Review

Hydroa vacciniforme and hydroa vacciniforme-like lymphoproliferative disorder: a spectrum of disease phenotypes associated with ultraviolet irradiation and chronic Epstein-Barr virus infection

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Abstract: Hydroa vacciniforme (HV) is a rare form of photosensitivity disorders in children and is frequently associated with Epstein-Barr virus (EBV) infection, whereas HV-like lymphoproliferative disorders (HVLPD) describe a spectrum of EBV-associated T-cell or NK-cell lymphoproliferations with HV-like cutaneous manifestations, including EBV-positive HV, atypical HV, and HV-like lymphoma. Classic HV occurs in childhood with vesiculopapules on sun-exposed areas, which is usually induced by sunlight and ultraviolet irradiation, and mostly resolves by early adult life. Unlike classic HV, atypical or severe HV manifests itself as recurrent papulovesicular eruptions in sun-exposed and sun-protected areas associated occasionally with facial edema, fever, lymphadenopathy, oculomucosal lesions, gastrointestinal involvement, and hepatosplenomegaly. Notably, atypical or severe HV may progress to EBV-associated systemic T-cell or natural killer (NK)-cell lymphoma after a chronic course. Although rare in the United States and Europe, atypical or severe HV and HV-like lymphoma are predominantly reported in children from Asia and Latin America with high EBV DNA levels, low numbers of NK cells, and T cell clones in the blood. In comparison with the conservative treatment used for patients with classic HV, systemic therapy such as immunomodulatory therapy is recommended as the first-line therapy for patients with atypical or severe HV. This review aims to provide an integrated, overview of current evidence and knowledge of HV and HVLPD to elucidate the pathophysiology, practical issues, environmental factors, and the impact of EBV infection.

Keywords: Epstein-Barr virus; hydroa vacciniforme; lymphoproliferative disorders; photodermatosis; sunlight; skin; ultraviolet radiation

1. Introduction

1.1 Hydroa vacciniforme

Hydroa vacciniforme (HV), first described in 1862, is a rare idiopathic photosensitive cutaneous disorder [1]. Photodermatoses are a heterogenous group of cutaneous disorders involving abnormal reactions to sunlight, usually caused or aggravated by ultraviolet (UV) components [2,3]. Initially, HV was believed to be a photodermatosis, intermediate in severity between hydroa aestivale and xeroderma pigmentosum [4]. Currently, HV is classified into the group of immunologically mediated (idiopathic) photodermatoses [2]. The prevalence of HV is 0.5 cases per 100,000 people in the Scottish population [5]. In the United States, HV constitutes 0.37% of all the patients with photodermatoses and is more prevalent in non-white, non-black patients [6]. In most cases, HV occurs in childhood with a bimodal distribution of early childhood (1 to 7 years old) and around or after puberty (12 to 16 years old) [7]. Classically, HV is characterized by chronic recurrent papulovesicles or vesiculobullous eruptions on sun-exposed areas after sunlight exposure, and is usually self-limited in adolescents or young adults. Patients may be sensitive to one kind of sunlight or to a wider range of wavelengths. Some studies suggest that UVB is the causal agent [4], while other studies report that longer wavelengths in the UVA spectrum are the more likely cause [7,8]. Subsequently, HV is seasonal and occurs typically in the summer.

1.2 Hydroa vacciniforme-like lymphoproliferative disorders

Patients with atypical or severe HV can present similarly to patients with classic HV in the early phase of disease, but recurrent cutaneous eruptions become more severe with age, progressing to involve both sun-protected and sun-exposed areas with facial swelling, ulcers, scarring, fever, hepatitis, hematologic abnormalities, and lymphadenopathy [9]. After a protracted clinical course with many recurrences, a subset of patients with atypical or severe HV may develop a systemic and often fatal EBV-positive T cell or NK cell lymphoma, although development of lymphoma is uncommon [10]. Regarding this phenomenon, the 2008 edition of the World Health Organization (WHO) classification of hematopoietic and lymphoid tumors described the HV-like lymphoma (HVLL) mostly carrying clonal rearrangements of the T cell receptor (TCR) genes and monoclonal Epstein-Barr virus (EBV) [11]. However, because of the inability to predict which patients will behave in an indolent fashion versus those patients who will develop overt lymphoma, the new designation hydroa vacciniforme-like lymphoproliferative disorder (HVLPD) has been established in the 2016 edition of the WHO classification [12,13]. This term encompasses chronic HV-like EBV-positive lymphoproliferative disorders of childhood with an increased risk of developing systemic lymphoma. By definition, HVLPD should include EBV-positive HV subtypes, particularly atypical or severe HV cases, and HVLL with a broad spectrum of clinical severity and a long disease course. HVLPD occurs mainly in children in Asia and Latin America without a significant sex bias [14], and the median age at diagnosis is 8 years (range: 1 to 15 years) [13].

In the early phase of disease, patients with HVLPD present with cutaneous disorders involving sun-exposed areas characterized by chronic papulovesicular skin lesions, ulcers, and scarring with an indolent behavior, similar to classic HV. However, some patients experience a long course of recurrences with disease extending to sun-protected skin areas, and progressing to systemic manifestations, including fever, hepatitis, lymphadenopathy, hepatosplenomegaly, and hemophagocytic syndrome [10,15,16]. Non-white patients with HVLPD are more likely to develop systemic disease than white patients [17]. Moreover, HVLPD may persist for dozens of years and over time about 15% of patients with HVLPD will develop HVLL with a higher mortality rate [10,18-20]. HVLL is predominantly reported in Latin America (Peru, Mexico, and Guatemala) and Asia (Korea, Japan, and Taiwan), and rarely occurs in whites [17,21]. In Taiwan, Lee *et al.* reported that HVLL constitutes 1% of all primary cutaneous lymphomas [22].

2. UV irradiation, chronic EBV infection, and the hypothetic pathogenesis

2.1 UV irradiation may induce HV

Among environmental hazards, UV irradiation is one of the most important factors involved in aging skin, photo-allergy, and phototoxic responses and tumor induction and progression [23]. UV irradiation can cause DNA damage, modulate the microbial landscape, and activate innate immunity by production of antimicrobial peptides and by stimulating innate cells and skin resident γδ T cells [24]. On the other hand, UV irradiation induces an immune suppressive environment in the skin, and subsequently inhibits effector T cells present in the skin, and shapes the persistence, phenotype, specificity, and function of resident memory T cells [24]. Moreover, high-dose UV irradiation may disrupt the barrier function of the skin, thereby facilitating the entrance of microbes that trigger cytokines production and modulate the immune system [24].

Since cutaneous lesions of HV patients can be induced by photoprovocation testing, the conceptually accepted hypothesis is that UV radiation with wavelengths between 320 and 390 nm may be the causal agent of HV [8,25-29]. A single high-dose of UVA irradiation does not induce HV, but repetitive photoprovocation tests at the same site, even with lower doses of UVA irradiation, result in the induction of erythema and vesiculation [29]. However, the mechanism and the chromophore resulting in UV-induced damage in HV are unclear and need further investigation.

*2.2 Biological nature of EBV and active EBV infection in HV*

EBV belongs to the γ-herpesviridae subfamily   and γ herpesviruses express virus cancer genes and immortalize infected-lymphocytes [30]. EBV has a double stranded DNA genome in its core that is 172 KB and has about 85 genes. Transferred via saliva in submucosal secondary lymphoid tissues, EBV has a tropism for B cells, but also can infect other types of human cells including T cells, NK cells and even epithelial cells [31]. Being the most widely distributed human pathogen, EBV is associated with various diseases including benign lymphoproliferative diseases (e.g., infectious mononucleosis), lymphoid malignancies (e.g., post-transplant lymphoproliferative disease, Hodgkin lymphomas and extranodal NK/T cell lymphoma), and epithelial tumors (e.g., nasopharyngeal carcinoma and gastric carcinoma) [30]. In healthy individuals, EBV infection is kept under tight control by EBV-specific immune regulators, particularly cytotoxic CD8+ T cells which can eliminate proliferating and lytically infected B cells [32]. Reactivation of viral replication plays an important role in the development of EBV-associated malignancy [33]. During EBV-driven tumor formation, early lytic EBV replication might condition the tumor microenvironment through attraction of monocytes via CCL5 and their differentiation into immune-suppressive tumor-associated macrophages (TAMs) [30]. These TAMs and early lytic EBV replication would promote IL-10 production to suppress protective cytotoxic lymphocyte responses, especially CD8+ T cells [30]. Moreover, EBV-encoded microRNAs (miRNAs) compromise the attraction of cytotoxic T-cells into the tumor microenvironment by downregulating CXCL11 expression, and also by inhibiting antigen presentation on MHC class I molecules on neoplastic cells [30]. Herein, early lytic EBV replication and viral miRNAs seem to collaborate to render the microenvironment of EBV-associated malignancies immune suppressive.

Regarding HV, EBV is highly involved in HV pathogenesis and frequently persists in patients with HV [9,18,34]. In comparison with extremely low EBV DNA loads in healthy individuals, the EBV DNA load in peripheral blood mononuclear cells (PBMCs) and plasma samples is much higher in all HV patients as compared with non-HV patients [35,36]. However, there is no correlation between EBV DNA loads in PBMC or plasma and HV subtype or severity [36]. EBV DNA load in PBMC or plasma also does not correlate with the survival rate of HV patients [36], but a high EBV DNA load in blood might be a useful biomarker in the diagnostic work-up [18]. In skin biopsy specimens, the number of EBV+ lymphoid cells shown by in situ hybridization for EBER is variable, although LMP-1 is usually negative (type I latency pattern). EBV-infected cells are mainly cytotoxic T-cells (CD3+, CD8 +, TIA-1+, granzyme B+, perforin+) or NK-cells (CD56+), whereas only a few are CD4+ or CD4-/CD8- [37]. By flow cytometric in situ hybridization, Kimura et al. found that EBV-infected cells in nearly half of HV or HVLL patients were γδ T cells that completely expressed molecules characteristic of cytotoxic cells [38]. Using electron microscopy, viral particles of EBV and

EBV DNA have been identified in lymphocytes and keratinocytes of phototest-induced skin of HV patients, but were absent in the surrounding normal skin [18]. . Notably, expression of EBV-encoded BZLF1 mRNA in skin is an EBV reactivation signal and correlates with a poorer prognosis [35,39]. Thus, although the mechanism remains unclear, EBV may play a key role in the pathogenesis and disease progression of HV and HVLPD.

2.3 Hypothetical pathogenesis and disease course

Although the pathogenesis of HV and HVLPD is unclear, based the long-term observational studies [10,18], we proposed a hypothetical course for the interplay between UV irradiation, EBV infection, HV subtypes, and HVLL (Figure 1). Cutaneous lesions of classic HV patients may be induced by UV irradiation and chronic EBV infection in childhood, usually with polyclonal T cells, and most of these lesions spontaneously remit in young adulthood. However, a subset of individuals may fail to develop immune tolerance to latent EBV infection, conferring a predisposition to acquire atypical/severe HV with UV-induced activation, and associated with atypical EBV-positive T cells. Clinically, patients with atypical/severe HV have recurrent papulovesicular eruptions and ulcerated indurated lesions on sun-exposed areas, and extending to sun-protected areas with systemic symptoms. Although most patients with atypical or severe HV have an indolent behavior with a long clinical course, a few patients with atypical or severe HV evolve into aggressive EBV-positive HVLL, usually associated with monoclonal EBV-infected T cells. With prolonged clinical follow up, the mortality rate for patients with EBV-positive HVLL is high.
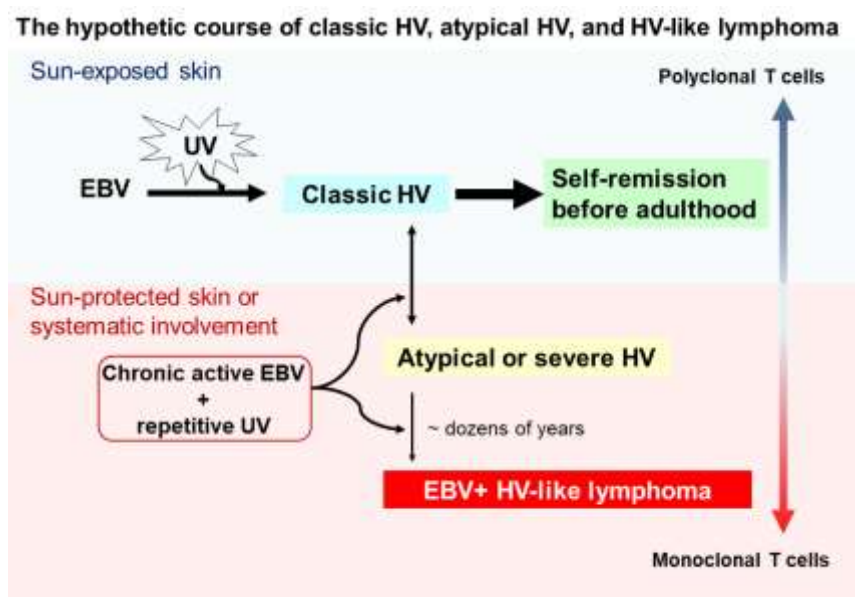

Figure 1. Schematic of a hypothetical suggestion regarding the onset and evolution of classic hydroa vacciniforme (HV), atypical or severe HV, and hydroa vacciniforme-like lymphoma (HVLL). Ultraviolet (UV) irradiation and chronic Epstein-Barr virus (EBV) infection likey contribute to the onset of classic HV skin lesions in children, but most of these lesions resolve spontaneously by the age of young adulthood. However, under chronic active EBV infection and repetitive UV exposure, some patients develop atypical or severe HV characterized by recurrent papulovesicular eruptions and ulcerated indurated lesions on sun-exposed areas. These lesions also may extend to sun-protected areas with systemic symptoms (e.g., fever), liver damage, lymphadenopathy, hepatosplenomegaly, and hemophagocytic syndrome. Despite most patients with atypical or severe HV having an indolent clinical course, a few patients with atypical or severe HV after dozens of years evolve into aggressive EBV-positive HVLL, associated with a monoclonal T cell proliferation.

**3. Clinical manifestations and laboratory characteristics**

The classic presentation of HV is that patients develop pruritus and a stinging sensation followed by hemorrhagic, umbilicated papulovesicular lesions and crusted bullae primarily on light-exposed areas [6]. Cutaneous lesions usually occur hours to days after sunlight exposure and are located mostly on the face, neck, forearms, and the dorsa of the hands [6]. The papulovesicular lesions or bullae most often develop an erythematous base and are initially tense, followed by progressive necrosis that leads to healing with a varioliform scar (Figure 2). In addition, a mixture of hyper- and hypopigmented lesions results in a polymorphous skin presentation. The differential diagnosis for HV at this stage includes erythropoietic and hepatic porphyrias,   which can be excluded by checking the level of porphyrins in the blood and urine, as well as phototoxic reactions, vesiculobullous form of polymorphous light eruption, and actinic prurigo [40]. Classic HV has no systemic symptoms and no abnormalities of routine laboratory tests, immune functions, anti-nuclear factors, vitamin metabolism, or porphyrin levels [9]. Classic HV usually remits during adolescence and is not associated with systemic disease or fatal morbidity.
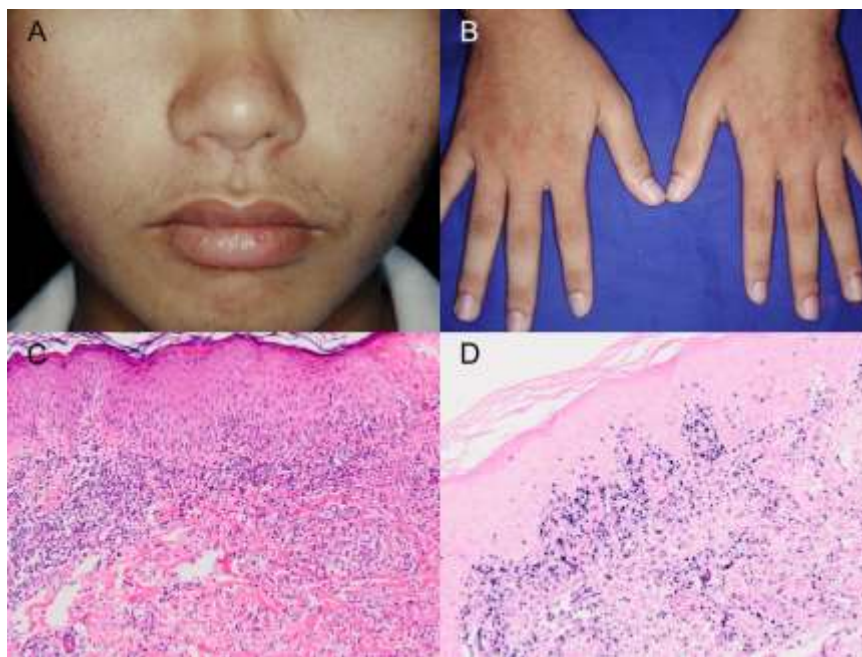
Figure 2. Clinical and pathologic features of classic HV. (A-B) The patient was a 17-year-old boy who presented with multiple papulovesicular eruptions, crusting and scarring over face and the dorsum of both hands for 4 to 5 years. The lesions were exacerbated in summer. (C) Hstological examination of the skin biopsy specimen shows a dense lymphocytic infiltrate, mostly confined to the upper dermis, and composed of small lymphoid cells with minimal atypia (H&E, 100X). (D) In situ hybridization for EBV-encoded RNA (EBER) shows   numerous positive cells in the skin (EBER, 100X).

Unlike classic HV, patients with atypical or severe HV may have skin lesions on sun-protected areas, and can present with systemic symptoms such as fever, lymphadenopathy, hepatosplenomegaly, anemia, and leukopenia, particularly late in the course of disease (Figure 3). The cutaneous signs of atypical or severe HV occur at older ages than those of patients with classic HV, and age of oncet of > 9 years is a risk factor [35]. In one study, conjunctivitis and oral aphthous stomatitis/gingivitis were observed in 26% of patients with classic HV versus 42% of patients with atypical/severe HV [35]. In addition, over 90% of patients with classic HV or atypical/severe HV have elevated γδ T-cell percentages > 5%, and all HV patients have a high EBV DNA load, although there were no statistically significant differences between classic versus atypical/severe HV [35]. By real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR) and flow cytometry immunophenotypic analysis, Cohen et al. described elevated levels of EBV DNA in the blood and high levels of EBV DNA in T or NK cells in all HVLPD patients, without any significant differences

between patients with classic versus atypical/severe HV [17]. Compared to classic HV patients, atypical/severe HV patients more frequently had abnormal antibody profiles to EBV antigens, such as elevated antiviral capsid antigen (VCA),elevated anti-early antigen (EA) and low EBV nuclear antigen (EBNA), and the serologic patterns were consistent with chronic active EBV infection [9]. However, anti-EBV antibody titres, EBV DNA load in PBMCs, number of Epstein-Barr encoding region (EBER) positive cells, and the subsets of infiltrating cells in skin biopsy specimens did not correlate with mortality [35].
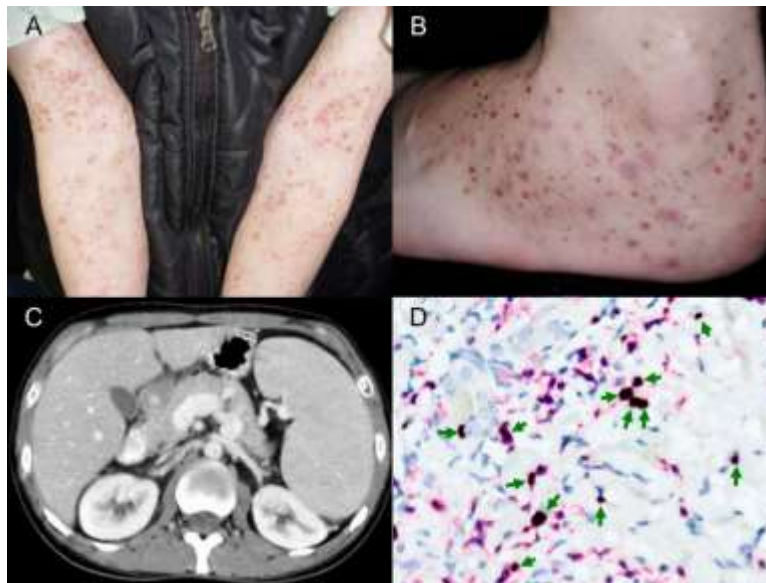
Figure 3. Clinical and pathologic features of a patient with HVLPD and development of HVLL. (A, B) The patient was a 31-year-old man who presented recurrent vesicles and papules on the face, hands and legs for 17 years. The cutaneous lesions extended to sun-protected areas, including upper arms and feet. (C) This patient had intermittent fevers, pancytopenia, and palpable neck lymph nodes, and the abdominal computerized tomography (CT) scan with contrast enhancement showed splenomegaly. (D) In the skin biopsy specimen, double staining of CD3 and EBER in situ hybridization proved   EBV infection in many T cells (green arrows, 400X).

When extracutaneous involvement occurs (hepatosplenomegaly, lymphadenopathy, bone marrow infiltration) with hematological abnormalities, others   recommend that these lesions be classified as HVLL [37]. Fever, weight loss, and asthenia can be present, and elevated serum LDH and/orliver function tests are noted in one-third of patients [37]. Clonality testing can be helpful because the presence of monoclonal T-cell receptor gene rearrangements correlates with progression of HVLPD to HVLL.

4. Phototesting and photoprovocation testing

Phototesting is an important method to confirm photosensitivity and provide an action spectrum, although the methodology employed for phototesting is different in different dermatology units. Generally, using a template with several exposable windows, unaffected skin (preferably on the back or abdomen) is exposed to different doses of UVA, broadband UVB, and /or visible monochromatic or broad-spectrum radiation. The assessment consists of immediate observation of possible urticarial lesions (for solar urticaria) and the minimal erythema dose (MED) reading performed 24 hours after the exposures [2,41]. The MED is defined as the dose of UVB, UVA, or visible light that induces   perceptible erythema on the irradiated area [41]. At least 2 weeks prior phototesting, systemic immunosuppressants and topical agents should be halted to avoid the interference [2]. In patients with HV, with a source of polychromatic UVA, the UVA MED can be low

[26]. With a source of monochromatic UVA, Sonnex et al. observed low MEDs between 340 and 380 nm in three patients [42], but others demonstrated normal UVA MEDs in HV patients [10,43].

Photopatch testing is diagnostically useful to evaluate patients with photoallergic contact dermatitis, and a positive reaction involving unirradiated and irradiated sites is consistent with allergic contact dermatitis. Photopatch test is usually negative in patients with HV [41]. Photo-provocation testing is employed to induce photosensitivity and can be performed by exposing the same skin site to three to five consecutive days of exposure. In about half of patients with HV, lesions can be reproduced by photoprovocative testing [18]. Lesions that develop after photoprovocation can be assessed clinically a and biopsied for histopathologic evaluation.

5. Pathological features and immunochemical profiles

Histopathological features of HV can vary according to clinical stage and the severity of different lesions. In the early stages of HV, characteristic histologic features in the skin include intraepidermal spongiotic vesiculation, varying degrees of lymphocytic infiltrate in the upper dermis (Figure 2) and areas of keratinocyte necrosis [7,10]. A histologic hallmark of HV, suggested by Iwatsuki et al., is a dense perivascular lymphocytic infiltration with reticulated degeneration of the epidermis [9]. The histologic features of classic HV and atypical/severe HV are essentially indistinguishable, such as reticulated epidermal degeneration and dense perivascular infiltration of mainly T cells, although the lymphoid infiltrate is often more dense and extensive, and extends deeply into subcutaneous tissue in atypical/severe HV [9]. Moreover, the clinical manifestations often deviate from the pathological features. Even with clinical features of aggressive disease or systemic involvement, lymphoid cells often show minimal or mild atypia (Figure 3) [44-46]. Thus, the diagnosis of HV versus HVLPD relies greatly on a careful history, physical examination, and phototesting, whereas histopathologic examination and laboratory tests are helpful in ruling out other photodermatoses.

Notably, in the skin biopsy specimens in situ hybridization for EBER shows positive cells in over 95% % of patients with classic HV and atypical/severe HV [9] and 100% patients with HVLPD [19]. Immunohistochemically, expression of CD5, CD7, CD43, and CD25 is variable, whereas CD57 is negative [37]. The lymphoid infiltrate is composed most frequently of cytotoxic CD8+ T cells, but in one-third of cases the infiltrate is derived from CD56+ NK cells [46]. The T cells can be positive for either T-cell receptor $\alpha\beta$ or $\gamma\delta$. The Ki-67 index is variable, and can be very low or as high as 50% [37].

Monoclonal rearrangement of TRG and/or TRB is regarded as a useful tool for distinguishing classic HV from severe HV [29]. In a large cohort study of HVLPD, 88% of patients carried monoclonal T-cell receptor gene rearrangements [19]. Xie et al. further recommended that clonal rearrangements of the T-cell receptor genes is a prognostic indicator; in their study all patients with monoclonal T-cell receptor gene rearrangements died [45]. Direct immunofluorescence is usually nonspecific, although there are a few reports describing granular deposition of C3 below the basement membrane and in the dermal papillae [8,42].

6. Molecular and genetic characteristics

Since Zhang et al. reported chromosome 6q deletion in a cell line (SNK-11) from a patient with HV [47], more and more genomic breakthroughs have been explored. In 2016, Cohen et al. reported that GATA2 deficiency is associated with EBV-positive HVLL [48]. Basically, GATA2 is a transcription factor crucial for both cellular immune responses and controlling the latent infection of herpesviruses, and is expressed in hematopoietic progenitors. Because one of GATA2 binding sites in EBV is located in a latency promoter, the Cp promoter for EBNA latency proteins, insufficiency of GATA2 may impair virus latency and result in more viral replication with prolonged active EBV infection and low numbers of monocytes, CD4 T cells, B cells, and NK cells [48]. To date, only one 24-

year-old Cantonese woman with HVLL was proven to have GATA2 deficiency and was successfully treated with a haplo-identical hematopoietic cell transplant from her unaffected sister [48]. Except the aforementioned case, Cohen et al. did not find mutations in GATA2 or other genes associated with severe EBV disease or repair of DNA in HVLPD patients [17].

Cohen and colleagues performed RNAseq analysis on a skin specimen of one patient with HVLPD. Compared with normal control tissue, skin of HVLPD revealed upregulation of genes encoding multiple chemokines [17], with the most upregulated genes being CXCL11, CXCL9, CXCL10, and CCL4/ These genes encode chemoattractants for activated T cells, activated monocytes, and NK cells. Other upregulated genes include IFNG, which encodes interferon γ to inhibit EBV outgrowth, and APOBEC3A, which encodes a member of the cytidine deaminase family to suppress replication of cytomegalovirus [17].

Moreover, Cohen et al. conducted a whole-exome sequencing study on a Caucasian patient with HVLPD and did not identify any pathogenic variants [17]. However, performing a whole-exome sequencing study in 5 Chinese patients with HVLPD, Xie et al. reported 8 mutant genes that might correlate with development of HVLPD [45]. The 8 mutant genes include 5 driver mutations involving STAT3, IKBKB, ELF3, CHD7 and KMT2D, as well as 3 passenger mutations involving ELK1, RARB, and HPGDS. All of these mutant genes and their downstream signaling pathways have been shown to be pathogenic factors in lymphoproliferative diseases [45]. The occurrence of these mutant genes and the potential mechanisms employed by these genes in HVLPD warrants further study.

7. Treatment and therapeutic agents

Traditionally, HV is treated conservatively, since classic HV usually undergoes spontaneous remission before adulthood. The therapeutic strategies consist of broad-spectrum sunscreens with a high sun protection factor and avoidance of the sunlight exposure [7,28,40]. In patients who do not respond to conservative treatment or have a prolonged refractory course, dermatologists should consider the possibility of HVLPD, particularly atypical/severe HV or HVLL. Currently, there are no guidelines to treat patients with HVLPD, mostly owing to the rarity of the disease. Several regimens, including phototherapy [41], immunomodulatory agents (antiviral agents, interferon, thalidomide, hydroxychloroquine, intravenous immunoglobulin, etc) [17,19,49-52], systemic corticosteroids [17,19], chemotherapy [19,53], and hematopoietic stem cell transplantation [19,53] have been used with variable rates of success. Regarding phototherapy, narrowband UVB (NBUVB) phototherapy 3 times weekly for 5 weeks is most often recommended [41], whereas psoralen-UVA (PUVA) photochemotherapy is not recommended for younger patients. In a report of 41 cases with HVLPD, Liu et al. suggested conservative treatment for most Chinese patients with HVLPD, and that chemotherapy should not be as a first-line treatment [19]. Similarly, studies from Latin American nations have reported poor outcomes in patients receiving chemotherapy [54]. If chemotherapy fails to eradicate lymphoma cells, this therapy may worsen the prognosis by inducing immunosuppression and reactivating EBV replication. Among a variety of therapeutic modalities, immunomodulatory therapy for HVLPD is often recommended [37]. Immunomodulator agents can modulate the host inflammatory response by enhancing innate immunity against viral replication, and can suppress disease aggressiveness.

8. Conclusions

HV (primarily cutaneous manifestations) and HVLPD (more often systemic or extracutaneous involvement) encompass a range of disease entities that typically occur in children or young adults who usually have a prolonged clinical course. HV and HVLPD are highly associated with EBV infection and UV radiation. Despite of the clinical and pathological similarities between HV and

HVLPD, prognosis is divergent. Establishing a diagnosis of HV, HVLPD or HVLL is multifactorial and therefore needs to incorporate history, clinical manifestations, phototesting results, histopathological features, presence and extent of EBV infection and assessment of T-cell clonality. Because patients with HVLPD exhibit a highly variable clinical course, close monitoring and systemic evaluation are essential to alleviate the potential risk of systemic lymphoma. Although there is no consensus on a first-line therapy for patients with HVLPD, immunomodulatory therapies may be associated with greater efficacy than chemotherapy. Molecular testing of HV and HVLPD is needed to identify biomarkers helpful in predicting clinical behavior, monitoring disease activity, and for identifying potential targets for drug development, thereby facilitating personalized treatment of patients with HVLPD. A major challenge in these efforts is the rarity of this disease, and therefore it seems likely that targeted funding and large cooperative efforts between multiple institutions will be required to more thoroughly study this disease.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

HV	Hydroa vacciniforme
UV	Ultraviolet
WHO	World Health Organization
HVLL	Hydroa vacciniforme-like cell lymphoma
HVLPD	Hydroa vacciniforme-like lymphoproliferative disorders
EBER	Epstein-Barr encoding region
EBV	Epstein-Barr virus
VCA	Viral capsid antigen
PUVA	Psoralen- ultraviolet A
NK	Natural killer
EBNA	EBV nuclear antigen
EA	Early antigen
qRT-PCR	Real-time quantitative reverse transcription polymerase chain reaction
PBMCs	Peripheral blood mononuclear cells
NBUVB	Narrowband ultraviolet B
MED	Minimal erythema dose
TAMs	Tumor-associated macrophages

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