HKASLD Bimonthly Scientific Meeting
Topic Review: IgG4 related disease

18th July 2013
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Outline

• Introduction
• Epidemiology
• Pathophysiology
• Clinical manifestations
• Diagnosis - radiological and histological features
• Treatment
• Prognosis
• Conclusion
What is IgG4?
Introduction – IgG4

- Least abundant among IgG subclasses
- Fragment antigen-binding (Fab) - arm exchange reaction
- IgG4 easily forms disulfide bonds within the heavy chains in the hinge region
- Lack of stability of the disulfide bonds permit chains to separate and recombine randomly
- Production primarily controlled by Type 2 Helper T cells (Th2).

History


1991: Similar pathological features involving common bile duct, gallbladder, minor salivary gland, suggesting systemic disorder. (Kawaguchi et al. Hum Pathol.)

1995: Presence of lymphocytic infiltration of pancreas tissue, coexistence of other manifestations e.g. sicca complex, and good responsiveness to glucocorticoids. (Yoshida et al. Dig Dis Sci.)


2003: Massive IgG4 plasmacytic infiltration in pancreatic tissue. (Kamisawa et al. J Gastroenterol.)

2012: Consensus statement on pathology of IgG4-related disease. (Deshpande et al. Mod Pathol.)
Epidemiology

• Few population-based studies available

• come from Japan and focus on autoimmune pancreatitis.

• male predominance and more patients were $>50$ years old

• Mayo clinic series: 11% of 245 patients who underwent pancreatic resection for benign indications $\rightarrow$ found to be autoimmune pancreatitis
Pathophysiology

**Genetic risk factors**
- HLA serotypes DRB1*0405 and DQB1*0401 increase susceptibility in Japanese
- DQβ1-57 without aspartic acid associated with disease relapse in Korean.
- Non-HLA genes: cytotoxic T-lymphocyte-associated antigen 4, TNFα and Fc receptor-like 3.

Pathophysiology

Autoimmunity
- Initial immunologic stimulus for the Th2-cell immune response.
- Serum IgG4 binds to normal epithelia of pancreatic ducts, bile ducts, salivary-gland ducts etc.
- Potential autoantigens at these sites include carbonic anhydrases, lactoferrin, pancreatic secretory trypsin inhibitor and trypsinogens.
- Antibodies expressed in various exocrine organs

Pathophysiology

Bacterial infection and molecular mimicry
- example: human carbonic anhydrase II & α-carbonic anhydrase of H. pylori.

- Patients of autoimmune pancreatitis have antibodies against plasminogen-binding protein of H. pylori.

- Behaves as autoantibodies.

- Stimulation with toll-like receptor ligands induces production of both IgG4 and IL-10 from peripheral-blood mononuclear cells (PBMCs )

Pathophysiology

Immune reaction

1) Th2-cell response
- Tissue mRNA expression levels of Th2 cytokines: IL-4, IL-5, IL-10, and IL-13 are substantially higher than in classic autoimmune conditions.
- Eosinophilia and elevated serum IgE levels, (~ 40% of IgG4 disease), are also mediated by Th2 cytokines.

2) Activate regulatory T (Treg) cells
- In contrast to classic autoimmune conditions
- Besides IL-10, Transforming growth factor β (TGF β) appears to be over-expressed in IgG4 disease -> promote fibrosis

Pathophysiology

- Massive infiltration by inflammatory cells results in organ damage.
- The inflammatory-cell infiltrate leads to tumefactive enlargement of the affected sites and organ dysfunction.
- Epithelial damage

Clinical manifestation

• Subacute development of a mass in the affected organ, or diffuse enlargement of an organ. Multiple organs are affected in 60-90% of patients. They share specific pathologic, serologic and clinical features.

• Allergic features such as atopy, eczema and modest peripheral blood eosinophilia. Up to 40% of patients have allergic disease e.g. bronchial asthma or chronic sinusitis.

• Lymphadenopathy is common

• Can be asymptomatic at the time of diagnosis and lack fever or other constitutional symptoms.
Clinical manifestation

- Obstructive painless jaundice
  - Cholestatic liver derangement
  - Sometimes can mimic biliary pathology or malignancy (e.g. CA pancreas/CA gallbladder)

- Portal hypertension
  - Retroperitoneal fibrosis
Radiological features – case 1

Swollen pancreatic head
Radiological features – case 1

Sausage shape, featureless swollen pancreas
Radiological features – case 1

Dilated intrahepatic ducts
Radiological features – case 2

Cholecystitis with significant wall thickening of gallbladder

After steroid treatment: Gallbladder wall thickening resolved
EUS – guided FNAC:
- 2.5cm hypoechoic lesion in gallbladder
- Dilated CBD to 1cm, with irregularly thickened wall to 3.4mm (FNA of thickened CBD wall negative for malignancy)
- Enlarged hypoechoic LNs in Celiac axis and pancreatoduodenal area. (Largest = 2cm)
ERCP:
- Beading appearance of CBD and IHD, DDx: Primary Sclerosing Cholangitis. No dominant biliary stricture noted.
IgG4-related disease is a systemic disease...

- IgG4-related hypophysitis
- Riedel’s thyroiditis
- IgG4-related interstitial pneumonitis and pulmonary inflammatory pseudotumors
- Chronic sclerosing aortitis and periaortitis
- Retroperitoneal fibrosis (Ormond’s disease)/mesenteritis
- Inflammatory orbital pseudotumor
- a) Sclerosing sialadenitis (Küttner’s tumor, IgG4-related submandibular gland disease)
- b) Chronic sclerosing dacryoadenitis (lacrimal gland enlargement)

Mikulicz’s disease = a + b

- IgG4-related kidney disease (tubulointerstitial nephritis and membranous glomerulonephritis)
Histological features

A: IgG4-related aortitis (H&E stain), with dense lymphoplasmacytic infiltrate on adventitial aspect. A vein obliterated by inflammation is indicative of obliterative phlebitis (arrow).

B: Storiform fibrosis in dacyoadenitis (H&E stain). Like a cartwheel, with bands of fibrosis (arrowheads) emanating from the centre (asterisk) representing the spokes of the wheel.

C & D: Immunoperoxidase staining showed all plasma cells in specimens are strongly positive for IgG4.

Histological features

E: A specimen of a venous channel with total obliteration - obliterative phlebitis (H&E stain)

F: A high-power image of the specimen in panel E shows lymphocytes, plasma cells (long arrow), eosinophils (arrowhead), and fibroblasts (short arrow)

- Consensus meeting about diagnosis in Boston MA 2011

- Purpose: practicing pathologists a set of guidelines about diagnosis of IgG4-related disease.

- Diagnosis primarily depends on morphology of biopsy. Tissue IgG4 counts are secondary in importance.

- Serum IgG4 level can aid the diagnosis, but it is neither sufficiently sensitive nor specific.

- Responses to treatment

Treatment

- Glucocorticoid
- Glucocorticoid-sparing agents:
  - Azathioprine/ mycophenolate mofetil (MMF)
- Rituximab

**No RCT trials have been conducted**
Glucocorticoid

• First line treatment
• Prednisolone at a dose of 0.6mg/kg/day for 2-4 weeks (consensus statement from 17 referral centers in Japan)
• Taper over a period of 3-6 months to 5mg/day, then continue at a dose between 2.5-5mg/day for up to 3 years

• Another approach suggested to discontinue glucocorticoids entirely within 3 months
Glucocorticoid-sparing agents

• For patients resistant to glucocorticoids or unable to reduce dose sufficiently (e.g. to below 10mg/day of prednisolone)

• Azathioprine (2mg/kg/day) or mycophenolate mofetil MMF (up to 2.5g/day as tolerated)

• However, the efficacy has not been evaluated adequately in clinical trials
Rituximab

- Chimeric monoclonal antibody against protein CD20
  → B-cell depletion

- Refractory to glucocorticoids and other medications

- IgG4 concentrations decline sharply, although concentrations of other IgG subclasses remain stable

- The decline in IgG4 level is associated with clinical improvement within weeks of treatment
Prognosis

• Lacking long-term data

• Causes of significant morbidity and mortality in untreated patients: cirrhosis and portal HT, retroperitoneal fibrosis, aortic aneurysms/dissection, biliary obstruction etc

• Relapse is common after discontinuation of treatment

• Reported to be associated with increased risk of cancers, e.g. gastric cancers (most common), lung, prostate, colon, lymphoma (esp. non-Hodgkin lymphoma)
Case 3 - Mr. Cheung, M/75


- **ENT**: followed up for bilateral parotid gland in 2003, biopsy showed reactive lymphoid follicle. Defaulted FU.

- **Oncology**: Incidental findings of multiple intra-abdominal lymph nodes since 2011 – ? Nodal metastasis from unknown origin or lymphoma.
Case 3 – Mr. Cheung

- Repeated episodes of biliary sepsis with multiple ERCPs and PTBDs done in these years – cholestatic liver derangement

- IgG4 checked in 7/2012: 28.4 g/L (reference: 0.03 – 2.01 g/L)

- EUS in 3/2013: swollen pancreatitis, thickened wall of abdominal aorta

- Treated with prednisolone and azathioprine -> liver function normalized
Conclusion

• IgG4-related disease is a recently recognized condition with pathological features that are consistent across a wide range of organ systems.

• This condition unifies a large number of medical disorders previously regarded as confined to single organ systems.

• More studies on the natural history, response to treatment and prognosis are warranted.

Do think of IgG4 disease as a differential diagnosis when we encounter a case of liver derangement or biliary disease!