Pathogenic Link Between Hydroa Vacciniforme and Epstein-Barr Virus–Associated Hematologic Disorders

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Objectives: To determine the pathogenic association of latent Epstein-Barr virus (EBV) infections with both typical hydroa vacciniforme (HV) and severe HV-like eruptions, and to survey the complications and outcomes of patients.

Design: Case series.

Patients: Twenty-nine patients with HV or severe HV-like eruptions.

Interventions: In situ hybridization and immunostaining of biopsy specimens; extraction of DNA samples from cutaneous lesions and/or peripheral blood mononuclear cells for EBV DNA assay.

Main Outcome Measures: Clinicopathologic manifestations, hematologic findings, complications, and outcomes; presence of latent EBV infection.

Results: T cells positive for EBV-encoded small nuclear RNA (EBER) were detected, to various degrees, in cutaneous infiltrates in 28 (97%) of 29 patients, including all 6 patients with definite HV with a positive phototest reaction, 11 of 12 patients with probable HV without evidence of photosensitivity, and all 11 patients with severe HV associated with systemic symptoms. In addition to EBER-positive T cells, many cytotoxic T lymphocytes expressing T-cell intracellular antigen 1 and granzyme B were present in the cutaneous lesions. Natural killer (NK) cells were absent or at a background level. The UV-induced cutaneous lesions showed histopathologic findings consistent with those of HV, containing many EBER-positive cells. Although no hematologic abnormalities were found in the definite and probable HV groups, the amounts of EBV DNA were increased in the peripheral blood mononuclear cells. By contrast, the severe HV group had markedly increased levels of EBV DNA associated with NK-cell lymphocytosis, and complications including chronic active EBV infection, hypersensitivity to mosquito bites, and hemophagocytic syndrome. Five patients with severe disease died of EBV-associated NK/T-cell lymphomas or hemophagocytic syndrome 2 to 14 years after onset.

Conclusion: Both typical and severe HV are included within the spectrum of cutaneous disorders mediated by EBV-infected T cells, and the severe HV group may have overt EBV-associated NK/T-cell lymphoproliferative disorders with a frequently fatal outcome.

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ing, indurated nodules on sun-protected as well as sun-exposed areas, high-grade fever, and liver damage. Histopathologic examinations of the eruptions demonstrated dense infiltration of lymphocytes containing a few atypical cells throughout the dermis and sometimes reaching into the subcutaneous tissue.

In addition to their clinical similarities, typical HV and severe HV-like eruptions have a close pathogenetic relationship on the basis of latent EBV infection. From the clinical point of view, however, typical HV should be distinguished from the severe disease because most patients with typical HV have a good prognosis, whereas patients with severe HV-like lesions frequently progress to have EBV-associated malignant complications. To understand the pathogenic similarities and differences between typical and severe HV-like eruptions, we examined the clinicopathologic findings, laboratory test results, immunophenotypes of infiltrating cells, amount of EBV DNA in the peripheral blood, and outcomes of the patients.

METHODS

PATIENTS

Twenty-nine patients with HV-like eruptions were divided into 3 groups: definite, probable, and severe. Patients with definite or probable HV fulfilled the following criteria: (1) repetitive vesiculopapular eruptions on exposed areas, including the face, lips, cheeks, and extensor surfaces of the hands and arms; (2) histologic features of reticulated degeneration of epidermis or blister formation associated with dense lymphocytic infiltration; and (3) exclusion of hereditary photosensitivity disorders. Six patients who had erythematous or vesiculopapular reactions to the photoprovocation test (cases 1-6) were diagnosed as having definite HV, and 12 patients (cases 7-18) who did not undergo the photoprovocation test or showed negative reactions were classified as having probable HV.

By contrast, 11 patients with severe HV (cases 19-29) presented with 1 or more of the following clinical and histopathologic findings in addition to the HV-like eruptions: (1) high-grade fever, (2) liver damage, (3) ulcerative indurated lesions, and (4) edematous swelling of the cheeks, eyelids, ears, and lips. Seven of 11 patients in the severe HV group have been described in case reports elsewhere,13,19-24 with differential diagnosis of pityriasis lichenoides et varioliformis acuta, lymphoepithelial lesions, pemphigus, sarcoidosis, vasculitis, and angiocentric lymphoma.

BIOPSY MATERIALS AND CELL PREPARATIONS

Paraffin-embedded biopsy specimens from 29 patients with HV or severe HV-like eruptions were used for in situ hybridization and immunostaining. Biopsy specimens from other lymphoproliferative skin disorders and resected hypertrophic tonsils were used as controls. They included 60 samples from lymphoproliferative disorders and 10 samples of hypertrophic tonsils. In addition, biopsy samples from pityriasis lichenoides (5 cases), chronic photosensitivity dermatitis (5 cases), panniculitis (5 cases), discoid lupus erythematosus (5 cases), and lip biopsy specimens containing salivary glands from patients with Sjögren syndrome (9 cases) were examined. All control samples were obtained from the pooled materials, and the patients’ biopsy samples were obtained, under informed consent, for the purpose of histopathologic diagnosis. Paraffin-embedded cell pellets of an EBV-infected cell line, B95-8, were prepared for positive controls for in situ hybridization and immunostaining.

DETECTION OF EBV-INFECTED CELLS BY IN SITU HYBRIDIZATION

Lymphoid cells containing EBER were detected by in situ hybridization on paraffin-embedded sections, with the use of fluorescein isothiocyanate–labeled nucleotide probes (Novocastra Laboratories Ltd, Newcastle upon Tyne, England). The EBER is synthesized in large quantities in the nuclei of cells latently infected with EBV. Deparaffinized sections were treated with 0.1N hydrochloric acid for 10 minutes, digested with proteinase K (10 mg/mL) or 0.8% pepsin (DAKO, Glostrup, Denmark) for 10 minutes at 37°C, and acetylated for 10 minutes with 0.1M triethanolamine containing 0.025% acetic acid. After prehybridization with salmon sperm DNA, the sections were hybridized with the fluorescein isothiocyanate–labeled probe overnight at 37°C. The sections were rinsed with 1× standard saline citrate (150mM sodium chloride and 15mM sodium citrate, pH 7.0) for 30 minutes and incubated with alkaline phosphatase–labeled anti–fluorescein isothiocyanate antibody (Novocastra Laboratories Ltd) for 30 minutes. Color development was performed by incubation with a substrate solution containing 5-bromo-4-chloro-3-indoxyl phosphate and nitroblue tetrazolium chloride. Specimens containing EBER-positive cells were classified into 4 groups according to the percentage of positive cells: 1+, 1% to less than 5% positivity in the infiltrates; 2+, 5% to less than 25%; 3+, 25% to less than 50%; and 4+, 50% or more.

QUANTITATIVE POLYMERASE CHAIN REACTION ASSAY FOR EBV DNA

Samples of DNA were extracted from the cutaneous lesions and/or peripheral-blood mononuclear cells of patients with HV, EBV-associated NK-cell lymphomas, and chronic active EBV infection, and from healthy volunteers. The plasmid DNA containing 1 copy of EBV–Epstein-Barr virus (EBV)–1 fragment was used as a template DNA for quantitative polymerase chain reaction (PCR) amplification. Samples of DNA (0.02 µg) were amplified by means of EBNA–1–specific primers: sense, 5’-GTCACTCATCATCGGGGTCCTG-3’; and antisense, 5’-TTCCGGTTGGAAACCTCTCCTTG-3’. Amplification was carried out at 96°C for 5 minutes, followed by 33 cycles consisting of 96°C for 1 minute, 59°C for 30 seconds, and 72°C for 45 seconds, which gave 250-base pair PCR products. The PCR products were subjected to gel electrophoresis with a 1.5% agarose gel, and positive signals were detected by ethidium bromide staining. The semiquantitative amounts of EBV DNA copies in patients’ samples were determined from the standard curve obtained by PCR amplification of the serial 10-fold dilutions of the template plasmid DNA solution.

For 9 samples, a real-time quantitative PCR assay was performed with a fluorescence-based real-time detection method (TaqMan PCR, PerkinElmer, Inc, Applied Biosystems, Foster City, Calif) as previously described.14 The amount of EBV DNA was calculated as the number of virus copies per microgram of DNA for cell preparations.

IMMUNOPHENOTYPING

Immunostaining was carried out to detect latent membrane protein 1 expressed by EBV-infected cells, and to determine the immunophenotype of the infiltrating cells. Preheated deparaffinized biopsy specimens were incubated with monoclonal antibodies to latent membrane protein 1, CD3ε, CD45RO, CD8, CD20 (DAKO, Glostrup, Denmark), granzyme B (Chemicon In-
ternational, Temecula, Calif), T-cell intracellular antigen 1 (Coulter Immunology, Miami, Fla), and CD4 and 56 (Novo-
castra Laboratories Ltd) for 2 hours at room temperature or over-
night at 4°C; then with biotin-labeled anti–mouse immuno-
globulins for 60 minutes; and finally with horseradish
peroxidase–labeled streptavidin for 30 minutes at room tem-
perature. The peroxidase activity was visualized by incubation
with diaminobenzidine in the presence of hydrogen peroxide.

### RESULTS

**SCREENING TEST RESULTS FOR LATENT EBV INFECTION IN CUTANEOUS LESIONS**

To determine the background levels of EBER-positive cells in lymphoid tissues and inflammatory skin disorders, we examined tissue sections from patients with hypertrophic tonsils (10 cases), pityriasis lichenoides (5 cases), panniculitis (5 cases), chronic photosensitivity dermatitis (5 cases), and discoid lupus erythematosus (5 cases), and from the lip biopsy specimens of patients with Sjögren syndrome (9 cases). Only a few EBER-positive cells (less than 0.1% of the infiltrates) were present in the 3 samples from hypertrophic tonsils, and no EBER-positive cells were found in other tissue sections, including those from the skin disorders (Table 1). Cells positive for EBER were found in all 11 patients with nasal and nasal-type NK-cell lymphoma, and in 5 (45%) of 11 patients with subcutaneous lymphoma with heterogeneous immunophenotypes. No EBER-positive cells were detected in primary CD30-positive cutaneous anaplastic large-cell lymphoma, mycosis fungoides, lymphomatoid papulosis, or lymphocytoma cutis.

Of the 29 patients with HV or HV-like eruptions, EBER-positive cells were found in all 6 patients with definite HV, 11 (92%) of 12 patients with probable HV (Figure 1 and Figure 2), and all 11 patients with severe HV (Figure 3) (Table 2). Two biopsy samples obtained from UV-A–induced eruptions (cases 5 and 6) had histologic features consistent with those of typical HV, with many EBER-positive cells in the dense lymphocytic infiltration. No EBER-positive cells were detected in one of the patients with probable HV (case 12), although the clinical and histologic features in this case were indistinguishable from those of other HV cases with EBER-positive cells. The EBER-positive cells ranged from 3% to 10% of the infiltrating mononuclear cells in most patients with definite and probable HV, while there were 2 patients with higher positivity ranging from 30% to 40% (cases 6 and 11). Patients with

| Table 1. Detection of EBER-Positive Cells in Cutaneous Lymphoproliferative Disorders |
|-----------------|-----------------|
| Diagnosis         | No. of EBER Positive/
|                   | Total Cases |
| Lymphoproliferative disorders |
| HV-like             |
| Definite HV (phototest positive) | 28/29 |
| Probable HV (phototest negative or not done) | 6/6 |
| Severe HV           | 11/11 |
| CD56-positive NK-cell lymphoma | 11/14 |
| Nasal type          | 2/2 |
| Blastic NK          | 9/9 |
| Subcutaneous lymphomas* | 0/3 |
| T-cell phenotype    | 5/11 |
| CD30-positive, pleomorphic | 4/10 |
| Primary cutaneous CD30-positive lymphoma |
| Anaplastic large cell | 0/7 |
| Mycosis fungoides   | 0/16 |
| Lymphomatoid papulosis | 0/7 |
| Lymphocytoma cutis  | 0/5 |
| Inflammatory skin disorders |
| Pityriasis lichenoides | 0/5 |
| Chronic photosensitivity dermatitis | 0/5 |
| Panniculitis         | 0/5 |
| Discoid lupus erythematosus | 0/5 |
| Miscellaneous         |
| Hypertrophic tonsil  | 31/10 |
| Lip salivary glands (Sjögren syndrome) | 0/9 |

*Defined as cases with extreme subcutaneous involvement with sparse infiltration in the dermis, excluding CD56-positive phenotype.
†A few EBER-positive cells (less than 0.1% of the infiltrates) were present.

Abbreviations: EBER, Epstein-Barr virus–encoded small nuclear RNA; HV, hydroa vacciniforme; NK, natural killer.

Figure 1. Vesiculopapules, crusty erythema, and shallow depressive scar on the face and earlobes (A) and forearms (B) (case 14).
severe HV had percentages of EBER-positive cells ranging from 3% to 30%. No clear differences were noted in the percentages of EBER-positive cells in the HV-like eruptions among the definite, probable, and severe HV groups.

DETECTION OF EBV DNA IN THE PERIPHERAL BLOOD

Epstein-Barr virus DNA was detected in the peripheral-blood mononuclear cells of 6 patients with probable HV and 4 patients with severe disease under a PCR condition in which no EBV DNA was amplified in healthy volunteers (Figure 2). The amounts of EBV DNA as determined by real-time PCR assay in the 4 patients with probable HV (cases 14, 15, 17, and 18) were 770, 2089, 2173, and 3400 copies per microgram of DNA, respectively (normal reference value, <50 copies per microgram of DNA). One patient (case 18) had no systemic symptoms except for the typical HV eruptions despite the higher level of EBV DNA load, with a slightly increased percentage of NK cells (33%; normal, <30%). Four patients with severe HV (cases 22, 25, 28, and 29) had larger numbers of EBV DNA copies in the peripheral blood: 15 136, 79 518, 544 000, and 11 200 copies per microgram of DNA, respectively.

IMMUNOPHENOTYPE OF INFILTRATING CELLS IN HV LESIONS

Immunostaining of all groups of HV-like eruptions demonstrated that most (more than 80%) of the infiltrating lymphoid cells expressed a T-cell phenotype such as CD3ε and CD45RO. No CD20-positive cells were demonstrated except in case 24, in which a small number of CD20-positive cells were present. In 10 patients examined in detail, many T cells with the CD4 or CD8 phenotype were present in the HV-like lesions, most of which were positive for cytotoxic molecules such as T-cell intracellular antigen 1 and granzyme B (Figure 4) and negative for EBER. An NK-cell marker, CD56, was absent or at a background level in the HV lesions. It is intriguing that EBER-positive and CD56-positive cells infiltrated into the subcutaneous lesions induced by insect bites, whereas no CD56-positive cells were present in the HV-like lesions on the face (case 29 in Table 3, data not shown). Therefore, both HV and HV-like lesions were composed of EBER-positive T cells and a larger number of EBER-negative cytotoxic T cells. The expression of latent membrane protein 1 antigen was absent or at a background level in the paraffin-embedded
tissue sections, whereas paraffin-embedded cell pellets of an EBV-infected cell line, B95.8, were positive for latent membrane protein 1.

LABORATORY TEST RESULTS

No abnormal findings were observed in the routine laboratory tests for complete blood cell counts and blood chemistry in the definite or probable HV group, except for elevated levels of antistreptolysin O titer in case 8 and serum IgA (559 mg/dL) in case 14. Patients with severe HV-like eruptions had elevated levels of aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase to various degrees and hematologic abnormalities such as leukopenia and thrombocytopenia suggestive of hemophagocytic syndrome in their clinical courses (Table 3). The percentages of CD36-positive cells were increased to more than 40% of the peripheral-blood mononuclear cells in 6 patients with severe HV (cases 20, 21, 23, and 27-29), resulting in the relative decrease of surface CD3-positive cell percentages.

Antibody titers against EBV were measured in 14 patients. Of 8 patients in the definite and probable HV groups, only 1 patient (case 14) had unusual serologic findings, showing positive IgA-class antibodies to EBV early antigen (EA) and EBV viral capsid antigen (VCA) at 1:40. Four of 6 patients with severe HV, however, had abnormal antibody patterns: a high level of anti-EBV-EA IgG antibody (1:320) without anti-EBNA antibody in case 19, increased levels of anti-VCA antibody (>1:1280) in cases 21 and 25, and the presence of IgA-class anti-EA and anti-VCA antibodies in cases 21 and 27, (Table 3). Therefore, abnormal antibody profiles to EBV antigens were more frequently associated with the severe HV group, and the serologic patterns were consistent with those of chronic active EBV infection: high antibody titers to EBV antigens of the lytic cycle such as VCA and EA, and low or negative antibody production to EBNA.

COMPLICATIONS AND OUTCOMES

Of the 18 patients with definite or probable HV, all 11 patients (cases 1, 2, 5-7, 11, and 14-18) whom we followed up for 2 to 9 years were alive without progression of the illness, although some patients still had recurrence of similar HV-like eruptions. By contrast, complications of the severe group included chronic active EBV infection in 6 patients (cases 20, 21, 25, and 27-29), hypersensitivity to mosquito bites in 5 patients (cases 21, 25, and 27-29), and virus-associated hemophagocytic syndrome in 4 patients (cases 19, 21, 23, and 26) (Table 3). Natural killer–cell lymphocytosis was present in the peripheral blood of 6 patients with severe HV. In our limited experience, the NK-cell lymphocytosis persisted even in the remission of the acute illness, while liver damage and leukopenia became manifest during exacerbation.

Three patients with severe HV (cases 21, 28, and 29) had repetitive episodes of mild to moderate vesiculopapular eruptions mimicking HV in the clinical course of EBV-associated systemic symptoms, but their cutaneous lesions were not severe. Two patients (cases 19 and 26) were initially diagnosed as having typical HV, but the eruptions became severe with age. The sequential change of the eruptions from typical to severe HV-like eruptions was recorded by photographs in patient 19, who had typical HV at the age of 8 years that became aggravated at the age of 12 years in association with high-grade fever and liver damage. The patient died of subcutaneous NK/T-cell lymphoma with hemophagocytosis (Figure 5 and Figure 6).

Of 11 patients with severe HV, 5 children progressed to overt EBV-associated malignant lymphoma with an NK/T-cell phenotype (cases 19, 21, 23, 24, and 26). CD36-positive tumor cells were detected in the nasal lymphoma (case 21) and subcutaneous lymphoma (case 24), although no significant numbers of NK cells were infiltrated into the vesiculopapular HV-like eruptions. Of the 5 patients who died, at least 4 (cases 19, 21, 23, and 26)
had fatal hemophagocytic syndrome characterized by leukopenia, thrombocytopenia, and liver damage. The fatal outcome occurred 2 to 14 years after the onset of disease.

**COMMENT**

In addition to the clinical similarity, biopsy specimens of HV and severe HV-like eruptions had essentially the same histologic features, such as reticulated epidermal degeneration and dense infiltration mainly composed of T cells (CD3ε-positive, CD45RO-positive, CD56-negative) around the blood vessels, although the infiltrate reached into the subcutaneous tissue and became dense in severe disease. Considerable numbers of EBER-positive T cells were present in the cutaneous infiltrates of 28 (97%) of 29 patients with HV or severe HV-like eruptions. No clear differences were observed in EBER-positive cell numbers among definite, probable, and severe HV. One EBER-negative case (case 12) might be diagnosed as a vesiculopapular variant of polymorphic light eruption. No clear differences were observed in EBER-positive cell numbers among definite, probable, and severe HV. One EBER-negative case (case 12) might be diagnosed as a vesiculopapular variant of polymorphic light eruption. The cutaneous infiltrates in HV lesions contained many T cells expressing cytotoxic molecules such as T-cell intracellular antigen 1 and granzyme B. These cell types usually outnumbered the EBER-positive cells. Therefore, cytotoxic T-cell responses against the virus-infected cells might be responsible for the development of HV and HV-like lesions. In the severe HV group, NK-cell lymphocytosis was frequently present in the blood, whereas no NK cells were involved in the development of HV-like lesions into which only T cells were infiltrated. These findings suggest that typical HV and the peculiar vesiculopapular eruptions in the severe HV group may represent different disease severities along the same spectrum of EBV-associated cutaneous disorders, although there may be differences in the systemic manifestations, laboratory test results, complications, and outcomes.

Cases in the severe HV group were frequently associated with liver damage, leukopenia, thrombocytopenia, and EBV-infected NK-cell lymphocytosis, and presented with various EBV-related complications, including hypersensitivity to mosquito bites, hemophagocytic syndrome, and chronic active EBV infection. Furthermore, the amounts of EBV DNA were markedly increased in the severe HV group, although they were also increased moderately in patients with typical HV without overt hematologic abnormalities (Table 4). In our experience, the severe HV group frequently had elevated levels of antibodies against EBV VCA and EA of the lytic infection cycle, while most patients with definite and probable HV had the usual antibody profile of post-EBV infection. These observations indicate a close pathogenic relationship between the severe HV

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**Figure 4.** Dermal infiltrates of hydroa vacciniforme composed mainly of lymphocytes expressing CD3-positive (A), CD4-positive (B), CD8-positive (C), T-cell intracellular antigen 1-positive (D), and granzyme B-positive (E) cells. CD56-positive cells are absent or at background level (F) (case 14).
group and chronic active EBV infection, suggesting that both diseases reside within the same spectrum of EBV-associated NK/T-cell lymphoproliferative disorders. Furthermore, to distinguish the severe disease from typical HV, the following laboratory tests are useful: hematologic and liver profiles, the percentage of NK lymphocyte subset, anti-EBV antibody titers, and EBV DNA load in the peripheral blood.34

Our histopathologic study demonstrated that HV-like cutaneous lesions were composed of T cells, but not of NK (CD56-positive) cells, although NK-cell lymphocytosis was usually present in the severe group. This discrepancy raises the question of whether the HV-like lesions and other EBV-associated complications are induced by different lymphocyte subsets. Patients with chronic active EBV infection often have a dominant NK-cell clone in the blood, although latent EBV infection is usually observed in various cell types, including NK, T, and B cells.29,30,34 Among EBV-associated symptoms, NK-cell lymphocytosis is closely related to the occurrence of hypersensitivity to mosquito bites,31-33 and EBV-infected CD8-positive T cells are responsible for that of hemophagocytic syndrome.29 These observations suggest that a variety of clinical manifestations result from the exis-
ence of various EBV-infected lymphocyte subsets in the blood, but are not induced by a dominant EBV-infected clone alone. It might be possible, therefore, that vesiculopapular eruptions mimicking HV are induced by EBV-infected T cells, and other systemic symptoms observed in the severe HV group are mediated by other EBV-infected NK-cell subsets. When there is no associated NK-cell lymphocytosis, only vesiculopapular eruptions may occur without systemic symptoms, as observed in the typical and probable HV groups.

Of the 11 patients with severe HV, 5 patients (cases 19, 21, 23, 24, and 26) progressed to overt EBV-associated malignant lymphoma 2 to 14 years after the onset. In addition, at least 6 patients (cases 20, 21, 25, and 27-29) had EBV-associated NK-cell lymphocytosis in the peripheral blood, and clonal proliferation of EBV-infected cells was found in 2 patients (cases 25 and 27) (data not shown). Although most patients with typical HV have had a good prognosis in our series, it is important to follow up these cases carefully since it may take many years for the disease to progress to malignant conditions, and some patients with a fatal outcome may present with typical HV eruptions initially, as exemplified by case 19 (Figure 5). The clinical and laboratory findings that predict progression include (1) lack of spontaneous resolution with age, (2) the aggravation of eruptions associated with facial swelling, (3) systemic complications such as a high-grade fever and liver damage, (4) dense and deep lymphocytic infiltration containing atypical cells, (5) an increased number of EBER-positive cells, (6) an episode of hypersensitivity to mosquito bites, (7) abnormal antibody titers to EBV, and (8) an increased level of EBV-DNA in peripheral blood.

In addition, we detected EBER-positive cells in 1 French and 1 Chinese patient with typical HV (data not shown). Therefore, latent EBV infection might be associated with typical HV in other countries. However, patients with malignant lymphoma with severe HV-like eruptions have been reported exclusively in Asia, Mexico, and Peru, whereas no specific epidemiologic distribution has been observed for typical HV. The endemic occurrence of severe HV might be correlated with the prevalence of other EBV-associated NK/T-cell lymphomas in Asians and Latin Americans. Therefore, the development of and progression to the severe HV-like lesions might occur endemically owing to the influences of the patient's genetic background, EBV subtypes, immunologic tolerance to EBV infection, or environmental factors. Our results indicate that both typical and severe HV exist along a spectrum of cutaneous manifestations mediated by cytotoxic T-cell responses against EBV-infected T cells, and severe HV may have EBV-associated NK/T-cell lymphoproliferative disorders with a fatal outcome.

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Table 4. Comparison Between Typical HV and Severe HV

<table>
<thead>
<tr>
<th>Variable</th>
<th>Typical HV</th>
<th>Severe HV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td>Worldwide</td>
<td>Prevalence in Asia and Latin America</td>
</tr>
<tr>
<td>Skin lesion</td>
<td>Exposed areas</td>
<td>Exposed and sometimes unexposed areas</td>
</tr>
<tr>
<td>Vesiculopapular</td>
<td></td>
<td>Ulcerative indurated lesions with facial edema and vesiculopapules mimicking HV</td>
</tr>
<tr>
<td>Photoprovocation</td>
<td>Usually positive</td>
<td>Usually negative</td>
</tr>
<tr>
<td>Histopathology</td>
<td>EBER-positive cells</td>
<td>T cells in HV-like eruptions, and NK (CD56-positive) cells in subcutaneous lesions</td>
</tr>
<tr>
<td>Other cells</td>
<td>Reactive CTLs</td>
<td>Reactive CTLs</td>
</tr>
<tr>
<td>Systemic symptoms</td>
<td>None</td>
<td>Fever, liver damage, lymphadenopathy</td>
</tr>
<tr>
<td>Hematologic findings</td>
<td>Usually normal</td>
<td>NK cell lymphocytosis, leukopenia, and thrombocytopenia</td>
</tr>
<tr>
<td>Anti-EBV Ab</td>
<td>Usually normal after EBV infection</td>
<td>Elevated Ab titers to VCA and EA; presence of IgA-class Ab; absence of anti-EBNA Ab</td>
</tr>
<tr>
<td>EBV DNA load</td>
<td>Increased</td>
<td>Highly increased</td>
</tr>
<tr>
<td>Complications</td>
<td>Usually none</td>
<td>HMB, CAEBVI, VAHS, and EBV-positive NK/T-cell lymphoma</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Usually benign</td>
<td>Poor in most but stable in some</td>
</tr>
</tbody>
</table>

Abbreviations: Ab, antibody; CAEBVI, chronic active EBV infection; CTLs, cytotoxic T lymphocytes; EA, early antigen; EBER, Epstein-Barr virus–encoded small nuclear RNA; EBNA, Epstein-Barr nuclear antigen; EBV, Epstein-Barr virus; HMB, hypersensitivity to mosquito bites; HPS, hemophagocytic syndrome; HV, hydroa vacciniforme; NK, natural killer; VAHS, virus-associated hemophagocytic syndrome; VCA, viral capsid antigen.
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