Case Reports
Acute retinal necrosis (ARN) in the context of neonatal HSV-2 exposure and subconjunctival dexamethasone: case report and literature review

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Summary
HSV-2 is an important cause of the acute retinal necrosis (ARN) syndrome in younger patients. We describe an atypical case of HSV-2 ARN in the context of neonatal exposure and subconjunctival steroid injection. Clinicians should be aware of the association of neonatal or congenital exposure to HSV-2 as a risk factor for this disease because early treatment may improve outcome and/or avoid involvement of both eyes.

Introduction
Acute retinal necrosis (ARN) is a potentially blinding condition, predominantly caused by varicella zoster (VZV), herpes simplex virus type 1 and 2 (HSV), and, infrequently, by cytomegalovirus (CMV).1 Clinical diagnosis is based on criteria published by the American Uveitis Society, independent of causative agent or patient immune status.2 ARN causes devastation, due not only to the fulminant vaso-occlusive retinitis but also to the high incidence of tractional and necrotic retinal tears leading to retinal detachment. Despite advances in surgical, laser, and antiviral therapy, the visual prognosis of ARN is poor, with a retinal detachment rate of up to 80%.3–4

The majority of cases of ARN, particularly HSV related, are caused by reactivation of a previous infection in immunocompetent or compromised individuals.5 In particular, ARN caused by HSV most often occurs in association with, or many years after, HSV encephalitis, meningitis, or following neurosurgery or trauma.6 We describe a case of an immunocompetent man with a history of neonatal herpes simplex virus exposure with HSV-2 ARN, the course of which was complicated by subconjunctival steroid injection.

Case Report
A previously well 30-year-old white man presented to the Ophthalmology Clinic at the Royal Brisbane and Women’s Hospital with a red, painful left eye and decreased visual acuity of 10 days’ duration. The patient had recently returned from Europe, where he had been hospitalized for 5 days with complicated left posterior uveitis, according to a translated discharge letter. During his hospitalization in Europe, the patient was diagnosed with posterior uveitis of unknown etiology and was treated with three subconjunctival injections of dexamethasone and gentamicin. Despite treatment, his vision continued to deteriorate rapidly during his admission. The patient had no history of ocular disease. He arrived at our facility with retinal photographs in hand.

On initial examination, his visual acuity was 20/80 in the left eye. Slit-lamp examination revealed a red eye with 1+ aqueous cell, mutton-fat keratic precipitates on the endothelium, and 1+ cell in the anterior vitreous. On indirect ophthalmoscopic examination, the posterior vitreous was clear and the fundus was characterized by peripapillary hemorrhages and retinitis (Figure 1A).
A presumptive diagnosis of unilateral ARN was made, based on satisfaction of the standard diagnostic criteria. Specifically, there were several foci of retinal necrosis with discrete borders in the peripheral retina showing circumferential spread. Additionally, there was evidence of occlusive vasculopathy and arteriolar involvement, with prominent anterior chamber flare. The patient had a history of unprotected male-male intercourse and was of unknown HIV status at presentation. The causative organism was thought to be CMV initially, and the patient was prescribed 350 mg intravenous ganciclovir twice daily. Symptoms did not improve over the next 48 hours, and the retinitis continued to progress. An aqueous tap was carried out for viral polymerase chain reaction (PCR) and fluorescein angiography (FA) was performed (Figure 2).

On day 3 of admission, a detachment of the peripheral retina was documented. Barrier laser was applied to the retina to arrest the detachment. Serology for HIV was negative, but PCR testing was positive for HSV-2. At this time, ganciclovir was ceased, and the patient was commenced on 840 mg intravenous acyclovir three times daily.

At day 8 of admission, the retina continued to detach inferiorly. A 3-port pars plana vitrectomy with barrier laser and insertion of silicone oil was carried out (Figure 1B).

The patient was discharged after 10 days of intravenous antiviral therapy, with a plan for 12 weeks of oral valacyclovir 1 g three times daily and topical prednisolone acetate 1% and phenylephrine 0.12% eyedrops (Prednefrin Forte; Allergan, Australia) four times daily. Visual acuity in the left eye at discharge was hand motions. The vitreous and retina of the right eye remained normal throughout treatment.

Although the patient denied any history of herpetic lesions, on further questioning, it was found that he had a twin sister who died at 8 weeks of age due to HSV-2 encephalitis.

No disease reactivation was observed during 12 months of follow-up; the patient maintained visual acuity of hand motion in the affected eye and 20/20 in his unaffected eye, with no abnormalities on clinical examination. Subsequently, he was followed at 3–6 month intervals.

**Discussion**

This case demonstrates an advanced presentation of multifocal ARN and highlights the importance of a thorough history of viral exposure in ARN patients. Typically in ARN, the peripheral retina is seen to contain the inflammatory response because of intact immune resistance to the virus. In this case, we believe that the injection of subconjunctival steroids early in the course of the disease may have altered the clinical picture. The literature describing ARN after injection of corticosteroids is limited. Toh and Borthwick propose that the presence of corticosteroids may reduce the eye’s immune response and increase the risk of infection or reactivation of dormant organisms.

Herpes simplex virus 2 is the most common cause of ARN identified in childhood, usually in children with a documented or suggested history of neonatal herpes exposure. Patients have been shown to have ARN associated with HSV-2 up to 30 years after neonatal infection, as seen in the current case. Cases of HSV-2 ARN reported in children with strongly suggestive or
documented histories of neonatal herpes infection are summarized in Table 1. Landry et al\textsuperscript{6} postulated that the risk of exposure to HSV-2 at birth would increase with increasing population prevalence of the disease. This is supported by the number of published cases of HSV-2 ARN with neonatal exposure, twice as many of which have been seen in the last decade, compared to those reported in the 1990s.\textsuperscript{3,5,6,9–21}

Although many documented cases of HSV-2 ARN in the literature have a history of neonatal exposure, some patients do not have such histories and the question of how the infection was acquired remains.\textsuperscript{21} Grose\textsuperscript{21} proposed that neonatal HSV-2 infections may be contracted perinatally as a subclinical skin, eye, or mouth infection. In particular, Grose suggests that the virus could enter via a fetal scalp monitor, conjunctiva, cornea, or nose. The viral pathogens travel to ganglia via the trigeminal or olfactory nerve, storing the potential for future reactivation in the optic nerve and retina.

Antiviral therapy is the accepted treatment for ARN, although a recent multicenter retrospective interventional series found no single treatment strategy as standard of care.\textsuperscript{22} The current recommended treatment for adults are intravenous acyclovir 10 mg/kg every 8 hours for 10 days followed by 1000 mg of oral valacyclovir three times a day for 6–14 weeks.\textsuperscript{22} The ideal duration and relative efficacy of this treatment remains unclear due to lack of randomized control trials. It is known that HSV is not eliminated by valacyclovir but merely suppressed to a level where the host immunity is balanced to virus replication. Delays of many years before involvement of the second eye have been reported, therefore long-term antiviral treatment is usually recommended.

A retrospective series at the Moorfields Eye Hospital showed that the incidence of retinal detachment decreased from 80% to 35% in eyes that were treated with prophylactic retinopexy.\textsuperscript{4} In contrast, many studies have found that the overall rate of retinal detachment remains high even in eyes having undergone laser treatment.\textsuperscript{4,8,23} Published reports have also suggested that eyes that do not receive laser are more likely to have extensive disease, consistent with a higher risk of retinal detachment.\textsuperscript{22,23} Although there is ongoing debate, most reports suggest that prophylactic barrier laser should be attempted in cases where there is limited vitritis and the retina can be visualized.\textsuperscript{4,22,23}

Other treatments include systemic corticosteroids, although they have not been proven to improve visual outcomes.\textsuperscript{22} Given that cytotoxic lymphocytes and other inflammatory cells are known to be involved in the destructive process in ARN, anti-inflammatory medication is thought to be an important component of treatment. This is controversial, however, given concern that steroid medication may enhance viral replication, especially in the acute phase.\textsuperscript{1,18} We believe that the subconjunctival steroid administered to our patient may have caused the atypical appearance (not contained to the peripheral retina) and progression of disease. Studies suggest that an antiviral should be commenced at diagnosis, and treatment with steroids should be delayed 24 to 48 hours.\textsuperscript{1}

The combination of severe posterior segment inflammation with peripheral retinal whitening in a patient of unknown immune status should alert the clinician to a possibility of underlying viral infection and prompt treatment with intravenous antiviral therapy should be commenced. With increasing infection rates of HSV-2 in the United States, a thorough history of infective exposure and consideration of any prior treatment should be considered in the diagnosis and management of ARN.\textsuperscript{6,13} In addition, patients with a known history of neonatal HSV disease, neurologic disease, or prior
ARN should be advised that any ocular pain, redness, or blurred vision should be promptly investigated by an ophthalmologist.

References


Table 1.
Published cases of ARN associated with HSV-2 in early childhood


