Grand Rounds

A 26-year-old man with renal failure and vision loss

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History

A 26-year-old Latino man with no past medical history of diabetes or hypertension presented to the emergency room complaining of nausea, back pain, fatigue, cough with yellowish sputum, and pleuritic chest pain. The review of systems revealed decreased urinary output.

The vital signs upon presentation are summarized in Table 1. The patient's physical exam showed bilateral costovertebral angle tenderness, and his laboratory tests are summarized in Table 2. A computed tomography scan was negative for nephrolithiasis, an electrocardiogram and an echocardiogram showed left ventricular hypertrophy, and a renal ultrasound showed small and echogenic kidneys bilaterally.

The patient was diagnosed with nephrotic syndrome and end-stage renal disease (ESRD). An extensive workup was carried out to define the etiology of the renal failure (Table 3). A kidney biopsy was not warranted given the ESRD and the potential complications associated with the procedure. His anemia was thought to be anemia of chronic disease secondary to renal failure and his dyslipidemia is consistent with nephrotic syndrome.

He was started on hemodialysis three times a week, plus Darbepoetin Alfa and Simvastatin for anemia and dyslipidemia, respectively. The patient was compliant with the hemodialysis schedule and the prescribed medications.

One year later, the patient presented to the emergency room complaining of severe headache and vomiting followed by sudden vision loss bilaterally. His vital signs are summarized in Table 4. A computed tomography scan of the head showed no evidence of bleeding, midline shift, or mass. A lumbar puncture was performed and acute meningitis was ruled out.

Table 1.

Vital signs at initial presentation

Blood pressure	116/67
Heart rate	81
Temperature	97° F
Respiratory rate	18

Table 2.

Laboratory Tests

BUN	68
Creatinine	10.5
Blood glucose	88
24 hour urine protein/Creatinine ratio	5.22
Proteinuria	>300 (nephrotic range)
Glucosuria	250
WBC	11.5
Hemoglobin	9.1
Hematocrit	27
Platelet	374
MCV	93.3
RDW	12.8

Table 3.

Laboratory work-up for cause of renal failure

Hemoglobin A1c	5.4
Antistreptolysin O antibodies titer	Normal
Complement C3 level	Normal
Complement C4 level	Normal
RPR	Non-reactive
Fasting lipid panel	Mild dyslipidemia
ANCA	Negative
ANA	Negative
Anti double stranded DNA	Negative
Hepatitis B serologies	Negative
Hepatitis C serology	Negative
HIV serology	Negative

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Table 4.

Vital signs at second presentation

Blood pressure	150/98
Heart rate	65
Temperature	97.8° F
Respiratory rate	16

Examination

On ophthalmologic exam, the patient had a fixed, irregular, non-reactive right pupil that measured 4 mm. A right relative afferent pupillary defect (RAPD) was present. The left pupil was reactive to light. The patient had visual acuities of counting fingers on the right, and 20/200 on the left without improvement by pinhole. The intraocular pressure measured 12 mm Hg on the right and 10 mm Hg on the left. The slit-lamp exam was significant for a fixed pupil on the right and iris touching the cornea on the left. The fundus examination of the right eye revealed extensive intraretinal hemorrhages in all 4 quadrants, dilated and tortuous retinal veins, cotton wool spots, and disc edema (Figure 1). The fundus examination of the left eye revealed severe inferior disc swelling, intraretinal hemorrhages, and cotton-wool spots (Figure 2).

Ancillary Testing

A fluorescein angiogram (FA) of the right eye (30 seconds post fluorescein injection) revealed extensive blockage of choroidal fluorescence by intraretinal heme, leakage correlating with areas of retinal edema, venous engorgement and tortuosity, and extensive non-perfusion involving the macula and mid-periphery (Figure 3).

FA of the left eye (65 seconds post fluorescein injection) revealed blockage of choroidal fluorescence by intraretinal heme, leakage correlating with areas of retinal edema, and areas of non-perfusion inferiorly (Figure 4).

Treatment

Patient was diagnosed with bilateral central retinal vein occlusions with ischemia.

Complete hematologic and coagulation workup came back negative (Table 5), but the homocysteine and CRP were both elevated. The patient was followed closely by ophthalmology for the first 6 months, including gonioscopy and undilated examination of the iris, to monitor

Figure 1. Color fundus photograph of the right eye shows extensive intraretinal hemorrhages in all 4 quadrants, dilated and tortuous retinal veins, cotton wool spots, and disc edema.

Figure 2. Color fundus photograph of the left eye shows severe inferior disc swelling, intraretinal hemorrhages, and cotton-wool spots.

for signs of neovascularization of the iris and neovascular glaucoma.

Differential Diagnosis

1. Central retinal vein occlusion (CRVO).
2. Ocular ischemic syndrome (carotid occlusion disease):

In ocular ischemic syndrome, the veins are usually dilated and irregular (but not tortuous). Although revascularization of the disc is present in one third of the cases, disc edema and hemorrhages are not characteristic. Retinal hemorrhages tend to be in the mid periphery. Patients may have a history of amaurosis fugax,

Figure 3. Fluorescein angiogram of the right eye (at 30 seconds post fluorescein injection) showing extensive blockage of choroidal fluorescence by intra-retinal hemorrhage and edema, leakage correlating with areas of retinal edema, venous engorgement and tortuosity, and extensive non-perfusion involving the macula and mid-periphery.

Figure 4. Fluorescein angiogram of the left eye (at 65 seconds post fluorescein injection) showing blockage of choroidal fluorescence by intra-retinal hemorrhage, leakage correlating with areas of retinal edema, and areas of non-perfusion inferiorly.

Table 5.

Coagulopathy workup

Lupus anticoagulant	Not detected
Protein C activity	Normal
Protein S activity	Normal
Cryoglobulin	Negative
Hemoglobin electrophoresis	Normal
Protein electrophoresis	Normal
ANCA	Negative
Prothrombin gene analysis for the G20210A mutation.	Negative
Homocysteine level	Elevated
C-reactive protein	Elevated

transient ischemic attacks, or orbital pain. The intra-ocular pressure is often low as is the central retinal artery perfusion pressure.

3. Diabetic retinopathy:

For diabetic retinopathy, hemorrhages and microaneurysms are usually concentrated in the posterior pole, exudates are more prominent, and the condition is typically bilateral. Intravenous fluorescein angiography may be required to distinguish this condition from central retinal vein occlusion.

4. Papilledema:

This is characterized by bilateral disc swelling with flame-shaped hemorrhages surrounding the disc but not extending to the peripheral retina. It results from increased intracranial pressure.

5. Radiation retinopathy:

A history of irradiation is critical for this diagnosis. Disc swelling with radiation papillopathy, and retinal neovascularization may be present. Generally, cotton-wool spots are a more prominent feature than hemorrhages.

6. Acute hypertensive retinopathy:

The blood pressure at presentation is critical for the diagnosis. It is characterized by focal or generalized vasoconstriction and breakdown of the blood-retinal barrier, with subsequent hemorrhages and exudates. Findings include:

- **Retinopathy:** This is characterized by arteriovenous nicking, copper or silver wire arterial changes, hemorrhages, exudates, and cotton wool spots.
- **Choroidopathy:** This is characterized by fibrinoid necrosis of choroidal arterioles. There may be Elschnig's spots (zones of nonperfusion of the choriocapillaris with pale white or red patches of the retinal pigment epithelium) and exudative retinal detachment. This is often due to an acute hypertensive episode (preeclampsia, eclampsia, or pheochromocytoma). FA shows early hypoperfusion and late staining.
- **Optic neuropathy:** This is characterized by florid disc edema with macular exudates.

The pathology is characterized by thickening of arteriolar walls, which leads to nicking of venules and endothe-

lial hyperplasia. Complications of hypertensive retinopathy include retinal vein occlusion, retinal macroaneurysm, nonarteritic anterior ischemic optic neuropathy, ocular motor nerve palsies, and worsening of diabetic retinopathy.

Diagnosis

The patient was diagnosed with bilateral central retinal vein occlusion (CRVO) with ischemia. The patient was noted to have a right relative afferent pupillary defect (RAPD), a high-risk characteristic of CRVO. The large retinal lesion seen in ischemic CRVO can explain this. Iridocorneal touch (a finding in the left eye) can be seen in trauma, after surgery, angle closure glaucoma, and inflammation. However, the history, review of systems, laboratory tests, fundus examination, fluorescein angiogram, and other exam findings were suggestive of CRVO rather than an inflammatory etiology.

Complete hematological and coagulation evaluations were performed (summarized in Table 5). The homocysteine level was found to be elevated, and this is associated with a hypercoagulable state in nephrotic syndrome. The C-reactive protein was elevated as well. A rheumatology consult was not entertained given the clinical picture, pertinent negative review of systems, and the negative laboratory workup. The patient was followed closely by ophthalmology for six months, including gonioscopy and undilated examination of the iris. Serial exams showed no signs of neovascularization of the iris or neovascular glaucoma. The patient, however, was lost to follow up due to a prolonged admission to an outside hospital for a dialysis catheter infection. The patient was called and encouraged to follow up once his acute line infection issues resolve.

Central retinal vein occlusion typically occurs in people over 50 years of age. Major risk factors are hypertension, diabetes mellitus, and atherosclerosis. Other risk factors are glaucoma, syphilis, sarcoidosis, vasculitis, increased intraorbital or intraocular pressure, hyphema, hyperviscosity syndromes (multiple myeloma, Waldenström's macroglobulinemia, and leukemia), high homocysteine levels, sickle cell, and HIV. Younger patients, especially those less than 45 years of age, who present with central retinal vein occlusion should have further hematologic and coagulation workup to rule-out an underlying thrombotic disorder.¹

CRVO has two types:

- The Nonischemic type (incidence of 70%) is defined as <10 disk diameters (DD) of capillary

nonperfusion. It is characterized by vision that is better than 20/200. Among this group, 16% progress to nonperfused CRVO and 50% resolve completely without treatment.

- The Ischemic type (incidence of 30%) is defined as more than 10 DD of nonperfusion. Patients are usually older and have worse vision. Iris neovascularization is seen in 60%. Up to 33% develop neovascular glaucoma. Ten percent are combined with branch retinal arterial occlusion (usually the cilioretinal artery is occluded due to low perfusion pressure of the choroidal system).²

The central vein occlusion study (CVOS) data did not support the recommendation for prophylactic panretinal photocoagulation (PRP). The CVOS found that early PRP decreased the rate of iris neovascularization (INV); however, the reduction was not statistically significant. Moreover, the study showed that early PRP reduced, but did not eliminate, the possibility of anterior-segment neovascularization. The CVOS recommended close follow-up of eyes with CRVO during the first 6 months (including gonioscopy and undilated slit-lamp examination of the iris) and prompt PRP of eyes in which iris neovascularization (INV) or angle neovascularization (ANV) develops.³

Risk factors for developing iris neovascularization in patients with CRVO are the amount of nonperfused retina, extent of retinal hemorrhages, male sex, and central vein occlusion of less than one month duration.³ The baseline visual acuity of patients with CRVO is a strong predictor for the development of INV/ANV, as is the amount of nonperfusion seen by fluorescein angiogram.⁴

Although PRP was better than selective PRP or photodynamic therapy at preventing INV and anterior segment neovascularization progression, selective PRP or PDT can also be safely used to treat anterior segment neovascularization secondary to ischemic CRVO.⁵

Every eye with CRVO is at risk for developing neovascular glaucoma. Lowering intraocular pressure helps to improve retinal circulation in an eye with CRVO,⁶ and there is a 10 % risk for development of BRVO or CRVO in the fellow eye.⁷

This case illustrates the potential importance of regular eye exams in young patients with end-stage renal disease on hemodialysis. Young patients with nephrotic syndrome and end-stage renal disease can develop CRVO.

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