Immunol Genet J, Vol. 4, No. 3, Sep 2021, pp.132-137 DOI: https://doi.org/10.18502/igj.v4i3.12113

Literature Review

Omenn Syndrome Caused by A Novel Mutation of the DCLRE1C Gene: Case Report and Review of Literature

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Received: 10 May 2021; Accepted: 19 July 2021

Abstract

We report a case of Omenn syndrome due to a novel mutation of the gene DCLRE1C(Artemis). He was referred to our hospital with a complaint of protracted diarrhea, erythematoexfoliative rash, urinary tract infection, pneumonia, and failure to thrive. He was 2 months old. At the first sight, the diagnoses of Omenn syndrome, graft versus host disease (GVHD), Netherton syndrome, and Atopic dermatitis came to mind. Laboratory evaluation showed lymphopenia, eosinophilia, high IgE, and whole-exome sequencing revealed a mutation of the DCLRE1C gene. After obtaining blood samples, he received broad-spectrum antibiotics, antifungals, antiviral, prophylaxis for pneumocystis Jirovecii pneumonia, and Intravenous immunoglobulin. He expired owing to delayed referral and overwhelming sepsis before receiving bone marrow transplantation. In every neonate infant presenting with erythematoexfoliative skin rash, refractory infection, and lymphopenia, Omenn syndrome should be considered.

Keywords: DCLRE1C Mutation; Omenn Syndrome; Erythematoexfoliative Rash; Esosinophilia

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How to cite this article
Cheraghi T, Safaee A, Esmaili E, Golshekan K, Ghavideldarestani M. Omenn Syndrome Caused by A Novel Mutation of the DCLRE1C Gene: Case Report and Review of Literature. Immunology and Genetics Journal, 2021; 4(3): 132-137. DOI: https://doi.org/10.18502/igj.v4i3.12113

Introduction

Omenn syndrome (OS) is a rare and autosomal recessive disease categorized as a subtype of severe combined immunodeficiency disease (SCID). It was initially reported by Gilbert S. Omenn as "Familial reticuloendotheliosis with eosinophilia" in 1965(1). OS is characterized by erythematoexfoliative dermatitis, soon after birth, failure to thrive, chronic diarrhea, eosinophilia, high IgE, lymphadenopathy, and hepatosplenomegaly(2).

Most patients have had in common, erythematoexfoliative rash, eosinophilia, and high IgE. Two genes; RAG1 and RAG2 have been reported as the main culprit genes for the disease but mutation of other genes has also been recognized as the causes of the syndrome (3) (4-7). Few reports are related to the DCLRE1C gene as the responsible gene. Interestingly, the different mutations of the DCLRE1C gene itself give rise to diverse immunologic phenotypes ranging from SCID to pure antibody deficiency (2, 8). Herein we report a case of Omenn syndrome due to mutation of the DCLRE1C (Artemis) gene.

Case presentation

The patient was referred to our hospital with the chief complaint of fever, generalized erythematoexfoliative rash, protracted diarrhea, and respiratory distress. Before admission, he had been visited by a general practitioner with the diagnosis of facial eczema due to food allergy, and hypoallergenic formula had been started for the infant. Afterward, he had been visited by a dermatologist with the diagnosis of atopic dermatitis and a prescription of hydrocortisone cream and emollient. He was an only child, born to far-consanguineous parents. The first pregnancy of the mother has been aborted at 14 weeks of gestation owing to lumbosacral agenesis and gastroschisis in prenatal ultrasonography study. For this patient, no any genetic counseling or prenatal and post-natal screening has been performed. At the admission, He had a generalized, erythematoexfoliative rash, (**Figure 1 and 2**), protracted diarrhea, failure to thrive, and respiratory distress. The hairs were sparse. On lung auscultation, diffuse rhonchi and crackles were heard.

During the admission, we encountered refractory diarrhea, metabolic acidosis, recurrent urinary tract infections with massive proteinuria and granular cast as well as unresolved pneumonia despite using broad-spectrum antibiotics. Stool calprotectin antigen was 863(normally less than 50micrgram/gram). He had proteinuria in the nephrotic range, urinary tract infection with E- Coli. Sonography of the kidneys revealed increased echogenicity with hydronephrosis. A portable chest x-ray showed bilateral multilobe pneumonia. Regarding severe lymphopenia and poor response to treatment, the prognosis did not seem favorable. He received broad-spectrum antibiotics for gram-negative, gram-positive, anaerobes, viral infections, fungi, as well as prophylaxis for pneumocystis Jirovecii pneumonia. Intravenous immunoglobulin (IVIG), was infused. He had Metabolic acidosis, thought to be a consequence of sepsis (urosepsis, chronic diarrhea, and persistent pneumonia) and sodium bicarbonate was used for the correction of metabolic acidosis. Laboratory findings are shown in **Table 1 and 2**. Complete blood count (CBC), showed leukocytosis, eosinophilia, and lymphopenia (**Table 1**). As is illustrated in **Table 1**, the patient had lymphopenia, eosinophilia, and high IgE. **Table 2** shows the absolute low CD3+, CD4+, normal CD8, and inversion of CD4/CD8 T cells.

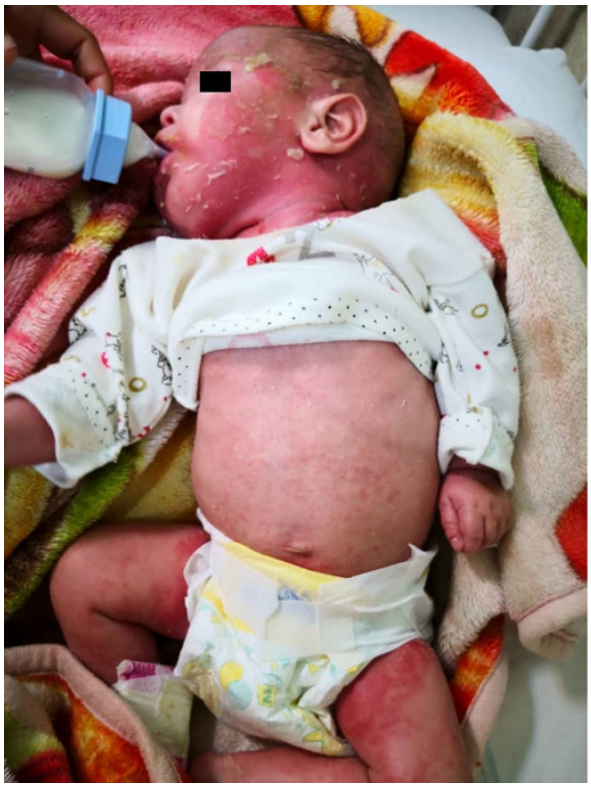

Figure 1: Generalized Erythematoexfoliative Rash seen on face, Scalp, trunk and limbs of the patient

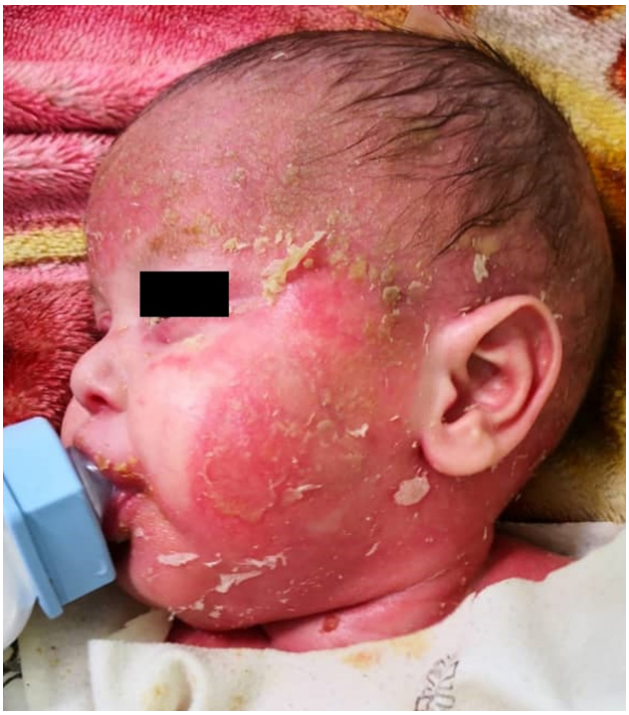

Figure 2: Erythematoexfoliative Rash seen on face and scalp

Table 1. Laboratory test results of the patient with Omenn syndrome

Laboratory Tests	WBC (10*3/ µl	Lympho-cyte%	Neutro-phil%	Eosino-phil%	Mono-cyte%	Platelets 10*3/ µl	Urine culture	IgA mg/ dl	IgE IU/ml
Patient Result	15.9	**13**	45	**30**	12	736	Ecoli > 100,000CFU/ mL	7	763
Normal Range	6.0-17.5	41–71	13-33	0-3	4-14	150-450	-	2.8-47	-

Since genetic testing was not available at our hospital, a blood sample in an EDTA-containing tube was sent to Microgen, Inc (South Korea) for Whole Exome Sequencing (WES) using Illumine high throughput DNA sequencing technology (Platform: NovaSeq6000). In the applied platform the read length was 150 bp with coverage of 100X and the library type was Sure Select V7-Post. Results of WES analysis indicated that the patient harbored a homozygous non-frameshift missense mutation in the DNA CROSS-LINK REPAIR PROTEIN 1C (DCLRE1C) gene, also known as ARTEMIS. This mutation in DCLRE1C (Chr10:14922990 A>T: NM_001289076: exon10: c.T707A) leads to an amino acid change (p.V236D). This finding has been verified using Sanger sequencing (**Figure 3**). Previous studies have found that various mutations in DCLRE1C gene are linked to Omenn Syndrome (OMIM: 603554) and Severe Combined Immunodeficiency, Athabascan type (OMIM: 602450). We were preparing him for bone marrow transplantation. Unfortunately, his condition worsened, leading to multiorgan failure. We used mechanical ventilation for respiratory support. Despite using all the above treatments, he did not respond to the therapeutic measures; his respiratory condition worsened, and ultimately succumbed to death before receiving bone marrow transplantation.

Table 2. Results of immunophenotyping of peripheral blood by flowcytometry

Marker/Age	Patient result (%)	Patient result (absolute count)	RI Child (%)	RI Child (absolute count)
CD3	81	1012	53-84	2500-5500
CD4	16	200	35-64	1600-4000
CD8	58	725	12-28	560-1700
CD4/CD8	0.27	-	1 or > 1	-
CD16	14	175	5-19	-
CD56	9	112	3-15	-
CD16+CD56	5	62	3-19	80-340

Discussion

The case we reported was referred too late to help optimally. Delayed diagnosis put the patient at maximum risk of multiorgan failure. Pertinent clinical and paraclinical findings, including erythematoexfoliative rash, multiorgan infection, eosinophilia, elevated IgE level, lymphopenia (**Table 1 and 2, and Figure 1, 2, and 3**), as well as detection of a homozygous non-frameshift missense mutation in the DCLRE1C gene, which was confirmed in patient and both parents by Sanger sequencing, led to the diagnosis of the Omenn syndrome

DCLRE1C gene encoding ARTEMIS, is involved in V(D)J recombination, as well as in nonhomologous end joining process; a process required for generating functional receptors for both B cells in pre- B cell stage in the bone marrow, and T cells in the thymus in pre- T cell stage. During V(D)J recombination, Variable(V), Diversity(D), and Joining(J) exons of coding genome that is located at the 5' and 3' end of the hairpin, flanking the recombination signal sequence (RSS), is recombined and assembled to code variable part of the receptors to recognize myriad of different antigens. In the first step of VDJ recombination, RAG1 and RAG2 genes, make nicks in the double stranded DNA, then, DNA protein kinase Catalytic subunit (DNA-PKcs) phosphorylates and make a complex with ARTEMIS, whereby Artemis gains the enzymatic endonuclease activity to open the already RAG complex generated hairpin. In the next step, the ligation phase, the processed broken DNA ends are ligated by DNA Ligase IV and XRCC4 (9-11).

Mutation of the DCLRE1C gene leads to the faulty V(D)J recombination and likewise, the defective generation of B and T cells with resultant severe and recurrent infections. Not all mutations of the DCLRE1C gene produce a similar phenotype. mutation of this gene generates many diseases from typical severe combined immunodeficiency (SCID) to pure antibody deficiency (2). Additionally, not all patients with Omenn syndrome are caused by mutation of DCLRE1C gene, other causative reported genes so far, are: RAG1, RAG2, ADA, IL2RG. CHD7, AK2, RMRP, IL7RA, ZAP70, and LIG4 genes, among which, RAG1, RAG2 are the most commonly reported(3, 4, 12-23).Therefore, Omenn syndrome is not a subtype of SCID, it is a phenotype caused by different genes(13). It is worth noting that different mutations of one gene may lead to diverse immunologic phenotypes. For instance, null mutation of the DCLRE1C(Artemis) gene causes Artemis-SCID, whereas, hypomorphous mutation of this gene gives rise to Omenn syndrome (22). The mutation we found was homozygous non-frameshift missense mutation in the (DCLRE1C) gene. Other researchers identified different muatations. Result of a study performed by Fel-

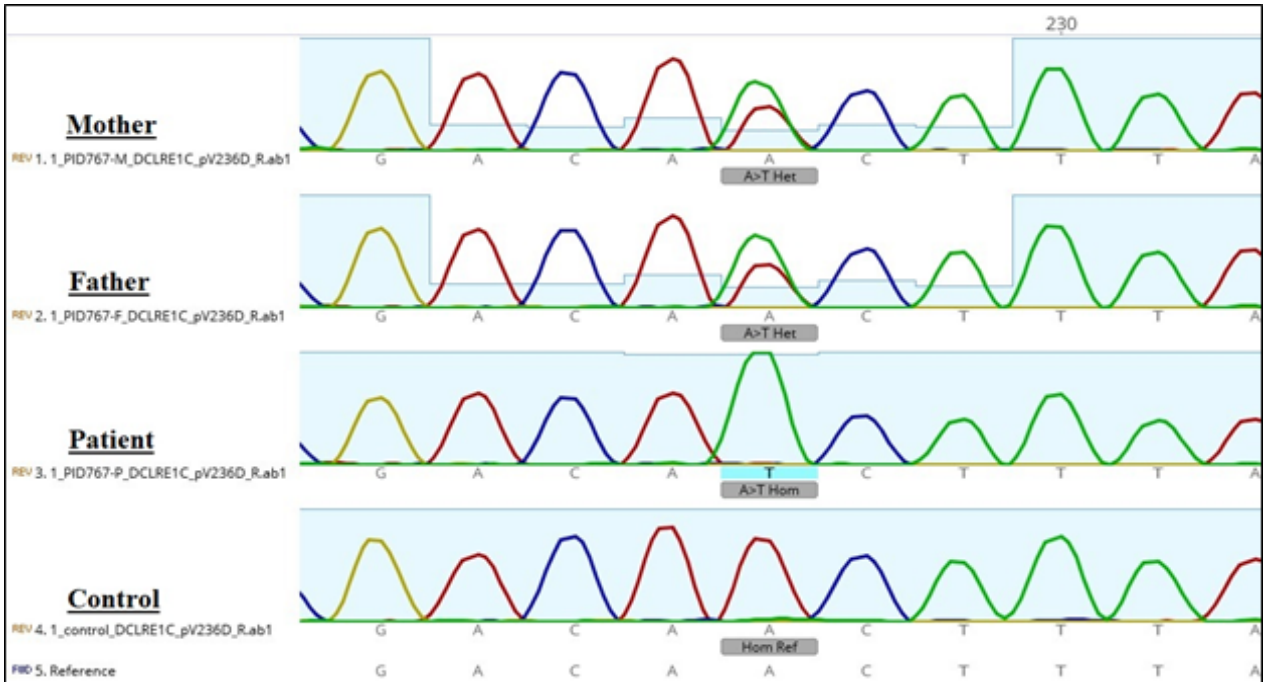

Figure 3. Sanger sequencing of the patient and his parents along with a control. The mutation found in the DCLRE1C gene (Chr10: 14922990 A>T: NM_001289076: exon10: c.T707A) via Whole Exome Sequencing was confirmed by Sanger sequencing confirming that the patient was homozygous while his parents are heterozygous carriers of this mutation.

gentreff et al. (2015) indicated a correlation between the nature and location of DCLRE1C mutations, functional activity, and the clinical phenotype (24). Earliest association of mutations of DCLRE1C gene with OS has been reported by Moshous et al. (2001) who have identified 8 different mutations in the DCLRE1C gene in 13 patients from 11 families with radiosensitive (RS)-SCID. However, none of the mutations were simple missense variants, and one of them could be considered as a true null allele (25). Moreover, Li et al. (2002) have identified a founder mutation in exon 8 of the DCLRE1C gene in 21 native Americans with Athabascan-type severe combined immunodeficiency (26). In 2003, a large genomic deletion and 3 missense mutations in conserved amino acid residues in the SNM1 homology domain of the Artemis protein have been identified in 4 RS-SCID patients(27) . Hence, Moshous et al. (2003) have identified hypomorphic mutations in exon 14 of the DCLRE1C gene in 4 patients from 2 families with partial SCID (27). In 2005, a compound heterozygous mutation has been detected in a patient with Omenn syndrome whose T cells expressed alpha/beta receptors with an oligoclonal repertoire but normal V(D)J recombination coding joints (28). Nonetheless, to the best of our knowledge, the detected mutation in our patient has not been previously reported.

In our patient absolute numbers of CD3+, CD4+ were low but, regarding the result of whole exome sequence result (**Figure 3**), and considering the placenta as an incomplete barrier, CD8+ T cells, unexpectedly was within the normal limit., this could be the result of maternofetal transfer of CD8 T cells (29, 30). Unfortunately, despite obtaining blood samples for IgG, IgM, and CD19, and CD20 they have not been performed by the laboratory owing to the early death of the patient. Regarding the results of mutation analysis and immunologic profile of the patient, the level of the IgG, IgM, as well as CD19 must be low.

The best practice for SCID variants is newborn screening using TREC (T cell Receptor Excision Circle), and other tests, timely diagnosis, and performing early hematopoietic stem cell transplantation, otherwise, the patient is put at risk of different infections, complications, and even, death. Confirmation of the inborn errors of immunity by Genetic study, provides both definitive diagnoses, and could help in family planning and prenatal diagnosis as well (31). Additionally, in countries like our country, where the rate of consanguineous marriages are high, autosomal recessive immune deficiencies are more prevalent (32, 33). Primary care physicians need to be trained for timely diagnosis of this group of diseases based upon updated warning signs of inborn errors of immunity (34).

Conclusion

Omenn syndrome should be considered in any neonate infant with erythematoexfoliative rash and for a better outcome, immunologic evaluation should be performed as soon as possible.

Conflict of interest

All authors declare that they have no conflict of interest.

Acknowledgment

The authors would like to thank PICU personnel of the

17th Shahrivar of Rasht for their compassionate care for patients.

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