Case Report

Essential Thrombocythemia Terminating in Myelofibrosis and Myeloblastic Transformation

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A 58-year-old man with essential thrombocythemia terminating in myelofibrosis and myeloblastic transformation is described. He was treated with busulfan and lived for 6 years and 6 months. At autopsy, significant osteomyelofibrosis was noted. Moreover, myeloblastic infiltration with proliferation of megakaryocytes and erythroblasts was seen in the bone marrow and spleen. In the lymph nodes, myeloid metaplasia was noted. The past reports on this disease terminating in myelofibrosis and/or blast transformation have been reviewed.

Key Words: Essential thrombocythemia, Myelofibrosis, Blast transformation

Essential thrombocythemia (ET) is one of the chronic myeloproliferative disorders. The main causes of death during the course of ET are hemorrhagic episodes and thrombosis. Occasionally, this disease terminates in myelofibrosis and/or blast transformation. This communication is concerned with a case of ET terminating in myelofibrosis and myeloblastic transformation.

CASE REPORT

A 58-year-old man was first admitted to the hospital on August 9, 1977, because of hypoesthesia and numbness of the extremities and around the mouth of one month duration. The first toe in the left foot had been amputated because of spontaneous gangrene in 1968, at the age of 50. On admission, he was found to have hepatosplenomegaly. Hematologic examination, as indicated in Table 1, showed no anemia, a white blood cell count of 16.8 x 10^9/l with immature cells of granulocytic series, and a markedly raised platelet count (1,032 x 10^9/l). The score of neutrophil alkaline phosphatase (NAP) was 73 by the method of Tomonaga. An aspiration of the sternal bone marrow revealed proliferation of the granulocytic series. Clot section of the same aspirate showed proliferation of the granulocytic series with preponderance of eosinophilic and megakaryocytic series (Fig. 1). Chromosome analysis showed no Ph1 chromosome. He was diagnosed as having essential thrombocythemia and cerebral infarction, and was treated with busulfan and urokinase with success. He was discharged on January 13, 1978. The hematologic findings returned to normal one year after discharge. The spleen decreased in size in February, 1980 and busulfan was discontinued. He remained well for 3 years until readmission. Hematologically, the platelet count increased to 476 x 10^9/l in November, 1982. However, it decreased gradually thereafter. Severe pancytopenia with leukoerythroblastosis occurred in October, 1983. He was readmitted on December 7, 1983. On admission, the liver was palpable 4 cm and the spleen, 3 cm, below the costal margins. Hematologic examination showed severe anemia, a
white blood cell count of $2.6 \times 10^9/l$ with 7% myeloblasts as listed in Table 1. His platelet count was $30 \times 10^9/l$. The NAP score was 306. Bone marrow aspiration was not successful. The serum lactic dehydrogenase activity was 279 mU/ml, vitamine B$_{12}$ 360 pg/ml, and serum iron...
Fig. 2. Post-mortem specimen of the sternum demonstrating marked myelofibrosis. (HE stain, x170)

Fig. 3. Post-mortem specimen of the femur showing myeloblastic infiltration. (HE stain, x340)

Fig. 4. Myeloblasts in a touch smear of the femur. (May/Grünwald-Giemsa stain, x1,700)
96 μg/ml. The total protein was 7.1 g/dl, of which 19.5% γ globulin. The Ig G was 1,535 mg/dl, Ig A 303 mg/dl, and Ig M 235 mg/dl. The immune complex was 1.5 μg/ml by C1q solid phase enzyme immunoassay. He was treated with anabolic steroids and blood transfusions. His clinical course rapidly deteriorated with increasing anemia, bleeding tendency due to disseminated intravascular coagulation, tarry stools, and high fever. He died on February 25, 1984.

At autopsy, the bone marrow of the sternum, vertebrae and femur was replaced by predominant fibrous tissues (Fig. 2). Moreover, myeloblastic infiltration with proliferation of megakaryocytic and erythroblastic series was noted in the fibrous background particularly in the femur (Figs. 3 & 4). The spleen weighed 660 g and showed marked proliferation of myeloblasts (Fig. 5). Some of the blasts in touch smear were positive for peroxidase reaction. The lymph nodes were not so enlarged, but showed intensive myeloid metaplasia. The liver weighed 1,620 g, and the kidneys showed disseminated intravascular coagulation. There were two aneurysms containing large laminated thrombi in the abdominal aorta and left external iliac artery.

**DISCUSSION**

Essential thrombocythemia is characterized by hyperplasia of megakaryocytic series and a marked excess of platelets. Since Dameshek's description, ET has been regarded as one of the chronic myeloproliferative disorders. Among these disorders, many transitional states exist. Some of the patients with this disease terminate in myelofibrosis and/or blast transformation. However, the incidence of this two problems in ET is not known.

Hattori et al. reviewed 50 patients with this disease reported in Japanese literature up to 1977. Three of the 50 cases had myelofibrosis during the course of the disease with transition into acute leukemia. On the other hand, there have been several reports, including Japanese literature since 1978, on this disease terminating in blast transformation. In this series of reported cases, the patients were treated with 32P, X-ray irradiation and cytostatic agents, i.e., busulfan and Thio-TEPA in the phase of thrombo-
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cythemia. The interval between diagnosis and blast transformation was from 16 months to 168 months (median value: 45 months). However, the blast transformation of ET was followed by a rapid downhill course and was refractory to chemotherapy. In 5 of the 10 reported cases, autopsy was done

In one case, there was extensive infiltration of poorly differentiated leukemic cells showing anaplasia, moderate pleomorphism and negative peroxidase reaction, in the bone marrow, lymph nodes, spleen, liver, kidneys and skin. In other case, there were infiltrates of primitive stem cells in the bone marrow, liver and kidneys. In Fukushima’s case, myeloblastic infiltration was seen in the bone marrow, liver and spleen. In contrast with above reports, one case developed osteomyelofibrosis with myeloid metaplasia in the lymph nodes, spleen and liver despite increasing number of myeloblasts in the peripheral blood. In the current case, myeloblastic infiltration was noted only in the bone marrow and spleen. Moreover, proliferation of blast cells in the spleen was more prominent than those in the bone marrow. The evidence suggests that extramedullary hematopoietic tissue are the important sites where blast transformation develops.

Lewis et al. believe that myelosclerosis will occur as a natural evolution of this disease and polycythemia vera. Murphy suggests that acute leukemia may develop as a natural history of ET and, moreover, the incidence of blast transformation increase in the patients with this disease treated with radioactive phosphorus or chemotherapy. In the current case, it remains uncertain whether cytostatic agents played a role in the development of myelofibrosis and/or blast transformation, or this phenemon was a natural history of this disease.

REFERENCES