CASE REPORT

Blueberry muffin baby with acute myeloid leukemia and spontaneous remission

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A B S T R A C T

Blueberry muffin baby is a rare neonatal skin disorder. Causes for the generalized hemorrhagic purpuric eruptions include congenital infections, hemolysis, and tumors. We report a 2.5-month-old female baby with a blueberry muffin appearance, respiratory distress, and decreased activity and appetite. Skin biopsy showed diffuse infiltrates of myeloperoxidase- and lysozyme-positive blast-like cells in dermis and superficial subcutis. Bone marrow study confirmed the diagnosis of acute monocytic leukemia with leukemia cutis. The skin nodules regressed spontaneously without chemotherapy over several days, and the peripheral blood cell counts normalized. This spontaneous remission lasted for 2 months. Spontaneous remission of infantile leukemia is rare, and its mechanism remains unknown. Although overt leukemia relapsed in some of these patients, a delay in chemotherapy spared these infants of the toxic effects of treatment.

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Introduction

Leukemia cutis occurs in 25–30% of infants with leukemia, most commonly with acute myelogenous leukemia of the French–American–British (FAB) classification M4 or M5.1,2 Skin lesions typically consist of bluish or purplish dermal nodules in a generalized distribution.1–3 The natural history of congenital leukemia is usually fatal despite aggressive chemotherapy, although a few patients have experienced temporary or permanent spontaneous remissions.1 We report an infant with leukemia-associated blueberry muffin syndrome, whose clinical course was unusual because of a temporary spontaneous remission.

Case report

A 2.5-month-old baby girl was brought to our hospital with a 7-day course of multiple bluish skin nodules and a 2-day history of poor activity, decreased appetite, and respiratory distress. She was born to a healthy 28-year-old woman after an uncomplicated pregnancy and had appeared healthy until 1 week ago. Physical examination revealed a phenotypically normal but floppy and unconscious female infant with multiple 0.3- to 3 cm-sized bluish-purpuric macules and subcutaneous nodules on the chest, abdomen, and back (Figure 1). Laboratory studies revealed a white blood cell count of 79 900/μL with 15% abnormal lymphocytes and monocytes, hemoglobin of 3.5 g/dL, and a platelet count of 50 000/μL. Skin biopsy under the clinical diagnosis of blueberry muffin syndrome showed diffuse infiltrates of monotonous blast-like cells with round, vesicular nuclei; granular cytoplasm; and many mitotic figures in dermis and superficial subcutis (Figure 2).

Immunohistochemically, the blast cells were positive for myeloperoxidase, lysozyme (Figure 3), CD43, and KP1. CD117, Terminal deoxynucleotidyl transferase (TdT), trypase, neuron-specific enolase, and synaptophysin were negative. The pathologic diagnosis was acute myeloid leukemia cutis. In the mean time, 41% blast cells were identified by peripheral blood smear. Bone marrow aspiration demonstrated 58.6% blast cells, most of them being large primitive cells with roughly circular nucleus and abundant basophilic cytoplasm. These blast cells are negative for periodic acid–Schiff and myeloperoxidase stains. They are positive for human leukocyte antigen (HLA)-DR, CD13, CD14, CD15, CD33, and CD34. Few of them expressed weakly for CD41. The cellular morphologic findings and staining were consistent with acute monocytic leukemia, FAB classification M5. Peripheral blood mutation of GATA 1 wild type was not detected. The admission course was complicated by tumor lysis syndrome with hyperkalemia, hypocalcemia, hyperphosphatemia, hyperuricemia, and acute renal failure. Supportive...
treatment instead of chemotherapy was given because of poor general condition. The skin nodules regressed spontaneously without chemotherapy over several days, and her blood cell counts gradually normalized. Peripheral blood showed spontaneous remission without immature blood cells in the subsequent weeks.

The spontaneous remission of leukemia raised the possibility of Down syndrome. However, there is no characteristic dysmorphic feature, and cytogenetic study of Down syndrome was not performed at that time.

Two months later, a relapse of acute myeloid leukemia occurred with hepatosplenomegaly, followed by multiple neck and inguinal lymphadenopathies. No cutaneous nodules were present. Laboratory evaluation showed a white blood cell count of 24,500/μL with 95.7% lymphocytes, 2.3% atypical lymphocytes, and 2% blast cells; hemoglobin of 6.6 g/dL; and a platelet count of 77,000/μL. Reverse transcriptase polymerase chain reaction studies of peripheral blood were positive for mixed-lineage leukemia (MLL)-AF9 fusion transcript [t(9;11)], whereas they were negative for MLL-AF6 [t(6;11)] and MLL-ENL [t(11;19)ENLα1] fusion transcript. These clinical and laboratory findings along with MLL rearrangement of peripheral blood confirmed a relapse of acute myeloid leukemia.

The patient was then enrolled into Taiwan Pediatric Oncology Group acute myeloid leukemia (AML) 97A protocol because of progression of disease and the presence of high-risk cytogenetic feature. She received four courses of chemotherapy with regimens of idarubicin, cytarabine (Ara-C), high-dose Ara-C (HD-Ara-C), and Etoposide (VP-16). Unfortunately, she died at 16 months of age because of Candida meningitis, and further study of Down syndrome was not performed.

**Discussion**

Blueberry muffin baby is a morphologic term used to describe the appearance of non-blanching, blue-red macules or firm papules, and nodules in young babies.\(^4\) The eruption is often generalized but favors the trunk, head, and neck.\(^4\) It had been reported to be a manifestation of either dermal erythropoiesis or neoplastic infiltrations.\(^4,5\) Dermal erythropoiesis may be caused by congenital virus infections, such as rubella, cytomegalovirus, coxackie virus B2, and parvovirus B19, or by severe hemolysis associated with Rh incompatibility, blood group incompatibility, hereditary spherocytosis, and twin–twin transfusion syndrome.\(^4\) Among the neoplastic diseases with the presentation of blueberry muffin babies, neuroblastoma was the most common, whereas rhabdomyosarcoma, Langerhans cell histiocytosis, and leukemia were less frequently reported.\(^4,5\)

A skin biopsy is invaluable in the diagnostic evaluation of blueberry muffin babies. If dermal collections of nucleated and nonnucleated red blood cells with a few myeloid precursors are seen, further studies to diagnose the causes of dermal erythropoiesis should include a peripheral blood cell count, hemoglobin level, congenital infection (TORCH) serologies, viral cultures, and Coombs’ test.\(^4\) If the histopathologic findings suggest neoplastic infiltrations, histochemical stainings, immunohistochemical

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**Figure 1** Multiple 0.3- to 3-cm-sized bluish and purpuric macules and subcutaneous nodules on the chest and abdomen.

**Figure 2** (A) Diffuse infiltrates in dermis and superficial subcutis. (B) Monotonous blast-like cells with round, vesicular nuclei; granular cytoplasm; and many mitotic figures (hematoxylin and eosin, original magnification 20× [A] and 400× [B]).
stainings, urinary catecholamines, peripheral blood smears, bone
marrow studies, and image studies may help confirm the diagnosis.

The skin nodules and peripheral blasts of our patient regressed
spontaneously over the course of several weeks without chemo-
therapy. Review of the English literature revealed several reports
of infants with spontaneously remitting leukemia, including four cases
with isolated skin involvement and 15 cases with widespread
diseases. The mechanism of spontaneous remission is not clear.
One of the proposed hypotheses is that the tumor burden is low
enough to be overcome by the patient’s immune system. Another
explanation corresponds to the “multiple-hit” theory of leukemo-
genesis. Once the abnormal leukocytes observed initially may rep-resent
a myeloid clone derived from a multipotent progenitor cell with
enhanced proliferative capacity but are incapable of indefinite self-
renewal and, thus, are not “fully malignant.” Trisomy 21,11q23, and
translocations are the most common chromosomal aberrations associated
with neonatal leukemia. These cytogenetic abnormalities found in the
leukemic cells of neonates and infants are clearly different from
those in older children and adults, and this may explain, in part, the
risk cytogenetic features that are associated with aggressive clinical
courses, such as MLL (11q23) rearrangement and breakpoint cluster
region (BCR)-c-abl oncogene 1(Abl) [t(9;22)] translocation. This
“watchful waiting” approach might spare very young infants the
severe morbidity of chemotherapy. Even if a relapse occurs after
spontaneous remission, such a postponement of chemotherapy
allows time for growth and development; hence, the infants are
less vulnerable to the toxic effects of chemotherapeutic agents.
However, to date, there are no distinguishing features to predict
the occurrence of spontaneous remission at the time of diagnosis.

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