Radiation-Induced World Health Organization Grade II Meningiomas in Young Patients Following Prophylactic Cranial Irradiation for Acute Lymphoblastic Leukemia in Childhood

—Three Case Reports—

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Abstract

Current chemotherapeutic regimens have been used to successfully treat many children with acute lymphoblastic leukemia (ALL), but have resulted in an increased risk of late central nervous system tumors, most commonly meningioma, particularly in patients who have received cranial irradiation. We treated 3 young patients with World Health Organization grade II meningiomas who had previously received cranial irradiation for the treatment of childhood ALL: a cerebellopontine angle tumor in a 19-year-old woman, a petroclival tumor in a 28-year-old man, and a frontal parasagittal tumor in a 19-year-old woman. These cases were difficult to treat due to the aggressive and invasive biology of the tumors. Therefore, we recommend systematic cranial imaging and long follow-up periods for leukemia survivors to detect brain tumors before progression.

Key words: acute lymphoblastic leukemia, atypical meningioma, cranial irradiation, radiation-induced meningioma, surgical removal

Introduction

Current chemotherapeutic regimens have been successfully used to treat children with acute lymphoblastic leukemia (ALL), but have resulted in an increased risk of late central nervous system tumors, most commonly meningioma, particularly in patients who have received cranial irradiation. We treated 3 young patients with World Health Organization grade II meningiomas who had previously received cranial irradiation for the treatment of childhood ALL: a cerebellopontine angle tumor in a 19-year-old woman, a petroclival tumor in a 28-year-old man, and a frontal parasagittal tumor in a 19-year-old woman. These cases were difficult to treat due to the aggressive and invasive biology of the tumors. Therefore, we recommend systematic cranial imaging and long follow-up periods for leukemia survivors to detect brain tumors before progression.

Recently we treated 3 young patients who presented with World Health Organization (WHO) grade II meningiomas. All three patients had been previously treated by cranial irradiation for childhood ALL. We report these cases and review the literature to investigate the incidence of radiation-induced meningiomas and evaluate the use of magnetic resonance (MR) imaging examination in long-term survivors of childhood leukemia.

Case Reports

Case 1: A 19-year-old woman presented with left facial nerve palsy and hearing loss. She was diagnosed with ALL at age 4 years and was treated using a protocol of the Tokyo Children’s Cancer Study Group.30) The ALL recurred at the age of 6 years. She received additional courses of chemotherapy and a bone marrow transplant with cranial irradiation of 18 Gy at the age of 7 years. MR imaging showed a tumor mass in the left cerebellopontine angle which was strongly compressing the brainstem and cerebellum with brain edema (Fig. 1A–C). The soft tumor was subtotally removed using a lateral suboccipital approach in March 2010. The tumor was severely adhered to the brainstem without arachnoid membrane, making it
Fig. 1 Case 1. Preoperative axial enhanced T<sub>1</sub>-weighted (A), axial T<sub>2</sub>-weighted (B), and coronal enhanced T<sub>1</sub>-weighted (C) magnetic resonance images showing a cerebellopontine angle tumor, strongly compressing the brainstem and cerebellum and causing brain edema (B). Postoperative axial enhanced T<sub>1</sub>-weighted (D) and axial T<sub>2</sub>-weighted (E) magnetic resonance images showing a remnant tumor.

Fig. 2 A: Case 1. Photomicrograph showing brain invasion of meningioma cells with cellular pleomorphism surrounded by lymphocytes, plasma cells, and foam cells compatible with invasive meningioma, World Health Organization (WHO) grade II, with lymphoplasmacyte-rich meningioma features (hematoxylin and eosin [HE] stain, original magnification ×200). Mitotic count and Ki-67 proliferating index using MIB-1 monoclonal antibody were 4/50 high power fields (HPFs) and 6.7%, respectively. B: Case 2. Photomicrograph showing increased cellularity and sheet-like growth pattern of small cells with geographic necrosis corresponding to atypical meningioma, WHO grade II (HE stain, original magnification ×100). Mitotic count and Ki-67 proliferating index using MIB-1 monoclonal antibody were 9/50 HPFs and 7.3%, respectively. C: Case 3. Photomicrographs showing meningothelial features of meningioma cells with necrosis and mitosis (arrows) (HE stain, original magnification ×200; inset: MIB-1 stain, original magnification ×400). Brain invasion, high mitotic count (21/50 HPFs), and moderately high Ki-67 proliferating index (18.7%) suggest aggressive type of meningioma, consistent with atypical meningioma, WHO grade II.
Fig. 3 Case 2. Preoperative axial enhanced T1-weighted (A), axial T2-weighted (B), and coronal enhanced T1-weighted (C) magnetic resonance images showing a left petroclival tumor, compressing the brainstem and cerebellum, extending subpially (A), and causing severe brain edema (B). Postoperative axial enhanced T1-weighted (D) and axial T2-weighted (E) magnetic resonance images showing partial removal of the tumor.

Fig. 4 Case 3. Preoperative sagittal (A) and coronal enhanced T1-weighted (B) and axial T2-weighted (C) magnetic resonance images showing a frontal parasagittal tumor compressing the right frontal lobe, causing brain edema (C), and occupying the superior sagittal sinus. Postoperative sagittal (D) and coronal (E) enhanced T1-weighted magnetic resonance images showing total removal of the tumor.

Discussion

Radiation-induced sarcomas in irradiated bone fulfill certain prerequisites. The following criteria have been proposed for radiation induced tumors: tumor in the irradiated field, different histological features from the original tumor, sufficient latency, no family history of phakomatosis, no recurrence or metastasis of the previous tumor, and no presence of the tumor before radiation treatment. Radiation-induced meningiomas are a clinically distinct subgroup from sporadic meningiomas. These tumors are often aggressive or malignant, are likely to be multiple, and show a high recurrence rate. Genetic analyses also reported fewer mutations in the neurofibromatosis type 2 gene and higher rates of 1p abnormalities.

Radiation-induced meningiomas have been categorized into three groups based on the amount of radiation administered: low dose (<10 Gy), moderate dose (10–20 Gy), and high dose (>20 Gy). The representative disease treated with low-dose cranial irradiation was tinea capitis. The calculated dose for tinea capitis in the upper layers of the brain has been reported as 1–2 Gy, which resulted in 4 to 9.5 times incidence of meningiomas. If the radiation dose for tinea capitis was greater than 2 Gy, the relative risk was 20,10,16,24. If the radiation dose was 7 fold increased risk of meningioma,13 Radiation-induced tuberculum sellae meningioma was reported after proton-beam radiotherapy for acromegaly. The survivors of the Hiroshima atomic bomb demonstrated about 2.5 times increased incidence of meningioma and the incidence was dose-dependent up to 36.3/100,000/year. Meningiomas after high dose irradiation have also been reported. The cumulative risk was 8.18% at 25 years after cranial irradiation ≥10 Gy.

The dose of cranial irradiation for CNS prophylaxis of childhood acute leukemia was changed from 24 to 18 Gy. Combined 24 Gy cranial irradiation and intrathecal methotrexate was widely employed in the 1970s, and reduced the incidence of CNS relapse from greater than 50% to approximately 10%. However, the adverse effects of CNS preventive therapy stimulated the search for alternative methods. In current regimens, 18 Gy of cranial irradiation is used only for high risk patients.

In 1991, the Children’s Cancer Study Group reported a 2.53% incidence of second neoplasms at 15 years after diagnosis of leukemia and a 22-fold increase in incidence of CNS neoplasms. Higher risk was evident in children who were 5 years of age or younger at the time of diagnosis. In 1998, the St Jude Children’s Research Hospital reported a 1.39% cumulative incidence of brain tumors at 20 years. However, recent investigations indicated a higher incidence of meningiomas if longer follow-up periods were analyzed. For example, 7 to 30 years follow up with MR imaging or computed tomography imaging every 3–6 years found 15 meningiomas in 88 irradiated grade II, atypical meningioma (Fig. 2C). Postoperatively the patient showed no neurological deficits and convulsion was controlled with an antiepileptic drug.
survivors, with an estimated incidence of 14.8% at 20 years. In comparison, only 1 meningioma was found in 122 non-irradiated survivors. A cohort study of 17980 survivors of childhood cancer found 137 meningiomas, 73 gliomas, and 37 other CNS tumors. Cumulative incidence of meningiomas was 6.3% with the increased risk related to the irradiated dose. Similarly, a 47% increased risk at 20 years after cranial irradiation treatment for childhood leukemia was found to justify systematic brain imaging.

The latency period before appearance of radiation-induced tumors is positively related to the age of the patient when treated with radiation, and inversely related to the radiation dose and the aggressiveness of the tumor. Male sex, initial diagnosis of leukemia, and use of whole brain or craniospinal fields were associated with a shorter latency time. The average time interval between the diagnosis of meningioma and irradiation for tinea capitis has been reported as 34 to 48 years. Latency following dental radiography was 22 to 30 years. However, patients who had been exposed to high-dose cranial irradiation presented with meningiomas at an average of 20 years. Shorter intervals ranging between 14 months and 15 years have also been reported. Younger age of the patient at irradiation (less than 5 years) was also related to shorter interval before presentation with meningioma. The mean latency of meningiomas after prophylactic irradiation for childhood ALL has been reported as 15 to 19 years. In the present cases, meningiomas were found at 12, 18, and 12 years after cranial irradiation. The relatively shorter latency periods in our cases might be related to the particularly malignant biology of the original meningiomas.

Although radiation-induced meningiomas are often aggressive or malignant, the recurrence rates of grade II or III meningiomas varied from around 15% to more than 50% following low-dose or high-dose irradiation. In meningiomas after prophylactic radiotherapy for childhood acute leukemia, rates of between 13% and 43% have been reported to be atypical. Identical rates of grade II or III radiation-induced meningiomas and survival were reported compared to adult primary meningiomas. In our institute, all radiation-induced meningiomas that have been presented to date have been WHO grade II. The atypical features of our cases might be related to the shorter follow-up periods of our surviving patients after treatment for childhood leukemia. We need longer follow-up periods to elucidate the incidence of meningioma as in our patients and the rate of malignant subgroups. We also need careful and regular follow-up examinations of our patients since high recurrence rates have been reported. Treatment strategies for these cases are difficult due to the aggressive or invasive biology of the tumor, deep location in the CNS, and large tumor size. The initial treatment consideration for radiation-induced meningiomas remains surgical resection. However, total removal is often difficult. Radiosurgery is a safe and effective treatment option for radiation-induced meningiomas either after resection or as an alternative to resection. The present cases suggest the importance of systematic cranial imaging and long follow-up periods for survivors after childhood leukemia to detect brain tumors before progress to the stage of being complex and difficult to treat.

References


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