IgG4-Related Disease: Challenges in Diagnosis and Management

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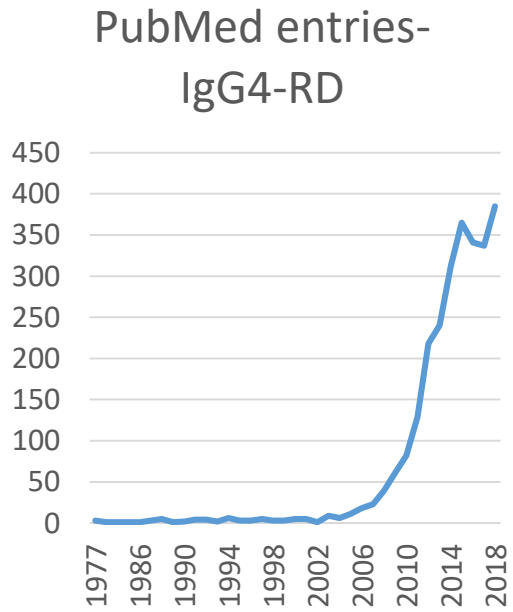
Relevant disclosures

- Clinical trials: Novartis, Bristol-Myers, Roche, Lilly
- Royalties: UpToDate
- Consultancies within the past 12 months:
  - Bristol-Myers Squibb
  - Sanofi
  - Viela Bio
- I will mention the use of rituximab for IgG4-related disease. This therapy is not approved by the FDA for this indication.

IgG4-related disease (IgG4-RD)

- Recently recognized fibro-inflammatory, immune-mediated disorder
  - First described in Japan in 2003
- Clinical presentation often one of tumor-like organ swelling or incidental biopsy findings
- May affect many organs



Timeline of discovery in Japan

IgG4 plasmacytic infiltration involves other organs (2003)

"IgG4-positive multiorgan lympho-proliferative syndrome" (2008)

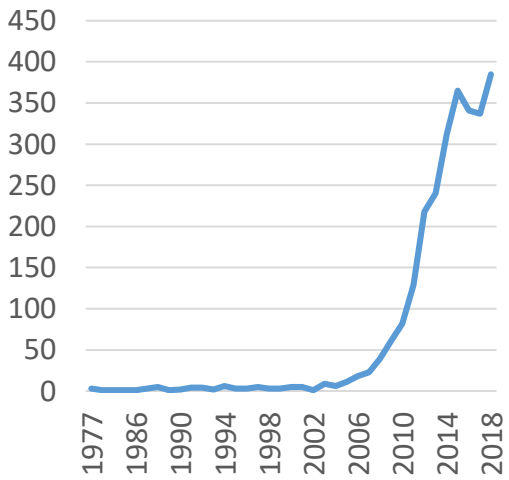
1990 — 2000 — 2010

Studies of Mikulicz disease (MD)

Autoimmune pancreatitis associated with high serum IgG4 levels (2001) and an IgG4-positive plasmacytic infiltrate (2002)

MD associated with high serum IgG4 levels and an IgG4-positive plasmacytic infiltrate (2004)

PubMed entries-IgG4-RD



Spectrum of IgG4-related disease

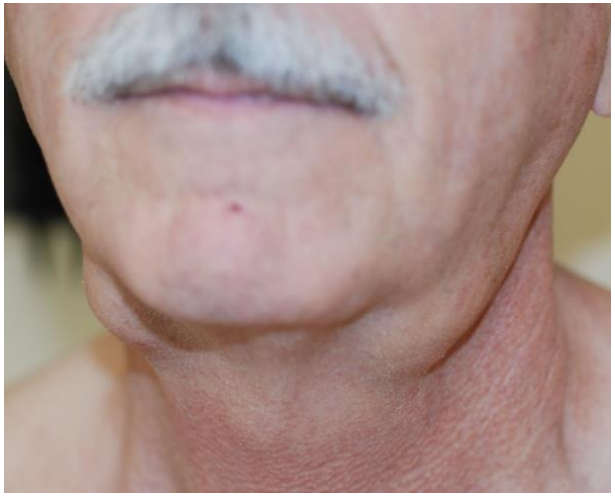
- Autoimmune pancreatitis (type 1)
- Sclerosing cholangitis
- Mikulicz syndrome
- Chronic sclerosing sialadenitis (Küttner tumor)
- Riedel's thyroiditis
- Tubulointerstitial nephritis
- Retroperitoneal fibrosis (Ormond disease)
- Mediastinal fibrosis
- Inflammatory pseudotumor (lung, breast, liver)
- Lymphoplasmacytic aortitis

IgG4-RD: An evolving experience

- Limited value of serum IgG4 as a diagnostic marker
- Increasing use of core needle biopsies and thus limitations on use of histopathologic criteria
- Emphasis on clinico-pathologic correlation and differential diagnosis
  - Clinical features
  - Serologic results
  - Radiologic findings
  - Pathologic interpretation

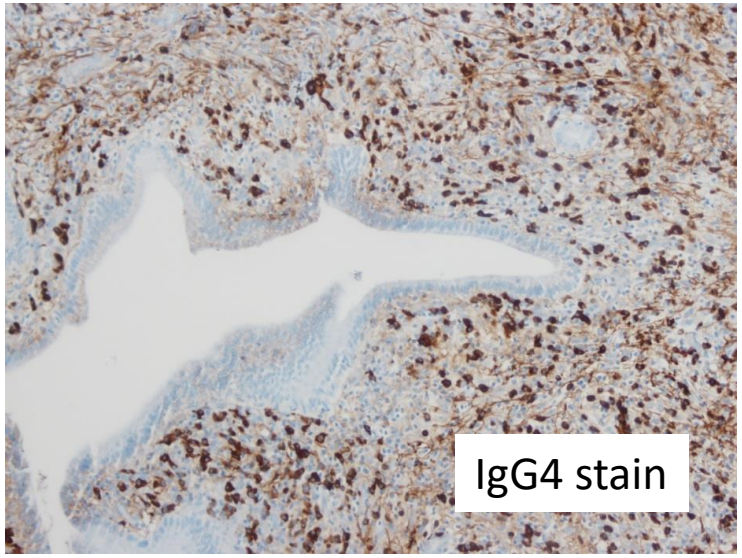
69 year old man

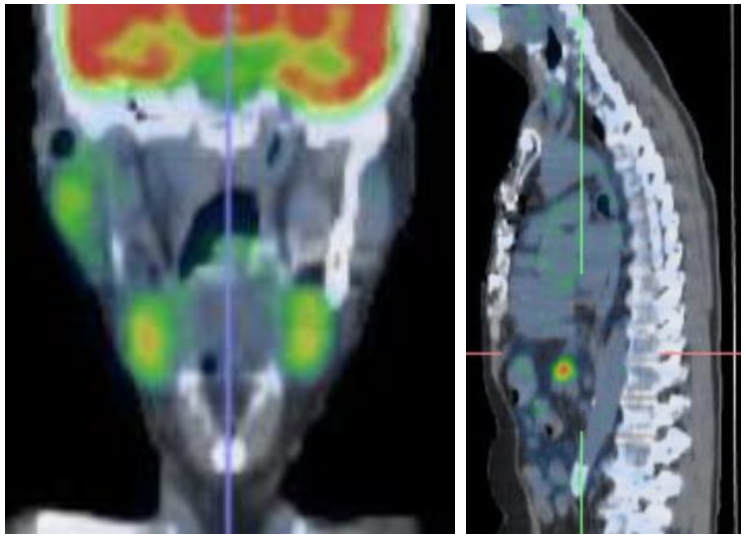
- January 2010: painless jaundice secondary to 2 cm bile duct stricture
- March 2010: Whipple procedure
  - Autoimmune pancreatitis on path
  - Normal serum IgG4
- November 2011: rheumatology referral
  - Dry eyes and mouth
  - Abnormal Schirmer's
  - Progressive enlargement of submandibular > parotid glands since 1/2010
  - Weak urinary stream
  - Rhinosinusitis



Case-cont'd

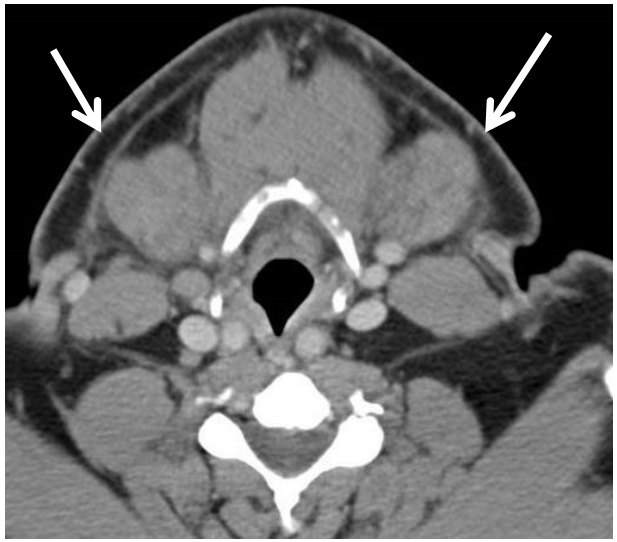
- Evaluation at JHH-April 2012
  - Induration and enlargement of parotid and submandibular glands
  - WBC 6200 (6% eosinophils)
  - IgG 2480, IgG4 36.9 mg/dl
  - ANA 1:40, negative SSA and SSB antibodies
  - Negative rheumatoid factor
  - IgE 569
- Treatment with prednisone and later rituximab

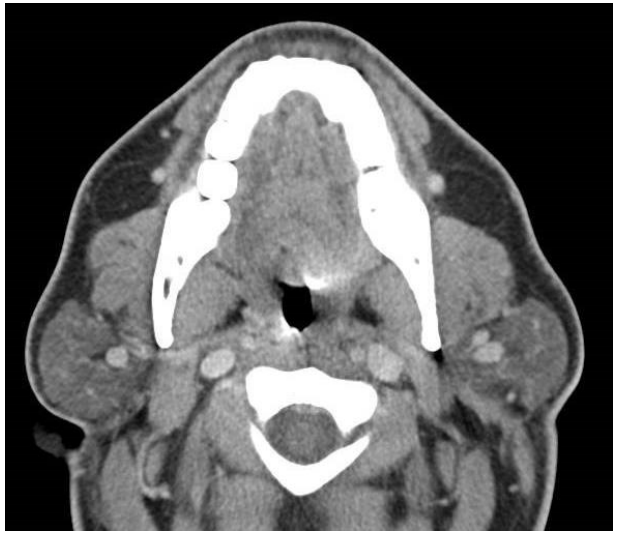




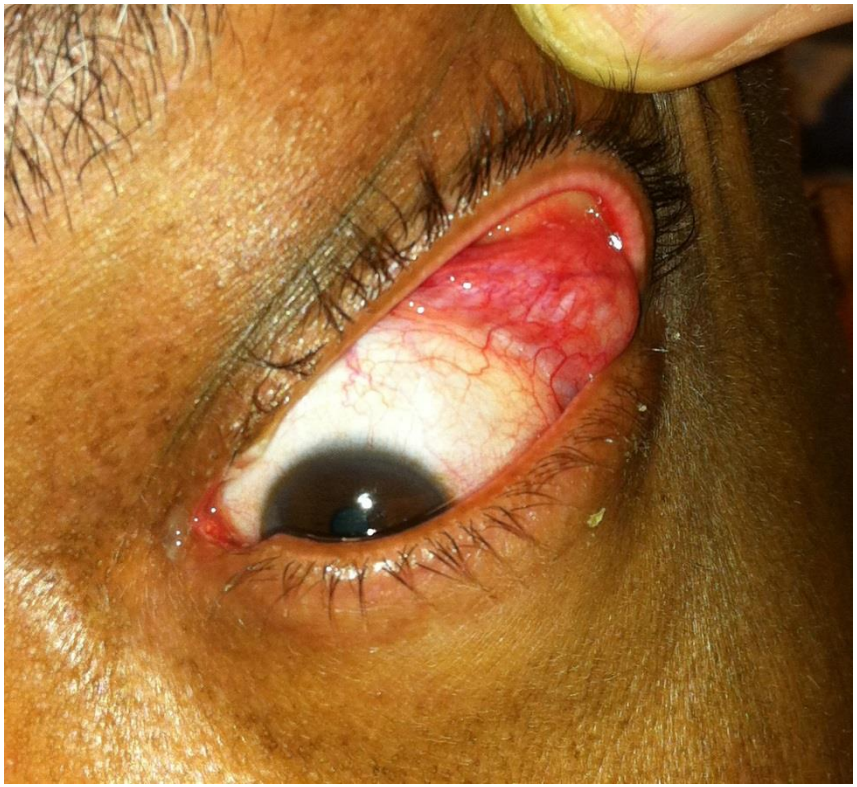
51 year-old man

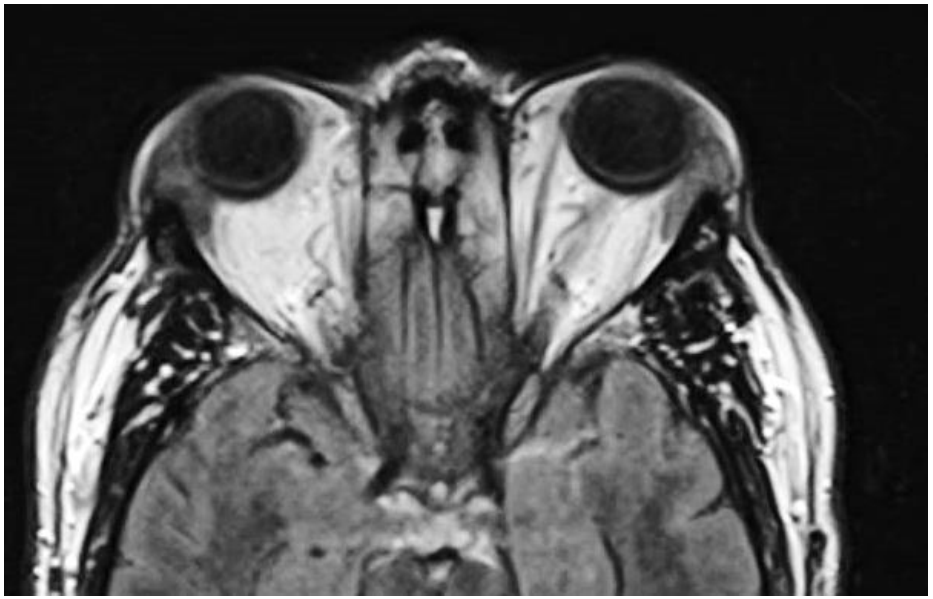
- Eczema and asthma as a child, chronic rhinosinusitis as an adult
- Early 2016: bilateral “neck lumps”
  - CT shows prominent submandibular glands
- Labs
  - ACE 26
  - WBC 10100/mm^3, 4.6% eos
- Referred by ENT physician to evaluate submandibular gland enlargement



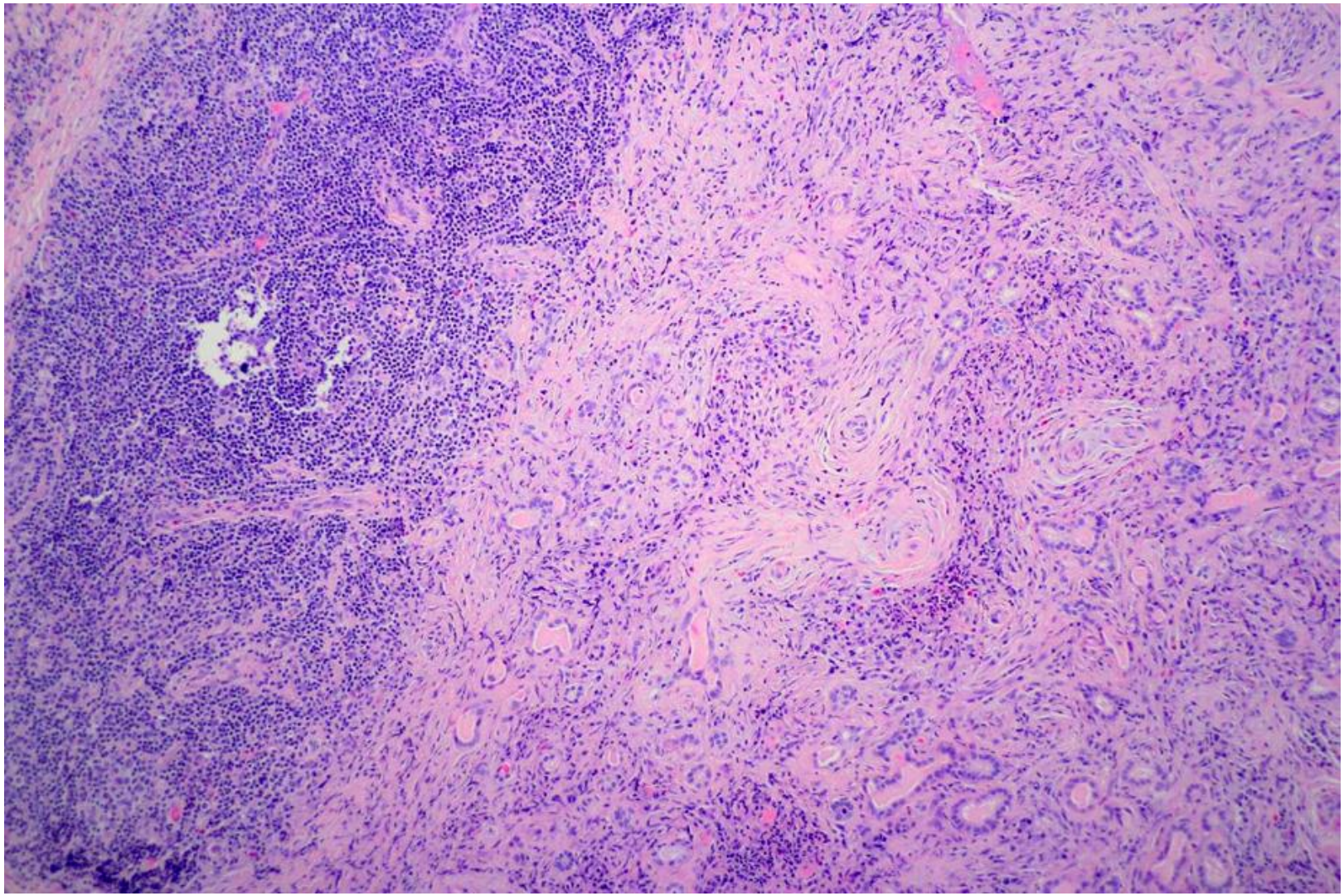


“Two years ago, they removed a tumor from my eye”



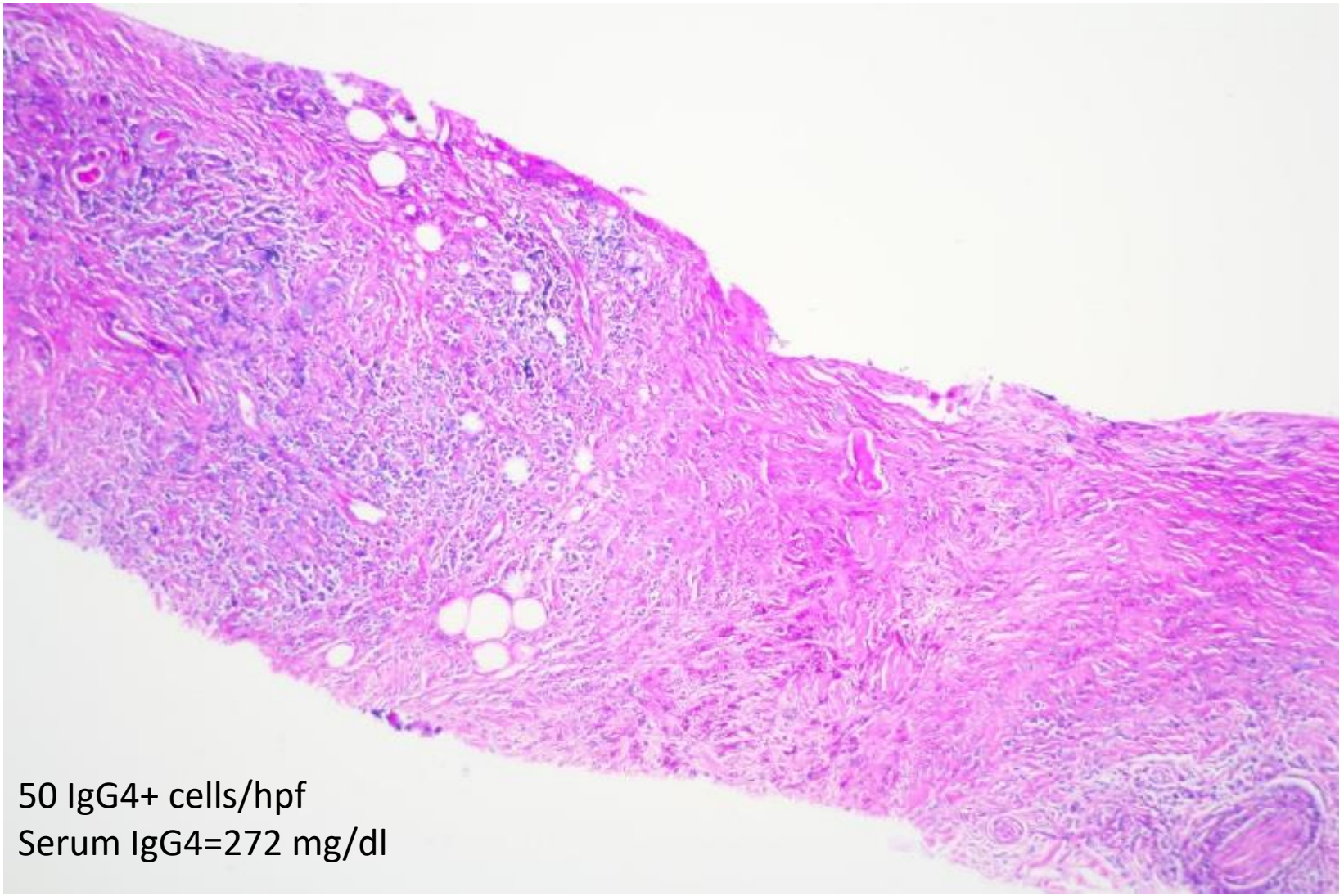


Lacrimal gland biopsy was read as non-specific dacryoadenitis.



116 IgG4+ plasma cells/hpf

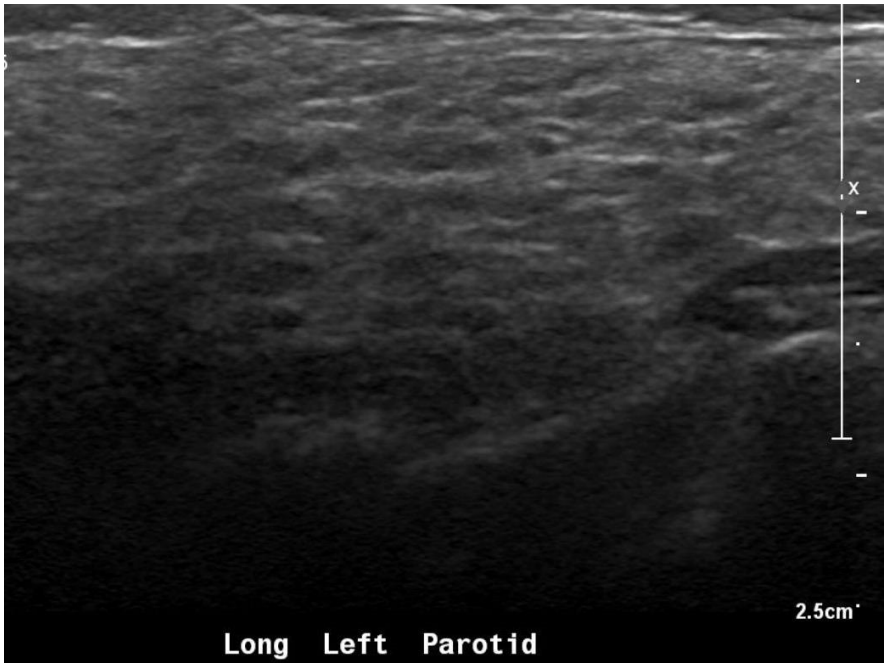
Core needle biopsy: submandibular gland

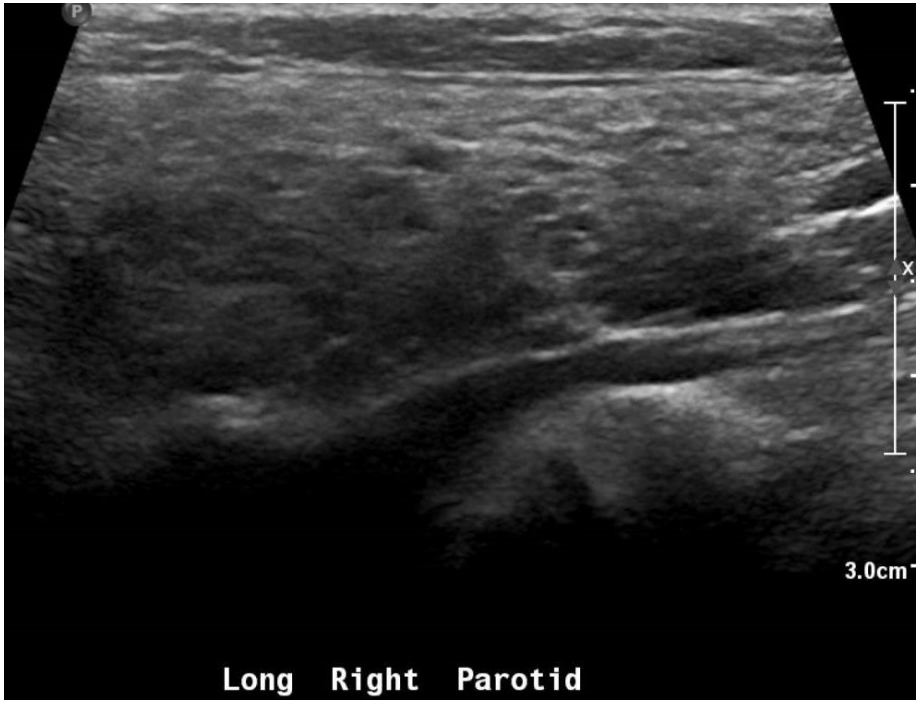


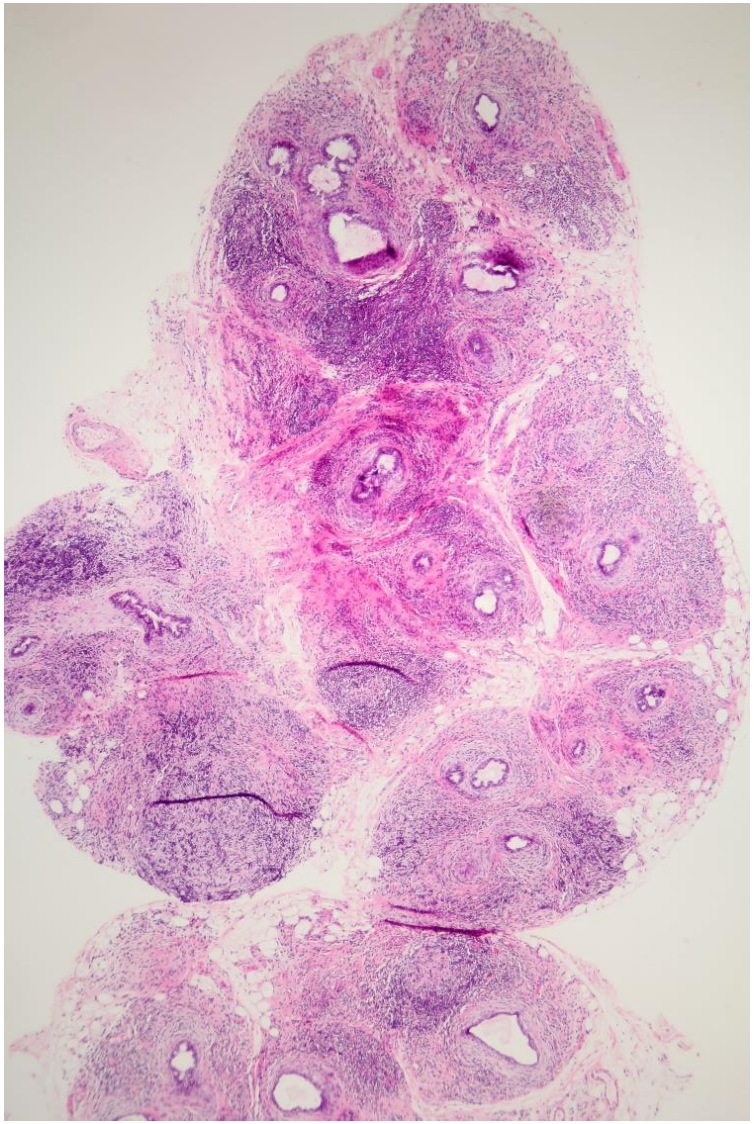
55 year old African-American woman

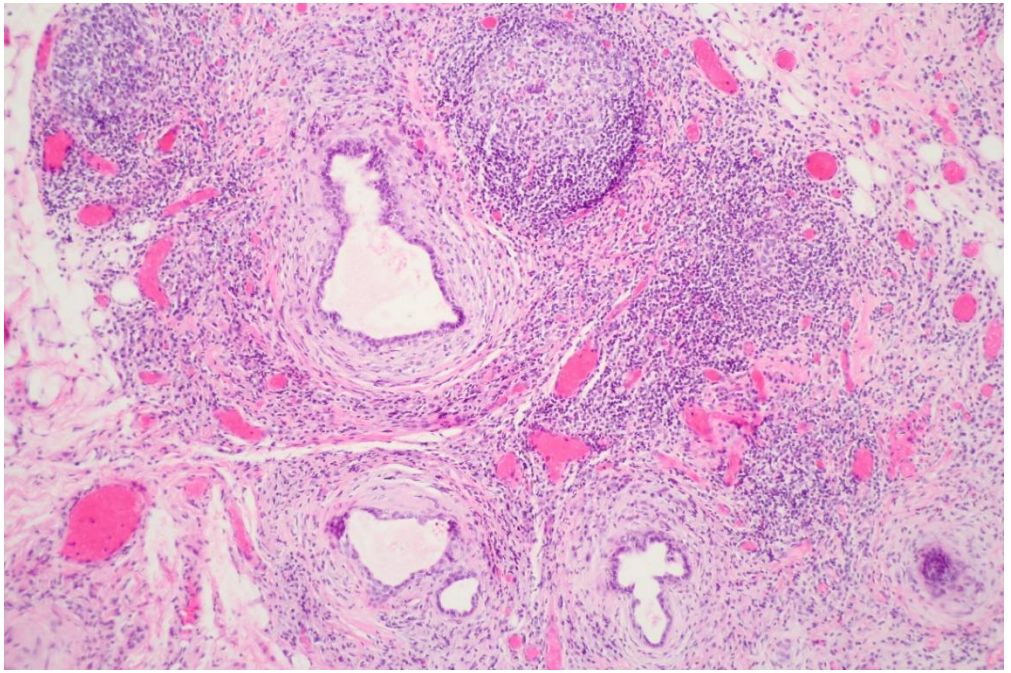
- History
  - 2 year history of chronic rhinosinusitis
  - 6 month history of severe dry mouth, leading to 35 lb weight loss
  - Intermittent chest tightness with normal PFTs
  - No dry eye symptoms
- Exam:
  - parotid and submandibular gland swelling
  - Severe dry mouth with atrophic glossitis
- CT scan sinuses: pansinusitis
- CT scan lungs: Minimal bronchial wall thickening with tree in bud opacities in the lower lobe
- WBC 9260, 5% eosinophils
- Anti-Ro, La negative, RF negative, IgG 1420, IgG4 231 mg/dl

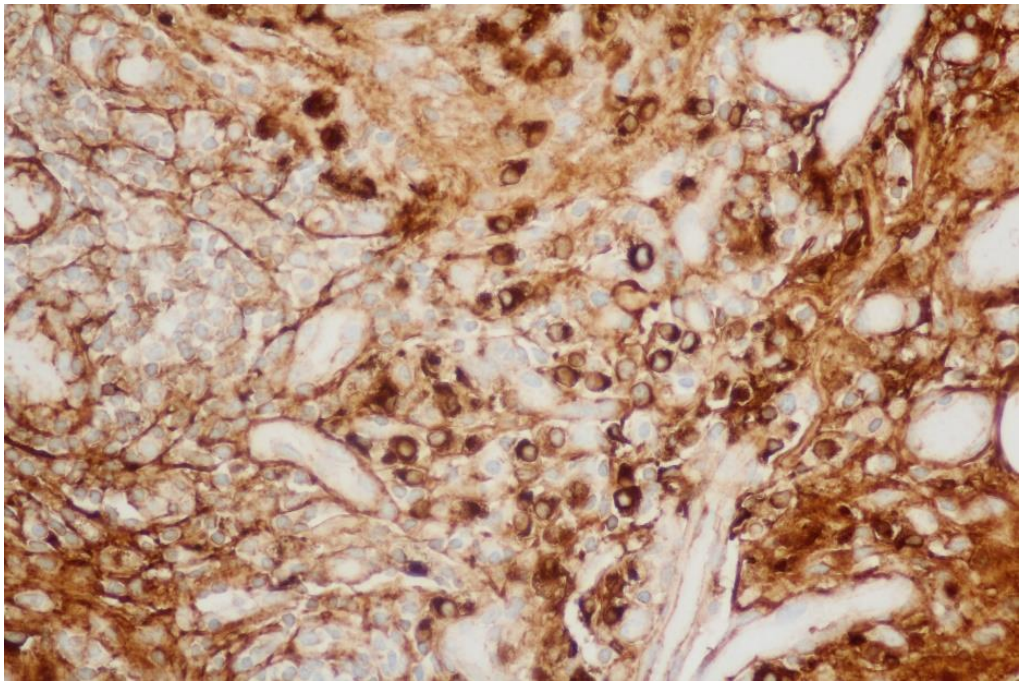
Parotid ultrasound











Rituximab, methotrexate
and later leflunomide

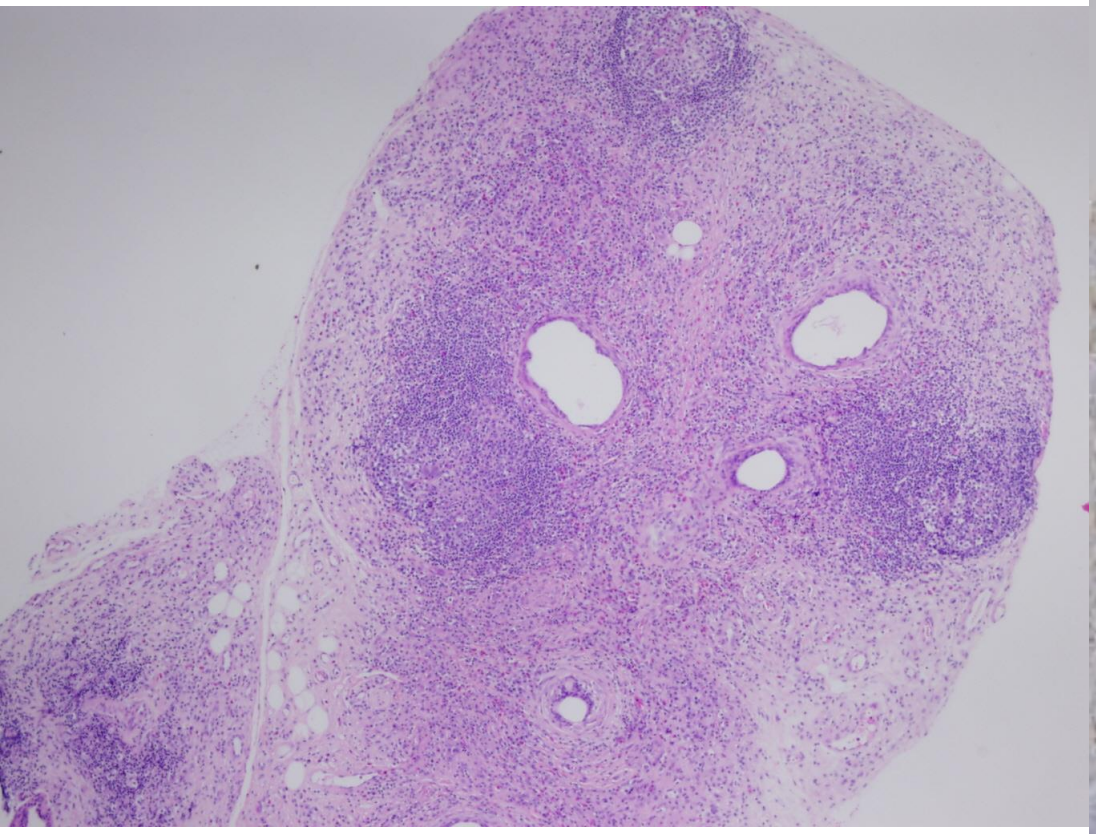
66 year-old man

- 9 months ago
  - two episodes of pneumonia, followed by a productive cough and dyspnea.
- 6 months ago
  - Onset parotid and submandibular gland enlargement, severe xerostomia, dry eyes, 25-pound weight loss, and night sweats.
- 1 month ago
  - Needle biopsy of the left parotid gland: polymorphous lymphocytic infiltrate, but no evidence of neoplasm.
- Initial evaluation at JHH ENT clinic:
  - diffuse enlargement and induration of his parotid (left > right) and submandibular glands.
  - Dry oral cavity
  - No palpable lymphadenopathy

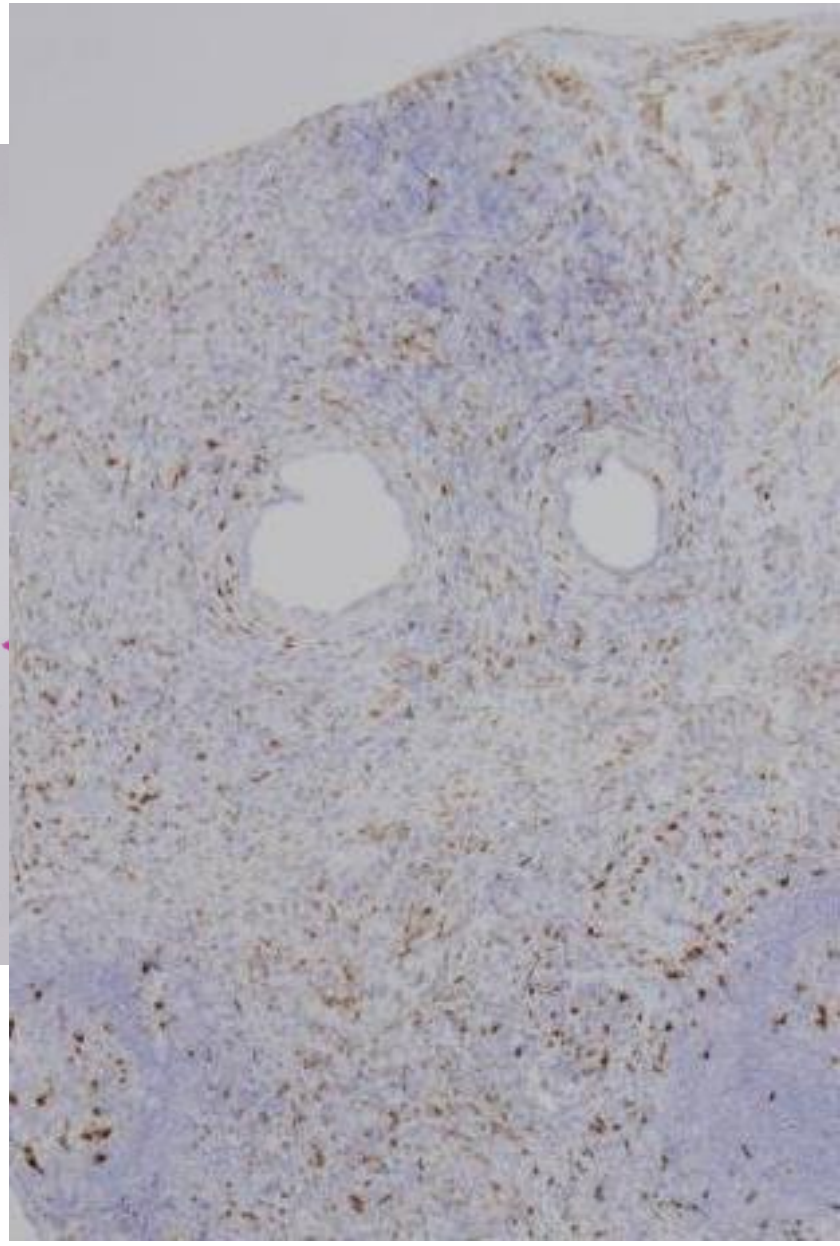
Diagnostic testing

- Evaluation for Sjögren's syndrome
  - Schirmer's test 7 mm OD, 5 mm OS
  - Stimulated and unstimulated saliva flow rates 0 ml/min
  - ANA 1:160, negative SS-A and SS-B antibodies
  - IgG 1395 mg/dl
  - WBC 13040 with 53% eosinophils
- Additional evaluation
  - CT imaging: ascending thoracic aortic aneurysm and mediastinal adenopathy
  - Bronchial lavage fluid 275 WBC (44% eosinophils).
  - Transbronchial lymph node biopsy: polytypic lymphocytes and increased eosinophils.

Serum IgG4: 348 mg/dl



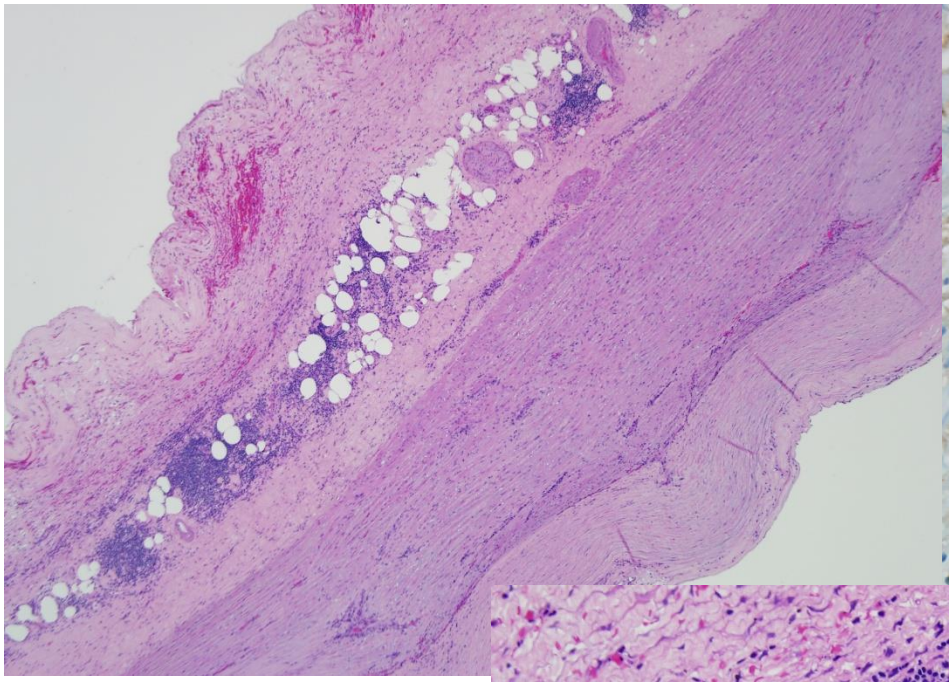
IgG4 stain, 4X

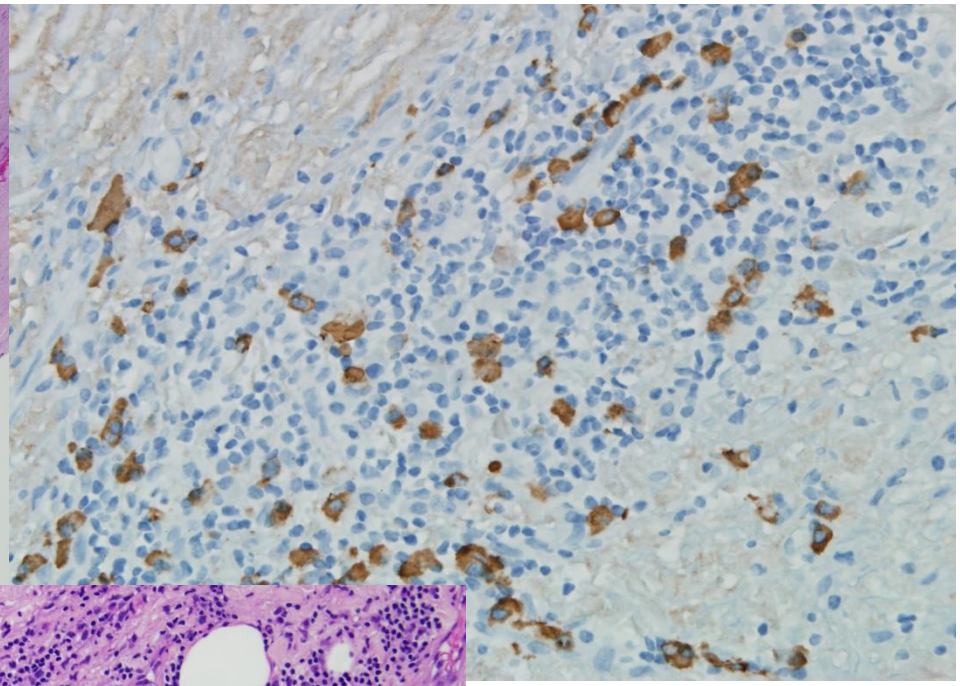


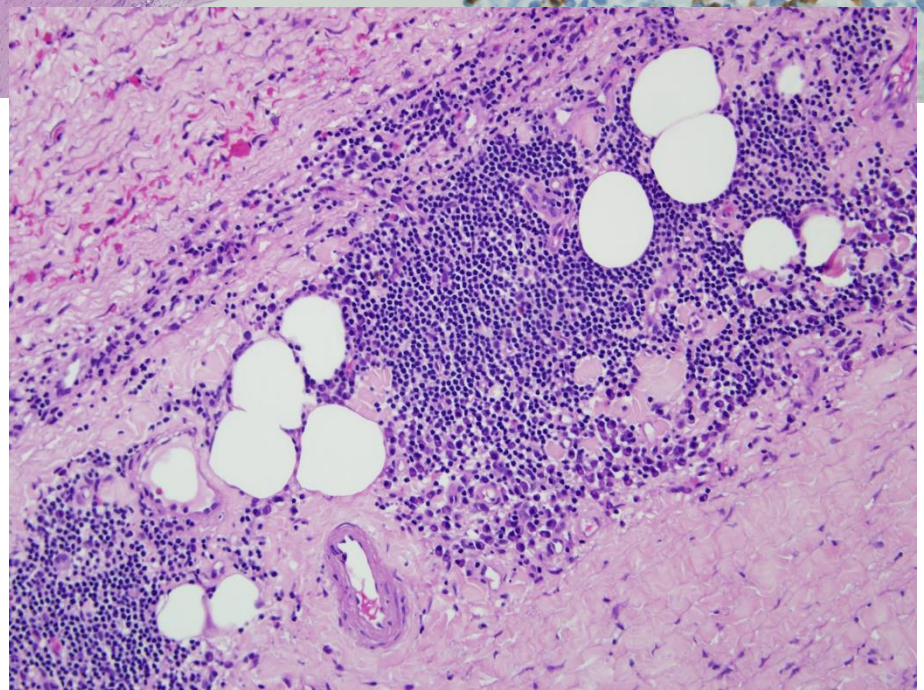
Clinical course

- Prednisone 40 mg qd, with tapering
  - The eosinophilia and salivary gland swelling resolved
  - His course over the next year was marked by
    - persistent xerostomia
    - weight stabilization
    - recurrent bronchitis
    - Hospitalization for panlobar pneumonia.
- June 2010
  - elective repair of his ascending thoracic aortic aneurysm using a Dacron graft .
  - lymphoplasmacytic aortitis and peri-aortitis with an increased number of IgG4 plasma cells.
  - Therapy with rituximab (1 cycle); maintained on prednisone 10 mg qd

Lymphoplasmacytic aortitis





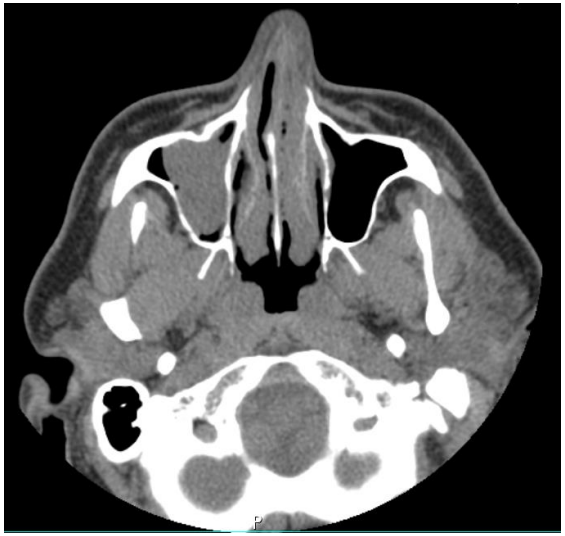


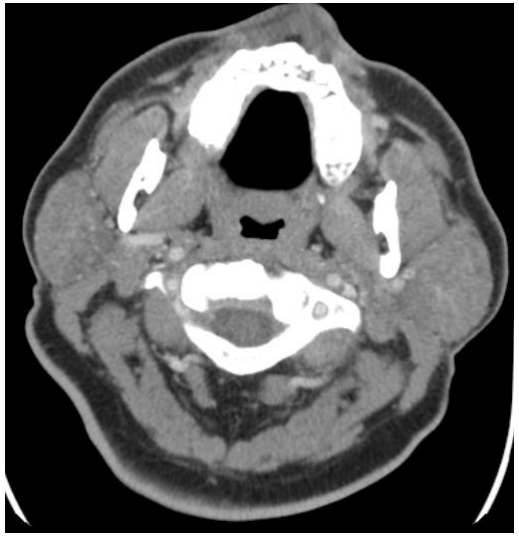
IgG4, 40X

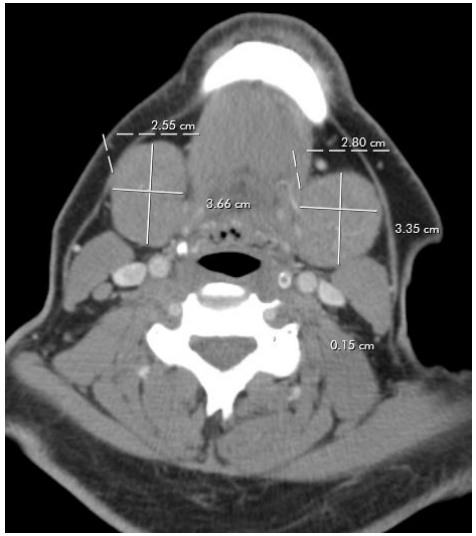
46 year old man

- Ulcerative colitis, currently on mesalamine
- 8/2016: angioedema, urticaria, allergic rhinosinusitis
- 3/2017: enlarged parotid and submandibular glands, cervical adenopathy; dryness of mouth; 45 lb weight loss

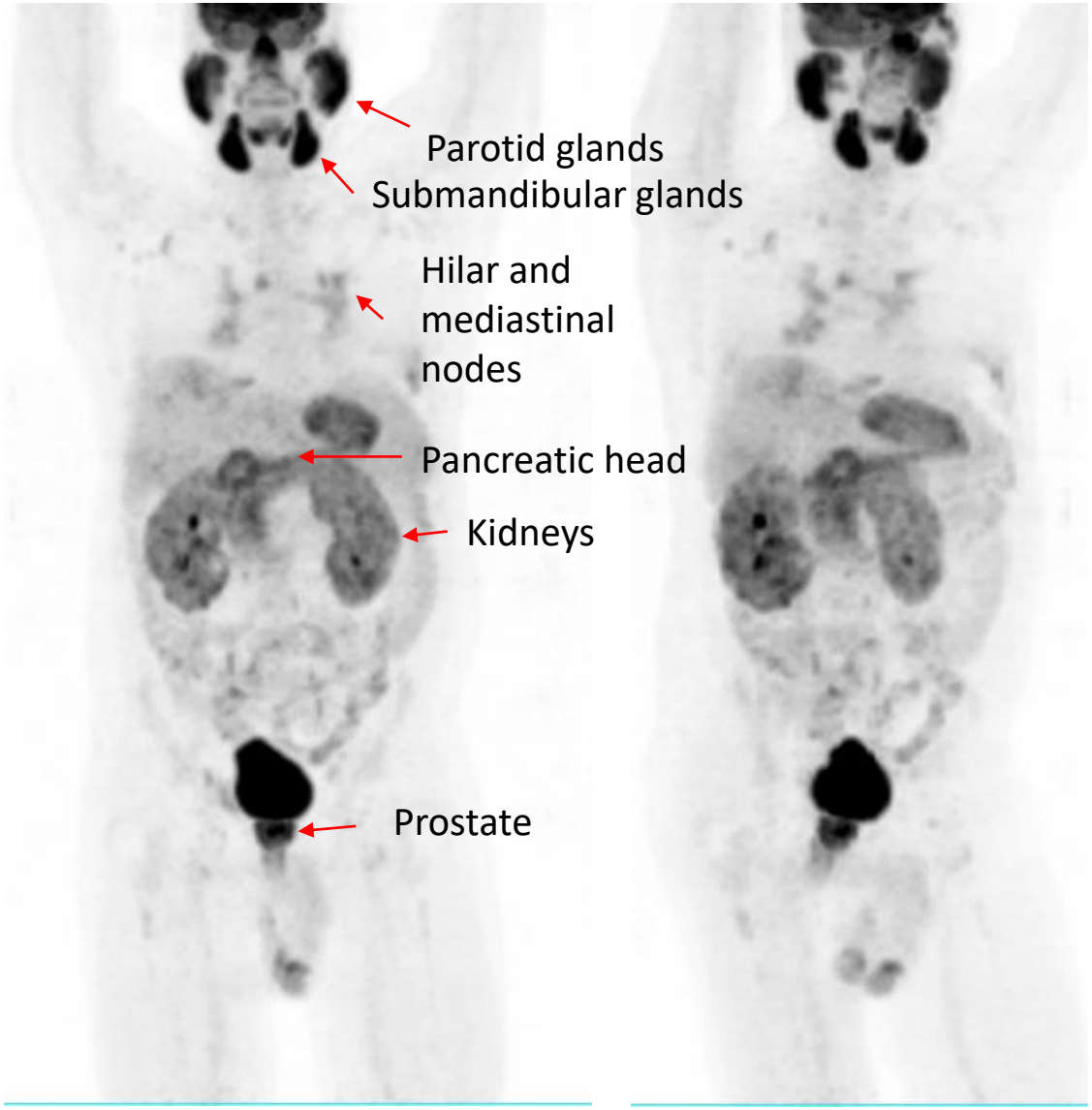
3/17 scans

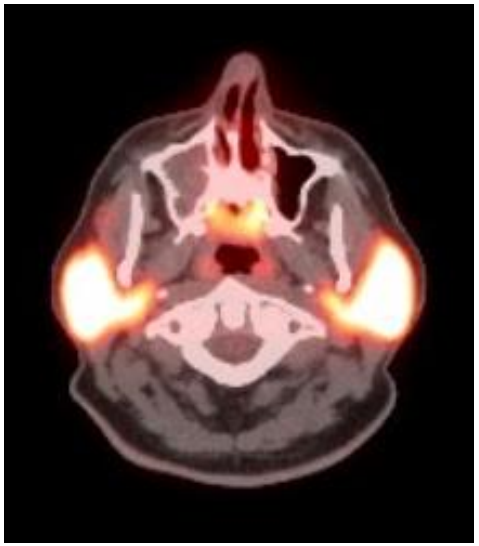


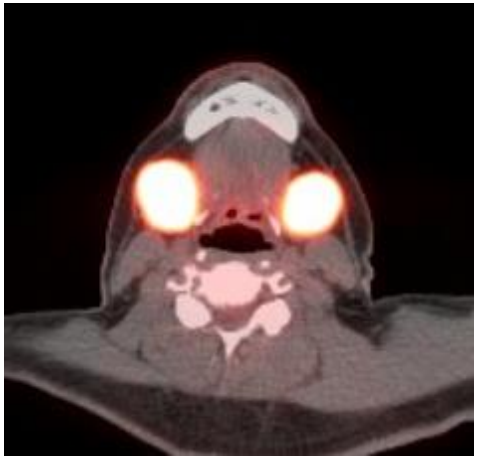


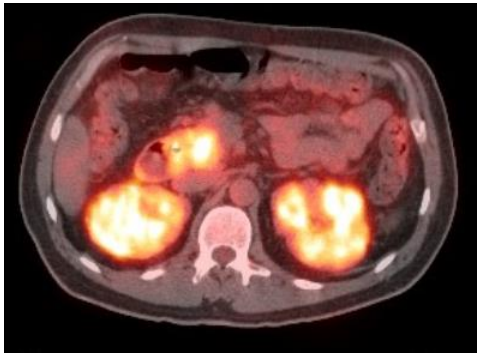


PET/CT scan 3/2017

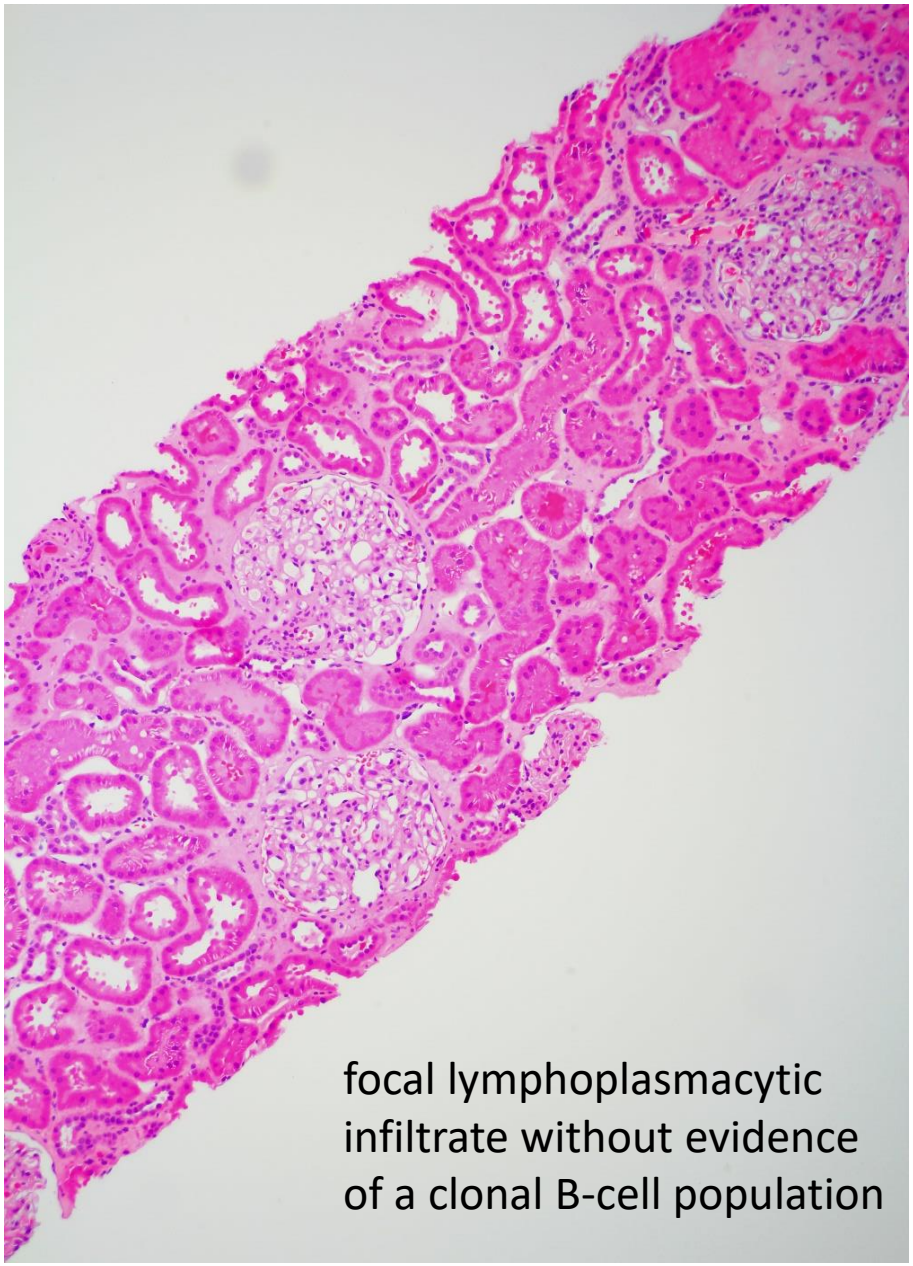


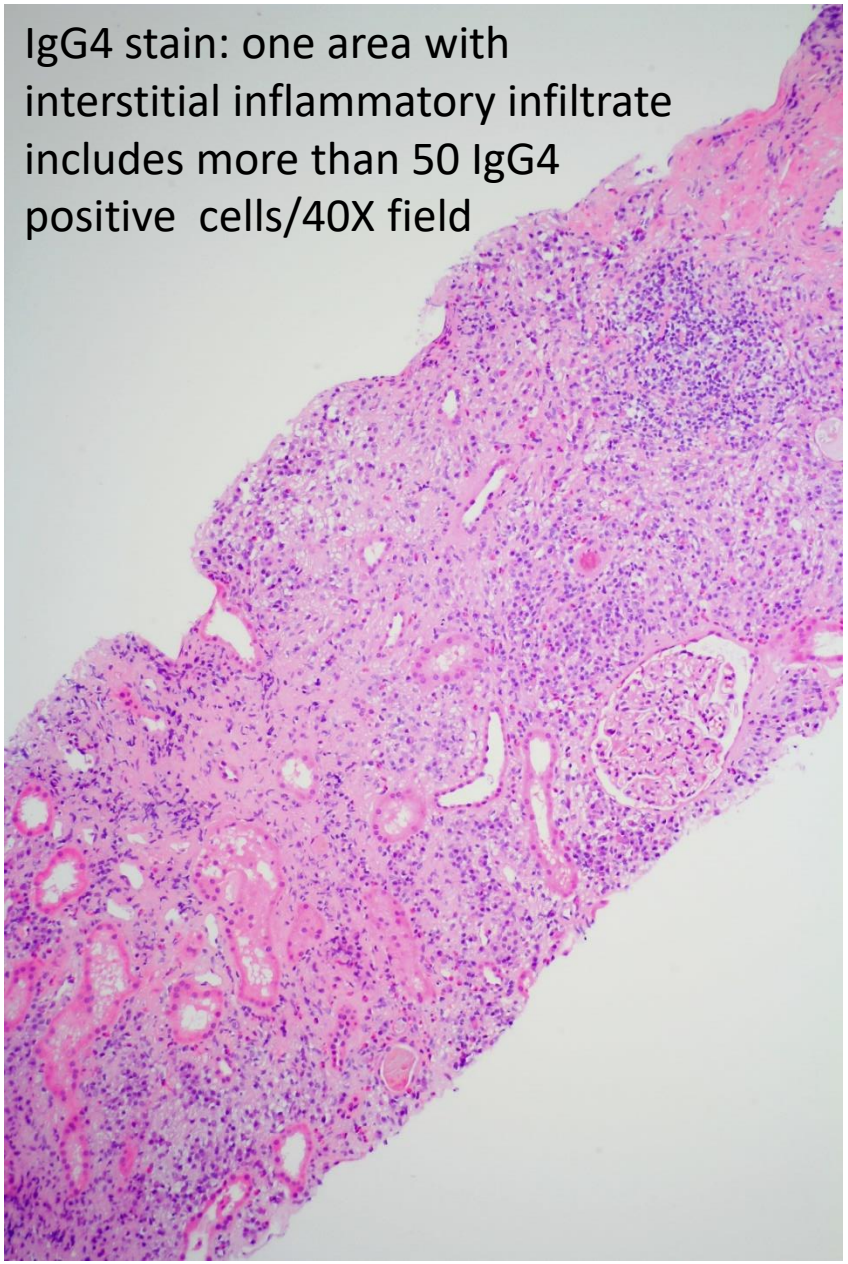




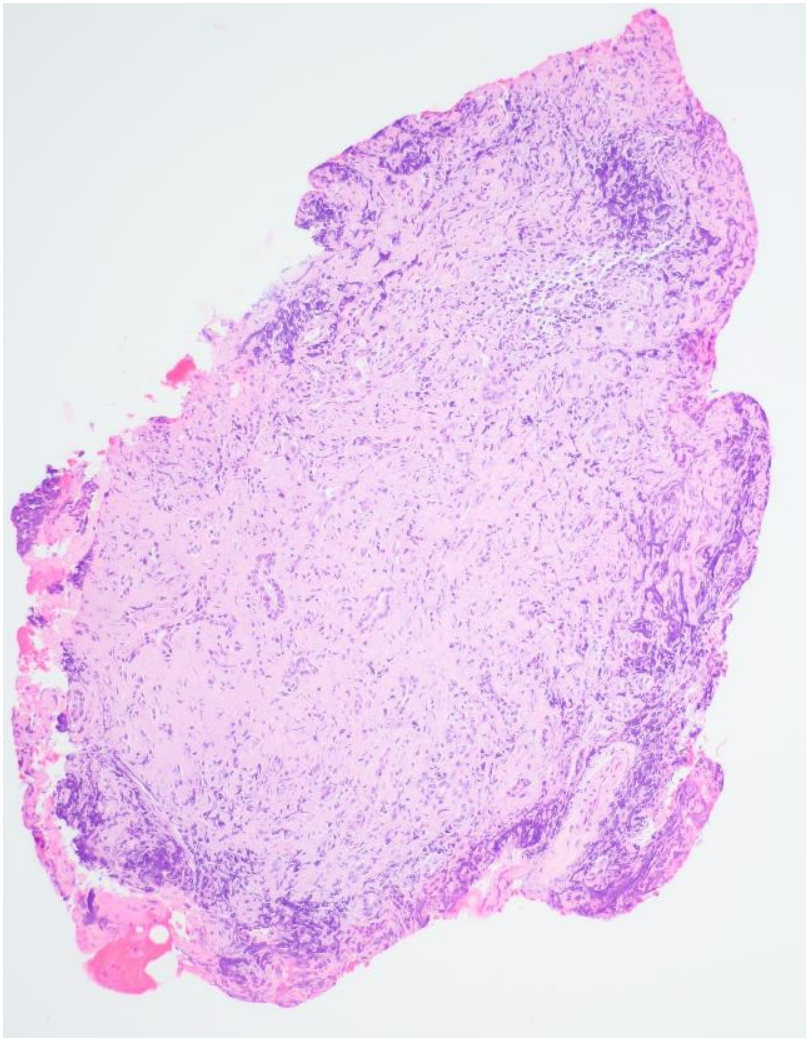


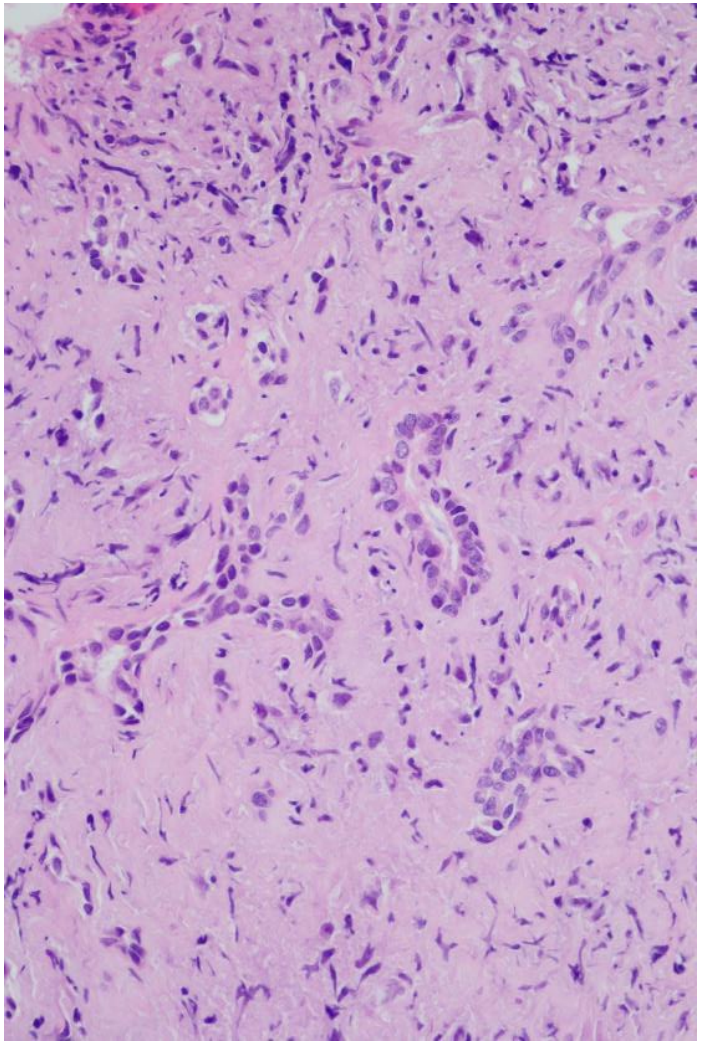
Kidney biopsy 4/2017





Right parotid gland biopsy 5/2017





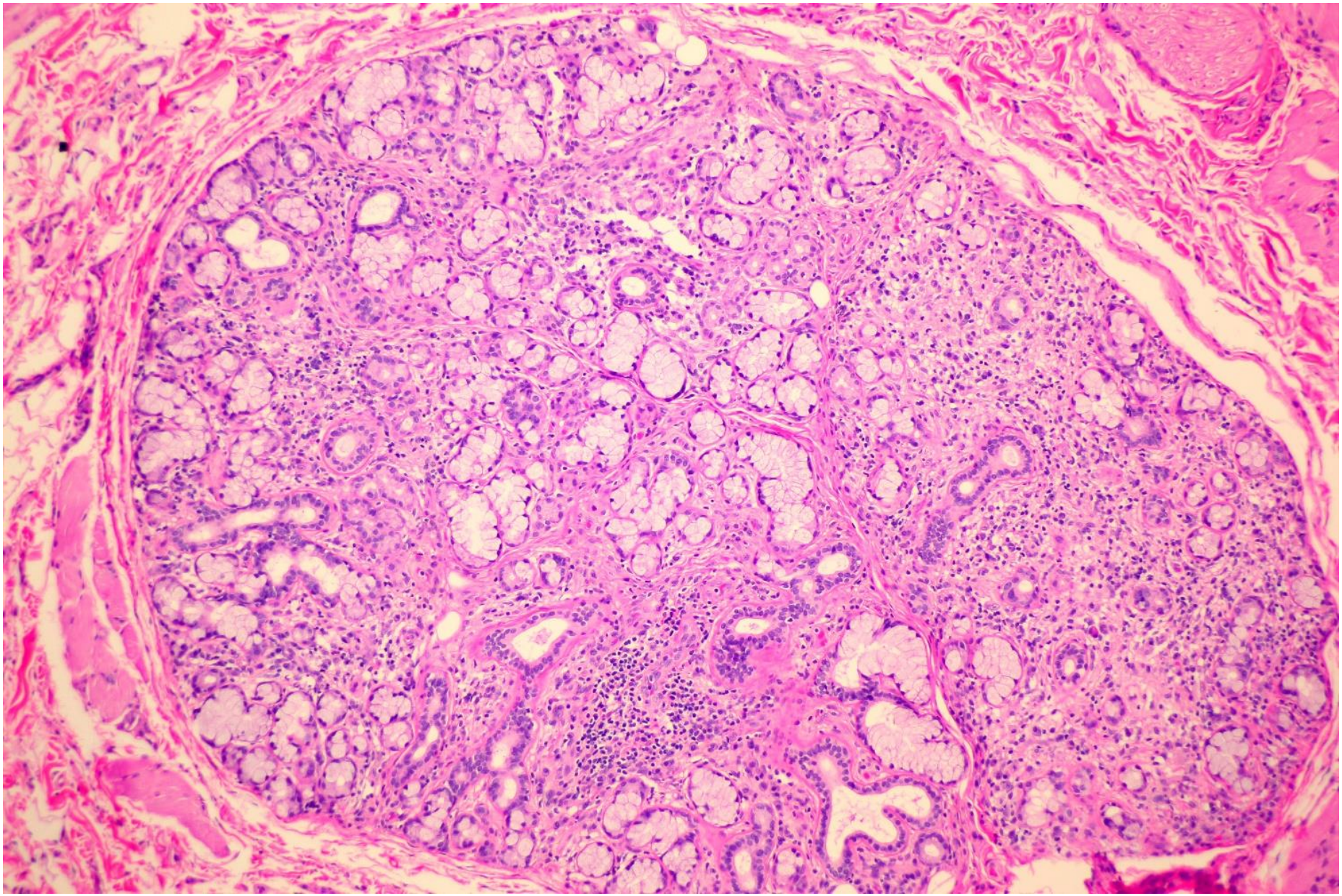
benign ductal epithelium with moderate fibrosis and chronic inflammation

Right inguinal lymph node biopsy-5/2017

- Reactive with markedly increased number and proportion of IgG4+ plasma cells.
- IgG4 cells >50% of the plasma cells

Rheumatology evaluation 6/2017

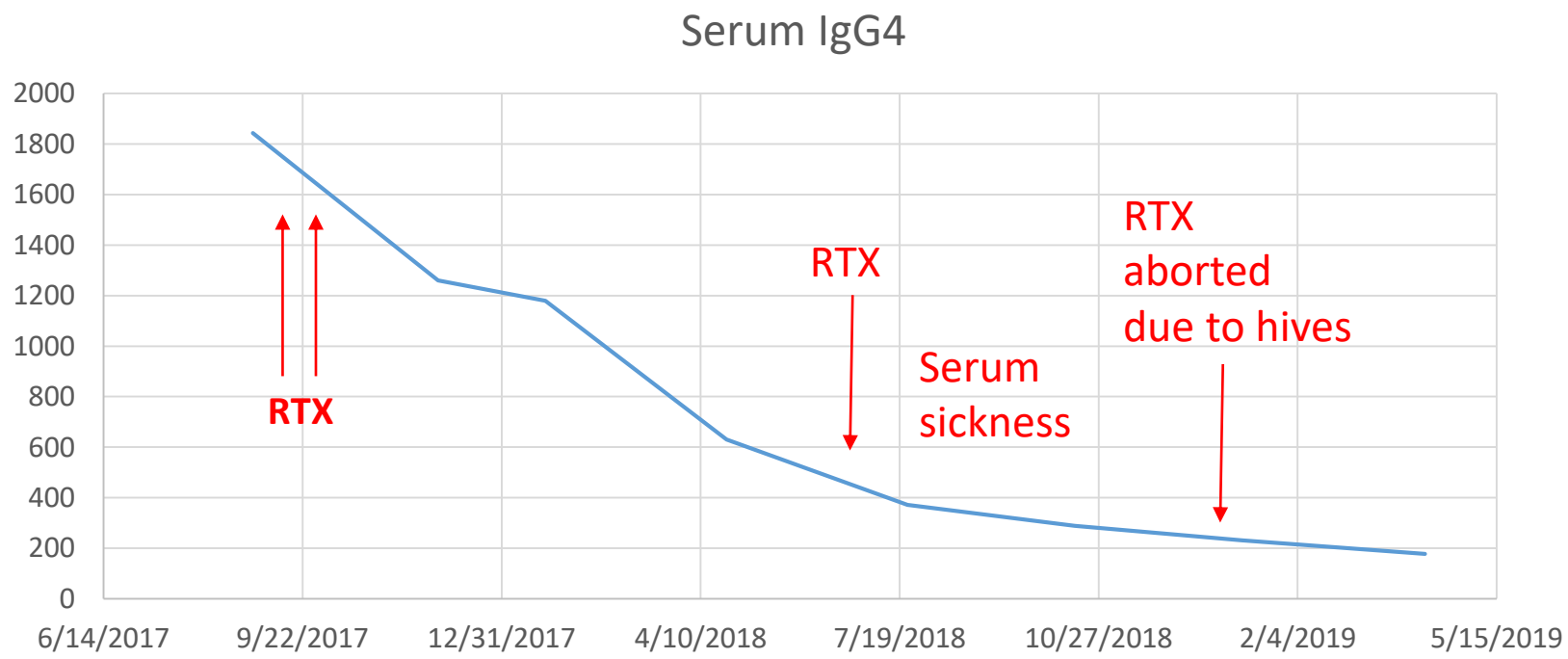
- Laboratory studies
  - WBC 9300, hemoglobin 12.4 g/dL, platelet count 277,000, eosinophil count 1800.
  - Creatinine 1.01 mg/dl
  - Alkaline phosphatase 515, AST 52, ALT 40.
  - SSA and SSB antibodies negative. ANA negative.
- Treated for presumptive Sjögren's with hydroxychloroquine and prednisone 20 mg daily for 2 weeks, followed by a taper
  - Improvement with 20 lb weight gain, less dry mouth, less sinus blockage
- Labial gland biopsy requested



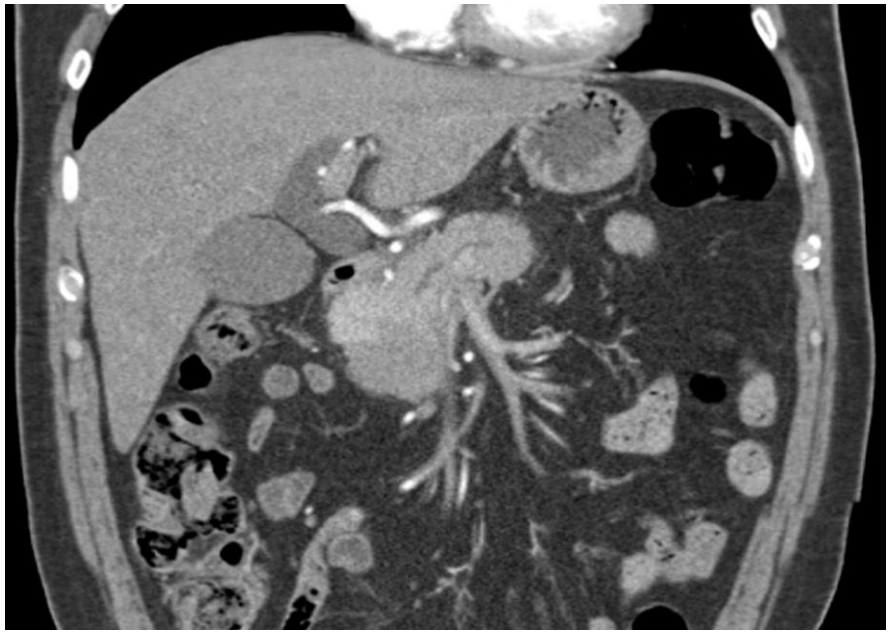
8/2017: several clusters of 40 or more lymphocytes, “compatible with Sjogren’s”.

Evaluation at Hopkins 8/2017

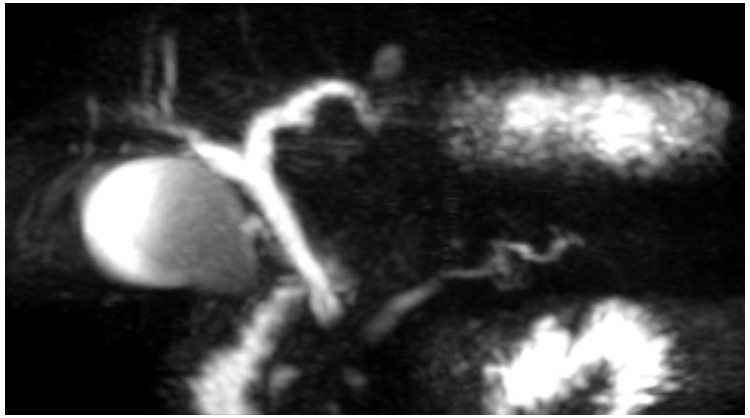
- IgG4 1843 mg/dl
- Continued on prednisone 10 mg qd; started on rituximab



56 year old man

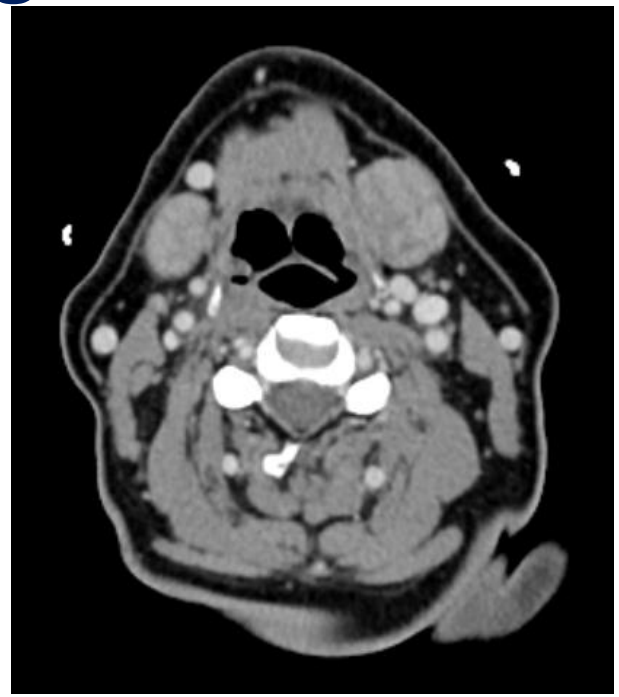


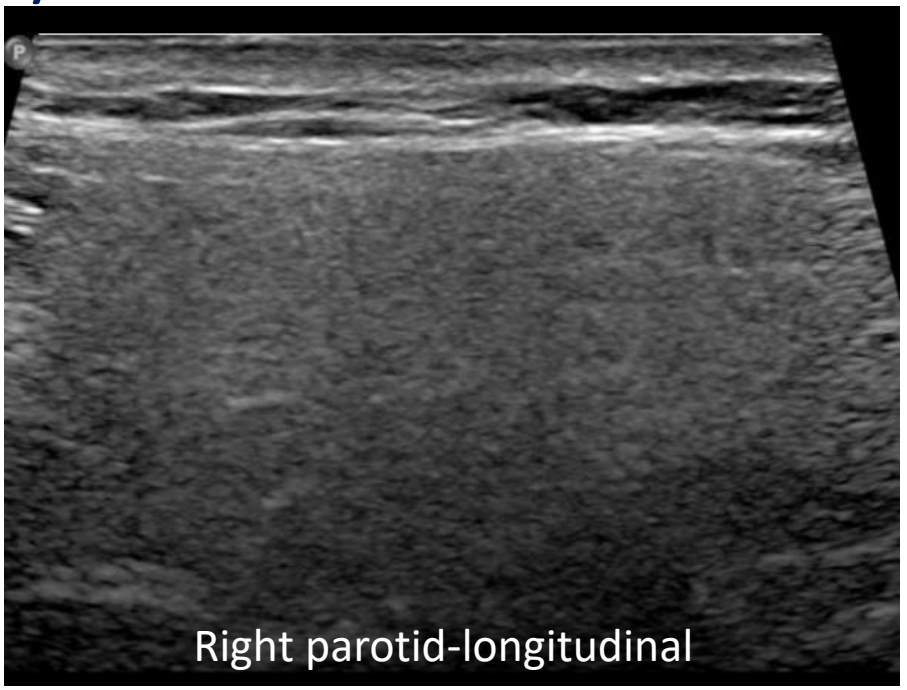
Pancreatic mass with long distal biliary stricture

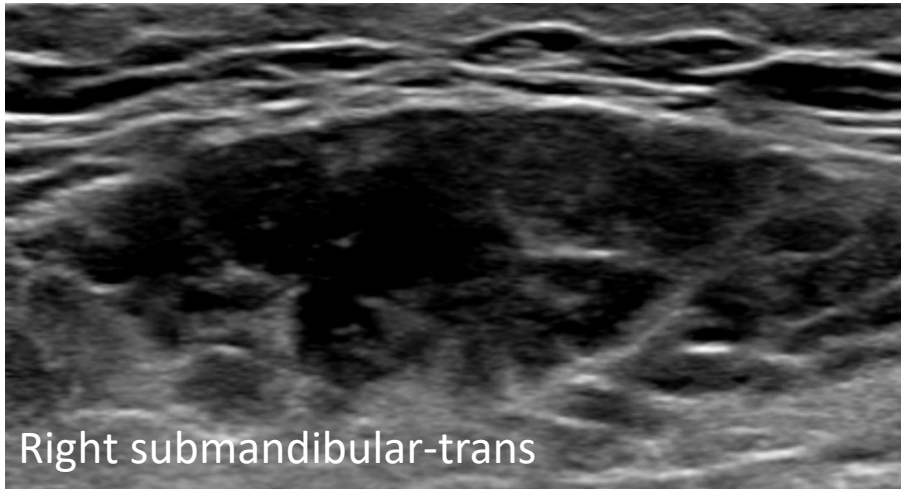


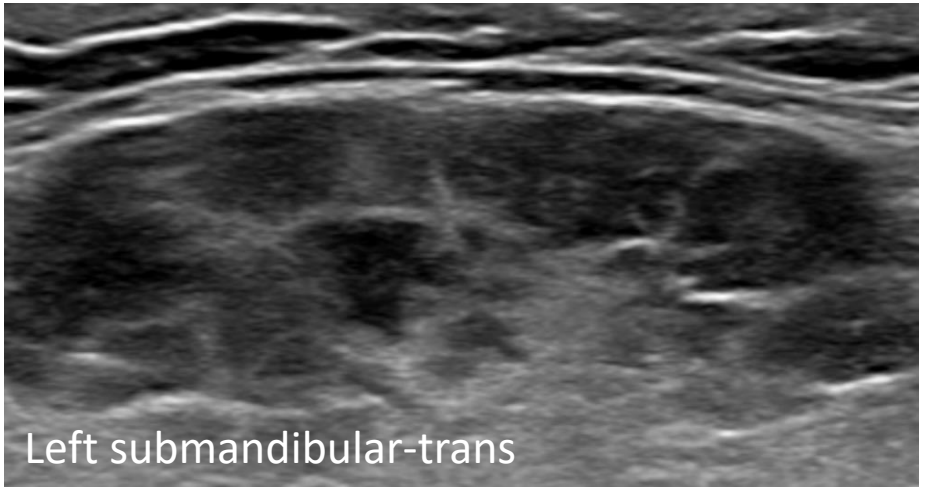
- 12/2014: acute painless jaundice
- Core biopsy of head of pancreas mass: fibrosis and inflammation with rare IgG4 staining cells
- IgG4 280 mg/dl
- Treated with corticosteroids with resolution of jaundice
- Intolerant of azathioprine and mycophenolate mofetil

Early 2016: submandibular gland enlargement with dry mouth

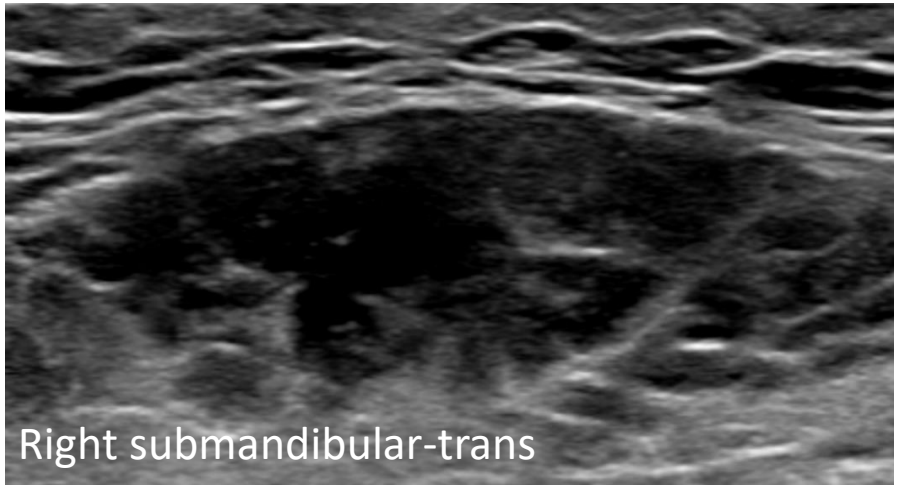


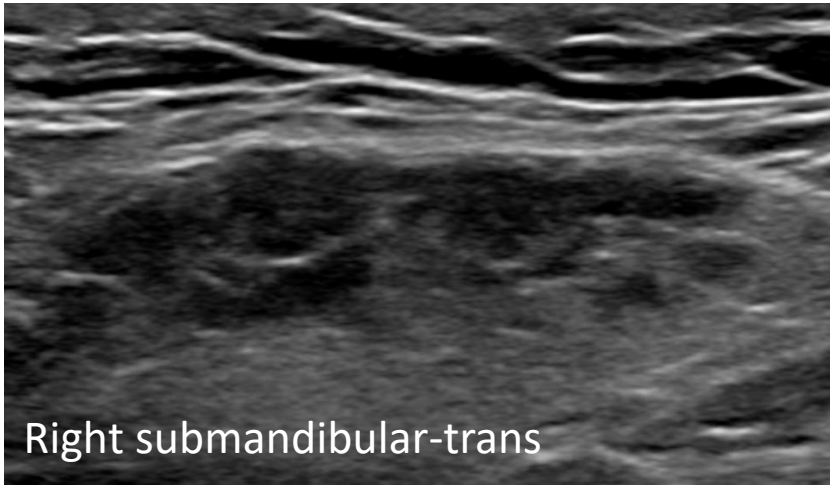


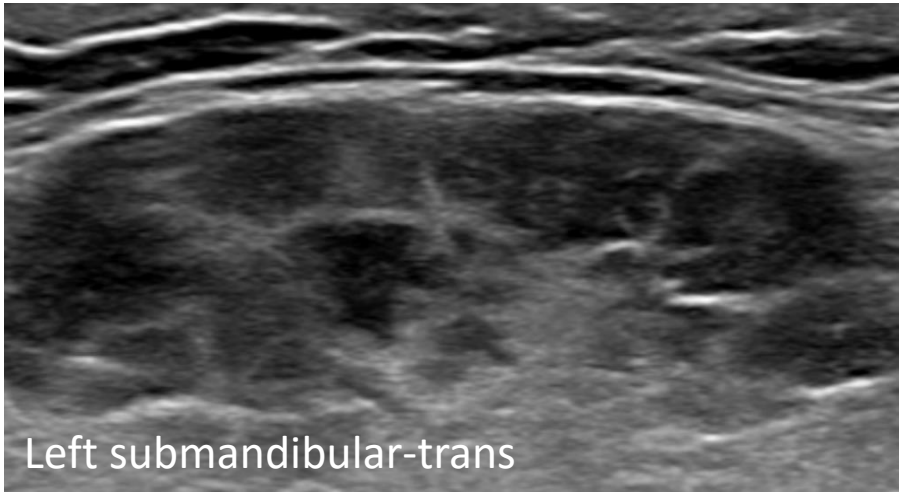


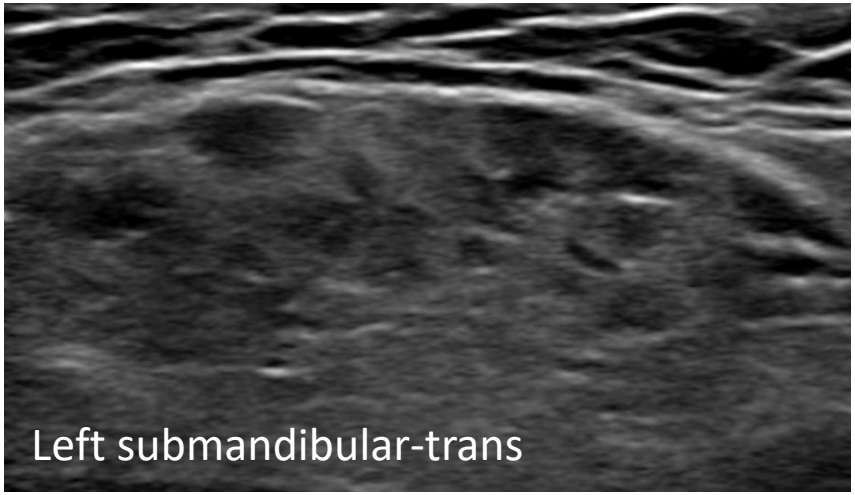


Treated with tapering course of prednisone; later azathioprine





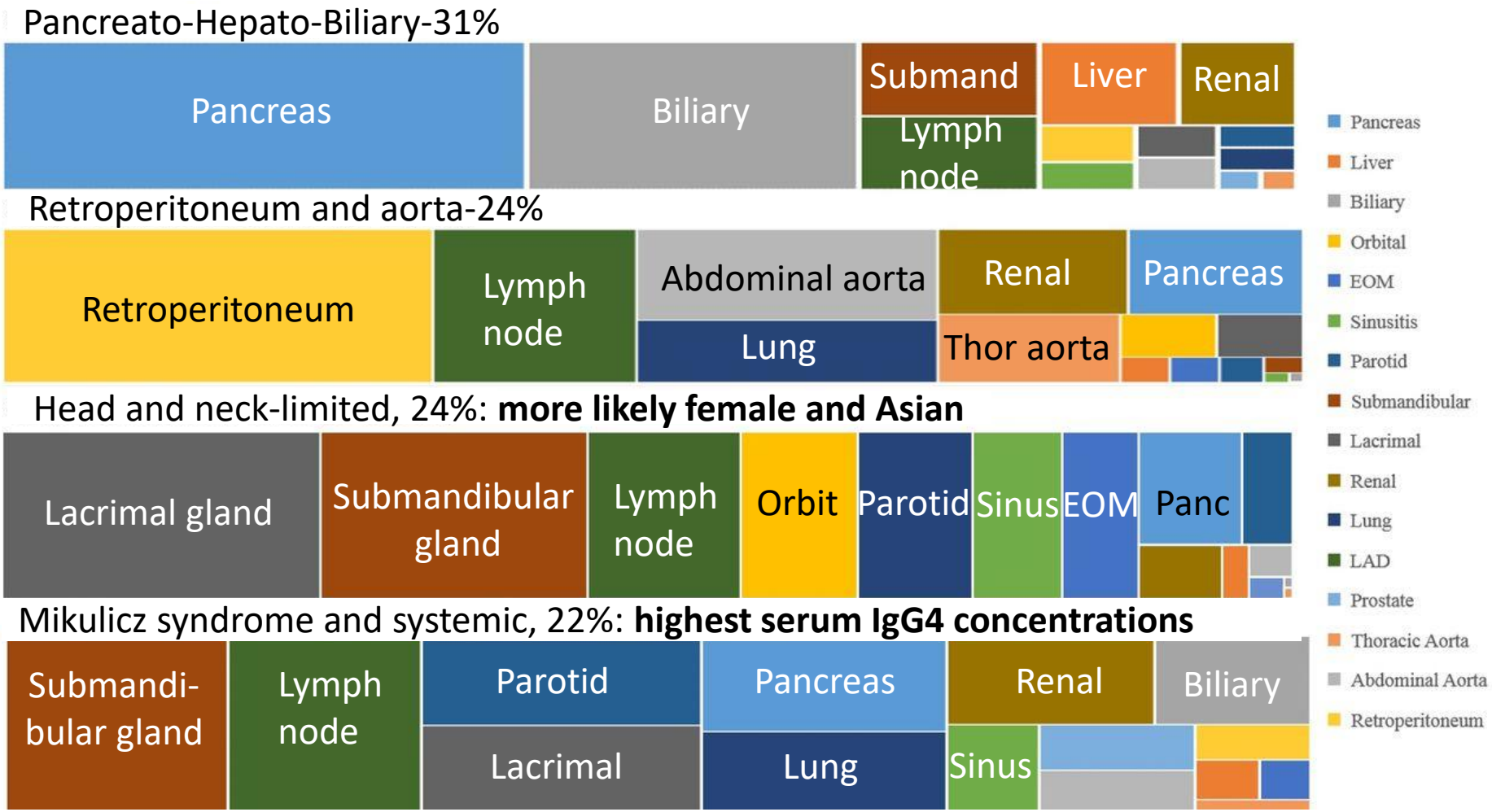




IgG4-RD is a chronic illness.

- Mainly affects middle-aged to elderly men
  - Male to female ratio of 3:1
  - More equal sex ratio for head and neck involvement
- Simultaneous or metachronous involvement of multiple organ systems
- Most have slow, indolent progression of disease

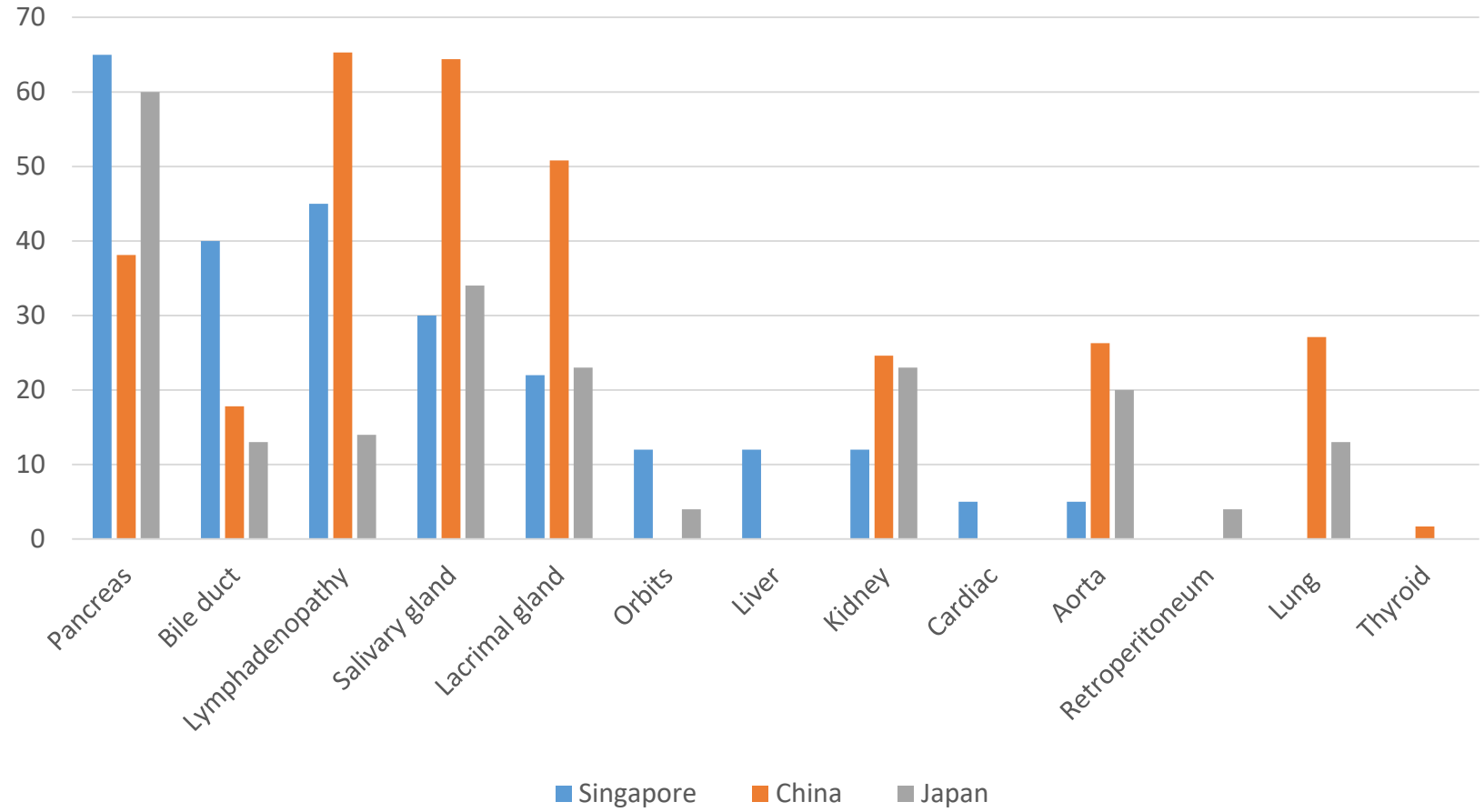
Clinical phenotypes of IgG4-RD



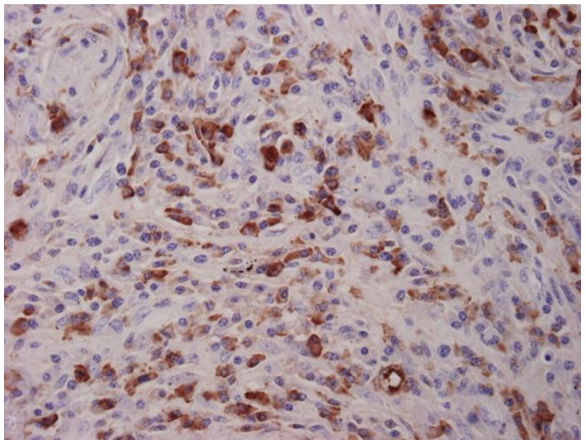
Latent class analysis of two cross-sectional cohorts; n=493 (derivation) and 272 (validation)

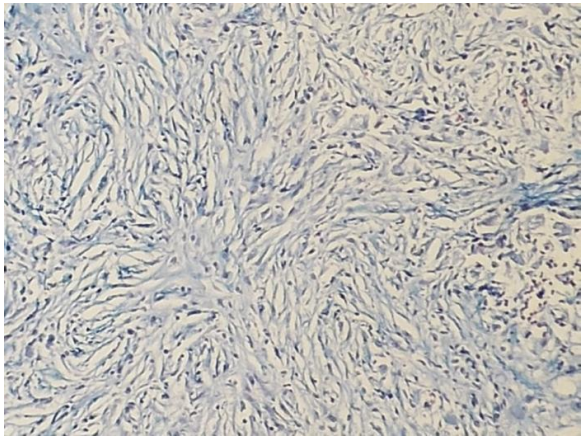
Ann Rheum Dis 2019;78:406-412

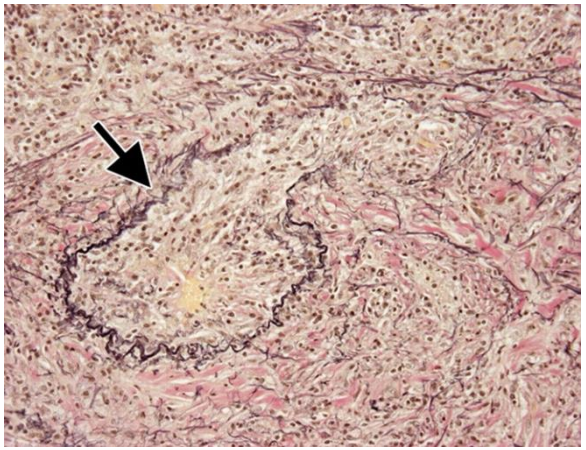
Organ involvement in IgG4-RD (Singapore cohort)



Clin Exp Rheumatol2018;36(Suppl 112):S89; Medicine. 94(15):e680, April 2015; Rheumatology 2015 Nov;54(11):1982-90.







Histopathology has 4 key elements.

- Lymphoplasmacytic infiltration rich in IgG4+ plasma cells
  - 10-200 IgG4+ cells/hpf
    - Varies by organ
  - **IgG4+/IgG+ plasma cell>40%**
- Storiform fibrosis (matted, irregularly whorled pattern)
- Obliterative phlebitis
- Eosinophilic infiltration

Rev Med Hosp Gen Med 2015; 78:99
Radiology 2009; 251:260

Be careful in interpreting the serum IgG4 level.

- Normal level does not exclude diagnosis (~40%)
  - Be aware of prozone effect.
- Mild elevations are common in a variety of conditions
- A high level (e.g. 6-8 fold greater than ULN) is strongly suggestive but not diagnostic
  - Also seen in hematologic malignancies
- Response of serum level to treatment does not reliably predict relapse
  - Does not normalize in 63% at remission
  - 10% may relapse with normal serum IgG4

Pathology of IgG4-RD

- IgG41 plasma cell tissue infiltrates are the sine qua non
- Number of IgG4+ plasma cells per hpf
  - Average the number of IgG4+ plasma cells within the three 40X high-power fields (hpf) with the highest number
  - Biopsy specimens of visceral organs
    - ≥10 IgG4+ plasma cells/hpf PLUS storiform fibrosis and/or obliterative phlebitis
  - Resection specimens
    - Pancreas: >50/hpf
    - Salivary and lacrimal gland: >100/hpf
    - Lung: >20/hpf
- Ratio of IgG4+/IgG+ plasma cells per hpf
  - Often difficult because of IgG background staining
  - Count cells in same region of the slide
  - >40% supports histopathologic diagnosis of IgG4+ RD

Mod Pathol 2012;25:1181

Umehara clinical diagnostic criteria for IgG4-RD

1. Characteristic diffuse/localized swelling or masses in single or multiple organs on clinical exam
2. Elevated serum IgG4 concentrations (>135 mg/dl)
3. Histopathologic examination shows:
   - Marked lymphoplasmacytic infiltration and fibrosis.
   - Infiltration of IgG4+ plasma cells:
     - IgG4+/IgG+ cells > 40% and
     - >10 IgG4+ plasma cells/HPF

Definite: 1 + 2+ 3
Probable: 1 + 3
Possible: 1 + 2

Adapted from Mod Rheumatol 2012; 22:21

Proposed ACR/EULAR classification criteria for IgG4-related disease

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

Source: Dr. Stone

Proposed ACR/EULAR classification criteria for IgG4-related disease: inclusion domains/points

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

MDedge News

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

Indications for treatment

- Urgent (to prevent irreversible organ damage)
  - Aortitis
  - Retroperitoneal fibrosis
  - Proximal biliary strictures
  - Tubulointerstitial nephritis
  - Pachymeningitis
  - Pancreatic enlargement
  - Pericarditis
- Asymptomatic disease
  - If waiting will lead to irreversible organ damage
  - Early treatment lead to faster and more complete remission with fewer long-term complications

Have a low threshold to treat active disease!

Treatment

- Corticosteroids (first-line agent)
  - Prednisone 0.6-1 mg/kg for 2-4 weeks, then taper by 5 mg every 1-2 weeks according to clinical response
  - Rapid clinical improvement is expected
  - May or may not maintain low-dose prednisone beyond 2-3 months
- Conventional steroid-sparing agents
  - Azathioprine, mycophenolate mofetil, methotrexate
  - Often used when steroid dose cannot be tapered due to persistently active disease
- B-cell depletion
  - Rituximab

Arthritis Rheumatol 2015; 67:1688

IgG4-RD patients often require maintenance therapy.

- Appropriate for patients at high risk of relapse
  - Multiorgan disease
  - Significantly elevated serum IgG4 levels
  - Involvement of proximal bile ducts
  - History of disease relapse
- Therapeutic options
  - Low-dose glucocorticoids
  - Conventional steroid-sparing agents
  - Rituximab
    - usually at time of disease flare

Management scenarios

- Single or pauci-organ involvement, mild IgG4 elevation
  - Expectant observation
  - Prednisone 20-40 mg qd x1 month; taper off during 2nd month
- Multi-organ involvement with high IgG4 with risk for irreversible organ damage
  - Prednisone 0.6 mg/kg/d for 2-4 weeks, taper by 10 mg qd every 2 weeks until 20 mg qd, then taper 5 mg every 2 weeks till off at end of 3 months
  - Start second-line agent at outset
    - MTX, AZA, MMF, RTX
  - Repeat PET/CT imaging in 3-6 months

Della-Torre and Stone; J Clin Immunol 2016:36:754

Management scenarios

- Retroperitoneal fibrosis (often with normal IgG4)
  - Ureteral stenting or ureteropexy
  - Prednisone 40-60 mg qd for 1 month, taper off by 2-3 months
  - Re-image at 3 months, preferably PET/CT
  - If no change on imaging, consider rituximab
- IgG4 tubulointerstitial nephritis with renal impairment
  - Prednisone 40-60 mg qd
  - Rituximab

Della-Torre and Stone; J Clin Immunol 2016:36:754

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