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Review Article

Ocular Lymphoma: Clinical, Diagnostic, and Therapeutic Aspects

H. Ashraf, M. Eghtedari

Abstract

Ocular involvement in lymphoma is a relatively rare condition that can result from a primary intraocular lymphoma or an intraocular manifestation of systemic lymphoma. Lymphoma manifestations frequently masquerade as other more benign intraocular conditions including allergic or infectious conjunctivitis, uveitis, multiple evanescent white dot syndrome, acute retinal necrosis, or herpetic retinitis. Accurate diagnosis depends on a high index of suspicion and frequently requires histopathological analysis of specimens, particularly vitreous biopsy, subretinal aspiration, or retinal biopsy with flow cytometry, polymerase chain reaction, or immunohistochemistry methods. Most of ocular lymphomas are of B lineage. Diagnosis is often complex and needs use of paraclinical evaluations. Treatment mainly consists of chemotherapy. It is important to review the ocular manifestations of lymphoma to assist ophthalmologists in prompt diagnosis of ocular lymphoma. And it also helps oncologists to recognize the need for a complete ophthalmic evaluation in the diagnosis, follow-up, and management of patients with lymphoma.

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Keywords ● B cell lymphoma ● tumor ● lymphoma ● eye neoplasm ● intraocular

Introduction

Lymphoid proliferations can affect the eye in various ways. Intraocular structures can be affected by non-Hodgkin's primary central nervous system lymphoma (PCNSL), reactive lymphoid hyperplasia, and systemic non-Hodgkin's lymphoma.[1-7] Hodgkin's lymphoma may also affect the ocular structures.[8]

There are two distinct forms of intraocular lymphoma originating from outside of the globe.[4] The first form originates within the central nervous system (CNS), called primary CNS lymphoma. The second form arises outside the CNS and metastasizes to the eye.[9] When primary CNS lymphoma initially involves the retina, it is named primary intraocular lymphoma (PIOL).[10]

On the other hand, chronic lymphocytic leukemia may involve the eye and its presentation is similar to lymphoma.[11] Intraocular lymphoma is probably the most elusive intraocular tumor to diagnose. It frequently masquerades as other more benign ocular lesions.[2,3,5,7,12] Diagnosis is often delayed (median time to diagnosis was 6 months in a study).[10] It is important to review the ocular manifestations of lymphoma to assist the ophthalmologists to play a pivotal role in prompt diagnosis and

Department of Ophthalmology, Poostchi Ophthalmology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.

Correspondence:
Masoomeh Eghtedari MD,
Department of Ophthalmology, Poostchi Ophthalmology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.
Tel: +98 711 2302830
Fax: +98 7116471479
Email: eghtedarim@gmail.com
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treatment of ocular lymphoma, which must be regarded as a sign of a life-threatening condition. Reviewing the manifestations of lymphoma would also assist the oncologists in recognizing the need for a complete ophthalmic evaluation in the course of diagnosis, follow-up, and management of the patients.[13]

Methods

All articles in the English or Persian languages utilizing the search words *intraocular lymphoma* in Pubmed as well as Magiran up to Feb 2008 were reviewed. These articles were reviewed along with the references cited in them. Those considered relevant and that contributed to the topics covered were included in this article.

Epidemiologic Characteristics

Most reports of ocular involvement in lymphoma are case reports or reports of a few patients. This may reflect its relative rarity. Meaningful data regarding the incidence and prevalence of this condition are not available. In general, the primary non-Hodgkin's lymphoma of the CNS is rare, accounting for 1% of all non-Hodgkin's lymphomas and less than 5% of intracranial tumors.[14,15] Also, less than 1% of all intraocular tumors have been diagnosed as lymphoma.[2] It typically affects elderly patients,[2,14,16,17] (in one study on 83 patients, median age was around 65 years).[10] But it can also occur in young children.[1,18] There is no report of racial predilection. Cancer registry is a recently founded issue in Iran and there is only few documented case reports of ocular lymphoma in our country.[19] It seems that systemic lymphoma is more common in northern provinces of Iran such as Mazandaran.[20]

Roots of Ocular Manifestations

In the case of systemic lymphoma, ocular involvement may be due to the disease itself as a direct result of metastatic neoplastic infiltration and/or compression, or caused by the act of circulating antibodies leading to paraneoplastic retinal degeneration.[21] It may also affect the eye with the side effects of treatment (maculopathy after blood brain barrier disruption for PCNSL).[22] Most ophthalmic manifestations are the consequences of direct infiltration of the intraocular, orbital, and adnexal tissues. Presence of a mass lesion in the orbit can result in compression of orbital tissues and displacement of the eyeball resulting in proptosis.[1,14] On the other hand, infiltrated intraocular tissues may mimic uveitis and this is largely responsible for the manifestations ranging from typical uveitis to retinitis and vasculitis that may be mistaken with an infective process.[23,24] Even an acute change of refractive error was reported, which has been attributed to lymphomatous deposits in the choroid with changes in refractive state.[25]

Cell Lineage

Lymphoma of the eye is frequently caused by B cell lineage. It is rarely affected by non-B cell non-Hodgkin's or T cell lymphomas.[26]

Although it is believed that PIOL is a variant of PCNSL, some authors suggested that it might differ in ontogeny with post germinal centre origin of PIOL of large B cell type.[27]

Ocular Manifestations

The lack of *pathognomonic* features, high clinical manifestations variability, and the limited value of imaging techniques often lead to serious delay in diagnosis.[23] Intraocular lymphoma often has a fatal outcome, but recognition of its modes of presentation facilitates early diagnosis and treatment that may improve prognosis.[7] Almost all ocular tissues may be affected by lymphoma. In this review, ocular manifestations will be grouped as conjunctival, anterior segment, posterior segment and neuro-ophthalmic manifestations and a summary of large case series findings is presented in table 1.

Conjunctiva

Infiltration of the conjunctiva may lead to conjunctival swellings or masses.[14,30] In a study of 39 children with leukaemias and malignant lymphomas, the most frequent ocular findings were found in the conjunctiva, occurring in 33.4% of the patients.[1] Marked chronic fol-

Table 1: Various clinical manifestations presented in major published case series of intraocular lymphoma.

Ocular Finding	Cases: Total number of enrolled patients				
	Rothova A et al[28]	Moll A et al[1]	Rihova E et al[3]	Shibata K et al[29]	Gill M et al[7]
Conjunctiva, sclera and episclera	-	7/10	-	-	-
Anterior segment(anterior uveitis, iritis, rubeosis)	6/19	-	-	1/3	1/4
Vitritis	11/19	-	12/14	1/3	2/4
Chorioretinal lesions	7/19	3/10	9/14	2/3	4/4
Neuro-opthalmic manifestations, Papillitis	2/19	-	-	-	2/4

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licular conjunctivitis has been reported in a patient with mantle cell lymphoma.[31] The follicular appearance of the lymphocytic hyperplasia may mimic the clinical picture of infectious or allergic conjunctivitis, and may cause diagnostic difficulties and delay in diagnosis and appropriate treatment.[1,14,30]

Conjunctival infiltration associated with intraocular involvement has also been reported.[32,33]

Anterior Segment

The cornea may be affected in adult T-cell leukemia/lymphoma that is caused by human T-cell lymphotrophic virus type 1 infection (HTLV-1).[34] This virus is an RNA retrovirus that primarily affects $CD4^+$ T-cells. Corneal involvement in HTLV-1 infection and adult T-cell leukemia/lymphoma include corneal haze, central corneal opacities with thinning, scarring, bilateral immunoprotein keratopathy, peripheral corneal thinning, scarring, and neovascularization.[34] It is believed that the novel corneal findings in these patients are most likely a consequence of the hypergammaglobulinemia induced by HTLV-1 infection or the T-cell malignancy. Keratoconjunctivitis sicca has also been reported in adult T-cell leukaemia/lymphoma.[34]

Episcleritis and scleritis may occur following lymphomatous infiltration.[35] The differential diagnosis of lymphoma should be considered when scleritis is resistant to corticosteroid therapy.[35] Mucosa-associated lymphoid tissue (MALT) lymphoma has been reported to masquerade as anterior scleritis.[35] The anterior scleritis may be associated with uveal effusion syndrome.[35]

Lymphoma may masquerade as iritis or iris nodule, anterior uveitis, posterior uveitis, or panuveitis.[2,3,7,16,19,28,34-36] Incorrect diagnosis of the uveitis syndromes may have severe consequences. Uveal involvement may be the initial manifestation of extra nodal lymphoma.[16] It is a differential diagnosis of recurrent uveitis-like symptoms evolving to painful blind eye. In a study of 40 patients with uveitis masquerade syndromes identified in a cohort of 828 consecutive patients with uveitis, 19 patients had intraocular malignancy (48% of all with uveitis masquerade syndrome; 2.3% of all with uveitis), mainly intraocular lymphoma (n=13) and leukemia (n=3).[28] The ophthalmologist was the first to recognize malignant disease in 11 of the 19 patients (58%). Lymphoma in this masquerade situation is resistant to corticosteroid therapy,[7] and may be associated with hypopyon.[37] A nodular lesion on iris has been reported in the evolution of non-Hodgkin's lymphoma.[18] Vogt-Koyanagi-Harada disease (VKH), an inflammatory ocular disorder characterized by bilateral granulomatous panuveitis and a variety of extraocular manifestations, has been reported to be associated with various immune disorders and recently with malignant lymphoma.[38] There is evidence that VKH can be induced by immune disorders caused by high soluble IL-2 receptor in malignant lymphoma.[38]

Glaucoma may also occur in lymphoma.[2,37] It may occur secondary to neovascularization of the iris and iridocorneal angle (neovascular glaucoma),[2] or may be due to direct obstruction of the trabecular meshwork by tumor cells.[37]

Posterior Segment

The vitreous may be infiltrated by malignant cells,[24] or there may be vitritis.[3,4] In a study of 14 patients with intraocular lymphoma, vitritis was present in 85.7% of cases.[3] Vitreous hemorrhage may also occur.[2]

The typical clinical presentation during posterior segment involvement include blurred vision and floaters.[4,39] The choroid may be involved by lymphoma either alone,[4,34] or as part of panuveitis.[2,7,35] A choroidal mass has also been reported in large B-cell lymphoma.[30] Posterior uveitis may be associated with retinochoroidal infiltration and in more severe cases may be associated with serous retinal detachment.[35,19]

The retina is frequently involved in ocular lymphoma. The various retinal lesions reported in lymphoma include retinal and subretinal infiltrates,[4,12,40] necrotizing granulomatous retinal vasculitis and retinitis,[5,7,23,41] retinal pigmentary degeneration,[17,34] hemorrhagic retinal necrosis,[24] retinal periphlebitis,[8] and perivascular exudates and sheathing.[24,42] The retinal and subretinal infiltrates and pigmentary alterations may mimic a diagnosis of multiple evanescent white dot syndrome.[12] The typical yellowish-white infiltrates may occur at the level of the subretinal pigment epithelial layer or they may clinically mimicking flecks or retinal pigment epithelium (RPE) detachment (figure 1).[7,39,41,43] However, other presentations may include multiple deep white dots in the retina secondary to tumor infiltration; retinal infiltration causing a necrotizing retinitis; or infiltration of the retinal vasculature causing arterial or venous obstruction.[7] Electrooculogram may show findings suggestive of widespread impairment of the retinal pigment epithelium.[41] In adult T-cell leukemia/lymphoma, ocular lesions may result from HTLV-1 infection, including direct infiltration by adult T-cell leukemia/lymphoma cells, cytomegalovirus retinitis and HTLV-1-associated uveitis.[29] The ocular lesion may simulate acute retinal necrosis or herpetic retinitis.[44]

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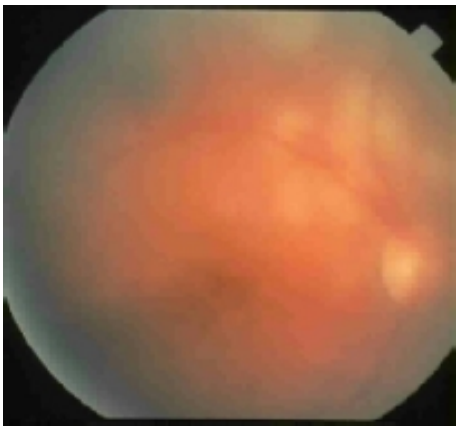

Figure 1: Multiple creamy yellow-white lesions at the level of the retinal pigment epithelium, superior to the optic disc and in the superior arcades. (Reproduced with permission from www.uveitis.org/images.)

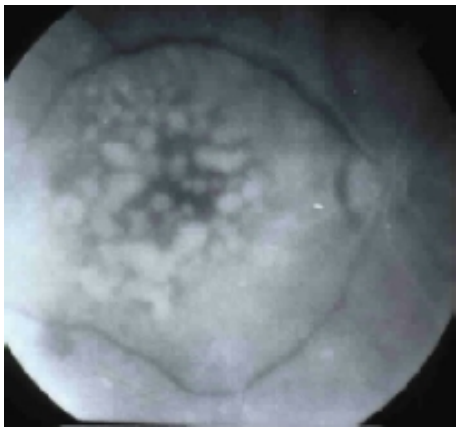

Figure 2: Fluorescein angiogram of the right fundus shows areas of hyperfluorescence in the central macula and superior to the disc, which corresponds to some of the lesions noted on exam. (Reproduced with permission from www.uveitis.org/images.)

Neuro-Ophthalmic Manifestations

Primary intraocular lymphoma is a variant of primary central nervous system lymphoma in which lymphoma cells are initially detected in the eyes before any evidence of the disease in the brain or cerebrospinal fluid.[39] The prognosis is mostly determined by later involvement of the central nervous system and/or visceral organs.[23] Different extra ocular features are induced by long-standing local infiltrates within basal ganglia or diffuse infiltration of the brain leading to an acute increase in intracranial pressure,[23] and therefore leading to neuro-ophthalmic manifestations. Meanwhile, optic nerve invasion may occur in primary intraocular lymphoma,[7,8,37,45] mimicking optic neuritis,[37,45] and this may progress to optic atrophy and visual loss.[45] In this situation, the clinical course may mimic multiple sclerosis.[45] Bilateral optic disc swelling has been reported in Hodgkin's disease.[8]

Diagnosis

Diagnosis can be difficult and frequently delayed as the clinical condition can mimic several other ocular conditions.[2,7]

Accurate diagnosis depends on a high index of suspicion and frequently requires prompt examination; however, sometimes imaging studies such as fluorescein angiogram may be beneficial (figure 2). Histological analysis particularly vitreous biopsy, subretinal aspiration or retinal biopsy for routine cytologic study, flow cytometric analysis, polymerase chain reaction, or immunohistochemistry are helpful in diagnosis (figure 3).[3-5,12,46]

CSF cytology showed positivity in 11% of the patients in one series reported by Grimm et al.[10] Cytopathology of fresh vitreous samples and performing immunohistochemistry (IHC) and polymerase chain reaction (PCR) lead to high yield of diagnosis.[46]

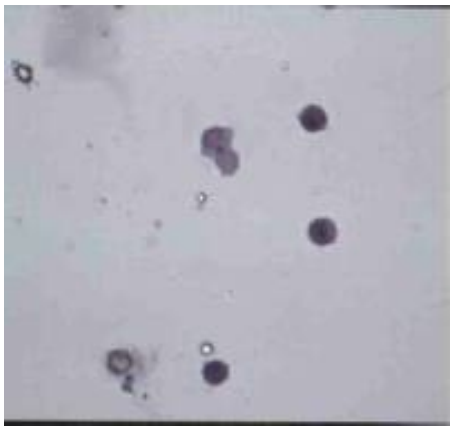

Figure 3: Cytologic study of the vitreous specimen showing markedly atypical lymphoid cells suspicious for lymphoma (Papanicolaou stain ×1000). (Reproduced with permission from www.uveitis.org/images.)

However, alcohol fixation may jeopardize the identification of PIOL cells in the vitreous sample.[47] Examination of the slides by an experienced cytopathologist is critical in the diagnostic evaluation of PIOL.[47]

PCR of immunoglobin heavy chain (IgH) locus, and search for translocation of bcl-2 gene can help to identify lesion clonality specially when IHC and flowcytometry fail to do so.[32,48] Likewise, it has been shown that measurement of IL-10 in the aqueous humor is a good screening test to reduce diagnostic delays.[49]

Treatment

Management of intraocular lymphoma needs joint efforts of ophthalmologists, oncologists, and radiotherapists.

Initial treatment was categorized as focal (intra-ocular chemotherapy, ocular radiotherapy) or extensive (systemic chemotherapy, whole brain radiotherapy).[10]

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Methotrexate (MTX) is the chemotherapeutic agent most commonly used to treat PCNSL and intraocular lymphoma.[50] MTX is delivered to the eye by intraocular injection,[51] or with iontophoretic treatment using MTX-loaded hydrogels.[52]

Other agents such as rituximab (anti CD20 antibody),[51,53] and 2-methoxyestradiol,[50] were experimentally used for treatment.

It has been shown that focal therapy may minimize treatment toxicity without compromising disease control or changing relapse pattern.[10]

External beam radiotherapy to the eye is rarely used for treatment of PIOL.[51]

Prophylactic whole-brain radiation in the absence of documented CNS disease may be indicated, because up to 85% of patients develop CNS lymphoma. However, there is insufficient evidence to evaluate its value.

Current studies are focused on eliminating antigenic load and inhibiting B cell chemokines as well as to determine the optimal local and systemic chemotherapy agents and immunotherapy options in the management of PIOL.[51]

Conflict of Interest: None declared

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