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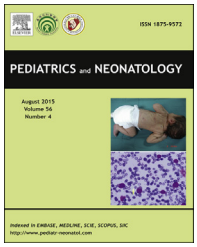

CASE REPORT

A Newborn with Congenital Mixed Phenotype Acute Leukemia After *In Vitro* Fertilization

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Congenital leukemia is a rare disease. The majority of cases of this disease are acute myelogenous leukemia (AML). Congenital acute lymphoblastic leukemia (ALL) is rare and most often is of B cell lineage. Rarely, some cases have been designated biphenotypic or mixed phenotype acute leukemia (MPAL). Herein, we report a preterm newborn referred to us as a result of the appearance of blue-violaceous dermal nodules on her body at birth. She was a twin and the product of an *in vitro* fertilization (IVF) pregnancy. Physical examination showed jaundice, hepatosplenomegaly, and peripheral facial nerve palsy in addition to dermal nodules. Bone marrow aspiration showed 40% blasts of lymphoid lineage; skin biopsy and its immunohistochemistry revealed myeloblastic infiltration of the dermis. Cytogenetic analysis (46,XX), fluorescence *in situ* hybridization (FISH) analysis, and cranial magnetic resonance were normal. The patient was diagnosed with congenital MPAL, and an association between IVF and congenital leukemia was suggested.

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1. Introduction

Leukemia diagnosed from birth to 6 weeks of age is defined as congenital leukemia.[1] Congenital leukemia cases are fewer than five per 1 million live births, and 80% of cases are nonlymphoblastic.[2] The majority of congenital leukemia cases are acute myelogenous leukemia (AML).[3] Congenital acute lymphoblastic leukemia (ALL) is rare and most often of B cell lineage (B-ALL).[3] Rarely, some cases (around 5%) of leukemias have been designated biphenotypic or mixed phenotype acute leukemia (MPAL).[4,5] Twenty-five to thirty percent of newborns with leukemia have leukemia cutis, which is a direct infiltration of skin and subcutaneous tissue by malignant cells. Leukemia cutis usually occurs in patients with AML but may also be seen in ALL.[4] Herein, a newborn with congenital MPAL is reported and an association between *in vitro* fertilization (IVF) and congenital leukemia is suggested.

2. Case Report

A 10-day-old female newborn was referred to our hospital owing to the appearance of blue-violaceous dermal nodules on her body at birth. The patient was the product of an uneventful pregnancy induced by IVF because of primary infertility. She was born by cesarean section following a 35-week pregnancy as a twin pair to a 24-year-old healthy mother and her unrelated 29-year-old healthy husband. Birth weight, length, and head circumference of the patient were between the 25th and 50th percentiles. Her brother was healthy. There was no history of maternal illness, malignancy, smoking, drug and alcohol use, exposure to X-rays or other known teratogens. It was learned that the mother had consumed just a small amount of tea, coffee, and cacao during pregnancy. Physical examination showed jaundice and multiple nonblanchable, firm, blue-violaceous dermal nodules, 3—10 mm in diameter, on her scalp, face, neck, chest, abdomen, back, buttocks, and extremities (Figure 1). The oral and ocular mucosa, palms, and soles were not affected. Petechiae/ecchymoses were absent. Liver and spleen were palpable 4 cm and 2 cm under the midclavicular line of the costa, respectively. No dysmorphic features were noted. Bilateral fundoscopic examination was normal. On the 6th day of hospitalization, peripheral facial nerve palsy was determined.

The initial complete blood count showed a white blood cell count of 10.200/mm^3, hemoglobin 12.2 g/dL, and a platelet count of 51.000/mm^3. A peripheral blood smear demonstrated circulating blasts (19%), while a bone marrow aspiration showed approximately 40% blasts of lymphoid lineage (Figure 2). Periodic acid Schiff and myeloperoxidase (MPO) stains were negative. Bone marrow flow cytometry showed surface cluster of differentiation 45 (CD45) 85.4%, CD3 62.8%, CD5 63.7%, and CD7 68.3%, while other markers [CD10, CD13, CD15, CD19, CD20, CD22, CD33, CD34, CD79a, CD117, terminal deoxynucleotidyl transferase (Tdt), and human leucocyte antigen-DR (HLA-DR)] were negative. A skin biopsy specimen demonstrated a dense papillary dermis and perivascular infiltrate composed of relatively uniform large neoplastic cells with round to oval nuclei, distinct nucleoli, and little basophilic cytoplasm. The epidermis was intact and a grenz zone was present under the epidermis. Dermal adnexes and subcutis were not involved. Immunohistochemistry of the skin biopsy specimen revealed myeloblastic infiltration with CD34 and MPO positive (Figure 3), whereas TdT/CD117/S-100 and CD1a were negative. The present patient was diagnosed with congenital mixed phenotype acute leukemia according to the World Health Organization (WHO) 2008 classification because CD3 was shown positive (by bone marrow flow cytometry, T-lymphoid lineage) and MPO was shown positive (by immunohistochemistry, myeloid lineage).[5] Cytogenetic analysis performed from a peripheral blood sample showed a normal female karyotype. There were no abnormalities in chromosome 21 or 11q23 region on 20 cells and five cells karyotyped, respectively. Fluorescence *in situ* hybridization (FISH) analysis was performed with an 11q23 region probe (LSI/MLL/DC/BAR-Vysis) and chromosome 7 (LSI/D7S522/CEP7-Vysis). The FISH results for translocations or deletions involving the *MLL* gene and for monosomy 7 or 7q deletions were negative. Serum transaminases and cranial magnetic resonance imaging were normal. Examination of cerebrospinal fluid cytology was free of malignant cells. Blood cultures and serum antibody titers against TORCH infections were negative. Total

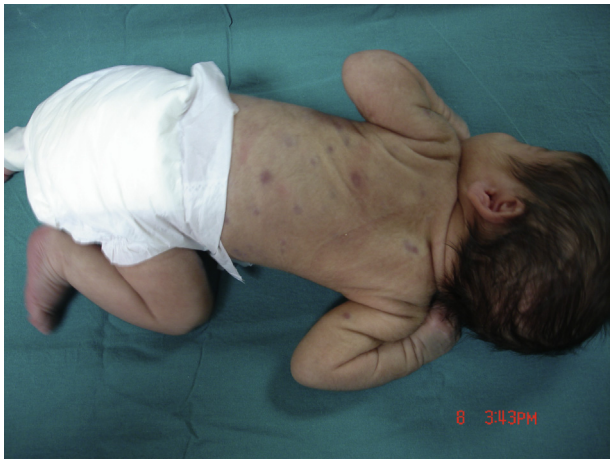

Figure 1 The appearance of dermal nodules.

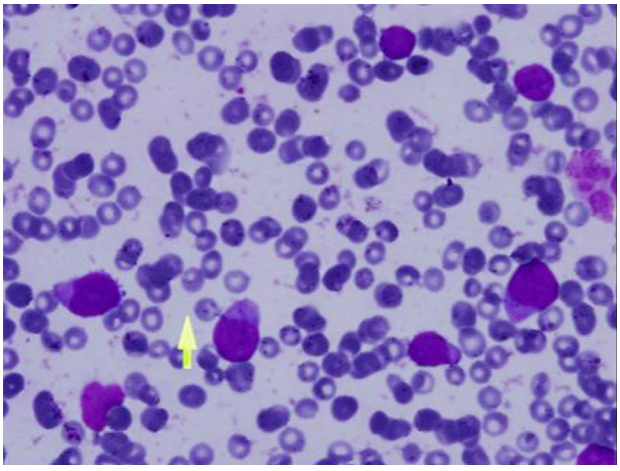

Figure 2 The bone marrow smear showing lymphoblastic cells (Wright's stain, 100×).

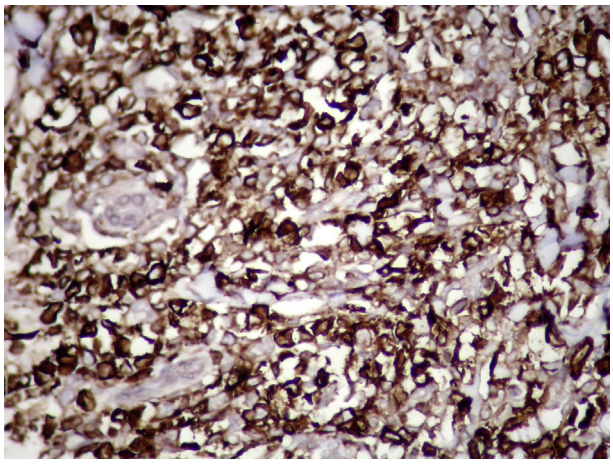

Figure 3 The myeloperoxidase (MPO) stain is positive in the neoplastic cells on the dermal infiltration (MPO, 400×).

bilirubin level was 16.2 mg/dL. Blood group incompatibility, glucose-6-phosphate dehydrogenase deficiency, hereditary spherocytosis, and hypothyroidism were not detected. The Interfant-99 protocol [induction phase including prednisone 60 mg/m^2 daily intravenous (IV) within the 1st week of hospitalization; dexamethasone 6 mg/m^2 daily IV from 8 days to 15 days; vincristine 15 mg/m^2 IV on the 8th day; cytarabine 75 mg/m^2 daily IV from 8 days to 15 days; and daunorubicin 30 mg/m^2 IV on the 8th and 9th days] was administered to the patient for MPAL. However, she died because of massive gastrointestinal hemorrhage on the 15th day following initiation of chemotherapy.

3. Discussion

The etiology of congenital leukemia is unknown.[1] However, several factors may be associated with the development of leukemia in the newborn period. These include maternal exposure to radiation, high birth weight (>4000 g), and high levels of insulin-like growth factors as well as exposure to topoisomerase-II inhibitors, such as coffee, tea, cocoa, wine, and soy products.[6] In this study, there were no leukemia-associated factors except for maternal consumption of small amounts of tea, coffee, and cacao during pregnancy.

The clinical features of congenital leukemia include nodular skin infiltrates, hepatosplenomegaly, lethargy, poor feeding, pallor, purpura/petechiae, and respiratory distress.[1] The present patient had only nodular skin infiltrates and hepatosplenomegaly. The diagnosis of congenital leukemia includes proliferation of immature leucocytes, infiltration of these cells into the extra hematopoietic tissue, absence of disease that can cause leukemoid or leukoerythroblastic reactions such as congenital infection, ABO incompatibility, and absence of chromosomal disorders that may be associated with unstable hematopoiesis, such as trisomy 21.[3] Our patient fulfilled all these criteria.

Leukemia cutis may be the first manifestation of congenital leukemia.[7,8] It presents as firm erythematous or blue-violaceous macules, papules, and nodules as a result of infiltrating leukemic cells in the skin.[8] Leukemia cutis is cited as occurring in 25—30% of patients. These lesions are observed most commonly in AML but may also be seen in ALL.[7,8] The lesions are typically multiple and distributed in a generalized pattern. Involvements of oral and ocular mucosa are quite rare.[8] There were widespread blue-violaceous dermal nodules on our patient's body except on the oral/ocular mucosa, palms, and soles.

Although a few cases with spontaneous remission have been described, congenital leukemia has a poor prognosis.[3,8,9] When congenital AML and ALL were compared, clinical characteristics and overall survival were not found to be significantly different.[9] Our patient died after a few days of the chemotherapy.

The classification of acute leukemias is based on a combination of morphology and cytochemical staining.[5] In most cases, the cells are of myeloid or lymphoid origin. However, in approximately 5% of cases, a single blast population coexpresses myeloid and lymphoid antigens. These cases are designated as acute biphenotypic leukemia, hybrid or mixed lineage leukemia.[4] Bilineage leukemia is defined as two different lineages of leukemic cell population in the same patient at the same time.[10] This type of leukemia, formerly designated as "bilineal acute leukemia" and "biphenotypic acute leukemia", is now collectively considered to be "mixed phenotype acute leukemia".[5] CD3 positive for T-lymphoid lineage by bone marrow flow cytometry and MPO positive for myeloid lineage by immunohistochemistry of skin biopsy specimen were determined in the present patient. According to the WHO 2008 classification, the present patient was diagnosed as MPAL. To our knowledge, this neonatal case report is the first case of congenital MPAL in the literature.

Chromosomal instability is a hallmark of congenital leukemia. The most commonly involved gene in infant leukemia is MLL, which encodes a 431-kDa protein. The most common translocations involving MLL are the t(4;11) and t(11;19) in ALL, and the t(9;11), t(6;11), and t(11;19) in AML.[11] There were no (LSI/MLL/DC/BAR-Vysis) deletions or translocations or monozomy 7 and 7q deletions (LSI/D7S522/CEP7-Vysis) in our patient.

Although IVF is not considered to be associated with an increased risk of pediatric malignancies, some cases with neuroectodermal tumors (neuroblastoma and medulloblastoma), embryonal cancers (hepatoblastoma and renal clear cell sarcoma), and retinoblastoma born after IVF have been reported.[12—15] Enhanced ovulation and spermatogenesis induced by various hormonal treatments, various manipulations performed on the germ cells and the fertilized ovum, and preservation of pregnancy by progestational hormones are prone to carcinogenic effects in these pregnancies.[14] A possible association between IVF and congenital leukemia may be suggested in the presented patient, who did not have any environmental, prenatal, or familial risk factors.

In conclusion, it should be kept in mind that skin nodules in a newborn may be a presenting sign of malignancy, and that the evaluation of these newborns using laboratory studies, peripheral blood smear, bone marrow aspiration, serologies, cytogenetics, and skin biopsy must be performed as soon as possible.

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