Refractory Anemia with an Excess of Blasts Developed into Overt Leukemia with Leukothrombocytosis

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A 72-year-old man with refractory anemia with an excess of blasts developed overt leukemia with leukothrombocytosis. Hematological and physical findings closely resembled those of an accelerated or blastic phase of chronic myelocytic leukemia. The cytogenetic anomaly of i(17q) was observed during the course. The present case is suggestive of the diversities of myelodysplastic syndromes (MDS), including relationships between MDS and myeloproliferative disorders (MPD) and acute leukemia.

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Introduction

Myelodysplastic syndromes (MDS) and myeloproliferative disorders (MPD) are thought to be the clonal origin in pluripotent stem cell (1–4). MDS are characterized by cytopenia in peripheral blood, normo- or hyperplastic marrow and morphological anomalies of hematopoietic cells (5). On the other hand, the hematological characteristics of myeloproliferative disorders (MPD) include the increase of some of blood cells in the peripheral blood resulting in leukocytosis, polycythemia or thrombocytosis (6). Thus, one of the main biological differences between MDS and MPD may be whether the maturation disturbance is present or not. In this paper, a case of refractory anemia with an excess of blasts (RAEB) developed overt leukemia with MPD-like findings such as leukocytosis, thrombocytosis and hepatosplenomegaly.

Case Report

The patient, a 72-year-old man, developed generalized weakness in mid April 1992. He visited another hospital because of weakness; iron was given intravenously under the diagnosis of anemia. On June 9, 1992, he was referred to our hospital because of an unfavorable course. The patient suffered from herpes zoster in 1990. Physical examination on admission

revealed a moderately nourished male. Body temperature was 36.5°C. Pulse was 89/min regular. Conjunctiva was anemic but not icteric. The heart was normal. Fine crackles were present at the bases of the lungs posteriorly. Hepatosplenomegaly, superficial lymphnodes and hemorrhagic tendency were not observed. The neurological examination was negative. Examination of the blood showed a red blood cell (RBC) count of $183 \times 10^4/\mu\text{l}$, hemoglobin (Hb) of 8.6 g/dl, a platelet (Plt) count of $2.8 \times 10^4/\mu\text{l}$, a white blood cell (WBC) count of 5,600/ μl with 1% myeloblasts, 70% neutrophils, 8% eosinophils, 2% monocytes and 9% lymphocytes. A few erythroblasts and megakaryocytes were found. Giant thrombocytes, neutrophils with hypersegmentation or pseudo-Pelger anomaly were also found (Fig. 1a, b, c). Findings of biopsied specimen of marrow were hyperplastic with an increase in megakaryocytes (Fig. 2a). Bone marrow smear revealed 15.0% myeloblasts, 6.0% promyelocytes, 8.8% myelocytes, 4.4% metamyelocytes, 28.8% neutrophils, 8.6% lymphocytes and 13.2% erythroblasts. The megakaryocyte count was increased to 540/ μl . Multinucleated erythroblasts, neutrophils with pseudo-Pelger anomaly and micromegakaryocytes were observed (Fig. 2b, c, d). Cytogenetic analysis was performed by Giemsa-banding technique. Twenty metaphases were analyzed, among which 15 showed a 46,XY, i(17q) karyotype (Fig. 3). Serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline

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Fig. 1. May-Giemsa staining of peripheral blood cells showing myeloblast and giant thrombocyte (a), hypersegmented neutrophil (b) and neutrophil with pseudo-Pelger anomaly ($\times 330$).

Fig. 2. Biopsied specimen of marrow showing hyperplastic marrow with an increase in megakaryocytes (a) ($\times 132$). May-Giemsa staining of marrow cells showing a multinucleated erythroblast (b), neutrophils with pseudo-Pelger anomaly (c) and micromegakaryocyte (d) ($\times 330$).

phosphatase (ALP), γ -glutamyl transpeptidase (γ -GTP), leucine aminopeptidase (LAP), blood urea nitrogen (BUN), cholinesterase (ChE) and total bilirubin were normal. Serum level of LDH was slightly increased to 655 IU/l. Anti-HTLV-I antibody was negative. On the basis of hematological findings the patient was diagnosed to be RAEB. From the end of October

1992 the Plt count gradually increased. On January 7, 1993 examination of the blood showed an Rbc count of $216 \times 10^4/\mu\text{l}$, Hb of 6.4 g/dl, Plt count of $61.3 \times 10^4/\mu\text{l}$, and Wbc count of $42,300/\mu\text{l}$ with 32.5% blasts; a diagnosis of acute leukemia was made. The liver was palpable 4 fingerbreadths (fbs) below the right costal margin and the spleen was also palpable 3 fbs below

Fig. 3. Cytogenetic analysis performed by Giemsa-banding technique. Twenty metaphases were analyzed, among which 15 showed a 46,XY,i(17q) karyotype.

H.O. 72 y/o Male MDS (RAEB→RAEB-t) →AML

Fig. 4. Hematological course. PRC: Packed red blood cells, PC: Platelet concentrate.

the left costal margin. The histological examination of bone marrow clot examined on January 11 showed hyperplastic marrow with the increase of blasts and megakaryocytes. From January 12, 1993 the oral administration of 300 mg/day of cytarabine ocfosfate was started. As shown in Fig. 4, Plt count fluctuated with WBC count. On February 7, 1993 the blood examination showed Plt count of $107 \times 10^4/\mu\text{l}$ and WBC count of $52,300/\mu\text{l}$ with 40% blasts. Results of marker analysis of blasts examined on March 11 were compatible with myeloblasts; CD13 63.9%, CD33 76.8% and CD41 0%. Blasts were also positive for anti-myeloperoxidase monoclonal antibody (AM-8) at 60.9%, for AM-9 at 65.2% and for AM-10 at 70.5%, respectively (7). On March 16, 1993 the oral administration of 2mg of melphalan was started. Leukothrombocytosis was improved without remission. On March 9, 1994, one year later, blood examination showed an RBC count of $244 \times 10^4/\mu\text{l}$, Hb of 7.3 g/dl, Plt count of $18.3 \times 10^4/\mu\text{l}$ and WBC count of 20,200/ μl with 6.5% blasts, 5.5% promyelocytes, 4.0% myelocytes, 1.5% metamyelocytes, 16.5% neutrophils, 2.0% eosinophils, 11.0% basophils, 39.0% monocytes and 14% lymphocytes. The liver and spleen were palpable 4 fbs and 5 fbs, respectively. Sequential analyses of chromosomes showed 47,XY,i(17q) in all of 20 cells examined. The patient is alive and was treated with transfusion and intermittent administration of melphalan.

Discussion

MDS which are hematological disorders with the potential of progression to acute leukemia, presumably result from the transformation of pluripotent stem cells giving rise to cytopenia, morphological anomalies and functional defects of erythroid, myeloid and megakaryocytic cells. MDS are classified into 5 groups: refractory anemia (RA), RA with ringed sideroblasts (RARS), RAEB, RAEB in transformation (RAEBt) and chronic myelomonocytic leukemia (CMML) (5). MPD is also thought to be a clonal disorder arising from a neoplastic transformation at the level of the pluripotent stem cell, resulting in an increase in some of the blood cells in the peripheral blood (4, 6). Thus, one of the differences in biological aspects between MDS and MPD is the presence or lack of a maturation disturbance. Although the appearance of MPD during the course of MDS is rare, some MDS showing MPD-like findings have been reported. Beris et al (8) reported a case developing polycythemia vera and two cases developing thrombocytosis. MDS cases developing leukothrombocytosis have been reported by Economopoulos et al (9), Yamaguchi et al (10) and Ohyashiki et al (11). Additional diagnoses such as Philadelphia chromosome-negative chronic myelocytic leukemia ($\text{Ph}^{\text{L}}\text{-CML}$), blastic crisis of $\text{Ph}^{\text{L}}\text{-CML}$, unclassified MPD (UMPD) have been given with the appearance of MPD-like characteristics, respectively. The present case also showed leukothrombocytosis during the sequential changes from RAEB to RAEB-t and acute leukemia. Hematological and physical findings such as

leukocytosis with the increase of blasts, thrombocytosis and hepatosplenomegaly closely resembled to those observed in the accelerated or blastic phase of CML. Recently, structural rearrangements of the long arm of chromosome 3 (3q anomalies) in hematological malignancies have been reported to be associated with megakaryocytic dysplasia, increased numbers of megakaryocytes and thrombocytosis (12). In the present case both megakaryocytic dysplasia and increased numbers of megakaryocytes were observed, however, sequential analyses of chromosomes revealed an isochromosome for the long arm of chromosome 17 [i(17q)], which has been frequently found prior to clinical or other evidences of blastic crisis of CML (13). Whether some biological bases common to MDS and MPD already coexisted in this case or whether some factors other than 3q further disturbed the status of MDS to evolve into overt leukemia with leukothrombocytosis are questionable. Further studies on these cases are thought to bring insight into the evaluation of the diversities of MDS, including the relationships between MDS, MPD and acute leukemia.

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