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LETTER TO EDITOR

# EBV-Related Hodgkin Lymphoma in an ICF2 Patient: Is EBV Susceptibility a Hallmark of This ICF Subtype?

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To the Editor,

Immunodeficiency, centromeric region instability, and facial anomalies syndrome (ICF) is a rare autosomal recessive disorder caused by defective DNA methylation. So far, approximately 70 cases have been reported: 56% have mutations in DNMT3B (ICF1), 31% in ZBTB24 (ICF2), and the remaining 13% in CDCA7 (ICF3) or HELLS (ICF4) [1].

Regardless of ICF subtype, the main clinical manifestations are recurrent and severe infections due to the underlying immunodeficiency, in particular T cell lymphocytopenia and/or hypo/agammaglobulinemia and facial abnormalities, such as epicanthus, low-set ears, hypertelorism, flat nasal bridge, telecanthus, and a round face.

We describe the history of an ICF2 patient who had a chronic EBV infection and developed aggressive Hodgkin lymphoma (HL). The clinical history and the revision of literature reveal that ICF2 patients have a predisposition to EBV infection with severe complications.

## Case Report

The patient was born from Italian, non-consanguineous parents. At 7 years of age, he underwent immunological investigations because of recurrent stomatitis and bronchopneumonias (3/year). Laboratory tests revealed hypogammaglobulinemia (IgG 425 mg/dl, IgA 147 mg/dl, IgM 27 mg/dl) and T cell alterations ($CD3^+$ 82%, $CD4^+$ 34%, $CD8^+$ 61%, $CD19^+$ 5%) with normal lymphocyte count (2200/$mm^3$). He had mild facial abnormalities, including mild dolichocephaly, high forehead, hypertelorism/telecanthus, downslanting palpebral fissures, and cryptorchidism. Cytogenetic analysis showed peculiar centromeric alterations on chromosomes 1, 9, and 16. Hence, the patient was diagnosed as affected by ICF syndrome [2]. Genetic testing for DNMT3B was negative, while recent ZBTB24 sequencing showed two heterozygous mutations: a nonsense mutation (c.909 dup, p. Lys304X) and a missense mutation in the BTB domain of ZBTB24 (c.175A > G, p.S59G). Regular intravenous immunoglobulin substitution therapy (400 mg/kg every 4 weeks) was started. At follow-up, no major infectious events were observed, but chronic sinusitis and rare upper respiratory tract infections successfully treated with antibiotic therapy.

At 19 years of age during routine analyses, an increase in liver enzyme levels (AST 50–98 U/l; ALT 58–183 U/l; GGT 228–443 U/l) was noticed. Ultrasound elastography demonstrated a mild, progressive fibrosis. HCV-PCR, HbsAg, CMV-PCR, ANA, ASMA, anti-LKM, ANCA, anti-endomysial, and tissue transglutaminase antibodies were all negative. Screening for cryptosporidium in stools, 24-h urinary copper, urine PBG, and dALA were also negative. From then on, EBV-DNA was constantly detected in PBMCs ranging from 5808 to 9983 copies/ml. Given the persistence of biochemical signs of hepatitis, although without evidence of progression at 24 years of age, a hepatic biopsy (initially refused as well as any immunosuppressive therapy) was performed, demonstrating a chronic cholangitis with marked portal inflammation and T lymphocyte infiltiration of biliary ductules. Multiplex/heteroduplex PCR analysis of TCRγ revealed the monoclonal nature of T lymphocyte that was not found in peripheral blood.

No significant clinical disturbances were reported until 27 years of age, when he developed persistent fever unresponsive to antibiotic therapy, weight loss, and asthenia.

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Laboratory investigations revealed mildly increased C-reactive protein (15 mg/dl, n.v. < 10), enhanced LDH concentration (1347 U/I), and high ferritin levels (9452 U/I). Blood, urine, and stool cultures were negative as well as chest X-ray and abdominal ultrasonography. A marked EBV viremia was noticed (99,000 copies/ml). A positron emission tomography showed multiple hyper-captation areas with involvement of both humeri, clavicles, ribs, sternum, shoulder blades, several vertebrae, pelvis, and both femurs. The bone marrow biopsy led to the diagnosis of nodular sclerosing HL, stage IVB. Reed-Sternberg cells were EBER+ by in situ hybridization analysis (Fig. 1). The patient was treated with doxorubicin + bleomycin + vinblastine + dacarbazine (ABVD) for 6 cycles plus rituximab (375 mg/m$^2$) which allowed a complete remission.

## Discussion

Twenty-nine patients with ICF2 have been reported so far in literature [1, 3–5]. All patients with ICF share common feature of immunodeficiency with recurrent bacterial infections. Viral infections are less common even if they may have a severe course [3].

Despite optimal substitutive therapy with IgG, our patient developed a chronic EBV infection and an EBV-related HL. It must be underlined that 3 other ICF2 patients have been reported with severe complications EBV infection: one patient had an EBV-induced hemophagocytic lymphohystiocytosis [4], another one developed "severe mononucleosis" [3], and a third patient with persistent EBV infection died of fatal infection [5]. Herein, we report a fourth case of EBV-related

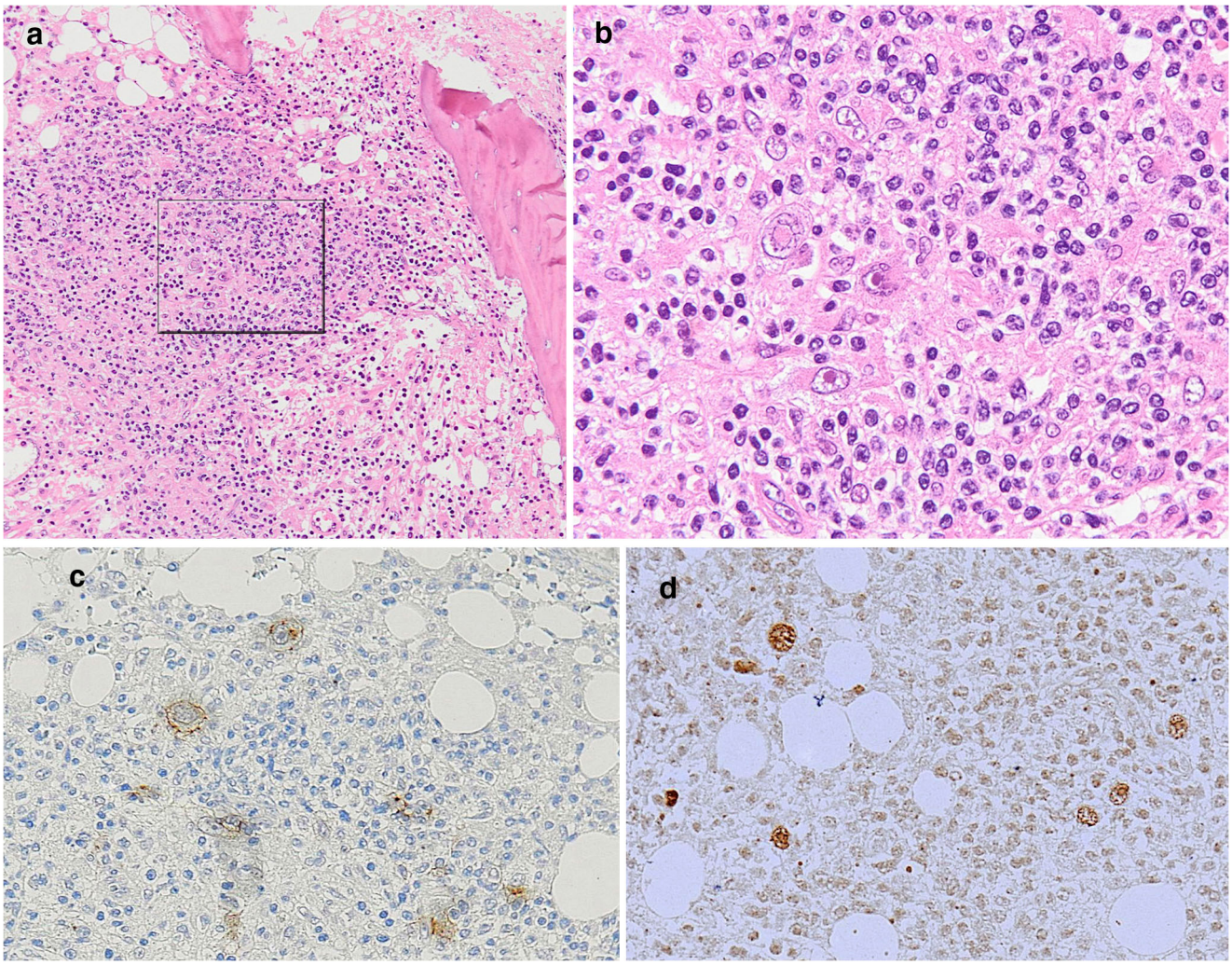


**Fig. 1** Nodular sclerosing HL, bone marrow biopsy microscopical view (original magnification: **a** × 100, **b** × 400, **c** and **d** × 200). **a**, **b** Hematoxylin and eosin stain of BM showing fibrotic areas and nodular clusters of small lymphocytes. Among these cells, we recognize small histiocytes and some large lymphoid cells with folded or multilobated nuclei and prominent eosinophilic nucleoli, called Reed-Sternberg cells. **c** CD30 staining is positive in large lymphoid cells. Reed-Sternberg cells are generally CD30+, CD15+, and Pax5+ positive (the latter immunohistochemical stainings are not shown in picture). **d** EBER in situ hybridation immunohistochemical staining showing strong EBER signal in Reed-Sternberg cells

complication in an ICF2 patient. In our patient, EBV viremia persisted over time, with marked increase during HL development with typical EBER+ Reed-Sternberg cells. Our case highlights that chronic EBV infection in ICF2 patients may evolve in malignancies. In this context, it should be stressed that ICF is a disease with chromosomal instability, such as Ataxia-Talangectasia and Nijmegen-breakage syndrome, and this may contribute to the accumulation of pro-neoplastic mutations. In summary, 4/29 patients (13.2%) of ICF2 patients published so far had abnormal control of EBV infection leading either to acute or chronic complications, that may manifest at diagnosis [4] or after more than 20 years, and may be lethal. Interestingly, EBV-induced complications seem to be a specific characteristic of ICF2 patients. Interactions between EBV-driven lymphocyte proliferation and DNA hypomethylation are widely recognized [6]. Whereas all ICF patients share the pericentromeric repeat hypomethylation, the subtelomeric methylation profiles differ among subtypes, in particular between ICF2 and ICF1 [7]. It may be possible that the peculiar methylome profile may account for the abnormal control of EBV infection in ICF2 patients.

In this context, HSCT may be considered in all ICF patients for its intrinsic capacity to solve not only the typical humoral defect but also the more extensive underlying impairment of the immune system that may result in fatal early and late complications. So far, 5 patients (4 ICF1, 1 ICF2) have been successfully treated with HSCT; this reverse the immunodeficiency and hopefully the risk of associated lymphocyte proliferations, such as the clonal T cell hepatic infiltration and HL observed in our patient.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.



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