Hydroa vacciniforme–like lymphoproliferative disorder: Clinicopathologic study of 41 cases

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Background: Hydroa vacciniforme–like lymphoproliferative disorder (HVLLPD) is a rare Epstein-Barr virus (EBV)-related disease that is usually found in East Asians and Latin Americans.

Objective: To report the characteristics of HVLLPD in Chinese patients.

Methods: Retrospective analysis of patients with HVLLPD from a single institute.

Results: A total of 41 patients were enrolled. All patients presented with papulovesicular lesions, mainly distributed on sun-exposed areas, with 26 patients showing systemic symptoms. Follow-up data were available for 20 patients, 16 patients were alive, and 4 patients died. Of the 4 deceased patients, 3 had taken a serum EBV DNA test that showed high viral loads. These 3 patients also received chemotherapy. Histopathology was characterized by dense proliferation of lymphocytes in the dermis. Angiotropism or angiodestruction was found in the majority of patients, whereas prominent cellular polymorphism was noticed in only 4 patients. All patients were positive for CD3, TIA1 cytotoxic granule associated RNA binding protein, and EBV-encoded RNA in situ hybridization.

Limitations: This was a retrospective study.

Conclusions: HVLLPD in Chinese patients showed indolent behavior in the majority of cases, which differed from the characteristics of HVLLPD in Latin Americans. Patients with high serum EBV DNA loads had an increased risk of their disease evolving into aggressive disease. Chemotherapy should not be considered as first-line treatment for most Chinese patients. (J Am Acad Dermatol 2019;81:534-40.)

Key words: cutaneous lymphoma; Epstein-Barr virus; hydroa vacciniforme; hydroa vacciniforme–like lymphoma; hydroa vacciniforme–like lymphoproliferative disorder.

Hydroa vacciniforme–like lymphoproliferative disorder (HVLLPD) is an Epstein-Barr virus (EBV)-associated disease, usually occurring in East Asia[1] and Latin America.[2,3] Many names, including hydroa vacciniforme,[4] severe hydroa vacciniforme,[5] hydroa vacciniforme–like lymphoma,[2] and hydroa-like cutaneous T-cell lymphoma,[6] have been used for this disease. The 2016 edition of the World Health Organization classification of hematopoietic and lymphoid tumors used the name HVLLPD.[3,7] HVLLPD normally occurs in children and young adolescents but is also found in adults[8] and rarely in the elderly.[9-11] It is characterized by vesicles or papules on sun-exposed areas of the body, including the face and dorsal aspect of the hands, which usually heal with pitted scars. Most patients develop systemic symptoms, including fever, wasting, lymphadenopathy, and hepatosplenomegaly.[1,6,12] HVLLPD is usually a rather aggressive disease, with fatal outcomes in most Latin American

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patients,[2,12-16] whereas most patients in East Asia have been shown to survive this disease.[8,17-19] In this report, we present our observations of 41 patients with HVLLPD in a single institute in China.

METHODS

This study was approved by the institutional review board of Xijing Hospital, Xi'an, China (No. KY20182028-1). All patients were seen in the dermatology department between 2007 and 2017. Diagnosis of HVLLPD was confirmed according to the 2016 edition of the World Health Organization classification of hematopoietic and lymphoid tumors.[7] Only patients with an available clinical record, clinical photography, and skin specimens with sufficient tissue for further studies were included. Hematoxylin and eosin–stained tissue sections were analyzed. Immunohistochemical studies were performed with antibodies against CD3, CD4, CD5, CD7, CD8, CD20, CD30, CD56, TIA1 cytotoxic granule associated RNA binding protein, and Ki67. Appropriate positive and negative controls were included for all antibodies tested. EBV-encoded RNA (EBER) in situ hybridization was performed with a kit from ZSGB-Bio (Beijing, China). Testing for T-cell receptor gene (*TCR*) rearrangement was performed by using the standard BIOMED-2 method.[20]

CAPSULE SUMMARY

- Hydroa vacciniforme–like lymphoproliferative disorder shows aggressive behavior in the majority of Latin Americans patients, whereas it shows chronic progression and a more indolent behavior in the majority of Chinese patients.
- Aggressive treatments, such as chemotherapy, should not be encouraged in the majority of Chinese patients.

RESULTS

Clinical features

The patients included 28 children (age, <18 years) and 13 adults (age, ≥18 years) (mean age, 14.6 years; median age, 13 years); 15 were male and 26 were female. Age of onset ranged from 1 to 42 years (mean age, 8.6 years; median age, 5 years), with 6 patients developing HVLLPD as an adult. The duration of clinical symptoms before diagnosis ranged from 1 month to 25 years (mean, 12.5 years).

All patients had skin lesions located in sun-exposed areas, including the face, auricle, dorsal aspect of the hand, and V-area of the upper part of the chest. Lesions usually were composed of small papules, vesicles, crusts, erosions, small ulcerations, and pitted scars (Fig 1). Facial edema was found in 7 patients. Prominent periorbital or perioral edema was not found in our patients. A total of 17 patients showed lesions in sun-protected areas, with all 17 having lesions on the arms and legs and 10 having lesions on the trunk. In

Fig 1. Hydroa vacciniforme–like lymphoproliferative disorder. Cutaneous presentation of a patient presented with papules and crusts at age 14 years. The patient showed relapse of lesions at age 22 years but showed no prominent papules and vesicles found at age 24 years.

Abbreviations used:

EBER: Epstein-Barr Virus–encoded RNA
EBV: Epstein-Barr virus
HVLLPD: hydroa vacciniforme–like lymphoproliferative disorder

21 patients, development of skin lesion was triggered or aggravated by sun exposure. Hypersensitivity to mosquito bites existed in 13 patients.

Otorhinolaryngologic symptoms were seen in 7 patients, which included nasal obstruction, nasal ulceration, dyspnea, rhinorrhea, otorrhea, hearing loss, and tinnitus. Nine patients developed ocular symptoms, including corneal nebula, conjunctival swelling, photophobia, tearing, and decreased visual acuity. One patient showed relapsing scrotal swelling and testicular pain during flare of skin lesions.

Five patients (12%) showed symptoms of cutaneous or mucosal bacterial infection, which usually presented as a prominent crust, erosion, or ulceration (Fig 2). Bacterial infections were confirmed by culture in all 5 patients, and their lesions healed with antibiotic therapy. In all, 26 patients (64%) showed systemic symptoms, including fever (body temperature >38.5°C) in 23 patients (56%), lymphadenopathy in 14 patients (34%), and hepatosplenomegaly in 7 patients (17%). EBV viral capsid antigen IgG antibodies were present in all 25 patients tested, whereas EBV viral capsid antigen IgM antibodies were present in only 1 of the 25 patients tested. Serum EBV DNA load was elevated in 14 of the 25 tested patients (>5000 copies/mL). Total serum IgE levels were elevated in 11 of the 13 tested patients (range, 17.2-83,700 IU/mL; mean, 15,600 IU/mL; normal value, <100 IU/mL).

Follow-up information on 20 patients was available; 16 of them were alive and 4 had died of their HVLLPD (Table I). Most patients in this study were treated with conservative therapy, which included sun protection, injections of interferon-α, topical corticosteroids, low-dose oral corticosteroids, or antibiotics when a bacterial infection was present. Only 3 patients received chemotherapy, including 1 patient who had a hematopoietic stem cell transplantation. The 3 patients who received aggressive treatments died of the disease.

Histopathology

Most patients showed dense lymphocyte infiltration in the dermis that was associated with reticular degeneration, spongiosis, or necrosis of the epidermis. In 21 patients focal areas of subcutaneous tissue were also involved. Lymphocytes usually showed perivascular dominant distribution. Angiotropism or angiodestruction was found in 31 patients. Proliferated lymphocytes were small and, in most cases, showed no cellular polymorphism. In 4 patients, prominent cellular polymorphism was found, and in 5 patients, prominent eosinophils were observed. Fibrosis was prominent in 6 patients with regressed lesions, and clinicopathological correlation and verification of EBER in situ hybridization were needed for diagnosis (Fig 3).

Immunohistochemistry

Proliferated lymphocytes were consistently positive for CD3, CD5, CD7, and TIA1 cytotoxic granule associated RNA binding protein in all patients. In 12 patients, $CD4^+$ cells were predominant, in 9 patients CD8 lymphocytes were predominant, in 18 patients $CD4^+$ and $CD8^+$ cells were mixed, and in 2 patients the results of testing for both CD4 and CD8 were

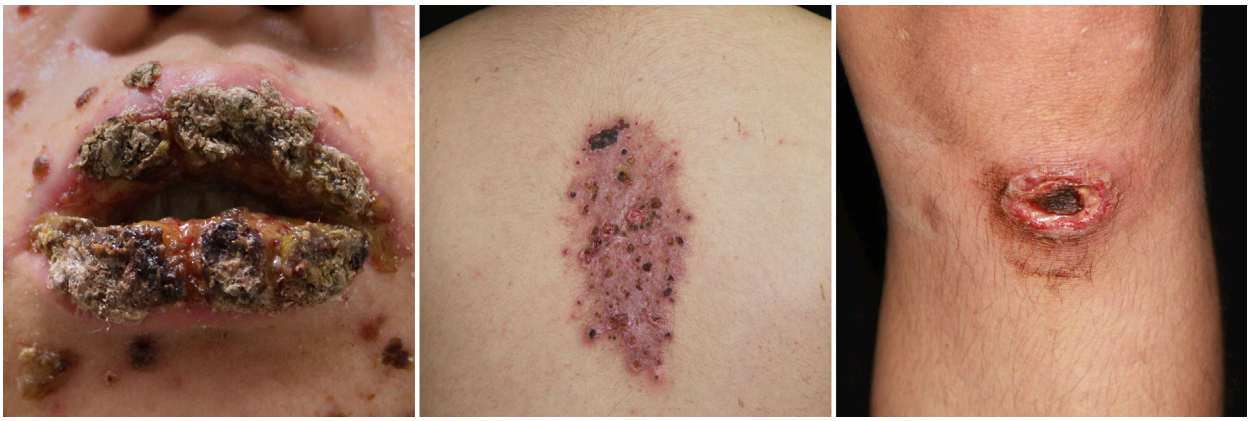

Fig 2. Hydroa vacciniforme–like lymphoproliferative disorder with concomitant bacterial infection. Prominent crusts, erosions, and ulcerations on the lip, back, and leg of 3 separate patients.

Table I. Clinical characteristics of the 4 dead patients

Patient	Sex/age at death/onset age, y	Systemic symptoms	Serum EBV DNA load, copies/mL	Treatment
1	Female/43/42	Fever, lymphadenopathy	1.05×10^5	Corticosteroids, chemotherapy, interferon α
2	Female/25/22	Fever, lymphadenopathy, hepatosplenomegaly	1.81×10^4	Chemotherapy
3	Female/21/20	Fever	Not done	Antibiotics
4	Male/4/4	Fever, lymphadenopathy, hepatosplenomegaly	2.15×10^4	Chemotherapy and then hematopoietic stem cell transplantation

EBV, Epstein-Barr virus.

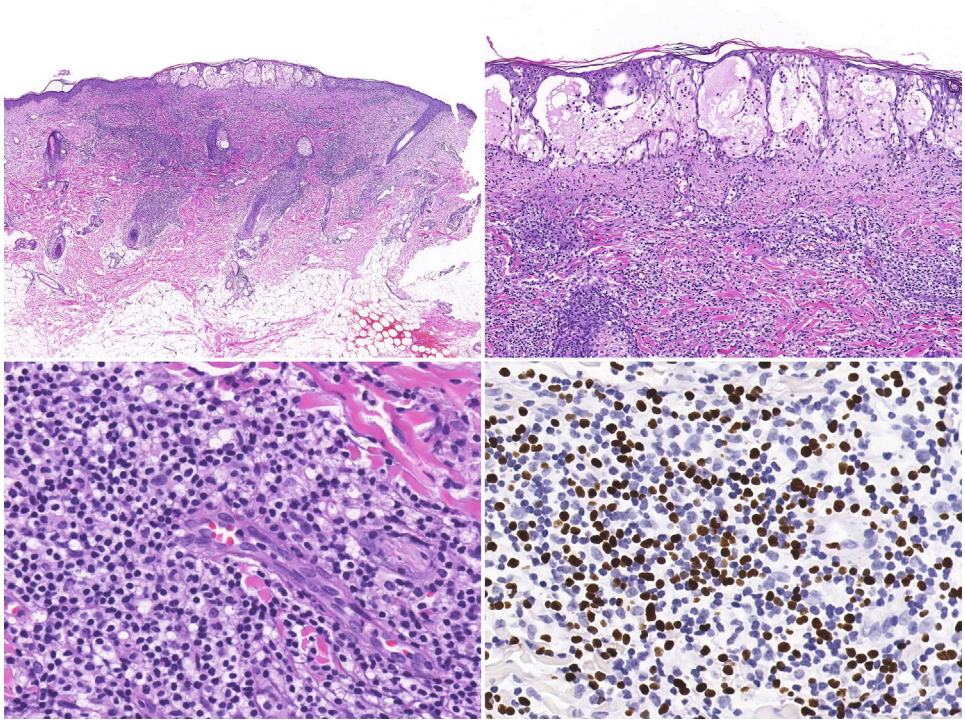

Fig 3. Hydroa vacciniforme–like lymphoproliferative disorder. Histopathology revealed reticular degeneration of the epidermis and formation of vesicles, as well as dense perivascular lymphocyte infiltration without prominent cellular polymorphism. Epstein-Barr virus–encoded RNA in situ hybridization showed scattered positive cells.

negative. The Ki67 proliferation index was less than 10% in 35 patients and higher than 10% in 6 patients. CD30 expression was noticed in 7 patients, and only 3 patients showed very focal or scattered positive staining for CD56.

Molecular studies

EBER in situ hybridization showed scattered positive cells in all patients. Testing for *TCR* gene rearrangement was successfully performed in 33 patients, with 29 patients showing positive results.

DISCUSSION

In this study, we examined the cases of 41 patients with HVLLPD in China. To the best of our knowledge, this study represents the largest collection of case reports of this rare disease. Similar to previous reports,[8,12] our patients were characterized by papulovesicular lesions located mainly in sun-exposed areas. However, lesions were also found in sun-protected areas. Facial edema was observed in only a small number of patients and periorbital and perioral edema were not prominent, whereas in Latin American patients, periorbital and perioral edema

Table II. Clinical and histological characters of large case reports of HVLLPD (≥6 patients)

Countries	Patients (male/female), n	Children/ adults, n	Cutaneous presentation	Systemic symptoms n/n, %	Cellular atypia	EBER positivity rate	Elevated serum EBV DNA load	Treatments (patients)	Death rate	Average follow-up time
Peru[6]	16 (7/9)	16/0	HV-like eruptions on the face	10/16 (63%)	Not obvious	16/16	N/A	CT (8)	50%	162 mo
Peru[13]	14 (9/5)	12/2	HV-like eruptions on sun-exposed and non—sun-exposed areas	2/14 (14%)	Not obvious	14/14	N/A	CT (12) CS (5)	28.6%	12.6 mo
Peru[2]	20 (14/6)	20/0	HV-like eruptions on sun-exposed areas	10/20 (50%)	Varied from patient to patient	20/20	N/A	CT (3) CS (13)	57%	77.5 mo
Bolivia[12]	12 (5/7)	8/4	HV-like eruptions on sun-exposed and non—sun-exposed areas. Facial and periorbital edema, swelling of the nose and lips	12/12 (100%)	Obvious in all patients	12/12	N/A	CT (12)	67%	36 mo
Bolivia[15]	7 (5/2)	7/0	HV-like eruptions on the face, arms and legs, periorbital edema	7/7 (100%)	Varied from patient to patient	7/7	N/A	CT (7) CS (7)	100%	3.3 mo
Mexico[16]	9 (6/3)	6/3	Facial edema with necrosis and pitted scars	9/9 (100%)	N/A	9/9	N/A	CT (2)	100%	N/A
France[31]	7 (4/3)	2/5	N/A	N/A	N/A	N/A	5/7	N/A	0%	96 mo
Japan[1]	29	28/1	HV-like eruptions on sun-exposed areas	9/29 (31%)	N/A	28/29	8/10	N/A	24%	N/A
Korea[8]	6 (3/3)	1/5	HV-like eruptions on sun-exposed and non—sun-exposed areas	3/6 (50%)	Obvious in some patients	6/6	N/A	CS (2)	17%	N/A
China[17]	7 (2/5)	7/0	HV-like eruptions on sun-exposed and non—sun-exposed areas, facial and lip edema	7/7 (100%)	Obvious in all	7/7	2/2	CT (2) CS (1) INF (2)	0/6	33.4 mo
China[19]	6 (5/1)	3/3	HV-like eruptions on sun-exposed areas	1/6 (17%)	Obvious in all	4/6	N/A	CS (4)	16.7%	106.3 mo
China*	41 (15/26)	28/13	HV-like eruptions on sun-exposed and non—sun-exposed areas, facial edema in a minority of patients	26/41 (64%)	Obvious in 4 of 41	41/41	14/25	CT (3) CS (12) INF (9) SCT (1)	20%	53.4 mo

HV-like eruptions include vesicles, blisters, ulcers, crusts, and pitted scars.
CS, Corticosteroids; *CT*, chemotherapy; *EBER*, Epstein-Barr virus—encoded RNA; *EBV*, Epstein-Barr virus; *HV*, hydroa vacciniforme; *HVLLPD*, hydroa vacciniforme—like lymphoproliferative disorder; *INF*, interferon-α; *LOF*, Lost to follow-up; *N/A*, not available; *SCT*, stem cell transplantation.
*Current report.

was very prominent in several studies.[12,15,21] In our study, otorhinolaryngologic and ocular symptoms were found separately in several patients. Ocular involvement of HVLLPD has been reported previously,[22-24] whereas the otorhinolaryngologic symptoms are rarely described.[18,25,26] One patient had a history of 20 years of scrotal swelling and testicular pain during flare of skin lesions, which was not reported in previous literature.

We found that patients with HVLLPD were prone to skin and mucosal bacterial infections. Rapid improvement after antibiotic treatment supported the coexistence of a bacterial infection. Interestingly, we noticed that a majority of our tested patients with HVLLPD (11 of 13 patients [85%]) had a prominently elevated serum IgE level. Several diseases with elevated serum IgE levels are prone to bacterial infection; these diseases include hyper-IgE syndrome,[27] Wiskott-Aldrich syndrome,[28] and atopic dermatitis.[29] It is possible that the elevated serum IgE level is pathogenically correlated with bacterial infections in our patients.

Histopathologically, proliferated lymphocytes in our patients were usually small and cellular polymorphism was noticed in only a small number of patients. EBV-positive cells usually constituted a minority of the proliferated cells, and the Ki67 proliferation index was usually less than 10%. In several reports from Latin America, cellular polymorphism was common and the Ki67 proliferation index was usually high.[12,13,16] These features may be related to the aggressive clinical behavior of the disease in Latin American patients. Among our patients, we found 7 with positive staining of CD30, which should be differentiated from lymphomatoid papulosis (for which EBER in situ hybridization is essential). In our study, only 3 patients showed very focal or scattered $CD56^+$ cells, whereas other reports have shown CD56-positive patients.[2,13,16,17] CD56-positive patients should be differentiated from those with extranodal NK/T-cell lymphoma, nasal type[30]; clinical characteristics are very important for the differentiation.

Only 4 of our patients died of HVLLPD, whereas the majority of Latin American patients died as a result of this disease (Table II).* Only 3 of our patients received chemotherapy, whereas chemotherapy was used in the majority of Latin American patients.[12] Chemotherapy seemed to be associated with poor prognosis in patients with HVLLPD, indicating that chemotherapy should not be routinely used as a treatment strategy for this disease.[2] At our institution, conservative treatments were typically used; they include injections of interferon α, topical or low-dose oral corticosteroids, or antibiotics when a concomitant bacterial infection is present. In a small number of patients, complementary treatments, such as Chinese herbal medicine, are used concomitantly. Among our patients, 3 of the 4 patients who died from HVLLPD had adult-onset disease, which was consistent with previous reports indicating that patients with adult-onset HVLLPD usually have a more aggressive disease course than do patients with childhood-onset HVLLPD.[32,33]All of our patients who died had very high serum EBV DNA loads (tested in 3 patients), whereas no patients with normal EBV DNA loads died of the disease. This result suggests that patients with high serum EBV DNA loads have an increased risk of aggressive disease, whereas the disease of patients with a normal serum EBV DNA load follows a more indolence disease course.

In conclusion, in most Chinese patients HVLLPD follows a more persistent and indolent clinical course, which differs from that of Latin American patients. We suggest conservative treatments for HVLLPD in most patients. The current challenge is to identify patients with a higher risk of progression to the more aggressive phases of disease and to effectively treat patients who are already in an aggressive phase.

*1,2,6,8,12,13,15-17,19,31.

REFERENCES

1. Iwatsuki K, Satoh M, Yamamoto T, et al. Pathogenic link between hydroa vacciniforme and Epstein-Barr virus-associated hematologic disorders. *Arch Dermatol*. 2006; 142(5):587-595.
2. Quintanilla-Martinez L, Ridaura C, Nagl F, et al. Hydroa vacciniforme-like lymphoma: a chronic EBV+ lymphoproliferative disorder with risk to develop a systemic lymphoma. *Blood*. 2013;122(18):3101-3110.
3. Quintanilla-Martinez L, Ko YH, Kimura H, Jaffe ES. Hydroa vacciniforme-like lymphoproliferative disorder. In: Swerdlow SH, Campo E, Harris NL, et al., eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissue*. Lyon, France: IARC; 2017:368-371.
4. Gupta G, Man I, Kemmett D. Hydroa vacciniforme: a clinical and follow-up study of 17 cases. *J Am Acad Dermatol*. 2000; 42(2 Pt 1):208-213.
5. Ruiz-Maldonado R, Parrilla FM, Orozco-Covarrubias ML, Ridaura C, Tamayo Sanchez L, Duran McKinster C. Edematous, scarring vasculitic panniculitis: a new multisystemic disease with malignant potential. *J Am Acad Dermatol*. 1995;32(1):37-44.
6. Barrionuevo C, Anderson VM, Zevallos-Giampietri E, et al. Hydroa-like cutaneous T-cell lymphoma: a clinicopathologic and molecular genetic study of 16 pediatric cases from Peru. *Appl Immunohistochem Mol Morphol*. 2002;10(1):7-14.
7. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127(20):2375-2390.

8. Cho KH, Lee SH, Kim CW, et al. Epstein-Barr virus-associated lymphoproliferative lesions presenting as a hydroa vacciniforme-like eruption: an analysis of six cases. *Br J Dermatol*. 2004;151(2):372-380.
9. Park S, Kim K, Kim WS, Yoo KH, Koo HH, Ko YH. Systemic EBV+ T-cell lymphoma in elderly patients: comparison with children and young adult patients. *Virchows Arch*. 2008;453(2):155-163.
10. Hamada T, Nakamura S, Ko YH, et al. Epstein-Barr virus-associated T/natural killer-cell lymphomas in the elderly: the first consensus meeting in Kofu 2013. *J Dermatol*. 2014;41(1):40-42.
11. Jung SE, Cho KH, Lee MW, Kim YC. Hydroa vacciniforme-like eruption associated with Epstein-Barr virus infection in an older adult. *Ann Dermatol*. 2015;27(6):789-791.
12. Sangueza M, Plaza JA. Hydroa vacciniforme-like cutaneous T-cell lymphoma: clinicopathologic and immunohistochemical study of 12 cases. *J Am Acad Dermatol*. 2013;69(1):112-119.
13. Rodriguez-Pinilla SM, Barrionuevo C, Garcia J, et al. EBV-associated cutaneous NK/T-cell lymphoma: review of a series of 14 cases from Peru in children and young adults. *Am J Surg Pathol*. 2010;34(12):1773-1782.
14. Rodriguez-Pinilla SM, Barrionuevo C, Garcia J, et al. Epstein-Barr virus-positive systemic NK/T-cell lymphomas in children: report of six cases. *Histopathology*. 2011;59(6):1183-1193.
15. Plaza JA, Sangueza M. Hydroa vacciniforme-like lymphoma with primarily periorbital swelling: 7 cases of an atypical clinical manifestation of this rare cutaneous T-cell lymphoma. *Am J Dermatopathol*. 2015;37(1):20-25.
16. Magana M, Massone C, Magana P, Cerroni L. Clinicopathologic features of hydroa vacciniforme-like lymphoma: a series of 9 patients. *Am J Dermatopathol*. 2016;38(1):20-25.
17. Xu Z, Lian S. Epstein-Barr virus-associated hydroa vacciniforme-like cutaneous lymphoma in seven Chinese children. *Pediatr Dermatol*. 2010;27(5):463-469.
18. Iwatsuki K, Xu Z, Takata M, et al. The association of latent Epstein-Barr virus infection with hydroa vacciniforme. *Br J Dermatol*. 1999;140(4):715-721.
19. Chen CC, Chang KC, Medeiros LJ, Lee JY. Hydroa vacciniforme and hydroa vacciniforme-like T-cell lymphoma: an uncommon event for transformation. *J Cutan Pathol*. 2016;43(12):1102-1111.
20. van Dongen JJ, Langerak AW, Bruggemann M, 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. *Leukemia*. 2003;17(12):2257-2317.
21. Magana M, Sangueza P, Gil-Beristain J, et al. Angiocentric cutaneous T-cell lymphoma of childhood (hydroa-like lymphoma): a distinctive type of cutaneous T-cell lymphoma. *J Am Acad Dermatol*. 1998;38(4):574-579.
22. Zamecki KJ, Friedman AH, Raab EL. Ophthalmic findings in a patient with CD8-positive T cell lymphoma and a hydroa vacciniforme-like eruption. *Br J Ophthalmol*. 2010;94(9):1266-1267.
23. Trikha S, Turnbull A, Srikantha N, Krishnan R, Tappin A. Anterior keratouveitis secondary to hydroa vaccineforme: a role for ophthalmic slit-lamp examination in this condition? *BMJ Case Rep*. 2011. https://doi.org/10.1136/bcr.09.2010.3309.
24. Mortazavi H, Hejazi P, Aghazadeh N, Esfandiari H, Ghanadan A, Jahanzad I. Hydroa vacciniforme with eye involvement: report of two cases. *Pediatr Dermatol*. 2015;32(1):e39-e41.
25. Yang YQ, Fan L, Wang L, et al. Systemic lymphoma arising from hydroa vacciniforme-like lymphoma: report of two cases with review of literature. *Int J Clin Exp Pathol*. 2014;7(9):6403-6408.
26. Picard C, Gouarin S, Comoz F, et al. Chronic active Epstein-Barr virus infection with cutaneous and sinus lymphoproliferation in a white female patient with 25 years' follow-up: an original case report. *Br J Dermatol*. 2015;173(5):1266-1270.
27. Grimbacher B, Holland SM, Gallin JI, et al. Hyper-IgE syndrome with recurrent infections—an autosomal dominant multisystem disorder. *N Engl J Med*. 1999;340(9):692-702.
28. Bosticardo M, Marangoni F, Aiuti A, Villa A, Grazia Roncarolo M. Recent advances in understanding the pathophysiology of Wiskott-Aldrich syndrome. *Blood*. 2009;113(25):6288-6295.
29. Bieber T. Atopic dermatitis. *N Engl J Med*. 2008;358(14):1483-1494.
30. Tse E, Kwong YL. The diagnosis and management of NK/T-cell lymphomas. *J Hematol Oncol*. 2017;10(1):85.
31. Verneuil L, Gouarin S, Comoz F, 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(1):174-182.
32. Miyake T, Yamamoto T, Hirai Y, et al. Survival rates and prognostic factors of Epstein-Barr virus-associated hydroa vacciniforme and hypersensitivity to mosquito bites. *Br J Dermatol*. 2015;172(1):56-63.
33. Kimura H, Ito Y, Kawabe S, et al. EBV-associated T/NK-cell lymphoproliferative diseases in nonimmunocompromised hosts: prospective analysis of 108 cases. *Blood*. 2012;119(3):673-686.