Pain, Proptosis and...Pitch Black!
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History and Exam
A 51-year old Caucasian woman presented to emergency ophthalmology clinic with bilateral sequential vision loss. She developed a sudden “dark spot” in the right eye on the morning of presentation, which she attributed her longstanding migraines. She denied any positive visual phenomena at the time of her vision loss, and denied any significant pain or discomfort. She opted to sleep for an hour in hopes that she would abort the onset of her typical migraine headaches. When she awoke 90 minutes later, she was “blind in both eyes.” She denied pain or retrobulbar discomfort other than her longstanding chronic daily headaches, which she experienced for years. She also denied scalp pain, jaw tenderness, or constitutional symptoms of giant cell arteritis. On further inquiry, the patient had previous medical problems, which began 6 years ago. She developed symptoms of xerostomia, rash, and arthralgias at that time. She saw a rheumatologist, and was diagnosed with hypersensitivity vasculitis and then Sjogren’s syndrome, based on the findings of an elevated serum sedimentation rate (70 mm per hour) and rheumatoid factor (606 KU/L, normal < 35). Cell count with differential, electrolytes, Sjogren’s specific antibodies (SS-A and SS-B), serum protein electrophoresis, anti-nuclear antibody (ANA) and anti-neutrophil cytoplasmic (ANCA) titres were normal, anti-DNA antibodies and complement levels were normal. The creatinine kinase (700) and aldolase (10) levels were elevated. Hepatitis serology was negative. Schirmer’s testing was normal at the time. Urinalysis showed trace protein, and mild hematuria. A chest x-ray and abdominal ultrasound were normal. Electromyography and nerve conduction studies were normal. The patient was treated with oral prednisone (1 mg per kg daily) with slow taper for approximately one and a half years, until her symptoms resolved. The patient remained well, except for symptoms of arthralgias 4 years later. The aforementioned serological tests were all within normal limits, as was the urinalysis. Three months prior to her vision loss, the patient developed pain, bilateral upper eyelid orbital swelling and diplopia. At that time, a CT scan of the orbits and orbit echography demonstrated enlarged lacrimal glands. The patient was treated with oral prednisone (1 mg per kg per day) at the time of her vision loss.

The examination demonstrated normal vital signs. Blood pressure was 130/70 mm Hg. The visual acuity measured hand motion vision in both eyes. Pupils measured 4.5 mm in both eyes, and constricted to 3 mm in bright light. There was no relative afferent pupil defect in either eye. The external ocular examination showed bilateral lacrimal gland enlargement, with proptosis in the left eye more so than the right eye. There was injection of the conjunctival and episcleral vessels of both eyes. Slit lamp biomicroscopy was normal, and the intraocular pressures measured 15 mm Hg by applanation tonometry in both eyes. There was mild limitation of abduction in both eyes. Dilated ophthalmoscopy demonstrated bilateral central retinal artery occlusions, with cherry red spots. The remaining cranial nerves were within normal limits, except for diminished auditory acuity in both ears. The patient wore hearing aids. There were no carotid bruits. The motor, sensory, coordination, and gait systems were normal. The cardiac examination was normal, and the only additional clinical findings included splinter hemorrhages in the distal nail beds of the upper and lower limbs.

Fundus angiography confirmed the presence of bilateral central retinal artery occlusions with partial reperfusion. A chest x-ray, carotid Doppler ultrasound testing, cranial magnetic resonance imaging and an echocardiogram were normal. Serum cell count with differential, electrolytes, ANA, complement levels, angiotensin converting enzyme, anti-phospholipid antibodies were within normal limits. Renal studies and urinalysis were normal. The serum sedimentation rate (60 mm per hour) was elevated.

A diagnostic procedure was performed.
Final Diagnosis
A limited form of Wegener’s Granulomatosis

Summary of Case Including Pathology
A left eyelid and orbital biopsy was performed, which demonstrated acute neutrophilic infiltrate and necrosis. There was evidence of chronic granulomatous inflammation, but unfortunately the results were non-specific. Repeat serological studies were of greater diagnostic value, because the c-ANCA level was positive with a markedly positive PR-3 EIA titre (100 units, normal 0-10). The p-ANCA and MPO EIA levels were negative.

Wegener’s granulomatosis (WG) is an inflammatory systemic vasculitic disorder affecting the upper airways, lungs, and kidneys with both classical and limited forms of expression. In the classical form, both the pulmonary and renal systems are involved. In limited forms of the disease, the renal system is spared, and ocular involvement may be the presenting feature. In our case, the diagnosis of WG was a diagnostic challenge, as the patient demonstrated neither pulmonary nor renal involvement. The eye may be involved in 52% of cases during the course of the disease, and in 8-16% of cases, ophthalmic disease is the presenting feature. Ophthalmologic manifestations include conjunctivitis, scleritis, episcleritis, optic neuritis, retinitis, central retinal artery ischemia, and cranial nerve paresis. Vision loss may occur through a number of mechanisms including vascular occlusion, macular edema, inflammation of the retina, glaucoma, and damage to the optic nerve or corneoscleral tissue. Our patient developed permanent vision loss from bilateral central retinal artery occlusions secondary to WG, which has been infrequently reported in the English language literature.

In addition to the clinical presentation, the diagnosis of WG is suggested by laboratory and radiological findings. Three major histopathological findings define WG including parenchymal necrosis, vasculitis, and granulomatous inflammation. The classical clinical findings may not be present in WG, and the absence thereof does not preclude the diagnosis, as was evident in our case. Additional serological tests may also be abnormal in WG, but not diagnostic. Non-specific findings of systemic inflammation may include normochromic anemia, leukocytosis, thrombocytosis, and decreased serum albumin. Creatinine clearance, urine chemistry, and examination of urine sediment may be useful to diagnose glomeronephritis, as three-fourths of patients with WG will develop renal involvement. In our case, and limited forms of WG, the renal screen may be negative.

Autoantibodies directed against cytoplasmic neutrophil antigens or proteinase 3 anti-PR3 have been well described in patients with WG. These antibodies are called antineutrophil cytoplasmic antibodies or ANCA. Of all the ANCA found in WG, 80-95% are C-ANCA anti-PR3. Most of the remaining 5-20% are p-ANCA anti-myeloperoxidase (MPO). The absence of c-ANCA does not preclude the diagnosis of WG, as 5-10% of cases may be serum c-ANCA negative. These autoantibodies are less common in limited forms of the disease, as was apparent in our case. The ANCA titre may parallel the course of the disease, and in our case the patient was seropositive for c-ANCA at the time of vision loss. The disappearance of ANCA can be associated with clinical remission, and patients who maintain negative or decreasing titres after therapy are at lower risk for clinical relapse. However this relationship is not absolute and the ANCA titre may be discordant with the disease process in one-third of patients.

Untreated, WG is fatal. Treatment with corticosteroids and immunosuppressive agents such as cyclophosphamide has improved the prognosis of the disease. For this reason, early recognition of atypical forms of WG is imperative to prevent serious morbidity and mortality among patients.

References
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