

# Case Reports: Chemokine and Cytokine Profiling in Patients with Herpetic Uveitis

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**Purpose:** To report cytokine/chemokine profiles of ocular fluid in two patients with herpetic uveitis.

**Methods:** Cytokine and chemokine profiling of ocular fluid was performed in two patients with herpetic uveitis. Ocular fluid findings were correlated with disease manifestations and the patients' clinical course.

**Observation:** Case 1 was a 45-year-old female, who was evaluated for an 11-day history of recurrent redness, and decreased vision in the right eye (OD) and was diagnosed with acute retinal necrosis. Ocular fluid from anterior chamber paracentesis was positive for varicella zoster virus (VZV) via PCR testing. Subsequently, the patient developed proliferative vitreoretinopathy requiring a pars plana vitrectomy. Ocular fluid sample cytokine/chemokine analysis detected IFN- $\gamma$ , TNF- $\alpha$ , IL-8, IL-18, MIP-1 $\beta$ , IP-10, and MCP-1 with MCP-1 being the most abundant cytokine. Case 2 was a 30-year-old female with a two-month history of progressive pain and decreased vision OD. She was diagnosed with hypertensive anterior uveitis after diagnostic anterior chamber paracentesis. Despite successful therapy for the anterior uveitis, her intraocular pressure remained elevated and required a glaucoma filtration procedure. Ocular fluid sample was collected at the time of surgery for cytokine/chemokine profiles analysis, and levels of 7 cytokines/chemokines were detected including IL-6, IL-8, IL-18, MIP-1 $\beta$ , IP-10, MCP-1, and IL-1RA with IL-1RA being the most abundant cytokine.

**Conclusion:** Cytokine/chemokine profiles of two patients with herpetic uveitis showed elevated levels of MCP-1, IP-10, IL-8, and IL-18 while IL-1RA was elevated in the chronic phase of hypertensive anterior uveitis. Further studies of cytokines and chemokines will improve our understanding of soluble mediators and potential targets for herpetic uveitis.

**Keywords:** case reports, cytokine, chemokine, acute retinal necrosis, anterior hypertensive uveitis

## Introduction

Herpetic anterior uveitis is the most common cause of infectious anterior uveitis accounting for 5–10% of all uveitis cases.<sup>1</sup> The disease is usually caused by herpes simplex virus (HSV-1 and HSV-2) or varicella zoster virus (VZV) and is characterized by unilateral anterior uveitis accompanied by high intraocular pressure. Acute retinal necrosis (ARN) is an uncommon viral uveitis syndrome that is also due to infection with VZV, HSV-1, or HSV-2. The exact epidemiology of ARN is unclear, but prior survey studies in the United Kingdom estimated an annual incidence of 1 case per 1.6 to 2.0 million, and the disease is characterized by severe and diffuse uveitis, retinal vasculitis, and retinal necrosis.<sup>2,3</sup> Herpetic anterior uveitis and acute retinal necrosis are often diagnosed via clinical examination by characteristic symptoms and signs;<sup>4</sup> however, polymerase chain reaction (PCR) of the anterior chamber fluid can aid the diagnosis in both conditions.<sup>5</sup>

The cytokine and chemokine profiles of herpetic uveitis have been incompletely studied in the literature. However, limited studies have described the detection of IL-10, TNF- $\alpha$ , and IFN- $\gamma$  in patients with herpetic uveitis,<sup>6–11</sup> shedding light on their potential involvement in the pathogenesis of the disease. Interestingly, a machine learning model has recently been developed to predict intraocular disease based on aqueous humor immune mediator profiles with great success,<sup>12</sup> therefore, further analyses of chemokine/cytokine profiles can be of interest in diagnosing intraocular inflammatory disease. Herein, we report cytokine chemokine profiles of the ocular fluid in two patients with herpetic uveitis, highlighting additional chemokines that may be involved in disease pathogenesis of the disease.

## Materials and Methods

The study was conducted in compliance with the Declaration of Helsinki, and informed consent was obtained from the patients participating in the study. A review of medical records was performed for data including ophthalmic examination findings, clinical presentation, patient management, and ophthalmic procedures performed. Ocular fluids were assessed for cytokine and chemokine profiles and were tested in triplicate using a multiplex chemiluminescent immunoassay according to the manufacturer's instructions (Meso Scale Diagnostics, Rockville, Maryland).

## Case Descriptions

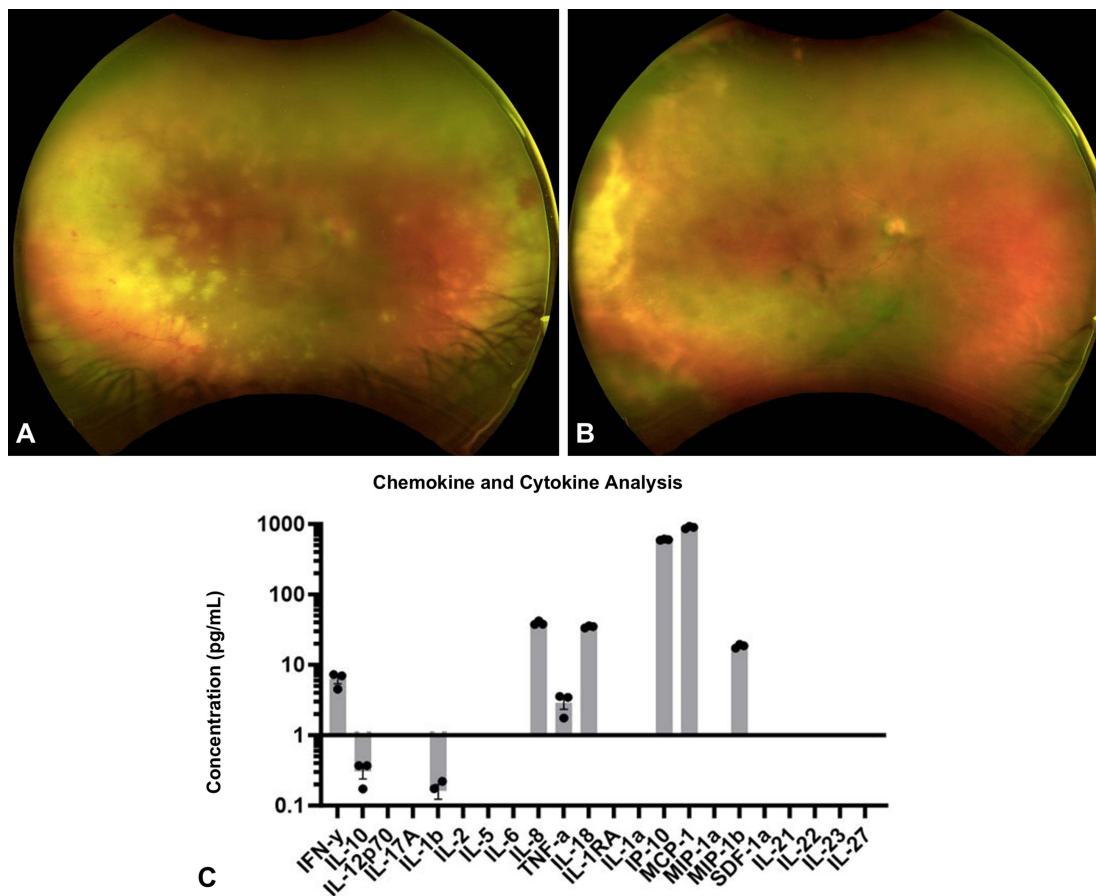
### Case 1

A 45-year-old female with a past medical history of rheumatoid arthritis and a remote history of chickenpox was referred for evaluation of an 11-day history of recurrent redness, blurriness, mild pain, pressure, discomfort, and decreased vision in the right eye (OD). Prior to her referral to our facility, she was evaluated at an outside clinic with a one-week history of redness and decreased vision OD. She was started on topical difluprednate and atropine for anterior uveitis which she began 2 days before her presentation to our facility.

On examination, best-corrected visual acuities (BCVA) were 20/100 OD and 20/25 in the left eye (OS). Pupillary examination showed a 1+ relative afferent pupillary defect OD. Intraocular pressures (IOP) were physiologic at 17 mmHg OD and 16 mmHg OS. Slit-lamp examination revealed 1–2+ granulomatous anterior chamber reaction and 3+ vitreous cells OD, and OS was unremarkable. Fundus examination showed optic disc edema and hemorrhages, diffuse retinal whitening, and necrosis with hemorrhagic vasculitis OD, and OS appeared unaffected (Figure 1A). A diagnostic anterior chamber paracentesis was performed, and the ocular fluid was positive for VZV by PCR testing. Given the examination findings, she was diagnosed with acute retinal necrosis prompting an in-office intravitreal injection of foscarnet (2.4 mg/0.1 mL) and ganciclovir (2 mg/0.05 mL) along with initiation of oral valacyclovir 2 grams TID. On a 2-week follow-up after the initial presentation, the patient reported improvement in central vision, and BCVAs improved to 20/50 OD and 20/20 OS. Examination revealed persistent vitreous opacity, but the retinitis has improved with consolidation and well-demarcated borders of the retinitis involving the temporal retina (Figure 1B).

On the 6-week follow-up, the patient complained of a sudden loss of vision in the right eye. BCVAs were counting fingers OD and 20/20 OS, and examination revealed retinal detachment OD. The patient underwent surgery for complex rhegmatogenous retinal detachment (RRD) repair and continued to be monitored closely. Postoperatively, the vision gradually improved until two weeks post-surgery when the patient was noted to develop a low-lying inferior retinal detachment with surface proliferative vitreoretinopathy (PVR), prompting a pars plana vitrectomy for retinal detachment repair. This surgery was performed seven weeks after the PVR diagnosis was made, and six months after the patient's initial presentation at our facility.

An aqueous humor (AqH) sample of the right eye was obtained during surgery for a chemokine/cytokine profile analysis. The levels of a panel of 22 cytokines and chemokines (ie, IFN- $\gamma$ , IL-10, IL-12p70, IL-17A, IL-1 $\beta$ , IL-2, IL-5, IL-6, IL-8, TNF- $\alpha$ , IL-18, IL-1RA, IL-1a, IL-1 $\alpha$ , IP-10, MCP-1, MIP-1 $\alpha$ , MIP-1 $\beta$ , SDF-1 $\alpha$ , IL-21, IL-22, IL-23, and IL-27) were tested in triplicate using a multiplex chemiluminescent immunoassay. The concentration of 7 cytokines/chemokines was detected including IFN- $\gamma$ , TNF- $\alpha$ , IL-8, IL-18, MIP-1 $\beta$ , IP-10, and MCP-1 (Figure 1C). MCP-1 was the most abundant cytokine (900 pg/mL), while IP-10 was the second most abundant cytokine (800 pg/mL). IL-8 and IL-



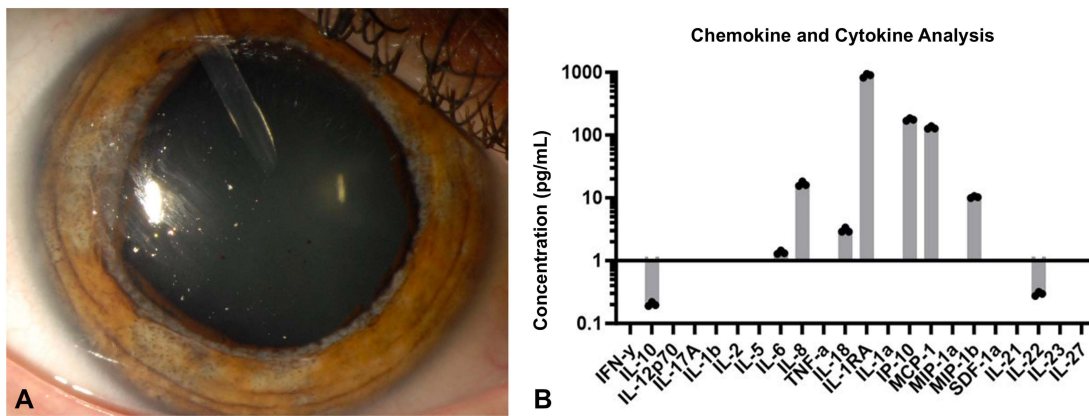
**Figure 1** Wide-field fundus photograph of patient 1 who has acute retinal necrosis due to varicella zoster virus shows moderate vitreous haze, diffuse multifocal whitening, and retinal hemorrhage at presentation (A). Following treatment, there is persistent vitreous opacity, but the retinitis has improved with consolidation and well-demarcated borders of the retinitis involving the temporal retina (B). Chemokine and cytokine analysis of ocular fluid at the time of retinal detachment shows elevated levels of MCP-1 and IP-10, as well as other soluble mediators (C).

18 were the third most abundant cytokines, each with a level of 40 pg/mL, while IFN- $\gamma$  and TNF- $\alpha$  levels of <10 pg/mL were recorded as the least abundant in this patient's AqH sample.

## Case 2

A 30-year-old female was evaluated for a two-month history of progressive pain and decreased vision OD. Two weeks before the development of ocular symptoms, the patient began prednisone taper as a treatment for her systemic inflammatory symptoms. Past medical history includes inflammatory arthritis, gastrointestinal symptoms suggestive of inflammatory bowel disease, and 20-pound weight loss prior to presentation. The complete details of the patient's case were reported previously and are summarized herein along with additional ocular fluid chemokine and cytokine analysis.<sup>13</sup>

On examination, BCVAs were 20/40 OD and 20/20 OS, and pupils were 9 mm and akinetic OD and 5 mm with brisk light reactivity OS. Intraocular pressures were 65 mmHg OD and 21 mmHg OS. Slit-lamp examination showed pigmented, granulomatous keratic precipitates (KP) within the inferior cornea, 3+ anterior chamber cell, diffuse iris atrophy with pigment on the zonules, and ectropion uveae OD, and OS was unremarkable. Gonioscopy showed 3+ pigmented cells within the inferior angle OD. Fundus examination was unremarkable in both eyes. A diagnostic anterior chamber paracentesis was positive for VZV DNA by PCR testing, and serologic testing was positive for VZV IgG antibody. Subsequently, she was diagnosed with VZV-associated hypertensive anterior uveitis, prompting initiation of oral acetazolamide and ophthalmic timolol, dorzolamide, and brimonidine for ocular hypertension, as well as



**Figure 2** High-magnification slit lamp photograph shows multiple areas of iris pigment loss, particularly along the inferior and temporal pupil. The tube shunt is also visible superotemporally (A). Cytokine and chemokine profiling shows elevated IL-1RA, MCP-1, IP-10 levels, as well as other soluble mediators (B).

valacyclovir 1g TID and prednisolone acetate 1% every 2 hours. The patient’s disease course and further details of her management were previously described.<sup>13</sup>

The patient was diagnosed with a cerebrovascular accident (CVA), thought to be due to VZV-associated CNS vasculopathy, and was hospitalized for 2 weeks during which her ocular symptoms gradually improved. She, however, developed worsening pain and vision in the right eye two months after her CVA, and her BCVA declined to 20/100 with an elevated IOP of 39 mmHg OD. Examination revealed 1+ ciliary injection and 3+ anterior chamber cell, and she was switched from prednisolone to difluprednate with minimal improvement. Subsequently, she underwent a glaucoma filtration procedure with an Ahmed shunt due to her persistent elevated IOP despite maximum tolerated ocular hypertensive therapy (Figure 2A). An aqueous humor sample of the right eye was obtained during filtration surgery for a chemokine/cytokine profile analysis. The levels of 22 cytokines and chemokines including IFN- $\gamma$ , IL-10, IL-12p70, IL-17A, IL-1 $\beta$ , IL-2, IL-5, IL-6, IL-8, TNF- $\alpha$ , IL-18, IL-1RA, IL-1a, IL-1 $\alpha$ , IP-10, MCP-1, MIP-1 $\alpha$ , MIP-1 $\beta$ , SDF-1 $\alpha$ , IL-21, IL-22, IL-23, and IL-27 were estimated using the multiplex bead immunoassay technique. Concentration levels of 7 cytokines/chemokines were detected including IL-6, IL-8, IL-18, MIP-1b, IP-10, MCP-1, and IL-1RA (Figure 2B). IL-1RA was the most abundant cytokine (1000 pg/mL), while IP-10 and MCP-1 were the second most abundant cytokines (150–200 pg/mL). IL-18 and MCP-1b levels of 10–20 pg/mL were detected but at minimal levels in this AqH sample. IL-6 and IL-8 were detected but found to be the least abundant cytokines, each with levels of <10 pg/mL.

## Discussion

In this article, we have described the chemokine/cytokine profiles of two patients with herpetic uveitis secondary to VZV, one patient with ARN and one patient with hypertensive anterior uveitis. In our ARN patient, MCP-1, IP-10, IL-8, IFN- $\gamma$ , and TNF- $\alpha$  were detected in the ocular fluid sample isolated during the surgery with MCP-1 being the most abundant cytokine. The detection of TNF- $\alpha$  and IFN- $\gamma$  is consistent with the previous reports in the literature evaluating acute stage of the disease.<sup>6–8,10,11,14</sup> Moreover, IFN- $\gamma$  has been described to play an important role in the clinical course of ARN,<sup>11</sup> and its level also correlates with the activity of the disease in a study reported by Ongkosuwito et al.<sup>8</sup>

Interestingly, the level of MCP-1 was persistently elevated in the ocular fluid sample at the time of collection several months after diagnosis in both patients. MCP-1 is a monocyte chemoattractant protein, which has been shown to play a pivotal role in the pathogenesis of inflammatory diseases and to be regulated by potent antiviral proteins, type I interferons.<sup>15,16</sup> A previous study established their role in predicting the severity of inflammatory diseases as well as in the pathogenesis of uveitis and retinal diseases including PVR and RRD.<sup>15</sup> The MCP-1 level in the ocular fluid of the ARN case was the most abundant (900 pg/mL) at the time of collection, and the patient subsequently developed PVR. Prior reports have documented a high rate of recurrent retinal detachment in association with ARN,<sup>17</sup> although the contribution of inflammatory cells and soluble mediators is incompletely understood. Whether MCP-1 and the

downstream effect of this chemokine are involved in the pathogenesis of PVR, which contributes to recurrent ARN-related retinal detachments, warrants further study.

Several studies have investigated chemokine/cytokine profiles in patients with herpetic uveitis. A study aimed at determining the intraocular cytokine profiles in different types of uveitis showed an increase in IL-1 $\beta$  and IL-10 levels among patients with viral uveitis, with no significant difference in cytokine profiles between HSV- and VZV-induced uveitis.<sup>9</sup> In another study of herpetic uveitis, the cytokine profiles in the aqueous humor of patients with herpetic uveitis demonstrated elevated intraocular IL-10, TNF- $\alpha$ , and IFN- $\gamma$  levels in eyes with VZV-associated uveitis when compared to healthy controls.<sup>10</sup> In animal models aimed at better understanding cytokine expression during ARN, HSV-1 infected eyes showed similar elevations in TNF- $\alpha$ , IFN- $\gamma$ , and IL-4 mRNA as compared to controls like those seen in patients with the disease.<sup>18,19</sup> Furthermore, in one of these studies in which the retina is directly infected with HSV-1, many of these chemokines and cytokines such as IFN- $\gamma$  and MCP-1 are significantly elevated within 2 days post-infection in wild-type mice but not in mice lacking a functioning type I interferon receptor suggesting some role in immunity and/or pathogenesis of these inflammatory proteins and their regulation by type I interferons.<sup>19</sup> However, the regulation and roles of these proteins are still not well understood in ARN.

In our patient with hypertensive anterior uveitis, concentration levels of IL-6, IL-8, IL-18, MIP-1 $\beta$ , IP-10, MCP-1, and IL-1RA were detected in the aqueous sample with IL-1RA being the most abundant cytokine (1000 pg/mL). While our findings of elevated IL-6, IL-8, IP-10, and MCP-1 are consistent with other studies of herpetic uveitis,<sup>6,7</sup> very little is known about the correlation between IL-1RA and ocular inflammation. Several studies have suggested that IL-1RA reduces the severity of uveitis.<sup>20,21</sup> In an animal model study of endotoxin-induced uveitis, overexpression of IL-1RA showed significantly lower inflammatory cell counts in the anterior and posterior chambers compared with controls.<sup>20</sup> Moreover, the treated mice also demonstrated significantly less *in vivo* fluorescein leakage from inner retinal vessels as compared to the controls.<sup>20</sup> In contrast, the level of IL-1RA was detected in the aqueous fluid at the time of clinically active disease in our patient as her glaucoma filtration surgery was performed due to elevated intraocular pressure despite maximally tolerated medical therapy. However, it is not certain whether IL-1RA provides any protective effect or contributes to the pathogenesis of the disease in our patients due to insufficient data. Thus, further studies are needed to elucidate the involvement of IL-1RA in the pathogenesis of the herpetic uveitis as well as potential therapeutic targets of this cytokine.<sup>20,21</sup>

In summary, we have reported cytokine/chemokine profiles of two patients with herpetic uveitis and their correlation with clinical disease. Cytokine/chemokine profiles of two patients with herpetic uveitis showed elevated levels of MCP-1, IP-10, IL-8, and IL-18 while IL-1RA was elevated in the chronic phase of hypertensive anterior uveitis. The analysis of cytokine and chemokine profiles of ocular fluid may be useful in investigating the immunopathogenesis of uveitis and potentially therapeutic targeting, given the high morbidity and sight-threatening nature of herpetic uveitis and retinitis.

## Ethical Approval

This case series was conducted in accordance with the Declaration of Helsinki. The collection and evaluation of all protected patient health information was performed in a Health Insurance Portability and Accountability Act (HIPAA)-compliant manner.

## Statement of Informed Consent

The written informed consent of research participants was obtained for this case series.

## Author Contributions

Nam V Nguyen, Susanne L Linderman and Tolulope Fashina are shared first authors. Rafi Ahmed and Steven Yeh are senior authors. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

Dr Christopher Conrady reports a patent IFN $\alpha$ 1 for viral retinitis pending to UNMC. The authors declare that there is no conflict of interest.

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