



Plasmablastic lymphoma in an HIV patient with cutaneous presentation: A case of remarkable remission in a typically refractory disease

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INTRODUCTION

Plasmablastic lymphoma (PBL) is a rare, aggressive lymphoma of B-cell lineage and is frequently but not always associated with HIV and Epstein-Barr virus (EBV) infection. Unlike diffuse large B-cell lymphoma, the most common aggressive lymphoma, PBL is associated with a dire prognosis when treated using regimens commonly adopted for diffuse large B-cell lymphoma. Most studies, albeit all small sample sizes, report survival in the range of 3 to 12 months. Long-term survival for patients with relapsed PBL is extremely rare, as the malignancy becomes highly resistant to chemotherapy. PBL rarely involves skin. Our case describes a patient with nodal and extranodal involvement of PBL, presenting in skin. Despite refractoriness to the initial combination chemotherapy, the patient has achieved a durable remission.

CASE REPORT

A 47-year-old HIV-positive man on antiretroviral treatment with an undetectable viral load a month prior, presented with persistent left leg swelling for 6 months, a 10-day history of a rapidly enlarging right leg mass, and a 2-day history of a left foot drop. The leg swelling began after a traumatic closed left tibial plateau fracture that required open reduction

Abbreviations used:

CT: computed tomography
 EBV: Epstein-Barr virus
 FDG: fluorodeoxyglucose
 PBL: plasmablastic lymphoma
 PET: positron emission tomography

and internal fixation. There was no evidence of pathologic fracture.

On admission, he had a 6-cm round red/purple flat-topped tumor nodule with central crusted depression on the right lateral shin (Fig 1). There was no lymphadenopathy, and he denied a history of fevers, chills, night sweats, anorexia, or weight loss. The left leg was larger in circumference than the right leg, and there was a left foot drop. Computed tomography (CT) of the right lower leg showed an irregular subcutaneous soft tissue lesion measuring 4.2 x 1.9 x 3.7 cm near the proximal calf. CT of the left leg in the region of the thigh showed a 7.2 x 8.0 cm (anteroposterior x transverse) lesion and a small subcutaneous enhancing lesion along the lateral aspect of the knee measuring 1.0 x 0.9 x 1.3 cm.

The skin nodule in the right leg was biopsied at the outset. Results showed a diffuse and dense dermal infiltrate of large plasmablastic tumor cells with irregular nuclei, clumped chromatin, prominent nucleoli, and abundant basophilic cytoplasm,

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associated with prominent mitoses and apoptotic bodies (Fig 2). Immunohistochemical analysis (Fig 3) performed on formalin-fixed paraffin-embedded tissue sections found expression of MUM-1, BCL-2, C-MYC, CD79a, CD138, CD38, and dim to absent expression of CD45. The neoplastic cells were negative for PAX-5, CD19, CD20, CD56, BCL-6, and human herpesvirus type 8. The proliferation rate as detected by the Ki67 antibody was greater than 90% in the atypical cells. A λ light chain restriction was identified by in situ hybridization. In situ hybridization for EBV-coded RNA was positive. These findings were consistent with plasmablastic lymphoma. An EBV quantitative polymerase chain reaction performed on the peripheral blood was 12,617 IU/mL. A concurrent test for HIV found a viral load of 3183 copies/mL and a CD4 count of 331 cells/mm³.

Subsequently, the patient underwent surgical exploration of the left lower extremity, which found diffuse infiltration by tumor with encasement of the hamstring muscles, the posterior cutaneous nerve of the thigh, and the sciatic nerve. A soft tissue biopsy was performed, and histologic and immunohistochemical analysis confirmed the presence of HIV-associated, EBV positive plasmablastic lymphoma in the soft tissue of left leg.

In subsequent staging workup, bone marrow biopsy showed 10% involvement by the plasmablastic lymphoma. CT of the abdomen and pelvis found several enlarged left femoral lymph nodes, the largest of which measured 21 x 12 mm.

A diagnosis was made of stage IV PBL, involving the lymph nodes, skin, bone marrow, and nerves. He received 4 cycles of etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin hydrochloride (EPOCH regimen) given every 3 weeks, and additionally received intrathecal treatments. The patient achieved a complete response after 4 cycles of EPOCH, confirmed by positron emission tomography (PET) and bone marrow biopsy. He received 2 more cycles of planned EPOCH for consolidation. However, within 4 weeks of completing cycle 6 of EPOCH, a restaging PET scan found several fluorodeoxyglucose (FDG) avid masses in the left lower extremity and relapse was confirmed by biopsy. He subsequently received dexamethasone, high-dose cytarabine, and cisplatin (DHAP regimen) with bortezomib and daratumumab for 3 cycles and again achieved complete remission. He then received carmustine, etoposide, cytarabine, and melphalan (BEAM regimen) prior to autologous stem cell transplantation, which he underwent approximately 9 months after his initial diagnosis. Because of the high risk of relapse and the proven activity of lenalidomide in plasma cell tumors

and certain lymphomas, the patient was placed on lenalidomide, 15 mg/d using a 3-weeks-on 1-week-off schedule. Approximately 1 year later, after missing 2 to 3 weeks of maintenance lenalidomide, a new FDG-avid right groin lymphadenopathy was found. He responded clinically to restarting lenalidomide at a higher dose (25 mg) and was eventually switched back to 15 mg/d for better tolerance. His most recent CT scan showed complete remission. The patient has survived 46 months since his initial diagnosis and remains in remission (Fig 4).

DISCUSSION

Plasmablastic lymphoma is an aggressive lymphoma of the B-cell lineage, which usually presents with fever, weight loss, and night sweats in a patient with HIV infection or AIDS. In a recent meta-analysis of 277 patients with plasmablastic lymphoma, 50% were found to be HIV positive and 66% of the biopsies performed on these patients were EBV positive.¹ Extranodal presentation is most frequent, with the oral cavity and gastrointestinal tract being the most common sites of disease. Primary cutaneous PBL is rare, accounting for approximately 6% of HIV-associated cases, but a large ulcerative or infiltrative multinodular tumor mass on the legs is a common pattern.^{2,3}

Histopathologic examination shows a tumor with a dense and diffuse growth pattern and a “starry sky” appearance, imparted by the presence of frequent mitoses, apoptosis, necrosis, and tingible body macrophages. The tumor cells resemble both B-immunoblastic lymphoma cells with large nuclei and prominent nucleoli and plasmacytoma cells with an abundant, basophilic, and often eccentric cytoplasm. The tumor cells are CD45⁻ (our case showed dim to absent positivity), express plasma cell markers (CD79, CD138, and CD38, with a restriction of a light-chain λ noted in our case) and are B-cell antigen (CD19, CD20, PAX-5) negative. This antigen profile indicates a differentiation stage in between immunoblasts and plasma cells, hence, the term plasmablastic lymphoma. EBV can be detected in up to 75% of cases and HHV-8 in less than 50% of cases. *MYC* gene rearrangements have been identified in 40% to 50% of patients.⁴

PBL presents with advanced-stage diseases in most patients and has a very poor prognosis with death occurring within the first year of diagnosis. For systemic PBL, there is no standard therapy that is proven to be highly effective. The most commonly used regimen for first-line treatment of PBL is cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like. More intense regimens, including high-dose chemotherapy and

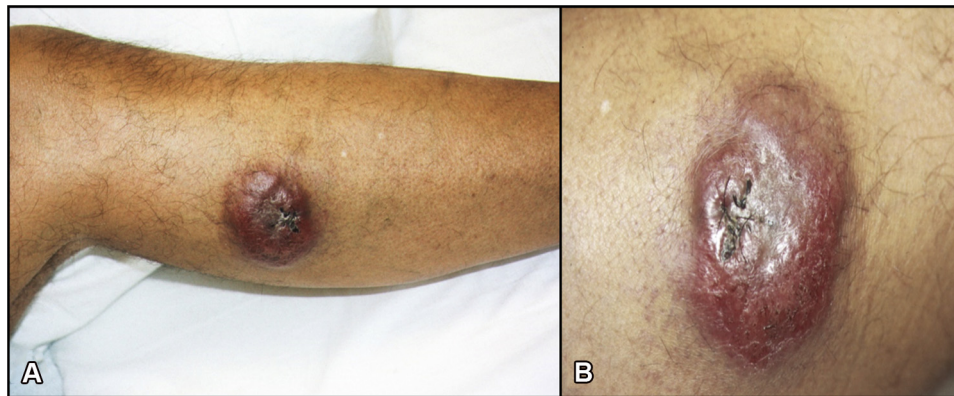


Fig 1. Clinical photographs of cutaneous manifestation of PBL. **A**, A 6-cm round, red, nodular flat-topped tumor with central crusted depression on the right lateral shin. **B**, Closer view of same image.

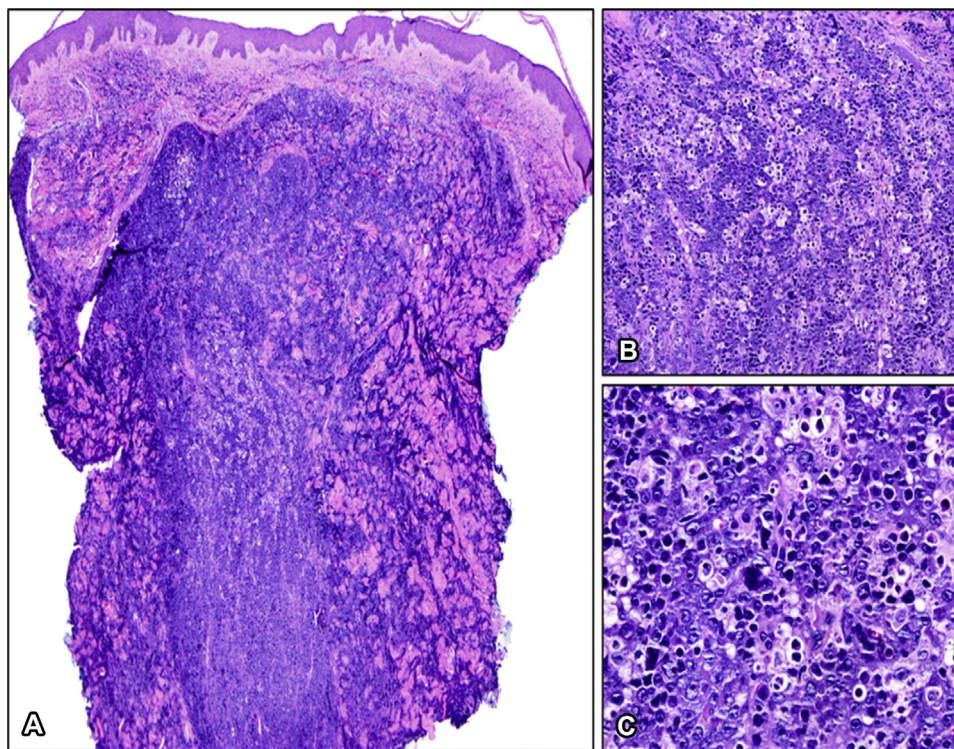


Fig 2. Histologic images of PBL. **A**, Punch biopsy of right lower leg lesion shows a dense, diffuse infiltrate in the dermis. **B**, Dense infiltrate of atypical cells with numerous mitotic figures and tingible body macrophages imparting a starry sky pattern. **C**, Neoplastic cells have a plasmablastic appearance with large nuclei, prominent nucleoli, and abundant basophilic and often eccentric cytoplasm. (Hematoxylin-eosin stain; original magnifications: **A**, x40; **B**, x200; **C**, x400.)

autologous stem cell rescue in first remission, have been reported in small studies, but the long-term benefits of dose intensification in PBL has yet to be confirmed.⁴⁻⁶ However, antimyeloma agents such as daratumumab and proteasome inhibitor bortezomib, alone and in combination with chemotherapy, have

produced responses in some patients with PBL.^{4,6} Lenalidomide, an immunomodulatory agent, has also shown efficacy in some patients with relapsed PBL. Our patient had refractory PBL, which is associated with a poorer prognosis than those with relapsed PBL. Fortunately, the patient has responded

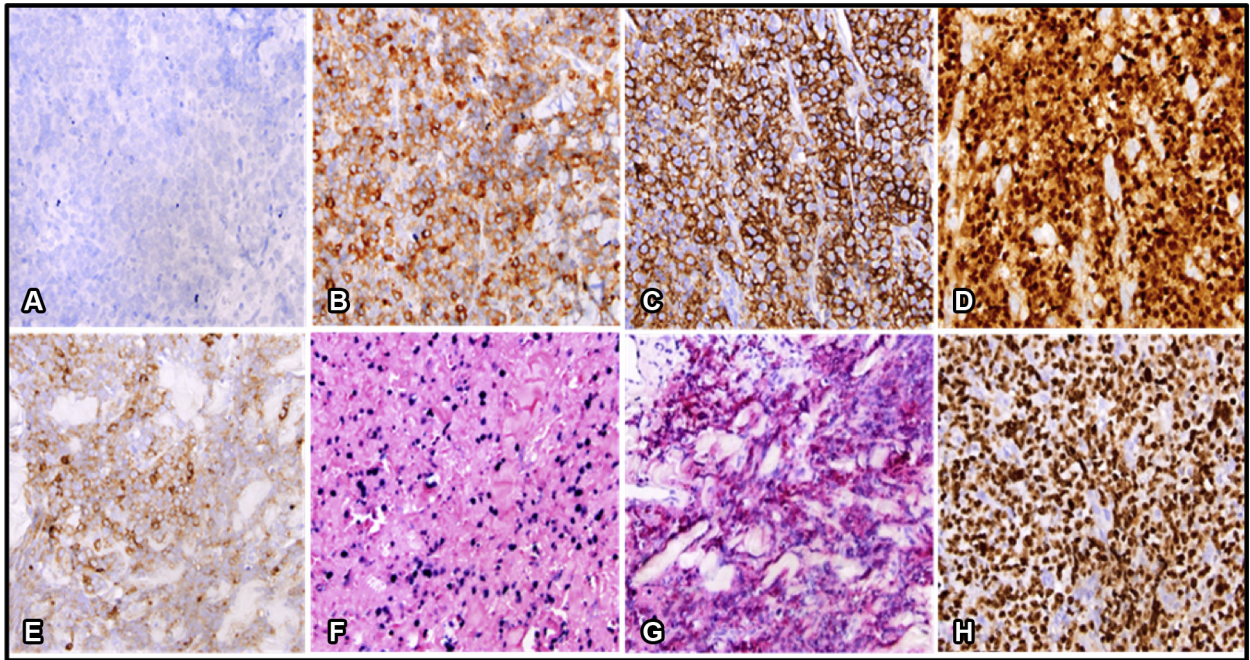


Fig 3. Immunostaining pattern of PBL. The neoplastic cells are negative for B-cell antigen CD20 (A), positive for plasma cell markers CD79a (B) and CD138 (C), and positive for MUM1 (D) and EMA (E). The neoplastic cells are also positive for EBV-encoded RNA by in situ hybridization (F) and show restriction of λ light chain (G). The Ki67 proliferative index exceeds 90%. (A through H, Hematoxylin-eosin stain; original magnification: x400.)

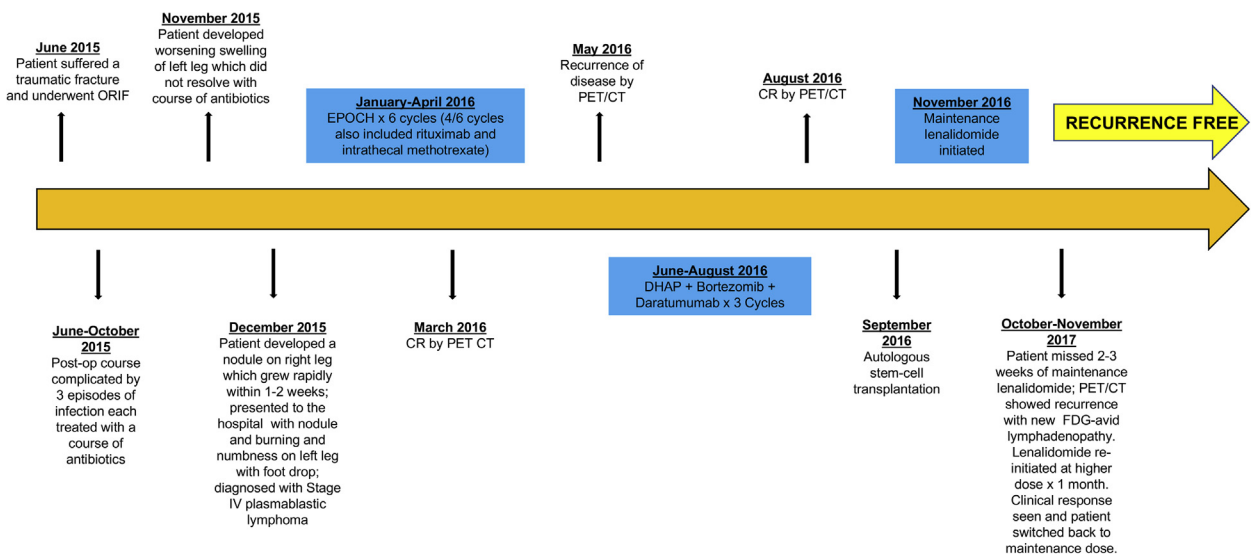


Fig 4. Timeline of the clinical course. Timeline of the patient’s clinical course from time of fracture to present. ORIF, open reduction internal fixation; CR, complete remission; DHAP, cisplatin, cytosine arabinoside and dexamethasone.

very well to the treatments given so far, including chemotherapy and 3 drugs active in plasma cell tumors. He remains lymphoma free 46 months from the initial diagnosis. The case shows that in carefully selected patients with PBL it is feasible and likely beneficial to incorporate bortezomib, lenalidomide,

and daratumumab into chemotherapy regimens, and such treatments may produce long-term survival even in refractory PBL. This strategy warrants further study in clinical trials.

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