Unilateral Thoracic Soft-Tissue Accumulation of Bone Agent in Lung Cancer

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One hundred thirty patients with lung cancer were studied to determine the incidence of unilateral thoracic soft-tissue accumulation (UTS) of ^{99m}Tc methylene diphosphonate (MDP). The finding was present in 60 of 130 (46%) of the patients. Of 52 patients who had received radiation therapy to the primary tumor in the chest, 46 (88%) had UTS, while six (12%) did not. Radiation therapy to lung tumors was the most significant of the factors studied in unilateral soft-tissue uptake of bone agent in the thorax of patients with lung cancer.

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Bone scans, using technetium-labeled phosphates and phosphonates have been reported to show soft-tissue accumulation in a number of disease states, including lung cancer (*1–4*) metastatic tumor to the lung (*5*), pleural effusions containing malignant cells (*6–9*), and malignant ascites (*10,11*). Speculation as to the etiology of this accumulation has been offered in some of these studies, and a number of possible mechanisms have been presented. The present investigation was prompted by the finding of unilateral soft-tissue accumulation in the thorax (UTS) of technetium-99m methylene diphosphonate ([^{99m}Tc]MDP) in a number of patients with lung cancer and pleural effusion, in order to determine the incidence of such activity, and to attempt to relate this finding to the underlying pathology and/or treatment.

MATERIAL AND METHODS

One hundred thirty-six (136) patients were selected for study: six of these patients were subsequently shown to have diseases other than lung cancer, and they were not studied further. Of the remaining 130 patients, all had complete clinical and pathologic documentation of lung cancer and included 90 males and 40 females, all in the fifth to seventh decade. Whole-body bone scans and a chest radiograph had been ordered either as prethoracotomy staging or in order to identify metastatic lung cancer to bone. Whole-body bone scans were performed using either a multicrystal scanner* or a large field-of-view camera† with a parallel hole, low-energy collimator. Twenty millicuries of ([^{99m}Tc]MDP) was injected intravenously, and the patient was imaged 2–3 hr later, using the 149-keV peak and a 20% window. The bone scans were examined for abnormal thoracic soft-tissue accumulation, and the findings were compared with those on the radiographs. In some cases, whole-body scans using gallium-67 (^{67}Ga) citrate were also available for comparison. While some of the studies showed intense soft-tissue activity of [^{99m}Tc]MDP, such accumulation was often subtle. If unilateral activity was clearly present, it was reported as "Present": if absent or equivocal, as "Absent", although quantitative or grading of soft-tissue uptake might be useful in the future prospective study.

Radiation therapy has been given to patients either with a Phillips Linear Accelerator or a cobalt source. Dosage and portals were individualized for each patient and ranged from 3,000 to 4,600 rad. Most of the treatments were in 15–18 fractions over 22–30 days, but they varied widely. The therapy was, in general, well tolerated.

RESULTS

Table 1 shows the relationship between UTS of MDP and therapy. Sixty of the 130 patients (46%) were found to have UTS of MDP (time interval between completion of radiation therapy and the bone scan in Table 2 and tissue diagnosis of UTS in Table 3), and in every case, this occurred in the hemithorax in which the tumor had been clinically and radiographically identified. UTS of MDP was not seen in the remaining 70 patients (56%). Twenty-five of 60 (42%) patients with UTS had pleural effusion identified on chest radiograph in the hemithorax in which the tumor was found, compared with 13 of 70 patients (18%) without UTS.

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TABLE 1
Findings in 130 Patients with Lung Cancer

	Present	Absent	Significance
Occurrence of UTS*	46% (60/130)	54% (70/130)	
Presence of pleural effusion	43% (25/60)	18% (13/70)	$p < 0.01$
Chemotherapy	18% (11/60)	13% (9/70)	N.S.†
Major surgery	43% (26/60)	43% (30/70)	0
Radiotherapy tumor	88% (46/52)	6% (6/52)	$p < 0.01$
Radiotherapy to nonlung metastases only	8.5% (5/60)	10% (7/70)	N.S.
Sex	Males - 62% Females - 38%	Males - 70% Females - 30%	N.S.

* Unilateral thoracic soft-tissue uptake of [^{99m}Tc]methylene diphosphonate.
† N.S. = Not significant.

This difference is significant. Cell studies had only been performed in three of the patients with UTS and two of these were reported to contain malignant cells (Class V).

Thoracotomies had been performed in 43% of the patients in each group, and chemotherapy carried out in 18% of the group with UTS and 13% of the group without UTS, a nonsignificant difference. Radiation therapy to the tumor clearly is associated with the appearance of UTS with MDP. Of 52 patients who received radiation therapy to the primary tumor prior to the performance of the bone scan, 46 (88%) had UTS (Fig. 1) and six patients (12%) did not have UTS, a highly significant difference with a p value of less than 0.01. Failure of these six patients to develop UTS after radiation therapy to the tumor is without explanation. Of patients receiving radiation therapy to sites other than the primary lung tumor, such as brain, adrenals, and metastases to bones, about the same occurrence (8.5% compared with 10.0%) was seen in patients with UTS as those without UTS. This indicates that the target region rather than radiation therapy per se is related to the development of UTS. Nine of 60 patients (15%) with UTS did not receive therapy: accumulation of MDP in these patients may be due to primary tumor uptake or to the presence of pleural effusion or both.

TABLE 2
Time Interval Between Completion of Radiotherapy and Bone Scan Compared in Patients With and Without Unilateral Thoracic Soft-Tissue Uptake

Time	UTS present	UTS absent	
Under 1 mo	8	1	
1 mo	2	1	
2 mo	4	0	
3 mo	1	1	
4–6 mo	8	1	
7–11 mo	11	3	
1–2 yr	5	0	
More than 2 yr	5	0	
Mean	9 mo	5 mo	N.S.

DISCUSSION

Soft-tissue uptake of bone imaging agents has been reported in a wide variety of clinical situations. When ectopic calcification cannot be demonstrated, the mechanism responsible for this uptake is unknown. Pleural effusions commonly occur in patients with breast cancer and malignant cells thought to be responsible for soft-tissue uptake of MDP (*12*). In this study, pleural effusions were more commonly seen in patients with UTS, but no such relationship is apparent with chemotherapy, thoracotomy, cell type of the cancer (Table 3), or sex of the patient (Table 1). Seventy-seven percent of all the patients with UTS with bone agent have had radiation therapy, compared with only 9% of those patients without UTS. Radiation therapy appears to be the most significant of those factors studied. Although chemotherapy is known to enhance the lung damage produced by radiation, the small numbers of patients who received chemotherapy did not suggest much influence in MDP accumulation by this mode of therapy.

Radiation fibrosis is said to require 6 mo to several years to develop fully, and we believe this may be related to unilateral MDP accumulation. While the reasons for patient selection and timing are clinical, our scans show a random distribution with regard to the occurrence of UTS and the time of therapy.

The relationship between radiation therapy and soft-tissue uptake of bone agent in our patients is a more

TABLE 3
Tissue Diagnoses in Patients With and Without Unilateral Thoracic Soft-Tissue Uptake of [^{99m}Tc]MDP

	UTS present	UTS absent
Squamous cell	22	22
Oat cell	11	13
Anaplastic	2	2
Large cell	6	5
Bronchoalveolar	2	0
Adenocarcinoma	13	18
All others	4	10

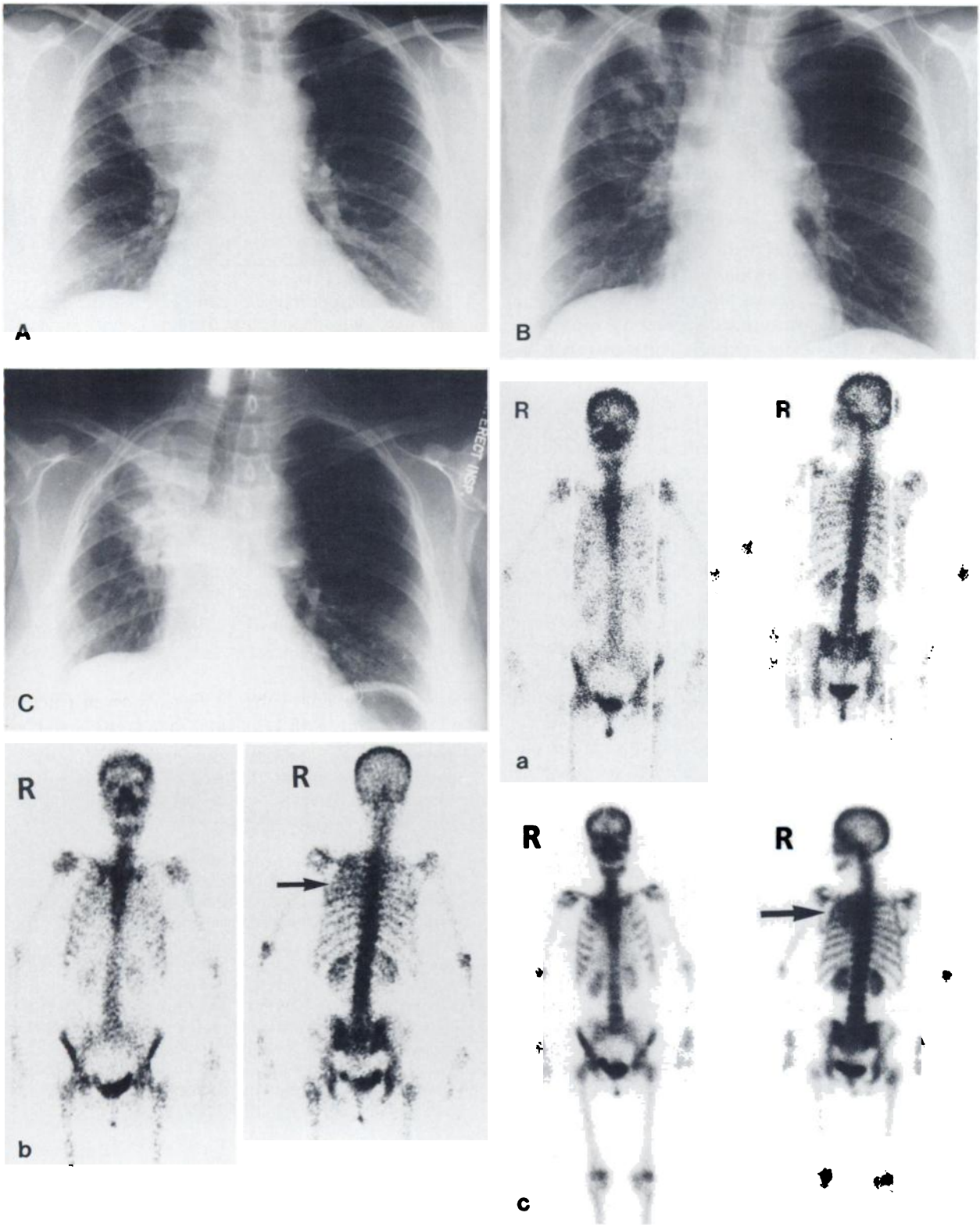

FIGURE 1
A 56-yr-old female had oat cell carcinoma of the right upper lobe with cerebral metastases. Radiographs (A, B, C) and simultaneous bone scans (a, b, c) show no UTS of MDP pretherapy (A), but 5 mo (B) and 1 yr (C) after therapy showed progressive UTS over the right upper lung (arrow).

consistent factor than other factors such as effusion, cell type of tumor, sex, etc. Both chemotherapy and radiation can damage normal lung tissues and tumor cells of rats as well as those of patients with cancer (*13*). Combinations of bleomycin and radiation therapy have been shown to enhance the lung damage produced by either agent alone (*8*). Other antineoplastic drugs have caused pulmonary toxicity as well. Since only 18% of the patients with localized MDP accumulation were known to have received these drugs, they would not appear to significantly contribute to such accumulation.

Silberstein (*14*) suggested that abnormal bone agent accumulation in breast tumors, myocardial infarction, and perhaps cerebral infarction is correlated with increased blood flow to the area and increased local tissue calcium and phosphorus. Siegel et al. (*7*) found that most of the activity was in the fluid and not the cellular portion of a malignant pleural effusion. Chaudhuri et al. (*15*) speculated that increased tumor phosphatases were responsible for uptake of bone agent, which was in agreement with the theory of Silberstein, as well as Lowenthal et al. (*1*). Two out of three patients with lung cancer showed progressive reduction in soft-tissue uptake in the region of the tumor following radiation therapy in a study by Hill (*16*). This decrease with time was not confirmed by our study. Despite these theories, the mechanism of accumulation of phosphates and phosphonates in malignancies and effusion remains unknown. Changes in blood flow, fibrosis, and damage to cells by radiation could all be responsible for our observations. In spite of our inability to demonstrate pleural effusions in many of the patients with UTS, the amount of fluid in some cases might be too small to be detected by conventional postero-anterior and lateral radiographs. The prognostic significance of UTS in radiation-treated lung cancer is obscure at this time. It may only represent a different marker of tissue response in patients with these tumors.

NOTES

* (Cleon whole body imager). Union Carbide Imaging Systems, Norwood, MA.

† (Nuclear Maxicamera 400 AT) General Electric Co., Milwaukee, WI.

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