

Case study

Unusual clinical and immunologic manifestations of transplacentally acquired maternal T cells in severe combined immunodeficiency

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The persistence of transplacentally transferred maternal T cells is common in infants with severe combined immunodeficiency (SCID), occurring in more than half of patients with SCID undergoing transplantation at our institution. These T cells respond poorly to mitogens *in vitro* but can cause cutaneous graft-versus-host disease; however, other effects of these cells are unknown. We describe 2 infants with SCID who had unusual problems associated with transplacentally transferred maternal T cells. Patient 1 was a 5-month-old girl with Janus Kinase 3-deficient SCID who had 4% circulating CD3⁺ T cells but no lymphocyte proliferative response to mitogens. Although the number of T cells increased after 2 nonchemoablated, T cell-depleted, haploidentical, paternal bone marrow transplantations, T-cell function failed to develop, and she became pancytopenic. Restriction fragment length polymorphism studies of flow cytometry-sorted blood T cells revealed all to be of maternal origin. A subsequent nonchemoablated, T cell-depleted maternal transplantation resulted in normal T-cell function and marrow recovery. Patient 2 was a 9-month-old girl with IL-7R α -deficient SCID who presented with autoimmune pancytopenia. She had 8% blood T cells (all CD45RO⁺) but no response to mitogens. High-resolution HLA sequence-specific priming typing detected both maternal haplotypes, indicating the presence of maternal cells. Her pancytopenia resolved after treatment with rituximab and was thought to be due to host B-cell activation by transplacentally acquired maternal T cells. Persistent transplacentally acquired maternal T cells in infants with SCID can mediate immunologic functions despite failing to respond to mitogens *in vitro*. We present evidence that these cells can cause allograft rejection and immune cytopenias. (*J Allergy Clin Immunol* ■■■■;■■■:■■■-■■■.)

Key words: Severe combined immunodeficiency, transplacentally transferred maternal T cells, graft-versus-host disease

Transplacentally acquired maternal T cells have been detected in the blood of healthy newborns¹ but are rapidly eliminated in those infants who are immunocompetent. However, because infants with severe combined immunodeficiency (SCID) do not produce T cells,² they cannot recognize or reject foreign cells and therefore frequently have persistence of maternal T cells. A recent report showed this to be the case in 40% of 121 infants with SCID undergoing transplantation at a single center.³ Of the 155 infants undergoing transplantation at our institution, 56% have had some T cells at presentation, and in most cases, these have been demonstrated to be of maternal origin (unpublished observations). Transplacentally acquired maternal T cells isolated from the blood of infants with SCID typically display a limited T-cell receptor repertoire, are dominantly CD8⁺CD45RO⁺,^{1,4} are not responsive to allogeneic cells *in vitro*, and have profoundly decreased or absent *in vitro* proliferative responses to mitogens and to recall antigens, such as *Candida* species and tetanus.^{3,5} In infants with SCID, these transplacentally acquired maternal T cells can be clinically silent or can cause graft-versus-host disease (GVHD). Previously described manifestations of GVHD caused by transplacentally acquired maternal T cells have been limited to mild or even severe dermatitis and, in rare cases, hepatic disease³; however, other clinical and immunologic manifestations of these cells have not been well recognized. We discuss 2 patients with SCID with transplacentally transferred maternal T cells that mediated allograft rejection and caused cytopenias.

METHODS

We studied 2 patients with SCID who received nonchemoablated, T cell-depleted, haploidentical bone marrow stem cell transplants from a maternal or paternal donor. Bone marrow was purged of mature T cells by means of soybean lectin agglutination and 2 cycles of sheep erythrocyte rosetting, as previously described.⁶ Four-color flow cytometry was performed on blood lymphocytes with the use of murine mAbs to CD3, CD4, CD8, CD16, CD45RA, and

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Abbreviations used

GVHD: Graft-versus-host disease

JAK3: Janus Kinase 3

RFLP: Restriction fragment length polymorphism

SCID: Severe combined immunodeficiency

CD45RO purchased from PharMingen (San Diego, Calif) and Becton Dickinson (San Jose, Calif). Lymphocyte proliferation was determined by measuring tritiated thymidine incorporation into PBMCs after *in vitro* culture with PHA, concanavalin A, and pokeweed mitogen. Each cellular study was run in parallel with PBMCs from healthy adult volunteers. Serum concentrations of IgG, IgM, IgA, and IgE were determined by means of nephelometry or single radial diffusion. Maternal lymphocytes were detected by using fluorescence *in situ* hybridization, restriction fragment length polymorphism (RFLP), or high-resolution HLA typing. High-resolution HLA class I and class II typing was performed by using the sequence-specific priming technique with commercial reagents from Pel-Freez Clinical Systems (Brown Deer, Wis). A set of alleles or group of allele-specific primers was used to amplify alleles of each HLA locus. A positive reaction of a primer pair indicates the presence of the allele or alleles that the primer specifically amplifies.⁷

Janus Kinase 3 (JAK3) sequence analysis

Exons 1 to 23 of the *JAK3* gene were PCR amplified and subjected to bidirectional sequence analysis (GeneDx, Inc, Gaithersburg, Md) by using genomic DNA isolated from patient 1's PBMCs (Qiaex DNeasy Tissue Kit; Qiagen, Inc, Santa Clarita, Calif) before bone marrow transplantation. The presence of the detected Y399X and R451X mutations in patient 1 was confirmed in new amplicons by means of restriction fragment analysis with StyI and sequencing, respectively (GeneDx). Mutations were further evaluated by means of sequence analysis of JAK3 exons 8 and 9 in our laboratory by using genomic DNA templates obtained from the patient's parents, as described below for patient 2's *IL7RA* sequence analysis. Nucleotide numbers refer to the published cDNA sequence (NM000215.2)⁸ with the start codon equaling 1.

IL7RA sequence analysis

Genomic DNA templates isolated from whole blood obtained from patient 2 before bone marrow transplantation (Qiaex DNeasy Tissue Kit, Qiagen) were PCR amplified with primer pairs (sequences available on request) spanning each of the 8 *IL7RA* gene exons and surrounding intronic splice sites. PCR products were purified (Qiaex II Gel Extraction Kit, Qiagen) and used as templates in sequencing reactions (Big Dye Terminator Cycle Sequencing System; Perkin-Elmer Life Sciences, Inc, Boston, Mass). Sequencing reactions representing both strands performed in our laboratory were electrophoresed and analyzed by using an ABI 377 Prism DNA (Perkin-Elmer) sequencing instrument and software package. Mutations were further evaluated by means of *IL7RA* sequence analysis in the region of interest of genomic DNA templates obtained from the patient's parents and 50 unrelated, anonymous healthy individuals of varied ethnic backgrounds (Alzheimer's Disease Research Center, Duke University Medical Center, Durham, NC). Nucleotide numbers refer to the published cDNA sequence (M29696)⁹ with the start codon equaling 1.

The studies were performed with the approval of the Duke University Committee on Human Investigations, and written informed consent was obtained from the parents.

TABLE I. Initial immunologic data

	Patient 1: JAK3-Def	Patient 2: IL-7R α -Def	Normal values
Absolute lymphocyte count	512/mm ³	572/mm ³	7300/mm ³ (4000-13,500/mm ³)
Lymphocyte subsets (%)			
CD3 ⁺	4	8.3	75.5 + 8.0
CD3 ⁺ CD45RA ⁺	6.5	2.2	34.5 + 9.6
CD3 ⁺ CD45RO ⁺	37.1	82.5	41.1 + 11.2
CD20 ⁺	92.5	73.5	9.5 + 3.2
CD16 ⁺	0.5	13.2	11.7 + 6.2
Lymphocyte proliferation responses*			
PHA	4401	1640	184,710 + 59,391
Con A	5712	653	138,202 + 61,340
Medium	8718	943	591 + 508
Immunoglobulins			
IgG (mg/dL)	561†	1520†	192-515
IgA (mg/dL)	0	5	12-31
IgM (mg/dL)	0	200	39-92
IgE (Iu/mL)	<2	27	0-74
Isohemagglutinins			
Anti-A	Negative	Negative	>1:4
Anti-B	Negative	Negative	>1:2

JAK3-Def, JAK3 deficiency; *IL-7R α -Def*, IL-7R α deficiency;

PHA, phytohemagglutinin; Con A, concanavalin A.

*Counts per minute of tritiated thymidine incorporation into DNA.

†After intravenous immunoglobulin.

RESULTS**Patient 1**

Patient 1 was a first-born biracial female referred at 5 months of age with respiratory distress caused by *Pneumocystis jiroveci* pneumonia. Studies revealed that the infant presented with a T⁺B⁺ natural killer cell-negative immunologic phenotype characteristic of JAK3-deficient SCID (Table I).^{2,10} DNA sequence analysis confirmed this diagnosis by demonstrating the patient was a compound heterozygote with 2 nonsense *JAK3* gene mutations, the first being a T > G substitution in exon 8 (Y399X) inherited from her mother and the second a C > T change in exon 9 (R451X) inherited from her father. Her first transplantation was performed at age 5 months; her father was used as the donor because of the gravid state of her mother. At 118 days after transplantation, lymphocyte enumeration revealed 62.5% CD3⁺ cells (959/mm³); most of these cells were CD8⁺CD45RO⁺ T cells (Fig 1, A and B). However, lymphocyte proliferative responses to mitogens remained extremely low (Fig 1, C).

The patient subsequently had marked pancytopenia requiring granulocyte colony-stimulating factor and regular transfusions of red cells and platelets. Bone marrow examination revealed marked aplasia of all lineages. A work-up for infectious causes revealed detectable EBV DNA, and therefore she was treated with 4 doses of anti-CD20 antibody (rituximab). However, she remained

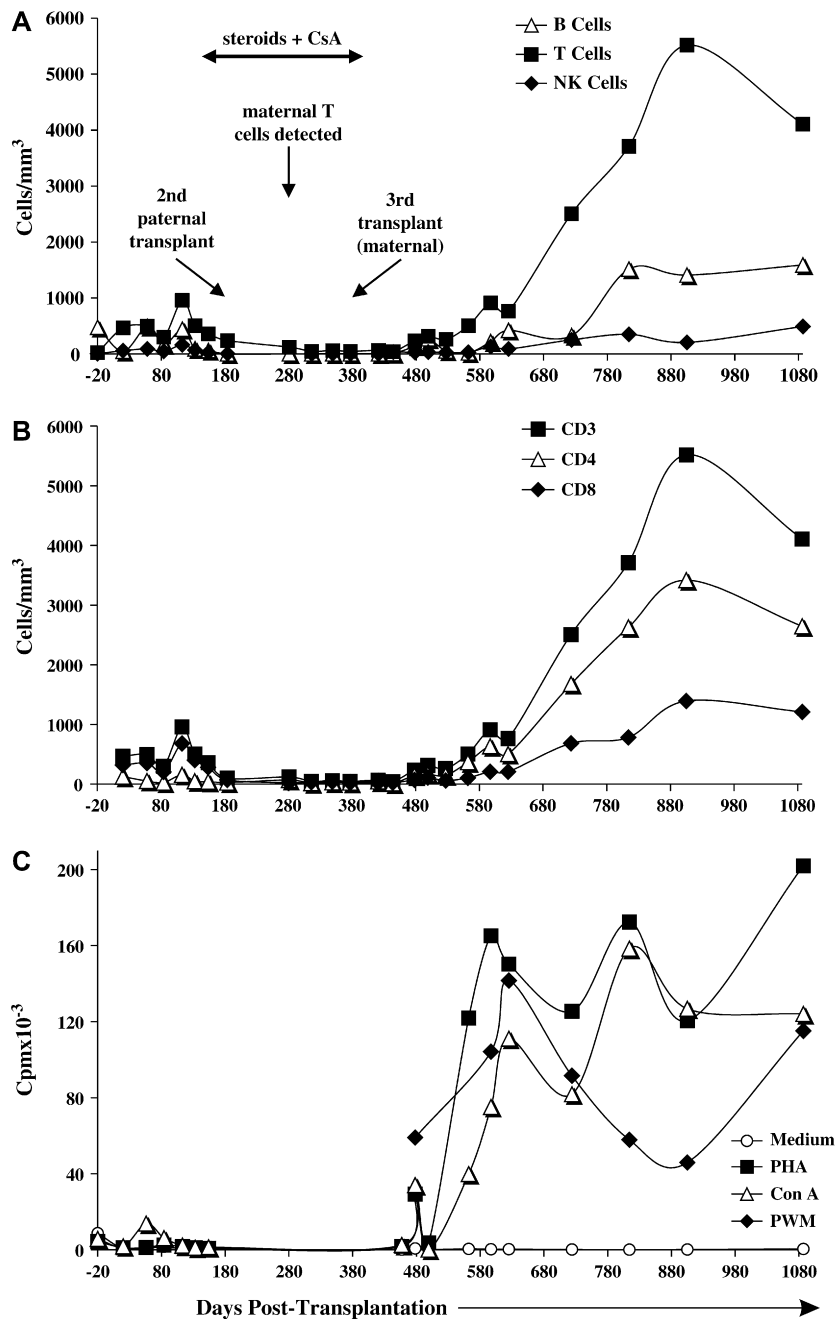


FIG 1. Patient 1's lymphocyte phenotype and function before and after transplantation. Shown are absolute numbers of T, B, and natural killer (NK) cells (**A**) and indicated T-cell subsets (**B**), along with tritiated thymidine incorporation by proliferating lymphocytes in response to PHA, concanavalin A (*Con A*), and pokeweed mitogen (*PWM*; **C**) at the designated time points. The times of the indicated transplantations and immunosuppressive therapies and the date when maternal T cells were first detected are shown in Fig 1, A. CsA, Cyclosporine.

pancytopenic, despite the lack of detectable circulating peripheral blood CD20⁺ B cells on subsequent flow cytometric analysis and the absence of demonstrable EBV DNA on repeat PCR studies. She was then treated with corticosteroids and cyclosporine for suspected GVHD (Fig 1). Although she remained pancytopenic, her transfusion requirements decreased after the initiation of immunosuppressive therapy.

At age 12 months, fluorescence *in situ* hybridization analysis of mitogen-stimulated PBMCs revealed all to be of female origin. She was then given a second paternal transplant; however, over the next 6 months, she remained profoundly pancytopenic and lymphopenic, with no evidence of T-cell function.

At 18 months of age, RFLP analysis of flow cytometry-purified CD3⁺ blood T cells revealed the presence of only

maternal alleles; no donor or recipient alleles were identified. Therefore a third nonchemoablated, T cell–depleted haploidentical transplant was given, this time using the mother as the donor. After the maternal transplant, the patient's pancytopenia resolved, allowing gradual weaning and eventual discontinuation of all immunosuppressants. She had some evidence of T-cell function beginning at 59 days after maternal transplantation and now has normal numbers of T cells and T-cell subsets, as well as normal T cell–proliferative responses to mitogens (Fig 1). Chimerism studies revealed that 100% of the T cells are currently of maternal origin. In addition, she also has normal levels of serum immunoglobulins and no longer receives intravenous immunoglobulin. She is currently 3½ years old, has no evidence of infection, and is growing and developing normally off of all medications.

Patient 2

Patient 2 presented to the hematology service at another hospital at 8 months of age with neutropenia, anemia, chronic cough, and failure to thrive. A bone marrow biopsy showed normal cellularity but myeloid arrest of uncertain cause. She was subsequently noted to be lymphopenic (absolute lymphocyte count was 572/mm³ on admission to our hospital) as well. Immune evaluation at our institution revealed the patient had T⁺B⁺ natural killer cell–positive SCID,² with 65% CD19⁺ cells, 13% CD16⁺ cells, 8.3% CD3⁺ cells, 5.3% CD4⁺ cells, and 3.3% CD8⁺ cells; her lymphocytes failed to respond to mitogens (Table I). *IL7RA* gene sequence analysis revealed she was a compound heterozygote with 2 different mutations in the exon 2/intron 2 boundary region. The maternal allele of patient 2 exhibited a G > A transition at nucleotide 221, the 3' terminal base encoded by exon 2. This 221 G > A mutation gave rise to substitution of tyrosine for cysteine at amino acid position 74 (C74Y). Patient 2 inherited a previously described T > G substitution at invariant position +2 in the 5' splice site of intron 2 (IVS2 +2T > G) from her father.¹¹ The patient's C74Y and IVS2 +2T > G sequence abnormalities were not detected in any of the tested 50 healthy individuals. Virtually all of the patient's T cells on initial examination were CD45RO⁺ (Table I), suggesting they were of maternal origin; this was confirmed by means of high-resolution HLA sequence-specific priming typing of her PBMCs that detected the presence of both maternal haplotypes (Table II).

After a T cell–depleted, maternal, haploidentical, bone marrow stem cell transplantation at our institution, the patient's anemia, lymphopenia, and neutropenia persisted. Her platelet count also decreased from normal levels to less than 20,000/mm³. The result of a direct Coombs test was positive, and after a red blood cell transfusion, the patient experienced significant hyperbilirubinemia. Because of the likelihood that her anemia, neutropenia, and thrombocytopenia were due to autoantibodies, she was given a 4-week course of rituximab, with subsequent improvement in her anemia, neutropenia, and thrombocytopenia associated with successful elimination of detectable circulating CD20⁺ cells.

TABLE II. Results of pretransplantation high-resolution HLA sequence-specific priming typing of patient 2 and parents

Sample	HLA-A	HLA-B	HLA-C	DRB1	DQB1
Patient 2	0101 2301	5701 5001 (0801) <i>chimerism</i>	0602 0602 (0701) <i>chimerism</i>	1101 0301	0301 0201
Mother	0101 2301	0801 5001	0701 0602	0301 0301	0201 0201
Father	0101 1101	5701 1801	0602 0501	1101 0301	0301 0201

Boldface type indicates inherited parental haplotypes.

In the first 30 days after transplantation, the patient experienced severe diarrhea, eosinophilia, and recurrent pneumatosis intestinalis, and she was started on cyclosporine and prednisone for presumptive GVHD. She remained lymphopenic, and her lymphocytes failed to respond to mitogens over the first 4 months after transplantation while she was receiving this immunosuppressive regimen (Fig 2).

At 7 months after transplantation, after she had been weaned from cyclosporine, patient 2 received a booster T cell–depleted haploidentical maternal bone marrow stem cell transplantation without pretransplantation chemotherapy. Over the following 6 months, she was weaned from steroids, which she had required because of recurrent pneumatosis. She subsequently had normal percentages of T cells and subsets and normal T-cell function (Fig 2). She continues to receive intravenous immunoglobulin but has intermittently had normal levels of IgA, IgM, and IgE. At 3½ years of age, she is clinically well and off all other medications.

DISCUSSION

It has long been recognized that children with SCID can have persistence of transplacentally acquired maternal T cells.^{12,13} In one series 60% of patients with SCID with detectable maternal T cells were asymptomatic; however, others had disease limited to the skin and liver.³ Although it has been hypothesized that these cells have other clinical and immunologic effects, these effects have not been well described. In the late 1980s, O'Reilly et al¹⁴ hypothesized that maternal cells could prevent engraftment of bone marrow transplants from nonmaternal donors. Our first case strongly supports this hypothesis. This patient did not have T-cell function and showed no evidence of paternal chimerism after 2 paternal marrow transplantations. The presence of transplacentally transferred maternal T cells was documented by means of RFLP, and immune reconstitution was only achieved after a third transplantation, using her mother as the donor for the first time. The transplacentally acquired maternal T cells, in this case, likely mediated rejection or caused resistance to engraftment of paternal stem cells. It is important

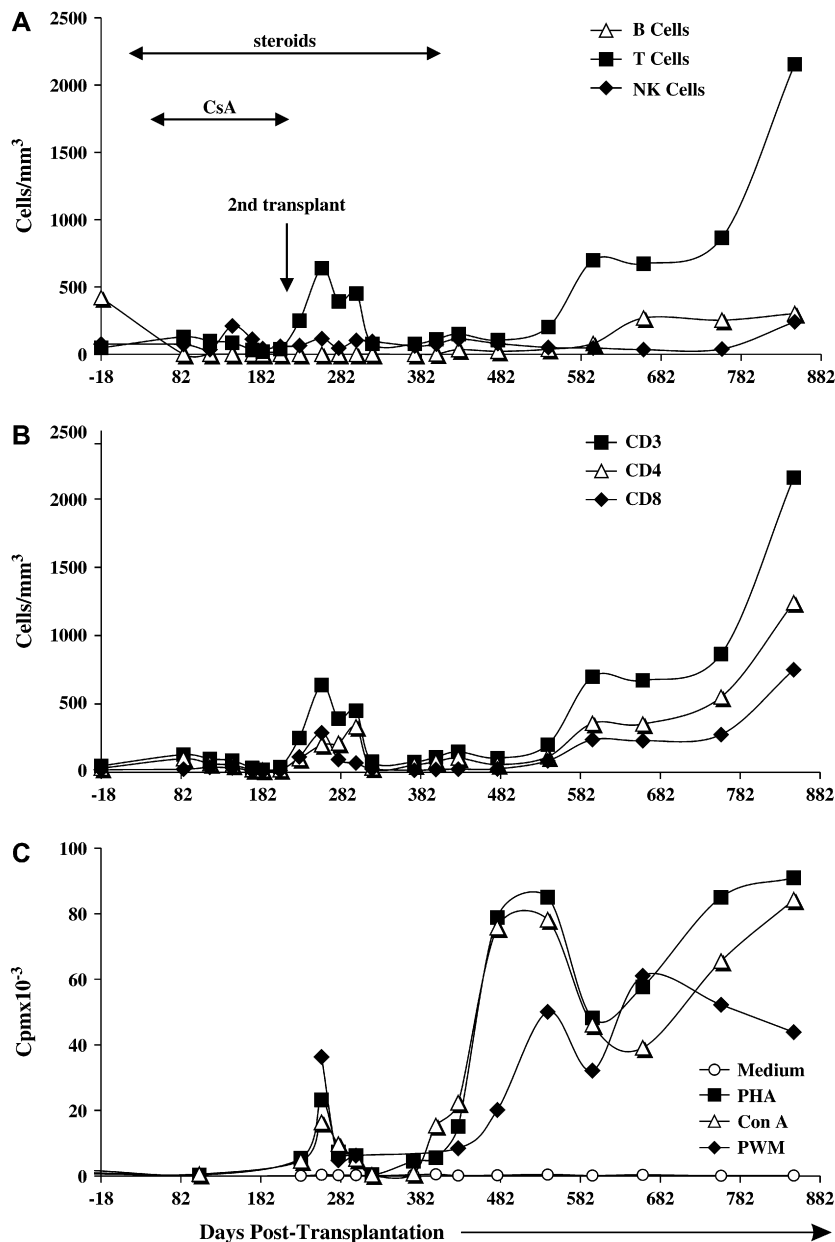


FIG 2. Patient 2's lymphocyte phenotype and function before and after transplantation. Shown are absolute numbers of T, B, and natural killer (NK) cells (**A**) and indicated T-cell subsets (**B**), along with tritiated thymidine incorporation by proliferating lymphocytes in response to PHA, concanavalin A (Con A), and pokeweed mitogen (PWM; **C**) at the designated time points. The times of the second transplantation and indicated immunosuppressive therapies are shown in Fig 2, A. CsA, Cyclosporine.

to note that at 118 days after the initial paternal transplantation, an increase in the number of circulating CD3⁺CD8⁺ T cells was detected (Fig 1). However, the patient did not have T-cell function at that time, and these cells soon decreased in number. Engrafted maternal T cells in SCID are preferentially CD8⁺,^{3-5,15} and therefore it is likely that this initial increase in CD3⁺CD8⁺ cells represented transplacentally transferred maternal T cells. Most transplacentally acquired maternal T cells are hyporesponsive to mitogenic stimulation,³⁻⁵ and the observation that

patient 1's CD3⁺CD8⁺ cells did not respond to these stimuli further supports their maternal origin.

It is likely that patient 1's pancytopenia was a manifestation of GVHD, graft-versus-graft disease, or both.^{16,17} Muller et al³ reported that transplacentally transferred maternal T cells that mediate GVHD are usually CD4⁺ and proliferate in response to mitogens. Because patient 1 had only CD8⁺ T cells that did not respond to mitogens, this makes GVHD from the maternal T cells less likely. Although EBV infection could have played a role,

several observations do not support this possibility. First, her cytopenias persisted after eradication of circulating B cells with rituximab and after EBV DNA levels became undetectable by means of sensitive PCR testing. Furthermore, her blood cell counts stabilized after the initiation of cyclosporine and steroid therapy. All of her cell lines normalized after the maternal transplantation, enabling discontinuation of immunosuppressants and granulocyte colony-stimulating factor. One other case of neutropenia likely mediated by maternal T cells in SCID has been reported.¹⁸

The presence of maternal cells in the blood of patient 2 was confirmed by means of detection of antigens representing both maternal haplotypes on high-resolution HLA typing of patient 2's PBMCs (Table II). The Coombs positive hemolytic anemia and resolution of pancytopenia after rituximab therapy support the notion that this process was autoimmune in nature. We have hypothesized that the transplacentally acquired T lymphocytes in this patient activated the B cells, leading to the autoimmune disease. A similar process of donor T cells activating host B cells was previously described in other patients with SCID from our institution who had multiple monoclonal serum immunoglobulins (multiclonal gammopathy) after T cell-depleted, haploidentical, bone marrow stem cell transplantation.^{19,20} However, the possibility also exists that the B cells were transplacentally acquired maternal B cells, as has been noted previously.²¹

In summary, we present 2 cases of transplacental T-cell engraftment leading to different clinical manifestations in patients with SCID. In the first case maternal cells were associated with failed paternal bone marrow engraftment and the subsequent development of pancytopenia thought to be caused by GVHD, graft-versus-graft disease, or both. In the second case maternal T cells were present in association with antibody-mediated pancytopenia. The recent report of a patient with JAK3-deficient SCID surviving to age 8 years with transplacentally acquired maternal T cells, partial antibody-producing capacity, and absent lymphocyte proliferation to mitogens suggests another example of the potential activities of these cells.²² The transfer of nucleated cells from mother to fetus has been shown to be common among healthy term newborns,²³ and a majority of patients with SCID at our institution (unpublished observation) have displayed maternally engrafted cells as well. The effects of these engrafted cells might be underrecognized, but they clearly have the potential to induce a variety of significant immunologic effects.

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