IgG4-Related Disease: Puzzles and Pitfalls

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Disclosures

• I have no relevant disclosures
• Consultant: Zebra Medical Technologies
Overview

- Case
- Criteria
- Pitfalls
- How to Proceed

Case

• 72 year-old woman with a 3-year history of pruritic rash on cheeks, neck, chest, and upper arms

• Treated with doxycycline, topical steroids without relief
Slide consult requested by clinician
Case

• My signout:

SUPERFICIAL AND DEEP PERIVASCULAR AND PERI-ADNEXAL LYMPHOPLASMACYTIC INFILTRATES WITH EOSINOPHILS (SEE COMMENT)
Case

Clinical Ddx

- Rosacea
- Photodrug
- Dermal hypersensitivity
- Granuloma faciale
Case

Clinical Ddx
• Rosacea
• Photodrug
• Dermal hypersensitivity
• Granuloma faciale

Histopathologic Ddx
• Rosacea (but bad distribution!)
• Dermal hypersensitivity
• Borrelia
• Granuloma faciale (no neuts!)
• Cutaneous lymphoid hyperplasia
• PMH:
  – Thyroiditis, unspecified
• ROS: 60 lb weight loss
• PMH:
  – Thyroiditis, unspecified

• ROS: 60 lb weight loss
Case

• Challenging fellowship case of patient with proptosis, weight loss, and similar-appearing biopsy specimens
IgG

IgG4
After treatment

Courtesy of Sotonye Imadojemu, MD
Back to our case

- Called the clinician and had a conversation
- Clinician thought it worth investigating
- Ordered outside block
IgG
Case

- 112 IgG4+ cells/HPF
- IgG4:IgG ratio ~70%
- Mixed B-cells and T-cells
- SPEP/UPEP negative, other labs normal
- Serum IgG4 301 mg/dL

**Diagnosis:** Probable IgG4 related-disease
IgG4-Related Disease

- Chronic fibroinflammatory disease
- Multiple organ systems
- Characteristic findings
- Increased IgG4+ cells
- Corticosteroid-responsive
# IgG4-Related Disease

**Table 1.** Previously Recognized Conditions Now Acknowledged to Fall within the Spectrum of IgG4-Related Disease.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mikulicz’s syndrome</td>
<td>(affecting the salivary and lacrimal glands)</td>
</tr>
<tr>
<td>Küttners tumor</td>
<td>(affecting the submandibular glands)</td>
</tr>
<tr>
<td>Riedel’s thyroiditis</td>
<td></td>
</tr>
<tr>
<td>Eosinophilic angiocentric fibrosis</td>
<td>(affecting the orbits and upper respiratory tract)</td>
</tr>
<tr>
<td>Multifocal fibrosclerosis</td>
<td>(commonly affecting the orbits, thyroid gland, retroperitoneum, mediastinum, and other tissues and organs)</td>
</tr>
<tr>
<td>Inflammatory pseudotumor</td>
<td>(affecting the orbits, lungs, kidneys, and other organs)</td>
</tr>
<tr>
<td>Mediastinal fibrosis</td>
<td></td>
</tr>
<tr>
<td>Retroperitoneal fibrosis (Ormond’s disease)</td>
<td></td>
</tr>
<tr>
<td>Periaortitis and periarteritis</td>
<td></td>
</tr>
<tr>
<td>Inflammatory aortic aneurysm</td>
<td></td>
</tr>
<tr>
<td>Idiopathic hypocomplementemtic tubulointerstitial nephritis with extensive tubulointerstitial deposits</td>
<td></td>
</tr>
</tbody>
</table>
Pathogenesis

- Oligoclonal, antigen-driven immune response
- Expansion of plasmablasts (CD19+ CD20- CD27+ CD38+)
- Expansion of CD4+ cytotoxic T-cells
- Expansion of Tfh2 T-cells
IgG4 disease criteria

- Evidence of organ involvement
- Pathology
  - Lymphoplasmacytic infiltrate with eosinophils
  - Storiform fibrosis (not everywhere)
  - Phlebitis
  - IgG4 predominance
    - IgG4/IgG cells >40%
    - Increased IgG4+ cells/ HPF
    - Cutaneous cutoffs remain ill-defined (10? 200?)
    - Bennett et al average of 133 IgG4+ cells/HPF (CI 33)
- Elevated IgG4 levels

Deshpande V et al., Mod Pathol 2012
Cutaneous IgG4 RD - a meta-analysis

- Charrow et al, JAAD 2016
- 58 Cases
  - 2 excluded
  - 15 definite
  - 7 probable
  - 18 possible
  - 16 neg for criteria
- 66% male
- Mean age: 59
- Head and neck
- Most common systemic involvement:
  - Head and neck (parotid, lacrimal, sialadenitis, proptosis)
• Bennett et al (Int J Derm 2016)
• 79% of pts with IgG4-RD w preceding systemic dz
• Most common sites
  – Salivary
  – Lymphatic
  – Lacrimal
  – Orbit

<table>
<thead>
<tr>
<th>Pathologic characteristic</th>
<th>Average (±95% CI)</th>
<th>Organ involved</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG4 + plasmacytes/HPF</td>
<td>133 ± 33</td>
<td>Salivary</td>
<td>53</td>
</tr>
<tr>
<td>IgG4/IgG plasmacyte ratio (%)</td>
<td>63 ± 7</td>
<td>Lymphatic</td>
<td>47</td>
</tr>
<tr>
<td>Serum IgG4 (mg/dl)</td>
<td>580 ± 184</td>
<td>Lacrimal</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prevalence in</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>reviewed cases</td>
<td></td>
</tr>
<tr>
<td>Venulitis</td>
<td>54%</td>
<td>Lung</td>
<td>7</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>76%</td>
<td>Hepatobiliary</td>
<td>3</td>
</tr>
<tr>
<td>Tissue eosinophilia</td>
<td>80%</td>
<td>Nasal cavity</td>
<td>3</td>
</tr>
</tbody>
</table>
Cutaneous IgG4-RD

Tokura et al, Brit J Derm, 2014
Cutaneous IgG4-RD

Bhabha FK et al, Australas J Derm 2016
## Cutaneous IgG4 disease: Manifestations

<table>
<thead>
<tr>
<th>Type</th>
<th>Symptoms</th>
<th>Differential diagnoses</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Cutaneous plasmacytosis</td>
<td>Multiple circular or ellipsoid patches with pigmentation</td>
<td>Multicentric Castleman disease</td>
<td>24–28, 30</td>
</tr>
<tr>
<td>2 Pseudolymphoma and angiolympoid hyperplasia with eosinophilia</td>
<td>Plaques and papulonodules mainly on the periauricular and facial areas</td>
<td>B-cell pseudolymphoma, mucosa-associated lymphoid tissue syndrome</td>
<td>2, 31, 32, 37</td>
</tr>
<tr>
<td>3 Mikulicz disease or IgG4-related dacrnyoadenitis and sialadenitis</td>
<td>Palpebral swelling, sicca syndrome, exophthalmos</td>
<td>Sjögren syndrome</td>
<td>6, 19, 24, 38–40</td>
</tr>
<tr>
<td>4 Psoriasis-like eruption</td>
<td>Scaly erythematous plaques</td>
<td>Psoriasis vulgaris</td>
<td>41, 42</td>
</tr>
<tr>
<td>5 Unspecified maculopapular or erythematous eruptions</td>
<td>Multiple maculopapular or exudative erythematous lesions</td>
<td>Drug eruption, toxic erythema</td>
<td>45, 46</td>
</tr>
<tr>
<td>6 Hypergammaglobulinaemia, purpura and urticarial vasculitis</td>
<td>Bilateral palpable purpuric lesions, prolonged urticarial lesions</td>
<td>Anaphylactoid purpura, Sjögren syndrome, lupus erythematosus</td>
<td>47–49</td>
</tr>
<tr>
<td>7 Ischaemic digit</td>
<td>Raynaud phenomenon, digital gangrene</td>
<td>Systemic sclerosis, thrombosis, antiphospholipid syndrome</td>
<td>52</td>
</tr>
</tbody>
</table>
Case 6-2017 — A 57-Year-Old Woman with Fatigue, Sweats, Weight Loss, Headache, and Skin Lesions

Paul A. Monach, M.D., Ph.D., John H. Stone, M.D., M.P.H., Amita Sharma, M.D., and Rosalynn M. Nazarian, M.D.
IgG4 disease: Serum tests

- IgG4 serum: >135mg/dL is elevated
- Elevated in 50% of pts with IgG4-RD
- Wide range of conditions with elevated IgG4

Wallace ZS et al. Arth Rheum 2015
<table>
<thead>
<tr>
<th>Final diagnoses</th>
<th>Number of cases (n=190)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite IgG4-RD</td>
<td>27</td>
</tr>
<tr>
<td>Probable IgG4-RD</td>
<td>38</td>
</tr>
<tr>
<td>Chronic sinusitis</td>
<td>46</td>
</tr>
<tr>
<td>Recurrent pneumonia</td>
<td>29</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>10</td>
</tr>
<tr>
<td>IgG deficiency</td>
<td>4</td>
</tr>
<tr>
<td>IgA deficiency</td>
<td>3</td>
</tr>
<tr>
<td>Common variable immunodeficiency</td>
<td>2</td>
</tr>
<tr>
<td>CD4 lymphocytopenia</td>
<td>1</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>11</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>3</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>2</td>
</tr>
<tr>
<td>Undifferentiated vasculitis</td>
<td>2</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>1</td>
</tr>
<tr>
<td>Churg-Strauss syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Behcet’s syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>1</td>
</tr>
<tr>
<td>Pancreato-biliary disease</td>
<td>9</td>
</tr>
<tr>
<td>Alcoholic pancreatitis</td>
<td>2</td>
</tr>
<tr>
<td>Alcoholic hepatitis</td>
<td>1</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>1</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Choledocholithiasis</td>
<td>1</td>
</tr>
<tr>
<td>Cholestatic hepatitis</td>
<td>1</td>
</tr>
<tr>
<td>Cholestatic hepatitis</td>
<td>1</td>
</tr>
<tr>
<td>Steatohepatitis</td>
<td>1</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>5</td>
</tr>
<tr>
<td>Interstitial pulmonary fibrosis</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary sarcoidosis</td>
<td>2</td>
</tr>
<tr>
<td>Bronchopulmonary aspergillosis</td>
<td>1</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>4</td>
</tr>
<tr>
<td>Invasive aspergillosis</td>
<td>1</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>1</td>
</tr>
<tr>
<td>Recurrent infection</td>
<td>1</td>
</tr>
<tr>
<td>Recurrent otitis media</td>
<td>1</td>
</tr>
<tr>
<td>Aortitis</td>
<td>3</td>
</tr>
<tr>
<td>Abdominal aortitis</td>
<td>2</td>
</tr>
<tr>
<td>Retroperitoneal fibrosis (asbestos)</td>
<td>1</td>
</tr>
<tr>
<td>Leukemia</td>
<td>2</td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>1</td>
</tr>
<tr>
<td>Chronic myelomonocytic leukemia</td>
<td>1</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>6</td>
</tr>
<tr>
<td>Chronic sialadenitis</td>
<td>1</td>
</tr>
<tr>
<td>Haemochromatosis</td>
<td>1</td>
</tr>
<tr>
<td>Hypereosinophilic syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Pachymeningitis (idiopathic)</td>
<td>1</td>
</tr>
<tr>
<td>Pompe disease</td>
<td>1</td>
</tr>
</tbody>
</table>
IgG4 RD: Serum tests

- Cutoff- 135 mg/dL
- Prozone phenomenon in up to 26% of pts
- Increasing cutoff to 270 mg/dL
  - decreased sensitivity to 35%
  - increased specificity to 90%
- Our patient: 301 mg/dL
IgG4-RD: Serum tests

• Wide variety of other changes *(varying frequency)*
  – Hypergammaglobulinemia
  – Hypocomplementemia
  – Eosinophilia

• Circulating plasmablasts may be better test
  – Flow cytometry *(cutoff 900/mL)*

Cutaneous IgG4-RD: Benign Mimics

Clinical

- Sarcoid
- Granuloma faciale
- Sjögren’s disease
- Cutaneous lymphoid hyperplasia
- EGPA
- Rosai-Dorfman
Cutaneous IgG4-RD: Benign Mimics

Clinical
- Sarcoid
- Granuloma faciale
- Sjögren’s disease
- Cutaneous lymphoid hyperplasia
- EGPA
- Rosai-Dorfman

Histopathological
- Cutaneous lymphoid hyperplasia
- Angiolymphoid hyperplasia with eosinophils
- Granuloma faciale
- Erythema elevatum diutinum
Pitfalls: Multicentric Castleman’s Disease

- Marked lymphadenopathy
- Much less fibrosis, glandular infiltration
- Thrombocytosis
- Elevated IL-6
- Elevated CRP

Courtesy of Ryanne Brown, MD, MBA
Cutaneous Castleman’s Disease

- Meets pathologic criteria
- Absent fibrosis, e/o hyper IL-6

Cutaneous lymphoid hyperplasia

- Cheuk W et al, 2009
  - 14 archival CLH cases
  - 2 w increased IgG4+ cells
  - Limited clinical info
Pitfalls: Malignant Mimics

Clinical
- MALT lymphoma
- Angioimmunoblastic T-cell lymphoma
- CTCL variants

Histopathological
- IgG4-restricted myeloma
- IgG4-restricted MZL

Pitfalls: Marginal Zone Lymphoma

- De Souza et al., 2017
  - 13% of cutaneous plasmacytic MZLs are IgG4
  - Light chain restriction
  - Systemic MZL
    - Lower IgG4 rate

- Orbital MALT lymphoma (clinical pitfall for IgG4RD
  - Light chain restriction
  - Clonality
IgG4-RD and Malignancy

- Malignancy 2.5x more common in IgG4-RD pts
  - 19% lymphoma
- Slightly different cohort
Challenging patients

http://discounicornss.tumblr.com/post/57403826324
Challenging patients

http://discounicornss.tumblr.com/post/57403826324
Diagnosis: Chronic actinic dermatitis
Diagnosis: Rosacea...for now
• 35 yo woman with proptosis, infiltrated plaques involving eyes, preauricular cheeks (parotid?)
Diagnosis: T-cell lymphoma

- Work in progress
Conclusions

1. IgG4 disease—varied morphologies, but esp think in clinical scenario with dermal nodules on face, neck, upper body
2. If thinking about CLH and pt has systemic sx, consider IgG4
3. Criteria are still evolving, but application of strict criteria probably best at present time (>100 IgG4+ cells/HPF, Ig4/IgG ratio >40%)
4. Serum IgG4 can be useful, but circulating plasmablasts may be better test
5. Thorough evaluation for malignancy
6. Beware of pitfalls!