Hydroa vacciniforme-like lymphoproliferative disorder in Korea

Byeol Han1,2, Keunyoung Hur3, Jungyoon Ohn1,2, Tae Min Kim3,4, Yoon Kyung Jeon4,5, You Chan Kim6 & Je-Ho Mun1,2

Hydroa vacciniforme-like lymphoproliferative disorder (HVLPD) is a rare Epstein–Barr virus (EBV)-associated lymphoproliferative disease. The disease course of HVLPD varies from an indolent course to progression to aggressive lymphoma. We investigated the characteristics of HVLPD in Korean patients. HVLPD patients at Seoul National University Hospital between 1988 and 2019 were retrospectively analyzed. This study included 26 HVLPD patients who all presented with recurrent papulovesicular and necrotic eruption on the face, neck, and extremities. EBV was detected from the skin tissues of all patients. HVLPD was diagnosed during childhood (age < 18 years) in seven patients (26.9%) and in adulthood (age ≥ 18 years) in 19 cases (73.1%). The median age at diagnosis was 24.0 years (range 7–70 years). HVLPD has various clinical courses, from an indolent course to progression to systemic lymphoma. Fourteen patients (53.8%) developed lymphoma: systemic EBV-positive T-cell lymphoma (n = 9, 34.6%); extranodal natural killer/T-cell lymphoma, nasal type (n = 3, 11.5%); aggressive natural killer/T-cell leukemia (n = 1, 3.8%); and EBV-positive Hodgkin lymphoma (n = 1, 3.8%). Mortality due to HVLPD occurred in five patients (26.3%) in the adult group, while it was one patient (14.3%) in the child group. As lymphoma progression and mortality occur not only in childhood but also in adulthood, adult-onset cases may need more careful monitoring.

Hydroa vacciniforme-like lymphoproliferative disorder (HVLPD) is a rare Epstein–Barr virus (EBV)-associated T-cell or natural killer (NK)-cell lymphoproliferative disease. According to the revised 4th World Health Organization (WHO) classification, the term HVLPD has been renamed from hydroa vacciniforme-like lymphoma to HVLPD owing to its relationship to chronic active EBV infection (CAEBV) and the broad spectrum of its clinical course. Although HVLPD usually affects children, adult and elderly cases have been reported. Clinically, it is characterized by recurrent erythematous papules and vesicles that leave pitted scars on sun-exposed areas, including the face and forearms. The disease course of HVLPD varies from an indolent course to systemic lymphoma. Our experience and the literature show that mortality or a fatal outcome from the progression of HVLPD to lymphoma can also occur in adults. In the present study, we report on 26 cases of HVLPD encountered at our hospital during the last three decades.

Results

Clinical features. A total of 26 cases were enrolled with diagnosis of HVLPD based on clinical and histopathologic features between 1988 and 2019 in the Department of Dermatology of Seoul National University Hospital (SNUH). Fifteen cases had been previously reported. There were seven children (age < 18 years) and 19 adults (age ≥ 18 years), with a median age of 24.0 years (range 7–70 years) at the time of diagnosis. The age at which the skin lesions of HVLPD first appeared varied, with a median age of 17.5 years (range 3–70 years). Among 19 adult patients, 6 (31.6%) reported that they had skin lesions in childhood. There were 16 male patients and 10 female patients (male-to-female ratio 1.6:1). All patients had recurrent vesicles, papules, crusted papulovesicles, necrotic ulcers, and pitted scars on sun-exposed areas (Fig. 1 and Tables 1 and 2). Besides lesions on the face and arms, skin lesions on non-sun-exposed areas, including the trunk, were present in seven patients.
(26.9%). Oral ulcer was noted in nine patients (34.6%), and facial swelling was observed in three patients (11.5%). At the first consultation, six patients (23.1%) had fever and cervical lymphadenopathy and two patients (7.7%) had splenomegaly. The median follow-up duration was 36.0 months (range 12–216 months). Ultraviolet (UV) A radiation provocation test was performed in seven patients. Among them, five patients (71.4%) had skin eruption with papulovesicles. Mosquito bite hypersensitivity was noted in three patients (11.5%). Serum EBV viral load was evaluated in 11 patients (42.3%). All patients showed serum EBV. High levels of viral load, ranging from 54,275 to 47,925,563 copies/mL (median 1,784,901 copies/mL), were observed during follow-up.

**Histopathologic features, immunohistochemical findings, in situ hybridization, and molecular studies.** The histopathologic features of cutaneous tissue were similar in all patients. Dense and diffuse infiltration of atypical lymphocytes was seen in the dermis and subcutaneous fat (Fig. 2). Epidermal necrosis, vesiculation, subepidermal edema, and perivascular and periappendageal atypical lymphocytic infiltration were found. The proliferated atypical lymphocytes were of small to intermediate size, with enlarged, round to oval nuclei. There were an inflammatory background with lymphocytes, eosinophils, histiocytes and plasma cells. The immunohistochemistry results and molecular study findings are summarized in Table 2. EBV-encoded small nonpolyadenylated RNA (EBER) was positive in all patients. EBER-positive cells were predominantly seen in the perivascular and periappendageal area in the dermis and subcutaneous fat. Detection of monoclonal T-cell receptor γ gene rearrangements was performed in 13 patients. Among them, four patients (30.8%) showed these rearrangements.
Treatment and disease course. Various treatments were applied. Sun exposure avoidance was recommended to all patients. Systemic steroid was used to control the disease in 14 patients (53.8%). Systemic acyclovir or minocycline was administered in three patients. Thirteen patients received chemotherapy as the first-line or second-line therapy because of disease activity exacerbation. Seven patients died during the follow-up (mortality rate 26.9%), six of whom died of the disease; one of whom (case no. 17) died of breast cancer. Therefore, HVLPD mortality occurred in seven patients (23.1%).

In the child group, one patient showed remission (14.3%) and three patients had partial remission and recurrence (42.9%). The disease progressed to systemic lymphoma or leukemia in three patients (42.9%), two of whom had a diagnosis of systemic EBV-positive (EBV+) T-cell lymphoma of childhood and one of whom had aggressive NK/T-cell leukemia. The mortality rate of HVLPD in the child group was 14.3% (1/7). The cause of death was aggressive NK/T-cell leukemia.

In the adult group, remission was noted in two patients (10.5%) and partial remission was observed in six patients (31.6%). Eleven cases (57.9%) were associated with systemic lymphoma, of which seven (36.8%) progressed to systemic EBV+ T-cell lymphoma; 3 (15.8%) to extranodal NK/T-cell lymphoma, nasal type; and 1 (5.3%) to EBV+ Hodgkin lymphoma. The mortality rate of HVLPD in the adult group was 31.6% (6 of 19). When we excluded the case of breast cancer death, the rate of disease-specific death was 26.3% (5 of 19) in the adult group. The causes of death were progression to systemic EBV+ T-cell lymphoma in four patients and extranodal NK/T-cell lymphoma, nasal type, in one patient.

Progression to lymphoma and mortality in relation to age at diagnosis, disease onset, and disease duration. We compared the rates of HVLPD progression to lymphoma and disease-related mortality between patients diagnosed during childhood and those diagnosed during adulthood. Although the rates of both were higher among those diagnosed during adulthood, the differences were not statistically significant (p = 0.665

Table 1. Summary of characteristics of patients with hydroa vacciniforme-like lymphoproliferative disease.

| Variable | Total N=26, n (%) |
|----------|------------------|
| Age at diagnosis, mean ± SD (range) (years) | 25.3 ± 12.8 (7–70) |
| Children (<18) | 7 (26.9) |
| Adult (≥18) | 19 (73.1) |
| Age at onset, mean ± SD (range) (years) | 19.8 ± 14.9 (3–70) |
| During childhood (<18) | 13 (50.0) |
| During adulthood (≥18) | 13 (50.0) |
| Disease duration, mean ± SD (range) (years) | 5.5 ± 5.2 (0–17) |
| Sex | |
| Male | 16 (61.5) |
| Female | 10 (38.5) |
| Anatomic location of cutaneous manifestations | |
| Sun-exposed area | 26 (100) |
| Non–sun-exposed area | 7 (26.9) |
| Extracutaneous involvement | |
| Yes | 16 (61.5) |
| No | 10 (38.5) |
| UVA provocation test [n = 7]a | |
| Positive | 5 (71.4) |
| Negative | 2 (28.6) |
| Serum EBV DNA load, mean ± SD (range) (copies/mL) [n = 11]b | 9,849,887.6 ± 15,824,779.4 (54,275–47,925,563) |
| Development of systemic lymphoma | |
| Yes | 14 (53.8) |
| Systemic EBV+ T-cell lymphoma | 9 (34.6) |
| Extranodal NK/T-cell lymphoma, nasal type | 3 (11.5) |
| Aggressive NK/T-cell leukemia | 1 (3.8) |
| EBV+ Hodgkin lymphoma | 1 (3.8) |
| No | 12 (46.2) |
| Outcome | |
| Alive with disease | 19 (73.1) |
| Mortality due to the disease | 6 (23.1) |
| Mortality due to another disease | 1 (3.8) |

aUV A provocation test was performed in seven patients. bSerum EBV DNA load was evaluated in 11 patients.
| Patient no. | Sex | Age at diagnosis, years (age at onset, years) | Cutaneous manifestations | IHC, EBER-1 ISH, TCRγ gene rearrangement | Serum EBV DNA load (copies/mL) | UVA provocation test | Extracutaneous involvement | Treatment | Disease course | Follow-up (months) | Last status during follow-up |
|------------|-----|-----------------------------------------------|--------------------------|------------------------------------------|-------------------------------|------------------------|-------------------------|-----------|----------------|---------------------|----------------------------------|
| 1          | F   | 7 (6)                                         | Erythematous crusted papulovesicles on the face and oral ulcer | CD3+, CD20+ a few, Ki-67 10%, EBV ISH+ | 15,462,763 | Positive | None | Observation | Partial remission and recurrence | 72 | AWD |
| 2          | M   | 10 (9)                                        | Erythematous crusted papulovesicles on the face | CD3+, CD20+ a few, CD56+, EBV ISH+ | ND | Negative | None | Systemic steroid, minocycline | Partial remission and recurrence | 216 | AWD |
| 3          | F   | 11 (5)                                        | Erythematous crusted papulovesicles on the face and arm, oral ulcer | CD3+, CD45RO+, CD8+, CD20−, CD56+ few, LMP-1−, EBV ISH+ | 1,784,901 | ND | None | Systemic steroid on recurrence | Partial remission and recurrence | 180 | AWD |
| 4          | F   | 12 (3)                                        | Erythematous crusted papulovesicles on the face, arm, and leg | CD3+, CD45RO+, CD56−, S-100−, lysozyme+ focal, EBV ISH+ | ND | ND | Liver, spleen, bone marrow | Oral acyclovir | Progressed to aggressive NK-cell leukemia | 108 | DOD |
| 5          | F   | 15 (10)                                       | Erythematous crusted papulovesicles on the face and arm | CD3+, CD4+, CD8+ focal, CD20−, CD56−, Ki-67+ 70%, EBV ISH+, TCR gamma gene rearrangement− | ND | Negative | None | Observation | Remission | 36 | AWD |
| 6          | M   | 17 (17)                                       | Erythematous crusted papulovesicles on the face and trunk, oral ulcer | CD3+, CD4+, CD8+ focal, CD20−, CD56−, TIA-1−, Ki-67+ 70%, EBV ISH+, TCR gamma gene rearrangement− | 8,463,700 | ND | Bone marrow | Systemic steroid→chemotherapy | Progressed to systemic EBV+ T-cell lymphoma | 12 | AWD |
| 7          | M   | 17 (8)                                        | Erythematous crusted papulovesicles on the face and forearm | CD45RO+, CD20−, EBV ISH+ | ND | Negative | Cervical lymph node, liver, spleen | Systemic steroid, chemotherapy | Progressed to systemic EBV+ T-cell lymphoma | NS | AWD |
| 8          | M   | 18 (6)                                        | Erythematous crusted papulovesicles on the face, arm, and trunk | CD3+, CD4+, CD8+ focal, CD20−, CD56−, S-100−, CD30−, EBV ISH+ | 47,925,563 | Positive | Cervical lymph node, spleen, iliac bone, bone marrow | Systemic steroid→chemotherapy | Progressed to systemic EBV+ T-cell lymphoma | 12 | DOD |
| 9          | F   | 19 (17)                                       | Erythematous crusted papulovesicles on the face and arm, oral ulcer, facial swelling | CD3+, CD4−, CD8−, CD20−, CD56−, CD30−, EBV ISH+ | 693,642 | ND | Right breast, lung, spleen, liver, pelvic bone, bone marrow | Systemic steroid→chemotherapy | Progressed to extranodal NK/T-cell lymphoma, nasal type | 24 | DOD |
| 10         | M   | 19 (4)                                        | Erythematous crusted papulovesicles on the face, arm, trunk, and ankle | CD20+ a few, CD56+ a few, LMP-1−, EBV ISH+ | 79,396 | ND | None | Observation | Remission | 204 | AWD |
| 11         | M   | 19 (4)                                        | Erythematous crusted papulovesicles on the face and forearm | CD45RO+, CD20−, EBV ISH+ | ND | Negative | None | Systemic steroid, oral acyclovir | Partial remission | NS | AWD |
| 12         | M   | 21 (19)                                       | Erythematous crusted papulovesicles on the face and oral ulcer | CD45RO+, CD20−, EBV ISH+ | ND | Negative | Cervical lymph node, liver | Systemic steroid | Progressed to Systemic EBV+ T-cell lymphoma | NS | DOD |

Continued
| Patient no. | Sex | Age at diagnosis, years (age at onset, years) | Cutaneous manifestations | HCL, EBER-1 ISH, TCRγ gene rearrangement | Serum EBV DNA load (copies/mL) | UVA provocation test | Extracutaneous involvement | Treatment | Disease course | Follow-up (months) | Last status during follow-up |
|------------|-----|------------------------------------------------|--------------------------|------------------------------------------|-------------------------------|---------------------|-----------------------------|-------------|-----------------|----------------|-----------------------------|
| 13         | M   | 24 (10)                                        | Erythematous crusted papulescences on the face, arm, and trunk | CD3+, CD34+, CD4+, CD8+, CD20+ a few, CD56+, granzyme B+ a few, Ki-67 1%, EBV ISH+, TCR γ gene rearrangement | 1,840,744 ND | Liver, spleen, bone marrow | Systemic steroid → chemotherapy | Progressed to Systemic EBV+ T-cell lymphoma | 120 | DOD |
| 1410       | M   | 24 (18)                                        | Erythematous crusted papulescences on the face and forearm | CD45RO+, EBV ISH+ | ND | Negative | Cervical lymph node, spleen | Systemic steroid | Progressed to peripheral T-cell lymphoma of adulthood | NS | DOD |
| 15         | M   | 26 (25)                                        | Erythematous crusted papulescences on the face | CD3+, CD4+, CD8+ focal, CD 20 + a few, CD30+ focal, CD56+, Ki-67 15%, TCR γ gene rearrangement | 30,917,751 ND | Cervical and axillary lymph node, spleen | Systemic steroid → chemotherapy | Progressed to peripheral T-cell lymphoma of adulthood | 204 | AWD |
| 16         | M   | 28 (22)                                        | Erythematous crusted papulescences on the face | CD3+, CD4+ | ND | Positive | None | Observation | Remission | 36 | AWD |
| 17         | F   | 28 (26)                                        | Erythematous crusted papulescences on the face and facial swelling | CD3+, CD45RO+, CD20+ a few, CD56+, Ki-67+ a few, LMP-1+, EBV ISH+, TCR γ gene rearrangement | ND | None | None | Systemic steroid | Partial remission and recurrence | 36 | Death |
| 18         | M   | 29 (25)                                        | Erythematous crusted papulescences on the face, arm, and trunk | CD3+, CD34+, CD20+ a few, CD56+, Ki-67+ (<5%), EBV ISH+, TCR γ gene rearrangement | ND | None | None | Systemic steroid | Partial remission and recurrence | 36 | AWD |
| 19         | F   | 30 (27)                                        | Erythematous crusted papulescences on the face and oral ulcer | CD3+, CD45RO+, CD20+ a few, CD56+, Ki-67+ (<5%), EBV ISH+, TCR γ gene rearrangement | ND | Cervical and axillary lymph node | Chemotherapy | Progressed to or accompanied extranodal NK/T-cell lymphoma, nasal type | 12 | AWD |
| 20         | M   | 32 (15)                                        | Erythematous crusted papulescences on the face and oral ulcer | CD3+, CD20+ a few, CD36+, granzyme B+, EBV ISH+, Ki-67 20% | 54,275 ND | Cervical lymph node, stomach | Chemotherapy, daratumumab | Progressed to extranodal NK/T-cell lymphoma, nasal type | 48 | AWD |
| 2111       | F   | 33 (30)                                        | Erythematous crusted papulescences on the face | CD3+, CD45RO+, CD20+, CD30−, CD56−, Ki-67 20%, EBV ISH+, TCR γ gene rearrangement | ND | Positive | Cervical lymph node, stomach | Chemotherapy | Progressed to Systemic EBV+ T-cell lymphoma | 18 | AWD |
| 2211       | M   | 34 (33)                                        | Erythematous crusted papulescences on the face, arm, and trunk, and oral ulcer | CD3+, CD45RO+, CD20−, CD30−, CD56−, Ki-67 20%, EBV ISH+, TCR γ gene rearrangement | ND | Bone marrow | Chemotherapy | Progressed to Systemic EBV+ T-cell lymphoma | 24 | AWD |
for progression and $p = 1.000$ for mortality). We further analyzed these parameters according to whether disease onset occurred in childhood (age < 18 years) or adulthood (age ≥ 18 years). There was no difference between the two groups with regard to either progression to lymphoma or disease-related mortality ($p = 1.000$ and $p = 0.645$, respectively). Additionally, we evaluated the effect of the period from disease onset to first diagnosis, comparing patients with a disease duration of < 10 years and those with a duration of ≥ 10 years. There were no differences in the rate of progression to lymphoma or disease-related mortality ($p = 1.000$ and $p = 0.218$, respectively) in relation to disease duration before first diagnosis.

### Discussion

Hydroa vacciniforme is a rare photodermatosis originally described by Bazin\(^{14}\). Although the pathogenesis of hydroa vacciniforme is not clearly established, sensitivity to UVB or UV A has been suggested as a pathologic mechanism\(^{15}\). In 1996, Cho et al. first suggested an association with EBV and recurrent necrotic papulovesicular eruptions of the face\(^{16}\). As most cases with hydroa vacciniforme manifestations have shown the presence of EBV, the question about the existence of classic hydroa vacciniforme without EBV infection remains unresolved\(^{16}\). Therefore, Quintanilla-Martinez and Fend suggested renaming the disease as hydroa vacciniforme EBV-associated lymphoproliferative disorder to encompass the broad clinical spectrum\(^{16}\).

HVLPD has been given various names, including hydroa vacciniforme-like lymphoma and EBV-associated vesiculopapular eruption on the face. In 2008, the WHO classification introduced 2 T-cell lymphoproliferative disorders associated with EBV in children: hydroa vacciniforme-like lymphoma and systemic EBV+ lymphoproliferative disease of childhood\(^{17}\). In 2016, the 4th WHO classification reclassified the disease into two groups: HVLPD and systemic EBV+ T-cell lymphoma of childhood (Table 3)\(^{18}\).

The EBV-associated T- and NK-cell lymphoproliferative diseases include EBV-associated hemophagocytic lymphohistiocytosis (HLH); CAEBV of T- and NK-cell type; systemic EBV+ T-cell lymphoma of childhood; aggressive NK-cell leukemia; extranodal NK/T-cell lymphoma, nasal type; and primary EBV+ nodal NK/T-cell lymphoma (Table 4)\(^{19,20}\). Primary EBV+ nodal NK/T-cell lymphoma is a new provisional entity defined as peripheral T-cell lymphoma with primary nodal presentation without nasal involvement\(^{20}\). Although splenomegaly and hepatic involvement can occur in 73% and 60% of the patients, skin and gastrointestinal involvement are rare\(^{21}\). EBV-associated HLH is a life-threatening inflammatory disease with symptoms including high fever, cytopenia, hypofibrinogenemia, elevated serum transaminases, hyperbilirubinemia, prolonged prothrombin time, and hyponatremia; it may occur as a primary condition or secondary to other conditions\(^{22}\). Secondary EBV-associated HLH may accompany CAEBV of T- and NK-cell type. HVLPD is classified as a cutaneous form of CAEBV of T- and NK-cell type. CAEBV of T- and NK- cell types has a broad range of clinical manifestations from indolent cutaneous form to a more severe systemic form\(^{20}\). Aggressive NK-cell leukemia is a fulminant

### Table 2. Clinical features and histopathologic findings in patients with hydroa vacciniforme-like lymphoproliferative disease at our institution. AWD alive with the disease, DOD died of disease, EBER-1 ISH EBV-encoded small nonpolyadenylated RNA (EBER)-1 by in situ hybridization, F female, IHC immunohistochemistry, M male, ND not done, NS not specified exact follow-up duration.

| Patient no. | Sex | Age at diagnosis, years (age at onset, years) | Sex | Age at diagnosis, years (age at onset, years) | Cutaneous manifestations | CD3+ | CD4+ | CD8+ | CD20+ | CD56- | CD56+ | gamma gene rearrangement | Serum EBV DNA load (copies/mL) | UVA provocation test | Extracutaneous involvement | Treatment | Disease course | Follow-up (months) | Last status during follow-up |
|-------------|-----|---------------------------------------------|-----|---------------------------------------------|-------------------------|-----|-----|-----|-----|-----|-----|--------------------------|--------------------------|--------------------------|--------------------------|-------------|----------------|----------------|--------------------------|
| 23\(\)     | M   | 37 (32)                                     | Erythematous crusted papulovesicles on the face, arm, and trunk | CD3+, CD4RO+, CD20+ a few, CD56- | Ki-67+ (>5%), EBV ISH+, TCR gamma gene rearrangement | ND | ND | Cervical lymph node | Chemo-therapy | Partial remission and recurrence | 36 | AWD |
| 24          | M   | 38 (38)                                     | Erythematous crusted papulovesicles on the face | CD3+, CD4+ | local, CD8+ | local, CD20-, CD56-, granzyme B+ | local, Ki-67+, EBV ISH+, TCR gamma gene rearrangement | 925,529 | ND | Lung (Hodgkin lymphoma), bone marrow, spleen, bone | Systemic steroid + chem-otherapy | Progressed to EBV+ Hodgkin lymphoma | 96 | AWD |
| 25\(\)     | F   | 39 (36)                                     | Erythematous crusted papulovesicles on the face, arm, and trunk | CD3+, CD4RO+, CD20+ a few, CD56- | Ki-67+ (>5%), EBV ISH-, TCR gamma gene rearrangement | ND | Positive | Cervical lymph node | Chemo-therapy | Partial remission and recurrence | 36 | AWD |
| 26\(\)     | F   | 70 (70)                                     | Erythematous crusted papulovesicles on the face, oral ulcer, and facial swelling | CD2+, CD3+, CD4+ | a few, CD5+, CD8+ | local, CD20-, CD30-, CD56-, EBV ISH | 200,500 | Negative | None | Topical steroid | Partial remission and recurrence | 12 | AWD |
A disease characterized by systemic neoplastic proliferation of NK-cells. It occurs in young to middle-aged adults. Extranodal NK/T-cell lymphoma, nasal type, is EBV+ aggressive lymphoma and occurs mainly in middle-aged adults. It occurs in 70–80% of all cases and primarily involves the nasal and nasopharyngeal region. Skin lesion presents as nodular ulcerative lesions, and gastrointestinal tract, testis and mucous membrane are involved. Systemic EBV+ T-cell lymphoma of childhood is a more rapidly progressive and fatal disease, characterized by EBV-encoded small nonpolyadenylated RNA was positive in the atypical mononuclear cells.

Table 3. Change of definition of hydroa vacciniforme and hydroa vacciniforme-like lymphoproliferative disease.

| Diagnosis                                      | Definition                                                                 | References                          |
|------------------------------------------------|---------------------------------------------------------------------------|-------------------------------------|
| Hydroa vacciniforme                           | Rare, sporadic, idiopathic photodermatosis characterized by papules, vesicles, and crusts which heal with vacciniform scarring after sunlight exposure. The pathogenesis is unclear although sensitivity of UVB or UVA has been suggested | First reported by Bazin14,15        |
| Hydroa vacciniforme-like lymphoma             | Proliferation of clonal T cells or, less frequently, NK cells infected by EBV with a latency type 1 profile. It has an indolent clinical course with long periods of recurrent skin lesions in sun-exposed areas that tends to regress spontaneously. After several years, the process may resolve or progress to systemic disease | 2008 WHO classification17          |
| Systemic EBV+ lymphoproliferative disease of childhood | Aggressive condition with rapid evolution to multiple-organ failure and death. It has overlapping features with aggressive NK-cell leukemia, but the cells have a T-cell phenotype and clonal TCR rearrangement. It may emerge in a background of chronic EBV infection and progress from a polyclonal, to an oligoclonal, and to a monoclonal EBV-driven proliferation |                                            |
| Hydroa vacciniforme-like lymphoproliferative disease | Name changed from lymphoma to lymphoproliferative disorder due to its relationship with chronic active EBV infection and the broad spectrum of its clinical course | 2016 WHO classification18          |
| Systemic EBV+ T-cell lymphoma of childhood   | Name changed from lymphoproliferative disorder to lymphoma owing to its fulminating clinical course and the desire to clearly distinguish it from chronic active EBV infection |                                            |
This study was approved by the institutional review board of...

Therefore, its use should be prudently considered in selected....

A 5 × 5 cm area on the buttock or upper arm was irradiated...radiologic imaging stud-

Although classic HVLPD usually occurs in the pediatric age group, there have been cases of systemic EBV + T-cell lymphoma in adults with HVLPD...

The prognostic factors of progression from HVLPD to systemic lymphoma have not been definitely established. Factors such as high serum EBV DNA loads, Latin American descent, systemic symptoms, adult onset, and chemotherapy were suggested to be associated with a more aggressive disease course...

In our database, among 19 adult cases, 11 (57.9%) were associated with systemic lymphoma, and this proportion was higher than that observed among childhood cases. Among these cases, seven progressed to systemic EBV + T-cell lymphoma; three to extranodal NK/T-cell lymphoma, nasal type; and one to EBV + Hodgkin lymphoma. Therefore, considering the higher possibility of adverse outcomes, adult-onset cases may also need careful monitoring as in childhood cases.

There is no established treatment guideline for HVLPD. Stringent sun protection is recommended for all patients using broad-spectrum sunscreens, sun-protecting clothing, and avoidance of sun exposure. Various treatments were tried including hydroxychloroquine, anti-viral drugs (acyclovir and valacyclovir), topical and systemic corticosteroids, and chemotherapy. For systemic HVLPD, although corticosteroids or thalidomide provided temporary improvements, the only curative treatment is hematopoietic stem cell transplantation...

There are some limitations. Although this study included one of the large cases with three decades data in SNUH, the sample size is small as HVLPD is an extremely rare disease. In addition, a detailed molecular analysis was not performed due to the retrospective study design. Lastly, it was challenging to distinguish between HVLPD and extranodal NK/T-cell lymphoma, nasal type, and primary EBV + nodal NK/T-cell lymphoma with extranodal involvement as some features are overlapped. However, the diagnosis was made based on clinical and pathologic findings by an experienced dermatologist, pathologist, and oncologist.

In summary, we described 26 cases of HVLPD encountered at our institution during the last three decades. HVLPD seems to have various disease courses. Fourteen patients (53.8%) in the present study had systemic T-cell lymphoma, NK-T cell lymphoma/leukemia, and EBV + Hodgkin lymphoma. Lymphoma progression and mortality can occur not only in childhood but also in adulthood.

**Methods**

We retrospectively reviewed cases of HVLPD diagnosed based on clinical and histopathologic features between 1988 and 2019 in the Department of Dermatology of SNUH. Patients who both gave and signed an informed consent to perform a skin biopsy were recruited (In cases of patients under 18 years of age, signed informed consent were given by parents and/or legal guardians). HVLPD was defined according to the revised 4th WHO classification...

A provisional entity.

| Disease                                                                 |
|------------------------------------------------------------------------|
| Aggressive NK-cell leukemia                                             |
| Chronic active EBV infection (CAEBV) of T- and NK-cell type            |
| Cutaneous CAEBV of T- and NK-cell type                                |
| Hydroa vacciniforme-like lymphoproliferative disease                   |
| Severe mosquito bite allergy                                            |
| Systemic CAEBV of T- and NK-cell type                                 |
| EBV-associated hemophagocytic lymphohistiocytosis                      |
| Extranodal NK/T-cell lymphoma, nasal type                             |
| Primary EBV + nodal NK/T-cell lymphoma†                               |
| Systemic EBV + T-cell lymphoma of childhood                            |

Table 4. Classification of EBV-associated T- and NK-cell lymphoproliferative diseases†,* A provisional entity.
SNUH (approval no. 1908-019-1053). All methods were carried out in accordance with relevant guidelines and regulations.

Statistical analyses were performed using SPSS 25 (SPSS Inc., IL, USA). Pearson’s chi-square test was performed to compare proportions, except when the expected values in the SPSS cells were < 5, in which case Fisher’s exact test was used. Student’s t-test was used to compare mean disease durations.

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Author contributions

Conceptualization, B.H. and J.H.M.; methodology, B.H. and J.H.M.; validation, K.H. and J.O.; formal analysis, B.H.; investigation, B.H., K.H., J.O. and J.H.M.; resources, Y.C.K and J.H.M.; data curation, B.H., K.H., J.O., T.M.K., Y.K.J., Y.C.K., and J.H.M.; writing—original draft preparation, B.H.; writing—review and editing, K.H., J.O., T.M.K., Y.K.J., Y.C.K., and J.H.M.; supervision, J.H.M. All authors have read and agreed to the published version of the manuscript.

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Additional information
Correspondence and requests for materials should be addressed to J.-H.M.

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