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Congenital Monoblastic Leukemia with 9;11 Translocation in Monozygotic Twins
: A Case Report

We report an autopsy case of congenital monoblastic leukemia that developed in monozygotic twins. The twin presented with progressive hepatosplenomegaly at 4 weeks after birth. One twin died of massive bleeding and hypovolemic shock before the treatment started. At autopsy, the liver was diffusely enlarged and showed a diffuse whitish discoloration except for the subcapsular and perivenular areas. Microscopic examination disclosed infiltration of histiocyte-like atypical cells along the sinusoids and portal areas of the liver. Spleen, lymph nodes and choroid plexus were also infiltrated by the tumor cells. However, bone marrow involvement of the tumor was minimal although multifocal. On immunohistochemical staining, these atypical cells were reactive for CD68 (PGM-1) and lysozyme, suggesting that the tumor cells might have been derived from monohistiocyte. Cytogenetic study revealed 9;11 translocation, which is frequently associated with acute monoblastic leukemia. To the best of our knowledge, this is the first report of congenital monoblastic leukemia of monozygotic twins in Korea.

Key Words : *Leukemia; Twins, Monozygotic; Hepatomegaly; Splenomegaly; Translocation (Genetic)*

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INTRODUCTION

Congenital leukemia is an extremely rare disease (1). Approximately 100 cases have been reported in the literature. It has several characteristics such as predominance of myeloid type, resistance to therapy, and frequent association with chromosomal abnormalities (2, 3). We report an autopsy case of a 4-week-old female monozygotic twin who died of acute monoblastic leukemia. She was born with a massive hepatosplenomegaly, and a long list of differential diagnosis was made even after the postmortem examination. The rarity of the case along with difficult differential diagnosis prompted this report.

CASE REPORT

A 35-day old female infant was presented to a local hospital with abdominal distension which was detected at 4 weeks after birth. She was the second co-twin of monozygotic twin pregnancy, and her sister showed the same clinical features. She was phenotypically normal with no gross congenital anomalies. Physical examination revealed hepatomegaly and ascites. Computed tomography of abdomen showed massive hepatomegaly and mild splenomegaly, but lymph node enlargement was not noted.

For further evaluation, she was transferred to Seoul National University Children's Hospital with presumptive diagnosis of glycogen storage disease. Hematologic laboratory values included hemoglobin 6.2 g/dL, platelets 32,000/μL and white blood cells 12,450/μL with 61% segmented neutrophils, 21% lymphocytes, 11% monocytes and no blasts. However, peripheral blood smears revealed atypical lymphocytes less than 5% of the total leukocytes. Liver function profiles were normal. Screening tests of disseminated intravascular coagulation showed severe coagulopathy with prothrombin time 2.72 (INR), activated prothrombin time 120 sec and fibrinogen 105 mg/dL.

To exclude a possibility of hematolymphoid malignancy including acute leukemia, bone marrow aspiration biopsy was performed from her sister because she showed hemorrhagic diathesis by a severe disseminated intravascular coagulation. The bone marrow was focally loaded with histiocyte-like atypical cells. Open liver biopsy of

her sister revealed infiltration of abnormal cells along the sinusoids. But identification of the nature of tumor cells could not be made.

At the 47th day of life, she presented with massive hematemesis, after which clinical course rapidly deteriorated. She expired for hypovolemic shock and pulmonary hemorrhage.

At postmortem examination, the body weighed 3,740 g with crown to rump length 35 cm and crown to heel length 54 cm. She showed severe abdominal distention. On abdominal incision, approximately 200 mL of serosanguineous fluid was drained. The liver was diffusely enlarged, weighing 850 g. It had smooth surface and rubbery-hard consistency without focal lesions. Cut surface showed diffuse whitish discoloration except for the bile-stained subcapsular and perivenular areas where normal texture was maintained (Fig. 1). The spleen was enlarged and congested, weighing 34 g. The lung showed patchy hemorrhage and there was punctate mucosal hemorrhage in the stomach. The lymph nodes were not found enlarged.

Microscopic examination revealed a diffuse infiltration of the tumor cells in the portal areas and the sinusoids of the liver. The sinusoids were markedly distended by massively proliferating intrasinusoidal tumor cells (Fig. 2). The surrounding hepatocytes showed atrophy and fatty change. Occasionally, the venules were filled with the tumor cells. In some areas, the hepatocytes were destroyed and invaded by the tumor cells. The area that was grossly bile-stained showed relatively preserved hepatic cell cords. A similar neoplastic infiltrate was present in the spleen. The sinuses in the red pulp were filled with the tumor cells. Dilated blood vessels in trabecula and pulp vein were also filled with the tumor cells. However, the white pulp was intact. The mesenteric lymph nodes revealed a focal involvement of tumor cells in the subcapsular and medullary sinuses. The bone marrow was hypercellular with residual hematopoiesis. The aggregates of the tumor cells were small and multifocal that their presence were accentuated by immunohistochemical staining for CD68 (PGM-1). Wright-Giemsa staining of bone marrow revealed the detailed tumor cell morphology (Fig. 3). The tumor cell was medium to large sized with a moderate amount of pale cytoplasm. The cytoplasmic border was indistinct. A few fine azurophilic granules were observed. The nucleus was round or slightly irregular in shape and slightly indented with moderately clumped nuclear chromatin. The nuclei contained one or two small indistinct basophilic nucleoli. In general, the tumor cell resembled histiocytes. However, hemophagocytic activity was not noted. Involvement of central nervous system was not observed, except the choroid plexus where focal infiltration of tumor cells along the capillaries was noted. The lung revealed a fresh intraalveolar hemorrhage.

Immunohistochemical studies using formalin-fixed and paraffin-embedded tissues indicated that the tumor cell was of mono-histiocytic origin. The tumor cell was focally reactive for CD68 (PG-M1) (Fig. 4A), lysozyme and CD31. And far less than 5% of tumor cells were reactive

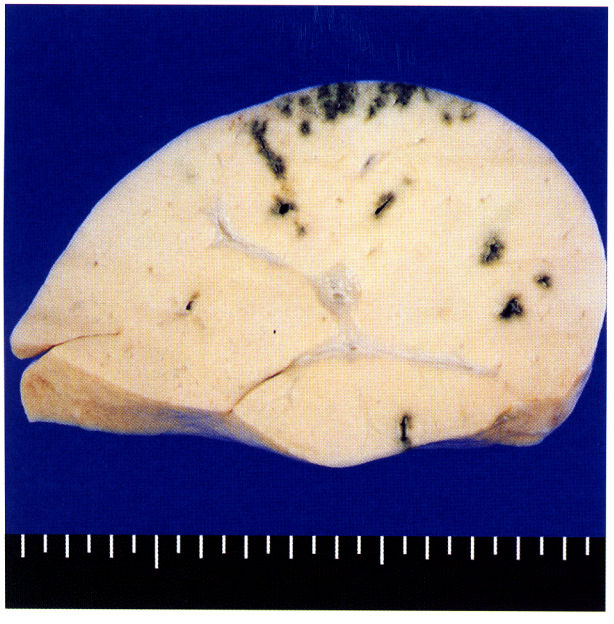

Fig. 1. Cross section of the liver reveals a diffuse whitish discoloration except for the bile-stained subcapsular and perivenular areas.

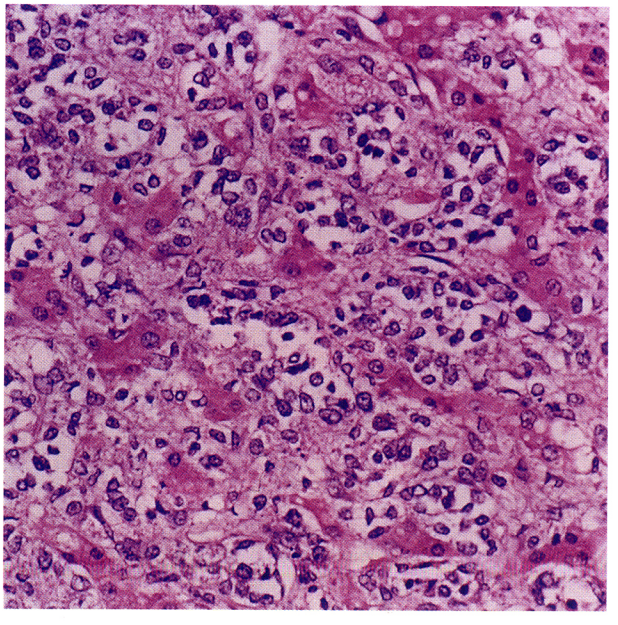

Fig. 2. Histology of the liver. The sinusoidal infiltration of the large pleomorphic tumor cells is characteristic (H-E).

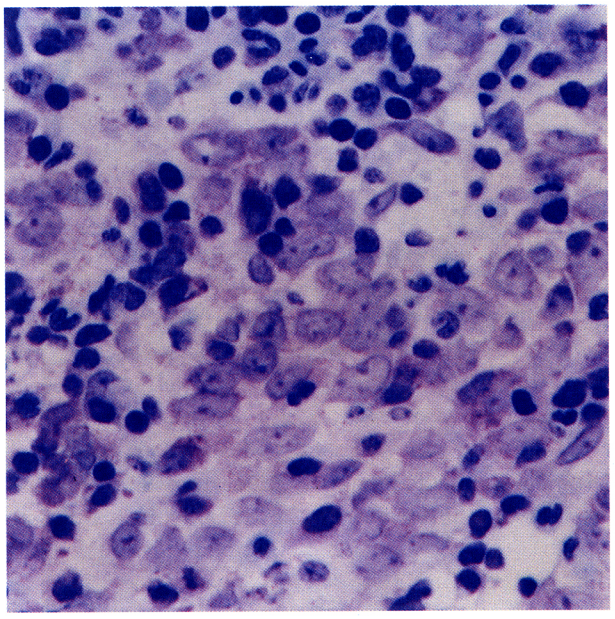

Fig. 3. Wright Giemsa staining of bone marrow section reveals detailed tumor cell morphology. The tumor cells are medium to large sized with prominent single or double nucleoli. Nuclear indentation and cytoplasmic azurophilic granules are also seen.

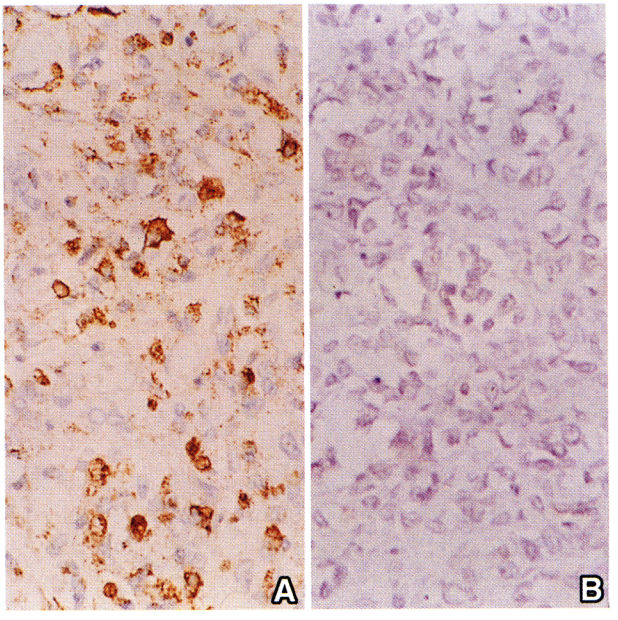

Fig. 4. The tumor cells are reactive for CD68 (PGM-1) (A) but not reactive for myeloperoxidase (B) by immunohistochemistry.

for myeloperoxidase (Fig. 4B). Periodic acid-Schiff staining showed no cytoplasmic granules.

T cell receptor gamma gene rearrangement by PCR disclosed no evidence of monoclonal band in liver and lymph nodes.

Cytogenetic study performed with bone marrow aspiration specimen of her sister revealed balanced translocation, t(9;11)(p21;q23) (Fig. 5).

The clinical course of the first co-twin baby also deteriorated, and she was discharged hopelessly. No further information was available.

DISCUSSION

This case is characterized by extensive hepatosplenic involvement of the leukemic cells. In microscopic examination, the cell morphology and invasion pattern in the liver raised several possibilities concerning the origin of the tumor cells. The areas of massive parenchymal destruction with minimal sinusoidal infiltration resembled infantile hemangioendothelioma. Infantile hemangioendothelioma is a benign neoplastic disease in the liver of infants that is characterized by single or multifocal lesion composed of thin vascular channels lined by plump endothelial cells (4). Our case showed diffuse involvement of the liver instead of localized tumefaction and the tumor cell was not reactive for CD34 and factor VIII-related antigen.

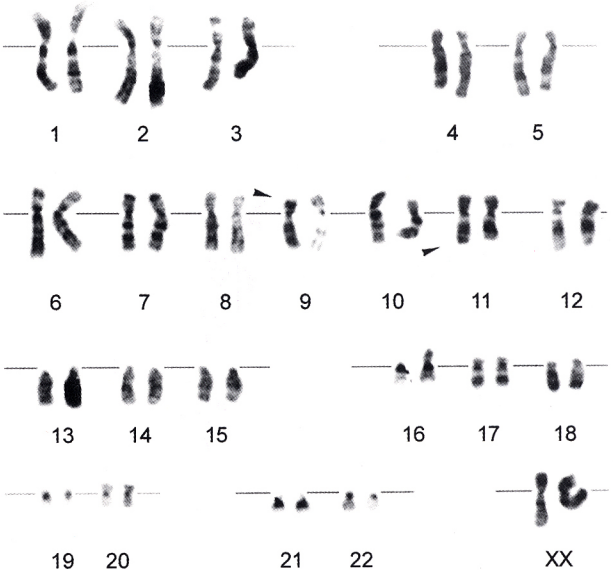

Fig. 5. Giemsa-banded karyotype from the tumor cells of bone marrow aspirates, 46, XX, t(9;11)(p21;q23).

The pattern of tumor cell infiltration along the sinusoids of the liver is well known in leukemia and γ/δ T cell lymphoma (5). The γ/δ T cell lymphoma is a distinct type of peripheral T-cell lymphoma characterized by hepatosplenic sinusal/sinusoidal infiltration and by γ/δ T-cell receptor gene rearrangement with a CD4/CD8 double negative phenotype (5, 6). We considered this

particular T cell lymphoma as the most possible diagnosis in this case. However, the tumor cell of our case was not reactive for CD3, UCHL-1 CD4, CD8, and CD56. Moreover, PCR technique showed no T cell receptor gamma gene rearrangement. Therefore, we were left with acute leukemia.

On morphologic characteristics alone, the differential diagnosis of acute leukemia was difficult, and such difficulty was resolved by observing cytochemical reactivity and immunophenotype. The possibility of acute lymphoblastic leukemia was ruled out due to the negative reactivity with lymphocyte-specific antibodies. The tumor cells were positive with antibody to CD68 (PG-M1) which is a marker of monocyte-macrophage and shows non-reactivity with granulocytes and their precursor cells (7). And less than 5% of tumor cells were myeloperoxidase positive by immunohistochemical staining, indicating the possibility of acute myeloblastic or myelomonoblastic leukemia to be low. The differential diagnosis with acute myeloblastic leukemia, minimally differentiated (AML-M0) was difficult. However, we ruled out AML-M0 by tumor cell morphology including cytoplasmic azurophilic granules and positive immunoreactivity to CD68 (PG-M1).

The leukemic cells in this case lack the morphologic features of monocytic differentiation such as multiple nucleoli, multiple nuclear lobulation, cytoplasmic tailing and aggregates of azurophilic granules (8, 9). In our case, the tumor cell was medium to large sized with round to oval nuclei, indistinct nucleoli and moderate amount of pale cytoplasm. However, monocytic differentiation characterized by folding or contouring and cytoplasmic azurophilic granules was present in some tumor cells. McKenna et al. (8) reported that the leukemic blasts of their ten cases failed to show clear evidence of monocytic differentiation and that the diagnosis of acute monoblastic leukemia was made only after the demonstration of intense neuron specific enolase activity by cytochemical studies. Cytogenetic analysis of our case revealed the balanced translocation, t(9;11)(p21;q23). Chromosomal abnormalities have been reported in a large number of patients with acute monoblastic leukemia. The most common rearrangements involve the MLL gene on chromosome 11q23 (10). In the majority of cases, a part of the long arm of chromosome 9 is lost, producing a balanced translocation, t(9;11)(p21;q23) (10-13). Although the translocation t(9;11)(p21;q23) has been described in acute myeloblastic and lymphoblastic leukemia (14, 15), it is the most common chromosomal abnormality of acute monoblastic leukemia, being associated with approximately 25% of the case. This suggests that the specific rearrangement may be involved in the pathogenesis of the disease. Monpoux et al. proposed that blastic karyotype analysis is essential to provide guidelines in difficult diagnosis caused by the immaturity of the tumor cells (13).

Congenital leukemia is extremely rare, and about 100 cases have been reported in the literature. Parental exposure to mutagens has been the subject of recent epidemiologic studies of infant leukemias, and the immunologic evidence suggests that many cases of infant leukemia, arise in utero (10, 16). The high concordance rate for leukemia in monozygotic twin, especially during the first year of life, indicates a common prezygotic or intrauterine genetic event, or perhaps metastasis via shared circulation (10). So far, a few cases of congenital leukemia occurring in monozygotic twin have been reported (17, 18). The presented case is characterized by diffuse hepatosplenic involvement with mild bone marrow involvement, immaturity of the monocytic phenotype of the tumor cells and occurrence in monozygotic twin. We postulate that the leukemic cell originated from the immature cell during the extramedullary hemopoiesis in utero by parental or intrauterine exposure to mutagen.

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