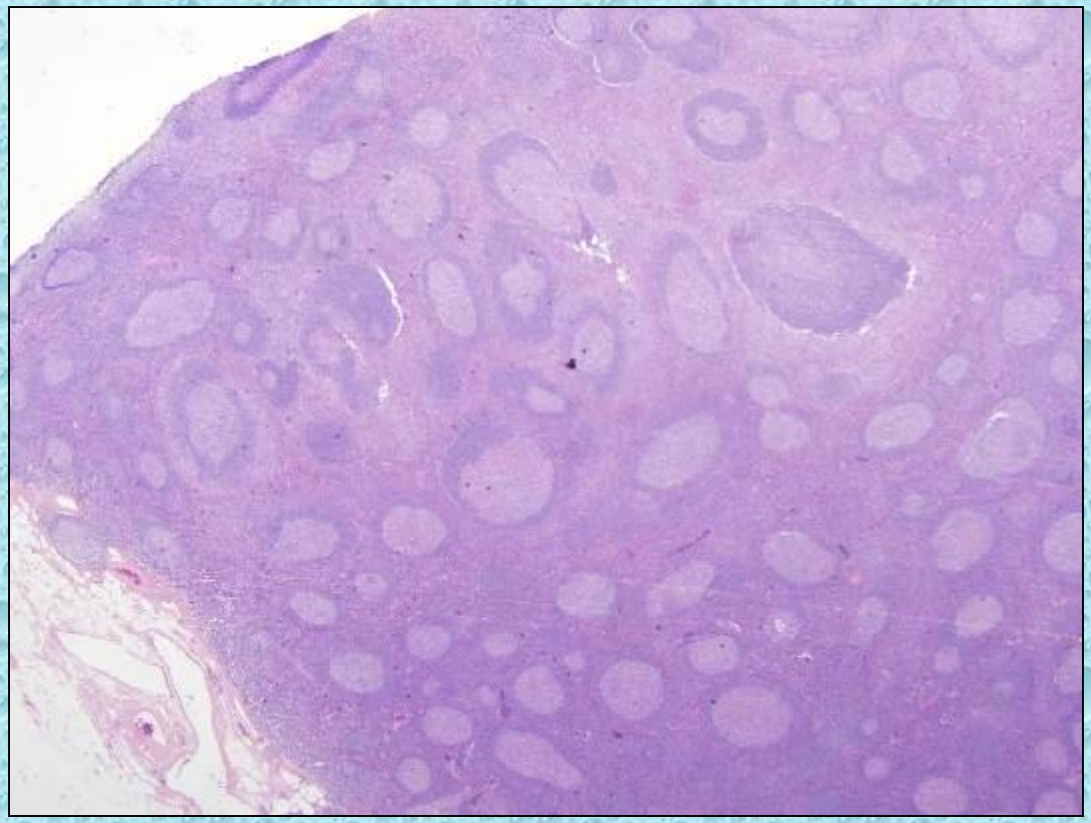
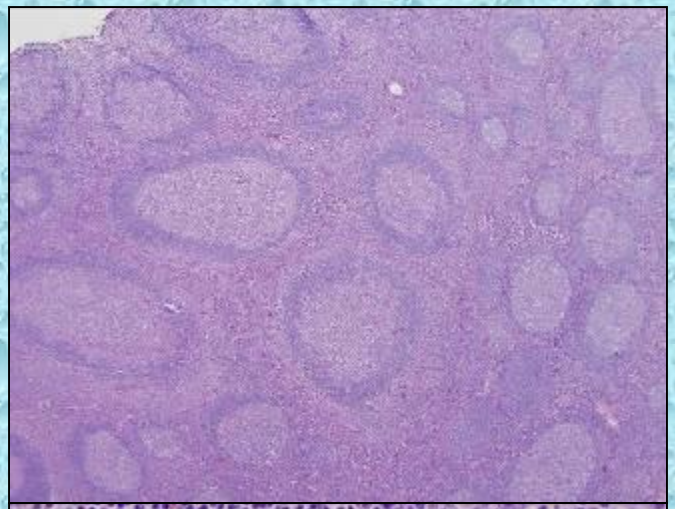
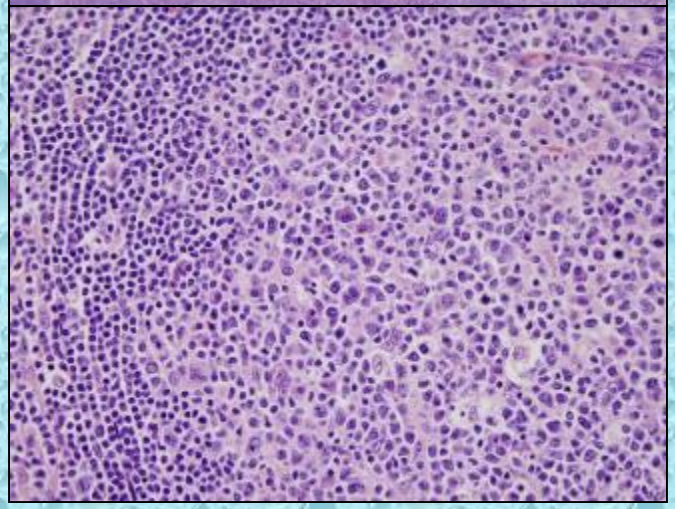
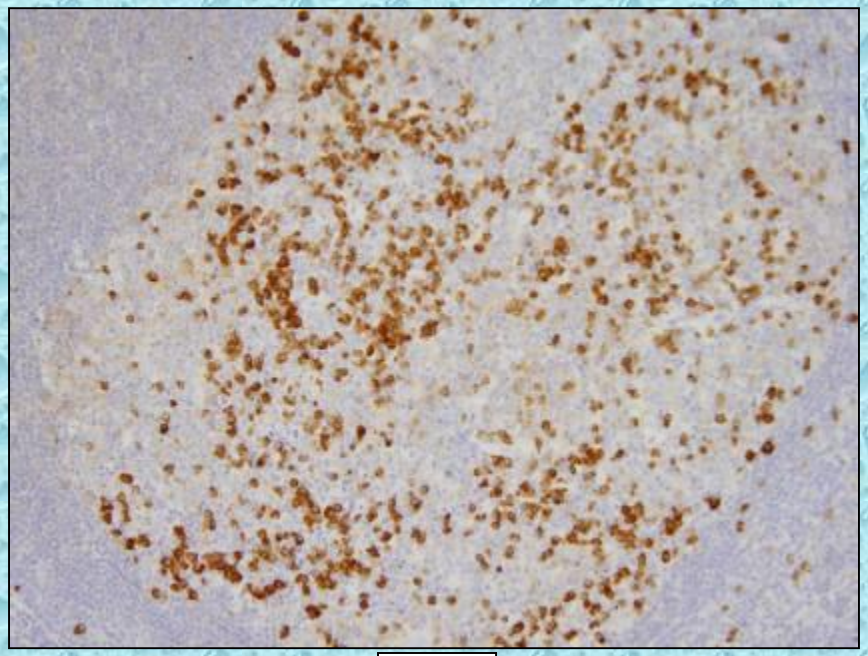
61 y/o male, generalized adenopathy. Axillary LN.



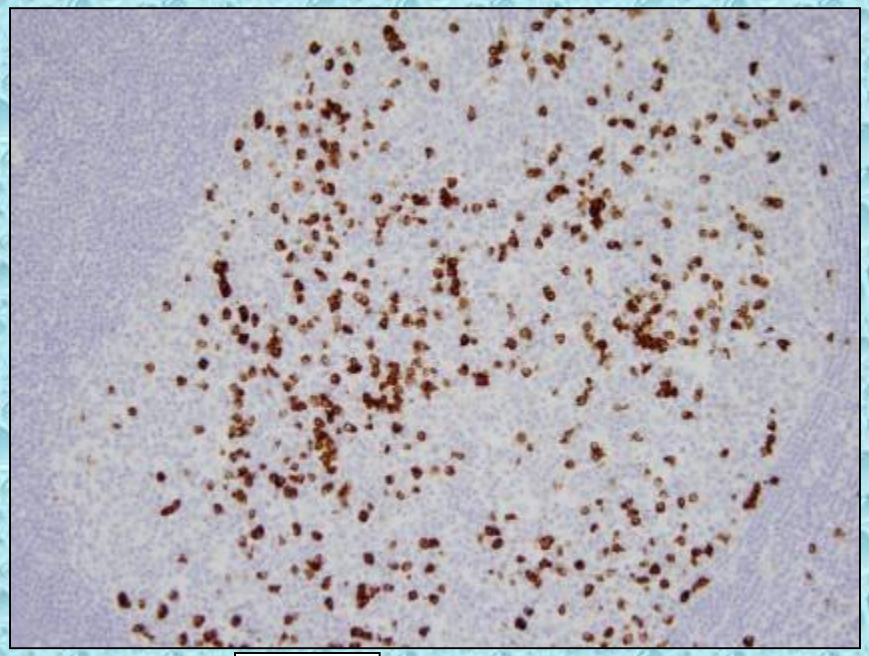




Follicular hyperplasia
Many plasma cells within germinal centers



IgG

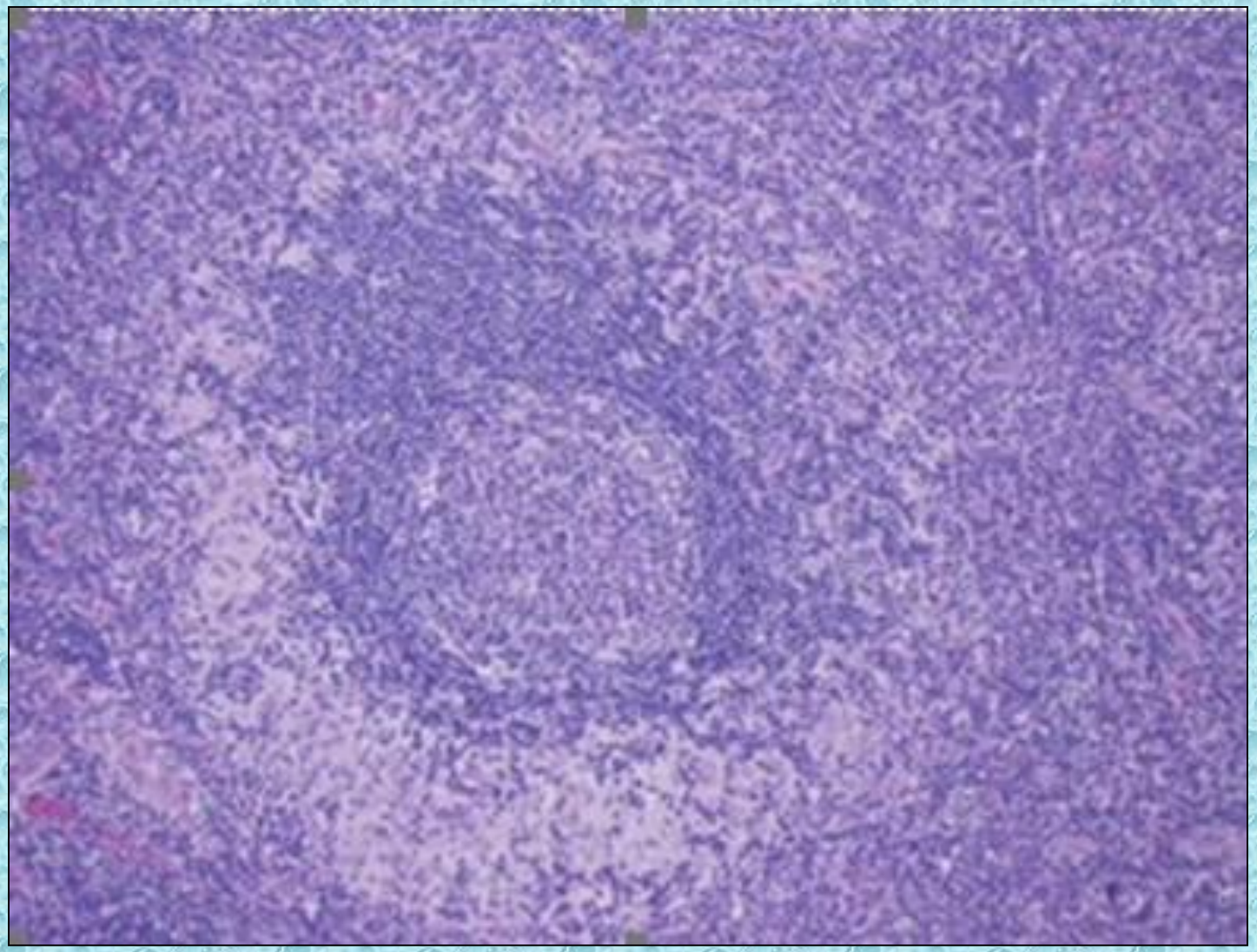


IgG4

61 y/o male, generalized adenopathy

- Case:

- My friend, Aaron Auerbach, at the Joint Pathology Center, sent this photo, and asked if I knew what it was – his colleague had seen it in a case…



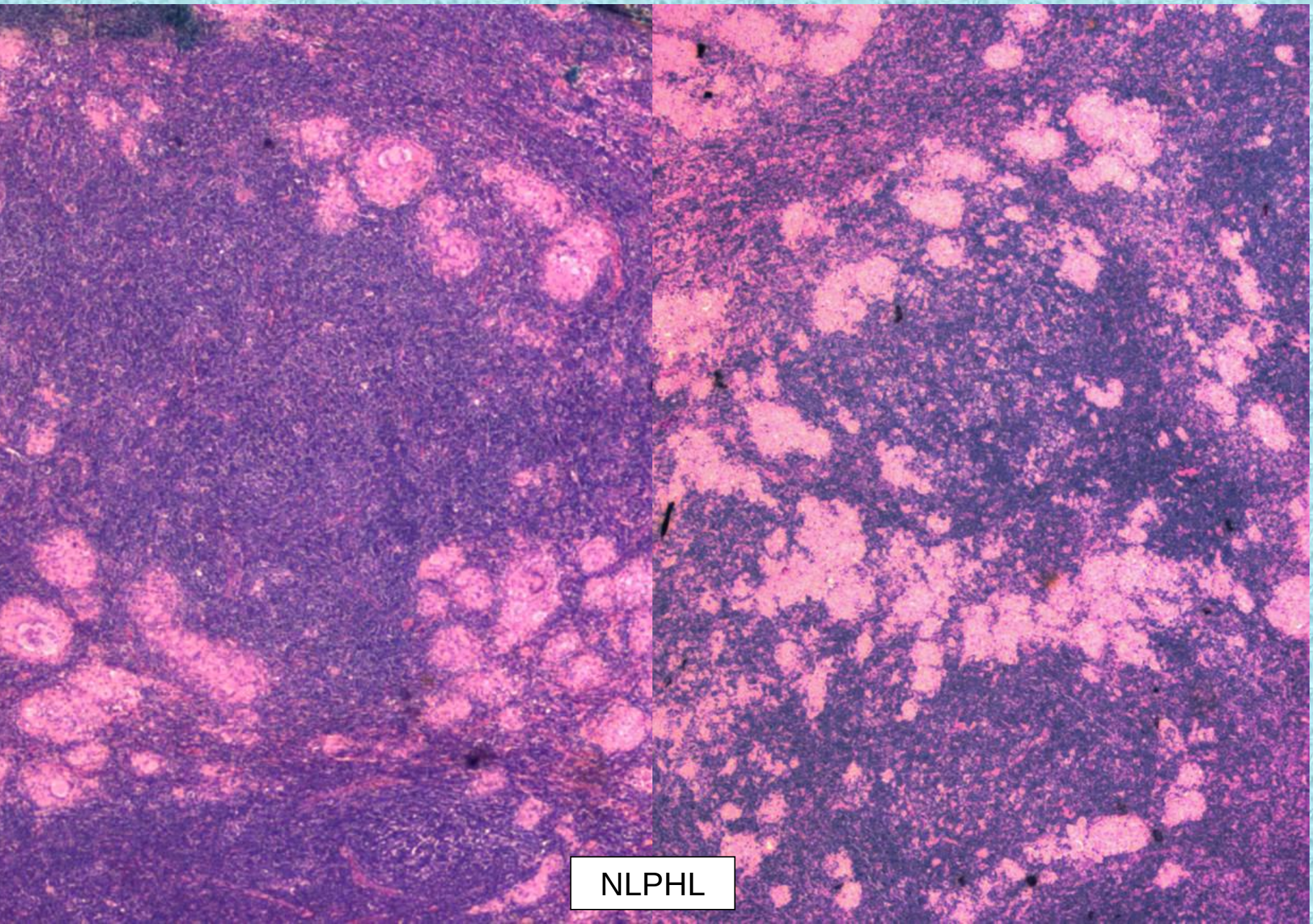
Reactive germinal center, with epithelioid histiocytes forming a ring around it

Table 1. Classifications of Hodgkin lymphoma over years.

JACKSON and PARKER 1944	LUKES AND BUTLER 1966	RYE 1966	REAL 1994 WHO 2001 2008	
Paragranuloma	L and H*			
	a. Nodular	Lymphocytic predominance	Nodular lymphocyte predominant	
	b. Diffuse			
Granuloma			Lymphocyte-rich	Classic HL
	Nodular sclerosis	Nodular sclerosis	Nodular sclerosis	
	Mixed	Mixed cellularity	Mixed cellularity	
	Diffuse fibrosis	Lymphocytic depletion	Lymphocyte depleted	
Sarcoma	Reticular		Lymphocyte depleted	

L and H, lymphocytic and/or histiocytic; REAL, Revised European-American Lymphoma; WHO, World Health Organization; HL, Hodgkin lymphoma

Paragranulomas in this diagnosis



- In 1944 Jackson and Parker called it in as "paragranuloma" to separate it from Hodgkin "granuloma".
- In 1966 Lukes and Butler (Lukes and Butler JJ, 1966) renamed paragranuloma "lymphocytic and/or histiocytic predominance HD", recognizing a nodular and a diffuse pattern and used the term of lymphocytic and histiocytic (L&H) RS-cell variant for the diagnostic cell (Lukes, Butler et al., 1966), now called LP cell.
- At the Rye symposium, it was decided to combine the nodular and diffuse types of the Lukes and Butler classification into LPHL (Lukes, Craver et al., 1966)

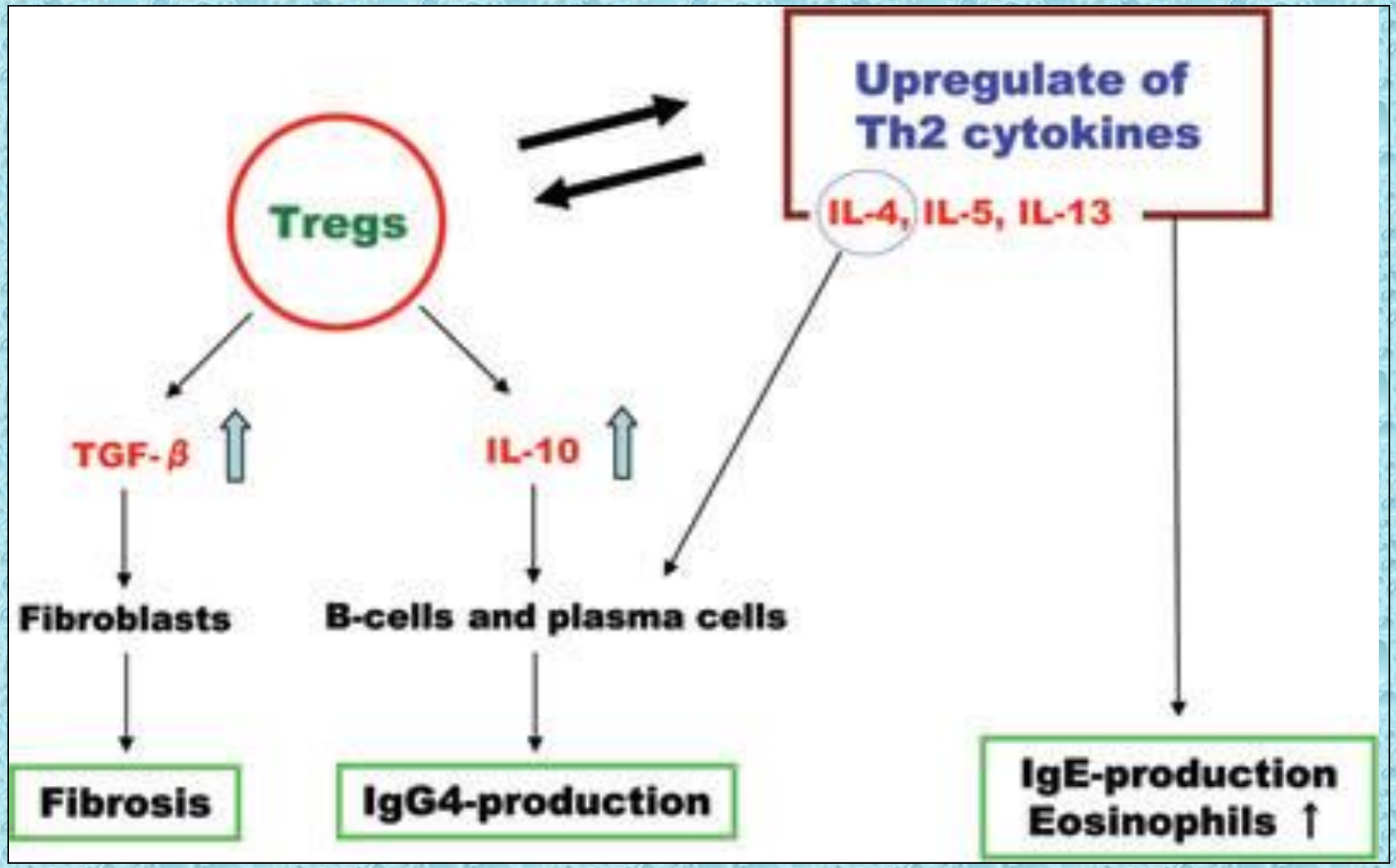
IgG4-related lymphadenopathy

IgG4-related sclerosing disease
IgG4-related plasmacytic exocrinopathy
IgG4 multi-organ lymphoproliferative syndrome

IgG4-related lymphadenopathy History

- Yoshida et al. 1995.
  - Autoimmune pancreatitis. Serum elevation of IgG4

IgG4-related lymphadenopathy



From: Sato et al. Pathology International. 2010.

Associations: IgG4-related diseases

- Pachymeningitis
- Hypophysitis
- Lacrimal gland lesion (Mikulicz's disease)
- Sclerosing sialadenitis
- Thyroid gland
- Mastitis
- Pulmonary disorders
- Autoimmune pancreatitis

- Hepatitis
- Sclerosing cholangitis
- Retroperitoneal fibrosis
- Prostatitis
- Inflammatory aortic aneurysm
- Tubulointerstitial nephritis
- Lymphadenopathy (80% of cases)
- Skin lesions

After: Sato et al. Pathology International. 2010.

Histology: IgG4 sclerosing disease, general*

- Pseudolymphomatous Pattern
  - Small lymphocytes
  - Plasma cells
  - Some eosinophils
- Mixed Pattern
  - Infiltrates of small lymphocytes and plasma cells with significant sclerosis
- Sclerosing Pattern
  - Predominant sclerosis with poorly defined borders
  - Patchy aggregates of lymphocytes and or plasma cells
  - Occasional obliterative phlebitis

Cheuk & Chang 2010

*Histologic findings are somewhat different in lymph nodes

Histology: Lymph Node

- Diverse findings
  - Reactive follicular hyperplasia
  - Plasma cell Castleman-like
  - Interfollicular plasmacytosis and immunoblasts
  - PTGC-like
  - Inflammatory pseudotumor-like
    - fibrosis

Sato et al. 2010. Cheuk & Chan. 2010.

Useful Note: IgG4 stains can only be interpreted easily with a concurrent IgG stain

A few new patterns

- Rosai-Dorfman like
- Infectious mononucleosis-like

Most specific for IgG4 RD

- Nodal fibrosis with IgG4 plasma cells
- Increased IgG4 positive plasma cells in interfollicular areas

DDx:

- MC-CD
- RA
- IMT
- RDD
- CHL

American Journal of Surgical Pathology

February 2021, Volume 45 (2), p 178–192

IgG4-related Lymphadenopathy

A Comparative Study of 41 Cases Reveals Distinctive Histopathologic Features

Jacob R. Bledsoe, MD, Judith A. Ferry, MD,† Azfar Neyaz, MD,† Leonardo Boiocchi, MD,† Cara Strock, MS,* Karen Dresser, BS,* Lawrence Zukerberg, MD,† and Vikram Deshpande, MD†*

Additional findings

- Perinodular granulomas
  - Can be a mimic of NLPHCL

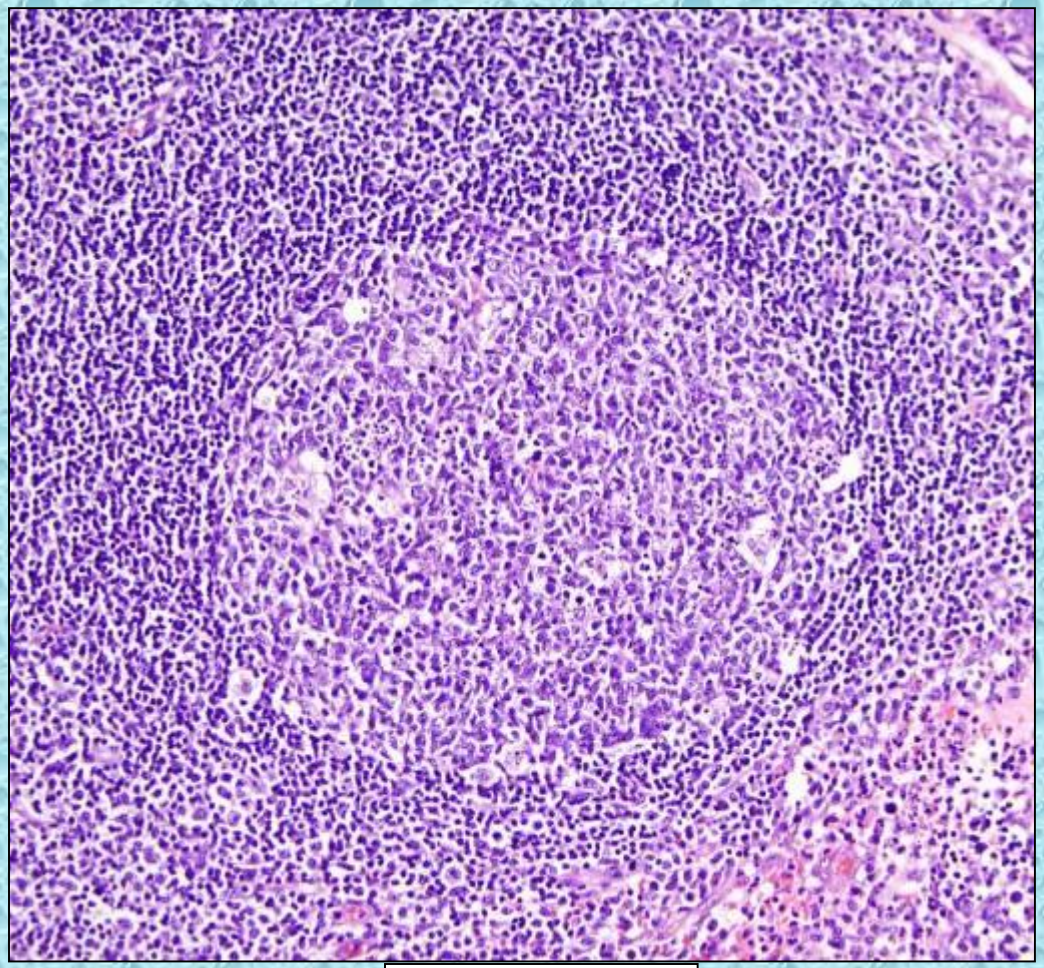
J Hematopathol (2011) 4:207–214
DOI 10.1007/s12308-011-0117-5

ORIGINAL ARTICLE

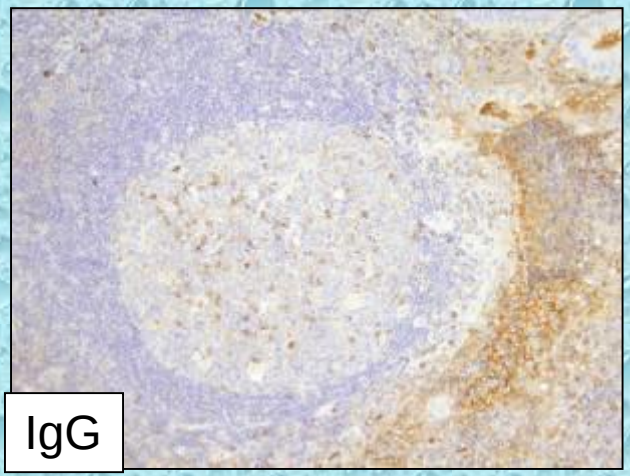
Perifollicular granulomatous inflammation in reactive lymph nodes: a possible morphologic marker for IgG4 plasmacytosis

Imran N. Siddiqi · Russell K. Brynes · Kate Grimm · Dennis P. O'Malley · Endi Wang

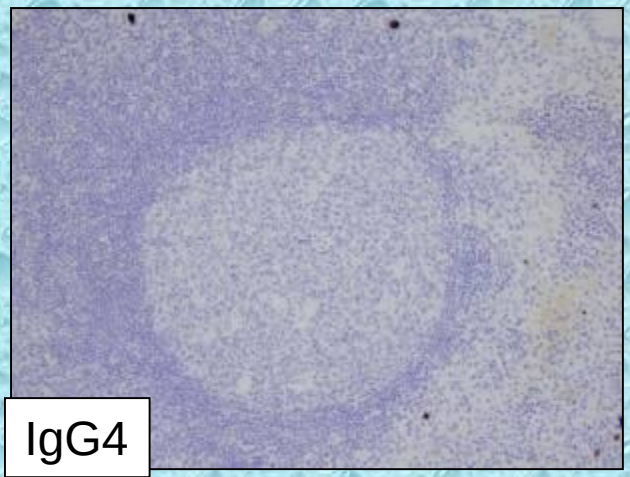
Normal IgG4 staining



Lymph Node

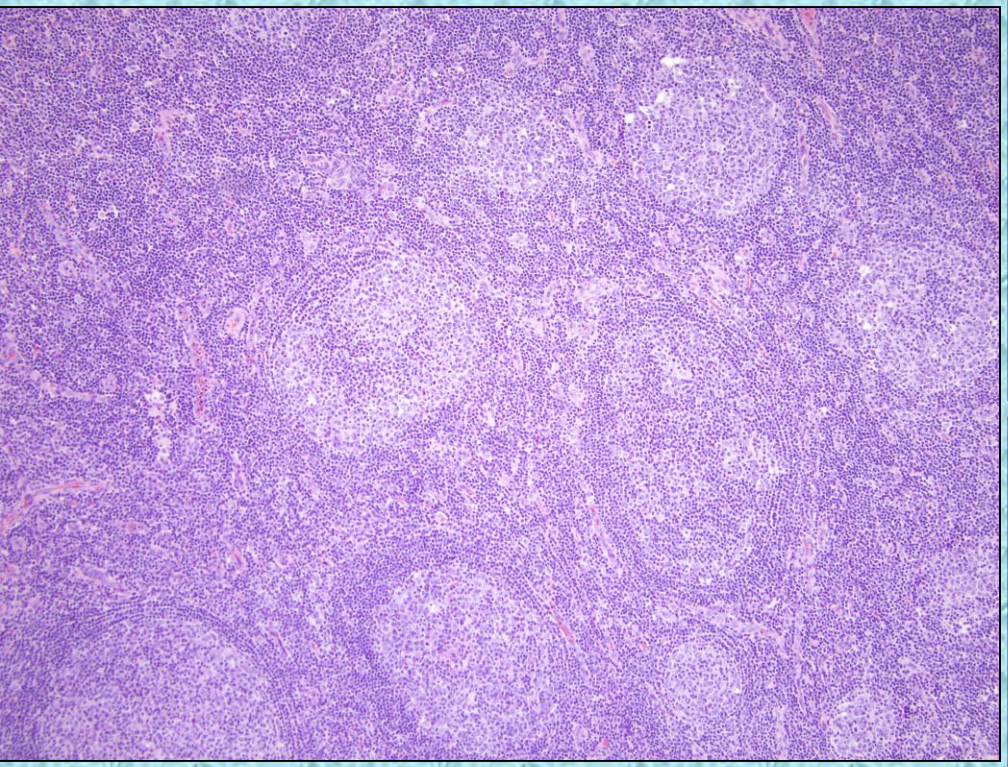


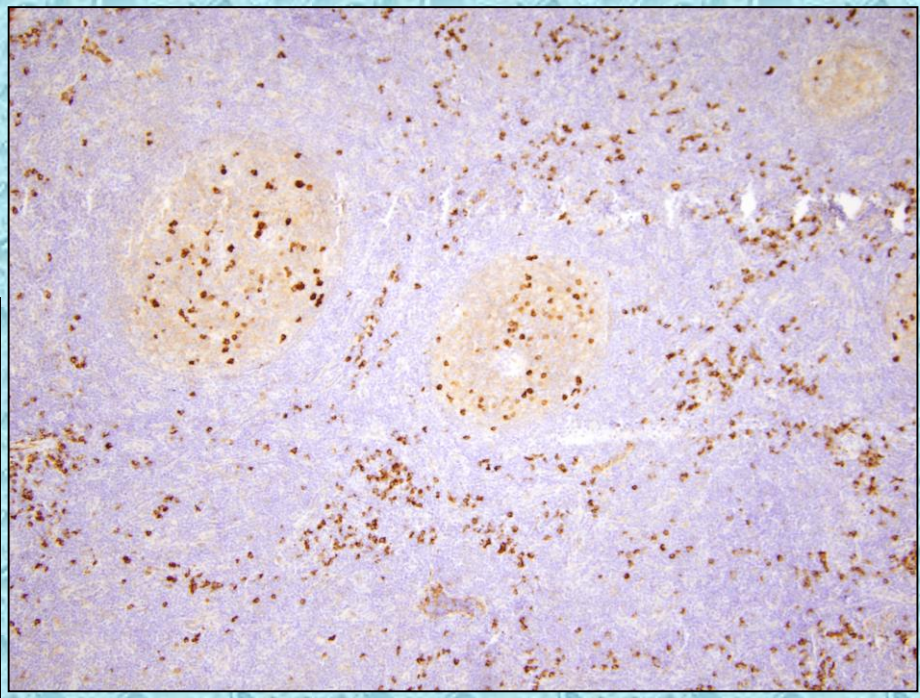
IgG

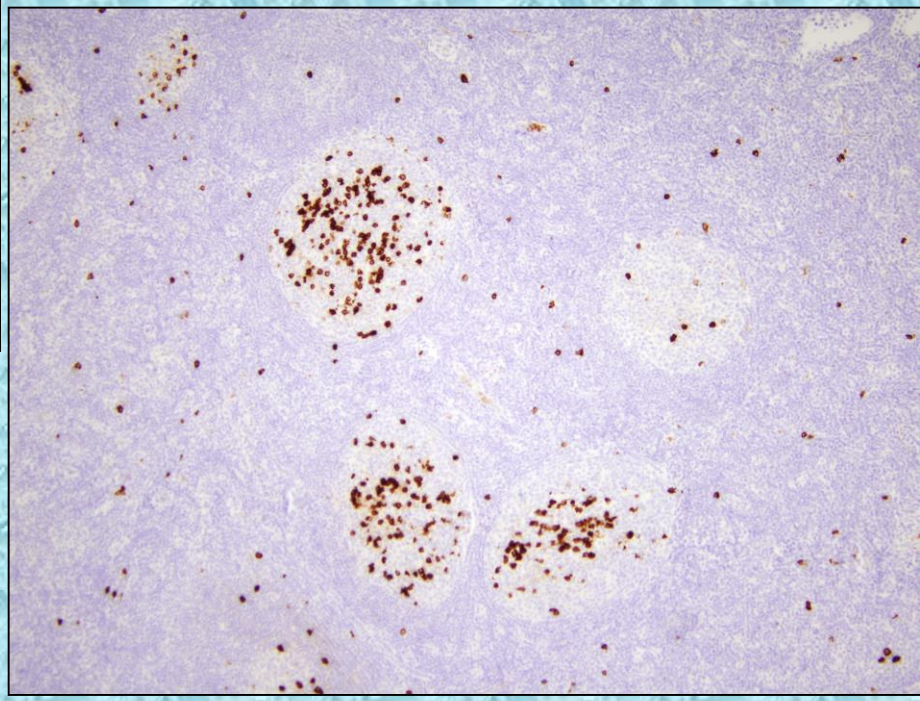


IgG4

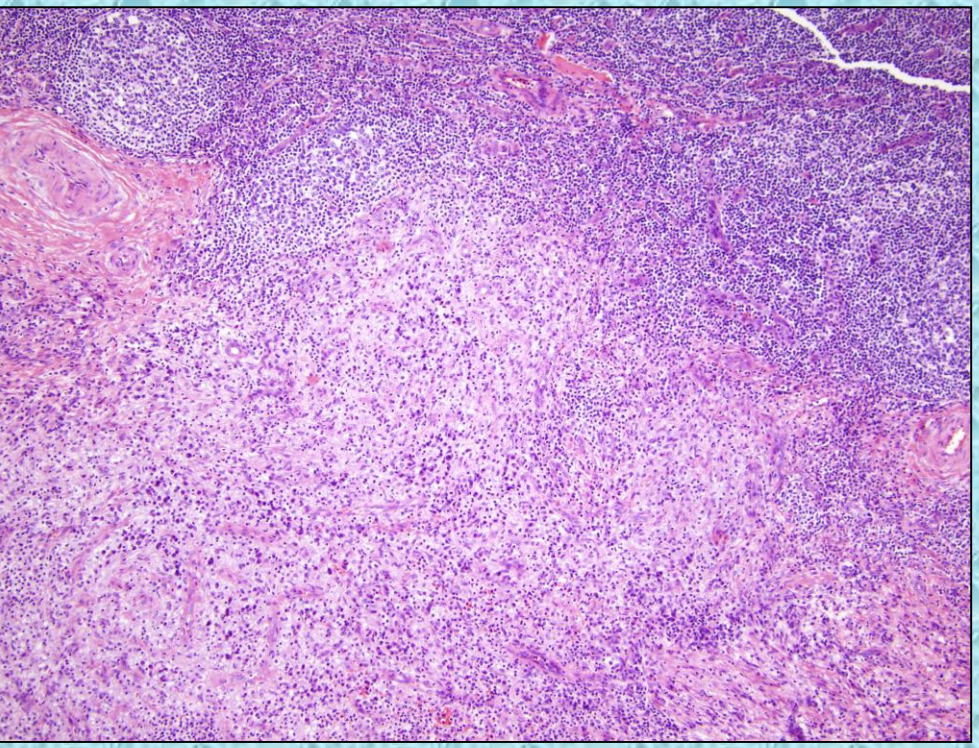
IgG4 follicular hyperplasia

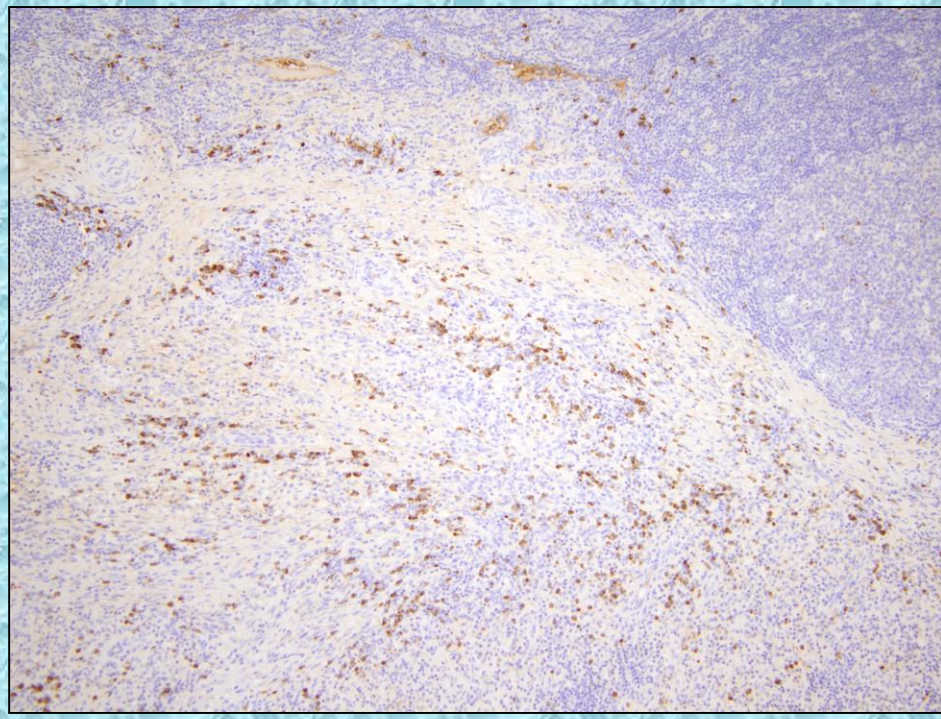


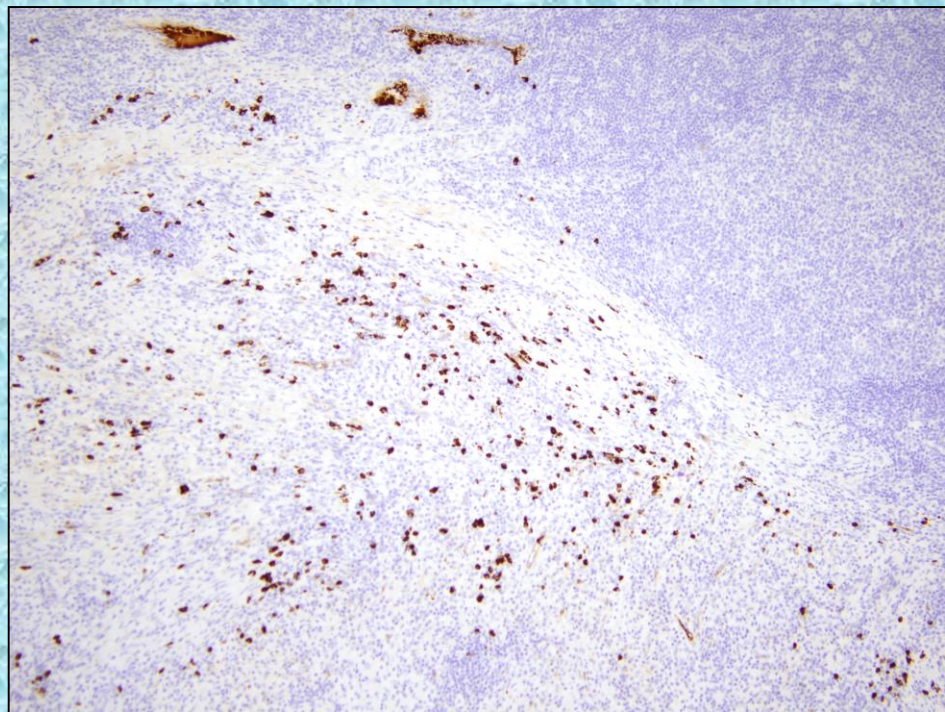




Inflammatory pseudotumor-like IgG4

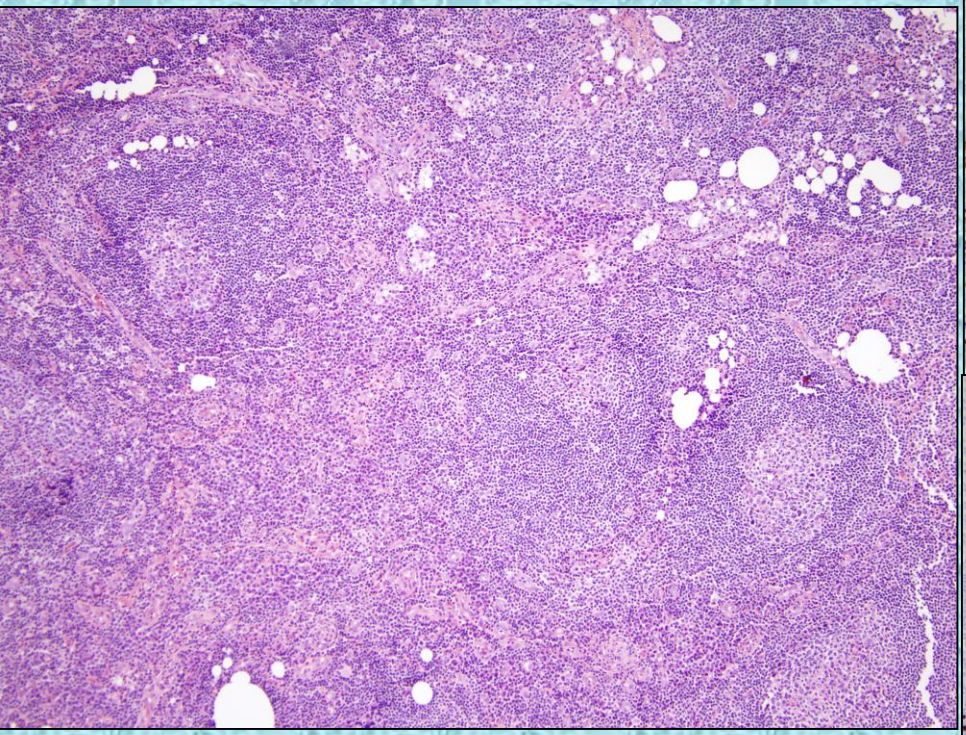


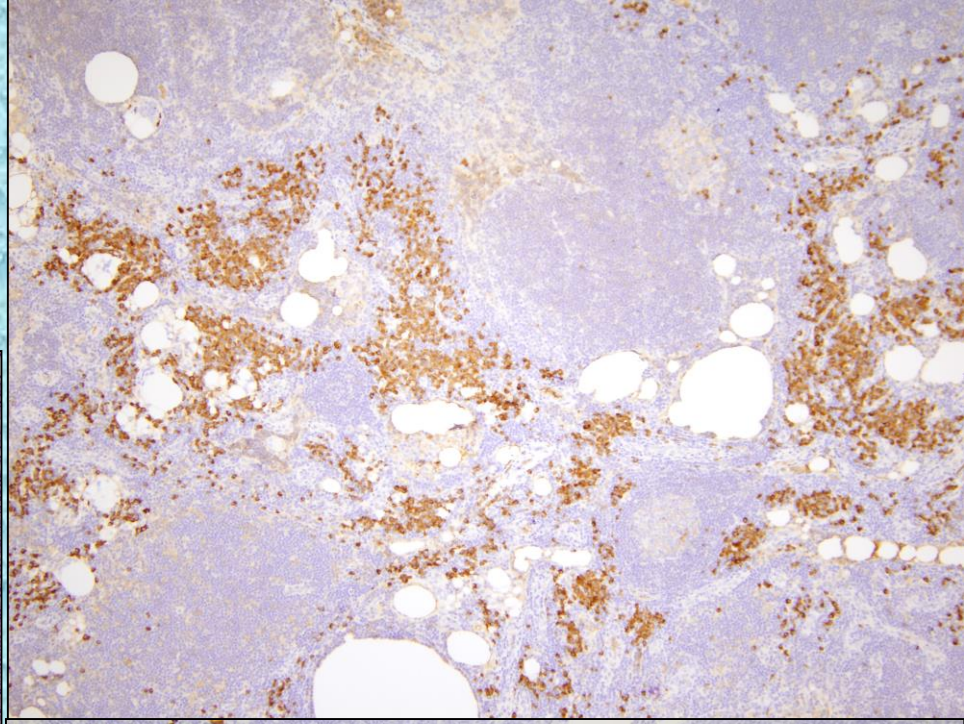


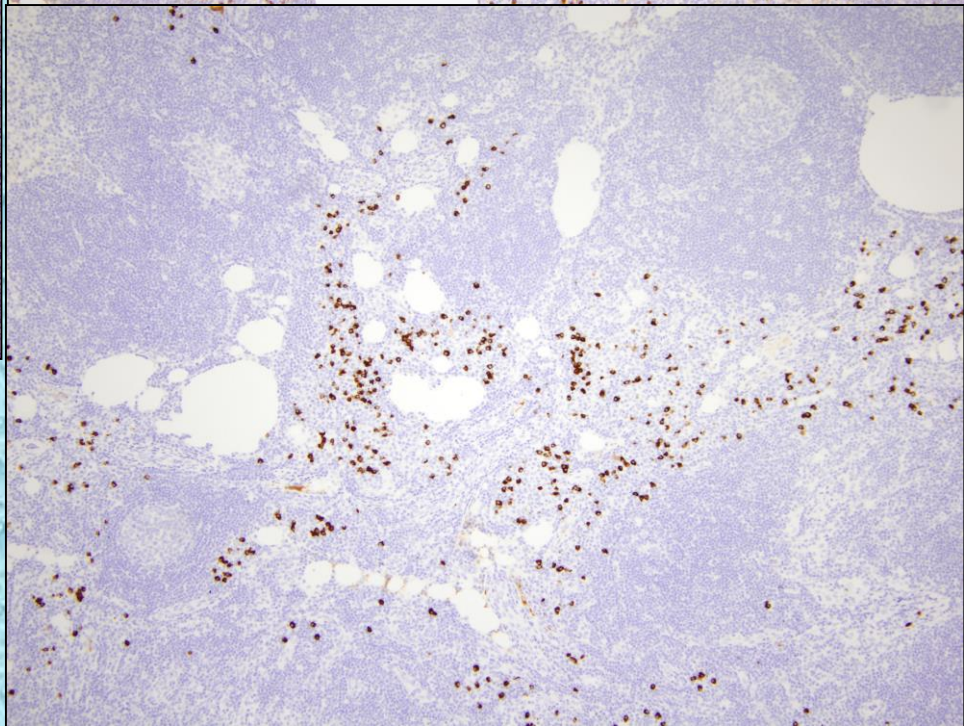


Fibrosis, plasma cells, mixed infiltrate
Most closely mimics syphilitic LAD

IgG4 Interfollicular

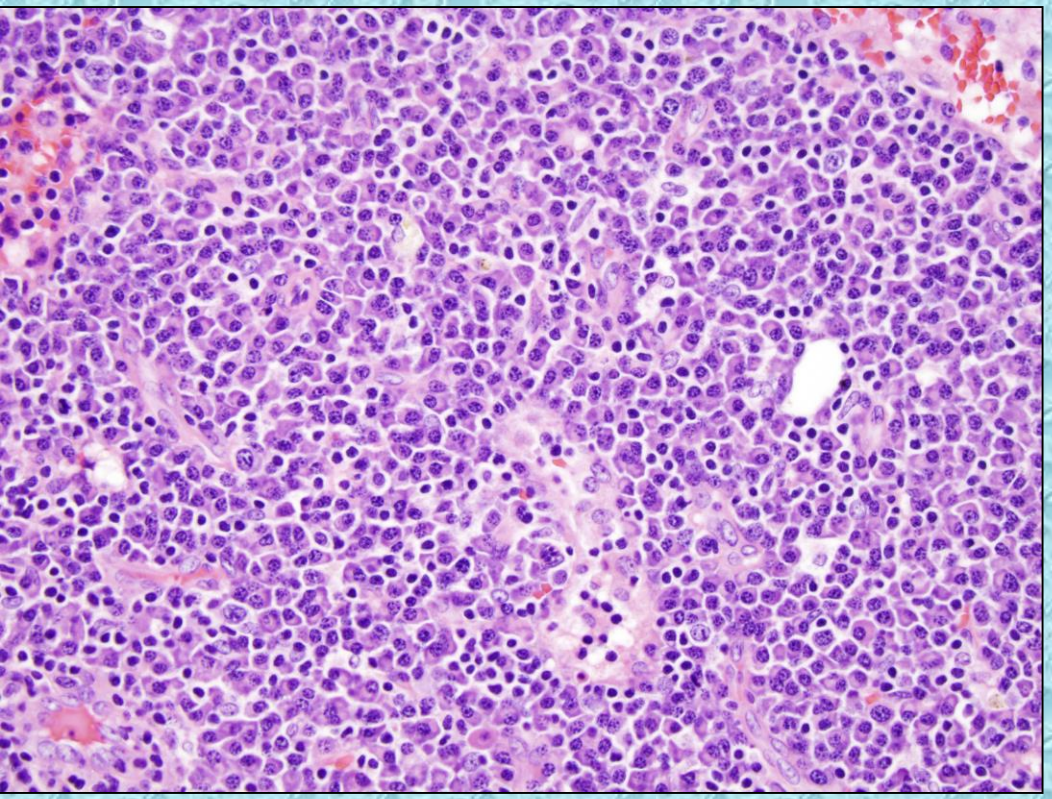


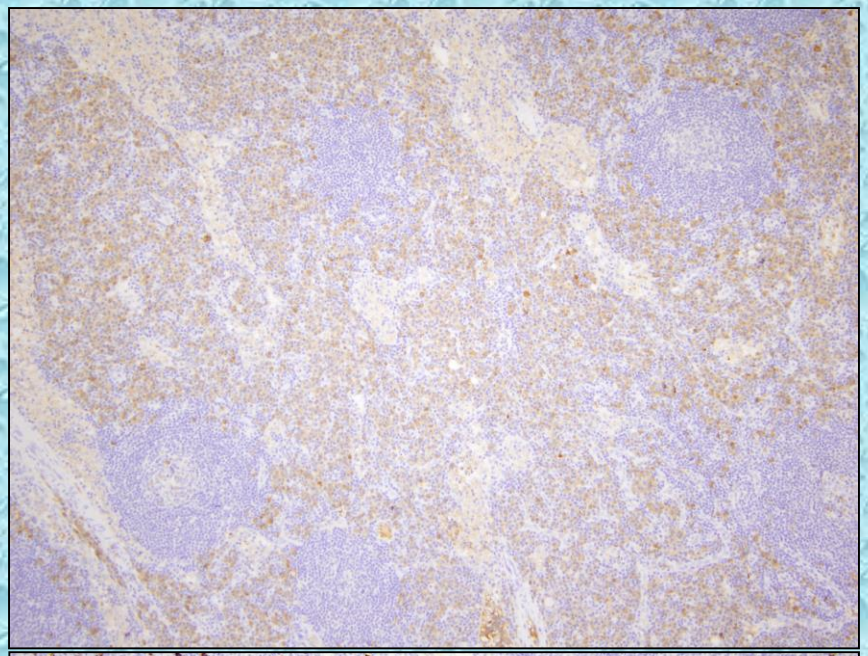


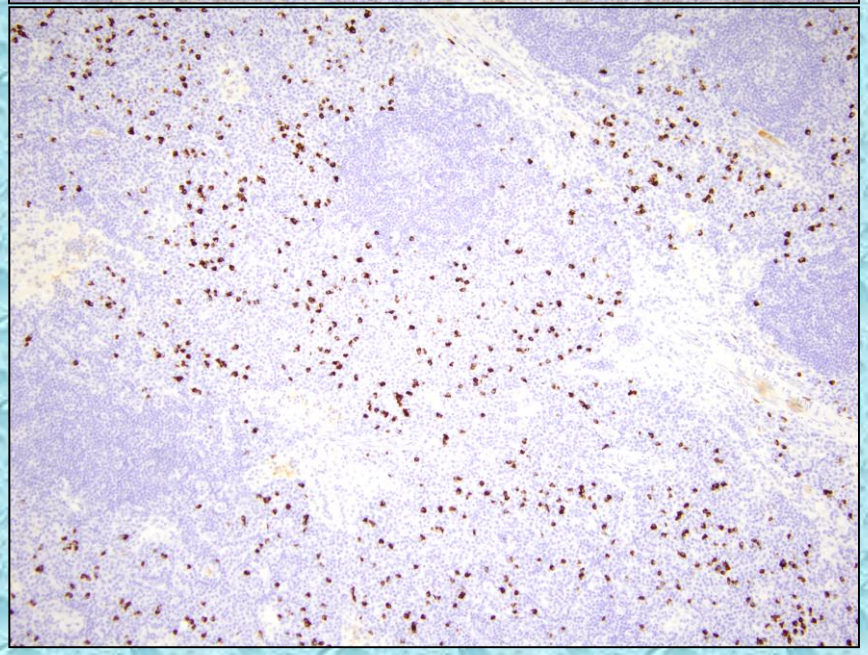


Increased immunoblasts in interfollicular areas

Plasma cell Castleman disease-like IgG4







IgG4-related lymphadenopathy Differential Diagnosis

- Autoimmune lymphadenitis
  - SLE, rheumatoid arthritis
- Plasma cell Castleman disease
- PTGC
- “True” inflammatory pseudotumor
- Inflammatory myofibroblastic tumor
- Marginal zone lymphoma*
- Lymphoplasmacytic lymphoma

*IgG4 positive lymphomas do occur

IgG4-related lymphadenopathy Therapy & Prognosis

Therapy

- Highly responsive to steroid and/or rituximab therapy

Prognosis

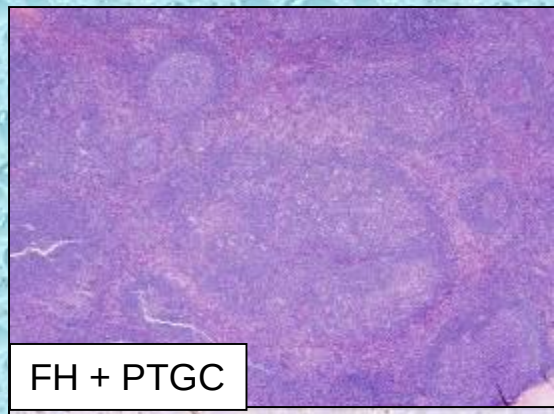
- Good although symptoms may persist or recur after cessation therapy

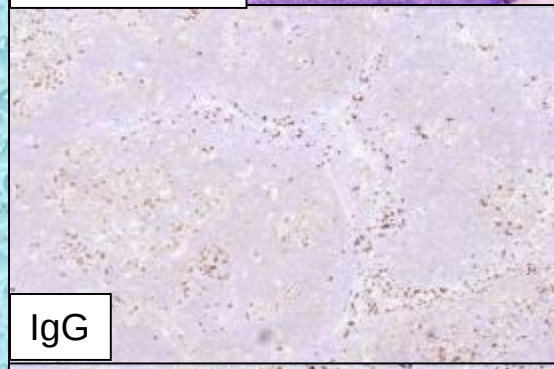
When do I perform IgG4 staining*

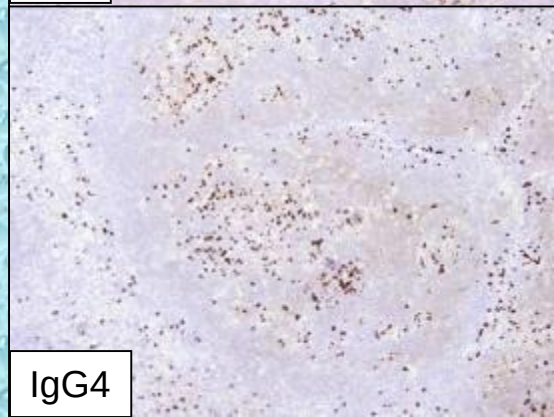
- Follicular or immunoblastic hyperplasias in older adults (50+)
- PTGC in older adults (50+)
- Fibrotic lesions with lymphoplasmacytic infiltrates (inflammatory pseudotumor)
- Anything that looks like Plasma Cell Castleman disease

IgG4-related lymphadenopathy SUMMARY

- Clinical: Older male
- Histology: Lymph nodes showing a broad range of reactive changes
- Possible etiologies: Unknown, possible autoimmune
- Therapy: Steroid/rituximab therapy very effective
- Prognosis: Good, but disease may persist despite therapy







Some practical advice

- Evaluate for this disorder
- If positive for IgG4, it is the beginning of a process, *not a specific diagnosis*
- My diagnosis will read "…with increased IgG4 positive plasma cells"
  - It also includes that it may be appropriate to evaluate for autoimmune disorders, serum IgG4 levels, and that these patients are usually managed by a rheumatologist
- "IgG related LAD" should only be used in cases of known IgG4 RD

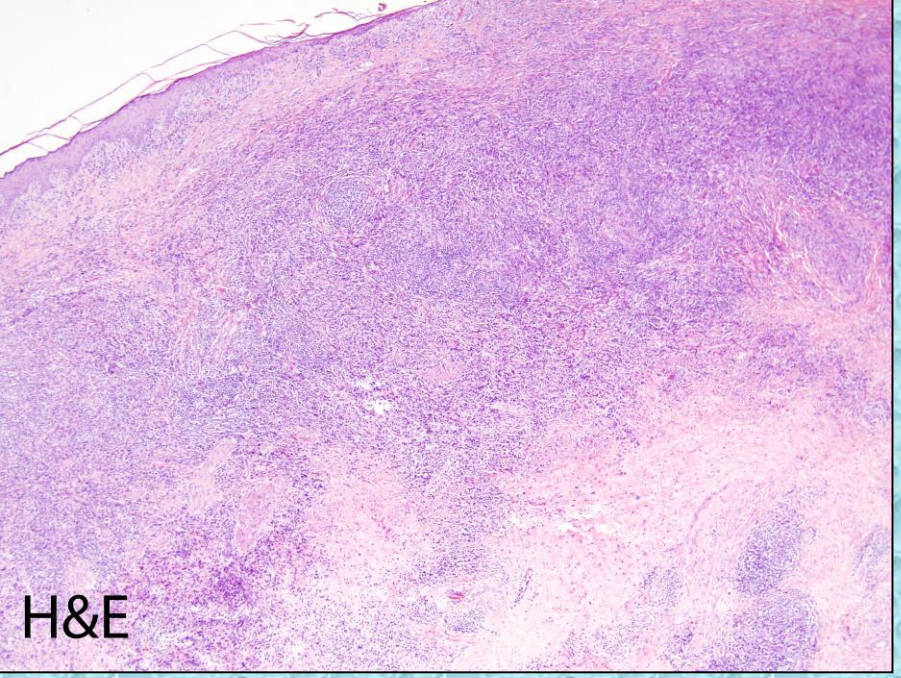
Some more practical advice

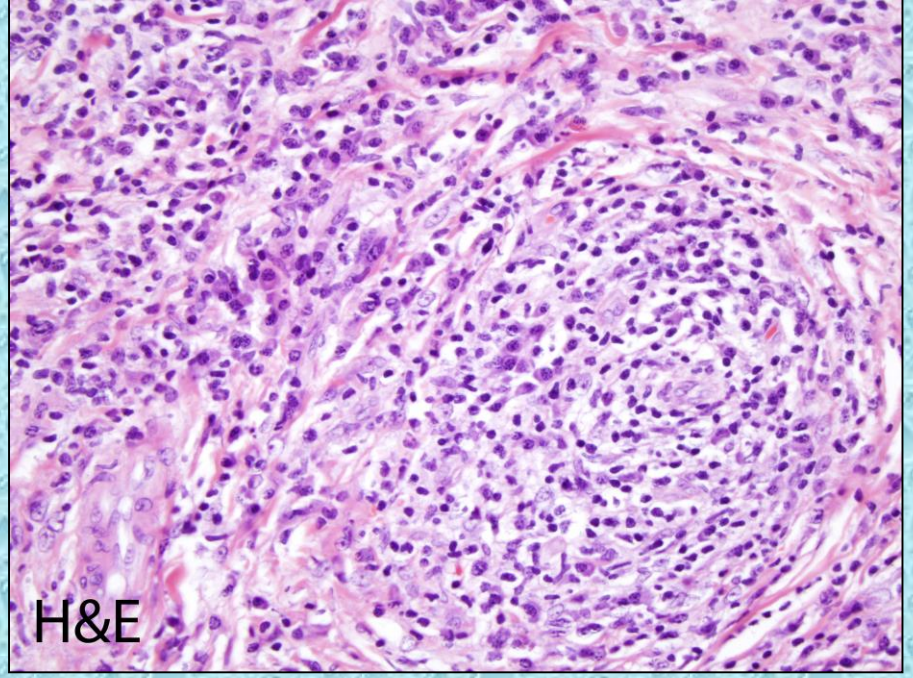
- Oral cavity lesions:
  - Have tons of IgG4 positive plasma cells, just don't do it unless there is evidence of IgG4 RD
- Syphilis
  - Has tons of IgG4 positive PCs (and can look just like IPT-like version – more later)
- Rosai-Dorfman
  - Has lots of IgG4 positive PCs – more later
- Nodular sclerosis Hodgkin lymphoma has lots
- Tuberculosis has lots

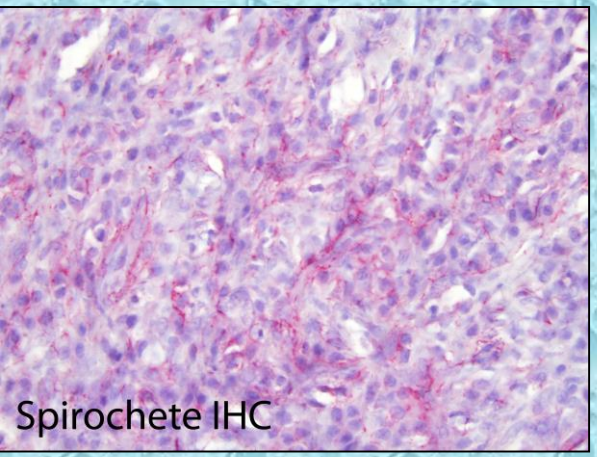
SYPHILIS

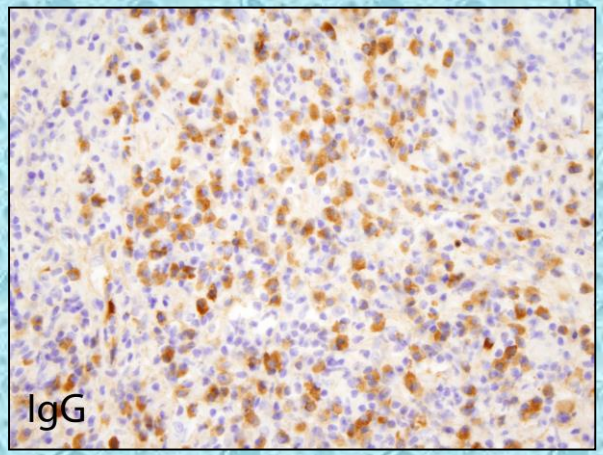
FALSE SHAME AND FEAR MAY DESTROY YOUR FUTURE

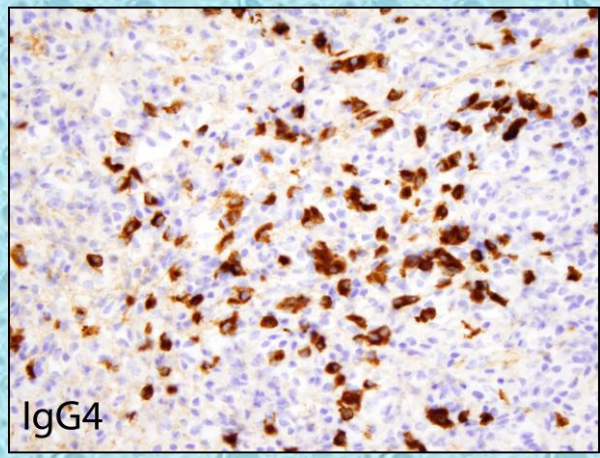
HAVE YOUR BLOOD TESTED











Reminder: Fibrosis, plasmacytosis, follicles, almost always groin/inguinal nodes or genital skin

Syphilis (luetic lymphadenitis)

- Clinical
  - Most frequently inguinal location
- Follicular hyperplasia
- Vasculitis, arteritis, phlebitis
- Capsulitis
- Prominent polyclonal plasmacytosis
- Epithelioid granulomas
- Capsular fibrosis
- Organisms seen with Warthin-Starry or IHC