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Mucosa-associated Lymphoid Tissue Lymphoma of the Lacrimal Gland – A Case Report

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Abstract. *MALT lymphoma of the ocular adnexa, an indolent B-cell lymphoma, rarely affects the lacrimal gland. The case of a 73-year-old man with ptosis and edema of the left upper eyelid, due to lacrimal gland swelling, is presented. Clinical evaluation and imaging examination led to excision biopsy. The mass histopathology, presenting organized lymphoid tissue, composed mainly of small B-cells, accompanied by immunophenotypic characteristics, was compatible with MALT lymphoma. Treatment with monoclonal antibody against CD-20 achieved a successful long-term disease control (4 years). The diagnostic approach is described and the pathological features and clinical signs of this rare entity are discussed, based on recent literature. The indolent clinical course of this lymphoma, either remaining localized or disseminating to other mucosal sites, is a distinct characteristic affecting prognosis.*

The eyelids, conjunctiva, orbital connective tissue and lacrimal structures have all proved to be potential sites of a spectrum of lymphoproliferative disorders, constituting one of the most unpredictable groups of lesions encountered in clinical ophthalmology. In the stroma of the above tissues lies a resident population of lymphocytes, which are not organized into follicular structures. These may give rise to extranodal lymphomas, which account for 9% of all orbital tumors (1).

The Revised European-American Lymphoma Classification (REAL) (2) of lymphoid malignancies, as well as the more recent classification of the World Health Organization (WHO) (3), included in the extranodal group of lymphomas the marginal zone B-cell lymphoma of MALT (mucosa-associated lymphoid tissue) type or MALT lymphomas. Histologically, the majority of orbital lymphomas are of MALT origin (4).

Few reports in the literature combine information concerning lymphomas of the lacrimal gland and MALT lymphomas, depicting such cases as rare. Differential diagnosis includes benign lymphoproliferation, such as lymphoid hyperplasia, pseudolymphoma and inflammatory pseudotumor (5, 6). We report on a patient with MALT lymphoma of the lacrimal gland and attempt to compare the information available with respect to the presentation, treatment and follow-up of our case.

Case Report

A 73-year-old male patient was referred to the University Clinic of Ophthalmology, Ioannina, Greece, 4 years ago after recurrent episodes of conjunctivitis, non responsive to treatment, in the previous 4 months. Ophthalmological examination revealed an excellent visual aquity of 10/10 sc in both eyes and measured a ptosis of the left upper eyelid of 4 mm. No other pathological findings were recorded.

Laboratory evaluation showed a normal complete blood count, normal liver and renal functions. Dacrioadenitis was diagnosed and the patient was treated with corticosteroids (Medrol) for 20 days. In addition, the patient was referred to the rheumatologists for possible systematic disease. A CT scan of the left orbit was advised, showing an elongated, intense enlargement of the left lacrimal gland with maximum width of 1 cm, that extended to the anterior as well as to the posterior segment of the left orbit. The depicted mass had a smooth contour and did not affect the adjacent bone structures. Based on the CT scan findings, both lacrimal gland and lower lip biopsy were performed, suggesting no traits of Sjogren's syndrome.

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The patient was followed for a year, in which time the left eyelid ptosis did not improve. Two years later, the eyelid ptosis increased to 5 mm, while edema of the left upper eyelid was added to the clinical signs. New ophthalmological evaluation revealed exophthalmos of the left eye, measured with Hertel's exophthalmometer at 23 mm, while the visual aquity remained excellent. There was no afferent pupillary defect. Systemic evaluation remained normal. A second CT scan of the left orbit showed further enlargement of the lacrimal gland but, more importantly, revealed a significant enlargement of the left superior rectus muscle to 9.1 mm, when compared to 5.1 mm of the right superior rectus muscle. Two months later, a third CT scan of the left orbit was ordered, revealing an infiltrating neoplasm of the left lacrimal gland, extending posteriorly in the orbit and infiltrating the left superior rectus muscle (Figure 1).

Excision biopsy of the mass was advised and surgery was performed under general anesthesia, providing biopsy material from the left superior rectus, the supraorbital tissue and part of the mass of the left lacrimal gland. Serial tissue sections 4-μm-thick were cut, fixed in 10% formaldehyde solution, embedded in paraffin and stained with hematoxylin and eosin. Immunohistochemistry was performed on one or two selected paraffin blocks, from the lacrimal gland placed on poly-L-lysine-coated glass slides. In brief, tissue sections were deparaffinized in xylene and dehydrated. A step of immersion in citrate buffer (0.1 m, pH 0.6), in plastic coplin jars and subjection to microwave irradiation twice for 15 min, was performed. Monoclonal antibodies directed against CD20, CD5, CD23, CD10, bcl-2, CD3, CD45RO, CD43 and Clg were applied. The labelled streptavidin avidin biotin (LSAB) method was used and the chromogen was developed with immersion of the slides in a diaminobenzidine-H_2O_2 substrate for 5 min. The slides were counterstained in Harris hematoxylin, dehydrated and mounted. To access the specificity of the reaction, positive control slides were included in all cases.

On gross examination, the lacrimal gland tissue appeared to have a bosselated surface. Histopathological examination revealed a dense infiltrate of small lymphocytes arranged in a pdeudonodular pattern (Figure 2). The normal glandular architecture was totally destroyed. Follicular center colonization by a neoplastic cell population was evident (Figure 3). These cells were CD20(+) (Figure 4), CD5(-), CD23(-), CD10(-), bcl-2(-) and CIg(-). A substantial proportion of the neoplastic population expressed the T-cell immunophenotype, positive for CD3, CD45RO, CD5 and CD43 antigens. The above morphological and immunohistochemical characteristics were consistent with MALT lymphoma from small lymphocytes.

Taking into consideration the pathological diagnosis, the patient was treated with 8 cycles of Rituximab. Rituximab is a monoclonal antibody against CD20 antigen. Clinical evaluation following treatment showed response of the patient, with lid ptosis being reduced to 2 mm. New imaging examination with MRI confirmed the above observation, showing significant reduction in the size of the left lacrimal gland. To date, the patient's clinical and imaging follow-up remains constant with the expected course of a MALT lymphoma, thus validating the pathologist's diagnosis.

Discussion

The lacrimal gland is the rarest of the potential ocular MALT sites, included in mucosal sites, that may acquire such characteristics following antigenic stimulation (7).

The histopathological and clinical features of low grade B-cell lymphoma of MALT are well described in the paper by Li and his colleagues (8), according to the criteria outlined by Issacson (9) and reviewed extensively in other papers.

Orbital lymphomas are more commonly seen in elderly patients aged 44 (10) to 64 years (11). It has been noted, in prior investigations, that women with ocular adnexal lymphoid proliferations outnumber men, in contrast to non-Hodgkin lymphoma, which in general affects men more frequently than women (12-14). Recent reports by Lee *et al*., however, show that women are outnumbered by men (10).

In organs normally devoid of MALT, lympoid tissue may be acquired as a result of chronic inflammatory or autoimmune disorder, *e.g.* Sjogren's syndrome. Previous reports disagree as to whether MALT lymphoma can occur as a primary disease, or as both a primary and secondary disease in the ocular adnexa (11, 15). It is, however, agreed that patients with primary ocular adnexal lymphoma have a better outcome than those with secondary disease (11, 13, 14). This also seems to be true in our case.

Regarding clinical symptoms, reports (16), consistent with the observation made in our case, show that the majority of patients examined presented with a mass, swelling or blepharoptosis, or a combination of these. This reflected the involvement of the anterior structure, including in our case the lacrimal gland. CT and MRI findings, important in the work-up of orbital lymphoid infiltrates, were also consistent with the literature. Lacrimal gland involvement is usually identified as diffuse enlargement and axial elongation of the gland, which conforms to the contour of the globe (17). On T1-weighted MRI, lymphoproliferative lesions have low signal intensity, whereas on T2-weighted imaging the signal intensity is low to intermediate due to the increased cellularity of the mass (17). Furthermore, CT scan of the chest, abdomen and pelvis is mandatory in order to ensure correct staging. This is given in terms of clinical stage, usually according to the

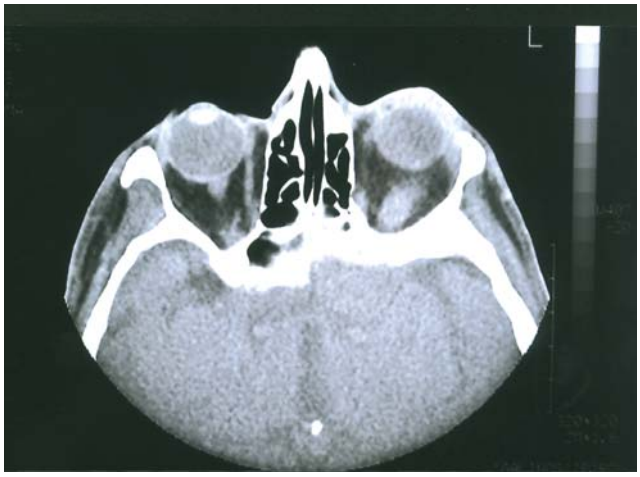

Figure 1. *MRI: Left lacrimal gland enlargement, extending posteriorly, infiltrating the left superior rectus muscle.*

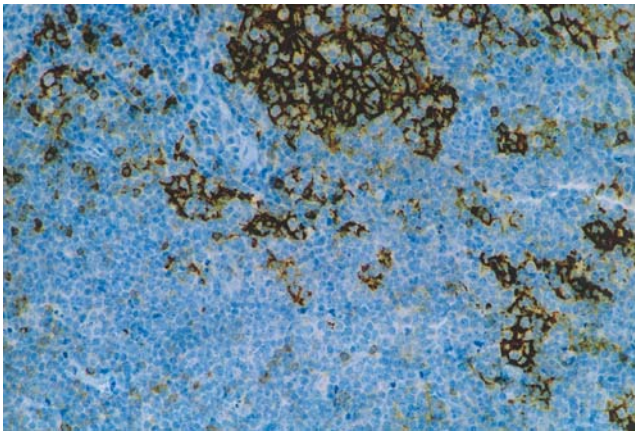

Figure 3. *Remnants of follicular dendritic reticulum cells of a lymphoid follicle colonized by neoplastic lymphoid cells (CD21, x200).*

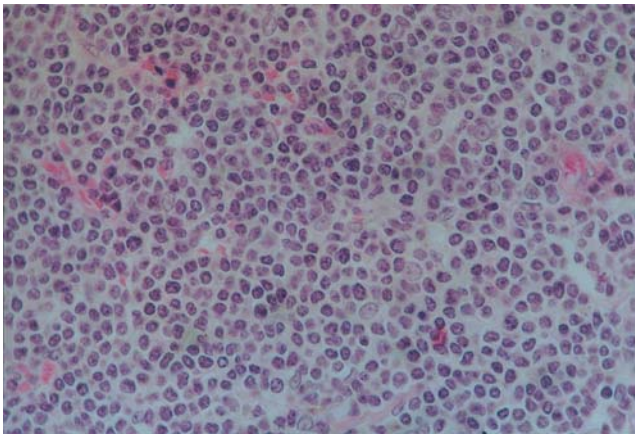

Figure 2. *Morphological spectrum of MALT lymphoma cells: small lymphocytes, centrocytoid lymphocytes, plasma cells and scattered transformed lymphocytes throughout the section (H&E x400).*

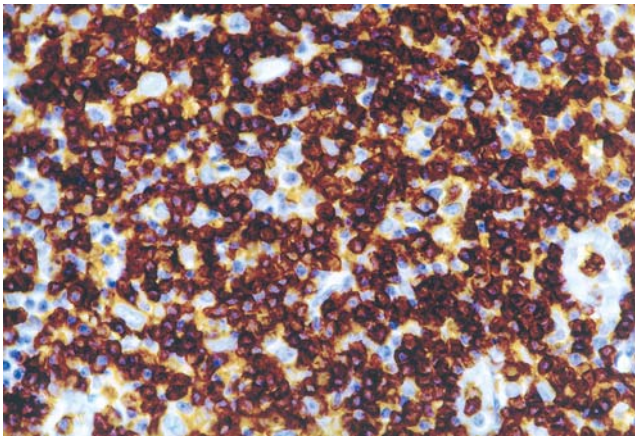

Figure 4. *Lymphocytes of MALT lymphoma with positive immunoreactivity to monoclonal antibody anti-CD20 (x400).*

Ann-Arbor Classification(18). Fung *et al*. (19) also reported that 19% of the patients with MALT lymphoma of the ocular adnexa (OA) had stage III or IV disease at diagnosis. Our case showed localization of the tumor, disease stage I. This supports the widely accepted view that MALT lymphomas have a tendency to remain confined to the orbit, probably because they share features of homing to their tissue of origin (9), or because there is no lymphatic drainage in the orbit and this may prevent the dissemination of the lymphatic cells (20).

Ocular adnexal MALT lymphomas in general, like their counterparts in other sites of the body, have a tendency to remain localized for prolonged periods and, when they do disseminate, the site of reccurence is another typical MALT site (11, 12). Prognosis is closely related to the clinical stage at presentation, patients with disseminated disease having worse prognosis than those with localized disease (17). Although not observed in larger studies, a recent smaller series suggested that lacrimal gland lymphoma presents a greater risk of subsequent systemic disease than orbital disease (21).

Apart from the clinical symptoms, it was only with the advent of immunohistochemistry and molecular biological studies that it was possible to distinguish between malignant lymphoma and reactive lymphoid hyperplasia. The immunophenotype of MALT lymphoma is not specific and, so far, seems to be one of exclusion: the cells are B-cells that are CD5(-), CD10(-) and cyclin D1(-); CD23 and CD43

are variable and monotypic cytoplasmic immunoglobulin may be present in plasma cells, but this is not a defining criterion (22, 23). The immunohistological characteristics of the ocular adnexal lymphomas of prognostic value include the MIB-1 growth fraction and, less convincingly, tumour cell positivity for p53 (6). In an analysis of 112 ocular adnexal lymphoid tumours with 99 malignant lymphomas, tumours with large growth fractions (>20%) correlated significantly with disease stage at presentation, disease stage at final follow-up and the occurrence of lymphoma-related death ($p<0.001$).

The neoplastic nature of the infiltrating lymphocytes in extranodal marginal zone B-cell lymphoma can be further supported (if necessary) through the demonstration of rearrangements of the immunoglobulin heavy chain gene with either Southern blot hybridization (24), PCR (6, 25), comperative genomic hybridization or fluorescent *in situ* hybridization (26).

Like non-Hodgkin lymphomas in other sites, surgery alone should not be employed as the main treatment of MALT lymphoma of the OA (27); radiation therapy has been reported to be very effective in MALT lymphoma of the OA (19, 28, 29). Fung *et al*. (19) showed a significant dose-response relationship in MALT lymphoma of the OA; the 5-year local control rate was 86% for less than 30 Gy and 100% for 30 Gy or more. This is in accordance with the results of later reports concerning stage I patients with lymphoma of the OA (30). It has been reported that combination chemotherapy is effective in orbital MALT lymphoma (31). However, because of the small number of patients who received chemotherapy alone, it is difficult to comment on the results of combination chemotherapy for advanced disease. Our case, treated with monoclonal antibody against the CD20 antigen, agrees with the above results with our patient reaching the fourth year of survival.

Long-term follow-up is needed to delineate the full spectrum of this unusual type of lymphoma and to understand its nature.

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References

1 Freeman C, Berg JW and Custler SJ: Occurrence and prognosis of extra-nodal lymphomas. Cancer *29*: 252-260, 1972.

2 Banfi A, Bonadonna G, Carnevali G, Oldini C and Salvini E: Preferential sites of involvement and spread in malignant lymphomas. Eur J Cancer *4*: 319-324, 1968.

3 Du M, Diss TC, Xu C, Peng H, Isaacson PG and Pan L: Ongoing mutation in MALT lymphoma immunoglobulin gene suggests that antigen stimulation plays a role in the clonal expansion. Leukemia *10*: 1190-1197, 1996.

4 Isaacson PG and Norton AJ: Lymphomas of the ocular adnexa and eye. *In*: Extranodal Lymphomas. Nuttall J, Daniels L, Singleton P (eds.). Churchill Livingstone: Edinburgh pp. 117-129, 1994.

5 Bahler DW, Miklos JA, Kapadia SB *et al*: Preferential use of specific immunoglobulin VH, D, and JH genes by salivary gland MALT lymphomas. Blood *88*: 375a Abstract, 1996.

6 Coupland SE, Krause L, Delecluse HJ *et al*: Lymphoproliferative lesions of the ocular adnexa. Analysis of 112 cases. Ophthalmology *105*: 1430-1441, 1997.

7 Yen MT, Pflugfelder SC, Crouse CA and Atherton SS: Cytoskeletal antigen expression in ocular mucosa-associated lymphoid tissue. Invest Ophthalmol Vis Sci *33*: 3235-341, 1992.

8 Li G, Hansmann ML, Zwingers T and Lennert K: Primary lymphomas of the lung: morphological, immunohistochemical and clinical features. Histopathology *16*: 519-533, 1990.

9 Isaacson PG and Norton AJ: Mucosa Associated Lymphoid Tissue (MALT) and the MALT Lymphoma Concept: Extranodal Lymphomas. Churchill Livingstone, Edinburg pp. 5-14, 1994.

10 Lee JL, Kim MK, Lee KH *et al*: Extranodal marginal zone B-cell lymphomas of mucosa associated lymphoid tissue- type of the orbit and ocular adnexa. Ann Hematol *84*: 13-8, 2005.

11 White WL, Ferry JA, Harris NL and Grove AS Jr: Ocular adnexal lymphoma. A clinicopathologic study with identification of lymphomas of mucosa-associated lymphoid tissue type. Ophthalmology *102*: 1994-2006, 1995

12 Knowles DM II and Jakobiec FA: Orbital lymphoid neoplasms: a clinicopathological study of 60 patients. Cancer *46*: 576-589, 1980.

13 Knowles DM II, Jakobiec FA, McNally L and Burke JS: Lymphoid hyperplasia and malignant lymphoma occuring in the ocular adnexa (orbit, conjunctiva, and eyelids): a prospective multiparametric analysis of 108 cases during 1977 to 1987 [see comments]. Hum Pathol *21*: 959-973, 1990.

14 Medeiros LJ and Harris NL: Lymphoid infiltrates of the orbit and conjunctiva. A morphologic and immunophenotypic study of 99 cases. Am J Surg Pathol *13*: 459-571, 1989.

15 Jakobiec FA, Iwamoto T, Patell M and Knowles DM II: Ocular adnexal monoclonal lymphoid tumors with a favorable prognosis. Ophthalmology *93*: 1547-1557, 1986.

16 Jenkins C, Rose GE, Bunce C, Cree I, Norton A, Plowman PN, Moseley I and Wright JE: Clinical features associated with survival of patients with lymphoma of the ocular adnexa. Eye *17*: 809-820, 2003.

17 Weber AL, Jakobiec FA and Sabates NR: Lymphoproliferative disease of the orbit. Neuroimaging Clin N Am *6*: 93-111, 1996.

18 Garbone PP, Kaplan HS, Musshoff K *et al*: Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res *31*: 1860-1861, 1971.

19 Fung CY, Tarbell NJ, Lucarelli MJ *et al*: Ocular adnexal lymphoma: clinical behaviour or distinct World Health Organization classification subtypes. In J Radiat Oncol Biol Phys *57*: 1382-1391, 2003.

20 Garner A: Orbital lymphoproliferative disorders. Br J Ophthalmol *76*: 47-48, 1992.

21 White VA, Gascoyne RD, McNeil BK, Chang WY, Brewer LV and Rootman J: Histopathologic findings and frequency of clonality detected by the polymerase chain reaction in ocular adnexal lymphoproliferative lesions. Mod Pathol *9*: 1052-1061, 1996.
22 Harris NL and Isaacson PG: What are the criteria for distinguishing MALT from non-MALT lymphoma at extranodal sites? Am J Clin Pathol *111(1 Suppl 1)*: S126-132, 1999.
23 Sharara N, Holden JT, Wojno TH, Feinberg AS and Grossniklaus HE: Ocular adnexal lymphoid proliferations: clinical, histologic, flow cytometric, and molecular analysis of forty-three cases. Ophthalmology *110*: 1245-1254, 2003.
24 Johnson TE, Tse DT, Byrne GE Jr *et al*: Ocular- adnexal lymphoid tumors: a clinicopathologic and molecular genetic study of 77 patients. Ophthal Plast Reconstr Surg *15*: 171-179, 1999.
25 Coupland SE, Foss HS, Anagnostopoulos I *et al*: Immunoglobulin VH gene expression among extranodal marginal zone B-cell lymphomas of the ocular adnexa. Invest Ophthalmol Vi Sci *40*: 555-562, 1999.
26 Wotherspoon AC, Finn TM and Isaacson P: Trisomy 3 in low-grade B-cell lymphomas of mucosa associated lymphoid tissue. Blood *8*: 2000-2004, 1995.
27 Esik O, Ikeda H, Mucai K *et al*: A retrospective analysis of different modalities for treatment of primary orbital non-Hodgkin's lymphomas. Radiother Oncol *38*: 13-18, 1996.
28 Bhatia S, Paulino AC, Buatti JM *et al*: Curative radiotherapy for primary orbital lymphoma. Int J Radiat Oncol Biol Phys *54*: 818-823, 2002.
29 Hasegawa M, Kojima M, Shioya M *et al*: Treatment results of radiotherapy for malignant lymphoma of the orbit and histopathologic review according to the WHO classification. Int J Radiat Oncol Biol Phys *57*: 172-176, 2003.
30 Uno T, Isobe K, Shikama N *et al*: Radiotherapy for extranodal marginal zone B-cell lymphoma of mucosa associated lymphoid tissue originating in the ocular adnexa: a multiinstitutional retrospective review of 50 patients. Cancer *98*: 865-875, 2003.
31 Galieni P, Polito E, Leccisotti A *et al*: Localized orbital lymphoma. Haematologica *82*: 436-439, 1997.

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