CLINICAL VIGNETTE

An Unusual Cause of Periorbital Edema: IgG4-Related Disease

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Clinical Case

A 50-year-old man complains of swelling of both upper eyelids. He reports onset of swelling 2 days prior. His left upper eyelid is slightly more swollen than his right. He did not notice significant redness or warmth nor any pain of his eyes or eyelids. His vision is unchanged and stable at baseline. He has no throat, lip or tongue swelling, hives or rash and denies any fevers or chills, chest pain and shortness of breath. He had a similar episode a few months ago but at that time the swelling was more pronounced and associated with redness. He was evaluated in the ER and diagnosed with periorbital cellulitis. He was given Cephalexin which seemed to help. There is recent travel, sick contacts, unusual new foods or new medications. His past medical history is significant for obstructive sleep apnea on nightly CPAP, hypertension, hyperlipidemia, mild intermittent asthma and Type 2 diabetes without complications. He has a strong family history of diabetes in multiple family members including his father and several brothers. Medications include atorvastatin 10 mg daily, dapagliflozin 10 mg daily, metformin 500 mg BID, fluticasone 44 mcg inhaled BID and losartan-hydrochlorothiazide 100-12.5 mg daily. He is married and lives with his wife and he works as a graphic designer. He has never smoked cigarettes or used recreational drugs. He drinks alcohol once every couple of weeks with dinner.

Exam revealed normal vitals: blood pressure 123/79, pulse at 93, temperature 37.1°C and oxygen saturation of 99% on room air. He appeared comfortable without distress. There was swelling of bilateral upper eyelids without erythema or warmth, with normal sclerae and conjunctivae. Pupils were equally reactive to light, clear oropharynx and nasal turbinates with moist mucus membranes. Lungs were clear to auscultation bilaterally, heart had regular rate and rhythm, with symmetric distal pulses, cranial nerves II-XII were intact with strength and sensation intact throughout.

Laboratory evaluation included normal chemistry panel, complete blood count and urinalysis. Hemoglobin A1c was 6.5, total cholesterol was 146 and LDL was 81. TSH was normal at 1.3.

There was no clear evidence of cellulitis based on exam. One working diagnosis was angioedema, possibly related to losartan, so losartan-hydrochlorothiazide was stopped and switched to amlodipine. Additional labs including a mildly elevated erythrocyte sedimentation rate of 35. C-reactive protein and C4 level were normal.

He was referred to Ophthalmology and comprehensive ocular exam found nothing of concern. An MRI of the orbits showed an "infiltrative T2-hypointense enhancing soft tissue involving both lacrimal glands and adjacent orbital soft tissues, non-specific, but which may represent lymphoma, granulomatous disease or fungal infection. There was extensive paranasal sinus disease involving the bilateral frontal sinuses, ethmoid air cells and right maxillary sinus with signal characteristics suggestive of fungal sinusitis. Subtle infiltration of the right pterygopalatine fossa suspicious for invasive sinusitis." The patient was referred to ENT. Comprehensive ENT exam showed no concern for possible fungal sinus disease. He underwent sinus surgery and cleaning with surgical culture showing no evidence of any infection. He was then started on budesonide rinses.

The patient's symptoms recurred, after surgery, with bilateral periorbital edema in addition to bilateral parotid swelling, dry mouth and DIP nodules on both hands. Additional laboratory testing included a positive rheumatoid factor at 119, but negative ANA and ANCA. The patient was then referred to Rheumatology. Rheumatology checked an IgG4 level which was elevated at 1120. Patient was then referred for lacrimal gland biopsy with pathology showing "severe chronic dacryoadenitis with predominant pattern of reactive lymphoid hyperplasia." Flow cytometry was negative. Patient was diagnosed with IgG4-related disease and started on prednisone 40 mg daily and Bactrim DS MWF for prophylaxis. His symptoms improved immediately on prednisone. Given the adverse effects of prolonged prednisone use including worsening hyperglycemia, patient was transitioned to methotrexate and prednisone was eventually tapered off. His IgG4-related disease has been well-controlled to date on methotrexate 20 mg weekly.

Discussion

Immunoglobulin G4-related disease (IgG4-RD) is an immune-mediated fibroinflammatory condition that can affect multiple organs. Common forms of IgG4-RD include Type 1 (IgG4-related) autoimmune pancreatitis, IgG4-related sclerosing cholangitis, IgG4-related Mikulicz disease which presents with combination of lacrimal, parotid and submandibular gland enlargement, orbital disease and retroperitoneal fibrosis with chronic periaortitis. IgG4-related disease is characterized by dense lymphoplasmacytic infiltrations with a predominance of IgG4-positive plasma cells on histopathology. It is often accom-

panied by some degree of fibrosis and an increased number of eosinophils. The serum IgG4 level is elevated in about two-thirds of patients, which means about one-third of patients with this condition have normal serum IgG4 levels.[1,2]

The pathogenesis of IgG4-related disease is likely autoimmune with both B and T cells, especially CD4+ cells, playing important roles. The IgG4 antibodies are unlikely to be pathogenic themselves, acting more as an epiphenomenon thereby having an anti-inflammatory role. The IgG4 antibodies seem to be produced in response to cytokine production and can be elevated in a number of disorders such as sarcoidosis, eosinophilic granulomatosis with polyangiitis, Castleman disease or allergic disorders. CD4+ cytotoxic T cells appear to play an important role in the pathophysiology of IgG4-related disease. Clonally expanded populations of CD4+ T cells are found in the peripheral blood and fibrotic lesions of IgG4-releated disease. These cytotoxic T cells make products such as perforin, granzyme B, IL-1, transforming growth factor (TGF)-beta and interferon gamma which are important mediators of fibrosis, a hallmark feature of IgG4-related disease. Tfh cells, another T-cell subset, also appear to play a role as high numbers of these cells are also found in affected tissues in IgG4-RD. The working hypothesis is that CD4+ cytotoxic T cells set up the disease and are sustained by continuous antigen presentation by B lymphocytes. The Tfh response is separate from this and may be responsible for the development of germinal centers within lymph nodes and involved organs, resulting in the creation of IgG4-secreting plasmablasts and plasma cells.[3]

IgG4-related disease appears to have a predominance in middle-aged and older males. However, IgG4-related disease that affects the head and neck appears to have a slight predilection for females.[4] A case-control study examining 234 patients with IgG4-RD and 1170 controls found that smoking was associated with an increased risk of developing IgG4-RD, especially in patients with retroperitoneal fibrosis.[5] Patients often present with subacute development of a mass in the affected organ or diffuse enlargement of an organ. The majority of patients with IgG4-RD (approximately 60 to 90 percent) present with multiple organ involvement. Lymphadenopathy is also common and symptoms of asthma or allergy are present in about 40 percent of patients.[1] Patients often feel well at the time of diagnosis with the exception of weight loss as a predominant presenting symptom for patients with multi-organ disease.[6] IgG4-related ophthalmic disease accounts for 17 to 23 percent of patients with IgG4-RD. The most typical presentation of this subtype is bilateral lacrimal gland involvement, as in our patient. Concurrent salivary gland involvement is also common, which also developed later on in our patient as his disease progressed.[1,2]

Glucocorticoids are the first-line agent for remission induction in all patients with active IgG4-related disease. Rituximab is sometimes used in combination with glucocorticoid to induce remission in patients with multiorgan disease and extremely high serum IgG4 level. Rituximab is also used as the agent of choice if glucocorticoid is contraindicated as an initial agent. There is no consensus on whether patients with IgG4-related disease should receive maintenance therapy. The international consensus guidance statement for IgG4-RD states that a glucocorticoid-sparing agent can be used as maintenance therapy however there is no consensus on how long such agents should be administered. Once in remission, patients should continue to be monitored closely with clinical and laboratory evaluations as well as periodic imaging.[7]

REFERENCES

1. **Stone JH, Zen Y, Deshpande V**. IgG4-related disease. *N Engl J Med*. 2012 Feb 9;366(6):539-51. doi: 10.1056/NEJMra1104650. PMID: 22316447.
2. **Kamisawa T, Zen Y, Pillai S, Stone JH**. IgG4-related disease. *Lancet*. 2015 Apr 11;385(9976):1460-71. doi: 10.1016/S0140-6736(14)60720-0. Epub 2014 Dec 4. PMID: 25481618.
3. **Mattoo H, Mahajan VS, Maehara T, Deshpande V, Della-Torre E, Wallace ZS, Kulikova M, Drijvers JM, Daccache J, Carruthers MN, Castelino FV, Stone JR, Stone JH, Pillai S**. Clonal expansion of CD4(+) cytotoxic T lymphocytes in patients with IgG4-related disease. *J Allergy Clin Immunol*. 2016 Sep;138(3):825-838. doi: 10.1016/j.jaci.2015.12.1330. Epub 2016 Mar 11. PMID: 26971690; PMCID: PMC5014627.
4. **Wang L, Zhang P, Zhang X, Lin W, Tang H, Li J, Wang M, Liu X, Fei Y, Chen H, Peng L, Zhang L, Lai Y, Zeng X, Li X, Xue H, Zhao Y, Zhang F, Zhang W**. Sex disparities in clinical characteristics and prognosis of immunoglobulin G4-related disease: a prospective study of 403 patients. *Rheumatology (Oxford)*. 2019 May 1;58(5):820-830. doi: 10.1093/rheumatology/key397. PMID: 30561747.
5. **Wallwork R, Perugino CA, Fu X, Harkness T, Zhang Y, Choi HK, Stone JH, Wallace ZS**. The association of smoking with immunoglobulin G4-related disease: a case-control study. *Rheumatology (Oxford)*. 2021 Nov 3;60(11):5310-5317. doi: 10.1093/rheumatology/keab172. PMID: 33751033; PMCID: PMC8783539.
6. **Cheuk W, Chan JK**. IgG4-related sclerosing disease: a critical appraisal of an evolving clinicopathologic entity. *Adv Anat Pathol*. 2010 Sep;17(5):303-32. doi: 10.1097/PAP.0b013e3181ee63ce. PMID: 20733352.
7. **Khosroshahi A, Wallace ZS, Crowe JL, Akamizu T, Azumi A, Carruthers MN, Chari ST, Della-Torre E, Frulloni L, Goto H, Hart PA, Kamisawa T, Kawa S, Kawano M, Kim MH, Kodama Y, Kubota K, Lerch MM, Löhr M, Masaki Y, Matsui S, Mimori T, Nakamura S, Nakazawa T, Ohara H, Okazaki K, Ryu JH, Saeki T, Schleinitz N, Shimatsu A, Shimosegawa T, Takahashi H, Takahira M, Tanaka A, Topazian M, Umehara H, Webster GJ, Witzig TE, Yamamoto M, Zhang W, Chiba T, Stone JH; Second International Symposium on IgG4-Related Disease**. International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease. *Arthritis Rheumatol*.

2015 Jul;67(7):1688-99. doi: 10.1002/art.39132. PMID: 25809420.