CASE REPORT & LITERATURE REVIEW

Lacrimal Gland Orbital Lobe Cystic Mucosa-Associated Lymphoid Tissue Lymphoma

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ABSTRACT

This report describes a case of cystic, extranodal, marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue of the orbital lobe of the lacrimal gland in a 70-year-old female. Initial clinical examination revealed bilateral dermatochalasis and a medial left upper lid contour deformity thought to be involutional ptosis. There was no suspicion for a mass lesion. Imaging and subsequent specialist clinical, pathologic, an immunochemical evaluation showed diagnostic features of cystic lacrimal gland orbital lobe MALT lymphoma. Clinical, radiographic, and immunohistopathologic and immunohistochemical findings are detailed. A review of the literature was performed and discussed. Cases of cystic MALT lymphoma isolated to the orbital lobe of the lacrimal gland are rare, with six cases reported in the literature.

The findings of this newly reported case provide a valuable addition to the small number of previously reported cases with a previously undescribed presentation mimicking involutional eyelid changes and no systemic autoimmune disease findings. It is important to consider this disease entity in the differential diagnosis for patients within this age group that present with eyelid morphology changes, especially if the changes have occurred over a short period of time.

Keywords: Lacrimal gland, lymphoma, MALT, cystic, orbital lobe

1. INTRODUCTION

Extranodal, marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) is a low-grade tumor that can occur in the lacrimal gland.[1-2] This condition generally has a good prognosis since it is a solid, slow-growing mass typically without cystic lesions.[2] Occurrence is prevalent between ages 50-70 with a slight female predominance. The pathogenesis is a result of persistent antigenic stimulation that becomes autonomous over time because of genetic instabilities.[3] This condition is usually asymptomatic early in the disease state, and the average interval between onset of symptoms to diagnosis often ranges from one month to 10 years.[3] The lack of symptoms can contribute to a delayed diagnosis, which is significant because the extent of disease at presentation is believed to be the strongest prognostic outcome factor.[4-5]

Cases of cystic, extranodal, marginal zone B-cell MALT lymphoma limited to the orbital lobe of the lacrimal gland are rare, with six cases reported in the literature. An additional case with a unique presentation, initially thought to be dermatochalasis and involutional ptosis, is described. A review of the literature with descriptions of clinical and histological features, diagnostic evaluation, and treatment was conducted with the findings reported in Table 1.

2. METHODS

A search was conducted in PubMed in September 2021 utilizing the terms "cystic MALT lymphoma," "orbital lobe lacrimal gland lymphoma," "lacrimal gland MALT lymphoma," and "MALT lymphoma orbit." The search terms produced 681 total results. Articles where then reviewed for inclusion based on the following criteria: 1. Immunohistopathology and immuno-histochemical confirmed MALT lymphoma; 2. Limited to orbital lobe of lacrimal gland; 3. Cystic morphology. There were two reports totaling six patients that met the inclusion criteria. The clinical, diagnostic imaging, and immunohistopathologic/ immunohistochemical findings were reviewed and summarized in Table 1.

An additional case of cystic orbital lobe MALT lymphoma is described in this report. The procedures reported in this case are in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

3. CASE REPORT

A 70-year-old Caucasian female was referred for evaluation of bilateral upper eyelid dermatochalasis with medial orbital fat prolapse and involutional ptosis of the left upper lid (Figure 1). The patient reported changes to her bilateral upper lids over the past two decades with noticeable worsening on the left side over the past 1-2 years. The patient reported no significant past medical or ocular history.

Clinical evaluation revealed 20/20 best corrected visual acuity bilaterally (OU), full extraocular motility, full visual fields to confrontation, orthophoric primary gaze, and pupils that constricted from 4mm to 2 mm in direct light with no afferent pupillary defect. External examination showed dermatochalasis bilaterally and a pliable mass involving the left upper eyelid causing a contour deformity of the medial lid. The vertical fissures were 9 mm right (OD) and 7mm left (OS) respectively. Margin to reflex distance 1 was 4mm OD and 2mm OS. Levator function was 15 mm OU. No lagophthalmos was appreciated. Slit lamp examination was normal except for 1+ nuclear sclerosis OU. Fundus examination was normal. The patient was sent for computed tomography (CT) of the orbits which revealed a 1.7cm x 1.0cm cystic mass in the region of the orbital portion of the left lacrimal gland. A subsequent biopsy was performed revealing a normal appearing palpebral and lateral orbital portion

of the lacrimal gland with a cystic appearing infiltrating lesion of the medial orbital portion of the gland (Figure 2).

Histopathological evaluation displayed fibrovascular tissue infiltrated with sheets of lymphocytes. The lymphocytes were small and round with occasional larger lymphocytes with open chromatin and prominent nucleoli (Figure 3). Immunohistochemical studies were performed including: CD3, CD5, CD10, CD20, CD21, CD23, CD43, BCL-2, BCL-6, cyclin D1, IgD, kappa and lambda Ig light chains, and Ki-67. The stains were positive for CD20, CD43 and BCL-2 in diffuse lymphocytes, CD3 and CD5 in scattered lymphocytes, and CD23, BCL-6, and CD10 in rare lymphocytes. Kappa and lambda light chains were present in approximately a 4:1 ratio. Testing was negative for CD21, cyclin D1, IgD, and Ki-67. These results were consistent with cystic, extranodal, marginal zone B-cell MALT lymphoma isolated to the orbital lobe of the lacrimal gland.

The patient's subsequent systemic oncology evaluation showed increased metabolic activity in the left upper eyelid on positron emission tomography (PET) scan and a positive bone marrow biopsy for lymphoma. The bone marrow biopsy was confirmed by histopathology and flow cytometry. The patient is currently receiving systemic treatment with Rituxan.

4. DISCUSSION

In the elderly adult population, orbital and eyelid abnormalities, particularly involution changes, are not uncommon. When evaluating these abnormalities, mass lesions are one of many important diagnoses that must be considered. In this patient cohort, masses are commonly malignant, with malignant lymphoma being the most common tumor.[6]

Cystic MALT lymphoma limited to the orbital lobe of the lacrimal gland is rare and associated with chronic, systemic autoimmune diseases in most cases.[7] It is believed that chronic dacryoadenitis from these conditions leads to cyst formation and the development of lymphoma, though the exact mechanism is not fully understood.[7] The assessment of these lesions begins with a clinical evaluation of the eyes, adnexa, and orbit.[7] Ptosis, proptosis, and ipsilateral limitations in ocular motility commonly occur, with visual acuity changes and ocular displacement being much less common.[7] Clinical examination is followed by diagnostic imaging if the presentation contains characteristics mentioned above or if other concerning clinical findings are present.[3] Computed tomography and magnetic resonance imaging (MRI) with contrast enhancement are the preferred imaging modalities.[3] These modalities can aid in the assessment of location, size, and degree of infiltration of disease.[3]

Biopsy and/or surgical excision are then performed to further evaluate the lesion, with particular collection methods to allow for immunochemical and immunohisto-pathologic analysis of the specimen.[3] Analysis includes testing for lymphocytic infiltrates, as well as CD3, CD5, CD10, CD20, CD21, CD23, CD68, CD79, BCL-2, BCL-6, cyclin D1, S100, IgD, kappa and lambda Ig light chains, and Ki-67.[2,7] The presence or absence of these markers can be used to make a preliminary diagnosis, but a PET scan and bone marrow biopsy are often performed to confirm the diagnosis.[3] Bone marrow biopsy findings are confirmed with histopathologic analysis and flow cytometry.[3] Treatment is variable depending on the individual presentation, including surgical resection, immunotherapy, radiotherapy, and single-agent or combination chemotherapy.[3] Non-localized disease typically requires more aggressive therapy, and more than one modality may be used as appropriate.[3]

4.1 Literature Review

Cassidy et al first reported three cases of cystic MALT lymphoma of the lacrimal gland orbital lobe (Table 1).[8] Patient number one had a 12-month history of progressive lid swelling. A cyst of the orbital lobe of the right lacrimal

gland was discovered, as well as mediastinal and abdominal lymphade-nopathy, eventually leading to the diagnosis of systemic lymphoma. She was treated with systemic combination chemotherapy and was in remission 18 months after treatment. Patient number two had a six-month history of progressive right proptosis and inferior globe displacement. The cystic lesion was removed, and she received local radiotherapy, remaining in remission after three years of follow up. Patient number three had a six-month history of painless swelling of the right upper lid. She underwent excisional biopsy with adjunctive radiotherapy and was disease free nine months after the completion of radiotherapy.

Dutton et al later reported a series of four cases, however one was indeterminate for MALT lymphoma (Table 1).[7] Patient number four had right upper lid swelling over two years. Following excisional biopsy and systemic treatment, the patient was disease free at six months. Patient number five had a six-month history of left upper lid changes. After evaluation, a biopsy was performed, and testing revealed MALT lymphoma. Definitive treatment had not yet been determined. Patient number six had 12 months of painless left eyelid swelling and underwent excisional biopsy. The cystic lesions were removed, and low dose orbital radiotherapy was administered.

Dutton et al also followed up on the three cases reported by Cassidy et al. Patient number two and three (Table 1) remained disease free 15 and 14 years later, respectively.[7] Patient number one was disease free for 10 years. She then developed left, noncystic, lacrimal gland MALT lymphoma. She was treated with orbital radiotherapy and six cycles of fludarabine and rituximab, followed by maintenance therapy with rituximab for two years. The patient was disease free for three years at the time of publication.

Including the case presented in this reported, there are only seven reported cases of immunohistochemical/ immunohisto-pathology confirmed cystic MALT lymphoma limited to the orbital lobe of the lacrimal gland. All seven patients were female, and there was an association with chronic systemic autoimmune conditions in the majority (71%) of cases. The mean age of presentation was 57 years of age, and the overall prognosis was good following all modalities of treatment. The findings of this newly reported case provide a valuable addition to the small number of previously reported cases with a previously undescribed presentation mimicking involutional eyelid changes and no systemic autoimmune disease findings. It is important to consider this disease entity in the differential diagnosis for patients within this age group that present with eyelid morphology changes, especially if the changes have occurred over a short period of time.

5. DECLARATIONS

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This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflicts of Interest
The authors have no conflicts of interest to declare that are relevant to the content of this article.

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7. FIGURE LEGEND

Figure 1. A. External photograph of the patient at initial presentation. Note the bilateral upper lid dermatochalasis with medial fullness initially thought to be orbital fat prolapse. There is also deformity in the contour of the left upper lid initially diagnosed as involutional ptosis. B. External photograph centered on the left upper eyelid in closed position. In this position the appearance of the mass is more similar to medial orbital fat prolapse with overlying dermatochalasis as the diagnostic clue of the abnormal contour of the upper lid is absent in this lid position.

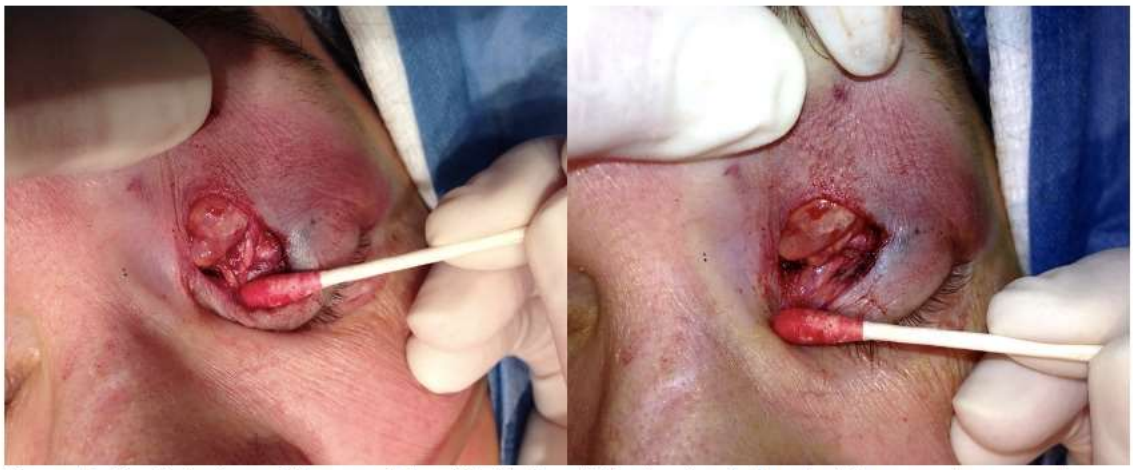

Figure 2. Cystic lesion of the medial orbital lobe of the lacrimal gland with a grossly normal appearing lateral orbital and palpebral lobe.

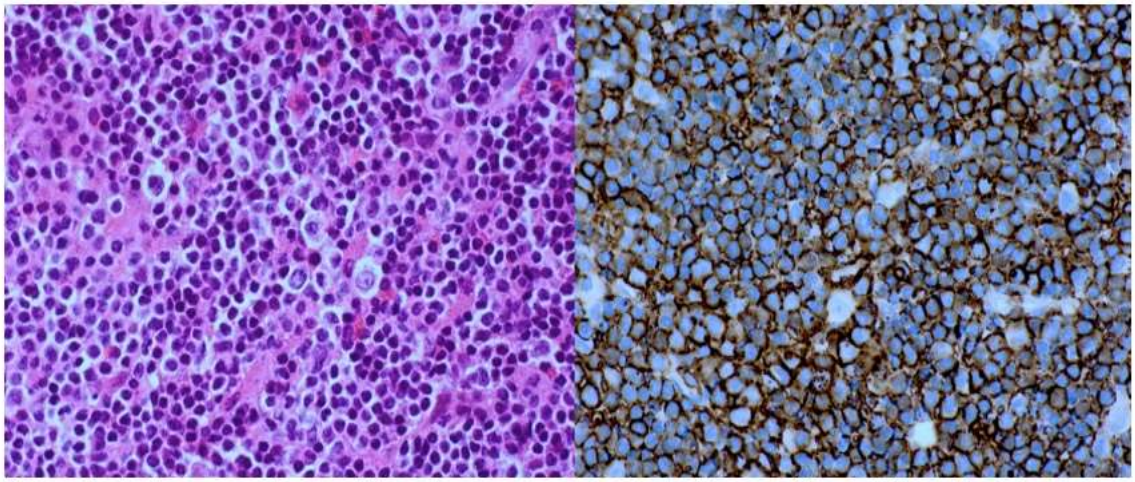

Figure 3. A. There are sheets of lymphocytes present, including small, round lymphocytes and larger lymphocytes with open chromatin and prominent nucleoli. (H&E, 150X). B. Immunohistochemical stains are positive for CD20 in the lymphocytes. (peroxidase anti-peroxidase, 150X).

Table 1. Reported Cases of Cystic Orbital Lobe Lacrimal Gland MALT Lymphoma

Publication (Year)	***Patient Number***	***Age/Sex***	***Autoimmune Condition***	***Presenting Symptoms***	***Imaging***	***Histology***	***Molecular Studies***	***Management***
Cassidy et al (2005)	1	41 F	Sjogren Syndrome	Progressive proptosis	CT- large cyst with some bony thinning of orbital roof and superolateral wall	Lymphocytes, plasma cells, lymphoid follicles with reactive germinal centers, monocytoid cells	Immuno-cytochemistry	3 cycles of chemotherapy with cyclophosphamide, doxorubicin, vincristine, prednisolone, and rituximab due to discovery of systemic lymphoma
	2	47 F	Sjogren Syndrome	Progressive proptosis, hypoglobus	MRI- large cyst with bone thinning of orbital roof, hypodense T1 and hyperdense T2	Lymphocytes, reactive follicles, plasma cells, monocytoid cells	None	Surgical excision with 3000 Gy local radiotherapy to resolution
	3	35 F	None	Progressive proptosis, hypoglobus, limited upgaze and abduction	MRI- displaced lacrimal gland outside orbital rim, hypodense T1 and hyperdense T2	Lymphocytes, dendritic cells	+ : S100 Polymerase Chain Reaction Analysis	Surgical excision with 3000 Gy fractionated adjunctive orbital radiotherapy to resolution

Table 1. Reported Cases of Cystic Orbital Lobe Lacrimal Gland MALT Lymphoma (Con't)

Publication (Year)	***Patient Number***	***Age/Sex***	***Autoimmune Condition***	***Presenting Symptoms***	***Imaging***	***Histology***	***Molecular Studies***	***Management***
Dutton et al (2019)	4	58 F	Sjogren Syndrome	Proptosis, hypoglobus, limited upgaze	MRI- multiloculated cystic lesion with adjacent solid components	Lymphocytes, prominent germinal centers and occasional giant cells	+ : CD3, CD5, CD20, CD79, CD21, CD23, CD68, Ki67 - : bcl-2, cyclin D1, S100	Surgical excision to resolution
	5	67 F	Sjogren Syndrome	Ptosis, proptosis, hypoglobus, limited upgaze	MRI- multiloculated cyst	Lymphoid tissue with mostly small lymphocytes	+ : CD20, CD10, bcl-6, CD21, CD35 - : CD5, bcl-16, bcl-2, Ki67	Surgical excision with further testing pending
	6	78 F	Seropositive Rheumatoid Arthritis	Proptosis, hypoglobus, limited upgaze and abduction	MRI- multiloculated cysts and displacement of optic globe	Lymphocytes, plasma cells, reactive follicles	+ : CD3, CD5, CD20, bcl-2 - : CD10, bcl-6, cyclin D1	Surgical excision with low-dose orbital radiotherapy to resolution
Czyz et al (2021)	7	70 F	None	Medial lid contour deformity	CT- cystic mass	Lymphocytes with open chromatin and prominent nuclei	+ : CD3, CD5, Cd10, CD20, CD23, CD43, bcl-2, bcl-6 - : CD21, IgD, Cyclin D1, Ki67	Chemotherapy with Rituxan

