Two cases of hydroa vacciniforme lymphoproliferative disorder in elderly patients: Excellent response to narrow-band ultraviolet B phototherapy

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INTRODUCTION

Hydroa vacciniforme lymphoproliferative disorder (HVLPD) is a rare chronic Epstein-Barr virus (EBV)-associated T/natural killer cell LPDs with a risk of progression to systemic lymphoma. It is further divided into HVLPD classic form, a benign subtype, and HVLPD systemic form which can be a life-threatening subtype. HVLPD mostly affects children and young adults, whereas HVLPD in people more than 65 years old is extremely rare. We herein describe 2 HVLPD cases who were both more than 80 years old and had a good response to narrow-band ultraviolet B (NBUVB) phototherapy.

Abbreviations used:

anti-VCA:	antiviral capsid antigen
CD:	cluster of differentiation
CT:	computed tomography
DNA:	deoxyribonucleic acid
EA:	early antigen
EBER:	EBV-encoded small nuclear RNA
EBNA:	EB nuclear antigen
EBV:	Epstein-Barr virus
HVLPD:	hydroa vacciniforme lymphoproliferative disorder
Ig:	immunoglobulin
LN:	lymph node
NVUVB:	narrow band ultraviolet B
RNA:	ribonucleic acid
TCI:	topical calcineurin inhibitor
TCR:	T-cell receptor
UV:	ultraviolet
UVA:	ultraviolet A

CASE REPORT

Case 1

An 85-year-old Japanese man visited us due to a 3-month history of rash and fever that was unresponsive to oral prednisolone (20 mg (=0.3 mg/kg)/day), antibiotics, and an antiviral. A physical examination revealed necrotic papulovesicular lesions on his face and trunk (Fig 1, *A* and *B*). His body temperature was 37.8 °C and he complained of fatigue. Routine laboratory tests were normal. Serological tests for EBV were as follows: antiviral capsid antigen IgM was negative (<x10), but antiviral capsid antigen IgG (x160), anti-early antigen IgG (x20), and EB-nuclear antigen (EBNA, x10) were positive. The viral load of EBV-DNA was less than 2.0×10^2 copies/ml of whole blood. A computed tomography scan revealed no hepatomegaly, splenomegaly, or lymphadenopathy. A skin biopsy taken from a papulovesicular lesion on the abdomen revealed focal epidermal necrosis (Fig 1, *C*), mild liquefaction degeneration, and dense infiltration of lymphoid cells of small and intermediate size without cellular atypia in the upper dermis (Fig 1, *D*). Immunohistochemical staining

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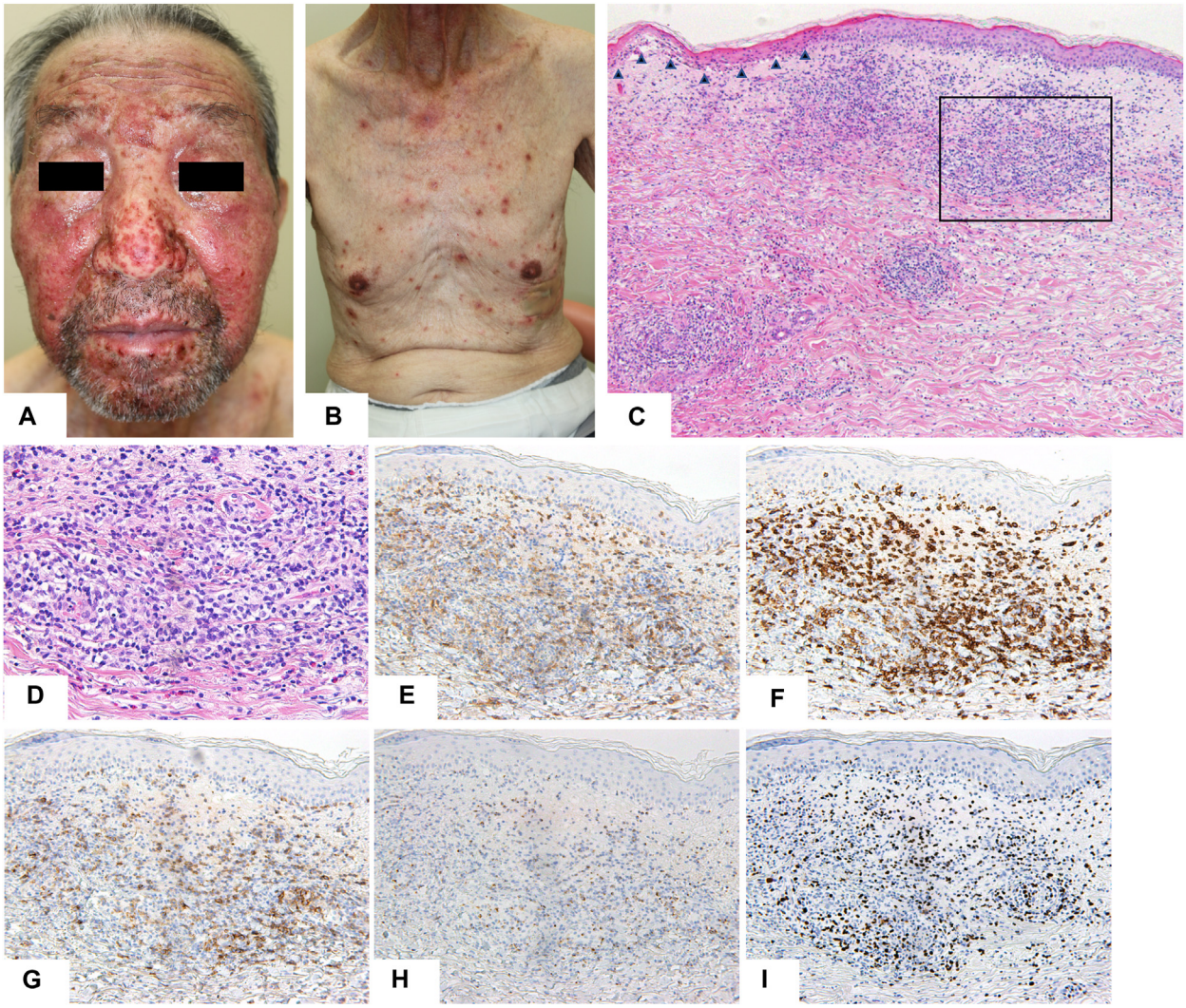

Fig 1. **A** and **B,** Clinical images of case 1 at the initial presentation were photographed. **C,** An image of lower magnification of hematoxilyn & eosin (H & E) staining of the erythema on the abdomen was shown (magnification ×10). *Arrowheads* indicate epidermal necrosis. **D,** An image of higher magnification of H & E staining squared area in (**C**) was shown (magnification ×40). **E-I,** Images of immunohistochemical staining of CD4 (**E**), CD8 (**F**), CD56 (**G**), Granzyme B (**H**), and EBER in situ hybridization (**I**) were shown (magnification ×20).

revealed that small lymphoid cells were positive for CD3, CD4, and CD8 (Fig 1, *E* and *F*), whereas sparsely positive for CD20. They were also positive for granzyme B (Fig 1, *H*). Large lymphoid cells were positive for CD56 (Fig 1, *G*) and EBV-encoded small nuclear ribonucleic acid (RNA) (EBER, Fig 1, *I*). Southern blot analysis of T-cell receptor (TCR) Jγ rearrangement in skin revealed no rearrangement band. Based on these findings, the diagnosis of HVLPD systemic form was made. NBUVB phototherapy was initiated once a week, along with a daily topical calcineurin inhibitor (TCI). NBUVB was chosen since the patient was resistant for oral prednisolone. In addition, due to the age of the patient, a therapeutic option with less toxicity was preferred. After 3 irradiations of NBUVB (total dosage of 2.0 J/cm^2), significant improvement in the skin eruptions was observed (Fig 3, *A* and *B*). NBUVB therapy was maintained at 1-2 times per month at 0.7-0.8 J/cm^2/time (Fig 3, *C*) without TCI for 18 months, until the patient relocated and stopped seeing us. There had been no recurrence of the skin eruptions while he received NBUVB therapy.

Case 2

An 83-year-old Japanese man developed necrotic papulovesicular lesions on his face and neck, subcutaneous nodules on the arms and abdomen, and tense bullae on the palms and soles (Fig 2, *A-C*) 3 months prior to visiting us. His body temperature was 37.6 °C

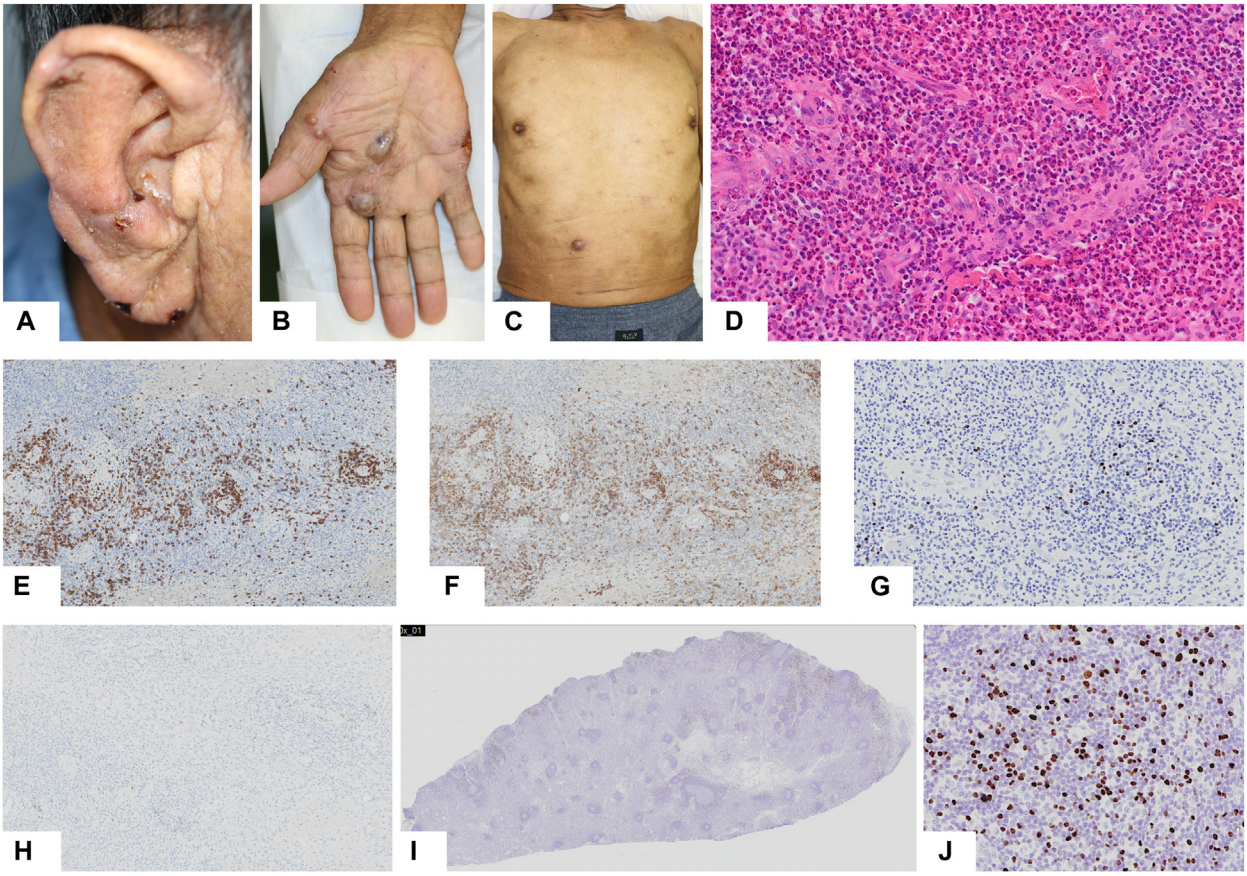

Fig 2. A-C, Clinical images of the case 2 at the initial presentation were photographed. **D,** An image of higher magnification of hematoxilyn & eosin (H & E) staining of the erythema on the dorsum of left hand was shown (magnification ×40). **E-I,** Images of immunohistochemical staining of CD3 (**E**) and CD4 (**F**), and EBER in situ hybridization (**G**) were shown (magnification ×20). **H-J,** An image of TCRβ was shown (magnification ×20) (**H**), EBER in situ hybridization stained on right inguinal lymph node was shown with lower magnification (**I**) and higher magnification (**J**).

and he complained of fatigue. Laboratory tests showed elevated white blood cell counts (11,200/μl) with an increase in eosinophils (5800/μl). Soluble interleukin-2 receptor was also increased (1647 U/ml). Serological tests for EBV were as follows: antiviral capsid antigen IgM was negative (<x10), but anti-EA IgG (x20) and EBNA (x40) were positive. The viral load of EBV-DNA was 5.0×10^5 copies/ml of whole blood. A computed tomography scan revealed multiple superficial and intraperitoneal lymphadenopathies, without hepatomegaly or splenomegaly. A skin biopsy taken from a papule with focal necrosis on the left dorsum of hand revealed focal epidermal and dermal necrosis, and dense infiltration of lymphoid cells with small and intermediate in size, with a massive eosinophil infiltration throughout the dermis (Fig 2, *D*). Immunohistochemical staining revealed that CD3 and CD4 were positive (Fig 2, *E* and *F*), but negative for CD56 and granzyme B (not shown). CD8 and CD20 were sparsely positive. EBER was positive for large infiltrating cells (Fig 2, *G*). TCRβ were weakly positive (Fig 2, *H*), whereas TCRγ were negative (not shown). A right inguinal lymph node biopsy identified EBER positive lymphocytes in the swollen lymph node (Fig 2, *I* and *J*). Southern blot analysis of TCR Jγ rearrangement in the skin and lymph node revealed no rearrangement band. Based on these findings, the diagnosis of HVLPD systemic form was made. TCI was applied with limited efficacy (Fig 3, *D* and *E*). Hence, NBUVB phototherapy was added to his hands and soles with an excellent response within 2 weeks (Fig 3, *F*). We used excimer light because he was not able to keep standing in the cabin-type NBUVB during the treatment. Although the skin lesions improved with the combined use of NBUVB and TCI, he died 18 months after disease onset due to the deterioration of his general condition. Histologic and TCR rearrangement evaluations did not support malignant transformation at the second skin biopsy which was performed 2 months before he died.

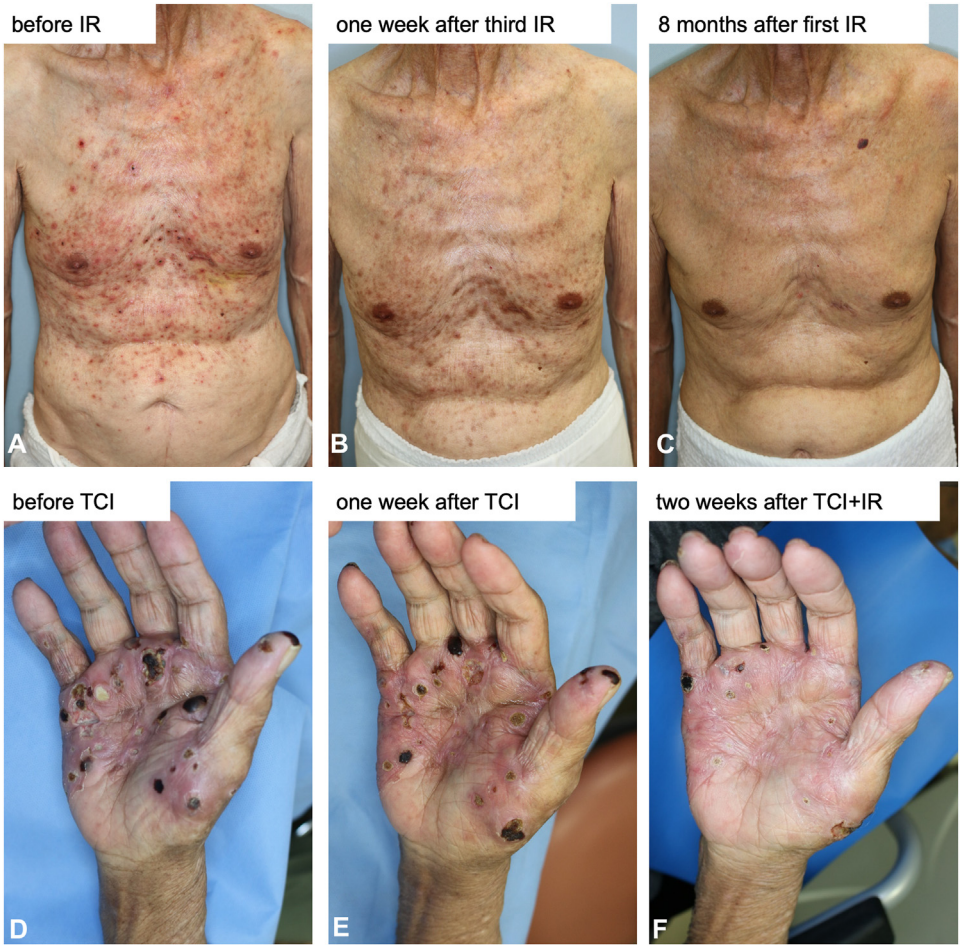

Fig 3. Rapid improvement of the papulovesicular eruptions on case 1 (**A**-**C**) and case 2 (**D**-**F**) were presented. *IR*, Irradiation; *TCI*, topical calcineurin inhibitor.

Table I. Summary of elder cases of HVLPD

Age	Sex	Distribution of the eruption	Systemic involvement	Treatment	Outcome	Reference
74	M	Head, face, and upper trunk	Liver	refused any treatment	died within 27 mo	1
70	F	Face	no	topical steroids	PR alive at 1.5-y follow-up	2
78	F	Face	no	unknown	alive at 1-y follow-up	3
70	F	Face	no	topical pimecrolimus	CR by 18-mo follow-up	4
77	M	Face	no	topical steroids	CR alive for 7 y	5
73	M	Face	Concomitant occurrence of CLL	systemic corticosteroid 1 mg/kg	CR	6
68	F	Face, Neck, Chest, Legs	fever, bone and lymph node involvement	unknown	died after 1.95 y	7
85	M	Face, Neck, Chest, back	fever	NBUVB	CR by 18-mo follow-up	Present case 1
83	M	Face, Arms, Hands, Abdomen, Soles	fever, lymph node involvement	NBUVB topical tacrolimus	died after 18 mo	Present case 2

CLL, Chronic lymphocytic leukemia; *CR*, complete remission; *NBUVB*, narrow-band UBV therapy; *PR*, partial remission.

DISCUSSION

To our knowledge, only 7 cases of HVLPD over the age of 65 have been reported in English literature (Table I).[1-7] Four out of 9 cases, including ours, were HVLPD systemic form. Among them, 3 cases died within 2.5 years from disease onset. Thus, there is a need to explore safe and effective treatment options for this population, who might be suffering from various co-morbidities and taking multiple drugs. The significance of our report was the prompt and excellent improvement of the skin lesions after NBUVB phototherapy. UV irradiation is a causative factor for the development of HV in children; hence, sun protection is generally recommended. The 320-390 nm UV wavelengths are suspected to be pathogenic.[8] One study demonstrated that approximately 53% of HV patients were sensitized to UVA and 40% of HV patients developed skin eruptions upon UVA irradiation.[9] In contrast, NBUVB has been shown to improve HV patients' tolerance to sunlight in a small number of cases, resulting in the prevention of new skin eruptions throughout the summer season.[2,9] Mechanisms by which NBUVB improved skin lesions of the present cases remain unclear. Induction of the immunosuppressive microenvironment in the skin by NBUVB phototherapy was suggested as one of the possible reasons.[8] Patients with HVLPD develop eruptions in both sun-exposed and sun-protected areas. Thus, the UV rays' pathogenic role in HVLPD remains debatable. However, the effectiveness of NBUVB in clearing existing papulovesicular eruptions has never been documented. The limitation of this report was the inability to procure long-term follow-up data and hence ascertain whether treatment with NBUVB may prevent disease progression to lymphoma. While the first case remained in good general health while receiving NBUVB, a previous report found that individuals with HVLPD exhibit HV-like eruptions for up to 15 years before progressing to systemic lymphoma.[10]

In summary, we present 2 cases of elderly patients with HVLPD systemic form whose skin lesions responded well to NBUVB. We propose that NBUVB phototherapy might be a therapeutic option for the skin lesions of elderly patients with HVLPD, but more research is needed.

Conflicts of interest

None disclosed.

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