Indium-111-Labeled Leukocyte and Technetium-99m-Sulfur Colloid Uptake by a Malignant Fibrous Histiocytoma: Phagocytosis by Tumor Cells?

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Indium-111-labeled leukocyte imaging, performed on a patient with a calcified mass in the right thigh, demonstrated labeled leukocyte accumulation in this mass. Technetium-99m-sulfur colloid imaging was performed to differentiate labeled leukocyte uptake in heterotopic bone marrow from uptake in a focus of infection. Leukocyte and sulfur colloid images were virtually identical, and the study was interpreted as without evidence of infection. Excision of the mass revealed an angiomatoid malignant fibrous histiocytoma with metaplastic bone formation. While no marrow elements were present in either the tumor or the metaplastic bone, phagocytosis of leukocytes by tumor cells was identified. Phagocytosis of leukocytes by tumor cells may be another cause of white cell accumulation in uninfected neoplasms.

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While indium-111- (^{111}In) labeled leukocyte scintigraphy is a useful method for investigation of infection in patients with neoplasm, leukocyte uptake by uninfected neoplasm does occur (*1–9*). Causes of leukocyte uptake by uninfected tumor may include local inflammatory reactions (*5,8*), leukocyte infiltration of tumor (*6,7*), and necrosis (*4*). We encountered an uninfected malignant fibrous histiocytoma that localized ^{111}In-labeled leukocytes and technetium-99m-sulfur colloid (^{99m}Tc-SC), suggesting an additional mechanism: phagocytosis by tumor cells.

CASE REPORT

A 28-yr-old male presented with a 2-mo history of night sweats, general malaise, fever to 39°C, weight loss of 30 lbs, and an enlarging right thigh mass, diagnosed as myositis ossificans five years previously. Physical examination revealed a 16 cm × 16 cm mobile, firm, slightly painful mass in the right mid-thigh, anterolaterally. Radiographs demonstrated a soft-tissue mass with branching calcifications, suggestive of ossification (Fig. 1). Laboratory values included: hemoglobin of 7.8 g/dl, hematocrit of 24%, with microcytosis and hypochromia, leukocyte count of 27,000 per mm^3 (54% polymorphonuclear leukocytes, 20% bands, 23% lymphocytes, 1% monocytes, 2% eosinophils), and an erythrocyte sedimentation rate of 130 mm/hr (normal <12 mm/hr).

To exclude infection, an ^{111}In-labeled leukocyte study was requested. Imaging was performed 24 hr after injection of 18.5 MBq (500 μCi) of autologous mixed leukocytes, labeled with ^{111}In-oxine according to the method of Thakur et al. (*10*).

Six-minute static images of the whole body were acquired on a large field of view gamma camera, using a medium-energy collimator and 20% windows centered over the 174 and 247 keV photopeaks of ^{111}In. Leukocyte accumulation in the mass was the only abnormality identified (Fig. 2A). Bone marrow scintigraphy was performed with ^{99m}Tc-SC to distinguish leukocyte localization in infection from localization in myositis ossificans, which may contain marrow elements (*11*). Following the leukocyte study, to ascertain the contribution of ^{111}In photons to the technetium image, a 6-min thigh image was obtained (through the medium-energy collimator) with a 7% window centered over the 140 keV photopeak of ^{99m}Tc; no discernible activity was present. The patient was then injected with 370 MBq (10 mCi) of ^{99m}Tc-SC and one hour later another image was acquired (Fig. 2B) with these same parameters. The ^{99m}Tc-SC and ^{111}In-labeled leukocyte images were virtually identical; based on their spatial congruency, the study was interpreted as consistent with heterotopic marrow accumulation of leukocytes without evidence of infection.
mulation of leukocytes without evidence of infection.

The thigh mass, subsequently excised, was diagnosed as an angiomatoid malignant fibrous histiocytoma. Areas of hemorrhage and necrosis surrounded by lymphocytes and plasma cells, with peripheral metaplastic bone formation, were present within the tumor. Phagocytosis of erythrocytes and leukocytes by tumor cells was seen (Fig. 3). No marrow elements were identified nor was there evidence of infection.

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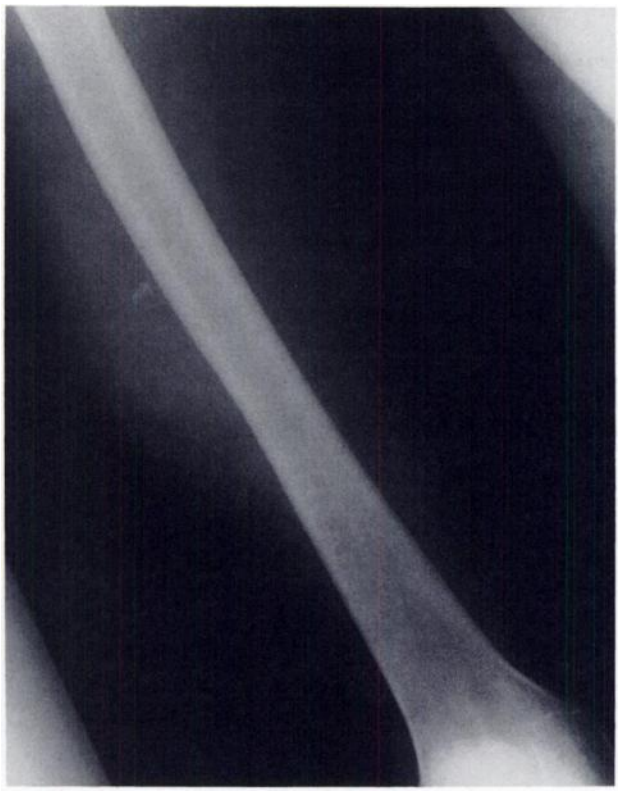

FIGURE 1
Anteroposterior radiograph of the right thigh. There is a large soft-tissue mass with branching calcifications suggestive of ossification. Differential diagnosis includes lipoma, myositis ossificans, and soft-tissue sarcoma.

DISCUSSION

Malignant fibrous histicytoma describes sarcomatous soft-tissue tumors characterized by histiocytic and fibroblastic cells arranged in a storiform (cartwheel-like) growth pattern (*12*). The cells of this tumor, though closely related to fibroblasts, are considered functional histiocytes, exhibiting ameboid movement and phagocytic capabilities (*13,14*).

The angiomatoid malignant fibrous histiocytoma, an unusual variant combining features of both a fibrohistiocytic and a vascular neoplasm, is a multinodular or cystic mass of the hypodermis or subcutis that generally occurs in an extremity in patients younger than 20 yr. It is characterized by irregular solid masses of histiocyte-like cells, interspersed with cystic hemorrhagic zones centrally, while lymphocytes and plasma cells form a peripheral cuff (*15*).

While ^{111}In-labeled leukocyte scintigraphy is useful for diagnosis of infection, labeled leukocyte accumulation in uninfected neoplasms does occur (*1–9*). Several mechanisms to explain this phenomenon have been suggested. Saverymuttu et al. (*5*) described ^{111}In-labeled granulocyte accumulation in two cases of colon carcinoma; histology revealed an acute inflammatory reaction in both. Balachandran et al. (*6*) identified labeled leukocyte accumulation in two cases of squamous cell carcinoma metastatic to brain; histology revealed abundant neutrophil accumulation in one case, while principally macrophages were present in the second case. Fortner et al. (*7*) noted tumor uptake of labeled leukocytes in six individuals: two carcinomas, two lymphomas, one sarcoma, and one bony metastasis. They speculated that tumor uptake may be due to several factors including free indium in the plasma (which binds to transferrin forming an ^{111}In transferrin complex, which has been suggested as a tumor imaging agent (*16*)), labeled lymphocyte uptake in lymph nodes involved with Hodgkin's disease, and macrophage uptake in tumors. Balachandran et al. (*8*) identified ^{111}In-labeled leukocyte uptake in 6 of 16 tumor sites. Histologic examination revealed granulocytic, lymphocytic, or macrophagic infiltration of tumor. Lamki et al. (*9*) described labeled leukocyte localization in uninfected neoplasms in 21 of 61 patients, including one with malignant fibrous histiocytoma. They suggested that labeled white cell localization in tumor could be associated with immunologic activity caused by fever and

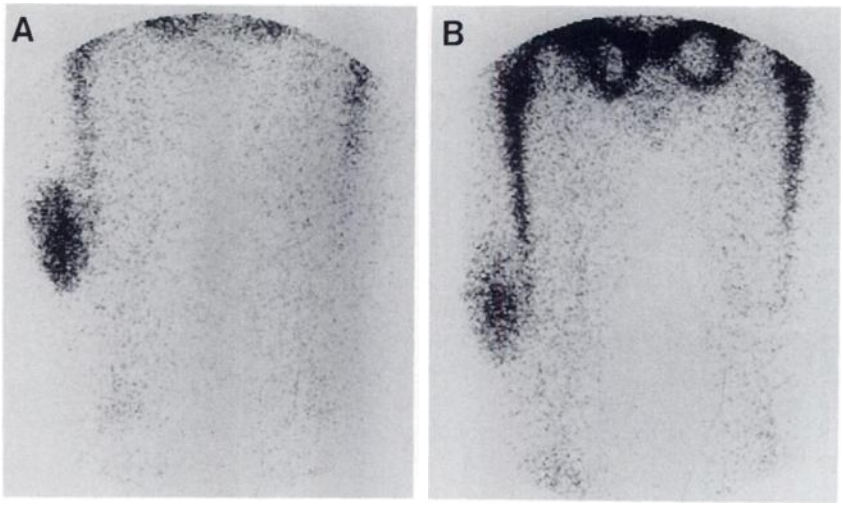

FIGURE 2
(A) Anterior 24-hr ^{111}In-labeled leukocyte image acquired for 6 min reveals a well-defined area of labeled white cell accumulation within the soft tissues of the right thigh, corresponding to the radiographic abnormality in Figure 1. Mild marrow expansion into the mid femora is also evident. (B) Anterior thigh image acquired for 6 min performed 1 hr after injection of 370 MBq of ^{99m}Tc-sulfur colloid: soft-tissue accumulation of sulfur colloid is virtually identical to the distribution of labeled leukocytes in (A). Mild marrow expansion into both mid femora is evident as well.

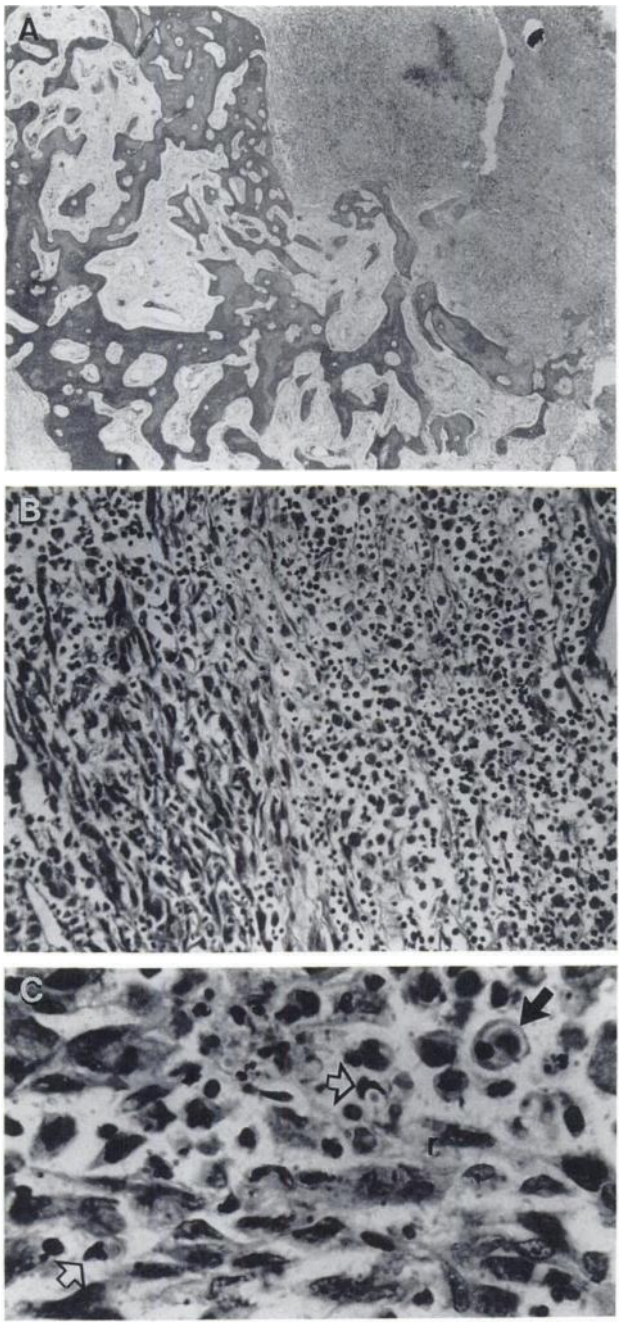

FIGURE 3
(A) Photomicrograph (24×) demonstrating metaplastic bone formation at the periphery of the tumor. No marrow elements are present. (B) Photomicrograph (200×) reveals inflammatory infiltrate (principally lymphocytes and plasma cells) interdigitating with spindle cells of the tumor. (C) Photomicrograph (787×) reveals leukocyte (solid arrow) and erythrocyte (open arrow) phagocytosis by tumor cells (i.e., functional histiocytes).

associated stress, or that perhaps leukocytes played a role in nonmetastatic effects of malignancies.

While any of these mechanisms could conceivably account for labeled leukocyte uptake in the tumor, they do not satisfactorily explain the sulfur colloid accumulation within it. Sulfur colloid imaging is typically characterized by decreased tracer uptake in those parts of the liver, spleen, and bone marrow replaced by tumor. A splenic hemangioma presenting as focally increased uptake on a ^{99m}Tc-SC study has been described; the postulated mechanism was that increased blood flow presented a greater portion of colloid to the reticuloendothelial cells surrounding the hemangioma (*17*). No reticuloendothelial cells were found in this soft-tissue tumor; therefore increased blood flow alone would not explain sulfur colloid uptake. While bleeding could account for uptake of sulfur colloid and labeled leukocytes, the identical uptake patterns of both radiotracers, injected 24 hr apart, makes this unlikely.

Indium-111-labeled leukocytes and ^{99m}Tc-SC normally accumulate in liver, spleen, and bone marrow through reticuloendothelial system phagocytosis, and the distribution of marrow activity on labeled leukocyte images is similar to that seen on sulfur colloid images (*18,19*). Complementary sulfur colloid imaging has been successfully used to differentiate normal variants of marrow activity identified on labeled leukocyte images from foci of infection (*20,21*).

While it could be argued that the sarcoma arose in an area of myositis ossificans (with marrow elements) that antedated it, there was no previous radiographic evidence to prove this assumption. Nor was there residual zoning maturation typical of myositis ossificans, and metaplastic bone is known to occur in malignant fibrous histiocytoma (*22*). We postulate that, in the absence of any reticuloendothelial cells, the congruent findings on the labeled leukocyte and sulfur colloid studies may be explained on the basis of phagocytosis by functional histiocytes of this tumor.

Phagocytosis by tumor cells has also been described in breast carcinoma and in Kaposi's sarcoma (*23,24*). This characteristic of certain tumor cells may be another mechanism of leukocyte accumulation in uninfected neoplasm. Further studies are necessary to determine if ^{99m}Tc-SC scintigraphy may help to confirm the presence or absence of infection in these cases.

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SELF-STUDY TEST

Radiobiology and Radiation Protection

Questions are taken from the *Nuclear Medicine Self-Study Program I*, published by The Society of Nuclear Medicine

DIRECTIONS

The following items consist of a question or an incomplete statement followed by five lettered answers or completions. Select the *one* lettered answer or completion that is *best* in each case. The answers may be found on page 1578.

1. The term *stochastic* is used to describe an effect of radiation
- **A.** that is dependent on age at exposure.
- **B.** in which the severity depends on the dose.
- **C.** in which the severity depends on the dose above a significant threshold.
- **D.** in which the probability of occurrence is a function of dose, with no threshold.
- **E.** in which the probability of occurrence is a function of dose, above a significant threshold.

2. What is the approximate percentage of "spontaneous" cancers and genetic mutations thought to be produced by exposure of the U.S. population to background radiation?
- **A.** 0.001%
- **B.** 0.1%
- **C.** 1%
- **D.** 10%
- **E.** 37%

3. The effects of radiation on health have been addressed by several advisory groups. What was the *most* significant aspect of the 1980 report of the National Academy of Sciences Advisory Committee on the Biologic Effects of Ionizing Radiation (BEIR III) that sets it apart from the previous reports?
- **A.** It uses the new atomic bomb dosimetry rather than the older T-65 data.
- **B.** It emphasizes radiation-induced genetic effects rather than radiation-induced cancer.
- **C.** It uses a linear-quadratic dose-response estimate as the preferred model rather than the more conservative linear dose-response model.
- **D.** The risk estimates for cancer induction by radiation are much higher than in previous reports.
- **E.** It uses the most conservative dose-response relationship as the preferred model for risk estimation.