Histological and Morphological Heterogeneity of Biliary Stenosis

Kirsten Muri Boberg
The Norwegian PSC Research Center and Department of Transplantation Medicine
Oslo University Hospital, Rikshospitalet
Oslo, Norway
I have no disclosures
Agenda

• Overview of causes of biliary stenosis
• Emphasis on the differentiation between strictures in the context of:
  – IgG4-sclerosing cholangitis (IgG4-SC)
  – Cholangiocarcinoma (CCA)
  – Primary sclerosing cholangitis (PSC)
• Diagnostic modalities
• Summary
Causes of biliary stenosis

**Benign causes**
- Iatrogenic bile duct injury
- Cholecystectomy
- Liver transplantation
  - Anastomotic stricture
  - Non-anastomotic stricture

**Autoinflammatory**
- Primary sclerosing cholangitis (PSC)
- IgG4-associated cholangitis
- Sarcoidosis
- Eosinophilic cholangitis
- Mast cell cholangitis
- Histiocytosis X

**Cholelithiasis (Mirizzi syndrome)**
**Chronic pancreatitis**
**Vascular**
- Ischemic cholangiopathy
- Vasculitis
- Intra-arterial chemotherapy
- Portal hypertensive biliopathy

**Infectious**
**AIDS cholangiopathy**

**Malignant causes**

**Cholangiocarcinoma**
- Sporadic
- PSC-associated

**Pancreatic adenocarcinoma**
**Metastatic cancer**
**Gall bladder cancer**
**Ampullary adenocarcinoma**
**Hepatocellular carcinoma**
**Lymphoma**

Bowlus CL et al. Nature Reviews 2017
Considerations in stricture diagnostics

• Type of stricture
  – Intrinsic/extrinsic
  – Benign/malignant
  – Fibrotic/inflammatory
  – Temporary/permanent
  – Symptomatic/asymptomatic

• Basic tools
  – Case history/clinical scenario
  – Biochemistry, tumor markers
  – CT findings
  – MRCP/ERCP cholangiography
  – Biopsy

• Supplementary tools
  – ……
# Characteristics of IgG4-SC, PSC and CCA

<table>
<thead>
<tr>
<th></th>
<th>IgG4-SC</th>
<th>PSC</th>
<th>CCA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yrs</strong></td>
<td>65</td>
<td>25 - 45</td>
<td>Peak 60 - 70</td>
</tr>
<tr>
<td><strong>Gender, male</strong></td>
<td>80%</td>
<td>65%</td>
<td>60%</td>
</tr>
<tr>
<td><strong>Associated diseases</strong></td>
<td>Autoimmune pancreatitis, IgG4-related diseases</td>
<td>IBD</td>
<td>-</td>
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<tr>
<td><strong>Histological findings</strong></td>
<td>Abundance of IgG4-pos. plasma cells</td>
<td>Obliterative cholangitis and cirrhosis</td>
<td>Adenocarcinoma, papillary tumors</td>
</tr>
<tr>
<td><strong>Cholangiography</strong></td>
<td>Long strictures, distal bile duct strictures</td>
<td>Band-like strictures with «beading»</td>
<td>Long, fixated, hard strictures</td>
</tr>
<tr>
<td><strong>Elevated serum IgG4</strong></td>
<td>90%</td>
<td>9 - 22%</td>
<td>8 - 14%</td>
</tr>
<tr>
<td><strong>Response to steroids</strong></td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Association with CCA</strong></td>
<td>?</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Good</td>
<td>Progressive disease</td>
<td>Poor</td>
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</table>

IgG4-SC vs PSC: Cholangiography

• IgG4-SC
  – Long, often distal strictures
  – Prestenotic dilatations

• PSC
  – Band-like, short strictures
  – Beaded pattern
  – Pruned-tree appearance
  – Diverticulum-like outpouchings

Kamisawa T et al. J Hepatobiliary Pancreat Sci 2019
### IgG4-SC: Subtypes and diff. diagnoses

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Involvement</th>
<th>Differential diagnosis</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Type 1</td>
<td>Distal common bile duct stricture</td>
<td>Pancreatic carcinoma, distal cholangiocarcinoma, chronic pancreatitis</td>
<td>Most frequent pattern, often with AIP</td>
</tr>
<tr>
<td>Type 2</td>
<td></td>
<td>PSC, SSC, pancreatic carcinoma, distal cholangiocarcinoma</td>
<td>Can exhibit additional extrahepatic strictures</td>
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<tr>
<td>Type 2a</td>
<td>* Diffuse intrahepatic cholangiopathy and a lower common bile duct stricture*</td>
<td>Hilar and distal common bile duct stricture</td>
<td>Hilar cholangiocarcinoma, pancreatic carcinoma, distal cholangiocarcinoma, gall bladder carcinoma</td>
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<tr>
<td>Type 2b</td>
<td>* Diffuse intrahepatic cholangiopathy and a lower common bile duct stricture*</td>
<td>Hilar stricture</td>
<td>Hilar cholangiocarcinoma</td>
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</tbody>
</table>

- Type 1: 64%
- Type 2a: 5%
- Type 2b: 8%
- Type 3: 10%
- Type 4: 10%

Patient with cholestasis and hilar stricture

52 yr old male

CT
Hilar tumor, most likely CCA

MRCP
Central occlusion of hilar bile ducts, suspicious of CCA

- Cholangiocarcinoma?
- PSC?
- IgG4-sclerosing cholangitis?

- Suspected CCA
- Liver resection: IgG4
- Liver failure
- Liver transplantation

Courtesy of Trygve Syversveen
IgG4-SC: Histology

- Immunohistochemical staining: Lymphoplasmacytic infiltrate
- IgG4-positive plasma cells (red) (>10/hpf)

Courtesy of K. Grzyb

- Infiltration of IgG4-pos. cells in the bile duct (brown)
- Storiform pattern of fibrosis
- Obliterative phlebitis
- Bile duct epithelium intact

Kamisawa T et al. J Hepatobiliary Pancreat Sci 2019
Diagnostic criteria of IgG4-related disease are based on a combination of findings

HISTORt criteria
- Histology
- Imaging
- Serology
- Other organ involvement
- Response to therapy

Reconsider if lack of response to 4 weeks of steroid therapy
Cholangiocarcinoma

- Long, fixated, irregular, hard strictures
- Asymmetrical, edgy limitations
- Strictures in the context of increased suspicion

Extrahepatic CCA

Growing longitudinally along the wall of large bile ducts causing wall thickening and strictures

Presenting as papillary tumors growing towards the duct lumen

Normal CCA

Kendall T et al. Liver Int 2019

Courtesy of Lars Aabakken
Cholangiocarcinoma

Preinvasive precursor lesions
- Periductal infiltrating CCA
  - Biliary intraepithelial neoplasm (BilIN 1-3)
- Intraductal papillary CCA
  - Intraductal papillary neoplasm of the bile duct (IPNB)

Molecular genetic alterations
- Genetic differences between distinct subtypes of biliary tract cancer - heterogeneous tumors
Primary sclerosing cholangitis (PSC)

- Bile duct inflammation and fibrosis
- Periductal fibrosis «typical»
- Diagnosis by MRCP or ERCP
- Males:females = 2:1
- Age at diagnosis 30-40 yrs
- IBD in up to 80%
- Progression to liver failure
- Transplant free survival
  - Median 12-21 yrs
Cholangiocarcinoma in PSC

- Life-time risk up to 20%
- Young patients
- Difficult to differentiate benign vs malignant strictures
- Most often diagnosed at advanced stage with poor prognosis
- Primary cause of PSC-related death
  - 32% of cases (Boonstra K et al. Hepatology 2013)
PSC-CCA: Examples of histopathology

- Irregular, atypical glandular structure and groups of neoplastic cells
- Bile duct with BIlIN3 (CCA in situ)
- Perineural infiltration
- Tumor with connective tissue stroma
- Complex glandular structure
- No normal bile ducts

Courtesy of H. Reims
PSC: Intraductal papillary neoplasm

Intraductal papillary neoplasm
Courtesy of B. Goeppert

Intraductal papillary neoplasm with invasive CCA

Intraductal papillary neoplasm
Courtesy of H. Reims
Indeterminate strictures: Supplementary tools

- **Ductal sampling**
  - Brush cytology
  - Forceps biopsy
  - Bile aspiration

- **Ductal imaging**
  - EUS
  - IDUS
  - Cholangioscopy
  - Confocal laser microscopy

- **PET scan**
Brush cytology

Bile duct in explanted liver

Low grade dysplasia

High grade dysplasia

Low grade dysplasia

High grade dysplasia

Cholangiocarcinoma
Brush cytology

- Poor sensitivity
- Questionable specificity in inflammatory tissues
- Sampling technique may matter

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>No. pts</th>
<th>Se</th>
<th>Spe</th>
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<tr>
<td>Foutch et al.</td>
<td>1991</td>
<td>30</td>
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<td>Lee et al.</td>
<td>1995</td>
<td>149</td>
<td>37%</td>
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<td>Ponchon et al.</td>
<td>1995</td>
<td>204</td>
<td>35%</td>
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<td>Pugliese et al.</td>
<td>1995</td>
<td>94</td>
<td>54%</td>
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<td>Glasbrenner et al.</td>
<td>1999</td>
<td>78</td>
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<td>Mansfield et al.</td>
<td>1997</td>
<td>43</td>
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<td>Jailwala et al.</td>
<td>1999</td>
<td>133</td>
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<td>Macken et al.</td>
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<td><strong>Total</strong></td>
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<td>837</td>
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Combined diagnostics

<table>
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<th>Sens</th>
<th>Spec</th>
<th>Accuracy</th>
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<td>100</td>
<td>76</td>
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<td>DNA analysis</td>
<td>52</td>
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<td>71</td>
<td></td>
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<tr>
<td>s-CA19-9</td>
<td>67</td>
<td>89</td>
<td>76</td>
<td></td>
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<tr>
<td>s-CEA</td>
<td>56</td>
<td>89</td>
<td>70</td>
<td></td>
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<tr>
<td><strong>All combined</strong></td>
<td>88</td>
<td>80</td>
<td>84</td>
<td></td>
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Lindberg B et al. Endoscopy 2002

FISH (loss or gain of chromosomes) analysis contributes to increase sensitivity

**ERCP/forceps biopsy**

Sensitivity: 43-81%
Specificity: 90-100%
Combine with brush cytology: sensitivity 73% ?
Access to stricture may be a limitation

**EUS**

- Features of malignancy
  - Presence of (pancreatic) mass
  - Irregular bile duct wall
  - Bile duct wall thickness >3mm

- FNA adds to diagnostic accuracy
- Distal>proximal lesions
- Seeding remains a concern
Cholangioscopy

• Appearance of stricture
  – Irregular surface
  – «Tumor vessels»

• Directed sampling of stricture
  – Visual forceps biopsies


CCA in PSC

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<tr>
<th>Test</th>
<th>Sens</th>
<th>Spec</th>
<th>Accuracy</th>
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<tr>
<td>Brush cytology</td>
<td>52</td>
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<td>87</td>
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<tr>
<td>FISH polysomony</td>
<td>50</td>
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<td>69</td>
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<tr>
<td>Cholangioscopy</td>
<td>65</td>
<td>97</td>
<td>96</td>
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</tbody>
</table>


• Normal
• PSC: inflamed bile duct
• PSC: inflamed bile duct and stricture

Courtesy of L. Aabakken
Molecular stratification and emerging biomarkers

- **Bile proteomic profile**
  - Lankisch TO. Hepatology 2011
  - AUC 0.87

- **Bush cytology: 4-gene methyl. DNA panel**
  - Andresen K. Hepatology 2015
  - Area under the curve: 0.944

- **Bile DNA methylation markers**
  - Vedeld HM. Unpublished

- **Blood microRNA markers**
  - miR-222, miR-483-5p
  - AUC 0.77

- **Serum metabolites**
  - Banales JM. Hepatology 2019

- **Urine peptide/protein markers**
  - Metzger J. Gut 2013

Proteomics, epigenomics, and metabolomics may prove to be useful, but need prospective validation.
Molecular alterations in bile tract cancer

Whole-exome sequencing of 260 biliary tract cancers

- PSC-CCA (International PSC Study Group) (n=186) (42 genes)
  - 30% intrahepatic CCAs
  - No FGFR alterations
  - IDH1: 1/186 (isocitrate dehydrogenase)

- PSC-CCA
  - Homogenous genomic CCA profile
  - Extrahepatic phenotype
  - Predominantly of extrahepatic/large duct origin?

- Clinical application with prognostic and therapeutic potential remains to be studied

32 genes sign. altered. Nearly 40% of cases harbored targetable genetic alterations (blue)

Nakamura H et al. Nature Genetics 2015

Goeppert B, Folseraas T et al. Unpublished
Surveillance for hepatobiliary cancers in PSC

- A number of algorithms for surveillance for hepatobiliary cancers in PSC patients proposed, but clinical utility unclear
- Patients diagnosed with hepatobiliary cancer (n = 79/830)
- 51% under surveillance, 49% without
- Probability of a hepatobiliary cancer event (recurrence or death) at 5 yrs higher with no surveillance (75% vs 32%)
- Survival at 5 and 10 yrs significantly higher in surveillance group

Ali AH et al. Hepatology 2018
Biliary strictures - Summary

• Clinical assessment along with a combination of radiological modalities and endoscopic procedures (ERCP with cholangioscopy, EUS) with tissue sampling (brush cytology, biopsies) is necessary to correctly diagnose biliary strictures

• IgG4-sclerosing cholangitis, PSC and CCA each presents specific features, but differential diagnosis may be challenging

• The potential of new biomarkers and genetic characteristics must be further studied

• Clinical trials with stratification of patients according to genetic drivers possible in the future?
Norwegian PSC Research Center

Leader:
Tom Hemming Karlsen

Clinical research

Experimental hepatology

Genomics and metagenomics