

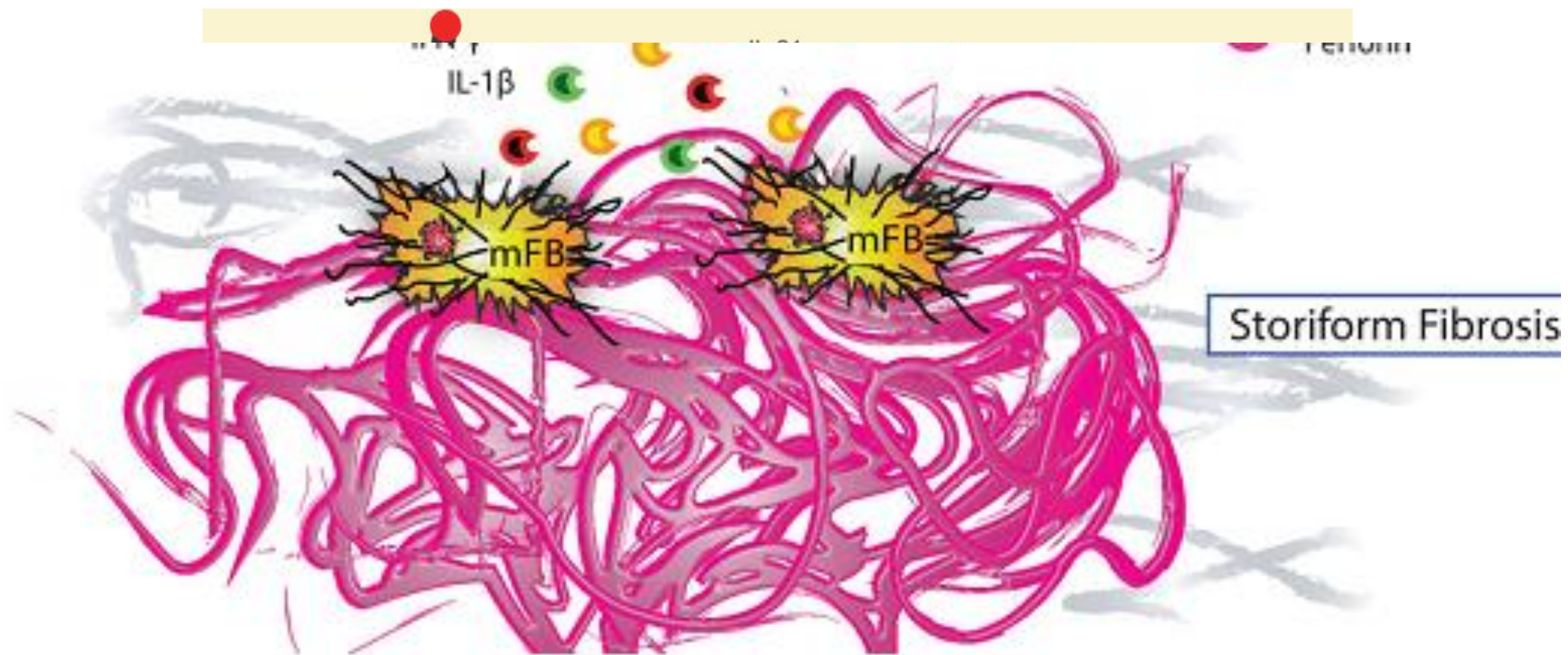


IgG4 Related Disease Diagnosis & Treatment

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IgG4 Related Disease Diagnosis

- **IgG4-RD should be clinically suspected in patients presenting with unexplained enlargement or swelling (Tumefactive lesion) of 1 or more organs or tissues**
- **Diagnosis of IgG4-RD remains a significant clinical challenge, and there is no simple diagnostic test for IgG4-RD**

Laboratory Tests : Routine Tests

- Mild-to-moderate peripheral eosinophilia is found in 34% of patients
- Elevated C-reactive protein levels were reported in 23% of cases.
Even in the setting of multiorgan disease, elevation in serum CRP concentrations is, however, generally modest and is less pronounced than is elevation in the ESR
- Hypergammaglobulinemia(61%),elevated IgG2, elevated serum IgE levels(58%), hypocomplementemia which is particularly common in patients with IgG4-related kidney disease, was observed in 41 %

Laboratory Tests : Serum IgG4

- Although most patients with IgG4-RD have elevated serum IgG4-levels, IgG4RD cannot be diagnosed solely on the basis of serum IgG4 levels for the following reasons
 - 1- elevated serum IgG4 levels (to greater than 135 mg/dl) were reported in 84 %
 - IgG4 levels found in serum using nephelometry can often be low in patients due to the prozone phenomenon(can be avoided by diluting the samples), cell binding and another unknown phenomenon
 - Newer forms of testing – enzyme-linked ImmunoSpot (ELISPOT) and quantitative reverse transcription polymerase chain reaction (RT-qPCR) – could be more telling

Laboratory Tests : Serum IgG4

Circulating IgG4/IgG ASC percentages >5% is a more sensitive and reliable marker for disease activity in patients with IgG4-RD both for diagnosis and disease activity monitoring

Laboratory Tests : Serum IgG4

2- elevation of serum IgG4 levels is not restricted to IgG4-RD and is also seen in other conditions .

- **A recent study reported that elevated serum IgG4 levels by themselves have a low specificity (60 %) and a low positive predictive value (34 %) for the diagnosis of IgG4-RD**

Vasculitis

- Eosinophilic granulomatous with polyangiitis (Churg-Strauss)
- Granulomatosis with polyangiitis (Wegener)
- Hypocomplementemic urticarial vasculitis

Hematological malignancy

- Castleman disease
- Extranodal marginal zone B-cell lymphoma
- Follicular lymphoma
- Angioimmunoblastic lymphoma

Solid-organ neoplasms

- Pancreatic cancer
- Lung cancer
- Sarcoma

Infections

- Pulmonary abscess
- Epstein-Barr virus-related lymphadenopathy
- Aortitis caused by chronic *Staphylococcus aureus* infection

Digestive diseases

- Inflammatory bowel disease
- Diverticulitis

Other systemic diseases

- Rheumatoid arthritis (synovium and lymph nodes)
- Histiocytosis (Rosai-Dorfman disease)

**If serum IgG4 levels are to be taken into account in
the diagnosis of IgG4-RD, then rigorous
clinicopathological correlation is required**

Laboratory Tests : Serum IgG4

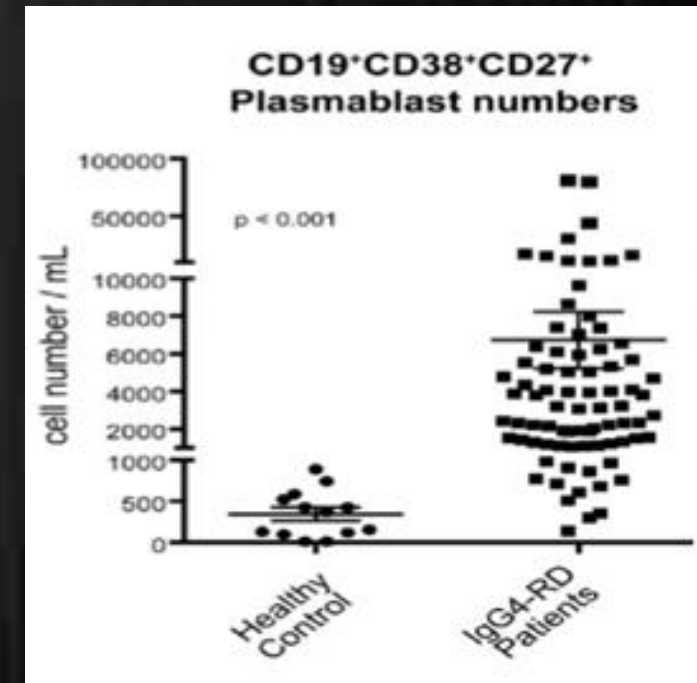
- Serum IgG4 concentration tends to correlate with **the number of organs involved**: the greater the number of organs affected, the higher the serum concentration.
- In addition, elevated serum IgG4 concentrations appear to identify a subset of IgG4-RDs that are more **“inflammatory”** low complement levels, and (possibly) greater refractoriness to treatment as compared with normal serum IgG4 levels

Laboratory Tests : FLOW CYTOMETRY

- Blood **plasmablast** concentrations may be superior to serum IgG4 concentrations for the diagnosis of IgG4-RD and offer important possibilities to follow disease activity in the longitudinal evaluation of patients.
- Plasmablasts can be identified through flow cytometry analysis of peripheral blood, gating on cells that are CD19^{low} CD38⁺CD20⁻CD27⁺

Laboratory Tests : FLOW CYTOMETRY

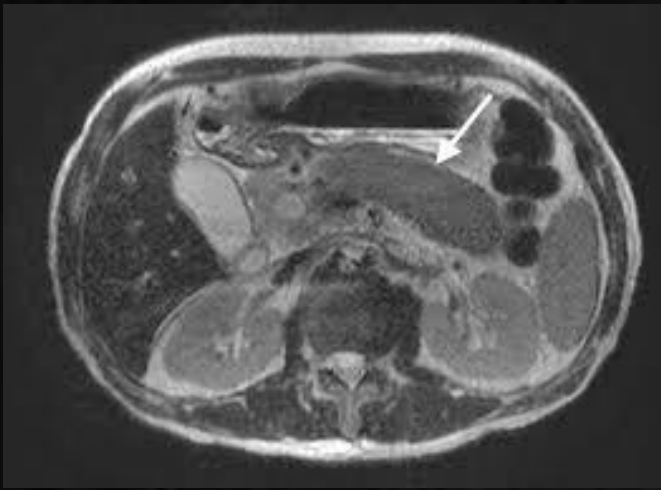
- Early studies of flow cytometry in IgG4-RD suggest that circulating plasmablasts are highly elevated even in patients with normal serum IgG4 concentrations.
- In addition, elevation in plasmablasts appears to decline sharply with therapy and rise again during disease flares.
- Therefore, plasmablast counts are a potentially useful biomarker for diagnosis, for assessing the response to treatment, and for determining the appropriate time for retreatment



Wallace ZS, Mattoo H, Carruthers M, et al. Plasmablasts as a biomarker for IgG4-related disease, independent of serum IgG4 concentrations. Ann Rheum Dis. 2015;74(1):190-195

Imaging In IgG4RD

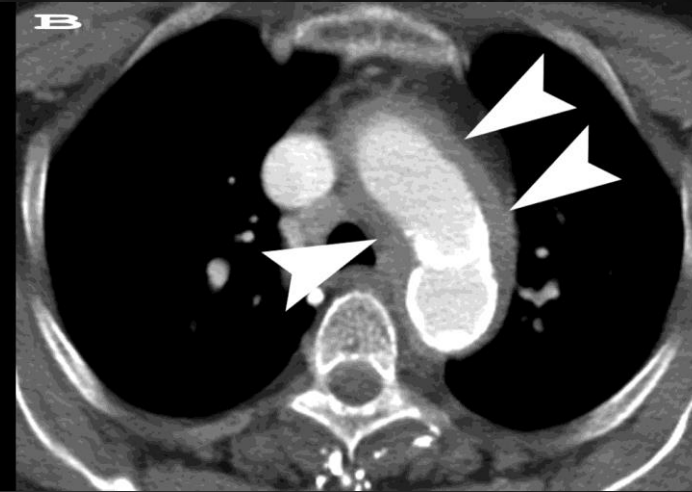
- CT scanning, MRI imaging, and FDG-PET/CT are popular methods of imaging IgG4-RD
- On enhanced CT images of IgG4-RD, a diffuse or focal swelling of organs or soft tissue masses appears with soft tissue attenuation, well-defined margins, and homogeneous enhancement at late stage
- In MRI present as iso- to hypointense on T2-weighted MRI and reflect increased cellularity and fibrosis
- FDG-PET/CT is useful for mapping the sites of IgG4-RD by highlighting hypermetabolic activity



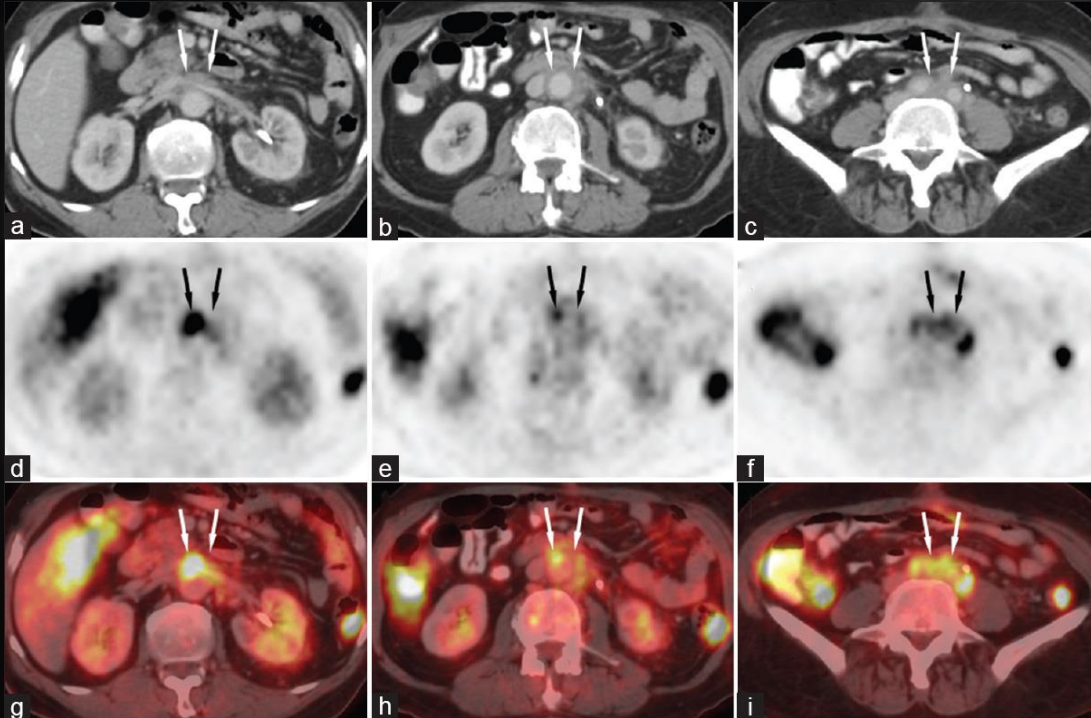
sausage shaped pancreas



diffuse pachymeningeal thickening



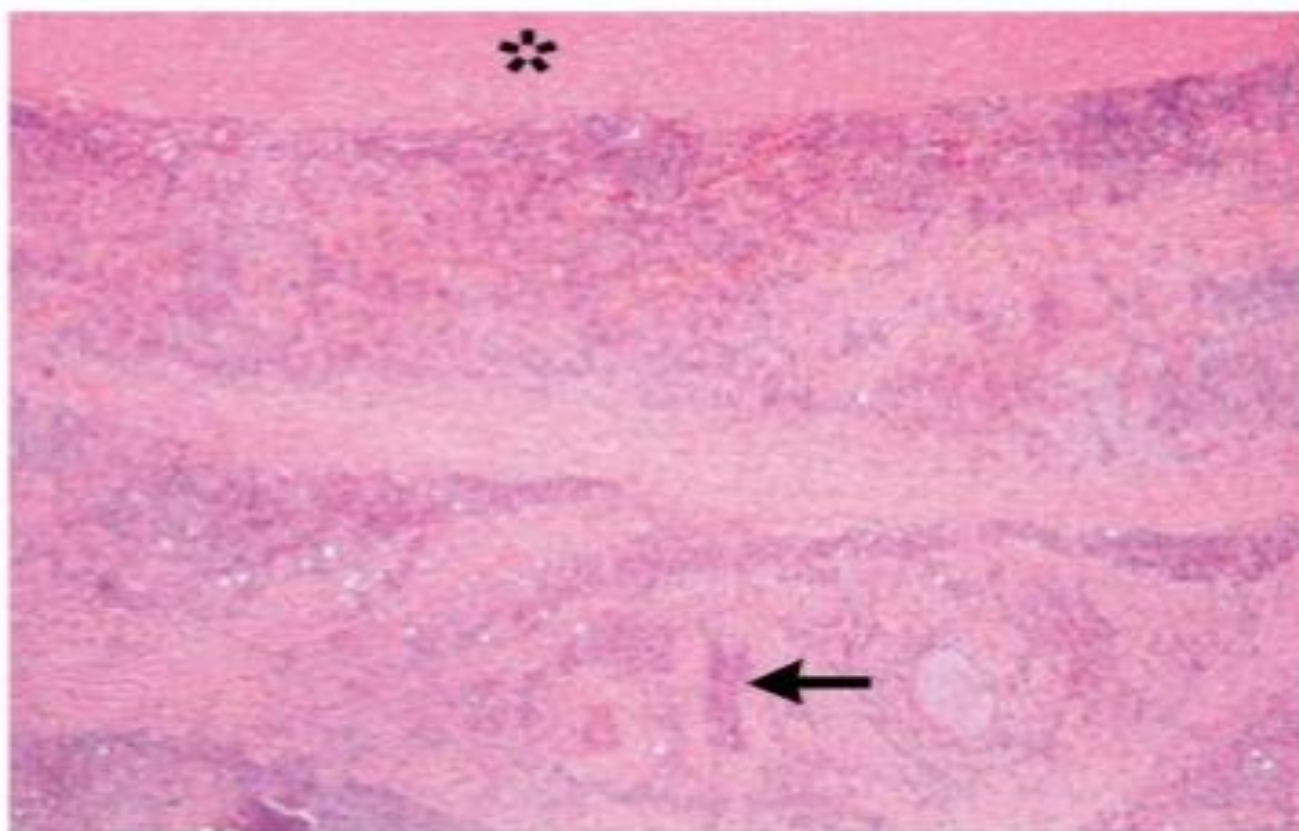
thickening surrounding the aortic arch



PET/CT findings, diagnosis of active retroperitoneal fibrosis

Histopathology In IgG4RD

- The current gold standard for the diagnosis of IgG4-RD is its characteristic histology and immunohistochemistry, which is almost the same regardless of the organs involved.
- Major histopathological features of IgG4-RD are dense lymphoplasmacytic infiltration

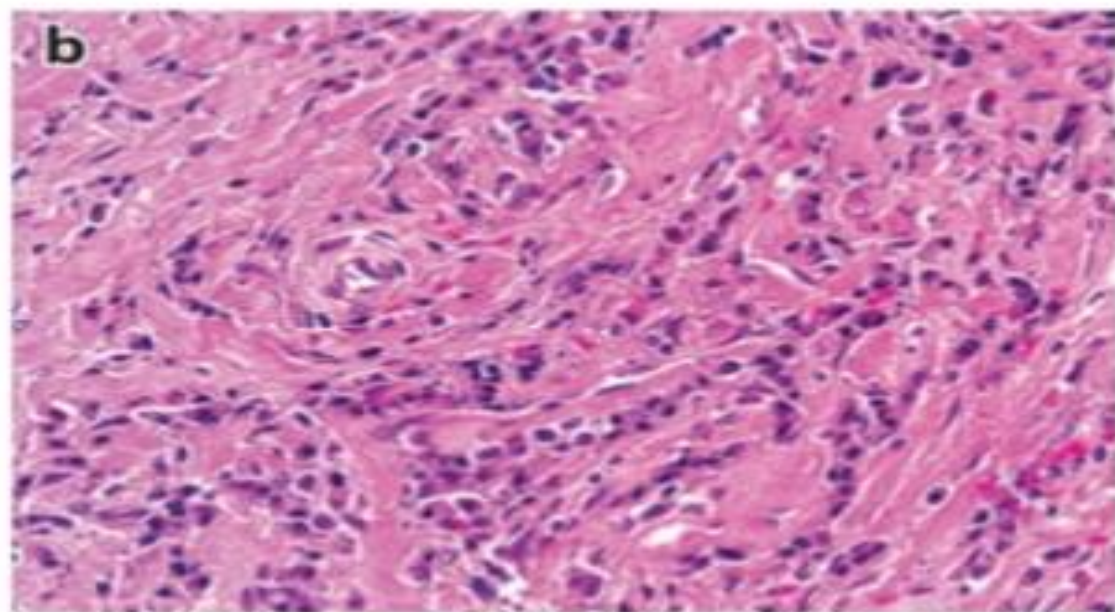
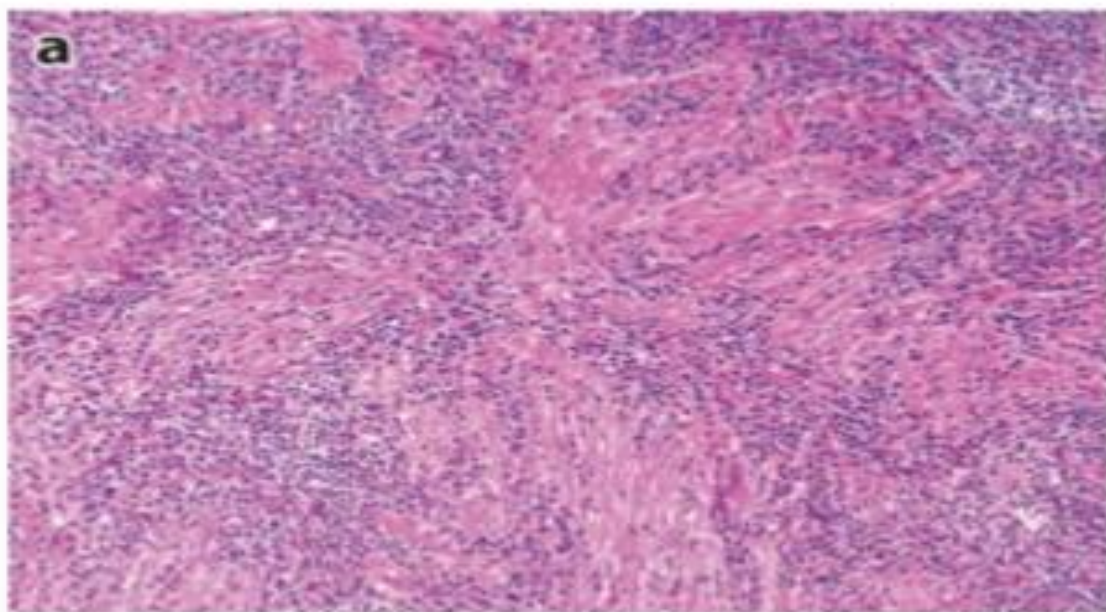


IgG4-related aortitis shows virtually entire wall of aorta. Although the media (inner layer, asterisk) is relatively unaffected, a dense lymphoplasmacytic infiltrate is present on adventitial aspect (outer layer) of aorta, and a vein obliterated by inflammation is indicative of obliterative phlebitis (arrow)

Histopathology In IgG4RD

- The current gold standard for the diagnosis of IgG4-RD is its characteristic histology and immunohistochemistry, which is almost the same regardless of the organs involved.
- Major histopathological features of IgG4-RD are dense lymphoplasmacytic infiltration with storiform fibrosis

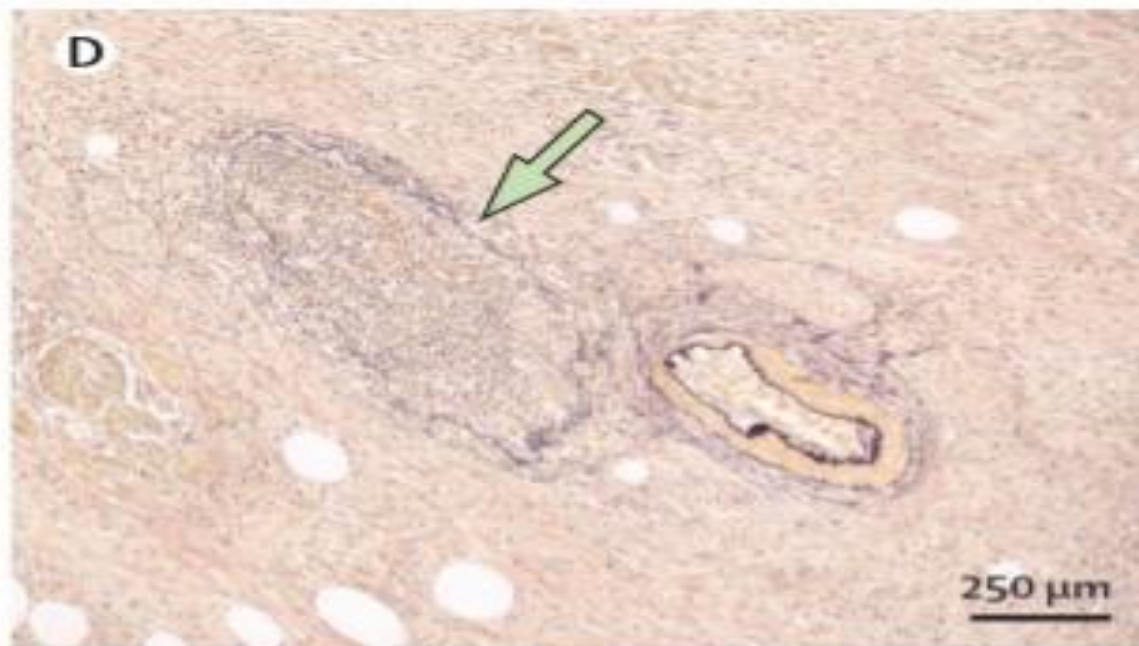
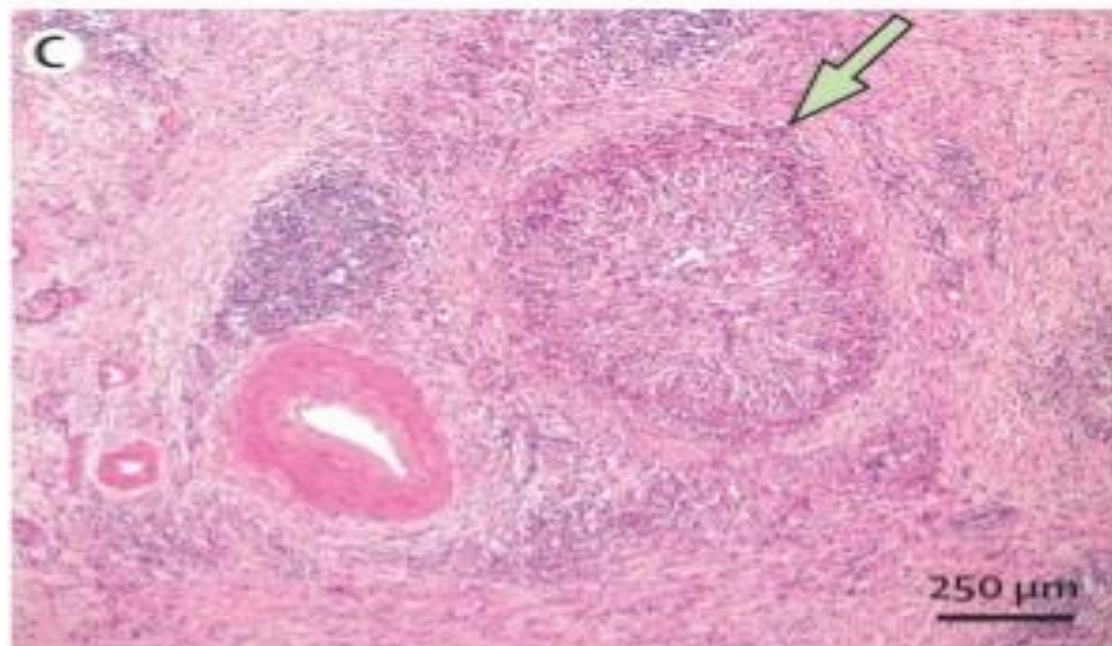
Storiform fibrosis



Histopathology In IgG4RD

- The current gold standard for the diagnosis of IgG4-RD is its characteristic histology and immunohistochemistry, which is almost the same regardless of the organs involved.
- Major histopathological features of IgG4-RD are dense lymphoplasmacytic infiltration with storiform fibrosis, **obliterative phlebitis,**

Obliterative phlebitis

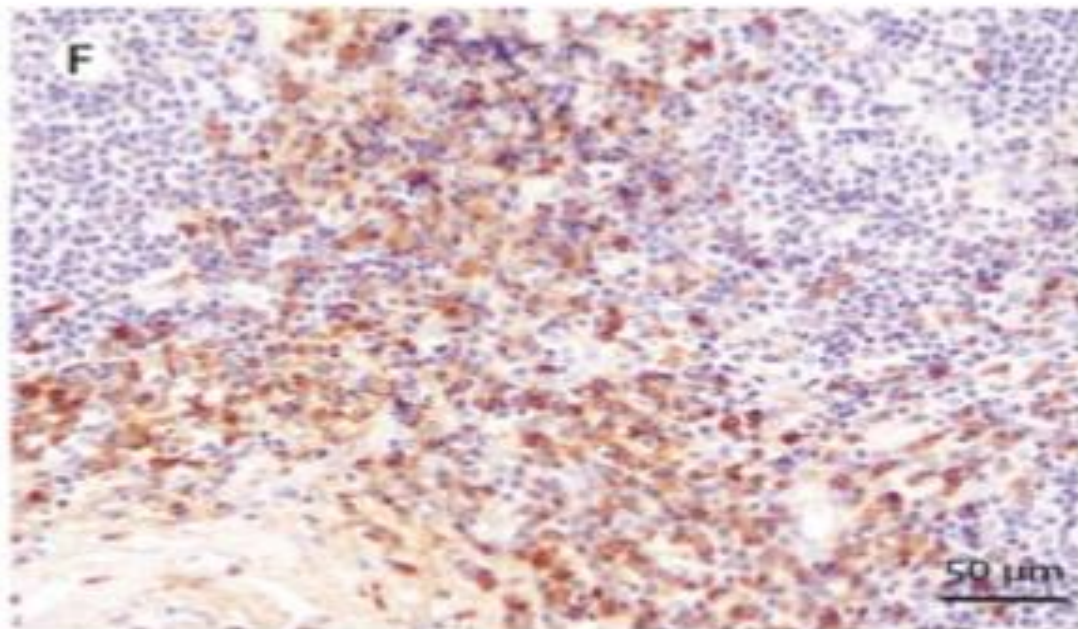
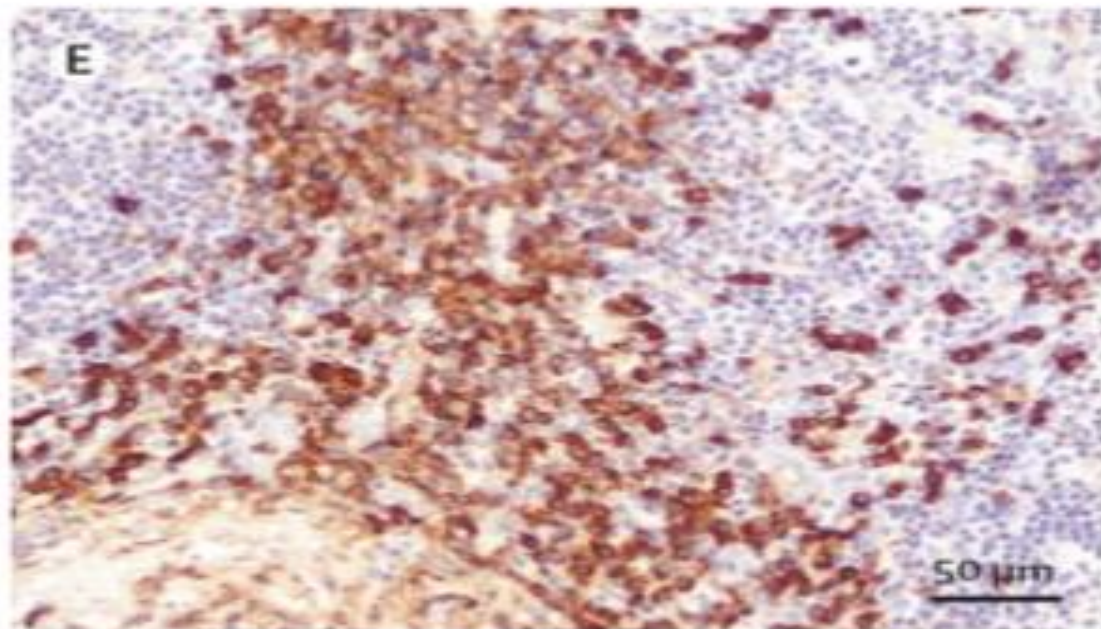


Obliteration of venous channels by extensive lymphoplasmacytic cell infiltration

Histopathology In IgG4RD

- The current gold standard for the diagnosis of IgG4-RD is its characteristic histology and immunohistochemistry, which is almost the same regardless of the organs involved.
- Major histopathological features of IgG4-RD are dense lymphoplasmacytic infiltration with storiform fibrosis, obliterative phlebitis, and **abundant infiltration of IgG4-positive plasma cells**

Immunostaining for IgG4 shows many IgG4-positive plasma cells



Histopathology In IgG4RD

- The presence of significant infiltration of IgG4-positive plasma cells in a biopsied specimen is not specific to IgG4-RD.
- Extensive IgG4-positive plasma cell infiltration has been described in other conditions that commonly mimic IgG4-RD
- One method that may help to distinguish IgG4-RD from other conditions is **semiquantitative** analysis of immunostaining. A frequently used cutoff value of infiltrated IgG4-positive plasma cells is more than **10 cells per high-power field (HPF)**, but the cutoff value varies according to the specific tissue

Histopathology In IgG4RD

- Confirmation of a diagnosis of IgG4-RD in long-standing IgG4-RD using histopathology can be **difficult**, since the tissue may have become predominantly **fibrotic**
- Measurement of the **IgG4-positive cell/total IgG-positive cell ratio**, in which a minimum ratio of **40 %** is usually used, may also be useful, especially in cases in which **fibrosis is predominant**
- Although malignancies can generally be excluded by needle biopsies, such biopsies often provide insufficient quantities of tissue to allow confirmation of a diagnosis of IgG4-RD. Samples from previous biopsied or resected specimens may be diagnostic if they are reviewed along with IgG4-immunostaining of paraffin-embedded specimens

Histopathology In IgG4RD

Biopsies of **lymph nodes** are often problematic to interpret with regard to the diagnosis of IgG4-RD because they **seldom undergo the storiform fibrosis** that is so highly characteristic of IgG4-RD, and large numbers of IgG4+ plasma cells can be found in multiple diseases in which IgG4-RD is not the diagnosis

Steroid Responsiveness

- Response to steroids can confirm a strong suspicion of the presence of IgG4-RD in patients with appropriate collateral evidence.
- In cases in which **sufficient biopsy specimens cannot be obtained**, such as cases where specimens are obtained from the biliary tract, it is difficult to differentiate IgG4-RD from malignancy, and, in such cases, a steroid trial can be applied.
- A steroid trial should **only** be applied to cases in which the effect of steroid **therapy can be evaluated** by imaging modalities, since symptomatic and hematological improvements occur nonspecifically in response to steroids, even in malignancy
- Those who respond poorly may include patients with more advanced fibrotic changes

ACR – EULAR first-ever classification

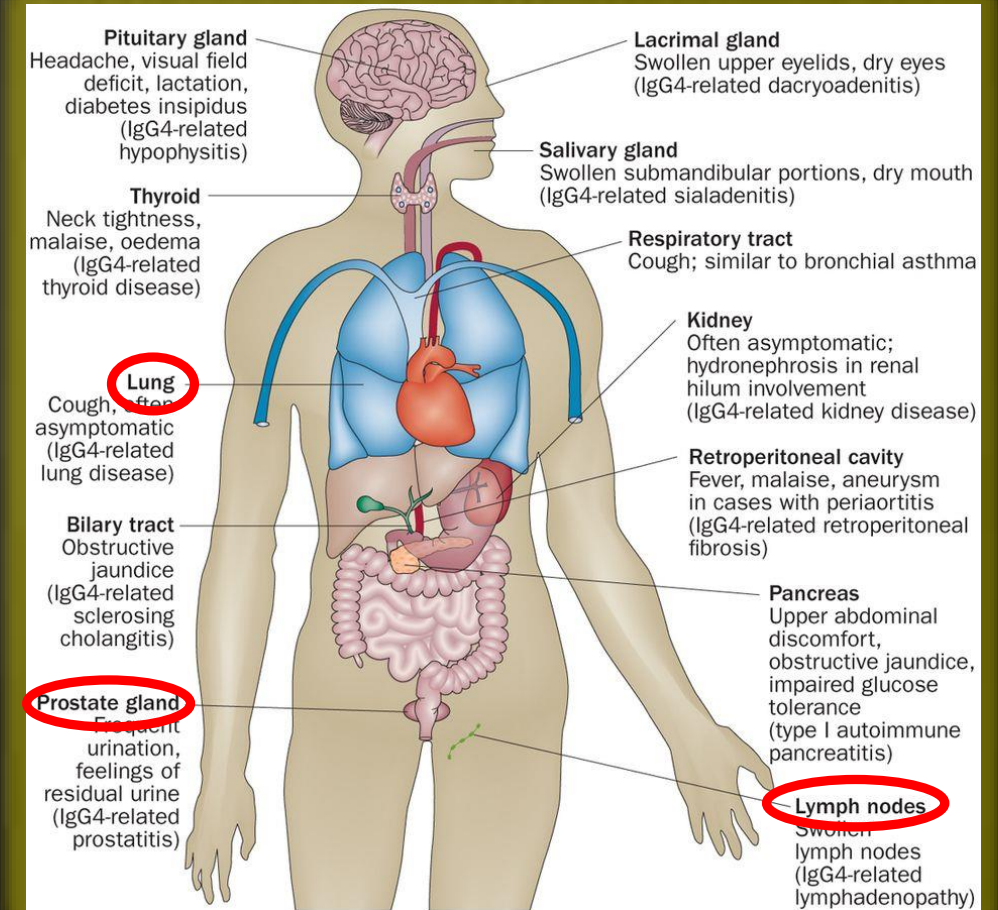
criteria for IgG4RD

99.2% specificity and 85.5% sensitivity

Nov2018 preliminary

1

- The first step in classifying a patient with IgG4-RD is to identify involvement of at least one organ from the list the panel compiled of 10 organs where involvement typifies the disease: pancreas, bile ducts, orbits, lacrimal glands, major salivary glands, retroperitoneum, kidney, aorta, pachymeninges, and thyroid gland



**Patients who do not have disease involvement in
at least one of these organs don't qualify as
having IgG4-RD**

2

- The next step is to rule out patients who have at least one exclusion criterion

Exclusion criteria for IgG4-related disease

Clinical exclusions	Fever Unresponsive to steroids Leukopenia and thrombocytopenia Peripheral eosinophilia ($>3,000$ per mm^3)
Serological exclusions	PR3 or MPO-ANCA positive Anti-Ro or La positive Extractable nuclear antibody positive Cryoglobulins Other disease-specific antibody
Radiology exclusions	Rapid radiographic progression Large bone abnormality (such as Erdheim-Chester disease) Splenomegaly Concern regarding infection, malignancy, or both
Pathology exclusions	Primarily granulomatous inflammation Necrotizing vasculitis Malignant infiltrate Prominent histiocytic infiltrate Prominent neutrophilic infiltrate Multicentric Castleman's pathology Prominent necrosis Inflammatory pseudotumor pathology

3

The last step is to identify enough individual classification hallmarks in the patient so that collectively they definitively identify IgG4-RD

IgG4-related disease inclusion domains and point assignments

Domains		Points
IgG4 level	Normal	0
	Above normal and less than 2× upper limit of normal	3.7
	2× to 5× ULN	6.1
	Above 5× ULN	10.8
Histopathology and immunostaining	Uninformative biopsy	0
	Dense lymphoplasmacytic infiltrate	3.7
	DLI plus obliterative phlebitis	6.1
	DLI plus storiform fibrosis	13.3
Lacrimal and major salivary gland enlargement	One set of glands involved	5.9
	Two or more sets of glands involved	13.8
Chest and thoracic aorta	Peribronchovascular and septal thickening	3.8
	Paravertebral band-like soft tissue in the thorax	9.8
Pancreas and biliary tree	Diffuse pancreas enlargement (loss of lobulations)	8.0
	Diffuse pancreas enlargement and capsule-like rim with decreased enhancement	10.5
	Pancreas and biliary tree involvement	18.7
Kidney	Hypocomplementemia	5.8
	Renal pelvis thickening or soft tissue or both	8.1
Retroperitoneum	Diffuse thickening of the abdominal aortic wall	4.1
	Circumferential or anterolateral soft tissue around the infrarenal aorta or iliac arteries	7.8

Note: A patient must tally at least 19.0 points to receive IgG4-related disease classification.

Source: Dr. Stone

Treatment IgG4RD

Who should be treated

- All symptomatic patients should be treated
- But Subclinical disease can lead to severe, irreversible sequelae in the biliary tree, kidney, aorta, mediastinum, retroperitoneum, mesentery, and other organs
- “Watchful waiting” may be appropriate, for example, in patients with asymptomatic lymphadenopathy , incidentally-detected lung nodules or mild submandibular gland enlargement?

Who should be treated

Watchful waiting ?

- The **metachronous** nature of IgG4-RD suggests that although the disease may appear to improve at least temporarily in one organ, it may re-emerge months or years later at a different site
- Approximately 50% of the relapse patients with IgG4-RD present with lesions in other organ
- Treatment leads to faster and more complete remission with fewer long-term complications of IgG4-RD than does waiting to treat

Treatment IgG4RD

- **Medical:**

Induction of remission

Maintenance therapy

- **Surgical**

Treatment Induction Therapy:

- **Glucocorticoids are the first-line agent for remission induction in all patients with active, untreated IgG4-RD, unless contraindications to such treatment are present typical starting prednisone dose is 40 mg/day**
- **Effective in controlling the disease in 90% of patients**

Induction Of Remission

➤ **Treatment response was defined by the presence of at least two of the following features**

improved clinical status

reduction in serum IgG4 concentration

improved radiologic findings

Induction Of Remission

Some but not all patients require the combination of glucocorticoids and a steroid-sparing immunosuppressive agent from the start of treatment

when add a steroid-sparing agent

- **when the patients are not able to taper glucocorticoid**

when add a steroid-sparing agent

- when the patients are not able to taper glucocorticoid
- **when the risks of recurrent flare during a glucocorticoid taper**
 - ★ **Multi-organ disease**
 - ★ **Significantly elevated serum IgG4 concentrations**
 - ★ **Involvement of the proximal bile ducts**
 - ★ **A history of disease relapse**

when add a steroid-sparing agent

- when the patients are not able to taper glucocorticoid
- when the risks of recurrent flare during a glucocorticoid taper
- **Patient who high risk for steroid complications?**

Azathioprine (AZA), mycophenolate mofetil (MMF),
6-mercaptopurine (6-MP),
methotrexate (MTX), tacrolimus and cyclophosphamide (CYC) have
all been employed as steroid-sparing agents

Maintenance Therapy:

- Continuing the initial glucocorticoid dose for 2–4 weeks followed by a gradual taper
- Many of the therapeutic studies cited above employed a taper of 5 mg per week until off in the US is to taper the glucocorticoid completely off within 2–3 months, Japanese clinicians often continue prednisone at a low to moderate dose (2.5–10.0 mg daily) for up to several years
- Without ongoing maintenance therapy, between 30% and 60% of patients relapse within 3 months of discontinuing glucocorticoid monotherapy

RTX for IgG4RD

- RTX is effective for both induction therapy and treatment of relapses in IgG4-RD, but relapses are frequent after B-cell reconstitution.
- Maintenance therapy with systematic RTX infusions is associated with longer relapse-free survival and might represent a novel treatment strategy.
- Yet, the high rate of infections and the temporary effect of RTX might be hindrances to such strategy.

Plasmablasts as a target of treatment

- **XmAb5871, a monoclonal antibody (homodimer) with a high-affinity variable region binding to CD19 and an enhanced Fc domain that binds to the FcγRIIb inhibitory receptor of B cells, is currently in phase II development for IgG4-RD treatment**

Surgical Treatment

- **Surgical debulking is an option for IgG4-RD involvement of some organs, but the suitability of surgical interventions is governed by the anatomic regions and adjacent structures involved.**
- **Some cases of highly fibrotic orbital disease are more amenable to surgical interventions than to medical therapy. As examples, some fibrotic orbital pseudotumors and sclerosing mesenteritis respond best to surgical resection when surgery is possible**

The background is a deep red with a soft, out-of-focus bokeh effect. Numerous small, glowing heart shapes in various shades of pink and red are scattered throughout the scene, creating a romantic and affectionate atmosphere. In the foreground, several red roses are visible; one is in sharp focus on the left, while others are blurred in the background. The overall color palette is dominated by reds and pinks, with some green from the rose leaves visible on the left.

Thank You