Diffuse Endothelioma of Bone*

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For some years I have been encountering in material curetted from bone tumors a structure which differed markedly from that of osteogenic sarcoma, was not identical with any known form of myeloma, and which had to be designated by the vague term "round cell sarcoma" of unknown origin and nature. I had no opportunity of following the course or learning the outcome of these cases, as most of them were treated by amputation of the limb.

Recently a case came under observation at the Memorial Hospital which revealed that this tumor is highly susceptible to radium, a fact that convinced me that the disease was entirely different from osteogenic sarcoma, which resists treatment by the physical agents.

The story of this case is briefly as follows:

A fourteen-year-old girl had been treated by an outside physician in 1918 for nasal discharge and occasional bleeding. Some ocular symptoms led to the suggestion of congenital lues, and a Wassermann reaction being weakly positive, salvarsan was administered. In November, 1918, while pulling on a rope, a spontaneous fracture of the ulna occurred, followed by swelling which gradually subsided. In January, 1919, the swelling recurred and continued with pain and disability until a well-marked tumor occupied the upper part of the arm. This tumor was noted to fluctuate in size. The veins of the skin were dilated, and the appearance led to the diagnosis of osteogenic sarcoma. Eight injections of Coley's toxins were administered at Mount Sinai Hospital, without notable effect.

On April twelfth at the Memorial Hospital a radium pack of 12,760 millicurie hours was applied to the arm, and followed by two other packs at intervals of two weeks. The tumor began to recede at once and at the end of five weeks no external swelling remained.

On admission the radiograph showed a peculiar diffuse fading of the upper half of the shaft of the radius, and a faint line from the old fracture. The outline of the slightly swollen shaft was smooth (Fig. 1); there was no bone formation, no point of perforation, or area of erosion of the shaft, all of which features told against osteogenic sarcoma. The prompt recession under radium was also quite unlike our experience with osteogenic sarcoma (Fig. 2). With the recession of the tumor the shaft was well restored and normal function regained. The patient left the hospital with instructions to return weekly for observation, which was continued for several months.

The patient then came under the care of her original physician who noted persistence of the nasal and ocular symptoms, and, regarding the tumor of the radius as luetic, he instituted vigorous treatment by salvarsan. The injections, however, were followed by severe toxic symptoms, vomiting, bloody urine, collapse, and

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progressive anemia. Later injections of cacodylate of sodium were administered for the anemia. The patient failed steadily and the tumor of the arm began to reappear. There was now an irregular fever up to 103°F. The urine failed to show Bence-Jones protein.

In October, 1920, the patient returned to the Memorial Hospital with a definite recurrence of the tumor, and owing to the conflict of opinion, a portion of tissue was removed for diagnosis. It proved to be a round cell growth of the above-mentioned type. Other tumors had now appeared plainly in the skull. There was exophthalmos. The eye grounds showed choked disc and nerve atrophy. The radiograph of the lungs was negative. Anemia and cachexia progressed rapidly, and death occurred on December 23, 1920. The total duration was about thirty months.

During the past four months I have seen six other cases of this disease. They occurred in subjects from fourteen to nineteen years of age. The bones affected were tibia, ulna, ischium, parietal and scapula. The tumors grew rather slowly, requiring some months to attract attention, but they were accompanied by attacks of pain and disability. One boy complained only of intermittent attacks of pain after exer-
exercise during the summer, but in November a smooth swelling appeared over the upper half of the leg. Several tumors were found to fluctuate in size, a symptom due to their vascularity. All were rather painful and tender.

The radiographs give characteristic features on which a diagnosis may be based with considerable certainty. A large portion or the whole of the shaft is involved, but the ends are generally spared, contrary to the rule with osteogenic sarcoma. The shaft is slightly widened, but the main alteration is a gradual diffuse fading of the bone structure. Bone production has been entirely absent. Some of the bones appeared honeycombed. Perforation of the shaft and sharp limitation of the process are wanting. The central excavation with widened bony capsule, as seen in benign giant cell tumors, is missing. The radiograph is therefore rather specific.

Under radium treatment the tumor recedes and the shaft gradually becomes well defined with little deformity and no eccentric bone formation.

In seven cases the tissue was examined microscopically, and in all the structure was nearly identical. The growth was composed of broad sheets of small polyhedral cells with pale cytoplasm, small hyperchromatic nuclei, well-defined cell borders, and complete absence of intercellular material. Hydropic degeneration often affects large islands of cells, in which only nuclei and cell borders are visible. Necrosis occurred after radium applications. There is very little desmoplastic quality, but the tumor cells readily infiltrate muscle and pass along the fasciae. In none were pulmonary or other forms of metastases observed. In the case cited the tumors of the skull were regarded as primary and of long standing. In some sections the cells were of increased size, while in others they were smaller and more compact, and approached the morphology of plasma cells. However, no definite areas of plasma cells have been seen in any case.

The probable endothelial nature of the tumor was suggested by the form of the cells, and especially by the appearance in broad sheets of polyhedral cells without intervening stroma (Fig. 3). This origin, however, did not seem to be fully supported until I encountered sections in one case in which the cells were found to line a complex series of fine channels inclosing intact blood (Fig. 4). Here the endo-
The thoracic character of the cells was quite pronounced, but they were much smaller than those occurring in angio-endothelioma, with which this tumor is doubtless closely related. In other portions of the same growth the cells appeared in diffuse sheets without capillary lumina, as seen in the other tumors of the series.

The exact point of origin of the growth is not clear, but the early rarefaction of the bone indicates that the disease begins in the blood vessels of the bone tissue. Yet an involvement, simultaneous or early, of the vessels of the bone marrow can not be excluded. In the discussions of multiple endothelioma in the literature some authors thought they could trace the origin to the vessels, blood or lymph, of the periosteum. Many multiple endotheliomas, as in Markwold's case, have appeared well within the bone marrow.

The designation of the tumor as endothelioma rather than as myeloma seems advisable, since myeloma is properly reserved for tumors derived from the specific cells of bone marrow.

The possible relation of the endothelial tumor to plasma cell or other forms of multiple myeloma deserves consideration, but the evidence at present available indicates that the two processes are distinct. I have found no definite plasma cells in any of the specimens. Plasma-cell myeloma is nearly always multiple and often very widespread. Bence-Jones protein has not appeared in any of the cases of endothelioma, but is often absent in myeloma. Multiple myeloma also perforates the bone rapidly and destroys it completely, while these tumors cause slow, rather diffuse rarefaction.

A relation to the angio-endotheliomas and other forms of endothelioma, solitary and multiple, described in the literature, must be assumed to exist. Most of these tumors accessible in the literature have occurred in adults and were clearly recognized as endothelioma. All the tumors of the present series have occurred in children, and with one exception they have been solitary.

The main point of the present communication lies in the demonstration that there is a rather common tumor occurring in young subjects, commonly identified with osteogenic sarcoma, and usually called round cell sarcoma, which is really of endothelial origin, and which is marked by such peculiar gross anatomical, clinical, and therapeutic features as to constitute a specific neoplastic disease of bone.

Special Announcement—Cancer Chemotherapy Conference

A National Conference on Cancer Chemotherapy, sponsored by the American Cancer Society and the National Cancer Institute, will be held at The Biltmore Hotel in New York City on June 1, 2 and 3, 1972. This conference will bring to the medical and related professions the most recent advances in the clinical application of chemotherapeutic agents in the management of cancer. For information, please contact Sidney L. Arje, M.D., Coordinator, American Cancer Society, 219 East 42nd Street, New York, N.Y. 10017.