Adult-onset hydroa vacciniforme-like lymphoma in a long-term resident of the United States

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INTRODUCTION

Hydroa vacciniforme-like lymphoproliferative disorders (HVLPDs) arise from chronic active Epstein-Barr virus (EBV) infection of T cells and natural killer cells. The term HVLPD was introduced in the 2016 World Health Organization classification of lymphoid neoplasms[1] to reflect the spectrum of EBV-related cutaneous disorders from classic hydroa vacciniforme (HV) to severe HV and HV-like lymphoma (HVLL). Although classic HV has no geographic predilection, severe HVLPDs (severe HV and HVLL) are endemic among children and young adults in Asia and Latin America.[2-5] Here we present an unusual case of severe HVLPD that arose in a Hispanic adult resident of the United States with no recent travel to endemic areas or childhood history of HV. With shifting patterns of global migration, it is important for American physicians to be familiar with this disease spectrum.

Abbreviations used:

EBER:	Epstein-Barr encoding region
EBV:	Epstein-Barr virus
HV:	hydroa vacciniforme
HVLL:	HV-like lymphoma
HVLPD:	HV-like lymphoproliferative disorders

CASE

A 33-year-old man had a 2-year history of diffuse eruptions of pruritic, painful papules over his entire body. The eruptions occurred periodically in association with sunlight and heat. Over the past year, they became more frequent with greater skin involvement and associated with fevers. He was originally from Mexico but immigrated to the United States >10 years ago and has not left this country since his arrival. He has no prior history of HV or other photodermatoses. Examination revealed cervical lymphadenopathy, splenomegaly, and numerous erythematous-to-brown papules with central necrosis and crusting over his trunk, face, and extremities distributed on a background of white, stellate scars (Fig 1).

Biopsies of the papules demonstrated a wedge-shaped, superficial, and deep dermal perivascular and periadnexal infiltrate of small atypical lymphocytes and eosinophils with necrosis of the epidermis and upper dermis (Fig 2, *A* and *B*). There was no vasculitis. The presence of numerous eosinophils was suggestive of a hypersensitivity reaction, such as to arthropod bites. The atypical small lymphocytes expressed CD2, CD3, CD7, CD8, and T-cell intracytoplasmic antigen 1. Rare $CD56^{+}$ lymphocytes were seen. Epstein-Barr encoding region (EBER) positivity was detected in a subset of the atypical lymphocytes by EBER in situ hybridization. T-cell receptor gene rearrangement studies by PCR demonstrated clonal rearrangements of the γ and β chains. Further evaluation to classify his HVLPD included

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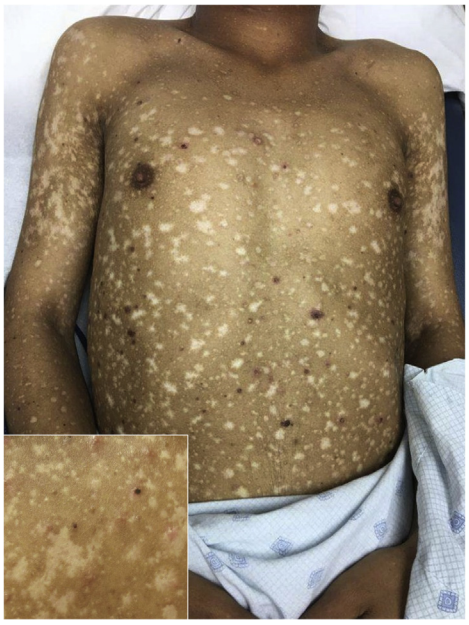

Fig 1. Lesions of patient with hydroa vacciniforme-like lymphoma. Erythematous-to-brown papules with central necrosis and hemorrhagic crust distributed on a background of white, stellate scars. Inset shows a close-up view of the characteristic hemorrhagic-crusted, erythematous, edematous papules, and white stellate scars.

flow cytometry, EBV PCR, and positron emission tomography–computed tomography scan. The patient had detectable levels of EBV DNA (53,900 copies/mL) in blood. Imaging revealed hypermetabolic cutaneous nodules on his head, neck, trunk, and scrotum and lymph nodes throughout the neck, thorax, abdomen, and pelvis. Due to concern for HVLL, the patient was referred to hematology-oncology for further management.

Six weeks after his initial presentation, the patient experienced 3 days of fever (102°F), nausea, vomiting, and the eruption of new skin lesions. He was admitted to a hospital to rule out infection or hemophagocytic syndrome, which is a known complication of severe HV and HVLL.[6,7] After extensive work-up, hemophagocytic syndrome was ruled out, and his symptoms were determined to be due to the progression of HVLPD. Interferon α-2b was initiated at 2 million units 3 times per week, which resulted in rapid defervescence and gradual resolution of his skin lesions.

The patient has continued to follow up with hematology-oncology on an outpatient basis. Interferon α-2b was titrated up to 7.5 million units 3 times per week with good control of his skin lesions. However, his disease burden on imaging is unchanged and his EBV DNA titers remain positive. We discussed the possibility of hematopoietic stem cell transplant to provide a potential long-term cure, but the patient has deferred this option due to lack of insurance coverage.

DISCUSSION

HVLPD encompasses a range of clinical entities that typically occur in children and young adults. They are linked by evidence of chronic active EBV infection and common histopathologic features, including epidermal vesicles and reticulate degeneration, with dermal perivascular lymphocytic infiltrates (Table I).[2-4,6,7] Severe HV extends to sun-protected skin and is often accompanied by systemic symptoms. Up to half of cases of severe HV progress to HVLL, a systemic malignancy that follows a rapidly progressive and usually fatal course.[5-8] This case describes the development of HVLPD in a man with no history of HV in childhood. His skin lesions did not correspond with a photodistribution and were accompanied by lymphadenopathy and fever. This constellation of symptoms raised concern for severe HVLPD and led to referral to hematology-oncology, where he was found to have lymphoma on the basis of findings from imaging (Table I).[2-4,6,7]

In HVLPD, repeated exposure to ultraviolet light is thought to cause continual activation of EBV and draw infected T cells and natural killer cells to sun-exposed skin.[4,5] Once there, these cells release cytotoxic molecules, such as T-cell intracytoplasmic antigen 1, causing local damage and the characteristic HV eruption.[5] Geographic variation in the incidence of severe HV and HVLL has been attributed to local differences in host human leukocyte antigen classes, EBV subtypes, and environmental factors, such as timing of initial EBV exposure.[2,9,10]

Severe HV and HVLL are managed medically and require close follow-up with hematology-oncology to monitor for disease progression. Severe HV has a chronic waxing and waning course, making it difficult to predict if and when lymphoma will evolve. Iwatsuki et al have proposed the following indicators of severe HV progression: facial swelling with eruptions, systemic symptoms, hypersensitivity to insect bites, increased levels of EBV DNA in peripheral blood or EBER-positive cells on biopsy, and presence of cellular atypia and deep infiltrates.[2] Although there are no randomized trials to guide treatment, immunomodulatory agents, including thalidomide, chloroquine, and interferon α, have emerged as first-line therapy for severe HV.[3] Anthracycline-based chemotherapy, such as CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisolone), can induce temporary remissions, but case series suggest higher than expected morbidity and mortality. Lastly, there is emerging