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Stromal Keratitis and Anterior Uveitis Due to Herpes Simplex Virus-2 in a Young Child

Saori Inoda*, Masato Wakakura*,
Joe Hirata*, Nobuyuki Nakazato* and Yuko Toyo-Oka†

*Department of Ophthalmology, Kanagawa, Japan; †Laboratory of Virology and DNA Research, Department of Clinical Laboratory, Kitasato University, Kanagawa, Japan

Background: An uncommon case of stromal keratitis and anterior uveitis due to herpes simplex virus type 2 (HSV-2) is reported.

Case: The patient was a 3-year-old boy admitted for conjunctival injection of the right eye of unknown cause, accompanied by corneal opacity and anterior uveitis.

Observations: High titers of antibodies against HSV and Epstein-Barr virus (EBV) were found in blood samples. Polymerase chain reaction (PCR) for the detection of HSV-1, -2, and EBV genome fragments was carried out using an anterior chamber sample as a template. An HSV-2 genome fragment was amplified by PCR. Administration of acyclovir and betamethasone was started, with the consequent elimination of corneal opacity, inflammatory cells, and keratic precipitates.

Conclusion: PCR clearly showed that HSV-2 was the causative pathogen of the stromal keratitis and anterior uveitis in this young patient. Systemic EVB infection may induce systemic immunocompromised conditions that can lead to reactivation of HSV-2 followed by ocular disorders. **Jpn J Ophthalmol 2001;45:618–621**

Key Words: Anterior uveitis, herpes simplex virus type 2, infectious mononucleosis, polymerase chain reaction, stromal keratitis.

Introduction

Many viruses are causative agents of keratitis and anterior uveitis. Infections due to herpes simplex virus type 2 (HSV-2) have been reported mostly in infants.[1,2] These patients appear to be infected through either a transplacental route or the maternal genital tract. However, evidence is quite difficult to obtain. There is only a single case report of a possible neonatal HSV-2 keratitis.[3] In this report, HSV-2 infection was confirmed through indirect evidence using immunohistochemistry. This study presents a case of stromal keratitis and anterior uveitis due to HSV-2 that was diagnosed by polymerase chain reaction (PCR). This is the first case report in a young child demonstrating HSV-2 DNA in the anterior chamber fluid.

Case Report

The patient, a 3-year-old boy, was admitted to this hospital for conjunctival injection and lid swelling of his amblyopic right eye. Closer inspection indicated the presence of corneal opacity. Slit-lamp examination disclosed mutton-fat keratic precipitates and inflammatory cells in the anterior chamber (Figure 1). The fundus of the right eye was invisible. On the

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Correspondence and reprint requests to: Saori INODA, MD, Department of Ophthalmology, Kitasato, University, 1-15-1 Kitasato, Sagamihara, Kanagawa 228-8555, Japan

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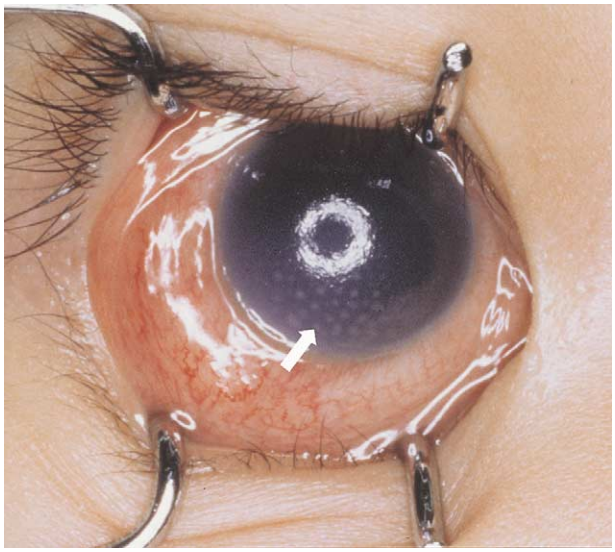

Figure 1. Photograph of right eye of 3-year-old patient taken under general anesthesia. Arrow indicates mutton-fat keratic precipitate. Conjunctival injection was prominent.

13th day after birth, the patient had undergone fundus examination for retinopathy of prematurity arising from a low birth weight (1,800 g). At this time the corneal opacity was first noted in the right eye. Seven days thereafter, this condition improved without any external intervention. Since treatment at our institution, the patient has been under continuous follow-up owing to the presence of the esotropia and amblyopia.

Computed tomography (CT) demonstrated inflammation in the bilateral maxillary and ethmoidal sinuses with a resulting diagnosis of paranasal sinusitis. The ocular inflammation was considered to be bacterial in origin and was treated with antibiotics systemically (intravenous cefazolin sodium, 480 mg daily for 2 weeks) and topically (eye drops of ofloxacin and tobramycin, four to six times daily) but without significant improvement. HSV antibody titers in blood samples were negative for HSV immunoglobulin M (IgM), and 1:26 for HSV IgG by enzyme immunoassay. Epstein-Barr virus (EBV) antibody titers in blood samples were 1:640 for viral capsid antigen (VCA) IgG, less than 1:10 for VCA IgM, less than 1:10 for Epstein-Barr nuclear antigen by indirect fluorescent antibody technique. Body CT scan indicated the presence of hepatosplenomegaly. Infectious mononucleosis was suspected from both findings, but atypical lymphocytes were not detected in blood samples. Recurrent corneal opacity prompted examination of the anterior chamber fluid for causative viruses. Endoscopic sinus surgery was performed under general anesthesia and at this time, 0.1 mL of anterior chamber fluid was extracted with his parents' consent for identification of HSV.

Following the method of Kimura et al[4] and Wright et al,[5] PCR was performed to detect HSV-1, HSV-2, and EBV genome fragments. Complementary primer sets for HSV-1 and HSV-2 were designed to amplify a specific part of the deoxyribonucleic acid (DNA) polymerase gene.[4] At this locus, there is a short sequence that is similar between the two types of HSV, while other sequences are different. The forward primer was complementary to the similar parts while each of the two reverse primers was specific to only one of the two types. To detect the EBV DNA fragment, primers were synthesized and used to amplify the IR3 region of the genome.[5] A volume of fluid (100 μL) containing inflammatory cells had been drawn from the right anterior chamber of the young child under general anesthesia and DNA was extracted from this solution.[6] PCR was carried out using the DNA as the template. As shown in Figure 2, a 391-base pair fragment constituting part of the HSV-2 genome was amplified. No evidence of HSV-1 and EBV fragments was found. Based on these results, the ocular symptoms were concluded to arise from HSV-2.

Acyclovir administration was started systemically (intravenous acyclovir, 360 mg daily for 2 weeks) and topically (3% acyclovir ointment, six times daily). Betamethasone administration was applied systemically (1 mg daily for 3 days) and topically (eyedrops, 0.1% Rinderon®, three times daily). This treatment markedly decreased the conjunctival injection and lid swelling. After several days of treatment, the large keratic precipitates and corneal opacity were seen to undergo gradual elimination. Ophthalmoscopy showed bilaterally normal fundi.

Discussion

Many viruses have been shown to cause ocular disorders such as keratoconjunctivitis, uveitis, retinitis, and optic neuritis. The HSV-2 virus has been detected mainly in infants in whom the infection may occur during the time of delivery.[1,2] Intrauterine transplacental infection was suspected in the present patient because the corneal opacity was evident soon after birth. The corneal lesion spontaneously remitted probably by reason of placentally transmitted maternal antibodies. However, maternal infection could not be confirmed because the mother refused to undergo examination.

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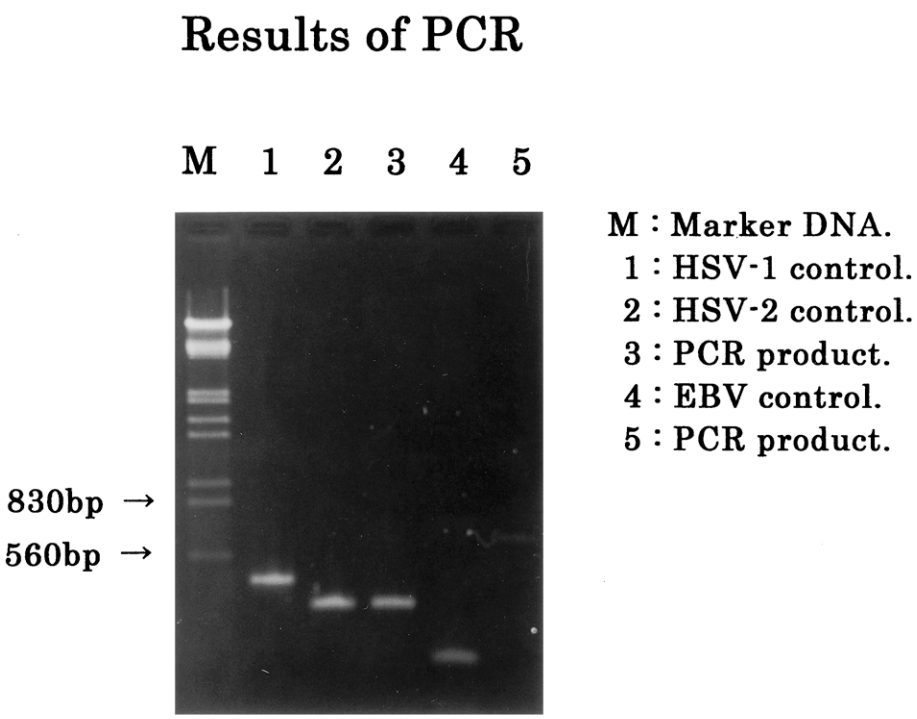

Figure 2. Results of polymerase chain reaction (PCR); 0.2 μg of DNA extracted from anterior chamber was used for one reaction as the template. PCR was carried out with specific primers designed to amplify each virus DNA fragment (see text). PCR products (4 μL) were loaded into 2% agarose gel and electrophoresed. M: marker DNA. Two examples of size marker (830 base pair ([bp] and 560 bp) are indicated. Lane 1: 469 bp herpes simplex virus (HSV)-1 DNA fragment (control). Lane 2: 391 bp HSV-2 DNA fragment (control). Lane 3: PCR product obtained with HSV-1 and -2 specific primers. As is shown, only HSV-2 DNA fragments were amplified. Lane 4: 239 bp EBV DNA specific primers (control). Lane 5: PCR product with EBV specific primers. No specific fragments were amplified. These results gave us direct evidence that ocular infection was caused by HSV-2.

HSV infection is generally diagnosed based on the results of the titration of specific antibodies in blood samples. In our case, HSV- and EBV-specific antibody titers were high. Blood sample examination failed to clearly indicate the causative viruses of the present ocular pathology. However, PCR clearly and directly showed HSV-2 to have caused the patient's infection, and thus is shown to be an effective means for diagnosis.

In contrast to the ocular disorders, the systemic symptoms noted, such as common cold and leukocytosis, were thought to be due to EBV, based on the findings of high titers of the EBV antibody. CT demonstrated hepatosplenomegaly, suggesting infectious mononucleosis. If systemic symptoms were caused by an EBV infection that occurred prior to any ocular ones, it could have possibly triggered the ocular recurrence. That is, an EBV infection may induce systemic immunocompromised conditions that can lead to reactivation of HSV-2 followed by an ocular disorder. In many reported cases of varied herpes infections, high antibody titers against EBV and HSV have been detected at the same time.[7]

In the present case, the rare causative pathogen was readily diagnosed by PCR using a sample from the anterior chamber, but was not seen in a blood test. Ophthalmologists should be alert for HSV-2 that may be a causative pathogen of stromal keratitis and anterior uveitis particularly in infants and young children.

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