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Review Article

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Ocular Lymphoma: Detection, Management, and Treatment

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Abstract

Primary intraocular lymphoma is a rare manifestation of primary central nervous system lymphoma. It most often affects patients in the sixth and seventh decades of life and has a predilection for immunocompromised patients, particularly males, whom it affects twice as often as females. Because of the ability of primary intraocular lymphoma to mimic less severe conditions such as uveitis, its detection can be difficult. The diagnosis should be suspected in all elderly patients with chronic uveitis unresponsive to corticosteroid or antibiotic therapy.

Although no therapeutic paradigm has been defined, combining chemotherapy and radiation therapy is the most effective treatment for the condition. Without multicenter clinical trials focused on improved treatment strategies, optimal disease management will continue to be challenging. The increasing frequency of ocular lymphoma has underscored the need to meet this challenge. In this article, the authors aim to provide ophthalmologists and primary care physicians with the tools necessary to hasten early recognition and prompt treatment of the disorder. Although no cure exists, recent studies with rituximab have shown promising results in treating intraocular lymphoma.

Keywords: Intraocular Lymphoma, Non-Hodgkin's Lymphoma, Primary Central Nervous System Lymphoma, PCNSL, PIOL, High-Dose Methotrexate, Rituximab.

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1. Introduction

Ocular neoplasms of any type are exceedingly rare, accounting for approximately 1.8 cases per million people [1,2]. Primary intraocular lymphoma (PIOL) is an ocular manifestation of primary central nervous system lymphoma (PCNSL). PIOL, also known as intraocular large cell lymphoma, is a high-grade variant of non-Hodgkin's B-cell lymphoma that tends to be confined to the central nervous system (CNS). PIOL mimics less severe conditions such as chronic vitreitis or uveitis but is usually more refractory to steroid and antibiotic treatment [3]. Although rare, PIOL is most commonly seen in the sixth and seventh decades of life [4]. Given its frequency in this age group, it should be considered in the differential diagnosis of retinal vasculitis or necrotizing retinitis in middle-aged or elderly patients [5,6]. Unfortunately, because of the difficulty associated with diagnosing the condition, it is often misdiagnosed until central nervous system (CNS) involvement occurs [7]. PIOL invades the brain, the vitreous body and nerves of the eye, the meninges, and the nerve roots of the central nervous system [8]. The posterior parts of the eye are most commonly affected in ocular lymphoma and can lead to systemic lymphoma dissemination in 7-8% of patients [9]. PIOL is associated with significant morbidity and mortality, but prompt recognition and early diagnosis may improve the prognosis [10].

2. Incidence

The exact incidence of PIOL remains uncertain. However, it is estimated to be less frequent than PCNSL, which has an incidence of 1/100,000 [11]. Although PCNSL is uncommon, the incidence of the disorder has dramatically increased over the past two decades

[4]. PCNSL affects the male gender more commonly than females and often affects patients in the sixth and seventh decades of life [4]. The prevalence of the condition has tripled in frequency during the last two decades, particularly amongst immunocompromised patient populations. It is expected to be the most common neurological neoplasm in the acquired immunodeficiency syndrome (AIDS) population on account of the commensurate increased prevalence of AIDS [12]. An estimated 3% of AIDS patients will acquire PIOL sometime [12]. Immunocompromised individuals, including transplant recipients and individuals with inherent immunodeficiency syndromes such as Wiskott-Aldrich syndrome, are also at increased risk of developing ocular lymphomas [4,12].

3. Pathogenesis

Primary intraocular lymphoma (PIOL) is a manifestation of PCNSL. Both represent rare extranodal non-Hodgkin lymphomas confined to the central nervous system and the eye, respectively [13]. Although the exact pathogenesis of PIOL remains obscure, two prominent hypotheses exist; one with an immunologic basis, the other microbiologic in nature. The prevailing hypothesis suggests that PIOL arises from activated lymphocytes that are transferred to the globe of the eye via recurrent pathogenic antigen responses. Chronic antigenic stimulation of these lymphocytes in the globe of the eye results in the development of a monoclonal lymphoproliferative response [14]. Upon initiating the lymphoproliferative response, tumor cells tend to colonize the retinal surface in preparation for invasion of the globe [15]. Once firmly latched onto the retinal surface, these cells expand preferentially into the subretinal space and, later, invade through the retinal pigment epithelium into the choroid [15]. If left undetected, the PIOL can potentially travel from the choroid of the eye directly into the central nervous system, resulting in a poorer prognosis.

4. Clinical Features

Patients with PIOL often complain of blurred vision, loss of visual acuity, and floaters [16,17]. The presentation is usually painless. However, pain in association with PIOL has been documented in rare cases, possibly due to increased intraocular pressure secondary to tumor growth. However, diplopia, proptosis, ptosis, conjunctival congestion, and glaucoma can also be seen in rare cases [18]. Fundoscopic examination usually reveals yellow subretinal infiltrates but can, in rare cases, demonstrate hemorrhagic retinal vasculitis and hemorrhagic retinal necrosis [3,5]. Optic atrophy and changes in the retinal pigment epithelium, may also be noted on fundoscopic exams. Some cases have presented with proptosis and chemosis [18]. Most patients may also exhibit posterior uveitis associated with retinochoroidal infiltration, anterior scleritis associated with uveal effusion syndrome, or bilateral pan-uveitis associated with serous retinal detachment [16]. Occasional or rare cases of uveitis documented by ophthalmologists result from PIOL and are thought to be associated with an increase in specific cytokines caused by the disease [14,19]. Therefore, distinguishing the type of interleukins is essential for differentiating between benign uveitis and PIOL masquerading as uveitis [19]. For instance, the inflammatory cells found in benign uveitis characteristically produce markedly elevated levels of interleukin 6 (IL-6) [19,20]. On the other hand, the malignant lymphocytes of PIOL release IL-10 and tend to result in an IL-10 to IL-6 ratio greater than 1.0, an essential characteristic of PIOL [19,20].

Incidentally, multifocal detachment of the retinal pigment epithelium is considered pathognomic for PIOL [21]. Further, ocular adnexal and intraocular involvement may be recognizable on orbital imaging [7]. Since intraocular lymphoma often mimics benign lesions such as chronic uveitis, the diagnosis should be suspected in patients whose supposed uveitis responds poorly to corticosteroids. Furthermore, the vision of patients with PIOL is often better than expected based on the clinical examination. Because of the intimate relationship between ocular and other brain structures, the occurrence of ocular lymphoma can lead to impingement on vital neurological structures and, as a result, frequently yields neurological deficits in affected patients [22].

Therefore, symptoms such as headache, memory loss, or reduced vision that arise in the setting of ocular lymphoma should raise the suspicion of central nervous system involvement. All individuals diagnosed with ocular lymphoma are, thus, recommended to undergo thorough neurological evaluation, including history, physical exam, and possibly neuroimaging to rule out cognitive or sensory impairment secondary to neoplasm [22].

5. Diagnosis

Prompt diagnosis and treatment may minimize visual loss and prolong life [5]. Primary intraocular lymphoma has a variable clinical course and frequently mimics benign inflammatory disease. Therefore, arriving at the correct diagnosis can be difficult even when it is suspected [23]. Ocular lymphoma can be diagnosed by slit lamp examination, lumbar puncture, vitreous biopsies, retinal biopsy, or analysis of immunoglobulin heavy chain gene rearrangements [5,9,10,24]. The use of lumbar puncture in patients suspected of PIOL stems from the fact that malignant cells are often present in the cerebral spinal fluid when ocular lymphoma is diagnosed [10]. Nevertheless, multiple vitrectomies and lumbar punctures may be necessary before the correct diagnosis is made, demonstrating the lack of sensitivity such diagnostic methods have for the condition [10].The ophthalmic examination of such patients usually reveals cellular infiltrates in the vitreous with or without subretinal infiltrates [17]. Determination of vitreous and fundus involvement can be achieved via fundoscopy and ultrasound examination [25,26]. Slit lamp examination often shows abundant cells in the anterior chamber [25]. Orbital computerized tomography (CT) and magnetic resonance imaging (MRI) have been used to achieve a diagnosis of PIOL and help determine the presence of extraocular involvement [7].

However, despite its widespread use as a diagnostic tool, imaging studies in ocular MRI and ultrasound have low sensitivity for ocular lymphoma. Nonetheless, they remain helpful in creating a reflective differential diagnosis against uveitis or ocular melanoma in the setting of PIOL [7]. In contrast to previous beliefs, the di-

agnosis of PIOL lesions cannot be confirmed histopathologically. Until recently, it was believed that cytology is frequently insufficient to confirm a suspicion of primary intraocular lymphoma (PIOL) [20]. Recent studies demonstrate that the opposite is true. Cytologic examination of cerebrospinal fluid and diagnostic vitrectomies, can yield accurate diagnostic evaluation in patients suspected of PIOL [17]. Furthermore, molecular and cytokine analyses are valuable adjuncts to cytology for diagnosing PIOL [17]. A recent study suggested that analysis of immunoglobulin heavy chain gene rearrangements (AIGHR) used alongside cytopathology and flow cytometry in systemic lymphoma have demonstrated increased diagnostic yield in PIOL signaling, a potentially valuable tool in diagnosing PIOL [24]. Thus, the use of radiological, nuclear medicine, molecular, and flow cytometric resources can improve early diagnosis, accurate staging, and response evaluation in patients with PIOL [27].

The ability of intraocular lymphoma to cause vitreous is associated with the reactive lymphocytic reaction it initiates in the vitreous of affected eyes. Vitreous biopsies of such lesions can often be nondiagnostic, leaving many experts needing clarification on a diagnostic paradigm for PIOL. The preferred method of obtaining a positive yield in such patients is via an aspiration biopsy through a retinotomy in the subretinal pigment epithelial space [29]. Notwithstanding, the morphologic diagnosis of primary and metastatic intraocular lymphoma (IOL) is made difficult by the paucity of fragile lymphocytes retrieved through pars plana vitrectomy (PPV) [24].

Diagnosing primary or secondary ocular lymphomas remains a challenge. This is partially because of the exceeding rarity of the disease, which has made obtaining tissues for pathologic analysis complicated [17,30]. According to the World Health Organization (WHO) classification for hematologic and lymphoid neoplasms, most PIOLs are classified as an immunohistologic subtype of diffuse large B-cell type of non-Hodgkin's lymphoma [31]. This classification corresponds with the distinctive histopathologic appearance of PIOL, which is frequently characterized by a constellation of sparsely distributed inflammatory cells in scant cytoplasm interspersed among large, atypical, neoplastic lymphocytic cells and necrotic debris [10, 32-34]. The morphologic appearance of the nuclei of the malignant cells characteristically has irregular contours, coarse chromatin, and nucleoli [10,32].

6. Treatment

Although optimal treatment has yet to be identified, recent studies have offered valuable insight into the management of PIOL [14,35,36]. Since PIOL is a type of CNS lymphoma, treating the entire brain rather than just the affected ocular structures are indicated. In order to slow down the progression of the lymphoma and to reduce the risks of complications, a standard combined-modality treatment approach is indicated. This treatment approach incorporates pharmacologic agents penetrating the CNS and whole-brain radiation therapy (WBRT). The most commonly used therapy for PIOL is high-dose methotrexate, along with radiation in severe cases [36-38]. Using a median of approximately 40 Gy radiation therapy alone on the eyes and CNS can yield high initial response rates. However, these patients eventually develop a recurrence of the disease [27,37,38]. WBRT rather than focused ocular radiation is far more effective and associated with less recurrence [39,40].

High-dosed methotrexate-based treatment regimens are more capable of significant regression rates than past treatment protocols [8,14,41]. A recent study using methotrexate-based treatment regimens for PIOL revealed induction of clinical remission in 26 of 26 patients (100%) with a median of 18.5 months follow-up [49]. Methotrexate-based regimens alone, even without radiation, have contributed to prolonged overall survival in the range of 5 years or more [8,12,36]. Notwithstanding, relapses occur in most cases, signaling the need for improved tools for earlier diagnosis of the disease [8]. Treating PIOL with traditional systemic chemotherapy alone is futile because of difficulties penetrating the blood-ocular barrier [22,42]. The ability to penetrate this problematic barrier has made agents such as methotrexate and cytosine arabinoside (Ara-C) essential treatment options for PIOL [43,44]. Even with the promise such agents offer, optimal management of PIOL remains undefined and largely anecdotal [35,45,46]. The current mainstay of treatment for PIOL consists of intravenous systemic methotrexate (8g/m2 IV) [44,35]. If the neoplasm does not respond to either treatment strategy, WBRT is warranted [46-48]. Intrathecal chemotherapy may be beneficial in treating leptomeningeal symptoms associated with PIOL, but high-dose methotrexate regimens without intrathecal treatment may have the same efficacy [14].

Complications associated with high-dose methotrexate include cataracts in as many as 73%, corneal epitheliopathy in 58%, maculopathy in 42%, vitreous hemorrhage in 8%, optic nerve atrophy in 4% and endophthalmitis in 4% [49]. Despite the numerous complications associated with treating ocular lymphoma, none of the patients in the aforementioned study experienced irreversible vision loss attributable to the methotrexate treatment [49]. Nonetheless, similar studies have demonstrated decreased visual acuity in patients with preexisting ocular pathology who were given intraocular methotrexate [50].

Although effective, the combination of WBRT and chemotherapy is associated with a significant risk of neurotoxicity, particularly in the geriatric population [39,40]. One recent study demonstrated neurotoxicity in 100% of the patients older than 60 years of age following a combined treatment with WBRT and a high-dose methotrexate regimen [14]. The various ocular structures that comprise the eye have varying sensitivities to irradiation. Prolonged exposure of ocular structures to high doses of external beam or plaque radiotherapy has been associated with reversible and irreversible ophthalmic complications [51]. For instance, while most patients tolerate radiation doses between 30-40 Gy, erythema and desquamation of the eyelids is commonly seen after radiation of 50-60 Gy. Radiation doses over 60 Gy often lead to eyelid scarring with resultant ectropion and entropion [51].

Further, increased doses of radiation also place the patient at risk of developing dry eye syndrome secondary to radiation-induced lacrimal gland atrophy [52,53]. The lacrimal gland's primary function is to lubricate the eye, and any failure to do so not only results in dry-eye syndrome but can ultimately result in loss of the affected eye [52,53]. Doses exceeding 60 Gy also result in conjunctivitis and scar formation within the corneal epithelium, leading to eye irritation and—in the case of corneal damage—visual severe impairment [54,55]. In cases where the radiation-induced scarring of the cornea is severe, the corneal perforation will arise, leading to endophthalmitis and permanent vision loss [55,56]. Radiation-induced cataracts and the associated decrease in visual acuity also threaten patients receiving PIOL irradiation [57,58]. Radiation optic neuropathy (RON), characterized by microaneurysms of ophthalmic capillaries and intraretinal exudates, can lead to atrophy of the optic nerve and permanent blindness [59,60]. The occurrence of RON and most ophthalmic complications of ocular irradiation can be avoided by strict compliance with low-dose radiation and avoidance of high-dose radiation regimens [52,58-60]. Radiation-induced dementia is also a common side effect of WBRT [39].

7. Prognosis

PIOL runs a usually fatal course. Recent studies have demonstrated prolonged median survival in patients receiving systemic high-dose methotrexate and WBRT [14]. In one study, the combination of methotrexate and WBRT prolonged the median survival duration from 12 months (with WBRT alone) to 33 months [55]. In another study, the combined-modality treatment approach with high-dose methotrexate and high-dose cytosine arabinoside combined with WBRT increased median survival to 42.5 months [56]. In cases without treatment, life expectancy can be as low as a few weeks [35]. Controversy exists about the clinical and prognostic significance of systemic dissemination in PIOL. Extensive systemic spread of the lymphoma can occur in the end stages of the disease, but unlike other neoplasms, staging of PIOL has proven futile and unreflective of clinical course [9]. Involvement of the central nervous system (CNS) often reflects a poorer prognosis with no effective treatment capable of offering long-term survival to such patients [13]. Median survival for cases of PIOL with CNS progression is approximately 23 months from initial diagnosis [36]. Patients not receiving treatment whose ocular disease was identified and treated before CNS progression had a significantly improved survival in 5 years or more [36]. Nonetheless, relapse of the disorder can be expected in up to 21% of previously treated patients [36]. Despite recent improvements in diagnosis and treatment, PIOL remains an aggressive disease with an overall 5-year survival rate of less than 25%. [19] Further, most patients die within two years of diagnosis due to progressive or recurrent CNS disease associated with PIOL [14].

8. Conclusions

It is not uncommon for PIOL to present as seemingly innocuous conditions such as uveitis. In elderly individuals with such conditions, the diagnosis should be suspected. The current diagnostic management of patients in whom ocular lymphoma is suspected includes a thorough neurological examination, including cerebral magnetic resonance imaging (MRI), lumbar puncture, and diagnostic vitrectomy, with the definitive diagnosis being based on the cytological analysis of a vitreous biopsy specimen [24]. Currently accepted treatment paradigms center on methotrexate-based chemotherapeutic regimens that, although imperfect, offer patients with PIOL improved survival rates. The increasing frequency of ocular lymphoma signals a need for dramatic improvement in therapeutic strategies [24]. Even with the significant improvement in treating ocular lymphoma during the past few decades, many critical therapeutic questions still need to be answered, including optimal dose, frequency, and duration of chemotherapeutic and irradiation strategies. Carefully designed multicenter clinical trials are warranted to build upon and improve the aforementioned therapeutic advances [28].

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