Glioblastoma Multiforme Following Prophylactic Cranial Irradiation and Intrathecal Methotrexate in a Child with Acute Lymphocytic Leukemia

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Cases of radiation-induced glioma in humans are extremely rare. A 2-year-old boy with acute lymphocytic leukemia had received prophylactic cranial irradiation (2400 rad/2½ weeks) and intrathecal methotrexate. Five years later he developed a glioblastoma multiforme on the left cerebral hemisphere while the leukemia was in remission. This is the first reported association of these disorders. It is possible that the glioma may have been induced by radiation and/or chemotherapy.

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THE INSTITUTION of specific central nervous system prophylaxis when the number of leukemic cells in that location is presumably low has greatly reduced occurrence of overt meningeal leukemia, thus increasing survival of children with acute lymphocytic leukemia.[1,2,19] Although the long-term sequelae of central nervous system prophylaxis have not been well defined, the therapeutic modality employed (cranial irradiation and intrathecal chemotherapy) have occasionally been associated with both acute and delayed neurotoxicity.[3-5] One of the most serious complications is a progressive leukoencephalopathy, the clinical manifestation of which includes confusion, somnolence, ataxia, spasticity, seizure, dementia, and more rarely, coma and death.[6,11,20,23]

This case report describes a patient who developed a cerebral glioblastoma five years after prophylactic cranial irradiation and intrathecal methotrexate for an acute lymphocytic leukemia. The particular association of these disorders has not been reported previously.

Case Report

On August 10, 1973, a 2-year-old boy was admitted to the Milton S. Hershey Medical Center of the Pennsylvania State University with a two-week history of tiring easily, fever, and black, tarry stools. Otherwise, he had been healthy. There was no family history of cancer or hereditary disease, including Von Recklinghausen's disease. Parents and two siblings were healthy. Physical findings included petechiae in the buccal mucosa, lymphadenopathy in the neck, epitrochlear and inguinal areas, hepatosplenomegaly, and bruises on both legs. No other skin lesions, dysmorphic features, or anomalies were found. Laboratory findings revealed a hemoglobin 4.9, hematocrit 10.5, platelets 21,000, leukocyte count 68,000 with 9% blasts, 72% promonocytes, 19% lymphocytes without polymorphonuclears or basophils. The bone marrow aspiration and biopsy from iliac crest revealed sheets of lymphoblasts consistent with the diagnosis of acute lymphocytic leukemia. On the second admission he was begun on vincristine 2 mg/M² intravenously (1.25 mg) weekly for six weeks and prednisone 40 mg/M² PO (25 mg) daily for six weeks as induction.

Remission was proven by bone marrow aspiration and physical examination on September 18, 1973. On September 23 he was readmitted for CNS prophylaxis: from September 25 to October 10, 1973, ^{60}cobalt irradiation was given to the whole brain utilizing lateral opposing fields (18 × 12 cm) with a daily dose of 200 rad at the midline. A total tumor dose of 2400 rad was delivered in 12 fractions over 15 elapsed days (981 ret. Nominal Standard Dose). Intrathecal methotrexate 12 mg/M² (7.8 mg) was given twice weekly for six doses. Maintenance therapy was 6-mercaptopurine daily, methotrexate weekly, and Cytoxan weekly. Until January 1975 he received vincristine and prednisone every three months for three consecutive doses. In February 1975, his regimen was changed to vincristine and prednisone pulses monthly until August 1976. He continued to receive 6-mercaptopurine daily and methotrexate weekly until August 1978. At that time all medication was stopped. He never had an exacerbation and continued to be in remission.

He was readmitted on November 5, 1978, for headaches,

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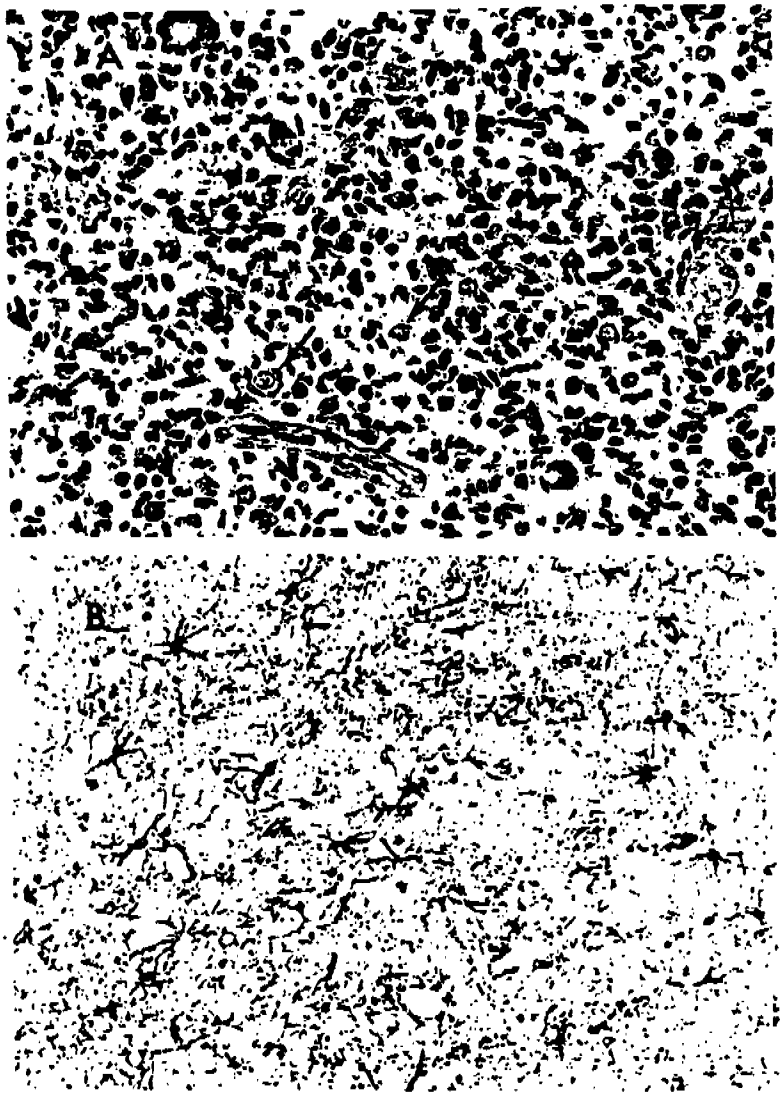

FIG. 1. Histology of the brain tumor. (A, Top) The tumor is highly cellular showing many mitoses, pleomorphic and giant cells. Arrows indicate entrapped neurons (H & E, ×100). (B, Bottom) Well-differentiated reactive astrocytes. Note lack of peroxidase (dark) staining of the tumor cells (PAP immunoperoxidase preparation for GFA protein, ×250).

vomiting, and lethargy of three weeks' duration. Physical examination revealed bilateral papilledema, difficulty with speech, and right hemiparesis. A computed tomography (CT) brain scan revealed a large cystic mass in the left parietal area. On November 7, 1978, the patient underwent left frontoparietal trephine craniotomy and needle aspiration of a large cystic lesion with xanthochromic contents. Subsequent CT brain scan revealed enlargement of what was thought to be a cystic mass.

On December 6, 1978, the patient was readmitted for progressive right hemiparesis and headaches. The arteriogram showed hypervascular tumor with suggestion of infiltrating as well as cystic components in left parietal area. On December 15, 1978, the patient underwent left frontoparietal craniotomy with subsequent resection of highly malignant and infiltrating glioma. Postoperatively the patient was treated with cranial irradiation: 4000 rad/4 weeks to whole brain followed by 1000 rad/1 week to gross tumor with reduced fields.

A CT brain scan on March 28, 1979, revealed significant improvement, and the patient initially improved in strength and coordination. However, he became disoriented and lethargic on June 1, 1979. His mental and neurologic status became progressively worse. He then had a high temperature and seizures and died on October 13, 1979. Unfortunately, autopsy was not performed.

Pathology

The tissue fragments obtained at surgery were formalin fixed and processed for paraffin sectioning. In addition to routine stains, the sections were also stained by peroxidase-antiperoxidase (PAP) method in order to demonstrate the presence of glial fibrillary acidic (GFA)

TABLE 1. Patients with Glioma following Irradiation (Review of Literature)

Authors	Reason for therapy	Age* (years)	Sex	Radiation dosage (rad)	Latent period† (years)	Radiation-induced glioma
Jones[19] (1960)	Meningioma (left frontal)	33	M	4000	10	Astrocytoma (right hemisphere)
Saenger[28] (1960)	Cervical adenitis	11	M	400	11	Glioblastoma
Albert[1] (1966)	Tinea capitis	4	M	500–800	4	Astrocytoma (light optic chiasm)
Albert[1] (1966)	Tinea capitis	10	M	500–800	1	Astrocytoma (cerebrum)
Kosmaki[16] (1977)	Craniopharyngioma	28	M	5400	6	Glioblastoma multiforme (temporal lobe)
Sogg[30] (1978)	Craniopharyngioma	9	F	6007	5	Malignant astrocytoma (right temporal lobe)
Robinson[26] (1978)	Teratoma (pineal)	10	M	4000	26	Astrocytoma, Grade 4 (right frontal lobe)
Robinson[25] (1978)	Meningioma	36	M	2750	21	Astrocytoma, Grade 3 (right temporal lobe)
Preissig[24] (1979)	Glomus jugular tumor (right middle ear)	43	M	4480	8	Anaplastic astrocytoma (right cerebellum)
Present series	CNS prophylaxis for acute lymphocytic leukemia	2	M	2400	5	Glioblastoma multiforme (left parietal lobe)

* Age at the time of therapy.

† Interval between irradiation and diagnosis.

protein in the tumor.[32] This antigen has been demonstrated to be specific for astroglia.[4]

Histologically the tumor was a highly cellular, anaplastic glial neoplasm with many giant cells, areas of necrosis, and vascular endothelial proliferation (Fig. 1A). The infiltrative nature of the tumor was indicated by the presence of many entrapped neurons in the neoplasm. The PAP method showed the presence of many well-differentiated astrocytes containing one or two nuclei (Fig. 1B). These astrocytes were interpreted as reactive rather than as a part of the neoplasm. The tumor cells did not contain a significant amount of GFA. On the basis of the above findings, the diagnosis of glioblastoma multiforme was made.

Discussion

The apparent induction of second malignant neoplasm by antineoplastic therapy is no longer a surprising observation. Though it is impossible to prove, the glioblastoma in this patient was most likely treatment-induced, whether by radiation, chemotherapy, or both. It may have been "spontaneous," although this was unlikely considering the low incidence of glioblastoma of cerebrum in children. The other possibility is a biologic predisposition to neural crest and neuroectodermal tumors such as is seen in Von Recklinghausen's disease.[23] The negative family history and lack of peripheral manifestations of Von Recklinghausen's disease suggests that it was not a factor in the present case. Radiation-induced brain tumors are well known. Modan *et al.*[21] reported on 11,000 children irradiated for ringworm of the scalp and two matched control groups were followed. Results of this study indicated that the increased risk of head and neck tumors is significant. Most radiation-associated intracranial neoplasms have been primarily sarcoma[11,31,35] and meningioma.[3,7,18,22,23,34,36] The examples of radiation-associated gliomas are rare, although these tumors have been produced experimentally in monkeys[12,15,17] and rats.[19] Only a few cases of radiation-associated gliomas in humans have been reported in the literature (Table 1): most were male patients with an average age of 15 years (range, 2–43). The radiation dosage ranged from 400–6000 rad with latent period of an average of nine (1–26) years.

Although the role of radiation in carcinogenesis has been well established in humans and experimental animals,[9,10] the exact mechanism of radiation-induced carcinogenesis remains to be elucidated. It was demonstrated that radiation-induced neoplasm appears to arise through mutagenic capacity and chromosome aberration, and the mechanisms leading to neoplastic transformation involve multistage processes (multihit kinetics) rather than a single, one-hit type of biochemical alteration. However, too little is known at this time about the cancer process to allow precise and detailed

statements concerning mechanisms of carcinogenesis for any human neoplasm.

The other possible etiologic factor in induction of this patient's tumor could be the combination of intrathecal methotrexate with cranial irradiation. It is known that administration of methotrexate in combination with 2000 rad or more cranial irradiation may result in multiple necrotic areas with or without gliosis disseminated throughout the cerebral white matter (leukoencephalopathy).[25-27] However, there is no evidence in man (Table 1) or experimental animals to indicate intrathecal methotrexate alone is carcinogenic or that it enhances the carcinogenic effect of radiation.

Based on the available evidence there is nothing to indicate that the rare occurrence of the long-term neoplastic hazard or other nonneoplastic complications of radiotherapy and/or chemotherapy in any way outbalances the benefits of their use for treatment of acute lymphocytic leukemia.

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