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Hydroa vacciniforme-like lymphoproliferative disorder: A clinicopathological, immunohistochemical, and prognostic study of 24 cases in China

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Abstract

Hydroa vacciniforme-like lymphoproliferative disorder (HV-LPD) is a rare cutaneous disease associated with Epstein–Barr virus infection. We retrospectively analyzed the clinical presentation, histopathological characteristics, and prognostic study of HV-LPD in 24 Chinese patients. All patients presented with recurrent papulovesicular and necrotic eruptions on the face, neck, and extremities, with 11 showing systemic symptoms. Twenty patients were diagnosed with HV-LPD in childhood (age < 18 years) and four in adulthood (age ≥ 18 years). The median age at diagnosis was 8.5 years old (range, 2–50). Histopathology revealed variably dense lymphocyte infiltration throughout the dermis. All cases were strongly positive for CD3 and Epstein–Barr encoding region based on *in situ* hybridization. Of 18 cases with a T-cell phenotype, 15 harbored monoclonal rearrangements in T-cell receptor (TCR) genes. Four cases with a natural killer cell phenotype carried polyclonal rearrangements in TCR genes. Among 24 patients, eight (33.3%) received chemotherapy, two (8.3%) allogeneic hematopoietic stem cell transplantation, and both are currently alive without disease. The median follow-up period was 24 months (range, 7–120) and 23 patients were available: 15 (62.5%) were alive, and eight (33.3%) had died. Fourteen cases had a relapse of disease and three developed lymphoma within 24 months of diagnosis. The mean survival time of childhood-onset patients was longer than that of adult-onset patients (36.4 vs. 20.8 months). In summary, the wide clinical course and representative presentation of cases in our center reflect the pedigree characteristics of HV-LPD. Allogeneic hematopoietic stem cell transplantation should be a preferred choice for relapse and refractory patients due to the poor effect of chemotherapy. Adult-onset and high serum EBV DNA loads may indicate an increased risk of aggressive disease in patients with HV-LPD.

KEYWORDS
cutaneous lymphoma, Epstein–Barr virus, hydroa vacciniforme, hydroa vacciniforme-like lymphoproliferative disorder, risk factors

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Xinhua Wang and Yuanzheng Liang contributed equally to this work.

1 | INTRODUCTION

Hydroa vacciniforme-like lymphoproliferative disorder (HV-LPD) is a rare cutaneous disease related to chronic active Epstein–Barr virus infection (CAEBV),[1] with an incidence of approximately 0.34/100 000.[2] It was once termed hydroa vacciniforme-like lymphoma (HVLL), which was changed from lymphoma to lymphoproliferative disorder mainly due to the broad spectrum of its clinical course.[3] Although HV-LPD more commonly occurs in children and adolescents, a number of adult cases have been reported recently.[4] HV-LPD is extremely rare in Western countries.[5] Most studies to date have described HV-LPD cases in Asian and Latin American countries. The clinical manifestations of HV-LPD typically manifest as a cluster of papulovesicles at onset, progressing to a fester and followed by healing with vaccinia-like scars on sun-exposed skin, including the face, back of hands, and lower limbs. Some cases show systemic symptoms such as fever, lymphadenopathy, and hepatosplenomegaly. The disease course of HV-LPD varies: it may have an indolent clinical course with long periods of recurrent skin lesions on sun-exposed areas that tend to regress spontaneously or progress to systemic malignant lymphoma with a fatal outcome.[6–8] Here, we report 24 cases of HV-LPD encountered at our hospital and investigate specific clinical features and prognostic factors.

2 | METHODS

Twenty-four patients with HV-LPD diagnosed by the Pathology Department were admitted to the First Affiliated Hospital of Zhengzhou University from July 2012 to July 2020. The pathological diagnosis was based on the classification of hematopoietic and lymphoid tissue tumors revised by the World Health Organization (WHO) in 2016 and independently confirmed by two senior pathologists in our hospital.[3] Complete clinical and laboratory data were obtained from medical records at the time of diagnosis.

2.1 | Histopathology and immunohistochemistry (IHC)

In the Department of Pathology, a piece of tissue was locally removed from the skin lesion of all patients for histopathological examination. The specimens were fixed in 10% formaldehyde solution, embedded in paraffin, cut into 4-μm thick sections and stained with hematoxylin–eosin. Immunophenotypes of CD3, CD4, CD8, CD20, CD30, CD56, T-cell intercellular antigen (TIA)-1, granzyme B, and Ki-67 (Maixin Biotech) were examined by the immunohistochemical SP method. For the above phenotypes, positive signals were brown staining. CD3, CD4, CD8, CD20, CD30, and CD56 were found in the cell membrane, granzyme B and TIA-I in the cytoplasm, and Ki-67 in the nucleus.

2.2 | *In situ* hybridization (ISH)

The kit used detected EBV-coded RNA (EBER) by in situ hybridization (OriGene Technologies), and the specific steps were carried out according to the kit instructions. The positive signal was brown and located in the nucleus.

2.3 | T-cell receptor (TCR) gene rearrangement

T-cell clonality was analyzed by polymerase chain reaction (PCR) amplification on the basis of BIOMED-2 protocols.[9] Primers (Yuanqi Biotech) were used for TCR-β, TCR-γ, and TCR-δ chain detection. Clonality analysis of the PCR products was performed using an ABI 3500DX genetic analyzer (Applied Biosystems). All experiments included appropriate positive and negative controls. A clear single-peak fluorescence signal at the target position was determined as a monoclonal rearrangement, whereas a continuous multipeak fluorescence signal was judged as a polyclonal rearrangement.

2.4 | Follow-up study

The survival status of 24 patients was confirmed by follow-up during hospitalization or telephone every 3 months, with the follow-up period ending in February 2021. Overall survival (OS) was defined as the time from diagnosis to death or the last follow-up. The efficacy of chemotherapy was evaluated at the end of 2, 4, and 6 cycles based on the Lugano classification.[10] The POD24 group (early progressive) was defined as developing lymphoma or relapse within 24 months of diagnosis, and conversely, the reference group was those experiencing no relapse or death at least 24 months of follow-up of diagnosis. Moreover, patients censored or with less than 2 years of follow-up both were excluded from the survival analysis. Overall survival time (OS*) was calculated from time of risk-defining event for the POD24 group or counted from 2 years after diagnosis for the reference group to the last follow-up time or the time of death provided.[11]

2.5 | Statistical analyses

SPSS version 23.0 (IBM) was used to perform statistical analyses. Fisher's exact test (two-tailed) was applied to compare correlations of variables between two groups, and quantitative variables were compared by the Mann–Whitney U-test. The Kaplan-Meier method was used for survival analysis. $p < 0.05$ was considered statistically significant. Cox proportional hazards models was applied to evaluate the association between POD24 and OS*.

3 | RESULTS

3.1 | Clinical characteristics

Among the 24 cases, there were 14 males and 10 females (male : female ratio, 1.4:1). Twenty patients were children (age < 18 years) and four adults (age ≥ 18 years); the median age of disease onset was 8.5 years (range, 2–50). All patients presented with small vesicles, ulcerations, crusts, and pitted scars on the sun-exposed areas, such as the face, upper limbs, and dorsal hands (Figures 1 and 2). The skin lesions were festered, hemorrhagic, and medial necrosis in most patients, and then the lesions usually scabbed, shed, and healed within a few weeks. As new skin damages appeared in the same area repeatedly, ulcers and necrosis continued to aggravate, involving deep tissues, and formed characteristic depressed scars after healing. Sixteen patients in our study, with a medical history of not less than 2 years, all showed pitted scars on the upper and lower extremities. Six patients experienced skin lesion aggravation after sun exposure, showing a clear photodistribution, which may present their photosensitivity indirectly. However, avoiding light daily cannot prevent the occurrence of skin lesions in our patients. Facial edema was found in two patients (case 20 and 23), the swelling of periorbital and lip tissues was only noted in one patient (case 13), and recurrent oral ulcers was exhibited in three patients (case 2, 5, and 13). One patient could not extend the metacarpophalangeal joint of the right hand, with movement limitation. At the time of diagnosis, 10 patients (41.7%) had fever, 11 (41.7%) lymphadenopathy, and 11 (45.8%) hepatosplenomegaly. Two cases were complicated with hemophagocytic syndrome (case 6 and 22). Severe mosquito bite allergy (SMBA) was not observed in our series. When comparing parameters between childhood onset and adult onset, no significant correlation was observed between the two groups. The full clinical data are shown in Tables 1 and 2.

3.2 | Laboratory examination results

At the time of diagnosis, serum EBV immunoglobulin (Ig)G was positive in 20 patients. Serum EBV DNA load was evaluated in 17 cases; 12 cases (70.5%) showed serum EBV DNA ≥ 1000 copies/mL, whereas the level was normal in five cases. Lactate dehydrogenase (LDH) levels were elevated in 15 patients (62.5%), ranging 297–560 U/L. Eight patients (33.3%) had abnormal liver function, which was mainly characterized by a transaminase level increase of more than 1.5-fold.

3.3 | Histopathological results

All skin samples exhibited blister formation in the epidermis and variably dense lymphocyte infiltration throughout the entire dermis, mainly surrounding the skin appendages and blood vessels. The lymphocytes were small or medium in size and characterized by mild atypia and irregular nuclei. The background usually showed reactive infiltration, sometimes admixed with eosinophils, neutrophils, and mast cells (Figure 3). Vascular destruction was observed in one case.

3.4 | Immunohistochemical results

All cases in the biopsy showed the proliferation of lymphoid cells with expression of CD3. Cytotoxic marker TIA-1 was predominantly

FIGURE 1 Cutaneous presentations of case 21 with hydroa vacciniforme-like lymphoproliferative disorder. (a) Scattered erythema, scab, atrophic scar, and pigmentation on the face. (b) Thick black-brown scabs of different sizes on the extended side of both forearms and the back of both hands. (c) The skin of the left leg is rough, peeling with brown uneven pigmentation, thick black scabs and bloody secretions on the outer ankle

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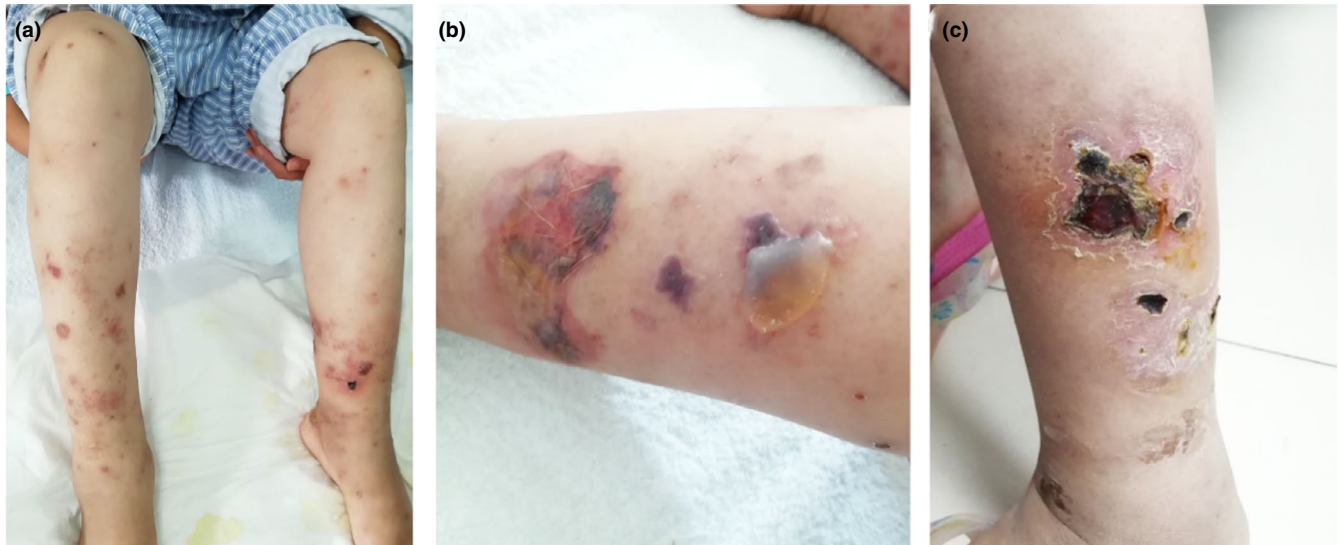
FIGURE 2 Cutaneous presentations of case 23 with hydroa vacciniforme-like lymphoproliferative disorder. (a) Scattered patchy erythema, papules, and partial surface scab and necrosis on both lower limbs. (b) Large blister in the left lower limb, tense blister wall, erythema edema, and bleeding at the base. (c) Dark brown sunken thick scab of the left lower limb with desquamation around it

positive in all 24 patients (Figure 4). Nine exhibited CD4$^+$ T cells, three were CD8$^+$ T cells, five were double positive for CD4 and CD8, one CD3$^+$ CD4$^-$CD8$^-$ T cells, and six were positive for CD56. Eight cases (44%) showed a variable number of neoplastic lymphocytes cells expressing CD30. The Ki-67 indicated variable proliferative activity of the atypical lymphoid cells ranging 10–80% (Table 3). The 24 cases were strongly positive for EBER by *in situ* hybridization. TCR gene rearrangement test was performed in 19 patients, with 15 (78.9%) showing a monoclonal T-cell population and four showing polyclonal rearrangement.

3.5 | Treatment and outcome

All 24 patients were initially treated with antiviral drugs such as arabinoside, ganciclovir, and interferon alone or in combination with oral immunosuppressants such as low-dose hormones and methotrexate. The commonly used hormones are prednisone and dexamethasone. However, the efficacy of conservative treatment in the advanced stage of the disease is poor. During the management of our patients, two cases (case 16 and 18) involved self-healing in adolescents; eight patients received chemotherapy due to repeated aggravation of skin lesions, but the efficacy was not satisfactory. In two cases (case 17 and 20), the disease progressed to EBV$^+$ natural killer (NK)/T-cell lymphoma, and the patients accepted allogeneic hematopoietic stem cell transplantation (AHSCT) when chemotherapy failed, both of whom are alive without disease.

In the pediatric group, 19 patients were available for the current status. Among them, four patients (21%) achieved complete remission (CR), three (15.8%) showed partial remission (PR), and six (31.6%) were in stable condition. Six patients (31.6%) had progressive disease (PD), and all died of the disease during the follow-up. The mortality rate of HV-LPD in the pediatric group was 31.6% (6/19). In the adult group, two patients (50%) achieved PR, and PD was observed in two patients (50%). Among the latter, one patient developed extranodal NK/T-cell lymphoma of the nasal type and died of intracranial infection during chemotherapy treatment, and the other died of the disease. The rate of HV-LPD mortality in the adult group was 50% (2/4).

The median follow-up period was 24 months (range, 7–120). During the follow-up time, one (4.2%) was lost follow up, 15 (62.5%) were alive, and eight patients (33.3%) died: six died of rapid disease progression, one (case 6) died of hemophagocytic syndrome, and one (case 21) died of extranodal NK/T-cell lymphoma of the nasal type. The mean survival time of childhood-onset patients was longer than that of adult-onset patients (36.4 vs. 20.8 months). The 1-year, 2-year, and 3-year OS rates were 95.0%, 68.6%, and 55.4%, respectively, excluding one patient who was lost during follow-up.

3.6 | Prognosis analysis

We compared OS rates between the clinical factors, as well as the pathological to confirm their association with mortality (Figure 5). However, Kaplan–Meier analysis showed that there was no statistical difference in EBV-infected T cells compared with those with NK cell infection (p = 0.544) in OS rate. There was no statistical difference in OS rate among serum EBV DNA load ≥ 1000 copies/mL and serum EBV DNA load < 1000 copies/mL (p = 0.155). Fever, lymphadenopathy, hepatosplenomegaly, LDH level elevation, abnormal liver function, and chemotherapy were all not significant factors with mortality.

TABLE 1 The clinical characteristics of 24 Chinese patients with HV-LPD

Case	Age of onset	Age at diagnosis, y (history)	Sex	Cutaneous presentation	Systematic symptoms at diagnosis	Serum EBV DNA load (copies/mL)	Treatment	Disease development course after diagnosis	OS, m	Status of last follow-up
1	Child-onset	2 (10 m)	M	Papules, vesicles, and pitted scars throughout the body	Fever	2.34E+05	Antiviral drugs, steroids	PD	14	D
2	Child-onset	3 (2y)	F	Papules, vesicles, and pitted scars throughout the body; ulcer on the tongue	Fever, hepatosplenomegaly, lymph node enlargement	7.52E+02	Antiviral drugs, steroids, chemotherapy	PR → PD → SD	20	A
3	Child-onset	3 (2y)	F	Papules, vesicles, and pitted scars on the face and limb	None	5.00E+02	Antiviral drugs, steroids	PR	8	A
4	Child-onset	4 (3 m)	M	Papules, vesicles, and pitted scars throughout the body	Lymph node enlargement	NA	Antiviral drugs → herbal treatment	PR → PD → SD	26	A
5	Child-onset	5 (2y)	M	Vesicles and pitted scars on the trunk, oral ulcer	None	1.43E+03	Antiviral drugs, steroids → herbal treatment → chemotherapy	PR → PD (relapse)	22	D
6	Child-onset	6 (9 m)	F	Papules and vesicle on the abdomen, hemophagocytic syndrome	Fever, hepatosplenomegaly, lymph node enlargement	1.34E+04	Antiviral drugs, steroids	PD	23	D
7	Child-onset	6 (4y)	F	Papules, vesicles, and pitted scars throughout the body	Fever, lymph node enlargement	1.43E+03	Antiviral drugs, steroids → thalidomide	NA	NA	L
8	Child-onset	7 (2y)	M	Papules, vesicles, and pitted scars throughout the body	None	NA	Steroids	PD	13	D
9	Child-onset	7 (5y)	F	Papules, vesicles, and pitted scars on the face and upper limb	Fever, hepatosplenomegaly	4.40E+03	Antiviral drugs, steroids	PD	13	D
10	Child-onset	7 (6y)	M	Papules, vesicles, and pitted scars on the face and hands	Lymph node enlargement	<5.00E+02	Antiviral drugs, steroids	PR → PD → SD	23	A
11	Child-onset	8 (1y)	M	Papules and vesicles on the face	None	5.00E+02	Antiviral drugs, steroids	PR → PD → SD	10	A
12	Child-onset	8 (3y)	F	Papules, vesicles, and pitted scars on the face and hands	None	NA	Antiviral drugs, steroids	PR → PD (relapse) → PR	42	A
13	Child-onset	9 (2y)	M	Papules, vesicles, and pitted scars on upper limb, periorbital edema, lip swelling, oral ulcer	None	<5.00E+02	Antiviral drugs, steroids → chemotherapy	PR → PD	25	D

(Continues)

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TABLE 1 (Continued)

Case	Age of onset	Age at diagnosis, y (history)	Sex	Cutaneous presentation	Systematic symptoms at diagnosis	Serum EBV DNA load (copies/mL)	Treatment	Disease development course after diagnosis	OS, m	Status of last follow-up
14	Child-onset	9 (5y)	F	Papules, vesicles, and pitted scars on the face and limb	Fever, hepatosplenomegaly	2.20E+07	Antiviral drugs, steroids	PR → PD → SD	56	A
15	Child-onset	11 (6 m)	M	Papules, vesicles on the trunk and limb	Fever, lymph node enlargement	3.96E+03	Antiviral drugs, steroids, and methotrexate	PR → PD → SD	19	A
16	Child-onset	11 (1y)	M	Papules, vesicles on the face	Hepatosplenomegaly, lymph node enlargement	NA	Steroids → herbal treatment	CR	42	A
17	Child-onset	12 (6 m)	M	Papules, vesicles, and pitted scars throughout the body	Fever, hepatosplenomegaly	7.55E+06	Antiviral drugs, steroids → chemotherapy → AHSCT	PR → PD (progressed to EBV+ T-cell lymphoma) → CR	35	A
18	Child-onset	12 (10y)	F	Papules, vesicles, and pitted scars on the limb	Lymph node enlargement	NA	Antiviral drugs, steroids	CR	103	A
19	Child-onset	14 (4y)	M	Papules, vesicles, and pitted scars on the face and limb	Hepatosplenomegaly, lymph node enlargement	4.21E+05	Antiviral drugs, steroids → chemotherapy	PR → PD → PR	120	A
20	Child-onset	14 (6y)	M	Papules, vesicles, and pitted scars on the face and ear; facial edema	Fever, hepatosplenomegaly, lymph node enlargement	NA	Antiviral drugs, steroids → chemotherapy → radiotherapy → AHSCT	PR → PD (Progressed to EBV+T-cell lymphoma) → CR	76	A
21	Adult-onset	22 (3y)	M	Papules, vesicles, and pitted scars throughout the body	Hepatosplenomegaly	NA	Steroids → chemotherapy	PR → PD (progressed to extranodal NK/T-cell lymphoma, nasal type)	30	D
22	Adult-onset	30 (1 m)	M	Ulcer on the anterior chest wall and lower limbs; Hemophagocytic syndrome	Fever, hepatosplenomegaly	1.54E+05	Antiviral drugs, steroids → chemotherapy	PR	9	A
23	Adult-onset	36 (1y)	F	Papules, vesicles, and pitted scars on the lower limb, facial edema	None	<5.00E+02	Steroids → chemotherapy	PR → PD (relapse) → PR	32	A
24	Adult-onset	50 (4y)	F	Papules, vesicles, and pitted scars throughout the body	Hepatosplenomegaly, lymph node enlargement	1.83E+07	Antiviral drugs	PD	12	D

Abbreviations: A, alive; AHSCT, allogeneic hematopoietic stem cell transplantation; CR, complete remission; D, dead; HV-LPD, hydroa vacciniforme-like lymphoproliferative disorder; L, lost follow-up; M, month; NA, not available; OS, overall survival; PD, progression of disease and PD is defined as recurrence or developing lymphoma; PR, partial remission; SD, stable disease; Y, year.

TABLE 2 Clinical and pathological characteristics of 24 HV-LPD patients based on the age of onset

	Total N = 24, n (%)	Child-onset N = 20, n (%)	Adult-onset N = 4, n (%)	p
Sex (male/female)	14/10	12/8	2/2	1.000
Age at onset (median, Y)	8.5	7.5	33	
Period from onset to diagnosis (median, M)	24	24	24	0.533
Symptoms at diagnosis				
Facial edema	3 (12.5)	2 (10.0)	1 (25)	0.437
Oral ulceration	3 (12.5)	3 (15)	0	1.000
Fever	10 (41.7)	9 (45.0)	1 (25.0)	0.615
Lymphadenopathy	11 (45.8)	11 (55.0)	0	1.000
Hepatosplenomegaly	11 (45.8)	8 (40.0)	3 (75.0)	0.300
Laboratory test results at diagnosis				
Serum EBV DNA load ≥ 1000 copies/mL (n = 17)	11 (64.7)	9 (64.3)	2 (66.7)	1.000
LDH level elevation (n = 20)[a]	15 (75)	12 (70.6)	3 (100.0)	0.539
Abnormal liver function (n = 21)[b]	8 (38.1)	6 (35.3)	2 (50.0)	0.618
Pathological results				
EBV-infected cell phenotype (T:NK)	18:6	15:5	3:1	1.000
TCR gene monoclonal rearrangement (n = 19)	15 (78.9)	12 (80)	3 (75)	1.000
Therapy				
Chemotherapy	8 (33.3)	5 (25)	3 (75)	0.721
AHSCT	2 (8.3)	2 (10)	0 (0)	1.000
Progression of disease within 24 months (POD24)				
Yes	9	7	2	0.615
No	15	13	2	0.615
Status				
Alive	15 (65.2)	13 (65)	2 (50)	0.589
Dead	8 (34.8)	6 (30)	2 (50)	0.589

Abbreviations: AHSCT, allogeneic hematopoietic stem cell transplantation; EBER, Epstein–Barr virus encoded RNA; HV-LPD, hydroa vacciniforme-like lymphoproliferative disorder; M, month; TCR, T-cell receptor; Y, year.

p: child-onset vs. adult-onset; $p < 0.05$ was considered statistically significant.

[a]LDH level elevation is defined as the level of lactate dehydrogenase in the serum higher than 240 U/L.

[b]Abnormal liver function was characterized by a transaminase level increase of more than 1.5-fold.

## 3.7 | POD24 and its relationship with the prognosis of HV-LPD patients

Of the 24 patients with HV-LPD, 14 cases had a relapse of disease and three developed lymphoma within 24 months of diagnosis, that is, the POD24 group (70.8%). Three cases (12.5%) with no relapse or death during the first 24 months after diagnosis were the reference group. One cases (4.2%) was lost to follow-up. Three patients (12.5%) were of less than 2 years of follow-up. Eight patients (33.3%) in the POD24 group died during follow-up.

Overall survival time rate at 2 years in the POD 24 group was 50.8%, compared with 66.7% for patients without early progression in the reference group (Figure 6). To further characterize the effect of POD24, the Cox proportional hazards models presented that patients who experienced early progression within 2 years (POD24) had no increased risk of death compared with those whose progression occurred after 2 years ($p = 0.964$; hazard ratio, 1.050; 95% confidence interval, 0.129–8.559).

4 | DISCUSSION

The nomenclature of HVLL originated from class hydroa vacciniforme (cHV). cHV is a photodermatosis that usually occurs in
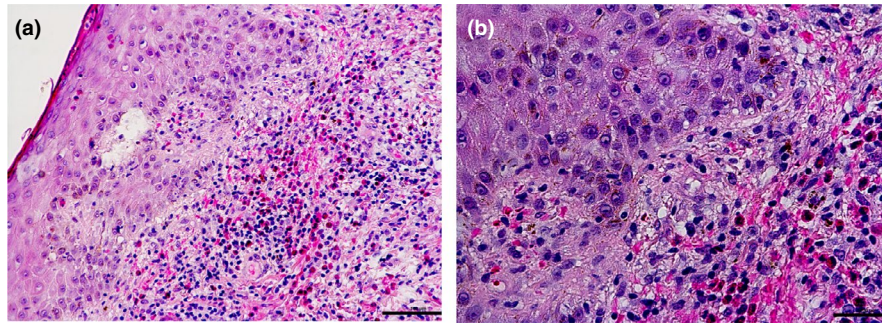
FIGURE 3 Histomorphological features on a skin biopsy sample of case 23 with hydroa vacciniforme-like lymphoproliferative disorder. (a) Epidermis blister formation and variably dense lymphocytes infiltration in the dermis (hematoxylin–eosin [HE], original magnification ×200). (b) Lymphocytes in the dermis are atypical, small to medium size, irregular nucleus (HE, ×400)
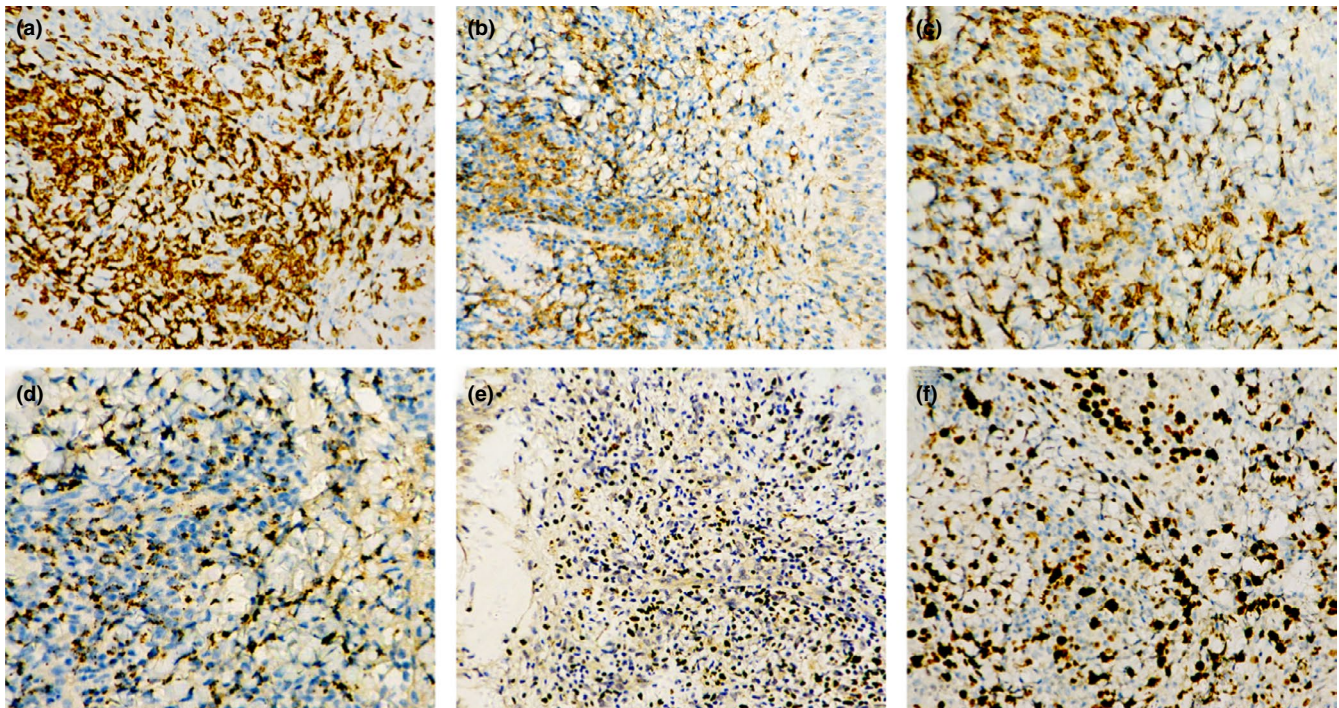
FIGURE 4 Immunophenotypical features of case 21 with hydroa vacciniforme-like lymphoproliferative disorder. (a–f) Positive expression of CD3, CD4, CD8, TIA-1, EBER, and Ki-67 proliferation index, respectively (hematoxylin–eosin, original magnification ×200)

pediatric patients and involves self-limited papulovesicle eruptions located in sun-exposed areas, with no apparent systemic manifestations. Although the clinical presentation of HVLL is similar to that of cHV, the skin lesions in the former are more severe and extensive, with systemic symptoms including fever, hepatosplenomegaly, and lymphadenopathy, and the prognosis is worse.[12] Thus, the 4th WHO classification introduced HV-LPD, which encompasses the broad spectrum of clinical manifestations. All patients with HV-LPD in our study had a similar disease process, from a mild stage to disease progression, which is consistent with the above description.

Chen et al. found that ultraviolet light plays a crucial role in the malignant transformation of HV-LPD and that sunlight can induce or aggravate skin lesions.[13] In our study, six of the patients experienced skin lesion aggravation after sun exposure. Verneuil et al. reported that the serum EBV DNA load increases in the active stage of the disease. The median serum EBV DNA load in patients with systemic HV-LPD is higher than that in classic HV-LPD.[4] In our study, the level of serum EBV DNA load clearly increased in eight patients when some new blisters started to appear but decreased with antivirus treatment, which suggested that the serum EBV DNA load is related to disease activity. No patients with normal EBV DNA loads died of the disease, whereas 50.0% (6/12) of our patients who died had very high serum EBV DNA loads, suggesting that patients with high serum EBV DNA loads have a more aggressive disease.

TABLE 3 Results of immunophenotype and molecular analysis in 24 patients with HV-LPD

| Case	CD3	CD4	CD8	CD56	CD7	TIA-1	GraB	CD20	Ki-67 (%)	EBER	TCR gene rearrangement
1	+	−	+	−	+	+	−	−	20	+	ND
2	+	−	−	+	+	+	+	−	100	+	−
3	+	−	+	−	+	ND	ND	−	15	+	+
4	+	+	−	ND	ND	+	−	−	10	+	+
5	+	−	−	+	+	+	−	−	30	+	−
6	+	+	−	−	+	+	−	−	60	+	+
7	+	−	−	+	ND	+	ND	−	40	+	−
8	+	+	+	−	+	+	+	−	40	+	+
9	+	+	−	−	ND	+	−	−	20	+	+
10	+	+	−	−	ND	+	−	−	15	+	+
11	+	−	+	−	+	+	−	−	60	+	ND
12	+	+	−	−	ND	+	−	−	20	+	+
13	+	+	−	−	+	+	−	−	10	+	+
14	+	−	−	+	−	+	−	−	70	+	ND
15	+	+	+	−	+	+	−	−	40	+	+
16	+	−	−	ND	+	+	+	−	30	+	+
17	+	+	+	−	+	ND	ND	−	40	+	+
18	+	+	−	−	ND	−	−	−	50	+	ND
19	+	+	+	−	ND	+	+	−	40	+	+
20	+	−	−	+	+	+	−	−	70	+	ND
21	+	+	+	−	+	+	−	−	40	+	+
22	+	−	−	+	+	+	+	−	56	+	−
23	+	+	−	−	ND	+	−	−	60	+	+
24	+	+	−	−	ND	+	+	−	80	+	+

Abbreviations: EBER, Epstein–Barr virus encoded RNA; GraB, Granzyme B; HV-LPD, hydroa vacciniforme-like lymphoproliferative disorder; ND, not done; TCR, T-cell receptor; TIA-1, T-cell-restricted intracellular antigen.

In our study, HV-LPD patients were EBER positive, directly confirming EBV infection of lymphocytes histologically. This phenomenon supports the view that EBV-infected T or NK cells play a pivotal role in the pathogenesis of HV-LPD.[14,15] Among our patients, nine exhibited CD4^{+} T cells, three CD8^{+} T cells, five CD4^{+} CD8^{+} T cells, one CD3^{+} CD4^{−}CD8^{−} T cells, and six CD56^{+} cells. A number of reports have described patients with the NK-cell phenotype and found that the disease course of the CD56 phenotype is more indolent than that of the T-cell phenotype.[7,16–18] In our study, patients with the CD56 phenotype were all alive at 24 months, and only one patient had disease progression. However, our survival analysis demonstrated no significant difference in OS rate for those with the T- or NK-cell lineage, which may account for our small sample size.

A total of 78.9% (15/19) of the patients in our study exhibited TCR gene monoclonal rearrangement, and we observed that some patients with TCR gene monoclonal rearrangement had a favorable outcome. Therefore, we must emphasize that it is necessary to clarify the nature of HV-LPD based on comprehensive consideration.

A variety of therapies have been attempted, including antiviral drugs, corticosteroids, chemotherapy, radiotherapy,

epigenetic regulation drugs, and hematopoietic stem cell transplantation; however, there are no established treatment guidelines for HV-LPD.[6,7,17] In our study, all patients with HV-LPD used antiviral drugs or steroids at the early-onset stage, but the effect was temporary. Moreover, a minority of patients chose Chinese herbal treatment. Sangueza et al. reported a retrospective analysis of 12 HV-LPD patients who received chemotherapy, with a median survival time of only 5.3 months; eight patients (66.7%) died of disease progression, indicating that chemotherapy is associated with poor prognosis in patients with HV-LPD.[8] In our study, the median survival time of eight patients who received chemotherapy was 31 months; one patient died of extranodal NK/T-cell lymphoma and one died of rapid disease progression, suggesting that chemotherapy may be more effective and prolong survival time in Chinese HV-LPD patients than in Latin American patients. Further research on which patients can benefit from chemotherapy is imperative. Only two patients received AHSCT; both achieved complete remission and are alive without disease. This supports the previous report that HSCT is a curative treatment for HV-LPD.[17,19] However, patients with relapsed or refractory HV-LPD in our hospital may prefer to receive
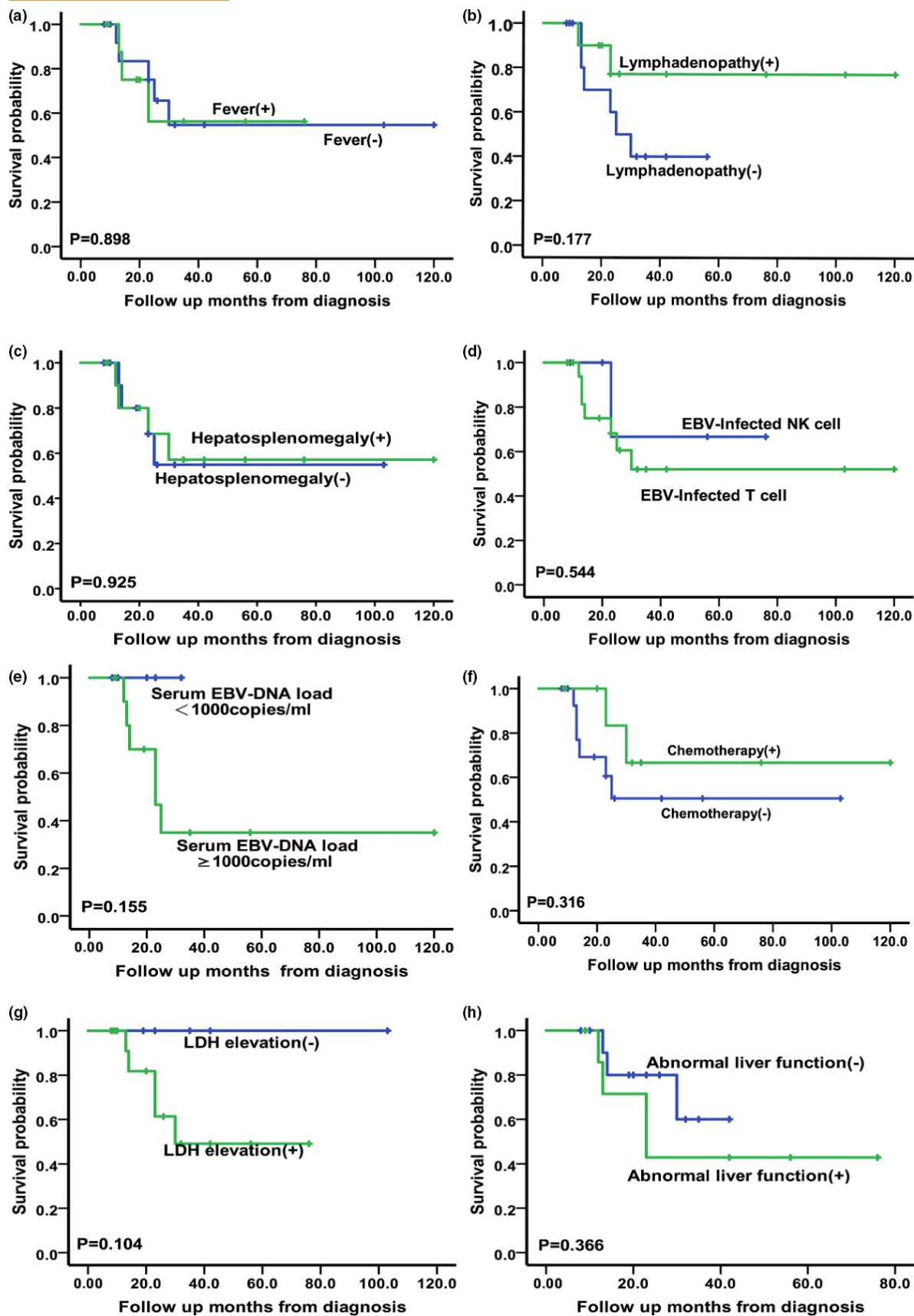
FIGURE 5 Kaplan–Meier survival curves of patients with hydroa vacciniforme-like lymphoproliferative disorder according to clinicopathological category. (a) Fever; (b) lymphadenopathy; (c) hepatosplenomegaly; (d) EBV-infected cell type (T vs. NK); (e) high and low serum EBV DNA load; (f) with and without chemotherapy; (g) with and without LDH level elevation; (h) with and without liver dysfunction
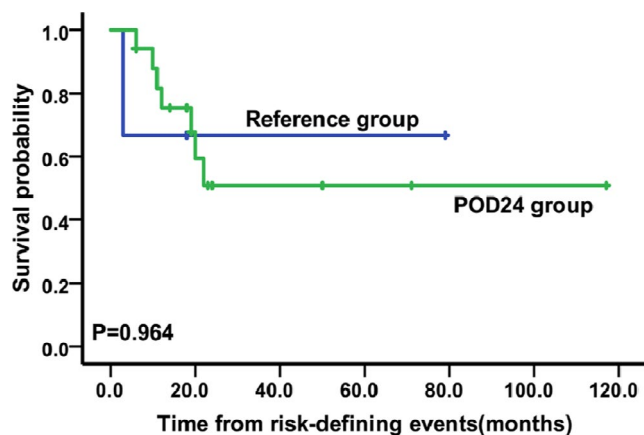
FIGURE 6 Overall survival for patients with POD24 group versus the reference group

chemotherapy regimens, as opposed to AHSCT, mainly for economic reasons. We used chidamide combined with etoposide in two cases for which CHOP chemotherapy failed (case 21 and 23); in these cases, the skin redness and swelling disappeared, the rash decreased, and the systemic symptoms were controlled. Both patients achieved PR for almost 3 months. Therefore, drugs targeting epigenetic regulation may constitute a new alternative, but their specific mechanism and efficacy are not clear, and we need to collect more data for further analysis.

Among our patients, the mortality rate of HV-LPD was 50% in the adult group compared to 31.6% in the pediatric group. Moreover, the mean survival time of childhood-onset patients was longer than that of adult-onset patients (36.4 vs. 20.8 months), suggesting that adult-onset patients with HV-LPD may have an increased risk of aggressive disease, which was consistent with previous report.[19] We can demonstrate that patients with early progression of disease (POD24) had poor survival; 2-year OS* rate was 50.8%, while in the reference group was 66.7%. However, the two groups had no significantly statistical difference in OS*. Kaplan–Meier analysis suggested that abnormal liver function was not a significant factor with mortality in our study, which may be a bias due to a limitation with sample size, so we will continue to accumulate more clinical cases to perform a study with a large sample patients of HV-LPD in the future.

In summary, the wide clinical course and representative presentation of cases in our center reflect the pedigree characteristics of HV-LPD, although the numbers were not enough. AHSCT should be a preferred choice for relapse and refractory patients due to the poor effect of chemotherapy. We demonstrate that adult-onset and high serum EBV DNA loads may indicate an increased risk of aggressive disease, but long-term follow-up is needed to accumulate more clinical data to further analyze the malignant transformation of HV-LPD. Moreover, future studies focused on genetic mutations might contribute to a better understanding of the biological behavior of HV-LPD and to establishing a more effective therapeutic strategy for these patients.

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