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The value of $^{99m}$Tc-MIBI whole body scintigraphy in active and in remission multiple myeloma

Abstract

Technetium-99m methoxy-isobutyl-isonitrile ($^{99m}$Tc-MIBI) has been proposed as an in-vivo marker of various active malignant diseases. The goal of this study was to evaluate the $^{99m}$Tc-MIBI whole body scintiscan for the early detection of multiple myeloma (MM), active or in remission. We have studied 43 patients with MM, 32 men and 11 women aged 52±10 years. Group A patients had active MM disease (29 cases) and Group B patients had MM disease in remission (14 patients). Plasma proteins, serum immunoelectrophoresis, bone marrow biopsy, whole body $^{99m}$Tc-MIBI scan and serum bio-chemical tests (ESR, and serum alkaline phosphatase) were examined out in each patient for the diagnosis of active or relapsed disease, or remission. Clinical and laboratory evaluation was made by two oncologists. Scintigraphic images were interpreted by three nuclear physicians who were blinded to the patients' clinical condition. The extension scale of the lesions on scintigraphy (E-score) was categorized into E0-E3. The intensity of radiotracer uptake throughout the skeleton (I-score) was also classified from I1-I3 as compared to the intensity of myocardial uptake. All patients were followed for at least one year and reassessed by the end of the year for confirming active-relapsed disease or remission. One-way analysis of variances and Spearman correlation coefficient were used for statistical data analysis. The sensitivity, specificity, positive and negative predictive values and accuracy of the $^{99m}$Tc-MIBI scan for determining active or relapsed cases were: 69%, 100%, 100%, 61% and 79%, respectively. There were significant differences in scan pattern, intensity, and extension of the lesions in patients with active-relapsed disease versus those in remission (P<0.001). It is concluded that the pattern of extension and intensity of $^{99m}$Tc-MIBI uptake in MM patients is associated with disease activity. Hence, in addition to the hematological and pathological findings, the $^{99m}$Tc-MIBI scan may be considered as a relatively accurate non-invasive technique for the differential diagnosis of active-relapsed from in remission MM.

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Introduction

Multiple myeloma (MM) is the most common primary bone malignancy in adults [1]. This neoplasm is a malignant myeloproliferative disorder characterized by accumulation and proliferation of plasma cells and secretion of a monoclonal immunoglobulin [1-4].

Several diagnostic procedures are used for MM patients. Conventional bone radiography is an important modality in the diagnosis of the lytic lesions and may be used for staging myeloma; however this method is notoriously insensitive especially in some locations such as ribs and sternum [1] and also can not differentiate active lesions from post-treatment changes, because radiographically visible lesions may persist for several months after successful treatment [1,5]. It is mentioned here that even the best diagnostic method for MM, bone marrow biopsy has its limitations, like sampling errors [6]. Nuclear medicine procedures such as bone and bone marrow scintigraphy have their own limitations. Although bone scan is occasionally helpful in the diagnosis of MM in areas that are difficult to evaluate with radiography, it is generally insensitive for demonstrating many active lesions confirmed by radiography and as a result, bone radiographs are more likely to show more extensive disease than do bone scans [2,5]. Focal defects on bone marrow scans with radiocolloids are non-specific and so the use of this method did not improve diagnostic accuracy [1]. Recently, several studies have suggested that technetium-99m methoxy-isobutyl-isonitrile ($^{99m}$Tc-MIBI) whole body scan could be an index of the disease activity in MM better than the other nuclear medicine methods [7-13].

The aim of this study was to evaluate $^{99m}$Tc-MIBI whole body scan in indicating different patterns of radiotracer uptake as to the intensity and extension of the MM lesions, relate
them to the clinical status and hematological markers of these patients and thus determine the diagnostic value of 
$^{99m}$Tc-MIBI in differentiating active disease from remission.

**Patients and methods**

Forty-three patients with MM (32 men and 11 women aged 52.3 ± 10.3 years) were enrolled in the study. These patients were divided into Group A, who had active MM disease (29 cases) and Group B patients who had MM disease in remission (14 patients). Six patients from Group A were new cases without history of previous treatment ($A_1$) and 23 cases were previously treated with chemotherapy, radiotherapy or bone marrow transplantation ($A_2$). The protocol of this study was approved by the methodological and ethical committee of the Research Institute for Nuclear Medicine of Shariati hospital and Tehran University of Medical Sciences. All patients gave their informed consent for this study.

The diagnosis of active or relapsed MM was confirmed by: plasma protein electrophoresis to quantify monoclonal M-component, serum immuno-electrophoresis, bone marrow biopsy, complete peripheral blood count, assessment of urinary excretion of Bence-Jones protein, ESR, and serum alkaline phosphatase (normal range: 100-290 IU/l). In the presence of local bone pain, radiography was performed, as the first-step imaging method. The $^{99m}$Tc-MIBI whole body scan was also performed on the following day.

Remission was defined by: a) improvement in signs and symptoms, b) at least 75% reduction of M-component and c) decrease in bone marrow plasma cell counts to less than 5% after chemotherapy or after bone marrow transplantation [3,6].

Active disease ($Group A_1$ and $A_2$) was described by two experienced oncologists according to the above-mentioned diagnostic procedures. Group $A_1$ patients were recently diagnosed as having MM and were not treated before and Group $A_2$ patients had evidence of relapse.

Twenty minutes following the intravenous (iv) injection of 555 MBq of $^{99m}$Tc-MIBI, a whole body scan was carried out in the anterior and posterior projections with a large field of view γ-camera, low energy all purpose collimator and scan speed of 15 cm/min. The pattern of uptake of the radiopharmaceutical was classified into the following four groups by three nuclear medicine physicians, who were blinded to the patients’ clinical condition: a) N-pattern: physiologic uptake in the heart, liver, spleen, kidneys, salivary glands, thyroid, and also faintly in the muscles with no evidence of activity in bone or bone marrow, b) D-pattern: diffuse bone marrow uptake, c) F-pattern: focal bone marrow uptake, d) D+F pattern: both focal and diffuse uptake.

Intensity (I-score) and extension (E-score) of the lesions were also evaluated as follows: I-score: a) I0: No bone marrow uptake, b) I1: Abnormal uptake less than in myocardium, c) I2: Abnormal uptake equal to myocardium, d) I3: Abnormal uptake more than in myocardium E-score: a) E0: No bone marrow uptake, b) E1: Uptake in the pelvis and spine, c) E2: Uptake in the pelvis, spine, ribs or proximal epiphyses of humerus and/or the femur d) E3: Uptake in the pelvis, spine, ribs or distal epiphyses of humerus and/or the femur. I-score was determined visually by view of all three nuclear physicians and in case of suspicion or controversial vision, the quantitative assessment was carried out to confirm the end result.

All patients were followed for at least one year and re-examined every 3 months, by all the above-mentioned tests in order to diagnose recurrence or active disease. None of the patients had any cardiac disease that might influence the I-score.

**Statistical analysis**

After calculation of sensitivity, specificity and accuracy, we processed our data statistically with SPSS (10) software. Chi-square analysis was used with multiple comparisons of qualitative variables such as scan patterns in different groups of patients. Analysis of variances between I-score and E-score in the different groups of patients was obtained by Kruskal-Wallis H test. Finally, Spearman-correlation coefficient was used to assess the presence of possible relationship between ordinal variables like bone marrow uptake scores and serum level of M-component. A P-value of less than 0.05 was considered significant.

**Results**

Twenty out of the 29 (69%) cases of Group A (active MM) had focal, diffuse or mixed pattern of abnormal $^{99m}$Tc-MIBI uptake and nine patients (31%) had normal scintigraphy. During the course of one year follow up, no response to treatment with multiple drugs and protocols was seen in six (67%) of these nine cases. All six patients of Group $A_1$ (new cases) showed abnormal scan which denotes 100% sensitivity in this group while this value for patients in Group $A_2$ was 61% (14 out of the 23 cases).

Chi-square analysis showed significant difference in the distribution of scan patterns among the patients with active disease and those in remission (P<0.001) (Fig. 1).

![Figure 1. Proportional frequency of various patterns of uptake in different clinical status of MM](image-url)
All patients with focal, diffuse or mixed, focal and diffuse, uptake were in Group A (active disease), while only 14 out of 23 patients (60.9%) with normal scan were in Group B (in remission).

The correlation between I-score or E-score and the values of hemoglobin and M-component of plasma proteins is found in Table 1. Analysis of variances by Kruskal-Wallis test revealed significant difference of I-score in patients with active/relapsed disease (Group A) versus those in remission phase (Group B), (P<0.001 and X² = 19.9) (Fig. 2). Also, a significant difference of E-score was noted between these two Groups (P<0.001 and X² = 18.15) (Fig. 3).

Finally the diagnostic value indices of ⁹⁹ᵐTc-MIBI scan for determining active disease were defined as sensitivity 69%, specificity 100%, positive predictive value 100%, negative predictive value 61% and accuracy 79.1%.

**Discussion**

The radiopharmaceutical ⁹⁹ᵐTc methylene-diphosphonate (⁹⁹ᵐTc-MDP) is the most commonly used agent to detect bone lesions in MM [1,2]. Due to poor osteoblastic response of the bones in MM, the sensitivity of bone scan is even lower than that of conventional radiography [5]. MRI is superior to standard radiography in the evaluation of some patients however, only advanced bone marrow infiltration in MM can be reliably detected by MRI [14] and also total-body MRI can be applied only in special clinical situations because it is time-consuming and cumbersome [13]. Nevertheless, MRI and other radiological procedures such as conventional radiography can not accurately differentiate active from inactive lesions, because the abnormalities that are noted by these techniques may be nonspecific [2,4,15,16]. The possibility of active multiple myeloma could not be excluded in patients with benign appearing vertebral compression fractures at MR imaging [15], and on the other hand the acute healing compression fractures may mimic the findings of malignant lesions [16].

In several other studies, the specificity and positive predictive value of ⁹⁹ᵐTc-MIBI was reported to be 75%-100% [7,9-13]. These results are in concordance with our study which revealed a specificity and positive predictive value of 100%. Also, all Group A₁ patients had abnormal ⁹⁹ᵐTc-MIBI whole body scan, which denotes 100% sensitivity, however the number of cases in this group was small in order to have significant statistics. In patients of Group A₂, sensitivity was less than 61%, while other studies report a range of sensitivity from 82% to 100% [7,9-13] which is dissimilar to our results. This difference may originate from disparity in the groups of patients designed. Most patients in our study had multiple treatments with variable protocols. In 67% of the patients with false negative ⁹⁹ᵐTc-MIBI scan, no response to different treatments was noted, so, low sensitivity of ⁹⁹ᵐTc-MIBI for the detection of MM lesions in our study may be due to multi-drug resistance, which is a problem interfering with ⁹⁹ᵐTc-MIBI uptake [17,18]. Hence, it may be suggested that this scintigraphic method could be used for predicting response to treatment [18].

We found no significant correlation between the amount of M-component and the uptake scores in scintigraphy and also between I-score or E-score and hemoglobin levels. In another study, correlation between the extension of the lesions (E-score) and the percentage of plasma cells in bone marrow, as well as the absolute amount of plasma M-component has been reported [7]. It is interesting to further study these findings in order to support the role of ⁹⁹ᵐTc-MIBI scan in MM disease. In addition to the above, we noted a significant difference of I-score and E-score in patients with active/relapsed disease (Group A) versus those in remission (Group B). What's
more, considering the results of other studies [9-13], our findings may indicate a potential role for 99mTc-MIBI scan in differentiating active/relapsed MM disease from remission.

In conclusion, the patterns, extension and intensity of the 99mTc-MIBI uptake in MM, may be associated with the disease activity of these patients. Whole body scan with 99mTc-MIBI has an accuracy of almost 80% for the detection of active MM. We suggest that 99mTc MIBI whole body scan may be used as a complementary imaging technique for the diagnosis and follow up of bone marrow lesions in MM patients.

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The value of $^{99m}$Tc-MIBI whole body scintigraphy in active and in remission multiple myeloma

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Abstract
Technetium-99m methoxy-isobutyl-isonitrile ($^{99m}$Tc-MIBI) has been proposed as an in-vivo marker of various active malignant diseases. The goal of this study was to evaluate the $^{99m}$Tc-MIBI whole body scintiscan for the early detection of multiple myeloma (MM), active or in remission. We have studied 43 patients with MM, 32 men and 11 women aged 52±10 years. Group A patients had active MM disease (29 cases) and Group B patients had MM disease in remission (14 patients). Plasma proteins, serum immuno-electrophoresis, bone marrow biopsy, whole body $^{99m}$Tc-MIBI scan and serum bio-chemical tests (ESR, and serum alkaline phosphatase) were carried out in each patient for the diagnosis of active or relapsed disease, or remission. Clinical and laboratory evaluation was made by two oncologists. Scintigraphic images were interpreted by three nuclear physicians who were blinded to the patients’ clinical condition. The extension scale of the lesions on scintigraphy (E-score) was categorized into $E_0-E_3$. The intensity of radiotracer uptake throughout the skeleton (I-score) was also classified from $I_0-I_3$ as compared to the intensity of myocardial uptake. All patients were followed for at least one year and reassessed by the end of the year for confirming active-relapsed disease or remission. One-way analysis of variances and Spearman correlation coefficient were used for statistical data analysis. The sensitivity, specificity, positive and negative predictive values and accuracy of the $^{99m}$Tc-MIBI scan for determining active or relapsed cases were: 69%, 100%, 100%, 61% and 79%, respectively. There were significant differences in scan pattern, intensity, and extension of the lesions in patients with active-relapsed disease versus those in remission ($P<0.001$). It is concluded that the pattern of extension and intensity of $^{99m}$Tc-MIBI uptake in MM patients is associated with disease activity. Hence, in addition to the hematological and pathological findings, the $^{99m}$Tc-MIBI scan may be considered as a relatively accurate non-invasive technique for the differential diagnosis of active-relapsed from in remission MM.

Keywords: $^{99m}$Tc-MIBI – Multiple myeloma diagnosis – Active disease – Follow up

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