Chiefs' Rounds

WillsEye Hospital

February 3rd, 2022

Charles Brodowski MD, PGY-4

Financial Disclosure

I have no financial relationships to disclose

31 year old female presents to Oculoplastics due to BUL and lacrimal gland swelling

- History of thyroid eye disease treated with RAI 3 years prior to presentation with mild periorbital swelling
  - Symptoms resolved following PO steroids
- Recurrent disease on tapering steroids
- Reports "seeing two" when "looking up"

Past Ocular History

- N/A

Past Medical History

- Graves Disease
- Adult onset asthma

Past Surgical History

- N/A

Medications

- Prednisone
- Escitalopram
- Levothyroxine

Social and Family History

- Non-smoker
- No EtOH use
- No IVDU
- FHx
- Diabetes – Father, Mother

Review of Systems

- WNL

1999 – s/p immediate completion steroids

2000 – 1 year after steroid treatment

Exam

V_{sc} < 20/25, 20/25

P < Reactive, no APD, Reactive, no APD

T_{Tpen} < WNL, WNL

CVF < Full, Full

EOM < Full, Full

UL edema w/ lacrimal fullness; Hertel 22-23/95

- Underwent radiation therapy
  - 2000 rads to supraorbital area
    - No retrobulbar XRT
  - Resolution of diplopia, persistent proptosis
- Underwent fatty orbital decompression
  - Pathology: minimal chronic inflammation
- 5 years later began experiencing recurrent sinus disease
  - CT Maxillofacial: pansinusitis, lacrimal glands WNL, still with mild enlargement SR & LR
- Underwent successful sinus surgery with marked improvement in periorbital edema and sinus disease

2007 No complaints

6 years later...

New periorbital swelling and xanthomatous deposits

2 years later...

Periorbital edema with severe swelling
and xanthomas lower lids
Hertel 15-16/95

Exam

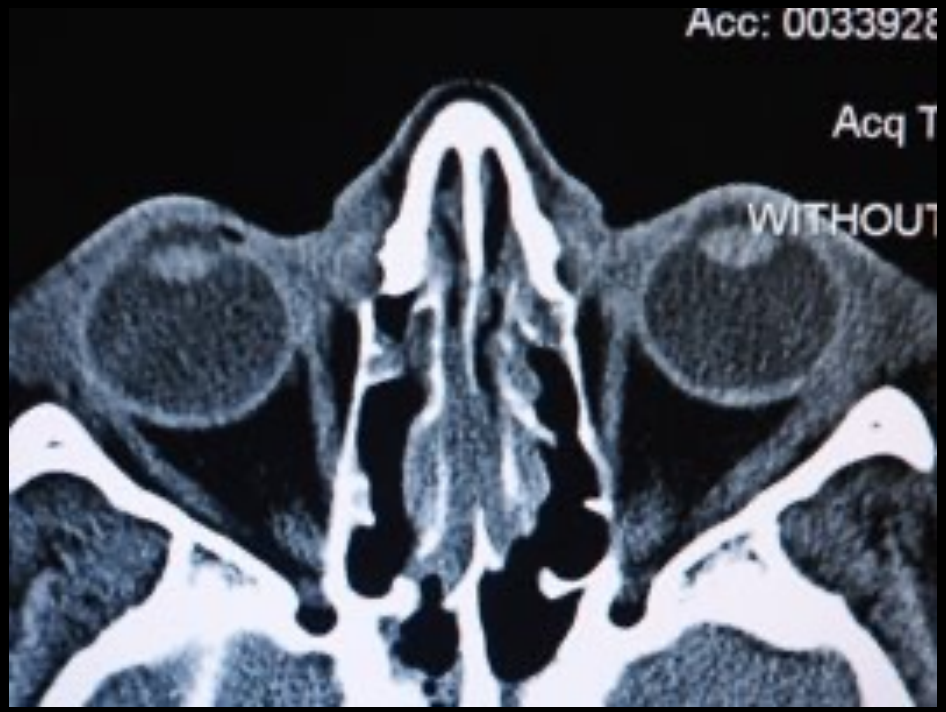
V_{sc} < 20/30 -2
20/30 -1

P < Reactive, no APD
Reactive, no APD

T_{Tpen} < 18
18

CVF < Full
Full

EOM < 10% upgaze limitation
10% upgaze limitation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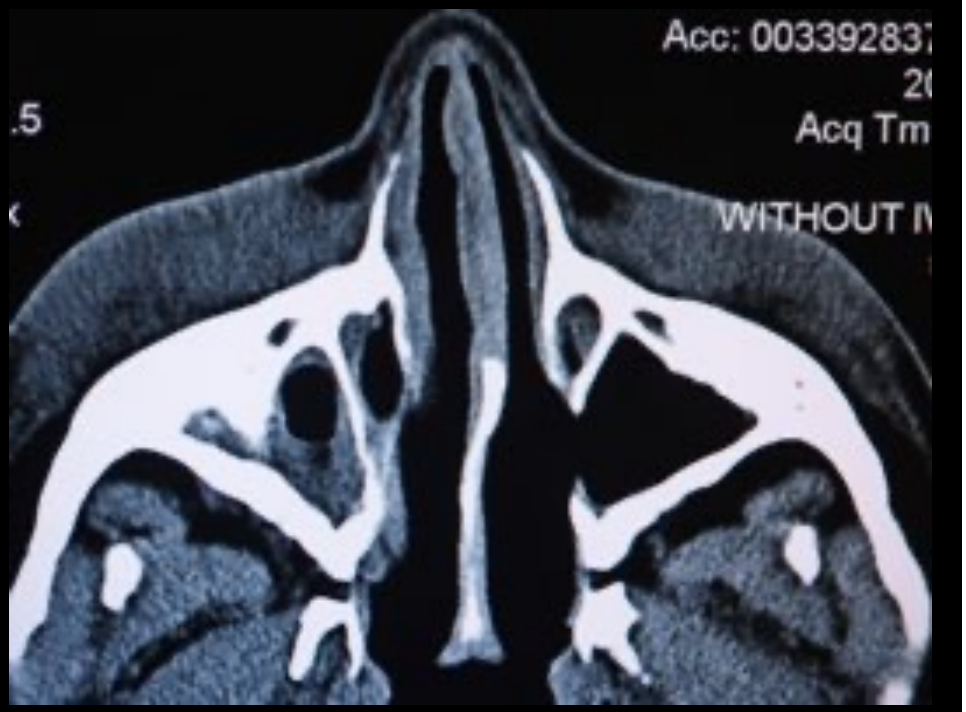
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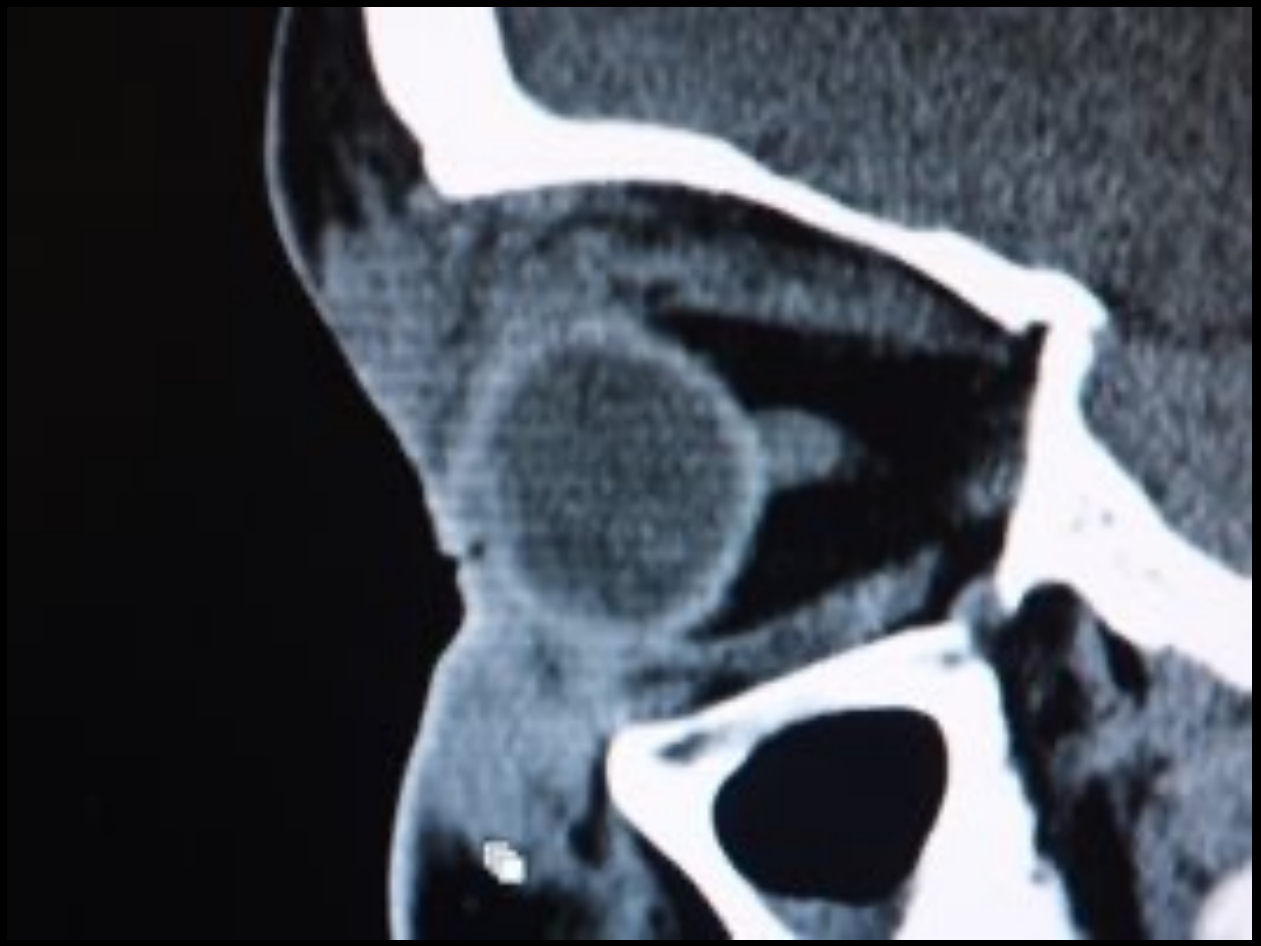


Massive infiltration of the lower periorbital area and cheeks, sparing of the superolateral radiated field

Differential Diagnosis?

Differential Diagnosis

Autoimmune/Inflammatory:

- Thyroid Associated Orbitopathy (TAO)
- Granulomatosis with polyangeitis (Wegener disease)
- IgG4-RD
- Sarcoidosis
- Idiopathic Orbital Inflammatory Disease

Malignant:

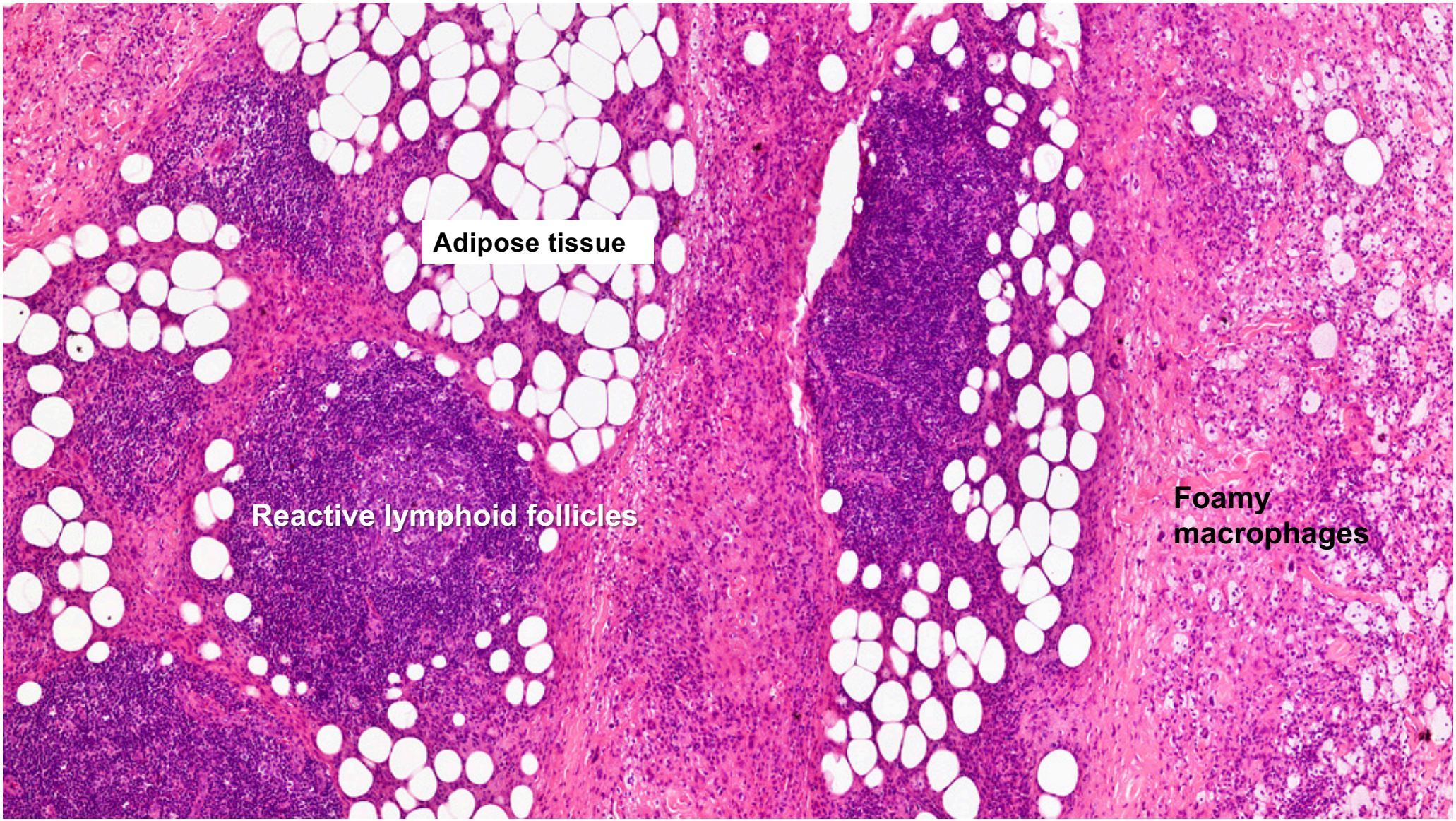
- Orbital Lymphoma
- Metastatic disease

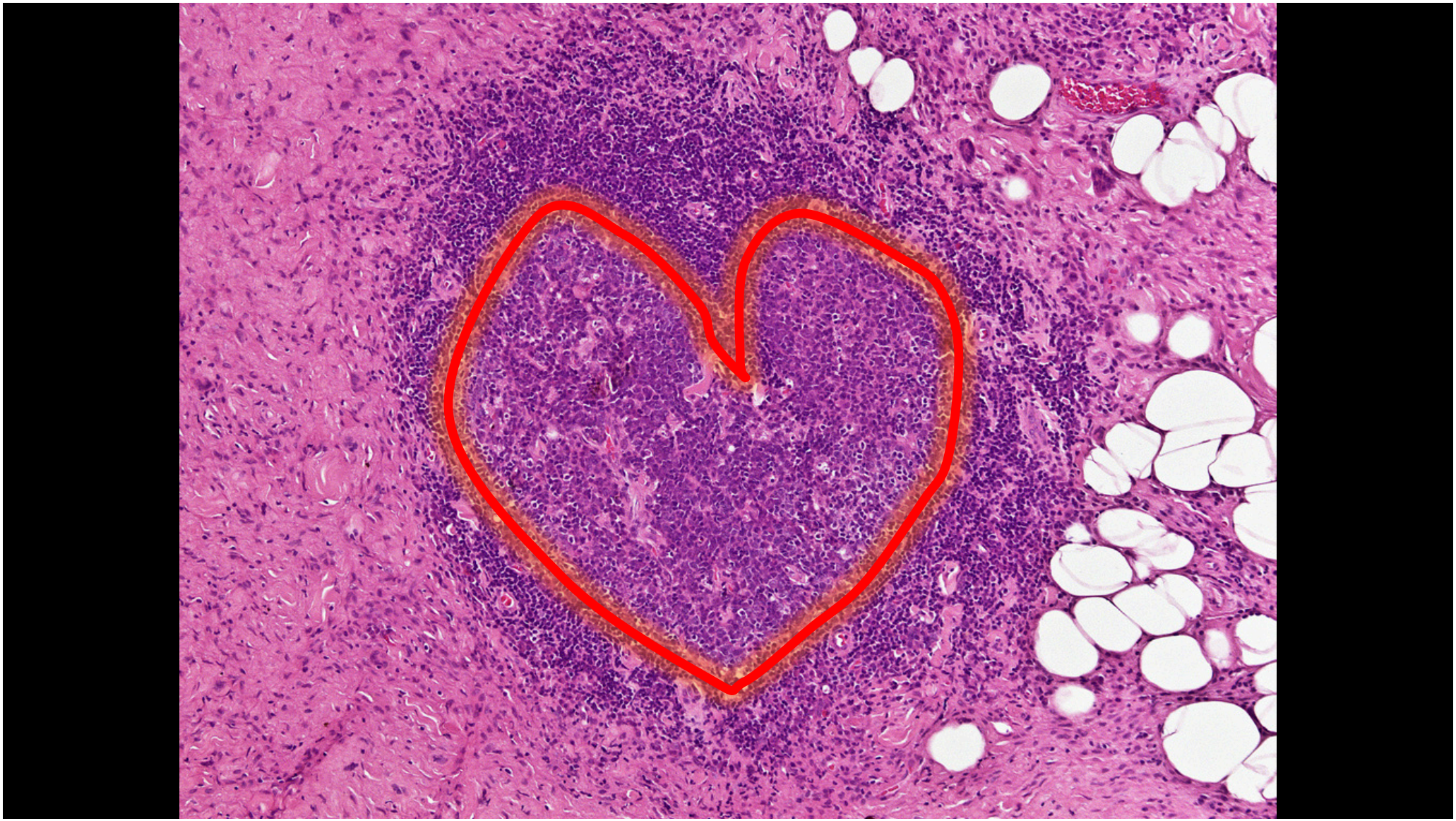
Miscellaneous:

- Adult Onset Xanthogranuloma
- Amyloidosis
- Kimura Disease

Next steps?

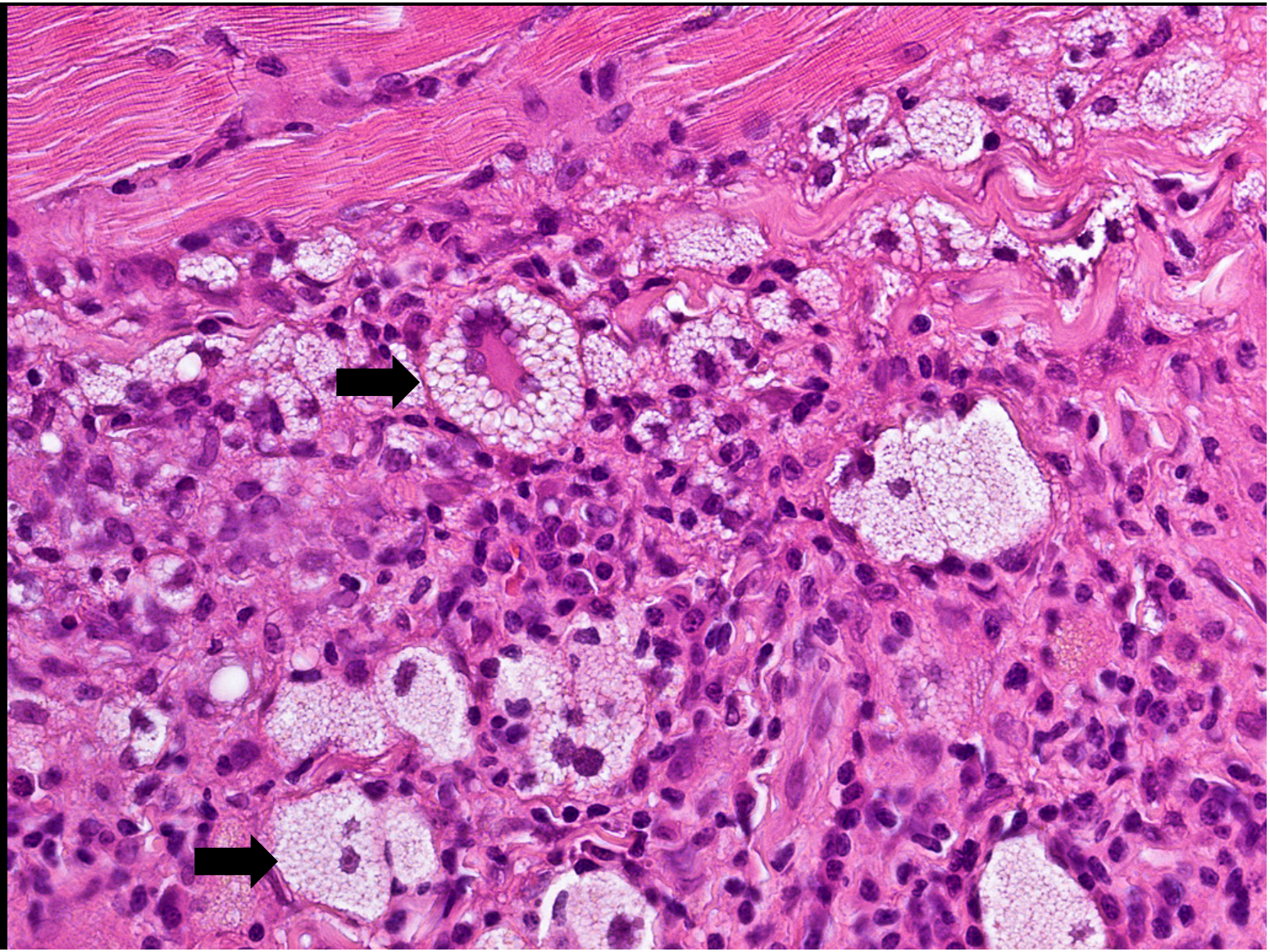
- Surgical intervention vs Observation?
- Lab testing?
- Treatment?

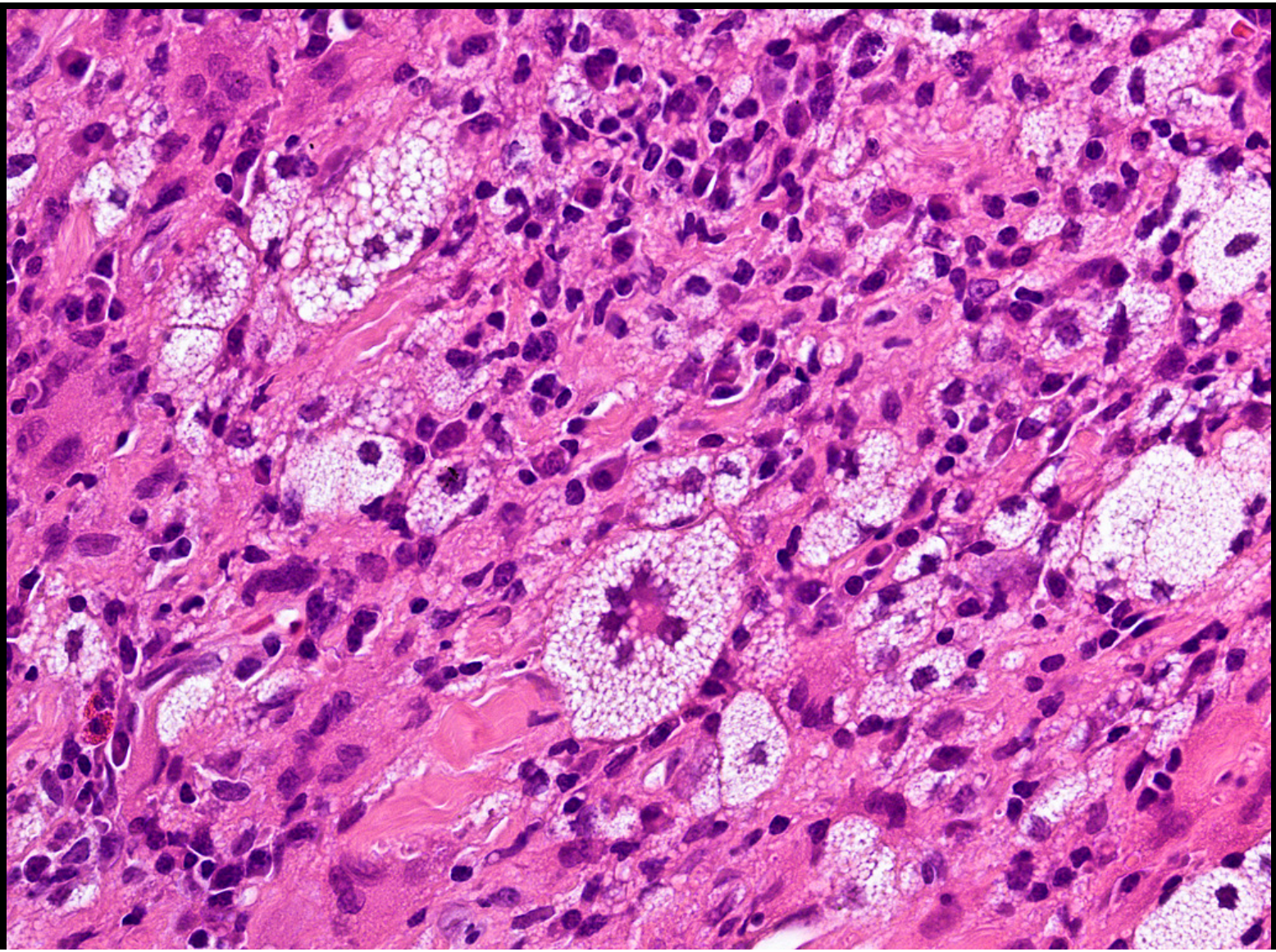

Adipose tissue
Reactive lymphoid follicles
Foamy
macrophages



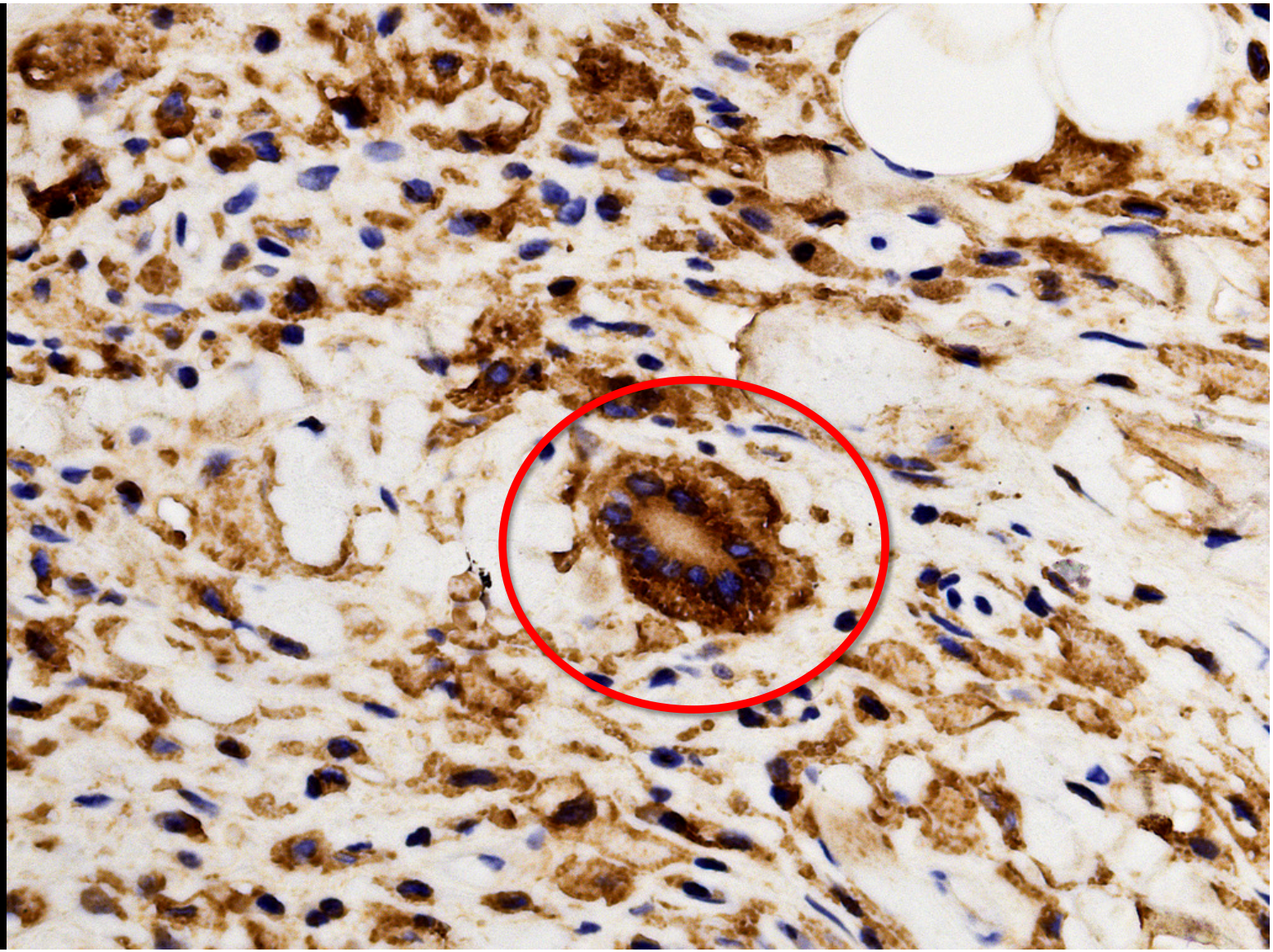
Touton-type giant cells

Foamy macrophages

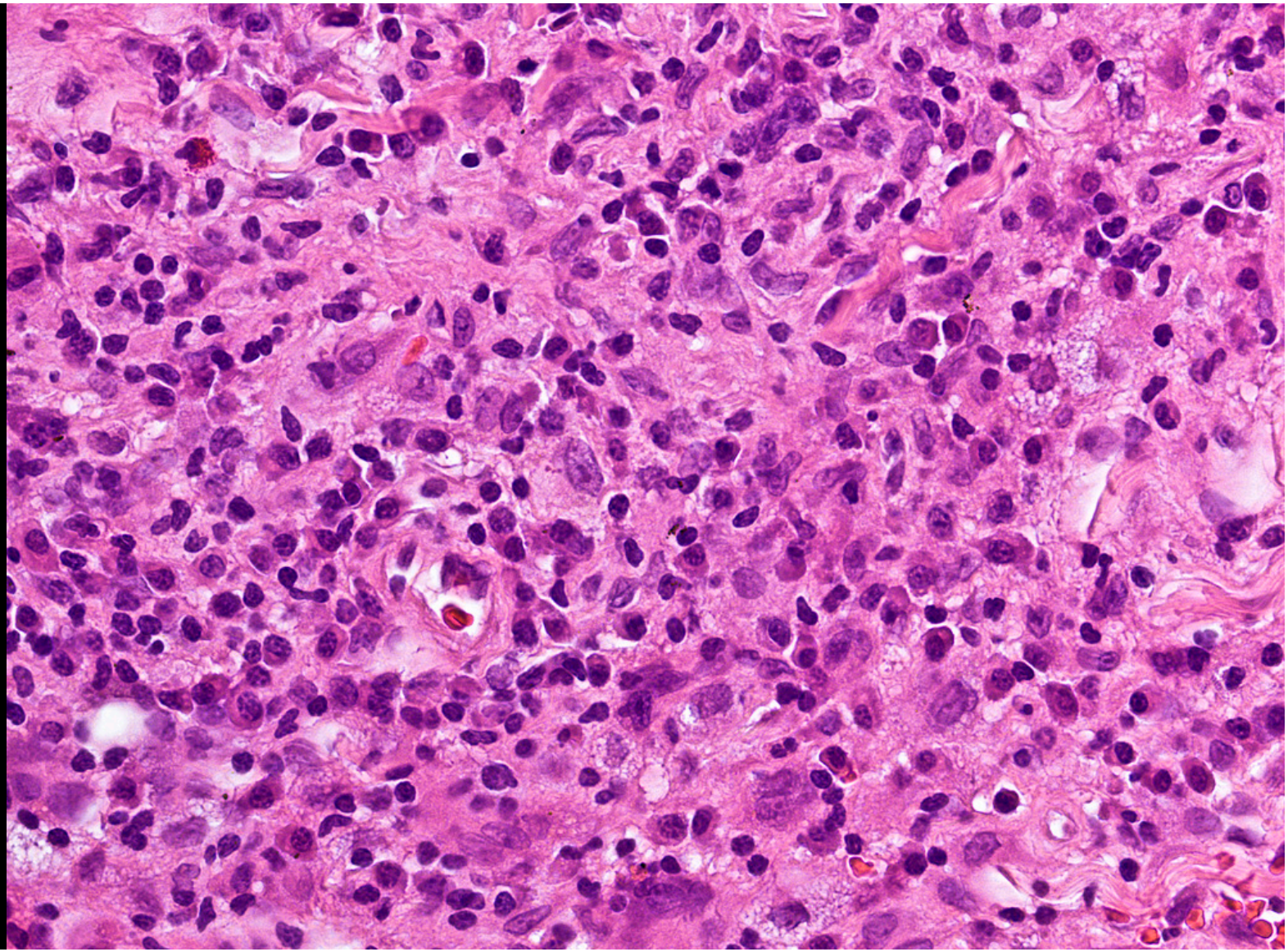




CD68

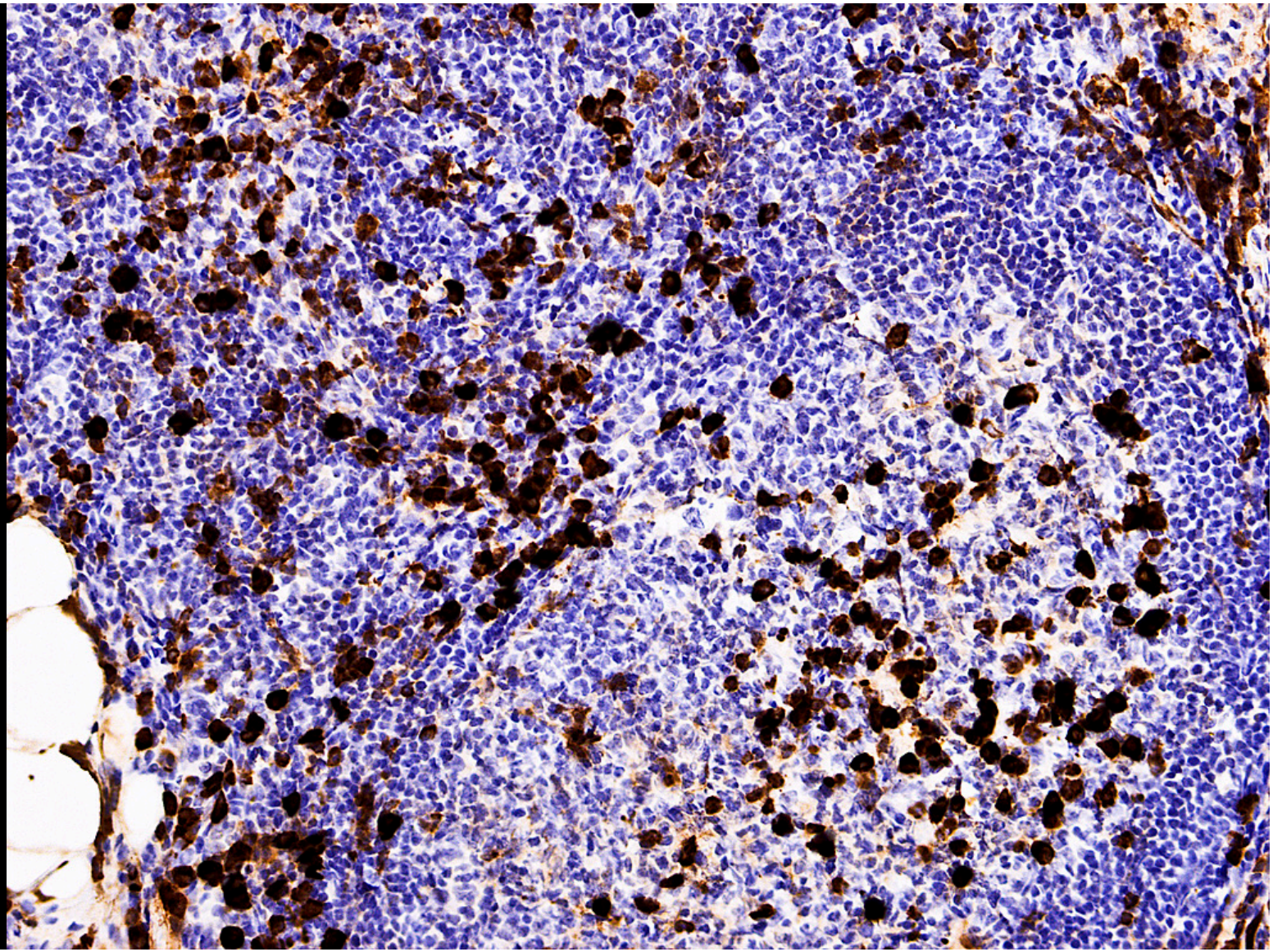


Lympho-plasmacytic infiltrate



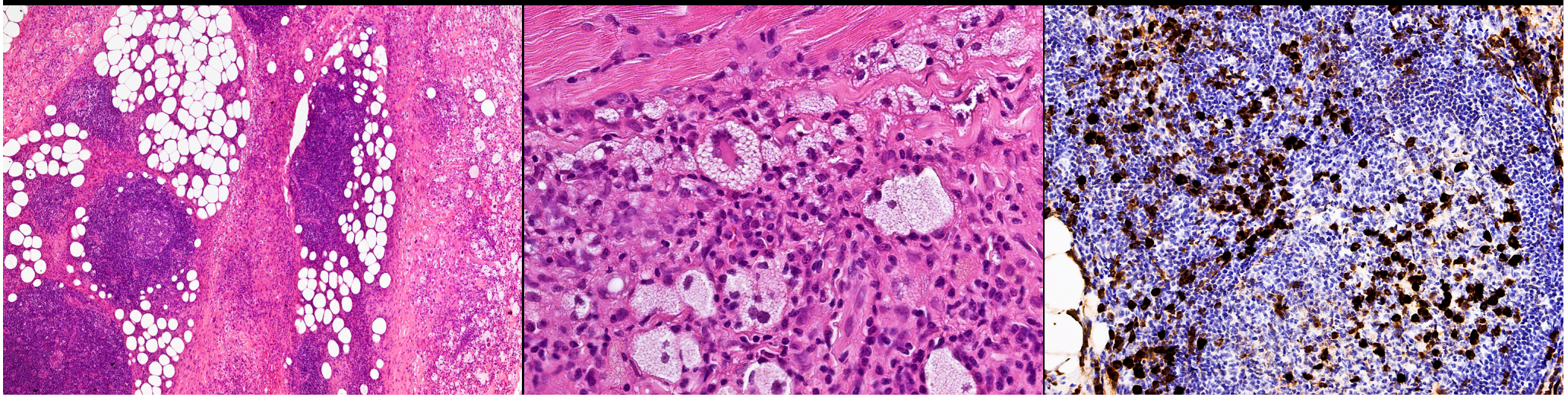
IGG4+ plasma cells
>100 / HPF

IgG4:CD138 >80%



Pathology Diagnosis

- Xanthogranuloma (likely adult onset asthma associated periocular xanthogranuloma)
- Elevated IgG4 plasma cells



Next Steps?

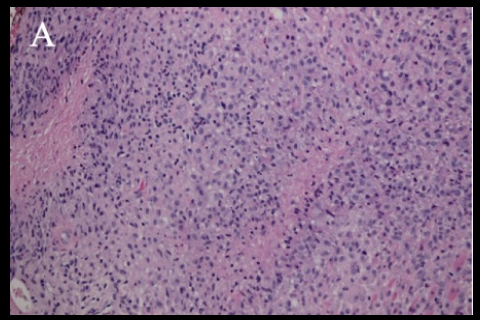
- Pathology demonstrating findings consistent with AAPOX
- Treatment options?
  - Systemic steroids?
  - Systemic immunosuppressant agents?
    - Methotrexate, Cyclophosphamide, RITUXIMAB

- Referred to Oncology for evaluation and consideration of Rituximab infusion

- Patient started on Rituximab infusions
  - 375 mg/m2 qweekly x 1 month
  - 375 mg/m2 q4 weeks x 6 months

Adult Onset Asthma and Periocular Xanthogranuloma (AAPOX)

- Rare systemic disease characterized by adult onset asthma, lymphadenopathy, periocular xanthogranulomatous disease
- Clinically presents with varying combination periocular swelling, xanthelasmas, asthma, systemic lymphadenopathy, glandular enlargement
  - Periocular involvement classically preseptal and anterior orbit ,can involve lacrimal gland and EOM
- Bx and labs demonstrate paraproteinemia and elevated IgG levels with Touton giant cells and cholesterol clefts
  - Unclear association w/ IgG4-RD
- Treatment: steroids, immunosuppressives, rituximab



Successful treatment with rituximab of IgG4-related disease coexisting with adult-onset asthma and periocular xanthogranuloma

Ioannis Asproudis, Maria Kanari, Ioannis Ntountas, Vasileios Ragos, Anna Goussia, Anna Batistatou & Paraskevi Vasileios Voulgari

- 36F w/ proptosis and periorbital edema
- Bx proven IgG4-RD AAPOX disease
- Treated with 2 cycles Rituximab + PO Steroids
  - Complete remission following Rituximab therapy

Sustained clinical response after single course of rituximab as first-line monotherapy in adult-onset asthma and periocular xanthogranulomas syndrome associated with IgG4-related disease

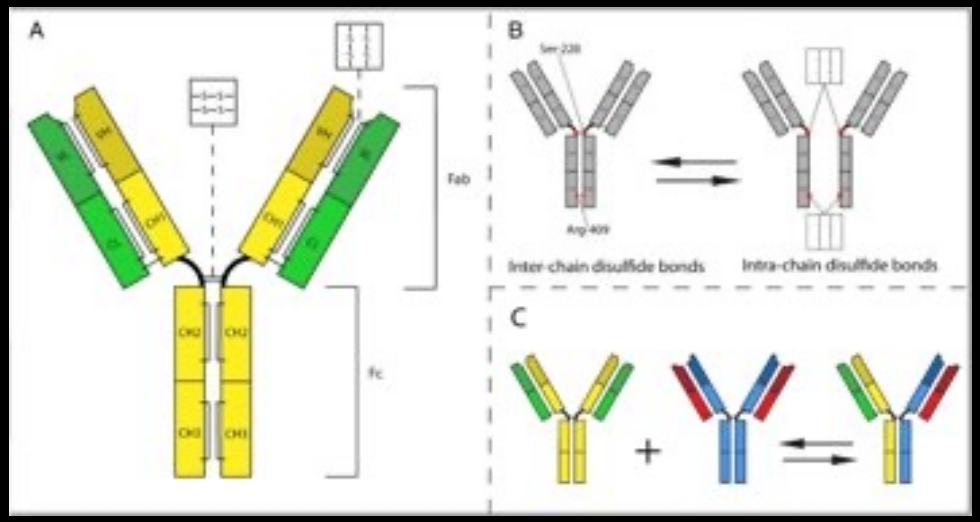
A case report

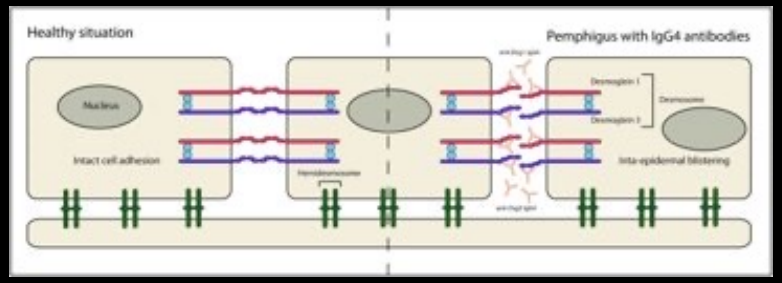
Giovanni Pomponio, MD,[a] Diletta Olivari, MD,[b,*] Massimo Mattioli, MD,[b] Alessia Angeletti, MD,[b] Giulia Rossetti, MD,[b] Gaia Goteri, MD,[c] and Armando Gabrielli, MD[b]

- 50F w/ eyelid xanthelasmas, adult onset asthma, lacrimal gland enlargement
- Bx proven IgG4-RD AAPOX disease
- Treated with single course Rituximab
  - "Near complete clinical remission" achieved w/o chronic steroid therapy

IgG4 Antibody

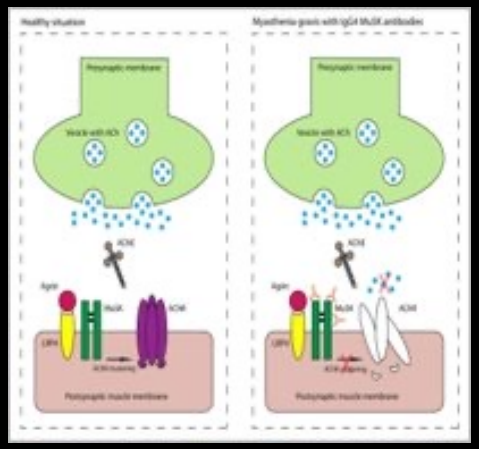
- FAB-ARM EXCHANGE: switch of inter-chain disulfide bonds to intra-chain bonds cause the heavy chains to dissociate resulting in two half molecules and form new molecules with another half molecule
- The resulting asymmetric antibody has two antigen-binding sites, is monovalent and can't form large immune complexes
- Minimal binding to activating receptors on effector cells and incapable of activating the complement pathway
- Interact with other immunoglobulins inhibiting the biologic effects of the complement-fixing IgG1 subclass





Pemphigus

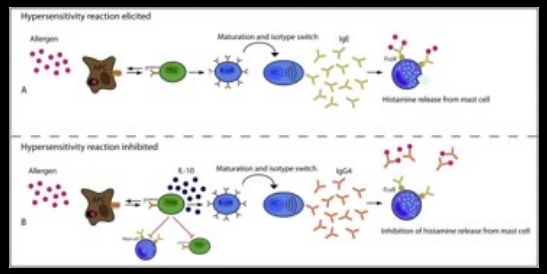
- Anti-Dsg1 and anti-Dsg3 IgG4 antibodies disrupt binding of intra-epidermal cell adhesion molecules Desmoglein 1 and Desmoglein 3: resulting in INTRAEPIDERMAL BLISTERING



Myasthenia

- Anti muscle-specific kinase IgG4 antibodies disrupt MuSK thus preventing acetylcholine receptor clustering and impairing synaptic transmission

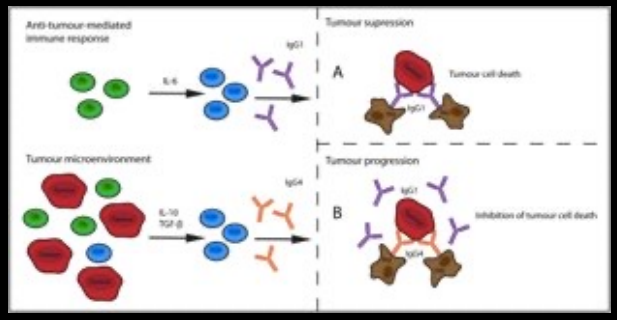
Allergy Exposure



Competitive binding with IgE to the allergen

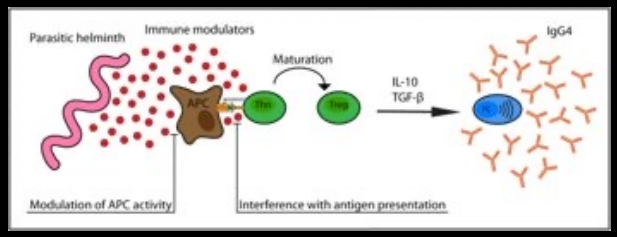
Preventing formation of IgE immune complexes and mast cell activation

Melanoma



- Melanoma cells initiate IgG4 production
- IgG4 is capable of blocking the antitumor activity of melanoma specific IgG1 through competitive binding

Parasitic Infection



- Parasite specific IgG4 create an immune-tolerant environment for helminths: causing a subclinical chronic infection

Allergies/hypersensitivities

Advantageous suppression
Beekeepers
Animal laboratory workers
Allergen-specific immunotherapy

Malignancies and Parasitic infections

Disadvantageous suppression
Melanoma and cholangiocarcinoma
Helminthic infections

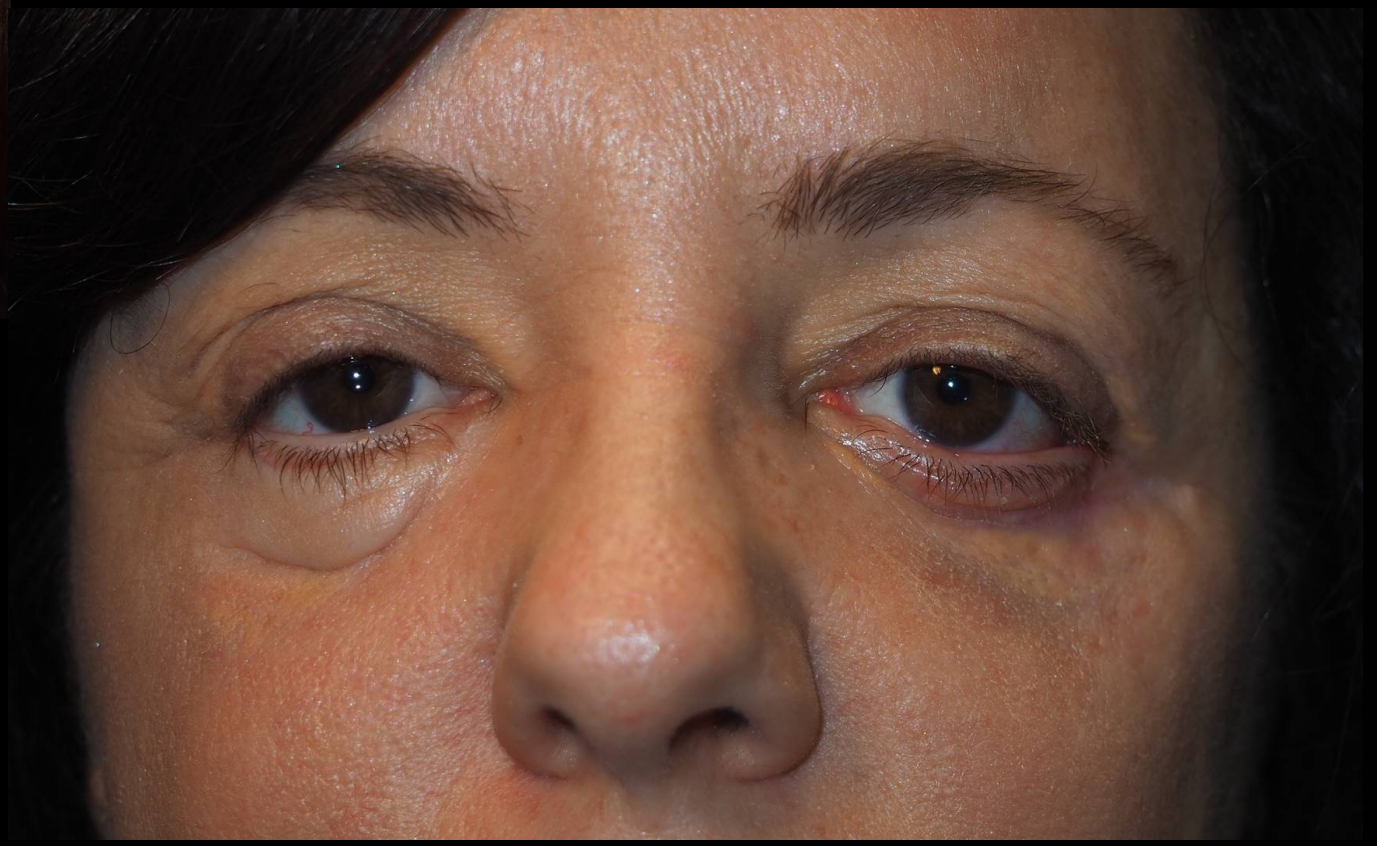
Autoimmune/immune-mediated diseases

Pathogenic
Pemphigus vulgaris and foliaceus
MuSK-myasthenia gravis

Following Rituximab Treatment

- Reports "significant improvement" in periorbital swelling
- Reduction in size of lower lid xanthelasmas
- Loss of tissue of cheek and lid resulting in lid deformities

2017 pre biopsy



2018 s/p rituximab

As of today...

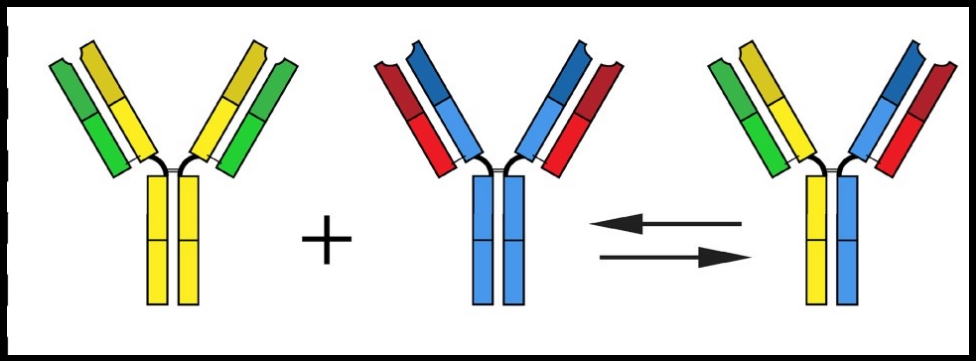
- Currently in remission off all systemic meds since Rituximab therapy
- Received 5-FU injections for periocular fibrosis and scarring
- Underwent multiple reconstructive surgeries following therapy
  - Canthoplasty w/ flap repositioning
  - B/l lateral lower lid reconstruction
  - Reconstruction BLL and Cheek lift
- Doing very well happy with appearance, no episodes of diplopia/periorbital edema/periocular xanthelasmas

Summary

- 31 year old female presenting w/ hx of thyroid eye disease and idiopathic orbital inflammation
- Underwent steroid treatment, radiation therapy, fatty decompression, lid surgery, sinus surgery, with stabilization of inflammatory disease
- 15 years later developed xanthomatous lesions and periorbital swelling with sudden progression
  - Ultimately underwent debulking with biopsy
  - Diagnosed with AAPOX
- Received Rituximab induction and maintenance therapy
  - Complete resolution of orbital symptoms and xanthomatous lesions
- Remains in remission off systemic therapy
  - Excellent cosmetic outcome following successful reconstructive surgeries

Role of IgG4 in XG and IgG4R-D

- PATHOGENIC
- PROTECTIVE
- PASSIVE OBSERVER



Resources

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- https://www.bing.com/images/search?view=detailV2&ccid=kGAjQpXk&id=4ED895F16A14F35E6977553A28240D11F48C7105&thid=OIP.kGAjQpXkMcUS1ydPZrO0sgHaFk&mediaurl=https%3a%2f%2fwww.idoj.in%2farticles%2f2020%2f11%2f5%2fimages%2fIndianDermatolOnlineJ_2020_11_5_792_295588_f7.jpg&cdnurl=https%3a%2f%2fth.bing.com%2fth%2fid%2fR.9060234295e431c512d7274f66b3b4b2%3frik%3dBXGM9BENJCg6VQ%26pid%3dImgRaw%26r%3d0&exph=609&expw=809&q=AAPOX+disease&simid=608011436639544125&FORM=IRPRST&ck=EF72E5DF5185D26786EC75DEE0897B7B&selectedIndex=3&ajaxhist=0&ajaxserp=0

Thank You

- Dr. Stefanyszyn
- Dr. Milman
- Dr. Shebaclo
- Wills Eye Class of 2023