IgG4-Related Disease

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Disclosures

I have no conflicts of interest to disclose.

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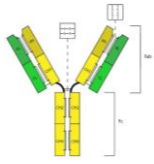
Outline

- Brief overview of IgG4-RD
- Case #1 – Classic example of IgG4-RD
- Case #2 – Lymph node involvement in IgG4-RD
- When to order IgG4/IgG IHC



OVERVIEW

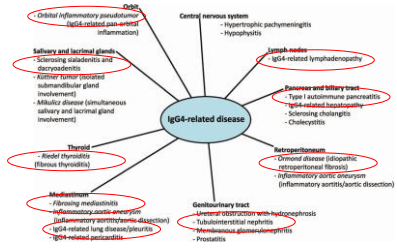
What is IgG4-Related Disease?

- A benign fibro-inflammatory disease with increased IgG4 plasma cells in the affected tissues
- Etiology and pathophysiology remain poorly understood
- Excellent response to steroids (or rituximab)
- Almost any tissue/organ system can be involved

Interesting Paradox

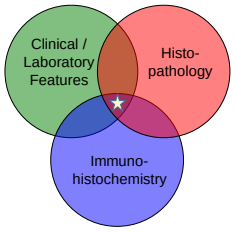
- Often underdiagnosed (lack of familiarity with the disease)
- Often overdiagnosed (avoid by remembering that IgG4-RD should almost never be your line diagnosis)

IgG4-RD: A "New" Disease that Explains Many "Old" Diseases



Weindorf SC, et al. *Arch Pathol Lab Med.* 2017;141:1476-1483

IgG4-RD: Diagnostic Triad



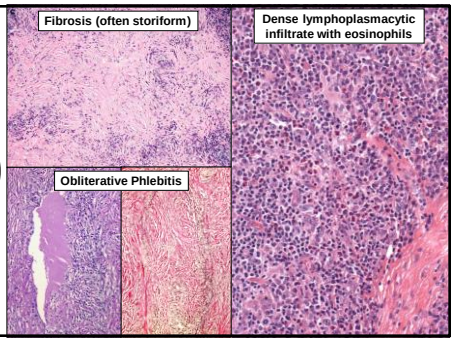
Clinical / Laboratory Findings

- Often older/elderly males
- Tumor-like enlargement of involved organs/tissues
- Lymphadenopathy, often generalized
- Usually no constitutional symptoms (no fever, weight loss, night sweats, etc.)

Clinical / Laboratory Findings

- Increased serum IgG4 (>135 mg/dL)
- Some patients have a normal serum IgG4 level

Histo-pathology



Immuno-histochemistry

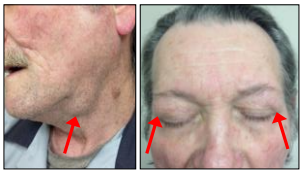
1. **Increased IgG4+ Plasma Cells**
   - Count 3 hpf with greatest number and average
   - Required number depends on the anatomic site (ranges from >10 to >200 per hpf)*
2. **IgG4/IgG ratio >40%**
   - Normal ratio is 5-10%
   - IgG stain: count the same 3 fields as the IgG4 stain

*Deshpande V, et al. *Mod Pathol.* 2012;25:1181-1192

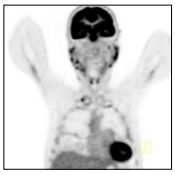
CASE #1

Case History

- 66M with soft tissue masses, lymphadenopathy
- No fever or weight loss
- Clinical concern for lymphoma



Bilateral enlargement of submandibular and lacrimal glands



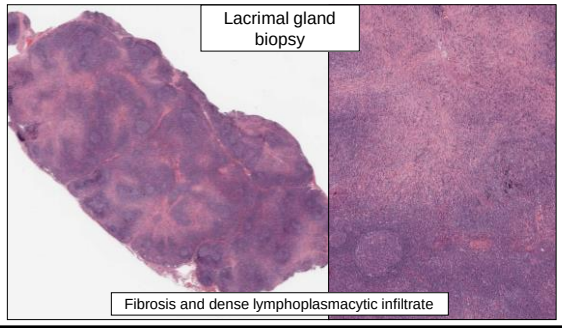
PET-avid:

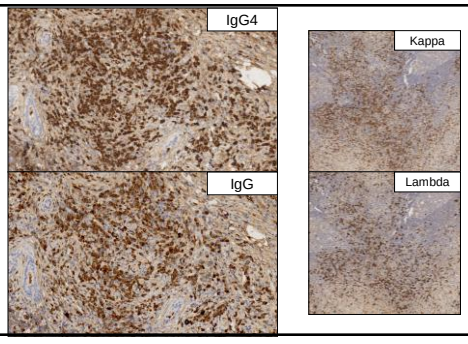
Submandibular, lacrimal, parotid glands

Multiple lymph nodes

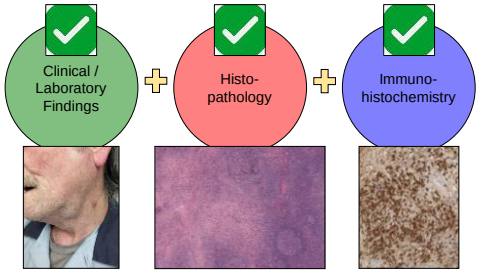
Thyroid, aorta, kidneys

Serum IgG4 = 600 mg/dL (normal <135 mg/dL)





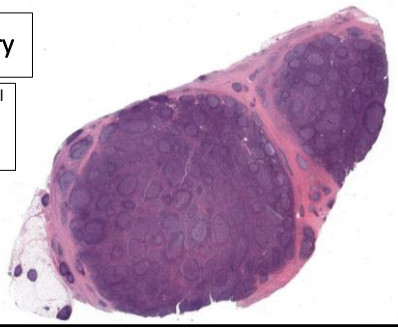
Diagnosis = IgG4-Related Disease

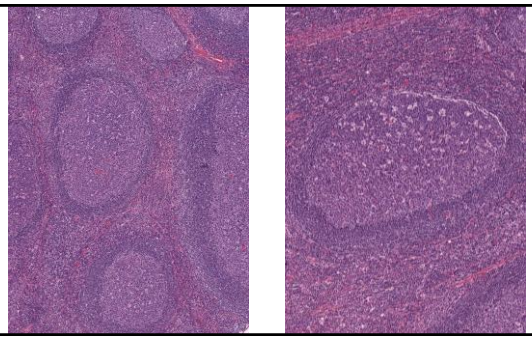


CASE #2

Case History

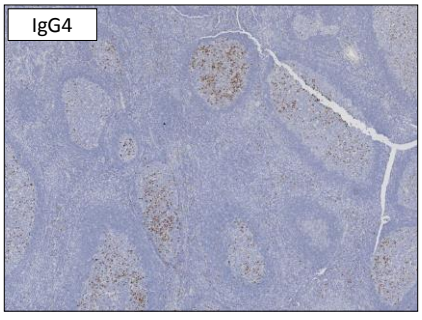
- 77M with cervical LAD for >1 year
- Flow cytometry negative

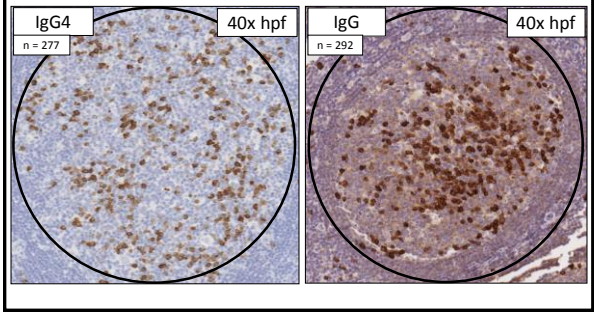




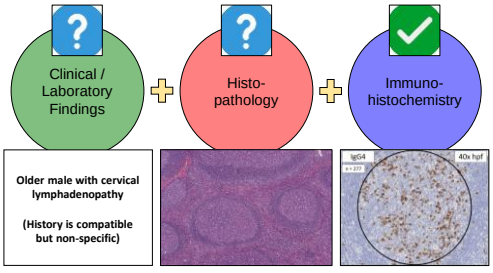
Differential Diagnosis

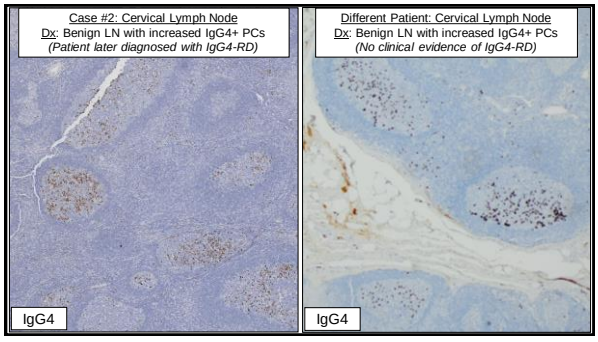
- Florid follicular hyperplasia
- IgG4-related disease
- Syphilis lymphadenitis
- Autoimmune lymphadenopathy





Diagnosis = Benign lymph node with follicular hyperplasia and increased IgG4+ plasma cells





IgG4-Related Lymphadenopathy

- In lymph nodes:
  - Negative IgG4/IgG stains exclude IgG4-related lymphadenopathy
  - Positive IgG4/IgG stains are not good predictors of IgG4-RD
- Increased IgG4+ plasma cells may be seen in:
  - Castleman disease
  - Rosai-Dorfman disease
- The 3 main histologic features of IgG4-RD (lymphoplasmacytic infiltrate, fibrosis, phlebitis) are not seen in lymph nodes

IgG4-Related Lymphadenopathy

5 Morphologic Patterns:

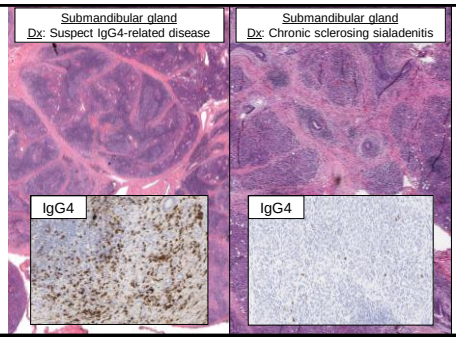
- Type I: Castleman disease-like
- Type II: Follicular hyperplasia
- Type III: Interfollicular expansion, often with increased immunoblasts
- Type IV: Progressive transformation of germinal centers (PTGC)
- Type V: Inflammatory pseudotumor-like

Cheuk W, et al. *Am J Surg Pathol.* 2008;32:671-681
Cheuk W, et al. *Semin Diagn Pathol.* 2012;29:226-234
Sato, et al. *Mod Pathol.* 2012;25:956-967

WHEN TO ORDER IgG4/IgG IHC

When to Order IgG4/IgG IHC

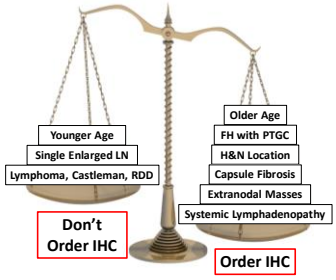
Tissues	Lymph Nodes
• Mass lesion with characteristic histopathology • Meeting IHC criteria is suggestive of IgG4-RD (still need clinical correlation)	



When to Order IgG4/IgG IHC

Tissues	Lymph Nodes
• Mass lesion with characteristic histopathology • Meeting IHC criteria is suggestive of IgG4-RD (still need clinical correlation)	• Can't rely on histopathology (aside from the LN being reactive) • Meeting IHC criteria is not a good predictor of IgG4-RD • Focus on other factors…

When to Order IgG4/IgG on Lymph Nodes



Take-Home Points

- The diagnosis of IgG4-RD requires clinical correlation
- Avoid an outright line diagnosis of IgG4-RD

- Non-LN Tissues:
  - Order IHC when the histopathology is compatible with IgG4-RD
  - Positive IHC is suggestive of IgG4-RD
- Lymph Nodes:
  - Much trickier…be judicious about ordering IHC
  - Positive IHC alone is not a good predictor of IgG4-RD