A patient with a recurrent epithelioid sarcoma of the hand was observed for five years with a diagnosis of nodular fasciitis. Eventually, the patient had a pulmonary metastasis and diffuse bone marrow spread, which was associated with a leukemoid reaction. Bone marrow dissemination by sarcoma is unusual, and its production of a leukemoid reaction very rare; this is its first reported occurrence in epithelioid sarcoma that the authors have been able to identify in the literature. (Key words: Epithelioid sarcoma; Bone marrow dissemination; Leukemoid reaction) Am J Clin Pathol 1988;90:723–726

EPITHELIOID SARCOMA is a distinctive malignant mesenchymal neoplasm of uncertain histogenesis that most frequently affects adolescents and young adults. It usually arises in the tendons, ligaments, and superficial soft tissues of the extremities and is probably the most common soft tissue sarcoma of the hand.

The natural history of epithelioid sarcoma is protracted and frequently terminates in eventual metastases and death. Although the original lesion may be small and clinically innocuous, as a rule, the tumor recurs locally or more proximally as multiple nodules. Regional lymph nodes and the lung are the most frequent sites of metastatic spread.

In general, soft tissue sarcomas metastasize via hematogenous routes. It is very unusual for soft tissue sarcomas other than rhabdomyosarcoma to metastasize to and diffusely infiltrate the bone marrow compartment with or without associated hematologic manifestations.

This case is the first report that we have been able to find in the literature of a metastatic epithelioid sarcoma diffusely infiltrating the bone marrow producing a leukemoid reaction.

Report of a Case
A 24-year-old male presented to his local physician in 1980 with a left palmar mass. The mass and three subsequent local recurrences were excised, the last in September 1984. The pathologic diagnosis of each specimen was nodular fasciitis.

In June 1985 the patient sought medical care for left shoulder pain and hemoptysis. A 1.0-cm left palmar firm mass with an adjacent 8-mm nodule covered by a blue–black eschar was noted on examination. A chest x-ray revealed a left upper lobe infiltrate with left hilar adenopathy. Bone scan showed uptake in the left ninth rib, left anterior iliac spine, and right ischium. Bronchoscopic examination demonstrated a fleshy pulsating lesion in the posterior apical segmental bronchus of the left upper lobe. A left upper lobectomy was performed. Consultative review of the hand and lung lesions by one of us (E.M.) yielded a diagnosis of epithelioid sarcoma, primary to the hand and metastatic to the lung and hilar lymph nodes.

The left chest pain persisted. Recurrent epistaxis over the next two weeks necessitated ligation of the left anterior ethmoid and internal maxillary arteries. The procedure was complicated by severe hemorrhage and fevers to 39.4 °C. No tumor or infectious process could be found, and the nature of the coagulopathy could not be defined because platelet count, protime, prothrombin time, bleeding time, and Factor VIII levels were repeatedly normal. Laboratory evaluation was remarkable for a white blood cell count of 45 × 10^9/L (45,000/mm³) with a differential of 0.70 (70%) polys, 0.16 (16%) bands, 0.05 (5%) lymphocytes, 0.04 (4%) monocytes, 0.02 (2%) eosinophils, 0.01 (1%) myelocytes, and 0.02 (2%) metamyelocytes, suggesting a leukemoid reaction. The hematocrit was 0.21 (21%) after severe epistaxis and the platelet count 357 × 10^9/L (357 × 10³/µL). The smear showed schistocytes, tear-drop erythrocytes, and nucleated red blood cells, consistent with a myelophthisic process. No tumor cells were seen. A left posterior iliac crest bone marrow aspirate and biopsy showed diffuse infiltration by epithelioid sarcoma cells. Multiple new skin nodules developed on the chest and scalp.

The patient was treated with two cycles of chemotherapy with doxorubicin, ifosfamide, and dacarbazine to which he had only transient partial response. He died of respiratory failure in September 1985. Permission for autopsy was not granted.

Pathology
Biopsy of the recurrent hand tumor in 1982 revealed a segment of tendon and attached synovial sheath infiltrated by an admixture of malignant epithelioid and spin-
FIG. 1 (upper, left). Biopsy of recurrent hand tumor showing a cluster of epithelioid cells with abundant cytoplasm merging with the spindle cell component. Hematoxylin and eosin (X313).

FIG. 2 (upper, right). Lung metastasis in which most of the tumor cells have epithelioid characteristics and increased cytologic atypia. Hematoxylin and eosin (X500).

FIG. 3 (lower). Posterior iliac crest bone marrow biopsy with the bone marrow replaced by tumor cells. Hematoxylin and eosin (X50).
dle cells (Fig. 1). The epithelioid cells were arranged in ovoid cords or short linear cords and merged with the spindle cell component. Small foci of tumor necrosis were present within both the epithelioid and spindle cell regions.

The metastasis to the lung consisted of a large hemorrhagic endobronchial mass with contiguous spread to peribronchial lymph nodes. The metastasis was composed almost entirely of the epithelioid component (Fig. 2).

The left posterior iliac crest bone marrow biopsy demonstrated metastatic epithelioid sarcoma diffusely infiltrating and replacing approximately 70% of the bone marrow (Fig. 3). The residual hematopoietic marrow was hypercellular with all cell lines present. The myeloid to erythroid ratio was increased to approximately six to one with a slight shift to the left. Reticulin was not increased.

Immunohistochemical studies demonstrated faint to focally intense granular cytoplasmic staining with antibodies directed against keratin in both the epithelioid and spindle tumor cells present in the hand lesion, and the metastases to the lung, and bone marrow. A similar pattern was seen with antibodies directed against the carcinoembryonic antigen except the tumor in the bone marrow had negative results. This latter finding may be an artifact of decalcification and tissue processing.

The tumor had negative results for leukocyte common antigen, immunoglobulin light and heavy chains, lysozyme, alpha-1-antitrypsin, alpha-1-antichymotrypsin, myoglobin, S-100, and desmin.

Discussion

This case report exemplifies the typical clinicopathologic characteristics of epithelioid sarcoma as well as the difficulty commonly encountered in its accurate diagnosis. It documents widespread bone marrow metastases and is the first reported case associated with a leukemoid reaction.

Classically, epithelioid sarcoma presents as a small nodule arising in the tendons, ligaments, aponeuroses, or superficial soft tissues of the distal upper extremity, commonly the hand, in patients who are in their second to fourth decades of life. Most tumors locally recur and spread along fascial planes, tendinogenuous structures, and the synovium. More proximal recurrences lacking continuity with the original lesional area are believed to be the result of lymphatic or vascular spread. Regional lymph node involvement is unusually frequent for soft tissue sarcomas, having a reported incidence of up to 42%. Distant metastases occur in 44–58% of patients and commonly involve the lung, skin (scalp), localized nodules in bone, and liver, reflecting hematogenous routes of spread.

In this case the original tumor and local recurrences were initially interpreted as reactive fibroblastic proliferations. Epithelioid sarcoma is notorious for its innocuous clinical presentation and histologically banal cytologic features, causing confusion with other benign entities such as necrobiotic granuloma, benign giant cell tumor of tendon sheath, fibromatosis, reactive fibrosis, fibrous histiocytoma, benign adnexal tumors, granular cell tumor, neurofibroma, and a ganglion.

The unique aspect of this case was the diffuse bone marrow spread complicated by a leukemoid reaction. Except for embryonal rhabdomyosarcoma, soft tissue sarcomas rarely metastasize to and replace the bone marrow. Bramwell and associates found bone marrow dissemination on initial assessment in 4 of 74 adults with soft tissue sarcomas; all had other evidence of metastatic disease. The histologic findings of these four were angiokeratoma, pleomorphic rhabdomyosarcoma, monophasic synovial sarcoma, and myxoid liposarcoma, and none was associated with a leukemoid reaction. Other isolated reports of bone marrow dissemination in patients with far advanced sarcoma rarely have been associated with a leukemoid response. Although our patient had focal abnormalities on bone scan, the bone marrow biopsy was from a radiographically uninvolved site. This in conjunction with the leukoerythroblastic anemia suggested that the bone marrow dissemination was diffuse.

A leukemoid reaction may be associated with infectious and inflammatory diseases, toxic exposures, and malignant neoplasms. Malignancies associated with leukemoid reactions are usually epithelial or lymphoid tumors. In addition to diffuse bone marrow dissemination, tumor-associated leukemoid reactions may result from tumor production of hematopoietic colony-stimulating factor. Other causes of a leukemoid reaction in this patient, leukemia and infection, were excluded by both the peripheral blood and bone marrow histologic results and the absence of any clinical or laboratory evidence of infection. We interpreted the phenomenon in this case as a manifestation of diffuse bone marrow replacement by metastatic tumor.

References

Lymphadenopathy and Entero-Vesical Fistula in Fabry’s Disease

DANIEL CARTER, M.D.,* HONGYUNG CHOI, M.D., GORDON TELFORD, M.D., MARRY OTTERSON, M.D., KEDAR CHITAPALLI, M.D., AND KARL PINTAR, M.D.

A case of a 55-year-old man with known Fabry's disease, complicated by entero-vesical fistula and associated with enlarged mesenteric lymph nodes, is reported. Histopathologic and ultrastructural findings of the involved lymph nodes are described, and pathogenesis of the entero-vesical fistula is briefly discussed. This is the first case, to the authors' knowledge, of urologic complication in Fabry's disease. (Key words: Fabry's disease; Entero-vesical fistula; Lymphadenopathy; Foamy cells; “Zebra-like” inclusion) Am J Clin Pathol 1988;90:726-731

FABRY’S DISEASE is an X-linked disorder of glycolipid metabolism, caused by a deficiency or lack of the lysosomal enzyme ceramide trihexosidase (alpha-galactosidase A). This enzyme defect results in progressive systemic accumulation of the substrate ceramide trihexose, which leads to skin lesions (angiokeratoma corporis diffusum) and cardiovascular, ocular, renal, cerebrovascular, and gastrointestinal dysfunction. Accumulation of this substrate in lymph nodes has been described in only a few cases in the literature. Urologic complications in Fabry's disease are extremely rare.

In this report, we describe a patient with well-documented Fabry's disease, in whom enterovesical fistula developed, a complication that has not been reported. Enlarged mesenteric lymph nodes were also encountered. Light microscopic and ultrastructural findings of the lymph nodes and the pathogenesis of enterovesical fistula, the most unusual complication of Fabry's disease, are discussed.

Report of a Case

A 55-year-old white man with known Fabry's disease presented to the hospital in May 1985 complaining of episodic epigastric and suprapubic cramping abdominal pain, worsened by eating. The patient also complained of an episode of pneumaturia and was admitted for evaluation. Urinalysis, intravenous pyelogram, cystoscopic examination, and bilateral retrograde urograms were all within normal limits. A retrograde cystogram demonstrated a posterolateral protrusion of the bladder to the right consistent with a large neck diverticulum. A barium enema revealed a segment of sigmoid diverticulitis, but no fistula was noted. A 24-hour collection of the patient's urine was performed after the barium enema, and no barium was found. The patient's symptoms resolved spontaneously, and he was discharged without a specific diagnosis.

The patient returned three months later with abdominal pain, anorexia, and nausea over a three-week period associated with a 15-pound weight loss and was readmitted in August 1985. On the evening of admission, fever and chills developed and he passed feculent-appearing urine. Blood and urine cultures obtained at the time of the febrile episode had negative results.

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Physical examination was remarkable for multiple nonpalpable telangiectasias and mild abdominal distention and guarding. A computed tomography (CT) scan of the pelvis demonstrated an abnormal soft tissue mass-like lesion with gas bubbles superior to the urinary bladder. A thickened small bowel loop and sigmoid colon were also seen. In the lower scans, air was seen in the urinary bladder. These findings were interpreted as an inflammatory lesion with communication to the urinary bladder (Fig. 1).