Neonatal acute myeloid leukemia with KMT2A/MLLT3 rearrangement revealed by a Blueberry Muffin syndrome

Canelle Koutny [a], Ludovic Legros [a], Anne Mostaert [a], Anne-Sophie Truant [a], Tzanca Vatcheva [a], Benoit Florkin [b], Sophie Gatineau [b,c], Julie Longton [b,c], Elisabeth Henrion [a]

[a] Departement of Neonatal Intensive Care, CHR Sambre et Meuse, 185 Avenue Albert 1E, 5000 Namur, Belgium
[b] Departement of Pediatric Hemato-oncology, Hôpital de la Citadelle, 1 Boulevard du Douzième de Ligne, 4000 Liège, Belgium
[c] Departement of Pediatric Hemato-oncology, CHU de Liège, Sart Tilman, 1 Avenue de l'hôpital, 4000 Liège.

canellekoutny@gmail.com

Keywords

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Abstract

Blueberry Muffin syndrome is a rare skin manifestation that can be observed during neonatal period. It should make pediatricians explore the differential diagnosis of extramedullary hematopoiesis, including congenital infections, intrauterine anemias and, more rarely, neoplastic pathologies.

We report the case of a late term newborn showing birth lesions suggestive of this syndrome. In the absence of other associated clinical signs and abnormalities in the blood count, diagnostic investigations were completed by a skin biopsy and a bone marrow aspiration which led to the diagnosis of acute myeloid leukemia with a KMT2A/MLLT3 rearrangement. As leukemic burden was low, a watch-and-wait approach was chosen, until chemotherapy needed to be initiated at eight weeks of life.

Introduction

Blueberry Muffin syndrome (BMS) is the clinical manifestation in a newborn of a cutaneous extramedullary hematopoiesis that persists or reappears after the physiological embryological one. Its causes include congenital infections, hemolytic anemias, twin-to-twin transfusion syndromes, Langerhans histiocytosis and neoplastic causes such as neuroblastoma and acute leukemia. We report the case of a newborn with Blueberry Muffin syndrome without any associated clinical signs nor blood count abnormalities. The diagnosis of myeloid leukemia cutis could be made with a biopsy of the skin lesions and was then confirmed by a bone marrow aspiration. The KMT2A/MLLT3 rearrangement present in our patient made the management and prognosis singular.

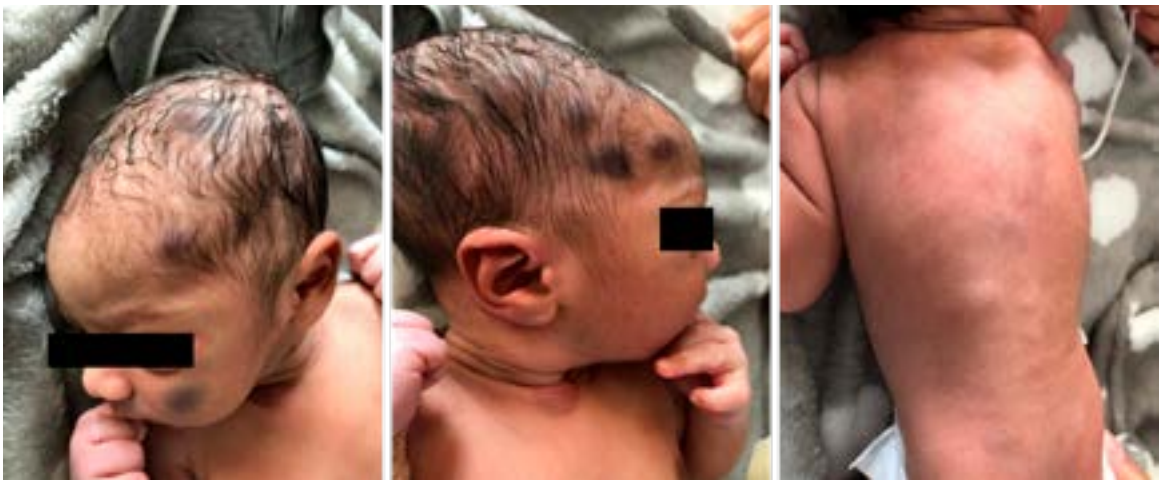
Case presentation

A male newborn, born at 41 weeks 2/7, eutrophic, presented himself at birth with erythematous-violaceous inflammatory macular, papular and nodular lesions of 1 to 1.5cm in diameter on the scalp, face, neck, trunk and limbs (Figure 1).

The pregnancy was triggered by artificial insemination and went without particularities. Family history was unremarkable, with non-consanguineous parents from Bangladesh. The mother was immune to rubella and cytomegalovirus (CMV) but not to toxoplasmosis. Prenatal ultrasounds were normal. The maternal screen for group B Streptococcus was negative. The delivery was induced for late-term pregnancy and was performed vaginally with vacuum instrumentation. The newborn presented a good adaptation to life and subsequently had cardiorespiratory parameters within standards and no fever. Apart from the skin lesions, his clinical examination was normal, with among others the absence of palpable intra-abdominal mass.

Because of the suspicion of BMS, an etiological workup was carried out. The blood tests showed a normal blood count without circulating blasts nor inflammatory syndrome. The infectious assessment was negative (toxoplasmosis, rubella, syphilis, herpes simplex, herpes zoster, parvovirus B19, Epstein-Barr virus, CMV, hepatitis B, and coxsackie serology and urinary CMV PCR). Hereditary spherocytosis and fetal-maternal incompatibility were also excluded. Lactate dehydrogenase and neuron-specific enolase were

Figure 1: Cutaneous erythematous-purplish infiltrated macules and papulonodules observed at birth.



normal. The abdominal ultrasound showed an absence of intra-abdominal mass and the chest X-ray showed no mediastinal enlargement.

In the absence of other etiological diagnosis, a skin biopsy was performed to exclude a tumoral etiology of the persistent skin lesions. This showed massive infiltration of the dermis by blast cells of the myeloid/monoblastic type, strongly positive for immunohistochemical labelling with CD33, CD68, CD123 and lysozyme, and weakly positive for CD56, CD43 and CD4, with a high index (>90%) of nuclear proliferation (Ki67) (Figure 2A-D). These results confirmed the diagnosis of myeloid leukemia cutis.

The bone marrow aspiration showed a moderate monocytoid-like blastosis consisting of monoblasts (12%) and promonocytes (10.5%) (Figure 2E). The immunological labeling was positive for CD45low, high SS, myeloperoxidase, HLA-DR, CD33, CD64, CD56, CD4 and negative for CD13, CD34, CD117 and CD11b. The cytogenetics study (FISH) revealed an abnormal clone characterized by a translocation involving part of the short arm of chromosome 9 and part of the long arm of chromosome 11 [t(9;11)(p21;q23)] leading to a KMT2A/MLLT3 rearrangement (formerly known as MLL-AF9). The lumbar puncture did not show any abnormal monoblastic population.

Because of the absence of peripheral blastosis, the low percentage of medullary blasts (< 30%) and the good general condition of the infant, a watch-and-wait approach was initially chosen in order to promote the growth of the infant and a better tolerance to chemotherapy.

Monitoring consisted of clinical and biological controls twice a week and a bone marrow aspiration every two weeks. The skin lesions involuted spontaneously after several weeks of life. The constitutional genetic workup for Down syndrome and Noonan syndrome then came back negative, when it would have modified the treatment if positive.

At eight weeks of life, the bone marrow aspiration showed an increase in the percentage of blasts (>30%), associated with neutropenia in the blood count, indicating the need to start chemotherapy for acute myeloid leukemia (AML) (following the NOPHO-DBH AML 2012 Protocol NCT01828489). The patient showed molecular remission 12 months after the end of treatment.

Discussion

Blueberry Muffin syndrome is the manifestation of a cutaneous extramedullary hematopoiesis. It presents as erythematous-purplish infiltrated macules or papulonodules (ranging from bright red to blue-grey), which are present at birth. It is often generalized but predominant in the trunk, head and neck (1).

The different etiologies are classified in table 1. Benign leukemoid reaction are due to the activation of the immune system in congenital infections or intrauterine anemias. Transient leukemoid reactions are due to constitutional chromosomic abnormalities responsible of an unstable hematopoiesis. They are associated with genetic syndromes or, more rarely, non-syndromic. Neoplastic causes are extremely rare and are due to an excessive production of immature or abnormal white blood cells (Table 1) (2).

In the case of skin nodules present during the neonatal period, clinicians have to look for malignancy characteristics such as the explosive nature (rapid multiplication) of the lesions, their indurated appearance and bluish color, an alteration of the general condition, and the presence of lymphadenopathies or hepatosplenomegaly (1).

Leukemia cutis or cutaneous leukemia is defined as the presence of leukemic cells in the dermis. It is the characteristic presentation of congenital leukemia, which is one of the causes of the so-called "Blueberry Muffin Syndrome. Around 2/3 of patients with neonatal leukemia have leukemic skin infiltration, and it is more often seen in acute myeloid leukemia (AML) than in acute lymphocytic leukemia (ALL).

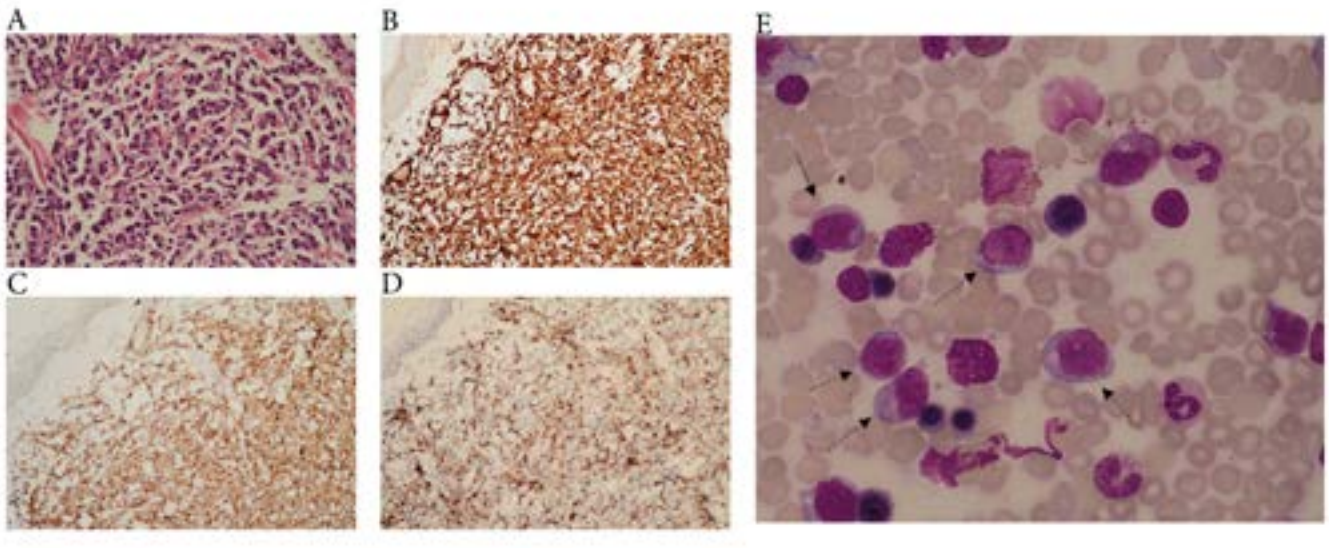
In 10% of newborns with leukemia cutis, no blasts are found at the bone marrow aspiration. In those cases, the term aleukemic leukemia cutis is used. A possible explanation for this phenomenon is the postnatal persistence of fetal physiological dermal hematopoiesis, which normally occurs during the first to fifth months of pregnancy but may be seen in cases of prematurity or intrauterine growth retardation, with a subsequent evolution to leukemic cells. Alternatively, leukemia cutis may represent skin metastases from unrecognized systemic leukemia (3).

Histologically, leukemia cutis classically appears as a dense and diffuse intra-dermal infiltrate of leukemic cells (as illustrated in our patient), of variable sizes and shapes. Their nuclei usually vary from an atypical aspect to a monomorphic appearance (3). In our patient, these cells presented a polymorphic appearance, showing either notches or a monocytoid appearance, sometimes accompanied by numerous nuclear debris.

A positive immunohistochemical labeling with CD68 and lysozyme has been described in 95% of adult cases of myeloid leukemia cutis regardless of the subtype of systemic leukemia (4). CD43 was found to be positive in 97% of patients with myeloid leukemia cutis in another study (4). These three markers were positive in our patient. In contrast, several studies which evaluated aleukemic myeloid leukemia cutis in adults and neonates showed no consistent markers (4).

Neonatal leukemia is defined by its onset within the first 28 days of life. It is a rare pathology (1 in 5 million births) which represents less than 1% of all pediatric

Figure 2: (A-D) Skin lesions biopsy on day 1. (A) Infiltration of the dermis and subcutaneous fat by blast cells. (B) Immunohistochemical labeling with lysozyme. (C) Immunohistochemical labeling with CD33. (D) Immunohistochemical labeling with CD68. (E) Bone marrow aspiration on day 7. Monocytoid-like blastosis consisting of monoblasts (dotted line arrows) and promonocytes (continuous arrow).



leukemias (3). It remains, however, the leading cause of neonatal death due to neoplasms. The majority of cases are congenital. In 66% of cases, neonatal leukemia is an AML with monocytic or monoblastic characteristics, while pediatric leukemias are mainly ALL (5).

Neonatal leukemia differs from pediatric leukemia by its clinical presentation (often presenting as a blueberry muffin appearance) and the frequency of associated cytogenetic abnormalities (such as KMT2A gene rearrangements) (6).

Clinically, neonatal leukemia can present with skin nodules (25-64% of cases), hepatomegaly (80% of cases), splenomegaly (75% of cases), lymphadenopathies (24% of cases) and central nervous system infiltration (50% of cases). Hyperleukocytosis is present in 49% of AML cases (7). Among these clinical and biological signs, only skin nodules were present in our patient.

The diagnosis was therefore made by the presence of medullary blastosis and skin infiltration in the absence of other causes of extramedullary hematopoiesis and genetic abnormalities.

Regarding the cytogenetics characteristics of neonatal leukemias, KMT2A gene rearrangements are found in 73-80% of neonatal ALL and in 32-50% of neonatal AML (8,9). The KMT2A gene is located at chromosome band 11q23 and encodes for the lysine-specific methyltransferase 2A that regulates gene expression (10). While wild-type KMT2A plays a major role in embryogenesis and maintenance of hematopoiesis, its rearrangements result in improper expression of genes involved in proliferation and lineage identity. Indeed, KMT2A rearrangements are acquired in hematopoietic precursors in utero and subsequently initiate a rapid progression to leukemia (9). There are currently approximately 100 different KMT2A fusion partner genes identified (9,10). The three most common partner genes in pediatric AML account for 66% of cases and are MLLT3 (22%), as seen in our patient, MLLT10 (27%) and ELL (17%) (9).

The prognosis for neonatal leukemia is poor. Moreover, KMT2A rearrangements are globally associated with inferior outcomes (10). In neonatal AML, the outcome significantly differs depending on the partner gene involved in the KMT2A rearrangements, unlike in neonatal ALL, in which KMT2A rearrangements are clearly associated with a poorer prognosis (9,11). Survival rates prior to 2000 were 23-26%, with a significantly better survival for AML (35%) than for ALL (9%) (5,7). In a more recent retrospective study of cases from 2001 to 2016, the two-year overall survival rate for congenital leukemia was 44.2%, and the two-years survival rate was 0% for patients with a KMT2A rearrangement and 69.5% for those without it (8). Recent multiomics analyses of KMT2A rearranged leukemia reveal higher lineage plasticity and stem-cell-like blasts in younger patients (12). These stem-cell-like blasts may contribute to the ability to evade chemotherapy and immune-mediated control, which explains the higher risk of relapse seen among younger patients with KMT2A ALL. As stated above, the outcome of pediatric AML with KMT2A rearrangements also differs according to the fusion partner genes. KMT2A/MLLT3 fusion is the most common rearrangement in children, but its prognosis remains controversial (10). Indeed, some reports have been able to demonstrate a better prognosis for AML associated with the KMT2A/MLLT3 rearrangement (11,13), while others have shown similar survival compared to the other KMT2A rearrangements (10,14). In many AML protocols, FISH screening for KMT2A rearrangements at diagnosis has thus become a standard approach (11). Finally, leukemia cutis, as described in our case, is also considered a factor of poor prognosis. Indeed, in the French ELAM02 cohort, they hypothesized that chemotherapy for AML may be sufficient to induce remission in bone marrow but not to penetrate the skin, thus leading to a higher risk of relapse (15).

Spontaneous remission is more likely to occur in neonates than in older infants and children, but it is unusual in neonates with KMT2A rearrangements (16,17). Nevertheless, due to its high toxicity during the first months of life and the possibility of spontaneous remission, the decision to initiate chemotherapy for the treatment of neonatal AML may be deferred in favor of a watch-and-wait attitude (16,17). Indeed, if the clinical and biological state of the patient allows it, a watch-and-wait attitude is advised until the potential remission or the progression to systemic leukemia (4). In this situation, regular clinical and biological (including bone marrow aspiration) follow-up is however essential for several years. Indeed, in the event of relapses during follow-up, some patients require chemotherapy as a second step. In two case reviews, Coenen et al. and Grundy et al. reported such relapses, respectively, in 4 out of 7 cases and in 10 out of 16 cases (16,18). The time to relapse was variable, ranging from several weeks to more than ten years. It is not clear which prognostic factors can predict these relapses, as the status of the bone marrow and the initial blood count cannot be used to predict a relapse or remission (18). In our patient, a watch-and-wait attitude was initially proposed to avoid the harmful impact of chemotherapy on the infant's growth. The decision to start chemotherapy was subsequently motivated in view of the progressive nature of the disease marked by the appearance of cervical, axillary and inguinal adenopathies, an increase in the percentage of bone marrow blasts (>30%), and the appearance of neutropenia and anemia. Besides, it would probably have been initiated anyways because of the KMT2A rearrangement present in our patient, as suggested by most authors (8-11).

In the latest published cases, chemotherapy usually associates cytarabine, etoposide, and an anthracycline, combined with intrathecal chemotherapy (in prophylaxis of an invasion of the central nervous system) (17). Our patient was treated with a similar protocol.

Table 1: Etiologies of Blueberry Muffin syndrome and associated diagnostic tests.

Etiologies	Diagnostic tests
Benign leukemoid reaction	
Congenital infections	
Toxoplasmosis, syphilis, herpes simplex, herpes zoster, rubella, CMV, parvovirus B19, EBV, coxsackies, hepatitis B, listeriosis	Serology or PCR
Intrauterine anemia	
Fetal-maternal incompatibility	Direct and indirect Coombs test, hemogram, reticulocytes, bilirubin, blood smear
Hereditary spherocytosis	MCHC/MCV rate, spherocytes at blood smear, osmotic fragility test, cryohemolysis test or 5'EMA test
Major anemia in twin-to-twin transfusion syndrome, fetal-maternal hemorrhage, intracranial perinatal bleeding	Hemogram
Transient leukemoid reactions due to chromosomic abnormalities	
Down syndrome, Noonan syndrome	Constitutional genetic workup
Neoplastic causes	
Langerhans histiocytosis	Hemogram, liver function tests, bilirubin coagulation tests, biopsy of skin lesions, abdominal ultrasound, chest and skeleton X-rays
Neonatal leukemia (leukemia cutis)	Hemogram, biopsy of skin lesions, bone marrow aspiration
Neuroblastoma	Urinary catecholamines, ferritin, neuron specific enolase, bone marrow aspiration
Congenital rhabdomyosarcoma	Biopsy of lesions

CMV: Cytomegalovirus. EBV: Epstein Barr Virus. MCHC: Mean Corpuscular Hemoglobin Concentration. MCV: Mean Corpuscular Volume.

Conclusion

This case highlights the importance of considering the hypothesis of neonatal leukemia in front of a Blueberry Muffin syndrome, even in the absence of other clinical signs, peripheral blastosis or abnormalities in the blood count. If no obvious etiology is found, investigation must be further conducted by a skin biopsy, supplemented subsequently by a bone marrow aspiration. Some neonatal acute myeloid leukemias show spontaneous remission. Due to the significant toxicity of chemotherapy in the first

months of life, a watch-and-wait approach can therefore be proposed at first, if the patient's condition allows it. However, in case of poor prognosis factors, such as KMT2A rearrangements, earlier chemotherapy should be applied. For those without KMT2A rearrangements, close biological and clinical monitoring is required for several years, due to the possibility of relapses. Chemotherapy is thus needed in the event of progressive disease.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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