

Letter to the Editor

Omenn syndrome is associated with mutations in DNA ligase IV*To the Editor:*

Omenn syndrome (OS) is a fatal variant of severe combined immunodeficiency (SCID), unless treated with allogeneic bone marrow transplant (BMT). Initially OS was associated with mutations in the recombination activating gene (RAG) 1 and 2.¹ Subsequently, we and others identified mutations in genes such as RNA component of ribonuclease mitochondrial RNA, adenosine deaminase, IL-2 receptor γ , and IL-7 receptor α in patients with OS.² We report here, for the first time, the occurrence of OS in a patient with a novel mutation in the DNA ligase IV gene, which was corrected after allogeneic bone marrow transplant.

The girl, born to nonconsanguineous parents after an uneventful pregnancy, weighed 2.5 kg (3rd percentile), and her head circumference was 30 cm (<3rd percentile). At 3 weeks of age, she developed protracted universal scaly erythroderma, hepatosplenomegaly, generalized lymphadenopathy, and diarrhea. The rash and diarrhea improved after treatment with cyclosporine A but worsened on discontinuation of treatment.

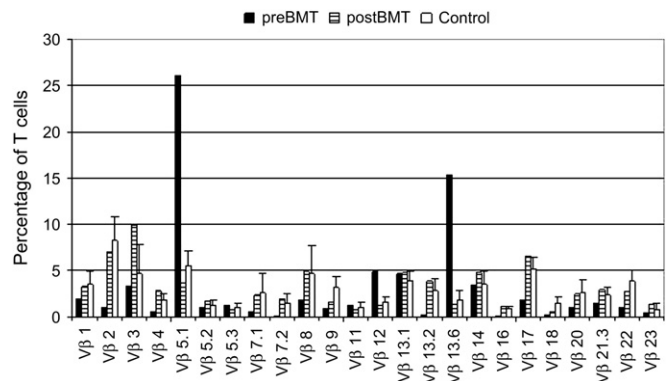
Eosinophils were markedly increased (2120 cells/ μ L; normal, 5-700 cells/ μ L). Evaluation of the immune system, performed as previously described,³ revealed a low but relatively preserved number of circulating CD3⁺ T cells coexpressing either CD4⁺ or CD8⁺ (Table I). T-cell response to mitogen stimulation and T-cell receptor excision circles were markedly reduced. Analysis of T-cell receptor V β families demonstrated skewed T-cell repertoire, with excessive expansion of 3 T-cell receptor families—V β 5.1, V β 12, and V β 13.6—while most other families were under-represented (Fig 1). B cells were practically absent, and serum IgA and IgM levels were reduced. There was no evidence for maternal engraftment. Sequences of the genes for RAG1 and RAG2, Artemis, RNA component of RNase mitochondrial RNA, adenosine deaminase, Ku70, Ku80, and IL-7 receptor α were normal (not shown). Sequencing of DNA ligase IV gene from the patient and the parents revealed 3 heterozygous mutations (Fig 2). One allele carried a C26T polymorphism and A845T transition resulting in H282L substitution near the ATP binding site, which were previously described.⁴ The other allele had a novel 5-nucleotide deletion (AAAGA) after the A nucleotide in position 1746, causing a frameshift at R581 and a downstream putative premature stop.

At 6 months of age, after myeloablative conditioning with 16 mg/kg busulphan and 200 mg/kg cyclophosphamide (each over a period of 4 days), the patient received unmodified HLA-matched unrelated donor BMT. She experienced graft-versus-host disease of the skin and gastrointestinal system, which resolved after prolonged treatment with cyclosporine, methylprednisolone, and mycophenolate mofetil. After transplant, she also had respiratory failure, cardiac chamber hypertrophy, EBV infection, hypertension, and renal abnormalities, which all resolved. Currently, 3.5 years posttransplant, she continues to have microcephaly with increased intracranial pressure, short stature, and developmental delay. Repeated analysis prior to and more than 3 years post BMT, demonstrated complete donor chimerism. Chimerism was determined by studying polymorphism in a variable number of

TABLE I. Immunity before and 3 years after BMT

	Before transplant	After transplant	Normal range
IgG (g/L)	6.6*	7.8	0.8-6.5
IgM (g/L)	<0.07	0.4	0.19-0.96
IgA (g/L)	<0.07	0.5	0.04-0.4
CD3 (cells/ μ L)	1275	4081	2000-6900
CD4 (cells/ μ L)	859	2589	1400-5100
CD8 (cells/ μ L)	438	1392	600-2200
CD19 (cells/ μ L)	3	1069	700-2500
CD56 (cells/ μ L)	188	367	100-1000
Phytohemagglutinin (stimulation index) patient/control	2/578	1010/878	>50
T-cell receptor excision circles (copies/0.5 μ g DNA)	5.3	3574	>300

*On intravenous immunoglobulin replacement therapy.

**FIG 1.** T-cell repertoire. Flow-cytometry analysis, represented as the percentage of cells, of various T-cell receptor V β families in CD3⁺ T cells obtained from the patient's peripheral blood before BMT (*preBMT*) and 3 years after transplant (*postBMT*) and normal control.

tandem repeats or a cytosine-adenine dinucleotide repeat (CA)_n in repeat in varying regions in the genome as previously described.³ Immune evaluations as long as 3 years after transplant showed normal T-cell and B-cell numbers, T-cell responses to mitogens, T-cell receptor excision circles, and immunoglobulin production (Table I). T-cell receptor repertoire has also normalized (Fig 1).

DNA double-strand breaks and repair are important for the rearrangement of genomic material, which is crucial for the maturation and diversification of T and B cells. The major mechanism for repair of double-strand breaks in mammalian cells is DNA nonhomologous end-joining, which occurs by the coordinated effect of at least 5 proteins, including Ku70, Ku80, DNA-dependent protein kinase (DNA-PK), Cernunnos, and DNA ligase IV.⁵ Mutations in DNA ligase IV have been previously described in patients ranging in age from 4 to 48 years, and a variety of clinical presentations, including leukemia, lymphoma, bone marrow failure, or developmental delay.^{6,7} A subset of patients with DNA ligase IV mutations and practically absent circulating T and B cells resulting in SCID have been recently reported.^{4,8,9} The patient described here, in addition to SCID, uniquely

presented with typical clinical and laboratory features of OS. Unlike mutations that completely abolish ligase IV assisted variable-diversity-joining chain recombination, such as the deletion found on 1 allele in our patient, the H282L mutation found on the other allele probably allowed residual signal-joint formation, resulting in leaky SCID. Indeed, in the 2 previous patients who had the DNA ligase IV H282L mutation, as many as 1074 CD3⁺ T cells/ μ L and wide V β -chain representation were found.⁴

BMT remains the treatment of choice for patients with SCID and OS. Among the few patients with DNA ligase IV–associated SCID who were transplanted, 1 died during conditioning, 2 died from veno-occlusive disease, and 1 died of posttransplant lymphoproliferative disease shortly after BMT.^{4,8,9} In contrast, another patient who received nonmyeloablative conditioning and subsequent matched unrelated donor BMT survived a year after BMT, but his immune reconstitution was not reported.⁴ The patient described here survived full myeloablative conditioning with no persisting long-term acute adverse effects, suggesting tolerance to chemotherapy despite ligase IV–deficient cells' increased sensitivity to ionizing radiation.

In conclusion, we demonstrate here that patients with mutations in DNA ligase IV can present with features of OS. The leaky SCID can be corrected with BMT in spite of the sizable number of circulating T cells, which can be effectively and safely erased with full conditioning.

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