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The usefulness of ^{99m}Tc-HMPAO-labeled leukocyte scintigraphy in the diagnosis of skeletal metastases of cancers

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The usefulness of bone marrow scintigraphy with ^{99m}Tc-HMPAO-labeled leukocytes (leukocyte bone marrow scintigraphy) in the diagnosis of skeletal metastases of cancers was investigated in 70 lesions in 27 patients with various types of cancer. The final diagnosis of skeletal metastases was based on one or more criteria consisting of histological confirmation, typical findings of metastases by bone radiograph, CT and MRI, or progressive swellings of the lesions with severe pain due to nerve compression. Of the 70 lesions, 55 were finally diagnosed as metastases, and 15 as benign lesions. Leukocyte bone marrow scintigraphy showed photopenic defects in 52 of the 55 metastatic lesions (sensitivity 95%), and the remaining 3 negative lesions were found positive for metastases by MRI. In contrast, MRI could evaluate only 39 of the 55 lesions because 16 lesions in the ribs, scapula and sternum were not visualized. Of these 39 lesions, MRI showed positive findings for metastases in 33 (sensitivity 85%), and negative findings in 6 with photopenic defects found by leukocyte bone marrow scintigraphy. Of the 15 benign lesions, 3 were false positive for metastases on leukocyte bone marrow scintigraphy (specificity 80%). We conclude that ^{99m}Tc-HMPAO-labeled leukocyte bone marrow scintigraphy may be useful in the diagnosis of skeletal metastases of cancers, particularly when MRI fails to evaluate the lesions.

Key words: ^{99m}Tc-HMPAO-labeled leukocyte scintigraphy, bone marrow scintigraphy, skeletal metastasis

INTRODUCTION

BONE SCINTIGRAPHY is usually used as a screening test to detect skeletal metastases of cancers, but this technique alone cannot differentiate the metastases from benign skeletal lesions.[1–5] Although MRI and CT are helpful in this differentiation,[6,7] systemic examination with them is not practical because of the excessive radiation dose, time consumption or cost benefit.[8]

Skeletal metastases of cancers occur via the bloodstream. Cancer cells are assumed to reach the bone marrow first, and then the bone,[9–11] suggesting that the early diagnosis of skeletal metastases of cancers may be made by evaluating bone marrow abnormalities on images. ^{111}In-chloride and ^{99m}Tc-colloid are commonly employed for bone marrow scintigraphy,[12] but such scintigraphy cannot always provide clear images to precisely analyze bone marrow lesions. ^{99m}Tc-HMPAO-labeled leukocyte scintigraphy is widely used in the detection of pathological conditions such as abdominal and skeletal inflammatory diseases.[13–15]

In the present study we evaluated the utility of ^{99m}Tc-HMPAO-labeled leukocyte scintigraphy (leukocyte bone marrow scintigraphy) in the diagnosis of skeletal metastases of cancers.

SUBJECTS

From among patients who were admitted to our hospital between 1996 and 1998 with histological or clinical diagnosis of cancers, 27 patients who had one to ten

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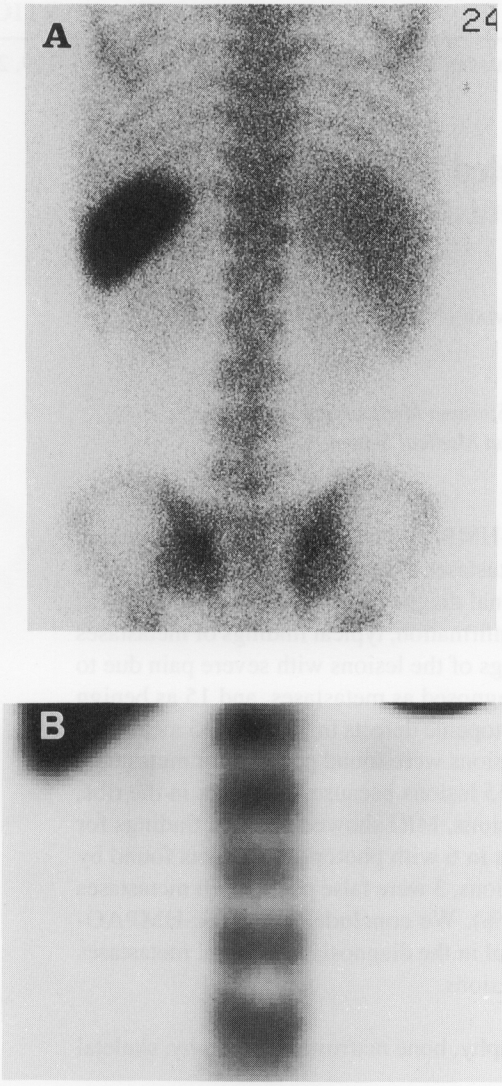


Fig. 1 ^{99m}Tc-HMPAO-labeled leukocyte bone marrow scintigrams in a healthy 20-year-old man. (A) Planar image of posterior view of the spine. (B) SPECT image of the thoracolumbar spine. Marked radionuclide accumulation is seen in the liver and spleen, but the bone marrow is clearly delineated with identified vertebral bodies.

suspicious skeletal metastases of cancers were selected as subjects. The primary cancers were hepatocellular carcinoma in 12 patients, gastric cancer in 7, gallbladder cancer in 2, and prostate cancer, lung cancer, breast cancer, colorectal cancer, esophageal cancer, and unknown primary tumor each in 1. Of these patients, 24 showed signs of abnormal accumulations on bone scintigraphy, and 3 had clinical symptoms characteristic of skeletal metastases of cancers despite having no abnormal accumulations on bone scintigraphy. In these 27 patients, altogether 73 skeletal lesions were evaluated. All the lesions consisted of those whose diagnosis of metastases were not definite on bone scintigraphy.

METHODS

Forty milliliter of venous blood was collected from each patient, and leukocytes were harvested according to the method of McAfee et al.[16] The leukocytes were labeled with ^{99m}Tc-HMPAO (550 MBq) by the modified method of Aburano et al.,[13] and administered intravenously back to the patient. At 4 hours after the intravenous administration, this leukocyte bone marrow scintigraphy could provide delineated clear planar anterior and posterior images, by using a dual-head gamma camera (Prism 2000 Picker) and a low-energy parallel-hole collimator. Spinal SPECT was performed under the following conditions: 360°, 72 steps, 128 × 128 matrix, 30 second intervals. Images were prepared with a ramp filter and Butterworth filter (order: 8, cut-off frequency: 0.25 cycle per pixel).

Focal photopenic defects found by leukocyte bone marrow scintigraphy were diagnosed as positive for skeletal metastases of cancers.

MRI was performed with a 1.5 T machine (Magnetom H15SP, Siemens, Erlangen, Germany). T1-weighted images were captured with a spin echo sequence (TR/TE = 500/12), and T2-weighted with a spin echo sequence (TR/TE = 4500/120). STIR images were obtained with a Short-Turn-Inversion Recovering (TR/TE/TI = 4000/30/150).

The final diagnosis of skeletal metastases of cancers in each patient was made when at least one of the following criteria was fulfilled.

1) Cancer tissue in the skeletal lesion was confirmed by histological examination.

2) Low signal T1-weighted and high signal T2-weighted images on MRI were detected in the skeletal lesions.

3) Bone destruction, osteogenic change, and tumor formation detected by CT or bone radiograph were detected in the skeletal lesions.

4) Patients were diagnosed as having skeletal metastasis when the results of follow-up tests confirmed skeletal metastasis even if the results of the initial tests were negative.

5) Even if the above four criteria were negative, progressive swellings of the lesions were seen with severe pain due to nerve compression during the follow-up observation period.

Verbal or written consent to participate in the study was obtained from each patient or members of his/her family.

RESULTS

Figure 1 shows a leukocyte bone marrow scintigram of a healthy man. On a planar image (posterior view) the entire bone marrow was clearly delineated, and on a SPECT image the spinal bone marrow was detectable without any interference by the liver and spleen.

In 27 patients both planar and spinal SPECT images by leukocyte bone marrow scintigraphy were obtained in 70

Table 1 Demographic and clinical features and imaging results in cancer patients with skeletal metastases†

Patient No./Age (Y)/Sex	Original cancer	Lesions studied	Numbers of positive lesions by HMPAO-L-Sci	Numbers of positive lesions by MRI	Numbers of metastases lesions by final diagnosis
1/26/M	HCC	6 (spine)*	6	6	6
2/38/F	GC	2 (spine)	2	2	2
		2 (pelvis)	2	2	2
3/62/M	HCC	2 (spine)	2	2	2
		5 (rib)	5		5
		1 (scapula)	1		1
		2 (sternum)	2		2
4/83/F	GC	1 (spine)	1	0	1
5/80/M	EC	2 (spine)	1	1	1
6/65/F	GBC	3 (spine)	0	3	3
7/77/M	HCC	2 (spine)	2	2	2
		6 (rib)	6		6
8/48/M	HCC	2 (spine)	2	2	2
		2 (rib)	2		2
9/57/M	GC	2 (spine)	2	2	2
10/78/F	LC	2 (spine)	2	2	2
11/65/F	GBC	3 (spine)	3	3	3
12/67/F	HCC	3 (spine)	3	0	3
13/59/F	GC	1 (spine)	1	0	1
14/59/M	GC	2 (spine)	2	2	2
15/71/M	GC	2 (spine)	2	1	2
16/67/M	U	3 (spine)	3	3	3
Total		56	52	33	55

† Y = years old, M = male, F = female, HCC = hepatocellular carcinoma, GC = gastric cancer, GBC = gall bladder cancer, EC = esophageal cancer, LC = lung cancer, U = unknown, HMPAO-L-Sci = ^{99m}Tc-HMPAO-labeled leukocyte scintigraphy, *Figures are numbers of abnormal lesions in skeletons indicated in parentheses.

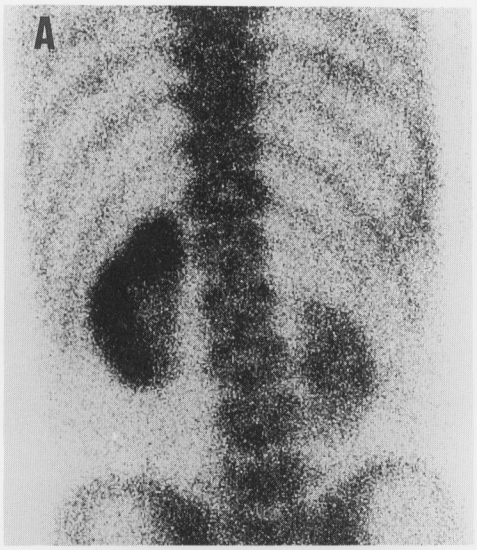
Table 2 Demographic and clinical features and imaging results in cancer patients without skeletal metastases†

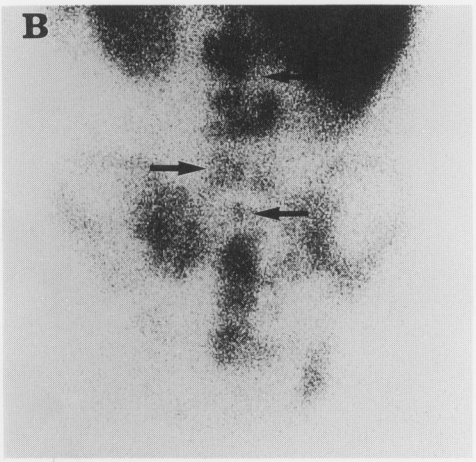
Patient No./ Age (Y)/Sex	Original cancer	Lesions studied	Numbers of negative lesions by HMPAO-L-Sci	Numbers of negative lesions by MRI
17/70/M	HCC	1 (spine)*	1	1
18/48/M	HCC	1 (scapula)	1	1
19/48/F	BC	1 (scapula)	1	1
20/76/M	GC	1 (spine)	0	1
21/64/M	HCC	2 (spine)	2	1
22/67/F	HCC	1 (spine)	1	1
23/47/F	HCC	1 (spine)	1	1
24/72/M	PC	1 (spine)	0	1
25/59/F	HCC	2 (spine)	1	2
26/74/F	HCC	1 (spine)	1	1
27/76/M	CC	2 (spine)	2	2
Total		14	11	13

† Y = years old, M = male, F = femal, HCC = hepatocellular carcinoma, BC = breast cancer, GC = gastric cancer, PC = prostate cancer, CC = colon cancer, HMPAO-L-Sci = ^{99m}Tc-HMPAO-labeled leukocyte scintigraphy, * Figures are numbers of abnormal lesions in skeletons indicated in parentheses.

of the 73 lesions. Two lesions in the thoracic vertebrae and one lesion in the cervical vertebra were too remote from other lesions to be examined at the same time.

Table 1 shows the results of leukocyte bone marrow scintigraphy in 55 skeletal lesions in 16 patients who had a final diagnosis of skeletal metastases of cancers. Of the 55 lesions, 52 were positive for metastases on leukocyte bone marrow scintigraphy (sensitivity 95%), and the remaining 3 negative lesions were positive for metastases on MRI. These 3 lesions were less than 0.5 cm diameter.





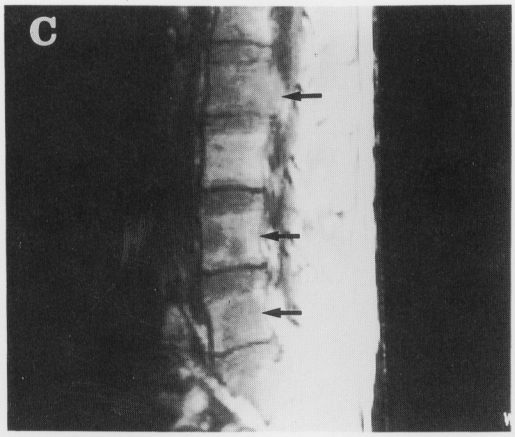


Fig. 2 Images of the lumbar spine in a 26-year-old man with hepatocellular carcinoma (patient No. 1) who complained of severe back pain, suspected of skeletal metastases. (A) ^{99m}Tc-MDP bone scan. There is no abnormal radionuclide accumulation. (B) ^{99m}Tc-HMPAO-labeled leukocyte bone marrow scintigram. There are photopenic defects in the third and fifth lumbar vertebrae and the first sacral vertebra (arrows). (C) MRI. Sagittal T1-weighted image shows multiple low signal regions in the third and fifth lumbar vertebrae and first sacral vertebra (arrows).

In contrast, MRI evaluated only 40 lesions, because 13 in the ribs, 1 in the scapula and 2 in the sternum could not be visualized. Of the 39 metastatic lesions, 6 lesions positive for metastases on leukocyte bone marrow scintigraphy were negative on MRI (sensitivity 85%).

Table 2 demonstrates the results of leukocyte bone marrow scintigraphy in 14 skeletal lesions in 11 patients who were finally diagnosed as having no skeletal metastases of cancers. Of these 14 lesions, 3 were positive for metastases on leukocyte bone marrow scintigraphy, but negative on MRI. Two of these 3 lesions were found in older patients with markedly deformed vertebrae. But MRI was positive for metastases in one lesion found negative on leukocyte bone marrow scintigraphy.

The specificity for the diagnosis of skeletal metastases of cancers by leukocyte bone marrow scintigraphy was 80%.

CASES

Patient No. 1

A 26-year-old man with hepatocellular carcinoma complained of severe back pain. ^{99m}Tc-MDP bone scintigraphy (posterior view) showed no abnormal accumulation anywhere in the body. Nevertheless, leukocyte bone marrow scintigraphy (posterior view) disclosed focal photopenic defects in the second and eleventh thoracic vertebrae, first, third and fifth lumbar vertebrae and first sacral vertebra. MRI detected several low signal intensities on T1-weighted images of the same regions. Figure 2 shows three of these lesions.

Patient No. 3

A 62-year-old man with hepatocellular carcinoma developed severe pain in the chest, back and both legs. ^{99m}Tc-MDP bone scintigraphy disclosed several accumulations in the ribs, sternum and thoracic and lumbar vertebrae. Leukocyte bone marrow scintigraphy also revealed focal photopenic defects in the same regions. Figure 3 shows such defects in the ribs and sternum.

Patient No. 15

A 71-year-old man with gastric cancer experienced severe back and lumbar pain. A bone radiograph showed compression fractures in the ninth thoracic vertebra and first lumbar vertebra. ^{99m}Tc-MDP bone scintigraphy revealed abnormal accumulations in the same regions. A

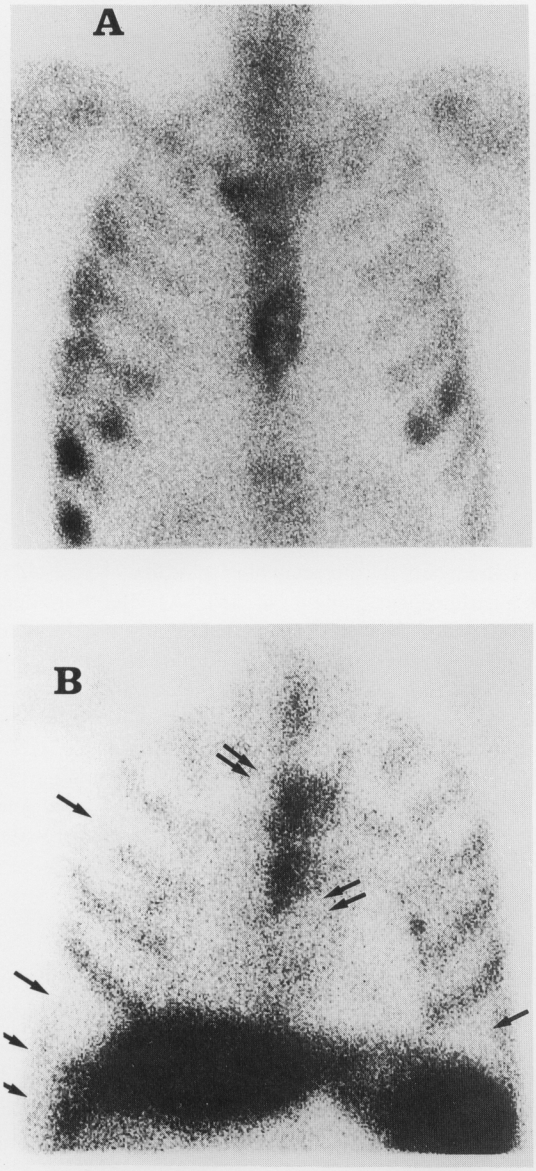


Fig. 3 Images of the thorax in a 62-year-old man with hepatocellular carcinoma (patient No. 3). (A) ^{99m}Tc-MDP bone scan. Abnormal radionuclide accumulations are seen in the ribs and sternum. (B) ^{99m}Tc-HMPAO-labeled leukocyte bone marrow scintigram. Anterior image shows clearly delineated focal photopenic defects in the ribs (arrows) and sternum (double arrows).

T1-weighted MRI image disclosed low signal intensity in the ninth thoracic vertebra. This site was enhanced by contrast imaging with Gd-DTPA. But in the first lumbar vertebra Gd-DTPA contrast imaging was negative despite a positive low signal intensity on MRI, characteristic of benign compression fracture. Leukocyte bone marrow scintigraphy (SPECT) showed focal photopenic defects in the ninth thoracic vertebra and first lumbar vertebra (Fig. 4).

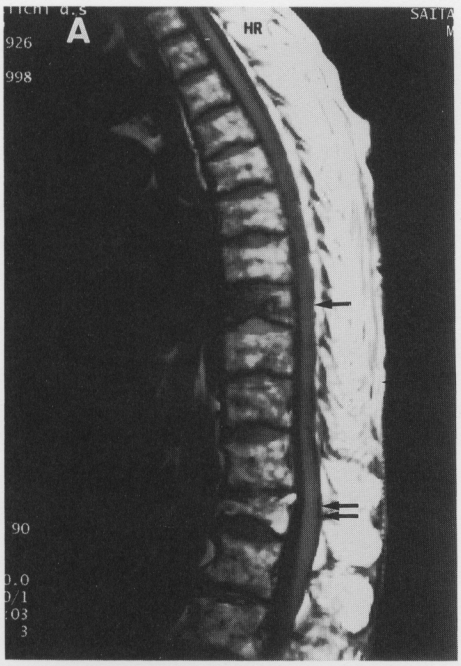
DISCUSSION

Based on the assumption that the early diagnosis of skeletal metastases of cancers may be made by analyzing bone marrow abnormalities on images, we studied the utility of ^{99m}Tc-HMPAO-labeled leukocyte scintigraphy in the present study.

In order to improve unsatisfactory bone marrow scintigraphy images obtained with ^{111}In-Cl_3, ^{99m}Tc-colloid preparations, etc.,[12] we employed ^{99m}Tc-HMPAO-labeled leukocyte scintigraphy, because granulocytes in the circulation derived from bone marrow are supposed to reach the reticuloendothelial system and accumulate in the bone marrow.[10] To prepare leukocytes and to label with ^{99m}Tc-HMPAO, we used standard methods established in the detection of inflammatory abdominal, bone and joint diseases.[13–17] Scans were performed 4 hours after intravenous administration of labeled leukocytes, as this leukocyte bone marrow scintigraphy provided delineated clear planar anterior and posterior images, by using a dual-head gamma camera (Prism 2000 Picker) and a low-energy parallel-hole collimator in our preliminary study. The subjects were selected from among patients with cancers who revealed abnormal accumulations on ^{99m}Tc-MDP bone scitigraphy routinely performed for cancerous patients and those who complained of severe pain despite having no such accumulations. The final diagnosis of skeletal metastases was made by fulfillment of one or more criteria consisting of histological confirmation, typical findings of metastases by bone radiograph, CT and MRI, or progressive swellings of the lesions accompanied by severe pain due to nerve compression.

As shown in Table 1, 52 of 55 skeletal metastatic lesions showed signs of focal photopenic defects on this bone marrow scintigraphy (sensitivity 95%). The present results were noteworthy, because 16 of these 55 lesions including 13 in the ribs, 1 in the scapula and 2 in the sternum which could not be visualized by MRI. Moreover, leukocyte bone marrow scintigraphy showed positive findings for skeletal metastases in 6 lesions which were negative for metastases on MRI. MRI is capable of detecting the replacement of adipose cells by tumor cells in bone marrow in the presence of skeletal metastases of cancers.[7] Similar replacement also occurs when bleeding exists in the bone marrow, suggesting that metastatic lesions cannot be detected clearly in cases of coexisting bleeding due to bone fractures.[18–21] This may explain the higher sensitivity of leukocyte bone marrow scintigraphy than that of MRI.

Of 14 skeletal lesions in 11 patients who were finally diagnosed as having no skeletal metastases of cancers, 3 revealed focal photopenic defects in the bone marrow on leukocyte bone marrow scintigraphy, as shown in Table 2. These false positive findings were not seen in MRI images. The exact reason for this false positive findings should be investigated in the future. Even if positive



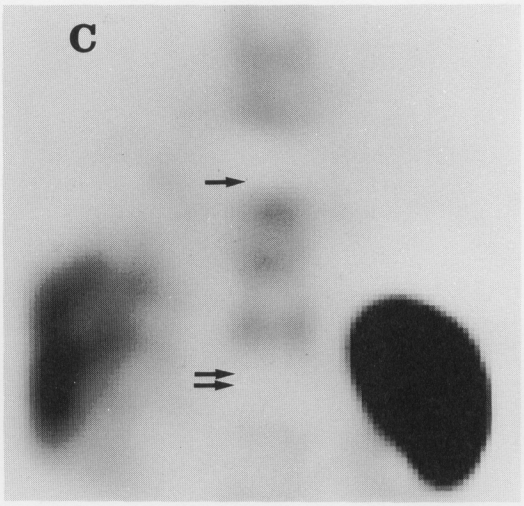


Fig. 4 Images of the thoracolumbar spine in a 71-year-old man with gastric cancer (patient No. 15). (A) MRI. Sagittal T1-weighted image shows compressed bone marrow in the thoracic ninth vertebra and first lumbar vertebra. (B) MRI. Post contrast sagittal T1-weighted image shows enhanced bone marrow compression in the ninth thoracic vertebra (arrow) and no enhancement in the first lumbar vertebra (double arrow). (C) ^{99m}Tc-HMPAO-labeled leukocyte bone marrow scintigram. SPECT image demonstrates clearly delineated focal photopenic defects in the ninth thoracic vertebra (arrow) and first lumbar vertebra (double arrow).

findings for metastases are obtained by leukocyte bone marrow scintigraphy, evaluation by MRI is advisable in cases of suspected benign compressions.

Bone marrow scintigraphy with ^{99m}Tc-labeled antigranulocyte monoclonal antibody has been used to provide better images than those obtained with ^{111}In-chloride scanning in the diagnosis of skeletal metastases as well.[8,22,23] But this scintigraphy involves such problems as image deterioration caused by repeated use and allergic reaction caused by high serum human antimouse antibody.[22] The use of ^{99m}Tc-HMPAO-labeled leukocyte scintigraphy in the evaluation of bone marrow was reported by Watanabe et al.[24] This is the only study that utilized the present scintigraphy in the diagnosis of skeletal metastases in a case of malignant lymphoma. The present study is the first attempt to investigate the utility of the method in a large number of cases.

For leukocyte bone marrow scintigraphy, as much venous blood as 40 m*l* is necessary, and separation and labeling of leukocytes take 2 hours. It would therefore be advisable to use this scintigraphy in the case of suspected skeletal metastases of cancers the diagnosis of which is undetermined by bone scintigraphy, along with conventional bone radiograph, particularly when skeletal metastases are present in multiple lesions including the ribs, sternum, scapula, and there are coexisting compression fractures.

CONCLUSION

^{99m}Tc-HMPAO-labeled leukocyte scintigraphy may be useful in the diagnosis of skeletal metastases of cancers. Its use is preferable when the diagnosis is undetermined by bone scintigraphy along with conventional bone radiograph, particularly in cases of multiple skeletal metastases existing in lesions undetectable by MRI and coexisting compression fractures.

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