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CASE REPORT

Human Herpesvirus 6A Infection-Associated Acute Anterior Uveitis

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Abstract: Human herpesvirus 6 (HHV-6) infection can cause ophthalmic diseases in immunocompetent patients, recipients of bone marrow transplants, and patients with acquired immunodeficiency syndrome (AIDS). This study describes the case of a healthy 37-year-old male who presented with unilateral anterior uveitis (AU), significant anterior chamber exudation, pupillary membrane closure, increased intraocular pressure, and eyelid edema. Notably, HHV-6A was the only pathogenic agent identified in the blood and aqueous humor. The patient was treated with foscarnet sodium and ganciclovir, showing effective results. Additionally, based on the literature review, the hypothesized mechanism underlying HHV-6A-associated AU was discussed. To the best of our knowledge, this is the first case report of HHV-6A involvement in ocular inflammation and may provide a theoretical basis for further investigations of occurrences of HHV-6A-associated acute AU in clinical settings.

Keywords: human herpesvirus 6A, acute anterior uveitis, secondary glaucoma

Introduction

Anterior uveitis (AU) is the most common type of uveitis and can be either infectious or noninfectious, and the noninfectious AU included immune-mediated or secondary to masquerade syndromes. The top four etiologies of anterior uveitis are as follows: idiopathic, rheumatic disease-associated uveitis, heterochromic cyclitis-associated uveitis, and herpetic uveitis.[1]

Herpesviruses, the causative agent of herpetic uveitis, are double-stranded, enveloped DNA viruses with a 125–230 kbp genome, which can encode approximately 80–180 viral proteins. They are categorized into three subtypes: alpha, beta, and gamma. To date, eight human-infecting herpesvirus types have been identified, collectively called human herpesviruses (HHVs) (Table 1). Notably, herpes simplex virus (HSV), varicella-zoster virus, cytomegalovirus (CMV), and rubella virus (RV) are commonly implicated in various ocular diseases, with HHV-6 being rarely involved.[2] A few studies have suggested an association between HHV-6 and various ocular diseases, including retinitis, keratitis, optic neuropathy, uveitis, and intraocular inflammation.[3–5] However, studies on HHV-6A-associated anterior uveitis are lacking. To the best of our knowledge, this study, for the first time, reports a case of AU with HHV-6A as the probable causative agent.

Case Report

A 37-year-old man who suffered from Mycoplasma pneumonia (M. pneumoniae) infection 2 months previously and was cured for more than a month, was referred to the outpatient clinic owing to complaints of increasing blurred vision and pain in the right eye (oculus dexter [OD]) for 2 weeks. For treatment, tobramycin and dexamethasone ophthalmic, atropine sulfate eye gel was topically applied, and oral prednisone (30 mg) was administered daily for a week. During the first visit, the best corrected visual acuity of the OD of the patient was only the hand movement. The patient underwent

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Table 1 Eight Human Herpesviruses and Their Subtypes

Alphaherpesvirinae Subfamily	Betaherpesvirinae Subfamily	Gammaherpesvirinae Subfamily
HSV-I	CMV	EBV
HSV-II	HHV-6	KSHV
VZV	HHV-7	

Abbreviations: HSV, herpes simplex virus; VZV, varicella zoster virus; CMV, cytomegalovirus; EBV, Epstein–Barr virus; KSHV, Kaposi's sarcoma-associated herpesvirus; HHV: human herpesvirus.

an ophthalmologic examination, revealing eyelid edema, along with conjunctival and ciliary congestion, with excess fibrinopurulent exudate in the anterior chambers (Figures 1A and 2A). Although a funduscopic examination could not be performed, the ocular B-ultrasound examination showed normal results (Figure 1D). Notably, the intraocular pressure (IOP) of the OD was recorded to be >50 mmHg, whereas that of the left eye (oculus sinister [OS]) was 18.6 mmHg. OS exhibited full visual acuity, with no detected abnormalities (Figure 3). The patient presented no systemic complaints or trauma history.

The blood tests showed a cell count of 13.7×10^9 leukocytes/L, with 84.2% neutrophils and 12.6% lymphocytes, and were negative for autoimmune diseases, including rheumatoid factor and antinuclear antibody. Furthermore, except for CMV-immunoglobulin (Ig)G, RV-IgG and HSV-I-IgG, serological tests were negative for human immunodeficiency virus-antibody (Ab), hepatitis C virus-Ab, hepatitis B surface antigen, treponema pallidum-Ab, CMV-IgM, *Toxoplasma gondii*–IgM/IgG, RV-IgM, HSV-I-IgM, and HSV-II–IgM/IgG. Additionally, the blood and aqueous humor samples were negative for bacterial and fungal cultures. Notably, the lung computed tomography revealed the presence of small benign

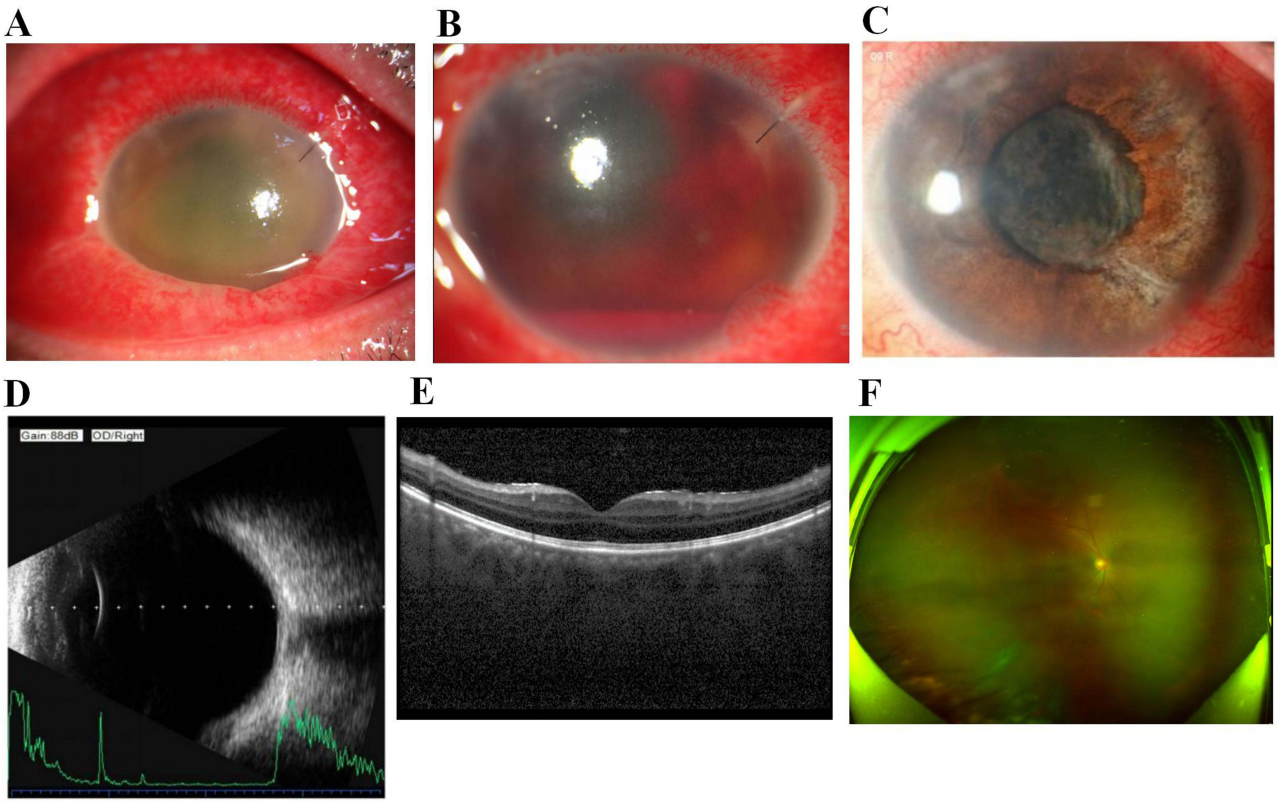

Figure 1 Images of the anterior segment of the right eye at initial diagnosis (**A**), the 1st day post-surgery (**B**), and 2 months post-treatment (**C**). The results of the B-ultrasound examination (**D**), optical coherence tomography (**E**), and fundoscopy (**F**) of the right eye, showing no significant abnormality.

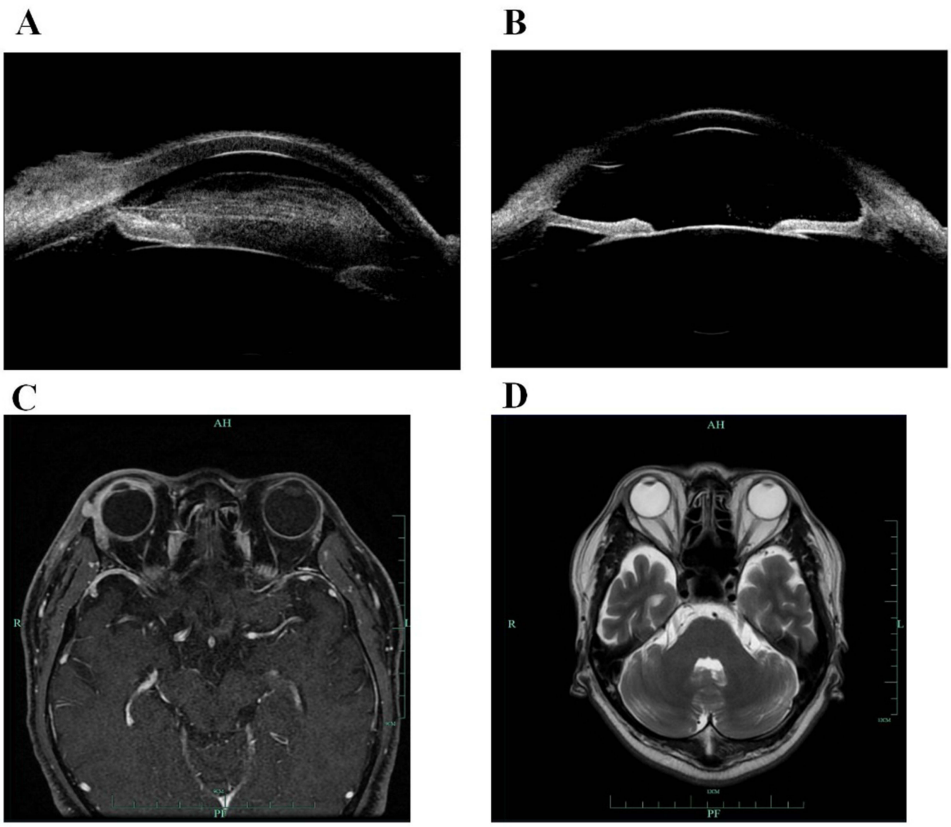

Figure 2 Ultrasound Biomicroscope images showing the change of the anterior chamber inflammation before (**A**) and after (**B**) antiviral treatment. The ocular magnetic resonance imaging showing the changes in the eyelids and lacrimal glands before (**C**) and after (**D**) antiviral treatment.

nodules. Cerebral nuclear magnetic resonance imaging (MRI) results were normal, with no clinical signs of meningitis or encephalitis. In contrast, ocular MRI revealed obvious swelling and inflammation of the OD eyelids and lacrimal glands (Figure 2C). The metagenomic next-generation sequencing (mNGS) of the aqueous humor was performed at another hospital (Affiliated Eye Hospital of Wenzhou Medical University) and only the genomic DNA of HHV-6 was identified.

Owing to worsening anterior chamber exudate formation, uncontrolled high IOP of the OD, and no detection of a definite pathogen, the patient was subjected to the douche of the anterior chamber to remove the exudative membrane. During the surgery, a yellow, dense fibrous exudate membrane (approximately 1 mm thick) was noted in the anterior chamber. The exudate membrane was tightly adhered to the iris, and after its removal, significant iridemia was observed (Figure 1B). The exudate was subjected to pathologic examination, and simultaneously, the aqueous humor and blood samples were subjected to another round of mNGS at another company. Interestingly, similar to previous round results, only the DNA of HHV-6A was detected. Additionally, hematoxylin–eosin staining of the removed exudate showed that the tissue was infiltrated by inflammatory cells, including mainly neutrophils; no tumor cells were found (Figure 4).

Notably, the worsening condition of the patient after hormone therapy suggested that an infection or tumor was the underlying cause of the symptoms. The pathological examination of the exudate membrane of the anterior chamber confirmed the absence of tumor cells, and mNGS analysis of the intraocular fluid from two different institutions identified the DNA of HHV-6A, albeit in low concentrations. Considering the non-detection of other pathogens and tumors, and the low positivity rate of HHV-6 in the normal intraocular fluid,[3] we assumed that HHV-6A was the causative agent of the uveitis in this patient. Thereafter, the patient received local and systemic antiviral treatments. In the following 2 weeks, and antiviral medications foscarnet (3 g/12 h) and ganciclovir (0.45 g/12 h) were intravenously administered. Subsequently, 1 g/ter in die (t.i.d). ganciclovir was orally administered, with the dose gradually being tapered off until discontinuation on day 35. Notably, no treatment-related adverse effects were observed.

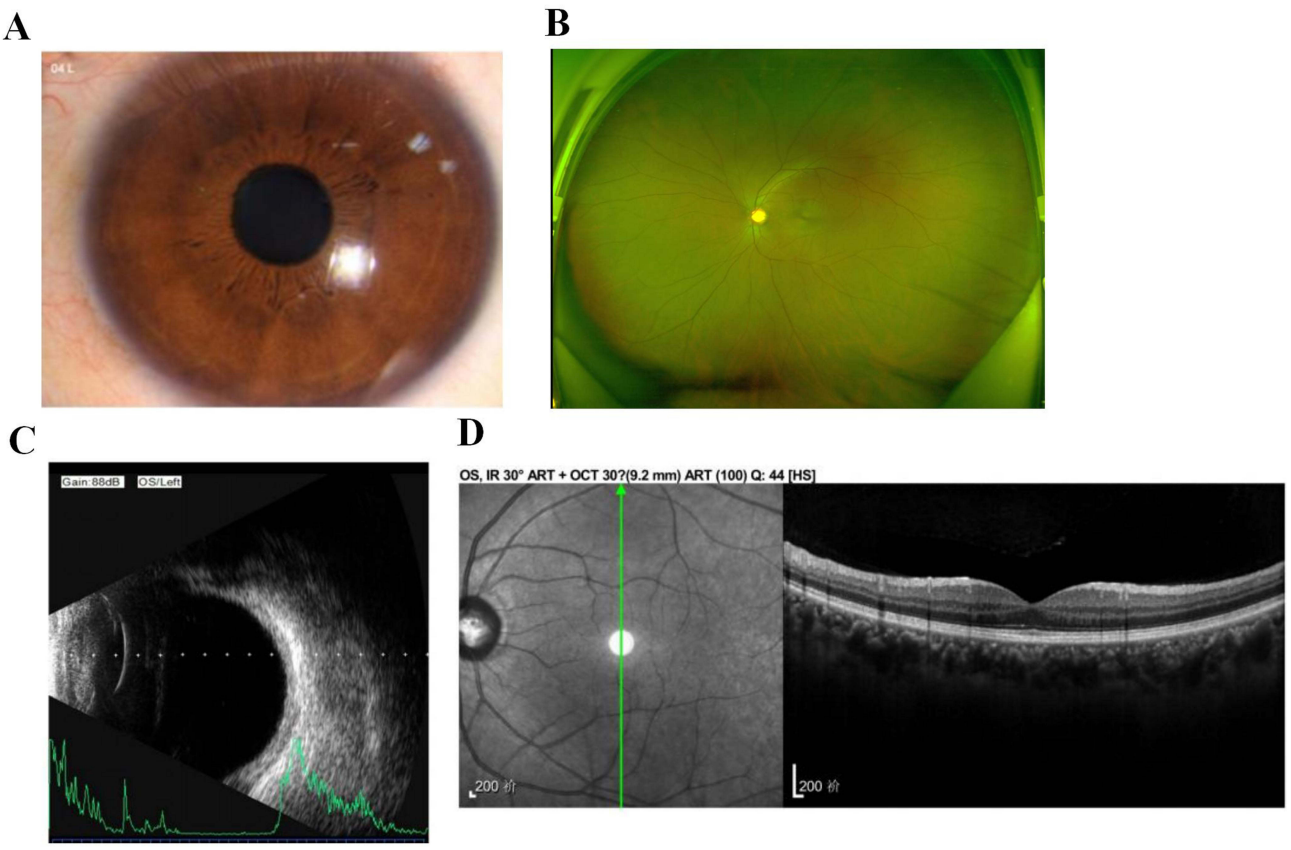

Figure 3 Images of the anterior segment (**A**), fundoscopy (**B**), B-ultrasound examination (**C**), and optical coherence tomography (**D**) of the left eye, showing no significant abnormality.

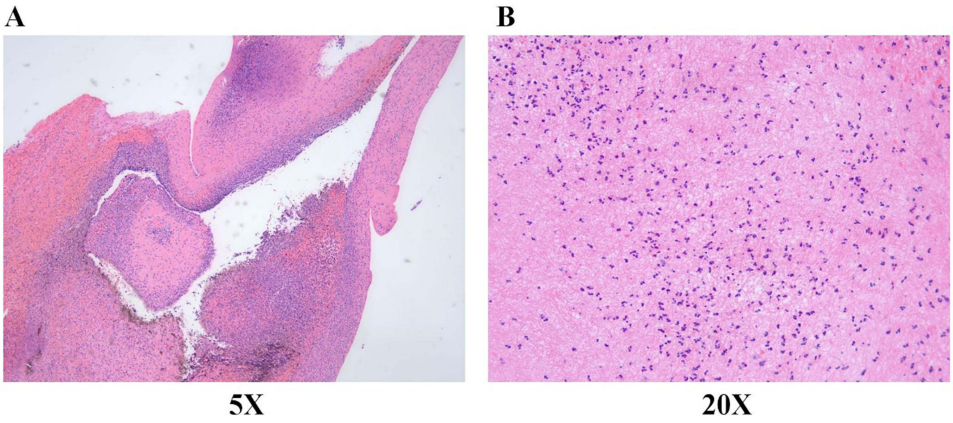

Figure 4 Representative 5x (**A**) and 20x (**B**) images of the removed exudate stained with hematoxylin and eosin.

The inflammatory status of the anterior segment markedly improved (Figures 1C and 2B), and the IOP of the OD returned to normal. After the inflammation disappeared, the fundus could be observed, and the retina and optic disc appeared normal (Figure 1E and F). Additionally, the visual acuity of the patient progressively improved, reaching 20/50 (Snellen visual acuity) in the OD at 2 months and 20/22 at 5 months post-treatment. However, the vision of the patient deteriorated to 6/12 at 12 months post-treatment due to secondary cataracts.

Discussion

HHV-6, also called human B-cell lymphotropic virus, is a ubiquitous lymphotropic and neurotropism virus that was isolated from cultured lymphocytes from individuals with lymphoproliferative disorders by Salahuddin et al in 1986.[6–8] The seroprevalence of HHV-6 antibodies is 80–100% among adults under 40 years old.[9,10] However, the detection of HHV-6 DNA is rare in aqueous fluids and less than 2% in vitreous samples from patients with ocular inflammation.[11,12] HHV-6 comprises glycoprotein H (gH), which interacts with the complement regulator CD46 (or membrane cofactor protein) for fusion and entry into the target cells.[13,14] Because CD46 is present on the membrane of all nucleated cells, HHV-6 can infect various cell types both in vitro and in vivo, including T lymphocytes, fibroblasts, epithelial cells, endothelial cells, oligodendrocytes, microglia, monocytes or macrophages, and dendritic cells.[15] Primary infections, endogenous reactivations, and exogenous reinfections may cause acute HHV-6 infections.[16]

HHV-6 is an etiologic factor for diseases such as exanthema subitum or roseola infantum, multiple sclerosis, encephalitis, epilepsy, and febrile seizures.[17] Reportedly, it has been identified as a potential causative agent of ophthalmic diseases in immunocompetent patients, recipients of bone marrow transplants, and patients with AIDS. Additionally, HHV-6 has been associated with ocular diseases, including retinitis, keratitis, optic neuropathy, uveitis, and intraocular inflammation.[3–5] To the best of our knowledge, to date, HHV-6 has been detected as the sole pathogen (through polymerase chain reaction [PCR] or mNGS) in only eight cases of uveitis (Table 2). Among them, the patients were previously healthy in four cases.[18–24] Furthermore, consistent with the observations of the presented case, the previously reported eight cases effectively responded to antiviral treatments and exhibited a good prognosis, with all the eyes presenting a visual acuity of more than 20/50 at the last follow-up. However, the ocular symptoms in previous cases were primarily manifested in the posterior eye segment, whereas in the case presented in this study, severe inflammation was observed in the anterior segment, with no symptoms in the vitreous body and retina.

There are two closely related HHV-6 variants: HHV-6A and HHV-6B; among them, subtype B is more clinically relevant. In our case, we identified a rare type of HHV-6A as the pathogen. In fact, the International Committee on Taxonomy of Viruses classified HHV-6A and HHV-6B as two distinct viruses in 2012.[25] Elham Bahramian et al have reported that HHV-6A and HHV-6B may exhibit different virulence levels on select cell types, with HHV-6A being more virulent, despite the apparent advantage of HHV-6B being able to more readily infect cells with high CD46 and CD134 expression.[26] The U94 gene product, a gene unique to HHV-6 that mediates site-specific DNA integration in human cells, can facilitate the establishment and/or maintenance of latent infection in these cells; this gene product is expressed at low levels during lytic replication; however, it is a major transcript during latent infection.[27,28] HHV-6A can induce CD46-mediated cell–cell fusion without viral replication via a tetrameric complex comprising glycoproteins gH, gL, gQ1, and gQ2.[29,30] Furthermore, the copy number of HHV-6A is lower than that of HHV-6B.[31] Therefore, we speculated that the acute severe anterior uveitis with a relatively low HHV-6A abundance in mNGS HHV-6A in this case was owing to the characteristics of HHV-6A infection.

Because HHV-6 can integrate into human chromosomes and transmit from parents to offspring,[32] differentiating between active and inactive HHV-6 infection is crucial to prevent misdiagnosis. The presence of chromosomally integrated HHV-6 (ciHHV-6), identified by Luppi et al in 1993,[33] can result in a high copy number of HHV-6, and thus, its persistent detection in the whole blood, cell-free plasma, serum, and other cell types.[34] Mori et al reported a case of misdiagnosis of ciHHV-6 variant A as an active infection because PCR repeatedly detected high copy numbers of HHV-6A DNA in the patient-derived plasma, and antiviral treatment was ineffective.[35] These findings highlight the importance of differentiating ciHHV-6 from active HHV-6 infection. The characteristics of ciHHV-6 are as follows: (a) ciHHV-6 DNA can be detected in non-blood cells such as oral swabs or hair follicles; (b) the ciHHV-6-to-human genome ratio is approximately 1:1; (c) at least one biological parent of the patient carries ciHHV-6; and (d) HHV-6 DNA remains positive in sequential testing, with antiviral treatment deeming ineffective.[36] In the case presented in this study, a serologic test for HHV-6 was not performed because of the lack of a diagnostic kit. Additionally, owing to cost and patient consent issues, HHV-6 DNA was not tested in the aqueous humor and blood samples after a good clinical treatment response was achieved. Nevertheless, the effectiveness of antiviral treatment with the detection of only HHV-6A DNA presents a strong argument for the etiology of an active HHV-6A infection.

Table 2 Summary of the Cases with HHV-6 Infection-Associated Ocular Inflammation

References	Age, Sex	Medical History	Diseased Eye	Ocular Anterior Segment	Ocular Posterior Segment	Intraocular Fluid	Body Fluid	Visual Acuity	Diagnosis
[18]	81, M	DM	OU	Retrodescemetic precipitates	Hyalitis, significant disc edema with hemorrhages	HHV6 (AH, PCR)	HHV6 (Serum, IgM, IgG)	OD: 20/40 Rossano 3; OS: 20/32 Rossano 2	Acute uveo-meningitis associated with HHV6
[5]	42, M	Heterochromia	OD	KPs	Vitreous cells and several peripheral snowballs	HHV6 (VB, PCR)	*Borrelia burgdorferi* (Serum, IgG)	–	–
[19]	59, F	HIV-1	OU	–	Slight pallor of the right optic disc	–	HHV6-B (PBMCs, CSF, PCR)	OU: 20/20	HHV6-Associated Retrobulbar Optic Neuritis
[20]	23, F	Healthy	OU	–	Optic disk edema and inferior SRD	–	HHV6-B (PBMCs, CSF, PCR)	–	Relapsing bilateral anterior optic neuritis; VKH?
[21]	42, F	Acute myelogenous leukemia	OD	No anterior uveitis or pseudohypopyon	Mild vitritis, an oval-shaped subretinal lesion, and several punctate hemorrhages	HHV-6B and HHV-7 (AH, mNGS)	HBsAg, TP-Ab (Serologic test)	OD: 20/20	Choroiditis
[22]	63, M	Healthy	OS	Moderate mutton-fat KPs	Vitreous opacities, significant optic disc edema surrounded by yellowish-white swelling in the inner retina, retinal arteritis, and cotton-wool-like exudates	HHV6 (AH, PCR)	VZV, CMV (Serum, IgG), HHV6 (Serum, IgM, IgG)	OS: 10/20	Uveitis with optic neuritis
[23]	22, M	Healthy, EBV infectious mononucleosis	OU	Fine KPs	Vitreous cells, retinal necrosis, confluent necrotic lesions, and retinal vasculitis	–	EBV (Serum, IgM), HHV6 (CSF, PCR)	OU: 20/20	HHV6 encephalitis and left fourth nerve palsy
[24]	31, M	DM	OU	A large left pupil	Significant disc edema and intraretinal lipid deposits in the macular region	HHV6 (AH, PCR)	HHV6 (Serum, IgM, IgG)	OD:20/25 OS: 20/20	
Our case	37, M	Healthy, *Mycoplasma pneumonia* infection	OD	Excessive amounts of fibrinopurulent exudate	–	HHV6A (AH, mNGS)	HHV6 (Serum, mNGS), CMV, RV, HSV-I (Serum, IgG)	OD: 20/50	

Abbreviations: M, male; F, female; DM, Diabetes Mellitus; KPs, keratic precipitates; AH, aqueous humor; VB, the vitreous body; CSF, cerebrospinal fluid; SRD, serous retinal detachment; HBsAg, hepatitis B surface antigen; TP-Ab, Treponema pallidum-specific antibodies; CS, corneal scraping; PCR, real-time polymerase chain reaction; HIV, human immunodeficiency virus.

Herein, one notable characteristic was the occurrence of significant anterior chamber exudation, which resulted in pupillary membrane closure and increased IOP. After surgically removing the exudative membrane, a tight adhesion between the membrane and the iris was observed, along with obvious hemorrhage. This suggested that HHV-6 may disrupt the blood–ocular barrier by damaging vascular endothelial cells, which have been reported to be fully permissive to HHV-6 infection and possibly form a reservoir for harboring HHV-6.[37] Arnaldo Caruso et al infected fetal human endothelial and other vascular endothelial cells with HHV-6A and observed the HHV-6A infection-mediated production of RANTES (regulated upon activation, normal T cell expressed and secreted) by regulating endothelial cells. RANTES is a proinflammatory chemokine that provides signals for local responses by inflammatory cells and subsequently recruits circulating monocytes and lymphocytes selectively. Notably, RANTES expression occurred independently of HHV-6 replication.[38] Based on the reviewed literature, the following mechanism is proposed for HHV-6A-associated AU development: HHV-6A infects vascular endothelial cells, leading to the production of chemokines such as RANTES and thereby inducing lymphocyte and monocyte accumulation in the eye, which results in exudative membrane formation. Carolyn B. Coulam et al reported a notable increase in neutrophil-specific CD16b messenger RNA levels in HHV-6-positive females with recurrent implantation failure compared to normal controls. This suggested that the virus recruited neutrophils to the site of infection.[39] Consistent with these results, the neutrophils were increased in the present case; however, the underlying mechanism needs further investigation.

In the present case, MRI revealed swelling of the right lacrimal gland. HHV-6 has been reported to be persistently present in the salivary glands, brain tissues, and peripheral blood mononuclear cells.[28,40,41] The lacrimal gland may be a site for latent HHV-6 infection and that the viral reactivation in the patient may have developed from the ocular adnexa.[42]

Our patient had a history of M. pneumoniae infection, which was cured before presentation. We need to define whether the M. pneumoniae infection was associated with our patient's ocular manifestation or HHV-6 infection. A few case reports have revealed an association between M. pneumoniae and uveitis and optic disc edema.[43,44] Only F Vianello et al have reported a case of meningoencephalitis and pneumonia infected by M. pneumoniae and HHV-6.[45] Three rounds of mNGS analysis of the aqueous humor and blood revealed the absence of M. pneumoniae DNA, which indicated that *M. pneumoniae* was not directly associated with uveitis in the patient. Nevertheless, *Chlamydia pneumoniae* infection may have weakened the immune system of the patient, facilitating the activation of latent HHV-6.

Conclusion

This study, to the best of our knowledge, for the first time, describes a case of HHV-6A-associated acute AU in a healthy patient who exhibited a good prognosis after antiviral treatment with foscarnet and ganciclovir. In ocular diseases, the pathogenic characteristics of HHV-6A can differ from those of HHV-6B, which necessitates their clear differentiation in clinical settings. Furthermore, differentiation should be made between acute HHV-6A infection and ciHHV-6A to avoid misdiagnosis. Herein, it was hypothesized that the mechanism underlying HHV-6A infection and severe anterior segment symptoms was as follows: HHV-6A may be present in the lacrimal glands or vascular endothelial cells, and when the immune system is compromised, it is reactivated, thereby leading to ocular inflammation. Altogether, the findings of this case study provide a theoretical basis for the management and further investigation of HHV-6A-associated acute AU.

Ethics and Consent

The patient provided written informed consent for the case details and images to be published. This study obtained approval from The First Affiliated Hospital of Zhejiang University School of Medicine to publish the present case details.

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Disclosure

The authors report no conflicts of interest in this work.

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