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LETTER TO EDITOR

Immune Reconstitution after Hematopoietic Stem Cell Transplantation in Immunodeficiency–Centromeric Instability–Facial Anomalies Syndrome Type 1

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Abbreviations

ICF	Immunodeficiency, Centromeric instability and Facial anomalies
HSCT	Hematopoietic stem cell transplant
RIC	reduced intensity conditioning

To the Editor:

Immunodeficiency, centromeric instability and facial anomalies syndrome (ICF) is a rare autosomal recessive condition (OMIM 242860) characterized by pericentromeric chromosome instability and a heterogeneous clinical presentation of recurrent infections, neurologic abnormalities, and facial dysmorphism (hypertelorism, macroglossia, and micrognathia) [1]. In ICF syndrome, defects in DNA methylation at the pericentromeric regions of chromosomes 1, 9, and 16 lead to cytogenetic abnormalities which are prone to breakage [1–3]. Pathogenic variants in four genes have been recognized to date; DNA methyltransferase 3B gene (*DNMT3B*) causing ICF1, Zinc-finger and BTB domain-containing 24 gene (*ZBTB24*) causing ICF2, and cell division cycle associated 7 gene (*CDCA7*) and helicase lymphoid-specific gene *(HELLS)* causing ICF3 and ICF4, respectively [2]. The most common subtype, affecting approximately 50% of patients, is ICF1 [1]. Immunologic abnormalities in ICF1 result from this epigenetic dysregulation and include defective lymphocyte differentiation, activation, and migration, as evidenced by absent $CD19^{+}CD27^{+}$ class switched memory (CSM) B cells, hypogammaglobulinemia, and sub-optimal T cell proliferation with antigen stimulation. Subsequently, patients suffer from recurrent pyogenic infections, opportunistic infections, and failure to thrive [3–5].

Treatment for the immunologic manifestations of ICF1 includes early immunoglobulin replacement and prophylaxis for opportunistic organisms; however, recurrent infections frequently lead to shortened lifespan, with affected patients rarely surviving beyond the second decade [4]. The only curative option for the immunodeficiency associated with ICF1 is hematopoietic cell transplant (HCT), which has been reported in less than 10 cases of ICF1 worldwide [3, 6–8]. All previously reported patients seemingly had successful correction of their hypogammaglobulinemia and reported full donor chimerism following either myeloablative or reduced intensity conditioning (RIC); however, data regarding long-term follow up after transplant is limited. Herein, we describe the case of a Caucasian male who presented at age 6 months with recurrent infections, was subsequently diagnosed with ICF1 syndrome, and underwent HCT at 22 months of life with immune

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reconstitution in the setting of mixed donor chimerism. We believe this to be among the first successfully transplanted case of ICF1 in the United States, and the first reported case of successful correction of the underlying immune deficiency despite mixed donor chimerism following HCT.

The patient is a Caucasian male born to non-consanguineous parents and product of a normal pregnancy. He presented at the age of 6 months with fever, respiratory symptoms, severe neutropenia (initial ANC 0), adenovirus, and coronavirus (subtype OC43) by PCR on nasopharyngeal swab, right middle lobe pneumonia on chest x-ray, as well as astrovirus gastroenteritis and adenoviremia. He was at 30th and 10th centiles for weight and height respectively, had gross and fine motor developmental delay, subtle hypertelorism, flat nasal bridge, epicanthal folds, and syndactyly of his second and third toes with no familial history of this trait. Work up for his neutropenia, including anti-neutrophil antibodies and *ELANE* sequencing analysis, was normal as was his TREC newborn screen. At 8 months of age, he had four admissions for recurrent neutropenic fevers, polyviral respiratory infection (rhinovirus and human metapneumovirus), and presumed superimposed bacterial pneumonia (bacterial and fungal cultures on bronchoalveolar lavage were ultimately negative, though obtained after antibiotic treatment). He was found to have panhypogammaglobulinemia (IgG < 30, IgM 7, IgA 7, all mg/dl) and absent vaccine antibody responses to tetanus and diphtheria, despite having received all age-appropriate immunizations (Table 1). Flow cytometry was notable for normal total CD19+ B cell counts but absent $CD19^{+}CD27^{+}$ $IgM^{-}IgD^{-}$ CSM B cells at age 10 months (Table 1). Lymphocyte proliferation to mitogens demonstrated normal response to ConA, PWM, and PHA. Bone marrow biopsy demonstrated normal marrow with trilineage hematopoiesis. He was started on intravenous immunoglobulin replacement at 9 months of age. A targeted next-generation sequencing (NGS) panel for inborn errors of immunity genes showed compound heterozygous variants *in trans* [c.1957G > A (p.Asp653Asn) and c.2292G > T (p.Arg764Ser)] in the *DNMT3B* gene, initially both classified as variants of unknown significance. One variant (c.2292G > T) was later reclassified as likely pathogenic (Fig. 1S). Karyotype assessment of phytohemagglutinin (PHA)-stimulated peripheral blood lymphocytes showed the classic chromosomal anomalies seen in patients with ICF1, confirming the diagnosis at age 12 months (Fig. 2S).

At age 22 months, the patient received 10/10 HLA MRD (matched related donor) bone marrow HCT (total nucleated cells of 6.88 × 10^8/kg) from his brother, age 4.5 years, who did not carry either of the *DNMT3B* variants. The patient underwent RIC [9, 10] with alemtuzumab of 0.9 mg/kg (day −14 to −12), fludarabine 150 mg/m^2 (day −8 to −4), melphalan 140 mg/m^2 (day −3 to-2) and thiotepa 10 mg/kg (day −1) and received methotrexate and tacrolimus for graft versus host disease (GvHD) prophylaxis. Absolute lymphocyte count (ALC) was 7191 cells/mm^3 pre-conditioning and 0 following alemtuzumab. Neutrophil engraftment was achieved on day +13. His initial post-transplant course was complicated adenovirus reactivation treated successfully with antivirals. The patient was discharged on day +26 after having received one additional dose of intravenous immunoglobulin, after which he did not require any additional immunoglobulin replacement post-transplant.

Sorted chimerism obtained on day 30 showed 98% donor cells in whole blood, CD3+ T cell and CD33+ myeloid fractions. However, on day 60 the patient started to develop mixed chimerism, and by 3 months post-transplant demonstrated 84% donor cells in peripheral blood with 59% sorted CD3+ T cells and 82% myeloid fractions (Table 1). Immune suppression was weaned from D+ 100 and discontinued on day 130. A CD34+ selected stem cell boost (6.3 × 10^6/kg) from his brother was given on day +198 with an intent to improve declining chimerism [11]. Chimerism has remained mixed but stable at 2.5 years post-transplant (Table 1). Despite this mixed chimerism, his immunologic studies demonstrated normalization of IgG, production of recent thymic emigrants, detection of CSM B cells and protective response to vaccines (Tables 1 and 2). At 2.5 years of follow up, the patient is doing well with complete immune reconstitution and no significant infections. At the time of this publication, he is 4 years old, attends pre-school, and continues to receive occupational, physical and speech therapies for developmental delay.

This case highlights the role of HCT in correcting the immune dysregulation in patients with ICF1, curing the underlying immunodeficiency and improving quality of life, even in the presence of mixed donor chimerism. There are very few reports of HCT for ICF1 in the literature. Five cases from Europe have reported HCT for patients with *DNMT3B* mutations using either RIC (three patients) or fully myeloablative conditioning (two patients), all of whom had immune reconstitution, and were able to discontinue immunoglobulin replacement [3, 6, 8]. Additional reports of transplant for ICF in the literature for unclear subtype include: two patients with ICFX (now classified as ICF3 or ICF4), one patient for unspecified ICF [12] and a patient transplanted for MDS with a history of ICF [1]. The only other report of HCT for ICF1 in the United States does not provide details of conditioning or post-transplant course [7]. There has also recently been report of successful HCT in the United States for a patient with ICF2 with 98–100% donor engraftment at 300 days post-transplant [13]. Of all cases for which chimerism data have been reported in HCT for ICF1, only one demonstrated decline in whole blood donor chimerism, which subsequently improved to 100% following unconditioned

Table 1 Immune reconstitution post-HCT

	Pre-HCT	3 months post-HCT	6 months post-HCT	Stem Cell Boost	9 months post-HCT	1 year post-HCT	18 months post-HCT	2 years post-HCT	2.5 years post-HCT
IgM (27-107mg/dL)	**7**	87	55		33	33	50	43	84
IgA (19-223 mg/dL)	**7**	15	18		**7**	**7**	**<7**	**<7**	**7**
IgG (402-1223 mg/dL)	**<30**	638	865		850	850	939	1,120	1,250
Diphtheria antibody Tetanus antibody	**<0.1** **<0.1**					>3.0 0.5		0.6 0.7	
Immunophenotyping									
CD3+ T cells *(1400-3700 cells//mm3) **(1204-2889)	6892*	**154***	1116*		1,977*	2,254*	2985*	1,641**	2,555**
CD4+ T cells *(700-2200 cells//mm3) **(505-1644)	3963*	**76***	**647***		1,127*	1,312*	1553*	655**	1,211**
CD8+ T cells *(490-1300 cells//mm3) **(336- 1296)	2809*	**58***	372*		761*	853*	1183*	752 **	1,089**
CD4/CD8 (>0.9)	1.4	1.3	1.7		1.5	1.5	1.3	0.87	1.1
CD56/CD16+ NK cells *(130- 720 cells// mm3) **(102-827)	**125***	**109***	155*		**95***	**74***	227*	102**	**51****
CD19+ B cells *(390-1400 cells//mm3) **(215- 1230)	1119*	**278***	864*		521*	758*	601*	468**	681**
CD19+CD7+IgM-IgD-isotype switched memory B cells (0.7-7.2%)	0.0%					2.74%			5.4%
CD45 RA/RO									
CD4+ RA+ % CD4 ≠ (median value for matched controls)	88.8%	20.3%				59.02% (38.35)≠			54.9%
CD4+RO+ %CD4 ≠ (median value for matched controls)	5.3%	73.3%				23.94% (42.32)≠			25.8%
CD8+RA+ % CD8 ≠ (median value for matched controls)		26.8%				78.33% (52.11)≠			68.7%
CD8+ RO+ % CD8 ≠ (median value for matched controls)		46.2%				6.98% (17.63)≠			3.2%
Chimerism (% Donor cells)									
Peripheral blood		84%	41%		50%	43%	44%	45%	44%
CD3+		59%	68%		79%	79%	78%	76%	75%
CD33+		82%	34%		34%	29%	25%	21%	22%
CD19+		97%						54%	62%

Comparison of baseline immunoglobulins, vaccine titers, immunophenotyping (T/B/NK and CD45 RO/RA), and donor chimerism were collected pre-transplant and monitored for 2.5 years post-transplant (Table 1). Patient had normal phytohemagglutinin-stimulated lymphocyte proliferation, T cell function, and percentages of naïve T cells (CD45 + RA) pre-transplant. Patient received CD34+ stem cell boost on day +197 with no effect on chimerism (between 6-month and 9-month data). At 1 year and 2.5 years following transplant, advanced immunophenotyping of T and B cells was performed (Table 2). At 2.5 years following transplant, additional evaluation for recent thymic emigrants (CD4 + CD45RA + CD31+) was performed which was appropriate for age at 43% of CD4+ T cells (Table 2). Reference ranges are shown in parentheses. Bolded values indicate outside of reference range

Flow Cytometry Methodology: Whole EDTA blood was used for multiparametric immunophenotyping. A large panel of T and B cell subset markers and regulatory T cells were assessed by flow cytometry at different time points. Clinical T cell panel analysis prior to transplant was performed on a BD Canto II instrument and data was analyzed with FCS Express v. 7 (De Novo software, Pasadena, CA). Advanced immunophenotyping after transplant was performed as follows: Briefly, one million cells, either from whole blood or PBMCs, were stained with either markers for T cell subsets, B cell subsets to identify naïve and memory T cells and recent thymic emigrants (CD45RA, CD45RO, CD62L, CCR7, CD27, and CD31), memory B cell subsets (CD27, IgD, IgM, IgG, and IgA). For analysis, 10,000 CD45+ lymphocytes for TBNK subset quantitation and 10,000 CD45+ for expanded T and B cell phenotyping were collected on a CytoFlex® flow cytometer (Beckman Coulter, La Brea, CA) with data acquisition using Kaluza C v. 1.1® software (Beckman Coulter).

Abbreviations: Ig indicates immunoglobulin; CD4+, T helper cells (CD4+); CD8+, Cytotoxic T cells; CD56+, NK cells; CD19+, B cells, CD45 + RA (naïve T cells).

* Initial reference range based on established values for our laboratory.

** Reference ranges adjusted after changes in laboratory methodology.

≠ Data collected for patient and compared with 45 matched control patients, median value for controls is shown in parentheses.

Table 2 Advanced immunophenotyping post-transplant

T cells							
(*Control value)*[≠]	**Naïve T cells % of CD4+** (CD4+ CD45 RA+ CD62L+ CCR7+) *(45.46%)*	**Central memory % of CD4+** (CD4+CD45 RO+ CD62L+ CCR7+) *(34.12%)*	**Effector memory % CD4+ T cells** (CD4+ CD45 RO+ CD62L- CCCR7-) *(9.41%)*	**Naïve T cells % CD8+** (CD8+ CD45 RA+ CD62L+ CCR7+) *(21.73%)*	**Central memory % CD8+** (CD8+CD45 RO+ CD62L+ CCR7+) *(6.03%)*	**Effector memory % CD8+ T cells** (CD8+CD45 RO+ CD62L-CCR7-) *(16.19%)*	**Recent thymic emigrants % CD4+ T cells** (CD4+CD45RA+CD31+)
1-year post--transplant	43.32%	31.23%	7.0%	34.12%	9.79%	16.31%	
2.5 years post--transplant	42.2%	51.1%	0.1%	28.3%	27.7%	0%	43%
B cells							
(*Control value)* [≠]	**Naïve B cells** %CD19+ B cells (CD19+CD27-) *(60.99%)*	**Total memory B cells** % CD19+ B cells (CD19+CD27+) *(30.91%)*	**Marginal zone B cells** %CD19+ B cells (CD27+IgM+IgD+) *(8.58%)*	**Switched memory B cells** %CD19+ B cells (CD27+IgM-IgD-) *(12.58%)*	**IgA+ memory B cells** % CD19+ B cells (CD27+IgA+) *(5.50%)*	**IgG+ memory B cells** % CD19+ B cells (CD27+IgG+) *(6.91%)*	
1-year post--transplant	92.78%	7.22%	2.55%	2.74%	0.05%	2.31%	
2.5 years post--transplant	77.2%	13.5%	3.7%	5.1%	0.1%	4.5%	

Comparison of baseline immunoglobulins, vaccine titers, immunophenotyping (T/B/NK and CD45 RO/RA), and donor chimerism were collected pre-transplant and monitored for 2.5 years post-transplant (Table 1). Patient had normal phytohemagglutinin-stimulated lymphocyte proliferation, T cell function, and percentages of naïve T cells (CD45 + RA) pre-transplant. Patient received CD34+ stem cell boost on day +197 with no effect on chimerism (between 6-month and 9-month data). At 1 year and 2.5 years following transplant, advanced immunophenotyping of T and B cells was performed (Table 2). At 2.5 years following transplant, additional evaluation for recent thymic emigrants (CD4 + CD45RA + CD31+) was performed which was appropriate for age at 43% of CD4+ T cells (Table 2). Reference ranges are shown in parentheses. Bolded values indicate outside of reference range.

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[≠] Data collected for patient and compared with 45 matched control patients, median value for controls is shown in parentheses.

boost infusion of marrow from the original donor [6]. In contrast, our patient had no response to a stem cell boost and has had persistent stable mixed chimerism, yet achieved effective immune reconstitution with no further chimerism decline or loss of graft.

This patient's mixed chimerism is likely related to the RIC preparative regimen for HCT. The use of RIC regimens for allogeneic HCT—particularly those containing alemtuzumab, fludarabine, and melphalan—in patients with nonmalignant disease is common. The use of these regimens is often complicated by the high incidence of mixed donor and recipient chimerism, as high as 80% [14]. In our patient the addition of Thiotepa to the conditioning did not change the outcome. Unlike hematologic malignancies where complete replacement with donor derived hematopoiesis is desirable for a cure, non-malignant disorders can often be controlled in the presence of mixed chimerism. Also, patient with nonmalignant disorders where single lineage abnormalities cause disease, relevant lineage specific engraftment is typically curative. Given that ICF is an immunodeficiency affecting the lymphoid linage, higher level of engraftment in the CD3 and CD19, as was seen in our patient, should be adequate to provide cure. This maybe the result of selective advantage for these lineages that would allow the use of RIC regimens to limit organ toxicity, late effects, and increase tolerability especially in young recipients. Serial tracking of chimerism and immune monitoring is necessary until stability is ensured. In the event of unstable or mixed chimerism, intervals between testing should be shorter to determine additional interventions such as donor lymphocyte infusions, stem cell boosts, or second transplant. We plan to continue chimerism testing, paired with immune monitoring, for our patient every 6 months until 5 years post-HCT if the values remain stable.

ICF1 is a rare disease, and it is difficult to draw conclusions from examination of a few patients. In our case, as in those reported previously, HCT was curative for the immunodeficiency associated with ICF1. Our patient has had improved quality of life and has been off immunoglobulin replacement, has not had any serious infections, and has not been hospitalized since transplant. It is important to note that HCT is unlikely to improve the extramedullary defects and neurological/developmental manifestations of ICF1. Other manifestations such as autoimmunity, for which HCT has an unclear effect, have been described in ICF1 but were not present in our patient. Ultimately, long-term follow up is crucial to better understand the impact of HCT for ICF1, and we hope our case provides additional insight into this rare disease.

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Declarations

Ethical Approval Not applicable.

Consent to Participate Not applicable.

Consent to Publish All authors have consented to the publication of this manuscript.

Competing Interests None of the authors have any conflicts of interest to disclose.

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