ejpmr, 2020,7(12), 200-209

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

PRIMARY INTRAOCULAR LYMPHOMA

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Article Received on 30/09/2020 **Article Revised on 20/10/2020** **Article Accepted on 10/11/2020**

ABSTRACT

Primary intraocular lymphoma (PIOL) is an ocular malignancy that is a subset of primary central nervous system lymphoma (PCNSL). Although rare, the incidence has been rising in both immunocompromised and immunocompetent populations. The majority of PIOL is diffuse large B-cell lymphoma, though rare T-cell variants are described. Diagnosis remains challenging for ophthalmologists and pathologists. PIOL can masquerade as noninfectious or infectious uveitis, white dot syndromes, or occasionally as other neoplasms such as metastatic cancers. Laboratory diagnosis by cytology has been much aided by the use of immunocytochemistry, flow cytometry, biochemical finding of interleukin changes (IL10:IL6 ratio>1) and cellular microdissection with polymerase chain reaction amplification for clonality. Use of several tests improves the diagnostic yield. This article is aimed at providing recent advances in diagnosing and management of PIOL.

KEYWORDS: microdissection, clonality, immunocompromised and immunocompetent.

1. BACKGROUND

The designation of intraocular lymphoma (IOL) includes primary intraocular lymphoma (PIOL), mainly arising from the central nervous system (CNS) and secondary intraocular lymphoma (SIOL, from outside the CNS as metastasis from a non-ocular neoplasm).[1,2] IOL incidence is very low.[3] Most cases are of B-cell origin and associated with primary CNS non-Hodgkin's lymphoma.[3] Fewer cases are of T-cell origin.[3] Intraocular T-cell lymphomas are uncommon, some are secondary to metastatic systemic T-cell lymphomas including primary cutaneous peripheral T-cell lymphoma (PCPTCL), the NK-T cell lymphoma, and rarely adult T-cell leukemia/lymphoma (ATL),[4-8] and the disease is usually confined to the iris and ciliary body and peripheral choroid. The most common PIOL by far is primary vitreoretinal lymphoma (PVRL). SIOL has different clinical features and prognosis[9] and the most common subtype is systemic diffuse large B cell lymphoma (DLBCL).[10]

2. Definition

2.1 Primary intraocular lymphoma

Primary intraocular lymphoma (PIOL) was initially defined as a subset of primary central nervous system lymphoma in which lymphoma cells grow initially only in the eyes, without evidence of disease in the brain or cerebrospinal fluid;[11] although concomitant as well as subsequent intracranial involvement occurs in majority of cases.[12] The lymphoma cells are seen within the vitreous and retina.

2.2. Secondary intraocular lymphoma

Secondary intraocular lymphoma arises outside the central nervous system and metastasizes to the eye.[1] The secondary type, which typically has different clinical features and prognosis.[11] The lymphoma cells are present mainly in the uvea. Ocular relapse of lymphoma of the testes, another immune privileged site, has been reported to mimic PIOL.[13] Systemic T-cell lymphoma with intraocular involvement shares some of the ocular clinical features of typical B-cell PIOL.[14]

3. Historical aspects

The entity now known as PIOL was called malignant lymphoma of the uveal tract, by Cooper in 1951[15] and Givner in 1955.[16] This terminology was replaced by the designation ocular reticulum cell sarcoma.[17]

4. Epidemiology

The incidence of IOL has been increasing in recent years, due to the increase in the patients of immunodeficiency and immunosuppression, the increase in life expectancy, and the improvements in diagnostic tools.[18] The overall incidence of IOL has been estimated to represent 1.86% of ocular malignant tumors.[18] The

median age of this disease is 50- 60y,[20-21] with a range between 15-85 years of age.[22] These are estimated to represent 4%-6% of primary brain tumors and 1%-2% of extranodal lymphomas.[23,24] Among IOL patients, the percentage of cases that involve the CNS is 60%-80%.[25] While 15%-25% of primary central nervous system lymphoma (PCNSL) patients develop ophthalmic manifestations of lymphoma, 56%-90% of PIOL patients have or will develop CNS manifestations of lymphoma.[26] In terms of gender, some reported that women were twice more affected than men.[27,28,29] But some reported that even greater cases occurred in men.[29] There appears to be no racial predilection for the disease.[30,31]

5. Etiology

The etiology of PIOL/PCNSL remains an enigma. Multiple factor interact to trigger an abnormal proliferation of T/B cells. One hypothesis suggests that in immunocompromised patients, a mutation in the Epstein-Barr virus attracts lymphocyte cells to the CNS, where transformation to neoplastic cells is initiated.[32] This is supported by the finding that Epstein-Barr virus is invariably found in AIDS patients with PCNSL and usually runs a more aggressive course,[33] but the same association in not documented in PIOL.[34] Toxoplasma gondii DNA has also been found in B-cell lymphoma cells in 2 out of 10 PIOL samples, leading to speculation on the role of this organism.[35] One suggestion is that an infectious antigen driven B-cell expansion is the primary trigger, which then becomes clonal.[36] Another hypothesis poses haematological transfer of neoplastic cells from nodal and extranodal sites to ocular and central nervous system structures.[28] In the chemokine hypothesis, B-cell chemokines may selectively attract lymphoma cells from the choroidal circulation to the retinal pigment epithelium (RPE). The B-cell chemokine receptors CXCR4 and CXCR5 were detected in lymphoma cells, whereas their ligands BLC and SDF-1 were detected only in the RPE.[37] A disturbance in the factors contributing to the immune privilege of the eye has also been implicated.[38]

6. Clinical features

Ocular features

PIOL is a masquerade syndrome that mimics uveitis, even responds to steroid therapy, which makes the diagnosis difficult. Ocular disease is bilateral in 64%-83% of cases.[39] Blurred vision, reduced vision, and floaters are the common initial subjective symptoms.[25] More than 50% of patients have significant vitreous haze and cells that can be seen insheets or clumps with vision impairment.[40] Posterior vitreous detachment and hemorrhage may occur occasionally.[41] Posterior uveitis is the most common presenting symptoms, and anterior segment inflammatory findings are frequently absent.[26] PIOL manifest as creamy lesions with orange-yellow infiltrates to the retina or retinal pigment epithelium Figure 1(A,B,C). They can give rise to a characteristic "leopard skin" pigmentation overlying the mass which may be seen in fluorescein angiography (FA).[42] There may be isolated subretinal lesions or associated exudative retinal detachment.[43] A single vitreous lesion is rare, sometimes simple vitreous inflammatory response or optic nerve infiltration may occur.[43] At presentation of PIOL, 56%- 90% patients have or will develop CNS manifestations of lymphoma.[22] Sometimes IOL may masquerade as bilateral granulomatous panuveitis.[45] When there is infiltration to the brain, behavioral changes and alteration in cognitive function may occur.[46] Intraocular T-cell lymphomas are uncommon, some of them are secondary to metastatic systemic T-cell lymphomas. SIOL should be considered when there is a bilateral sudden and severe inflammatory reaction of the anterior segment that does not respond to treatment or recurs. Anterior reaction and keratic precipitates may be presented especially in SIOL.[47] The most common ocular manifestation of this disease is nongranulomatous anterior uveitis and vitritis. Other rare ocular symptoms include inflammatory glaucoma, neurotrophic keratopathy, fully dilated pupil, and choroidal detachment.[48] Previous systemic primary site reported indicated that the skin was the most common site. Concurrent CNS involvement was reported in 31.0% cases.[49]

CNS features

Symptoms of CNS involvement may emerge at any time of the disease course and can be focal and/or diffuse.[50] At presentation of PIOL, 16-34% have CNS involvement.[31] Tumors of the frontal lobe can induce behavioral changes and alteration in cognitive function.[51] Common focal neurological findings are hemiparesis in 51% and cerebellar signs, including ataxia, in 23%.[24] A strong indicator of CNS involvement is new-onset seizures.[41] Lymphomatous meningitis without intracerebral involvement is one variant.[52] From 13% to 25% of patients with primary central nervous system lymphoma (PCNSL) have ocular signs on diagnosis.[31] Conversely, it is estimated that between 42% and 92% of PIOL cases go on to exhibit intracranial lymphoma within a mean interval of 8-29 months.[53] Widespread dissemination of PCNSL can also occur in 7-8% of patients, usually late in the course.[54] The concurrent involvement of CNS with ocular involvement in a case of bilateral granulomatous uveitis in elderly patient should raise a strong suspicion of PIOL and the investigation should be directed toward the same.

Differential diagnosis of PIOL

As it is a "masquerade syndrome[31], **(Table 1)**, the differential diagnosis of PIOL is wide and includes both infectious and noninfectious uveitis.[31]

DIAGNOSIS

The key to diagnosis is a high index of suspicion for any chronic posterior uveitis that is atypical or refractory to therapy, especially in middle-aged or older patients. Intense ocular inflammation without significant pain, photophobia or conjunctival hyperemia should be

investigated. Sub-RPE infiltrates, sheets or clumps of vitreous cells (Figure 2 A) and steroid resistance (allowing for an initial response) are other features of possible PIOL.

In cases of suspected PIOL, evaluation of central nervous system should be undertaken. This includes a history with emphasis on neurological signs and symptoms, neurological examination, neuroimaging with magnetic resonance imaging and lumbar puncture for cerebrospinal fluid cytology.

Fluorescein and indocyanine green angiography

Indocyanine green angiography showed small hypofluorescent lesions in the early phase, becoming less apparent in the late phases. The hypofluorescent lesions were more numerous on fluorescein than indocyanine green angiography.[41] Figure 1(D,E,F). Together, the fluorescein and indocyanine green angiographic findings had a positive predictive value of 89% and a negative predictive value of 85%.[42]

Fundus autofluorescence

In 5 eyes with PIOL the clinically observed brown "leopard spotting" over yellow lesions beneath the RPE had a bright hyperautofluorescence appearance, whereas white lesions above the RPE were hypoautofluorescent.[55] This is thought to be the result of lipofuscin in RPE cells.

Optical coherence tomography

Optical coherence tomography (OCT) findings include nodular hyper-reflective lesions in retinal pigment epithelium layer, reduced foveal thickness compared to uveitis cases, and is useful for confirming the absence of cystoid macular edema.[42] Recently, the use of spectral domain OCT has demonstrated lymphomatous subretinal or sub-RPE deposition.[56] Further research on the use of OCT to monitor treatment response of such lesions is necessary, but its use is likely to be limited to central, rather than peripheral, fundus involvement.

On EDI-OCT, there was an irregular, undulating appearance to the choroidal surface that has been described as seasick,[101] with compression of the choriocapillaris inward. Other features on EDI-OCT included deep optical shadowing and numerous clumps of optically dense material at the level of the RPE, presumed to represent macrophages with lipofuscin. Overlying subretinal fluid with a homogeneous, optically dense, and widened photoreceptor band in some areas was noted, as was photoreceptor loss in other areas. These features were suggestive of choroidal lymphoma.

B mode ultrasound scan

Ophthalmic ultrasonography can be used to narrow the differential where the posterior segment is difficult to visualize. Abnormal ultrasonographic findings are frequent, although none of the changes are specific for PIOL.[29] The most common are vitreous debris, retinal detachment, elevated chorioretinal lesions, and widening of the optic nerve.

Neuroimaging- Magnetic resonance imaging (MRI) with contrast is more sensitive than computed tomography (CT) for detecting lymphomatous lesions in the CNS, but both are limited in evaluating ophthalmic disease.[57] CT and MRI show unifocal or multifocal (in one-third of cases) periventricular, homogenously enhancing lesions.[58] With CT the lesions are isodense or hyperdense, and with MRI, the lesions are hypodense on T1-weighted and hyperdense on T2-weighted images.[59] PET/CT has been used to identify CNS lesions as well as ocular activity, both of which take up the 2-[(18)F] fluoro-2- deoxy-D-glucose dye, though the same lesions were identifiable either on MRI or on funduscopy.[60]

Blood testing- Blood tests should be used to rule out conditions in the differential diagnosis, including markers of infectious and noninfectious uveitis. Additionally a complete blood count and human immunodeficiency virus test are useful.[31]

Biopsy

Biopsy remains one of the hallmark procedures in diagnosing PIOL.[61] Tissue biopsy, especially of the vitreous, is performed, especially if PCNSL lesions cannot be found on neuroimaging or when cerebrospinal fluid (CSF) evaluation remains negative. The corticosteroid treatment must be discontinued as least 2 weeks before biopsy. Specimens can be obtained by fine needle vitreous aspiration or pars plana vitrectomy.[61] Vitreous sampling should be taken with infusion off. Multiple biopsies may be required to reach a definite pathological diagnosis.[62] The main site of involvement is the sub-RPE space (between RPE and Bruch membrane). The retina, vitreous, and optic nerve head are affected to various degrees.[63] The uvea may show a reactive inflammatory cell infiltrate, and uveal biopsies are often non-diagnostic. Fine needle aspiration of the vitreous is performed with a 21- to 25-gauge needle inserted through the pars plana, although the sample size is small. Generally this is a safe clinical procedure, with a high success rate in differentiating between infectious, inflammatory, and malignant causes of uveitis.[64] An initial diagnosis of intraocular malignancy or infection was confirmed in 40% of patients.[65]

Vitreous biopsy specimens need to be transported quickly for laboratory analysis.[61] Lymphoma cells undergo morphological degradation within 60 minutes, but an appropriate preservative may be used if transport time exceeds this.[62]

If subretinal lesions are present, a retinotomy can be performed using the vitreous approach[52] or they can also be aspirated.[66] Subretinal tumors may consist largely of necrotic tissue, and so specimens are ideally taken from the deeper part of the lesion, near the choriocapillaris, where viable lymphoma cells are most likely to be

found.[10] Transcleral biopsy using a partial scleral thickness flap is described.[61]

Lumbar puncture

A lumbar puncture to obtain CSF is indicated in suspected PCNSL. Up to 25% of patients with identifiable lesions on MRI will have positive CSF cytology.[67] As a standard protocol, papilloedema should be ruled out.

Cytological and histological findings

The diagnosis of PIOL requires a multidisciplinary approach. From the pathologist's viewpoint this involves morphological assessment in conjunction with traditional immunocytochemistry and molecular analysis (such as flow cytometry and polymerase chain reaction [PCR] analysis). Morphologically the typical lymphoma cells are large B-cell lymphoid cells with scanty basophilic cytoplasm, an elevated nucleus:cytoplasm ratio, hypersegmented, round, oval, bean, or clover shaped nuclei with a coarse chromatin pattern and prominent or multiple nucleoli (figure 2B).[53] The concordance between clinical features and pathological diagnosis is as high as 96%.[53] For lymphoma, the positive predictive value of cytologic evaluation was 99-100% and the negative predictive value was 61-81%.[68] Sparse number of cells is the main reason for an inconclusive result.[69] Vitreous specimens contain many reactive T-lymphocytes, necrotic cells, debris, and fibrin that can also confound the identification of malignant cells.[53]

Immunocytochemistry and flow cytometry

The phenotyping of cells by their surface markers is useful for identifying lymphomatous cells, particularly if cytology is scanty.[70,71] Immunocytological techniques use a cell-mounted slide with antibodies directed at specific cell markers.[70] Flow cytometry works in a similar fashion, except that the cells are separated using a fluorescence activated cell-sorter in a fluid medium. Immunocytology increases the rate of diagnosis from 30% (using cytology alone) to 70%,[71] but requires more cells. Flow cytometry allows for multiple monoclonal antibodies to be applied to an aliquot of suspected lymphoma cells simultaneously, which allows the use of a larger detection panel.[72] Most PIOL are monoclonal B cell lymphomas that stain positively for B cell markers, such as CD19, CD20, and CD22 and show restricted expression of either kappa or lambda chain (figure 2C,D).[73] In T-cell lymphomas, the T-cell population stains positively for T-cell markers (CD3, CD4).[74]

Biochemical and PCR analysis

B-cells secrete high amounts of IL-10, an immunosuppressive cytokine. IL-10 to IL-6 ratios greater than 1.0 are highly suggestive of PIOL.[75] Wolf et al. showed that intravitreal IL-10/IL-6 >1.0 was used to correctly distinguish PIOL from uveitis with approximately 75% sensitivity and specificity.[76] The mean IL-10 to IL-6 ratio in 35 PIOL vitreous specimens was 5.23 whereas it was 0.23 for uveitis patients.[77] IL-10 levels in the aqueous have also been found to be significantly elevated in PIOL patients.[78]

Treatment

Due to the rarity of IOL, standard and optimal therapy is not defined. Treatment modalities for IOL include intravitreal chemotherapy, targeted chemotherapy/immunotherapy and radiotherapy, which is used alone or in an appropriate combination. The therapies vary according to the disease stage, the presence or absence of CNS involvement, and performance status of the patients.[79] The current recommendation for the treatment of IOL without CNS or systemic involvement should be limited to local treatment, including intraocular methotrexate and/or ocular radiation in order to minimize systemic toxicities.[46]

Ocular irradiation with prophylactic CNS treatment is used to control IOL, maintain vision, and prevent CNS involvement.[32] The average external beam radiation dose is close to 40 Gy, but can range from 30 to 50 Gy.[40] The complications of radiotherapy include radiation retinopathy, vitreous hemorrhage, dry eye syndrome, conjunctivitis, neovascular glaucoma, optic atrophy, punctate epithelial erosions or cataract. While the treatment of the patients with CNS involvement includes a combination of radiotherapy and chemotherapy.[80]

Intravitreal methotrexate

As with systemic chemotherapy, the mainstay of intravitreal chemotherapy is methotrexate.[81] Weekly methotrexate (400 micrograms in 0.1 cc) injected into the vitreous cavity (intravitreal methotrexate) and was shown by Fishburne to be useful in the treatment of VRL.[82] Others have verifed this fnding.[83] The problem is that it takes on average 6.4 methotrexate injections to develop a remission.[83] If intravitreal methotrexate will be used, it is critical that it is the intrathecal form and that the right concentration (400 mcg/0.1 cc) be used. In addition, it is important that a paracentesis first be performed because that will decrease the chances of subconjunctival extravasation of the methotrexate.

Intravitreal methotrexate therapy is extremely effective in inducing clinical remission of vitreoretinal involvement in PVRL with acceptable morbidity. In a 10-year study using intravitreal injections of methotrexate as first line treatment in PVRL, none of the total 26 patients had an intraocular recurrence.[83]

Intravitreal rituximab

Rituximab is an anti-CD20 monoclonal antibody. Intravitreal injections of 1mg/0.1mL rituximab weekly for 4 weeks as a onecourse protocol showed encouraging results in 20 eyes with CD20-positive PVRL. However, 50% of the cases showed recurrences in the study.[84] Relapses following intravitreal rituximab may require treatment with intravitreal methotrexate and radiation.[85]

Intravitreal rituximab is often used to decrease the frequency of methotrexate injections or for methotrexate-resistant IOL.[85] Initial response was good with clearance of PIOL, but subsequent relapse required intravitreal methotrexate and radiation. High dose methotrexate is the most active drug, producing a response rate of up to 72% when used alone and up to 94%-100% in combinations.[86] Combined intravitreal methotrexate and systemic high-dosemethotrexate treatment is effective in patients with PIOL.[87] In addition, intravitreal chemotherapy with 0.4 mg methotrexate in 0.1 mL achieved local tumor control in relapsed IOL.[88] The intravitreal chemotherapy is a primary treatment in combination with systemic chemotherapy.[82] For relapsed or refractory PIOL with PCNSL has been treated with intrathecal methotrexate and cytarabine.[89] These treatment decisions are often complex and require personalized treatment for different patients.

Emerging therapies

Stem cell transplantation

The use of stem cell transplantation for PVRL has been described.[90] Originally, it was used for refractory or recurrent cases of vitreoretinal and/or CNS lymphoma. The patients that were able to complete the treatment regimen had a median overall survival was 58.6 months compared to 18.3 months for the overall group. The two-year survival rate was 69% for the transplant group compared to 45% for the entire group.[90]

Lenalidomide plus rituximab

A recent abstract presented at the American Society of Hematology Annual Meeting in 2016 from the French LOC Network reviewed results from a phase II trial of lenalidomide plus rituximab for relapsed or refractory PCNSL or PVRL.[91] Of the 45 enrolled patients, 9 patients had PVRL and 10 patients had secondary VRL; 6 of the 19 patients achieved a complete remission.

Pomalidomide

Pomalidomide (a similar agent but with better penetration into the CNS) has shown efficacy in an animal model of CNS lymphoma.[92] An ongoing study being conducted at Mayo Clinic sites and DanaFarber Cancer Institute was developed to investigate the use of pomalidomide for refractory or recurrent CNS or vitreoretinal. Enrollment continues with promising results.[93]

Ibrutinib

Ibrutinib was originally utilized for the treatment of chronic lymphocytic leukemia (CLL).[94] It is an oral targeted agent whose mechanism of action is inhibiting Bruton's tyrosine kinase (BTK). In addition, it inhibits the HCK tyrosine kinase protein. Ibrutinib is approved for the treatment of Waldenström's macroglobulinemia WM.[95] An interim analysis of a phase II clinical trial utilizing single agent ibrutinib in relapsed or refractory PCNSL and PVRL was recently presented.[91] Eleven patients with PCNSL and seven patients with PVRL at time of study entry were included in the analysis. Te median number of treatment cycles was fIve, with an overall response rate of 56% and 3 of 18 patients achieving a CR as best response.

Prognosis

IOL is a rare lymphocytic malignancy, the reported mortality rate range between 9% and 81% in follow-up periods, and the survival time is 12-35months.[96] However, the reported mortality rate of IOL is very inconsistent because of the rare patient populations, variation in treatment modalities, and the delayed diagnosis. Tumor recurrence is common, and sometimes the existing treatment cannot effectively prevent the local recurrence and the CNS involvement. The prognosis depends on the following aspects: 1) whether the CNS is involved. A trend toward better survival was seen among patients with isolated ocular presentation.[97,98]

Table 1: Differential diagnosis of primary intraocular lymphoma.

Inflammatory disorders	
Posterior or intermediate uveitis or panuveitis	**Infectious causes**
Multifocal choroiditis	Tuberculoma
Behcet disease	Cytomegalovirus retinitis
Acute posterior multifocal placoid pigment epitheliopathy (AMPPE)	Endophthalmitis
	Herpetic uveitis
Multiple evanescent white dot syndrome	Toxoplasmosis
Birdshot choroidopathy	Acute retinal necrosis
Serpiginous chorioretinopathy	Syphilis
Retinal arterial and venous obstruction or vasculitis	
Frosted branch angiitis	**Neoplasms**
Vogt-Koyanagi-Harada disease	Metastatic cancers
Sarcoidosis	Amelanotic melanoma

Figures

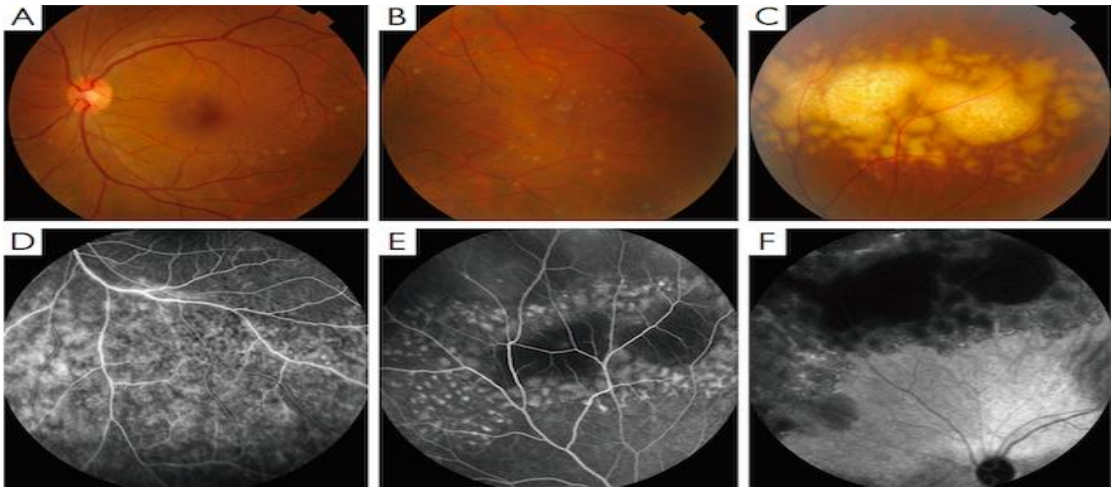

Figure 1. Funduscopy and angiogram imaging in the left eye of the primary vitreoretinal lymphoma patient. (A) Multiple small yellowish subretinal spots in the posterior pole; (B) multiple small yellowish subretinal spots in the temporal peripheral retina; (C) a large, confluent and ill-defined yellowish subretinal lesions in the superior periphery; multiple similar small subretinal lesions surrounding the large lesion; (D) middle phase fluorescence angiography (FA) illustrating mild leakage along some of the retinal vessels and diffuse retinal pigment epithelium (RPE) granularity; (E) late phase FA showing a large hypofluorescence area of lymphoma cell deposits corresponding to the large lesion in (C); multiple hyperfluorescent window defects of RPE damage corresponding to the small lesions in (C); (F) indocyanine green angiography illustrating the corresponding large and multiple small sub-retinal lesions with hypofluorescence in late phase.[99]

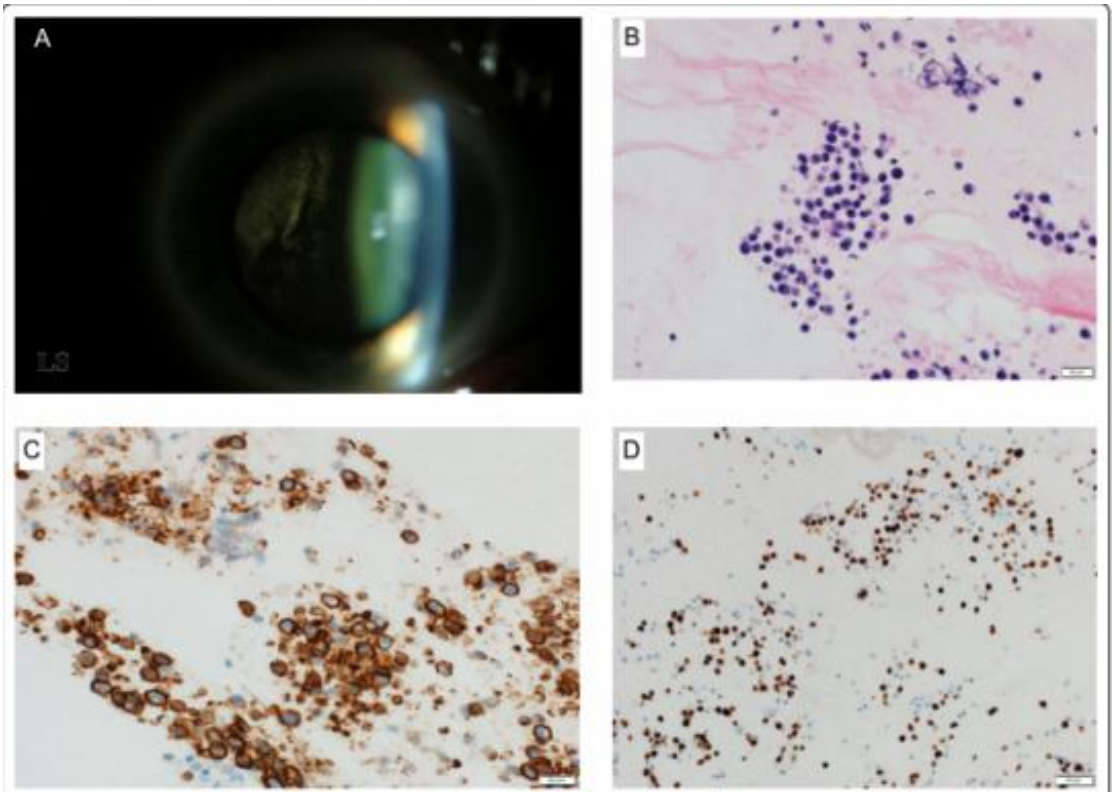

Figure. 2 (A) Diffuse large B cell lymphoma in the vitreous of a patient. (B) Cytomorphology of the vitreoretinal difuse large B cell lymphoma cells (H&E ×400). (C) Immunostaining for CD20 of the vitreoretinal lymphoma cells (×400). (D) Ki-67 staining of the vitreoretinal cells; note the extensive staining which is consistent of marked local replication (×200).[100]

CONCLUSION

PIOL is a masquerading ocular disease, making it difficult to diagnose and treat. With recent advances in diagnostic imaging and molecular techniques, the detection of this highly aggressive disease has improved. High relapse rates and CNS involvement are common,

which result in poor prognosis of PIOL, despite aggressive treatment with chemotherapy and/or radiotherapy.

With the advent of newer modalities of treatment, the survival rate has improved. It is hence imperative that ophthalmologist should keep PIOL as a differential diagnosis in granulomatous or non-granulomatous uveitis in elderly patients.

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