Progressive outer retinal necrosis after rituximab and cyclophosphamide therapy

Mohit Dogra, Priya Bajgai, Ashok Kumar, Aman Sharma

We report a case of progressive outer retinal necrosis (PORN) in a patient of microscopic polyangitis (MPA), being treated with immunosuppressive drugs such as cyclophosphamide and rituximab. Her aqueous tap was positive for Varicella Zoster virus and she was treated with oral and intravitreal antivirals, along with discontinuation of one of the immunosuppressive agents, i.e. rituximab, which might have led to reactivation of the virus causing necrotizing retinitis lesions. Rituximab and cyclophosphamide are extremely potent drugs, which are necessary to manage immunological disorders such as MPA. However, they may predispose the patient to serious complications like viral infections, including PORN.

Key words: Cyclophosphamide, progressive outer retinal necrosis, rituximab, viral retinitis

Varicella zoster virus (VZV)-induced progressive outer retinal necrosis (PORN) is a devastating ocular complication responsible for severe visual loss, occurring almost exclusively.

In patients with AIDS.[1] Intraocular inflammation and vasculitis are usually absent, which differentiates PORN from VZV-induced acute retinal necrosis (ARN) affecting nonimmunosuppressed patients.[2] Although PORN was first described in a human-immunodeficiency virus (HIV) positive patient in 1990, cases have been reported in HIV-negative patients treated with immunosuppressive therapies as well.[3]

Rituximab is a B-cell-depleting anti-CD20 monoclonal antibody that is increasingly being used to treat autoimmune disorders and B-cell non-Hodgkin lymphoma.[4,5] The rituximab versus cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis (RAVE) trial strongly supports rituximab as an alternative/adjunct to cyclophosphamide for the treatment of relapse of microscopic polyangiitis (MPA).[6] As with other immunosuppressive agents, there is a risk of opportunistic infections, including herpes viruses.[7,8] Schuler *et al*. reported a case of ARN in a patient of rheumatoid arthritis with scleromalacia following rituximab therapy.[9]

We report a potential association between use of rituximab and cyclophosphamide in a patient of MPA and development of PORN.

Case Report

A 52-year-old Indian female presented with profound diminution of vision in both eyes of 2-week duration. She was a known case of MPA for the last 3 years. Her anti-nuclear antibody and anti-myeloperoxidase antibody were positive and renal biopsy showed pauci-immune chronic glomerulonephritis. She was treated with cyclophosphamide infusion 900 mg for 10 monthly pulses followed by oral azathioprine 150 mg once a day and tapering doses of oral prednisolone with good response. She had a relapse 2 months before her ocular complaints for which she received rituximab infusion 1 g followed by 2nd cycle, 2 weeks later. One month post-2nd cycle of rituximab patient developed diminution of vision in the right eye (RE) first followed by left eye, a week later. On presentation to us, her best corrected visual acuity (BCVA) was no light perception in the RE and 20/200 in the left eye. There was no associated pain, redness, or floaters. Anterior segment examination showed a relative afferent pupillary defect in the RE with quiet anterior chamber in both eyes. Fundus examination revealed grade 1 media clarity, multiple whitish creamy lesions with ill-defined margins involving the peripheral and outer retina with absence of any vitreous inflammation in both the eyes with disc pallor in the RE [Fig. 1]. In view of necrotizing retinal lesions involving peripheral and outer retina a working diagnosis of herpes virus induced PORN was made and the patient was admitted. She was started on intravenous acyclovir 750 mg three times a day along with oral aspirin 150 mg once a day. Oral azathioprine 150 mg OD was continued and rituximab was stopped, after consultation with a rheumatologist. Low-dose oral steroids (0.5 mg/kg body weight) were added 2 days after starting acyclovir.

Laboratory investigations revealed leucopenia with mild anemia. Serum IgG was positive for both cytomegalovirus (CMV) and herpes simplex virus (HSV), while other investigations were normal, including IgM for CMV and HSV. The patient was continued on intravenous acyclovir; however, there was deterioration in the left eye. Left eye BCVA decreased to 1/60 with increase in number of retinitis lesions along with confluence of lesions in both eyes [Fig. 2]. At this stage, anterior chamber tap was done from the RE and it showed the presence of VZV DNA by polymerase chain reaction [Fig. 3]. Intravitreal ganciclovir (2.0 mg/0.1 ml) was injected in the left eye and systemic acyclovir was continued. After 14 days of systemic acyclovir and 4 intravitreal injections of ganciclovir, the retinitis lesions in both eyes healed and BCVA in the left eye improved

Access this article online

Quick Response Code:

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_811_17

Advanced Eye Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Correspondence to: Dr. Mohit Dogra, Advanced Eye Centre, Post Graduate Institute of Medical Education and Research, Sector 12, Chandigarh - 160 012, India. E-mail: mohit_dogra_29@hotmail.com

Manuscript received: 01.09.17; Revision accepted: 22.12.17

Cite this article as: Dogra M, Bajgai P, Kumar A, Sharma A. Progressive outer retinal necrosis after rituximab and cyclophosphamide therapy. Indian J Ophthalmol 2018;66:591-3.

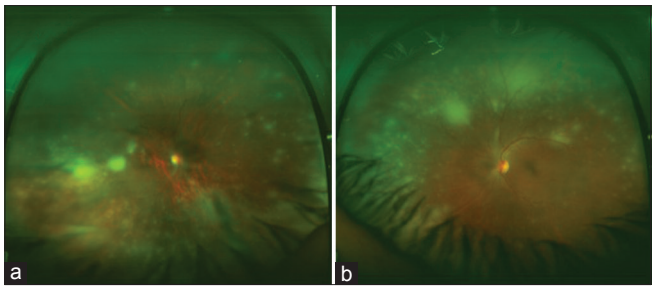

Figure 1: Fundus pictures of both eyes at presentation showing multiple whitish creamy lesions with ill-defined margins involving the peripheral, mid peripheral and outer retina while sparing the retinal vessels. Right eye shows temporal disc pallor and left eye shows a healthy disc (a and b)

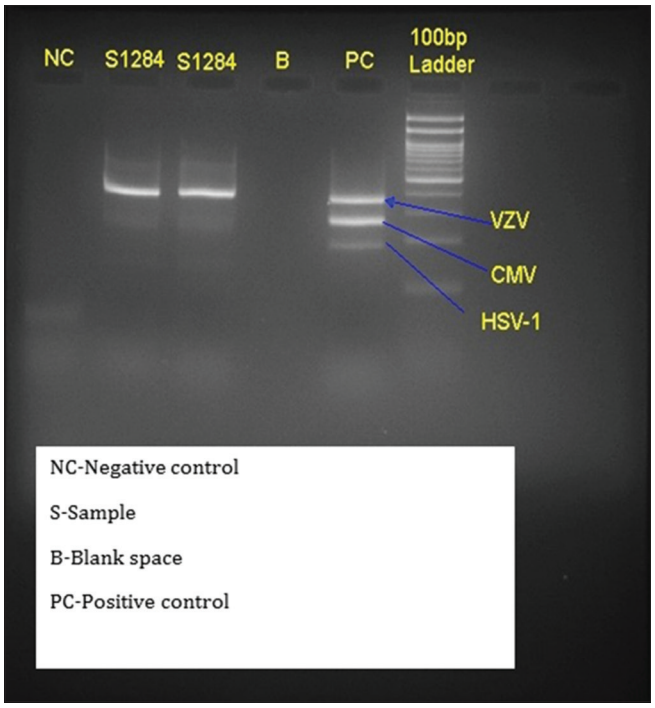

Figure 3: Polymerase chain reaction showing Varicella Zoster virus genome positivity from aqueous tap

to 3/60. At this juncture, she was started on oral valacyclovir 1 g three times a day and intravenous acyclovir was stopped. Oral steroids were tapered while azathioprine was continued, after consultation with a rheumatologist. At 3-month follow-up, the patient maintained BCVA of 3/60 in the left eye with no recurrence and healed retinitis lesions in both eyes [Fig. 4].

Discussion

Rituximab is an anti-CD20 antibody which is increasingly been used to treat immunological disorders. Use of cyclophosphamide has declined, owing to the fear of secondary malignancies and sterility, and it is now reserved for severe attacks and attacks not responding to other immunosuppressive agents.[6] Our patient had a clinical, immunological, and pathological diagnosis of MPA with renal and pulmonary involvement. As she had a very severe attack, cyclophosphamide was used along with azathioprine. However, after she had a relapse 10 months later, rituximab was used owing to its favorable safety profile as compared to cyclophosphamide. The patient developed PORN lesions in both eyes, RE followed by the left, 1 month after 2nd rituximab infusion.

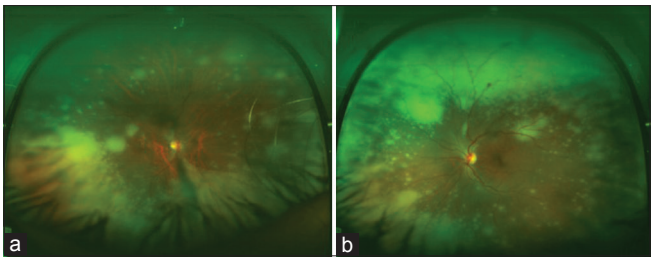

Figure 2: Fundus pictures of both eyes, 4 days after starting intravenous acyclovir, showing appearance of new retinitis lesions and confluence of old lesions (a and b)

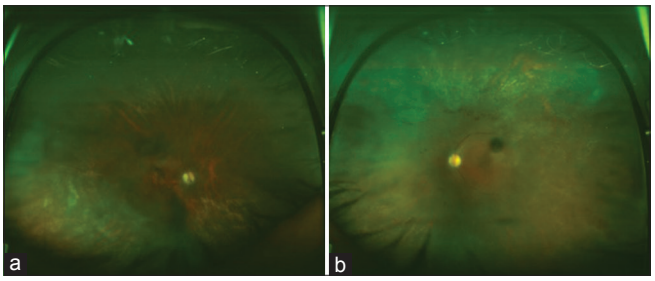

Figure 4: Fundus pictures at 3 months showing healed retinitis lesions represented by atrophic retina in the periphery and mid periphery, vitreous degeneration and disc pallor in both eyes (a and b)

Management of PORN includes both intravenous and intravitreal antiviral therapy and is aimed at prevention of second eye involvement, reducing incidence of retinal detachment, and causing resolution of retinitis lesions.[10] Our patient presented late when her left eye got involved, so we could not salvage her RE. Intravitreal ganciclovir and intravenous acyclovir were administered to our patient and led to resolution of retinitis lesions in both eyes and preservation of vision in the left eye without any recurrence over the next 3 months.

Conclusion

To the best of our knowledge, this is the first reported case of PORN in a patient of MPA, who was being managed with rituximab and cyclophosphamide, successfully treated with intravenous and intravitreal antiviral therapy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Engstrom RE Jr., Holland GN, Margolis TP, Muccioli C, Lindley JI, Belfort R Jr., *et al.* The progressive outer retinal necrosis syndrome. A variant of necrotizing herpetic retinopathy in patients with AIDS.

Ophthalmology 1994;101:1488-502.

2. Austin RB. Progressive outer retinal necrosis syndrome: A comprehensive review of its clinical presentation, relationship to immune system status, and management. Clin Eye Vis Care 2000;12:119-29.
3. Forster DJ, Dugel PU, Frangieh GT, Liggett PE, Rao NA. Rapidly progressive outer retinal necrosis in the acquired immunodeficiency syndrome. Am J Ophthalmol 1990;110:341-8.
4. Miserocchi E, Pontikaki I, Modorati G, Gattinara M, Meroni PL, Gerloni V, *et al*. Anti-CD 20 monoclonal antibody (rituximab) treatment for inflammatory ocular diseases. Autoimmun Rev 2011;11:35-9.
5. Huerva V, Sanchez MC, Traveset A, Jurjo C, Ruiz A. Rituximab for peripheral ulcerative keratitis with Wegener granulomatosis. Cornea 2010;29:708-10.
6. Calabrese LH, Molloy ES. Therapy: Rituximab and PML risk-informed decisions needed! Nat Rev Rheumatol 2009;5:528-9.
7. Kroll JL, Beam C, Li S, Viscidi R, Dighero B, Cho A, *et al*. Reactivation of latent viruses in individuals receiving rituximab for new onset type 1 diabetes. J Clin Virol 2013;57:115-9.
8. Aksoy S, Harputluoglu H, Kilickap S, Dede DS, Dizdar O, Altundag K, *et al*. Rituximab-related viral infections in lymphoma patients. Leuk Lymphoma 2007;48:1307-12.
9. Schuler S, Brunner M, Bernauer W. Rituximab and acute retinal necrosis in a patient with scleromalacia and rheumatoid arthritis. Ocul Immunol Inflamm 2016;24:96-8.
10. Cunningham ET Jr., Wong RW, Takakura A, Downes KM, Zierhut M. Necrotizing herpetic retinitis. Ocul Immunol Inflamm 2014;22:167-9.