Hodgkin's Disease in a Child with Acute Lymphoblastic Leukemia

Ho Seong Kim, Hye Ok Roh, Shin Heh Kang, Chuhl-Joo Lyu, Kir-Young Kim, Soon Won Hong and Woo Ick Yang

Hodgkin's disease, manifested as a second malignant neoplasm in acute lymphoblastic leukemia, rarely occurs, with seventeen cases reported including this case. We presented the clinical and pathologic features of a nine-year-old male child with acute lymphoblastic leukemia in remission. He had cervical lymph node involvement 22 months after the diagnosis of leukemia as an initial presentation of Hodgkin's disease of mixed cellularity.

A brief review of related literatures was also done.

Key Words: Hodgkin's disease, acute lymphoblastic leukemia, second malignant neoplasm

Recent advances in the treatment of childhood cancer have increased the survival rate for many malignant diseases. As survival improves, late effects of the disease and/or its therapy may increase. One of these effects is the development of second malignant neoplasms (SMN). Acute lymphoblastic leukemia (ALL) is the most common cancer in children, but the occurrence of SMN in patients with ALL is rare (Moscik and Rymann 1981; Ellerbroek et al. 1984). Particularly, the development of Hodgkin's disease in patients with ALL as a SMN is quite unusual, with just sixteen reported cases (Grant and Coleman 1975; Woodruff et al. 1977; Lampert and Boosen 1977; Garwicz et al. 1978; Harousseau et al. 1978; Wingen et al. 1979; Hagmann et al. 1981; Horbar et al. 1981; Labotka et al. 1983; Zuible et al. 1986; Peeters et al. 1986; Sabatine et al. 1986).

We report on a patient with acute lymphoblastic leukemia, treated with standard chemotherapy and central nervous system irradiation, who subsequently developed Hodgkin's disease while in remission.

CASE REPORT

A nine-year old boy was admitted to the Department of Pediatrics because of fever and pain in his right hip for three months. The peripheral white blood cell count was 2,800/mm^3 with 14% lymphoblasts. There was no lymphadenopathy or splenomegaly. A bone marrow aspirate confirmed the diagnosis of ALL L1 morphology (FAB criteria) (Fig. 1). Immunological markers were not done. Chromosome studies showed a normal male karyotype. He was treated with vincristine, prednisone, and L-asparaginase, which led to complete remission. Cranial irradiation (total dose of 1,800 cGy) and intrathecal methotrexate were given for central nervous system prophylaxis.

Maintenance therapy consisted of daily oral 6-mercaptopurine and weekly methotrexate intramuscular injections. He remained in generally good health until 22 months following diagnosis, when he was admitted again due to four-month old masses in his right submandibular area. There were no complaints of fever, weight loss, or night sweats. On admission, body temperature was 36.4°C, pulse rate 100/min, and respiration rate 26/min. On physical examination, two lymph-nodes were palpable in his right submandibular area. These were 1 x 2.5 cm, 2 x 3 cm in size, firm, fixed, and non-tender.
Fig. 1. Bone marrow aspiration smear shows predominantly small lymphoblasts having dark, ovoid homogenous nuclear chromatin, some of which are slightly indented, and inconspicuous nucleoli. The cytoplasm is scanty and indistinct (Wright-Giemsa stain, × 1,000).

Fig. 2. Bone marrow aspiration smear shows normal maturation and cellularity (Wright-Giemsa stain, × 400).

Fig. 3. Hodgkin’s disease with mixed cellularity; lymphocytes are lower in number, and Reed-Sternberg cell (arrow) is readily identified (H&E stain, × 400).

Fig. 4. Frequent mitosis (M) and Hodgkin’s cells (H) are found in the background of plasma cells (P) and eosinophils (E) infiltration (H & E stain, ×400).

There was no enlargement of the liver, spleen, or other lymph-nodes. The hemoglobin was 12.2 gm/dl, hematocrit 34.8%, and white blood cell count 7,550/mm³ with 73% neutrophils, 18% lymphocytes, and 9% monocytes. The platelet count was 275,000/mm³, and the erythrocyte sedimentation rate was 4 mm per hour. Blood chemistries, urinalysis, and chest X-ray were normal. A bone marrow aspiration showed normocellularity with lymphoblasts less than 5% compatible with the remission state of ALL (Fig. 2). Microscopic examination of the biopsied specimen of cervical lymph nodes revealed Hodgkin’s disease of the mixed cellularity type (Fig. 3 and 4). The normal lymphoid tissue was largely replaced by a diffuse infiltrate of lymphocytes, histiocytes, eosinophils, and plasma cells with irregular areas of necrosis and disordered fibrosis. Characteristic Reed-Sternberg cells were easily identified. Further investigations were made to determine the extent of the Hodgkin’s disease. On the neck, chest, and abdominal CT scan, there were many enlarged lymph-nodes only along the right internal jugular vein. The whole body bone scan was normal. He was clinically assessed as stage IA. He was treated with two courses of MOPP protocol (nitrogen mustard, vincri-stine, procarbazine, and prednisone), which was well tolerat-
ed, he continued to receive maintenance therapy for leukemia, concurrently. After two courses of MOPP chemotherapy, radiotherapy to an involved field (2,400 cGy) was undertaken and the remaining four courses of MOPP chemotherapy will be resumed (Donaldson and Link 1987).

**DISCUSSION**

Recent therapeutic advances have improved the survival rate in childhood cancer. As a result, occurrence of SMN in children is seen with increasing frequency (Li 1997; Mike et al. 1982; Meadows et al. 1985). Individuals with a history of childhood cancer have an estimated ten to twenty times the lifetime risk of a SMN when compared to age-matched controls (Meadows et al. 1985). Although the lifetime incidence of SMN has not yet been defined, within the first twenty years after the initial diagnosis, it is between 3% and 12% (Moertel et al. 1961; Li 1977; Mike et al. 1982; Meadows et al. 1985). However, these figures, as well as the types of SMN, differ considerably according to the diagnosis of primary cancer, patient age, specifics of therapy, and presence of genetic conditions (Blatt and Bleyer 1989).

Today, more than 70% of all children with ALL who are younger than then years of age at diagnosis can be cured with modern therapy (Poplack and Reaman 1988; Bleyer 1990). As a result of this improvement, the possibility of SMN occurring in patients with ALL is increasing. Still, SMN in patients with ALL is rare (Mosijczuk and Ruymann 1981; Ellerbroek et al. 1984). The most frequent SMN in patients with ALL are histiocytic medullary reticulosis, acute nonlymphoblastic leukemia, Hodgkin’s disease, chronic myelogenous leukemia, and various solid tumors (Cited from Ellerbroek et al. 1984). Curiously, the occurrence of Hodgkin’s disease in ALL was not observed until 1975 (Grant and Coleman 1975), but subsequently sixteen more patients, including this case, have been described (Table 1).

The ages of the seventeen reported patients ranged from 4 to 53 years, with all but three under twenty, as expected. The ratio of male to female was equal. The mean interval between diagnosis of ALL and Hodgkin’s disease was 24.7 months (range: 10~70 months), much shorter than the mean interval of 38 months between the diagnosis of ALL and solid tumors (Mosijczuk and Ruymann 1981). Eight

<table>
<thead>
<tr>
<th>Source</th>
<th>Age/Sex (yrs)</th>
<th>Interval* (mo)</th>
<th>Histology</th>
<th>Stage</th>
<th>Sites</th>
<th>Radiation</th>
<th>Chemotherapy**</th>
</tr>
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<tr>
<td>Grant &amp; Coleman, 1975</td>
<td>17/M</td>
<td>15</td>
<td>LD</td>
<td>IVB</td>
<td>Ce,In,S,B</td>
<td>C,Sp</td>
<td>V,D,P,M,6MP</td>
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<td>Woodruff et al. 1977</td>
<td>18/F</td>
<td>11</td>
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<tr>
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<td>22</td>
<td>MC</td>
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<td>C</td>
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<tr>
<td>Harousseau et al. 1978</td>
<td>24/F</td>
<td>12</td>
<td>MC</td>
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<td>Wingen et al. 1979</td>
<td>10/F</td>
<td>16</td>
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<td>C</td>
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<td>53/F</td>
<td>20</td>
<td>MC</td>
<td>IIb</td>
<td>In</td>
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<td>Current Case</td>
<td>10/M</td>
<td>22</td>
<td>MC</td>
<td>IA</td>
<td>Ce</td>
<td>C</td>
<td>V,P,A,M,6MP</td>
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* Interval from diagnosis of ALL to onset of Hodgkin’s disease.

**For ALL

C: cranial; Sp: spinal; Me: mediastinal; LD: Lymphocyte depletion; MC: mixed cellularity; NS: nodular sclerosis; LP: lymphocyte predominant; V: vincristine; P: prednisone; A: L-asparaginase; D: doxorubicin; D: daunorubicin; M: methotrexate; 6MP: 6-mercaptopurine; Cy: cyclophosphamide; Ce: cervical node; In: inguinal node; Su: supravacular node; Mes: mesenteric node; Pa:Paraortic node; N: node; B: bone; L: lung; Liv: liver; S: spleen; Sb: small bowel; T: tonsil

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of the seventeen patients had mixed cellularity, four had nodular sclerosis, three had lymphocyte depletion, and one patient had lymphocyte predominant Hodgkin's disease. This distribution of histologic type is unusual because nodular sclerosis is the most common form of Hodgkin's disease (Sullivan et al. 1984).

Although the factors playing a role in the development of Hodgkin's disease in patients with pre-existing ALL are far from clear, one or more of the following hypotheses is plausible. First, radiation therapy and chemotherapy for ALL may be oncogenic. Radiation therapy is known to cause damage to deoxyribonucleic acid, leading to genetic mutations and the appearance of tumors such as acute myelogenous leukemia and osteosarcoma (Tefft et al. 1968; Hutchinson 1976). However, because the SMN associated with radiation therapy generally have arisen in the irradiation field (Hutchinson 1976), it is unlikely that the radiation therapy these patients have received played a major role in the development of the SMN. It is possible, however, that chemotherapy may potentiate the oncogenic effect of radiotherapy (Rosner and Grunwald 1975). Methotrexate and mercaptopurine, the two agents most frequently used for maintenance in ALL, can result in hepatic damage (Einhorn and Davidsohn 1964; Hersh et al. 1966). Methotrexate-associated hepatic fibrosis preceded the development of a hepatoma in a child five years after the diagnosis of ALL (Penn 1978). The carcinogenicity of the chemotherapeutic agents used in the treatment of ALL has long been suspected (Penn 1976; Rosner 1976; Penn 1978), but not proven. Secondly, therapy for ALL or the disease itself may sufficiently impair host immunity allowing an environmental oncogenic factor to induce a SMN. The appearance of a lymphoreticular malignancy such as histiocytic reticulosis and Hodgkin's disease with a brief latency supports this hypothesis (Mosijczuk and Ruymann 1981). And clinical evidence that suppression of the immune system contributes to oncogenesis of lymphoreticular tumors is derived primarily from surveys of renal transplant recipients. These individuals have a 35-fold increased risk of cancer development, usually histiocytic lymphoma, as a result of immunosuppressive therapy (Starzl et al. 1970; Penn 1974). Thirdly, patients with ALL may have an underlying genetic inherited disorder which predisposes them to malignancies, possibly triggered by environmental factors. The brief interval before the appearance of SMN in some patients with ALL suggests that an additional malignant clone may be present but not clinically apparent at the time of diagnosis of ALL. Another possibility is that a common neoplastic stem cell that initially gives rise to ALL may subsequently differentiate to anther malignant cell type as a result of therapy (Mosijczuk and Ruymann 1981). In addition, these patients may possess constitutional factors that lower the threshold and latency period required for a malignancy such as ALL or a subsequent tumor to appear. Finally, the occurrence of two tumors in one person may be coincidental.

The oncogenic potential of the therapy in ALL, constitutional predisposition, and the increased survival resulting from newer methods of treatment should alert clinicians to the possibility of SMN occurring in patients of all ages with the initial diagnosis of ALL. Therefore, periodic examination of the lymph node, liver, spleen, and bone marrow is essential for all patients with ALL.

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