



**EMORY UNIVERSITY SCHOOL OF MEDICINE**  
Department of Pathology and Laboratory Medicine

**EMORY**


# IgG4-Related Disease

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**GAP**  
Georgia Association of Pathology

## Kyle Bradley, MD Disclosures

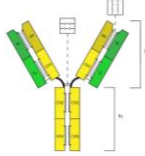
I have no conflicts of interest to disclose.

 @KyleBradleyMD

Emory University School of Medicine, Department of Pathology

## 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

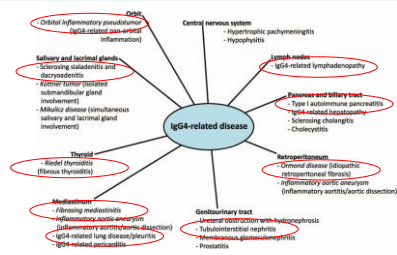
## What is IgG4-Related Disease?

- 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

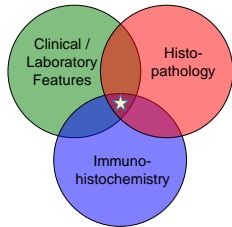


**Central node: IgG4-related disease**

- Orbit**
  - Orbital inflammatory pseudotumor (IgG4-related eye disease/inflammation)
- Central nervous system**
  - Hypertrophic pachymeningitis
  - Hypophysitis
- Lymph nodes**
  - IgG4-related lymphadenopathy
- Salivary and lacrimal glands**
  - Sclerosing sialadenitis and dacryoadenitis
  - Autoimmune dacryocystitis (involvement)
  - Mikulicz disease (simultaneous salivary and lacrimal gland involvement)
- Thyroid**
  - Riedel thyroiditis (Riedel thyroiditis)
- Mediastinum**
  - Fibrosing mediastinitis
  - Immunohistochemical overexpression (inflammation) (immunohistochemical overexpression)
  - IgG4-related lung disease (inflammation)
  - IgG4-related pericarditis
- Genitourinary tract**
  - Chronic interstitial nephritis/hypertrophic glomerulonephritis
  - Tubulointerstitial nephritis
  - Cholelithiasis
  - Prostatitis
- Retropneumonia**
  - Orbital disease (idiopathic, organometastatic fibrosis)
  - Inflammatory atrophic atelectasis (inflammatory atelectasis/benign dissection)
- Pancreas and biliary tract**
  - Type 1 autoimmune pancreatitis
  - IgG4-related hepatopathy
  - Sclerosing cholangitis
  - Cholecystitis

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

Fibrosis (often storiform)

Dense lymphoplasmacytic infiltrate with eosinophils

Obliterative Phlebitis

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

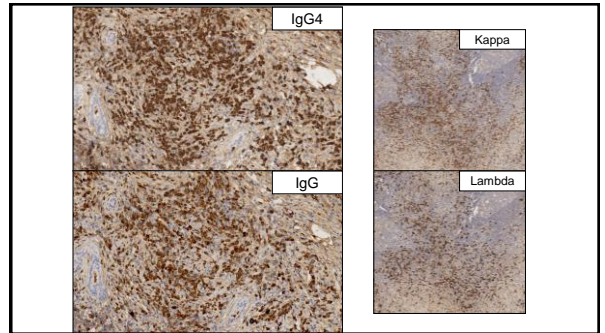
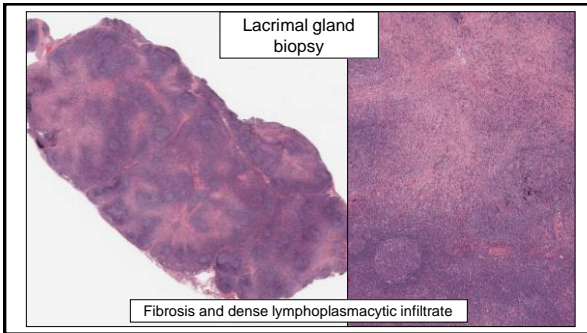


Bilateral enlargement of submandibular and lacrimal glands

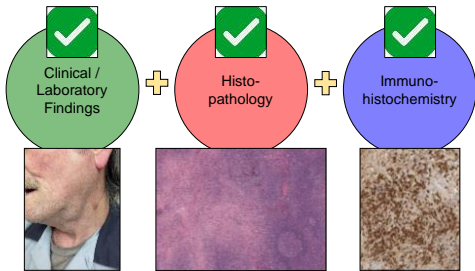
PET-avid:

Submandibular, lacrimal, parotid glands  
Multiple lymph nodes  
Thyroid, aorta, kidneys

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



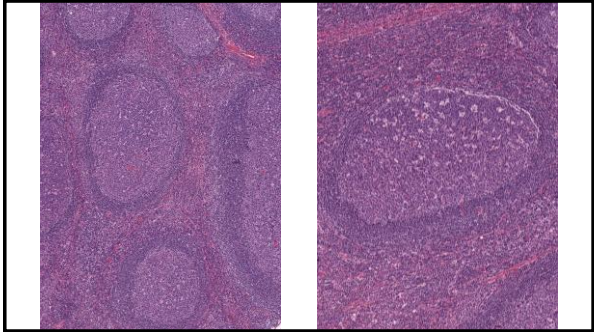
### Diagnosis = IgG4-Related Disease



CASE #2

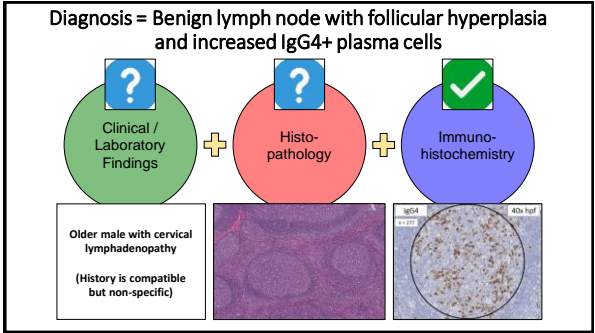
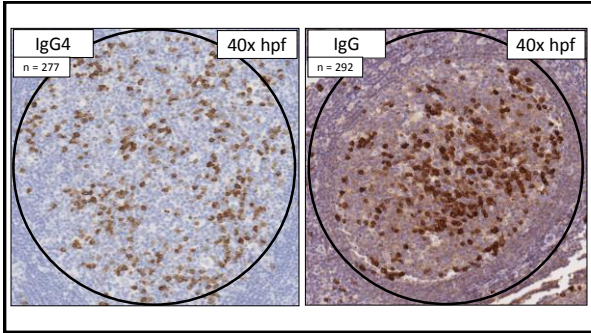
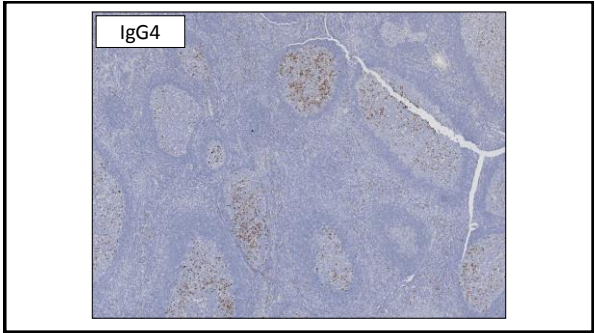
**Case History**

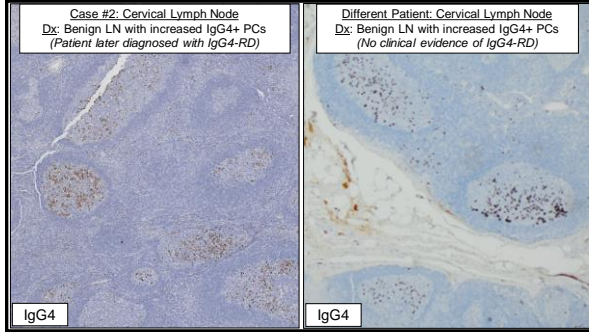
- 77M with cervical LAD for >1 year
- Flow cytometry negative



**Differential Diagnosis**

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





### 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:

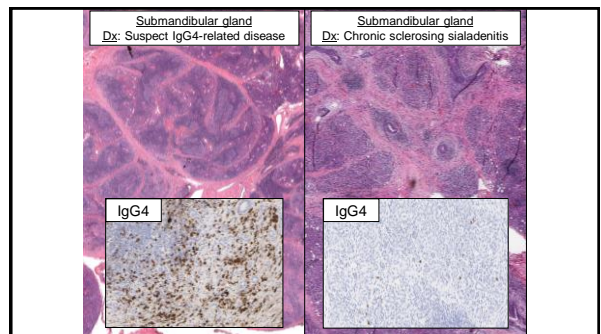
- **Type I:** Castleman disease-like
- **Type II:** Follicular hyperplasia
- **Type III:** Interfollicular expansion, often with increased immunoblasts
- **Type IV:** Progressive transformation of germinal centers (PTGC)
- **Type V:** Inflammatory pseudotumor-like

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
<ul style="list-style-type: none"> <li>• Mass lesion with characteristic histopathology</li> <li>• Meeting IHC criteria is suggestive of IgG4-RD (still need clinical correlation)</li> </ul>	<div style="border: 1px solid black; height: 100px; width: 100%;"></div>





## When to Order IgG4/IgG IHC

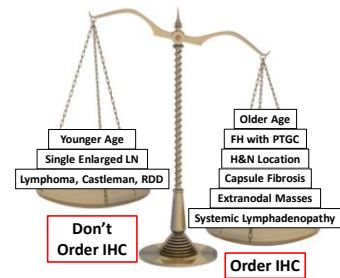
### Tissues

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

### Lymph Nodes

- 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

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