Title:

Hyperviscosity syndrome secondary to Multiple Myeloma leads to devastating vision loss after sequential central retinal vein and central retinal artery occlusion.

Abstract:

Central retinal vein occlusion followed by a central retinal artery occlusion in the setting of multiple myeloma. The causative agent is hyperviscosity syndrome leading to in-situ venous and in-situ arterial thrombus.

Case History:

A 74 year old Hispanic male presented for his annual diabetic eye examination with the chief complaint of blurry vision for the past several months more so in his right eye than the left eye. His last eye examination was one year ago at which the patient's ocular history was remarkable for only a few mild crossing changes O.U.

His medical history was significant for multiple myeloma, non-insulin dependent diabetes mellitus, essential hypertension, hyperlipidemia, benign prostatic hyperplasia and 4 levels of lumbar disc herniation. His medications included: finasteride, glipizide, lisinopril, simvastatin, terazosin, and aspirin.

Pertinent Findings:

The patient's best-corrected visual acuity was 20/20 in both eyes. Confrontation fields were full O.D. and O.S. Pupils were equal, round and reactive to light with no afferent pupillary defect. Extraocular muscles were smooth and accurate O.U. Slit lamp examination revealed temporal pingueculas O.U., and 2+ nuclear sclerotic cataracts in both eyes.

Intraocular pressures were 17 mmHg in both eyes using Goldmann applanation tonometry. Dilated fundus examination showed a cup-to-disc ratio of 0.45/0.45 O.D. and 0.4/0.4 O.S. with distinct margins in both eyes. The right eye was noted to have multiple flame shaped hemorrhages on the rim tissue of the optic nerve, scattered dot, blot and flame shaped hemorrhages scattered throughout the four quadrants of the posterior pole with blot hemorrhages extending into the periphery. In addition, there were 2 cotton wool spots and retinal venules were noted to have marked tortuosity and segmentation of the vascular column. The left eye was only remarkable for one cotton wool spot. There were no hemorrhages or vascular tortuosity noted in the left eye. The patient was diagnosed with a non-ischemic central retinal vein occlusion (CRVO) O.D.

On serial follow-ups over the next 8 weeks the patient's best-corrected visual acuity decreased from 20/20 to 20/200 O.D. and remained stable at 20/20 O.S. The dilated fundus examination noted continued venous dilation and pan hemorrhages O.D. with the addition of macular edema O.D. Fundus evaluation of the left eye remained stable. OCT of the right eye revealed subretinal fluid under the papillomacular bundle extending to the fovea. The patient received a 2 mg intravitreal injection of Kenalog (triamcinalone) O.D. to solicit resolution of the macular thickening.
Six weeks post intravitreal Kenalog O.D. the patient presents with best-corrected visual acuity as count fingers at three feet O.D. and 20/20 O.S. Dilated fundus evaluation revealed flame shaped, dot and blot hemorrhages in all four quadrants, twelve cotton wool spots concentrated in the superior and inferior temporal arcades and a ring of retinal whitening surrounding the macula with a cherry red spot O.D. The fellow eye showed two cotton wool spots with a few blot intraretinal hemorrhages OS. OCT exhibited massive cystic foveal edema O.D. Fluorescein fundus angiography (FFA) showed delayed transit time, enlargement of hypofluorescent foveal avascular zone, classic petaloid macular edema, a large area of retinal non-perfusion greatest temporal to the macula with no late stage leakage. The patient was diagnosed with a now sequential central retinal artery occlusion (CRAO) O.D. Upon initial presentation the patient did not display an afferent papillary defect (APD) as expected with a CRAO, but upon follow up for the 2 weeks after onset a 1+ APD was noted O.D.

Differential diagnosis:

Upon initial evaluation the patient's differential diagnoses were diabetic retinopathy, branch retinal vein occlusion and central retinal vein occlusion. The patients other co-morbidities included hypertension, anemia, and chemotherapy treatment all of which may be contributing to the patients initial presentation and retinopathy.

When the patient presented with a sequential central retinal artery occlusion following his central retinal vein occlusion, it was speculated to be thrombotic in nature. The literature notes that a majority of patients with a CRAO is more than likely secondary to an embolic event. These emboli typically consist of cholesterol (74%), calcified material (10.5%), or platelet-fibrin (15.5%). Upon presentation, the patient did not show any other clinical signs or symptoms of stroke, hence the medical team did not believe the patient was at risk for an embolic event and no further investigations were warranted. Also, it was reassuring that the recent carotid non-invasive study (Duplex ultrasound) was bilaterally unremarkable with no significant stenosis of either the right or left internal carotid arteries. In addition, the patient's recent echocardiogram reported sinus bradycardia with first degree A-V block, but was otherwise unremarkable.

Diagnosis and Discussion:

The patient was diagnosed with a non-ischemic central retinal vein occlusion with sequential central retinal artery occlusion secondary to hyperviscosity syndrome in the setting of multiple myeloma IgA kappa. It is suspected that the causative agent of this ophthalmic presentation was in-situ venous and in-situ arterial thrombus.

One year prior to his initial eye examination, the patient was diagnosed with Multiple Myeloma IgA Kappa subsequent to a hospital admission complaining of 1-2 week of progressive fatigue associated with an unintentional eleven pound weight loss and recent onset cough. His workup revealed a previously undocumented anemia associated with diminished creatinine clearance, elevated serum total protein and a large monoclonal IgA kappa serum protein electrophoresis (SPEP) The patients IgA fraction was 5820 mg/dL (Normal 82-453 mg/dL) and kappa fraction was 8070 mg/dL (Normal 629-1350 mg/dL). The patient’s initial treatment was chemotheraphy with Bortezomib (Valcade) and dexamethasone. At the end of his fifth round of treatment he
exhibited poor gastrointestinal tolerance and dehydration that delayed the sixth round of treatment [which was scheduled to begin two months prior to his eye examination.]

Multiple myeloma is the most common form of bone malignancy. The frequency is increased in older patients with the median age of diagnosis in the 7th decade (1). Multiple myeloma is a disease in which there is an uncontrolled proliferation of cells involved in antibody synthesis known as plasma cell dyscrasias. These dyscrasias demonstrate excessive production of monoclonal gammopathy with a concurrent decrease in normal immunoglobulins.(2). Immunoglobulins are composed of four polypeptide chains: two "light" chains (lambda or kappa), and two "heavy" chains (alpha, delta, gamma, epsilon or mu). The type of heavy chain determines the immunoglobulin isotype (IgA, IgD, IgG, IgE, IgM, respectively). IgA paraproteinemias are responsible for approximately 29% of cases of multiple myeloma, sixty-six percent of which are shown to be kappa (3).

The associated increase in blood proteins seen in MM leads to increased global blood viscosity, which is an important determinant of blood flow (4). The delay in initiating the patient's sixth round of chemotherapy resulted in a relapse in his multiple myeloma and therefore increased his total serum concentration of IgA kappa. At the time of his central retinal vein occlusion laboratory testing shows that his IgA fraction was 4120 mg/dL and his kappa fraction was 5090 mg/dL. The increased serum IgA kappa lead to the patient developing hyperviscosity syndrome. Hyperviscosity syndrome refers to the clinical sequelae of increased blood viscosity usually resulting from increased circulating serum immunoglobulins(5). This syndrome rarely occurs in Multiple myeloma, having an incidence of only 2-4%. Of these patients who usually have IgA paraprotein peaks show that it typically needs to be greater than 5000 mg/dl (6). Of this small percentage, IgA paraproteins have shown to be more commonly associated with hyperviscosity because the tendency of the IgA molecules to form polymers (5).

The symptoms of hyperviscosity syndrome are spontaneous mucous membrane bleeding, retinopathy, pulmonary symptoms, and neurologic symptoms including dizziness, headache, and stroke (7). Ophthalmic examination may reveal decreased visual acuity, dilated retinal veins, "sausage-linked" or "boxcar segmentation" of the retinal veins, or retinal hemorrhages (8). Symptoms usually are not seen at viscosities of less than 4 units, and the hyperviscosity syndrome typically requires a viscosity greater than 5 units (9). Normal relative serum viscosity ranges from 1.4-1.8 units (10). Upon laboratory testing it was shown that our patient had an increased serum viscosity of 3.4 units. The patient displayed no other remarkable symptoms besides the vision loss in his right eye. The literature noted that severity of the hyperviscosity syndrome is not directly related to the serum viscosity; each patient responds differently to hyperviscosity (11).

The patient's increase in serum viscosity incited venous stasis. The stasis evoked resistance that damaged the endothelial cells lining the blood vessel walls culminating leaking and thrombus formation. The overall turbulent flow interfered first with small vessels showing intraretinal hemorrhages, followed by larger vessels in the retina. Once the larger vessels became involved thrombi formed leading to the central retinal vein occlusion (12). Ultimately the severity of retinopathy is dependent on the site of occlusive event. The more posterior the occlusion occurs manifests a milder form of retinopathy, similar to this patient's initial presentation. This
can be attributed to the availability of more collateral channels draining the inner retina (13). Conversely, the more anterior occlusions present with greater amounts of hemorrhages and increased ischemia (14).

During the time that the patient was being closely monitored for sequelae related to the CRVO, chemotherapy was not re-initiated which fostered further elevation in the patients IgA Kappa to 6330 mg/dL and 6800mg/dL, respectively. This further augmentation of continued stasis throughout the retinal vasculature caused more insidious damage. Concurrently the underlying vein occlusion caused an increase in intravenous pressure across the capillary bed impairing retinal arterial filling (15). This environment synergized arterial thrombosis formation leading to the central retinal artery occlusion. It is speculated that in this case the central retinal artery was only transiently occluded secondary to the causative nature in which it manifested. Hayreh states that a transient non-arteritic central retinal artery occlusion (NA-CRAO) will produced the classic fundus findings of attenuated arterioles, ring of retinal whitening and cherry red spot with normal FFA findings (16). The increased perfusion is the reason the patient did not initial present with an afferent pupillary defects. He also goes on to say that in patients with transient NA-CRAO the visual outcomes can be completely different from any of the other types of CRAO (17). The patient's outcome is solely dependent upon the duration of the transient NA-CRAO, which may vary from several minutes to many hours (18).

**Treatment:**

The patient was admitted for three sessions of urgent plasmaphoresis before transitioning to alternative chemotherapy, Revlimid (lenalidomide). The change in therapeutic agents was incited to reduce the stress on the renal system. The initiation of plasmaphoresis also helped reduce the associated risk of central retinal vein occlusion and/or central retinal artery occlusion in the fellow eye. Upon discharge from the hospital, the patient's serum plasma levels post-plasmaphoresis was 1.7 mg/dl. The patient was instructed to continue with aspirin and Lovenox (enoxaparin) as continued prophylaxis against further thrombotic events.

In a 23 case retrospective study by Brown et al, it was reported that 81 % of patients with combined CRVO-CRAO developed rubeosis iridis (19). Retinal ischemia is thought to play a major role in the pathogenesis of the disease process, which is probably more severe that that seen with either entity independently. The mean time required to develop rubeosis iridis was 11.8 weeks with the median being 6 weeks. (11). Neovascular glaucoma can result in further visual decline as well as significant morbidity in the form of eye pain. The authors suggest aggressive laser therapy to be considered soon after the obstructive event.

The visual prognosis for the patient's right eye is poor secondary to extensively enlarge foveal avascular zone present on FFA. The patient was issued new polycarbonate lenses due to his new monocular status. The patient will continue to be monitored closely for neovascularization at 2-3 week intervals (20).
Conclusion:

Although hyperviscosity syndrome in multiple myeloma is rare it is important to understand the disease process to prevent its visually devastating effects. This uncommon clinical entity which typically has poor visual outcomes may be prevented with proper awareness. I suggest that all multiple myeloma patients receive dilated fundus evaluation at six month intervals, I advocate for antithrombotic prophylaxis and monitoring of each patients serum viscosity levels.
References: