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Pancytopenic Prodrome (pre-ALL) of Acute Lymphoblastic Leukemia in Adults: Possible Pathogenesis

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We report two cases of adult acute lymphoblastic leukemia presenting with preleukemic phase of pancytopenia with a few abnormal lymphoid cells in bone marrow aspirates. The initial diagnosis of each case was suspicious aplastic anemia and hypoplastic anemia. Both cases progressed to overt acute lymphoblastic leukemia within 1 year. We suggest that initial pancytopenic phase (pre-ALL) may precede the diagnosis of acute lymphoblastic leukemia in adults and differential diagnosis from myelodysplastic syndrome and primary aplastic anemia will be needed. We also suggest that primary bone marrow lymphoma and "primary unknown metastatic lymphoma of bone marrow" may be possible as the pathogenesis in a case like ours.

Key words : *Acute lymphoblastic leukemia, preleukemic phase, bone marrow lymphoma.*

INTRODUCTION

Pancytopenic phase(pre-ALL) associated with a hypocellular or normocellular bone marrow may precede the diagnosis of acute lymphoblastic leukemia(ALL). There have been several reports about names to describe this condition, usually in childhood, which include aleukemic prodrome, preleukemic ALL, aplastic presentation of ALL, hypoplastic preleukemia[1-4]*. There are also several reports*[5-7, 22]* that present the pathogenesis of pre-ALL and conclude that the pre-leukemic aplasia in childhood is a feature of ALL. Only a few reports*[8-10, 24]* about the pathogenesis of adult pre-ALL have been published. It may be difficult to distinguish adult pre-ALL from aplastic anemia or hypoplastic myelodysplastic syndrome and, actually, the patients are often treated as if they had hypoplastic anemia.*

We discuss several possibilities such as myelodysplastic syndrome, primary bone marrow lymphoma, pre-ALL and primary aplastic anemia, and "primary unknown metastatic lymphoma of bone marrow" as the causes of preceeding pancytopenic phase with or without a few circulating blasts in adult ALL.

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MATERIALS

Two adult cases of acute lymphoblastic leukemia, which had previously a course of hypoplastic anemia, were finally diagnosed according to FAB criteria in the Hematology Department of Kyungpook University Hospital.

CASE 1

A 41-year-old man presented in May 1994 with severe anemic symptoms of recently aggravated dyspnea and dizzness. He did not have any history of drug medication, hemolytic disease and previous illness. Physical examination showed pallor and chronically ill appearance. He did not have fever, lymphadenopathy and organomegaly. The initial complete blood count showed Hb 4.7g/dl with 1.3% reticulocytes, WBC 1.2×10^9 /L with a differential of 36% neutrophils, 60% lymphocytes, 4% monocytes and platelet 55×10^9/L. Peripheral blood examination showed normocytic normochromic red

Table 1. The Progress of Peripheral blood counts According to Serial Phase in case 1.

Progress (Phase)	Hb (g/dL)	WBC ($\times 10^9$/L)	Platelet ($\times 10^9$/L)	Duration (Months)	Treatment
Pancytopenic (pre-ALL)	4.7	1.2	55	3	steroid androgen
Recovery	11.8	4.5	166	3	none
Relapsing pancytopenic	4.1	1.2	45	6	steroid folate
Leukemic (ALL)	4.0	24.6	15		chemotherapy (AOP)

cell and normal white cell morphology. Laboratory results showed serum iron level (287 ug/dL: normal range; 35-150 ug/dL) TIBC (352 ug/dL: normal 260-400 ug/dL) ferritin (461 ug/L: normal 20-400 ug/L), erythropoietin (307 mU/mL: normal 10-25 mU/mL). Ham's test was negative and sucrose lysis test revealed 15% positive lysis. Leukocyte alkaline phosphatase score was 146. Cytogenetic study for bone marrow sample showed normal 46 XY. Given the concern that this clinical picture could represent anemia of bone marrow failure, two bone marrow aspirates and biopsies were performed. One was a dry tap and the other aspirate showed a scanty marrow particle with a few lymphoid cells (Fig. 1). The bone marrow biopsy revealed a hypocellular marrow (Fig. 2) with many T-lymphoid cells stained by monoclonal pan-T cell antibody. Because we wondered where a few abnormal cells in bone marrow aspirate are from, CT scan and tumor seeking scans, including Tl-201, Ga-67, MIBI scan, were checked to find out lymphatic mass which might exist somewhere in the body. All imaging studies were negative except the bone scan showed small hot uptake in right knee area. The patient was maintained with low dose steroid and decadurabolin injection for presumed aplastic anemia. Three months after initial presentation, his CBC showed normal counts and he was well for 3 months. After that, he again manifested more severe pancytopenia for 6 months (Table 1). Bone marrow studies during the second six months also showed hypocellular marrow with a few abnormal lymphoid cells. One year after initial presentation, he presented with fever and hemoptysis. Chest x-ray showed superior mediastinal widening and right pleural effusion. Chest CT scanning showed homogenous, irregular margined soft tissue mass in the antero-superior mediastinum and mass lesion encasing the right-sided bronchus(Fig. 3). His WBC rose to 25$\times 10^9$/L with 25% circulating lymphoblasts. Physical examination showed huge hepatomegaly (1 palm breath palpable). Bone marrow aspirate at this time showed infiltration with PAS positive lymphoblasts (73.4%). Immunophenotyping study revealed 95.1% positive for T lymphoid marker(CD7). A diagnosis of ALL was made and adriamycin-vincristine-prednisolone therapy was started, but he died of sepsis and respiratory failure six days later.

CASE 2

A 20-year-old lady presented with easy fatigability, dizziness and menorrhagia of one month duration. Physical examination revealed no organomegaly and lymphadenophathy. A routine blood count revealed: Hb,5.4 g/dL with 1.1 % reticulocytes; WBC, 2.2$\times 10^9$/L with 34 % neutrophils, 56 % lymphocytes, 6 % monocytes and 4 % blast like cells, platelet count, 14$\times 10^9$/L. Three bone marrow aspirates at different sites revealed dry tap and the bone marrow biopsy showed normocellular marrow with some dysplastic cells. The T2-weighted image of spine MRI in pancytopenic phase showed relatively high signal in the marrow suggesting "reconversion" rather than diffuse marrow disease with tumor cell infiltration (Fig. 4). Initially, a diagnosis of hypoplastic anemia was made. After six week well-being period, she presented again with fever and arthralgia. Her WBC rose to 290$\times 10^9$/L with circulating 50% lymphoblasts. Bone marrow aspirate was diluted with peripheral blood. Immunophenotyping study showed the blasts were lymphoid lineage, pre-B (CD10:68.7%, CD19:94.9%, CD22: 93.3%) or pre-B with some CD33 (myeloid), CD34 (stem cell) activity. A diagnosis of ALL L2 was made at this time and she has been in complete remission for 4 months after having five serial chemotherapeutic cycles

with adriamycin- vincristine- prednisolone and intrathecal chemotherapy with methotrexate for CNS prophylaxis.

DISCUSSION

Preleukemic states characterized by pancytopenia and bone marrow hypoplasia are widely recognized in adults with nonlymphocytic leukemia, but have rarely been associated with adult ALL. The aplastic phase (pre-ALL) in children is transient and remission may be spontaneous or rapidly induced by corticosteriod[11, 12]. This type of presentation is observed in about 1.3-2.2 % of pediatric ALL[2, 4, 12, 13]. Recently, there has been a report saying aplastic presentation as pre-leukemic state of ALL should be suspected not only in children but also in adults[8]. We observed the adult pre-ALL patient (case 1) who had pancytopenia at presentation, a subsequent recovery phase, and finally terminal ALL one year after initial presentation. Possible explanations have been proposed for the pathogenesis of an aplastic presentation (pre-ALL): 1) an exogenous factor (infection or toxic agents) that causes the bone marrow depression and simultaneously a mutation of a hematopoietic stem cell transforming it into leukemic cell[14-16, 22]; 2) the presence of endogenous corticosteroids in quantities sufficient to temporarily eliminate lymphoblasts[17]; 3) the existence of a clonal disorder with a true preleukemic state[5, 18-20, 22]; 4) the possible inhibitory properties intrinsic to the leukemic cells rather than to other host factors (paraneoplastic syndrome)[21, 23]. The spontaneous recovery may be explained by the development of resistance to the putative inhibitory factor by the normal hematopoietic progenitor cells or neoplastic cells losing their inhibitory properties as a result of further clonal evolution[23]; 5) folate deficiency in ALL. Folate deficiency status in ill patients is known to produce rapidly developing pancytopenia and actually folate status may contribute to the aplastic phase in ALL[24]. We wondered where a few abnormal lymphoid cells, resembling a lymphoma cell, a bit, seen in bone marrow aspirate of case 1 were originated from. Several scenario about pathogenesis, besides pre-ALL, may be possible in this case. First, primary bone marrow lymphoma which cells were initially indolent within 1 year. In this hypothesis, pancytopenic phase may be due to the myelophthisic or paraneoplastic effects of lymphoma cells on normal hematopoietic system. Clear diagnostic definition and further research for primary bone marrow lymphoma will be needed. Second, "unknown primary metastatic lymphoma of bone marrow", which is an unfamiliar diagnostic terminology, may be possible as the pathogenesis in patients who have pre-ALL like manifestations. All possible studies, including tumor seeking scans, whole body CT, serologic marker studies in our case to seek an occult lymphatic mass which might exist, were negative. It might be possible that indolent metastatic lymphoma in bone marrow had myelophthisic impacts and finally transformed into highly aggressive lymphoma/leukemia. At the time of ALL phase in our case, he eventually manifested a mediastinal mass that has been the origin of some lymphoid cells in bone marrow observed at initial presentation. Third, the developing leukemia, often within a few months following aplastic anemia, might in fact have had a hypocellular myelodysplastic syndrome[25].

We were in a diagnostic dilemma when we encountered case 2. She had pancytopenia and three bone marrow aspirates showed dry tap. We also were not able to get marrow particles in case 1, even though we tried to aspirate bone marrow particles from three other aspiration sites. In patients showing a few lymphoid cells in bone marrow, the possibility of pre-ALL must be taken into consideration for diagnosis and the MRI of bone marrow may be helpful for guessing what kind of disease is progressing in bone marrow[26, 27]. Strictly, case 2 may not be an aplastic one and, otherwise, may be a familiar picture of ALL presenting as pancytopenia with few circulating blasts temporarily. One author[4] reported on terminology relating to pre-ALL that the prodrome could more usually be described as 'aleukemic' than as 'aplastic'. The pancytopenic phase observed for 6 weeks in case 2 may represent a preleukemic phase of ALL which is applicable to myelodysplastic syndrome, preleukemic phase of AML. It may be confusing to do differential diagnosis between myelodysplastic syndrome and primary aplastic anemia in a case like this. Hypercellular marrow and reticulin fibrosis in the bone marrow biopsy may help to distinguish pre-ALL from aplastic anemia[4]. It is impossible to determine the effect of the preleukemic state upon long-term prognosis of the leukemic process. Details of prognostic factors and treatment are unavailable in most cases.

In summary, aplastic presentation (pre-ALL) with or without abnormal lymphoid cells within the bone marrow, followed by later development of ALL, must be differentiated from primary aplastic anemia and myelodysplastic anemia, especially in adults. In addition, primary bone

marrow lymphoma and "primary unknown metastatic lymphoma of bone marrow" may be possible as the pathogenesis in pre-ALL.

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