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Diagnostic Evaluation in Primary Intraocular Lymphoma : A Review

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ABSTRACT

Background: Although very rare, there has been an increasing incidence of primary intraocular lymphoma (PIOL) in recent years. In addition, PIOL is often missed in diagnosis and is often treated without a standard, resulting in frequent recurrence and involvement of the central nervous system. Investigations have an important role in establishing the diagnosis of this case.
Contents: The latest diagnostic supporting tests applied to PIOL are optical coherence tomography, fundus fluorescence angiography, indocyanine green angiography, fundal autofluorescence, ocular ultrasonography, vitrectomy sampling, and head MRI. Histopathological examination with Giemsa stain or hematoxylin-eosin is the gold standard in this case. Molecular studies and genetics have also recently played an important role in supporting PIOL diagnosis.
Conclusion: PIOL has similarities with other vitreoretinal and uveal tract diseases, so it is not easy to diagnose. High clinical suspicion needs to be followed up with the latest investigations to establish PIOL diagnosis.

Keywords: Diagnostic approach, intraocular lymphoma, primary

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Introduction

Primary Intraocular Lymphoma (PIOL) or often called primary vitreoretinal lymphoma (PVRL), is a neoplasm, most commonly B-cell, and rarely T-cell, that originates from or initially arises in the subretinal pigment epithelium (RPE), retina, and vitreous.[1-4] Definitions PIOL is a subset of PCNSL and a heterogeneous group of malignant lymphocytic neoplasms affecting the retina with or without vitreous or optic nerve involvement and evidence of brain or cerebrospinal fluid involvement. Hodgkin's lymphoma is from a large diffuse network of B-cell histologic types, and the difference is that PIOL is a subtype of primary central nervous system lymphoma (PCNSL).[6] Once there is a manifestation of central nervous system involvement, the disease entity changes to PCNSL.[7]

Although primary orbital tumours are very rare compared to other tumours, this subtype of PIOL is the most common primary ocular lymphoma malignancy.[8] In the United States, the incidence of PCNSL was 0.46 per 100,000 population in the period 2004-2007. The incidence was higher in males (0.54) than females (0.39), with a male: female ratio of 1.38. Although there are contradictory reports that intraocular lymphoma is more common in women.[9] PCNSL with ocular involvement and PIOL is estimated to account for 1% of non-Hodgkin's lymphomas, 1% of intracranial tumours, and ocular involvement and PIOL are estimated to account for 1% of non-Hodgkin's lymphoma, 1% of intracranial tumours, and <1% of intraocular tumours.10 There is a trend of increasing incidence of PIOL in recent years which may be due to the increase in cases of immunodeficiency, immunosuppression, and the development of diagnostic tools.[7]

PIOL commonly presents in older patients as non-specific, chronic and relapsing uveitis known as Masquerade's syndrome that does not respond to steroid therapy, making the diagnosis sometimes difficult.[11] Eye disorders are usually bilateral (64-83% of cases).[12] Although Unilateral involvement is present in 30% of cases but may be bilateral in about 85% of patients. Approximately 25% of patients with PCNSL will have a PIOL, and at least 60% of patients presenting with a PIOL will have central nervous system disease. The patient's most frequent symptoms are decreased visual acuity and floaters, and infrequent complaints include redness of the eye, photophobia, and ocular pain.[13]

The gold standard in establishing PIOL diagnosis is the finding of lymphoma cells in the intraocular compartment by histopathological examination.[7] However, starting the diagnostic procedure must be based on a high clinical suspicion. Some clinical indications that increase the suspicion of PIOL according to Chan et al. (2011)[10] are older adults with

non-infectious uveitis who do not respond to inflammatory therapy, visual acuity that is not correlated and is better than the severity of the vitreous found on fundoscopic examination, and there are a characteristic yellow-white subretinal infiltrate lesion on fundoscopic examination. This article will then review further investigations to establish the diagnosis of PIOL.

Optical Coherence Tomography (OCT)

Direct infiltration of the retina by lymphoma cells with focal proliferation creates a semi-opaque appearance that appears homogeneous on optical coherence tomography (OCT). Infiltrating lymphomatoma can be seen as a hyperreflective signal in the form of dots, bands and nodules at or above the RPE with the spectral-domain OCT2 (Figure 1). This hyperreflective signal must be distinguished from age-related macular degeneration or diabetic macular oedema.[14,15] Granular subretinal lesions (between Bruch's membrane and the retinal pigment epithelium) may be seen when a subretinal lesion is present. OCT can be used to monitor lymphoma progression or regression.[16]

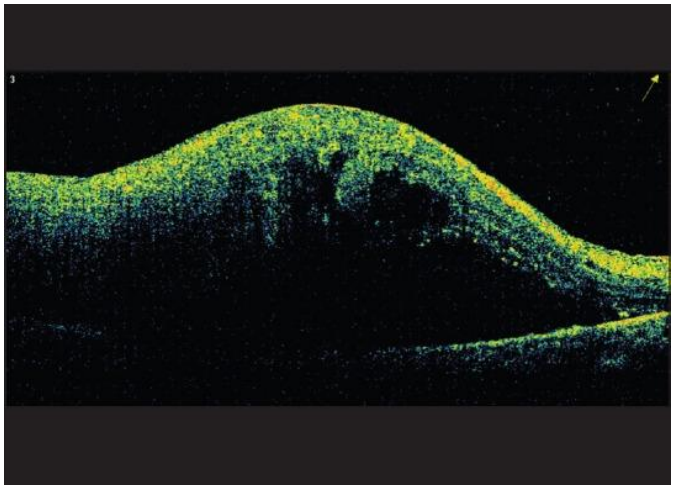

Figure 1. Overview of Subretinal Lymphoma Cell Infiltration on OCT imaging.[7]

Fundus Flourescence Angiography (FFA) and Indocyanine Green Angiography (ICGA)

FFA can be used to demonstrate hypofluorescence in the early to late stages of PIOL involving the outermost retinal layer (Fig. 2). Other signs that can be seen on this examination are punctuated hyperfluorescent window defects, round hyperfluorescent lesions, vasculitis, fluorescence leakage along the retinal veins, and periarteriolar staining.[17,18] In the early stages of PIOL, hypofluorescent lesions will appear on ICGA examination but become less visible in the late stages of PIOL.[19] The FFA and ICGA examinations simultaneously had sensitivity and specificity values of 89% and 85%, respectively.

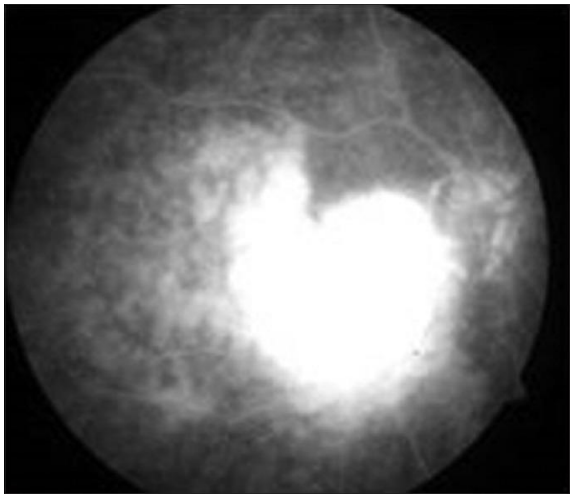

Figure 2 Small hypofluorescent lesion in the lesion area with fluorescent leak seen in late stage PIOL on FFA examination.[21]

Fundal Autoflorescence

This examination is to determine where the lymphoma infiltrating the RPE is located. On fundal autofluorescence (FAF) examination, the typical finding in PIOL cases is a granular pattern consisting of hyperautofluorescent patches surrounded by a hypoautofluorescent ring as shown in Figure 3. In the lymphomatous infiltration in the sub-RPE space, a hyperautofluorescent spot is seen surrounded by a hypoautofluorescent ring. On the other hand, if the lymphomatous infiltrate is above the RPE, it will produce a granular pattern of hypoautofluorescent dots surrounded by a hyperautofluorescent ring. The hypofluorescent spots (leopard spots) seen in FFA are identical to the hyperautofluorescent spots in FAF.[19,22]

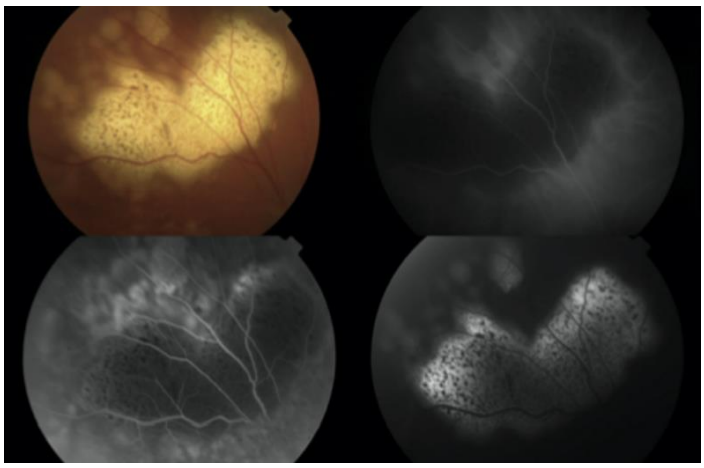

Figure 3. PIOL lesion on fundus autofluorescence.[22]

Ultrasound B-Scan

Ocular ultrasonography is not specific for PIOL but can be used in cases where the posterior segment is difficult to visualize. Ultrasound findings suggesting a PIOL include vitreous debris, retinal detachment, enhancement of the chorioretinal lesion, and optic nerve widening, as shown in Figure 4.[19] B-scan ultrasound allows objective measurements with good repeatability, descriptive and easy follow-up. Therefore, ultrasonographic B scan of the eye should provide the basis for clinical diagnosis and follow-up of PCNSL with intraocular involvement as a cost-effective method with high accuracy and efficiency for diseases with high and low malignancy rates.[23]

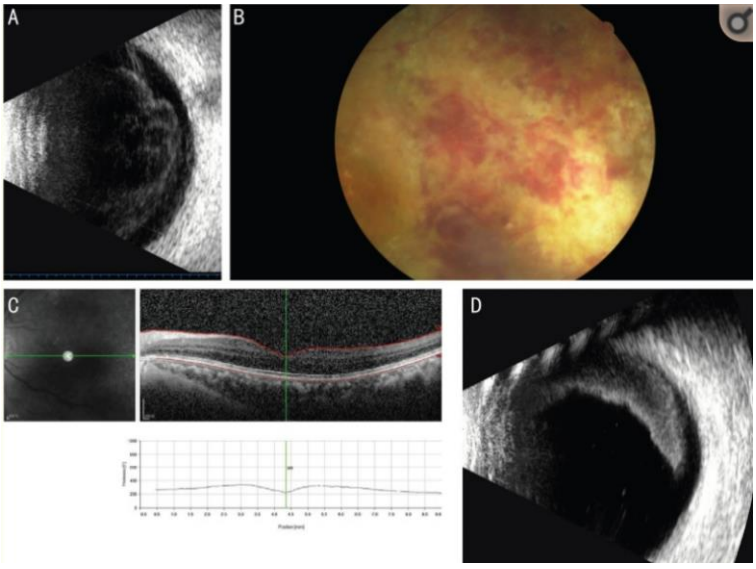

Figure 4. PIOL lesions on Ultrasound B scan and OCT. A: The punctate echo group with moderate and high peaks was observed on ultrasound B-scan of the eye; B: Yellow deposits on the retina observed on fundoscopy; C: Normal central foveal thickness detected by OCT scan; D: Suspected eccentric mass observed on ultrasound but not on slit-lamp examination.[23]

Sampling Vitrectomy

Two methods can be used to perform vitrectomy sampling: vitreous biopsy and pars plana vitrectomy (Pars Plana Vitrectomy, PPV). The vitreous biopsy takes a sample from the central vitreous of 1-2 ml of the undiluted specimen while in PPV samples from the central vitreous and cortical 50-100 ml of diluted vitrectomy cassette fluid.[24] To ensure adequate and maximum cellular viability, samples should be taken to the laboratory without delay within 30 minutes of sampling. Suppose the sample cannot be brought to the laboratory. In that case, fixatives such as ethanol, methanol, propranolol solutions (8:1:1 ratio), Shandon cytofix or HEPES-glutamic acid-mediated organic-solvent protection effect (HOPE) buffer can be used.

PPV examination has advantages over vitreous biopsy because it can maximize sample volume, improve patient vision by cleaning vitreous debris, and PPV's greater cellularity than vitreous biopsy, allowing additional tests such as immunohistochemistry, DNA extraction for monoclonal studies and polymerase chain reaction (PCR) to be performed.[24]

Head Magnetic Resonance Imaging (MRI)

Since PIOL is part of PCNSL, it is necessary to perform a systemic neurologic examination to exclude the possibility of central nervous system involvement. This aim can be done by magnetic resonance imaging (MRI) of the brain, examining the cerebrospinal fluid, and a brain biopsy.[7] CNS lesions that may be seen on brain MRI are uni- or multi-focal hypodense on T1-weighted and hyperdense on TRI-weighted MRI as shown in Figure 5.[19,25] Cerebrospinal fluid examination for the detection of lymphoma is important to avoid invasive diagnostic procedures such as vitrectomy. 25% of patients with CNS lesions have positive cerebrospinal fluid cytology.[26] Imaging-guided brain biopsy should be performed in patients with suspicious MRI lesions but negative CSF cytology.[7]

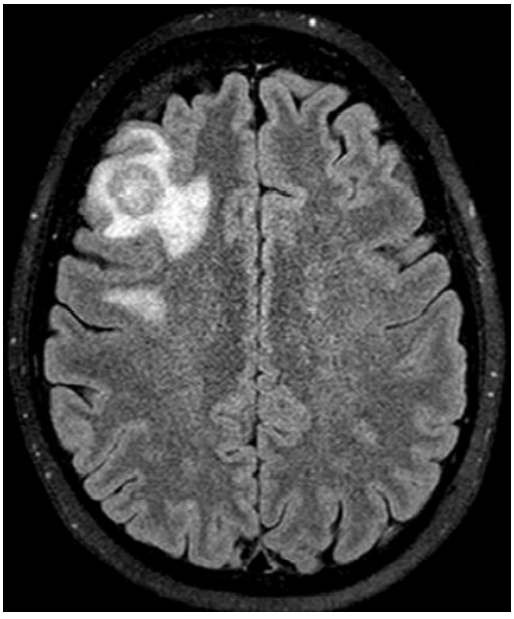

Figure 5. MRI image of PIOL with CNS involvement, showing a mass in the right medial frontal gyrus accompanied by vasogenic oedema.[27]

Standard Histopathologic Examination

Standard histopathological examination of PIOL using a light microscope. The most

recommended tissue stains are Giemsa or Diff-Quick because they can give a better picture of the characteristics of lymphoma cells. However, other stains such as Papanicolou or Hematoxylin-eosin can also be used. Under light microscopy, PIOL or PVRL cells are seen clustered in the sub-RPE space and appear as large lymphoid cells with little basophilic cytoplasm and a large visible nucleus that may be round, oval, or granular or hyper-segmented with dense prominent nucleoli and mitoses (Figure 6). In addition, a background image of inflammatory cells and necrotizing lymphoma cells can also be seen.[7]

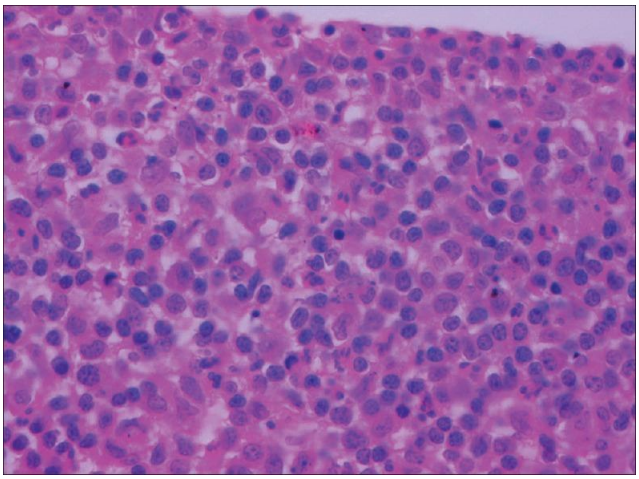

Figure 6. Vitreous biopsy examination in PIOL cases. Large cells have scanty or moderate cytoplasm and prominent nucleoli (HE staining 400x magnification).[7]

Immunohistochemistry and Flow Cytometry

The immunohistochemical examination determines whether lymphoma originates from B cells or T cells. In addition, this examination aims to determine the ability of lymphoma cell proliferation, which shows the degree of aggressiveness. Most cases originate from B cells where the markers CD20, CD79α are positive, and CD3 are negative. Rarer cases where lymphoma originates from T cells where the markers are CD3 positive and CD20 negative. These two subtypes generally show high expression of the Ki-67 marker so that they have extensive proliferative abilities (Fig. 7-9).[11]

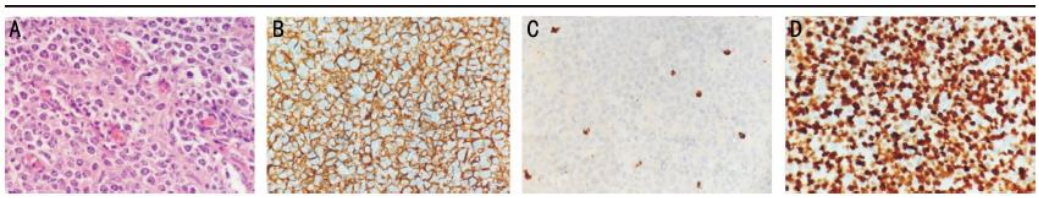

Figure 7. Histopathological and immunohistochemical examination of PIOL derived from B cells. (A) Atypical cells with pleomorphic nuclei with prominent nuclei and very little cytoplasm (HE staining 200x magnification); (B) Immunohistochemical examination which

showed positive CD20 (200x magnification); (C) Immunohistochemical examination which showed negative CD3; (D) Immunohistochemical examination which showed high expression of the proliferative marker Ki-67 (>80%) indicated its extensive proliferative nature.[11]

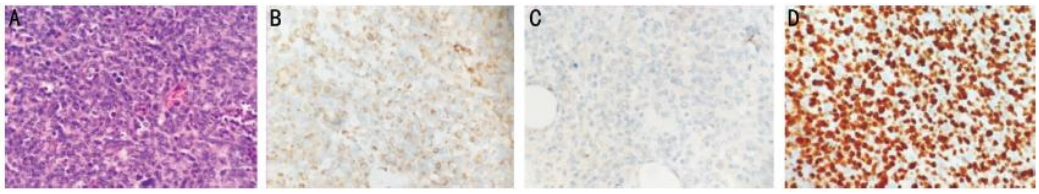

Figure 8. Histopathological and immunohistochemical examination of T cell-derived PIOL. (A) Moderate to large lymphoid cells with atypical nuclei (HE staining 200x magnification); (B) Immunohistochemical examination which showed positive CD3 (200x magnification); (C) Immunohistochemical examination, which showed negative CD20; (D) Immunohistochemical examination which showed high expression of the proliferative marker Ki-67 (>80%) indicated its extensive proliferative nature.[11]

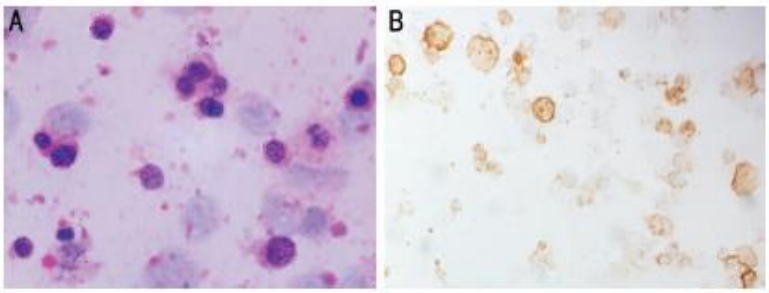

Figure 9. Cytological examination of the vitreous specimen of a PIOL patient. (A) large, atypical and highly stained lymphoid cells with irregular nuclei and coarse chromatin (400x magnification); (B) After an immunocytochemical examination, a positive CD20 expression was found, indicating B cells' origin.[11]

The flow cytometry examination can examine the cell surface marking and show a monoclonal B cell population. IOLs usually consist of monoclonal B cells with restricted chains. The ratio 2 : 3 or 0.6 is a very sensitive marker for lymphoma.[28]

Other Laboratory Examinations and Genetic Test

The molecular examination detects immunoglobulin genes involved in lymphoma cells and the cytokines expressed. On vitreous fluid analysis will show an increase in interleukin (IL-10) with a ratio of IL-10: IL-6> 1.0 very helpful for diagnosis. PCR was used to examine the amplification of the immunoglobulin heavy chain DNA. In B-cell lymphoma, molecular analysis can detect rearrangements of the IgH gene, whereas, in T-cell lymphoma, rearrangements of genes making up the T-cell receptor can be detected. PCR analysis of the EB virus in aqueous humour may be useful to support the diagnosis of intraocular NK cell lymphoma.[11]

PIOL detection can also be done through chromosomal analysis. The presence of a BCL-2 translocation (14;18) is suggestive of an IOL diagnosis. Microdissection with a minimum of 15 atypical lymphoid cells has been shown to have a diagnostic efficiency of 99.5% using PCR.[29,30] In addition, HIV tests, complete blood counts, and specific tests can also be performed to determine the cause of uveitis.[7]

Conclusion

PIOL is a rare clinical entity that is often misdiagnosed as an infectious or inflammatory condition. There is a high index of clinical suspicion, especially when there is a suboptimal response to standard steroid treatment or recurrence in suspected vitreous/uveitis. This high clinical suspicion needs to be continued with the latest investigations to establish PIOL diagnosis. Initial investigations that can be performed are optical coherence tomography, fundus fluorescence angiography, indocyanine green angiography, fundal autofluorescence, ocular ultrasonography, vitrectomy sampling, and head MRI. Molecular and genetic testing can also support the diagnosis of PIOL. In addition, histopathological examination with Giemsa stain or hematoxylin-eosin is the gold standard in this case.

Conflict of Interest

Nothing to declare

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