

<table>
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<tr>
<th></th>
<th>Presentation</th>
<th>Referral</th>
<th>7 y</th>
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<tr>
<td>AST</td>
<td>110</td>
<td>291</td>
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<tr>
<td>GGT</td>
<td>&lt;20</td>
<td>437</td>
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<tr>
<td>T Bil</td>
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<td>0.5</td>
<td>0.6</td>
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<tr>
<td>ALB</td>
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<tr>
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Now what?
- UDCA
- Abx
- Prednisone
- Pred + Azathioprine
- Tacrolimus
- Transplant Evaluation

6½ yo F bloody stools ➔ Crohn colitis

<table>
<thead>
<tr>
<th>Age:</th>
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<th>Referral</th>
<th>7 y</th>
<th>8 y</th>
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<tr>
<td>AST:</td>
<td>-</td>
<td>437</td>
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<td>53</td>
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<td>Plat:</td>
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<td>322</td>
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Other labs:
- ANA NEG
- α-SMA + (46)
- pANCA ++

Balsalazide
Metronidazole
UDCA – 20 mg/kg/d
11 year old boy with bloody stools

Dx: UC

11 yo M bloody stools   Dx UC

Age: 11 y

ALT: 109
AST: 56
GGT: 153
T Bili: <0.1
ALB: 3.6
Plat: 490

Liver Bx

Other labs:
ANA NEG
α-SMA NEG
Now what?
- UDCA
- Azax
- Prednisone
- Pred + Azathioprine
- Tacrolimus
- Transplant Evaluation

Serial MRE’s & Labs reveal rapid progression
Age: 11 y 14½ y 15 y

<table>
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<tr>
<th></th>
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<th>GGT</th>
<th>TBili</th>
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<td>63</td>
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Hgb 3.6

Ascites,
Variceal bleed
Transplant List

Liver Disease in IBD

Q: **Why liver disease** & **Why are they so different?**
1947: 1st report of Cirrhosis in a child with UC

HEPATIC CIRRHOSIS AS A COMPLICATION OF CHRONIC ULCERATIVE COLITIS


Case Reports

Case 1. M.C.S. Female. Age 14.
This patient was first admitted to the Graduate Hospital in April 1939. Diarrhea had begun one year prior to this. A diagnosis of anemia had been made, although the basis for this diagnosis is unknown. Seven months before this admission, pain had developed in the right upper abdomen. Because this was thought to be due to possible amebic abscess, laparotomy was performed. Symptoms of the gall-bladder were discovered and the liver was found to be small and cirrhotic.

Comment. This 14 year old patient had been found to have hepatic cirrhosis a few months after the onset of the symptoms of chronic ulcerative colitis. During the subsequent course of her illness, the developed splenomegaly, jaundice, enlargement of the liver, and evidence of liver dysfunction.

Albumin 2.0 Hepatosplenomegaly Jaundice Emaciation


Thoughts from 1947 & 1949

A study of our patients has convinced us, on the other hand, that severe and prolonged colitis may readily produce changes in the patient which lead to the development of cirrhosis. We, therefore, believe that cirrhosis may occur occasionally as a true complication of colitis.

It is also necessary to mention the possible effect on the Liver of the constant absorption of toxic material and bacteria from the bowel.

1949 BMJ Editorial: Cirrhosis & Colitis

In most of the published reports the attempt to relate the cirrhosis or other hepatic lesion to the coexisting colitis is most unconvincing.

A curious and fallacious argument has been followed by both Johnson and Turner.


Topics for 2013: 66 years later

- Incidence, prevalence, potential etiology
  - Adults vs. Children
- Recognition of clinical manifestations
  - Signs & Symptoms
  - Labs & Imaging
- Relevant clinical consequences
- Genetic, immunological, microbial contributions
- Therapies
- Future & Long-term issues
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Liver Disease in IBD – 4 Q’s

- Q1: How can I identify liver disease?
  - Signs & Symptoms
  - Labs & Imaging
  - Invasive procedures (ERCP, PTC, Bx...)
- Q2: Does the Liver “track” with the bowel?
  - Or, if the bowel is better, is the liver better too?
- Q3: What does liver disease mean for the child with IBD?
- Q4: Where does the field need to go?
  - Etiologies
  - Treatments

Why is the Liver a target in IBD?

- Inflammation
  - From the gut
- Microbial products
  - LPS & others
  - Reprocessed molecules
- Commonalities between cholangiocytes & enterocytes.
**1947: 1st report of Cirrhosis in a child with UC**

*HEPATIC CIRRHOSIS AS A COMPLICATION OF CHRONIC ULCERATIVE COLITIS*  

It is also necessary to mention the possible effect on the liver of the constant absorption of toxic material and bacteria from the bowel.

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**Etiologies & Roles for Genes & Guts**

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**Adult onset PSC: Basics**

- Incidence ~ 1/100,000  
  Prevalence ~ 10/100,000
- Median age 41 y (~ 50% asymptomatic at Dx)
  - Within 5 years ~ 22% have symptoms
    - fatigue, pruritus, jaundice, abdominal pain
- 60-80% have IBD & 4% of UC have PSC
- 6% have overlap PSC+AIH
- Symptomatic on presentation→ 9y to death/LT
- IgG4+ with AI Pancreatitis
- Screening for Colon CA, Cholangio CA (1%/yr)

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**Notes:**


**Adult IBD: Abnormal LFTs → Survival**


**Prevalent autoantibodies in PSC in Adults**

- pANCA 26-94%
- ANA to 83%
- α-SM Ab to 80%
- α-LKM Ab 0%

**Pediatric Liver Disease in IBD: Single Center Study**

- Reported prevalence ~ 5%
- 8 years: 52 children Dx with Colitis. Ages 9-16 y
- 17 (11 M) with Liver Indices in [32%]
- 14/17 (82%) had liver labs on presentation
  - Liver Bx during Colonoscopy
  - GGT: 83-1401
  - ALT: 51-1435
  - MRCP: Abnormal in 12/17
  - All 12 with Auto-Immune "features" (10 + pANCA, 8 αSMAb )
  - Rx with Pred +/- AZA
- 15/17 normal liver labs 3 y of f/U
- No association of severity of colitis with liver disease

Pediatric PSC: Mt. Sinai referral series

- 12 year retrospective study
- 47 patients with PSC
  - Med 12 y (2-20 y)
    - IBD dx 1st: 26%
    - PSC dx 1st: 15%
    - IBD + PSC dx together: 59%
- Liver bx in 45
  - Fibrosis 1/2: 16 (35%)
  - Bridging Fibrosis: 25 (56%)
  - Cirrhosis: 4 (9%)
  - AIH: Features 12 (25%)
- MRCP in 39
- ERCP Interventions in 8
  - Papillotomies, Stents


Adult onset PSC: Medical Treatment

- Medications without efficacy in PSC (no AIH):
  - Steroids
  - Etanercept
  - Infliximab
  - Tacrolimus
  - Cyclosporine
  - Azathioprine
  - Methotrexate
  - UDCA

... In adult patients with PSC, we recommend against the use of UDCA as medical therapy (1A). ...

... UDCA (15-20 mg/kg/d) improves serum liver tests ... but does not reveal a proven benefit on survival...

... does not yet allow a specific recommendation for the general use of UDCA in PSC...
Adult onset PSC: UDCA Meta-analysis

<table>
<thead>
<tr>
<th>AUTHOR-YEAR</th>
<th>UDCA PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindor 1997</td>
<td>1:51 / 1:51</td>
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<tr>
<td>Mitchell 2001</td>
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<tr>
<td>D'usso 2003</td>
<td>1:16 / 1:16</td>
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<tr>
<td>Lindor 2009</td>
<td>9:73 / 9:73</td>
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Pooled (Fixed effect): 30:237 31:228 0.841 (0.493-1.418)

Better Placebo/No Rx Better UDCA


HD UDCA (28-30 mg/kg/d) → Worse Outcomes in Early PSC

Early stage PSC Cr = YD

UDCA Placebo

Endpoints

Antibiotics → Improved Liver Indices in PSC

14 patients on po Vanco (50 mg/kg/d) → Improved Liver Indices in PSC

• 2-17 y (mean 12 y)
• 11 UC, 3 CD  No AIH
• Variable Rx lengths: 5-56+ months
• Less effective in cirrhotics

PSC: Clinicaltrials.gov → 41 trials (8 for children)

Select Pediatric Trials:
• UDCA withdrawal: NCT01088607: WUP PSC (Black, U Tenn)
• Vancomycin: NCT01802073: Microbiome (Cox, Stanford)
• Genomics: NCT01161992: ages 5-90 (Lazaridis, Mayo)

Select Adult Trials:
• Endoscopic U/S, ERCP (Spyglass, Narrow Band Imaging, Stents...)
• NorUDCA NCT01755007: Ph II double-blind Europe (Trauner, Falk)
• Fenofibrate NCT01142323: Pilot study (Alk Phos (Levy, Miami))
• Simtuzumab NCT01672853: Ph II anti-LoxL2 (anti-fibrotic) Gilead
• Rifaximin NCT01695174: Ph II (Talkwalker, Mayo)
• UDCA + ATRA NCT01456468: Ph I (Boyce, Yale)

October 6, 2013: search terms "sclerosing cholangitis AND children"
Summary: Liver Disease in IBD – 4 Q’s

Q1: How can I identify liver disease?
- Look for it at presentation of IBD, mainly colitis
- Labs (GGT +) & Imaging (MRCP)
- Invasive procedures for obstruction (ERCP, PTC)
- Biopsy for those with AIH features, or not sure.

Q2: Does the Liver “track” with the bowel?
- No → PSC is often linked to quiescence of colitis.

Q3: What does liver disease mean for the child with IBD?
- Potential for complications or transplant.
- UDCA & Abx treatments require better studies.

Q4: Where does the field need to go?
- Etiologies: Genes, Microbes, Immune cells, Diet
- Treatments: Antibiotics, Anti-fibrotics, FXR Agon., NorUDCA
- Longitudinal studies of children with IBD
Liver Disease in IBD – Unmet needs

• True Incidence, prevalence data
• Roles for Clinical Best Practices
• UDCA, Vancomycin, Nor-UDCA, FXR agonists ...
• True etiologic gut-liver connections
  • Genomics (e.g. TGR5, Immune pathways)
  • Microbial products and prokaryotic derived metabolites
• Transplant Evals & Post-Transplant care
• Future & Long-term issues
Mechanism of high GGT cholestasis

- Retention of bile acids within hepatocytes
- Presence of bile acids within bile ducts

(GGT released from apical membrane into serum)