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CASE REPORT

Atypical Omenn Syndrome Due to RAG2 Gene Mutation, a Case Report

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ABSTRACT

Severe Combined Immunodeficiency (SCID), characterized by a profound decrease in both the number and function of T cells, is related to more than 20 different mutations. Recombination-activating gene (RAG) 1 and 2 seem to be two of the most common forms presenting with various manifestations, including typical SCID, Omenn syndrome (OS), atypical SCID (AS), or delayed onset combined immunodeficiency with granulomas. One interesting manifestation in RAG mutation is the change in the immunophenotype over time, even after hematopoietic stem cell transplantation (HSCT). As bone marrow transplantation (BMT) is the only curative treatment of SCID, it is necessary to differentiate between SCID and OS due to the different conditioning regimens (CR). We present a novel case of atypical SCID (SCID manifestations with more than 300 $CD3^{+}T$ cells) caused by RAG 2 gene mutation whose immunophenotype changed to atypical Omenn syndrome (all Omenn syndrome manifestations except rash, eosinophilia, and elevated IgE) over time. Differentiation of leaky SCID, SCID and Omenn syndrome in RAG mutation genes and overlap manifestations is important in treatment plan and prognosis.

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Keywords: Atypical Omen Syndrome, Atypical SCID, RAG 2 Mutation, Severe Combined Immunodeficiency

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INTRODUCTION

SCIDs are severe forms of primary immunodeficiency diseases characterized by the absence or very low number of T cells ($CD3^+$ T cells <300/mL) and absent or very low T cell function (<10% of the lower limit of normal). This is measured by the response to phytohaemagglutinin (PHA) via contrast Atypical SCID (AS) characterized by $CD3^+$ T cell of more than 300/ml and less than 1000/ml and T cell function impairment (<30% of the lower limit of normal) (1). Omenn syndrome (OS) refers to conditions presenting a generalized skin rash, early manifestations of erythroderma, diarrhea, lymphadenopathy, hepatosplenomegaly, FTT, eosinophilia, hypogammaglobulinemia, increased IgE, absence of B-cells, presence of oligoclonal T cells, detectable $CD3^+$ T cells ≥300/mL, absent or low T cell proliferation to exposed antigens(≤30% of the lower limit of normal), and absence of maternal engraftment (1). In AOS, one or more clinical manifestations of OS are absent, but oligoclonal T-cells are present (2). With more than 20 different mutations described as related genes in literature, recombination-activating gene (RAG) 1 and 2 seem to be two of the most common forms of autosomal recessive SCID. RAG defects lead to immunoglobulin and T cell receptor formation impairment. This condition presents with various manifestations, including T-B-NK+SCID, Omenn syndrome (OS), atypical SCID/atypical Omenn (AS/AOS), or delayed onset combined immunodeficiency with granulomas and/or autoimmunity (CID-G/AI) (3). These manifestations may also occur or change from one form to another one even after bone marrow transplantation (4). In this study, we described an atypical SCID which was finally presented as atypical Omenn syndrome.

CASE REPORT

The patient was a 13 months boy born to consanguineous parents, with a family history of frequent and severe infections in his sister. SCID was considered based on her T-B-NK+ immunophenotype without genetic testing, and she died at the age of 18 months due to sepsis. Our patient did not receive any live vaccine at birth (Bacillus Calmette-Guerin (BCG) and oral poliovirus (OPV) based on routine national vaccination) due to the history of sibling death with immunodeficiency probability. Two weeks after birth, he was assessed for immunodeficiency, when immunophenotype was compatible with AS or SCID was compatible with maternal T cell engraftment (Immunologic assays are shown in Table 1); therefore, prophylactic antibiotics and Intravenous Immunoglobulin (IVIG) were prescribed. He was asymptomatic until the age of 4 months when he developed pre-orbital cellulitis and dacryocystitis associated with pseudomonas, oral thrush, and recurrent diarrhea. He was visited at eight months of age for the first time in our clinic with failure to thrive (FTT), hepatomegaly, and lymphadenopathy without skin lesions. The immunophenotype was altered through increasing $CD8^+$ class more than 2,200/mL without any significant difference in $CD4^+$ count (Figure 1). Although IgA and IgM were reduced, IgG was within a normal range due to regular IVIG infusion, and serum IgE level did not change significantly (Table 1).

Antibody responses to tetanus and diphtheria before receiving IVIG as well as lymphocyte transformation test to PHA, BCG, and Candida were completely impaired, and maternal T cell engraftment was excluded by human leukocyte antigen (HLA) typing.

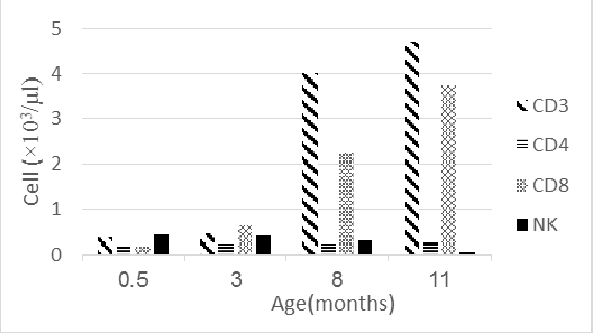

Figure 1. Serial change in CD3, CD4, CD8, NK during the time.

Whole-exome sequencing test followed by mutation confirmation by direct Sanger revealed a heterozygous RAG2 gene mutation in parents while a homozygous mutation p. R229Q in the patient (Table 2). At the age of eleven months, the patient underwent bone marrow transplantation (BMT) from his matched sibling donor using a minimal dose of busulfan as the BMT conditioning regimen. However, he deceased two months later due to severe infection.

Table 1. Patient immunological data in different age.

Age(months)	1/2	3	8	11
WBC ($\times10^3/\mu L$)	4.4 (5-21)	1.26 (5.5-18)	8.25 (6-17.5)	7.6 (6-17.5)
LYM ($\times10^3/\mu L$)	0.79 (3.5-13.1)	0.88 (3.7-9.6)	4.78 (3.8-9.9)	5 (2.6-10.4)
CD3 ($\times10^3/\mu L$)	0.395 (2.3-7)	0.465 (2.3-6.5)	4 (2.4-6.9)	4.7 (1.6-6.7)
CD4 ($\times10^3/\mu L$)	0.205 (1.7-5.3)	0.235 (1.5-5)	0.240 (1.4-5.1)	0.27 (1-6.4)
CD8 ($\times10^3/\mu L$)	0.190 (0.4-1.7)	0.645 (0.5-1.6)	2.24 (0.6-2.2)	3.75 (0.4-2.1)
CD19 ($\times10^3/\mu L$)	0 (0.6-1.9)	0 (0.6-3)	0.02 (0.7-2.5)	0.75 (0.6-2.7)
CD16/56 ($\times10^3/\mu L$)	0.44 (0.2-1.4)	0.41 (0.1-1.3)	0.3 (0.1-1)	0.05 (0.2-1.2)
EOS ($\times10^3/\mu L$)	0.090	0.25 (0.05-0.51)	0.25 (0.05-0.51)	0.057 (0.05-0.51)
IgE (IU/ml)		57 (<200)	65 (<200)	
Hb (gm/dl)	14 (10-20)	9.1 (9.5-14)	11.3 (10.5-13.5)	10.9 (10.5-13.5)
Plt ($\times10^3/mm^3$)	268 (150-450)	408 (150-450)	188 (150-450)	203 (150-450)

WBC; White Blood Cell, LYM; Lymphocyte, EOS; Eosinophil, Hb; hemoglobin, Plt; Platelet

DISCUSSION

Our patient was RAG2 gene deficient with homozygote R229Q mutation who was primarily diagnosed as AS due to higher than 300 cells/mL circulating autologous T cell count (5,6). Circulating B cells are absent in RAG-deficient patients presenting with OS/AOS or SCID as shown in our patient (Table 1) whereas they are often detected in those with AS and CID-G/AI (7). Patients with AS may present some features of OS that most frequently involve the skin and the liver; however, these patients lack severe lymphoproliferation and hepatosplenomegaly. The patient in the present study developed hepatomegaly followed by lymphadenopathy. In R229Q mutation, which is

indeed a missense mutation, protein function is not completely lost, presenting with either SCID or OS. Notarangelo *et al.* determined the activity of each RAG2 variant and analyzed the recombination activity of compound heterozygosity. They showed that the mean recombination activity level (MRAL) of R229Q homozygote mutation was 8.9%. The mean recombination activity of mutant alleles correlated with severity and clinical phenotype (8). And, MRAL was about 20% in AS and significantly lower than 10% in OS and SCID.

Table 2. Genetic testing report. Whole Exome Sequencing Test Followed by Mutation Confirmation by Direst Sanger Sequencing.

Platform	Read Length	Coverage	Gene	DNA Change	dbSNPrsID	OMIM	Zygosity
Illumina HiSeq4000	101	100X	RAG2	NM_001243786: Exon3:c.G686A	Rs121917894	179616	Patient:Hom Father:Het Mother:Het

Hom; Homozygote, Het; Hetrozygote

It is important to differentiate SCID and OS although Haddad *et al.* reported no differences between OS and SCID after HSCT regarding survival, the need for the second procedure, Graft-versus-host disease, or immune reconstitution. SCID patients lack T cells, hence unable to reject allogeneic stem cells; in such cases, conditioning regimen (CR) is not required while it is necessary to employ CR for the typical and atypical OS (9). Based on our literature review, R229Q homozygote mutation often causes OS or AOS, and only a few studies report typical T− B−SCIDs (8,10). Homozygous R229Q mutation in mice was also associated with OS and AS (10). Villa *et al.* reported that mice Rag2R229Q/R229Q mutation mimicked most symptoms of human OS (11). According to the study conducted by Roifman *et al.*, all RAG mutant patients with CD3 of more than 500 had Omenn syndrome (5). Two studies reported OS with the absence of one or more manifestations; in one of them, ADA deficiency was shown without eosinophilia and normal IgE while in the other, RAG1 deficiency case was reported with the absence of rash but the presence of other features (12,13). According to the previous reports, our case is the first reported RAG2 deficiency with AOS manifestations without skin involvement.

CONSENT

Written informed consent was obtained from the patient`s legal guardians for publication of this case report and its accompanying information. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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