Sideroblastic Anemia Associated with Multiple Myeloma in Turner’s Syndrome

Kuniaki Itoh, Tadahiko Igarashi, Hisashi Wakita and Masako Minamihisamatsu*

A 67-year-old female was admitted to our hospital because of pancytopenia. Forty-six percent of erythroblasts in the bone marrow were ringed sideroblasts. Laboratory findings showed an IgG-κ monoclonal gammopathy. She was diagnosed as having sideroblastic anemia associated with multiple myeloma in mosaic (45, X/46, XX/47, XXX) Turner’s syndrome. There was no response to therapy. The chromosomal pattern of the patient was varied, and was accompanied by the development of refractory anemia with an excess of blasts from refractory anemia with ringed sideroblast 4 months after presentation. Cytogenetic studies suggested that the abnormal clone was restricted to the monosomic cell line.

Key words: chromosome, ringed sideroblast, monoclonal gammopathy

Introduction

The most common disorder of gonadal development in females is Turner’s syndrome; Extragonadal neoplasia in Turner’s syndrome has been sporadically reported (1–3). Hematologic neoplasia, however, is very rare in Turner’s syndrome. Here, we report a case of refractory anemia with excess of blasts (RAEB) which developed from refractory anemia with ringed sideroblast (RARS) associated with multiple myeloma in Turner’s syndrome.

Case Report

A 67-year-old female was admitted to our hospital because of anemia in October 1988. She was diagnosed as having multiple myeloma at a university hospital in May 1984 based on osteoporosis, IgG-κ monoclonal gammopathy and increased plasma cells (14.8%) in the marrow. Initial blood findings were as follows: hemoglobin 10.6g/dl, WBC 4.9 x 10^9/l, platelet count 329 x 10^9/l, IgG 3,875mg/dl, IgA 206mg/dl and IgM 10mg/dl. Bence-Jones proteinuria was present. Melphalan was given with a total dose of 84mg over 2 months with the serum IgG level declining to 2,547mg/dl. The patient remained asymptomatic for four years and was seen on a follow-up basis by a local hospital.

In May 1988, hematological evaluation revealed hemoglobin 11.0 g/dl, WBC 4.3 x 10^9/l and platelet count 90 x 10^9/l. Her height was 127.5 cm and she weighed 33.6 kg. On physical examination, the positive findings were anemia, a systolic murmur and petechiae of the lower extremities. She did not have a webbed neck. Peripheral blood count showed hemoglobin 5.1 g/dl, WBC 2.7 x 10^9/l (myeloblasts 1%, myelocytes 1%, metamyelocytes 5%, neutrophils 37%, lymphocytes 44%, monocytes 11% and basophils 1%), and platelet count 51 x 10^9/l. Peripheral blood film revealed 13 nucleated red cells per 100 white cells. Bone marrow aspirate was hypercellular with 4.4% myeloblasts, 1.4% plasma cells and 59.0% erythroblasts. Of erythroblasts, 46% were ringed sideroblasts. The bone marrow smear showed dyserythropoiesis with megaloblastoid cells and dysmyelopoiesis with pseudo-Pelger Huët anomaly. There were increased numbers of small hypolobulated megakaryocytes. Neutrophil alkaline phosphatase score was 282. Laboratory findings were as follows: LDH 369 IU/l, Ca 4.3/mEq/l, Fe 87 μg/dl and ferritin 390 ng/ml. The serum albumin was 3.9 g/dl, serum immunoglobulin levels were: IgG 2,180 mg/dl, IgM 150 mg/dl, IgA 240 mg/dl, and an IgG-κ monoclonal gammopathy was present without Bence-Jones proteinuria. Vitamin B₆ was 3.1 mg/ml. Folic acid was 2.4 mg/ml. Radiological
evaluation showed systemic osteoporosis.

There was no response to therapy with pyridoxine, folic acid, vitamin D₃ and oxymetholone, and blood transfusions were required. In February 1989, the number of myeloblasts in the marrow reached 6.8% and she was diagnosed as having RAEB which developed from RARS. The patient died in March 1989 due to bronchopneumonia. Serum immunoglobulin levels had not changed. At autopsy, focal proliferation of plasma cells in the spleen and lymph nodes was observed. The ovaries were atrophic bilaterally without neoplasia.

### Cytogenetic Studies

In October 1988, a bone marrow sample of this patient was examined for cytogenetic analysis. Seventeen of 19 G banded metaphases were 43, X, -X, -7, -17, -18, +der (17q, 21q). The remaining two metaphases were 45, X, -X (Table 1). In February 1989, chromosome analysis of the patient's peripheral blood lymphocytes revealed 45, X/46, XX/47, XXX mosaicism. Direct marrow preparations revealed 25 of 37 mitosis to have 43 chromosomes, 4 with 45 chromosomes, 3 with 41, 3 with 40 and 2 with 42 (Fig. 1).

### Discussion

In Turner's syndrome with mosaic karyotypes, the presence of a Y chromosome or Y chromosome material is associated with a high incidence of gonadoblastoma and dysgerminoma (4, 5). A tendency for developing neurogenic tumors has also been suggested in Turner's syndrome, however, the occurrence of other extragonadal tumors is rare (1). The risk of hematologic neoplasia is increased in patients with certain congenital chromosome abnormalities, e.g., Down's syndrome and Klinefelter's syndrome (6). A few cases of hematologic neoplasia, such as acute myeloblastic leukemia (1, 7), acute lymphoblastic leukemia (8), chronic lymphocytic leukemia (9) and chronic myelocytic leukemia (10–12), have been reported in Turner's syndrome. To our knowledge, Turner's syndrome accompanied by myelodysplastic syndrome (MDS) and multiple myeloma has not been reported. When the present patient was diagnosed as having sideroblastic anemia, there was no evidence of multiple myeloma, namely the IgM and IgA levels were normal and the number of plasma cells was not increased in the marrow on admission. There have been similar cases describing a lack of evidence of multiple myeloma when sideroblastic anemia associated with multiple myeloma developed into leukemia (13). The reason for this condition is unknown. Whether the association between multiple myeloma and Turner's syndrome is merely coincidental is unclear.

In the present case, it was hypothesized that MDS was caused by the antineoplastic chemotherapy for multiple myeloma (14). However, the administration of only 84 mg of melphalan would seem to make this less likely. Although a high incidence of monoclonal gammopathy in MDS has been reported (15), the most convincing hypothesis seems to be that Turner's syndrome with multiple myeloma developed MDS. The gene for the granulocyte-macrophage colony stimulating factor receptor has been mapped to the sex chromosome (16). From the viewpoint of their report, in which the chromosome localization of this gene may be important in the leukemogenesis of acute myeloid leukemia, the present patient is an interesting rare case of RAEB developing from RARS in Turner's syndrome.

Furthermore, the occurrence of the development of an abnormal karyotype in patients with constitutional chromosome mosaicism provides an experiment of nature which may clarify the clonality and evolution of tumors. The present case suggested that the abnormal clone did

### Table 1. Sequential Analysis of Karyotype

<table>
<thead>
<tr>
<th>Date</th>
<th>Numbers of metaphases</th>
<th>Karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>October 1988</td>
<td>BM 2 45, X, -X</td>
<td>45, X, -X</td>
</tr>
<tr>
<td></td>
<td>February 1989 17</td>
<td>43, X, -X, -7, -17, -18, +der(17q 21q)</td>
</tr>
<tr>
<td></td>
<td>PB 24 45, X</td>
<td>45, X, -X</td>
</tr>
<tr>
<td></td>
<td>4 46, XX</td>
<td>46, XX</td>
</tr>
<tr>
<td></td>
<td>13 47, XXX</td>
<td>47, XXX</td>
</tr>
<tr>
<td>BM 4</td>
<td>45, X, -X</td>
<td>45, X, -X</td>
</tr>
<tr>
<td>25</td>
<td>43, X, -X, -17, -18, -21, +der(17q 21q), +mar</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>42, X, -X, -4, -6, -7, -10, -17, -17, -18, -21, +der(10)(10?):(q26:?), +mar1, +mar2, +mar, +r(?)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>42, X, -X, -4, -6, -7, -10, -17, -17, -18, -20, -21, +der(10)(10?):(q26:?), +mar1, +mar2, +mar, +r(?)</td>
<td></td>
</tr>
<tr>
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<td>41, X, -X, -4, -6, -7, -10, -17, -17, -18, -20, -21, +der(10)(10?):(q26:?), +mar1, +mar2, +mar, +r(?)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>41, X, -X, -4, -6, -7, -10, -17, -17, -18, -21, +der(10)(10?):(q26:?), +mar1, +mar2, +r(?)</td>
<td></td>
</tr>
<tr>
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<td>40, X, -X, -4, -6, -7, -10, -17, -17, -18, -20, -21, +der(10)(10?):(q26:?), +mar1, +mar2, +r(?)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>40, X, -X, -4, -6, -7, -10, -17, -17, -18, -20, -21, +der(10)(10?):(q26:?), +mar1, +mar2, +mar</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>40, X, -X, -4, -6, -7, -10, -17, -17, -18, -19, -20, -21, +der(10)(10?):(q26:?), +mar1, +mar2, +mar, +r(?)</td>
<td></td>
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BM: bone marrow, PB: peripheral blood
not develop from a cell of the 46, XX or 47, XXX lineage, but from a cell of the 45, X, −X lineage. It is accordingly suggested that MDS is a clonal disorder (17).

Acknowledgments: We would like to thank Professor M. Omine and Dr. H. Niikura of Fujigaoka Hospital, Showa University for providing the clinical data.

References