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INVITED REVIEW

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INVITED REVIEW

Primary Vitreoretinal Lymphoma in HIV Infection

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ABSTRACT

HIV-related primary vitreoretinal lymphoma (PVRL) is a subset of primary central nervous system lymphoma (PCNSL), which is an AIDS-defining disease. Patients are younger than immunocompetent patients who present with PVRL, and generally have very low CD4-counts. Vitritis with multifocal cream-colored subretinal or sub-retinal pigment epithelial infiltrates, and absence of cystoid macular edema is typical. Vitreous cytology remains the gold standard for diagnosis, but supplementary tests such as flow cytometry and genetic analyses of tumor cells in vitreous samples, and measurement of interleukin-10 level in aqueous or vitreous, may improve diagnostic yields. Diagnosis may also be established by identifying concurrent brain involvement. Treatment includes antiretroviral therapy (ART), systemic chemotherapy (usually methotrexate-based) and local ocular treatment (including intravitreal methotrexate, intravitreal rituximab and ocular external beam radiotherapy). The value of systemic chemotherapy in the absence of associated PCNSL is uncertain. Prognosis is poor but has improved significantly compared to the pre-ART era.

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Primary vitreoretinal lymphoma (PVRL) is a subset of primary central nervous system lymphoma (PCNSL) that is first detected within the eye, and most often is localized to the vitreous and/or retina.[1] It is an aggressive lymphoma that is associated with a poor prognosis, as many patients ultimately develop intracranial involvement.[2] PVRL needs to be differentiated from uveal lymphoma, which affects the choroid, ciliary body or iris, and may occur as a primary malignancy, as well as from a secondary manifestation of systemic lymphoma.[3] In this review we focus on PVRL, and specifically PVRL that occurs in the setting of human immunodeficiency virus (HIV) infection.

PVRL in HIV-positive patients has many similarities to PVRL in immunocompetent individuals. However, several important differences exist in epidemiology, pathogenesis, differential diagnosis and management, which necessitates an adjusted approach in these patients.

Epidemiology

HIV-related PVRL is rare, and the scarce literature on the subject consists of small case series and case reports.[4–12] Even in immunocompetent patients, the incidence of PVRL is low, estimated at approximately 0.021 to 0.048 in 100 000 people.[1,13]

PCNSL is one of the acquired immune deficiency syndrome (AIDS) defining diseases.[14] In the United States, where epidemiology has been well documented, the incidence of HIV-associated PCNSL increased during the AIDS pandemic in the 1990 s, and then declined with the introduction of antiretroviral therapy (ART).[15] However, the risk of PCNSL remains elevated amongst HIV-infected persons, who have a 17-times greater risk of developing the disease compared to the general population.[16] How this increased risk of PCNSL translates to the risk of PVRL has not been studied.

In immunocompetent patients, the median age of presentation with PVRL is between 65 and 70 years, with a reported range of 15–85 years.[2,13] In contrast, HIV-related PVRL presents at a younger age. The median age in published studies is 38 years, with a range of 26–71 years.[4–12] Similar to those with HIV-related PCNSL, patients with HIV-related PVRL are severely immunocompromised at presentation with a median CD4 count of 14 x 10^6/L (range 0–44 x 10^6/L).[4–8,17,18]

Pathogenesis

Histopathologically, PVRL is usually a high-grade, non-Hodgkin's lymphoma of diffuse large B-cell lymphoma subtype, although T-cell rich B-cell lymphomas and T-cell lymphomas have also been described.[2,13,19] The pathogenesis of HIV-related PVRL is poorly understood, but insights may be gained from studies conducted on specimens obtained from patients with PCNSL.

HIV-associated PCNSL is strongly linked to Epstein-Barr virus (EBV) infection. EBV can be detected in virtually all histopathologic specimens and in 80% of cerebrospinal fluid (CSF) specimens of HIV-positive patients with PCNSL.[20,21] In laboratory studies, EBV-infected B-lymphocytes produce latent membrane protein-1 (LMP-1) which upregulates anti-apoptosis proteins (bcl-2, bcl-x) and cell cycle regulation

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proteins (cyclin D2), and inactivates the tumor suppressor gene, p53, causing the cells to proliferate continuously.[22] In immunocompetent persons, this proliferation is held in check by T cell immunity, but in HIV-patients, there is loss of EBV-specific CD4 + T cell function, leading to proliferation that is not regulated and ultimately results in monoclonal malignant transformation.[23]

The role of EBV in HIV-associated PVRL is less well-defined due to the rarity of the disease and paucity of biopsy specimens. Mittra *et al.* published a case report of PVRL in an HIV-positive patient, whose retinal biopsy specimen contained EBV, as detected by *in situ* hybridization.[5] In a case series by Chan *et al.*, EBV was identified on the enucleation specimens of one of the two patients with HIV-related PVRL.[24]

HIV infection may directly promote lymphomagenesis. Vascular endothelial cells are permissive to infection with the virus, and monolayers of endothelial cells expressing HIV Tat and Vpu transgenes support adhesion and growth of malignant B cells isolated from cerebrospinal fluid (CSF) of patients with PCNSL.[25,26]

In almost all cases, PVRL and PCNSL occur exclusively within the central nervous system, including the eye compartment. Immunohistochemical studies of tissue samples from HIV-infected and non-infected persons, have demonstrated the presence of B cell chemokines, including CXCL12 and CXCL13, in local cell populations, as well as lymphomatous B cells, suggesting these proteins contribute to localization of the tumor.[27–30]

Clinical Presentation

At first presentation, PVRL typically masquerades as a chronic intermediate or posterior uveitis. It may show an initial response to corticosteroid therapy, but subsequently becomes resistant to this treatment.[31]

The most common ocular symptoms are floaters and blurred vision; eye redness and pain are rare.[2] Although the visual acuity may be reduced, it is often much better than would be expected from that level of intraocular leukocyte infiltration. The initial presentation is bilateral in 80% of cases.[13,32,33]

On slit-lamp examination, the hallmark of PVRL is vitritis and/or multifocal cream-colored subretinal or sub-retinal pigment epithelial deposits of lymphoma cells (Figure 1a).[34,35] When these deposits are present, the index of suspicion for PVRL should be very high. The vitreous cells tend to not clump, but rather form strings or sheets of cells along the vitreous fibrils in an aurora borealis-type pattern that may obscure details of the posterior pole.[36,37] The subretinal infiltrates vary in size from small punctate lesions to larger plaque-like confluent areas, and may be associated with retinal pigment epithelial changes. Other presentations include retinal infiltration, retinal vasculitis that may be occlusive, and optic disc swelling.[32,33,38]

Cystoid macular edema is usually absent.[32] This is an important diagnostic clue, since patients with inflammatory or infectious uveitis entities with marked vitritis typically have macular edema. The posterior segment findings may be accompanied by mild anterior segment inflammation with

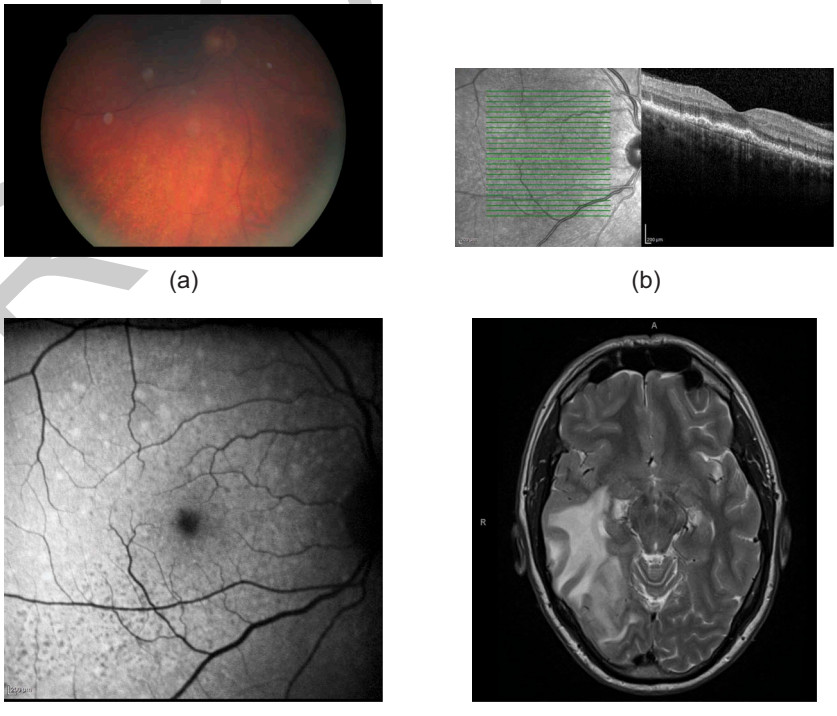

Figure 1. Presentation of a patient with PVRL and concurrent PCNSL. (a). Fundus photograph demonstrating vitreous haze and inferotemporal multiple cream-colored punctate subretinal infiltrates. (b). Spectral domain OCT showing hyperreflective material in the subretinal and sub-RPE space. (c). Fundus autofluorescence demonstrating hyperfluorescent spots corresponding to lymphoma infiltrates, and hypofluorescent spots corresponding to RPE atrophy. (d). Contrasted T1-weighted MRI showing a space-occupying lesion in the left parieto-occipital lobe with vasogenic edema and mild midline shift.

aqueous cells and flare, and keratic precipitates, but posterior synechiae are typically absent.[32,38]

Approximately 40% of immunocompetent patients with PVRL have concurrent PCNSL at presentation.[13] Similarly, concurrent PCNSL in HIV-related PVRL has also been reported, but the frequency of the association is unknown.[4,6,7,12] The most common neurological symptoms are cognitive deterioration and behavioral changes, but patients may also present with headaches, hemiparesis, aphasia, seizure and/or ataxia.[32,39]

Differential Diagnosis

PVRL has a wide differential diagnosis, but for patients with HIV-related PVRL, who are severely immunocompromised, infectious causes are the most important.[40]

When diffuse subretinal infiltration of lymphoma cells occurs, the clinical signs may be easily confused with a viral retinitis. In fact, most of the published cases of HIV-related PVRL were initially misdiagnosed and treated as cytomegalovirus (CMV) retinitis.[6,7,10,12] For those patients in whom the subretinal infiltrates are punctate and multifocal, PVRL may present as a multifocal chorioretinitis, and when perivascular infiltration of lymphoma cells occurs, the tumor may masquerade as a retinal vasculitis. These presentations may then be incorrectly attributed to infections, such as ocular syphilis, tuberculosis or toxoplasmosis, or fungal endophthalmitis.[5,10]

Infectious uveitis and PVRL may also occur concomitantly or sequentially in HIV-positive individuals. Stanton *et al.* reported a patient with simultaneous CMV retinitis and PVRL that were diagnosed on vitreous biopsy cytology, and confirmed at autopsy.[12] Rivero *et al.* described a patient with CMV retinitis that was successfully treated with intravenous ganciclovir, who developed PVRL one year later.[7] At the second presentation, the eyes had more dense vitritis and areas of retinal perivasculitis, which would be atypical of CMV retinitis but could easily be misdiagnosed as an immune reconstitution uveitis.

Diagnosis

PVRL is notoriously difficult to diagnose, particularly in patients with concomitant HIV infection. The average duration of symptoms preceding definitive diagnosis varies between 13 and 24 months in literature published in the 1990 s.[41,42] More recent studies indicate that diagnosis is now achieved in 80% of patients within 6 to 12 months due to an increased awareness of the disease and improved diagnostic techniques.[2,33,34,39]

Ocular Imaging

Ocular imaging may aid considerably when making the diagnosis of PVRL. Optical coherence tomography (OCT) most commonly demonstrates the lymphomatous infiltrates as hyperreflective material in the subretinal space, either as discrete nodules or confluent plaques (Figure 1b). Similarly, hyperreflective material may also be seen in the sub-RPE space, either as RPE undulations or confluent plaques between the retinal pigment epithelium and Bruch's membrane.[43] OCT demonstrates choroidal sparing in PVRL, which is a particularly useful diagnostic feature. Vertical hyperreflective columns that extend between the retinal nerve fiber layer and retinal pigment epithelium have also been described, hypothesized to represent early micro-infiltration extending from the retinal vessels into the subretinal and subretinal pigment epithelial spaces, where the lymphoma cells subsequently proliferate.[44]

Fundus fluorescein angiography may demonstrate hypofluorescence in areas of lymphomatous infiltration, creating a "leopard-spot" appearance, and window defects in areas of retinal pigment epithelial atrophy.[45,46] On fundus autofluorescence the inverse is observed, with hyperfluorescent spots corresponding to the tumor infiltrates, and hypofluorescent areas corresponding to the epithelial atrophy (Figure 1c).[47]

Diagnostic Vitrectomy

The gold standard for PVRL diagnosis in HIV-positive patients, like HIV-negative patients, is the identification of PVRL cells on ocular samples, which may include vitreous or chorioretinal biopsy, or rarely, an enucleated globe. Corticosteroid treatment should be held for approximately one month prior to vitrectomy to minimize the lympholytic effect that may reduce cell yield.[48,49]

Typically, a 23- or 25-gauge 3-port diagnostic vitrectomy is performed, and 1–2 ml of undiluted vitreous is obtained before the infusion is opened. Lymphoma cells are extremely fragile and degenerate quickly. Therefore, a low vitrector cutrate with gentle manual aspiration should be used, and the unfixed sample should be delivered to the cytologist within one hour.[49] If a delay is anticipated, the sample should be placed in a mild fixative such as Hepes-glutamic acid buffer mediated Organic solvent Protection Effect (HOPE), which is preferable to alcohol or formalin fixation.[50,51] Many vitreoretinal surgeons also provide dilute vitreous and the vitreous cassette as additional samples for pathological testing.[52]

Prior experience in evaluating cytopathological specimens is valuable, since it is easy to miss the small numbers of malignant lymphoma cells amongst the larger numbers of reactive lymphocytes and degenerate cells that are invariably present (Figure 2). Regardless, the sensitivity of vitreous cytology alone in the diagnosis of PVRL may be as low as 30%, and many patients require more than one diagnostic vitrectomy.[13,53] Histopathology of a chorioretinal biopsy has a higher sensitivity, but also a considerably higher ocular morbidity than vitrectomy, and is reserved for exceptional situations.[54]

In recent years, several supplementary tests on ocular samples have become extremely beneficial adjuncts to reaching a diagnosis of PVRL. Interleukin (IL)-10 is a cytokine expressed by malignant B-cells, whereas inflammatory cells produce IL-6. Thus, an elevated IL-10 level, or a relatively high IL-10:IL-6 ratio in the aqueous or vitreous fluid is quite suggestive, albeit not diagnostic, of PVRL.[55,56] The identification of immunoglobulin heavy chain gene rearrangements by PCR testing on vitreous samples or chorioretinal biopsy specimens have also proven useful,[55,57] and several groups have demonstrated that a high percentage of PVRL harbor a mutation in the *MYD88* gene, which may be another helpful

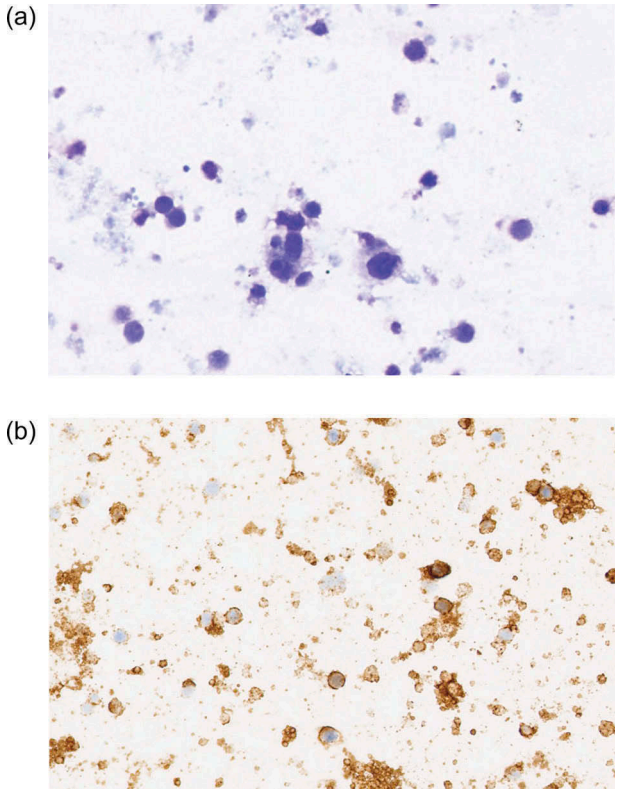

Figure 2. Vitreous biopsy of a patient with PVRL. (a). Mai-Grunewald Giemsa (MGG) stain of the cytospin of a vitrectomy sample demonstrating atypical lymphocytic blasts on a background of lytic cells. The atypical blasts are pleomorphic with varying-sized nuclei and with narrow cytoplasmic rims. (b). CD20 stain using DAB chromogen highlighting the atypical cells as neoplastic B-cells. The background lytic cells are also positive with this stain.

diagnostic aid.[58–60] Although EBV infection has been associated with PVRL, role of PCR for EBV on vitreous as an adjunct to the diagnosis of HIV-related PVRL has not been established. However, the diagnostic vitrectomy provides an important opportunity to rule out the presence of intraocular infection in HIV-positive patients.

Evaluation for PCNSL

Due to the strong association between PVRL and PCNSL, all HIV-positive patients suspected of having PVRL should undergo brain magnetic resonance imaging (MRI), as well as CSF analysis for cytology, flow cytometry and EBV PCR.[61]

On MRI, HIV-related PCNSL presents with single or multiple supratentorial lesions, most commonly with ring enhancement (Figure 1d).[62] If lesions are found, stereotactic brain biopsy may be used to establish the diagnosis of PCNSL with concurrent PVRL. However, since this procedure has a high morbidity and mortality in these severely immunocompromised HIV patients, vitreous biopsy is often the diagnostic procedure of choice.[63]

Positive CSF cytology and/or flow cytometry identifying lymphoma cells is diagnostic of PCNSL and could obviate the need for diagnostic vitrectomy.[61] A high titer of EBV on CSF PCR is highly suggestive, but not diagnostic, of PCNSL and may be used as an indication for diagnostic vitrectomy, even with normal neuroimaging.[4] Notably, HIV-positive patients who have previously been treated with ganciclovir may have a false-negative CSF PCR for EBV in the presence of PCNSL.[64]

Treatment

The optimum treatment of HIV-related PVRL remains undefined, and the limited evidence on the topic is derived from retrospective case series. Current approaches involve the combination of ART and local ocular therapy (intravitreal methotrexate, intravitreal rituximab or ocular external beam radiation), and in selected cases, systemic chemotherapy.[65–69]

ART forms a critical component of any successful treatment regime in HIV-related PVRL with or without PCNSL. Improvements in CD4 count and reduction in HIV viral load are associated with better disease control and improved overall survival.[70]

HIV-positive patients with PVRL and associated PCNSL should be treated with systemic chemotherapy, as well as ART and local ocular chemotherapy or radiotherapy.[39] Following the British HIV Association Guidelines, patients who are sufficiently fit should receive a high-dose methotrexate-containing chemotherapy regimen as first-line systemic treatment.[61,71,72] Whole-brain radiotherapy has fallen out of favor due to high recurrence rates and neuro-cognitive adverse effects, and is reserved for palliative cases, or those patients in whom the risks of toxicity from high-dose chemotherapy is considered unacceptable.[73] Although rituximab has effectiveness as a systemic treatment in HIV-related systemic non-Hodgkin's lymphomas, it does not appear to have similar therapeutic activity in PCNSL and is associated with high rates of toxicity in HIV-positive patients with low CD4 counts.[74,75]

HIV-positive patients with PVRL without associated PCNSL should be treated with ART and local ocular treatment, but the addition of systemic chemotherapy remains uncertain. The local approach minimizes systemic toxicity, which is a major advantage in HIV-positive individuals, but a concern is that potential subclinical sites of PCNSL remain untreated and could lead to earlier CNS involvement with reduced survival time.[66] In one large early case series of immunocompetent patients, the International PCNSL Collaborative Group found that the use of local ocular treatment alone did not compromise disease control or overall survival.[2] In contrast, several small recent studies suggest that omission of systemic therapy may lead to earlier CNS involvement.[76,77]

It is unclear whether the addition of EBV treatment in HIV-related PVRL may have value. Small retrospective studies on HIV-associated PCNSL utilized IL-2 to induce EBV to break from latency in the tumor cells and render the virus susceptible to ganciclovir or foscarnet treatment, and showed potential benefit.[78,79]

Prognosis

Although not specifically addressed in the literature, the prognosis of HIV-related PVRL may be worse than that of PVRL in immunocompetent patients, with CNS involvement or other AIDS-related illnesses being the most common sources of mortality.[80] However, prognosis has improved significantly

compared to the pre-ART era, when survival was only a few months.[4–7,12] Recent studies of HIV-related PCNSL have shown mean overall survival of up to 60 months.[61,72,81]

Conclusion

HIV-related PVRL is a rare condition, which is difficult to diagnose and has a poor prognosis. The ophthalmologist should always consider this diagnosis in HIV-positive patients with severe immunosuppression who present with undifferentiated intermediate or posterior uveitis. Large multinational collaborative clinical studies are needed to consolidate optimal diagnostic investigations and treatment regimens for this serious condition.

Declaration of interest

Q7 The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper

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