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ORIGINAL ARTICLE

Hydroa Vacciniforme-Like Lymphoproliferative Disorder in Korea: Prognostic Implication of Clinical Signs and Whole Blood Epstein-Barr Virus DNA

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Background: Hydroa vacciniforme-like lymphoproliferative disorder (HVLPD) is rare Epstein-Barr virus (EBV)-associated disease. The classic form of HVLPD is a self-resolving disease, whereas the systemic form can progress to malignant lymphoma, resulting in fatal outcomes. However, the prognostic factors remain unclear. **Objective:** This study aimed to evaluate the clinical characteristics of HVLPD and the association between whole blood EBV DNA and clinical outcomes. **Methods:** We retrospectively reviewed our 25-year experience involving 11 patients with HVLPD from a single tertiary center in South Korea and evaluated the clinical characteristics of HVLPD and the correlation between whole blood EBV DNA and clinical outcomes. **Results:** Of the total 11 patients, 54.5% (6/11) manifested classic HVLPD that resolved with conservative treatment, while 45.5% (5/11) patients had systemic HVLPD, four of whom died of progressive disease or hemophagocytic syndrome. Five patients with systemic HVLPD manifested severe skin lesions such as prominent facial edema, deep ulcers and necrotic skin lesions involving sun-protected areas. Median EBV DNA levels at initial diagnosis were higher in three dead patients than in those alive (2,290 vs. 186.62 copies/ μl). **Conclusion:** When EBV DNA levels were high, patients showed severe skin lesions and when EBV DNA levels were low, skin lesions tended to improve. Thus, patients with high EBV DNA levels showed an increased risk of severe skin lesions and disease progression. **(Ann Dermatol 33(3) 222～227, 2021)**

-Keywords-
DNA, Epstein-Barr virus, Hydroa vacciniforme, Lymphoma, Prognosis

INTRODUCTION

Hydroa vacciniforme-like lymphoproliferative disorder (HVLPD) is closely associated with Epstein-Barr virus (EBV) infection, which is extremely rare and mostly prevalent in East Asia and Latin America[1-4]. It is characterized by recurrent papulovesicles in sun-exposed areas, particularly the face or dorsum of the hands, which show crusts and healing with scarring, and typically high levels of EBV DNA in the blood[5]. HVLPD mainly occurs during childhood and early adolescence, and is partially resolved in adolescence, while it may persist as a systemic form of HVLPD with symptoms such as fever, lymphadenopathy, and hepatosplenomegaly and may progress to malignant lymphoma[4-6].

Although HVLPD is a rare disease, several studies have tried to evaluate risk factors for the poor prognosis[7,8]. According to Paik et al.[7], T-cell lineage and cytopenia were associated with poor prognosis while age higher than 8 years at onset of disease and liver dysfunction were related to increased mortality in a Japanese study by Kimura et al[8]. Cohen et al.[9] reported that white patients diagnosed with HVLPD were less likely to develop sys-

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temic disease or require hematopoietic stem cell transplant (HSCT) than nonwhites. Several studies have shown that Latin American patients usually show aggressive courses with fatal outcomes, while most patients in East Asia have indolent courses[4,6,10,11]. Since patients with HVLPD exhibit variable clinical courses and may often have fatal outcomes, we authors believe that it is critical to evaluate the factors in addition to racial susceptibility underlying disease progression and predict the prognosis. Here, we report our 25-year observations of 11 patients with HVLPD in a single tertiary center located in South Korea. To identify patients at higher risk of advancing to more aggressive courses, we analyzed the clinical features and whole blood EBV DNA level of HVLPD patients.

MATERIALS AND METHODS

Patient data collection

Eleven biopsy-proven cases of HVLPD diagnosed at Samsung Medical Center from 1994 to 2019 were identified and retrospectively reviewed. This study was approved by the Institutional Review Board of Samsung Medical Center (SMC 2019-07-019). Clinical records, clinical photographs, laboratory data and biopsy specimens were analyzed. Diagnosis of HVLPD was based on the 2016 edition of the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissue[12]. The following clinical data were collected for analysis: age, sex, site of skin involvement, clinical features of the skin lesion, systemic symptoms, extracutaneous involvement, initial whole blood EBV DNA levels, and survival outcome.

Patient 4[13] and 7[14] were reported previously. Patients with classic HVLPD had no persistent systemic symptoms such as lymphadenopathy, hepatosplenomegaly, hepatitis, or hemophagocytic syndrome, while those with systemic HVLPD had ≥1 of these persistent symptoms or signs of extracutaneous disease (based on prior criteria[5]).

Whole blood EBV DNA quantification

Whole blood samples were collected from HVLPD patients at the time of initial diagnosis. Venous blood was collected into 3.5 ml tubes containing ethylenediaminetetraacetic acid as an anticoagulant (BD Biosciences, Franklin Lakes, NJ, USA). Within 24 hours of blood collection, EBV DNA was isolated from 200 μl of whole blood using the High Pure polymerase chain reaction (PCR) Template Preparation Kit (Boehringer Mannheim, Mannheim, Germany) and eluted in 200 μl of elution buffer as recommended by the manufacturer. Real-time PCR was performed using the LightCycler EBV Quantification Kit on the LightCycler Instrument (ver. 1.2; Roche Diagnostics, Mannheim, Germany) using the software ver. 3.5. Hybridization probes were used to detect a gene fragment encoding a single copy of the EBV gene *EBNA1*. The primer and probe sequences are specific for amplifying and detecting the EBV DNA. These methods of EBV quantification were as reported previously[15].

RESULTS

Clinical features

We analyzed 11 patients with HVLPD (Table 1). The male-to-female ratio was 6:5, and the median age of onset was 8 years (range, 3～68 years). At initial presentation, 10 patients were children and young adult (<40 years) and 1 was an elderly patient (≥40 years). Five patients (#1, 4, 5, 8, and 10) had systemic HVLPD with persistent fever and involvement of the lymph nodes, bone marrow, liver, spleen or larynx, and their mean onset age was 21 years. The other six patients had classic HVLPD with a mean onset age of 8.3 years.

All patients had skin lesions in sun-exposed areas (head, neck, V-area of the upper part of the chest, or dorsum of hand), and five (#1, 4, 5, 8, and 10) had additional lesions in sun-protected areas involving the lower extremities. Patients presented with papulovesicles, crusts, erosions, ulcers, or pitted scars. Five patients (#1, 4, 5, 8, and 10) manifested severe skin lesions such as prominent facial edema, deep ulcers, and necrosis. Of 11 patients, 5 patients (#2, 6, 7, 8 and 10) developed skin lesions triggered or aggravated by sun exposure. Hypersensitivity to mosquito bites occurred in 2 patients.

Follow-up

The mean duration since onset of disease for all 11 patients was 8 years (range, 0.14～25 years). The total duration of follow-up since the onset of disease for the entire cohort was 87 patient-years. Seven of 11 patients with HVLPD were alive and 4 patients (#1, 4, 5, and 8) who received aggressive chemotherapy died of their HVLPD. The causes of death were hemophagocytic syndrome or multiorgan failure in 4 patients. Patient #10 with systemic HVLPD underwent HSCT. He is currently in remission after HSCT with immunosuppressive therapy. The remaining patients who carried the classic HVLPD were treated with conservative therapy and manifested no new HVLPD skin lesions.

Whole blood EBV DNA level and skin manifestation

Whole blood EBV DNA levels were elevated in all the 6 tested patients (>10 copies/μl) at diagnosis. The median EBV DNA levels at initial diagnosis were higher in 3 dead

Table 1. Demographic and clinical data of patients with hydroa vacciniforme-like lymphoproliferative disorder

Patient no.	Sex	Onset age (yr)	Site of skin involvement	Edema	Vesicle	Ulcer	Crust	Scar	HMB	Photo sensitivity	Systemic symptoms	Extracutaneous involvement	Initial whole blood EBV DNA (copies/μl)	Outcome	Duration of survival (yr)
1	Female	68	Face, neck, chest, legs	N	Y	Y	Y	Y	N	N	Y	BM(+), LN(+) hepato-splenomegaly	7,248.71	D	1.95
2	Male	12	Face	N	Y	Y	Y	Y	N	Y	N	-	-	A	8.64
3	Male	3	Face	N	Y	N	N	Y	-	-	N	-	-	A	19.67
4	Male	12	Face, hands, arms, legs	Y	Y	Y	Y	Y	Y	N	Y	Ileum(+), BM(+), splenomegaly	2,290	D	4.59
5	Female	11	Face, scalp, chest, back, buttock, legs	Y	Y	Y	Y	Y	-	-	Y	LN(+)	236.62	D	6.64
6	Male	4	Face, hands	N	Y	Y	Y	Y	N	Y	N	-	-	A	25.33
7	Female	4	Face, hands	N	Y	Y	Y	Y	N	Y	N	-	-	A	12.35
8	Female	3	Face, arms	Y	Y	Y	Y	Y	N	Y	Y	Larynx(+)	-	D	1.66
9	Female	5	Face, scalp, arms	N	Y	Y	Y	Y	N	N	N		186.62	A	4.81
10	Male	11	Face, arms, legs	N	Y	Y	Y	Y	Y	Y	Y	BM(+)	4,304.16	A	1.24
11	Male	22	Face, arms	N	Y	N	Y	Y	N	N	N	-	25.97	A	0.14

EBV: Epstein-Barr Virus, Y: yes, N: no, HMB: hypersensitivity to mosquito bites, BM: bone marrow, LN: lymph node, D: dead, A: alive, -: unknown.

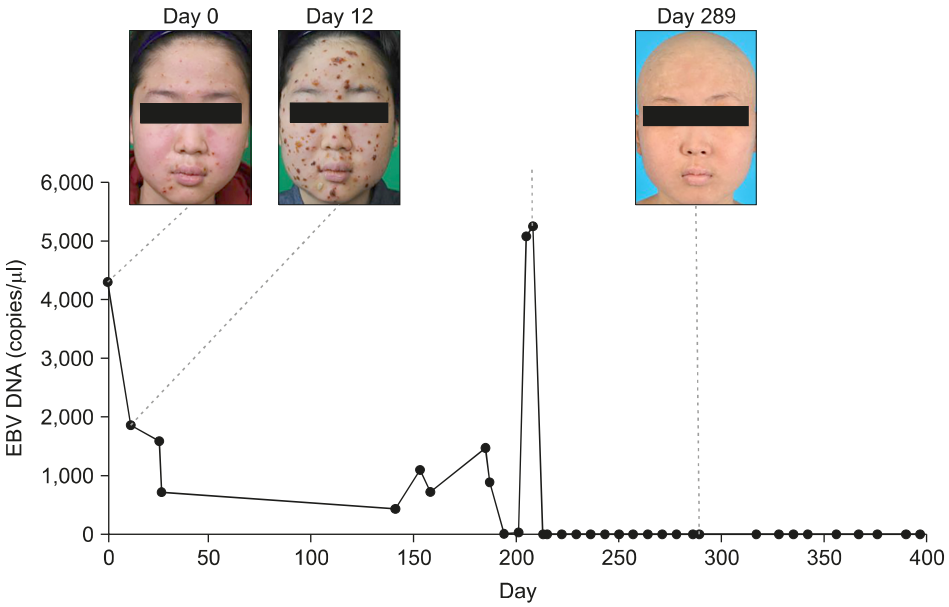

Fig. 1. Sequential changes in whole blood EBV DNA level and associated clinical course. Patient #10 initially showed facial edema and ulcers with the EBV DNA level of 4,304.16 copies/μl on day 0, and developed deep ulcers and crusts when the EBV DNA level was 1,868 copies/μl on day 12. After hematopoietic stem cell transplant on day 194, skin lesions healed as EBV DNA levels decreased to undetectable level. EBV: Epstein-Barr virus.

patients (2,290 copies/μl) than in 3 living patients (186.62 copies/μl). One of the three patients alive had a high level of EBV DNA (4,304.16 copies/μl). However, treatment with HSCT controlled systemic HVLPD, and the EBV DNA is undetectable.

Clinical photographs and whole blood EBV DNA levels over time are shown in Fig. 1. Both clinical photographs and measurements of whole blood EBV DNA of 4 patients were available for analysis. Patient #10 showed facial edema and ulcers when the EBV DNA level was 4,304.16 copies/μl on day 0, and deep ulcers, necrosis, and crusts were severe when the EBV DNA level was 1,868 copies/μl on day 12. After HSCT on day 194, facial edema improved and ulcers healed as EBV DNA declined to undetectable level. The patient remains symptom-free so far. We received the patient's consent form about publishing all photographic materials. The other two patients (#1 and #4) also showed tendency to develop severe skin lesions when EBV DNA levels were highly elevated.

DISCUSSION

In this study, we reviewed our 25-year experience with HVLPD in a single tertiary center in South Korea. Approximately 54.5% (6/11) of patients in our study had classic HVLPD that resolved with conservative treatment, while 45.5% (5/11) patients had systemic HVLPD. Four patients (36.4%), all of whom had systemic HVLPD, died of progressive disease or hemophagocytic syndrome despite chemotherapy. The remaining one patient with systemic HVLPD is currently in remission after receiving HSCT. Previous reports suggested a high risk of developing systemic disease and death in the order of Caucasian, East Asian, and Latin American patients[4,6,10,11,16]. Similarly, in this study, the mortality rate was higher than that of whites[9] and lower than that of Latin Americans[4,17].

In this study, 1 of 11 patients (9.09%) was older than 40 years and belonged to systemic HVLPD. On average, patients with classic HVLPD were younger than those with systemic HVLPD. Previous reports showed that older age was associated with a poor prognosis for EBV-positive T/NK cell lymphoproliferative disease[7,18]. Cohen et al.[19] recently reviewed that HVLPD was not confined to children or young adults and its clinical courses varied widely. Also, they reported that HVLPD with early onset had a favorable prognosis, while systemic HVLPD had a poor prognosis[18-20]. The differential diagnosis between systemic HVLPD with elderly onset and extranodal natural killer (NK)/T cell lymphoma (ENKL), nasal type can be difficult because both diseases show EBV encoded RNA in situ hybridization-positive cells and, ENKL, nasal type with extra-nasal disease also has poor prognosis[19,21]. However, these two diseases should be differentiated since ENKL, nasal type was the most common subtype of non-Hodgkin lymphoma in South Korea[22]. In our case, patient #1 did not show destructive lesion of nose and middle of face and positron emission tomography revealed that there was no hypermetabolic lesion of nasal cavity.

Patients with severe skin lesions were prone to have poor prognosis in this study. All patients showed characteristic papulovesicular lesions mainly in sun-exposed area. Five patients with systemic HVLPD had prominent facial edema, deep ulcers and necrotic skin lesions involving sun-protected areas when they first visited the hospital. In

the study reported in China[11] where the mortality rate (20%) was lower than in this study, only 4 out of 40 patients showed facial edema, but the association between facial edema and prognosis was not reported. In the Latin American study of systemic HVLPD, which developed into lymphoma[6], the mortality rate was 66.7% and all 12 patients exhibited skin lesions in both sun-exposed and sun-protected areas. Of them, 58.3% (7/12) patients had facial edema, and others showed periorbital edema or perioral edema. Therefore, we believe that severe skin lesions of HVLPD may be associated with disease progression and poor prognosis of HVLPD, which is consistent with previous reports when comprehensively considered.

The median EBV DNA level at initial diagnosis was higher in 3 dead patients than that in living patients (2,290 vs. 186.62 copies/μl). Although some studies reported the lack of correlation between EBV DNA levels and prognosis[5], several recent studies have reported that HVLPD patients carrying higher levels of EBV DNA are more likely to suffer from systemic HVLPD and have poor prognosis[9,11]. We believe that the small sample size may have resulted in inconsistent findings in various studies due to the rarity of the disease and the variable timing of initial presentation and measurement of EBV DNA in each patient. Therefore, we decided to analyze EBV DNA levels over time and evaluated the changes in clinical course. Guo et al.[23] showed that EBV DNA levels decreased during the treatment and increased to high levels upon disease progression. To the best of our knowledge, this study represents the first report involving a consecutive series of clinical changes in patients with HVLPD according to EBV DNA load. Four patients had clinical photographs and underwent continuous measurement of EBV DNA levels in this study. All four cases showed severe skin lesions, such as deep ulcers, necrosis, and prominent facial edema when EBV DNA levels were high, and skin lesions tended to improve when EBV DNA levels were low. Therefore, we suggest that the quantification of EBV DNA plays a crucial role in understanding the clinical course and determining the treatment strategy for HVLPD.

EBV DNA can be extracted from plasma, whole blood and peripheral blood mononuclear cells (PBMC). Selection of the optimal blood specimen is still controversial[24]. Most previous studies examined the association between HVLPD and EBV DNA load in PBMCs[5,16]. In addition, Liu et al.[11] found that patients with high serum EBV DNA loads had an increased risk of aggressive course. We thought that whole blood containing both cell-related and cell-free EBV DNA could also be used for diagnosis. There are many advantages to measuring EBV DNA load in whole blood over other blood specimen. Whole blood is easily obtained and contains whole blood compartment which harbor EBV. EBV load is also not affected by leukocyte variability over time, and requires only a small amount of whole blood. In addition, due to possible preparation artifacts such as cell lysis or apoptosis during preparation, serum specimen can lead to unsatisfactory and unreliable results, whereas EBV DNA load of whole blood are free from these problems[15]. Our data suggests the value of measuring EBV DNA in whole blood may be valuable for patients with HVLPD. However, there are no comparison data from large populations, so further study is needed.

The study has several limitations. First, the number of patients is so small that statistical analysis is lacking. Second, not all patients' medical photographs were acquired or EBV DNA levels measured. Third, dominant cell type wasn't analyzed although dominant lymphocyte subsets (T, T or NK cells) in the peripheral blood are known to be related to the clinical subtypes and prognosis[25].

In summary, HVLPD patients with severe skin lesions such as prominent facial edema, deep ulcers, and necrosis manifest systemic disease and poor prognosis. In addition, whole blood EBV DNA reflects the clinical course of the disease. Further studies are needed to determine the relationship between EBV DNA level and HVLPD prognosis.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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