HIV-Associated “Double-Hit” Lymphoma of the Tonsil: A First Reported Case

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Abstract

Double-hit lymphoma (DHL) is a unique subtype of non-Hodgkin lymphoma characterized by at least two rearrangements involving *MYC*, *BCL2*, and/or *BCL6*. These lymphomas are uncommon and aggressive, responding poorly to typical chemotherapy regimens. Lymphomas rarely arise from the oral cavity or tonsils, and those presenting as a neck mass are predominantly diffuse large B-cell lymphoma. To date, primary DHL of the tonsils has yet to be described in the literature. Here, we report a case of a 44 year-old male patient with well-controlled human immunodeficiency virus (HIV) who presented with a sore throat. He subsequently developed acute respiratory compromise due to a rapidly enlarging tonsillar mass. Pathologic and genetic analysis confirmed the presence of *BCL6* and *MYC* rearrangements suggestive of DHL of the tonsils. In a young patient with HIV and a neck mass, it is essential that lymphoma remains on the list of differential diagnoses as prompt diagnosis and treatment may prevent complications from its rapid expansion.

Keywords Double hit · Lymphoma · Tonsil · DLBCL · Large B-cell lymphoma

Introduction

Neck masses are a common occurrence in children and adult populations and are caused by various etiologies. Masses may be cystic, such as a thyroglossal duct cyst or lymphangioma, or solid, such as a lymphoma, neuroblastoma, or neurofibroma. Rarely, masses arise in the tonsils with diagnoses

ranging from unilateral enlarged lymph nodes to primary carcinomas. Squamous cell carcinoma (SCC) is the most common malignant neoplasm of the tonsils, with long-term tobacco and heavy alcohol use being major contributors, as well as human papillomavirus [1, 2]. Lymphomas occur less frequently than SCC and represent 5% of oral malignancies [3]. While the classification of lymphomas is complex, the typical nomenclature begins by identifying if the mass is a Hodgkin lymphoma or non-Hodgkin lymphoma (NHL), with the former characterized by the binucleated Reed–Sternberg cell [4]. Diffuse large B-cell lymphoma (DLBCL) is a type of NHL and the most common to arise in the oral cavity [3]. Another, more rare type is the high-grade B-cell lymphoma (HGBL) which encompasses all large B-cell lymphomas (LBCL) with rearrangements in *MYC*, *BCL2*, and/or *BCL6*. When HGBLs contain more than one of these rearrangements, they are called ‘double-hit lymphomas’ (DHL) and are associated with increased aggression and worse outcome [5–8].

Among human immunodeficiency virus (HIV)-positive individuals, DLBCL is the most common NHL variant. An increased rate of *MYC* and *BCL6* rearrangements portends an aggressive phenotype compared to lymphomas affecting the general population [9]. Despite these genetic influences, the mechanisms between HIV infection and subsequent

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development of DHL remain largely unknown. To our knowledge, DHL of the tonsils has not yet been described in the literature. Awareness of DHL occurrence at this site is necessary due to the rapid growth of these tumors with potential to cause acute airway compromise. Herein, we describe the first case of primary tonsillar DHL in a patient with HIV, a rapidly enlarging neck mass, and acute respiratory compromise.

Case Description

A 44-year-old male with a medical history significant for active HIV, treated with ongoing antiretroviral therapy, and *Helicobacter pylori* peptic ulcer disease presented to our clinic with a chief complaint of a sore throat. A social history was negative for smoking, tobacco, and alcohol use, and a family history was significant for maternal throat cancer. The patient denied fever, symptoms of an upper respiratory infection, shortness of breath, or hemoptysis. A subsequent throat culture was positive for group B streptococcus for which he was given a course of antibiotics. Despite the medications, the patient experienced worsening odynophagia and developed a muffled voice. Over the course of a month, he changed to a soft food and liquid diet and reported a weight loss of 35 lbs. His HIV viral load remained undetectable through the entirety of his work-up with a CD4+ count of 491.

Prior to arriving at our clinic, the patient had visited the emergency department (ED) for his symptoms. A peritonsillar abscess drainage was attempted but did not yield significant fluid for culture. A computed tomography (CT) scan performed at that time revealed a 3.1×2.5 cm mass (Fig. 1). The patient was scheduled for an outpatient fine needle aspiration (FNA); however, due to increased breathing difficulties, he returned to the ED 10 days later. A CT neck with IV contrast showed a 4.6×4.3 cm right tonsillar mass (Fig. 2). Right levels 2A and 1B/submandibular lymph nodes were enlarged.

Examination of the oropharynx revealed a large exophytic tumor with a smooth capsule. The tumor was obstructing 80 to 90% of the oropharyngeal inlet. The patient underwent a right tonsillectomy with significant tumor debulking whereby the mass was grasped and excised down to the tonsillar fossa using Bovine electrocautery. The histopathologic findings were characteristic of an aggressive LBCL, non-germinal center derived (Fig. 3). Fluorescence in situ hybridization (FISH) showed *BCL6* and *MYC* rearrangements, including a t(8;14) chromosomal translocation (Fig. 4). These results confirmed a double-hit HGBL. Additionally, the tumor was negative for Epstein-Barr virus (EBV) infection by Epstein-Barr encoding region in situ hybridization (EBER-ISH). The patient underwent six cycles of R-EPOCH (Rituximab, Etoposide, Prednisone, Vincristine Sulfate, Cyclophosphamide, and Doxorubicin Hydrochloride) and responded well initially.

Fig. 1 Initial computed tomography images revealed a 3.1×2.5 cm mass in the **a** axial (orange arrows) and **b** coronal (green arrows) planes

Fig. 2 Computed tomography images revealed a 4.6×4.3 cm right tonsillar mass in the **a** axial (blue arrows) and **b** coronal (red arrows) planes. Increased airway impingement as compared to previous CT scan 10 days prior is noted

Five months later, the patient developed a right-sided facial swelling. CT showed an enlarging mass in the right parotid space with increased metabolic activity on positron emission tomography (PET) scan. FNA confirmed recurrence and EBER-ISH was again negative. He was started on DHAP (Dexamethasone, Cytarabine and Cisplatin) and tolerated it well with an impressive resolution of the facial swelling. The patient is undergoing continuous follow-up.

Discussion

Previously, LBCLs with *MYC* and *BCL2* and/or, less commonly, *BCL6* translocations were thought of as hybrid malignancies between Burkitt lymphoma (BL) and DLBCL. They were designated “B-cell lymphoma, unclassifiable”. In the updated 2016 World Health Organization (WHO) classification system, this nomenclature was modified to the umbrella term HGBL which includes all LBCLs with *MYC*, *BCL2*, and/or *BCL6* known as “double-/triple-hit” lymphomas [5–8]. The distinction becomes clinically significant as it is known that HGBLs tend to act aggressively and respond poorly to standard CHOP (cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisone) or rituximab-CHOP therapy [3, 6, 8, 10–13]. Rather, first-line treatment with R-EPOCH has been shown to reduce progression and disease burden [10, 13]. Like many other NHLs, HGBLs with *MYC/BCL6* translocations, as seen in

our patient, frequently present as extranodal masses with documented cases of involvement of the central nervous system, nasopharynx, palate, ribs, ovaries, liver, and, in one case, an effusion-based lymphoma [3, 7, 10–12, 14].

In general, lymphoma is the second most common primary malignancy to arise within the head and neck region after SCC. The rising rate of SCC in younger populations, due to an increase in high-risk HPV infections, contributes to the misdiagnosis of lymphoma-based tonsillar masses [15]. Both tonsillar lymphoma and SCC present with non-specific findings early in the disease course which pose diagnostic challenges for clinicians. Risk factors such as heavy alcohol and tobacco use are known to be associated with SCC but their absence does not necessarily suggest lymphoma due to the increased prevalence of HPV-mediated cancers in the region [1]. Not only should clinicians consider lymphoma in the evaluation of tonsillar masses, other possibilities include those of benign origin including lymphangiomas. These benign lesions may resemble their malignant tonsillar counterparts as they may be locally destructive. However, unlike the malignant tonsillar masses, lymphangiomas are usually congenital and present early in life with a smooth and pedunculated gross appearance [2]. The distinction in etiology and clinical presentation is crucial as it guides the treatment course and choice of chemotherapy.

Of the malignant tonsillar masses, most have a site predilection for Waldeyer’s ring (WR), a region comprising the lymphoid tissue of the pharynx including tonsillar

Fig. 3 Histologic studies show solid sheets of atypical large lymphoid neoplastic cells with vesicular nuclei and prominent nucleoli, brisk mitotic activity, and frequent apoptotic bodies. **a** H&E $\times 40$, and immunohistochemical stains ($\times 20$), **b** Ki67, **c** PAX5 and **d** CD5

confirm overall findings consistent with an aggressive large B-cell lymphoma with non-germinal center derived phenotype (CD10–, BCL6–, MUM1+, data not shown)

Fig. 4 Fluorescence in situ hybridization (FISH) analysis was performed using split-signal probes to identify rearrangements in *BCL2*, *BCL 6*, *MYC*, *t(8;14)*, and *t(14;18)*. *BCL6* rearrangements were detected (**a**) with 1 red, 1 green, and 1 yellow fusion (1R1G1F, yel-

low circle) probes, indicating splitting of one yellow probe. *MYC* rearrangements (**b**) were also detected with 1R1G1F probes, indicated by the red circle. *t(8;14)* (not shown) was also detected in the analysis. The *BCL2* rearrangement and *t(14;18)* were not present

tissues of the nasopharynx, oropharynx, and base of the tongue [16–18]. The palatine tonsils appear to be the highest occurring primary site within WR for NHL to manifest and DLBCL represents the most frequently encountered NHL subtype [17–20]. However, the authors are unaware of any reports of primary DHL of the tonsils to date. There is one published case report of tonsillar follicular lymphoma expressing *BCL2* which subsequently underwent transformation into a triple-hit lymphoma of the frontal bone with a *MYC/BCL2/BCL6* phenotype [10, 11]. Nonetheless, the involvement of the tonsils by HGBL with *MYC/BCL6* translocations is a novel finding, especially in a patient with HIV.

Given the relatively new classification schema, there is scarce evidence describing the propensity of HIV-infected individuals to develop DHL. Previous evidence comparing DLBCL between HIV-infected patients and the general population demonstrates differing molecular characteristics between the two groups. HIV-infected patients with DLBCL tend to have a higher rate of *MYC* and *BCL6* abnormalities and thus a worse prognosis compared to those without HIV [9]. Additionally, of the different translocations noted in HIV-infected patients, *MYC* appears to be the most common and confers a more aggressive clinical course [9, 21]. There is one case report of an HIV-related DHL that presented as peripheral blood involvement with both *BCL2* and *MYC* translocations [22]. Further research is required to delineate the association between HIV-infection and subsequent development of DHL, with emphasis on the genetic phenotype as it pertains to treatment and prognosis. We describe a patient with HIV who developed primary DHL of the tonsils. While uncommon, this entity should be included on the differential diagnosis for neck and tonsillar masses due to its rapid growth and the potential for airway compromise.

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Compliance with Ethical Standards

Conflict of interest The authors declare that there is no conflict of interest regarding the publication of this paper.

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