LEUKEMOID REACTION IN CARCINOMATOUS SKELETAL AND SPLENIC METASTASES

A Case Report

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Leukemoid reactions have been reported as occurring in a wide variety of pathologic conditions. The reaction may be indistinguishable from a true leukemia, or it may be a hyperleukocytosis with relatively few immature cells giving no great difficulty in diagnosis. Heck and Hall (1) observed leukemoid reactions of the myeloid type in pyogenic and non-pyogenic infections, miliary tuberculosis, hemolytic anemias, pernicious anemia, polycythemia vera, and Hodgkin's disease, in active regeneration of the bone marrow, massive hemorrhage, granulocytopenia, diseases of the bone and bone marrow, malignant metastases, multiple myeloma, and osteosclerosis, and in such miscellaneous conditions as diabetic coma and chemical poisoning (mustard gas). The lymphatic type of leukemoid reaction has been observed by Krumbhaar (2) in infectious mononucleosis, pertussis, measles, typhoid fever, and acute infections, such as puerperal sepsis.

Carcinoma causing a leukemoid reaction simulating true leukemia has been reported by only a few observers. Heck and Hall observed only two instances, a case of breast carcinoma and a carcinoma of the prostate. In both, skeletal metastases were present, and in the first, splenic metastases as well. Jackson (3) reports two cases in which gross hyperplasia of the bone marrow followed bony metastases from intrathoracic cancer. In a case recorded by Sala and Stein (4) splenic and skeletal metastases from carcinoma of the breast produced an unusual leuko-erythroblastic leukemoid picture of chronic lymphatic character.

The presence of immature myeloid cells in the circulating blood has been observed more frequently than the leukemoid reaction. In a series of 50 cases of cancer with roentgen evidence of skeletal metastases, Heck and Hall found myeloid cells in one third. In a considerable number of these cases the cells were observed before the roentgen findings became positive. These authors suggested that leukemoid reactions should occur as a terminal manifestation in a fairly high percentage of patients with malignant disease. A comparatively low incidence has been observed, however, in this hospital in cases with bone metastases. In the Cancer Hospital, Welfare Island, where custodial care is given to large numbers of such patients, the experience has been similar (Sala, personal communication). Leukemoid reactions in the presence of bone metastases have been only rarely encountered.

The cause of a leukemoid reaction associated with metastases in the bones is still obscure. Sala and Stein believe it is independent of the extent of bone marrow replacement by malignant cells. They advance the premise that
there is one fundamental cause, at present obscure, for the cellular changes in the peripheral blood. It may be (a) stimulation of hemopoiesis by the skeletal metastasis; (b) a regenerative process to counteract destruction of hemopoietic elements; (c) impeded maturation of the blood cells because of a starvation process due to greedy tumor cells.

The case recorded here is a further example of a leukemoid reaction occurring in the presence of cancer metastases to bone marrow and spleen. The picture was indistinguishable from lymphatic leukemia.

**FIG. 1. PRIMARY BRONCHOGENIC CARCINOMA, EXTREMELY ANAPLASTIC**

A forty-six-year-old white woman was admitted to City Hospital, Welfare Island (1st Medical Service of Dr. John Carroll), on July 2, 1939, because of hemoptysis of nine hours' duration. She had had a non-productive cough for fifteen years and had lost sixty pounds of weight during the past two years. Two months before admission, an episode of hemoptysis led to a diagnosis of bilateral pulmonary tuberculosis, and roentgen examination showed mottling of the left upper and lower lobes, with slight peribronchial thickening in the right lung. Nine hours before admission, the patient expectorated voluminous quantities of bright red blood. She had never noticed undue shortness of breath.

Her past history revealed a tendency to bleed freely when cut and, in recent years, to develop large bruises following the slightest trauma.

There were numerous petechiae and large ecchymoses on the skin of the body and extremities. The mucous membranes were clear but pale. There were no enlarged lymph nodes. Examination of the chest revealed lagging inspiration on the left side, inspiratory retraction, dullness, and normal vocal fremitus in the left second and third interspaces. The heart was enlarged to the left with an apical impulse in the anterior axillary line, fifth interspace. Systolic murmurs were prominent over all valvular areas. Blood pressure was 150/90. The liver edge could be palpated two fingers' breadth below the costal cage.

Blood findings were as follows: hemoglobin 70 per cent (Sahli), red cell count 3,350,000; white cell count 28,450, with 27 per cent granulocytes, 13 per cent monocytes, and 60 per cent lymphocytes, chiefly prolymphocytes. The granulocytes were largely poly-
Fig. 2. Widespread Minute Carcinomatous Deposits in the Bone Marrow

Fig. 3. Diffuse Carcinomatous Invasion of the Spleen without Tumor Formation
morphonuclear cells, with a few myelocytes and metamyelocytes. The blood smear also showed occasional erythroblasts. The blood platelets numbered 110,000. Bleeding time was 8.5 minutes; coagulation time 2.2 minutes. A tourniquet test was positive, petechiae being produced rapidly. The urine and blood Wassermann reactions were negative. Non-protein nitrogen was 43 mg. per cent; blood sugar 148 mg. per cent.

The hemorrhagic tendency was evidenced by petechiae persistently appearing at the site of venipunctures, and epistaxis during the first four days in the hospital. The blood pressure fell to 120/85, but the heart sounds remained of fair quality. A roentgenogram of the lungs showed ill-defined shadows at the left hilum, suggestive of tuberculosis. Death occurred six days after admission. The final clinical diagnoses were: pulmonary tuberculosis with massive hemorrhage; purpura hemorrhagica; lymphatic leukemia.

At autopsy purpuric hemorrhages, discrete and confluent, were observed over all portions of the body, especially the limbs and anterior surface of the trunk. Mucous membranes and serosal surfaces were mottled by hemorrhagic spots. Large left subpleural hemorrhages, hemorrhagic infiltration of the wall of the cecum, and a large blood clot enclosed in the leaves of the sigmoid mesentery were particularly remarkable.

The heart weighed 335 gm. There was extensive fatty degeneration of the myocardium, with focal collections of lymphocytes and myxomatous fibrous tissue.

The lungs weighed 400 gm. each. Cut section of the left lung revealed a hard, pinkish-white, gritty mass in the bifurcation of the primary bronchus, extending into the anterior secondary bronchus and those radicles supplying the lower portion of the upper lobe. The lumen of the secondary bronchus was narrowed to 2 mm. for a distance of 1.5 cm. Distal to this was a bronchiectatic dilatation with shaggy, granular mucosa and greenish-yellow purulent contents. The lung parenchyma was invaded for 0.5 cm. on either side of the tumor. Microscopic sections through the stenotic area revealed a complete replacement of normal bronchial mucosa by cords of small, dark, anaplastic cells separated by dense strands of fibrous tissue. These cells varied in size and staining quality, did not tend to mimic glandular tissue, and showed no mitoses. Invasion of lymph spaces and adjacent tissue was noted. A section through the bronchiectatic area showed lymphocytic infiltration and emphysema, with some atelectasis. Groups of anaplastic cells were found in the peribronchial regions in lymph spaces adjacent to an arterial branch, and infiltrating the parenchyma itself. The right lung showed no noteworthy changes.

The liver weighed 2600 gm. It was enlarged, nodular and diffusely studded with malignant metastases of various size. Microscopically there were nodules of dark, anaplastic cells in a fibrous stroma grouped in glandular and alveolar arrangement. Some cells which infiltrated adjacent liver tissue singly and in groups resembled true leukemia cells.

The spleen weighed 150 gm. and was firmer than normal, with prominent fibrotic bands and malpighian corpuscles. The corpuscles, sinusoids, and fibrous stroma were invaded by islands and cords of dark anaplastic tumor cells similar to those in the lung and liver. The gallbladder, pancreas, adrenals, pituitary, and brain were normal grossly and histologically. Except for submucosal hemorrhages in the esophagus, the gastro-intestinal tract was normal. Hemorrhagic areas were present in the pelves of both kidneys.

The bone marrow was scant, very fluid, pale-pink to yellow in color; it contained many islands of tumor cells similar to those found elsewhere, with a desmoplastic reaction. The adjacent bone marrow cells and the bone itself appeared normal.

Sections of the skin through hemorrhagic areas showed marked lymphocytic and plasma-cell infiltration, extending up into the dermis and down into the subcutaneous tissue. The epithelial tissue was edematous.

Anatomical diagnosis: Bronchogenic carcinoma with metastases to liver, spleen, and bone marrow.

References