Primary Conjunctival Follicular Lymphoma: A Case Report and Literature Review

Ruby Maini*, Manjari R Regmi1, Nitin Tandan1, Priyanka Parajuli1, Odalys Lara Garcia1, Fawwad Zaidi1,2 and Aziz Khan1,2

1Department of Internal Medicine, Southern Illinois University School of Medicine, USA
2Department of Hematology-Oncology, Southern Illinois University School of Medicine, USA

Abstract

Background: Extranodal non-Hodgkin lymphoma accounts for approximately 20% to 30% of reported cases of lymphoma. Of these, roughly 8% occur within the orbit with a smaller portion occurring within the conjunctiva. Ocular manifestations of conjunctival lymphoma are quite variable and can mimic common ocular pathologies, thus requiring a high degree of suspicion for diagnosis.

Case Presentation: A 68-year-old male patient with a history of papillary urothelial cancer who underwent transurethral resection of the prostate in 2014 presented to the outpatient clinic for left neck swelling. During this evaluation, the patient’s provider noted right medial canthus swelling. The patient reported that this area was bothersome. He denied symptoms of changes in vision, pain with extraocular movements, and dryness. On physical examination, the right lacrimal caruncle appeared enlarged and protruded through the eyelid. Magnetic resonance imaging of the orbits revealed an asymmetric thickening of the right lacrimal caruncle (13 mm). On biopsy, the diagnosis of follicular (non-Hodgkin lymphoma) of the conjunctiva was made.

Conclusion: A literature review was performed in order to investigate unique presentations and management approaches for primary conjunctival lymphoma. This report highlights the various manifestations of conjunctival follicular lymphoma, the difficulties of diagnosis, and unique management strategies.

Keywords: Non-Hodgkin lymphoma; Ocular adnexal lymphoma; Conjunctival lymphoma

Introduction

Non-Hodgkin lymphoma includes a variety of malignancies that involve the lymph nodes. Extranodal non-Hodgkin lymphoma of the conjunctiva encompasses a minor percentage of cases. Initial presentations vary and can be non-specific, including but not limited to ptosis, discoloration of the eye, and a characteristic “salmon patch” appearance [1]. Here, we report a case of an incidental finding of right canthus swelling as the only manifestation of primary follicular lymphoma of the conjunctiva.

Case Presentation

A 68-year-old Caucasian male with a previous history of papillary urothelial cancer who underwent transurethral resection of the prostate in 2014 presented to the ear, nose and throat clinic for concern of left neck swelling. The patient denied any tobacco, alcohol, or recreational drug use. During this evaluation, the patient’s provider noted right medial canthus swelling. The patient reported that this area was bothersome. He denied symptoms of changes in vision, pain with extraocular movements, and dryness. On physical examination, the right lacrimal caruncle appeared enlarged and protruded through the eyelid. The remainder of the exam was unremarkable.

He underwent Computed Tomography (CT) of the neck, which revealed a mass inferior to the left parotid gland, suggestive of Warthin’s tumor. This was surgically removed. Magnetic resonance imaging of the orbits with and without contrast was performed, which revealed asymmetric thickening of the right lacrimal caruncle noted to be 13 mm in size, with isointense T1/T2 signal and minimal enhancement after contrast. No invasion or infiltration of the adjacent structures was observed. The globe, optic nerves, and extraocular muscles appeared normal and symmetric.

The patient underwent excisional conjunctival biopsy and the largest mass (medial) was removed and sent for pathologic evaluation. Microscopic examination showed small to medium sized...
Ki-67 showed proliferation of about 15% to 20%. Whole body Positron Emission Tomography (PET) was negative for disease. Bone marrow biopsy demonstrated no atypia. Ultimately, a diagnosis of grade 1-2 follicular non-Hodgkin lymphoma was made. Our patient did well with localized radiation therapy to his right orbit and obtained a

<table>
<thead>
<tr>
<th>Author</th>
<th>Title Name</th>
<th>Study Details</th>
<th>Age</th>
<th>Laterality</th>
<th>Histological Type</th>
<th>Treatment</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akpek EK et al. [2]</td>
<td>Conjunctival lymphoma masquerading as chronic conjunctivitis</td>
<td>Case report</td>
<td>Unknown</td>
<td>Bilateral</td>
<td>Follicular Lymphoma</td>
<td>Radiation Therapy</td>
<td>No recurrence for 16 months</td>
</tr>
<tr>
<td>Alkatan HM et al. [4]</td>
<td>Ocular adnexal lymphoproliferative disorder in an ophthalmic referral center in Saudi Arabia</td>
<td>Retrospective study of 40 patients who underwent incisional biopsy from 2000-2012 at the King Khalid Eye Specialist Hospital, 1 case excluded</td>
<td>Median age 36 years (range 11-91), 70% males and 30% females</td>
<td>Bilateral 7.5%, right eye 48%, left eye 45%</td>
<td>Follicular lymphoma (1 patient)</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Azumi A et al. [5]</td>
<td>A case of follicular lymphoma derived from the conjunctiva</td>
<td>Case report</td>
<td>65-year-old female</td>
<td>Left eye</td>
<td>Follicular Lymphoma</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Baldini L et al. [6]</td>
<td>Treatment and prognosis in a series of primary extranodal lymphoma of the ocular adnexa</td>
<td>19 patients with localized primary ocular adnexal lymphomas followed for median of 96 months, 1 patient had conjunctival follicular lymphoma</td>
<td>20-year-old, female</td>
<td>Left eye</td>
<td>Follicular Lymphoma</td>
<td>Radiation Therapy</td>
<td>No recurrence at 125-month follow-up</td>
</tr>
<tr>
<td>Bellesio M et al. [7]</td>
<td>A rare case of primary conjunctival Follicular Lymphoma Grade 3B</td>
<td>Case report</td>
<td>31-year-old, female</td>
<td>Right eye</td>
<td>Follicular Lymphoma grade 3 B</td>
<td>Excision and rituximab, cyclophosphamide, vincristine and prednisolone, intraflechal methotrexate</td>
<td>Unknown</td>
</tr>
<tr>
<td>Bianciotto C et al. [8]</td>
<td>Cyberknife radiosurgery for the treatment of intraocular and periocular lymphoma in Philadelphia, Pennsylvania</td>
<td>Retrospective case series of 13 patients who underwent CyberKnife radiosurgery</td>
<td>Mean age 68 years (range 46-91); 14 eyes of 13 patients</td>
<td>Two eyes (unknown side)</td>
<td>Follicular lymphoma (2 eyes)</td>
<td>Treatment with radiation therapy</td>
<td>No recurrence</td>
</tr>
<tr>
<td>Cackett P et al. [9]</td>
<td>Isolated conjunctival lymphoma metastasis from previous low-grade non-Hodgkin's lymphoma</td>
<td>Case report</td>
<td>47-year-old, male</td>
<td>Right eye</td>
<td>Grade 3 Follicular Lymphoma</td>
<td>Excision</td>
<td>No recurrence for 4 years</td>
</tr>
<tr>
<td>da Cunha LP [10]</td>
<td>Conjunctival follicular lymphoma after treatment for invasive squamous cell carcinoma</td>
<td>Case report</td>
<td>79-year-old, female</td>
<td>Right eye</td>
<td>Follicular lymphoma, stage 3 with retroperitoneal involvement.</td>
<td>Immunotherapy with rituximab and chemotherapy with cyclophosphamide and vincristine</td>
<td>Patient did well on first follow-up visit</td>
</tr>
<tr>
<td>Duncan et al. [11]</td>
<td>Follicular lymphoma presenting solely as chronic follicular conjunctivitis</td>
<td>Case report</td>
<td>Unknown</td>
<td>Bilateral</td>
<td>Low grade conjunctival follicular lymphoma</td>
<td>Radiation therapy</td>
<td>Unknown</td>
</tr>
<tr>
<td>Farmer JP et al. [12]</td>
<td>Characterization of lympho proliferative lesions of the conjunctival; Immunohistochemical and molecular genetic studies</td>
<td>Retrospective case series of 16 patients</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Follicular lymphoma (1 patient)</td>
<td>Primary lymphoma treated with radiation or topical chemotherapy</td>
<td>No recurrence</td>
</tr>
<tr>
<td>Gou P et al. [14]</td>
<td>Features of clinical presentation, pathology and magnetic resonance or computed tomography imaging for ocular lymphoma</td>
<td>Retrospective study of 73 cases with ocular complaints at Beijing Tong’ren Hospital from June 2006-September 2012</td>
<td>Mean age 60 years, 47 males and 26 females</td>
<td>24 bilateral, 23 right eye, 26 left eye</td>
<td>Follicular lymphoma (1 patient)</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Kirkegaard MM et al. [15]</td>
<td>Conjunctival lymphoma – An international multicenter retrospective study</td>
<td>Retrospective study design, data collected through January 1, 1980-December 31, 2010. Seven eye cancer centers were involved. Total of 268 patients, 5 were excluded</td>
<td>Mean age 61.3 years, 55.1% females</td>
<td>Unknown</td>
<td>Follicular lymphoma in 16.3 %, 43 of 263</td>
<td>Localized disease stage IIE or IIE treated with EBRT ± chemotherapy. Wide-spread lymphoma IIE IVE chemotherapy ± EBRT</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Table 1: Study characteristics of conjunctival follicular lymphoma.
complete remission. He did well on his 6-month follow-up.

Discussion

 Conjunctival follicular lymphoma is challenging to diagnose and treat due to the limited number of reported cases in the scientific community. After reviewing PubMed articles, 11 case reports, 6 retrospective studies, and 1 prospective study were found (Table 1).

 There did not seem to be predilection for gender or laterality. Mean age of diagnosis was 52.7 years with age ranging between 20-years-old to 70-years-old. It is worth noting, however, that patients who initially presented with early disease could later present with bilateral conjunctival involvement and even systemic disease.

 Conjunctival lymphomas account for 2% to 8% of extranodal lymphomas [1]. Conjunctival tumors frequently consist of squamous cell carcinoma, melanoma, or lymphoma. An international retrospective study from January 1980 to December 2010 was performed to investigate the subtypes of conjunctival lymphoma. After analysis of histopathological findings from seven different eye cancer centers, B-cell non-Hodgkin lymphomas are one of the most frequent causes of conjunctival lymphomas [15]. The most common subtypes reported in the study were marginal zone lymphoma, followed by follicular lymphoma, mantle cell lymphoma, and finally diffuse large B-cell lymphoma [15].

 The inconsistency and variability in presentation is what makes the diagnosis challenging. Some commonly reported symptoms include an abnormal sensation of the eye, ptosis, and often seen is a pinkish discoloration of the conjunctiva. Conjunctival lymphomas are typically localized to conjunctival fornix or bulbar regions and are usually found unilaterally. Rarer presentations are bilateral and/or involve lesions in the caruncle or limbus [1]. Four case reports describe the difficulty of diagnosing conjunctival lymphoma due to the simplicity of symptoms, where the initial diagnosis was conjunctivitis [2,11,13,16-18]. Velandia et al. [18] reported the initial diagnosis of chronic conjunctivitis with preliminary biopsy revealing only reactive lymphoma hyperplasia. Due to the patient’s persistence of symptoms for a year, a biopsy was performed which brought forward the diagnosis of conjunctival follicular lymphoma.

 The diagnostic modality of choice is magnetic resonance imaging of the orbit; however, optical coherence tomography can also be used for optical surface lesions [19,20]. Biopsy and histopathological analysis are the most important steps necessary to confirm the diagnosis. Upon diagnosis, staging is assessed classically via Ann Arbor and Cancer Tumor, Node, Metastasis-based staging systems.

 The gold standard treatment for isolated conjunctival lymphoma is external beam radiation therapy commonly administered with 30 to 36 gray [20]. There has been use of intraslesional interferon alfa-2b, which is a cell membrane receptor binder which alters gene transcription preventing cellular differentiation and oncogene expression [1]. There has been a limited use of intraslesional rituximab, a CD20 inhibitor, in achieving complete remission [1]. Systemic disease requires the use of chemotherapeutics and/or immunologic therapy; however, there is insufficient data with regards to chemotherapy and/or immunologic regimens. Bendamustine has shown encouraging results both as a solitary agent as well as when it is used in combination with rituximab [21]. Chlorambucil in combination with Cyclophosphamide, Vincristine, and Prednisone (CVP) with or without doxorubicin has also shown to have a promising response while maintaining a lower toxicity profile [22].

 Although the aforementioned strategies may be effective, there are concerns that these therapies may lead to significant chances of relapse [22]. A retrospective international cohort study identified 24 patients with conjunctival follicular lymphoma. This study demonstrated that 11 patients had primary disease whilst 7 patients had systemic disease at diagnosis [16]. Of these patients, those that received initial therapy with radiotherapy alone, chlorambucil ± CVP and CVP alone resulted in a relapse of 6 patients. Of the literature reviewed, 11 out of 18 studies reported findings of either some or no recurrence, with a majority reporting no recurrence [16,19]. Common modalities of treatment that were associated with no signs of recurrence included treatment regimens with radiation therapy ± intraslesional rituximab; however, administration of radiation therapy did not eliminate recurrences completely. Optimal treatment regimens are still being discovered; further prospective trials are needed to optimize treatment for conjunctival lymphoma and minimize instances of recurrence.

 Conclusion

 Due to the rarity of this condition, conjunctival lymphoma can often be overlooked and misdiagnosed. However, it is imperative to consider conjunctival lymphoma on the differential if clinically indicated.

 References


