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BRIEF COMMUNICATION

Drug reaction with eosinophilia and systemic symptoms during primary Epstein–Barr virus infection

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We report a drug reaction with eosinophilia and systemic symptoms case of primary Epstein–Barr virus (EBV) infection, in which the diagnosis was first confirmed by lymphocyte transformation tests (LTT). LTTs were positive for cefditoren–pivoxil and acetaminophen. LTT, EBV load, and anti-EBV antibodies could allow early diagnosis of drug reaction with eosinophilia and systemic symptoms, which masquerades with the clinical features of infectious mononucleosis.

Introduction

Drug allergy occasionally causes a severe, multiorgan systemic reaction. Drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS) is a severe drug hypersensitivity reaction that is characterized by fever, skin eruption, cervical lymphadenopathy, leukocytosis with atypical lymphocytosis and/or eosinophilia, and liver dysfunction.[1] Causative drugs range widely and include anticonvulsants and antimicrobial agents. DRESS is often associated with the reactivation of the herpes virus family represented by human herpes virus (HHV)-6, Epstein–Barr virus (EBV), and cytomegalovirus.[1] By contrast, DRESS has rarely been reported in patients during acute primary infection of the viruses. The diagnosis of high-risk drug eruption is challenging because the sensitivity tests would give false negative results in patients

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with Stevens—Johnson syndrome, toxic epidermal necrolysis, and DRESS/DIHS.[2]

We report herein a case of DRESS, which developed during the course of primary EBV infection. The early diagnosis of DRESS was first made by the positive lymphocyte transformation test (LTT) for acetaminophen and cefditoren—pivoxil (CDTR-PI).

Case report

A previously healthy 4-year-old boy was admitted to our hospital on the 14th day of illness because of prolonged fever, jaundice, and generalized skin eruption. The patient had received oral CDTR-PI and acetaminophen suppository from the 6th day to the 12th day of illness. Despite the defervescence on the 11th day of illness, jaundice and abdominal pain emerged. On the 13th day of illness, he presented to a practitioner again because of developing generalized skin rash. The laboratory findings showed increased levels of: aspartate aminotransferase, 1821 U/L; alanine aminotransferase, 1777 U/L; total bilirubin, 6.8 mg/dL; and direct bilirubin, 5.1 mg/dL. He was then referred to us for further management.

On admission, his body temperature was 38.0°C. Skin and bulbar conjunctiva were icteric. Pruritic maculopapular eruption spread confluently on the trunk, extremities, palms, and soles (Fig. 1). Mucous membranes and conjunctivas were spared. There was cervical lymphadenopathy, hepatomegaly, but no splenomegaly. Complete blood counts showed a leukocyte count of 3.99 $\times$ 10^9/L with 26% segmented neutrophils, 55% lymphocytes, 10% monocytes, 4% eosinophils, and 5% atypical lymphocytes, a hemoglobin concentration of 11.7 g/dL and a platelet count of 143 $\times$ 10^9/L. Blood chemistry showed: total bilirubin, 7.8 mg/dL; direct bilirubin, 5.6 mg/dL; aspartate aminotransferase, 570 U/L; alanine aminotransferase, 894 U/L; lactate dehydrogenase, 637 U/L; and γ-glutamyl transpeptidase, 348 U/L. C-reactive protein concentration was 0.09 mg/dL. Serum levels of ferritin (1492 mg/dL) and soluble interleukin-2 receptor (6061 U/mL) were both high. Immunoglobulin levels and coagulation studies were unremarkable (immunoglobulin E $<$ 10 U/mL). Surface maker analysis of the peripheral blood lymphocytes showed a reversed CD4/CD8 ratio (0.45) and a prominently increased proportion of activated CD8$^+$T cells (72.2%). There were past inactive infections, but no reactivations of cytomegalovirus or HHV-6. Positive antiviral capsid antigen immunoglobulin M with negative anti-EBV nuclear antigen antibody indicated primary EBV infection. A high copy number of EBV-DNA (3 $\times$ 10^6 copies/L of peripheral blood) was detected by real-time polymerase chain reaction. LTT for acetaminophen [stimulation index (SI) 555%] or CDTR-PI (SI 314%) was highly positive. The diagnosis of DRESS was made because the patient fulfilled all but one criteria of eosinophilia. Dexchlorpheniramine and glycyrrhizinate were started with no use of the other drugs including antipyretics. All symptoms resolved until the cessation of therapy on the 19th day of illness. Negative LTT for acetaminophen (SI 81%) or CDTR-PI (SI 71%) was confirmed 2 months later. Thereafter, skin eruption did not appear when acetaminophen was administered at the chance of fever.

Discussion

Drug reactions in childhood are often challenging to diagnose because of accompanying viral diseases presenting cutaneous manifestation. The diagnostic criteria of DRESS/DIHS overlap the representative manifestations of infectious mononucleosis (IM). DRESS was first confirmed by the positive LTT in this pediatric patient with primary EBV infection. This observation suggests an unexpected utility of LTT for the correct diagnosis of DRESS associated with primary EBV infection.

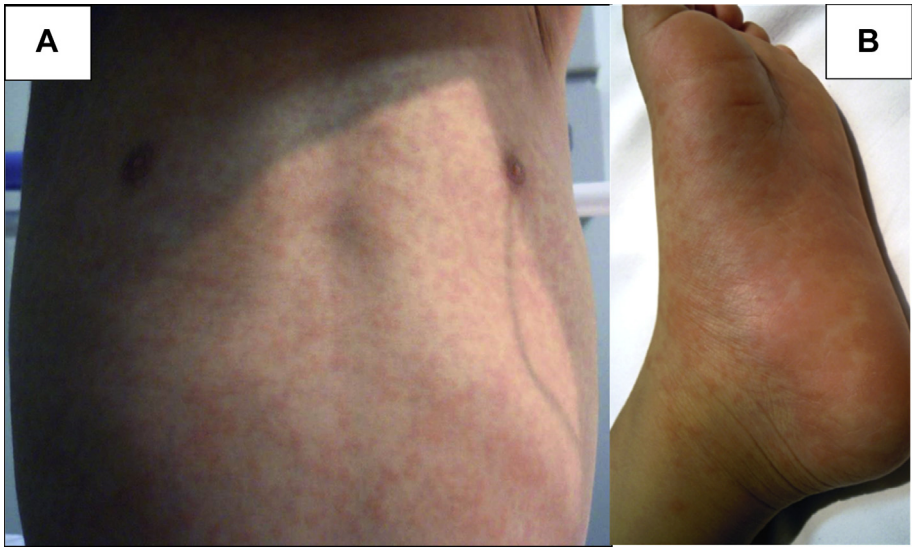

Figure 1. Maculo-papular eruption confluently spreading over (A) the whole body and (B) extremities involving palms and soles. The photographs were taken at the time of admission.

Reactivation of herpes virus infection concurrent with drug hypersensitivity is considered specific to DRESS. Only three patients have been previously reported to develop DRESS during primary EBV infection.[3–5] As shown in Table 1, there was no LLT recorded. These patients had prolonged fever, skin rash, and atypical lymphocytosis, but not always other typical expressions of acute IM. The present patient showed slight neutropenia and thrombocytopenia, but no eosinophilia. High serum levels of soluble interleukin-2 receptor and ferritin during the acute phase indicated the excessive immune activation leading to hemophagocytic syndrome, when eosinophilia is unusual. Pituitary adrenal axis might result in the modest increase of eosinophil counts during the convalescent phase (18th day of illness: 0.29 $\times$ 10^9/L).[6] Severe immune responses to the virus reactivation may explain the clinical manifestations of DRESS. Picard et al[1] found that the reactivation of HHV-6, HHV-7, and EBV and the proliferation of activated CD8$^+$T cells, which recognize EBV epitopes in most patients. The culprit drugs triggered the virus replication in EBV-transformed B cells from the patients. Picard et al[1] indicated that cutaneous and visceral symptoms of DRESS are mediated by activated CD8$^+$T cells largely directed against herpes viruses such as EBV. Therefore, primary EBV-infected patients might be at risk of developing drug reaction augmented by the activated CD8$^+$T cells. Both LTT for acetaminophen and CDTR-PI were definitely positive in the present patient. These drugs are chemically different and are metabolized through different pathways. Multidrug hypersensitivity rather than the cross reaction may explain the distinct manifestation although no skin patch test was performed.

Ampicillin (or amoxicillin) administration precipitates exanthema in >95% of adults, but is less common in children, with EBV-associated IM. Exanthema develops in 3–15% of IM patients not treated with β-lactam antibiotics. "Ampicillin rash" is explained by the mechanism of the proliferation of EBV-reactive CD8$^+$ T cells enhances the sensitivity to the drug. Renn et al[7] reported that the drug eruption occurs as the aminopenicillin-specific reaction. However, commonly used β-lactam antibiotics (cefotaxime), along with ampicillin, could be culprit drugs of DRESS.[8] With this background, exanthema in IM patients should be cogently differentiated from the prodrome of DRESS.

In the present patient, the positive result of LTT came to be negative with the favorable clinical course. Kano et al[2] reported that positive LLT was obtained at an acute phase of toxic epidermal necrolysis or Stevens–Johnson syndrome, but was later observed 5–8 weeks after the onset of DRESS. The proportion of circulating T cell subsets from patients affects the *in vitro* result of LTT. Functional regulatory T cells at the acute stage of DRESS may serve to prevent the activation and expansion of drug-specific T cells.[9] However, the proportion of regulatory T cells was reported to decrease in patients with primary infection, but not with reactivation of EBV.[10] Further study is needed to determine the sensitivity of LLT during the acute and convalescent phase of primary EBV infection assessed by the analysis of functional T cell subpopulations. Sequential LLT may be useful to determine the ominous hypersensitivity to drugs in patients with the primary infection of EBV.

Table 1 Reported patients with drug reaction with eosinophilia and systemic symptoms during primary Epstein–Barr virus (EBV) infection[a]

Pt	Sex	Age (y)	Causative drug	EBV DNA	Fever/ rash	Tonsillitis	Lymph-adenopathy	Hepato-megaly	WBC counts (×10^9/L)	Atypical lymphocytes	Eosino-philia[b]	LLT	Steroid therapy	Outcome	Refs
1	M	40	Allopurinol	High	Yes	No	No	No	13.7	Yes	Yes	NR	No	Alive	3
2	M	8	Carbamazepine	NR	Yes	No	Yes	Yes	19.9	Yes	Yes	NR	Yes	Alive	4
3	M	8	Azithromycin	NR	Yes	No	No	No	Normal range	Yes	Yes	NR	Yes	Alive	5
4	M	4	Acetaminophen Cefditoren–pivoxil	High	Yes	No	Yes	Yes	3.99	Yes	No	Positive	No	Alive	Ours

[a] Primary EBV infection was determined based on the pattern of anti-EBV antibodies.
[b] Eosinophil counts > 0.7 × 10^9/L.
LLT = lymphocyte transformation test; NR = not recorded; Pt = patient; WBC = white blood cells.

Conflicts of interest

The authors state that they have no conflicts of interest.

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