Fatal CAEBV-Associated Vasculitis in ICF Syndrome Type 2

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To the Editor:

Immunodeficiency, centromeric instability, and facial anomalies (ICF) syndrome is an extremely rare autosomal recessive disorder caused by DNA hypomethylation. In 2019, Licciardli et al [1] reported that ICF type 2 (ICF2), which is caused by mutations in the *ZBTB24* gene, increases susceptibility to Epstein-Barr virus (EBV). To date, 43 cases of ICF2 have been documented. These include 2 recent cases with EBV-associated lymphoproliferative disorders (EBV-LPDs) reported since 2016, raising the total to 6 EBV-related complications. We report on 1 of the 6 cases. The patient presented novel aspects of EBV-related disease in ICF2, specifically chronic active EBV disease (CAEBV) leading to vasculitis, a first of its kind. The patient's parents gave their permission for this letter to be published.

The patient, a Japanese boy described by Nitta et al [2], displayed typical craniofacial features of ICF and additional symptoms, including hypoplastic primary teeth, bilateral hydronephrosis, hypopituitarism, and delayed motor development. He had experienced chronic diarrhea and frequent respiratory infections from childhood. At age 4 years, he developed recurrent fevers with vesicles on his trunk and arms. As reported by Makay et al [3], production of B-cell antibody to combined stimulation with IL-4, IL-10, and CD40 was very poor. Immunoglobulin replacement therapy was started at age 5 years owing to the in vitro results and deficient CD27-positive memory B cells and specific immunoglobulins. The diagnosis of ICF syndrome was confirmed based on chromosomal abnormalities and DNA hypomethylation, with no *DNMT3B* mutations. Biopsy of the vesicle revealed the presence of giant cells suggestive of viral infection, and high EBV-DNA load was detected in peripheral blood (PB). Despite a decrease in the frequency of fever following immunoglobulin therapy, high

EBV-DNA loads persisted in PB, ranging from 168 800 to 661 160 copies/µgDNA. At age 6, contrast-enhanced computed tomography scans showed no abnormalities (Suppl. Fig. 1A), and CD4-positive cells were identified in PB as EBV-infected through double staining and EBER-ISH (Suppl. Fig. 2). Southern blot analysis using an EBV terminal probe revealed a monoclonal band, indicating monoclonal proliferation of EBV-infected lymphocytes. A monoclonal peak pattern was detected in PB for T-cell receptor γ but not for B-cell receptors. Hematopoietic stem cell transplantation was considered but deferred because of the limited success rates for ICF in 2010 and clinical improvement with immunoglobulin therapy.

At age 7, the patient contracted respiratory syncytial virus infection, and his fever resolved in 3 days, although his cough worsened. X-ray revealed cardiac enlargement, and echocardiography showed marked dilation of the enlarged aortic root, aortic regurgitation, enlargement of the left ventricle, and enlargement of the coronary arteries (Suppl. Fig. 1B). Contrast-enhanced computed tomography revealed dilatation of the aortic root, descending thoracic middle aorta, bilateral common iliac arteries, celiac artery, superior iliac artery, and inferior mesenteric artery, as well as bilateral coronary aneurysms and multiple nongranulomatous vasculitis in the lung field (Suppl. Fig. 1C and Figure). EBV-DNA in PB remained high. Although the only diagnostic criterion for Kawasaki disease was fever, the patient had coronary artery aneurysms and was given immunoglobulin (400 mg/kg for 5 days) according to the usual treatment for Kawasaki disease. However, the enlargement of the aortic root and aortic regurgitation progressed. A respiratory syncytial virus antigen test became negative on the 13th day after admission, but the patient became febrile again. He died of heart failure 2 months after hospitalization. Posthumously, ICF2 was confirmed by a homozygous c.1148G>A mutation in the *ZBTB24* gene confirmed ICF2. The patient's parents were heterozygous for this mutation, although they were not consanguineous [2].

This report details a case of ICF2 syndrome complicated by vasculitis amid persistent EBV viremia. The patient's persistently high EBV-DNA levels in PB, identification of $CD4^+$ T cells as infected cells, and monoclonal expansion of EBV align with the pathogenesis of CAEBV. CAEBV is a rare subtype of LPD caused by EBV that can lead to cardiovascular complications such as coronary aneurysms and aortitis. Muneuchi et al [4] reported that 60% of CAEBV patients experienced cardiovascular conditions such as aortitis and coronary artery lesions. Hematopoietic stem cell transplantation is the only known treatment to halt progression of CAEBV [4]. However, in the case we report, rapid progression of vasculitis within a year precluded timely transplantation, leading to severe vascular complications. As in the present case, vasculitis can progress quietly in CAEBV, underlining the need for screening by PCR-based EBV quantification in ICF2 patients and rapid transplantation to prevent cardiovascular complications if high levels of EBV-DNA persist. In the case of persistent EBV infection, we also emphasize the importance of genetic analysis, including that of *ZBTB24*, to improve diagnosis and therapy.

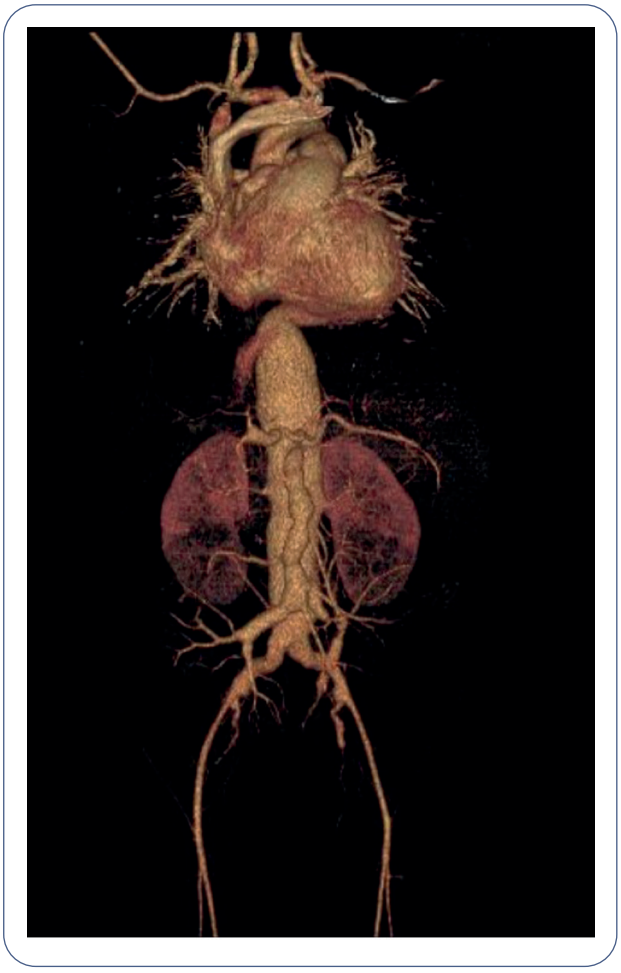

Figure. Three-dimensional computed tomography reconstruction of the vascular system showing the affected vasculature.

In contrast to ICF2, no EBV-related disorder has been reported in ICF1, which is caused by *DNMT3B* mutations and accounts for more than half of all cases of ICF syndrome [5]. EBV-LPDs are known to be associated with DNA hypomethylation [6], and both *DNMT3B* and *ZBTB24* mutations result in DNA hypomethylation at pericentromeric repeats. However, the pattern of methylation abnormalities differs between the two [7]. Although other ICF types are also involved in methylation abnormalities [8], there are no reports of susceptibility to EBV, except in ICF2; susceptibility to EBV is likely to be specific to ICF2. This means that the unique methylation patterns seen in *ZBTB24* mutations are strongly linked to increased susceptibility to EBV infection. Furthermore, as both ICF2 and CAEBV are extremely rare diseases, their co-occurrence may not be coincidental, but rather the methylation abnormalities caused by the *ZBTB24* mutation may contribute to the development of CAEBV. Epigenetic changes akin to those in *ZBTB24* mutations could contribute to the etiology of many cases of CAEBV in which no genetic cause has been found. The present case might provide new insights into the etiology of the disease.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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