Secondary gluoblastoma multiforme with a new translocation t (3; 3) (q21; q26) following treatment of acute lymphoblastic leukemia

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The cure rate for acute lymphoblastic leukemia (ALL) has significantly increased in the past 30 years. In this regard, treatment-related late side effects, including secondary malignant tumors, have gained considerable importance. The risk of the development of a second malignant tumor is 14-fold higher in ALL than expected in aged-matched controls. Brain tumor constituted 25% of all secondary tumors developed after treatment of ALL[1]. Here we report a case that developed a cerebral glioblastoma multiforme six years after treatment for ALL. Our case is interesting because he presented with a translocation t (3; 3) (q21; q26) at the time of diagnosis of glioblastoma, which was previously described in acute myeloid leukemia (AML).

A 13-year-old boy had been diagnosed as high-risk common ALL six years previously and had been treated successfully with the modified St. Jude Study XI chemotherapy protocol[2] and prophylactic cranial irradiation with a total dose of 18 Gy. Chromosomal preparation had not been performed for cytogenetic analysis from bone marrow at the time of diagnosis of ALL, since sufficient number of metaphases on the smears could not be obtained. He was admitted to the hospital after he suffered a generalized epileptic seizure three years after cessation of the treatment. Neurological examination revealed no abnormality except bilateral papiledema. Magnetic resonance imaging (MRI) showed a large mass of the corpus callosum reaching the right frontal lobe (Fig. 1). The bone marrow aspirate was in remission. Cytogenetic studies revealed an abnormal karyotype of 46, XY t (3; 3) (q21; q26) in his marrow aspirate (Fig. 2). A craniotomy was performed and the tumor was removed partially. Histopathological diagnosis was glioblastoma multiforme. Postoperatively, a total dose of 30 Gy [60]Cobalt irradiation to the tumor location was delivered. He was started on a chemotherapy program

consisting of CCNU 100 mg/m^2, vincristine 1 mg/m^2 and prednisolone 40 mg/m^2. Nevertheless, his neurological status progressively worsened and he died within six months.

Secondary brain tumors are mainly associated with prior radiotherapy. Cranial irradiation is used for both prophylaxis and treatment of central nervous system (CNS) disease in ALL.
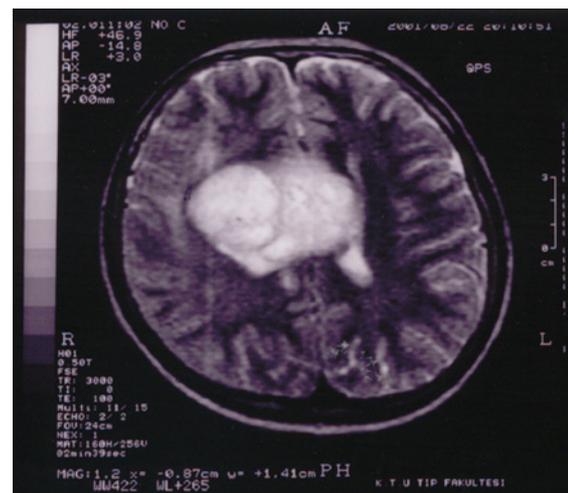

Fig. 1. Magnetic resonance imaging (MRI) showing a large tumoral mass in the right frontoparietal area extending to the left through the corpus callosum.
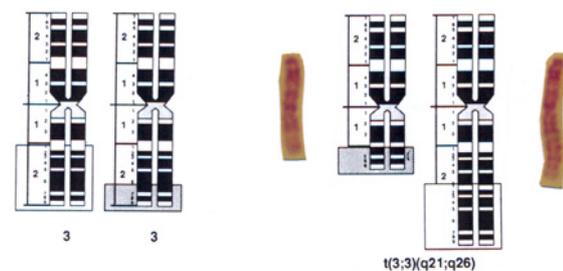

Fig. 2. Partial karyotype and ideogram of the t(3; 3) identified in the case's bone marrow cells, after GTG banding gpresence of t(3; 3) (q21; q26).

The most common primary/secondary tumor combinations are ALL/brain tumor (13% of all secondary tumors)[3]. Most of the radiation-associated intracranial neoplasms are sarcoma and meningioma. There are few reported cases with gliomas, including glioblastoma multiforme, after ionizing radiation[4]. The cumulative risk for developing secondary brain tumor among survivors of childhood ALL is 1% at 15 years[1]. The median time to development of a CNS tumor following diagnosis of ALL is 9 (1-26) years. The previous radiation dosage in radiation-induced brain tumors ranged from 3 to 95 Gy (mean 36.7 Gy). The mean age of those patients at the time of radiotherapy was 12.9 years (2 weeks-52 years)[4]. Radiation dosage applied to our patients was 18 Gy when he was seven years old and the latent period was six years.

Our patient also received intensive chemotherapy, including etoposide and alkylating agents and intrathecal methotrexate. There is no evidence to indicate intrathecal therapy alone or combined with radiotherapy contributes to the development of neoplasm. Although a correlation with certain chemotherapeutic agents and secondary myeloid leukemia is well known, there are very few reports on a relationship between the systemic chemotherapy and brain tumor. Relling et al.[5] reported an unusually higher incidence of secondary malignant brain tumor in children with ALL treated with Total Therapy Study XII. They conclude that use of higher dose (75 mg/m^2) 6-mercaptopurine and genetic defect in thiopurine metabolism were responsible for this high incidence[5]. however, variability in antimetabolite metabolism was not obtained as a risk factor in the BFM study[6]. Our patient similarly received 6-mercaptopurine at doses of 75 mg/m^2.

Chromosomes 3, 7, 9, and 17 are most frequently involved in structural abnormalities in pediatric gliomas[7]. Gains of chromosomes 7 and 3, and loss of chromosomes 10 and 18 have been reported in some pediatric cases with glioblastoma multiforme[7,8]. Translocation (3; 3) (q21; q26) has been reported in AML associated with dysmegakaryopoiesis and poor prognosis[9]. We could not find any reported case with primary or secondary brain tumor and any other secondary malignant neoplasm who had chromosomal translocation involving chromosome 3q21 and 3q26. Recently, Chang et al.[10] identified a brain specific protease inhibitor, neuroserpin (PII2), at chromosome 3q26. This novel serpin gene expression was found to be down-regulated in brain cancer cell lines and in brain tumor tissues[10]. It was suggested that breakpoints in the 3q26 region might affect various tissue-specific cancer-related serpin genes.

In our case, this chromosomal aberration may have been created by radiotherapy and/or chemotherapy, or he could have already carried this alteration in this somatic cells that were shared by multiple organs. The mechanisms leading to neoplastic transformation involve a multistage procedure. It may be speculated that translocation including chromosome 3q21 and 3q26 caused a biological predisposition to development of the secondary glioblastoma multiforme in our case. Since reporting every case with a different chromosomal aberration is essential to understanding the underlying mechanism of development of a secondary malignancy, we share our experience with this case.

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