



Presumed herpes simplex virus keratouveitis in a 2-year-old child: a case report

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ABSTRACT

Background: Ocular herpes simplex virus (HSV) disease is uncommon in very young children and may be difficult to recognize because history and examination are limited and early manifestations can resemble bacterial conjunctivitis. Pediatric disease may involve multiple corneal layers, extend into the anterior chamber, recur, and threaten visual development. We describe presumed HSV keratouveitis in a 2-year-old child.

Case Presentation: A 2-year-old girl presented with a two-month history of right-eye pain, photophobia, and tearing after an episode diagnosed elsewhere as HSV blepharoconjunctivitis. Previous topical treatments, including antibiotics, had produced little improvement. Examination revealed right eyelid edema, conjunctival congestion, and an inferior geographic epithelial defect involving one-third of the cornea; the anterior chamber was quiet. Suspected HSV epithelial keratitis was treated with topical acyclovir 3% ointment, moxifloxacin, and lubrication. Although the epithelium healed, stromal edema, infiltration, and endotheliitis developed. Topical prednisolone acetate and therapeutic-dose oral acyclovir were commenced after normal renal function was confirmed. Serological testing showed reactive cytomegalovirus (CMV) IgG and IgM; Epstein-Barr virus IgG and IgM, HSV-1 IgG, HSV-2 IgG, rubella IgM, and Toxoplasma IgG and IgM were non-reactive. Initial improvement was followed by acute recurrence one week after transition to prophylactic acyclovir. Examination under anesthesia revealed a recurrent 3-mm epithelial defect, diffuse stromal edema and infiltration, 2+ anterior chamber cells, and right-eye intraocular pressure of 29 mmHg; no keratic precipitates, iris atrophy, synechiae, or posterior-segment abnormalities were identified. Ocular-surface HSV-1/HSV-2 polymerase chain reaction (PCR), obtained after four weeks of topical and three weeks of systemic acyclovir, was negative, and bacterial cultures showed no growth. Ocular CMV and varicella-zoster virus testing was not performed, and the parents declined aqueous-humor sampling. The child received intravenous acyclovir (10 mg/kg every 8 hours) and methylprednisolone (1 mg/kg/day) for five days, with topical anti-inflammatory, cycloplegic, pressure-lowering, lubricating, and initially empirical antibacterial treatment. At discharge, the eye was quiet, intraocular pressure had normalized, and a 4-mm paracentral stromal opacity remained. At six months there was no recurrence; intraocular pressure was 15 mmHg, refraction was stable, and no fixation preference or ocular misalignment was observed.

Conclusions: The sequential unilateral epithelial, stromal, endothelial, and anterior uveal involvement favored HSV, but absent aqueous-humor testing and negative post-treatment surface PCR precluded virological confirmation. This case supports longitudinal assessment of persistent unilateral corneal inflammation in young children and surveillance for recurrence, corneal sequelae, and impaired visual development.

KEYWORDS

keratitis, herpetic; uveitis, anterior; child, preschool; acyclovir

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INTRODUCTION

Herpes simplex virus (HSV) is a common cause of corneal morbidity and the leading infectious cause of corneal blindness in developed countries [1]. Herpes simplex virus type 1 (HSV-1) accounts for most ocular herpetic disease and may involve the corneal epithelium, stroma, or endothelium, with extension to the anterior chamber manifesting as keratouveitis [2]. Pediatric disease can be particularly difficult to recognize because primary infection may be missed or initially diagnosed as blepharoconjunctivitis, while geographic epithelial ulcers, stromal involvement, recurrent disease, corneal scarring, and amblyopia may occur more frequently than in adults [2].

Primary ocular HSV infection may present as blepharoconjunctivitis, particularly in children and adolescents, while pediatric anterior-segment disease may include epithelial, stromal, or endothelial keratitis and iritis [3]. Recognition and management may be particularly challenging in children because difficulties in obtaining a reliable history and performing a comprehensive examination can contribute to misdiagnosis and treatment delay. Pediatric HSV keratitis may also follow a more severe or recurrent course, resulting in stromal scarring, irregular astigmatism, corneal thinning or perforation, and an increased risk of amblyopia; consequently, close follow-up and frequent ocular assessment are important for preserving vision [4]. HSV-1 keratitis is particularly uncommon in infancy and may initially resemble bacterial conjunctivitis, potentially delaying appropriate antiviral treatment and increasing the risk of corneal scarring and amblyopia [5]. Moreover, polymerase chain reaction (PCR)-confirmed HSV-1 anterior uveitis without corneal involvement, keratic precipitates, iris changes, or ocular hypertension has been reported in a child, illustrating that pediatric disease may lack the features conventionally associated with herpetic anterior uveitis [6].

The etiological assessment becomes more complex when keratitis is accompanied by anterior uveitis. HSV-1, varicella-zoster virus (VZV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV) may be detected in ocular samples, although their PCR detection patterns vary substantially by anatomical sampling site [7]. The distribution of anterior-uveitis etiologies also varies among populations and clinical settings. In a tertiary-center study from Singapore, infectious causes accounted for 18.5% of anterior uveitis cases, with HSV and VZV among the most frequently identified infectious etiologies [8]. In a study of otherwise unexplained anterior uveitis in Thailand, intraocular-fluid analysis identified HSV, VZV, and CMV as important viral etiologies [9]. Because both studies were conducted in geographically and clinically selected populations, their findings may not be directly generalizable to other settings. Herpetic anterior uveitis may be caused by HSV, VZV, or CMV; and although keratitis, keratic precipitates, elevated intraocular pressure, and iris atrophy can suggest a herpetic etiology, substantial clinical overlap among these viruses may preclude reliable pathogen-specific attribution without aqueous-humor analysis [10]. HSV-associated anterior uveitis is usually unilateral; nevertheless, uncommon bilateral and otherwise atypical presentations have been reported, including clinically presumed bilateral disease in an immunocompetent patient [11].

The objective of this report was to describe the diagnostic and therapeutic challenges of presumed herpetic keratouveitis in a 2-year-old child, including delayed recognition, sequential involvement of multiple corneal layers, early recurrence, and residual corneal opacity, and to present the management approach and clinical outcome over six months of follow-up.

CASE PRESENTATION

A 2-year-old girl presented to the Cornea Clinic at Farwaniya Hospital, Farwaniya, Kuwait with a two-month history of pain, photophobia, and tearing in the right eye. According to her parents, the symptoms began after an episode of right-sided HSV blepharoconjunctivitis, characterized by unilateral blepharoconjunctivitis accompanied by vesicular eyelid lesions, that had been clinically diagnosed by a physician at a private hospital two months earlier. Before presentation she had received multiple topical treatments, including topical antibiotics and frequent ocular lubrication, with minimal clinical improvement.

The patient had a history of congenital nasolacrimal duct obstruction (CNLDO) in the right eye, associated with recurrent ocular discharge and redness, as well as a history of strabismus. She had worn spectacles since the age of 1 year. Her family history was notable for distal renal tubular acidosis type 1, affecting her 6-year-old sister. There was no other relevant medical or ocular history.

The initial examination was challenging because of poor cooperation; reliable quantitative visual acuity could not be obtained. Examination was performed using a portable slit lamp at 10× and 16× magnification (Keeler™ Classic PSL Portable Hand-Held Slit Lamp, Keeler Ltd., Windsor, UK) and an eyelid speculum following instillation of Benox® eye drops (Oxybuprocaine Hcl 0.4%; EIPICO, Egyptian International Pharmaceutical Industries Company, Cairo, Egypt).

Examination of the right eye revealed eyelid edema, conjunctival congestion, and an inferior geographic corneal epithelial defect involving approximately one-third of the corneal surface. The anterior chamber was quiet, with no cells or flare. The pupil was round, regular, and reactive; the lens was clear; and a good red reflex was present. A presumptive clinical diagnosis of HSV epithelial keratitis was made.

Treatment was initiated with topical acyclovir 3% ophthalmic ointment (Zovirax®, Glaxo SmithKline – Glaxo Wellcome Operations, London, UK) five times daily, topical Vigamox® (moxifloxacin 0.5%; Alcon, Geneva, Switzerland) one drop three times daily for 10 days, and intensive lubrication with Systane® eye drops (Hydroxypropyl guar 0.18%; Alcon Laboratories, Inc., Fort Worth, TX, USA) one drop four times daily. Weekly follow-up was arranged.

At the first follow-up visit, one week after treatment initiation, the conjunctival congestion and eyelid edema had improved markedly. The epithelial defect had healed completely, with negative fluorescein staining; however, significant underlying corneal edema, stromal infiltration, and endotheliitis were observed. Herpetic stromal keratitis and endotheliitis were suspected. Pred Forte® eye drops (Prednisolone acetate 1.0%; Allergan, Inc., Irvine, CA, USA), one drop six times daily for 10 days, was therefore initiated, and the topical antibiotic was continued. Pediatric consultation was requested to determine the appropriate systemic acyclovir dosage. Concurrently, a comprehensive laboratory evaluation comprising a complete blood count, liver function tests, renal function tests, and viral serology was requested.

Serological testing showed reactive CMV IgG and IgM antibodies. Epstein-Barr virus IgG and IgM antibodies, HSV-1 IgG, HSV-2 IgG, rubella IgM, and Toxoplasma IgG and IgM antibodies were non-reactive. The complete blood count and liver and renal function test results were within normal limits. The differential diagnosis included HSV and CMV keratouveitis. The pediatric and infectious-disease teams considered the positive serum CMV results insufficient to establish active ocular or systemic CMV infection in the absence of compatible systemic findings, and no further CMV-directed investigations were considered clinically indicated.

Oral acyclovir suspension (200 mg/5 mL) was initiated at a therapeutic dose of 6.5 mL per dose (260 mg/dose; approximately 17.3 mg/kg/dose for a child weighing 15 kg), administered three times daily for 10 days. Two weeks later, further clinical improvement was observed, with resolution of the corneal edema. The stromal infiltration had been replaced by a faint inferotemporal paracentral anterior stromal corneal opacity with a horizontal diameter measuring $\approx$ 4 mm. The condition was considered to represent resolving herpetic keratitis. Oral acyclovir suspension (200 mg/5 mL) was continued at a prophylactic dose of 10 mg/kg (150 mg per dose, equivalent to 3.75 mL per dose) twice daily.

Despite this initial improvement, the patient returned one week later with acute worsening characterized by severe photophobia, blepharospasm, eyelid edema, and a 3-mm paracentral corneal epithelial defect with underlying diffuse corneal edema. The anterior chamber could not be visualized because of corneal haze. The patient was admitted for examination under general anesthesia (EUA), microbiological sampling of the tear film, conjunctiva, and cornea, cycloplegic refraction, and multidisciplinary evaluation.

The EUA was performed jointly by the cornea; pediatric ophthalmology; oculoplastic; uveitis; and ear, nose, and throat (ENT) teams. Intraocular pressure, measured using iCare PRO rebound tonometer (iCare Finland Oy, Vantaa, Finland), was elevated in the right eye at 29 mmHg, compared with 16 mmHg in the left eye. This was the first documented elevation of intraocular pressure in the affected eye during the course of the disease. The elevated pressure was considered potentially attributable to inflammatory or trabeculitic ocular hypertension associated with anterior uveitis, corticosteroid-related ocular hypertension, or both.

Anterior-segment examination of the right eye using a portable slit lamp at 10 $\times$ and 16 $\times$ magnification (Keeler™ Classic PSL Portable Hand-Held Slit Lamp) revealed conjunctival injection and multiple diffuse areas of superficial punctate keratopathy, together with an inferior paracentral epithelial defect measuring $\approx$ 3 mm. The defect was surrounded by substantial corneal edema and infiltration involving an area measuring $\approx$ 4 mm (Figure 1). The anterior chamber was deep and formed, with 2+ cells. No keratic precipitates, flare, hypopyon, endothelial deposits, iris atrophy, or synechiae were observed. The pupil was pharmacologically dilated, and the crystalline lens and vitreous were clear, with a good red reflex. Examination of the left eye was unremarkable. Bilateral fundus examination with an indirect ophthalmoscope (Welch Allyn Inc., Skaneateles Falls, NY, USA) and a 30-diopter lens (VOLK Optical, Mentor, OH, USA) revealed well-defined optic disc margins, normal retinal vasculature, and preserved foveomacular reflexes in both eyes.

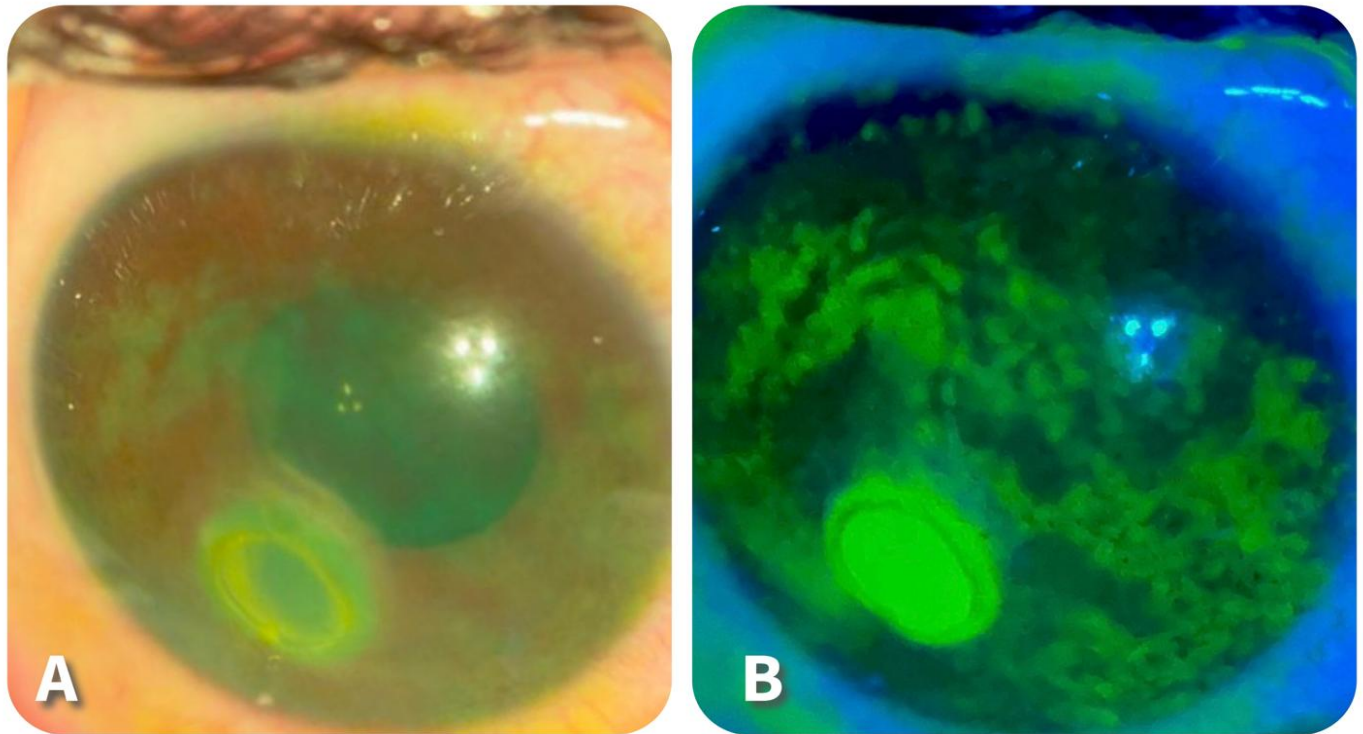


Figure 1. Anterior-segment photographs of the right eye during examination under anesthesia for the acute recurrence. (A) Conjunctival injection, diffuse superficial punctate keratopathy, an inferior paracentral epithelial defect measuring ≈ 3 mm, and surrounding corneal edema and infiltration involving an area measuring ≈ 4 mm. (B) Fluorescein staining highlighting the diffuse superficial punctate keratopathy and the ≈ 3 -mm inferior paracentral epithelial defect.

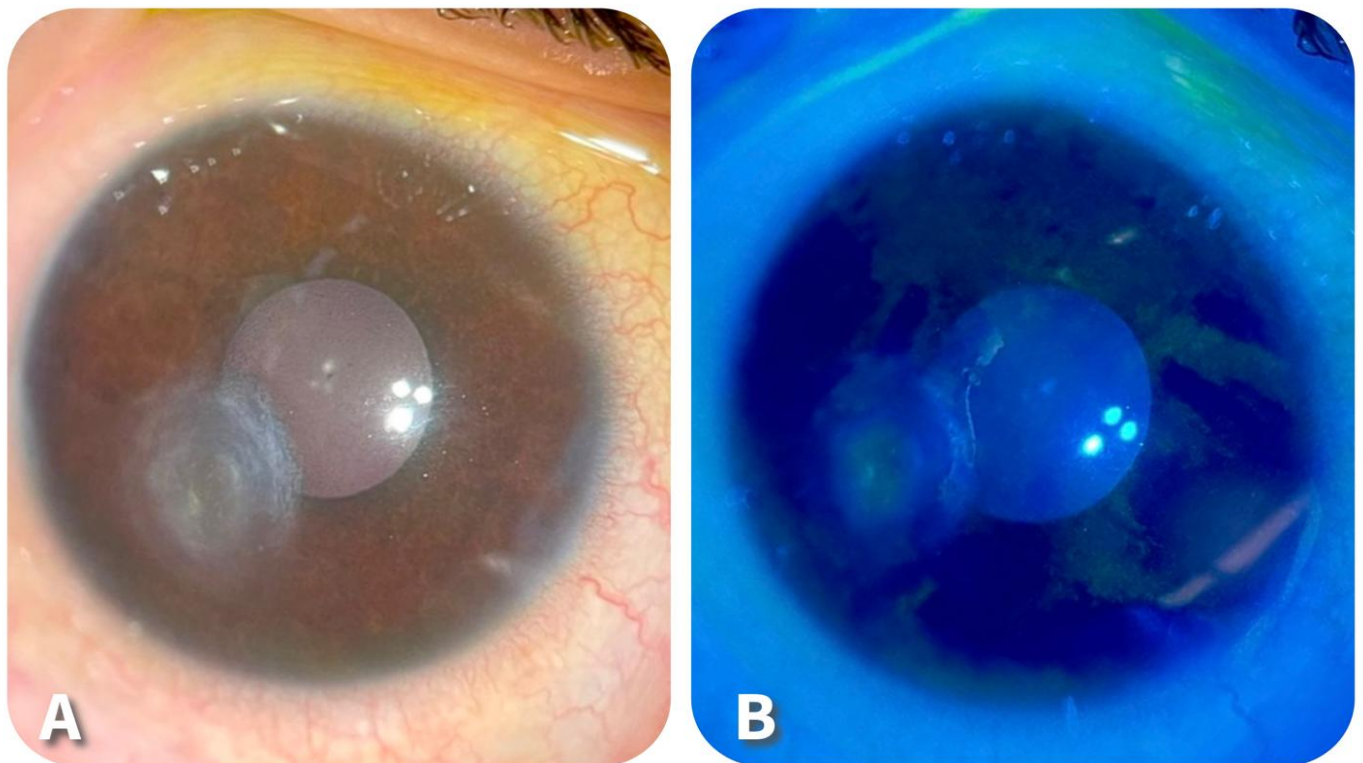


Figure 2. Anterior-segment photographs of the right eye at the final pre-discharge examination under anesthesia following 5 days of inpatient treatment. (A) Residual 4-mm paracentral anterior stromal corneal opacity. (B) Fluorescein staining demonstrating residual superficial punctate keratopathy.

Concurrent oculoplastic evaluation confirmed a membranous obstruction of the right nasolacrimal duct, which was successfully opened by probing and syringing. Nasal endoscopy performed by the ENT team revealed no abnormalities. Cycloplegic refraction was +6.00 DS/−3.25 DC × 107° in the right eye and +6.00 DS/−3.00 DC × 73° in the left eye. Keratometry readings were K1 41.00 D/K2 45.75 D in the right eye and K1 41.00 D/K2 43.25 D in the left eye.

Corneal, conjunctival, and tear-film specimens were collected for bacterial culture and antimicrobial-susceptibility testing and for HSV-1/HSV-2 PCR. Sampling was performed after four weeks of topical acyclovir and three weeks of systemic acyclovir treatment. PCR testing for VZV, CMV, adenovirus, and enteroviruses was not performed. Aqueous-humor PCR testing for HSV and CMV was considered; however, the parents declined all intraocular sampling. Consequently, ocular CMV infection could not be molecularly ruled out.

Following multidisciplinary discussion involving the infectious-disease, rheumatology, pediatric ophthalmology, uveitis, and cornea teams, the decision was made to continue inpatient management. Intravenous methylprednisolone was initiated at 1 mg/kg/day in two divided doses (7.5 mg twice daily; total daily dose, 15 mg for a body weight of 15 kg) for 5 days to control the severe inflammatory keratouveitis, after instituting systemic antiviral therapy and empirical antibacterial coverage. Intravenous Losec® (omeprazole) was administered at 1 mg/kg/day once daily for 5 days after ruling out contraindications. Intravenous acyclovir was administered at 10 mg/kg every 8 hours, with adequate hydration and renal function monitoring maintained throughout treatment.

Fortified vancomycin ophthalmic solution (50 mg/mL; Zermacin, vancomycin hydrochloride 0.5-g lyophilized powder for solution; Arwan Pharmaceutical Industries, Lebanon) and fortified ceftazidime ophthalmic solution (50 mg/mL; Fortum®, ceftazidime 2 g; GlaxoSmithKline, Rueil-Malmaison, France) were administered hourly during the daytime. Additional topical treatment comprised cyclopentolate hydrochloride 1% ophthalmic solution three times daily, intensive ocular lubrication with Systane® lubricant eye drops, Maxitrol® ophthalmic ointment (neomycin sulfate, polymyxin B sulfate, and dexamethasone; distributed by Novartis Pharmaceuticals Corporation, NJ, USA) at bedtime, and Cosopt® eye drops (dorzolamide hydrochloride 2% and timolol maleate 0.5% ophthalmic solution) twice daily. This treatment regimen was initiated immediately after the EUA.

HSV-1 and HSV-2 DNA were not detected by real-time PCR in the submitted corneal, conjunctival, or tear-film specimens. Bacterial cultures of the corneal and conjunctival swabs showed no growth after 48 hours, after which the fortified antibiotic eye drops were discontinued.

Daily examinations during hospitalization showed progressive improvement, including reduced blepharospasm, decreased conjunctival injection, and stabilization of the corneal findings. Intravenous acyclovir and methylprednisolone were continued for a total of five days together with the topical therapy.

At the final pre-discharge EUA the anterior chamber was quiet, with no active stromal edema or infiltration. Residual superficial punctate keratopathy with fluorescein staining and a 4-mm paracentral anterior stromal corneal opacity remained (Figure 2). Intraocular pressure had normalized to 9 mmHg while the patient was receiving Cosopt®, which was subsequently discontinued. She was discharged on frequent ocular lubrication and prophylactic oral acyclovir at 150 mg per dose (3.75 mL of the 200 mg/5 mL suspension) twice daily. Monthly follow-up was arranged in both the cornea and pediatric ophthalmology clinics. The patient was compliant with topical and systemic treatment. No treatment-related systemic adverse events were documented.

At the six-month follow-up, the patient's ocular condition remained stable. There were no epithelial defects, epithelial or stromal edema, or endotheliitis. A 4-mm paracentral anterior stromal opacity remained. Intraocular pressure was 15 mmHg, and the anterior chamber was quiet, with no cells or flare. There was no evidence of relapse or recurrence. Cycloplegic refraction was unchanged from that obtained during the recurrence EUA. Best-corrected monocular grating acuity measured with Teller Acuity Cards at a testing distance of 55 cm was 19 cycles per degree (cpd) in the right eye and 26 cpd in the left eye. The patient remained orthotropic with spectacle correction and showed no fixation preference. Spectacle wear was continued, and no patching or other amblyopia treatment was initiated. Prophylactic acyclovir was discontinued. Adherence to outpatient topical and oral treatment and overall treatment tolerability were not formally assessed. No systemic treatment-related adverse events were documented in the available medical records. The chronological clinical course and management are summarized in Table 1.

This case report was reviewed and approved by the Ophthalmology Department Review Board, Farwaniya Hospital, Kuwait. The case report was prepared in accordance with the principles of the Declaration of Helsinki. Written informed consent for publication of the case details and accompanying clinical images was obtained from the patient's parent.

Table 1. Chronological summary of the clinical course and management

Time	Clinical events
Two months prior to presentation	- Clinically diagnosed herpes simplex blepharoconjunctivitis at a private hospital
At presentation	- Presumptive herpetic epithelial keratitis - Topical acyclovir 3% ointment 5x daily, moxifloxacin 0.5% one drop 3x daily for 10 days, Systane® one drop 4x daily were started - Weekly follow-up arranged
One week after treatment initiation	- Epithelial defect healed completely, conjunctival congestion and eyelid edema markedly improved - Corneal edema, stromal infiltration, and endotheliitis raised suspicion of herpetic stromal keratitis/endotheliitis - Prednisolone acetate 1% one drop 6x daily for 10 days added, topical antibiotic continued - Complete blood count, liver and renal function tests, and viral serology requested - After pediatric consultation, oral acyclovir suspension started at 260 mg/dose (6.5 mL of 200 mg/5 mL; approximately 17.3 mg/kg/dose) 3x daily for 10 days
Two weeks after initiation of therapeutic-dose oral acyclovir	- Corneal edema resolved, stromal infiltration replaced by a faint inferotemporal paracentral anterior stromal opacity measuring $\approx$ 4 mm horizontally - Condition considered as resolving herpetic keratitis - Oral acyclovir reduced to prophylaxis at 150 mg/dose (3.75 mL of 200 mg/5 mL; 10 mg/kg/dose) 2x daily.
One week after transition to prophylactic oral acyclovir	- Acute recurrence of presumed herpetic keratouveitis with severe photophobia, blepharospasm, eyelid edema, a 3-mm paracentral epithelial defect, and diffuse corneal edema - Multidisciplinary evaluation and EUA showed diffuse superficial punctate keratopathy; a 3-mm inferior paracentral epithelial defect with $\approx$ 4 mm of surrounding corneal edema/infiltration; 2+ anterior chamber cells; and intraocular pressure 29 mmHg OD and 16 mmHg OS - Corneal, conjunctival, and tear-film specimens obtained for bacterial culture/antimicrobial susceptibility and HSV-1/HSV-2 PCR - Inpatient treatment: intravenous methylprednisolone 1 mg/kg/day in two divided doses for 5 days, intravenous omeprazole 1 mg/kg/day once daily for 5 days, intravenous acyclovir 10 mg/kg every 8 hours, fortified vancomycin and ceftazidime 50 mg/mL hourly during daytime, cyclopentolate hydrochloride 1% 3x daily, intensive Systane® lubrication, Maxitrol® ointment at bedtime, Cosopt® 2x daily - Hydration and renal function monitored during intravenous acyclovir therapy
Final pre-discharge EUA after five days of inpatient treatment	- Quiet anterior chamber with no active stromal edema or infiltration; residual superficial punctate keratopathy with fluorescein staining and a 4-mm paracentral anterior stromal opacity - Intraocular pressure 9 mmHg on Cosopt®, which was then discontinued - Discharge treatment: frequent ocular lubrication and prophylactic oral acyclovir 150 mg/dose (3.75 mL of 200 mg/5 mL) 2x daily - Monthly cornea and pediatric ophthalmology follow-up arranged
At the six-month follow-up	- Stable ocular status with no epithelial defect, epithelial or stromal edema, endotheliitis, relapse, or recurrence - Persisting 4-mm paracentral anterior stromal opacity - Intraocular pressure 15 mmHg; anterior chamber quiet without cells or flare - Cycloplegic refraction unchanged from the recurrence EUA - Patient remained orthotropic with spectacle correction, showing no fixation preference - Spectacle wear continued; no patching or other amblyopia treatment required - Prophylactic acyclovir discontinued

Patient/caregiver perspective: The patient's parent described the prolonged clinical course, repeated examinations, hospital admission, and frequent administration of ocular and systemic medications as challenging for both the child and the family. At the six-month follow-up, the parent expressed satisfaction with the child's clinical improvement and the absence of further recurrence and acknowledged the importance of continued ophthalmic follow-up to monitor for recurrence and visual-development concerns.

DISCUSSION

This case illustrates the diagnostic and therapeutic challenges posed by presumed herpetic keratouveitis in early childhood. A 2-year-old girl presented after a two-month history of unilateral ocular symptoms that had initially been clinically diagnosed as HSV blepharoconjunctivitis and treated with topical antibiotics. The subsequent course, including geographic epithelial keratitis followed by stromal edema and infiltration, endotheliitis, anterior chamber inflammation, ocular hypertension, early recurrence, and residual stromal opacity, was compatible with the recognized spectrum of ocular HSV disease. Nevertheless, because the preceding blepharoconjunctivitis was not virologically confirmed, ocular-surface PCR was negative after antiviral treatment, and the parents did not consent to anterior chamber paracentesis, the diagnosis should be regarded as presumed HSV keratouveitis rather than PCR-confirmed HSV infection.

The preceding unilateral blepharoconjunctivitis with vesicular eyelid lesions provided relevant clinical context. Primary HSV infection may manifest as blepharoconjunctivitis in children and may subsequently involve the cornea and anterior uvea [3]. HSV infection may also initially present as nonspecific blepharoconjunctivitis, with dendritiform corneal lesions becoming apparent later [12]. The initial episode in our patient should therefore be considered supportive—but not diagnostic—evidence of HSV infection as it was not virologically confirmed.

Recognition of ocular HSV infection can be particularly difficult in young children because clinical history and slit-lamp examination may be limited, and early disease may be mistaken for bacterial conjunctivitis [5, 13]. Casanova et al. reported PCR-confirmed, noncongenital HSV-1 keratitis in an immunocompetent 9-month-old infant who was initially treated for presumed bacterial conjunctivitis before progressive corneal opacity prompted reconsideration of the diagnosis [5]. Similarly, our patient had persistent unilateral disease despite previous topical antibiotic treatment but unlike that infant she subsequently developed stromal, endothelial, and anterior uveal involvement, while virological confirmation could not be obtained. These cases emphasize that HSV should remain in the differential diagnosis of persistent unilateral corneal inflammation in young children, including those without systemic illness or recognized immunodeficiency.

The clinical course was also consistent with the broader spectrum reported in pediatric anterior-segment HSV disease. In a pediatric series, diagnosis was based predominantly on compatible history and examination, with culture or PCR performed in selected cases; epithelial, stromal, endothelial, and uveal manifestations were documented, together with clinically important rates of recurrence and amblyopia [14]. Pediatric HSV keratitis may exhibit geographic epithelial ulceration, stromal involvement, recurrence, corneal scarring, and amblyopia more frequently than adult disease. Extension of inflammation to the anterior chamber may produce keratouveitis and ocular hypertension, which are recognized complications of HSV keratitis in both children and adults [2]. Our patient's young age, sequential involvement of multiple corneal layers, recurrence, and residual stromal opacity therefore place her at particular risk of long-term visual morbidity.

This presentation was clinically distinct from neonatal HSV disease. Neonatal HSV generally becomes clinically apparent within the first six weeks of life and is classified as skin, eye, and/or mouth disease, central nervous system disease, or disseminated infection [15]. Presentation at 2 years of age with localized anterior-segment disease and no evidence of systemic involvement was therefore more consistent with post-neonatal ocular HSV disease than with neonatal HSV infection.

At the initial corneal-clinic assessment, examination revealed right eyelid edema, conjunctival congestion, and an inferior geographic epithelial defect involving approximately one-third of the corneal surface. Given these findings and the recent history of clinically diagnosed unilateral HSV blepharoconjunctivitis with vesicular eyelid lesions, the corneal lesion was considered clinically compatible with HSV epithelial keratitis. Topical acyclovir 3% ophthalmic ointment (Zovirax®) was administered five times daily. This management was consistent with the recommended use of antiviral therapy for active HSV epithelial keratitis [16]. Topical corticosteroid therapy was not introduced while the epithelial defect remained active, as corticosteroids should generally be avoided or minimized in the presence of HSV epithelial ulceration [16–18]. Weekly follow-up was arranged to monitor epithelial healing and detect progression or treatment-related complications. At the subsequent review, the epithelial defect had healed completely, with negative fluorescein staining. However, underlying stromal edema and infiltration had become apparent, accompanied by clinical evidence of endotheliitis. HSV epithelial, stromal, and endothelial keratitis represent anatomically distinct manifestations that require different therapeutic approaches [14, 16, 18], although combined involvement of different corneal layers is well documented in pediatric HSV disease and appears to occur more frequently in children than in adults [14, 16]. In our patient, these findings indicated sequential progression from epithelial keratitis to deeper corneal involvement.

Prednisolone acetate 1% ophthalmic suspension (Pred Forte®), administered as one drop six times daily, was therefore initiated together with oral acyclovir. The therapeutic components of this regimen were consistent with the guideline recommendation that HSV stromal and endothelial keratitis be treated with topical corticosteroid therapy under antiviral coverage [16]. Because of the family history of renal disease, pediatric consultation was obtained before systemic acyclovir was commenced. Renal function was assessed before treatment in view of the known risk of acyclovir-associated nephrotoxicity [19, 20]; the patient's renal function results were normal. In view of the progression to stromal keratitis and endotheliitis at an unusually young age [13, 21], a comprehensive laboratory evaluation was also undertaken to assess the patient's general health and investigate alternative infectious etiologies [22].

The development of unilateral anterior chamber inflammation and elevated intraocular pressure further raised suspicion of herpetic keratouveitis. Corneal involvement and ocular hypertension have been reported more frequently in HSV-associated than in VZV-associated anterior uveitis; however, no individual clinical finding reliably identifies the causative herpesvirus [10]. Hence the absence of keratic precipitates, iris atrophy, and posterior synechiae in our patient did not rule out herpetic anterior uveitis, but reduced the specificity of the clinical diagnosis.

Pediatric HSV anterior uveitis may also lack findings conventionally associated with adult disease. Murthy et al. reported PCR-confirmed HSV-1 anterior uveitis in a healthy 5-year-old child who presented without corneal involvement, keratic precipitates, iris changes, or elevated intraocular pressure [6]. Our patient similarly lacked keratic precipitates and iris atrophy but differed by having prominent epithelial, stromal, and endothelial corneal involvement and subsequently elevated intraocular pressure. Resolution following oral acyclovir and topical corticosteroid treatment was also documented in the PCR-confirmed pediatric case reported by Murthy et al. [6]; however, treatment response in our patient cannot independently establish HSV as the cause because several antiviral, anti-inflammatory, antibacterial, and pressure-lowering therapies were being administered concurrently.

Although herpetic anterior uveitis is generally unilateral, variability beyond the typical phenotype has been reported. Chu and Gilhotra described bilateral chronic presumed HSV anterior uveitis in an immunocompetent adult despite the absence of detectable HSV DNA in aqueous humor [11]. In contrast, our patient had unilateral keratouveitis, which is more typical of herpetic disease. Chu and Gilhotra's report illustrates atypical laterality, but because its HSV attribution was also presumptive [11], it does not provide independent evidence about the diagnostic sensitivity of aqueous-humor PCR.

CMV remained a key differential given endotheliitis, anterior uveitis, and ocular hypertension [23–25], plus had positive serum CMV IgG and IgM results. Nevertheless, peripheral serology alone cannot establish active ocular CMV infection; definitive diagnosis generally depends on demonstration of CMV DNA in aqueous humor [23, 26, 27]. The limited specificity of serum antibody results for intraocular disease is further illustrated by the absence of a relationship between serum herpesvirus antibody titers and pathogen-specific aqueous-humor findings in patients with herpetic anterior uveitis [28]. High background CMV seropositivity has also been documented in some populations: for example, CMV IgG seropositivity reached 87% in a cohort of pregnant women in Singapore, although that adult antenatal estimate cannot be extrapolated directly to a 2-year-old child [29]. Positive serum CMV IgM alone does not necessarily establish active CMV infection, and serological results may require cautious interpretation [30, 31]. In this patient, following pediatric and infectious-disease consultation and in the absence of compatible systemic findings, the serum CMV results were considered insufficient to establish active systemic or ocular CMV infection; no additional systemic CMV investigations were considered clinically indicated at that time. Ocular CMV infection nevertheless could not be excluded because the parents declined aqueous-humor sampling.

The phenotype in our patient was less typical of CMV corneal endotheliitis. CMV endotheliitis is characteristically associated with localized or diffuse corneal edema, coin-shaped or linear keratic precipitates, anterior uveitis, and elevated intraocular pressure, with a generally intact corneal epithelium [32]. By contrast, this child initially had geographic epithelial ulceration and stromal infiltration and did not display coin-shaped or linear keratic precipitates. Published regimens for CMV endotheliitis have primarily used topical, intravitreal, or systemic ganciclovir, or oral valganciclovir, frequently in combination with topical corticosteroids; however, no consensus has been established on the optimal agent, route, dosage, or treatment duration [32, 33]. In one series [34] cited in Alfawaz's review [33], topical acyclovir was co-administered in four of eight patients receiving multidrug antiviral and corticosteroid regimens; however, these observations do not establish acyclovir alone as effective CMV-directed therapy [33, 34]. Accordingly, improvement during acyclovir-containing treatment was clinically compatible with HSV but was not diagnostically conclusive, because pathogen-specific attribution generally requires integration of the clinical phenotype with

virological testing, and corticosteroids and other concurrent therapies may also have contributed to the observed improvement [35, 36]. Taken together, these considerations favored HSV over CMV but were not definitive.

The negative HSV PCR results from the corneal, conjunctival, and tear-film specimens did not definitively rule out HSV infection [37]. HSV keratitis is diagnosed primarily on clinical grounds, and the likelihood of PCR detection is influenced by clinical phenotype, timing and source of sampling, specimen-collection technique, and prior antiviral treatment. Studies have shown that HSV DNA is detected less consistently in stromal or atypical keratitis than in typical dendritic or geographic epithelial disease. Tear samples also tend to have lower PCR detection rates than corneal scrapings, while PCR analysis of conjunctival swabs has shown limited concordance with clinical diagnosis [38–40]. The timing of tear-sample collection can substantially influence the diagnostic yield of HSV testing, because viral detection varies during the course of disease and may be reduced by prior antiviral therapy [39]. In patients with dendritic or geographic keratitis, tear HSV-specific secretory IgA levels increased with disease duration, peaked on days 9–10, and decreased sharply after day 11 of illness [41]. In our patient, the ocular-surface specimens were collected after approximately four weeks of topical and three weeks of systemic acyclovir treatment, when stromal and anterior-chamber inflammation predominated. The negative PCR results therefore provided no virological confirmation but should be interpreted cautiously and not regarded as evidence to rule out HSV as the underlying etiology.

In cases of suspected viral keratouveitis or anterior uveitis, aqueous-humor analysis using PCR and/or intraocular antibody testing can improve pathogen-specific diagnosis, including differentiation among HSV, VZV, and CMV; this may be particularly valuable in diagnostically challenging pediatric cases [6, 42–45]. In a Singapore tertiary-center cohort, aqueous-humor PCR for HSV, VZV, and CMV was used selectively in cases of hypertensive uveitis or when infectious or undiagnosed systemic disease was suspected [8]. Similarly, the combination of anterior chamber inflammation and elevated intraocular pressure in our patient prompted consideration of aqueous-humor PCR for HSV and CMV. However, the parents did not consent to anterior chamber paracentesis.

PCR and intraocular antibody analysis may provide complementary evidence [41, 42, 46]. De Groot-Mijnes et al. found that PCR alone would have missed 34% of herpesvirus infections identified through combined aqueous-humor testing and that viral DNA was detected more readily during the earlier phase of disease, whereas intraocular antibody production remained detectable later [46]. In a selected Thai adult population with otherwise unexplained anterior uveitis and an inadequate response to topical corticosteroids, combined PCR and Goldmann-Witmer coefficient analysis identified a viral etiology in 20 of 30 patients [9]. However, that cohort comprised highly selected adults and excluded keratouveitis [9], so its etiological frequencies cannot be extrapolated to this patient. Because the parents did not consent to aqueous-humor sampling, neither HSV nor CMV could be confirmed or definitively ruled out; accordingly, the diagnosis remained presumed HSV keratouveitis, with HSV considered the most likely etiology based on the overall clinical phenotype and disease course.

During the acute recurrence, EUA documented recurrent epithelial disease, diffuse stromal edema, 2+ anterior chamber cells, and an intraocular pressure of 29 mmHg. The elevated pressure may have resulted from herpetic trabeculitis, corticosteroid exposure, or both. In a selected series of recurrent unilateral anterior uveitis with sectoral iris atrophy, elevated intraocular pressure during active inflammation occurred in 90% of patients and was considered likely to reflect trabecular inflammation [28]. Ocular hypertension is a recognized feature of viral anterior uveitis, including HSV-associated disease [47]. Because our patient had also received topical corticosteroids, the respective contributions of inflammatory trabeculitis [48] and a corticosteroid-associated pressure response [49] could not be determined.

The hospitalized recurrence was treated with antiviral, anti-inflammatory, pressure-lowering, cycloplegic, lubricating, and initially empirical antibacterial therapy. Fortified vancomycin and ceftazidime at 50 mg/mL were administered while secondary bacterial keratitis was ruled out; both were discontinued after cultures showed no growth. In the cohort reported by Neumann et al., HSV- and VZV-associated anterior uveitis was managed with oral acyclovir, topical corticosteroids, and mydriatic therapy, using pressure-lowering treatment when intraocular pressure was elevated [10]. In our patient, intravenous methylprednisolone was administered for the severe inflammatory component after instituting systemic antiviral therapy and empirical antibacterial coverage [50, 51].

Intravenous acyclovir was administered at 10 mg/kg every 8 hours for 5 days, equivalent to 30 mg/kg/day. This dosage falls within the reported parenteral range of 30–45 mg/kg/day in three divided doses for children older than three months [52]. As nephrotoxicity and intravenous-line complications have been reported with parenteral acyclovir in children [53, 54], adequate hydration and renal function monitoring were maintained throughout treatment. Although Berkhout et al. [53] support the dosage and safety-monitoring measures used in this patient, they do not

specifically establish intravenous acyclovir as standard treatment for isolated ocular HSV disease.

Recurrence one week after transition to prophylactic oral acyclovir does not necessarily argue against HSV. Suppressive therapy reduces but does not eliminate recurrence [55, 56]. In the Herpetic Eye Disease Study, the cumulative probability of recurrent ocular HSV disease during 12 months was 19% with oral acyclovir and 32% with placebo, corresponding to a rate ratio of 0.55 [55]. However, participants in that trial were at least 12 years old and had experienced an episode of ocular HSV disease within the preceding year; therefore, its efficacy estimate and dosing regimen should not be directly extrapolated to a 2-year-old child. More directly relevant pediatric evidence was provided by Liu et al. [21], who reported at least one breakthrough recurrence in six of 16 children receiving long-term oral acyclovir prophylaxis; in at least one child, recurrence followed a growth-related reduction in the adequacy of the baseline dose, emphasizing the need for periodic dose reassessment as children grow. Though Liu et al.'s small retrospective case series evidences that breakthrough recurrence can occur, it does not establish the efficacy of prophylaxis or explain the mechanism of recurrence in our patient. Furthermore, the early recurrence in our patient occurred shortly after treatment de-escalation and should not be interpreted as evidence of antiviral resistance in the absence of virological testing or susceptibility analysis [57]. These observations underscore the importance of close follow-up during suppressive therapy and after treatment de-escalation so that recurrences and associated complications can be detected and managed promptly [55].

Following intensified treatment, the epithelial defect, stromal edema, infiltration, anterior chamber inflammation, and ocular hypertension resolved, leaving a 4-mm paracentral anterior stromal opacity. At six months, the eye remained quiet without recurrence, intraocular pressure was normal, cycloplegic refraction was stable, and the child remained orthotropic with spectacles, showing no fixation preference. These findings were reassuring, and no additional amblyopia treatment was considered clinically indicated at that time. Nevertheless, fixation-preference testing has limited sensitivity and does not definitively rule out amblyopia in preschool children [58, 59]. Given the residual paracentral corneal opacity and the recognized risks of recurrence, corneal scarring, refractive sequelae, and amblyopia in pediatric HSV keratitis, continued pediatric ophthalmic surveillance of fixation behavior, age-appropriate monocular visual acuity, cycloplegic refraction, ocular alignment, and corneal clarity remain important [13, 21, 60, 61].

A strength of this report is the longitudinal documentation of the evolving corneal and anterior-chamber findings, acute recurrence, multidisciplinary assessment, and ocular outcome over six months. The principal limitation of this case is the absence of pathogen-specific intraocular confirmation. The prior blepharoconjunctivitis was diagnosed clinically; ocular-surface HSV PCR was performed only after prolonged antiviral exposure; no ocular-surface PCR testing for CMV or VZV was performed; and aqueous-humor PCR and intraocular antibody analysis were unavailable because parental consent for anterior chamber paracentesis was not provided. In addition, improvement occurred during multidrug treatment and cannot be attributed specifically to acyclovir. The limited six-month follow-up also precludes conclusions about long-term recurrence, refractive effects, amblyopia, or permanence of the stromal opacity. Despite these limitations, the chronological evolution from clinically diagnosed unilateral blepharoconjunctivitis with vesicular eyelid lesions to geographic epithelial keratitis, stromal keratitis, endotheliitis, anterior uveitis, and ocular hypertension made HSV the most clinically plausible etiology. The case emphasizes that ocular HSV should be considered in young children with persistent unilateral blepharoconjunctivitis or corneal inflammation, that negative post-treatment ocular-surface PCR does not reliably rule out the diagnosis, and that atypical pediatric keratouveitis requires cautious integration of clinical phenotype, disease evolution, laboratory limitations, treatment response, and continued visual-development surveillance.

CONCLUSIONS

This case illustrates the diagnostic and therapeutic challenges of presumed HSV keratouveitis in a 2-year-old child. In young children, limited cooperation and nonspecific early manifestations may complicate recognition of ocular HSV disease. Persistent unilateral blepharoconjunctivitis or corneal inflammation, particularly when followed by sequential epithelial, stromal, endothelial, or anterior uveal involvement, should prompt consideration of HSV while alternative etiologies are appropriately evaluated. Because recurrence may occur after treatment de-escalation or during suppressive therapy, close follow-up is warranted to detect reactivation, monitor corneal and intraocular-pressure sequelae, and assess visual development. In the absence of aqueous-humor testing, the diagnosis in this case remains presumptive. Further pediatric studies are needed to refine diagnostic approaches and establish age-appropriate treatment and suppressive strategies for HSV keratouveitis in very young children.

ETHICAL DECLARATIONS

Ethical approval: This case report was reviewed and approved by the Ophthalmology Department Review Board, Farwaniya Hospital, Kuwait. The case report was prepared in accordance with the principles of the Declaration of Helsinki. Written informed consent for publication of the case details and accompanying clinical images was obtained from the patient's parent.

Conflict of interest: None.

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