



## Case Report

# Brentuximab Vedotin Induces Long-Term Remission in T-cell PTLD without Evidence of Graft Rejection

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## Abstract

A 63-year-old male with a history of bilateral lung transplant in 2013 for end-stage COPD, presented with constitutional symptoms, and a paraspinal soft tissue lesion at the T10 level, lymphadenopathy, and lung and liver nodules on imaging. Liver biopsy confirmed EBV-negative T-cell PTLD with positive CD30. The patient's immunosuppressant regimen was reduced and immunochemotherapy was initiated with BV-CHP (Brentuximab vedotin, cyclophosphamide, doxorubicin and prednisone). Symptoms improved remarkably after starting chemotherapy and no change in lung function. PET scan after two cycles demonstrated a complete response (CR) which persisted on follow-up imaging after completion of 6 cycles. The physiologic role of CD30 is not fully understood in transplant recipients however, it was exploited therapeutically in this case. BV-CHP was safe, well-tolerated, and efficacious in treating patients with T-cell PTLD with positive CD30.

**Keywords:** PTLD; Brentuximab vedotin; CD30

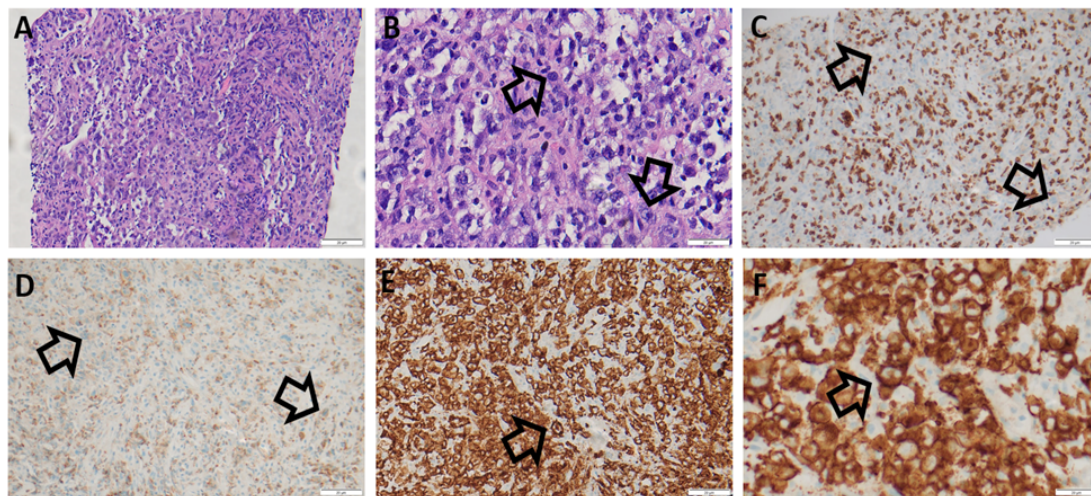
## Introduction

Post-transplant lymphoproliferative disorders (PTLDs) are typically of B-cell lineage and EBV-driven. However, PTLDs of T-cell or NK-cell lineage can rarely be seen, but they are less likely to be associated with EBV.

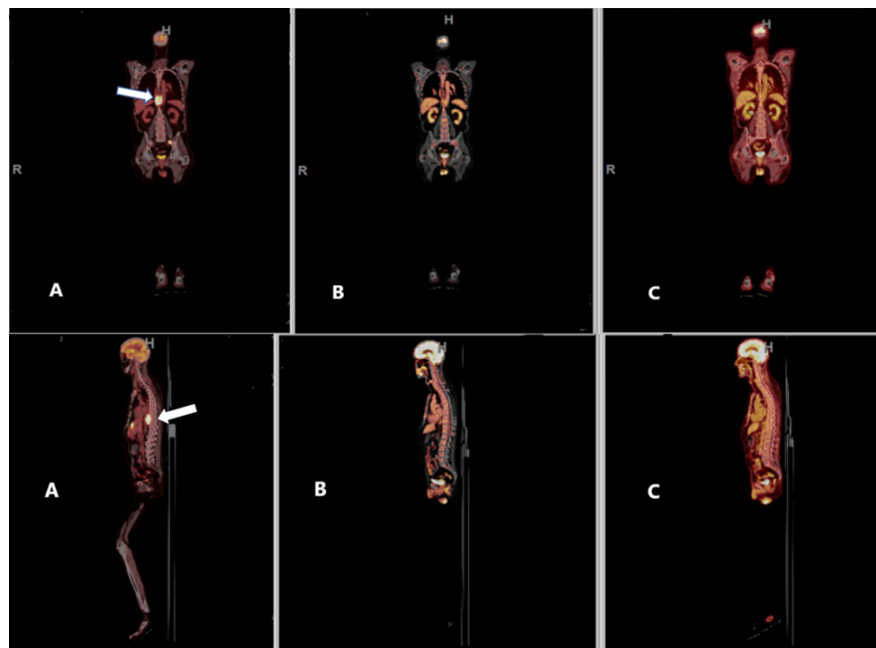
## Case Description

A 63-year-old male with a history of bilateral lung transplant in 2013 for end-stage COPD, complicated by acute rejection in the peri-operative phase, presented with constitutional symptoms and a paraspinal soft tissue lesion at the T10 level, lymphadenopathy, and lung and liver nodules on imaging. LDH was 304 U/L (normal reference range 85-277 U/L). Epstein-Barr virus (EBV) was detectable in the blood at 1,324 copies/mL by quantitative PCR. A liver biopsy revealed an abnormal T cell lymphoproliferative disorder that expressed CD2 (partial), CD4, CD5, perforin, and

TIA, but lacked CD3, CD7, CD8, ALK-1, and PAX-5. These cells formed abnormal sheets of large cells which were CD30positive and EBV ISH negative, establishing a diagnosis of monomorphic post-transplant lymphoproliferative disorder (PTLD) (Image 1). The International Prognostic Index (IPI) score was high-risk, with extranodal sites (involving liver and bone), in addition to elevated LDH and Ann Arbor stage IV. The patient was subsequently treated with a reduction in immunosuppression and BV-CHP (Brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone) as described in the ECHELON-2 protocol, every 3 weeks and planned for 6 cycles [1]. PET scan after two cycles revealed complete remission (Figure 1). Brentuximab vedotin was dose reduced to 1.2 mg/kg in the fourth cycle, then omitted in the last two cycles due to grade 2 neuropathy. Subsequent PET scan after completion of 6 cycles of chemotherapy demonstrated persistent complete remission (CR), and the patient remains in CR one year after completion of therapy without any evidence of lung compromise.



**Image 1:** Hematoxylin and eosin-stained slides demonstrate diffuse sheets of large, atypical cells (examples indicated by open arrows) infiltrating liver parenchyma at 20x objective view (A), with vesicular nuclei, prominent nucleoli, single cell necrosis, and mitotic activity apparent at 50x objective view (B). Immunohistochemistry at 20x objective views show the larger neoplastic cells are negative for CD3 but are found interspersed with normal T cells (C), are partially positive for CD2 (D), and are diffusely positive for CD30 (E). A 50x objective view demonstrates large atypical cells with diffuse CD30 positivity (F).



**Figure 1:** PET scan at diagnosis showed increased FDG-uptake in the paraspinal soft tissue lesion at the T10 level (white arrows) (A); PET scan after 2 cycles of BV-CHP (B) and 6 cycles of BV-CHP (C) showed resolution of the paraspinal mass. Coronal views on the top. Sagittal views on the bottom.

## Discussion

PTLDs are lymphoid and/or plasmacytic proliferations that develop in patients who undergo solid-organ or allogeneic bone marrow transplantation and are on immunosuppressive agents. Only about 7-15% of PTLT are of T-cell or NK cell origin [2]. PTLTs of T/NK type are reported to be EBV-associated in 37% of cases [3]. In this case, the T lymphoproliferation had morphologic and immunophenotypic aberrancies (including loss of CD3 and CD7, as well as strong CD30 expression) and would be considered a monomorphic PTLT

(resembling anaplastic large cell lymphoma, ALK-negative). The physiologic role of CD30 is not fully understood, and in transplant recipients is not defined at all. It is thought to be expressed on activated T cells, NK cells, and B cells and serves in negative selection of T-cells and secondary antibody production [4]. In this case, the tumor cells expressed CD30, and we were able to exploit that therapeutically. Treatment of PTLT represents a challenge due to patients' transplant history, comorbidities and immunosuppression. The risk-stratified sequential treatment (RSST) trial represented a novel strategy to maximize benefit while reducing treatment-related toxicity [5]. Immunosuppression reduction alone can yield responses in about 25% of PTLTs even though that varies by type of PTLT. The addition of monoclonal antibodies can also augment these responses. Brentuximab vedotin (BV) is an antibody-drug conjugate that binds to target tumor cells expressing CD30. The linked chemotherapeutic agent, monomethyl auristatin E (MMAE), is released causing cell cycle arrest and cell death. BV has demonstrated efficacy in treatment for CD30-positive peripheral T-cell lymphomas (PTCL) in combination with cyclophosphamide, doxorubicin, and prednisone (CHP). In the ECHELON-2 study, BV-CHP regimen for 6-8 cycles was compared with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) for the treatment of CD30- positive peripheral T-cell lymphomas. The hazard ratios for overall survival and progression-free survival favored BV-CHP (HR=0.66 and 0.71 respectively) [6]. However, there is very little data regarding the resultant immune manipulation of targeting CD30-positive cells in the post-transplant setting. Intratumoral regulatory T-cells (Tregs) have been shown to express CD30, and there was a concern about whether eliminating a significant portion would result in rejection. After careful discussion with the transplant and the patient, we elected to give one cycle with immediate improvement in constitutional symptoms and no change in lung function. We herein present this case where BV-CHP was safe, well-tolerated, and efficacious to add to the body of literature.

## Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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