

## ANCA-associated granulomatous vasculitis\* (Wegener's granulomatosis)

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**Chief Complaint:** Diplopia and “darkening of vision” in the right eye

### History of Present Illness:

*(Note what occurs to which eye, right(OD) or left(OS), in the HPI)*

A 54 year-old gentleman noticed binocular vertical diplopia 4 months prior to presentation. The patient felt his symptoms were progressively worsening.

Furthermore, over the last week, while driving on the interstate, he noticed the vision in the **RIGHT** eye was starting to “darken.”

During this four-month period, the patient was followed by an otolaryngologist for his sinus disease and nosebleeds. These symptoms had been present for the past 10 months. He was treated with cautery for the epistaxis, and ultimately, a polypectomy/anastomosis was performed. On post-operative day #1, he notified the otolaryngologist that his diplopia was still present, although his nosebleeds and sinus disease had improved. One week post-operatively, the patient awoke with a “bulging” **LEFT** eye. This was accompanied by a **LEFT** facial droop. He was believed to have a Bell's palsy and was started on doxycycline and prednisone 40mg daily by a local emergency room physician. The patient followed up with his otolaryngologist the next day, and the prednisone was increased to 80mg daily.

With no improvement after one week of the above treatment, he underwent decompression of the **LEFT** facial nerve. During these events, his diplopia was persistent and he was referred to a neuro-ophthalmologist. The “darkening of vision” in the **RIGHT** eye remained throughout this entire time period.

The following is a summary of the laterality in this patient's symptoms prior to presenting to us.

- Initial symptom: binocular diplopia
- Then “darkening vision” in the **RIGHT** eye
- Then post operatively, **LEFT** eye proptosis accompanied by **LEFT**-sided facial droop

**Past Ocular History:** Presbyopia

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\* **ANCA-associated granulomatous vasculitis** has been proposed as a more appropriate and descriptive term for this condition rather than eponym of Wegener's granulomatosis.

**Past Medical History:**

- Deviated septum
- Nasal polyps
- Hernia repair
- Tonsillectomy
- Polypectomy
- R and L maxillary antrostomy

**Medications:**

- Ciprofloxacin and Dexamethasone Otic (Ciprodex®) drops to ears
- Refresh PM

**Allergies:** No known drug allergies

**Family History:** Non contributory

**Social History:** No alcohol use. Tobacco use: 1 pack per day for 30 years

**Ocular Exam****Visual Acuity:**

- 20/100 pinhole 20/60 OD
- 20/40 pinhole 20/25 OS

**Pupils:** 4mm → 2mm, brisk, equal OU, 1.2 log unit RAPD OD

**Intraocular pressure by applanation:** 15mmHg OD, 20mmHg OS

**Motility:** Full, orthotropic OU

**Confrontation visual fields:** Inferotemporal deficit OD, full OS

**External:** (Figure 1)

Normal OD. Facial droop, ptosis, proptosis, 3mm inferior scleral show OS

Hertel exophthalmometry measurement at base of 95mm:  
20mm OD, 24mm OS

**Slit lamp examination**

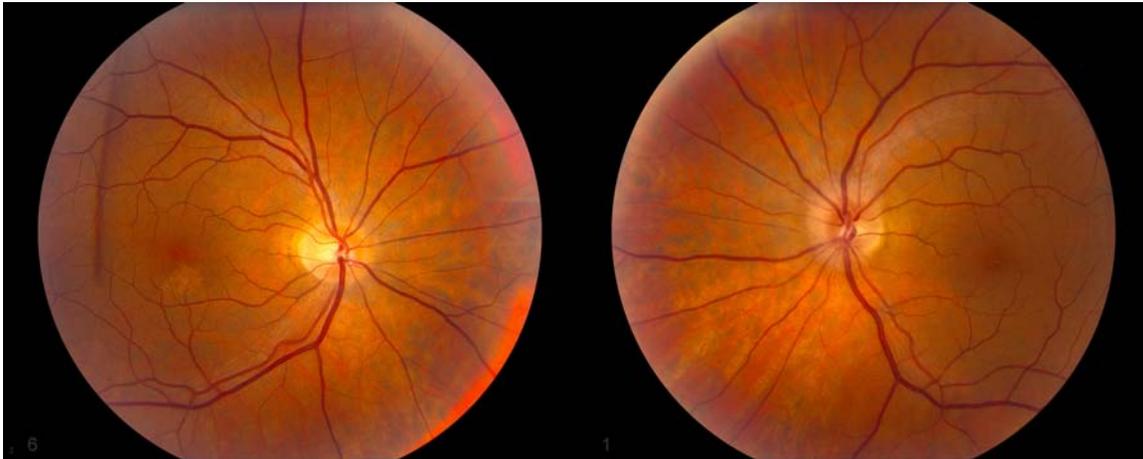
- **Lids/Lashes:** Normal OU
- **Conjunctiva/Sclera:** Normal OD, dilated episcleral veins inferiorly OS
- **Cornea:** Clear OU
- **Anterior Chamber:** Deep and quiet OU
- **Iris:** Normal architecture OU
- **Lens:** Trace nuclear sclerosis, cortical cataracts OU
- **Vitreous:** Normal OU



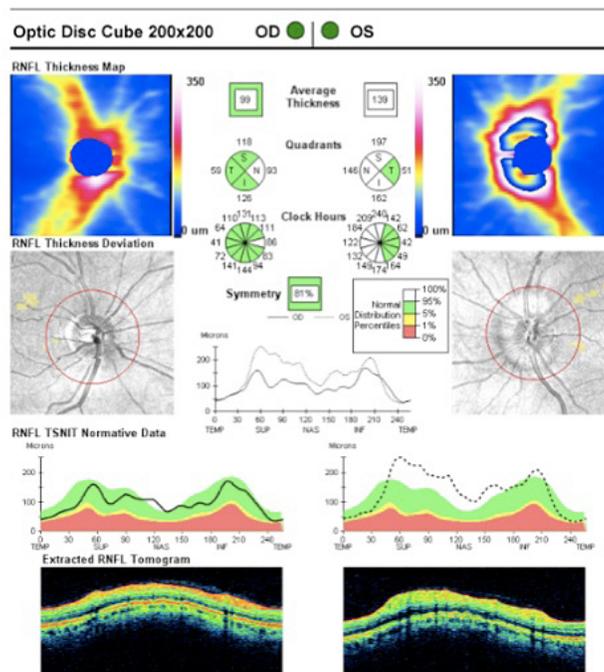
**Figure 1.** External photograph

**Dilated fundus examination:** (Figure 2)

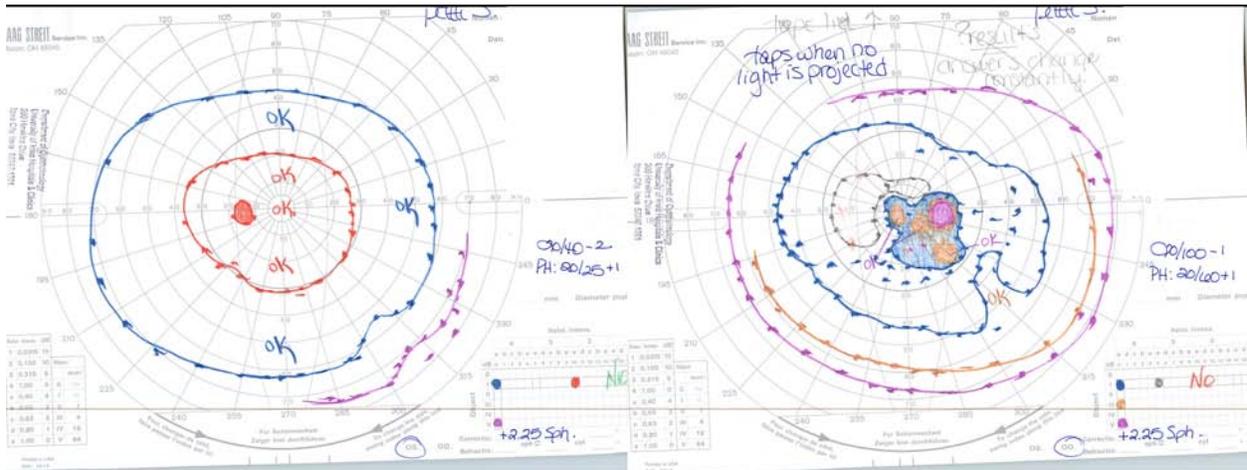
- **Disc:** Mild temporal pallor OD, optic disc edema OS
- **Cup to disc ratio:** 0.35 OD, 0.25 OS
- **Macula:** Flat OU
- **Vessels:** Normal OD, arteriovenous nicking OS
- **Periphery:** Normal OD, dot hemorrhages and chorioretinal scar inferotemporally OS



**Figure 2:** Fundus photographs demonstrating the optic disc edema of the left optic nerve; mild temporal pallor OD



**Figure 3.** Optical coherence tomography demonstrating increased nerve fiber layer thickness in the left optic nerve



**Figure 4.** Initial Goldmann visual field illustrating a dense relative cecocentral scotoma OD



**Figure 5.** MRI brain with gadolinium. Coronal T2 fat suppressed image showing the hyperintense lesion between the medial rectus and the lamina papyracea in the left orbit

### Hospital Course:

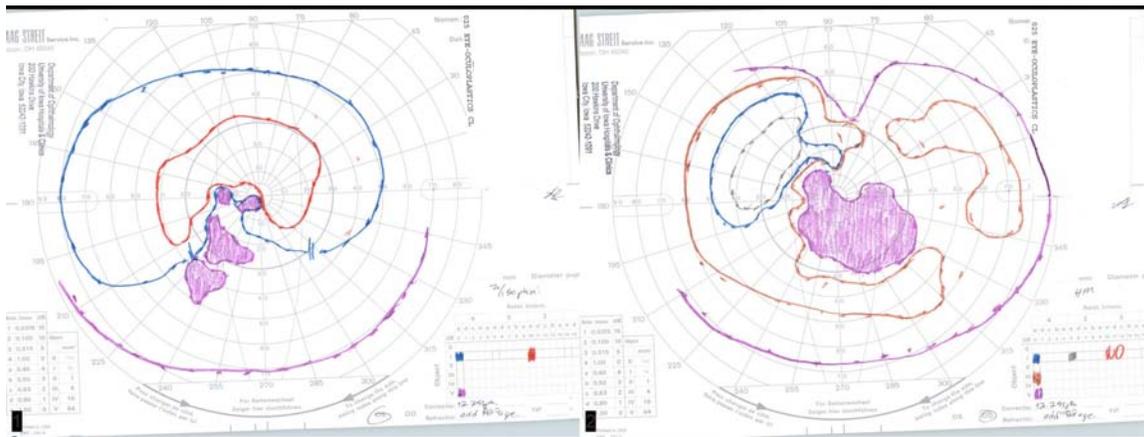
The patient underwent extensive examination and testing by multiple services including neuro-ophthalmology, oculoplastics, and otolaryngology. He initially underwent an endoscopic biopsy, which demonstrated acute and chronic inflammation with fibrosis.

In the meantime, the patient's visual acuity worsened to hand motion OD and 20/150 OS with worsening visual fields (Figure 6).

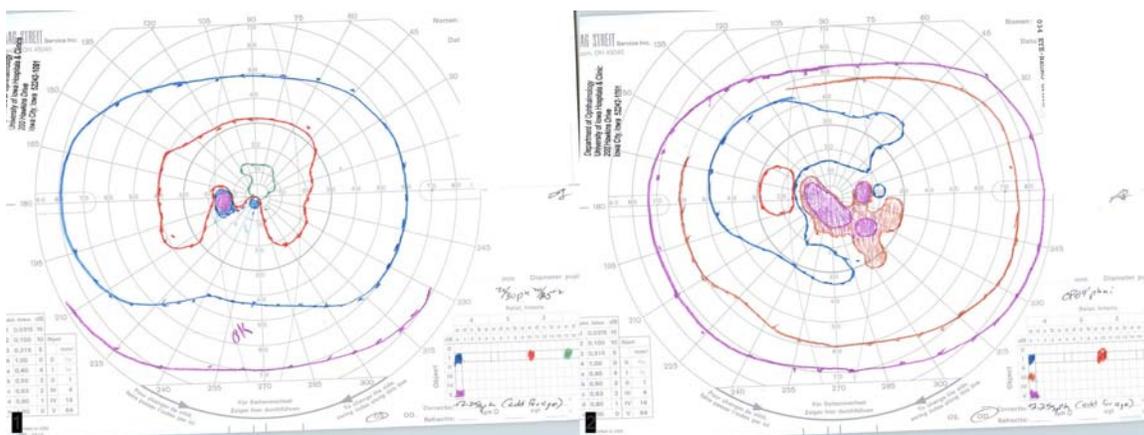
Given the pathology report above, the leading working diagnosis was idiopathic orbital inflammatory syndrome (IOIS); therefore, high dose steroids were started. The patient received methylprednisolone 1000mg intravenously for 3 days then started a slow oral prednisone taper starting at 80mg.

With steroid therapy, the patient's visual acuity and visual field testing initially improved over the short term.

**A.**



**B.**



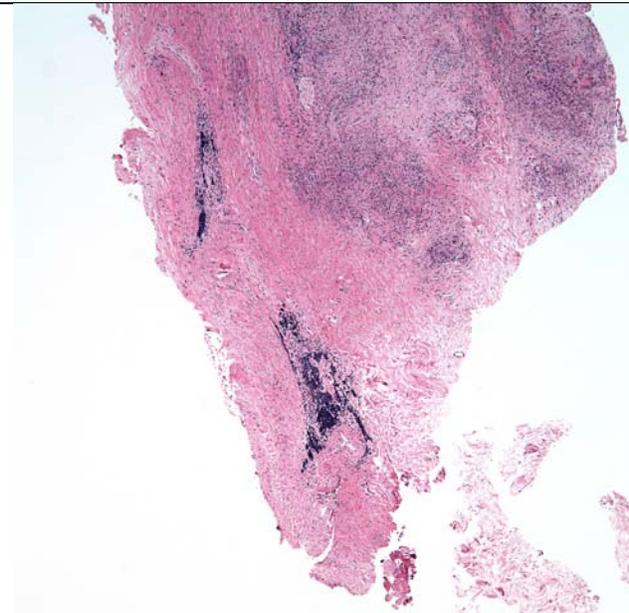
**Figure 6.** Goldmann visual field pre-(A) and post-(B) high dose steroids

However, over the following month, the patient failed to improve. If the correct diagnosis had been IOIS, he would have expected a rapid resolution of his symptoms.

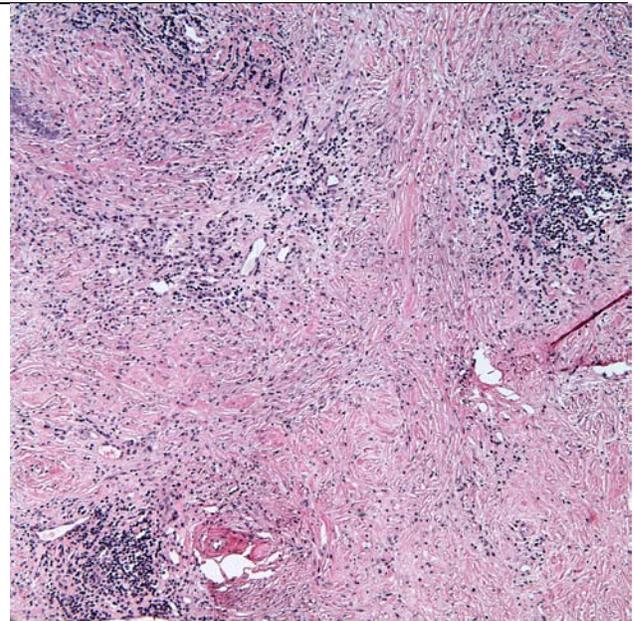
At this point, the various involved medical teams re-evaluated the situation, which should always be done when the patient does not respond as expected to the management. The situation was discussed between the oculoplastic surgeons, neuro-ophthalmologists, and otolaryngologists, and the decision was made to re-biopsy the lesion.

An anterior orbitotomy was performed through a transcaruncular approach by the oculoplastics team.

The biopsy showed sclerotic tissue with a scattered chronic granulomatous inflammation with patchy infiltrates and necrosis. The differential diagnosis included Wegener's granulomatosis and idiopathic orbital inflammatory syndrome.



**Figure 7.** Hematoxylin and eosin stain. 20X magnification of the biopsy specimen demonstrating a patchy infiltrative pattern. The sclerotic tissue showed scattered chronic granulomatous inflammatory infiltrate and focal areas of necrosis



**Figure 8.** Hematoxylin and eosin stain at 50X magnification. Patchy infiltrates show polymorphologic groups of cells including plasma cells, lymphocytes, and monocytes with focal areas of necrosis

Lymphoma was ruled out with immunohistochemistry stains with CD20 and CD79a.

Of note, the more typical pathology seen in Wegener's granulomatosis shows occlusions of the vessels representing a vasculitis as well as interstitial granulomas. There are also polymorphic inflammatory infiltrates. The absence of these entities does not necessarily rule out the diagnosis of Wegener's granulomatosis.

Disease limited to the orbit alone or orbit and sinuses, such as in our patient, has been reported to show a more polymorphous pattern of infiltrative cells, which includes plasma cells, histiocytes, epithelioid cells and eosinophils compared to patients with systemic Wegener's granulomatosis (Ahmed 2008, Fecher 2002).

Laboratory work up was performed including an anti-neutrophil cytoplasmic antibody (cANCA) titer, which is 93% sensitive and 97% specific for systemic Wegener's granulomatosis (Nolle 1989). In limited orbital or orbital/sinus disease, the sensitivity is variable, between 32-67% (Nolle 1989, Woo 2001).

Our patient's cANCA titer was > 1:80 (normal < 1:20)

He was referred to the rheumatology service and started on cyclophosphamide with the intention to transition to methotrexate, once in remission.

### **Discussion:**

ANCA-associated granulomatous vasculitis\* (Wegener's granulomatosis) is a granulomatous necrotizing vasculitis (Godman 1954). Godman and Churg described in a review the pathological features of this disease in the small arteries of the lungs and kidneys. In 1983, McClusky and Fienberg described independent areas of extravascular necrotizing granulomatous lesions that are now recognized as a classic pathologic finding (see above), especially in pulmonary tissue (McClusky 1983). The condition's eponym is named after Dr. Friedrich Wegener, who first described the disease in detail in 1936, although Peter McBride (1854-1946) in 1897 and Heinz Karl Ernst Klinger (born 1907) in 1931 reported similar disorders earlier.

Up to 50% of systemic ANCA-associated granulomatous vasculitis can have ocular/orbital involvement. Sixteen percent of patients will present with ocular inflammation. However, orbital or orbital/sinus involvement alone is rare. According to the largest study thus far, only 13 patients over 23 years (Ahmed 2008) have had disease limited to this area.

Of note, patients initially present with signs and symptoms, which can be extremely variable and nonspecific. Consequently, the diagnosis can be severely delayed.

### **Classification: 2 criteria**

- A. **American College of Rheumatology (ACR) 1990** – classification criteria for ANCA-associated granulomatous vasculitis. Two or more of these criteria have a sensitivity of 88% and a specificity of 92% (Leavitt 1990)
  - a. Nasal or oral inflammation
    - i. Painful or painless oral ulcers
    - ii. Purulent or bloody nasal discharge
  - b. Lungs (X-ray)
    - i. Nodules
    - ii. Infiltrates
    - iii. Cavities

- c. Kidneys
    - i. Hematuria
    - ii. Red cell casts
  - d. Biopsy showing granulomatous inflammation
    - i. Within arterial walls
    - ii. In perivascular areas
- B. Chapel Hill Consensus Conference (CHCC) 1992** – Establishing the diagnosis of Wegener’s granulomatosis requires:
- a. A granulomatous inflammation involving the respiratory tract and
  - b. A vasculitis of small to medium-sized vessels

**DIAGNOSIS:** ANCA-associated granulomatous vasculitis (Wegener’s granulomatosis)

In our patient, the diagnosis of ANCA-associated granulomatous vasculitis was somewhat delayed because of visits to multiple physicians in different areas of medicine. However, this is a not uncommon way of presentation. Because the initial presenting symptom may be highly nonspecific, a high index of suspicion is required. It also usually requires the professional collaboration of multiple medical teams including otolaryngologists, rheumatologists, pathologists, neuro-ophthalmologists, oculoplastic surgeons, as well as the patient’s primary care physician.

The epistaxis our patient experienced initially was treated; however, the source of the presenting sign was not definitively determined. Furthermore, recall that his presenting symptom of decreased vision was in the RIGHT eye. Therefore, when he developed new symptoms in the LEFT eye, the working diagnosis needed to be readdressed and questioned.

In addition, when our patient did not respond as expected to steroid therapy alone, we questioned our leading working diagnosis at that time, which was IOIS. It is critical to reassess the situation if treatment does not deliver the expectant result.

Consequently, as mentioned above, many different medical departments worked together to re-evaluate the case. We collaborated with the otolaryngologists to perform the biopsy, first, in the least invasive manner with an endoscope. Because the pathology was inconclusive, a more invasive biopsy, then, was performed via an anterior orbitotomy. The ocular pathologist played a key role in diagnosing the disease as did the oculoplastics service, who performed the biopsy and ordered the laboratory testing. After the repeat biopsy and the blood work confirmed the diagnosis of ANCA-associated granulomatous vasculitis, our rheumatologists played an integral role in initiating the appropriate therapy promptly. This case is a great example of how multidisciplinary collaboration can lead to accurate diagnosis and prompt treatment.

<p><b>EPIDEMIOLOGY:</b></p> <ul style="list-style-type: none"> <li>• Incidence – 10 cases per million per year (Bosch 2007)</li> <li>• 90% patients are Caucasian</li> <li>• Middle-aged population, but can be seen in younger or older patients</li> </ul>	<p><b>SIGNS:</b></p> <p><i>Ocular:</i></p> <ul style="list-style-type: none"> <li>• Proptosis</li> <li>• Eyelid edema</li> <li>• Ophthalmoplegia</li> <li>• Scleritis</li> <li>• Conjunctivitis</li> <li>• Uveitis</li> <li>• Episcleritis</li> </ul> <p><i>Systemic:</i></p> <ul style="list-style-type: none"> <li>• Rhinitis</li> <li>• Renal failure</li> <li>• Epistaxis</li> <li>• Perforated septum (causing “saddle-nose” deformity)</li> <li>• Gingivitis</li> <li>• Subglottal stenosis</li> <li>• Pulmonary nodules/cavitary lesions/hemorrhage</li> </ul>
<p><b>SYMPTOMS:</b></p> <p><i>Ocular:</i></p> <ul style="list-style-type: none"> <li>• Diplopia</li> <li>• Eye pain</li> <li>• Decreased vision</li> <li>• Decreased visual field</li> </ul> <p><i>Systemic:</i></p> <ul style="list-style-type: none"> <li>• Hearing loss</li> <li>• Hemoptysis</li> <li>• Joint pain</li> <li>• Neuropathy</li> </ul>	<p><b>CURRENT TREATMENT OPTIONS:</b></p> <p>Cyclophosphamide (first line of treatment for most in conjunction with corticosteroids.)</p> <ul style="list-style-type: none"> <li>• 1mg/kg/day corticosteroid</li> <li>• 2mg/kg/day for oral cyclophosphamide. IV pulse doses of cyclophosphamide can be given in more severe disease with corticosteroids. (Monitor the WBC)</li> </ul> <p>Once in remission switch to methotrexate or azathioprine.</p> <p>Corticosteroids can be tapered to a low maintenance dose, once remission is achieved.</p> <p>Plasmapheresis (in very severe disease, including pulmonary involvement or other end-organ damage)</p> <p>Alternative options in severe disease unresponsive to the above treatments:</p> <ul style="list-style-type: none"> <li>• Mycophenolate mofetil</li> <li>• 12-Deoxyspergualin</li> <li>• Anti-thymocyte globulin</li> <li>• Rituximab</li> <li>• Infliximab</li> </ul>

**DIFFERENTIAL DIAGNOSES:**

- ANCA-associated granulomatous vasculitis\* (Wegener's granulomatosis)
- Lymphoma
- Idiopathic orbital inflammatory syndrome
- Churg strauss syndrome
- Microscopic polyangiitis
- Relapsing polychondritis

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