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Primary Conjunctival Follicular Lymphoma: A Case Report and Literature Review

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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. On examination, the heath care provider incidentally noted right medial cantus swelling of the right eye. Computed tomography of the neck revealed Warthin's tumor which required surgical excision. 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

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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 cantus 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

Table 1: Study characteristics of conjunctival follicular lymphoma.

Author	Title Name	Study Details	Age	Laterality	Histological Type	Treatment	Relapse
Akpek EK et al. [2]	Conjunctival lymphoma masquerading as chronic conjunctivitis	Case report	Unknown	Bilateral	Follicular Lymphoma	Radiation Therapy	No recurrence for 16 months
Al-Kader LA et al. [3]	A case of conjunctival follicular lymphoma mimicking mucosa-associated lymphoid tissue lymphoma	Case report	68-year-old, female	Left eye	Stage 1 follicular lymphoma	Radiotherapy of 30 Gy/15 fractions	No recurrence
Alkatan HM et al. [4]	Ocular adnexal lympho proliferative disorder in an ophthalmic referral center in Saudi Arabia	Retrospective study of 40 patients who underwent incisional biopsy from 2000-2012 at the King Khalid Eye Specialist Hospital, 1 case excluded	Median age 36 years (range 11-91), 70% males and 30% females	Bilateral 7.5%, right eye 48%, left eye 45%	Follicular lymphoma (1 patient)	Unknown	Unknown
Azumi A et al. [5]	A case of follicular lymphoma derived from the conjunctiva	Case report	65-year-oldm female	Left eye	Follicular Lymphoma	Unknown	Unknown
Baldini L et al. [6]	Treatment and prognosis in a series of primary extranodal lymphoma of the ocular adnexa	19 patients with localized primary ocular adnexal lymphomas followed for median of 96 months, 1 patient had conjunctival follicular lymphoma	20-year-old, female	Left eye	Follicular lymphoma	Radiation Therapy	No recurrence at 125-month follow-up
Bellesso M et al. [7]	A rare case of primary conjunctival Follicular Lymphoma Grade 3B	Case report	31-year-old, female	Right eye	Follicular lymphoma grade 3 B	Excision and rituximab, cyclophosphamide, vincristine and prednisolone, intrathecal methotrexate	Unknown
Bianciotto C et al. [8]	Cyberknife radiosurgery for the treatment of intraocular and periocular lymphoma in Philadelphia, Pennsylvania	Retrospective case series of 13 patients who underwent CyberKnife radiosurgery	Mean age 68 years (range 46-91); 14 eyes of 13 patients	Two eyes (unknown side)	Follicular lymphoma (2 eyes)	Treatment with radiation therapy	No recurrence
Cackett P et al. [9]	Isolated conjunctival lymphoma metastasis from previous low-grade non-Hodgkin's lymphoma	Case report	47-year-old, male	Right eye	Grade 3 Follicular Lymphoma	Excision	No recurrence for 4 years
da Cunha LP [10]	Conjunctival follicular lymphoma after treatment for invasive squamous cell carcinoma	Case report	79-year-old, female	Right eye	Follicular lymphoma, stage 3 with retroperitoneal involvement.	Immunotherapy with rituximab and chemotherapy with cyclophosphamide and vincristine	Patient did well on first follow-up visit
Ducan et al. [11]	Follicular lymphoma presenting solely as chronic follicular conjunctivitis	Case report	Unknown	Bilateral	Low grade conjunctival follicular lymphoma	Radiation therapy	Unknown
Farmer JP et al. [12]	Characterization of lympho proliferative lesions of the conjunctival: Immunohistochemical and molecular genetic studies	Retrospective case series of 16 patients	Unknown	Unknown	Follicular lymphoma (1 patient)	Primary lymphoma treated with radiation or topical chemotherapy	No recurrence
Goebels S et al. [13]	Follicular Conjunctivitis of Unknown Origin	Case report	40-year-old, female	Bilateral	Follicular lymphoma	Radiotherapy and remission	Patient did well on 18-month follow-up
Gou P et al. [14]	Features of clinical presentation, pathology and magnetic resonance or computed tomography imaging for ocular lymphoma	Retrospective study of 73 cases with ocular complaints at Beijing Tong'ren Hospital from June 2006-September 2012	Mean age 60 years, 47 males and 26 females	24 bilateral, 23 right eye, 26 left eye	Follicular lymphoma (1 patient)	Unknown	Unknown
Kirkegaard MM et al. [15]	Conjunctival lymphoma – An international multicenter retrospective study	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	Mean age 61.3 years, 55.1% females	Unknown	Follicular lymphoma in 16.3 %, 43 of 263	Localized disease stage IE or IIE treated with EBRT ± chemotherapy. Wide-spread lymphoma IIIE IVE chemotherapy ± EBRT	Unknown

lymphoid cells with angulated and cleaved nuclei. The cells showed reactivity to CD20, CD79A, CD10 and CD23 with overexpression of BCL2. There was no reactivity for BCL1, CD3, CD5, CD30 or CD43. 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

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 intralesional 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 intralesional 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 ± intralesional 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.

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