IGG4-RELATED DISEASE: A BROAD OVERVIEW AND CURRENT CONCEPTS

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Stanford University, Division of Immunology and Rheumatology
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Disclosures

None
Outline

■ What is IgG4-related disease (IgG4-RD)?
■ Historical Perspective
■ Making the Diagnosis
■ Epidemiology
■ Clinical Presentation
■ Pathogenesis
■ Treatment
■ Prognosis
■ Future Directions
IgG4-related disease is a systemic, immune-mediated disease that manifests as fibroinflammatory, tumefactive lesions that can affect virtually any organ in the body.

For centuries individual organ manifestations were given eponymous designations and thought to be distinct entities, but in fact all share common histopathologic features.
Conditions Now Recognized as IgG4-RD

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mikulicz disease</td>
</tr>
<tr>
<td>Küttnertumor</td>
</tr>
<tr>
<td>Riedel thyroiditis</td>
</tr>
<tr>
<td>Eosinophilic angiocentric fibrosis</td>
</tr>
<tr>
<td>Multifocal fibrosclerosis</td>
</tr>
<tr>
<td>Lymphoplasmacytic sclerosing pancreatitis/</td>
</tr>
<tr>
<td>autoimmune pancreatitis</td>
</tr>
<tr>
<td>Inflammatory pseudotumor</td>
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<tr>
<td>Fibrosing mediastinitis</td>
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<tr>
<td>Sclerosing mesenteritis</td>
</tr>
<tr>
<td>Retroperitoneal fibrosis (Ormond disease)</td>
</tr>
<tr>
<td>Periaortitis/periarteritis</td>
</tr>
<tr>
<td>Inflammatory aortic aneurysm</td>
</tr>
<tr>
<td>Cutaneous pseudolymphoma</td>
</tr>
<tr>
<td>Idiopathic hypertrophic pachymeningitis</td>
</tr>
<tr>
<td>Idiopathic tubulointerstitial nephritis</td>
</tr>
<tr>
<td>Idiopathic hypocomplementemic tubulointerstitial nephritis with extensive tubulointerstitial deposits</td>
</tr>
<tr>
<td>Idiopathic cervical fibrosis</td>
</tr>
</tbody>
</table>

Historical Perspective: 1888

Historical Perspective: 1979

Primary Sclerosing Cholangitis
Associated with Fibrosis of the Submandibular Glands and the Pancreas

Ingela Sjögren, Bo Wengle and Magnus Korsgren

From the Department of Internal Medicine, University Hospital, Uppsala, and Falu Hospital, Falun, Sweden
Fig. 1. Symptoms, including malaise, itching, clay-coloured stools, dark urine and frank icterus (⊗), recurred following reduction of the prednisolone dosage, together with an increase of serum alkaline phosphatase (○—○), serum alanine aminotransferase (▲—▲), and serum bilirubin (×—×).
Historical Perspective: A New Disease Is Born

Hydronephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis

Hideaki Hamano, Shigeyuki Kawa, Yasuhide Ochi, Hiroshi Unno, Nobuhiko Shiba, Masahisa Wajiki, Koh Nakazawa, Hisashi Shimojo, Kendo Kiyosawa

Close relationship between autoimmune pancreatitis and multifocal fibrosclerosis

T Kamisawa, N Funata, Y Hayashi, K Tsuruta, A Okamoto, K Ameminya, N Egawa, H Nakajima

A new clinicopathological entity of IgG4-related autoimmune disease

Terumi Kamisawa¹, Nobuaki Funata², Yukiko Hayashi³, Yoshinobu Eishi³, Morio Koike³, Kouji Tsuruta⁴, Atsutake Okamoto⁴, Naoto Egawa¹, and Hitoshi Nakajima¹

¹Department of Internal Medicine, Tokyo Metropolitan Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan
²Department of Pathology, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan
³Department of Pathology, Tokyo Medical and Dental University School of Medicine, Tokyo, Japan
⁴Department of Surgery, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan

“It looks as if she has autoimmune pancreatitis in her submandibular gland!”

“A black crow flying through the dark night.”
IgG4-RD

- Lymphadenopathy
- Subcutaneous nodules
- Pachymeningitis
- Dacryoadenitis
- Chronic thyroiditis
- Hypophysitis
- Sialadenitis
- Nephritis
- Aortitis
- Sclerosing cholangitis
- Interstitial pneumonia
- Retroperitoneal fibrosis
- Autoimmune pancreatitis
IgG4-RD: Making the Diagnosis

- Chronic, systemic fibroinflammatory disease
  - Immune-mediated
  - Essentially every organ can be affected

- Tumefactive lesions
  - Aorta, pachymeninges, bile ducts are exceptions

- Typical histopathology
  - Lymphoplasmacytic infiltrates with IgG4+ plasma cells
  - Storiform fibrosis
  - Obliterative phlebitis

- Elevated serum IgG4

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40% of patients have single organ disease

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40% of patients have single organ disease
60% of patients have multi-organ involvement

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Lymphoplasmacytic Infiltrate

Storiform Fibrosis

Obliterative Phlebitis

IgG4-RD: Making the Diagnosis

Get tissue!

Request an IgG4 stain
Making the Diagnosis: Histopathology

- **Histopathology compatible with diagnosis if ≥ 2 are present:**
  
  1. Dense lymphoplasmacytic infiltrate (100%)
    - IgG4+ plasma cells
      - >10 to >50 per high-power field (mean 120/HPF)
      - IgG4+/IgG+ ratio of 30-50% (mean 60%)
  
  3. Storiform fibrosis (74%)
  
  4. Obliterative phlebitis (40%)
  
  5. *Eosinophilic infiltration* (40%)

- Large variation between organs

Making the Diagnosis: Histopathology

- **Arteritis** does not exclude the diagnosis
  - Occasionally seen in autoimmune pancreatitis and lung lesions
  - Necrotizing arteritis not seen

- **Granulomatous** inflammation not seen

- A prominent **neutrophilic** infiltrate not seen

- Giant cells rarely seen

Inflammatory bowel disease

Hypocomplementemic urticarial vasculitis

Multicentric Castleman’s disease

Oral inflammatory diseases

Rheumatoid arthritis

Anti-neutrophil cytoplasmic antibody-associated vasculitis

Rhinosinusitis

Tissue IgG4+ Plasma Cells Can Be Seen in Other Conditions

Lymphoma

Rosai-Dorfman disease

Xanthogranulomatous disease

EBV-related lymphadenopathy

Primary sclerosing cholangitis

Staphylococcus aureus infection


Tissue IgG4+ Plasma Cells In Various Tissues

IgG4-RD: Making the Diagnosis

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IgG4-RD: Making the Diagnosis

- Elevated serum IgG4

IgG4-RD: Making the Diagnosis

<table>
<thead>
<tr>
<th>TABLE 1. Main Laboratory Abnormalities and Immunological Features Detailed in the Main Series (n&gt;10) of Patients With IgG4-Related Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated C-reactive protein levels</td>
</tr>
<tr>
<td>Eosinophilia</td>
</tr>
<tr>
<td>Serum IgG levels (mg/dL)</td>
</tr>
<tr>
<td>&gt;1800</td>
</tr>
<tr>
<td>Mean of individual values (n=192)</td>
</tr>
<tr>
<td>Range of mean IgG values (26 studies) (mg/dL)</td>
</tr>
<tr>
<td>&lt;1800</td>
</tr>
<tr>
<td>1800-3600</td>
</tr>
<tr>
<td>3601-5000</td>
</tr>
<tr>
<td>Serum IgG4 levels (mg/dL)</td>
</tr>
<tr>
<td>&gt;135</td>
</tr>
<tr>
<td>Mean of individual values (n=192)</td>
</tr>
<tr>
<td>Range of mean IgG4 values (42 studies) (mg/dL)</td>
</tr>
<tr>
<td>&lt;135</td>
</tr>
<tr>
<td>135-270</td>
</tr>
<tr>
<td>271-540</td>
</tr>
<tr>
<td>541-1080</td>
</tr>
<tr>
<td>&gt;1080</td>
</tr>
</tbody>
</table>

IgG4-RD: Making the Diagnosis

- Elevated serum IgG4

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Test characteristics of serum IgG4 concentration elevation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic (%)</td>
<td>IgG4 &gt;135 mg/dL</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>90</td>
</tr>
<tr>
<td>Specificity</td>
<td>60</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>34</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>96</td>
</tr>
</tbody>
</table>

Making the Diagnosis: Serum IgG4

- Majority above 135 mg/dL but negative in 10-30% of cases
  - Mean reported value is 4-6 times the ULN
  - Elevation is not specific for IgG4-RD!

- Disease activity may correlate with IgG4 level
- Number of organs involved may also correlate
- The trend is more important than the absolute number
- Be aware of the prozone effect and falsely low IgG4 levels (26%)

### Serum IgG4 and The Prozone Effect

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Original report</th>
<th>Retest</th>
<th>IgG4 value, mg/dl</th>
<th>Fold increase after dilution</th>
<th>No. of affected organs</th>
<th>Active disease</th>
<th>Presence of prozone effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.3</td>
<td>2,470</td>
<td>247</td>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
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<tr>
<td>2</td>
<td>28.4</td>
<td>941</td>
<td>33</td>
<td>3</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>29.3</td>
<td>219</td>
<td>7.5</td>
<td>1</td>
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<tr>
<td>4</td>
<td>59.8</td>
<td>337</td>
<td>5.6</td>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
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<tr>
<td>5</td>
<td>12.7</td>
<td>5,340</td>
<td>420</td>
<td>3</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>17.6</td>
<td>1,850</td>
<td>105</td>
<td>4</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
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<tr>
<td>7</td>
<td>8.0</td>
<td>5,160</td>
<td>645</td>
<td>7</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>43.9</td>
<td>1,030</td>
<td>23</td>
<td>4</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
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<tr>
<td>9</td>
<td>14.4</td>
<td>1,910</td>
<td>132</td>
<td>7</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>37.5</td>
<td>819</td>
<td>22</td>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

Serum IgG4 Response to Rituximab

Elevated Serum IgG4 Can Be Seen in Other Conditions

Inflammatory bowel disease
Sarcoidosis
Sjögren syndrome
Systemic lupus erythematosus
Systemic sclerosis
Liver cirrhosis
Rheumatoid arthritis
Anti-neutrophil cytoplasmic antibody-associated vasculitis
Sjögren syndrome
Interstitial lung disease
Rheumatoid arthritis
Liver cirrhosis
Rheumatoid arthritis
Anti-neutrophil cytoplasmic antibody-associated vasculitis
Liver cirrhosis
Rheumatoid arthritis
Anti-neutrophil cytoplasmic antibody-associated vasculitis
Liver cirrhosis
Rheumatoid arthritis
Anti-neutrophil cytoplasmic antibody-associated vasculitis

Making the Diagnosis: Plasmablasts

- CD19\textsuperscript{low} CD20\textsuperscript{neg} CD38\textsuperscript{high} CD27\textsuperscript{high} antibody secreting cells

Making the Diagnosis: Plasmablasts

- May be the best marker of IgG4-RD disease activity

Making the Diagnosis: Plasmablasts

- Oligoclonal
- Autoreactive

Making the Diagnosis: Other Laboratory Values

- **ANA and/or RF** positive in 30% of patients
  - ANA is not of the IgG4 subclass
  - Not positive for anti-Ro/SSA, anti-double stranded DNA, or anti-neutrophil cytoplasmic antibodies

- **CRP** elevated in 25% of patients
  - More common to have a high ESR from elevated IgG with a normal CRP

Making the Diagnosis: Other Laboratory Values

- **Hypocomplementemia** in **40%** of patients
  - Particularly common in IgG4-related kidney disease

- **Hypergammaglobulinemia** in **60%** of patients
  - Elevated **IgE** in **60%** of patients
    - IgA and IgM often low

- **Eosinophilia** in **33%** of patients

Making the Diagnosis: Imaging

■ Cross-sectional imaging
  - CT and MRI useful for detecting organ enlargement and pseudotumors
  - After diagnosis, **CT chest/abdomen/pelvis to assess extent of disease**

■ Potential diagnostic role for $^{18}$F-FDG PET/CT
  - **More sensitive** for detecting salivary gland, lymph node, and blood vessel disease
  - PET identified **more extensive disease in nearly 70% of cases** compared to standard evaluation of exam, ultrasound, CT

IgG4-RD: Making the Diagnosis

Making the Diagnosis: A Rare Exception

Lymphoplasmacytic sclerosing pancreatitis without IgG4 tissue infiltration or serum IgG4 elevation: IgG4-related disease without IgG4

Phil A Hart¹, Thomas C Smyrk² and Suresh T Chari¹

¹Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA and ²Department of Pathology, Mayo Clinic, Rochester, MN, USA
Epidemiology of IgG4-RD

- Review of 3500 cases
  - Mean age at diagnosis: 63 years
    - Rare pediatric cases reported
  - Male predominance accounting for 73% of cases
  - Roughly 75% of reported cases are Japanese
    - Approximately 8000 patients had IgG4-RD in Japan in 2009
      - Prevalence of 6 cases per 100,000 people
    - IgG4-RD has been identified in all races and ethnicities

Reported IgG4-RD Cases in the Literature as of 2014

Epidemiology of IgG4-RD

Possible association with chronic exposure to industrial dusts, gases, oils, solvents and pesticides in ‘blue-collar’ professionals

Table 1. Job History and Occupational Exposures of the Amsterdam Cohort of Patients With IgG4-RD
(IgG4-Associated Cholangitis, Autoimmune Pancreatitis)

<table>
<thead>
<tr>
<th>Job History of 25 Patients from the Amsterdam Cohort (&gt; 1 year)</th>
<th>Recalled Regular Occupational Exposures (&gt; 1 year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Musician, painter, metal worker, carpenter</td>
<td>solvents, car paint, metal, pigments</td>
</tr>
<tr>
<td>2. Carpenter</td>
<td>solvents, sawdust, wood, chipboard</td>
</tr>
<tr>
<td>3. Glass worker, project manager at multinational</td>
<td>glass dust, glass components, lead, barium, cobalt, nickel, lead, silica, industrial dust, building sites</td>
</tr>
<tr>
<td>4. Plasterer</td>
<td>solvents, chalk dust, sawdust, wood, chipboard</td>
</tr>
<tr>
<td>5. Industrial warehouse forklift driver</td>
<td>unknown (deceased)</td>
</tr>
<tr>
<td>6. Industrial fuel/waste oil laboratory, skipper</td>
<td>solvents, crude oil, ship waste oil, chemicals</td>
</tr>
<tr>
<td>7. Miner, tiler, beth superintendent</td>
<td>solvents, silica dust, mine dust, asbestos, glue</td>
</tr>
<tr>
<td>8. Metal worker, textile worker</td>
<td>solvents, metal dust, textiles, pigments, paints</td>
</tr>
<tr>
<td>9. Shipping</td>
<td>solvents, asbestos, crude oil</td>
</tr>
<tr>
<td>10. Painter, army officer, flight arrangements, tomato farmer</td>
<td>solvents, paint, pigments, kerosene, pesticides, friction plate dust</td>
</tr>
<tr>
<td>11. Painter</td>
<td>solvents, paint, pigments, dust</td>
</tr>
<tr>
<td>12. Small machine factory owner</td>
<td>solvents, car paint, metal dust, asbestos, oils</td>
</tr>
<tr>
<td>13. Builder, plumber</td>
<td>plumbing materials, dust, sawdust, glue, lead</td>
</tr>
<tr>
<td>14. Self-employed optometrist</td>
<td>dense glass dust, dense plastic dust, acetone</td>
</tr>
<tr>
<td>15. Carpenter</td>
<td>solvents, sawdust, chipboard, glue</td>
</tr>
<tr>
<td>16. Bricklayer, industrial cleaner of house walls</td>
<td>solvents, silica dust, concrete dust, brick dust, asbestos</td>
</tr>
<tr>
<td>17. Mud worker, shipping, mud industry manager</td>
<td>solvents, oil products, dust</td>
</tr>
<tr>
<td>18. Builder, painter</td>
<td>solvents, sawdust, chipboard, paints</td>
</tr>
<tr>
<td>19. Car industry worker</td>
<td>solvents, oil products</td>
</tr>
<tr>
<td>20. Historian, rebuilt 3 houses during last 20 years</td>
<td>solvents, sawdust, silica dust, paint</td>
</tr>
<tr>
<td>21. Builder, wall miler</td>
<td>cleaning products</td>
</tr>
<tr>
<td>22. Hospital cleaner</td>
<td>no known exposures</td>
</tr>
<tr>
<td>23. Teacher</td>
<td>no known exposures</td>
</tr>
<tr>
<td>24. Nurse</td>
<td>unknown (deceased)</td>
</tr>
</tbody>
</table>

IgG4-RD Clinical Presentation

- Consider IgG4-RD when a patient presents with tumor-like lesions in one or more organs
  - Visible on exam or detected by imaging
- Constitutional symptoms such as fever are rare
  - Not critically ill at first presentation
  - Subacute weight loss relatively common
- Allergy or asthma in 30-40% of patients
- Organ specific manifestations

Pancreas

- Type I autoimmune pancreatitis (AIP) reported in 41% of systemic cases
- Present with jaundice, abdominal pain, pruritus, steatorrhea, new-onset diabetes
- CT scan with **diffuse swelling** of the pancreas with late phase enhancement and **low-density rim**

Major Salivary Glands

- Reported in 40% of systemic cases
- Present with glandular swelling and sicca symptoms
  - Unlike Sjögren’s, responds to glucocorticoid treatment
- Submandibular > parotid > sublingual gland involvement

Ophthalmic Involvement

- Reported in 29% of systemic cases
- Dacryoadenitis (lacrimal gland enlargement) most common
  - Usually bilateral
- Orbital psuedotumor, optic neuropathy, ptosis, scleritis

Lymph Nodes

- Lymphadenopathy in 26-41% of systemic cases
- Often near an organ that is involved
- Mainly periaortic and periiliac

Problematic for making the diagnosis; minimal fibrosis

Biliary Tree and Gallbladder

- Reported in 19.5% of systemic cases
- 83% of IgG4-RD sclerosing cholangitis also have AIP
  - The converse is 40%
- IgG4-RD cholecystitis often asymptomatic

Allergy

- Atopic background in 17-40% of systemic cases
- Asthma, dermatitis, urticaria, conjunctivitis, rhinitis, sinusitis, nasal polyposis

Retroperitoneum

- Retroperitoneal fibrosis reported in 13% of systemic cases
- Present with back pain, lower extremity swelling, hydronephrosis
- Mainly periaortie and periiliac

Kidneys

- Reported in 13% of systemic cases
- **Tubulointerstitial nephritis most common**
  - Azotemia, rise in creatinine, low C3, C4, CH50 (60%)
- Glomerular disease and nephrotic syndrome uncommon

Chest

■ Reported in 12% of systemic cases

■ Often asymptomatic
  - Cough, dyspnea

■ Interstitial lung disease, nodular pleural thickening, hilar lymphadenopathy, mediastinal fibrosis possible

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Vascular Involvement

- Aortitis in 9% of systemic cases
- Aneurysms, dilation, periaortitis, dissection
- Carotid, coronary, pulmonary, mesenteric, intracerebral, peripheral arteries possible

Neurologic Involvement

■ CNS disease in 1-2% of systemic cases

■ Present with headache, palsies, vision change, weakness, numbness, sensorineuronal hearing loss, seizures

■ **Hypertrophic pachymeningitis**
  - Imaging shows dural thickening or bulging mass

■ Cranial nerves affected by adjacent masses

Prostate

- Reported in 2% of systemic cases
- Present with severe urinary retention
  - Diagnosed after transurethral resection
- Can also present as a prostate mass seen on imaging

Hypophysis

- Hypophysitis in 1.5% of systemic cases
- Hypopituitarism or diabetes insipidus
- MRI shows enlargement of the anterior pituitary or stalk

Skin

- Reported in 1% of systemic cases
- Erythematous plaques and subcutaneous nodules
  - Occasionally brown papules
- Mostly involve skin of the head
- Eczema frequently reported

Thyroid

■ Riedel’s and fibrosing Hashimoto’s thyroiditis are IgG4-RD

■ 81% of Riedel’s thyroiditis in women

Rare IgG4-RD Manifestations

- **Thoracic paravertebral mass**
- Mastitis
- Scrotal mass
- Esophageal/gastric/duodenal/ileal/colonic pseudotumors → strictures
- Sclerosing mesenteritis
- Hepatic pseudotumor
- Midline-destructive lesion
- Cardiac valve pseudotumor
- Pericardial pseudotumor

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- Scrotal mass
- Esophageal/gastric/duodenal/ileal/colonic pseudotumors → strictures
- **Sclerosing mesenteritis**
- Hepatic pseudotumor
- Midline-destructive lesion
- Cardiac valve pseudotumor
- Pericardial pseudotumor

Rare IgG4-RD Manifestations

- Thoracic paravertebral mass
- Mastitis
- Scrotal mass
- Esophageal/gastric/duodenal/ileal/colonic pseudotumors --> strictures
- Sclerosing mesenteritis
- Hepatic pseudotumor
- Midline-destructive lesion
- Cardiac valve pseudotumor
- **Pericardial pseudotumor**

IgG4-RD Pathogenesis

■ Th2 cells initially implicated
  - Increased IL-4, IL-5, IL-13, IgG4, IgE
  - Only increased in atopic patients (~30%)

■ CD4+ CTLs \((\text{CD}4^+ \text{CD}27^{\text{low}} \text{CD}62L^{\text{low}})\) expanded
  - Express granzyme, granulysin, and perforin
  - Express IL-1\(\beta\), TGF-\(\beta\), and interferon-\(\gamma\)
  - Up-regulate signaling lymphocytic activation molecule 7 (SLAMF7)

CD4+ CTLs Undergo Large Clonal Expansions

CD4+ CTLs Secrete Inflammatory and Pro-Fibrotic Cytokines and Decline After Rituximab

T follicular helper cells

- Circulating Tfh2 cells are expanded
  - Correlate with plasmablasts, IgG4, IL-4, disease activity
- In vitro, Tfh2 cells induce differentiation of naïve B cells into plasmablasts
- Tfh2 cells do not decline after glucocorticoid treatment

IgG4-RD Pathogenesis: The IgG4 Molecule

IgG4-RD Pathogenesis: The IgG4 Molecule

- **Anti-inflammatory/tolerance-inducing**
  - Beekeepers, patients receiving allergen immunotherapy

- **Pathogenic**
  - Pemphigus vulgaris, MuSK–myasthenia gravis, idiopathic membranous nephritis

- **Disadvantageous suppression**
  - Inhibit clearance of malignancies such as melanoma and cholangiocarcinoma
  - Inhibit clearance of infectious agents such as helminths

- IgG4 antibodies may be directly pathogenic or a protective response that prevents binding of harmful IgG1 autoantibodies

IgG4-RD Pathogenesis: Autoantibodies

- Autoantibodies reported in the literature
  - Carbonic anhydrase II, lactoferrin, pancreatic secretory trypsin inhibitor, pancreatic trypsinogens, annexin A11
  - Unclear significance
  - Most are IgG1 or unknown subclass
  - Anti-annexin A11 is both IgG1 and IgG4 targeting the same epitope

IgG4-RD Pathogenesis

- **Mouse model**
  - BALB/c mice injection with IgG from AIP patients
  - Injury to both pancreatic and salivary tissue
  - Damage from IgG1
    - Less from IgG4 alone
  - Damage partly abrogated by simultaneous injection of IgG1 with IgG4

IgG4-RD Pathogenesis: Response to Rituximab

Serum IgG4 = 1560 mg/dL (nl <135 mg/dL)

Two months later, Serum IgG4 = 390 mg/dL

Images courtesy of Dr. John Stone
IgG4-RD Skin Biopsy Pre- and Post-Rituximab

IgG4-RD Pathogenesis

IgG4-RD Treatment

- Prednisone 0.6mg/kg tapered over 12 weeks
  - Dramatic response to glucocorticoids
  - ~50% will relapse within 1 year after initial response if no additional treatment is given
  - Japanese providers often maintain prednisone 2.5 to 10mg daily after taper

32% relapsed at 6 months
56% relapsed at 1 year
76% relapsed at 2 years
92% relapsed at 3 years

IgG4-RD Treatment

■ Disease Modifying Anti-Rheumatic Drugs (DMARDs)
  - No controlled trials comparing DMARDs
  - Small studies and anecdotal reports support the use of azathioprine, methotrexate, mycophenolate mofetil

■ B cell depletion
  - Rituximab evaluated in a prospective, open-label trial ($n = 30$)
  - Disease response in 97%, primary outcome in 77% and complete remission in 47% at 6 months

■ B cell inhibition
  - XmAb5871 binds CD19 and FcγRIIb
  - Recent open-label, single-arm study suggests efficacy

■ Experimental therapies
  - Abatacept
  - Elotuzumab to target SLAMF7 on CD4+ CTLs

### Manifestations Requiring Urgent Treatment

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Rationale for urgent treatment</th>
</tr>
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<tbody>
<tr>
<td>Aortitis</td>
<td>Inflammatory aortic aneurysms can continue to enlarge and are at risk for dissection.</td>
</tr>
<tr>
<td>Retroperitoneal fibrosis</td>
<td>Progressive disease may lead to irreversible nerve damage/pain and/or ureteral obstruction/renal failure.</td>
</tr>
<tr>
<td>Proximal biliary strictures*</td>
<td>Untreated disease may lead to superimposed infectious cholangitis and eventually irreversible fibrosis and cirrhosis.</td>
</tr>
<tr>
<td>Tubulointerstitial nephritis</td>
<td>Untreated disease may lead to irreversible chronic kidney disease.</td>
</tr>
<tr>
<td>Pachymeningitis</td>
<td>Untreated disease puts the patient at risk for neurologic deficits and/or seizures.</td>
</tr>
<tr>
<td>Pancreatic enlargement</td>
<td>Untreated disease may lead to irreversible pancreatic exocrine and endocrine failure.</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>Untreated disease may lead to tamponade or constrictive pericarditis.</td>
</tr>
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Monitoring Treatment: IgG4-RD Responder Index

IgG4-RD Treatment: My Approach

■ Prednisone 0.6mg/kg for 1 month
  - Taper over subsequent 2-3 months pending response
■ If prednisone response complete, and manifestation non-life-threatening, follow clinically
  - If flare, repeat short course of steroids and add azathioprine
■ If prednisone response complete, and manifestation potentially life-threatening, add azathioprine to steroid taper
■ If relapse while on azathioprine, stop and treat with rituximab
■ If prednisone response incomplete, and manifestation is symptomatic or life-threatening, treat with rituximab
IgG4-RD Prognosis

- Natural history has several trajectories:
  - Occasional spontaneous remission
  - Indolent, progressive organ enlargement
  - Additional organ involvement over time
  - Irreversible damage of vital organs
- Increased risk of death compared to the general population (OR 2.07)
- Roughly 50% of patients will relapse within 1 year after initial remission
  - Lower rate of relapse with DMARDs (likely) and rituximab (definitely)
- Conflicting reports about IgG4-RD developing into cancer
  - Likely does not represent a premalignant state
- A prior history of malignancy roughly 3-fold higher in IgG4-RD patients compared to matched controls

IgG4-RD: Future Directions

- Official American College of Rheumatology/European League Against Rheumatism Classification Criteria for IgG4-Related Disease coming soon
- Efforts to discover a common autoantigen ongoing
  - A reliable mouse model of disease is needed
- Further investigation into the role of CD4+ CTLs
  - Targeted therapy with Elotuzumab (anti-SLAMF7)
- A randomized, placebo-controlled, double-blind clinical trial with XmAb5871 is being planned
- New therapies that target the inflammatory cell infiltrate (CCR), glycocalyx (galectin), hepatic stellate cell activation (PPAR), and matrix crosslinking (LOX) are in development
THANK YOU!

IgG4-RD
QUESTIONS
References

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