CASE REPORT

Congenital Leukemia: A Rare Cause of Blueberry Muffin Rash

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Abstract

Congenital leukemia is an extremely rare disease occurring within the first 28 days of life. The disease prognosis is poor with high mortality rates. We describe a case of congenital acute monocytic leukemia in a female infant whose disease underwent rapid progression and culminated in death due to multiple organ failure. Our patient presented at birth with leukemia cutis, hepatomegaly, and abnormal neurological examination. She also had evidence of cardiac and respiratory dysfunction. Laboratory results revealed severe anemia, hyperleukocytosis with monocytic predominance, coagulopathy, and findings consistent with tumor lysis syndrome. The autopsy showed diffuse multiorgan infiltration by acute monocytic leukemia. Congenital leukemia has distinctive clinical presentations which make it a diagnostic and therapeutic challenge. We aimed to draw attention to this rare disease and its differential diagnosis with other common causes of blueberry muffin rash associated with hepatosplenomegaly and leukocytosis.

Keywords: Infant, Newborn; Leukemia, Monocytic, Acute/complications; Leukemia, Monocytic, Acute/congenital; Leukemia, Monocytic, Acute/diagnosis

Keypoints

What is known:
- Congenital leukemia is an extremely rare disease with a high mortality rate.
- Leukemia cutis is a common presentation, while congenital leukemia encompasses a wide range of clinical manifestations.

What is added:
- The diagnosis can be challenging since it can mimic other disorders such as congenital infections, hemolytic diseases, and other tumors.
- Further studies are needed to improve the outcome of this rare disease.

Introduction

Congenital leukemia is an extremely rare disease occurring within the first 28 days of life, and accounting for less than one percent of all childhood leukemias.[1]

It should be noted that congenital leukemia has distinctive features from childhood leukemia, both in terms of disease biology and response to treatment. In contrast to the predominance of acute lymphoblastic leukemia in older children, the majority (up to two-thirds) of neonatal cases are of myeloid origin, particularly monocytic type.[2] Of the remaining cases, most are acute lymphoblastic leukemia and few cases are mixed phenotype or blastic plasmacytoid dendritic cell neoplasms.[2]

Congenital leukemia encompasses a wide phenotypic range that can be mimicked by other disorders such as congenital infections, hemolytic diseases, disseminated neuroblastoma, histiocytic syndromes, and transient myeloproliferative disorder with or without Down syndrome. Leukemia cutis is a common presentation, occurring in 50% of neonates.[3] It is the infiltration of the skin and subcutaneous tissue by leukemic cells, resulting in variable clinically identifiable cutaneous lesions, such as blueberry muffin rash characterized by multiple reddish-blue papules or nodules in the skin due to extramedullary hematopoiesis in the dermis. There are many underlying causes of blueberry muffin rash including congenital infections like toxoplasmosis, rubella, cytomegalovirus, and *herpes simplex* (TORCH complex) and syphilis, hemolytic diseases (*rhesus* or ABO incompatibility, hereditary spherocytosis) and tumors

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(congenital leukemia, disseminated neuroblastoma, congenital rhabdomyosarcoma, Langherhans cell histiocytosis). Hyperleukocytosis, hepatosplenomegaly and central nervous system infiltration, expressed by bulging fontanelle, papilledema, and retinal hemorrhages as well as a reduced level of consciousness, are also common features of congenital leukemia.[4]

The prognosis is poor, with higher mortality rate than any other congenital cancer.[5] However, there are some reports of spontaneous remission.[6,7] The ideal therapeutic approach has not yet been established, and collaborative international clinical trials are ongoing to determine a better therapeutic approach and improve poor outcomes and treatment-related toxicity.

We describe a case of congenital acute monocytic leukemia in a female newborn whose disease underwent a rapid progression culminating in death due to multiple organ failure.

Case Report

A female infant weighing 2795 g was born at 34 weeks of gestation by urgent cesarean section due to fetal distress. Her Apgar scores were 3/2/4 and she needed advanced resuscitation. Her 28-year-old mother was healthy, 0Rh negative, immune to rubeola, and the remainder routine serologic studies (toxoplasma, syphilis, and human immunodeficiency virus) were negative. Genital herpes was diagnosed during first trimester. The pregnancy was complicated by gestational diabetes at 28 weeks that was poorly controlled with insulin. Obstetric ultrasounds were normal until 34 weeks when fetal macrosomia and hydramnios were diagnosed. There was no family history of malignancy and no mother exposure to radiation, other medications, or toxins.

Physical examination revealed a non-dysmorphic, ill-appearing infant, with a distended abdomen due to marked hepatomegaly, spontaneous oral and nasopharyngeal hemorrhage, and a diffuse, non-blanching, bluish-red, macular rash with some palpable nodes and multiple petechiae (Figs. 1 and 2). There was no lymphadenopathy. She had a bulged anterior fontanelle, no spontaneous movements, no primitive reflexes, no reaction to pain and the pupils were fixed and dilated.

Laboratory studies at birth showed a hemoglobin of 7.4 g/dL, platelet count of 196 000 cells/µL, white blood cell count of 58 160 cells/ µL with monocytic predominance (72%), without blast visualization on peripheral blood smear examination. Coagulopathy was also present with partial thromboplastin time of over 100 s, prothrombin time of 42.8 s, international normalized ratio of 3.67 and fibrinogen of 62 mg/dL. Bone marrow aspirate was not performed due to severe coagulopathy. Laboratory findings compatible with tumor lysis syndrome were present, including elevated lactate dehydrogenase (22 875 U/L), hyperkalemia (7.1 mmol/L), hyperphosphatemia (8.1 mg/dL) and creatinine rise from 0.71 to 0.98 mg/dL. Uric acid was not measured. Ferritin was significantly elevated (> 2000 ng/mL) and transaminases were also abnormal (aspartate aminotransferase 2772 U/L, alanine aminotransferase 195 U/L). She had mixed severe acidemia (pH 6.9, partial pressure of carbon dioxide 61.7 mmHg, bicarbonate 8.3 mmol/L) and hyperlacticemia (maximum 253 mg/dL). Hyperammonemia was noted (281 µmol/L). An extensive metabolic study was performed, finding an abnormal lysosomal biochemical analysis suggestive

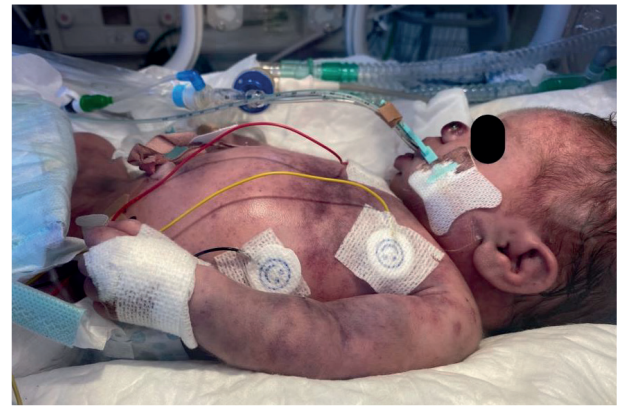

Figure 1. Widespread non-blanching, bluish-red, macular rash with some palpable areas and multiple petechiae.

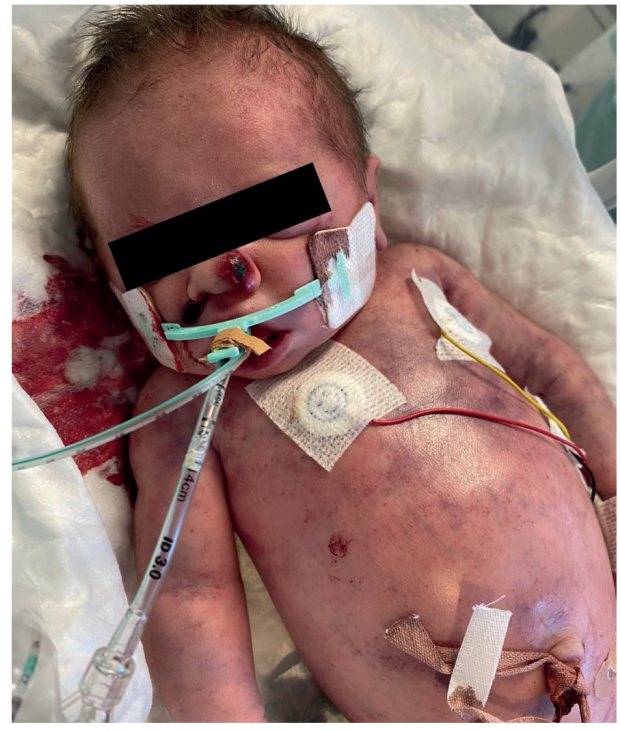

Figure 2. Firm left nasal nodule of approximately 1 cm and active hemorrhage of right nasal fossa.

of type II or III mucolipidosis. However, no genetic variants were found in the molecular study of the infant and both parents. C-reactive protein and bacterial culture of blood were negative. The infant blood group was 0Rh positive, with negative Coombs test. Serologic tests for rubella, *Toxoplasma* and syphilis were unremarkable. *Cytomegalovirus* and *Herpes simplex* 1 and 2 deoxyribonucleic acid were not detected in urine and in plasma, respectively.

From the imaging studies performed, extensive heterogeneous peri-intraventricular hemorrhage with ventricular dilation, left cerebellar hemorrhage and inverted diastolic flow on Doppler were found on cerebral ultrasound (Figs. 3 and 4). Abdominal ultrasound showed marked hepatomegaly, small amount of intraperitoneal fluid and small volume right pleural effusion.

The patient needed fluid resuscitation and inotropic support with dopamine and dobutamine. Empirical therapy with ampicillin, gentamycin and acyclovir was started within the first hours of life. Despite several blood product transfusions (erythrocyte, platelets, plasma, and fibrinogen), the infant maintained significant active hemorrhage. Severe neonatal hypoglycemia (minimum 16 mg/dL) was treated with intravenous dextrose.

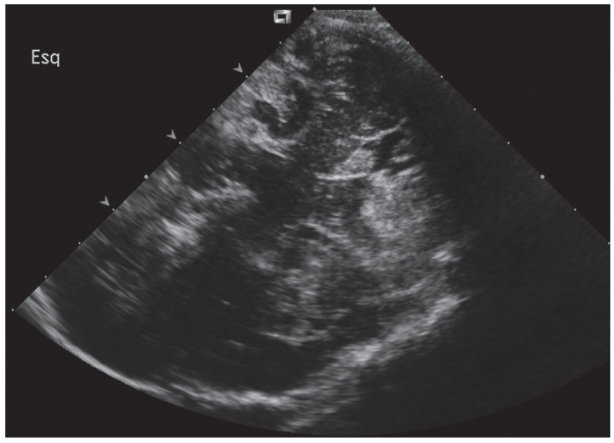

Figure 3. Cerebral ultrasound showing left cerebellar hemorrhage.

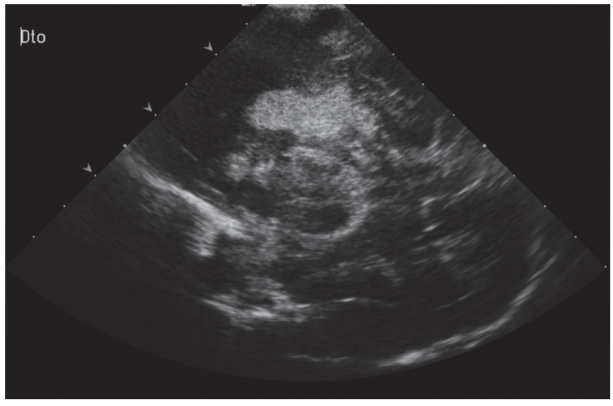

Figure 4. Cerebral ultrasound showing extensive heterogeneous peri-intraventricular hemorrhage.

The infant died of multiple organ failure at 28 hours of life. Post-mortem liver biopsy revealed massive liver infiltration by acute myeloid leukemia, with immunophenotyping compatible with monocytic lineage. The autopsy demonstrated extensive multisystemic leukemic involvement. Cytogenetic analysis showed rearrangement of *KMT2A* gene resulting from t(9;11).

Discussion

Congenital leukemia is a rare disorder that needs a high suspicion index for its early diagnosis. The criteria that contribute to the diagnosis include infiltration of extra hematopoietic tissues, absence of any other diseases that cause leukemoid reactions, and absence of constitutional chromosomal disorders associated with unstable hematopoiesis such as Down syndrome.[8]

Our patient presented with classical findings of congenital leukemia at birth, such as blueberry muffin rash, hepatomegaly, hyperleukocytosis and severe anemia, in addiction to abnormal neurological examination due to leukemic infiltration or leukostasis, and coagulopathy due to liver infiltration. Leukostasis syndrome can be responsible for both the cardiac and respiratory failure with hypoxia and acidosis.

Hydramnios has been described as a prenatal presentation of congenital leukemia.[9] However, it can also be justified by poorly controlled gestational diabetes or even fetal heart failure.

Our diagnostic workup excluded some diseases that can mimic these symptoms, such as TORCH infections, hemolytic disease of the newborn, and other malignancies. White blood differential cell count can be used to distinguish congenital monocytic leukemia from leukemoid reactions since in the latter there is a shift to the left with all stages of developing granulocyte precursors. Rather, our patient had a monocytic-predominant hyperleukocytosis. Peripheral blood smear evidencing blasts and/or a compatible peripheral blood flow cytometry immunophenotyping can also be crucial and simple diagnostic tools. The false positive result of the lysosomal biochemical assay might be explained by hyperleukocytosis.

Congenital leukemia can be a rapidly progressive illness, as in our case. *KMT2A* rearrangements are frequent and have been associated with poorer outcomes.[9] Although spontaneous remission has been reported, its mechanism is still unclear. Therefore, management of congenital leukemia is challenging with a high-risk mortality and treatment related toxicity.[10] Further international collaborative studies are needed to improve outcomes of this rare disease.

Author Contribuitions

ADC and MA participated in the study conception or design. ADC and AMG participated in acquisition of data. ADC, MR and MA participated in the analysis or interpretation of data. ADC participated in the drafting of the manuscript. MJP, AMG and MA participated in the critical revision of the manuscript. All authors approved the final manuscript and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this study.

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Confidentiality of data

The authors declare that they have followed the protocols of their work center on the publication of patient data.

Consent for publication

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Leucemia Congénita: Uma Causa Rara de *Blueberry Muffin Rash*

Resumo

A leucemia congénita é uma doença extremamente rara, manifestando-se até aos 28 dias de vida. O seu prognóstico é reservado, estando associado a uma mortalidade elevada. Descrevemos o caso de uma recém-nascida com leucemia monocítica aguda com progressão fulminante, que culminou com disfunção multiorgânica e morte. Ao nascimento, verificou-se *blueberry muffin rash*, hepatomegália e coma. Apresentava ainda sinais de insuficiência respiratória e cardíaca. Analiticamente, salientava-se hiperleucocitose com predomínio monocítico, anemia grave, coagulopatia e achados compatíveis com síndrome de lise tumoral. A autópsia demonstrou infiltração difusa multiorgânica por leucemia monocítica aguda.

A leucemia neonatal tem apresentações clínicas muito distintas, sendo um desafio diagnóstico e terapêutico. Alertamos para esta patologia rara e o seu diagnóstico diferencial com outras causas mais comuns de *blueberry muffin rash* associado a organomegálias e leucocitose.

Palavras-Chave: Recém-Nascido; Leucemia Monocítica Aguda/complicações; Leucemia Monocítica Aguda/congénita; Leucemia Monocítica Aguda/diagnóstico