

Clinicopathological analysis of the hydroa vacciniforme-like lymphoproliferative disorder with natural killer cell phenotype compared with cutaneous natural killer T-cell lymphoma

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Abstract. Hydroa vacciniforme-like lymphoproliferative disorder (HVLDP) is defined as a distinctive clinicopathological type of cutaneous lymphoma and a subset of patients with this disease exhibit the natural killer (NK)-cell phenotype. The HVLDP-NK cell phenotype may be difficult to distinguish from cutaneous natural killer T-cell lymphoma (CNKTL), as these two diseases share similar immunophenotypic markers. Therefore, the aim of the present study was to analyze the clinicopathological features of this rare disease and compare these features with those of CNKTL. The clinical, histopathological and molecular features of 5 patients with the HVLDP-NK cell phenotype and 11 patients with CNKTL were evaluated. As well as certain subtle histopathological differences, there marked differences the age, distribution of lesions and clinical course differed between patients with these two diseases. These results suggest that the HVLDP-NK cell phenotype should be classified as a separate disorder and treated accordingly.

Introduction

The 2008 World Health Organization (WHO) classification defines hydroa vacciniforme-like lymphoma (HVLL) as a clinicopathological type of cutaneous lymphoma with Epstein-Barr virus (EBV) infection (1). HVLL is a type of EBV+ T-cell lymphoproliferative disorder (LPD) that generally occurs during childhood (1). Studies have demonstrated that the prevalence of HVLL is particularly high across Asia, and Central and South America (2-6). The 2016 revision of the WHO classification now formally classifies childhood systemic EBV+ T-cell LPD as childhood systemic EBV+ T-cell lymphoma, in order to emphasize its aggressive clinical course (7). Furthermore, HVLL is no longer categorized as a subtype of childhood EBV+ T-cell lymphoma and 'HVLL' is now referred to hydroa vacciniforme-like lymphoproliferative disorder (HVLDP) in the 2016 WHO classification, since this disease has distinctive clinicopathological features (7). HVLDP is a primarily cutaneous disorder with a broad spectrum of clinical aggressiveness and HVLL is considered a syndrome accompanying this disease. Unlike in classical hydroa vacciniforme (HV), HVLDP skin lesions are located on sun-exposed and non-sun-exposed areas of the skin and tend to worsen with age. The majority of patients with HVLDP present with systemic symptoms, including fever, lymphadenopathy and hepatosplenomegaly (5,8,9). The majority of patients with HVLDP exhibit a T-cell phenotype, however some also exhibit the positive expression of cluster of differentiation (CD)56 in tumor cells, suggesting that HVLDP may originate from natural killer (NK) cells (10-14). Differentiating between HVLDP with CD56+ expression and cutaneous natural killer T-cell lymphoma (CNKTL) remains challenging. These two diseases share many histopathological features, particularly as they exhibit similar immunophenotypic markers (11). Therefore, in the 2005 WHO classification, the HVLDP-NK cell phenotype is considered to be a variant of NK/T-cell lymphoma, nasal type.

The present study investigated the clinicopathological features of 5 patients with a HVLDP-NK cell phenotype and compared these to the clinicopathological features of

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11 patients with CNKTL, to emphasize that the HVLPD-NK cell phenotype should be considered as a separate entity to CNKTL and evaluated with caution.

Patients and methods

Patients. The biopsied tissues of 5 patients (4 females and 1 male) with the HVLPD-NK cell phenotype attending the First Affiliated Hospital of Zhengzhou University (Zhengzhou, China) between February 2011 and December 2014 were obtained. The median age of these patients was 7 years old (range, 4-14 years old). Tissues from patients diagnosed with CNKTL were also obtained and analyzed as the control group. A total of 11 patients with CNKTL were included in the current study, of which 7 were male and 4 were female. The median age of these patients was 53 years old (range, 35-69 years old). All cases were diagnosed according to the 2016 WHO classification criteria (7). Among the 5 cases of HVLPD, one case was initially considered to be NK/T cell lymphoma; the final diagnosis of HVLPD was reached following a review of the patient's tissue specimen. All specimens were routinely processed, embedded in paraffin, sectioned and stained with hematoxylin and eosin.

Immunohistochemistry (IHC). Paraffin-embedded tissue was fixed using 10% formalin at 37°C for >6 h, which were divided into 4- μ m-thick sections on an automated immunostainer (Ventana Medical Systems, Inc., Tucson, AZ, USA). Endogenous peroxidase and phosphatase activity was blocked by 3% hydrogen peroxide for 4 min at 37°C. The following antibodies were used: CD20 (dilution, ready-to-use; cat. no. 14357208), CD4 (dilution, ready-to-use; cat. no. 15367406), CD8 (dilution, ready-to-use; cat. no. 15456809), CD56 (dilution, ready-to-use; cat. no. 14004708), Granzyme-B (dilution, ready-to-use; cat. no. 16691906), CD30 (dilution, ready-to-use; cat. no. 15331003), Ki-67 (dilution, ready-to-use; cat. no. 14567378) were purchased from (OriGene Technologies, Inc., Beijing, China). CD3 (dilution, ready-to-use; cat. no. 130801543E) and TIA-1 (dilution, ready-to-use; cat. no. 160426599E) were purchased from Fuzhou Maixin Biotech, Co., Ltd. (Fuzhou, China). Endogenous peroxidase activity blocked by 3% hydrogen peroxide for 4 min at 37°C. Secondary anti-rat antibodies (dilution, ready-to-use; cat. no. 760-500; Roche Diagnostics, Basel, Switzerland) conjugated to horseradish peroxidase were applied for 30 min at 37°C. The sections were counterstained with hematoxylin at 37°C for 2 min and a coverslip was applied.

In situ hybridization (ISH) for EBV. EBV RNA was detected using the ISH technique using the Epstein-Barr Virus Early RNA kit (cat. no. ISH-5021; OriGene Technologies, Inc.), following the manufacturer's protocol. Briefly, 4-6 μ m sections were cut from paraffin-embedded tissues, deparaffinized with xylene at 37°C for 10 min, rehydrated, predigested with proteinase K (OriGene Technologies, Inc.) and hybridized with DIG-labeled RNA probe. Following washing, the reaction was accomplished using anti-DIG horseradish peroxidase conjugate (OriGene Technologies, Inc.), followed by staining with 3,3'-diaminobenzidine substrate at 37°C for 5 min.

Polymerase chain reaction (PCR). PCR was performed on all 5 cases of HVLPD and only certain cases of CNKTL (the tissues from a number of cases were not sufficient for PCR due to necrosis or amounts) to evaluate T-cell receptor gene rearrangement, following the BIOMED-2 protocol as previously described (15). The 56 primers for the clonal rearrangement analysis of the TCR gene were all selected from the BIOMED-2 primer system (cat. no. 200008; Shanghai Yuanqi Biotechnology Co., Ltd., Shanghai, China), which was used to detect the TCR β , TCR γ , and TCR δ chains. The BIOMED-2 primer system also contained five internal control primers. Total DNA from the tissue samples was amplified using GoldStar Best DNA Polymerase (CWBIO, Beijing, China) according to the manufacturer's protocol. The thermocycling conditions were as follows: 7 min at 95°C, followed by and 40 cycles for 45 sec at 95°C and 1 min at 72°C. The primer sequences reference to commercial kit (Shanghai Yuanqi Biotechnology Co., Ltd., Shanghai, China).

Results

Clinical features. The clinical features of the 5 patients are summarized in Table I. All patients presented with skin lesions that were marked by recurring outbreaks, including papulovesicular eruption, ulceration and scarring. In 4 of the 5 patients, cutaneous lesions were present on the face (Fig. 1); another patient (case 1) had lesions in the trunk and extremities but did not present with lesions on the face involvement. All patients presented with systemic symptoms, including fever, lymphadenopathy and hepatosplenomegaly. The median duration of the disease from the occurrence of skin lesions to the onset of systemic symptoms was 33 months. None of the patients had bone marrow involvement. Of the 5 cases, 2 (cases 2 and 5) received cyclophosphamide, adriamycin, vincristine, prednisone (CHOP) chemotherapy; the other two cases (cases 3 and 4) received glucocorticoids (dexamethasone) as symptomatic treatment for ~1 week. Case 1 was lost prior to follow up. At the end of the study, 3 patients were alive; however, case 4 succumbed to systemic disease, including infection and hepatic failure <13 months after being admitted to the First Affiliated Hospital of Zhengzhou University.

Histopathological features. The histopathological features of patients are presented in Table II. Histopathologically, all cases exhibited polymorphic lymphoid infiltration throughout the dermis and subcutaneous tissue. In the majority of cases (4/5), the squamous epithelium was not infiltrated or destroyed (Fig. 2A). There was a patchy or nodular dense lymphoid infiltrate, with prominent skin adnexa involvement and vascular destruction in the majority of cases. However, tumor necrosis was only observed in one case (case 4; Table III). Lymphoid cells were small-to-medium-sized, exhibiting mild atypia and irregular nuclear contours (Fig. 2B). In case 2, a large number of neutrophils were found within the corium layer.

Immunohistochemical analysis and ISH for EBV. Neoplastic lymphoid cells from all cases expressed T-cell- and NK-cell-associated antigens, including CD3 and CD56 (Fig. 2C); however they were all negative for CD20 (Table III). Weak expression of CD3 was observed in two

Table I. Clinical features of the HVLPD-NK cell phenotype.

Patient	Sex	Age (years)	Distribution of lesions	Fever	Bone marrow involvement	Initial treatment	Status	Duration prior to progression to systemic symptoms (months)	Survival following diagnosis (months)
1	F	4	Haunch and extremities	Yes	No	-	-	24	-
2	F	4	Face	Yes	No	CHOP	Alive	19	N/A
3	F	9	Face and extremities	Yes	No	Ganciclovir/Steroids	Alive	33	N/A
4	M	14	Face and extremities	Yes	No	Steroids	Succumbed	54	13
5	F	7	Face and upper limbs	Yes	No	CHOP	Alive	36	N/A

HVLPD-NK, Hydroa vacciniforme-like lymphoproliferative disorder-natural killer; N/A, not applicable; CHOP, cyclophosphamide, adriamycin, vincristine, prednisone; M, male; F, female.



Figure 1. Case 4. Ulceration and scars on the face with marked edema.

cases (cases 2 and 3). One case (case 5) was weakly positive for CD8 and two cases (cases 1 and 3) were positive for CD4. The other two cases (cases 2 and 4) were negative for CD4 and CD8. The cytotoxic markers TIA-1 and Granzyme-B were positive in all cases. CD30 was heterogeneously expressed in cases 3 and 5 (Fig. 2D). Proliferative activity was assessed by Ki-67, which ranged between 30 and 70% of the tumor cells. All 5 cases were determined to be EBV positive following ISH detection.

Molecular studies. All 5 cases were analyzed via PCR. Four cases revealed evidence of polyclonal T cell receptor gene rearrangement, while 1 case (case 4) was positive for monoclonal T cell receptor γ chain gene rearrangement (Table III).

Comparison of clinicopathological features of patients with HVLPD-NK compared with patients with CNKTL. Table IV provides an analysis of the clinicopathological features of patients with CNKTL (n=11) compared with those that had the HVLPD-NK cell phenotype (n=5). A total of 8 patients (73%) with CNKTL presented with nodules or plaques on the extremities and only 1 case (9%) had lesions on the trunk alone. A further 2 cases (18%) revealed the involvement of the trunk and extremities. Infiltrations of the nasal cavity were observed in 2 cases. One case was admitted to the hospital with a presumptive diagnosis of skin cancer, as it revealed a large crateriform ulcer on the leg.

A total of 9 patients (82%) received at least one of the following therapies: Chemotherapy alone (45%; 5 of 11), radiotherapy alone (18%; 2 of 11) and concurrent chemo-radiotherapy (18%; 2 of 11). Out of the 11 patients, 5 (45%) had succumbed by the end of the follow-up period and the median follow-up period was 23 months.

Skin adnexa involvement and vascular destruction were observed in all patients with CNKTL (Table IV), which was also the case in HVLPD-NK (Fig. 3A). A total of 7 cases with CNKTL (64%) exhibited epidermis involvement and necrosis (Fig. 3B) was observed in the majority of cases with CNKTL (91%). Tumor cells had a monomorphic appearance and were medium-to-large or large sized with obvious atypia. All CNKTL cases were EBV positive.

Table II. Histopathological features of HVLPD-NK cell phenotype.

Patient	Epidermis involvement	Skin adnexa involvement	Vascular destruction	Necrosis	Subcutaneous infiltrate	Cellular morphology
1	No	Yes	Yes	No	Yes	Small
2	No	Yes	No	No	Yes	Small-medium
3	No	Yes	Yes	No	Yes	Small-medium
4	Yes	Yes	Yes	Yes	Yes	Medium
5	No	Yes	Yes	No	Yes	Small-medium

HVLPD-NK, Hydroa vacciniforme-like lymphoproliferative disorder-natural killer cell.

Table III. Immunohistochemical analysis and EBER results of this series.

Patient	CD20	CD3	CD4	CD8	CD56	Gran-B	TIA-1	CD30	Ki-67 (%)	EBV	TCR
1	-	+	+	-	+	+	+	-	30	+	Polyclonal
2	-	+/-	-	-	+	+	+	-	40	+	Polyclonal
3	-	+/-	-/+	-	+	+	+	-/+	60	+	Polyclonal
4	-	+	-	-	+	+	+	-	60	+	Monoclonal
5	-	+	-	-/+	+	+	+	+	40	+	Polyclonal

CD, cluster of differentiation; Gran-B, granzyme B; EBV, Epstein-Barr Virus; TCR, T-cell receptor gene rearrangement.

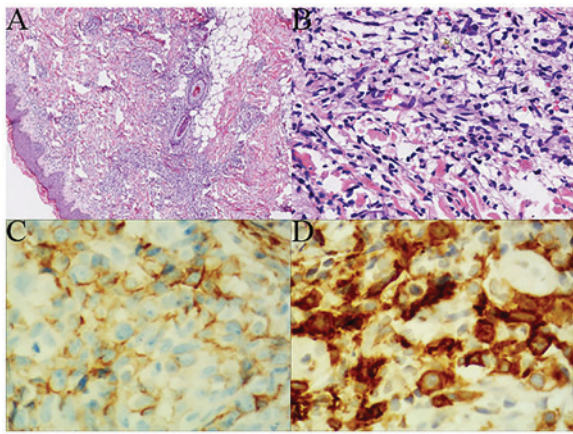


Figure 2. Case 5. (A) Squamous epithelium was not infiltrated by tumor cells (H&E staining, magnification, x50). (B) Lymphoid cells were small-medium in size, mixed with some plasma cells and neutrophils (H&E staining, magnification, x200). Neoplastic cells were positive for (C) CD56 and (D) CD30 (immunoperoxidase with hematoxylin counterstain; magnification, x400). CD, cluster of differentiation; H&E, hematoxylin and eosin.

Discussion

There have been few studies regarding the HVLPD-NK cell phenotype and half of these have been case reports (10,12,13). The current study assessed 5 patients with HVLPD-NK and indicated that all 5 cases exhibited clinical and histological features similar to the typical HVLPD-T phenotype. The difference was that these cases revealed an unusual immunophenotype of CD56 expression, revealing that they had a NK cell phenotype of HVLPD. Although

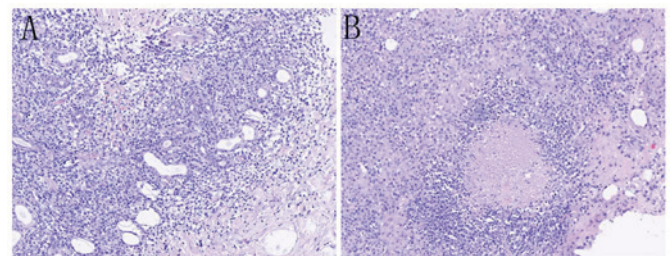


Figure 3. Histopathological features of cutaneous natural killer/T-cell lymphoma. (A) Skin adnexa involvement by large sized cells with marked atypia (H&E staining, magnification, x100). (B) Coagulative necrosis within the subcutaneous tissue (H&E staining, magnification, x100). H&E, hematoxylin and eosin.

all cases exhibited positive expression of CD3, 2 of the 5 cases exhibited weak expression of CD3. Two cases exhibited the CD4-/CD8- immunophenotype, highlighting the NK cell origin. However, another two cases exhibited CD4 expression and one case had a weak CD8 expression, which revealed it to be a T cell phenotype. Thus, CD4/CD8 immunophenotype expression could not be used to diagnose HVLPD. These results differ from the results of studies by Doeden *et al* (10) and Magaña *et al* (14) and demonstrate that a variety of CD4/CD8 immunophenotypes may be observed in the HVLPD-NK cell phenotype.

The HVLPD-NK cell phenotype may be particularly difficult to distinguish from CNKTL for the reason that these two diseases share similar immunophenotypic markers for CD3, CD56, Granzyme-B and TIA-1. These two diseases are also EBV positive and have a high Ki-67 proliferation index (11).

Table IV. Comparison of the clinicopathological characteristics of patients with HVLDP-NK cell phenotype and those with CNKTL.

Characteristics	HVLDP-NK cell phenotype (n=5)	CNKTL (n=11)
Median age (years)	7 (4-14)	53 (35-69)
Distribution of lesions (%)		
Face	80 (4/5)	18 (2/11)
Trunk	20 (1/5)	27 (3/11)
Extremities	80 (4/5)	91 (10/11)
Initial treatment (%)		
CHOP (or other chemotherapies)	50 (2/4)	45 (5/11)
Radiotherapy	0 (0/4)	18 (2/11)
Chemo-radiotherapy	0 (0/4)	18 (2/11)
Steroids	50 (2/4)	0 (0/11)
No treatment	0 (0/4)	18 (2/11)
Epidermis involvement	20 (1/5)	64 (7/11)
Skin adnexa involvement	100 (5/5)	100 (11/11)
Vascular destruction	80 (4/5)	100 (11/11)
Necrosis	20 (1/5)	91 (10/11)
Cellular morphology		
Small-medium	100 (5/5)	0 (0/11)
Medium-large	0 (0/5)	82 (9/11)
Large	0 (0/5)	18 (2/11)

HVLDP-NK, hydroa vacciniforme-like lymphoproliferative disorder-natural killer cell; CNKTL, cutaneous natural killer T-cell lymphoma; CHOP, cyclophosphamide, adriamycin, vincristine, prednisone.

Among the 5 cases included in the current study, case 2 was initially misdiagnosed as NK/T cell lymphoma and the patient received an inappropriate treatment.

The clinicopathological features of these two diseases have been summarized in the current study to identify the differences between them. Firstly, there was a marked difference regarding the median age of patients with these two diseases. The HVLDP-NK cell phenotype was more likely occur in children and adolescents, whereas patients with CNKTL were generally middle-aged or elderly. Secondly, there was a difference in the distribution of lesions between these two diseases. The current study demonstrated that patients with the HVLDP-NK cell phenotype were more likely to present with cutaneous lesions on the face, whereas patients with CNKTL generally exhibited lesions on the trunk and extremities. Consistent with the results of the current study, Mraz-Gernhard *et al* (16) reported that 70% of patients with CNKTL presented with lesions on one or more extremities and only a few cases (13%) presented with lesions in the head or neck regions. Furthermore, in the current study, 2 cases with CNKTL exhibited systemic symptoms and revealed nasal cavity involvement. The nasal skin of these 2 cases exhibited swelling and ulceration. However, these symptoms differed

between those exhibited by patients with HVLDP presenting with lesions on the face, which were marked by multiple papulovesicular eruption and scarring.

Furthermore, the clinical manifestations and courses of these two diseases differ markedly. HVLDP is marked by slow progression prior to the development of systemic symptoms; subsequently patients present with fever and erythema, which recur repeatedly. The lesions of patients with HVLDP are often characterized by papulovesicular eruption, ulceration and scarring (6). All 5 young patients with HVLDP in the current study experienced acute erythema, which may be relieved with the use of anti-viral drugs in the early stages of the disease. The duration of the disease prior to progression to systemic symptoms, including fever, lymphadenopathy and hepatosplenomegaly, was ~1.5 years in the current study. By contrast, NK/T-cell lymphoma presenting in the skin generally exhibits an aggressive clinical course without remission following diagnosis and the outcome of the majority of such patients is poor and may lead to mortality (16-19). Skin lesions of patients with NK/T cell lymphoma are generally nodular or present with large plaques and sometimes with ulcers (16).

The histopathological features of the two diseases may be differ somewhat, although the immunohistochemical expression of the HVLDP-NK cell phenotype may mimic that of NK/T cell lymphoma. The results of the current study indicated that the involvement of the epidermis in HVLDP, as well as tumor necrosis, is rare; the opposite was the case regarding skin lesions in patients with CNKTL. Patients with HVLDP usually exhibit multiple skin lesions (6). The fact that the epidermis is not involved in 4 out of 5 cases may be due to the biopsy site-in the current study, the majority of biopsy sites were skin rashes, where early pathological changes were observed. Skin adnexa involvement and vascular destruction occurred in patients with HVLDP and CNKTL. Lymphoid cells from patients in the HVLDP group were small-to-medium-sized with mild atypia, whereas in the majority of cases from the CNKTL group, the tumor was composed of medium-sized or large cells exhibiting marked pleomorphism. Taken together, these subtle histological clues may provide an additional diagnostic basis to distinguish between these two diseases.

In addition to CNKTL, the differential diagnosis for the HVLDP-NK cell phenotype includes benign inflammatory diseases and primary cutaneous CD30-positive T-cell LPD. Inflammatory disorders of the skin may microscopically resemble HVLDP. In the current study, the lymphocytes of all 5 cases were small-to-medium-sized with less atypia, which closely mimics chronic inflammation. The lesions of 1 case were accompanied by a large number of neutrophils, meaning that it was difficult to detect the tumor cells. The majority of cases (4/5) with the HVLDP-NK cell phenotype in the current study exhibited a polyclonal gene arrangement that closely mimicked benign lesions. Furthermore, patients with HVLDP tend to exhibit lymphocytic vascular destruction, which is very rare in inflammatory disorders, such as cutaneous eczema (20). Investigating the clinical course and performing ISH for EBV may help to distinguish between HVLDP and inflammatory disorders (20). Furthermore, CD30+ T-cell LPD should also be excluded. Primary cutaneous CD30+ T-cell LPD includes lymphomatoid papulosis, primary cutaneous anaplastic large cell lymphoma and borderline cases,

which is characterized by CD30+ EBV- T-cells. In the current study, 2 cases with HVLPD exhibited heterogeneous expression of CD30. The phenotype of these 2 cases may mimic that of CD30+ T-cell LPD. However, these 2 cases also exhibited positive EBV expression, meaning that it was determined to be HVLPD.

The sample size in the current study was very limited; therefore, further studies involving larger samples are required to confirm the results. The optimal approach for treatment remains unknown and previous studies have demonstrated that the prognosis of patients with HVLPD is variable (11,14,21,22). Patients in the current study received different treatments; even so, one case succumbed even following treatment with CHOP.

In conclusion, the current study revealed marked differences in the clinicopathological features between patients with HVLPD-NK and those with CNKTL, particularly regarding the clinical course, even though these two diseases share similar immunophenotypes and some histopathological features. Therefore, the results of the current study suggest that the HVLPD-NK cell phenotype should be classified as a separate entity.

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Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Authors' contributions

GNW, WCL and MZZ designed and directed the research. GNW and YCu performed the experiments and drafted the manuscript. WGZ, LL and XDZ analyzed and interpreted data. YCh and XZG collected the clinical data. YL collected the experimental data. All authors read and approved the final for publication.

Ethics approval and consent to participate

The current study was approved by the Ethics Committee of The First Affiliated Hospital of Zhengzhou University (Zhengzhou, China). Signed informed consents were obtained from all patients prior to the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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