American Journal of Ophthalmology Case Reports 19 (2020) 100859

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Intravitreal methotrexate and fluocinolone acetonide implantation for Vogt-Koyanagi-Harada uveitis

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ARTICLE INFO

Keywords:
Intravitreal methotrexate
Fluocinolone acetonide implant
Retisert®
Vogt-koyanagi-harada syndrome

ABSTRACT

Purpose: To report a case of intravitreal methotrexate treatment and fluocinolone acetonide (Retisert®) implantation in a patient with Vogt-Koyanagi-Harada syndrome (VKH).

Observations: A 34-year-old male was referred for worsening vision and bilateral panuveitis consistent with VKH. He was treated with prednisone, mycophenolate mofetil, prednisolone acetate eye drops, and injections of triamcinolone and adalimumab. He failed to improve with these therapies and developed multiple adverse effects, including hepatotoxicity, severe eye pain, cataracts, and cystoid macular edema. We treated him with intravitreal methotrexate injections in both eyes, which rapidly improved his eye pain, inflammation, and vision. He subsequently underwent fluocinolone acetonide (Retisert®) implantation, cataract extraction with intraocular lens insertion, and Ahmed tube placement for long-term intraocular pressure control. His vision improved from hand motions to 20/30, intraocular pressure remained stable at 17, there was complete resolution of his panuveitis and uveitic macular edema, and his systemic medications were able to be discontinued.

Conclusions: /Importance: This case demonstrates intravitreal methotrexate may successfully treat intraocular inflammation, pain, and macular edema in VKH. Excellent long-term vision and reduction of adverse effects of systemic medications were also achieved with subsequent fluocinolone acetonide implantation. Combining these two targeted therapies may be an effective strategy in treating VKH in patients who have severe pain and cannot tolerate systemic therapy.

1. Introduction

Vogt-Koyanagi-Harada (VKH) syndrome is an inflammatory disease characterized by bilateral granulomatous panuveitis. Although the exact etiology is not known, VKH can occur after a virus trigger in the presence of an HLA-DRB1*0405 allele, and can lead to a Th1 lymphocyte-mediated attack on melanocytes in the eye, inner ear, meninges, skin and hair.[1] The acute uveitic stage is typically treated with systemic corticosteroid therapy with or without immunomodulatory agents.[2–5] Patients who develop severe side effects from systemic therapy can be very challenging to manage. Targeted intraocular treatment may be an underutilized strategy in these patients.

Intravitreal methotrexate is one potential treatment option. Methotrexate is an antimetabolite that competitively inhibits dihydrofolate reductase. It induces immunosuppression through the inhibition of leukocyte differentiation and was utilized as one of the first curative therapies for metastatic cancer. Methotrexate was proposed for use in leukemia in 1950, shortly after Sidney Farber demonstrated that aminopterin, a chemical analogue of folic acid, could induce remission in acute lymphoblastic leukemia.[6,7] It was first used intravitreally for intraocular lymphoma in 1995.[8] Today intravitreal methotrexate is used most commonly for intraocular lymphoma, but it has more recently shown promise in uveitis as well.[9,10] In a large retrospective cohort study, Gangaputra et al. found methotrexate to be well tolerated by most patients and to be an effective corticosteroid-sparing agent for several types of uveitis.[11]

Here we present a case of intravitreal methotrexate to treat panuveitis in a patient with VKH, and subsequent fluocinolone acetonide (Retisert®) implantation resulting in vision improvement and symptom control.

2. Methods

Retrospective case report. The study protocol was approved by the

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https://doi.org/10.1016/j.ajoc.2020.100859
Received 29 July 2019; Received in revised form 14 June 2020; Accepted 26 July 2020
Available online 2 August 2020

Institutional Review Board for Human Subjects Research at Stanford University. Wide angle fundus and fluorescein angiography photos were obtained with the Optos imaging system. Optical coherence tomography photos were obtained with the Zeiss Cirrus OCT imaging system. Intravitreal methotrexate injections were given at 400 μg/0.1 mL through the pars plana using sterile technique with application of betadine and use of lid speculum. The fluocinolone acetonide (Retisert®) device was implanted as previously described.[12] Briefly, a limbal peritomy was performed to expose the inferotemporal quadrant. A double-armed 8–0 prolene suture was passed through the hole in the strut of the implant. A scleral incision was made with a keratome blade 3.5 mm from the limbus and 4.0 mm in length. The implant was then placed with the drug tablet anteriorly into the vitreous cavity. To secure the implant, each arm of the 8–0 Prolene suture was placed through the inner scleral wound at half-depth and tied in a 3-1-1 fashion.

2.1. Case report

A 34-year-old Hispanic male was referred for one year of worsening vision in both eyes secondary to panuveitis. At presentation to our clinic, his vision was hand motions (HM) OD and 20/100 OS. There was no relative afferent pupillary defect, the intraocular pressure (IOP) was 13 OD, 18 OS. The right eye had 2+ injection, numerous medium sized keratic precipitates (KP), anterior chamber had 4+ cell and 3+ flare, posterior synechiae, 2+ posterior subcapsular cataract (PSC), 3+ vitreous cell, a hyperemic optic disc, cystoid macular edema (CME), and scattered peripheral yellow nodules (Fig 1A,C). The left eye had a few KP, trace cell and flare, trace PSC, 1+ vitreous cell, optic disk edema, and scattered peripheral yellow nodules (Fig. 1B). B-scan ultrasonography showed choroidal thickening (Fig. 1D). Fluorescein angiography demonstrated multifocal leakage, hyperfluorescent staining of peripheral nodules, and late optic disc leakage (Fig. 1E and F). Samples from the patient's blood, aqueous and vitreous were tested. Complete blood count, basic metabolic profile, erythrocyte sedimentation rate, rapid plasma reagin, fluorescent treponemal antibody absorption, quantiferon, lyme antibody, and angiotensin converting enzyme were unremarkable. Vitreous fluid yielded rare polymorphonuclear neutrophils and no organisms, and chest x-ray was normal. After exclusion of infectious, neoplastic, and other inflammatory etiologies, the patient was diagnosed with Vogt-Koyanagi-Harada (VKH) syndrome.

At presentation, the patient was taking prednisone 25 mg daily, mycophenolate mofetil 500 mg twice daily, and prednisolone acetate 1% three times daily in both eyes. The side effects of the steroids were becoming intolerable for the patient, and included hip necrosis and difficulty sleeping. He had developed hepatotoxicity with elevated liver function test enzymes from the mycophenolate. He had also previously received two injections of sub-tenon's triamcinolone acetate as well as six treatments of subcutaneous adalimumab. Despite this treatment, he suffered from constant and severe eye pain, recurrent inflammation, and worsening vision with cystoid macular edema and cataracts.

Given the complex and worsening clinical course, the decision was made to first treat the right eye with 400 μg/0.1 mL intravitreal methotrexate. He reported that the intravitreal methotrexate was immediately effective for his pain and inflammation. The patient's vision improved from HM to 20/400 OD within 1 week, and 20/150 after 4 weeks, with improvement of the CME. The decision was made to perform surgery for cataract extraction and intravitreal fluocinolone acetonide (Retisert®) implantation (Fig. 2A and B). He had a subsequent surgery for Ahmed tube placement and a second vitrectomy for a mild non-clearing vitreous hemorrhage. His symptoms improved dramatically, and 6 months after surgery, his right eye vision stabilized to 20/30, IOP 17, with resolution of the panuveitis and macular edema (Fig. 2C).

During the postoperative course of his right eye, the patient developed worsening vision and CME in the left eye. He received an injection of intravitreal methotrexate OS, which resulted in reduced vitreous cells and mild improvement of the CME. He was taken to the operating room 3 months later for repeat intravitreal methotrexate, pars plana vitrectomy, and fluocinolone acetonide (Retisert®) implantation in his left eye. His postoperative course was unremarkable, and 2 months after surgery in his left eye, his vision had improved to 20/30, IOP 21, and there was no intraocular inflammation or macular edema (Fig. 2D).

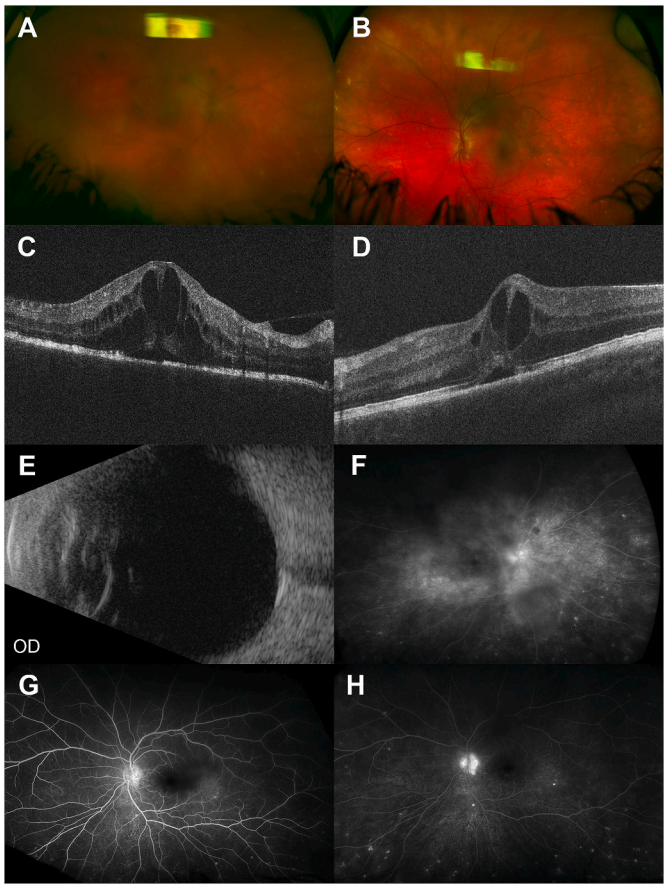

Fig. 1. 34-year-old male with Vogt-Koyanagi-Harada syndrome. **A-B)** Wide field fundus photos with 3+ vitreous cells and hyperemic disc OD, and scattered peripheral yellow nodules OU. **C)** Optical coherence tomography of the macula with extensive cystic macular edema OD. **D)** B-scan ultrasonography showing diffuse choroidal thickening without posterior scleritis. **E-F)** Fluorescein angiography demonstrating diffuse multifocal areas of leakage, staining of peripheral nodules, and late optic disc leakage OU. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3. Discussion

Vogt-Koyanagi-Harada syndrome can be very difficult to manage in patients who have failed systemic therapy and who develop severe side effects from treatment. Most cases of VKH are treated with oral corticosteroids alone or in combination with immunomodulatory agents. Our patient was initially treated with such a regimen, including prednisone, mycophenolate mofetil, and adalimumab. Although all of these agents have been shown to be effective in treating VKH,[4,13] our patient did not respond to these combined therapies. His uveitis was not controlled, and he was developing severe side effects, including worsening eye pain, cataract, cystoid macular edema, and liver toxicity. Given this challenging clinical course, we did not pursue further systemic therapy which could lead to worsening adverse effects. We instead decided to offer more aggressive local therapy with intravitreal methotrexate and fluocinolone acetonide implantation.

Intravitreal methotrexate was first used in the eye to treat intraocular

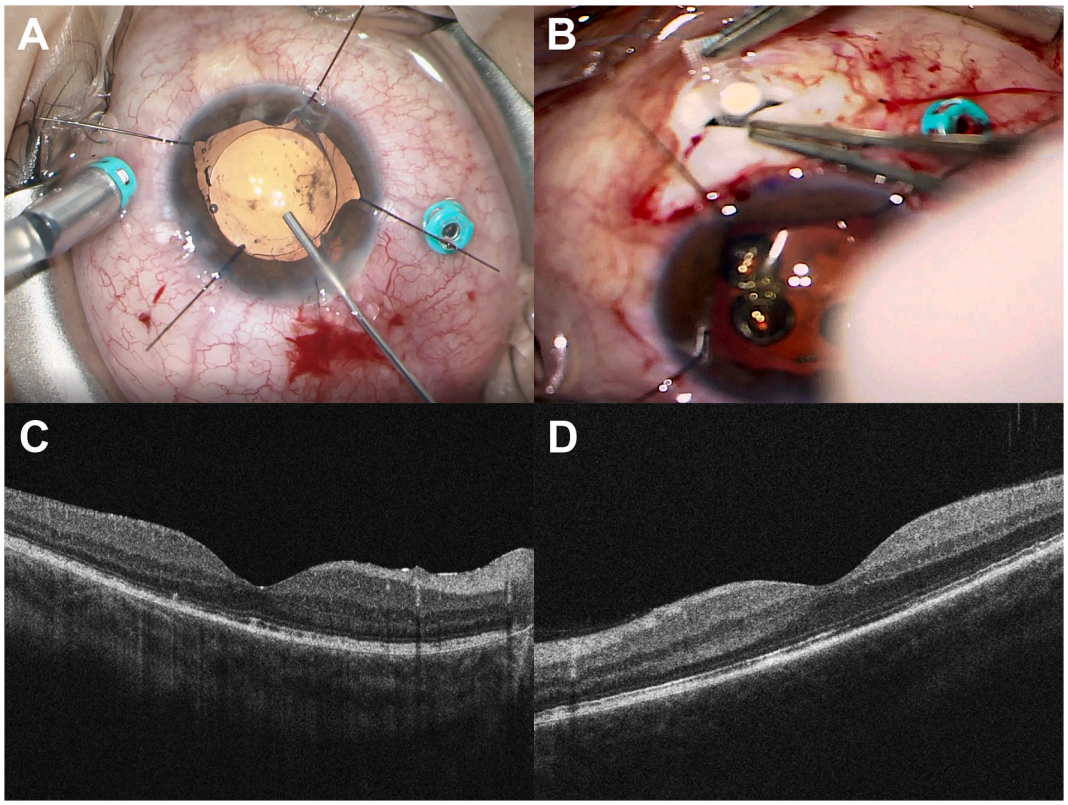

Fig. 2. Surgical management with postoperative improvement in visual acuity. **A-B)** Cataract extraction, intraocular lens placement, and fluocinolone acetonide (Retisert®) implantation. **C-D)** Postoperative optical coherence tomography showing resolution of cystoid macular edema in both eyes after intravitreal methotrexate injections and intravitreal fluocinolone acetonide (Retisert®) implants.

lymphoma,[14] and was subsequently demonstrated to be effective in patients with non-infectious uveitis and uveitic cystoid macular edema.[10] In VKH, systemic methotrexate has resulted in some success when combined with systemic corticosteroids.[15] However, the use of intravitreal methotrexate in VKH has not been previously reported, and, to our knowledge, this may be the first case of intravitreal methotrexate therapy in a patient with VKH.

In our patient, intravitreal methotrexate was successful in rapidly improving his eye pain, visual acuity, and macular edema within 1–2 weeks in his more severely affected right eye. Intravitreal methotrexate was not given in his left eye until he developed CME months after the initial therapy in his right eye. The intravitreal methotrexate rapidly resolved the CME, consistent with previous findings that demonstrated efficacy in treating uveitic CME.[10] The methotrexate injections were well tolerated without any further systemic side effects. Importantly, the resolution of the panuveitis and macular edema facilitated the placement of the fluocinolone acetonide implant, which would have been challenging given the severity of the patient's active intraocular inflammation.

Fluocinolone acetonide intravitreal implants, which can deliver intravitreal corticosteroid for up to 30 months, have been used to treat VKH but with mixed results.[16,17] The main adverse outcomes are increased intraocular pressure and cataract formation. Anticipating these complications is important. In our patient, we performed the steroid implantation in conjunction with cataract extraction and Ahmed tube placement. Our results were positive, and 6 months after surgery, the patient's visual acuity improved from HM to 20/30, with stable IOP and complete resolution of the panuveitis and macular edema. Given such a positive outcome, it is possible that combining intravitreal methotrexate with fluocinolone acetonide implants may increase the efficacy of the steroid. However, further studies are needed to determine if these two therapies act on synergistic anti-inflammatory pathways.

4. Conclusions

Vogt-Koyanagi-Harada syndrome can be a challenging condition to manage with systemic therapy alone, especially in patients who develop intolerable side effects. Localized treatment with intravitreal methotrexate can be effective in controlling intraocular inflammation, and fluocinolone acetonide implantation with appropriate measures for intraocular pressure control can result in excellent long-term visual outcomes.

Patient consent

This report does not contain any information that could lead to the identification of the patients.

Authorship

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

Funding

VBM is supported by NIH grants [R01EY031952, R01EY026877, R01EY024665, R01EY025225, P30EY026877], Research to Prevent Blindness (RPB), New York, NY, and the Stanford ChEM-H Testing Molecular Hypotheses in Human Subjects Seed Grant.

CRediT authorship contribution statement

Jong G. Park: Supervision, Conceptualization, Funding acquisition, Formal analysis, Writing - original draft, Writing - review & editing. **Natalia F. Callaway:** Supervision, Conceptualization, Funding

acquisition, Formal analysis, Writing - original draft, Writing - review & editing. **Cassie A. Ludwig:** Supervision, Conceptualization, Funding acquisition, Formal analysis. **Vinit B. Mahajan:** Supervision, Conceptualization, Funding acquisition, Formal analysis, Writing - original draft, Writing - review & editing.

Declaration of competing interest

None reported.

Acknowledgements

The authors would like to acknowledge Dr. Kuldev Singh who performed the Ahmed tube surgery.

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