IgG4-Related Disease in the Pancreatobiliary System:

How Good is Histopathology as the Gold Standard of Diagnosis?

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IgG4-related disease/IgG4-RD – key facts

Fibro-inflammatory condition
Rare
Systemic
Tumefactive

Unique pathology
Glucocorticoid responsive
IgG4-RD – Clinical presentation

• Subacute: swelling of organ with e.g. local obstruction/dysfunction suggestive of tumour/neoplasm

• Four clinical phenotypes:
  • Pancreato-Hepato-Biliary disease: 31%
  • Retroperitoneal Fibrosis and/or Aortitis: 24%
  • Head and Neck-Limited disease: 24%, more likely female and Asian
  • Classic Mikulicz syndrome with systemic involvement: 22%, higher serum IgG4

• DM, allergic diseases, autoimmune diseases common

IgG4-RD – Pathophysiology and Diagnosis

- Aberrant T-cell activity: T-fh and T-reg inducing plasma cell class switch, plasmablasts, lymphoid follicles; CTLs leading to fibrosis
- IgG4 likely secondary reactive

- HISORt = Histology, Imaging, Serology (IgG4), Other Organ involvement, Response to treatment (steroids)

- Only 50% of patients with IgG4-RD have IgG4 elevation in serum
- Only 10% of patient with IgG4 elevation in serum have IgG4-RD

- Laboratory findings not specific: ↑ Ig, ↑IgE, ↑ eosinophils, ANA, RF
- Circulating plasmablasts
- Histopathology gold standard of diagnosis
IgG4-RD – Characteristic histopathology

1. Dense lymphoplasmacytic infiltrate
2. Fibrosis, arranged at least focally in a storiform pattern
3. Obliterative phlebitis
4. Increased IgG4 plasma cells and increased ratio of IgG4 to IgG positive plasma cells

Dense lymphoplasmacytic infiltrate

- Mature lymphocytes and plasma cells
- Eosinophils can be prominent
- Lymphoid follicles may be present
- Histiocytes present but not prominent

Storiform fibrosis

- Cart-wheel or whorled
- Bland spindle cells
- Intimate association of fibrosis with inflammation = appears stream-like

Obliterative phlebitis

- Least often found but most specific feature
- Luminal obliteration by inflammation and fibrosis
- Unaccompanied artery may give clue
- Elastic stains useful

Phlebitis without obliteration

- Additional clue seen on H&E
- Obliterative arteritis also seen in pancreatic IgG4-RD
• Required number of IgG4 positive plasma cells site specific
• In biopsies at least 10/HPF
• Average count of 3 HPF with highest number IgG4 and IgG
• IgG4 to IgG positive plasma cell ratio >40% mandatory
IgG4-RD – Histopathology cautions

- Venous obliteration by luminal fibrosis without inflammation does not represent IgG4-RD but more likely organised thrombus
- Background staining, especially IgG, often precludes accurate counting
- Isolated elevation of IgG4 positive plasma cells is non-specific
- Plasma cells in IgG4-RD are polytypic warranting low threshold for evaluation of light chain restriction
- Histomorphology trumps IgG4/IgG immunohistochemistry
IgG4-RD – DD of ↑ IgG4+ plasma cells

• Tumours: peritumoural changes, Inflammatory myofibroblastic tumour

• Lymphoproliferative disorders: MALT, plasma cell

• Infections

• Eosinophilic disorders

• Inflammatory/Autoimmune disorders: Castleman Disease, Rosai-Dorfman disease, Vasculitis (ANCA+, granulomatosis with polyangiitis etc)
IgG4-RD – the things you don’t see

• Epithelioid granulomas (except in some lymph nodes)
• Giant cells
• Necrosis (except when ulcerated)
• Neutrophilic microabscesses
• Necrotising arteritis
IgG4-RD – Proposed diagnostic terminology

1. **Histologically highly suggestive of IgG4-RD**
   - Two or three features, ↑IgG4+ plasma cells, IgG4/IgG >40%

2. **Probable histological features of IgG4-RD**
   - Single feature, ↑IgG4, often in biopsies, IgG4 to IgG positive plasma cell ratio most specific

3. **Insufficient histological evidence of IgG4-RD**
   - Does not fit into 1 or 2, does not exclude IgG4-RD
   - Insufficient evidence for Cytology in diagnosis of IgG4-RD

Clinicopathological correlation is critical
IgG4-RD – Hepatopancreatobiliary presentation

- Autoimmune pancreatitis type 1/ AIP type 1
- IgG4-related sclerosing cholangitis
- (IgG4-related cholecystitis)
- IgG4-RD in the liver

IgG4-RD in the pancreas

- Type 1 AIP (IgG4-related pancreatitis)
- Commonest presentation of IgG4-RD (60%)
- Elderly men
- Painless jaundice, acute pancreatitis rare
- Diffuse enlargement of the pancreas with a capsule-like low-density rim and narrowing of pancreatic duct on imaging
- Diffuse process, pancreatic duct epithelium preserved
- Differential diagnosis: Type 2 AIP, Pancreatic cancer, Groove and follicular pancreatitis, Granulomatosis with polyangitis, RA

### IgG4-RD - The ICDC criteria

#### TABLE 2. Level 1 and Level 2 Criteria for Type 1 AIP

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Level 1</th>
<th>Level 2</th>
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<tbody>
<tr>
<td><strong>P</strong> Parenchymal imaging</td>
<td>Typical: Diffuse enlargement with delayed enhancement (sometimes associated with rim-like enhancement)</td>
<td>Indeterminate (including atypical): Segmental/focal enlargement with delayed enhancement</td>
</tr>
<tr>
<td><strong>D</strong> Ductal imaging (ERP)</td>
<td>Long (&gt;1/3 length of the main pancreatic duct) or multiple strictures without marked upstream dilatation</td>
<td>Segmental/focal narrowing without marked upstream dilatation (duct size, ≤5 mm)</td>
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<td><strong>S</strong> Serology</td>
<td>IgG4, &gt;2× upper limit of normal value a or b</td>
<td>IgG4, 1–2× upper limit of normal value a or b</td>
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</table>
| **OOI** Other organ involvement | 1. Histology of extrapancreatic organs | 1. Histology of extrapancreatic organs including endoscopic biopsies of bile duct:
| | a. Marked lymphoplasmacytic infiltration with fibrosis and without granulocytic infiltration | a. Histology of extrapancreatic organs including endoscopic biopsies of bile duct:
| | (2) Storiform fibrosis | Both of the following:
| | (3) Obliterative phlebitis | (1) Marked lymphoplasmacytic infiltration without granulocytic infiltration |
| | (4) Abundant (>10 cells/HPF) IgG4-positive cells | (2) Abundant (>10 cells/HPF) IgG4-positive cells |

#### Histology of the pancreas

**LPSP (core biopsy/resection)**

At least 3 of the following:

1. Periductal lymphoplasmacytic infiltrate without granulocytic infiltration
2. Obliterative phlebitis
3. Storiform fibrosis
4. Abundant (>10 cells/HPF) IgG4-positive cells

**LPSP (core biopsy)**

Any 2 of the following:

1. Periductal lymphoplasmacytic infiltrate without granulocytic infiltration
2. Obliterative phlebitis
3. Storiform fibrosis
4. Abundant (>10 cells/HPF) IgG4-positive cells

#### Diagnostic steroid trial

Response to steroid (Rt)*

Rapid (<2 wk) radiologically demonstrable resolution or marked improvement in pancreatic/extrapancreatic manifestations

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Type 1 AIP/IgG4-RD – Resection specimen

- 66 year old gentleman
- 2006 weight loss and jaundice
- EUS 3x2cm mass in head of pancreas
- FNA suspicious of malignancy
- Whipple’s procedure
2013: IgG4 3.5 g/l

2019: 79 years well with stable disease, on Creon, no other treatment

IgG4 2.9 g/l

Developed Alzheimer
Type 1 AIP/IgG4-RD – Biopsy specimens

- Pancreatic FNA: Only to rule out malignancy
- Biliary brush: Only to rule out malignancy
- Ampullary biopsy: Low sensitivity and specificity
  May be helpful but morphological features almost always absent
  Elevated IgG4 positive cells not specific

- Pancreatic core biopsy/FNB: Possible but can be limited
  IgG4/IgG ratio most specific

- Gallbladder:
  Very useful to review previous cholecystectomy including nodular
  fibroinflammatory infiltrate at the serosal aspect

Type 1 AIP/IgG4-RD – Core biopsy

• 60 year old female
• 2009 Epigastric pain
• >3cm mass in uncinate process of pancreas
• Pancreatic core biopsy
2010: IgG4 1.35 g/l

2019: 70 years
Stable disease,
No treatment, IgG4
0.7 g/l

Had breast cancer
and temporal arteritis

Up to 25 IgG4 positive cells per hpf
Type 1 AIP/IgG4-RD – EUS FNB

• 41 year old male
• 12/2016: epigastric discomfort, reflux and heartburn followed by obstructive jaundice
• Serology: Bili 45 umol/l, AlkP 717 IU/l, ALT 600 IU/l, IgG 8.3 g/l, IgG4 1.147 g/l, ANA negative
• PMH: previous salivary gland enlargement, dry eyes, mild asthma, stage 1 malignant melanoma
Histopathology – EUS FNB
Pancreatic parenchyma
Storiform fibrosis
Obliterating phlebitis – Elastic stain (EVG)
IgG4 (25/hpf) 55%

After 4 weeks steroids (Jan 17): Bili 8 umol/l, AlkP 90 IU/l, ALT 20 IU/l, IgG4 0.765 g/l

2019: 44 years, flare of symptoms with dark urine but normal LFTs, IgG 0.77 g/l, MRI burnt out disease
IgG4-related sclerosing cholangitis (IgG4-RSC)

• IgG4-sclerosing cholangitis presenting feature in 6-10% of patients
• Commonly associated with type 1 AIP
• 8-17% isolated hepatobiliary lesions – require biopsy
• 10-20% of IgG4-RSC normal serum IgG4
• Longer and combined low bile duct and intrahepatic strictures
• Hilar involvement with expansion between ducts and vessels
• Differential diagnosis: **PSC, bile duct carcinoma**, secondary sclerosing cholangitis, lymphoproliferative disorders, follicular cholangitis, fibrohistiocytic variant of inflammatory pseudotumours

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<th>PSC</th>
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<td>• Outer/entire wall of bile ducts</td>
<td>• Inner wall of bile duct with ulceration</td>
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<td>• Lumen intact (except stent)</td>
<td>• Subepithelial inflammation</td>
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<td>• Inflammation around periductal glands</td>
<td>• Loss of bile ducts</td>
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<td>• Rare duct loss</td>
<td>• Onion skinning</td>
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<tr>
<td>• Intense lymphoplasmacytic inflammation</td>
<td>• Rarely increased IgG4</td>
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<tr>
<td>• Obliterative phlebitis</td>
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<tr>
<td>• Fibrosis</td>
<td></td>
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<tr>
<td>• &gt;10 IgG4 positive cells/hpf</td>
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<td>• IgG4:IgG ratio &gt;0.4</td>
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IgG4-RD in the liver

• IgG4-hepatopathy
  • Collective term covering hepatic lesions primarily or secondarily related to IgG4-related sclerosing cholangitis and type 1 autoimmune pancreatitis
  • Five categories: portal inflammation, large bile duct damage, portal sclerosis, lobular hepatitis, and cholestasis

• IgG4-autoimmune hepatitis
  • Only 3 cases reported in absence of AIP and IgG4-RSC

• IgG4-inflammatory pseudotumour

IgG4-RSC + hepatopathy – Biopsy diagnosis

- **Biliary brush:** Only to rule out malignancy
- **Bile duct biopsy:** Mainly to rule out malignancy as characteristic pathology of IgG4-RD at hilum adjacent to bile ducts
- **Liver biopsy:** Often not specific and no fibrosis. Expanded portal tracts in peripheral liver with lymphocytes, plasma cells and eosinophils, expansive fibroinflammatory nodule characteristic but usually not on biopsy
- **Ampullary biopsy:** Low sensitivity and specificity
- **Gallbladder:** Fibroinflammatory infiltrate at the serosal aspect, often as well circumscribed nodule
IgG4-RSC – Diagnostic biopsy challenges

• 62 year old lady, no PMH
• November 2015: Presented with obstructive jaundice secondary to pancreatic mass abutting portal vein
• Stented – atypical brush cytology
• Whipple planned for 31/12/2015
• EUSx2: benign histology
• MDM decision to proceed to surgery but bile duct abnormal at operation
• Frozen section benign
• Cholecystectomy and Hepaticojejunostomy
• Serology: Bili 22 umol/l, AlkP 166 IU/l, ALT 21 IU/l, IgG 8.8 g/l, IgG4 0.31 g/l, ANA not known
Histopathology – EUS FNB
No phlebitis
IgG4 (<10/hpf)  IgG
Intraoperative frozen section core biopsy
Vague storiform fibrosis and inflammation
IgG4 (just >10/hpf)
BD: expanded, inflamed and storiform fibrosis
Cystic duct: expanded wall, narrow lumen
Cystic duct: inflamed and storiform fibrosis
Gallbladder

- April 2017: extremely well, improved type 3c DM, stopped insulin
- April 2018: patient doing great, normal LFTs, IgG4 0.29 g/l
- 2019: 66 years, well IgG 0.3 g/l
IgG4-hepatopathy – Liver biopsy

• 74 year old gentleman
• April 2016: “Decompensated liver disease” triggered by chest infection
• Allergic to fish, melon and rabbit fur
• March 2017: malnourished, TP 96, Alb 25, IgG4 >7.1
• Liver biopsy
Dense inflammation

Portal fibrosis

Obliterated vein

IgG4

Started steroids, 2017: gained weight,
TP 75,
Alb 41,
IgG4 2.5 g/l

2019: 76 years
IgG4 1.2 g/l
Near normal LFTs
7.5 mg Prednisolone
IgG4-RD – Take home messages

- IgG4-RD is rare
- Histopathology is an “imperfect gold standard” and needs close clinicopathological correlation
- Isolated increased IgG4-immunohistochemistry not specific; IgG4/IgG ratio most useful
- Critical role of histopathology to exclude malignancy
- EUS FNB diagnosis challenging but new EUS FNB needles with promising diagnostic performance
- No role for cytology in diagnosis of IgG4-RD
- Review of archival gallbladder pathology may be helpful
- Histopathology has no role in assessing prognosis or treatment response
Thank you for your attention