Bulletin of the

University of Minnesota Hospitals
and
Minnesota Medical Foundation

Ewing's Bone Sarcoma

Volume XIX | Friday, April 16, 1948 | Number 22

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UNIVERSITY OF MINNESOTA HOSPITALS
and
MINNESOTA MEDICAL FOUNDATION
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Published for the General Staff Meeting each week during the school year, October to June, inclusive.

Address communications:

Staff Bulletin
332-M University of Minnesota Hospitals
Minneapolis 14, Minnesota

UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS

Visitors Welcome

April 19 - April 24, 1948

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Monday, April 19

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; Interns' Quarters, U. H.

9:15 - Fracture Rounds; A. A. Zierold and Staff; Ward A, Minneapolis General Hospital.

10:00 - 12:00 Neurology Ward Rounds; A. B. Baker and Staff; Station 50, U. H.

11:00 - 11:50 Physical Medicine Conference; Occupational Therapy with Orthopedic Conditions; Betty Johnson; E-101, U. H.

11:00 - 11:50 Roentgenology-Medicine Conference; Staff; Veterans' Hospital.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and D. State; Eustis Amphitheater, U. H.

12:15 - 1:20 Obstetrics and Gynecology Journal Club; M-435, U. H.

12:50 - 1:20 Pathology Seminar; Studies on the Bone Marrow; J. A. Williams; 104 I. A.

12:30 - 1:30 Physiology Seminar; Hyaluronidase and its Inhibition in Normal and Pathological Conditions; David Glick; 214 M. H.

12:30 - 1:50 Surgery Grand Rounds; A. A. Zierold, Clarence Dennis and Staff; Minneapolis General Hospital.

1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U. H.

2:00 - 3:00 Surgery Problem Case Conference; C. Dennis and Staff; Small Class Room, General Hospital.

4:00 - 5:00 Pediatric Seminar; Electrophoresis of Proteins; Miss Doeden; 6th Floor Seminar Room, U. H.

4:00 - 5:00 School of Public Health Seminar; Dysentery Studies in the Rio Grande Valley; James Watt; 113 MeS.

5:00 - 6:00 Urology-Roentgenology Conference; D. Creevy and H. M. Stauffer and Staffs; M-515, U. H.

Tuesday, April 20

8:30 - 10:20 Surgery Reading Conference; Lyle Hay; Small Conference Room, Bldg. I, Veterans' Hospital.

9:00 - 9:50 Roentgenology Pediatrics Conference; L. G. Rigler, I. McQuarrie and Staff; Eustis Amphitheater, U. H.

10:30 - 11:50 Surgical Pathological Conference; Lyle Hay and Robert Hebbel; Veterans' Hospital.

12:30 - 1:20 Pathology Conference; Autopsies; Pathology Staff; 102 I. A.

2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III, Veterans' Hospital.

3:15 - 4:20 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U. H.

3:30 - 4:20 Clinical Pathological Conference; Staff; Veterans' Hospital.

4:00 - 5:30 Surgery-Physiology Conference; O. H. Wangensteen and M. B. Visscher; Eustis Amphitheater, U. H.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

5:00 - 5:50 Roentgenology Diagnosis Conference; L. G. Rigler and Staff of University Hospitals; M-515, U. H.

Wednesday, April 21

8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-515, U. H.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker and Joe R. Brown; Veterans' Hospital.

11:00 - 11:50 Pathology-Medicine-Surgery Conference; Primary Amyloidosis; O. H. Wangensteen, C. J. Watson and Staff; Todd Amphitheater, U. H.

4:00 - 5:00 Infectious Disease Rounds; Todd Amphitheater, General Hospital, Veterans' Hospital.

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8:15 - 9:00 Roentgenology-Surgical-Pathology Conference; Walter Walker and H. M. Stauffer; M-515, U. H.

8:30 - 10:20 Surgery Grand Rounds; Lyle Hay and Staff; Veterans' Hospital.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:50 Surgery-Radiology Conference; Daniel Fink and Lyle Hay; Veterans' Hospital.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and D. State; Eustis Amphitheater, U. H.

11:30 - 12:30 Clinical Pathology Conference; Steven Barron, C. Dennis, George Fahr, A. V. Stoesser and Staffs; Large Class Room, General Hospital.

12:00 - 12:50 Physiological Chemistry Seminar; Subject to be announced; 214 M. H.

1:00 - 1:50 Fracture Conference; A. A. Zierold and Staff; Minneapolis General Hospital.

4:00 - 4:50 Bacteriology Seminar; Techniques of Tissue Culture; Richard Lyon; 111 MeS.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.

5:00 - 5:50 Roentgenology Seminar; Thoracic Surgery Conference; Richard Varco; M-515, U. H.

Friday, April 23

8:30 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:20 Medicine Grand Rounds; Staff; Veterans' Hospital.

10:30 - 11:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.

11:00 - 12:00 Surgery-Pediatric Conference; C. Dennis, A. V. Stoesser and Staffs; Minneapolis General Hospital.

11:30 - 12:50 University of Minnesota Hospitals General Staff Meeting; Radiation Therapy for Vaginal and Uterine Prolapse; John L. McKelvey; New Powell Hall Amphitheater.

12:00 - 1:00 Surgery Literature Conference; Clarence Dennis and Staff; Minneapolis General Hospital, Small Class Room.

1:00 - 1:50 Dermatology and Syphilology; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312, U. H.

1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

Saturday, April 24

7:45 - 8:50 Orthopedics Conference; Wallace H. Cole and Staff; Station 21, U. H.

8:00 - 9:00 Pediatric Psychiatric Rounds; Reynold Jensen; 6th Floor West Wing, U. H.

8:00 - 9:30 Psychiatry and Neurology Grand Rounds; Staff; University Hospitals.

9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:00 - 9:50 Surgery-Roentgenology Conference; O. H. Wangensteen, L. G. Rigler, and Staff; Todd Amphitheater, U. H.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; M-515, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; M-515, U. H.

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

II. EWING'S BONE SARCOMA

David J. Nelson

Following the classic article by Gross[10] in 1879 which grouped several tumors under "round-cell sarcoma" a number of papers were published describing endothelial tumors of bone but it wasn't until 1921 that Ewing separated them as a distinct group and presented a series[21].

Ewing originally classified it as an endothelioma, but later (in 1924) adopted the classification of Borst as an endothelial myeloma or diffuse endothelioma[24] since he believed the tumor originated from the medullary cavity or mainly so[21].

It is a tumor which forms 27% of primary bone tumors. 72% are found in males and a definite relationship to trauma has been mentioned in many large series of cases, usually in about 35%. Pathological fractures are rather rare, sited variously as occurring in 5-15%[34].

It is a disease of young individuals. 95% of cases are under 25-30 years of age[13]. The youngest patient reported was 2½ years of age, the oldest 79. Ages 10-30 predominate[47].

It should be stated at the outset that persistent bone pain in children without an obvious diagnosis should be considered a tumor until proved otherwise[5].

History

The cyclic recurrence of pain and swelling is highly suggestive of this disease.

Pain is the outstanding symptom in about 80% of cases and usually it is the symptom which brings the patient to the doctor.

Characteristically, pain beings with or without trauma in one of the long bones in a male 10-30 years of age. It tends to disappear, at first, with or without treatment only to recur more severely at ever decreasing intervals. Severe nocturnal pain became an outstanding symptom in most cases. Pain is present from 6 weeks to 7 months before the patient seeks help and usually 8-12 months elapse before a diagnosis is made.

90% of cases will show a mass. This mass tends to spontaneously decrease in size with cessation of pain only to reappear when symptoms recur. These changes are probably due to hemorrhage and reabsorption within the tumor.

Physical

There are usually signs of both local and systemic disturbance. Fever, averaging 100°, mild leucocytosis, slight albuminuria, secondary anemia and weight loss cause confusion with infectious diseases.

The mass varies from a small localized one to a large fusiform one extending along almost the entire shaft. The soft parts are freely moveable over the tumor but tend to be edematous, show local elevation of temperature and display dilated superficial veins. The tumor is usually tender to palpation and feels firm but less hard than bone.

Later in the disease when metastases have occurred the temperature is more elevated, weight loss more marked and chest pain with hemoptysis occurs in many. Vertebral metastases are occasionally accompanied by paraplegia[24].

The pulse rate is believed to be accelerated as long as the growth of tumor is active. A high pulse rate is a poor prognostic sign.

Pathology

In a discussion of the pathology it will soon become apparent that much controversy exists throughout but that in spite of this many points of agreement have been resolved.

Ewing's tumor affects the long bones most frequently, and, generally speaking, only the shaft part except for secondary invasion of the epiphysis. The flat bones, including the clavicles are occasionally involved.

The upper two-thirds of the tibia,

the lower and upper thirds of the femur and the upper half of the humerus are the most frequent sites of this tumor.

It begins slowly and metastasizes slowly to the lungs, skull, and lymph nodes. It is important to note that dissemination of secondary growths to other bones occurs. Some view this as evidence of multiple primary foci but the majority of pathologists do not support this opinion. The bones most frequently involved in metastases are the skull, spine, ribs, scapula and clavicle. Less commonly in the long bones. Metastases to the skull are unusual in that they usually form multiple subperiosteal lesions which indent but don't erode the outer and inner tables. Sometimes they are found on the under side of the dura depressing, but not invading, the brain. Brain metastases are relatively rare. In a patient dying of other causes, autopsy revealed tumor tissue in retroperitoneal nodes nine years after the primary lesion had been treated and apparently "cured"[32].

Whether biopsy procedures give rise to metastases is a rather hotly disputed question and will be dealt with later.

Grossly, the major part of the tumor is found to be situated subperiosteally. The soft part is usually encapsulated by a thin fibrous tissue layer. It is firm, grayish-white, brainlike tissue which is divided into characteristic lobules by a number of connective tissue strands. Occasionally cysts are seen filled with a dark jelly-like material due to hemorrhage[24].

Perhaps the gross appearance is more readily recognizable on x-ray. Characteristically, it is found more toward the center of the shaft. There is often a well circumscribed shadow where the tumor invades the muscle. It doesn't appear to be a tumor primarily destructive or of medullary origin from an x-ray standpoint. In the young patient, three characteristic changes occur in the shaft. The first or earliest sign is condensation of the bone with reaction of the periosteum. This is followed by invasion with expansion, striation and destruction of the cortex and the so'called "onion-peel" formation which is usually considered the typical picture of Ewing's sarcoma but is certainly not present in all of the cases. This stage is then followed by disintegration of the periosteal layers and shaft with extension of the tumor into surrounding parts. The remains of the periosteum are apparent by a rather marked lipping near the junction of normal shaft and tumor[10].

The cortex appears thickened, not only due to expansion of the bone but also to narrowing of the medullary cavity. Some mottling of the medullary cavity region occurs later. The tumor gives the appearance of extending most readily in the long axis of the bone[24].

Osteophytes may be seen to arrange themselves irregularly or at 90° angles to the cortex due to the disturbed relationship of periosteum to cortex. The latter arrangement is probably due to bone being laid down along the vessels of Volkmann which have been stretched out by the elevation of the periosteum.

Probably the onion-skin layers are due to growth of tumor and subsequent hemorrhage and a desperate attempt on the part of the periosteum to wall off the tumor tissue. The tumor may break thru and the cycle be repeated many times[24]. Some authors, however, feel that this laminated condition occurs because the tumor pushes the cortex outward, infiltrating it, sometimes forcing it apart into layers[28].

Bone destruction is usually not a prominent feature. The tumor infiltrates the bone rather than destroys it and the periosteum and endosteum reacts vigorously with ossification. The destruction which occurs late in the disease is due to circulatory disturbance.

Microscopically, the typical example of Ewing's sarcoma is sheets of uniform sized and shaped cells. They are small polyhedral cells with round or oval nuclei. The cytoplasm is scanty and practically stainless. In areas where the cells are not packed so closely, the cytoplasm is seen and found to be faintly eosin staining. The nuclei are darkly staining, rarely contain nucleoli

and mitotic figures are fairly frequent. Osteoclasts are not infrequently seen near dead bone or near bone out in the tumor tissue[24]. Altho Ewing's sarcoma is usually the "diffuse" tupe just described, some are: 1. interfascicular (thin layers of cells between strands of connective tissue), 2. alveolar (composed of large groups of cells resembling adenoma), 3. plexiform (composed of columns showing papillary projections)[21].

There is no intracellular substance demonstrable except septae which often separate the tumor into lobules and give it an alveolar appearance. The tumor tends to be encapsulated by fibrous tissue. The degree of vascularity varies[24]. Rosettes (or pseudorosettes by some authors) are fairly common in many cases of Ewing's sarcoma--those proved at autopsy to be Ewing's and not neuroblastoma[23]. Some Haversian canals will show infiltration of tumor cells both in and about the vessel walls. This finding is often pointed out as evidence of the origin of this tumor.

The periphery of the tumor is often infiltrated by PMN's and monocytes, especially if the tumor is of long duration or has been biopsied. This occasionally leads to a wrong diagnosis of osteomyelitis.

A group of tumors occurring in the same age group with the same symptoms but presenting certain atypical features microscopically and on x-ray have been classified as atypical Ewing's sarcoma or reticular cell variants of Ewing's sarcoma.

They involve the metaphyseal part of the bone and tend to invade the marrow cavity early in the course of the disease without giving rise to much periosteal reaction. The cells vary in size, many have prolongations of the cytoplasm. Tumor giant cells resembling Dorothy Reed cells are present. Histologically, they are identical with reticulum cell sarcoma of lymph nodes. Occasionally the cells may be medium or large lymphocytes two times the size of the Ewing's tumor cells.

Response to x-ray therapy and the absence of bone formation in the tumor favors their being grouped with Ewing's tumor. They are rapidly fatal in almost 100% of cases.

Ewing's sarcoma of soft tissues are rapidly growing, microscopically identical with that of bone and appear to arise immediately adjacent to the periosteum[24]. It may then secondarily involve the bone if it wasn't an extension from the bone in the first place[38]. The clinical course is similar to Ewing's tumor of bone and is similarly sensitive to x-ray therapy[24].

That these tumors begin slowly and metastasize slowly seems well established.

Whether bone production is a feature of this disease has been debated, but it seems in accordance with the pathology noted that the tumor cells do not produce bone, but rather a very active periosteum proliferates it to a greater or lesser extent in an attempt to wall off the tumor's spread[13].

Histogenesis

At the present time, most of the available information seems to indicate that the cell of origin of Ewing's sarcoma is in some way closely related to the lymphoid type of cell. It responds to x-ray therapy like the lymphoid group, histologically, the cells resemble lymphoblasts and lymphocytes, the early x-ray picture is similar to the multiple bone involvement seen in lymphatic leukeima, and the tissue culture characteristics are lymphoid rather than endothelial[24]. The tendency to involve other bones rather than metastasize to other organs suggests lymphosarcoma of lymph nodes.

The probable origin of this lymphatic tissue seems to be most likely the perivascular lymphatic endothelium. One author has observed proliferation of this endothelium into multiple layers and some sprouts growing out into the connective tissue. Further, the tumor maintains its angioblastic arrangement and produces a secretion of lymph fluid[21].

Whether the tumor originates intracortically or subperiosteally has not been ascertained. However, it is quite certain that it does not originate within the medullary cavity.

Experimental work has shown that lymphatics exist in the cortex and the periosteum and that they have intercommunications, but no one has ever proved the existence of lymphatics within the medullary cavity[21].

Also, the shape of the tumor is against its being of medullary origin. It is not round or centrally placed on the x-ray, it narrows rather than expands the central cavity and the periosteal reaction occurs early. Sections usually show only a small part of the tumor in the marrow cavity.

If one assumes it to be intracortical or primary in the Haversian system, this would explain the rapid infiltration by tumor producing early endosteal and periosteal reaction. With this hypothesis one could also explain the widened Haversian canals and the laminated cortical bone. It would also be easy to see how the tumor could infiltrate under the periosteum and later into the medullary cavity as well as its apparent ease of spread longitudinally along the shaft of the bone.

If one assumes it arises subperiosteally, this would help explain: the tumor's limitation to the shaft of the bone, since the active subperiosteal layer ends at the epiphyseal line; why the bulk of the timor is located subperiosteally; the tendency of the Haversian systems to be infiltrated, the reactive formation of the bone and the tendency to extend up and down the shaft.

Reticulum cell sarcoma and Ewing's sarcoma are most likely variants of the same tumor[45].

Atypical cases show transitions from reticulum cells thru lymphoblasts to lymphocytes, the small lymphocytes constituting the small round cells of typical cases.

Tissue cultures reveal development of some cells with prolongations of cytoplasm which are like reticulum cells as seen in these atypical Ewing's sarcomas[24].

Some pathologists feel that the many microscopic forms of Ewing's are apparently the results of variations in growth and in blood supply rather than varying modes of histogenesis. The commonest form of cell being the small round cell and the reticular cell second. Spindle type, lymphocytic and myelocytic types are rare.

The chief opposition to the lymphatic endothelium theory of origin comes from the group who believe Ewing's finds its origin in the reticulo-endothelial system. They believe the tumor arises from a very undifferentiated mesenchymal cell capable of differentiating into adult reticulo-endothelium, into hemohistioblasts or endothelium. They'a are almost forced to believe the origin is in the medullary cavity and much later goes to the cortex. The tumor cells of Ewing's should then be able to become osteoblasts and form bone[16].

It has never been demonstrated whether this more primitive type of reticulum cell occurs in the Haversian canals[24].

When these primitive cells become more differentiated, they resemble fibroblasts, fibrocytes and even osteocytes. Therefore, the cell of origin in Ewing's sarcoma, fibrosarcoma, osteogenic sarcoma and lymphoblastoma is the same, depending on the line and extent of differentiation.

Therefore, the diagnosis of Ewing's tumor could not be a separate and complete entity but is interrogated with lymphoblastoma and myeloblastic tumors on one hand and fibrosarcoma and osteogenic sarcoma on the other[31].

Another study reveals that practically all instances of Ewing's tumor occur in those parts of the skeleton where ossification begins toward the end of the second month of fetal life (therefore in the shaft and not the epiphysis). Consequently, the source of the primitive mesenchymal cells, being embryonal,

rests[3].

It has been noted that in the pathological section of these tumors as well as the clinical picture, evidences of infection are to be found. Consequently, it is only to be expected that this possible cause or at least contributary factor should be investigated.

One worker injected dried endothelial myeloma chicken virus into the tibial marrow of week old chicks and produced typical endotheliomas. He then inoculated a series of chicks with this tumor material and produced five different varieties of bone sarcoma found in man; endothelial myeloma, plasma cell myeloma, osteogenic sarcoma, giant cell tumor and an epithelial tumor[14].

This led to the trial of various substances to ascertain their systemic effect on the disease. A chance observation of a patient with Ewing's tumor who apparently improved when afflicted with erysipelas began the use of Coley's toxins to be mentioned later.

Finally there is the opinion that this disease represents only bone metastases from internal or visceral sources.

Bronchiogenic carcinoma and especially neuroblastoma are most frequently sited as the primary lesion. The first need not concern us here as it is the latter which has caused the greatest amount of comment.

After several cases which had been diagnosed Ewing's sarcoma from the clinical, x-ray and biopsy observations as well as the tumor's response to x-ray therapy had been proved by autopsy to be neuroblastoma or sympathicoblastoma, a doubt arose as to how many were being misdiagnosed thus, or even if they might all be neuroblastomas.

Certainly there is no doubt of the existence of an entity such as neuroblastoma.

Briefly, neuroblastoma is a tumor of the sympathetic chain or the adrenal. They usually occur before the age of five and the microscopic picture characteristically shows cells almost identical to those described for Ewing's sarcoma excepting for their arrangement in circles or rosettes.

However, the "characteristic" rosettes have been unequivocally demonstrated to occur in Ewing's tumors on which thorough autopsy has been performed and no neuroblastoma found.

The fact that a fair number of ten year cures have followed removal of a primary tumor diagnosed as Ewing's should certainly counteract the assumption that they are all neuroblastomas.

The conclusion we draw from this, then, is that the two diseases resemble each other very closely and some new diagnostic procedure is necessary to distinguish them and clarify the treatment as well as the statistics.

Treatment

Treatment of this disease falls mainly into two types, x-ray therapy and surgery.

In Ewing's original description of the tumor, he mentioned its radiosensitiveness. Since then, use of x-ray therapy has been tried quite extensively. Since the widespread use of x-ray therapy, the per cent of cures has decreased rather than increased, possibly due to the false sense of security the initial regression gives. The benefits of irradiation are transient[24].

In a general way, the shorter the life cycle of a cell, the greater its sensitivity to x-ray therapy and the converse is also generally true. Altho the range of sensitivity to x-ray therapy is extensive, no cell is wholly invulnerable. The life cycle of the lymphocyte is the shortest of human cells and therefore it is the most sensitive[28].

The individual sensitivities in a group of Ewing's tumors seems rather more uniform than that of other varieties of neoplasm[20]. However, radiosensitivity doesn't parallel radiocurability[29].

It is the general feeling that irradiation alone is not sufficient to control the disease in a majority of cases.

The maximum normal tissue tolerance doses are advised[6] and one roentgenologist doesn't feel adequate treatment has been given unless he can deliver 4,500r into the tumor[47]. This seems to be in agreement with the opinions at the University of Minnesota.

Also, it is felt by many that the entire bone should be treated as if it were all tumor even though x-rays show it to be rather localized.

Microscopic examination of tumors twelve hours after 750r had been delivered revealed at least two thirds of the cells showed destruction with large numbers of crumbling nuclei. It should be possible to notice clinical regression of a tumor after two or three treatments.

One must not be misled, however, into believing, as some do, that the tumors treated adequately with irradiation don't recur and that recurrence is an absolute sign of inadequate treatment[20]. It has been definitely shown at autopsy that some tumors exhibit a maximum degree of radioresistance in that, altho receiving maximum normal tissue tolerance doses, tumor cells were still found in the primary tumor[6].

The status of preoperative irradiation is somewhat controversial but is generally approved both for diagnostic and treatment purposes. Those who object, do so on the grounds that delay in amputation means loss of valuable time. If one contemplates a resection rather than amputation (which, incidentally, gives better results than either irradiation or resection alone), preoperative irradiation is of great value in shrinking the soft tissue mass and making the operation technically easier[36].

Postoperative irradiation is often advised, but without very thorough consideration of the subject. What structures should be irradiated?

The regional lymph nodes of course. But there are those who feel that one cannot be sure of the diagnosis between neuroblastoma and Ewing's and so should routinely irradiate the abdomen whether a mass is felt or not[2].

One author has even advocated the routine irradiation of the lung fields since this is the most common place for metastases[41]. This view is not held by many, however, including our x-ray therapy department.

In the irradiation of soft tissue Ewing's sarcoma, it has been advised to give sufficient dosage to treat the bone and not just the soft tissue mass as it has a tendency to metastasize and recur locally as if being "seeded" by the bone[38].

Coley's toxins were mentioned previously. There is sufficient undisputable data on this subject to show that some cases have been markedly improved by the use of this material, either alone or combined with irradiation even after the disease has reached the inoperable stage and developed metastases.

However, on the basis of statistics, of any single treatment, amputation gives the most favorable results. Yet, a combination might be expected to improve results to some extent.

The general outline of treatment in operable cases which seems to be most logical consists of:

1. Early diagnosis
2. Biopsy and frozen section diagnosis under tourniquet to help prevent metastases.
3. While waiting for the results, carefully close wound and discard all instruments used. Change gown and gloces.
4. If it proves to be a Ewing's tumor, do an immediate amputation before removing the tourniquet.
5. Post-operative irradiation of regional lymph nodes.
6. A trial of Coley's toxins.

Inoperable cases should be treated with the maximum dose of x-ray therapy and followed with an extensive course of

Coley's toxins. Weekly injections for six months is considered adequate for one course of therapy. This may be repeated.

After x-ray treatment, marked bone production is usually noted to take place.

Prognosis

Several large groups of cases have been followed a sufficiently long period of time to draw a few definite conclusions as to prognosis.

It is becoming increasingly evident that a five year survival does not mean a cure. Cases dying of metastases seven, eight and nine years later are being reported.

A few clinical signs of prognostic value are:

A patient with a duration of symptoms of twenty months or more before seeking medical aid fared better than those of shorter duration[8]. This apparently indicates a less rapidly growing tumor. However, symptoms do not always precede the fatal stage of the disease[24].

Location of the tumor is of great prognostic significance. When the tumor is within or close to the trunk, including the upper femur, mortality is practically 100%[10].

Cell differentiation plays an important role in the prognosis[45].

In an excellent article based on the study of four hundred cases in the Registry of Bone Sarcoma and on fifty-one cases of tue author's, certain microscopic signs were found to be of value.

The author graded the tumors as to malignancy on the basis of the average number of mitotic figures per high powered field. Grade I--1-5/hpf, Grade II--6-10/hpf, Grade III--11-15/hpf, and Grade IV--16 & up/hpf. On the basis of this grading, some interesting observations were made.

The shorter lived cases had an average mitotic-figure count of 7.2 as compared to 6.3 in the others.

As was stated previously, patients with a tumor of the torso lived a shorter life than those with a tumor of the extremity.

It was found, torso tumors had an average count of 7.4 and those in the extremities had 6.4

It was noted that patients seen early had a higher count. If these patients were treated with x-ray only, a longer survival resulted than if treated with amputation. However, cures with x-ray therapy were rare.

The author had four, five-year survivals out of fifty-one cases. Those living had the lowest mitotic counts. That is, three fell into Grade I and the fourth was classified Grade II since it had a count of six/hpf.

The presence of few or many oat-cell or spindle-shaped nuclei didn't seem to influence the grade of malignancy.

Altho not very well substantiated, it would appear that those tumors showing heavy chromatin content may be considered more malignant.

No significance can be attached to the presence or absence of nucleoli.

Differential Diagnosis

Briefly other bone tumors and low-grade inflammatory conditions cause most of the trouble in differentiation.

Osteogenic sarcoma is perhaps the most frequent offender[13]. This tumor tends to show more bone production early, in the form of spicules instead of lamina. It is usually in the metaphysis of the long bones and it doesn't respond to x-ray therapy.

Osteomyelitis, chronic, and especially Garré type of sclerosing osteomyelitis has long been a difficult differential. Even biopsy doesn't always solve the problem. An example is B.B., a case at the U. of M. who for two years was diagnosed as Garré's, both on x-ray and

biopsy. A subsequent review of the first biopsy after the diagnosis became obvious still showed no evidence of Ewing's sarcoma. However, careful history, physical and laboratory findings including x-ray and biopsy usually gives the correct diagnosis.

Syphilis is occasionally confusing on the x-ray picture, as was one of our cases. The Wassermann, the older age group and its lack of response to x-ray but improvement to antiluetic treatment gives the diagnosis[24].

T.B. and multiple myeloma will rarely cause confusion.

Neuroblastoma has already been discussed and it may be impossible until autopsy is performed to differentiate this condition. However, they tend to be multiple, occur during the first five years of life and are more likely to show rosettes on biopsy[25].

Biopsy

Whether the biopsy procedure gives rise to tumor cell emboli and aids in the formation of metastases has never been proved. There are both experimental evidence and case histories which argue against it, however.

Experimental needle biopsies of rat carcinoma and even maceration of the tumor with the needle showed no increase of metastases over a control group[27].

One case of Ewing's sarcoma was diagnosed as osteomyelitis and a drilling procedure done. The symptoms returned and a trapdoor was cut in the bone. A diagnosis of Ewing's was tentatively made, but two more biopsies were done to confirm it. The patient was finally treated with x-ray therapy and Coley's toxins. The patient was living and well nine years later[27].

Aspiration biopsy has proved very successful in some hands and may be a safer procedure[13,22].

Altho there are many who argue against biopsy, positive evidence of spread of the tumor is lacking.

Many authorities feel that if there is a difference of opinion on the diagnosis as arrived at from the biopsy and results of x-ray therapy, the latter is most reliable[33,17].

Serum Alkaline Phosphatase

Occasionally one may get an increase in the serum phosphatase. This may indicate multiple bone involvement. In these cases, follow-up determinations may aid in determining the degree of inactivity caused by x-ray therapy or extirpation of the tumor if they return and remain at normal levels.

Serum phosphatase is likely to be increased if pathological fracture occurs or if treating with Coley's toxins.

Series

In order to show the results being obtained in this very grave disease, some of the larger series reported in the literature will be briefly mentioned.

1. A series of 99 cases followed, showed 86 dead and 13 living.

   a. of the 13 living, 6 are 5 years or more.

      (1) 2 had surgery (amputation) and irradiation.
      (2) 3 had surgery (amputation) only.
      (3) 1 had irradiation alone.

2. A series of 24 treated by x-ray therapy alone had 6 survivals of 3-12 years.

3. There were no 5 year cures in a series of 150 treated with x-ray alone.

4. A series of 54 cases treated with surgery alone had 4 five year survivals.

5. A series of 35 consecutive cases treated by irradiation or surgery--all died.

Our series consists of 15 cases, the

Case	Age	Sex	# Mo. between Onset & Rx	History of Trauma	Bone Affected	Pathologic Fract.	Temp.	W.B.C.	X-Ray Diag.	Biopsy Diag.	Metas. before Rx	Rx	Tumor Life (Mo's.)	Autopsy	Average m-f Count
1.	16	M	3	+	L 1/3 femur	-	102°	10,300	Ewing's	No biop.	+	X-ray	9	-	
2.	16	M	12	+	U 1/3 femur	-	(r) 99.1	10,250	1.Ewing's 2.Osteo.	No biop.	-	X-ray	12	-	
3.	51	M	13	-	U 1/3 femur	-	?	6,700	Osteo.Sar.	Ewing's	-	X-ray	14	-	
4.	12	M	1	-	U 1/3 femur	+	102	14,600	Ewing's	No biop.	-	X-ray	?	-	
5	8	F	1	-	L 1/3 tibia	-	101	12,000	Leukemic Infiltration	No biop.	+	None	2	+	4 (Grade I)
6.	14	M	3	+	U 1/3 tibia	-	(r) 99.8	8,100	1.Ewing's 2.Scl.Osteo.	No biop.	-	X-ray	12	-	
7	13	M	3	+	L 1/3 fibula	-	100.5	9,000	Ewing's	No biop.	-	Refused Amp. X-ray	35	+	
8	19	M	16	-	Os Calcis	-	99	7,200	Osteo.Sar.	Ewing's	-	Amputation L 1/3 femur	20	+	10 (Grade II)
9	18	M	2	+	Livert.	-	98.6	9,350	Ewing's	Ewing's	-	X-ray	7	-	
10.	14	M	13	-	U 1/3 tibia	-	100.4	6,350	Ewing's	Retic.Var. of Ewing's	-	X-ray & Amp. of M 1/3 femur	72 c Met.	L	1.7 (Grade I)
11.	14	F	6	-	U 1/3 femur	-	98.6	8,050	Scl.Osteo.	1.Osteo. 2.Ewing's	-	Penicillin X-ray	28	L	2.5 (Grade I
12	26	F	24+	-	L4&S.Vert.	-	98.6	9,100	Malig. Tumor	Ewing's	-	X-ray	63	L	12 (Grade III)
13.	74	M	2	-	M 1/3 fibula	-	98.6	8,000	Osteo.	Retic.Var. of Ewing's	-	Local ex. X-ray	Died of Other Causes		4.0 (Grade I)
14.	36	F	10	+	U 1/3 femur	+	98.6	7,800	Ewing's	Ewing's	-	X-ray	24	L	9.7 (Grade II)
15	13	F	3	-	U 1/3 tibia	-	(r) 99.6	9,850	1.Ewing's 2.Osteo.Scl.	Ewing's	-	Ref.amp. X-ray	14	-	

outcome of which is known in every case.

An attempt has been made to analyse them from the standpoint of those factors which constitute a poor prognosis.

The ages vary from 8 to 74. Males predominate 2:1. Only one patient had symptoms lasting more than 20 months before seeking medical attention. This patient is the only 5-year survival of the series apparently free of the disease.

History of trauma was noted in six. A high per cent of cases with tumors situated in unfavorable parts of the body were encountered in this series.

Two pathological fractures occurred. More than half of the temperatures and W.B.C.'s were normal.

The x-ray diagnosis proved accurate in 60%. Biopsy was done in eight cases, including the three still living.

An objection might be raised to one case included in this series since some felt it should be considered a reticulum cell sarcoma on the basis that no tumor tissue was found in the medullary cavity. However, since it is felt that this case, accidentally discovered on an x-ray taken for another purpose, is a very early one, the tumor had not had time to invade the center of the bone. It was admittedly typical of Ewing's in all other respects, and therefore was included here.

At least two patients had metastases before treatment could be instituted.

X-ray was used in ten cases. All but one of these were inoperable because of location or advanced state of the process.

Of the two cases treated with combined removal of the primary lesion and x-ray therapy, one died of other causes too soon to be of value in regards to treatment. The other is living six years later, but has metastases.

One case treated with surgery alone, which should have been best suited for this form of treatment, died twenty months later.

Of the four patients living at the present time, one is too recent to be of statistical value, two have metastases and the fourth is living and well as of March, 1948. (Five years after the onset of symptoms.)

Autopsy was performed on three cases and the findings agreed with the diagnosis of Ewing's sarcoma except in case #5, where one might seriously consider it a possible case of neuroblastoma.

Microscopically, cells seem to be arranged in rosettes in some areas altho this is true of some proved cases of Ewing's.

No conclusions can be reached from the attempt at grading these tumors due to an insufficient number, but case #10 was considered a Grade I and has lived six years. Case #11, also a Grade I has lived 28 months with a tumor which took two years to become evident. Case #12, (a Grade III) would be expected to have a more malignant appearance since it occurred in the torso, but the good results on x-ray therapy are a little difficult to understand.

It is common for these tumors to be less malignant when they occur in the older age group and this was found to be so in case #13.

The outcome in case #14 can only be guessed at, but it will probably be fatal. Case #5 certainly doesn't fit the grade which was assigned to it, but no plausible explanation is found except this was an atypical case of Ewing's in every way.

In conclusion

1. The histogenesis of Ewing's Tumor is still in dispute, but its status as a separate entity is well established.

2. If confronted with a case of persistent bone pain, without obvious cause, in a young individual, it is sarcoma till proved otherwise.

3. Perhaps it would prove to be of value to attempt classification of tumors as to malignancy on a histological basis.

4. In treatment, a combination of amputation and x-ray therapy should be used whenever possible. Perhaps Coley's toxins should be tried until something more effective is found.

List of Cases

1. ..-age 16-Male.

Admitted April 30, 1932 complaining of pain in the right thigh for 3 months and swelling of same for 5 weeks.

Injured in January 1932 while playing basketball. Limped for a month and then was fairly good until March when he twisted his knee while running.

Anorexia and a 20 lb. weight loss. Quite weak.

Examination: Large, hard, eliptical tumor of lower one-third right femur about 19 cm. long. Measurement of right thigh (in spite of muscle atrophy) was $38\frac{1}{4}$ cm. Left side was 32 cm. Definite bruit over mass.

X-ray: Ewing's tumor. No lung metastases. Possible Ewing's of right ischium. W.B.C.-10,300, Temperature 102°, Pulse 120 to 130.

Treatment: X-ray ' 145% S.E.D. right thigh and hip. 5/10 to 5/25/32. X-ray - 145% S.E.D. right thigh and hip, 7/27/32.

Note: August 15, 1932 - No change in general condition. Tumor unchanged.

Patient gained weight during July and not having any pain.

October 8, 1932 - Died of metastases.

2. - age 16 - Male

Admitted November 4, 1932 with pain in right hip and knee, pain in chest, night sweats and weight loss. History of injury to right hip 4 years ago. In bed because of pain and stiffness for 1 year prior to admission.

Tumor in right upper thigh. Hard and non-tender. W.B.C.- 10,250.
X-ray - Ewing's sarcoma or possible osteo.

Treatment- 110% S.E.D. to 3 fields right upper femur. 11/18/32.

Note- Multiple metastases to both lungs. Primary tumor showed good response to x-ray treatment.

3. W.P. - Age 51 - Male.

Pain and swelling appeared in June, 1933. It recurred in October, 1933. Lasted until February 1934.

Three weeks prior to first admission to a hospital noted swelling of leg and a 10 lb. weight loss.

X-ray of chest was normal. X-ray of left upper femur compatible with Ewing's sarcoma.

Biopsy - Ewing's sarcoma.

Treatment - Radium needles inserted into tumor and later radium blocks to skin.

Several courses of X-ray later, (dosage not known).

Patient died August 16, 1934.

4. - Age 12 - Male.

Admitted June 25, 1937. Noted limp and pain in right upper femur during December, 1936. Treated for rheumatism.

In January, 1937 was given deep X-ray therapy elsewhere.

February 27 film showed pathological fracture thru tumor. This subsequently healed.

Further X-ray treatment in May.

In June a new lesion noted in lower end of femur.

Patient began losing weight and appetite. X-rays of femur, knee, and chest revealed destructive bone lesions.

Temperature 100-103°. W.B.C.-14,600.

Exact date of death not known.

5. - Age 8 - Female

Admitted July 25, 1937 complaining of scalp tumors and weakness. She was apparently well until July, 1937. Then rapidly developed pain and swelling in multiple parts of her body including shoulders, skull and lumbo-sacral region. Lost weight and appetite. Swelling in lower right leg was probably the primary tumor.

Examination - Temperature 99-102°. W.B.C. 4,000-12,000. Clinical diagnosis was leukemia or Hodgkins.

Expired on August 23, 1937.

Autopsy- Pneumonia right lung- no tumor found. Pneumonia left lung - 1 cm. tumor nodule.

Tumor attached to left kidney, 2 cm. in diameter and not involving kidney tissue.

Both kidneys involved with tumor tissue.

Tumors of scalp eroded skull and attached to dura.

Two tumors within cranium- One was $2\frac{1}{2}$ cm. in anterior fossa behind left eye and another 2 cm. in posterior fossa midline. T8-T9 vertebra involved.

Tumor 8 b 6 cm. attached to pelvis-sessile.

Tumor 9 x 4 cm. fusiform on left leg just above ankle, attached to periosteum of tibia and fibula.

Tumor tissue consistent with Ewing's sarcoma.

6. - Age 14 - Male.

Admitted on March 9, 1938. All right until December, 1937 when kicked by horse. Swelled and remained tender for 2 weeks. Then subsided only to reappear in February, 1938.

W.B.C.- 8,100. X-ray diagnosis- Ewing's sarcoma.

Treated with X-ray. Patient died January, 1939 with metastases.

7. - Age 13 - Male.

All right until November,1938 except for poor appetite. Then injured left lower fibula in fall. Swelling fluctuated some till January, 1939 when he injured it again.

Chest X-ray normal. W.B.C.-9,000.

Treatment X-ray February, 1939. Amputation refused.

More X-ray in May, 1939. Improved.

Mass in groin noted August, 1939. This was also treated with X-ray. At this time more was given to fibula.

Metastases to chest August, 1939.

Expired October, 1941.

Autopsy- Mass bulging diaphragm into abdomen.

Lung fields almost filled. Liver normal except for one nodule of tumor.

8. . - Age 19 - Male.

First seen by M.D. for painful heel, especially on weight bearing, February, 1939. Had similar attack in fall of 1938. Some edema over lateral maleolus at that time, No X-ray taken.

June 7, 1939 - X-ray film negative.

September, 1939- Swelling of ankle began.

November, 1939- Very swollen and painful. Limited motion.

Biopsy 12/6/39 - Ewing's sarcoma.

Amputated lower thigh 12/7/39. Chest film negative.

June, 1940 - Metastases to Pubis.

July, 1940 - Metastases to sacrum, first lumbar and possibly thoracic spine.

Examination- October 22, 1939. Lumps in scalp, ribs, scapulae and arms. Bloody fluid in chest. Expired October 1939.

Autopsy- Scalp metastases, masses of tumor tissue in lungs. Metastasis in spleen. Mass of tumor tissue 2.5 by 3 by 3 cm. at costovertebral junction of 4th thoracic vertebra.

9. . - Age 18 - Male

Well until October 28, 1942, when exposed to bad weather. Developed malaise and weakness, especially of lower extremities. December 4, 1942 had acute retention and could move legs only a little and by the next day was completely paralyzed, Sensory level at Lumbar 1.

W.B.C. - 9,350. Gibbus at T12 with tendernesss. X-ray Destructive lesion of Lumbar 1. Chest, negative.

Treatment - Laminectomy - tissue- Ewing's sarcoma.

X-ray therapy.

Note- May, 1943 revealed little improvement and gradual down-hill course til death 5/43.

10. - Age 26 - Female.

Two years before admission on 12/5/44 had typical signs and symptoms of herniated disc. Gradual onset. Pain also in coccyx. A.J. absent bilateral.

X-ray- malignant lesion.

Treatment- Laminectomy of Lumbar 5 and Sactal 1. Tissue- Ewing's sarcoma.

X-ray therapy.

Last note on 3/24/47- living and well, gaining weight, no symptoms.

11. - Age 14 - Male.

Admitted January 20, 1943 with history of lump on right leg just below knee for 1 yr. Now growing and is the size of an egg.

X-ray- destructive lesion of upper right tibia involving half of the shaft.

Biopsy - Ewing's sarcoma.

Treatment - Deep X-ray and mid-thigh amputation in February, 1943.

Chest X-ray March, 1945- metastases. Treated with X-ray.

Further metastases treated with X-ray and local segmental excision.

Last seen January, 1948 with more metastases of lungs but fairly good general condition.

12. - age 14- Female.

August, 1945 developed pain in right thigh with limp. Some weight loss. X-ray diagnosis February 1946 - chronic sclerosing osteo.

Biopsy- 2/16/46 - chronic osteo.

Pain worse in 2/47 and treated with penicillin. Pain relieved.

Thigh began gradually enlarging in 7/47. Biopsy revealed Ewing's sarcoma. X-ray revealed involvement of femur, ischium and T 10 vertebra. Review of first biopsy still can only be osteo.

Treatment- X-ray with marked improvement. Later recurred and more X-ray therapy given.

13. ... - Age 74 - Male.

Admitted 10/23/47 because of prostatism. Circulation poor in legs and venogram done to determine circulation of deep veins. Process in fibula seen and investigated.

X-ray diagnosis- osteo.

Treatment- Fibulectomy, partial, done and diagnosis of Ewing's made. This was later changed to reticulum cell sarcoma because "no tumor found in medullary cavity".

X-ray therapy given.

Patient expired 1/24/48 of other causes.

14. - Age 36 - Female.

Admission 11/21/47 with history of fall on 2/12/46. Had pain in upper left thigh intermittently since, with a limp. Pain became constant last three months.

Chest film- negative.

X-ray diagnosi- Ewing's sarcoma tumor upper one-third of left femur. W.B.C. 7,800.

Biopsy- Ewing's sarcoma.

Treatment- X-ray. Hip spica for pathological fracture.

15. - Age 13- Female.

Admitted Feb. 14, 1945 complaining of pain and gradual enlargement of the right tibia just below the knee since Dec., 1944. A course of treatment with sulfa drug had been given originally by L.M.D. and it improved. It then began to enlarge again very rapidly.

W.B.C.- 9,800, Temp. 99°.

X-ray diagnosis- 1. Ewing's, 2. Osteogenic Sarcoma.

Biopsy - Ewing's Sarcoma.

Amputation was refused by the parents so two courses of deep x-ray were given. The first was in 2/26/45, the second 7/19/45.

X-rays on 7/20/45 showed some improvement but the tumor was considered to be still active. Chest neg.

X-ray of chest on 9/12/45 showed metastases to the hilum bilaterally, to the left lung and to the ribs.

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III. MEDICAL SCHOOL NEWS

Pathology Conference

One of the functions which it is hoped that these pages will perform is to inform physicians who are not on the campus of the Medical School of the many worthwhile conferences and meetings to which they are cordially invited. One such meeting is the Pathology Conference held each Tuesday at 12:30 in the Anatomy Building. Clinical material chiefly from Twin City hospitals is briefly presented in such a way that the diagnosis becomes a challenging problem. Physicians and medical students in the conference are invited to give their diagnostic impressions. Only after everyone has had their say does the Pathologist give the results of the autopsy. X-ray films, if available, are discussed by Dr. Rigler or one of the other Radiologists. The conference is presided over by Dr. E. T. Bell, Professor of Pathology, or some member of his staff. The deep interest in clinical medicine of our staff in Pathology always assures pertinent comments correlating clinical and pathological findings. A great deal of stimulation can be assured any physician or medical student who attends these conferences and such visitors are welcome.

American College of Physicians Meeting

Dr. Cecil J. Watson, Head of the Department of Medicine and Dr. Wesley Spink, Professor of Medicine will have a busy week in San Francisco during the annual meeting of the American College of Physicians, April 19 to 23. Dr. Watson will be giving a lecture on Prognosis and Treatment of Hepatitis Insufficiency and will take part in a Panel Discussion on Liver Diseases. Dr. Spink will give a lecture on The Pathogenesis of Human Brucellosis with Respect to Prevention and Treatment and will also take part in a Panel Discussion on Fhemotherapy.

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New Aid In Visual Education

Dr. Leo Rigler, Chief of the Department of Radiology has recently exhibited an apparatus for projecting x-ray films on the screen. This apparatus, called a Vu-graph, throws a greatly enlarged x-ray shadow on the screen in such a way that minute details are readily visible to an audience of a large amphitheater. This should add greatly to the many conferences held in the University Hospitals in which a demonstration of x-ray findings plays such an important role.

Dr. Glick Receives Grant

Dr. David Glick of the Department of Physiological Chemistry has recently received a grant of $9,000.00 from the United States Public Health Service. These funds will be used to help him continue his studies on the Inhibition of Hyaluronidase in Health and Disease.

Kellogg Course

The course in the applied medical sciences offered by the medical school and sponsored by the W. K. Kellogg Foundation will be completing its third year in June. The course for 1947-48 was originally planned as a nine month course with Anatomy being presented in the summer and other preclinical and clinical departments taking part in the fall and winter quarters. Seventeen physicians wished to take further work during the spring quarter. A course was arranged for this group using a seminar type of presentation with the registrants taking an active part in the preparation and presentation of the material. It is hoped that extensive use of this type of presentation may be used in the Kellogg course for next year.

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