Radiation-induced gliosarcoma

Case report and review of the literature

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A 13-year-old boy presented with a cerebral gliosarcoma 12 years after having acute lymphoblastic leukemia treated by chemotherapy and central nervous system prophylaxis treated by radiation therapy (24 Gy) and intrathecal methotrexate. A review of the literature disclosed 129 possible radiation-induced glialomatous and/or sarcomatous brain tumors: namely, 89 gliomas, 36 sarcomas, and four gliosarcomas, including the present case. An analysis of these cases revealed several characteristics that differentiate them from similar spontaneous brain tumors, thus providing arguments for the carcinogenic effect of radiation therapy on intracranial tumors.

KEY WORDS • radiation-induced tumor • brain neoplasm • glioma • gliosarcoma • acute lymphoblastic leukemia

SIDE-EFFECTS of radiation therapy on the central nervous system (CNS) are most frequently radiation therapy necrosis, postirradiation arteritis, or progressive leukoencephalopathy. Various radiation-induced tumors have been described, such as leukemias and lymphomas, thyroid carcinomas, or peripheral fibrosarcomas. Possible radiation-induced intracranial tumors have also been reported, the most frequent of which are radiation-induced meningiomas, with 296 cases collected from the literature by Harrison, et al., in 1991.

In the present paper, we describe the case of a young boy who presented with a very rare brain tumor that could have been induced by previous radiation therapy. On this occasion, we have reviewed the published data on most of the radiation-induced gliomas and brain sarcomas to study their specific characteristics and to compare them with similar histological types of tumors appearing without any previous treatment. This analysis of possible radiation-induced tumors involves 89 gliomas, 36 sarcomas, and four gliosarcomas, including the present case.

Case Report

Patient History. In October 1974 an 18-month-old boy presented with acute lymphoblastic leukemia with no signs of CNS involvement. Remission was attained by treatment with vincristine and prednisolone. Prophylaxis of the CNS included whole-brain irradiation (24 Gy) and five intrathecal injections of methotrexate (12 mg/m² each) over a period of 5 weeks. Consolidation polychemotherapy, including vincristine, methotrexate, mercaptopurine, and prednisolone, was continued until 1979. In 1980, a routine control computerized tomography (CT) scan showed a right frontal hyperdense nodule without contrast enhancement. No change was observed on follow-up examinations in 1981 and 1982, and a diagnosis of granuloma was provided (Fig. 1 upper).

Examination. The patient was readmitted in May 1986 for headaches, vomiting, neck stiffness, left hemiparesis, and hemihypesthesia. A CT scan (Fig. 1 lower) showed the unchanged right frontal nodule and a 4-cm right temporoparietooccipital hypodense lesion with mass effect and peripheral contrast enhancement.

Operation and Postoperative Course. On May 21, 1986, a right parietal craniotomy was performed, and a poorly delineated intraparenchymatous cystic tumor, including 45 cc of xanthochromic fluid and necrotic areas, was totally removed; no adherence to the dura was observed. Postoperatively, the patient’s neurological signs improved and a control CT scan showed no signs of residual tumor. Complementary radiation therapy was given on the right parietal region for a total dose to tumor of 32 Gy.
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In November 1986, despite a normal neurological examination, a CT scan showed tumor recurrence and an “eight-drugs-in-one-day” polychemotherapy (vincristine, procarbazine, hydroxyurea, cisplatinum, methylprednisolone, cytosine-arabinoside, and carmustine) was begun. In April 1987, the patient deteriorated rapidly, with somnolence, anorexia, and left hemiparesis, which corresponded to an extensive tumor progression as seen on CT scan. At no time was there evidence of metastatic lesion. He died at home on June 3, 1987. No autopsy was performed.

Pathological Findings. Surgical specimens included several solid irregular pieces of various sizes, which were submitted to light microscopic examination only. With conventional stainings, the tumor appeared to be very heterogeneous but exhibited two main intermingling areas (Fig. 2A and B). On one side, the most cellular areas had a gliomatous aspect: they were composed of a proliferation of small astrocytic cells, which showed important nuclear polymorphism, and giant multinucleated cells (Fig. 2C). Mitoses were abundant and vascular endothelial proliferation was prominent in some areas. These regions included numerous microcalcifications, necrotic areas, and few reticulin fibers (Fig. 2A and D).

On the other side (Fig. 2B), the tumor was less cellular, composed of irregular elongated fusiform cells arranged in loose fascicles. This pattern was particularly marked at the periphery of the gliomatous component, in which ribbons of fusiform cells were infiltrating surrounding cerebral parenchyma and seemed to proliferate independently from gliomatous tissue. These sarcomatous areas contained abundant reticulin (Fig. 2D). Microcalcifications were also present in these areas, as well as in the surrounding normal brain.

Immunohistochemical findings demonstrated in the gliomatous areas a majority of cells testing positive for glial fibrillary acid protein (GFAP) (Fig. 2F) and some cells that were positive for S-100 protein stainings; only the vascular structures were vimentine positive. The sarcomatous areas exhibited a majority of vimentine-positive cells (Fig. 2E) with only some S-100 protein– or GFAP-positive cells. Other immunoperoxidase stainings for desmine, α-1-antitrypsine, neurofilaments, keratines, and epithelial and lymphocytic markers were negative.

The irregular combination of undifferentiated gliomatous malignant areas and fibroblastic sarcomatous perivascular areas suggested the diagnosis of gliosarcoma.

Review of the Literature

The criteria for radiation-induced neoplasms were established in 1948 by Cahan, et al., and were later modified in 1972 by Schrantz and Araoz as follows: 1) the tumor must appear in the irradiated area, 2) the tumor was not present prior to irradiation, 3) a sufficient latency period must elapse between irradiation and the appearance of the tumor, and 4) the radiation-induced tumor must be histologically proven and must be of a different histological type from the original first tumor treated by radiation therapy.

According to Fajardo, the existence of animal models of radiation-induced tumors, a higher incidence of tumors among individuals treated with radiation therapy compared with a matched control group, and the demonstration of a dose–response relationship are other important criteria. Generally excluded from the category are patients suffering from a polytumoral genetic syndrome, such as phakomatoses or polyadenomatoses.

Radiation-induced brain tumors meet all these criteria. First, brain tumors resembling glioblastoma have been induced in Rhesus monkeys after whole-brain irradiation. Next, one major argument is found in a retrospective study covering 10,834 patients who received radiation therapy for tinea capitis (mean dose 1.5 Gy) and two matched control populations: the study documented 60 neural tumors in the patients who received radiation therapy, with a 30-year cumulative risk of 0.8%.

The incidence of tumors was 1.8 per 10,000 children who received radiation therapy per year. The estimated relative risk compared to the control populations was 6.9 for all tumors, 8.4 for neural tumors of the head and neck, 9.5 for meningiomas, and 2.6 for gliomas. The authors found a strong dose–response relationship, with the relative risk approaching 20.0 after estimated doses of approximately 2.5 Gy. For brain tumors, the excess absolute risk was 0.6 per 10,000 person-years per Gray, and the relative risk estimate at 1 Gy was 3.0. In the same way, Shore and colleagues, in a study including 2215 children who received radiation therapy for tinea capitis, reported an excessive

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FIG. 2. Photomicrographs. a: Highly cellular mixed tumor exhibiting sarcomatous (bottom) and gliomatous (top) aspects. Large irregular black “dots” correspond to scattered microcalcifications. H & E, original magnification × 60. b: Continuous areas of sarcomatous (right side) and gliomatous (left side) aspects of the tumor. H & E, original magnification × 100. c: Detail of atypical glial cells and several mitotic figures. H & E, original magnification × 200. d: Abundant fascicles of reticulin fibers in the anaplastic sarcomatous area, but not in the gliomatous area (top left). Reticulin, original magnification × 200. e: The same field showing vimentine-positive fascicles in the sarcomatous area. Immunoperoxidase for antivimentine, original magnification × 200. f: Several large and small cells stained for glial fibrillary acid protein (GFAP) in the gliomatous area. Immunoperoxidase for anti-GFAP, original magnification × 400.
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TABLE 1
Radiation-induced gliosarcomas: clinical data*

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>Age at XRT (yrs), Sex</th>
<th>Primary Condition</th>
<th>XRT Dose (Gy)</th>
<th>Latency (yrs)</th>
<th>Age at Diagnosis (yrs)</th>
<th>Location of Gliosarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Averback, 1978</td>
<td>36, M</td>
<td>PA</td>
<td>58</td>
<td>1</td>
<td>37</td>
<td>rt temporal</td>
</tr>
<tr>
<td>Beute, et al., 1991</td>
<td>26, F</td>
<td>ALL</td>
<td>10–15</td>
<td>8</td>
<td>34</td>
<td>rt cerebellar</td>
</tr>
<tr>
<td>Kaschten, et al., 1995</td>
<td>1, M</td>
<td>ALL</td>
<td>24</td>
<td>12</td>
<td>13</td>
<td>rt parieto-occipital</td>
</tr>
</tbody>
</table>

* XRT = radiation treatment; M = meningioma; PA = pituitary adenoma; PC = parotid carcinoma; ALL = acute lymphoblastic leukemia.

Risk of intracranial tumors, including two meningiomas, three gliomas, and one schwannoma.

Other reports,3,13,25,69 although covering lower numbers of patients, estimated the relative risk of malignant brain tumors between 20 and 226 after whole-brain irradiation for acute lymphoblastic leukemia (mean dose 24 Gy).

Last, Harrison, et al.31 in a review of the literature reported 296 cases of radiation-induced meningiomas with unique features that distinguished them from spontaneous meningiomas, such as sex ratio, average age, localization, presence of multiple tumors, and recurrence rate; these authors also found a relationship among radiation dosage, latency period, and age at appearance of the meningioma: for high doses (more than 20 Gy), the age at diagnosis and latency period are reduced. This relationship had already been found by Iacono and coworkers.24

In support of our reported case of radiation-induced gliosarcoma, and according to the required criteria, we collected from the literature 129 well-documented cases (including ours) of intracranial or spinal gliomatos and/or sarcomatous radiation-induced tumors. Eighty-nine of these cases were gliomas (63 high-grade and 14 low-grade gliomas; four ependymomas; eight tumors with nonspecified histology), 36 were sarcomas (20 fibrosarcomas of sella turcica; eight meningioma, and five osteogenic sarcomas; one malignant fibrous histiocytoma; and two intraparenchymatous sarcomas, one of which was a fibrosarcoma and the other a cerebellar chondrosarcoma), and four were gliosarcomas. Because only a sufficient number of documented cases were analyzed, it is likely that the total number of radiation-induced tumors is higher. On this basis, meningiomas represent approximately 70%, gliomas 20%, and sarcomas 10% of radiation-induced brain tumors.

The main characteristics of these 129 gliomatous and sarcomatous radiation-induced tumors have been detailed and compared with histologically similar spontaneous tumors. Data concerning the four radiation-induced gliosarcomas are summarized in Table 1.

Primary Pathology Justifying Irradiation. Except for 11 patients with benign pathologies, most of the patients were subjected to radiation therapy for primary intracranial (59%) or extracranial (33%) tumors (Table 2). The two most important groups were gliomas after radiation therapy for acute lymphoblastic leukemia and sella turcica fibrosarcomas after radiation therapy for pituitary adenoma.

Age of Patients at Tumor Irradiation. The mean age of patients when their tumors were irradiated was 18.1 years (Fig. 3 upper left). This age was significantly lower for glial tumors (13.8 years) than for sarcomas (27.2 years); it was also lower for low-grade gliomas (9.8 years) than for high-grade gliomas (14.6 years). The higher mean for fibrosarcomas after irradiation for pituitary adenomas (37.8 years) depended on the age of the patients at the time these adenomas appeared. There was no evident predilection age for the induction of the four gliosarcomas (1, 26, 36, and 52 years). In total, 60% of the patients received radiation therapy before the age of 20 years (70% for gliomas).

Sex Ratio. Males were slightly more affected by radiation-induced gliomas (55%), whereas females exhibited more radiation-induced sarcomas (53%).

Radiation Dosage. Doses of radiation ranged from 3 to 140 Gy (mean 40.5 Gy) (Fig. 3 upper right). The mean dose was significantly higher for sarcomas (59.5 Gy) than for gliomas (34.5 Gy) and for high-grade gliomas (39 Gy) than for low-grade gliomas (22.1 Gy). The mean dose for radiation-induced ependymomas was 28.5 Gy. Contrary to cases of gliomas and meningiomas, no radiation-induced sarcoma occurred for doses lower than 20 Gy. Gliosarcomas appeared after doses ranging from 10 to 58 Gy (mean 37.2 Gy).

Latency Period. The mean latency period between irradiation and appearance of a secondary tumor was 9.6 years, slightly lower for gliomas (9.2 years) than for sarcomas (11 years) (Fig. 3 lower left). There was no significant difference between high- and low-grade gliomas. In comparison, the mean latency period for radiation-
induced meningiomas varied between 20 and 35 years, depending on the radiation dosage.\textsuperscript{31,34} The mean latency period for radiation-induced gliosarcomas ranged from 1 to 12 years (mean 5.5 years).

**Histological Type.** Among the 81 well-documented radiation-induced gliomas, 78\% were high-grade gliomas, 17\% were low-grade gliomas, and 5\% were ependymomas. Among radiation-induced sarcomas, 58\% were fibrosarcomas, almost all of them originating from the sella turcica; 22\% were meningeal sarcomas; 14\% osteogenic sarcomas; and there was one malignant fibrous histiocytoma and one cerebellar chondrosarcoma. Only two of these sarcomas were intraparenchymatous tumors (one occipital fibrosarcoma and one cerebellar chondrosarcoma). Apart from our case, only three other cases of radiation-induced gliosarcomas have been described (Table 1).\textsuperscript{6,10}

**Age of Patients at Diagnosis of Radiation-Induced Tumors.** The mean age of patients when diagnosed as having radiation-induced tumors was 27.8 years. The age was significantly lower for patients with gliomas (23.4 years), especially for low-grade gliomas (18.6 years), compared with high-grade gliomas (24.2 years) (Fig. 3 lower right). Fifty-three percent of all gliomas appeared before the patient reached 20 years of age. The mean age at diagnosis of sarcomas was 37.5 years and was higher for sella turcica fibrosarcomas (47.8 years). The age at diagnosis of radiation-induced gliosarcomas ranged from 13 to 53 years (mean 34.2 years).

**Location of Radiation-Induced Tumors.** Most of the radiation-induced gliomas were supratentorial (77\%) and some were infratentorial (18\%); four spinal gliomas were also included in this study. Thirteen and one-half percent of gliomas exhibited multiple locations. Most sarcomas were sella turcica fibrosarcomas (56\%) and only two of the sarcomas were intraparenchymatous. Three of the four gliosarcomas were supratentorial, the last one located in the cerebellum.

Radiation-Induced Glioma Location According to Age at Diagnosis. Most of the infratentorial radiation-induced gliomas appeared in patients between 10 and 20 years of age (Fig. 4), but the peak incidence of supratentorial radiation-induced gliomas also occurred at this same age, which is radically different from spontaneous gliomas whose maximum incidence extends between 30 and 50 years of age. Eighty-two percent of radiation-induced gliomas that appeared before 20 years of age and all gliomas that appeared in the first decade of life were supratentorial, whereas spontaneous gliomas in young people are preferentially infratentorial.

Radiation-Induced Glioma Location According to Histological Grade. Most of the radiation-induced supratentorial gliomas were high-grade gliomas (86\%), but the majority of infratentorial gliomas were also high-grade gliomas (62\%) (Table 3).

**Discussion**

Gliosarcoma\textsuperscript{24,44,48,56,72,76,86} is a very rare form of malignant brain tumor, resulting from the contiguous development of gliomatous and sarcomatous areas in a single lesion. Its predilection for the temporal lobe, its surgical presentation as a firm lesion often attached to the dura and sometimes mistaken for a meningioma, and the possibility of its resulting in remote metastases are well known. Pathological findings include both gliomatous areas with GFAP-positive anaplastic glial cells and sarcomatous areas with vimentine-positive cells and many reticulin fibers, often at the periphery of the lesion and predominantly perivascular. Beute, et al.,\textsuperscript{10} reported 79 cases of gliosarcomas in the literature until 1987. In one series, however, gliosarcomas represented approximately 8\% of all anaplastic astrocytomas.

The origin of "spontaneous" gliosarcoma is supposed to occur in the neoplastic transformation of the perivascular cellular proliferation often seen in malignant gliomas.\textsuperscript{24,72}
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This hypothesis is strengthened by the possible presence in these tumors of all the intermediate forms from a slight perivascular proliferation to an invading sarcomatous transformation, often keeping a perivascular predominance. Lalitha and Rubinstein, postulated that a primary sarcoma could induce the neoplastic transformation of adjacent glial cells and proposed to name it “sarcomatoid glioma,” in which they could also find all the intermediate forms from banal reactive to highly anaplastic astrocytes; this transformation could arrive in or around an intra-parenchymatous or even a meningeal sarcoma. The possibility of simultaneous carcinogenesis in the two cellular types or the malignant transformation of a precursor cell that could differentiate into glial or mesenchymal cells are less credible.

According to these considerations, the carcinogenic role of radiation therapy in the genesis of the four described radiation-induced gliosarcomas could apply either by promoting the appearance of the initial tumor (glioma or sarcoma) or by inducing the neoplastic transformation of the vascular or astrocytic reactive component of the initial tumor.

In our case, the predominance of gliomatous areas with marked vascular hyperplasia and the peripheral location of sarcomatous parts were consistent with a sarcomatous transformation in an initial malignant glioma. That radiation-induced gliosarcoma appeared after acute lymphoblastic leukemia in our case may also imply secondary sarcomatous transformation, because all reported radiation-induced brain tumors appearing after acute lymphoblastic leukemia have been gliomas except for one meningeal sarcoma. With regard to the three other radiation-induced gliosarcomas, the two cases described by Averback only had a latency period of 1 year between irradiation and the diagnosis of the secondary tumor, a period that is somewhat short with regard to carcinogenesis. Moreover, his first case presented initially as a meningioma with incomplete removal of the tumor and postoperative radiation therapy; the secondary tumor was adherent to the dura, its superficial part was sarcomatous and its deeper part exhibited features of a glioblastoma. In this case, it is possible that the secondary lesion was a metastasis of the sarcomatous transformation of the meningioma, with anaplastic transformation of the underlying glial reactive tissue; the role of radiation therapy in the genesis of this secondary lesion is not clearly demonstrated. The case described by Beute, et al., represents, to our knowledge, the first case of gliosarcoma, with or without previous irradiation, described in the posterior fossa; unfortunately, no histological data were illustrated or discussed. Our case fulfills all the criteria for radiation-induced tumors and the latency period (12 years) is compatible with carcinogenesis. Regarding our review of the literature, the characteristics of our case make it closer to the radiation-induced gliomas than to sarcomas, and this is a further argument for the sarcomatous transformation in an initial radiation-induced glioblastoma.

The role of radiation therapy in the induction of brain tumors has remained questionable for a long time. Analyses of large series from the literature, clearly show an increased incidence of brain tumors among people who received radiation therapy compared with a matched control population. Moreover, in our analysis of 129 well-documented cases of possible radiation-induced gliomatous or sarcomatous brain tumors, we found that these tumors presented unique features distinguishing them from histologically similar “spontaneous” lesions, particularly in the case of gliomas: earlier age at diagnosis, high number of multiple gliomas, predominance of supratentorial and malignant gliomas in young people, and the relationship between radiation dosage and the histological type of radiation-induced tumors. However, we did not find any relationship between radiation dosage and latency period before the diagnosis of the secondary tumor, as was previously described for meningiomas.

The role of chemotherapy in inducing these secondary tumors seems less evident. First of all, a great number of the cases described previously included no chemotherapy. Furthermore, although numerous radiation-induced brain tumors were recognized after combined treatment by radiation therapy and chemotherapy for acute lymphoblastic leukemia, no such brain tumors were reported after Hodgkin’s disease, for which only chemotherapy is usually applied. In some cases, however, chemotherapy could play an adjuvant role.

Children suffering from acute lymphoblastic leukemia and treated by prophylactic CNS irradiation and intrathecal methotrexate can also exhibit abnormal cerebral CT scans, showing dilation of the ventricles, widening of the subarachnoid spaces, leukoencephalopathy, or intracerebral dystrophic calcifications. Our case presented a right frontal hyperdense nodule on cerebral CT scan, and, on microscopic examination, numerous microcalcifications within the tumor but also in the surrounding brain parenchyma. These are probable sequelae of the previously applied combined treatment, but no relationship has ever been demonstrated between such anomalies and a possible carcinogenesis. As described above, this frontal lesion remained unchanged for 7 years and had no interference with the radiation-induced gliosarcoma that predominated in the parietal lobe.

Conclusions

Although radiation-induced meningiomas are the most frequently reported, numerous cases of radiation-induced gliomas and brain sarcomas have been published. We report the fourth case of radiation-induced gliosarcoma, which is also the first to appear after treatment of acute lymphoblastic leukemia and to be submitted to immunohistochemical investigation. The analysis of an increasing number of reports concerning possible radiation-induced brain tumors provides further evidence on the primordial role of radiation therapy in the induction of these tumors.
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