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LIFECHANGINGMEDICINE

Natural History of PSC

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Liver Clinic Consultation: True Story

- 26/Female
- Routine lab tests – elevated serum alkaline phosphatase; elevated gamma GTP
- Diarrhea with bleeding – Crohn's disease
- ERCP – PSC
- Started on Urso

- Return visit:
- Engaged – to be married in six months
- Mother-in-law and fiance

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Liver Clinic Consultation: True Story

- Should I get married?
- Should I have children?
- Will I be alive to see my children grow up?
- At what rate will my PSC progress?
- When will I need a liver transplant?
- How do you know that I need a liver transplant?
- Use of Urso during pregnancy?

- Questions……
- This clinic visit lasted almost two hours!!!!

Liver Clinic Consultation: True Story

- Eleven years later:

- She did get married
- She has gone through two successful pregnancies
- She has two healthy children
- She has no symptoms from her PSC
- Her liver function tests are almost normal
- Her liver sonogram; liver MRI show mild PSC
- I see her in the liver clinic once a year

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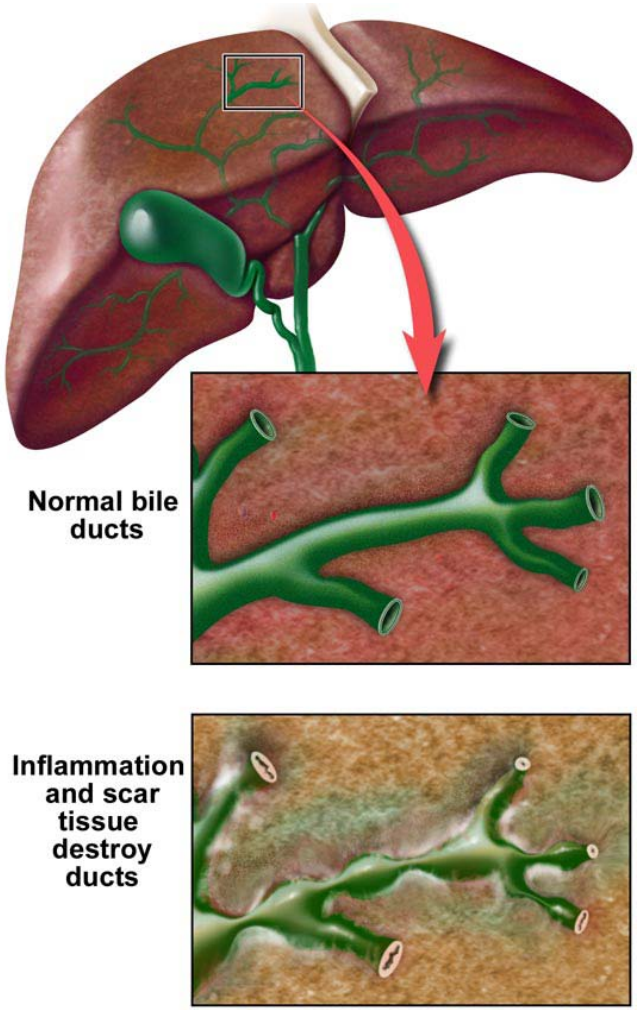
PSC

- Primary sclerosing cholangitis is a progressive chronic cholestatic liver disease of unknown etiology that is commonly associated with chronic colitis
- PSC usually leads to advanced liver disease and liver failure, and is an important indication for liver transplantation
- Unfortunately, no effective medical therapy currently exists for PSC



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Overview

- Epidemiology and Natural History of PSC
- Clinical Features
- Variant Forms of PSC
- Pregnancy and PSC
- Liver Transplantation and PSC

Etiopathogenesis of PSC

- It is thought that PSC results from the combination of **genetic predisposition** and **immune-mediated** events that lead to ongoing biliary duct damage

- It has been postulated that the initial insult leading to the sustained immune-mediated injury in genetically susceptible individuals might be triggered by bacteria-related injury

- Evidence of a genetic susceptibility to PSC was initially suggested by reports of familial occurrence of PSC1 and further supported by data demonstrating an **increased risk of PSC, up to 100-fold**, among siblings of PSC patients compared with the general population

Dense genotyping of immune-related disease regions identifies nine new risk loci for primary sclerosing cholangitis

- The study was headed by Tom Karlsen and involved an international effort of investigators (including US, Canada, and Europe) and of course, PSC patients

- The findings have resulted in a better understanding of the genetic basis of PSC and how the **genes of PSC overlap with the genes of several other autoimmune diseases**

- The hope is that these findings can lead to new insights for targeting drugs that might already be in use for these more common diseases

Nature Genetics; published online 21 April 2013; doi:10.1038/ng.2616

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Epidemiology of PSC

- Population-based studies few – North America and Europe

- Overall incidence of PSC: 0 to 1.3 per 100,000 inhabitants
- Overall prevalence: 0 to 16.2 per 100,000 inhabitants

- Wide variation in the geographic distribution of PSC
- Highest frequency in Northern Europe, New Zealand and North America
- Variation related to differences in genetic susceptibility to the disease among different ethnic groups

Epidemiology of PSC

- PSC predominantly affects men
- Male: Female ratio is 2 : 1
- Median age – 40 years
- Strong association with inflammatory bowel disease (IBD) – most patients have concurrent IBD – 70% = most commonly Ulcerative Colitis (UC)

The prevalence, incidence and natural history of primary sclerosing cholangitis in an ethnically diverse population

- Primary sclerosing cholangitis (PSC) is a rare chronic cholestatic liver disease often associated with inflammatory bowel diseases (IBD)

- Current epidemiological data are limited to studies of predominantly Caucasian populations

- Aim: to define the epidemiology of PSC in a large, ethnically diverse US population

BMC Gastroenterol. 2011 Jul 18;11:83. doi: 10.1186/1471-230X-11-83

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The prevalence, incidence and natural history of primary sclerosing cholangitis in an ethnically diverse population

- We identified 169 (101 males) cases fulfilling PSC diagnostic criteria with a mean age at diagnosis of 44 years (range 11-81).

- The age-adjusted point prevalence was 4.15 per 100,000 on December 31, 2005

- The age-adjusted incidence per 100,000 person-years was not significantly greater in men 0.45 (95% CI 0.33-0.61) than women 0.37 (95% CI 0.26-0.51)

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The prevalence, incidence and natural history of primary sclerosing cholangitis in an ethnically diverse population

- IBD was present in 109/169 (64.5%) cases and was significantly more frequent in men than women with PSC (73.3% and 51.5%, respectively, p = 0.005)

- The cumulative average yearly mortality rate was 1.9%

- Age and serum sodium, creatinine and bilirubin at diagnosis and albumin at last entry were identified as significant factors associated with death, liver transplant or cholangiocarcinoma

The prevalence, incidence and natural history of primary sclerosing cholangitis in an ethnically diverse population

- The incidence and prevalence of PSC observed in a representative Northern California population are lower compared to previous studies in Caucasian populations and this might reflect differences in the incidence of PSC among various ethnic groups

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The prevalence, incidence and natural history of primary sclerosing cholangitis in an ethnically diverse population

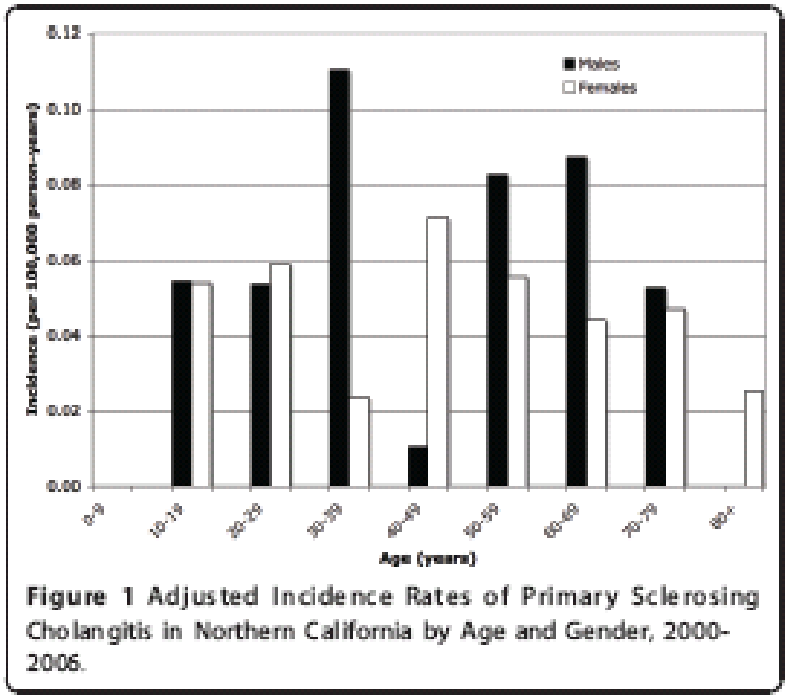

Figure 1 Adjusted Incidence Rates of Primary Sclerosing Cholangitis in Northern California by Age and Gender, 2000-2006.

Table 1 Demographic, biochemical, and clinical characteristics of 169 PSC cases diagnosed within a northern Californian HMO in the 2000-2006 period

Age at diagnosis, *years*	44.2 ± 17.4	(11-81)
Males, *n* (%)	101 (59.8)	
Ethnicity,*n* (%)		
White	51 (30.2)	
African American	15 (8.9)	
Hispanic	9 (5.3)	
Asian/Pacific Islander	3 (1.8)	
Other/Unknown	91 (53.8)	
Laboratory Values at Diagnosis		
Alkaline Phosphatase, *IU/L*	283.4 ± 256.8	(30 - 1355)
Aspartate Aminotransferase, *IU/L*	66 ± 65.7	(13 - 407)
Alanine Aminotransferase, *IU/L*	70.3 ± 71.9	(11 - 339)
Total bilirubin, *g/dL*	2.3 ± 3.7	(0.2 - 19.7)
Serum albumin, *g/dL*	3.8 ± 0.8	(1.3 - 5.1)
International Normalized Ratio	1.1 ± 0.2	(0.9 - 2.7)
MELD	9.6 + 4.1	(6.4 - 27.4)
IBD, *n* (%)	109 (64.5)	
Ulcerative colitis	95 (56.2%)	
Crohn's disease	13 (7.7%)	
Indeterminate colitis	1 (0.6%)	
Outcomes, *n*		
Liver Transplantation	23	
Cholangiocarcinoma	7	
Death	25	

All continuous variables are expressed as mean ± standard deviation (range).

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Causes of death in PSC patients from 2000 - 2006

- Liver-related

- Liver failure
- Hepatorenal syndrome
- Cholangiocarcinoma
- Liver cancer
- Cholangitis/Sepsis

- Non Liver-Related

- Colon cancer
- Myocardial infarction
- Squamous cell cancer
- Pulmonary fibrosis
- Pulmonary embolism
- Urosepsis
- Unknown

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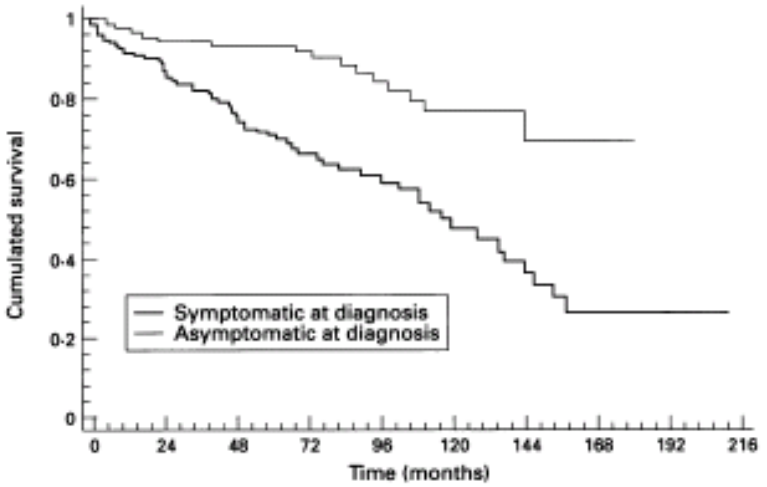
Natural History of PSC

- Can vary significantly in individual patients
- Follows a **progressive course** that affects survival
- **Mean survival** from the time of diagnosis to death free of liver transplantation ranges from **7 and 18** years
- Patients who are **asymptomatic** at the time of diagnosis may have better survival compared with those with symptoms



Natural History of PSC

- Several prognostic models have been proposed in an attempt to predict clinical outcome in patients with PSC , the highly variable course of the disease limits their applicability in the clinical setting

- Variable identified in prognostic models include:
- Age
- Liver test results
- Cholangiographic findings
- Histologic stage
- Clinical manifestations of advanced disease

PSC: Clinical Features

- PSC primarily affects young and middle-aged men especially patients with underlying inflammatory bowel disease
- Approximately 70% to 80% of PSC patients have ulcerative colitis (UC)
- Approximately 2% to 7.5% of patients with UC and 1.4% to 3.4% of patients with Crohn’s disease develop PSC
- IBD can be diagnosed at any time during the course of PSC and PSC can occur at any time during the course of IBD
- In general, IBD is diagnosed several years earlier than PSC

PSC: Clinical Features

- PSC may also develop many years after proctocolectomy for colitis and IBD can develop many years after liver transplantation for advanced PSC
- Majority of patients (> 55%) have asymptomatic elevations in liver enzymes
- Due to its close association to IBD, many cases come to medical attention when patients with IBD are screened for liver disease

PSC: Clinical Features

- Clinical course of PSC – insidious worsening of cholestasis and eventual development of jaundice and end-stage liver disease
- Asymptomatic patients with PSC are at increased risk for developing symptoms over time
- Most common symptoms: fatigue and pruritus
- Uncommon initial manifestations: jaundice; pain; fever; weight loss; cholangiocarcinoma or manifestations of portal hypertension

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PSC: Clinical Features

- Common presenting symptoms

• Abdominal pain	20%
• Pruritus	10%
• Diarrhea	8%
• Jaundice	6%
• Fatigue	6%
• Fever	4%

PSC: Clinical Features

- Recent trends: more patients without IBD are identified; patients are older at diagnosis
- Bacterial cholangitis may manifest after endoscopic intervention or surgical exploration of the biliary tree
- Cholangiocarcinoma develops in up to 23% of patients and can occur relatively early and before onset of cirrhosis
- Impairments in health-related quality of life among individuals with PSC when compared to the general population

PSC: Biochemical features

- Cholestatic picture with elevations in serum alkaline phosphatase are the biochemical hallmark of PSC
- Increases between 3 and 10 times the upper limit of normal occur in 95% of cases
- Serum ALT and AST are usually 2-3 fold higher than normal
- Serum bilirubin is normal in 60% of individuals at diagnosis

PSC: Biochemical features

- The liver function tests, however, may be normal and can fluctuate during the course of the disease
- Prognostic models for PSC have been developed eg, the Mayo model for predicting survival
- The limitations of prognostic models include the inability to account for the development of cholangiocarcinoma and health-related quality of life

PSC: Biochemical features

- Once decompensated cirrhosis develops, the Model for End-Stage Liver Disease (MELD) score more accurately predicts survival and is more appropriately used in prioritizing patients for liver transplantation

PSC: Mayo Risk Score

- To estimate patient survival in PSC
- R = 0.03 (age [yrs]) + 0.54 $\log_e$ (bilirubin [mg/dl]) + 0.54 $\log_e$ (AST [u/l]) + 1.24 (variceal bleeding [0=no/1=yes]) – 0.84 (albumin [g/dl])
- Used to obtain survival estimates upto 4 years of follow-up
- Obviates the need for a liver biopsy

Kim WR et al. *Mayo Clin Proc* 2000;75:688-694
http://www.mayoclinic.org/gi-rst/mayomodel3.html

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Model for End-stage Liver Disease (MELD)

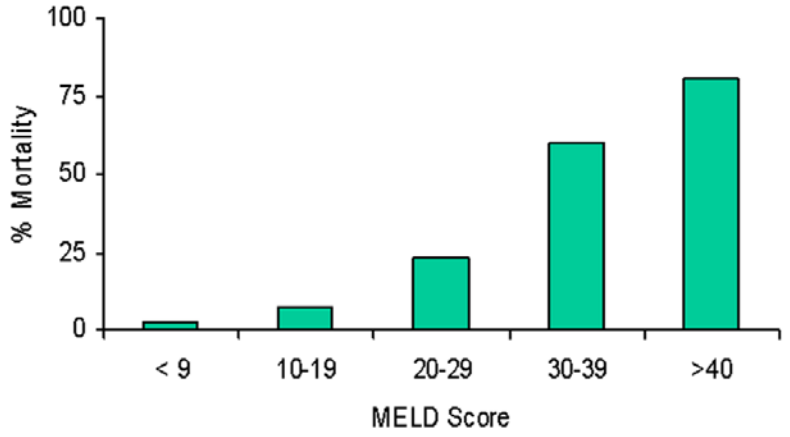
- MELD score

- 0.957 x Log (creatinine mg/dl) +
- 0.378 x Log (bilirubin mg/dl) +
- 1.120 x Log (INR) +
- 0.643

- MELD calculator: www.unos.org

- Date of implementation: February 27, 2002

Figure X-2. Three-Month Mortality Based on Listing MELD in Patients on the OPTN Waiting List



Source: Wiesner et al, 2003. (14)

Association Between Reduced Levels of Alkaline Phosphatase and Survival Times of Patients With Primary Sclerosing Cholangitis

- There is no significant difference in long-term survival between patients with PSC given UDCA (17-23 mg/kg/day) or placebo for 5 years.

- However, patients who have reduced or normal levels of Alkaline Phosphatase (ALP) have longer survival times, regardless of whether they receive UDCA or placebo

- Scandanavian PSC UDCA trial

Clin Gastroenterol Hepatol. 2013 Jan 22. pii: S1542-3565(13)00090-6. doi: 10.1016/j.cgh.2012.12.032. [Epub ahead of print]

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Improvement of serum alkaline phosphatase to <1.5 upper limit of normal predicts better outcome and reduced risk of cholangiocarcinoma in PSC

- Improvement in Serum Alkaline Phosphatase (SAP) to below 1.5 ULN is associated with better outcome and reduced risk of cholangiocarcinoma (CCA) in PSC
- This was comparable to the achievement of complete normalization of SAP
- Oxford PSC database

J Hepatol. 2013 Feb;58(2):329-34. doi: 10.1016/j.jhep.2012.10.013. Epub 2012 Oct 22

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PSC: Additional diagnostic studies

- Serologic tests
  - pANCA; ANA; ASMA
- Radiographic tests
  - Cholangiography: ERCP; MRC
- Histologic tests
  - Liver biopsy

PSC: Disease-Related Complications

- Fatigue and Pruritus
- Metabolic bone disease
- Gall bladder stones and polyps
- Peristomal varices
- Dominant stricture
- Bacterial Cholangitis
- Malignancy
  - Cholangiocarcinoma
  - Colonic dysplasia and carcinoma
  - Gallbladder neoplasia
  - Hepatocellular carcinoma

Variant Forms of PSC

- Small duct PSC
- Overlap with Autoimmune hepatitis
- IgG4-related sclerosing cholangitis

Small duct PSC

- Biochemical and histology findings of PSC
- Normal cholangiogram
- Milder clinical course; longer survival; less likely to develop cholangiocarcinoma
- 25% of cases progress to classic PSC

Autoimmune hepatitis-PSC overlap

- Should be suspected in
  - PSC patients with ANA or ASMA
  - PSC patients with AIH on histology
  - AIH patients with IBD
  - AIH patients with IBD and cholestatic profile

- Suboptimal response to steroid therapy

IgG4-related sclerosing cholangitis

- Serum IgG4 should be measured in all PSC patients
- IgG4 levels are elevated in approximately 10% of PSC patients
- Associated with more severe clinical disease
- May have clinical response to steroid therapy

Pregnancy and PSC

- Little is known regarding the natural history and potential complications of pregnancy in patients with PSC
- Hepatic disease activity is not significantly worsened during the gestational period
- Close monitoring required: blood tests; ultrasound; MRC or ERCP

Pregnancy and PSC

- Fertility did not seem to be reduced in PSC since the number of children did not differ between PSC patients and healthy controls
- 25 pregnancies in 17 female PSC patients (median age at conception 31 years)
- An increase in liver enzymes was documented during five pregnancies (20%) and eight times (32%) post-partum
- There were no serious maternal complications

Gut. 2011 Aug;60(8):1117-21. doi: 10.1136/gut.2010.228924. Epub 2011 Feb 21

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Pregnancy and PSC

- All 21 live births presented with a normal perinatal and postnatal development over a median observation time of 50 months

- Two pregnancies were delivered pre-term and four fetal losses occurred early in pregnancy (<12 wk)

- Continuation of treatment with ursodeoxycholic acid (15/21) or azathioprine (2/21) had no negative effects on pregnancy outcome

Liver transplantation and PSC

- Excellent survival rates of 90%-97% at one year, and 83%-88% at five years
- Retransplantation rates seem to be higher for patients with PSC than other diagnoses
- Recurrence of PSC in the liver graft has been documented

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Liver transplantation and PSC

- Frequency of recurrent PSC after liver transplantation – estimated between 10% to 20% - publication bias
- PSC might recur earlier after living donor liver transplantation, particularly when the liver graft is obtained from a biologically related living donor
- Retransplantation for recurrent disease and graft loss – considered in select patients

Summary (1)

- Primary sclerosing cholangitis (PSC) is a chronic immune-mediated disease of the liver of unclear etiology, characterized by chronic inflammation and fibrosis of bile ducts

- It primarily affects middle aged men, and is associated with 4-fold increased mortality as compared to age- and gender-matched population

- Progressive biliary and hepatic damage results in portal hypertension and hepatic failure in a significant majority of patients over a 10-15 year period from initial diagnosis

Summary (2)

- In addition, PSC confers a markedly increased risk of hepatobiliary cancer, including cholangiocarcinoma and gallbladder cancer as compared to the general population, and cancer is the leading cause of mortality in patients with PSC

- It is associated with inflammatory bowel disease in 70% patients, and increases the risk of colorectal cancer almost 10-fold

Summary (3)

- Despite significant research efforts in this field, the pathogenic mechanisms of PSC are still incompletely understood, although growing evidence supports the role of genetic and immunologic factors

- There are no proven medical therapies that alter the natural course of the disease

- Thus, liver transplantation is the only available treatment for patients with advanced PSC, with excellent outcomes in this population

Thank you – Have a wonderful time in Pittsburgh……..