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Case report

Effective treatment of refractory sympathetic ophthalmia with glaucoma using adalimumab

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ABSTRACT

Purpose: Sympathetic ophthalmia (SO) is an autoimmune, bilateral, granulomatous panuveitis, which occurs following penetrating eye injury or eye surgery. We report two cases of refractory SO in patients with a history of trabeculectomy, which were treated effectively with adalimumab.

Observations: Case 1: A 69-year-old male with a history of trabeculectomy for rubeotic glaucoma of the right eye, secondary to diabetic retinopathy 8 years prior, presented with a decrease in visual acuity of the left eye due to SO. After two rounds of pulse corticosteroid therapy (intravenous infusion of 1 g methylprednisolone/day for 3 days), serous retinal detachment (SRD) was resolved. As oral prednisolone was tapered to avoid deterioration of the diabetes mellitus, we shifted to other immunosuppressive therapies to control inflammation. Methotrexate 6mg/week (0.1 mg/kg) was introduced first, but was discontinued owing to side effects. After 6 months of cyclosporine 100 mg/day (1.5 mg/kg, max. dose 2.3 mg/kg), the SRD relapsed. Adalimumab was then introduced, which led to remission of SRD, and inflammation was controlled for 7 months.

Case 2: A 43-year-old male, with a history of trabeculectomy for primary open-angle glaucoma of the right eye 4 years prior, presented with blurred vision in the right eye. Optical coherence tomography revealed SRD and choroidal thickening in both eyes. Pulse corticosteroid therapy (intravenous infusion of 1 g methylprednisolone/day for 3 days) was initiated, followed by oral prednisolone. SRD gradually improved, but it did not resolve completely. Given the severe visual loss the patient had experienced due to the primary open-angle glaucoma, oral prednisolone was tapered quickly to avoid steroid-induced intraocular pressure (IOP) elevation. Cyclosporine 125 mg/day (1.8 mg/kg, max. dose 2.1 mg/day) was introduced first, but was later discontinued because of side effects. Adalimumab was then administered, causing the SRD to disappear; and IOP was well-controlled. After the introduction of adalimumab, control of intraocular inflammation was achieved and IOP remained within the target range for 7 months.

Conclusions and importance: SO requires long-term immunosuppressive treatment. Adalimumab is an effective treatment in cases of steroid or immunosuppressant refractory SO, particularly for glaucoma patients, in whom long-term steroid therapy should be avoided.

1. Introduction

Sympathetic ophthalmia (SO) is an autoimmune, bilateral, granulomatous panuveitis, which occurs following penetrating eye injury or eye surgery.[1] Although the true incidence is unknown, the estimated incidences after penetrating ocular injuries and intraocular surgery are 0.2%–0.5% and 0.01%–0.05%, respectively.[2] The pathogenesis of SO is not fully understood, but a T-cell-mediated immune reaction against ocular antigens is suspected; notably, it has similar pathogenesis to Vogt–Koyanagi–Harada disease (VKH). A history of penetrating ocular trauma or surgery is an essential diagnostic criterion of SO, largely because of the similarity to clinical manifestations of VKH.[3] SO and VKH have been reported to exhibit a greater likelihood of HLA-DR4 expression in the Japanese population.[4]

Systemic and topical corticosteroid therapy for controlling inflammation has been the mainstay of SO treatment.[5] If patients are intolerant or do not respond to the corticosteroid treatment, other immunosuppressive agents are used. Cyclosporine, methotrexate, azathioprine and mycophenolate mofetil are reported to be effective for controlling the inflammation associated with SO.[6]

Recently, several reports have demonstrated the effectiveness of a tumour necrosis factor alpha (TNFα) antagonist for the treatment of

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non-infectious uveitis.[7] Adalimumab is a fully human anti-TNFα antibody used for the treatment of various inflammatory conditions, including non-infectious uveitis.[8] Until 2016, cyclosporine was the sole approved steroid-sparing immunosuppressive drug for non-infectious uveitis in Japan, thus, it is often chosen as a first-line steroid-sparing immunosuppressive drug. Notably, the approval of adalimumab in 2016 dramatically changed the treatment strategy for non-infectious uveitis in Japan.

Here, we report the use of adalimumab for the treatment of two cases of SO combined with glaucoma in patients who had a history of filtration surgery. To reduce the risk of corticosteroid induced intraocular pressure (IOP) elevation, adalimumab appeared to be beneficial for SO patients with glaucoma.

2. Findings

2.1. Case 1

A 69-year-old male with diabetic retinopathy presented with progressive and persistent blurriness of the left eye. The patient had a history of cataract surgery in both eyes 12 years prior, as well as vitrectomy and trabeculectomy in the right eye for rubeotic glaucoma 8 years prior. At presentation, the right eye demonstrated no light perception and the best-corrected visual acuity of the left eye was 0.02. IOP was 8 mmHg in the right eye and 13 mmHg in the left. Slit-lamp examination showed a filtering bleb with underlying uvea and a 3-mm hyphaema in the anterior chamber with severe iris rubeosis in the right eye. The left eye had numerous granulomatous keratic precipitates and an anterior chamber cell grading of 2+, based on the Standardization of Uveitis Nomenclature Working Group classification.[9] Fundus examination showed serous retinal detachment (SRD) and choroidal detachment with panretinal photocoagulation for diabetic retinopathy in the left eye (Fig. 1-A). Fundus of the right eye was invisible due to the presence of a hyphaema. Fluorescein angiography revealed multiple hyperfluorescent leakage dots and multiple chorioretinal scars from panretinal photocoagulation; indocyanine green angiography (ICG) showed multifocal hypofluorescent dots at late phase (Fig. 1-C, 1-D). Optical coherence tomography (OCT) showed bullous SRD with loss of choroidal vascular structure, suggestive of choroidal inflammation (Fig. 1-B). The patient noticed auditory disturbance, but did not experience headaches or dermatological disorders such as alopecia, vitiligo, or poliosis. Human leukocyte antigen (HLA) testing revealed that the patient was HLA-DR4 positive. The patient was diagnosed with SO. Pulse corticosteroid therapy (intravenous infusion of 1 g methylprednisolone/day for 3 days) was initiated, followed by slow tapering. The hyphaema soon resolved and SRD was observed in the right eye, which also improved following corticosteroid treatment. The patient soon developed severely uncontrolled hyperglycaemia and corticosteroid-induced IOP elevation. To avoid side effects, prednisolone was rapidly tapered, and methotrexate was introduced with the starting dose of 6 mg/week (0.1 mg/kg) However, methotrexate treatment was discontinued owing to side effects, such as pancytopenia and hepatic insufficiency. Cyclosporine 100 mg/day (1.5 mg/kg, max dose 2.3 mg/kg) was then initiated, but inflammation persisted. SRD recurred 6 months later, while the patient was receiving 150 mg/day (2.3 mg/kg) cyclosporine and 20 mg/day oral prednisolone. Subcutaneous injection of adalimumab was then introduced, with a loading dose of 80 mg, followed by a dose of 40 mg every 2 weeks. There was no recurrence of SRD for 7 months and oral prednisolone administration was tapered from 20 mg/day to 2.5 mg/day (Fig. 2). The blood glucose level of the patient was well-controlled and IOP remained within the target range. There were no side effects associated with the adalimumab therapy.

2.2. Case 2

A 43-year-old male presented with bilateral blurred vision. The patient had a history of trabeculectomy in the right eye 3 years prior for primary open angle glaucoma. At presentation, best-corrected visual acuity was 0.05 in the right eye and 1.2 in the left eye. IOP was 7 mmHg in the right and 12 mmHg in the left eye. Slit-lamp examination revealed numerous granulomatous keratic precipitates in both eyes, with a 4 + cell grading in the right anterior chamber and a 2 + cell grading in the left anterior chamber. Fundus examination showed SRD in both eyes (Fig. 3-A). Fluorescein angiography detected vascular leakage from neovascularisation in the right fovea, but no hyperfluorescent leakage was detected. ICG showed multifocal hypofluorescent dots in the both eyes (Fig. 3-C, 3-F). OCT revealed SRD in the right eye and choroidal thickening in both eyes (Fig. 3-B, 3-E) The patient was positive for HLA-DR4. The patient experienced headaches and auditory disturbance for a few weeks before developing ocular symptoms. Poliosis had been noticed 1 year prior. The patient was diagnosed with SO and pulse corticosteroid therapy (intravenous infusion of 1 g methylprednisolone/

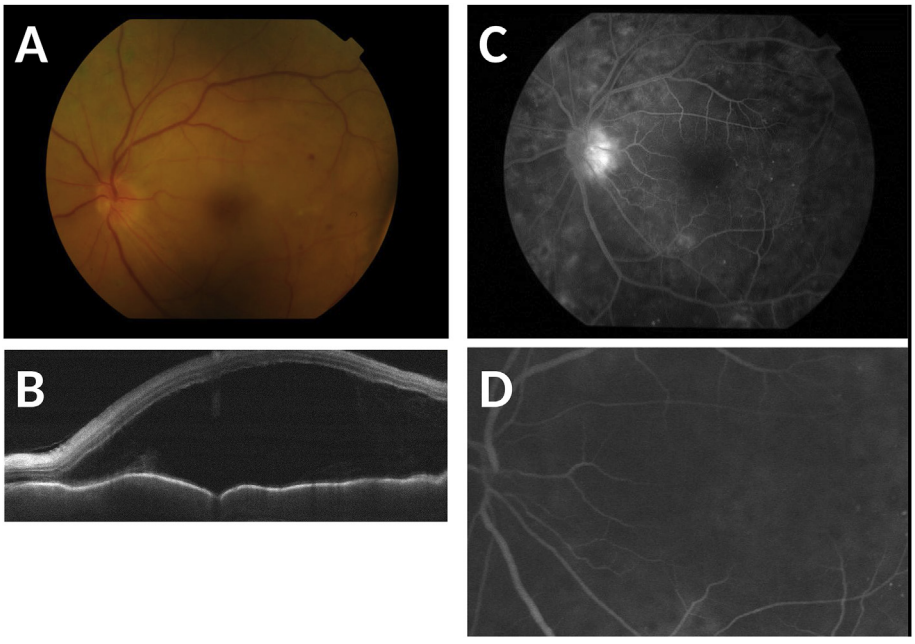

Fig. 1. Clinical appearance of Case 1 at presentation.
A. Fundus photography of the left eye. The image reveals serous retinal detachment (SRD) and laser scars from panretinal photocoagulation for diabetic retinopathy.
B. Optical coherence tomography scan of the left eye. The image demonstrates SRD with hyper-reflective material in the subretinal fluid. The choroid is extremely swollen and the thickness is immeasurable. The image also reveals a loss of hyper-reflectivity in the inner choroid.
C. Fluorescein angiography of the left eye. The image reveals multiple hyperfluorescent leakage dots and multiple chorioretinal scars from panretinal photocoagulation.
D. Indocyanine green angiography of the left eye. The image reveals multiple hypofluorescent dark spots during the late phase of the angiography. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

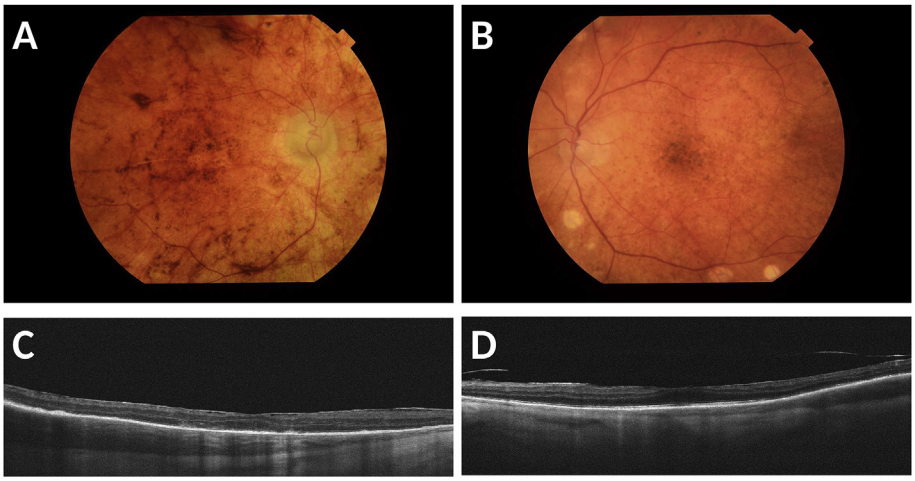

Fig. 2. Clinical appearance of Case 1 after adalimumab administration.
A, B. Fundus photographs of the right and left eyes, respectively. The images show that serous retinal detachment (SRD) was resolved; loss of normal pigmentation can be observed.
C, D. Optical coherence tomography scans of the right and left eyes, respectively. Bullous SRD was resolved and choroidal thickness decreased in both eyes.

day for 3 days) was initiated. The patient was promptly administered 50 mg/day oral prednisolone and 125 mg/day cyclosporine (1.8 mg/kg, max. dose 2.1 mg/kg), because the patient had severe visual field loss and a history of corticosteroid-induced IOP elevation as a response to topical and systemic corticosteroid. However, 2 months after the resolution of SRD by pulse corticosteroid therapy, SRD relapsed when the patient was on 20 mg/day oral prednisolone and 150 mg/day (2.1 mg/kg) cyclosporine. Additionally, side effects including hypertension, angular cheilitis, oral ulcer and fatigue were noted, thus, cyclosporine was discontinued. Adalimumab was initiated with a loading dose of 80 mg followed by a dose of 40 mg every 2 weeks; subsequently, the patient achieved IOP within the target range and complete control of the uveitis over 7 months, without any side effects. Prednisolone was successfully tapered to 0 mg.

3. Discussion

The cases described in this report indicate the benefits of adalimumab therapy for refractory SO, particularly in glaucoma patients who must avoid corticosteroid-induced IOP elevation. In both cases, introduction of adalimumab led to the attainment of target IOP, as well as an improvement in inflammation and remission of SRD.

Vitreoretinal surgery and cataract surgery are the main surgical causes of SO.[10] Trabeculectomy is also a risk factor for SO, which is supported by experimental studies demonstrating that immunization with melanocyte specific proteins (tyrosinase-related protein) induces ocular inflammation.[11] In case 2, SO was most probably triggered by trabeculectomy; however it is unclear whether vitrectomy or trabeculectomy was directly associated with SO in case 1. Notably, there was an incarceration of uveal tissue at the surgical site, which may have caused exposure of the uvea to extraocular antigens and led to SO. It is important to consider the possibility of SO even 3–8 years after trabeculectomy.

Because serum and ocular TNFα levels are reported to be elevated in SO, it is plausible that therapy with TNFα antagonists may be effective for the treatment of SO.[12,13] Gupta et al. reported the case of a 7-year-old patient with refractory SO who was successfully treated with infliximab.[14] Soheilian et al. first reported on the effectiveness of

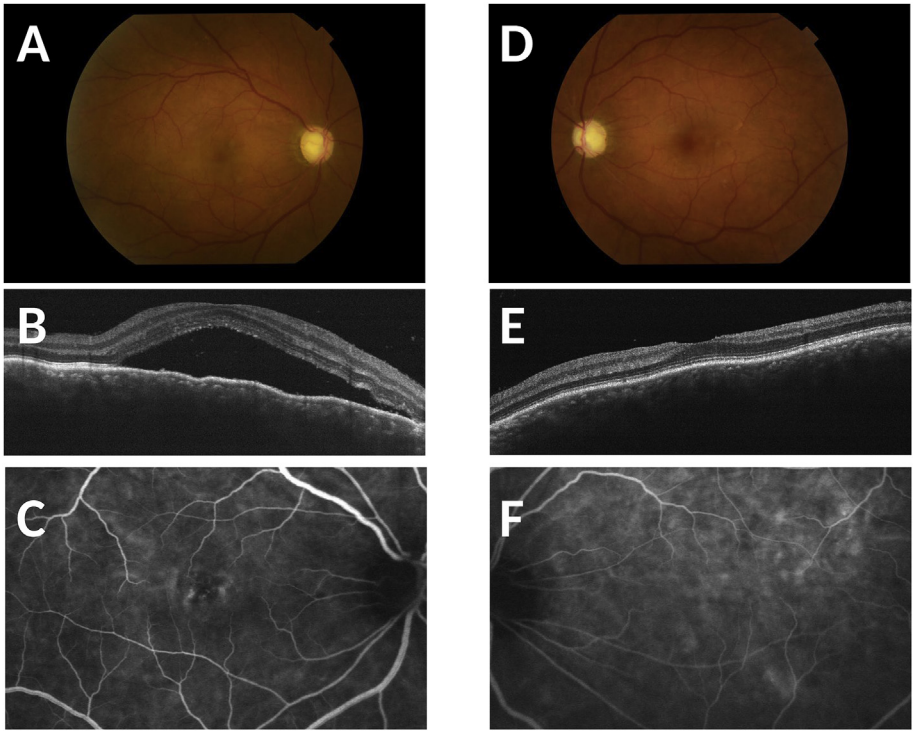

Fig. 3. Clinical appearance of Case 2 at presentation.
A. Fundus photography of the right eye at presentation. Serous retinal detachment (SRD) and glaucomatous optic nerve cupping can be observed.
B. Optical coherence tomography scan of the right eye. The image revealed bullous SRD with hyperreflective material in the subretinal fluid, along with choroidal thickening.
C. Indocyanine green angiograph of the right eye showing multifocal hypofluorescent dots and vascular leakage from neovascularisation at the fovea.
D. Fundus photography of the left eye. SRD is not clearly visible. Glaucomatous optic nerve damage is present.
E. Optical coherence tomography of the left eye. No SRD was observed but choroidal fold and choroidal thickening are shown.
F. Indocyanine green angiograph of the left eye. Multifocal hypofluorescent dots are present. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

adalimumab for a patient with refractory SO after phakic intraocular lens implantation.[15] Kase et al. described the use of adalimumab therapy for refractory paediatric SO after trauma.[16] These cases show the successful use of adalimumab therapy for SO patients with a history of glaucoma filtration surgery.

Infliximab is solely approved for Behcet's disease in Japan; in contrast, adalimumab can now be widely used for the treatment of non-infectious uveitis in Japan. Vallet et al. reported that adalimumab and infliximab are equally effective for the treatment of non-infectious uveitis.[17] Previous studies have shown that adalimumab use was associated with a higher rate of long-term quiescence compared with infliximab.[18] There was also a nonsignificant trend towards a higher rate of serious side effects during the use of infliximab, including infections, hypersensitivity reactions, autoimmune disease, and neoplasia.[17] While infliximab requires hospitalization for intravenous administration, adalimumab is administered subcutaneously, which is more comfortable for patients.[18]

SO is a relatively rare and difficult disease to treat. The efficacy and safety of adalimumab treatment in patients with non-infectious uveitis was described in the VISUAL (I, II, III) trials.[19] However, the number of SO patients is limited; thus, such encounters are limited to case reports.[15,16,19] Despite the limited availability of approved non-steroidal immunosuppressive therapy for non-infectious uveitis in Japan, these two detailed cases show the successful treatment of SO with adalimumab. These two cases also reveal the importance of the early initiation of adalimumab in glaucoma or diabetic patients, in order to avoid the side effects of corticosteroid treatment.

4. Conclusions

In summary, to control non-infectious uveitis in which TNFα is thought to play a role in the pathogenesis, such as SO, adalimumab may be a strong candidate as a first-line corticosteroid-sparing agent, particularly for glaucoma and diabetic patients. Adalimumab was first approved for use in Japan in 2016. Long-term follow-up with a large group of patients is required to clarify the possible adverse effects and efficacy of adalimumab. It is also essential to elucidate whether adalimumab can be tapered or discontinued in patients whose inflammation has been successfully controlled.

Patient consent

Both patients gave written consent to publish case details.

Conflicts of interest

The following authors have no financial disclosures: TH, YH, YK.

Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

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References

1. Chu XK, Chan CC. Sympathetic ophthalmia: to the twenty-first century and beyond. *J Ophthalmic Inflamm Infect.* 2013;3(1):49.
2. Gasch AT, Foster SC, Grosskreutz CL, Pasquale LR. Postoperative sympathetic ophthalmia. *Int Ophthalmol Clin.* 2000;40(1):69–84.
3. Rao NA, Sukavatcharin S, Tsai JH. Vogt-Koyanagi-Harada disease diagnostic criteria. *Int Ophthalmol.* 2007;27(2-3):195–199 E pub 2017 Mar 24.
4. Ohno S. Immunological aspects of Behcet's and Vogt-Koyanagi-Harada's disease. *Trans Ophthalmol Soc UK.* 1981;101:335–341.
5. Chan CC, Roberge RG, Whitcup SM, Nussenblatt RB. 32 cases of sympathetic ophthalmia. A retrospective study at the National Eye institute, Bethesda,Md., from 1982 to 1992. *Arch Ophthalmol.* 1995 May;113(5):594–600.
6. Kilmartin DJ, Dick AD, Forrester JV. Prospective surveillance of sympathetic ophthalmia in the UK and Republic of Ireland. *Br J Ophthalmol.* 2000;84(3):259–263.
7. Garnier BM, Vallet H, Seve P, et al. Efficacy and safety of TNF-α inhibitors in non-infectious uveitis: a multicentre retrospective study. *Investig Ophthalmol Vis Sci.* 2014 April;55:5303.
8. Jaffe GD, Dick AD, Brezin AP, et al. Adalimumab in patients with active noninfectious uveitis. *N Engl J Med.* 2016;375:932–943.
9. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature (SUN) working group. Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. *Am J Ophthalmol.* 2005;140(3):509–516.
10. Lubin JR, Albert DM, Weinstein M. Sixty-five years of sympathetic ophthalmia: a clinicopathologic review of 105 cases (1913 to 1978). *Ophthalmology.* 1980;87:109–121.
11. Kondo I, Nakamura H, Miyano M, Konno S, Sakuragi S. Ocular and extraocular inflammation induced by immunization of tyrosinase related protein 1 and 2 in Lewis rats. *Exp Eye Res.* 2000;71(4):361–369.
12. Palexas GN, Sussman G, Welsh NH. Ocular and systemic determination of IL-1 beta and tumour necrosis factor in a patient with ocular inflammation. *Scand J Immunol Suppl.* 1992;11:173–175.
13. Santos LM, Marcos MC, Gallardo JM, et al. Aqueous humor and serum tumor necrosis factor-alpha in clinical uveitis. *Ophthalmic Res.* 2001;33:251–255.
14. Gupta SR, Phan IT, Suhler EB. Successful treatment of refractory sympathetic ophthalmia in a child with infliximab. *Arch Ophthalmol.* 2011;129(2):250–252.
15. Soheilian M, Jabbarpourbonyadi J, Soheilian R, Peyman GA. Bilateral uveitis after phakic intraocular lens implantation and management with adalimumab. *J Cataract Refract Surg.* 2012;38:1094–1096.
16. Kase S, Shinohara T, Kase M. Adalimumab for pediatric sympathetic ophthalmia. *JAMA Ophthalmol.* 2014;132(8):1022–1024.
17. Vallet H, Seve P, Biard L, et al. French Uveitis Network.Infliximab versus adalimumab in the treatment of refractory inflammatory uveitis. *Arthritis Rheumatol.* 2016;68:1522–1530.
18. Simonini G, Taddio A, Cattalini M, et al. Prevention of flare recurrence in childhood-refractory chronic uveitis: an open label comparative study of adalimumab versus infliximab. *Arthritis Care Res (Hoboken).* 2011;63:612–618.
19. Suhler EB, Adan A, Brezin AP, et al. Safety and efficacy of adalimumab in patients with noninfectious uveitis in an ongoing open-label study: VISUAL III. *Ophthalmology.* 2018 Jul;125(7):1075–1087.