CLINICO-PATHOLOGIC CONFERENCES

Tracheal Epstein-Barr virus-associated smooth muscle tumour in an HIV-positive patient

Giulio S Dominelli MD FRCPC1, Rachel Jen MD FRCPC1, Kirily Park MD PhD FRCPC2, Tawimas Shaipanich MD FRCPC3


Epstein-Barr virus-related smooth muscle tumours (EBV-SMTs) are a rare but well recognized non-AIDS-defining malignancy that can also be found in several other immunosuppressed states. Pulmonary involvement of EBV-SMTs is not uncommon, but it can present with multifocal lesions in any anatomical site. The present article describes an HIV-positive woman with dyspnea who was found to have a large tracheal EBV-SMT. The authors discuss their approach to diagnosis and management, and present unique follow-up bronchoscopic imaging.

Key Words: Epstein-Barr virus; HIV; Intervention bronchoscopy; Tracheal tumour

Learning objectives
• To learn which immunosuppressed states place patients at risk for Epstein-Barr virus-related smooth muscle tumours (EBV-SMTs).
• To develop a differential diagnosis for pulmonary malignancy in HIV patients.

Can Meds Competency: Medical Expert

Pretest
• What are the common malignant pulmonary manifestations of HIV?
• What immunosuppressed states can be associated with EBV-SMT?

CASE PRESENTATION

A 38-year-old woman was referred to her respirologist for evaluation of a two-month history of worsening exertional dyspnea. She had been seen by otolaryngology several months earlier for a right tonsilar mass and an incidental tracheal lesion 8 mm in size. The tonsil was biopsied, with pathology showing benign features that were managed conservatively. Unfortunately, she was lost to follow-up. Her current presentation was associated with a productive cough, occasional dysphagia and scant hemoptysis. Although there were no associated fever or chills, the patient reported a 4.5 kg weight loss over the previous two months. There were remote tuberculosis contacts, although work-up at that time proved negative. Her medical history was significant for HIV diagnosed six years previously. There was no history of AIDS-defining illness or previous opportunistic infections. She was not currently on antiretroviral therapy (CD4 count 2.20 \times 10^9/L). Other comorbidities included hepatitis C and a remote 10 pack-year smoking history.

Physical examination in the seated position revealed a respiratory rate of 16 breaths/min and oxygen saturation of 96%. There was good air entry bilaterally, with no stridor, wheeze or other adventitious sounds. However, when supine, there was significant cough, associated with the development of loud stridor and a minor oxygen saturation drop to 92%. Head and neck examination revealed an enlarged right tonsil and no palpable cervical lymph nodes. The remainder of the cardiovascular and abdominal examination was unremarkable.

Given the concern for airway obstruction, a computed tomography (CT) scan of the neck, chest and abdomen was performed (Figure 1). Compared with a scan performed several months earlier, there was significant interval increase in the polypoid tracheal mass from 8 mm to 1.5 cm in diameter, an increase in the right tonsil mass to 1.1 cm and a left upper lobe nodule measuring 11 mm. Flexible bronchoscopy was performed in an intensive care unit setting. It revealed a near-obstructing lesion with no distal central airway narrowing or lesions (Figure 2A). Given its size and location, the decision was made to resect via rigid bronchoscopy in the operating room. The tracheal tumour was successfully removed via rigid bronchoscopy using loop electrocautery and retrievable basket through a flexible bronchoscope. The patient tolerated the procedure well and examination of the distal airways following removal showed no abnormalities. Pathology from the resection demonstrated a well-circumscribed mass composed of tightly packed fascicles of mildly atypical short spindle cells with numerous mitotic figures (up to 20 mitoses per 10 high-power fields). There was no necrosis present and lymphocytes were scattered throughout the tumour. According to immunohistochemistry, the tumour was strongly positive for smooth muscle actin and myosin and was negative for desmin, keratin, p63, S100, CD34, human herpes-virus 8 and epithelial membrane antigen. The CD45 stain was negative in tumour cells, but highlighted the interspersed lymphocytes.

Figure 1) Computed tomography scan with representative axial images showing the 1.5 cm polypoid tracheal tumour and left upper lobe nodule

Figure 2A) Rigid bronchoscopy with 5 mm diameter flexible bronchoscope through a right ventricular cannula and 2 mm rigid bronchoscope with 15 mm diameter retrieval basket

1Department of Medicine, Respiratory Division, University of British Columbia, Vancouver; 2Department of Medicine, Nanaimo Regional General Hospital, Nanaimo, British Columbia

Correspondence: Dr Giulio S Dominelli, Pacific Lung Health Centre, St Paul’s Hospital, 88 Providence Wing, 1081 Burrard Street, Vancouver, British Columbia V6Z 1Y6. Telephone 604-806-8818, fax 604-806-8839, e-mail dominell@alumni.ubc.ca
The stain for Epstein-Barr virus-encoded RNA in-situ hybridization showed positive staining for nuclei of most of the spindle cells. The negative CD34 and human herpesvirus 8 excluded Kaposi's sarcoma. This pathology was compatible with an EBV-SMT (Figure 3). The patient subsequently underwent a repeat biopsy and right tonsillectomy. Pathology demonstrated the same EBV-SMT observed in the trachea, 1.7 cm in size with clean margins.

Medical oncology was consulted for considering adjuvant chemotherapy or radiation. Due to multifocal disease, the recommendation was to treat with antiretroviral therapy at the present time. Because the resection margin of the tumour was positive, follow-up bronchoscopy was performed at four weeks. Flexible bronchoscopy showed no significant intraluminal narrowing (Figure 2B). An optical coherence tomography (OCT) study revealed disruption of epithelium and thickening of basement membrane layers, but an intact cartilage ring at the resection site (Figure 4). These findings were suggestive of fibrotic tissue from previous electrocautery treatment and no further invasion of the tumour beyond the cartilage ring. A repeat biopsy at time of this particular OCT bronchoscopy confirmed the OCT finding and showed no residual tumour at the tracheal resection site at the four-week interval. The left upper nodule was not biopsied and assumed to be an additional site of EBV-SMT. A six-month follow-up CT scan showed a decrease in size from 11 mm to 9 mm. The patient is now asymptomatic, but continued surveillance will be critical because EBV-SMTs tend to be multifocal and recur.

**DISCUSSION**

EBV-SMTs are a well-recognized malignancy associated with HIV and other immunocompromised states such as post-transplant, common variable immunodeficiency, glucocorticoid and tumour necrosis factor inhibitor administration (1-4). Typical histology consists of well-differentiated smooth muscle cells with cigar-shaped nuclei, a low level of mitotic activity and positive stains for smooth muscle actin and Epstein-Barr virus (EBV) encoding RNA (5). The exact pathogenesis remains under investigation, but appears to be related to neoplastic transformation and clonal expansion of smooth muscle cells by EBV infection (4). Whether this occurs via CD21 upregulation or plastic transformation and clonal expansion of smooth muscle cells by EBV infection (4). Whether this occurs via CD21 upregulation or fusion of EBV-superinfected lymphoblastoid cells is unclear (3).

EBV-SMT in HIV can occur at any anatomical site and tend to be multifocal in nature in contrast to the solitary lesions observed in immunocompetent individuals. However, the multiple tumours are believed to be multifocal disease and not truly metastases because tumours do not share the same clonal origin (4). A recent review by Purgina et al (4) demonstrated the lung to be the third most common site, behind central nervous system and soft tissue. With pulmonary involvement, EBV-SMTs can present with a variety of symptoms depending on size and anatomical location. New-onset stridor, recurrent atelectasis or postobstructive pneumonia should trigger consideration of an endobronchial lesion. In addition to the present report, there exists a very small number of case reports documenting primary endobronchial involvement in adult patients (1,6,7). Other patients have presented with hemoptysis, dyspnea, wheeze or incidental nodules on CT scan. On bronchoscopy, EBV-SMT appear as white polypoid lesions attached to the bronchi or trachea. The differential diagnosis of an endobronchial lesion in an HIV-positive patient should include both neoplastic (Kaposi's sarcoma, adenoid cystic carcinoma, carcinoid, non-Hodgkins lymphoma, primary lung malignancy) and non-neoplastic causes (mycobacteriosis, foreign body, inflammatory polyp) (6).

The outcomes of HIV EBV-SMT are quite variable and cannot be accurately predicted from tumour histology (5). Reports show only a small subset (6%) of HIV EBV-SMT patients dying as a result of the tumour. Surgical resection is the mainstay of treatment in these patients, but is often limited by the anatomical location and multifocal nature of the disease. Endobronchial lesions can be removed via loop cautery or laser resection (1). Detailed planning for the resection of these tumours is critical given the concerns over airway stability and bleeding. The data regarding ancillary therapy, including antiretroviral therapy and chemotherapy, are minimal. There have been reported successes using antiretroviral therapy. These tumours appear to be resistant to conventional cytotoxins (4).

OCT is an optical imaging method that can offer real-time near-histological resolution for visualizing cellular and extracellular structures at and below the tissue surface. OCT is similar in concept to ultrasound, except light waves instead of sound waves are used for imaging. The OCT device (Lightlabs C7XR, St Jude Medical Inc, USA) used in the present study has an axial resolution of 12 µm to 15 µm and an imaging range of up to 5 mm in diameter. Previous studies have shown the ability of OCT to reliably differentiate in vitro benign, inflammatory and neoplastic bronchial tissue (8). However, the clinical role of OCT remains under investigation, but shows promise in areas of detection and therapy for early central lung cancers and
tracheal stenosis. To our knowledge, the present report is the first to describe OCT as part of postresection surveillance for EBV-SMT. The noninvasive nature and real-time ability of this technology makes it ideal for future research in the area of postresection surveillance.

ACKNOWLEDGEMENTS: GSD, RJ, KP and TS identified the case, managed the patient and contributed to the writing and editing of the manuscript. The authors thank Dr H Masoudi for providing the histopathology images.

Post-test
• What are the common malignant pulmonary manifestations of HIV?
EBV-SMT are a rare malignant complication of HIV infection. The more frequent malignant manifestations that one should consider are: Kaposi’s sarcoma, lymphoma, bronchogenic carcinoma and metastasis (9). Both Kaposi’s and non-Hodgkin’s lymphoma are considered to be AIDS-defining malignancies (9).
• What immunosuppressed states can be associated with EBV-SMT?
Case reports have identified EBV-SMT related to several immunosuppressed states. These include, but are not limited to: HIV/AIDS, post-transplant, common variable immunodeficiency, glucocorticoid and tumour necrosis factor inhibitor administration (2-4).

REFERENCES
Submit your manuscripts at http://www.hindawi.com