

CASE REPORT

Infantile pyknocytosis, a rare cause of hemolytic anemia in newborns: report of two cases in twin girls and literature overview

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Introduction

Hemolytic disease of the newborn has several generally well-known causes. Among them, Rhesus incompatibility, ABO factors incompatibility, and red cell enzymatic defects, such as G6PD, pyruvate kinase deficiencies and red blood cell spectrine defects, are the most common. In rare cases, hemolysis may be due to antigens such as c, E, Kell, and Duffy. Infections (e.g. CMV, toxoplasmosis, rubella, syphilis) may also present with jaundice, hemolytic anemia and hepatosplenomegaly, but with a negative Coombs test. In a study by Palmer et al. [1], the incidence of jaundice was reported to be 10.7%, and the most common etiological factors were prematurity (19.9%), ABO erythroblastosis (7.1%), sepsis (3.4%), Rhesus erythroblastosis (2.7%), bruising (2.2%), multifactorial (1.0%), and G6PD deficiency (0.5%). Similar results were reported 10 years later by Guaran et al. [2]. Among the lesser known causes is infantile pyknocytosis, a rare but not exceptional cause of early neonatal jaundice that is

Key Clinical Message

Infantile pyknocytosis is a rare cause of neonatal jaundice and hemolytic anemia. We report on two cases in twin girls that were diagnosed on peripheral blood smear reading. Pyknocytosis should be considered in cases of early unexplained severe hemolytic anemia, and systematic peripheral smear review performed. Its management consists of phototherapy and RBC transfusion.

Keywords

Early jaundice, etiologies, hemolytic anemia, neonates, pyknocytosis.

associated with transient neonatal hemolytic anemia, and whose management may require one or several packed red blood cells transfusions. This condition was first described by Tuffy et al. [3] in 1959 after they discovered peculiar red blood cells with irregular margins and rare short projections, which they called pyknocytes, on peripheral blood smear analysis.

We report two new cases to emphasize that clinicians should include infantile pyknocytosis in the differential diagnosis of hemolytic anemia, especially in cases with unclear etiology.

Patients & Methods

This is a retrospective review of the medical records of two twin sisters who were hospitalized in our Neonatal Medicine Unit in 2011 for persistent early jaundice, associated with hemolytic anemia. Both infants were products of bi-chorionic, bi-amniotic twin pregnancy following ovarian stimulation. They were delivered by cesarean

section at 36 weeks gestation and adapted well to the extra-uterine environment, with Apgar scores of 9 and 10 (first and fifth minutes of life, respectively). Birth weights were 2840 g (twin 1) and 2800 g (twin 2). Early postnatal life was marked by rapid-onset jaundice managed favorably with phototherapy. Both infants were discharged on postnatal day 5, with normal bilirubin levels (140 $\mu\text{mol/L}$ (8.18 mg/dL) for T1, and 152 $\mu\text{mol/L}$ (9 mg/dL) for T2) on mixed feeding (breast and bottle). The parents were of Algerian origin and were not consanguineous. The mother was 39 years of age and had experienced several spontaneous abortions, and neither parent had a past history of jaundice, blood transfusion, splenomegaly, cholelithiasis, or other related conditions.

History of Illness

Case 1

Twin 2 was brought to us at 15 days old for persisting jaundice and poor feeding. Upon clinical examination, a diagnosis of jaundice was confirmed: she looked pale, her cardiac and pulmonary functions were unremarkable, and she had no hepato-splenomegaly. Weight gain since birth was poor (+20 g since discharge), and her remaining vital functions were unremarkable. Her initial blood tests showed a total bilirubin level of 265 $\mu\text{mol/L}$ [15.5 mg/dL; conjugated 8 $\mu\text{mol/L}$ (0.47 mg/dL)], with severe anemia (hemoglobin 5.5 g/dL, hematocrit 18%, reticulocytes count 22.6% (384,000/ mm^3), MCV 105 fl, and low haptoglobin (<0.15).

Additional blood tests showed the following: absence of blood group incompatibility in ABO and Rhesus systems (baby O Rh (+), mother A Rh (+), negative Coombs, and elution tests. Thyroid and liver function tests and G6PD activity were within normal ranges, and urinalysis was unremarkable. Blood smear review (by Dr. Picard at Kremlin Bicêtre Hospital, Paris) revealed numerous pyknocytes (Fig. 1); unfortunately ektacytometry (method for measuring red blood cell deformability) could not be performed as the baby had been given an emergency blood transfusion.

Posttransfusion control, the hemoglobin level was stable (12 g/dL) 3 days later, and phototherapy was maintained for 72 h. A few days after admission, the child presented with pustular skin lesions compatible with cutaneous staphylococcal infection (treated with local antibiotics). She fully recovered and was discharged. Control hemoglobin a month after discharge was 9.3 g/dL.

Case 2

Twin 1, a 21-day-old was admitted for skin lesions similar to those presented earlier by her sister, and for which she also received local antibiotics. A diagnosis of jaundice was confirmed, with unremarkable physical examination. Routine blood tests showed a hemoglobin level of 12 g/dL, white blood count 17,710/ mm^3 , platelets count 450,000/ mm^3 , reticulocytes count 61,200/ mm^3 , total bilirubin 122 $\mu\text{mol/L}$ [7.13 mg/dL; conjugated 5 $\mu\text{mol/L}$ (0.30 mg/dL)], normal blood urea and electrolytes, and negative C-reactive protein (<1 mg/L). Peripheral blood

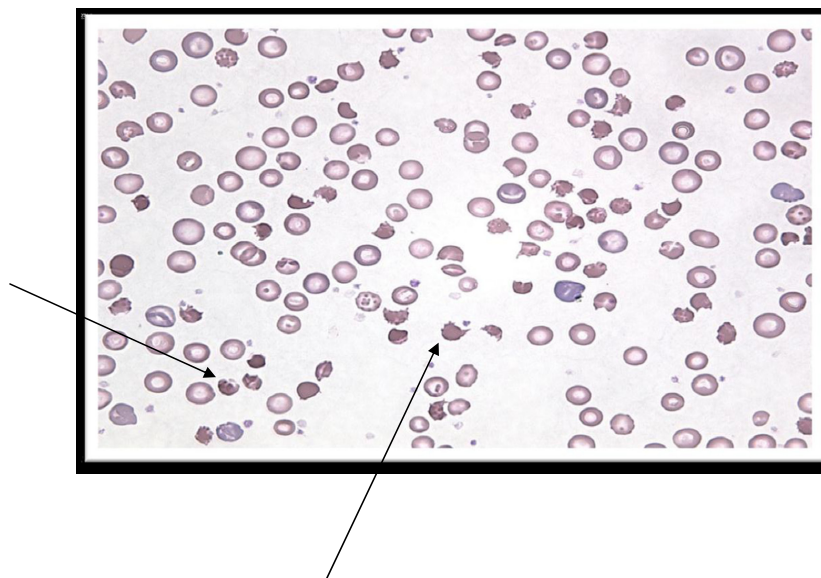


Figure 1. Blood smear film of twin 2 showing numerous pyknocytes.

smear and ektacytometry tests, prior to RBCs transfusion, supported pyknocytosis with hyper dense cells in excess (11%). The reticulocytes count was 144,000/mm³, hemoglobin level was 8 g/dL, and MCV was 107 fl. Coombs test, erythrocytes assays for G6PD, pyruvate kinase enzymes, liver and thyroid function tests, and urinalysis were all normal. Both parents' blood tests revealed no abnormality (normal hemoglobin levels and erythrocytes count, normal haptoglobin levels). The child's jaundice progressively intensified [total bilirubin 263 μ mol/L (15.4 mg/dL)] and was associated with severe hemolytic anemia (Hb 6.6 g/dL), requiring phototherapy and packed red cell transfusion. This child fully recovered, and control hemoglobin and ektacytometry were both normal 3 months after the acute phase.

Discussion

Infantile pyknocytosis is a neonatal syndrome first described by Tuffy *et al.* [3] in 1959 in a case series of term newborns. Since this report, only 55 other cases, including ours have been reported [3, 4]. Although this condition is rare, Eyssette-Gerreau *et al.* [5] have reported that the diagnosis was made in 14 of 149 children (9.4%) referred for hemolytic anemia of unknown cause. Gender distribution shows a male predominance with a ratio of 2:1.

The etiology of infantile pyknocytosis remains unknown. However, the underlying cause could be an extra corpuscular factor that is yet to be identified. This hypothesis is plausible, considering research by Ackerman *et al.* [6], who showed transfused red blood cells being converted into pyknocytes during an exchange transfusion in two patients. In another experiment, Kulapongs *et al.* [7] incubated normal red blood cells with a patient's plasma and observed the transformation of normal cells into pyknocytes. An increase in the percentage of hyperdense cells (3–15%) on the peripheral blood smear during pyknocytosis reflects the existence of some cellular dehydration and the probable presence of oxidative stress. Our cases have two unexplained particularities: first, the occurrence in twin children, and secondly, a maternal history of unexplained miscarriages. The probability of inheritance has previously been suggested by Limme *et al.* [8] in a study of five children, in two of whom pyknocytosis had been diagnosed within the same family in association with a past history of several miscarriages in two mothers. In another 1983 report, Maxwell *et al.* [9] described cases of pyknocytosis with intrauterine hemolysis in two brothers. These reports strongly lead us to speculate on the probable existence of familial susceptibility or a hereditary factor, which may promote the occurrence of this affliction under certain circumstances.

Whether the supposed triggering factor is environmentally acquired (bacteria or virus) or intrinsic remains to be determined.

Clinically, the first sign of infantile pyknocytosis is early jaundice, which occurs within the first 48 h of life, consisting of unbound bilirubin with maximum mean indirect bilirubinemia of 255 μ mol/L (25–500 μ mol/L), requiring intensive phototherapy in most cases. Cases resistant to phototherapy, and thus requiring exchange transfusion, have also been reported [3].

The second clinical sign of this condition is severe hemolytic anemia, which may occur between the second and fourth weeks of postnatal life and is characterized by a low hemoglobin level (below 8.0 g/dL), hyperleukocytosis (not constant), low haptoglobin level and increased plasma LDH level. Other biological abnormalities, such as minimal increase in leukocytes count along with moderately increased liver enzymes, may also be present [10]. Physical examination does not contribute to the diagnosis. The absence of splenomegaly in affected infants suggests that the spleen does not play a pivotal role in red blood cells destruction and strongly supports the hypothesis that hemolysis could be induced by an independent factor (genetic or environmental), that is yet to be discovered. Infantile pyknocytosis is diagnosed only by careful analysis of peripheral blood smear, which reveals numerous small irregular and contracted red blood cells with hyper-dense spikes (the pyknocytes), that progressively increase in number to peak at approximately 3–6 weeks postnatal age, and then spontaneously disappear (at an average age of 4–6 months).

Notably, however, 5.6% (0.3–5.6%) of physiologically preterm infants may present with pyknocytes within their first weeks of life. In term infants, these abnormal cells can be seen in 0.3 to 1.9% of cases (3). Similar red blood cell morphology has also been reported in conditions, such as heat stroke in adults, elliptocytosis, and neonatal anemia, due to vitamin E, G6PD, and pyruvate kinase deficiencies in both humans and horses [5, 10]. Infantile pyknocytosis should be added to the differential diagnosis of hemolytic jaundice in newborn infants, especially in those cases with no splenomegaly or negative history of infection and after the elimination of known common causes.

The management of infantile pyknocytosis is mainly supportive, and while a single red blood cells transfusion (15 mL/kg) may be sufficient (our cases), several blood transfusions may be necessary. In a recent study, recombinant erythropoietin was used (dose of 1000 UI/kg per week) in association with oral iron therapy to manage persisting anemia despite several blood transfusions in two infants [11]. Although the latter modality had no side effects, it remains preliminary, and more studies are

needed before its generalization. The long-term prognosis of this condition is favorable and self-limiting, with no recurrence reported so far. Rare cases of death, possibly related to incomplete medical support, have been reported [12]. Fatal outcome secondary to pulmonary hypertension due to or aggravated by very severe hemolytic anemia has also been reported [13]. Early recognition of this condition and its appropriate management can be life-saving and are of utmost importance.

Conclusion

Infantile pyknocytosis is a rare neonatal condition that needs to be considered in a child with precocious jaundice that becomes rapidly associated with severe hemolytic anemia. A high level of suspicion remains the only way to confirm this diagnosis. Routine peripheral blood smear review in all cases of hemolytic jaundice is warranted, as this would assist in the early diagnosis of this condition. The management of infantile pyknocytosis consists of phototherapy for jaundice and correction of anemia by packed red blood cells transfusion. The overall outcome is favorable in a large majority of cases.

Conflict of Interest

None declared.

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