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CASE REPORT

Frosted branch angiitis caused by Varicella Zoster virus in an immunocompetent patient

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ABSTRACT

Introduction: Frosted branch angiitis(FBA) is a panuveitis with sheating of all retinal vesssels.

Case presentation: Herein we report an immunocompetent person who presented with fever, headache, atypical rash, and hazy vision. Ophthalmoscopy of both eyes revealed perivascular sheathing with frosted branch angiitis pattern in veins, patchy retinal hemorrhages. Aqueous PCR analysis turned positive for VZV.

Discussion: This case illustrates that VZV should be considered in the differential diagnosis of retinal perivasculitis. Since a rapid and accurate diagnosis is crucial for prompt administration of antiviral therapy, PCR-based analysis of aqueous humor is a valuable tool for detecting viruses.

Keywords: *Varicella zoster virus;* Frosted branch angiitis; blurred vision

INTRODUCTION

Frosted branch angiitis (FBA) is a panuveitis associated with sheating of all retinal vesssels. FBA is basically divided into four different groups. The first comprises patients affected by lymphoma (e.g. large cell lymphoma) and leukemia (e.g. acute lymphoblastic leukemia). The second group includes patients with associated autoimmune disorders including systemic lupus erythematosus, Crohn's disease, Behcet disease which can have FBA as a clinical sign of the underlying disease.The third group includes patients with viral infections such as cytomegalovirus (CMV), herpes simplex (HSV), varicella zoster (VZV) or non-viral infections like toxoplasma retinochoroiditis. Finally the last group comprises patients with acute idiopathic disorder (1,2).

ARN is caused mainly by VZV and HSV, and patients present by decrease in vision, photophobia, and eye pain (3). FBA secondary to viral infection can progress to acute retinal necrosis with poor and permanent damage to vision (4,5). Vasculitis may be an important mechanism in development of acute retinal necrosis(ARN).

The treatment of FBA aims to prevent further damage by VZV and HSV infection. We describe a 33-year-old woman who was diagnosed with a severe case of meningitis and eye infection by VZV. Treatment by corticosteroid and acyclovir preserved the patient's vision.

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CASE PRESENTATION

A 33-year-old woman was seen by a clinician because of fever, chills, myalgia and arthralgia that started 2 weeks prior to the visit. After 5 days, she developed maculopapular rash on her abdomen and right flank. She was treated with levofloxacin and ceftriaxone. After several days, she reported pulsatile headache, nausea, vomiting and progressive blurring of her vision and was admitted to Rasoul-e-Akram Hospital in Tehran, Iran.

She had no history of rheumatic disease but had recurrent oral ulcerations whose frequency was less than 3 times per year. She contracted chicken pox 15 years before. She was not smoker or had no use of alcohol or illicit drugs. She admitted consumption of non-pasteurized dairy products. She was married, living with his husband and had a technical office job with no relevant exposure.

On examination, her temperature was 39°C, blood pressure was 110/70 mm Hg, the weight 101 kg. Her body-mass index was 34.6 (BMI: the weight in kilograms divided by the square of the height in meters. On eye examination the visual acuity was 20/2000 in both eyes). Intraocular pressure was within normal range. Anterior segment examination showed mild ciliary injection, fine granulomatous keratic precipitates and no posterior synechiae. Both eyes had mild inflammatory reactions in anterior chamber (1+ cell) and vitreous (1+ cell). In funduscopy there was diffuse and extensive retinal perivascular sheathing (mostly phlebitis) and scattered intraretinal hemorrhage along with severe macular edema in both eyes. The optic discs were swollen bilaterally with blurred margins (Fig.1). Her clinical feature was compatible with a diagnosis of frosted branch angiitis. She had limitation in abducting both of her eyes. There was no other neurologic deficit.

Based on an inconclusive initial work up, an anterior chamber paracenthesis was performed to investigate the presence of viral footsteps. Aqueous specimen was subjected to HSV, VZV and CMV PCRs and intravitreal (2000 microgram in 0.004ml) and systemic ganciclovir was given to patient because of high suspicion about CMV infection. Her symptoms and clinical condition improved significantly. Aqueous PCR analysis (qualitative) turned positive for VZV (done in a private laboratory by conventional procedure) therefore, ganciclovir switched to acyclovir 10 mg/kg every 8hr along with oral prednisolone 60 mg daily for 7 days that followed by tapering doses. No lesion was seen on brain MRI or brain CT scan. Patient's laboratory data are summarized in Table 1. Laboratory data in Table 1 show increased ALT and LDH that is usual in viral infection. CSF analysis shows patient suffered from aseptic meningitis. Tests for rheumatologic diseases (Anti-Smooth Muscle Ab, Anti-SSa, Anti-SSb, Anti-Cardiolipin IgM, IgG, Anti-B2 Glycoprotein IgM, IgG, ANA, Anti-ds DNA, Anti-CCP, ACE, RF) were negative. Tests for infectious diseases (Wright's test, Anti-Brucella IgG Ab, VDRL, R PR, Anti-Toxoplasma Ab IgM, IgG, Anti-CMV Ab IgM, IgG, Anti- VCA Ab IgM, IgG, Anti-HSV Ab 1,2 IgM, IgG, Anti-HIV Ab, HBsAg, Anti-HCV Ab, Anti VZV IgM) were negative. Serum Anti-VZV Ab IgG and VZV DNA on aqueous sample by PCR method were positive.

Fig. 1. Retinal examination showed perivascular sheathing with frosted branch angiitis pattern in veins and patchy retinal hemorrhages.

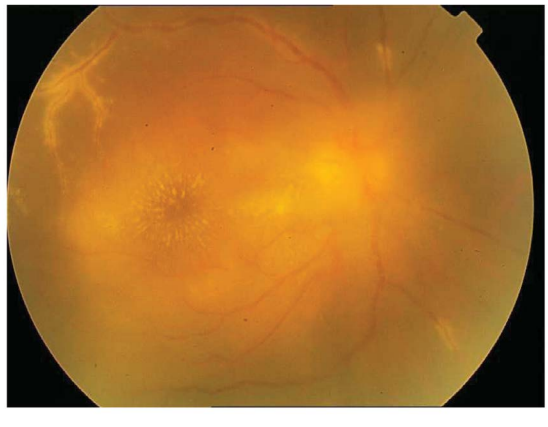

Table 1. Laboratory Data for Patient with frosted branch angiitis

Variable	Reference range	On presentation
White-cell count(per mm^3)	4,000- 10,000	4800
Hb(gr/dl)	12-16	11.3
PLT(per mm^3)	140,000-440,000	214
INR*	0.9-1	1.2
PTT	25-40	30
BUN(mg/dl)	5-23	12
Cr(mg/dl)	0.5-1.5	1.18
AST(IU/L)	6-40	40
ALT(IU/L)	6-40	80
ALK phosphatase(IU/L)	30-120	152
Total Bilirubin(mg/dl))	0.2-1.2	0.7
Direct Bilirubin(mg/dl)	0-0.4	0.27
CPK(IU/L)	60-174	159
Alb(g/dl)	3.5-5.5	3.2
Sodium(mmol/liter)	136-145	132
Potassium(mmol/liter)	3.7-5.5	3.4
Calcium(mmol/liter)	7-11	8.2
ESR(mm/hr)	<20	61
LDH(IU/L)	225-500	765
Urinalysis		Normal
CSF analysis		
		WBC 350/mm^3(PMN55%)
		RBC 1700mm^3
		GLU 47mg/dl
		Pro 161mg/dl
		CSF pressure 19cm/H2O
		Gram's stain Negative

*INR: International normalized ratio

One week later, the patient's systemic condition improved, however, no significant improvement in visual acuity was noticed. Repeated ocular coherence tomography (OCT) revealed the persistence of macular edema in both eyes. Therefore, the second intravitreal ganciclovir injection (2000 microgram in 0.004 ml) was combined with intravitreal bevacizumab injection (1.25 mg in 0.05 ml).

Two weeks after second injection, the visual acuity improved to 20/1000 and 20/1000, bilaterally. Anterior chamber and vitreous reaction decreased and vascular sheathing and macular edema resolved partially. Parenteral acyclovir was replaced by oral valacyclovir (12 weeks) and systemic corticosteroid was tapered off gradually over a month. The clinical improvement continued up to last visit (6 month after injection).

DISCUSSION

Herein we report a case of an immunocompetent person who presented with VZV meningitis and FBA. Frosted branch angiitis is a rare disease characterized by visual disturbance associated with anterior chamber and vitreous inflammation and severe sheathing of retinal vessels resembles the

appearance of frosted branches of a tree. FBA can be associated with ocular and systemic diseases (2).

It is postulated that the clinical picture of FBA can be caused by direct invasion of infective agent or secondary to immunologic response. Shenoy *et al.* reported a 26-year-old lady who presented with fever, headache and sudden loss of vision in her right eye. Fundus examination showed a yellow infiltrate above the fovea with minimal surrounding retinal edema in the right eye. There was no vitreous exudate or hemorrhage. She was diagnosed as acute HSV infection by positive IgG and IgM antibodies to HSV (6). In our case, the initial examination and fluorescein angiography findings was compatible with a diagnosis of FBA. However, the haze media prevents us to examine the peripheral retina completely to detect any probable area of retinal necrosis. Together with systemic antiviral therapy, an intravitreal injection of ganciclovir was administered at same session after anterior chamber paracenthesis to further combat any undetected area of retinal necrosis.

Our case proves that FBA is only a descriptive fundus finding and not a disease entity by itself and physicians must try to identify a possible etiology. VZV, HIV, EBV, CMV, Rubella, toxoplasma and streptococci group A can be the triggering antigen source, so only after effective and proper antiviral coverage, systemic steroid would result in controlling inflammation (7).

The reactivation of VZV infection in immunocompetent persons that presented by aseptic meningitis or other neurological disease with or without rash, is reported previously (8). Given the atypical rash in our patient, we didn't think of VZV reactivation at the outset which resulted in delayed institution of antiviral agent. Therefore, awareness of the protean VZV manifestations is of utmost importance to prevent permanent damage.

Diagnosis of VZV-induced neurological and ocular disease may be facilitated by using PCR technology to detect VZV DNA in CSF and aqueous humor of patients with uveitis. Anterior chamber paracentesis is easy and without serious complications (9,10).

Unfortunately, we didn't look for anti-VZV antibody in the CSF that is thought to be superior to the detection of VZV DNA in CSF in the diagnosis of VZV meningoencephalitis (11).

In our case, the initiation of the systemic steroid together with anti-viral agent improved her systemic condition as well as intraoculr inflammation. The anterior chamber and vitreous inflammation subsided, vascular sheathing resolved and retinal hemorrhages gradually disappeared. However, the visual acuity did not improved because of the presence of a recalcitrant macular edema. Intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) has been widely used in recent years to treat macular edema secondary to diabetic retinopathy, central and branch retinal vein occlusion and uveitis. Because of inheriting immunosuppressive potential of anti-VEGF agent, we combined bevacizumab intravitreal injection, with ganciclovir intravitreal injection from a different site, to prevent potential chance of viral proliferation and invasion.

Most patients with FBA have been treated with systemic steroids and acyclovir has been used with unknown effect because herpes virus group may cause frosted branch retinal angiitis(1,12).

In our patient with blurred vision, aseptic meningitis, positive PCR for VZV in aqueous humor and positive serum varicella IgG, the diagnosis of reactivation of VZV is confirmed. This case illustrates that VZV should be considered in the differential diagnosis of retinal perivasculitis.

Ziyaeyan showed that a significant proportion of children and adults are at risk of VZV infection (13) so, VZV vaccine should be incorporated in childhood vaccination program in Iran.

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