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Multiple myeloma: predictive value of Tc-99m MIBI scintigraphy and MRI in its diagnosis and therapy

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Abstract

BACKGROUND: We assessed the validity of ^{99m}Tc-MIBI scintigraphy and MRI in the diagnosis and prediction of the effect of therapy in patients with multiple myeloma (MM) and monoclonal gammopathy of unknown significance (MGUS), in whom both examinations were performed within 14 days.
MATERIALS AND METHODS: Forty-seven consecutive patients with MM and 5 with MGUS were enrolled in the study. Out of 47 MM patients, 6 were in Durie-Salmon stage I and 41 had active disease in stage II or III. Fifteen patients were examined before and within 2 months of intensive chemotherapy. Anterior and posterior whole-body scans were obtained 10 min after IV administration of 740 MBq (20 mCi) ^{99m}Tc-MIBI. MRI of Th and LS spine, T1 w.i. and STIR in the sagittal plane were performed.
RESULTS: Bone marrow pathological changes in 41 MM patients with active disease were detected in 39 (95%) scintigraphic examinations and in 38 (94%) of MRI. Among 41 MM patients with active disease, 21 showed diffuse patterns of ^{99m}Tc-MIBI uptake, 8 showed focal patterns and 10 showed both focal and diffuse patterns, while 34 patients exhibited focal lesions in MRI and 4 both focal and diffuse findings. Moreover, 5 of 38 patients had epidural mass and 18 had vertebrae compression. Out of 15 patients after therapy, 13 reached complete remission and 2 had stable disease. Normal ^{99m}Tc-MIBI scintigraphy was found in 11 (85%) patients with complete remission, 2 presented both focal and diffuse patterns of ^{99m}Tc-MIBI uptake. Two patients with stable disease also had focal and diffuse radiotracer uptake. MRI findings were normal only in 3 (23%) patients in complete remission. Eight patients exhibited focal lesions and 2 showed partial conversion in MRI.
CONCLUSIONS: ^{99m}Tc-MIBI scintigraphy and MRI are methods of equal sensitivity in detecting active MM and complement each other. The advantage of ^{99m}Tc-MIBI scintigraphy is the possibility of whole body examination, which allows superiority in detection of MM in appendicular skeleton and extramedular lesions, and faster response to therapy, while the advantage of MRI is the detection of epidural masses and vertebral compressions influencing the therapeutic strategy.
Key words: multiple myeloma, ^{99m}Tc-MIBI scintigraphy, MRI, prediction of therapy effect

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Introduction

Multiple myeloma (MM) is a clonal B-lymphocyte neoplasm of terminally differentiated plasma cells. It accounts for approximately 1% of all malignant diseases and represents about 10% of haematologic malignancies. The annual incidence of newly diagnosed cases is approximately 3 to 4 per 100,000 population per year, with an estimated 14,000 new cases each year [1]. The cause of MM is unknown. Data from cloning and gene-sequencing studies strongly imply that the malignant clone in MM arises from a late cell in B-cell development [2, 3].

The hallmark of MM is the detection in blood and/or urine of a monoclonal protein, M protein, produced by the abnormal plasma cells. By using the more sensitive techniques of immunofixation and immunoelectrophoresis, M protein (in serum and/or urine) will be detected in most patients [4] .

Once the diagnosis is suspected, an X-ray skeletal survey and bone marrow aspiration biopsy are performed. Minimal criteria for establishment of a diagnosis of MM should be the detection of at

least 10% abnormal plasma cells in a random bone marrow biopsy specimen and M protein in either the serum and/or urine. Osteolytic lesions on a skeletal survey may be found. In most patients, the diagnosis of MM is established without difficulty [4] .

Whole body X-ray skeletal survey (WBXR) and marrow plasmacytosis have well-known limitations [5]. In particular, the persistence of radiological abnormalities cannot be considered evidence of active disease, since they may represent residual osteolysis in the absence of plasma cell proliferation. In addition, radiography is not able to detect disease in bone marrow or soft tissues. On the other hand, bone marrow biopsy is an invasive technique with potential difficulties in evaluating accurately and reproducibly plasma cell infiltration, and is susceptible to sampling errors.

^{99m}Tc-2-methoxyisobutylisonitrile (MIBI) has recently been proposed as a potential tracer in patients with multiple myeloma (MM). Its increased uptake in bone marrow and soft tissue has beeen reported as a sensitive and specific indicator of myeloma activity [6–8] . This observation has been explained by the localization of ^{99m}Tc-MIBI inside the plasma cells infiltrating the bone marrow and soft tissue [9].

The superiority of MRI over plain radiographs for the detection of MM spinal bone lesions, the prognostic significance in early and advanced MM, and its role in the staging of disease has also been repeatedly demonstrated [10, 11].

The aim of the study was to evaluate and compare the validity of ^{99m}Tc-MIBI scintigraphy and MRI in the diagnosis and prediction of therapy effects in patients with MM and monoclonal gammopathy of unknown significance (MGUS), in whom both examinations were performed within 14 days.

Materials and methods

Fifty-two consecutive patients (35 male, 17 female, median age 61 years; 47 patients with MM and 5 with MGUS) were enrolled in the study.

Out of 47 MM patients, 6 were in Durie-Salmon stage I, not requiring therapy, and 41 had active disease in stage II or III. Fifteen patients were examined before and within 2 months of intensive chemotherapy (Table I).

Diagnosis and staging were made according to standard criteria [12]. All patients underwent WBXR survey and bone marrow plasma cell count. Haematological and biochemical examination included monoclonal immunoglobulin level (MIG) and further MM activity markers including serum thymidinkinase (sTk), beta2-microglobulin (B2M), labelling index (LI), C-reactive protein (CRP), telopeptid-1CTP, haemoglobin level (HB) and apoptotic index (Apo).

Restaging was performed at the time of the second ^{99m}Tc-MIBI scintigraphy , within 2 months of completing the intensive chemotherapy. A patient was considered to have complete remission when a bone marrow plasma cell percentage $< 5\%$ and monoclonal component reduction $> 75\%$ had been achieved, to have reached partial remission when a monoclonal component reduction of between 50% and 75% had been achieved, and to have progressive disease when there was an increase in the monoclonal component and/or in plasma cell infiltration. If other changes did not meet these criteria, the patient was classified as having stable disease [5].

^{99m}Tc-MIBI scintigraphy and MRI were performed within 14 days.

Table 1. Patient characteristics

	Number of patients
MM stage I	6
MM stage II and III	41
MGUS	5
Total	52
Before and after therapy	15

^{99m}Tc-MIBI scintigraphy

Studies of all patients were performed using a dual-head gamma camera (e-CAM, Siemens) equipped with low-energy, high resolution, parallel hole -collimators. Whole body scans were obtained 10 minutes after IV injection of 740 MBq (20 mCi) ^{99m}Tc-MIBI in anterior and posterior view. The scans were classified according to Pace et al classification [13] as pattern N, when physiological distribution of tracer uptake was present, pattern D with diffuse bone marrow tracer uptake, pattern F with areas of focal uptake, and F + D, when combinations of both tracer uptakes were observed. In addition, the scans were graded according to extension (E) and intensity (I) of the diffuse bone marrow uptake. A summed score (S = E + I) was also computed for each patient.

MRI

1.5 Tesla (Siemens Symphony) equipment was used. MRI of thoracic (Th) and lumbar/sacral spine (LS), T1 weighted images (w.i.), and fat suppression sequences (STIR) in sagittal plane were performed. Selected vertebrae T1 w.i. in transversal plane, T2 w.i., and opposed phase GRE (fast sequences) were performed when needed.

Main pathological signs were T1 hypointensity (focal and diffuse) and STIR hyperintensity.

Results

Bone marrow pathological changes in 41 MM patients with active disease were detected in 39 (95%) scintigraphic examinations and in 38 (94%) MRI examinations.

All 5 MGUS patients had negative ^{99m}Tc-MIBI scan and MRI.

All 6 patients in the initial stage (st. I) of disease (not requiring therapy) had negative ^{99m}Tc-MIBI scan and negative STIR but positive T1 w.i. in MRI (Table 2).

Among the 41 MM patients with active disease, 21 showed D-pattern of ^{99m}Tc-MIBI uptake, 8 F, 10 F+D, and 2 patients N pattern, while 34 patients exhibited focal lesions in MRI and 4 patients had combined focal and diffuse findings (Table 3; Figure 1 and 2AB). Moreover, 5 of 38 patients had epidural mass and 18 vertebral compression in MRI.

Out of 15 patients after intensive chemotherapy, 13 reached complete remission and 2 were classified as having stable disease.

Normal ^{99m}Tc-MIBI scintigraphy was found in 11 (85%) patients with complete remission, and 2 patients presented F+D pattern of ^{99m}Tc-MIBI uptake. Two patients with stable disease also showed F+D pattern of radiotracer uptake (Table 4; Figures 3 and 4).

MRI findings were normal only in 3 patients (23%) with complete remission. Eight patients exhibited focal lesions and 2 showed

Table 2. Results of ^{99m}Tc-MIBI and MRI examination (n = 52)

	^{99m}Tc-MIBI scintigraphy		MRI — STIR		MRI — T1 w.i.	
	Positive	Negative	Positive	Negative	Positive	Negative
MM stage I	–	6	–	6	6	–
MM stage II and III	39	2	38	3	38	3
MGUS	–	5	–	5	–	5
Total	39	13	38	14	44	8

Table 3. Distribution of ^{99m}Tc-MIBI and MRI scan patterns

Scan pattern	^{99m}Tc-MIBI positive results (n = 39)	MRI positive results (n = 39)
D	21	–
F	8	34
F + D	10	4

D — diffuse pattern; F — focal pattern; F + D — combined focal and diffuse pattern

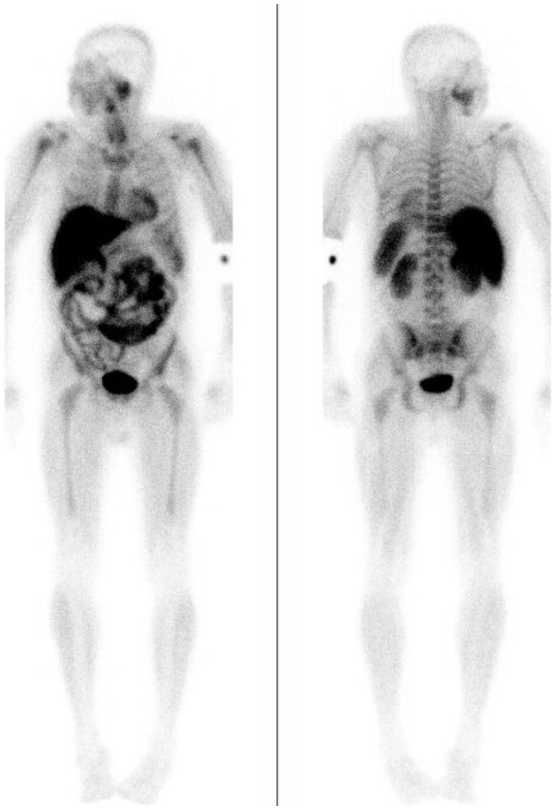

Figure 1. ^{99m}Tc-MIBI scintigraphy in active (stage III) MM patient. D pattern of ^{99m}Tc-MIBI uptake.

partial conversion (Table 4, Figure 5AB). Two patients with stable disease exhibited focal lesions.

Discussion

The equal sensitivity of both ^{99m}Tc-MIBI scintigraphy and MRI in the detection of active disease was revealed in our study. Both examinations complement each other.

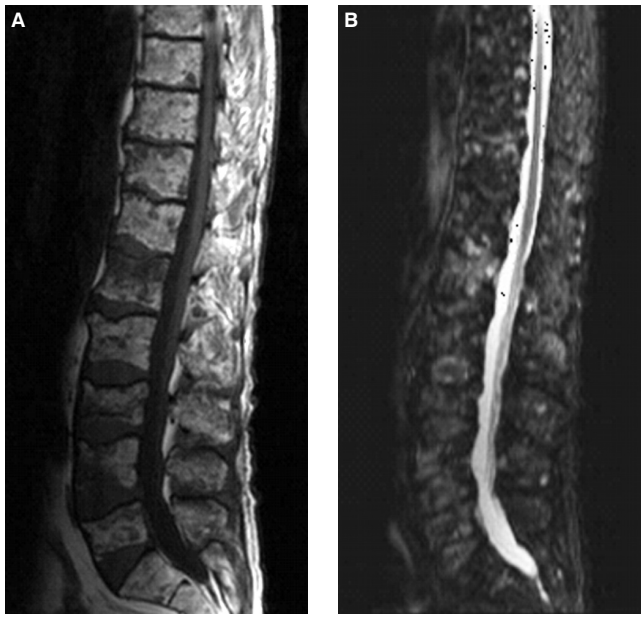

Figure 2. Sagittal T1-weighted MR image (A) and STIR (B) in the active MM patient, stage III (the same patient as in Figure 1). Multifocal involvement of spine is present. Focal lesions are best seen against the background of bone marrow conversion (A).

The assessment of the proportion of D and F patterns in both ^{99m}Tc-MIBI scintigraphy and MRI has been very problematic as most MM foci are usually smaller than 10 mm, which is below the scintigraphic resolution. Therefore, findings of D pattern predominated in 99mTc-MIBI scintigraphy. The work of Wakasugi et al [14] is also very informative, who found mild diffuse bone marrow uptake of ^{99m}Tc-MIBI in 90% patients in the control group.

Our study has also shown that ^{99m}Tc-MIBI scintigraphy, unlike MRI, provides "real-time" information about tumour response to therapy, which enables very effective monitoring of therapy results. Out of 13 patients in remission, 8 exhibited focal lesions and 2 partial conversion in MRI, while 11 patients had no pathological uptake of radiotracer in ^{99m}Tc-MIBI scintigraphy. While MRI is very sensitive for detection of disease in the skeletal system, the focal lesions seen by MRI take some months to years to resolve, even with the patient with complete clinical response. Thus, while new lesions on MRI indicate relapse or progression, an unchanging examination may be present for some time despite excellent clinical response by the patient [11].

The advantage of ^{99m}Tc-MIBI scintigraphy is the possibility of the whole-body examination, which allows superiority in detection of MM (especially focal lesions) in appendicular skeleton and extramedular localization.

Table 4. ^{99m}Tc-MIBI and MRI after intensive chemotherapy (n = 15)

Therapy result	^{99m}Tc-MIBI scintigraphy		MRI	
	Positive	Negative	Positive	Negative
CR (n = 13)	2	11 (85%)	10	3 (23%)
SD (n = 2)	2	–	2	–

CR — complete remisiion; SD — stable disease

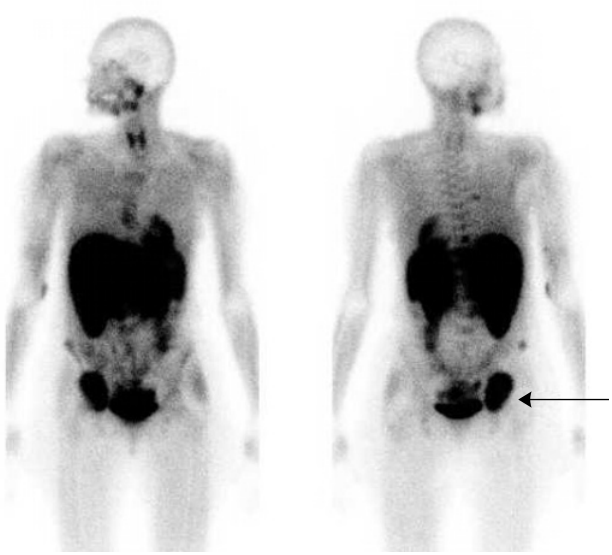

Figure 3. ^{99m}Tc-MIBI scintigraphy (F+D pattern of 99mTc-MIBI uptake) before intensive chemotherapy. Large area of focal uptake of 99mTc-MIBI on the right side of pelvis (arrow).

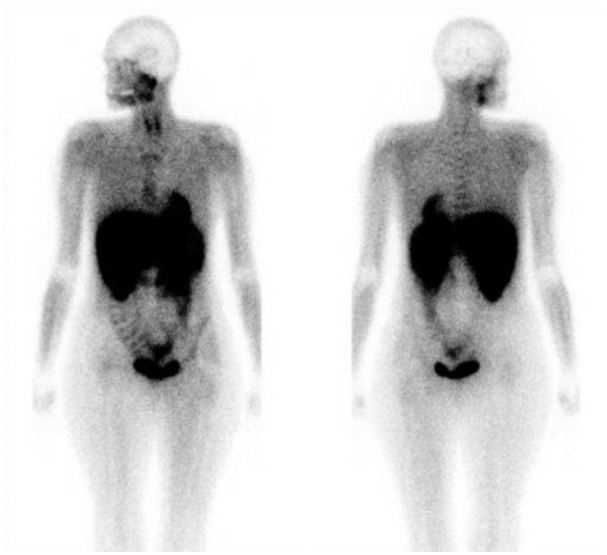

Figure 4. ^{99m}Tc-MIBI scintigraphy 2 months after intensive chemotherapy (the same patient as in Figure 3). Complete clinical remission was reached. Early effect of therapy was apparent in ^{99m}Tc-MIBI scintigraphy — focal lesions disappeared.

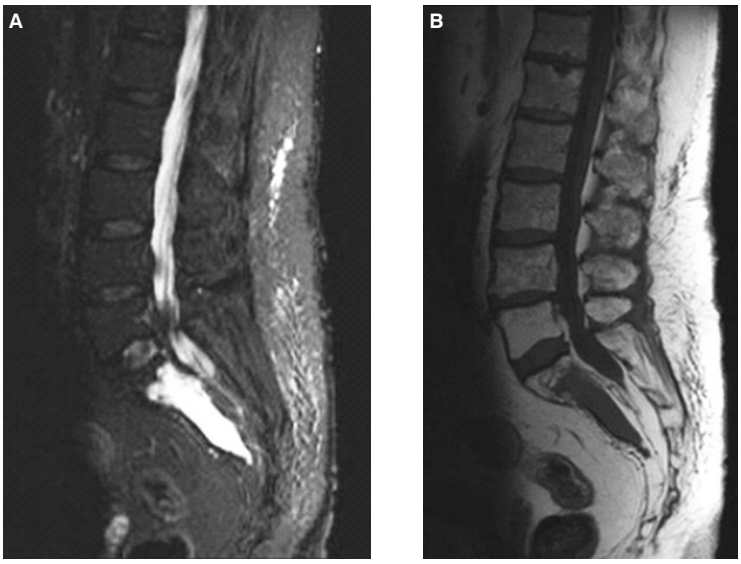

Figure 5. Sagittal STIR (**A**) and T1-weighted MR image (**B**) in patient 2 years after therapy of active MM. Normal clinical findings and 99mTc-MIBI scintigraphy. The STIR focal lesion persists.

In our study, 5 epidural masses and 18 vertebral compressions were detected in MRI. This examination provides superior spatial and contrast resolution of the skeletal system compared to ^{99m}Tc-MIBI scintigraphy. This is in accordance with statement of Walker [11] , who, moreover, suggests that MRI is important for baseline examination of the calvarium, vertebral column, pelvis (with proximal femora), sternum, shoulder girdles and, when indicated, other selected structures.

Conclusions

^{99m}Tc-MIBI scintigraphy and MRI are methods of equal sensitivity in detecting active MM in the axial skeleton, and they complement each other.

The advantage of ^{99m}Tc-MIBI scintigraphy is the possibility of whole-body examination, which allows superiority detection of MM (especially focal lesions) in appendicular skeleton and extramedullar localization, and faster response to therapy. The disadvantage of ^{99m}Tc-MIBI scintigraphy in comparison with MRI is the lower resolution of the equipment. Most focal lesions in MM are smaller than 10 mm and are bellow the resolution of scintigraphy. Therefore, assessment of the proportion of diffuse and focal lesions in both examinations is very problematic.

The advantage of MRI is the ability to detect epidural masses and vertebral compressing, significantly influencing the therapeutic strategy.

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