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Clinical report

Progressive outer retinal necrosis in an immuno-compromised patient presenting with bilateral retrobulbar optic neuritis

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Background: Progressive outer retinal necrosis (PORN) is a necrotizing chorioretinopathy caused by herpes simplex virus, varicella-zoster virus, or cytomegalovirus.
Objective: To describe the clinical morphology of PORN presenting with asymmetrical isolated bilateral retrobulbar optic neuropathy.
Method: The medical records of a 45-year-old human immunodeficiency virus infected patient presenting with bilateral visual loss at King Chulalongkorn Memorial Hospital were reviewed with respect for the privacy of patient.
Result: Gradual visual loss progressed to no light perception in the right eye and 20/200 in the left eye within 1 month. The patient was initially diagnosed with retrobulbar optic neuritis in both eyes. The investigations included MRI, vitreous tapping, lumbar puncture, and serological testing. MRI elicited enhancement around both optic nerves, which suggested optic neuritis. Thereafter, multifocal areas of retinal necrosis developed with rapid progression and additional cutaneous zoster lesions were established. These findings led to a diagnosis of PORN. The patient was promptly treated with intravenous ganciclovir, anti-retroviral therapy, and vitrectomy with endophotocoagulation and silicone injection. Unfortunately, his visual prognosis in the left eye was still poor.
Conclusion: PORN was uncommonly present with bilateral isolated optic neuropathy before retinal lesions developed. Retrobulbar optic neuropathy from herpetic infection in immunocompromised patients should be considered despite a normal fundus at initial presentation. Early diagnosis and prompt intervention may preserve vision. This case demonstrates the importance of careful physical examination and follow up of retinal lesions.

Keywords: Bilateral optic neuropathy, HIV infection, immunocompromised patient, progressive outer retinal necrosis, retrobulbar optic neuritis

Progressive outer retinal necrosis (PORN) is a necrotizing herpetic retinopathy, caused by herpes simplex virus (HSV), varicella-zoster virus (VZV), and cytomegalovirus (CMV) [1, 2]. The disease primarily presents with choroid and outer retina involvement with minimal inflammatory intraocular reaction and the inner retina is affected in the late stage [3]. This article presents a case with uncommon presentation of bilateral isolated optic neuropathy before a retinal lesion developed.

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Materials and methods

The medical records of a 45-year-old human immunodeficiency virus (HIV) infected patient who presented with bilateral visual loss at King Chulalongkorn Memorial Hospital were reviewed with respect for the privacy of patient. The history, clinical features, clinical course and all investigations were collected. Our Institutional Review Board approved the review of patient records and this clinical report.

Results

A 45-year-old male patient with known HIV infection (CD4 19 cells/mm^3), with a history of previous pulmonary tuberculosis and cutaneous herpes simplex infection presented at our hospital. He had a

complete standard tuberculosis (TB) treatment for 6 months. He also had oral acyclovir 800 mg 5 times per day for 1 month with poor compliance. However, he had not been treated with antiretroviral drugs.

This patient presented at a secondary care hospital with history of progressive visual loss in both eyes over a period of one month. He also had a right side headache for 10 days. At that time his best corrected visual acuity (BCVA) was 20/70 in the right eye and 20/50 in the left eye. The eye examination appeared normal for both eyes. A lumbar puncture was normal (open pressure 5 cmH_2O, protein 74 mg/mm^3, sugar 79 mg/mm^3 (blood sugar = 124 mg/mm^3), white blood cells (WBC) 0 cells/mm^3, red blood cells (RBC) 0 cells/mm^3, acid fast bacilli (AFB), cryptococcus antigen (Ag), and india ink result were all negative). Brain computed tomography (CT) without contrast showed mild cortical atrophy with unremarkable other features. He was admitted to the secondary care hospital for 4 days. The provisional diagnosis was bilateral progressive visual loss with unknown cause, and he did not receive any medical treatment. Because his vision was still getting worse he was referred to our hospital for further investigation and treatment.

At King Chulalongkorn Memorial Hospital, his best corrected visual acuity (BCVA) was no light perception (NLP) in the right eye and 20/200 in the left eye. He had full extraocular movements. The corneas were clear with no cell in anterior chambers of either eye. The lenses were clear and pupils were 5 mm and sluggish reaction to light in both eyes. A fundus examination of the right eye found a few deep small yellow whitish lesions at the temporal site of about 5,000 μm to the macula. The optic disc, macula and peripheral fundus appeared normal. The fundus of the left eye appeared normal. Computerized visual field 30-2 with target size V showed a deep scotoma of the inferonasal and temporal regions in the left eye. Color vision was impaired. Magnetic resonance imaging of the brain and orbit showed an enhancement around the bilateral distal optic nerves and chiasm suspected diffuse meningeal enhancement relating to meningitis and bilateral optic neuritis (**Figure 1**). The visual acuity (VA) of his left eye had deteriorated to hand motion with good light projection. The inflammatory reactions appeared with cellular reaction 1+ in the anterior chamber of the right eye and 2+ in the left eye. The right pupil was 7 mm with no reaction to light and the left was 6.5 mm with sluggish react to light. There was mild vitreous reaction in the left eye. Both fundus showed multiple yellow whitish choroidal lesions in the posterior pole with pallor peripheral retina (**Figure 2A, 2B**). The optic disc and macula area appeared normal with positive spontaneous venous pulsation. The provisional diagnosis was focal retinitis with bilateral optic neuritis, with infection most likely the cause. Other diseases involved were pansinusitis, herpes simplex skin infection, and partial treatment of pulmonary tuberculosis. Using underlying data from the patient, and deep lesions of the fundus, herpes virus, tuberculosis, or fungal etiology were suspected.

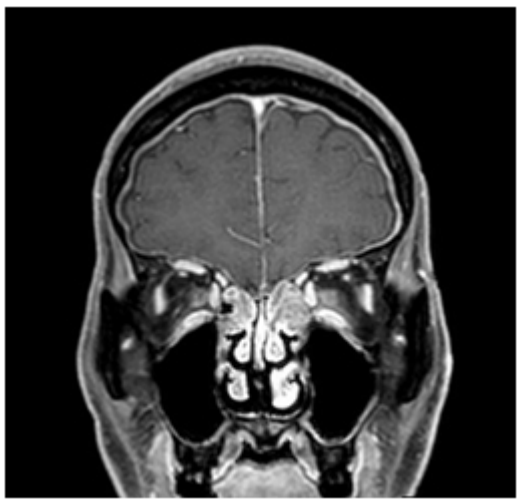

Figure 1. Magnetic resonance imaging (MRI), contrast-enhanced coronal T1-weighted image with fat suppression show abnormal enhancement of bilateral optic nerves

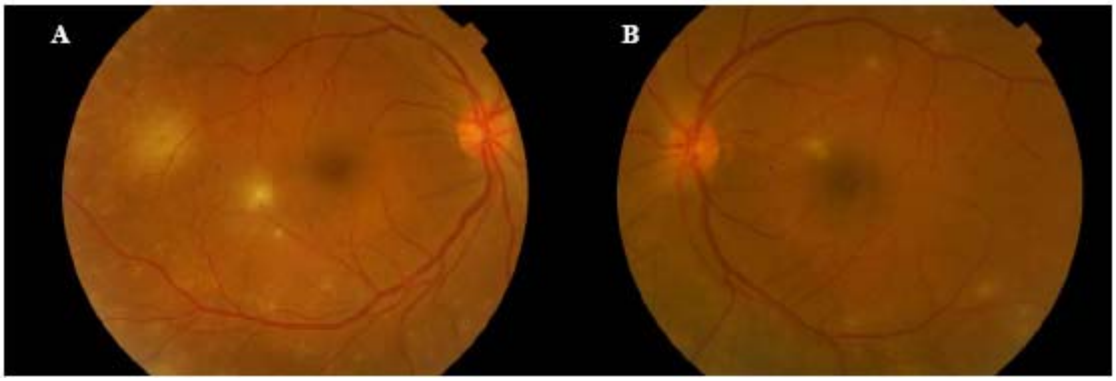

Figure 2. Fundus photography, **A** (right eye) and **B** (left eye): fundus pictures at 1 week after presentation showing deep small multiple whitish deep retina infiltration at temporal to macular and along arcade

This patient was scheduled for vitreous tapping in the left eye, sinuscopy, chest X-ray imaging, lumbar puncture, Tzanck smear, and a blood test for serological workup. A vitreous specimen for Gram staining, potassium hydroxide preparation, acid fast bacilli (AFB), modified AFB, bacterial and fungal cultures included polymerase chain reaction (PCR) for TB, mycobacteria growth indicator tube (MGIT) all showed negative results. Cerebrospinal fluid (CSF) profile was normal, clear appearance, open pressure 5 cmH_2O, sugar 66.1 mg/dL (blood sugar = 55 mg/dL), protein 0 g/dL. Chest X-ray imaging showed no evidence of active pulmonary TB. A Venereal Disease Research Laboratory test (VDRL) and *Treponema pallidum* hemagglutination assay (TPHA) were nonreactive. For the differential diagnosis above, we started treatment with acyclovir 450 mg intravenous every 8 hour, amphotericin B 30 mg per day (0.7 mg/kg/day) intravenous and anti-TB drugs (isoniazid 250 mg daily, rifampicin 450 mg daily, pyrazinamide 500 mg daily, and ethambutol 400 mg daily). Additional treatment included amoxicillin/clavulanic acid (Augmentin) 1,000 mg every 12 hours for pansinusitis therapy and TobraDex eye drops applied to the left eye four times a day for after vitreous tapping care. A few days later, his vision was not changed, but chorioretinal lesions had progressed (**Figure 3A and B**) corresponding to a clinical picture of PORN. Ganciclovir 200 mg intravenous every 12 hours was started instead of acyclovir. Antiretroviral medication had been started at the sixth day of admission with tenofovir 300 mg daily, lamivudine 150 mg daily, and efavirenz 600 mg daily. Multiple breaks with peripheral retinal detachment of both right and left fundus were found at the seventh day of admission. A 20 gauge pars plana vitrectomy (PPV) with fluid gas exchange with endophotocoagulation with silicone oil (Oxane HD) injection of left eye was done. A vitreous specimen was collected for PCR of HSV, VZV, and CMV. All showed negative results.

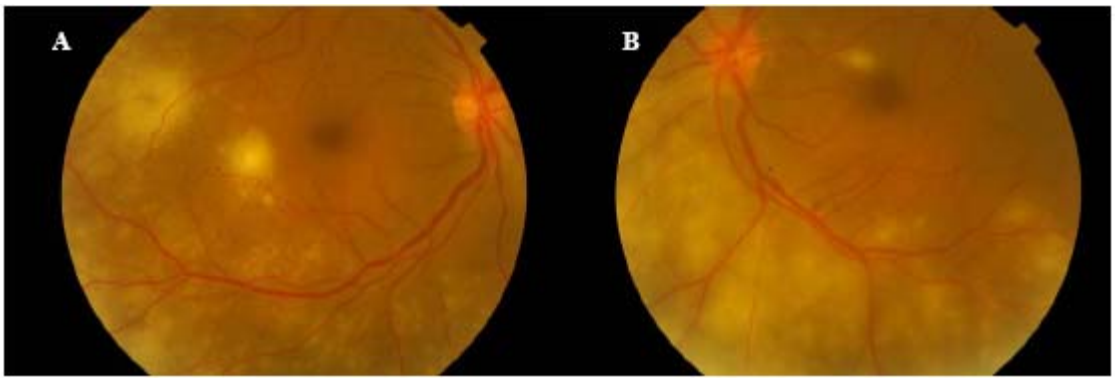

Figure 3. Fundus photography, **A** (right eye) **and B** (left eye): fundus pictures at 2 weeks after presentation, show enlargement of yellow white subretinal lesions, deep yellow white confluent lesions along mid periphery and peripheral retina. Retinal necrosis was noted.

Post operatively, VA of counting finger 2 foot in the left eye and no light perception (NLP) in the right eye. Fundus of left eye revealed a pale disc with circumferential laser reactions with silicone filled. Retina was attached, with multiple retinal hemorrhage and necrosis along vessels in mid peripheral and peripheral areas.

TobraDex eye drops were applied to the left eye four times and 1% atropine eye drops applied to the left eye twice daily. Ganciclovir 200 mg intravenous every 12 hours was continued for 17 days then switched to acyclovir 450 mg intravenous every 8 hours for 1 month with no side effect. At 1 month follow up period, VA of the left eye was hand motion with poor light projection and NLP in the right eye. The fundus of the left eye showed attachment at the posterior pole with a chorioretinal scar circumferentially. The right eye had total retinal detachment. Oral acyclovir 800 mg 5 times per day was replaced with intravenous acyclovir at the third month of the treatment course.

Discussion

Necrotizing herpetic retinopathies have been considered to be a spectrum of disorders caused by HSV, VZV, and CMV. There are two common spectrums included in acute retinal necrosis (ARN) occurring in apparently immunocompetent patients [1] and PORN described in severely immunocompromised patients [2]. Forster et al. were the first to describe "rapidly progressive outer retinal necrosis", they observed that only the outer retina was involved initially with minimal to no intraocular inflammation and then inner retinal layer and retinal vessels affected late stage [3].

PORN was generally presented in immuno-compromised patients with preceding VZV, HSV, or CMV infection. Typical presenting symptoms are acute or subacute visual loss compatible with absent to mild anterior chamber cells or vitritis, outer retinal necrosis with spare the perivascular and large retinal breaks leading to retinal detachment [4]. These uncommonly present with isolated optic neuropathy before retinal lesions develop.

Engstrom et al. reported a variant of necrotizing herpetic retinopathy in 38 acquired immunodeficiency (AIDS) patients (65 involved eyes) and median CD4 cell count was 21 cells/mm^3. The most common presenting symptom was unilateral decreased vision in 35 of 65 eyes (54%). Typical retinal lesions were multifocal, deep opacities scattered throughout the periphery and in 11 (17%) of 65 eyes had optic nerve involvement at diagnosis. The findings of optic neuropathy in this report are optic disc swelling, disc hyperemia, and optic atrophy. Retinal lesions progressed rapidly and developed retinal detachment in 43 (70%) of 61 eyes. Initial intravenous antiviral therapy did not alter final visual outcome that resulted in NLP in 42 (67%) of 63 eyes within 4 weeks after diagnosis [5].

In the current case, the patient presented with isolated bilateral optic neuritis without any other ocular involvement. Typical chorioretinal lesions developed as a consequence. This is a very uncommon presentation. A diagnosis of PORN was made on the basis of the fundus and clinical appearance.

Atypical presentations of PORN following optic neuritis have been reported in few case series. All patients presented with asymmetrical acute profound loss of vision despite having anterior and posterior segments that were normal or only mildly inflamed. Ten patients had a positive VZV PCR in vitreous or cerebrospinal fluid, despite that some patients never having had a history of herpes zoster infection before. Two patients had a positive CMV PCR, one from blood and the other from an unspecified source [6-13]. There was one patient with PORN who had a positive PCR for both HSV and CMV. Presumed CMV retinitis and PORN was ultimately diagnosed [14]. Currently, PCR of the intraocular fluid remains a main laboratory technique to confirm viral retinitis infection in the posterior segment with a sensitivity of 80%–88% [15]. However, in our case, a negative viral PCR result in typical clinical presentation may be the result of treatment with antiviral medication that can result in lower viral replication that PCR might not detect. It should be noted that a history of immune status, clinical presentation, and careful serial fundus evaluations are important clues for the diagnosis of PORN, even if the laboratory PCR is negative. Although PCR has high sensitivity for HSV, VZV and CMV, false negative results may also occur if there is a low inoculum in the clinical specimen or an inadequate sample [16].

Optimal treatment of PORN with optic neuropathy remains unclear. The treatment usually includes systemic acyclovir, intravenous followed by the oral route [9]. Some reports show the excellent visual recovery after combined intravenous steroid and acyclovir treatment [13, 17].

Conclusion

We herein report the rare case that presented with bilateral retrobulbar optic neuritis before retinal findings that may cause misdiagnosis and wrong initial treatment. The diagnosis is very challenging. Therefore awareness of PORN in immuno-compromised patients presented with bilateral retrobulbar optic neuritis and prompt treatment will be beneficial.

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