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Intense Uptake of Technetium-99m-MDP in Primary Breast Adenocarcinoma with Sarcomatoid Metaplasia

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Focal soft-tissue accumulation of bone-seeking radiopharmaceuticals has many causes but is usually less intense than skeletal activity. Extraskeletal new bone formation, as seen in myositis ossificans and extraskeletal osteosarcoma, represents an exception where markedly increased uptake can be seen. Technetium-99m-MDP uptake in primary breast carcinoma has been recently investigated using scintamammographic techniques to differentiate malignant from benign lesions. The mechanism of uptake remains unclear but is likely multifactorial and nonspecific. We present a case of primary breast carcinoma with florid ^{99m}Tc-MDP activity relative to normal bone. Tumor histopathology in this patient demonstrates malignant new bone formation as the likely mechanism for the marked radiotracer avidity.

Key Words: breast carcinoma; technetium-99m-MDP; bone scintigraphy; sarcomatoid carcinoma

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Technetium-99m-methylene diphosphonate (MDP) uptake in extraosseous malignancies is occasionally seen on delayed imaging but is typically less intense than skeletal activity. The following case illustrates striking accumulation of ^{99m}Tc-MDP in primary adenocarcinoma of the breast.

CASE REPORT

A 61-yr-old woman was admitted to the hospital with bleeding from a large breast mass. Sixteen months before this admission, she was involved in a motor vehicle accident, suffering multiple pelvic fractures. The patient, a Jehovah's witness, eventually went on to recovery without transfusion despite moderate blood loss. Physical examination during that hospitalization demonstrated a 10-cm right breast mass; the patient had been aware of this mass for several years but had not sought medical attention. Fine-needle aspiration of the lesion revealed a high-grade ductal adenocarcinoma. Immunoperoxidase staining for estrogen and progesterone receptors was negative. These findings were confirmed on a subsequent core biopsy, which also revealed extensive sarcomatoid metaplasia with a spindle and pleomorphic cell population as well as areas of cartilaginous and osseous differentiation (Fig. 1). Immunoperoxidase staining confirmed the presence of cytokeratin in areas of conventional ductal carcinoma. Sarcomatoid regions were negative for cytokeratin but decorated with vimentin.

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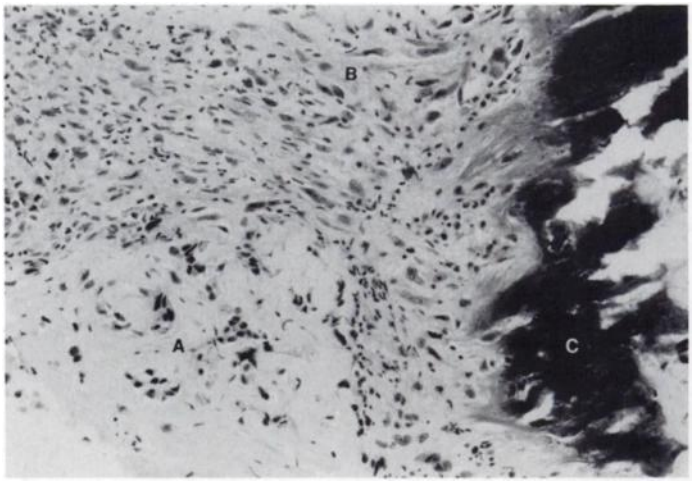

FIGURE 1. (A) Pathologic specimen from breast tumor demonstrates areas conventional ductal adenocarcinoma, (B) spindle sarcomatoid population and (C) extraosseous bone formation.

The patient refused all treatment options and was lost to follow-up, having failed to keep multiple clinic appointments. However, 2 wk prior to the current admission, she eventually presented to the outpatient clinic complaining of diffuse pain, which had worsened over a period of several weeks. Laboratory studies at that time were remarkable for a hemoglobin of 9.9 gm/dl, alkaline phosphatase of 2202 IU/liter (normal range 38–126 IU/liter) and a normal serum calcium. A chest radiograph demonstrated multiple new pulmonary nodules, consistent with metastatic disease (Fig. 2). She again refused treatment and returned home until presenting 2 wk later with bleeding from the breast tumor. In the interim, the primary cancer had enlarged to approximately 24 cm in diameter and was now adherent to the chest wall. Skeletal scintigraphy was requested to determine the presence of osseous metastatic involvement. Delayed images obtained 2 hr after injection of 20 mCi ^{99m}Tc-MDP demonstrated intense uptake of the radiopharmaceutical within the primary breast carcinoma, vastly out of proportion to skeletal uptake (Fig. 3). Limited osseous metastatic disease was seen in the skull and possibly the shoulders. There was no evidence of uptake within the lung metastases seen on the plain radiograph.

Since that time, the patient has agreed to intervention and is receiving chemotherapy consisting of cyclophosphamide, 5-FU and adriamycin, before palliative surgery (toilet mastectomy).

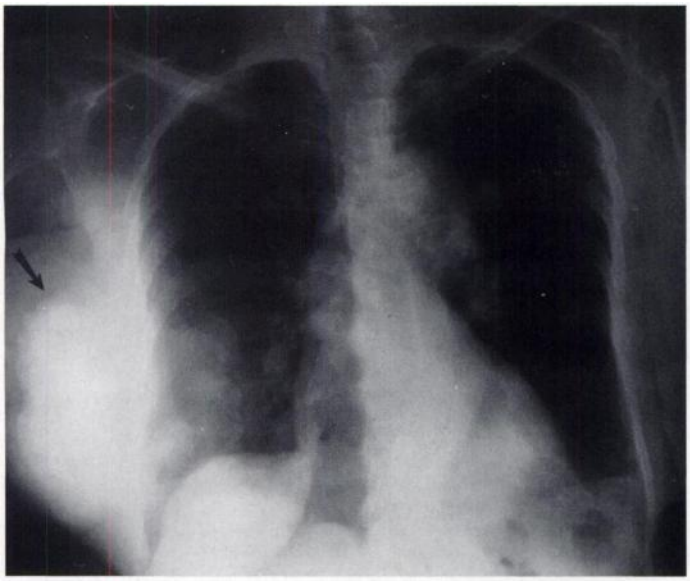

FIGURE 2. Chest radiograph demonstrates large right breast mass with evidence of calcification (arrow). Bilateral pulmonary nodules reflect metastatic disease.

Erythropoietin injections will be administered as necessary to stimulate red blood cell production.

DISCUSSION

Localization of ^{99m}Tc-MDP in soft-tissue malignancies is well-documented but is typically much less intense than skeletal activity. An exception is seen with the extraskeletal variant of osteosarcoma, which comprises approximately 1% of soft-tissue sarcomas and 4% of all osteosarcomas, where marked radiotracer accumulation reflects new bone formation (*1,2*). Myositis ossificans, a self-limited form of soft-tissue new bone production, represents a benign cause of intense extraskeletal, nongenitourinary ^{99m}Tc-MDP activity (*3*).

Radionuclide uptake in breast cancer was first reported by Low-Beer in 1946 using ^{32}P (*4*). Scintigraphic imaging of a primary breast carcinoma was accomplished in 1966 with ^{99m}Tc-pertechnetate (*5*). Concentration of bone-seeking radiopharmaceuticals within such tumors that is visible on delayed imaging has been previously reported (*6–9*). However, unlike the present case, tumor activity was invariably less than that of bone. More recently, ^{99m}Tc-MDP scintimammography with early imaging at 10–20 min after injection has demonstrated encouraging accuracy in differentiating malignant from benign breast lesions due to increased tumor-to-background activity of the radiotracer (*10*). With delayed imaging at 2 hr postinjection, the sensitivity for detecting breast cancer fell from 92% to 38%, reflecting the relative paucity of primary sites visualized on delayed images during routine metastatic evaluations. Scintamammography using ^{201}Tl or ^{99m}Tc-sestamibi has also shown favorable results (*11–16*).

Metaplastic breast carcinoma is an umbrella term which describes a heterogeneous group of tumors in which the glandular differentiation of conventional ductal carcinoma is partly or wholly replaced by a different histological pattern. The majority of cases of metaplastic breast carcinoma are conventional adenocarcinomas exhibiting areas of sarcoma-like growth. The histogenesis of these "biphasic" tumors has been the subject of a protracted literature debate. However, substantial immunohistochemical and ultrastructural evidence now exists to support the contention that these lesions are essentially epithelial tumors which have undergone metaplasia (*17*). This metaplastic process may be focal or so extensive as to require exhaustive sampling in order to identify areas of conventional breast carcinoma. Heterologous elements (those that exhibit a tissue phenotype not native to the breast) may also be identified and most frequently, as in this case, consist of areas of bone or cartilage (*17*). These heterologous foci may be directly contiguous with conventional ductal carcinoma or be associated with and separated by a spindle or pleomorphic sarcomatoid population (*18*).

The postulated causes of ^{99m}Tc-MDP uptake in extraosseous neoplasms are many and include tumor vascularity, inflammation, local pH factors, altered calcium metabolism, hormonal influences and cell wall damage (*19,20*). The histopathology in this case report offers extraskeletal new bone formation as a plausible mechanism for the intense radiotracer accumulation, in addition to the aforementioned causes. The mesenchymal metaplasia of the epithelial neoplasm with chondroid and osseous differentiation would conceivably behave much like a chondrosarcoma or osteosarcoma in terms of ^{99m}Tc-MDP uptake. Although unproven, the absence of discernable activity within the lung metastases may reflect the absence of a significant metaplastic component in these deposits. While sarcomatoid carcinomas may display dramatic histological and, in this case, scintigraphic findings, these heterologous elements do not appear to significantly alter the overall clinical prognosis (*17*).

CONCLUSION

We present a case of intense uptake of a bone-seeking radiopharmaceutical within a primary breast adenocarcinoma. Histopathologic evidence of sarcomatoid metaplasia suggests extraskeletal new bone formation as the likely cause for this finding.

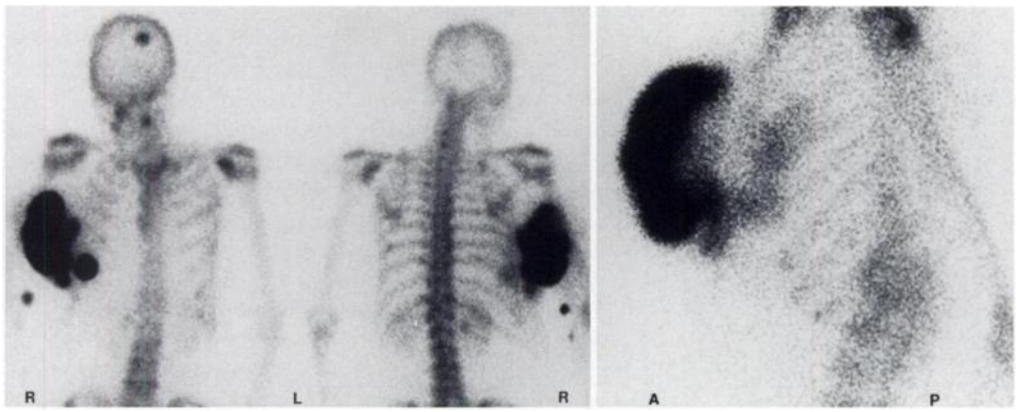

FIGURE 3. (A) Anterior and posterior images obtained 2 hr after ^{99m}Tc-MDP injection shows intense activity in primary breast tumor, which is confirmed on lateral projection (B). Evidence of limited osseous metastatic disease is present.

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Sentinel Node Imaging Via a Nonparticulate Receptor-Binding Radiotracer

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Technetium-99m-labeled polydiethylenetriamine pentaacetic acid polymannosyl polylysine (DTPA-*man*-PL) was synthesized and tested for lymph node scintigraphy by subcutaneous administration. The agent was designed for receptor-mediated uptake by mannose-binding protein, which resides on the plasma membrane of reticuloendothelial cells. **Methods:** Subcutaneous injections of a ^{99m}Tc-labeled agent having 18 DTPA and 82 mannosyl groups attached to a polylysine of 100 units ([^{99m}Tc]DTPA$_{18}$-*man*$_{82}$-PL$_{100}$) were made at the level of the metacarpus and metatarsus of three healthy rabbits. Images were acquired at 1, 6, 12 and 24 hr. Popliteal and axillary nodes were then assayed for percent of injected dose (%ID). A negative control study was performed in three normal rabbits with [^{99m}Tc]DTPA$_{18}$-PL$_{100}$. **Results:** Significant differences in mean 24-hr %ID between the receptor specific and nonspecific agents were observed for both the popliteal ($p < 0.006$) and axillary ($p < 0.012$) nodes. Popliteal percent injected dose at 24 hr was 3.00 ± 0.72% for [^{99m}Tc]DTPA-*man*-PL and 0.13 ± 0.08% for [^{99m}Tc]DTPA-polylysine. Axillary accumulation at 24 hr was 2.84 ± 0.83% for [^{99m}Tc]DTPA-*mannosyl*-polylysine and 0.22 ± 0.12% for [^{99m}Tc]DTPA-polylysine. Percent injected dose of the receptor-specific agent was highest (4%) during the 6-hr scan. Accumulation of the nonspecific agent by the popliteal and axillary nodes at 6-hr postinjection was approximately 0.5%. **Conclusion:** This study provides proof of principle for lymphoscintigraphy by receptor-mediated delivery of a nonparticulate imaging agent.

Key Words: lymphoscintigraphy; receptor-binding radiopharmaceutical; sentinel node imaging

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Sentinel node imaging is a nuclear medicine examination that identifies the first lymph node to receive lymphatic flow from the primary tumor site. Because this node will be invaded first by malignant cancer cells, its removal and microscopic examination is an extremely sensitive index of metastatic disease (*1*). Also, using an intraoperative probe, sentinel node scintigraphy can be used as a basis for accurately detecting and excising regional lymph nodes for cancer staging (*2–6*). These procedures entail administering a particulate radiopharmaceutical intradermally or subcutaneously and localizing radiopharmaceutical uptake in targeted regional lymph nodes using a planar gamma camera as well as a gamma-probe intraoperatively at the time of staging lymphadenectomy. Advantages of these procedures include preoperative or intraoperative localization of the sentinel node which reduces extent of surgical intervention; verification of excision of the sentinel node increasing accuracy of cancer staging; and real-time detection of additional lymph nodes at the surgical site.

With the withdrawal of ^{99m}Tc-labeled antimony-trisulfide from the U.S. market, clinicians were left without an agent specifically designed for lymphoscintigraphy. Filtered ^{99m}Tc-sulfur colloid (*7,8*), ^{99m}Tc-labeled colloimdal albumin (*9*) and ^{99m}Tc-human serum albumin are used as replacements, but do not possess the attributes of an ideal sentinel node imaging agent. Such an agent would provide a 100% detection rate for the sentinel lymph node. The current agents do not achieve this goal. In patients with breast cancer, ^{99m}Tc-antimony-trisulfide (*10*) and unfiltered technetium-sulfur colloid have detection rates of 91% and 82%, respectively. Filtered technetium-sulfur colloid yields a detection rate of 84% in patients with melanoma (*11*). This rate was increased to 96% when both preoperative