Sclerosing diseases of the biliary tree

Reiner Wiest M.D.
PSC
Histomorphology

concentric ductal fibrosis
“onion skinning”
involving bile ducts
within portal tract areas
What can cause sclerosing of biliary tree?
What can cause sclerosing of biliary tree?

Sclerosing cholangitis of unknown origin

**PSC:** Primary sclerosing cholangitis
**IgG4-SC:** IgG4-related sclerosing cholangitis

Secondary sclerosing cholangitis

**Infection:** bacterial/parasitic/pyogenic cholangitis
**Immunodeficiency:** e.g. congenital, AIDS patients
**Mechanical/toxic:** stone, surgical, trauma, CTx, drug
**Cholangiocarcinoma:** diffuse metastasis
**Ischemic:** vascular trauma, arterial insuff., PNH
**Pancreatobiliary** disease: CF, CP, ABCB4-CP
**Systemic inflammatory** disease: Sarcoidosis, GvHD, Eosinophilic
**Others:** Portal-hypertensive Biliopathy, Mastozytosis, Caroli,

.............
Pathogenesis of Primary Sclerosing Cholangitis?
Pathogenesis of Primary Sclerosing Cholangitis?

**Immune-mediated mechanisms**
- Autoantibodies
- HLA association
- Autoimmune diseases

**MHC-Haplotypes**
- CFTR variants
- Ccr5Δ32
- ICAM polymorphism
- MST1 variants
- TGR5 variants
- GPC5/GPC6

**Genetics**
- Exogenous triggers
- Infectious agents
- Helicobacter species
- Viruses (CMV, reovirus T3)
- Fungi (candida albicans)

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**The Victim Cholangiocyte**
- IL-6, CD44, MCP-1
- Activation of neutrophils
- ROS and lymphocytes

**Chronic Cholangitis**
- Chemokines
- PDGF, CTGF
- TGFb1, FGF, TLR ligands

**Cholangiocellular carcinoma**
- Periductal onion-skin type fibrosis
- Obstructive cholestasis
- Biliary cirrhosis

**Toxic Bile**
- ABCB4 mutations
- CFTR variants
- SXR/PXR variants

**Gut-derived CCR9^+^T-cells**
- Sinusoidal MAdCAM-1 expression
- CCL25 production
- Bacterial translocation/antigens

**IBD**
Most difficult questions in the bible class history!

Which genes are shared between UC and PSC?
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IL2, CARD 9 and REL

Hanse et al. Hepatology 2011
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Hanse et al. Hepatology 2011

Which cell-type is responsible for PSC development after colectomy?

Memory $a4b7$-CCR9+CD8+T-cells primed by retinoic dependent iDC

Eksteen B et al. Gastroenterology 2009
Factors modulating risk for PSC?
Factors modulating risk for PSC?

- IBD, mostly UC
  - 2-4% (max 8%) of IBD patients, in their lifetime
  - up to 88% of PSC-patients suffer IBD

- male predominance
- Sometimes family history of disease
- smoking protects against PSC
Symptoms in PSC?
Prognosis in patient with and without symptoms?
Symptoms in PSC?
Prognosis in patient with and without symptoms?

- often asymptomatic (about 50%)
- right upper quadrant pain, abdominal discomfort,
- fatigue, pruritus, fever/chills and weight loss.
  (very variable)
- If symptoms: time till death or transplantation reduced
  9 years vs. 12-18 years
Mayo Risk Score for PSC?
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R = (0.0295 * (age in years)) + (0.5373 * LN(total bilirubin in mg/dL)) - (0.8389 * (serum albumin in g/dL)) + (0.5380 * LN(AST in IU/L)) + (1.2426 * (points for variceal bleeding))

Points for variceal bleeding: 0 if none, 1 if present.

Each unit increase in the Mayo Risk Score (R) is associated with a 2.5-fold increase in the risk of death. The score shows very slight upward slope over time in stable patients, but during the terminal phase it shows an acceleration in progression (http://www.medal.org/)

R ≤ 0 = low" risk
R = 0-2 = "intermediate" risk
R > 2 = "high" risk

Kim et al. Mayo Proc 2000
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| R < 0 | Low risk |
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Kim et al. Mayo Proc 2000
Lab tests of Primary Sclerosing Cholangitis?
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- cholestatic (↑GGT, ↑AP, bilirubin)

+ high transaminases (2-3x normal value) in a majority of patients
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Other lab tests?

-Serology: Antibodies

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<th>Prevalence</th>
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<tbody>
<tr>
<td>Anti-neutrophil cytoplasmic antibody</td>
<td>50%-80%</td>
</tr>
<tr>
<td>Anti-nuclear antibody</td>
<td>7%-77%</td>
</tr>
<tr>
<td>Anti-smooth muscle antibody</td>
<td>13%-20%</td>
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<tr>
<td>Anti-endothelial cell antibody</td>
<td>35%</td>
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<tr>
<td>Anti-cardiolipin antibody</td>
<td>4%-66%</td>
</tr>
<tr>
<td>Thyroperoxidase</td>
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</tr>
<tr>
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<tr>
<td>Rheumatoid factor</td>
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Diagnosis of Primary Sclerosing Cholangitis?
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- Lab: CHOLESTASIS (not otherwise explained…)

PSC
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- MRC (P) Method of choice

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What is small duct PSC?
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- Disease variant which is characterized by typical cholestatic and **histological features** of PSC but **normal bile ducts** on cholangiography
- Survival is longer
- Lower risk for CCA
- 20% develop large duct diseases over 7-10 years
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**Normal cholangiogram but high suspicion → perform?**

→ Liver Biopsies (small duct PSC and/or Overlap-Syndrom with AIH)
Validation of the Prognostic Value of Histologic Scoring Systems in Primary Sclerosing Cholangitis: An International Cohort Study

Elisabeth M. G. de Vries,1* Manon de Krijger,1* Martti Färkkilä,2 Johanna Arola,3 Peter Schirmacher,4 Daniel Gotthardt,5

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Most common complications of PSC?
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- **Cholangiocarcinoma**
  (5-10% of PSC patients)

- **Biliary (secondary) Cirrhosis**
  → portal hypertension/ liver failure
  → hepatocellular carcinoma
  (about 2% per year)

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  5-10 fold increase
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Colon and PSC: When colonoscopy in PSC?
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- **Every PSC** patient at least once, at ED even asymptomatic patients
- **Plus Biopsy** even if macroscopically intact (4 quadrant in each colon segment + Ileum)
- **Every (3-)5 year** after PSC diagnosis or when symptoms develop to seek IBD
- **IBD: annual** surveillance colonoscopy with chromoendoscopy (also after LTx)
When to go for ERCP?
When to go for ERCP?

- **Established PSC:**
  i) therapeutic indication or ii) risk of CCA
  - clinically relevant or worsening symptoms: jaundice, cholangitis, pruritus, weight loss
  - rapid increase of AP and/or bilirubin
  - new or progression of known dominant stricture (MR)

- **Persistent PSC suspicion** despite normal high-quality MR/MRCP and normal liver biopsy

In advanced stage/cirrhosis: benefit maybe limited
ERCP-findings: Amsterdam-classification
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Full occlusion cholangiogramm mandatory:
Type I (intra- and extrahepatic)
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Type II intra-
Type III extrahepatic
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## ERCP-findings: Amsterdam-classification

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<tr>
<td>0</td>
<td>No visible abnormalities</td>
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<tr>
<td>I</td>
<td>Multiple caliber changes; minimal dilatation</td>
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<tr>
<td>II</td>
<td>Multiple strictures; saccular dilatations, decreased arborization</td>
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<td>III</td>
<td>Only central branches filled despite adequate filling pressure; severe pruning</td>
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ERCP-findings: Amsterdam-classification
Dominant stricture?
- definition, frequency, risks
Dominant stricture? - definition, frequency, risks

**Definition**: stenosis with a diameter of

< 1.5 mm in the CBD

< 1 mm in the right or left hepatic duct

Mostly associated with increased cholestasis and pruritus

**Frequency**: 45% to 58% of PSC patients during follow up.

**Risks**: CCA, cholangitis
ERCP: management of dominant stricture?
ERCP: management of dominant stricture?

- Always use peri-interventional antibiotics!
- **Sphincterotomy** not routinely - only small if at all done when difficult access and/or therapeutic interventions.
- Before any endoscopic therapy: **brush cytology and/or biopsy**

- **Dilatation** preferred method because majority of studies only dilated.
  - significant improvement in LTx-free survival only shown for dilatation scheme: repeat every 1-4 weeks, CBD 8mm, DHR/L 6 mm till success.
- **Stenting**: Perforation rate higher and hence, only in selected cases and only short-term (1-2 weeks).
PSC and CCA: epidemiology, risk, prognosis
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- Life-time risk up to 15-20% (=400-fold increased)
- 10-year cumulative risk: 6-9%
- Up to 50% discovered at initial diagnosis of PSC (or < 1 year FU)
- Prognosis dismal: ≤ 2 years median overall survival

- **Risk factors for CCA:**
  - Presence and duration of IBD (but not PSC)
  - UC with colorectal cancer/ dysplasia
  - Elevated serum bilirubin, variceal bleeding
  - NKG2D gene polymorphism
Stricture – diagnostics – Brush + FISH + Cholangioscopy?
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**Brush-cytology:**
Sensitivity 43%; Specificity 97%, NPV 87%
Chance of CCA in dominant stricture: ca. 5%
> 90% CBD or perihilar in location
Lack of dominant stricture does not rule out CCA-> always do Brushing!

**FISH/chromosomal assessment:**
- Polysomy prognostic as relevant as proven CCA
- Dominant stricture: polysomy: 88% specificity for CCA
- Persistent polysomy-> 69% develop CCA

**Cholangioscopy with SpyBite-Biopsy**
- Improves diagnostic yield
- Triple (Brush+Biopsy+FISH):
  increased sensitivity to 82% (NPV 87%)
PSC and Gallbladder: Polyps and Cancer
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- 286 PSC patients: 18 (6%) GB mass lesion (21+9 mm)
- 10 cases (56%) GB cancer

Said K et al. J. Hepatol 2007

- 102 PSC patients undergoing cholecystectomy
- 8 GB adenocarcinoma

Buckles AJG 2002

- 72 PSC patients (66 removed at LTx)
- > 50% abnormal histology of GB:
- Dysplasia in 37% and adenocarcinoma 14%

PSC and Gallbladder: Polyps and Cancer

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Said K et al. J. Hepatol 2007

Annual ultrasound recommended

Any mass lesion (> 10 mm): cholecystectomy

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- Yearly MR/MRCP most experts recommend
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- Corticosteroids, Immunosuppressants for AIH (overlap-patients)
Potential future Medical Treatment of PSC?
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- **New form of UDCA**: 24-norUrsodeoxycholic acid (norUDCA) is the C23 homologue of the 3a,7b-dihydroxy C24 bile acid UDCA hydrophilic, anti-fibrotic, anti-inflammatory, anti-proliferative

- **FxR-agonists**: e.g. Obeticholic acid, INT-767
  - also choloretic, cholangiocyte modulator, gut-barriere etc.

- **Vedolizumab**: α4 β7 inhibitors / anti-Integrin (Trial ongoing)
  - aberrant gut-homing lymphocyte hypothesis focuses on the relationship between PSC and IBD.

*Traumer M et al. Dig Dis Sci 2016*
Liver Transplantation in PSC: when, how...
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- One of the best indications per se: 5y survival > 80%
- Listed due to complications of cirrhosis, portal hypertension
- Specific of PSC (rarely): Recurrent/ refractory cholangitis, intractable pruritus
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- CCA: perihilar and < 3 cm
- Mayo-Protocol: neoadjuvant radiation, radiation-sensitization chemotherapy, oral capecitabine, laparoscopy before LTx
- Re-PSC of graft: 20-25% in 5-10 years
- UC: Colectomy seems to protect from recurrence of PSC (controversial, not recommended)
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<td>suggestive of autoimmune pancreatitis</td>
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<tr>
<td>(S) Serology</td>
<td>(IgG4 $\geq$ 2 times the upper limit of normal)</td>
</tr>
<tr>
<td>(O) Other organ involvement</td>
<td>Biliary strictures, parotid/lacrimal gland involvement, mediastinal lymphadenopathy, retroperitoneal fibrosis</td>
</tr>
<tr>
<td>(Rt) <strong>Response to steroid treatment</strong></td>
<td>Resolution/marked improvement of pancreatic and extrapancreatic manifestations</td>
</tr>
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Microscopic characteristics in IgG4-hepatobiliary disease
Microscopic characteristics in IgG4-hepatobiliary disease

- lymphoplasmacytic infiltration
- storiform pattern of fibrosis
- obliterative phlebitis with a variable presence of eosinophils

- >10 IgG4+ plasma cells per HPF in a biopsy specimen
- >50 IgG4+ plasma cells per HPF in a resection specimen
- Plus an IgG4+ : IgG+ plasma cell ratio of >40%
IgG4-sclerosing cholangitis: classification
IgG4-sclerosing cholangitis: classification

Distal CBD
Most frequent
Often with AIP

A: with Pre-stenotic dilatation

B: without Pre-stenotic dilatation

Hilar + CBD
Hilar alone

Type 1

DD: pancreatic Ca, Distal CCC, CP

Type 2

DD: PSC, SSC

Type 3

DD: Hilar CCA

Type 4

Okazaki et al. J. Hepatol 2014
IgG4-hepatobiliary disease – epidemiology, risk factors
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- Most frequent extra-pancreatic manifestation of IgG4-related diseases
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- Male (7:1!), > 60 year of age,

- Risk factors: chemicals/toxins (blue-collar-worker),
  allergy/atopy/eosinophilia, other autoimmune disease (thyroid, coeliac..)
Pathogenesis of IgG4-sclerosing cholangitis
Pathogenesis of IgG4-sclerosing cholangitis

Kamisawa et al. Lancet 2015
IgG4-serum levels - how useful? Differentiate PSC
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- > 1.4 g/l: 65-80% of IgG4-SC (but 20% normal levels)
- > 2.5 g/l: IgG4-SC vs. PSC: sensitivity 70-89%, specificity 95%
- 1.4-2.8 g/l: ratio IgG1:IgG4 > 0.24: sensitivity 86%, specificity 95%, NPV 90%
- > 5.6 g/l: specificity and PPV 100% (?) vs. PSC (+ CCA)
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PSC per se:

- > 20% liver explants present with IgG4+cell infiltrate
- > 10% present with increased serum IgG4 (> 1.4 g/l)
- both conditions associate with worse prognosis/= seek CCC
- + associates with: reduced HLA-B*08, increased –B*07, DR-B1*15 frequency
Typical ERCP-features in IgG4-sclerosing cholangitis?
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Strictures in cholangiogramm:
Typical ERCP-features in IgG4-sclerosing cholangitis?

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- thin diffusely narrowed pancreatic duct
Typical ERCP-features in IgG4-sclerosing cholangitis?

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How helpful for differential diagnostic purpose?
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Sensitivity 45% = forget it!
Typical ERCP-features in IgG4-sclerosing cholangitis?

Strictures in cholangiogramm:

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- Mild dilatations upstream
- Thin diffusely narrowed pancreatic duct

Malignancy must be excluded

Sensitivity 45% = forget it!
Diagnostic endoscopic optimized work-up ?

IgG4
Diagnostic endoscopic optimized work-up?

**All you can do:**
- ERCP (plus cholangioscopy)
- Brush-cytology, biopsy
- Bile fluid
- EUS (plus FNA)
- Ampullary biopsy
- Liver biopsy

**Caveats/problems:**
- patchy disease
- insufficient tissue/cells
- reduced numbers IgG4-cells
  
  E.g. in fibrotic stages
  
  ✔ IgG4-cells in other diseases
  
  e.g. malignancy, inflammation
How to differentiate PSC/CCA from IgG4-SC?
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NGS-> qPCR for expanded B-Cell-Clone and IgG4+-RNA

Sensitivity 94%, Specificity 99%

Breuers et al. Curr Opin Gastroenterol 2017
How to differentiate PSC/CCA from IgG4-SC?

NGS-> qPCR for expanded B-Cell-Clone and IgG4+-RNA

Circulating Plasmablast-number can help differentiate IgG4-RD from other diseases
= Biomarker for IgG4-RD (even when normal serum IgG4)

Breton-Zeron et al. BestPractGastro 2017

Sensitivity 94%, Specificity 99%

Breuers et al. Curr Opin Gastroenterol 2017
Treatment for IgG4-sclerosing cholangitis?
Treatment for IgG4-sclerosing cholangitis?

Corticosteroid 0.6 (-1) mg/kg KG

(30-40mg/Tag) for 4 weeks

Tapering: 5mg/week, ending at week 12

Maintenance therapy (2.5.-5 mg/d) for 3 years

reduces relapse rate compared to stop at 26 weeks (23% vs. 57%)
Treatment-success for IgG4-sclerosing cholangitis?
Treatment-success for IgG4-sclerosing cholangitis?

- Re-assess after 4-6 weeks
  - Serum IgG4: only minority will normalize
  - Complete resolution of strictures and liver tests = response
    - Achieved in about 2/3 of IgG4-SC
Recurrence/Refractory IgG4-sclerosing cholangitis
Risk ? Treatment-Options ?

- Ca. 50% will show some recurrence (majority < 6 months after EOT)
- Risk-factors:
  
  high IgG4, multi-organ-involvement, prior recurrence
  
  Typ 2-4 (hilar and intrahepatic disease manifestation)
- Immunmodulators: best evaluated azathioprine
- Rescue: Rituximab (Anti-CD20-> killing expanded B-cell-clone)
IgG4-SC differs from PSC in.......
IgG4-SC differs from PSC in........

- Rare disease
- Usually multi-organ-disease
- Histology needed to confirm diagnosis
- More benign disease
  - less malignant development (2-fold*), infrequent end-stage cirrhosis
- Good response to steroids

*: presumably only if chronically active disease
Danke für die Aufmerksamkeit
Diagnostic items

1. Biliary tract imaging reveals diffuse or segmental narrowing of the intrahepatic and/or extrahepatic bile duct associated with the thickening of the bile duct wall

2. Hematological examination shows elevated serum IgG4 concentrations (≥135 mg/dl)

3. Coexistence of autoimmune pancreatitis, IgG4-related dacryoadenitis/sialadenitis, or IgG4-related retroperitoneal fibrosis

4. Histopathological examination shows:
   a. Marked lymphocytic and plasmacyte infiltration and fibrosis
   b. Infiltration of IgG4-positive plasma cells: >10 IgG4-positive plasma cells/HPF
   c. Storiform fibrosis
   d. Obliterative phlebitis

Option: effectiveness of steroid therapy

A specialized facility, in which detailed examinations such as endoscopic biliary biopsy and endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) can be administered, may include in its diagnosis the effectiveness of steroid therapy, once pancreatic or biliary cancers have been ruled out

Diagnosis

Definite diagnosis

1. + 3.

1. + 2. + 4.a., b.

4.a., b., c.

4.a., b., d.

Probable diagnosis

1. + 2. + option

Possible diagnosis

1. + 2.