Leukemic Tumors Composed of Basophilic Precursors in Chronic Granulocytic Leukemia

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Summary. Three patients with Philadelphia chromosome positive chronic granulocytic leukemia (CGL) complicated by leukemic tumors mimicking malignant lymphoma are reported. These leukemic tumors are considered in extramedullary blast crisis. The most interesting point in the present cases is that the proliferating neoplastic cells are composed of basophilic precursors. Cytochemical, electron microscopic and immunological studies are necessary to differentiate the leukemic tumor from malignant lymphoma.

INTRODUCTION

Chronic granulocytic leukemia (CGL) is divided into two different clinical phases: the chronic phase and blast crisis phase. Blast crises are heterogenous, in which proliferating cells are not only myeloblasts but also lymphoblasts, monoblasts, basophilic precursors, megakaryoblasts and a mixture of these cells. Localized or multiple tumors resembling malignant lymphoma have also been often experienced.1-7)

We here report on three patients with Philadelphia chromosome (Ph1) positive CGL with extramedullary tumors resembling malignant lymphoma. Of special interest in this report is the finding that the infiltrating neoplastic cells are composed of basophilic precursors.

OBSERVATIONS

Case 1. A 38-year-old man was first confirmed to have leucocytosis and a small number of blasts in his peripheral blood in September 1979. He was diagnosed as CGL on the basis of anemia, thrombocytosis, extensive leucocytosis with a nuclear shift to the left, marked hepatosplenomegaly and positive Ph1 chromosome in December 1980. On admission, his white blood count (WBC) was $15.6 \times 10^3$ /cmm, with 5% blasts, 12% promyelocytes, 13% myelocytes, 9% metamyelocytes, 11% bands, 16% segmented neutrophils, 15% basophils, 7% eosinophils, 3% erythroblasts and 1% megakaryocyte. As a result of ultrastructural examination of the bone marrows including 3.0% blasts, a transition of morphologic features from the more immature blastic cells into basophilic precursors was observed (Figs. 1a, b, c). After treatment with busulfan 2 mg/day, his WBC gradually decreased and the hepatosplenomegaly reduced. In early July 1981, he complained of severe right back pain and was readmitted to the hospital. On July 30, he suffered from complete palsy of the lower half of his body. At that time, hematological data revealed a chronic phase of CGL. A solid tumor in the 10th and 11th thoracic vertebrae was found on myelography. A laminectomy and removal of the tumor were performed.

The histologic section of the tumor demonstrated the diffuse proliferation of large neoplastic cells surrounded by hyalinous connective tissue (Fig. 2). These cells had a vesicular, round nucleus with a single nucleolus. The cytoplasm was scanty and basophilic.

Cytochemical staining on tumor imprints revealed that these neoplastic cells had variably positive reaction with periodic acid-Schiff, acid phosphatase and $\beta$-glucuronidase stains. Moreover, the cells contained small granules in the cytoplasm, which exhibited metachromatic staining with toluidine blue (Fig. 3).
Fig. 1. Electron micrographs of blasts in the bone marrow in an early stage from Case 1. The cells show a transition of morphologic features from less mature cells (Fig. 1a, ×5,400) into basophils (Fig. 1b, c, ×5,400).
Fig. 2. Case 1. Section obtained from the solid tumor in the 10th thoracic vertebra, showing the diffuse proliferation of large neoplastic cells with a vesicular nucleus and prominent single nucleolus (×660).

Fig. 3. Toluidine blue metachromasia present in the tumor cells (×1,600).
Fig. 4. Electron micrographs of the tumor cells from Case 1. Correspondance with those of blasts in the bone marrow. Note the prominent nucleoli, many profiles of rough endoplasmic reticulum, polysomes, scattered glycogen particles and small granules (more immature basophil, 4a, 4b, ×7,300). A more mature basophil, showing specific granules surrounded by a unit membrane and containing electron dense particles and an occasional myelin-like figure (4c, ×6,100). 4c right: higher-power view of the granules (×18,200).
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Fig. 5. The cross section of the thoracic tumor from Case 1 at autopsy, showing a marked diffuse and/or lobulated appearance, greyish white in color with small necrotic foci.

Fig. 6. Basophils observed in the pleural effusion of Case 2 (×1,500).

On the other hand, myeloperoxidase, Sudan black B, naphthol AS-D chloroacetate esterase and naphthyl butyrate esterase stains were completely negative.

Electron microscopy of the neoplastic cells demonstrated a round or indented nucleus with a single prominent nucleolus, many profiles of rough endoplasmic reticulum, numerous free ribosomes, a few small granules and a large accumulation of glycogen particles throughout the cytoplasm (Figs. 4a, b).

Characteristic granules which displayed a basophilic nature were also observed; namely, the granules were surrounded by a unit membrane and contained electron-dense particles and/or occasional myelin-like figures (Fig. 4c).

After laminectomy, the patient was irradiated and given vincristin and prednisolon without any effect. In October, the blasts in the peripheral blood increased gradually to 17% and later to 37%. Marked
splenomegaly was noted, and death occurred 3.5 months after the detection of the thoracic tumor.

At autopsy, massive leukemic cell proliferation in the examined bone marrows, spleen (2.720 g), liver (2.420 g) and systemic lymph nodes was observed. A tender mass, 6 cm in diameter and greyish white in color, occupied the 11th thoracic vertebra (Fig. 5).

Case 2. A 59-year-old female was found to have leucocytosis in December 1979. In October 1980, the patient was admitted to a hospital. On admission, her hematological data were as follows: red blood cell count (RBC) 435 x 10^4 /cmm, platelet count 127.5 x 10^4 /cmm, WBC 46.0 x 10^3 /cmm. Her hemogram revealed 5% myelocytes, 3% metamyelocytes, 8% bands, 42% segmented neutrophils, 4% eosinophils, 24% basophils, 2% monocytes and 12% lymphocytes. The neutrophil alkaline phosphatase (NAP) score was very low and a chromosomal analysis of bone marrows showed a Ph1 chromosome. Under the diagnosis of CGL, she was administered busulfan (4 mg/day). The patient remained well until January 1982 when back pain, bilateral leg palsy and incontinence developed. Laminectomy and removal of the tumor were carried out under the diagnosis of epidural tumor in the 8th thoracic vertebra. Histologically it mimicked a picture of malignant lymphoma. Radiation therapy was given to the thoracic vertebra. Although she was administered 6-mercaptopurine, 100 mg/day, a solid tumor was later found in the left inguinal and the upper mediastinal regions. In April, she developed right pleural effusion in which a great number of large bizarre mononuclear cells were noted. Almost all of the cells had distinct basophilic granules in the cytoplasm upon a May-Giemsa stain (Fig. 6). Electron microscopy of the cells demonstrated a large, indented nucleus with a distinct nucleolus, numerous polysomes, long strands of rough endoplasmic reticulum, clusters of glycogen, small mitochondria and scattered granules which had basophilic characteristics (Fig. 7). Finally, dyspnea was observed and death occurred on April 30, 1982.

At autopsy, tender masses were identified in the periosteal regions of the right ribs, right sternoclavicular muscle and right lung. On microscopic examination, these tumors showed extensive infiltration of large neoplastic cells which were completely negative for naphthol AS-D chloroacetate esterase stain, but exhibited metachromatic stain with toluidine blue (Fig. 8). The bone marrow was hypercellular with a predominance of granulocytes. A small lesion of a blast crisis was recognized in only the sternum. There were slight leukemic infiltrates in the spleen...
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Fig. 8. Case 2. Periosteal tumor of the right rib with infiltration by large neoplastic cells (×690). Insert: immature basophil exhibiting metachromasia staining with toluidine blue (×1,700).

Fig. 9. Case 3. Dense infiltrate of large neoplastic cells in the subcutaneous tissue with numerous mitosis (9a, ×340). 9b: Higher-power view of neoplastic cells (×520).
Case 3. A 47-year-old man developed anemia and arthralgia in December 1983. He was admitted to the hospital in April 1984. On admission, hematological findings of the peripheral blood were as follows: RBC 343 x 10^4 /cmm, platelet count 18.2 x 10^4 /cmm, WBC 16.1 x 10^9 /cmm. The hemogram revealed 6.5% blasts, 1.0% metamyelocytes, 0.5% bands, 57.5% segmented neutrophils, 2.0% eosinophils, 14.5% basophils, 18.0% lymphocytes, 6.0% monocytes and 1.0% of erythroblasts. Moreover, his NAP score was very low and a Ph1 chromosome was detected. He was diagnosed as CGL, and busulfan later vincristin and prednisolon were administered. One month after the diagnosis, multiple subcutaneous nodules were recognized. The histologic pictures of the nodule corresponded with those of Case 1 (Fig. 9), except for the mixing of a very small amount of blasts stained with naphthol AS-D chloroacetate esterase. Immunological study using monoclonal antibody revealed the proliferated cells reacting with anti-My 7, which indicated granulocytes or monocytes.

In electron microscopic examination, most of the cells were presumed basophilic precursors (Fig. 10). Although combined chemotherapy (BHAC-DMP; Behenoyl ara-C, Daunomycin, 6-Mercaptopurin, Prednisolon) was given, the subcutaneous nodules became larger —up to 10 cm in diameter— and spread throughout the body. Furthermore, a right subpleural tumor was found in July. Finally, the blasts in the peripheral blood increased up to 34.5% and death occurred on September 14, 1984. Autopsy was not performed.

DISCUSSION

The cases presented were all Ph1 positive CGL, complicated by leukemic tumors. The tumors had the following characteristics: 1) the histologic sections appeared to mimic malignant lymphoma; 2) they had a tendency to occur in many places; 3) they were recognized before any hematological blast crisis; and 4) they indicated a poor prognosis for the disease.

There have been some reports on the pathogenesis of tumors during the course of CGL. The following possibilities have been reported: 1) malignant lymphoma coexist accidentally with leukemia; 2) the malignant change in reactive reticulosis is associated with CGL; or 3) acute myeloblastic transformation of CGL alters into the proliferation of more undifferentiated blast cells (leukemic tumors). The sec-
ond opinion was proposed by Fukuda and Ohnishi, because the histologic pictures and morphology of proliferating cells containing fat droplets and phagocytized red cells in the cytospasm resembled those of reticulum cell sarcoma. On the other hand, Pascoe reported two patients with CGL who developed leukemic tumors of the breast. He mentioned the demonstration of eosinophilic precursors was important for making a diagnosis of leukemic tumor. Additionally, he emphasized that imprints stained with one of the Romanowski stains might greatly facilitate the identification of immature granulocytic cells. Furthermore, Ota demonstrated a case presenting Ph chromosome in the tumor cells and considered the possibility that an acute leukemic transformation occurred in cells less mature than myeloblasts.

As a result of cytochemical, electron microscopic and immunological studies, the proliferating neoplastic cells in the tumors have been concluded to be non-lymphocytes. The most interesting point in the present cases was that the cells were composed of basophilic precursors. In general, it is accepted that CGL is a stem cell disorder and the blast crisis is a heterogenous condition inducing not only myeloblastic proliferation but also several kinds of hematopoietic cell proliferation. Basophilic crisis in CGL has also been recognized. As to the incidence of basophilic crisis in blast crisis with CGL, Muehleck et al. reported such in 4 of 41 patients (9.8%); our own data was 4 in 22 cases (18.2%). There is, however, only one case report in the literature presenting Ph chromosome in the tumors. Concerning the basophilic tumor, we do not support the theory that the leukemic cells transformed into more primitive cells, because a small number of the same blasts had been already observed in the bone marrow in earlier stages. Therefore, we considered the present cases to be a peculiar type of basophilic crisis occurring in the extramedullary sites. Moreover, as a sequel to the culture of the peripheral blood of Case 1, Kishi established a new leukemia cell line (KU 812) characterized as basophilic precursors. We confirmed that this KU 812 could be transplanted to nude mice easily and form a tender mass composed of basophilic precursors. These findings suggest that the basophils in Case 1 have a very extensive proliferative ability and a tendency to form solid masses.

Although it is believed that the basophilic tumor is a very rare complication in CGL, its incidence will increase through detailed examination using cytochemical, electron microscopic and immunological studies.

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