Hydroa vacciniforme-like lymphoma: a case report and literature review

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ABSTRACT

Hydroa vacciniforme (HV) is a photosensitivity disorder in childhood characterized by recurrent vacciniform vesicles, necrotic ulcers, and scars on sun-exposed areas. HV-like lymphoma is a rare variant of cutaneous T-cell lymphoma. HV, atypical HV and HV-like lymphoma belong to the spectrum of Epstein-Barr virus (EBV)-associated lymphoproliferative disorders. We report a fatal case of HV-like lymphoma in a 31-year-old man with a 16-year history of recurrent vacciniform papulovesicular eruption with crusts and scarring. The rash initially was confined to the sun-exposed areas. Histopathology revealed focal necrosis of the epidermis and subjacent dermis with a superficial lymphocytic infiltrate, consistent with HV. Toward the end of the clinical course, the skin lesions became persistent and spread to nonsun-exposed areas. Repeated biopsies revealed epidermal necrosis with infiltration of CD4+ CD56− lymphocytes in the dermis, some with atypical nuclei, and small blood vessel vasculitis. EBV-encoded RNA (EBER-1)-positive lymphocytes were detected. Progression of his skin lesions was associated with colon ulcers, gingival ulcers, fever, splenomegaly, leukopenia and thrombocytopenia. EBER-1-positive lymphocytes were detected in all biopsy specimens, including the skin, gingiva, and bone marrow; the last also showed infiltrate of atypical lymphocytes with T-cell receptor-γ gene rearrangement. The pathogenic role of UV-irradiation is discussed.

KEYWORDS

Hydroa vacciniforme
Hydroa vacciniforme-like lymphoma

Introduction

Hydroa vacciniforme (HV) is a rare, acquired photosensitivity disorder first described by Bazin in 1862.¹ It is characterized by recurrent vesicles, necrotic crusts and vacciniform scars on sun-exposed areas. The disease is usually sporadic with onset in childhood and resolution by early adult life. HV-like lymphoma is a rare, newly-classified cutaneous T-cell lymphoma in association with chronic latent Epstein-Barr virus (EBV) infection.² In this report, we describe the clinical and pathologic findings of a case of childhood-onset HV that progressed to fatal HV-like lymphoma in young adulthood. A brief review of reported cases of HV-like lymphoma is given and the pathogenic role of UV-irradiation is discussed.

Case report

A 14-year-old Taiwanese boy first presented in February of 1980 with a 6-month history of recurrent, pruritic vesiculo-papules on the face, ears and the dorsal aspect of the hands (Figures 1A and 1B). The skin lesions were exacerbated by sun exposure. The patient was lost to follow-up for 9 years until 23 years of age when he returned for medical examination before military service. Physical examination revealed many erythematous papules, some with central necrotic
crusts and scarring, distributed on the sun-exposed areas (Figures 1C and 1D). There was no cervical or axillary lymphadenopathy or hepatomegaly. A skin biopsy specimen from a crusted papule revealed focal necrosis of the epidermis and upper dermis, consistent with late lesion of HV. Phototesting for minimal erythema dose (MED) revealed a borderline reduction MED for UVA and normal MED for UVB. Photo-provocation test was not performed. The patient was advised to avoid sun exposure, use a broad-spectrum sunscreen and wear appropriate clothing for sun protection. After the evaluation, he was enrolled for military service for 1 year. Since then, the sunlight-provoked vacciniform eruptions became purpuric and more confluent, but were limited to the sun exposure areas. Histopathologic examination of a purpuric macule revealed changes of HV. Only a few infiltrating lymphocytes were Ki-67+

In the ensuing 5 years, he was hospitalized twice for colon ulcers with lower gastrointestinal bleeding and cellulitis of the right thigh, respectively. At 31 years of age, he was admitted again because of intermittent fever of unknown origin for 1 month. Laboratory study revealed leukopenia (white blood cell count: $2 \times 10^9/L$) and thrombocytopenia (platelet count: $105 \times 10^9/L$) without atypical lymphocytes in the peripheral blood. The serum aspartate aminotransferase, 81 U/L (1.35 μkat/L; normal range: 5–35 U/L [0.08–0.58 μkat/L]) was slightly elevated with normal alanine aminotransferase. An abdominal sonography showed splenomegaly. The skin lesions became persistent and spread to the sun-protected areas (Figure 2A). Two additional skin biopsy specimens from inner aspect of both thighs showed confluent necrosis of lower half of the epidermis with suprabasal and subepidermal vesiculation, edema with extravasation of erythrocytes, and necrosis or thrombosis of small blood vessels in the dermis. A superficial and deep, moderately-dense perivascular infiltrate of lymphocytes was present in the dermis, some of them having atypical large hyperchromatic oval nuclei (Figures 2B and 2C). Immunohistochemical staining showed that most infiltrating lymphocytes were CD3+ and CD4+ with a few CD8+ cells (Figure 3). Stain for CD56 was negative. In situ hybridization for EBV-encoded RNA (EBER-1) detected some positive cells in the dermal infiltrate (Figure 2D). About 5% of the infiltrating lymphocytes were Ki-67+

Approximately 1 year later, he developed poor-healing gingival ulcers with persistent fever and impaired cognition, and was hospitalized again. The skin lesions were similar to those described earlier. The EBV anti-viral capsid antigen (VCA) IgM was negative and anti-VCA IgG was positive at 1:640. Specimens obtained from a gingival ulcer and bone marrow revealed dense diffuse infiltrate of atypical lymphocytes with some EBER-1-positive cells. Up to 90% of
the infiltrating lymphocytes were Ki-67+. T-cell receptor-γ gene rearrangement was detected in the bone marrow specimen by polymerase chain reaction. In situ hybridization for EBV was performed on all other biopsy specimens; variable amounts of EBER-1-positive cells in each one. During his last hospitalization in July of 2007, he died of a sudden onset of apnea. No autopsy was granted by the family.

**Figure 2**  (A) Persistent erythematous papules and confluent plaques with crusts spread to sun-protected areas. (B) A low-power view of a biopsy specimen from the thigh reveals a moderately-dense perivascular infiltrate of lymphocytes in the dermis. (C) Some lymphocytes have atypical large hyperchromatic oval nuclei (arrows; H&E, 400×). (D) Some lymphocytes in the dermal infiltrate are EBER-1-positive (400×).

**Figure 3**  Immunohistochemical staining reveals that the majority of the infiltrating lymphocytes are CD4+ with a few CD8+ cells (100×, 200×).
Discussion

We described the clinicopathological findings of a case of typical childhood onset EBV-associated HV in a Taiwanese boy that progressed to fatal EBV-positive HV-like T-cell lymphoma with involvement of gastrointestinal tract and bone marrow. It was not clear how strictly our patient had carried out photo-protection during his military service period. However, the worsening of his skin lesions after military service raised the suspicion that UV exposure might have deleterious effect on the progression of his disease. Clinically, HV is characterized by recurrent pruritic vesiculopapules 12–24 hours after sun exposure. The skin lesions are mainly distributed on sun exposed areas, especially the face and dorsal aspect of the hands. As the lesions resolve, they enter a dry crusting phase followed by permanent vacciniform scars. Typically, there is no systemic involvement except for mild and transient malaise, and on rare occasions, fever or headache accompanying the more severe attacks. The disorder improves under appropriate sun protection, indicating a benign nature of the disease.

Recent investigations have found that the cutaneous lesions of HV are associated with latent EBV infection. In addition to the typical HV, atypical form of HV has been reported in Latin American countries (Mexico and Peru) and Asia (Taiwan, Japan and Korea). In the 29 patients with HV reported by Iwatsuki et al various degrees of T cells positive for EBER were detected in the cutaneous infiltrates in 28 (97%) patients, including 11 patients with atypical HV. They concluded that both typical and atypical HV are diseases with different severity in the same spectrum of EBV-associated disorder. Compared with the typical form of HV, atypical HV usually has more extensive skin lesions and is associated with high fever, lymphadenopathy, liver damage or HV-like lymphoproliferative disorders (LPD), including malignant lymphoma. It is important to distinguish between the typical and atypical forms of HV by clinical features and laboratory findings for prediction of disease outcome. Increased number of EBER-1-positive cells is one of the indicators to suggest atypical HV. In the present case, we did not find obvious increase of EBER-1-positive cells in the specimens biopsied over time.

The spectrum of EBV-associated LPDs in nonimmunocompromised hosts includes EBV-driven B-cell LPDs and aggressive T-cell and NK-cell LPDs, which are often put under the heading of chronic active EBV (CAEBV) infection. CAEBV can involve B, T or NK cells. The B-cell type includes EBV+ large B-cell lymphoma of elderly and lymphomatoid granulomatosis. The T/NK-cell type includes HV, HV-like lymphoma, severe mosquito bite allergy, and systemic EBV+ T-cell LPD of childhood. The previously documented cases of lymphoma with HV-like lesions had been grouped under EBV-positive T-cell LPDs of childhood in the WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues, 2007 and specified as HV-like lymphoma (ICD-O 9725/3). HV-like lymphoma is very rare. Table 1 summarizes the 29 cases reported in the literature.

Table 1 Hydroa vacciniforme-like lymphoma reported in the literature.2,4,5,10–14

<table>
<thead>
<tr>
<th>Author</th>
<th>Number</th>
<th>Pathologic diagnosis</th>
<th>Phenotype</th>
<th>Mean age</th>
<th>Gender (F/M)</th>
<th>Race</th>
<th>Status on reporting</th>
<th>EBER-1(+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oono et al (1986)2</td>
<td>1</td>
<td>HV coexists malignant lymphoma</td>
<td>CD4(+)&gt;CD8(+)</td>
<td>6</td>
<td>0/1</td>
<td>Japanese</td>
<td>D (1)</td>
<td>NA</td>
</tr>
<tr>
<td>Magaña et al (1998)4</td>
<td>4</td>
<td>Angiocentric cutaneous T-cell lymphoma</td>
<td>Variable; CD30(+)</td>
<td>8</td>
<td>0/4</td>
<td>Mexican</td>
<td>L (2)</td>
<td>4/4</td>
</tr>
<tr>
<td>Cho et al (2001)10</td>
<td>2</td>
<td>T-cell lymphoma</td>
<td>NA</td>
<td>33</td>
<td>1/1</td>
<td>Korean</td>
<td>A (2)</td>
<td>2/2</td>
</tr>
<tr>
<td>Chen et al (2002)11</td>
<td>1</td>
<td>T-cell lymphoma</td>
<td>CD8(+)</td>
<td>8</td>
<td>1/0</td>
<td>Taiwanese</td>
<td>A (1)</td>
<td>Negative</td>
</tr>
<tr>
<td>Yoon et al (2005)12</td>
<td>1</td>
<td>Nodal marginal zone lymphoma</td>
<td>NA</td>
<td>46</td>
<td>0/1</td>
<td>Korean</td>
<td>A (1)</td>
<td>Negative</td>
</tr>
<tr>
<td>Feng et al (2008)13</td>
<td>1</td>
<td>T-cell lymphoma</td>
<td>CD8(+)</td>
<td>3</td>
<td>1/0</td>
<td>Chinese</td>
<td>A (1)</td>
<td>Negative</td>
</tr>
<tr>
<td>Doeden et al (2008)14</td>
<td>2</td>
<td>Hydroa-like lymphoma</td>
<td>CD30(+) CD4(-) CD8(-)</td>
<td>6</td>
<td>0/2</td>
<td>Guatemalan Hispanic</td>
<td>A (2)</td>
<td>2/2</td>
</tr>
<tr>
<td>Present case</td>
<td>1</td>
<td>HV progressed to HV-like T-cell lymphoma</td>
<td>CD4(+)</td>
<td>14</td>
<td>0/1</td>
<td>Taiwanese</td>
<td>D (1)</td>
<td>1/1</td>
</tr>
</tbody>
</table>

NA = not available; HV = hydroa vacciniforme; EBER = EBV-encoded RNA; D = died; A = alive; L = lost.
Among the EBV-associated LPDs, HV and HV-like lymphoma are unique in that the skin lesions show a clear photodistribution or photoaccentuation, and in most HV patients, the disease improved with adequate sun protection. These findings suggest a pathogenic role of UV irradiation. In view of the photosensitivity and chronic EBV infection in HV and HV-like LPD, one may wonder whether there is any direct interaction between the two, and whether repeated or excessive UV irradiation plays a critical role in the development of HV-like lymphoma. We did a literature search and could only find scant reports that address these important issues. Some authors reported positive photoprovocation test with development of erythematous edematous or vesicular skin lesions in patients with HV, and detection of EBV+ lymphocytes in irradiated area. Ohtsuka et al.15 and Cho et al.7 detected EBV DNA in the peripheral blood of HV patients. They speculated that the development of UV-induced skin lesions may be related to the circulating EBV-infected lymphocytes activated by repeated UV exposure. Three different clinical courses were observed in the six cases of EBV-associated HV or atypical HV: spontaneous remission, clearing after photoprotection, and continuous recurrence irrespective of sun exposure. The last pattern was seen in the cases of atypical HV. The authors suggested that other factors, such as immune status of the host may be involved in perpetuating the skin lesions. Several studies suggest that disease progression may be related to the EBV and Ki-67 positivity,7,8 and high positivity of EBV and Ki-67 was found in the infiltrating lymphocytes of the skin lesions from patients who progressed to lymphoma.10

Both quantity and quality of CD8+ T-cell response to EBV virus are critical to the control of EBV infection.9 CD8+ T cells isolated from healthy seropositive individuals or individuals recovered rapidly from infectious mononucleosis recognize a wide variety of EBV epitopes.16 CD8+ T cells from patients with persistent infectious mononucleosis, on the contrary, recognize only a few epitopes. The diversity of T-cell repertoire (as defined by Vβ T-cell receptors) is more expanded in individuals with asymptomatic EBV infection, compared to the symptomatic patients. It seems reasonable to suspect that repeated or excessive sun exposure might lead to continuous activation of the latent EBV infection in selected HV patients who are genetically predisposed to chronic EBV infection and have not practiced strict sun protection.

Ataxia telangiectasia and Rad3 related (ATR) is an important gene in DNA damage response and chromosomal stability. Liu et al.17 studied the role of ATR gene alterations in the pathogenesis of nasal NK/T-cell lymphoma and CAEBV, and found ATR gene mutations in some of the nasal NK/T-cell lymphoma and CAEBV cell lines. The mutations were associated with a delay or abrogation in repair of ultraviolet-induced DNA single-strand breaks, and a defect in p53 accumulation. We did not perform mutation analysis for ATR in our patient because we do not have fresh frozen tissue. However, it would be interesting to investigate whether ATR mutation is involved in the progression of HV to HV-like lymphoma in the future. If ATR mutation with defective repair of UV-induced DNA is proven to be involved in the pathogenesis of HV-like lymphoma, then a strict photoprotection may help to reduce the risk of lymphomatous progression.

Although most patients with typical HV have good prognosis, regular follow-up is recommended because of the possibility of eventual progression to malignant lymphoma, which was exemplified by our case. In the case of a 6-year-old boy with chronic EBV infection, HV-like skin eruptions, and chronic hepatitis reported by Wu et al.,6 the chronic hepatitis was thought to be part of an ongoing smoldering process of clonal T-cell LPD and the possibility of malignant transformation is a concern. For EBV-associated LPD, numerous anecdotal treatments had been reported, including immunosuppressants (e.g. systemic corticosteroid, cyclosporine), eradication of chronic EBV infection and strict UV protection, but the effects have been limited.7

In summary, we described the clinicopathological findings of a fatal case of EBV-positive HV-like T-cell lymphoma in a Taiwanese young man with childhood onset HV. More studies are needed to elucidate the pathogenetic role of UV irradiation in chronic activation of EBV and the progression to HV-like lymphoma.

References
1. Bazin E. Lécons théoriques et cliniques sur les affections génériques de la peau, Vol I. Paris: Delahrage, 1862;132. [In French]


