**Concomitant orbital tumors: Small lymphocytic lymphoma involving the lacrimal gland of a patient with clinical diagnoses of Muir-Torre syndrome and extensive sebaceous gland carcinoma of the ipsilateral eyelid.**

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*Short title: Concomitant orbital tumors in the lacrimal gland of a Muir-Torre syndrome patient.*

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**Abstract**

***Background/Aims****:* We present a case of 2 concomitant tumors – i.e. a Sebaceous Carcinoma (SC) and small lymphocytic lymphoma (SLL) - in the lacrimal gland of a patient with Muir-Torre syndrome.

***Methods****:* Clinical history, orbital examination, diagnostic biopsy, excisional biopsy and histopathologic analysis were utilized.

***Results****:* An 89-year-old female presented in the eye casualty with corneal ulcer, anterior uveitis, proptosis and restricted ocular motility. She has a clinical history of breast cancer, colon carcinoma and SC of the eyelid, which had been resected completely 2 years before. Clinical examination, imaging and diagnostic biopsy confirmed orbital SC recurrence. Exenteration and subsequent histopathologic analysis of the specimen revealed lymphocytic infiltrates consistent with SLL within the lacrimal gland.

***Conclusion****:* We report for the first time a case of Muir-Torre syndrome patient who developed an orbital recurrent SC with an incidental finding of a lacrimal gland B- non-Hodgkin lymphoma consistent with SLL. Clinicians should be aware of the possibility of this co-existence of multiple cancer types in patients with sebaceous carcinoma and Muir Torre syndrome.

**Concomitant orbital tumor: Small lymphocytic lymphoma in the lacrimal gland of a Muir-Torre syndrome patient with extensive sebaceous gland carcinoma of the eyelid.**

**Introduction**

Sebaceous carcinoma (SC) is a rare cutaneous malignancy that is characterized by aggressive behavior and is often associated with extensive local invasion, including perineural and bony infiltration, recurrence and metastasis to regional lymph nodes and distant organs [1]. Most SCs occur in the periocular region, commonly in the eyelid [2]. SC can occur in patients with an autosomal-dominant condition called Muir–Torre syndrome (MTS), who have additional visceral malignancies, such as colorectal, endometrial, urologic, and gastrointestinal tumors, in the absence of other predisposing factors. There are two types of MTS. The most common is characterized by defects in mismatch repair genes and the early-onset of these tumors. The second type of MTS does not show deficiency in mismatch repair and its pathogenesis remains undefined [3].

**Case History**

An 89-year-old woman presented to the eye emergency in 2015 with increasing pain and redness of the right eye over the previous several months. Visual acuity was 6/120 in the right eye and 6/12 in the left. On examination, she had a corneal ulcer, anterior uveitis with hypopyon, gross proptosis and restricted ocular motility to the right side (Fig.1 a). Her past medical history included diabetes type 2, diverticulosis, kidney stones as well as both breast carcinoma, colon carcinoma whilst in her 4th decade of life. In Sept. 2013, she had been diagnosed with a right upper eyelid poorly-differentiated SC. This was resected with 4mm margins and reported as completely excised. The upper eyelid was reconstructed with a Cutler Beard flap several days later after confirmation of pathological clearance on paraffin sections. Conjunctival mapping biopsies were clear of tumor cells, and there was no palpable lymphadenopathy. The patient recovered well, and follow-up examinations revealed only some punctate corneal erosions due to poor closure of the reconstructed upper lid; these were treated with topical lubricants. However, when she re-presented in February 2015 with the above symptoms, she was suspected to have microbial keratitis and orbital cellulitis. She was admitted to hospital and treated with intravenous antibiotics and topical antibiotics. Initially this responded to antibiotics, but as the infection settled her orbital signs failed to resolve, with 6mm persistent proptosis, hypotropia, restricted eye movements, hypoglobus and fullness in the superior orbit (Fig.1 b). A CT and MRI scan of the head and orbits were undertaken and revealed an extensive soft tissue mass occupying the superior aspect of the right orbit and extending to the apex, measuring 31 x 19 x 34 mm (Fig.1 c). There was no bony destruction or erosion (Fig.1 d) and no local lymphadenopathy. An orbital biopsy was performed and pathology results confirmed a local recurrence of her previously-treated SC. Her systemic staging scans showed no evidence of any pelvic or abdominal lymphadenopathy, or metastatic tumour. A FBC that was done prior to surgery did not reveal any lymphocytosis. We proceeded to total orbital exenteration. The produced specimen was sent for histopathologic examination, while the socket was left to granulate, with pro-granulation packing. The orbital exenteration specimen confirmed an extensive, partially necrotic SC, which involved the bulbar conjunctiva, with intraepithelial pagetoid spread, and extended superiorly and posteriorly with destruction of orbital adipose tissue and striated muscle, to the posterior surgical margin. Tumour infiltration of blood vessels, lymph vessels as well as peripheral nerve sheaths was seen. Immunohistochemical stains were performed and the SC cells demonstrated positivity for Ber-EP4 (M0804; 1:50;Dako UK), EMA (M0614; 1:400; Dako UK), perforin (clone 5B10;1:20; Leica Biosystems) and partially for adipophilin (clone PLIN2;1:500;Lifespan Biosciences) (Fig. 2). Although the latter marker was negative in the poorly differentiated areas of the tumor, it did highlight pagetoid spread within the conjunctival epithelium and epidermis (Fig. 2). Because of the medical history, we performed immunohistochemistry for the known microsatellite instability markers (MLH1, MSH2, MSH6 and PMS2). Both MLH1 and PMS2 demonstrated clear nuclear positivity whilst the other markers were negative, in the presence of a positive control (Fig.3).

In addition, the lateral surgical margin in the region of the lacrimal gland was characterized by dense lymphocytic infiltrates. On immunohistochemistry, a clear B-cell dominance was observed, with the lymphocytes showing an aberrant expression for CD5 (clone 4C7;1:100;Leica) and CD23 (clone 1B12;1:200;Leica). They were negative for cyclin D1 (clone SP4;A:50;ThermoScientific) (Fig. 4). In addition, IgH-PCR was performed on the DNA extracted from the microdissected lymphocytes, demonstrating a monoclonal B-cell population, confirming the diagnosis of a secondary manifestation a low-grade B-Non Hodgkin Lymphoma (NHL) in the lacrimal gland.

Given the involved surgical margins for both SC and SLL cells, the patient was treated with low-dose external radiotherapy. More than two years later, the patient is alive with no signs of local SC recurrence or metastatic disease.

**Discussion**

Herein we report a case of a MTS patient who developed a recurrent SC in the orbit as well as a focal infiltration of a low-grade B-NHL in the lacrimal gland, consistent with SLL. This case is of interest because the tumors arise concomitantly in very close adjacency to each other. They do not quite represent ‘collision’ tumors: i.e. two different neoplasms coexisting within a single lesion, either because two different types of cancer have independently and metachronously arisen at the same place, or because one or both malignancies have metastasized to the same location [4].

The phenomenon of NHL patients developing additional skin cancers, particularly if they are immunosuppressed, has been described previously [5].  Indeed Chang et al. presented six cases of patients with NHL, some of whom had MTS, who later developed SCs [6]. The authors proposed that a lymphoma-related immunosuppression and MTS-related abnormal tumor surveillance may predispose such patients to SC formation. Supporting this notion is the recent finding that the lymphoid enhancer-binding factor-1 (LEF1) that is highly overexpressed and associated with CLL/SLL [7], has also been found to play a role in the etiology of SC [8]. However, in our patient the SC preceded the SLL by several years, which is unusual.

Atypical also in our case compared to the series reported by Chang is the anatomical co-location of the two tumors, and the incidental nature of the SLL. The case is of interest for other reasons, including: a) the extensive degree of orbital invasion of this SC, despite the relative small initial nodular tumour of the eyelid. This may be explained by large components of the tumour being poorly differentiated with extensive perineural infiltration and the high number of mitoses; b) the use of a combined immunopanel when confirming the tumor type, particularly in the poorly differentiated areas. The strong expression of Ber-EP4 and perforin in the SC cells, despite the patchy staining of adipophilin, aided the differentiation of SC from its main mimics (e.g. squamous cell carcinoma, basal cell carcinoma, Merkel cell carcinoma and amelanotic melanoma) [10].

In conclusion, this patient had adjacent co-existent sebaceous carcinoma and SLL within the same orbit. Clinicians should remain vigilant for the other associated tumors of Muir-Torre syndrome in any patient with SC.

**Statements and Acknowledgments**

The patient consented to the use of the clinical data and photographs as well as the use of the histopathological images for publication.

This case report has not been simultaneously submitted for publication elsewhere.

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**FIGURE LEGENDS**

**Figure 1**: a) Anterior uveitis with hypopyon. b) Proptosis with associated right hypotropia. c) MRI Head: Coronal T1-weighted image with fat suppression enhanced with Gadolinium showing a soft tissue mass measuring 31 x 19x 34 mm which is extending along the roof of the right orbit and displacing the globe anteriorly and inferiorly. There is enhancement of the lesion post contrast. Normal appearances of the left globe and orbit. d) CT Orbits bone window showing an extensive soft tissue mass within the superior aspect of the right orbit which is causing proptosis and hypoglobus. There is no bony destruction or erosion.

**Figure 2** - Histological examination of a sebaceous gland carcinoma. (A) Haematoxylin and eosin (H&E) staining of a sebaceous carcinoma (SC) with the inset of (A) demonstrating cellular morphology at higher power magnification. (B) Epithelial membrane antigen (EMA) staining visible in the SC cells and at the epithelial surface. (C) Ber-Ep4 immunoreactivity of the tumor cells; (D) Adipophilin – patchy within the bulk of the tumor but demonstrating pageotid spread within the surface epithelium (inset); and (E) perforin expression in the SC (B-E: DAB immunostaining).

**Figure 3**: Immunohistochemical staining of the sebaceous carcinoma cells for microsatellite instability markers. It can be seen that the tumor cells are positive for MLH1 (clone ES05;1:100;Leica) (A) and PMS2 (clone A16-4;1:100;Leica) (B); however negative for MSH2 (FE11;DAKO;RTU) (C), and MSH6 (clone EP49;DAKO;RTU) (D) (DAB immunostaining).

**Figure 4**: Histological examination of a low-grade B-Non-Hodgkin Lymphoma (NHL) of the lacrimal gland. (A) Haematoxylin and eosin (H&E) staining of lacrimal gland showing areas of dense lymphocytic infiltration. Immunohistochemistry with 3,3’-diaminobenzidine (DAB) showing: (B) areas of proliferation with Ki67 staining; B-cell aggregates with positive staining for (C) CD20 staining at low-power magnification, (D) CD20 at high-power magnification and (E) CD23 identifying infiltrating B-cells of an abnormal phenotype. (F) CD5 positivity, a pan-lymphocyte marker, was also present. Cyclin D1 highlighted the macrophages within the tumor only (inset): the neoplastic lymphocytes were negatove for this marker (B-F: DAB immunostaining).