Brain sarcoma of meningeal origin after cranial irradiation in childhood acute lymphocytic leukemia

Case report

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The authors report their experience with an unusual case of intracerebral sarcoma of meningeal cell origin in an 8-year-old girl. This tumor occurred 6 years after cranial irradiation at relatively low dosage (2200 rads) had been delivered to the head in the course of a multimodality treatment for acute lymphocytic leukemia. The tumor recurred approximately 10 months after the first surgical intervention. Macroscopic total excision of the recurrent growth followed by whole-brain irradiation (4500 rads) failed to eradicate it completely and local recurrence prompted reoperation 18 months later. This complication of treatment in long-term childhood leukemia survivors is briefly discussed, as well as the pathology of meningeal sarcomas.

KEY WORDS • lymphocytic leukemia • radiation-induced neoplasia • brain sarcoma

ADMINISTRATION of effective anti-leukemic drugs in combination with central nervous system (CNS) prophylaxis has dramatically improved the prognosis of acute lymphocytic leukemia (ALL) in children. Possible CNS prophylaxis includes intrathecal chemotherapy (methotrexate) and cranial irradiation (up to 2400 rads). Such treatment has resulted in complete remission. Serious complications, including radiation-induced sarcomas, have been reported following therapeutic cranial irradiation for scalp lesions, pituitary adenomas, and primary malignant brain tumors.

We are not aware of any reports of meningeal sarcomas following low-dose cranial irradiation in leukemic patients. Since such an occurrence may be related to the improved survival rate in children with ALL, we may anticipate the appearance of more cases of brain sarcoma in the future.

Case Report

This 2-year-old girl was diagnosed in October, 1974, as having ALL. She was referred for treatment at the Pediatric Hematology-Oncology Department of the Beilinson Medical Center, Petah Tikva. Remission was induced after a month of prednisone and weekly vincristine therapy. Central nervous system prophylaxis was then carried out, consisting of six injections of intrathecal methotrexate (12 mg/sq m) and 2200 rads of cranial irradiation.

She was maintained with daily 6-mercaptopurine and weekly methotrexate for 5 years, with six monthly then six 3-monthly pulses of vincristine, cyclophosphamide (Cytoxan), and prednisone. There was never any evidence of meningeal leukemia. A routine computerized tomography (CT) scan 3 months after completion of the 5-year course of chemotherapy did not reveal any significant abnormality. In April, 1981, electroencephalography was performed to evaluate the child for reading problems and was reported as showing the presence of a disturbance in the right frontal lobe. A CT scan was scheduled for the following week but, while returning to Beer-Sheba, she was involved in an automobile accident and was brought to the Soroka Medical Center.

First Admission. On admission she was pale and
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drowsy and actively bleeding from the left ear. There was complete ophthalmoplegia on the left, and a mandibular fracture with deformation was noted. Funduscoppy revealed fresh subhyaloid and flame-shaped retinal hemorrhages bilaterally. The right limbs were hypotonic. The deep tendon reflexes were weak and a positive Babinski sign was elicited on the right. A basal skull fracture complicated by subdural hematoma was diagnosed initially. Selective bilateral carotid and left vertebral angiograms were obtained. An unexpected, well delineated, and highly vascular tumor was demonstrated in the right frontal region (Fig. 1 left).

First Operation and Course. With the patient under general anesthesia, controlled respiration, and osmolar diuresis, a right frontotemporal craniotomy was performed 2 hours after admission. The tumor was entirely embedded within the brain. Its superficial surface, found at a depth of 1.0 to 1.5 cm under the cerebral cortex, was adherent to the surrounding white matter. The mass was removed in one piece, and surgery was concluded after tracheostomy and satisfactory reduction of the mandibular fracture.

A stormy postoperative course was complicated by development of meningitis, pyocephalus, and secondary hydrocephalus. The patient’s condition responded to appropriate antibiotics and to insertion of a medium-pressure ventriculostomy shunt. Three months after surgery, the child was transferred to an institution for rehabilitation. Her condition continued to improve and she was able to return home 6 months later. Repeat CT scans of the brain in July and September, 1981, as well as in March, 1982, showed progressive dilatation of the ventricular system with porencephalic enlargement of the right frontal horn. In one of the 12 tomographic slices obtained at the March, 1982, examination, a circumscribed area of hyperdensity was visible in front of and lateral to the frontal horn of the right ventricle. In retrospect, this finding should have alerted us to the possibility of tumor recurrence.

Second Admission. Five months later, in August, 1982, the patient was readmitted to the hospital because of clinical deterioration. Cerebral angiography and CT of the brain confirmed the recurrence of a huge growth at the site of the tumor excised 15 months previously (Fig. 1 right).

Second Operation and Course. A second surgical procedure was performed and the recurrent tumor was completely removed. In view of the aggressive biological behavior and malignant cytological features of the recurrent growth, it was thought that the admittedly oncogenic hazard of ionizing irradiation to the patient’s brain did not outweigh its potential therapeutic value as far as survival time and palliation were concerned, and a total dose of 4500 rads was given over 6 weeks. In the 1½ years since that time she has remained mentally alert and able to walk with the aid of a pair of Canadian crutches, and she could successfully participate in a full-year regular school program.

Third Operation and Course. A second local recurrence prompted us to revise the right frontal operative wound in January, 1984. The recurrent growth was completely resected without apparent damage to the adjacent brain tissue, resulting in a rapid and steady improvement in her general condition. Obviously, in our patient neither surgery nor cranial irradiation, alone or in combination, were curative or could prevent local recurrence. Nevertheless, the rewarding functional re-
covery after each surgical intervention is noteworthy. At the time of writing, the patient is alive and symptom-free, having had a postoperative survival that has already extended 3 years after the original tumor was diagnosed and 18 months after the excision of the first recurrent growth.

Pathological Examination. The original surgical specimen consisted of a large, well delineated, firm rubbery tumor mass, measuring 8.0 cm in diameter. The cut surface was tan-gray in color, homogeneous in texture, and had a fleshy appearance (Fig. 2). Numerous small hemorrhages dotted the cut surface. The tumor was not encapsulated. Multiple blocks of tissue from various areas of the tumor were fixed in 10% neutral formalin, embedded in paraffin, and stained with hematoxylin and eosin. Selected sections were later deparaffinized and stained with lead citrate and uranyl acetate. Semi-thin sections were cut on an LKB ultramicrotome with glass knives and stained with methylene blue-azure II and basic fuchsin. Selected blocks were cut for ultra-thin sections and examined on a Philips 201 transmission electron microscope. The areas examined showed a cellular tumor comprised of large ill-defined cells with prominent round to oval central nuclei. Cytoplasmic borders were poorly preserved. Nuclei showed chromatin clumping at the periphery of a distinct nuclear envelope. The cytoplasm was rich in organelles, mitochondria, and dilated small cisterns of rough endoplasmic reticulum. The Golgi apparatus was prominent in most cells.

Material for pathological examination was also obtained from the recurrent tumor removed at the last surgical procedure. Compared to previously examined tissue, that tumor appeared much better defined and much more malignant histologically.

Numerous histological sections showed a predominantly spindle-cell tumor producing collagen in abundance. Pleomorphism and atypia were of a moderate degree. Electron microscopic examination confirmed the fibroblastic nature of the tumor cells. The final pathological diagnosis is a moderately well differentiated fibrosarcoma of meningeal origin.

Discussion

Prior to the institution of effective CNS prophylaxis in children with ALL, 60% to 70% developed CNS leukemia, followed by bone marrow relapse and death. The addition of cranial irradiation in combination with intrathecal methotrexate to the systemic anti-leukemic therapy has reduced the recurrence rate in the CNS to 5% to 10%. This has resulted in an increase of complete remissions and long-term leukemia-free survival. The modalities used for CNS prophylaxis have been occasionally associated with serious complications. Early postirradiation clinical deterioration has been reported in relation to a process of demyelination. Radionecrosis, disseminated necrotizing leukoencephalopathy, mineralizing microangiopathy, and irradiation-induced neoplasia have been described as delayed complications in patients receiving ionizing irradiation. In one group of children, 53% showed evidence of brain atrophy, ventricular dilatation, and basal ganglia calcification on CT scanning. Subtle changes in abstract thinking, fine coordination, and learning disabilities may later be...
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CRANIAL IRRADIATION AND MENINGEAL SARCOMAS

Cranial irradiation during childhood has been shown to be associated with a significant risk of developing meningiomas at sites of exposed mesenchymal tissues. Postirradiation occurrence of malignant tumors within or adjacent to tissues exposed to ionizing radiation have also been reported. Development of fibrosarcomas in patients with pituitary irradiation has long been recognized. Primary intracranial sarcomas may originate from mesenchymal cells in the dura mater, from leptomeningeal infoldings, and from adventitia of intraparenchymal blood vessels. Brain sarcomas and extracerebral sarcomas of meningeal origin are histologically identical and are distinguished only by their location. Until 1972, only four acceptable cases of radiation-induced meningeal sarcoma had been reported and, according to Schrantz and Araoz, who added their own case, these cases were similar histologically to fibrosarcomas of other soft tissues. More recently, Bojesen-Møller and Knudsen reported a sixth, very similar, case of meningeal sarcoma following ionizing radiation of the head. They concluded that children receiving cranial irradiation must be closely observed, and that the possibility of radiation-induced neoplasia should be considered whenever a space-occupying lesion is suspected.

Our case, in common with the other six cases mentioned above, satisfies the criteria set forth by Schrantz and Araoz for irradiation-induced meningeal sarcomas: 1) The tumor appeared in a treated area; 2) Absence of intracranial sarcoma was established prior to irradiation; 3) A latent period of years existed between irradiation and the appearance of the sarcoma; and 4) The existence of the sarcoma was histologically proven.

A thorough review of the available literature dealing with irradiation-induced neoplasia revealed no reports on meningeal sarcomas following prophylactic or therapeutic cranial irradiation in leukemic patients. One explanation why such a serious complication has not been encountered until now may be the relatively short survival of leukemic patients in the past. If this assumption is correct, we may witness additional reports in the future, because during the last two decades effective anti-leukemic chemotherapy has allowed an increasing survival rate of childhood ALL.

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References


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