

Case Report: MALT1 Mutation in a Patient with Severe Combined Immunodeficiency

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Abstract

Severe combined immunodeficiency (SCID) is one of the most serious and life-threatening forms of primary immunodeficiency disorders (PID). SCID patients manifest a large clinically heterogeneous group of monogenic disorders caused by a defect in human innate and adaptive immune response. It leads to an increased susceptibility to a variety of infections, sometimes with fatal outcomes. To date, *more than 30* candidate *genes* and *mutations* in patients with SCID phenotype have been identified. We found a homozygous variation (c.1454 A>G_p. Asn485Ser) in the MALT1, identified by WES in an expired infant with SCID. The mutation in MALT1 is associated with the absence of T cell activation, which produces immature lymphocytes leading to SCID.

Keywords: Whole exome sequencing, Severe Combined Immunodeficiency, Mucosa associated lymphoid lymphoma translocation gene 1

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Severe combined immunodeficiency (SCID) is an inherited condition and potentially fatal primary immunodeficiency (PID) which is characterized by the absence of T cells resulting in a profound deficiency of adaptive immune function (2). SCID patients are susceptible to severe infections including pneumonia, gastrointestinal infections, sepsis, recurrent or persistent thrush and chronic diarrhea. The absence of lymph nodes is mostly seen in these patients (3). Opportunistic infections are observed in the respiratory tract and the gastrointestinal tract of SCID patients. Different viral and fungal infections manifest during the life of SCID patients (4). SCID is inherited in forms of X-linked autosomal recessive or autosomal dominant traits (5). More than 30 known mutation genes in SCID patients have been identified (6). During the pathogenesis of SCID, different mutations in a single gene may give rise to distinct clinical symptoms (7). Indeed, mutation in genes involved in T cell, or both T and B cell development lead to the manifestation of broad spectrum infections such as bacterial, viral and fungal infections (8, 9). In the majority of infants with SCID it is often unknown at birth and their genetic defects are not diagnosed until life threatening infections occur (10). Mucosa associated lymphoid tissue lymphoma translocation gene 1 (*MALT1*) encoded for caspase like cysteine proteinase mucosa associated lymphoid tissue lymphoma translocation protein, is a requisite for nuclear factor kappa b activation downstream of antigen receptors, other receptors with immune receptor tyrosine-based activation motifs, and G protein coupled receptors (11-13). The Nuclear factor kappa B (NF- κ B) is a chief regulator of lymphocyte activation, survival, and proliferation that signals through various receptors including the T cell receptor (TCR) and B cell receptor (BCR), the tumor necrosis factor receptor (TNFR), and the B-cell-activating factor receptor (BAFF-R) (14). Impairment in MALT1

protein expression affects the NF κ B signaling pathway. Therefore, these data reinforce the association between *MALT1* deficiency and SCID (15). Inborn errors of the CARD11-BCL10-MALT1 (CBM) signalosome complex consisting of caspase recruitment domain containing (CARD) family adaptors, B cell CLL/lymphoma 10 (BCL10), and *MALT1* have recently been shown to underlie SCID and CID with immunological and clinical phenotypes (17). The mutation in *MALT1* is associated with the absence of T cell activation, which in turn produces immature lymphocytes leading to SCID (18). The advent of next generation sequencing, especially whole exome sequencing has significantly facilitated the rapid identification of variants causing mutations (19). In the present study, we describe a newborn CID patient with mutation in the *MALT1* gene.

Case presentation

The patient was a five-month old Iranian girl, the second child of consanguineous parents. The first child in this family was a girl who expired five months after birth following similar symptoms to that of our patient. In addition, the cousins of the patient's mother also expired due to the same symptoms. Also, the grandson of the patient's aunt expired after having similar symptoms.

The first clinical manifestation started at the age of 10 days with a cutaneous rash and desquamation. The patient was hospitalized at once due to chronic diarrhea and received broad-spectrum antibiotics.

At 4 months of age, the BCG vaccine and recommended age-specific vaccines were not administered to the patient but she was given the oral polio vaccination (OPV). At the age of 5 months, the patient was suspected of having cellular immunodeficiency; therefore, the patient was referred to the Pediatrics Center of Excellence, Children's Medical Center, Tehran, Iran for further immunological and evolutionary tests. Laboratory and immunological findings at the date of diagnosis are presented in details in **Table 1**.

Table 1. Laboratory and immunological findings at date of diagnosis.

Parameters	Result	Normal Range
WBC	13800	6.0–17.5 (10 ³ /μl)
Lymph	30	47-77 %
PMN	65	15-45 %
Hb	17.1	11.3-14.1 (gr/dl)
PLT	398000	250-450 (10 ³ /μl)
CD3	76	30-78% Lymph
CD 4	74	22-58 % Lymph
CD 8	2	10-37 % Lymph
CD11a	100%	85-100% Lymph
CD11b	5%	25-35 % Lymph
CD11a	95%	>90 PMN+Mono
CD11b	59%	>90 % Lymph
CD18	97%	>90 PMN+Mono
CD 19	5%	9-38 % Lymph
CD4/ CD8	3.8	1-3 % Lymph
CD 16	11%	8-22 % Lymph
PHA	0	3.0≥
NBT	95%	>90 %

At the age of 5 months, the patient was diagnosed with combined immunodeficiency (CID), and genetic analysis was performed on her. Genetic evaluation confirmed molecular diagnosis of MALT1 deficiency due to a homozygous c.1454 A>G mutation that leads to an Asn485Ser in the caspase domain. At this age, the patient suffered from skin disorders. The blood culture of the patient was positive for *Staphylococcus epidermidis*. Skin biopsy revealed irregular acanthosis with neutrophil accumulation in the epidermis and also moderate Aspergillosis in the lower dermis. Seborrheic dermatitis was seen on the patient's epidermis. Unfortunately, the patient expired due to the erythroderma and lymphadenopathy at 6 months of age.

Discussion

SCID includes a broad spectrum of gene defects with an underlying susceptibility to bacterial, viral, and fungal infections with regular numbers or an absence of B and T lymphocytes and impaired humoral and cellular immunity. This disorder is marked by a lack of autologous T cells, even

while patients with CID have T cells (23, 24). Inborn defects of the CBM complex (CARD11/BCL-10/MALT1) can underlie CID, SCID, and other immunological phenotypes (25, 26).

Our awareness of *MALT1* is based on rare case reports previously recorded to date, which were characterized by the failure to thrive, inflammatory bowel disease, recurrent systemic infections, dermatitis, and other different features (27-30). The NF-κB plays a crucial role in the maintenance of innate and adaptive immune responses. Therefore, aberrant NF-κB activity due to *MALT1* deficiency may result in cancer, immunodeficiency, autoimmunity, severe immunological symptoms, as well as skin barrier and dysfunction of the epidermal differentiation.

In this manuscript, we report a female infant with a novel *MALT1* homozygous mutation (c.1454 A>G) who passed away due to erythroderma and lymphadenopathy at 6 months of age. Her clinical presentations were a cutaneous rash, desquamation, bacterial infections, irregular acanthosis, mononucleosis, along with erythroderma and lymphadenopathy. Some of these complications have been recorded previously among *MALT1* deficiency patients (15, 31). The patient's sister and cousin, who died from similar symptoms, probably suffered from the same defect. This case study explains the phenotype of the skin in *MALT1* deficiency. Although several publications were published on *MALT1* deficiency, the causes and mechanisms involved in the skin complications of these patients have only been reported in a few studies in the literature (29, 31-34).

It has been revealed that atopic-like dermatitis in aging *MALT1*-deficient mice may result from a reduction in the number and function of Tregs, which causes a disturbance in the normal immune homeostasis and leads to the activation of effector T cells and skin inflammation (34). Moreover, defect in T-cell activation by antigens increases the patients' susceptibility to opportunistic infections like *C. Albicans* and *cytomegalovirus*. Also, it has been reported that defective CARD11 has been seen in a

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patient with *Pneumocystis jiroveci* pneumonia and hypogammaglobulinemia; therefore our patient showed that host defense against pathogenic environmental factors may be affected by *MALT1* deficiency, indicating that the CBM complex can play the critical role in host defense (26, 27).

Surprisingly, a few phenotypes that can be found in *MALT1* deficiency (such as in viral infections, sinopulmonary infections, and atopy) can also be found in patients with dominant-negative CARD11 mutations. Thus, it is suggested that glutamine supplementation, which can repair the defects in patients with mutant cells, may be a treatment target for some of the *MALT1* deficiency symptoms (15, 35-37)

Conclusion

Overall, the clinical and immunological findings propose that *MALT1* deficiency results in autosomal recessive CID in humans. This case report gives a more detailed characterization of the histological and clinical skin phenotype of *MALT1* deficiency and a description of a new *MALT1*-deficiency-causing mutation. This novel immunodeficiency syndrome shows the significance of *MALT1* in the phenotype of disease and highlights the importance of screening for gene mutations in CID patients (26, 38, 39).

Conflicts of interest

The authors declare no conflicts of interest regarding this study.

Acknowledgment

The patient's legal guardians signed a written informed consent for the publication of this case report and its accompanying information.

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