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Case Report Open Access

β-Thalassemia Intermedia with Immune Hemolysis during Pregnancy: A Report of Two Cases

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Abstract

Blood transfusion to treat β-Thalassemia Intermedia (BTI) during pregnancy carries a major risk of eliciting alloantibodies that cause hemolysis, which can progress to severe refractory hemolytic anemia. Moreover, autoimmune hemolytic anemia can develop either concurrently or shortly after alloimmunization induced by a blood transfusion. Here, the course and successful outcome of pregnancy is reported for two sisters with BTI who developed severe hemolysis following blood transfusion. Case 1 had heart failure at 31 weeks gestation necessitating a Caesarean section and splenectomy. She received rituximab and responded well. Case 2 was induced at 28 weeks of gestation due to non-reassuring fetal status. Neither case received blood transfusions early in childhood, which could have contributed to the severe alloimmune hemolysis observed when they received transfusions during pregnancy. However, both patients gave birth to viable offspring. The current case report is the first to describe both maternal and fetal outcome after an episode of immune hemolysis in pregnant BTI patients.

Keywords: Thalassemia intermedia; Hemolysis; Pregnancy; Alloantibodies; Blood transfusion

Introduction

The term 'β-Thalassemia Intermedia' (BTI) was first coined to describe patients showing clinical manifestations that were too severe to be termed 'β-thalassemia minor', but too mild to be termed 'β-thalassemia major' [1]. Consequently, BTI encompasses a wide spectrum of clinical phenotypes ranging from being symptomatic from as young as 2 years old to being asymptomatic until adulthood. The diagnosis of BTI has evolved significantly, and now involves both clinical and molecular analyses [2,3].

Women with BTI who have never been transfused or have had only minimal transfusions prior to pregnancy are at risk of severe alloimmune hemolytic anemia if transfusions are required during pregnancy [4-8]. Moreover, autoimmune hemolytic anemia can develop either concurrently or shortly after alloimmunization induced by a blood transfusion [9]. With a paucity of literature on this subject, management of immune hemolysis in BTI patients during pregnancy presents a significant challenge for the attending physician. This case report details the successful outcome of pregnancy in two sisters with BTI who developed severe immune hemolysis following blood transfusion during pregnancy.

Case 1

An Iranian female was diagnosed with BTI at the Dubai thalassemia center at the age of 9 years. She had experienced a severe hemolytic episode following a blood transfusion at the age of 12, which was treated with a short course of prednisolone and a further blood transfusion. Thereafter, her hemoglobin (Hb) levels remained stable at 8-10 g/dl.

At 22 years-of-age, she presented to the emergency room complaining of shortness of breath, fatigue, and dizziness. At this time the patient was primigravida at 25 weeks of gestation. She reported that, during a visit to Iran 1 week earlier, she had been transfused with two units of blood. She had no symptoms of infection during her pregnancy, and the only drugs she was taking were oral iron and multivitamins. On admission, the patient was afebrile but tachycardic, tachypnoic, pale, and deeply jaundiced. Her blood pressure was 110/60, with a grade 1/6 systolic murmur at the apex and no signs of cardiac failure. The liver and spleen were palpable 2 cm below the costal margin, and the uterus size corresponded with a gestation stage of 25 weeks. The hemoglobin level was 3.5 g/dl and the laboratory results were consistent with an acute hemolytic episode (Table 1, Case 1). The patient was typed as B Rh-positive, and an antibody screen with 11 cells on an ID-Dia Panel (Japan) showed a mixed reaction with a positive auto control. The patient had life-threatening anemia and required an urgent transfusion; therefore, after providing informed consent, she received 2 units of the least incompatible B Rh-positive pre-storage leukodepleted packed red blood cells (PRBC) and was treated with prednisolone (60 mg/day). Within the first 2 weeks she received 18 units of PRBC. Her Hb level remained at around 6 g/dl and she suffered congestive heart failure at Week 29 of gestation. Anti-heart failure therapy was started immediately and she received two doses of intravenous immunoglobulins (1 g/kg body weight/day), administered 1 week apart. The patient continued to show symptoms of refractory hemolytic anemia; therefore, a Caesarean section (CS) and splenectomy were performed at gestational Week 31. She delivered a live infant weighing 1140 g and, although she became hemodynamically stable, her Hb level remained at around 6 g/dl and she was still transfusion-dependent. Weekly intravenous infusions of rituximab (500 mg) were started at 1 week postpartum, which were continued for 4 weeks. At 4 weeks postpartum, her Hb returned to pre-gestational levels (8-10 g/dl) and no further transfusions were necessary. Anti-heart failure therapy was stopped at 8 weeks postpartum and the corticosteroids were tapered gradually before being withdrawn. Both mother and infant were alive and healthy 1 year later.

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	Case 1	Case 2
Hemoglobin, g/dl (lowest)	2.9	5.7
Reticulocytes (%)	2.8	5.6
Mean corpuscular volume (fL)	74	69
White blood cells ($\times 10^6$/L)	11.8	8.3
Platelets ($\times 10^3$/L)	196	224
Bilirubin, Total (mg/dL)	8.4	8.0
Bilirubin, Direct (mg/dL)	0.6	0.8
Coombs test, Direct	Positive	Positive
Coombs test, Indirect	Positive	Positive
Serum ferritin (ng/mL)	2123	435
Lactate dehydrogenase (U/L)	2874	834
Serum B12 and folate	Normal	Normal
Electrolytes, blood sugar, blood urea nitrogen, and creatinine	Normal	Normal
Anti-nuclear, anti-DNA, anti-smooth muscle, and anti-mitochondrial antibodies	Negative	Negative
Cytomegalovirus and Epstein-Barr virus (IgM, IgG)a	Negative	Not done
Mycoplasma antibodies	Positive, titer 1:80	Weak positive, titer 1:40
Hepatitis B virus, hepatitis C virus, and human immunodeficiency virus (HIV)	Negative	Negative
Blood type	B Rh-positive with negative C, E, K, Fy(a), and S antigens	B Rh-positive with anti-c antibodies
Hemoglobinuria	Positive	Positive

[a]IgM: immunoglobulin M; IgG: immunoglobulin G

Table 1: Laboratory workup of Cases 1 and 2.

Case 2

The patient was a 25-year-old Iranian female with BTI (Hb of 8-9 g/dl), who was the elder sister of Case 1. She had previously had two successful pregnancies and no abortions. Her first delivery was complicated by a hemolytic episode following a blood transfusion, which responded very quickly to a short course of prednisolone. She was not transfused during her second pregnancy, which progressed uneventfully to a normal full-term vaginal delivery. However, by week 20 of her third pregnancy she presented with symptoms of anemia (Hb, 6.5 g/dl). She was hospitalized by the obstetrician and transfused with three units of pre-storage leukodepleted PRBC. However, her Hb levels continued to drop (5.7 g/dl) and laboratory tests suggested acute hemolysis. The laboratory test results are summarized in the (Table 1, Case 2). The patient was treated with prednisolone (60 mg/day) and typed as B Rh-positive with anti-c antibodies. She then received 2 units of phenotypically-matched pre-storage leukodepleted PRBC. Although she improved clinically, she showed a non-reassuring fetal status and oligohydramnios at Week 28 of gestation, which prompted the induction of labor. She gave birth to a live infant weighing 1190 g. Postpartum, the patient's Hb returned to pre-gestational levels (8-10 g/dl). Prednisolone was withdrawn gradually and then stopped 3 months later. Both mother and infant were alive and healthy 1 year later.

Discussion

Pregnancy is rare among women with BTI [10,11] and is associated with both fetal and maternal complications. Maternal complications include preeclampsia, cardiac dysfunction, and immune hemolysis [4,11-18]. The largest published study of pregnancy in women with BTI shows that anemia is common; of the 44 pregnant women studied, transfusion was required in 35 (79.5%) women during pregnancy, with 27.3% requiring transfusion during pregnancy for the first time [12]. BTI patients who have never been transfused, or who have received only a minor transfusion, are at risk of developing severe alloimmune hemolytic anemia if they then receive a transfusion when pregnant [4,12,13,19,20]. The risks are reduced if transfusion therapy is initiated before the age of 12 months [2]. Other risk factors for alloimmunization include being female [21], being Rhesus negative [21], the use of a limited phenotype match rather than an extended phenotype-matching protocol [19,20,22,23], and prior splenectomy [21,22,24]. Splenectomized patients have higher alloantibody levels due to immune system stimulation by damaged RBCs in the absence of effective filtering via the spleen [22].

Neither of the two cases reported here received an early transfusion during childhood, which could have contributed to the severe alloimmune hemolysis that occurred after the transfusions during pregnancy. Although both cases had a complicated antepartum course and were ultimately delivered by CS or induced, both gave birth to viable offspring and recovered well postpartum. This is consistent with a previous study of pregnancy in patients with BTI, which found that more than 50% were able to tolerate vaginal delivery [13]. It is interesting to note that Case 1 in the present report did not show a good response to splenectomy, but did show a good response to rituximab treatment postpartum. It is unfortunate that she underwent a splenectomy, because this will increase the risk of developing alloimmune hemolysis in the future, making further management more difficult. Rituximab administration during the third trimester appears to be safe for the child [25]; therefore, rituximab (rather than splenectomy) could have been used to treat case 1. Further studies are warranted.

Five similar cases of immune hemolysis in pregnant BTI patients have been described [4,12,13]. Two cases from Lebanon also received a first transfusion during pregnancy, after which they developed alloantibodies and required repeated blood transfusions; however, neither patient was hemodynamically unstable and both required splenectomy (one at 31 weeks of gestation following a CS, and the other at 8 weeks postpartum) [12,13]. Of three similar cases reported in Italy, one received steroid therapy and had an induced abortion [4], the second experienced heart failure at 35 weeks of gestation and was delivered by CS, and the third was delivered by CS after non-reassuring fetal heart rate patterns were detected [4,12]. The latter two cases experienced a similar course to those in the present report (although Case 2 in the present study was successfully induced).

Conclusion

Blood transfusions lead to complications in pregnant BTI patients who receive their first transfusion later in life and, unless strongly indicated, it is best avoided. It is appropriate that these patients are managed in a high-risk pregnancy facility equipped with a neonatal intensive care unit. In addition, to increase the chances of a successful pregnancy, these patients should be under the joint care of a hematologist and an obstetrician from the start. Rituximab should be considered during the postpartum period; this may remove the need for splenectomy, which may increase the risk of alloimmunization in the future. However, due to the paucity of reported cases, evidence-based management of pregnant women with BTI will continue to be difficult.

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