• Review •

Intraocular lymphoma

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Abstract

• Intraocular lymphoma (IOL) is a rare lymphocytic malignancy which contains two main distinct forms. Primary intraocular lymphoma (PIOL) is mainly a subtype of primary central nervous system lymphoma (PCNSL). Alternatively, IOL can originate from outside the central nervous system (CNS) by metastasizing to the eye. These tumors are known as secondary intraocular lymphoma (SIOL). The IOL can arise in the retina, uvea, vitreous, Bruch's membrane and optic nerve. There are predominantly of B-cell origin; however there are also rare T-cell variants. Diagnosis remains challenging for ophthalmologists and pathologists, due to its ability to masquerade as noninfectious or infectious uveitis, white dot syndromes, or occasionally as other metastatic cancers. Laboratory tests include flow cytometry, immunocytochemistry, interleukin detection (IL-10: IL-6, ratio >1), and polymerase chain reaction (PCR) amplification. Methotrexate-based systemic chemotherapy with external beam radiotherapy and intravitreal chemotherapy with methotrexate are useful for controlling the disease, but the prognosis remains poor. Therefore, it is important to make an early diagnose and treatment. This review is focused on the clinical manifestations, diagnosis, treatment and prognosis of the IOL.

• **KEYWORDS:** intraocular lymphoma; central nervous system; diagnosis; treatment; prognosis
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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. Most cases are of B-cell origin and associated with primary CNS non-Hodgkin's lymphoma. Fewer cases are of T-cell origin. 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)[3-7], 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[8], and the most common subtype is systemic diffuse large B cell lymphoma (DLBCL)[9]. Although still rare, the incidence of IOL has increased in the recent years, and prognosis remains poor. Here, we summarize mainly the current literature on IOL.

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[8,10]. The overall incidence of IOL has been estimated to represent 1.86% of ocular malignant tumors[11]. The median age of this disease is 50-60y[12-13], with a range between 15-85 years of age[14]. These are estimated to represent 4%-6% of primary brain tumors and 1%-2% of extranodal lymphomas[15-16]. Among IOL patients, the percentage of cases that involve the CNS is 60%-80%[17]. 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[18]. In terms of gender, some reported that women were more commonly affected than men by 2:1[19-21]. But some reported that even greater cases occurred in men[22]. There appears to be no racial predilection for the disease[22-23].

ETIOLOGY

The etiology of IOL remains unclear. Multiple hypotheses of lymphomagenesis are involved. Immunocompromise, Epstein-Barr virus, and Toxoplasma gondii infection may be the related factors[24-26]. Moreover, an infectious antigen driven B-cell

expansion may be the primary trigger, which then becomes cloned[8]. Thus, genetic, immunologic, and microenvironmental factors are probably necessary in order to induce malignant B-cell phenotype[27]. Proofs of causation are still lacking, and the lymphomagenesis requires further investigation.

CLINICAL 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[28]. Blurred vision, reduced vision, and floaters are the common initial subjective symptoms[17]. More than 50% of patients have significant vitreous haze and cells that can be seen insheets or clumps with vision impairment[29]. Posterior vitreous detachment and hemorrhage may occur occasionally[30]. Posterior uveitis is the most common presenting symptoms, and anterior segment inflammatory findings are frequently absent[18]. Another characteristic from optical coherence tomography (OCT) is the development of creamy lesions with orange-yellow infiltrates to the retina or retinal pigment epithelium (RPE)[1,31-32]. They can give rise to a characteristic "leopard skin" pigmentation overlying the mass which may be seen in fluorescein angiography (FA)[32-35]. There may beisolated subretinal lesionsor associated exudative retinal detachment[23,33]. A single vitreous lesion is rare, sometimes simple vitreous inflammatory response or optic nerve infiltration may occur[36]. At presentation of PIOL, 56%-90% patients have or will develop CNS manifestations of lymphoma[14]. Sometimes IOL may masquerade as bilateral granulomatous panuveitis[37]. When there is infiltration to the brain, behavioral changes and alteration in cognitive function may occur[38].

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[39]. The most common ocular manifestation of this disease is non-granulomatous anterior uveitis and vitritis. Other rare ocular symptoms include inflammatory glaucoma, neurotrophic keratopathy, fully dilated pupil, and choroidal detachment[40]. Previous systemic primary site reported indicated that the skin was the most common site. Concurrent CNS involvement was reported in 31.0% cases[41].

DIAGNOSTIC TESTS

The delay between a positive diagnosis and the onset of ocular or neurological symptoms usually ranges from 4-40mo[23,28,42], although more rapid progression may occur[43]. The diagnosis of IOL requires a multidisciplinary approach, involving morphological assessment in conjunction with traditional immunocytochemistry and molecular analysis [such as flow cytometry and polymerase chain reaction (PCR) analysis]. Histologic identification remains one of the essential procedures in diagnosing IOL[44-45]. Morphologically and immunohistochemically, the typical lymphoma cells are usually with scanty cytoplasm, an elevated nucleus: cytoplasm ratio, round, oval, bean, or irregular shaped nuclei with a coarse chromatin and prominent or multiple nucleoli[46-47] (Figure 1A). In B cell lymphoma the predominance of lymphoma cells were identified as CD20, CD79α positive and CD3 negative (Figure 1B, 1C). And in T cell lymphoma, medium to large sized lymphoid cells with atypical nuclei are visualized with HE staining (Figure 2A). While the tumor cells are identified as CD3 positive and CD20 negative (Figure 2B, 2C). Both the two types of IOL are with high Ki-67 positive rate (average >80%) indicates extensive proliferation (Figures 1D, 2D). Specimens can be obtained by fine needle vitreous aspiration or pars plana vitrectomy. And multiple biopsies may be required to reach a definite pathological diagnosis. Removed ocular fluids (*via* aqueous tap, vitreous tap, or diagnostic vitrectomy) need to be delivered quickly for laboratory analysis, to prevent cell degeneration that can make diagnosis difficult[47]. Furthermore, a negative vitrectomysample is common, sparse number of cells is also the main reason for misdiagnosis. In addition, vitreous specimens contain many reactive T-lymphocytes, necrotic cells, debris, and fibrin that can also confound the identification of malignant cells[46]. Then, retinal or chorioretinal biopsies may be required. Microscopically, the typical lymphoma cells are large B-cell lymphoid cells with scanty cytoplasm, an elevated (nucleus:cytoplasm) ratio, heteromorphic deeply stained nuclei with a coarse chromatin pattern and prominent nucleoli can be seen (Figure 3). Pars plana vitrectomy has several advantages, including improved vision by clearance of vitreous debris and maximizing the sample size[44,48-49], although the lymphoma may extend to the epibulbar space through the sclerotomy port following vitrectomy[50].

Molecular analysis detecting immunoglobulin gene rearrangements in the lymphoma cells and ocular cytokine analysis of vitreous fluid show elevated interleukin (IL-10) with an IL-10:IL-6 ratio >1.0 are helpful for the diagnosis, while inflammatory conditions typically show elevated IL-6[17,51-53]. In addition, if the eyes have no function or conservative treatment is impossible, a diagnostic enucleation may become necessary[54]. Flow cytometry can examine cell surface markers and demonstrate monoclonal B-cell populations. IOL is typically comprised of amonoclonal B-cell population with restricted κ or λ chains. A κ:λ ratio of 3 or 0.6 is a highly sensitive marker for lymphoma[55]. PCR has been used to amplify the immunoglobulin heavy chain DNA. In

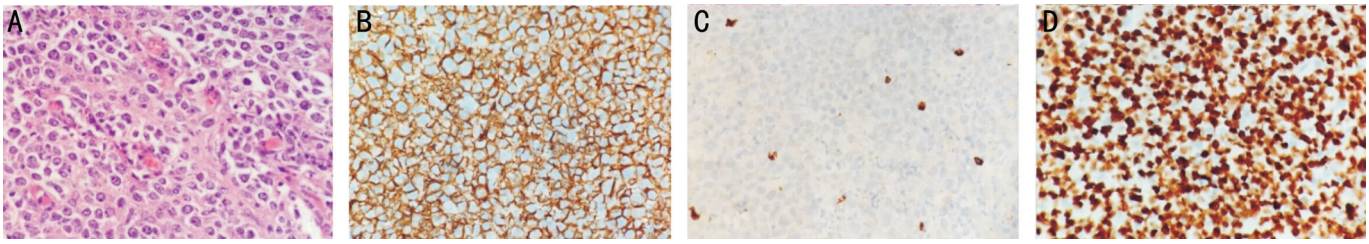

Figure 1 Histopathological and immunohistological of IOL origining from B cell The atypical cells have pleomorphic nuclei with conspicuous nucleoli and scanty cytoplasm (A, HE staining, 200×). It is positive for CD20 (B, 200×) and negative for CD3 (C, 200×); the high Ki-67 positive rate (average >80%) indicates extensive proliferation (D, 200×).

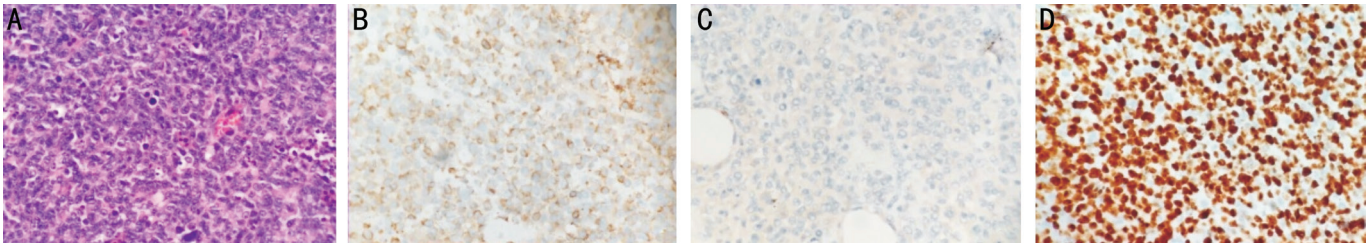

Figure 2 Histopathological and immunohistological of IOL origining from T cell Medium-to-large-sized lymphoid cells with atypical nuclei are visualized with HE staining (A, 200×) and identified as CD3 positive (B, 200×), CD20 negative (C, 200×); the high Ki-67 positive rate (average >80%) indicates extensive proliferation (D, 200×).

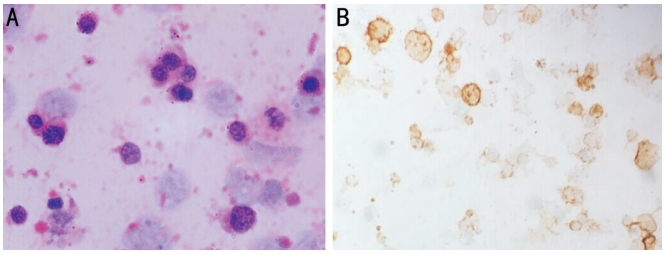

Figure 3 Cytology of the vitreous specimen reveals some atypical, large lymphoid cells, with large, deeply stained, irregular nuclei and coarse chromatin (A, 400×), which is identified as CD20 positive (B, 400×).

B-cell lymphomas, molecular analysis can detect IgH gene rearrangements, while in T-cell lymphomas, T-cell receptor gene rearrangements can be detected[56]. Detection of the bcl-2 t (14;18) translocation is also an effective method to diagnose IOL. Wallace *et al*[57] reported that 40 of 72 (55%) PIOL patients expressed the bcl-2 t (14;18) translocation at the major breakpoint region. A PCR analysis of EB virus with aqueous humor might be useful for supporting the diagnosis of intraocular NK-cell lymphoma[58]. Microdissection with a minimum of 15 atypical lymphoid cells has been shown to have a diagnostic efficiency of 99.5% by using PCR[59].

Besides, ophthalmological examinations frequently demonstrate the presence of vitritis, usually in association with infiltrates of the retina and the retinal pigment epithelium. Hyperfluorescense on fundus autofluorescence imaging can demonstrate active sub-retinal pigment epithelium deposits, while hypofluorescent spots can correspond to areas where tumor cells were suspected to have once been[60]. Fluorescein angiography (FA) may show mottling, granularity, and late staining patterns with a characteristic "leopard spotappearance"[23,32,34-35,61]. OCT demonstrates hyper reflective lesions at the level of the RPE in PVRL. The valuable diagnostic tools include fundoscopy, FA, OCT, fundus autofluorescence, and fluorescein and indocyanine green angiography. There has been reported that ophthalmological examinations finding had a positive predictive value of 88.9% and a negative predictive value of 85%[32]. In addition, once cerebral lymphoma is suspected, contrast-enhanced cranial magnetic resonance imaging (MRI) is the best imaging modality. Lesions are often isointense to hypointense on T2-weighted MRI, with variable surrounding edema and a homogeneous and strong pattern of enhancement[62-63].

TREATMENT

Due to the rarity of IOL, standard and optimal therapy is not defined. Treatment modalities for IOL include intravitreal chemotherapy, systemic chemotherapy, and radiotherapy, which is used alone or in an appropriate combination. The therapies vary according to the disease degree, the presence or absence of CNS involvement, and performance status of the patients[64]. 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[38]. Ocular irradiation with prophylactic CNS treatment is used to control IOL, maintain vision, and prevent CNS involvement[24]. The average external beam radiation dose is close to 40 Gy, but can range from 30 to 50 Gy[29]. The complications of radiotherapy include radiation retinopathy, vitreous hemorrhage, dry eye syndrome, conjunctivitis, neovascular glaucoma, optic atrophy, punctate epithelial erosions or cataract[29]. While the

treatment of the patients with CNS involvement includes a combination of radiotherapy and chemotherapy[63,65]. As with systemic chemotherapy, the mainstay of intravitreal chemotherapy is methotrexate[66]. Rituximab is an anti-CD20 monoclonal antibody. And intravitreal rituximab is often used to decrease the frequency of methotrexate injections or for methotrexate-resistant IOL[67-69]. Initial response was good with clearance of PIOL, but subsequent relapse required intravitreal methotrexateand radiation[67]. Methotrexate can also use alone or in combination with other medications, such as thiotepa and dexamethasone[34,70-72]. 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[73-74]. Combined intravitreal methotrexate and systemic high-dosemethotrexate treatment is effective in patients with PIOL[75]. However, polychemotherapy is also associated with higher drug toxicity[29]. In addition, intravitreal chemotherapy with 0.4 mg methotrexate in 0.1 mL achieved local tumor control in relapsed IOL[76-77]. Also the intravitreal chemotherapy is a primary treatment in combination with systemic chemotherapy[70]. Drug resistance may occur with repeated injections[78]. For relapsed or refractory PIOL with PCNSL has been treated with intrathecal methotrexate and cytarabine[79]. These treatment decisions are often complex and require personalized treatment for different patients.

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 12-35mo[19,80-82]. 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[83-84]. Moreover, the IOL patients with CNS involvement are almost died in the short term. Neuroimaging is important for the patients after treatment since the IOL patients carry a risk for recurrence or CNS involvement[85]; 2) histopathologic type is another important factors. Generally T cell type has poorer prognosis than B cell type; 3) treatment opportunity, early treatment after onset of symptoms may improve the prognosis for a better visual outcome[86]. In PCNSL, median survival of patients treated with radiotherapy alone or chemotherapy plus radiotherapy ranges from 10 to 16mo[38]; 4) the vision and survival rates are both poor in recurrent patients. Due to the rarity of the disease, there is often misdiagnosis, delay in diagnosis, and mismanagement of IOL.

CONCLUSION

In conclusion, IOL often masquerades as intraocular inflammation resulting in misdiagnosis or delayed diagnosis, with subsequent inappropriate management and high mortality rates. Patients with suspected IOL should undergo cytopathologic examination of vitreal fluid or vitrectomy before therapy. On the ocular cytokine levels, mainly IL-10:IL-6 ratio and molecular analysis can provide useful supplementary data for the diagnosis. Once IOL is diagnosed, all patients are required to be examined the subtle neurological symptoms and signs with the oncologist. Meanwhile, neuroimaging is performed to detect any evidence of CNS involvement. Optimal therapy for IOL is considered a great challenge to the clinical. Intravitreal chemotherapy with more than one agent may be proved to be useful in controlling the ocular disease. When the CNS involved, methotrexate-based systemic chemotherapy with external beam radiotherapy should be undertaken. Because of the rarity of this disease, multicenter studies are needed to obtain optimized treatment methods in order to get better vision and prognosis.

METHOD OF LITERATURE SEARCH

PubMed (1970 to end of 2016) database was searched using the search terms IOL, PIOL and SIOL. Removing duplicate articles, excluding articles that clearly related to extraocular lymphoma, and removing foreign language papers provided a total of 86 unique articles in English.

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