Three cases of primary myelodysplastic syndrome (MDS) associated with myelofibrosis were initially diagnosed as refractory anemia by the presence of bicytopenia or pancytopenia and having normo- or hypercellular marrow with dysplastic features. The bone marrow aspiration of these patients showed dry tap a few months after admission, or on admission. Their bone marrow biopsy specimens revealed various grades of increased formation of reticulin fibers. One patient entered into complete remission in response to metenolone, while the other two patients died of cerebral hemorrhage several months after admission. These results indicate that this disease should be classified as a distinct subgroup of MDS.

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**Key words:** bone marrow, dry tap

**Introduction**

Myelofibrosis is usually associated with myeloproliferative disorders, including chronic granulocytic leukemia, agnogenic myeloid metaplasia, polycythemia vera and megakaryocytic leukemia (1). Secondary myelofibrosis is usually seen in patients with hematological malignancies, secondary to chemotherapy or radiotherapy (2). Involvement of fibrosis of the bone marrow in the cases of primary MDS not associated with previous chemotherapy or radiotherapy has been recently reported by Sultan et al (3), Pagliuca et al (4), Lambertenghi-Deliliers et al (5), and others (6-13). The cause of the association of myelofibrosis and primary MDS remains to be determined. However, the significance of this complication deserves attention from the standpoint of the clinical diversity of MDS and the relating factors responsible for the pathogenesis of fibrosis in the field of hematopoiesis. We present three cases of primary MDS which were associated with myelofibrosis.

**Case Report**

Profiles of the patients are shown in Table 1. The peripheral blood counts revealed various degrees of pancytopenia. The bone marrow revealed various grades of cellularity, from normo- to hypercellular marrow with various types of dysplastic cells in the trilineage components. The cytogenetic abnormalities or rearrangements of the oncogenes studied (N-ras, Ha-ras and Ki-ras) in the peripheral blood or bone marrow cells did not reveal abnormalities in any of the patients. No hepatosplenomegaly was seen in any of the patients on admission which was confirmed by echography or computed tomography. The bone marrow aspiration became dry tap in two patients (patients 1 and 2) at 2 or 3 months after admission, and was dry tap in patient 3 on admission. The bone marrow biopsy specimens of these patients revealed various grades of increased reticulin fibers, stained with Gomori's silver impregnation for reticulin fibers (Fig. 1a-c). The increase in megakaryocytes was observed in patient 3 (Fig. 1c), and was not observed in the other patients. Patient 1 was treated by administration of metenolone, resulting in complete hematological remission which has lasted until present. Patients 2 and 3 were administered granulocyte-macrophage colony-stimulating factor (GM-CSF). Patient 2 did not respond to this therapy, and an increasing number of leukocytes was observed in patient 3; they died of cerebral hemorrhage 7 and 2 months after admission, respectively. Autopsy findings of patient 3 revealed marked hepatosplenomegaly and microscopic infiltration of the blood cells indicating extramedullary hematopoiesis (Fig. 2a, b).

**Discussion**

Myelofibrosis is a relatively rare finding in primary MDS (3-13). However, in one report, an increase in reticulin fibers was seen in 65% of MDS cases, although it was not clarified whether
Table 1. Profiles of the Patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex (Years)</th>
<th>FAB</th>
<th>Hb (g/dl)</th>
<th>Leukocyte (10⁹/L)</th>
<th>Platelet (10⁹/L)</th>
<th>Diagnosis to MF (Months)</th>
<th>Outcome (Cause of death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52/F</td>
<td>RA</td>
<td>5.7</td>
<td>3.4</td>
<td>330</td>
<td>Normo</td>
<td>E</td>
</tr>
<tr>
<td>2</td>
<td>69/F</td>
<td>RA</td>
<td>7.0</td>
<td>2.4</td>
<td>23</td>
<td>Hyper</td>
<td>E,G</td>
</tr>
<tr>
<td>3</td>
<td>51/M</td>
<td>RA</td>
<td>4.4</td>
<td>1.0</td>
<td>10</td>
<td>Hyper</td>
<td>E,G,M</td>
</tr>
</tbody>
</table>

RA denotes refractory anemia according to the criteria of myelodysplastic syndrome by the French-American-British (FAB) group. *Cellularity was determined by the clot section of bone marrow aspirate or biopsy specimen. Dysplasia denoted dyserythropoiesis (E), dysgranulopoiesis (G), and dysmegakaryopoiesis (M). MF denotes myelofibrosis.

these cases consisted solely of primary MDS or also contained cases of secondary MDS (6).

The acute progressive fatal course of MDS associated with myelofibrosis had been first reported as acute myelodysplasia with myelofibrosis by Sultan et al (3). However, Pagliuca et al (4) reported a relatively longer survival. In general, the presence of myelofibrosis seems to confer a poor prognosis, although the survival rates are still related to the French-American-British (FAB) subtype (longer survival in patients with refractory anemia and chronic myelomonocytic leukemia compared with those of refractory anemia with excess of blasts). Many of the MDS patients with myelofibrosis had cytogenetic abnormalities and a significantly shorter survival than those without myelofibrosis (12). Indeed, one of the present patients (patient 1) responded to the administration of metenolone and is still alive after more than 4 years. However, our other two patients died of hemorrhagic complications soon after admission.

Patient 3 of the present report might need the differential diagnosis from malignant fibrosis. These were formerly called malignant myelosclerosis (14, 15), acute myelofibrosis (16), or acute megakaryocytic myelofibrosis (17). Methods of phenotyping megakaryoblasts indicated that these cases were variants of AML, rather than myelofibrosis, and had been designated as acute megakaryoblastic leukemia, referred to as M7 by the FAB classification (18, 19). Furthermore, some MDS patients with myelofibrosis eventually develop acute megakaryoblastic leukemia (9, 12). Our case was different from those in that the bone marrow biopsy and autopsy specimens revealed mainly fibrosis, and infiltration by immature megakaryocytes was not evident. Agnogenic myeloid metaplasia was also denied in this patient by the rapid clinical course, and by the absence of hepatosplenomegaly and leukoerythroblastosis at the initial diagnosis (20).

The pathogenesis of the complication of myelofibrosis in MDS remains to be elucidated. A polypeptide growth factor capable of inducing fibroblast proliferation and collagen synthesis isolated from human platelets including platelet-derived growth factor (21) and transforming growth factor beta (22) could be responsible for the formation of myelofibrosis; further increased numbers of megakaryocytes were observed in most of the reported cases in the bone marrow biopsy specimens (4). The multipotential stem cell origin of the pathogenesis of MDS might accompany myelofibrosis as in other myeloproliferative disorders (1). However, in our patients, an increase in megakaryocytes was observed only in patient 3.

The increasing numbers of such case reports indicate that primary MDS with myelofibrosis represents a distinct clinical entity, and should be classified as a subgroup of MDS, or should be considered as an addendum.

The association of extramedullary hematopoiesis in cases of MDS with myelofibrosis has been recently reported (10). In those cases, the location of hematopoiesis was switched to extramedullary sites by the fibrosis of the bone marrow. The marked extramedullary hematopoiesis observed in our patient 3 might also suggest the effect of GM-CSF in enhancing extramedullary hematopoiesis.

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References

Biopsied bone marrow specimens stained with Gomori’s silver impregnation, when the bone marrow aspiration was dry tap. Various grades of the increased formation of reticulin fibers were observed in patient 1 (a), patient 2 (b) and patient 3 (c). An increased number of megakaryocytes was observed in patient 3 (c).

Fig. 2 Extramedullary hematopoiesis observed in the liver (a) and in the spleen (b) in patient 3. An increased number of hematopoietic cells including erythroid, myeloid and megakaryocytic series are observed.


Myelodysplastic Syndrome and Myelofibrosis