IgG4 Disease

General Principles of IgG4-related disease. EL Cluvar, AC Bateman

Diagnostic Guidelines for IgG4-related disease with a focus on histopathological criteria. V Deshpande, A Khosroshahi

Diagnostic Histopathology

J B King,
ST4 Histopathology

Definition

- Systemic fibro-inflammatory condition
- Tumefactive lesions with characteristic histopathological features
  - Dense lymphoplasmacytic infiltate
  - Storiform fibrosis
  - Obliterative phlebitis

History

- 1961 first description – pancreatitis with hypergammaglobulinaemia
- 1995 concept of ‘autoimmune pancreatitis’
- 2001 increased IgG4 serum levels with AI pancreatitis
- 2003 multiple extra-pancreatic lesions
- 2004 evolution of IgG4 – RD concept

By sarles et al

Epidemiology

- Older males, most > 60 yrs
- In Japan Estimated prevalence of AIP 0.8 cases / 100,000 per year
- Incidence 0.28-1.08 cases / 100,000 per year
- In US - 11% of pancreatic resections for benign disease had AIP

Organs involved in IgG4 disease

- Pancreas
- Bile duct
- Liver
- GI tract
- Salivary and lacrimal glands
- Orbit
- Retroperitoneum and mesentery
- Thyroid
- Lung
- Kidneys
- Breast
- Skin
- Pituitary gland
- Meninges
- Prostate
- Lymph nodes
- Pericardium
- Aorta

Conditions once viewed as separate disease entities and now recognized as a manifestation of IgG4-RD (adapted from Khosroshahi & Stone, 2011)

- Autoimmune pancreatitis
- Sclerosing cholangitis
- Mikulicz's syndrome – salivary and lacrimal glands
- Kuttner's tumour – submandibular glands
- Riedel's thyroiditis
- Retroperitoneal fibrosis (Ormond's disease)
- Mediastinal fibrosis
- Chronic sclerosing aortitis

Continued ...

- Inflammatory abdominal aortitis
- Orbital pseudotumour
- Eosinophilic angiocentric fibrosis – orbits, sinuses and nasal cavities
- Multifocal fibrosclerosis – orbits, thyroid gland, retropertioneum, mediatinum and others
- Idiopathic hypocomplementaemic tubulointerstitial nephritis with extensive tubulointerstitial deposits

Clinical characteristics

- Can affect most organ systems – symptoms depend on activity of disease and pattern of involvement
- Most subacute symptoms related to swelling of the organ
- Urgent – biliary disease, aortitis, pachymeningitis
- Incidentally – radiology, biochemistry, immunology, histology
- History of atopy in 40% – asthma, eczema, sinusitis
- Chronic dx – can occur over a long time – follow up

IgG4-related intracranial hypertrophic pachymeningitis with skull hyperostosis: a

- IgG4-related sclerosing disease represents a subset of cases previously diagnosed as idiopathic hypertrophic pachymeningitis.
- This rare inflammatory disorder causes localized or diffused thickening of intracranial dura mater.
- Headache, cranial nerve palsy, and ataxia are the most common clinical manifestations.
- dural biopsy is usually essential for a definitive diagnosis
- thick fibrous dura associated with chronic inflammation cell infiltrate consisting of lymphocytes and plasma cells;
- compression of neural structures by the thickened fibrous dura results in neurological defects

The Mayo Clinic HISORt criteria for the diagnosis of AIP – 2007

- Histopathology – one or both required
  - Characteristic appearances within biopsy or resection material
  - At least 10 IgG4-positive plasma cells per high power field within areas of lymphoplasmacytic infiltrate
- Imaging and serology – all 3 required
  - Diffusely enlarged pancreas with delayed and 'rim' enhancement
  - Irregular pancreatic duct
  - Increased serum IgG4 concentration

Mayo clinic criteria continued …

- Response to steroid therapy – all 3 required
  - Unexplained pancreatic disease after a full clinical workup including exclusion of cancer
  - Raised serum IgG4 concentration and/or extra-pancreatic organ involvement with increased numbers of tissue IgG4-positive plasma cells
  - Resolution or marked improvement in disease with steroid therapy

The Japanese Comprehensive diagnostic criteria for IgG4-rd

1. Clinical examination showing characteristic diffuse/localised swelling or masses in single or multiple organs
2. Elevated serum IgG4 >135mg/dl
3. Histology
   - Marked lymphocytic and plasma cell infiltration and fibrosis
   - Infiltration of IgG4 + plasma cells; ratio of IgG4+ : IgG+ > 40% and >10 IgG4 + plasma cells /hpf

- Definite = 1+2+3, probable = 1+3, possible 1+2
- Exclude malignancy

Lab findings

- Serological dysfunction
- Elevated Serum IgG4 80% of patients
- x2 upper limit specificity of 99% in AIP
  - Normal 1.4g/l
  - Sig fn rate – the patients more benign disease
  - False pos rate – 10% with pancreaticobiliary malignancy; 5% healthy individuals

    also allergic diseases, Parasitic infections, Immunotherapy, beekeepers

- ANA in 50%
- IgE, ESR, CRP, eosinophilia – not specific

Radiological findings

- Diffuse or focal
- Mass forming – may simulate tumours
- AIP characteristic – diffusely enlarged pancreas, delayed and rim enhancement, irregular pancreatic duct
- Changes may resolve with treatment depending on stage and how much fibrosis – scarring won't resolve

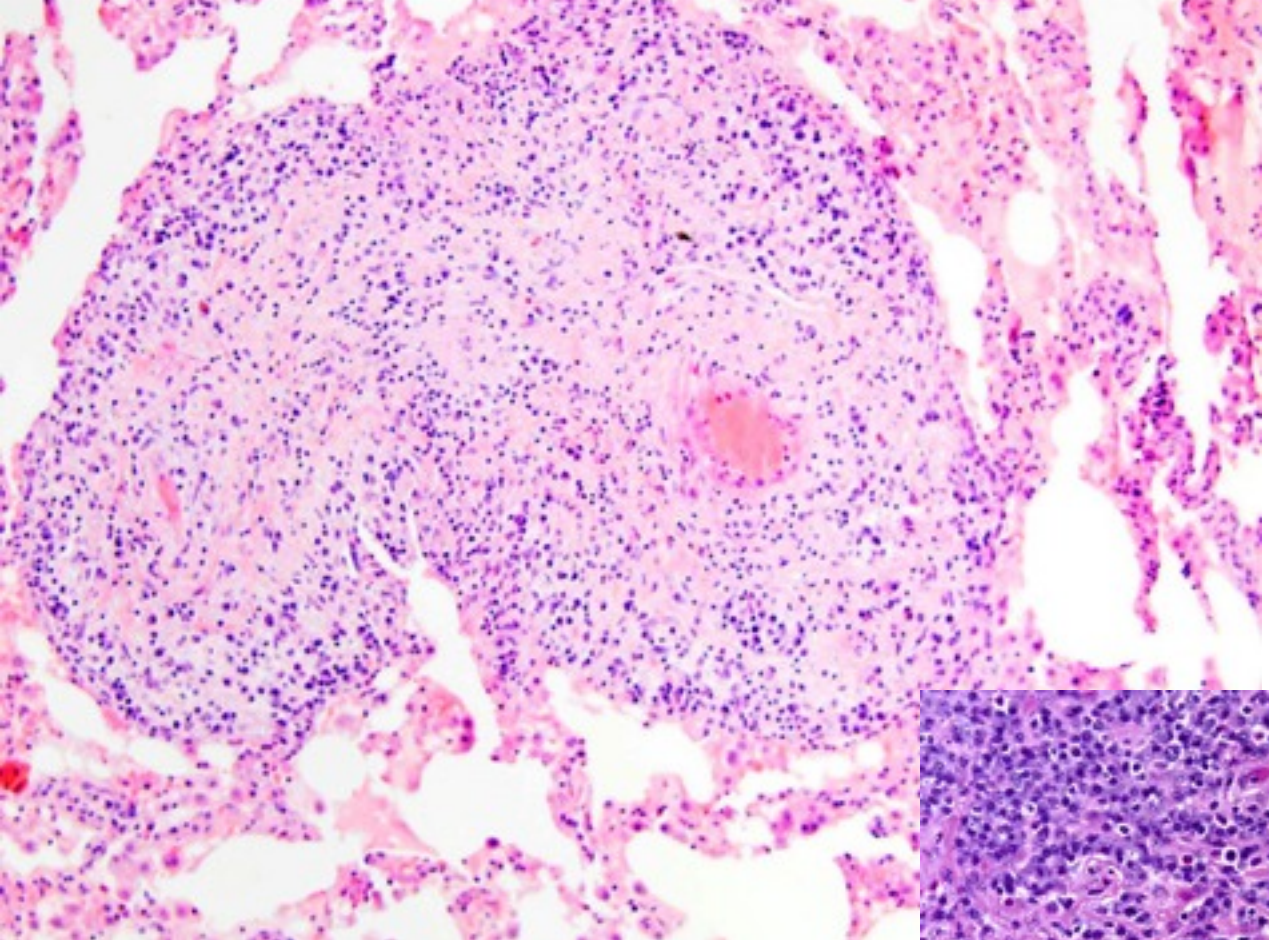
Histopathological features

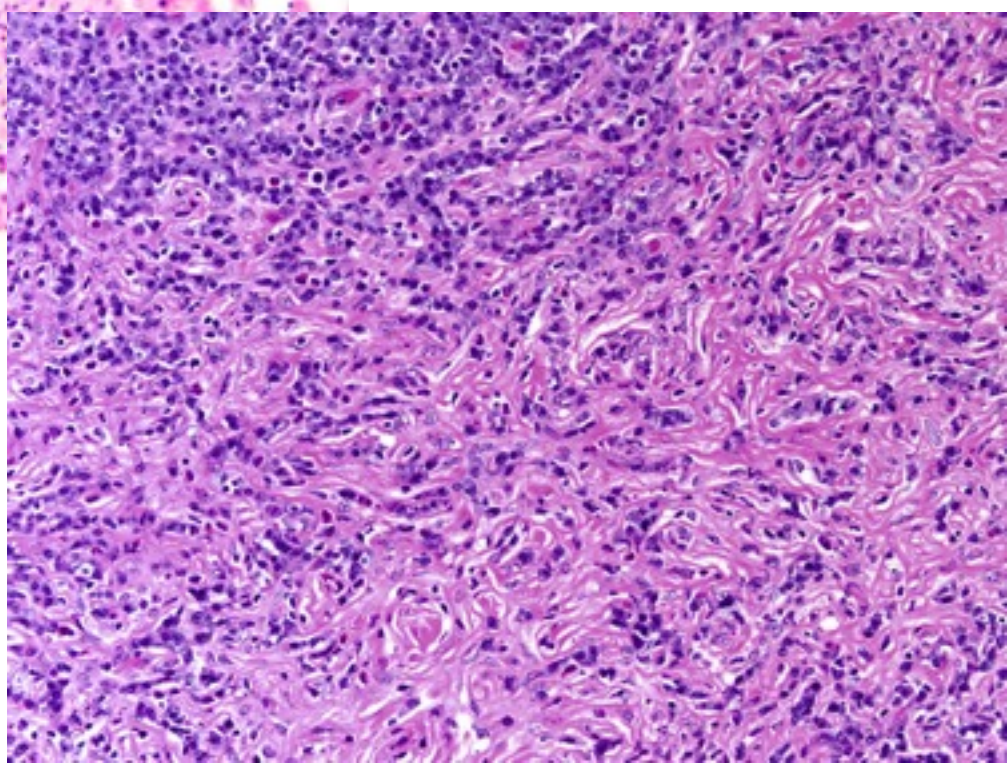
- Triad of key morphological features
  - Lymphoplasmacytic inflammation
    - Dense usually associated with germinal centre formation
    - Eosinophils may be prominent
    - Mass-forming or diffuse
    - Prominent IgG4+ plasma cells
    - High IgG4+ / IgG+ ratio – 40%
    - Granulomas not feature – if present unlikely to be IgG4

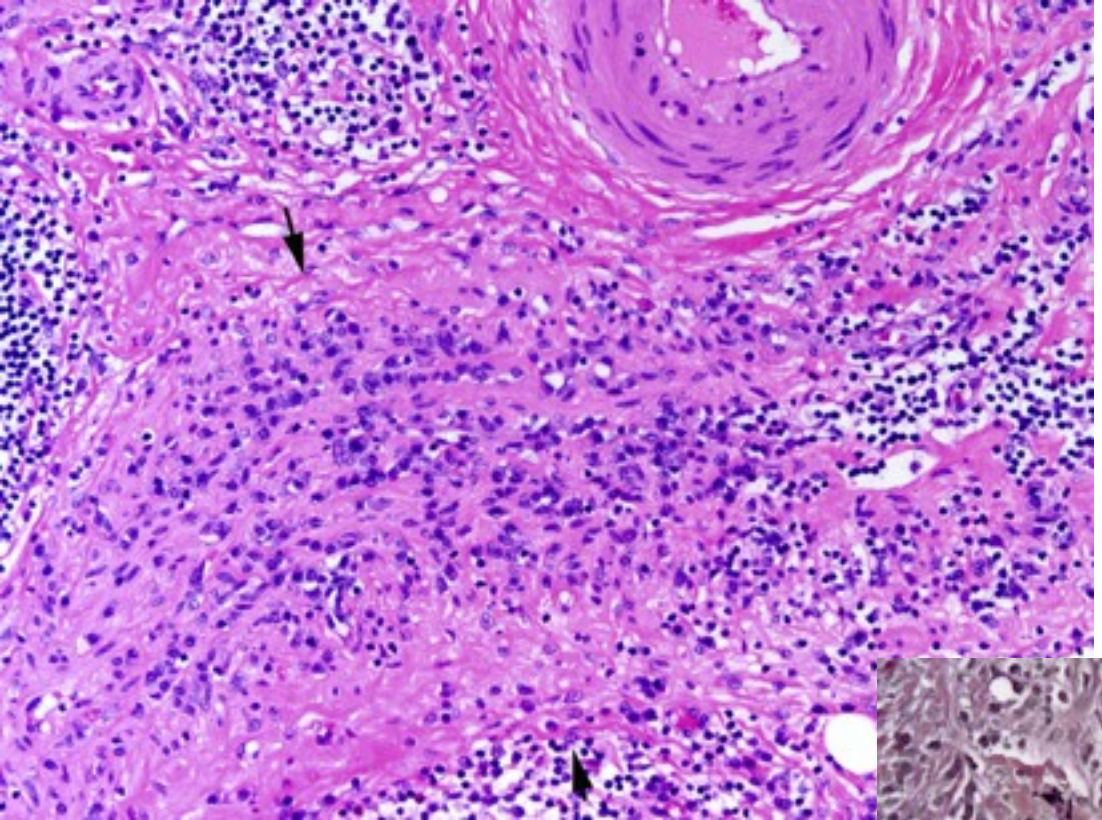
Histopath features continued ...

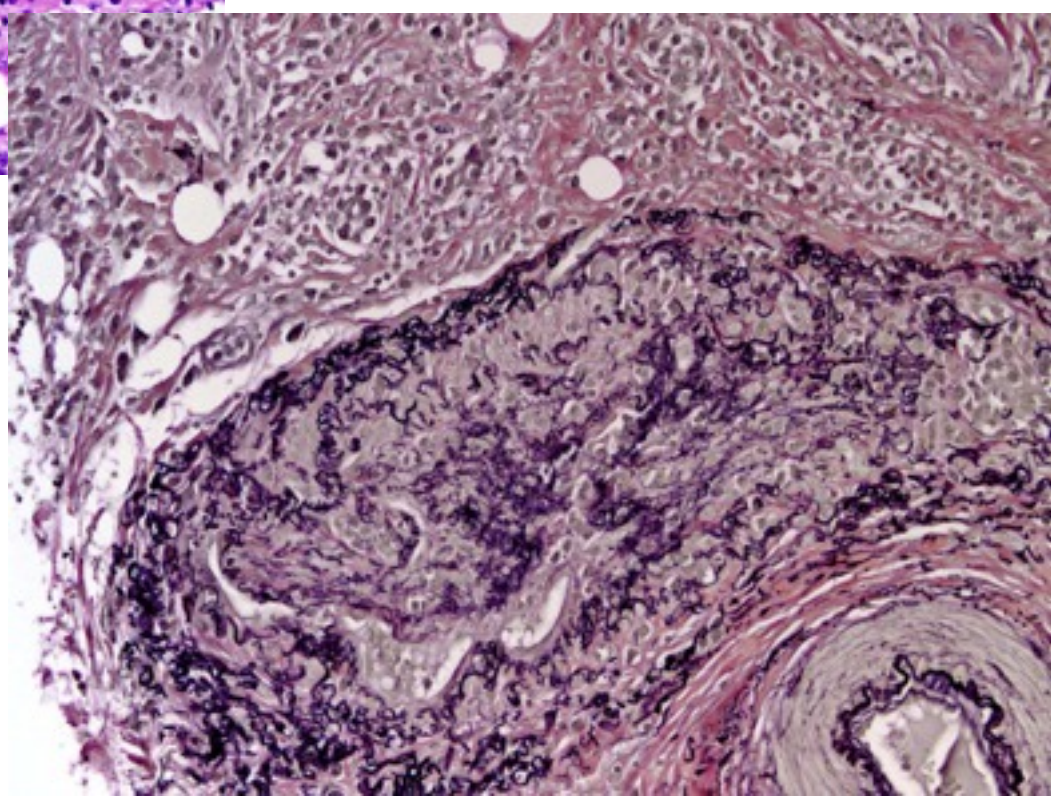
- Storiform fibrosis
  - Closely packed myofibroblasts and fibroblasts
  - Hyaline and keloidal fibrosis may be seen
- Lymphocytic / obliterative venulitis
  - EVG may be helpful

  - Obliterative arteritis is less common – can be seen in pulmonary and pancreatic lesions
  - Lack fibrin and necrotising inflammation



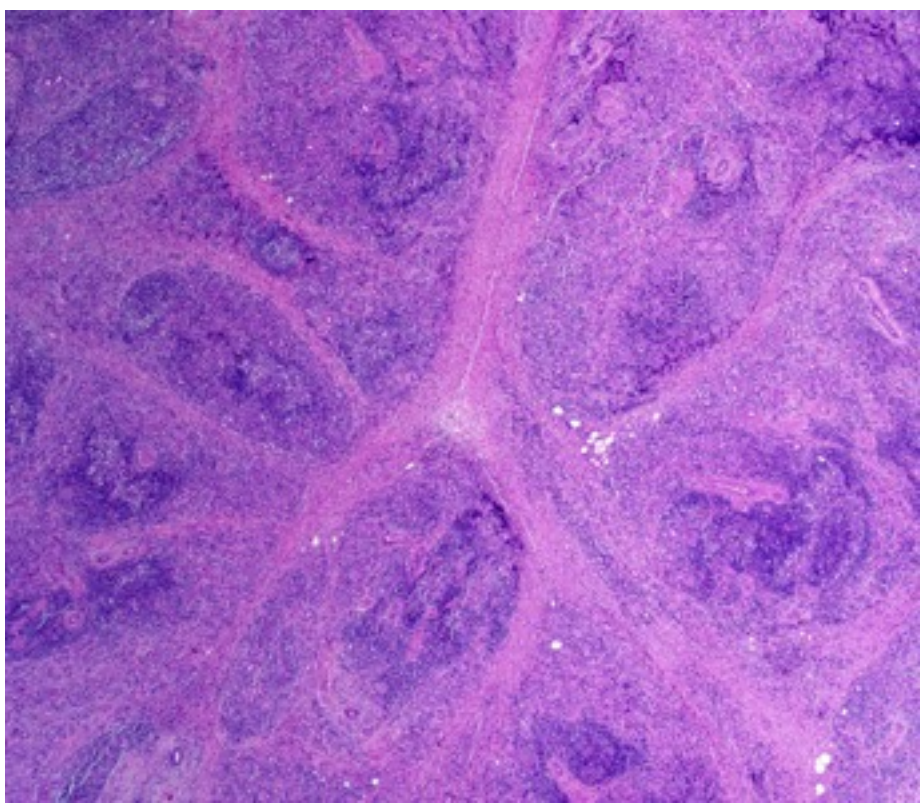






- Some variation in morphology
  - Lack of fibrosis or obliterative phlebitis in LN dx
  - Orbital disease – lacks obliterative phlebitis

  - Jigsaw puzzle-like low power appearance pancreas and submandibular gland



IgG4 plasma cell counts

- Mean count within 3 hpfs containing the greatest number of IgG4+ plasma cells
- 20 cells/hpf more specific
- Minimum counts vary between tissues and the amount of tissue
- Total IgG cells to calculate the ratio – 40%
- IgG difficult to do because of background staining
- Nos will reduce if pt has been on treatment

Suggested cut off points for IgG4 Counts

- Lacrimal gland >100
- Salivary gland >100
- Lymph node >100

- Lung (surgical specimen) >50
- Lung (biopsy) >20
- Pleura >50
- Pancreas (surgical specimen) >50
- Pancreas (biopsy) >10
- Bile duct (surgical specimen) >50
- Bile duct (biopsy) >10
- Liver (surgical specimen) >50
- Liver (biopsy) >10
- Kidney (surgical specimen) >30
- Kidney (biopsy) >10
- Aorta >50
- Retroperitoneal >30
- Skin >200

Autoimmune aeitology?

- Evidence for an autoimmune aetiology
- Multisystem disease is common
- Serum IgG often raised
- Involved organs show CI and scarring
- Assn with particular HLA genotype
- Immune complex deposition often present within involved tissue
- Many show response to anti inflam therapy

- 4 subclasses of IgG
- IgG4 least common
- 1-3 activate complement
- 1,3,4 opsonise bacteria
- 4 prob immunoregulatory
- Th2 response

- Th2 response and increased expression of related cytokines
- IL-4
- IL-5 – eosinophilia
- IL-13
- IL-10 – class switch

} production of IgG4

- Activation of regulatory T cells – TGF-β – fibrosis

Treatment

- Corticosteroids
- Relapse = 35.8%
- Recurrent and refractory disease
  - Azathioprine, mycophenolate, and methotrexate
  - Retuximab – B-cell depletion
  - Those with fibrosis have less of a response

Differential diagnosis

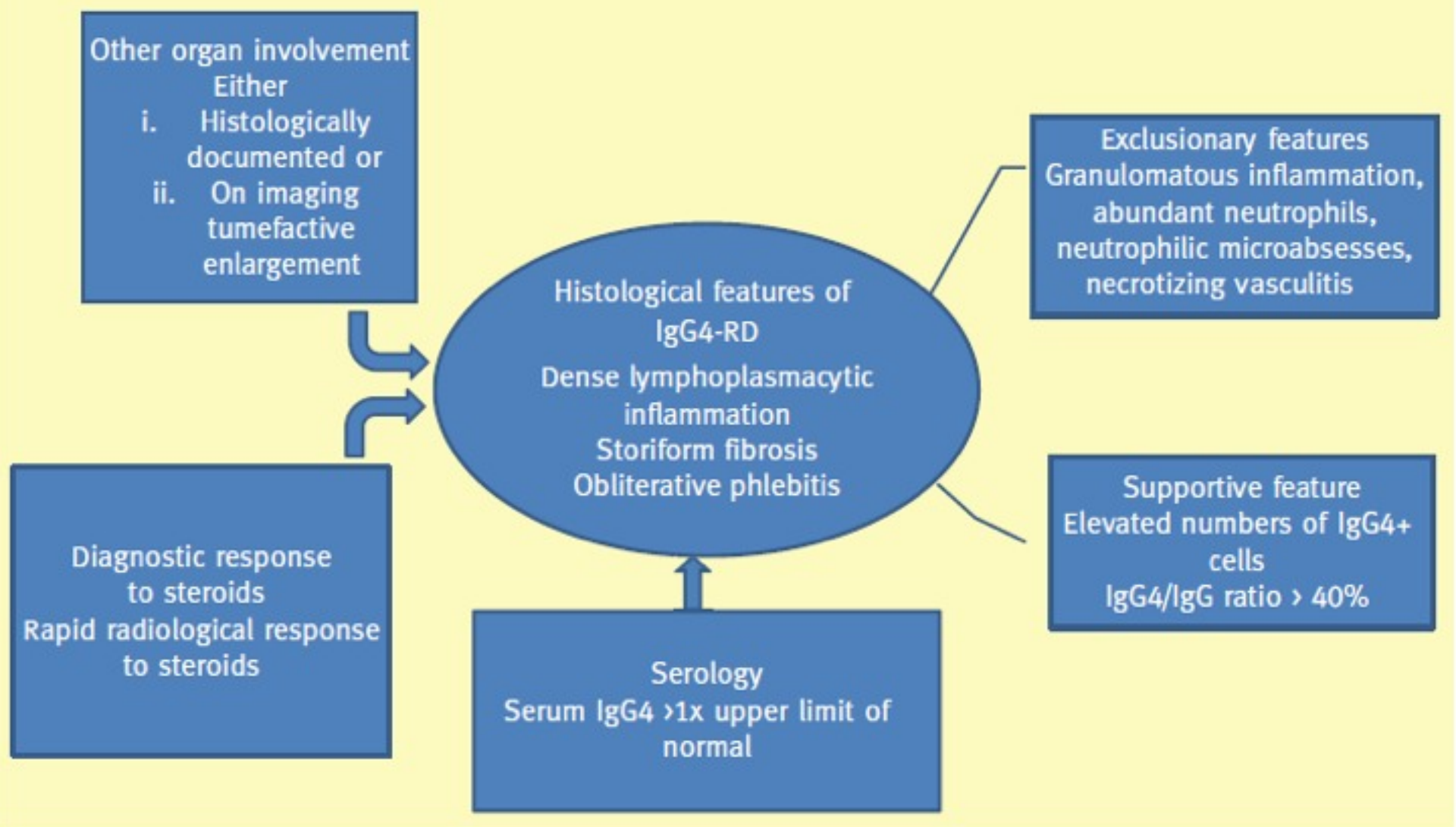
- immune-mediated conditions mimic IgG4-RD:
  - Sjögren's syndrome,
  - ANCA-associated vasculitides (granulomatosis with polyangiitis),
  - microscopic polyangiitis,
  - Churg Strauss syndrome,
  - sarcoidosis
  - Behcet's disease

DD: lack histological profile but assn with high IgG4

- Tumefactive lesions of pancreas + liver
- Lymphomas – low grade B cell
- Oral inflammatory disease
- Allergic rhinitis
- Rheumatoid arthritis
- Primary sclerosing cholangitis

DD: disease show both histologic appearance and high IgG4

- Granulomatosis with polyangitis
- Atypical features for IgG4 :
  - Granulomatous inflammation
  - Giant cells
  - Necrosis
  - Neutrophilic microabscess



Proposed algorithm for the diagnosis of IgG4-related disease (adapted from 1: Deshpande V. The pathology of IgG4-related disease: Critical issues and challenges. Semin Diagn Pathol. 2012 Nov; 29 (4): 191e6. http://dx.doi.org/10.1053/j.semdp.2012.08.001. PubMed PMID: 23068297.).

Diagnostic criteria

- Mayo Clinic 2007
- Diagnosis requires the presence of features within at least one of these groups
  - Histopathology
  - Imaging and serology
  - Response to steroid therapy

- Spectrum of presentation
- Orbit, thyroid, lung, AI pancreatitis – classical
- Liver – sclerosing cholangitis, pseudotumour, hepatitis
- Kidney – Mass, nephritis
- Retroperitoneal fibrosis

- Stomach = gastric ulceration
- Colorectal polyps
- Intraductal papillary mucinous neoplasm of the pancreas – assn with

Boston census criteria

- Highly suggestive can't rely on IgG4 count on its own
- Probable
- insufficient