Clinical Utility of Bone Scan Features of Pleural Effusion: Sensitivity and Specificity for Malignancy Based on Pleural Fluid Cytopathology

E. Dayan Sandler, Robert S. Hattner, Marguerite T. Parisi and Theodore R. Miller

Department of Radiology, Nuclear Medicine Section and Pathology, University of California San Francisco, San Francisco, California

Asymmetric chest activity with malignant and benign pleural effusions has been described in bone scans. However, the clinical utility of this finding is not elucible from the literature. We developed specific scintigraphic criteria for malignant pleural effusion and retrospectively assessed their sensitivity and specificity in a group of patient scans. **Methods:** Pleural fluid was submitted for cytopathology from 850 patients over a 5-yr period. Bone scans were done within 2 mo of the thoracentesis in 74 patients. As a consensus panel, we reread the scans and reviewed the cytology. **Results:** The effusions were cytologically malignant in 25/74 patients (34%), indeterminate in 9/74 (12%) and benign in 40/74 (54%). Based on cytopathology, malignant pleural effusions were detected by bone scans with a sensitivity of 34%–50% and a specificity of 78%–89%; true sensitivity and specificity was somewhere in between averaging 42% (95% confidence interval 24%–60%) and 84% (95% confidence interval 73%–95%), respectively. **Conclusions:** The bone scan is frequently the first examination suggesting pleural metastasis, and when it is detected it should be pursued beyond pleural fluid cytology, if negative or indeterminate.

Key Words: skeletal scintigraphy; malignancy; pleural effusion

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Diffusely increased hemithoracic activity ipsilateral to malignant and benign pleural effusions has been described in radionuclide bone scans (*1–9*). At least sixteen such patients have been reported to date, two of whom were cytologically negative or benign (*8,9*). The sensitivity and specificity of bone scans for detection of malignant pleural effusions (MPE) is not eluctable from the literature since the incidence of scan negative pleural effusions, benign and malignant, has not been previously reported. We sought to develop specific scintigraphic criteria for the presence of pleural effusions in bone scans and to assess objectively their sensitivity and specificity for malignancy. Using a retrospective study design, we chose a population of patients who had pleural effusions diagnosed clinically who also had bone scans.

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For correspondence contact: R.S. Hattner, MD, Nuclear Medicine Section L 340, University of California San Francisco, San Francisco, CA 94143-0252.

MATERIALS AND METHODS

Patients

All 850 patients from whom pleural fluid specimens were submitted for cytological evaluation at UCSF during the 5 yr from 1985 to 1990 were enrolled. Of these, 74 were selected because they had had bone scans within 2 mo of pleural fluid cytology. Table 1 summarizes the patients' primary clinical diagnoses.

Scans

Bone scans were obtained 4 hr after the administration of 0.30 mCi (11 MBq)/kg ^{99m}Tc-MDP. A 40-cm diameter scanning scintillation camera was used with a 20% energy window symmetric about 140 keV along with an all-purpose collimator optimized for 200 keV to create anterior and posterior scans of the entire skeleton at 24 cm/min. These scans contained about two million counts.

Scintigraphic Criteria

Diagnostic criteria for pleural effusions on bone scans were developed by consensus. They were:

1. Posterior view: hemithoracic asymmetry, decreased costal/intercostal contrast.
2. Anterior view: "triangle sign", asymmetrically increased activity in a triangle formed by the lateral sternal border, the costochondral junctions and the level of diaphragm.
3. Anterior or posterior view: a steep activity gradient at the level of the diaphragm.

Each scan was evaluated in accordance with these criteria by consensus.

Cytology

The cytologic specimens were independently rereviewed by an experienced cytopathologist (TRM) and classified as benign, malignant or indeterminate. The cytopathologist was blinded to the bone scan results.

RESULTS

Our data are presented in Table 2, a contingency table that compares bone scan and cytopathological outcomes, and examples of true-positive studies are shown in Figures

TABLE 1
Primary Clinical Diagnosis in 74 Patients with Pleural Fluid Cytology and Bone Scans

Diagnosis	No. of patients
Breast cancer	16
Bronchogenic cancer	15
Benign	12
Cytologic malignancy, unknown primary	8
Lymphoma	5
Renal cell cancer	5
Leukemia	2
Prostate cancer	2
Colon/GI cancer	2
Ewing's sarcoma	2
Neuroblastoma	1
Melanoma	1
Osteosarcoma	1
Head and neck squamous-cell cancer	1
Cervix cancer	1

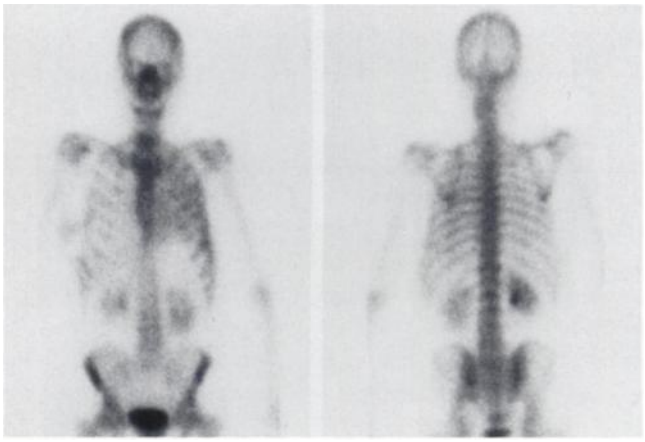

FIGURE 1. (Left) Anterior and (right) posterior bone scans of a 48-yr-old female with breast cancer shows the three criteria for left-sided malignant pleural effusion. Note involvement of the T-11 vertebral pedicles.

1 and 2. Cytology results were used as a reference standard to calculate sensitivities and specificities under various scenarios to consider the possibilities permitted by inclusion or exclusion of indeterminate cytopathological outcome. These are presented in Table 3.

As seen in Table 3, the true sensitivity of bone scan detection of malignant pleural effusions in this series ranges from 0.34 to 0.50; the specificity from 0.78 to 0.89. True values are somewhere in between: sensitivity 0.42 (95% confidence interval 0.24–0.60) and specificity = 0.84 (95% confidence interval 0.73–0.95).

DISCUSSION

Malignant pleural effusion on bone scans was first described by Siegel (*1*) and postural layering of malignant pleural effusion on bone scans was later noticed by Lamki (*3*). Figure 3 shows postural layering of an effusion in one of our patients. A pleural effusion associated with benign disease, coccioidomycosis, was found by Babbel (*8*), and a cytologically negative sympathetic pleural effusion in a patient with an abdominal lymphoma has also been reported (*9*). Figure 4 shows a benign pleural effusion in one of our patients. In 1991, Cole et al. were able to find bone scan-positive pleural effusions in sixteen patients (*9*).

TABLE 2
Contingency Table Comparing Bone Scans and Cytopathologic Outcomes

	Cytopathology			
	(−)	Indet.*	(+)	Total
(−)	35	4	15	54
Bone Scans				
(+)	5	5	10	20
Total	40	9	25	74

*Cytologically indeterminate.

We know several things about the mechanism of this phenomenon. First, some studies have shown that pleural fluid radioactivity when compared to a simultaneously obtained blood sample yields a ratio of about 3:1. Secondly, the activity is in the fluid, not the cellular phase, and lastly, the activity is due to ^{99m}Tc-MDP, not TcO_4^- or a metabolite (*1,2,5*). Excessive vascular permeability, a theory first posed by Kida, fits the observations best (*5*).

It is likely that malignant lesions abutting and invading the visceral pleura express the excessive capillary permeability which characterize the vessels of cancer. This would permit rapid permeation of the radiopharmaceutical into the effusion initially when the blood concentration is high. The relatively large distribution volume would result in slow backdiffusion, resulting in a dynamically high relative concentration in the effusion which happens to coincide with the typical imaging delay.

Although this is a fine explanation, it does not seem to

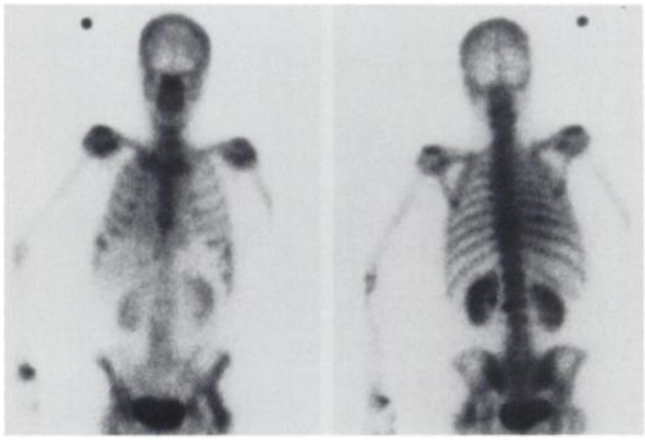

FIGURE 2. (Left) Anterior and (right) posterior bone scans of a 52-yr-old female with small-cell lung cancer shows the three criteria for a right-sided malignant pleural effusion. Note: involvement of multiple vertebrae, a left hip arthroplasty prosthesis with heterotopic bone, and abnormally increased renal activity from chemotherapy.

TABLE 3
Sensitivity and Specificity of Bone Scans Using Five Scenarios for Classifying Indeterminate Cytopathology

	Sensitivity (Fract.)	Specificity (Fract.)
1. Exclude indeterminate cytology . . .	0.40 (10/25)	0.83 (35/40)
2. Indeterminate cytology is negative . . .	0.40 (10/25)	0.80 (39/49)
3. Indeterminate cytology is positive . . .	0.44 (15/34)	0.88 (35/40)
4. Bone scan result is correct . . .	0.50 (15/30)	0.89 (39/44)
5. Bone scan result is incorrect . . .	0.34 (10/29)	0.78 (35/45)

account for the infrequent observations of apparently benign pleural effusions on bone scans, as we found in five cases (13%), or ten (20%), if the cytopathologically indeterminate effusions were indeed from benign causes. This might be explained by Apriles data and the limitations of cytopathology (*2*).

Aprile found a correlation between ^{99m}Tc-pyrophosphate pleural effusion-to-blood ratios ranging from low to high in pleural effusions in benign as well as malignant effusions. However, the overlap suggested that some benign effusions might be evident on bone scans.

Cytology is inherently dependent on adequate sampling. A negative result does not necessarily rule out the presence of disease. It may merely indicate that an inadequate sample was examined, a low cell count or degenerated material. We did not attempt to assess the degree to which these factors might have influenced our cytopathologic outcome.

Previous reports of pleural effusions in bone scans do not permit estimation of sensitivity and specificity for malignancy, but our data suggest a sensitivity of about 0.40 and a specificity of 0.80 or greater. This suggests that bone scanning is not a useful diagnostic test for malignant pleural effusion itself. However, finding a scan positive for malignant pleural effusion is a bonus.

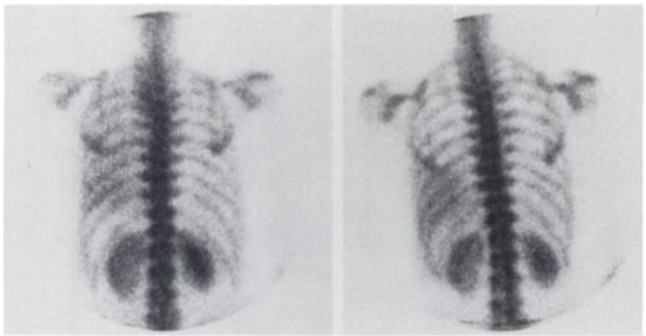

FIGURE 3. Posterior thoracic bone scans. (Left) supine, and (right) erect of a 63-yr-old male with renal cell carcinoma demonstrates layering of his malignant pleural effusion.

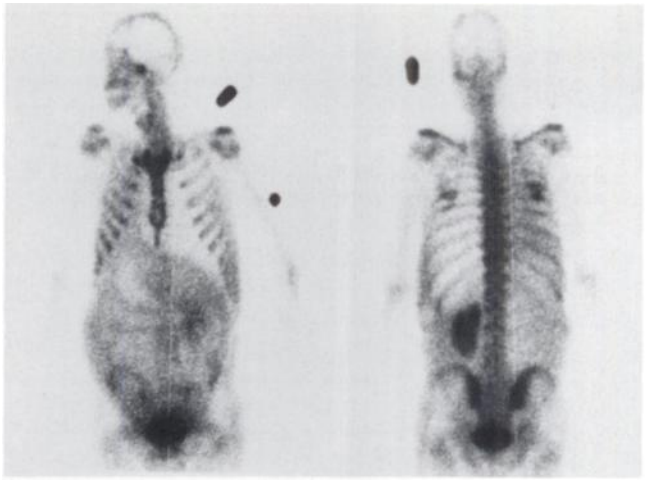

FIGURE 4. (Left) Anterior and (right) posterior bone scans. This 42-yr-old male has a past history of right nephrectomy for renal cell carcinoma. He now has hepatic insufficiency with cytopathologically benign ascites and right-sided pleural effusion which are evident in this scan. Increased left renal activity from hepatorenal syndrome is also shown.

The scan criteria we developed to diagnose malignant pleural effusion are easy to use. Moreover, their use has significantly improved interobserver precision in the bone scan diagnosis of malignant pleural effusion in our clinic.

CONCLUSION

Our data show that bone scans are only moderately sensitive, but quite specific for the detection of malignant pleural effusion. Bone scintigraphy is frequently the first examination that suggests pleural metastasis. Our results support the recommendation of Cole et al. that when pleural effusion is detected on bone scans, the diagnosis should be pursued beyond pleural fluid cytology if it is negative or indeterminate (*9*).

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