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Case Report

Ocular Adnexal Lymphoma, a Bump in the Eye

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Abstract: Ocular adnexal lymphomas are a heterogeneous group of malignancies, composing approximately 1-2% of non-Hodgkin lymphomas (NHLs) and 8% of extranodal lymphomas. Ocular adnexal lymphoma can involve conjunctiva, orbital soft tissues, eyelid or adnexal structures such as lacrimal gland and lacrimal drainage system. We describe two cases of ocular adnexal lymphoma involving lower eyelid and superior bulbar conjunctiva. They presented with painless swelling over these regions. Ocular examinations revealed salmon-coloured conjunctival patch in both the patients. The histopathology of the excisional biopsy revealed eyelid grade 1 follicular lymphoma and extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) respectively. Both patients underwent successful radiotherapy.

Keywords: ocular adnexal lymphoma, follicular lymphoma, mucosa-associated lymphoid tissue.

INTRODUCTION

Lymphomas of orbital and ocular adnexa are indeed rare. However, they represent the majority of orbital malignancies (Coupland, S. E. *et al.*, 1998; Ferry, J. A. *et al.*, 2007; Rootman, D. B. *et al.*, 2011). Ocular adnexal lymphomas are mostly seen in the 5th to 7th decade of life with female predominance. The most frequently involved sites are the orbit (40%), followed by conjunctiva (35-40%), lacrimal gland (10-15%) and eyelid (10%) (Moslehi, R. *et al.*, 2006). The majority of ocular adnexal lymphomas are B-cell non-Hodgkin lymphomas. The predominant subtypes of non-Hodgkin lymphoma involving this region are low-grade B-cell lymphomas, of which the majority are extranodal marginal zone lymphomas (Coupland, S. E. *et al.*, 1998; Nola, M. *et al.*, 2004). The less common B-cell lymphoma subtypes include follicular lymphoma, diffuse large B-cell lymphoma, plasmacytoma, lymphoplasmacytic lymphoma mantle-cell lymphoma and hairy cell leukemia (Coupland, S. E. *et al.*, 1998; Nola, M. *et al.*, 2004). Here, we report two cases of ocular adnexal lymphoma involving the conjunctiva and eyelid respectively.

CASE PRESENTATION

Case 1

A 58-year-old woman with known case of diabetes mellitus and hypertension, presented with left lower eyelid swelling which was progressively increasing in size for one month. There was no other associated symptoms. She denied any other systemic disease or trauma history. Ophthalmological examination revealed a best corrected visual acuity (BCVA) of 6/12 in both eyes. There was a fixed, rubbery mass measuring 3.5cm x 2.0cm palpable in the inferolateral aspect of left lower eyelid [Figure 1]. The anterior segment examination of both eyes was normal. Fundus examination of both eyes showed mild non-proliferative diabetic retinopathy changes with right maculopathy. Systemic examination was unremarkable. Excisional biopsy was performed from inferior tarsal conjunctiva and the histopathology revealed a grade 1 follicular lymphoma. Full blood picture revealed mildly increased white blood cells with lymphocytosis and reactive lymphocytes. Other laboratory results were in normal range. Computed tomography (CT) of brain and orbit did not show intraorbital or intracranial extension of the mass. Patient was referred to hematologist for further management and has undergone one cycle of

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radiotherapy. The swelling has significantly reduced in size post radiotherapy treatment [Figure 2].

Case 2

A middle-aged female presented to us with a complaint of painless swelling in her left eye for two months. There was no increased discharge or discomfort. Patient denied any history of trauma or foreign body entering her eye. She denied any antecedent history of pyrexia. On examination, visual acuity over the right and left eye is 6/12 and 6/9 respectively. Her extraocular movements were full. Slit lamp examination over both eyes revealed a confined hyperemic "salmon patch" swelling over the superior bulbar and fornix of her left conjunctiva [Figure 3]. The rest of the ocular and systemic examinations were unremarkable. Blood investigations were normal. Imaging of brain and orbit did now any intraorbital or intracranial extension. Excision biopsy of the subconjunctival tissue revealed extranodal marginal zone lymphoma (MALT Lymphoma). She was referred to hematologist and has completed 12 sessions of radiotherapy within two weeks.

Figure 1: Rubbery mass at inferolateral aspect of left lower eyelid

Figure 2: The reduction of left eyelid swelling after radiotherapy.

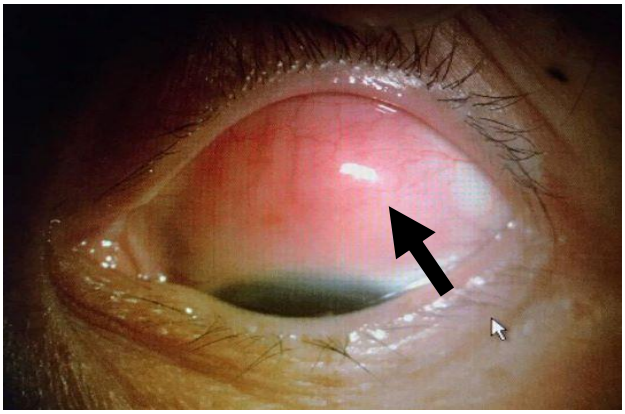

Figure 3: Hyperemic salmon patch swelling over superior bulbar and fornix of left conjunctiva

DISCUSSION

Ocular adnexal lymphomas represent 6–8% of all orbital tumours (Bardenstein, D. S. 2005) and they are predominantly primary extranodal neoplasms. However, about 10-32% of patients have secondary ocular involvement with systemic lymphoma (McKelvie, P. A. *et al.*, 2001; Coupland, S. E. *et al.*, 2005). The most common subtype seen in the clinical settings are extranodular marginal zone lymphoma of MALT (35-80%), followed by follicular lymphoma (20%), diffuse large B-cell lymphoma (8%) and the less common mantle cell lymphoma, small lymphocytic lymphoma and lymphoplasmacytic lymphoma (McKelvie, P. A. *et al.*, 2001; Jenkins, C. *et al.*, 2000).

The ocular adnexa comprise the tissues and structures surrounding the eye and include the following entities: the conjunctiva, eyelids, lacrimal gland, and orbital soft tissues. Conjunctival lesions typically present as mobile pink infiltrates in the substantia propria ("salmon-pink patch"), causing conjunctival swelling, redness, and irritation. Orbital lymphoid proliferations are characterized by a palpable, firm or rubbery mass causing insidious, progressive proptosis, occasionally associated with periorbital edema, decreased visual acuity, motility disturbances, and diplopia. Our patients presented with conjunctival swelling and rubbery eyelid lesion which were suspicious and have led to the histopathological diagnosis of lymphoma.

MALT lymphomas typically arise in tissues or organs that are normally devoid of any organized lymphoid tissue, such as the orbital region, but acquire reactive lymphoid tissue in response to persistent antigenic stimulation, as a result of chronic inflammatory or autoimmune disorders. Analyses of somatic mutations in the immunoglobulin (Ig) gene segment have suggested a role of chronic antigen stimulation in the pathogenesis of ocular adnexal MALT lymphoma (OAML) (Coupland, S. E. *et al.*, 1999). Chronic antigenic stimulation may eventually progress to genetic instabilities with successive chromosomal abnormalities, causing transformation of

a clone of normal lymphoid cells to MALT lymphoma. Microbial pathogens that underlie chronic inflammatory processes and eventually lead to the acquisition of MALT may also play an important role in both malignant transformation and subsequent clonal expansion of the lymphoma (Chan, C. C. *et al.*, 2006; Lee, S. B. *et al.*, 2008).

Follicular lymphomas exhibit a nodular pattern of growth, and on immunohistochemistry neoplastic follicle centre cells are positive for CD10, Bcl-2, and Bcl-6 antigens (Coupland, S. E. *et al.*, 2002). Follicular lymphomas are often slow growing tumours and indolent in comparison to other lymphoma variants such as mantle cell and diffuse large B-cell lymphomas (Bardenstein, D. S. 2005). However, Nicolo ´ *et al.*, (1999) describe a case of follicular lymphoma with an aggressive course resulting in multiple recurrences despite chemotherapy and radiotherapy.

Comparison between follicular and MALT lymphomas showed that follicular lymphomas arise from germinal centre B cells where antigen exposure occurs, whereas lymphomas of mucosa-associated lymphoid tissue are believed to develop from post–germinal centre lymphocytes. Both entities are low-grade lymphomas, but follicular lymphomas have an 8-year survival of 60% to 65% with a failure-free survival of approximately 35% (Lister, T.A, *et al.*, 2004), whereas lymphomas of mucosa-associated lymphoid tissue have an 8-year survival of approximately 80% and a failure-free survival of 65% (Lister, T.A, *et al.*, 2004). Both of our cases were low grade lymphomas as described above.

The initial evaluation of these patients requires careful ophthalmic examination and adequate tissue sampling for histopathological diagnosis. Further assessment for accurate staging and therapeutic planning include thoughtful history taking and physical examination, laboratory studies, serum protein electrophoresis, serum LDH, β2-microglobulin, chest x ray, bone marrow biopsy and CT thorax, abdomen and pelvis. Unfavourable prognostic features include advanced stage (Esik, O. *et al.*, 1996), old age, nodal involvement (Zucca, E. *et al.*, 2003), B symptoms (fever, night sweats and weight loss) (Meunier, J. *et al.*, 2004), performance status > 1, elevated serum LDH or β2-microglobulin levels (Martinet, S. *et al.*, 2003) and p53 gene expression (Coupland, S. E. *et al.*, 2005).

The treatment modalities for patients with ocular adnexal lymphoma include surgical resection, radiotherapy, single agent or combined regiments of chemotherapy and interferons immunotherapy (Blasi, M. A. *et al.*, 2001). Surgical resection is indicated for encapsulated tumours but the risk of recurrence is relatively high. Radiotherapy for localized MALT lymphoma in ocular adnexa offers excellent local control with a prolonged clinical course (Uno, T. *et al.*, 2003). Systemic chemotherapy should be considered in patients with advanced disease or systemic manifestations. Blasi *et al.*, suggested that local immunotherapy with IFN-α seems to be an effective and lasting treatment method and provides an alternative for radiotherapy for conjunctival MALT lymphomas (Blasi, M. A. *et al.*, 2001).

Our cases here involved two middle-aged women who presented with insidious onset of eyelid mass and conjunctival swelling respectively with no prior history of lymphoma. Histopathology results of both conjunctival excision biopsy revealed follicular and MALT lymphoma which showed favourable outcome with subsequent radiotherapy sessions. They are good clinical example of cases of how diagnostic dilemma occur which gives great impact on the clinical management of a patient. Therefore, these cases emphasize the importance of utilizing the concerted efforts of clinical with histological analyses to achieve the correct diagnosis for proper patient care.

CONCLUSION

A rigorous approach to accurate diagnosis and systemic staging is fundamental for optimal treatment planning and outcome. Conjunctival and eyelid lymphomas seemed to have better outcome from previous reports but the ocular adnexal lymphoma involving orbits or lacrimal gland demands more vigorous treatment. The standard of care in patients with orbital and ocular adnexal lymphomas requires a thorough workup with the integration of clinical, histological, immunophenotypical, and genomic data in every case because one never knows what diagnostic rarity will surface. Ocular adnexal lymphoma should always be included in the differential diagnosis of any patient presenting with progressive swelling of eyelid or ocular region despite it being a rare diagnosis.

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