A Survey Examination of Patients With Hydroa Vacciniforme

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Hydroa vacciniforme is a rare acquired photosensitivity disorder that manifests in childhood. We sought to identify the demographics, disease progression, symptoms, risk factors, and treatment efficacy associated with hydroa vacciniforme using a questionnaire. Nineteen surveys were included in the data analysis. Symptoms occurred throughout the year and the most common dermatologic manifestations included redness, blisters, bumps, scars, itching, and burning, predominantly on sun-exposed areas. The most common associated symptoms included oral ulcers, abdominal pain, and eye ulcers. Most participants limited their sun exposure to less than 10 hours weekly and stated sunscreen somewhat helped prevent breakouts. Most participants had no to limited improvement of their symptoms with treatments.

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Hydroa vacciniforme is a rare acquired photosensitivity disorder that manifests in childhood. The disease is characterized by erythematous macules, which usually appear a few hours after sun exposure, especially on the dorsal hands and face. These macules routinely progress into vesicles and bullae, which crust and can form atrophic scars.[1,2] The scars can result in hand and earlobe deformity.[3,4] Conjunctivitis,[5] photophobia,[5] corneal ulceration, and partial absorption of nasal cartilage[6] also have been reported. Skin manifestations can be accompanied with fever and malaise.[2] Although the condition spontaneously resolves over a period of years, various forms of therapy have been tried. Patients have been reported to respond to antimalarial agents,[2,7] β-carotene,[8] cyclosporine,[9] and narrowband UVB (NB-UVB).[10] However, the efficacy of these treatments remains unknown. In the last 10 years, hydroa vacciniforme also has been shown to be associated with latent Epstein-Barr virus (EBV) infection.[11]

Our knowledge of hydroa vacciniforme is limited by the low prevalence of the disease and lack of specific diagnostic tests. Retrospective studies have not defined the associated symptoms of hydroa vacciniforme during the first and subsequent episodes of the disease or the relationship between sun exposure and the onset of symptoms.[1,2,10] In addition, mucosal ulcers have not been frequently reported[12] but were noted in our analysis. Consequently, the purpose of this study is to identify the demographics, disease progression, symptoms, risk factors, and treatment efficacy associated with hydroa vacciniforme.

Methods

Survey Design—A comprehensive questionnaire consisting of 35 questions, including a combination of multiple-choice and open-ended questions, was generated. The impact of the disease on the participants' quality of life was measured using the Skindex-16 survey.[13]

Survey Administration—After approval for the study was obtained from the St. Luke's-Roosevelt Hospital Center institutional review board (protocol number 08-107), an invitation to participate in the survey was posted on a hydroa vacciniforme support group on the Internet (http://health.groups.yahoo.com/group/HydroaVacciniforme). The questionnaire was posted on a Web site and participants were provided a link to the survey. A number of participants had the questionnaire completed by a guardian and all responses were completed anonymously.

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The authors report no conflict of interest.

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Results

Demographics of Participants—Among the 23 surveys collected, 4 were excluded due to a failure of completion of more than 60% of the questions. Nineteen surveys were included in the data analysis. Table 1 lists and summarizes the demographic information of the participants. The participants had a mean age (standard deviation [SD]) of 18.1 (11.0) years, with 11 males and 8 females. Female participants had an earlier mean age of onset (SD) compared with males (4.4 [2.6] years vs 6.0 [3.2] years). Most participants (84.2% [16/19]) reported they were currently symptomatic at the time of the survey. As a result, the mean duration of disease could not be calculated among participants. When asked about their ethnic background, 94.7% (18/19) of participants identified themselves as white, 10.5% (2/19) identified themselves as Asian, 15.8% (3/19) identified themselves as Native American, and 5.3% (1/19) identified themselves as Hispanic. Most participants (63.2% [12/19]) resided in the United States.

Disease Course—Although most participants reported symptoms in the spring (89.5% [17/19]) and summer (84.2% [16/19]), a number of participants also noted symptoms in the autumn (73.7% [14/19]) and winter (63.2% [12/19]). Figure 1 highlights the recurrence of symptoms.

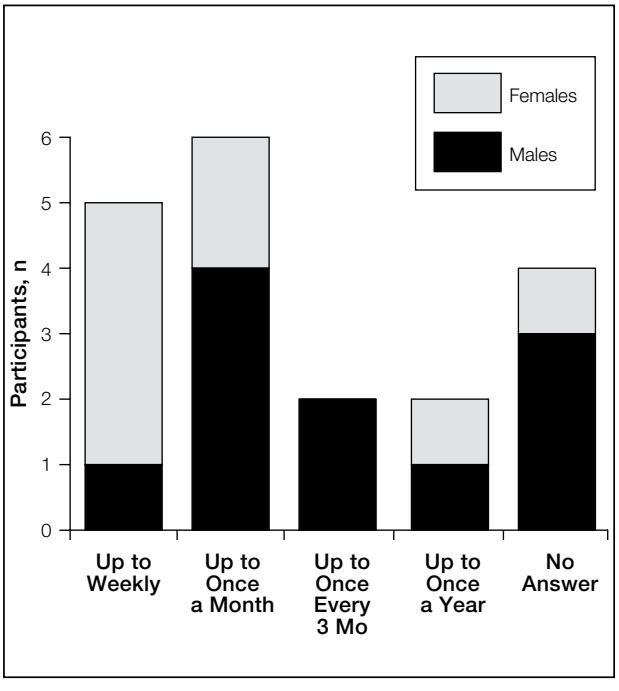

Figure 1. The recurrence of symptoms (N=19).

Responses ranged from up to weekly (26.3% [5/19]), up to once a month (31.6% [6/19]), up to once every 3 months (10.5% [2/19]), and up to once a year (10.5% [2/19]). No answer was reported in 4 participants.

The most common dermatologic manifestations included redness (94.7% [18/19]), blisters (84.2% [16/19]), bumps (84.2% [16/19]), scars (84.2% [16/19]), itching (73.7% [14/19]), and burning (63.2% [12/19]). The most common anatomic locations during the first episodes were the cheeks (84.2% [16/19]), ears (78.9% [15/19]), arms (73.7% [14/19]), hands (63.2% [12/19]), and lips (57.9% [11/19]). These results were consistent between first and subsequent episodes (data not shown).

The most common symptoms associated with hydroa vacciniforme were oral ulcers (52.6% [10/19]), abdominal pain (36.8% [7/19]), eye ulcers (31.6% [6/19]), and pain on exposure to light (26.3% [5/19]). Symptoms associated with EBV, including throat swelling (26.3% [5/19]), enlarged lymph nodes (21.1% [4/19]), undocumented fever (10.5% [2/19]), documented fever (temperature >38.1°C)(5.3% [1/19]), also were reported. These symptoms were similar between first and subsequent episodes (data not shown).

The mean duration (SD) needed for resolution of outbreaks was 2.3 (1.3) weeks. When asked about the progression of symptoms, 47.4% (9/19) of participants noted their symptoms improved, 36.8% (7/19) stated their symptoms remained the same, and 15.8% (3/19) reported worsening of their symptoms over the course of the disease.

Sun Exposure and Sunscreen Use—When asked about the relationship between sun exposure and onset of symptoms, most participants reported the onset of symptoms within 24 hours (63.2% [12/19]) or between 24 and 72 hours (31.6% [6/19]) of sun exposure. Furthermore, most participants limited their sun exposure to 0 to 5 hours (42.1% [8/19]) or 5 to 10 hours (31.6% [6/19]) weekly. Most participants reported symptoms occurring after sun exposure through glass windows (68.4% [13/19]) or outdoor sunbathing (63.2% [12/19]), while fewer respondents (26.3% [5/19]) noted symptoms occurring after tanning in booths.

When asked about sunscreen use, 63.2% (12/19) reported to always use sunscreen, while 31.6% (6/19) of participants noted occasional sunscreen use. Most participants (84.2% [16/19]) stated sunscreen somewhat help prevent breakouts, while most participants reported they use a sun protection factor greater than 50 (52.6% [10/19]) or between 31 and 50 (26.3% [5/19]).

Treatments—When asked about the treatments attempted, 26.3% (5/19) tried antibiotics, another

Table 1.

Participant Demographics[a]

Participant No.	Gender	Age at Review	Age of Onset	Currently Symptomatic	Duration of Disease	Ethnicity	Patient Location
1	M	9 y	6 y	Yes	3 y	White	Ohio
2	M	14 y	3 y	Yes	11 y	White	New York
3	M	17 y	2 y	Yes	15 y	White	Australia
4	M	17 y	2 y	Yes	15 y	White	Australia
5	M	18 y	6 y	Yes	12 y	White	Missouri
6	M	19 y	11 y	No	7 y	White	South Africa
7	M	30 y	11 y	Yes	19 y	White	United Kingdom
8	M	40 y	2 y	Yes	38 y	White	Bosnia
9	M	10 y	7 y	Yes	3 y	Asian, White	California
10	M	15 y	8 y	No	4 y	White, Hispanic, Native American	California
11	M	21 y	8 y	Yes	13 y	White, Native American	California
12	F	5 y	2 y	Yes	3 y	White	Pennsylvania
13	F	7 y	3 y	Yes	4 y	White	United Kingdom
14	F	11 y	5 y	Yes	6 y	White	Georgia
15	F	12 y	3 y	Yes	9 y	White	Germany
16	F	14 y	8 y	Yes	6 y	White	Utah
17	F	28 y	6 y	No	22 y	White	Oklahoma
18	F	12 y	8 y	Yes	4 y	Asian	Maryland
19	F	44 y	6 mo	Yes	43 y	White, Native American	Missouri

Abbreviations: M, male; F, female; SD, standard deviation.

[a]Mean age at review (SD), 18.1 (11.0) years; mean age of onset (SD), 5.3 (3.2) years (males, 6.0 [3.2] years; females, 4.4 [2.6] years); participants currently symptomatic, 84.2%.

26.3% (5/19) used antimalarial agents, 21.1% (4/19) did not try any treatments, 15.8% (3/19) tried NB-UVB, and 5.3% (1/19) attempted psoralen plus UVA. Other treatments attempted by the participants not listed in our survey included β-carotene (26.3% [5/19]), sun avoidance (10.5% [2/19]), and sunscreen (10.5% [2/19]). When asked about the efficacy of the listed treatments, 2 of 3 participants stated they had no improvement with NB-UVB, while 1 participant reported up to 25% improvement. One participant who attempted psoralen plus UVA and 3 participants who tried antibiotics reported no improvement. The other 2 participants who tried antibiotics provided no answer. Furthermore, 3 of 4 participants who attempted antimalarial treatment reported no improvement, while 1 participant reported up to 50% improvement. The fifth participant provided no answer. When asked about the efficacy of treatments not listed in the survey, all 5 participants who tried β-carotene reported no improvement. The 2 participants who listed sun avoidance as a treatment modality noted up to 25% improvement. One of 2 participants who utilized sunscreens reported no improvement, while the other participant reported resolution of symptoms.

Personal and Family History of Hydroa Vacciniforme and Atopy—Most participants (89.5% [17/19]) did not have a family history of hydroa vacciniforme, while 2 participants (10.5%) were uncertain about other family members having the condition. When asked about a personal history of atopy, 42.1% (8/19) reported a history of allergies, 26.3% (5/19) reported a history of asthma, 5.3% (1/19) reported a history of eczema, and 21.1% (4/19) reported a history of hay fever. Overall, 57.9% (11/19) noted a personal history of allergies, asthma, eczema, or hay fever. When asked about a family history of atopy, 47.4% (9/19) reported a family history of allergies, 42.1% (8/19) reported a family history of asthma, 31.6% (6/19) reported a family history of eczema, and 52.6% (10/19) reported a family history of hay fever. Overall, 63.2% (12/19) noted a family history of allergies, asthma, eczema, or hay fever.

Diagnosis of Hydroa Vacciniforme—All participants noted their dermatologists made the diagnosis of hydroa vacciniforme.

EBV Testing—Most participants (78.9% [15/19]) did not seek EBV testing, while only 3 participants (15.8%) had the test performed. One participant provided no answer. Of the 3 participants, 2 had a positive EBV test and 1 had a negative EBV result.

Phototesting—Eight participants (42.1%) sought phototesting; of these participants, 7 (87.5%) had a positive UVA phototest, while 6 (75%) had a positive UVB phototest. One participant (12.5%) could not recall the phototest result.

Quality of Life—Thirteen participants (68.4%) stated that the disease interfered with their daily activities. Additionally, 13 participants (68.4%) stated they were always bothered by the persistence or reoccurrence of their skin condition, while 12 participants (63.2%) noted they were always bothered by their frustration with their condition. Eleven participants (57.9%) were always concerned about the consequences of their skin condition. Furthermore, 11 participants (57.9%) expressed always being annoyed with their condition. Ten participants (52.6%) were always bothered by the appearance of their skin, while a different set of 10 participants (52.6%) were always embarrassed by their skin condition.

Comment

In 1963, McGrae and Perry[1] published a retrospective study of 29 cases of hydroa vacciniforme and concluded the disease was a rare, chronic, photosensitive disorder with 90% (26/29) of cases occurring in childhood, characterized by discrete vesicles on sun-exposed areas that left scars on healing. Patients were otherwise healthy with no evidence of porphyria, and there was a 2:1 ratio of affected males and females.[1] Because these conclusions were made more than 40 years ago, only 3 large studies have been published and management of the disease remains a challenge.[2,8,10]

Hydroa vacciniforme is thought to present during childhood and spontaneously involute during the late teenaged years.[8] Specifically, 1 study identified a bimodal age distribution between 1 and 7 years of age and 12 and 16 years of age.[10] All participants in our study reported the onset of symptoms before their teens with a mean age of onset (SD) of 5.3 (3.2) years. Although 1 prior study stated males had a longer duration of disease compared to females (11 years vs 5 years),[10] the duration of disease could not be calculated in our study, as 84.2% (16/19) of participants were symptomatic at the time the survey was conducted. Five participants (26.3%) still had symptoms beyond their teens. The reasons for the chronicity of disease are unclear; however, in our study, 3 of 5 participants who still had symptoms beyond their teenaged years admitted to tanning in booths. Other case reports have noted a late onset of hydroa vacciniforme beyond the teenaged years among males who had prolonged sun exposure while serving in the army after many years of sun avoidance.[14]

In our study, there was a greater ratio of males to females, and this ratio has been inconsistent among prior studies.[1,2,10] Prior studies also have reported an earlier age of onset in females compared to males.[2,10] This conclusion was supported in our study, as females had a mean age of onset (SD) of 4.4 (2.6) years, while males had a mean age of onset (SD) of 6.0 (3.2) years.

Although the skin types of our participants were not recorded, the vast majority of our participants were white (94.7%). These results are consistent with the predominance of photodermatoses in melanocompromised individuals.

As expected, most outbreaks were reported predominantly during the spring (89.5%) and summer (84.2%) months; however, most participants still reported symptoms during the autumn (73.7%) and winter (63.2%) months, which could be attributed to the penetration of UVA and UVB rays through the atmosphere and the warm climates of the participants' location during the traditionally colder months. Additionally, there was a wide range of answers when participants were asked about the frequency of their symptoms, which may be a product of the participant's sun exposure (cannot be defined by a specific time frame).

Our study confirmed the polymorphic presentation of hydroa vacciniforme. Most participants reported redness, blisters, bumps, scars, itching, and burning during the first and subsequent episodes. Fewer participants noted ulcers. As expected, most skin lesions were located on sun-exposed areas, including the cheeks, ears (Figure 2), and arms during the first and subsequent episodes. The most common associated symptoms were oral ulcers, abdominal pain, eye ulcers, and pain on exposure to light during the first and subsequent episodes.

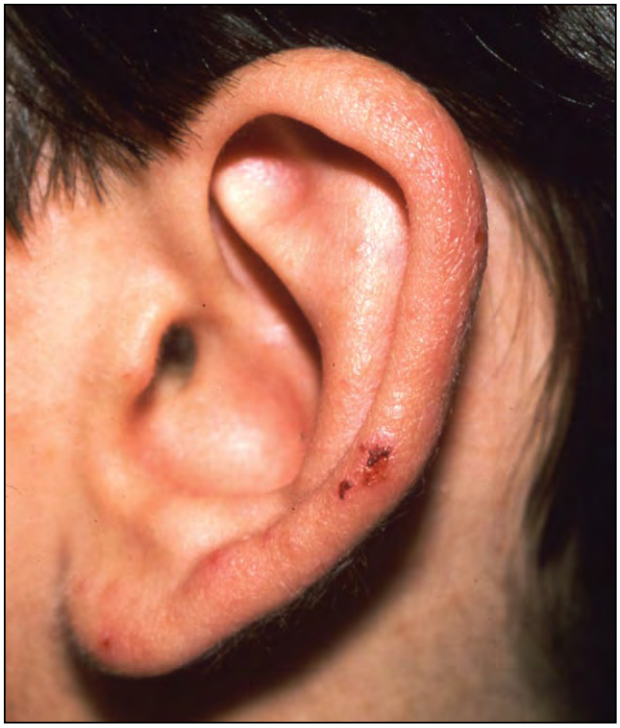

Figure 2. Helix of patient showing an ulcer with hemorrhagic crust.

Symptoms associated with EBV were not prominent among participants during their first episodes of hydroa vacciniforme. However, more participants reported throat swelling (26.3%) and enlarged lymph nodes (21.1%) during subsequent attacks. Among the 4 participants (21.1%) who reported both throat swelling and enlarged lymph nodes, only 2 had EBV testing and both tested positive. Overall, only 3 participants (15.8%) sought EBV testing and 2 had positive results.

The association between latent EBV infection with hydroa vacciniforme was established in 1999 when a study demonstrated 6 children with hydroa vacciniforme had a considerable number of EBV-encoded small nuclear RNA detected in T cells in the dermal infiltrates by in situ hybridization, though these participants did not present with throat swelling or enlarged lymph nodes.[11] Latent EBV, the virus implicated in infectious mononucleosis,[15] has been shown to be associated with a number of malignancies, including Burkitt lymphoma,[16] nasopharyngeal carcinoma,[16] T-cell lymphoma,[17] EBV-associated hemophagocytic syndrome,[18] natural killer cell lymphoma,[19] and Hodgkin disease.[20] As a result, Iwatsuki et al[11] concluded hydroa vacciniforme may be a cutaneous lymphoproliferative disorder mediated by latent EBV infection. In contrast to that study, our study demonstrated 2 participants with positive EBV test results who were symptomatic for infectious mononucleosis. Furthermore, 2 other participants who were symptomatic for infectious mononucleosis with enlarged lymph nodes did not have EBV testing. These findings may support the possibility that EBV has a role in the pathogenesis of hydroa vacciniforme, and patients who are suspected to have hydroa vacciniforme, especially those with numerous outbreaks, should have EBV testing performed.

The mean duration (SD) needed for resolution of outbreaks was 2.3 (1.3) weeks. This result was comparable to Sonnex and Hawk[2] who estimated a range of 1 to 6 weeks for the progression of skin lesions into scars. Furthermore, when our participants were asked about the progression of symptoms, most stated their symptoms either improved (47.4%) or remained the same (36.8%). It remains unclear if this outcome could be attributed to the natural progression of the disease or sun-protection measures.

Hydroa vacciniforme has been suspected to be a delayed-type hypersensitivity (DTH) response because of the dermal perivascular lymphocytic infiltrate seen on pathology.[21] Specific chromophores are suspected to be transformed into antigens after

light exposure and consequently induce this DTH response. Our study may support the theory that hydroa vacciniforme is a DTH response based on the timing between sun exposure and the onset of symptoms. Most participants stated they developed symptoms within 24 hours (63.2%) or between 24 and 72 hours (31.6%) of sun exposure.

Most participants had limited their sun exposure to 0 to 5 hours (42.1%) or 5 to 10 hours (31.6%) weekly, suggesting they believed that sun avoidance was an important means to preventing further symptoms. However, when asked about how they received sun exposure, most stated through glass windows (68.4%) or outdoor sunbathing (63.2%). A few participants had admitted tanning in booths (26.3%), which was most notable among participants who had symptoms beyond 20 years of age. Greater emphasis on sun avoidance from glass windows and tanning booths is needed to prevent further outbreaks.

Sunscreen was a common form of sun protection, as most participants either always (63.2%) or sometimes (31.6%) used sunscreen. Most participants (84.2%) stated sunscreen somewhat helped prevent breakouts and most used a sun protection factor greater than 50 (52.6%). However, our study did not ask if the participants used sunscreen with protection from UVA rays and did not ask participants to quantify the number of times and amount of sunscreen applied. Although anecdotal reports have been published regarding the successful treatment of hydroa vacciniforme with azathioprine,[22] antimalarial agents,[2,7] β-carotene,[8] cyclosporine,[9] fish oil,[22] and NB-UVB,[10] most participants had no to limited improvement of their symptoms with these treatments. Therefore, the resolution of symptoms associated with hydroa vacciniforme may be a result of the spontaneous remission of the disease instead of use of the aforementioned modalities. Consequently, the efficacy of these modalities will likely be difficult to assess. Because most cases of hydroa vacciniforme occur in the pediatric population, the risks for using systemic agents likely outweigh the benefits. Aggressive sun avoidance, broad-spectrum sunscreen, protective clothing, and UV window blockers remain the treatments of choice.[10]

Most cases of hydroa vacciniforme are acquired; however, a few case reports have documented familial cases.[23,24] In our study, most participants (89.5%) denied having a family history of the disease. Furthermore, in contrast to another case series,[10] most participants had a personal history (57.9%) or family history (63.2%) of atopy.

All participants were diagnosed by a dermatologist, which reflects the importance of the dermatologist to recognize, diagnose, and properly manage hydroa vacciniforme, as well as educate patients and their families about proper sun protection.

Prior studies have shown the clinical and histologic reproduction of lesions of hydroa vacciniforme with repetitive UVA irradiation, and most cases demonstrated no change in the minimal erythema dose in the UVA and UVB range.[4,7,10,25-29] In one case series, the 3 patients with the most severe symptoms were reported to have the lowest minimal erythema doses to monochromatic UVA.[2] However, there was variability in the results among patients receiving repetitive UVB irradiation. One case report stated UVB irradiation only produced erythema,[29] while another case cited increased tolerance to UVA erythema by multiple UVB exposure.[26] Two case reports showed no induction of lesions by UVB.[27,28] In our study, most participants did not seek phototesting (57.9%). Although our study confirms UVA irradiation likely reproduces clinical lesions of hydroa vacciniforme, further studies may be needed to clarify the effects of repetitive UVB exposure.

The modified Skindex-16 scale demonstrates the profound impact of the dermatologic manifestations of hydroa vacciniforme on the participants' quality of life. Most participants (68.4%) stated the disease interfered with their daily activities. Furthermore, more than 50% stated they were always bothered by the persistence, consequence, appearance, frustration, embarrassment, and annoyance with their skin condition, which represents 6 of 7 questions included in the emotion scale of the Skindex-16.

The differential diagnosis of hydroa vacciniforme is listed in Table 2. A notable differential is the much more severe hydroa vacciniforme–like eruption (HVLE), which usually is found in children from Latin America and Asia and is characterized by the presence of lesions in non–sun-exposed and sun-exposed areas.[30-35,43] However, in contrast to patients with hydroa vacciniforme, patients with HVLE present with fever, facial edema, extensive tissue loss and disfigurement from primary skin lesions, hypersensitivity to mosquito bites, hepatosplenomegaly, and frequent progression to malignant lymphoma or leukemia.[30-35,43] Histologic findings have demonstrated a dense infiltration of atypical lymphocytic cells expressing CD3,[33,43] CD4,[32] CD8,[35] CD30,[32,33] or CD45RO,[33,43] as well as the presence of EBV-encoded small nuclear RNA.[43,44] Patients often experience a relapsing and remitting course and mortality usually is due to complications of malignancy and infections.[30-35,43] Another HVLE but with natural killer cell phenotype has been described in 2 patients.[45] Clinical features are similar to HVLE, but histology shows a dense dermal infiltrate for CD56, CD30, and natural killer cells, and in situ hybridization of the

Table 2.

Differential Diagnosis of Hydroa Vacciniforme

	Dermatologic Manifestations					Location		
Disease	Crust	Papules	Pruritus	Scarring	Vesicles	Sun-Exposed Areas	Non–Sun-Exposed Areas	Systemic Findings
Hydroa vacciniforme[1-6]	++	–	++	++	++	+	–	Conjunctivitis, oral ulcers, photophobia
HVLE[30-35]	++	+	++	++	++	+	+	Fever, hepatosplenomegaly, leukemia, lymphoma
Actinic prurigo[36]	++	++	++	+	+	+	+	Cheilitis, conjunctivitis, photophobia
Bullous LE[37,38]	++	–	+	–	++	+	+	Alopecia areata, anemia, arthritis, oral ulcers, pericarditis, psychosis, renal failure, seizures, thrombocytopenia
Erythropoietic protoporphyria[39]	+	–	++	+	+	+	–	Cholelithiasis
Hartnup disease[40]	++	++	++	++	++	+	–	Ataxia, glossitis, mental retardation, tremors
PLE[41]	–	++	++	–	+	+	–	Fever, malaise
Primary HSV[42]	++	–	+	–	++	+	+	Fever, lymphadenopathy, malaise

Abbreviations: ++, frequent manifestation; –, rare manifestation; +, occasional manifestation; HVLE, hydroa vacciniforme–like eruption; LE, lupus erythematosus; PLE, polymorphic light eruption; HSV, herpes simplex virus.

lymphocytic infiltrate was positive for EBV.[45] However, the disease course is unknown.

The main limitations of our study were the small sample size and lack of confirmation of the patient's diagnosis. Participants also were recruited from a support group on the Internet, took an active interest in their condition, completed numerous quality of life questions, and demonstrated sun-protection measures. Therefore, it is unclear if the results were representative of all individuals with hydroa vacciniforme. Furthermore, recall bias could have affected the results, especially because a number of questionnaires were completed by the participant's guardian. Finally, responses to the Skindex-16 portion of the survey were modified so that participants could only respond with always, sometimes, or never. Prior studies utilizing the Skindex-16 contained a numeric system with a scale of 1 (for never) to 7 (for always).[13] As a result, the quality of life of certain conditions could not be compared. Additionally, not all participants completed the Skindex-16 portion of the survey, which would have provided inaccurate calculations to compare the quality of life among other conditions.

Conclusion

Our study confirms a number of findings from prior studies. Hydroa vacciniforme occurs predominantly in the pediatric population, earlier in females, and can persist for many years. However, in contrast to other studies, oral ulcers and eye involvement are more common than reported. Despite limited sun exposure, patients are still symptomatic and can experience scarring. No effective treatment exists aside from sunscreen and sun avoidance, and the disease spontaneously remits. The efficacy of proposed treatments will likely be difficult to assess in future studies. Finally, the disease's relationship with EBV remains undefined and future studies are needed to clearly define this relationship.

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