IJMS
Vol 32, No 4, December 2007

Case Report

Blueberry Muffin Rash in a Patient with Hemolytic Disease of the Newborn Due to Anti-Cw

M. Kadivar, H. Samaee[1],
A. Arab Hoseini[1], Sh. Nourbakhsh[2]

Abstract
Blueberry muffin rash is a characteristic multiple bluish skin nodules associated with perinatal infection, severe and chronic anemia, and neoplastic infiltrative diseases. We present an unusually severe case of hemolytic disease of the newborn. He required exchange transfusions for several times. The complete work up led to the diagnosis of anti-Cw. The skin lesion regressed spontaneously within one month.
Iran J Med Sci 2007; 32(4): 251-253.

Keywords ● Isoantibodies ● newborn ● hemolytic disease of the newborn

Introduction

The blueberry muffin rash can be seen with intrauterine infection, severe and chronic anemia, and neoplastic infiltrative diseases.[1-10] These lesions can be found in various hematological disorders and hemolytic syndromes such as twin-to-twin transfusion, Rh hemolytic disease of the newborn, diffuse neonatal hemangiomatosis, congenital leukemia, and neuroblastoma.[4,6,8,11,12] Blueberry muffin rash is never idiopathic and the prognosis depends on the cause. Cw is a low frequency red cell antigen, which belongs to the Rh antigen system.

We report blueberry muffin rash in a patient with hemolytic disease of the newborn due to anti-Cw. To the best of our knowledge this association has not been previously reported.

Case Report

A full-term male neonate was born through a cesarean section to a 29-year-old mother (gravida 4, para 3, living 0). The neonate's blood group was O positive. He weighed 2600 gram and his Apgar scores at 1 and 5 minutes were 6 and 9 respectively. He had been resuscitated at the time of birth because of thick meconium stained amniotic fluid. He was then transferred to the neonatal intensive care unit for further management within a few hours of life.

The parents had no consanguinity and did not have any previous medical diseases. Both of them were of Afghani immigrants. The mother had three previous deliveries in which all of the neonates – a girl and two boys– had died one day after birth due to unknown causes but all had pallor and presented with severe jaundice. There was not any data available from the previous birth history in Afghanistan.

Physical examination of the neonate on admission revealed a pale and yellowish skin, edematous infant with many

Department of Pediatrics,
Children's Medical Center,
Tehran University of Medical Sciences,
[1]Department of Pediatrics,
Division of Neonatology,
Iran University of Medical Sciences,
Aliasghar Children's Hospital,
[2]Department of Pediatrics,
Milad General Hospital,
Tehran, Iran.

Correspondence:
Maliheh Kadivar MD,
Department of Pediatrics,
Division of Neonatology,
Children's Medical Center,
Medical Sciences/University of Tehran,
Tehran, Iran.
Tel: +98 21 66917648
Fax: +98 21 66930024
Email: kadivarm@sina.tums.ac.ir

scarlet-bluish macule, papule, and nodules on his face, chest, abdomen, and extremities (figure). He had hepatosplenomegaly with a liver and spleen palpable 6 cm (with liver span of 9 cm) and 8 cm below costal margins, respectively. His heart was hyperdynamic and a systolic murmur (grade III/VI) was detected. He was supported by mechanical ventilation.

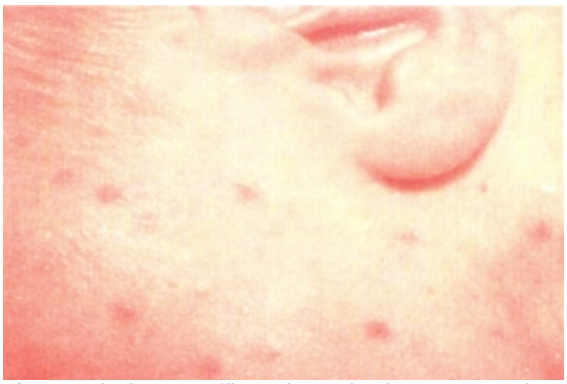

Figure: Blueberry muffin rash on the face presented at birth due to extramedullary hematopiesis.

Initial lab data showed: white blood cell count (WBC)=21000/mm^3, hemoglobin=12.3 g/dl, hematocrit=36.9%, reticulocytes=17.8%, and platelet count=13000/mm3. The peripheral smear revealed nucleated red blood cells (NRBC), spherocytosis, and anisocytosis. There were 350 NRBC per 100 WBC. The coagulation times were within normal limits. Blood chemistry revealed normal electrolytes, elevated creatinine (1.6 mg/dl), AST 245 U/l (normal: 0-40), ALT 118 U/l (normal: 0-40), and albumin 2.8g/dl (normal: 3.5-5). Total and direct bilirubin were 12.1 and 2.1mg/dl respectively, which were increased to 21 and 6.8 after 3 hours of birth.

Prenatal screening for infectious diseases was negative. Antinuclear and Antiphospholipid antibodies were negative. Vaginal culture was also negative. Both father and mother had blood group O positive. An assay for maternal antibodies against red cells was not done during pregnancy.

All the cultures obtained for bacterial infections in the patient were negative. Serological evaluations for syphilis, cytomegalovirus (CMV), and herpes simplex type 1 and 2, rubella, human immune deficiency virus (HIV), Epstein-Barr virus, and toxoplasma were also negative. The patient had microscopic hematuria with rare red blood cells compatible with hemoglobinuria that became negative later.

The infant's blood group was O positive and he had a positive direct antiglobulin test. On panel study, anti Cw was detected on the infant's red cells. Direct Coombs' test was strongly positive. Abdominal ultrasound showed; both liver and spleen were larger than normal with normal echogenicity, increased echogenicity of renal cortex, and some free fluid in costophrenic angle. The echocardiography revealed mild left ventricular dysfunction and tricuspid regurgitation. The brain ultrasound was normal.

Despite institution of intensive phototherapy, total bilirubin continued to rise, and the infant underwent double exchange transfusions for three times in the first 48 hours of his life. Because of presumed hemolytic disease of the newborn, he also received intravenous immunoglobulin (IVIG) for two times at the second and third day of life in order to stop the hemolytic process. The infant's hyperbilirubinemia gradually resolved with continued phototherapy for a week. In addition, he underwent artificial ventilation for three days after birth. Because of his unstable general condition, and the result of echocardiography he was digitalized, which was discontinued three weeks later after normal follow-up echocardiography.

Histology of skin biopsy was revealed nodular aggregation of nucleated and mature red blood cells and scattered elements of myelopoietic and megapoeitic systems especially in perivascular regions in the deep dermis and subcutaneous area. The skin lesions regressed spontaneously within two weeks.

The infant was discharged from hospital after three weeks and at that time his laboratory data were: WBC=8400/mm^3 with normal differentiation, reticulocyte count=4%, hemoglobin= 8.9 g/dl, platelet count=213000/mm3, bilirubin= 8.1mg/dl, AST=120 U/l, and ALT=76. He was discharged on folic acid and multivitamins and was followed up to his first birthday. His hemoglobin was raised to 10.8 g/dl, his reticulocyte decreased to 1.7%, and no hepatosplenomegaly was further detected. His growth and development were appropriate for his age.

Discussion

Blueberry muffin is a petechial, purpuric, magenta colored macules, papules, and plaques as well as blueberry colored ecchymoses, which resolve gradually over a period of several days to weeks.[4] The clinical significance and prognosis of this lesion in the newborns is variable and depends on its etiology. The hemorrhagic-purpuric looking skin lesions reflect extramedullary hematopiesis. These may reactivate hematopoiesis in organs where it previously occurred in embryonic and fetal life due to compensatory demand, deficient replacement, or either loss or dysfunction of corpuscular blood elements.[7,11,12] Therefore the skin lesions are due to the presence of hematopoietic aggregations within the dermis and not due to true hemorrhage.[4,6,11]

These lesions must be differentiated from those seen in malignant diseases such as con-

genital monoblastic leukemia, neuroblastoma, congenital alveolar rhabdomyosarcoma, and congenital histiocytosis or neonatal hemangiomatosis.[7-9,12] The blueberry muffin baby can be seen in utero infections with rubella, toxoplasmosis, varicella, cytomegalovirus, herpes simplex, coxsackievirus B-2, human parvovirus B19, and HIV.[1-3]

Chronic prenatal anemia leading to blueberry muffin lesions have been reported in association with severe hemolytic anemia such as congenital spherocytosis, hemolytic disease of the newborn due to Rhesus immunization and ABO incompatibility, or in anemia caused by twin-to-twin transfusion, fetomaternal hemorrhage and severe perinatal intracranial bleeding.[1,4,5,10-13] Our patient provides another cause of prenatal anemia leading to blueberry muffin lesions namely hemolytic disease of the newborn due to anti-C antibody.

C protein is a low frequency red cell antigen that belongs to the Rh antigen system (Rh8) and is present in about 2% of general Caucasian population.[14] It is usually inherited in combination with the common Rh haplotype, CDe, and may show reduced expression of the C antigen.[14,15] Anti–Cw occurs in about 0.1% of pregnant women, and maybe either naturally occurred or acquired through sensitization via transfusion or pregnancy.[14] Anti–Cw rarely produces hemolytic disease of the newborn. It may be mild to severe requiring phototherapy or exchange transfusion. In the case of this disease, severe anemia or hydrops fetalis have not been reported previously.[13-15] Although anti–Cw usually is not associated with clinically severe hemolytic diseases of the newborn but unrecognized anti–Cw can result in severe hyperbilirubinemia, kernicterus, and fetal death if left untreated.[15]

Our patient was an unusually severe case of hemolytic disease of the newborn due to anti–Cw in his previously sensitized mother. He was presented with signs of erythroblastosis fetalis and severe hyperbilirubinemia who underwent exchange transfusions for several times. Chronic intrauterine anemia was the cause of dermal hematopoiesis presented as blueberry muffin rash.

Blueberry muffin rash is never idiopathic and it may occur because of various causes. It represents a postnatal re-expression of normal fetal extramedullary hematopoiesis. According to our case anti-C antibody as an agent causing hemolytic disease of the newborn can cause these lesions with a similar mechanism.

References

1 Bowden JB, Hebert AA, Rapini RP. Dermal hematopoiesis in neonates: report of five cases. *J Am Acad Dermatol* 1989; 20: 1104-10.

2 Hendricks WM, Hu CH. Blueberry muffin syndrome: cutaneous erythropoiesis and possible intrauterine viral infection. *Cutis* 1984; 34: 549-51.

3 Klein HZ, Markarian M. Dermal erythropoiesis in congenital rubella. Description of an infected newborn who had purpura associated with marked extramedullary erythropoiesis in the skin and elsewhere. *Clin Pediatr (Phila)* 1969; 8: 604-7.

4 Hebert AA, Esterly NB, Gardner TH. Dermal erythropoiesis in Rh hemolytic disease of the newborn. *J Pediatr* 1985; 107: 799-801.

5 Schwartz JL, Maniscalco WM, Lane AT, Currao WJ. Twin transfusion syndrome causing cutaneous erythropoiesis. *Pediatrics* 1984; 74: 527-9.

6 Smets K, Van Aken S. Fetomaternal hemorrhage and prenatal intracranial bleeding: two more causes of blueberry muffin baby. *Eur J Pediatr* 1998; 157: 932-4.

7 Godambe SV, Rawal J. Blueberry muffin rash as a presentation of alveolar cell rhabdomyosarcoma in a neonate. *Acta Paediatr* 2000; 89: 115-7.

8 Meuleman V, Degreef H. Acute myelomonocytic leukemia with skin localizations. *Dermatology* 1995; 190: 346-8.

9 Shown TE, Durfee MF. Blueberry muffin baby: neonatal neuroblastoma with subcutaneous metastases. *J Urol* 1970; 104: 193-5.

10 Pizzaro A, Elorza D, Gammalo C, et al. Neonatal dermal erythropoiesis associated with severe rhesus immunization: amelioration by high-dose intravenous immunoglobulin. *Br J Dermatol* 1995; 133: 334-6.

11 Waldron P, de Alarcon P. ABO hemolytic disease of the newborn: a unique constellation of findings in siblings and review of protective mechanisms in the fetal-maternal system. *Am J Perinatol* 1999; 16: 391-8.

12 Evole-Buselli M, Hernandez-Marti MJ, Gascó-Lacalle B, et al. Neonatal dermal hematopoiesis associated with diffuse neonatal hemangiomatosis. *Pediatr Dermatol* 1997; 14: 383-6.

13 Mogilner BM, Berrebi A, Levy A, Levene C. Hemolytic disease of the newborn caused by the rhesus antigen Cw. *Acta Paediatr Scand* 1982; 71: 703-4.

14 Sacks MO, Schlutz C, Dagovitz L, Vanecko M. Hemolytic disease of the newborn due to the rare blood factor, rhw (Cw). *Pediatrics* 1958; 21: 443-4.

15 Reiner AP, Teramura G, Aramaki KM. Use of a PCR-based assay for fetal Cw antigen genotyping in a patient with a history of moderately severe hemolytic disease of the newborn due to anti-Cw. *Am J Perinatol* 1999; 16: 277-81.