Primary Intraocular Lymphoma

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Introduction

Primary intraocular lymphoma (PIOL) is a subset of primary central nervous system lymphoma (PCNSL). PCNSL is usually a diffuse large B-cell non-Hodgkin's lymphoma in which malignant lymphoid cells involve the retina, vitreous, or optic nerve, with or without concomitant CNS involvement.[1,2] Because PIOL remains confined to neural structures, it is distinguished from primary orbital lymphoma and systemic non-Hodgkin's lymphomas that either involve or metastasize via the circulation to the uvea and ocular adnexa of the orbit, lacrimal gland, and conjunctiva.[3]

The incidence of PCNSL has increased in both immunocompetent and immunocompromised people from 0.027/100,000 in 1973 to 1/100,000 in the early 1990s.[4] The cause for the increased incidence in immunocompetent patients is unknown.[5] Ocular disease is bilateral in 80% of cases.[6] Previous reports suggested that approximately 80% of patients with PIOL subsequently will develop brain lymphoma.[7-9]

This report highlights the need for collaboration to improve our understanding and management of rare malignancies such as PIOL.

Case Report

A 50-year-old male, initially presented for blurred vision, more pronounced on the left, of three weeks duration. Ophthalmologic exam confirmed the presence of scattered vitreous cells. The eye angiogram was within normal limits and no findings were suggestive of papillitis.

A workup, including complete blood count (CBC), angiotensin-converting enzyme level, Human Leukocyte Antigen-B 27 and 51, antinuclear antibody test, and Rapid Plasma Reagin, was within normal limits except for a mild lymphocytosis. A hematology consult was requested.

The workup for lymphoproliferative disorders included an erythrocyte sedimentation rate (ESR), a positron emission tomography (PET) scan, a magnetic resonance imaging (MRI) of the brain, a bone marrow biopsy, blood flow cytometry, a lumbar puncture with flow cytometry and cytology, and a computed tomography (CT) scan of the chest, abdomen, and pelvis. All exams were within normal limits.

Over the next few months, the patient was treated with different modalities for vitreitis, including methotrexate, without improvement. Left vitrectomy was done 14 months after initial presentation. The flow cytometry on the vitreous fluid showed 11% monoclonal type B lymphocytes with lambda light chain restriction. Another workup, including ESR, PET scan, MRI of the brain, bone marrow biopsy, blood flow cytometry, lumbar puncture with flow cytometry and cytology, CT scan of the chest, abdomen, and pelvis, was within normal limits. The radiation oncologist was reluctant to consider this case as a primary intraocular lymphoma and to treat it as such.

The patient's vision improved after vitrectomy. However, he had right-sided blurriness. Right vitrectomy was done five months later. Cytology and flow cytometry on the vitreous fluid confirmed the presence of a large B cell lymphoma with lambda light chain restriction. The workup for systemic involvement was again negative.

The patient was treated with bilateral ocular radiation (6MV photons, 5 by 5.5 cm, to a dose of 3000 cGy in 200 cGy per fraction for 15 fractions). He was followed every six months with brain MRI, CBC, and a lumbar puncture with fluid cytology and cytometry without evidence of recurrence.

The patient reported headaches two years later (almost four years from the initial presentation). An MRI of the brain showed a large left frontal lobe tumor. He was treated with two cycles of CHOP-R for a presumed large B cell lymphoma relapse. CHOP-R is named after the chemotherapy drugs used in the treatment. It involves the monoclonal antibody ***r***ituximab, and the drugs: ***c***yclophosphamide, doxorubicin (chemical name ***h***ydroxydaunorubicin), vincristine (originally known as ***O***ncovin®) and ***p***rednisone.

The repeat MRI after the two CHOP-R cycles showed regression of the lesion. The patient completed a total of four cycles of CHOP-R, then underwent debulking surgery followed by whole brain radiation therapy. The pathology confirmed the diagnosis of diffuse large B cell lymphoma. The patient underwent autologous stem cell transplantation eight months after beginning CHOP-R therapy, followed by five courses of intrathecal cytarabine. The patient remained disease free four years later.

Discussion

At presentation, PIOL often is misdiagnosed as uveitis and may respond initially to corticosteroids, resulting in a delay of definitive diagnosis.[10] Patients may complain of blurred vision and floaters. Visual acuity often is better than would be expected based on the clinical examination.[10-13]

Given the nonspecific nature of eye findings in PIOL, patients being considered for this diagnosis should be examined for other causes of uveitis, including sarcoidosis, intermediate uveitis, multifocal choroiditis, acute posterior multifocal placoid pigment epitheliopathy, birdshot chorioretinopathy, toxoplasmosis, ocular tuberculosis, and acute retinal necrosis.[3] A diagnosis often is not made until there is brain progression at which time the prognosis is poor.[14] The most common finding on ocular examination is vitreitis. The posterior segment examination usually reveals vitreous cells, which may form clumps or sheets.[12,13]

PIOL is closely related to PCNSL. It seldom involves other organs, therefore, neuroimaging of the brain, orbits, and a lumbar puncture are required.[15,16] For patients with no evidence of disease by neuroimaging or cerebrospinal fluid (CSF), a diagnostic vitrectomy should be performed on the eye with the most severe vitreitis or poorest visual acuity.[17]

It is difficult to arrive at a pathologic diagnosis of PIOL.[7,18] Thus, research has focused on developing other methods to assist in the diagnosis of PIOL. These methods include immunohistochemistry, flow cytometry, molecular analysis, and cytokine evaluation.

Immunohistochemistry and flow cytometry rely on the finding that most PIOLs are monoclonal populations of B lymphocytes that stain for B-cell markers (CD19, CD20, CD22) and have restricted expression of kappa or lambda chains.[13,19,20] Immunohistochemistry also has been used to demonstrate expression of B-cell lymphoma-6 (BCL-6) and multiple myeloma oncogene 1 (MUM1) in PIOL cells.

BCL-6 is a B-cell marker that is normally turned off as B cells move from the germinal center into the marginal zone during B-cell differentiation.[21] MUM1 is a protein involved in the control of plasma cell differentiation. While B cells usually express one of these proteins at a time, concomitant expression has been shown in systemic diffuse large B-cell lymphoma.[22] Similar patterns of expression also have been demonstrated in five patients with PIOL.[23] Many still believe that a pathologic diagnosis is required to confirm the presence of PIOL and immunophenotyping plays a supportive role in diagnosis.[3]

Ocular specimens from patients with PIOL revealed immunoglobulin heavy (IgH) rearrangements in the third complementarity-determining region (CDR3) of the IgH variable region that can serve as a molecular marker of clonal expansion of lymphocytes.[24] Cytokines may play a role in distinguishing PIOL from uveitis. While interleukin 6 (IL-6) is produced in high levels by inflammatory cells in uveitis, IL-10 is produced by malignant B lymphocytes in intraocular and CNS lymphoma. PIOL is associated with an increased IL-10 to IL-6 ratio (greater than 1.0).[25]

These patients should undergo neuroradiologic imaging and CSF examination. No further ocular diagnostic tests are required in patients with positive CSF. In patients with negative CSF, a vitrectomy or vitreous tap should be performed in the eye with more severe vitreitis or worse visual acuity. This sample should be sent for cytology, cytokine analysis, IgH rearrangements, Bcl-2/IgH translocations, and immunohistochemistry/ flow cytometry.

Chorioretinal biopsies may be required when vitrectomy specimens are nondiagnostic. Because of the cytolytic nature of corticosteroids on lymphoma cells, corticosteroid treatment should be withheld until all diagnostic procedures are completed.[3]

The optimal method of treatment for PIOL or PCNSL with ocular involvement is yet to be determined. Local ocular treatments include ocular radiotherapy[6,26] and intravitreal methotrexate.[27] Due to radiation complications and the fact that this treatment cannot be repeated if the patient relapses, intravitreal treatment has become more desirable for both isolated and recurrent ocular disease.[27,28] Extensive treatments include whole brain radiotherapy (which includes the posterior retina), high-dose methotrexate[29], cytarabine alone and in combination with methotrexate[30-32], as well intrathecal chemotherapy.

Grimm et al. retrospectively studied 83 HIV negative, immunocompetent PIOL patients from 16 centers in seven countries.[14] All had disease confined to the eyes at diagnosis with no evidence of brain, systemic, or spinal cord lymphoma. Initial treatment was categorized as focal in 23 (intra-ocular methotrexate, ocular radiotherapy) or extensive in 53 (systemic chemotherapy, whole brain radiotherapy) patients. Six patients received no therapy and the details were unknown in one. Forty-seven patients relapsed (brain 47%, eyes 30%, brain and eyes 15%, and systemic 8%). Median time to relapse was 19 months. There was no statistically significant difference in progression free survival (PFS) or overall survival (OS) regardless of the treatment modality. Median PFS and OS were 29.6 and 58 months, respectively, and unaffected by treatment type.

Intensive chemotherapy followed by autologous stem-cell transplant was reported to rescue patients with refractory or recurrent PCNSL and PIOL. A study of 22 patients with PCNSL included 11 patients with PIOL (3 with isolated ocular disease and eight with concomitant CNS

involvement).[33] Five of the eight patients with CNS disease had partial or complete response and had survival times of 18+ to 70+ months. One of these patients had systemic progression and died in 3 months. Two had ocular recurrences. One had complete response with subsequent ocular radiotherapy, while the other died due to a second tumor. Two of the three patients with isolated ocular disease had complete response, while the other patient with isolated ocular disease had intraocular lymphoma recurrence at three months, then died of a second tumor. Only one of the 11 patients with PIOL experienced neurotoxicity. Seven of the 22 patients experienced this side effect. In addition, this treatment was not recommended for patients older than 60 years of age, because 5 of 7 patients in this age group died of treatment complications.

Conclusions

PIOL often is misdiagnosed and patients should be examined for other causes of eye disease when considering this diagnosis. A pathologic diagnosis of PIOL may not be found. Cytokines help to distinguish PIOL from uveitis. Neuroradiologic imaging, CSF examination, vitrectomy, and/or vitreous tap each may play a role in diagnosis. Depending on the patient, treatment of the PIOL may be focal or extensive. Chemotherapy also may be necessary. Often, prognosis is poor because of the disease progression that occurs before diagnosis.

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Keywords: B-cell lymphoma, central nervous system neoplasms, eye diseases, case report