The Management of Intraocular Lymphoma Resistant to Intravitreal Methotrexate Injection

In a patient who presented with asymmetric involvement in both eyes, each eye responded to different management strategies.

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Primary intraocular lymphoma (PIOL) is the most common ocular masquerade syndrome.[1,2] It is a rare non-Hodgkin lymphoma and is categorized as a subtype of primary central nervous system (CNS) lymphoma (PCNSL).[1] Vitritis, subretinal and subretinal pigment epithelium (RPE) yellowish infiltrates are the most common presenting signs.

We report a case of PIOL with PCNSL in a patient who presented with asymmetric involvement in both eyes and in whom each eye responded to different management strategies. To the best of our knowledge, this is the first report to highlight the management of PIOL by therapeutic vitrectomy.

CASE REPORT

A 49-year-old woman was referred with a diagnosis of biopsy-proven PIOL. She also had a history of behavior and cognitive dysfunction, loss of appetite, weight loss, and right-side facial palsy and hemiparesis. Her best corrected visual acuity (BCVA) was no light perception in the right eye and 6/18 in the left.

Ocular adnexa, ocular motility and anterior segment examination in both eyes were normal, except for the observation of retrolental cells and membranes in the left eye. Fundus examination of the right eye revealed marked blurring of the disc margins and areas with subretinal creamy infiltrates (Figure 1A). There was also a scar from previous subretinal biopsy undertaken at another center. The left eye had grade 2 media haze with no retina or disc involvement (Figure 1B).

Fluorescein angiography revealed disc leakage and venous beading along the inferior arcades in the right eye (Figure 1C) and no retina or disc involvement in the left eye (Figure 1D). Neurologic examination revealed right upper motor neuron facial palsy and increased tone in the right upper limb and lower limb.

Magnetic resonance imaging of the brain showed multiple nonenhancing focal and confluent areas of T2-weighted/FLAIR hyperintense lesions in bilateral periventricular and subcortical white matter, the left thalamocapsular region, and the left cerebral peduncle. Cerebrospinal fluid cytology showed clusters of lymphoid cells with high nuclear-cytoplasmic ratio that were CD3 positive and CD22 negative. Blood count, blood chemistry, serum lactate dehydrogenase (LDH), and antinuclear antibodies were within normal limits, and serology for HIV was negative. Computed tomography (CT) of the chest and abdomen and pelvis and bone marrow biopsy were negative for lymphoma involvement.

A clinical diagnosis of PIOL with PCNSL was made, and the patient was treated with the recommended DeAngelis protocol.[3] Following treatment with this pro-

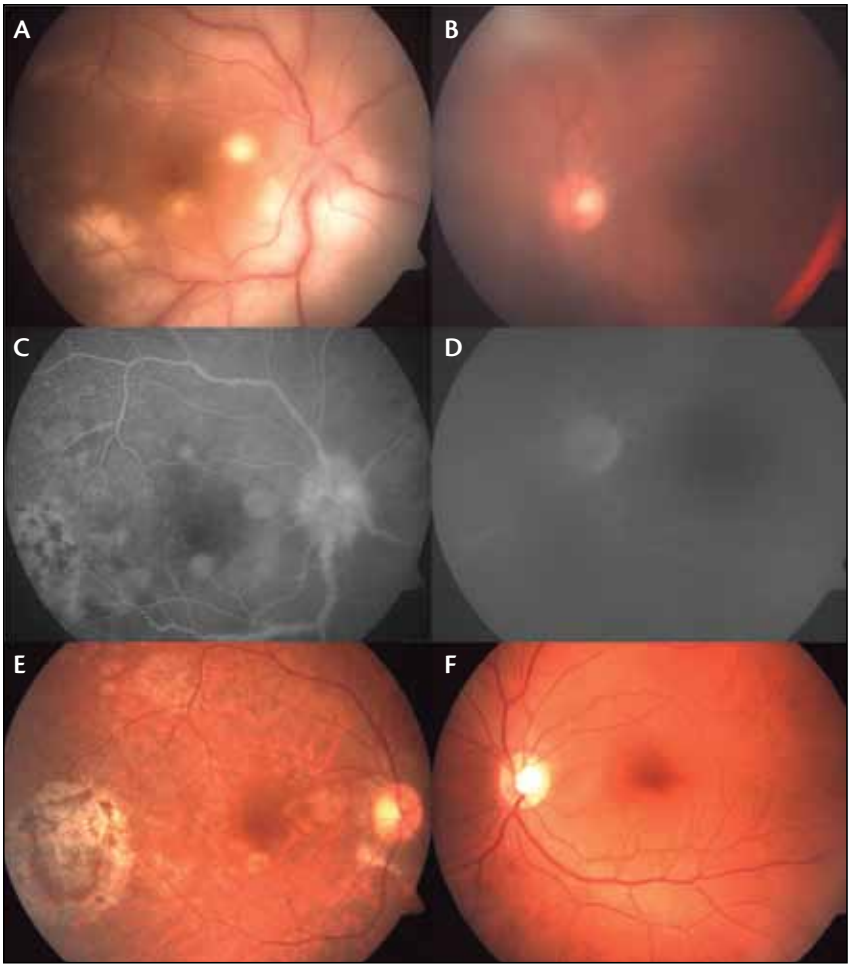

Figure 1. Fundus photograph of the right eye (A) shows optic disc infiltration and subretinal infiltration with vascular changes, while that of the left eye (B) shows significant vitreous membranes and no involvement of the optic disc, subretinal space, and retinal vessels. The above features are highlighted in the corresponding fluorescein angiographic images (C and D). Complete resolution of the optic nerve and retinochoroidal involvement is seen in the right eye (E) and of vitreous membranes in the left eye (F).

tocol, there was complete resolution of the CNS as well as intraocular involvement in both eyes (Figures 1E and 1F).

At 3-month follow-up, the right eye showed complete remission, with visual acuity improvement to 6/18. In the left eye, however, severe recurrence was noted with the formation of extensive vitreous membranes that reduced the visual acuity to 3/60 (Figure 2A). There was, again, no retinochoroidal involvement during this relapse in the left eye.

As there was only vitreal involvement in left eye, we decided to treat this with intravitreal methotrexate (MTX) injections. The patient received 9 intravitreal MTX injections (400 µg/0.1 mL) depending on activity (based on vitreous haze).

With this treatment, the patient was in clinical remission with no disease activity in both eyes after 18 months of follow up (Figure 2B). Three months after the ninth injection of intravitreal MTX, she again developed vitreal relapse in the left eye. Despite two further intravitreal injections of MTX, no significant resolution of the vitreous membranes was noted (Figure 2C). We hypothesized that this lack of response was an indication of resistance to MTX, and therefore we performed a complete therapeutic vitrectomy using a 23-gauge microincision vitrectomy system.

Nine months after vitrectomy, no relapse has been observed (Figure 2D), and the patient maintains a visual acuity of 6/18 in the right eye and 6/12 in the left.

DISCUSSION

PIOL typically presents as a posterior uveitis with nonspecific findings of vitreous debris, optic nerve infiltration, subretinal infiltration, elevated chorioretinal lesions, and retinal detachment.[4] It is usually bilateral, and CNS is involved in 60% of cases. There are 3 main treatment options for PIOL: systemic high-dose MTX injection, orbital irradiation, and intravitreal chemotherapy with MTX.[5-7]

The patient described here had bilateral but asymmetric involvement, with retinal and optic nerve involvement in the right eye and only vitreal involvement in the left eye. She received standard management for PCNSL including systemic chemotherapy and cranial irradiation, excluding the eye fields. Initial response was noted in both eyes; however, the right eye, with predominant retinal disease, resolved completely, and the left eye continued showing activity. This highlighted the fact that retina and optic nerve involvement paralleled CNS disease, and, due to significantly lower levels of chemotherapeutic agent in the vitreous cavity, remission could not be sustained in the left eye.

Chan et al have reported therapeutic levels of MTX for up to 5 days after intravitreal injection as compared with

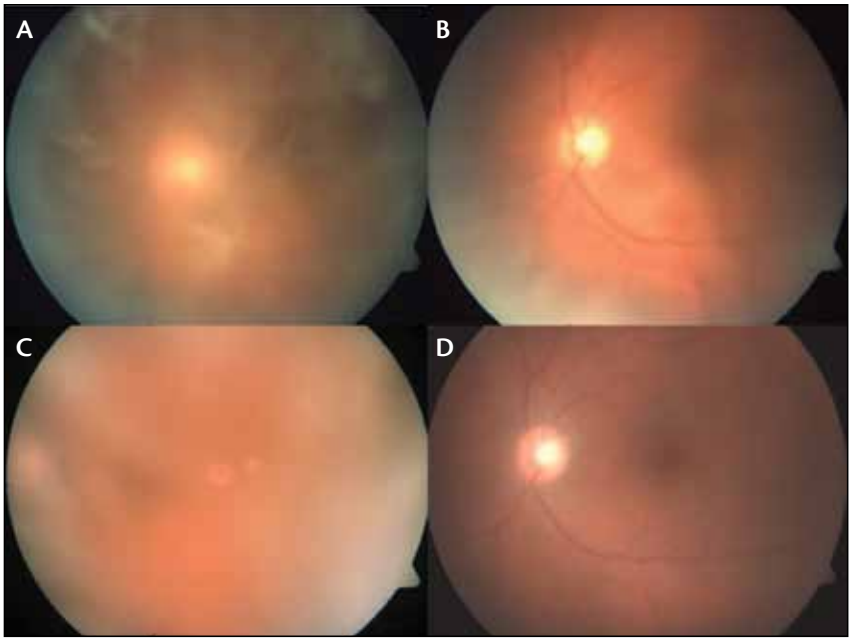

Figure 2. Severe relapse of vitreous membranes in the left eye 3 months after systemic therapy (A). Partial resolution is seen following the third intravitreal methotrexate (MTX) injection (B). Fundus appearance immediately prior to vitrectomy manifesting relapse of vitreal lymphoma and resistance to further MTX injections (C). Clear media and absence of any vitreous relapse following therapeutic vitrectomy (D).

a few hours with systemic administration.[8] Numerous reports have also described poor response to systemic MTX-based regimens due to poor penetration into ocular tissues and have recommended intravitreal MTX as a treatment modality for PIOL with good response and fewer complications.[9-16]

With incomplete response in our patient, and involvement limited to vitreous only, we treated the patient with multiple intravitreal MTX injections in the left eye. Frenkel et al demonstrated clinical remission after a mean of 6.4 ±3.4 (range, 2–16) injections of MTX.[11] In our patient, after an initial satisfactory response to 9 intravitreal MTX injections, there was a severe relapse that was resistant to further MTX injections. Because the disease was primarily limited to the vitreous, we decided to do a complete pars plana vitrectomy, with the hope that we could achieve complete remission of the disease after surgery.

Although diagnostic vitreous biopsy is routinely performed to confirm a suspicion of PIOL, to the best of our knowledge, complete vitrectomy as a treatment modality for PIOL has not been previously described. Diagnostic vitreous biopsy has been in use for several decades as part of the management algorithm of intraocular lymphomas, and no concerns of systemic spread as a result have been raised, unlike with retinoblastoma.

The prolonged remission seen in our patient following complete vitrectomy prompts us to wonder whether microincisional therapeutic vitrectomy should become the treatment of choice in patients with the vitreal form of PIOL. Observations from a larger number of patients following such intervention would be necessary before coming to a firm conclusion on this matter. ■

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The authors report no conflicts of interest relevant to the material discussed in this article. *Dr. Venkatesh may be reached at venkyprao@yahoo.com.*

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