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Late Hypoproliferative Anemia of Hemolytic Disease of Newborn (HDN) - Post Rhesus Isoimmunisation - A Case Report

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ABSTRACT

Introduction: Hemolytic disease of the fetus and newborn (HDFN) is caused by maternal IgG–mediated destruction of fetal erythrocytes, most commonly due to RhD incompatibility, and can present with a spectrum ranging from fetal anemia to neonatal hyperbilirubinemia. Late-onset anemia, a common complication, typically occurs between 2–6 weeks of age. We report a case of late onset hyporegenerative anemia secondary to Rhesus isoimmunization.

Case Description: A two-and-a-half-month-old female infant presented with progressively increasing pallor, initially noticed over the face subsequently involving the upper and lower extremities over a period of 3 days. She was born late preterm to an Rh-negative mother with isoimmunization and had required intrauterine transfusions, followed by postnatal phototherapy and IVIG for hyperbilirubinemia. On follow-up, she was found to have severe isolated anemia (Hb 5.5 g/dL) with reticulocytopenia and mild indirect hyperbilirubinemia, suggestive of late onset hyporegenerative anemia secondary to hemolytic disease of the newborn. A positive indirect Coombs test supported ongoing immune-mediated pathology. The infant was managed with packed red cell transfusions, showing hematological improvement on follow-up, and is under close monitoring.

Discussion: Hemolytic disease of the fetus and newborn (HDFN), most commonly due to RhD alloimmunization, results in immune-mediated destruction of fetal erythrocytes and may lead to complications ranging from fetal anemia to neonatal hyperbilirubinemia and kernicterus. Late-onset anemia is a frequent complication, particularly in infants who undergo intrauterine transfusions, typically presenting between 2–6 weeks of age and resolving by 3 months. It is classified into hyporegenerative and hemolytic types, with the former characterized by reduced erythropoiesis and low reticulocyte counts. Management of hyperbilirubinemia includes intensive phototherapy and exchange transfusion, while anemia is treated with packed red cell transfusions. Adjunct therapies such as erythropoietin and nutritional supplementation have limited and variable benefits. Close follow-up with serial hematological monitoring is essential to guide management and ensure recovery.

Conclusion: This case underscores the need for heightened awareness of late-onset hyporegenerative anaemia in infants with Rh isoimmunization. This atypical delayed presentation at 10 weeks highlights the variable clinical spectrum of late hyporegenerative anemia and the need for continued clinical suspicion beyond the usual age range. Bone

marrow aspiration is indicated in atypical neonatal anemia with persistent reticulocytopenia or suspected alternative marrow pathology.

Keywords: Hyporegenerative marrow, hemolytic disease of newborn, intrauterine transfusion

INTRODUCTION

Hemolytic disease of the fetus and newborn (HDFN) results from immune-mediated destruction of fetal and neonatal erythrocytes due to transplacental transfer of maternal IgG alloantibodies, most commonly against the RhD antigen. The pooled prevalence of maternal alloimmunization among antenatal women in India, as reported by Shastri et al., was 2.0 per 100 (95% CI: 1.5–2.5) (1). Following the introduction of anti-D prophylaxis in the United Kingdom in the 1970s, alloimmunization rates in at-risk pregnancies reduced from approximately 13–16% to 0.5–1.8% (2). Clinical severity ranges from fetal anaemia and hydrops fetalis to neonatal hyperbilirubinemia. Late-onset anaemia is a common complication. It typically presents between 2 and 6 weeks of age and resolves by 3 months. Two forms are recognised: hyporegenerative anaemia and hemolytic anaemia. Here we report a case of late-onset hyporegenerative anaemia of the newborn secondary to rhesus isoimmunisation.

CASE REPORT

A two-and-a-half-month-old female infant presented with progressively pallor, initially noticed over the face subsequently involving the upper and lower extremities over a period of 3 days. It was insidious in onset and gradually worsened during this period. There was no history of bleeding manifestations from any site, melena, or hematuria. There was no history of vomiting, abdominal distension, lethargy, decreased activity, fast breathing, facial puffiness, pedal edema, or abnormal body movements. There was no history of yellowish discoloration of urine, poor feeding, or reduced breastfeeding. The infant was exclusively breastfed, developmentally appropriate for age, and immunized up to 1.5 months according to the national immunization schedule.

The infant was the second child of a non-consanguineous marriage, born to an Rh-negative mother with Rh isoimmunization and an Rh-positive father. The baby was delivered late preterm at 35 + 2 weeks of gestation via lower segment caesarean section (LSCS) in view of previous LSCS, with a birth weight of 2.6 kg, and cried immediately after birth. Mother DCT was positive at 12 weeks of period of gestation (POG) with titres crossing critical value at 20-week POG after which fetal PSV was monitored which was > 1.5 MOM (multiple of median) at 29 week of period of gestation (POG) and hemoglobin less than 10g/dL requiring 3 blood transfusion at 29 week POG, 31week POG and 33 week POG after which the PSV was <1.5 MOM. After birth, serial monitoring revealed that the neonate's bilirubin levels exceeded the threshold for phototherapy; accordingly, the infant received 48 hours of phototherapy along with a single dose of IVIG for the management of hyperbilirubinemia. The baby was discharged. The parents were counselled regarding the elevated risk of complications in future pregnancies. This time, the child was noticed to have severe anaemia (haemoglobin 5.5 gm/dl) without other lineage affection. The child was worked up for the same, which revealed indirect hyperbilirubinemia (indirect bilirubin – 3.4 mg/dl), schistocytes of 1.6% with reticulocytopenia (corrected reticulocyte count- 0.22 %) and other markers of hemolysis being normal, which is suggestive of previous hemolysis and raises the possibility of Late hypoproliferative anaemia of HDN or Bone marrow suppression due to IVIG. ICT positive favours the former over the latter diagnosis. The child was transfused with two units of PRBC and planned for follow-

up for 3 months. Parents have been counselled about the condition and the need for top-up transfusion until 3 months of life, and the requirement for further evaluation if no resolution is observed after 3 months of life. A repeat complete blood count done after 10 weeks revealed an improved haemoglobin of 10.6 gm/dl, a schistocyte count of 0.6%, and a corrected reticulocyte count of 1.8% without transfusion support. All the important laboratory values are included in table 1.

Table 1: Important laboratory findings.

Parameter	On presentation	After 10 weeks
Hb	5.5 g/dL	10.6g/dl
Corrected retic count	0.22%	1.8%
Indirect bilirubin	3.4 mg/dL	1.1 mg/dl
ICT	Positive	Not available
DAT	Negative	Not available
LDH	355.8 U/L	230 U/L

DISCUSSION

Hemolytic disease of the fetus and newborn (HDFN) is characterised by immune-mediated destruction of fetal and neonatal erythrocytes due to transplacental transfer of maternal IgG alloantibodies (3). Maternal alloimmunization may occur against more than 50 erythrocyte antigens; however, the most severe cases are commonly associated with the Rhesus-D (RhD) antigen (4). Rh Isoimmunization may cause severe fetal and neonatal complications due to immune-mediated hemolysis, including fetal anemia, hydrops fetalis, and intrauterine fetal demise, severe hyperbilirubinemia, kernicterus, respiratory distress, and long-term neurodevelopmental impairment. Late-onset anaemia, defined as anaemia developing after the first week of life, is a well-recognised complication of RhD-associated HDFN. It has been reported in up to 83% of affected neonates, with the highest incidence observed among those who undergo intrauterine transfusions (5). This form of anaemia typically manifests between 2 and 6 weeks of age and generally resolves by 3 months (5).

Two main subtypes of late-onset anaemia are described: late hyporegenerative anaemia and late hemolytic anaemia. Late hyporegenerative anaemia is characterised by ineffective erythropoiesis, reflected by low or absent reticulocyte counts and normal bilirubin levels. Usual age of presentation is 2- 6 weeks of age (6). In our case, the child was presented at 10 weeks of age. Proposed mechanisms include antibody-mediated intramedullary destruction of erythroid precursors, suppression of bone marrow activity following intrauterine or postnatal transfusions, and relative erythropoietin deficiency, reduced survival of transfused erythrocytes, and relative anaemia resulting from expansion of intravascular volume during neonatal growth, although the exact pathogenesis remains incompletely understood (7). In contrast, late hemolytic anaemia is associated with ongoing peripheral red cell destruction, characterised by elevated reticulocyte counts and increased bilirubin levels, indicating active bone marrow compensation (7).

Management of neonatal hyperbilirubinemia in HDFN primarily involves intensive phototherapy, using high spectral irradiance and maximal body surface exposure, alongside adequate fluid supplementation to enhance bilirubin elimination. Exchange transfusion remains the definitive therapy for severe cases by reducing bilirubin levels and removing antibody-coated erythrocytes and circulating maternal antibodies. Also study conducted by Al-Alaiyan et al. reported that IVIg administration did not result in a statistically significant reduction in the incidence of late hyporegenerative anaemia or the requirement for top-up blood transfusions, and thus, routine use of IVIg in

the management of HDFN cannot be recommended (8).

The primary treatment for anaemia in HDFN is the administration of packed red blood cells, known as a top-up transfusion. Intrauterine transfusions (IUTs) are associated with an increased risk of postnatal anaemia (9). The exact mechanism remains unclear; however, it is likely related to suppression of erythropoiesis (9). To enhance erythropoiesis, the administration of EPO, folate, iron, and vitamin E has been shown to benefit the treatment of anaemia in HDFN (10). Recombinant human erythropoietin (rhEPO) has been evaluated in small studies and case reports, showing variable effects on the development of anaemia and the requirement for top-up transfusions in neonates with hemolytic disease of the fetus and newborn (HDFN). However, given the limited clinical significance of the reported benefits, its routine use is not currently recommended (11).

In our case, late hyporegenerative anaemia was identified as the primary cause of anaemia. This form of anaemia may persist for several weeks after birth. Affected infants require close monitoring for clinical signs of persistent anaemia, as reticulocyte production from the fetal bone marrow may be reduced, and other hematopoietic cell lines, such as neutrophils, can also be involved. Serial weekly assessment of reticulocyte count and hematocrit can guide transfusion decisions and provide reassurance of hematopoietic recovery (12).

However, bone marrow aspiration may be considered in selected cases where the clinical course is atypical, when alternative etiologies such as inherited bone marrow failure syndromes, marrow infiltration disorders, congenital infections, or aplastic conditions of neonatal anaemia are suspected, or when anaemia and reticulocytopenia persist despite poor response to standard supportive management.

CONCLUSION

This case underscores the need for heightened awareness of late-onset hyporegenerative anaemia in infants with Rh isoimmunization. This delayed presentation highlights the variability in clinical manifestation and suggests that clinicians should maintain a high index of suspicion for hyporegenerative anemia even beyond the conventional age window, particularly in infants with persistent anemia and suppressed reticulocyte response. The diagnosis is generally established based on clinical history, evidence of maternal alloimmunization, a positive direct antiglobulin test (DAT), prior history of hemolytic disease, and characteristic laboratory findings of anaemia with reticulocytopenia. In most cases, the condition is transient and results from the temporary suppression of erythropoiesis following immune-mediated hemolysis and prior transfusions; therefore, structured follow-up protocols are essential to ensure early diagnosis and appropriate management, thereby preventing complications associated with severe anaemia. Bone marrow aspiration may be reserved for atypical neonatal anaemia cases with persistent anaemia and reticulocytopenia or when alternative etiologies such as marrow failure syndromes, congenital infections, or infiltrative disorders are suspected.

Declaration by Authors

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