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Immunodeficiency, centromeric instability, and facial anomalies (ICF) syndrome with NK dysfunction and EBV-driven malignancy treated with stem cell transplantation

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To the Editor:

Immunodeficiency, centromeric instability, and facial anomalies syndrome (ICF) is a rare autosomal recessive disorder characterized by DNA hypomethylation at the pericentromeric regions of several chromosomes.[1] Variants in *DNMT3B* (ICF-1) account for over half of cases, and variants in *ZBTB24* (ICF-2),[2] *CDCA7* (ICF-3), and *HELLS* (ICF-4)[3] comprise the other half of cases. The majority of patients have hypo- or agammaglobulinemia with normal B cells, though additional defects have been reported.[4–6] We present the case of a female patient with impaired NK cell function, decreased NK cell numbers, and abnormal NK cell phenotype who was found to have a novel homozygous *ZBTB24* pathogenic variant. She subsequently developed EBV-driven lymphoproliferative disease and was

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successfully treated with chemotherapy followed by hematopoietic stem cell transplantation (HSCT).

The patient presented at 3 months of age with fever and respiratory distress. After brief hospitalization for presumed bronchiolitis, she returned with new fever, worsening of respiratory symptoms, hepatosplenomegaly, leukopenia, and diffuse hazy infiltrates on chest radiograph (Figure 1A). Further evaluation revealed a whole-blood CMV PCR of 125,257 copies/mL and she was diagnosed with CMV pneumonitis.

She was born full-term and Pennsylvania newborn screen was normal, including T cell receptor excision circles. She had received her 2-month vaccinations—including live oral rotavirus vaccine—without issue, was formula-fed, and had no allergies. Her parents are first cousins from Saudi Arabia, and she has a healthy older brother. Her family history was significant for “blood cancers” in two female cousins and a maternal aunt.

Initial workup (summarized in Table E1 in the Online Repository) was significant for undetectable IgA, low IgG, low $CD8^+$ cells, low NK cells, and low B cells. She received IVIG and valganciclovir. She was discharged on hospital day 32 after CMV PCR was undetectable and continued valganciclovir prophylaxis as an outpatient.

Immunoglobulins and T and B cells normalized over the 9 months after admission. CMV remained undetectable (Table E1). NK cell number remained low, and NK cell function was decreased when repeated three times as a clinical send-out lab to the Cancer & Blood Diseases Institute Clinical Laboratories at Cincinnati Children’s Hospital. Further NK cell analysis at 17 months of age on a research basis (laboratory of EMM and JSO, then at Texas Children’s Hospital) confirmed this functional abnormality and showed an increased percentage of $CD56^{bright}$ cells and a decreased percentage of $CD16^+$ cells (Figure 2). These findings suggest either impaired transition from immature to mature NK cells or impaired survival of mature NK cells. NK phenotype was further defined by 5 flow cytometry panels designed to interrogate human NK cell phenotype and function[7] that confirmed that the over-represented $CD56^{bright}$ subset were bona fide immature NK cells (Figure E1 in the Online Repository).

Medical Genetics evaluation noted hypotonia, arched eyebrows with blepharophimosis, telecanthus, ptosis, saddle-shaped nose, recessed chin, and gross motor and speech delays at age 17 months. Whole exome sequencing revealed a novel homozygous frameshift variant in *ZBTB24* (c.1492_1493del, p.Q498Vfs) consistent with a diagnosis of ICF-2 (MIM phenotype number 614069), which was confirmed with Sanger sequencing. Karyotyping, C-banding, and centromeric instability studies were normal.

Continued evaluation at 32 months of age was significant for low NK cells, low memory B cells, and low pneumococcal titers (Table E1). PPSV23 was administered shortly thereafter.

At 34 months of age, she developed fever and respiratory distress. Initial evaluation revealed bilateral infiltrates on chest radiograph (Figure 1B), respiratory viral panel positive for rhinovirus/enterovirus, and elevated whole-blood EBV PCR of 6,500 copies/mL. CMV PCR was negative. Immunological evaluation showed loss of previously protective tetanus and

diphtheria titers, no response to PPSV23, low IgG, and additional abnormalities in lymphocyte subsets (Table E1). Due to persistent high fevers and lack of clinical improvement, chest CT and bronchoscopy with bronchoalveolar lavage (BAL) were pursued. EBV PCR from the BAL specimen was elevated at 83,000 copies/mL, and CT was concerning for lymphoproliferative disease. Due to her tenuous clinical status, one dose of rituximab was administered for presumptive EBV-driven lymphoproliferative disease. She subsequently underwent thoracoscopic lung wedge resection biopsy which was consistent with EBV-driven lymphoproliferative disorder with features of a CD20-negative large B cell lymphoma.

At the time of diagnosis, both HSCT and medical therapy for lymphoma were considered and discussed. Due to the previous success of HSCT for ICF, [8] the evolution of the patient's immunodeficiency to include persistent hypogammaglobulinemia and a memory B-cell defect in addition to NK abnormalities, and the occurrence of a second severe, life-threatening infection at a young age, HSCT to correct the underlying immunodeficiency was considered an clinically-relevant therapeutic option for this patient. Chemotherapy was initiated, however, due to the patient's severe illness, the large tumor burden, and the time necessary to orchestrate HSCT.

Chemotherapy was administered per protocol ANHL1131, group B (pre-phase with cyclophosphamide, vincristine, prednisone, intrathecal methotrexate/hydrocortisone; courses 1 and 2 with cyclophosphamide, vincristine, prednisone, doxorubicin, high-dose methotrexate, intrathecal methotrexate/hydrocortisone; and courses 3 and 4 with cytarabine, high-dose methotrexate, intrathecal methotrexate/hydrocortisone, intrathecal cytarabine/hydrocortisone). She ultimately underwent reduced-intensity conditioning per institutional protocol with hydroxyurea, alemtuzumab, fludarabine, melphalan, and thiotepa followed by CD34-selected, 12/12 HLA-matched, unrelated-donor peripheral blood HSCT. Her early post-transplant course was complicated by adeno-, EBV, and CMV viremia which responded quickly to antiviral medications, donor lymphocyte infusion, and rituximab.

She is now greater than 300 days post-transplant, off immunosuppression with 98–100% donor engraftment, without evidence of organ toxicity or graft-versus-host disease, and with excellent immune reconstitution. Recent CMV and EBV whole-blood PCRs were undetectable, and she is receiving IVIG for mild hypogammaglobulinemia thought to be secondary to rituximab given several times throughout her course.

Previously described immune defects in patients with ICF other than hypogammaglobulinemia include decreased $CD4^+$ T cells[5] and defective lymphocyte mitogen response.[6] This is the first report of impaired NK cell number and function with likely related EBV-driven lymphoma. Little is known about NK cells in ICF, with one patient with ICF-2 who gradually developed decreased NK cells,[6] and an additional patient with ICF-2 with low NK cell number and hemophagocytic lymphohistiocytosis.[9] Further investigations may include NK phenotyping of other patients with ICF.

This case adds an unexpected disorder to the differential diagnosis of an infant with low NK cell number and/or function and also adds a new presenting phenotype to the known clinical

spectrum of ICF-2. Of interest, though this patient had characteristic facies and a novel pathogenic variant in a gene associated with ICF, she had neither centromeric instability nor the typical hypogammaglobulinemia associated with the disorder. The absence of centromeric instability has important implications for diagnosis – a negative centromeric instability test may not rule out ICF. This case also demonstrates a novel requirement for *ZBTB24* in human NK cell maturation and function.

Regarding the relationship between this patient's immunodeficiency, her susceptibility to EBV, and her ultimate diagnosis of EBV-driven malignancy, we suggest that her NK dysfunction was most clinically significant. It has been described that surveillance by NK and antigen-specific $CD8^+$ T-cells are the main protectors against primary EBV infection, and that lymphoproliferative disorders (LPDs) can emerge when EBV infection escapes the cellular immune response. It has recently been reported that two-thirds of EBV-associated LPDs occur in patients with B- and T-cell deficiency, highlighting the importance of cellular immunity in protection against EBV-driven processes.[10] In a recent review by Tangye et al, the importance of NK cells in human anti-EBV immunity is reviewed, in addition to several recent studies in mice which suggest that NK dysfunction leads to higher incidence and increased severity of EBV driven lymphoproliferation compared to NK-sufficient mice. [11] Regarding the patient's hypogammaglobulinemia, EBV-specific antibodies have been shown to possibly modulate disease severity rather than to prevent disease, and cellular-based mechanisms appear to play the largest role in EBV immunity.[11]

It has been suggested that HSCT should be considered for patients with ICF with evidence of T cell dysfunction.[8] This case suggests that patients with ICF-2 syndrome should have their NK cell function thoroughly investigated and transplant should be considered as a potential therapeutic option if NK cell defects are found.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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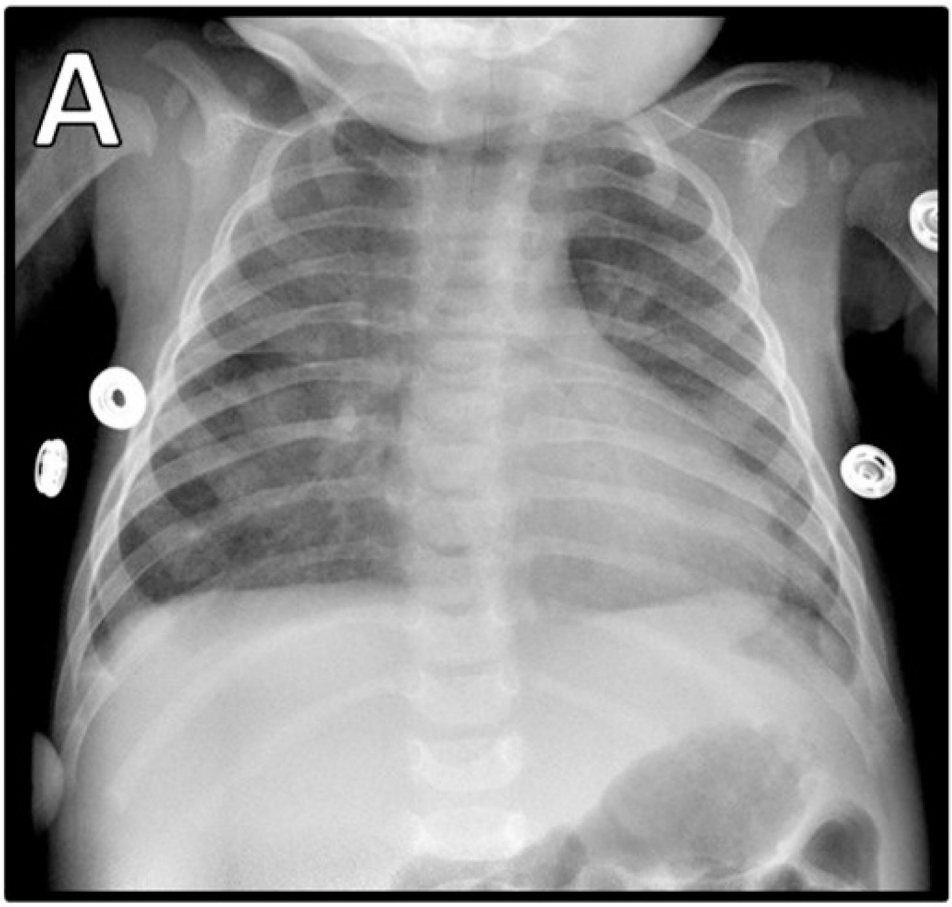
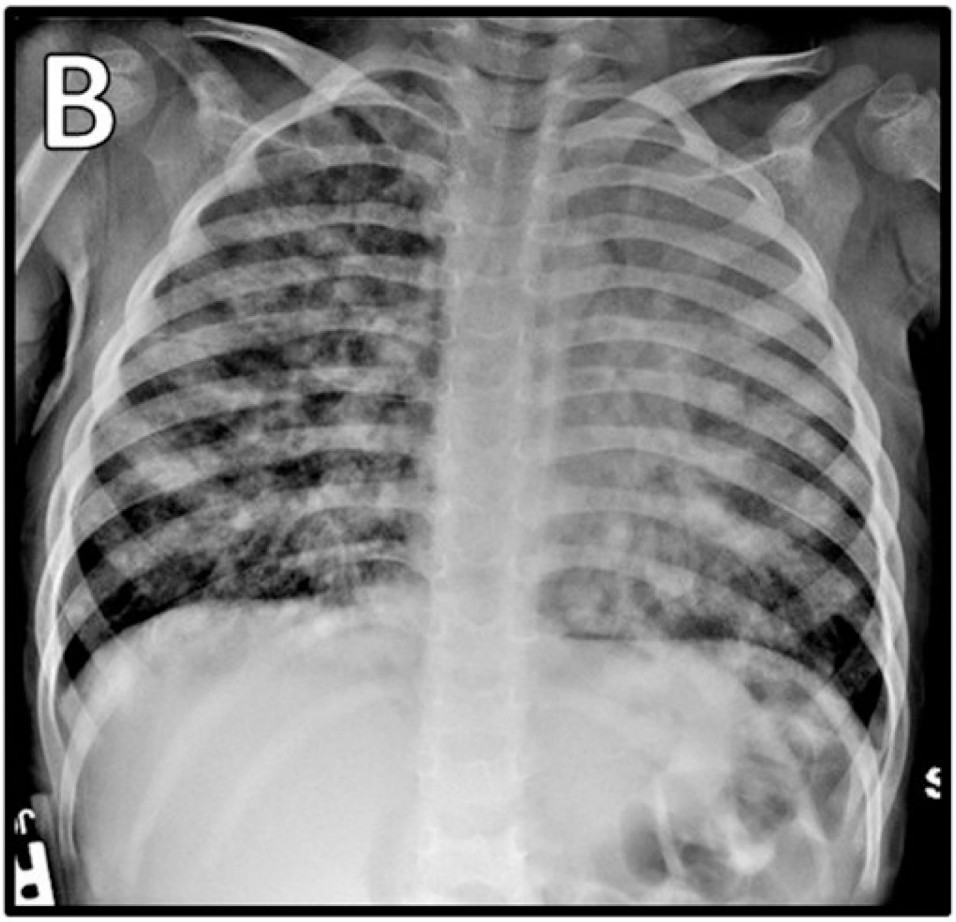
Clinical implications:

This is the first reported case of both 1) ICF syndrome presenting as NK dysfunction and 2) EBV-driven malignancy in ICF syndrome. Hematopoietic stem cell transplantation treated the immunodeficiency and should be considered early in ICF-2 with NK cell defects.





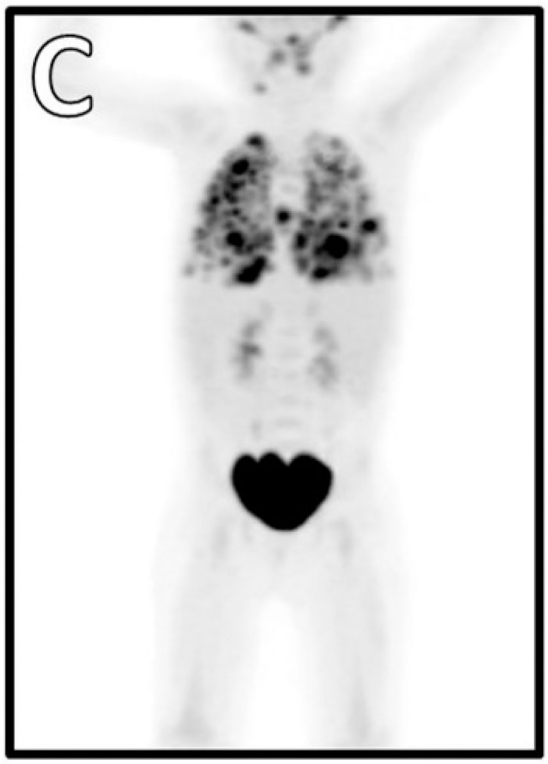


Figure 1. Imaging during hospitalizations.

A) CMV pneumonitis. EBV-driven lymphoproliferative disease B) radiograph, C) PET.

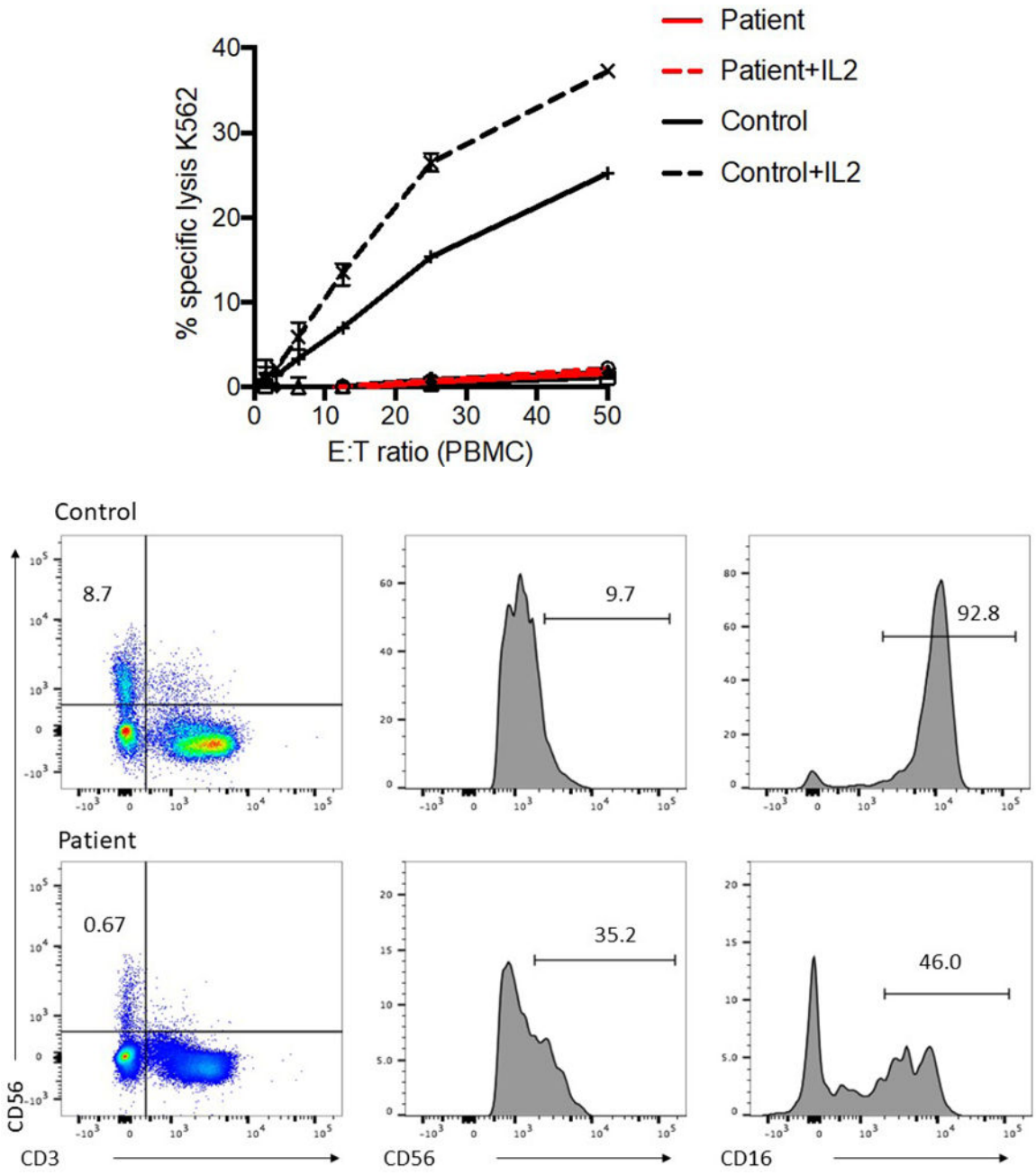


Fig. 2. Impaired NK cell phenotype and function.

PBMC isolated by standard Ficoll density centrifugation. A) ^{51}Cr cytotoxicity assay against K562 target cells in the presence (dashed line) or absence (solid line) of IL-2. B) FACS analysis of PBMC demonstrating NK cell frequency within the lymphocyte gate (left) and frequency of CD56^{bright} (center) and CD16^{+} NK cells (right).