Metachronous Diffuse Large B-Cell Lymphoma and Kaposi Sarcoma of the Right Eyelid and Lacrimal Gland in a Patient with Granulomatous Common Variable Immunodeficiency

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Key Words

Common variable immunodeficiency · Kaposi sarcoma · Lymphoma · Lacrimal gland

Abstract

Purpose: To describe the ophthalmic and histopathological features of a female with granulomatous common variable immunodeficiency (CVID) who presented with upper-lid swelling. **Procedures:** The patient underwent a biopsy of the right upper lid/palpebral lacrimal gland with imaging showing a left-sided nasopharyngeal mass, multiple lymph nodes within the mediastinum, bilateral lung nodules and a peritoneal nodule in the right iliac fossa. The right upper-lid swelling progressed and was subject to a second biopsy. **Results:** The first right upper-lid biopsy revealed a diffuse large B-cell lymphoma (DLBCL), confirmed with clonal IgH gene rearrangement with PCR. The nasopharyngeal mass and lymph nodes were suspected clinically to be DLBCL. However, a biopsy of the nasopharyngeal mass showed Kaposi sarcoma (KS). The second biopsy of the right upper lid/palpebral lacrimal gland revealed KS with no evidence of DLBCL. **Conclusion:** This is the first documentation of periocular/orbital metachronous DLBCL and KS in a patient with granuloma-

tous CVID. We discuss the role of fluctuating immunity in CVID to explain the spontaneous regression of the DLBCL and the varying clinical picture.

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Introduction

Common variable immunodeficiency (CVID) encompasses a heterogeneous group of primary immune deficiencies characterised by reduced serum levels of immunoglobulins, absent or impaired specific antibody production and recurrent infections. The majority of patients present as adults with recurrent respiratory tract infections, gastrointestinal disturbances or autoimmune conditions [1–5]. CVID has two main phenotypes; one in which infections are characteristic and the other in which impressive inflammatory and/or hematologic complications also develop, including lymphadenopathy, splenomegaly, autoimmune cytopenias, enteropathy, and/or granulomatous disease [4, 6, 7]. Multi-systemic granulomatous disease is a well-documented complication of CVID, and its presence is associated with significant morbidity and early mortality. Granulomas are found fre-

quently in lung, skin, liver, spleen, and the gastrointestinal tract [3–7]. CVID patients also have an increased risk of malignancy, both haematological neoplasms and solid tissue carcinomas [1–5, 8–11], and these complications now appear to be the major cause of morbidity and death in CVID.

We report a unique case of a patient with granulomatous CVID who developed dual pathology of the right lacrimal gland/right eyelid region.

Case Report

A 43-year-old female with known granulomatous variant CVID presented to the orbital clinic with a 3-month history of bilateral upper-eyelid pain and swelling (fig. 1a). She denied any visual disturbance. The patient had an extensive past medical history related to her CVID that included hepatosplenomegaly, oesophageal varices, recurrent respiratory tract infections, bronchiectasis, previous cytomegalovirus (CMV) infection (non-ophthalmic) and coeliac disease. A CT scan confirmed bilateral lacrimal gland swelling (lacrimal and palpebral parts) which was worse on the right, with soft tissue upper-eyelid swelling (fig. 1b). She underwent a biopsy of the palpebral part of the right lacrimal gland and surrounding right upper-eyelid soft tissue. The biopsy was fixed in standard buffered formalin, processed to paraffin wax, cut into 4-µm sections and stained with haematoxylin and eosin (H&E).

Histology revealed variably sized aggregates of neoplastic lymphocytes surrounded by smaller lymphocytes and non-caseating granulomas (fig. 1c, d). The neoplastic lymphocytes expressed CD20 (fig. 1e), CD30, BCL6, BCL2, and MUM1, with a Ki-67 proliferation fraction around 80% (fig. 1f). The neoplastic cells did not express CD10, CD5, human herpes virus 8 (HHV8), EBV or cyclin D1. PCR revealed an unequivocal clonal B-cell population, confirming the diagnosis of a diffuse large B-cell lymphoma (DLBCL) with a non-germinal centre phenotype. A staging of bone marrow showed CVID-related lymphoid proliferation without lymphoma.

A PET scan showed intense uptake by a 2-cm left-sided nasopharyngeal mass and by multiple lymph nodes within the mediastinum, bilateral lung nodules and a peritoneal nodule in the right iliac fossa. In the context of the radiological findings, negative bone marrow trephine biopsy and lack of B symptoms, chemotherapy was postponed to enable biopsy of the nasopharyngeal mass. Histology of the nasopharyngeal mass confirmed the diagnosis of HHV8-positive Kaposi sarcoma (KS). The latter was treated with targeted palliative radiotherapy (interestingly, there was spontaneous resolution of the right lacrimal gland mass during the treatment of the nasopharyngeal KS).

The patient re-presented 3 months later with increasing swelling and discomfort in her right upper eyelid (fig. 1g). An MRI of the orbits confirmed the recurrent enlargement of both lacrimal glands with the clinical suspicion of recurrent DLBCL. The patient underwent a repeat biopsy of the right palpebral part of the lacrimal gland and surrounding eyelid soft tissue. On this occasion, histology revealed a KS, without evidence of DLBCL (fig. 1h–j). She received palliative radiotherapy to the right eye for symptom-

atic relief. Unfortunately, she developed multiple subcutaneous nodules and intermittent abdominal pain. A CT scan done for disease re-staging confirmed increased cervical, axillary and mediastinal lymphadenopathy, infiltration of the mesentery and multiple subcutaneous nodules, all being compatible with disseminated KS. This was confirmed by an axillary lymph node biopsy.

On review of all her previous biopsy material, a subcutaneous biopsy from the right side of her neck taken 3 years previously was reclassified as HHV8+ epithelioid KS, and not the 'likely myopericytoma' as initially diagnosed. These subcutaneous neck lesions pre-dating the lacrimal gland disease had spontaneously disappeared and appeared to be related to periods during which she was relatively immunologically well.

She received palliative chemotherapy for the disseminated KS, but over the next 6 months, her liver function deteriorated further. She continued to have repeated admissions for neutropenic sepsis and massive ascites, leading to her death. No autopsy was performed.

Discussion

CVID predisposes to an increased risk of malignancy, particularly gastric cancer and lymphoma [1–5, 8–11]. Estimating exactly how great the risk of malignancy is in CVID has proven challenging given the low prevalence of the condition. This has led to great variation in estimate. The risk of lymphoma in CVID patients was found to be increased by 30-fold in a British study and 259-fold in an American study [10, 11]. In a combined Danish and Swedish study of 176 CVID patients, the incidence of malignancy was increased when compared with the general population, with a standard incidence ratio (SIR) of 1.8. This was largely due to lymphoma (SIR 12.1) and gastric cancer (SIR 10.3) [8]. Granulomatous CVID accounts for 8–22% of all CVID [6, 7] and shows systemic non-caseating granulomas (often misdiagnosed as sarcoidosis). This subset of CVID shows an increased prevalence of the HHV8 genome within the blood and lymphoma lesional tissue [12, 13]. It has been postulated that the granulomatous disease in CVID represents a spectrum of lymphoproliferative disorder, driven by HHV8 [12, 13].

The commoner types of lymphoma documented in CVID patients include DLBCL (as in this case report), marginal-zone lymphoma and Hodgkin lymphoma [5]. The histological diagnosis of lymphoma in a CVID setting requires the confirmation of clonality by PCR testing.

Our patient had been diagnosed with CVID in 2003; however, the granulomatous component was diagnosed several years later. A colonic biopsy performed 1 year before the orbital disease showed poorly formed granulomas associated with a dense lymphocytic infiltrate. She

Fig. 1. **a** First presentation of the patient with upper-eyelid swelling (the right eye showed larger swelling). **b** Coronal CT scan showing bilateral lacrimal gland swelling. **c** H&E-stained biopsy section showing granulomatous inflammation. **d** H&E showing highly atypical lymphoid blast cells. **e** CD20 immunohistochemistry showing a positive signal on the lymphoid blast cells (membranous positivity). **f** Ki-67 immunohistochemistry showing a high proliferation fraction (around 80%). **g** Worsening of the right upper-eyelid swelling. **h** Repeat biopsy of the same region showing a bland spindle cell lesion, alternating with plumper cells (**i**) and positive for HHV8 on immunohistochemical staining (**j**), indicating a diagnosis of KS.

Table 1. Summary of ophthalmic CVID presentations

Infectious	Inflammatory/autoimmune	Granulomatous	Malignancy	Other
CMV retinitis [14, 15]	Placoid choroidopathy [22]	Granulomatous uveitis [19–21]	Uveal B-cell lymphoma [32]	Orbital inflammation and follicular hyperplasia of the orbit [29, 30]
Ocular toxoplasmosis [13]	Retinal vasculitis [23]			Retinitis pigmentosa [31]
Keratoconjunctivitis [16, 17]	Uveitis [19, 24–26] Orbital inflammation [29, 30] Birdshot-like chorioretinopathy [27]			

also had a long-standing waxing and waning lymphadenopathy of the mediastinal and cervical lymph nodes. This fluctuating clinical picture is likely related to an underlying variability in her immune state. The latter could explain the absence of lymphoma (through spontaneous regression in the absence of active intervention) in the second biopsy, which surprisingly contained only KS.

Ocular manifestations of CVID are limited and only described in case reports and small case series. Only 1 patient developed an ocular CVID-related complication in a study of 248 CVID patients (intraocular toxoplasma infection) [3]. Indeed, in most of the case studies, the subjects were treated for recurrent or opportunistic infections such as CMV retinitis and multi-drug resistant keratoconjunctivitis [14–17]. Table 1 summarises the ocular manifestations of CVID found in the literature. There are several reports of ocular manifestations of granulomatous CVID, including granulomatous uveitis [18–21]. Autoimmune and non-granulomatous chronic inflammatory complications of CVID include uveitis, diffuse placoid chorioretinopathy, bird-shot chorioretinopathy, bilateral corneal ulcerations and orbital inflammations [22–30]. Starr et al. [31] noted an unusual pattern of retinitis pigmentosa and CVID in one family.

The only report of an ocular malignancy related to CVID was of a 28-year-old female with known systemic B-cell lymphoma [32]. She presented with painful right-sided subacute visual loss, and examination of the eye showed a bullous, macula-off retinal detachment, a choroidal infiltrate and atrophy of the retinal pigment epithelium, suggestive of ocular lymphoma.

In summary, ocular complications, particularly malignant manifestations of CVID, are very uncommon, with only one CVID-related lymphoma previously reported in the eye. Our patient had a unique clinical presentation with sequential tumours of DLBCL and KS in the right lacrimal gland/right upper-eyelid region, complicated by

a fluctuating course reflective of probable varying immunity. Lastly, granulomatous inflammation in biopsies is not uncommon in the orbit and eyelid region and has a long list of causes. If a patient has a history of multiple infections and tumours, especially those that wax and wane, granulomatous CVID should be added as a differential to the histopathology report, especially if the presentation involves multiple systems, as in this case.

Statement of Ethics

The subjects have given their informed consent. The study protocol has been approved by the institute's committee on human research, and animal experiments conform to institutional standards. The study was performed in accordance to the Declaration of Helsinki.

Disclosure Statement

The authors have neither conflicts of interest nor financial interests to disclose.

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