

# Post-transplant lymphoproliferative disorder presenting as CD20-negative plasmablastic lymphoma in the lung

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## Abstract

Post-transplant lymphoproliferative disorders (PTLD) are a serious complication of transplantation with a high mortality. Most PTLD present within the first year of transplantation and are associated with Epstein-Barr virus (EBV) infection. Plasmablastic lymphoma (PBL) is a rare but aggressive disease originally described in patients with HIV, presenting most commonly in the jaw and oral mucosa. To our knowledge, this is the first case of PBL presenting as PTLD of the lung in a HIV and EBV negative patient. Given the increasing number of transplants performed, we would like to share this uncommon presentation of PTLD as PBL.

## Introduction

Post-transplant lymphoproliferative disorders (PTLD) are lymphoid or plasmacytic proliferations that develop as a consequence of immunosuppression in a recipient of a solid organ, bone marrow, or stem cell graft. It is one of the most serious complications of transplantation with a mortality of 40-70%.<sup>1</sup> The majority of lesions are most commonly driven by Epstein-Barr (EBV) infection, but recently several cases have reported EBV-negative status.<sup>2-4</sup> Three main types of PTLD, as described in transplant patients, include early lesions, polymorphic PTLD, and monomorphic PTLD.<sup>5</sup> Early lesions encompass infectious mononucleosis-type acute illness characterized by polyclonal B-cell proliferation. Polymorphic PTLD are made of immunoblasts, plasma cells, and lymphoid cells that demonstrate malignant transformation and do not fulfill criteria for any of the recognized types of lymphoma described in immunocompetent hosts. Finally, monomorphic PTLD are monoclonal proliferations that are recognized in the immunocompetent host.

PTLD occurs in about 5% of patients receiving heart-lung/lung allografts.<sup>5</sup> Most PTLD presents within the first year of transplantation, especially in the context of immunosuppressive

agents, and is associated with EBV infection.<sup>5</sup> EBV-negative PTLD tends to present 4-5 years after transplantation.<sup>6,7</sup> Diagnosis is made under the circumstance of recent transplantation and tumor biopsy to evaluate histopathology, immunophenotype, and EBV *in situ* hybridization. Plasmablastic lymphoma (PBL) is a rare but aggressive disease originally described in patients with human immunodeficiency virus (HIV), presenting most commonly in the jaw and oral mucosa.<sup>8</sup> Morphologically, cells are described as large and centroblastic or immunoblastic. Tumors frequently are CD20 and CD45 negative and are positive for EBV virus and plasma cell related antigens CD138, P63, and CD79A. Prognosis is usually poor, with a median overall survival of 11 months, regardless of the intensity of chemotherapy.<sup>9</sup> Recently, several reports have expanded the disease spectrum and describe PBL manifesting in extranodal sites such as the colon, skin, and lungs in HIV positive and negative patients.<sup>10,11</sup> However, to our knowledge, this is the first reported case of PTLD presenting as PBL in the airway.

## Case Report

A 63-year-old, white male with a history significant for a single left lung transplant for interstitial fibrosis, a second bilateral lung transplant for primary graft failure secondary to pulmonary venous stenosis, and a third right lung transplant for bronchioles obliterans was admitted for fever and productive cough. His review of systems was also significant for a 10 pound weight loss over the prior 3 months. At the time of presentation, his vital signs were all stable; he was afebrile and had an oxygen saturation of 98% on 1 L of supplemental oxygen via nasal cannula. On examination, he was alert and oriented to time and place. Heart, lung, and abdominal exams were normal. No cervical, supraclavicular, axillary, or inguinal lymphadenopathy was appreciated. Complete blood count (CBC) was significant for low hemoglobin of 10.8 (Normal: 12.0-15.5 g/dL) and remained at this level throughout the hospitalization. The remainder of the CBC with differential was normal. Chemistry values were unremarkable. Other significant infectious laboratory values included a positive EBV DNA polymerase chain reaction (PCR) titer (low copy levels <2000 copies/mL), negative EBV *in situ* hybridization, negative cytomegalovirus PCR, negative HIV serology, and negative human T-cell lymphotropic virus serology. Broad-spectrum antibiotics, including imipenem, doxycycline, and vancomycin, were initiated for presumed pneumonia. Due to his significant transplant history, a bronchoscopy was performed and revealed granulation tissue completely occluding the left main bronchus. This obstruct-

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ing endobronchial tissue was debulked and sent for pathology evaluation along with a specimen from the right transplanted lung. The preliminary report of the left endobronchial tissue was consistent with malignancy, suspicious for PTLD. Overnight, he developed a fever and subsequently underwent another bronchoscopy, which showed the left main stem bronchus was obstructed again with tissue. Several hours after this bronchoscopy, the patient became hypoxic and was intubated and mechanically ventilated. He was successfully weaned and extubated after two days, at which time a repeat bronchoscopy revealed a patent left main bronchus. Final pathology report of the left endobronchial biopsy showed PBL with tumor cells staining positively for CD79a and CD138 (Figure 1). Markers CD3, CD20, PAX-5, CD30, MPO, S-100, cytokeratin, and CD56 were all negative. EBV *in situ* hybridization stains were negative. Ki-67 highlighted approximately 90% of tumor cells. The biopsy from the transplanted right lung revealed no acute rejection, granulomata, or malignancy. Based on the endobronchial biopsy results, and after discussing prognosis with the patient, a treatment plan was formulated to start standard dose R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy outpatient. In order to elucidate any other possible

locations of malignancy, a Positron Emission Tomography-Computerized Tomography (PET-CT) was ordered. Unfortunately, the patient continued to have multidrug-resistant pneumonia, and after discussion with the lung transplant team, the patient elected to pursue hospice care where he subsequently passed away 4 days later.

## Discussion and Conclusions

PBL was first described as a B-cell lymphoma occurring in the oral cavity in the context of HIV infection.<sup>8</sup> Recently, more cases of PBL have been reported in extra oral sites, including the stomach, bone, skin, and colon in HIV-negative patients as well.<sup>10</sup> In fact, there is a recent report of cutaneous presentation of PBL as PTLD.<sup>12</sup> The lungs, however, are a rare extra oral site of involvement of PBL, especially in the context of a HIV-negative patient. In the review of literature, this is the first case report of PBL presenting in the lung as PTLD in an HIV-negative individual. PBL is most commonly associated with immunodeficiency, such as HIV, and EBV plays an important role

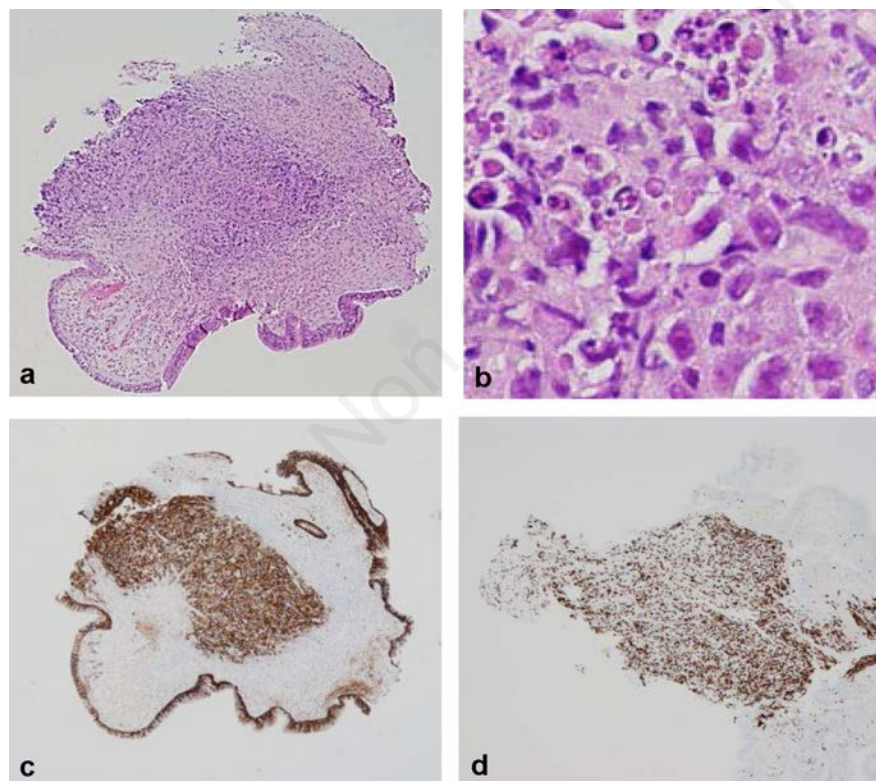
in transforming B cells to become malignant. Immunosuppression secondary to HIV provides an environment for EBV infection to promote tumorigenesis. But some reports suggest EBV infection is present in only 17% of HIV-negative PBL cases, indicating that EBV may not be the only virus responsible for tumorigenesis. Our patient presented in an immunosuppressed state post-transplant due to immunosuppressive agents, and EBV infection was not detected by *in situ* hybridization analysis. This may indicate another unknown virus or other factors that are responsible for the tumorigenesis of PBL. PTLD is usually treated with rituximab with success. Other cases of PBL presenting as cutaneous PTLD were treated with rituximab given a portion of positive CD20 cells.<sup>12</sup> However, our patient was CD20-negative and thus was proposed to be treated under a protocol for PBL, not strictly PTLD. Our patient opted to not pursue chemotherapy and elected to pursue hospice care.

We report a unique case of PTLD presenting as CD20-negative PBL in the lung. The disease was characterized by aggressive proliferation as seen with need for repetitive debulking. This was also illustrated histopathologically with the high presence of proliferative mark-

ers. Given the increasing number of transplants performed, we would like to share the importance of recognition of an uncommon presentation of PTLD as an aggressive form of PBL. Immediate treatment in accordance to histopathology and immunophenotyping can protract progression of the disease. More work is required to understand the mechanism of PBL presenting as PTLD in the context of HIV-negative, EBV-negative disease.

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**Figure 1.** Composite histology and immunohistochemistry of left main bronchus biopsy. a) Tumor biopsy was measured 0.2 in greatest dimension. Histologic hematoxylin and eosin section revealed malignant neoplasm with diffuse growth pattern (40 $\times$ ). b) High power magnification (400 $\times$ ) of neoplastic cells reveal atypical intermediate to large size lymphoid cells with one or more distinct nucleoli. Plasmacytoid features present. c) Neoplastic cells positive for CD138 (40 $\times$ ) and d) Ki67 stains approximately 90% of tumor cells (40 $\times$ ).