Extraosseous Osteogenic Sarcoma

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THE OCCURRENCE of osteogenic sarcoma outside the skeletal system is quite rare, whereas extraskeletal bone formation under a variety of different stimuli is not at all infrequent. After Wilson's[18] report in 1941, Schaffer[17] in 1952 collected from the literature 44 patients presumed to be suffering from extraosseous osteogenic sarcoma. Fine and Stout[7] found only one case in a review of 147 instances of osteogenic sarcoma and reports of 864 surgical specimens and 9,065 autopsies. However, they obtained histories and pathological material of 12 acceptable new cases from various hospitals. They[7] made a critical study of published cases and were reluctant to accept several as genuine extraosseous osteogenic sarcomas. Kauffman and Stout[11] in 1963 further reported two instances of this tumor in children. Subsequent to this only occasional cases have been reported.[10, 12]

Nine patients with extraosseous osteogenic sarcoma have been treated at Memorial Hospital through the years. This apparently is the largest single series treated in one institution. The rarity of this tumor prompted us to analyze our material in retrospect, with respect to histological characteristics, natural history, and management of this unusual tumor. It is recognized that if strict criteria for the diagnosis of extraosseous osteogenic sarcoma are not followed, the apparent incidence will be much greater.

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Pathology

Macroscopic. These tumors are usually surrounded by a tough connective tissue capsule which is intimately adherent to surrounding structures making dissection extremely difficult. The overlying skin is occasionally ulcerated. The size of the tumors varies from 1.5 cm. in maximum diameter to 20 cm. The color of the cut surfaces of the tumors varies between red, gray, grayish white, whitish gray or yellowish white; often several combinations can be seen in different areas of the same tumor. Areas of hemorrhage and necrosis are frequent.

The central part is usually cystic, whereas the periphery is firm and rarely specks of calcification or bone formation can also be seen. The remarkable ability of this tumor to infiltrate the surrounding muscles, tendons and adipose tissue should be borne in mind during gross examination of the tumor. In rare instances the lesion is in contact with the periosteum of the underlying long bone.

Microscopic. A striking histological feature is the nodular arrangement of the tumor (Fig. 1). The nodules are quite cellular and contain both spindle and giant cells, and these cells are frequently arranged in cords similar to fibrosarcoma (Fig. 2). The nuclei in the spindle cells vary in shape, size, and staining quality and frequently are hyperchromatic. Al-

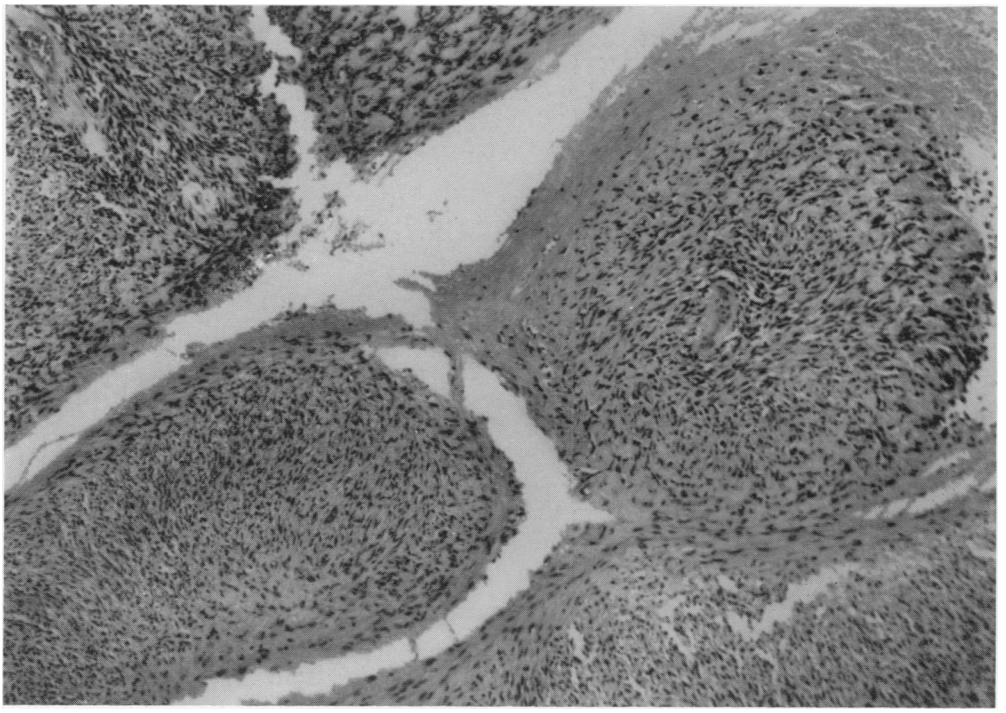

FIG. 1. Marked nodular arrangement of spindle cells. (H & E ×75.)

though the degree of cellular pleomorphism and the number of giant cells vary from field to field, there is uniformity in cellular morphology throughout the tumor. Tumor giant cells with multiple nuclei are most commonly seen in the fibrous part of the tumor; in some instances 25 or more nuclei can be seen in a single giant cell (Fig. 3). Mitoses, however, are infrequent (Fig. 4).

Bone formation can be seen in all parts of the tumor (Fig. 5) and often a transformation zone from fibrous stroma can be demonstrated. Calcification of osteoid and fibrous tissue can also be observed at various sites in the lesion. Vascularity is not a marked feature and often blood vessels are not seen in several sections. Malignant cells may invade and penetrate the capsule, and extension into the surrounding tissue can often be seen. However, invasion of blood vessels by tumor cells is not a marked feature.

The nodular arrangement of distinctive cell types, giant cells, and osteoid formation with osteoblasts have been seen in all cases reported.

Material

Nine records of patients with extraosseous osteogenic sarcoma were found. Seven were women and two were men. The youngest was 31 years old and the oldest 67.

Case Reports

Case 1. A 48-year-old woman was first seen in December 1964. In 1950, she noticed a lump in the right elbow which was apparently cured by aspiration. However, in 1955, a scaling appeared in the aspiration site which was surrounded by multiple small nodules. These lesions were excised and a histological diagnosis of neurofibroma was made. There were two subsequent recurrences in 1957 and in 1963; on both occasions the diagnoses of neurofilromata were made. In June 1964 the third recurrence was associated with a painful elbow joint. Biopsy at this time showed malignant tumor and the patient came to Memorial Hospital.

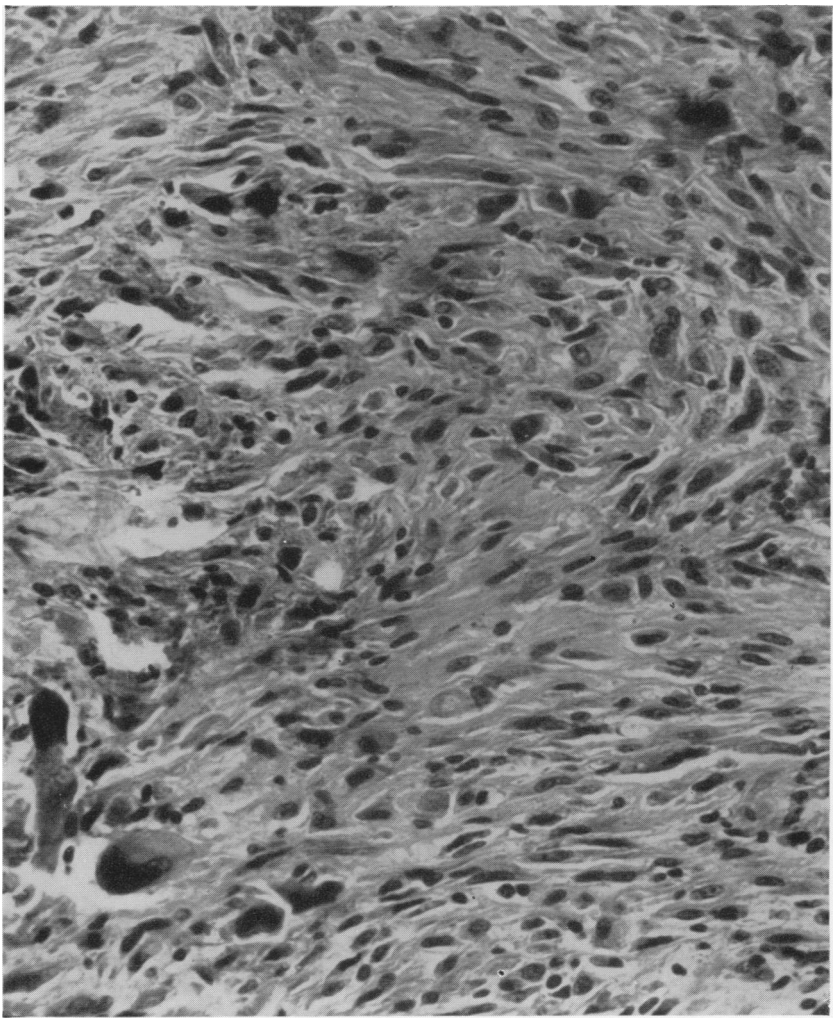

FIG. 2. Many areas of the tumor had a cellular fibrosarcomatous appearance. (H & E ×320.)

Significant findings were limited to the right elbow. There was a healed 9-cm. scar with edema and induration (Fig. 6). The epitrochlear and axillary nodes were unremarkable. Elbow function was limited. X-rays showed an area of bone destruction in the right ulna (Fig. 7). The soft tissues in the region of the right elbow, the distal end of the humerus and the proximal end of the ulna were excised.

The pathological specimen measured 28 × 9 × 4 cm. and contained about 9 cm. of the distal end of the humerus, 4 cm. of the proximal end of the ulna and the skeletal muscles. The elbow joint was apparently free of gross tumor. The ulnar fragment was secondarily invaded by a 2.5 × 4-cm. whitish, firm tissue that extended to the skin surface posteriorly. A histologic diagnosis of extraosseous osteogenic sarcoma was made. In view of the history of multiple local recurrences and site of the tumor, bone invasion was considered secondary. She is living free of disease, 2 years after operation.

Case 2. A 67-year-old man was first seen with a tender swelling of the left thigh in October 1962. In July 1962 he first became aware of tenderness in the back of the left thigh. Five weeks later a lump was detected by his physician. X-ray examination showed faint calcification within the tumor. The femur was normal. The mass was considered myositis ossificans and no active treatment was instituted. However, pain, swelling and tenderness progressively became worse.

On physical examination there was a tender mass approximately 9 cm. in maximum diameter beginning at a point 5 cm. below the infragluteal fold. The rest of the examination was negative.

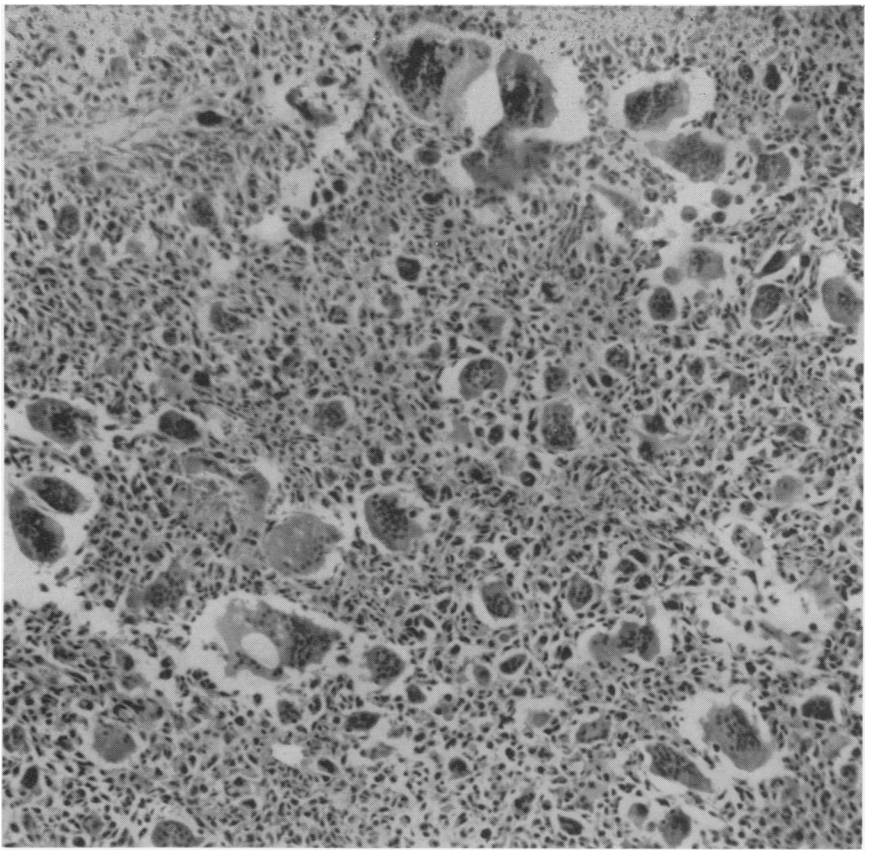

FIG. 3. Large and biziarre multinucleated giant cells. (H & E ×115.)

The only significant laboratory findings was elevated serum alkaline phosphatase (24 Bodansky units). In view of the calcification in the tumor and elevated serum alkaline phosphatase, a clinical diagnosis of extraosseous osteogenic sarcoma was made. Wide soft tissue resection was performed on October 30, 1962.

The specimen which was 25 cm. long and 12 cm. wide (Fig. 8) included parts of semitendinosus, semimembranosus, the abductor muscles and the biceps femoris. The biceps femoris, however, was the only muscle infiltrated by tumor. In the upper portion of the biceps femoris there was a sharply delineated, whitish encapsulated 8 cm. × 6 cm. ovoid tumor, the center of which was necrotic and contained cystic and hemorrhagic areas.

After an uneventful postoperative course the serum alkaline phosphatase returned to normal within six weeks. After six months he was readmitted because of local recurrence. This was a hard 4 cm. × 3 cm. plaque-like mass in the middle of the scar (Fig. 9). This local recurrence was preceded by a rise in alkaline phosphatase activity to 11.2 Bodansky units at the time of admission. Chest x-rays showed what were presumed to be metastatic deposits in both lung fields. Wide excision was performed (Fig. 10), but the lesion promptly recurred (Fig. 11). During a third admission alkaline phosphatase activity was 27.7 Bodansky units. The patient was treated with intra-arterial instillation of nitrogen mustard (0.6 mg./Kg.). A short-term regression of the tumor followed (Fig. 12). He complained of low back pain for which an empiric course of radiation therapy was given. He died on November 19, 1963, 16 months after initial therapy. An autopsy was performed.

At autopsy, recurrence in posterior thigh, direct extension within psoas major muscle and metastases to lungs, heart, pancreas and small bowel were found. It was believed that the immediate cause of death was due to replacement of lung parenchyma by metastases and bilateral pulmonary effusion.

Case 3. A 53-year-old woman was admitted to Memorial Hospital in July 1953. In March 1951 a growth was excised from the right posterolateral chest wall. Pathological diagnosis of the first tumor is not available. The lesion promptly

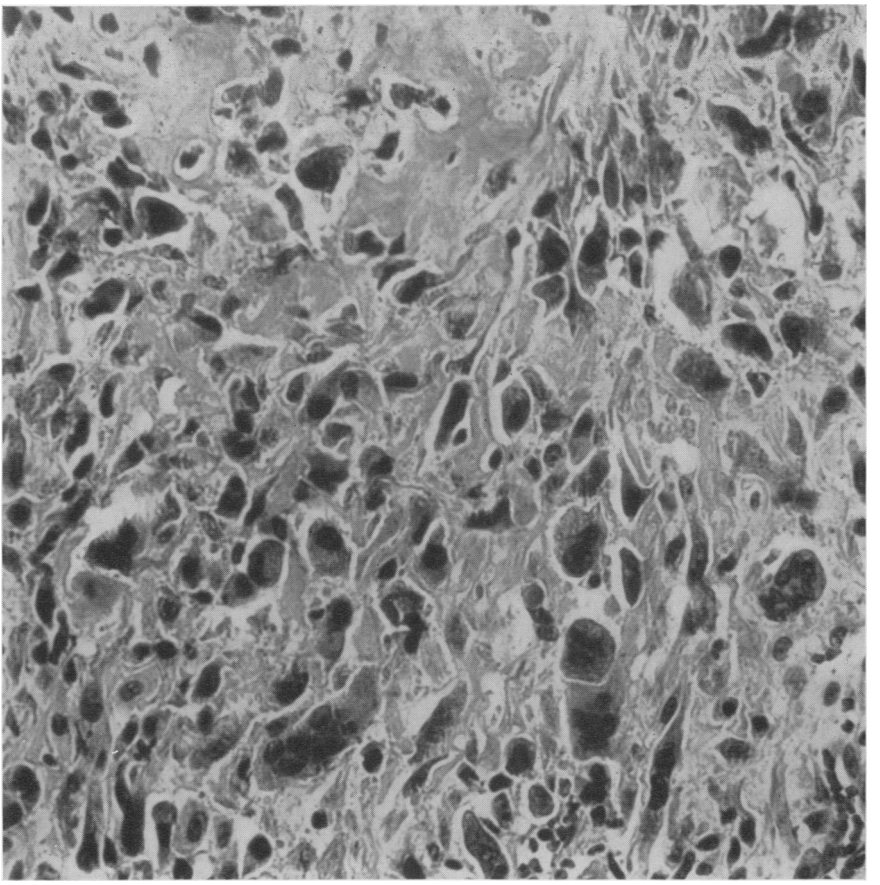

FIG. 4. Giant cells and immature osteoid formation. (H & E ×375.)

recurred and in November 1951 a wide excision of the mass was performed. A diagnosis of malignant tumor was made at this time. The tumor subsequently recurred twice and both times was locally excised. The lesion recurred for the fourth time in May 1953. This time the tumor was excised and axillary dissection was performed. The area operated upon never healed and the patient was referred to Memorial Hospital.

There was a large punched out ulcer at the base of the axilla. The tissues were indurated and immobile under the ulcer and surrounding it circumferentially for at least 10 cm. A biopsy was diagnosed as extraosseous osteogenic sarcoma. All routine laboratory studies were normal. On August 20, 1953 wide excision of the tumor mass was performed. This required excision of segments of the third to eighth ribs. The chest wall defect was closed with tantalum mesh and the wound was covered by mobilizing the breast anteriorly and skin flaps posteriorly.

The operative specimen was 26 cm. × 19 cm. A 2 cm. × 1 cm. centrally located ulcer involved the periosteum of two of the six ribs in the specimen. The inferior part of the scapula measuring 6 × 4 cm. and located at the posterior border of the specimen, was free of tumor. The specimen contained a hard, grayish-white tumor 13 cm. × 9 cm. × 3 cm. The edges of the specimen were free of both macroscopic and microscopic tumor.

The patient remained well for 10 months. At examination in July 1954 she had a nodule in the right arm. By December 1954 she had developed distant metastases and she died in January 1955. Autopsy showed diffuse pulmonary and hepatic metastases. At the time of death there was no evidence of local recurrence at the site of chest wall resection.

Case 4. A 31-year-old woman was admitted with a locally recurrent mass in her left buttock in December 1953. Approximately seven years ago a "fatty tumor" was removed from her left buttock. In the early part of 1951, an orange-sized tumor recurred at the site of the previous excision. This tumor was removed and a diagnosis of possible malignant tumor was made. Two fur-

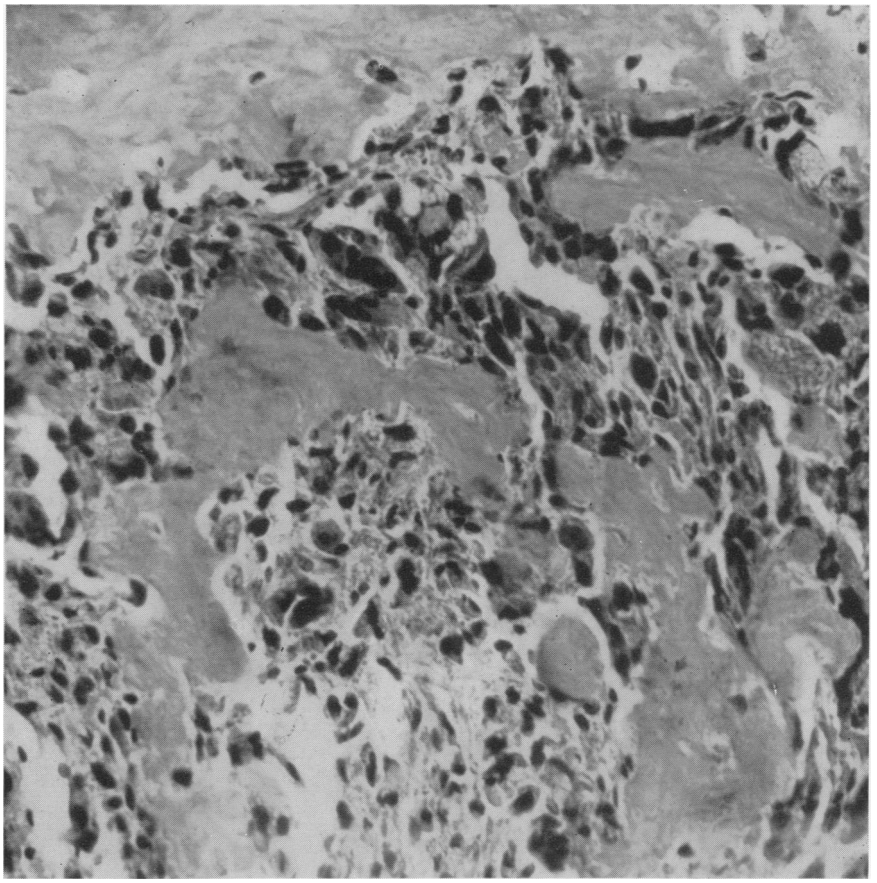

FIG. 5. Atypical and malignant osteoids. (H & E ×285.)

ther recurrences were also excised. About a month prior to this admission, she noticed some small nodules alongside the scar.

There was a 6-cm. oval mass in the region of the previous scar and five satellite nodules extending up to the sacroiliac ligaments. A wide soft tissue resection was performed.

The operative specimen consisted of a mass of fibrofatty connective tissue in continuity with underlying muscles which measured 20 cm. × 18 cm. × 7 cm. and the overlying skin measured 12 cm. × 13 cm. The specimen contained several subcutaneous tumor masses, some of which were adherent to the muscles. The largest mass measured 7 cm. × 4 cm. The cut surface was whitish-gray with varying degrees of necrosis.

The patient survived for 2 months and died of diffuse pulmonary metastases with recurrence in the primary site. Autopsy was not performed.

Case 5. A 50-year-old woman was admitted to Memorial Hospital in September 1963 with a recurrent lump in the right thigh. A lump was first noticed in 1962 and was removed. The tumor recurred promptly and was re-excised. Subsequently, the lesion recurred several times and each time was locally excised. After the last excision she received radiation therapy. By August 1963 the mass recurred again and started to grow larger.

There was a diffusely indurated swelling of the right thigh, and the skin showed signs of radiation reaction. An 18-cm. oval mass could be palpated under the scar of previous operations. Since the remainder of the physical examination and all the laboratory tests were normal, right hemipelvectomy was performed. She was discharged from the hospital in good condition.

The operative specimen consisted of the right lower extremity and the hemipelvis. The entire antero-lateral compartment of the thigh was indurated and hard, and in the center there was a large ulcerated area measuring 8 cm. × 7 cm. × 2.5 cm. The base of the ulcer was necrotic. Cut sections of the tumor revealed areas of yellowish-gray tissue and multiple hemorrhage spots. The margin of resection was apparently free of any tumor. She remained well for one year but died

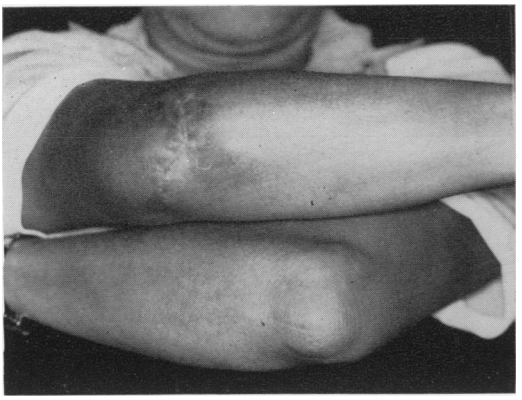

FIG. 6. Scar, induration and swelling in the right elbow of Patient 1.

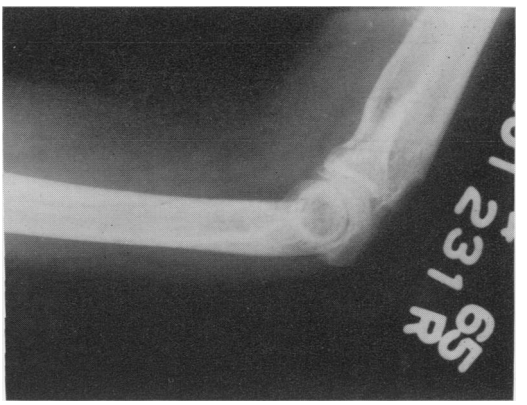

FIG. 7. Preoperative x-ray of right elbow joint in Patient 1. Note the bone destruction in the ulna.

shortly thereafter of pulmonary metastases. No autopsy was performed.

Case 6. A 33-year-old woman was admitted here in December 1966 with a diagnosis of sarcoma. In October 1966 a small walnut-sized lump was excised from her thigh and a diagnosis of a soft tissue sarcoma was made. Review of submitted slides established the diagnosis of extraosseous osteogenic sarcoma.

On admission there was no evidence of gross tumor in the thigh. The remainder of the physical and laboratory examination was negative. She was irradiated with a 250-kv. machine using a 14 × 11 cm. oval port covering the site of the primary tumor, 500 rads daily, for a total dose of 2,000 rads. Left retroperitoneal node dissection and hip joint disarticulation were then performed.

There was no evidence of residual tumor in the extremity and the lymph nodes were negative for metastatic tumor.

She remains well to date, 16 months after operation.

Case 7. A 41-year-old man was seen in October 1955 with a tumor in the right zygomatic region of three weeks' duration. An aspiration biopsy had been taken from the tumor and was reported as fragments of spindle cell tumor which could not be classified because of insufficient material. On admission there was a 3-cm. subcutaneous nodule directly over the zygoma. Wide excision of the tumor with primary closure was performed.

The operative specimen consisted of an elipse of tissue measuring 3.5 × 8 cm.; the skin measured 2.5 × 0.8 cm. The tumor was well encapsulated, about 1.7 cm. in diameter, and was located in subcutaneous tissue. The cut surface of the tumor was yellowish-grey with areas of hemorrhage. A diagnosis of extraosseous osteogenic sarcoma was established. He remains well to date, 12 years after operation.

Case 8. A 64-year-old woman was first seen in Memorial Hospital in March 1951 with a recurrent lesion in the lower end of the left thigh. About four years previously a walnut-size lump was excised from the same site. This tumor recurred and was re-excised at which time, it was diagnosed as fibrosarcoma. Following another recurrence six months ago she came to Memorial. There was a 6 cm. × 8 cm. recurrent tumor under the old scar in the region of the adductor tubercle. All the other investigations were negative and the lesion was widely excised.

The specimen consisted of the patella and attached tendon of quadriceps femoris, other muscles and subcutaneous tissue and measured 18 cm. × 13 cm. × 5 cm. There were four tumor nodules in the specimen. Two were in association with the quadriceps muscle and measured approximately 1.5 cm.× 1 cm. × 0.5 cm. One was in the subcutaneous tissue and measured 1.5 cm. in diameter and one measuring 0.5 cm. in diameter was lateral in the substance of the vastus lateralis muscle.

Although the margins of the excised specimen were microscopically free of tumor, the lesion recurred within five months. Another wide excision was performed. She remained well for 16 months when another 2-cm. nodular recurrence was excised. This excision was followed by recurrence, treated by local excision and radiation therapy; a dose of 2,700 rads was given. In September 1955 the lesion recurred for the fourth time. Amputation was then suggested but by the time the patient agreed, the lesion was fungating. A subtrochanteric amputation was performed in December 1955. The lesion measured 18 × 5 ×6.5 cm. and

TABLE 1

Patient	Age/ Sex	Location	Initial Therapy	Status of Primary at M. H.	1st Treatment at M. H.	Local Recur. after 1st M. H. Therapy	End Result
1	48 F	Elbow	Multiple local excisions	Recurrent tumor	Excision of rt. elbow jt.	None	2 Years. Living N.E.D.
2	68 M	Thigh	None	9 cm. oval tumor in infragluteal fold	Wide excision	Yes, multiple recurrences	16 months. Dead with diffuse metastases
3	53 F	Lateral chest wall	Multiple local excisions	Recurrent ulcerating tumor	Chest wall resection	None	17 months. Dead with pulmonary and hepatic metas t
4	31 F	Buttock	Multiple local excisions	6 cm. oval tumor in the region of previous scar	Wide excision	Yes	2 months. Dead with pulmonary metast.
5	50 F	Thigh	Multiple local excisions	Recurrent 18 cm. tumor	Hemipelvectomy	None	1 year. Dead with pulmonary metast.
6	33 F	Thigh	Primary tumor locally excised for biopsy	No obvious primary tumor	Groin dissection and hip joint disarticulation	None	16 months. N.E.D.
7	41 M	Zygomatic region	None	3 cm. tumor	Wide excision	None	12 years. N.E.D.
8*	64 F	Thigh	Multiple local excisions	Recurrent 6 cm. × 8 cm. tumor	Wide excision	Yes	5 years. Dead of disease
9**	44 F	Thigh	None	20 × 15 cm. primary tumor	Refused any form of oper. at at first— later hemipelvectomy	None	6 months. Dead of disease

* Patient 8 had a subtrochanteric amputation at a later date.
** Patient 9 consented to a hemipelvectomy as a last resort.

involved almost all the anterior, lateral and medial compartment muscles of the lower thigh. She was readmitted in March 1956 with multiple metastases in both lung fields and died in April 1956. Autopsy was not performed.

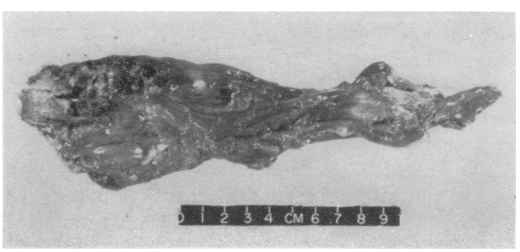

FIG. 8. Surgical specimen of first soft tissue resection in Patient 2. The whitish tumor in the biceps femoris muscle can be seen in the right end of the specimen. Apparently, this was a wide resection of the tumor.

Case 9. A 44-year-old woman was first admitted in August 1961. She noticed a painful lump in the posterior part of her left thigh about one year prior to admission. No active treatment was administered. The tumor grew, however, and she came to Memorial. There was a somewhat indistinct mass 20 cm. × 15 cm. at the posteromedial aspect of the left thigh. Aspiration biopsy showed soft tissue sarcoma. Hemipelvectomy was proposed but the patient refused any form of operation. Consequently, the tumor was radiated with 5,300 rads but it continued to increase in size. Because she still refused operation the mass was frozen with a cryogenic probe apparently without effect. In June 1962 she finally consented to a local operation. The lesion which was histo-

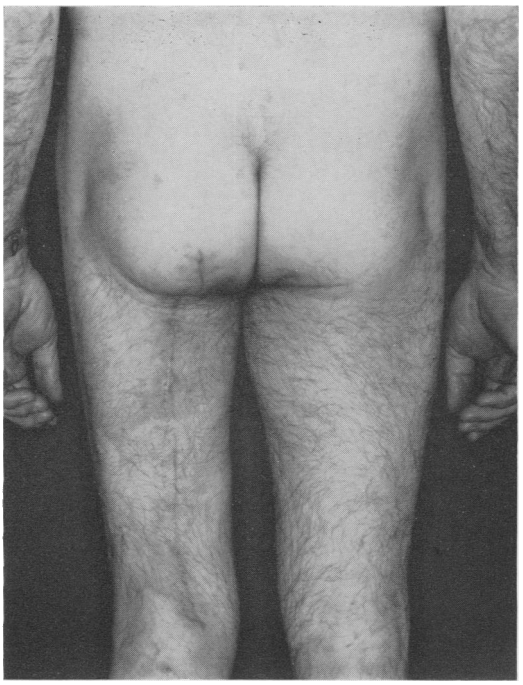

FIG. 9. The first recurrence in Patient 2. The recurrence can be seen in the middle of this long scar, characterized by change in skin color and presence of a scab.

logically diagnosed as extraosseous osteogenic sarcoma recurred promptly, and by February 1963 it was large and ulcerated (Fig. 13). At that time she consented to amputation and hemipelvectomy was performed. She tolerated the procedure well and was discharged in good condition.

The operative specimen consisted of the left lower extremity and hemipelvis. The ulcerated tumor measured 18 × 15 cm. with necrotic material seen throughout the base. The lesion involved all the posterior compartment muscles. The sciatic nerve was involved. The bones were free of tumor. Lung metastases developed and she succumbed in March 1964. Autopsy consent was not obtained.

Results and Prognostic Factors

Of nine patients with extraosseous osteogenic sarcoma one (Patient 7) is living free of disease 12 years after initial treatment. A second (Patient 8) lived for 5 years with disease. Four patients were dead within 2 years (Patients 2, 3, 4 and 5). One died 31 months after treatment (Patient 9). Two are living free of disease two years (Patient 1) and 16 months (Patient 6), respectively (Table 1).

What influences the prognosis of these highly malignant tumors is difficult to discern. Five of nine patients had recurrences after multiple local excisions. Four of these died before five years. One (Patient 1) is alive 2 years after operation. It is reasonable, therefore, that local recurrence after inadequate excision indicates poor prognosis. To avoid local recurrences and multiple inadequate excisions, it is suggested that adequate biopsy diagnosis of the primary lesion be made at the onset, following which wide excision be performed.

Review of operative specimens in wide excisions has shown that even when there was no microscopic evidence of malignant cell infiltration in the margins of resection three of five patients had locally recurrent disease at the time of death. The exceptions were Patient 2 who had a chest wall resection and Patient 8 who ultimately had an amputation. It is thus suggested that oftentimes a wide excision, is in fact inadequate therapy. Since most of these tumors occur in the extremities, theoretically the ideal treatment to improve survival rates is major amputation. It is true that in our patients amputations have not salvaged any patient, but in all but one, am-

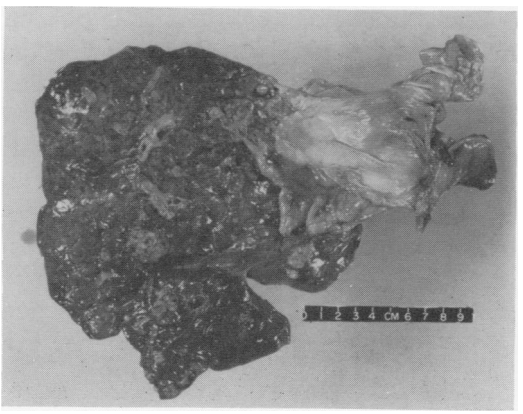

FIG. 10. Surgical specimen of the excision of the local recurrence as shown in Figure 9 in Patient 2. Note the large necrotic tumor which was underneath the scar in Figure 9.

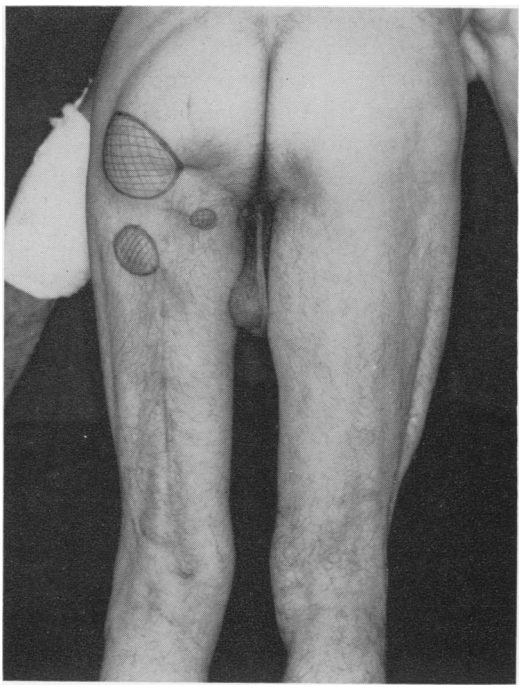

FIG. 11. Second local recurrence in Patient 2. Tumor masses are marked by crosshatches.

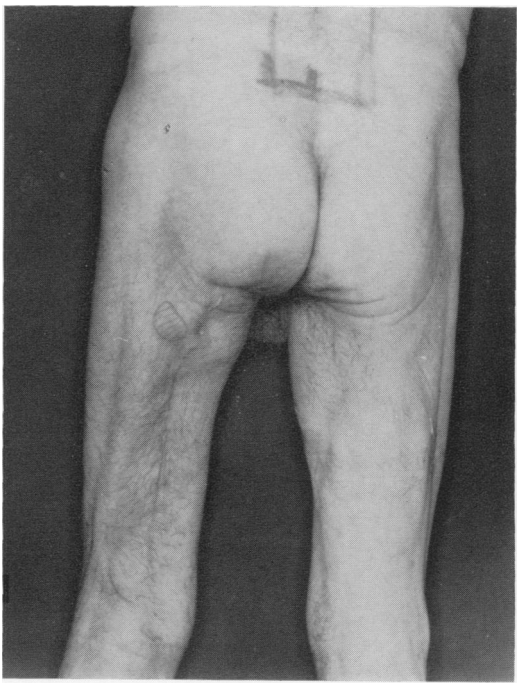

FIG. 12. The tumor masses shown in Figure 11 showed partial regression after intra-arterial instillation of nitrogen mustard. However, this regression was extremely short lived. The marked area in the lumbar region shows the size of x-ray port used.

putation was performed as a desperate measure to control local disease and not as an elective operation. Patient 6 had an elective amputation and did not have residual tumor in the extremity. She is living free of disease for 16 months. The overall prognosis is poor and an aggressive approach is possibly best.

The role of radiation therapy is difficult to assess in such a small series, but the clinical impression is that there is some beneficial effect of preoperative radiation (Patient 6). No chemotherapeutic drug is known to be of value.

The quantity of osseous tissue in the tumor and degree of mitosis does not necessarily indicate the course of the tumor or its likelihood to metastasize. No prediction of the course or prognosis of a tumor can be made by histological examination.

Discussion

The existence of extraosseous osteogenic sarcoma is clearly established.[4, 7, 17, 18] Bonneti[1] in 1700 described an osteoma of the mammary gland. Morgagni[4] in 1763, Johanes Müller[15] in 1838 and Astley Cooper[5] in 1845 described ossified tumors of the female breast. In the early part of this century Coley,[6] Rhoades and Blumgart[16] and Mallory[13] described osteogenic tumors occurring in soft tissues. Many of these tumors were histologically similar to osteogenic sarcoma of bones. Most of the tumors were described as clinically benign. Unfortunately, patients were inadequately followed. This lack of follow up gave many authors a sense of false security. Fine and Stewart[7] on the other hand after a good follow up, stated that ten of 12 patients were dead within 3 years of initial therapy. Experience with the present group of patients also shows that this type of tumor has a grave prognosis and is worse than the

prognosis in chondrosarcoma of the extraskeletal tissues.[8]

The histogenesis of extraosseous osteogenic sarcoma is not yet settled. Metaplastic ossification is known to occur in voluntary muscles[4] and in other locations.[19] Huggins[9] stressed the concept of metaplasia of connective tissue into bone due to unknown influences. Binkley and Stewart[4] in 1940 made an extensive study on the morphogenesis of extraskeletal osteogenic sarcoma and pseudo-osteosarcoma. They proposed that the most important alteration leading to the assumption of the structure of osteogenic sarcoma was laying down of dense hyaline tissue, resulting in probable ischemia and the development of a cavernous telangiectatic type of circulation favoring stasis and consequent probable anoxia. Brookes[2] in 1966 showed that in experimental animals elevation of carbon dioxide tension and red cell count promotes bone formation in an osteogenic area. Furthermore, Brookes[3] produced increased experimental osteogenesis in an environment where the pH ranged from 6.8 to 7.2, P_{O_2} about 40 mm. Hg and P_{CO_2} 50 mm. Hg. These studies are well controlled and complementary. Consequently, we feel that histological[4] and experimental[2, 3, 9] evidence is available to support the concept of metaplasia of connective tissue cells into bone.

The histopathological characteristics of this tumor have been alluded to and these criteria must be strictly adhered to in diagnosis of extraosseous osteogenic sarcoma. Radiographic evidence of calcification in a soft tissue tumor *per se* is not unusual, but concomitant elevation of the level of serum alkaline phosphatase in the absence of any demonstrable cause should suggest the diagnosis of extraosseous osteogenic sarcoma. This was the finding in Patient 2 and a correct clinical diagnosis was made. Extraosseous osteogenic sarcoma must be differentiated from benign osseous tumors of the soft tissues and atypical forms of myositis ossificans. Other ossifying lesions of the soft tissue which should be considered in the differential diagnosis include giant cell tumors of soft tissue and parosteal osteoma. The final accurate diagnosis, however, should always be made by biopsy.

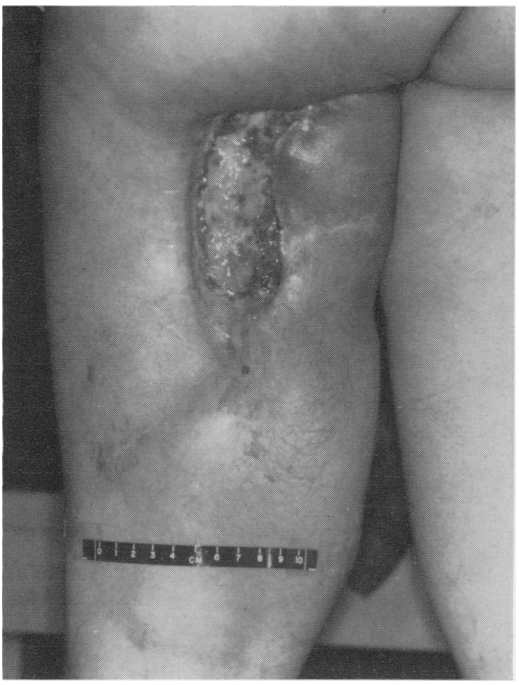

FIG. 13. Recurrent ulcerating tumor in Patient 9.

The location of the tumors correspond with that of osteogenic sarcomas of the extremities. The lower extremities were involved in six of nine patients.

Summary

Nine records of patients with extraosseous osteogenic sarcomas have been studied. Seven were women. The pathological criteria used in diagnosing these tumors have been described. Unless strict histological criteria are followed the apparent clinical incidence will be much greater. One of nine patients survived 12 years free of disease and one lived for 5 years with disease. Five patients died of cancer within 3 years. Two are living free of disease two

years and 16 months, respectively. The ultimate prognosis in patients with extraosseous osteogenic sarcoma is not favorable. Local recurrence following inadequate local excision possibly contributes to the poor prognosis. An aggressive surgical approach including major amputation is recommended as the primary form of therapy.

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