Diagnostic Role of Combined 99mTc-Hmpao Leucocyte Scintigraphy and 99mTc-MDP Bone Scintigraphy in the Diagnosis of Osteomyelitis in the Diabetic Foot

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Abstract

Background: The aim of this study was to assess the role of 99mTc-HMPAO leucocyte scintigraphy combined with 99mTc-MDP bone scintigraphy in the diagnosis of osteomyelitis in the diabetic foot.

Methods: 50 diabetic patients with suspected osteomyelitis were included. The HMPAO-Leucocytes/MDP scan was considered to be consistent with osteomyelitis when the HMPAO-Leucocytes uptake was concordant with MDP bone uptake. A HMPAO-Leucocytes uptake without concordant bone MDP activity was considered as a soft-tissue infection. The results of the HMPAO-Leucocytes/MDP scan were compared to the following diagnostic criteria: bone infection was confirmed by radiological follow-up or bone biopsy; the absence of bone infection was confirmed by clinical (healing of the ulcer without antibiotic therapy) and radiological follow-up.

Results: According to these criteria, among the 56 ulcers, bone infection was observed in 27 (48.2%): the HMPAO-Leucocytes/MDP scan was positive in 25 cases, including 7 ulcers with normal or equivocal radiographs at inclusion. In the group of 29 ulcers without proven bone infection, the HMPAO-Leucocytes/MDP scan was negative in 28 cases, including 8 lesions with a soft-tissue infection.

Conclusion: With a sensitivity of 92.6%, a specificity of 96.5%, the HMPAO-Leucocytes/MDP scan is a reliable tool for the diagnosis of osteomyelitis in the diabetic foot. Neuroarthropathy did not affect the performances of the HMPAO-Leu/MDP scan. Owing to a high spatial resolution this test is very helpful to differentiate bone infection from soft-tissue infection especially in case of neuroarthropathy.

Key Words: Diabetic foot – Bone infection – Bone/leucocyte scan.

Introduction

The diagnosis of osteomyelitis remains difficult in diagnosis in the diabetic foot. Routine radiographic techniques have a low sensitivity since they do not reveal changes until the bone has been significantly violated; moreover a concomitant neuroarthropathy may mask the radiological interpretation.

Three-phase bone scan with 99mTc-MDP has a 100% sensitivity but a very low specificity due to the high incidence of neuroarthropathy or traumatic fractures [1]. White blood cells labeled with various radionuclides, especially 111Indium oxine [2,3] have been shown to be useful for the diagnosis of bone infection when combined with a 99mTc-MDP bone scan. In addition, recent studies have reported that 99mTc-HMPAO may contribute significantly to the diagnosis of bone and joint infections [4,14-16]. Therefore the current study is to evaluate the efficacy of the 99mTc-HMPAO-Leucocyte scintigraphy combined with a 99mTc-MDP bone scintigraphy (HMPAO-Leucocytes/MDP scan) for the diagnosis of osteomyelitis in the diabetic foot.

Patients and Methods

Patients:

50 diabetic patients with suspected osteomyelitis from a foot ulcer (30 males, 20 females; median age: 59.1 years; median duration of diabetes: 10 years, HbA1c: 8.7% range 6.9-12) were included from November 2006 to November 2008. 22 were treated with insulin and 28 with oral antidiabetic agents. Other significant medical history in this population included peripheral vascular or coronary diseases (n=29), peripheral neuropathy (n=33), previous foot ulcers (n=28), neuroarthropathy with Charcot joint (n=3). Inclusion criteria were: suspected bone or joint infection from a single or multiple foot ulcers and no history of vascular or foot surgery during the previous three months.
Patients with acute limb infection at clinical presentations are medical emergencies and require immediate antibiotic therapy and are not included.

**Imaging protocol:**

Dorsal-plantar and lateral radiographs were taken on the day of inclusion, then repeated when they were equivocal for the diagnosis of osteomyelitis. Three-phase bone scintigraphy was performed using 20 mCi of 99mTc-MDP. Immediately after injection, dynamic images of the feet were obtained for one minute. Blood pool images were obtained in the five minutes after the injection. After two hours, delayed five minutes images of the feet (dorsal, plantar and lateral views) were acquired.

Leucocytes labelling with 99mTc-HMPAO: blood samples (45 ml) were collected on heparin. A Cell-rich plasma was obtained after sedimentation for 30-60 minutes at 37°C in the presence of 2.5 ml dextran. After sedimentation at 200 g for 15 minutes, leucocytes were isolated. The leucocytes were labelled with 15 mCi of freshly prepared 99mTc-HMPAO; incubation lasted for 15 minutes at room temperature. The labelled cells were washed and resuspended in cell poor plasma, then injected intravenously with a delay of less than 2 hours after the initial blood sampling.

The mean injection dose was 10 mCi. The labelling efficiency was 69%±11%. Scintigraphic images were acquired 1/2 and 3 hours after injection with a special care was taken to place the patients in the same position as for bone scintigraphy.

The ulcer dressing was carefully changed between the leucocytes injection and the first images acquisition. The 99mTc-HMPAO-Leucocytes scan and 99mTc-MDP scans were performed within a 2-3 day interval.

**Data analysis:**

Each imaging study was independently evaluated by one experienced radiologist and one nuclear medicine physician who knew the site of interest but did not have any additional information. The HMPAO Leucocytes/MDP scan was considered to be positive for osteomyelitis when there was an accumulation of leucocytes concordant with an abnormal uptake on bone scintigraphy (Fig. 1). The HMPAO-Leucocytes/MDP scan was considered to be negative for bone infection when no leucocytes accumulation was observed (absence of infection Fig. 2) or when there was an accumulation of leucocytes closed to the foot ulcer without concordant abnormal uptake on bone scintigraphy (soft-tissue infection) in 28 ulcers a needle bone biopsy for bacteriological and histological studies was performed when the radiograph at inclusion was negative with a positive bone scintigraphy. The absence of bone infection was confirmed by radiological follow-up and by healing of the ulcer without antibiotic treatment. Most of the 56 ulcers included are in the Forefoot and neuropathic (86%) 10% were in the hind foot and 4% in mid foot while 12% was neuroischemic and 2% non neuropathic non neuroischemic with size range 0.8-3 cm2).

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**Fig. (1):** Ulcer of the left second toe. Focal MDP uptake on bone scintigraphy (A) concordant with HMPAO accumulation on leucocyte scintigraphy (B): Osteomyelitis of the left second toe.
Among the 56 foot ulcers, 27 (48.2%) were associated with osteomyelitis diagnosed by radiology (n=17) or bone biopsy (n=10). The HMPAO-Leucocytes/MDP scan was positive in 25 cases (Fig. 1) (two false negatives) including 7 lesions with negative radiography at inclusion but showed scintigraphic evidence of bone infection during follow-up. For the 29 ulcers without proven bone infection, the HMPAO-Leucocytes/MDP scan was negative for 28 (Fig. 2) (one false-positive), including 8 ulcers with soft-tissue infection. The HMPAO-Leucocytes/MDP scan has the best overall diagnostic performances with sensitivity of 92.6%, specificity of 96.5% and accuracy of 94.9% as compared to plain radiography at inclusion with sensitivity of 49% specificity of 79% and accuracy of 60% or MDP scintigraphy alone has a very high sensitivity (100%) but a low specificity (29%) and accuracy of 63% especially in cases of previous foot ulcers or neuroarthropathy in the same site.

Moreover, neuroarthropathy, traumatic fractures or hyperemia that result from RSD results in positive bone scan images which remain positive for months so it can not be differentiated from bone infection by three-phase bone scintigraphy alone.

Labelled leucocyte scan along with bone scintigraphy have been reported to have a sensitivity ranging from 86% to 100% and a specificity from 69 to 94% [2,6,14-16]. The method used for leucocytes labeling Leucocytes labelled with various radionuclides have been used for the detection of foot osteomyelitis. Several authors have recently reported that 99mTc-HMPAO-Leucocytes scan combined with a 99mTc-MDP bone scan is helpful in the detection of peripheral bone and joint infection [8] even in chronic osteomyelitis [4]. A very few studies have for negative scintigraphic studies in cases with a high clinical suspicion of infection. 99mTc-HMPAO WBC scanning has been shown to be an accurate technique for the diagnosis of osteomyelitis in the setting of violated bone, with a sensitivity of 100% and a specificity of more than 95% [14]. In a group of patients appearing quite similar to our population, with suspected osteomyelitis, Devillers et al. reported an overall sensitivity, specificity, and accuracy of 93%, 100%, and 96%, respectively, for 99mTc-HMPAO WBC scanning and 100%, 17%, and 53.3%, respectively, for 99mTc-MDP bone scanning [18]. Nasser S. Ballani et al. reported also, combined 99mTc-HMPAO/MDP imaging had proved to be useful in diagnosing osteomyelitis with specificity of 99mTc-MDP bone scanning improved from 30% to 78% on the addition of 99mTc-HMPAO WBC scanning [16]. Previous studies have reported that leucocyte imaging may prove useful for the detection of bone infection in the diabetic foot [3,6,7] . However the major limitation of leucocyte imaging is the poor spatial resolution when performed without bone scintigraphy since this procedure cannot reliably separate a bone from a soft-tissue infection [6-8]. In our study, the negative bone scintigraphy allowed to exclude osteomyelitis was confirmed by the clinical and radiological follow-up since the HMPAO-Leucocytes scintigraphy alone was of poor value for distinguishing between soft-tissue infection and osteomyelitis.

Discussion

This study confirms and demonstrates that the 99mTc-HMPAO Leucocytes scintigraphy combined with a 99mTc-MDP bone scintigraphy is effective in the diagnosis of osteomyelitis of the diabetic foot. Since the advent of infection-specific radiopharmaceuticals, the standard approach in cases of suspected osteomyelitis has been to perform plain radiography followed by 3-phase bone scintigraphy using such infection-specific radiopharmaceuticals to increase the specificity of bone scan findings in cases of violated bone. MRI and CT are reserved
focusing on the accuracy of the 99mTc-HMPAO-Leucocytes scintigraphy for the detection of pedal osteomyelitis in diabetic patients [10,11]. The performances of the combined HMPAO-Leucocytes/MDP scan (sensitivity: 92.5%, specificity: 96.5%, accuracy: 94.9%) reported in our study likely better than those with 111 Indium-Leucocytes scintigraphy combined with a bone scintigraphy. In our study, the only false-positive scan resulted from leucocytes accumulation in an ulcer dressing following minor trauma occurred between the leucocytes injection and the acquisition of the first images.

The two false-negative scans occurred in ulcers involving the extremity of the toes and the Tc-99m HMPAO-Leucocytes scintigraphy was negative. Histological and bacteriological examinations from a bone biopsy were positive for these two ulcers; and an antibiotic treatment was started.

The diagnosis of foot osteomyelitis is often difficult in patients with neuroarthropathy since many of the radiographic findings are similar because of the bone remodeling which results in increased 99mTc-MDP uptake on bone. In these patients a combined 111In-Leucocytes/99mTc-MDP scan has been reported to prove useful for the detection of osteomyelitis [2,9,13]. Seabold [12] has reported several false-positive images at sites of rapidly progressing neuroarthropathy without proven bone infection. The mechanism of this 111 In leucocytes uptake at noninfected acute fracture sites remains unclear. It could result from a late Indium marrow accumulation as well as the poor spatial resolution of Indium. In our study, among the three patients with severe neuroarthropathy (one metatarsal osteomyelitis proven by bone biopsy, one soft-tissue infection and one negative histological and bacteriological examinations), the exact concordance between 99mTc-MDP and 99mTc HMPAO accumulation in an ulcer dressing following minor trauma occurred between the leucocytes injection and the acquisition of the first images.

In conclusion the HMPAO-Leucocytes/MDP scan is a very sensitive and specific method to detect bone infection in the diabetic foot. After plain radiography, the 99mTc-MDP bone scintigraphy is the first step. If negative, osteomyelitis is unlikely. If positive, a 99mTc-HMPAO-Leucocytes scintigraphy should be performed in order to exclude or to confirm the diagnosis of bone infection.

References