

GUIDELINES

Diagnostic and disease severity determination criteria for hydroa vacciniforme lymphoproliferative disorders and severe mosquito bite allergy

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Funding information

Ministry of Health, Labour and Welfare, Grant/Award Number: 20FC1004 and 22FC1004

Abstract

Hydroa vacciniforme lymphoproliferative disorder (HV-LPD) and severe mosquito bite allergy (SMBA) are both cutaneous forms of Epstein–Barr virus (EBV)-associated T/natural killer (NK) cell LPDs and are closely related to chronic active EBV disease (CAEBV) and EBV-associated hemophagocytic lymphohistiocytosis (EBV-HLH). HV-LPD is further divided into classic HV, a benign subtype mediated by EBV-positive $\gamma\delta$ T cells, and systemic HV, another life-threatening subtype mainly associated with EBV-positive $\alpha\beta$ T or $\gamma\delta$ T cells. The vast majority of patients with SMBA have increased numbers of EBV-infected NK cells in the blood. Clinical symptoms of HV-LPD and SMBA often overlap in the same patient and may progress to more serious disease conditions equivalent to the systemic form of CAEBV. To define the disease spectrum of HV-LPD and SMBA, we propose the diagnostic criteria and the determination criteria for disease severity. The proposed diagnostic criteria are consistent with those for CAEBV and EBV-HLH in the guidelines for the management for CAEBV and related disorders 2023.

KEYWORDS

diagnostic criteria, disease spectrum, Epstein–Barr virus, hydroa vacciniforme lymphoproliferative disorder, severe mosquito bite allergy

This is the first English version of the diagnostic and disease severity determination criteria for hydroa vacciniforme lymphoproliferative disorder and severe mosquito bite allergy in a full set of revised Japanese guidelines for the management of chronic active Epstein–Barr virus disease and related disorders (2023).

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1 | INTRODUCTION

Hydroa vacciniforme lymphoproliferative disorder (HV-LPD) and severe mosquito bite allergy (SMBA) represent two cutaneous variants of Epstein-Barr virus (EBV)-positive T/natural killer (NK) cell LPDs. Given that both diseases occasionally overlap and progress to the serious condition comparable with chronic active EBV disease (CAEBV), they have also been classified into the cutaneous form of CAEBV.¹

Before the terms HV-LPD and SMBA were introduced, various diagnostic names had been used in previous studies.²⁻⁴ Furthermore, both diseases still have no consensus diagnostic criteria that can distinguish them clearly from CAEBV. In 2018, a consensus meeting on the disease spectrum and terminology for HV-LPD was held in Madison, USA.⁵ Thereafter, the 5th edition of the World Health Organization (WHO) classification adopted the newly proposed nomenclatures and defined the spectrum of HV-LPD, SMBA and "systemic" CAEBV separately.⁶ The term systemic CAEBV (ICD-O coding: 9725/1) is synonymous with the term CAEBV used in this report.

In line with the consensus terminology and definition,^{6,7} the Ministry of Health, Labour and Welfare (MHLW) research team for CAEBV and related disorders in Japan redefined the disease spectrum of HV-LPD and SMBA, and proposed the diagnostic criteria and the determination criteria for disease severity. A full set of guidelines for the management of CAEBV, HV-LPD, SMBA, and EBV-associated hemophagocytic lymphohistiocytosis (EBV-HLH) has been published

elsewhere.⁸ In this report, we summarize the diagnostic criteria and the disease severity determination criteria for HV-LPD and SMBA.

2 | MATERIALS AND METHODS

For the diagnostic and determination criteria for disease severity, we conducted a literature review on etiologically related disorders, including HV-LPD, SMBA, CAEBV, HLH, and EBV-related lymphoma/leukemia. Through expert meetings, the disease spectrum and nomenclature were revised to be consistent with those adopted in the 5th edition of the WHO classification⁶ and the newly launched terminologies and definitions for CAEBV and related diseases.⁷

3 | HV-LPD: DISEASE SPECTRUM AND DIAGNOSTIC CRITERIA

Hydroa vacciniforme (HV) was first described by EH Bazin in 1862 as a benign photosensitivity dermatosis of childhood, characterized by herpetic vesicles on sun-exposed areas.⁹ In 1999, EBV-positive T cells were detected in skin lesions with classic HV,¹⁰ and then EBV-positive γ T cells were found to be increased in the patient's blood (Figure 1).¹¹⁻¹³ The term "classic" HV is used in this report to represent the certain type of HV-LPD mentioned above.

On the contrary, life-threatening cases with severe HV-like eruptions and systemic symptoms such as fever and liver damage

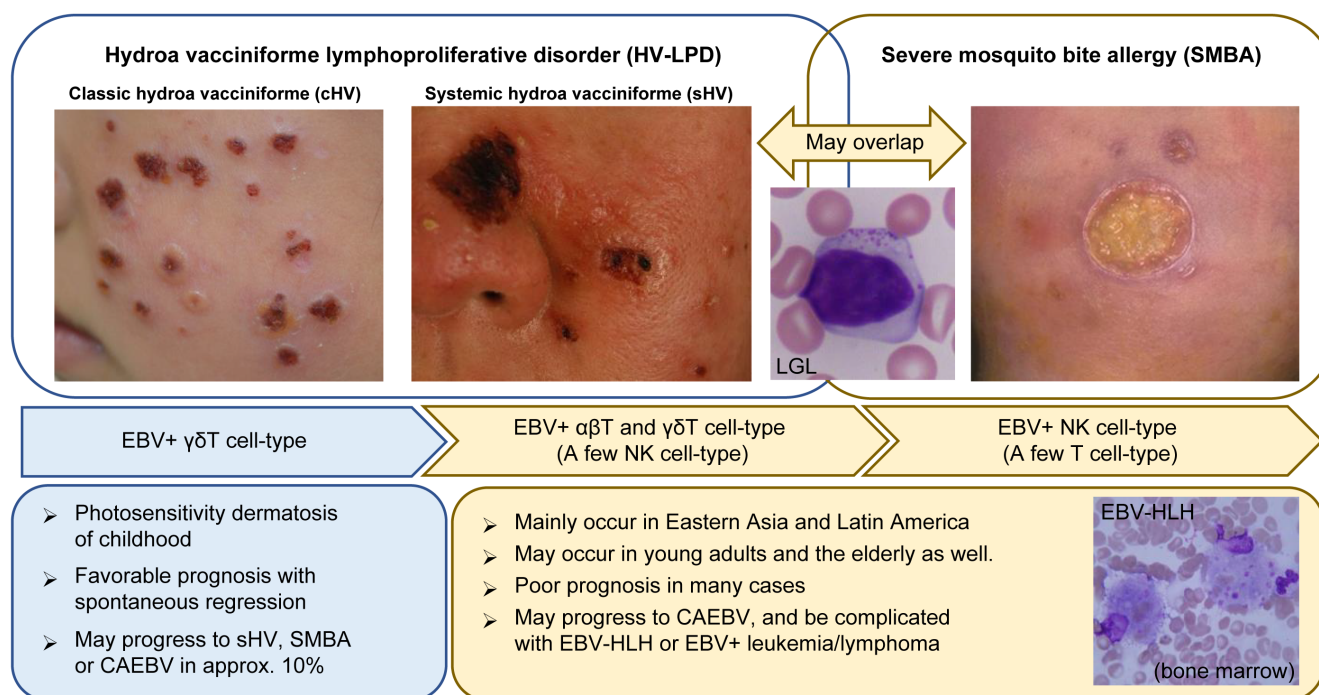


FIGURE 1 Disease spectrum of hydroa vacciniforme lymphoproliferative disorder and severe mosquito bite allergy. CAEBV, chronic active Epstein-Barr virus disease; cHV, classic hydroa vacciniforme; EBV, Epstein-Barr virus; EBV-HLH, EBV-associated hemophagocytic lymphohistiocytosis; HV-LPD, hydroa vacciniforme lymphoproliferative disorder; LGL, large granular lymphocyte; shV, systemic hydroa vacciniforme; SMBA, severe mosquito bite allergy.

have been reported in Eastern Asia and Central America under different names: recurrent necrotic papulovesicles of the face, severe or systemic HV, and HV-like lymphoma.^{2,3,14,15} Many of those patients have an increased number of EBV-positive $\alpha\beta$ T or $\gamma\delta$ T cells in the peripheral blood, and may overlap with SMBA or have a history of SMBA associated with an increased number of EBV-positive NK cells. Those patients often progress to severe disease conditions such as CAEBV and fatal EBV-related lymphomas.

Based on the similarity of cutaneous manifestations, the term hydroa vacciniforme-like LPD has long been used to encompass classic HV and severe forms.^{1,5,16} In the 5th edition of the WHO classification,⁶ the term hydroa vacciniforme LPD (HV-LPD) has been adopted instead because EBV infection can be confirmed to be present in all HV lesions, including the classic form.¹⁰⁻¹²

HV-LPD is classified into classic HV (or classic HV-LPD), a major subtype occurring among Caucasians, and systemic HV (or systemic HV-LPD), which is mainly encountered in Asians and

Hispanics (Table 1).¹⁶ Classic HV is a self-limiting skin disease without systemic symptoms or extracutaneous organ involvement, whereas systemic HV may exhibit severe cutaneous manifestations and systemic symptoms, and extracutaneous organ involvement which often leads to an unfavorable outcome.¹⁵⁻²⁰

From therapeutic and prognostic points of view, classic HV must be clearly distinguished from the systemic HV, although approximately 10% of patients with an initial diagnosis of classic HV may progress to the systemic type.^{15,21}

4 | HV-LPD: DISEASE SEVERITY AND DIAGNOSTIC ALGORITHM

Disease severity is categorized into mild, moderate, and severe forms according to clinical subtypes that are closely related to prognosis, the presence of systemic complications, and disease complications

TABLE 1 Diagnostic criteria for HV-LPD

I. Classic hydroa vacciniforme

- (1) Herpetic vesicles and papules/crusts on sun-exposed areas including face, auricles, and dorsal surfaces of the hands.
 - (2) EBV-infected cells or the virus-gene products can be detected in the skin lesions.
 - (3) The number of EBV-positive T cells is increased in peripheral blood.
 - (4) The level of EBV DNA load in the blood is high.
 - (5) The following diseases are excluded: other known skin diseases, CAEBV, and SMBA.
- The definite case fulfills all of (1)–(5).
The probable case fulfills (1) and has at least one of (2) and (3).
The possible case fulfills (1) and (4).

II. Systemic hydroa vacciniforme

- In addition to (1)–(4):
- (6) Swollen edematous face and lips, transient fever, liver damage, and lymphadenopathy are present.
 - (7) The following diseases are excluded: other known skin diseases and EBV-associated lymphoma/leukemia.
- The definite case fulfills all of (1)–(7).
The probable case fulfills (1) and (6), and has at least one of (2) and (3)*.
The possible case fulfills (1), (4), and (6).

*NK-cell-dominant cases can be included in systemic hydroa vacciniforme.

Supplementary explanation

Classic hydroa vacciniforme

- (1) In addition to herpetic vesicles, cHV may be accompanied with conjunctival hyperemia and aphthous stomatitis of the lips and gingiva.
- (2) Detection of EBER-positive cells in the skin biopsy samples is a standard method, but when biopsy is difficult, the blister roof or crusts can be used instead for EBER detection by RT-PCR (at a research level).
- (3) cHV usually occurs in childhood, associated with an increased number of EBV-infected $\gamma\delta$ T cells (>5% of all lymphocytes). sHV may occur even in young and old adults as well as in children, and include either EBV-infected $\alpha\beta$ T-cell-dominant or $\gamma\delta$ T-cell-dominant type. Flow cytometry-fluorescent in-situ hybridization or immunomagnetic bead-aided quantitative PCR is performed at a research level to confirm EBV infection in the T-cell fraction.
- (4) The standardized value of elevated EBV DNA load in whole blood is $>1 \times 10^4$ IU/mL.
- (5) The following diseases should be excluded: herpes simplex, varicella-zoster virus infection, Kaposi's varicelliform eruption, porphyria, polymorphic light eruption, impetigo contagiosum, acne, and lymphomatoid papulosis. The overlapping of CAEBV should be considered according to the diagnostic algorithm if patients have the following symptoms: infectious mononucleosis-like symptoms for >3 months, persistent fever, and organ involvement (see the CAEBV algorithm).

Systemic HV

- (6) Swelling of the face, eyelids, and lips can occur in ENKTL-NT and aggressive NK-cell leukemia, but both diseases usually lack herpetic vesicles.
- (7) HV-LPD, especially sHV, may overlap SMBA associated with systemic symptoms, thereby is often included in the category of cutaneous CAEBV. The cutaneous form, however, is not the same as CAEBV defined in the present diagnostic criteria. HV-LPD may progress to ENKTL-NT and aggressive NK-cell leukemia.

Abbreviations: CAEBV, chronic active Epstein-Barr virus disease; cHV, classic hydroa vacciniforme; EBER, EBV-encoded small nuclear RNA; EBV, Epstein-Barr virus; ENKTL-NT, extranodal NK/T-cell lymphoma, nasal type; HV-LPD, hydroa vacciniforme lymphoproliferative disorder; NK, natural killer; RT-PCR, reverse transcription PCR; sHV, systemic hydroa vacciniforme; SMBA, severe mosquito bite allergy.

TABLE 2 Determination criteria for the disease severity of HV-LPD

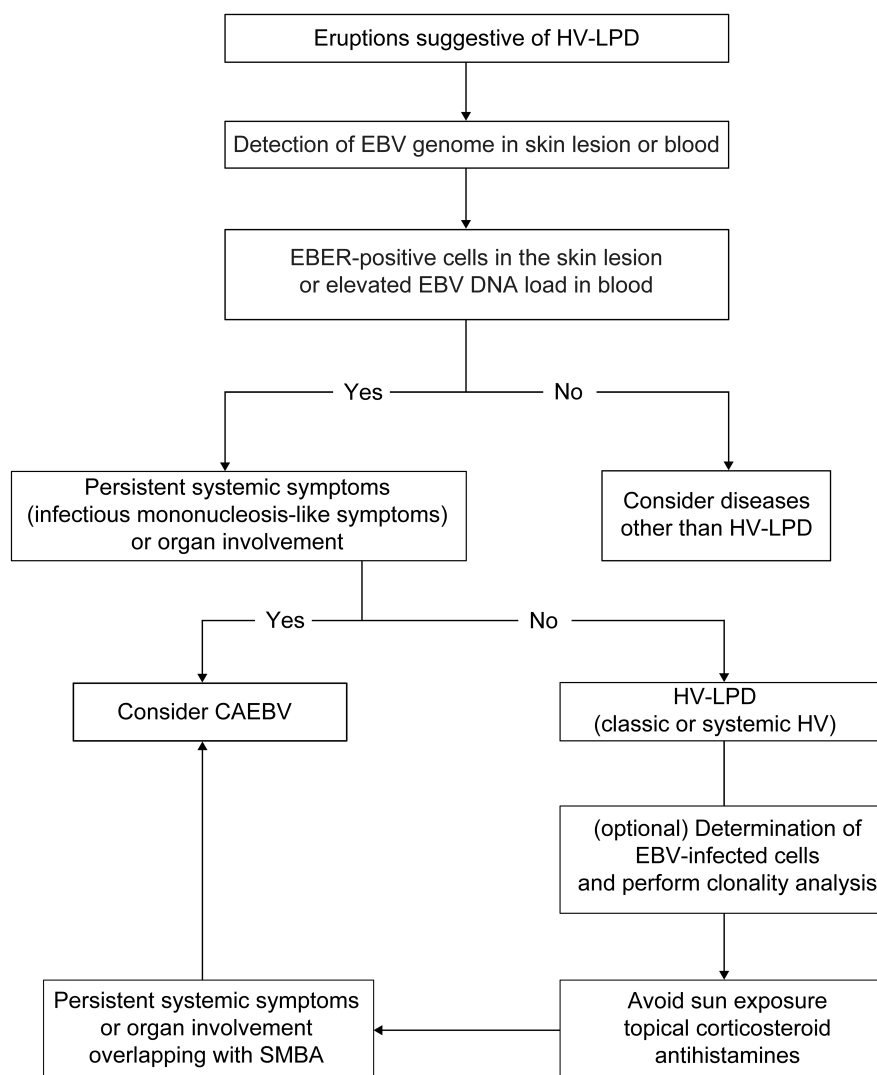
Mild	No systemic symptoms* or organ involvement, except for the characteristic mucocutaneous lesions
Moderate	Characteristic mucocutaneous lesions associated with edema of the face, eyelids, or lips Characteristic mucocutaneous lesions associated with transient systemic symptoms*
Severe	Overlapping with SMBA Fulfilled diagnostic criteria for CAEBV Complicated with EBV-HLH or progression to EBV-related T/NK lymphoma/leukemia

Abbreviations: CAEBV, chronic active Epstein-Barr virus disease; EBV, Epstein-Barr virus; EBV-HLH, EBV-associated hemophagocytic lymphohistiocytosis; HV-LPD, hydroa vacciniforme lymphoproliferative disorder; SMBA, severe mosquito bite allergy; T/NK, T cell or natural killer cell.

*Systemic symptoms include fever $>37.5^{\circ}\text{C}$, liver damage, and lymphadenopathy, excluding specific organ involvement. The disease severity is classified into mild (exclusively classic hydroa vacciniforme), moderate or severe disease by the most severe item.

and progression (Table 2). The mild category exclusively includes classic HV, and the severe category includes life-threatening disease conditions comparable with CAEBV and EBV-positive T/NK lymphoma or leukemia.

CAEBV is a progressive, life-threatening disease that fulfills the following four major diagnostic criteria: (1) infectious mononucleosis-like symptoms persisting more than 3 months, (2) increased EBV DNA levels in the blood or tissues, (3) the presence of EBV-infected T/NK cells, and (4) the exclusion of known diseases. Unlike CAEBV, patients with systemic HV have neither sustained organ involvement, except for the typical skin lesions on examination, nor infectious mononucleosis-like symptoms persisting for >3 months, one of the major diagnostic criteria for CAEBV. A recent study, however, showed that some patients with CAEBV, HV-LPD, and SMBA share similar somatic mutations such as *DDX3X*, as also observed in other EBV-associated T/NK-cell lymphomas, and that the cases carrying a driver mutation showed a significantly poor prognosis.²² Therefore, patients with severe HV-LPD are closely related to CAEBV, and need careful follow-up and management for CAEBV (Figure 2).^{6,8,17,18}

**FIGURE 2** Diagnostic algorithm for hydroa vacciniforme lymphoproliferative disorder. CAEBV, chronic active Epstein-Barr virus disease; EBER, EBV-encoded small nuclear RNA; EBV, Epstein-Barr virus; HV-LPD, hydroa vacciniforme lymphoproliferative disorder; SMBA, severe mosquito bite allergy.

5 | SMBA: DISEASE SPECTRUM AND DIAGNOSTIC CRITERIA

SMBA is characterized by a swollen erythematous skin reaction followed by deep ulcers on the sites of mosquito or insect bites and even vaccine injection (Figure 1). Previously, SMBA was termed

TABLE 3 Diagnostic criteria for SMBA

- (1) Skin redness, swelling, and ulcers occur in the sites of mosquito bites and vaccine injection accompanied with fever, followed by scar formation, but patients are asymptomatic without such provocative factors.
 - (2) EBV-infected cells or virus-gene products can be detected in the skin lesions.
 - (3) The level of EBV DNA load is elevated in the blood.
 - (4) The number of LGLs or EBV-infected NK cells is increased in the peripheral blood.
 - (5) Skin reactions caused by a known allergic mechanism or underlying diseases are excluded.
- The definite case fulfills all of (1)–(5).
The probable case fulfills (1) and has at least one of (2) and (4).
The possible case fulfills (1) and (3).

Supplementary explanation

- (1) SMBA is mostly induced by mosquito bites, but it can also be caused by other insect bites and vaccine injection. Patients may present with transient systemic symptoms including fever, lymphadenopathy, and liver dysfunctions. Scar formation resulting from previous episodes of SMBA can be present.
- (2) Detection of EBER-positive cells using skin biopsy samples is a standard method, but when biopsy is difficult, EBER can be detected in the crusts and lesional skin tissue by RT-PCR at a research level.
- (3) The standardized value of elevated EBV DNA load in whole blood is $>1 \times 10^4$ IU/mL.
- (4) Flow cytometric analysis reveals that most patients with SMBA have an increased total number of NK cells ($\geq 30\%$ of the total lymphocytes). Flow cytometry–fluorescent in-situ hybridization or immunomagnetic bead-aided quantitative PCR is performed at a research level to confirm EBV infection in the NK cell fraction. Some patients may have an EBV-infected T-cell-dominant type of SMBA.
- (5) Diseases to be excluded: blisters, redness, swelling, and generalized rash related to common insect bite allergy, and pathergy reactions associated with neutrophilic dermatoses including Behçet's disease, Sweet disease, and pyoderma gangrenosum.

The overlapping of CAEBV should be considered in line with the diagnostic algorithm if patients have the following symptoms: infectious mononucleosis-like symptoms for >3 months, persistent fever, and organ involvement (see the CAEBV algorithm).

SMBA may overlap HV-LPD associated with systemic symptoms, thereby being included in the category of cutaneous CAEBV. The cutaneous form, however, is not the same as CAEBV defined in the present diagnostic criteria.

SMBA may progress to ENKTL-NT, and aggressive NK-cell leukemia.

Abbreviations: CAEBV, chronic active Epstein–Barr virus disease; EBER, EBV-encoded small nuclear RNA; EBV, Epstein–Barr virus; ENKTL-NT, extranodal NK/T-cell lymphoma, nasal type; HV-LPD, hydroa vacciniforme lymphoproliferative disorder; LGL, large granular lymphocyte; NK, natural killer; NK/T, natural killer cell, or T cell; RT-PCR, reverse transcription PCR; SMBA, severe mosquito bite allergy.

hypersensitivity to mosquito bites.^{4,20,23} Presumably, mosquito bites induce an initial inflammation, which provokes the secondary severe cutaneous reactions due to the infiltration of activated EBV-positive NK cells.²³ The number of EBV-infected NK cells showing a cell type of large granular lymphocytes (LGL) is usually increased ($>30\%$ of lymphocytes) in the peripheral blood.^{21,24} Even though the skin reaction is severe, an allergic reaction to mosquito bites without the involvement of EBV-positive NK/T cells should be excluded from SMBA's diagnostic criteria (Table 3).

6 | SMBA: DISEASE SEVERITY AND DIAGNOSTIC ALGORITHM

Patients with definite SMBA who have been in remission for more than 1 year, with or without residual hematological abnormalities, are classified as mild SMBA (Table 4). Patients who have ongoing or recurrent SMBA with transient systemic symptoms, without extracutaneous organ involvement, are classified as moderate SMBA. The severe form of SMBA is defined if the patients overlap with HV-LPD, and/or at least one of life-threatening disease conditions such as CAEBV, HLH and EBV-positive T/NK lymphoma, or leukemia (Figure 3).⁸

7 | PROGNOSTIC INDICATORS AND MANAGEMENT

Patients with HV-LPD and SMBA can be classified into four clinical subtypes: classic HV, systemic HV, SMBA, and HV-LPD overlapping with SMBA (Figure 1). These clinical subtypes are closely related to the dominant EBV-positive lymphocyte subset in the peripheral blood: classic HV associated with EBV-positive $\gamma\delta$ T cells

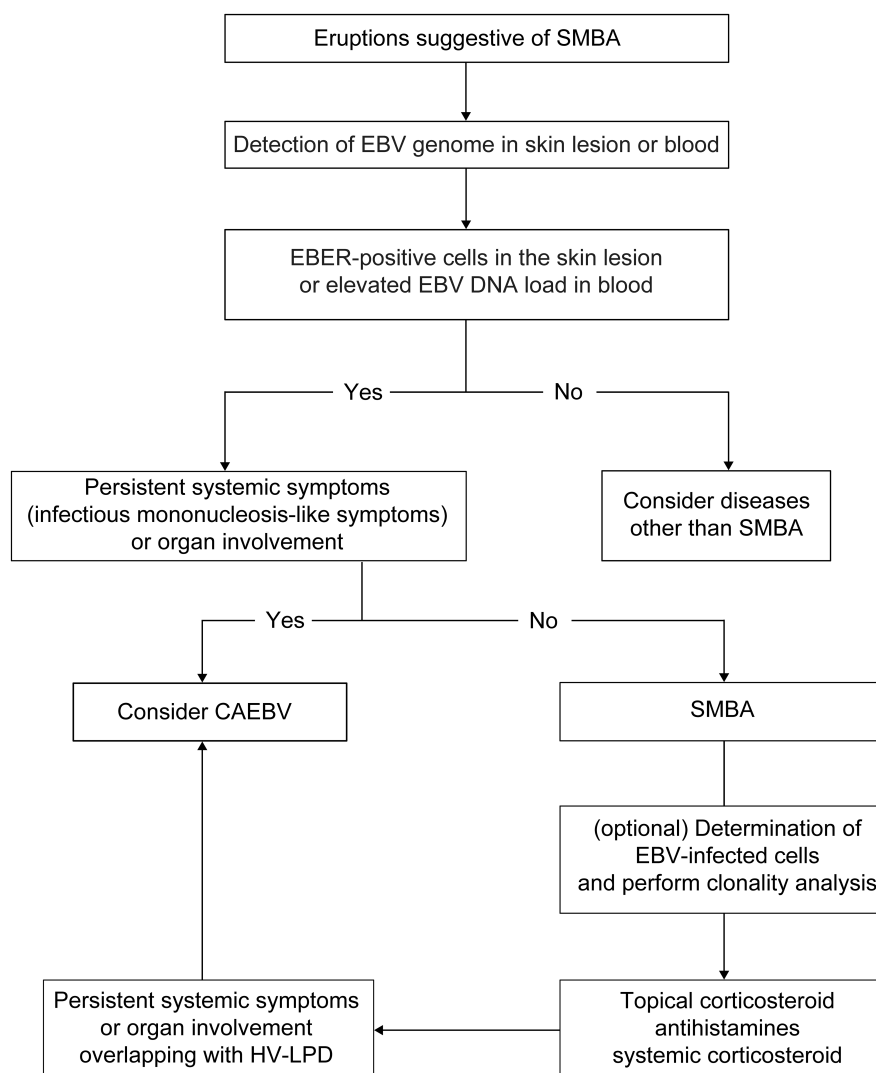
TABLE 4 Determination criteria for the disease severity of SMBA

Mild	Definite case of SMBA showing clinical improvement without extracutaneous organ involvement for over 1 year
Moderate	Recurrent SMBA associated with transient systemic symptoms*, but no persistent extracutaneous organ involvement
Severe	Overlapping with HV-LPD Fulfilled diagnostic criteria for CAEBV Complicated with EBV-HLH or progression to EBV-related T/NK lymphoma/leukemia

Abbreviations: CAEBV, chronic active Epstein–Barr virus disease; EBV, Epstein–Barr virus; EBV-HLH, EBV-associated hemophagocytic lymphohistiocytosis; HV-LPD, hydroa vacciniforme lymphoproliferative disorder; SMBA, severe mosquito bite allergy; T/NK, T cell, or natural killer cell.

*Systemic symptoms include fever $>37.5^\circ\text{C}$, liver damage, and lymphadenopathy, excluding specific organ involvement. The disease severity is classified into mild (exclusively a stable disease of SMBA), moderate or severe disease by the most severe item.

FIGURE 3 Diagnostic algorithm for severe mosquito bite allergy. CAEBV, chronic active Epstein-Barr virus disease; EBER, EBV-encoded small nuclear RNA; EBV, Epstein-Barr virus; HV-LPD, hydroa vacciniforme lymphoproliferative disorder; SMBA, severe mosquito bite allergy.



(>5% of lymphocytes), systemic HV with either EBV-positive $\gamma\delta$ T- or $\alpha\beta$ T-cell-dominant type, and the vast majority of SMBA with an increased number of EBV-infected NK cells (>30% of lymphocytes). The prognosis is favorable in patients with classic HV and $\gamma\delta$ T-cell-dominant systemic HV in childhood, but poor in patients with other subtypes such as $\alpha\beta$ T-cell-dominant systemic HV and SMBA (mortality rate 11.5 vs 3.51 in 100 person-years).²¹ Since the definition of the dominant EBV-positive lymphocyte subset differs in each clinical subtype, the prognosis might not be related to the property of the EBV-positive cell subset, but rather the net tumor burden of EBV-positive lymphocyte subsets and acquired epigenetic alterations or somatic gene mutations.

Other prognostic indicators include an onset age over 9 years (over 8 years in Okuno et al.²²), the mRNA expression of *BZLF1*, a reactivation marker,^{19,25} and the presence of a somatic driver mutation such as *DDX3X*.²² These prognostic indicators, however, are excluded from the present criteria because the onset age is not determined clearly by medical interview alone, and the detection of molecular and genetic markers has not widely been used in a clinical setting.

The elevated EBV DNA load ($>1 \times 10^4$ IU/mL) in the whole peripheral blood sample is useful for a diagnosis of HV-LPD and SMBA, but not applicable as a prognostic indicator. However, extremely high levels of EBV DNA load in the plasma are found to be related to hemophagocytic syndrome complications.²⁶

In the present diagnostic criteria, classic HV can be separated from systemic HV and classified into the mild form of HV-LPD in the disease severity determination criteria because of its favorable prognosis.^{16,19,21} Since approximately 10% of classic HV patients may progress to a severe form,¹⁹ careful follow-up is necessary. Most patients with SMBA progress to more serious conditions, but stable disease or spontaneous remission could occur in some cases. To identify the self-limited cases of SMBA by a follow-up study using annual registry data, we have included a category of the mild form in the disease severity determination criteria (Table 4).

At present, systemic HV and SMBA still have no standard therapy, although some therapeutic attempts have been made with or without benefits; these therapies include cytotoxic chemotherapy,²⁷ interferon- α ,²⁸ photoprotection,²⁹ and thalidomide.³⁰ For patients

with CAEBV, therapeutic regimens are currently under clinical trial,³¹⁻³³ but there is no effective drug and hematopoietic stem cell transplantation is the only curative treatment.^{34,35} According to the present diagnostic criteria, systemic HV and/or SMBA with sustained systemic symptoms, extracutaneous organ involvement, or overlapping with other clinical subtypes are all categorized into the severe forms, equivalent to the spectrum of CAEBV. The patients with severe disease should be followed up in line with the guidelines for the management of CAEBV.⁸

8 | PROSPECTIVE

Consensus diagnostic criteria are important to perform the patient's registry, statistical analysis, and therapeutic effect evaluation. We hope that the present diagnostic criteria can contribute to these purposes.

ACKNOWLEDGMENTS

The authors would like to thank the members of the MHLW Research Team in Japan for their contribution to the review process of the current diagnostic criteria.

FUNDING INFORMATION

This study was supported by the grant (20FC1004 and 22FC1004) from the Ministry of Health, Labour and Welfare (MHLW), Japan.

CONFLICT OF INTEREST STATEMENT

None.

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How to cite this article: Hirai Y, Asada H, Hamada T, Kawada J-i, Kimura H, Arai A, et al. Committee for Guidelines for the Management of Chronic Active EBV Disease and Related Disorders (the MHLW Research Team in Japan). Diagnostic and disease severity determination criteria for hydra vacciniiforme lymphoproliferative disorders and severe mosquito bite allergy. *J Dermatol.* 2023;50:e198–e205. <https://doi.org/10.1111/1346-8138.16842>