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Vitreoretinal lymphoma presenting as frosted branch angiitis in a patient with diffuse large B-cell lymphoma

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ABSTRACT

Purpose: To describe the evaluation, diagnosis, and treatment of vitreoretinal lymphoma presenting as frosted branch angiitis in a patient with diffuse large B-cell lymphoma (DLBCL).

Observations: A 57-year-old woman with a history of non-Hodgkin lymphoma and recent DLBCL relapse presented with frosted branch angiitis that raised suspicion for an infectious retinitis but was found to be vitreoretinal lymphoma.

Conclusions and Importance: This case primarily highlights the importance of considering vitreoretinal lymphoma on the differential diagnosis of etiologies of frosted branch angiitis. Despite suspicion for vitreoretinal lymphoma, it is also important to treat empirically for infectious etiologies of retinitis in cases of frosted branch angiitis. In this case where the diagnosis was ultimately vitreoretinal lymphoma, weekly alternating intravitreal injections of methotrexate and rituximab led to improvement in visual acuity and retinal infiltration.

1. Introduction

There are three subtypes of intraocular lymphoma: vitreoretinal, choroidal, and iridial.[1] Vitreoretinal lymphoma was known in the 1980s–1990s as reticulum cell sarcoma,[1] and it is often classified as either primary or secondary.[1,2] Vitreoretinal lymphoma is rare, as there are between 30 and 380 cases yearly in the United States, of which 95% are CD20$^+$, DLBCL.[1,3] Whereas choroidal and iridial lymphomas are usually low-grade with favorable prognoses, vitreoretinal lymphoma is typically high-grade with a worse prognosis.[2,4,5] The brain is ultimately involved in 80% of cases, with one-third of patients showing CNS involvement within five years of diagnosis.[2,6]

The combination of low incidence, advanced disease at the time of presentation, and occult presentation make vitreoretinal lymphoma a difficult diagnosis and a devastating disease. The presentation can be occult, because vitreoretinal lymphoma tends to masquerade as other entities such as anterior, intermediate, and posterior uveitis before the correct diagnosis is made.[1,5,7,8]

Ocular findings in vitreoretinal lymphoma can include optic disc infiltration,[9] deep yellow subretinal infiltrates,[9] yellowish perivascular infiltrates,[10] retinitis-like lesions with retinal hemorrhages and RPE mottling,[10] and sub-retinal and sub-RPE infiltrates.[10] One atypical presentation of vitreoretinal lymphoma is frosted branch angiitis, which is a rare retinal vasculitis characterized by translucent perivascular sheathing of retinal arterioles and venules.[11] Frosted branch angiitis is more commonly associated with infectious etiologies such as CMV retinitis,[11] but has also been reported in association with paraneoplastic phenomena, T-cell lymphoma, and Hodgkin Lymphoma.[12–15] The presentation here of DLBCL-related vitreoretinal lymphoma presenting as frosted branch angiitis is especially rare.[8]

We highlight the diagnostic evaluation and management of vitreoretinal lymphoma by reporting a rare case of vitreoretinal lymphoma related to DLBCL relapse that presented as frosted branch angiitis.

2. Case report

A 57-year-old woman presented with painless left eye vision loss. In 1992 she received ProMACE-CytaBOM followed by mediastinal radiation for primary mediastinal non-Hodgkin lymphoma. She achieved complete remission until 2015 when core needle biopsy of a new left axillary mass revealed DLBCL. She therefore underwent six cycles of RCHOP with residual DLBCL on left axillary lymph node excisional

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biopsy, for which she was then treated with two cycles of RICE and autologous stem cell transplant. New FDG avid lymphadenopathy on PET-CT in 2018 prompted core needle biopsy of a left inguinal lymph node, which showed recurrent DLBCL. Initially ibrutinib achieved complete metabolic response, but she subsequently required Kymriah CAR T-cell therapy in 2019. Further disease progression prompted six cycles of rituximab-bendamustine-polatuzumab followed by sibling allogenic stem cell transplant with complete metabolic response by May 2020. However, a few months later she developed a new biopsy-proven DLBCL right frontal mass. She then underwent 3000 cGy radiation to the whole brain and the bilateral eyes with lens-sparing (Fig. 1) as well as an additional isolated higher dose of 500 cGy to the brain to a focal area of her tumor burden. Subsequent Brain MRI showed no evidence of disease and she was monitored without further chemotherapy or radiation, although she did continue to receive ongoing prophylactic acyclovir and intravenous immunoglobulin in the setting of pancytopenia and hypogammaglobulinemia. She remained medically stable and her ocular history was unremarkable for four months until she then presented to her ophthalmologist with new painless left eye vision loss.

Examination of the right eye was normal. Left eye visual acuity was 20/150 with a central scotoma. Color plates were 1/10 and there was an afferent pupillary defect. The anterior chamber was quiet. There was disc swelling with splinter hemorrhages, possible early retinitis-like lesions inferior to the fovea, and perivascular infiltrates (Fig. 2). Her ophthalmologist referred her to obtain urgent MRI orbits with and without IV contrast, which demonstrated focal enhancement of the left optic nerve head without lesions elsewhere (Fig. 3). Her clinical presentation, ophthalmologic examination, and radiographic findings raised suspicion for lymphomatous retinal and optic nerve infiltration, an infectious optic neuritis and retinitis, or radiation optic neuropathy. She was, however, lost to follow-up for six weeks at which time she presented now as a new patient to the retina service and her visual acuity had deteriorated to counting fingers at 2 feet and examination revealed mild anterior chamber cell, 1+ vitreous cell, diffuse pallid disc swelling and infiltration, and frosted branch angiitis (Fig. 4).

The differential diagnosis at this point was most concerning for ocular involvement of DLBCL or infiltration by herpes simplex virus (HSV), cytomegalovirus (CMV), or toxoplasma. Important in pursuing a work-up in such a case is prioritizing those elements of the differential diagnosis that pose the most imminent risk of irreversible morbidity. Diagnosing and empirically treating a possible infectious optic neuritis and retinitis is commonly more time-sensitive than identifying

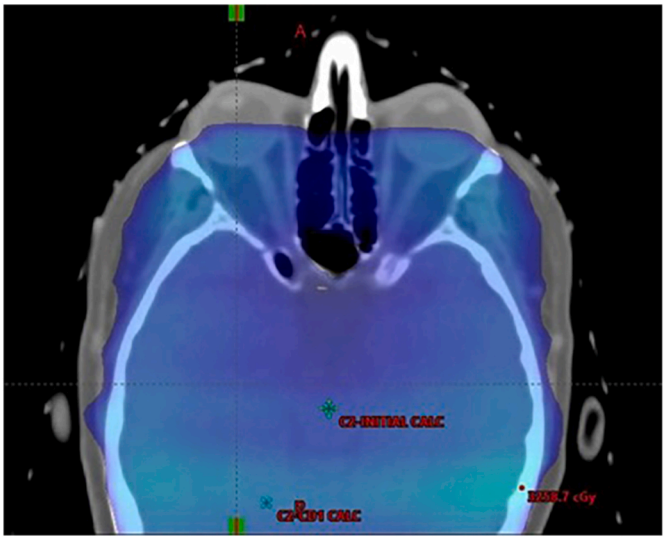

Fig. 1. Distribution of 3000 cGy radiation to the whole brain and the bilateral eyes with lens-sparing.

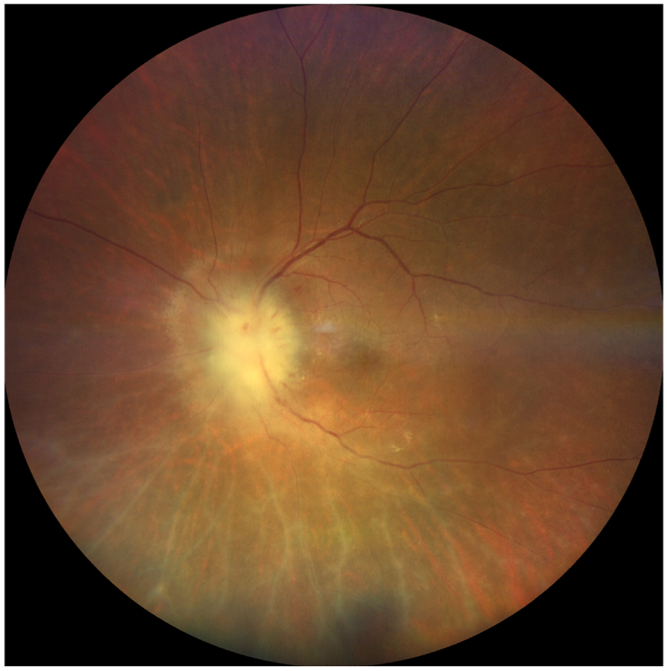

Fig. 2. Initial fundus photograph of the left eye.

intraocular lymphoma, and empiric work-up and treatment of a viral etiology can be immediately performed in the clinic while preparation is made for vitreous biopsy for lymphoma diagnosis. Therefore, an aqueous fluid sample was sent for PCR testing for CMV, HSV, and toxoplasma, and she was treated empirically for both CMV and HSV with intravitreal foscarnet and for toxoplasma with intravitreal clindamycin. Furthermore, her prophylactic systemic acyclovir was switched to therapeutic valganciclovir as empiric systemic therapy for CMV retinitis.

Aqueous HSV, toxoplasma, and CMV PCR and serum HSV and toxoplasma IgM and CMV PCR were negative. There was no improvement in subjective examination and fundus appearance after the intravitreal injection of foscarnet and clindamycin and one week of therapeutic valganciclovir. Furthermore, OCT revealed characteristic sub-retinal infiltrates (Fig. 5) and "rounded roof" retinal thickening (Fig. 6) both suggestive of lymphoma. She underwent urgent pars plana vitrectomy with vitreous biopsy and intra-operative intravitreal methotrexate. Vitreous biopsy yielded atypical mononuclear cells consistent with vitreoretinal lymphoma. Subsequent lumbar puncture and whole-body imaging were without evidence of lymphoma elsewhere. While ocular relapse is associated with a high risk of CNS relapse, the decision was made in consultation with her medical oncologist to treat her localized relapse with weekly alternating intravitreal injections of methotrexate 0.4 mg/0.1 mL and rituximab 1 mg/0.1 mL without reintroduction of systemic therapy. After her second intravitreal injection, visual acuity in the affected left eye had improved to 20/400 and optic nerve and retinal infiltration resolved with resultant atrophy (Fig. 7). She remained stable through the subsequent six intravitreal injections. However, her intravitreal injections were paused when work-up of a new headache led to the discovery of new bilateral temporo-occipital white matter lesions with associated vasogenic edema and new posterior fossa leptomeningeal spread for which she was transferred to inpatient hospice without further oncologic care.

3. Discussion

The tendency of vitreoretinal lymphoma to masquerade as other entities has been widely described.[1,5,7,8] It can be misdiagnosed as anterior uveitis and more frequently as intermediate and posterior uveitis.[1,5,9,10] Treatment of presumed uveitis with corticosteroids lyses

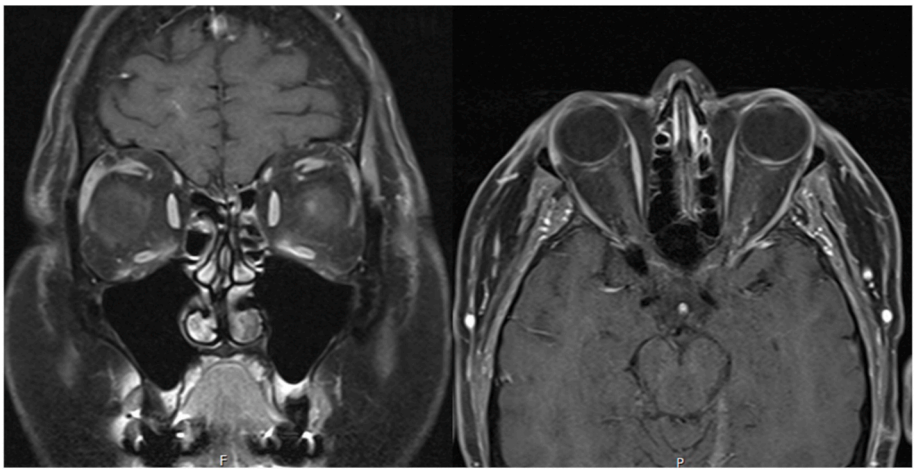

Fig. 3. MRI orbits with and without IV contrast demonstrating focal enhancement of the left optic nerve head.

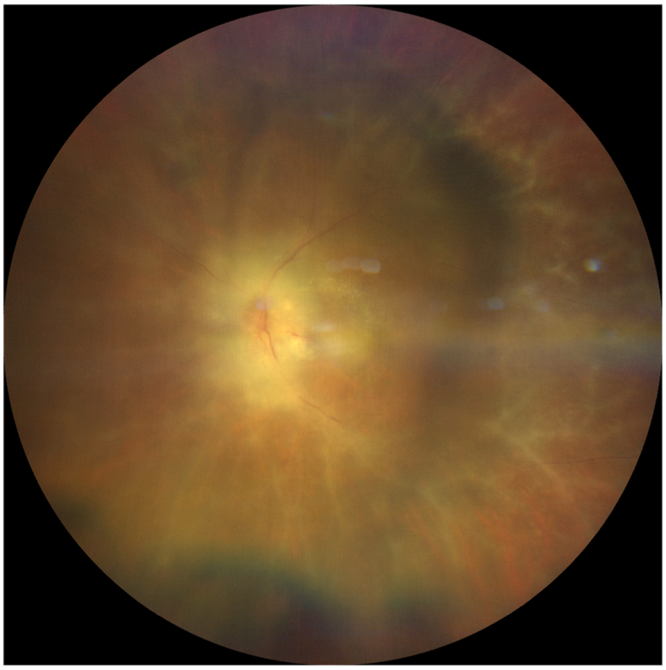

Fig. 4. Fundus photograph of the left eye six weeks later revealing disease progression.

the lymphoma cells, which decreases the yield of a vitreous biopsy and further delays diagnosis.[1] As in this case, vitreoretinal lymphoma can present with frosted branch angiitis concerning for an infectious retinitis and vasculitis.[7]

In many cases, immediate empiric treatment for viral retinitis is important because viral etiologies may be more common in an immunosuppressed patient and would potentially be more rapidly sight-threatening. The best course of action may involve immediate empiric treatment of viral etiologies while preparing for vitreous biopsy to evaluate for vitreoretinal lymphoma. Diagnosing vitreoretinal lymphoma is also time-sensitive, because subretinal and sub-RPE infiltrates can be rapidly increase in size leading to hemorrhagic masses and retinal detachments if not treated expediently.[16] Lymphoma infiltration of the optic disc can also lead to a poor prognosis if not treated promptly.[9]

If the cellular pathology on vitreous biopsy is equivocal, detection of MYD88 mutation in ocular fluid obtained at the time of surgery can help confirm the diagnosis of vitreoretinal lymphoma as it is present in 80% of cases.[1,17] A high IL-10/IL-6 ratio is suggestive but not diagnostic, and IL-10 levels can be monitored for evidence of recurrence after treatment.[1,17]

There are no randomized controlled clinical trials for vitreoretinal lymphoma.[6] One center favors systemic therapies, reserving intravitreal therapy or vitrectomy for cases with dense vitreous infiltrates.[2,18] Others advocate for intravitreal methotrexate and rituximab for unilateral involvement and for systemic therapy in bilateral cases with further therapies as adjuncts.[1] Monitoring for response is challenging, and formal guidelines for treatment and for defining residual disease after treatment remain to be established.[1,19] The mean 5-year survival rate is 41.4–71%, and recurrence and relapse are common despite treatment.[3]

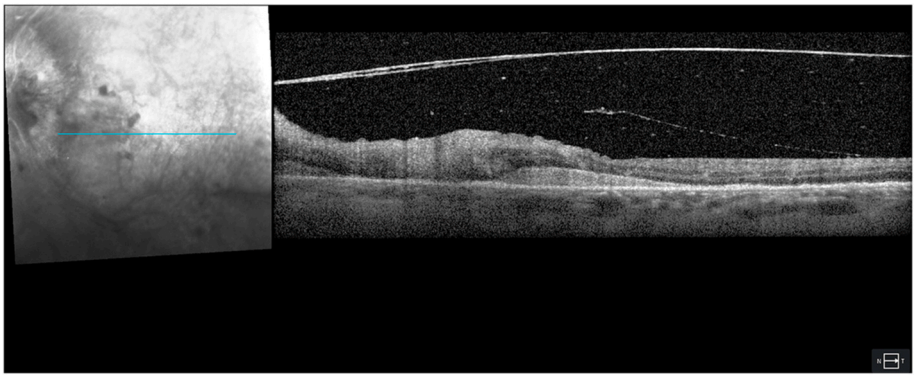

Fig. 5. Optical coherence tomography of the left eye with sub-retinal deposits concerning for vitreoretinal lymphoma.

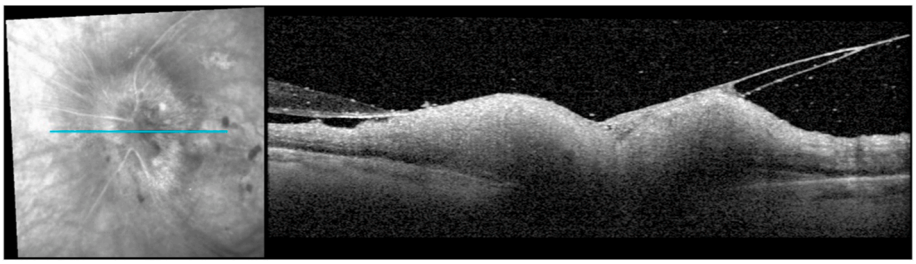

Fig. 6. Optical coherence tomography of the left eye with "rounded roof" retinal thickening concerning for vitreoretinal lymphoma.

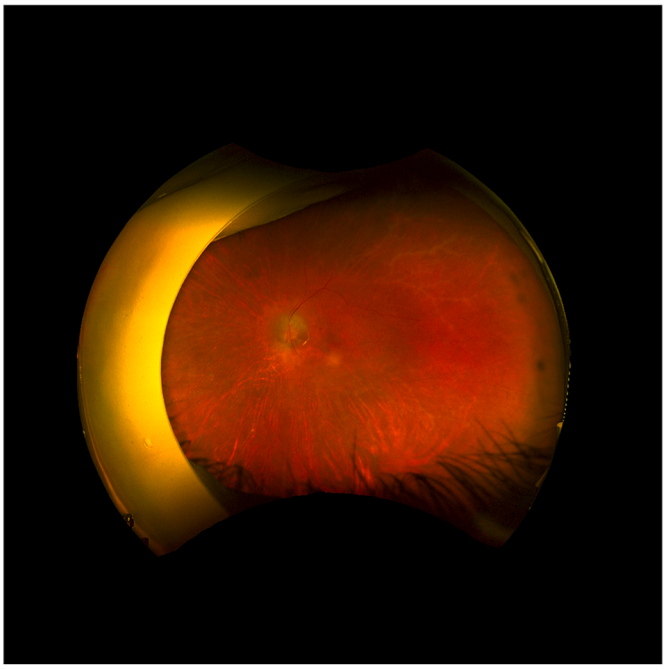

Fig. 7. Fundus photograph of the left eye after the second dose of weekly alternating intravitreal methotrexate and rituximab.

4. Conclusions

This case demonstrates a rare presentation of frosted branch angiitis as a manifestation of vitreoretinal lymphoma. Frosted branch angiitis is more commonly seen in CMV retinitis, which occurs in immunosuppressed patients. However, frosted branch angiitis can also rarely occur in the setting of vitreoretinal lymphoma related to DLBCL and must therefore be considered in the differential diagnoses in such clinical scenarios. Prompt empiric treatment of possible viral retinal and optic nerve infiltration is essential while preparing for prompt vitreous biopsy to diagnose suspected lymphoma.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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