www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2023;12(2):e120204
doi: 10.7363/120204
Received: 2022 Dec 13; revised: 2023 Apr 22; rerevised: 2023 May 05; accepted: 2023 May 18; published online: 2023 Aug 24

Case report

Severe neonatal anemia: looking at the whole picture

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Abstract

Neonatal anemia is an important cause of newborn morbimortality. Its causes fall into three categories: hemorrhagic, hemolytic or hypoplastic. Prompt recognition and acute care are crucial for good outcomes. Its etiological investigation is also essential to prevent further complications for the newborn and its mother.

We report a case of a full-term neonate born after an uneventful pregnancy of a mother with a significant medical history of ulcerative colitis under mesalazine treatment. He was delivered by an emergency c-section for a non-reassuring fetal status with an Apgar score of 5-8-9. Investigation revealed severe neonatal anemia with high reticulocyte count and a positive Kleihauer-Betke test. After an effective blood transfusion, he was discharged home under iron supplementation and later reevaluations showed normalization of blood parameters and regular growth and neurodevelopment.

Many causes of neonatal anemia have been described. The presence of fetal erythrocytes in maternal blood occurs in nearly all term pregnancies, but massive fetomaternal hemorrhage occurs only in 0.5% of cases. Active inflammatory bowel disease is also associated with adverse pregnancy outcomes and, in recent years, mesalazine, one of its main treatments, has been linked to neonatal anemia and hydrops fetalis. Regardless of the patient's clinical presentation and predicted anemia etiology, we highlight the importance of identifying and acting on further possible causes.

Keywords

Neonatology, anemia neonatorum, fetomaternal transfusion, inflammatory bowel diseases, mesalazine, drug-related side effects and adverse reactions.

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How to cite

Sousa Dias M, Meneses M, Viveiros C, Ferraz C, Noites P, Santos J. Severe neonatal anemia: looking at the whole picture. J Pediatr Neonat Individual Med. 2023;12(2):e120204. doi: 10.7363/120204.

Introduction

Neonatal anemia is an important cause of newborn morbimortality. Its causes fall into three categories: hemorrhagic, the most frequent; hemolytic; or hypoplastic [1].

Within the hemorrhagic causes, small fetomaternal hemorrhages are common events, occurring in nearly all term pregnancies, although large bleeds leading to neonatal anemia are rare. When there is no history of trauma, including the need for invasive pregnancy tests like amniocentesis, or evidence of placental abruption, this entity is classified as spontaneous. It can occur at any time during pregnancy, resulting in abortion, fetal demise, hydrops fetalis or fetal anemia. When it occurs in the third trimester, decreased or absent fetal movement is the most common symptom. Its diagnosis is made through the Kleihauer-Betke test and the prognosis depends on the rate and amount of blood loss [2].

Inside hemolytic and hypoplastic anemias, infections are the main relevant etiologies, but hemolysis can also occur through immunological mechanisms, drugs being one possible trigger [1]. In recent years, mesalazine, a well-established treatment for inflammatory bowel disease, has been linked to fetal anemia and hydrops fetalis [3, 4]. In adults, this drug is associated with hematological side effects such as aplastic anemia, hemolytic anemia, agranulocytosis, leukopenia and pancytopenia. It has been proved that mesalazine can be found in the umbilical cord at similar concentrations to maternal blood and in low concentrations in breast milk, although no correlation with worsened neonatal outcomes has been proved [5].

Case report

A 34-year-old G2P1A1 woman was admitted to the hospital for labor induction at 39 weeks of gestation. Her medical history was significant for a 7-year diagnosis of ulcerative colitis, under control with mesalazine 4 grams daily, which she kept during the whole pregnancy, and a vegetarian diet, for which she took oral multivitamins including iron and folic acid and cobalamin injections, with normal blood controls. The pregnancy was supervised and uneventful: her blood group was 0 Rh positive, third-trimester serologies had no signs of active infection and routine ultrasounds and cardiotocography evaluations were normal.

Due to a non-reassuring fetal status during cardiotocography monitoring, an emergency c-section was performed. A markedly pale, respiratory distressed and hypotonic baby boy was born, with an Apgar score of 5-8-9, at first, fifth and tenth minutes, respectively. After stabilization with positive pressure ventilatory support, he was admitted to the Neonatal Intensive Care Unit. Anthropometry was adequate to gestational age and physical examination showed a persistent pale appearance and a systolic murmur, with no other abnormalities.

Investigation revealed 5.3 g/dL hemoglobin normocytic normochromic anemia with 14.5% reticulocytes and 5.5% fetal hemoglobin in the mother's blood on the Kleihauer-Betke test, corresponding to 320 mL of fetal blood in the maternal circulation. Leucogram, platelet count, inflammatory markers and hemolysis parameters were normal, no blood group incompatibility was found, Coombs test was negative, there was not evidence of parvovirus, German measles, toxoplasmosis or cytomegalovirus infection and histopathological examination of the placenta showed no signs of abruption. A transfontanellar ultrasound was performed and was normal.

The infant underwent an effective 10 mL/kg blood transfusion, with a hemoglobin level rise to 11.3 g/dL, and remained hemodynamically stable without any other specialized care during his admission.

On day 5 of life, he was discharged home under 2 mg/kg/day iron supplementation. Later reevaluations until his first year of life showed normalization of blood parameters and regular growth and neurodevelopment.

Discussion

Many causes of neonatal anemia have been described. The presence of fetal erythrocytes in maternal blood is common, but massive fetomaternal

hemorrhage, defined as the loss of more than 150 mL of fetal blood, occurs in only 0.5% of cases. The cause for spontaneous fetomaternal hemorrhage remains mostly unknown and the episode is largely unpredictable because of the absence of specific symptoms. The rate and amount of blood loss will determine neonatal outcome and, at minimal antepartum suspicion, emergent cesarean birth is recommended to prevent any further deterioration in the fetal status. The amount of fetal blood in the maternal circulation can be calculated using the formula suggested by Salim et al. and the rate of blood loss can be estimated through the reticulocyte count [2]. In our case, the fetomaternal hemorrhage was massive but it must have occurred over a large period, as evidenced by the active bone marrow, hence the good neonatal outcome.

Active inflammatory bowel disease is associated with adverse pregnancy outcomes and mesalazine, one of its main maintenance treatments, has been considered safe during pregnancy and breastfeeding, albeit the growing number of reported cases of adverse maternal and fetal reactions [5]. Bokström et al. and Ek and Rosenborg reported two cases of fetal anemia and hydrops fetalis potentially related to 5-aminosalicylic acid drugs, the second having remitted after mesalazine discontinuation [3, 4]. Furthermore, Prieto et al. described a case of maternal thrombocytopenia which resolved after suspension of mesalazine and Levi et al. stated a case of reversible congenital neutropenia in a mother with Crohn's disease under sulphasalazine [6, 7].

Our case potentially illustrates neonatal anemia due to spontaneous massive fetomaternal hemorrhage induced by mesalazine. Although the determination of mesalazine level in the newborn's blood was not performed, fetomaternal hemorrhage was confirmed and other possible causes were excluded, leading to the suspicion of mesalazine as a possible major contributor to the anemia.

Regardless of the patient's predicted anemia etiology, we highlight the importance of identifying and acting on further possible causes. More studies regarding immunomodulating drugs' safety in pregnancy are needed and close cooperation between gastroenterologists, obstetricians and pediatricians is required in the management of pregnant women with inflammatory bowel disease.

Declaration of interest

The Authors declare that there is no conflict of interest.

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