Ophthalmology Grand Rounds

Christopher Adam, M.D. (PGY2)

August 6, 2015

Case Presentation

- 39 y/o BF who presented to UHB-ED with c/o painless right upper and lower eyelid swelling x 2 days.

History

- Pertinent positives (+): multiple past episodes of eyelid swelling which resolved with steroids.
- Pertinent negatives (-): denied decreased vision, pain, diplopia, trauma, discharge, insect bites, HA, fevers, weight loss, arthralgias/myalgias, rash.

History

- PMH: SLE (Dx 2008), Anemia, Sickle cell trait.
- POH: multiple past episodes of eyelid swelling.
- PSH: LEEP, Myomectomy.
- Meds: Prednisone and Ciprofloxacin (started by Rheum PTA), Bosentan, Omeprazole, Vitamin D. *Previously on Hydroxychloroquine*.
- All: NKDA.
- SH: no use of tobacco products, alcohol, or illicit drugs.
- FH: no glaucoma, blindness, auto-immune disease.

Exam Findings

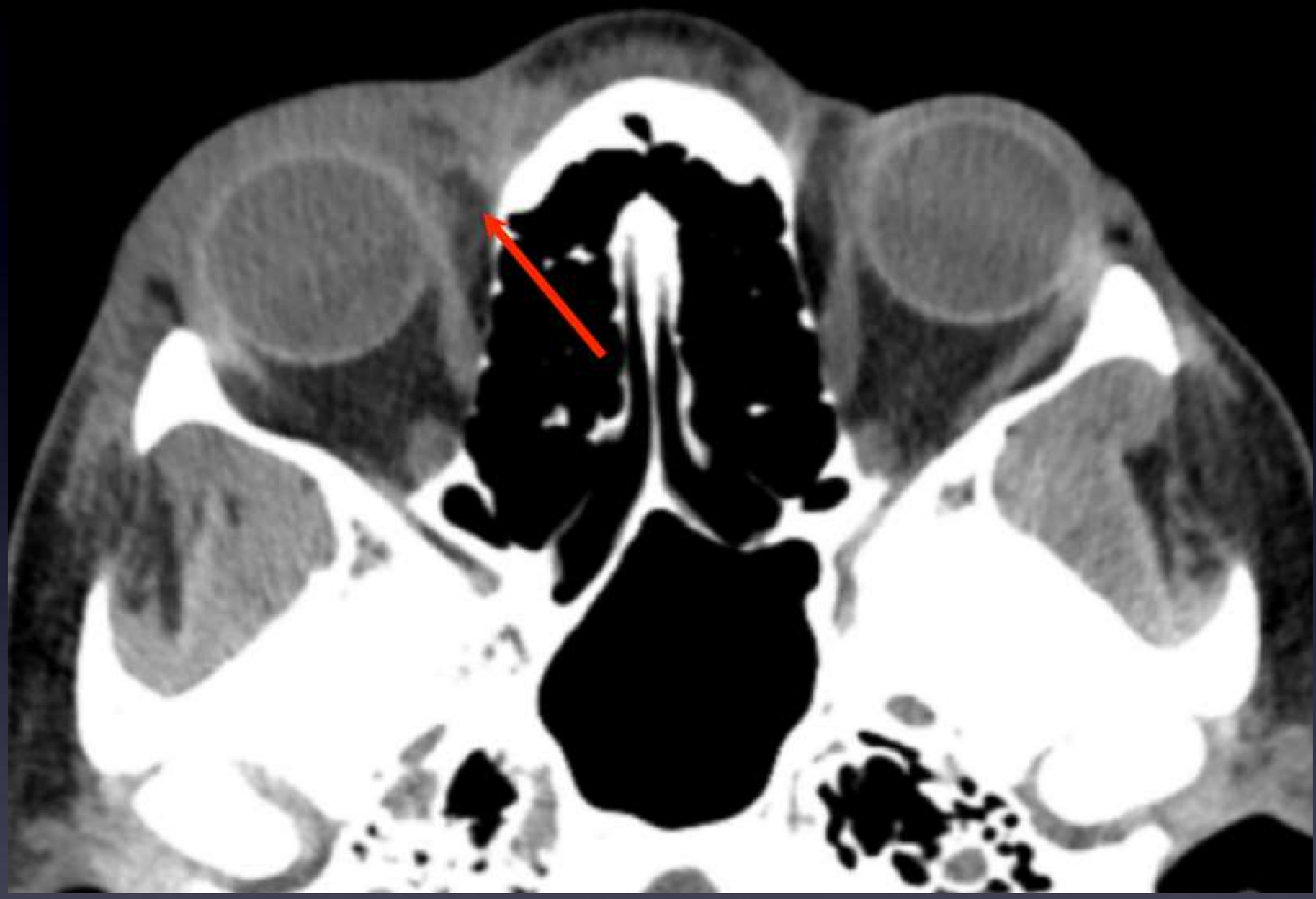
- NVasc: 20/20- OD, 20/20 OS
- Pupils: 5-3mm err OU, no APD
- EOMs: full OU; no pain/diplopia/limitations
- CVF: ftfc OU
- Tpen: 13/13

Slit Lamp Exam

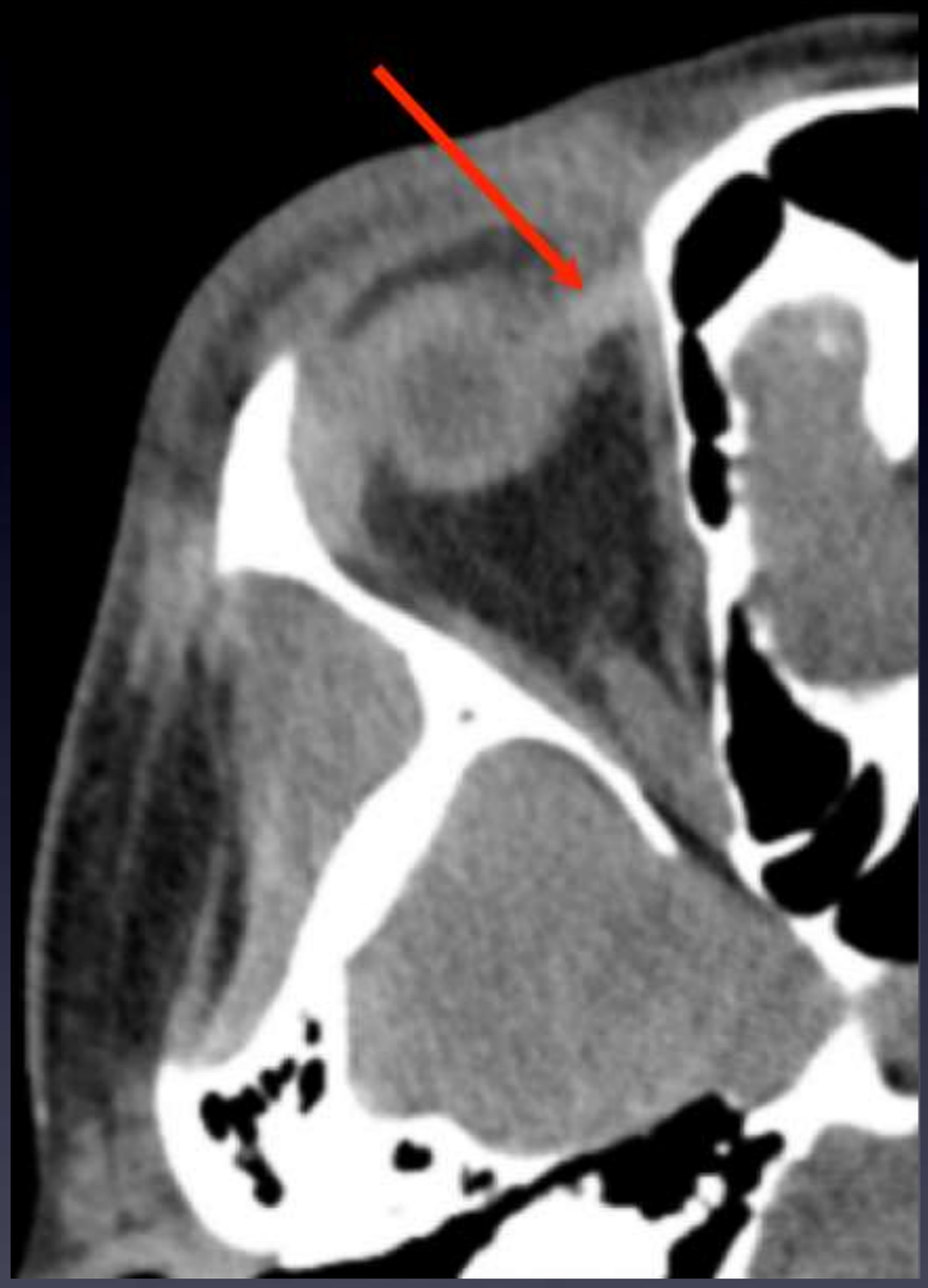
- L/L/A: +right upper/lower eyelid edema with thickened SQ tissue. +warmth/erythema. +Focal point tenderness of superior trochlea region on deep palpation of right orbit.
- C/S: w/q OU.
- Cornea: clear OU.
- A/C: d/q OU.
- Iris/Pupils: rr OU.
- Lens: clear OU.

Dilated Fundus Exam

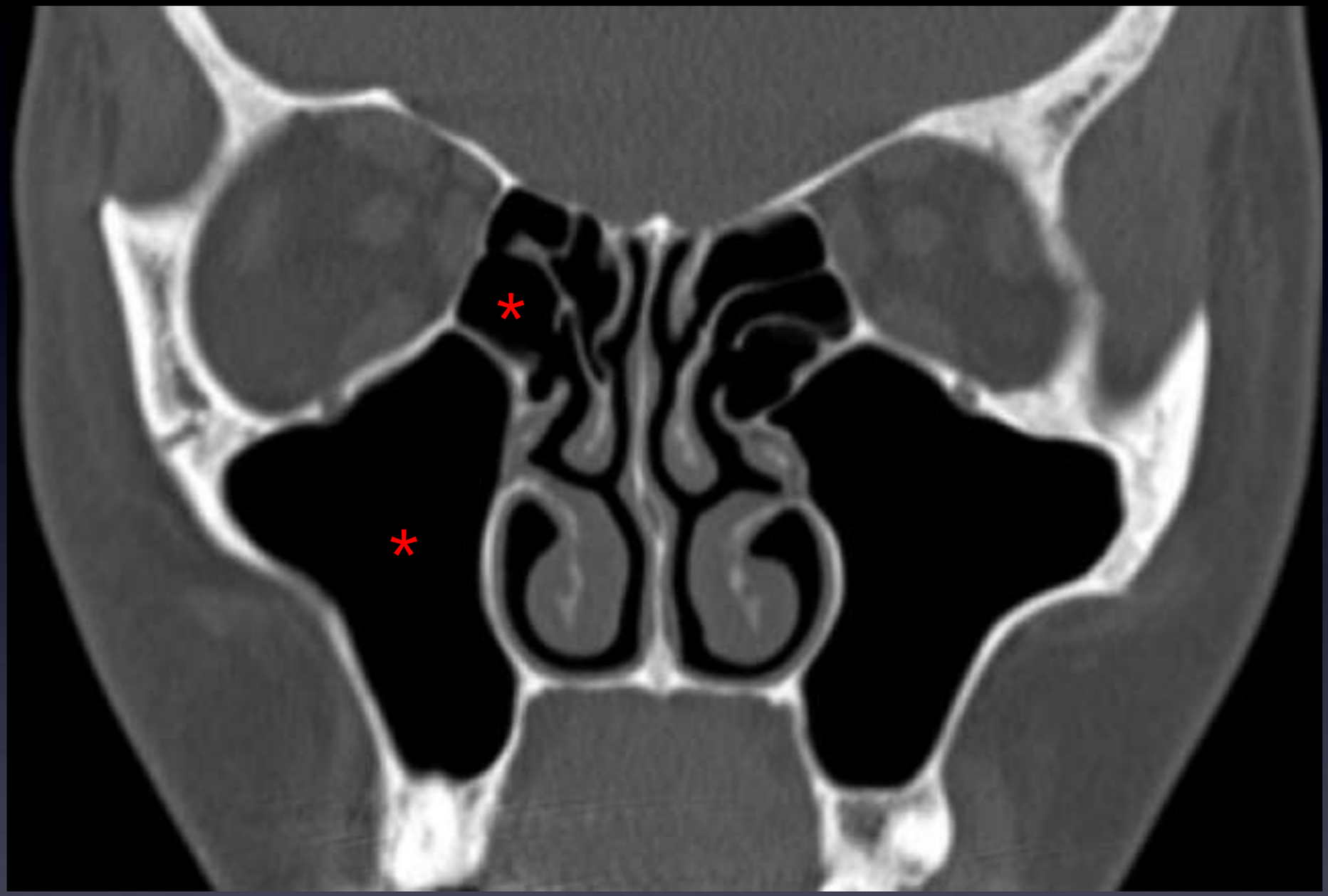
- Vitreous: clear OU.
- C/D: 0.4, s/p OU.
- Macula: flat OU.
- V/P: normal caliber, no heme/holes/tears OU.



Axial CT w/o contrast showing soft tissue thickening of the right preseptal region and orbital fat standing (arrow). Thickening of the MR insertion. Absence of sinus disease.



Axial CT w/o contrast showing right SO and trochlea hyperdensity (arrow).



Coronal CT w/o contrast showing absence of sinus disease (asterisks).

- Differential Diagnosis?

Differential Diagnosis

- **Infection (cellulitis, abscess)**
- **Angioedema/Urticaria**
- **Nonspecific orbital inflammation (idiopathic; associated with systemic inflammatory syndrome/autoimmune disease)**
- **Neoplasm**
- **Trauma**

Diagnosis?

Nonspecific Orbital Inflammation

- Definition: A benign (non-neoplastic, non-infective) inflammatory space occupying infiltration of the orbit.

History

- Nonspecific orbital inflammation was first described in 1905 by Birch-Hirschfeld.

NSOI

- Also known as Orbital Pseudotumor or Idiopathic Orbital Inflammatory Disease.

Incidence

- Difficult to assess given the wide range of manifestation and lack of universally accepted definition.
- NSOI thought to account for 6.3% of orbital disorders (Yuen et al., 2002).

NSOI

- Pathogenesis remains controversial.
- Believed to be an immune-mediated process.
- Often associated with systemic autoimmune disease: Crohn’s, SLE, granulomatosis polyangiitis, RA, DM, MG, and AS.
- Exquisitely sensitive to systemic steroids.

NSOI

- Occurs in 5 orbital locations/patterns:
  - - Extraocular muscles *(myositis)*
  - - Lacrimal gland *(dacryoadenitis)*
  - - Anterior orbit (e.g., *scleritis)*
  - - Orbital apex
  - - Diffuse orbital inflammation

Presentation

- Depends on location/pattern of involved tissue.
- Acute or subacute ocular and periocular redness, swelling, and pain (deep/boring).
- EOM limitation, proptosis, conjunctival injection, chemosis, eyelid erythema, and soft tissue swelling.
- Pain with ocular movement suggests myositis.
- Va may be impaired if the optic nerve or posterior sclera are involved.

Atypical Presentation

- *Sclerosing variant* (limited inflammation, extensive fibrosis).
- b/l orbital inflammation in adults suggests systemic vasculitis.
- In children 1/3 of cases are b/l and rarely associated with systemic disorders.
- Children commonly present with HA, fever, vomiting, and abdominal pain. Uveitis, elevated ESR, and eosinophilia more common in children.

Disease Course

- Natural history is highly variable.
- Spontaneous remission without sequelae.
- Intermittent episodes of activity.
- Prolonged inflammation leading to fibrosis of orbital tissues and ophthalmoplegia.
- Chronically associated with ptosis and visual impairment.

Investigation

- Extensive History/Physical exam
- Characterization of symptoms (7 dimensions)
- PMH focusing on systemic disease
- FH of autoimmune disease
- Medications/Allergies
- Detailed Ophthalmic exam
- Laboratory and Radiologic studies

Work-up

- After a differential diagnosis has been formulated and potential etiologies ruled out based on your detailed history and exam, laboratory and radiologic testing can be used to aid in the identification of the underlying disease process.

Labs

- CBC, ESR, CRP, ANA, ANCA, RF, IgG panel (subclasses), ACE, Thyroid panel.

IgG-4

- **IgG4-related orbital disease is a recently defined inflammatory process:**
- **1) Inflammatory infiltration of IgG4-producing plasma cells.**
- **2) Tendency to form tumorous lesions at different sites.**
- **3) Increased serum IgG4 levels, although not a required condition.**
- **Mombaerts et al., 1996**

IgG4

- **Wong et al., 2014** analyzed gene expression and the prevalence of IgG4 immunostaining among subjects with orbital inflammatory diseases.
    - Concluded that IgG4+ plasma cells are common in orbital tissue from patients with sarcoidosis, GPA (Wegener's), or NSOI.
    - IgG4 staining correlates with increased inflammation in the lacrimal gland based on histology and gene expression.
- **Oles et al., 2015** investigated IgG4 related inflammatory orbital pseudotumors.
    - Measured IgG4+/CD138+ and IgG4+/IgG+ ratios.
    - Found IgG4-related orbital disease presenting as dacryoadenitis, orbital inflammatory pseudotumor, and orbital myositis.

IgG4 Immunostaining and Its Implications in Orbital Inflammatory Disease

Amanda J. Wong[1], Stephen R. Planck[1,2,3], Dongseok Choi[1,4], Christina A. Harrington[5], Megan L. Troxell[6], Donald C. Houghton[6], Patrick Stauffer[1], David J. Wilson[1], Hans E. Grossniklaus[7], Roger A. Dailey[1], John D. Ng[1], Eric A. Steele[1], Gerald J. Harris[8], Craig Czyz[9], Jill A. Foster[10], Valerie A. White[11], Peter J. Dolman[11], Michael Kazim[12], Payal J. Patel[12], Deepak P. Edward[13], Hind al Katan[13], Hailah al Hussain[13], Dinesh Selva[14], R. Patrick Yeatts[15], Bobby S. Korn[16], Don O. Kikkawa[16], James T. Rosenbaum[1,2,3]*

1 Casey Eye Institute, Oregon Health & Science University, Portland, Oregon, United States of America, **2** Department of Medicine, Oregon Health & Science University, Portland, Oregon, United States of America, **3** Devers Eye Institute, Legacy Health Systems, Portland, Oregon, United States of America, **4** Department of Public Health and Preventive Medicine, Oregon Health & Science University, Portland, Oregon, United States of America, **5** Integrated Genomics Laboratory, Oregon Health & Science University, Portland, Oregon, United States of America, **6** Department of Pathology, Oregon Health & Science University, Portland, Oregon, United States of America, **7** Department of Ophthalmology, Emory University, Atlanta, Georgia, United States of America, **8** Department of Ophthalmology, Medical College of Wisconsin, Milwaukee, Wisconsin, United States of America, **9** Division of Ophthalmology, Ohio University, Columbus, Ohio, United States of America, **10** Department of Ophthalmology, The Ohio State University, Columbus, Ohio, United States of America, **11** Department of Ophthalmology and Visual Sciences, University of British Columbia, Vancouver, BC, Canada, **12** Department of Ophthalmology, Columbia University, New York, New York, United States of America, **13** Research Department, King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia, **14** Ophthalmology Network, Royal Adelaide Hospital, Adelaide, SA, Australia, **15** Department of Ophthalmology, Wake Forrest University, Winston-Salem, North Carolina, United States of America, **16** Department of Ophthalmology, University of California San Diego, San Diego, California, United States of America

Abstract

Objective: IgG4-related disease is an emerging clinical entity which frequently involves tissue within the orbit. In order to appreciate the implications of IgG4 immunostaining, we analyzed gene expression and the prevalence of IgG4-immunostaining among subjects with orbital inflammatory diseases.

Methods: We organized an international consortium to collect orbital biopsies from 108 subjects including 22 with no known orbital disease, 42 with nonspecific orbital inflammatory disease (NSOI), 26 with thyroid eye disease (TED), 12 with sarcoidosis, and 6 with granulomatosis with polyangiitis (GPA). Lacrimal gland and orbital adipose tissue biopsies were immunostained for IgG4 or IgG secreting plasma cells. RNA transcripts were quantified by Affymetrix arrays.

Results: None of the healthy controls or subjects with TED had substantial IgG4 staining. Among the 63 others, the prevalence of significant IgG4-immunostaining ranged from 11 to 39% depending on the definition for significant. IgG4 staining was detectable in the majority of tissues from subjects with GPA and less commonly in tissue from subjects with sarcoidosis or NSOI. The detection of IgG4+ cells correlated with inflammation in the lacrimal gland based on histology. IgG4 staining tissue expressed an increase in transcripts associated with inflammation, especially B cell-related genes. Functional annotation analysis confirmed this.

Conclusion: IgG4+ plasma cells are common in orbital tissue from patients with sarcoidosis, GPA, or NSOI. Even using the low threshold of 10 IgG4+ cells/high powered field, IgG4 staining correlates with increased inflammation in the lacrimal gland based on histology and gene expression.

IgG4-related inflammatory orbital pseudotumors – a retrospective case series

Krzysztof Oles[1], Wojciech Szczepanski[2], Jacek Skladzien[1], Krzysztof Okon[2], Joanna Leszczynska[1], Emilia Bojanowska[1], Magdalena Bialas[2], Agnieszka Wrobel[3], Joanna Mika[4]

[1]Department of Otolaryngology, Head and Neck Surgery of the Jagiellonian University, Krakow, [2]Department of Pathomorphology, Medical College Jagiellonian University, Krakow, [3]Department of Otolaryngology, Medical College Jagiellonian University, Krakow, [4]Department of Pain Pharmacology, Institute of Pharmacology, Krakow, Poland

Folia Neuropathol 2015; 53 (2): 111-120 DOI: 10.5114/fn.2015.52407

Abstract

Orbital diseases may be divided into congenital defects of the orbit, infectious and inflammatory diseases, orbital tumors (including malignant and benign tumors) and injuries. Idiopathic inflammatory syndromes are often encountered within the orbit and are usually classified as orbital pseudotumors. The etiology of pseudotumors of the vision organ is unknown. Infectious agents, autoimmune disorders and improper healing are taken into consideration in the pathogenesis of this disorder. Thanks to detailed studies conducted in recent years, a new disease syndrome was identified in 2001. It is known as IgG4-related disease, and its differentiation is based on the analysis of IgG4 levels in the affected tissues. Orbital locations of the disease were first reported in Japan as late as at the end of 2009. This finding triggered the European studies on this subject. To date, no such studies have been conducted in Poland. The starting study population consisted of 167 patients with isolated infiltrative tumor diseases within the orbital region treated at the Department of Otolaryngology, Head and Neck Surgery of the Medical College Jagiellonian University in Krakow. Detailed analysis and diagnostic screening for IgG4-related disease was performed in a total of 17 patients diagnosed with orbital pseudotumor.

Ocular Manifestation of SLE

- Common, potentially sight threatening, and may be the presenting feature.
- Affects any part of the eye or visual pathway.
- Mechanisms include IC deposition and other Ab related mechanisms, vasculitis, thrombosis, medication toxicity.

Ocular Manifestation of SLE

- **Eyelid**: discoid lupus rash
- **Lacrimal**: keratoconjunctivitis sicca (1/3 of SLE patients)
- **Orbital**: edema, myositis, panniculitis, ischemia/infarction
- **Corneal**: DES, corneal erosions, peripheral ulcerative keratitis
- **Episclera/Sclera**: episcleritis, scleritis
- **Retina**: retinopathy, cotton-wool spots, exudates, hemorrhages, tortuosity, vasculitis, occlusions)
- **Optic and Cranial nerves:** optic neuritis, atrophy, ischemic optic neuropathy, CN palsies

Trochleitis in SLE

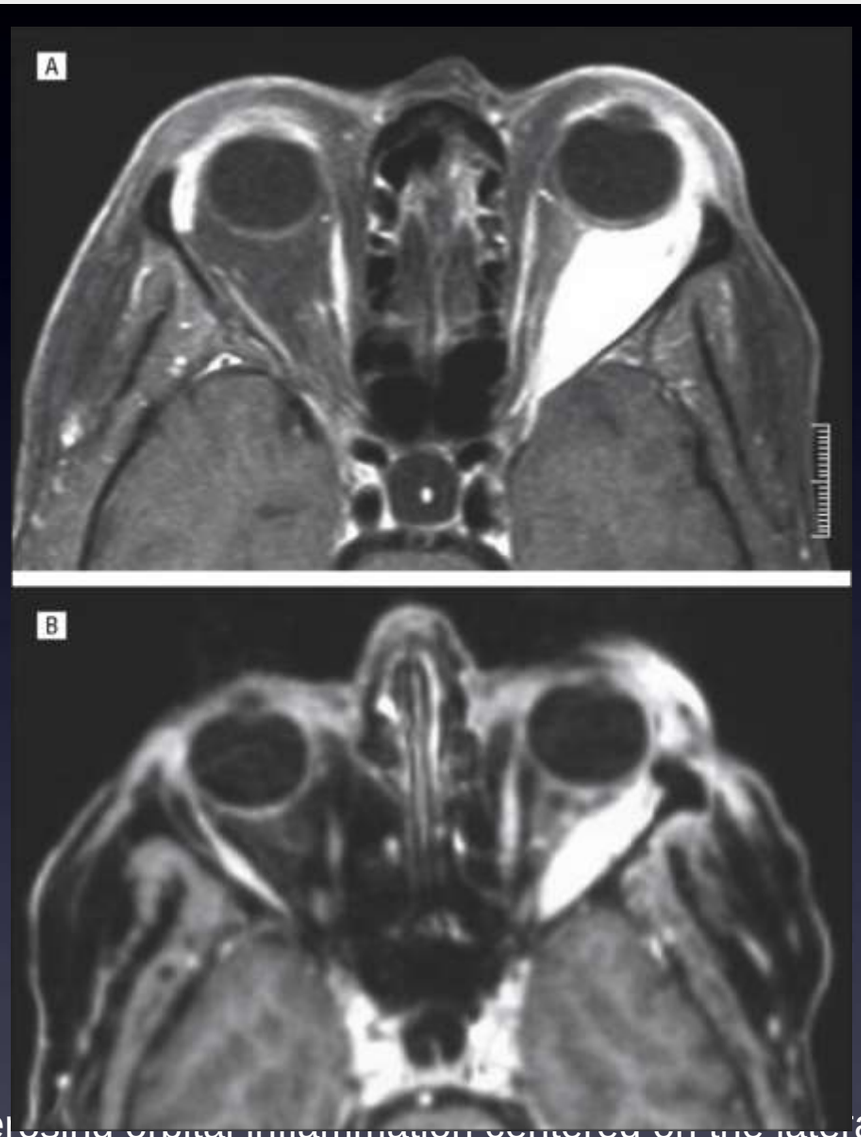
- Case reports of trochleitis as first manifestation of SLE (Fonseca et al., 2013).
- Pain with eye movement (adduction, supraduction), diplopia, focal pain on deep palpation of superior-nasal orbital rim.
- Idiopathic, RA, SLE, Scleritis, Brown syndrome, Myositis, Psoriasis, Migraine.

Imaging

- Radiographic evaluation of the orbit typically involves CT and MRI.
- Kapur et al., 2009 noted different DWI signal intensities between NSOI, orbital cellulitis, and orbital lymphoid.
- Orbital US is helpful in evaluating the insertions of extraocular muscles (absent in TED), identifying intraocular and lacrimal gland tumors, lymphangiomas, and scleritis (T-sign).

From: **Idiopathic Sclerosing Orbital Inflammation**

Arch Ophthalmol. 2006;124(9):1244-1250. doi:10.1001/archopht.124.9.1244



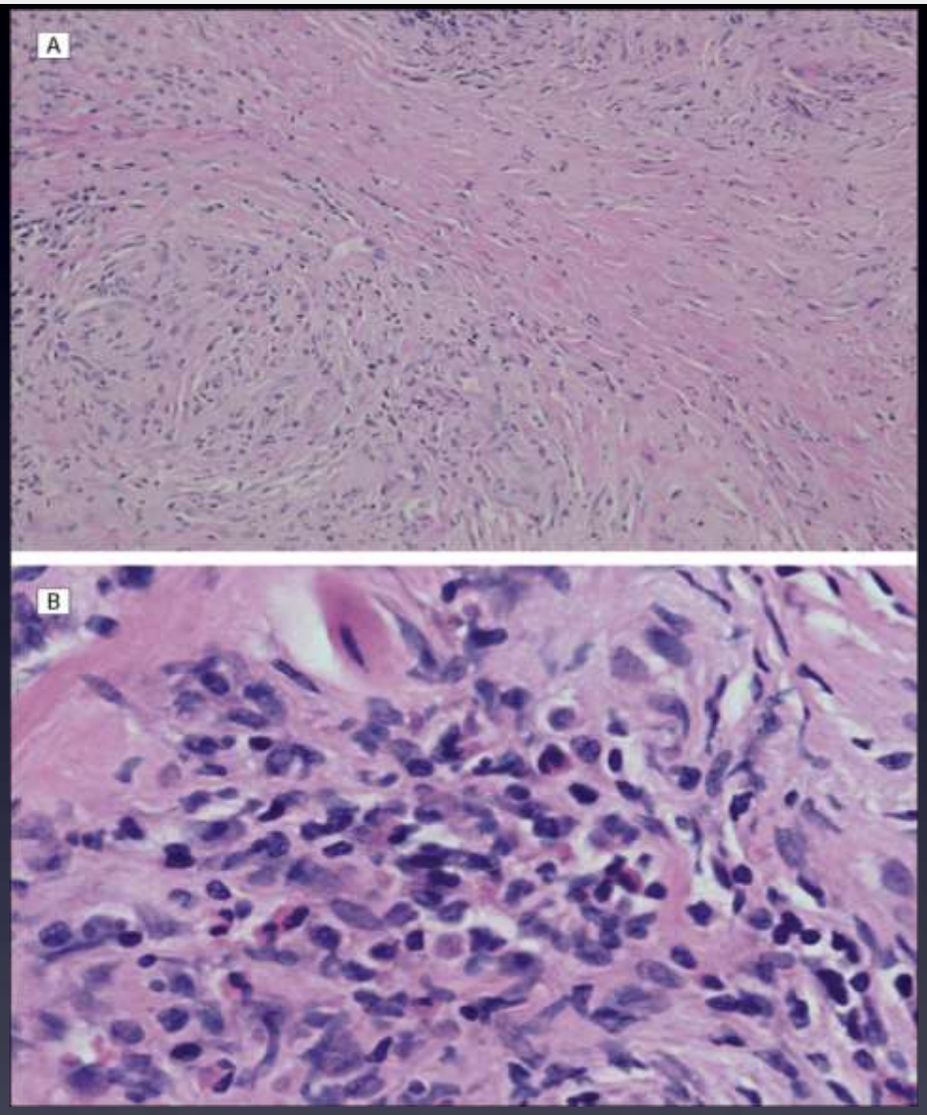
Magnetic resonance image of idiopathic sclerosing orbital inflammation centered on the lateral rectus muscle in a 60-year-old woman. A, At presentation, the muscle is markedly enlarged and inflamed. B, After treatment with oral prednisolone, there is an obvious reduction in the muscle swelling, which was accompanied by improvement in the patient's symptoms and signs.

Histology

- Histopathological analysis reveals pleomorphic inflammatory cellular infiltration: lymphocytes, plasma cells, and eosinophils with variable reactive fibrosis w/o a known cause.
- *Sclerosing NSOI* subtype with predominant fibrosis and minimal inflammation. Responds poorly to steroids and radiotherapy. Typically requires aggressive

From: **Idiopathic Sclerosing Orbital Inflammation**

Arch Ophthalmol. 2006;124(9):1244-1250. doi:10.1001/archopht.124.9.1244



Photomicrographs show the histological appearance of idiopathic sclerosing orbital inflammation. A, Low magnification shows diffuse inflammation with marked sclerosis (hematoxylin-eosin, original magnification ×100). B, At higher magnification, there is a polymorphous inflammatory infiltrate with prominent eosinophils (hematoxylin-eosin, original magnification ×400).

Diagnosis

- NSOI is a diagnosis of exclusion.
- Typical clinical presentation combined with orbital imaging and negative laboratory w/u suggest the diagnosis of NSOI.
- Prompt response to systemic steroids supports the diagnosis.
- Note: inflammation associated with other orbital processes (e.g., metastases, ruptured dermoid cysts, infections) may also improve with systemic steroid administration.
- A thorough systemic evaluation should be undertaken if there is any uncertainty regarding the diagnosis.

Treatment

- The goal of treatment in NSOI is to preserve vision, orbital function, and reduce the acute inflammatory process.
- High dose corticosteroids are the standard initial therapy for NSOI.

Treatment

- Observation: mild disease, anticipation of spontaneous remission.
- NSAIDs: often effective in mild disease prior to steroid therapy.
- Systemic corticosteroids
- Orbital depot steroid injection: may be useful in some cases.

Treatment

- Resistant cases cytotoxic drugs (e.g. methotrexate, azathioprine), calcineurin inhibitors (e.g. cyclosporin, tacrolimus) and biological blockers (anti-TNF-alpha)
- Surgical resection: inflammatory focus in highly resistant cases.
- Radiotherapy: no improvement after steroid therapy. Successful in recurrent myositis. Low-dose (e.g. 10 Gy) may produce remission.

Corticosteroids

- Once other diagnoses are excluded, initial therapy generally consists of systemic corticosteroids.
- Initial daily adult dosage is typically **Prednisone 1 mg/kg/day**.
- Acute cases generally respond rapidly, with abrupt resolution of the associated pain and symptoms.
- Steroids are tapered based on clinical response, tapering should proceed slowly below 40 mg/day and very slowly below 20 mg/day.
- Rapid reduction of systemic steroids may cause a recurrence of inflammatory symptoms and signs.
- Some believe the use of pulse-dosed IV dexamethasone followed by oral prednisone may produce clinical improvement when oral prednisone alone fails to control the inflammation.

Biopsy?

- Incomplete response or recurrent disease suggests the need for orbital biopsy.
- Can provide histologic confirmation and exclude specific inflammatory diseases.
- Some advise biopsy before initiating empiric steroids to avoid delayed or missed diagnoses.
- Others advocate biopsy of all infiltrative lesions; except orbital myositis or orbital apex syndrome.
- Biopsy is recommend for isolated

Back to our patient...

- Admitted by Medicine.
- Ophthalmology and Rheumatology consulted.
- Initial working diagnosis was Pre-septal cellulitis vs. Angioedema vs. NSOI.
- Patient initially received antibiotics in ED.
- Was subsequently started on Prednisone 60mg daily and Clindamycin 600mg IV q8h.

Labs

- Total IgG 2918 (nl 694-1618).
  - *IgG subclasses pending.*
- Remaining laboratory w/u including PPD, RPR, Lyme, C3/C4, and ACE were negative/wnl.

Imaging

- CT showed soft tissue thickening of the right preseptal region and orbital fat standing.
- Thickening of the MR insertion on the globe with adjacent orbital attenuation.
- Right SO hyperintensity and trochleitis.

Discharge Planning

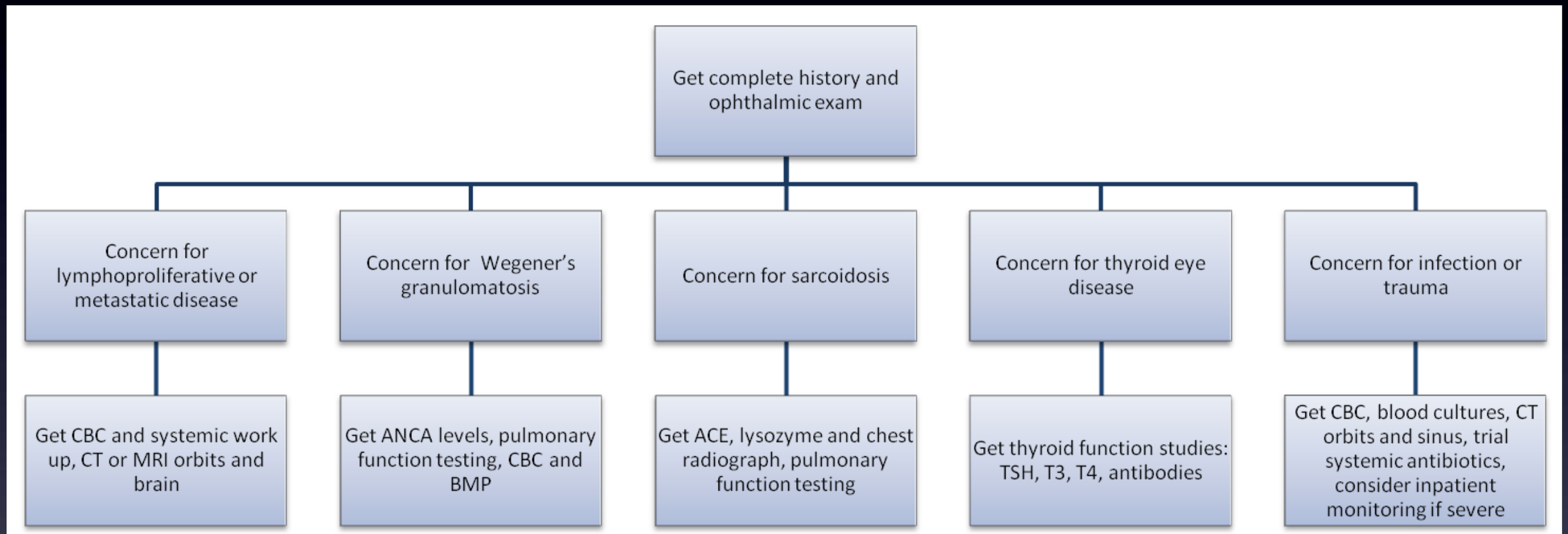
- Prednisone 60mg daily with plan for slow taper over 2 months.
- Omeprazole 40mg daily.
- Artificial Tears 2/2.
- Close f/u with Ophthalmology, Rheumatology and PCP.

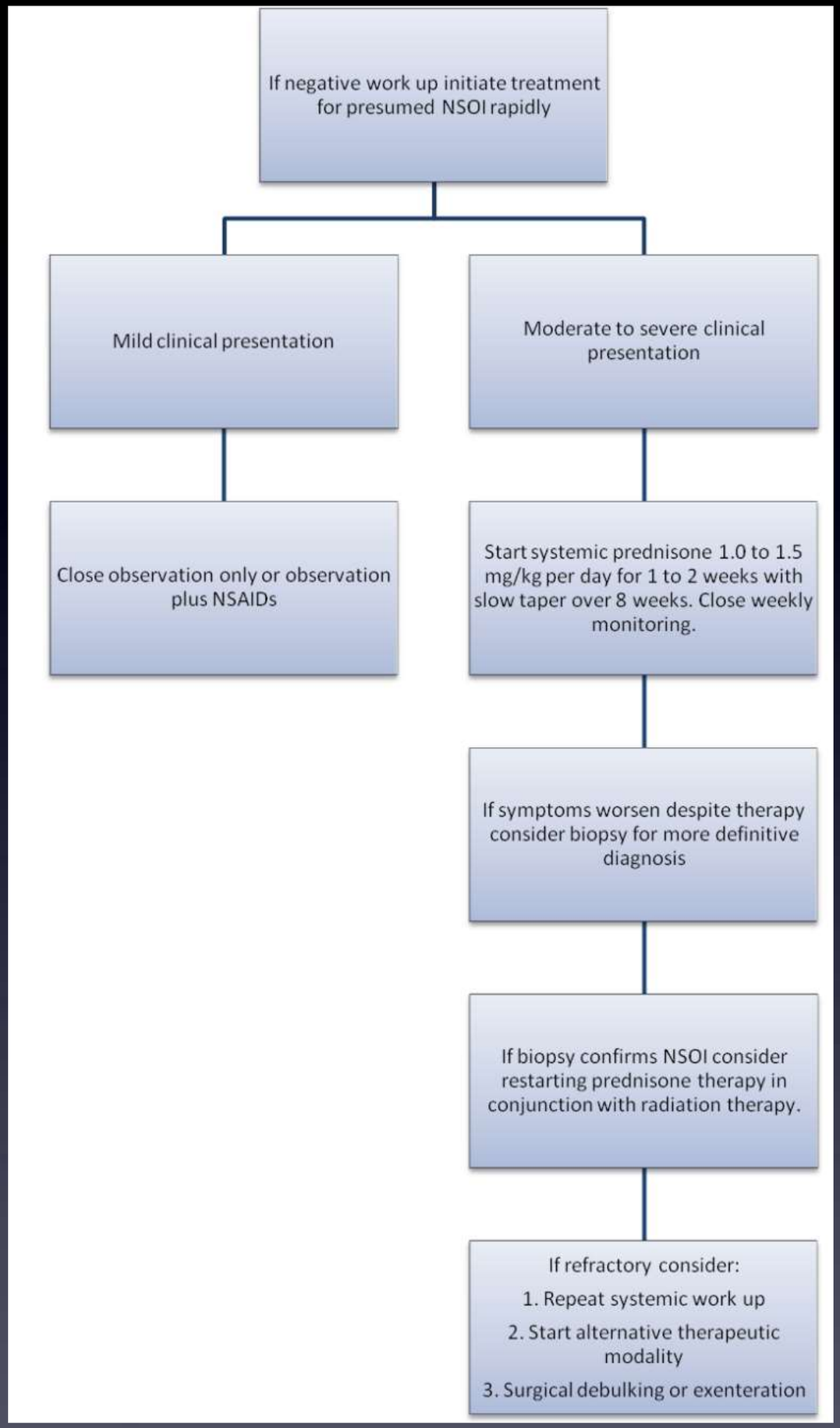
Outpatient

- At one week follow-up our patient has shown significant improvement in symptomatology.
- c/o mild sensitivity to light and eyelid swelling.
- f/u appointment in one month.

Summary

- Previous similar episodes
- Favorable rapid response to steroids
- Known autoimmune disease (SLE)
- Acute eyelid swelling, myositis, trochleitis, pre- and post-septal inflammation on imaging
- Elevated IgG


Get complete history and ophthalmic exam
Concern for lymphoproliferative or metastatic disease
Concern for Wegener's granulomatosis
Concern for sarcoidosis
Concern for thyroid eye disease
Concern for infection or trauma
Get CBC and systemic work up, CT or MRI orbits and brain
Get ANCA levels, pulmonary function testing, CBC and BMP
Get ACE, lysozyme and chest radiograph, pulmonary function testing
Get thyroid function studies: TSH, T3, T4, antibodies
Get CBC, blood cultures, CT orbits and sinus, trial systemic antibiotics, consider inpatient monitoring if severe


If negative work up initiate treatment for presumed NSOI rapidly
Mild clinical presentation
Moderate to severe clinical presentation
Close observation only or observation plus NSAIDs
Start systemic prednisone 1.0 to 1.5 mg/kg per day for 1 to 2 weeks with slow taper over 8 weeks. Close weekly monitoring.
If symptoms worsen despite therapy consider biopsy for more definitive diagnosis
If biopsy confirms NSOI consider restarting prednisone therapy in conjunction with radiation therapy.
If refractory consider:
1. Repeat systemic work up
2. Start alternative therapeutic modality
3. Surgical debulking or exenteration

Reflective Practice

- This case demonstrated the importance of a thorough history, ophthalmic exam, and diagnostic workup along with developing a wide differential diagnosis. This case allowed me to learn more about a these disease entities, their presentations, treatment strategies and their complications.
- This case also allowed me to evaluate the literature for the differential diagnoses of this disease entity while keeping in my mind my patient's prognosis and expectations.

Core Competencies

- Patient Care: The case involved thorough patient care and careful attention to the patient's past medical history. Once diagnosed the patient received proper management and follow up care.

- Medical Knowledge: This presentation allowed me to review the presentation, differential diagnosis, proper evaluation, workup and treatment options for nonspecific orbital inflammation (NSOI).

- Practice-Based Learning and Improvement: This presentation included a current literature search of current studies in the clinical and radiographic presentation of NSOI.

- Interpersonal and Communication Skills: The patient was treated with respect and every effort was made to communicate with the patient in a timely manner.

- Professionalism: The patient was diagnosed in a timely manner. She was informed of his diagnosis and explained current treatment options.

- Systems Based Practice: The patient was discussed with the Oculoplastics service about prognosis and treatment options.

References

- Mottow-Lippa L, Jakobiec FA, Smith M. Idiopathic inflammatory orbital pseudotumor in childhood. II. Results of diagnostic tests and biopsies. *Ophthalmology. 1981;88(6):565-574.*
- Mombaerts I, Goldschmeding R, Schlingemann RO, Koornneef L. What is orbital pseudotumor? *Surv Ophthalmol.* 1996;41:66-78.
- Mombaerts I, Koornneef L. Current status in the treatment of orbital myositis. Ophthalmology. 1997;104:402-408.
- Rootman J. *Orbital Disease- Present Status and Future Challenges.* Boca Raton, FL: Taylor & Francis; 2005:1-13.
- Rootman J, McCarthy M, White V, Harris G, Kennerdell J. Idiopathic sclerosing inflammation of the orbit: a distinct clinicopathologic entity. *Ophthalmology.* 1994;101:570-584.
- Rootman J, Nugent R. The classification and management of acute orbital pseudotumors. *Ophthalmology.* 1982;89(9);1040-1048.
- Kanski JJ, Bowling B. Clinical Ophthalmology: A Systematic Approach. 8th ed. Philadelphia: Elsevier/Saunders; 2016:89-92.
- Oles K, Szczepanski W, Skladzien J, Okon K, Leszczynska J, Bojanowska E, Bialas M, Wrobel A, Mika J. IgG4-related inflammatory orbital pseudotumors - a retrospective case series. *Folia Neuropathol*. 2015;53(2):111-20.

Thank You!!!

- Patient
- Dr. Elmalem
- Dr. Mamta Shah