Pathological Society/IAP meeting, Ghent
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The (under) diagnosis of IgG4-related systemic sclerosing disease

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Acute pancreatitis

- Causes
  - Gallstones
  - Alcohol
  - Trauma
  - Viruses
  - Drugs
- Serious condition, often fatal
- May receive material from necrosectomy
Chronic pancreatitis

**Causes**
- Alcohol

**Chronic inflammation and fibrosis**
- Early exocrine loss
  - Malabsorption
- Late endocrine loss
  - Diabetes mellitus

*M May receive material from decompression*
Autoimmune pancreatitis

- IgG4-related (systemic) sclerosing disease
- 2-6% of cases of chronic pancreatitis
- 1961 First description
- 1995 Autoimmune aetiology
- 2001 Value of serum IgG4 levels
- 2003 Tissue IgG4-positive plasma cells
Clinical presentation

- May be limited to pancreas or multi-organ
- History shorter than for alcoholic variant
- Presentation depends on pattern of organ involvement
- Unusual distributions of disease may lead to considerable difficulty in diagnosis
IgG4

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Autoimmune pancreatitis
IgG4 related sclerosing disease
## Patterns of involvement

<table>
<thead>
<tr>
<th>Organ</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>Chronic pancreatitis</td>
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<tr>
<td>Liver</td>
<td>Sclerosing cholangitis</td>
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<tr>
<td>Gallbladder</td>
<td>Chronic cholecystitis</td>
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<tr>
<td>Colon</td>
<td>IBD-like colitis</td>
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<tr>
<td>Kidney</td>
<td>Interstitial nephritis</td>
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<tr>
<td>Lung</td>
<td>Interstitial pneumonia</td>
</tr>
<tr>
<td>Orbit</td>
<td>Pseudotumour</td>
</tr>
<tr>
<td>Meninges</td>
<td>Chronic meningitis</td>
</tr>
</tbody>
</table>

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Radiological features
Radiological features
Radiological features
Radiological features
Serological markers

- Serum IgG
- Serum IgG4
- Anti-carbonic anhydrase antibody
- Others
  - Anti-nuclear antibody
  - Anti-smooth muscle antibody
  - Anti-mitochondrial antibody
  - Anti-neutrophilic cytoplasmic antibody
Serum IgG & IgG4 levels

A Korean study

- Serum IgG
  - 71.1% sensitivity / 83.7% specificity
- Serum IgG4
  - 73.3% sensitivity / 95.1% specificity
Utility of serum IgG4 levels

A UK study (Oxford)

- 196 serum IgG4 level requests
- Retrospective sorting according to diagnosis
- Mean serum IgG and IgG4 levels higher in autoimmune pancreatitis than other groups (including cancer) (p < 0.001)
Utility of serum IgG4 levels

Å Italian meta-analysis (Bologna)

- Morselli-Labate AM & Pezzilli R. *J Gastroenterol Hepatol* 2009; 24: 15-36
- 7 studies; 159 patients & 1099 controls
- Receiver operating curve (ROC) characteristics analysis
- Suggested that raised serum IgG4 shows ‘good accuracy’ for diagnosis although some ‘heterogeneity’ existed

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Serum anti-carbonic anhydrase antibody level

A Japanese study

- Titre raised in 88.9% of AIP
- Not raised in cancer
- Not specific
  - Sjogren’s syndrome
  - Alcoholic chronic pancreatitis
Pathophysiology

Evidence for an autoimmune aetiology

- Multi-system disease involvement is common
- Some involved organs are common sites for autoimmune disease
- Serum IgG concentration often raised
- Involved organs show chronic inflammation and scarring
- Disease association with a particular HLA genotype
- Immune complex deposition is often present within involved tissue
- Molecular mimicry may occur during disease initiation
- Many patients show response to anti-inflammatory therapy
Role of IgG4

- Four subclasses of IgG
  - IgG4 least common
- IgG1-3 can activate complement
  - IgG4 cannot
- All except IgG2 can opsonise bacteria
- Is there a pathogenetic role?
Role of IgG4

- Immunofluorescence study
  - Detlefsen S, et al. Histopathology 2010; 57: 825-835
- C3c, IgG & IgG4 are present within immune complexes in basement membranes of involved pancreatic tissue
- Suggests pathogenetic role for IgG4
Role of IgG4
Histopathological features

- Appearances depend on involved tissues
- Lymphoplasmacytic inflammation
- Fibrosis
  - Often storiform
- Vascular changes
  - Particularly described within the pancreas
  - Obliterative phlebitis
  - Granulocytic epithelial lesion
IgG4-positive plasma cells

Å IgG4-positive plasma cell numbers

ï Kloppel G, et al. J Gastroenterol 2007; 42(Suppl XVIII); 28-31

ï >10/hpf was original criterion

ï >20/hpf – 43% sensitivity / 100% specificity

ï >50/3 hpf – 70% sensitivity / 100% specificity

Å Plasma cell counts may be patchy
Patterns of AIP

- Patterns of pancreatic involvement
- Honolulu consensus document
- Type 1
  - Lymphoplasmacytic sclerosing pancreatitis
- Type 2
  - Idiopathic duct-centric chronic pancreatitis
Type 1

- More common
- Wide geographical distribution
- Males >> females
- Increased serum IgG4 & IgE concentrations
- Presence of autoantibodies
- Extra-pancreatic involvement common
- Steroid-responsive
Type 1

- Lymphoplasmacytic infiltration
  - Periductal and perilobular
- Fibrosis
- Obliterative phlebitis
- Inflammation extends beyond pancreas
- IgG4-positive plasma cells present
Type 2

- Less common
- Appears limited to Western countries
- Gender distribution equal
- Extra-pancreatic manifestations uncommon
  - Apart from inflammatory bowel disease
- Steroid-responsive
Type 2

• Lymphoplasmacytic infiltration
  Ù Mainly periductal
• Fibrosis
• Granulocytic epithelial lesions
  Ù Neutrophilic infiltration of ductular epithelium
• Inflammation limited to pancreas
• IgG4-positive plasma cells not present
Extra-pancreatic involvement

- Diagnostic criteria imprecise
  - Inflammatory pseudotumour-like
  - Non-specific lymphoplasmacytic inflammation
  - May mimic other diseases e.g. IBD, PSC
  - IgG4-positive plasma cell count used

- Some tissues may be *more accessible* than the pancreas
Colonic involvement
Refractory gastric ulcer
Refractory gastric ulcer
Utility of ampullary biopsy

A Korean study

- 19 symptomatic AIP patients, 16 AIP patients in remission & 84 controls
- >10 IgG4-positive plasma cells/hpf in 53% symptomatic AIP; none in controls
- Increased IgG4-positive plasma cells most common when serum IgG4 level also raised
IgG4/IgG ratio

Å Ratio of plasma cells that are IgG4-positive
   ï Suggested IgG4/IgG ratio >40%

Å Evaluation of ampullary biopsies
   ï An IgG4/IgG ratio of >0.1 appears useful
Diagnostic guidelines

Japan-Korea consensus criteria 2008

- Diagnosis requires the presence of criteria I-1 and I-2 plus either criterion II or criterion III

  1. Pancreatic parenchymal imaging reveals diffuse/segmental/focal gland enlargement, occasionally with a mass and/or a rim of hypoattenuation

  2. Pancreaticobiliary duct imaging reveals diffuse/segmental/focal duct narrowing, often with stenosis of the bile duct

  II. Elevated serum IgG or IgG4 concentration and detection of autoantibodies

  III. Lymphoplasmacytic infiltration of pancreatic tissue with abundant IgG4-positive plasma cells
Diagnostic guidelines

MAYO Clinic (HISORt) 2007

Diagnosis requires the presence of features within at least one of these groups

1. Histopathology
   - Similar to the Japan-Korea consensus criteria

2. Imaging & serology
   - Similar to the Japan-Korea consensus criteria

3. Response to steroid therapy
Differential diagnosis

Alcoholic chronic pancreatitis

- Shorter history, multi-system involvement
- Morphological features
- IgG4-positive plasma cells

Pancreatic adenocarcinoma

- *May contain prominent IgG4-positive plasma cells*
Relationship to neoplasia

- Adenocarcinoma
- Non-Hodgkin’s lymphoma
  - B-cell lymphoma
  - Peripheral T-cell lymphoma

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Treatment

- Good clinical response to steroids
  - Resolution of duct stricturing
  - Reduction in serum IgG4 level
- Relapse may occur
- Other agents may be required
  - Azathioprine
  - Mycophenolate
Summary

Â IgG4-related sclerosing disease is a rapidly ‘emerging’ condition
Â Important to recognise as may mimic malignancy and usually steroid-responsive
Â Presentation is often multi-system and commonly but not always involves the pancreas
Â Disease may be localised to one organ
Summary

Â Important not to over-diagnose the entity
Â Care needed especially if malignancy is also suspected
Â Other much more common causes of chronic pancreatitis should not be missed
Â Pathologists can help with the diagnosis!
References

Â Morselli-Labate AM & Pezzilli R. J Gastroenterol Hepatol 2009; 24: 15-36
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