

# A Rare Case of Transient Erythroblastopenia of Infancy with Parvovirus B19 Infection

## Parvovirüs B19 Enfeksiyonuna Bağlı Geçici Eritroblastopeni: Nadir Bir Olgu

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**ABSTRACT** Transient erythroblastopenia of childhood is a slowly developing anemia that occurs in early childhood and is characterized by a gradual onset of pallor. The etiology of transient erythroblastopenia of childhood is unknown. However, researchers have proposed numerous viral and immunologic mechanisms. We describe a rare case with transient erythroblastopenia of childhood in whom human parvovirus antibodies were detected in her serum. The diagnosis of TEC was suspected with temporary cessation of red blood cell production resulting in normocytic normochromic anemia, reticulocytopenia, and bone marrow erythroblastopenia. Detection of human parvovirus antibodies indicated its causal relation to the development of transient erythroblastopenia of childhood. The possibility of human parvovirus infection should be considered in the assessment of anemia of the newborn.

**Key Words:** Anemia; infant; 11-kDa protein, human parvovirus B19

**ÖZET** Çocukluk çağıının geçici eritroblastopenisi, erken çocukluk çağıında meydana gelen ve soluklukla bulgu verip yavaş ilerleyen bir anemidir. Çocukluk çağıının geçici eritroblastopenisinin etiyojisi bilinmemektedir. Ancak araştırmacılar bir takım viral ve immünolojik mekanizmaları öne sürmüşlerdir. Burada, parvovirüs B19 enfeksiyonuna bağlı nadir olarak gelişen bir geçici eritroblastopeni olgusu bildirilmiştir. Normositik normokrom anemiye yol açan geçici eritrosit üretim duraksaması, retikülositopeni ve kemik iliği incelemesinde eritroblastopeni ile geçici eritroblastopeniden şüphelenildi. Human parvovirüs antikorlarının tespiti parvovirüse bağlı geçici eritroblastopeni olabileceğini akla getirmekteydi. Yenidoğan döneminde anemi nedenleri arasında parvovirüs enfeksiyonları da akılda tutulmalıdır.

**Anahtar Kelimeler:** Anemi; bebek; 11-kDa proteini, insan parvovirüs B19

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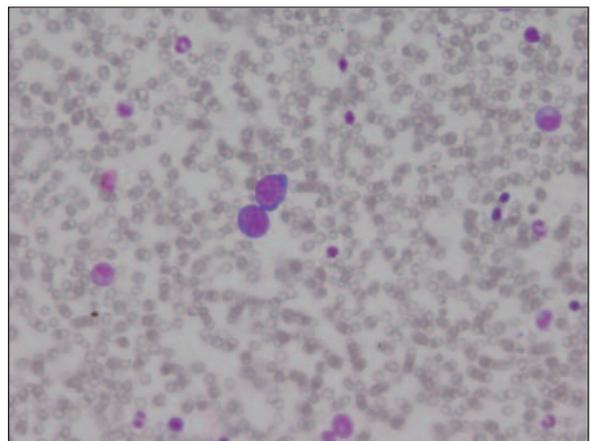
**T**ransient erythroblastopenia of childhood (TEC) is a disorder of young children, aged 3 months to 4 years, characterized by anemia with reticulocytopenia and decreased red blood cell precursor. An association with viral infections has been proposed.<sup>1</sup> The relationship between TEC and parvovirus B19 infection still remains uncertain. Large series using primarily serologic evaluation have not shown an association, whereas smaller series have reported parvovirus B19 infection in such patients.<sup>2,3</sup>

We describe an infrequent case with congenital parvovirus B19 infection presenting with transient erythroblastopenia in early infancy.

## CASE REPORT

A preterm female infant was born vaginally at 32 weeks of gestation to a 35-year-old gravida 2 mother with no prenatal pathological findings. Her mother had been followed-up routinely by her private obstetrician, had shown a normal pregnancy course until delivery, and had received antenatal steroids for the prevention of respiratory distress syndrome. Apgar scores were 4 at 1 minute and 6 at 5 minutes. Her birth weight was 1860 g, height 37 cm. On admission to our neonatal unit on the second day of life, the infant was tachypneic and had severe retractions, nasal flaring, and grunting. A chest radiograph showed opaque lungs; therefore one dose of surfactant was administered within 1 hour after birth and she was put on mechanical ventilation. Routine laboratory measurements revealed; hemoglobin (Hb) 13 g/dL, hematocrit (Hct): 41%, mean corpuscular volume (MCV): 113 fL, white blood cell (WBC) count 14.600/L and platelet count was 94.000/L. Peripheral blood smear (PBS) revealed 54% neutrophils, 46% lymphocytes and 16% normoblasts. Her blood biochemical parameters were all normal except hypoglycemia. Hypoglycemia (plasma glucose level: 42 mg/dL) and metabolic acidosis (pH 7.12, PCO<sub>2</sub> 13.4 mmHg, PO<sub>2</sub> 132 mmHg, bicarbonate 3.9 mEq/L) was corrected with appropriate medication rapidly. C-reactive protein was negative. On 13th day of hospitalization, her spontaneous respiration was sufficient and mechanical ventilation was discontinued. On the 20th day of life; pancytopenia was detected possibly as a consequence of nosocomial sepsis. Hemoglobin level decreased to 10 g/dL, white cell count to 2.200/L and platelet cell count to 31.000/L. High sensitive C-reactive protein was high (64 mg/l; N: 0-6 mg/l). Erythrocyte sedimentation rate was 68 mm/hr. Anemia was corrected with multiple transfusions. Alpha Haemolytic streptococci and *Candida albicans* were isolated from blood cultures. Intravenous cephalexin 100 mg/kg/d and amphotericin b 0.5 mg/kg/d were administered. She was discharged from the hospital after recovery on the 45th day of life with supplementary iron treatment (2 mg/kg/d).

When she came to routine hospital control on the 75<sup>th</sup> day of life, severe anemia was detected. Her physical examination was normal. Laboratory evaluation showed normochromic, normocytic anemia with a Hb level of 5.4 g/dL, Hct 16.4%, platelet count 431.000/L, WBC count 8.900/L (lymphocytes 51%, neutrophils 43%, monocytes 4%, eosinophils 1%, basophils 1%), MCV 78.8 fL, mean corpuscular hemoglobin 26.6 pg, and reticulocyte count 0.1%. Corrected reticulocyte count was low (0.7%). The peripheral blood smear did not provide evidence of hemolysis. In addition, the results of direct and indirect Coombs tests were negative. Hemoglobin electrophoresis pattern was normal (HbA 95.3%, HbA2 2.8%, HbF 1.9%). Serum ferritin values, iron level, iron binding capacity, transferrin saturation and bilirubin levels were normal. Toxoplasmosis, Rubella, Cytomegalovirus, Herpes simplex virus and Epstein-Barr virus serology were negative. Bone marrow aspiration revealed marked erythroid hypoplasia (M:E ratio:17.5) and giant proerythroblasts, suggesting parvovirus B19 infection (Figure 1). Serum parvovirus IgM, IgG (1/16) and DNA by polymerase chain reaction (PCR) ( $4.3 \times 10^6$  B19 DNA copies/ml) were positive. Parvovirus B19 IgM was negative but IgG and parvovirus B19 DNA by PCR ( $3.7 \times 10^6$  B19 DNA copies/mL) were positive in the maternal serum. When her mother was asked for any complaints during pregnancy, she mentioned severe edema on her feet, malaise, myalgia and weakness without



**FIGURE 1:** Bone marrow aspiration of the patient demonstrating giant proerythroblasts, suggesting parvovirus B19 infection (microscope ocular, 40x). (See for colored form Bkz. <http://pediatri.turkiyeklinikleri.com/>)

fever or rash two or three weeks before delivery. She was transfused once, with packed red blood cells; this increased the Hb to 8.7 g/dL. Over the next weeks, the child exhibited progressive recovery of erythropoiesis, as suggested by a parallel increase of reticulocyte count, Hb and Hct of the peripheral blood. No additional transfusions were given. When the infant was 90 days old, her hemoglobin level was normal (12 g/dL) and anemia was not detected in the follow up. She is now 15 months old with normal growth and development.

## DISCUSSION

The hematological profile of our case was interpreted as transient erythroblastopenia. Bone marrow aspiration revealed marked erythroid hypoplasia and giant proerythroblasts. Hemolytic anemia was ruled out because reticulocytosis was absent, the direct Coombs test was negative, and bilirubin levels were within the normal range. Preterm delivery and erythroblastopenia were considered to have developed secondary to parvovirus B19 infection.

Transient erythroblastopenia of childhood is characterized by a slowly developing anemia due to decreased production of red blood cell precursors. The cause of TEC is unknown. However, researchers have proposed numerous viral and immunologic mechanisms. Previous case reports have noted pure red cell aplasia with concomitant human parvovirus B19 infection.<sup>1,4</sup> However, a prospective case series of 10 patients failed to identify a single viral causative agent for transient erythroblastopenia of childhood.<sup>5</sup>

Human parvovirus B19 is a small-DNA virus belonging to the Parvoviridae family that infect red blood cell precursors in the bone marrow. It mainly manifests in an asymptomatic pattern but may cause extremely wide variety of clinical syndromes, such as erythema infectiosum, pure red cell aplasia, transient aplastic crisis, transient erythroblastopenia of childhood, persistent anemia and arthropathies. In the normal host, the disease is generally mild with conclusive recovery. In utero Parvovirus B19 infection may result in fetal death, hydrops fetalis, congenital anemia, or leukoery-

throblastosis.<sup>6,7</sup> Parvovirus B19 infects the erythroid progenitor cells and causes transient erythroblastopenia and is usually associated with red cell aplasia, leukopenia, and thrombocytopenia. However, transient increases in leukocyte and platelet counts have also been reported.<sup>8,9</sup>

Examination of bone marrow specimens can also be useful in diagnosing parvovirus B19 infection and reveals decrease or absence of erythroid precursors. Giant proerythroblasts with prominent cytoplasmic vacuoles and intranuclear inclusions limited to erythroid line cells on bone marrow smears can be observed.<sup>10</sup> Our patient came to control with a more severe hemoglobin decline than expected in physiological anemia at the third month of age. There was no evidence of hemolysis or acute blood loss. Bone marrow aspiration revealed erythroid cell hypoplasia and giant proerythroblasts, suggesting parvovirus B19 infection.

Parvovirus B19 may be transmitted through inhaled particules, hand to mouth contact, transfusion with contaminated blood products and through transplacental transmission.<sup>11</sup> Transmission of virus via blood may be suspected in our patient because she had received multiple transfusions in the neonatal period. But maternal history of myalgia, weakness, severe edema on her feet just 2-3 weeks before labor led us to vertical transmission of parvovirus during the last trimester of pregnancy.

The diagnosis of parvovirus B19 induced red cell aplasia requires the demonstration of an IgM antibody response or the presence of the virus. However, the most appropriate diagnosis of parvovirus B19 infection is the simultaneous determination of B-19 DNA by PCR and demonstration of specific IgM. Infection with parvovirus B19 virus is followed by production of specific neutralizing antibodies, first the IgM class and a few days later IgG class.<sup>12,13</sup> While parvovirus IgM disappears in 60 to 90 days period, IgG may persist for years. The infant's serum IgM and PCR DNA positivity demonstrated acute parvovirus infection. Maternal serum IgM negative but IgG and PCR DNA were positive. Recently, it has been shown that PCR DNA positivity may be prolonged

for about 7 months and absence of IgM with IgG positivity doesn't always show an earlier transmitted infection.<sup>14</sup> Specific antibodies and parvovirus DNA by PCR were diagnostic for intrauterine infection in our case.

Miller R identified six infants smaller than 6 months of age with TEC. All patients presented with moderate to severe anemia, reticulocytopenia, and age-appropriate mean corpuscular volume and fetal hemoglobin level. They suggested that TEC may occur more commonly in infants smaller than 6 months of age than has heretofore been recognized and that it has a clinical and hematologic picture similar to that seen in older children. Recognition of the occurrence of TEC in very young infants may help avoid an inappropriate diagnosis of Diamond-Blackfan anemia.<sup>15</sup>

Patients with TEC frequently do well in a noteworthy manner and often require only close follow-up and reassurance. No interventions have been proven to shorten its course and treatment is

supportive.<sup>16</sup> Packed red cell transfusions are required in patients with severe TEC when signs of clinical decompensation are evident as in our patient. Treatment with corticosteroids and erythropoietin is unnecessary. Only cases with prolonged parvoviral erythroid cytotoxicity have to be treated with intravenous IG immunoglobulin. Our patient recovered completely within six weeks.

## CONCLUSION

This is one of the few documented cases of classical TEC attributable to parvovirus B19 infection. Parvovirus B19 infection should be assessed in infants presenting with severe anemia accompanied by reticulocytopenia in the very early stage of life. Cases where parvovirus B19 infection is suspected should be handled in an appropriate manner and should include serology of mother and infant with both neutralizing antibodies (both acute and convalescent) and detection of parvovirus B19 DNA by PCR.

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