IGG4-RELATED DISEASE
Overview

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- Histology
- Clinical manifestations
- Diagnosis
- Treatment
Definition

IGG4-RD is a multifocal, fibroinflammatory disorder that can affect almost all organs and tissues.

It is characterized by tendency to form tumefactive lesions, a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, and often an elevated serum IgG4.
IgG4-RD

It is a collection of disorders that have specific pathologic, serologic, and clinical features in common.
IgG4-RD

- Classical features:
  - Tumor-like swelling of involved organs
  - Lymphoplasmacytic infiltrate with IgG4+ plasma cells
  - Variable degrees of fibrosis in a “storiform” pattern
  - Elevated IgG4 (occurs in 60-70%)
    - Unreliable diagnostic marker, as 3-7% of healthy individuals may have an elevated IgG4
  - Good initial response to glucocorticoids
IgG4-RD

- HALLMARK = Isolated submandibular gland enlargement

- Pts may have parotid or lacrimal gland enlargement as well, mimicking Sjogren's syndrome, however antibodies are usually negative.
A 26-year-old woman with three months of bilateral submandibular gland swelling. Her condition, once misdiagnosed as Sjogren's syndrome or termed "Mikulicz disease" or "Kuttner tumor", is now known as IgG4-related sialadenitis. IgG4-related sialadenitis is part of the larger spectrum of IgG4-related systemic disease.

Lacrimal gland swelling
Orbital IgG4-Related Disease: Clinical Features and Diagnosis. ISRN Rheumatology Volume 2012 (2012), Article ID 412896, 5 pages http://dx.doi.org/10.5402/2012/412896
IgG4-RD

It is a disease similar to that of Sarcoidosis in that many or all organs systems may be involved, but the diagnosis is unified by distinct histologic findings.
Elevated IgG4-positive plasma cells in the affected tissue is the sine qua non of the diagnosis.
Table 2: Previously Recognized Conditions That Comprise or May Comprise Parts of the IgG4-RD Spectrum.\textsuperscript{19}

IgG4-RD accounts for some or all of the cases known previously by the following names:

- Mikulicz’s disease
- Küttners tumor
- Riedels thyroiditis
- Eosinophilic angiocentric fibrosis
- Multifocal fibrosclerosis
- Lymphoplasmacytic sclerosing pancreatitis/autoimmune pancreatitis
- Inflammatory pseudotumor
- Fibrosing mediastinitis
- Sclerosing mesenteritis
- Retroperitoneal fibrosis (Ormond’s disease)
- Periaortitis/periarteritis
- Inflammatory aortic aneurysm
- Cutaneous pseudolymphoma
- Idiopathic hypertrophic pachymeningitis
- Idiopathic tubulointerstitial nephritis
- Idiopathic hypocomplementemic tubulointerstitial nephritis with extensive tubulointerstitial deposits
- Membranous glomerulonephritis
- Idiopathic cervical (paravertebral) fibrosis
In October 2011, an International symposium was held in Boston. World’s leading experts from 35 countries and various subspecialties met, including pathologists, rheumatologists, gastroenterologists, allergists, immunologists, nephrologists, pulmonologists, oncologists, ophthalmologists, and surgeons.

Nomenclature was a specific focus of the meeting. Japanese investigators came to a consensus as to what the disease should be named, and the committee at the symposium agreed with them on calling the disorder IgG4-related disease.
Epidemiology

- Largely undefined
- Usually in middle aged and older men, but depends on the organs involved, e.g…
  - Type 1 autoimmune pancreatitis is more prevalent in older men
  - IgG4-related siadenitis has equal distribution between men and women
  - Isolated head and neck disease have equal distribution among sexes
Pathogenesis

- Etiology unknown, but thought to be both an autoimmune and allergic disorder

- Evidence for an autoimmune etiology, as studied in AIP
  - It is associated with specific class II histocompatibility antigen genotype
  - ANA may be present
  - Molecular mimicry involving H. pylori has been suggested
  - Immune complex deposition seen in affected organs
Pathogenesis

- Evidence for an allergic etiology
  - Elevated levels of Th2 cytokines, serum IgE, Tregs, and increased cytokines including IL10, TGF-beta.
  - Th2 cytokines, Tregs, and IL-10 support IgG4 production
  - Peripheral eosinophilia is seen in ~40% of pts

- Pts have an increased prevalence of allergic rhinitis, bronchitis, asthma, and sinusitis
Histology

- Lymphoplasmacytic tissue infiltration with predominance of IgG4-positive plasma cells and T lymphocytes with fibrosis and obliterative phlebitis
- Fibrosis pattern is “storiform” (cartwheel appearance of arranged fibroblasts and inflammatory cells called “nuclear streaming artifact”)
- Eosinophilia is common

**No necrosis, No granulomatous inflammation**
Fibrosis in “storiform pattern”

Collagen stain (blue) demonstrating fibrosis within the renal interstitium. The fibrosis has a storiform pattern.

Clinical manifestations

- May involve one or multiple organs systems
- 60-90% of pts have multi-organ involvement
- Often pts have subacute development of a mass and frequently have lymphadenopathy, but lack constitutional symptoms
- Often asymptomatic, and found incidentally on x-rays and biopsy
Clinical manifestations

- **Lymphadenopathy**
  - LNs usually <2 cm but may be up to 5 cm
  - Occurs in 80% of pts with autoimmune pancreatitis
  - Symptoms occur from mass effect, and there is the absence of constitutional symptoms
  - **Great response to corticosteroids**
  - Usually multiple sites involved i.e. mediastinal, hilar, intrabdominal, axillary
  - Patients may have elevated IgG4, serum IgG/IgE, ESR, polyclonal hypergammaglobulinemia
Clinical manifestations

- Salivary/Lacrimal gland involvement
  - Previously referred as Mikulicz disease or Kuttner tumor,
    - Originally thought to be subset of Sjorgen’s syndrome. However it is differentiated from SS, by mild dryness of eyes/mouth, a higher frequency of allergic rhinitis/bronchial asthma, AIP, and interstitial nephritis, lower frequency of autoantibodies (ANA, SSA/SSB, RF)
  - Common in pts with IgG4-related pancreatitis up to 40%
  - Pt may have low complement levels
  - Several cases have been reported that show an a/w MALT lymphoma and other lymphomas
Clinical manifestations

- Autoimmune pancreatitis
  - Prototypical form of IgG4-RD
  - Type 1 autoimmune pancreatitis is a/w IgG4
  - Patient presents with painless obstructive jaundice or pancreatic mass
  - Can be associated with diabetes mellitus
  - Pts with IgG4-related pancreatitis usually have another IgG4 related condition as well
  - Pancreatic cancer may also cause an elevated serum IgG4, so does not exclude cancer!
  - Xray/CT shows “sausage-shaped pancreas” or diffuse enlargement, with a halo of edema
Sausage-shaped pancreas

Clinical manifestations

- IgG4-related sclerosis cholangitis
  - Most frequent extra pancreatic manifestation of Type 1 AIP seen in ~70%
  - Rare in absence of pancreatitis

- Retroperitoneal fibrosis
  - Can be seen by itself, but often pts have fibrosis of other organs such as pancreas, salivary glands, lymph nodes
  - May be responsive to steroids
Clinical manifestations

- Aortitis/periaortitis
  - Noninfectious, thoracic lymphoplasmacytic aortitis or inflammatory abdominal aortic aneurysms or abdominal periaortitis
  - Maybe assoc. with retroperitoneal fibrosis

- Thyroid disease
  - Riedel’s thyroiditis and fibrous variant of Hashimoto’s thyroiditis
Lung manifestations

- Nodules
- Ground glass opacities
- ILD/honeycombing
- Brochovascular thickening
- Pleural thickening
Clinical manifestations

- Lung/pleural disease
  - Maybe asymptomatic or present with cough, hemoptysis, pleurisy, chest pain, dyspnea
  - May mimic sarcoidosis with hilar adenopathy and nodules
  - Pleural thickening, obliterative arteritis, interstitial pneumonias are associated with AIP
Clinical manifestations

- Tubulointerstitial nephritis
  - Mostly middle aged and elderly men
  - Pts may also have masses/nodules that mimic RCC
  - Pts usually have extrarenal manifestations of IgG4-RD
  - Can also get membranous glomerulonephritis

- Other organs - skin, liver, pituitary, etc.
<table>
<thead>
<tr>
<th>Organ System</th>
<th>Clinical Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes</td>
<td>Chronic sclerosing dacryoadenitis, orbital pseudotumor, orbital myositis, scleritis</td>
</tr>
<tr>
<td>Ears</td>
<td>Destructive disease of middle ear</td>
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<tr>
<td>Nose</td>
<td>Eosinophilic angiocentric fibrosis</td>
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<tr>
<td>Salivary glands</td>
<td>Chronic sclerosing sialadenitis (submandibular &amp; parotid glands)</td>
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<tr>
<td>Lymph nodes</td>
<td>Generalized or localized lymphadenopathy</td>
</tr>
<tr>
<td>Thyroid gland</td>
<td>Fibrosing variant of Hashimoto’s thyroiditis, Riedel’s thyroiditis</td>
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<tr>
<td>Lungs</td>
<td>Lung nodules, ground-glass opacities, alveolar/interstitial inflammation, bronchovascular bundle thickening, pleural thickening</td>
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<tr>
<td>Heart</td>
<td>Pericarditis (sometimes with constriction)</td>
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<tr>
<td>Aorta</td>
<td>Thoracic aortitis, abdominal aortitis, inflammatory aortic aneurysms, aortic dissection</td>
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<tr>
<td>Retroperitoneum</td>
<td>Retroperitoneal fibrosis</td>
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<tr>
<td>Pancreas</td>
<td>Type 1 autoimmune pancreatitis</td>
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<tr>
<td>Biliary tree</td>
<td>Sclerosing cholangitis mimicking primary sclerosing cholangitis</td>
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<tr>
<td>Skin</td>
<td>Erythematous or flesh-colored papules or plaques on the face or head</td>
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<tr>
<td>Central nervous system</td>
<td>Hypopituitarism, hypertrophic pachymeningitis</td>
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<tr>
<td>Peripheral nervous system</td>
<td>Perineural inflammation</td>
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<tr>
<td>Other</td>
<td>Prostatism, sclerosing mesenteritis, fibrosing mediastinitis</td>
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</tbody>
</table>
Organs not involved

- Brain parenchyma (can involve meninges!)
- Bone marrow
- Joints
- ?Bowel
Diagnosis

- Need tissue for diagnosis
  - Needle biopsy with immunohistochemical staining for IgG4+ plasma cells
  - A high IgG4:total IgG ratio (>0.5) and substantial amount of IgG4-positive plasma cells is necessary for the diagnosis. The exact number of IgG4+ plasma cells needed for diagnosis varies by the organ
  - If tissue c/w IgG4-RD usually do not need to biopsy other sites especially if there is good response to steroids
Diagnosis

Usually the minimum for making diagnosis from most tissues is 30 – 50 IgG4+ cells per hpf. However in some organs only need 10 cells per hpf.
Diagnosis

- Serum IgG4 levels should be ordered, but do not need to be elevated for a diagnosis
  - In one study, serum IgG4 was elevated (>135 mg/dl) in 86% of pts
  - May correlate with disease activity and decrease with steroids administration
When to think of IgG4 –RD...

- Pts with pancreatitis of unknown etiology, and/or sclerosing cholangitis
- Pts with bilateral lacrimal and salivary enlargement
- The presence of allergic symptoms, chronic bronchitis, retroperitoneal fibrosis are a helpful hint!
Other lab studies to order

- CBC w/ diff including eosinophils
- Chemistries
- Amylase/lipase
- Complement C3/C4
- Urinalysis
- IgE
- ESR/CRP
- IgG4 subclasses
Additional testing

CT chest/abd/pelvis and/or PET scan to determine the extent of the disease activity, as well as response to treatment.
This PET study demonstrates diffuse uptake within both parotid glands and lymph nodes throughout the axillae and mediastinum.

Treatment

- If symptomatic then immediate treatment is recommended
- Watching and waiting is reasonable if asymptomatic
Treatment

Initiate Prednisone at approx. 40 mg/day or 0.6 mg/kg day

Pts usually start responding in 2-4 weeks, once good response is achieved then taper dose over approximately 3-6 months with goal of discontinuing after 3 months
Treatment

- If not responsive or unable to taper below 10 mg/day then consider treatment with:
  - Azathioprine at 2 mg/kg/day
  - Mycophenolate mofetil up to 2.5g/day as tolerated
  - Methotrexate

- If still not responding then consider B-cell depletion tx with Rituximab at 1 g IV (RA protocol).
Rituximab therapy leads to rapid decline of serum IgG4 levels and prompt clinical improvement in IgG4-related systemic disease.
Prognosis

- Pts may improve spontaneously however relapses are common after stopping treatment
- An increased risk of lymphoma has been reported, as well as pancreatic cancer, salivary duct cancer, pulmonary adenocarcinoma, SCLC, gastrointestinal clear cell cancer
References


- Uptodate. Overview of IgG4-related disease