Autoimmune Pancreatitis & Cholangiopathy

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Goal and Objectives

• AIP
  – Subtypes
  – Pathophysiology
  – Clinical presentation
  – Diagnosis and diagnostic challenges
  – Treatment

• AIC
  – Brief overview of diagnosis and treatment
AIP- Introduction

• AIP introduced in 1995 by Yoshida as:
  – “corticosteroid-responsive disease associated with features of autoimmunity”

• The association of AIP and elevated serum IgG4 levels was recognized in 2001

AIP-Introduction

• In 2003, involvement of extrapancreatic organs (abundant infiltration with IgG4 plasma cells) led to the notion that AIP was part of a multi-organ disease, named IgG4-related disease (IgG4-RD).
AIP – simple definition

• A form of chronic pancreatitis that is characterized:
  – clinically by frequent presentation with obstructive jaundice
  – histologically by a dense lymphoplasmacytic infiltrate and fibrosis
  – therapeutically by a dramatic response to corticosteroid therapy

Shimosegawa, Pancreas, 2011
Hart, Gut, 2013

Subtypes of AIP

• Two distinct histological subtypes:
  – Lymphoplasmacytic sclerosing pancreatitis (LPSP), considered AIP type 1.
  – Idiopathic duct-centric pancreatitis (IDCP), considered AIP type 2.
Subtypes of AIP

• IDCP (AIP type 2) is most often **NOT associated** with elevated serum IgG4 levels. It is clinically and histologically very different from IgG4-related pancreatitis.

• The term “AIP” is now reserved more for AIP type 1 and IDCP has replaced the term AIP type 2.

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Comparison of AIP and IDCP

<table>
<thead>
<tr>
<th></th>
<th>AIP</th>
<th>IDCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, mean</td>
<td>7th decade</td>
<td>5th decade</td>
</tr>
<tr>
<td>Male sex</td>
<td>75%</td>
<td>50%</td>
</tr>
<tr>
<td>Elevation of serum IgG4 level</td>
<td>~ 66%</td>
<td>~ 25%</td>
</tr>
<tr>
<td>Other organ involvement</td>
<td>50%</td>
<td>N/A</td>
</tr>
<tr>
<td>Histological findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoplasmacytic</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>infiltration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periductal inflammation</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Storiform fibrosis</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Obliterative phlebitis</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>GEL</td>
<td>–</td>
<td>+++</td>
</tr>
<tr>
<td>IgG4 tissue staining</td>
<td>Abundant(≥10 cells/high-power field)</td>
<td>Scant(&lt;10 cells/high-power field)</td>
</tr>
<tr>
<td>Response to corticosteroids</td>
<td>~ 100%</td>
<td>~ 100%</td>
</tr>
<tr>
<td>Risk of relapse</td>
<td>High(20%–60%)</td>
<td>Low(&lt;10%)</td>
</tr>
<tr>
<td>Associated with IgG4-RD</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Pathophysiology

1. Genetic predisposition

2. Possible immunologic triggers

3. Subsequent immune reactions

Genetic predisposition

• HLA haplotypes predispose to AIP:
  – DRB1*0405 and DQB1*0401.
  – Validated only in Japanese population
  – No data on European or US population
Immunologic triggers

- 40% are ANA+
- High titers of autoantibodies against trypsinogens, PRSS1, and PRSS2
- Molecular mimicry with *H. Pylori*
- Environmental factors???
  - High incidence of IgG4-RD in blue-color population

Subsequent immune reactions
Epidemiology

• AIP is rare

• Estimated prevalence of 1 per 100,000 in Japanese population

Clinical Manifestation

• Mean age at diagnosis > 60 years
• 3:1 male predominance
• Most common presentation:
  – painless jaundice (60%–75%)
  – pancreatic mass or focal pancreatic enlargement
• Pancreatic insufficiency (hyperglycemia and steatorrhea)
• Acute pancreatitis (rare)
Clinical Features

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

“HISORt”

Histology

Macro:
1. Diffuse enlargement of the gland
2. Localized “pseudotumor” or small discrete nodules

Micro:
- LPSP is characterized by
  1. Dense lymphoplasmacytic infiltrate predominantly involving lobules
  2. Obliterative phlebitis
  3. Storiform fibrosis

Phil A. Hart, Yoh Zen, Suresh T. Chari
Recent Advances in Autoimmune Pancreatitis
Gastroenterology, Volume 149, Issue 1, 2015, 39–51
Improving tissue diagnosis

- EUS-FNA, often results in suboptimal tissue acquisition

- Attempts have been made to improve tissue acquisition using core needle biopsies

<table>
<thead>
<tr>
<th>Study</th>
<th>Needle size</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
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<tbody>
<tr>
<td>Morishima</td>
<td>22</td>
<td>8%</td>
<td>100%</td>
<td>100%</td>
<td>33%</td>
</tr>
<tr>
<td>Kanno</td>
<td>22</td>
<td>25%</td>
<td>100%</td>
<td>100%</td>
<td>45%</td>
</tr>
<tr>
<td>Iwashita</td>
<td>19</td>
<td>43%</td>
<td>95%</td>
<td>-</td>
<td>-</td>
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</tbody>
</table>

Kanno, GIE 2016
Morishima, GIE 2016
Iwashita, CGH 2012
Comparison of diagnostic performance of EUS-FNA and TCB in focal pancreatic mass

<table>
<thead>
<tr>
<th>Final diagnosis</th>
<th>EUS-FNA</th>
<th>EUS-TCB</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatitis (n = 3)</td>
<td>1/3</td>
<td>3/3</td>
<td></td>
</tr>
<tr>
<td>LPSP (n = 2)</td>
<td>1/2</td>
<td>2/2</td>
<td></td>
</tr>
<tr>
<td>ICP (n = 1)</td>
<td>0/1</td>
<td>1/1</td>
<td></td>
</tr>
<tr>
<td>PC (n = 14)</td>
<td>14/14</td>
<td>10/14</td>
<td></td>
</tr>
<tr>
<td>Sensitivity(^a)</td>
<td>33%</td>
<td>100%</td>
<td>0.0833</td>
</tr>
<tr>
<td>Specificity(^a)</td>
<td>100%</td>
<td>71%</td>
<td>0.0308</td>
</tr>
<tr>
<td>Accuracy(^a)</td>
<td>88%</td>
<td>76%</td>
<td>0.3683</td>
</tr>
</tbody>
</table>

\(^a\) Sensitivity, specificity and accuracy for diagnosis of pancreatitis

Impact of the needle size

<table>
<thead>
<tr>
<th></th>
<th>19g group</th>
<th>22g group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before-PCB</td>
<td>After-PCB</td>
</tr>
<tr>
<td>Definite type 1 AIP</td>
<td>6 (35.3%)</td>
<td>15 (88.2%)</td>
</tr>
<tr>
<td>Change in sensitivity of definite AIP</td>
<td>10 (58.8%)</td>
<td>7 (18.9%)</td>
</tr>
</tbody>
</table>

-No complication

Mizuno, J Gastro 2009

Oh et al, DDW 2016
Imaging-Parenchymal

- Classic findings (30-50%):
  - Diffuse enlargement of the pancreas with loss of the normal lobulated contour “sausage-shaped pancreas”

Case courtesy of Dr Erik Ranschaert, Radiopaedia.org, rID: 11060

Imaging-Parenchymal

- Less typical (10-20%):
  - Focal or multifocal enlargement of the gland
Imaging-ductal

- Long (> 1/3 the length of the pancreatic duct) or multifocal strictures without upstream dilation (<5 mm)
- Side branches arising from a strictured segment
- MRCP is not reliable

Role of EUS (other than FNA)

- Differential diagnosis of AIP, particularly focal type AIP, and pancreatic cancer has been challenging

- Preliminary studies have been done to evaluate the usefulness of contrast-enhanced harmonic endoscopic ultrasound (CEH-EUS) for differentiating focal type AIP from PAC

Cho et.al, DDW 2016
CEH-EUS

- Novel technology which observes both parenchymal perfusion and microvasculature in the pancreas
- Uses microbubble blood pool agents (Sono-Vue, Levovist)
  - (sulphur hexafluoride microbubbles)

Pancreatic Cancer
CEH-EUS
Proof of Concept

• 27 AIP patients and 53 PC patients.
• Hyperechoic enhancement in arterial phase (AIP, 89 % vs. PC, 13 %; P<0.001)
• Homogenous distribution of contrast agent (AIP, 82 % vs. PC, 17%; P<0.001)
• Absence of irregular internal vessel (AIP, 85 % vs. 30 %; P<0.001)
• The sensitivity and specificity were 88.9 % and 86.8 %

Serum IgG4

• 2/3 of patients have elevated serum IgG4 levels
• Mild elevations of serum IgG4 levels (1–2 x ULN) in 10% to 15% of patients with pancreatic cancer, cholangiocarcinoma, and PSC
• Low PPV

Cho et.al, DDW 2016
Other organ involvement  
(manifestation of IgG4-RD)

- proximal bile duct strictures
- retroperitoneal fibrosis
- bilateral submandibular enlargement
- characteristic renal parenchymal lesions

Response to therapy.

- The inflammatory component of AIP/IgG4-RD is very responsive to corticosteroids
- Lack of a convincing radiographic improvement after corticosteroid therapy should prompt additional investigation for malignancy (4-6 weeks)
Diagnostic criteria for AIP

• **Histology**

  or

• Use various combinations of diagnostic findings (No other solitary feature is pathognomonic for AIP)

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Diagnostic criteria

• International Consensus Diagnostic Criteria (ICDC) for diagnosing autoimmune pancreatitis (AIP)-2011
• Japanese Pancreatic Society (JPS) 2006
• HISORt
• Korean
• Asian
• Italian
• JPS 2011
Japanese Clinical Diagnostic Criteria for Autoimmune Pancreatitis, 2011

A. Diagnostics criterion

I. Enlargement of the pancreas:

- Diffuse enlargement of the pancreas
- Segmental/local enlargement

II. ERCP (endoscopic retrograde cholangiopancreatography) shows irregular narrowing of the main pancreatic duct

III. Serological findings

- Elevated level of serum IgG4 (≥135 mg/dl)

IV. Pathological findings: among (i)-(iv) listed below, three or more are observed

- Prominent infiltration and fibrosis of lymphocytes and plasmacytes
- Ten or more diffuse IgG4-positive plasmacytes per high-power microscope field
- Storiform fibrosis
- Obliterative phlebitis
- Sclerosing cholangitis
- Sclerosing dacryoadenitis/sialoadenitis (Mikulicz disease)
- Retroperitoneal fibrosis

V. Other organ involvement (OUI): sclerosing cholangitis, sclerosing dacyroadenitis/sialoadenitis, retroperitoneal fibrosis

Clinical lesions

- Extra-pancreatic sclerosing cholangitis, sclerosing dacyroadenitis/sialoadenitis (Mikulicz disease), or retroperitoneal fibrosis can be diagnosed with clinical and imaging findings.

Pathological lesions

- Pathological examination shows characteristic features of sclerosing cholangitis, sclerosing dacyroadenitis/sialoadenitis, or retroperitoneal fibrosis.

<Option> Effectiveness of steroid therapy

A specialized facility may include in its diagnosis the effectiveness of steroid therapy, once pancreatic or bile duct cancers have been ruled out. When it is difficult to differentiate from malignant conditions, it is desirable to perform cytopathologic examination using an endoscopic ultrasound-guided fine needle aspiration (EUS-FNA). Failing therapeutic diagnosis by steroids should be avoided unless the possibility of malignant tumor has been ruled out by pathological diagnosis.
Japanese Clinical Diagnostic Criteria for Autoimmune Pancreatitis, 2011

B. Diagnosis

I. Definite diagnosis
1. Diffuse type
   Ia + <III / IVb / V(a/b)>

2. Segmental focal type
   Ib + II + two or more of <III / IVb / V (a/b)>
   Ib + II + <III / IV b / V (a/b)> + Option

3. Definite diagnosis by histopathological study
   IVa

II. Probable diagnosis
   Segmental/focal type: Ib + II + <III / IV b / V (a/b)>

III. Possible diagnosis*
   Diffuse type: Ia + II + Option
   Segmental/focal type: Ib + II + Option

When a patient with a focal/segmental image of AIP on CT/MRI without ERCP findings fulfill more than one of III, IVb and V(a/b) criteria, he/she can be diagnosed as possible AIP only after the negative workup for malignancy by EUS-FNA, and confirmed as probable one by an optional steroid response.

Possible diagnosis*: A case may be possibly type 2, although it is extremely rare in Japan.

"+" refers to “and”, and "/" refers to “or”.

Which Guideline to use?
Comparison of Diagnostic Abilities Guidelines

- A cohort of 51 patients with the diagnose patients as definitive or probable type 1 AIP, type 2 AIP, or unclassifiable based pathologically confirmed AIP or presumed AIP

- The goal compare the diagnostic ability of ICDC with other published guidelines were re-evaluated with Japanese Pancreatic Society (JPS) 2006, HISORT, Korean, Asian, Italian, and JPS 2011 guidelines

<table>
<thead>
<tr>
<th></th>
<th>ICDC</th>
<th>JPS-2006</th>
<th>Korean</th>
<th>Asian</th>
<th>HISORT</th>
<th>Italian</th>
<th>JPS-2011</th>
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</thead>
<tbody>
<tr>
<td>Definitive Type 1</td>
<td>33 (65%)</td>
<td>39 (76%)</td>
<td>39 (76%)</td>
<td>39 (76%)</td>
<td>37 (73%)</td>
<td>21 (41%)</td>
<td>36 (71%)</td>
</tr>
<tr>
<td>Probable Type 1</td>
<td>1 (2%)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Definitive Type 1</td>
<td>4 (8%)</td>
<td>4 (8%)</td>
<td>4 (8%)</td>
<td>4 (8%)</td>
<td>4 (8%)</td>
<td>4 (8%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Unclassifiable</td>
<td>13 (25%)</td>
<td>8 (16%)</td>
<td>8 (16%)</td>
<td>8 (16%)</td>
<td>10 (20%)</td>
<td>26 (51%)</td>
<td>11 (22%)</td>
</tr>
<tr>
<td>Total</td>
<td>51</td>
<td>51</td>
<td>51</td>
<td>51</td>
<td>51</td>
<td>51</td>
<td>51</td>
</tr>
</tbody>
</table>

- Dependence of ICDC on histology and diagnostic ERCP, and the lack of acknowledgment of waxing-waning symptoms and imaging limits its applicability

Madhani et al, DDW 2016
Management

• Goal of anti-inflammatory treatment is to:
  1. provide relief of symptoms
  2. confirm the diagnosis

Corticosteroid therapy

• High-dose corticosteroid therapy (equivalent prednisone dosing of 30–40 mg/day) results in rapid and consistent induction of disease remission
• 3 to 4 weeks duration
• Followed by an assessment of clinical response
Corticosteroid therapy

- Japan Pancreas Society recommends:
  - Slow, prolonged taper over several months to a low maintenance dose (2.5–10 mg/day of prednisone) continued for 1-3 years

- Retrospective studies show lower relapse rates in low-maintenance compared to no-maintenance regimen (23% vs 34%; P=0.045).

Role of Steroid Trial

- As a diagnostic adjunct
- When histology is inconclusive
- Distinguish between AIP and pancreatic adenocarcinoma (PAC)
  - Atypical CT finding for AIP without classic imaging criteria for PAC
  - Only if EUS-FNA has been negative
Relapse

• Recrudescence
  – increase in corticosteroid dosing followed by a prolonged taper

• True relapse
  – 20% to 60%

Treatment of Relapse

1. High-dose corticosteroids, followed by maintenance treatment with low-dose corticosteroids
2. High-dose corticosteroids without maintenance treatment
3. High-dose corticosteroids followed by maintenance treatment immunomodulator
4. Rituximab induction with or without maintenance rituximab
Immunomodulators for AIP

<table>
<thead>
<tr>
<th>Author; Country</th>
<th>n</th>
<th>Steroid free remission</th>
<th>Relapse</th>
<th>Median follow-up</th>
<th>Drugs used</th>
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</thead>
<tbody>
<tr>
<td>Ghazale; US</td>
<td>7</td>
<td>7/7</td>
<td>2</td>
<td>6 mo</td>
<td>AZA (4) MMF(2) CTX (1)</td>
</tr>
<tr>
<td>Sandanayake; UK</td>
<td>10</td>
<td>7/8</td>
<td>0</td>
<td>4 mo</td>
<td>AZA</td>
</tr>
<tr>
<td>Raina; US</td>
<td>10</td>
<td>10/10</td>
<td>1</td>
<td>NR</td>
<td>AZA (9) MTX (1)</td>
</tr>
<tr>
<td>Frulloni, Italy</td>
<td>6</td>
<td>6/6</td>
<td>0</td>
<td>17</td>
<td>AZA (4) MTX (2)</td>
</tr>
<tr>
<td>Hart; US</td>
<td>41</td>
<td>21/38</td>
<td>17/38</td>
<td>NR</td>
<td>AZA 6-MP MMF</td>
</tr>
</tbody>
</table>

Ghazale, Gut 2007
Sandanayake, CGH 2009
Raina, AJG 2009
Frulloni, AJG 2009
Hart, Gut 2013

Rituximab

- Monoclonal CD20 antibody
- B cell depletion from peripheral blood
- For AIP and IgG4-RD
- Both for induction and maintenance of remission
  - Intolerant to high dose steroids
  - Risk factors for relapse
Rituximab for Type 1 AIP/ IgG4-RD

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>AIP</th>
<th>Induction Rx</th>
<th>Steroids</th>
<th>Maintenance Rx</th>
<th>Response</th>
<th>Complete Remission</th>
<th>Relapse</th>
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<tbody>
<tr>
<td>Hart</td>
<td>12</td>
<td>12</td>
<td>375 mg/m² x4</td>
<td>5/12</td>
<td>Yes</td>
<td>92%</td>
<td>83%</td>
<td>8%</td>
</tr>
<tr>
<td>Carruthers</td>
<td>30</td>
<td>18</td>
<td>1000 mg x 2</td>
<td>4/30</td>
<td>No</td>
<td>97%</td>
<td>67%</td>
<td></td>
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<tr>
<td>Wallace</td>
<td>60</td>
<td>12</td>
<td>1000 mg x 2</td>
<td>19/60</td>
<td>No</td>
<td>95%</td>
<td></td>
<td>40%</td>
</tr>
</tbody>
</table>

Hart, Gut 2012
Carruthers, Ann Rheum Dis 2015
Wallace J, Rheumatol 2015

Rituximab

- Effective for AIP
- Useful in relapsing, recrudescent, or refractory disease
- Patients need to be screened for chronic infections.
Summary

- AIP and IDCP are two distinct steroid-responsive pancreatitides.

- The initial triggering events and predisposing factors to AIP remain elusive

- A diagnosis of AIP requires a high index of clinical suspicion and is established by combining diagnostic evidence from radiographic imaging of the pancreatic parenchyma and pancreatic duct, serum IgG4 levels, other organ involvement, histology, and response to corticosteroid therapy

- Controlled studies are needed to better understand the optimal treatment approach to these patients
Autoimmune Cholangiopathy

- The sixth common manifestation of IgG4-RD

- Pancreatitis (60%)
- Sialadenitis (34 %)
- Tubulointerstitial nephritis (23 %)
- Dacryoadenitis (23 %)
- Periaortitis (20 %)
- Proximal bile ducts cholangiopathy (13 %)

Inoue, IgG4-related disease: dataset of 235 consecutive patients. Medicine. 2015

Involvement of Bile Duct

- Intra-pancreatic cholangiopathy
  - Mostly associated with AIP
  - Direct extension of the inflammatory process from the pancreas
  - 78% of cases

- Proximal cholangiopathy
  - In association with pancreatitis (20%)
  - isolated bile duct disease (2%)
Magnetic resonance cholangiography in a patient with autoimmune cholangiopathy and autoimmune pancreatitis


MR cholangiopancreatography shows severe stricture of the perihilar bile duct

Clinical features

• Similar to other IgG4 disease
• Male-to-female ratio of 4:1
• 90% of patients are in their 60s or older
• Present with obstructive jaundice

Diagnosis- Serology

• IgG4 level:
  – > 135 - 140 mg/dl
    • sensitivity of 80%
    • specificity ~ 50%
  – > 270-280 mg/dl
    • sensitivity of 50%
    • specificity over 90%

Oetini AM. Hepatology 2011
Diagnosis-Serology

- Other markers
  - hyper-gamma globulinemia (50 %)
  - ANA (40 %)
  - Rheumatoid factor (20 %)
  - AMA (negative)
  - ANCA (negative)

Diagnosis-Imaging

- US and CT both of limited value

- Enhanced MRI with MRCP
  - location, distribution, and degree of the biliary strictures
  - bile duct wall thickening
  - AIP findings in patients with concomitant disease
MRCP- multifocal pancreatobiliary strictures

Nakazawa, J Pancreas, 2010

CE-MRI
Thickening of the bile duct wall
ERCP

• ERCP is superior to MRCP for demonstrating luminal changes in the bile duct
• More invasive than MR
• Risk of post-ERCP pancreatitis

IAC:
- Dilation after confluent stricture (>10 mm) is a characteristic feature of ISC

PSC:
- Band-like stricture
- Beaded appearance
- Pruned tree appearance,
- Diverticulum-like outpouching
Intraductal Ultrasound

Large duct cholangiopathy:
- Transmural fibroinflammatory processes
- Rich in lymphocytes and plasma cells
- Storiform fibrosis
- Obliterative phlebitis
Diagnosis

• Very similar to AIP
  – HISORt
  – JSP
  – International Consensus Diagnostic Criteria

Differential Diagnosis

• Cholangiocarcinoma
  – Localized or mass-forming cholangitis
  – Bile duct biopsy and biliary cytology
  – Lack of response to steroids in 2-3 weeks

• PSC
  – Demographics
  – IgG4-positive plasma cells are not present in PSC
Treatment

• The treatment strategy is basically similar to that for type 1 AIP
• High-dose steroids (prednisone at a dose of 30–40 mg per day)
  – slow taper over several months to a low maintenance dose