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SEVERE HYPOCHROMIC MICROCYTIC ANEMIA IN A PATIENT WITH CONGENITAL ATRANSFERRINEMIA

Bibi Shahin Shamsian, MD □ *Department of Pediatric Hematology—Oncology, Mofid Children's Hospital, Shahid Beheshti Medical University, Tehran, Iran*

Nima Rezaei, MD □ *Growth and Development Research Center, Centers for Excellence for Pediatrics, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran*

Mohammad Taghi Arzanian, MD, Samin Alavi, MD, Omid Khojasteh, MD, and Aziz Eghbali, MD □ *Department of Pediatric Hematology—Oncology, Mofid Children's Hospital, Shahid Beheshti Medical University, Tehran, Iran*

□ *Congenital atransferrinemia or hypotransferrinemia is a very rare autosomal recessive disorder, characterized by a deficiency of transferrin, resulting in hypochromic, microcytic anemia and hemosiderosis. The authors describe a 10-year-old Iranian girl with hypochromic microcytic anemia. The age presentation of anemia was 3 months. Further evaluations indicate severe hypochromic microcytic anemia with decreased serum levels of iron, TIBC, and increased serum level of ferritin in this patient. The serum level of transferrin was decreased. The diagnosis of atransferrinemia was confirmed. Although atransferrinemia is a rare condition, it should be considered in the cases with hypochromic microcytic anemia, decreased serum levels of iron, TIBC, and increased serum level of ferritin.*

Keywords atransferrinemia, hemosiderosis, hypochromic microcytic anemia

Congenital atransferrinemia or hypotransferrinemia is a very rare autosomal recessive disorder, characterized by a deficiency of transferrin, resulting in a severe hypochromic, microcytic anemia in early infancy [1–4]. Mutations in the *TF* gene (3q21) have been associated with this condition, which result to defective expression of transferrin, decreased accessibility of iron to RBC precursors and at last hypochromic, microcytic anemia [1–4].

Clinical manifestations of atransferrinemia include pallor, anorexia, irritability, tachycardia, systolic murmer, and hepatomegaly [1, 3–5]. Some

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Address correspondence to Bibi Shahin Shamsian, MD, Department of Pediatric Hematology—Oncology, Mofid Children's Hospital, Shariati Avenue, Tehran, Iran. E-mail: Shamsianb@yahoo.com

affected patients could be complicated due to hemosiderosis, including hepatic fibrosis, cirrhosis, arrhythmias, congestive heart failure, and even death to heart failure. Endocrinopathies disorders such as diabetes mellitus, secondary hypopituitarianism, hypoparathyroidism, and hypothyroidism could be seen in some patients. Cutaneous darkening of the skin due to iron-stimulated melanin production may also have occurred [1, 3–5]. An increased numbers of infections appear in the affected patients [1].

To best of our knowledge, there is not any reported case with atransferrinemia in our country and the region. We here describe a patient who presented with gastroenteritis and anemia as a first manifestation, but further evaluations confirmed the diagnosis of atransferrinemia.

CASE REPORT

The patient is a 10-year-old girl from consanguineous parents. There was no history of any serious disorder in the family and she has a healthy 8-year sister. The first presenting manifestation of the patient was gastroenteritis, which occurred at the age of 3 months. Complete blood cell count (CBC) indicated severe anemia with hemoglobin (Hb) of 4 g/L at that time. Consequently, the patient was admitted to a medical center and blood transfusion was performed. As she continued to have anemia, she was referred to our referral center with severe pallor at the age of 6 months. CBC showed severe hypochromic microcytic anemia at the time of admission (Table 1), whereas CBC, Hb electrophorasis, and serum iron, total iron binding capacity (TIBC), and ferritin of her parents were normal. Study of bone marrow aspiration indicated an increased in erythroid series without any evidence of hemosiderosis pigments. Blood transfusion was performed and then supplementation of folic acid (1 mg/day) and ferrus sulfate (3 mg/kg/day), irrespective of laboratory findings were tried. After blood transfusion, her Hb increased to 9.8 g/dL (reticulocytes = 0.5%). Three months follow-up of the patient with treatment of ferrus sulfate and folate did not change the Hb level, and hypochromic microcytic anemia remained (Hb = 9.4 g/dL, MCV = 73 fL, MCH = 24 pg); so, ferrus sulfate was discontinued, but folic acid continued.

Subsequently, she was under follow-up; she received 3 transfusions until the age of 3, when her serum transferrin was 24 mg/dL (Table 1) and the diagnosis of atransferrinemia was made. Serum transferrin levels of parents were also measured and were subnormal: 109 mg/dL the in father and 169 mg/dL in the mother (normal range: 200–360 mg/dL). Continuing the therapy with folic acid was prescribed. Although she was advised to come in for regular follow-up, she came only irregularly for further visits. Mild to moderate anemia continued. The results of laboratory investigations at the age of 5 are shown in Table 1.

TABLE 1 Patient characteristics at different ages

	6 months	3 years	5 years	9 years
WBC (/mm^3)	5,700			4,500
PMN (%)	18			46
Lymphocyte (%)	78			54
Eosinophil (%)	4			
RBC (/mm^3)	2,230,000			2,620,000
Hb (g/dL)	5.3			4.5
MCV (fL)	71			61.8
MCH (pg)	23			17.2
Platelet (n/mm^3)	303,000			126,000
Reticulocyte (%)	0.5			0.3
Alanin amino transferase (u/L)	Normal			84
Aspartate amino transferase (u/L)	Normal			30
Bilirubin total(mg/dL)	Normal			0.9
Bilirubin direct(mg/dL)	Normal			0.2
Direct Coombs test	Negative			Negative
Indirect Coombs test	Negative			Negative
Hb electrophoresis	HbA = 96.7% HbF = 1.5% HbA2 = 1.8%			HbA = 96.7% HbF = 0.7% HbA2 = 2.5%
Serum iron (μg/dL)	Normal	17 (normal range: 50–120)	21 (normal range: 50–120)	18 (normal range: 35–155)
Total iron-binding capacity (μg/dL)	Normal	53 (normal range: 250–400)	81 (normal range: 250–400)	56 (normal range: 250–400)
Serum ferritin (ng/mL)	Normal	250 (normal range: 9–90)	837 (normal range: 9–90)	837 (normal range: 9–90)
Serum transferrin (mg/dL)		24 (normal range: 192–312)	10 (normal range: 200–360)	2 (normal range: 200–360)
Serum copper (μg)			120 (normal range: 78–131)	
Serum Zn (μg)			87 (normal range: 59–117)	
Bone marrow spiration	Erythroid hyperplagia		Erythroid hyperplasia	Normocellular active erythropoisis No hemosiderosis
Bone marrow biopsy	No hemosidero-sis			
Chest X-ray	Normal			Normal
Abdominal sonography	Normal			Mild splenomegaly

Finally, she was admitted to our hospital once again in April 2007, when she was 9 years old. She was very pale and had mild splenomegaly. She had mild upper respiratory tract infection about 1 week before visit. The results

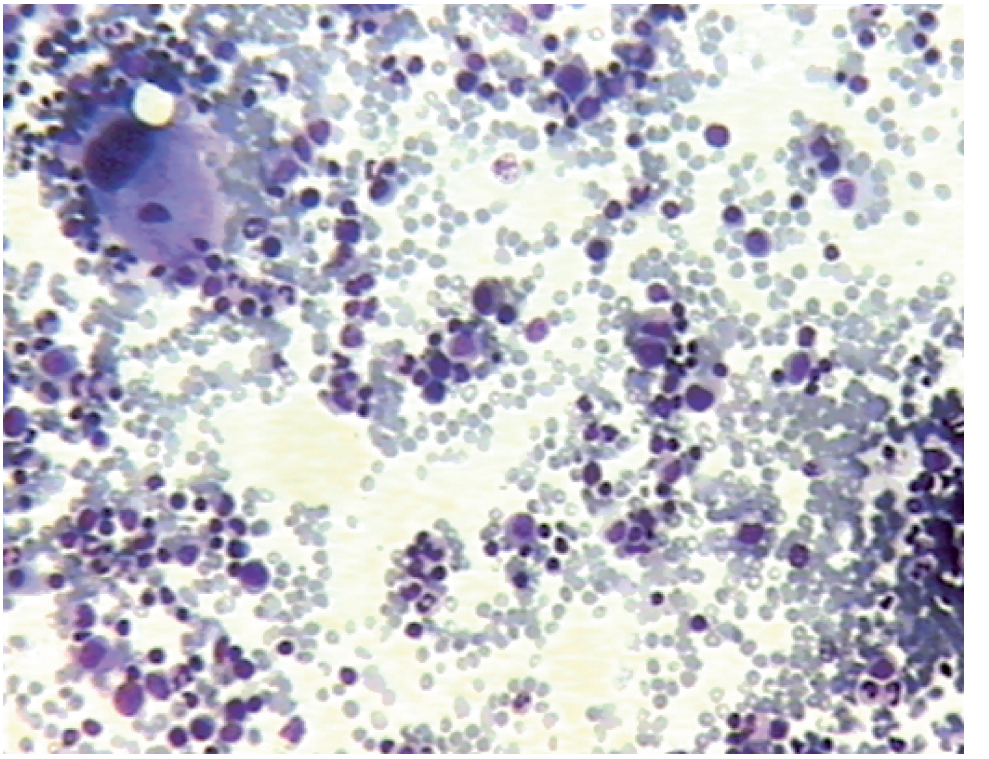

FIGURE 1 Increased erythroid series in bone marrow aspiration.

of laboratory investigations are shown in Table 1. Bone marrow aspiration and biopsy showed normal cellularity, while erythropoiesis was active without any evidence of hemosiderosis pigments (Figures 1 and 2). Because of past history of infection and splenomegaly, other evaluations were also done: HBs antigen, hepatitis C virus (HCV) Ab, HIV test, Epstein-Barr virus (EBV) IgG and IgM, and cytomegalovirus (CMV) IgG and IgM were negative. Echocardiographic study showed mild mitral valve prolapse (MVP) with normal left ventricular ejection fraction (LVEF). She was given two blood transfusions and discharged in good condition.

Since that time, she has been under regular follow-up. Magnetic resonance imaging (MRI T2*) was performed, which showed normal myocardial dimension (34.45 ms; normal myocardial T2* > 20 ms) with normal cardiac iron load. However, liver T2* was 1.65 ms (normal hepatic T2* > 6.3 ms) and moderate iron loading (8.53 mg/g/dw; normal <2 mg/g/dw). For treatment, human purified transferrin was not available for her. Becuase of increased level of serum ferritin (960 ng/mL), deferoxamine was prescribed, but unfortunately the patient did not use. Thus, iron chelator of oral deferiprone (L1) 50 mg/kg/day was started for her.

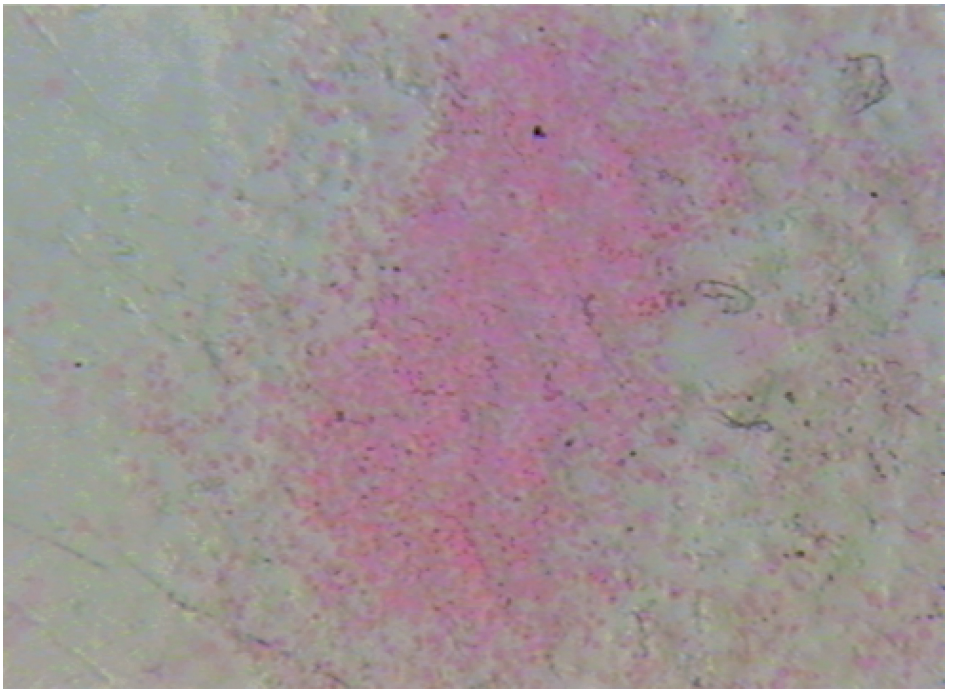

FIGURE 2 Prussian blue staining of bone marrow biopsy without any evidence of hemosiderosis.

Now she is good condition and has no organomegaly. The last laboratory test results were as follow: Hb = 9.7 g/dL, MCV = 71 fL, MCH = 22 pg, ferritin = 640 ng/mL. The results of second MRI T2* after 6 months of treatment with deferiprone (L1) was cardiac T2* of 22.53 ms (normal myocardial T2* > 20 ms) with normal cardiac iron load. Liver T2* was 1.54 ms and loading of 9.06 mg/g/dw (normal hepatic T2* > 6.3 ms and <2 mg/g/dw); thus, the hepatic iron load was moderate. Therefore, the dosage of deferiprone was increased.

DISCUSSION

Congenital atransferrinemia is characterized by abnormal synthesis of transferrin, a plasma protein that transports iron through the blood. Lack of transferrin synthesis leads to reduction of iron delivery to developing erythroid precursors in bone marrow, resulting in reduced hemoglobin synthesis, as well as iron storage in peripheral tissues (secondary hemochromatosis); therefore, hypochromic, microcytic anemia is one of the most important clinical signs of the disease [1–5].

Heilmeyer et al. described total absence of transferrin in a 7-year-old girl, who presented with severe hypochromic anemia. Death occurred from heart failure due to severe hemosiderosis of the heart [5]. Goya et al. described a

patient with low serum transferrin, who responded well to parenteral administration of transferrin [6]. Hayashi et al. restudied this family; the proband showed late onset of anemia and growth retardation and the patient was found to have a healthy brother and a sister with very low transferrin levels [7]. Supplementary therapy with apo-TF resulted in gradual disappearance of the anemia and improvement in growth. It seems that recovery from anemia and the resumption of growth were dependent on the transferrin level [7]. They suggested that the condition, termed "hypotransferrinemia," is a recessive trait and that the subjects with the recessive phenotype may be compound heterozygotes of a variant allele and a null allele [7].

Beutler et al. indicated that atransferrinemia had been reported in only 8 patients in 6 families till the year 2000. They reported the first known case in the United States and identified mutations in the *TF* gene [1].

Our patient is a 10-year old Iranian girl from consanguineous parents. Her first transferrin level was 24 mg/dL, the second one was 10 mg/dL, and the last one was less than 2 mg/dL. Except for a history of severe anemia and 3 blood transfusions from infancy until 3 years old, she has had moderate anemia. At her last visit, at the age of 10 years, she had severe hypochromic microcytic anemia, mild splenomegaly, and mild thrombocytopenia with history of recently respiratory infection. The severity of anemia and mild splenomegaly in this phase may be due to recent infection.

Infusion of fresh frozen plasma or human purified apotransferrin may stabilize or correct the anemia, but these treatments have only a transient effect [1, 3–5]. The 2 Japanese patients had been given highly purified apotransferrin intravenously with good effect and without the development of antitransferrin antibodies [8]. The infusion of either normal plasma or purified apotransferrin seems to have an effect in raising hemoglobin concentration in the 10–14 days follow-up [1]. Our patient is also under follow-up and a candidate for fresh frozen plasma and iron chelator therapy.

Although atransferrinemia is a rare condition, it should be considered in the cases with hypochromic microcytic anemia, decreased serum levels of iron, TIBC, and increased serum level of ferritin.

Declaration of Interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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