



Epstein-Barr virus reactivation is induced, but abortive, in cutaneous lesions of systemic hydroa vacciniforme and hypersensitivity to mosquito bites



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ABSTRACT

Background: Epstein-Barr virus (EBV)-associated T/natural killer (NK)-lymphoproliferative disorders (LPDs) include hydroa vacciniforme (HV) and hypersensitivity to mosquito bites (HMB). The pathomechanisms of these diseases are still unclear.

Objective: To understand the inflammatory process, we examined EBV reactivation markers, *BZLF1* and *BDRF1* mRNA in the tissue and blood from patients with EBV-associated T/NK-LPDs.

Methods: Sixty-four patients with EBV-associated LPDs and epithelial neoplasms, and EBV+ cell line cells were studied. DNase-treated and resistant EBV DNA load in blood and cell culture supernatants were calculated. An EBV reactivation signal was analyzed in the tissue, blood and cell line cells.

Results: In the tissue, *BZLF1* mRNA was detected in 5 of 6 (83%) samples of EBV+ epithelial neoplasms, 16 of 21 (76%) of EBV+ lymphomas, and 5 of 15 (33%) of systemic HV and/or HMB, but negative in all 15 patients with classical HV. In the blood, *BZLF1* mRNA was detected in only one of 19 (5.3%) samples of EBV-associated T/NK-LPDs. A down-stream reactivation signal, *BDRF1* mRNA was expressed in all 6 samples of EBV+ epithelial neoplasms, but it was positive in only one of 15 (6.7%) samples from systemic HV and HMB in the tissue. EBV+ T/NK-cell line cells treated with phorbol 12-myristate 13-acetate produced *BZLF1* and *BDRF1* mRNA, and encapsidated EBV DNA was detected in the culture supernatants of cell line cells.

Conclusion: Stimulation-induced EBV reactivation occurred both *in vivo* and *in vitro*, but it was almost abortive *in vivo*. Reactivation-related EBV antigens might be responsible for induction of systemic HV and HMB.

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1. Introduction

Epstein-Barr virus (EBV)-associated T/natural killer (NK)-lymphoproliferative disorders (LPDs) are a group of diseases including hydroa vacciniforme (HV) and hypersensitivity to mosquito bites (HMB). Patients with classical HV (cHV) present with vesiculopapules on sun-exposed areas such as cheeks, ears and the dorsal surfaces of the hands, without systemic symptoms, whereas patients with systemic HV (sHV) usually show ulceronecrotic lesions associated with systemic symptoms such as fever and lymphadenopathy [1–3]. In patients with both classical and

systemic HV, the EBV DNA load and the level of EBV+ $\gamma\delta$ T cells are usually increased in the peripheral blood mononuclear cells (PBMCs) [2,4].

HMB is characterized by intense local skin reactions and systemic symptoms including high fever, lymphadenopathy, hepatosplenomegaly and hemophagocytic syndrome [5]. These clinical symptoms are induced by mosquito bites, insect bites or vaccinations. Patients with HMB are usually associated with EBV+ NK-cell lymphocytosis [2,6], and HV-like eruptions may coexist or occur during the clinical courses. Patients with chronic active EBV infection (CAEBV) may present with HV or HMB in the clinical course [7].

We described different cellular events between HMB and HV-like eruptions [2]. EBV-associated HV lesions contained various numbers of EBV-encoded small RNA (EBER)+ T-cells, together with

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Table 1
Summary of EBV-associated diseases examined.

	No	EBV infected cell type	Tissue		PBMC		Plasma			Interpretation (Naked DNA, virions or mixed)	
			<i>BZLF1</i>	<i>BDRF1</i>	EBV load		<i>BZLF1</i>	<i>BDRF1</i>	EBV load		%EBV remaining post-DNase
			mRNA	mRNA	copies/ μ gDNA		mRNA	mRNA	copies/ml		
cHV	1	NK	neg	neg	35500	neg	neg	un			
	2	T	neg	neg	16500	nt	nt	un			
	3	$\gamma\delta$ T	neg	neg	nt	nt	nt	nt			
	4	$\gamma\delta$ T	neg	neg	3060	neg	neg	un			
	5	nt	neg	neg	4790	nt	nt	un			
	6	$\gamma\delta$ T	neg	neg	12400	nt	nt	2120	0%	Naked	
	7	T	neg	neg	770	nt	nt	nt			
	8	$\gamma\delta$ T	neg	neg	nt	nt	nt	nt			
	9	nt	nt	nt	nt	neg	neg	nt			
	10	$\gamma\delta$ T	neg	neg	73000	nt	nt	nt			
	11	nt	neg	neg	114	neg	neg	3910	nt	nt	
	12	nt	neg	neg	nt	nt	nt	nt			
	13	nt	neg	neg	1100	nt	nt	870	nt	nt	
	14	$\gamma\delta$ T	neg	neg	2180	neg	neg	un			
	15	$\gamma\delta$ T	neg	neg	nt	nt	nt	nt			
	16	nt	neg	neg	nt	nt	nt	nt			
sHV	1	nt	neg	neg	3230	neg	neg	772	0%	Naked	
	2	$\gamma\delta$ T	pos	neg	39600	neg	pos	644	0%	Naked	
	3	T	pos	neg	35500	pos	neg	1730	0%	Naked	
	4	$\gamma\delta$ T	nt	nt	27300	neg	neg	un			
	5	nt	neg	neg	nt	nt	nt	nt			
	6	T	neg	neg	79900	neg	neg	16980	5%	Mixed	
	7	T and NK	nt	nt	34600	neg	neg	801	0%	Naked	
	8	NK	neg	neg	13500	neg	neg	un			
	9	nt	pos	neg	4500	nt	nt	nt			
	10	T	neg	neg	1220	nt	nt	899	nt	nt	
HMB	1	NK	pos	pos	1900	nt	nt	3680	14%	Mixed	
	2	NK	nt	nt	41000	neg	neg	6234	nt	nt	
	3	NK	nt	nt	5720	neg	neg	nt			
	4	NK	neg	neg	5580	neg	neg	un			
	5	nt	neg	neg	nt	nt	nt	nt			
	6	NK	neg	neg	nt	nt	nt	nt			
HMB + HV	1	NK	nt	nt	2770	neg	neg	552	0%	Naked	
	2	NK	pos	neg	31700	neg	neg	1070	0%	Naked	
	3	NK	neg	neg	21400	neg	neg	8160	nt	nt	
	4	NK and $\gamma\delta$ T	neg	neg	208	neg	neg	un			
Lymphoma	1	B	pos	pos	nt	nt	nt	nt			
	2	B	pos	neg	nt	nt	nt	nt			
	3	NK	pos	neg	nt	nt	nt	nt			
	4	T	neg	neg	nt	nt	nt	nt			
	5	NK	pos	pos	nt	nt	nt	nt			
	6	T/NK	pos	neg	88000	nt	nt	11800	0%	Naked	
	7	T/NK	pos	neg	nt	neg	neg	1360	0%	Naked	
	8	T	pos	pos	nt	nt	nt	nt			
	9	T	pos	neg	1450	neg	neg	un			
	10	T	neg	neg	nt	nt	nt	nt			
	11	T	pos	neg	446	neg	neg	811	0%	Naked	
	12	T/NK	neg	neg	nt	nt	nt	nt			
	13	T/NK	pos	neg	nt	nt	nt	nt			
	14	T/NK	pos	neg	nt	nt	nt	nt			
	15	NK	nt	nt	472	neg	neg	4810	nt	nt	
	16	T	neg	neg	1340	neg	neg	4559	nt	nt	
	17	T	pos	pos	341	nt	nt	31570	nt	nt	
	18	B	pos	neg	nt	nt	nt	nt			
	19	T	pos	neg	196	neg	neg	un			
	20	B	pos	pos	nt	nt	nt	nt			
	21	T	pos	neg	nt	nt	nt	909	nt	nt	
	22	B	neg	neg	nt	nt	nt	nt			
Epithelial	1	NPC	pos	pos	nt	nt	nt	nt			
	2	GC	pos	pos	nt	nt	nt	nt			
	3	GC	pos	pos	nt	nt	nt	nt			
	4	NPC	pos	pos	nt	nt	nt	nt			
	5	NPC	pos	pos	nt	nt	nt	nt			
	6	NPC	neg	pos	nt	nt	nt	nt			

NPC: Nasopharyngeal carcinoma, GC: Gastric carcinoma, pos: positive, neg: negative, un: undetectable, nt: not tested.

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