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CLINICAL VIGNETTE

Profound Pancytopenia and Bullous Skin Eruption after Brentuximab Vedotin

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Introduction

Brentuximab vedotin was approved by the FDA in 2011 for patients with anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen. The accelerated approval was based on a phase II study demonstrating an overall response rate of 86%, complete response 57%, and median duration of overall and complete response of 12.6 and 13.2 months respectively.[1] We report a case of fatal and profound pancytopenia associated with severe bullous skin eruption one week after the first dose of brentuximab vedotin in a patient with recurrent anaplastic large cell lymphoma.

Case History

A 78-year-old female initially presented with multiple skin nodules in December 2008. An excisional biopsy confirmed anaplastic CD30-positive ALK-negative T-cell lymphoma. Bone marrow biopsy showed no involvement of lymphoma. PET/CT scan showed multiple enlarged hypermetabolic nodes in the neck, axillae, mediastinum, abdomen, and pelvis, in addition to the cutaneous nodules. She was treated with infusional chemotherapy etoposide, doxorubicin, vincristine, cyclophosphamide, and prednisone for six cycles and achieved complete remission. She developed small erythematous skin nodule under left axillary fold in July 2012. Excisional biopsy showed T-cell lymphoma, CD30+, CD4+, CD2+ with loss of CD7, Ki67 20%, ALK negative. PET/CT scan showed hypermetabolic 1.4x0.5cm right axillary node. Bone marrow examination showed no evidence of lymphoma involvement. Cytogenetic study of the bone marrow showed 46,XX,inv(9)(p12q13)c[20] that is a known constitutional abnormality of little clinical significance. The skin lesion resolved with topical steroid cream and the right axillary node was non-palpable. Repeat PET/CT scan three months later showed stable right axillary node 1.8 x 0.7cm. Systemic chemotherapy was not offered. A year later, she developed erythematous maculopapular skin rash over the chest and abdomen. PET/CT scan showed multiple hypermetabolic neck and axillary nodes, in addition to multiple hypermetabolic skin lesions. Skin biopsy showed anaplastic CD30+ T-cell lymphoma, positive for CD3, CD4, and CD30 and negative for CD8 and CD20. Bone marrow examination revealed hypercellular marrow with 25% involvement by CD30+ T-cell lymphoma that was confirmed by flow cytometric findings of CD30+, CD5+, CD2+, but CD4-, CD7- and CD8- lymphoma cells. Fluoresence in situ hybridization of the bone marrow was negative for TCR/14q11.2, or ALK gene rearrangement. Cytogenetic study of the bone marrow showed 46-47,X,-X, add(2)(p25),del(6)(q21q27),del(9)(q21q22),del(10)(q24q26),+ 12,+mar,inv(9)(p12q13)c[cp4]/46,XX,inv(9) (p12q13)c [16]. In mid-January 2014, she developed worsening maculopapular skin rash with serum creatinine increased to 3 mg/dL, uric acid 10.8 mg/dL, and LDH 1850 IU/L, for which she was treated with hydration and prednisone 100mg daily for 5 days. She was found to be allergic to allopurinol, and febuostat was given. The erythematous skin rash of the lymphoma gradually resolved. Serum creatinine decreased to 1.3 mg/dL and uric acid to 3.8 mg/dL; WBC 3,900/µl, hemoglobin 10.3 g/dL, platelet 45,000/µl, with neutrophils 44%, lymphocytes 25%, and monocytes 27%. She was finally started on Brentuximab vedotin at 1.8mg/kg. A week later, she developed bullous skin rash of both legs (Figure 1). WBC decreased to 300/µl, hemoglobin 8 g/dL, platelet 134,000/µL; serum creatinine 1.3 mg/dL, uric acid 4.1 mg/dL, and LDH 662 IU/L. Broad-spectrum antibiotics were started, and filgrastim was initiated. Urine culture grew drug resistant E. coli and vancomycin resistant Enterococcus. The leg wound culture grew Klebsiella pneumoniae, Staphylococcus aureus, and Enterococcus species. Platelet count decreased to less 20,000/µl by day 20. Her condition further deteriorated, and she eventually required ventilator support. The blood counts slowly recovered with ANC >1000/µL by day 27 after Brentuximab. However, her condition continued to deteriorate. Tracheal aspirate culture subsequently grew Aspergillus fumigatus. She finally succumbed to sepsis on day 42.

Discussion

Two features are worth discussing in this case. The first is the bullous skin eruption. The original skin rash of the lymphoma was of erythematous maculopapular type, and it had improved with prednisone two weeks before brentuximab vedotin was started. The new bullous skin eruption is most likely due to brentuximab vedotin and is not part of the anaplastic lymphoma. Steven-Johnson syndrome has been reported with brentuximab vedotin. However, the bullous skin eruption in our patient was mainly confined to the legs, and there was no mucocutaneous involvement that is characteristic of Steven-Johnson syndrome.

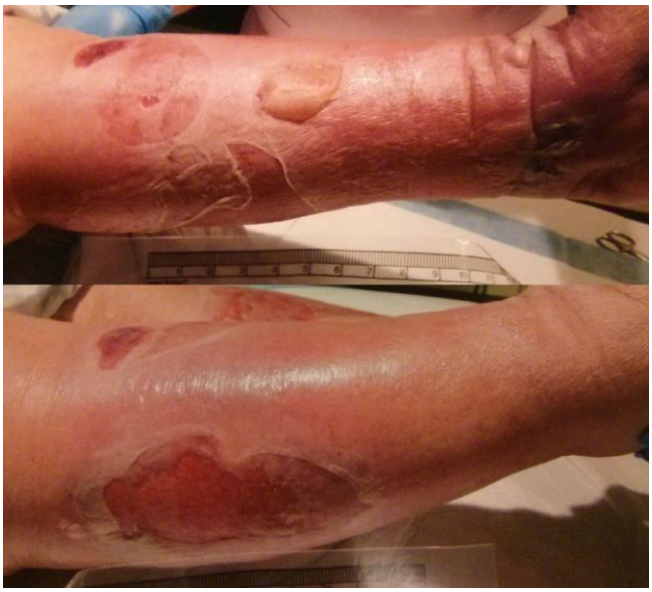
The second is the profound pancytopenia that developed one week after brentuximab. Grade 4 neutropenia <500/µL has been reported in 9% cases receiving brentuximab vedotin, and it is mostly self-limiting. In our patient, the profound

neutropenia that lasts for 20 days is unusual. The profound pancytopenia may also be related to the marrow involvement of anaplastic lymphoma. Alternatively, the profound neutropenia may be related to the presence of constitutional pericentric inversion of chromosome 9. Constitutional inv(9) has been implicated in delayed engraftment after transplantation though not without controversy.[2-4] The patient did not have any problem recovering the marrow after receiving infusional chemotherapy EPOCH in 2009. It is unlikely for inv(9) to play a major role in causing the severe pancytopenia though it is not improbable as a contributory factor.

We report the first case of profound pancytopenia and severe bullous skin eruption a week after brentuximab vedotin in a patient with anaplastic large cell lymphoma. The profound and prolonged neutropenia may be related to the marrow involvement of lymphoma, marrow toxicity of brentuximab vedotin and/or constitutional pericentric inversion of chromosome 9.

Figures

Figure 1: Bullous skin eruption a week after brentuximab vedotin confined below the knees.



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