La Pancreatitis Autoimmune

Italo Vantini
Pancreatologia felix
Autoimmune Pancreatitis

Long time ago...(late 70s)

“Why should the pancreas be the human organ not involved by an autoimmune process only?”

More than 1000 papers on Autoimmune Pancreatitis published so far)

Ludovico Antonio Scuro
1924 – 1989
Chronic pancreatitis

Eterogeneity

- alcoholic
- obstructive
- genetic
- paraduodenal
- idiopathic
- senile
- autoimmune
Autoimmune Pancreatitis

Autoimmune pancreatitis is a recently identified clinical entity of pancreatitis.

1. in which not well understood autoimmune mechanisms are involved in the pathogenesis

2. that dramatically responds to steroids
Chronic pancreatitis: Report from a multicenter Italian survey (PANCROINF/AISP) on 893 patients

<table>
<thead>
<tr>
<th>Associated factor</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>≥80 g of ethanol consumption a day for at least 5 years.</td>
</tr>
<tr>
<td>Obstruction</td>
<td>Fibrotic stenosis of either the papilla of Vater or the main pancreatic duct with its upstream uniform dilation at radiology (MRCP, ERCP or CT).</td>
</tr>
<tr>
<td>Autoimmunity</td>
<td>Association with autoimmune diseases, histological or cytological findings, clinical and instrumental response to steroid therapy [24].</td>
</tr>
<tr>
<td>Cystic dystrophy of the duodenal wall/groove pancreatitis</td>
<td>Thickening of the duodenal wall or cyst(s) within the duodenal wall at radiology (CT, MRCP and EUS) or histology.</td>
</tr>
<tr>
<td>Genetic</td>
<td>CFTR, SPINK1 or PRSS1 gene mutations.</td>
</tr>
</tbody>
</table>

MRCP: magnetic resonance cholangio-pancreatography and EUS: endoscopic ultrasound.

Chronic pancreatitis: Report from a multicenter Italian survey (PanCroInfAISP) on 893 patients

### Definition of associated factors.

<table>
<thead>
<tr>
<th>Associated factor</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>≥80 g of ethanol consumption a day for at</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distribution of patients with CP according to associated factors and alcohol consumption at enrolment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>Obstruction</td>
</tr>
<tr>
<td>Alcohol + obstruction</td>
</tr>
<tr>
<td>Autoimmunity</td>
</tr>
<tr>
<td>Cystic dystrophy duodenal wall⁹/groove pancreatitis</td>
</tr>
<tr>
<td>Hereditary/genetic</td>
</tr>
<tr>
<td>None/idiopathic</td>
</tr>
</tbody>
</table>

⁹ or groove pancreatitis.

Genetic

<table>
<thead>
<tr>
<th>Genetic</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRCP</td>
<td>magnetic resonance cholangio-pancreatography and EUS: endoscopic ultrasound.</td>
</tr>
</tbody>
</table>

Autoimmune pancreatitis (AIP)

about 30-40% of those formerly classified as “idiopathic chronic pancreatitis”
Autoimmune pancreatitis: an entity with different features and presentations:

- **Pathological features**
  - 2 types
    - Type 1
    - Type 2

- **Organ involvement**
  - Pancreatic disease only
  - Other organs involved

- **Clinico-pathological and imaging features**
  - Focal and mass forming
  - Diffuse

- **Clinical presentation**
  - Jaundice
  - Acute, relapsing (chronic) pancreatitis

A “dual” system
AIP: a chronic pancreatitis
Periductal inflammation with IgG4 positive plasmacells
Duct destruction and narrowing
Storiform fibrosis

From Zamboni G et al

Type 1
Lympho-Plasmacytic Sclerosing Pancreatitis (LPSP)
AIP: a chronic pancreatitis
Periductal inflammation with IgG4 positive plasmacells
Duct destruction and narrowing
Storiform fibrosis
Type 1 Lympho-Plasmacytic Sclerosing Pancreatitis (LPSP)

Type 1 Autoimmune Pancreatitis is part of a (IgG4): multiorgan fibroinflammatory syndrome
- biliary tract
- Kidney
- retroperitoneum
- lung
- salivary glands

From Zamboni G et al
In Type 2 autoimmune pancreatitis the histologic findings are typical for the disease: granulocyte inflammatory infiltration into the pancreas, mainly around the ducts, with rupture of the basal membrane and secondary destruction of pancreatic ducts.
Type 2 Autoimmune Pancreatitis can be associated with inflammatory colitis pathologically resembling ulcerative colitis.

In autoimmune pancreatitis the histologic findings are typical for the disease: inflammatory infiltration into the pancreas, mainly around the ducts, with rupture of the basal membrane and secondary destruction of pancreatic ducts.
Autoimmune pancreatitis:
a single disorder with different features and presentations

- **Pathological features**
  - 2 types
    - Type 1
    - Type 2

- **Organ involvement**
  - Pancreatic disease only
  - Other organs involved

- **Clinico-pathological and imaging features**
  - Focal and mass forming
  - Diffuse

- **Clinical presentation**
  - Jaundice
  - Acute, relapsing (chronic) pancreatitis
Autoimmune pancreatitis

Diffuse

Focal and mass forming

Pre-contrastographic

mild pancreatitis

Early arterial phase

jaundice

University of Verona: Dpt. of Radiology
### Focal and diffuse AIP: clinical pictures (Verona)

<table>
<thead>
<tr>
<th></th>
<th>Focal</th>
<th>Diffuse</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>N.</td>
<td>44 (54%)</td>
<td>37 (46%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Gender (males)</td>
<td>32 (73%)</td>
<td>20 (54%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Age at onset*</td>
<td>46.6 ± 13.6</td>
<td>39.6 ± 16.5</td>
<td>(&lt; 0.025)</td>
</tr>
<tr>
<td>Heavy drinkers (&gt;80 g/day)</td>
<td>1 (2,4%)</td>
<td>1 (2,7%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Smokers</td>
<td>19 (46%)</td>
<td>15 (41%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Duration of the disease</td>
<td>6.9 ± 4.8</td>
<td>7.6 ± 6.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Autoimm. Associated disorders</td>
<td>18 (41%)</td>
<td>23 (59%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Jaundice at presentation</td>
<td>25 (57%)</td>
<td>10 (27%)</td>
<td>(&lt; 0.013)</td>
</tr>
<tr>
<td>Pancreatitis at presentation</td>
<td>6 (4%)</td>
<td>22 (60%)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Calcifications</td>
<td>2 (5%)</td>
<td>7 (19%)</td>
<td>0.072</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13 (29%)</td>
<td>9 (24%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Steatorrhoea</td>
<td>12 (27%)</td>
<td>9 (24%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Resection surgery</td>
<td>17 (21%)</td>
<td>0</td>
<td>(&lt;0.001)</td>
</tr>
</tbody>
</table>

*years (average ± SD)

Mass-forming AIP: response to steroid therapy

CT before steroid trial  15 day trial with steroids
Diffuse AIP
Pancreatic atrophy and exocrine insufficiency

2003, May

Just after the first flare of pancreatitis

2004, July

One year later on
(after treatment with steroids)
atrophy of the pancreas

Dpt of Radiology, Verona 2006
**Exocrine and Endocrine Pancreatic Function in 21 Patients Suffering from Autoimmune Pancreatitis before and after Steroid Treatment**

Luca Frulloni\textsuperscript{a} Chiara Scattolini\textsuperscript{a} Anna Maria Katsotourchi\textsuperscript{a} Antonio Amodio\textsuperscript{a} Armando Gabbrielli\textsuperscript{a} Giuseppe Zamboni\textsuperscript{b} Luigi Benini\textsuperscript{a} Italo Vantini\textsuperscript{a}

Departments of \textsuperscript{a}Biomedical and Surgical Sciences, and \textsuperscript{b}Pathology, University of Verona, Verona, Italy

**Fig. 1.** Fecal elastase 1 before and after steroid therapy. Horizontal lines represent the upper normal limit (>200 µg/g stool), mild pancreatic insufficiency (100–200 µg/g stool) and severe pancreatic exocrine insufficiency (<100 µg/g stool).

Pancreatology 2010;10:129–133
Autoimmune pancreatitis
clinical identikit

- Painless jaundice (focal-mass forming)
- “Atypical” acute pancreatitis (diffuse)*
- Association with other immunological disorders or inflammatory colitis

Response to steroid therapy

- Calcifications, diabetes and steatorrhoea are unfrequent
  - No heavy drinker
  - No or moderate smoker

* more often mild in young people
<table>
<thead>
<tr>
<th>Definition</th>
<th>Pathology</th>
<th>Clinic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AIP Type 1 (70-85%)</strong></td>
<td>Lympho-Plasmacytic Sclerosing Pancreatitis (LPSP)</td>
<td>Relapses YES</td>
</tr>
<tr>
<td><strong>AIP Type 2 (15-30%)</strong></td>
<td>Idiopathic Duct-Centric Pancreatitis (IDCP)</td>
<td>Relapses NO</td>
</tr>
<tr>
<td>IgG4+ (ICH) – GEL−</td>
<td>IgG4 systemic disease</td>
<td></td>
</tr>
<tr>
<td>IgG4− (ICH) – GEL+</td>
<td>Inflammatory Bowel Disease</td>
<td></td>
</tr>
</tbody>
</table>

Pancreatology 2010;10:664–672
IgG4 cannot be used as a diagnostic marker of Autoimmune Pancreatitis.

Increased IgG4 levels also in patients with chronic pancreatitis, recurrent pancreatitis, and pancreatic cancer.

(Frulloni L. et al., Pancreas 2003)
Long-term outcomes of autoimmune pancreatitis: a multicentre, international analysis

**RELAPSE RATE**

<table>
<thead>
<tr>
<th>23 institutions</th>
<th>1064 patients</th>
<th>ICDC criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 countries</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Type 1: 978
- Type 2: 86

*Relapse rate*

- **Type 1**: 31% (in IgG4–related sclerosing cholangitis)
- **Type 2**: 9%

Autoimmune pancreatitis: aetiology and pathogenesis

- **It is still unknown** (under investigation in animal models)
  
- **Antibodies**: Carbonic Anydrase II, Lactoferrin, amylase alfa, plasminogen-binding protein; SPTI antibodies (against host antigens);
- **T cell abnormalities**
- **Genetics**: association with haplotype DRB1 0405 DQB1 0401 (in Japan), but not in Korean);
- **Polymorphism of Cytotoxic Lymphocyte-associated antigen-4**
- TNF- alfa
The mimicry in AIP

Table 1

<table>
<thead>
<tr>
<th>A. Synthetic peptides</th>
<th>AIP peptide_{1-12}</th>
<th>AIP peptide_{1-7}</th>
<th>AIP peptide_{6-12}</th>
</tr>
</thead>
<tbody>
<tr>
<td>S K D E R R F E Q P R V</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S K D E R R F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R F E Q P R V</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A K E E R R Y</td>
<td></td>
<td></td>
<td>H. Pylori plasminogen binding protein (298-304 O25249)</td>
</tr>
</tbody>
</table>

| B. Sequence homology between AIP peptide and H. Pylori plasminogen binding protein |
|----------------------------------|---------------------------------------------------------------|
| S K D E R R F                    | AIP peptide_{1-7}                                            |
| A K E E R R Y                    | H. Pylori plasminogen binding protein (298-304 O25249)       |

| C. Sequence homology between H. Pylori plasminogen binding protein and UBR2 |
|-------------------------------|-------------------------------------------------------------------|
| A K E E R R Y                  | H. Pylori plasminogen binding protein (298-304 O25249)          |
| : : : : : * : : :             |                                                                  |
| A K E Q R R Q                  | E3 ubiquitin-protein ligase UBR2 (1186-1197 Q8IWV8)             |

Proteins reacting with AIP serum

Identification of a Novel Antibody Associated with Autoimmune Pancreatitis

Luca Frulloni, Claudio Lunardi, Rita Simone, Marzia Dolcino, Chiara Scattolini, Massimo Falconi, Luigi Benini, Italo Vantini, Roberto Corrocher, Antonio Puccetti.


<table>
<thead>
<tr>
<th>Training Group</th>
<th>Validation Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IgG Antibodies (IU/μl)</strong></td>
<td><strong>IgG Antibodies (IU/μl)</strong></td>
</tr>
<tr>
<td>250,000</td>
<td>250,000</td>
</tr>
<tr>
<td>225,000</td>
<td>225,000</td>
</tr>
<tr>
<td>200,000</td>
<td>200,000</td>
</tr>
<tr>
<td>175,000</td>
<td>175,000</td>
</tr>
<tr>
<td>150,000</td>
<td>150,000</td>
</tr>
<tr>
<td>125,000</td>
<td>125,000</td>
</tr>
<tr>
<td>100,000</td>
<td>100,000</td>
</tr>
<tr>
<td>75,000</td>
<td>75,000</td>
</tr>
<tr>
<td>50,000</td>
<td>50,000</td>
</tr>
<tr>
<td>25,000</td>
<td>25,000</td>
</tr>
</tbody>
</table>

AHP derived peptide contains an epitope reacting with nearly all AIP patients sera.
Autoimmune pancreatitis (mice model for Type 1 AIP): a T cell mediated disease

The mechanism of AIP may be **biphasic**:

1. **Induction**: response to a self-antigen that may be induced by a decrease in Treg and a Th1 cytokine response

2. **Progression**: increase in Teff and a Th2 cytokine response

The imbalance between Treg and Teff may be associated with a mutation or polymorphism in CTLA-4, a surface Ig protein that is a potent attenuator of the T lymphocite response, regulating the immunological tolerance

More the imbalance, more severe the experimental pancreatic damage

*Theresa Schweiger et al Gut 2014, 63; 494-505*
Autoimmune pancreatitis

practical questions and actions

1. properly diagnosing autoimmune pancreatitis, differentiating them from other types of pancreatitis
   – interpretation of clinical, lab and imaging features by using international criteria

2. differentiating AIP from cancer (in focal and mass forming AIP) and reducing unnecessary resection surgery

3. treating AIP
   – managing acute phase
   – preventing relapses
The criteria for the diagnosis
The criteria for differentiating the types of AIP
Two levels of probability for the diagnosis
## Autoimmune pancreatitis type 1: cardinal diagnostic criteria and levels of reliability

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Level 1</th>
<th>Level 2</th>
</tr>
</thead>
</table>
| **P** (parenchimal imaging) | Diffuse enlargement  
Delayed enhancement | Segmental/focal enlargement  
Delayed enhancement |
| **D** (ductal imaging) | Single long stenosis of MPD  
Multiple stenosis of MPD | Segmental/focal narrowing  
without upstream dilation |
| **S** (serology) | sIgG4 > 2x UNL | sIgG4 1-2x UNL |
| **OOI** (other organ involvement) | Intrahepatic bile duct stricture(s)  
Retroperitoneal fibrosis | Salivary/lacrimal glands  
Kidney |
| **H** (histology) | 3 criteria | 2 criteria |
| **Rt** (response to steroids) | Resolution/marked improvement  
of the pancreatic/extrapancreatic involvement | |

### Autoimmune pancreatitis type 2: cardinal diagnostic criteria and levels of reliability

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Level 1</th>
<th>Level 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P</strong> (parenchimal imaging)</td>
<td>Diffuse enlargement&lt;br&gt;Delayed enhancement</td>
<td>Segmental/focal enlargement&lt;br&gt;Delayed enhancement</td>
</tr>
<tr>
<td><strong>D</strong> (ductal imaging)</td>
<td>Single long stenosis of MPD&lt;br&gt;Multiple stenosis of MPD</td>
<td>Segmental/focal narrowing without upstream dilation</td>
</tr>
<tr>
<td><strong>S</strong> (serology)</td>
<td>sIgG4 &gt; 2x UNL</td>
<td>sIgG4 1-2x UNL</td>
</tr>
<tr>
<td><strong>OOI</strong> (other organ involvement)</td>
<td></td>
<td>Clinically diagnosed inflammatory bowel disease</td>
</tr>
<tr>
<td><strong>H</strong> (histology)</td>
<td>(1) GEL$^+$ ductal&lt;br&gt;(2) absent or scant IgG4$^+$</td>
<td>(1) GEL$^+$ acinar&lt;br&gt;(2) absent or scant IgG4$^+$ cells</td>
</tr>
<tr>
<td><strong>Rt</strong> (response to steroids)</td>
<td>Resolution/marked improvement of the pancreatic/extrapancreatic involvement</td>
<td></td>
</tr>
</tbody>
</table>
Three types of AIP: overlaps among diagnostic features
Diagnosis according to ICDC criteria
Diagnosis according to ICDC criteria and assuming that all the patients have undergone steroids and responded to it

A steroid trial enhances (by 20 to 73%) the possibility of correctly diagnosing AIP without histology (7/8 type 1 and 3/3 type 2 would have been classified into the right type of AIP)

BUT

27% of patients, also assuming a positive response to steroids, did not fulfill ICDC criteria

In these patients core biopsy is needed

Diagnosis by ICDC assuming a positive response to steroids

Histological diagnosis based on resected specimen

Type 1 AIP (n=7)
Type 2 AIP (n=1)
Type 2 AIP (n=4)
Type 1 AIP (n=10)
Type 1 AIP (n=6)
Type 2 AIP (n=2)
Autoimmune pancreatitis: the role of pathology in the diagnosis

• The gold-standard for diagnosis is the full spectrum of pathological changes (LPSP) on a pancreatic specimen

BUT

• in no more than 22-27% of the cases the non-surgical biopsy is diagnostic for AIP
  – Patchy distribution
  – Absence of the full spectrum of changes
  – Insufficient sampling
Narrowed and irregular duct in autoimmune pancreatitis

Associated with a clinical picture
Autoimmune pancreatitis

- MRCP: irregular narrowing -

MRCP and/or ERCP changes may be useful in diagnosing non-mass-forming type 2 AIP
The problem is to distinguish focal AIP from pancreatic cancer.
The problem is to distinguish focal AIP from pancreatic cancer.
mass in the head of the pancreas

Autoimmune pancreatitis
5-10 %

Pancreatic Cancer
90-95%

(Moreover → metastasis of renal/lung cancer, chronic pancreatitis, sarcoidosis, Tbc..)
Contrast-enhanced US (CEUS)

Cancer

Mass forming AIP

- Basal Hypoechochogenic mass
- Basal Hypoechochogenic mass
- Basal Hypoechochogenic mass

- Sensitivity 88.6%
- Specificity 97.8%

D’Onofrio et al. W J Gastroenterol 2006
Endoscopic Ultrasound Sonography

- **EUS guided FNA (citology)**: can confirm pancreatic cancer more quickly than core biopsy, but **cannot confirm** AIP
- **EUS trucut** (19 gauge EUS TCB) (histology): 27% probability to diagnose AIP by histological specimen

(Levy et al. Gastrointest End, 2005)
Endoscopic Ultrasound Sonography

- **EUS guided FNA (citology)**: can confirm pancreatic cancer more quickly than core biopsy, but cannot confirm AIP. 

  - **EUS trucut (19 gauge EUS TCB) (histology)**: 27% probability to diagnose AIP by histological specimen (Levy et al. Gastrointest End, 2005)

The real target of EUS is to exclude a pancreatic cancer. A negative test does not exclude either malignancy or AIP.

Contrast-enhanced EUS improves the detection and characterization of mass-forming inflammatory lesions.

EUS should always associated with specimen collection because there are not “patognomonic” features for AIP.
Autoimmune pancreatitis **type 1 and 2**: cardinal diagnostic criteria and levels of reliability

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Level 1</th>
<th>Level 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>P (parenchimal imaging)</td>
<td>Diffuse enlargement</td>
<td>Segmental/focal enlargement Delayed enhancement</td>
</tr>
<tr>
<td>D (ductal imaging)</td>
<td>Single long stenosis of MPD</td>
<td>Multiple stenosis of MPD</td>
</tr>
<tr>
<td>S (serology)</td>
<td>sIgG4 &gt; 2x UNL</td>
<td>sIgG4 1-2x UNL</td>
</tr>
<tr>
<td>O (other organ involvement)</td>
<td>Intrahepatic bile duct stricture(s)</td>
<td>Retroperitoneal fibrosis</td>
</tr>
<tr>
<td>K (kidney)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H (histology)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rt (response to steroids)</td>
<td>Resolution/marked improvement of the pancreatic/extrapancreatic involvement</td>
<td></td>
</tr>
</tbody>
</table>

Diagnosis of Type 1 Autoimmune Pancreatitis

Algorithm in patients with mass or jaundice

Patients presenting with obstructive jaundice and/or pancreatic enlargement/mass

CT/MRI: Pancreatic Findings Indeterminate/Atypical for AIP

Work-up for cancer: Negative

- Review CT/MRI/Physical Examination for other organ involvement
- Measure serum IgG4 levels
- If not sufficient evidence based on above two, perform the following
  - Endoscopic pancreatogram
  - Ampullary biopsies with stain for IgG4
  - Review previous biopsy/resection specimen of pancreas or other organs

No cardinal criteria for type 1 AIP on serology, OOI

Follow algorithm for type 2 AIP

Two or more from Level 1 (+ ductal Level 2) Criteria for Type 1 AIP

- Pancreatic core biopsy

  - Inconclusive/Not performed
    - Any Level 1 S/OOI or Level 1 D + Level 2 S/OOI/H
      - No
      - Yes
  
- Surgical resection

  - LPSP

  - Other diagnosis
    - Yes
    - No

- Steroid Trial

  - Yes
  
- Other diagnosis

AIP: Definitive Type 1

- Reconsider diagnosis

AIP: Probable Type 1
Diagnosis of Type 2 Autoimmune Pancreatitis

**Algorithm in patients with mass or jaundice**

1. **Patients presenting with obstructive jaundice and/or pancreatic enlargement/mass**
   - If any cardinal criteria for type 1 AIP on serology, other organ involvement:
     - Yes: Follow algorithm for Type 1 AIP
     - No: Work-up for cancer: Negative
   - Pancreatic core biopsy
     - Level 1 H (IDCP)
     - Level 2 H
       - Steroid Trial
         - Reassess CA 19-9, pancreatic morphology
           - Response to steroids:
             - Yes: IBD present?
               - Yes: AIP: Definite type 2
               - No: AIP: Probable Type 2
             - No: Reconsider diagnosis
       - Inconclusive/Not performed
         - Endoscopic pancreatogram
           - Level 1/2 D
             - Steroid Trial
               - Reassess CA 19-9, pancreatic morphology
                 - Response to steroids:
                   - Yes: IBD present?
                     - Yes: IDCP
                     - No: AIP-NOS
                   - No: Other diagnosis
                 - No: Reconsider diagnosis
         - Surgical resection
Autoimmune pancreatitis

practical questions and actions

• properly diagnosing autoimmune pancreatitis, differentiating them from other types of pancreatitis
  – interpretation of clinical, lab and imaging features by using international criteria
• differentiating AIP from cancer (in focal and mass forming AIP) and reducing unnecessary resection surgery
• treating AIP
  – treating acute episode(s)
  – preventing relapses
Initial feature

Clinical presentation:
mild acute pancreatitis followed by persisting increase in serum pancreatic enzymes

To consider the steroid trial effective, the imaging response should be:
- prompt
- unequivocal
- complete

After 4-week steroid trial
Current treatment in Type 1 AIP

I. Initial attack

- Induction of remission with high-dose steroid
  - Tapering of steroid over several months
    - Complete withdrawal of steroid
    - Maintenance therapy with low-dose steroid

II. In relapses

- In cases of relapse
  - Dose-up and/or prolonged induction steroid therapy
    - More gradually taper
  - Steroid plus immunomodulator such as azathioprine
    - Tapering steroid while maintaining immunomodulator
  - Rituximab in refractory cases (A monoclonal antibody, directed against the CD 20 antigen on B lymphocytes)

Recent advances in autoimmune pancreatitis: type 1 and type 2
Terumi Kamisawa,1 Suresh T Chari,2 Markus M Lerch,3 Myung-Hwan Kim,4 Thomas M Gress,5 Tooru Shimosegawa6
GUT 2013; 62: 1373-80
PA Hart et al: Long-term outcomes of autoimmune pancreatitis: a multicentre, international analysis
Gut 2013; 62: 1071-6

23 institutions
10 countries
1064 patients

ICDC criteria
Type 1
978
Type 2
86

Table 1  Initial treatment strategies and treatment details for those treated with steroids

<table>
<thead>
<tr>
<th>Initial treatment</th>
<th>Type 1 AIP (n=901†)</th>
<th>Type 2 AIP (n=85†)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Successful remission, n</td>
<td>%</td>
</tr>
<tr>
<td>Steroids *</td>
<td>681/684</td>
<td>99.6</td>
</tr>
<tr>
<td>Surgical resection</td>
<td>125/127</td>
<td>98.4</td>
</tr>
<tr>
<td>Palliative surgical bypass</td>
<td>22/23</td>
<td>95.7</td>
</tr>
<tr>
<td>Conservative</td>
<td>37/67</td>
<td>55.2</td>
</tr>
</tbody>
</table>

Relapse rate
Type 1
31%
Type 2
9%

(> in IgG4–related sclerosing cholangitis)

* reatreatment with steroids was equally effective
Autoimmune pancreatitis*

- 36-month maintenance therapy with azathioprine -

*2 patients with type 2 AIP, 2 patients with NOS AIP
In IgG4-Related Disorders a Th2-mediated immune response is involved leading to excessive or inappropriate B-cell activation.

**RITUXIMAB** a monoclonal antibody directed against the CD20 antigen on B cells → depletion of B cells.

(Rituximab already used in other immunological and IgG4 related disorders)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Treatment protocols used for steroid, immunomodulator and rituximab (RTX) therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction regimen</strong></td>
<td><strong>Taper</strong></td>
</tr>
<tr>
<td>Steroids</td>
<td>Prednisone 40 mg daily × 4 weeks</td>
</tr>
<tr>
<td>Immnomodulator</td>
<td>Azathioprine 2.0–2.5 mg/kg/day (alternate: 6-MP 1 mg/kg/day) (alternate: MMF 750–1000 mg twice daily)</td>
</tr>
<tr>
<td>RTX</td>
<td>375 mg/m² intravenous BSA weekly × 4 weeks Coadminister: oral diphenhydramine 50 mg and oral paracetamol 1000 mg once</td>
</tr>
</tbody>
</table>

12/38 Type 1 AIP non-responder to immunosuppressants → Rituximab maintenance

10/12 (83%) in remission for a median of 47 months (no relapse)

*Hart PA et al, Gut 2013; 62: 1607-15*
Rituximab: antiCD20 antibody (treatment against B cells) the mature form of which (plasma cells) are responsible for antibody production
Rituximab: antiCD20 antibody (treatment against B cells) the mature form of which (plasma cells) are responsible for antibody production
Cenotaffio di Johann George Wirsung

Padova,
Basilica del Santo,
Chiostro del Capitolo
George Wirsung........Wirsung duct
Padova: giardino dei semplici
(botanic garden)
Autoimmune pancreatitis in a mice model: a T cell driven disease

- CTLA-4 (a surface protein of Ig superfamily) is a potent attenuator of the T cell response

- Blockage or deletion of CTLA-4 in MRL/Mp mice:
  - Suppressed regulatory T cell (Treg)
  - Raised effector T cell (Teff)

  with subsequent organ destruction and increasing severity of pancreatitis

* suggested also by the pronounced increase in IgG4 in type 1 AIP

Schwaiger T. et al GUT 2014; 63: 494-505
Autoimmune pancreatitis in a mice model: a T cell driven disease

- CTLA-4 (a surface protein of Ig superfamily) is a potent attenuator of the T cell response

- Blockage or deletion of CTLA-4 in MRL/Mp mice:
  - Suppressed regulatory T cell (Treg)
  - Raised effector T cell (Teff)

  Treatment that either expands the Treg or inhibits the Teff may have a beneficial effect on autoimmune pancreatitis

  * suggested also by the pronounced increase in IgG4 in type 1 AIP

Schwaiger T. et al GUT 2014; 63: 494-505
Autoimmune pancreatitis in a mice model: a T cell mediated disease

- **CTLA-4** (a surface protein of Ig superfamily) is a potent attenuator of the T cell response

- Blockage or deletion of **CTLA-4** in MRL/Mp mice:
  - Suppressed regulatory T cell (Treg)
  - Raised effector T cell (Teff)

- with subsequent organ destruction and increasing severity of pancreatitis

* suggested also by the pronounced increase in IgG4 in type 1 AIP

Schwaiger T. et al GUT 2014; 63: 494-505