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

1Departments of Allergy and Immunology, 3Internal Medicine, 4Hematology and Oncology, Gunma Children’s Medical Center, 2Gunma Prefectural Institute of Public Health and Environmental Sciences, Gunma, 5Department of Pediatrics and Developmental Biology, Graduate School, Tokyo Medical and Dental University, Tokyo, 6Department of Pediatric Oncology, Institute of Development, Aging and Cancer, Tohoku University, Miyagi, 7Department of Pediatrics, Ehime University School of Medicine, Ehime, 8Department of Pediatrics/Developmental Pediatrics, Nagoya University Graduate School of Medicine, Aichi and 9Department of Laboratory Sciences, School of Health Sciences, Faculty of Medicine, Kanazawa University, Ishikawa, Japan.
Correspondence: Dr. Masahiko Kato, Departments of Allergy and Immunology, Gunma Children’s Medical Center, 779 Shimohakoda, Hokkitsu, Gunma 377-8577, Japan.
Email: mkato@shibukawa, gmc.pref.gunma.jp
Received 28 September 2005.
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immunological observations of V (D) J recombination in different ways. Villa et al. reported the clinical and immunological observations of V (D) J recombination defects in lymphocytes due to RAG mutations. They analyzed 44 such patients from 41 families, and concluded that: (1) null mutations on both alleles lead to the T-B-SCID phenotype; (2) patients manifesting classic OS have missense mutations on at least one allele and maintain partial 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.

**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. 

OS is an unusual severe immunodeficiency with T cells but no B cells, and peculiar features also due to a defect in RAG1 or RAG2 genes. All these three forms are characterized by an impairment of the V (D) J recombination, the process that insures the somatic diversification of immunoglobulin and T cell receptor-encoding genes. Recent findings have enabled us to better understand the pathophysiology of these three immunodeficiencies, which affect the V (D) J recombination process to a different extent and in different ways. Villa et al. reported the clinical and immunological observations of V (D) J recombination defects in lymphocytes due to RAG mutations. They analyzed 44 such patients from 41 families, and concluded that: (1) null mutations on both alleles lead to the T-B-SCID phenotype; (2) patients manifesting classic OS have missense mutations on at least one allele and maintain partial 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-splenomegaly, lymphnode swelling, eczema, eosinophilia, IgE elevation. He was diagnosed with typical Omenn syndrome. The genomic analysis revealed that he carried a missense mutation in the Artemis gene, R897stop. This mutation was inherited from his mother. His sister, who was 2 years old at the time of diagnosis, was also found to carry the same mutation. Both of them were treated with hematopoietic stem cell transplantation and showed favorable outcomes. This case highlights the importance of identifying the genetic basis of SCID and the potential for personalized treatment strategies.

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**Table 1** Major phenotypes of SCID

<table>
<thead>
<tr>
<th>Phenotypes</th>
<th>Diagnosis</th>
<th>Bearing gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>T (−) B (−) NK (−) SCID</td>
<td>ADA deficiency</td>
<td>ADA</td>
</tr>
<tr>
<td>T (−) B (−) NK (+) SCID</td>
<td>RAG1, RAG2 deficiency</td>
<td>RAG1, RAG2</td>
</tr>
<tr>
<td>T (−) B (+) NK (−) SCID</td>
<td>Artemis deficiency</td>
<td>Artemis</td>
</tr>
<tr>
<td>T (−) B (+) NK (+) SCID</td>
<td>X-SCID</td>
<td>γc chain</td>
</tr>
<tr>
<td>T (+) B (−) NK (+) SCID</td>
<td>IL-7Rα deficiency</td>
<td>IL-7Rα</td>
</tr>
<tr>
<td>T (+) B (+) NK (+) SCID</td>
<td>Ommen syndrome</td>
<td>RAG1, RAG2</td>
</tr>
</tbody>
</table>

ADA: adenosine deaminase, SCID: severe combined immunodeficiency, RAG: recombination activating genes

**Table 2** Clinical features of six cases of RAG1/RAG2 mutations in Japan

<table>
<thead>
<tr>
<th>Case</th>
<th>Age at Diagnosis</th>
<th>Clinical Feature</th>
<th>Mutation</th>
<th>Outcome</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 *</td>
<td>2 m</td>
<td>Hepatosplenomegaly, lymphnode swelling, eczema, eosinophilia, IgE elevation</td>
<td>RAG1; R396C, L885R</td>
<td>Dead at 5 m</td>
<td>Typical Omenn syndrome</td>
</tr>
<tr>
<td>2 *</td>
<td>0 m</td>
<td>Hepatosplenomegaly, lymphnode swelling, eczema, eosinophilia, IgE elevation</td>
<td>RAG1; R396C, L885R</td>
<td>Dead at 21 days</td>
<td>Typical Omenn syndrome</td>
</tr>
<tr>
<td>3</td>
<td>4 m</td>
<td>Lymphnode swelling, eczema, eosinophilia, IgE elevation</td>
<td>RAG1; R559S, R897stop</td>
<td>post SCT, live at 10 y</td>
<td>Materno-fetal transplantation</td>
</tr>
<tr>
<td>4</td>
<td>0 m</td>
<td>Hepatosplenomegaly, lymphnode swelling, eczema, eosinophilia, IgE elevation</td>
<td>RAG2; A73H, Q258stop</td>
<td>post SCT, live at 2 y 10 m</td>
<td>Typical Omenn syndrome</td>
</tr>
<tr>
<td>5</td>
<td>10 m</td>
<td>Poor growth weight, respiratory distress</td>
<td>RAG1; R142stop, R396H</td>
<td>post BMT, live at 2 y 11 m</td>
<td>Atypical Omenn syndrome</td>
</tr>
<tr>
<td>6</td>
<td>3 m</td>
<td>Hepatosplenomegaly, eczema, eosinophilia</td>
<td>RAG1; del 2441 framshift</td>
<td>post SCT, live at 1 y 8 m</td>
<td>2nd site mutations</td>
</tr>
</tbody>
</table>

* sibling

SCT: stem cell transplantation, BMT: bone marrow transplantation, m: month, y: year
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. 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. 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 OMENN SYNDROME**

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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