CASE REPORT

Congenital B-cell Acute Lymphoblastic Leukemia with Congenital Rubella Infection

Dhan Raj Bagri[1], Krapal Singh Yadav[1], Rambabu Sharma[1] and Sandhya Gulati[2]

From Departments of Pediatrics[1] and Pathology[2], Sir Padampat Mother and Child Health Institute, JK Lon Hospital, SMS Medical College, Jaipur, Rajasthan, India.

Correspondence to: Dr Dhan Raj Bagri, Departments of Pediatrics, SMS Medical College, Jaipur, Rajasthan, India. meena.drdhanraj6@gmail.com
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Background: Congenital B-cell Acute lymphoblastic leukemia (ALL) is a rare malignancy. **Case Characteristics**: A newborn infant presented with purpuric spots and ecchymotic patches, blueberry muffin rash, depressed neonatal reflexes, respiratory distress and hepatosplenomegaly. Peripheral smear revealed atypical blast cells. Serum ELISA was positive for Rubella IgM and IgG antibodies. Flow cytometry suggested congenital B-cell ALL. **Outcome**: The baby died after 3 days due to suspected intracranial hemorrhage. **Message**: Congenital leukemia may be rarely associated with congenital rubella infection.

Keywords: *Acute leukemia, MMR vaccine, Rubella virus*.

Congenital leukemia is extremely rare, with a reported incidence of 1 in 5 million; it develops *in utero* and is diagnosed at birth or within one month of life [1]. It has a poor prognosis with only 23% survival being reported at 24 months [2]. Congenital leukemia may manifest at birth with petechiae, ecchymosis and hepatosplenomegaly; specific cutaneous infiltrates (leukemia cutis), which usually appear as firm blue or red nodules (blueberry muffins) are seen in 25-30% of infants [3]. Blueberry muffin rash is also seen in congenital rubella and cytomegalovirus infection, and in metastatic neuroblastoma [4]. A wide variety of single gene traits, constitutional and familial conditions are associated with an increased risk of developing hematological malignancies [5].

Case Report

A full-term appropriate for gestational age female infant born at our hospital (birthweight 3 kg) out of a consanguineous marriage, to a 27-year-old mother by lower segment cesarian section with an unremarkable antenatal history, presented at birth with pallor, palpable purpuric spots and ecchymotic patches, diffuse blueberry muffin rash of 1 to 3 cm (***Fig*. 1**), and depressed neonatal reflexes. The craniofacial configuration was normal, but the anterior fontanelle was full. She had tachypnea and tachycardia. The abdomen was mildly distended; hepato-splenomegaly was evident on palpation.

Maternal TORCH profile during the second trimester done at another hospital was positive for Rubella IgG. Other routine maternal antenatal investigations, including

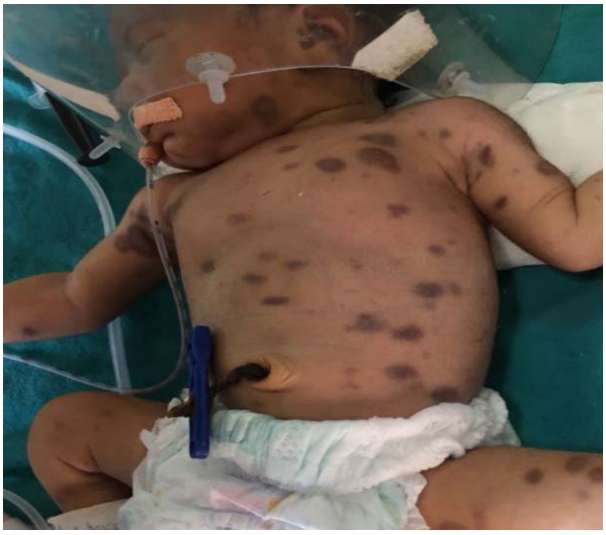

Fig. 1. *Blueberry muffin rash in a newborn with congenital leukemia and rubella infection. (color image at website)*

HbsAg, VDRL, HIV, urine microscopy, antenatal ultrasound and TSH were normal. Complete blood count of the child suggested anemia (Hb 5.8 g/dL), thrombocytopenia (platelet count 14×10^9/L), leuco-cytosis (total leukocyte count 44.3×10^9/L) with blasts 60%, polymorphs 18%, lymphocytes 20% and eosinophils 2%. Peripheral blood film findings were suggestive of acute leukemia, showing clumped red blood cells, leucocytosis, blast cells and markedly reduced platelets, with no hemoparasites.

Blood sugar (85 mg/dL), urea (13 mg/dL), creatinine (0.4 mg/dL) and bilirubin (total 2.7 mg/dL, indirect 2.1 mg/dL)

were normal. SGOT (331 U/L), SGPT (120 U/L), alkaline phosphatase (1596 U/L), LDH (6189 IU/L) and GGT (337 U/L) were raised. Uric acid was 4 mg/dl, calcium was low (7.4 mg/dL), total protein was 5.5 gm/dL (albumin 3.5 gm/dL), and C-reactive protein was non-reactive. INR was raised (2.55), aPTT was 55 sec, and d-dimer levels were 8.5 µg/mL. Chest *X*-ray was normal. Ultrasound abdomen revealed an enlarged liver (7 cm), contracted gall bladder, and enlarged spleen (6.1 cm). Ultrasound brain revealed a dilated left lateral ventricle with slight midline shift to left side, suggestive of intracranial involvement. Skin biopsy was not done. TORCH profile by Pict Array TORCH ELISA (Nanoplex) was suggestive of positive Rubella IgM and IgG antibodies.

Flow cytometric immunophenotyping showed 60% circulating blasts, which expressed CD19, CD20, CD79a, HLA DR, CD34, and were negative for CD3, CD5, CD7, CD13, CD33, CD117, CD14, cytoplasmic CD3, and Myeloperoxidase. A diagnosis of B-Cell acute lymphoblastic leukemia (ALL) with congenital rubella infection was made. Despite ventilation in neonatal intensive care unit and blood component therapy, the baby survived only for 3 days.

DISCUSSION

This case fulfilled the criteria for diagnosis of congenital leukemia: (*i*) disease presentation at or shortly after birth, (*ii*) raised number of immature white blood cells, (*iii*) infiltration of cells into extra hemopoietic tissues, (*iv*) absence of other conditions like congenital syphilis, blood group incompatibility, which can cause leukemoid reaction [2].The differential diagnosis of congenital leukemia includes sepsis and intra-uterine infections, hemolytic disease of the newborn (HDN) and transient myeloproliferative disease (TMD) [1]. Infections are ruled out by serology and culture, while in HDN numerous erythrocyte precursors are seen in the peripheral smear. TMD is seen usually with Down syndrome, often with associated transient polycythemia and/or thrombocytosis, which were not found in this case.

Thrombocytopenia may be seen in up to 80% infants with CRS, which may be due to decreased megakaryocyte production [6]. Elevated leucocyte counts and severe thrombocytopenia, as seen in this child, are unusual for rubella. Patients can also develop a hemolytic anemia that can persist for months and potentially progress to red cell aplasia with variable leukocyte count [7]. There is paucity of reports of association of congenital rubella infection with malignancy; one case of lymphoblastoma has been reported after maternal rubella infection [8]. Acute myelomonocytic leukemia has also been reported with atypical congenital rubella [9]. Assembly, maturation and three-dimensional helical structure of the teratogenic rubella virus using cryo-electron tomography has also been described [10].

In any newborn presenting with palpable purpura, besides other causes like common neonatal rashes, leukemoid reactions, TORCH infection, and bleeding disorder, congenital leukemia should be considered as a differential diagnosis. On suspicion, immuno-phenotyping by flow cytometry, together with morphology and cytochemical stains should be performed. Association of ALL with rubella in this case suggest that the virus itself may have the potential to cause congenital leukemia.

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