CASE REPORT

The Detection of Malignant Melanoma by Bone Marrow Aspiration

A Report of Two Cases

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Since 1936, when Rohr and Hegglin first recognized tumor cells in the bone marrow, numerous articles have appeared reporting bone marrow metastases in neuroblastomas, sarcomas and a wide variety of carcinomas including tumors of the prostate, breast, lung, stomach, colon, kidney, other organs and undetermined primary sites. The value of sternal and iliac marrow aspirations as diagnostic and prognostic aids has been emphasized by many investigators, yet there is little information recorded on melanoma cells in the marrow. A search of the literature revealed only 8 cases, to which we are recording 2 additional cases.

Historical Review

In 1941 Battle and Stasney made the diagnosis of malignant melanoma by sternal puncture in a 60 year old housewife who had lost her right eye enucleated two years previously. She entered the hospital with severe back pains, anemia and weight loss. A roentgenologic survey of her skeletal system and lungs revealed no abnormalities. An unequivocal diagnosis could not have been made before death without the bone marrow studies. In 1942 Dicker and Dubois-Ferriere reported 2 patients with generalized melanoma with bone marrow metastases. The aspirated marrow was grossly black in color. Two additional patients were reported by Dubois-Ferriere in 1946. One had a melanoma of the left shoulder with metastases to axillary lymph nodes. The other patient, a 62 year old man, had a primary lesion on the right heel without involvement of the inguinal lymph nodes as shown by biopsy. Sternal puncture revealed metastases of the tumor eight months prior to the appearance of clinical signs. Had it not been for the discovery of pigmented tumor cells in the marrow biopsy, this patient would have had an extensive operation.

Within the past four years, three similar instances have been recorded. Rubinstein reported a 47 year old woman who entered the hospital with pain in the right leg, anemia, weight loss and a mass in the lower abdomen. X-rays showed some destruction of the lumbar spine. The material obtained by sternal puncture was normal, but aspirations from the iliac crest were ink black. Micro-
scopie examination of the iliac marrow revealed "numerous melanin-laden cells." In a series of 152 patients with malignant disease, Jonsson and Rundles did bone marrow aspirations on 2 patients with malignant melanoma and obtained a positive result in one case. Durkee and Wilson recently diagnosed disseminated malignant melanoma by sternal marrow aspiration in a 48 year old man who had undergone enucleation of his left eye two years previously.

**Case Reports**

**Case 1**

A 67 year old white retired farmer entered the University Hospitals on January 28, 1952, with a five month history of severe back pain, weakness, anorexia and a loss of 30 pounds. Two months prior to admission he had developed severe pain in the lower anterior ribs bilaterally and vomited intermittently. In November 1950, a dark "wart" on his back had been removed by electrocautery.

Physical examination revealed a chronically ill, anemic man who held his back stiff and moved with difficulty. In the interscapular area a flat scar measuring 7 by 15 mm. was found. At the upper margin of the scar extending cephalad was a 1.0 by 1.5 cm., brown-black, slightly indurated lesion which was elevated superiorly. Nearby were several yellowish-tan seborrheic warts. Examination of the fundi with the pupils dilated failed to reveal any abnormalities. There was no adenopathy. The chest was somewhat emphysematous but otherwise normal. Careful palpation of the abdomen did not reveal any masses. The liver and spleen could not be felt. Rectal examination was normal. A complete neurologic examination was normal. Percussion over the middle and lower thoracic vertebrae and lower ribs was painful. The initial working diagnoses were malignant melanoma, multiple myeloma or widespread carcinoma from an undetermined source.

Laboratory data: The blood Wassermann was negative. A complete urinalysis was normal. Melanuria was not present. The hemoglobin was 8.0 Gm. per 100 ml., erythrocyte count 3,060,000, white cell count 3,450 per cu. mm. with a normal differential, hematocrit 29 per cent, sedimentation rate by the Westergren method 96 mm. in one hour, platelet count 142,000 (Sanford's direct method) and the reticulocyte count 1.2 per cent. The bleeding time, coagulation time and erythrocyte fragility tests were normal. Clot retraction was complete. Liver function studies were normal. The serum calcium, phosphorus and the alkaline phosphatase were normal. A lumber puncture was normal except for a slightly elevated protein of 50 mg. per 100 ml. A teleoroentgenogram of the chest showed clear lung fields. Special films for rib detail were normal. X-rays of the pelvis showed questionable erosion of the left pubis. Antero-posterior and lateral films of the thoracolumbar spine revealed generalized demineralization, wedge-shaped narrowing of the fifth thoracic vertebra and collapse of the ninth thoracic vertebra with erosion of the left pedicle.

Upon completion of the above laboratory tests a sternal puncture was performed. The marrow specimens contained large clumps of ink black material easily seen with the naked eye (fig. 1). Microscopic examination of smears fixed by Wright's stain revealed extensive infiltration by tumor cells (figs. 2 and 3). These cells were arranged singly or in clumps and varied in shape, being round, rectangular or spindle-shaped with the cytoplasm extending out as a tail. A large, bluish-violet nucleus was made up of loose, evenly distributed, rather heavy chromatin strands with an occasional nucleolus. The cytoplasm was pale blue in color, somewhat mottled, frequently vacuolated and often had an indistinct border. In most cells the cytoplasm contained a variable number of pigment deposits ranging from small, faint, greenish-black granules to heavy clumps of black material. Some of the pigment was extracellular. An occasional reticulo-endothelial cell containing similar dark cytoplasmic granules was noted.

Bone marrow aspirations from the right and left iliac crests and the dorsal spine of the first lumbar vertebra had the same appearance as the sternal marrow both grossly and microscopically. A small amount of heparinized marrow was centrifuged in a Wintrobe hematocrit tube, and it was observed that a mixture of tumor elements and white cells lay-
Fig. 1 (Case 1)—Aspirated bone marrow as it appeared on gross inspection. Note the large clumps of ink black material (×3).

Fig. 2 (Case 1)—Photomicrograph of the bone marrow showing extensive infiltration by pigmented tumor cells, many being spindle-shaped. (×700)

...ered out as the “buffy coat” above the packed red cells (fig. 4). Concentrated samples of peripheral blood were checked carefully for tumor cells without success.
The pigmented interscapular skin lesion, though it appeared benign, was totally excised and sectioned longitudinally. Microscopic examination revealed normal epidermis succeeded by irregular acanthosis in which the basal cells and adjacent cells of the rete mucosum showed heavy pigmentation and extreme loss of polarity. Scattered pigmented cells extended up through the rete mucosum, many going past the granular layer into the stratum corneum. Masses of melanoblasts without polarization occurred in loose clusters at the tips of the rete pegs. Mitoses were few, or obscured by pigment. In one zone there was an extension of the tumor cells into the upper dermis; these were mostly of the fusiform type, although many round pigmented cells with huge vesicular nuclei were also present. In the dermis under the most active portion of the epidermal growth were groups of plasma cells and lymphocytes.

The patient's condition has progressively deteriorated.

Case 2

An 18 year old white postal clerk entered the University Hospitals on February 8, 1952, complaining of weakness, vomiting and shortness of breath of three months' duration. A black mole had been present on his left neck beneath the angle of the jaw all his life. The mole had been traumatized frequently and bled on several occasions. Three years previously the lesion began to grow and was removed surgically. Microscopic examination of the tissue was not done. Several months later a subcutaneous nodule appeared at the upper end of the scar and gradually increased in size during the next year. The "lump" was excised and sections revealed malignant melanoma with scanty pigment. X-ray therapy was given to the left neck area after which the patient felt well until three months before admission when he developed left pleural effusion and lost 15 pounds. In January 1952, a thoracentesis was performed with recovery of an unknown amount of fluid. The patient was sent to the hospital for possible operation.

Physical examination revealed a chronically ill, apprehensive young man. There was a thin, flat scar 5 cm. long on the upper left side of the neck with an adjacent subcutaneous
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nodule 6 mm. in diameter. No lymph nodes were palpable. The fundi were normal. The entire left hemithorax was dull to percussion and breath sounds were absent. The liver was enlarged 4 cm. below the right costal margin, firm to palpation and questionably nodular. Rectal and neurologic examinations were normal.

Laboratory data: The blood Wassermann was negative. The hemoglobin was 12.5 Gm. per 100 ml., the erythrocyte count 4,160,000 and the white cell count 7,500 per cu. mm. with a normal differential. Melanuria was present, otherwise the urine was normal. Postero-anterior and lateral films of the chest showed a homogeneous density over the entire left

chest. X-rays of the pelvis disclosed multiple osteolytic lesions involving the right ischium, right pubis and left ilium. Films of the thoracolumbar spine were normal. A thoracentesis of the left chest yielded 2,800 ml. of blood-tinged, straw-colored fluid. Cytologic studies on the fluid were negative for tumor cells.

Bone marrow aspirations from the right and left iliac crest appeared normal but on microscopic examination showed almost complete replacement of normal marrow elements by tumor cells (fig. 5). Morphologically these cells were similar to those described in Case 1 except for being somewhat larger with a finer, more reticular nuclear chromatin pattern, more obvious nucleoli and much less cytoplasmic pigment. Many of the melanoma cells contained no pigment. No extracellular pigment was seen.
Our patients had widespread disease. In Case 1 an unequivocal diagnosis was not established before the withdrawal of ink black material from the sternum. Multiple marrow aspirations from different sites in both patients showed heavy infiltration with abnormal cells in all smears, indicating a diffuse process.

The marrow of the two patients differed, notably in cell morphology and quantity of pigment. In Case 2 the nuclear chromatin of the tumor cells was finer and more reticular, with pigment deposits in only an occasional tumor cell. The spindle-shaped cells, present in Case 1 were absent in Case 2. The melanoma cells in either case could not have been differentiated from other tumor cells, excluding multiple myeloma, but for the dark pigment granules in the cytoplasm. This makes malignant melanoma unique since we have been unable to identify the origin of other tumor cells in the bone marrow. The amelanotic type would not be identifiable since it is without pigment.

The diagnosis of malignant melanoma metastasizing to the bone marrow is made by the following criteria: (1) clumping of the cells, (2) cell morphology, plus (3) the presence of black pigment in the cytoplasm. From a single cell it is
hazardous to attempt positive identification. Reticulo-endothelial cells containing hemosiderin deposits may be mistaken for malignant melanoma cells (fig. 6). The reticulo-endothelial cell has a large nucleus composed of dense reticular chromatin surrounding one or two nucleoli. The cytoplasm is abundant, has indistinct irregular borders, is pale blue or light slate gray in color and may contain pigment granules similar to those in melanoma cells, although the granules in the tumor cells usually are much finer. Sometimes the cytoplasm of the reticulo-endothelial cell appears to be washed away with only the nucleus and granules remaining. These cells do not collect into large clumps like the tumor cells but are found scattered over the slide. Occasionally two or more reticulo-endothelial cells occur together.

A marrow showing evidences of melanoma involvement is of value not only diagnostically but also prognostically. It indicates generalized involvement and thus may prevent costly diagnostic examinations or extensive surgical procedures. It may give the correct diagnosis when no obvious lesion is available for biopsy. Our interest in bone marrow aspirations in malignant melanoma was stimulated by finding these 2 cases within two weeks. We are now making a bone marrow survey of other patients known to have melanoma. The practical value of such a procedure as a routine diagnostic test has yet to be determined.

Fig. 6 (Case 2)—A reticulo-endothelial cell, from the marrow of another patient, which may be mistaken for a malignant melanoma cell. (×900)
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SUMMARY

We have presented 2 cases of disseminated malignant melanoma with bone marrow metastases which are, so far as we have been able to find, the ninth and tenth cases reported in the literature. In Case 1 the cytoplasm of the tumor cells contained abundant dark pigment, whereas in Case 2 the pigment deposits were rare. A study of the morphology of the bone marrow smears reveals that the melanoma cell usually differs from other tumor cells by the presence of deposits of dark pigment in the cytoplasm. The amelanotic type would not be easily identifiable since it is without pigment. Caution is needed not to confuse the melanoma cell with the reticulo-endothelial cell. A study of other patients with malignant melanoma is now in progress.

ADDENDUM

Since finding these 2 patients with positive marrows we have obtained bone marrow aspirations from the sternum and both iliac crests on 15 additional patients with proven malignant melanoma. Six of the patients had localized lesions, 4 had involvement of the regional nodes and 5 had hematogenous spread. None of the marrow aspirations contained tumor cells, including 1 patient with osteoblastic lesions of the pelvis and spine.

REFERENCES

Case Report: The Detection of Malignant Melanoma by Bone Marrow Aspiration: A Report of Two Cases

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