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# Progressive Outer Retinal Necrosis and Immunosuppressive Therapy in Myasthenia Gravis

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## Key Words

Retinitis · Progressive outer retinal necrosis · Varicella zoster retinitis

## Abstract

**Introduction:** Progressive outer retinal necrosis (PORN) is a rare but devastating infectious retinitis associated with varicella zoster virus (VZV) and responsible for severe visual loss.

**Case Report:** A 59-year-old man treated for generalized myasthenia with oral azathioprine and prednisone presented with severe unilateral necrotizing retinitis. Polymerase chain reaction of the aqueous and vitreous humors was diagnostic for VZV PORN. **Conclusion:** VZV PORN is a severe potential ocular complication of immunosuppression, prompting urgent diagnosis and appropriate treatment.

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## Introduction

Varicella zoster virus (VZV) progressive outer retinal necrosis (PORN) is a devastating ocular complication responsible for severe visual loss, occurring almost exclusively in patients with AIDS. Affected patients complain of blurring vision or vague visual loss (54%), constriction of the visual field or loss of peripheral vision (28%), floaters (1%), pain (6%), or are asymptomatic (11%) [1]. The fundoscopic examination is characterized by multifocal retinal opacities starting at the peripheral retina, involving the posterior pole in 30% of cases, being rapidly coalescent and progressing to complete retinal necrosis [1, 2]. The retinitis tends to be bilateral with time (61% of patients), i.e. within 4 weeks in the study by Engstrom et al. [1]. Intraocular inflammation and vasculitis are usually absent, which differentiates PORN from VZV acute retinal necrosis affecting non-immunosuppressed

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patients [3]. The diagnosis is based on isolating VZV DNA by polymerase chain reaction in the aqueous and/or vitreous humor [3]. Even if this affection was first described in a human immunodeficiency virus (HIV)-positive patient in 1990 by Forster et al. [4], a few cases have been reported in HIV-negative patients treated with immunosuppressive therapies.

Here we report a case of VZV PORN in a patient treated with immunosuppressive therapies for a generalized myasthenia.

## Case Report

A 59-year-old man was admitted with unilateral progressive visual loss in the right eye occurring over the last 7 days and evolving to counting fingers. He had been diagnosed with generalized myasthenia 2 years earlier and during the last 20 months he had been treated with oral prednisone (60 mg/day at first for 4 weeks with subsequent tapering down to 20 mg/day, which was his regimen during 14 months). Oral azathioprine (150 mg/day) was added 1 month prior to visual loss to treat complete ophthalmoplegia and ptosis in the left eye. The right eye's intraocular pressure was 18 mm Hg. There was no corneal opacity and no iris anomaly. Ophthalmic examination of the right eye disclosed no anterior chamber inflammation and no retinal vasculitis; however, mild vitritis, an optic disc edema and macular and peripheral necrotizing retinitis in the right eye (fig. 1, fig. 2). Visual acuity of the left eye was 20/20, and the remainder of the ophthalmic examination was normal. Polymerase chain reaction of the aqueous and vitreous humors performed in the right eye was positive for VZV and negative for cytomegalovirus and herpes simplex virus 1 and 2. The diagnosis was consistent with VZV PORN. HIV serology was negative, and the CD4 lymphocyte count (1,389/mm<sup>3</sup>) and CD4/CD8 ratio (1.74) were normal. Lumbar puncture and cerebral MRI found no signs of central nervous system zoster meningitis, encephalitis or vasculitis. Oral azathioprine therapy was discontinued, and steroid doses were progressively decreased. Two intravitreal injections of ganciclovir were followed by 10 intravitreal injections of foscarnet. High doses of intravenous foscarnet (180 mg/kg/day) and acyclovir (30 mg/kg/day) were also administered. As acute renal failure occurred after 2 weeks, foscarnet was discontinued and half of the dose of acyclovir was given for one more week. The patient was then discharged on oral acyclovir (15 mg/kg/day) for 3 months. After 10 months of follow-up, his best vision was counting fingers in the right eye and 20/20 in the left eye. The patient had no other ocular complications such as retinal detachment.

## Discussion

The main finding of this report is that VZV PORN can occur in a patient affected by another ophthalmic condition, i.e. ocular myasthenia gravis. The retinal symptoms could have been initially misleading, but the immunosuppressed status of the patient prompted the exploration of PORN in this non-HIV-infected patient. The patient's symptoms (painless rapidly progressive visual loss), the appearance of retinal lesions (multifocal, coalescent and peripheral), the lack of anterior and posterior inflammation, the lack of response to treatment and the presence of VZV in aqueous and vitreous humors without another herpes virus (cytomegalovirus, herpes simplex virus) were typical of PORN [1–4], in a context of immunosuppressive treatments recently introduced with azathioprine and prednisone. The context of recently introduced azathioprine associated with corticosteroids supports this diagnosis. It is well known that the use of azathioprine and/or steroids is associated with an

increased risk of herpes zoster, and that this association is stronger among new users than persistent users of these drugs [5, 6].

Indeed, this case is illustrative of a rare but serious complication of immunosuppressive therapy. To our knowledge, no other case of VZV PORN in a patient with another ophthalmic condition and/or with azathioprine has been reported. Only 10 other cases secondary to immunosuppressive therapies have been described (table 1) [6–17], but none secondary to azathioprine and none in a patient treated for myasthenia. The patients described in table 1 were treated for allogeneic stem cell transplants [7–10], idiopathic thrombocytopenic purpura [11], cutaneous non-Hodgkin's lymphoma [12], rheumatoid arthritis [13, 14], multiple sclerosis [13], nephrotic syndrome [15] and lymphocytic lymphoma [16]. Another case has been reported on a non-HIV patient with a transient decrease in CD4 lymphocyte count and CD4/CD8 ratio, who has been treated at first with prednisolone only (table 1) [17]. The reports on patients after stem cell transplantation were all bilateral and associated with disseminated cutaneous herpes zoster or local cutaneous VZV (table 1) [7–10]. The reports on patients with rheumatoid arthritis and on the one patient with idiopathic thrombocytopenic purpura were also bilateral [11, 13, 14]. PORN tends to be bilateral with time in HIV patient series (61–70% of patients) [1, 2], which was not the case in our patient. In addition, our patient could not report a previous or concurrent extraocular VZV manifestation, unlike 67–75% of patients in HIV patient series [1, 2]. Unfortunately, no VZV PORN cases in non-HIV patient series are available, probably because they are too rare. No accurate data as in HIV patients is available to assess how often the retinitis is bilateral in these patients. However, a careful monitoring of the other eye seems essential to detect PORN and to treat it early.

The current recommendations for PORN include antiviral intravitreal injections 3 times a week for 2 weeks (ganciclovir or foscarnet), followed by injections once or twice a week until the retinitis is stabilized. High doses of intravenous antiviral double therapy (ganciclovir or valganciclovir at induction doses for 3 weeks and foscarnet at induction doses for 2 weeks) are required to protect the other eye and the central nervous system, followed by maintenance antiviral therapy (oral valganciclovir and intravenous foscarnet) until complete healing. Oral valganciclovir or valacyclovir can then be continued [18]. Our patient was treated twice a week with intravitreal antiviral injections and intravenous high doses of antivirals (foscarnet and acyclovir) during 2 weeks and with half of the doses of intravenous acyclovir for 1 additional week. The visual outcome in HIV-patients is poor: 67 and 49% of patients had a final visual acuity of 'no light perception' within 4 weeks and 6 months after the initial diagnosis, respectively [1, 2]. The visual outcome may be better in patients treated with more than 1 intravenous antiviral agent, and even more so when using both intravenous and intravitreal antiviral agents [18]. In Scott et al.'s study, 45% of eyes treated with both intravitreal and intravenous antivirals had a final visual acuity of 20/80 or better [18].

One of the aims of the treatment in our patient was to prevent the involvement of the left eye and to preserve the right eye from retinal detachment. Indeed, about 70% of eyes develop rhegmatogenous retinal detachment [1, 2] within a median time of 30 days to 3 months after presentation [3]. Without laser treatment, our patient did not develop retinal detachment after 10 months; indeed, prophylactic demarcating laser treatment is controversial in this setting [3, 18].

## Conclusion

VZV PORN is a devastating ocular complication, typically occurring in severely immunosuppressed patients (in particular HIV patients) and characterized by multifocal peripheral and posterior retinal lesions which rapidly coalesce without anterior inflammation and vasculitis. In a patient with visual loss, while on longstanding immunosuppressive therapy, PORN is a rare albeit possible cause, beyond several common diagnoses (i.e. keratitis, uveitis, toxoplasmosis, syphilitic chorioretinitis), which needs prompt treatment. Thus, a careful examination of the peripheral retina is required for an early diagnosis. A delayed diagnosis may result in retinal necrosis and detachment, affecting both eyes and potentially leading to irreversible blindness. The treatment requires antiviral intravitreal injections and intravenous therapy.

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**Table 1.** Case reports of PORN in non-HIV patients treated with immunosuppressive therapies

Ref.	Cases, n	Unilateral/bilateral	Diagnosis	Immunosuppressive therapy	PORN treatment
[10]	1	Bilateral	Acute lymphoblastic leukemia	Hematopoietic stem cell transplantation and steroids	Intravenous ganciclovir and foscarnet, followed by intravenous cidofovir and intravitreal foscarnet
[7]	1	Bilateral	Acute myeloid leukemia	Methylprednisolone, ciclosporin, mycophenolate mofetil, anti-thymocyte globulin for stem cell transplantation	Intravitreal ganciclovir and intravenous high-dose acyclovir
[9]	1	Bilateral	Refractory anemia with excess blasts type 1	Ciclosporin, prednisolone, mycophenolate mofetil after stem cell transplantation	Intravenous foscarnet, ganciclovir and cidofovir, intravitreal foscarnet injections and 1 dose of human immunoglobulin (0.4 g/kg)
[8]	1	Bilateral	T-lymphoblastic lymphoma	Thiotepa, fludarabine and anti-thymocyte globulin for stem cell transplantation	Intravenous and intravitreal foscarnet
[17]	1	Unilateral	Transient immune deviation	Prednisolone	Intravitreal foscarnet injection, intravenous acyclovir
[13]	2	Unilateral/bilateral	Multiple sclerosis/rheumatoid arthritis	Steroids	Intravenous acyclovir, intravitreal injections of ganciclovir and foscarnet
[16]	1	Unilateral	Small lymphocytic lymphoma	Corticosteroids and alkylating agent therapy (chlorambucil and cyclophosphamide)	Intravenous foscarnet and ganciclovir, intravenous gammaglobulin (0.5 mg/kg/day) for 5 days and oral decadron (16 mg/day)
[15]	1	Unilateral	Nephrotic syndrome	Prednisolone	Intravenous high-dose acyclovir
[11]	1	Bilateral	Idiopathic thrombocytopenic purpura	Methylprednisolone, gammaglobulin, vincristine	Intravenous acyclovir
[12]	1	Unilateral	Cutaneous non-Hodgkin's T-cell lymphoma	Chlorambucil and prednisone	Intravenous acyclovir
[14]	1	Bilateral	Rheumatoid arthritis	Chlorambucil and prednisone	Intravenous acyclovir



**Fig. 1.** Fundus appearance of the right eye showing multifocal retinal opacities and superficial retinal hemorrhages involving the posterior pole. There is an associated optic disc swelling and mild vitritis.



**Fig. 2.** Right retinal photograph showing multifocal and coalescent retinal opacities in the temporal retina.