

Infantile pyknocytosis: effectiveness of erythropoietin treatment

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Abstract

Infantile pyknocytosis is a rare form of neonatal haemolytic anaemia with unusual red cell morphology. Anaemia is mostly severe and red blood cells transfusion is often needed. In this report, we have described a male child aged 10 days, born at 37 weeks + 3 days, who presented neonatal jaundice and severe anaemia. After a careful peripheral blood smear examination, infantile pyknocytosis was diagnosed. A treatment with recombinant subcutaneous erythropoietin (1,000 UI/prokg/week) in conjunction with iron supplementation (6 mg/kg/day) was started. The therapy was reduced 6 weeks after the beginning and discontinued 4 weeks after the reaching of a steady state of the haemoglobin values. After 12 months of follow up, the patient showed no anaemia and pyknocytosis.

Keywords

Haemolytic anaemia, jaundice, pyknocytosis, recombinant erythropoietin, newborn, infant.

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Introduction

In 1959, for the first time Tuffy et al. described haemolytic anaemia in early infancy associated with an increased number of pyknocytes. These cells were distorted, irregular erythrocyte that stained densely on peripheral blood smear [1]. Little has been written about the above mentioned disorder since

the initial report and the cause of this pathology has not been fully understood yet [2]. This form of anaemia has generally been considered a rare disease; however, a recent retrospective study stated that infantile pyknocytosis represents about 9% of unexplained neonatal anaemias [3]. We described a newborn with infantile pyknocytosis who underwent a treatment with recombinant erythropoietin (rHu-Epo), resulting in an improvement in the clinical and haematological status, thus preventing further transfusion.

Case

A 10 day old male newborn was admitted to our Paediatric Department because of the appearance of jaundiced complexion. He was born at 37 weeks + 3 days by caesarean section for non-reassuring cardiotocographic trace and oligoidramnios, after a reported uncomplicated pregnancy. Family history was negative for haematological diseases. Birth weight was 2,650 g; APGAR score 9-10. He was discharged from the nursery at the age of 3 days with exclusive breast feeding on demand. The patient serum bilirubin level at the age of 5 days was 12.9 mg/dl.

On admission (age 10 days) the patient appeared pale and icteric, the cardio-respiratory objectivity was normal; there was no organomegaly. Total bilirubin level was 28.5 mg/dl.

Laboratory tests showed a hematocrit (Ht) of 35%, with a red blood cells (RBCs) count of 3,380,000/ml, haemoglobin (Hb) level of 11.7 g/dl; liver and renal tests were within normal range. The child's blood type was 0 +, and his mother's 0 +. The patient underwent phototherapy but, at the following controls, bilirubin levels remained between 17-23 mg/dl. Coombs test, glucose-6-phosphatedehydrogenase activity, haemoglobin electrophoresis, osmotic fragility test, liver and renal function tests, levels of lactate dehydrogenase, piruvate kinase, thyroxine, thyroid-stimulating hormone were normal. Haptoglobin was 0.08 g/l. Pyknocytes weren't found in the first peripheral blood smear performed. Cerebral and abdominal ultrasonography appeared normal. On the third day of hospitalization, Ht levels decreased to 30%, with a RBCs count of 2,900,000/ml, reticulocyte count of 3.5% and Hb 9.7 g/dl. During the following days, laboratory tests worsened: Hb value dropped to 6.1 g/dl, with Ht levels at 18%, a RBCs count of 1,700,000/ml, reticulocyte of 1.5% and a total bilirubin level of 21 mg/dl.

A new peripheral blood smear was performed and the patient was transferred to a 1st level haematology centre, where he was transfused for severe anaemia. Transfusion of packed RBCs gave no results and the following controls showed a slow and progressive anaemia with a Ht of 26.5%, Hb level of 8.4 g/dl, and a reticulocyte count of 13.2%. His serum bilirubin level was 5.93 mg/dl. The second peripheral pre-transfusion blood smear highlighted several distorted, irregular, small RBCs, and infantile pyknocytosis was finally diagnosed (**Fig. 1**). After the informed consent of the child's parents, the patient started hormone therapy with recombinant subcutaneous erythropoietin (rHu-Epo) (1,000 UI/kg/week) in conjunction with iron supplementation (6 mg/kg/day). The total Erythropoietin (rHu-Epo) dose of 1,000 UI/kg/week was divided into two doses a week according to literature studies [4]. Due to the increasing trend of the Hb level (9.0 g/dl) and reticulocyte count (4.4%), the infant was discharged and included in a follow-up program. Gradually, a satisfactory plateau in Hb values was observed: after 6 weeks, Hb = 11.2 g/dl and reticulocyte count = 3.7%; at 10 weeks, Hb = 11.5 g/dl and reticulocyte count = 3%. Therapy was reduced 6 weeks after and discontinued after other 4 weeks, due to the reaching of a steady-state (**Fig. 2**). No side effects were observed. In addition, no further transfusion support was necessary. At 12 months of age, the Hb level and the reticulocyte count were into the normal range and the patient seemed to have fully recovered.

Discussion

Infantile pyknocytosis is a rare form of neonatal anaemia. Little is known about its aetiology,

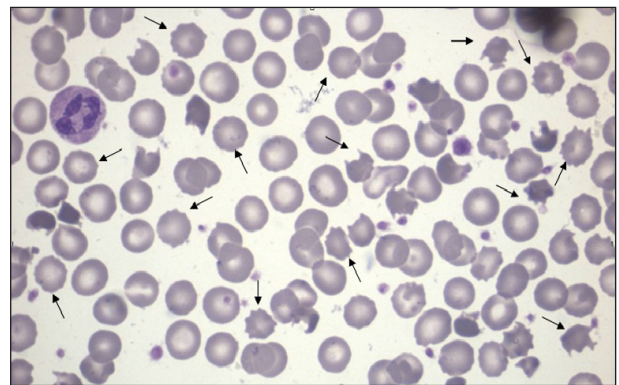


Figure 1. The second pre-transfusion peripheral blood smear. Arrows show numerous pyknocytes.

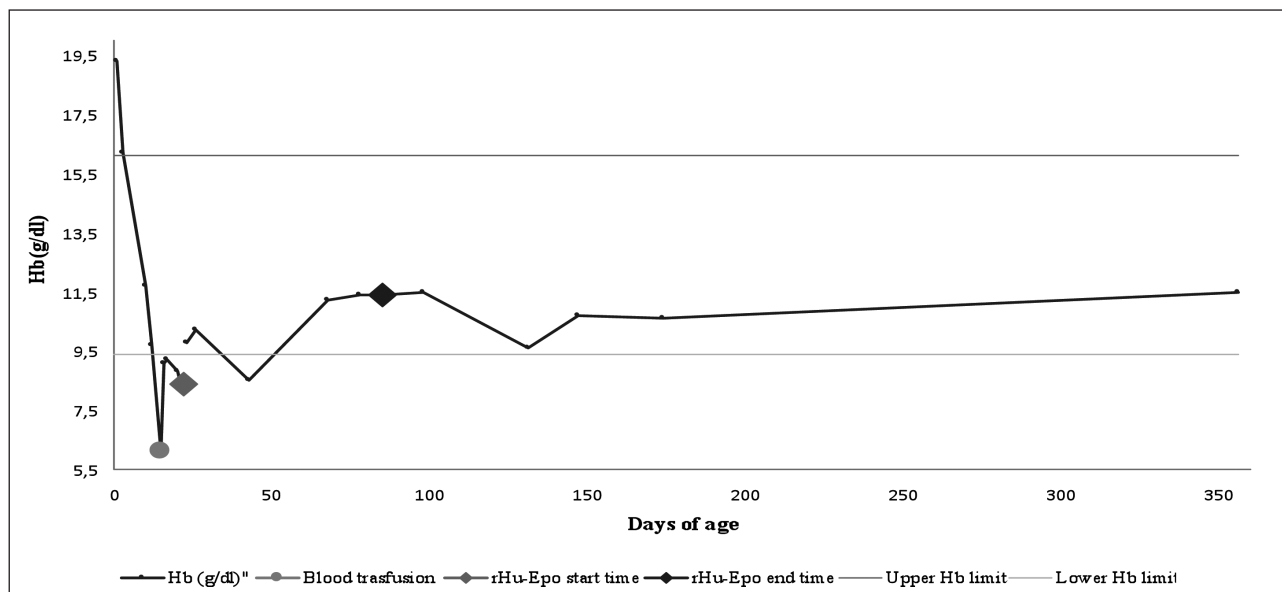


Figure 2. Changes of Hb levels from birth to 12 months of age. The circle indicates the moment in which the patient received blood transfusion and rhombuses indicate the rHu-EPO treatment (starting and end times).

epidemiology and clinical features. The disease manifests with early jaundice without splenomegaly and transient haemolytic anaemia, which peaks at 3-4 weeks of age and resolves by the age 4-6 months [2]. During these years, the diagnosis of the infant pyknocytosis has been infrequent, but the clinical manifestation, especially anaemia is severe in most of the cases, and a correct diagnosis appears extremely important. Pyknocytes have also been observed in association with glucose-6-phosphate dehydrogenase and pyruvate kinase deficiency, elliptocytosis, and in neonatal anaemia related to vitamin E deficiency [2, 3]. None of these pathological conditions was observed in the present case.

The aetiology of pyknocytosis is still completely unknown. Although most cases are thought to be sporadic, the diagnosis of the above mentioned pathology in several patients with consanguineous parents, point at a possible genetic cause for this disorder [1, 3, 5]; a recent study supports the theory of an autosomal recessive mode of transmission [6]. Other researches questioned the hypothesis of a toxic effect of bilirubin on red cells in jaundiced infants. In some experimental studies, in which adult red cells have been exposed to serum from a severely jaundiced infant with pyknocytosis, changes in morphology were not pointed out, suggesting that the original pyknocytosis was not caused by bilirubin [7]. The hypothesis that bilirubin might predispose red cells of neonates to haemolysis or phagocytosis

is certainly plausible, but stronger evidence than that recently presented is needed to support the above mentioned theory [8]. Whether bilirubin is the cause or the end result of the pyknocytosis, or even both, still remains an unanswered question. Several findings suggest that infantile pyknocytosis results from the interaction of the erythrocyte membrane with a transient extra-corporeal factor. On the one hand, this hypothesis is based on the evidence that haemolysis is a transient process, not depending from the spleen; on the other hand, it is based on the finding that normal transfused erythrocytes soon assumed the distorted morphology of the recipients' RBC, as reported in a recent study [3]. As regards the treatment, the majority of cases reported in literature required several blood transfusions [1-9], and also our patient needed a transfusion, although this did not improve his anaemia.

However, according to a recent study, treatment with erythropoietin seems to be able to significantly ameliorate the clinical and haematological status of patients affected by pyknocytosis [10, 11].

Due to the fact that the cause of the disease is not directly linked to intrinsic erythrocyte alteration, the treatment with rHu-Epo may constitute a better therapy than blood transfusion, since it increases the reticulocyte response. Similar results were obtained in premature neonates and in patients with hereditary spherocytosis [10, 12]. Therefore, beyond the obvious advantage of avoiding the risk of blood-borne infections or other transfusion-related

risks, rHu-Epo treatment appears to be also cost-effective [12]. Importantly, side effects of rHu-Epo therapy have not been generally observed in infants. Even in the absence of defined guidelines, when diagnosis of pyknocytosis has been established in a newborn, the presence of anaemia or of a rapid fall in Hb values, together with inappropriate reticulocyte counts, should trigger the decision to start the rHu-Epo therapy aiming at anticipating the onset of severe anaemia and preventing any transfusion. Further studies are needed to better define the most appropriate time to start the therapy, in order to establish the optimal dosage and duration of the treatment.

Declaration of interest

The Authors declare that there is no conflict of interest.

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