A FURTHER CONSIDERATION OF EWING’S SARCOMA

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Since Ewing’s first report of a previously unrecognized tumor of bone derived from endothelial elements (1), there have been numerous reports of tumors which have conformed with his endothelial myeloma, and others which have sought to deny the existence of such a tumor. Among these was an article by the present writer (2) agreeing almost entirely with Ewing’s conclusions. Kolodny (3) believed that this tumor should be put into a different group from the purely endothelial or angio-endothelial tumors. Geschickter and Copeland (4), in 1930, suggested that Ewing’s tumor might arise from the vessels of the haversian system, but in their book (5), published the following year, classified it as a primary lymphosarcoma. Hirsch and Ryerson (6) have taken particular exception to the contention that the Ewing sarcoma may be a specific type of tumor and have reported cases to support their opinion that most or perhaps all of these growths are metastatic from an internal or visceral source. More recently Colville and Willis (7) have reported tumors of the neuroblastoma type which gave rise to bone metastases simulating Ewing’s tumor of bone. These writers believe that many such tumors have been erroneously classified as endotheliomas.

I am now certain that among the group of tumors reported by me in 1926 (2) as Ewing’s tumor, there were a number which were undoubt edly cases of multiple myeloma or lymphosarcomatosis with metastases to bones. The usual and just criticism has been that autopsies were not performed on most of the recorded cases, and that without a complete examination post mortem, a primary visceral tumor could not be excluded. Since my earlier report I have had the opportunity of performing autopsies upon several important cases which may clarify the subject somewhat.

CASE REPORTS

Case 1: Solitary Diffuse Endothelial Myeloma (Ewing’s Sarcoma) of the Scapula: 1

A. B., a white woman of thirty-one, began to have pain in the right arm and shoulder in August 1931. In November of the same year an x-ray diagnosis of Ewing’s sarcoma of the scapula was made. There was a rarefying tumor of the bone producing a laminated structure and the periosteal fraying considered typical of Ewing’s tumor (Fig. 1). X-ray treatments slightly reduced the size of the tumor, but in a few months it began to grow rapidly and shortly exceeded its original size. By Jan. 5, 1932, a marked destruction of the bone was visible roentgenographically, and a large extra-osseous tumor was palpable. The patient, who was of a nervous temperament, went into a condition of

1 Recorded through the courtesy of Professor A. C. Reed of the University of California Medical School.
FIG. 1. CASE 1: RAREFYING TUMOR OF THE SCAPULA AND SOFT TISSUES AROUND IT, A RATHER CHARACTERISTIC ENDOTHELIAL MYELOMA

FIG. 2. CASE 1: ANTERO-POSTERIOR VIEW OF TUMOR SHOWN IN FIG. 1
cyclic vomiting following x-ray therapy, and in spite of treatment instituted with full knowledge of the physiological conditions involved, developed a paralytic ileus, peritonitis, and bronchopneumonia, with death six months after the onset of her illness. There had been no Bence-Jones protein in the urine, and the blood showed only a slight terminal rise in leukocytes.

The autopsy was performed forty-five minutes post mortem. There was a remarkable dilatation of the stomach and duodenum (paralytic), with an early colon bacillus (by culture) peritonitis, and diffuse bronchopneumonia. The tumor was single, no metastases being found, although a head examination was not permitted. Skull metastases could not be found by palpation. Skull metastases could not be found by palpation. The tumor involved all of the scapula, projecting backward about 6 cm. and forward about the same distance. Laterally it projected into the axilla, and several extensions had grown between the ribs. It was covered by a pseudo-capsule of muscle and fascia.

**FIG. 3. CASE 1: PHOTOMICROGRAPH OF TUMOR (× 400)**

The cells of the tumor in no way resemble those of a metastatic tumor; they do not conform to the type found in multiple myelomas, and all characteristics of an osteogenic sarcoma are lacking.

On section the tumor was of a creamy-gray color, very cellular, and in places necrotic (Fig. 2). There was a moderate amount of connective tissue running through it in narrow bands. The bone had largely been destroyed and was easily broken.

Histologically the tumor cells were relatively small, contained round or oval nuclei with sparse, scattered chromatin particles. The cytoplasm in many cells was abundant and did not stain (hematoxylin and eosin, and Giemsa), but in others took a slightly bluish tinge. The cells were uniform in size, formed no intercellular substance, and no fibrillae. These were not the irregularly shaped cells of an undifferentiated myeloblastoma and none of them displayed the features of the lymphocyte series of cells (Fig. 3).

This is the only case, so far as I can find, of an endothelioma of bone which was single at autopsy. Due to an unusual chain of circumstances, the patient died before the full effects of x-ray treatment could
be demonstrated, and before metastases could occur. Since all of the body was examined except the contents of the skull, it seems reasonably certain that the primary tumor was in the scapula, and, from the histology, that it was not an osteogenic sarcoma. The tumor does not in the least resemble a lympho- or myelosarcoma. It ought to be, by exclusion if for no other reason, an endothelial tumor of bone or, in other words, a Ewing's sarcoma.

Case 2: Endothelial Myeloma with Multiple Bone Metastases and Metastasis to the Lungs: R. M., a boy of six, complained of pain and swelling of the left leg beginning about Aug. 10, 1929. For a month this was treated as inflammatory. The child was admitted to the University Hospital (service of Dr. H. H. Markel) on Nov. 6, 1929, with the diagnosis of a bone tumor. The roentgenologist (Dr. R. S. Stone) reported a marked bulging of the upper half of the shaft of the left fibula, which increased the diameter of the bone to about three times its normal size. The position of the original shaft could still be seen, but the entire structure had been destroyed by an osteolytic process. Outside the line of the shaft was new bone laid down in radiating spicules. The periosteum was elevated at the edge of the tumor and formed a slight lipping. The tumor extended to, but not beyond the epiphyseal line. It was not definitely limited to the shaft end (Fig. 4).

There was slight benefit from x-ray treatment, but metastases occurred to the left jaw, right femur, skull, and lungs. The lung shadows responded temporarily to x-ray

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Fig. 4. Case 2: A Tumor Which has Some of the Characters of an Osteogenic Sarcoma and Others Which are Said to Be Peculiar to an Endothelial Myeloma

Much of the new bone formation followed x-ray treatment.
treatment, but rapidly reappeared, and the child died March 28, 1930, less than eight months after the apparent onset.

At autopsy the tumors recorded above were found, and the lung shadows proved to be of neoplastic origin. There were no other metastases to internal organs, and none to lymph nodes. The primary tumor (Fig. 5) occupied fully half the fibula, was fusiform in shape, filled the marrow cavity, and had grown around and up and down the shaft beneath the periosteum. The subperiosteal portion was composed largely of rather firm tissue having a radiating pattern, while the remainder of the tumor (in the medulla and surrounding soft tissues) was soft, very cellular, and in places necrotic.

Histologically the tumor is composed of rather undifferentiated cells, which at the same time are characteristic (Fig. 6). The absence of stainable cytoplasm, the lack of cell membrane, and the absence of intercellular structures are features constantly linked with undifferentiated endothelial tumors. The nuclei are roughly oval, slightly elongate, or round. Some contain indentations, and some are definitely kidney-shaped. The relatively sparse, scattered endothelial granules are likewise characteristic of primitive types of endotheliomas.

This is a rather usual type of tumor occurring in a boy and first diagnosed as osteomyelitis or osteo-arthritis. The x-ray picture is somewhat irregular, as it displays radiating spicules of bone. However, this character, which has been erroneously assigned exclusively
to osteogenic sarcoma, may be displayed by any bone tumor, primary or metastatic. I have shown that a transplantable endothelioma of chickens (9) may produce new bone in exactly the same manner as a transplantable fibrosarcoma, and that both types of cells may become osteoblasts upon occasion. We no longer wonder at the ability of mesenchymal cells to differentiate into a variety of adult types which may be endothelial cells forming capillaries, fibroblasts forming connective tissue, osteoblasts forming bone, or chondroblasts forming cartilage. It is not surprising, therefore, that an endothelial-cell tumor, under the influence of radiation (which may destroy cells completely or possibly cause a cell to become more mature) may become an osteoblastic tumor, and so present the external characters of an osteogenic tumor.

**FIG. 6. CASE 2: PHOTOMICROGRAPH OF TUMOR (X 800)**

Cells with faint or non-staining cytoplasm with oval or indented vesicular nuclei are believed to be characteristic of this type of tumor. There is no intercellular substance and the cells do not resemble those of the lymphoblastic or myeloblastic series.

**CASE 3: Endothelial Myeloma of the Femur with Metastases to the Skull and Lungs.**

R. P., a boy of five, began to limp with the left leg six months before admission to the Children's Hospital, San Francisco, Oct. 16, 1929. Tenderness developed at the same time, but although an operation had been advised, nothing had been done in the way of treatment. Five months later the left eye began to protrude.

Upon examination there were pain and limitation of motion in the left hip with the foot turned out. There was no palpable swelling. The left eye was protuberant, the eyeball elongated, and the muscles distorted. Other organs were essentially negative. Red blood cells and white blood cells were present in normal numbers. A blood Wassermann test was negative. The urine was negative.

An x-ray of the left femur, Oct. 16, 1929, showed a destructive process involving the upper third of the bone, with elevation of the periosteum, new bone regeneration, and soft tissue swelling. The presumptive diagnosis was malignant tumor, probably osteogenic sarcoma (Fig. 7). On Oct. 24, 1929, x-ray pictures were made of the chest, skull,

2 Case of Dr. George McChesney, San Francisco.
CASE 3: DESTRUCTIVE TUMOR OF THE HEAD AND SHAFT OF THE FEMUR WHICH WAS DIAGNOSED ENDOTHELIOMA FROM A BIOPSY SECTION

FIG. 7. CASE 3: DESTRUCTIVE TUMOR OF THE HEAD AND SHAFT OF THE FEMUR WHICH WAS DIAGNOSED ENDOTHELIOMA FROM A BIOPSY SECTION

FIG. 8. CASE 3: TUMOR SHOWN IN FIG. 7 FOLLOWING X-RAY TREATMENT
This tumor remained stationary for a period of over two years.
sinuses, and bones of the lower legs, all of them proving negative. A biopsy specimen from the femoral tumor was diagnosed Ewing's sarcoma, and x-ray treatments were started Nov. 6, 1929. Two treatments to the eye, and four to the femur caused marked improvement, but on Jan. 30, 1930, the eye again became swollen. One other treatment caused a complete return to normal. Lumps appeared in the skull during April 1930. One of these was removed, and all of them were radiated, with improvement. Recurrences disappeared again under treatment, and the child was apparently quite well for fifteen months. On March 8, 1932, a cough developed and an x-ray picture showed masses in the lungs. Further treatment checked the process somewhat, but death occurred on Oct. 28, 1932, three years and a half after the onset.

The x-ray treatments were as follows: 3 to the orbit; 8 to the femur; 21 to the skull; and an unrecorded number to the chest. The doses, with little variation, were as follows: dose, 100; voltage, 200; filtration, 0.5 Cu; distance, 55 cm. Figure 8 shows the effect of the treatment on the femoral tumor.

At autopsy tumors were found in the skull and both lungs. The femur was not examined, but continued x-ray observation had shown this tumor to be quiescent for over two years. There were two skull tumors, soft and white, with a lobulated structure. They were subgaleal and had not invaded the scalp or dura. The lower lobe of the right lung was entirely replaced by tumor. Several smaller metastases were present in both lobes of the left lung. The mediastinal, retroperitoneal, mesenteric, and subcutaneous lymph nodes did not contain tumor.

Sections of the tumors showed them to consist of sheets of fairly small cells with a delicately staining vacuolated cytoplasm, and nuclei with a fine chromatin network, and no recognizable nucleoli. There was no definite intercellular substance, although the cells were forming fine vascular channels in some places.

This tumor would appear to be a definite endothelial myeloma. The slow onset, with symptoms pointing to no specific disease, the presence of a single lesion for a considerable period of time, the development of skull tumors, and finally death by pulmonary metastases are classical. This case might have been classified clinically as a Hutchison type of neuroblastoma because of the early involvement of the orbit, but autopsy disclosed no such tumor. Histologically one ought, also, to differentiate such tumors from the small round-celled, intensely hyperchromatic neuroblastomata of the adrenal anlage.

Metastasis to the orbital regions can in no way be considered as peculiar to neuroblastoma. Lymphosarcoma of any type, endothelial myeloma and chloroma very often localize in this region. Because of the fact that lymphomatous tumors, chloromas, and myelomas of all types are more common than retroperitoneal neuroblastoma, a retrobulbar metastasis is probably less likely to arise from neuroblastoma than from a member of this latter group of tumors. A Hutchison type of tumor can, therefore, hardly describe a tumor of any particular origin.

DISCUSSION

The origin of Ewing's sarcoma has been widely discussed. With the exception of Hirsch and Ryerson, and Colville and Willis (loc. cit.), most writers agree that such a tumor, differing in certain definite fundamental features from all other tumors, does indeed exist. Its clinical, roentgenological, and pathological characters are fairly con-

* Hutchison mentions that chloromas can be differentiated by the presence of abnormal cells in the blood, which is usually but not always the case.
stant. There are, however, several related tumors of slightly different histologic appearance, as cellular angio-endotheliomas and reticulated round-cell sarcomas, which probably originate from the same stem cell. Kolodny denies any relationship between the diffuse endothelioma (Ewing's sarcoma) and angio-endothelioma. Melnick (10) says that, of course, an angio-endothelioma is not an Ewing's sarcoma. Probably in the strict sense, this is true, but if an Ewing's sarcoma is an endothelioma, its close relationship to malignant cellular angio-endotheliomas is obvious.

Oberling (11) reported 5 cases of bone tumors which he believed to be Ewing's sarcoma because of the characteristic histories, the histological appearance, the disposition of the neoplastic elements, and the connection with connective and vascular types of tissue. He differentiated these from osteoblastic tumors, myelomas, and lymphoblastomas. Included among them was an angio-endothelioma.

I believed that I could recognize three histological types among the 52 cases previously reported, namely, a completely undifferentiated diffuse endothelioma, a cellular endothelial type forming vessels (angioendothelioma), and a reticular type. All of these tumors had the same clinical and roentgenological features, with no more variation than one might expect to find in osteogenic sarcomas, for example. Oberling thought that he could recognize these three types in his collection and compared the diffuse endothelioma type to what he called undifferentiated reticulosarcoma, the angio-endothelioma type to his reticuloendotheliosarcoma, and the reticular type to differentiated reticulosarcoma. In other words, in the last two types there was some differentiation toward an endothelial cell in one case, and toward a reticulum cell in the other, each being actually only one short step removed from the indifferent mesenchymal cell element which gives rise to the reticulo-endothelial system and to the hematopoietic system.

Melnick quotes Oberling's classification and interprets the latter's reticulosarcome indifferencie as a tumor composed of cells which ought to form a reticulum. However, an undifferentiated reticulum cell, if actually undifferentiated, would not form anything which would disclose its character. Melnick, with many others, regards the reticuloendothelial system as consisting of mature cells having specific functions, and for this reason only reticulum cell sarcomas should arise from it. He recognizes a reticulum-cell lymphosarcoma, and the hematopoietic potentiality of the reticulum. Oberling goes further, recognizing the possibility of the evolution of the undifferentiated reticular cell into an hematopoietic reticular cell, becoming the multipotential hemocytoblast from which myelosarcomas and lymphosarcomas may arise. It may be a needless pursuit of an unimportant

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4 The term angio-endothelioma has been used to designate so many different types of growth that everyone using it should define his interpretation of it. It has been used for ordinary benign hemangiomas as well as for the most cellular endotheliomas which only appear to form vascular channels. Any type of tumor between these two extremes, as regards cellularity and degree of malignancy, may or may not be called angio-endothelioma according to the whim of the interpreter.
question, but if endothelial tumors cannot arise from the reticulo-endothelial system, the second part of the latter term ("endothelial") should be dropped.

In a more recent paper Oberling, with Raileanu (12), has reported the results of special staining methods upon a group of 12 tumors generally classified as Ewing's sarcomas. They describe the formation of reticulin fibrils, endothelium, erythroblasts, myelocytes, plasma cells, and even macrophages. In other words, Ewing's sarcoma arises from a very undifferentiated mesenchymal cell capable of differentiating into adult reticulo-endothelium, into the hemohistioblast, or into endothelium. There can be no general disagreement about this now, and fundamentally the contentions of Melnick, Oberling, and the present writer are exactly the same. I would further suggest that this cell of the undifferentiated reticulosarcoma (Ewing's sarcoma) can on occasion form a cement substance and produce a relatively undifferentiated angio-endothelioma, and that it may become an osteoblast.

Whether these tumors arise in the cortex or the medulla of bone is perhaps of no particular importance. Geschickter and Copeland thought at one time they had demonstrated (from x-ray pictures) that Ewing's sarcoma arose in the cortex. Melnick accepted this as proved, but I have shown (9) that transplanted endotheliomas in chickens may grow in the medulla of bone for as long as eighteen days (out of a total life history of twenty-two to twenty-four days) before their presence can be demonstrated in any way except by cutting through the cortex and direct observation. Thus, over two-thirds of the course of the disease has passed before there is x-ray evidence of its presence. It is quite impossible to evaluate these results in terms of similar tumors of man, but one might suggest that because a tumor is first demonstrable by clinical means in the cortex of a bone, it need not necessarily have arisen there. It would be fortunate for the patient if this were so, as it would mean an earlier diagnosis and more prompt treatment in most cases.

From the three cases recorded here I believe we may say that the endothelioma of bone is much like the malignant endothelioma found elsewhere; that it does not respond rapidly and readily to x-ray treatment but disappears gradually and slowly as compared, for instance, with a metastatic lymphosarcoma or a neuroblastoma in a bone, but at the same time much more rapidly and surely than an osteogenic sarcoma or the average metastatic carcinoma. Since my previous report (2) I have discovered that metastatic lymphomatous tumors have been the most difficult to differentiate from endothelial myelomas. The former tumors may manifest themselves first as bone tumors, and it may not be until generalized lymphadenopathy in superficial areas occurs that the question of a lymphoma is raised. Perhaps we have more evidence that this tumor differs from lymphosarcoma and other hematocytoblastic tumors in the fact that lymph node metastases were not present in any of these cases. Ewing's sarcomas constantly metastasize to the lungs, behaving in this respect like connective-tissue sar-
comas, in contrast to lymphosarcomas and myelomas. We may find
upon further study that lymph node metastases are not common, and so
have to revise an opinion to the contrary, previously expressed. An-
other revision can be made with the evidence at hand. The tumor cell
of Ewing's sarcoma can become an osteoblast and form bone.

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