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CaseReport:

Undiagnosed Anemia after 9 years: Diamond-Blackfan (homozygous Variant c.140G>T; p.Gly47Val in ADA2 Gene)

Narges Obeidi[1], Zeynab Gharehdaghi[1*], GholamReza Fathpour[2], Mohadeseh Rostamipoor[1,3]

1. Department of Hematology, School of Para Medicine, Bushehr University of Medical Sciences, Bushehr, Iran
2. Hematology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
3. The Persian Gulf Marine Biotechnology Research Center, The Persian Gulf Biomedical Sciences Research Institute, Bushehr University of Medical Sciences, Bushehr, Iran

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*** Corresponding author:**

Zeynab Gharehdaghi, PhD.

Address: Department of Hematology, School of Para Medicine, Bushehr University of Medical Sciences, Bushehr, Iran

E-mail:
z.gharehdaghi1993@gmail.com

Abstract

Context: Diamond-Blackfan anemia (DBA) is a rare autosomal recessive disorder characterized by erythroblastopenia and pure red cell aplasia. The condition typically results from an abnormality in a ribosomal protein gene.

Case presentation: Cases of cytopenia have been linked to ADA2 deficiency caused by CECR1 mutations. In the current case study, a child presented with severe anemia requiring multiple RBC transfusions due to the condition going undiagnosed. After 8 years, the patient developed elevated ferritin levels, severe neutropenia, and a serious infection that complicated the clinical picture. Molecular analysis revealed homozygous variants (c.140G>T p.Gly47Val) in the ADA2 gene inherited from heterozygous parents.

Conclusion: This case represents the first documented instance in Iran, highlighting the importance of screening for congenital defects in seemingly healthy couples, especially emphasizing the need for prenatal diagnosis (PND) using molecular methods and genetic sequencing.

Keywords: Adenosin Deaminase 2, Hematopoiesis, Diamond-Blackfan anemia, Delayed diagnosis

1. Context

Diamond-Blackfan anemia (DBA) is an inherited bone marrow failure syndrome characterized by a rare congenital pure red cell aplasia. The incidence of anemia is estimated at 5-7 cases per million live births [1, 2]. Anemia symptoms typically manifest within the first year of an individual's life, particularly between 2-3 months [3]. It was marked by macrocytic RBCs, with less than 5% erythroid progenitors. Leukopoiesis and megakaryopoiesis are typically normal, but thrombocytopenia or thrombocytosis has been noted in some cases. [1]. Approximately 30-50% of individuals with DBA exhibit congenital physical abnormalities, with notable occurrences including cleft lip and palate, as well as malformations affecting the head, heart, neck, and urogenital regions. [4]. The incidence of neoplasia, including solid tumors, acute myeloid leukemia (AML), and myelodysplastic syndrome (MDS), was elevated. [5, 6]. Autosomal dominant mutations in RP genes were the most common mutations in DBA patients. Less frequent were other mutations in EPO, TSR2, CECR1, and GATA1 genes. [7]. Mutations in the CECR1 gene, which encodes ADA2, lead to Deficiency of Adenosine Deaminase 2 (DADA2). This loss of ADA2 function

was initially identified as a syndrome in 2014. [7]. Severe manifestations included stroke, immunodeficiency, autoimmunity, neutropenia, vasculopathy, liver and neurological disorders, and erythroid aplasia. [8, 9]. The study reported the case of a 10-year-old girl from Iran with the homozygous DBA variant c.140G>T; p.Gly47Val in the ADA2 gene for the first time.

2. Case presentation

A two-month-old infant was admitted to Zeynabie Hospital in Khormooj, Bushehr, Iran on June 7, 2012, presenting with symptoms of paleness, reluctance to feeding, and lethargy. Further examination revealed a low hemoglobin level of 3.6 g/dL and a reduced RBC count of 1.19 million/L as per Table 1,2, based on a complete blood count (CBC) test. Investigations indicated an absence of hemolysis. Unfortunately, there was no further investigation into the causes of severe anemia, and the child received RBC transfusions at irregular intervals (every 1-3 months) due to undiagnosed anemia.

Table 1. Laboratory Data of CBC in first visit

CBS	WBC	Neutrophil (%)	Lymphocyte (%)	RBC (x106/L)	Hb (g/dl)	Hematocrit (%)	MCV (fl)	MCH (pg)	MCHC (g/dl)	Platelet (x10³/L)
Result	6.7	21.7	72.0	1.19	3.6	10.0	84.0	30.3	36.0	882

Table 2. Laboratory Data in first visit

CRP	SGOT/ AST (U/l)	SGPT/ ALT (U/l)	ALP(U/l)
Negative	42	44	1427

After 8 years, she referred to a hematologist-oncologist with ferritin level of 5000 ug/L. Initially, desferrioxamine and desferal were prescribed by the physician due to elevated liver enzyme levels instead of exjade. Shortly after, she was hospitalized with fever, severe neutropenia, intense tenderness, and typhlitis. Treatment with antibiotics was initiated, during which she acquired an Aspergillus infection, necessitating a 3-month treatment. Further specific tests were conducted for a precise diagnosis after partial improvement. Noteworthy erythroid hypocellularity was noted in her bone marrow biopsy. Fanconi anemia was ruled out through chromosomal breakage analysis and a physical examination. Subsequently, molecular analysis and polymerase chain reaction (PCR) amplification were utilized by the physician, coupled with Sanger sequencing, to ascertain complete family genotypes. Sanger PCR revealed the presence of variant c.140G>T; p.Gly47Val in the ADA2 gene situated on chromosome 22/exon 1. This variant existed in a heterozygous state in both parents but was inherited homozygously by the child.

3. Discussion

Diamond-Blackfan anemia (DBA) is a rare autosomal recessive disorder characterized by a lack of red blood cell production leading to severe anemia due to low reticulocyte count. Patients with DBA also face an increased risk of cancer [10]. Treatment options include erythrocyte transfusions, glucocorticoids, and hematopoietic stem cell transplantation, with the latter being the most effective [11]. DBA is often associated with abnormalities in ribosomal protein genes. Mutations in CECR1 have been linked to vasculopathy and cytopenias due to ADA2 deficiency [12].

In the current report, the child was admitted to the hospital due to severe anemia. Subsequently, she received multiple RBC transfusions without determining the underlying cause of her anemia. Over the course of a few years, the situation became further complicated by severe neutropenia and a serious infection. At this time, molecular techniques facilitated the discovery of c.140G>T point mutations in the ADA2 gene among all family members, marking the first such instance in Iran. Furthermore, Garg et al. in 2014 documented the presence of the heterozygous variant p.Gly47Val in the ADA2 gene mutation in a child afflicted with fatal vasculopathy [13]. In the same year, Navan et al. reported the heterozygous variant in Turkish patients with Polyarteritis nodosa vasculopathy. Their study suggested the role of p.Gly47Val mutation in vasculitis, autoinflammation, immunodeficiency, and hematologic defects syndrome (VAIHS) [14]. The discovery showed a consistent autosomal recessive inheritance pattern. There is a 25% chance of the fetus being affected in each pregnancy if both parents carry the gene. Some individuals exhibit mild or even no symptoms of the disease. Consequently, asymptomatic parents can unknowingly pass on these mutations to their offspring due to misdiagnosis [10].

4. Conclusion

This was the initial report of variant c.140G>T; p.Gly47Val in the ADA2 gene in Iran. The case highlighted severe anemia and erythroblastopenia in the patient. PCR testing is essential for prompt and precise diagnosis. Furthermore, the research highlights the need for thorough screening for congenital abnormalities in seemingly healthy couples, especially emphasizing the importance of prenatal diagnosis (PND) using molecular techniques and gene sequencing.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of the Bushehr University of medical science (Code IR.BPUMS.REC.1402.271).

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Author's contributions

The authors equally contributed to preparing this article.

Conflict of interest

There is no conflict of interest in the manuscript.

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