Immunosuppression-associated primary cutaneous plasmablastic lymphoma secondary to romidepsin

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INTRODUCTION

Plasmablastic lymphoma (PBL) is a rare subtype of large B-cell lymphoma most commonly seen in immunocompromised patients, particularly in those with HIV infection. In these patients, PBL often affects the oral mucosa.1 Other immunocompromised states, including immunosuppression for organ transplant and immunosenescence, have been linked to PBL.1 Epstein-Barr virus (EBV) reactivation is thought to be a major driver of PBL.1 PBL is characterized histologically by an absence of B- and T-cell markers and expression of plasma cell markers CD38 and CD138. The median overall survival of HIV-positive and HIV-negative patients with PBL is 15 months and 9 months, respectively.1 Some patients with PBL present with primary cutaneous disease (pcPBL), defined as no systemic involvement. These patients have a unique clinical presentation and an indolent course. We report the first case of iatrogenic pcPBL secondary to romidepsin therapy for primary cutaneous peripheral T-cell lymphoma not otherwise specified (pcPTCL-NOS).

CASE

A 72-year-old woman with pcPTCL-NOS, diagnosed in 2013, presented to the dermatology clinic in 2015 with progressive disease (Fig 1, A). She had a history of non-Hodgkin lymphoma diagnosed and treated in 2004 and myeloproliferative disorder diagnosed in 2013, both at an outside institution, and neither diagnosis was independently confirmed at our institution.

Romidepsin (14 mg/m² on days 1, 8, and 15 of 28-day cycles) was initiated in December of 2015 for the pcPTCL-NOS with near complete resolution. Treatment was stopped in May of 2016 due to cytopenia after 6 cycles. At the same time, an asymptomatic, 9-mm erythematous nodule was discovered on her left anterior leg (Fig 1, B).

Biopsy found a dense and diffuse infiltrate throughout the dermis (Fig 2, A) composed of large atypical plasmacytoid cells, mature-appearing plasma cells, and small lymphocytes (Fig 2, B). In situ hybridization found diffuse λ positivity (Fig 2, C and D) with a λ/κ ratio of 500:1 and EBV positivity in 10% of cells. Immunohistochemistry found CD38 and CD138 positivity, minimal CD20 positivity, and

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Ki67 positivity in 60% to 80% of the cells. The findings were most consistent with PBL.

Workup for PBL included positron emission tomography/computed tomography, bone marrow biopsy, serum protein electrophoresis, and flow cytometry, was unremarkable. HIV testing was negative. Because of chronic health issues and family circumstances, the patient opted not to undergo treatment. The patient returned 3 months later and was noted to have slow enlargement of her left leg plaque to 3.0 cm and a new 4.5-cm plaque on her right lower leg. A new biopsy taken
from the right leg plaque was consistent with PBL, showing EBV positivity in 10% of cells and a λ/κ ratio of 10:1. The patient received local radiotherapy of 2400 cGy to both lower leg lesions with complete resolution.

Although the patient remained clear of PBL, she was found to have a recurrence of her PTCL-NOS in February 2017. At that time, the patient declined treatment. The patient remained off treatment for several months and presented to the hospital with symptomatic anemia in November 2017. During her hospitalization, she had increasing lymphadenopathy. A lymph node biopsy showed PTCL-NOS, and a bone marrow biopsy found hemophagocytic lymphohistiocytosis. Unfortunately, she continued to decompensate and transitioned to hospice in December 2017.

**DISCUSSION**

PBL is an aggressive subtype of large B-cell lymphoma and is often an immunosuppression-associated lymphoproliferative disease. Using the 3-part unifying nomenclature, our case would be described as pcPBL, EBV⁺, iatrogenic (romidepsin). Diagnosis and treatment can be challenging because of morphologic and immunohistochemical similarities to extramedullary plasma cell myeloma, high rates of relapse, and poor prognosis.¹ Distinction is difficult; myelomas are not usually EBV⁺, and distribution and primary bone marrow involvement in myeloma are often helpful discriminators. A high Ki-67 proliferative rate is more likely seen in PBL than plasmacytoma.

Nineteen cases, including the current case, of pcPBL without systemic involvement have been reported.²⁻⁹ The median age of onset is 56 (range, 32-85). The male/female ratio is 5:4, and 74% of the cases occurred in immunosuppressed patients. The 2 major causes of immunosuppression were HIV/AIDS (9 of 14) and solid organ transplant (4 of 14). Our case is the only reported case secondary to an anticancer agent, EBV positivity was reported in 16 of 19 of the cases and HHV-8 was positive in 4 of 6 patients.

Systemic PBL has a poor prognosis, and anthracycline-based chemotherapy is often the treatment of choice.¹ Unlike systemic PBL, pcPBL has an excellent prognosis. pcPBL can be managed with adjustment of immunosuppression, initiating/optimizing antiretroviral therapies, or chemotherapy and/or radiation. A total of 16 of 19 reported pcPBL cases had clinical follow-up; 13 had remission or no further progression of the disease, and 3 patients died of the disease. More aggressive disease was seen with large tumor size, multiple lesions, and advanced local disease with skin breakdown. Two cases had multiple risk factors yet achieved complete remission with systemic chemotherapy.⁴⁻⁷ In our case, romidepsin was stopped, and the lesions were treated with local radiation therapy with disease remission. The effects of immunosuppression on the clonal expansion of the plasmablastic cells were seen with a substantial reduction of κ/λ restriction from 500:1 to 10:1 with cessation of immuno-suppression.

To the best of our knowledge, this is the first case describing PBL secondary to romidepsin. Chemotherapy is associated with secondary non-Hodgkin lymphomas.¹⁰ The direct mechanism is debated but likely related to both direct drug damage to DNA and immunosuppressive effects.¹⁰ In our case, the patient received 6 cycles of romidepsin without additional maintenance dose—sparing regimens. This finding suggests that the normal dosing regimen of romidepsin may carry a small risk for immunosuppression associated PBL.

All patients with PBL should be evaluated for systemic disease with positron emission tomography/computed tomography, serum protein electrophoresis, bone marrow biopsy, flow cytometry, and HIV testing. In HIV-positive patients, antiretroviral therapies should be initiated or optimized. Immunosuppressants should be reduced or stopped. For localized disease, excision or radiotherapy should be considered. Anthracycline-based therapies should be reserved for multifocal, advanced, and progressive disease. Close clinical follow-up is recommended.

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