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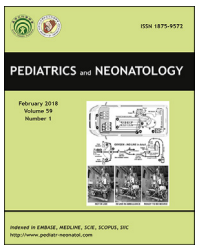

Short Communication

A case of severe combined immunodeficiency caused by adenosine deaminase deficiency with a new mutation

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1. Introduction

Adenosine deaminase (ADA) deficiency is among the most common causes of severe combined immunodeficiency, characterized by dysfunction of the T, B, and natural killer (NK) cells (T-B-NK-SCID) and severe lymphopenia.[1] ADA is a key enzyme in the purine salvage pathway, the absence of which causes lymph-toxic deoxyadenosine triphospate (dATP) accumulation, inhibiting ribonucleotide reductase, a critical enzyme for DNA replication and repair. This effect impairs the lymphocyte development and function resulting in severe combined immune deficiency (SCID).[1,2]

ADA deficiency is autosomal recessively inherited through mutations in the *ADA* gene, which is located on chromosome 20q13.12. Herein, we will describe the identification of a novel splicing mutation in the *ADA* gene in a patient with SCID.

2. Case presentation

A 3-month-old girl was referred for recurrent fever, pneumonia, diarrhea, chronic dermatitis, failure to thrive, and motor retardation. The patient was the daughter of consanguineous parents and had a female sibling who had died due to recurrent infections. On a physical examination, her weight, height, and head circumference were all less than the third percentile. She suffered from oral thrush and a diffuse brownish colored macular rash on the trunk. Chest auscultation revealed bilateral crackles at the lower zones. Chest X-ray, indicated the absence of thymus shadow; a para-cardiac infiltration and an inferolateral squaring scapulae were demonstrated (Fig. 1).

Laboratory tests revealed mild anemia with profound lymphocytopenia, and hypogammaglobulinemia (Supplementary Table 1). A lymphocyte subgroup analysis revealed a severe combined immunodeficiency. Purine nucleoside phosphorylase (PNP) and adenosine deaminase (ADA) enzyme activities were measured in the extracts of

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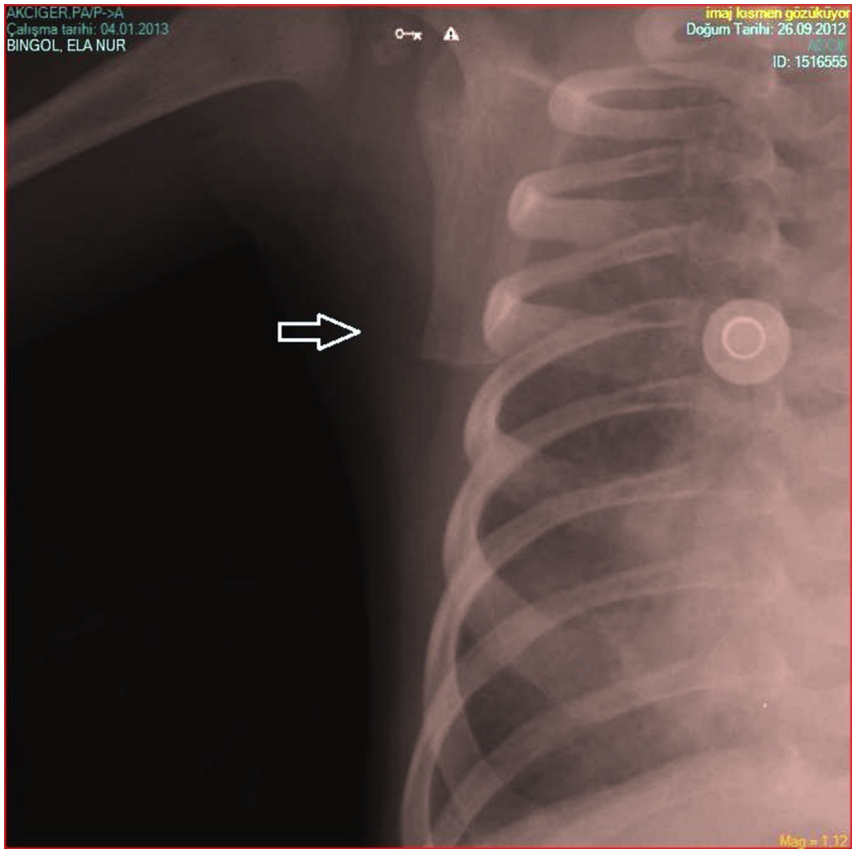

Figure 1 A chest X-ray indicating the absence of thymus and squaring scapulae, the mutation result of the patient.

dried blood spots on filter paper by a laboratory in the Duke University Medical Center in Durham, NC, USA. ADA activity was absent, whereas PNP activity was in the normal range. The total deoxyadenosine nucleotides (dAXP) in the erythrocytes were markedly elevated, confirming the diagnosis of ADA deficiency.

To define the mutation, genomic DNA was amplified, and the entire coding region, along with the exon-intron boundaries of the *ADA* gene, was sequenced. The patient was found to be homozygous for a point mutation c.478+3G>C, which causes an IVS5 splicing mutation (IVS5+3G>C) (Fig. 1). Her mother, father, and sister were carriers of this mutation, and her brother was wild-type (no mutation). To our knowledge, this is a novel mutation.

As she had no matched family donor, hematopoietic stem cell transplantation (HCT) was unavailable. Enzyme replacement therapy with polyethylene glycol-modified bovine ADA (PEG-ADA) was initiated. During the follow-up, the level of ADA activity significantly increased, and dAXP were almost normal.

3. Discussion

The prevalence of SCID is estimated to be approximately 1:50,000 live births in western countries,[1] whereas it is reported as 4:40,000 in Turkey.[3] The relatively higher prevalence of immunodeficiencies may be explained by the high rate of consanguineous marriages. T-B-NK+ is the most common type of SCID in our country, but the rate of ADA deficiency is only 4%.[3]

The disease is characterized by severe lymphopenia with low numbers of T, B, and NK cells. Although eosinophilia is a typical feature of Omenn syndrome, eosinophilia accompanied by absolute lymphopenia has also been reported, as in the present case.[4]

ADA-SCID patients suffer from recurrent infections, a failure to thrive, and neurologic manifestations. Extensive dermatitis, and persistent diarrhea can also develop. In individual patients it is often unclear whether an involvement of these organs is caused by the metabolic effects of ADA deficiency itself or if it is secondary to the immunodeficiency.

Patients may also have prominent metaphyseal changes that are suggested to be reversible by enzyme replacement therapy.[5] Our patient had a flaring of costochondral junctions. The skin rash of the patient was interpreted as a maternal engraftment syndrome that develops by a mechanism similar to a graft a versus host disease as a response to maternal lymphocytes.[6] However, maternal engraftment in patients with SCID due to ADA deficiency has not been directly documented.

More than 70 mutations of the ADA gene including missense, splicing, deletion and nonsense type have been described for ADA deficiency.[7] Our patient was homozygous for a 5′ splice site mutation in IVS5, which was

detected in other family members who were carriers. The consanguinity of parents and history of a similar sibling strongly suggest that both patients had the same immunological defect. The mutation in our patient appears to be novel.

HCST is the only curative treatment for patients with ADA deficiency. In the absence of an HLA, an identical donor enzyme replacement with PEG-ADA could provide a temporary solution, as in our case.

In conclusion, ADA deficiency is a medical emergency and should be suspected in every patient with lymphopenia. The diagnosis should be confirmed by the detection of low enzymatic activity, an elevated dAXP and a mutation analysis.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.pedneo.2016.10.008.

Abbreviations

ADA	Adenosine deaminase
dATP	deoxyadenosine triphospate
HCT	Hematopoietic stem cell transplantation
Ig	Immunoglobulin
NK	Natural killer
PNP	Purine nucleoside phosphorylase
SCID	Severe combined immunodeficiency