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Utility of ^{99m}Tc dextran scintigraphy in diabetic patients with suspected osteomyelitis of the foot

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Purpose: Osteomyelitis of the foot is a frequent complication of diabetes mellitus and its diagnosis is often difficult. The goal of this study was to demonstrate the utility of ^{99m}Tc dextran scintigraphy in suspected diabetic foot infections. ***Materials and Methods:*** Twenty-six patients (20 males, 6 females, age range 18–80 years) with diabetes mellitus who had a total of 36 foot ulcers or necrosis were studied. All the patients underwent both three phase bone scan and ^{99m}Tc dextran scintigraphy. Final diagnosis was based upon either pathologic examination or clinical follow-up at least four months. ***Results:*** On bone scan increased uptake was seen in 55 sites, and among these there were 11 lesions of proven osteomyelitis. There were 11 true-positive, 0 false negative, 0 true negative and 44 false positive results for bone scan. The sensitivity, specificity and accuracy of bone scan were 100%, 0% and 20%, respectively. With regard to ^{99m}Tc dextran scan, nine lesions produced true-positive results with two lesions indicating false negatives resulting in a sensitivity of 82%. Thirty-six true negative and eight false positive results produced a specificity of 82%, and an accuracy 82% from ^{99m}Tc dextran studies was obtained. Eight false-positive results were possibly due to neuroarthropathy, pressure points and deep penetrating ulcers. A patient with one false-negative result had angiopathy while other had neither neuropathy nor angiopathy. ***Conclusions:*** According to these results, ^{99m}Tc dextran scintigraphy seems to be a sensitive and specific diagnostic method, and because of its advantages over other radiopharmaceuticals (shorter preparation time, highly stability *in vivo/in vitro*, early diagnostic imaging and low cost), it may be a radiopharmaceutical of choice for diagnosing in diabetic foot infections.

Key words: diabetic foot, infection, scintigraphy, ^{99m}Tc dextran

INTRODUCTION

DIABETES MELLITUS is frequently complicated by skin ulceration, cellulitis, or both, especially involving the lower extremities. Establishing the diagnosis of osteomyelitis in the foot may, at times, be difficult. Concurrent conditions, such as peripheral vascular disease, cellulitis, neuropathy, and osteoarthropathy, may obscure the clinical manifestations of osteomyelitis. Thus, diagnostic imaging modalities can provide useful adjunctive information. A variety of nuclear medicine techniques including bone scintigraphy and/or gallium-67 (^{67}Ga) scintigraphy, labeled IgG, white cell and antigranulocyte antibodies scintigraphy are currently employed.

Technetium-99m (^{99m}Tc) dextran is a inflammation-seeking radiotracer and nonspecifically concentrates in lesions with increased capillary permeability like other agents such as ^{67}Ga, ^{99m}Tc IgG and ^{99m}Tc nanocolloid.[1–3] The aim of this study was to determine the usefulness of ^{99m}Tc dextran scintigraphy in diabetic patients referred for investigation of possible pedal osteomyelitis.

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Table 1 Patients data summary

Pat. no (age/sex)	Clinical ulcer localizations	Increased uptake sites at bone scan	^{99m}Tc dextran findings	X-ray	Culture	Diagnostic Method	Final (OM)	Surgical Intervention
1 (60/M)	Plantar ulcer-R	Midfoot-R	–	–	+	Follow-up	–	STD-R
		Hindfoot-R	–	–	+	Follow-up	–	
		Midfoot-L	–	–	NA	Follow-up	–	
		Hindfoot-L	–	–	NA	Follow-up	–	
2 (61/M)	Dorsal-L ulcer	2nd mttr-L	+	–	–	Histology	+	AKA-L + A-V
		3rd mttr-L	+	–	–	Histology	+	fis + FF
3 (63/F)	Amputed 1st toe-R + base ulcer	Midfoot-R	–	–	NA	Follow-up	–	Amputation of
		1st mttr-R	–	–	–	Histology	–	1st mttr-R
		Midfoot-L	–	–	NA	Follow-up	–	
4 (72/M)	Amputed all-R mttrs + dorsal ulcer	Midfoot-R	+	+	–	Histology	+	BKA-R
5 (66/M)	Amputed 5th toe-R + base necrose + Amputed all mttrs-L	1st toe-R	–	–	–	Histology	–	AKA-R + A-V
		5th mttr-R	–	–	+	Histology	–	fis + FF
		Midfoot-L	–	–	NA	Follow-up	–	
6 (65/M)	Amputed 2345 toes-L + base ulcer	4th mttr-L	+	–	+	Follow-up	–	STD-L
		5th mttr-L	+	–	+	Follow-up	–	
		Midfoot-R	–	–	NA	Follow-up	–	
		Midfoot-L	–	–	NA	Follow-up	–	
7 (67/F)	Amputed all toes-R + base ulcer	Midfoot-R	–	–	+	Histology	–	AKA-R
8 (69/M)	1st toe-L necrose	1st toe-L	+	–	–	Histology	+	Amputation of
		1st toe-R	+	–	NA	Follow-up	–	1st toe-L
		Midfoot-L	+	–	NA	Follow-up	–	
9 (64/M)	1st toe-L + R ulcers	1st toe-R	–	–	–	Follow-up	–	STD-R
10 (80/M)	Plantar + heel-L ulcers	Midfoot-L	–	–	–	Histology	–	BKA-L
		Calcaneus-L	+	+	+	Histology	+	
11 (64/F)	Midfoot-L ulcer	Midfoot-L	–	–	–	Follow-up	–	STD-L
12 (60/F)	1st toe-R necrose	Midfoot-R	–	–	NA	Follow-up	–	TMA-R
		1st toe-R	–	–	+	Histology	–	
		2nd toe-R	–	–	+	Histology	–	
		3rd toe-R	–	–	–	Histology	–	
13 (71/M)	2345 toes-L necrose	1st mttr-L	–	–	–	Histology	–	BKA-L
14 (52/M)	Amputed 2nd toe-L + base ulcer	2nd mttr-L	+	–	+	Histology	+	Amputation of
		1st toe-L	–	–	NA	Follow-up	–	2nd mttr-L
		1st toe-R	–	–	NA	Follow-up	–	
15 (73/M)	Amputed 3rd toe-R + plantar/dorsal ulcers	Hindfoot-R	–	–	+	Histology	–	AKA-R
16 (60/F)	Amputed 5th toe-R + base ulcer	5th mttr-R	–	–	+	Histology	–	TMA-R
		Hindfoot-R	–	–	NA	Follow-up	–	
17 (70/M)	Amputed foot-L + 5th toe-R necrose	Hindfoot-R	–	+	–	Histology	–	AAA-R + A-V
		Midfoot-R	–	+	–	Histology	–	fis + FF
18 (57/M)	Heel-L ulcer	Calcaneus-L	+	–	+	Follow-up	–	STD-L

19 (18/M)	1st toe-R necrose	5th toe-R Midfoot-R Midfoot-L	– – –	– – –	+ NA NA	Histology Follow-up Follow-up	+ – –	Amputation of 1st toe-R
20 (59/M)	Amputed 5th toe-L + dorsal/plantar ulcers	1st mttr-L 4th mttr-L	– –	– –	NA +	Follow-up Histology	– –	Amputation of 4th mttr-L
21 (51/F)	2nd toe-L necrose	2nd toe-L Midfoot-L	– –	– –	– NA	Histology Follow-up	– –	Amputation of 2nd toe-L
22 (45/M)	Heel-L ulcer	Calcaneus-L	+	–	+	Follow-up	–	STD-L
23 (65/M)	1st toe-R + 1st + 5th toe-L ulcers	1st mttr-R 1st mttr-L	– –	– –	– –	Follow-up Histology	– +	STD-R + TMA-L
24 (58/M)	5th mttr-L ulcer	5th mttr-L	+	–	+	Histology	–	Amputation of 5th mttr-L + FF
25 (50/M)	5th toe-R ulcer	5th mttr-R Midfoot-R	+ +	– –	+ NA	Follow-up Follow-up	– –	STD-R
26 (31/M)	2nd + 3rd mttr-L ulcers	2nd mttr-L 3rd mttr-L Midfoot-L	+ + –	+ + –	+ + NA	Histology Histology Follow-up	+ + –	Amputation of 2nd + 3rd mttrs-L

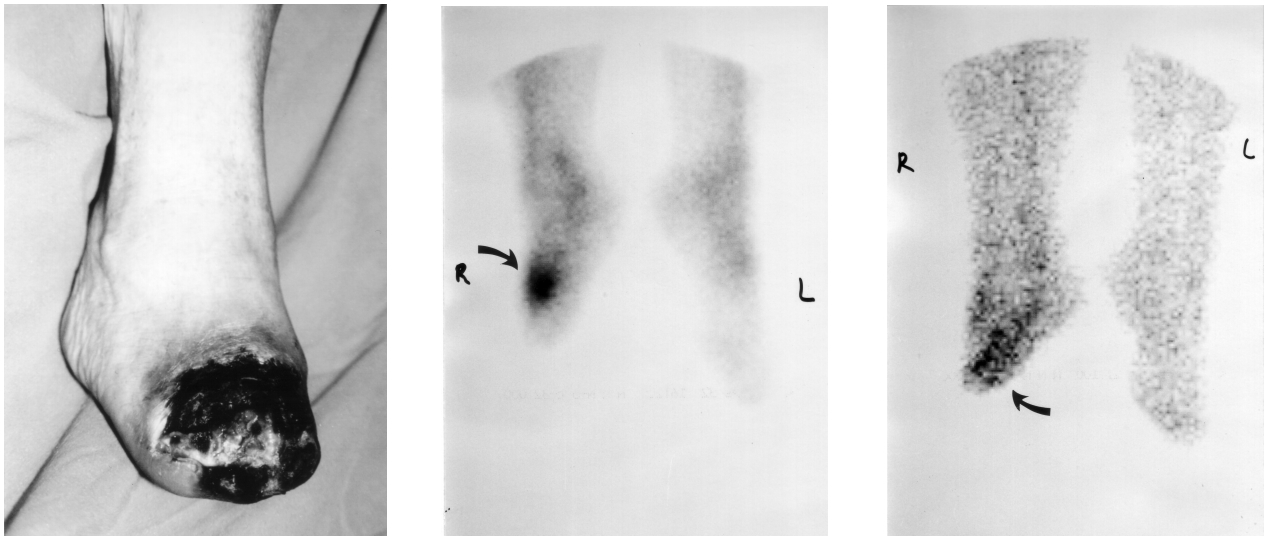
Abbreviations of Table 1.
M, male; F, female; L, left; R, right; mttr, metatarsal; NA, not available; STD, soft tissue debridement; AKA, above-the-knee amputation; BKA, below-the-knee amputation; AAA, above-the-ankle amputation; A-V fis, arteriovenous fistulae; FF, free flap; TMA, transmetatarsal amputation; OM, osteomyelitis

MATERIALS AND METHODS

Twenty-six patients, clinically suspected to have osteomyelitis, were included 6 women and 20 men; their mean age is 59 years old, ranging from 18 to 80 years. All patients had diabetes mellitus (1 of type I and 25 of type II) for at least 4 years (mean 13 years). There were nonhealing ulcers or gangrenes adjacent to suspected areas of osteomyelitis in all patients (36 lesions). Patients with normal bone scans were not included in this study since three phase bone scintigraphy has very sensitive in assessing of osteomyelitis. None of the patients had received antibiotics for at least 1 week before the imaging studies and cultures. Soft tissue or bone cultures were obtained within 1 to 2 weeks of imaging. Presence or absence of neuropathy and arteriopathy were assessed by clinical examination, electromyelography and duplex Doppler for each patient.

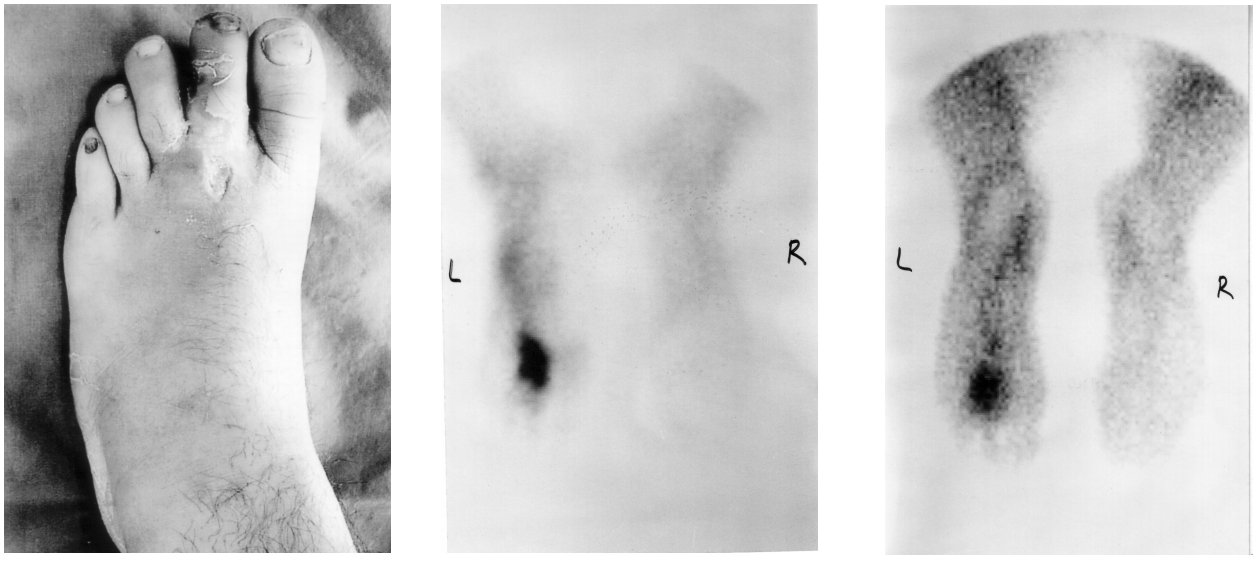
Three-phase bone scintigraphies were obtained following injection of 740 MBq (20 mCi) of ^{99m}Tc methylene diphosphonate (MDP) and included flow, blood pool and delayed images. Static images (plantar, anterior and lateral) were acquired with a preset time of 5 min. ^{99m}Tc dextran was prepared in our laboratory according to the kit preparation method.[4] Labeling efficiency was more than 95%. Four hours after 370 MBq (10 mCi) ^{99m}Tc dextran were injected intravenously, feet images were acquired with a preset time of 5 min. Both scintigraphic studies were always obtained within 3 days of each other. All scintigraphic images were interpreted by two experienced observers unaware of the results of clinical and roentgenological findings. ^{99m}Tc MDP images were interpreted as positive for osteomyelitis when increased flow, hyperemia, increased uptake on delayed images. A ^{99m}Tc dextran scan was judged to be abnormal (degree of slight, moderate or intense) if, in the suspected area, ^{99m}Tc dextran uptake was greater than the uptake in the surrounding normal tissue or the contralateral side. ^{99m}Tc dextran scintigraphy was considered to be positive for osteomyelitis when there was moderate-to-intense uptake of ^{99m}Tc dextran in a zone concordant with the area of uptake on bone scan. ^{99m}Tc dextran scan was considered to be negative for osteomyelitis when there was abnormal accumulation in a zone not concordant with the area of uptake on bone scan or when no ^{99m}Tc dextran accumulation was observed. Slightly increased activity of ^{99m}Tc dextran was also evaluated as being negative. Each uptake was determined to correspond to bone or only to soft tissue by comparing with bone scan anatomical landmarks. In order to reduce the number of false-positive results secondary to the activity in dressings,[5] all patients underwent wound-dressing changes immediately before imaging.

All radiographs were interpreted by one experienced radiologist. Cortical distruption in the area of a foot ulcer was considered indicative of osteomyelitis. A final diagnosis was confirmed by either surgery and pathologic examination or clinical course and radiographic follow-up (minimum 4 months). Patients who were diagnosed by clinical means were considered not to have osteomyelitis if their signs and symptoms responded to local treatment and/or a brief (less 2 weeks) course of antibiotics with no



a **b** **c**

Fig. 1 (a) A patient with diabetes mellitus (No. 7) whose all toes of the right foot were previously amputed had ulcer at the base of amputation site. (b) Bone scan show increased uptake in the midfoot (*arrow*), (c) whereas ^{99m}Tc dextran accumulation was located in the soft tissues inferior to the bone (*arrow*). No osteomyelitis was confirmed and there was only a soft tissue infection (true negative ^{99m}Tc dextran study).



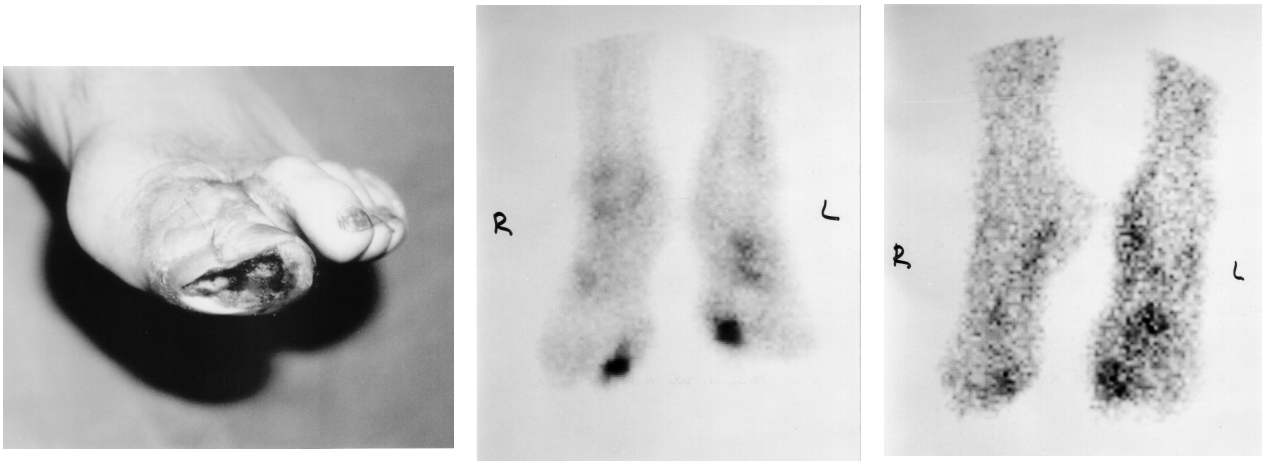
a **b** **c**

Fig. 2 (a) Infected ulcer at the base of second toe of left foot (No. 26). Both (b) bone and (c) ^{99m}Tc dextran scan in plantar projection show intense focally increased uptake in the distal of second and third metatarsal. There is also diffusely moderate uptake in the midfoot of left foot on the bone scan, whereas no ^{99m}Tc dextran uptake is seen in this regions. Osteomyelitis was subsequently confirmed pathologically after amputation of second and third toes. This study was accepted as true positive and true negative for ^{99m}Tc dextran.

subsequent relapse. Positive bacteriology and positive histology led to the diagnosis of osteomyelitis.

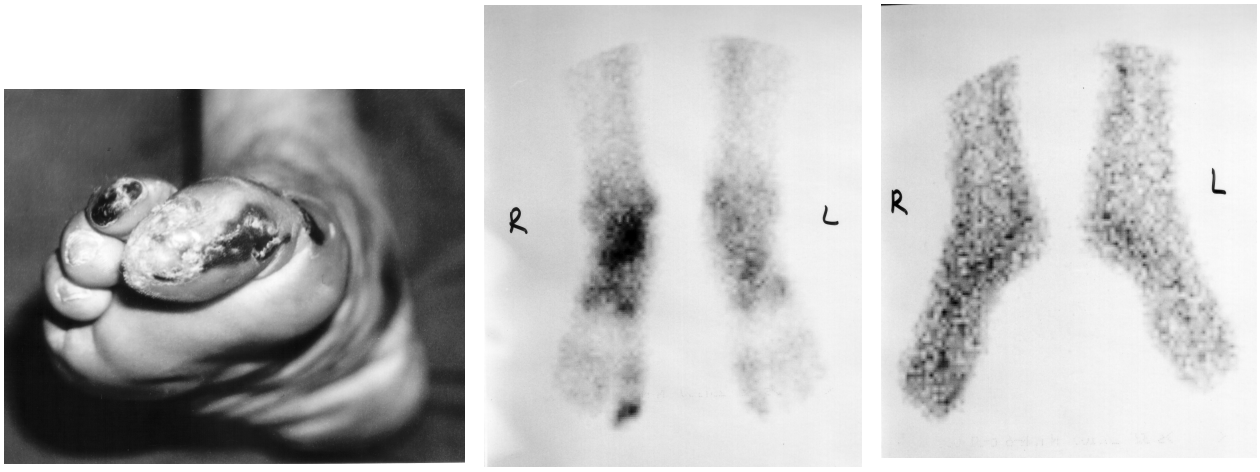
RESULTS

The clinical and imaging results for 26 patients are summarized in Table 1. All cases except one had evidence of neuropathy and ten patients had angiopathy. ^{99m}Tc MDP



a b c

Fig. 3 (a) Necrosis at the first toe of left foot (No. 8). On both bone (b) and ^{99m}Tc dextran scan (c), there was increased uptake in the first toe and midfoot of left foot and first toe of right foot. Osteomyelitis was proven pathologically after amputation of first toe of left foot. Thus, ^{99m}Tc dextran study was categorized as true positive in the left first toe and as false positive in the right first toe and left midfoot for osteomyelitis.

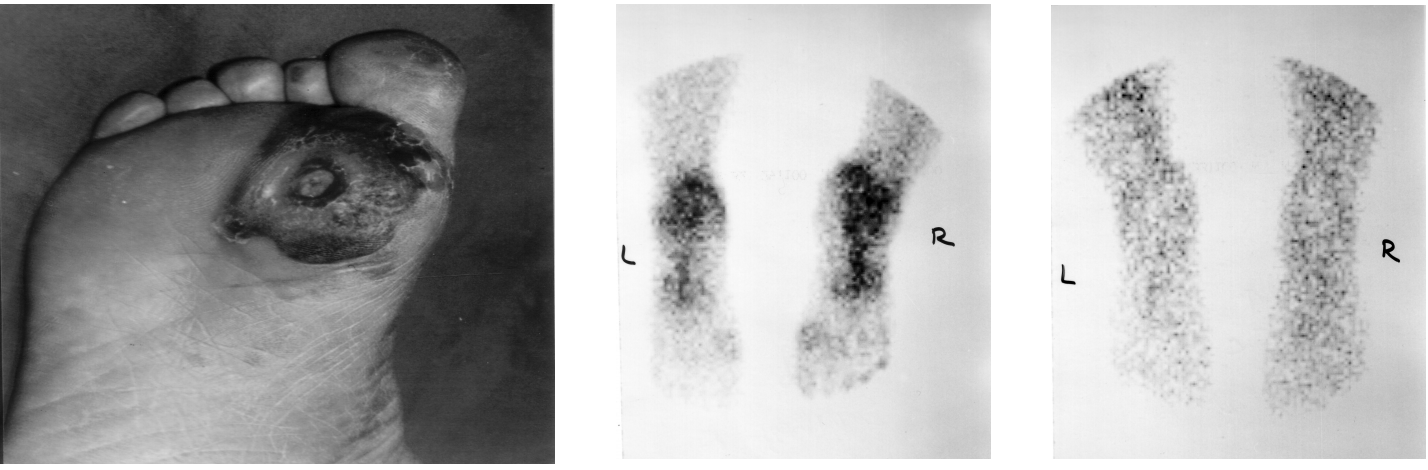


a b c

Fig. 4 (a) Necrosis at the first toe of right foot (No. 19). (b) Increased uptake on bone scan is seen in the right first toe and both midfoot, (c) whereas ^{99m}Tc dextran scan is normal. Histologic examination showed osteomyelitis after amputation of right first toe, indicating that ^{99m}Tc dextran scan was falsely negative. However, it was considered as true negative for both midfoot.

bone scan showed increased uptake in 33 out of 36 localizations clinically suspected for osteomyelitis and also determined 22 additional possible osteomyelitic foci. Among these 55 lesions, there were 11 foci of proven chronic osteomyelitis. The other 44 increase uptake sites without osteomyelitis were caused by degenerative osteoarthritis, uninfected pressure points and soft tissue lesions. ^{99m}Tc MDP bone scan produced 11 true positive (TP), 0 true negative (TN), 0 false negative (FN) and 44 false positive (FP). The sensitivity, specificity, and accuracy were 100%, 0% and 20%, respectively. Since there were increased ^{99m}Tc MDP uptakes in all suspected osteomyelitis areas, values of specificity and accuracy were very low.

By using the bone scan as a landmark for the osseous structures, ^{99m}Tc dextran uptake could be correctly localized to soft tissue or bone in most of cases (Fig. 1). ^{99m}Tc dextran scintigraphies were positive in 9 out of 11 proven osteomyelitic foci (Fig. 2 and Fig. 3). There were eight false-positive results in five patients (Fig. 3). ^{99m}Tc dextran accumulation in these patients were possibly due to pressure points (No. 6), neuroarthropathy (No. 8), penetrating ulcers with deep soft tissue infections (No. 22 and No. 25). There were two false-negative results in 2 patients. One (No. 23) of these had vascular angiopathy while other (No. 19) had neither neuropathy nor



a b c

Fig. 5 (a) Right plantar ulcer (No. 1). (b) bone scan shows bilaterally increased uptake in the mid- and hindfoot, (c) ^{99m}Tc dextran scan is normal, and it was acceped as true-negative for osteomyelitis.

angiopathy (Fig. 4). Sixty-six lesions without osteomyelitis showed normal or slightly increased ^{99m}Tc dextran accumulation that was accepted as true-negative results (Figs. 1, 2, 4 and 5). The sensitivity, specificity and acuracy were 82%, 82% and 82%, respectively, for ^{99m}Tc dextran scan.

Soft tissues or bone cultures were obtained from 36 lesions. The cultures revealed bacterial growth in 20 lesions. There was osteomyelitis in six of these lesions and five of negative cultures. Plain radiography produced 4 TP, 42 TN, 7 FN, and 2 FP. The sensitivity, specificity, and accuracy were 55%, 44% and 47%, respectively, for culture results and 36%, 95% and 84%, respectively, for plain radiography.

DISCUSSION

Diagnostic imaging methods useful in the evaluation of the diabetic foot include some scintigraphic and radiologic techniques. The cost-effectiveness of approaches to the diagnosis is important because imaging studies are expensive.[6] In this circumstance, plain radiography and even magnetic resonance (MR) are not very specific[7,8] and MR is much more expensive than nuclear medicine studies.[9] If clinically neuropathy is present, specific nuclear medicine imaging should be performed.[10,11] Which technique should be preferred is dependent the availability and the price of the different agents.

Bone scintigraphy is very sensitive but not specific as it is positive in cases of neuroarthropathy as well. ^{67}Ga, either alone or in combination with bone scanning, is of little diagnostic value. Indium-111 (^{111}In) labeled leukocyte scintigraphy has been shown to be able to enhance diagnostic specificity, however, this techniques have a certain number of disadvantages.[12] Labeled leukocytes do accumulate in uninfected Charcot joint and a major drawback is always the low count rate of the images and the poor spatial resolution.[13,14] ^{99m}Tc HMPAO leukocyte scan has been found to be an excellent method and it has certain advantages over ^{111}In scan in terms of dosimetry, availability and spatial resolution and also offers same-day imaging with comparable results.[15] However, only in patients with chronic osteomyelitis in which very late images are necessary for evaluation, the physical half-life and the instability of HMPAO label is disadvantageous compared to ^{111}In scan.[10] Other disadvantages of labeled leukocyte include high radiation dose to spleen and bone marrow, long preparation time and expense. ^{99m}Tc labeled anti-granulocyte monoclonal antibody (BW 250/183) scintigraphy has high sensitivity and specificity,[16] and the advantages of this technique over autologous leukocyte techniques are the simplicity of its use compared with techniques that require the isolation of autologous white blood cells.[10] Whole antibodies such as IgG and IgM are potentially strong inducers of human anti mouse antibody reaction (HAMA), which could theoretically make repeated injection of the tracer dangerous or, more likely, result in image degradation due to rapid hepatic clearance of immunoconjugates.[10,11] One way to minimize the likelihood of such undesirable events is the use of antibody fragments, which are much weaker inducers of HAMA. However, ^{99m}Tc labeled antigranulocyte monoclonal antibody fragment Fab scintigraphy appears to be poorly adapted to the detection of bone infection in diabetics and is less specific than ^{99m}Tc labeled leukocyte scintigraphy. Uptake mechanism of labeled IgG and nanocolloid is related to increased vascular permeability into expanded extracellular fluid space.[17] Although Oyen et al. found an high sensitivity and specificity using ^{111}In IgG scan, major limitations of labeled IgG are its cost and antigenic properties (human antihuman antibody reaction).[18] ^{99m}Tc nanocolloid, which is another nonspecific agent, scan

showed lower specificity because of its uptake in hematopoietically active marrow.[19]

Dextran is used clinically as a plasma expander and has a high molecular weight (81,000 dalton). ^{99m}Tc dextran is a blood pool labeling and lymphoscintigraphy agent,[20,21] but it has been used only recently to evaluate inflammation.[1–3] ^{99m}Tc dextran can easily be prepared within 5 to 15 minutes in every nuclear medicine laboratory, and once prepared in the kit form, it can be stored at 2 to 4°C for several weeks and can be used routinely by adding ^{99m}Tc pertechnetate. It has numerous advantages such as being quite cheaper than other agents, having a long intravascular half-time, high stability *in vivo* and *in vitro*, having a quick background clearance and no penetration to normal capillary membrane.[4,21] It has also a relative chance of early diagnostic imaging.

Many investigators suggested that slightly increased tracer uptake should be considered as having doubtful pathologic significance and categorized as negative result for diagnosis.[10,16,18] In our study, although ^{99m}Tc dextran uptake was not observed in most of the patients which were considered as true negative, there was minimal-to-mild increased activity in some patients. We accepted only "moderate-to-marked increased ^{99m}Tc dextran uptake" as positive result of imaging for diagnosis. Eight false-positive and two false-negative ^{99m}Tc dextran findings occurred, resulting in a sensitiviy of 82% and a specificty of 82%. In three of eight false positive results ^{99m}Tc dextran activity was mistakenly attributed to the bone in clinically diagnosed deep soft tissue infection, while other false-positive results were probably due to noninfected neuroarthropathy and pressure points. It was not possible to discriminate osteomyelitis from soft tissue involvement in deeply penetrating soft tissue infections by using the bone scan as a landmark for the osseous structures when additional bone scan were also obtained. Same problems have been also reported in other studies.[18,22] In these cases, it was found that SPECT may help to overcome these problems.[23] ^{99m}Tc dextran accumulation in pressure points and neuroarthropathy may be possibly related with increased capillary permeability, locally increased extracellular space and macromolecular entrapment in the these regions. Neuroarthropathy and other increased turnover lesions have been responsible for false positive cases with other imaging techniques.[14,18,19] Of our two false negative results, one is probably due to severe vascular angiopathy, while the other one, who had neither neuropathy nor angiopathy, the reason may be related to the degree of chronicity of osteomyelitis. Since only the patients with positive bone scan were included in our study, sensitivity of bone scan was very high and specificity was extremely low. This is not a new finding, and the performance of bone scintigraphy in this study is in agreement with reports in the literature.[14,15,18] In fact, goal of present study was to determine the performance of ^{99m}Tc dextran scan as a new imaging technique. Therefore, bone scan was used both in determining the likelihood of osteomyelitis and for attributing of ^{99m}Tc dextran uptake to either bone or soft-tissue, as a landmark osseous structures.

There are similarities in diagnostic efficacy between the results of our study and other nuclear medicine studies reported previously. Further studies comparing ^{99m}Tc dextran scintigraphy with other imaging methods such as labeled leukocyte scintigraphy are needed to determine its diagnostic role better. Because of certain advantages, particularly the shorter preperation time and its low cost, we suggest that ^{99m}Tc dextran scan may be used as alternative diagnostic tool over other agents for evaluation of suspected diabetic foot infections.

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