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BRIEF COMMUNICATION

An Asian Patient with Intraocular Lymphoma Treated by Intravitreal Methotrexate

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Abstract

Background: To demonstrate the efficacy of intravitreal methotrexate for treating intraocular lymphoma.

Case: A 55-year-old immunocompetent Asian man was diagnosed with intraocular lymphoma.

Observations: The patient was initially managed by intravenous administration of high-dose methotrexate. Because vitreous cells persisted after systemic chemotherapy, methotrexate was given intravitreally thereafter. There was only self-limited corneal epitheliopathy without major complications following intraocular injections. Ocular remission was sustained during a 21-month follow-up.

Conclusion: Intravitreal methotrexate is an effective, repeatable, and safe treatment for intraocular lymphoma. **Jpn J Ophthalmol** 2006;50:474–478 © Japanese Ophthalmological Society 2006

Key Words: chemotherapy, intraocular lymphoma, intravitreal injection, methotrexate, primary central nervous system lymphoma

Introduction

Intraocular lymphoma (IOL) is a rare but lethal disease. It is defined as infiltration of malignant lymphoid cells of the uveal tract, retina, vitreous, or optic nerve[1] and is considered a subset of primary central nervous system lymphoma (PCNSL); 80% of cases of IOL are associated with PCNSL.[2] PCNSL has a poor prognosis, with a 5-year survival rate of less than 5%.[3] Presentations of IOL can occur before or after neurological manifestations. The most common symptoms are floaters and blurred vision.[4] It can masquerade as chronic uveitis or vitritis. When uveitis presents with unknown origin in elderly patients, or is refractory to steroid treatment, IOL should be considered.[5,6] A definite diagnosis can be made by cytopathologic examination of a vitreous biopsy specimen. Sometimes, repeated diagnostic vitrectomy is needed because lymphoma cells are scanty and fragile.[2] In addition, diagnosis also requires the skill of an experienced cytologist. Treatment of IOL is usually chemoradiotherapy.[1] Systemic chemotherapy, such as intravenous high-dose methotrexate, can result in remission of PCNSL, either with or without intrathecal chemotherapy. Micromolar concentrations of methotrexate were present in both ocular chambers 4 h after completion of intravenous high-dose methotrexate in eight patients.[4] Even 74 h after intravenous administration, a cytotoxic level was present in the aqueous humor, according to a single case report.[7] However, IOL can persist after 2–3 cycles of high-dose methotrexate or may relapse after an initial response to systemic chemotherapy.[4] Therefore, ocular relapse or persistence causes major morbidity after successful systemic chemotherapy. Orbital irradiation is an effective treatment strategy for IOL. However, it has several drawbacks. It may lead to local complications after radiotherapy, such as retinopathy, optic neuropathy, dry eye, or cataract.[2] Moreover, it precludes ocular retreatment and further radiation of brain, if the dose of radiation is maximal. In recent limited studies, intraocular chemotherapy for IOL had fair

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therapeutical results without vision-threatening complications.[8–11] Intravitreal methotrexate directly elevates the concentrations to effective levels in the vitreous while avoiding systemic complications. Because methotrexate is well tolerated by intraocular tissues, repeated injections are feasible without retinal toxicity.[8] In this article, we report on the first immunocompetent Asian patient with IOL treated by systemic and intravitreal methotrexate. Remission of ocular manifestations was found at a 21-month follow-up.

Case Report

A 55-year-old male patient complained of blurred vision in the right eye for several months. His medical history was unremarkable except that he was a carrier of hepatitis B virus. Best-corrected visual acuity was 2/20 in the right and 12/20 in the left eye. Intraocular pressure was normal in both eyes. Anterior chamber and vitreous showed 3+ cells in both eyes. Multiple, yellow-white subretinal infiltrates were scattered around the posterior pole and midperipheral retina in the right eye. The inferior part of the fundus showed retinal necrosis, sheathing of vessels, and retinal hemorrhage. Fluorescein angiography revealed diffuse retinal pigment epithelium (RPE) disturbance, which included granularity, that is, punctate hypofluorescence and hyperfluorescence lesions, and late staining of larger subretinal infiltrates (Fig. 1A). Perivascular leakage in the inferior part of the retina was also found (Fig. 1B). No subretinal infiltrates were discovered in the left eye. An electroretinogram (ERG) revealed nearly nondetectable rod and cone responses in the right eye. Subnormal rod and normal cone responses were recorded in the left eye (Fig. 1C). Diffuse retinal and RPE dysfunction was supported by abnormal ERGs in both eyes. Serological tests were all negative or within normal limits, including Venereal Disease Research Laboratory test, antinuclear antibodies, human immunodeficiency virus antibodies, toxoplasma IgG, complete blood cell count, creatinine, glutamic pyruvic transaminase, and rheumatoid factor. Uveitis masquerade syndromes was inferred, and diagnostic vitrectomy was performed (Fig. 1D). Lymphoma cells, characterized by scanty cytoplasm and a large nucleus with fine chromatin and prominent nucleoli, were discovered by cytological examination (Fig. 2A). A large B-cell intraocular lymphoma was diagnosed. Negative findings on brain magnetic resonance images and in a cerebrospinal fluid evaluation indicated no involvement of the central nervous system. A systemic work-up, including chest and abdominal computed tomography and bone marrow biopsy, showed no extraocular spread of lymphoma. The patient underwent systemic chemotherapy with high-dose intravenous methotrexate (6–10 g/m^2) once a month for 3 months. Reactions in the anterior chamber and vitreous subsided in both eyes temporarily during systemic chemotherapy. Bilateral iritis and vitritis worsened 2 months after completion of chemotherapy. Before the first intravitreal methotrexate injection, we obtained informed consent from the patient and approval from the ethical committee of National Taiwan University Hospital. Intravitreal injections of methotrexate were given with a dose of 400 μg in 0.1 ml twice weekly for 3 weeks, after which the vitreous of both eyes was cleared of lymphoma cells. Then the patient underwent injections once weekly for 1 month. Following the 7-week course, corneal epitheliopathy occurred bilaterally, even under topical lubricants. The patient refused further injections because of ocular pain. The remission persisted 1 year after intraocular chemotherapy. Best-corrected visual acuity was 1/20 in the right and 14/20 in the left eye with normal corneal status at the last follow-up. The severity of the nuclear sclerosis of the lens remained stable, similar to that at the initial diagnosis, in both eyes. The ERG revealed partial recovery in the right and full recovery in the left eye of both rod and cone responses (Fig. 2B). Punctate atrophy of RPE and chorioretinal scars without vitritis were found on the right eye, and normal fundus in the left eye, 21 months after the initial diagnosis (Fig. 2C).

Discussion

This patient initially had vitritis, multiple fundus lesions, and focal necrotic retina. Numerous punctate lesions on the fundus simulated white dot syndrome (e.g., multifocal choroiditis or multiple evanescent white dot syndrome). Retinal necrosis, hemorrhages, and vasculitis mimicked viral retinitis, possibly acute retinal necrosis or cytomegalovirus retinitis. Serological tests also showed negative results. Because of the complicated presentation, uveitis masquerade syndromes were inferred. These are a group of ocular disorders that present as intraocular inflammatory processes but are in fact noninflammatory diseases.[12] Following cytological evaluation of a vitreous biopsy specimen, the patient was accurately diagnosed with IOL. Multiple yellow-white spotty lesions corresponded to granularity on the angiography, which is the most common and characteristic finding in IOL.[13] These lesions indicated diffuse sub-RPE infiltration of lymphoma cells. Focal retinal vasculitis and necrosis correlated with angiographic perivascular leakage, which are less common findings and indicate secondary involvement of the retina.[5]

In an animal study on intravitreal chemotherapy, an effective concentration of methotrexate in the vitreous could last 48 to 72 h.[8] According to one case report, intraocular tumor cells were absent on cytological examination after a 3-week treatment course (twice a week), and no subsequent recurrence was found in the following 30 months.[9] The largest scale study included 16 immunocompetent patients with IOL treated by intravitreal methotrexate.[11] A dose of 400 μg was given twice weekly for 1 month during the induction phase. Subsequently, a weekly consolidation for 1 month was followed by monthly maintenance for 1 year. Twenty-six eyes of 16 patients were all cleared clinically of malignant cells after a median of 8.5 injections, with a range of 4 to 12 injections. After a follow-up of 6 to 35 months (median, 18.5 months), three patients suffered a

Jpn J Ophthalmol
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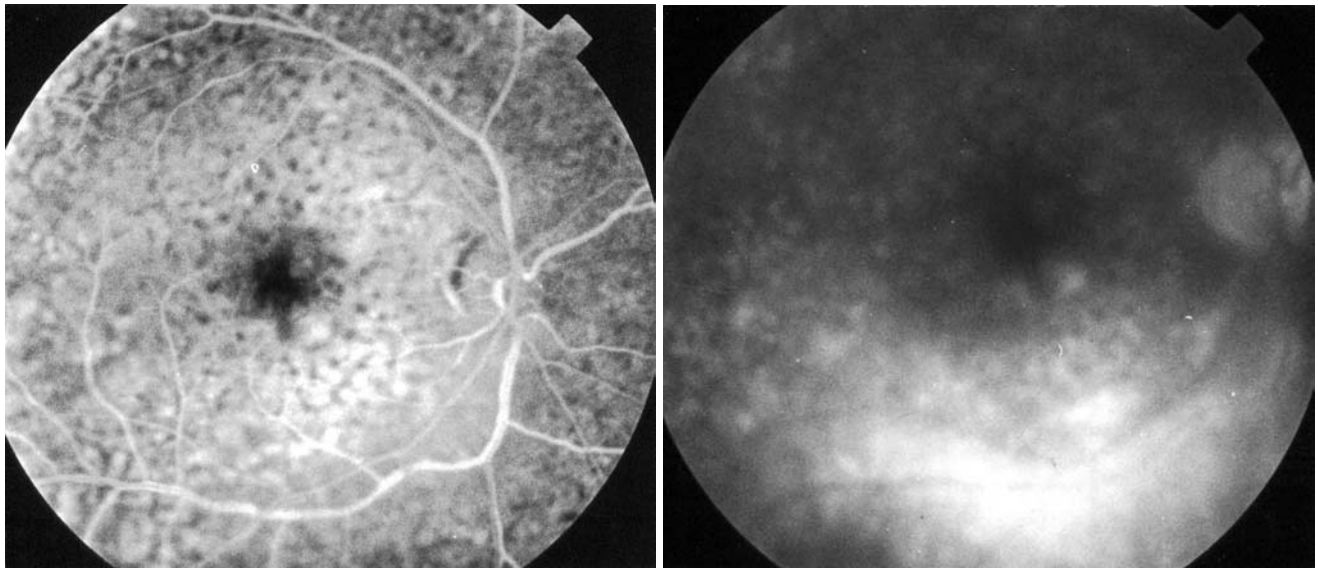

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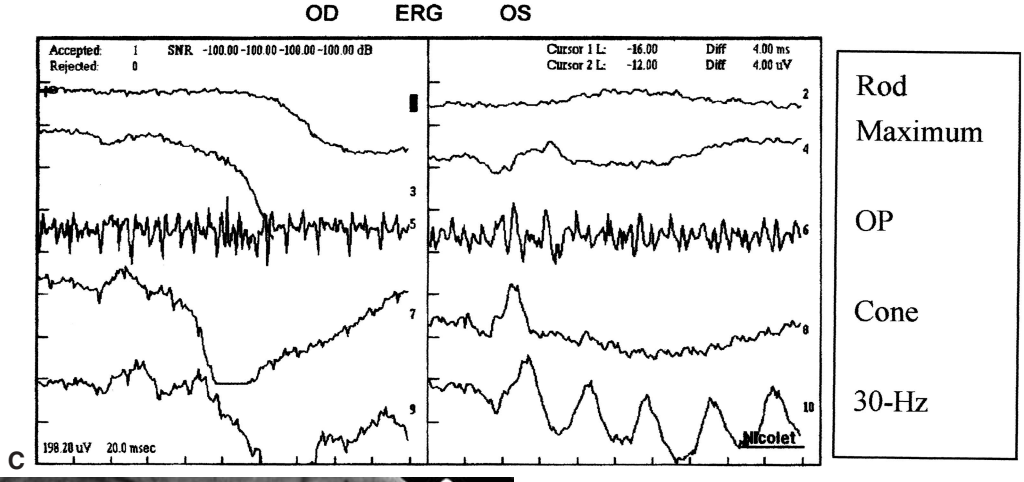
B



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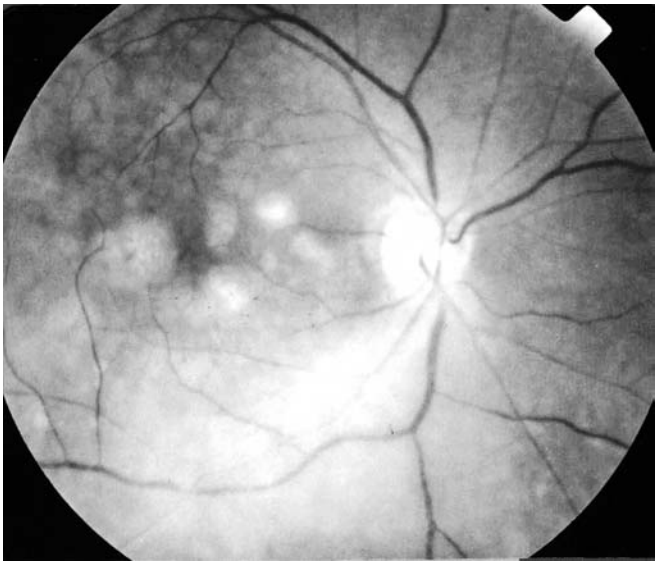

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Figure 1. A Diffuse retinal pigment epithelium (RPE) disturbance presenting as punctate hypofluorescence and hyperfluorescence lesions in the early phase of fluorescein angiography (FA). **B** Staining of larger subretinal infiltrates and perivascular leakage at inferior retinal vessels in the late phase of FA. **C** The electroretinogram (*ERG*) before treatment. *Rod*, rod responses; *Maximum*, rod responses by maximal stimuli; *OP*, oscillatory potentials; *Cone*, cone responses; *30-Hz*, 30-Hz flicker response. Rod and cone responses were barely detectable in the right eye. Subnormal rod and normal cone responses were recorded in the left eye. **D** Multiple yellow-white subretinal infiltrates on the posterior pole accompanied inferior retinal necrosis and vascular sheathing, shown by diagnostic vitrectomy.

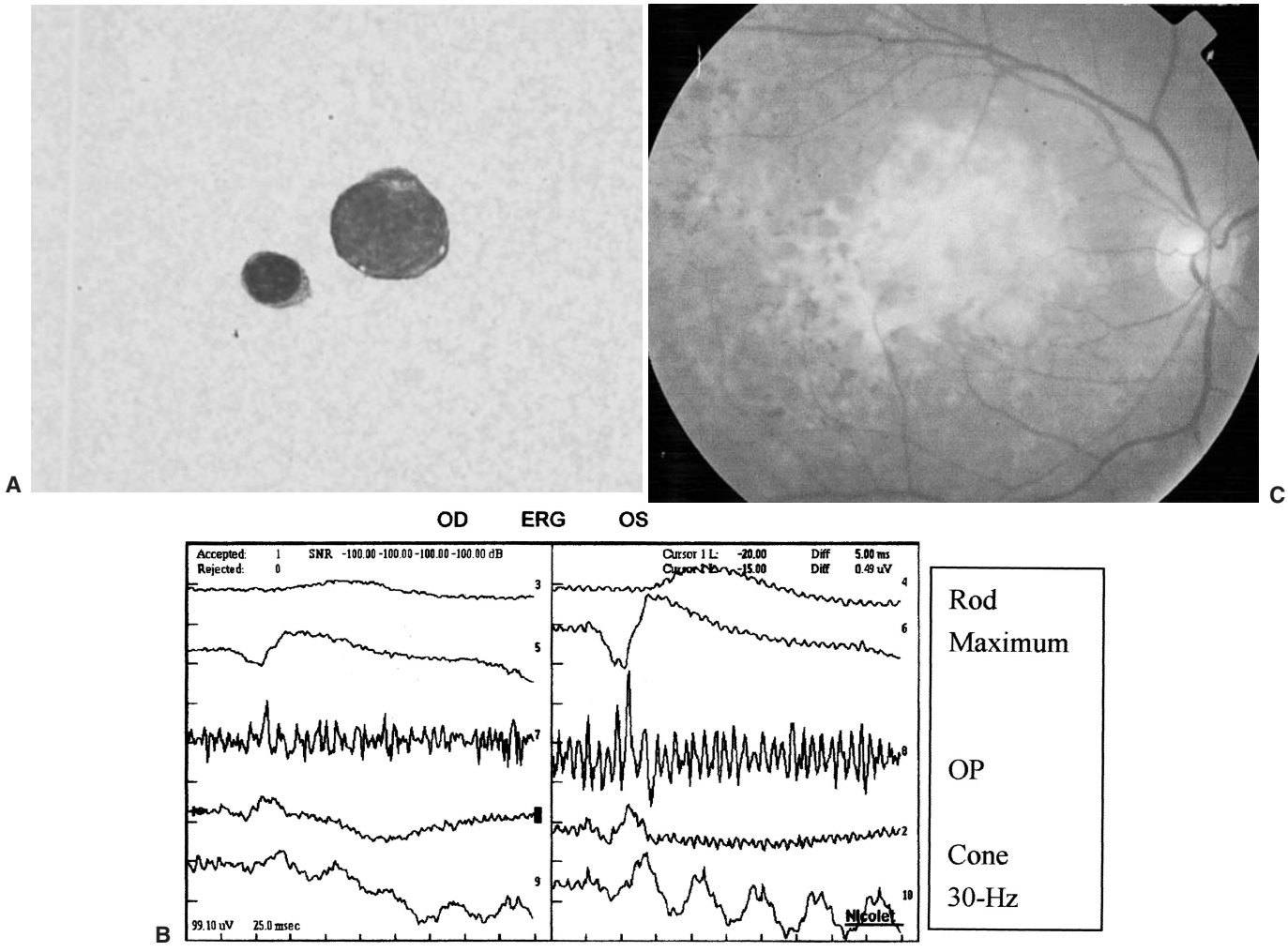

Figure 2. **A** Cytological analysis in this patient revealed many lymphoblasts with a high nucleus/cytoplasm ratio, fine chromatin, prominent nucleoli, and more than twice the size of accompanying normal, mature lymphocytes, which were about 7–8 μm in diameter. **B** Rod and cone responses were subnormal in the right eye and normal in the left. **C** Punctate atrophy of RPE and macular chorioretinal scars shown by fundus photography.

recurrence of disease. A second remission was induced by an additional course of intravitreal chemotherapy. No major complication such as retinal detachment or infectious endophthalmitis was observed. Cataract and corneal epitheliopathy occurred in 73% and 58% of patients. All corneal epitheliopathy was well treated by lubricating eye drops or topical folinic acid, without limbal stem cell failure. Mild vitreous hemorrhage occurred in two eyes and was self-limited. One patient had sterile endophthalmitis after injections and responded to corticosteroid management. Maculopathy, presenting as retinal pigment epithelium disturbances, was reported in 42% of patients. Most of them were identified as sequel to lymphoma infiltrates because they were present before intraocular chemotherapy. The authors concluded that intravitreal methotrexate was effective in inducing clinical remission of IOL, with acceptable morbidity. Nevertheless, this approach did not extend life expectancy. Six of 16 patients died from progression to intracranial tumor. Two patients with isolated IOL had intravitreal methotrexate as the sole treatment, and one developed evidence of intracranial lymphoma. Therefore, intravitreal chemotherapy did not have a protective effect against systemic or brain occurrence of lesions.

In previous reports, neither orbital irradiation nor intraocular chemotherapy could prevent possible future involvement of the central nervous system.[4,11] Therefore, this immunocompetent Asian patient with isolated IOL was first treated by systemic chemotherapy. However, intravenous high-dose methotrexate failed to control the ocular conditions, and intravitreal methotrexate was chosen to manage the ocular persistence of lymphoma. The technique not only avoided adverse effects caused by traditional radiotherapy on eyes, but also possessed advantages, including low intraocular toxicity, no vision-threatening complications, a high initial response rate, no systemic side effects, and repeatability. After a 3-week induction phase, the vit-

reous was shown cleared of cells by biomicroscopic examination. Although consolidation of remission was given during the following 4 weeks, the whole course was stopped prematurely without a maintenance phase during the following year. The patient quit the treatment because of corneal epitheliopathy, which might have been due to the effect of antimetabolites on rapidly proliferating epithelium.[11] Vision did not recover in the eye with diffuse involvement of lymphoma, but, fortunately, ocular remission continued without relapse after more than 1 year of follow-up. Cataract, the most common complication after intraocular methotrexate, did not occur, possibly because fewer injections were given. The corneal epitheliopathy also healed without sequelae.

In summary, an Asian patient with persistent ocular lymphoma initially managed with systemic chemotherapy was treated effectively by intravitreal methotrexate. Only self-limited corneal epitheliopathy without major complications was observed following the intraocular injections. Ocular remission was sustained after an 18-month follow-up. Intravitreal methotrexate is a useful, repeatable, and safe treatment for IOL.

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