NEUROBLASTOMA METASTASES IN BONES, WITH A CRITICISM OF EWING'S ENDOTHELIOMA *

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INTRODUCTION

The characteristics of Ewing's sarcoma or diffuse endothelioma of bone, as described by Ewing [1] and other writers, are as follows. The patient is usually a child. The tumour appears most frequently in a short or long bone of a limb and, if in a long bone, affects the shaft diffusely. The onset is with pain and disability, and later enlargement of the segment of the limb. Intermittent mild pyrexia is often present. These features lead in many cases to an initial diagnosis of osteomyelitis, a diagnosis that skiagrams, unless interpreted by workers familiar with this class of tumours, may be held to confirm. Exploratory operation reveals a soft tumour mass surrounding the bone and often infiltrating surrounding soft tissues. Histological examination of an excised specimen reveals a richly cellular tumour composed of closely aggregated, small spheroidal cells of uniform size and shape, each with a spherical hyperchromatic nucleus. These cells appear in diffuse sheets or masses usually devoid of any specific structural arrangement. Purely histological diagnosis, therefore, is not possible. The tumour is highly susceptible to adequate doses of X-radiation, which produces prompt diminution or disappearance of the growth. This favourable response is held to be almost diagnostic of Ewing's tumour. Recurrence, however, is the rule and death usually occurs within two or three years. Almost invariably secondary growths, regarded by some as metastases and by others as multiple new formations, appear in many other bones, especially in the skull and, unlike other bone tumours, Ewing's tumour frequently yields metastases in lymph glands.

The object of this paper is to report a tumour that presented all

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the accepted features of Ewing's tumour, but which careful autopsy study revealed to be one of many skeletal metastases from a small adrenal neuroblastoma.

Report of Case

Clinical History: J. T., a well developed girl 8 years old, had had previous good health and had suffered no noteworthy illnesses. In June 1932 persistent pain in the right thigh began and in August a swelling of the upper part of the thigh was noticed. The child was admitted to the hospital with the diagnosis "chronic osteomyelitis." Save for a slightly tender, diffuse enlargement of the upper half of the right thigh, general examination disclosed no other abnormalities. The skiagraphic report was: "Area of bone destruction and periosteal reaction in upper third of shaft of femur, appearance suggestive of osteomyelitis. A leukocyte count gave 10,400 cells per cmm. The Wassermann test yielded no reaction. Slight pyrexia was present, the evening temperature frequently reaching 99° F, and sometimes 100° F. On Sept. 17, 1932 the skiagraphic report was as follows: "There has been some extension of the bone involvement, the upper two-thirds of the shaft now being affected." (See Fig. 1.)

On September 21 exploratory operation was performed, revealing a large soft tumour enveloping the shaft of the femur and invading the surrounding soft tissues. A fragment was excised for histological diagnosis. The report on this specimen was: "Richly cellular, round-celled, highly malignant tumour invading skeletal muscle; specific nature cannot be affirmed, possibly a soft tissue sarcoma, possibly a metastatic growth."

A skiagram of the thorax on October 5 disclosed no evidence of lung metastases. On the same day a course of deep X-radiation to the tumour was commenced, and was continued until Nov. 21, 1932. Within four days of the commencement of this treatment pronounced reduction in the size of the growth was apparent and pain and tenderness were much relieved. The rapidity of diminution of the tumour following the initial applications of X-rays was dramatic. During this course of treatment, and thereafter until her death, the patient had increased pyrexia up to 101° F in the evenings, and sometimes to 102° and 103°.

In skiagrams taken on Oct. 27, 1932 no pulmonary metastases were visible but a paravertebral tumour was noted (Fig. 2). The subsequent course was one of emaciation, cachexia and further increase in the size of the femoral tumour. Death occurred on Nov. 29, 1932. The clinical diagnosis was "Ewing's sarcoma of the femur."

Postmortem Examination

Autopsy was performed six hours after death. There was an enormous, fusiform, soft white growth surrounding the whole of the shaft and neck of the right femur and invading the surrounding muscles. The tumour tissue was easily detached from the femur, the exposed surface of which was eroded and roughened and resembled coarse sandpaper to the touch (Fig. 3). At the lower limit of the

growth there was a slight degree of periosteal new bone formation. The medullary cavity was occupied by tumour tissue. All other bones of the skeleton that were examined presented similar but less conspicuous tumour deposits, situated chiefly beneath the intact periosteum. The inner and outer surfaces of nearly all the cranial bones, mandible, all vertebrae, all ribs, sternum, right humerus, clavicles, pelvis and left femur were involved. Only on the lumbar and thoracic vertebrae did the subperiosteal growths produce tumour masses readily visible externally; elsewhere they formed a thin stratum only discovered on incising the periosteum. The vertebrae and several ribs were sectioned and were found to contain medullary deposits of tumour also. The peripheral bones of the limbs were not examined.

Numerous discrete white tumour nodules were present in the lungs and liver. Both kidneys contained a few tiny points of growth. There were small metastases in the iliac and lumbar lymph glands. The medulla of the left adrenal contained two or three tiny discrete white nodules. The right adrenal was the seat of a group of white nodules occupying the medulla; these, though they appeared to be separate when viewed on a single cut surface (Fig. 4), were connected for the most part with one another, forming a lobulated tumour 3 cm. in maximum diameter with a few smaller, separate satellite nodules. All other organs, including the skull contents, appeared normal.

Histological Examination

Microscopic study of haematoxylin-eosin sections of all of the tumours described above, as well as of various viscera, was carried out. Frozen sections of the adrenal growth were stained also by Bielschowsky's method and by Cajal's silver pyridine method for nerve fibres.

The growths in all situations consisted of diffuse masses of rounded cells, each 10 or 12 microns in diameter, with a spherical, deeply stained but vesicular nucleus that sometimes presented a single small nucleolus. Mitotic figures were numerous. The bulk of the tumours exhibited no special arrangement of the cells, but in parts of the right adrenal growth distinct rosette formation was present (Fig. 5). The same feature was observed also, though less clearly, in some of the hepatic metastases. No nerve fibres were found in the Bielschowsky and Cajal-stained sections, and there was no evidence

of any tendency of the tumour cells to differentiate toward the adult nerve cell type.

Of the viscera that appeared macroscopically normal, only the spleen exhibited abnormalities. The vascular spaces of the splenic pulp contained sparsely scattered, small clumps of tumour cells, which were found also in a small accessory spleen.

Discussion

The identity of the tumour in this case is scarcely open to doubt. The primary growth was a highly malignant but small neuroblastoma of the right adrenal that had produced bulky metastases in the other viscera, and especially in the skeleton. The cytology and rosette formation of the adrenal tumour are characteristic of the neuroblastomas of childhood. That the adrenal tumour was small is no argument against its primary character, for the primary growths in the Hutchison [2] and Pepper [3] types of adrenal neuroblastoma are notorious for their small size, compared with that of their metastases in the skull or liver. The possible suggestion that because the left adrenal contained metastatic nodules the right adrenal tumour was also metastatic in nature does not accord well with the much larger size of the right-sided tumour. If, in spite of the cytology of the adrenal growth, it is assumed that the femoral tumour was primary, it is still necessary to admit that all the other skeletal growths were secondary, and this admission greatly detracts from the argument for the primary nature of the femoral tumour. That this tumour was much larger than any other of the skeletal deposits, and that it was the clinically predominant tumour, provide no argument for its primary character, for the Hutchison skull tumours also are in the forefront of the clinical picture and are much larger than the coexistent deposits in other parts of the skeleton.

As regards this clinical predominance of one out of many metastases in bone, a possible cause may be found in the relations of tumour to periosteum in the various situations. It may be that the reason why one metastasis grew luxuriantly while the others remained clinically dormant is that for some cause, possibly traumatic, the periosteum had undergone a solution of continuity at the site of the dominant growth, thereby releasing it from a restraining influence and allowing the neoplasm to flourish unchecked in the

surrounding tissues. In other words, the tumour developed precociously in one particular situation because the restraining periosteum suffered penetration. However, we can see no escape from the conclusion that the case described was one of adrenal neuroblastoma with prolific skeletal metastases, one of which outstripped the others and simulated a large primary tumour of the femur.

Clinically the femoral tumour was diagnosed as a Ewing's sarcoma. How valid was this diagnosis? The accepted characteristics of Ewing's tumour have been summarised in our introduction, and our case presented all of these characteristics. The patient was a child, the tumour affected diffusely a large part of the shaft of a long bone, the onset was with pain and disability, the course of the disease was febrile, the initial clinical and skiagraphic diagnosis was osteomyelitis, metastases developed in other parts of the skeleton including the skull, pulmonary metastases were late in their appearance, biopsy revealed a diffuse spheroidal-celled growth with small spherical hyperchromatic nuclei, and the initial response to X-ray therapy was prompt and striking. In all these respects our tumour conforms to Ewing's description, and further, the skiagraphic features of our case and also the gross appearance of the eroded bone shaft closely resemble those depicted in Ewing's Figures 127 to 129.[1] We believe then that, on all possible clinical grounds, the diagnosis of Ewing's tumour was fully justified, and this diagnosis might easily have received false corroboration from the autopsy, had this not been complete.

It is pertinent then to inquire whether other alleged instances of Ewing's sarcoma or endothelioma may not also have been of a nature similar to ours, and whether adequate autopsy study has been made in any of the cases that have received this clinical designation. In pursuing this inquiry it is disappointing to find that neither in Ewing's accounts nor in those of Connor,[4] Coley and Coley,[5] Kolodny,[6] and Clopton and Womack [7] is there any detailed autopsy record of any of their cases, and that in the majority of instances the diagnosis rested on clinical and biopsy findings only. Thus, Ewing [8] records no details of autopsy findings. Connor, discussing 52 bone tumours classified as Ewing's sarcoma in the Registry of Bone Sarcoma, states that "necropsies were done in less than one-third of the cases," and his paper gives no indication as to how complete these autopsies were. Coley and Coley describe many

cases of "endothelial myeloma" diagnosed on clinical and biopsy findings, but autopsy is recorded in only one case (No. 49), of which it is stated: "A necropsy was performed, revealing very extensive metastases in nearly every bone and organ." Kolodny gives a full account of clinical and skiagraphic findings on which, along with the radiotherapeutic response, he would rely entirely for the diagnosis. He considers that clinical distinction from metastatic growths in bones can be made because "metastases occur in the very young or after the age of 40, while most Ewing's sarcomata are seen in early adolescence," a statement with which we venture to think very few pathologists will agree. No autopsies were performed on Clopton and Womack's cases. In the only postmortem record specifically mentioned by Ewing in his Neoplastic Diseases (page 361), it is perhaps noteworthy that "retroperitoneal lymphatic metastases were found." On page 352 Ewing says "the diagnosis of endothelioma of bone should not be made until a thorough search for a primary tumor has proved unsuccessful, and this search may, at times, not be regarded as complete without autopsy." We concur with this view, but would modify the latter half of Ewing's statement to read, "this search may *never* be regarded as complete without *thorough* autopsy."

Since no adequate records of autopsies of cases classed as Ewing's tumour are available, we may turn to earlier literature for possible information on the subject. Of much interest is a paper by Roman [9] who described under the title "myeloplastic sarcoma" two cases of widespread round-celled growths of many bones in children. In one case there was a supposedly metastatic growth involving the left adrenal, and in the other a tumour completely replacing the adrenal. Roman reviewed also several recorded tumours that resembled his own, those of Gussenbauer, Dittrich, and Schmidt, in all of which it is of interest to note that tumour nodules were present in the adrenals. Indeed, it is clear that the tumours described and reviewed by Roman were not, as he supposed, "myeloplastic sarcomas," but instances of adrenal neuroblastoma with widespread bone metastases in the same category as the Hutchison tumours. Evidently Roman was not aware of Hutchison's work of five years previously.[2] Yet, strange to say, Kaufmann [10] accepts Roman's interpretation.

A purely histological diagnosis of Ewing's tumour is not possible.

All writers on the subject admit that there is nothing distinctive about the cytology or architecture of the growths. As MacGuire and McWhorter [11] say: "Most pathologists would call these tumors round-celled sarcomas." However, of possible significance (as regards a neuroblastic nature) is Ewing's [1] observation (see page 359) that "rosette structures without lumina" are present in some of the tumours.

MacGuire and McWhorter confess themselves perplexed by the scope and identity of the group of tumours under discussion, and they conclude: "Ewing's tumor is not yet established as a clinical entity." Hirsch and Ryerson [12] also severely criticise the records of alleged cases, and they suspect that most of them were instances of metastases from undiscovered primary tumours. With this criticism we agree and, while we think it probable that a variety of different conditions has been included in the group of Ewing's tumours, we would urge strongly the claim of adrenal neuroblastoma as the responsible tumour in many instances. This claim is supported by the general characteristics of cytology and metastatic distribution of Ewing's tumours. The multiplicity of skeletal growths, their diffuseness and often predominantly subperiosteal situation, the frequent involvement of the skull, and the frequent presence of lymph gland metastases (a rare feature with all primary bone tumours), are all reminiscent of the malignant neuroblastomas as described by Hutchison,[2] Tileston and Wolbach,[13] Frew,[14] Wollstein,[15] and others. It may be recalled that Hutchison's tumours were formerly called "sarcomas" of the skull. We believe that future careful autopsy work will furnish a revelation regarding the Ewing sarcomas similar to that furnished by Hutchison's work for the skull tumours. If, in a case of the Hutchison type, we imagine the bulky skull tumours to be transferred to a long bone, a Ewing tumour would result. The age incidence of the two classes of growth is slightly different, Hutchison's tumours appearing usually in infants, and Ewing's tumours chiefly in older children. It is possible, however, that this very difference may be related in some way to the different sites of preference of the apparent "primary" tumours.

We would draw attention also to the significant fact that "Ewing's sarcoma, primary in the skull" has rarely if ever been recorded, although all writers on the subject comment on the remarkable frequency with which secondary growths appear in the skull. Perhaps

the explanation of this seeming anomaly is that when skull growths are the first to appear the case is recognised correctly as belonging to the Hutchison group and thereby escapes the designation "Ewing's sarcoma."

Finally, we have searched in vain for observations other than our own on the radiosensitivity of neuroblastic tumours, but, from the truly embryonal qualities of their cells and from their high mitotic activity, we would not be surprised to learn that they frequently possess the susceptibility to X-radiation that has been regarded as almost diagnostic of the Ewing tumour.

Summary and Conclusions

1. A case is described in which a tumour presenting all the accepted characteristics of a Ewing's sarcoma of bone was shown at autopsy to be one of many metastases from an adrenal neuroblastoma.

2. Review of certain adequately recorded autopsy cases of supposed multiple bone sarcomas leads to the conclusion that these also were instances of adrenal neuroblastoma with skeletal metastases.

3. The term "Ewing's sarcoma," while possessing clinical value as defining a syndrome presented by a certain group of tumours affecting bones, has no established claim as designating a pathological entity.

4. While not denying the *possible* existence of a primary bone tumour presenting the Ewing syndrome, we believe that further study will disclose the metastatic nature of most of the tumours with this syndrome, and we strongly suspect that adrenal neuroblastomas will prove to be the primary growths in many of the cases.

We are indebted to Dr. L. Love for his interest in the skiagraphic aspect of the case reported and for preparing prints of the skiagrams shown in Figures 1 and 2.

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DESCRIPTION OF PLATE

PLATE 65

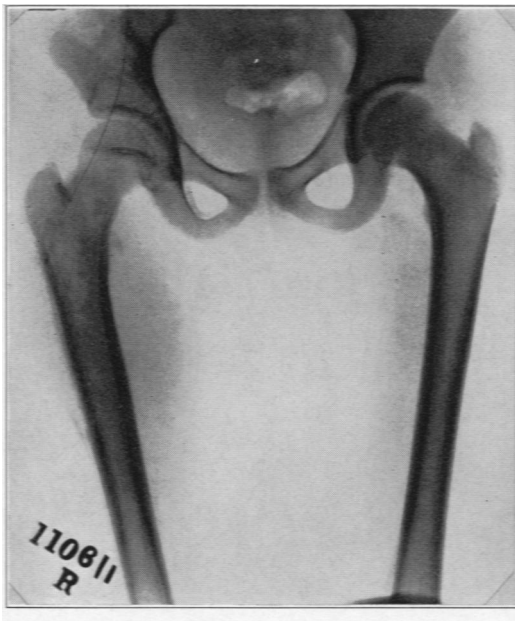
FIG. 1. Skiagram of femur on Sept. 17, 1932.

FIG. 2. Skiagram of thorax on Oct. 27, 1932, showing paravertebral tumour.

FIG. 3. Anterior view of femur after removal of soft tumour tissue. Half natural size.

FIG. 4. Vertical section of right adrenal. Natural size.

FIG. 5. Two views of haematoxylin-eosin stained sections of adrenal tumour showing rosettes.



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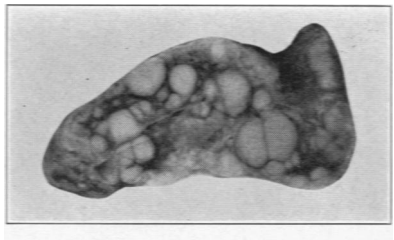

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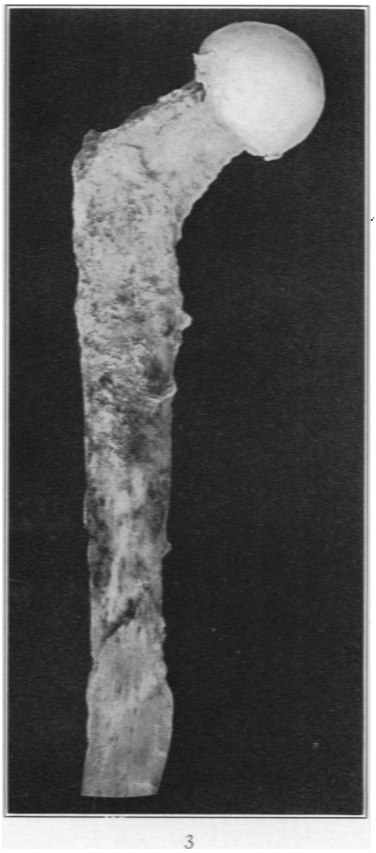

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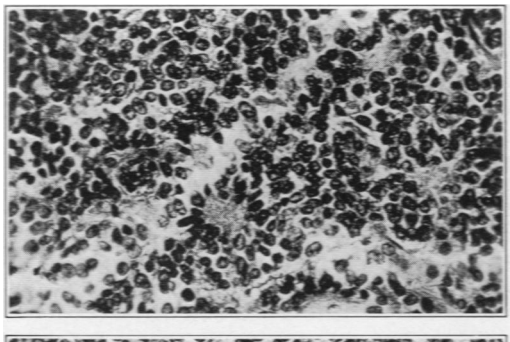

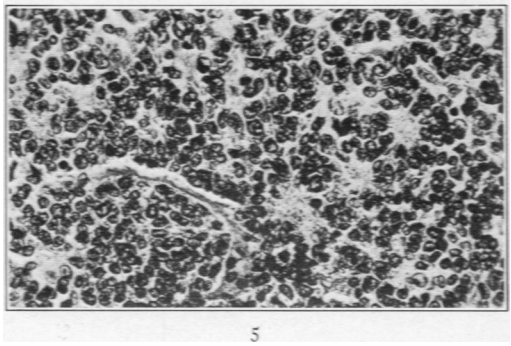

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Colville and Willis

Neuroblastoma Metastases in Bones