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Case report

Atypical herpes simplex virus type 2 acute retinal necrosis presentation with large subretinal lesion

Daniel Wang[a], Justin D. Bloomberg[b], Lucia Sobrin[c], Debra Goldstein[d], Dimitra Skondra[e,*]

[a] Department of Ophthalmology, New York Eye and Ear Infirmary, 310 E. 14th Street, New York, NY, USA
[b] Department of Ophthalmology, John H Stroger Jr. Hospital of Cook County, 1969 Ogden Avenue, Chicago, IL, USA
[c] Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA, USA
[d] Department of Ophthalmology, Northwestern University, 645 N. Michigan Avenue, Chicago, IL, USA
[e] Department of Ophthalmology, The University of Chicago, 5841 S. Maryland Avenue, Chicago, IL, USA

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ABSTRACT

Purpose: To report the unique clinical findings of a case of Herpes Simplex Virus Type 2 herpetic retinitis manifesting as a large elevated subretinal lesion.

Observations: A 26-year-old Hispanic male with no significant past medical history presented with a one-week history of right eye pain and endorsement of worsening vision. Ophthalmic examination of the right eye identified a markedly elevated white subretinal lesion with associated findings of vitritis and hypotony. Ultrasound biomicroscopy demonstrated a diffusely thickened choroid and confirmed the observed subretinal mass. Examination of the fellow left eye was largely unremarkable with the exception of lesions suggestive of inactive chorioretinal scars. Diagnostic vitrectomy and vitreous PCR (polymerase chain reaction) was positive only for HSV-2 (herpes simplex virus type 2) and verified by two independent laboratories. The observed subretinal lesion of right eye improved on intravenous acyclovir and intravitreal foscarnet treatment.

Conclusions and Importance: Presented here is an unusual, novel clinical presentation of HSV-2 acute retinal necrosis manifesting as an elevated subretinal lesion along with findings of panuveitis. This case suggests that consideration should be given to the diagnosis of HSV ARN (acute retinal necrosis) when a subretinal elevation is concomitantly appreciated in the setting of vitritis and chorioretinal lesions.

1. Introduction

Acute retinal necrosis (ARN) is a rare, yet aggressive and potentially devastating posterior infectious uveitis that was first described by Urayama and colleagues in 1971.[1] The principle and most common causative agent of ARN is Varicella Zoster Virus (VZV) followed by Herpes Simplex Virus (HSV-1 and HSV-2).[2–4] Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) have also been implicated as potential causative etiologies.[4,5] The syndrome affects both immunocompetent or immunosuppressed individuals of either gender and at any age.[6]

ARN has a rapidly destructive course that may result in permanent vision loss as consequence of macular or optic nerve damage and retinal detachment (RD). Functional outcomes of patients are poor with 48% of affected eyes having a visual acuity worse than 20/200 6-months after disease onset.[7] The disease is classically defined as a syndrome of acute panuveitis with progressive retinal periarteritis and patchy or confluent areas of necrotizing retinitis. Retinal atrophy resulting from necrosis often leads to secondary rhegmatogenous retinal detachment with rates of occurrence as high as 20%–85% of treated eyes.[3,4,8,9] Despite the syndrome's varied clinical manifestations and presentations, to our knowledge, we are reporting the first case of ARN to manifest with a large elevated subretinal lesion.

2. Case report

A 26-year-old incarcerated Hispanic male presented with severe pain and worsening vision of the right eye during the course of one week. The patient was otherwise healthy and denied a prior history of intravenous drug use, human immunodeficiency virus, tuberculosis, syphilis or sexually transmitted diseases, and other systemic infections. Review of systems was positive for a mild right-sided headache that was accompanied by intermittent episodes of blurry vision and generalized discomfort of the right eye over the course of the past year prior to presentation.

* Corresponding author. University of Chicago Medical Center, 5841 S. Maryland Avenue, AMB S426, MC 2114, Chicago, IL, 60637, USA.
E-mail address: dskondra@bsd.uchicago.edu (D. Skondra).

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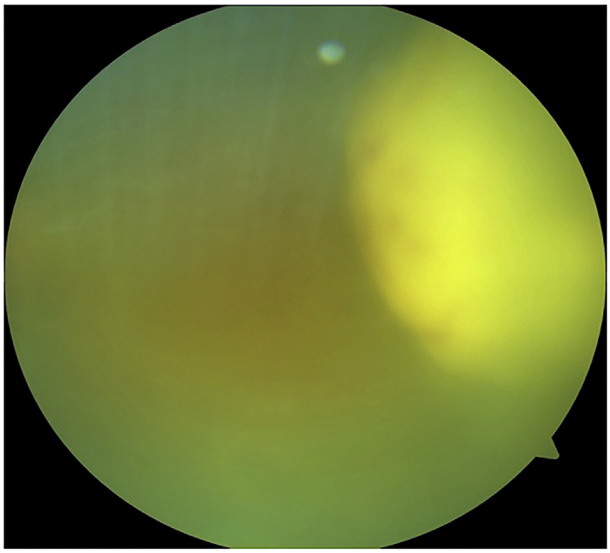

Fig. 1. Fundus photo of the right eye demonstrates a large white elevated subretinal lesion nasally with overlying dense vitritis.

On examination, visual acuity was 20/400 in the right eye and 20/30 in the left eye. A mildly dilated pupil and afferent pupillary defect was noted in the right eye. Intraocular pressures were measured at 4 mm Hg in the right eye and 16 mm Hg in the left eye respectively. Slit lamp examination revealed diffuse conjunctival injection with non-granulomatous keratic precipitates and nasal band keratopathy of the right eye. Furthermore, 2 + cell and flare was present along with 360° of posterior synechiae in the right eye. Exam of the fellow left eye demonstrated an area of focal posterior synechiae and rare cells throughout the anterior segment.

Dilated fundus examination of the right eye was largely limited secondary to dense vitritis, but revealed a hyperemic optic disc as well as a large, elevated subretinal lesion nasally that was accompanied by overlying vitreous membranes and pigmented chorioretinal scars in the inferior and superior quadrants (Fig. 1). Ultrasound of the right eye demonstrated a diffusely thickened choroid and a hyperechoic 5mm subretinal mass that corresponded to the observed lesion (Fig. 2). Fundus examination of the left eye showed evidence of multiple chorioretinal scars along the superior arcade with concurrent demonstration in the nasal, superior and inferior peripheries (Fig. 3). Fluorescein

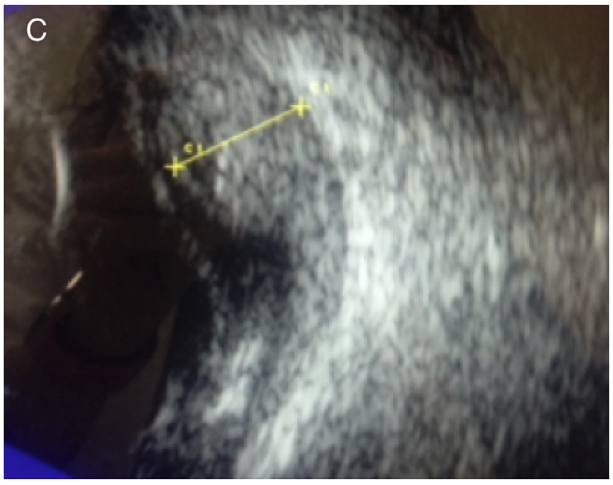

Fig. 2. Ultrasonography performed at the time of presentation revealing a diffusely thickened choroid and 6.7mm hyperechoic subretinal mass corresponding to the lesion observed clinically.

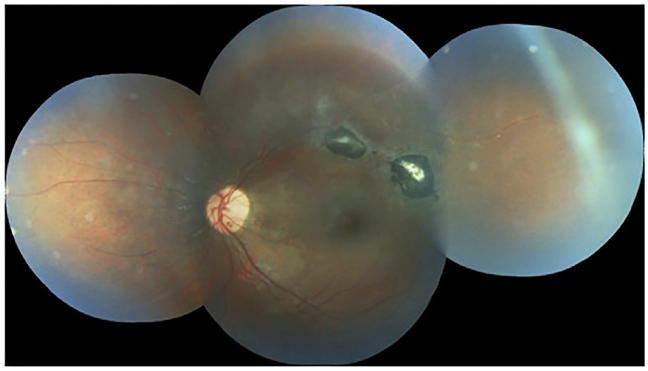

Fig. 3. Montage fundus photo of the left eye demonstrating pigmented chorioretinal scars along the superior arcade.

angiography of the right eye was limited and unrevealing due to overlying vitritis. The left eye exhibited staining of the observed chorioretinal scars, but no evidence of active vasculitis or optic disc leakage was appreciated.

Given the unique presentation and uncertain diagnosis, the patient was started on empiric intravenous acyclovir, intravenous vancomycin and cefepime, sulfamethoxazole-trimethoprim, as well as topical prednisolone drops and atropine drops in the right eye. An extensive laboratory workup was pursued. Subsequent HIV testing, blood cultures, syphilis, QuantiFERON-TB, serum toxoplasma IgG and IgM, and vasculitic work up (anti-neutrophil cytoplasmic antibody, antinuclear antibody, rheumatoid factor) were all negative. Computerized tomography (CT) of the orbits was also largely unremarkable, demonstrating a thickened sclera in the right eye with no optic nerve enhancement. Systemic manifestations and malignancy were further ruled out with negative findings on CT chest and abdomen imaging.

Patient underwent a diagnostic pars plana vitrectomy of the right eye with concurrent intravitreal injection of vancomycin, ceftazidime, and clindamycin. Intraoperatively appreciable periarteritis and focal areas of retinitis at the edges of chorioretinal scars superiorly and inferiorly were noted. On post-operative day one the patient's vision of the right eye was reduced to count fingers with examination demonstrating stable vitritis and unchanged subretinal lesion. After the induction dose of intravenous acyclovir was completed, patient was switched to oral valacyclovir. On post-operative day three, the patient's vision declined further to light perception with examination demonstrating worsening vitritis and a stable subretinal lesion. Vitreous polymerase chain reaction (PCR) and culture studies returned positive only for HSV-2 while toxoplasmosis, VZV, CMV, and vitreous bacterial and fungal cultures were negative. Intravenous acyclovir was restarted and intravitreal injection of foscarnet was performed the same day. Samples from the vitreous biopsy was sent to a second laboratory which also confirmed positive HSV-2 PCR ($3.25 \times 10\wedge5$ copies/microliter) and was negative for Toxoplasmosis, VZV, CMV PCRs.

In light of these results, intravitreal injections of foscarnet were administered twice weekly. The patient's visual acuity unfortunately remained at light perception, but the subretinal lesion was observed to steadily decrease to approximately 3mm on ultrasound (Fig. 4). After ten days of IV acyclovir the patient was discharged from the hospital with oral valacyclovir along with a tapering dose of oral prednisone and combination of prednisolone and atropine drops. The patient additionally received intravitreal foscarnet injections weekly as an outpatient. Ten days after discharge, the patient's vision was reduced to no light perception. Performed ultrasound of the right eye at the time demonstrated the subretinal lesion, but new retinal and choroidal detachment were appreciated. Given the poor prognosis, no further surgical intervention was performed. The patient remained on prophylactic oral valacyclovir to prevent re-activation of retinitis in the left eye.

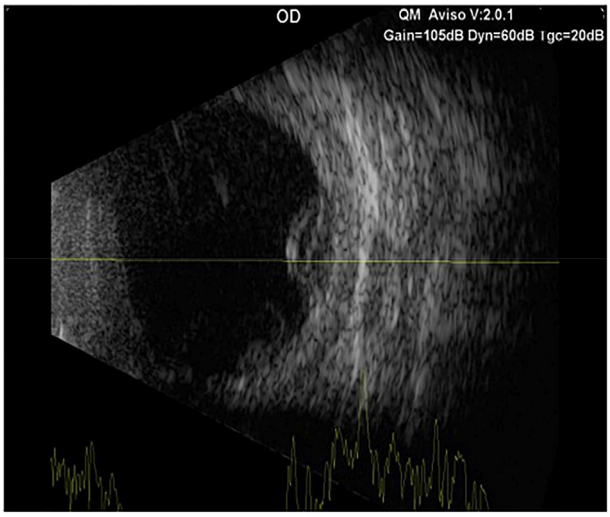

Fig. 4. Ultrasonography performed after intravitreal and systemic viral therapy demonstrating improvement in size and morphology of the observed subretinal lesion.

3. Discussion

Although epidemiologically uncommon, ARN is a serious, potentially blinding syndrome that carries a wide constellation of findings including a triad of peripheral necrotizing retinitis, retinal arteritis, and a prominent inflammatory reaction.[10] ARN requires prompt diagnosis and management as the disease is rapidly progressive and often ends with devastating visual outcomes as a result of macular ischemia and edema, optic nerve neuropathy, and retinal detachment.[6]

A number of clinical findings and features of ARN have been characterized but we are reporting the first case to manifest with large elevated subretinal lesion. The observed lesion was without associated hemorrhage and appeared morphologically consistent with a possible toxoplasmosis granuloma or subretinal abscess in setting of endogenous bacterial or fungal endophthalmitis; however, interestingly, both toxoplasmosis serologies and vitreous PCR were negative. Extensive systemic infectious work-up including vitreous bacterial and fungal cultures was unremarkable, excluding the possibility of endogenous endophthalmitis.

Despite having an atypical presentation, the case does come to meet several of the key defining clinical criteria of ARN set forth by the Executive Committee of the American Uveitis Society. Based on the patient's presenting clinical history, there was a lapse in time between the initial onset of visual symptoms to the time of presentation and treatment, thus delaying antiviral therapy and permitting the rapid progression of the disease course observed.[10] A prominent panuveitis presentation was appreciated as there was significant evidence of inflammation throughout the vitreous and anterior chamber on ocular examination.[10] Unfortunately, due to the marked inflammation and dense vitritis, there were limitations in the ability to directly characterize areas of retinal necrosis and occlusive vasculopathies; however, during vitrectomy of the right eye, appreciable areas of periarteritis and retinitis were seen at the margin of chorioretinal scars which could be supportive of ARN. The observed chororetinal scars of the fellow left eye could also be suggestive of previous ARN involvement as bilateral ARN occurs in up to 70% of untreated individuals,[11] though they did not have the typical appearance of resolved retinitis. Antiviral treatment appeared to lead to clinical morphological improvement of the subretinal lesion.

The diffusely thickened choroid with enhancement of the sclera observed on CT scan could be suggestive of posterior scleritis in addition to the panuveitis. In Foster's[12] review of the etiology of 500 cases of anterior and posterior scleritis, herpetic infection was not associated with any cases of posterior scleritis, but it was responsible for 7.8% of anterior scleritis. Machado et al.[13] have reported a series of 23 cases of posterior scleritis in which herpes simplex infection was associated with 2 cases, but none of the cases demonstrated an elevated subretinal mass. The large subretinal mass in our patient could represent an atypical nodular posterior scleritis as part of ARN, but the ultrasound images do not support the lesion arising from the sclera.

ARN has historically been a clinical diagnosis made on examination, but the severe consequences of underdiagnosis, misdiagnosis, and delays in treatment of atypical presentations has prompted the use of laboratory methods to aid in the process. Serum and intraocular fluid antibody testing, retinal biopsy, viral culture, and immunocytochemistry have all been modalities traditionally utilized, but their use has largely been limited by their poor sensitivity or specificity and other confounding factors.[6] Numerous reports have demonstrated the functionality of PCR testing in the diagnosis and management of ARN. PCR HSV sensitivity reported between 80% and 96% in clinically defined ARN cases.[5,14–16] Furthermore, because ARN presents with overlapping clinical features that may resemble other etiologies, a negative PCR result may lead to a prompt diagnosis of another entity.[17,18] Our patient underwent diagnostic vitrectomy which yielded two compelling positive HSV-2 PCR samples that was verified by two independent laboratories.

ARN associated HSV-2 has been linked to a number of risk factors including young age, previous history of meningitis or encephalitis, neonatal HSV infection, and specific triggering factors such as periocular trauma or steroid use.[5,19,20] In a study by Tran et al., twenty-four immunocompetent patients with PCR confirmed HSV-2 ARN, presented with first eye involvement at a mean age of thirty-six years.[14] All the patients in the study had active necrotizing retinitis, and three patients had inactive chorioretinal scarring in the fellow eye, a finding that was also observed in our patient.[14] Rhegmatogenous retinal detachment early in a clinical course has been suggested as a marker for HSV driven retinitis.[21] Visual acuity of our patient unfortunately reduced to no light perception likely secondary to optic nerve involvement in addition to retinal and choroidal detachment despite aggressive intravenous and intravitreal antiviral treatment.

4. Conclusion

In conclusion, our case demonstrates that HSV ARN should be considered in the differential when a patient presents with an elevated subretinal lesion in the context of concurrent of vitritis and chorioretinal lesions. Early diagnosis and treatment is critical to prevent potentially devastating visual complications in suspected cases.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Disclosures

None of the authors have financial disclosures or conflicts of interest relating to this topic.

Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajoc.2019.100501.

References

1. Urayama A, Yamada N, Sasaki T, et al. Unilateral acute uveitis with retinal periarteritis and detachment. *Jpn J Clin Ophthalmol.* 1971;25:607–619.
2. Muthiah MN, Michaelides M, Child CS, et al. Acute retinal necrosis: a national population-based study to assess the incidence, methods of diagnosis, treatment strategies and outcomes in the UK. *Br J Ophthalmol.* 2007;91:1452–1455.
3. Hillenkamp J, Nolle B, Bruns C, et al. Acute retinal necrosis: clinical features, early vitrectomy, and outcomes. *Ophthalmology.* 2009;116:1971–1975.
4. Lau CH, Missotten T, Salzmann J, Lightman SL. Acute retinal necrosis features, management, and outcomes. *Ophthalmology.* 2007;114:756–762.
5. Ganatra JB, Chandler D, Santos C, et al. Viral causes of the acute retinal necrosis syndrome. *Am J Ophthalmol.* 2000;129:166–172.
6. Schoenberger S, Kim S, Thorne J, et al. Diagnosis and treatment of acute retinal necrosis. *Ophthalmology.* 2017;124:382–392.
7. Cochrane TF, Silvestri G, McDowell C, et al. Acute retinal necrosis in the United Kingdom: results of a prospective surveillance study. *Eye.* 2012;26:370–377.
8. Meghpara B, Sulkowski G, Kesen MR, et al. Long-term follow-up of acute retinal necrosis. *Retina.* 2010;30:795–800.
9. Blumenkranz MS, Culbertson WW, Clarkson JG, et al. Treatment of the acute retinal necrosis syndrome with intravenous acyclovir. *Ophthalmology.* 1986;93:296–300.
10. Holland GN. Standard diagnostic criteria for the acute retinal necrosis syndrome. *Am J Ophthalmol.* 1994;117:663–667.
11. Palay DA, Sternberg Jr P, Davis J, et al. Decrease in the risk of bilateral acute retinal necrosis by acyclovir therapy. *Am J Ophthalmol.* 1991;112:250–255.
12. Gonzalez-Gonzalez LA, Molina-Prat N, Doctor P, et al. Clinical features and presentation of infectious scleritis from herpes viruses: a report of 35 cases. *Ophthalmology.* 2012;119:1460–1464.
13. Machado O, Curi AL, Bessa TF, et al. Posterior scleritis: clinical features, systemic association, treatment and evolution of 23 patients. *Arq Bras Oftalmol.* 2009;72(3):321–326.
14. Tran THC, Rozenberg F, Cassoux N, et al. Polymerase chain reaction analysis of aqueous humor samples in necrotizing viral retinitis. *Br J Ophthalmol.* 2003;87:79–83.
15. de Boer JH, Verhagen C, Bruinenberg M, et al. Serologic and polymerase chain reaction analysis of intraocular fluids in the diagnosis of Infectious uveitis. *Am J Ophthalmol.* 1996;121:650–658.
16. Abe T, Tsuchida K, Tamai M. A comparative study of the polymerase chain reaction and local antibody production in acute retinal necrosis syndrome and cytomegalovirus retinitis. *Graefes Arch Clin Exp Ophthalmol.* 1996;234:419–424.
17. Knox CM, Chandler D, Short GA, et al. Polymerase chain reaction-based assays of vitreous samples for the diagnosis of viral retinitis. Use in diagnostic dilemmas. *Ophthalmology.* 1998;105:37–45.
18. Gargiulo F, De Francesco MA, Nascimbeni G, et al. Polymerase chain reaction as a rapid diagnostic tool for therapy of acute retinal necrosis syndrome. *J Med Virol.* 2003;69:397–400.
19. Kychenthal A, Coombes A, Greenwood J, et al. Bilateral acute retinal necrosis and herpes simplex type 2 encephalitis in a neonate. *Br J Ophthalmol.* 2001;85:629–630.
20. Ahmadieh H, Sajjadi SH, Azarmina M, et al. Association of herpetic encephalitis with acute retinal necrosis syndrome. *Ann Ophthalmol.* 1991;23:215–219.
21. Duker JS, Blumenkranz MS. Diagnosis and management of the acute retinal necrosis (ARN) syndrome. *Surv Ophthalmol.* 1991;35:327–343.