Diagnostic Testing of Primary Vitreo-Retinal Lymphoma

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Abstract: Primary Vitreo-Retinal Lymphoma (PVRL) or Primary Intra-Ocular Lymphoma (PIOL) is a rare malignancy often seen as a context of primary central nervous system lymphoma (PCNSL). This article reviews the diagnostic approach of PVRL.

The techniques for diagnosing PVRL from ocular biopsy specimens includes cytologic analysis, immuno-cytochemistry, flow-cytometry, polymerase chain reaction (PCR) to detect V-J Ig gene re-arrangements, and analysis of IL6, IL10 in aqueous or vitreous fluid.

Currently, cytology in combination with immunohistochemistry is considered the gold standard for the diagnosis of PVRL. But ancillary tests including IgH, TCR gene rearrangements and cytokine analysis are reliable biomarkers for B and T cell PVRL. Genetic testing with t(14:18) detection may show promising results in future.

Keywords: Primary vitreoretinal lymphoma, intraocular lymphoma, diagnosis, CNS lymphoma.

INTRODUCTION

Several types of lymphomas can involve the eyes. These include systemic non-Hodgkin's lymphoma or systemic Hodgkin's disease, both of which can metastasize to the eye. However, intraocular Hodgkin's disease is exceptionally rare, with only a handful of reported cases [1]. The most common lymphoma of the eye is non-Hodgkins B-lymphocyte lymphoma involving the eye and the central nervous system (CNS). Primary vitreoretinal lymphoma (PVRL), also known as primary intraocular lymphoma (PIOL), is a rare subset of primary central nervous system lymphoma (PCNSL).

Intraocular lymphoma may arise in different parts of the eye, expressing various clinical manifestations. They can be divided into four major groups [28]:

(1) PVRL is the most common type, which is high grade, aggressive non-Hodgkin's lymphoma, usually of B cell type.

(2) Primary choroidal lymphoma is typically low grade B cell lymphoma, similar to extranodal marginal zone B cell lymphoma elsewhere in the body. It does not have any association with CNS disease.

(3) Primary iridal lymphoma is a rare malignancy that can be either B or T cell type. Interestingly B and T cell lymphomas arise in the iris in equal measures.

(4) Secondary uveal lymphoma, is usually of diffuse large B cell lymphoma type (DLBCL)

HISTORY

Intraocular-CNS lymphoma, previously termed reticulum cell sarcoma or microgliomatosis, was first described by Givner in 1955 [2]**.** In the earlier studies, definitive diagnosis of intraocular-CNS lymphoma was based on histopathologic examination of enucleated eyes, or brain biopsy and studies at autopsy. In 1975, Klingele and Hogan published the first report of the use of vitreous biopsy specimen for its diagnosis, which has since become a widely performed procedure [2-4].

EPIDEMIOLOGY

The incidence of PVRL is difficult to estimate because of the lack of a central database for this disease. The incidence for all eye and orbital malignancies was 0.8 per 100,000 person years in 2007, and were more common in patients aged ≥ 50 years [5]. From 1999 to 2002 there were approximately 100 new cases of PVRL reported in the United States [6]. According to another report, the incidence of intraocular-CNS lymphoma has trebled over the last decade, an increase not correlated with a correspondingly large increase in known predisposing factors [7].

There are no known racial or ethnic associations. Among immunocompetent individuals, the peak incidence of PVRL is in 5th to 7th decades of life. In immunocompromised patients such as those infected with human immune deficiency virus, PVRL tends to occur in a younger population [8-10].

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Better data exist for PCNSL. The incidence recorded between 2004 to 2007 was 0.46 per 100,000 person years, with a male to female ratio of 1.38 [11].

The remainder of this review will focus on the diagnostic approach of PVRL.

CLINICAL MANIFESTATIONS

Systemic Features

PVRL is commonly associated with CNS lymphoma, which can manifest before, concurrent with, or after ocular diagnosis. It has been estimated in multiple case series that intraocular involvement occurs in 15-25% cases of PCNSL [12-14].

In a series of 32 patients with intraocular lymphoma, 62% had co-existent CNS lymphoma [15]. In another study, 11 of 12 patients (92%) showed CNS involvement [16]. Nodal or visceral lymphoma developed in a minority of PVRL patients [15, 17]. It has also been reported that 65-90% of patients presenting with PVRL subsequently developed CNS lymphoma within 29 months [11].

Because intraocular-CNS lymphoma is more likely to involve the deeper brain structures than the cerebral cortex, seizures and motor symptoms, although they do occur, are less common than in patients with other kinds of brain tumors. Therefore, evaluation of patients suspected of PVRL should always include careful medical history, focusing on cognitive changes, such as alterations in personality and level of alertness are common at the time of presentation. CNS findings, such as headaches, confusion, focal neurological deficit, diplopia, imbalance, right-left confusion and difficulty with gait have been reported [18]. New onset of seizures is also a strong indication of CNS involvement. Thus, careful history taking and thorough neurologic examination are vitally important.

Ophthalmic Features

Insidious onset and delay in the diagnosis of PVRL is common. Patients may be asymptomatic or may report blurred vision and floaters. A variety of clinical ophthalmic signs have been reported [11, 19, 20]. Most of the cases have little anterior segment inflammation. The eye is usually white and quiet. Reactive T lymphocytes may contribute to iritis and even keratic precipitates. Iris nodules rarely may be present.

The most classic findings are those of the posterior segment, including white cell infiltration of the vitreous and sub-retinal pigment epithelial deposits composed of infiltrating lymphoma cells. The vitreous cells may appear larger than the ordinary inflammatory cells. The vitreous cells are reported to clump into reactive clusters causing aurora borealis appearance as the cells line along the vitreous fibrils. Vitreous haze is usually less than expected. Other retinal findings include perivascular sheathing, and sub-retinal and intra-retinal white cell infiltration mimicking retinitis. Choroidal mass can occasionally be seen, but this is most typical of secondary intraocular lymphoma [8]. RPE hyperplasia has also been reported [21]. More commonly, lymphoma cells grow along the Bruch's membrane and can cause focal or solid detachment of RPE. Leopard-spot pigmentation occurs with early or diffuse involvement as cells proliferate under the retina in large sheets of yellow white cells; it is better appreciated on fluorescein angiogram (FA) [22].

Differential Diagnosis

PVRL is one of the masquerade syndromes of uveitis because of its non-specific presentation. The differential diagnosis of PVRL includes acute retinal necrosis (ARN), cytomegalovirus (CMV) retinitis, retino-choroidal toxoplasmosis, syphilitic retinitis, pneumocystis choroiditis, Vogt Koyanagi Harada (VKH) syndrome, Acute Posterior Multifocal Placoid Pigment Epitheliopathy (APMPPE), benign vitritis, sympathetic ophthalmia, Whipples disease or other malignant or infectious uveitides [23-26].

DIAGNOSTIC TESTS

The cornerstones of diagnosis of PVRL are thorough CNS evaluation [including a history and neurologic examination, as well as magnetic resonance imaging (MRI)], CNS cytology and diagnostic vitrectomy.

Non-Specific Tests

FA often shows clusters of round hyper- or hypofluorescent lesions ~100 μm in size in early and late phases [28]. FA may also reveal vascular leakage, indistinguishable from uveitis. It may also show diffuse RPE alterations suggestive of PVRL. CME, which is commonly found in non-lymphomatous uveitis, is rare in PVRL.

Fundus auto fluorescence may demonstrate multiple weak or bright hyperfluorescent spots or hypofluorescent areas [27].

Optical coherence tomography (OCT) of the retina may show nodular hyper-reflective lesions at the level of RPE or sub-RPE space [28]. Farzin Forooghian *et al*. have reported a case report of usage of high definition spectral domain OCT (HD SD OCT) in prompt decision to perform diagnostic PPV leading to diagnosis of PVRL [29]. In a recent report, Yeh and Wilson described the SD OCT features of a patient with PVRL with clear visualization of fundus detail. The sub-retinal lesions were seen to resolve on SD OCT following treatment. Thus, in addition to supporting the diagnosis of PVRL, SD OCT can be useful to monitor response to treatment [30].

B-scan ultrasonography has a limited role in evaluating PVRL, except in cases with elevated mass, where ultrasound may help to rule out other conditions, such as, uveal melanoma, metastatic cancer, or choroidal hemangioma [26].

Systemic Evaluation

Any recent onset CNS symptoms or findings on neurologic examination raise the suspicion of CNS spread. An MRI is warranted, however, in all patients suspected of having CNS lymphoma, even if history and examination are negative. On MRI the appearance of PCNSL is characteristic, with the tumor being supratentorial in 50% of cases [31]. Unlike brain metastasis and malignant gliomas, which show ring enhancement on administration of contrast, these lesions characteristically have dense and diffuse enhancement with distinct borders. Testing for HIV is also required when warranted.

A lumbar puncture must be performed on all patients suspected of having intraocular-CNS lymphoma, regardless of the results of the neurologic evaluation, since this is the least invasive form of tissue testing, and results may obviate the need for further invasive testing. Lumbar puncture is estimated to be positive in about 25% of cases with documented brain involvement on neuroimaging, and a much smaller percentage of patients with no brain involvement on neuroimaging [32]. Ten milliliters of cerebrospinal fluid (CSF) is appropriate for cytology. A repeat lumbar puncture may be required for diagnosis. Lymphoma cells are extremely fragile, and to optimize results, specimens should be transported to the laboratory immediately. Lumbar puncture can be negative in a patient with intraocular-CNS lymphoma, since CNS disease may lag ocular disease by months to years [33]. Even in the presence of CNS involvement, lumbar puncture can give false-negative results as a consequence of mishandling of the specimens or employment of systemic corticosteroid therapy prior to the diagnostic vitrectomy; corticosteroids are cytolytic for lymphocytes and for intraocular-CNS lymphoma cells and may even cause intraocular-CNS lymphoma lesions to decrease in size [59].

Although physical examination and ocular imaging are useful adjuncts, the gold standard for PVRL diagnosis has been identification of PVRL cells in the eye. This requires surgical intervention including diagnostic vitrectomy and/or diagnostic retinal or chorioretinal biopsy.

Laboratory Diagnosis of PVRL; Diagnostic Vitrectomy

Cytology

Morphological evidence of PVRL is characterized by large, anaplastic, atypical lymphoid cells with large irregular, lobulated nuclei, coarse chromatin, prominent nucleoli and scanty basophilic cytoplasm. Mitoses may be present, rare or absent [39].

Rajgopal and Harbour [26] reported that when an expert cytopathologist is available, the gold standard remains the cytologic examination. When characteristic lymphoma cells are found in the biopsy sample, the specificity is quite high [36-38]. According to a study reported by Davis, this standard is controversial and depends on local expertise [35].

Much of the challenge in diagnosing PVRL arises from a paucity of lymphoma cells and abundance of reactive lymphocytes. Also, PVRL cells may easily undergo necrosis, so careful and prompt processing of the specimen is of critical importance. To increase the diagnostic yield, it is critical to immediately place the specimen on ice and hand carry it to the pathology laboratory for analysis, and to notify the cytopathologist in advance so that specimen can be immediately processed and analysed. Even so, multiple vitreous samples may be needed to make a definitive diagnosis [40-42].

Molecular Analysis

Monoclonality, either a B cell population, with κ or λ restriction or a T cell population with T cell receptor (TCR) is observed using immunohistochemistry or flow cytometry. Missotten *et al*, have recently reported that multicolor flowcytometric analysis had 82.4% sensitivity and 100% specificity in patients with suspected

intraocular lymphoma. This is comparable to reported IL-10-IL-6 testing sensitivity of 0.8 and sensitivity of 0.65 to 0.95 by immunoglobulin heavy chain (IgH) gene rearrangement testing in clinical cohorts [58].

Immunohistochemistry is helpful in showing CD 20+ cells, which in general are rarely a part of non malignant autoimmune uveitis [28]. According to a study conducted at National Eye Institute, by Wang *et al*, molecular analysis of IgH and TCR gene rearrangements using microdissection and polymerase chain reaction (PCR) technique has the highest sensitivity, specificity, predictive value and efficiency for the diagnosis of PVRL, when compared with morphological identification of atypical lymphoid cells or IL-10-IL-6 ratio analysis [34]. In another study, flow cytometry identified intraocular lymphoma in 7 of 10 patients as compared to only three diagnosed by cytology [43]. In an additional study, it provided corroborative support in six patients diagnosed by both modalities [44]. More recently, Davis and colleagues have reported that CD-22+ B lymphocytes comprising greater than or equal to 20% of total cells had a positive predictive value of 88% for lymphoma, while a CD4:CD8 T lymphocyte ratio of greater than 4 had a similarly positive predictive value of 70% for immunologically mediated uveitis [45].

Moreover, detection of IgH or TCR gene rearrangements in micro dissected atypical lymphoid cells greatly facilitates the diagnosis and classification of PVRL with only a small number of lymphoma cells, whereas routine cytological and cytokine analysis may not be able to provide such information from small specimens. Because B and T cell lymphomas respond differently to certain therapeutic agents such as rituximab (monoclonal anti-CD 20 antibody), which is effective in B cell lymphoma [46], oncologists can choose the most effective targeted treatment for each individual PVRL patient based on specific lymphoid cell origin.

Cytokine Analysis

Elevation of IL-10 levels in ocular fluids and/or IL-10:IL-6 ratio > 1 is highly suggestive but not diagnostic of, B cell lymphoma [48-50], although T cell PVRL may also be associated with higher IL-10 levels in the vitreous [51]. Aqueous IL-10 levels are reported to correlate with the clinical response to local chemotherapy [28]. Specifically, elevated relative ratios of IL-10 to IL-6 were found in 24 of 31 ocular lymphoma cases, supporting the diagnosis of lymphoma [52]. However, a study at Massachusetts Eye Research and Surgery Institution shows that IL-10 can be detected even in vitreous specimens of patients with non-neoplastic uveitis and that, conversely, IL-10 levels are not always elevated in patients with intraocular-CNS lymphoma [53]. Thus high IL-10 levels are suggestive, but not diagnostic of lymphoma, with vitreous biopsy cytopathology still being the only definitive means of diagnosing ocular involvement in intraocular-CNS lymphoma. However, as an adjunct that is performed on the supernatant, pipetted off after spinning the cells, which does not require additional vitreous specimen, but can instead be performed on the residuum remaining after the cytopathology specimen is removed, a high ratio of IL-10 to IL-6 may provide additional supportive information in confirming the diagnosis.

The author [47] has previously reported a positive response to intravenous and intravitreal methotrexate in a patient reported to have pars plana vitrectomy (PPV) cytology negative for lymphoma cells but positive for monoclonality with IgH gene rearrangements, and high IL-10 to IL-6 ratio. Therapy was initially denied because of lack of cytologic proof for the diagnosis of lymphoma. The patient subsequently, over a period of 6 months, developed a constellation of neurological symptoms which eventually prompted a brain biopsy. This showed unequivocal lymphoma. High dose intravenous methotrexate, coupled with bilateral multiple intravitreal methotrexate resulted in remission. According to this case report, it is mandatory that if there is a strong clinical suspicion of lymphoma, and all other possible etiologies have been excluded, and adjunctive examinations provide evidence for lymphoma, the patient should be afforded the opportunity to decide between observation and aggressive lymphoma treatment. Furthermore, demonstration of monoclonality with IgH rearrangement together with IL level analysis support the diagnosis of PIOL with a high degree of certainty and should lead to MTX based therapy, despite absent malignant cells in the vitreal biopsy.

Genetic Tests

Several investigators have identified the t(14;18) locus by PCR in ocular specimens of patients with intraocular-CNS lymphoma. This translocation brings the antiapoptotic *BCL2* gene under the control of the IgH enhancer causing deregulated expression of the antiapoptotic *BCL2* gene. Detection of the *BCL2* gene

in an intraocular lymphoma specimen can be used as a marker for the presence of malignant cells and of monoclonality [54, 55]. Since microdissection allows for the procurement of very specific small populations of cells from larger histologic specimens, combining microdissection with PCR amplification for a marker of malignancy, such as the t(14;18) translocation, may be a powerful tool in the diagnosis of intraocular lymphoma, as well as providing clues to its pathogenesis. However, this translocation is not present in all cases of primary intraocular lymphoma. Reports suggest that it may be present in 40–60% of cases, and so even though it is a useful and powerful adjunct in the diagnosis of lymphoma, its absence does not rule out primary intraocular lymphoma [56, 57].

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