RADIOTHERAPY FOR ENDOTHELIAL MYELOMA 1

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Like the movement of radiant energy, the acquisition of knowledge seems to proceed by quanta. For long periods knowledge in certain directions may remain at a standstill, while at other times it may increase either by small accretions or by one or a series of more important steps. In the field of bone tumors, knowledge had been practically stationary for many years. Most malignant tumors affecting the skeleton were designated as one or another variety of sarcoma, and for a pathologist to violate this tradition was to risk incurring discredit. With reference to the character of neoplasms in general, the medical profession had largely come to accept, and still accepts, the dictum of the pathologist as law. In many quarters, in fact, the verdicts of the pathologist are accepted altogether too blindly, and often clinical, radiologic, and other factors are not given due consideration.

In 1921 Ewing described a variety of bone tumor usually affecting the tibia, fibula, humerus, ulna, femur, ischium, and skull or scapula of young subjects, growing rather slowly, requiring months to attract attention, and accompanied by swelling, intermittent pain, disability, and sometimes by fever. Such growths commonly involve a large portion of the shaft of long bones, although flat bones also may be affected; they usually spare the extremities of the bones, and present roentgenologic features which, at certain stages and in the majority of cases, are almost pathognomonic. These roentgenologic characteristics include absence of bone production, fading and sometimes honeycombing of the bony structure, comparatively slight widening of the shaft, and a peculiar laminated appearance of the peripheral portion of the bone corresponding to the periosteum (except in flat bones). In some cases, however, the roentgenologic appearance for some time after the onset is inconclusive and not infrequently is thought to represent an inflammatory condition of the bone. Another significant and distinctive feature is that, unlike all other bone tumors, the neoplasm

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in question is remarkably sensitive to radium and roentgen rays. Indeed, the exceptional susceptibility of the tumor to radium was one of the peculiarities which convinced Ewing that this variety of neoplastic disease is entirely different from osteogenic sarcoma.

Although Ewing's classical description was published ten years ago, and although many other communications on the subject have appeared during the interval, many otherwise well informed members of the profession are unfamiliar with this neoplasm, and pathologists continue to classify such tumors as osteogenic or as round-cell sarcomas. Unfortunately, the classification of bone tumors in general remains one of the most confusing phases of medicine. Even among those pathologists who agree with Ewing that this neoplastic disease deserves to be classified separately, few have accepted his designation of "diffuse endothelioma of bone." Kolodny suggested the term "endothelial myeloma," under which the tumor is now most commonly known, but others still follow Ewing's lead in rejecting the implication of myeloma, which he thought should be "reserved for tumors derived from the specific cells of bone-marrow." Many continue to designate such tumors as endothelial myelomas or hemangio-endotheliomas, probably because they are waiting until a larger series is available for critical study. Another reason undoubtedly is that few pathologists are familiar with the difference in radiosensitivity between different varieties of normal and malignant cells and, consequently, are unable to estimate the relative import of this factor. Pathologic clarification, therefore, must await the scrutiny of a larger number of cases and increasing realization of the significance of the specific radiosensitivity of different kinds of cells as an aid in their identification.

Among tumors of bone, only three varieties show an appreciable degree of radiosensitiveness. The so-called benign giant-cell tumor reacts to radium or roentgen rays in a peculiar and characteristic manner. Two or three weeks after irradiation, the growth, instead of undergoing gradual retrogression for a time or remaining unaffected, as do all malignant neoplasms of bone or soft tissues, begins to swell, and the swelling is accompanied by redness and pain. This may continue for a number of weeks. If the patient or the attending physician has not been forewarned, he may quite naturally conclude that the rays have actually stimulated the tumor to increased growth, and this assumption may result in unnecessary sacrifice of the affected limb. After from three to six
weeks this acute reaction subsides spontaneously, and after the lapse of several months roentgenograms of the bone generally show deposition of fresh bone. In time the entire tumor may be replaced by solid bone. This kind of reaction differs entirely from the behavior of malignant tumors and supports the view that giant-cell growths are chronic inflammatory lesions, at least at the outset. The fact that some of these tumors ultimately acquire malignant features does not affect the apparent validity of this deduction. All true tumors, benign as well as malignant, regress rapidly or slowly, remain stationary, or continue to grow at the same rate as before irradiation.

Of the malignant tumors of bone, the diffuse endothelioma of Ewing is by far the most radiosensitive. The rate at which such neoplasms regress after exposure to the rays suggests a more than coincidental relation to lymphogenous disorders, such as those observed in lymphoblastoma. The rate of regression of endothelioma so closely approximates that of lymphosarcoma or Hodgkin’s disease that one is led to infer a definite relationship. At any rate, among bone tumors the susceptibility is quite exceptional. The only other bone tumor which can be said to be radiosensitive is chondrosarcoma, but the susceptibility of the latter variety is much less than that of the former. The difference is so great that confusion is practically impossible. Osteogenic sarcoma, on the contrary, can hardly be said to be radiosensitive. Rather, it is characterized by its great resistance to radiation. Few such tumors can be made to regress to an appreciable degree, even by the most intense irradiation. In fact, increasing experience with radiotherapy for bone tumors makes it seem more and more likely that, whenever such a tumor proves unusually sensitive and diminishes rapidly in size or disappears, temporarily or permanently, after irradiation, it is an endothelioma, regardless of any classification based on microscopic appearance. It will be interesting to see whether this somewhat heretical assumption will be sustained by future investigations.

There cannot be any question that the condition described by Ewing represents a specific disease. Even if its course and symptoms, as well as its anatomic and roentgenologic peculiarities, were not so characteristic as they usually are, its reaction to irradiation is so absolutely different from the reaction of any other kind of bone tumor that this feature alone would be sufficient to serve as a distinctive sign if we could be certain that the radiosensitiveness of
all growths of this kind is uniform and unvariable. Until the range of such variation can be ascertained, the value of radiosensitivity for identification cannot be regarded as absolute. In the meantime, no one can deny that this feature is more important for differential purposes than either the history or roentgenologic data alone. Some of those who have written on the subject have stressed the multiplicity of such tumors. Some have even expressed the idea that the condition may be multiple from the start.

But, as Connor has pointed out, in only three of the fifty-four cases studied by him were multiple tumors present. On the other hand, the frequency with which, at necropsy, multiple lesions are found in the skull, vertebrae, other bones, lungs, and lymph nodes, points to metastasis rather than to simultaneous, independent involvement.

The main object of this communication is to bring out the diagnostic significance of radiosensitivity. Certainly, biopsy does not invariably settle the diagnosis. As expressed by Syca- more and Holmes, the "discouraging results obtained in osteogenic sarcoma by even the most radical surgery" and "the difficulty which most pathologists seem to have in differentiating endothelial myeloma from osteogenic sarcoma" give point to Ewing's advocacy of irradiation as a diagnostic test as well as a therapeutic procedure. But if such a test is to be made, the manner of irradiation is as important as the dose of rays administered. The mere exposure of
such a tumor to a roentgen tube or to a small quantity of radium for a short time does not necessarily constitute an adequate test. The following cases are presented as examples.

**Case 1:** A man aged forty-eight years registered at The Mayo Clinic July 28, 1930. He complained of swelling of the right shoulder. One day, four years previously, while he was attempting to start his motor by manual cranking, the handle suddenly and forcefully reversed. He was immediately conscious of a sharp pain around the right shoulder, and

![Fig. 3. Case 1: Roentgenogram, July 29, 1930, Showing Massive Disintegration of Bones of the Right Shoulder](image)

The volume of the tumor was so great as to obscure some of the bone features. The pain persisted several months. Then he noticed in the scapular region a small lump which gradually increased in size and became tender. One year following the accident, the mass was removed surgically, and the patient was told it was a sarcoma. One year later, a small lump appeared in the right suprascapular region and was promptly excised. One year prior to his arrival at the clinic, another mass had appeared in the right scapular region and a third attempt at excision was made, the patient being told that the mass represented a necrotic abscess. Later in the same year, another recurrence developed, and the patient was subjected to a fourth operation. Four months had not elapsed before the tumor had again recurred. Since then it had grown steadily. Constant and severe
pains had interfered with sleep; mechanical hindrance by the growth and the resulting weakness had made all work impossible for some time. In spite of the disability, however, the general health had not been appreciably affected.

When the patient undressed for examination, the right scapular region was abnormally prominent. A large, bulky, hard and fixed tumor appeared to have originated in the upper half of the scapula but now projected not only backward but upward (supraclavicoloscapular space), and even anteriorly, where it caused the right pectoral muscles to bulge forward (Figs. 1 and 2). Roentgenologic examination, July 29, 1930,

![Figs. 4 and 5. Case 1: Arrangement of the Treatment Fields over the Posterior, Superior, and Anterior Surfaces of the Region Occupied by the Tumor](image)

The arrows indicate that the beam of rays directed to each of the fields was to converge toward the center at an angle of 45°.

revealed a neoplasm affecting the upper part of the right scapula and giving the impression of osteogenic sarcoma (Fig. 3). When a piece of tissue from the neoplasm, obtained from the surgeon who had tried several times to excise it, was examined by the pathologist, it was found to be hemangio-endothelioma, otherwise known as Ewing's tumor.

The site of the growth and its projection backward and upward were such as to offer an excellent opportunity for treatment by the method of multiple converging beams. As may be seen from Figs. 4 and 5 the posterior and superior aspects of the mass were divided by indelible lines marked on the skin into five fields, and two additional fields were outlined on the anterior or pectoral surface. Through the five posterior and superior fields the posterior, or proximal, half of the tumor was exposed to as many beams of rays of short effective wave-length, each directed toward the center of the growth at an angle of 45° for the posterior fields and perpendicularly to the surface for the superior field. Through the two anterior fields the neoplasm received in addition two beams of rays
of short effective wave-length, focused as accurately as possible on the center of the tumor. Such was the scheme of treatment as outlined. The first course of roentgen irradiation according to this plan was given between July 31 and August 14, 1930, in seven daily sessions, except for an interval of nine days between the third and fourth sessions. The interval of nine days was not originally intended. Shortly after the third daily irradiation, the patient complained of severe and almost constant pain around the right hip. The treatment was perforce interrupted. After three days the pain in the right hip, for which a satisfactory explanation could not then be found, began to subside. Roentgenologic

examination of the pelvis brought a negative report. Nevertheless, the circumstances suggested the possibility of metastasis so strongly that the pelvic roentgenograms were reviewed (Fig. 6) and a metastatic lesion of the ilium, at the anterior superior spine, was found; this had previously been mistaken for gas in the colon.

The primary tumor melted away with astonishing rapidity, as may be seen from the photographs taken six weeks later (Figs. 7 and 8).

The patient received a second course of treatment between Oct. 8 and 13 and a third course between Dec. 16 and 18, 1930. Each time several beams of rays of medium effective wave-length were directed, at an angle of 45° through as many separate fields, toward the posterior, proximal surface of the tumor (prominent scapular aspect), but the growth having retrogressed so much, the number of fields was reduced from five to four.
and at the third course of treatment only one large anterior field was exposed to rays of short effective wave-length. The metastatic focus in the right ilium also was irradiated and retrogressed quite as rapidly.

During the last year the patient has been entirely well and has been able to pursue all the arduous labors associated with life on the farm. Repeated examinations have failed to give any indication of recurring malignant activity. The case is cited mainly to illustrate the rapidity of regression so characteristic of this variety of tumor. The lapse of time

![Figs. 7 and 8. Case 1: Patient Six Weeks after the First Course of Roentgen-Ray Treatment](image)

Marked retrogression of the tumor with corresponding improvement in general condition and in the function of the right shoulder.

has been altogether too short to warrant speaking of cure. This is not an impossible hope, however, since another patient with similar but even larger tumors affecting the same bones has been free from any sign of neoplastic activity for eight years.

**Case 2:** A man, aged fifty-six years, registered at the clinic June 11, 1923. In December 1922, the patient had begun to suffer from pain in the back and around the right shoulder; the pain seemed to be more severe during inclement weather. Later the pain in the back shifted to the left hip and was accompanied by pruritus and slight nocturia. At times the pain was severe and radiated toward the scrotum. In January 1923, after an attack of severe pain followed by hematuria for twenty-four hours, the patient had passed a renal stone, but the bleeding and pain subsided and did not recur. During the first six months of 1923, a swelling of the left buttock and of the right scapular region was noticed, and this gradually increased.

General examination disclosed moderate pallor, functional disability of the right upper extremity caused by a large, firm tumor measuring 11 by 12 cm. in the region of the right scapula, and partial disability of the left lower extremity caused by a second tumor, measuring 15 cm. in
FIG. 9.  CASE 2: THE RIGHT SHOULDER, JUNE 13, 1923
A destructive process affecting the right scapula may be noted.

FIG. 10.  CASE 2: THE PELVIS, AUGUST 9, 1923
A destructive process in the left ilium, corresponding to the large overlying tumor in the soft parts may be noted.
diameter, in the left posterior iliac and gluteal regions. Both tumors were fixed firmly to the corresponding bones, roentgenologic examination of which revealed a destructive process (Figs. 9 and 10).

Each tumor was exposed to roentgen rays of short wave-length in June, August, and November, 1923, and March, 1924. Both tumors decreased rapidly in size and disappeared completely, and the functional disability was entirely relieved; the patient returned to work and has worked regularly ever since. The patient is still well. The second series of roentgenograms, made May 18, 1927, shows remarkable regeneration of both bones (Figs. 11 and 12).

Figs. 11 and 12. Case 2. The Right Scapula and Left Half of the Pelvis
May 18, 1927

In the scapula complete regeneration of the bone has taken place. Retrogression of the tumor in the ilium has occurred, but abnormal repair of bone has taken place, probably because treatment was a little too intense.

Both neoplasms unmistakably originated in the respective bones. The fact that, in the second case, the tumor in the left ilium was larger than the growth in the right scapula probably means that the latter was secondary to the former, but the possibility of multiple independent tumors cannot be excluded forthwith. In the first case, on the contrary, there can hardly be any doubt that the growth in the right scapula was the primary lesion and that the lesion in the left ilium represented metastasis.

Case 3. A girl, aged nine years, had a tumor involving the upper third of the right humerus, with spontaneous fracture. In this case, also, the neoplasm retrogressed rapidly and completely, and as far as the tumor is concerned, she has been quite well ever since. However, so intent were we on destroying the tumor that treatment by the method of multiple converging beams was pushed to the utmost limit of tissue tolerance.
The result has been abnormal, although solid, repair of the affected portion of the humerus. Also, such intense irradiation at her age has interfered with the growth of the bone and the muscles around the shoulder girdle. Nevertheless, the child is able to swim and to play tennis.

**CASE 4.** A girl, aged eight years, had a tumor involving the lower third of the femur. Roentgen irradiation caused this to retrogress at the rate peculiar to endothelial myeloma. The growth and symptoms disappeared and the child recovered completely. She was well for more than a year. At her next examination, evidence of malignant activity at the

![Fig. 13. Case 4. Photomicrograph (from Frozen Section) Showing Microscopic Appearance of the Tumor](image)

site of the primary tumor or of metastasis to other bones or to the lungs could not be found, but the thoracic roentgenograms disclosed an abnormally large heart. Electrocardiographic studies gave indications of a lesion in the wall of the left ventricle. For a few weeks the symptoms were ambiguous, but later decompensation set in and when the child died soon afterward, a metastatic focus in the wall of the left ventricle was discovered; this was the only evidence of metastasis.

In the first and fourth of these cases microscopic examination of tissue showed endothelial myeloma or hemangio-endothelioma;
in the second and third cases biopsy was not performed. It may be objected that, since the character of the neoplasm in these two cases was not verified by microscopic inspection, they cannot be accepted as authentic examples. But it may not be impertinent to reply that until pathologists can be more consistent in the histopathologic identification of bone tumors in general, and until sufficient light has been shed on this type of tumor to enable pathologists to recognize it with greater accuracy, the history and radiosensitivity of diffuse endothelioma (Ewing) or endothelial myeloma (Kolodny, Sycamore and Holmes) must be regarded as more significant diagnostic features than microscopic examination. Moreover, the increasing significance of the specific radiosensitivity of different varieties of cells makes it essential that, in any future attempt to establish differential criteria for this group of tumors, this factor should receive due consideration. In the four cases which have been recorded the tumors retrogressed at almost exactly the same rate. Any difference between them in this respect could be accounted for by variation in the conditions of irradiation.

In a recent review of the so-called proved cases of this kind examined and treated in The Mayo Clinic between 1920 and 1930 I found a total of 43 cases. Seven of the patients were aged less than ten years, 11 were from ten to twenty, 9 from twenty to thirty, 5 from thirty to forty, 7 from forty to fifty, 2 from fifty to sixty, and 2 were from sixty to seventy. The comparative frequency with which different bones were involved was as follows: femur, 18 cases; humerus, 4 cases; scapula, 3 cases; clavicle, 3 cases; fibula, 3 cases; tibia, 2 cases; ulna, 2 cases; radius, 1 case; bones of foot, 2 cases, and other bones, 2 cases.

The original intention had been to analyze this series of cases with reference to different phases, including specifically the value of radiotherapy. On reviewing the pathologic diagnoses recorded, it was at once obvious that, before any real analysis could be made and before anything like reliable data could be derived from the cases of this group, a thorough and painstaking scrutiny of the pathologic material must be undertaken. Among the pathologic designations given at the time of examination were endothelioma, hemangio-endothelioma, endothelial sarcoma, angiosarcoma (Ewing), malignant endothelioma, and lympho-angio-endothelioma-sarcoma. In the majority of cases, also, surgical measures (partial or complete excision of the tumor, or amputation) were the first therapeutic step, and radiotherapy was instituted sooner or later
after operation in an attempt to prevent recurrence. Therefore, any data gathered from the records of these cases could be of little value until the pathologic classification of the tumors has been carefully revised. As long as such classification remains as uncertain as it now is, the end-results of treatment by radium or roentgen rays cannot be ascertained.

BIBLIOGRAPHY


