Postirradiation cerebellar glioma

Case report

COREY RAFFEL, M.D., PH.D., MICHAEL S. B. EDWARDS, M.D., RICHARD L. DAVIS, M.D., and ARTHUR R. ABLIN, M.D.

Departments of Neurological Surgery, Pathology, and Pediatrics, School of Medicine, University of California, San Francisco, California

A 13-year-old girl developed an anaplastic astrocytoma of the cerebellum 7 years after irradiation of the central nervous system and prophylactic chemotherapy for acute lymphocytic leukemia. The fact that the astrocytoma was anaplastic and infiltrative was unusual for astroglial tumors at this site. It is proposed that this is a radiation-induced glioma.

KEY WORDS · malignant glioma · radiation · lymphoblastic leukemia · radiation-induced tumor · astrocytoma

Radiation therapy is an established cause of secondary neoplasia in the central nervous system (CNS). Both benign and malignant tumors can develop after cranial irradiation. Benign postirradiation tumors, of which meningiomas are the most common, have a relatively long latency period, defined as the interval from the start of radiation therapy to clinical recognition of the tumor, whereas postirradiation sarcomas develop after a shorter latency.

Reports of glial neoplasms after radiation therapy are rare. We present the unusual case of a child who developed an anaplastic astrocytoma of the cerebellum after CNS irradiation and chemotherapy for acute lymphoblastic leukemia. We also review the literature on radiation-induced gliomas.

Case Report

This 13-year-old girl presented in 1982 with a 3-week history of morning headache frequently associated with vomiting, difficulty with balance, and blurring of vision. Her parents had noted that she was increasingly somnolent. In 1975, she had been treated for acute lymphoblastic leukemia with systemic prednisone, vincristine, and L-asparaginase at the University of California, San Francisco. Cerebrospinal fluid (CSF) obtained by lumbar puncture that same year contained no malignant cells. She had received 2400 rads of craniospinal irradiation in conjunction with six intrathecal methotrexate injections (9 mg each), and had followed a 5-year course of oral vincristine and 6-mercaptopurine. The patient remained asymptomatic until the onset of her current symptoms.

Examination. The results of her physical examination were unremarkable. The patient was alert and oriented, but found neck flexion painful and could not touch her chin to her chest. Sensation and cranial nerves were intact. Motor examination revealed hypotonia of the lower extremities, a right pronator drift, and slowed fine motor movements of the right hand. Mild dysmetria, more marked on the right, was also present. Deep tendon reflexes of both legs were hyperactive, and sustained bilateral ankle clonus was observed.

The CSF obtained at lumbar puncture was clear; the glucose level was 67 mg/dl, total protein content 62 mg/dl, and the white cell count 10/cu mm, of which 27% were lymphocytes and 73% monocytes or histiocytes. Cytological examination of the CSF showed atypical cells that were larger than lymphocytes and distinguished by unusual pleomorphic nuclei, which had convoluted nuclear membranes and occasional prominent nucleoli. The ratio of nucleus to cytoplasm in the aberrant cells was greater than normal.

A computerized tomography (CT) scan revealed a diffusely enhancing mass in the right cerebellar hemisphere (Fig. 1). The fourth ventricle was effaced by the mass and displaced to the left, and the lateral and third ventricles were dilated. Examination of a bone marrow specimen documented sustained remission of the leukemia.
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FIG. 1. Computerized tomography scan showing an enhancing cerebellar mass. The fourth ventricle is displaced and effaced, and the temporal horns of the lateral ventricles are enlarged.

Operation. On July 29, 1982, a ventriculoperitoneal shunt was placed. Three days later, the patient underwent suboccipital craniectomy, which disclosed a reddish-gray tumor superficially coating and diffusely infiltrating the right cerebellar hemisphere. Because there was no demarcation between normal tissue and the tumor, a subtotal resection was performed. The postoperative course was uneventful. She was treated with 4000 rads of irradiation to the whole head and adjuvant hydroxyurea chemotherapy.

Postoperative Course. One year after her operation, the patient is doing well. Her only neurological symptom is persistent mild dysmetria on the right, and CT scans show no enhancement in the posterior fossa, indicating tumor regression.

Pathological Examination. The biopsy specimen showed diffuse cerebellar infiltration by cells with round-to-oval to elongated nuclei. The tumor spread under the pia and extended into the subarachnoid space (Fig. 2 left). The tumor was hypercellular, and marked mitotic activity was noted (one to six mitotic figures per high-power field). The nuclei were eccentrically placed; the nucleoplasm was dusky and nucleoli were not prominent. Cell-enclosed cytoplasm was amphophyllic and extruded into stellate processes stained by phosphotungstic acid-hematoxylin (Fig. 2 right). Immunohistochemical staining showed glial fibrillary acidic protein in these cell processes.

Discussion

The production of intracranial tumors, both benign and malignant, by cranial irradiation has been well documented.26 In establishing a causal relationship between therapeutic irradiation and the development of a secondary tumor, significant histological differences must be apparent to reduce the possibility that the later tumor evolved from its predecessor. Reliance on the guideline of histological dissimilarity, however, limits the number of cases that can support a correlation between radiation and subsequent glial neoplasms.

Low-dose irradiation (150 rads to the surface of the brain) has been suggested as a factor accounting for the increased incidence of meningiomas in adults who were irradiated as children for tinea capitis 16 to 45 years previously.2,3,16,24 Higher doses of irradiation (1500 to 5600 rads) have also been implicated in the development of meningiomas;1,18,20 latency in these cases ranged from 12 to 47 years.

High-dose irradiation, especially of pituitary tumors, has been causally linked with fibrosarcomas.1,5,7,19,28 Waltz and Brown28 reported three cases of fibrosarcoma after radiation therapy for pituitary adenomas and reviewed 10 other cases from the literature. The irradiation dose in these cases ranged from 2400 to 7800 rads and the latency period was 2 to 20 years. Goldberg, et al.,7 reported that two of 75 acromegalic patients treated with irradiation subsequently devel-
The idea that radiation might play a causal role in the formation of malignant glial tumors was first suggested in 1958 by Kent and Pickering, who reported the appearance of a glioblastoma in a monkey 863 days after thermal neutron irradiation to its whole head with 2473 rads. Traynor and Casey later reported three cases of malignant ependymoblastoma in monkeys that had received 600 to 800 rads of proton radiation (55 Mev); three of the 10 monkeys that survived 3 years or longer developed glioblastomas. In a 9-year follow-up review of 72 similarly irradiated monkeys, Haymaker, et al., irradiated monkeys with 200 to 800 rads of proton radiation (55 Mev); three of the 10 monkeys that survived 3 years or longer developed glioblastomas. In a 9-year follow-up review of 72 similarly irradiated monkeys that received no more than 1200 rads, Krupp found seven cases of glioblastoma.

The causal relationship between radiation therapy and subsequent development of glioma is better established in animals than in humans. Our review of the literature revealed only six, or possibly seven, cases of malignant gliomas occurring after human cranial irradiation (Table 1). In 1960, Jones described a patient in whom a right hemispheric astrocytoma developed 10 years after treatment with 4000 rads of external beam radiation therapy for a left frontal angioblastic meningioma.

Robinson reported two cases of malignant astrocytoma after cranial irradiation. The first patient, at 10 years of age, had received 400 rads of external beam therapy before surgical removal of a pineal teratoma; 27 years later, the patient had a right frontal glioblastoma. The second patient, at 36 years of age, was treated with 2750 rads after partial resection of a meningioma that was totally excised at a second operation; 21 years later, a malignant astrocytoma was identified. The second patient must be considered cancer-prone, as he also had rectal adenocarcinoma at 50 years old.

Two reports document the occurrence of astrocytoma after radiation therapy for craniopharyngioma. In the first, a 21-year-old patient received 5400 rads, and 6 years later developed a right temporal glioblastoma. In the second, a 9-year-old patient was treated with 6007 rads; a right temporal glioma appeared 6 years later.

Klæriga, et al., reported a case of astrocytoma after treatment for a cerebellar medulloblastoma. This patient received 5000 rads of cranial irradiation at the age of 10 months for a desmoplastic medulloblastoma identified at biopsy, and a cerebellar malignant astrocytoma was identified 11 years later. We do not know whether this case represents a radiation-induced glioma or astrocytic differentiation of the original tumor.

Haselow, et al., presented the only case of a young child who possibly had a radiation-induced glioma. Diagnosed as having histiocytosis at 9 months, the patient received seven courses of radiation therapy totaling 500 to 600 rads to the fourth ventricle over 8 years, as well as chemotherapy with multiple agents (vinblastine, 6-mercaptopurine, 5-fluorouracil, prednisone, and amethopterine). Fifteen years after the initial treatment, the patient developed an ependymoma in the fourth ventricle. Although this patient received only a small dose of radiation over a long period of time, low-dose irradiation has been implicated in the induction of meningiomas.

In our patient, an anaplastic astrocytoma was diagnosed 7 years after CNS irradiation for acute lymphoblastic leukemia. This is the first reported case of glioma in a child who received CNS irradiation for leukemia. The unusual pathological features of the tumor, which does not resemble the cerebellar astrocytomas typically seen in children or those seen in adults, suggest that it was induced by radiation. However, our patient and the patient reported by Haselow, et al., both received chemotherapy in addition to radiation therapy. The role of chemotherapy in the induction of their tumors is unclear and cannot be excluded.

Postoperative management of our patient presented a difficult dilemma. The occurrence of an astrocytoma after radiation therapy suggests that a radiation-induced mutation led to the appearance of a malignant genotype. As shown by the few reported cases of radiation-induced glioma, such mutations are very rare. Whether this patient's genotype predisposed her to radiation-induced malignancy remains moot. The established benefit of postoperative radiation therapy for anaplastic tumors outweighed the risk of inducing a second malignancy.

### TABLE 1

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Initial Tumor</th>
<th>Age (yrs)</th>
<th>Radiation Dose (rads)</th>
<th>Latency (yrs)</th>
<th>Second Tumor</th>
</tr>
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<tr>
<td>Jones, 1960</td>
<td>meningioma</td>
<td>?</td>
<td>4000</td>
<td>10</td>
<td>astrocytoma</td>
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<td>Komaki, et al., 1977</td>
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<td>5400</td>
<td>6</td>
<td>glioblastoma</td>
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<tr>
<td>Haselow, et al., 1978</td>
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<td>600</td>
<td>15</td>
<td>ependymoma</td>
</tr>
<tr>
<td>Klæriga, et al., 1978</td>
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<td>1</td>
<td>5000</td>
<td>11</td>
<td>astrocytoma</td>
</tr>
<tr>
<td>Sogg, et al., 1978</td>
<td>craniopharyngioma</td>
<td>9</td>
<td>6007</td>
<td>6</td>
<td>astrocytoma</td>
</tr>
<tr>
<td>Robinson, 1978</td>
<td>pineal teratoma</td>
<td>10</td>
<td>4000</td>
<td>27</td>
<td>glioblastoma</td>
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<tr>
<td></td>
<td>meningioma</td>
<td>36</td>
<td>2750</td>
<td>21</td>
<td>astrocytoma</td>
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</table>
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neoplasm, and the patient was treated accordingly. Her postirradiation scans document tumor regression after therapy.

The role of radiation therapy in the induction of gliomas can be accurately assessed only by a prospective, controlled study of age-matched irradiated and nonirradiated patients.

References


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Address reprint requests to: Michael S. B. Edwards, M.D., c/o The Editorial Office, Department of Neurological Surgery, 1360 Ninth Avenue, Suite 210, San Francisco, California 94122.