Blueberry Muffin Syndrome in a Newborn. A Case Report of Transient Extramedullary Hematopoiesis

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Abstract
Blueberry Muffin Syndrome (BMS) is a rare condition in newborns characterized by distinctive skin lesions often associated with transient extramedullary hematopoiesis. We present a case of a newborn with BMS focusing on the diagnostic challenges, especially in distinguishing it from acute leukemia. Despite extensive investigations, no specific etiology was found. The skin lesions resolved spontaneously. This case highlights the importance of a multidisciplinary approach in the diagnosis of BMS and underscores the need for a thorough evaluation to exclude severe underlying conditions.

Introduction

Blueberry Muffin Syndrome (BMS) is a rare neonatal condition characterized by red-blue papules, macules, or nodules on the skin. The lesions mostly consist of reactive extramedullary hematopoiesis or neoplastic skin infiltration and are related to underlying conditions, including acute leukemia or metastatic tumors. The term 'blueberry muffin syndrome' (BMS) derives from the purplish maculopapular skin lesions resembling the surface of a blueberry muffin. However, this seemingly innocuous term can mask underlying serious conditions, including malignancies, and therefore requires careful clinical evaluation to identify the cause.

Early and accurate diagnosis is critical due to the broad differential diagnosis (1,2). This report describes a newborn with BMS and transient extramedullary hematopoiesis, emphasizing the diagnostic challenges and the importance of ruling out malignancy.

Clinical Case

A male Caucasian newborn was delivered vaginally at 39 weeks after induction due to decreased fetal movement and altered fetal monitoring. The pregnancy was otherwise uneventful, with no ABO or Rh incompatibility and no family history. Maternal infectious serologies (expanded after delivery) were negative for cytomegalovirus (CMV), toxoplasmosis, hepatitis B, hepatitis C, syphilis, HIV, *Chlamydia trachomatis*, coxsackievirus and human T-lymphotropic virus (HTLV). The mother was immune to rubella and parvovirus and not immune to varicella-zoster virus (VZV).

At birth, the newborn had a low birth weight of 2,345 grams (below the second percentile, consistent with severe hypotrophy) and had experienced perinatal hypoxia-ischemia events with transient acidosis, followed by a good recovery. The Apgar score was 9 at 1, and 7 at 5 minutes of life. At birth, the infant's skin was erythemic and there was no pallor or jaundice. There was no lymphadenopathy on physical examination. A bluish rash on the face, limbs, and back led to the diagnosis of BMS (Figure 1.A).

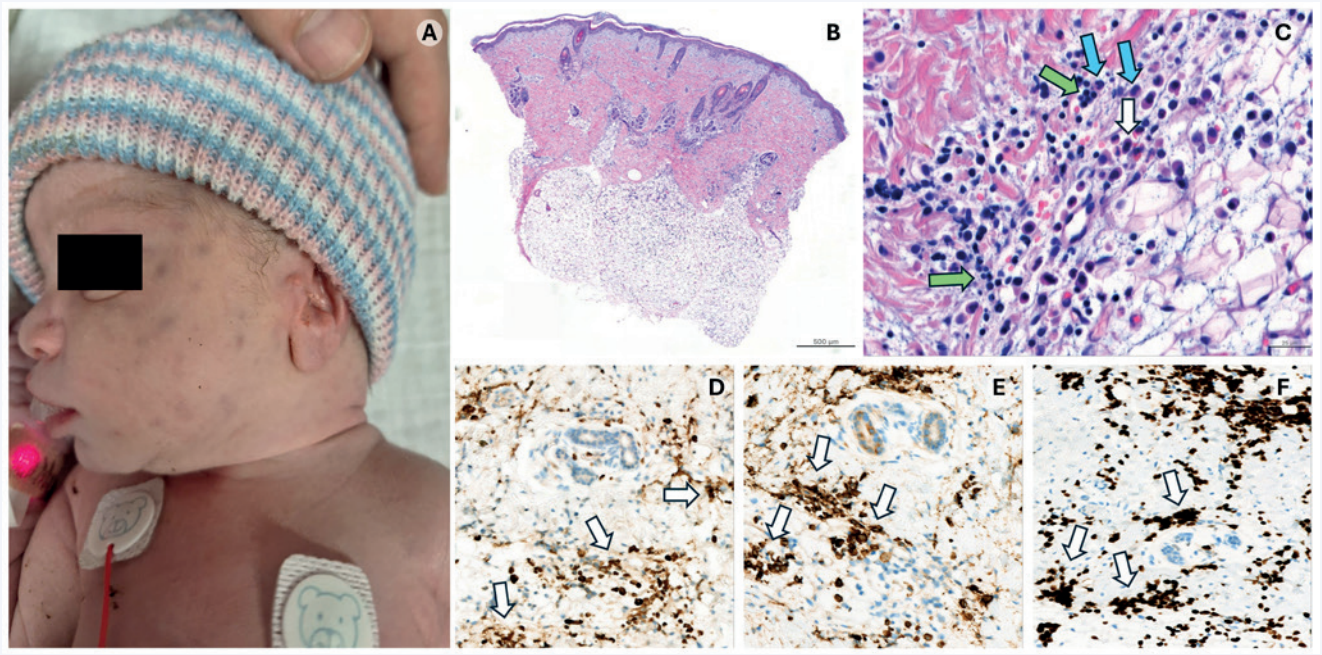
Initial blood tests revealed polycythemia with a hemoglobin level of 22.1 g/dL and a hematocrit of 60.5%, with significant erythroblastosis. The child's direct Coombs test was negative.

Biological analysis revealed mild thrombocytopenia. The white blood cell count showed transient neutropenia and moderate lymphopenia. The absence of hyperleukocytosis in this case indicated a lower probability of leukemia or infection.

The direct bilirubin level was 0.6 mg/dL on the first day of life, and the total bilirubin level was 18.4 mg/dL on the fifth day of life. Other blood parameters, including CRP and creatinine, were normal. Moderate biological disturbances in prothrombin time were observed and returned spontaneously to the expected neonatal range within one week.

Infectious workup, including multiplex PCR for various respiratory viruses, enterovirus PCR on stool, VZV and herpes simplex virus PCR, were negative. Urine CMV PCR was also negative. Imaging

FIGURE 1: A. Infiltrated violaceous macules on the face. B. Skin biopsy (Hematoxylin and Eosin stain, 20x magnification): Dermal-hypodermal infiltration. C. Skin biopsy (Hematoxylin and Eosin stain, 400x magnification): Immature granulocytic population (white arrow) showing granulocytic maturation (blue arrow) associated with an erythroblastic population (green arrow). D-F. Skin biopsy (Immunohistochemistry, 200x magnification): Myeloperoxidase (MPO) staining (D) highlights granulocytic lineage cells (white arrow), and CD71 staining (E) identifies erythroblastic clusters (white arrow). Ki67 staining (F) indicates a high proliferative index (white arrow).



studies, including abdominal ultrasound, chest X-ray, and brain MRI, were performed to investigate potential hepatosplenomegaly or bone abnormalities but did not reveal any significant findings.

Bone marrow aspiration revealed 3.5% blasts without significant morphologic or phenotypic abnormalities. A skin biopsy from the left buttock showed dermal and hypodermal infiltration by immature myeloid cells. The initial differential diagnosis included acute myeloid leukemia (AML) and extramedullary hematopoiesis (Figure 1.B through F). Immunohistochemical analysis revealed CD43, myeloperoxidase, and lysozyme positivity, and a high proliferation index confirmed by anti-Ki67 antibody. The absence of CD34, CD117, and TdT, and the presence of erythroblastic clusters expressing CD71, suggested extramedullary hematopoiesis.

Genetic analysis of mutations was performed to rule out inherited conditions associated with extramedullary hematopoiesis or other hematologic abnormalities. Mutational analysis of *FLT3* and *NPM1* genes in the skin biopsy, and *FLT3*, *NPM1*, *CEBPA*, and *IDH1/2* genes in the bone marrow found no pathogenic variants. These genes are frequently mutated in acute myeloid leukemia (AML), with *CEBPA* in particular being associated with familial AML. The absence of detectable mutations in these genes allowed for the exclusion of approximately 35% of pediatric AML cases. Furthermore, karyotyping of the bone marrow ruled out the presence of the *t(8;16)(p11;p13) (KAT6A-CREBBP)* translocation, which is linked to spontaneously remitting neonatal AML.

The skin lesions resolved spontaneously after eight days of life, and the child was discharged with pediatric follow-up. No specific etiology for the extramedullary hematopoiesis was identified.

TABLE 1: Etiologies of Blueberry Muffin Syndrome.

Non-neoplastic etiologies	Neoplastic etiologies
• **Congenital (TORCH) Infections:** - **T**oxoplasmosis - **O**ther (Syphilis, …) - **R**ubella - **C**ytomegalovirus - **H**erpes simplex virus **Other viral infections**: not classified within the TORCH group : enterovirus (coxsackievirus, …), parechovirus, …	• **Acute Leukemias**: - Acute myeloid leukemia - Acute lymphoblastic leukemia • **Lymphomas** • **Histiocytosis** - **Langerhans cell histiocytosis** - **Juvenile xanthogranuloma** • **Mastocytosis** (cutaneous or systemic) • **Infantile myofibromatosis** • **Metastatic tumors**: - Metastatic neuroblastoma - Metastatic rhabdoid tumor - Metastatic rhabdomyosarcoma - Metastatic tumors acquired via transplacental route • Choriocarcinoma • Melanoma • **Vascular tumors or malformations**: - Hemangioma
• **Hemolytic disease of the newborn**: - ABO and Rh Incompatibility - Hereditary spherocytosis • **Vascular hemodynamic conditions** - Twin-to-Twin transfusion syndrome	

Discussion

BMS can be one of the first manifestations of an underlying systemic pathology, whether reactive or neoplastic, necessitating thorough investigation. The characteristic skin nodules observed in BMS result from reactive extramedullary hematopoiesis or infiltration

TABLE 2: Etiological workup for Blueberry Muffin Syndrome.

Step	Purpose	Tools
Clinical assessment	Identify maternal history, prenatal risk factors, and newborn signs	Physical examination
Laboratory tests	Detect hematological abnormalities: • **Anemia/hemolysis**: Evaluate hemoglobin levels and markers of hemolysis • **Erythroblastosis and leukocytosis**: Assess the number of erythroblasts and leukocytes in the blood • **Evaluation of lymphocyte population**: Determine the dominant lymphocyte subtype (e.g., T-cells, B-cells, NK cells) • **Coagulation disorders**: Assess for abnormalities in clotting factors and platelet function Detect infections (e.g., TORCH,...)	Complete blood count Blood smear Serology PCR
Radiological imaging	Assess visceral involvement: • **Hepatosplenomegaly**: Check for liver and spleen enlargement, which may suggest underlying systemic disease • **Mediastinal mass**: Look for any masses in the mediastinum, possibly indicating lymphoma or other tumors • **Brain or spinal mass**: Identify any intracranial or spinal lesions that may be related to neoplastic processes	**Abdominal ultrasound** **Magnetic resonance imaging (MRI)** **Chest X-ray**
Bone marrow aspiration	Evaluate marrow function and rule out malignancy • **Aberrant marrow population/blasts**: assess for the presence of abnormal cells or blasts, indicating possible leukemia or other marrow pathology • **Genetic abnormalities**: Conduct cytogenetic or molecular tests to detect chromosomal anomalies or specific gene mutations	Morphology Flow cytometry Cytogenetics Molecular analysis
Skin biopsy	Differentiate extramedullary hematopoiesis from malignancies (e.g., leukemia cutis, Langerhans cell histiocytosis, ...)	Histology Immunohistochemistry Molecular analysis

by neoplastic cells depending on the underlying etiology (1,2) (Table 1). Understanding the mechanisms behind these lesions is essential for accurate diagnosis and management.

During fetal development, erythropoiesis begins in the yolk sac between 2 and 10 weeks of gestation, transitions to the liver from 10 to 18 weeks, and shifts primarily to the bone marrow by the third trimester. Extramedullary hematopoiesis occurs when normal bone marrow function is insufficient or disrupted, leading to hematopoietic activity in former hematopoietic sites or new secondary sites such as the skin. This compensatory mechanism can be seen in congenital infections or hematologic disorders, as well as in neoplastic conditions where marrow function is impaired.

Among the most frequent causes of BMS with extramedullary hematopoiesis in the skin are congenital infections and hematologic disorders. Intrauterine infections, including viral agents from the TORCH group (toxoplasmosis, rubella, CMV, herpes), as well as bacterial infections like syphilis, can disrupt normal fetal hematopoiesis. These infections may lead to direct bone marrow suppression, inflammation-driven hematopoietic dysfunction, or immune-mediated hemolysis, all of which may trigger extramedullary hematopoiesis. Similarly, hematologic disorders such as neonatal hemolytic diseases (e.g., ABO or Rh incompatibility, hereditary spherocytosis) and twin-twin transfusion syndrome (TTTS) may result in anemia, stimulating increased erythropoietin (EPO) production, which in turn drives extramedullary hematopoiesis and the development of BMS lesions (3–5). Notably, in TTTS, BMS is typically observed in the donor twin, who experiences chronic anemia.

Neoplastic causes of BMS include both benign and malignant neoplasms. Among hematologic malignancies, acute myeloid leukemia and acute lymphoblastic leukemia are commonly presenting as BMS, either through direct neoplastic infiltration of the skin or due to marrow dysfunction leading to compensatory extramedullary hematopoiesis. Congenital histiocytosis, including juvenile xanthogranuloma (JXG) and Langerhans cell histiocytosis (LCH), can also present with BMS-like lesions, with varying degrees of systemic involvement. In some cases, solid tumors such as neuroblastoma or rhabdomyosarcoma (6,7) may metastasize to the skin, causing a BMS. Transplacental metastases from maternal malignancies, such as melanoma or choriocarcinoma, are rare but should also be considered (7). Other rare neoplastic causes include infantile myofibromatosis and multifocal vascular lesions (8).

Mechanistically, neoplastic processes might impair hematopoiesis through several pathways, including direct marrow infiltration leading to spatial crowding, the release of inhibitory cytokines, and alterations in the bone marrow microenvironment, such as fibrosis. These mechanisms contribute to ineffective hematopoiesis and necessitate compensatory extramedullary hematopoiesis, which manifests clinically as BMS.

The diagnostic approach to BMS relies on differentiating between reactive/secondary extramedullary hematopoiesis, its etiology and neoplastic infiltration (1-2). A structured evaluation begins with a detailed maternal history, including prenatal screening results and infectious exposures, followed by a thorough newborn clinical examination to identify additional warning signs such as hepatosplenomegaly or lymphadenopathy. Laboratory investigations play a key role, with blood tests assessing hematologic parameters and markers of infection, while virological and serological assays help confirm congenital infections. Imaging studies, including ultrasound, X-ray, and MRI, can reveal visceral involvement such as hepatosplenomegaly or the presence of a mediastinal mass (9).

Bone marrow aspiration is crucial to assess the presence of blasts and bone marrow alterations, and to perform cytogenetic and molecular analyses to help distinguish between leukemia and

non-malignant causes of BMS (7). Skin biopsy, as a less invasive and more accessible procedure, plays a key role in distinguishing extramedullary hematopoiesis from neoplastic infiltrations such as histiocytosis, metastatic tumors or leukemic infiltration, which are not necessarily excluded by a negative bone marrow aspiration (9,10). While bone marrow aspiration can often rule out leukemia, cutaneous involvement - termed myeloid sarcoma or leukemia cutis - may arise independently. This dermatologic manifestation can precede, coincide with, or follow the diagnosis of leukemia, highlighting the complementary roles of bone marrow aspiration and skin biopsy in the clinical evaluation. Each of these diagnostic steps, summarized in Table 2, contributes to determine the underlying cause of BMS and guiding appropriate management.

BMS management requires a multidisciplinary approach involving pediatricians, dermatologists, hematologists, and pathologists. While skin manifestations are a key feature, BMS itself is usually asymptomatic. Treatment should target the underlying systemic condition responsible for BMS. In cases of extramedullary hematopoiesis with no definite underlying etiology, regular follow-up is necessary to monitor resolution and detect any evolving pathology (9).

In our case, the skin lesions resolved spontaneously. The favorable progression of the patient's health over an eight-month period argues against the presence of BMS-related complications. Continued clinical monitoring remains essential to detect any potential late-onset manifestations. No specific etiology for the extramedullary hematopoiesis was identified. The hypothesis proposed by clinicians is that potential chronic fetal hypoxemia in late pregnancy, which led to restricted growth, may have promoted extramedullary hematopoiesis. The absence of other symptoms and the normalization of laboratory values supported a favorable clinical course.

Conclusion

BMS, though rare, presents a significant diagnostic challenge due to its broad differential diagnosis. Accurate diagnosis involves a thorough evaluation to differentiate between non-neoplastic and neoplastic causes. This case highlights the importance of a detailed diagnostic approach and multidisciplinary management in ensuring favorable outcomes.

Conflict of interest

The authors and co-authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Patient informed consentient

The authors and co-authors declare that they informed the patient's family of the redaction of this article. The parents consented to the use of the clinical images and clinical information related to this case report.

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