Omenn Syndrome—Review of Several Phenotypes of Omenn Syndrome and RAG1/RAG2 Mutations in Japan

Masahiko Kato¹,², Hirokazu Kimura², Mitsuru Seki³, Akira Shimada⁴, Yasuhide Hayashi⁴, Tomohiro Morio⁵, Satoru Kumaki⁶, Yasushi Ishida⁷, Yoshiro Kamachi⁸ and Akihiro Yachie⁹

ABSTRACT
Omenn syndrome (OS) is a form of severe combined immunodeficiency (SCID) characterized by erythrodermia, hepatosplenomegaly, lymphadenopathy, and alopecia. In patients with OS, B cells are mostly absent, T-cell counts are normal to elevated, and T cells are frequently activated and express a restricted T-cell receptor (TCR) repertoire. Thus far, inherited hypomorphic mutations of the recombination activating genes either 1 or 2 (RAG1/2) have been detected in most OS patients. We have recently experienced a rare case of OS showing the revertant mosaicism due to multiple second-site mutations leading to typical OS clinical features with RAG1-deficient SCID. In this review, we will focus on the variation of several phenotypes of OS.

KEY WORDS
immunodeficiency, Japan, Omenn syndrome, RAG1 or RAG2 mutation

INTRODUCTION
The common characteristic of severe combined immunodeficiency (SCID), a group of rare monogenic disorders, is the occurrence of a block in T cell differentiation, always associated with a direct or indirect impairment of B cell immunity.¹,² The resulting combined immunodeficiency is responsible for the clinical severity of SCID, which, without treatment, leads to death within the first year of life. At least, eleven distinct SCID phenotypes have been identified to date. Mutations of several genes have been found to cause SCID as shown in Table 1. Identifying the pathophysiological basis of most SCID conditions has led to the possibility of molecular therapy as an alternative to allogeneic hematopoietic stem cell transplantation.

Omenn syndrome (OS), was first reported by Omenn in 1985, one of a rare SCID characterized by the presence of a substantial number of oligoclonal, activated T cells, and the lack of B lymphocytes, associated with particular clinical features such as generalized erythroderma, lymphadenopathy, hepatosplenomegaly, and increased occurrence of life-threatening infections.³ In OS patients, circulating B lymphocytes are usually absent, whereas various numbers of activated and oligoclonal T lymphocytes are present in peripheral blood and infiltrate the skin, gut, liver and spleen, causing a graft-versus-host-like disease.⁴,⁷ OS is caused by mutations of the recombination activating genes (RAG1 and RAG2) ² that are essential for V(D)J recombination.⁸,⁹ Unless treated with hematopoietic stem cell transplantation, OS patients usually succumb early in life to overwhelming opportunistic infections.⁷
SEVERAL PHENOTYPES OF OMENN SYNDROME

SCID represent a heterogeneous group of hereditary defects of the immune system that affect both T and B cells and whose etiology has only recently begun to be understood. A portion of these SCID patients bear a defect in either of the two recombination-activating genes, RAG1 or RAG2, while others have mutations in a newly identified gene, Artemis. All these three genes, RAG1 or RAG2, and Artemis, are characterized by an impairment of the V(D)J recombination activity, which accounts for the generation of residual, oligoclonal T-lymphocytes; (3) in a third group of patients, findings were only partially compatible with OS, and these patients, who also carried at least one missense mutation, may be considered to have atypical SCID/OS; (4) patients with engraftment of maternal T cells as a complication of a transplacental transfusion represented a fourth group, and these patients, who often presented with a clinical phenotype mimicking OS, may be observed regardless of the type of RAG gene mutation. These results suggest that clinical and immunologic phenotypes of patients bearing RAG mutation are more diverse than previously reported and that this diversity is related to the specific type of RAG mutation.

OUR RECENT CASE AND REVIEW OF RAG1/RAG2 MUTATIONS IN JAPAN

Recently, we encountered a 3-month-old boy with generalized exudative erythroderma, hepato-
Omenn Syndrome in Japan

Fig. 1 Various phenotypes of Omenn syndrome. Omenn syndrome (OS) shows various phenotypes. Typical OS has the generation of residual RAG activity, resulting in oligoclonal expansion of autoreactive T cells (Typical Omenn). Atypical OS may result if expansion of activated, oligoclonal T cells do not become predominant. As shown in OS with MFT, patients with engraftment of maternal T cells as a complication of a transplacental transfusion often presented with a clinical phenotype mimicking OS, and may be observed regardless of the type of RAG gene mutation. Our case showed oligoclonal expansion of T lymphocytes with multiple second-site mutations leading to typical OS with RAG1-deficient SCID shown in B- T-SCID with reversions.

tosplenomegaly, draining otitis externa, and alopecia, with a history of *Pseudomonas aeruginosa* bactremia requiring systemic antibiotic treatment. Laboratory evaluation found mild anemia, leukocytosis with marked lymphocytosis and eosinophilia, low serum immunoglobulin levels, and hypoalbuminemia. Analysis of T cell receptor Vβ repertoire in the periphery showed extremely restricted heterogeneity. There was no evidence of maternal lymphocyte engraftment due to the result of HLA typing and FISH analysis. Finally, mutation in the RAG1 gene was detected by DNA sequencing.11 The diagnosis of OS was established. Immunosuppressive therapy with prednisolone was started and then cyclosporin A was added to correct autoimmune manifestations. Four months after admission, the patient underwent allogeneic stem cell transplantation (SCT) with a full matched unrelated cord blood unit, because no matched related donor was available.12 Although the patient is infected with *Mycobacterium avium complex* and received anti-
mycobacterium therapy with ethanbutol, rifampin, and azithromycin, he no longer suffers from high fever and is in good condition on day +300 post-transplant.

So, far in Japan, six cases, including ours, of mutations of recombination activating genes (RAG1 or RAG2) were reported. As shown in Table 2, we summarized clinical features and mutation sites of RAG1 and RAG2. Cases 1 and 2, which were siblings with typical Omenn phenotype, were found to be compound heterozygotes of R396C and L885R mutations in RAG1.13 In case 3, with RAG1 mutation, maternofetal transplantation was detected14 as shown by Villa et al.,4 Case 4 is the only one of RAG2 mutation in Japan. Case 5 showed atypical OS without eosinophilia, hyper-IgE, and lymphadenopathy. The case 6 (our recent case) showed oligoclonal expansion of T lymphocytes with multiple second-site mutations leading to typical OS with RAG1-deficient SCID11 as shown in Figure 1. The patient is homozygous for a single base C deletion predicted to cause frameshift and premature termination of the RAG1 protein. Six compensatory second-site mutations were found in his revertant T cells, which showed an activated phenotype with a restricted TCR repertoire, expanded in peripheral blood, and might have contributed to the modification of his clinical features, suggesting that the patient’s revertant T cell mosaicism is responsible for OS phenotypes switched from T-B-SCID.

A NOVEL PHENOTYPE OF OMENNSYN

DROME

Somatic revertant mosaicism is a rare phenomenon that is increasingly being reported in human genetic disorders.15,16 Both back mutations resulting in restoration of wild-type sequences and second-site mutations leading to compensatory changes have been reported in revertant patients. Interestingly, in all cases with somatic revertant mosaicism reported to date, revertant cells carried a single revertant sequence.15,16 It is also well recognized that revertant mosaicism is an additional basis for milder phenotype in several primary immunodeficiencies such as adenosine deaminase deficiency,17 X-linked SCID,18 and Wiskott-Aldrich syndrome,19 where revertant lymphocytes of patients showed selective growth advantage in vivo.

From these observations, this patient is the first case showing somatic revertant mosaicism in OS. The present studies provide significant implications of revertant mosaicism in the pathogenesis of OS, and further support the possibility that genetic reversions may be more common than previously thought.

In conclusion, OS is a fatal disease if untreated. Therapeutic options include bone marrow transplantation or cord blood stem cell transplantation; however, the mortality is still 46%.7 The mortality might be more reduced if diagnosis is established early and treatment is initiated rapidly by using early compatible bone marrow transplantation or cord blood stem cell transplantation.

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