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Mycophenolate Mofetil–Induced Lymphoproliferative Disorder in a Young Adult With Chronic Posterior Uveitis

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Abstract

Purpose: To present a case of a young adult with bilateral chronic posterior uveitis resulting from Vogt-Koyanagi-Harada (VKH) disease treated with mycophenolate mofetil who subsequently developed vitreoretinal lymphoma in the right eye. **Methods:** A case and its findings were analyzed. **Results:** A 34-year-old Hispanic woman presented with an 8-year history of chronic recurrent posterior uveitis in both eyes secondary to VKH disease. A vitreous infiltrate that was treatment resistant occurred in the right eye. Subsequently, a diagnostic vitrectomy was performed and it was determined that the patient had developed unilateral vitreoretinal lymphoma. **Conclusions:** Masquerade syndromes should remain in the differential in patients with well-established uveitis who are on immunomodulatory treatment. A diagnostic vitrectomy should be considered when the treatment response is uncharacteristic. Furthermore, guidelines are lacking for central nervous system prophylaxis for isolated unilateral ocular intraocular lymphoma in young adults.

Keywords

diffuse large B-cell lymphoma, lymphoproliferative disorder, Vogt-Koyanagi-Harada, masquerade syndrome, primary vitreoretinal lymphoma, mycophenolate mofetil

Introduction

Noninfectious uveitis is a common cause of blindness worldwide, especially when it affects the posterior segment. Vogt-Koyanagi-Harada (VKH) disease is a rare granulomatous inflammatory disorder that more commonly affects Hispanics, Asians, Middle Easterners, and Native Americans.[1] VKH classically follows 4 stages, including prodromic, acute uveitis, convalescent, and chronic or recurrent periods.[2] Management of VKH often involves long-term steroid-sparing immunomodulatory medication in steroid-refractory or intolerance cases.

Although several autoimmune conditions are associated with lymphoma, the benefits of immunomodulatory therapy often outweigh the risks, such as the rare but potentially life-threatening complication of a lymphoproliferative disorder.[3] Many presentations of ocular lymphoproliferative disorders exist; however, medication associations and case presentations are less well characterized in the literature. Intraocular lymphoma is often considered a variant of central nervous system (CNS) lymphoma and often presents a diagnostic challenge because it can masquerade as uveitis.

We report a case that highlights the importance of maintaining an ongoing differential diagnosis and high suspicion for vitreoretinal lymphoma in younger adult patients with a well-established uveitis condition treated chronically with mycophenolate mofetil.

Case Report

A 34-year-old Hispanic woman presented with an 8-year history of chronic recurrent posterior uveitis. After previous workups at multiple academic centers, she was determined to have Vogt-Koyanagi-Harada (VKH) syndrome, which manifested as bilateral noninfectious posterior uveitis and lower cheek vitiligo. Serologic testing for angiotensin-converting enzyme, *Mycobacterium tuberculosis* complex organisms (QuantiFERON-TB Gold), syphilis antibody, and antineutrophil cytoplasmic antibodies were unremarkable. She had been treated with prednisone and topical corticosteroids. Her ocular history included cataract extraction with intraocular lens placement in both eyes and a trabeculotomy procedure in the left eye.

She presented to our clinic with active posterior uveitis in both eyes with an exudative retinal detachment (RD) and hypotony in the left eye (Figure 1). The visual acuity (VA) was

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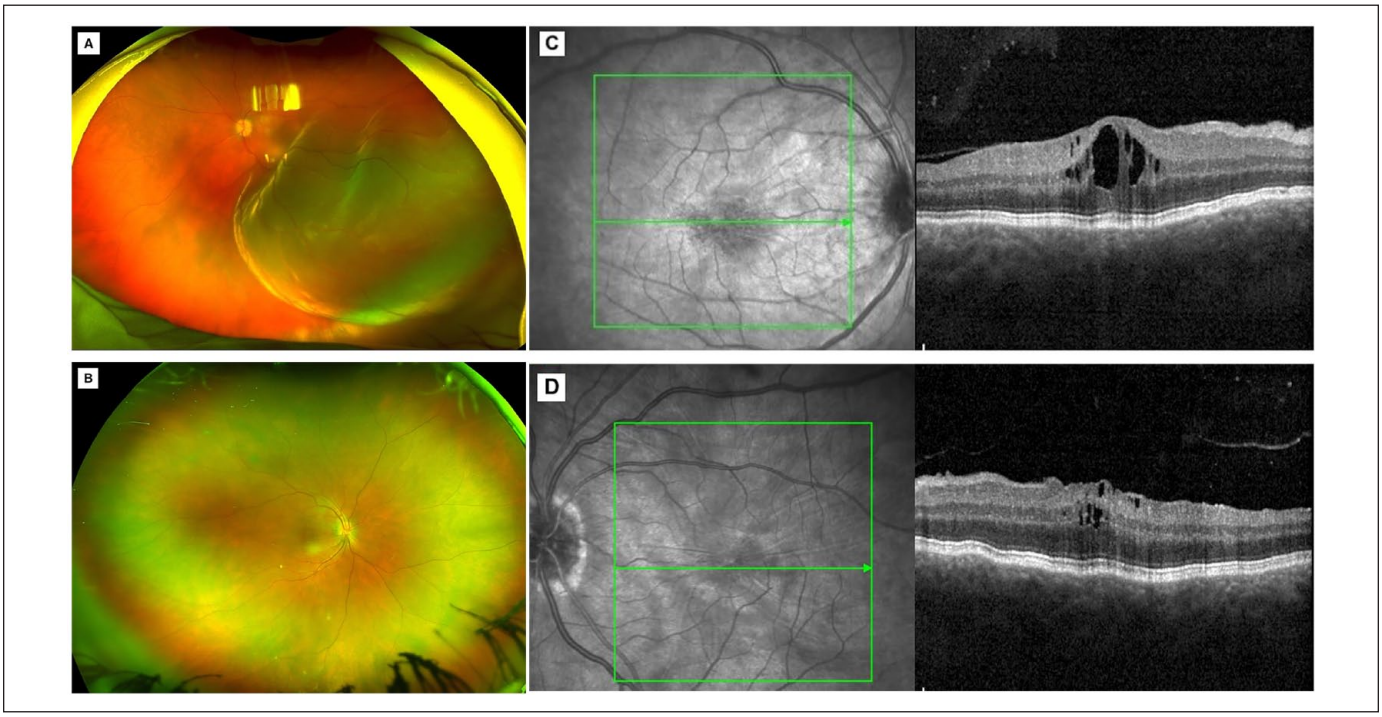

Figure 1. (A) Ultra-widefield fundus photograph of the left eye shows an inferotemporal serous retinal detachment resulting from Vogt-Koyanagi-Harada disease. (B) Ultra-widefield fundus photograph of the right eye at initial presentation. (C) Spectral-domain optical coherence tomography (SD-OCT) horizontal raster of the macula in the right eye at presentation shows cystoid macular edema (CME) and a pachychoroid. (D) SD-OCT horizontal raster of the left eye at presentation shows low-grade CME and a pachychoroid.

20/30 OD and counting fingers OS, and the intraocular pressure was 10 mm Hg and hypotony, respectively. She was treated with intravenous methylprednisolone sodium succinate (Solu-Medrol, Pfizer) (1g/daily for 3 days) and prednisone (80 mg/day with a 10 mg taper) and was started on low-dose methotrexate (10 mg/week); however, the exudative detachment in the left eye failed to respond. Methotrexate was discontinued within 1 month because of intolerance.

Given the concern for a secondary rhegmatogenous nature of the lattice with atrophic holes and a lack of improvement with medical therapy during the previous 3 months of treatment, the patient subsequently had RD repair with a scleral buckle, 25-gauge pars plana vitrectomy, fluocinolone acetonide intravitreal (IVT) implant (0.59 mg) placement, and silicone oil (SO) tamponade in the left eye. Three months later, the right eye developed hypotony, choroidal folds, and recurrent posterior inflammation. The right eye was treated with a sub-Tenon triamcinolone acetonide injection followed by placement of an IVT dexamethasone implant (0.7 mg), which led to significant improvement. However, there was an immediate recurrence after resolution of the treatment effect.

Subsequently, the patient had placement of an IVT fluocinolone acetonide implant (0.59 mg) in the right eye. Months later, the SO in the left eye was removed. However, recurrent posterior uveitis developed and was treated with high-dose prednisone (60 mg/day on a 10 mg/week taper) and a sub-Tenon triamcinolone acetonide injection. Mycophenolate mofetil treatment was initiated and titrated up to 1500 mg twice a day.

After 15 months of controlled inflammation, the patient developed recurring posterior uveitis in the right eye, which was treated with an IVT dexamethasone implant (0.7 mg), and the mycophenolate mofetil was discontinued. After an initial treatment response to the dexamethasone implant in the right eye, she developed a dense vitreous infiltrate approximately 5 months later once the treatment response diminished (Figure 2). An examination of the left eye did not show signs of vitreous cells or infiltrate or of subretinal lesions. Given the atypical lack of treatment response, the decision was made to pursue a diagnostic vitrectomy in the right eye to further investigate the vitreous infiltrate.

The diagnostic aspirate was consistent with a neoplastic mature B-cell lymphoproliferative disorder with features favoring large B-cell lymphoma (CD20+, PAX5+, CD3−, CD138−, MYD88−). Flow cytometry was also used to confirm the diagnosis and showed CD19+/B− lymphoid-type events, a λ immunoglobin light chain restriction, and a reversed CD4/CD8. Findings of a systemic workup, including magnetic resonance imaging of the brain, a lumbar puncture, and a bone marrow biopsy, were normal. Limited guidance existed in the literature on the benefits of systemic chemotherapy for CNS prophylaxis for isolated unilateral vitreoretinal lymphoma in a young adult without extraocular involvement. Thus, a diagnostic vitrectomy was performed in the left eye to assess for additional locations of activity to guide systemic treatment decisions; the assessment found no evidence of a malignancy.

The patient was successfully treated with 8 consecutive weekly regional serial IVT methotrexate injections in the right eye followed

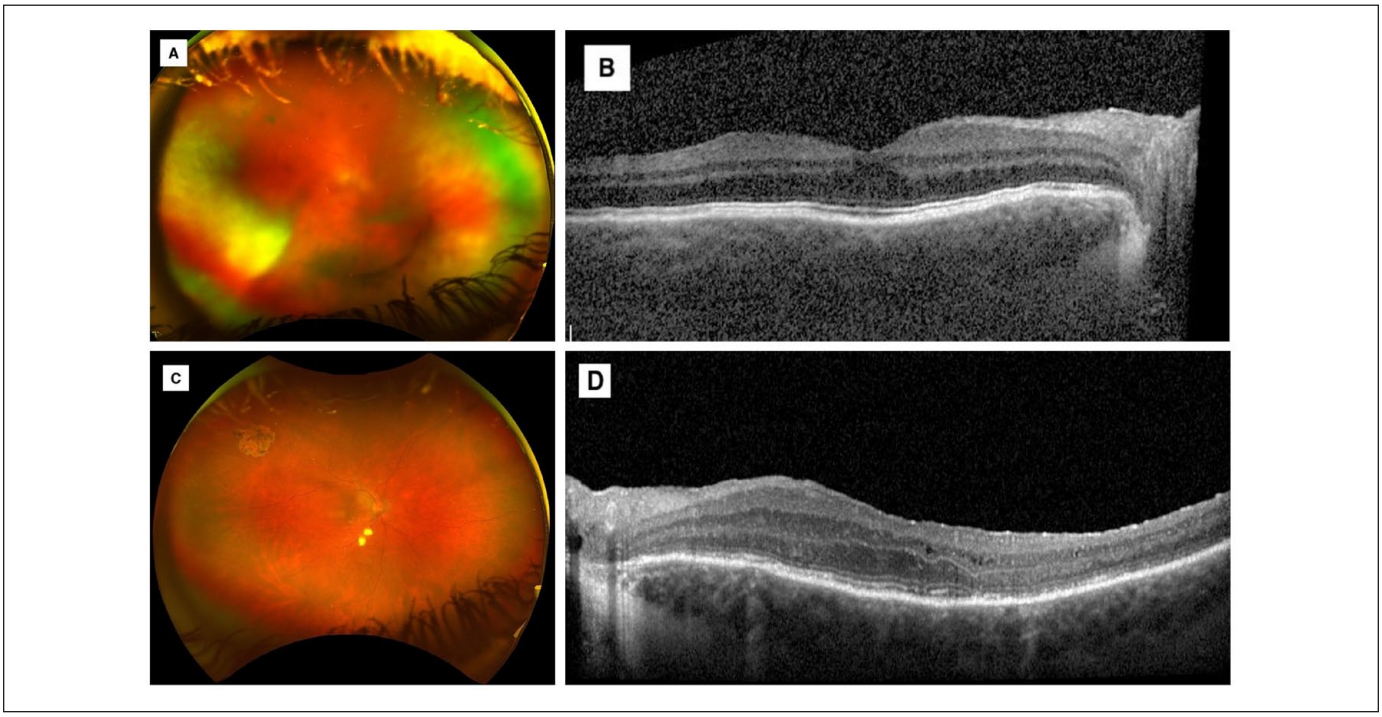

Figure 2. (A) Ultra-widefield fundus photograph of the right eye shows a white vitreous infiltrate. (B) Macular spectral-domain optical coherence tomography (SD-OCT) B-scan of the right eye shows resolved macular edema with an improved retinal pigment epithelium contour and a persistent pachychoroid. (C) Ultra-widefield fundus photograph of the right eye after a diagnostic vitrectomy and a course of intravitreal methotrexate injection shows resolution of the vitreous infiltrate. Superotemporal laser scarring is present from a treated operculated tear. (D) Macular SD-OCT scan of the left eye shows nonclinically significant hyporeflective cystoid cavities without subretinal material or vitreous cavity hyperreflective dots. There are no signs of lymphoma.

by systemic high-dose methotrexate and rituximab for CNS prophylaxis. The VA at last follow-up was 20/100 OD and 20/30 OS.

Conclusions

Vitreoretinal lymphoma, or intraocular lymphoma, is a rare malignancy that is regarded as a variant of primary CNS lymphoma. Vitreoretinal lymphoma most commonly presents in older individuals. Roughly 95% of vitreoretinal lymphoma is diffuse large B-cell lymphoma.[4] First described in 1991, lymphoproliferative disorders can occur at a younger than typical age from chronic administration of immunomodulatory medications.[5,6]

Intraocular lymphoma presents a diagnostic challenge; it is often initially misdiagnosed and treated as uveitis involving the posterior segment. For this reason, it is commonly referred to as a masquerade syndrome. However, patients with chronic uveitis treated with systemic immunomodulatory agents can develop vitreoretinal lymphoma at a younger than expected age. These patients represent an even more difficult diagnostic challenge. Differentiating underlining noninfectious uveitis activity from a new-onset intraocular lymphoproliferative disorder is difficult; however, it is crucial given the potentially life-threatening effect. Thus, it is imperative to keep masquerade syndromes in the differential diagnosis, not only as the primary cause of intraocular inflammation but also in the setting of chronic uveitis treated with systemic immunomodulatory agents with new inflammatory findings and an atypical treatment response. Although multimodal imaging combined with a careful ocular examination can help in the assessment of patients for whom there is a concern for vitreoretinal lymphoma, a diagnostic vitrectomy should be considered for a definitive diagnosis.

The vitreous infiltrate presented in the right eye after 15 months of mycophenolate mofetil use despite an active fluocinolone 0.59 mg implant that failed to replicate the previous response seen with the adjunctive IVT dexamethasone 0.7 mg implant. Thus, the decision was made to pursue a diagnostic vitrectomy, which led to the diagnosis of diffuse large B-cell lymphoma. This is a rare presentation of vitreoretinal lymphoma in a young adult with longstanding posterior uveitis secondary to VKH who is on chronic mycophenolate mofetil. In the setting of chronic pharmacologic immune dysregulation, this can further be considered a B-cell lymphoproliferative disorder.

Although many lymphoproliferative disorders have been reported and linked to immunomodulatory drugs, few reports have been related to mycophenolate mofetil.[6,7] To the our knowledge, this case represents the first known mycophenolate mofetil–induced intraocular lymphoproliferative disorder. The only other immunomodulatory agent the patient was exposed to during her course was low-dose methotrexate (10 mg/week) for a total of only 4 weeks nearly 2 years before she developed intraocular lymphoma; thus, we believe there was no direct causal relationship to methotrexate use.

Vitreoretinal lymphoma has a propensity for the CNS, with up to 90% of patients developing CNS and/or spinal cord disease within 1 year.[8] Although the best method of treatment for intraocular lymphoproliferative disease has yet to be determined, intraocular lymphoma with CNS involvement is, in general, treated with chemotherapy with or without radiation as the first-line option. However, IVT methotrexate is often considered to be a regional option. (Regional options would be the IVT injections directed toward just treating eye pathologies related to VKH.) Although the patient had chronic recurrent posterior uveitis in both eyes, the location of vitreoretinal lymphoma was isolated to 1 eye without CNS or systemic involvement. The literature lacks defined guidelines and recommendations regarding the benefit of systemic CNS prophylaxis in unilateral vitreoretinal lymphoma in young adults without extraocular malignancy. However, after the patient had oncologic consultations at multiple centers, the decision was made to treat with systemic chemotherapy for CNS prophylaxis.

Although masquerade syndromes are often thought to be the primary cause of intraocular inflammation, this case shows the need to consider the additional development of a lymphoproliferative disorder in the differential in patients with established noninfectious uveitis on chronic immunomodulatory agents. Determining remission and recurrence of intraocular lymphoma after local and systemic chemotherapy in a patient with a known chronic posterior uveitis condition and an intraocular lymphoproliferative disorder is difficult, but vital. Differentiating persistent or recurrent uveitis activity from relapsing or undertreated lymphoma represents further challenges.

This report describes a young adult with bilateral chronic, severe posterior uveitis resulting from VKH disease treated with mycophenolate mofetil and requiring systemic and regional corticosteroids who subsequently developed vitreoretinal lymphoma in the right eye. This case highlights the need for improved guidance on CNS prophylaxis in ocular lymphoproliferative disorders in young adults without extraocular malignancy.

Ethical Approval

This case report was conducted in accordance with the Declaration of Helsinki. The collection and evaluation of all protected patient health information were performed in a US Health Insurance Portability and Accountability Act–compliant manner.

Statement of Informed Consent

Informed consent, including permission for publication of all photographs and images included herein, was obtained before the procedure was performed.

Declaration of Conflicting Interests

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