Immunol Genet J, Vol. 6, No. 4, December 2023, pp.137-140 DOI: https://doi.org/10.18502/igj.v6i4.17101

Case Report

The *RAG1* Mutation Presenting as Early Onset SLE in an Iranian Patient

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Received: 18 September 2023; Accepted: 09 December 2023

Abstract

It has been established that mutations of the Recombinase activating genes (*RAG1* and *RAG2*) are responsible for classic T-B-NK+ severe combined immunodeficiency (SCID). On the other hand, it has now become evident that certain mutations within these genes can also lead to other forms of combined immunodeficiency, antibody deficiency, and even autoimmunity.

In this report, we present a case involving a 9-month-old female patient who presents with clinical and laboratory findings indicative of systemic lupus erythematosus (SLE). Following the diagnosis of early-onset SLE and considering the presence of concurrent infections, it was considered necessary to investigate potential underlying monogenic disorders associated with inborn errors of immunity. Immunological evaluations demonstrated a combined immunodeficiency and whole exome sequencing confirmed that the patient has a mutation in the *RAG1* gene.

Keywords: Systemic Lupus Erythematosus; RAG1; SCID; Immunodeficiency

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How to cite this article

Cheraghi T, Mir Emarati A, Moradkhani A. The RAG1 Mutation Presenting as Early Onset SLE in an Iranian Patient. Immunology and Genetics Journal, 2023; 6(4): 137-140. DOI: https://doi.org/10.18502/igj.v6i4.17101

Introduction

Immunodeficiency and autoimmunity may be two different features of the same monogenic disorder (1, 2). Traditionally, we learned that recurrent or severe infections are an alarming sign of immunodeficiency. However, a growing body of literature highlights that late and particularly, early-onset autoimmunity may be a presentation of an inborn error of immunity (3-7). Two genes that have been detected to be involved in tolerance and autoimmunity, are the recombination-activating genes (*RAG1*, and *RAG2*). They are expressed in the cells of the adaptive immune system. encoding two enzymes involved in B and T cell development, expressed in pre-B and pre-T cells, start the gene rearrangement to provide the repertoire of functional receptors for B and T cells to recognize a vast array of antigens (8, 9). It has long been established that mutations within these genes lead to T-B-NK+ severe combined immunodeficiency (SCID) (10, 11). However, in recent years, many researchers investigated patients

with *RAG* mutation and have found that the mutation of these two genes may lead to a spectrum of diseases ranging from other variants of SCID to antibody deficiency, and autoimmunity (4, 12-14). Reported diseases include Omenn syndrome (15), atypical SCID (16), autoimmunity and CD4 T lymphopenia, combined immunodeficiency with granuloma (12), antibody deficiencies from IgA deficiency, common variable immunodeficiency, polysaccharide antibody deficiency in adults (16). In this report, we present a patient exhibiting predominant autoimmune manifestations.

Case presentation

A 9-month-old female was referred to our clinic with a pruritic maculopapular skin rash, fever, petechiae, hematuria, and proteinuria. She had a history of thrombocytopenia, urinary tract infections, pulmonary infections, and otitis media. The patient was born prematurely to non-consanguineous parents with no family history of similar diseases. Her 10-year-old sister was healthy. She was not receiving anticoagulants, antibiotics, or immunosuppressants. The family history was negative for hematological disorders or immunodeficiency, and there was no evidence of splenomegaly or lymphadenopathy on examination. With written informed consent obtained from her parents, an extensive workup for underlying causes was initiated.

A complete blood count (CBC) confirmed thrombocytopenia. Coagulation studies, including prothrombin time (PT) and activated partial thromboplastin time (aPTT), were normal, ruling out coagulopathy. Autoimmune evaluation revealed positive antinuclear antibodies (ANA) and anti-double-stranded DNA (anti-dsDNA). Screening for chronic infections, including HIV, EBV, CMV, and hepatitis viruses, was unremarkable. Complement levels (C3 and CH50) were below normal. Given the clinical manifestations of thrombocytopenia, anemia, hematuria, positive ANA, and anti-dsDNA, early-onset systemic lupus erythematosus (SLE) was suspected. Based on previous experiences with patients with early-onset autoimmune diseases, we further evaluated the patient for underlying immunodeficiency **(Figure 1)**. Immunologic evaluation revealed panhypogammaglobulinemia, and flow cytometry showed low levels of CD3, CD4, CD8, CD19, and CD20. Key laboratory findings are summarized in **Table 1**. The diagnosis of SLE was confirmed based on the criteria of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR). Additionally, coexistent infections, very low B and T cells, and low immunoglobulins suggested combined immunodeficiency. Genetic testing identified a homozygous mutation in the *RAG1* gene (c.2095C>T, p.Arg699Trp), confirming *RAG1* deficiency as the underlying cause.

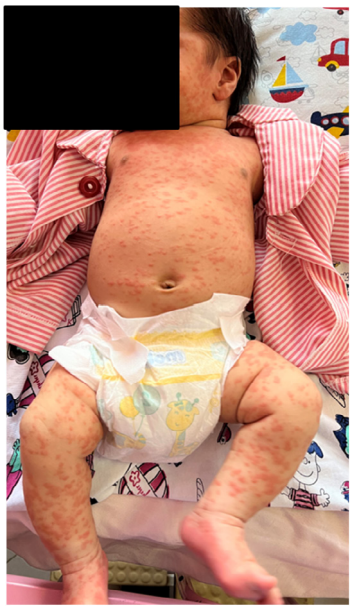

Figure 1. A 9-month-old girl presented with generalized maculopapular rash, thrombocytopenia, and hematuria

Despite renal involvement characterized by hematuria and proteinuria, the parents did not consent to a renal biopsy. Treatment with intravenous immunoglobulin (IVIG) and prednisone was initiated due to the profound hypogammaglobulinemia and confirmed SLE. Although we were concerned about the potential side effects of corticosteroids, especially the exacerbation of infections given the patient's low immunoglobulin levels, the treatment outcomes were positive. Corticosteroid therapy successfully ameliorated refractory thrombocytopenia without significantly worsening infections. Prednisone was initially administered at 20 mg/day in two divided doses, then tapered to 5 mg in the morning. Hydroxychloroquine at 50 mg/day was added to control exacerbations. Rituximab was used twice and

Table 1. Laboratory findings of the patient

Laboratory data	Results	Normal Range	Laboratory data	Results	Normal Range
Hb (g/dl)	8.7	12.3-15.3	IgM (mg/dl)	25	40-143
Plt, *1000/µl	45	150-450	IgE (IU/ml)	0.7	<68
C3	77	90-180	CD3 %	27	50-90
C4	12	51-150	CD4 %	18.3	20-69
CH50	32.4(0-50)	51-150	CD8 %	23.9	5-40
ANA titer	1/160	<1/80	CD16 %	56.7	3-15
U/C > 100000	E. Coli	Negative	CD56 %	28	3-15
Anti-ds-DNA	72.1	<25	CD19 %	0.2	3-40
IgG (mg/dl)	62	345-1213	CD20 %	0.1	3-40
IgA (mg/dl)	39	14-106			

then discontinued.

Discussion

Traditionally, *RAG* have been recognized for their role in causing severe combined immunodeficiency. However, advancements in genetic technology have revealed that inborn errors of metabolism can manifest with clinical signs and symptoms other than recurrent infections (12). In our report, we present a case characterized by clinical and laboratory findings indicative of systemic lupus erythematosus (SLE), which, through genetic analysis, was determined to be attributable to a monogenic disorder related to inborn errors of immunity. While SLE is generally understood to be a polygenic condition, this case has opened new windows for improving understanding of disease pathogenesis, suggesting that what has traditionally been classified as polygenic may also be caused by a monogenic disorder (1, 2, 18). Apart from typical SCID, it has been proven that mutation of *RAG* genes could give rise to three categories of diseases. The first one is combined immunodeficiency including atypical SCID, typical and atypical omenn syndrome, leaky SCID, and combined immunodeficiency with granulomas, and CD4 T lymphopenia (12, 13, 15, 16). The second category is antibody deficiencies: IgA deficiency, common variable immunodeficiency, polysaccharide antibody deficiency in adults (19-22), and the last one is autoimmunity (5, 12, 23). The outcome of *RAG* mutations is influenced by a combination of well-characterized and yet-to-be-characterized genetic and epigenetic factors and remains incompletely elucidated. However, it has been noted that null mutations in the *RAG* genes are associated with classic severe combined immunodeficiency (SCID)(24), whereas, the hypomorphic mutation may lead to other variants (14, 25).

Based on available data (17), presence of high NK cells, and immune dysregulation (as in our case) makes the chance of rejection of bone marrow transplantation more likely. It is important to emphasize that a significant limitation of our report is that the kidney biopsy was not performed, because parents did not consent for it.

Furthermore, the process of tolerance and the prevention of autoimmunity are linked to the essential functions of RAG in V(D)J recombination. A substantial body of evidence exists indicating that mutations in these genes are associated with a variety of autoimmune disorders (5, 14), It appears that further research is needed to shed light on this partially understood domain.

Conclusion

When we faced with cases of early-onset autoimmunity, it is essential to investigate potential monogenic disorders associated with inborn errors of immunity.

Conflicts of interest

The authors declare that they have no conflict of interest.

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