The Value of Combined Radionuclide and Magnetic Resonance Imaging in the Diagnosis and Conservative Management of Minimal or Localized Osteomyelitis of the Foot in Diabetic Patients

Lydia Vesco, Hatem Boulahdour, Selim Hamissa, Sandrine Kretz, Jean-Luc Montazel, Leon Perlemuter, Michel Meignan, and Alain Rahmouni

Early diagnosis of osteomyelitis is helpful for a successful conservative treatment. The value of bone scanning combined with granulocytes labeled with hexamethylpropylene amine oxime (HMPAO) granulocyte-Tc99m (GN) radionuclide imaging (combined [RI]) with magnetic resonance imaging (MRI) for the diagnosis of osteomyelitis was assessed in 24 diabetic patients with foot ulcers. Evidence of osteomyelitis was based on the presence of at least one of the following criteria: (1) clinical bone involvement, (2) radiological bone involvement, (3) both positive combined RI and MRI, and (4) evidence of clinical bone involvement during the follow-up period. Thirteen patients had osteomyelitis. Seven patients had clinical bone involvement (sensitivity, 54%), five had radiological bone involvement (sensitivity, 38%), and 10 had positive combined RI for osteomyelitis (sensitivity, 77%). MRI demonstrated a higher sensitivity (100%). The specificity for combined RI and MRI was 82%. These results lead to a new diagnostic strategy for the early detection of minimal or localized osteomyelitis to avoid amputations. MRI is most appropriate following a negative x-ray in determining whether to treat osteomyelitis, since a negative MRI result rules out osteomyelitis. Antibiotic therapy should be used in the case of a positive MRI result, but Charcot joint disease can lead to false-positive MRI results. In this case, combined RI should be performed.
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OSTEOMYELITIS of the foot is a common complication of diabetes, occurring in 15% of patients.[1-4] The clinical diagnosis of osteomyelitis is based on palpation of exposed bone,[2] but this criterion is not always found and is unreliable for early diagnosis.[5] Plain radiography can detect osteomyelitis, showing localized areas of mottled osteolysis below a superficial ulcer. This osteolysis usually appears after several weeks.[6] Magnetic resonance imaging (MRI) signal changes in bone marrow have a high sensitivity and specificity for osteomyelitis, particularly when they are associated with soft tissue abnormalities.[7-16] Bone scintigraphy with Tc99m-methylene diphosphonate reflecting osteoblast activity is sensitive but lacks specificity.[17-19] Higher specificity has been reported for the Tc99m bone scan agent combined with labeled granulocytes that accumulate at the infection site through the processes of chemotaxis.[20-26]

Early diagnosis of osteomyelitis is the key to conservative treatment.[27] The goals of this prospective study were (1) to compare clinical and radiological findings with combined radionuclide imaging (combined RI) and MRI findings, (2) to compare the sensitivity and specificity of imaging modalities for the early detection of osteomyelitis, and (3) to assess the contribution of combined RI and MRI to the choice of conservative treatment in a series of 24 diabetic patients with foot ulcers.

SUBJECTS AND METHODS

Study Population

Twenty-four consecutive patients (17 men and seven women) with diabetes mellitus (16 type 1 and eight type 2) were admitted to our institution for treatment of a foot ulcer. For all patients, combined RI and MRI were performed with a 5-day delay after admission. The mean age was 59 years (range, 31 to 78), and the mean duration of diabetes was 18 years (range, 1 to 46). Five patients had Charcot's joint disease, defined as tarsal and metatarsal bone deformities. Two had acute-phase Charcot's foot. Wagner's classification was used to grade the ulcerations,[28] which were superficial in eight patients (grade 1), deep to the level of tendon with limited cellulitis in nine patients (grade 2), and deep to the level of tendon with abscess or bone involvement in seven patients (grade 3). Patients with grade 4 or 5 ulcerations (with local gangrene confined to the digits or forefoot lesions with gangrene of the entire foot) underwent immediate surgery and were thus excluded from this study. Plain radiographs of the feet were obtained in every case, and radiological abnormalities related to diabetic arthropathy and/or osteomyelitis were noted (Table 1).

RI

Two RI procedures were performed 2 days apart with hexamethylpropylene amine oxime (HMPAO) granulocyte-Tc99m (GN) and hydroxymethylene diphosphonate (HMDP)-Tc99m (HDP).

Protocol for leucocyte labeling with HMPAO-Tc99m. Blood samples (100 mL) were collected on citric acid dextrose A. Cell-rich plasma was obtained after sedimentation for 30 to 45 minutes at 37°C in the presence of 2.5 mL plasmagel. After centrifugation at 200× *g* for 10 minutes, granulocytes were isolated on the Ficoll gradient (Pharmacia, Uppsala, Sweden). The autologous granulocytes were labeled with 555 MBq HMPAO-Tc99m (Ceretec; Amersham, Bucks, UK). The duration of incubation was 15 minutes at ambient temperature. The labeled cells were washed and resuspended in cell-poor plasma. Reinjection was performed intravenously 2.5 hours after the initial sample. The mean reinjection dose was 450 MBq. The labeling efficiency was 78% ± 9%. Cell viability was based on the trypan blue test (>95%). On the first day, 450 MBq (12 mCi) GN was injected intravenously, and images were acquired 4 and 24 hours later. On the third day, 555 MBq (15 mCi) HDP was injected intravenously and the feet were placed in the same position for the two radionuclide examinations. The images were acquired 6 hours after the injection using a Helix camera (Elscint, Israel) with a high-resolution collimator for HDP and a high-sensitivity collimator for GN, with a matrix of 256 × 256 pixels. For GN, anterior, posterior, plantar, and lateral views of the feet were obtained with a preset time of 20 minutes. The duration of each examination at 4 and 24 hours was 60 minutes. For HDP, 2-second images were acquired at 2

From the Service d'Endocrinologie, and Service de Médecine Nucléaire et Service d'Imagerie Médicale, Hôpital Henri Mondor, Créteil, France.

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Address reprint requests to Lydia Vesco, MD, 51 Ave du Marechal de Lattre de Tassigny, Hôpital Henri Mondor, 94000 Créteil, France.

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Table 1. Patient Characteristics

Patient No.	Sex/ Age (yr)	Location of the Ulcer/Phase	Wagner's Grade	Arthropathy on X-Ray	HDP
1	M/70	Metatarsal head	3	+	+
2	M/71	First toe	3	−	+
3	M/50	Metatarsal head	3	−	+
4	M/62	Metatarsal head	3	−	+
5	M/53	Calcaneus	3	+	+
6	F/59	Calcaneus	3	Charcot's foot	+
7	M/69	Fourth toe	1	+	+
8	M/68	First toe	2	+	+
9	M/64	First toe	2	+	+
10	M/60	Metatarsal head	1	+	+
11	M/66	Metatarsal head	1	+	+
12	F/55	Acute phase	2	Charcot's foot	+
13	F/71	Metatarsal head	1	+	+
14	F/57	Calcaneus	1	Charcot's foot	+
15	M/41	First toe	1	+	+
16	M/53	Second toe	2	+	+
17	M/64	First toe	1	+	+
18	F/64	Acute phase	1	Charcot's foot	+
19	M/51	Tibial stump	2	−	+
20	M/59	First toe	2	−	+
21	M/31	First toe	2	+	+
22	F/61	Ankle	3	−	+
23	F/69	Metatarsal head	2	Charcot's foot	+
24	M/61	Second toe	2	−	+

Abbreviations: arthropathy: +, presence of lesions; −, absence of lesions; HDP: +, presence of hyperactivity.

minutes after injection on an anterior view during the vascular phase. Six hours after injection, 1,000-kilo-count anterior, posterior, plantar, and lateral views of the feet were acquired. RI positivity for osteomyelitis was based on the presence of a hot spot of radioactivity in the same area with the GN and HDP methods. GN was considered negative when there was no granulocyte accumulation or when granulocytes accumulated in an area unrelated to the area of HDP uptake.

MRI

All patients were studied with a 1.5-T magnet (Siemens Medical System, Erlangen, Germany). Patients were positioned comfortably supine with both feet in the head coil. Oblique coronal images perpendicular to the metatarsal long axis or midfoot were chosen from sagittal images. In each study, at least two orthogonal planes were acquired. The field of view was 200 mm, matrix 160 × 256, and thickness 3 to 5 mm. The following images were always acquired: a T1-weighted spin echo (SE) image (repetition time [TR], 400 to 500 ms; time of echo [TE], 15 ms; two acquisitions) and a fat-suppressed T2-weighted SE image (TR, 2,000 to 2,500 ms; TE, 45 and 90 ms; two acquisitions). Fat-suppressed T1-weighted SE images were acquired before and after intravenous administration of gadolinium tetraazacyclododecane tetraacetic acid ([Gd-DOTA] Laboratoire Guerbet, Aulnay-sous-Bois, France) at a dose of 0.1 mmol/kg. MRIs were analyzed by two radiologists (A.R. and J.L.M.). Criteria for the diagnosis of osteomyelitis were based on criteria determined in previous studies,[8-10,13,16] ie, focally decreased marrow signal intensity on T1-weighted images corresponding to an increased signal intensity on T2-weighted images, with marrow enhancement on postcontrast T1-weighted images and an adjacent inflammatory soft tissue mass or ulcer or a sinus tract. The extension of the marrow signal abnormality was assessed.

Diagnostic Criteria for Osteomyelitis

Osteomyelitis was diagnosed on the basis of at least one of the following criteria: (1) clinical bone involvement, ie, the ability to reach bone by advancing a probe through the ulcer, (2) radiological bone involvement, ie, mottled osteolysis in front of the ulcer, (3) both positive combined RI and MRI, and (4) clinical evidence of bone involvement during follow-up evaluation.

Treatment and Follow-up Evaluation

Treatment of osteomyelitis included daily wound cleansing, debridement, and antibiotic therapy for 10 weeks. In patients without osteomyelitis, treatment involved deep wound debridement and daily dressing only. Clinical examination was performed every week for 3 months after the initial admission to assess local outcome. Two patients had combined RI and MRI 3 months after the initial diagnosis.

RESULTS

Clinical outcomes are presented in Table 2. Thirteen patients had osteomyelitis (Figs 1 to 3). Clinical bone involvement was found in seven patients, radiological bone involvement in five, both positive combined RI and MRI in 10, and clinical evidence of bone involvement during follow-up evaluation in three (no. 1, 8, and 9).

Six of seven patients with clinical osteomyelitis had positive combined RI and MRI findings, while the other patient (no. 1) had a negative combined RI and a positive MRI. Among 11 patients who did not have osteomyelitis, combined RI was positive in two (no. 17 and 20) and MRI was positive in two (no. 18 and 23).

The diagnostic criteria sensitivity was as follows: clinical

Table 2. Clinical and Imaging Evaluation and Clinical Outcome

Patient No.	Clinical Osteomyelitis	Radiological Osteomyelitis	Combined RI	MRI	Clinical Follow-up Evaluation	Final Diagnosis
1	+	+	−	+	B*	Osteomyelitis
2	+	+	+	+	G*	Osteomyelitis
3	+	+	+	+	G*	Osteomyelitis
4	+	+	+	+	G*	Osteomyelitis
5	+	−	+	+	G*	Osteomyelitis
6	+	+	+	+	G*	Osteomyelitis
7	−	−	+	+	G*	Osteomyelitis
8	−	−	−	+	B	Osteomyelitis
9	−	−	−	+	B	Osteomyelitis
10	−	−	+	+	G*	Osteomyelitis
11	−	−	−	−	G	—
12	−	−	−	−	G	—
13	−	−	−	−	G	—
14	−	−	−	−	G	—
15	−	−	−	−	G	—
16	−	−	−	−	G	—
17	−	−	+	−	G	—
18	−	−	−	+	G	—
19	−	−	+	+	G*	Osteomyelitis
20	−	−	+	−	G	—
21	−	−	−	−	G	—
22	+	−	+	+	G*	Osteomyelitis
23	−	−	−	+	G	—
24	−	−	+	+	G*	Osteomyelitis

Abbreviations: +, presence of osteomyelitis; −, absence of osteomyelitis; G, good results; B, bad results.

*Antibiotic therapy prescribed.

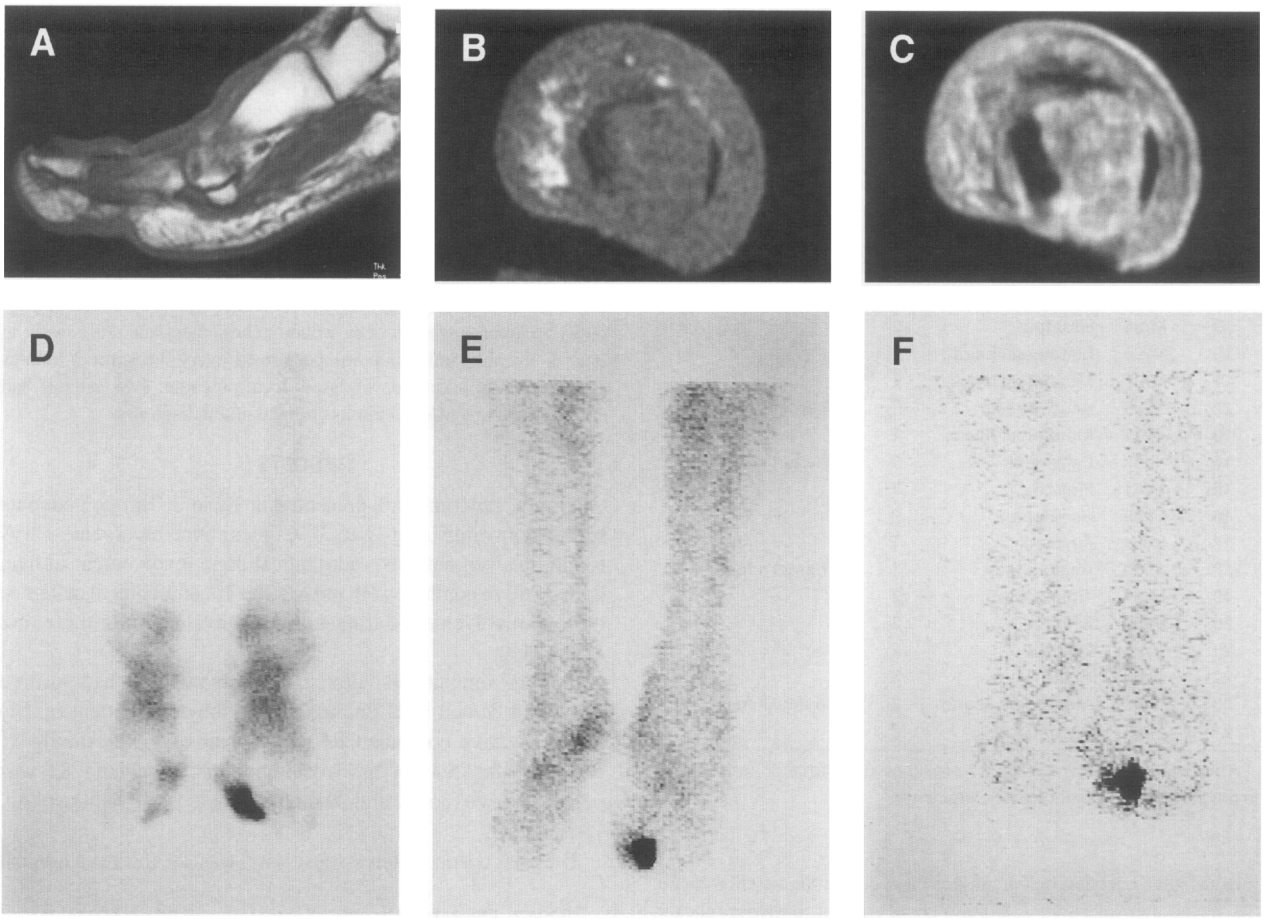

Fig 1. Patient no. 2, a 71-year-old man with a diabetic foot ulcer of the first toe (Wagner 3). (A) Sagittal T1-weighted MRI shows the soft tissue ulcer with decreased enhanced signal of the bone marrow of P1. Axial T1 fat-suppressed images before (B) and after injection of Gd-DOTA (C) show low signal intensity of bone marrow enhancement after injection with cortical interruption and disruption of the cutaneous signal (ulcer). (D) HMDP scan showing increased uptake of the first and second toe. GN scan at 4 hours (E) and 24 hours (F) shows increased uptake in the same area.

bone involvement, 54%; radiological bone involvement, 38%; and positive combined RI and MRI, 85%. The sensitivity was 77% for combined RI and 100% for MRI (Fig 2), and the specificity was 82% for combined RI and 82% for MRI.

The bone marrow signal abnormality corresponding to osteomyelitis involved the whole calcaneum in two patients and a limited part of one bone segment in 11 patients (metatarsus in five, phalanx in three, calcaneus in one, tibial stump in one, and tibial malleolus in one).

After 10 weeks of treatment as previously described, all patients but one (no. 1) were cured of disease (Table 3). An amputation of the first metatarsal bone related to bacteriological resistance was performed in this patient.

In two patients (no. 8 and 9), the diagnosis of osteomyelitis was made at clinical evaluation 3 weeks after combined RI and MRI. Combined RI and MRI were performed 3 months after the initial diagnosis of osteomyelitis in two cases (no. 6 and 24). Clinical outcome at 3 months was good. RI was negative in cases 6 and 24. MRI was negative in case 24 but positive in case 6 (Fig 3). Clinical outcome at 6 months was good.

DISCUSSION

No false-negative MRI results for the diagnosis of osteomyelitis were observed in this study. Other investigators have reported similar results, but most of their patients had large areas of osteomyelitis involving several bones and requiring surgery, whereas a majority of our patients had focal osteomyelitis.[9,15,29] The sensitivity was higher for MRI versus combined RI (77%) and equal to that for HDP alone (100%). One false-negative result for combined RI (no. 1) may have been due to a decrease in the local blood supply owing to severe arteriopathy, hampering granulocyte accumulation in the infected tissue. The two false-positive radionuclide scans (no. 17 and 20) may have been due to the difficulty in acquiring the same area of the foot in the two scans. This inconvenience has been previously reported.[25] The positive results on GN may have been due to soft tissue infection associated with chronic arthropathy, leading to a positive HDP result.

Two false-positive MRI examinations (no. 18 and 23) were observed. Both patients had Charcot's joint disease with severe soft tissue edema of the foot. Focal dislocations were found on

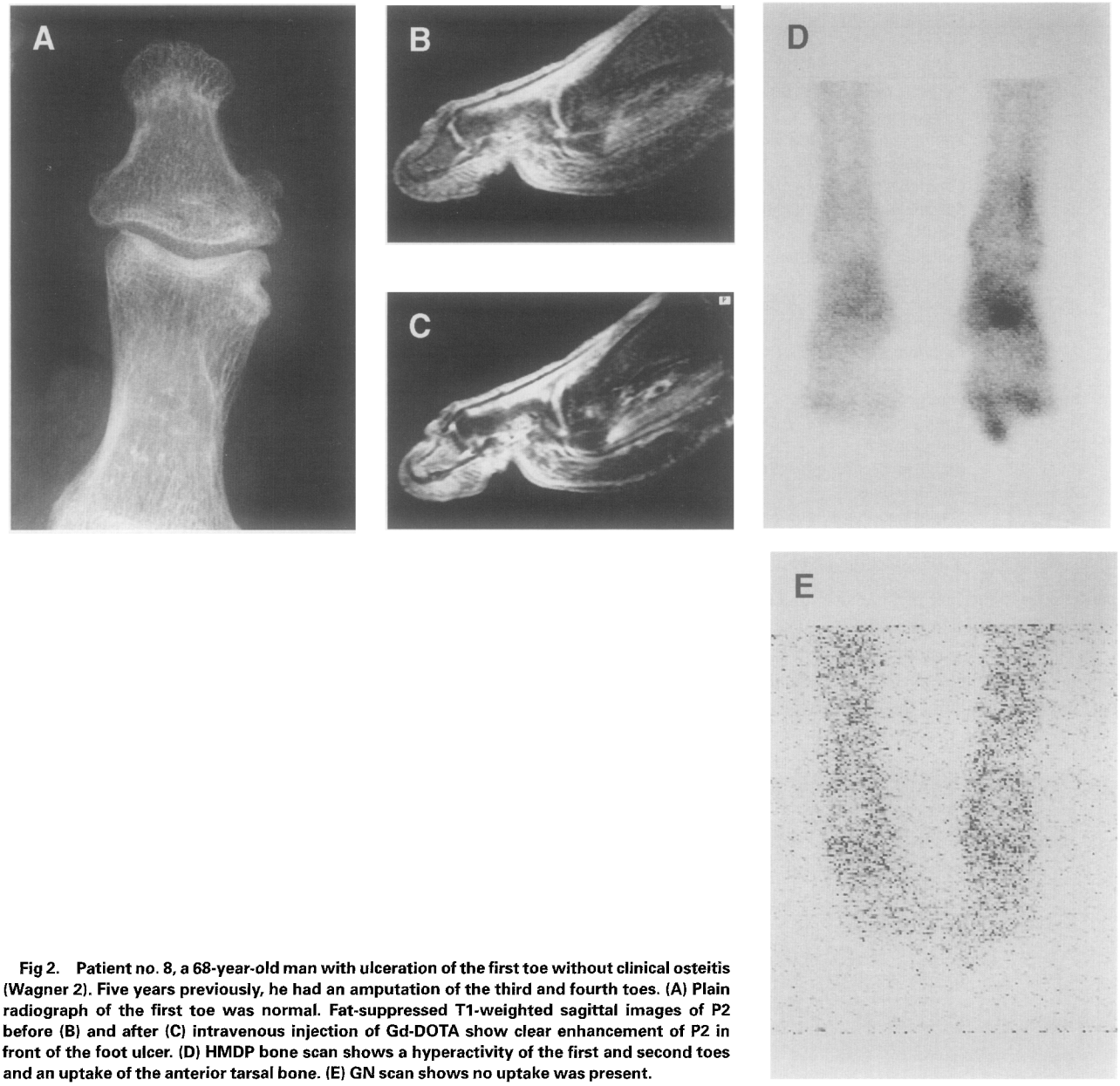

Fig 2. Patient no. 8, a 68-year-old man with ulceration of the first toe without clinical osteitis (Wagner 2). Five years previously, he had an amputation of the third and fourth toes. (A) Plain radiograph of the first toe was normal. Fat-suppressed T1-weighted sagittal images of P2 before (B) and after (C) intravenous injection of Gd-DOTA show clear enhancement of P2 in front of the foot ulcer. (D) HMDP bone scan shows a hyperactivity of the first and second toes and an uptake of the anterior tarsal bone. (E) GN scan shows no uptake was present.

x-ray examination. The limitations of MRI in the diagnosis of osteomyelitis in patients with neuropathic osteoarthropathy have been reported elsewhere.[12-16] Two main MRI patterns of neuropathic osteoarthropathy have been reported[14]: (1) chronic disease easily diagnosed by MRI, with fragmentation and dislocation of the bones, osteosclerosis, and cyst-like lesions; edema within the bone and subcutaneous fat with joint effusion can also be observed, but are located some distance from the ulcer; and (2) recent-onset rapidly progressing neuropathic osteoarthropathy with signal-intensity changes identical to those observed in osteomyelitis, ie, inflammation of the bone marrow and adjacent soft tissue. Location in the midfoot, polyarticular impairment, absence of localized cortical interruption, and soft tissue infection some distance from the bone changes favor a diagnosis of acutely progressive neuropathic osteoarthropathy.

Physical examination and plain x-ray examination have low sensitivity even when combined (54%), confirming the need for combined RI and MRI for the early diagnosis of osteomyelitis. None of the patients had positive plain x-ray results without clinical signs of osteomyelitis. Furthermore, two patients had negative plain x-ray findings despite clinical osteomyelitis. The value of plain radiography is thus limited unless the examination is repeated several weeks later, during which time osteomyelitis can progress considerably. Follow-up imaging was performed in two patients (no. 6 and 24). The good clinical outcome in patients no. 6 and 24 was associated with combined RI negativity. In one of these patients (no. 6), an abnormal bone marrow signal was still present 3 months later on MRI (Fig 3). This could be explained by persistent bone marrow edema despite successful treatment. Combined RI may thus be preferred to MRI for monitoring the response to treatment,

Table 3. Treatment Characteristics of the Patients

Patient No.	Wagner's Grade	Bacteriology	Intravenous Antibiotic Therapy	Oral Antibiotic Therapy	Surgery
1	3	Penicillin resistance *Staphylococcus, Pseudomonas*	Vancomycin, fucidic acid, ciprofloxacin	Pyostacin, rifampicin	+
2	3	*Staphylococcus aureus, Enterococcus faecalis, Morganella*	Amoxicillin/clavulanic acid, ciprofloxacin	Ciprofloxacin	–
3	3	*Corynebacter, Escherichia coli*	Ciprofloxacin, pyostacin, fucidic acid	Pyostacin, fucidic acid	–
4	3	*Serratia marcescens, Enterococcus faecalis*	Ofloxacin	Ofloxacin	–
5	3	Penicillin resistance *Staphylococcus, Pseudomonas*	Amoxicillin/clavulanic acid, ciprofloxacin	Amoxicillin/clavulanic acid, ciprofloxacin	–
6	3	*Pseudomonas, Proteus, Escherichia coli, Streptococcus*	Amoxicillin/clavulanic acid, nitromycin	Amoxicillin/clavulanic acid	–
7	1	*Pseudomonas*	Amoxicillin/clavulanic acid, ciprofloxacin	Ciprofloxacin	–
8	2	*Enterococcus*	Amoxicillin/clavulanic acid	Amoxicillin/clavulanic acid	–
9	2	*Staphylococcus aureus, Streptococcus*	Amoxicillin/clavulanic acid	Amoxicillin/clavulanic acid	–
10	1	*Enterobacter*	Amoxicillin/clavulanic acid	Amoxicillin/clavulanic acid	–
19	2	*Staphylococcus aureus, Streptococcus*	Pyostacin, ofloxacin	Pyostacin, ofloxacin	–
22	3	*Pseudomonas*	Ciprofloxacin	Ciprofloxacin	–
24	2	*Staphylococcus aureus, Enterococcus*	Amoxicillin	Amoxicillin	–

particularly in the case of Charcot's joint disease, but this needs to be confirmed in a larger study.

In conclusion, this study confirms that combined RI and MRI are valuable techniques for the early diagnosis of localized osteomyelitis; antibiotic treatment can be started rapidly, thereby avoiding the need for amputation. In our opinion, MRI should be the first imaging modality, as osteomyelitis can be ruled out if MRI is negative. In patients with suspected osteomyelitis and chronic neuropathic osteoarthropathy, combined RI and MRI both should be used and the results carefully compared.

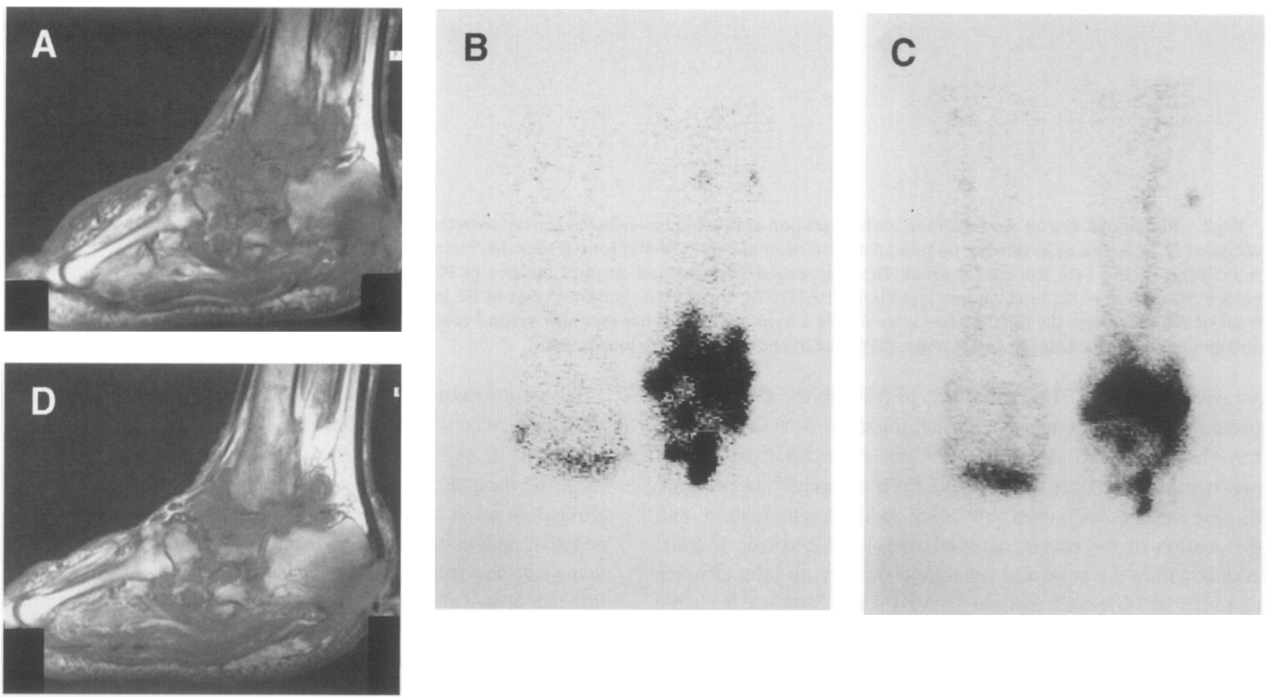

Fig 3. Follow-up evaluation of patient no. 6, a 59-year-old woman with Charcot's joint disease with foot ulcer (Wagner 3). Before treatment, (a) sagittal T1-weighted MRI shows thickening of soft tissue of the talus with a large low–signal-intensity area within the posterior part of the calcaneus and the tibia. Marked tibiotarsal arthropathy is also present with widening of the joint corresponding to fluid effusion. Combined RI including HDP (b) and GN (c) shows marked increased uptake of the foot. Three months after antibiotic therapy, (d) sagittal T1-weighted image shows that low–signal-intensity area within the calcaneus and tibia decreased in size. Tibiotarsal arthropathy was unchanged. GN scan was negative without uptake.

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