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LETTER TO THE EDITOR

Bilateral Blepharoconjunctivitis as the Presenting Sign of Disseminated Herpes Simplex 1 Infection in a Preterm Neonate

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A 1056-g female infant was delivered via cesarean section at 26 weeks and 2 days of gestation to a 20-year-old gravida 2 para 2 woman with spontaneous early rupture of membranes for 6 days. The mother and her partner had no history of herpes simplex virus (HSV) infection before, at the time of, or after birth. No visible lesions were present at delivery.

GENERAL FINDINGS

The infant had APGAR scores of 8 and 9 at 1 and 5 min, respectively. She was asymptomatic and her physical examination was normal until day 7. On day 7, the infant developed conjunctival infection and yellow discharge with clear cornea on both eyes; netilmycin eyedrops were started empirically. No skin lesions were present at that time. One day later, scanty and indistinct hyperemic rash was noted on the anterior chest wall lateral to the right nipple. It appeared in clusters. Ocular findings did not improve on topical antibiotics. On day 9, a small vesicle with an erythematous base was seen on the face of the infant, diagnosed by the dermatologist as a herpetic infection. The girl was quarantined with contact precautions to avoid direct contact with skin and mucosal lesions, excretions, and body fluids. Treatment with intravenous high-dose acyclovir (60 mg/kg per day in 3 divided doses) and topical ophthalmic acyclovir 5% pomade were started immediately after blood and cerebrospinal fluid (CSF) samples were taken from the patient.

On day 11, new vesicles were seen on the anterior chest wall, back, both axillae, the perioral and periorbital region, and the oral mucosa. The patient experienced lethargy, apnea, and bradycardia as signs of CNS involvement of disseminated infection but no signs of seizures, opistotonus, abnormal posturing, or coma were seen.

Systemic acyclovir treatment was continued for 30 days until the result of CSF polymerase chain reaction (PCR) for HSV 1 DNA was negative, whereas topical ophthalmic treatment with acylovir was for 21 days. On day 40, oral prophylactic acylovir therapy was started in order to suppress recurrence of HSV 1 infection. The patient was discharged from the hospital with both virological and clinical cure on day 46.

OPHTHALMOLOGICAL FINDINGS

The ophthalmologist was consulted when bilateral palpebral edema and few eyelid vesicles were noticed on day 9. Examination of the anterior segment was performed by portable slit lamp and revealed bilateral corneal haze, more prominent on the right eye, consistent with epithelial keratitis. On day 12, ophthalmologic examination was repeated and revealed bilateral geographic corneal epithelial defect with heaped edges. The edges of the defect

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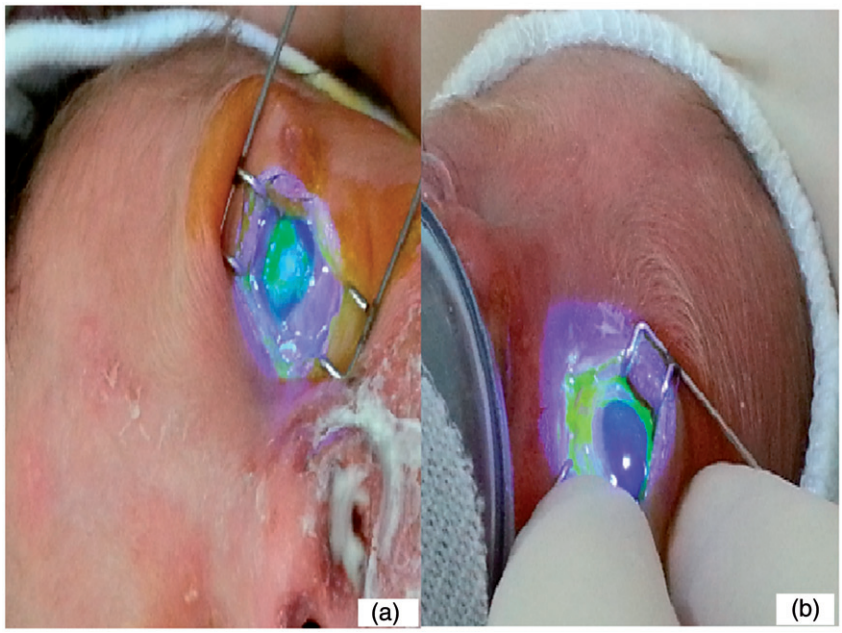

FIGURE 1. Corneal fluorescein staining before (a) and after (b) treatment.

had a rolled appearance and were stained with fluorescein (Figure 1a). The underlying cornea of both eyes was hazy and therefore fundus examination could not be performed. The patient's corneal epithelial defect had resolved by day 25 and corneal opacification improved daily (Figure 1b). Bilateral corneal haze had resolved on day 31 and fundus examination revealed bilateral zone 1 ROP with preplus disease. Also, there was no sign of HSV retinitis. Intravitreal bevacizumab treatment was performed on day 32. Retinal vessels reached to zone 2 and preplus disease was resolved in 10 days after injection.

LABORATORY TESTS

Gram stain of scrapings from the lesions taken on day 7 showed epithelial cells and polymorphonuclear leucocytes but no microorganisms. Immunofluorescence staining of lesion scrapings was not performed. Bacterial, fungal, and chlamydial cultures were obtained from each eye and were negative. Lumbar puncture was performed on day 9 and there were 200 red blood cells/mm^3, with 104 mg/dL protein and 48 mg/dL glucose. Serologic tests, which were sent on day 9, for HSV type 1 IgM, IgG and type 2 IgM, IgG from both the mother and the baby were negative. TORCH-S (toxoplasma, rubella, cytomegalovirus, HSV type 1, type 2, and syphilis) was negative. Complete blood count, biochemical blood markers, and ultrasonographic examination of abdominal organs and adrenal glands were normal. Both blood and cerebrospinal fluid (CSF) were sent for analysis with real-time PCR for HSV DNA type 1 and 2. HSV type 1 DNA was detected in the plasma as 144,000 copies/mL and in the CSF as 100 copies/mL. Polymerase chain reactions of plasma and CSF of HSV type 2 DNA were negative. Bacterial cultures of blood and CSF were negative and empirical antibiotic treatment was discontinued. Diagnosis of disseminated herpetic infection was made due to central nervous system (CNS) involvement. Cranial ultrasonography and MRI were normal. Pneumonia with negative cultures of direct tracheal aspirate and gastrointestinal bleeding as a sign of disseminated intravascular coagulation (DIC) were seen in the patient.

Maternal antibody titer for HSV type 1 Ig G was found positive, indicating seroconversion in the mother on day 40. The results of both serological and polymerase chain reaction of the patient and mother are shown in Table 1.

HSV infection occurs in 1 in 2000–5000 neonates per year.[1] Seventy to eighty-five percent of neonatal HSV infections are caused by HSV 2, whereas the remaining cases are due to HSV 1.[2] Neonatal herpes is much more frequent (50%) in babies from mothers with a primary HSV infection in respect to babies from mothers with recurrent HSV infection (<3%).[3,4] In our case, diagnosis of HSV 1 infection was confirmed by PCR of the blood and CSF. Serology, on the other hand, was negative. At the time of diagnosis, maternal serology was also negative, indicating first-episode primary infection.

Half of the infants with HSV infection are born prematurely, usually between 30 and 37 weeks of gestation.[5] Our patient was born at 26 weeks of gestation. To our knowledge, our case is the youngest premature neonate presenting initially with ocular

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TABLE 1. Serological and polymerase chain reaction results of the patient and mother.

Lab test	Day performed	Results
Patient		
HSV type 1 IgM, IgG	9	Negative
HSV type 2 IgM, IgG	9	Negative
TORCH-S	9	Negative
HSV type 1 DNA (blood)[a]	9	144,000 copies/mL
HSV type 1 DNA (CSF)[a]	9	100 copies/mL
HSV type 2 DNA (blood)[a]	9	Negative
HSV type 2 DNA (CSF)[a]	9	Negative
HSV type 1 DNA (blood)[a]	39	Negative
HSV type 1 DNA (CSF)[a]	39	Negative
Mother		
HSV type 1 IgM, IgG	9	Negative
HSV type 2 IgM, IgG	9	Negative
HSV type 1 IgG	40	Positive

[a]Detected with polymerase chain reaction.
Note. CSF, cerebrospinal fluid; HSV, herpes simplex virus; TORCH-S, toxoplasma, rubella, cytomegalovirus, HSV type 1, type 2, and syphilis.

findings of HSV infection in the literature. The prolonged premature rupture of membranes (PPROM) and maternal age less than 21 years are also risk factors for neonatal HSV infection.[6] Our case presented with young maternal age and PPROM history.

Herpes simplex virus infections of the newborn can be acquired in utero (5%), intrapartum (85%), and postnatally (10%). Clinically, neonatal infections are classified as (1) localized to the skin, eyes, or mouth (SEM disease); (2) disseminated, involving multiple organs, with or without CNS involvement; and (3) encephalitis with or without skin, eye, or mouth involvement. Approximately 45% of these infections are localized to the skin, eyes, or mouth, 25% as disseminated disease, and 30% as encephalitis.[7] Mortality was significantly greater with disseminated infection (57%) than with encephalitis (15%) and did not occur with disease limited to the skin, eyes, or mouth.[8] The SEM disease, although it seems benign, carries risk of dissemination, as in our case. Kimberlin et al. demonstrated that 24% of neonates with clinical SEM disease actually had positive CSF PCR for HSV DNA.[9] Therefore, systemic workup, rapid diagnosis, and early initiation of acyclovir treatment are essential to preventing morbidity and mortality in these cases.

At the time of diagnosis of neonatal herpetic infection, symptoms and signs are found with the following frequency: skin vesicles 68%, fever 39%, lethargy 38%, seizures 27%, blepharoconjunctivitis 19%, pneumonia 13%, and DIC 11%.[7,10] Bilateral blepharoconjunctivitis on day 7 was the initial presentation in our case. Skin vesicles, oral mucosal lesions, and sequential bilateral epithelial keratitis appeared in 2 days. With all of these findings, diagnosis of SEM disease was considered at first and acyclovir treatment, both systemic and topical, was initiated immediately. Development of lethargy, apnea, bradycardia, CNS involvement, pneumonia, and GIS bleeding due to DIC in the following days warned us about possible visceral dissemination.

Active ocular infection occurs in 20–25% of neonates with HSV 1 infection. Typical findings are corneal ulceration, anterior uveitis, cataract, vitritis, chorioretinitis, and optic atrophy.[11] Wang et al. reported unilateral keratitis as the presenting sign of neonatal disseminated HSV 1 infection on day 3.[12] Neonatal HSV is a bilateral disease occurring in infants between 2 days and 2 weeks of age.[13] Our case first developed bilateral blepharoconjunctivitis on day 7, progressing to geographic corneal ulceration on day 9, consistent with the diagnosis of bilateral epithelial herpetic keratitis, which resolved rapidly with systemic and topical acyclovir treatment. To our knowledge, this is the first described case with bilateral blepharoconjunctivitis unresponsive to topical antibiotic treatment as the presenting sign of disseminated neonatal HSV 1 infection. Therefore, HSV 1 infection should be kept in mind in the differential diagnosis of bilateral neonatal conjunctivitis unresponsive to topical empirical antibiotic treatment.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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