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Commentary

Sting and Aversion-Severe Mosquito Bite Allergy

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Received: February 23, 2023; **Published:** March 04, 2023

Severe mosquito bite allergy manifests as an uncommon cutaneous manifestation of natural killer (NK) cell subtype of chronic active Epstein Barr viral (CAEBV) infection. Predominantly documented in Japan, severe mosquito bite allergy characteristically delineates hypersensitivity to mosquito bites.

Severe mosquito bite allergy is designated as an Epstein Barr virus (EBV+) induced NK cell lymphoproliferative disorder and represents as a cutaneous variant of chronic active Epstein Barr virus (CAEBV) infection. Severe mosquito bite allergy characteristically denominates an exaggerated allergic reaction to mosquito bites, incriminates diverse cutaneous surfaces and demonstrates a prolonged clinical course. Severe mosquito bite allergy is accompanied by complications such as hemophagocytic lymphohistiocytosis (HLH), hydroa vacciniforme-like lymphoproliferative disorder or systemic chronic active Epstein Barr virus (CAEBV) infection. Besides, enhanced possible emergence of overt NK/T cell lymphoma or aggressive NK cell leukaemia is encountered. The exceptionally discerned severe mosquito bite allergy predominantly incriminates Asians or Japanese.

Severe mosquito bite allergy preponderantly arises within children and young adolescents. Mean age of disease emergence is 6.7 years although the condition may appear between 0 to18 years. A specific gender predilection is absent [1,2].

Severe mosquito bite allergy is engendered due to hypersensitivity reaction following mosquito bites. Majority of incriminated subjects delineate elevated serum immunoglobulin E (IgE) along with enhanced Epstein Barr viral deoxyribonucleic acid (EBV DNA) load and circulating NK cell lymphocytosis confined to peripheral blood.

Of obscure aetiology, severe mosquito bite allergy is associated with cogent genetic predisposition and environmental factors which influence disease pathogenesis [1,2].

Mosquito bite can induce expression of Epstein Barr virus latent membrane protein 1 (LMP1) within NK cells. Proliferation of mosquito antigen specific CD4+ T cells is associated with reactivation of latent Epstein Barr virus confined to NK cells. A proportion of infiltrating NK cells appear immune reactive to Epstein Barr virus (EBV).

Hypersensitivity to mosquito bite is engendered on account of proliferating CD4+ T lymphocytes arising as a reaction to secretions of mosquito salivary gland. Aforesaid secretions contribute to reactivation of Epstein Barr virus (EBV) within NK cells with the induction of latent membrane protein 1 (LMP1). Constituent NK cells appear infected with monoclonal Epstein Barr virus (EBV) as delineated upon terminal repeat analysis. Besides, Epstein Barr virus terminal repeat analysis demonstrates monoclonal Epstein Barr virus in a majority of instances.

Akin to *in situ* hybridization (ISH) of hydroa vacciniforme-like lymphoproliferative disorder, a fraction of NK cells exhibit Epstein Barr virus encoded small RNAs (EBERs) [3,4].

Simulating hydroa vacciniforme-like lymphoproliferative disorder, peripheral blood of severe mosquito bite allergy demonstrates latent membrane protein 1 (LMP1), as discerned with polymerase chain reaction (PCR), thereby indicating the emergence of type 2 Epstein Barr viral latency [3,4].

Acute episodes frequently appear associated with pyrexia and general malaise. The condition exhibits acute, severe, localized cutaneous lesions manifesting as erythema, bullae, cutaneous ulcers or focal necrosis along with scarring. Besides, systemic symptoms as pyrexia, lymphadenopathy, liver abnormalities or hepatosplenomegaly may ensue. Lymphadenopathy and hepatosplenomegaly can be occasionally encountered [3,4].

The hypersensitivity reaction simulates hypersensitivity encountered upon injection site following vaccination. Upon resolution of hypersensitivity or symptomatic recovery, incriminated subjects appear asymptomatic until subsequent mosquito bite occurs.

Severe mosquito bite allergy may progress to systemic chronic active Epstein Barr viral (CAEBV) infection with eventual emergence of aggressive NK cell leukaemia.

Upon microscopy, cutaneous tissue obtained from incriminated site demonstrates epidermal necrosis, cutaneous ulceration and configuration of bullae. A dense infiltrate of lymphoid cells may extend into subjacent subcutaneous tissue [3,4].

Lymphoid infiltrate is polymorphous and comprised of miniature lymphocytes along with enlarged atypical cells admixed with diverse reactive inflammatory cells as histiocytes and eosinophils.

Morphological countenance simulates hydroa vacciniforme-like lymphoproliferative disorder. Reactive CD4+ or CD8+ T lymphocytes appear intermingled within neoplastic lymphoid infiltrate [3,4].

	Clinical Features	Histological Features	Immuno-phenotype
EBV associated HLH	Pyrexia, splenomegaly, cytopenia, liver dysfunction. EBV DNA or RNA detected within tissues. Exclusion of EBV+ T/NK LPDs.	Hemophagocytosis by activated histiocytes in BM, lymph node, spleen. Few EBV+T cells	Predominantly cytotoxic CD8+ T cells
CAEBV systemic	Persistent IM-like illness > 3 months. Pyrexia, liver dysfunction, hepatosplenomegaly, HV-like eruptions, hypersensitivity to mosquito bite, uveitis, diarrhoea, lymphadenopathies, cytopenia. Peripheral blood EBV DNA copies>102.5/mg or EBV RNA or viral protein in affected tissues.	Non specific inflammation devoid of histological evidence of malignant lymphoproliferations	CD4>>CD8>> γδ T cells, CD56+
Hydroa vacciniforme (HV)-like LPD	Cutaneous form of CAEBV. Recurrent vesiculopapular eruptions in sun-exposed skin. Indolent, self limited clinical course with progression into EBV+ T/NK cell LPDs.	Intra-epidermal spongiotic vesicles. Lymphoid infiltrate with angiocentric and periadnexal involvement. Small lymphocytes with minimal or absent atypia	Predominantly cytotoxic CD8+ T cells, CD56+

Severe mosquito bite allergy	Cutaneous form of CAEBV. Exaggerated hypersensitivity reaction to mosquito bites as erythema, bullae, ulcers, scarring, pyrexia, lymphadenopathy, hepatosplenomegaly, liver anomalies. Prolonged clinical course with progression to EBV+ T/NK cell LPDs.	Epidermal necrosis, ulcer and bullae. Polymorphous infiltration of small lymphocytes, large atypical cells, reactive inflammatory cells as histiocytes and eosinophils	CD3ε+, CD56+ NK cells
Systemic EBV+ T cell lymphoma of childhood	Pyrexia, hepatosplenomegaly, coagulopathy, pancytopenia, abnormal liver function. Monoclonal proliferation of EBV+ T cells in tissues and peripheral blood. Follows acute primary EBV infection in healthy children or CAEBV setting. Fulminant clinical course, death within days or weeks.	Increased infiltration of small lymphoid cells, histiocytic hyperplasia, striking haemophagocytosis in BM, spleen and liver. Small lymphocytes with minimal or absent atypia	Predominantly CD8+ cytotoxic T cells, CD2+, CD3+
Aggressive NK cell leukaemia	Pyrexia, malaise, hepatic failure, hepatosplenomegaly, pancytopenia. Systemic neoplastic proliferation of NK cells in peripheral blood, BM. Fulminant clinical course. EBV-subset	Variable leukemic cell infiltration in BM, LN, liver, spleen. Cells ranging from normal large granular lymphocytes to atypical pleomorphic lymphocytes	CD3ε+, CD56+ NK cells, CD2+, FASL+, sCD3-, CD5-, CD16+
Extra-nodal NK/T cell lymphoma, nasal type	EBV+ aggressive lymphoma. Nasal type (80%) occurs in nasal and nasopharyngeal area, minimally aggressive. Extra-nasal type (20%) occurs in skin, GIT, testis. Aggressive disease. Extensive ulceration and necrosis in mucosal sites	Diffuse infiltration of atypical lymphoid cells, angiocentricity, angiodestruction. Frequent coagulative necrosis. Broad cytological spectrum. Variable inflammatory cells.	CD3ε+, CD56+ NK cells (CD25+, FAS+, FASL+, HLADR+, sCD3-, CD4-, CD5-. Few CD3ε+, CD56- cytotoxic T cells (CD8+, CD5+, TCR γδ+ or αβ+)
Primary EBV+ nodal T/NK cell lymphoma	Rare EBV+ PTCL with primary nodal presentation. Generalized lymphadenopathy. Limited extra-nodal lesions without nasal involvement	Monomorphic population of large, atypical cells with centroblastic feature or diffuse proliferation of pleomorphic small, medium and large atypical cells	Predominantly CD8+ cytotoxic T cells, CD56+, CD4+, γδ T cells

Table: *Pathological features of EBV+ T/ NK cell lymphoproliferative disorders [3,4].*

EBV: Epstein Barr Virus; PTCL: Peripheral T Cell Lymphoma; HLH: Hemophagocytic Lymphohistiocytosis; NK: Natural Killer; BM: Bone Marrow; CAEBV: Chronic Active Epstein Barr Virus Infection; LN: Lymph Nodes; TCR: T cell Receptor; GIT: Gastrointestinal Tract; LPD: Lymphoproliferative Disorder; IM: Infectious Mononucleosis

Although the morphological countenance is identical to hydroa vacciniforme-like lymphoproliferative disorder, infiltrating lymphoid cells exhibit an NK cell immuno-phenotype with expression of CD56 or cytotoxic granules T cell intracellular antigen1 (TIA1) and granzyme B. Epstein Barr virus infected neoplastic T lymphoid cells are frequently immune reactive to CD30+. However, cells are exceptionally immune reactive to latent membrane protein 1 (LMP1) [5,6].

Neoplastic lymphoid cell infiltrate expands into subjacent subcutaneous tissue. Reactive CD4+ and C8+ T cells appear intermingled with infiltrating lymphoid cells.

Infiltrating NK lymphoid cells appear immune reactive to CD3ε+, CD56+ or cytotoxic molecules T cell intracellular antigen 1 (TIA1) and granzyme B [5,6].

Thus, as latent membrane protein 1 (LMP1) is discerned within peripheral blood with polymerase chain reaction (PCR), severe mosquito bite allergy as a hypersensitivity reaction is contemplated to be an Epstein Barr virus latency type 2 disease [5,6].

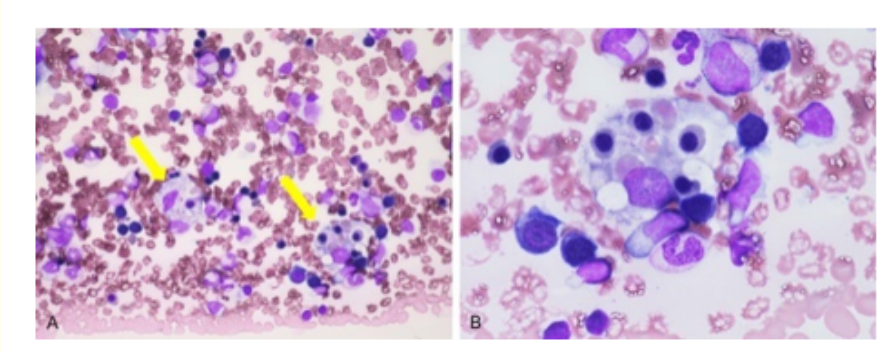

Figure 1: *Severe mosquito bite allergy demonstrating EBV+ hemophagocytic T lymphocytes engulfing red blood cells and granulocytes [7].*

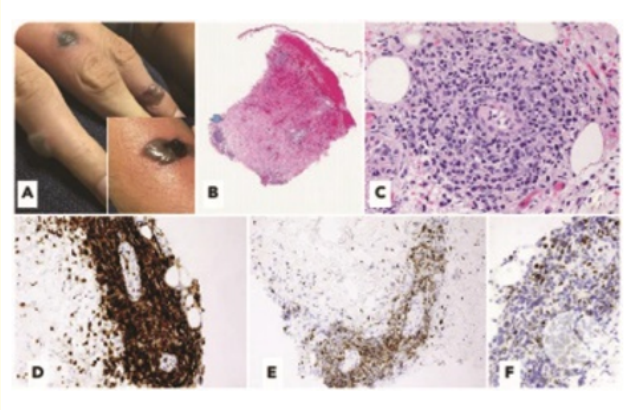

Figure 2: *Severe mosquito bite allergy delineated erythema, bullae and cutaneous ulcers infiltrated by EBV+ T lymphoid cells admixed with enlarged atypical cells, reactive lymphoid cells as histiocytes and eosinophils confined to cutis with expansion into subcutaneous zones. Immune reactivity to diverse T cell markers is denominated [8].*

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7. Image 1 Courtesy: Semantic scholar.

8. Image 2 Courtesy: ASH.com.

Volume 22 Issue 4 April 2023
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