Int J Clin Exp Pathol 2014;7(9):6403-6408
www.ijcep.com /ISSN:1936-2625/IJCEP0001270

Case Report

Systemic lymphoma arising from hydroa vacciniforme-like lymphoma: report of two cases with review of literature

Yu-Qiong Yang, Lei Fan, Li Wang, Ji Xu, Run Zhang, Zheng Ge, Jian-Yong Li, Wei Xu

Department of Hematology, The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital, Nanjing 210029, China

Received July 1, 2014; Accepted August 20, 2014; Epub August 15, 2014; Published September 1, 2014

Abstract: Hydroa vacciniforme-like lymphoma (HVLL) is an extremely rare lymphoma described in children that occurs mainly in Asia and Latin American countries. It is an Epstein-Barr virus (EBV)-positive lymphoproliferative disease (LPD) characterized by a monoclonal proliferation of T or NK cells. In this study, we report the clinical and pathological features of two Chinese patients with HVLL showed T-cell phenotype expressing CD4. The two patients generally presented with similar clinical histories of waxing and waning ulcerative blistering lesions for ten years or more until progression to systemic lymphoma. One patient died two months after progression and another is alive with disease. In the two cases, persistence infection of EBV may be attributed to the disease progression, and systemic lymphoma arising from HVLL behaves in an aggressive fashion and is predisposing to chemotherapeutic agent resistance.

Keywords: Hydroa vacciniforme, lymphoma, Epstein-Barr virus infections

Introduction

Hydroa vacciniforme-like lymphoma (HVLL) is an uncommon type of lymphoma occurring in children and often develops with long-standing hydroa vacciniforme (HV). This entity is associated with hypersensitivity to mosquito bites and sun sensitivity. HVLL and systemic Epstein-Barr virus (EBV)-positive T-cell lymphoproliferative disease (T-LPD) of childhood were incorporated in the subgroup of EBV-positive T-LPD of childhood in the 2008 World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues. Central to the disease was the relatively long clinical course before developing systemic lymphoma [1]. Very few cases of HVLL progression to systemic lymphoma have been reported so far, and the current study describes two cases of HVLL advancing to systemic lymphoma, with similar presentation with "HV"-like skin lesions for ten years or over. In order to sustain our findings and improve the knowledge on this disease, related literatures were reviewed.

Case reports

Case 1

The patient was a 19-year-old Chinese female, admitted to our hospital on June 13, 2013, due to recurrent rash for sixteen years. Upon admission, she presented with fever and shortness of breath for three weeks. Her mother described that the patient initially presented with erythematous, papules, nodules and blisters with distribution over the face, truck and extremities without fever at the age of three (**Table 1**). In July 2012, the skin lesions were intensified with itching, and skin biopsy of a papule obtained from the right leg was performed. Diffuse small-to-medium-sized lymphocytes without atypia were observed in the dermis that extends into the subcutaneous fat. The infiltrate pattern of perivascular was found (**Figure 1A**, **1B**). Diagnosis of HVLL was established on morphology, immunophenotype (**Figure 1C-E**), T cell receptor (TCR) gene rearrangement (**Table 2**), and clinical manifestations, by which the patient

Table 1. Clinical features of two patients with HVLL

Case	Sex	Age, y	Clinical diagnosis	Characteristics of lesions	Systemic symptoms	HMB	Treatment	Follow-up
1a	F	3	-	Erythematous, papules, nodules and blisters with distribution over the face, truck and extremities, exacerbating in summer season	No	Yes	-	
1b		18	HVLL	Skin lesions intensified with itching	No		IFN-α	
1c		19	T-cell lymphoma	Systemic skin with extensive brownish patches and part healed with atrophic scar	Yes		Chemotherapy	DoD
2a	F	8	HV	Facial edema, erythemtous, papules and blisters, worseing in summer	No	Yes	Thalidomide, chloroquine, systemic steroids	
2b		16	HVLL	Facial lesions with charateristics of waxing and waning	No		Methotrexate, systemic steroids, IFN-α	
2c		18	HVLL (systemic)	Facial edema and flaky rash erythematous	Yes		Chemotherapy	AwD

AwD, alive with disease; DoD, died of disease; HMB, hypersensitivity to mosquito bites; IFN, interferon. Case (1-2) a: at the onset of the disease; b: in the stage of diagnosis of HVLL; c: in the phase of HVLL developing systemic lymphoma.

was treated with interferon (IFN)-α. Although the lesions were relieved and seemingly healed with depressed atrophic scars, she complained of fever accompanying with shortness of breath ten months later, and computed tomography (CT) examination showed generalized lymphadenopathy, pericardial and bilateral pleural effusion, abdominal and pelvic effusion, hepatosplenomegaly and pelvic huge lumps. By antibiotic therapy and drainage of pericardial and pleural effusion, her temperature dropped down to normal, but remaining symptoms showed no sign of improvement.

Physical examination after admission revealed systemic skin with extensive brownish patches and atrophic scar partially healed with dander at the surface (**Table 1**). Swollen lymph nodes were palpable under the jaw, the right axillary and inguen (maximum diameter being 2 cm). Stethoscopic chest examination revealed decreased breath at the bilateral lungs and distant cardiac sounds. Moderate hepatomegaly (3 cm below the right costal margin) was palpable by abdominal examination.

Laboratory work confirmed EBV infection with mild anemia, extremely high tumor burden and liver dysfunction (**Table 2**). Bone marrow involvement was possible because of positive TCRβ and TCRγ rearrangement detected by PCR. Echocardiographic assessment left ventricle ejection fraction (LVEF) was 59%. Biopsy of the pelvic mass by histopathology revealed highly invasive T-cell lymphoma (**Table 2**), for which the patient was diagnosed as T-cell lymphoma (stage IV, group B).

The patient's disease was refractory to multiple chemotherapy regimens, and persisted despite two cycles of CHOP-like (cyclophosphamide, liposomal doxorubicin, vincristine and prednisone) and additional one cycle of GDP (gemcitabine, dexamethasone and cisplatin). Her clinical condition was deteriorating, and EBV load remained uncontrolled. The patient died from disease progression on August 21, 2013.

Case 2

The patient was an 18-year-old Chinese female, referred to our hospital on January 18, 2014. She described a ten-year history of recurrent facial erythema and blisters, and was diagnosed as "HV" a decade ago (**Table 1**). After treatment with prednisone, thalidomide and chloroquine, the lesions were improved but recurred with waxing and waning nature. In January 2011, facial skin biopsy was performed, revealing lymphocytes infiltration without atypia and moderate amounts of eosinophils in the superficial dermal around the blood vessels.

She was initially diagnosed as HVLL based on her clinical manifestation and skin biopsy histopathology (**Table 2**), and responded to combined prednisone, methotrexate and IFN-α, but relapsed soon after drug withdrawal. In November 2013, she developed bilateral nasal congestion and fever. Physical examination revealed nasal neoplasm, and biopsy identified infiltration of abnormal proliferation of lymphocytes into a large number of dead tissue. Pathological diagnosis of HVLL involving the nasal cavity was made on her clinical features (**Table 2**).

On examination after admission, the patient had edema and flaky rash erythematous on her

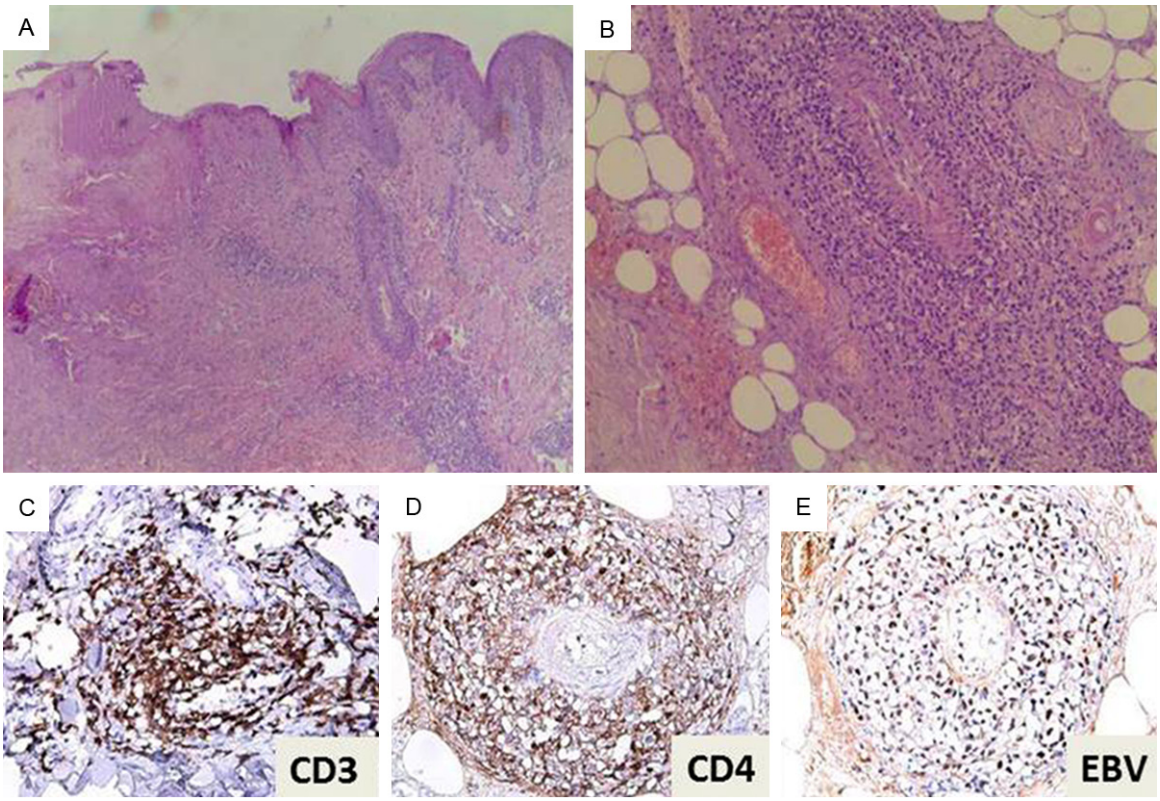

Figure 1. Morphology, immunophenotype and in situ hybridization (ISH) for EBV-encoded small RNA (EBER) of HVLL (Case 1). A. Skin biopsy showing an infiltrate mainly in the dermis that extends into the subcutaneous fat. Note that the infiltrate surrounds the vascular. (Haematoxylin and eosin [H&E], original magnification stain×40); B. Higher power examination shows small-to-medium-sized lymphoid infiltrate without atypia surrounding a blood vessel. (H&E stain, original magnification×100); C. CD3 staining reveals many positive cells. (immunoperoxidase, original magnification×400); D. CD4 stain shows that the cells surrounding the vascular are CD4 positive. (immunoperoxidase, original magnification×400); E. EBER ISH is positive in the infiltrating lymphocytes. (original magnification×400).

face, and developed a fever of 38.9. Moderate splenomegaly (1 cm below the left costal margin) was palpable, but superficial lymph nodes and the liver were not enlarged.

Routine laboratory examinations showed elevated levels of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH), and higher EBV load was measured (**Table 2**). Positron emission tomography (PET)-CT revealed thickened mucosa in the right side of the rear wall of the nasopharynx with a maximum standardized uptake value (SUV) of 8.0 (a maximum SUV of liver is 2.3). The patient was diagnosed as HVLL (systemic) in compliance with the symptoms, signs, laboratory findings and biopsy histopathology. After therapy with one cycle of CEOP (cyclophosphamide, etoposide, vincristine and prednisone), her temperature fell down to normal level and nasal congestion was relieved. The skin lesions on the face improved during chemotherapy but recurred soon without therapy. She is alive with disease in the follow-up time with the end up date of June 2014.

Discussion

HVLL is an extremely rare lymphoma that occurs mainly in children and adolescents, yet uncommonly seen in adults [1]. HVLL had been called angiocentric cutaneous T-cell lymphoma of childhood. The European Organization for Research and Treatment of Cancer (EORTC) in 2005 subclassified HVLL as a variant of extranodal NK/T-cell lymphoma, nasal type (ENKTCL-N), and defined it as a rare type of EBV-associated lymphoma of CD8 cytotoxic T cells. In this classification, HVLL was categorized as LPD with a uniformly poor prognosis. However, the 2008 WHO classification for the first time classified HVLL as childhood EBV-

Table 2. Laboratory examination, immunophenotype and molecular analysis in the two cases

	Case 1		Case 2	
	1b	1c	2b	2c
Abnormal results of laboratory examination				
Hb (normal, 110-150 g/L)		108		normal
ALT (normal, 7-40 U/L)		115.4		44.1
AST (normal, 13-35 U/L)		109.4		39.1
LDH (normal, 140-271 U/)		1217		297
EBV-DNA (normal, < 5000 copies/ml detected by qPCR)		5.02E+05		1.77E+06
Immunophenotype and molecular analysis	skin lesion	pelvic mass	Skin lesion	Nasal neoplasm
CD3	+	+	+	+
CD4	+	-	+	+
CD8	-	ND	-	-
CD56	-/+	+/-	-	-
CD30	+	ND	ND	ND
TIA-1	-/+	-	+	+
Ki-67	ND	80%+	ND	ND
CD20	-	-	-	-
EBER-ISH	+	+	+	+
TCRγ	Mono	ND	Mono	ND
TCR-VJ2	ND	ND	ND	Mono

ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hb, hemoglobin; LDH, lactate dehydrogenase; qPCR, quantitative polymerase chain reaction; TCR, T cell receptor. Mono, monoclonal; ND, not done; -/+, a minority of cells; +/-, many cells; +, most cells; ISH, in situ hybridization.

positive T-LPD [2]. This reflects the increasing awareness of EBV associated T/NK-cell LPD and HVLL being considered as indolent lymphoma with a chronic course, contrary to the previous 2005 EORTC classification. This entity is mainly prevalent in population of Asia, and Native American from Central and South America, and Mexico. The median age was 7 years (range, 3-15 years) in a study from China, and more boys are affected than girls [3]. The mean age of patients in Peru was 11 years (range, 5-17) [4]. Nevertheless, the annual incidence of HVLL is not accurately estimated [5].

HVLL, characterized by a papulovesicular eruption, generally proceeds to ulceration and scarring. The cutaneous manifestation is similar to that of "classic" HV. Nevertheless, the lesions are larger and deeper and not only occur on light-exposed skin, but also on non-exposed sites. Meanwhile, lesions cannot resolve in adolescence or young adulthood unlike typical HV [6]. Two patients in our cases had a "HV"-like lesion history for a decade or more. They presented with similar clinical features to those in previous descriptions, including edema, blistering, ulceration, and scarring, and features of exaggerated bite reactions. Moreover, the lesions showed no remission but aggravated in adolescence. Currently a specific morphologic division is not seen between HV and HVLL. Both two entities are EBV associated, and differential diagnosis mainly depends on clonal analysis of the TCR genes [7]. If a clonal TCR gene rearrangement is observed, a diagnosis of HVLL should be rendered. Clonality and EBV status were not investigated at the early attack in our two cases. Hence, it is unclear that whether the diagnosis of HVLL was established at the onset of the disease, or developed in the long-standing HV. In a recent study, Kimura et al. [8] reported four cases of "classic" HV, defined as patients with a characteristic dermatosis without systemic symptom. However, based on the monoclonality of the TCRγ genes, all four cases were reclassified as HVLL. Therefore, the detection of TCR gene rearrangement is needed in patients with HV even without systemic symptom.

Characteristically, HVLL remains indolent or prolonged clinical course, and patient may have recurrent skin lesions for some time, up to

10-15 years, before progression to systemic disease. In most reports, the disease is in recurrent state but does not progress. In few cases, the disease potentially underwent a longer aggressive clinical course. For HVLL patients, prolonged follow-up is necessary even if the disease initiates remission. Two patients in our report, with a history of HVLL, were developed into systemic lymphoma, and biopsy of different tissues except skin by in situ hybridization (ISH) revealed EBER-positive cells (**Table 2**). In compliance with the clinical course, diagnosis of systemic lymphoma arising from HVLL was made in these two cases. Nevertheless, it is hard to predict what patients will eventually progress to systemic lymphoma due to unclear specific prognosis factors available, and current criteria such as presence of systemic symptoms and severity of the lesions are not useful, either [1]. By previous reports, the clinical course for this entity may be indolent in patients with NK-cell phenotype when compared with those with a T-cell phenotype characterized by intermittent fever and hepatosplenomegaly [6]. However, patients with an NK-cell phenotype seem to have a higher risk to develop a systemic lymphoma during the long clinical course, such as ENKTCL or aggressive NK-cell leukemia [8]. Yet, our two cases showing CD4 T-cell phenotype developed into systemic lymphoma are inconsistent with previous reports. Few reports have ever showed that high titers of serum EBV-related antibodies often are capable of predicting a progressive clinical course [9]. Similarly, our cases presented significantly elevated EBV-DNA during the progression of the disease. Quantification of circulating EBV-DNA can be an accurate biomarker of tumor load, and some studies suggest that the EBV-DNA load was correlated with the number of EBER-positive cells [10]. In the case 1, the amounts of EBV load in the peripheral blood had been rising during treatment, which eventually resulted in death of the patient. Therefore, we consider that patients with persistently greater amounts of EBV-DNA may be in higher risk to develop a systemic lymphoma with poorer prognosis.

Currently, treatment options for HVLL remain uncertain. Chemotherapy seems effective in some patients with partial remission rate by 30%, but the effects are usually transient, and sustained complete remission is impossible for most cases [8]. In addition, it had been reported that patients receiving chemotherapy had a worse prognosis with short survival. Xu et al [11] described worsened conditions in 2 of 7 patients with HVLL undergone chemotherapy, and another study reported 8 deaths of 11 patients who received chemotherapy and/or radiotherapy, in whom 5 were secondary to infectious complications [12]. Barrionuevo et al. [13] also described 5 deaths from liver failure and sepsis in 8 cases received chemotherapy. In contrast, conservative strategies including (IFN)-a [11], prednisolone, cyclosporine A [8], chloroquine and thalidomide [14], are recommended as first-line therapy. A recent study reported that 13 patients with HVLL were primarily treated with immunosuppressive or immunomodulating therapy, such as steroids, thalidomide, and/or chloroquine. The skin lesions were generally improved with medication, and the extent of lesion infiltration as well as EBV cell count was found decreased in follow-up biopsies [1]. As is in our case 2, the patient had received the conservative treatment for ten years by admission, and even though new skin lesions developed, the lesions responded in general to the therapy by the time of her doctor's office visit. Nevertheless, the above therapy strategies should not work much, if a HVLL progressed to aggressive lymphoma, for the clinical course would be much more aggressive with systemic context, as is shown by the death of the case 1 in two months and two deaths from Mexican reports in 2 to 4 years [1], respectively, after progression to aggressive lymphoma. Systemic lymphoma with a history of HVLL is probably resistant to chemotherapeutic agents; whereas a report described that a child with refractory HVLL obtained long remission for two years after allogenic hematopoietic stem cell transplantation (allo-SCT) [15]. This therapy may improve the condition, and yet more research is needed to confirm whether allo-SCT can be effective in the treatment of refractory HVLL or HVLL progressed systemic lymphoma.

Acknowledgements

This study was supported by National Natural Science Foundation of China (30971296, 81170488, 81370657), Natural Science Foun-

dation of Jiangsu Province (BK2010584), Key Projects of Health Department of Jiangsu Province (K201108), Jiangsu Province's Medical Elite Program (RC2011169), Project Funded by The Priority Academic Program Development of Jiangsu Higher Education Institute (JX10231-801), National Public Health Grand Research Foundation (201202017), Development of Innovative Research Team in The First Affiliated Hospital of NJMU, and State Key Clinical Department Construction.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Wei Xu, Department of Hematology, The First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital, Nanjing 210029, China. Tel: +86-25-83781120; Fax: +86-25-83781120; E-mail: xuwei10000@hotmail.com

References

[1] Quintanilla-Martinez L, Ridaura C, Nagl F, Sáez-de-Ocariz M, Durán-McKinster C, Ruiz-Maldonado R, Alderete G, Grube P, Lome-Maldonado C, Bonzheim I and Fend F. Hydroa vacciniforme-like lymphoma: a chronic EBV+ lymphoproliferative disorder with risk to develop a systemic lymphoma. Blood 2013; 122: 3101-3110.

[2] Sangueza M and Plaza JA. Hydroa vacciniforme-like cutaneous T-cell lymphoma: clinicopathologic and immunohistochemical study of 12 cases. J Am Acad Dermatol 2013; 69: 112-119.

[3] Park S and Ko YH. Epstein-Barr virus-associated T/natural killer-cell lymphoproliferative disorders. J Dermatol 2014; 41: 29-39.

[4] Cohen JI, Kimura H, Nakamura S, Ko YH and Jaffe ES. Epstein-Barr virus-associated lymphoproliferative disease in non-immunocompromised hosts: a status report and summary of an international meeting, 8-9 September 2008. Ann Oncol 2009; 20: 1472-1482.

[5] Jang MS, Kang DY, Park JB, Kim ST and Suh KS. Cutaneous T-cell lymphoma in Asians. ISRN Dermatol 2012; 2012: 575120.

[6] Doeden K, Molina-Kirsch H, Perez E, Warnke R and Sundram U. Hydroa-like lymphoma with CD56 expression. J Cutan Pathol 2008; 35: 488-494.

[7] Quintanilla-Martinez L, Jansen PM, Kinney MC, Swerdlow SH and Willemze R. Non-mycosis fungoides cutaneous T-cell lymphomas: report of the 2011 Society for Hematopathology/European Association for Hematopathology workshop. Am J Clin Pathol 2013; 139: 491-514.

[8] Kimura H, Ito Y, Kawabe S, Gotoh K, Takahashi Y, Kojima S, Naoe T, Esaki S, Kikuta A, Sawada A, Kawa K, Ohshima K and Nakamura S. EBV-associated T/NK-cell lymphoproliferative diseases in nonimmunocompromised hosts: prospective analysis of 108 cases. Blood 2012; 119: 673-686.

[9] Wang M, Wang S, Yang QP, Liu YM, Gao LM, Sun H and Liu WP. Hydroa vacciniforme-like lymphoma of an adult: a case report with review of the literature. Diagn Pathol 2013; 8: 72.

[10] Kawabe S, Ito Y, Gotoh K, Kojima S, Matsumoto K, Kinoshita T, Iwata S, Nishiyama Y and Kimura H. Application of flow cytometric in situ hybridization assay to Epstein-Barr virus-associated T/natural killer cell lymphoproliferative diseases. Cancer Sci 2012; 103: 1481-1488.

[11] Xu Z and Lian S. Epstein-Barr virus-associated hydroa vacciniforme-like cutaneous lymphoma in seven Chinese children. Pediatr Dermatol 2010; 27: 463-469.

[12] Rodríguez-Pinilla SM, Barrionuevo C, Garcia J, Martínez MT, Pajares R, Montes-Moreno S, Casavilca S, Montes J, Bravo F, Zaharia M, Zevallos-Giampietri E, Sanchez L and Piris MA. 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: 1773-1782.

[13] Barrionuevo C, Anderson VM, Zevallos-Giampietri E, Zaharia M, Misad O, Bravo F, Cáceres H, Taxa L, Martínez MT, Wachtel A and Piris MA. Hydroa-like cutaneous T-cell lymphoma: a clinicopathologic and molecular genetic study of 16 pediatric cases from Peru. Appl Immunohistochem Mol Morphol 2002; 10: 7-14.

[14] Ruiz-Maldonado R, Parrilla FM, Orozco-Covarrubias ML, Ridaura C, Tamayo Sanchez L and Duran McKinster C. Edematous, scarring vasculitic panniculitis: a new multisystemic disease with malignant potential. J Am Acad Dermatol 1995; 32: 37-44.

[15] El-Mallawany NK, Geller L, Bollard CM, Wistinghausen B, Mussai F, Wayne AS, Alobeid B and Cairo MS. 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 2011; 46: 759-761.