IgG4 related cholangiopathy

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Introduction

- IgG4 associated cholangitis (IAC) is one manifestation of IgG4 related disease (IgG4 RD)
  - Immune mediated inflammatory disease characterized by inflammatory lesions in the pancreaticobiliary tract with massive infiltration of lymphocytes (typically IgG4 positive plasma B cells) in the bile duct wall, elevation of the serum IgG4 and a good response to corticosteroid treatment

- IAC is associated with type 1 autoimmune pancreatitis (lymphoplasmocytic sclerosing pancreatitis)

- IAC and autoimmune pancreatitis (AIP) may mimic sclerosing cholangitis, cholangiocarcinoma or pancreatic carcinoma

- As IAC and AIP may be difficult to diagnose and mimic malignancy, unnecessary hepatic / pancreatic resections may take place

Hubers 2015
Pathogenesis

- Poorly understood
- IAC belongs to **spectrum** of IgG4 **related disorders**, which include a number of medical conditions sharing similar histopathological characteristics
  - **Multiple organs** can be affected simultaneously / consecutively with swelling, loss of function and inflammatory features including lymphocytic infiltration
  - **Pancreaticobiliary** tract is one of the major localisations; IAC is often accompanied by autoimmune pancreatitis
    - >½ AIP have hepatobiliary manifestations
      - Kanno 2012
    - Most IAC have involvement of the pancreas
      - Ghazale 2008

<table>
<thead>
<tr>
<th>Abdominal and pelvic manifestations</th>
<th>Extra-abdominal/extra-pelvic manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile ducts (IAC), gallbladder, and liver</td>
<td>Hypophysis</td>
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<tr>
<td>Pancreas (AIP)</td>
<td>Eye, retro-orbital tumor</td>
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<td>Stomach, intestine, and ileal pouch</td>
<td>Salivary and lacrimal glands</td>
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<tr>
<td>Retroperitoneum (fibrosis)</td>
<td>Thyroid gland</td>
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<tr>
<td>Kidney</td>
<td>Lung</td>
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<tr>
<td>Pseudotumor</td>
<td>Lymphatic system (especially lung hilus)</td>
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<td>Prostate</td>
<td>Vascular system (aortitis)</td>
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<td>Testis</td>
<td>Joint</td>
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</tbody>
</table>

Hubers 2015
Pathogenesis

• Histologically - IAC / type 1 AIP
  • Dense lymphoplasmacytic infiltrate
  • Abundant IgG4 positive plasma cells
  • Specific pattern of storiform fibrosis
  • Obliterative phlebitis
Pathogenesis

Deshpande 2012
Clinical picture

- Older males
  - Generally >60 yrs
  - Male / female 8:1

- Association with IBD is controversial

- Possible role for environmental factors (solvents, gases)

- Mild to moderate abdominal pain, weight loss, obstructive jaundice and pruritus
- New onset DM, steatorrhea
Imaging

• Mass forming lesions vs biliary strictures/ sclerosing lesions
  • May be difficult to distinguish from malignancy, sclerosing cholangiopathies (PSC)

• Cholangiography – variable with corresponding differential
  • Hilar stenosis – klatskin
  • Distal CBD stenosis – chronic pancreatitis, pancreatic cancer, cholangiocarcinoma
  • Diffuse structuring in intra- & extra-hepatic systems - PSC
• Elevated serum bilirubin, ALP, GGT, Ca 19-9, IgG4 - Fluctation!
  • IgG4 <4x ULN non-diagnostic (can be elevated in ca, PSC)
  • 20-25% of IAC / AIP can have normal IgG4
  • Ca 19-9 frequently elevated

• Rheumatoid factor, ANA may be positive but lack specificity, sensitivity
Diagnosis

• No accurate diagnostic test for IAC / IgG4 RD – leads to diagnostic delay

• Serum IgG4 only diagnostic when raised > 4x the upper limit of normal

• Diagnostic criteria
  • Organ manifestation patterns
  • Imaging findings
  • Serum tests
  • Histological features
  • Response to immunosuppressive therapy
Diagnosing pancreaticobiliary manifestations of IgG4-RD

**Autoimmune pancreatitis (type I)**
- Clinical suspicion of pancreatic disease
  - Absence of classical imaging for AIP
- Classical imaging for AIP + one of the following:
  - elevated serum IgG4
  - other organ involvement
  - compatible FNA histology
- Negative work-up for cancer
- One of the following:
  - serum IgG4 > 2 x ULN
  - (histologically) proven other IgG4-RD spectrum organ involvement
- Two of the following:
  - elevated serum IgG4
  - clinical / radiological evidence for other organ involvement
  - compatible FNA histology
- Response to 2 weeks of adequate steroid treatment:
  - significant decrease in serum IgG4
  - markedly improved morphology as objectivated by imaging (CT, ultrasound, MRCP)

**Definite diagnosis of AIP**

**Definite diagnosis of IAC**

**IgG4-associated cholangitis**
- Stricture(s) of intra-hepati, proximal extra-hepati or intra-pancreatic ducts, with:
- Classical imaging for AIP + elevated serum IgG4
- Two or more of the following:
  - elevated serum IgG4
  - suggestive pancreatic imaging findings
  - other organ involvement
  - bile duct biopsy with > 10 IgG4 positive cells / hpf
  - Combined with following findings after 4 weeks of adequate steroid treatment:
    - markedly improved biliary strictures allowing stent treatment
    - liver enzymes < 2 x ULN
    - significant decrease in serum IgG4 and CA19.9
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**IgG4-associated cholangitis**

- Stricture(s) of intra-hepatic, proximal extra-hepatic or intra-pancreatic ducts, with:
  - Previous pancreatic/ biliary resection or core biopsy of pancreas showing diagnostic features of AIP/IAC

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- Response to 2 weeks of adequate steroid treatment:
  - Significant decrease in serum IgG4
  - Markedly improved morphology as objectivated by imaging (CT, ultrasound, MRCP)

**Definite diagnosis of IAC**

- In all cases of non-response to adequate steroid treatment:
  - Withdraw steroids!
  - Reconsider presence of malignant disease

**Two or more of the following:**

- Elevated serum IgG4
- Suggestive pancreatic imaging findings
- Other organ involvement
- Bile duct biopsy with >10 IgG4 positive cells / hpf

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Chari 2009
Hubers 2015
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Case 1 – Mr NM

- 64 yr old man, African extraction
- BG: DM, Hpt, blind L eye, PS1
- 1\textsuperscript{st} seen 2010
  - Obs jaundice, 10kg LOW
  - Bili 198/121, ALP 448, GGT 1651, AST 127, ALT 89, Ca 19-9 200,8
  - CT distal obstruction, no mass
  - ERCP – stricturing of hilum, intrahepatic ducts – stent placed
  - Brushings – benign cells, lymphocytes
  - IgG 33,52 (7-16)
  - Thought to be malignant

- 2012 - no pain, jaundice, loss of PS, LOW – bili 24/15, ALP 651, GGT 2300, Ca 19-9 57
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Case 2 – Mr LB

- 54 year old man, mixed extraction
- BG: DM
- 1st presented April 2009
  - Abdominal pain, LOW
  - Bili 17/6, ALP 313, GGT 763, ALT 180, AST 116, Ca 19-9 245
  - CT: enlarged, sausage shaped pancreas
  - Subsequently Bili 36/19
  - ERCP: CBD stricture, diffuse intra-hepatic strictures
  - Serum IgG4 6 (0.084 – 0.888)
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- Rxed with oral prednisone
- CT 5/12 post end of Rx
Case 2 – Mr LB

• 54 year old man, mixed extraction
• BG: DM
• Returned 2014
  • Obstructive jaundice
Case 3 – Mrs NT

• 49 year old woman, African extraction
• BG: nil
• Presented May 2012
  • Fluctuating clinical jaundice, progressive pruritus, mild LOW
  • Bili 74/43, ALP 211, GGT 86, ALT 34, AST 41, alb 28, Ca 19-9 normal
  • CT: HOP mass
  • MRI/MRCP: multifocal caliber variation of intra- & extra-hepatic biliary tree, dilated GB, dilated CHD, stenosed CBD
  • ERCP: long distal CBD stricture
  • Surgical resection: Histo: IgG4 RD AIP.
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Case 4 – Mr BD

- 64 year old man; compatriot of Solly Marks; of mixed extraction
- BG: hpt, hyperchol, IHD, good baseline
- Presented Jan 2013
  - Obstructive jaundice, LOW
  - Bili 181/102, GGT 150, AST 48, ALT 61
  - Ca 19-9 5.7
  - CT: dilated CBD tapers abruptly within bulky HOP
  - ERCP: distal benign CBD stricture
  - IgG4 21.6 (0.84-0.888)
  - EUS: ill defined mass
- Good response to steroids; relapse on completion. Subsequent response on re-initiation
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Case 5 – Mr YH

• 58 year old man, mixed ancestry

• BG: DM; dxed chronic sclerosing sialadenitis (on histolology) prev year

• Presented Jan 2014
  • LOW, Obstructive jaundice / pruritus
  • Bili 40/34; ALP 313, ALP 405, GGT 292, ALT 77, AST 64, Ca 19-9 1721
  • U/S: thickened GB wall, hepatomegaly
  • CT: thickened GB / CBD walls
  • MRCP: sclerosed intra-hepatic ducts
  • IgG4: 37.1 (0.03 – 2.01)
  • Liver bx: proliferating bile ductules, absent normal caliber interlobular duct, lymphocytes >10 IgG4-positive plasma cells / HPF
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<th>ALP</th>
<th>GGT</th>
<th>ALT</th>
<th>AST</th>
<th>Ca 19-9</th>
<th>IgG4</th>
</tr>
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<tbody>
<tr>
<td>Case 1</td>
<td>198</td>
<td>590</td>
<td>1886</td>
<td>127</td>
<td>157</td>
<td>200</td>
<td>33.5 (IgG 7-16)</td>
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<td>Case 2</td>
<td>17</td>
<td>313</td>
<td>763</td>
<td>180</td>
<td>116</td>
<td>247</td>
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<td>Case 3</td>
<td>74</td>
<td>211</td>
<td>86</td>
<td>34</td>
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<td>N</td>
<td>0.71</td>
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<tr>
<td>Case 4</td>
<td>286</td>
<td>276</td>
<td>42</td>
<td>91</td>
<td>94</td>
<td>5.7</td>
<td>21.6 (0.084-0.888)</td>
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<tr>
<td>Case 5</td>
<td>42</td>
<td>405</td>
<td>292</td>
<td>77</td>
<td>64</td>
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Conclusion

• IgG4 cholangiopathy is uncommon
• The clinical and radiological picture is varied
• Diabetes is a prominent clinical feature
• Early diagnosis requires a high index of suspicion
• Histology remains the gold standard
• Important clues include
  • a prolonged clinical course
  • fluctuating clinical / biochemical picture
  • clinical / radiological features not in keeping with malignancy
  • multifocal / benign appearance on cholangiography
• Of particular note:
  • Ca 19-9 may be elevated
  • Elevation of the serum IgG4 is variable
• Therapeutic trial of steroids only once malignancy has been excluded