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CASE REPORT

Two cases of subfoveal choroidal neovascularization with tubulointerstitial nephritis and uveitis syndrome

Yuko Takemoto[1], Kenichi Namba[1], Kazuomi Mizuuchi[1], Shigeaki Ohno[2], Susumu Ishida[1]

[1]Department of Ophthalmology, Hokkaido University Graduate School of Medicine, Sapporo - Japan
[2]Department of Ocular Inflammation and Immunology, Hokkaido University Graduate School of Medicine, Sapporo - Japan

PURPOSE. *Tubulointerstitial nephritis and uveitis (TINU) syndrome usually shows anterior segment intraocular inflammation, but severe posterior segment intraocular inflammation is rarely observed. We report 2 children with TINU syndrome complicated by subfoveal choroidal neovascularization (CNV).*
METHODS. *Case reports.*
RESULTS. *Patients were a 12-year-old girl and a 12-year-old boy diagnosed with probable TINU syndrome on the basis of typical ocular findings and high value of urinary β2 microglobulin even though renal biopsy was not performed. The girl showed development of CNV with subretinal macular hemorrhage along with the exacerbation of anterior chamber inflammation in her left eye. Subretinal macular hemorrhage recurred frequently even with oral prednisolone; therefore, intravitreal injection of bevacizumab (IVB) was performed. After IVB, the subretinal proliferative tissue shrunk and subretinal hemorrhage has not recurred for 5 years. The boy showed subretinal hemorrhage from CNV with severe anterior chamber inflammation in his left eye. With oral prednisolone, anterior chamber inflammation and subretinal hemorrhage disappeared, but shrunken subretinal fibrosis in the macula remained. Final visual acuity was poor due to residual subretinal fibrosis in both cases.*
CONCLUSIONS. *Tubulointerstitial nephritis and uveitis syndrome has a potential to develop CNV that leads to severe visual loss; therefore, prompt anti-inflammatory therapy is required, and IVB should be regarded as a potential choice of treatment.*

KEY WORDS. *Bevacizumab, Choroidal neovascularization, Recurrence, Tubulointerstitial nephritis and uveitis syndrome*

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INTRODUCTION

Tubulointerstitial nephritis and uveitis (TINU) syndrome typically occurs in ~15-year-old girls, and is characterized by a combination of idiopathic acute TINU (1, 2). As ocular findings, patients usually present with anterior segment inflammation and sometimes with mild posterior segment lesions, such as mild vitreous opacity (opacitas corporis vitrei; OCV) and optic disk hyperemia. By contrast, severe posterior segment intraocular inflammation is rarely observed. In this report, we present 2 cases of TINU syndrome with subfoveal choroidal neovascularization (CNV).

Case 1

A 12-year-old girl presented with a 3-month history of ocular pain and redness in both eyes. At the first examination, she showed mild anterior chamber inflammation with keratic precipitates and posterior synechia, redness and swelling of the optic disk, snowball OCV, and periphlebitis OU. Corrected visual acuity was 24/20 OU. Laboratory tests were normal except for the extra-high value of urinary β2 microglobulin (2.429 mg/L; normal 0.027–0.275 mg/L). On the basis of typical ocular findings and in accordance with the diagnostic criteria for the disease, the patient was diagnosed with probable TINU syndrome without renal bi-

opsy (3). At that time, ocular inflammation was mild and gradually controlled without topical corticosteroids.

Two months later, however, the patient showed exacerbated bilateral intraocular inflammation. Visual acuity was 14/20 OD and 2/20 OS. Severe anterior chamber inflammation with posterior synechia OU and fibrin exudate OD were observed. The posterior segment was also inflamed. In addition to exacerbated OCV, snowball vitreous opacity and swollen optic disk (OU), as well as subfoveal exudates with subretinal macular hemorrhage, were present (OS) (Fig. 1A).

Subfoveal lesion was hyperfluorescent on fluorescein angiography (FA) (Fig. 1B). The lesion was hypofluorescent in the early phase and hyperfluorescent in the late phase on indocyanine green angiography (ICGA). Optical coherence tomography (OCT) showed proliferative tissue with slight serous retinal detachment (SRD) in the subretinal space (Fig. 1C). These results suggest that CNV with exacerbated inflammation had developed.

The patient was treated with systemic administration of 60 mg prednisolone per day and sub-Tenon injection of 40 mg triamcinolone acetonide (STTA). With these treatments, subretinal hemorrhage and SRD disappeared, and the subfoveal tissue shrank.

Four months later, subretinal hemorrhage suddenly recurred, but diminished with a treatment of 60 mg prednisolone and STTA.

Another 3 months later, however, subretinal hemorrhage recurred with the enlargement of CNV and SRD (OS). The patient's visual acuity decreased to 3/20 (OS). After informed consent was obtained, intravitreal injection of 1.25 mg bevacizumab (IVB) was performed twice at a 2-month interval (OS) in addition to the increase in prednisolone dose.

Since then, subretinal hemorrhage and SRD have disappeared and the subretinal proliferative tissue has shrunk. Prednisolone was successfully tapered off. The CNV has not recurred for 5 years.

Case 2

A 12-year-old boy complained of persistent hyperemia in both eyes. On the first examination, mild anterior chamber inflammation with keratic precipitates (OU) and posterior synechia (OS) were observed. Redness of the optic disk and diffuse OCV were also observed (OS). Laboratory tests were normal except for the extra-high value of urinary β2

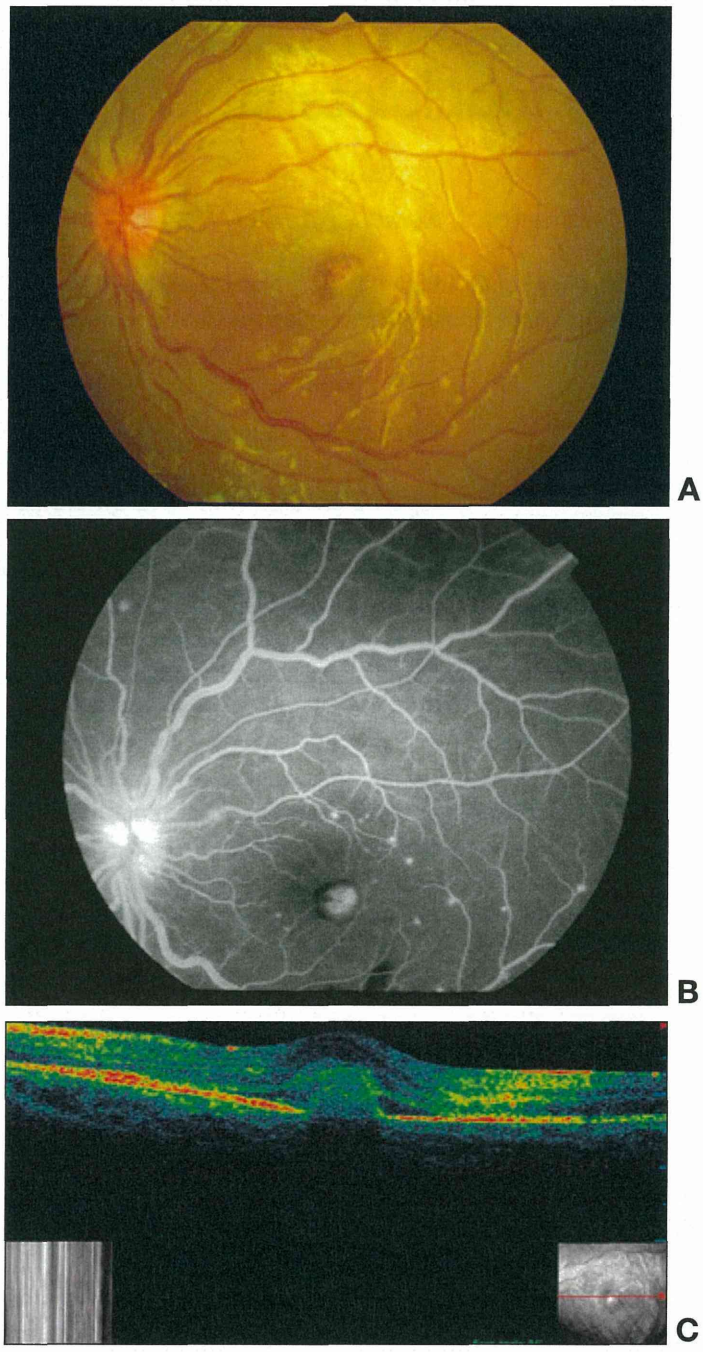

Fig. 1 - *Imaging study for case 1.* **(A)** *Subfoveal proliferative tissue with subretinal hemorrhage and serous retinal detachment.* **(B)** *Subfoveal lesion was hyperfluorescent on fluorescein angiography.* **(C)** *Proliferative tissue with slight serous retinal detachment was observed with optical coherence tomography.*

microglobulin (1.457 mg/L). Fluorescein angiography and ICGA could not be performed because the patient could not tolerate them due to anamnesis of Asperger syndrome. He was diagnosed with probable TINU (without renal biopsy).

With topical corticosteroid treatment, ocular inflammation gradually subsided, but intraocular inflammation (OS) was exacerbated 4 months later. Visual acuity decreased from 24/20 to 10/20. Severe anterior chamber inflammation with posterior synechia was observed. In addition to a swollen optic disk, subfoveal proliferative tissue with subretinal hemorrhage and SRD were observed. The development of CNV was suspected from these findings.

With oral administration of 40 mg prednisolone per day, anterior chamber inflammation, subretinal hemorrhage, and SRD disappeared, but subretinal fibrosis in the macula (OS) remained.

Although the patient experienced 2 recurrences of anterior chamber inflammation, he has not shown recurrence of subretinal hemorrhage. His visual acuity has remained at 3/20 (OS).

DISCUSSION

The clinical course of ocular inflammation in TINU syndrome is usually chronic, but sometimes, recurrences are observed, requiring systemic corticosteroid administration. Ocular findings at recurrence are usually limited to the anterior chamber and sometimes combined with mild posterior segment symptoms, such as diffuse vitreous opacities, optic disk swelling, and periphlebitis (2). In this article, 2 cases of secondary CNV complication in TINU were reported. The results indicate that TINU syndrome has the potential to develop CNV with severe inflammatory recurrence.

The development of CNV in TINU syndrome is rare; in our clinic, 4.3% of 46 TINU syndrome cases developed CNV. Moreover, no case of secondary CNV related to other forms of uveitis in children was observed, except for one case diagnosed with sarcoidosis.

For case 1, IVB was performed to treat refractory CNV. After the procedure, the patient no longer showed recurrent CNV-induced bleeding and CNV enlargement. Although several reports about IVB for secondary CNV with uveitis have been published, no study has been conducted on IVB for children.

Only a few reports describe long-term efficacy and safety after IVB (4). Menstrual irregularities and teratogenicity are indicated as potential side effects of IVB for young girls (5), but incidences have not been reported. Case 1 showed repeated hemorrhaging from enlarged CNV and lost visual acuity (OS); she urgently needed effective treatment at that time. With informed consent and full awareness of the risks of IVB, IVB was performed. The patient has not reported any side effects, including menstrual irregularities, for 5 years. However, the patient still requires careful monitoring because of uncertainty regarding the long-term influence of IVB.

Given that CNV can result in severe visual loss, patients should be carefully monitored to manage recurrence. The administration of systemic corticosteroids from the early stage of the disease should be considered. Intravitreal bevacizumab should be regarded as a potential course of treatment even for young patients who present with CNV.

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Address for correspondence:
Kenichi Namba, MD, PhD
Department of Ophthalmology
Hokkaido University Graduate School of Medicine
N-15, W-7, Kita-ku
Sapporo 060-8638
Japan
knamba@med.hokudai.ac.jp

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CLINICAL INVESTIGATION

Trabecular meshwork depigmentation in Vogt–Koyanagi–Harada disease

Kazuomi Mizuuchi · Nobuyoshi Kitaichi · Kenichi Namba · Yukihiro Horie · Susumu Ishida · Shigeaki Ohno

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Abstract
Purpose Since some patients develop depigmentation of the trabecular meshwork in the course of Vogt–Koyanagi–Harada (VKH) disease, we examined the incidence of trabecular depigmentation and its correlation with other ocular findings and systemic symptoms.
Methods We retrospectively reviewed the clinical charts of 53 Japanese patients diagnosed with VKH disease. The scores of trabecular and limbal pigmentation of all patients were recorded. We then examined the correlation between trabecular pigmentation and the presence of sunset glow fundus or skin lesions.
Results Trabecular pigmentation was significantly lower in the patients with sunset glow fundus than in those without it ($P = 0.022$), whereas limbal pigmentation showed no significance. However, there were no significant differences in trabecular and limbal pigmentation between the patients with and those without skin lesions. Furthermore, there was no correlation between trabecular and limbal pigmentation.
Conclusions Depigmentation of the trabecular meshwork develops in some patients in the course of VKH disease. This depigmentation is significantly correlated with sunset glow fundus, but not with limbal depigmentation or skin lesions.

Keywords Vogt–Koyanagi–Harada disease · Trabecular depigmentation · Sunset grow fundus · Limbal depigmentation · Skin lesion

K. Mizuuchi · K. Namba (✉) · Y. Horie · S. Ishida
Department of Ophthalmology, Hokkaido University Graduate School of Medicine, Kita-15, Nishi-7, Kita-ku, Sapporo 060-8638, Japan
e-mail: knamba@med.hokudai.ac.jp

N. Kitaichi · S. Ohno
Department of Ocular Inflammation and Immunology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

N. Kitaichi
Department of Ophthalmology, Health Sciences University of Hokkaido, Sapporo, Japan

Introduction

Vogt–Koyanagi–Harada (VKH) disease is a systemic disorder considered to be a cell-mediated autoimmune disease against melanocytes in systemic organs [1–5]. The onset of the disease is acute, and patients show severe inflammation including bilateral intraocular inflammation, sensorineural hearing loss and meningitis. Intensive systemic corticosteroid therapy is the mainstay of the treatment for this disease. However, some patients develop prolonged chronic inflammation. These patients often exhibit depigmentation such as vitiligo, alopecia, poliosis, sunset glow fundus and Sugiura's sign.

Sunset glow fundus is seen as a result of depigmentation of the choroids and is typified by the fundus exhibiting an orange–red discoloration that simulates the appearance of sunset [1, 6, 7]. Sugiura's sign is the depigmentation of corneal limbs [2]. These findings are seen in the prolonged stage of VKH disease.

We found that some patients show depigmentation of the trabecular meshwork in the course of VKH disease. This is the first report describing trabecular depigmentation in VKH disease. In this report, we examined the incidence of trabecular depigmentation and correlation with Sugiura's sign and other systemic symptoms.

Patients and methods

We retrospectively reviewed the clinical charts of 53 Japanese patients (21 men and 32 women) diagnosed with VKH disease who attended the Uveitis Survey Clinic of the Hokkaido University Hospital, Japan, between 1991 and 2011. VKH disease was diagnosed based on the revised criteria proposed by the Committee of the 2nd VKH Disease Symposium [6]. Patients with a history of intraocular surgery or diagnosed as having sympathetic ophthalmia were excluded. The age at disease onset ranged from 20 to 73 years of age, and the average was 46.0 years. The mean follow-up period was 59.9 months (range 0–237).

All patients who visited our clinic with the symptoms of the early stage of VKH disease were immediately treated with systemic corticosteroids. High-dose corticosteroids, usually starting with 200 mg/day of prednisolone, were administered intravenously. No patients were initially treated with methyl prednisolone pulse therapy. The dosage of prednisolone was gradually tapered according to the improvements shown in the clinical findings, and then replaced by oral prednisolone.

This is not a consecutive case series study. VKH patients who visited our hospital in the period from June 2010 to September 2011 were investigated for trabecular and limbal pigmentation with gonioscopy and slit-lamp microscopy, and the amount of pigmentation was scored. Also, the presence of sunset glow fundus and/or skin lesion such as vitiligo, alopecia or poliosis were investigated.

To evaluate the trabecular pigmentation, each eighth of the trabecular meshwork was scored from 0 to 4 based on the Scheie classification [8]. All eight scores (0–4) were summed up to calculate the trabecular pigmentation score (maximum 32) in each eye. In the same way, we observed four quadrants of the corneal limbus using slit-lamp microscopy to evaluate the limbal pigmentation. The pigmentation of each quadrant was scored from 0 to 2. Zero denoted no limbal pigmentation; 1, mild pigmentation; and 2, standard pigmentation. The standard picture of score 2 is shown (Fig. 4c). The summation of the four quadrant-scores was the limbal pigmentation score (maximum 8) of each eye.

Statistical analyses were performed using the Mann–Whitney U test or t test. P values of <0.05 were considered statistically significant.

This study followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Hokkaido University Hospital.

Case reports

The following four cases showed typical trabecular depigmentation (Cases 1, 2 and 3) and limbal depigmentation (Sugiura's sign; Case 4) in the clinical course of VKH disease.

Case 1

A 40-year-old man presented with bilateral granulomatous iridocyclitis and sunset glow fundus at his initial visit. Despite having no exudative retinal detachment and pleocytosis, complete VKH disease was diagnosed due to the typical sunset glow fundus, headache, decreased hearing, poliosis and vitiligo. Although he was treated with high-dose systemic corticosteroids, mild anterior uveitis was seen in both eyes while tapering the corticosteroids. Gonioscopic examination revealed trabecular pigmentation OS initially graded score 2 (Fig. 1a) and scored 1 (Fig. 1b) 1 month after his initial visit. The scores decreased to score 1 (Fig. 1c) and 0 (Fig. 1d) over 19 months. Later, vitiligo and apparent sunset glow fundus were seen.

Case 2

A 53-year-old woman presented with mild iridocyclitis with exudative retinal detachment OU and swelling and hyperemia of the right optic disc at her initial visit. Based on the findings of pleocytosis and hearing loss, incomplete VKH disease was diagnosed. Although she was treated with high-dose systemic corticosteroids, she relapsed twice with bilateral granulomatous anterior chamber inflammation while tapering the amount of the corticosteroids. The trabecular pigmentation OD was graded score 2 at 1 month after the disease onset (Fig. 2a, b), and decreased to score 1 (Fig. 2c, d) within the first 4 months. Depigmentation was observed OS. Sunset glow fundus also developed later.

Case 3

A 51-year-old woman presented with bilateral mild iridocyclitis, serous retinal detachment and optic disc swelling with hyperemia at her initial visit. Although pleocytosis was not detected, incomplete VKH disease was diagnosed according to the typical ocular findings of VKH, sensorineural hearing loss, tinnitus and headache. She was treated with high-dose systemic corticosteroids, which were gradually tapered. Corticosteroid therapy was successfully terminated without any recurrence of ocular inflammation. Her right trabecular pigmentation was scored 3 (Fig. 3a, b) at 1 month, and decreased to 0 (Fig. 3c, d) at 27 months after onset. Similar depigmentation was also seen OS. Skin lesions and sunset glow fundus were never seen.

Case 4

A 26-year-old man presented with bilateral iridocyclitis, serous retinal detachment, and optic disc swelling with

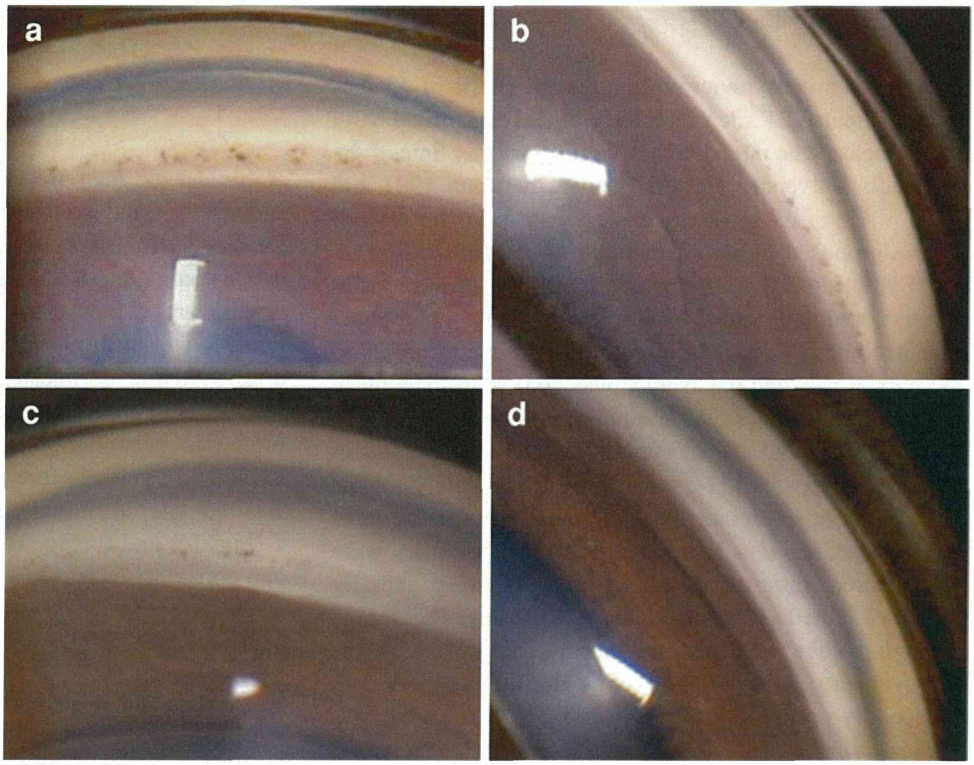

Fig. 1 Change of trabecular depigmentation in Case 1. **a** Score of trabecular pigmentation was 2 and, **b** 1 at 1 month after his initial visit. **c** 20 months after his initial visit, trabecular pigmentation was reduced to scores 1 and, **d** 0

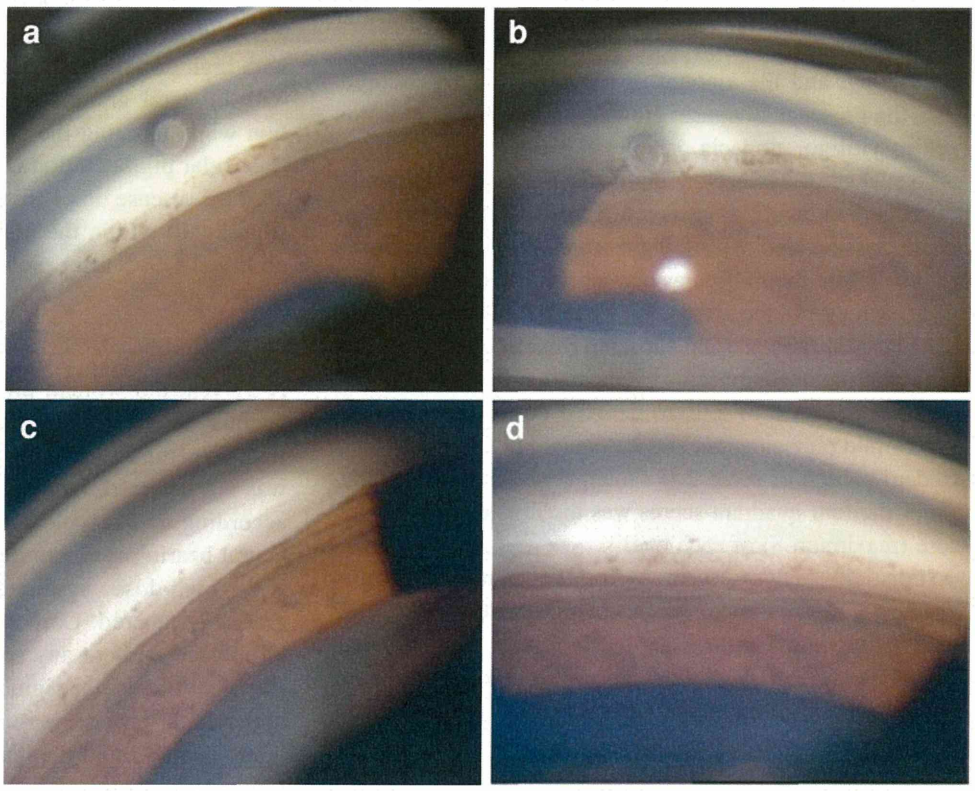

Fig. 2 Change of trabecular depigmentation in Case 2. **a**, **b** Score of trabecular pigmentation was 2 at 1 month after the disease onset. **c**, **d** Five months after the disease onset, trabecular pigmentation was reduced to score 1

hyperemia at his initial visit. In addition to the typical ocular findings of VKH disease, headache, pleocytosis, and alopecia were recorded. Complete VKH disease was diagnosed. He was treated with high-dose systemic corticosteroids, which were gradually tapered. However, bilateral granulomatous anterior uveitis relapsed 6 months after

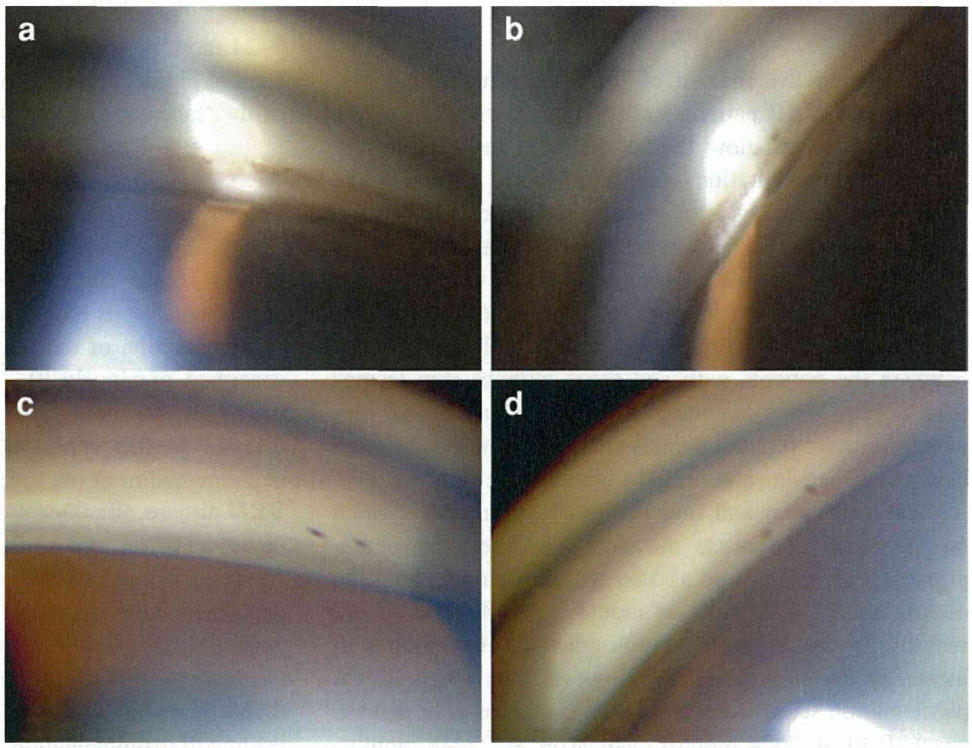

Fig. 3 Change of trabecular depigmentation in Case 3. **a**, **b** Score of trabecular pigmentation was 3 at 1 month after the disease onset. **c**, **d** Twenty-seven months after the disease onset, trabecular pigmentation was reduced to score 0

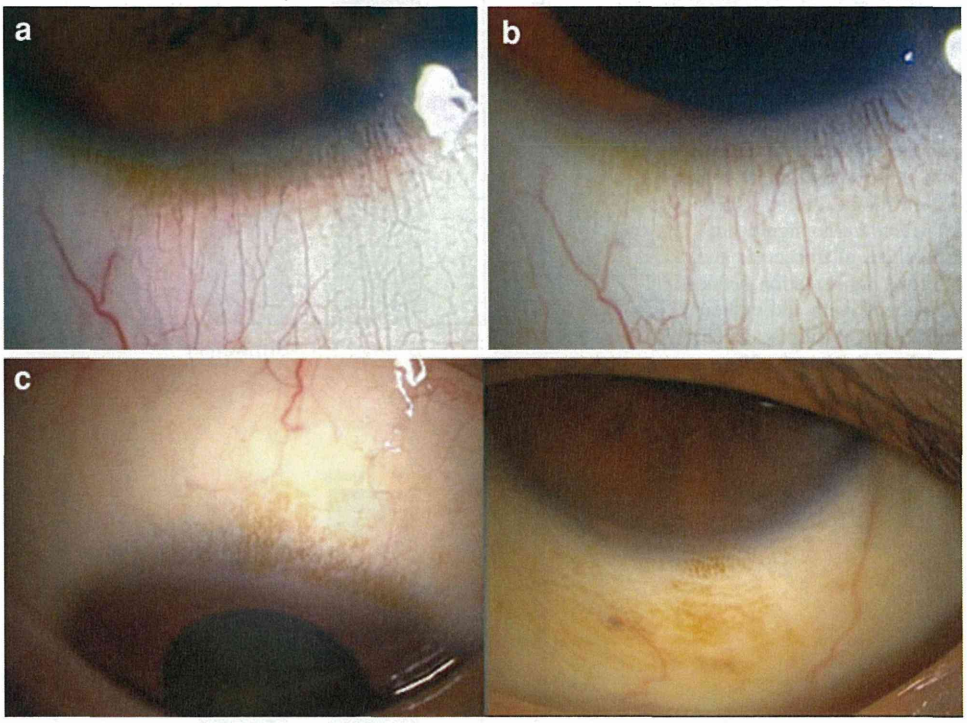

Fig. 4 Change of limbal depigmentation in Case 4. Score of limbal pigmentation was 2 at his initial visit (**a**). Twenty-one months after his initial visit, limbal pigmentation was reduced to score 1 (**b**). **c** Score 2 of limbal pigmentation (standard picture)

his initial visit. In addition to the development of the sunset glow fundus, his limbal pigmentation decreased (Sugiura's sign) in the course of the disease. According to our original scoring, the limbal pigmentation was graded as score 2 at his initial visit (Fig. 4a), but was decreased to score 1 (Fig. 4b) after 21 months.

Results

We evaluated the amount of trabecular and limbal pigmentation in VKH patients both in the presence of and the absence of sunset glow fundus and skin lesions (Fig. 5). Trabecular pigmentation was significantly lower in the patients with sunset glow fundus than those without it (Fig. 5a, $P = 0.022$). However, limbal pigmentation scores showed no significance between the patients with and those without sunset glow fundus (Fig. 5b). There were no significant differences in trabecular and limbal pigmentation between the patients with and those without skin lesions (Fig. 5c, d). When amounts of trabecular and limbal pigmentation were plotted, there was no significant correlation between trabecular and limbal pigmentation (Fig. 6).

Next, trabecular and limbal pigmentation were divided on the basis of disease duration. The mean trabecular pigmentation was scored as 5.69 within 6 months after the disease onset, 4.89 at 7–24 months, and 4.13 at 25–48 months. Trabecular pigmentation gradually decreased with increased duration (Fig. 7a). However, the mean limbal pigmentation score was 1.31 within 6 months after disease onset, 0.39 at 7–24 months, and 0.69 at 25–48 months. Limbal pigmentation was significantly reduced at 7–24 months after disease onset ($P = 0.003$, Fig. 7b). Limbal pigmentation decreased rapidly compared with that of the trabecular meshwork (Fig. 7).

Discussion

In the course of VKH disease, development of limbal depigmentation is known as Sugiura's sign [2]. Atrophy and depigmentation of the iris in VKH disease have also been described previously [9, 10]. However, depigmentation of the trabecular meshwork has never been reported in VKH disease. In this study, we showed a tendency toward a depigmentation of the trabecular meshwork in the course of VKH disease. Significant correlation between the trabecular depigmentation and sunset glow fundus was also found, whereas no significant correlation between the limbal depigmentation and sunset glow fundus was seen. It is now generally accepted that the underlying immunopathologic mechanism in VKH disease is a T cell-mediated autoimmune reaction against melanocyte-related antigens [11] leading to depigmentation of the tissue by phagocytosis. The

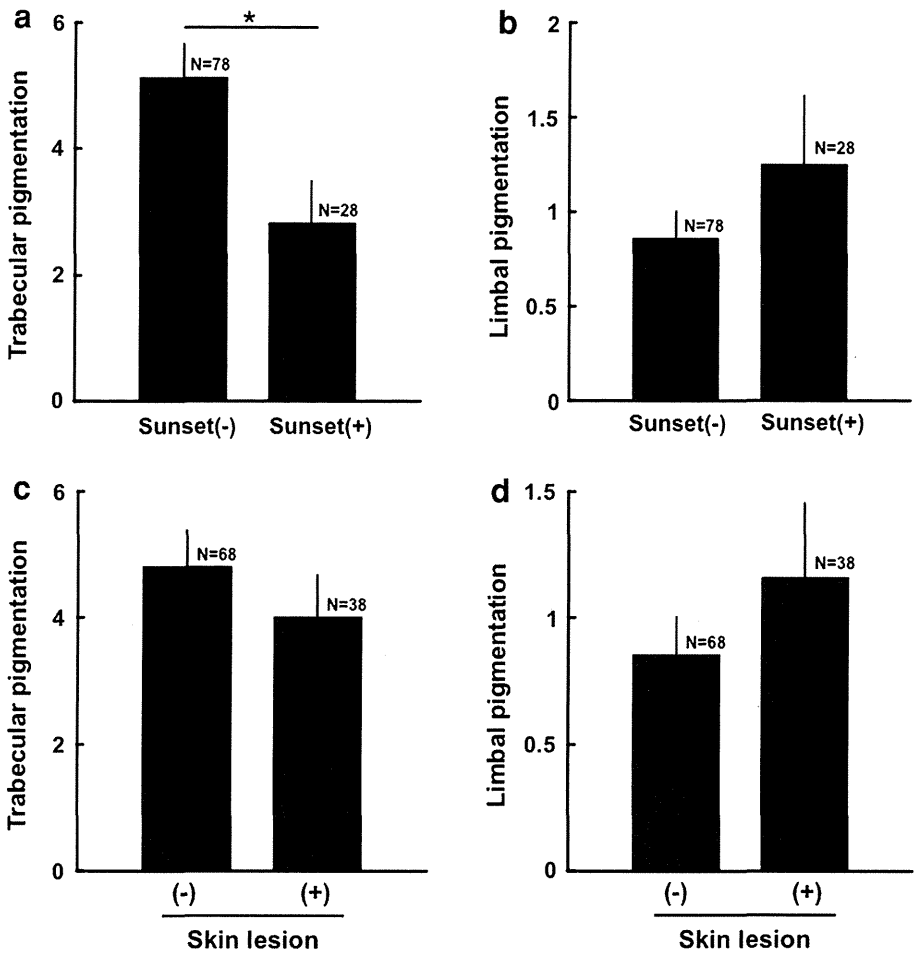

Fig. 5 Correlation of trabecular and limbal pigmentation with the sunset glow fundus and skin lesions. **a** Trabecular and, **b** limbal pigmentation were scored in the presence or absence of sunset glow fundus. Trabecular pigmentation was significantly lower in patients with sunset glow fundus than those without it ($P < 0.05$). **c** There were no significant differences of trabecular and, **d** limbal pigmentation between the patients with and without skin lesions (vitiligo, alopecia, or poliosis). *$P = 0.022$

trabecular meshwork and choroid are target tissues inside the eye in VKH disease, and it is suspected that they are commonly affected at the same time and with the same mechanisms in the disease. Therefore, it is consistent that the development of the trabecular meshwork and choroidal depigmentation (sunset glow fundus) are significantly correlated. On the other hand, depigmentation of the limbus, located at the ocular surface, may develop by some other mechanism. And, we found that the trabecular depigmentation developed later than the limbal depigmentation. Although we do not have an explanation for the phenomenon, we know that some kinds of immune suppression mechanisms maintain immune privilege in the eye. They may delay immune reaction toward the trabecular pigments.

The presence or absence of skin lesions correlated poorly with trabecular and limbal depigmentation in the present study. This suggests that depigmentation is induced through different local mechanisms in these two organs.

Sunset glow fundus is one of the characteristic ocular findings of VKH disease. Therefore, it can be decisive for diagnosis in atypical cases. It is sometimes hard to diagnose the disease in its early stage, particularly in Vogt–Koyanagi type (iridocyclitis type), because characteristic ocular findings, e.g., exudative or serous retinal detachment, are absent. Sunset glow fundus sometimes confirms the diagnosis at 2–6 months after disease onset. Trabecular depigmentation can also be a decisive finding in the diagnosis of VKH disease. As shown in this report, development of trabecular depigmentation was significantly correlated with the development of sunset glow fundus. For the cases of less pigment patients, e.g., Caucasian, trabecular depigmentation may be more helpful than sunset glow fundus. Furthermore, in patients with bilateral invisible ocular fundi due to total posterior synechia and/or cataract, the presence of trabecular depigmentation can be a suggestive sign for the convalescent stage of VKH disease. Prolongation of intraocular inflammation is also an important issue in VKH disease. We examined the relationships between trabecular or limbal pigmentation and prolongation, but we could not find any significant differences between them (data not shown). Further examination with an increased number of patients is required.

In this study, scores for trabecular and limbal pigmentation were obtained from only one examination of most of the enrolled patients; therefore, they were not serially observed. All cases are now carefully followed up at our Uveitis Clinic. Further examinations are required to confirm depigmentation in the enrolled patients a few years later. The correlations between trabecular or limbal depigmentation and other parameters, e.g., gender, genetic background, age of disease onset and recurrence of the disease, may also be analyzed in the future.

This is the first report describing the development of trabecular depigmentation in the convalescent stage of VKH disease. Limbal depigmentation of VKH disease is called Sugiura's sign worldwide after Seiji Sugiura (1915–2003), who first reported the phenomenon.

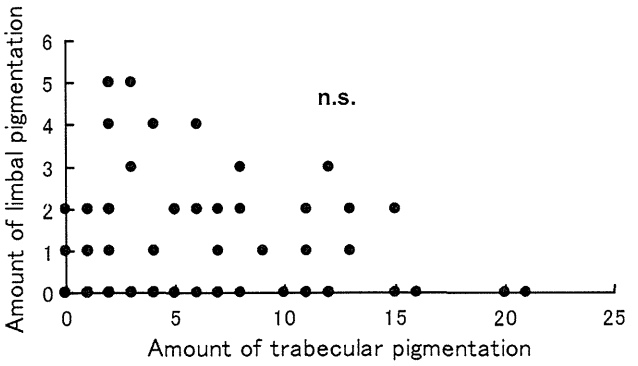

Fig. 6 Correlation between trabecular and limbal pigmentation in VKH patients. There was no correlation between the amount of trabecular and limbal pigmentation

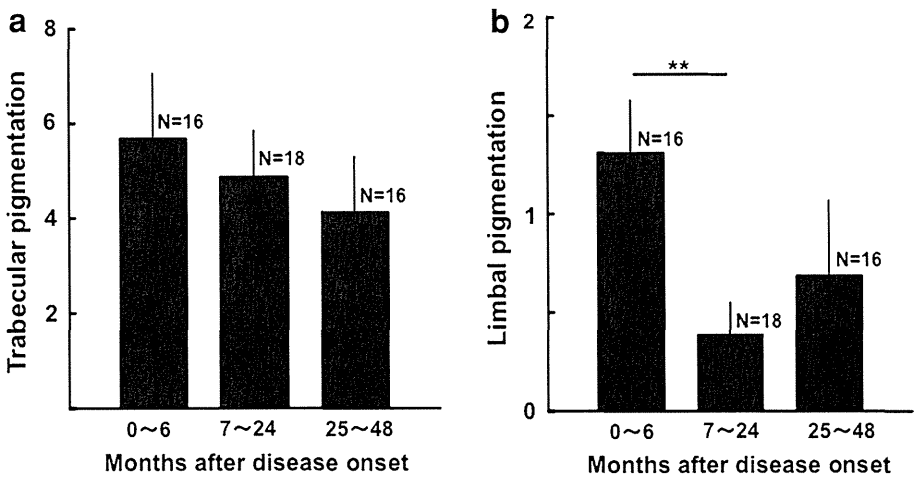

Fig. 7 Trabecular and limbal pigmentation divided on the basis of disease duration. **a** Trabecular pigmentation was gradually reduced with time. However, **b** limbal pigmentation was significantly reduced at 7–24 months after disease onset. Limbal pigmentation decreased rapidly compared with that of the trabecular meshwork. $^{**}P = 0.003$

Following the example of Sugiura's sign, we propose calling this phenomenon 'Ohno's sign.'

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BRIEF REPORT Open Access

Bacterial endophthalmitis caused by an intraocular cilium in a patient under treatment with infliximab

Xue-hai Jin, Kenichi Namba*, Wataru Saito, Daiju Iwata and Susumu Ishida

Abstract

Background: We report a case of bacterial endophthalmitis caused by an intraocular cilium in a patient without any history of trauma or ocular surgery.

Findings: A 32-year-old Caucasian male showed symptoms of orbital myositis and scleritis, with no intraocular inflammation in the right eye. The patient had been treated with infliximab for Crohn's disease. Three weeks after initiation of oral prednisolone therapy, he developed bacterial endophthalmitis. During pars plana vitrectomy, a cilium in the massive vitreous opacity was found. A focal scleral necrosis was detected just outside where the cilium was intraoperatively observed. Vitreous culture showed the presence of *Staphylococcus aureus*.

Conclusions: The intraocular cilium seemed to be the aetiology of the endophthalmitis in this case, which suggests that anti-tumour necrosis factor-α therapy may play a role in the migration of cilia into the globe and the occurrence of endophthalmitis.

Keywords: Cilium, Endopthalmitis, Anti-tumour necrosis factor-α antibody therapy, Crohn's disease

Findings

Introduction

The presence of intraocular cilia is rare but is sometimes reported as a complication from a penetrating ocular injury. The response of the eye to the retained intraocular cilia may be an early severe inflammation or delayed inflammatory reaction in the form of plastic iridocyclitis, granulomatous inflammation or foreign-body reaction [1]. Up to now, there are only three case reports in the literature of an intraocular cilium without any history of trauma or surgery; there was no evidence of an external entrance site for the intraocular cilium detected in these three cases [2-4].

We present a rare case of bacterial endophthalmitis suspected to be caused by an intraocular cilium without any history of penetrating ocular trauma or ocular surgery. The cilium is speculated to migrate gradually into the vitreous cavity via necrotised sclera induced by chronic infection, finally to cause exogenous endophthalmitis. This case was treated with anti-tumour necrosis factor (TNF)-α antibody for Crohn's disease before the onset of endophthalmitis.

Case report

A 32-year-old Caucasian male complained of redness with tenderness that lasted for 3 days in his right eye. He received oral prednisolone therapy for 2 weeks on the diagnosis of presumed orbital myositis without intraocular abnormality in an eye clinic. However, his symptoms gradually worsened, so he was referred to our hospital. He had been treated with infliximab, an anti-TNF-α antibody, for 2 years for Crohn's disease, and the disease was well controlled. There was no history of trauma or ocular surgery.

His decimal visual acuity was 1.0 OU. Slit-lamp examination revealed marked temporal conjunctival and scleral injections OD, with no anterior chamber inflammation (Figure 1a). Funduscopic examination revealed a tiny creamy intraretinal infiltration at the supero-temporal periphery without vitreous opacity OD. Nothing appeared abnormal at OS. Ultrasonic B-mode imaging and MRI

* Correspondence: knamba@med.hokudai.ac.jp
Department of Ophthalmology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

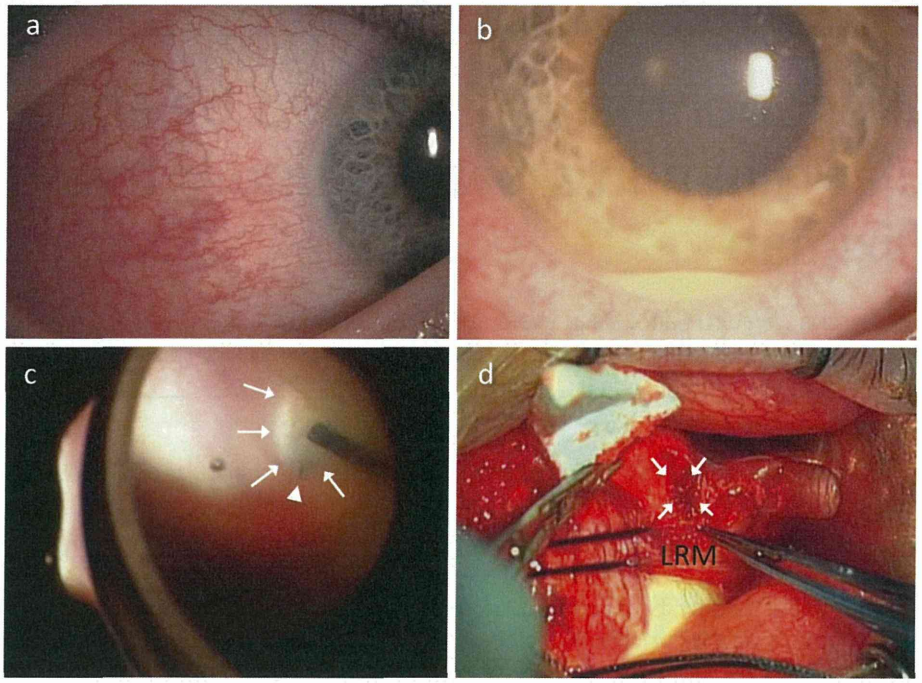

Figure 1 Photographs of the right eye. Photographs of the right eye showing marked temporal conjunctival and scleral injections at the first visit (**a**) and anterior chamber inflammation with hypopyon 1 week after the first visit (**b**). Intraoperatively, a yellow-white massive vitreous opacity (white arrows) was observed at the supero-temporal retina and a foreign body (white triangle) resembling a cilium was found in the vitreous opacity (**c**). A focal scleral necrosis (arrows) was detected just outside where the foreign body was observed (**d**). LRM, lateral rectus muscle.

showed no abnormalities. The white blood cell count and C-reactive protein level were within normal limits.

Administration of prednisolone (40 mg/day) was orally initiated for scleritis. However, he returned 1 week later with complaints of blurred vision and exacerbated pain OD. Examination revealed a visual acuity of 1.0, 3+ cells in the anterior chamber and massive vitreous opacity above the temporal intraretinal infiltrate OD. On the following day, his visual acuity had deteriorated to hand motion OD. Anterior chamber inflammation worsened to 4+ cells with hypopyon (Figure 1b), and the fundus was invisible due to exacerbated vitreous opacity. As suspicious endophthalmitis was diagnosed, he immediately underwent pars plana vitrectomy. Intraoperatively, a yellow-white mass, suggestive of subretinal abscess, was observed at the retina, peripheral to the pars plana of the supero-temporal side; and a foreign body resembling a cilium was found in the massive vitreous opacity (Figure 1c). A focal scleral necrosis was detected at exactly the same site where the foreign body was observed (Figure 1d). Histopathological examination later confirmed the foreign body to be a human hair (cilium) (Figure 2). Vitreous culture showed the presence of *Staphylococcus aureus*. After the surgery, endophthalmitis

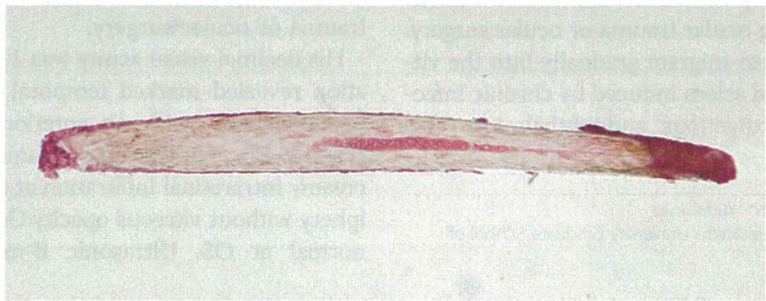

Figure 2 Histopathological examination confirming the foreign body as a human hair (hematoxylin and eosin, ×4).

became silent with the treatment of intravenous antibiotics; however, the retina was partially detached due to the occurrence of secondary proliferative vitreoretinopathy.

Discussion

We encountered a case of bacterial endophthalmitis caused by an intraocular cilium. This case was unique because of the absence of any history of penetrating ocular trauma and the history of treatment with an anti-TNF-α antibody for Crohn's disease. Although the possibility of remotely unrecalled ocular trauma may have been involved in the cilium migration, there were no intraocular foreign bodies except the cilium detected during surgery. Moreover, the clinical course of scleritis - without intraocular inflammation antecedent to the onset of endophthalmitis - suggests that it may take time for the cilium migration, rather than a sudden trauma. During surgery, a focal scleral necrosis was found at the same site where the cilium was detected, suggesting that necrotized sclera gave the migrating cilium entrance to the globe. Such conditions are unlikely to be due to a sudden penetrating ocular trauma. We speculate that the accidentally migrated cilium under the conjunctiva caused chronic bacterial infection and then focal scleral necrosis and that subsequently, the cilium migrated into the vitreous cavity via the necrotised sclera, finally to cause exogenous endophthalmitis.

Cilium migration into the subconjunctival space usually does not cause chronic infection in immunocompetent people because microorganisms around the cilia are eliminated easily with innate immune responses. In this case, the history of treatment with infliximab, an anti-TNF-α antibody, may play a role in the migration of the intraocular cilium. TNF-α is a central key cytokine that mediates inflammatory response. Therefore, the anti-TNF-α drugs are highly effective treatment for chronic inflammatory diseases such as rheumatoid arthritis and Crohn's disease. Meanwhile, TNF-α is also an important cytokine that plays a central role in the innate immune response towards microorganisms [5]. The immune response eliminates them by inducing strong inflammation. However, under treatment with an anti-TNF-α drug, microorganisms survive easily, and the focal infection tends to persist with a mild inflammation [6]. In this case, therefore, we speculate that a chronic infection in the subconjunctival space is prolonged due to the increased vulnerability to infection by the anti-TNF-α drug administration, which led to focal scleral necrosis subsequently.

This case indicates that intraocular cilia may be an aetiology of endophthalmitis even in patients without any history of trauma or surgery. Furthermore, anti-TNF-α drug therapy may play a role in the migration of the intraocular cilium and the development of endophthalmitis.

Abbreviation

TNF: Tumour necrosis factor.

Competing interests

All authors declare that they have no competing interest.

Authors' contributions

XJ managed the case and drafted the manuscript. KN managed the case, also participated in the design of the study and revised the manuscript critically. WS was involved in treating the case, also reviewed the paper and gave valuable comments. DI was involved in the medical care of the case and contributed to the collection of data. SI supervised the management of the case, also revised the manuscript and made the best possible comments. All authors read and approved the final manuscript.

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CLINICAL INVESTIGATION

Clinical features of human T lymphotropic virus type 1-associated uveitis in Hokkaido, Japan

Satoru Kase · Kenichi Namba · Nobuyoshi Kitaichi · Daiju Iwata · Shigeaki Ohno · Susumu Ishida

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Abstract
Purpose To clarify the clinical features of human lymphotropic virus type 1 (HTLV-1)-associated uveitis (HAU) in patients of Hokkaido University Hospital, Hokkaido, northern Japan.
Methods We reviewed the records of a consecutive series of 21 patients with HAU who were followed up for more than 12 months at Hokkaido University Hospital.
Results Of the 21 patients enrolled in this study, 19 as well as their parents (90.5 %) were born in Hokkaido. One patient was a member of the Ainu ethnic group. Unilateral involvement was found in 16 cases (76 %). In the ophthalmological examinations, vitreous opacity was most frequently followed by keratic precipitate, iris/gonio nodules, and posterior synechiae, while hypopyon, retinal vasculitis, and neovascularization were rarely observed. Intraocular inflammation was controlled by topical treatment, while systemic corticosteroids were required in less than one-fourth of patients. Visual acuity improved in 15 patients, remained unchanged in four patients, and deteriorated in two patients. HAU was observed in two patients with adult T-cell leukemia/lymphoma (ATLL). Three out of the four patients (75 %) for whom HLA typing was available had HLA-A26.
Conclusions A number of clinical features were unique to Hokkaido, namely, predominant unilateral involvement, as well as two HAU patients with ATLL. The phylogenetic difference of HTLV-1 and HLA typing may correlate with different clinical manifestations in HAU.

Keywords HTLV-1 · Uveitis · Adult T-cell leukemia · Hokkaido

S. Kase · K. Namba (✉) · D. Iwata · S. Ishida
Department of Ophthalmology, Hokkaido University Graduate School of Medicine, Kita 15, Nishi 7, Kita-ku, Sapporo 060-8638, Japan
e-mail: knamba@med.hokudai.ac.jp

N. Kitaichi · S. Ohno · S. Ishida
Department of Ocular Inflammation and Immunology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

N. Kitaichi
Department of Ophthalmology, Health Sciences University of Hokkaido, Sapporo, Japan

Introduction

The human T-lymphotropic virus type 1 (HTLV-1) was the first human retrovirus to be discovered [1], and it is estimated that 10–20 million people worldwide are infected with it [2]. Although the majority of infected people remain asymptomatic, the virus is associated with exceptionally severe diseases, including adult T-cell leukemia/lymphoma (ATLL) and an inflammatory disease of the central nervous system called HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) [2]. Irregardless of the clinical status of the patient, the HTLV-1 provirus is predominantly detected in CD4+ T lymphocytes. It thus appears that the main vivo cellular targets of HTLV-1 are cells from the adaptive immune system [3].

HTLV-1-associated uveitis (HAU) is believed to account for 1.1 % of all uveitis patients in Japan [4]. In a recent prospective multi-center epidemiologic survey of uveitis involving 3,830 uveitis patients in Japan, the frequency of HAU was 0.8 % [5]. Mochizuki et al. [6] report that HTLV-1 infection was more frequent in patients with uveitis of unknown etiology than in the general population in Southern Japan. HAU was found in a relatively high

proportion of the population in the Kyushu area compared with other areas in Japan [4]. As ATLL is also common in the same area [7], this increased frequency of HAU is probably due to a high prevalence of HTLV-1 carriers in the southern island of Kyushu [8]. On the other hand, Goto et al. [4] report that HAU is also present in other areas outside of Kyushu. Moreover, Goto et al. [9, 10] demonstrate that the prevalence of HAU in HTLV-1 carriers in central Japan differs from that in southwestern Japan, suggesting that the incidence of HAU could be influenced by environmental or hereditary factors, including human leukocyte antigen (HLA). Hokkaido is the northernmost island in Japan with a population of 5.6 million [11]. Many residents are descended from migrants coming from other parts of Japan after the middle of the nineteenth century. In an earlier study, we reported the clinical features of 1,240 uveitis patients in Hokkaido, Japan, in which HAU was observed in 12 patients (1.0 %) [11]. To date, however, the clinical features of HAU in the area remain unknown.

In this study, we reviewed the clinical features of HAU in patients of Hokkaido University Hospital, Hokkaido, northern Japan, and also investigated the place of birth, ophthalmological findings, visual outcome, and related systemic disorders of each patient.

Materials and methods

This study was approved by the institutional review board of Hokkaido University. We reviewed the medical records of a consecutive series of 21 patients with HAU, who were followed up for more than 12 months between January 1991 and March 2011 at the Uveitis Survey Clinic of the Hokkaido University Hospital. Diagnostic criteria were based on clinical findings and the presence of serum antibodies to HTLV-1 as well as on the exclusion of other distinct uveitis entities [12]. Laboratory tests, including white blood cell count, C-reactive protein, liver and renal functions, fasting blood sugar, serum angiotensin converting enzyme, KL-6, urinary beta2-microglobulin, and the tuberculin skin test or interferon release assay test for tuberculosis, were run to exclude the other etiologies of uveitis. To differentiate from other causes of anterior uveitis, we also did HLA-B typing, tested for the presence of Herpes viruses in the aqueous humor by PCR methods, and evaluated the patients for the clinical features of ankylosing spondylitis and diabetes mellitus.

Routine follow-up examinations were performed and included history recording, testing of visual acuity and intraocular pressure, slit-lamp biomicroscopy, and ophthalmoscopy. Fluorescein angiography, perimetry, electroretinography, and ocular ultrasonography were also performed in selected patients. Serological, neurological, and endocrinological studies were also conducted where indicated. HLA-A alleles were examined in selected patients after written informed consent was obtained.

The mean follow-up period of the 21 cases was 84.5 months (range 15–208 months). Additional information available from previous medical history that enabled us to estimate the onset and course of HAU or related systemic disorders, such as, ATLL, HAM/TSP, and hyperthyroidism, was also collected.

Results

Place of birth

Of the 21 patients, 19 and their parents (90.5 %) were born in Hokkaido, Japan. Among the 19 patients, one patient was a member of the Ainu ethnic group [13]. Of the two remaining patients, one was born in Yamagata, in the north-east of Japan, and had moved to Hokkaido, and the other was born in Hokkaido, but his parents were born in Kyushu.

Ophthalmological findings

This study included 21 cases involving 15 women and six men. The average age at the onset of HAU ranged from 22 to 83 (mean 56.0) years. There were 16 cases of unilateral involvement [left eye (OS) 10 cases, right eye (OD) 6 cases] and five cases of uveitis in both eyes. In terms of the type of uveitis, our examinations revealed 15 cases of panuveitis, three cases of intermediate uveitis, two cases of posterior uveitis, and one case of anterior uveitis. Therefore, 26 eyes of 21 patients (cases) were investigated in this study. At onset, all patients complained of blurred vision and/or floaters. Corrected visual acuity was between 0.02 and 1.5 at onset. Ophthalmological findings revealed diffuse vitreous opacity in 23 eyes (88.4 %), keratic precipitates in ten eyes (38.5 %), iris/gonio nodules in four eyes (15.3 %), posterior synechiae in four eyes (15.3 %), fibrin exudates in the anterior chamber in two eyes (7.7 %), hypopyon in one eye (3.8 %), retinal periphlebitis in four eyes (15.3 %), retinal exudates in two eyes (7.7 %), iris rubeosis and retinal neovascularization in one eye (3.8 %), and hyperfluorescence of the optic disc detected by fluorescence angiography in three eyes (11.5 %).

Treatment

Topical eyedrops of 0.1 % betamethasone were administered to all eyes (100 %). Five of the 21 patients (23.8 %)

required oral prednisolone starting at 30 or 40 mg/day. Posterior sub-Tenon's injection of triamcinolone acetonide and of dexamethasone was performed in five (19.2 %) and one (3.8 %) eye, respectively, of the 26 eyes. Subconjunctival injection of dexamethasone was performed in one eye (3.8 %). Four eyes (15.4 %) had complicated secondary glaucoma and were treated with topical anti-glaucoma agents, and two patients eventually needed to undergo either glaucoma filtering surgery or trabeculotomy.

Outcome of visual acuity

Changes in visual acuities from initial to final presentations were reviewed. Visual acuity improvement of more than one line was found in 15 cases. The visual acuity remained unchanged in four cases during follow-up. In contrast, two patients showed <0.5 in the final visual acuity examination, with subsequent deterioration of visual acuity due to secondary glaucoma and epiretinal membrane formation, respectively (Fig. 1).

Systemic complications

Of the 21 patients, eight (38 %) had a medical history of hyperthyroidism. Uveitis was noted in two patients who had been followed-up by an internal medicine physician due to ATLL. Two subtypes of ATLL were noted: one patient had the smoldering type and the other patient the chronic type. These two patients also had a medical history of hyperthyroidism. In contrast, HAM/TSP was not detected in any of the HAU patients.

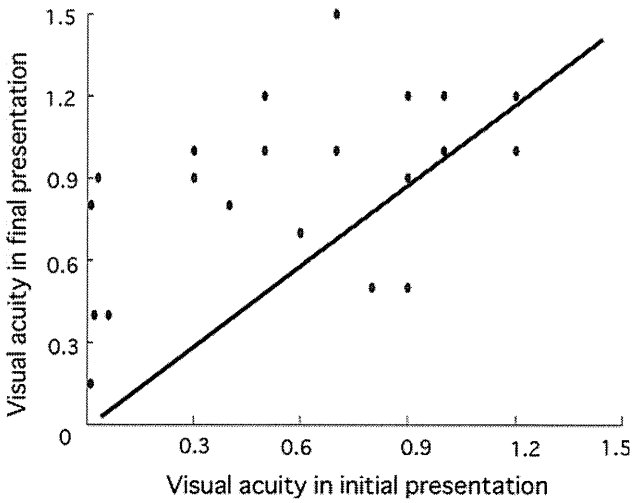

Fig. 1 *Dot graph* of visual acuities in initial and final presentations in patients with human lymphotropic virus type 1 (HTLV-1)-associated uveitis

HLA alleles

Four patients could be investigated for the determination of HLA-A alleles. The presence of HLA-A26 was determined in three of these patients (75 %), while the fourth patient was a carrier of HLA-A2 and A24. One HAU patient with complicating ATLL had HLA-A26, whereas HLA-A typing was not available in the other ATLL patients. Moreover, no patients carried HLA-B27 or B51.

Case reports

Case 1

A 53-year-old woman complained of floaters in both eyes (OU) in June 2004. Since uveitis was noted, she was referred to our University hospital. She had a medical history of hyperthyroidism since March 2004. She was born in Hokkaido and was half-Ainu. Her corrected visual acuities was 1.2 OD, and 1.5 OS with normal intraocular pressure. There was anterior segment inflammation with 1+ flare and 2+ cells OS. Diffuse vitreous opacity was noted OU (Fig. 2). Fundus findings were negative. Laboratory data revealed a high titer of anti-HTLV-1 antibody (8,192×) in the serum. She was treated with topical betamethasone as well as oral prednisolone 30 mg. The uveitis showed gradual remission. Neurological and hematological examinations revealed that she had not shown any symptoms of HAM/TSP or ATLL.

Case 2

A 61-year-old woman complained of blurred vision OD in July 1997. She has been followed-up by oncologists due to ATLL. Her corrected visual acuity was 0.8 OD. Mild anterior segment inflammation with vitreous opacity was observed OD. The blood test revealed the presence of anti-HTLV-1 antibody. She was born in Hokkaido. Since her ocular symptoms had gotten worse, she visited our hospital in 2001. Visual acuity was 0.6 OD with normal intraocular pressure. Slit-lamp examination demonstrated anterior segment inflammation with 3+ flare and 2+ cells. Posterior synechiae and fibrin exudates on the lens were observed OD (Fig. 3). Diffuse vitreous opacity was noted OD. She was treated with topical betamethasone as well as oral prednisolone 30 mg. The vitreous opacity gradually diminished in 2006 (Fig. 3). She has been well without any exacerbation in the uveitis (up to 2011). HLA typing revealed that she carried HLA-A26.

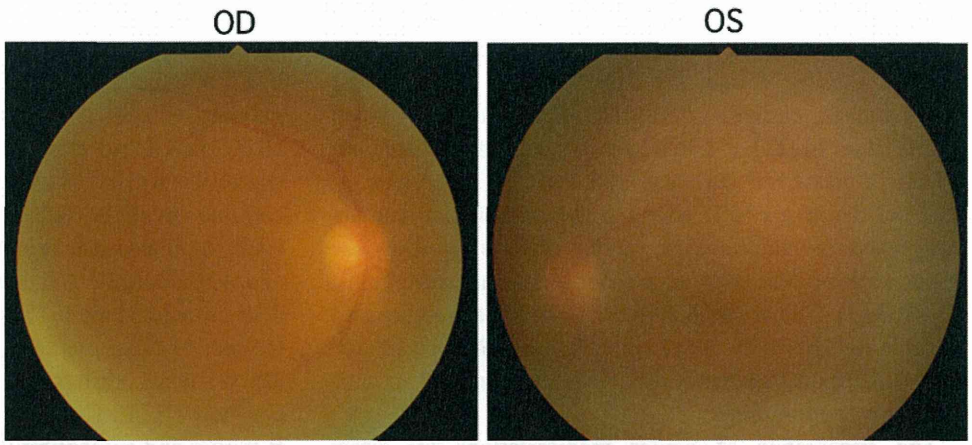

Fig. 2 Fundus examination in case 1 of HTLV-1-associated uveitis. Diffuse vitreous opacity was noted in both eyes. *OS* Left eye, *OD* right eye

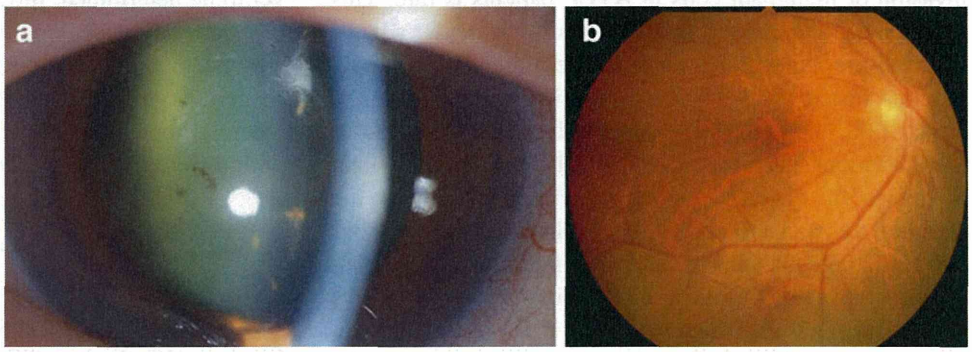

Fig. 3 Case 2 of HTLV-1-associated uveitis: **a** slit-lamp examination in 2001, **b** fundus in 2006. Anterior segment inflammation with 3+ flare and 2+ cells, posterior synechiae, and the presence of fibrin on the lens were observed in right eye. **a** Pigmentations and fibrous membrane on the lens remained after relief of posterior synechiae. **b** Post-treatment vitreous opacity is not apparent

Discussion

In a previous study, we estimated the prevalence of HAU to be 1.0 % in uveitis patients in Hokkaido, Japan [11], with being more frequent in middle-aged women. Visual prognosis was overall favorable or stable in the majority of patients. In terms of ophthalmological findings, vitreous opacity was most frequent condition, followed by keratic precipitate, iris/gonio nodules, and posterior synechiae, while hypopyon, retinal vasculitis, and neovascularization were rarely observed. Intraocular inflammation was basically controlled by topical treatment, while systemic corticosteroid was required in less than one-fourth of patients. These clinical findings are similar to those reported in studies from other areas [14–16], which enabled us to completely differentiate HAU from uveitis with other etiologies, such as Behçet's disease and sarcoidosis [11]. It has been demonstrated that in HAU cases bilateral uveitis is as frequent as unilateral inflammation [14, 15], whereas in our present study we found that the uveitis was predominantly unilateral. It is therefore possible that unilateral inflammation is a characteristic feature in patients with HAU in this area.

In the present study, 38 % of patients had a medical history of hyperthyroidism. Case studies of HAU have demonstrated an association with hyperthyroidism or Graves' disease in several patients, ranging from 7.9 to 20.0 % [16–18]; our study confirms this previously reported association. Indeed, HAU occurs not only as an isolated ocular disorder in otherwise healthy HTLV-1 carriers, but also as a part of HTLV-1-related systemic diseases, such as HAM/TSP [19]. In contrast, our study showed that two of the 21 cases of HAU also had ATLL, while none of the HAU patients had a medical history of HAM/TSP. This seems to be a characteristic of our results, since it is considered that individuals with HAU present immunological disturbances similar to those of HAM/TSP, but with no ATLL [20]. In our two ATLL patients, diffuse vitreous opacity was noted, which is typically found in isolated HAU patients. One of these two patients had anterior segment intraocular inflammation with fibrin exudates and posterior synechiae, as shown in case 2. The uveitis was completely resolved after topical and/or systemic corticosteroid administration. These findings indicate that the migrated cells were inflammatory rather than neoplastic cells. Interestingly, both ATLL patients had a medical history of hyperthyroidism, suggesting a concomitant association of HAU, ATLL, and hyperthyroidism. A concomitant association of HAU, HAM/TSP, and hyperthyroidism has been reported, in which the characteristic uveitis in HTLV-I carriers is caused by either an immune-mediated or autoimmune pathological mechanism modified by the retrovirus [16]. An immune-mediated intraocular reaction is thought to be relevant to the pathogenesis of

HAU: intraocular activated T cells in HTLV-1-associated myelopathy contribute to constitutive cytokine production, thereby causing intraocular inflammation [21]. Unlike asymptomatic carriers or HAM/TSP, monoclonal T-cell proliferation in HTLV-1 infection is noted in patients with ATLL. It has been demonstrated that the expression of HTLV-1 can trigger alterations in the cell markers that are recognized by natural killer (NK) cells, suggesting the importance of NK cells as a defense mechanism against HTLV-1 [3]. Therefore, it is likely that the pathogenesis of HAU in patients with ATLL is different from that of isolated HAU and that the former may be involved in activated innate immunity.

The appearance of ocular manifestations by direct invasion of malignant cells in ATLL patients is rare. This invasion can manifest as mass lesions in the ocular adnexa as well as ocular inflammation-like findings, including vitreous opacity [22–24], iritis, cyclitis, vasculitis in the retina [25], and choroidal thickening [26]. The latter manifestations may mimic HAU. The visual acuity and prognosis of diffuse vitreous opacity, as well as the favorable response to corticosteroid therapy shown by our two HAU patients are typical ocular findings in HAU, but the direct invasion of malignant cells in the eye is not. This study also highlights that if uveitis is to be observed in patients with ATLL, ophthalmologists should consider the possibility of not only HAU or uveitis of other etiology, but direct invasion of malignant cells in the eye.

In this study, we elucidated the clinical features of HAU patients at Hokkaido University Hospital in which 21 patients (90.5 %) were born in Hokkaido, including one ethnic Ainu. As shown above, a number of the clinical features of our patients from Hokkaido differed from those reported in previous studies, such as predominant unilateral involvement, no complication with HAM/TSP, and two HAU patients with ATLL. These characteristic manifestations may result from the different origins of HTLV-1 and/or HLA alleles. Indeed, HTLV-1 is endemic among the three ethnic populations of Japan that account for most of the present-day Japanese population, namely, Ainu, Ryukyuan, and Wajin, with the latter being the majority population [27]. HTLV-1a, one of the subtypes of HTLV-1, was introduced into Japan relatively recently as a result of Portuguese explorations and the African slave trade [28]. Several reports postulate the presence of HTLV-1a in Japan since ancient times, a view supported by the detection of HTLV-1 infection in Japanese Ainu, considered to be direct descendants of the oldest migrating Mongoloid populations [29]. Yamashita et al. [27] prove the predominance of subgroup A in the Ainu and Ryukyuans; this subgroup belongs to a transcontinental subgroup and both groups share a common origin of HTLV-1. In contrast, the Japanese subgroup is the major subgroup among the Wajin. Indeed, there is a bias in the prevalence of HTLV-1 subtypes among the inhabitants of Kyushu and Okinawa [30].

HLA class I and II genes have been examined in 51 patients with HAU: their results, however, suggest that HLA class I and class II genes did not contribute to susceptibility to HAU in south Kyushu [31]. In contrast, susceptible levels of either ATLL or HAM/TSP of human HLA-A alleles are reported. Again, although HLA-A26 and A36 could be ATLL associated, HLA-A24 is a HAM/TSP-associated allele [32]. In our study, despite the limited number of cases available, three out of four HAU patients (75 %) were carriers of HLA-A26, of whom one patient also had ATLL. However, since the correlation with HLA-B typing and susceptibility to ATLL and/or HAM/TSP has yet to be determined, further studies are required to clarify the correlation. Taking all of our results together, we suggest that the phylogenetic difference of HTLV-1 and modern large migration (HLA alleles) in the comparatively recently populated part of Japan, Hokkaido, may correlate with different clinical manifestations in HAU.

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