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CLINICAL CASE

Chronic active EBV infection: the experience of the Samsung Medical Center in South Korea

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KEYWORDS
Epstein-Barr virus;
Children;
Chronic active infection;
NK lymphocytosis;
Mosquito-bite hypersensitivity

Abstract
Background: Chronic active EBV infection (CAEBV) of T-cell or NK-cell type is an EBV+ polyclonal, oligoclonal or often monoclonal lymphoproliferative disorder (LPD) recognized as representing the spectrum of EBV-associated T-cell and NK-cell LPD with different clinical presentations; one systemic and two cutaneous disorders including hydroa vacciniforme-like T-cell LPD and mosquito bite hypersensitivity. The systemic form of the disease is characterized by fever, persistent hepatitis, hepatosplenomegaly and lymphadenopathy, which shows varying degrees of clinical severity depending on the immune response of the host and the EBV viral load.
Case reports: We described the clinicopathological findings of two children with CAEBV with a brief review of the literature.
Conclusions: Recognition of the disease is important for adequate management of the patient. EBV analysis should be included in the principal diagnostic tests for febrile children.

PALABRAS CLAVE
Virus de Epstein-Barr;
Niños;
Infección crónica activa;
Linfocitosis de células NK;
Hipersensibilidad por picadura de mosquito

Infección crónica activa por virus de Epstein-Barr: experiencia del Centro Médico Samsung en Corea del Sur

Resumen
Introducción: La infección crónica activa (CA) de células T o células tipo NK por virus de Epstein-Barr (VEB) es un desorden linfoproliferativo (DLP) VEB+ policlonal, oligoclonal o, frecuentemente, monoclonal reconocido como representación del espectro del DLP de células T y células NK asociado con VEB que tiene diversas presentaciones clínicas: un padecimiento sistémico y dos cutáneos que incluyen el DLP de células T que semeja hidroa vacciniforme y la hipersensibilidad por picadura de mosquito. Los síntomas de la enfermedad sistémica incluyen

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fiebre, hepatitis persistente, hepatoesplenomegalia y linfadenopatías que muestran diferente grado de severidad clínica, dependiendo de la respuesta inmune del hospedero y de la carga viral del VEB.
Casos clínicos: Se describen los hallazgos clínico-patológicos de dos niños con CAVEB y una breve revisión de la literatura.
Conclusiones: Es importante reconocer esta enfermedad para proporcionar el manejo adecuado al paciente. El análisis de VEB debería incluirse como una de las principales pruebas diagnósticas en niños con fiebre.

1. Introduction

Chronic active Epstein-Barr virus infection (CAEBV) is a clinical term initially defined by Straus as a disease related to chronic or persistent infection of EBV. Suggested criteria for diagnosing severe chronic EBV infection includes the following: 1) severe illness of >6 months duration that began as primary EBV infection and is associated with grossly abnormal EBV antibody titers [IgG to viral capsid antigen (VCA) = ∼1:5120; antibody to early antigen (EA) = ∼1:640; or antibody to EBV nuclear antigen (EBNA) <2], and 2) histological evidence of major organ involvement such as interstitial pneumonia, hypoplasia of some bone marrow elements, uveitis, lymphadenitis, persistent hepatitis or splenomegaly, and 3) detection of increased quantities of EBV in affected tissues by anticomplementary immunofluorescence for EBNA or nucleic acid hybridization[1]. In early reports, the cellular lineage of EBV-infected cells has not drawn attention; however, subsequent reports documented that EBV mainly exists in T-cells[2,3] but not in B-cells, as revealed by dual staining immunofluorescence analysis[3]. Just as the accumulation of clinical and laboratory data for CAEBV, it has been recognized that clinical and laboratory findings of CAEBV are of a broader spectrum than initially thought. Because individual cases do not fulfill the diagnostic criteria initially proposed, Kimura and colleagues modified the diagnostic criteria for CAEBV as follows: (1) illness ≥3 months duration [EBV-related illness or symptoms including fever, persistent hepatitis, extensive lymphadenopathy, hepatosplenomegaly, pancytopenia, uveitis, interstitial pneumonia, hydroa vacciniforme (HV), and hypersensitivity to mosquito bites (HMB)]; (2) increased amounts of EBV DNA or grossly abnormal levels of EBV antibodies, for instance, detection of EBV DNA in tissues or peripheral blood by Southern blot hybridization; EBV-encoded small RNA-1-positive cells in affected tissues or peripheral blood, $>10^{2.5}$ copies of EBV DNA/μg of DNA of peripheral blood mononuclear cells; and grossly abnormal levels of EBV antibodies (anti-VCA IgG titers ≥5120 or anti-EA IgG titers ≥640), and (3) no evidence of previous immunological abnormalities or other recent infection that might explain the observed condition.[4]

Based on the accumulated data, CAEBV of T-cell or NK-cell type has been recently defined as a systemic EBV+ polyclonal, oligoclonal or often monoclonal lymphoproliferative disorder (LPD) characterized by fever, persistent hepatitis, hepatosplenomegaly and lymphadenopathy, which shows varying degrees of clinical severity depending on the immune response of the host and the EBV viral load.[5,6]

CAEBV is often accompanied by cutaneous lesions such as severe mosquito bite allergy and hydroa-vacciniforme (HV)-like T-cell lymphoproliferative disease. Mosquito bite hypersensitivity (or mosquito bite allergy, MBH) is a unique cutaneous manifestation of CAEBV infection characterized by abnormally intense local reaction at arthropod bite area associated with systemic symptoms and signs like fever, lymphadenopathy and liver dysfunction. EBV genome is mainly found within NK cells of peripheral blood of MBH patients who often show NK cell lymphocytosis.[7–10]

HV-like LPD is an EBV-associated polyclonal, oligoclonal, or monoclonal cutaneous T-cell lymphoproliferative disease characterized by recurrent vesiculopapular eruptions, mainly on the face and arms. It shows a broad spectrum of clinical aggressiveness and usually a long clinical course with risk to develop systemic lymphoma. As the disease progresses patients develop severe and extensive skin lesions with systemic symptoms including fever, hepatosplenomegaly and lymphadenopathy. Classic HV, severe HV and HV-like T-cell lymphoma constitute a continuum spectrum of EBV-associated HV-like LPD.[5,11–14]

Recently, the three disorders indicated above have been recognized as representing the spectrum of EBV-associated T-cell and NK-cell LPD with different clinical presentations; one systemic and two cutaneous disorders including HV-like T-cell LPD and MBH.[14]

2. Case reports

The patients described in the following two case reports depict typical clinical manifestations of CAEBV with MBH in children. Case 2 was reported previously.[15]

2.1. Case 1

A 15-year-old Korean boy was admitted to the hospital with chronic intermittent dermatological and various systemic symptoms and signs since he was 5 years old. Birth weight was normal and adequate for gestational age. At a recent visit to a pediatric department, he showed adequate height of 163.7 cm for his age, but a low body weight of 39.6 kg.