IgG4-related disease and lymphadenopathy

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Disclosures

- None

Outline

- Epidemiology & pathogenesis
- Clinical & laboratory findings
- Pathology of IgG4-related disease
- IgG4-related lymphadenopathy
- Differential diagnosis
- Lymphomas in IgG4-RD, and IgG4+ lymphomas
- Summary

IgG4-related disease

- A systemic sclerosing disease of uncertain etiology
- Often diagnostically challenging given it's rarity and overlap with other inflammatory processes
- A clinicopathologic entity with characteristic features that allow for diagnosis

Epidemiology

- Predominantly a disease of middle aged to elderly men[1]
  - Median age at diagnosis: 50-70 years
  - M:F ratio of 2-4:1
- Estimated incidence of about 0.3-1 per 100,000 people[2]

Pathophysiology[3]

- Initial studies demonstrating the utility of B cell depletion suggested a central role of activated B cells
- However, aberrant T cell activity is now favored to be the underlying immunological defect
  - IL-4 secreting Tfh cells are implicated in driving class switching of IgG4+ B cells and plasmablasts
  - Fibrosis is thought to be driven by cytokines from activated B cells, CD4+ cytotoxic T cells, and M2 macrophages
- The IgG4 molecule is a relatively inactive immunobulin subclass and it is hypothesized that the frequent IgG4+ plasma cells are a secondary phenomenon rather than intrinsically pathogenic

1. Wallace ZS, et al. Arthritis Rheumatol 2015
2. Uchida K, et al. Int J Rheumatol 2012
3. Perugino CA & Stone JH. Nat Rev Rheum 2020

Clinical features

- Subacute or chronic presentation
- Tumor-like mass or enlargement of one or more organs
  - Clinically visible mass
  - Signs of organ dysfunction, i.e. jaundice due to bile duct obstruction in IgG4-related pancreatitis
  - Orbit, salivary glands, and pancreatobiliary tract most common
  - Multifocal organ involvement in 30-60% of cases[1-3]
- Systemic symptoms are uncommon and include weight loss and weakness
- Clinically apparent lymphadenopathy reported in 25-75% of cases[1-2]

1. Wallace ZS, et al. Arthritis Rheumatol 2015
2. Zen Y & Nakanuma Y. Am J Surg Pathol 2010
3. Martinez-Valle F, et al. Autoimmun Rev 2017
4. Uchida K, et al. Int J Rheumatol 2012

Laboratory findings

- Elevated serum IgG4
  - An imperfect marker - issues with sensitivity and specificity.
  - Up to half of patient's with biopsy proven and clinically active IgG4-RD may have normal serum IgG4.[1]
  - Only 10% of patients with elevated serum IgG4 levels were diagnosed with IgG4.[2]

1. Wallace ZS, et al. Arthritis Rheumatol 2015
2. Ebbo M, et al. Int J Rheumatol 2012

Laboratory findings

Other common but non-specific laboratory abnormalities[1,2]

- Peripheral eosinophilia
- Polyclonal hypergammaglobulinemia
- Elevated serum IgE
- Elevated CRP
- Hypocomplementemia

1. Della-Torre E, et al. Allergy 2014
2. Stone JH, et al. Mayo Clin Proc 2015

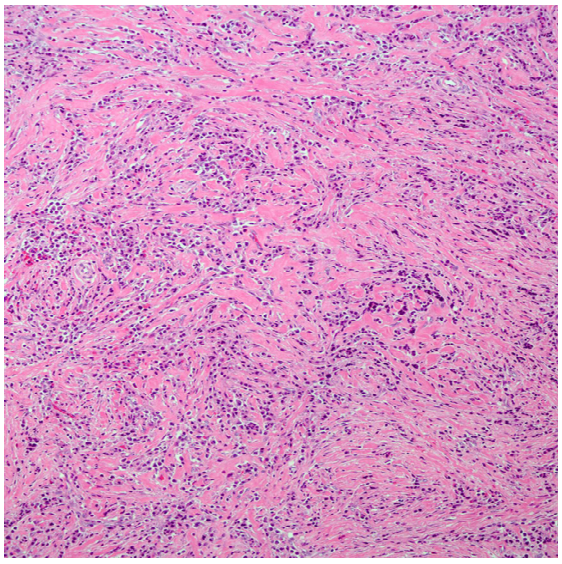
Histopathology

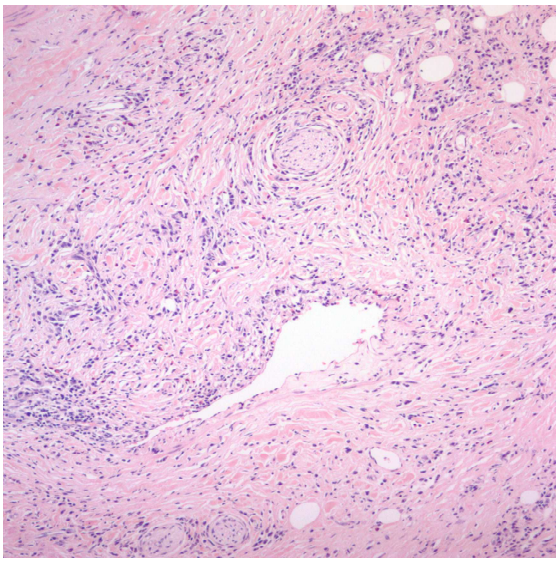
1. Increased IgG4+ plasma cells and an increased IgG4/IgG plasma cell ratio (>40%)
   - Useful stains:
     - IgG, IgG4
     - CD138, kappa, lambda to establish polyclonality
2. Storiform fibrosis
3. Obliterative phlebitis
   - Useful stain: elastic stain

- Other: admixed eosinophils

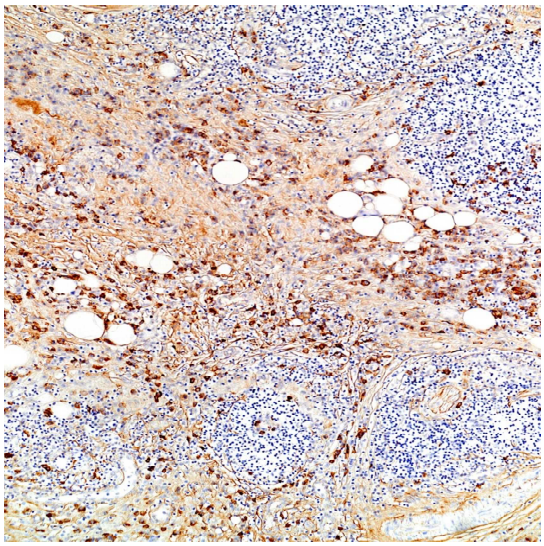
Deshpande V, et al. Mod Pathol 2012
Bledsoe JR, et al. APMIS 2018

Storiform fibrosis

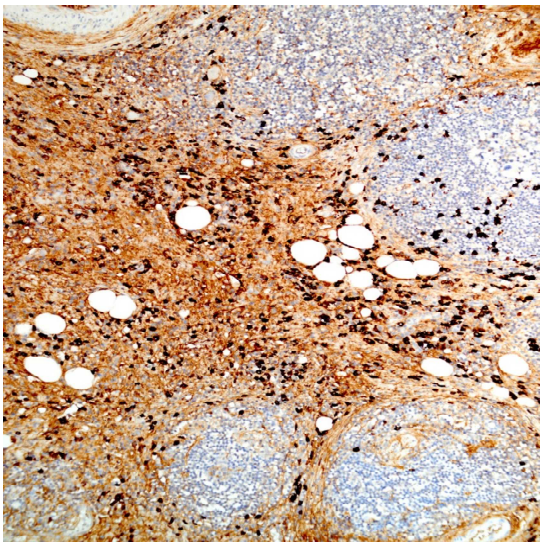




IgG4



IgG



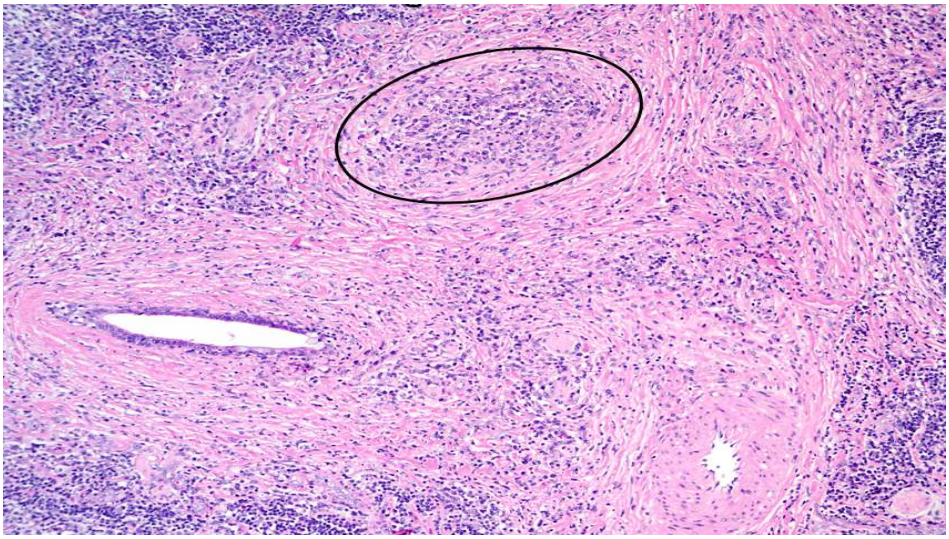
Bledsoe JR, et al. APMIS 2018

Method of calculating IgG4/IgG ratio

- Count three HPF (40x) with the highest number of IgG4+ plasma cells and take the average
- Count the same three HPF for IgG and take the average
- Calculate the IgG4/IgG ratio using the average counts

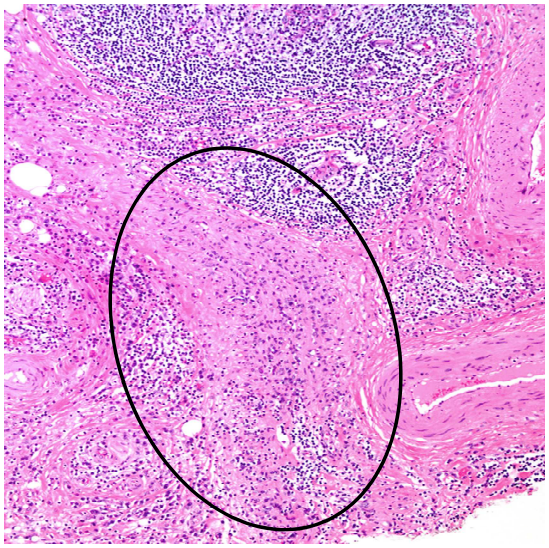
Deshpande V, et al. Mod Pathol 2012

Obliterative phlebitis

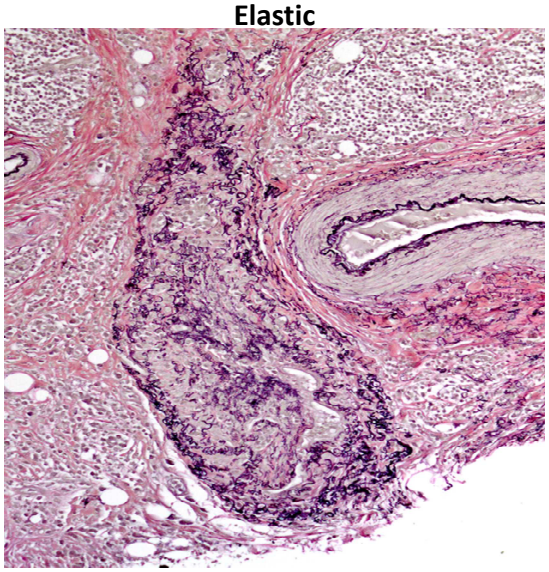


Bledsoe JR, et al. APMIS 2018

Obliterative phlebitis

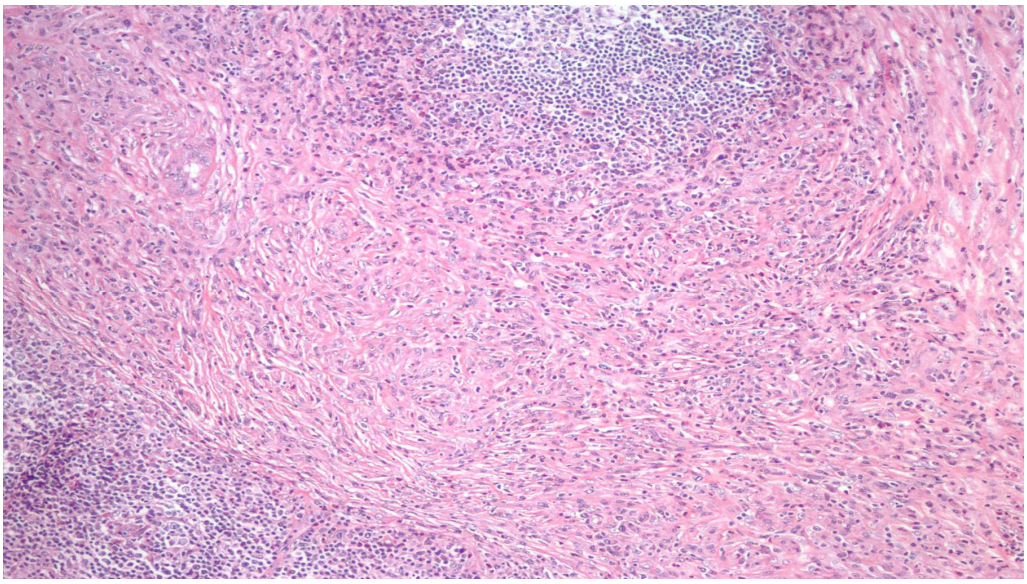


Elastic



Bledsoe JR, et al. APMIS 2018

Eosinophils



Diagnostic Terminology

1. Histologically highly suggestive of IgG4-RD
2. Probable histologic features of IgG4-RD
3. Insufficient histopathological evidence of IgG4-RD

Characteristic histological features
1. Dense lymphoplasmacytic infiltrate
2. Fibrosis, usually storiform in character
3. Obliterative phlebitis

Cases with ≥ 2 pathology features | Cases with 1 pathology feature

	Numbers of IgG4+ plasma cells (/hpf)		Ref
Meningus	>10	>10	55
Lacrimal gland	>100	>100	28
Salivary gland	>100	>100	17,34
Lymph node	>100	>50	27
Lung (surgical specimen)	>50	>50	10,35
Lung (biopsy)	>20	>20	10,35
Pleura	>50	>50	6
Pancreas (surgical specimen)	>50	>50	30,32
Pancreas (biopsy)	>10	>10	56,57
Bile duct (surgical specimen)	>50	>50	49
Bile duct (biopsy)	>10	>10	58,59
Liver (surgical specimen)	>50	>50	49
Liver (biopsy)	>10	>10	12,60
Kidney (surgical specimen)	>30	>30	15
Kidney (biopsy)	>10	>10	61
Aorta	>50	>50	16,51,52
Retroperitoneum	>30	>30	8
Skin	>200	>200	62,63

IgG4+/IgG+ plasma cell ration >40% a mandatory for histological diagnosis of IgG4-RD

Green boxes = Histologically highly suggestive of IgG4-RD
Orange boxes = Probable histological features of IgG4-RD

Deshpande V, et al. Mod Pathol 2012

Diagnostic Terminology

- Cases classified as 'histologically highly suggestive of IgG4-RD' are much more likely to be truly IgG4-RD than the other categories
- Definitive diagnosis of IgG4-RD involves correlation of histopathologic features with clinical and laboratory features, particularly serum IgG4 and imaging studies showing mass-like enlargement of one or more organs
- In most cases a comment is warranted that correlation with clinical and imaging findings is recommended for further evaluation of IgG4-RD

Bateman AC and Culver EL. Histopathology 2017
Deshpande V, et al. Mod Pathol 2012

Lymphadenopathy in IgG4-RD

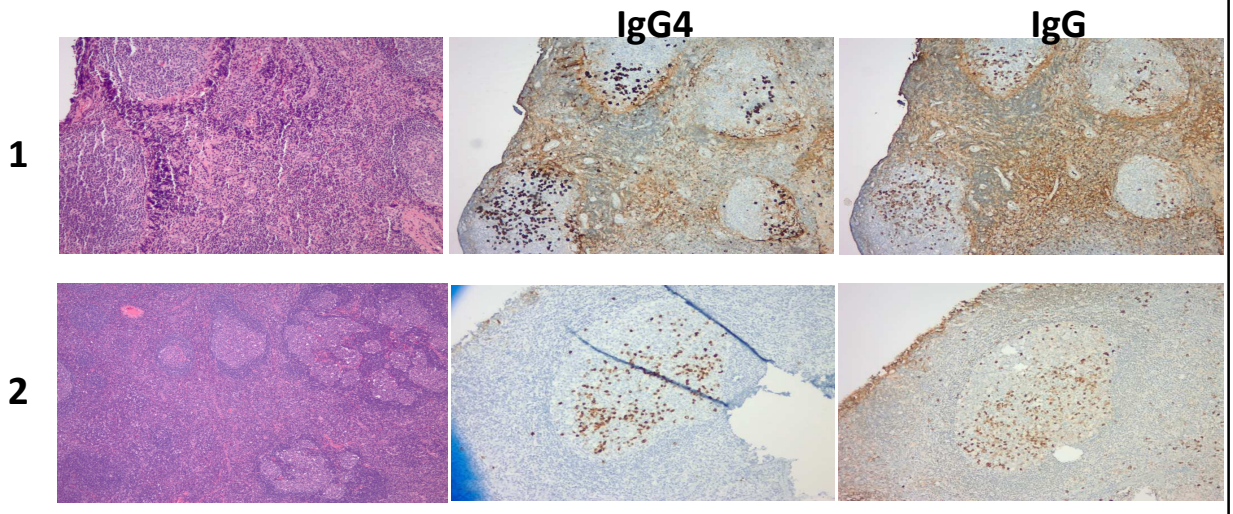
- Many patients with IgG4-RD, including known and undiagnosed IgG4-RD, have lymphadenopathy, which may be clinically suspicious for malignancy/lymphoma and lead to lymph node sampling

Terminology

"IgG4-related lymphadenopathy"

- Enlarged lymph nodes in a person with established IgG4-RD
- This term should not be used in patients without established IgG4-RD who have increased IgG4+ plasma cells in lymph nodes
- Increased IgG4+ plasma cells and an increased IgG4/IgG plasma cell ratio are not specific for IgG4-RD in lymph nodes
  - Castleman disease
  - Rosai-Dorfman disease
  - Rheumatoid arthritis
  - ALPS, JIA, other chronic inflammatory diseases
  - Lymph nodes in patients with carcinoma and other neoplasms

Two lymph nodes from patients without IgG4-RD



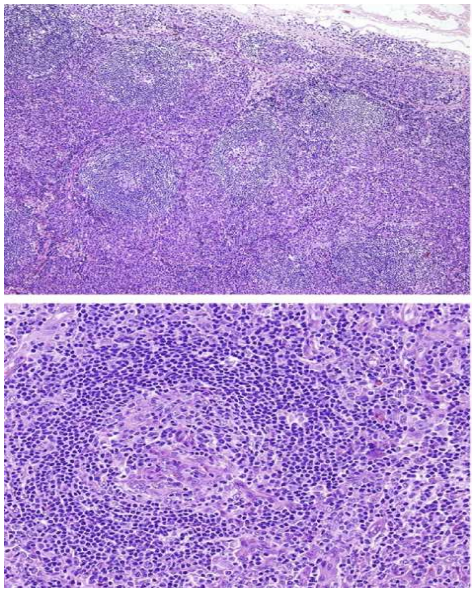
IgG4-related lymphadenopathy

Patients with known IgG4-related disease

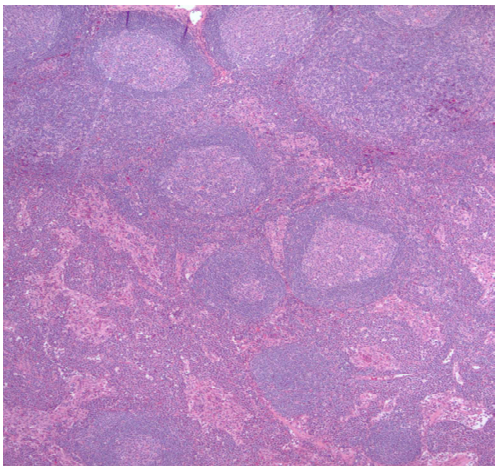
- Five described patterns, all with increased IgG4+ plasma cells
  1. Follicular hyperplasia pattern
  2. Castleman disease-like pattern
  3. **Interfollicular expansion pattern**
  4. PTGC-like pattern
  5. **Inflammatory pseudotumor-like pattern**
- Issue: these morphologic patterns are largely not specific for IgG4-related disease

Cheuk W and Chan JKC. Semin Diagn Pathol 2012
Bledsoe JR, et al. Am J Surg Pathol 2021

Castleman disease-like Pattern

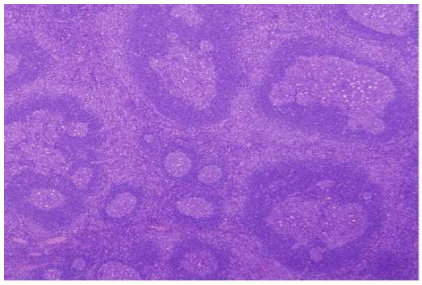


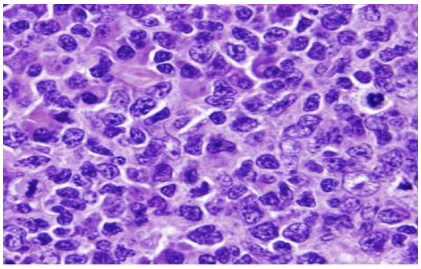
Follicular Hyperplasia Pattern

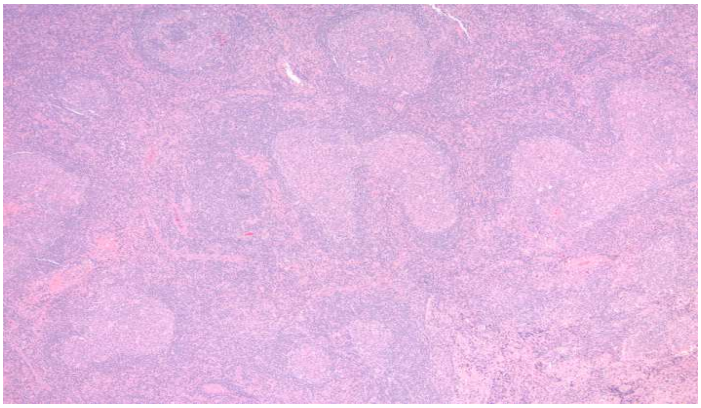


Cheuk W and Chan JKC. Semin Diagn Pathol 2012
Bledsoe JR, et al. Am J Surg Pathol 2021

PTGC-like Pattern

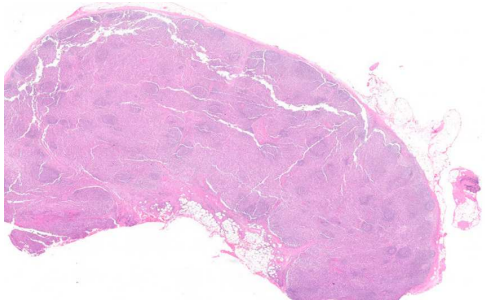


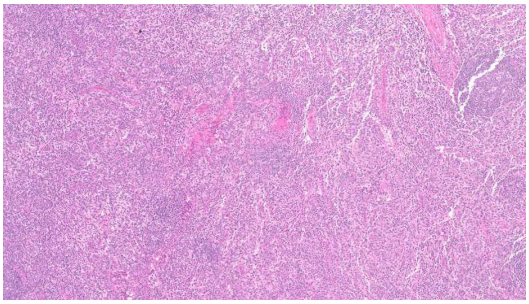


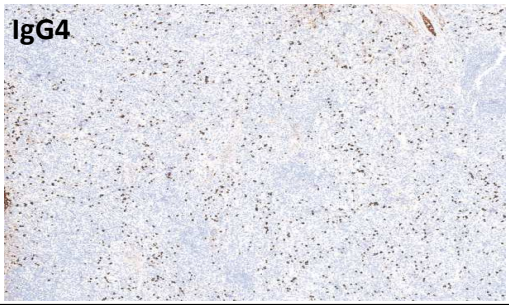


Cheuk W and Chan JKC. Semin Diagn Pathol 2012
Bledsoe JR, et al. Am J Surg Pathol 2021

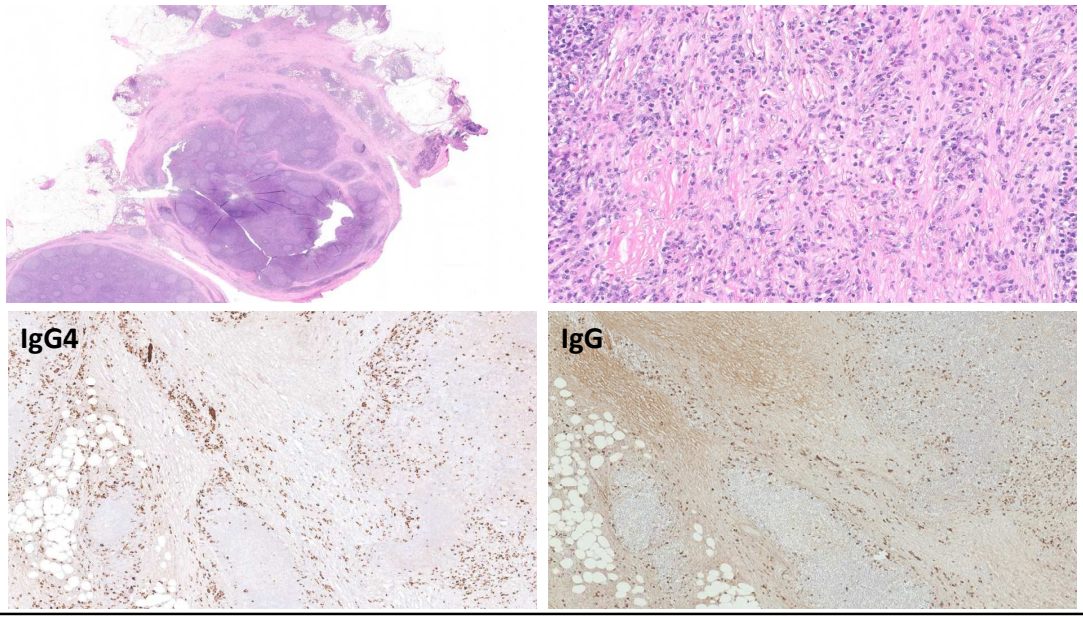
Interfollicular Expansion Pattern







Inflammatory Pseudotumor Pattern

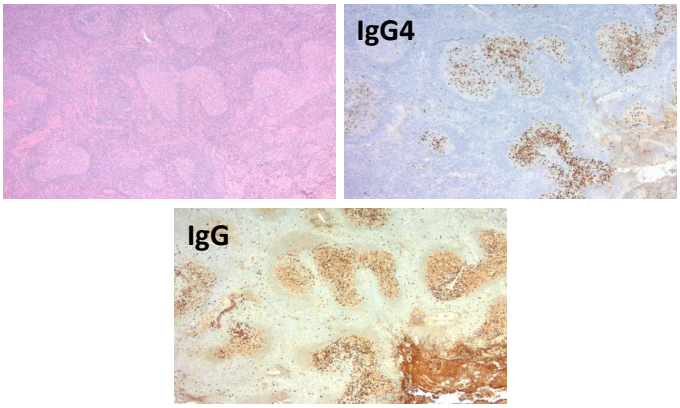


IgG4-related lymphadenopathy

- Issues:
  1. Follicular hyperplasia, Castleman-disease-like changes, PTGC, and interfollicular expansion are relatively common morphologies in non-specific causes of lymphadenopathy
  2. Increased IgG4+ plasma cells and IgG4/IgG ratio in lymph nodes are not specific for IgG4-RD
- Question: Which patterns of lymphadenopathy are more specific for true IgG4-related disease?

Non-specific patterns of lymphadenopathy

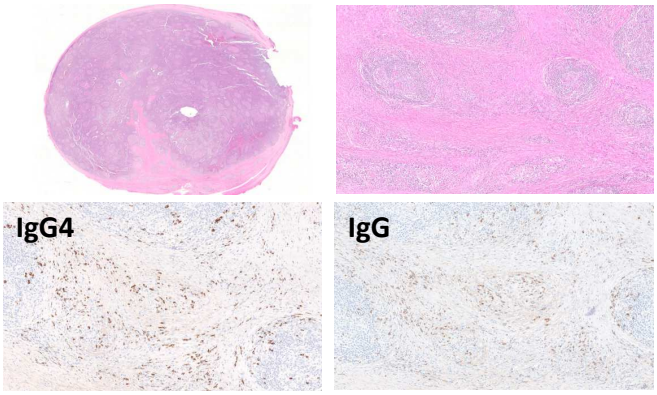
- In general FH, PTGC, and CD-like patterns are not specific
- An isolated increase in IgG4+ plasma cells and IgG4/IgG ratio within germinal centers is not specific
  - See more frequently in control cases than IgG4-RD
  - Usually seen in the context of follicular hyperplasia, PTGC, or CD-like patterns



Bledsoe JR, et al. Am J Surg Pathol 2021

Specific patterns of IgG4-related lymphadenopathy

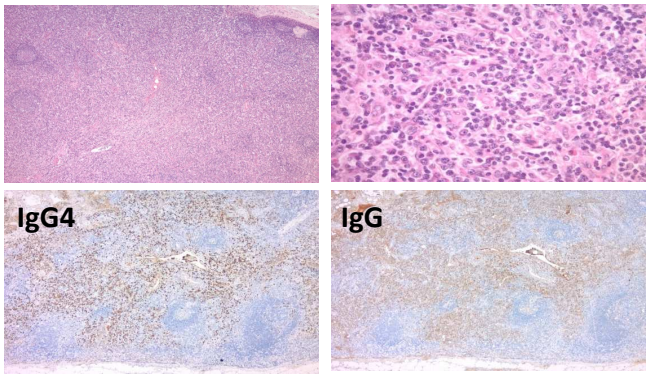
- Features highly specific for IgG4-RD:
  - Increased IgG4+ plasma cells and IgG4/IgG ratio in areas of nodal fibrosis or “inflammatory pseudotumor-like pattern” ($p<0.0001$)
  - Specificity: 98%
  - Sensitivity: 31%



Bledsoe JR, et al. Am J Surg Pathol 2021

Specific patterns of IgG4-related lymphadenopathy

- Features highly specific for IgG4-RD:
  - Increased IgG4+ plasma cells and IgG4/IgG ratio in extrafollicular zones or “interfollicular expansion pattern” ($p<0.0001$)
  - Specificity 97%
  - Sensitivity 51%

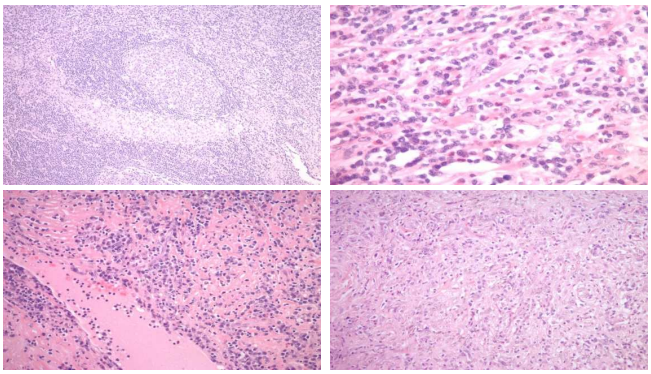


Bledsoe JR, et al. Am J Surg Pathol 2021

IgG4-related lymphadenopathy

Other useful features

- Perifollicular granulomas
- Eosinophils admixed with IgG4+ plasma cells
- Phlebitis
- Storiform fibrosis



Differential Diagnosis of IgG4-RD

Table 1: Pathologic differential diagnosis of IgG4-RD

- Infections
  - Bacterial
  - Mycobacterial
  - Viral
  - Spirochetal - e.g. syphilis
  - Infections involving specific sites:
    - Aortitis
    - Otitis media/mastoiditis
- Tumors
  - Inflammatory myofibroblastic tumor
  - Inflammatory infiltrate in background of various visceral tumors
- Lymphoproliferative disorders
  - MALT lymphoma with plasmacytic differentiation
  - Plasma cell neoplasm
- Inflammatory/Autoimmune disorders
  - Many sites
    - Multicentric Castleman disease
    - Rosai-Dorfman disease
    - Sarcoidosis
    - ANCA-associated vasculitis
      - Granulomatosis with polyangiitis
      - Eosinophilic granulomatosis with polyangiitis
    - Inflammatory pseudotumor
  - Hepatobiliary tract
    - Primary sclerosing cholangitis
    - Type 2 autoimmune pancreatitis
    - Follicular cholangitis
  - Orbit/Salivary glands
    - Sjögren syndrome
  - Eosinophilic angiocentric fibrosis
    - Kimura disease
    - Angiolymphoid hyperplasia with eosinophilia
  - IgG4-related sialadenitis
    - Chronic sialadenitis, NOS

Bledsoe JR, et al. APMIS 2018

Differential diagnosis

Inflammatory Myofibroblastic Tumor

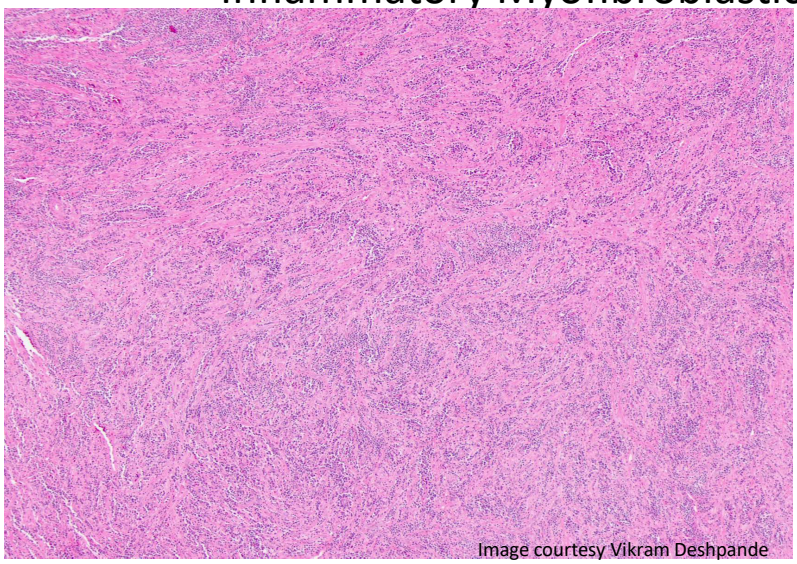
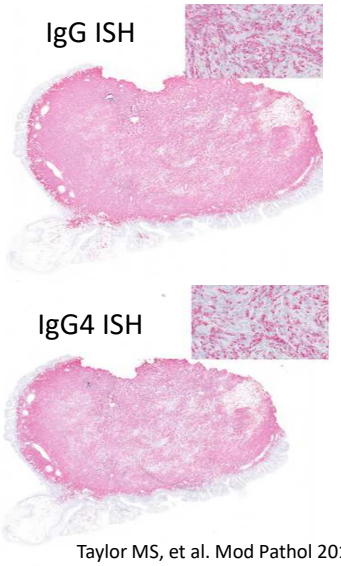


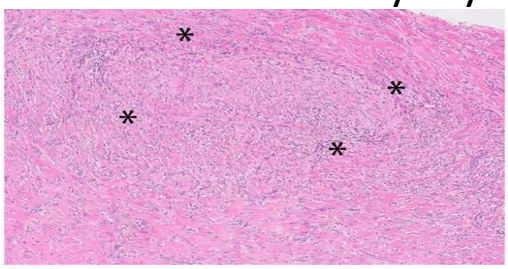
Image courtesy Vikram Deshpande

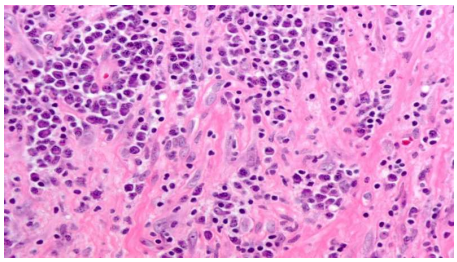


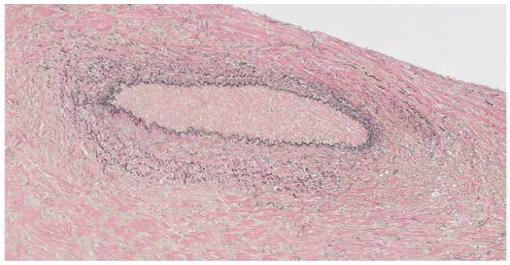
Taylor MS, et al. Mod Pathol 2019

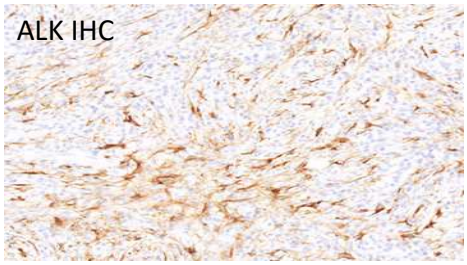
Differential diagnosis

Inflammatory Myofibroblastic Tumor







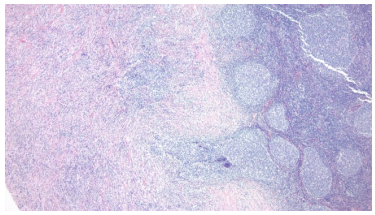


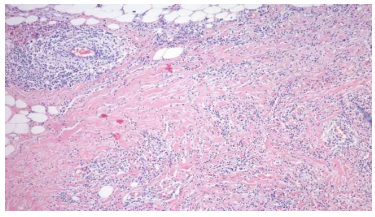
Taylor MS, et al. Mod Pathol 2019

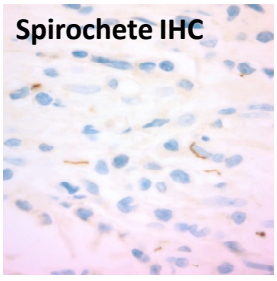
Differential diagnosis

Syphilitic lymphadenitis

- Fibrosis, plasmacytosis, phlebitis
- IgG4+ plasma cells usually not increased, but may rarely be[1]
- Spirochete IHC or silver stain useful







1. Tse JY, et al. Mod Pathol. 2018

Pediatric IgG4-related disease

- Very rare, <50 cases reported
- Median age of 11-13 years
- Possible slight female preponderance
- Elevated serum IgG4 in 70-80%
- 40-50% with orbital disease, ~20% with hepatobiliary, ~10% with salivary gland
- Good response to prednisone or rituximab in most cases
- Pediatric IgG4-related lymphadenopathy: most reports are in patients without extranodal IgG4-RD, consist of increased intrafollicular IgG4+ cells, and probably are not true IgG4-RD

Karim et al. Pediatric Rheumatology 2016.
Martin-Nares et al. ACR/ARP abstract 2019.

IgG4, IgG4-RD, and lymphoma

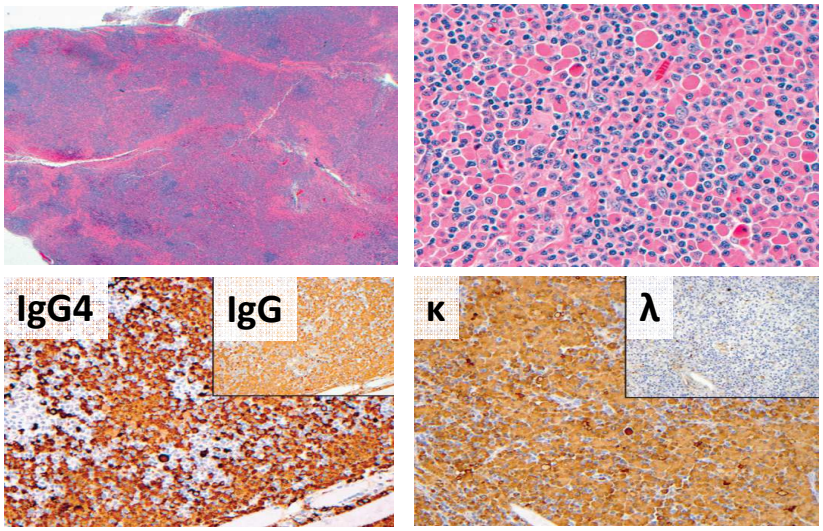
Two categories of lymphoma cases to consider

1. Lymphomas/plasma cell neoplasms that express IgG4
   - B-cell lymphomas with plasmacytic differentiation, primarily MALT lymphomas[1]
   - **Does not indicate concurrent or pre-existing IgG4-RD**
   - **May mimic IgG4-RD** - clonality assessment of plasma cells by kappa/lambda staining is recommended in all cases where IgG4-RD is considered
   - **Serum IgG4 may be elevated** – clonal on SPEP/IFE
   - IgG4+ MALT lymphomas are common in the:
     - Meninges/dura: 6/13 (33%) of cases were IgG4+. None had IgG4-RD[2]
     - Skin: 19/49 (39%) of cases were IgG4+. None had IgG4-RD[3]
     - Often have prominent IgG4+ Mott cells[1,2]
   - IgG4+ plasma cell myeloma
     - 6 cases, similar features as non-IgG4+ myeloma but a higher rate of plasmablastic morphology. None had IgG4-RD[4]

1. Bledsoe JR, et al. AJCP 2017
2. Venkataraman G, et al. Mod Pathol. 2011
3. Brenner I, et al. Mod Pathol. 2013
4. Geyer JT, et al. Mod Pathol 2014

85 year old man with an orbital mass

IgG4+ MALT lymphoma w/ plasmacytic differentiation



Bledsoe JR, et al. AJCP 2017

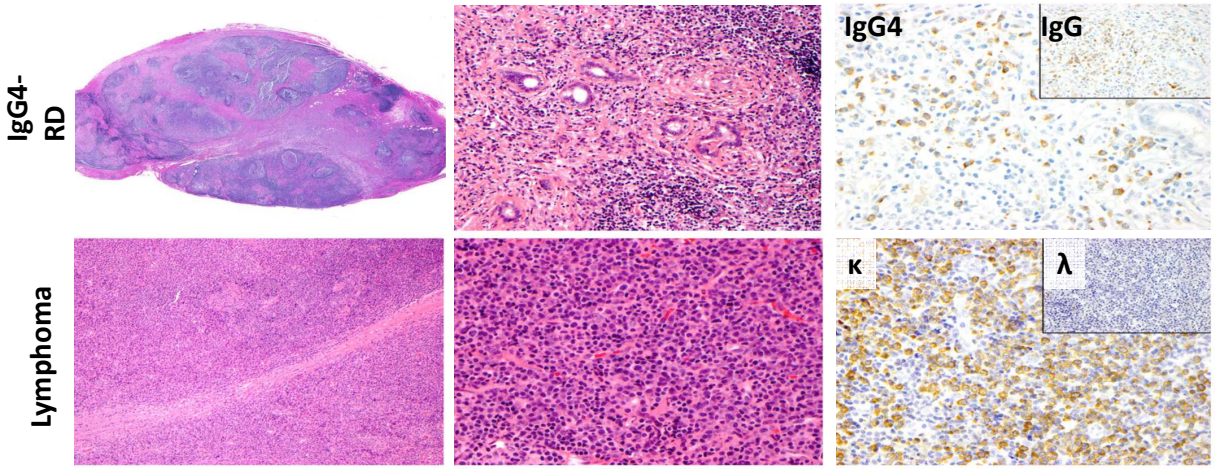
IgG4, IgG4-RD, and lymphoma

Two categories of lymphoma cases to consider

2. Lymphomas that occur in people with known IgG4-related disease[1]
   - Some studies have suggested that patients with IgG4-RD have an increased risk of developing lymphoma[1,2]
   - However, a definitive clonal relationship between IgG4-RD infiltrate and subsequent lymphoma has never been proven
   - **Most of such lymphomas do not express IgG4**
   - Predominantly MALT lymphomas or DLBCL

1. Bledsoe JR, et al. Virchows Archiv 2018
2. Cheuk W, et al. Am J Surg Pathol 2008

A 33 year old woman with a history of IgG4-related dacryoadenitis, who developed EMZL of the contralateral lacrimal gland 11 years later



Bledsoe JR, et al. Virchows Archiv 2018.

IgG4, IgG4-RD, and lymphoma

Evidence to suggest an etiologic link between IgG4-RD and lymphoma:[1,2]

- Some lymphomas occur at the site of IgG4-RD involvement
- Some patients have intervening IgG4-related lymphadenopathy – suggesting chronic antigenic stimulation/lymphoproliferation
- Rare cases of IgG4+ MALT lymphoma occur in patients with IgG4-related disease
- Oligoclonal expansions of monotypic IgG4+ plasma cells have been described in lymph nodes of patients with and without IgG4-RD[1]

1. Bledsoe JR, et al. AJCP 2017
2. Bledsoe JR, et al. Virchows Archiv 2018

Summary

Take home points:

- IgG4-related disease has characteristic histopathologic features but diagnosis requires clinical and laboratory correlation
- Increased IgG4+ plasma cells ≠ IgG4-RD
- When you consider the diagnosis of IgG4-RD, excluding an IgG4+ lymphoma is prudent
  - Clonality assessment using kappa/lambda, SPEP/IFE, molecular testing
- Increased IgG4+ plasma cells in a lymph node are non-specific unless in fibrosis or diffusely increased in extrafollicular zones
- In most cases a comment is warranted that correlation with clinical, laboratory, and imaging findings is recommended for further evaluation for IgG4-related disease

References

Bateman AC and Culver EL. IgG4-related disease-experience of 100 consecutive cases from a specialist centre. Histopathology 2017;70(5):798-813

Bledsoe JR, et al. IgG4-related disease: review of the histopathologic features, differential diagnosis, and therapeutic approach. APMIS 2018;126:459-476.

Bledsoe JR, et al. Atypical IgG4+ plasmacytic proliferations and lymphomas – characterization of 11 cases. AJCP 2017;148:215-235

Bledsoe JR, et al. Lymphomas in IgG4-related disease: clinicopathologic features in a Western population. Virchows Archiv 2018;472(5):839-852.

Bledsoe JR, et al. IgG4-related lymphadenopathy – A comparative study of 41 cases reveals distinctive histopathologic features. Am J Surg Pathol 2021;45(2):178-192.

Brenner I, et al. Primary cutaneous marginal zone lymphomas with plasmacytic differentiation show frequent IgG4 expression. Mod Pathol. 2013;26(12):1568-1576.

Cheuk W and Chan JKC. Lymphadenopathy of IgG4-related disease: an underdiagnosed and overdiagnosed entity. Semin Diagn Pathol 2012;29:226-234.

Cheuk W, Yuen HKL, Chan ACL, Shih LY, Kuo TT, Ma MW, Lo YF, Chan WK, Chan JKC. Ocular adnexal lymphoma associated with IgG4+ chronic sclerosing dacryoadenitis: a previously undescribed complication of IgG4-related sclerosing disease. Am J Surg Pathol 2008;32(8):1159–1167.

Ebbo M, et al. Pathologies associated with serum IgG4 elevation. Int J Rheumatol 2012;2012:602809

Della-Torre E, et al. Prevalence of atopy, eosinophilia, and IgE elevation in IgG4-related disease. Allergy 2014;69:269-272.

Deshpande V, et al. Consensus statement on the pathology of IgG4-related disease. Mod Pathol 2012;25:1181-92.

References

Geyer JT, et al. IgG4 plasma cell myeloma: new insights into the pathogenesis of IgG4-related disease. Mod Pathol 2014;27:375-381

Karim F, et al. IgG4-related disease: a systemic review of this unrecognized disease in pediatrics. Pediatric Rheumaology. 2016;14:18.

Martin-Nares E, et al. Juvenile-onset IgG4-related disease: a systematic review. 2019 ACR/ARP annual meeting abstract.

Martinez-Valle F, et al. IgG4-related disease: evidence from six recent cohorts. Autoimmune Rev 2017;16:168-172.

Perugino CA & Stone JH. IgG4-related disease: an update on pathophysiology and implications for clinical care. Nat Rev Rheum. 2020;16:702-714.

Stone JH, et al. Diagnostic approach to the complexity of IgG4-related disease. Mayo Clin Proc 2015;90:927-39.

Taylor MS, et al. Morphologic overlap between inflammatory myofibroblastic tumor and IgG4-related disease: lessons from next-generation sequencing. Mod Pathol 2019;43(3):314-324.

Tse JY, et al. Syphilis of the aerodigestive tract. Am J Surg Pathol 2018;42(4):472-478.

Uchida K, et al. Prevalence of IgG4-related disease in Japan based on nationwide survey in 2009. Int J Rheumatol 2012;2012:358371.

Wallace ZS, et al. IgG4-related disease: clinical and laboratory features in one hundred twenty-five patients. Arthritis Rheumatol 2015;67:2466-75.

Venkataraman G, et al. Marginal zone lymphomas involving meningeal dura: possible link to IgG4-related diseases. Mod Pathol. 2011;24(3):355-366.

Zen Y & Nakanuma Y. IgG4-related disease: a cross-sectional study of 114 cases. Am J Surg Pathol 2010;34:1812-1819.

Questions?