Vitreoretinal Lymphoma

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Introduction

Primary central nervous system lymphoma (PCNSL) originates in the brain parenchyma, spinal cord, leptomeninges, and the eyes. Primary vitreoretinal lymphoma (PVRL) is a variant of PCNSL with predominantly ophthalmic involvement. The relationship between PVRL and PCNSL is variable with intraocular involvement preceding, occurring simultaneously or following CNS manifestations. Diagnosis is challenging, particularly as the clinical findings (vitreous cells, subretinal pigment epithelial, and/or retinal infiltrates, optic disc edema, aqueous cells, flare, and others) can be nonspecific and misdiagnosed as uveitis. Biopsy should be performed in suspected cases that often are of steroid-resistant uveitis, particularly in older or immunocompromised individuals. Detection of highly elevated interleukin-10 (IL-10) in ocular fluids is helpful in the diagnosis of B-cell PVRL.

Case 1: Diffuse Large B-Cell PVRL

A 56-year-old Caucasian woman presented with a 6 month history of decreased vision in both eyes and poor balance. Magnetic resonance imaging (MRI) of the brain was unremarkable. She was initiated on oral and periocular steroids but her symptoms persisted. Diagnostic vitrectomy was negative for infection or malignancy. Upon referral to ophthalmic oncology clinic, her visual acuity was 20/32 in the right eye and hand motions in the left eye. On slit-lamp examination, non-granulomatous keratic precipitates were

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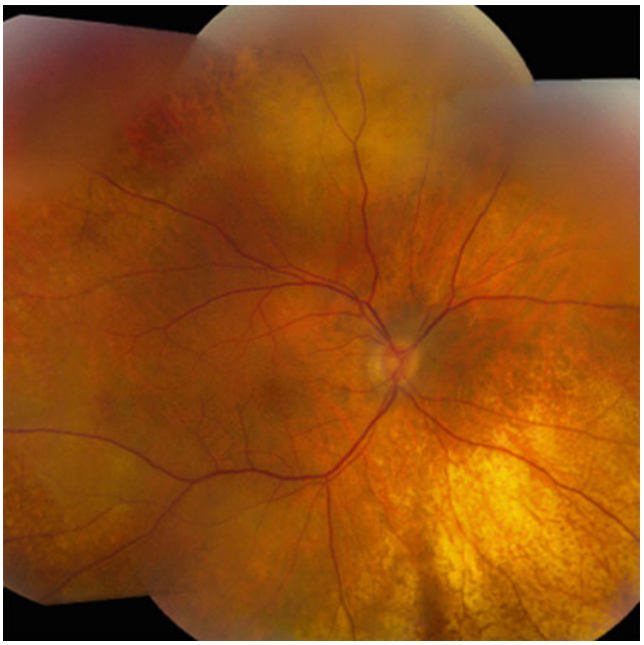

Fig. 1 Color fundus photograph of the right eye demonstrating mild vitreous haze

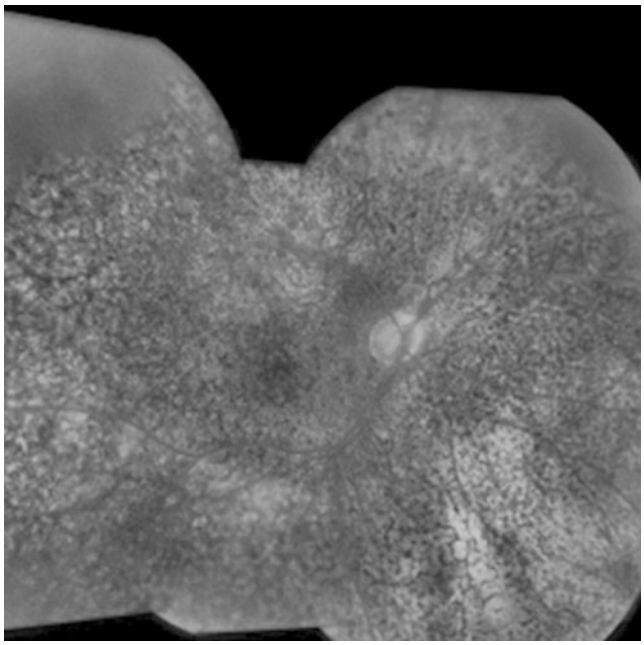

Fig. 3 Fluorescein angiogram of the right eye showing stippled pattern of hyperfluorescence

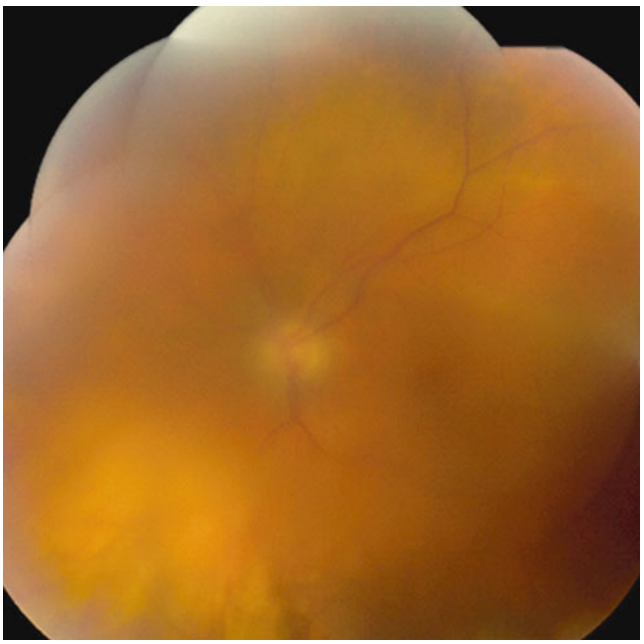

Fig. 2 Color fundus photograph of the left eye demonstrating significant vitreous cells and haze

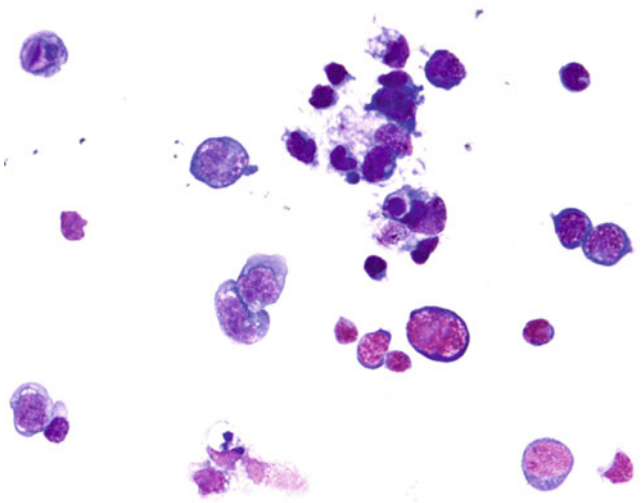

Fig. 4 Vitreous biopsy demonstrating large, atypical lymphoid cells with scanty basophilic cytoplasm with large irregular nuclei

observed in the right eye, and there were 1+ anterior chamber cells in the right eye and 0.5+ cells in the left eye. On dilated examination, there were trace cells in the vitreous of the right eye and 3+ cells in the vitreous of the left eye (Figs. 1 and 2). Optical coherence tomography (OCT) showed absence of cystoid macular edema and fluorescein angiography (FA) revealed a stippled pattern of hyperfluorescence in both eyes (Fig. 3). Diagnostic vitreous sampling was

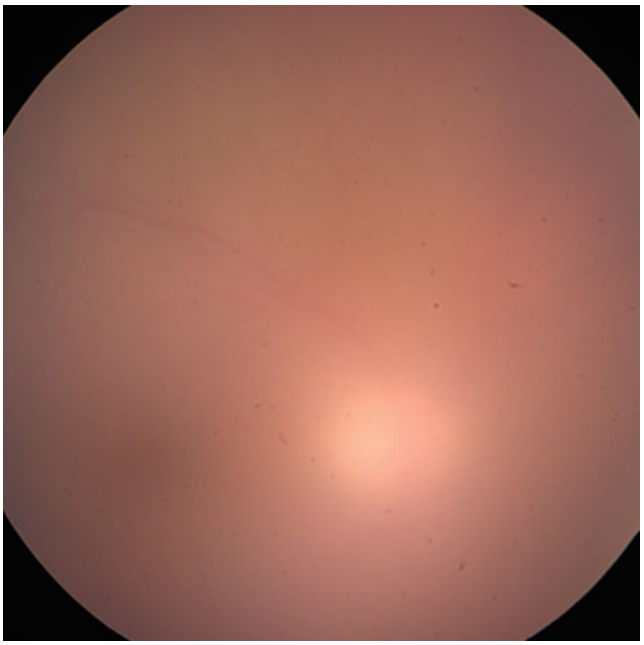

Fig. 5 Color fundus photograph of the right eye demonstrating significant vitreous cells and haze

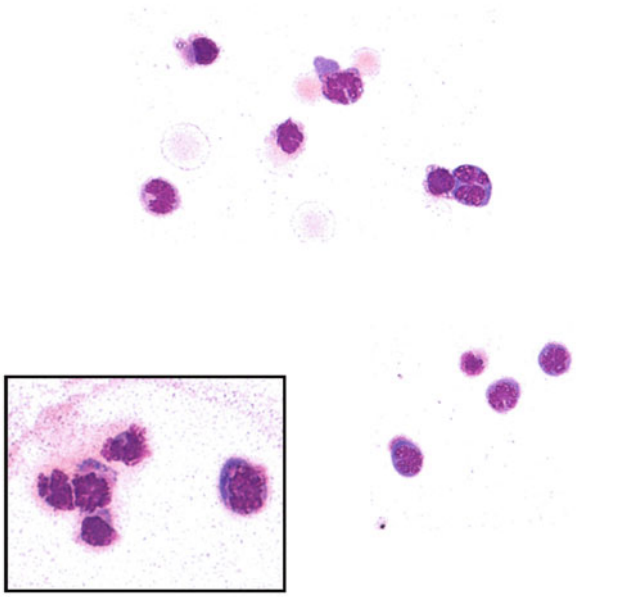

Fig. 6 Vitreous biopsy showed large, atypical lymphoid cells with scanty basophilic cytoplasm with large segmented nuclei

performed in the left eye. Cytology revealed large, atypical lymphoid cells with scanty basophilic cytoplasm and large segmented nuclei (Fig. 4). Microdissection and polymerase chain reaction (PCR) from the atypical lymphoid cells revealed the presence of IgH gene rearrangement. Vitreous cytokine analysis by enzyme-linked immunosorbent assay (ELISA) revealed an IL-6 of less than 78 pg/ml, while the IL-10 was elevated at 24,890 pg/ml (normal undiluted vitreous <23.4 pg/ml). Diagnosis of diffuse large B-cell lymphoma (DLBCL) was confirmed.

Case 2: PVRL with Subsequent Development of CNS Lymphoma

A 71-year-old Caucasian woman presented with blurred vision and floaters in both eyes. Her visual acuity was 20/32 in both eyes. On examination, there were fine keratic precipitates and vitreous cells in both eyes (Fig. 5). Diagnostic vitrectomy was performed in the left eye. Cytology revealed large, atypical lymphoid cells with large nuclei and scanty basophilic cytoplasm which stained positively for the lambda chain (Fig. 6). Microdissection and PCR from the atypical lymphoid cells revealed IgH gene rearrangement. Vitreous cytokine analysis by ELISA revealed an IL-6 of less than 15.6 pg/ml and an elevated IL-10 of 266 pg/ml. Cerebral spinal fluid (CSF) cytokine analysis from a lumbar puncture (LP) showed an IL-6 of less than 7.8 pg/ml and an IL-10 of less than 11.7 pg/ml. A diagnosis of DLBCL was established. She was treated with high-dose intravenous methotrexate (3.5 g/m^2). Two years later, she developed a left infiltrative optic neuropathy and secondary glaucoma. She subsequently developed fever, fatigue, and neurocognitive changes. An MRI brain revealed numerous sites of recurrent central nervous system lymphoma including the optic chiasm and right frontal lobe. Palliative care was initiated.

Case 3: T-Cell Vitreoretinal Lymphoma with Cutaneous Involvement

A 78-year-old Caucasian male developed blurry vision in the left eye of 4 months duration. He had previously been diagnosed with cutaneous T-cell lymphoma of the left leg 3 years before the onset of ocular symptoms. On examination, the best corrected vision was 20/25 in the right eye and count fingers in the left eye. On dilated examination of the right eye, there were trace vitreous cells. Superior nasal to fovea, there was a small area of retinal pigment epithelium (RPE) atrophy (Fig. 7). In the left eye, there were 2+ vitreous cells (Fig. 8). MRI of the brain was unremarkable. Vitreous biopsy of the left eye demonstrated atypical, intermediate to large lymphoid cells with enlarged, round, irregular nuclei, visible nucleoli, and basophilic cytoplasm (Fig. 9). T-cell markers (CD3, CD4) were strongly positive, while B-cell markers

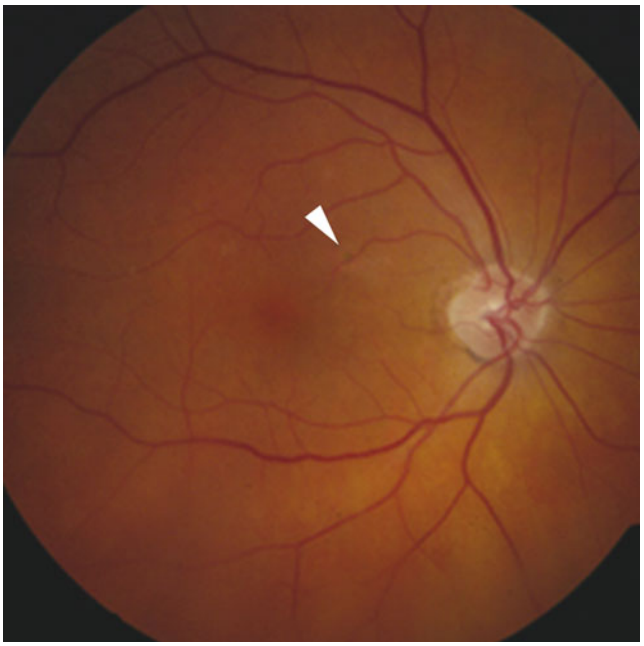

Fig. 7 Color fundus photograph of the right eye showing a small area of retinal pigment epithelium (*RPE*) atrophy superior nasal to fovea (*arrow*)

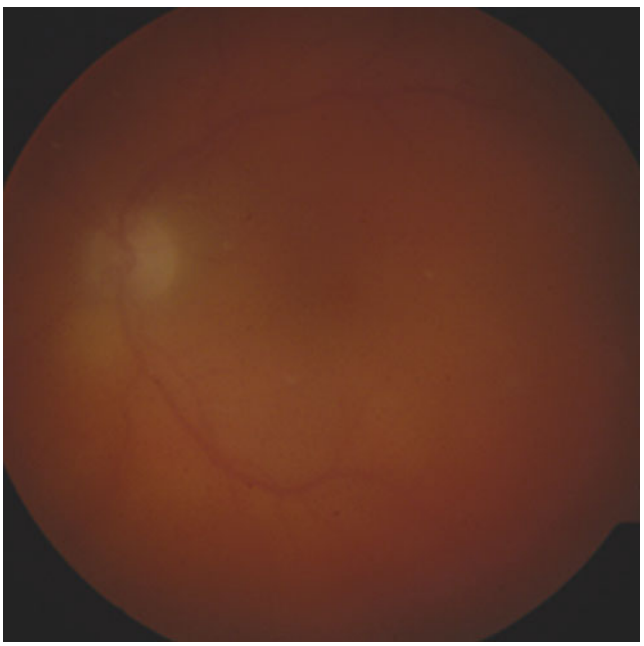

Fig. 8 Color fundus photograph of the left eye demonstrating dense vitreous cells and haze

(CD20) were negative (Fig. 10). T-cell receptor (TCR)-γ gene rearrangement was supportive of a clonal population of T-cells (Fig. 11). Review of tissue from the patient's skin biopsy revealed near identical molecular analysis.

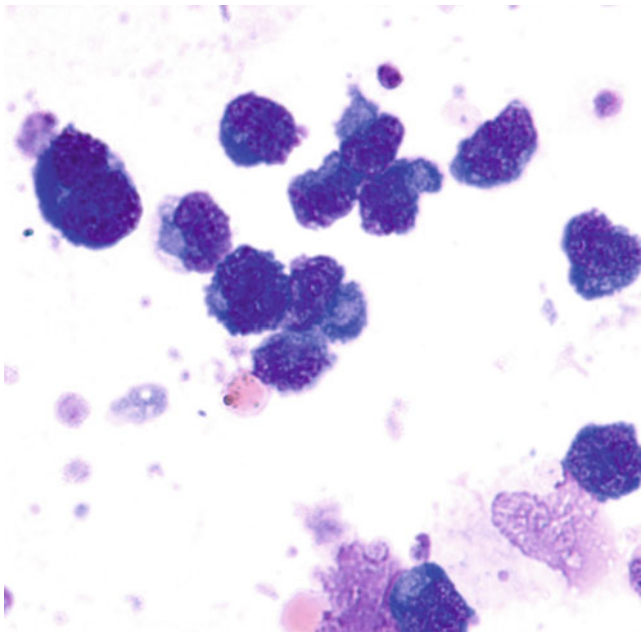

Fig. 9 Vitreous biopsy of the left eye revealing atypical, lymphoid cells in variable sizes with enlarged, irregular nuclei, visible nucleoli, and basophilic cytoplasm

Case 4: PVRL in a Patient with HIV

A 42-year-old male with known human immunodeficiency virus (HIV) infection presented with decreased vision in the right eye. His most recent CD4 count was 954 cells/mm^3 and his viral load was 5400 IU/ml. On examination, his best corrected visual acuity was 20/63 in the right eye and 20/20 in the left eye. On dilated fundus examination, there were vitreous 2+ cells and haze in the right eye (Fig. 12). The left eye was essentially normal. Laboratory studies were negative for any active infectious etiology; therefore he was treated empirically with topical corticosteroids. His vision in the right eye worsened to 20/200. He underwent diagnostic vitrectomy of the right eye which confirmed the diagnosis of vitreoretinal B-cell lymphoma (Fig. 13). Subsequent MRI of the brain and systemic work-up was unremarkable. PCR for Epstein Barr virus (EBV) was positive in both vitreous and cerebral spinal fluid.

Case 5: Vitreoretinal Lymphoma Masquerading as Uveitis

A 64-year-old Caucasian male presented with decreased vision and floaters in the right eye of several weeks duration. On examination, he was noted to have a dense vitritis

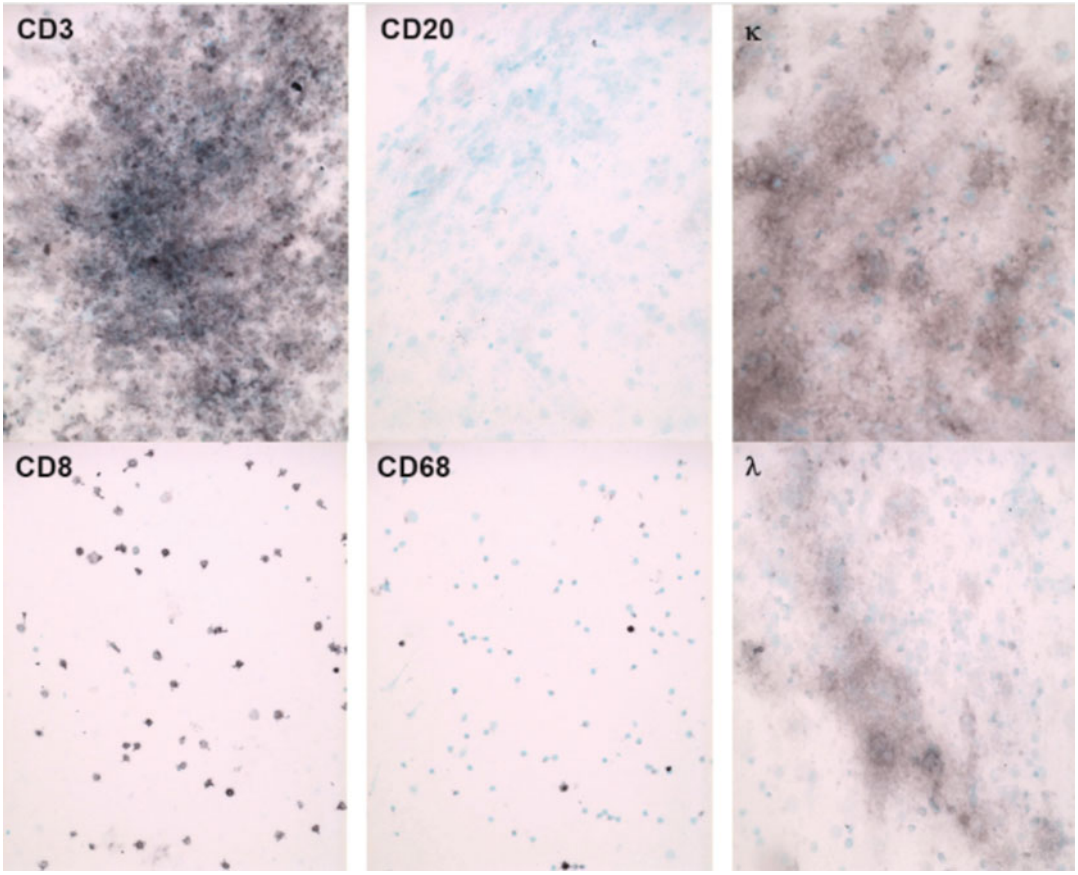

Fig. 10 T-cell markers (CD3 shown) were strongly positive, while B-cell markers (CD20) were negative. The cytoplasm stained positively for the kappa chain and also lightly positive for the lamda chain. CD8 positive T-cells and few macrophages (CD68) are also found

in the right eye. He was treated empirically with intravitreal antibiotics and antifungals for suspected infectious posterior uveitis; however, the vitritis persisted. Vitreous biopsy was performed but was nondiagnostic. Vitreous cultures were negative for bacteria and fungi. An inflammatory etiology was suspected, and the patient was started on oral steroids; however, his vision continued to decline. He was referred to ophthalmic oncology clinic for suspected lymphoma. The vision was no light perception in the right eye and 20/50 in the left eye. On examination of the right eye, there was no anterior chamber or vitreous cell. There was marked chorioretinal atrophy (Fig. 14). Examination of the left eye demonstrated mild mottling of the RPE but was otherwise unremarkable. OCT of the left eye showed an abnormality of the RPE with an infiltrative appearance of the subRPE space (Fig. 15). MRI of the brain was unremarkable. Following tapering of corticosteroids, the decision was made to perform enucleation of the right eye for diagnostic purposes, as the patient was actively losing vision in the left eye and diagnosis had not yet been established. Histopathology of the enucleated globe demonstrated marked chorioretinal

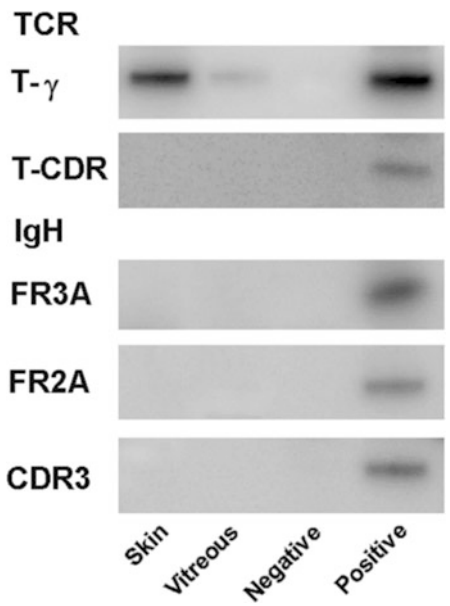

Fig. 11 T-cell receptor (TCR)-γ PCR was supportive of a clonal population of T-cells. Review of tissue from the patient's skin biopsy revealed near identical molecular analysis

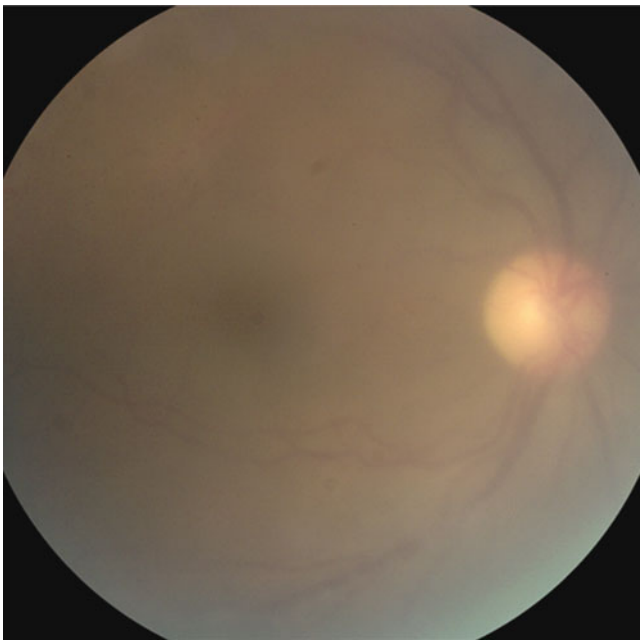

Fig. 12 Color fundus photograph of the right eye demonstrating vitreous 2+ cells and haze

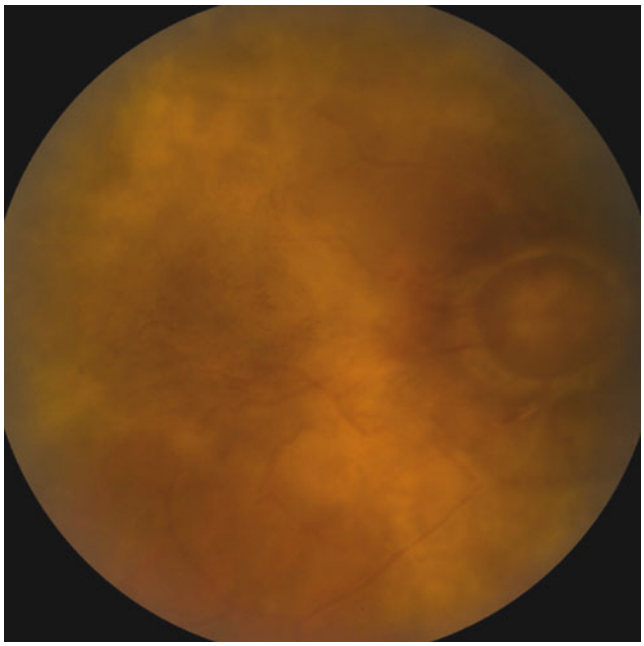

Fig. 14 Fundus photograph of the right eye demonstrated marked chorioretinal atrophy, attenuation of the vasculature, and pallor of the optic nerve

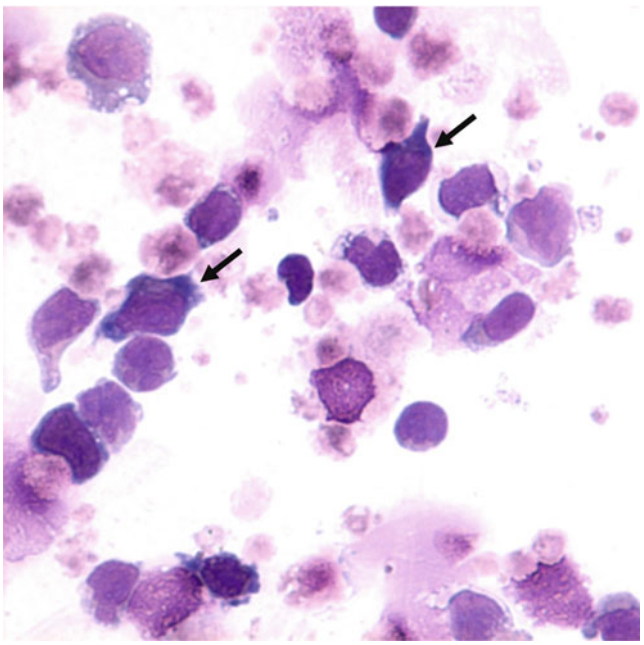

Fig. 13 Vitreous biopsy revealing scattered, atypical lymphoid cells (*arrows*) in a background of small lymphocytes and macrophages

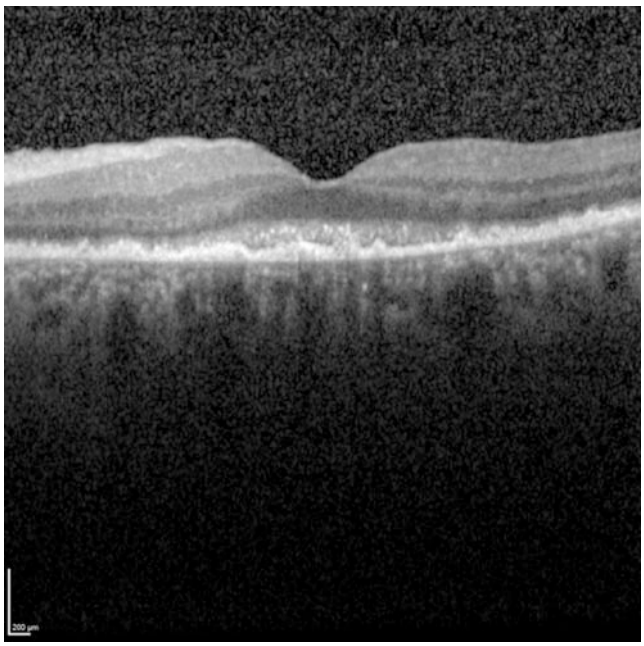

Fig. 15 OCT of the left eye shows an irregular subRPE infiltrate beneath the fovea

atrophy. Histopathology, flow cytometry, and gene-rearrangement studies showed no evidence of malignancy. Six weeks later, the patient developed mental status changes and repeat MRI revealed a lesion in the pituitary gland involving the optic pathway. A second biopsy, obtained from the remaining right optic nerve stump, revealed DLBCL. He was treated with high-dose intravenous methotrexate and rituximab.

Case 6: Neoplastic Lymphomatous Submaculopathy

A 63-year-old Asian Indian female presented with blurring of vision in her left eye. The patient was a diagnosed case of central nervous system (CNS) primary diffuse large B-cell lymphoma (DLBCL). She had received 6 cycles of R-MPV (rituximab, methotrexate (3.5 g/m^2), procarbazine, and vincristine). The visual complaints were noted 6 weeks after cessation of her chemotherapy. Her visual acuity was 20/50 in the right eye and counting fingers at 1 m in the left eye. Fundus examination of the left eye revealed large, hazy indistinct yellowish submacular lesion. Fluorescein angiography showed diffuse hyperfluorescence in the macular region in the late phase. OCT of the left eye revealed a subretinal hyperreflective band which was uniform in configuration (Fig. 16). Magnetic resonance imaging (MRI) of the brain revealed residual CNS disease. The patient was treated with intravitreal methotrexate 400 μg/0.1 ml. Further cycles of systemic chemotherapy were also initiated. Intravitreal methotrexate was repeated after 2 weeks. Four weeks after the first injection, there was a complete regression of the submacular deposition. Her visual acuity in the left eye improved to 20/20 after intravitreal methotrexate and systemic chemotherapy. SS-OCT revealed complete resolution of the hyper-reflective subretinal band with no disruption in that area.

Key Points

- Vitreoretinal lymphoma is an ophthalmic variant of primary central nervous system lymphoma.
- The majority of cases are high-grade diffuse large B-cell lymphoma.
- Typical clinical features include vitreous cells and subretinal pigment epithelial infiltrates.

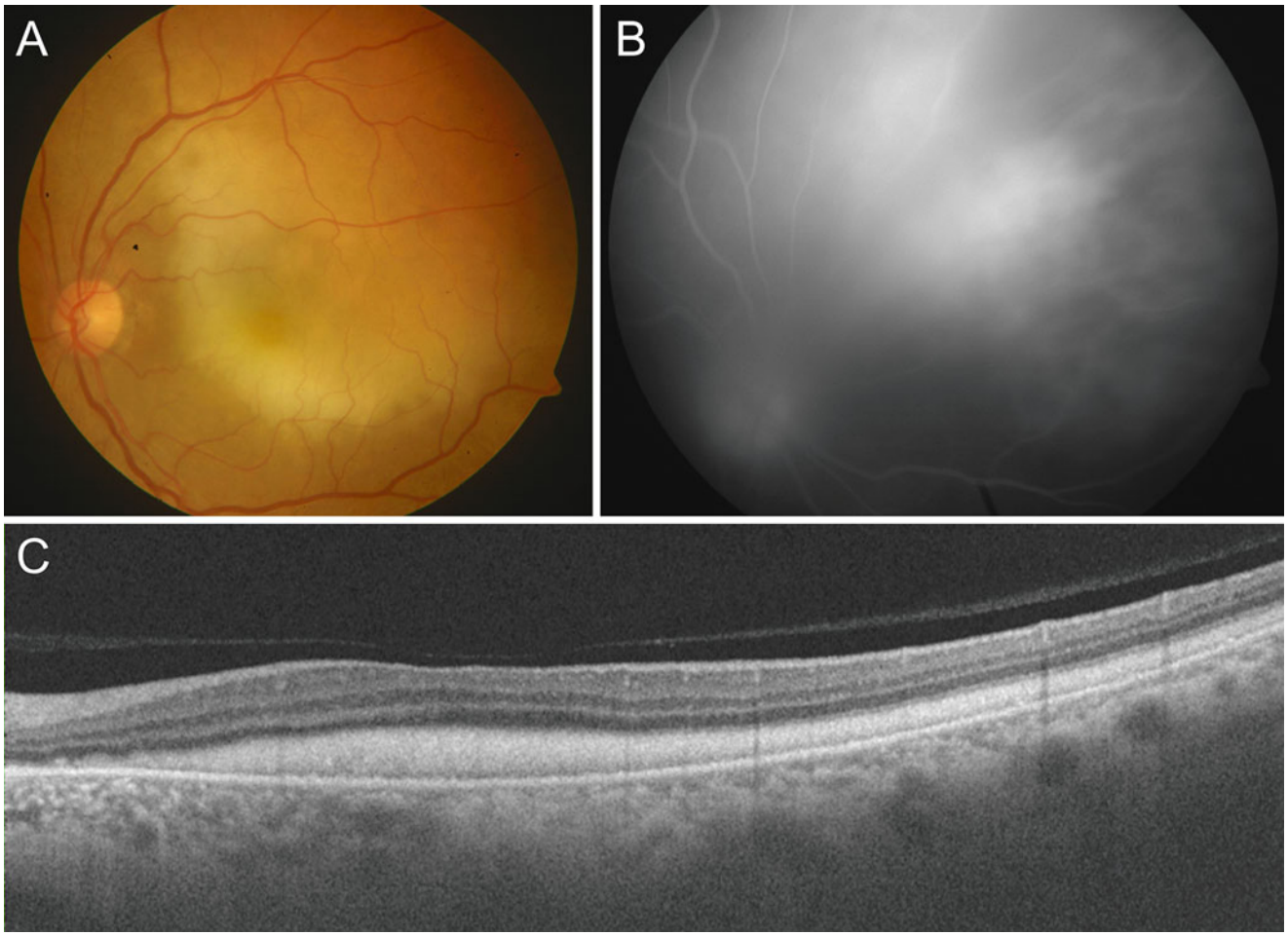

Fig. 16 Fundus photograph of the patient with neoplastic lymphomatous submaculopathy shows the characteristic yellowish subretinal deposits in the macular area (**a**). The fluorescein angiography shows diffuse hyperfluorescence in the macular region (**b**). The scan passing through the macula on optical coherence tomography shows diffuse subretinal yellowish deposition (**c**)

- Biopsy (vitreous or subretinal) is the gold standard for establishing the diagnosis.
- Ancillary techniques including immunohistochemistry, flow cytometry, gene rearrangement studies, and cytokine profiles can be useful in supporting the diagnosis.
- Local ocular treatment may consist of intravitreal chemotherapy (methotrexate), and/or immunotherapy (rituximab for B-cell PVRL), and/or radiation.
- Treatment for PCNSL is complex and consists of various combination regimens which typically include high-dose methotrexate and rituximab.

Suggested Reading

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