Table 3. False-Negative Results for Polymerase Chain Reaction

Clinical Diagnosis	False-Negative Results*
Corneal endotheliitis (cytomegalovirus)	1
Herpetic keratouveitis	1
Herpetic anterior uveitis	2
Ocular toxoplasmosis	3
Bacterial endophthalmitis	12
Fungal endophthalmitis	2

*False-negative results indicate negative polymerase chain reaction results, with a final diagnosis of ocular infection as determined by other examinations, clinical findings, or responses to treatment.

in the anterior chamber are observed.[11,12] In these types of cases, both the retina and fellow eye usually are intact. However, CMV-related corneal endotheliitis exhibits corneal endothelium edema but not anterior uveitis.[12–15] Recently, several investigators have reported finding cases of CMV-associated corneal endotheliitis when using this new PCR technique.[12,15,16] It additionally was reported that this inflammation could be well controlled through the use of antiviral agents.[12–16]

In both our previous and present studies, we observed a few cases with positive HHV-6 results. As reported previously, we also have encountered a patient with apparent severe unilateral panuveitis.[17] After further examination of this particular case, we finally determined the patient had ocular toxocariasis and HHV-6–associated panuveitis. In addition, we also found 2 HHV-6–positive cases with bacterial endophthalmitis in our present study, with neither of the patients found to be immunocompromised. Thus, at the present time there is no conclusive evidence that clarifies whether viral replication of HHV-6 occurs in the eye. Of all of the patients examined in the present study, there were no HHV-7– or HHV-8–positive cases.

This study examined many bacteria-positive endophthalmitis cases. Sample analysis led to the detection of bacterial 16S rDNA in 26 of 38 patients with clinically suspected bacterial endophthalmitis. With the exception of the PCR-negative cases, high bacterial DNA copy numbers were detected in all of these patients. Our broad-range real-time PCR detected bacterial 16S rDNA in samples from 3 patients with idiopathic uveitis, which were false-positive results (Table 4). However, bacteria 16S copy numbers were not very high in these patients. It has been suggested that amplification of bacteria species may occur in patients undergoing long-term steroid treatments. In fact, the 3 cases in our present study all had received subconjunctival injections, systemic steroids, or both over a long period. Other explanations for our present results could be contamination caused by technical errors during the PCR preparation or bacterial exposure that occurred when collecting the samples (e.g., contamination resulting from conjunctival ocular flora present when collecting the ocular sample). Other than these 3 cases, we did not observe any PCR false-positive results resulting from herpes virus, fungi, or parasites.

In this study, we used 2 PCR methods to detect fungal infections, one for fungal 18S and one for 28S rDNA. For the 18S, we designed pan-fungal primers and probes that were complementary to the 18S rRNA sequences present in the *Candida* and *Aspergillus* species.[5] Our PCR system detected 6 *Candida* species, along with 5 *Aspergillus* species. In another study, we used several different primers and probes to detect separately each of these fungal species.[5] Additionally, although our PCR examination was able to detect all species of *Candida* and *Aspergillus* DNA, it did not detect any other fungi DNA. Therefore, we prepared a separate assay that targeted a part of the 28S large subunit rRNA genes for others.[6,18] *Candida* ocular infection is very similar to endogenous endophthalmitis, and in the past, we have encountered some rare *Aspergillus*-positive cases, for example, retinal vasculitis, endogenous endophthalmitis, late postoperative endophthalmitis, and post-traumatic keratitis-associated endophthalmitis. Fungal DNA was detected in 9 of the 11 ocular samples obtained from fungal endophthalmitis patients (Table 2). One fungal keratitis case also had positive results for fungal 28S rDNA in the aqueous humor. These PCR-positive samples all had significantly high copy numbers of *Candida*, *Aspergillus*, or *Cryptococcus* DNA. In 2 patients who were clinically suspected of having *Candida* endophthalmitis, our PCR analysis did not detect any fungal genome in the ocular sample. However, it should be noted that this sample was aqueous humor, and if we had obtained a vitreous sample instead, we might have detected *Candida* DNA because *Candida* endophthalmitis often results from hematogenous dissemination. This finding suggests that the type of sample collected could be very important with regard to the ability to make an accurate diagnosis.

In our bacterial 16S PCR study, we found false-negative results in 12 of the 38 samples obtained from clinically suspected bacterial endophthalmitis patients (Table 3). The false-negative results were defined as being negative for PCR even though there was a clinically suspected bacterial infection, for example, culture positive, having an inflammation that was well-controlled by antibiotics, or both. Once again, it is necessary to consider how the samples were actually obtained in these cases. Bacterial 16S rDNA was not detected in a few of the endogenous bacterial endophthalmitis patients. However, because endogenous endophthalmitis results from hematogenous dissemination, it might have been possible to detect bacterial genome if we had collected vitreous samples. Although the proper DNA extraction procedure required for verifying bacterial infec-

Table 4. False-Positive Results for Polymerase Chain Reaction

Polymerase Chain Reaction for Infectious Antigens	False-Positive Results*
Bacteria 16S	3

*False-positive results indicate positive polymerase chain reaction results, with a final diagnosis of clinically noninfectious disease. These patients with bacteria 16S false-positive resuts ultimately were diagnosed with idiopathic uveitis.

tion by PCR remains controversial, we have attempted to use various approaches for the DNA extraction that will upregulate the PCR sensitivity. In general, a bactericidal enzyme pretreatment (e.g., lysozyme pretreatment) is required for bacterial cell wall destruction, and several investigators have reported previously finding lysozyme resistance in gram-negative and gram-positive bacteria species.[19,20] However, we did not pretreat any of our samples with enzyme because of the limited amount of sample that was available and the fact that our PCR examination included other infectious agents, such as viruses, fungi, and parasites. Therefore, it possible that bacterial 16S rDNA might not have been detected in a few of the endogenous bacterial endophthalmitis patients because of difficulties in collecting samples from patients with infectious agglomeration.

In conclusion, our results indicate that a comprehensive PCR system can be used to verify ocular disease diagnoses definitively. Furthermore, this PCR system also is able to exclude ocular infections as the potential cause of ocular disorders and, based on the confidence of the diagnosis, can be used to help design appropriate early treatments for ocular disease. Because it is important to be able to exclude noninfectious uveitis or endophthalmitis, the PCR-negative results can help to simplify the clinical workups in these cases. Additionally, because PCR examinations can be used to exclude infectious agents, this makes it easier to determine which cases are applicable for use of steroids. Although unfortunately this laboratory approach is not commercially available at the present time, we currently are pursing plans to create a simple examination kit that can be used for ocular infectious diseases in the near future.

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CLINICAL INVESTIGATION

Acute retinal necrosis: factors associated with anatomic and visual outcomes

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Abstract

Purpose To examine the factors associated with anatomic and visual outcomes in Japanese patients with acute retinal necrosis (ARN).

Methods One hundred four patients with ARN who were followed for more than 1 year at nine referral centers were reviewed. Retinal involvement at initial presentation was classified into four groups: zone 1 (posterior pole, $n = 22$), zone 2 (midperiphery, $n = 54$), zone 3 (periphery, $n = 25$), and unknown ($n = 3$). Forty-eight eyes underwent prophylactic vitrectomy before development of retinal detachment (vitrectomy group); 56 eyes were treated conventionally without prophylactic vitrectomy (observation group).

Results The retina was attached in 28 of 48 eyes (58.3 %) in the vitrectomy group and 42 of 56 eyes (75.0 %) in the observation group at the final visit ($P = 0.071$). At 1 year, 56 eyes (53.8 %) had a best-corrected visual acuity (BCVA) of 20/200 or worse. Multivariate logistic regression analyses identified zone 1 disease (odds ratio = 4.983) and optic nerve involvement (odds ratio = 5.084) as significantly associated with BCVA of 20/200 or worse. Among the zone 3 eyes, significantly ($P = 0.012$) more eyes in the observation group than in the vitrectomy group had an attached retina.

Conclusions Prophylactic vitrectomy did not improve the final BCVA in any eyes. Zone 3 eyes had better outcomes without prophylactic vitrectomy.

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Keywords Acute retinal necrosis · Retinal detachment · Visual outcome · Prophylactic vitrectomy

Introduction

In 1971, Urayama et al. [1] first reported acute retinal necrosis (ARN), a devastating, potentially blinding, necrotizing retinitis. ARN is diagnosed on the basis of the clinical appearance and disease course as well as the standard diagnostic criteria proposed by the American Uveitis Society [2]. Because varicella zoster virus (VZV), herpes simplex virus (HSV), and Epstein-Barr virus are implicated in the pathogenesis of ARN [3–6], the standard treatment for ARN is intravenous acyclovir 10 mg/kg every 8 h or 1500 mg/m^2 daily for 5–10 days, followed by oral acyclovir 800 mg five times daily for 6 weeks [7]. Furthermore, systemic treatment with corticosteroids [8] and/or an antiplatelet agent [9] is often given empirically. Recently, prophylactic laser retinopexy [10] or prophylactic vitrectomy [11–13] before development of a retinal detachment has been reported to reduce the incidence of retinal detachment, which is predictive of the visual outcome in ARN [14, 15]. However, disappointing results have also been reported after these treatments [16, 17]. Conducting a study of treatments for ARN is difficult because the disease is rare. Indeed, ARN was diagnosed in only 53 of 3830 patients (1.4 %) with endogenous uveitis referred to university hospitals in Japan over a 1-year period [18].

In this study, we retrospectively investigated 104 patients diagnosed with ARN in Japan to determine the anatomic and visual outcomes as well as the indication for prophylactic vitrectomy.

Patients and methods

This study was a retrospective observational case series of 104 consecutive patients who were negative for the human immunodeficiency virus and who had been diagnosed as having ARN at nine referral centers in Japan (Hokkaido University, Kobe University, Kyorin University, Kyushu University, Osaka University, the University of Tokyo, Tokyo Medical University, Tokyo Medical and Dental University, and Yokohama City University) between 2002 and 2008 with a minimal follow-up time of 1 year. In cases of bilateral involvement, only the first involved eye was included. A clinical diagnosis of ARN was based on the standard diagnostic criteria proposed by the American Uveitis Society [2]. The institutional review board of each center approved the study protocol.

The patients' medical records were reviewed for age, sex, best-corrected visual acuity (BCVA) at the initial presentation, retinal necrotic lesions, optic nerve involvement (redness and/or edema), presence of prophylactic vitrectomy, BCVA at 1 year, retinal status at the final visit, and duration of follow-up. Eyes without silicone oil removal were considered to have a retinal detachment.

The sites of retinal necrosis were classified into three groups according to the classification of cytomegalovirus (CMV) retinopathy of Holland et al. [19]. Zone 1 was defined as the portion of the retina in which infection was immediately sight-threatening and corresponded to the area 3000 μm from the fovea or 1500 μm from the margins of the optic nerve head; zone 2 extended anteriorly from zone 1 to the clinical equator; zone 3 extended anteriorly from zone 2 to the ora serrata.

We compared the anatomic and functional outcomes of the two groups of patients. The vitrectomy group included patients who underwent prophylactic vitrectomy before the development of a retinal detachment. The observation group included patients who did not undergo prophylactic vitrectomy.

The VA was converted to logarithm of the minimum angle of resolution (logMAR) values for statistical analysis. On the basis of a previous report [20], the following logMAR values were assigned: counting fingers, 2.6 logMAR; hand motions, 2.9 logMAR; light perception, 3.1 log MAR; no light perception, 3.4 logMAR. According to the Standardization of Uveitis Nomenclature (SUN) criteria [21], patients were classified as having severe visual loss at a visual acuity of 20/200 or worse. Each variable with a significant association ($P < 0.05$) was introduced into a forward, stepwise, logistic regression model to identify the baseline factors that were independent predictors of ARN. The odds ratio (OR) and its 95 % confidence interval (CI) for each possible risk factor were also calculated. When appropriate, the Mann-Whitney and Fisher exact tests were used to compare the differences between the groups. Statistical analyses were performed using JMP version 8.0 for Windows (SAS Institute, Cary, NC, USA). Probability values less than 0.05 were considered significant.

Results

A total of 106 patients with a diagnosis of ARN were reviewed. Two patients did not meet the inclusion criteria because they were positive for the human immunodeficiency virus. One hundred four patients (61 men, 43 women) met the inclusion criteria. The median patient age at disease onset was 55 years (51.2 ± 15.5; range, 12–79 years). The causative virus was HSV in 18 eyes, VZV in 84 eyes, and unknown in 2 eyes. According to the

classification of CMV retinopathy of Holland et al. [19], the eyes were classified as having zone 1 disease (posterior) in 22 cases, zone 2 disease (midperiphery) in 54 cases, and zone 3 disease (periphery) in 25 cases; the zone was unknown in 3 cases because of vitreous opacity. Optic nerve involvement was detected in 79 eyes. The median follow-up time was 45 months (46.4 ± 23.1; range, 12–106 months).

Antiviral treatment (acyclovir or valacyclovir) was administered in all cases. A corticosteroid was prescribed for 95 eyes, and the initial doses of corticosteroid in prednisolone equivalents ranged from 7.5 to 1250 mg daily. Forty-eight eyes (46.2 %) underwent prophylactic vitrectomy before a retinal detachment developed on 0–186 days (median, 11 days) after the initial visit (vitrectomy group). Fifty-six eyes (53.8 %) did not undergo a prophylactic vitrectomy (observation group).

Development of retinal detachment in the observation group

In the observation group, 39 of 56 eyes (69.6 %) developed a retinal detachment during the follow-up period. The associations of six explanatory variables with development of RD (age, sex, causative virus, BCVA at presentation, site of retinal necrosis, and optic nerve involvement) were individually examined. Simple logistic regression analyses identified male sex, severe visual loss at the initial presentation, and optic nerve involvement as the factors associated with development of RD. In addition, stepwise multivariate logistic regression analyses identified optic nerve involvement as the sole predictor of development of RD ($P = 0.002$; OR, 9.481; CI 2.251–50.74). Of the 41 eyes with optic nerve inflammation at presentation, 32 (78.1 %) developed RD. In contrast, of the 11 eyes without optic nerve inflammation at presentation, 3 (27.3 %) developed RD.

Final retinal attachment

Retinal attachment was achieved in 70 eyes. In the vitrectomy group, 28 of 48 eyes (58.3 %) achieved retinal attachment. In the observation group, 42 of 56 eyes (75.0 %) achieved retinal attachment. In the 39 eyes that underwent reparative surgery in the observation group, 25 (64.1 %) achieved retinal attachment. Overall, 34 eyes did not achieve retinal attachment; they comprised 22 eyes that did not undergo silicone oil extraction and 12 eyes that developed a tractional retinal detachment after silicone oil removal. The associations of seven explanatory variables with final RD (age, sex, causative virus, BCVA at presentation, site of retinal necrosis, optic nerve involvement, and presence of prophylactic vitrectomy) were individually examined (Table 1). Simple logistic regression analyses identified older age, VZV infection, and severe visual loss at the initial presentation as the factors associated with final RD. In addition, stepwise multivariate logistic regression analyses identified severe visual loss (visual acuity of 20/200 or worse) at presentation as the sole predictor of final RD ($P = 0.004$; OR, 3.507; CI: 1.486–8.491).

Table 1 Univariate logistic regression analysis of potential predictors of final retinal detachment

	Odds ratio	95 % CI	*P* value
Age	1.042	1.012–1.076	0.006
Male	0.981	0.441–2.350	0.981
VZV infection	4.923	1.286–32.44	0.018
SVL at initial presentation	3.507	1.486–8.491	0.004
Zone 1 disease	2.302	0.857–6.144	0.097
Optic nerve involvement	2.207	0.730–8.247	0.168
Prophylactic vitrectomy	2.143	0.938–5.012	0.071

CI confidence interval, *SVL* severe visual loss, *VZV* varicella zoster virus

Visual acuity at 1 year

The mean (SD) BCVA at initial presentation was 0.76 ± 0.89 (range, −0.18 to 3.4) and at 1 year was 1.06 ± 1.01 (range, −0.18 to 3.4). The mean (SD) logMAR BCVAs at the initial presentation were 0.92 ± 0.99 in the vitrectomy group and 0.64 ± 0.78 in the observation group, which did not differ significantly ($P = 0.172$). The mean BCVAs at 1 year were 1.23 ± 1.09 in the vitrectomy group and 0.92 ± 0.93 in the observation group, which also did not differ significantly ($P = 0.129$). The BCVA in 23 patients gained more than three lines, remained unchanged in 34 patients, and lost more than three lines in 47 patients. Those who lost more than three lines of vision included 13 of the 22 patients with zone 1 disease (59.1 %), 26 of the 54 patients with zone 2 disease (48.1 %), 7 of the 25 patients with zone 3 disease (28.0 %), and 3 patients in which the zone was unknown. The associations of seven explanatory variables with severe visual loss at 1 year (age, sex, causative virus, BCVA at presentation, site of retinal necrosis, optic nerve involvement, and presence of prophylactic vitrectomy) were individually examined (Table 2). Simple multivariate logistic regression analyses identified VZV infection, severe visual loss at the initial presentation, zone 1 disease, and optic nerve involvement as related to severe visual loss at 1 year. In addition, stepwise multivariate logistic regression analyses identified two baseline factors: zone 1 disease ($P = 0.010$; OR, 4.983; CI 1.440–23.35) and optic nerve involvement ($P = 0.005$; OR, 5.084; CI 1.589–19.93; Table 3). The BCVAs of eyes without retinal attachment at the final visit are shown in Table 4.

Table 2 Univariate logistic regression analysis of potential predictors of severe visual loss at 1 year

	Odds ratio	95 % CI	*P* value
Age	1.012	0.987–1.038	0.354
Male	1.451	0.664–3.192	0.351
VZV infection	3.900	1.339–13.09	0.012
SVL at initial presentation	1.662	1.057–2.768	0.027
Zone 1 disease	7.741	2.400–34.82	0.0003
Optic nerve involvement	5.265	1.870–17.35	0.001
Prophylactic vitrectomy	1.400	0.645–3.068	0.395

CI confidence interval, *SVL* severe visual loss, *VZV* varicella zoster virus

Table 3 Multivariate logistic regression analysis of potential predictors of severe visual loss at 1 year

	Odds ratio	95 % CI	*P* value
Zone 1 disease	4.983	1.440–23.35	0.010
Optic nerve involvement	5.084	1.589–19.93	0.005

CI confidence interval

Table 4 Best-corrected visual acuity at 1 year in eyes that did not achieve retinal attachment

Eyes with tractional retinal detachment after silicone oil removal ($n = 12$)	
Better than 20/200	2
20/2000 to 20/200	8
Hand motions	1
Light perception	1
Eyes without silicone oil removal ($n = 22$)	
Better than 20/200	1
20/2000 to 20/200	9
Counting fingers	3
Hand motions	3
Light perception	3
No light perception	3

Prophylactic vitrectomy and extent of retinal necrosis

The efficacy of prophylactic vitrectomy was also evaluated on the basis of the extent of the retinal necrosis at the initial presentation. The anatomic and visual outcomes are shown in Table 5. Seven of 25 eyes with zone 3 ARN underwent prophylactic vitrectomy before a retinal detachment developed, and three of the seven eyes achieved retinal attachment. Nine of the 18 eyes in the observation group developed a retinal detachment, and 8 of the 9 eyes achieved retinal attachment following surgery. Overall, 3 of 7 eyes (42.9 %) in the vitrectomy group and 17 of 18 eyes (94.4 %) in the observation group achieved retinal attachment ($P = 0.012$). Zone 3 eyes had better anatomic outcomes without prophylactic vitrectomy. The anatomic and visual outcomes of zones 1 and 2 eyes did not differ significantly between the vitrectomy and observation groups.

Discussion

This is the first report on anatomic and visual outcomes of ARN in multiple uveitis centers in Japan. The visual prognosis of patients with ARN is generally poor and in Japanese patients is reported to be correlated with the presence of retinal detachment and VZV infection [14]. Simple logistic regression analyses showed that severe visual loss at 1 year in our patients was also correlated with VZV infection, severe visual loss at the initial presentation, zone 1 disease, and optic nerve involvement. Prophylactic vitrectomy was not correlated with the visual prognosis. These results suggest that irreversible damage to the retina and optic nerve before antiviral treatment strongly affects the visual prognosis.

In particular, the anatomic success rate of zone 3 eyes was better without prophylactic vitrectomy than with prophylactic vitrectomy. Three of 7 eyes (42.9 %) with zone 3 ARN in the vitrectomy group and 17 of 18 eyes (94.4 %) in the observation group achieved final retinal attachment ($P = 0.012$). Ishida et al. [22] also reported that all three eyes with zone 3 disease received only antiviral medical therapy and did not develop a rhegmatogenous retinal detachment. In eyes with zone 3 disease, the area of retinal necrosis was small, and intravenous antiviral treatment seemed sufficient to control the infection.

In the natural course of ARN, rhegmatogenous retinal detachment was observed in approximately 75 % of the untreated eyes [10]. RD also developed in about 70 % of the observation group eyes of our study. We found that eyes with optic nerve redness or edema had a risk of RD. In eyes with optic nerve redness or edema, the retinal necrosis extended posteriorly from the peripheral retina, suggesting longer duration of the necrosis after the onset of symptoms than in eyes without optic nerve redness and that this severe damage to the retina is related to the risk of RD development.

Previous studies have reported that prophylactic vitrectomy prevented retinal detachment [13, 22]; however, at the same time, prophylactic vitrectomy did not improve the mean final VA [13]. The eyes in these reports were treated from 1998 to 2006 [22] and from 1987 to 2008 [13]. Recent advances in retinal surgeries, i.e., vitrectomy using a high-speed vitreous cutter with intravitreal injection of triamcinolone acetonide to visualize the vitreous gel and locate vitreoretinal adhesions [23], are expected to reduce

Table 5 Anatomic status and logMAR BCVA at 1 year based on the extent of retinal necrosis at the initial presentation

Zone	RA	RD	Total
Vitrectomy group ($n = 48$)			
1	1.66 ± 1.02 ($n = 4$)	2.55 ± 0.83 ($n = 4$)	2.11 ± 0.98 ($n = 8$)
2	0.58 ± 0.56 ($n = 21$)	2.03 ± 0.96 ($n = 11$)	1.08 ± 0.72 ($n = 32$)
3	0.10 ± 0.09 ($n = 3$)	1.76 ± 1.31 ($n = 4$)	1.05 ± 1.28 ($n = 7$)

Zone	RA without RD development	RA after RD repair surgery	RD	Total
Observation group ($n = 56$)				
1	0.56 ± 0.51 ($n = 4$)	1.13 ± 0.26 ($n = 4$)	2.03 ± 1.05 ($n = 6$)	1.36 ± 0.96 ($n = 14$)
2	−0.01 ± 0.11 ($n = 4$)	1.10 ± 0.89 ($n = 13$)	1.52 ± 0.74 ($n = 5$)	1.00 ± 0.91 ($n = 22$)
3	0.11 ± 0.23 ($n = 9$)	0.54 ± 0.42 ($n = 8$)	1.00 ($n = 1$)	0.35 ± 0.46 ($n = 18$)

The zones of one eye in the vitrectomy group and of two eyes in the observation group were unknown because of vitreous opacity

BCVA best-corrected visual acuity, *RA* retinal attachment, *RD* retinal detachment

postoperative inflammation and achieve favorable anatomic success. Therefore, we limited our search to Japanese patients diagnosed as having ARN after 2002 and retrospectively evaluated their anatomic and visual outcomes. However, our results were similar to those of previous reports: prophylactic vitrectomy did not improve the visual prognosis in any eyes.

In the current study, we investigated the functional outcomes using the prediagnostic conditions and therapeutic approaches as variables. As a result, zone 1 disease and optic nerve involvement were associated with severe visual loss at 1 year. We predicted the visual prognosis of our patients from these factors but, unfortunately, could not improve the visual prognosis because we could not change those factors. The damage at the initial presentation might have mostly affected the outcome.

As with previous studies on ARN, the present study is limited by its relatively small sample size. The starting dose of steroid treatment, history of laser photocoagulation, timing of the prophylactic vitrectomy, and surgical procedures differed among the referral centers. The retrospective data collection may also have influenced the consistency of the available data. Nevertheless, we collected the clinical data of 114 cases from major referral centers in Japan, and our data described the characteristics of this rare disease in Japanese patients.

In conclusion, the anatomic and functional success in the treatment of ARN was determined primarily by the condition of the retina and optic nerve at the initial presentation. Regarding the indication for prophylactic vitrectomy, this therapy should not be administered for zone 3 ARN. Further studies with a larger number of patients with longer follow-up are needed to determine the treatment of ARN.

Acknowledgments The authors thank Hiroshi Keino and Takayo Watanabe (Kyorin University School of Medicine), Kimiko Okinaga (the University of Tokyo), and Norihiko Ito (Yokohama City University) for data collection.

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Goodbye From the Editor

IT HAS BEEN A PRIVILEGE TO SERVE AS EDITOR IN chief of the *Archives of Ophthalmology*, now *JAMA Ophthalmology*, for the past 20 years. The goal I shared with my outstanding editorial board during this time is given in our mission statement: "To be the indispensable source of ophthalmic knowledge for the generalist, specialist, and trainee. . . . " I believe we succeeded in our aim, and I extend a heartfelt thanks to our contributors and our editorial staff for making this possible and to our readers for their continuing interest and support.

Our journal has a proud heritage, dating back to its founding in 1869. I have had the personal good fortune to know 5 of the 7 previous editors—starting with Francis Heed Adler, MD, and David Cogan, MD—as teachers, colleagues, and friends. Each editor put his mark on the journal and left it changed for the better. I hope this was the case for my tenure as well. I am pleased that Neil Bressler, MD, from our editorial board was chosen as my successor and am confident that he will maintain this tradition.

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Conflict of Interest Disclosures: None reported.

The Standardization of Uveitis Nomenclature Project

The Future Is Here

IN 1996, AN EDITORIAL IN THE *ARCHIVES OF OPHTHALMOLOGY* entitled "Uveitis and the Tower of Babel" bemoaned the inconsistent use of vocabulary to describe even quite common cases of uveitis.[1] Members of the American Uveitis Society were given clinical vignettes and informally surveyed for this editorial[1]; they revealed a striking difference in opinion regarding whether a particular term was appropriate to describe a hypothetical clinical situation. For example, for the first vignette, members were asked if the term *pars planitis* should be used in reference to a 25-year-old woman with bilateral findings of anterior chamber cells, vitreous cells, and "snowbanks" over the inferior pars plana. Of those surveyed, 33% thought that *pars planitis* was the preferred term, 39% thought that it was an acceptable term, and 28% thought that it was an unacceptable term. One can imagine that if uveitis specialists around the world were surveyed in a similar fashion, the discord would be even greater. This state of "discommunication" is by no means unique to uveitis. However, when one considers that each uveitic disease is of relatively low prevalence, that disease prevalences differ greatly depending on the part of the world, and that typical features of the same disease differ depending on a patient's ethnicity, perhaps there was little opportunity for a common language of communication to spontaneously develop.

The Standardization of Uveitis Nomenclature (SUN) Project was started a few years later by a working group of uveitis specialists intent on developing an international consensus for the use of terms to report on uveitis at academic meetings and in the literature. Certainly the time was ripe for forging such a consensus, given the explosion of knowledge in immunology with the opportunity for disease-specific immunopathogenesis research and the influx of new potential treatments, particularly biologic agents that would require rigorous multicenter clinical trials. A clear vocabulary would be necessary to ensure the successful completion of such studies and trials. Importantly, this endeavor was endorsed by 3 major uveitis organizations: the American Uveitis Society, the International Uveitis Study Group, and the International Ocular Inflammation Society.

The SUN Working Group held a 2-day workshop in Baltimore, Maryland, in 2004 that was attended by 45 uveitis specialists from around the world. Using nominal group techniques, this workshop managed to achieve a consensus on the definition of several commonly used terms. These were published in 2005 as "Standardization of Uveitis Nomenclature for Reporting Clinical Data: Results of the First International Workshop."[2] Although still a work in progress and therefore subject to periodic revision, investigators appear to be adopting these guidelines. This, in turn, will allow some measure of comparability between articles and/or clinical trials. The terms defined included many that we take for granted, such as *acute*, *recurrent*, and *chronic*. These SUN guidelines also

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affirmed the classification of uveitis by location within the eye and standardized the use of clinical grading as a tool for assessing degree of inflammation, for the most part by adopting previously published single-institution "expert panel"–driven definitions.[3-5] Consensus was also achieved on how to document and report intraocular pressure abnormalities, outcomes of treatment, and visual acuity. For example, prior to the first workshop, there were 4 grading schema for anterior chamber cells, 4 schema for anterior chamber flare, and 3 schema for vitreous haze or debris in use, each with a variable number of steps, resulting in poor comparability between studies.[2] As a consequence of the first SUN workshop, there was international agreement on a single grading scheme each for anterior chamber cells, anterior chamber flare, and vitreous haze. The reproducibility of these schemata has been demonstrated in a study[6] showing excellent interobserver agreement. Widespread acceptance of the results of the first SUN workshop is indicated by the fact that, in the first 2 years since its publication in the *American Journal of Ophthalmology*, it was the most cited article from that journal (T. Liesegang, MD, oral communication, November 2008).

In a major bid to stay ahead of the information technology curve, the SUN Working Group has embarked on a second phase. The goal of this second phase is to create a classification of specific uveitic entities in a manner that will be compatible with various medical informatics systems. For example, SNOMED CT, which is short for Systemized Nomenclature of Medicine–Clinical Terms, is a structured collection of medical terms that are used internationally for recording clinical information and that are coded to be computer processable.[7,8] It covers areas such as diseases, symptoms, operations, treatments, devices, and drugs and is meant to appear in several languages such that use is interchangeable between countries and regions of the world. Another example is the Sentinel System developed by the US Food and Drug Administration; this system can analyze standardized data files (files on more than 60 million people already exist) created by participating health plans and other organizations in order to investigate drug safety in near "real time" or at least much quicker than previously possible.[9,10] Eventually, one can imagine that standardized formats for electronic medical records used by physicians and medical institutions may allow similar computer-based reviews of records, allowing for the possibility of not only identifying adverse effects but also quantifying clinical outcomes.

Whether one agrees with such "computerization of medicine" or not, in point of fact, it is already happening. Thus, rather than waiting for a classification system to be handed down from an organization without in-depth knowledge of uveitis, the SUN Project aims to proactively offer a classification system already agreed on by most international uveitis specialists and created using current bioinformatics methodology. To conform to the bioinformatics methodology, uveitic disease entities need to have descriptors. To this end, a second international workshop was held over 2 days in 2009 in Miami, Florida, this time attended by 59 uveitis experts from various regions of the world. Before the workshop, an initial terminology was developed via web-based surveys, broadband Delphi techniques, and teleconferences. This terminology was then revised by workshop participants using nominal group techniques and supermajority voting. At the end of this process, a total of 193 terms were identified and mapped to 28 major uveitic disease entities.[11] Successfully achieving a supermajority consensus on the mappings of terms to diseases validated the utility of the vocabulary developed and permitted the development of a computerized, "drop-down menu" database to collect cases for each of the syndromes. This database will be used to optimize and validate classification criteria for each of the disease entities, in a manner similar to that used by the American College of Rheumatology for classification criteria for the rheumatic diseases. An example of mapping of terms into dimensions for a given disease are the following mapping for birdshot chorioretinitis: posterior uveitis (anatomic class of uveitis), insidious (onset), persistent (duration), chronic (course), bilateral (laterality), choroid and retinal vasculature (primary site of inflammation), multifocal spots (morphology), ovoid, indistinct 50 to 250 μm, yellow-orange or cream-colored (descriptors of spots), posterior and midperipheral (2-dimensional fundus location), undetectable to faintly hyperfluorescent on fluorescein angiography (imaging), hypofluorescent on indocyanine green angiography (imaging), etc. These mappings, plus any previously proposed "diagnostic criteria,"[12] will provide the bases for the development of an optimized (in terms of sensitivity and specificity) and parsimonious set of classification criteria for the major uveitic diseases. By defining the "phenotype" of each disease in an internationally accepted manner, the SUN process will facilitate future disease-specific research.

Finally, it is important to note that the SUN Project is not being developed to supersede any decision-making process of practicing ophthalmologists. Specifically, the SUN classification would differ intrinsically from criteria for diagnosing a patient's condition. As described in a recent best-seller, *How Doctors Think*, physicians in reality rarely use algorithms or criteria to make that decision anyway. Rather, "an expert clinician usually forms a notion of what is wrong with the patient . . . based on pattern recognition."[13(p34)] Uveitis specialists, in particular, have been using pattern recognition for decades to diagnose rather obscure diseases. The problem was that they were then unable to communicate this activity accurately to their colleagues in universally understandable terms. With the SUN Project, one of the most opaque corners of ophthalmology may catapult into becoming one of the most clearly elucidated. The future is here.

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Additional Information: The authors serve in organizational positions for the SUN Working Group (Dr Okada as a steering committee member and Dr Jabs as principal investigator).

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LETTER TO THE EDITOR

Enhanced depth imaging optical coherence tomography of the choroid in new-onset acute posterior scleritis

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Dear Editor,

Posterior scleritis is a painful and potentially blinding inflammatory disease of the posterior segment of the eye [1]. Recently, spectral-domain optical coherence tomography (OCT) with enhanced depth imaging (EDI) has been used to visualize choroidal thickness in inflammatory disorders including Vogt–Koyanagi–Harada disease and posterior scleritis [2–5]. In this report, we describe two patients with new-onset acute posterior scleritis in whom choroidal thickening was observed by EDI-OCT.

The first patient was a 58-year-old woman referred to us for ocular pain and serous retinal detachment in the left eye. On examination, the best-corrected visual acuities (BCVAs) were 1.2 OD and 0.7 OS. The intraocular pressures (IOPs) were normal for both eyes, as was the remainder of the examination for the right eye. However, the left eye showed mild conjunctival injection and serous retinal detachment (Fig. 1a) without anterior chamber or vitreous cells. EDI-OCT (Heidelberg Engineering, Heidelberg, Germany) was performed by scanning along horizontal and vertical planes through the fovea. Subfoveal choroidal thickness was determined by measuring the distance between the outer border of the hyper-reflective line corresponding to retinal pigment epithelium and the outer border of the choroid, and was found to be 202 μm OD and 548 μm OS (Fig. 1b, c). Magnetic resonance imaging showed a thickened posterior eye wall on the left (Fig. 1d). Blood tests were positive for antinuclear antibodies; however, syphilis serologies, antineutrophil cytoplasmic antibody and the angiotensin converting enzyme level were negative or normal. A tuberculin skin test (TST) was also negative. The patient was tentatively diagnosed as having posterior scleritis of noninfectious etiology, and started on 20 mg/day of prednisolone. The serous retinal detachment resolved within 2 weeks of initiating therapy, and the choroidal thickness in the left eye gradually decreased (308 μm at 2 weeks; 276 μm at 1 month). There was no recurrence of ocular pain or inflammation during corticosteroid tapering. By 6 months, the prednisolone had been tapered to 5 mg/day, and the choroidal thickness was found to be 215 μm OD and 226 μm OS (Fig. 1e, f).

The second patient was a 65-year-old woman referred to us for bilateral ocular pain and injection. On examination, the BCVAs were 1.2 OD and 1.2 OS, with normal IOPs OU. Both eyes had conjunctival injection and retinochoroidal folds without anterior chamber or vitreous cells (Fig. 2a, b), and B-mode ultrasonography showed a thickened posterior eye wall bilaterally. Although the C-reactive protein was elevated, other systemic examinations were negative, including the TST. The patient was given a tentative diagnosis of bilateral posterior scleritis of noninfectious etiology, and started on 20 mg/day of prednisolone which was slowly tapered. EDI-OCT performed before treatment showed a subfoveal choroidal thickness of 447 μm OD and 446 μm OS (Fig. 2c, d). The ocular pain and injection improved, and the retinochoroidal folds resolved by 2 weeks. The choroidal thickness was noted to be 393 μm OD and 375 μm OS at 2 weeks, and 372 μm OD and 374 μm OS at 2 months (Fig. 2e–h).

EDI-OCT in these two patients with new-onset acute posterior scleritis showed marked choroidal thickening in affected eyes. Indocyanine green angiography has demonstrated diffuse zonal hyperfluorescence in the choroid of posterior scleritis, indicating increased choroidal vascular permeability in this disease state [6]. We previously reported that choroidal thinning develops after repeated episodes of posterior scleritis [5], suggesting that recurrent inflammation of the sclera can

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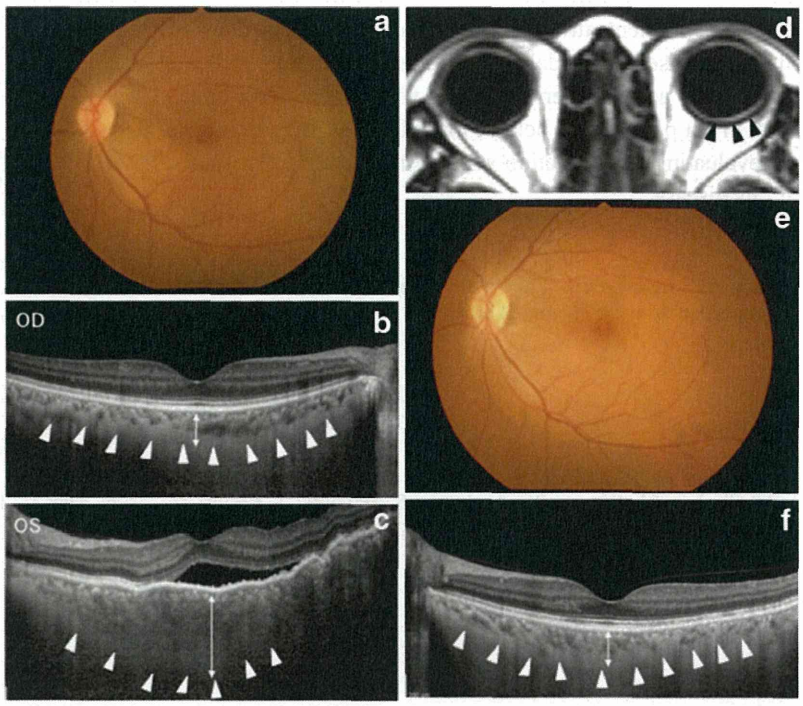

Fig. 1 Patient 1 with new-onset acute posterior scleritis in the left eye. **a** Fundus photograph of the left eye revealing serous retinal detachment and retinochoroidal folds. **b**, **c** Enhanced depth imaging optical coherence tomography (EDI-OCT) at presentation, showing the subfoveal choroidal thickness to be 202 μm OD and 548 μm OS. *White arrowheads* delineate the external choroidal margin. **d** Magnetic resonance imaging showing a thickened posterior eye wall OS (*black arrowheads*). **e**, **f** Fundus photograph and EDI-OCT image of the left eye after 6 months of treatment, at which time the subfoveal choroidal thickness was found to have decreased to 226 μm

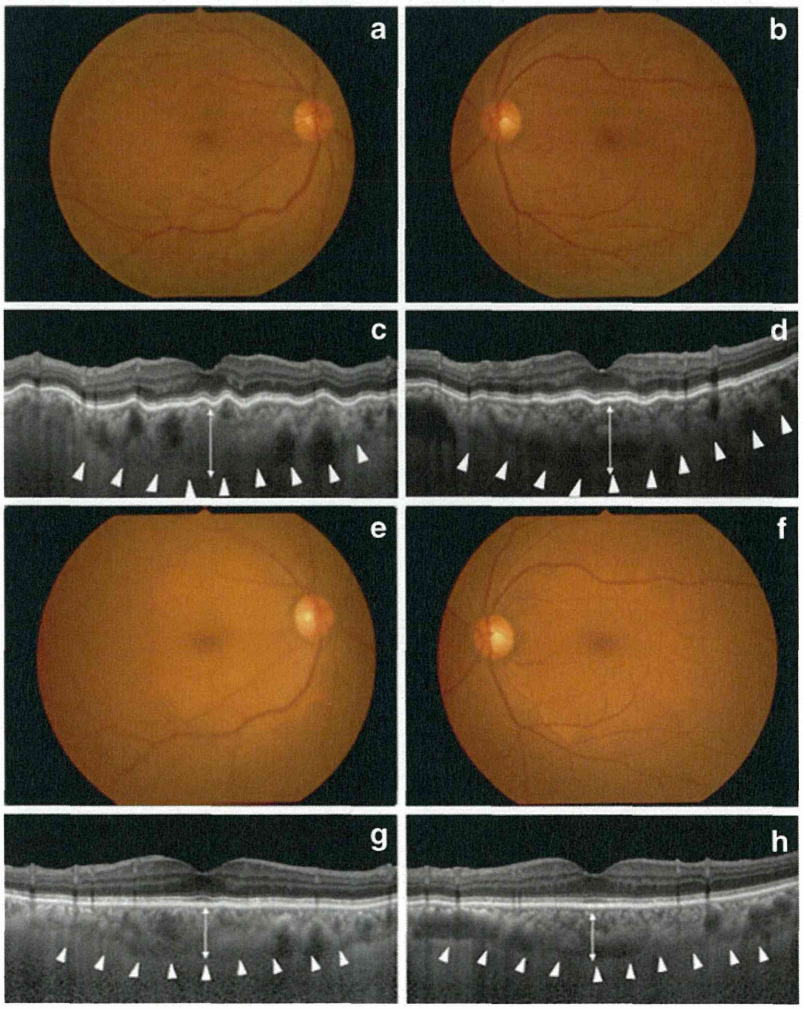

Fig. 2 Patient 2 with bilateral new-onset acute posterior scleritis. **a**–**d** Fundus photographs and EDI-OCT showing retinochoroidal folds in both eyes at presentation. *White arrowheads* delineate the external choroidal margin, and the subfoveal choroidal thickness was measured to be 447 μm OD and 446 μm OS. **e**–**h** Fundus photographs and EDI-OCT images after 2 months of treatment, at which time the subfoveal choroidal thickness had decreased to 372 μm OD and 374 μm OS

induce permanent atrophic alterations to adjacent choroid. Since decreased choroidal thickness correlated with improvement of the acute posterior scleritis with corticosteroid treatment in our patients, we believe that EDI-OCT may be helpful for evaluating inflammation severity and treatment response in this disease.

Commercial associations The authors have no conflict of interests in connection with the submitted article.

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LETTER TO THE EDITOR

Enhanced depth imaging optical coherence tomography of the choroid in recurrent unilateral posterior scleritis

Wakako Taki · Hiroshi Keino · Takayo Watanabe · Annabelle A. Okada

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Dear Editor,

Posterior scleritis is a painful and potentially destructive ocular inflammation caused by infectious agents or non-infectious immune reactions [1]. Recently, spectral-domain optical coherence tomography (OCT) using enhanced depth imaging (EDI) has been shown to reliably visualize the full thickness of choroid in normal and highly myopic eyes [2, 3]. In this report, we describe two patients with recurrent unilateral posterior scleritis in whom thinning of the choroid was observed by EDI–OCT.

Patient 1

A 33-year-old man was referred for scleritis refractory to systemic corticosteroids. On examination, visual acuities (VAs) were 1.2 OD without correction and 0.9 OS with correction of −0.50 diopter. The intraocular pressures (IOPs) were normal OU. The right eye was normal, but the left eye was mildly injected, with serous retinal detachment noted in the fundus (Fig. 1a). B-mode ultrasonography showed a thickened posterior eye wall (Fig. 1b). Syphilis serologies, antineutrophil cytoplasmic antibody, and angiotensin converting enzyme level were unrevealing. The tuberculin skin test (TST) was positive, but the QuantiFERON®-TB 2G (QFT; Cellestis, Carnegie, Australia) was negative. The patient was diagnosed with posterior scleritis of unclear etiology, and started on 40 mg/day of prednisolone on a taper, and later on oral methotrexate (MTX) for steroid sparing. The patient was recurrence-free for over 2 years. However, 29 months after presentation while still on MTX 8 mg/week, ocular pain serous retinal detachment recurred OS (Fig. 1c). EDI–OCT was performed using the Heidelberg Spectralis instrument (Heidelberg Engineering, Heidelberg, Germany), with retinal scans performed along horizontal and vertical planes through the center of the fovea. Choroidal thickness was determined manually by measuring the

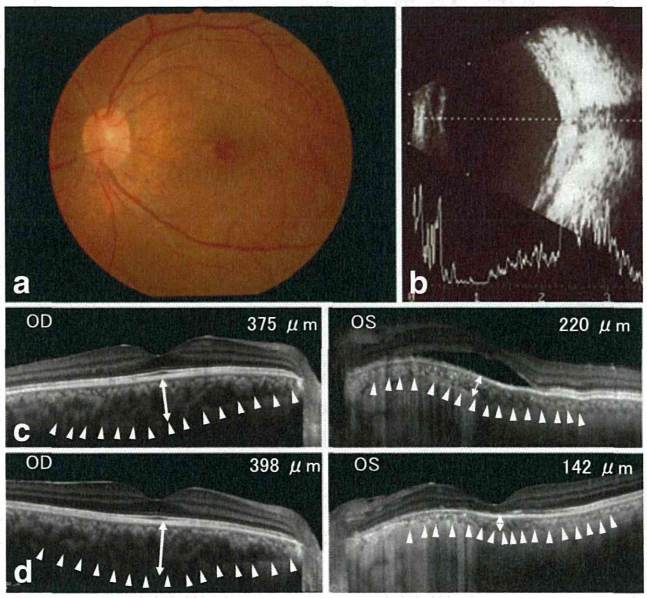

Fig. 1 **a** Fundus photograph of the left eye in patient 1, revealing serous retinal detachment and a hyperemic optic disc. **b** B-mode ultrasonography showed a thickened posterior eye wall. **c** EDI–OCT images at 29 months after presentation during a bout of active, recurrent inflammation. **d** EDI–OCT images at 35 months during a period of quiescence. *White arrowheads* delineate the external choroidal margins

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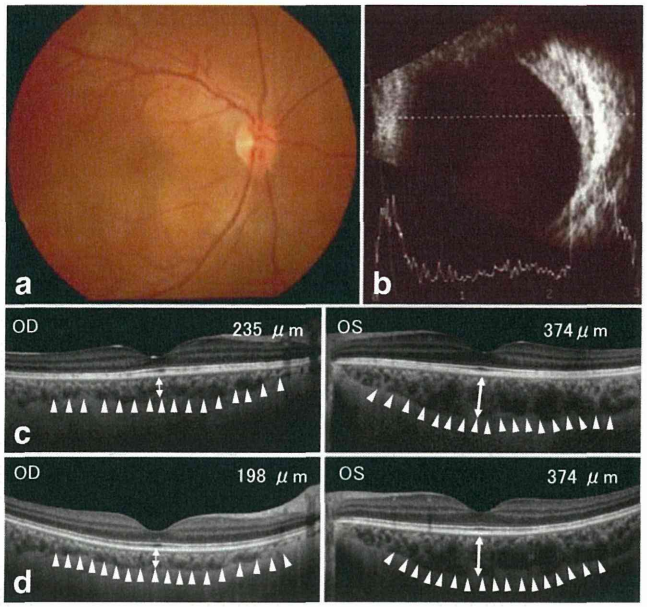

Fig. 2 **a** Fundus photograph of the right eye in patient 2, revealing serous retinal detachment and a hyperemic optic disc. **b** B-mode ultrasonography showed a thickened posterior eye wall. **c** EDI–OCT images at 53 months after presentation, at a time of resolution of recurrent posterior scleritis. **d** EDI–OCT images at 59 months after presentation during a period of quiescence. *White arrowheads* delineate the external choroidal margins

distance, under the center of the fovea, between the outer border of the hyper-reflective line corresponding to the retinal pigment epithelium and the outer border of the choroid. Subfoveal choroidal thicknesses were found to be 375 μm OD and 220 μm OS (Fig. 1c). The treatment regimen was increased to prednisolone 30 mg/day and MTX 10 mg/week, and the posterior scleritis again resolved. Follow-up EDI–OCT at 35 months revealed choroidal thicknesss of 390 μm OD and 143 μm OS (Fig. 1d). There was no difference in axial length between the two eyes (23.58 mm OD and 23.44 mm OS) as measured at 46 months after initial presentation.

Patient 2

A 21-year-old woman was referred for scleritis refractory to topical corticosteroids. On examination, the VAs were 0.06 OD with correction of +1.00 diopter and 0.8 OS with correction of −0.50 diopter. The IOPs were normal OU. The left eye was normal, but the right eye had a serous retinal detachment (Fig. 2a) and B-mode ultrasonography showed a thickened posterior eye wall OD (Fig. 2b). Ancillary investigations were notable for presence of antinuclear antibodies and a positive TST, although the chest X-ray was normal; QFT testing was not available. The patient was diagnosed with posterior scleritis of unclear etiology, and treated with prednisolone 100 mg/day intravenously for 3 days, followed by an oral dose of 40 mg/day tapered to zero by 12 months. The posterior scleritis resolved within 1 month, with no recurrence for roughly 4 and a half years. However, at 53 months after presentation, the patient had recurrence of posterior scleritis OD, and was restarted on prednisolone 30 mg/day on a gradual taper. The posterior scleritis resolved by 1 month (Fig. 2c), and EDI–OCT performed at that time showed a subfoveal choroidal thickness of 235 μm OD and 374 μm OS. No recurrences were observed during the subsequent 6 months, and the choroidal thickness was noted to be 198 μm OD and 374 μm OS (Fig. 2d) at 59 months after presentation. Both eyes had the same axial length (22.5 mm OU) as measured 68 months after initial presentation.

In this report, EDI–OCT in two patients with recurrent unilateral posterior scleritis showed marked choroidal thinning in the eye with the scleritis compared to the non-involved eye. To our knowledge, this represents the first report to measure choroidal thickness in posterior scleritis. Scleral inflammation can readily spread to the choroid [4], and indocyanine green angiography has demonstrated diffuse zonal hyperfluorescence in the choroid with posterior scleritis [5]. We speculate that recurrent inflammation of the posterior sclera induces alterations to the adjacent choroid, gradually resulting in choroidal atrophy.

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CLINICAL INVESTIGATION

Behçet's disease ocular attack score 24: evaluation of ocular disease activity before and after initiation of infliximab

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Abstract

Purpose We developed a novel scoring system for uveitis due to Behçet's disease (BD), termed Behçet's disease ocular attack score 24 (BOS24), and examined its validity and usefulness by estimating changes in ocular disease activities both before and after initiation of infliximab therapy.

Methods BOS24 consists of a total 24 points divided into 6 parameters of ocular inflammatory symptoms. To examine the validity of our scoring system, 5 uveitis specialists examined the severity of 50 ocular attacks in clinical charts using both our system and a physician's impression score (grade 1–10). In addition, ocular disease activities both before and after initiation of infliximab were retrospectively examined in 150 cases of ocular BD using BOS24.

Results The average BOS24 for the 5 doctors was highly correlated with the average physician's impression score ($p < 0.0001$), whereas the coefficient of variance for BOS24 among doctors was much lower than that for the physician's impression score ($p < 0.0001$). Summation of BOS24 over a 6-month period (BOS24-6M) was significantly reduced after starting infliximab therapy ($p < 0.0001$). The average BOS24 for individual ocular attacks was also significantly decreased after starting infliximab, with scores for the posterior pole and fovea notably improved.

The members of the Ocular Behçet's Disease Research Group of Japan are listed in the Appendix.

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Conclusions BOS24 was highly related to severity noted by the physician's impression and had a low level of variability among the examined doctors. Using our novel scoring system, infliximab therapy was shown to reduce not only the frequency of ocular attacks, but also the severity of each attack. BOS24 is a promising tool for evaluating ocular BD activities.

Keywords Behçet's disease · Ocular attack · Score · Disease activity · Infliximab

Introduction

Behçet's disease (BD) is a systemic inflammatory disease characterized by intraocular inflammation, oral and mucosal ulcerations and skin lesions, as well as a variety of disorders involving multiple organ systems throughout the body. In a recent prospective multicenter survey of uveitis patients in Japan, BD was found in 3.9 % of all newly arrived patients with uveitis [1]. Ocular involvement in BD patients in Japan is reported to range from 47.4 to 69 % [2] and is characterized by recurrent explosive attacks of intraocular inflammation, including iritis, hypopyon, chorioretinitis, retinal vasculitis, retinal vein occlusion, optic neuritis, retinal neovascularization and vitreous hemorrhage. Panuveitis or posterior uveitis occurs in the majority of these patients, while anterior uveitis is reported in some (approximately 10 %) [3]. Colchicine, cyclosporine, corticosteroid, azathioprine and other immunosuppressive agents are used to manage ocular inflammatory attacks [4]. Recent reports note that continuous therapy with infliximab, an anti-tumor necrosis factor-α (TNF-α) antibody drug, dramatically reduces the frequency of ocular attacks in BD patients with refractory uveoretinitis, indicating it as very promising for treatment of ocular BD [5–7]. However, anti-TNF-α therapy has adverse effects, and patients receiving such therapy are at risk of developing serious systemic infections, such as tuberculosis and pneumocystis pneumonia and infusion reactions. Moreover, several cases of new-onset psoriasis in association with anti-TNF-α treatment are also reported [8, 9].

Recurrent intraocular inflammation in BD patients is characterized as intermittent and episodic, and referred to as inflammatory ocular attacks. Evaluations of disease activity and the efficacy of drugs for ocular disease related to BD are primarily based on the frequency of ocular attacks [5–7, 10, 11], with the secondary endpoints generally being best-corrected visual acuity (BCVA) [10], location of inflammation sites (posterior uveitis and panuveitis more severe than anterior uveitis) [11, 12], presence or absence of severe ocular inflammatory signs (hypopyon, involvement of inflammation on the retina, macula, or optic disc) [11] and the physician's impressions of the severity of each ocular attack (mild, moderate, severe) [13, 14]. However, because frequency does not reflect the severity of ocular attacks, it also may not represent the exact activities of the ocular disease. Meanwhile, a systemic evaluation method has been established. The Behçet's Disease Current Activity Form (BDCAF), one of the most popular methods of measuring the activity of BD, uses a 5-point scale (0–4) to classify clinical features (oral ulcers, genital ulcers, skin lesions, etc.) by doctors during the 4 weeks prior to the day of assessment [13, 14]. However, the definition of each point in that scale is obscure, especially regarding ocular disease activity.

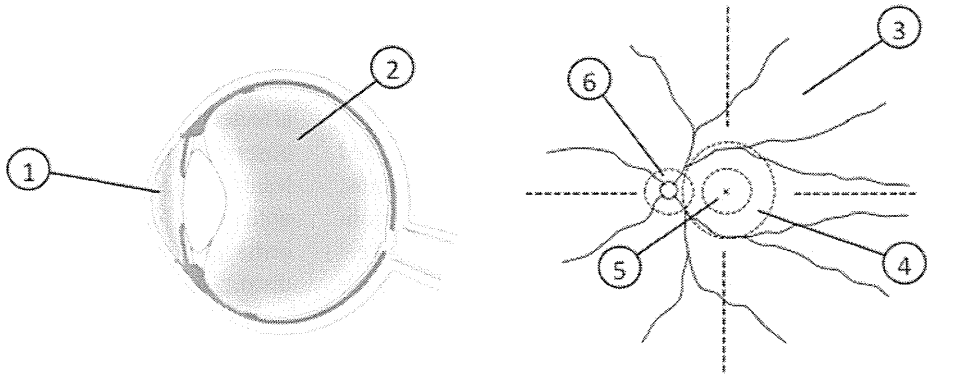
Several precise scoring systems have been established for evaluation of disease activity related to rheumatoid arthritis (RA), and are widely used in clinical practice [15]. For example, the disease activity score 28 (DAS28) is a widely used scoring system for RA, calculated from values obtained for 28 different joints regarding tenderness, swelling, erythrocyte sedimentation rate and assessment of general health with a 0–100 visual analog scale (VAS) [16]. High disease activity is defined as a DAS28 value greater than 5.1, while moderate activity is greater than 3.2 and less or equal to 5.1, low activity is less or equal to 3.2 and greater than 2.6, and remission is less than 2.6. The simplified disease activity index (SDAI) [17] and its modified version, the clinical disease activity index (CDAI) [18], are also popular and easily calculable scoring systems that use the same 28-joint counts for tender and swollen joints, along with overall disease activity noted on a 0–10 VAS completed by the patient and physician, with/without C-reactive protein levels. These scoring systems allow for objective and unbiased evaluations of patients seen in everyday practice, reduce measurement error, and help with analysis and interpretation of clinical trials of new potential disease-modifying drugs.

To develop a precise and easily used system for evaluation of disease activity related to ocular BD, we established a novel scoring system termed Behçet's disease ocular attack score 24 (BOS24), which consists of a total 24 points divided into 6 parameters of ocular inflammatory symptoms. In this study, we examined the validity of this scoring system among physicians. In addition, ocular disease activities before and after initiation of infliximab were retrospectively examined in 150 patients with ocular BD using BOS24.

Patients and methods

Behçet's disease ocular inflammatory score 24 (BOS24)

The Ocular Behçet's Disease Research Group of Japan, consisting of 10 major uveitis referral centers, recently



1. Anterior chamber cells	0, 1, 2, 3, 4 point
2. Vitreous haze	0, 1, 2, 3, 4
3. Peripheral retina lesions	0, 2, 4, 6, 8
4. Posterior pole lesions	0, 2, 3, 4
5. Foveal lesions	0, 2
6. Optic disc lesions	0, 2
	total 24 points

Fig. 1 BOS24 scoring system. The BOS24 consists of a total 24 points summarized from 6 parameters of ocular inflammation symptoms, including anterior chamber cells (maximum 4 points), vitreous opacity (maximum 4 points), peripheral fundus lesions (maximum 8 points), posterior pole lesions (maximum 4 points), subfoveal lesions (maximum 2 points), and optic disc lesions (maximum 2 points). For scoring retinal inflammatory signs, the retinal field is divided into the posterior pole (areas *inside* of arcade vessels) and peripheral retina (areas *outside* of arcade vessels), with the latter further divided into 4 areas for each quadrant; temporal superior, temporal inferior, nasal superior, and nasal inferior

Table 1 Behçet's disease ocular inflammation score: BOS24

(1) Cells in the anterior chamber[a] (max. 4 points)
Cell 0: 0 point, cell 0.5+ or 1+: 1 point, cell 2+: 2 points, cell 3+: 3 points, cell 4+ or hypopyon: 4 points
(2) Vitreous haze[a,b] (max. 4 points)
Haze 0: 0 point, haze 0.5+ or 1+: 1 point, haze 2+: 2 points, haze 3+: 3 points, haze 4+: 4 points
(3) New inflammatory changes in the peripheral retina (max. 8 points)
Give each 2 points in each quadrant of peripheral retina if new inflammatory changes (exudates, hemorrhages, vasculitis) are seen
(4) New inflammatory changes in the posterior pole of retina (max. 4 points)
The percentage of areas occupying new inflammatory changes in the posterior pole of retina: 0 %: 0 point, >0 and <10 %: 2 points, ≥10 and <25 %: 3 points, ≥25 %: 4 points
(5) New inflammatory changes in the fovea (max. 2 points)
Give 2 points if new inflammatory changes (exudates, hemorrhages, vasculitis) are seen in the fovea
(6) New inflammatory changes in the optic disc (max. 2 points)
Give 2 points if new inflammatory changes in the optic disc (redness and edema, sometimes accompanied by hemorrhages, exudates and edema of retina surrounding the optic disc) are seen

[a] Using the grading scale determined by the SUN Working Group [16]

[b] Using the grading scale determined by Nussenblatt et al. [17]

established the BOS24 scoring system (Fig. 1; Table 1). The concepts of BOS24 are as follows: (1) BOS24 is used to indicate the severity of each ocular attack. (2) BOS24 is determined in eyes suffering from ocular inflammatory attacks on the day when the patient is seen by a doctor and judged as the most severe period of inflammation during an exacerbation stage. If the ocular attack is binocular, the score is separately determined in both eyes. (3) BOS24 consists of only objective ocular findings, such as cells in the anterior chambers or areas of retinal exudates/hemorrhages, and does not include patient complaints or subjective examination tests such as BCVA. (4) The score is determined only based on new emerging inflammatory signs and is not influenced by chronic inflammation signs, such as flaring in the anterior chamber, chronic vitreous opacity and macular edema. (5) The scoring system was designed for use in both prospective and retrospective studies, therefore, the items utilized are simple and can be checked in usual clinical practice for eyes with uveitis. (6) High scores are assigned for retinal inflammatory signs,