Myelodysplastic Syndrome Following Therapy for Brain Tumor
—Two Case Reports—

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Abstract

A 3-month-old boy and a 29-year-old woman presented with myelodysplastic syndrome (MDS) following therapy for primary malignant brain tumor. Both received intensive alkylating agent doses for induction and maintenance chemotherapy combined with craniospinal or cranial radiation for medulloblastoma and anaplastic astrocytoma, respectively. They developed refractory anemia and pancytopenia. Approximately 9 years after the completion of induction chemoradiotherapy, chromosomal analysis of bone marrow cells resulted in the diagnosis of MDS. The boy died of leukemic evolution 15 months later, the woman died of hematopoietic failure 3 months later. The most common symptom of MDS is refractory anemia, either alone or as part of bi- or pancytopenia. Clonal proliferation with chromosomal analysis of bone marrow cells establishes the diagnosis of MDS. Patients with malignant brain tumors are at risk of the development of MDS as a late complication of chemotherapy based on high cumulative doses of alkylating agents.

Key words: myelodysplastic syndrome, primary brain tumor, chemotherapy, alkylating agent, secondary malignancy

Introduction

Myelodysplastic syndrome (MDS) is a heterogeneous group of hematologic disorders broadly characterized by cytopenia associated with dysmorphic and usually cellular bone marrow and consequent ineffective blood cell production.26,27) Idiopathic MDS is a disease of the elderly; the mean age at onset is 68 years.4) MDS following therapy for cancer (therapy-related MDS: t-MDS) is not age-related and may occur in as many as 15% of patients within a decade after intensive combined-modality treatment for the malignancy.4,16,19,23) This study describes the neuro-oncologic characteristics of t-MDS in two patients with primary malignant brain tumors treated in Japan.

Case Reports

Case 1: A 3-month-old boy with retarded developmental milestones was referred to our department in January 1983. Computed tomography of the brain revealed a tumor in the posterior fossa. He underwent a craniotomy and subtotal excision of the tumor. The histological diagnosis was medulloblastoma. He received chemotherapy consisting of 1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride (ACNU) and 1-(2-tetrahydrofuryl)-5-fluorouracil (tigafur) and craniospinal radiation including 10 Gy to the entire craniospinal axis and 30 Gy boost to the posterior fossa. The tumor disappeared completely after this treatment. Maintenance chemotherapy comprised of ACNU, tigafur, and N-[4-[[2,4-diamino-6-pteridinyl]methyl]methylamino]benzoyl]-L-glutamic acid (MTX) was administered until September 1985. The cumulative doses were 650 mg ACNU, 50 g tigafur, and 6.8 g MTX. However, he became in-
creasingly less active due to refractory anemia starting in 1988.

In January 1992, he developed frequent bleeding from the nasal mucosa and gingiva. A complete blood count showed hemoglobin 5.9 g/dl, platelets $6.9 \times 10^9$/mm$^3$, and white blood cells (WBCs) $3.46 \times 10^9$/mm$^3$. The provisional diagnosis was idiopathic thrombocytopenic purpura. A bone marrow aspirate contained normocellular marrow with dyserythropoietic change and ringed sideroblasts in the erythroid lineage, hypogranulation, and hyposegmentation in granulocyte precursors, and an increase in myeloblasts (11%). Cytogenetic analysis of cultured bone marrow cells revealed abnormal karyotype in 16/23 cells, all showing 47, XY, +1, der(15)t(1;15)(p10;q10). These findings confirmed the diagnosis of MDS (refractory anemia with excess blasts: RAEB). He died 15 months later of multiple organ failures because of leukemic evolution.

Case 2: A 29-year-old woman presented with headache and left hemiparesis in September 1990. Magnetic resonance (MR) imaging showed a heterogeneously enhanced irregular mass in the right frontal lobe, which was subtotally removed. The histological diagnosis was anaplastic astrocytoma. External beam radiotherapy (54 Gy) to the extended local field was completed in November 1990. She received 125 mg methyl 6-[3-(2-chloroethyl)-3-nitrosoureido]-6-deoxy-β-D-glucopyranoside (MCNU) on two occasions during radiotherapy. The residual tumor was resolved after these treatments. After discharge, she was given 11 courses of maintenance chemotherapy (MCNU 100 mg) every 3 to 4 months.

Follow-up MR imaging demonstrated local recurrence as a small enhanced mass in September 1995. She underwent total removal followed by combined chemotherapy consisting of ACNU and cis-diaminedichloroplatinum (CDDP) and began five cycles of ACNU maintenance chemotherapy (100 mg) which was completed in July 1997. The cumulative doses were 1425 mg MCNU, 740 mg ACNU, and 100 mg CDDP. In September 1997, a routine complete blood count showed WBCs 2800/mm$^3$ (55% lymphocytes, 43% neutrophils, 2% monocytes), hemoglobin 8.5 g/dl with macrocytosis, and platelets $1.12 \times 10^5$/mm$^3$. By September 1999, several episodes of pancytopenia had occurred, and she required frequent blood transfusions. The complete blood count 5 months later revealed WBCs 2100/mm$^3$ (35% lymphocytes, 34% monocytes, 27% neutrophils, 2% myelocytes, 2% metamyelocytes), hemoglobin 6.5 g/dl with macrocytosis, and platelets $7.5 \times 10^4$/mm$^3$. In April 2000, a bone marrow aspirate revealed hypercellularity with increased blasts (10%), dyserythropoiesis, nuclear hyposegmentation in the granular lineage, and megakaryocytic hyperplasia with atypical forms. Cytogenetic analysis of cultured bone marrow cells demonstrated abnormal karyotype in 15 of 20 tested cells, all showing 46, XX, +1, der(1;7)(q10;p10), i(21)(q10). The diagnosis was MDS (RAEB). She died of acute renal failure and disseminated intravascular coagulopathy 3 months after the diagnosis of MDS.

Discussion

Secondary malignancy due to chemotherapeutic agents was not broadly recognized until the discovery that several cancer patients had developed acute myeloid leukemia (AML) after the administration of alkylating agents. Classical AML developed following the administration of alkylating agents, or the administration of topoisomerase-II inhibitor. Half of the first group of patients characteristically manifested MDS prior to leukemic evolution. The second group underwent rapid leukemic change without MDS within a few years of receiving the chemotherapy.

MDS is a clonal hematopoietic stem cell disorder leading to impaired cell proliferation and differentiation. The clinical symptoms of MDS are nonspecific, but anemia dominates the early course. Most symptomatic patients complain of gradual onset of fatigue, weakness, dyspnea, and pallor. However, at least half of the patients are asymptomatic, and MDS is discovered only incidentally by routine blood cell counts. A routine complete blood count frequently detects macrocytic anemia in patients with MDS, either alone or as part of bi- or pancytopenia, whereas isolated neutropenia or thrombocytopenia is more unusual. The smear may be dimorphic with a distinctive population of large red blood cells.

The diagnosis of MDS is based on morphologic dysplastic changes in the peripheral blood and bone marrow cells identified by smear examination and clonal proliferation in the bone marrow. The French-American-British (FAB) Cooperative Group proposed a classification based on easily obtainable laboratory information (Table 1). According to these criteria, both of our cases were RAEB. The median survival time of patients with RAEB is approximately 15 months. RAEB, a subtype of MDS, is a refractory disease with a poor prognosis (Table 1). Since the establishment of the FAB classification for MDS in 1982, only 11 patients with MDS after therapy for malignant brain tumor including our patients have been reported (Table 2).

However, a number of neuro-oncology studies have
Table 1  FAB classification and prognosis of myelodysplastic syndrome

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Blood</th>
<th>Marrow</th>
<th>% of MDS cases</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory anemia (RA)</td>
<td>blasts &lt;1%</td>
<td>blasts &lt;5%</td>
<td>27</td>
<td>50</td>
</tr>
<tr>
<td>Refractory anemia with ringed sideroblasts (RARS)</td>
<td>blasts &lt;1%</td>
<td>blasts &lt;5%</td>
<td>20</td>
<td>65</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts (RAEB)</td>
<td>blasts &lt;5%</td>
<td>blasts 5–20%</td>
<td>26</td>
<td>15</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts in transformation (RAEB-t)</td>
<td>blasts &gt;5%</td>
<td>blasts 20–30%</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Chronic myelomonocytic leukemia</td>
<td>&gt;100000/ml monocytes</td>
<td>any number</td>
<td>14</td>
<td>23</td>
</tr>
</tbody>
</table>

Cited from references 2 and 3.

Table 2  Myelodysplastic syndrome after malignant brain tumor therapy

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Age/Sex</th>
<th>Histological diagnosis</th>
<th>Chemotherapy</th>
<th>Subtype of MDS</th>
<th>Interval to MDS (months)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genot et al. (1983)¹¹</td>
<td>42 yrs/F</td>
<td>anaplastic astrocytoma</td>
<td>teniposide, CCNU</td>
<td>RAEB</td>
<td>43</td>
<td>died of complication during induction chemotherapy for leukemia</td>
</tr>
<tr>
<td>Pui et al. (1990)²³</td>
<td>16 mos/M</td>
<td>unknown</td>
<td>nitrogen mustard, procarbazine</td>
<td>RAEB</td>
<td>19</td>
<td>died 10 mos after diagnosis of MDS without treatment</td>
</tr>
<tr>
<td>Hayani et al. (1992)¹³</td>
<td>12 mos/F</td>
<td>medulloblastoma</td>
<td>nitrogen mustard, vincristine, prednisolone, procarbazine</td>
<td>RAEB-t</td>
<td>19</td>
<td>leukemic evolution 7 mos, and died 19 mos after diagnosis of MDS</td>
</tr>
<tr>
<td>Perry et al. (1998)²²</td>
<td>39 yrs/F</td>
<td>glioblastoma</td>
<td>BCNU, 6-MP, CDDP, etoposide</td>
<td>RAEB</td>
<td>17</td>
<td>alive 8 mos after diagnosis of MDS without treatment</td>
</tr>
<tr>
<td>Duffner et al. (1990)⁹</td>
<td>23 mos/?</td>
<td>choroid plexus carcinoma</td>
<td>vincristine, cyclophosphamide, CDDP, etoposide</td>
<td>?</td>
<td>92</td>
<td>died</td>
</tr>
<tr>
<td></td>
<td>7 mos/?</td>
<td>desmoplastic infantile ganglioglioma</td>
<td>vincristine, cyclophosphamide, CDDP, etoposide</td>
<td>?</td>
<td>57</td>
<td>died</td>
</tr>
<tr>
<td>Akyuz et al. (1998)¹¹</td>
<td>15 yrs/M</td>
<td>medulloblastoma</td>
<td>procarbazine, CCNU, vincristine</td>
<td>RAEB</td>
<td>28</td>
<td>leukemic evolution 1 mo, and died 8 mos after diagnosis of MDS</td>
</tr>
<tr>
<td>Rogers et al. (2001)²⁴</td>
<td>34 yrs/F</td>
<td>anaplastic astrocytoma</td>
<td>procarbazine, CCNU, vincristine</td>
<td>RAEB</td>
<td>54</td>
<td>alive 3 yrs after allergenic bone marrow transplant for MDS</td>
</tr>
<tr>
<td>Present Case 1</td>
<td>3 mos/M</td>
<td>medulloblastoma</td>
<td>ACNU, tegafur, MTX</td>
<td>RAEB</td>
<td>108</td>
<td>died of MOF 15 mos after diagnosis of MDS</td>
</tr>
<tr>
<td>Present Case 2</td>
<td>29 yrs/F</td>
<td>anaplastic astrocytoma</td>
<td>MCNU, ACNU, CDDP</td>
<td>RAEB</td>
<td>115</td>
<td>died of DIC 3 mos after diagnosis of MDS</td>
</tr>
</tbody>
</table>


documented cases of therapy-related AML. The patients presented with aplastic anemia, persistent anemia, prolonged thrombocytopenia, or refractory anemia.⁷,⁸,¹²,¹³,¹⁴,¹⁵,¹⁷ We suggest that the current nomenclature developed by FAB is not entirely satisfactory. More information on t-MDS is necessary to develop accurate diagnostic procedures.

MDS may occur in as many as 15% of patients within a decade of intensive combined-modality treatment for malignancy.⁴,¹⁶,¹⁹,²³ Advances in therapeutic multimodalities, especially those involving chemotherapeutic agents, have resulted in longer
patient survival.\textsuperscript{5,6,20} Neuro-oncologists need to be aware that patients with medulloblastoma, oligodendroglioma, anaplastic astrocytoma, or intracranial germ cell tumors are at higher risk for therapy-related MDS and AML because they can survive for more than 5 years after effective chemotherapy consisting of high cumulative doses of alkylating agents and topoisomerase-II inhibitor.\textsuperscript{2,10,18,21,25}

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References


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