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Blast Crisis associated with Episodic Febrile Attacks in a Patient with Chronic Lymphatic Leukemia

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A seventy-five year-old female with 17 years' clinical history of chronic lymphatic leukemia was described. An immunologic analysis revealed that leukemic lymphocytes of the patient have surface markers consisting of μ-chain positive cells 88%, δ-chain positive cells 3% and γ-chain cells 1%. As to light chain of surface Ig, κ-chain positive cell 7% and λ-chain cells of 85% out of 100 lymphocytes were recorded. Acid phosphatase staining showed 95% positive in lymphocytes, and non-specific esterase staining revealed 51% positive in lymphocytes, without any combination chemotherapies when examined. She was then well controlled only with low-dose cyclophosphamide 20 mg-50 mg a day, for the initial 15 years' stable course. She developed a blast crisis of CLL at the last stage of her clinical course. It is interesting that a febrile episode over 38°C was noted for a few days, followed by an abrupt increase of Lymphoblasts in the peripheral blood of short duration. This type of combined episodes of fever and lymphoblastosis subsided for a while, but the similar phenomenon was repeatedly seen in the subsequent course of her illness. She eventually died of chronic heart failure. On autopsy, the diagnosis of CLL blast crisis was confirmed, with pathological findings of infiltrations of lymphocytes, lymphoblasts and some plasma cells in various tissues including the marrow, spleen, liver, adrenals, heart, kidneys, lungs, intestines and lymph nodes. The episodic fever associated blastic crisis discussed.

Key Words
Chronic lymphatic leukemia (CLL), Surface Ig positive lymphocyte, Febrile episode, Blast crisis in CLL.

INTRODUCTION

Leukemic lymphocytes in chronic leukemia (CLL) are known to proliferate very slowly (1-6). CLL is a hematologic malignancy characterized by the accumulation of lymphocytes in the peripheral blood, bone marrow, spleen and lymphnodes. Fever greater than 38°C is usually seen among neutropenic patients with hematologic malignancy during chemotherapy or aplastic anemia, due to bacterial, fungal and viral infections. However, there could be a rare occasion of a non-infectious febrile episode over 38°C followed by an abrupt blast crisis lasting only for a few days. In the present paper, repeated fever and blast crisis of leukemic lymphocytes are documented.
CASE PRESENTATION

Y. Nak., an 86-year-old female, had a clinical history of 17 years from the age of 70 to 86. Her clinical onset appeared to be at the age of 70 in 1973 in association of occasional purpura without any medical check-up for several years, followed by severe nasal bleeding recurrently occurred in August and October 11, 1973 at the age of 75. Her family history disclosed heart disease with her father, colon cancer with her daughter, and tuberculosis with her son. The past history of the patient was non-contributory. On admission, the temperature was 36.7°C, and there was nothing remarkable on physical examination. There was no lymphadenopathy or no hepatosplenomegaly. Laboratory examinations included an elevated peripheral leucocyte count of 140,800/μl (consisting of lymphoblast 2%, lymphocyte 95% and neutrophil 3%), a red blood cell count 296 X 10⁴/μl, hematocrit 25%, and a platelet count 11.5 X 10⁴/μl. A bone marrow aspiration revealed that a nuclear cell count was 86.8 X 10³/μl consisting of erythropoiesis 3.4%, granulopoiesis 2.8%, eosinophil 0.2%, monocyte 0.4%, reticulum cell 0.2%, lymphoblast 2.4% and lymphocyte 90.6%. An immunological analysis of the peripheral blood revealed the distributions of surface immunoglobulins of peripheral lymphocytes demonstrated 87.5% of μ-chain-positive cells, 3.0% of δ-positive cells and 4.7% of γ-positive cells out of 100 peripheral lymphocytes, without any positive surface Ig of α-chain, by using cell-suspensions mixed with anti-serum at 37°C for 30 minutes, followed by 3 times washing with PBS, and then analyzed lymphocytes on smear films under fluorescence microscopy. An another immunological analysis on surface marker revealed μ-chain-positive cells 88%, δ-chain cells 3% and γ-chain cell 1% out of 100 peripheral lymphocytes, with light chain surface marker of κ-chain positive cytoplasmic cell 7% and λ-chain positive cells 85% out of 100 peripheral blood lymphocytes. For acid-phosphatase staining, an immunohistochemical analysis revealed a result of 95% positive (moderately positive 22%, weakly positive 68%, and granular reaction 5%) cells out of lymphocytes examined in the peripheral blood material. A non-specific esterase staining of the peripheral lymphocytes recorded 51% of positive cells. Thus, the immunologically-defined surface marker of μ-chain-positive and λ-chain positive cells ranging approximately 85% among the peripheral lymphocytes was presumed to be a signal of malignant lymphocyte series. An additional data showed that both peroxidase. An additional data showed that both peroxidase reaction and Sudan-Black staining were negative on lymphocytes in the peripheral blood as well as bone marrow aspirated material. Intradermal tests for PPD, candida antigen and SK-SD antigen were all positive after 48 hours measurements of the forearm of the patient, suggestive of no abnormality of cellular immunity.

On the basis of these findings, a clinical diagnosis of chronic lymphatic leukemia (IgM type B cell CLL) was established. Other laboratory data included a total serum protein 6.1g/dl,
GOT 21 IU, GPT 11 IU, cholesterol 234 mg/dl, triglyceride 100 mg/dl and LDH 501 IU, with an isozyme pattern of I 27.4%, II 40.1%, III 19.1%, IV 7.0% and V 6.1%. There were BUN 26 mg/dl, Na 146 mEq/1, K 5.4 nEq/1, Cl 109 mEq/1, prothrombin time 10.4 sec., partial thromboplastin time 34.6 sec., plasma fibrinogen 205 mg/dl and FDP 5 µg/ml. Chest X-ray and an electrocardiogram showed nothing abnormal. An electrophoresis of the serum protein revealed a pattern with albumin 4.2 g/dl, α₁-globulin 0.1, α₂-globulin 0.5, β-globulin 0.8 and γ-globulin 0.5 g/dl, showing hypo-γ-globulinemia. Although the clinical state during hospitalization was stable in an inactive phase of CLL, a therapy was instituted on only prednisolone 20 mg/day for 4 weeks. A gradual improvement of peripheral blood was shown, and there was a leucocyte count of 75,000/µl, a red blood cell 329 count X 10⁴/µl, hemoglobin 9.8 g/dl, a hematocrit 33.8% and a platelet count 10.3 X 10⁵/µl, without any lymphadenopathy or hepatosplenomegaly at the time of discharge from the hospital on December 3, 1978.

At the out-patient clinic, she was instituted on the low-dose continuous administration of cyclophosphamide 30 mg/day, for the following 10 years (1978-1987). Occasional episodes of infections during the course required antibiotics as well as intravenous immunoglobulins. Hematological data were under control with a range
Y. NAK. 86F.  CLL

Cyclophosphamide

30 mg x 3 days

100 mg x 1 day

30 mg x 23 days

WBC

Lymphocytes

Lymphoblasts

Granulocytes

CRP

0.3 1.8 <0.3 <0.3 <0.3 0.3 0.3 3.9 3.6 <0.3 1.5 0.3 0.8 2.9 0.4 0.3 7.7

Jan Feb Mar Apr May Jun Jul

Figure 2. Clinical course of the patient's late stage, with noted episodes of leucocytosis, lymphocytosis and blastcrisis, in association of febrile episodes.

of 12,000 ~ 19,000/μl of white cell count with peripheral lymphocytes of 80 ~ 90% out of total white cells, 8.8 ~ 9.5 g/dl of hemoglobin, 250 ~ 270 X 10^6/μl of red blood cells, and 10.5 ~ 14.5 X 10^4/μl of platelet counts.

On December 25, 1986, she had cough and fever (38.0 ~ 39.3°C). The second admission of her clinical course was recorded from January 3, 1987 to February 21, 1987. On admission, the body temperature 36.1°C, regular pulse 88/min, and the physical examination showed no lymphadenopathy or no hepatosplenomegaly. A chest X-ray showed no abnormality, although a cardio-thoracic ratio was 64.0% with a suspicion of chronic heart failure without any significant abnormality in ECG. A bone marrow aspiration at this time showed a nucleated cell count of 57.7 X 10^6/μl, consisting of erythropoiesis 5.4%, granulocyte 8%, and lymphocyte series 93.2%. A peripheral blood count included a total leukocyte count of 8,800/μl with granulocyte 8%, eosinophil 3% and lymphocyte 89%, red blood cells 154 X 10^6/μl, a hemoglobin 4.8 g/dl, a hematocrit

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15.7% and a platelet count of 7.3 X 10^4/μl. There were negative CRP, plasma fibrinogen 80 mg/dl, LDH 327 IU/ml, a serum total protein 4.6 g/dl with albumin 2.6g/dl and hypo-γ-globulin of 0.6 g/dl, IgG 559 mg/dl, IgA of less than 33 mg/dl, IgM of less than 25 mg/dl, serum iron 78μg/dl and TIBC 239μg/dl. Without any obvious inflammatory findings in a stable CLL state, she was discharged with a continuous low dose 30 mg/day of cyclophosphamide for the following the out-patient clinic until 1989 January, when a blast crisis of lymphocytic series was observed in the peripheral and bone marrow blood. Therefore she had the third admission from January 18, 1989 at the age of 85.

On admission, she had no lymphadenopathy and no splenomegaly. The entire profile of major changes of clinical course were shown in Figure 1. The blast crisis was confirmed just before admission with a peripheral leucocytosis of 48,000/μl including 69% lymphoblasts and 24% of lymphocytes. It was obviously a blast crisis as shown in Figure 2, where the second marrow aspiration showed a definite increase of lymphoblasts up to 84.0% out of nucleated cell counts, compared with findings of 1.6% in the marrow of last admission. A loading administration of cyclophosphamide 100 mg for 2 days showed a noted effect on a reduction of leucocyte and lymphocyte. However, as shown in Figure 1, she had an episode of general fatigue and high fever, just before the elevations of lymphocytes and high fever, just before the elevation of lymphocytes and lymphoblasts, in association with only slightly elevated CRP, suggestive of no severe infections. These episodes rapidly subsided towards normal range of body temperature followed by hematological normalization of leucocytosis, lymphocytosis and diminution of abnormal lymphoblast, without intensive care therapy (such as multi-drugs chemotherapy or moderately high dose prednisolone), except an administration of 30mg cyclophosphamide for 3 days. Without chest X-ray abnormalities during these recurrent episodes of fever and lymphocytosis, she was administered by different schedule of antibiotics including penicillin, and cephalosporin, anti-fungal agents, intravenous immunoglobulin and others, all of which appeared to be not effective to the febrile attacks. With an increased cardio-thoracic ratio with slight pleural effusion, she died of chronic heart failure on July 18, 1989 at the age of 86.

On autopsy, the diagnosis of CLL blastic crisis was confirmed, with pathological findings of macroscopically diffuse whitish bone marrow, and microscopically with high density of nucleated cells of mainly mature lymphocyte, lymphoblasts and plasma cells. There were lymphocytic infiltrations to the spleen (230gm), liver (1,600mg), bilateral adrenals (right 130gm, left 100gm), lungs, intestines, and lymphnodes (paraortic, peripancreatic and parabronchial). Accessory findings included bronchopneumonia, gastric ulcer, multiple cysts in the liver, pancreas and thyroid, and 180 ml of pleural fluid.

In summary, this patient had a clinical course of CLL of B cell type with 16 years' survival, and finally had a blastic crisis of CLL with an
interesting observation of recurrent febrile (more than 38°C) attacks followed by abrupt increase of lymphocytes and lymphoblasts, lasting only a few days with recovery to normal body temperature and lymphocyte reduction in the peripheral blood, with no infectious state.

**DISCUSSION**

Chronic lymphatic leukemia (CLL) is a hematologic neoplasm characterized by the accumulation of mature-looking lymphocytes in the peripheral blood as well as in the bone marrow, spleen and lymph nodes. CLL is usually common in patients over 50 years of age. CLL is the most common form of chronic leukemia in western countries, while it is rare in orientals including Japan. As CLL represents a clonal, neoplastic B lymphocytes in most cases, the diagnosis is made on the basis of (1) reviewing of the peripheral blood and its smear film, (2) monoclonal surface IgM immunoglobulin with or without surface IgD lymphocytes, and B cell marker, (3) some degree of hypogammaglobulinemia with or without very small amount of IgM-M-protein, and (4) infiltration of the lymphocyte in the marrow (1,2).

Because the leukemic lymphocytes in CLL proliferate very slowly, as is also true of normal B-lymphocytes and other are in Go stage. Because of the leukemic cells have a very long life-span, though only a small portin of total leukemic cells is proliferating, CLL cells than continue to accumulate and continue to recirculate in the peripheral blood (1–5). Rai et al (6) classified CLL with prognostic remarks into 5 types, on the basis of progressive-accumulative hematologic disorder; ① stage 0 of lymphoproliferation in the peripheral and marrow with an estimated survival of more than 150 months, ② stage I of increased lymphocyte with lymphadenopathy with survival of 101 months, ③ II stage of hepatosplenomegaly with survival rate of 71 months, ④ III stage of lymphocytosis with anemia with survival of 19 months and ⑤ IV stage of lymphocytosis with thrombocytopenia with survival of 19 months. It is known that the disease becomes progressively less responsive to previously effective treatment.

As to febrile episodes as shown in Figure 2, fever in the present case was recurrently observed at the last stage of her course, in accordance with blastic crisis of lymphocytic proliferation, in the peripheral blood. Fever over 38°C occurred among febrile neutropenic patients of hematological malignances such as AML, CML, and acute lymphoblastic crisis during chemotherapy (7,8). Fungal pulmonary infection, supposed viral pneumonia, and in a few cases documented bacterial infection were noted in one study (7). Febrile episodes in CLL consisted of 22 proved septicemias due to Gram-positive organisms in 11 cases and to Gram-negative organisms in 10 cases, where the mean duration of treatment (timentin & tobramycin) was 11.1 days (range 4–20 days) in another study (8). Although granulocytopenia persisted in the last stage of clinical course in the present study as in Figure 2, fever had duration of only several days and blastic crisis was definitely followed just after feb-
rile episode, without any chemotherapy. The febrile episode appeared to be directly related to a term of "periodical increase & decrease" of lymphoblasts and lymphocytes, and appeared not to be related to infections without any marked increase of CRP. This type of fever is not commonly seen in clinical course of leukemia. Thus, the precise mechanism is worthy of pursuit.

REFERENCES