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Differential Diagnosis of Atypically Located Single or Double Hot Spots in Whole Bone Scanning

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Our study assessed the predictive value of atypically located hot spots in routine ^{99m}Tc -DPD (3,3 diphosphono-1, 2-propane dicarboxylic acid tetrasodium salt) bone scanning for osseous tumor spread in patients with a history of malignant tumor. **Methods:** Of 1286 scans in consecutive patients with a history of malignant tumor, but with no current evidence of osseous tumor spread, 172 displayed one or two hot spots in the following locations: transverse process of a single vertebra, manubriosternal junction, unilateral process of L5/S1, unilateral shoulder, costal cartilage, single rib, and unilateral sternoclavicular joint. The final diagnosis could be established by a control bone scan after at least 6 mo, biopsy and/or postmortem, respectively, in 135 patients. **Results:** Of the atypical hot spots, 11.1% were the first indication for osseous tumor spread. This diagnosis was most probable for single hot spots in the rib (25%) and shoulder (21%). Conversely, hot spots in the sternoclavicular joint never indicated malignancy. **Conclusion:** The likelihood of atypically located isolated hot spots indicating osseous tumor spread is higher than expected during routine investigations in patients with a history of malignant tumor but no current evidence for malignant disease. Only hot spots in the sternoclavicular joint did not indicate metastatic disease in our study.

Key Words: bone scintigraphy; hot spots; metastases

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In 1942 Treadwell et al. (1) described the use of radiotracers for assessing bone metabolism and provided the basis for detecting metastatic disease by nuclear medicine imaging procedures. Bone scintigraphy with ^{99m}Tc -labeled diphosphonates has been used for more than 30 yr to evaluate primary and metastatic bone lesions. Scintigraphic imaging identifies pathophysiological processes such as regional perfusion, permeability and bone metabolism. These processes precede morphological changes and account for the high sensitivity of nuclear medicine procedures for early detection of inflammatory, traumatic and neoplastic diseases (2-6) as well as for the low specificity for differential diagnosis of various diseases with similar pathophysiological characteristics. Such low specificity is a particularly problematic clinical dilemma in tumor patients who demonstrate isolated increased tracer uptake in locations such as the manubriosternal junction, ribs, lower neck or sacrum that may occur as a result of inflammatory or post-traumatic changes (6-12) but also may indicate incipient metastatic disease.

The purpose of our study was to assess the predictive value of

isolated and atypically located hot spots in routine ^{99m}Tc -DPD (3,3 diphosphono-1, 2-propane dicarboxylic acid tetrasodium salt) bone scanning for osseous tumor spread in patients with a history of malignant tumor but with no current evidence of metastatic disease.

MATERIALS AND METHODS

Patient Selection

Between October 1993 and May 1994, 1286 whole-body bone scans were performed on patients with a history of malignant tumor but with no current evidence of metastatic disease during routine follow-up. Patients with central hot spots in the vertebral column or skull but without signs of degenerative changes or trauma were assumed to have a higher likelihood for metastatic disease and were not included in our study.

In 172 patients (92 women, 80 men; age range 19-89 yr; mean age 59.62 yr \pm 14.00 yr s.d.; median age 60.5 yr) there was normal tracer distribution with the exception of one or two areas of focally increased tracer uptake in the following locations: (a) transverse process of a cervical vertebra; (b) manubriosternal junction; (c) transverse process of the fifth lumbar vertebra and/or sacrum; (d) shoulder; (e) costal cartilages, up to four spots; (f) single rib; and (g) sternoclavicular joint.

In 135 patients (77 women, 58 men; age range 19-84 yr; mean age 57.93 yr \pm 13.98 yr s.d.; median age 57 yr) of the above mentioned 172 patients (78.5%), a final diagnosis could be established by follow-up bone scintigraphy at least 6 mo later and/or by histological diagnosis after surgery or by postmortem examination. Restitution of a lesion without specific therapy was considered to confirm its benign nature. Persistence and the occurrence of additional (typically located) hot spots with corresponding radiographs was considered to represent malignancy. All other patients were diagnosed by biopsy. The sites of their primary tumors are shown in Table 1. In stable lesions under therapy, the confirmation was based on biopsies in all patients.

Bone Scintigraphy

Bone scintigraphy was performed in all patients 3 hr after the intravenous injection of 600 MBq ^{99m}Tc -DPD (Teceos Behringwerke AG, Frankfurt, Germany) through an antecubital vein. Anterior and posterior whole-body images were obtained using a double-headed, large-field-of-view gamma camera (GCA 901A, Toshiba Corp., New York, NY) equipped with low-energy, parallel-hole, high-resolution collimators at a scan speed of 15 cm/min so that about 1000 kcounts were accumulated per image and stored in a 256 \times 1024 matrix. The images were reviewed by three physicians in consensus.

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TABLE 1
Incidence of Skeletal Metastases Correlated with Primary Tumor Site

Primary tumor	Malignant*	Not malignant*	Total†
Prostate	0 (0%)	16 (100%)	16 (11.9%)
Breast	4 (8.5%)	43 (91.5%)	47 (34.8%)
Lymphoma	0 (0%)	3 (100%)	3 (2.2%)
Bronchi	3 (20.0%)	12 (80.0%)	15 (11.1%)
Melanoma	1 (4.5%)	21 (95.5%)	22 (16.3%)
Ewing's sarcoma	0 (0%)	5 (100%)	5 (3.7%)
Kidney	1 (14.3%)	6 (85.7%)	7 (5.2%)
Sarcoma	1 (16.7%)	5 (83.3%)	6 (4.4%)
Others	5 (35.7%)	9 (64.3%)	14 (10.4%)
Total	15 (11.1%)	120 (88.9%)	135 (100%)

*Numbers in parentheses are percentages according to the primary tumor site subgroup.

†Numbers in parentheses are percentages according to all 135 patients.

Statistical Analysis

Chi-square tests were performed to compare different groups. The level of statistical significance was set at $p \leq 0.05$.

RESULTS

Of the 135 patients who fulfilled the selected criteria, 23 (17.0%) had two hot spots on their bone scans, and the remaining 112 patients (83.0%) showed only a single hot spot in one of the previously defined locations. The primary tumor site was breast carcinoma in 47 of 135 patients (34.8%); melanoma in 22 of 135 patients (16.3%); carcinoma of the prostate gland in 16 of 135 patients (11.9%); carcinoma of the bronchus in 15 of 135 patients (11.1%); renal cell carcinoma in 7 of 135 patients (5.2%); sarcoma in 6 of 135 patients (4.4%), including 4 osteosarcomas, 1 chondrosarcoma and 1 sarcoma without specified histology; Ewing's sarcoma in 5 of 135 patients (3.7%); and lymphoma in 3 of 135 patients (2.2%). Of the 135 patients, 14 (10.4%) had other primary tumors (including bladder carcinoma, pharyngeal carcinoma, hepatocellular carcinoma, histiocytosis X, malignant mesothelioma, pheochromocytoma, carcinoma of the pancreas, carcinoma of the thyroid gland, rectal carcinoma, seminoma, vaginal squamous cell tumor and unknown primary tumor) (Table 1). The incidence of double or single hot spots did not differ significantly between the primary tumor sites ($p > 0.05$) (Table 2).

There were 120 patients (88.9%) with known malignancies and atypical hot spots in the initial bone scintigraphy who remained negative for the diagnosis of osseous tumor spread for a follow-up of at least 6 mo (Figs. 1, 2). In the remaining 15 patients (11.1%), bone metastases were confirmed. This group

TABLE 2
Incidence of Single or Double Hot Spots Correlated with Primary Tumor Site

Primary tumor	Double hot spot	Single hot spot	Total
Bronchi	1 (6.7%)	14 (93.3%)	15
Ewing's sarcoma	0 (0%)	5 (100%)	5
Kidney	2 (28.6%)	5 (71.4%)	7
Lymphoma	0 (0%)	3 (100%)	3
Breast	8 (17.0%)	39 (83.0%)	47
Melanoma	2 (9.1%)	20 (90.9%)	22
Prostate	6 (37.5%)	10 (62.5%)	16
Sarcoma	1 (16.7%)	5 (83.3%)	6
Others	3 (21.4%)	11 (78.6%)	14
Total	23 (17.0%)	112 (83.0%)	135

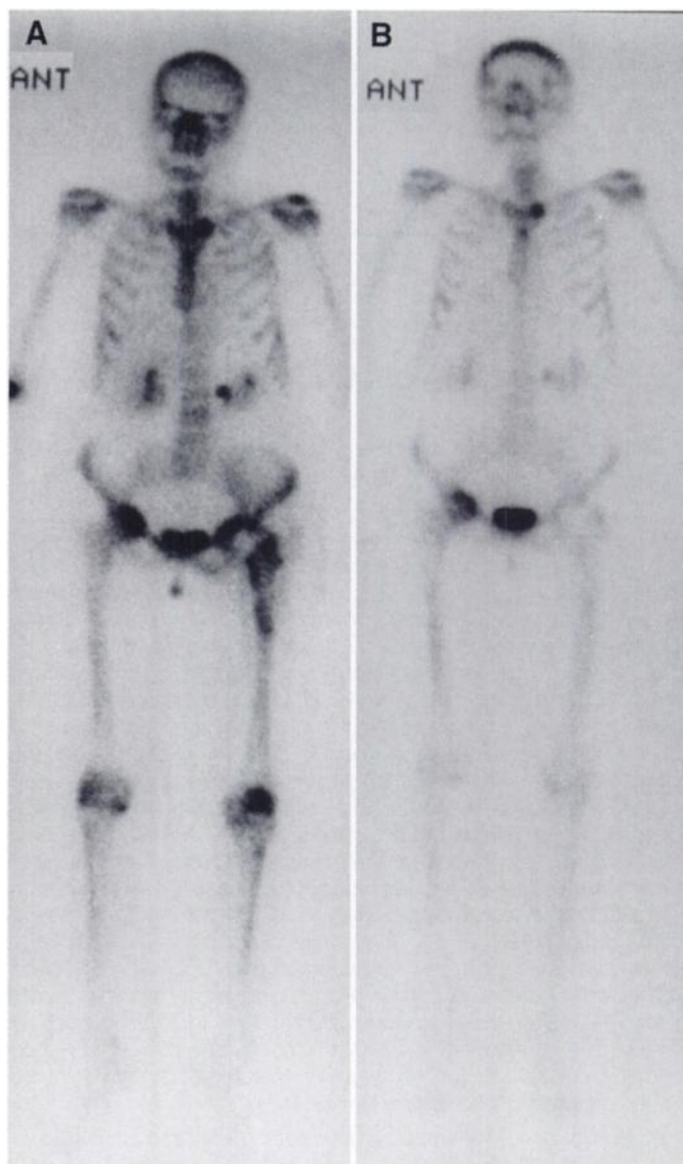


FIGURE 1. (A) Nonmalignant hot spots in 60-yr-old woman with hyper-nephroma show increased tracer uptake in left shoulder and manubriosternal joint. (B) No scintigraphic changes 10 mo later confirmed degenerative disease. Tracer uptake in hips and right femur was due to orthopedic surgery.

included 4 of 47 women with breast cancer (8.5%), 3 of 15 patients with bronchus carcinoma (20%), 1 of 22 patients with melanoma (4.5%), 1 of 7 patients with renal cell carcinoma (14.3%) and 1 of 6 patients with sarcoma (16.7%). Of the 15 patients, 5 (33.3%) had other primary tumor sites (Fig. 3).

All patients with prostate cancer ($n = 16$), lymphoma ($n = 3$) or Ewing's sarcoma ($n = 5$) remained negative for the diagnosis of bone metastases. Due to the small number of patients in some groups, the differences between the malignancy rates of the individual primary tumors did not reach a level of statistical significance. Age and gender did not have any predictive value for possible malignancy ($p > 0.05$).

Location of the hot spots did show a predictive value for metastases (Table 3): None of the hot spots detected at the sternoclavicular joint ($n = 31$) were malignant. One patient (5.3%) with a hot spot on the transverse process of the fifth lumbar vertebra ($n = 19$), 2 patients (6.7%) with a hot spot on the transverse process of a cervical vertebra ($n = 30$), 3 (9.1%) with a hot spot on the manubriosternal junction ($n = 33$), 3 (20.0%) with focal tracer uptake on the shoulder ($n = 15$) and

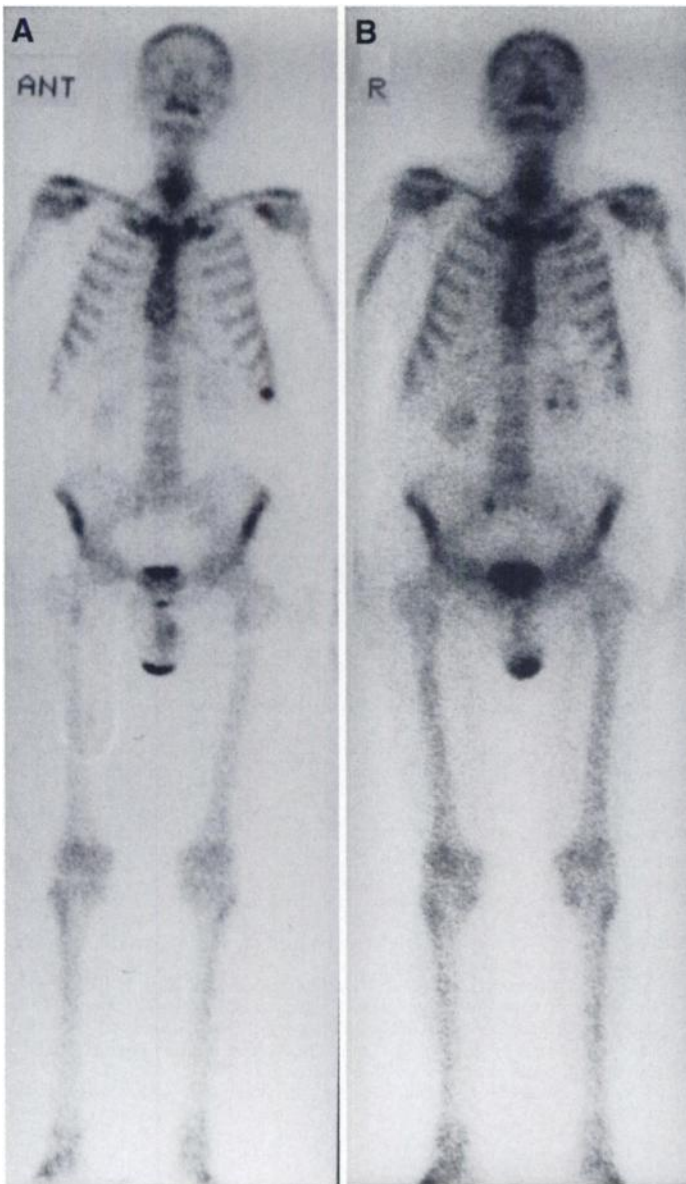


FIGURE 2. (A) Nonmalignant hot spot in 69-yr-old man with prostate cancer shows solitary tracer uptake in costal cartilage of tenth rib on left side. (B) Normal scan 2 yr later.

6 (25.0%) with a hot spot on the entire length of a single rib (n = 24) did have bone metastases. Again, these differences did not reach a level of statistical significance.

DISCUSSION

Bone scintigraphy is a highly sensitive technique for detecting bone metastases in the absence of trauma, inflammation or degenerative changes. Multiple lesions, especially in the vertebral column and skull, are strongly suggestive of metastatic disease, whereas other solitary lesions pose diagnostic problems in patients with known malignancies (6-8,10-15). Any single or double hot spot in a patient with a history of malignant tumor indicates the need for further examinations, such as conventional radiography, CT, bone marrow scanning, MRI or biopsy, and will impose physical strain and distress on the patient and cause additional costs. The aim of our study was to assess the likelihood of atypical hot spots for indicating osseous tumor spread.

Consistent results were found for hot spots in the sternoclavicular joint, which were never caused by metastases in our



FIGURE 3. Malignant hot spot in 54-yr-old man with malignant mesothelioma shows single hot spot on lateral aspect of fourth rib on left side. Histological specimen was positive for bone metastases.

study and, thus, might not require additional investigation. The findings for other locations were less consistent.

A hot spot in the manubriosternal junction was due to metastases in 3 of 33 patients (9.1%). This rate is significantly ($p < 0.01$) lower than that reported by Kwai et al. (14), who found 76% of isolated sternal lesions, the majority in the manubriosternal joint, due to metastatic disease in patients with

TABLE 3
Incidence of Skeletal Metastases Correlated with Localization of Hot Spots

Hot spot location	Malignant*	Not malignant*	Total†
Transverse process of cervical vertebra	2 (6.7%)	28 (93.3%)	30 (19%)
Manubriosternal junction	3 (9.1%)	30 (8.9%)	33 (20.9%)
Transverse process of fifth lumbar vertebra and/or sacrum	1 (5.3%)	18 (94.7%)	19 (12%)
Shoulder	3 (20%)	12 (80%)	15 (9.5%)
Costal cartilages (up to four spots)	1 (16.7%)	5 (83.3%)	6 (3.8%)
Rib	6 (25%)	18 (75%)	24 (15.2%)
Sternoclavicular joint	0 (0%)	31 (100%)	31 (19.6%)
Total	16 (10.1%)	142 (89.9%)	158 (100%)

*Numbers in parentheses are percentages according to hot spot localization subgroup.

†Numbers in parentheses are percentages according to all 158 hot spots.

breast cancer. A comparison of these two populations revealed that our study population comprised only 47 patients with confirmed breast cancer. Twenty-three women of this group (48.9%) showed sternal lesions, of which 9 were located on the manubriosternal junction, 11 on the sternoclavicular joint and 3 in both locations. None of them was due to osseous tumor spread. A bias toward higher tumor stages in Kwai's study might explain the differences, but this is uncertain since they did not report the patients' characteristics in their study. The 3 patients in our study who had metastases in the manubriosternal junction had bronchus carcinoma, osteosarcoma and histiocytosis X as their primary tumors.

Three of the 15 patients (20%) with a single hot spot in the shoulder and 6 of the 24 patients (25%) with a hot spot on the rib had bone metastases. These findings are consistent with McNeil et al. (15), who reported that 17% of solitary rib lesions in patients with a known primary tumor are due to osseous tumor spread. Tumeh et al. (12) found a lower incidence of only 9.8% for osseous metastases in patients with a single hot spot in the rib. However, since their findings were based on 41 patients compared to the 24 patients in our study, the difference between the two proportions does not reach a level of statistical significance. In addition, their study population comprised more patients with breast cancer than our study (70% versus 35%; $p < 0.05$). Since the spine is the primary site of osseous metastases in breast cancer (6), it might be presumed that this population bias influenced their incidence of rib metastases. The primary tumors in the 6 patients with rib lesions in our study were carcinoma of the breast, bronchi, melanoma, malignant mesothelioma, renal clear cell carcinoma or carcinoma of the adrenal gland. The patient with the breast carcinoma had a second hot spot on the transverse process of the fifth lumbar vertebra.

Even if the location of the primary tumor failed to reach a statistical level of significance for the prediction of malignancy in atypically located hot spots, the following results appear noteworthy. Single or double hot spots in the 16 patients with prostate cancer and in the 5 patients with Ewing's sarcoma

never indicated osseous tumor spread. This was remarkable since patients with prostate carcinoma showed a high incidence of presenting two areas of increased focal tracer uptake (6 of 16; 37.5%).

CONCLUSION

Single or double hot spots in atypical locations other than in the sternoclavicular joint are more often due to skeletal metastases than generally assumed except in patients with prostate cancer. The causes of hot spots in the shoulder, costal cartilage, rib, manubriosternal junction and transverse processes of the cervical or lumbosacral region must be evaluated further with other appropriate imaging or invasive procedures to exclude incipient metastatic disease.

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