Chronic lymphocytic leukaemia (CLL)/small-cell lymphocytic lymphoma (SLL) of the lacrimal sac: a case series

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Abstract

Background: Lymphomas of the lacrimal sac are rare accounting for less than 10% of lacrimal sac malignant tumours. They may present with symptoms typical of secondary acquired nasolacrimal duct obstruction and are thus often misdiagnosed.

Methods: Case series and literature review.

Results: Herein we describe 3 cases of chronic lymphocytic leukaemia (CLL)/small-cell lymphocytic lymphoma (SLL) of the lacrimal sac with immunohistochemical and in 1 case molecular confirmation.

Conclusion: Lymphomas of the lacrimal sac should be suspected in patients with known CLL presenting with epiphora and dacryocystitis. During dacryocystorhinostomy (DCR), an incisional biopsy of the lacrimal sac is essential for confirming CLL/SLL involvement and may guide treatment.

Key Words: Lacrimal sac, lymphoma, chronic lymphocytic leukaemia, dacryocystitis, epiphora.

Malignant tumours of the lacrimal sac are uncommon with close to 90% of these being of epithelial origin. Lymphomas of the lacrimal sac are rare [1-3]. They may present with symptoms typical of secondary acquired nasolacrimal obstruction including epiphora with a medial canthal mass and thus often misdiagnosed. It should be suspected in patients with known CLL presenting with epiphora and dacryocystitis. During DCR an incisional biopsy of the lacrimal sac is essential for confirming CLL/SLL involvement and may therefore guide adjuvant treatment [1-7].

All patients had signed a written informed consent form and the study was conducted in accordance with the declaration of the Declaration of Helsinki.

Case Reports

Case 1: An 89 year-old male, with past medical history of CLL and left external DCR, presented to the eye department with a painful, discharging, cystic swelling in the right lacrimal sac area. He was treated with antibiotics for his right-sided dacryocystitis, and later listed for a right external DCR. Perioperatively, the lacrimal sac was noted to be inflamed, and hence an incisional biopsy taken.

The specimen extended 8x5x3mm. Histological examination revealed: a diffuse atypical lymphocytic infiltrate with mild nodularity; intermediate-sized cells with coarse nucleus and prominent nucleoli and large cells with prominent nucleoli in proliferation centres (Fig. 1A&B). Ki67 immunostaining showed a moderate growth fraction with mitotic cells localized in proliferation centres (Fig. 1C). Further evaluation with immunohistochemistry (IHC) confirmed monotypical B cells with positive staining for: CD5; CD20; CD23; CD79a; (Fig. 1D-F) BCL-2 with synthesis of IgM, IgD and equivalent staining of kappa and lambda light-chains, with a moderate background scattering of CD3+ T-cells. The following immunostains were negative: cyclin-D1, CD21, CD10 and BCL-6. Histological and IHC features were consistent with diffuse, well-differentiated CLL/SLL. Immunoglobulin heavy-chain polymerase chain reaction (IgH-PCR) demonstrated a monoclonal B-cell population. Furthermore, next generation sequencing was performed as previously described [8]. Briefly, target exons of 15 selected genes relevant to CLL were sequenced using Ion Torrent Personal Genome Machine (PGM) and Torrent Suite Pipeline v4 (Life Technologies, UK). Genes included were: *TP53* (exons 2-11) and *SF3B1* (exons 8-20); *ATM* (exons 2-63); *MYD88* (exons 2-5);

BIRC3 (exons 2-9); *NOTCH1* (exon 34); *XPO1* (exons 11-16); *LRP1B* (exons 34-86); *FBXW7* (exons 5-12); *HIST1H1E* (exon 1); *ZFPM2* (exon 8); *SAMHD1* (exons 1-16); *CHD2* (exons 12-36); *POT1* (exons 5-19) and *PCLO* (exons 2-24). This molecular panel has previously been reported to be associated with extensive nodal involvement indicating advanced stages of CLL and thus relevant for its prognosis [8]. Next generation sequencing was performed in this case to ascertain whether or not lacrimal sac involvement is associated with any of these gene mutations. No somatic gene mutations were detected in the sample.

The patient was already under the care of haematologists and had received chemotherapy – previous course of chlorambucil followed by bendamustine. He was given a further single lower dose of bendamustine. His lacrimal stents were removed 6 months post successful DCR and he was given a further 6 month follow up appointment. Prior to his appointment at the eye department, the patient had surgery for a sebaceous cell carcinoma on his calf involving excision and grafting, which unfortunately failed and found to be infected with Pseudomonas. He subsequently developed sepsis and was treated with intravenous antibiotics but rapidly deteriorated, and died within 4 days of admission.

Case 2: A 66 year-old male, with known CLL in the past, presented with a 6 month history of epiphora and a painless hard mass over the right lacrimal sac. Computed tomography revealed a soft tissue mass, measuring approximately 20x22x16mm, in the medial canthal region extending into the lacrimal fossa and nasolacrimal duct into the nasal cavity. A right external DCR with an incisional biopsy of the lacrimal sac was performed.

Histopathological analysis showed: a nodular and diffuse infiltration by intermediate-sized, round lymphocytes punctuated by pale-staining proliferation centres containing pro-lymphocytes and para-immunoblasts. There was an unusual degree of stromal fibrosis, marked perineural and perivascular sclerosis. Tumour cells had a classical CLL phenotype: CD5+; CD20+; CD21+; CD23+; CD79a+; MUM-1+ and BCL-2+ with synthesis of IgM. CD3, CD10, cyclin-D1 and BCL-6 stains were negative. The Ki-67 growth fraction was <5%. Plasma cells within sclerotic areas showed indeterminate light-chain staining. Overall, features were consistent with lacrimal sac involvement by SLL/CLL.

The patient had low-dose local radiation of the lacrimal sac area alone, as further disease was not detected elsewhere on staging. The patient was re-referred to the eye department 2 years later for persistent epiphora secondary to post irradiation scarring. There was a complete response locally but the patient suffered a relapse of the CLL elsewhere, received further chemotherapy, and was subsequently lost to follow up at the eye department.

Case 3: A 75 year-old female, with a past medical history of: CLL (p53 deletion) treated with fludarabine and cyclophosphamide; successful left external DCR for recurrent dacryocystitis but local drainage of the right lacrimal sac due to relapse of her CLL, presented with a recent 6-month history of intermittent right eye epiphora. Clinically there was right nasolacrimal duct obstruction but no palpable mass. During external DCR, the right nasal process of frontal bone was noted to have a soft consistency with a spongy mucoid appearance and therefore prompted a biopsy. There was no obvious tumour noted in the lacrimal sac.

Histological assessment was limited due to a very small specimen and marked traction artefact. Of note, however, small fragments of trabecular bone showed dense infiltration of the intratrabecular stroma by lymphoma (Fig 2A&B). The tumour comprised small lymphocytes with scanty pale cytoplasm and small, round nuclei with condensed chromatin and no nucleoli. The cell infiltrate were CD20+, CD79a+, CD5+, CD23+ (Fig 2C-E), BCL-2+, IgM+, IgD+ with kappa light-chain restriction; but negative for CD10, p53, MUM-1, CD43 and cyclin D1. The Ki-67 growth fraction was <5%. There was marked reduction of CD3+ and CD5+ reactive T-cells. Histological and IHC appearances were consistent with involvement by SLL/CLL.

The patient was referred back to haematologists and treated with chlorambucil and ofatumumab. She has been in remission for 5 years.

Discussion

Lymphomatous involvement of lacrimal sac may be primary or secondary. There are <70 primary cases and few case reports/series of secondary involvement. Previous reporting would have been variable due to lack of global consensus regarding lymphoma classifications until the Revised European-American Classification

of Lymphoid Neoplasms, the WHO classification, and later the EORTC ophthalmic oncology task force study defining the clinical and histopathological characteristics [1-3, 9-10]. From the EORTC study of 15 primary lacrimal sac lymphoma cases, 33% of cases were classified as diffuse large B cell lymphoma (DLBCL; non-Hodgkin's lymphoma), 33% as extranodal marginal zone B cell lymphoma of mucosa associated lymphoid tissue (MALT lymphoma), 20% were classified as transitional MALT lymphoma with features between MALT lymphoma and DLBCL, and 13% as unclassified B cell lymphomas [10]. Of the other in the literature, it appears that DLBCL and MALT lymphomas occur with approximately equal frequency [1-3, 5, 7, 9-11]. However, DLBCL has been more frequently described in association with systemic lymphoma [2-3, 7].

Lymphomas account for ~2-6% of lacrimal sac malignant tumours, present in generally older patients with symptoms typical of secondary acquired nasolacrimal obstruction including epiphora, medial canthal mass; thus often misdiagnosed as acute or chronic dacryocystitis [4-7]. It should be suspected in patients with known CLL presenting with epiphora and dacryocystitis. DCR with stenting is well-tolerated and effective at alleviating symptoms. During DCR an incisional biopsy of the lacrimal sac is essential for confirming CLL/SLL involvement, even in the absence of obvious swelling (as in 1 of our cases), and may guide adjuvant chemo- and/or radiotherapy treatment [1-4, 6]. Treatment is usually a combination of surgery, irradiation and /or chemotherapy (notably regimens involving chlorambucil) but no commonly agreed treatment regimen for periocular lymphoma exists because of the limited number of patients seen [2-3, 7, 10-11].

In keeping with earlier reports [2-3], our patients had systemic CLL with secondary lacrimal sac infiltration, were elderly but one had presumed bilateral involvement (2 DCRs) and one with bony destruction which are rare. Two of the patients had been treated with chemotherapy (including chlorambucil) whilst one had low-dose local area irradiation as no further disease was detected.

In summary, CLL/SLL infiltration of the lacrimal sac is rare and should be suspected in any patient with systemic CLL presenting with epiphora and/or lacrimal sac area mass. Herein we present 3 cases with immunohistochemical confirmation and one where molecular testing was available – which, to our

knowledge, has not been previously reported. However, we do recognize that no somatic mutations were detected even though this molecular panel has previously been reported to be relevant for CLL prognosis and treatment response [8]. Whether or not lacrimal sac involvement is associated with the same somatic gene mutations requires further evaluation.

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