Tumor Metastases in Bone Marrow

By Ulfar Jonsson, M.D.,* and R. W. Rundles, M.D.

The notorious tendency of some tumors to metastasize by way of the blood stream and lodge in the bone marrow has been discussed in a previous communication dealing with carcinomas arising from the prostate gland.14 Individuals who have fever, pain, weight loss, etc., due to widespread neoplastic disease before there are local signs or symptoms of tumor growth usually present difficult diagnostic problems. Infiltration of the bone marrow with tumor tissue may lead to blood abnormalities such as progressive anemia, sometimes with immature granulocytes and nucleated red cells in the circulating blood, thrombocytopenic purpura,10 etc. Skeletal disease, another common result of blood-borne metastases, may resemble primary bone tumor, multiple myeloma, hyperparathyroidism,17 lipid granuloma, or Paget’s disease.4

The possibility of recognizing tumor cells in bone marrow aspirated from the sternum was first studied in 1936 by Rohr and Heglin.14 They found tumor cells in 11 of 75 patients with neoplastic disease. Many investigators were subsequently able to identify tumor implants in aspirated bone marrow.2, 11, 12, 18-21 After Henning6 suggested using bones other than the sternum and choosing the site for aspiration by the presence of tumor nodules, roentgen abnormalities or areas of bone pain, an even higher percentage of positive findings was obtained.

The present study was undertaken (1) to ascertain the reliability and practical usefulness of bone marrow aspiration in the diagnosis of tumor metastases in a large series of patients, (2) to correlate the morphology of tumor cells if possible with the site of their origin, and (3) to study the role of marrow infiltration in producing the anemia commonly associated with neoplasm. One hundred and fifty-two patients with tumors of different types were chosen for study (table 1). Many had tumors that had spread locally or were suspected of having metastasized. A considerable number were first seen as diagnostic problems.

The technical procedures were those previously employed.16

Case Histories

F. L. M., C49481, a 29 year old white housewife, was first admitted to Duke Hospital on November 30, 1948. She had been well until one year earlier when she hit her left breast while carrying wood. A mass appeared at the site of injury and about three months later she noted a nodule under her left arm. Her physician advised no therapy unless the mass increased in size or became painful.

Two months before her admission to the hospital she began to feel weak and had mild aching in the lumbar region. Her physician found that she was anemic and gave her 15 units of liver extract intramuscularly and 1.8 Gm. of ferrous sulfate daily for one week. There was no improvement. She was then given eight blood transfusions of 500 cc. each, and 10 mg. of folic acid was added to her daily medications.
On admission to the hospital she was thin, pale and chronically ill. A hard, irregular fixed mass was present in the left breast and two firm lymph nodes measuring 2 cm. in diameter were palpable in the left axilla. There was moderate tenderness to pressure over the sternum. The liver and spleen were not palpable.

Examination of the blood showed the hemoglobin to be 7.0 Gm. per 100 cc., red blood count 2,300,000, white blood count 13,230, hematocrit 19.5 per cent, reticulocytes 6.2 per cent, and platelets 50,000–120,000 per cu. mm. The white blood cells were distributed as follows: Segmented neutrophils 8 per cent, nonsegmented neutrophils 37 per cent, metamyelocytes 3 per cent, neutrophilic myelocytes 4 per cent, lymphocytes 34 per cent, eosinophils 3 per cent, basophils 3 per cent, and monocytes 8 per cent. There were 9 normoblasts per 100 white blood cells.

Roentgen films showed extensive osteolytic lesions in the skull, ribs, scapulae, clavicles, humeri, spine, pelvis and upper femora (fig. 1, A). The serum calcium was 13.3 mg. per cent, phosphorous 2.6 mg., and alkaline phosphatase 11.8 Bodansky units.

<table>
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<th>Primary site</th>
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<tr>
<td>Kidneys, etc.</td>
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<td><strong>71</strong></td>
<td><strong>90</strong></td>
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Bone marrow was aspirated with difficulty from the iliac crest. The marrow was almost completely replaced with clumps of foreign cells with pyknotic nuclei varying greatly in size and shape (fig. 2, A).

A lymph node was removed from the left axilla and showed infiltration with scirrhous carcinoma.

She was given testosterone propionate, 100 mg. three times a week, intramuscularly. Her blood values continued to fall rapidly. Purpuric lesions appeared on the arms and feet and she bled from the gums and nose. She was given five blood transfusions of 500 cc. each. She was discharged from the hospital twenty-three days after admission with the hemoglobin 13.2 Gm. per 100 cc. and the red blood count 4,300,000. During the next six weeks the blood values continued to fall but then improved for several weeks.

She was readmitted on April 4, 1949. On examination she was again pale and chronically ill. There were numerous soft tissue metastases. Roentgen films showed conspicuous progression in her bone lesions (fig. 1, B). The blood values were as follows: Hemoglobin 4 Gm. per 100 cc., RBC 1,27 M., WBC 13,150, hematocrit 12.3 per cent, platelets 200,000, and reticulocytes 30.5 per cent. Immature granulocytes were present in the circulating blood as before and there were 35 nucleated red blood cells per 100 white blood cells.

The bone marrow was examined for the second time and again only a small amount of
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marrow could be aspirated. There was almost complete replacement with huge clumps of tumor cells similar in morphology to those present before hormone therapy. The patient expired at home on July 25, 1949.

Fig. 1.—(A) Roentgen film of upper femur, Case F. L. M., C49481, December 1, 1948. (B) Same, 4 months later.

Fig. 2.—(A) Photograph of tumor cell clumps in bone marrow of Case F. L. M., C49481, ×420. (B) Photograph of "signet ring" tumor cells surrounded by normoblasts from Patient O. H. D., C65285, ×420.

H. L. W., B49974, a 69 year old business man, was admitted to Duke Hospital for his final illness on August 19, 1949. At the age of 16 he had developed tuberculosis of the right hip which in the course of ten years and after multiple operations healed with deformity. During the ten years before admission he had had two to three episodes of right shoulder pain lasting one to two months. Eight weeks before admission he developed pain in the left hip that radiated down the leg posteriorly. Four weeks later he began to have aching about his right shoulder and arm.
On physical examination he was obese and not apparently ill. There were scars and deformity about the right hip. Movement of the right shoulder and left hip was limited and painful. Roentgen films showed numerous calcifications in the hilar areas of the lungs and at the right apex, as well as along the lumbar vertebrae on the right side. There was extensive scarring about the right hip with a false joint between the femur and ilium above the acetabulum. Films of the right shoulder showed demineralization and narrowing of the joint space.

His hemoglobin was 12.4 Gm. per 100 cc., and WBC 7,100. The sedimentation rate was rapid. Urinalysis was negative. Serum calcium was 8.3 mg. per 100 cc., phosphorous 3.0 mg., alkaline phosphatase 12 King-Armstrong units and acid phosphatase 2 King-Armstrong units.

He was treated for twelve days in the hospital with traction applied to the left leg, following which the treatment was continued for a month at home. It was then necessary to readmit him to the hospital because of increasingly severe joint pain. He had developed in addition pain about his chest and severe constipation.

He had also at this time developed pronounced rib and sternal tenderness. Roentgen examination of the skeleton showed no new findings. The hemoglobin was 12.1 Gm. per 100 cc., RBC 4,650,000, hematocrit 41 per cent, and WBC 7,100. There were no immature granulocytes or nucleated red cells in the circulating blood. Urinalyses showed small amounts of protein. Stool examinations were negative for blood. The serum calcium was 8.4 mg. per cent, phosphorous 2.8, and alkaline phosphatase 6.6 Bodansky units.

A bone marrow examination was requested because of the pronounced tenderness of the superficial bones. Marrow was aspirated in small quantity from a tender area of the sternum. In the stained films the cellular elements were almost exclusively large clumps of tumor cells varying in size with eccentric nuclei and abundant vacuolated cytoplasm. Abdominal distention, fever and bone pain rapidly became worse. There was no improvement with nitrogen mustard therapy. He died on October 30, 1949.

At autopsy there were metastatic tumor implants in the liver, adrenal glands, omentum, lymph nodes, peritoneum, diaphragm and bones containing red marrow. A slight thickening of the gastric mucosa was observed and histologic sections showed the primary tumor to be a small mucus producing carcinoma.

O. H. D., 65285, a 65 year old white school janitor, was admitted to Duke Hospital on July 16, 1949. Six months earlier he had the onset of progressive weakness and ease of fatigue. Two months before admission he developed spontaneous bruising over his legs and became too weak to work. Three weeks before admission he vomited blood amid tarry stools. He was given seven blood transfusions. There was little improvement and after returning home he began to have severe nose bleeds.

On admission to the hospital he was thin, chronically ill, pale, jaundiced and dyspneic. There were many large ecchymotic areas over the extremities. There was no definite increase in bone tenderness. The liver edge was palpable 6 cm. below the right costal margin, but the spleen was not palpable. The urine was dark red in color and contained a trace of protein. Two barium chloride strip tests for bilirubin were negative. A 2-4 p.m. urine specimen contained 2.7 Ehrlich units of urobilinogen. The total serum bilirubin was 2.1 mg. per 100 cc., 0.5 mg. reacted at 1 minute and 0.7 mg. at 15 minutes. The stools gave positive guaiac tests for occult blood.

The hemoglobin was 4.2 Gm. per 100 cc., RBC 1,300,000, and WBC 13,200 with the following differential: Segmented neutrophils 71 per cent, nonsegmented neutrophils 22 per cent, metamyelocytes 4 per cent, lymphocytes 3 per cent. There were 16 normoblasts per 100 white cells. The hematocrit was 12 per cent, reticulocytes 12.0 per cent, and platelets 50,000. In the stained films the red blood cells varied moderately in size and shape. There were no spherocytes. The Coombs test was negative.

Bone marrow aspirated from the sternum was of normal cellularity. There was an ex-
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An extraordinary increase in erythroid precursors with a leukocyte-erythroid ratio of 1:3. Scattered among the bone marrow elements were several clumps of foreign cells with abundant gray cytoplasm and eccentric "signet ring" nuclei (fig. 2, B).

After admission to the hospital the patient was given three blood transfusions of 500 cc. each. On the second hospital day he developed a severe headache, rapidly became comatose and died.

On autopsy the anatomic diagnoses were: Small ulcerated carcinoma of the stomach with metastases to the retroperitoneal and hilar lymph nodes, both lungs, and the bone marrow of the sternum, ribs, vertebrae and femur; splenic and hepatic hematopoiesis and hemosiderosis; and massive intracerebral and subarachnoid hemorrhage. Microscopic study showed that the tumor cells contained a great deal of mucin. Many had a typical "signet ring" appearance.

H. W. E., C61971, a 53 year old salesman, was admitted to Duke Hospital on May 27, 1949. He had been very obese throughout most of his adult life, was known to have had arterial hypertension for 5 years and had had hemiplegia of sudden onset one and a half years before admission.

Four months before admission he developed severe low back pain after lifting. The pain became progressively more severe. A few weeks later he developed chills and fever, was thought to have pneumonia, and was given penicillin and aureomycin. The fever subsided within a week, but soon returned and persisted in spite of antibiotic therapy.

After entering the hospital his temperature ranged from 38.2 to 39.5 C. He was too obese to permit an accurate physical examination. He was critically ill, and breathed rapidly with loud expiratory wheezes. Blood pressure was 180/104 mm. mercury. His chest was emphysematous. Wheezes and rhonchi were audible throughout the lung fields. The liver was palpable 7 cm. below the right costal margin. Rectal examinations by several observers showed no evidence of prostatic or other neoplasm. A mild spastic hemiparesis was present on the right. There was increased tenderness over the sternum and pelvic bones.

Examination of the blood showed his hemoglobin to be 8 Gm. per 100 cc., RBC 3,840,000, hematocrit 30.5 per cent, and WBC 10,900 with the following differential count: Segmented neutrophils 58 per cent, nonsegmented neutrophils 21 per cent, metamyelocytes 4 per cent, eosinophils 1 per cent, lymphocytes 8 per cent, and monocytes 8 per cent. Platelets were normal in number. The urine contained nearly 1 Gm. of protein per 24 hours that precipitated at pH 5.0 below 60 C. and when acidified with nitric acid cleared at boiling and reprecipitated on cooling. His stools gave negative tests for occult blood. The serum proteins were 5.3 Gm. per 100 cc., with the albumin 3.3 Gm. and globulin 2.0 Gm. Serum calcium was 6.0 mg. per 100 cc., phosphorous 3.5 mg., alkaline phosphatase 75-82, and acid phosphatase 3.5-4.0 King-Armstrong units. Roentgen films of the chest and abdomen showed dense proliferative bone changes in the pelvis, spine and ribs. A barium enema showed no abnormality.

Bone marrow was aspirated from the sternum. Virtually no cells were present except metastatic tumor cells, some of which had eccentric nuclei and abundant foamy cytoplasm.

He rapidly became worse and died three weeks after admission. At autopsy the anatomic findings included: Benign polyps of the descending and sigmoid colon; anaplastic polypoid carcinoma of the rectum with metastases to the psoas muscles, prostate, pelvic and abdominal lymph nodes, adrenals, pancreas, liver, heart and bones; extreme osteosclerosis and splenic anl hepatic hematopoiesis.

The preceding cases illustrate typical clinical problems presented by patients with widespread neoplastic disease where the demonstration of tumor cells by bone marrow aspiration was obviously useful. Tumor implants were demonstrated by aspiration in 71 of the 152 patients (table 1). This high percentage of positive findings was due in part to the selection of patients, but probably more
to the careful selection of the site for marrow aspiration. The sternum, ribs and other superficial bones were carefully examined for nodules or tender areas which suggested local tumor growth and a favorable site for aspiration. When collapsed vertebrae or roentgen evidence of disease in deeper bones was present, a long number 18 spinal needle was implanted and its correct position verified by roentgen films before the aspiration was done. Tumor cells were found in the sternal marrow in 50 instances, and in 21 cases elsewhere—skull, clavicles, vertebrae, etc.

Metastases to bone marrow were found most frequently in patients with neuroblastoma, carcinoma of the prostate, breast and in those in whom the primary tumor could not be located during life. The 3 patients with carcinoma of the colon were not representative of all patients with this neoplasm. One had multiple polyposis and presented with a tumor involving the sterno-clavicular joint. A second patient, though, was found to have metastatic cells in an area of bony destruction in the ischium and a carcinoma of the descending colon was discovered in a search for the primary tumor.

The hemoglobin was less than 12 Gm. per 100 cc. in 90 patients. In 29 individuals, anemia was present without evidence from roentgen study or bone marrow aspiration of tumor metastases. Bleeding, infection, fever, etc., seemed to adequately account for the anemia in these patients. In 30 individuals without anemia, localized tumor metastases were present in bone marrow. In only one patient (Case O. H. D.) the anemia seemed to result from increased red cell destruction.

Twenty-two patients had so-called leukoerythroblastic anemia with immature granulocytes and nucleated red cells in the circulating blood. All of them had bone marrow metastases. Nucleated red cells and immature granulocytes were not seen in the blood of patients in whom the hemoglobin was 12 Gm. per 100 cc. or more, and usually not until the hemoglobin was reduced below 8.5 Gm. per 100 cc. The most severe degrees of anemia occurred in those with most extensive bony involvement as judged by marrow films and by roentgen abnormalities. Metastases from prostatic carcinoma and neuroblastoma tended to produce generalized infiltration of the bone marrow and were the tumors most frequently productive of leukoerythroblastic anemia. When the response to hormone therapy was good in patients with prostatic carcinoma the anemia regressed and fewer tumor cells could be demonstrated in the bone marrow. The tumor cells that persisted developed eccentric and pyknotic nuclei, and basophilic cytoplasm as previously described.

The demonstration of tumor metastases by bone marrow aspiration was in many instances a valuable supplement to roentgen methods in demonstrating bony metastases which have been almost exclusively relied upon in the past. Of the 71 patients in whom tumor implants were found in the bone marrow, there were 12 with no x-ray evidence of skeletal involvement, and equivocal changes in 3. Of the 81 patients in whom tumor implants were not demonstrated in the marrow, 23 were thought to have x-ray evidence of neoplastic skeletal involvement, and in 6 the changes were doubtful.
This suggests that bone marrow examinations should be performed in patients thought to have malignant disease before extensive surgery is performed. This is particularly true if the patient is thought to have a tumor that is likely to spread to the skeleton or has any symptoms or signs suggesting bone involvement.

The criteria by which tumor cell implants can be reliably recognized in bone marrow films have been generally agreed upon. Tumor cells are first of all foreign cells unlike normal marrow elements or any derived from the hematopoietic tissues in common pathologic conditions. In films they tend to be seen in clusters in areas in which cells from the bone marrow are well spread. Tumor cells vary in size, are generally larger than normal cells, except the megakaryocytes, and often have poorly delimited boundaries. The nuclei are large, hyperchromatic and have prominent nucleoli.

Inferences as to the site of the primary tumor have sometimes been made from the study of the morphologic features of the metastatic cells. Rohr and Hegglin in their small number of cases found that tumor cells in the bone marrow tended to be either large cells or small. The former seemed to arise largely from the stomach and prostate, the latter from bronchial neoplasms. Later investigators, however, studied more extensive material and were unable to correlate the size of tumor cells with their site of origin. In some instances other features were helpful in this regard. Tischendorf and Frank studied metastases from squamous epithelial tumors in aspirated lymph node material and in bone marrow. With the Giemsa stain these cells were colored red along the edges while the cytoplasm closer to the nucleus was basophilic. This finding was confirmed by Francke, who described, in addition, characteristic features of spindle-cell sarcoma and melanomasarcoma. Metastases from the former were composed of spindle shaped cells with thin protoplasmic protrusions at the ends. The latter contained prominent melanin pigment granules described also by Rubinstein and by Batte and Stasney. Metastases from neuroblastoma were first reported in aspirated marrow by Kato and Wachter. Landolt later studied this type of implant present in 12 of 17 patients with neuroblastomas and regarded their mosaic arrangement and fine chromatin pattern somewhat similar to myeloblasts as characteristic of the tumor.

In our material adenocarcinoma implants from different sources were remarkably similar in appearance. Occasionally the structure of the tumor could be inferred from rosette shaped groups resembling transected acini. In 9 of our patients the tumor cells contained mucous, evidenced by vacuolated, foamy cytoplasm, usually gray or faintly blue staining and sometimes an eccentric nucleus with typical "signet ring" appearance. The primary tumor arose from the stomach in 3 instances (fig. 2,B), the bronchus in one (fig. 3,A–B), the colon in 3 (fig. 3,C), and unknown in 2. Pigment granules were observed in cells of one patient with melanosaarcoma that had metastasized to the skull. The only patient with hypernephroma in our series in whom metastases were found appeared to have a characteristic type of cell with small to medium sized nucleus and abundant lacy, gray staining cytoplasm with granules (fig. 3,D). Fleisch-
hacker and Klima described a similar patient with cells of this type. In 2 of our 3 patients with metastatic neuroblastoma the cells were apparently smaller than those described by Landolt, Kato and Wachter. The nuclear chromatin pattern resembled that of myeloblasts (fig. 3,E). In the third patient the metastatic cells were larger (fig. 3,F).
The origin of metastases can thus occasionally be inferred from the morphologic features of the aspirated tumor cells, especially in mucus producing or squamous cell carcinomas, some adenocarcinomas, many cases of metastatic neuroblastomas or melanomas. Histochemical stains, such as Gomori's method for demonstrating acid phosphatase activity, etc., apparently have not been applied to the study of tumor implants in bone marrow. Valuable information might be obtained by such methods in certain instances.

Many authors have described secondary bone marrow reactions in patients with neoplastic disease with or without marrow infiltration. These reactions include increase in number of plasma cells and/or reticulum cells, a shift toward immaturity in the myeloid series, an increased number of megakaryocytes, etc. In our material these changes were so variable that little diagnostic value could be attached to them. Occasionally the percentage of plasma cells has been increased to the extent that the diagnosis of multiple myeloma has been considered. In our patients plasma cells were increased to 10 per cent or more in some instances but were normal in morphology. Six of the 7 patients with hypernephroma were among those with increased plasma cells in the bone marrow.

**Conclusions**

Since aspiration biopsy of the bone marrow is often helpful in demonstrating tumor metastases it is recommended as a diagnostic procedure for the presence of widespread malignant disease, especially when extensive surgery is being contemplated.

By carefully selecting the site for aspiration, positive findings were obtained in 71 of 152 patients with different types of malignancies. Carcinoma of the prostate and neuroblastomas were especially prone to infiltrate the marrow diffusely. Gross marrow infiltration was found in patients with leukoerythroblastic anemia. The primary site of tumor growth can sometimes be inferred from the appearance of the metastatic cells.

**REFERENCES**

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