Churg-Strauss Syndrome with Orbital Inflammation

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Chief Complaint: Double vision, bulging eyes and drooping of the left upper eyelid.

History of Present Illness: A 56 year old male patient presented to the oculoplastics clinic reporting a two month history of progressive proptosis and drooping of the left upper eyelid. He had also been experiencing binocular diplopia for several weeks. He had constant generalized redness around the eye for several years that was ascribed to chronic seasonal allergies. Furthermore, over the last several months, he had noticed that his eyes began to bulge (on the left side more than the right), and he began experiencing pain around the left eye. He did not describe any other changes in his vision aside from the diplopia and proptosis.

Past Medical History:

- Asthma, poorly controlled, diagnosed at the age of 11. Maintained on albuterol and fluticasone/salmeterol inhalers. Hospitalized 25 times for management of acute exacerbations.
- Chronic seasonal allergies.
- Episode of sinusitis with eosinophilia several years prior to presentation, thought to be consistent with allergic sinusitis.
- Chronic fibrosing inflammation of submandibular salivary gland at age 54.
- Chronic inner ear effusions with tympanostomy tube placement at age 54.

Past Ocular History: Strabismus, status post surgical correction at the age of 3.

Medications: Dexamethasone 1mg BID, albuterol, fluticasone, fluticasone/salmeterol, doxepin

Allergies: NKDA.

Family History:

- Father with lung cancer, passed away at age 53.
- Numerous first cousins with Crohn's disease.
- Several distant relatives with chronic respiratory disease.

Social History: Patient denies tobacco or alcohol use. The patient is an attorney and is married, without children. There is no recent or remote history of travel outside of the United States.

Exam:

Visual Acuity: 20/25 OD; 20/25 OS
Pupils: Normal size and reaction OU. No relative afferent pupillary defect OU.
Motility: Normal OD, Mild abduction deficit OS.
Visual fields: Full to confrontation OU.

External exam: Erythematous and flaky periorbital skin OU. Mild periorbital edema OU. (Figure 1). Left sided proptosis (Figure 2).
Slit Lamp Exam:

- Ptosis, left side greater than right.
- Mild conjunctival hyperemia OU.
- Clear corneas OU.
- Anterior chambers deep and quiet OU.
- Normal lenses OU

Dilated Fundus Exam:
Disc, macula, vasculature and periphery were normal OU.

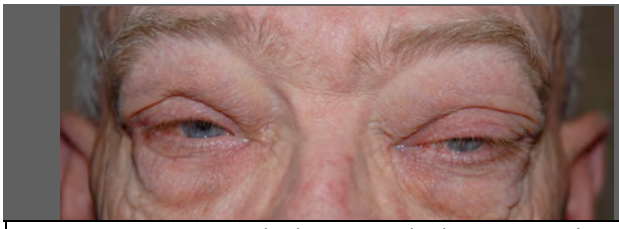

Figure 1: External photograph demonstrating periorbital erythema, mild periorbital edema, and left sided ptosis.

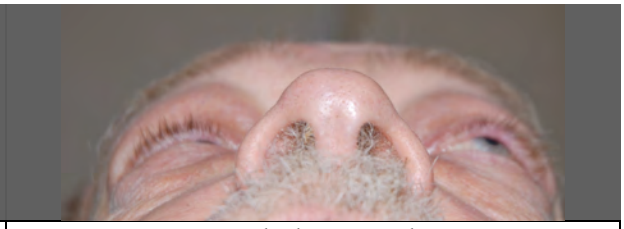

Figure 2: External photograph demonstrating axial proptosis of the left eye.

As part of the patient's workup for what appeared to be bilateral orbital inflammation, an orbital CT was performed and a complete blood count was obtained.

Labs:
CBC:

WBC 10.7 x10E^3/mm^3

Neut 36%
Lymph 17%
Mono 7%
Eos 40%
Baso 0%

RBC 4.73 x10E^6/mm^3
Hgb 15.5 gm/dL
HCT 46%
Plt 394 x10E^3/mm^3

- The WBC was normal and there was no neutrophil predominance to suggest an infection.
- The WBC differential demonstrated peripheral eosinophilia.

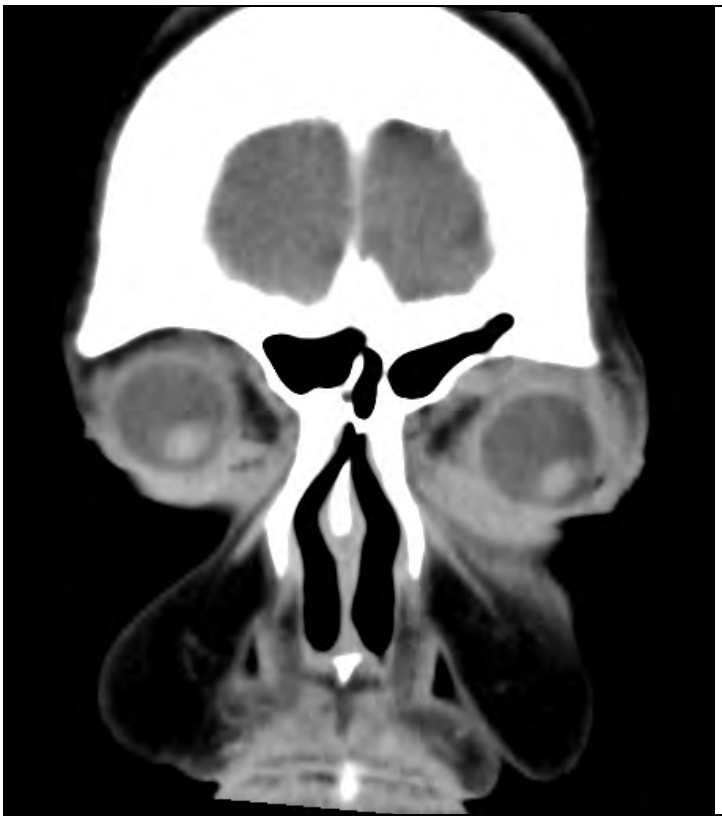

Figure 3: Maxillofacial CT without contrast demonstrating a diffuse mass in the superior aspect of the left orbit.

As part of his workup for eosinophilia, the patient underwent a bone marrow biopsy that demonstrated an abnormally high number of eosinophils. The bone marrow was otherwise normal with no evidence of other blood dyscrasias.

Given that the etiology of the inflammation and eosinophilia was unclear, a left anterior orbitotomy was performed and a biopsy of orbital mass was obtained.

Histopathologic analysis of the biopsied tissue revealed an inflammatory infiltrate in the orbital fat composed of numerous eosinophils, epithelioid histiocytes, lymphocytes, and occasional multinucleated giant cells. Focal areas of necrosis were present in some of the granulomatous areas. In some areas, inflammatory cells surrounded small and medium-sized blood vessels. Periodic acid Schiff (PAS), Ziehl-Neelsen, Gomori methenamine silver (GMS), Warthin-Starry, Giemsa, Gram and Fite-Faraco stain were all negative for organisms.

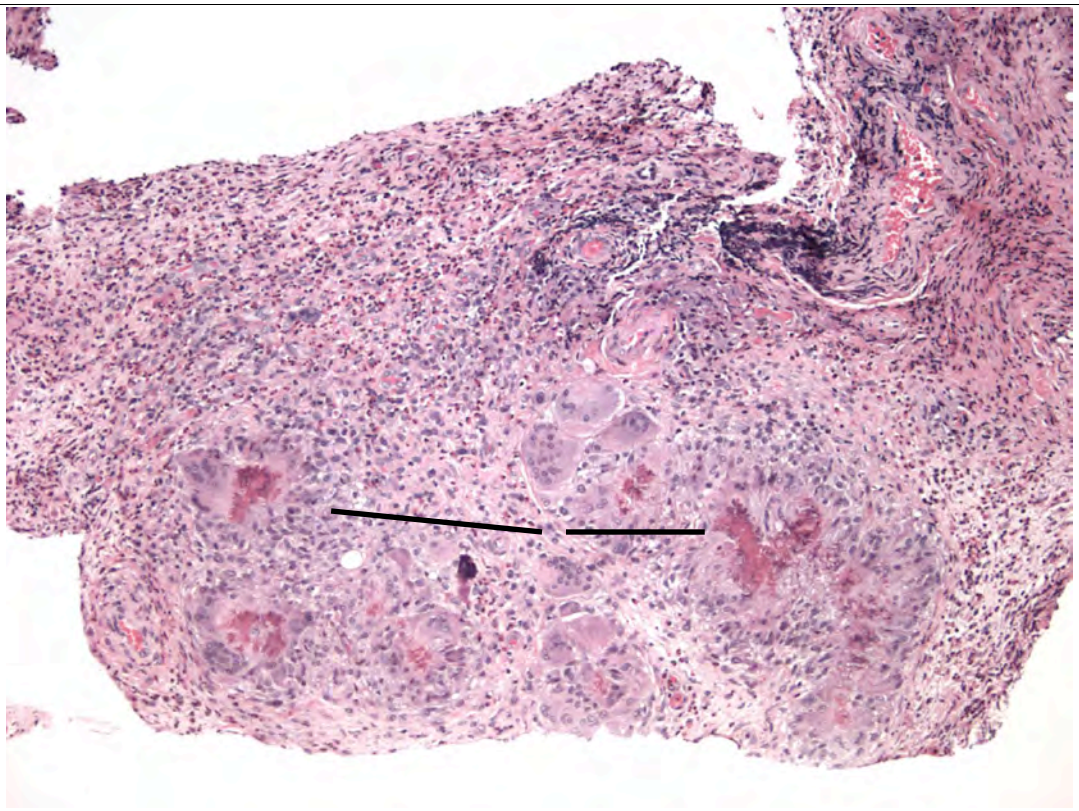

Figure 4: Hematoxylin and eosin stain at 50X magnification of orbital tissue reveals multinucleated giant cells arranged into granulomas (arrows) with necrotic centers (caseating granuloma).

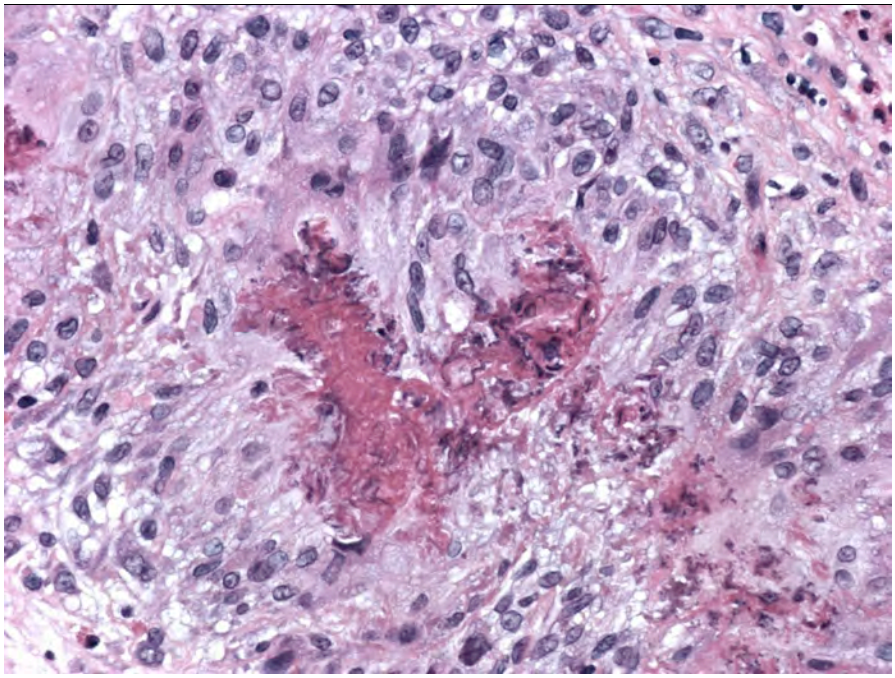

Figure 5: A granuloma (100X) with a highly eosinophilic (bright pink) necrotic center (caseation).

Course:
The patient's constellation of clinical and laboratory findings satisfied the American College of Rheumatology criteria for **Churg-Strauss Syndrome (CSS) (Table 1)** Specifically, his asthma, peripheral eosinophilia, paranasal sinusitis and histologic proof of eosinophilic perivasculitis made CSS the leading diagnosis for this patient.

The patient was referred to rheumatology and was treated with high-dose corticosteroids. He reported complete resolution of his symptoms after a few weeks of treatment. At one year, he remained symptom-free, but required a daily dose of steroid to keep his symptoms under control. The managing rheumatologist is considering transitioning the patient to a steroid-sparing agent for long-term disease control.

Diagnosis: Churg-Strauss Syndrome with orbital inflammation

Differential Diagnosis:
Wegener's granulomatosis
Microscopic polyangiitis
Hypereosinophilic syndrome
Orbital cysticercosis or other chronic parasitic infection

Discussion:
Churg-Strauss syndrome (CSS) was first described by Churg and Strauss in 1951 as a small and medium-vessel vasculitis characterized by asthma, hypereosinophilia and multi-system vasculitis (Sehgal, 1995). CSS is a rare disorder with an incidence of 1.3 to 6.8 cases per 1 million patients per year (Scott, 2000). The mean age of presentation is approximately 50 years, and there appears to be a slight male predominance.

There are three distinct clinical phases of CSS. The disease begins with asthma and atopic allergies that may begin in childhood. The first phase may be present for months to years before progression to the second, eosinophilic phase, which is characterized by eosinophilic infiltration with granulomatous inflammation and can have an array of clinical presentations, including granulomatous pneumonia, gastroenteritis, or, as in this case, orbital pseudotumor. The final third phase of the disease is the vasculitic phase, which typically involves small- and medium-sized vessels of the eyes, skin, gastrointestinal tract and heart. Coronary arteritis and myocarditis are the primary causes of morbidity and mortality (Noth, 2003). These phases do not always occur in a step-wise fashion, making the diagnosis a challenging one to make definitively. Patients are often treated for multiple distinct conditions before the unifying diagnosis of CSS is made.

The classic histologic findings in CSS are necrotizing arteritis, eosinophilic infiltration and extravascular granulomas. Our patient demonstrated a peri-arteritis along with eosinophilic infiltration and extravascular granulomas in both the orbit and in his bone marrow.

The ophthalmic manifestations of CSS are varied and can result from granulomatous inflammation, vasculitis or both. Numerous neuro-ophthalmic manifestations of CSS have been reported, including cranial neuropathies, amaurotic episodes, arteritic ischemic optic neuropathy, and orbital pseudotumor. Vascular involvement can also present as a central or branch retinal

artery occlusion secondary to vasculitis. Anterior segment involvement can present as conjunctivitis, scleritis, or keratouveitis (Golnik, 2004). Chronic conjunctivitis and conjunctival granulomas have also been reported (Figure 6).

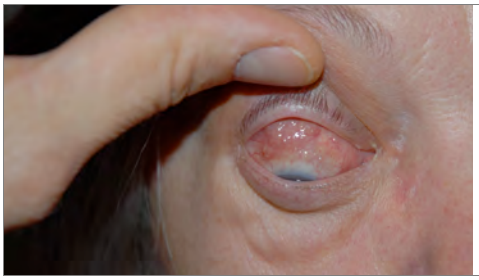

Figure 6: Note the conjunctival granulomas on the bulbar conjunctiva of this patient with known CSS.

Establishing a diagnosis can be difficult given the phasic nature and the often prolonged and sequential development of clinical and pathological features. CSS is distinguished from other granulomatous, vasculitic and eosinophilic syndromes by a clinical history that includes asthma, eosinophilia and rhinosinusitis, as well as other characteristic signs and symptoms (Table 2). Establishing a diagnosis depends on the presence of a constellation of findings, rather than any single feature. When the diagnosis was first described by Churg and Strauss in 1951, all patients examined had the following three findings: blood and tissue eosinophilia, necrotizing vasculitis and necrotizing granulomas centered on necrotic eosinophils (Churg, 1951). However, finding all three features in any single patient is rare and cannot be relied upon for diagnosis. The American College of Rheumatology set forth the most widely utilized criteria for diagnosing and classifying CSS; the presence of 4 or more criteria yields a sensitivity of 85% and a specificity of 99.7% (Table 1) (Masi, 1990).

CSS is typically treated with systemic steroids alone. However, in 20% of patients, cytotoxic drugs are required to stop progression of the disease. Major life-threatening organ involvement may require emergent treatment with pulse doses of intravenous corticosteroids combined with other cytotoxic medications (Grau, 2008).

Table 1: American College of Rheumatology Criteria for Diagnosis of Churg-Strauss (Masi, 1990)
1. Asthma
2. Eosinophilia > 10% in peripheral blood
3. Paranasal sinusitis
4. Pulmonary infiltrates
5. Histologic proof of vasculitis with extravascular eosinophils
6. Mononeuritis multiplex or polyneuropathy

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Table 2: Features distinguishing CSS from other clinical entities (Sinico and Bottero, 2009)				
	CSS	**WG**	**MPA**	**HES**
Asthma	Yes	No	No	No
Eosinophilia	Yes	No	No	Yes
Rhinosinusitis	Yes	No	No	No
Lung involvement	Yes	Yes	Yes	Yes
Skin involvement	Yes	Yes	Yes	Yes
Heart involvement	Yes	Rare	Rare	Yes
ANCA positivity	Yes (40%, myeloperoxidase)	Yes (90%, proteinase 3)	Yes (80%, myeloperoxidase)	No
Vasculitis	Yes	Yes	Yes	No
Eosinophilic-rich infiltrate	Yes	No	No	Yes
Granuloma	Yes	Yes	No	No

Abbreviations: Churg-Strauss Syndrome (CSS), Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), hypereosinophilic syndrome (HES).

Epidemiology	**Signs**
• Mean age 50 years old • Possible slight male predominance • 1.3- 6.8 cases per 1 million per year	• Peripheral eosinophilia • Granulomatous or necrotizing vasculitis of small vessels with marked infiltration of eosinophils
Symptoms	**Treatment**
• Asthma and/or allergic rhinitis • Mononeuritis multiplex • Pseudotumor • GI bleeding • Purpura	• Glucocorticoids (effective in 80% as sole therapy) • Cyclophosphamide • Infliximab

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