Case Reports in Ophthalmology

Case Rep Ophthalmol 2014;5:444–450

DOI: 10.1159/000369963
Published online: December 10, 2014

1663–2699/14/0053–0444$39.50/0
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Conjunctival Follicular Lymphoma after Treatment for Invasive Squamous Cell Carcinoma

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Key Words
Lymphoma · Follicular lymphoma · Eye neoplasms · Conjunctiva · Cytological techniques · Case report

Abstract
Backgrounds/Aims: The authors describe the case of a 79-year-old Caucasian woman who presented an ocular adnexal lesion as the first clinical manifestation of a systemic follicular lymphoma, highlighting the clinicopathological features of this rare entity and its potential to be misdiagnosed as marginal zone lymphoma of the mucosa-associated lymphoid tissue. ***Methods:*** Conjunctival impression cytology was performed for a rapid initial diagnosis of lymphoma, and subsequent histopathological and immunohistochemical studies were carried out for its confirmation and to identify the best therapeutic regimen. ***Results:*** After the initial presentation and diagnosis, she was submitted to complete clinical evaluation; confluent retroperitoneal lymphadenopathy was detected through abdominal computed tomography, characterizing clinical stage III. ***Conclusion:*** Awareness of this lymphoma is important when making a diagnosis of ocular adnexal lymphoid neoplasms for its appropriate evaluation and management.

Introduction

Ocular adnexal lymphoma (OAL) is defined as a lymphoma that can involve the eyelid, the conjunctiva, the orbit, the lacrimal gland or the lacrimal sac. OAL comprises 2.5% of all extranodal (i.e., originating outside lymph nodes and other lymphoid organs) non-Hodgkin lymphomas, and the most common type is the marginal zone B-cell lymphoma of the

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mucosa-associated lymphoid tissue subtype (MALT lymphoma). MALT lymphomas usually occur as a primary disease of the ocular adnexa whereas other lymphoma types are often systemic with secondary involvement of the ocular adnexa. This group of diseases affects both genders equally, but the incidence varies in different ethnic groups [1].

Follicular lymphoma is a monoclonal B-cell neoplasm that consistently exhibits a follicular pattern. In the ocular adnexa, follicular lymphomas constitute about 15–20% of OALs. Follicular lymphoma typically presents in older patients (about 60 years old), and the disease course is indolent with a long-term overall survival [2].

Case Report

The authors describe the case of a 79-year-old female patient, Caucasian, smoker, from Sao Paulo (SP, Brazil). In July 2013, she was evaluated by one of the authors (M.M.) due to the complaint of an abnormality and swelling of the inferior conjunctiva and the medial canthus of her right eye for a period between 4 and 6 months. She had a history of previous cataract surgery and corneal transplantation for the treatment of Fuchs endothelial dystrophy in 2008, and also an excisional biopsy for an ocular surface squamous neoplasia that was histologically graded as invasive squamous cell carcinoma in the inferior conjunctiva of the same eye in 2011. On examination, the visual acuity of both eyes was 20/25 on the Snellen chart. She had a salmon patch swelling extending from the nasal fornix to the inferior fornix and involving the bulbar conjunctiva in the medial canthus of her right eye (fig. 1). There was no pain and no history of trauma. The patient's intraocular pressure was measured at 12 mm Hg in both eyes. The rest of the exam was unremarkable. A previous hysterectomy with salpingo-oophorectomy due to her bilateral benign ovarian cysts and her treatment for an in situ carcinoma of the breast with conservative surgery, followed by radiotherapy, were recorded as her past medical history. Her family history was positive for breast cancer. Based on a slit-lamp examination and also to rule out an eventual recurrence of her previous ocular surface squamous neoplasia, impression cytology (IC) was performed to aid in the initial diagnosis. Following the administration of topical anesthesia with 0,5% proxymetacaine hydrochloride (Anestalcon® 0.5%, Alcon, Sao Paulo, Brazil), a membrane filter (Millipore HAWG01300, Bedford, Mass., USA) was placed onto the lesion surface, gently pressed for 5 s, and then peeled off. The sampling was performed 3 consecutive times in order to increase the sensitivity of the IC and to access the deeper layers. The filters were immediately fixed in a solution containing glacial acetic acid, formaldehyde 37%, and ethyl alcohol in a 1:1:20 volume ratio. All strips were processed for the periodic acid-Schiff and Gill's hematoxylin stain. Glass slides were mounted with Entellan (Merck, Darmstadt, Germany) and cells were analyzed under light microscopy by an experienced professional (J.N.B.).

IC samples (fig. 2) revealed an abrupt transition from the adjacent normal bulbar conjunctiva and a fairly monomorphic population of cells resembling lymphocytes, almost equal to or slightly larger than a mature lymphocyte, with scant cytoplasm, predominantly condensed chromatin and inconspicuous nucleoli over the lesion surface. Based on the cytomorphological findings, a hypothesis of a lymphoma was made and a differential diagnosis of lymphoid hyperplasia was considered [3].

An incisional biopsy was performed for subsequent histopathological and immunohistochemical studies to define the final diagnosis and to identify the best therapeutic regimen. The fragments obtained measured 0.3 × 0.2 × 0.2 cm on average and histologically demonstrated (fig. 3) a vaguely nodular and diffuse monomorphic infiltrate of small to medium

lymphoid cells with slightly nuclear irregularities in lamina propria of the conjunctival mucosa, with cytomorphologies similar to those seen in the cytologic samples. These lymphoid cells were diffusely positive for CD20, a B-cell marker and a CD21 immunostain highlighted the nodular pattern of the proliferation, revealing neoplastic follicles of various sizes. The neoplastic lymphoid cells within the follicles were positive for Bcl-6 and Bcl-2, as well those outside them, in the interfollicular region. A diagnosis of grade 1 follicular lymphoma was rendered.

After the surgery, the patient was referred to the A.C. Camargo Cancer Center for a complete clinical evaluation, staging of the disease, and for further treatment. She underwent a full systemic clinical workup including a complete clinical examination, peripheral blood film, bone marrow evaluation, chest radiographic study, magnetic resonance imaging (MRI) of the orbit, positron emission tomography, computed tomography (CT) scans of the chest, thorax, pelvis and abdomen. MRI scans of the orbit revealed a localized mass with densification in the inferior right eyelid. She was diagnosed with stage IIIA (by the conventional Ann Arbor clinical staging system) follicular lymphoma after the finding of confluent retroperitoneal lymphadenopathy through an abdominal CT scan. The bone marrow was not involved. Considering all these results, the patient was treated with a combination of immunotherapy with anti-CD20 antibody (rituximab) [4] and with the cytotoxic chemotherapy agents [5] cyclophosphamide and vincristine. Periodic follow-up with a repeated workup every 6 months was recommended. The patient was doing well during her first follow-up visit.

Discussion

The vast majority of literature's data on ocular adnexal lymphomas focus on the most frequent encountered histotype, i.e., marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue. However, when a physician encounters less common histologic types of lymphoma in this anatomical site, difficulties in their recognition and management may arise [5]. Besides, the usual clinical appearance of a benign lymphoid hyperplasia or a malignant lymphoma is normally a 'salmon patch'-like conjunctival swelling, without any specific clinical signs that can aid with the differentiation between the 2 lesions [6].

The association between follicular lymphoma and a previous invasive squamous cell carcinoma has never been reported on the conjunctiva. Nevertheless, there are reports that evidenced new malignancies (including lymphoma) after squamous cell carcinoma of the skin. According to Robsahm et al. [7], a history of skin cancer increases the risk of lymphoma. Although the mechanism for such associations is not fully understood, several mechanisms have been suggested. First, ultraviolet radiation impairs the immune system, both locally in the skin and systemically. Moreover, immunodeficiency as a result of the disease itself, genetic factors or previous treatment with radiation or chemotherapy are potentially shared risk factors [7, 8]. In our particular patient, there was a history of a previous radiotherapy for breast cancer as an adjuvant treatment.

The authors in the present report describe the case of a follicular lymphoma of ocular adnexa and highlight the features of this rare entity showing that IC performed before the treatment gave the first clue for a lymphoma diagnosis confirmed later by histopathology. On cytology alone, it may be difficult to distinguish between the lymphoma subtypes [3]. In the case described, the initial suggestion of a lymphoma was offered by a trained professional through IC over the lesion surface, and then subsequent histopathological and immunohistochemical studies confirmed the diagnosis and defined its histotype. To the best of our knowledge, there is no previous report on IC suggesting an initial diagnosis of a lymphoid

lesion at the conjunctiva preceding a surgical biopsy. Initial suggestions of another lymphoma were described through an imprint cytology of the biopsy material from a retrobulbar bilateral lesion from another patient [3]. In the present report, the initial suggestion of a lymphoid lesion was offered through IC performed directly over the unilateral conjunctival lesion, differing from the previous report that also used cytology for diagnostic purposes, but not directly over the lesion.

The role of the cytological result by the preoperative IC in the present case was the exclusion of the possibility of a recurrence of her previous ocular surface squamous neoplasia [9] on the conjunctiva, as well as the suggestion of a lymphoid tumor based on the cytomorphological findings described above. IC with the aid of a piece of cellulose acetate paper offers a simple and relatively noninvasive method for acquiring sequential samples of the superficial conjunctival epithelium, from the superficial lamina propria, from patients directly [9].

The differentiation of follicular lymphoma from mantle cell lymphoma, marginal zone lymphoma, and reactive lymphoid hyperplasia is important because these lymphomas exhibit different clinical behaviors and outcomes and lymphoid hyperplasia is a benign condition. Immunophenotyping is crucial to confirm the lymphoid lineage and lymphoma subtype. In difficult cases, additional ancillary studies such as in situ hybridization and polymerase chain reaction can also be performed [10] to define the histologic type or to prove the clonal nature of the process, respectively.

Our patient was diagnosed with stage IIIA follicular lymphoma after abdominal lymphadenopathies were found following her ocular manifestation. This finding is in accordance with the literature since the majority of patients have extensive disease above and below the diaphragm at the time of diagnosis [2]. As shown in the present case, the conjunctiva seems to be one of the most commonly affected extranodal sites [5]. Awareness of this lymphoma is important when making a diagnosis of ocular adnexal lymphoid neoplasms for appropriate management. A rigorous approach to initial diagnosis, including histopathological and immunohistochemical staining, followed by full staging evaluation for lymphoma, are recommended in patients with this disease.

Acknowledgement

No specific financial support was available for this study.

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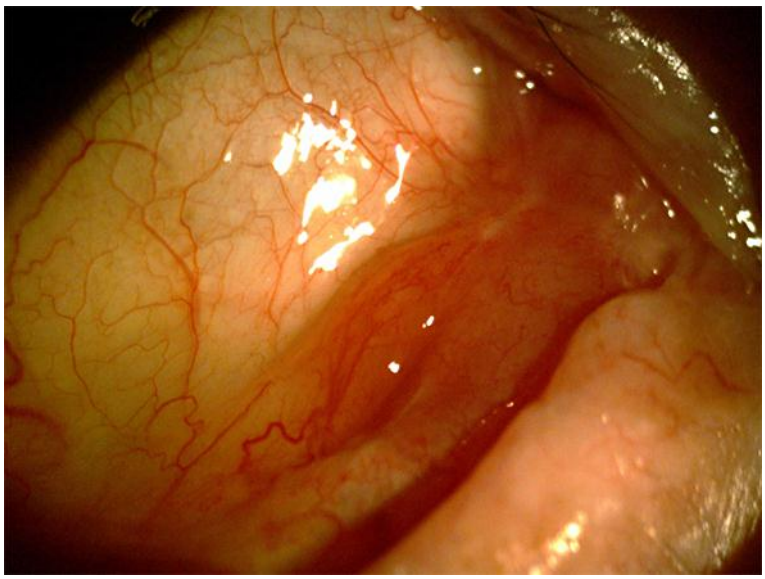

Fig. 1. A slit-lamp biomicroscopy appearance of the lesion showing a salmon patch swelling extending from the nasal fornix to the inferior fornix and involving the bulbar conjunctiva in the medial canthus of the right eye.

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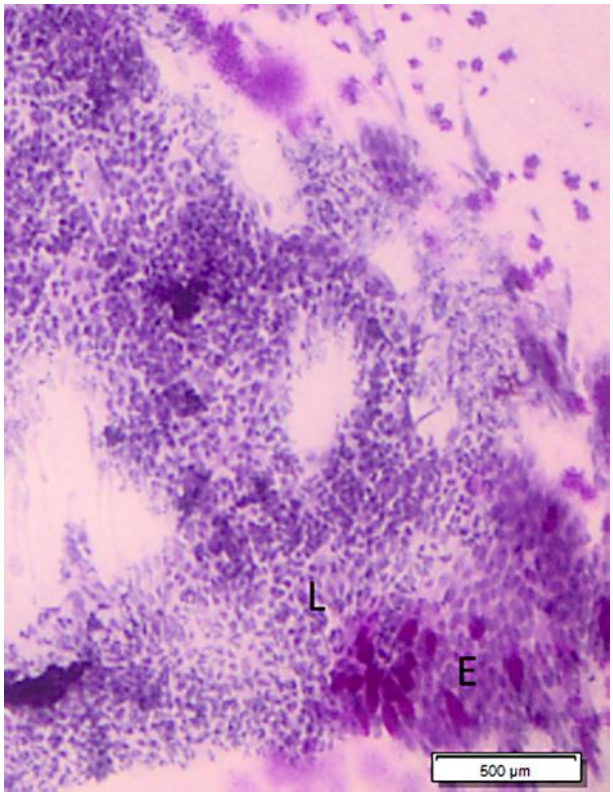

Fig. 2. An impression cytology demonstrating an abrupt transition from the adjacent normal bulbar conjunctiva with goblet cells (E) and a fairly monomorphic population of lymphoid cells (L), almost equal to or slightly larger than a mature lymphocyte, with a scanty cytoplasm, predominantly condensed chromatin and inconspicuous nucleoli over the lesion surface (HE. Original magnification. ×200).

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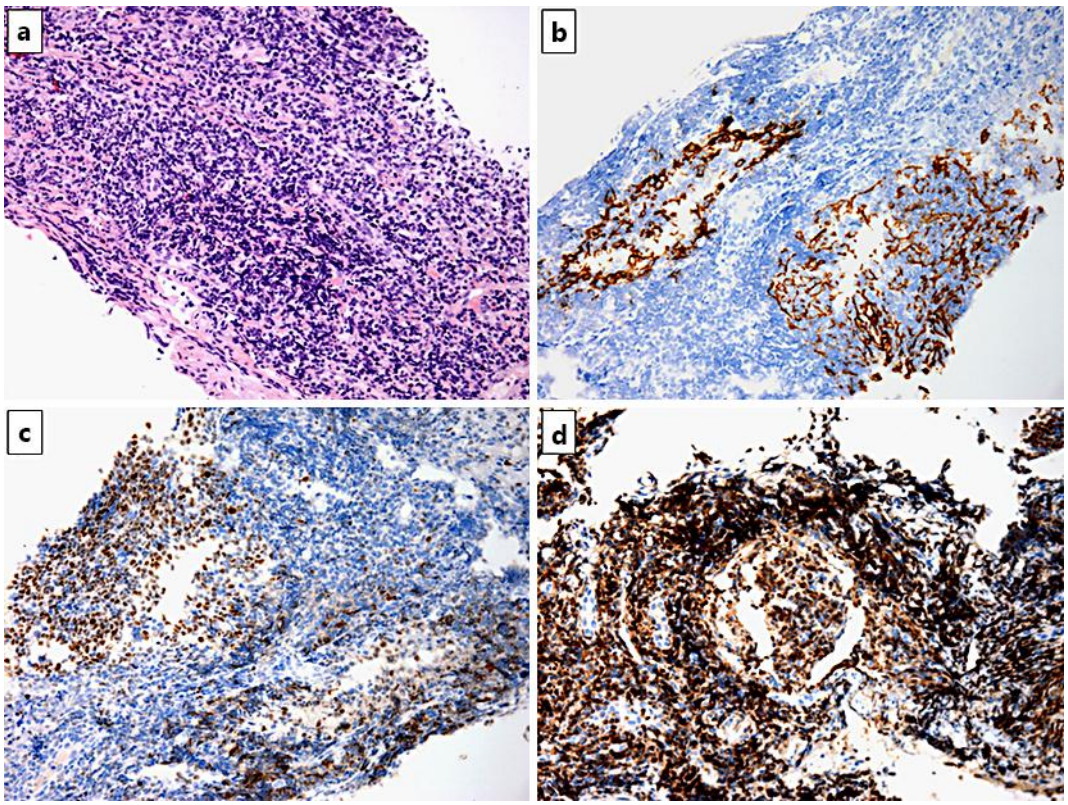

Fig. 3. Histopathological study: an interstitial and vaguely nodular lymphoid infiltrate in the lamina propria (**a**; HE. ×200). It was composed mostly by small to medium lymphocytes with slightly nuclear irregularities, being diffusely positive for CD20 (not shown), with CD21 highlighting the neoplastic follicles (**b**; CD21 antibody. ×200). The neoplastic cells were positive for Bcl-6 (**c**; Bcl-6 antibody. ×200) and Bcl-2 (**d**; Bcl-2 antibody. ×200).