Autoimmune Pancreatitis

“Papillas, Pancreatograms, and Plasma Cells”

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Indiana University

Case History

• 77 year old male retired physician with new onset of painless jaundice
• He also has 20 # weight loss, which is intentional due to swimming and dietary changes.
• He has no anorexia and no early satiety
• Tbili: 16 ALP 501 and CA 19-9 112
• CT scan shows “fullness in head of pancreas and no discrete mass”
EUS shows a 22 x 23 mm mass in the HOP. Ten passes with FNA showed no evidence of malignancy. Inflammatory cells. No atypia.

Do we suspect AIP?

- What further diagnostic tests would we do?
  - IgG total nl, IgG4 nl, ANA –
  - Papilla bx: Results-Immunohistochemical staining for IgG-4 is negative
- Should the patient go to surgery for diagnosis and treatment?
- Should I use corticosteroids?
- If this is AIP, what is the natural history?
- What is likelihood of relapse?
**Autoimmune Pancreatitis**

- Historical Perspective
- Epidemiology
- Clinical Presentation
  - Type I and Type II
- Making the diagnosis
  - Satisfying the criteria: Japan, Korea, HISORt
- Treatment regimen

**AIP Historical Perspective**

- 1961: Sarles¹
  - 1st description non-ETOH pancreatitis
  - Diffuse enlargement of pancreas
  - Marked lymphoplasmacytic infiltration
  - Elevated gammaglobulins
- 1995: Yoshida²
  - Proposed AIP as concept
- 1997: Ito³
  - 3 cases AIP dramatic response to steroids
- 2001: Hamano⁴
  - Serum IgG 4 as marker

AIP Definition

- “A unique form of chronic pancreatitis characterized by swelling of the gland, irregular narrowing of the pancreatic duct, lymphoplasmacytic infiltration of pancreas, and favorable response to steroids”

aka: lymphoplasmacytic sclerosing pancreatitis (LPSP)

AIP Epidemiology

- Worldwide
- Uncommon
  - 2007 Japan nationwide survey
    - 4.6% prevalence AIP in c pancreatitis
    - Total: 2790 AIP patients, 1120 newly diagnosed cases 2007
    - Incidence: 0.9 / 100,000 population
  - 2005 Korea
    - 5.4 % prevalence (17/315) AIP in c pancreatitis
  - 2005: Italy
    - 6.0 % prevalence (23/383) AIP in c pancreatitis
  - 2003: Mayo1
    - 11.0 % prevalence (27/254) AIP in c pancreatitis

1 Pancreas 2003;27:3-13
2 Pancreas 2012;41:835
AIP

- Who does it affect?
  - older males > older females
  - Japan Kawa, Gastro 2002;122:1264-9
    - n = 40
    - Male 82% (n=33)
    - Age 61 yrs (32-76)

AIP

Clincial Presentation

- New onset jaundice (70%) - common
- Asymptomatic or Mild epigastric discomfort
- Acute pancreatitis – very rare
- Weight loss

CT scan
- Incidental pancreas mass, “fullness”
- Diffuse enlargement pancreas “Halo Sign”
- Fluctuating pancreas masses

ERCP
- Diffuse or segmental narrowing of PD
- Biliary stricture - distal or proximal
CT Scan in AIP

Pancreatogram Findings
ERCP in AIP

AIP Histology
Pathogenesis

- **Not well understood**
  - ? Allergic ..... IgG-4 released in response to an antigen often occurs in allergic disorders

- **Target antigen** for AIP not detected

- **Release cytokines** → up-regulate HLA class II expression by duct epithelial cells → ab to CA II ag’s (duct epithelium) and lactoferrin (acinar cells) → lymphocyte infiltration

Identification of a Novel Antibody associated with AIP

- random library of dodecamer peptides with pooled serum samples from 20 patients with focal AIP

- Most promising peptide they detected was recognized by the serum of
  - 18 of 20 patients (90%) with pathologically proven AIP
  - 4 of 40 pancreas cancer patients (10%)
  - Other pancreatitis or healthy controls was 0%

Identification of a Novel Antibody associated with AIP

- Peptide has homology to PBP protein of H pylori and human UBR2 protein highly expressed in pancreatic acinar cells
  - independent AIP group, 33 of 35 + PBP ab (94%)
  - 5 of 110 patients with pancreatic cancer + PBP (5%)
  - 22 of 35 patients with AIP were + for UBR2 (acinar cells)
  - 0 of 35 patients with other pancreatic diseases.

- Needs validation in larger cohort of patients from different countries with different genetic backgrounds


Type 1 vs Type 2 AIP

<table>
<thead>
<tr>
<th></th>
<th>Type 1 AIP</th>
<th>Type 2 AIP</th>
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</thead>
<tbody>
<tr>
<td>Gender distribution</td>
<td>M &gt; F</td>
<td>M = F</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoplasmacytic infiltrate</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Storiform fibrosis</td>
<td>Present</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Obliterative phlebitis</td>
<td>Present</td>
<td>Infrequent</td>
</tr>
<tr>
<td>IgG4 + cell infiltrate</td>
<td>Present</td>
<td>Scant/min</td>
</tr>
<tr>
<td>Pancreatic duct destruction</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>GEL lesions</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Histologic confirmation need for diagnosis</td>
<td>Not in all cases</td>
<td>Yes</td>
</tr>
<tr>
<td>Serum IgG4 elevated</td>
<td>Mostly</td>
<td>No</td>
</tr>
<tr>
<td>Other organ involvement</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Responds to steroids</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Disease relapse</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Association with IBD</td>
<td>Some</td>
<td>Strong</td>
</tr>
</tbody>
</table>

Abbreviations: GEL, granulocyte epithelial lesion; IBD, inflammatory bowel disease.

Sugumar Gastroenterol Clin N Am 2012; 41:9-22
Type 1: IgG-4 Related Sclerosing Systemic Disease?

- **Proposal:** AIP is not simply pancreatitis but pancreatic lesion reflecting systemic disease
- **Supported by:**
  - Clinically bile duct (IAC), kidneys, lungs, thyroid, prostate, retroperitoneum, liver, and gallbladder are also involved
  - Most IgG-4 related sclerosing disease associated with AIP, but may occur without pancreas
  - IgG-4 staining cells > 10 / HPF in affected tissues
  - All tissues respond similarly to steroid therapy

Kamasawa World J Gastroenterol, 2008; 14:3948-55
AIP
Making the Diagnosis

• For Research Purposes
  – Japan Criteria 2000
    • Revised 2006
  – Korean Criteria 2003
  – Mayo HISORT Criteria 2006
    • Histology, Imaging, Serology, Other organ involvement, Response to therapy

• For Clinical Purposes
  – In the appropriate clinical setting
    • typical findings on ERCP +/- CT scan along with
    • supportive serology +/- histology

Diagnostic Yield in AIP Serology

- Autoantibodies in 10-100% pts with AIP
- 4 series from Japan/Korea

<table>
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<tr>
<th>Autoantibodies</th>
<th>IU</th>
<th>Mayo</th>
<th>UK</th>
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</thead>
<tbody>
<tr>
<td>ANA</td>
<td>39%</td>
<td>25/63</td>
<td></td>
</tr>
<tr>
<td>Lactoferrin</td>
<td>76%</td>
<td>16/21</td>
<td></td>
</tr>
<tr>
<td>ACA II</td>
<td>62%</td>
<td>13/21</td>
<td></td>
</tr>
<tr>
<td>RF</td>
<td>26%</td>
<td>10/36</td>
<td></td>
</tr>
<tr>
<td>AMA</td>
<td>4%</td>
<td>1/18</td>
<td></td>
</tr>
<tr>
<td>Antithryoglobulin</td>
<td>34%</td>
<td>14/41</td>
<td></td>
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Kim, Am J Gastroenterol 2004;99:1605

Indiana University Experience

<table>
<thead>
<tr>
<th>Metrics</th>
<th>IU</th>
<th>Mayo</th>
<th>UK</th>
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<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>29</td>
<td>11</td>
</tr>
<tr>
<td>Age (mean/range)</td>
<td>50 (18-76)</td>
<td>63 (14-85)</td>
<td>53 (28-78)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>60</td>
<td>83</td>
<td>100</td>
</tr>
<tr>
<td>Elevated Total IgG</td>
<td>33%</td>
<td>38%</td>
<td>-</td>
</tr>
<tr>
<td>Elevated IgG 4</td>
<td>13%</td>
<td>71%</td>
<td>64%</td>
</tr>
<tr>
<td>Response to Steroids</td>
<td>92%</td>
<td>100%</td>
<td>100%</td>
</tr>
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Serology IgG 4 and IgG IU Results

Serum IgG4 quandry

• Should ALL patients undergoing resection have serum IgG 4 testing?
  – Prevalence of AIP in Whipple resections
    • 2.5%
  – 40 patients need to be screened to prevent one from going to surgery
    • (if elevated IgG-4 was 100% accurate in AIP)
  – $ 50 cost of serology
  – It would cost $ 2000 for each patient pre-op
**Papillas**

- **Pancreas adenocarcinoma**
- **AIP**
- **cbd stone**

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**Diagnostic Yield of Ampulla Biopsy**

- IgG-4 Immunostaining > 10 / HPF

<table>
<thead>
<tr>
<th>Diagnostic</th>
<th>AIP</th>
<th>Pancreas Ca</th>
<th>Papillitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIP</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- All diagnostic specimens were in patients with head of pancreas involvement
- 2 negative ampulla bx – body and tail

Kamisawa, Gastrointest Endosc 2008: in press
Pancreas Core Biopsy

- **Benefit:**
  - able to obtain histology and preserved architecture

- **Drawback:**
  - invasive, higher risk, duct-centric nature of inflammatory process, obliterative phlebitis may be missed, sampling error

- Transabdominal U/S Core Biopsy
  - 18 gauge, IgG-4 staining, mean 2 passes (1-3), core obtained
  - 21% (4/19)

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EUS Core Biopsy

- **EUS core biopsies**
  - 7/16 (44%) diagnostic histology
  - 15/16 (96%) diagnostic IgG-4 immunostain

- **Resection specimens**
  - 12/13 (94%) diagnostic histology
  - 13/13 (100%) diagnostic IgG-4 immunostain

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Bang, Pancreas 2008;36:84

Chari, Clin Gast Hepatol 2006;4:1010
IgG-4 tissue immunostaining

- Technique standardized
- Must be performed on tissue
  - no standard for cell block
- Many tissues including pancreas cancer have scarce IgG-4 staining plasma cells
- > 5 high-power fields examined
- Positive if: + IgG-4 plasma cells > 10 / HPF

Steroids and AIP

- Some patients improve spontaneously
- Steroid effect is dramatic
  - Clinically effective
  - Morphologically effective
  - Serologically effective
- Optimum dose/duration not fully established
- Relapse in approximately 1/3rd

UK Deheragoda, Clin Gas Hepatol 2007;5:1229
Steroids and AIP

- **Regimen**
  - Begin: Prednisone 30 – 40 mg/day x 4 wks
  - Follow-up at 1 month
    - If responding by CT or ERCP (objective criteria)
      - Taper: week 4, decrease 5 mg q wk
      - Total duration of treatment: 12 weeks (3 months)
  - Follow-up at 6 months
    - Warning: Proximal bile duct involvement predictive of relapse
Steroids and AIP

- **Follow-up at 12 months**
  - If relapse, reinstitute prednisone 40 mg/day and add azathioprine 1.5 – 2.5 mg/kg/day
  - IAC (IgG-4 associated cholangitis) biliary strictures (proximal > distal) are more likely to have incomplete response or relapse
  - Retroperitoneal fibrosis or nephritis may relapse
  - Rituximab IV infusion (B cell depletion) has been encouraging for treatment of azathioprine relapsers
  - Cytoxan and MTX use has also been reported

**2 week trial of Steroids**

- **Discriminator?**
- **22 patients**
  - ? AIP
  - **2 week**
  - 0.5 mg/kg prednisolone
  - **+ response**
    - n = 15
    - n = 15 (100%)
    - Rx trial confirmed AIP
    - f/u 27 mos (6-47 mos)
  - **- response**
    - n = 7
    - 6 pts OR \(\rightarrow\) pan ca
    - 1 pt 7 mo f/u \(\rightarrow\) pan ca liver mets

Moon, Gut 2008;57:1704
So What Happened to our Patient?

• Bile duct stent placed. Jaundice resolved
• Treated with steroids x 5 months
• Pancreatogram reverted to near normal
• Fullness on CT scan resolved
• Has persistent smooth distal biliary stricture treated with FC-SEMS
• No evidence of malignancy at 2.5 years

AIP – Lessons Learned

• In patients with jaundice, enlarged pancreas or mass . . . . be vigilant, consider AIP
• Cannot rely on elevated serum IgG-4 in Western Populations to establish diagnosis
• IgG-4 immunostaining on histology specimen is most accurate
• If you are treating with steroids for suspected AIP, have SOMETHING to MEASURE!
AIP – Lessons Learned

• AIP is not simply pancreatitis, but an IgG-4 related sclerosing systemic disease
  – Consider biopsy of liver, bile duct, lung, kidney
• EUS core biopsy, ampulla biopsy may be diagnostic
• Consider AIP or IgG-4 cholangitis before pancreatic/biliary surgery