Published in final edited form as:

J Am Acad Dermatol. 2018 March ; 78(3): 637–642. doi:10.1016/j.jaad.2017.08.005.

RECURRENT SCARRING PAPULOVESICULAR LESIONS ON SUN-EXPOSED SKIN IN A 22-YEAR-OLD MAN

Melissa A. Levoska, BS^{a,b}, Jeffrey I. Cohen, MD^c, Irini Manoli, MD, PhD^d, Chyi-Chia Richard Lee, MD, PhD^e, Steven S.T. Ching, MD^f, Jessica Shand, MD, MHS^g, Deborah Tamura, RN, MS^a, Kenneth H. Kraemer, MD^a, and John J. DiGiovanna, MD^a

^aLaboratory of Cancer Biology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

^bMedical Research Scholars Program, National Institutes of Health, Bethesda, MD, USA

^cLaboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA

^dMedical Genomics and Metabolic Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA

^eLaboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

^fFlaum Eye Institute, University of Rochester, Rochester, NY, USA

^gDivision of Pediatric Hematology-Oncology and Wilmot Cancer Center, University of Rochester, Rochester, NY, USA

Keywords

Epstein-Barr Virus; Hydroa Vacciniforme; photosensitivity; photodermatitis; EBV-associated lymphoproliferative disorders

CASE SUMMARY

History

A 22 year old Caucasian male has been followed in the Clinical Center at the National Institutes of Health (NIH) for recurrent outbreaks of scarring herpetiform lesions on sun-exposed areas.^{*} He reported itching and burning within fifteen minutes of sun exposure

Corresponding Author: John J. DiGiovanna, MD, Laboratory of Cancer Biology and Genetics, National Cancer Institute, NIH, 37 Convent Drive, Rm. 4002, Bethesda, MD 20892-4262 Telephone: 240-760-6340 Fax: jdg@nih.gov.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflicts of interest: none

This work has not been previously published, not currently submitted elsewhere, nor presented at a national/international meeting. Reprints will not be requested.

evolving into fluid-filled blisters over the next day, then darkly colored crusts and healing over 1–2 weeks, sometimes with pox-like depressions (Figure 1 A–E).

Living in the northeastern part of the United States, outbreaks occurred in the spring and summer with upwards of twenty lesions, and intermittently throughout the year. Sitting near windows (predominantly UVA) in school, or riding in a car, could precipitate lesions, however fireplaces or fluorescent bulbs did not. He continued to participate in outdoor activities.

His first outbreak occurred at age 3 years during the spring in the southeastern part of the United States (US) when he and two siblings had a varicella infection. The summer outbreaks continued, but resolved in winter after moving to the northeast. At 5 years of age, his parents recognized that the lesions were precipitated by sun and began protection with hats, long sleeves, and sunscreen. Outbreaks tended to occur at the beginning of spring or when he did not use photoprotection, and two were associated with fever and pharyngitis. Bacterial and viral cultures of active skin lesions for HSV and VZV were negative. Some episodes were treated with antivirals, antibiotics or prednisone with inconsistent improvement. UVA and UVB provocative testing was negative. Testing for porphyrins in his urine and blood during skin eruptions were negative as was direct immunofluorescence of a skin biopsy.

Severe inflammation and blistering of his lips [Figure 1F] occurred in association with sun exposure. At 14 years of age, he had gingival inflammation treated with gingivectomies. Oral cultures were negative for adenovirus, CMV, HSV and VZV. He had multiple episodes of bilateral follicular conjunctivitis associated with skin lesions and occasionally, non-painful corneal lesions [Figure 1G, H] but denied photophobia.

He denied fatigue, weight loss, night sweats, joint symptoms, skin infections, hypersensitivity to mosquito bites, abnormal reactions to vaccinations, and cold sores. He did not have evidence of immunodeficiency.

The patient's mother had pruritic sun-induced rashes without blisters or scarring, and several family members had autoimmune related abnormalities including Raynaud's syndrome, Sjogren's syndrome, gestational lupus, Hashimoto's thyroiditis, gluten enteropathy, multiple sclerosis, and positive antinuclear antibody (ANA) tests.

Physical Examination

At age 22 years, examination at the NIH Clinical Center showed active lesions in various stages (small vesicles, umbilicated papules, and papules with crusts) over the neck, superior helices of the ear and dorsal surface of the hands [see Figure 1]. There were hypopigmented scars (1 mm to 2 cm) on his cheeks, nose, neck, dorsum of his hands and upper trunk, and larger scars on his shoulders. He had a few facial lentigines and three café au lait macules (2

*The patient, and/or parents, signed consents and were followed under NIH protocols that were approved by the Institutional Review Boards of the National Human Genome Research Institute, National Institute of Allergy and Infectious Diseases, and the National Cancer Institute.

to 4 cm) on the right chest and right upper arm but no oral nor ocular lesions. A small (0.5-cm) right inguinal lymph node was palpable but no hepatosplenomegaly.

Laboratory Studies

A skin biopsy (Figure 2A) obtained from an active lesion (Figure 1C) showed epidermal spongiosis with vesiculation and necrosis overlying a superficial and deep perivascular inflammatory chronic inflammation. The epidermal necrosis was focally confluent and infiltrated by a mixture of acute and chronic inflammatory cells (Figure 2B). EBV-encoded RNA (EBER) positive lymphocytes are shown in Figure 2C. His blood was positive for antibody to Epstein-Barr nuclear antigen (EBNA) and Epstein-Barr virus capsid antigen IgG (EBVCA-IgG), and negative for EBVCA-IgM. EBV DNA levels in his blood were markedly elevated up to 1,325,500 copies/mL [Reference value approximately < 200 copies/mL]. EBV in the blood was predominantly localized to T-cells and T-cell receptor PCR detected a clonal T-cell population in the peripheral blood. CD4, CD8, CD20, and NK cell counts were within normal limits. A panel of autoimmune antibodies were negative; thyroid function tests and immunoglobulin levels were within normal range. Testing for antibodies to VZV was positive for IgG but not IgM, consistent with prior infection.

Diagnosis

Hydroa vacciniforme (HV) with chronic active Epstein-Barr virus (CAEBV) infection.

Management/Course/Work-up

Typical HV may resolve in late adolescence or young adulthood, or have features of CAEBV with progression to lymphoproliferative disease, including lymphoma. This patient had a markedly elevated EBV load, presence of EBV in T cells, and a persistent clonal T-cell population in his peripheral blood. Bone marrow biopsy showed a T-cell clonal population with some EBV-positive cells (4–5% of the cellular marrow) and a hypocellular bone marrow without increased blasts or lymphoid aggregates. An 18-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) scan did not identify a lymphoproliferative process.

Serum levels of the storage forms of vitamin D (25-OH, D2 and D3) were in the range of mild to moderate deficiency. A dual-energy x-ray absorptiometry (DEXA) scan showed mild osteopenia, consistent with chronic photoprotection. Vitamin D supplementation was recommended.

DISCUSSION

HV is a rare childhood photodermatosis associated with latent EBV infection.¹ Typical HV has outbreaks that begin during childhood or early adolescence without systemic involvement and usually resolve by young adulthood.^{2, 3} Some cases persist into adulthood with elevated levels of EBV in the blood.^{4, 5} Most patients with typical HV have been diagnosed in the United States, Europe, Australia, South Africa and Asia.^{5–8} In contrast, patients with severe HV-like eruptions are often from Asia,^{9–12} and South America.^{13–16} Severe HV-like eruptions involve both sun exposed and sun protected areas, penetrate

deeper, form necrotic ulcers with deep scarring and are associated with multisystem clinical abnormalities.^{6, 17, 18}

The etiology of HV may involve immunologic, genetic and environmental factors, and is related to infection with EBV⁵ (human herpesvirus-4), an enveloped, double-stranded DNA virus with B-cell tropism.¹⁹ In the US, EBV infection is prevalent (>60%) in children ages 6 to 19, and is usually asymptomatic in young children.^{20 19, 21} Infection during adolescence or adulthood usually manifests as acute infectious mononucleosis, with fever, pharyngitis, and lymphadenopathy.^{22, 23} After the primary infection, EBV remains latent in memory B cells in immunocompetent hosts, allowing the virus to persist and be shed from the oropharynx.⁶

Diagnosis of HV is based on clinical, histopathological, and laboratory findings. The gold standard test is EBV-encoded ribonucleic acid (EBER) positive lymphocytes in the dermis by *in situ* hybridization.^{1, 6, 8} In HV patients EBV is typically found in $\gamma\delta$ -T-cells²⁴ or NK cells, whereas in healthy individuals, EBV is localized in B cells. After primary infection, circulating levels of EBV DNA may be elevated for a few months²⁵ and previously infected healthy individuals usually have low or undetectable levels. With typical HV, EBV DNA levels are often markedly elevated and even higher in severe HV-like eruptions.^{8, 24}

While EBV infection in most immunocompetent individuals resolves into a latent phase, rarely, as in our patient, persistent active infection (CAEBV) can occur,⁶ with recurrent or long-lasting infectious mononucleosis-like symptoms.¹⁹ CAEBV has been associated with severe hydroa vacciniforme-like eruptions and hypersensitivity to mosquito bites (HMB).⁶ Patients with HMB develop necrotic vesicles or bullae triggered by mosquito or insect bites that often result in scarring and systemic abnormalities.^{26, 27}

HV may be part of a spectrum of EBV-associated lymphoproliferative disorders (LPDs), caused by the clonal proliferation of T-cells or NK cells.²⁸ To avoid confusion with true lymphomas the World Health Organization (WHO) re-classified HV-like lymphoma as “HV-like lymphoproliferative disorder.” in 2016.^{29, 30} The severe form of HV is associated with fever, lymphadenopathy, hepatosplenomegaly, liver damage,⁶ and hematologic abnormalities.⁸ Oral lesions are more common, and there can be cartilage destruction or bone absorption.^{31, 32} Patients with severe HV-like lymphoproliferative disorder have a monoclonal T-cell receptor gene rearrangement by PCR and/or monoclonal NK-cell proliferation.^{14, 16, 28} They can progress to EBV-associated NK or T-cell lymphomas.^{8, 15, 17, 33}

Genetic variations have been associated with severe EBV disease including polymorphisms in HLA-A01³⁴ and interleukin-10 (IL-10),³⁵ and mutations in a variety of genes: *SH2D1A*, *ITK*, *BIRC4*, *CD27*, *MAGT1*, *LRBA*, *CORO1A*, *PIK3CD*, *STK4*, *PRF1*, *UNC13D* and *STXBP2*.^{36, 37} Recently, GATA2 deficiency has been linked to severe EBV infection, CAEBV infection, HV-like lymphoproliferative disorder and EBV-associated lymphoma.³⁸ We did not find mutations in any of these genes in our patient.

Our patient developed typical HV lesions continuing into his early twenties, with elevated blood levels of EBV DNA, and EBV detected in tissue (skin biopsies) with lymphocytic

infiltrates, consistent with CAEBV infection.³⁹ In patients with persistent disease activity, following EBV DNA levels in the blood can help assess for the development of aggressive systemic disease. Our patient had T-cell clonality in the peripheral blood which is monitored annually for evidence of malignant lymphoproliferation.

Disease management of typical HV involves prevention of outbreaks through sun avoidance and photoprotection, including hats, clothing, sunscreen and tinted windows that block UV exposure.^{6, 7, 40} A variety of treatments have been reported with little or inconsistent benefit including antibiotics,⁷ thalidomide,⁴⁰ antivirals (acyclovir and valacyclovir),^{41, 42} hydroxychloroquine,⁷ azathioprine, cyclosporine, corticosteroids,⁷ fish oils,^{7, 43} beta carotene,^{3, 7} and prophylactic narrow-band UVB phototherapy.^{3, 7} Hematopoietic stem cell transplantation is usually required for patients with severe HV with systemic disease. Vaccines for prevention of EBV infection are currently being developed.⁴⁴

Acknowledgments

We would like to thank Kennichi Dowdell, Ph.D., National Institute of Allergy and Infectious Diseases, NIH for determining EBV viral loads in purified lymphocyte subpopulations and Alexandra A. Herzlich, M.D. for obtaining the eye images. We would also like to thank Francis S. Collins, M.D., Ph.D. and William A. Gahl, M.D., Ph. D. for their efforts in the initiation and support of these studies, and Edward W. Cowen, M.D., M.H.Sc for his role in the initial diagnosis of this patient.

The patient, and/or parents, signed consents and were followed under NIH protocols that were approved by the Institutional Review Boards of the National Human Genome Research Institute, National Institute of Allergy and Infectious Diseases, and the National Cancer Institute.

Funding Sources: This research was supported by the Intramural Research Programs of the Center for Cancer Research, National Cancer Institute, National Institute of Allergy and Infectious Diseases, and National Human Genome Research Institute, National Institutes of Health (NIH). Support for Ms. Levoska was made possible through the NIH Medical Research Scholars Program (MRSP), a public-private partnership supported jointly by the NIH and generous contributions to the Foundation for the NIH from the Doris Duke Charitable Foundation, the American Association for Dental Research, the Colgate-Palmolive Company, Genentech, and other private donors. For a complete list, visit the foundation website at <http://www.fnih.org>.

Abbreviations

NIH	National Institutes of Health
EBNA	Epstein-Barr Nuclear Antigen
EBER	Epstein Barr Virus-associated RNA
FISH	Fluorescence In-situ Hybridization
LMP	Latent Membrane Protein
EBV	Epstein-Barr Virus
CMV	Cytomegalovirus
HSV	Herpes simplex virus
VZV	Varicella Zoster Virus
UV	Ultraviolet

Ig	Immunoglobulin
CAEBV	Chronic Active Epstein Barr Virus
WHO	World Health Organization
TdT	terminal deoxynucleotidyl transferase
FDG-PET	18-Fluorodeoxyglucose Positron Emission Tomography

References

1. Iwatsuki K, Xu Z, Takata M, Iguchi M, Ohtsuka M, Akiba H, et al. The association of latent Epstein-Barr virus infection with hydroa vacciniforme. *Br J Dermatol*. 1999; 140:715–21. [PubMed: 10233328]
2. Goldgeier MH, Nordlund JJ, Lucky AW, Sibrack LA, McCarthy MJ, McGuire J. Hydroa vacciniforme: diagnosis and therapy. *Arch Dermatol*. 1982; 118:588–91. [PubMed: 7103528]
3. Gupta G, Man I, Kemmett D. Hydroa vacciniforme: A clinical and follow-up study of 17 cases. *J Am Acad Dermatol*. 2000; 42:208–13. [PubMed: 10642674]
4. Xie JL, Chen GY, Jin Y, Zheng XD, Wei XJ, Zheng YY, et al. Hydroa vacciniforme present for 48 years with cytotoxic CD4+ T-cell infiltration and Epstein-Barr virus infection. *Br J Dermatol*. 2012; 166:449–51. [PubMed: 21801161]
5. Verneuil L, Gouarin S, Comoz F, Agbalika F, Creveuil C, Varna M, et al. Epstein-Barr virus involvement in the pathogenesis of hydroa vacciniforme: an assessment of seven adult patients with long-term follow-up. *Br J Dermatol*. 2010; 163:174–82. [PubMed: 20367637]
6. Hall LD, Eminger LA, Hesterman KS, Heymann WR. Epstein-Barr virus: dermatologic associations and implications: part I. Mucocutaneous manifestations of Epstein-Barr virus and nonmalignant disorders. *J Am Acad Dermatol*. 2015; 72:1–19. quiz -20. [PubMed: 25497917]
7. Huggins RH, Leithauser LA, Eide MJ, Hexsel CL, Jacobsen G, Lim HW. Quality of life assessment and disease experience of patient members of a web-based hydroa vacciniforme support group. *Photodermatol Photoimmunol Photomed*. 2009; 25:209–15. [PubMed: 19614900]
8. Iwatsuki K, Satoh M, Yamamoto T, Oono T, Morizane S, Ohtsuka M, et al. Pathogenic link between hydroa vacciniforme and Epstein-Barr virus-associated hematologic disorders. *Arch Dermatol*. 2006; 142:587–95. [PubMed: 16702496]
9. Cho KH, Lee SH, Kim CW, Jeon YK, Kwon IH, Cho YJ, et al. Epstein-Barr virus-associated lymphoproliferative lesions presenting as a hydroa vacciniforme-like eruption: an analysis of six cases. *Br J Dermatol*. 2004; 151:372–80. [PubMed: 15327544]
10. Shi JQ, Chen QX, Li SF, Li W. Hydroa vacciniforme-like cutaneous T-cell lymphoma. *Indian J Dermatol*. 2014; 59:91–3. [PubMed: 24470671]
11. Xu Z, Lian S. Epstein-Barr virus-associated hydroa vacciniforme-like cutaneous lymphoma in seven Chinese children. *Pediatr Dermatol*. 2010; 27:463–9. [PubMed: 20497358]
12. 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; 43:1102–11. [PubMed: 27531667]
13. Magana M, Sanguenza P, Gil-Beristain J, Sanchez-Sosa S, Salgado A, Ramon G, 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; 38:574–9. [PubMed: 9580256]
14. Quintanilla-Martinez L, Ridaura C, Nagl F, Saez-de-Ocariz M, Duran-McKinster C, Ruiz-Maldonado R, et al. Hydroa vacciniforme-like lymphoma: a chronic EBV+ lymphoproliferative disorder with risk to develop a systemic lymphoma. *Blood*. 2013; 122:3101–10. [PubMed: 23982171]
15. Plaza JA, Sanguenza 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; 37:20–5. [PubMed: 25162933]

16. Barrionuevo C, Anderson VM, Zevallos-Giampietri E, Zaharia M, Misad O, Bravo F, 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; 10:7–14. [PubMed: 11893040]
17. Magana M, Massone C, Magana P, Cerroni L. Clinicopathologic Features of Hydroa Vacciniforme-Like Lymphoma: A Series of 9 Patients. *Am J Dermatopathol*. 2016; 38:20–5. [PubMed: 26368647]
18. Eminger LA, Hall LD, Hesterman KS, Heymann WR. Epstein-Barr virus: dermatologic associations and implications: part II. Associated lymphoproliferative disorders and solid tumors. *J Am Acad Dermatol*. 2015; 72:21–34. quiz 5–6. [PubMed: 25497918]
19. Cohen JI. Epstein-Barr virus infection. *N Engl J Med*. 2000; 343:481–92. [PubMed: 10944566]
20. Dowd JB, Palermo T, Brite J, McDade TW, Aiello A. Seroprevalence of Epstein-Barr virus infection in U.S. children ages 6–19, 2003–2010. *PLoS One*. 2013; 8:e64921. [PubMed: 23717674]
21. Straus SE, Cohen JI, Tosato G, Meier J. NIH conference Epstein-Barr virus infections: biology, pathogenesis, and management. *Ann Intern Med*. 1993; 118:45–58. [PubMed: 8380053]
22. Cohen JI. Optimal treatment for chronic active Epstein-Barr virus disease. *Pediatr Transplant*. 2009; 13:393–6. [PubMed: 19032417]
23. Straus SE. Acute progressive Epstein-Barr virus infections. *Annu Rev Med*. 1992; 43:437–49. [PubMed: 1316095]
24. Hirai Y, Yamamoto T, Kimura H, Ito Y, Tsuji K, Miyake T, et al. Hydroa vacciniforme is associated with increased numbers of Epstein-Barr virus-infected gamma delta T cells. *J Invest Dermatol*. 2012; 132:1401–8. [PubMed: 22297643]
25. Balfour HH Jr, Holman CJ, Hokanson KM, Lelonek MM, Giesbrecht JE, White DR, et al. A prospective clinical study of Epstein-Barr virus and host interactions during acute infectious mononucleosis. *J Infect Dis*. 2005; 192:1505–12. [PubMed: 16206064]
26. Tokura Y, Tamura Y, Takigawa M, Koide M, Satoh T, Sakamoto T, et al. Severe hypersensitivity to mosquito bites associated with natural killer cell lymphocytosis. *Arch Dermatol*. 1990; 126:362–8. [PubMed: 1689990]
27. Tokura Y, Ishihara S, Tagawa S, Seo N, Ohshima K, Takigawa M. Hypersensitivity to mosquito bites as the primary clinical manifestation of a juvenile type of Epstein-Barr virus-associated natural killer cell leukemia/lymphoma. *J Am Acad Dermatol*. 2001; 45:569–78. [PubMed: 11568749]
28. Cohen JI, Kimura H, Nakamura S, Ko YH, 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; 20:1472–82. [PubMed: 19515747]
29. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood*. 2011; 117:5019–32. [PubMed: 21300984]
30. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016; 127:2375–90. [PubMed: 26980727]
31. Yamamoto T, Hirai Y, Miyake T, Yamasaki O, Morizane S, Iwatsuki K. Oculomucosal and gastrointestinal involvement in Epstein-Barr virus-associated hydroa vacciniforme. *Eur J Dermatol*. 2012; 22:380–3. [PubMed: 22361979]
32. Gu H, Chang B, Qian H, Li G. A clinical study on severe hydroa vacciniforme. *Chin Med J (Engl)*. 1996; 109:645–7. [PubMed: 9206069]
33. Sanguenza M, Plaza JA. Hydroa vacciniforme-like cutaneous T-cell lymphoma: clinicopathologic and immunohistochemical study of 12 cases. *J Am Acad Dermatol*. 2013; 69:112–9. [PubMed: 23541598]
34. McAulay KA, Higgins CD, Macsween KF, Lake A, Jarrett RF, Robertson FL, et al. HLA class I polymorphisms are associated with development of infectious mononucleosis upon primary EBV infection. *J Clin Invest*. 2007; 117:3042–8. [PubMed: 17909631]

35. Helminen M, Lahdenpohja N, Hurme M. Polymorphism of the interleukin-10 gene is associated with susceptibility to Epstein-Barr virus infection. *J Infect Dis*. 1999; 180:496–9. [PubMed: 10395868]
36. Cohen JI. Primary Immunodeficiencies Associated with EBV Disease. *Current topics in microbiology and immunology*. 2015; 390:241–65. [PubMed: 26424649]
37. Cohen JI, Niemela JE, Stoddard JL, Pittaluga S, Heslop H, Jaffe ES, et al. Late-onset severe chronic active EBV in a patient for five years with mutations in STXBP2 (MUNC18-2) and PRF1 (perforin 1). *J Clin Immunol*. 2015; 35:445–8. [PubMed: 25947952]
38. Cohen JI, Dropulic L, Hsu AP, Zerbe CS, Krogmann T, Dowdell K, et al. Association of GATA2 Deficiency With Severe Primary Epstein-Barr Virus (EBV) Infection and EBV-associated Cancers. *Clin Infect Dis*. 2016; 63:41–7. [PubMed: 27169477]
39. Park S, Ko YH. Epstein-Barr virus-associated T/natural killer-cell lymphoproliferative disorders. *J Dermatol*. 2014; 41:29–39. [PubMed: 24438142]
40. Sonnex TS, Hawk JL. Hydroa vacciniforme: a review of ten cases. *Br J Dermatol*. 1988; 118:101–8. [PubMed: 3342168]
41. Pahlow Mose A, Fisker N, Clemmensen O, Bygum A. Antiviral treatment of a boy with EBV-associated hydroa vacciniforme. *BMJ Case Rep*. 2014; 2014
42. Lysell J, Wiegand Edstrom D, Linde A, Carlsson G, Malmros-Svennilson J, Westermarck A, et al. Antiviral therapy in children with hydroa vacciniforme. *Acta Derm Venereol*. 2009; 89:393–7. [PubMed: 19688153]
43. Modeste AB, Cordel N, Balguerie X, Leroy D, Lauret P, Joly P. Hydroa vacciniforme: dietary fish oil. *Ann Dermatol Venereol*. 2001; 128:247–9. [PubMed: 11319390]
44. Cohen JI. Epstein-barr virus vaccines. *Clin Transl Immunology*. 2015; 4:e32. [PubMed: 25671130]

Key Teaching Points

- Typical Hydroa Vacciniforme is a self-limited EBV-associated disorder of children and adolescents characterized by recurrent outbreaks of scarring papulovesicular lesions. The gold standard diagnostic test is biopsy of an active lesion showing reticular degeneration and demonstrating EBV RNA (EBER+) in lymphocytes.
- Avoiding sun exposure using photoprotection can reduce outbreaks.
- Patients typically have high levels of circulating EBV DNA best detected from whole blood rather than serum or plasma.
- In patients with persistent skin disease activity, following EBV DNA levels in the blood can help assess for the development of aggressive systemic disease.
- Severe HV disease associated with chronic active EBV may progress to lymphoproliferative disorders or lymphoma with increased mortality.

Figure 1.

Hydroa Vacciniiforme. Lesion evolution begins as a vesicle on a red base (1A), which umbilicates (1B), continues to erode (1C) eventually leading to crusting (1D).

E. Larger vesicle (6 mm in size) on the helix.

F. Ulcerations of the lower lip that were associated with sun exposure at 9 years of age.

G. Conjunctival involvement at 10 years of age. The conjunctiva is injected. In the center of the injected conjunctiva is an area of fluorescein staining indicating an epithelial defect, which is also demonstrated in Fig 1H visualized with cobalt blue light. The denuded epithelium is consistent with a ruptured conjunctival vesicle.

Figure 2.

Hydroa Vacciniforme. A. Skin biopsy taken from a papulovesicular lesion on the dorsal surface of the hand (lesion shown in Figure 1C) revealed prominent vesiculation along the basal epidermal layers with partial detachment of epidermis from the subjacent papillary dermis, and a moderately dense perivascular inflammatory infiltrate in the superficial and deep dermis. (H&E stain; magnification: 40×)

B. High magnification view of the affected epidermis showed prominent intraepidermal vesiculation and necrotic epidermal keratinocytes with reticular degeneration (H&E stain: original magnification: 400×). Immunohistochemistry stains (not shown) revealed a dermal inflammatory infiltrate composed of mostly CD3 positive T cells that were predominantly a mixed population of CD4 and CD8 positive T lymphocytes with a small subset of lymphocytes that are positive for CD25 and FOXP3 (which represent regulatory T-cells). Most of the inflammatory cells were negative for CD20 and CD56. Staining was positive for EBV latent membrane protein (LMP) and negative for HSV. PAS (post diastase) stain was negative for fungal hyphae.

C. In situ hybridization showing EBV-encoded RNA (EBER) positive lymphoid infiltrate with nuclear staining in a subset of lymphocytes (original magnification: 600×).