



## Uveo-meningeal syndrome secondary to Herpes Simplex Virus related acute retinal necrosis

Megan Haghnegahdar<sup>a</sup>, Dante Pennipede<sup>a</sup>, Brenton Massey<sup>b</sup>, Mary Champion<sup>a</sup>,  
Radwan Ajlan<sup>a,\*</sup>

<sup>a</sup> Department of Ophthalmology, University of Kansas School of Medicine, 7400 State Line Road, Prairie Village, KS, 66208, USA

<sup>b</sup> Department of Neurology, University of Kansas School of Medicine, 3901 Rainbow Boulevard, Mailstop 2012, Kansas City, KS, 66160, USA

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### ABSTRACT

**Purpose:** To present a rare case of uveo-meningeal syndrome secondary to herpes simplex virus (HSV-1) in a patient with acute retinal necrosis.

**Observations:** A 49-year-old female with a past medical history of herpes simplex encephalitis 18 years prior presented with a 3-day history of right sided headache and decreased vision of the right eye. Her visual acuity was 20/30 in the right eye and 20/20 in the left eye. Clinical examination revealed right relative afferent pupillary defect, panuveitis, and retinal necrosis. Examination of the left eye was unremarkable. Cerebral spinal fluid (CSF) analysis by polymerase chain reaction (PCR) was negative for herpes simplex virus 1 (HSV-1) but did reveal pleocytosis consistent with meningitis. The patient was admitted and empirically treated with intravenous acyclovir (10 mg/kg every 8 hours) and systemic steroids. Topical steroids and cycloplegia were also started. Magnetic resonance imaging revealed no leptomeningeal, pachymeningeal, or parenchymal enhancement. Systemic autoimmune and infectious workup were unremarkable. Based on clinical exam findings and negative PCR results, an anterior chamber tap was performed with aqueous fluid PCR testing which revealed 71,000 copies of HSV-1. A repeat lumbar puncture was performed on day three of admission and revealed a decrease in pleocytosis after initiation of acyclovir therapy and remained negative for HSV on PCR testing. She was discharged home on intravenous acyclovir, topical steroids, and topical cycloplegics. Her retinal necrotic lesions continued to regress and her headaches continued to improve.

**Conclusions and importance:** Uveo-meningeal syndromes are a rare clinical entity that involve the uvea, retina, and meninges. This case highlights the importance of aqueous fluid PCR testing despite negative CSF PCR, as it may hasten treatment with antiviral therapies to preserve vision and limit neurologic sequelae.

### 1. Introduction

Uveo-meningeal syndrome is a rare clinical entity that involves the uvea, retina, and meninges. Etiologies of this syndrome include infectious, inflammatory, and neoplastic causes. Of these causes, inflammatory and autoimmune disease are the most common, such as granulomatosis with polyangiitis, sarcoidosis, Behcet's disease, and Vogt-Koyanagi-Harada syndromes.<sup>1</sup> Infectious causes of uveo-meningeal syndromes are more rare and include bacterial, viral, and mycobacterial organisms. Of the viral infections, cytomegalovirus (CMV), herpes simplex virus (HSV), and varicella-zoster virus (VZV) are most commonly recognized. Features of uveo-meningeal syndrome include meningitis or meningoencephalitis in the presence of uveitis.

The meningeal involvement is oftentimes chronic, leading to cranial neuropathies, polyradiculopathies, and hydrocephalus.<sup>1</sup>

Acute retinal necrosis (ARN) is defined as peripheral necrotizing retinitis classically due to infection with either VZV or HSV. It is characterized by sudden onset of decreased vision, floaters, ocular pain, and photophobia. The incidence of ARN is estimated to be 0.63 cases per million population per year to 1 case per 1.6 to 2.0 million population per year based on two separate studies based in the United Kingdom.<sup>2,3</sup> Prevalence is equal between sexes and patients affected are usually immunocompetent. The mean age of ARN due to HSV-1 infection is 40 years, whereas the mean age for ARN due to HSV-2 infection is below 25 years. The disease may arise without systemic prodrome and may occur months or years after primary infection or following cutaneous or

\* Corresponding author. KU Eye, 7400 State Line Road, Prairie Village, KS 66208, USA.

E-mail address: [rajlan@kumc.edu](mailto:rajlan@kumc.edu) (R. Ajlan).

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systemic herpetic infection. Interestingly, there is higher risk of encephalitis and meningitis among patients with ARN due to HSV1 than VZV infection. The American Uveitis Society criteria for diagnosis of ARN includes one or more foci of retinal necrosis with discrete borders located in the peripheral retina, rapid progression in the absence of antiviral therapy, circumferential spread, and occlusive vasculopathy with arteriolar involvement. Supportive clinical criteria include prominent vitritis and anterior chamber inflammation, optic neuropathy or atrophy, scleritis, and pain. If there is diagnostic uncertainty, aqueous polymerase chain reaction (PCR) sampling for identification of causative organism is recommended.<sup>4</sup>

Various cases describing ARN due to HSV report preceding HSV encephalitis (HSE) days to years prior to the development of HSV ARN. Examples include a 68 year old male who developed HSV ARN nine months after HSE,<sup>5</sup> a 64 year old female who developed HSV ARN ten days after HSE,<sup>5</sup> a 25 year old male who developed HSV ARN one month after HSE,<sup>6</sup> a 45 year old female who developed HSV ARN six years after HSE,<sup>7</sup> and a 59 year old male who developed HSV ARN one month after HSE.<sup>8</sup> Each of these cases had documented positive HSV infection by PCR testing of cerebrospinal fluid and had neuroimaging findings consistent with HSE, suggesting axonal spread of infection from the brain to the retina. However transmission from the retina to the brain is less understood and not well documented. Here we present a case of HSV uveo-meningitis that originated from HSV acute retinal necrosis.

## 2. Case report

A 49-year-old female with a past medical history of herpes simplex encephalitis 18 years prior presented with a 3-day history of right sided headache and decreased vision of the right eye. Her visual acuity was 20/30 in the right eye and 20/20 in the left eye. Clinical examination revealed right relative afferent pupillary defect, panuveitis, superior-temporal branch retinal artery occlusion, and inferior retinal necrosis (Fig. 1A). Examination of the left eye was unremarkable.

She was admitted to the inpatient medicine service for further evaluation. Systemic autoimmune and infectious workup were

unremarkable. Cerebral spinal fluid (CSF) analysis by polymerase chain reaction (PCR) was negative for herpes simplex virus 1 (HSV-1), but did reveal pleocytosis consistent with meningitis. Magnetic resonance imaging (MRI) revealed no leptomeningeal, pachymeningeal, or parenchymal enhancement. Given concern for HSV meningitis in the setting of CSF pleocytosis and a prior history of herpes simplex encephalitis, she was empirically initiated on intravenous acyclovir 10 mg/kg every 8 hours. Topical steroids and cycloplegia were also started. IV steroids were also started per neurology's recommendations. Based on clinical exam findings and negative CSF PCR results, anterior chamber (AC) tap was performed with aqueous fluid PCR testing which ultimately revealed 71,000 copies of HSV-1. A repeat lumbar puncture was performed on day three of admission and revealed a decrease in pleocytosis after initiation of acyclovir therapy and remained negative for HSV on PCR testing. She was continued on intravenous acyclovir 5mg/kg every 8 hours for four additional weeks after discharge. Topical steroids and topical cycloplegics were also continued.

She was closely followed in clinic after discharge. Subjectively, her headaches improved over time. Serial exams revealed regression of her retinal necrotic lesions and stable vitritis (Fig. 1C). Optical coherence tomography (OCT) macula showed poorly distinguished outer retinal layers (Fig. 1D). Five months after her initial evaluation, she underwent pars plana vitrectomy for persistent vitreous membranes in her right eye. Final visual acuity post vitrectomy with 20/60 in the right eye.

## 3. Discussion

Here we present a case of uveo-meningitis syndrome associated with HSV ARN. After consulting with the neurology service involved in the patient's care, the leading hypothesis is that the patient's meningitis was secondary to HSV ARN (a.k.a. uveo-meningeal syndrome). This is further supported by a decrease in CSF pleocytosis and clinical improvement of headaches while receiving acyclovir and steroids. HSV ARN is usually treated with intravenous acyclovir 10mg/kg every 8 hours for 10–14 days followed by extended antiviral therapy with oral acyclovir 800mg five times daily, valacyclovir 1g three times daily, or



**Fig. 1.** Multimodal imaging of the right eye. Initial ultrawide field fundus photography of the right eye demonstrating media opacity and retina necrotic lesions (A). Initial OCT macula of the right eye demonstrating poorly differentiated retinal layers and increased interstitial hyperreflectivity (B). Ultrawide field fundus photography of the right eye 4 months later demonstrating media opacity and retinal scars in previously necrotic retina locations (C). Macular OCT scan 4 months later shows decreased retinal layer hyperreflectivities and residual focal thinning (D).

famciclovir 500mg three times daily for 3 months.<sup>4</sup> The extended antiviral therapy may reduce incidence of contralateral disease or bilateral ARN by 80% over one year.<sup>4</sup>

Diagnosis of uveo-meningeal syndrome requires extensive ocular and medical history and examination. Screening laboratory and imaging may be tailored to various potential etiologies elicited on history and physical exam. Patients at minimum should undergo lumbar puncture and MRI of the brain with gadolinium.<sup>1</sup> It may be necessary to obtain special studies when routine laboratory and imaging are unrevealing for a potential etiology. Examples of special testing include vitreous or meningeal biopsy. Treatment is targeted to the causative agent in conjunction to appropriate consultation to various specialties depending on the nature of the cause, such as rheumatology, infectious diseases, and hematology/oncology. A multidisciplinary approach is typically required for diagnosis and treatment.<sup>1</sup>

PCR detection of HSV by lumbar puncture sampling of cerebrospinal fluid has an estimated sensitivity of 98%, specificity of 94%, positive predictive value (PPV) of 95%, and negative predictive value (NPV) of 98%.<sup>9</sup> PCR detection of HSV by anterior chamber (AC) tap has an estimated sensitivity of 98.8%, specificity of 98.5%, PPV of 98.8%, and NPV of 98.5%.<sup>10</sup> Alternative testing to AC tap includes vitreous specimen PCR testing, however this is associated with increased risk of further retina pathology and thus AC tap is usually preferred.<sup>4</sup>

The patient's history of previous HSE carried the risk of HSV reactivation as a cause of her headaches. Our neurology colleagues excluded HSV reactivation based on their clinical examination and extensive work up (two negative CSF HSV PCR tests and lack of encephalitis findings on brain MRI with gadolinium). Furthermore, the patient had extensive ARN (Fig. 1A) and positive aqueous fluid HSV PCR to support uveo-meningeal syndrome as the diagnosis. Choroidal contact with the pia matter at the optic nerve is believed to be the route where the inflammation reaches the subarachnoid space and meninges resulting in uveo-meningeal syndrome.<sup>11</sup>

This case is significant due to the very few documented accounts of HSV infection spreading from ARN to the brain.<sup>12,15</sup> Our literature review revealed four previous cases of patients who developed acute retinal necrosis due to HSV-1 and later went on to develop CNS infection. Three of the cases were found to have positive HSV-1 PCR testing on both vitreous and CSF samples, one of which was found on post-mortem testing.<sup>12-14</sup> The fourth case report had positive HSV-1 PCR testing of a vitreous sample, however there was no mention of CSF PCR HSV testing.<sup>15</sup> Three of these patients had been receiving systemic steroids and one was chronically immunosuppressed.

Our case is unique to these cases in that the AC tap was positive for HSV-1 while CSF testing was negative for HSV-1. However there was high suspicion by our consulting neurology colleagues that the headaches and CSF pleocytosis were caused by CSF HSV-1 infection. Our case highlights the importance of AC fluid PCR testing despite negative CSF PCR when uveo-meningitis syndrome remains in the differential diagnosis, as it may hasten treatment with antiviral therapies to preserve vision and limit neurologic sequelae.

#### 4. Conclusion

We present a case of HSV uveo-meningitis secondary to HSV ARN discovered by AC fluid PCR testing in the setting of two negative CSF examinations. This case highlights the importance of AC fluid PCR testing despite negative CSF PCR when uveo-meningitis syndrome is suspected.

#### Patient consent

Written consent was obtained from the patient to include ultrawide

field fundus photography and optical coherence tomography macula in this case report.

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#### Authorship

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

#### Declaration of competing interest

None.

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