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

Xinhua Wang1 | Yuanzheng Liang1 | Yanxin Yang1 | Wencai Li2 | Guannan Wang2 | Shuangfeng Wang3 | Yan Li4 | Mingzhi Zhang1

1Department of Oncology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China
2Department of Pathology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China
3Department of Dermatology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China
4Department of Dermatology, Henan Provincial People’s Hospital, Zhengzhou, China

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
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.\(^5\) 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-1 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
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 autologous 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 $\geq$ 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.
| 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 | 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 | 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 | 23 | A |
| 11   | Child-onset 8 (3y) | M | Papules and vesicles on the face | None | 5.00E+02 | Antiviral drugs, steroids | PR → PD | 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)
| 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)   | 15 (75)             | 12 (70.6)                 | 3 (100.0)                | 0.539 |
| Abnormal liver function (n = 21) | 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 case (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
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. 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. 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. 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.
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. 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. 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. 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. 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. However, patients with relapsed or refractory HV-LPD in our hospital may prefer to receive

### 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    | ND   | −    | 40        | +    | −                      |
| 8    | +   | +   | +   | −    | +   | +     | −    | −    | 40        | +    | +                      |
| 9    | +   | +   | −   | ND   | ND  | −     | −    | −    | 20        | +    | +                      |
| 10   | +   | +   | −   | ND   | ND  | +     | −    | −    | 15        | +    | +                      |
| 11   | +   | −   | +   | −    | +   | +     | −    | −    | 60        | +    | ND                     |
| 12   | +   | +   | −   | ND   | ND  | −     | −    | −    | 20        | +    | +                      |
| 13   | +   | +   | −   | +    | −   | +     | −    | −    | 10        | +    | +                      |
| 14   | +   | −   | −   | +    | −   | +     | −    | −    | 70        | +    | ND                     |
| 15   | +   | +   | +   | −    | +   | +     | −    | −    | 40        | +    | +                      |
| 16   | +   | −   | −   | ND   | ND  | +     | +    | −    | 30        | +    | +                      |
| 17   | +   | +   | +   | −    | +   | +     | ND   | ND   | 40        | +    | +                      |
| 18   | +   | +   | −   | ND   | ND  | −     | −    | −    | 50        | +    | ND                     |
| 19   | +   | +   | +   | −    | ND  | +     | −    | −    | 40        | +    | +                      |
| 20   | +   | −   | −   | +    | +   | +     | −    | −    | 70        | +    | ND                     |
| 21   | +   | +   | +   | −    | +   | +     | −    | −    | 40        | +    | +                      |
| 22   | +   | −   | +   | −    | ND  | +     | +    | −    | 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.
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.
chemotherapy regimens, as opposed to AHSC, 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. AHSC 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.

ACKNOWLEDGMENTS
This work was supported by the National Natural Science Foundation of China (grant no. 81970184) and National Science and Technology Major Project of China (grant no. 2020ZX09201-009).

CONFLICT OF INTEREST
None declared.

ORCID
Mingzhi Zhang https://orcid.org/0000-0003-3581-551X

REFERENCES
1. Cohen J, Iwatsuki K, Ko Y, Kimura H, Manoli I, Ohshima K, et al. Epstein-Barr virus NK and T cell lymphoproliferative disease: report of a 2018 international meeting. Leukemia Lymphoma. 2020;61:808–19.
2. Gupta G, Man I, Kemmett D. Hydroa vacciniforme: A clinical and follow-up study of 17 cases. J Am Acad Dermatol. 2000;42:208–13.
3. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127:2375–90.
4. Verneuil L, Gouarin S, Comoz F, Agbalika F, Creveuil C, Varna M, et al. Epstein-Barr virus involvement in the pathogenesis of hydroa vacciniforme: an assessment of seven adult patients with long-term follow-up. Br J Dermatol. 2010;163:174–82.
5. Cohen JI, Manoli I, Dowdell K, Krogmann TA, Tamura D, Radecki P, et al. Hydroa vacciniforme-like lymphoproliferative disorder: an EBV disease with a low risk of systemic illness in whites. Blood. 2019;26:2753–64.
6. Liu Y, Ma C, Wang G, Wang L. Hydroa vacciniforme-like lymphoproliferative disorder: clinicopathologic study of 41 cases. J Am Acad Dermatol. 2019;81:534–40.
7. Magaña M, Massone C, Magaña P, Cerroni L. Clinicopathologic features of hydroa vacciniforme-like lymphoma: a series of 9 patients. Am J Dermatopathol. 2016;38:20–5.
8. Sangueza M, Plaza JA. Hydroa vacciniforme–like cutaneous T-cell lymphoma: clinicopathologic and immunohistochemical study of 12 cases. J Am Acad Dermatol. 2013;69:112–9.
9. Jv D, Langerak A, Brüggemann M, Evans P, Hummel M, Lavender F, et al. Design and standardization of PCR primers and protocols for detection of clonal immunoglobulin and T-cell receptor gene recombinations in suspect lymphoproliferations: report of the BIOMED-2 Concerted Action BMH4-CT98-3936.
10. Casulo C, Byrtek M, Dawson K, Zhou X, Farber C, Flowers C, et al. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: an analysis from the National LymphoCare Study. J Clin Oncol. 2015;33:2516–22.
11. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano Classification. J Clin Oncol. 2014;32:3059–67.
12. Casulo C, Byrtek M, Dawson K, Zhou X, Farber C, Flowers C, et al. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: an analysis from the National LymphoCare Study. J Clin Oncol. 2015;33:2516–22.
13. Chen C-C, Chang K-C, Medeiros LJ, Lee JY-Y, Hydroa vacciniforme: a distinctive form of Epstein-Barr virus-associated T-cell lymphoproliferative disorders. Eur J Dermatol. 2019;29:21–8.
14. Ohshima K, Kimura H, Yoshino T, Kim CW, Ko YH, Lee S-S, et al. Proposed categorization of pathological states of EBV-associated T/natural killer-cell lymphoproliferative disorder (LPD) in children
and young adults: Overlap with chronic active EBV infection and infantile fulminant EBV T-LPD. *Pathol Int.* 2008;58:209–17.

15. Quintanilla-Martinez L, Ridaura C, Nagl F, Sáez-de-Ocariz M, Durán-Mckinster C, Ruiz-Maldonado R, et al. Hydroa vacciniforme-like lymphoma: a chronic EBV+ lymphoproliferative disorder with risk to develop a systemic lymphoma. *Blood.* 2013;122:3101–10.

16. Doeden K, Molina-Kirsch H, Perez E, Warnke R, Sundram U. Hydroa-like lymphoma with CD56 expression. *J Cutan Pathol.* 2008;35:488–94.

17. Guo N, Chen Y, Wang Y, Huang Y, Feng Y, Li M, et al. Clinicopathological categorization of hydroa vacciniforme-like lymphoproliferative disorder: an analysis of prognostic implications and treatment based on 19 cases. *Diagn Pathol.* 2019;14:82–92.

18. Xu Z, Lian S. Epstein-Barr virus-associated hydroa vacciniforme-like cutaneous lymphoma in seven Chinese children. *Pediatr Dermatol.* 2010;27:463–9.

19. El-Mallawany N, Geller L, Bollard C, Wistinghausen B, Mussai F, Wayne A, et al. Long-term remission in a child with refractory EBV+ hydroa vacciniforme-like T-cell lymphoma through sequential matched EBV+-related allogeneic hematopoietic SCT followed by donor-derived EBV-specific cytotoxic T-lymphocyte immunotherapy. *Bone Marrow Transplant.* 2010;46:759–61.

How to cite this article: Wang X, Liang Y, Yang Y, et al. Hydroa vacciniforme-like lymphoproliferative disorder: A clinicopathological, immunohistochemical, and prognostic study of 24 cases in China. *J Dermatol.* 2021;00:1–12. [https://doi.org/10.1111/1346-8138.15944](https://doi.org/10.1111/1346-8138.15944)