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Second Malignant Neoplasms Following the Treatment of Brain Tumors in Children

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Abstract and Introduction

Abstract

We investigated retrospectively 992 children with central nervous system tumors who were treated at our center between 1970 and 2004. All of the patients were treated by surgery, chemotherapy, and/or radiotherapy. Six patients developed second malignant neoplasms, and their clinical and histopathologic characteristics are reviewed in this article. The second malignant neoplasms were diagnosed as non-Hodgkin lymphoma, myelodysplastic syndrome, basal cell carcinoma, malignant melanoma, Kaposi sarcoma, and high-grade neuroectodermal tumor. The initial diagnoses were ependymoblastoma in one, medulloblastoma in three, and low-grade astrocytoma in two patients. The median latency time was 3.03 years (range 0.39–22.93 years). The outcome varied according to the histopathologic type of the second tumor. The patients who developed non-Hodgkin lymphoma and myelodysplastic syndrome died of progressive disease. The patients with second skin neoplasms are alive as of the time of this writing. The patient with Kaposi sarcoma developed one of the rare reported second malignant neoplasms following a primary brain tumor in childhood. A wide spectrum of second malignant neoplasms was detected after treatment of primary brain tumors with surgery, radiotherapy, and chemotherapy. Long-term follow-up is therefore necessary for the child who has survived a primary central nervous system tumor.

Introduction

Central nervous system tumors are the most common solid tumors in children.^[1] Second malignant neoplasms are a possible management-related complication of tumors that are treated with radiotherapy and chemotherapy. A genetic predisposition has been documented in a number of cases.^[2] Several multicenter studies have reported the occurrence of second malignant neoplasms after cranial radiotherapy for the prophylaxis of leukemias.^[3-7] However, there are a few studies on the occurrence of second malignant neoplasms after the treatment of central nervous system tumors.^[2,8-12] In this article, we present our center's experience with second malignant

neoplasms that have developed as a result of the treatment of primary central nervous system tumors.

Patients and Methods

We evaluated retrospectively 992 patients with central nervous system tumors who were treated at our center between 1970 and 2004. The primary treatment strategy was gross total surgery whenever possible. Histopathologic examination was done according to the World Health Organization criteria. Patients who had postoperative residue received adjuvant radiotherapy and/or chemotherapy. The malignant tumors that developed in a remote location with histopathologic features that differed from the primary brain tumor were considered to be second malignant neoplasms. We documented the clinical characteristics, the latency times of the second malignant neoplasms, and the outcomes of the patients.

Results

Patient Characteristics

Of 992 patients with central nervous system tumors, 6 developed second malignant neoplasms. The clinical characteristics are shown in Table 1. There were five boys and one girl. The age of the patients at the time of the initial diagnosis ranged between 2 and 7.4 years (median 5.6 years). The initial diagnoses were ependymoblastoma in one, medulloblastoma in three, and low-grade astrocytoma in two patients. The tumors were located at the posterior fossa and fourth ventricle in the majority of cases. Gross total surgery was the main treatment in five cases, whereas a biopsy was performed in one patient. Four patients received chemotherapy consisting of lomustine, vincristine, and procarbazine. All of the patients were treated with adjuvant radiotherapy, except the one with a left parietal grade II astrocytoma. The median latency time to the development of the second malignant neoplasms was 3.03 years (range 0.39–22.93 years). The histopathologic diagnoses of the second tumors were myelodysplastic syndrome, Kaposi sarcoma, non-Hodgkin lymphoma, basal cell carcinoma, malignant melanoma, and a high-grade primitive neuroectodermal tumor. Four patients are alive and two had died of disease progression at the time of this writing.

Clinical and Histopathologic Features of the Second Malignant Neoplasms

The patient with the primary diagnosis of ependymoblastoma was treated with gross total surgery followed by craniospinal radiation and six courses of chemotherapy with lomustine, procarbazine, and vincristine. Seventeen months after the cessation of treatment, he was admitted with fever and bleeding from the nose. Pancytopenia and atypical myeloid cells were detected in the differential count. Bone marrow examination revealed significant myelodysplastic changes, such as fatty infiltration with huge myeloid cells and findings of dyserythropoiesis, normoblasts with nuclear atypia, and myeloblasts. The diagnosis was myelodysplastic syndrome. Chemotherapy consisting of methylprednisolone, etoposide, and mitoxantrone was started. The family refused further therapy after 1 month, and the patient died of progressive disease 8 months later.

The first patient with medulloblastoma was treated with craniospinal radiation and nine courses of lomustine and vincristine after the subtotal resection. She stayed in remission for 23 years and was then admitted with a mass on the skin of her left breast. Surgical resection of a 3.5 x 2.5 cm mass revealed a histopathologic appearance of spindle-shaped cells arranged in fascicles and vascular channels with extravasated blood cells. The diagnosis was Kaposi sarcoma. She is alive with no evidence of disease 7 months after the surgical treatment of the second tumor.

The second patient with an initial diagnosis of medulloblastoma was treated by gross total resection, craniospinal radiation, and eight courses of lomustine, vincristine, and procarbazine. He was admitted with cough and fever 21 months later. The chest radiography and computed tomography of the thorax revealed mediastinal enlargement and massive pleural effusion. Cytologic evaluation and fine-needle aspiration biopsy of the mediastinal mass led to the diagnosis of non-Hodgkin lymphoma, lymphoblastic type. He received the induction phase of chemotherapy, including vincristine, doxorubicin, cyclophosphamide, L-asparaginase, and cytarabine with

radiation to the mediastinum. He died of progressive disease in the second month of treatment.

The third patient with medulloblastoma had gross total surgery, radiation to the posterior fossa, and six courses of lomustine and vincristine. He was lost to follow-up after the completion of treatment. Ten years later, he had skin lesions within the radiotherapy field. A biopsy of these lesions yielded a diagnosis of basal cell carcinoma with superficial multicentric infiltration of spindle cells, with hyperchromatic nuclei in clusters and bundles. This patient was diagnosed as having Gorlin syndrome with the prominent features of growth retardation, macrocephaly, and radiologic evidence such as cystic lesions in the mandible, bridging of the sella turcica, and fusion of the second and third ribs. He underwent surgery and received radiotherapy as therapy for the lesions. He has been alive and disease free for 8 years after the diagnosis of the second malignant neoplasm and was the subject of a previous case study.^[1,3]

The first patient with fibrillary astrocytoma developed the second tumor only 3 months after treatment of the primary tumor. Interestingly, this patient received no radiotherapy or chemotherapy. The biopsy performed on lesions on the neck and scalp revealed malignant melanoma with the appearance of round and oval-shaped fusiform neoplastic cells in bundles crossing each other. In all layers of the epidermis and penetrating the dermis and multinucleated giant cells in the dermis were significant nucleoli and frequent atypical mitosis. Immunoperoxidase staining showed S-100 and HMB-45 positive staining, but cytokeratin and glial fibrillary acidic protein were negative. With the diagnosis of malignant melanoma level 5, surgery was performed for the mass on the neck, and he was treated with interferon- α 2b for 1 year. He is still alive 6.7 years after the cessation of therapy.

In the second patient with the previous diagnosis of grade I astrocytoma, the primary lesion was located at the fourth ventricle adjacent to the medulla oblongata. Four years after surgery and radiotherapy, he presented with vomiting. Magnetic resonance imaging showed a tumor located at the right cerebellar hemisphere that was remote from the site of the primary tumor. Gross total resection was performed, and pathologic examination of the secondary tumor revealed highly cellular, monomorphic, small round cells with a perinuclear halo and significant palisades. Immunocytochemical studies showed negative staining with glial fibrillary acidic protein, Neu-N, synaptophysin, and neuron-specific enolase; Ki-67 was highly positive. These findings led to the diagnosis of neuroectodermal tumor resembling primitive neuroectodermal neoplasm with morphologic features. Cisplatin and etoposide were started. He is still alive and under treatment for 3 months.

Discussion

Second malignant neoplasms are a serious and delayed complication in children who survive cancer. Because of significant improvements in the survival rates of childhood cancer, they would be expected to occur more frequently. However, there are a few reports about second malignant neoplasms that developed in children after the treatment of primary central nervous system tumors.

Meningiomas, nerve sheath tumors, and gliomas were reported as the most common tumors by Ron et al.^[3] Their data included those patients who were irradiated because of tinea capitis. There are two reports of patients with acute lymphoblastic leukemia who were treated with chemotherapy, intrathecal methotrexate, and/or craniospinal radiation. Of the 13 patients treated at the Dana-Farber Cancer Institute between 1972 and 1995, 4 developed astrocytomas and 3 had acute myelogenous leukemia.^[6] In a German study, the most common second malignant neoplasms after the Berlin-Frankfurt-Munster therapy of acute lymphoblastic leukemia in childhood were leukemia and lymphoma in 23 of 52 patients.^[7] In the same study, central nervous system tumors were found in 13 patients, in whom high-grade malignant gliomas were the most common histopathologic subtype. Broniscer et al from St. Jude Children's Hospital reported 24 second malignant neoplasms following the treatment of brain tumors.^[2] Of these cases, 42% were gliomas and 21% were meningiomas.

Other tumors, such as sarcomas, malignant fibrous histiocytomas, skin tumors, and, rarely, primitive neuroectodermal tumors, were also reported in children and adults who received radiotherapy.^[3,5,7-11,14,15] Although several authors have reported that one of the most common tumors following radiation for central nervous system tumors was meningioma,^[3,5,8] we found no meningioma after the treatment of primary central nervous system tumors in our cases. One of our patients was 3 years old when he was exposed to radiotherapy. Ten years later, he had skin lesions on the scalp and trunk, which were in the field of the previous radiotherapy. The histopathologic

diagnosis was basal cell carcinoma. Then the patient was diagnosed as having Gorlin syndrome, as reported previously.^[1,5]

The patient with pilocytic astrocytoma developed a high-grade neuroectodermal tumor resembling a primitive neuroectodermal tumor according to morphologic criteria but at a different location within the previous radiotherapy field. Sixteen cases of primitive neuroectodermal tumors have been reported that occurred 5 to 18 years after radiation treatment.^[4,7,9,11,14,16] Although they are extremely rare, primitive neuroectodermal tumors must be kept in mind in patients receiving cranial radiation. Our patient developed a primitive neuroectodermal tumor 4 years after receiving radiation. In our study, the occurrence of five tumors in patients with a history of cranial and/or spinal radiotherapy supports the association of radiotherapy in the development of second cancer. The patients treated by cranial radiation for other types of tumors were not included in this study.

In a report by Duffner et al, 5 of 198 children with central nervous system tumors developed second malignant neoplasms that were considered to be the result of prolonged postoperative chemotherapy and delayed radiotherapy.^[12] All of these patients had 12 to 26 cycles of chemotherapy containing etoposide, cyclophosphamide, and cisplatin because of their young age at admission. Three of the five malignant neoplasms were myelodysplastic syndrome and acute myelogenous leukemia, which can be induced by alkylating agents and topoisomerase II inhibitors.^[17-19] Etoposide has been associated with the development of acute myelogenous leukemia.^[20,21] Two of our patients who received lomustine, procarbazine, and vincristine developed myelodysplastic syndrome and lymphoblastic lymphoma about 1.4 to 1.8 years after the cessation of the chemotherapy, which is earlier than the rest of the cases. Both of these patients had chemotherapy with alkylating agents for six and eight cycles, respectively, and received large doses of craniospinal radiation. A synergistic effect of radiotherapy and chemotherapy in inducing second malignant neoplasms has been reported.^[9,12]

Kaposi sarcoma that is not a sequela of acquired immune deficiency syndrome (AIDS) has rarely been reported as a second malignant neoplasm following cancer.^[22,23] Iscovich et al reported an odds ratio of 0.5 for Kaposi sarcoma after central nervous system neoplasms.^[22] In our study, a mass on the skin of the left breast was diagnosed as Kaposi sarcoma in one patient nearly 23 years after the primary medulloblastoma. Nine cycles of chemotherapy with alkylating agents should be taken into consideration as the possible cause of the second tumor in this patient. This patient developed one of the rare cases of Kaposi sarcomas following a primary brain tumor experienced in childhood.

The patient who had a malignant melanoma as a second neoplasm was previously managed by surgery for low-grade fibrillary astrocytoma. The malignant melanoma in this patient should not be considered therapy related. The two tumors in this patient were thought to be coincidental processes.

In our study, the outcome of patients with second malignant neoplasms was found to be associated primarily with their histopathologic diagnosis. The survival period of the patients with myelodysplastic syndrome and non-Hodgkin lymphoma was 9 and 3 months, respectively, after the diagnosis. Broniscer et al reported that their three patients with second hematologic malignancies died at a median of 0.3 years (range 0.1–1.1 years) after diagnosis.^[2] In another study, the outcomes of the patients with second myelodysplastic syndrome and acute myelogenous leukemia were also poor.^[1,2] In contrast, patients with second basal cell carcinomas or malignant melanomas were reported alive in several studies.^[2,4,6,7] The three children in our study with second tumors involving the skin were all alive and disease free at the time of this writing.

Second malignant neoplasms after central nervous system tumors are associated with therapies for the primary tumor and can be in a wide spectrum ranging from radiation-associated cranial neoplasms to hematopoietic malignancies. Rigorous and prolonged follow-up of these patients is warranted, particularly in children in whom survival continues to improve significantly.

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Table 1. Clinical Information of the Patients With Second Malignant Neoplasms Following Primary Central Nervous System Tumors

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Initial Case	Age (yr)	Sex	Primary Tumor Histology	Primary Tumor Site	Surgery	Chemotherapy	Radiotherapy Site	Latency (yr)	Second Tumor Histology	Second Tumor Site	Treatment	Outcome
1	6.9	Male	Ependymbioblastoma	Posterior fossa	Gross total	Lomustine-vincristine-procarbazine	Craniospinal	1.4	Myeloidysplastic syndrome	Bone marrow	Methylprednisolone-etoposide-mitoxantrone	Exitus
2	3.3	Female	Medulloblastoma	Posterior fossa	Subtotal	Lomustine-vincristine-procarbazine	Craniospinal	22.9	Kaposi sarcoma	Pectoral region	Surgery	Alive
3	5.9	Male	Medulloblastoma	Posterior fossa	Gross total	Lomustine-vincristine-procarbazine	Craniospinal	1.8	Non-Hodgkin lymphoma (lymphoblastic)	Mediastinum pericardium	Methylprednisolone-vincristine-doxorubicin-cyclophosphamide-prednisolone	Exitus
4	2	Male	Medulloblastoma	Posterior fossa	Gross total	Lomustine-vincristine	Craniospinal	9.1	Basal cell carcinoma	Skin (scalp, trunk)	Cyclophosphamide, radiotherapy to trunk, cervical	Alive
5	7.4	Male	Astrocytoma, grade II	Left parietal	Gross total	—	—	0.4	Malignant melanoma	Skin (neck) and lymph node	Surgery, interferon- α 2b	Alive
6	5.3	Male	Pilocytic astrocytoma, grade I	Fourth ventricle	Gross total	—	Posterior fossa	4.3	Primitive neuroectodermal tumor	Cerebellar hemisphere	Surgery, dispiatin-etoposide	Alive (under chemotherapy)

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