The Value of Polymerase Chain Reaction in a Diagnostic Challenge: An Atypical Posterior Herpetic Uveitis

Polimeraz Zincir Reaksiyonunun Tanısal Değeri: Atipik Bir Herpetik Arka Üveit Olgusu

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Case Report *Olgu Sunumu*

ABSTRACT

An atypical posterior uveitis caused by Herpes Simplex Virus (HSV) is presented in this case report. Initially no specific etiology could be specified and posterior segment findings were progressive despite oral steroid therapy. Thereafter, a diagnostic vitrectomy was performed and polymerase chain reaction (PCR) for HSV-DNA was found to be positive in the vitreous sample. Visual acuity improved from finger counting to 20/30 after vitrectomy and intravenous acyclovir therapy. HSV may play an important role in nonspecific, atypical ocular inflammations and the existence of HSV-DNA can be detected in ocular fluids and membranes with PCR, which can serve as an exceptionally valuable diagnostic tool for HSV infections.

Key Words: Atypical viral uveitis, herpes simplex virus, polymerase chain reaction, vitreous biopsy.

ÖZ

Bu çalışmada, herpes simpleks virüsün (HSV) neden olduğu atipik bir arka üveit sunulmaktadır. Başlangıçta, üveitin spesifik bir etiyoloji saptanamamış ve ampirik olarak oral steroid tedavisi başlanmıştır. Ancak, arka segment bulgularının ilerleyici olması nedeniyle tanısal bir vitrektomi yapılmış ve alınan vitre örneklerinde HSV-DNA'sı polimeraz zincir reaksiyonu (PCR) ile saptanabilmiştir. Vitrektomi sonrası intravenöz asiklovir tedavisi de başlanmış ve hastanın başlangıçta parmak sayma düzeyinde olan görme keskinliği 20/30'a kadar yükselmiştir. HSV, atipik oküler inflamasyonlarda önemli bir role sahip olabilir. Oküler sıvı örneklerinde veya membran gibi oküler doku örneklerinde HSV-DNA'sının PCR ile saptanması mümkündür. PCR'nin, atipik herpetik üveitlerin tanısında çok değerli bir araç olduğu düşünülmektedir.

Anahtar Kelimeler: Atipik viral uveit, herpes simpleks virüs, polimeraz zincir reaksiyonu, vitre biyopsisi.

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INTRODUCTION

Infections with Herpes Simplex Virus (HSV) can cause a wide spectrum of eye diseases, including uveitis with devastating sequels.[1] HSV uveitis usually presents as anterior uveitis. Posterior uveitis and panuveitis are less commonly caused by HSV. HSV uveitis includes iridocyclitis, vitritis, retinitis, choroiditis, optic neuritis and acute retinal necrosis (ARN).

The challenges in diagnosis and management of HSV disease in the anterior ocular tissues are more profound in the posterior segment. Clinically, chorioretinitis and ARN associated with HSV may be easily confused with diseases caused by other agents.[2-6] A variety of laboratory techniques are valuable in diagnosis, including electron microscopic study of vitreous, retinal biopsy, viral culture, local antibody production and polymerase chain reaction (PCR).[7-11] PCR can provide high sensitivity and specificity in detection of HSV in vitreous and aqueous humor samples,[12-15] and was exceptionally helpful in the diagnosis of HSV in the following case.

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CASE REPORT

The patient was a 31 year old female, complaining of visual loss in the left eye. Visual acuity (VA) in the left eye was finger counting. In the slit-lamp examination, 1-2 (+) cell reaction was noted in the anterior segment. Funduscopy revealed mild papillitis, retinitis involving the fovea with overlying fine epimacular membrane and mild vitritis neighboring the retinal inflammation (Figure 1A). The right eye of the patient was free of any symptoms and signs, with a VA of 20/20 (Figure 1B).

Upon diagnosis of posterior uveitis, detailed clinical and laboratory tests, and consultations to rheumatology, dermatology, internal medicine (respiratory diseases and infectious diseases departments) and neurology departments were carried out. Consultations could not give any clue of a specific etiology. Biochemical and hematological parameters including sedimentation rate, serum C-reactive protein and angiotensin-converting enzyme levels were within normal limits, PPD was anergic, and pathergy test gave negative result. In serologic examination, HSV-1 IgM and Cytomegalovirus (CMV) IgG were found to be positive, while serologic markers for HSV-2, Toxoplasma gondii, Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV); antinuclear antibody (ANA), anti-double stranded deoxyribonucleic acid (anti-dsDNA), antiphospholipid antibody, Venereal Disease Research Laboratory (VDRL) test, Fluorescent Treponemal Antibody Absorption (FTA-ABS), anti-neutrophil cytoplasmic antibody (ANCA), rheumatoid factor (RF) were all negative. Oral prednisolone was initiated at 1 mg/kg soon after.

Inflammatory reaction progressed despite oral steroid therapy. Therefore, the patient was hospitalized, and a diagnostic as well as therapeutic vitrectomy was performed with the suspicion of an atypical infection. During vitrectomy, membranes overlying macula were carefully excised, and cellular debris was aspirated.

PCR evaluation of the vitreous samples yielded a highly positive titer for HSV-DNA; whereas PCR evaluations for CMV and Varicella Zoster Virus (VZV) were negative. The PCR technique in our laboratory works on the gene sequence in DNA polymerase, which is common to both HSV-1 and HSV-2; therefore discrimination between these two agents could not be made. Fungal and bacterial cultures and microscopy of vitreous samples were negative.

Intravenous acyclovir treatment was initiated, and five days later oral steroid therapy was added. Two weeks after vitrectomy, ocular findings resolved; intravenous acyclovir treatment was substituted with 5x200 mg oral acyclovir and the patient was discharged.

VA of the left eye improved to 20/40 at 1 month. Fundus examination revealed fine membranes over the optic nerve and central macula, and a little focus of scarring temporal to the fovea (Figure 2A). The patient's visual acuity in the left eye improved to 20/30 at 1 year, with residual scarring temporal to the fovea and fine epiretinal membranes (Figure 2B).

CONCLUSION

Herpetic posterior segment infection usually takes the form of ARN, which starts as peripheral necrotizing retinitis with multiple foci, becomes confluent and progresses posteriorly.[16-17] A more severe form of herpetic posterior segment involvement is progressive outer retinal necrosis (PORN), which occurs in immunodeficiency, particularly in AIDS.[18] Herpes viruses causing ARN and PORN include varicella zoster virus (VZV), HSV-1 and HSV-2.[18-21] In this case, retinitis began at the posterior pole, involving the macula. The inflammatory reaction was not necrotizing and mild in nature. This clinical picture did not remind a typical herpetic posterior uveitis.

Ocular findings of the patient at presentation could not direct us to a specific etiology. Such findings could be associated with many diverse diseases; so detailed examinations were performed but no specific etiology could be identified. Although HSV-1-IgM positivity on serology was suggestive of herpetic infection, it does not constitute a powerful evidence for eye disease and its association with eye involvement is controversial.[22]

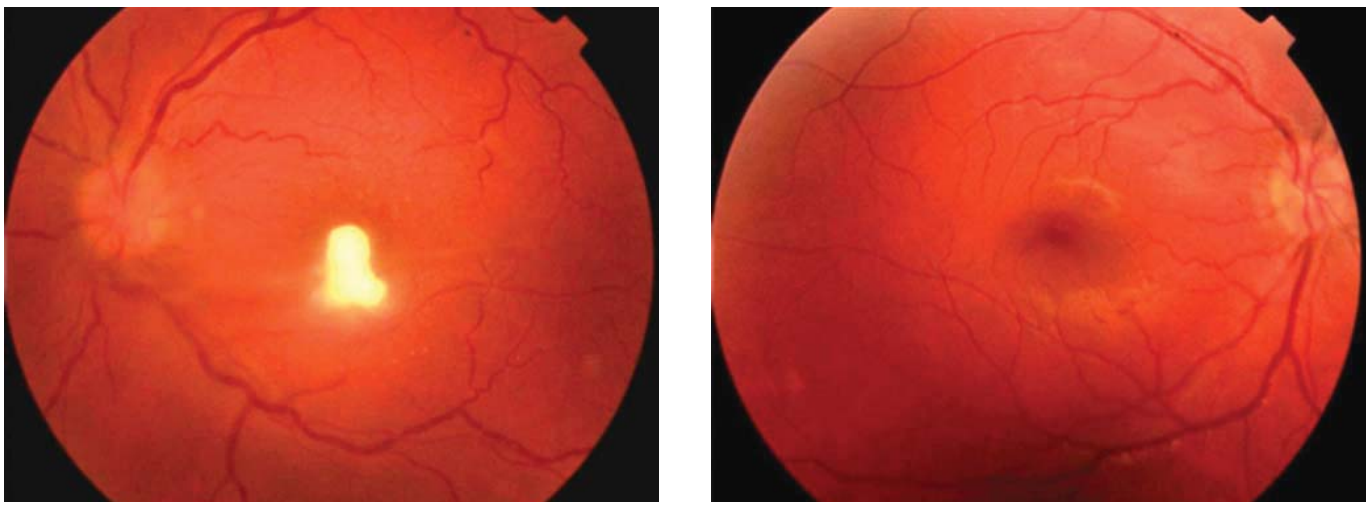

Figure 1: A: Left eye demonstrating retinitis, papillitis, cell infiltration and mild membrane formation over the fovea. Figure. **B:** Right eye with normal fundus findings.

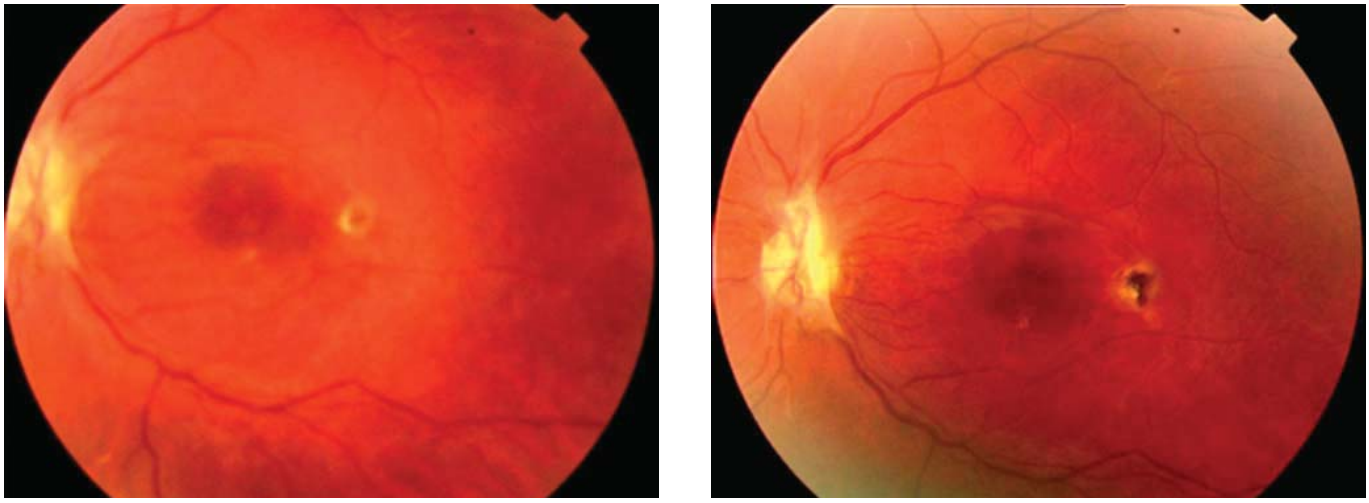

Figure 2: Fundus photography of the left eye with no active inflammation but residual findings: Scarring temporal to the fovea, a fine epiretinal membrane superior to the fovea and also at the papilla, at 1 month (Figure 2A) and 1 year (Figure 2B) postoperatively.

It was the unresponsiveness to systemic steroids that led us to a diagnostic and therapeutic vitrectomy in this case. A positive PCR result for HSV-1 in the vitreous sample, together with clinical improvement with systemic acyclovir therapy confirmed the diagnosis. In vitreous samples, false positive results are very low with PCR for HSV-DNA, provided that contamination is avoided.[23] Pendergast et al.[24] found a very low incidence of HSV-PCR positivity in vitreous samples from eyes without uveitis.

HSV uveitis may present as nonspecific, atypical inflammations of the posterior segment of the eye, which can be diagnostic and therapeutic challenges. In such conditions, the existence of HSV-DNA can be detected in ocular fluids and membranes by PCR, which is an important diagnostic tool for HSV infections.

KAYNAKLAR/REFERENCES

1. Green LK, Pavan-Langston D.: Herpes simplex ocular inflammatory disease. Int Ophthalmol Clin. 2006;46:27-37.
2. Elkins BS, Holland GN, Opremcak EM, et al.: Ocular toxoplasmosis misdiagnosed as cytomegalovirus retinopathy in immunocompromised patients. Ophthalmology. 1994;101:499-507.
3. Cubillan LD, Cubillan EA, Berger TG, et al.: Syphilitic uveitis and dermatitis. Arch Ophthalmol. 1998;116:696-697.
4. Mendelsohn AD, Jampol LM.: Syphilitic retinitis. A cause of necrotizing retinitis. Retina. 1984;4:221-224.
5. Duker JS, Nielsen JC, Eagle RC Jr, et al.: Rapidly progressive acute retinal necrosis secondary to herpes simplex virus type 1. Ophthalmology. 1990;97:1638-1643.
6. Chiquet C, Bodaghi B, Mougin C, et al.: Acute retinal necrosis diagnosed in a child with chronic panuveitis. Graefes Arch Clin Exp Ophthalmol. 2006;244:1206-1208.
7. Rummelt V, Rummelt C, Jahn G, et al.: Triple retinal infection with human immunodeficiency virus type 1, cytomegalovirus, and herpes simplex virus type 1. Light and electron microscopy, immunohistochemistry, and in situ hybridization. Ophthalmology. 1994;101:270-279.
8. Freeman WR, Stern WH, Gross JG, et al.: Pathologic observations made by retinal biopsy. Retina. 1990;10:195-204.
9. Yamamoto S, Pavan-Langston D, Kinoshita S, et al.: Detecting herpesvirus DNA in uveitis using the polymerase chain reaction. Br J Ophthalmol. 1996;80:465-468.
10. de Boer JH, Verhagen C, Bruinenberg M, et al.: Serologic and polymerase chain reaction analysis of intraocular fluids in the diagnosis of infectious uveitis. Am J Ophthalmol. 1996;121:650-658.
11. Knox CM, Chandler D, Short GA, et al.: Polymerase chain reaction-based assays of vitreous samples for the diagnosis of viral retinitis. Use in diagnostic dilemmas. Ophthalmology. 1998;105:37-44.
12. Westeneng AC, Rothova A, de Boer JH, et al.: Infectious uveitis in immunocompromised patients and the diagnostic value of polymerase chain reaction and Goldmann-Witmer coefficient in aqueous analysis. Am J Ophthalmol. 2007;144:781-785.
13. Chan CC, Shen D, Tuo J.: Polymerase chain reaction in the diagnosis of uveitis. Int Ophthalmol Clin. 2005;45:41-55.
14. Madhavan HN, Priya K, Biswas J.: Current perspectives of herpesviral retinitis and choroiditis. Indian J Pathol Microbiol. 2004;47:453-468.
15. Rothova A, de Boer JH, Ten Dam-van Loon NH, et al.: Usefulness of Aqueous Humor Analysis for the Diagnosis of Posterior Uveitis. Ophthalmology. 2007 Jul 30; [Epub ahead of print].
16. Lau CH, Missotten T, Salzmann J, et al.: Acute retinal necrosis features, management, and outcomes. Ophthalmology. 2007;114:756-762.
17. Fisher JP, Lewis ML, Blumenkranz M, et al.: The acute retinal necrosis syndrome. Part 1: Clinical manifestations. Ophthalmology. 1982;89:1309-1316.
18. Holland GN.: The progressive outer retinal necrosis syndrome. Int Ophthalmol. 1994;18:163-165.
19. Rahhal FM, Siegel LM, Russak V, et al.: Clinicopathologic correlations in acute retinal necrosis caused by herpes simplex virus type 2. Arch Ophthalmol. 1996;114:1416-1419.
20. Culbertson WW, Blumenkranz MS, Pepose JS, et al.: Varicella zoster virus is a cause of the acute retinal necrosis syndrome. Ophthalmology. 1986;93:559-569.
21. Lewis ML, Culbertson WW, Post JD, et al.: Herpes simplex virus type 1. A cause of the acute retinal necrosis syndrome. Ophthalmology. 1989;96:875-878.
22. Sambrook J, Fritsch EF, Maniatis T.: Molecular cloning: a laboratory manual, 2nd edition. Cold Spring Harbor Laboratory. Cold Spring Harbor, NY 1989, P:E.3-E.4.
23. Garweg J, Fenner T, Böhnke M, et al.: An improved technique for the diagnosis of viral retinitis from samples of aqueous humor and vitreous. Graefes Arch Clin Exp Ophthalmol. 1993;231:508-513.
24. Pendergast SD, Werner J, Drevon A, et al.: Absence of herpesvirus DNA by polymerase chain reaction in ocular fluids obtained from immunocompetent patients. Retina. 2000;20:389-393.