CLINICAL VIGNETTE

Varicella Induced Acute Retinal Necrosis

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A 48-year-old male with type II diabetes mellitus, hypertension and migraine headache, was admitted to the inpatient service with new progressive left eye vision loss. He noted that about one week prior, his central vision was hazy and he felt as if he was looking through a "dirty window." When this first started, he had preserved peripheral vision and was able to read the numbers on his watch using his peripheral vision, but not when looking directly at his watch with his right eye closed. Over the prior week, his left eye vision continued to worsen. By day four he was unable to see any details and was only able to perceive large shapes and changes in light. By the morning of admission to the hospital he had absolutely no vision on the left eye. He was not able to even appreciate the penlight directly into his left eye. He also reported a constant dull left eye pain rated 5/10 severity with sharper 6-7/10 pain on lateral gaze. He remarked that the pain radiated out to involve the area around his orbit into his forehead. He denied any other headache and had no recent illnesses or exposure to people with known illness. He denied fever, chills, nausea, vomiting, cough, dyspnea, chest pain, abdominal pain. He also denied any focal weakness, sensory changes, slurred speech, aphasia. He has never experienced anything like this in the past. His past medical history was negative for malignancy, blood clots, or HIV risk factors. No history of myocardial infarction or stroke in the past. His family history was significant for a maternal grandmother with Type II Diabetes Mellitus. His current medications included alogliptin 25mg daily, lisinipril 20mg daily, metformin 1gram twice a day. He currently works as an administrator at a security firm. He is active and walks every day. He is a non-smoker and does not drink alcohol and denies any recreational drug use. His physical exam was remarkable for a pulse of 84 b/min, blood pressure of 120/70 mmHg, and a BMI of 29.2. He had bilateral scleral injection and his pupils were equal and reactive to light. Mental Status: Awake and alert and fully oriented. Speech was fluent and without dysarthria or aphasia and he had intact naming, reading, and repetition. He was able to follow complex commands and participate in a goal directed conversation. On examination of his cranial nerves, his right eye had no visual field deficits but he had complete loss of vision in the left eye and was unable to perceive light directly shone into his left pupil. His extra ocular movement was intact bilaterally and his left eye dilated with direct light. He had intact consensual constriction when light was shone into the right eye. His fundoscopic exam revealed diffuse pallor of the retina on the left eye, scattered retinal hemorrhages and edema of the optic disk with blurred margins (Figure 1). His right optic disc had clear margins. The remainder of his neuro and physical exam was unremarkable. Specifically, no vesicular rash, genital ulcerations, nor hepatosplenomegaly. Initial labs were only significant for elevated HbA1c at 7.6. Given the clinical, presentation, both ophthalmology and neurology were consulted. MRI brain was notable for diffusion restriction in the cannicular and intra-orbital portions of the left optic nerve concerning for acute versus subacute left optic nerve infarction. Increased signal involving the left portion of the optic chiasm and intracranial portion of the left optic nerve on diffusion-weighted imaging was noted. Dedicated MRI of the left orbit was consistent with left infectious versus noninfectious optic neuritis. There were no findings to suggest intracranial demyelination disease. The patient underwent a lumbar puncture which was unremarkable and had a negative Covid-19 test. Fluorescein angiography on his left eye revealed peripheral retinal whitening with involvement of posterior pole, with hemorrhage, and occlusive arteritis. Serum studies were negative for Toxoplasma and IgG, IgM, and IgG subclasses were normal, rapid plasma regain (RPR), Human T-lymphotropic virus (HTLV) IgG, Human immunodeficiency virus (HIV), Cerebrospinal (CSF) white blood cell count, Biofire, venereal disease research labs (VDRL) were all negative. The biofire is a polymerase chain reaction (PCR) multiplex for simultaneous and rapid identification of 14 pathogens, including 6 bacteria, 7 viruses, and Cryptococcus. The CSF culture from admission was negative. At this point, the differential was narrowed to infections causes of acute retinal necrosis including herpes simplex (HSV), varicella zoster virus (VZV) and cytomegalovirus (CMV) and ophthalmology was asked to obtain samples from the vitreous and the patient was started on empiric antiviral coverage with acyclovir. Shortly thereafter the vitreal sample VZV PCR returned positive and he was started on antiviral infusions.

Discussion

The pathogenesis of Acute retinal necrosis (ARN) is a peripheral necrotizing retinitis caused by Varicella-zoster virus (VZV) or Herpes simplex virus (HSV) infection. It predominantly affects immunocompetent individuals, but can occur in immunocompromised patients. The condition was initially described in a paper by Urayama in 1971. This seminal article was published in the Japanese Journal of Clinical Ophthalmology and described a panuveitis with vitritis, retinal periarteritis with areas of peripheral confluent retinal necrosis in six patients.[1] Some of these patients also had retinal detachments.[2] The condition can be unilateral or bilateral. If it becomes

bilateral, it is known as bilateral ARN or BARN. ARN has also been described in the literature due to cytomegalovirus (CMV), or Epstein-Barr virus (EBV).[3] The condition affects men and women equally. It is more common in older patients as immunity to VZV decreases. HSV-induced ARN affects younger patients especially those with a history of herpes encephalitis. Acute retinal necrosis can also occur in immuno-competent patients taking corticosteroids, non-corticosteroid immunosuppressants, and after chemotherapy. The virus infects retinal cells and necrosis occurs from cytolysis and the occlusion of retinal capillaries. Dead retinal cells detach and leave areas of residual disc pallor. The initial inflammation caused by viral infection damages the retinal cells. Further progression causes arteriolar constriction which exacerbates retinal necrosis. Later as the retina scars, retinal detachment may occur in up to three quarters of patients with ARN.[4] As in our case, patients often present with ocular pain or periocular pain, with pain exacerbated by eye movement. Redness, photophobia or light sensitivity, floaters, decreased vision, or blurred vision, and visual field deficits may also occur.

When assessing patients, risk factors for AIDS, immune compromise, any prior systemic or ocular therapies or surgical procedures, systemic diseases, and any previous herpes infection including encephalitis should be sought. On physical exam the internist can assess the eye for conjunctival injection or scleritis and perform a dilated fundoscopic examination for focal areas of retinal pallor, retinal hemorrhage, optic disc edema, and retinal detachment. Ophthalmologic consultation can assess for prominent inflammatory reaction within the vitreous and anterior chamber as well as measurement of intraocular pressure.

The ARN diagnostic triad is arteritis/phlebitis of the retinal and choroidal vessels, a confluent necrotizing retinitis usually of the peripheral retina, and a moderate to severe vitritis.[5]

When ARN is suspected, testing should include complete blood count with differential, baseline liver and kidney function, HIV serology, FTA-ABS (fluorescent treponemal antibody absorption), and RPR (rapid plasma reagin), erythrocyte sedimentation rate, toxoplasmosis titers, purified protein derivative skin test (PPD), and chest x-ray as part of the initial evaluation.[6] The ophthalmologist can perform an anterior chamber/vitreous paracentesis for herpesviruses (VZV, HSV, CMV, and EBV) and toxoplasmosis polymerase chain reaction (PCR). Positive VZV or HSV PCR in is seen in 79-100% of cases of ARN. Serum Viral titers (VZV, HSV, CMV), Lumbar Puncture CT/MRI of Brain and intravenous fluorescein angiography can also be considered depending on the patient's presentation.[7]

ARN is an ophthalmologic emergency and once suspected or confirmed anti-viral therapy should be initiated immediately. The goal is to decrease spread to the opposite eye. One study showed that 75% of the patients treated with acyclovir remained disease-free in the opposite eye at 2 years versus 35% of patients not treated with acyclovir.[8] Unfortunately, treatment does not reduce the rate of retinal detachment in the eye which was infected initially. Acyclovir should be started at 10-13 mg/kg every 8 hours or 1500mg/m2/day intravenously (IV) for 5-10 days and followed by acyclovir 800 mg five times daily orally for 6 weeks to 3 months. Alternate treatment options include Valacyclovir which can be taken orally three times daily avoiding the need for intravenous access. Other oral options include Famciclovir and Valganciclovir. As in our patient sight-threatening retinitis or optic disc involvement, may involve intravitreal injections.

Concurrent with IV antivirals, oral prednisone 0.5-2.0 mg/kg/day for one and a half to two months should be started two days after the start of antiviral therapy or once regression of necrosis is demonstrated on fundoscopic exam. Also, antiplatelet therapy (aspirin 81 mg to 650 mg daily) or warfarin may prevent further ischemia of the optic nerve and retina. Finally, laser photocoagulation posterior to the zone of active retinitis may be performed prophylactically to wall off or prevent subsequent retinal detachment, this however remains controversial. The visual prognosis of ARN is poor and 64% of affected eyes achieve a final acuity of worse than 20/200 due to multiple complications including retinal detachment, optic neuropathy, macular abnormality, and retinal ischemia.[9] Visual outcomes may improve with prompt diagnosis and treatment. Up to 92% of eyes may achieve at least 20/400, and 46% of eyes may achieve a final vision of at least 20/40 and involvement of the other eye may reduce.[10] A large series noted that when the macula and the optic disc were involved, a final vision of 20/200 or worse could be expected.[11]

ARN is a vision threatening disease and internists and hospitalists who diagnose patients with herpes simplex infection of the eye should refer these patients to an ophthalmologist immediately. The main goal of rapid diagnosis, as in our patient, is to reduce the chances of spread to the opposite eye. The prognosis of ARN is poor and about two thirds of affected eyes have a final visual acuity of worse than 20/200.[12] Retinal detachment, optic neuropathy, macular involvement, and retinal ischemia are associated consequences.

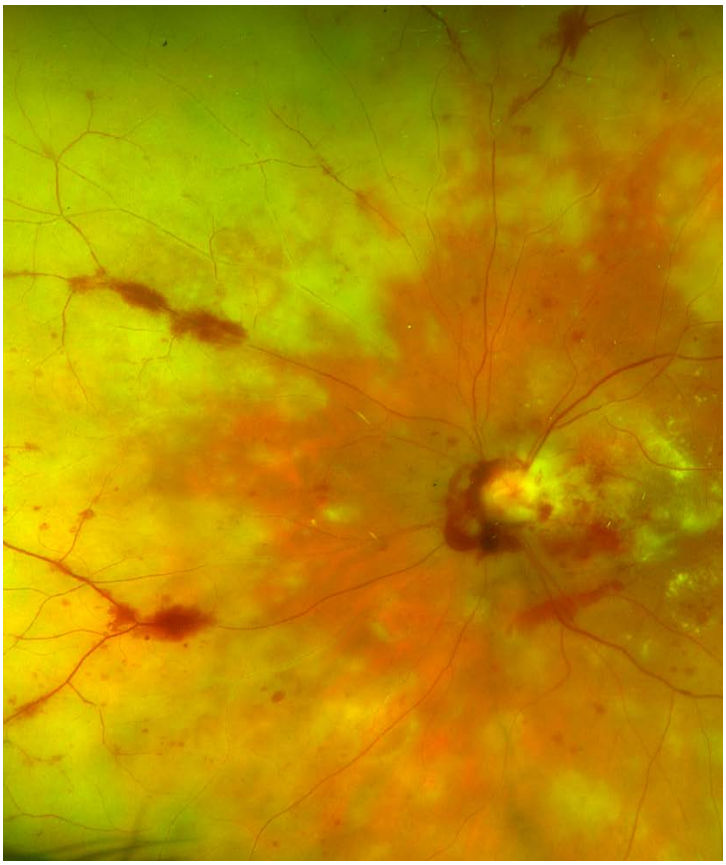

Figure 1. Area of optic disc at center. Diffuse pallor of the retina of the left eye, scattered retinal hemorrhages and edema of the optic disk with blurred margins and hemorrhages.

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