Congenital nephrotic syndrome in IL7Rα-SCID: A rare feature of maternofetal graft-versus-host disease

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Clinical Implications

Maternofetal graft-versus-host disease in severe combined immunodeficiency may manifest as congenital nephrotic syndrome, with edema and proteinuria. In patients with only a single allelic hit in *IL7R*, but phenotypic IL7Rα SCID, genetic analysis of intronic regions may identify mutations in compound heterozygosity.

Biallelic mutations in *IL7R*, encoding the IL-7 receptor α-chain, typically present as T−B+NK+ severe combined immunodeficiency (SCID) owing to the protein's role in early T-lymphocyte development,[1] accounting for 5% to 10% of SCID cases with variation by population.[2] Rarely, hypomorphic *IL7R* mutations may cause Omenn's syndrome (OS), manifesting as erythroderma, lymphadenopathy, hepatosplenomegaly, and raised IgE, generated by autologous autoreactive T lymphocytes.[1] An important differential diagnosis is engraftment of maternal T lymphocytes causing graft-versus-host disease (maternofetal engraftment [MFE]).

One case of nephrotic syndrome associated with OS has been previously described.[3] Nephrotic syndrome, comprising of edema, hypoproteinemia, heavy proteinuria, and hyperlipidemia, may arise from inherited defects in glomerular filtration or acquired from immune-mediated glomerular damage, and is treated with intravenous albumin transfusion and immunosuppression.[4]

We report a case of an infant with compound heterozygous *IL7R* mutations, presenting with congenital nephrotic syndrome and subsequently demonstrating features of MFE. Data were collected retrospectively from medical records, with written consent from the family.

The patient was born at term by forceps delivery to healthy nonconsanguineous parents of Portuguese descent, without antecedent family history suggesting primary immunodeficiency. At age 2 weeks, he presented with generalized edema. Investigations demonstrated heavy glomerular proteinuria (>400 mg/m^2/d) with albuminuria (194 mg/L), hypoproteinemia (34.2 g/L), and normal lipid profile (Table I), initially improving with regular albumin transfusion. Cytomegalovirus DNA was not detected in blood or urine. He subsequently developed blood-stained stools: colonoscopy demonstrated mild hemorrhagic colitis, which resolved with introduction of a milk-free formula. He was commenced on thyroxine for hypothyroidism (Table I).

At age 3 months, he developed significant exudative seborrheic dermatitis with generalized erythroderma, as well as hepatosplenomegaly (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Laboratory investigations were remarkable for hypereosinophilia (>10,000 cells × 10^9/L). Flow cytometry demonstrated a T-low, B-low, and NK-positive immunophenotype. Naive CD3$^+$ T lymphocytes were absent, with 100% of detectable T lymphocytes of maternal origin and of CD45RO$^+$ phenotype, consistent with MFE (Table I). He was commenced on antimicrobial prophylaxis (cotrimoxazole and itraconazole), intravenous immunoglobulin, and immunosuppression with methylprednisolone and ciclosporin A. His proteinuria improved with immunosuppression, though remained above normal limits. Imaging revealed bilateral echobright kidneys; a renal biopsy was considered, but not undertaken because of clinical improvement with immunosuppression.

Initial whole-exome sequencing demonstrated heterozygous deleterious mutations in *JAK3* and *IL7R*. Subsequent whole-genome analysis identified a second, intronic hit in *IL7R* in compound heterozygosity with the previously sequenced missense variant (chr5:35,867,751G>A, c.379+288G>A, and chr5:35,867,437G>A, c.G353G>A, p.C118Y, respectively). Strikingly, the same combination of pathogenic variants was previously described in another patient of Portuguese descent with IL7Rα-SCID.[5] The maternally inherited missense variant in exon 3 results in substitution of tyrosine for cysteine, and has been described in other patients with SCID and OS.[1] The paternally inherited mutation creates a novel splice-site, leading to insertion of garbage sequence and a stop codon, with resultant nonsense-mediated decay of *IL7R* mRNA.

Our patient underwent a matched unrelated donor hematopoietic stem cell transplant (HSCT) at age 8 months. Transplant data are summarized in Table II. His transplant course was remarkable only for the development of fever with patchy focal lung consolidation, suggesting fungal pneumonia. Cultures were negative. He improved with intravenous meropenem, teicoplanin, and liposomal amphotericin B. Throughout his transplant course, renal function was stable with mild proteinuria, and he did not require albumin replacement.

Immunoglobulin replacement stopped approximately 1-year posttransplant. Four and a half years later, he is euthyroid, off thyroxine, and his proteinuria has not relapsed. Despite normal immune reconstitution, he has recently been hospitalized for an isolated episode of small-joint polyarthritis, treated with a short course of corticosteroids. Autoantibodies were negative, aside from weakly positive (1/640) antinuclear antigen titers. His laboratory and immunologic data are summarized in Table I.

In this report, we present the first described case of nephrotic syndrome associated with MFE in a patient with SCID and maintained resolution of proteinuria post-HSCT.

Persistence of transplacentally acquired maternally derived T lymphocytes denotes SCID, due to an absence of neonatal T lymphocytes able to recognize and reject foreign cells. Despite being detectable in 40% of patients with SCID, including those with *IL7R* mutations, their manifestation clinically is less frequent, and may be heterogeneous, ranging from an Omenn's-like syndrome with multiorgan graft-versus-host disease to being

TABLE I. Laboratory data and immunophenotype pretransplant and posttransplant

Test	Pre-HSCT	Post-HSCT (4.5 y)	Reference range
Hematology			
Hemoglobin (g/L)	133	136	115-135
Platelet count (cells $\times 10^9$/L)	781	245	150-450
Neutrophil count (cells $\times 10^9$/L)	5.78	6.56	6-17.5
Total lymphocyte count (cells $\times 10^9$/L)	0.61	2.39	4-10.5
Eosinophil count (cells $\times 10^9$/L)	10,000	0.00	0.3-0.8
Biochemistry			
Sodium (mmol/L)	137	137	135-145
Potassium (mmol/L)	4.9	4.3	3.5-4.5
Urea (mmol/L)	4.0	12.1	5.4-12.9
Serum creatinine (μmol/L)	17	41.5	17.0-38.0
Serum cholesterol (mmol/L)	3.9	—	<4.40
Serum triglycerides (mmol/L)	2.1	—	0.5-1.70
Serum albumin (g/L)	18.1	43.1	36.0-55.0
Serum protein (g/L)	34.2	78.8	60.0-80.0
Urine protein (g/L)	0.94	0.08	<0.15
Urine albumin (mg/L)	194	—	—
Urine protein:creatinine ratio (mg/mmol)	470	29	0-56
TSH (UI/mL)	0.04	2.8	0.7-6.0
Free T4 (pmol/L)	10.4	14.1	12.3-22.8
Anti-TPO (UI/mL)	17	<1	0-34
Immunoglobulins			
IgA (g/L)	<0.04	<0.26	0.4-2.00
IgG (g/L)	<0.06	11.7	4.9-16.1
IgM (g/L)	<0.05	1.94	0.5-2.00
IgE (kUI/L)	6.8	34.7	0-60
Lymphocyte susets			
Total $CD3^+$ (cells/μL)	650 (72%)	2251 (90%)	2300-7000
$CD3^+CD4^+$ (cells/μL)	612 (68%)	1463 (58%)	1400-5300
$CD3^+CD8^+$ (cells/μL)	41 (5%)	622 (25%)	400-2200
$CD19^+$ (cells/μL)	50 (6%)	165 (6%)	600-3000
$CD16^+56^+$ (cells/μL)	189 (21%)	88 (3.5%)	100-1400
$CD4^+CD45RA^+$	0%	1156 (79%)	—
$CD8^+CD45RA^+$	0%	565 (90%)	—
$CD3^+CD45RO^+$	100%	—	—
HLA^-DR^+	67%	5%	—
Chimerism			
$CD3^+$	100% maternally derived	100% donor	—
$CD15^+$	—	92% donor	—
$CD19^+$	—	92% donor	—
Vaccine-specific antibody titers			
Diphtheria IgG (UI/mL)	—	0.76	—
Tetanus IgG (UI/mL)	—	2.90	—

TPO, Thyroid peroxidase; *TSH*, thyroid-stimulating hormone; —, not checked.
Chimerism data obtained by Quadplex PCR microsatellite analysis of pretransplant and posttransplant short tandem repeat markers of patient compared with donor.

clinically silent.[6] Indeed, one report of preserved humoral immunity in an 8-year-old child with maternally derived $CD4^+$ T lymphocytes and JAK3-SCID suggests that these cells may rarely contribute to immune competence in SCID.[7] Hypereosinophilia is described in both OS and MFE , and may reflect skewed expansion of T_H2 lymphocytes seen in these syndromes.[8]

The shared pathology of dysregulated T-lymphocyte—mediated damage explains the similarities between MFE and OS, and Rybojad et al[3] attributed their case of nephrotic syndrome to this aberrant cellular response. Our patient did not undergo renal biopsy; in the case with OS, histology demonstrated minimal change nephropathy without a lymphocytic infiltrate[3] while T-lymphocyte peritubular infiltration has been described in 1 patient with MFE, skin involvement, and nephritis.[6] Our patient's improvement in proteinuria with immunosuppression and sustained remission following HSCT exclude true congenital nephrotic syndromes,[4] implying that this pathology was mediated by maternally engrafted lymphocytes.

TABLE II. Transplant characteristics, graft details, and peritransplant morbidity and clinical course

Characteristic	Details
Age at HSCT	8 mo
Weight	6.9 kg (<0.4th centile) on admission, 9.3 kg (25th centile) at discharge
Graft details	10/10 MUD PBSC $CD34^+$ cells: 4.6×10^6/kg
Conditioning regimen	Alemtuzumab 0.2 mg/kg × 3 d Treosulfan 12 g/m^2 × 3 d Fludarabine 30 mg/m^2 × 5 d
Engraftment	Neutrophils: D+25 Platelets: D+12 Whole blood chimerism: 100% donor on D+26
Peri-HSCT morbidity	Mild mucositis Minor increase in proteinuria but no albumin replacement required Fever with raised inflammatory markers and patchy consolidation on CT thorax, treated as fungal pneumonia (cultures negative)
Current status	Well, biochemically euthyroid, and without thyroxine supplementation Recent episode of small-joint polyarthritis, treated with nonsteroidal anti-inflammatories

CT, Computed tomography; *MUD*, matched unrelated donor; *PBSC*, peripheral blood stem cell.

We postulate that our patient's hypothyroidism was secondary to protein loss, which is well established in nephrotic syndrome.[4] Following resolution of his proteinuria post-HSCT, our patient is now biochemically euthyroid.

It is notable that the mutations identified in our patient are identical to those described by Butte et al[5] in a patient also of Portuguese descent. The complete absence of the paternal intronic variant from population databases, demonstrating its rarity, might suggest a founder mutation inherited from a common ancestor from the Iberian Peninsula. Similarly, the maternal missense variant is recorded at very low frequencies in Latino/admixed American (2/34,488) and non-Finnish European (1/113,314) populations in the gnomAD allele frequency database (https://gnomad.broadinstitute.org/variant/5-35867539-G-A?dataset=gnomad_r2_1). We previously reported that exonic deletions are a relatively common mutation type in IL7Rα-SCID.[9] The present case emphasizes the further possibility of deep intronic mutations, supporting the role of wider genomic analysis in patients with phenotypic IL7Rα-SCID who lack coding variants in the expected zygosity. Introduction of newborn screening for SCID may aid diagnosis in cases with atypical presentations, such as this one.

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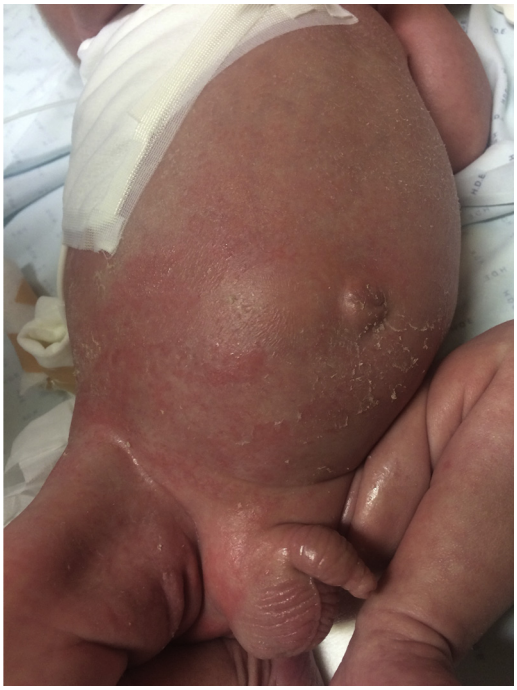

FIGURE E1. Photograph showing generalized erythroderma with some desquamation and abdominal distension due to hepatosplenomegaly. Image captured shortly after initial presentation in infancy.