A unique UC phenotype

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4 key thoughts...

• The jaundiced IBD patient
• The role of the multi-disciplinary team
• When to transplant?
• What to do with the colon?
Clinical Case

• 24 year old male

• Family history of colorectal carcinoma (CRCa)

• Inflammatory bowel disease in 2010 (IBD)
  – Pan-colitis (mild)
  – Sigmoid/rectal < right sided inflammation
  – Ulcerative colitis (UC)

• Management
  – 5 ASA oral + suppositories
Clinical course

- Mostly asymptomatic, uncomplicated UC

- 2015
  - Severely fatigued
  - Yellow discoloration
  - Severe pruritus
• Cholestatic picture
• Synthetic function preserved
• No recent drug history
• Hepatitis studies all negative
• Autoimmune studies negative
• Ferritin normal
• HIV negative
• Ceruloplasmin normal

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Imaging

MRCP 2015

Beading and irregularities
Focal narrowing
Dominant stricture
Hepatomegaly
Primary sclerosing cholangitis (PSC)
Primary sclerosing cholangitis (PSC)

- Chronic cholestatic liver disease
- Intra and extrahepatic bile duct
- Bile duct obliteration, cirrhosis and liver failure
- > 50% require liver transplant in 10-15yrs
Pathological themes in PSC

**Histopathology**

- Progressive injury to small and large ducts
- Inflammation confined to portal tracts
- Concentric periductal fibrosis (onion skinning)
- Loss of bile ducts and cirrhosis

*Sleisenger and Fordtran's Gastrointestinal and Liver Disease. Chp. 68 10th edition*
The PSC-IBD relationship

- Strongly associated to inflammatory bowel disease (IBD)

- 67% to 73% of patients with PSC have IBD
  - 85 to 90% have UC
  - 10 to 15% have CD

- Patients with IBD
  - PSC in 2 – 8% of UC
  - PSC in 3% of CD

Pathogenesis of PSC-IBD

**Leaky GUT**
- Increased permeability
- Bacterial metabolites to Liver

**Genetics**
- 200 IBD loci
- 16 PSC loci
- < 50% overlap

**GUT lymphocyte homing**
- Shared chemokines and adhesion molecules
- Activated lymphocytes via entro-hepatic circulation

**Microbiome / metabolome**
- Dysbiosis
- Veillonella ++
- Eschieria ++

IBD-PSC
PSC-UC demographics

• Incidence is higher in young males

• Mean age for IBD diagnosis is significantly earlier
  – 24.5yrs vs. 33.8yrs

• The PSC occurs at a younger age
  – 33.6yrs vs. 58.9yrs (p<0.001)

The unique PSC-UC phenotype

Quiescent to mildly symptomatic

Lower grade inflammation (Right > Left)

Reduced steroid use

Decreased rate of hospitalization

Inversely related PSC: IBD activity
The colon concern in PSC-UC

Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and inflammatory bowel disease: a meta-analysis of 16 observational studies

Han-Han Zheng^ab and Xue-Liang Jiang^b

PSC-UC versus UC alone

• 3 fold risk of colorectal neoplasia and cancer
  • Dysplasia – OR 2.98 (95% 1.54 – 5.76)
  • Cancer – OR 3.01 (95% 1.44 – 6.29)
Biliary Cancer risk in PSC-IBD

Duration of Inflammatory Bowel Disease Is Associated With Increased Risk of Cholangiocarcinoma in Patients With Primary Sclerosing Cholangitis and IBD

- 33% increased risk per 10 years of IBD
- Not modified by colectomy
- Associated with hepatocellular Ca

Management – UC component

• Step up approach – mostly responds to 5-ASAs (lowers the cannilicular enzymes)

• Surveillance is the key
  – Annual colonoscopy
  – Annual imaging of the gall bladder (+Ca 19.9)
  – 6 monthly HCC screening when cirrhotic
  – Regular bone marrow density testing
Management of the PSC component
Ursodeoxycholic acid

• Low dose suggested an improvement in LFTs, not survival (used in Sweden)
  – Possible reduced risk of CRCa and CholangioCa

• High dose UDCA RCT was terminated.
  – Improved LFTS **BUT** increase in adverse events (sepsis)
Management of the PSC component Immunomodulation

• No benefit

Future work

• Gut specific α4β7 (vedolizumab) targets to primed gut lymphocytes

• Small molecule inhibitors against CCR9

• ‘Mabs’ against fibrosis
Management of the PSC component
ERCP and Surgery

• Balloon dilation with/out stent placement

• Orthotopic liver transplantation (OLT)
  – Only potential cure
  – Survival rates of 85% at 5 years / 70% at 10 years
  – Without OLT – symptomatic patients die within 12-15 years.
  – Less based on MELD scores
Course of IBD after liver transplant (LT)

- Worsening of colitis in 30% of patient
- Colectomy rate post LT 4 -20%
- Higher rate of overall clinical IBD activity
- 3 fold increased risk in CRCa

A PSC liver is somewhat protective
Case clinical progression (2017)

• Annual colonoscopy with random biopsies
  – chronic colitis with focal activity

• 6 monthly varices screen
  – Grade 1 oesophageal varices
  – Portal hypertensive gastropathy

• Co-managed with HPB and Liver
  – Prepared for OLT

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Case clinical progression

MRCP 2017

- Massive hepatomegaly
- Biliary fibrosis and obliteration
- Marked narrowing of common hepatic duct
- Features of portal hypertension
- Splenorenal shunting
Clinical Questions?

1. When to do a liver transplant?
   - High risk surgery
   - MELD
   - Good baseline versus sick patient

1. Do we consider a subtotal colectomy before liver transplant?
   - Risk of UC flaring
   - High risk of CRN / CRCa
   - Risk the graft – Tacro and stoma…
   - Risk for pouchitis
Conclusion

- Cholestasis in IBD must be fully investigated
- PSC - IBD shares a close, unexplained relationship
- The UC phenotype is unique
- OLT is the only cure
- Early multi-disciplinary team
- What one does with the colon is based on risk of cancer