Case Report

Ocular Adnexal Lymphoma Presenting with Visual Loss

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Abstract

Context: Elderly patients with visual loss often have age-related macular degeneration, diabetic retinopathy, glaucoma, and cataract as common causes of visual loss. Other less common etiologies should be considered, especially in those presenting with systemic associations. **Case Report:** The patient discussed in our review is an 80-year-old female, with a history of diabetic retinopathy and macular degeneration who presented with a sudden deterioration of vision. While this was initially attributed to diabetic retinopathy, she was eventually noted to have a salmon patch lesion in her conjunctiva, diagnosed on biopsy to be a diffuse large B-cell lymphoma. **Conclusion:** Because of the significant rate of disseminated disease among patients with lymphomas in the orbit that carries a worse prognosis, early diagnosis is essential to promote better overall survival of these patients. We describe here a patient diagnosed with conjunctival lymphoma associated with pronounced visual loss and review the literature on this subject.

Keywords: Elderly, eye, mucosa-associated lymphatic tissue (MALT), ocular lymphoma (OL), salmon patch

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Introduction

Although more prevalent causes of loss of vision in elderly patients such as age-related macular degeneration, glaucoma, cataract, and diabetic retinopathy have been widely discussed in the medical literature, clinicians should keep in mind other less common etiologies when evaluating a patient with this complaint, especially those in which prompt treatment can potentially improve the overall clinical outcomes. One such scenario is discussed through our case presentation of an elderly lady who presented with acute onset of loss of vision to her ophthalmologist and was diagnosed with a conjunctival lymphoma.

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Case Presentation

An 80-year-old woman with a history of coronary artery disease, atrial fibrillation, hypertension, diabetes mellitus, basal cell carcinoma removed via Mohs procedure on the nose, diabetic retinopathy, and macular degeneration presented with a history of a recent increase in the number of falls she had been sustaining due to a recent, sudden deterioration of vision bilaterally. She was initially seen by the ophthalmologist 2 months ago for loss of vision in her right eye that was thought to be related to her previously diagnosed diabetic retinopathy. She underwent focal laser photocoagulation for diabetic retinopathy in her

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right eye, with no significant improvement in vision. Upon further ophthalmic evaluation, a fleshy, salmon colored conjunctival tumor was identified in her left eye [Figure 1]. She was referred to the ocular oncology service and subsequently the conjunctival tumor was biopsied. Histopathologic examination of the specimen revealed sheets of large neoplastic lymphoid cells with moderate nuclear pleomorphism, vesicular chromatin, and large nucleoli underlying the normal conjunctival epithelium [Figure 2]. Small lymphocytes were observed admixed with the previously described atypical ones. Immunohistochemical studies showed the large lymphoid cells stained positive (diffuse, strong) for CD20 and MUM-1, less intensely positive for Pax-5, weakly positive for Bcl-6, and negative for CD10. The small background lymphocytes were CD3-positive [Figure 3]. Histopathological findings were consistent with diffuse large B-cell lymphoma (DLBCL) with an immunophenotypic profile consistent with nongerminal center origin. Proliferation index estimated by Ki-67 labeling was found to be 80% and were positive for c-myc rearrangement.

The patient's laboratory workup including complete blood count with a differential, comprehensive metabolic panel, and coagulation profile, was within normal limits. Serum lactate dehydrogenase (LDH) level was 506 U/L (normal range: 313-618 U/L). Her hepatitis screen was negative. She underwent orbital computed tomography (CT) and magnetic resonance imaging (MRI) scans that failed to reveal any discrete masses although the MRI revealed a mild asymmetric thickening and enhancement of the sclera in the anterior left globe. Additionally, both positron emission tomography-CT (PET-CT) and an MRI of her brain failed to reveal any other systemic central nervous system (CNS) involvement. Cerebrospinal fluid (CSF) analysis after an uncomplicated lumbar puncture (LP) did not reveal any malignant cells.

Since the patient had a biopsied conjunctival tumor on the left side but had unexplained loss of vision on the right side as well, she was presumed to have CNS involvement and was treated with high dose systemic methotrexate in addition to rituximab. She received three cycles of methotrexate at 1.5 g/m^2 (50% dose reduction due to age and low creatinine clearance) and rituximab at a dose of 375 mg/m^2. The first cycle was complicated by severe diarrhea related to *Clostridium difficile* infection and dehydration and the third cycle was complicated by acute renal insufficiency, fluid overload, insufficient methotrexate clearance, and prolonged hospital stay. Further chemotherapy had to be stopped in view of the side effects. Ophthalmic follow-up revealed improved vision in her right eye. Interval MRI revealed interval improvement in nonspecific scleral thickening and enhancement along the anterior aspect of the left globe. Based on the documented improvement, the patient was to be continued on the same chemotherapy regimen; however, she declined further treatment. The patient was evaluated by radiation oncology but she opted to decline further treatment at this time. She has not followed up by physicians at this hospital after that and has been lost to follow-up.

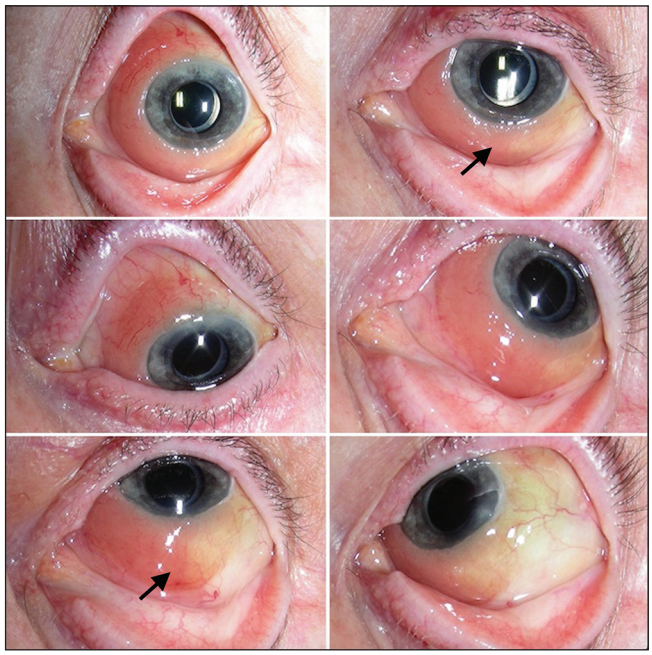

Figure 1: Initial clinical presentation—clinical composite photograph of the patient's left eye reveals an extensive fleshy salmon solid tumor of the conjunctiva extending into the orbit inferonasally

Discussion

Non-Hodgkin's lymphoma (NHL) is a group of malignant neoplasms that involve excessive proliferation

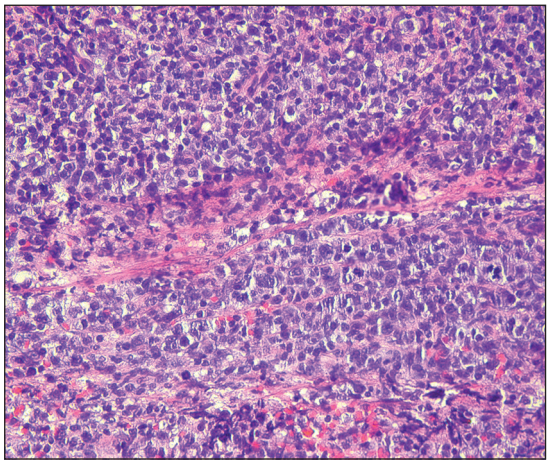

Figure 2: Histopathology from biopsied conjunctival lesion—photomicrograph reveals sheets of large neoplastic lymphoid cells with moderate nuclear pleomorphism, vesicular chromatin, and large nucleoli underlying normal epithelium. (H&E, 30×)

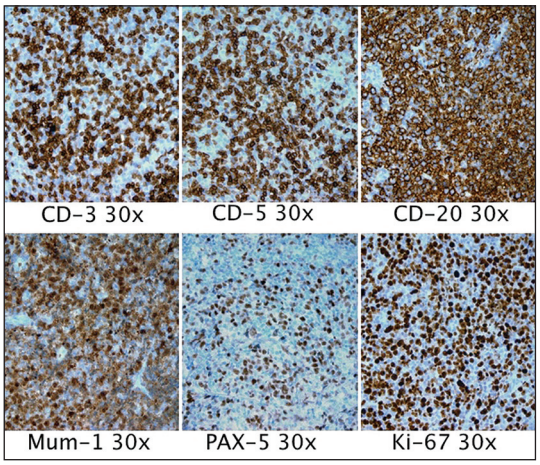

Figure 3: Immunohistochemical stains of conjunctival lesion—photomicrographs of multiple immunohistochemical assays showed that the large lymphoid cells stained strongly positive for CD20 and MUM-1; it was also positive for Pax-5 and weakly positive for Bcl-6. The large lymphoid cells were negative for CD10. The small background lymphocytes stained positive with CD3

of B- or T-lymphocytes. NHL cases account for 4.3% of all new cancer cases in the US according to the Surveillance, Epidemiology, and End Results (SEER) database.[1] Ocular lymphoma (OL) accounts for 5-10% of cases of extranodal lymphomas.[2] The SEER database also suggests that there has been a rapid increase in the number of cases of OLs since 1975, with an annual increase of around 6%.[3] This could be attributed to the availability of better imaging modalities as well as better diagnostic techniques including flow cytometry, immunohistochemistry, and molecular analysis among others. Due to a significant overlap between the modes of presentation of OL with other benign diseases of the eye, it is important to recognize the clinical-pathological aspects of these tumors. Early recognition is also important because many patients with orbital lymphomas will progress to develop systemic lymphomas and hence, need close surveillance.[4]

Non-Hodgkin's lymphoma subtypes involving the eye

According to the 2008 World Health Organization (WHO) classification, there are about 70 different subtypes of lymphoma.[5] These have been classified based on their clinical features, morphological characteristics, genetics, and immunophenotypic features. A complete discussion of all lymphoma subtypes is outside the scope of this paper but it is essential to summarize the most common subtypes of lymphoma that affect the ophthalmic structures.

NHL Subtypes Involving the Adnexal Structures: Ocular adnexal lymphoma (OAL), a rare form of NHL, comprises about 5-10% of all cases of OLs.[2,6] OAL most commonly affects the orbit (up to 40%) followed by the conjunctiva (35-40%) and the eyelids (up to 10%).[7] Of the various WHO subtypes of NHL, the three most common ones to affect the adnexal structures include extranodal marginal zone lymphoma (ENMZL), follicular lymphoma, and diffuse large B-cell lymphoma (DLCBL).

ENMZL of mucosa-associated lymphatic tissue (MALT) is the most common among these, encompassing close to 50% of cases in a recent Danish study.[2] Through their studies on cadaveric eyes, Knop *et al*. have demonstrated that the conjunctiva, lacrimal gland, and the lacrimal drainage system are also a part of MALT; hence, the most common lymphoma type in these structures is the ENMZL.[8,9] This lymphoma has been associated with *Chlamydia psittaci* infection in some studies with good response to antibiotic therapy.[10-12]

Follicular lymphoma and DLBCL are the second and third most common types of NHL to affect the adnexal structures.[13] Many other NHL subtypes can manifest in adnexal structures including mantle cell lymphoma, small lymphocytic lymphoma, lymphoplasmacytic lymphoma, and anaplastic large T-cell lymphoma.[2]

Interestingly, the lacrimal gland has been shown to have an equal incidence of ENMZL and DLBCL.[2]

NHL subtype involving the retina/vitreous structure is generally of the DLBCL type and is classified and managed as primary CNS lymphoma.[14]

Clinical features

OAL has been described as a masquerader of other benign diseases affecting the eyes; hence, it needs to be carefully considered when evolving the differential diagnosis of common ophthalmological clinical syndromes. The most common age for the onset of OAL is between the 5th and 7th decades.[15] The disease has more commonly been reported in females.[16] Close to 20% of all OALs have been reported to be bilateral.[16-20] Bilateral involvement is more common in the ENMZL subtype than the DLBCL.[21] More than 15% patients with orbital lymphoma present with disseminated disease.[3] Systemic symptoms such as fever, fatigue, weight loss, and night sweats are rarely associated with OAL.[14] They most commonly present with symptoms from the mass including reduced visual acuity, double vision, ptosis, proptosis, dry eye, and eyelid swelling.[15,20,22] Pain is a rare clinical feature reported in only 36% of the patients.[16] On examination, OAL patients were seen to have a conjunctival mass/salmon patch similar to our patient.[22,23] Rarely do these patients have an erosion of the orbital wall, most commonly associated with the DLBCL type.[24]

Management

The National Comprehensive Cancer Network (NCCN) guidelines suggest that standard diagnostic tests for NHL should include a detailed history for assessment of presenting clinical features, physical examination looking for systemic involvement, performance status assessment, laboratory workup including complete blood count with a differential, comprehensive metabolic panel, serum LDH level, and tests for viral infections such as human immunodeficiency virus (HIV), hepatitis-B if rituximab-based regimens are planned and hepatitis C in some cases.[25] A unilateral bone marrow biopsy with aspirate prior to starting therapy may be performed but the biopsy may not be needed in cases where the PET scan is negative unless finding another lymphoma subtype will change the management of that patient. Imaging studies of the orbit such as a CT scan/MRI scan are needed and finally confirmation of the diagnosis is done with biopsy, molecular analysis, and flow cytometry.

Patients thought to have limited stage disease of the ocular structures should be further evaluated by slit lamp biomicroscopy, gonioscopy, and dilated fundus examination. Considering the fact that CNS features could be the presenting symptoms of OL (e.g., in our patient), the standard evaluation of any presumed CNS lymphoma includes an ophthalmic evaluation preferably by an experienced ophthalmologist. CNS involvement, as such, is difficult to diagnose in NHL patients. Studies including CSF analysis and MRI scans commonly miss CNS involvement.[26] Sensitivity of CSF studies can be improved by serial LPs to analyze several specimens.[26] MRI for suspected CNS disease needs to be timed prior to the LP to prevent picking up of false positive signals in the leptomeningeal region after an LP.[27]

The treatment of OAL depends on several factors associated with an OAL that include several features of the tumor such as subtype of the lymphoma, CNS involvement, adverse biological factors such as c-myc rearrangements with or without bcl-6 mutations and prognostic factors pertaining to the patient such as performance status and organ function.[25] While guidelines for the treatment of lymphoma are subtype-specific, initial treatment of lymphoma in the eye ranges from surgical excision, radiation therapy for local disease control to chemotherapy for systemic disease or a combination of these modalities. ENMZL type of OAL needs consideration for *Chlamydia psittaci* treatment because studies have shown regression of this lymphoma type with antibiotic use.[11]

Therefore, the treatment of OAL involves management of these patients in a multidisciplinary center with the availability of expert hematologists and experienced ophthalmologists to diagnose and assess response to treatment especially in atypical presentations such as in our patient.

Conclusion

Because of the significant rate of disseminated disease among patients with lymphomas in the orbit that carries a worse prognosis, early diagnosis is essential to promote better overall survival of these patients. It is important to recognize that our patient had an underlying visual deficit caused by her diabetic retinopathy and macular degeneration. Although she was found to have a salmon-patch conjunctival tumor in the left eye, there was no suitable explanation for why she had experienced a sudden loss of vision in her right eye (since there was no intraocular or epibulbar involvement detected clinically or on imaging studies) other than hypothetical CNS involvement by her lymphoma. Thus, this differential diagnosis should be considered when evaluating patients presenting with vision complains in order to provide a timely referral to the ophthalmologist and hematologist for further assessment, possible biopsy, and early therapeutic intervention. Moreover, when managing such patients, it is important to have the resources of a specialized multidisciplinary approach found in centers with expertise in managing both ocular and hematologic malignancies.

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Conflicts of interest

There are no conflicts of interest.

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