The Turkish Journal of Pediatrics 1998; 40: 131-134

MYELODYSPLASTIC SYNDROME IN A CHILD WITH A HISTORY OF MEDULLOBLASTOMA*

*Canan Akyüz MD***, Suna Emir MD****, Nilüfer Güler MD*****

*Alev Türker MD******, Münevver Büyükpamukçu MD*******

SUMMARY: Akyüz C, Emir S, Güler N, Türker A, Büyükpamukçu M. (Oncology Unit, Department of Pediatrics and Adult Oncology Unit, Department of Internal Medicine, Hacettepe University Faculty of Medicine, Ankara, Turkey). Myelodysplastic syndrome in a child with a history of medulloblastoma. Turk J Pediatr 1998; 40: 131-134.

We present a case of myelodysplastic syndrome (MDS) following treatment for medulloblastoma. The tumor was diagnosed at 15 years of age and managed with surgery, craniospinal radiation and a triple-durg regimen [chloroethylnitrosourea (CCNU), vincristine (VCR), procarbazine]. Fifteen months after the completion of therapy, the patient developed MDS with monosomy 5 and monosomy 7 on chromosome analysis of bone marrow cells. Two weeks later, MDS evolved into acute myeloblastic leukemia (AML). Therapy-related MDS or AML may be a complication for patients with past brain tumors. Therefore, they should be carefully followed up by regular physical examinations and complete blood counts. *Key words: medulloblastoma, myelodysplastic syndrome, second malignancy, monosomy 5, monosomy 7.*

Several reports suggest that the development of leukemic disorders as a second neoplasm may be related to the treatment of the first malignancy[1,2]. This association has reported mainly for Hodgkin's disease and non-Hodgkin's lymphoma[3]. A similar association is not well recognized in children receiving chemotherapy and radiotherapy for brain tumors. We report a case who showed myelodysplastic syndrome (MDS) and acute myeloblastic leukemia (AML) following treatment for medulloblastoma because of the rarity of leukemic disorders such as these two in patients treated for brain tumors.

Case Report

In August 1991, a 15-year-old, previously healthy boy came to Hacettepe University Children's Hospital with complaints of headache, vomiting and ataxia. During the radiological evaluatilon of the patient, a posterior fossa tumor was

* From the Oncology Unit, Department of Pediatrics and Adult Oncology Unit, Department of Internal Medicine, Hacettepe University Faculty of Medicine, Ankara.

** Associate Professor of Pediatrics and Pediatric Oncologist, Hacettepe University Faculty of Medicine.

*** Research Assistant in Pediatrics, Hacettepe University Faculty of Medicine.

**** Associate Professor of Oncology, Hacettepe University Faculty of Medicine.

***** Assistant Professor of Oncology, Hacettepe University Faculty of Medicine.

****** Professor of Pediatrics and Pediatric Oncologist, Hacettepe University Faculty of Medicine.

recognized in the cranial computed tomography. Histopathologic diagnosis of medulloblastoma was established after the surgical removal of the tumor. Residual tumor was not present on the postoperative cranial tomography. The patient was further managed with radiotherapy (3600 cGy to the neuroaxis, 1800 cGy boost to the tumor bed) in another centre. Chemotherapy cycles consisting of chloroethylnitrosourea (CCNU), vincristine (VCR), and procarbazine were given every six weeks for one year and terminated in November 1992. At the end of the treatment, reevaluation revealed no evidence of residual or recurrent tumor. Fifteen months after the completion of therapy, the patient complained of pallor and fatigue. Complete blood count (CBC) showed Hb: 6.1 g/dl, platelet count: 77,000/mm^3, and WBC: 2,400/mm^3 with 34 percent neutrophils, 64 percent lymphocytes, and 2 percent eosinophiles. Bone marrow examination revealed hypercellularity with increased blasts (17%) and dyserythropoiesis. Bone marrow biopsy was reported as normocellular with an excess of eosinophilic leukocytes. Rare ringed sideroblasts were shown in bone marrow with the iron stain. Bone marrow synchronized cultures revealed a karyotype of 45, XY with the deletion of the fifth and seventh chromosomes and presence of marker chromosome in 18 of the 25 metaphases analyzed (45, XY, -5, -7, +mar). The diagnosis of myelodysplastic syndrome (MDS) was established. Two weeks later, MDS evolved into acute myeloblastic leukemia. The patient was treated with anti-leukemic therapy, (VCR + ARA - C + mitoxantrone + prednisolone). However, the patient did not achieve a remission and became refractory to the therapy and died with disease progression eight months after the diagnosis of MDS.

Discussion

Brain tumor is the second most common neoplasm in children after leukemia[4]. Medulloblastomas represent twenty to thirty percent of all childhood brain tumors. New therapeutic approaches have improved the outcome in medulloblastoma. Radiation to the craniospinal region and addition of multidrug regimens led to this improvement, replacing the application of local radiotherapy[5]. In general, this aggressive approach consisting of radiotherapy and chemotherapy forms the basis of the principal treatment of neoplastic disorders. In the long-term follow up of these patients, complications of this therapy have been increasingly recognized. Secondary malignancies have high morbidity and mortality. Common risk factors for the development of secondary malignancies are the primary tumor, type of chemotherapy, radiotherapy and underlying genetic diseases. The increased risk of second malignancies, most commonly AML, has been reported in treated cases of different types of tumors, especially in Hodgkin's disease[1-3]. However, few cases with a history of brain tumors have been reported to date[6-10]. In our patient, the onset of acute leukemia was preceded by a phase of myelodysplasia. Myelodysplasia preceding leukemia has been reported before[6, 8].

Myelodysplastic syndrome is rare in children. The most widely recognized classification is the one proposed by the French-American-British (FAB) Cooperative Group, and it is based on morphological findings of the peripheral blood smear and bone marrow[11]. The FAB classification for our patient was refractory anemia with excess blasts (RAEB).

Secondary MDS, due to previous toxic chemical exposure or chemoradiotherapy, may occur at all ages. This secondary form of MDS, with or without progression to AML, is emerging as a significant clinical problem, and may cause substantial morbidity and mortality. Use of more intensive treatment regimens combining high-dose chemotherapy and radiotherapy and broader utilization of adjuvant chemoirradiation in solid tumor therapy are some of the reasons for increased incidence. In secondary MDS, abnormal karyotypes are evident in virtually all patients. Multiple chromosome aberrations are the rule. Chromosomes 5 and 7 are involved in 85 percent of the secondary MDS patients[12-13]. Cytogenetic analysis of the bone marrow in our patient revealed monosomy 5 and monosomy 7, which is characteristic of therapy-related MDS and AML. Nitrosourea is one of the durgs accused causing the development of leukemias after the treatment of primary brain tumors[8-9]. In animals, nitrosoureas have a mitogenetic, carcinogenic and teratogenic action. The role played by alkylating agents in the induction of iatrogenic acute leukemia is well known.

In different studies by Baram et al.[14] and Pui et al.[15], it was reported that two cases treated with MOPP (nitrogen mustard, vincristine, prednisolone, and procarbazine) chemotherapy for brain tumor developed acute lymphocytic leukemia and MDS. In another study by Hayani et al.[16], two of eight children who survived medulloblastoma developed MDS. One of them had received MOPP chemotherapy for a brain tumor at the age of 12 months, completing a total of 24 courses, and 19 months later developed MDS with monosomy 7. The other who developed MDS was a seven-year-old boy treated with craniospinal radiation and MOPP chemotherapy. In both cases, MDS evolved into AML. Although we cannot conclude that chemotherapy with CCNU caused MDS in our patient, it is most likely that the chemotherapy played a major role in the pathogenesis of MDS. Radiation therapy may also have been a contributory factor in our patient. The time interval between the therapy and the evolution of MDS was short, a similar finding as noted in the previously reported cases. This is unlike cases involving adults where such a latent period is usually more than three years. As a major immunosuppressant, procarbazine is certainly an important factor in the induction of leukemia in Hodgkin's diseases[17]. Therefore, we must consider the possible role of procarbazine, along with CCNU, in the development of MDS and leukemia in our patient.

In conclusion, we report a case who developed myelodysplastic syndrome and acute myeloblastic leukemia after treatment for medulloblastoma. We consider radiotherapy and chemotherapy responsible for this complication. Those children who have been treated with radiotherapy and chemotherapy need to be closely followed up with regular physical examinations and peripheral blood counts. Bone marrow examination including cytogenetic analysis should be performed when peripheral cytopenia is detected.

REFERENCES

1. Green DM, Zevon MA, Reese PA, et al. Second malignant tumors following treatment during childhood and adolescence for cancer. Med Pediatr Oncol 1994; 22: 1-10.
2. Meadows A, D'Angio G. Incidence of second malignant neoplasms in children: results of an international study. Lancet 1982; ii: 1326-1331.
3. Kushner BH, Zauber A, Tan CT. Second malignancies after childhood Hodgkin's disease. The Memorial Sloan-Kettering Cancer Center experience. Cancer 1988; 62: 1364-1370.
4. Duffner PK, Cohen ME, Myers MH, Heise HW. Survival of children with brain tumors: SEER Program, 1973-1980. Neurology 1986; 36: 597-601.
5. Duffner PK, Cohen ME. Changes in the approach to central nervous system tumors in childhood. Pediatr Clin North Am 1992; 39: 859-877.
6. Blatt J, Penchansky L, Phebus C, Horn M. Leukemia in a child with a history of medulloblastoma. Ped Hem Oncol 1991; 8: 77-82.
7. Pai MR, Advani SH, Gopal R, et al. Acute leukaemia following malignant ependymoma: a case report. J Surg Oncol 1985; 29: 1-4.
8. Genot JY, Krulik M, Poisson M, et al. Two cases of acute leukemia following treatment of malignant glioma. Cancer 1983; 52: 222-226.
9. Hildebrand J, Malarne M, et al. Acute nonlymphoblastic leukemia in a patient treated for brain tumor. Arch Neurol 1982; 39: 664-665.
10. Sayli T, Cemeroğlu AP, Tuncer AM, Gürgey A. Acute lymphoblastic leukemia following optic glioma treated by radiotherapy and surgery. Acta Paediatr 1993; 82: 327-328.
11. Bennet JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol 1982; 51: 189-199.
12. Kantarjian HM, Keating MJ. Therapy-related leukemia and myelodysplastic syndrome. Semin Oncol 1987; 14: 435-443.
13. Negrin RS, Greenberg PL. Myeloproliferative and myelodysplastic syndromes. In: Haskell CM (ed). Cancer Treatment. Philadelphia: W.B. Saunders Company; 1995: 927-931.
14. Baram TZ, van Eys J, Dowell RE, et al. Survival and neurologic outcome of infants with medulloblastoma treated with surgery and MOPP chemotherapy. A preliminary report. Cancer 1987; 60: 173-177.
15. Pui CH, Hancock ML, Raimondi SC, et al. Myeloid neoplasia in children treated for solid tumors. Lancet 1990; 336: 417-421.
16. Hayani A, Mahoney DHJr, Taylor LO. Therapy-related myelodysplastic syndrome in children with medulloblastoma following MOPP chemotherapy. J Neurooncol 1992; 14: 57-62.
17. Reimer RR, Hoover R, Fraumeni JF. Acute leukemia following treatment of Hodgkin's disease. Cancer 1982; 50: 676-679.