A Man with Pruritic Nodules on the Face, Trunk, and Extremities

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Introduction
Cutaneous B-cell lymphomas represent a group of lymphomas derived from B-lymphocytes in different stages of differentiation. The skin can be the site of primary or secondary involvement of B-cell lymphomas. Primary cutaneous B-cell lymphomas (PCBCL) are cutaneous B-cell lymphomas that present in the skin with no evidence of extracutaneous disease at the time of diagnosis. The World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues recognizes five distinct PCBCL subtypes:

- Primary Cutaneous Follicle Center Lymphoma (PCFCL).
- Primary Cutaneous Marginal Zone Lymphoma (PCMZL).
- Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type (PCDCLBL-LT).
- Diffuse Large B-Cell Lymphoma NOS.
- Intravascular Diffuse Large B-Cell Lymphoma.

The diffuse large B-cell lymphoma NOS category includes less common provisional entities with insufficient evidence to be recognized as distinct diseases at this time. EBV-positive diffuse large B-cell lymphoma is a rare subtype in this group.

History
An 84-year-old man with a past medical history significant for prostate cancer successfully treated with radiation therapy in 2008, presented with a five-month history of a pruritic eruption on the arms, legs, back, neck, and face. The patient denied any constitutional symptoms and review of systems was otherwise negative. The patient was taking prednisone, which alleviated his pruritus, but the lesions persisted.

Examination
Physical examination revealed multiple pink to erythematous papules and subcutaneous nodules on the face, neck, back, and upper and lower extremities. No cervical, supraclavicular, axillary, or inguinal lymphadenopathy was present.

Laboratory
A peripheral blood smear showed a population of circulating CD10 positive T-helper lymphocytes suspicious for a T-cell lymphoproliferative process. A bone marrow biopsy was performed and did not show evidence of B-cell lymphoid neoplasia, but did show atypical lymphoid aggregates composed of CD4 and CD10 positive T-cells, which were identical to the abnormal population in the peripheral blood. Peripheral blood T-cell rearrangement and JAK2 were negative.

Histopathology
Punch biopsies of representative lesions of the upper back and right arm revealed diffuse and nodular infiltrates of atypical lymphoid cells with scattered centroblasts and neoplastic cells. The Ki-67 proliferative index was >90%. The neoplastic cells were negative for CD5, CD10, CD20, CD21, CD30, CD56, CD123, CD138, PAX5, C-MYC, BCL-2, BCL-6, cyclin D1, TCL-1A, and TDF. PCR showed a clonal B-cell population.

Course and Therapy
Based on clinical and histologic findings, a diagnosis of primary cutaneous EBV-positive diffuse large B-cell lymphoma was made. The patient was started on CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy for the treatment of this aggressive cutaneous lymphoma, which resulted in clinical improvement of his lesions. Clinical follow-up and monitoring in conjunction with this treatment will likely be of benefit in determining the clinical significance of the T-cell findings.

Discussion
EBV-positive diffuse large B-cell lymphoma was initially described in 2003 by Oyama et al and was included as a provisional entity in the 2008 WHO classification system as a rare subtype of the diffuse large B-cell lymphoma NOS category. It is defined as an EBV-positive mononodal large B-cell proliferation that occurs in immunocompetent patients over 50 years old. EBV is a human herpesvirus that demonstrates tropism for lymphocytes and survives in human hosts by establishing latency in B-cells. Under normal immune conditions, the proliferation of EBV-infected B-cells is prevented by cytotoxic T cells; therefore, it has been postulated that EBV-positive DLBCL of the elderly might be caused by age-related senescence of the immune system.

EBV-positive DLBCL is more common in Asia than in Western countries and there is a slight male predominance. A majority of patients present with extranodal disease at the time of diagnosis and the skin is the most common extranodal site of involvement. Rare cases of primary cutaneous involvement have also been described. Cutaneous manifestations include erythematous papules and subcutaneous nodules. Other sites of extranodal involvement include the lungs, oral cavity, pharynx, GI tract, and bone marrow. However, it is an aggressive lymphoma and prognosis is poor irrespective of the primary site of involvement.

Two morphologic subtypes can be seen on histology. The polymorphic pattern is characterized by a broad range of B-cell maturation along with admixed reactive cells (lymphocytes, histiocytes, and plasma cells). The monomorphic or large-cell pattern is characterized by monotonous sheets of large transformed B-cells. However, many cases show both histologic patterns and these morphologic variants do not impart any clinical or prognostic significance. Regardless of the histologic subtype, the neoplastic cells express pan B-cell antigens (CD19, CD20, CD79a, and PAX-5) as well as MUM1, BCL2, and EBER. Cases with plasmablastic features show weak or absent CD20 (as in our patient). Detection of EBV by in situ hybridization is required for the diagnosis.

Workup of a suspected cutaneous lymphoma should include a complete history and physical exam, lab studies, and relevant imaging evaluation. In addition, a bone marrow biopsy and aspirate should be performed in all cutaneous lymphomas with intermediate to aggressive clinical behavior. Accurate staging evaluation is integral to confirm the absence of extracutaneous involvement and to provide prognostic and anatomic information for the appropriate selection of treatment.

Primary cutaneous lymphomas tend to have different clinical behaviors and prognoses compared to histologically similar systemic lymphomas, and therefore require different therapeutic strategies. EBV-positive DLBCL has an aggressive clinical course with median survival of 2 years. Patients with EBV-positive DLBCL have a poorer overall survival and treatment response when compared to patients with EBV-negative diffuse large B-cell lymphomas. No standard treatment exists, but R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), which is the standard treatment for PCDCLBL-LT may provide a survival benefit. However, further studies are required to determine optimal treatment strategies.

Conclusion
Although rare, EBV-positive DLBCL is an important entity to consider when evaluating a patient with a suspected primary cutaneous lymphoma. Workup to rule out an underlying systemic lymphoma with labs, imaging, and bone marrow biopsy is critical. Prognosis is poor and treatment is difficult, as standard treatment protocols have yet to be determined.

References