

Short communication

# Progressive outer retinal necrosis in the era of highly active antiretroviral therapy: Successful management with intravitreal injections and monitoring with quantitative PCR

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## Abstract

**Background:** Progressive outer retinal necrosis (PORN) is an ocular disease in individuals with AIDS and is associated with substantial morbidity. The optimal management of PORN and its clinical course in the HAART era is unclear.

**Objective:** We report a case of successfully managed PORN that provides insight into the monitoring and treatment of this disease.

**Study design:** Intravitreal injections and intravenous therapy targeted towards varicella zoster virus (VZV) were used to treat PORN. HAART was initiated for HIV-1 therapy. Serial PCR for VZV was performed on aqueous humor to monitor the clinical course.

**Results:** The presence of VZV DNA from aqueous humor correlated with clinical exacerbations of disease. Initiation of twice weekly intravitreal injections with dual antiviral drugs appeared to be an important therapeutic intervention that resulted in remission of PORN. Secondary prophylaxis against VZV was successfully withdrawn after HAART induced partial immune recovery.

**Conclusion:** In addition to aggressive therapy with intravitreal injections, HAART and quantitative measurements of VZV DNA from aqueous humor have important roles in the management of PORN. A multidisciplinary approach involving specialists in infectious diseases, ophthalmology, and clinical microbiology will improve the chances for successful long-term outcomes.

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**Keywords:** AIDS; HIV-1; Varicella Zoster virus; HAART; Acute retinal necrosis syndrome; retinitis

## 1. Introduction

Progressive outer retinal necrosis (PORN), also known as rapidly progressive herpetic retinal necrosis (RPHRN) (Ormerod et al., 1998), causes devastating vision loss and

is difficult to treat. It was first described as a unique clinical entity that occurred almost exclusively in patients infected with human immunodeficiency virus 1 (HIV-1) (Forster et al., 1990). PORN is distinguished from acute retinal necrosis (ARN) early in its course by PORN's minimal inflammatory features seen in the aqueous and vitreous humor, sparing of retinal vasculature, and multiple peripheral lesions that clinically appear to be located in the outer retina. However, lesions can rapidly coalesce, cause full thickness retinal necrosis, and subsequent retinal detachment. In the majority

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of cases, PORN occurs in patients co-infected with HIV-1, and Varicella Zoster virus (VZV) is usually the causative agent.

Although some small case series have described limited success with systemic antivirals alone (Ciulla et al., 1998; Spaide et al., 1996), others have shown that this is insufficient for the long-term management of PORN (Engstrom et al., 1994; Galindez et al., 1996). There is little information in the ophthalmologic or infectious disease literature to guide management of PORN in the highly active anti-retroviral therapy (HAART) era, where the number of patients surviving beyond their initial diagnosis of AIDS and associated opportunistic infections has increased. Therefore, it is important to understand the clinical course of PORN during HAART-induced immune recovery, and to establish the clinical utility of PCR amplification of VZV DNA from aqueous humor samples.

We describe the case of an antiretroviral-naïve HIV-1 infected patient with bilateral PORN who sustained a favorable outcome in one eye via management with HAART, intravenous plus intravitreal dual antiviral treatment directed against VZV, and aqueous humor quantitative VZV PCR monitoring.

## 2. Case report and results

A thirty-year-old woman from Thailand with a history of an episodic vesicular rash on her buttocks since age 18, was diagnosed with AIDS in 2002 (CD4 count: 69 cells/mm<sup>3</sup>, HIV viral load (VL): 60,000 copies/mm<sup>3</sup>). She had declined antiretroviral therapy and remained without symptoms until October 2003 when a clinical diagnosis of right buttock cutaneous zoster was made at an outside institution. She developed tearing and photophobia in the right eye (OD: oculus dexter) shortly afterward, and was treated with a 2 month course of oral acyclovir and topical steroids. By report, it was thought that these episodes represented recurrence of latent VZV infection, although the possibility of Herpes Simplex virus (HSV) as the etiology could not be excluded.

However, in January 2004, she developed a rapid deterioration of vision OD, and was referred to our institution. The retinal exam was consistent with unilateral PORN OD (Table 1). DNA from VZV was amplified from aqueous humor OD by qualitative PCR (40–140 µl aqueous humor brought up to 200 µl with phosphate buffered saline; DNA extraction by NucliSens Isolation Kit (bioMerieux, Inc., Durham, NC) to final elution volume of 50 µl). Amplification of cytomegalovirus (CMV), HSV-1, and HSV-2 was negative (PCR primers and FRET probes specific for each of these have been described elsewhere (Cortez et al., 2003; Marques et al., 2001)). There was no evidence of PORN in the left eye (OS: oculus sinister), but a single, hypo-pigmented, atrophic scar of uncertain significance lateral-temporal to the vascular arcades was noted (Fig. 1A). Except for a CD4 count of 34 cells/mm<sup>3</sup> and mild anemia, the remaining physical exam,

basic laboratory tests, and imaging studies were unrevealing. RPR, hepatitis serologies, mycobacterial culture, toxoplasma serologies and PPD were negative.

On admission, induction therapy was initiated with intravenous (IV) foscarnet (90 mg/kg) twice daily, IV ganciclovir (5 mg/kg) twice daily (Galindez et al., 1996; Kuppermann et al., 1994; Moorthy et al., 1997; Morley et al., 1994; Ormerod et al., 1998), and twice weekly intravitreal injections OD of ganciclovir (2 mg/0.05 ml) and foscarnet (1.2 mg/0.05 ml) (Roig-Melo et al., 2001; Scott et al., 2002). Ganciclovir was switched to oral valganciclovir (900 mg twice daily) on hospital day 4 (Martin et al., 2002; Peck et al., 2003). HAART was also initiated (stavudine, lamivudine, lopinavir/ritonavir). However, despite 3 weeks of therapy, right eye vision was deemed unsalvageable. A new concern arose when a new left eye lesion was first noted (Day 20). This necrotic, white lesion with surrounding edema in the outer retinal layers, occurred adjacent to the atrophic scar described at admission and was consistent with a new diagnosis of OS PORN (Fig. 1B). Fortunately, vision remained stable at 20/20. Intravenous foscarnet was continued at induction doses, valganciclovir was changed back to twice daily IV ganciclovir, and twice weekly intravitreal injections of foscarnet and ganciclovir were switched from OD to OS.

Small amounts of aqueous humor were removed at the time of intravitreal injections in order to prevent the buildup of intraocular pressure. VZV quantification of OS aqueous humor was used as an adjunct to ophthalmologic exams to track the clinical disease course and response to treatment in the left eye over the next 4 months, with 16 samples collected between Days 24 and 151. Primers VZV-gb-1 (5'-CGG-TGC-GAA-CAC-GGG-AGT-ATC-CTC-G-3') and VZV-gb-2 (5'-ATC-CCT-TTG-CCG-AGA-AAC-CCA-ACG-C-3') were designed to amplify a 267-bp segment of the VZV glycoprotein B gene using an assay similar to what has been described previously (Larsen et al., 2002). FRET detection probes were designed to anneal with a 1-base gap between the probes. The following probes were commercially synthesized (Idaho Technology) and labeled with Red 640 as the reporter: VZV-gb.FRET.up (5'-CAG-ATA-CTA-ACG-TCA-TAT-ATT-TAA-TCA-TTT-C-Fluorescein 3') and VZV-gb.FRET.dn (5'-Red640-TGG-GCT-TCT-CGA-AAT-TTA-TCG-GGA-TCA-AAC-Phosphate 3'). Under these conditions, 1–10 copies of VZV genomic equivalents per micro liter extracted DNA were detected using VZV whole organisms spiked in lysis buffer as a positive control. This assay shows no cross-reactivity with human genomic DNA, cytomegalovirus (CMV), HSV-1, or HSV-2, or Epstein Barr virus (EBV).

Between Days 32 and 67, no VZV PCR samples were taken because the left eye lesion appeared stable after the initial enlargement, and because three serial VZV samples on Days 24, 27 and 32 were negative. Intravitreal injections were decreased to weekly and laser photocoagulation was performed to prevent retinal detachment on Day 37. However, on Day 60, new inferior lateral extension of PORN

was noted (Fig. 1C), and injections were increased again to twice weekly. Subsequent VZV PCR on Day 67 was positive.

Serial quantitative PCR performed between Days 70 and 81 reached a maximum value of 384 copies/mm<sup>3</sup> of VZV DNA, before falling below the level of detection of <1 copy/mm<sup>3</sup> on Day 84 (remained negative on multiple assays through Day 151). On Day 81, progression of PORN OS was noted to have stopped when VZV DNA was 87 copies/mm<sup>3</sup> and CD4 count was 41 cells/mm<sup>3</sup>, and laser photocoagulation was again performed.

CD4 count gradually increased to 61 (Day 101) and 99 (Day 196). By Day 217, the patient was off all anti-VZV treatment: IV ganciclovir was tapered to once daily (Day 84) then discontinued (Day 164); IV foscarnet was tapered to once daily (Day 209) and discontinued (Day 217); and intravitreal injections were decreased to once weekly (Day 164), then discontinued after 58 administrations (Day 185). At the time of this writing, 2 years after stopping all therapy for VZV, the patient maintains 20/20 vision in her left eye, while CD4 cell count has improved to 360 cells/mm<sup>3</sup> (VL <50 copies/mm<sup>3</sup>).

Table 1  
Summary of VZV viral load, CD4 lymphocyte count, and clinical course

Day	VZV VL (copies DNA/ml <sup>a</sup> )	CD4 count (cells/mm <sup>3</sup> )	Clinical course/therapy
1			<i>R eye:</i> <b>PORN diagnosed clinically</b> ; gross movements only; intravitreal injections <sup>b</sup> initiated BIW <i>L eye:</i> no PORN; single, isolated, atrophic lesion peripherally Initiated induction IV therapy BID (FOS/ValGCV), HAART
4	R: pos (ND)	34	Discontinue IV GCV; initiate ValGCV
7	R: pos (ND)		
20			<i>L eye:</i> <b>PORN diagnosed clinically</b> Initiated IV GCV BID (discontinued ValGCV); continued IV FOS BID
24	L: neg		<i>R eye:</i> discontinued injections in R eye <i>L eye:</i> <b>Initiated intravitreal injections BIW</b> for 1st time
27	L: neg		<i>L eye:</i> lesion enlarged
32	L: neg		<i>L eye:</i> slight enlargement of lesion occurred
37			<i>L eye:</i> lesion stabilized (smaller, less confluent); <b>tapered</b> injections to once/week
60			<i>L eye:</i> <b>2nd new lesion (PORN) noted; reinitiated BIW</b> injections
63			<i>L eye:</i> lesion stabilized
67	L: pos (ND)		<i>L eye:</i> 1st <b>positive PCR</b>
70	L: pos (384)		
74	L: neg (<1)		
77	L: pos (206)		
81	L: pos (87)	41	<i>L eye:</i> all lesions stabilized
84	L: neg (<1)		Began tapering IV therapy (GCV to QD); continued IV FOS BID
87	L: neg (<1)		
90	L: neg (<1)		
97	L: neg (<1)		
101	L: neg (<1)	61	
115	L: neg (<1)		
129	L: neg (<1)		
151	L: neg (<1)		
164			<i>L eye:</i> Tapered intravitreal injections to once/week Discontinued IV GCV; remained on IV FOS BID
185			All intravitreal injections stopped
196		99	
209			Tapered IV FOS to QD
217			<b>Discontinued all therapy for VZV</b>
>600			<b>No further disease progression</b>

ND: not done; IV (intravenous); FOS (foscarnet); GCV (ganciclovir); ValGCV (oral valganciclovir); pos (positive); neg (negative); BIW (twice weekly); QD (once daily); BID (twice daily); L (left); R (right).

<sup>a</sup> Copies of VZV DNA is corrected for a total volume of 1 ml aqueous humor, as samples varied in volume.

<sup>b</sup> Intravitreal injections: include both FOS/GCV; text in bold indicate key events in clinical history.

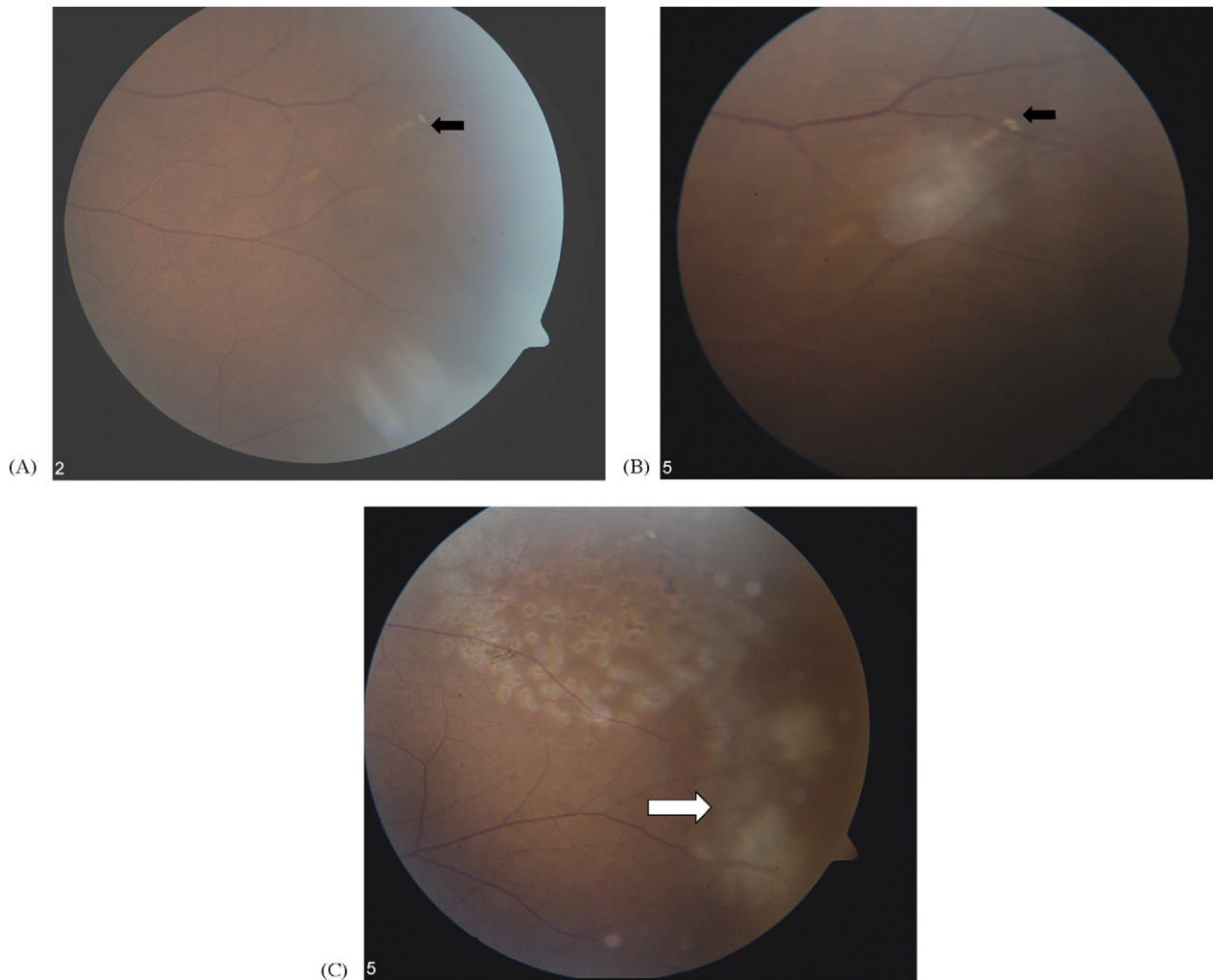


Fig. 1. Progression of PORN in left eye. (A) Day 1, hypopigmented, atrophic scar (arrow) located temporolaterally to vascular arcades. (B) Day 20, new intraretinal whitening adjacent to atrophic scar (arrow indicates scar). (C) Day 60, extension of PORN (indicated by arrow) inferior laterally to initial lesion. The uniform round scars superior to the arrow are the result of laser photocoagulation procedures.

### 3. Discussion

This report adds to the growing body of evidence that intravitreal injections are a key element in the successful management of PORN (Ormerod et al., 1998; Pavesio et al., 1995; Perez-Blazquez et al., 1997; Roig-Melo et al., 2001; Scott et al., 2002). Although intravenous or oral systemic agents may have a role in preventing visceral or central nervous system dissemination of VZV in an immunocompromised host, caution is recommended in their use, even in combination, as the sole therapy for PORN. The patient here developed PORN OS and had re-exacerbation of disease despite the use of combination systemic agents at induction doses. Progression of PORN OS attenuated only after twice weekly intravitreal injections were initiated. An attempt to taper injections to once weekly on Day 37 (CD4 count: 34 cells/mm<sup>3</sup>) was followed by a clinical exacerbation of PORN approximately 3 weeks later (first noted on Day 60). For the second time, increasing the intravitreal injections to twice weekly was

associated with disease remission. The patient received a total of 58 intravitreal injections into the left eye before successful discontinuation. We conclude that aggressive management with frequent intravitreal injections is critical for delivering effective levels of antiviral drugs to the affected eye. The length of time that these injections need to be continued is unclear.

In addition, the role of HAART in the management of HIV-1 infected patients with PORN cannot be overemphasized. In HIV-1 infected individuals, HAART-induced immune recovery can allow the safe discontinuation of primary and secondary prophylaxis for many opportunistic infections, including herpes viruses such as CMV (Whitcup et al., 1999). In our patient, all anti-VZV therapy for PORN was tapered off successfully only after a partial immune recovery on HAART occurred (CD4 count: 99 cells/mm<sup>3</sup>). It is notable that no evidence of active PORN was detected once CD4 count was 61 cells/mm<sup>3</sup> on Day 101. Thus, similar to AIDS patients with CMV retinitis who respond immunologically

to HAART, there may be a CD4 count threshold where the host immune system may be capable of controlling VZV-associated PORN. It cannot be determined from this single report nor from a review of the previous literature what this threshold might be. Previous case series demonstrate that the CD4 counts of patients diagnosed with PORN are low (20–50 cells/mm<sup>3</sup>) (Engstrom et al., 1994; Moorthy et al., 1997; Ormerod et al., 1998). However, because these were written in the pre-HAART era, there is little information correlating the clinical course of PORN with CD4 count after initiation of HAART. Two recent case reports describe PORN diagnosed at higher CD4 counts than what has been previously described. In both cases, this occurred during a period of rapid HAART induced immune recovery (Ramsay et al., 2001; Woo et al., 2004). The inability to detect VZV replication by PCR in either of the cases suggests that these may be examples of immune reconstitution syndrome rather than disease caused by active VZV replication (Hirsch et al., 2004). The case reported in this paper is one of the first to extensively document the relationship between HAART induced-improvements in CD4 count with the clinical course of PORN.

Finally, we demonstrate the utility of quantitative real time PCR in monitoring the clinical course of PORN. Our patient developed PORN in the left eye despite 3 weeks of systemic antiviral agents. VZV DNA was not detected initially, which might have been the result of antiviral therapy suppressing VZV replication below the level of detection for quantitative PCR (Asano et al., 2004; Short et al., 1997; Tran et al., 2003). However, despite the ongoing administration of systemic antivirals as well as initiation of intravitreal injections into the left eye, VZV DNA in the aqueous humor was detected at a later time-point when fundoscopic exam simultaneously demonstrated clinical exacerbation of PORN. The use of quantitative real time PCR for monitoring PORN activity has been described previously (Asano et al., 2004). Asano reported two cases of VZV ARN and one case of HSV ARN. One patient had severe VZV ARN with aqueous PCR VL of  $(4.4\text{--}5.5) \times 10^6$  copies/ml, that later became undetectable after 1 month of antiviral therapy. The other patient with VZV ARN had a much milder clinical presentation. Initial VZV VL on presentation for this patient was only 900 copies/ml, decreased to 80 copies/ml after 8 days of therapy, and became undetectable at 28 days. This work demonstrates that the quantitative VL correlates well with both severity of disease and the response to therapy. The low VZV VL seen in our patient likely reflects the effect of anti-viral therapy preventing full-blown disease and correlates with the low VL seen by Asano in their patient with mild VZV ARN. We conclude that aqueous humor quantitative PCR for VZV DNA appears to have sufficient sensitivity and specificity to warrant further investigation as a possible surrogate marker of disease progression in PORN, and demonstrate that VZV DNA can be detected even with the use of high concentrations of antiviral drugs. Repeatedly negative VZV VL loads, together with improved clinical features on ophthalmologic

exam, and HAART-induced improvements in CD4 counts together could help guide the withdrawal of therapy, as it did with our patient. On the other hand, increases in VZV VL or persistence at high levels could signal the need for more aggressive intervention.

Case reports and case series of patients with PORN will continue to provide the most useful information regarding management, given the relatively small number of cases and narrow window of time in which therapy must be initiated in order to be successful. Although the ophthalmologist's role in managing PORN is paramount, this work demonstrates that a multidisciplinary approach involving specialists in infectious diseases, ophthalmology, and clinical microbiology will improve the chances for successful long-term outcomes.

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