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Case Report

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Allogeneic stem cell transplantation in a child with thalassemia major and severe factor V deficiency: Case report and review of the literature

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Abstract

Simultaneous occurrences of thalassemia and Factor V (FV) deficiency have been reported in only three cases to date. Of them, two with thalassemia intermedia and one with thalassemia trait were diagnosed. Mild to moderate FV deficiencies have also been described in these cases. Among them, only one underwent allogeneic stem cell transplantation (allo-SCT). No data were available about the outcome of allo-SCT. This is the first report of coexisting thalassemia major and severe FV deficiency in a child who was successfully treated with allo-SCT only for thalassemia major. Our experience with this case suggests that allo-SCT is well known curative treatment for patients with thalassemia major; however, it is not considered an effective treatment strategy for patients with severe FV deficiency.

Introduction

Thalassemia is the most known inherited hemoglobin disorder in Mediterranean countries including Turkey [1]. Patients with thalassemia major have several risks of chronic hemolytic anemia, splenomegaly, transfusional hemosiderosis, and bile duct stone if they are not performed allogeneic stem cell transplantation (allo-SCT) from a suitable donor. Allo-SCT is the only curative treatment for patients with thalassemia major today [2]. In contrast to thalassemia, severe factor V deficiency (FV) is a rare inherited coagulation disorder in the world. Fresh frozen plasma is used for serious bleeding episodes because specific factor concentrate has not existed for patients with severe FV deficiency yet [3]. According to the literature search, simultaneous occurrences of thalassemia and FV deficiency have been reported in only three cases to date [4,5].

We report the simultaneous occurrences of homozygous thalassemia major and severe FV deficiency in the same child who was treated with allo-SCT from an uncle with heterozygous FV deficiency.

Case Report

We presented a 10-year-old boy with thalassemia major who underwent allogeneic stem cell transplantation in another transplant center five years ago. He was referred to our center for circumcision. His hemoglobin (Hb) concentration 13.9g/dL, mean corpuscular volume (MCV) 88fL, reticulocyte 1.2% were normal ranged in our center. Hb electrophoresis (Hb F: 0.8%, Hb A2: 2.1%), Ferritin (mg/dl):229, Indirect bilirubin (mg/dl):0.3 and LDH (IU/L):211 were found to be normal. His prothrombin time (PT)[25.2 seconds (sec) (normal range between 10-14 sec)] and activated partial thromboplastin time (APTT) [68.5 seconds (sec) (normal range between 20-32 sec)] were prolonged before surgery. The severe FV deficiency for definitive diagnosis was firstly based on a specific FV assay (FV:C level below 0.9 U/dL). In his history, he had been successfully transplanted from an HLA-matched uncle donor with peripheral stem cell mobilization at 5 years old. He achieved full donor chimerism. Prolonged PT and APTT were also detected at the time of allo-SCT. His parents stated that fresh frozen plasma was used for catheter insertion before allo-SCT. However, detailed clinical and laboratory data were not available during allo-SCT. His parents were first-degree relatives, but they had a negative family history of thalassemia and FV deficiency. Thus, we have analyzed the patient's DNA extracted directly from a skin biopsy for thalassemia major and FV deficiency. Molecular genetic analyses revealed the homozygous variants in the HBB gene (NM000518.5); c.135del, (p. Phe46LefsTer16, the other name as codon 44) and FV gene (NM_000130.5); c.6304C>T (p. Arg2102Cys) in the patient. The variants in both genes were known pathogenic variants that have been previously described in the literature (PMID: 20301599, PMID: 31064749). His uncle was found to be asymptomatic heterozygous for the same FV genetic defect. His uncle's Hb concentration 17.1g/dL, MCV 91fL, reticulocyte 0.9% were normal ranged in our center. Hb electrophoresis (Hb F: 0.5%, Hb A2: 2.2%) was found to be normal. His PT [15.2 seconds (sec) (normal range between 10-14 sec)] and APTT [34.5 sec (normal range between 20-32 sec)] were slightly prolonged. His uncle's FV:C level was ranged between 30 and 50 U/dL. Circumcision was successfully performed with fresh frozen plasma and tranexamic acid in the patient. At the time of writing, the patient was well with full donor chimerism.

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Table 1. Summary of the previously reported cases and the presented case with Factor V deficiency who had thalassemia

Authors	Year	Patient age/ gender	Thalassemia phenotypes	Pretransplant clotting tests/ Patient FV level	Pretransplant Donor FV level	Allo-SCT	Thalassemia Outcome	Posttransplant clotting tests/ FV level
Giannini, *et al.* [4]	1998	Unknown	Trait	Unknown	-	-	-	-
Mourad, *et al.* [5]	2004	12 years/girl	Intermedia	21%	17%	Yes	ND	ND
Mourad, *et al.* [5]	2004	17 years/boy	Intermedia	18%	-	No	-	-
Present case	2022	10 years/boy	Major	Prolonged PT and APTT	30%- 50%.	Yes	Curative 100% chimerism	Prolonged PT and APTT/2%

Allo-SCT: Allogeneic stem cell transplantation; FV: Factor V; PT: Prothrombin time; APTT: Activated partial thromboplastin time; ND: Not described

Discussion

The simultaneous occurrences of inherited thalassemia and FV deficiency have been reported in only three cases to date [4,5]. Of them, only one underwent allo-SCT. However, the outcome of allo-SCT, as described in our case, has not been reported in this case [5]. Similar to our child, two of three cases were also children, but their thalassemia types were different from our case. The first reported case was diagnosed with the thalassemia trait and the remaining two siblings were diagnosed with thalassemia intermedia. As well, mild to moderate FV deficiencies have been reported in these cases in contrast to our case with severe FV deficiency [4,5] (Table 1). We presented the coexistence of thalassemia major and FV deficiency in a child who was successfully treated with allo-SCT only for thalassemia major.

The thalassemia major accompanying severe FV deficiency was a very rare condition, and complete chimerism was obtained for thalassemia major after allo-SCT, but stem cell transplant did not work to correct clotting abnormalities in our case. However, approximately 80% of FV was produced in the liver and the remaining 20% was stored in the alpha granule of megakaryocytes [3]. Thus, we were expected to increase in FV level after platelet engraftment due to the platelet-derived FV in allo-SCT, but we did not observe any changes in prolonged PT/ APTT with low FV level after allo-SCT. It could be related to the donor status who had a heterozygous FV genetic defect. In parallel with these data, Despain, *et al.* reported a case with severe FV deficiency diagnosed after circumcision in the neonatal period and developed recurrent intracranial hemorrhage at age 2 months and successfully treated with orthotopic liver transplantation at age 5 months [6]. FV is produced by the liver; thus, liver transplantation may be a good choice for refractory bleedings as in a previously reported case with severe FV deficiency [6]. A preclinical study has shown that healthy murine donor bone marrow-derived mononuclear or mesenchymal stromal cells which were expressed FVIII mRNA or FVIII protein have been used with variable success in hemophilic mice undergoing allo-SCT [7]. However, there are six cases with hemophilia A documenting FVIII activity after allo-SCT [8]. No alteration in factor VIII level after allo-SCT has been reported in most of these patients. It is speculated that allo-SCT may not correct properly clotting factor deficiency in patients with inherited coagulation disorders if it is not used in alternative cell types such as bone marrow-derived mononuclear cells and/or mesenchymal stromal cells [7]. However, our case was transplanted from an uncle with peripheral stem cell mobilization instead of bone marrow. These stem cell sources are important and need to be verified in future studies using bone marrow sources to address this issue.

Our experience with this case suggests that allo-SCT is well known curative treatment for patients with thalassemia major; however, it is not considered an effective treatment strategy for patients with severe FV deficiency.

Compliance with Ethical Standards

Conflicts of interest

The authors have no conflict of interests.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

Informed consent was obtained from patient and his parents.

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