OSTEOGENIC SARCOMA OF THE SKULL FOLLOWING ROENTGEN-RAY THERAPY FOR BENIGN PITUITARY TUMOR

JOHN M. MEREDITH, M.D., F. B. MANDEVILLE, M.D., AND SAUL KAY, M.D.

Departments of Neurological Surgery, Radiology, and Surgical Pathology, Medical College of Virginia, Richmond, Virginia

(Received for publication April 1, 1959)

Osteogenic sarcoma of the skull is rare whether of spontaneous origin or following irradiation. In fact, it is almost unknown after irradiation of the skull or intracranial contents in any period of life. As a primary development, not associated with irradiation, it is also extremely rare, particularly in the later decades of life and in individuals who do not have an associated Paget’s disease of the skull. The patient in the present report did not have Paget’s disease of the skull, was 57 years of age at the time of death, and, 6 years after the beginning of roentgen-ray therapy for a verified chromophobe pituitary adenoma, had an osteogenic sarcoma of the skull, which was verified at necropsy. The case report is accompanied by photomicrographs of the pituitary tumor and also several of the osteogenic sarcoma of the skull. It is believed worthy of report because of its rarity and interest, and also to stress the importance of irradiating intracranial structures or neoplasms therein only when such therapy seems definitely or strongly indicated, as there always would appear to be a slight chance, and potential danger at least, of osteogenic sarcoma developing in the overlying skull when such roentgen therapy is carried out.

CASE REPORT

Mrs. A.D., a white woman aged 51, was first admitted to the hospital on Oct. 22, 1951. She had begun to notice visual disturbance in August 1951. A diagnosis then was made of pituitary adenoma on the basis of an enlarged sella. She had had headaches, and visual fields had revealed a bitemporal hemianopsia at that time.

She was given roentgen-ray treatment to the pituitary gland over a period of 8 days, and the headaches disappeared. Basal metabolic rate was −20 per cent and blood pressure was 110/90. She was discharged on Oct. 31, 1951.

2nd Admission, May 15, 1952. On May 16, a right frontal craniotomy was carried out (J.M.M.) with removal of a pituitary tumor between the optic nerves. Diagnosis: chromophobe adenoma of pituitary gland.

It was thought before operation that she had shown marked signs of panhypopituitarism (anterior lobe) which had been present for an indefinite period. The optic discs were very pale and well outlined, showing primary atrophy. She was discharged on May 31, 1952.

Course. In July 1952, she was treated in the Department of Internal Medicine for hypopituitarism, and was thought to have anterior pituitary insufficiency, with secondary hypothyroidism and adrenal cortical deficiency. Her basal metabolic rate on July 1, 1952 was −31 per cent.

3rd Admission, June 18, 1955. This time she was on the medical service of Dr. Elam Toone for treatment of arthritis. The diagnosis of postoperative pituitary insufficiency was made again and myxedema was well controlled with thyroid therapy. Roentgenograms of her cervical-upper dorsal spine, lumbar spine and pelvis, including the right hip, showed sacroiliac changes suggesting old rheumatoid arthritis and generalized demineralization of the cervical and lumbar spine. The basal metabolic rate was −15 per cent. She was discharged on June 22, 1955.

4th Admission, April 28, 1956, again was to the medical service. The diagnosis at that time
was adrenal cortical insufficiency with pituitary insufficiency incidental to surgical removal of the pituitary adenoma in May 1952, and hypothyroidism. Roentgenograms of the skull showed the sella turcica to measure 18 by 21 mm. with ballooning of the intrasellar space. Basal metabolic rate was −16 per cent. She was discharged on May 8, 1956.

5th Admission, Sept. 21, 1957. About 6 weeks previously, she had noticed the presence of a painless mass in the left temporal region. This had become as large as a small lemon by the time of admission, was doughy in consistency, rather fixed to the surrounding skull, and entirely painless on firm palpation and compression. There were no severe headaches or other distress associated with the condition. She was then receiving cortisone and thyroid therapy, this having been administered continuously since the operation for pituitary tumor in 1952. Roentgenograms of the skull showed evidence only of the old right-sided craniotomy: “There are no other remarkable roentgen findings in the skull.” The lungs were clear as shown in a film of the chest although there was mild enlargement of the heart with an arteriosclerotic aorta. Hemoglobin was 14 gm., count of white blood cells was 8,900, and urine was normal.

On Sept. 24, 1957, under endotracheal anesthesia, an extradural mass was explored in the left temporal region. The mass definitely perforated both tables of the skull. A generous biopsy of the lesion was made, and the wound was closed entirely dry without drainage.

A quotation from the operative note reads as follows: “The temporal muscle was gently dissected, disclosing a rather massive collection of yellowish, granular, necrotic tissue apparently coming from the deeper layers of muscle, having its base and source of origin in the left temporal bone. This portion of the skull presented a defect of irregular shape and contour, partly disintegrated, and of stellate appearance. It is rather remarkable it was not seen in films of the skull. The dura mater was apparently intact and was not opened. As much as possible of the tumor was excised, and a frozen section biopsy was reported as showing an osteogenic type of sarcoma. All bleeding was readily controlled with the electrosurgical apparatus, and closure of the scalp was made, there being no excessive loss of blood at any time. The patient withstood the procedure well and left the operating room in good condition.”

She died, however, on Sept. 25, 1957, 15 hours after operation, without ever having regained consciousness, primarily of a massive extradural hemorrhage from an eroded left-sided middle meningeal artery which occurred after operation at some unknown time during the 15 hours she was in the recovery room.

Pathologic Reports (from the Department of Surgical Pathology). 1. Surgical specimen of pituitary tumor removed in 1952 (S-52-3314).

Microscopic. A few capillaries surrounded by swollen cells are seen. The latter are thought to represent chromophobe tumor cells.

2. Surgical specimen of left temporal bone, Sept. 24, 1957 (S-57-7338). Specimen consisted of many pieces of yellowish-gray, soft tissue with minute hemorrhages. They varied from 3 to 11 mm. in maximal diameter.

Microscopic. Sections are of a malignant tumor which is markedly cellular and composed of extremely pleomorphic cells. The cytoplasm is indistinct, but most of the cells are spindly with ovoid and elongated nuclei, and many of they are monster forms (Fig. 1). Nucleoli are generally prominent. In addition, multinucleated tumor cells are present (Fig. 1). Mitoses are numerous and atypical. In some areas the tumor shows very little intercellular stroma. In other areas, there is an abundance of dense eosinophilic stroma, sometimes with distinct osteoid formation (Fig. 2).

Diagnosis. Osteogenic sarcoma of temporal bone, left, arising in previously (6 years) irradiated bone.

3. Autopsy (A-9811). Examination of the head only was allowed. When the scalp was reflected, an area of swollen tissue 4 cm. in diameter was found over the left temporal region. In the center of this area was a defect, admitting one finger, which extended through the cranium. The edges of this defect were fragile and of egg-shell consistency. The right side of the cranium revealed an old (1952) frontal craniotomy bone flap. The sites of old burr holes in both parietal bones were also identified. After sawing through the cranium, a diffuse erosion of bone, approximately 6 cm. in circumference, was noted beneath the soft-tissue abnormality
Fig. 1. Photomicrograph of soft-tissue tumor from left temporal bone. Note pleomorphic cells and several multinucleated giant cells. (×300)

Fig. 2. Photomicrograph of tumor to show osteoid matrix. (×400)
POSTRADIATION OSTEOSTEOGENIC SARCOMA OF SKULL

in the left temporal region. This erosion occurred between the tables of the skull, and extended down toward the petrous portion of the temporal bone. The diploic bone in this area was replaced by pink, fleshy, friable tumor tissue. The center was excavated, admitted one finger, and was partially filled with blood clot. The two bony tables were fragile where they were expanded by the tumor tissue. This was particularly true of the inner table which had an egg-shell sensation to palpation. An epidural hematoma of approximately 200 cc. was found beneath the bone involved by tumor. The left cerebral hemisphere was markedly flattened and displaced by the hematoma. Both hemispheres seemed softer than normal. Examination of the sella turcica revealed a large, smooth, soft, brownish, globular mass, 1.5 by 1 cm., surrounded by the dural lining of the sella turcica (Fig. 3). The hypophysis could not be recog-

Fig. 3. Coronal section of brain in vicinity of hypophysis. Note pituitary tumor displacing third ventricle upwards.

nized separately from the neoplastic mass. There was no evidence of invasion of surrounding structures. The contents of the cavernous sinus were markedly displaced laterally. The floor of the third ventricle was displaced upwards with moderate flattening of the hippocampal gyri. The lateral ventricles were slit-like. On cut section, the pituitary mass had a uniform, fleshy consistency with a pink-red color, and could be separated from the surrounding dura mater.

Microscopic. There was persisting sarcoma between the tables of the cranium (Fig. 4). Tumor had extended into the blood clot overlying the dura mater. Several sections made of the cranial bone adjacent to the tumor showed no changes typical of Paget's disease of the bone.

The pituitary gland was largely replaced by sheets of tumor cells, arranged in a trabeculated pattern, and separated by blood-filled sinuses. The cells of the pituitary tumor were fairly uniform, but occasional bizarre large nuclei were seen (Fig. 5). The cytoplasm was finely granular and the cytoplasmic borders were indistinct. The cells were identified as chromophobe in type, and the uninvolved pituitary tissue was atrophic and displaced to the periphery.

Diagnosis. (1) Osteogenic sarcoma (? postirradiation) of left temporal bone, with extension to epidural space, and (2) residual chromophobe adenoma of pituitary gland.
Fig. 4. Photomicrograph of persisting sarcoma between the tables of the cranial bone. (X150)

Fig. 5. Photomicrograph of pituitary tumor showing sheets of chromophobe cells. (X350)
Roentgenologic Report (from the Department of Radiology). The case of postirradiation osteogenic sarcoma in the vault of the skull herein reported meets four requirements set forth in the few reviews on the subject that have appeared in recent medical literature. First, roentgenographic evidence of a normal vault of the skull was obtained before the irradiation. Secondly, deep roentgen therapy was given to a benign pituitary tumor, and the sarcoma that developed later arose in the area included within the radiotherapeutic beam. Thirdly, a relatively long symptom-free latent period, 6 years in our case, elapsed. Fourthly, the sarcoma in the previously normal bone was proved histologically.

In 1922, Beck\(^1\) reported 3 cases of sarcoma developing in normal bone in the beam of roentgen rays administered for tuberculous arthritis. Cahan et al.\(^2\) in 1948 listed 17 cases from the European literature, 16 of sarcoma in bones 3 to 11 years after treatment with external radiation and 1 after intra-articular injection of radium chloride. In 1957, Cruz et al.\(^3\) reported 11 cases of postirradiation bone sarcoma, none of which was in the skull.

No case of postirradiation osteogenic sarcoma of the vault of the skull was found in the several reports in the literature on this subject. The total tumor doses ranged from 1,000 r to 5,280 r given in periods ranging from 1 month to 9 years. In our case, the tumor dose was 2,052 r delivered in a period of 8 days to a (subsequently verified) chromophobe adenoma of the pituitary gland. A large right frontal bone flap was made 7 months following roentgen therapy for surgical attack on the pituitary tumor. The osteogenic sarcoma, proven 6 years after roentgen-ray therapy, was found in the left temporal region.

Roentgen therapy was administered through anterior frontal, right and left temporal portals, each 6 by 8 cm. in diameter and rectangular, with the center of the beam angled to the sella turcica. Each of the three portals was treated daily for a period of 8 days from Oct. 23, 1951 to Oct. 31, 1951. Treatment factors were 200 kilovolts, 20 milliamperes, 59 cm. distance, 1/2 mm. copper and 1 mm. aluminum filter, half-value layer 1 mm. copper; 150 r measured, in air, were given through each portal daily with a total air dose of 1,200 r, in air, to each. The depth dose to the pituitary was 2,052 r. The width of the skull was 13 cm. in the temporal region.

DISCUSSION

As stated above, previous articles in the literature have disclosed scarcely any, if any, truly authenticated case or cases of postirradiation osteogenic sarcoma of the skull.

A number of authorities on bone tumors\(^2,4,6-9\) were consulted, and in no specific instance was a similar lesion found. Most of the sarcomas were in bones other than the skull, whether produced experimentally or found in clinical cases. Coley\(^4\) stated that, according to Hatcher, the literature up to 1945 contained a report of 19 human beings with osteogenic sarcoma occurring as a sequel to therapeutic exposures to radium or roentgen rays. In all but 3 of these the sarcoma developed in the course of treatment of tuberculous arthritis. Eighteen of the patients had roentgen therapy and 1 had radium. The time interval elapsing between the beginning of roentgen-ray treatment and the recognition of the bone sarcoma in the clinical cases of Hatcher was 6.6 years (average); in our patient, it was 6 years. Coley then (1948) described briefly his personal series reported with Cahan et al.\(^2\), who studied 11 cases in which osteogenic sarcoma or chondrosarcoma developed in irradiated bones after a lapse of from 6 to 22 years following roentgen or gamma treatment. They concluded that while such a situation is unusual or uncommon, it does occur, nevertheless. It may take place in previously normal bone (as in our patient) or in a benign bone tumor. In their experience, there was a latent period of from 5 to more than 20 years between exposure to irradiation and recognition of a frank sarcomatous alteration in the involved bone. It is also seldom observed following moderate roentgen-ray ther-
apy, and probably requires a tissue dose of 3,000 r or more, although 1 patient had received only 1,550 r. Our patient, as noted above, received a depth dose to the pituitary of 2,052 r.

Coley4 further believed that when a suspicious mass develops in an area of bone that has been irradiated, it is probably best to carry out an aspiration biopsy rather than open surgical biopsy because of danger of incising irradiated tissue, which is notoriously slow to heal. This would certainly have been, in retrospect, the desired method of diagnosis in our case instead of open biopsy because, although that procedure was simple and easy, and at the time of closure the wound was perfectly dry, apparently the operative procedure permitted (in some manner) erosion of the middle meningeal artery by the malignant sarcomatous process during the night, and the patient succumbed actually to a large extradural hemorrhage which occurred in the region of the tumor. At all events, the malignant sarcomatous tumor in this case was large and had invaded the dura mater and other tissues, so that a cure would not have been possible.

Coley concluded that the late development of bone sarcoma, rare as it is following irradiation, is another reason for his belief that roentgen therapy is not ordinarily to be recommended for benign tumors of bone. The same reasoning would prevail for irradiating questionable lesions of the brain so far as a beneficial effect is concerned. Although the incidence of bone sarcoma after irradiation apparently is very small, the possibilities are most serious when it does occur. Coley also stated that the calvarium is only very rarely the seat of primary osteogenic sarcoma. At the Memorial Hospital in New York, there have been only 7 such cases in a period of 20 years. He cites Geschickter and Copeland who stated that in a series of over 500 cases of primary (spontaneous) bone sarcoma, there were only 8 examples of osteogenic sarcoma of the cranial bones. Also, in general, primary osteogenic sarcoma of the skull is seen mostly in children and young adults with the exception of osteogenic sarcoma that is associated with Paget’s disease, and which occurs usually in individuals past middle life; our patient showed no clinical, radiologic or pathologic evidence of Paget’s disease. Coley stated that the roentgenographic appearance of the skull may enable one to make the correct diagnosis preoperatively, but, as in our case, this often is not possible.

According to Snapper,5 it is well known that osteogenic sarcoma as a primary disease in any bone is an uncommon lesion in patients over the age of 50. Snapper even stated that sarcomas of the skull in patients over 50 years of age have been found only in skulls already affected by Paget’s disease (unless previously irradiated). In the 11 cases of postirradiation bone sarcoma reported by Cruz et al.6 in 1957, none of them was in the skull. Furthermore, only 6 of the tumors in their 11 cases were osteogenic, 5 were fibrosarcomatous, and they were usually in the bones of the trunk or the extremities. As noted above, Beck1 was the first to report sarcoma arising in bone previously subjected to irradiation. He reported 8 cases in which the tumor originated in previously normal bone included within the beam of roentgen-ray therapy for tuberculous arthritis. In the paper by Cruz et al.,6 the four criteria for the acceptance of the diagnosis of postirradiation bone sarcoma were laid down and are the same as those cited in the roentgenologic discussion of our case. We believe that these criteria were fulfilled in our case and that it represents one of the rare instances of osteogenic sarcoma developing in the skull after irradiation. The latent interval between roentgen-ray therapy and development of sarcoma in other reported cases varied from 32 months to 30 years. The latent interval between the completion of
irradiation and establishment of the microscopic verification of osteogenic sarcoma varied from 4 to 34 years. The 11 cases reported by Cruz et al. originated as follows: 2 were in the femur, 2 in the humerus, and 1 each was in the clavicle, mandible, phalanx of the hand, fibula, rib, scapula, and lumbar spine.

Cruz et al. concluded their paper with the statement that the relationship between exposure to large doses of ionizing radiation and development of sarcoma in the bone included within the beam of therapy has been established experimentally by several workers. They further stated that there is undoubted clinical evidence that sarcoma occurs in man as a rare complication following completion of roentgen-ray therapy. They also believed that the absence of changes in the skin following irradiation may encourage the therapist to deliver unusually high doses of radiation.

It may be noted among reports in the literature that osteogenic sarcoma in irradiated bone did develop as soon as 32 months in 1 case after roentgen therapy, and in another case 4 years after irradiation. In our case the interval was 6 years. It is generally agreed, however, that there is usually a longer interval than this between the last irradiation of the normal bone or benign lesion in it, and the development of postirradiation osteogenic sarcoma in the same area. Apparently, osteogenic sarcoma of the skull, particularly in middle-aged or elderly patients who do not have Paget’s disease, is quite rare, or almost unknown, whether it follows irradiation, as in our case, or develops spontaneously. Postirradiation osteogenic sarcoma occurs much more frequently in extracranial bone (in the extremities, etc.) than in the skull.

SUMMARY

The case of a middle-aged white woman is presented in whom postirradiation osteogenic sarcoma of the skull developed approximately 6 years after roentgen-ray therapy was given for a benign lesion of the pituitary (chromophobe adenoma). The four criteria by which this occurrence is determined are given and are believed to have been fulfilled in this case. It is emphasized that adult-type osteogenic sarcoma of the skull, whether of the rare postirradiation type or even of spontaneous origin, is very unusual; in middle-aged individuals who are free of Paget’s disease, as in our case, it develops much more frequently in extracranial bones in the extremities or spinal-pelvic axis.

REFERENCES