Comparison of Technetium-99m-MDP, Technetium-99m-WBC and Technetium-99m-HIG in Musculoskeletal Inflammation

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This study compared three radionuclide techniques in distinguishing musculoskeletal infection from noninfectious inflammation. **Methods:** Thirty-five orthopedic patients with suspected musculoskeletal infection were examined using three radionuclide techniques in sequence: triphasic bone scintigraphy, ^{99m}Tc radioleukocytes (^{99m}Tc-WBC) scintigraphy and ^{99m}Tc human immunoglobulin (^{99m}Tc-Hig) scintigraphy. Two "early" and "late" acquisitions were performed, at 4–6 hr and 20–24 hr postinjection, respectively. Patients who were diagnosed as suffering from noninflammatory lesions became the controls. We calcu"late"d for all studies one index of inflammation (Infl) as the ratio between counts in the uptake area and counts in an equal area of normal tissue. **Results:** The "early" radiolabeled leukocytes and "late" Hig scintigraphy allowed the greatest ability to distinguish between infections and noninfectious inflammations ($p < 0.011$and $p < 0.016$) with a sensitivity of 96.6% and 96.5% and specificity of 71% and 100%, respectively. Hig and radioleukocytes allowed distinguishing infections from noninflammatory diseases at both examinations. **Conclusion:** The "early" radioleukocyte scintigraphy allowed us to separate infections from noninfectious inflammations. In contrast, the same result can be obtained only with the "late" scan in the Hig study, but Hig mapped the spread of the inflammation into soft tissues better. Hig might be an alternative to radioleukocytes because of its simple preparation, similar accuracy and safety.

Key Words: inflammation; orthopedic disease; triphasic bone scan; leukocyte scan; immunoscintigraphy

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Despite severe sterilizing procedures and routine preventive antibiotic treatment, musculoskeletal infections are still the most worrisome complications in orthopedic surgery. Detecting a muscle and/or bone infection may be difficult and creates diagnostic and therapeutic problems particularly when other pathologies, such as the sclerosing effects of osteomyelitis, latent chronic osteitis, prosthetic loosenings, arthritis and vascular diseases (i.e., diabetic vasculitis) coexist. In these cases, the orthopedist must make a therapeutic decision according to the presence or absence of an infective process. A correct therapeutic approach is possible only if the diagnosis of infection is rapid and accurate.

Clinical examination, laboratory assays, planar radiological studies (very sensitive in the acute phase of disease) lose accuracy in the chronic stages, especially in complicated cases. CT and MRI give information about the extent of the lesions and can detect very small foci of infection, but they have relatively low specificity. In addition, MRI cannot be used with metallic implants and prosthesis, and CT images are often impaired by artifacts (*1*).

Radionuclide methods are being used more and more in diagnosing skeletal and soft tissue infections, as well as for evaluating the intensity and diffusion of the process itself (*2*). These methods consist of three phases of bone scintigraphy and scans by tracers of inflammations such as colloids, leukocytes, antigranulocytes antibodies (AbAG) and human immunoglobulin (Hig), usually performed in sequential mode.

Leukocytes labeled with ^{111}In and ^{99m}Tc have diagnostic superiority, but they also have the disadvantage of low availability, high cost and, in the case of ^{111}In, relatively high dosimetry. In addition, they may give false-positive results due to physiologic marrow uptake and false negatives in the case of chronic osteomyelitis or osteonecrosis (*3*).

Hig, first labeled with ^{111}In and recently with ^{99m}Tc, has been developed and used in the last few years (*4,5*). Its advantages and limitations are still a matter of research and discussion. There is a lack of research comparing Hig with the radioleukocytes in a homogeneous group of orthopedic patients. There are scientific papers only dealing with heterogeneous inflammatory pathologies (*6*).

We undertook our prospective study to compare the accuracy of ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP), ^{99m}Tc leukocytes (^{99m}Tc-WBC) and ^{99m}Tc human immunoglobulin (^{99m}Tc-Hig) in distinguishing musculoskeletal infections from noninfectious inflammations.

MATERIALS AND METHODS

Thirty-five orthopedic patients, who were presumed to have infections of the musculoskeletal system after clinical examination of the involved musculoskeletal region, were selected for the study. Clinical criteria for enrollment were the presence of at least two of the following signs: drainage, edema, erythema, warmth, induration, tenderness and painful motion. Most of the patients showed signs of previous trauma or surgery. The patients' clinical and scintigraphic data are summarized in Table 1.

After informed written consent of each patient, we performed three radionuclide examinations with different radiopharmaceuticals on the following chronological schedule: (a) ^{99m}Tc-MDP three-phase scan, (b) ^{99m}Tc-Hig scintigraphy and (c) ^{99m}Tc-WBC scintigraphy. Patients in whom orthopedists had already identified lesions by MRI, CT scan or planar radiography did not have MDP scintigraphy performed. All examinations were performed after clinical diagnosis within six days, at suitable intervals to avoid radioactive overlapping between them. All examinations were acquired on a large field-of-view digital gamma camera equipped with a low-energy, high-resolution collimator. The three-phase bone scan was executed centering the gamma camera head above the area of interest indicated by the orthopedic surgeon and, if possible, above the contra"late"ral site for a visual and semiquantitative comparison. We administered a dose of 666–740 MBq ^{99m}Tc-MDP as a bolus and registered 5-sec frames for 120 sec with

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TABLE 1
Clinical Cases and Results of Visual and Computerized Analysis

Age (yr)	Sex	Group	Final clinical diagnosis	Visual analysis Hig-score	Visual analysis leukocytes-score	Hig Inflammation-index Early	Late	Leukocytes inflammation index Early	Late	MDP-Infl
32	M	S	Osteomyelitis right tibia	++ TP	++ TP	1.65	1.66	1.74	1.58	
73	F	N	Hyperplastic marrow left femur in myelofibrosis	− TN	++ FP	0.98	1.01	1.4	1.2	1.02
48	M	S	Infection right hip	++ TP	−+ TP	2.88	3.58	0.98	—	
41	M	S	Osteomyelitis right femoral head	++ TP	++ TP	1.62	2.44	1.55	—	4.5
15	M	S	Tubercolous spondylitis D5-D6	− FN	+ TP	1.13		1.50		1.74
19	M	S	Osteomyelitis right tibia	++ TP	++ TP	2.8	4.5	3	4.8	17.7
79	F	S	Infected loosening right hip	++ TP	++ TP	1.06	—	0.95	—	1.9
61	F	S	Infected loosening left hip	−+ TP	−+ TP	1.64	1.4	1.4	—	1.12
80	F	I	Inflammation right thigh	++ TP	++ TP	1.92	1.95	2.17	2.4	2.16
83	F	I	Arthritis left hip	++ TP	++ TP	1.18	1.12	1.40	1.33	0.91
67	F	S	Osteomyelitis right hip (p)	++ TP	++ TP	1.72	1.89	2.23	—	2.99
18	M	S	Osteomyelitis right tibia	++ TP	++ TP	1.49	2	2.02	—	1
31	M	S	Infected left femoral fracture	++ TP	++ TP	2.32	—	2.34	—	4.6
82	F	S	Chronic osteomyelitis left hip	++ TP	++ TP	1.46	1.62	3	—	
78	M	S	Chronic osteomyelitis right hip (p)	++ TP	+ TP	1.50	—	1.30	—	
39	M	N	L4-L5 posterior arthrodesis	− TN	− TN	0.9	0.78	0.84	—	1.29
56	M	S	Infected right femoral fracture	++ TP	++ TP	1.2	1.4	1.41	1.64	2.83
50	M	I	Right perifemoral inflammation (f)	++ TP	++ TP	1.88	2.3	1.72	1.50	
19	M	I	Inflammation left femoral fracture	−+ TP	−+ TP	1.61	1.50	2.03	2.04	
54	M	I	Inflammation right femoral fracture	−+ TP	−+ TP	1.64	1.60	1	1.38	2.7
49	M	S	Osteomyelitis right femor	++ TP	++ TP	2.05	2.27	2.86	4.90	
73	F	S	Osteomyelitis right tibia	++ TP	++ TP	2.05	2.35	2.66	3.05	2.78
74	M	I	Inflammation right neck femoral fracture	−+ TP	−+ TP	1.28	1.31	1.11	1.16	
48	M	I	Inflammation right tibia fracture	++ TP	−+ FN	2.20	1.60	0.97	1.01	
68	M	S	Infected right tibia fracture	++ TP	++ TP	2.30	1.13	1.12	1.30	2.63
84	M	N	Loosening prosthesis right hip	− TN	− TN	0.82	0.81	0.90	0.88	
63	M	I	Inflammation right coxitis	++ TP	++ TP	1.63	2	1.52	1.65	
52	M	S	Infected left trochanteric femoral segment	++ TP	++ TP	1.95	1.77	1.39	1.31	
54	M	I	Traumatic right femoral necrosis	++ TP	++ TP	1.60	1.66	1.18	1.12	
73	F	N	Osteoporotic spine fracture	− TN	− TN	—	—	0.98	—	
86	F	N	Left femoral neck fracture	− TN	− TN	—	—	1.17	1.02	
48	M	N	Neurodysthrophy left hip	− TN	−+ FP	—	—	1.12	1.14	
32	M	I	Osteitis left tibia in fracture	++ TP	++ TP	1.65	1.66	1.74	1.58	
73	M	S	Infected prosthesis right knee	++ TP	++ TP	2.05	2.35	2.66	3.05	2.78
59	M	N	Reticoloisthiocitoma T8	− TN	− TN	1.14	1.00	0.82	0.78	1.20

S = infection; I = noninfectious inflammation; N = noninflammatory disease; p = prosthesis; f = fracture.

matrix of 64 × 64 and six blood pool 20-sec frames starting from the fifth minute with the patient in a fixed position. Three hours later static multiple views of the same body segment were collected in a 256 × 256 matrix with the high-resolution collimator.

For scintigraphy with ^{99m}Tc-Hig, 610 ± 112 MBq was slowly injected intravenously acquiring scans at 4–6 hr and 20–24 hr postinjection in a matrix 256 × 256 with the high-resolution collimator. There were no adverse reactions.

Scintigraphic study with the leukocytes, labeled according to the method of Peters et al. partially modified, was performed 2–6 hr ("early" scan) and 20–24 hr ("late" scan) after the injection of 487 ± 127 MBq of the tracer. Table 2 gives full details of the leukocyte labeling procedures with an average yield of 46.5% ± 11.5% s.d.

TABLE 2
Steps of Radioleukocyte Labeling Procedure

- Withdrawing 100 ml blood in ACD (6:1)
- GR sedimentation by Plasmasteril (10:1) within 45 min
- Centrifugation 150 × g and leukocytes separation
- Preparation of ^{99m}Tc-HMPAO 1.11–1.29 GBq/3cc
- Radiochromatography of ^{99m}Tc-HMPAO: yield > 85%
- Selective labeling and washing of leukocytes by an autologous cell-free serum: mean yield of labeling 46.5% ± 11.5%

The scans were visually interpreted by three independent observers and scored for activity on a four-point scale: − = negative, ± = faint uptake, + = moderate uptake, ++ = marked uptake. A semiquantitative analysis was performed for all the radiotracers by dividing the average counts per pixel in an area of interest circumscribing the musculoskeletal foci of accumulation, by the average counts per pixel in an equal size area drawing in an unaffected symmetrical site or in a site of same-tissue composition assessed as uninjured, on both the "early" and "late" scan (Fig. 1). The numerical value obtained was named the inflammation index (Infl). The scintigraphic results were compared with the confirming final diagnosis, as determined by surgery, biopsy, drainage and culture, to evaluate the accuracy of any single radionuclide method.

For each tracer, analysis of variance (ANOVA) was used to assess the Infl differences between the three groups of pathology: infections, noninfectious inflammations and noninflammatory diseases. Graphic intergroup comparison was made using 95% confidence intervals. Pearson's correlation coefficient was used to examine the relationship between the tracers. Statistical significance was assumed when the probability value p was less than 0.05.

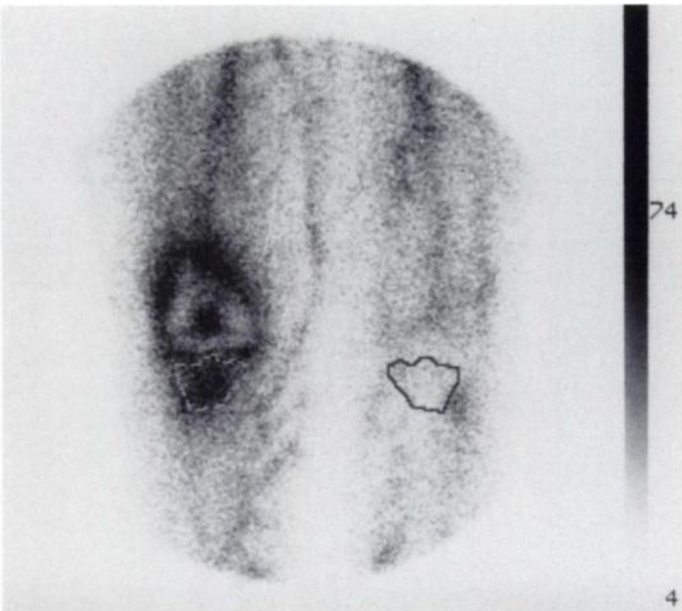

FIGURE 1. This image illustrates the analysis method used to calcu"late" the inflammation index (Infl). Two ROIs of equal size are selected, one on the area of the anomalous uptake and one on a contralateral area supposed normal. The inflammation index is expressed as the ratio between the mean counts per pixel of the pathologic and the normal areas.

RESULTS

The final diagnoses were 18 patients with infections, 10 with noninfectious inflammations and seven with noninflammatory diseases. The grades of sensitivity, specificity and accuracy of the radiotracers used are reported in Table 3.

One case of chronic tubercolous spondylitis was not revealed by Hig (Fig. 2), and one of noninfectious inflammation around a right tibia fracture was not detected by the radiolabeled leukocytes (false-negatives). Radiolabeled leukocytes were false-positive in one case of neurodysthrophy and in one of hyperplastic marrow isle in a left femoral diaphysis, not far from the area of sterile arthritis in the knee, in a patient with myelofibrosis (Fig. 3).

Statistical evaluation of the results by ANOVA (Fig. 4) has highlighted that:

1. The "early" leukocytes study can differentiate between infections and noninfectious inflammations ($p = 0{,}011$), whereas the "early" Hig study cannot; the same ability was observed even for "late" Hig and "late" radioleukocytes studies: p values were 0.016 for "late" Hig and 0.021 for "late" radioleukocytes studies, respectively.
2. Infls distinguished the infections from the noninflammatory diseases at both times of examination with Hig and radioleukocytes.
3. The "early" Hig study can differentiate between inflammatory processes (infections and noninfectious inflammations) and noninflammatory diseases ($p = 0{,}001$), whereas "early" radioleukocytes cannot.

TABLE 3
Scintigraphic Results and Descriptive Statistics

	^{99m}Tc-MDP	^{99m}Tc-Hig	^{99m}Tc-Leukocytes
Sensitivity (%)	93.7	96.5	96.6
Specificity (%)	66.0	100.0	71.0
Accuracy (%)	89.0	97.2	91.8
Positive predictive value (%)	93.7	100.0	93.0
Negative predictive value (%)	66.0	87.5	83.3

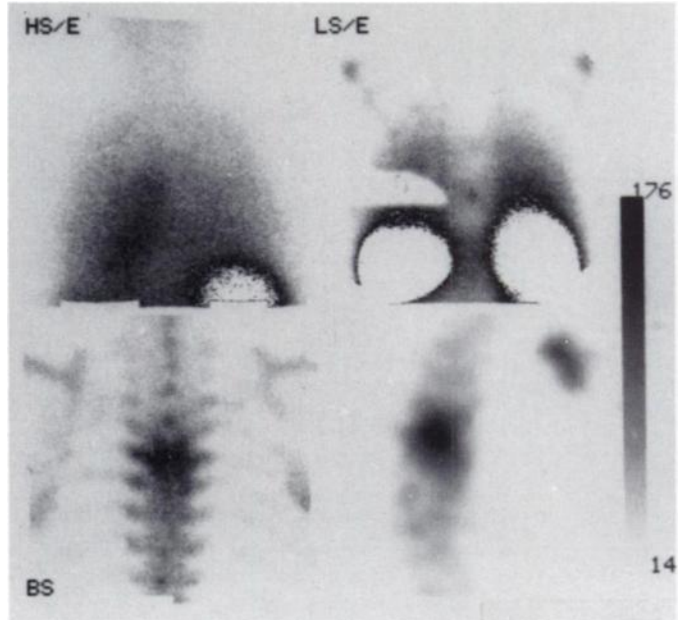

FIGURE 2. These are the scans performed in a 15-yr-old patient suspected of having metastases of malignant germinoma on T5 and T6 vertebral bodies. The radiolabeled leukocytes, at the top right, were positive for inflammation process, whereas Hig, top left, was not. The final microbiological diagnosis concerning the lesion was of tubercolar spondylodiscitis T5 T6. At the bottom right there is a sagittal slice of the dorsal spine of a bone tomoscintigraphy. HS/E = "early" Hig scintigraphy; LS/E = "early" leukocyte scintigraphy; BS = bone scintigraphy.

4. Infl did not differ between the "early" and "late" studies with both radioleukocytes and Hig, in the patients affected by noninfectious inflammation and noninflammatory diseases.

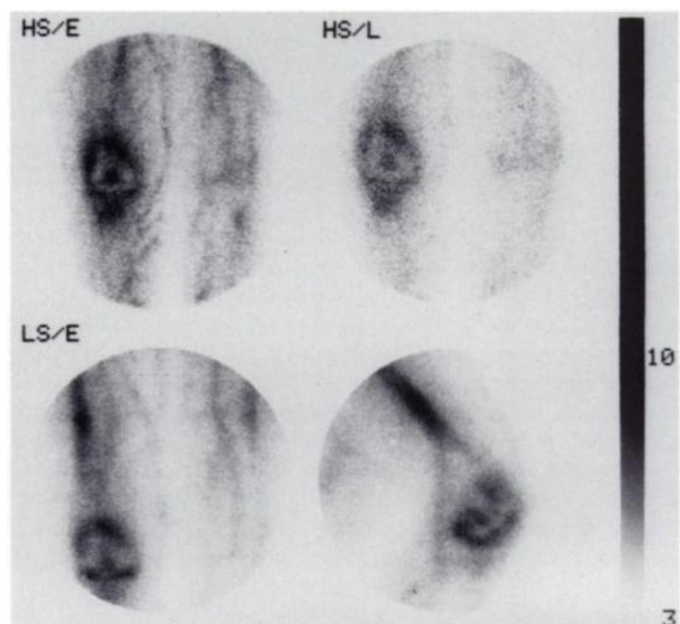

FIGURE 3. Scintigraphy of a 73-yr-old woman with suppurative arthritis of the right knee in total arthroprosthesis by *Staphilococcus aureus*. An intense uptake of radiolabeled leukocytes in the periprosthetic bony tissues and in the soft articular and periarticular tissues was detected. The focal radioleukocyte concentration in the femoral diaphysis was a false-positive finding due to hyperplastic bone marrow (myeloid metaplasia in myelofibrosis). The patient had an inflammation of the distal femoral epiphysis and a concomitant infection of the proximal tibial epiphysis. HS/E = "early" Hig scintigraphy; HS/L = "late" Hig scintigraphy; LS/E = "early" leukocyte scintigraphy; anterior view on the left and "late"ral view on the right.

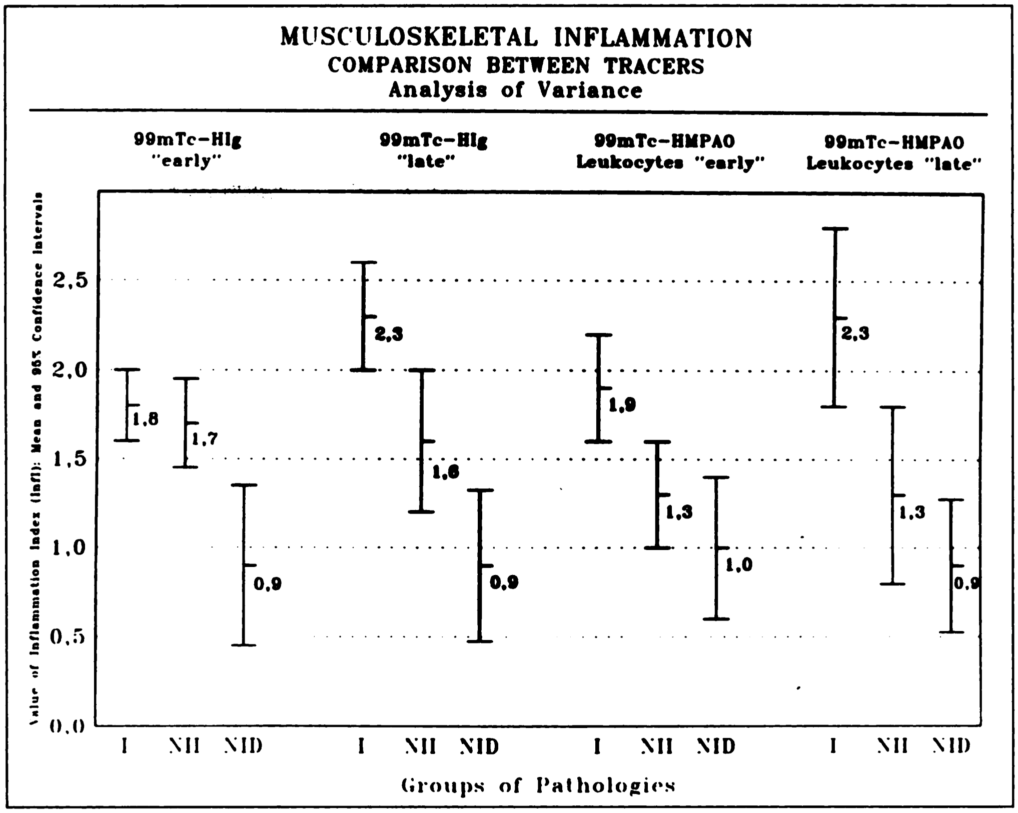

FIGURE 4. The graph illustrates the index of inflammation expressed as a mean value and 95% intervals of confidence of all groups of pathologies obtained in the "early" and "late" scintigraphic studies with Hig and leukocytes. I = infections; NII = noninfectious inflammations; NID = noninflammatory diseases.

5. Both "early" and "late" radioleukocytes Infl and "late" Hig were comparable in detecting the grade of infection ($p = 0.001$).
6. MDP Infl did not correlate with Hig and radioleukocytes.

Different scintigraphic findings between Hig and leukocytes uptake in the lesion were observed: the point of the leukocytes uptake was well marked, whereas in the Hig scan it generally had faint limits and it was more extended, particularly when a cellulitis was present (Figs. 5 and 6).

DISCUSSION

An ideal radiopharmaceutical agent for detecting infection or noninfectious inflammation, able to grade the activity of inflammatory lesions in nuclear medicine has not been found despite the many radionuclide imaging techniques which have been advocated and justified over the years, such as ^{67}Ga (*7*), nanocolloids (*8*), ^{111}In leukocytes (*9*), ^{99m}Tc-HMPAO leukocytes (*10*) and Ab antigranulocytes labeled with ^{123}I (*11*) and, recently, with radiotechnetium (*12*).

In patients suffering from musculoskeletal inflammations only the use of a radiomarker of great sensitivity and specificity allows for the "early" detection of a possible infection. At present, all of the radionuclide techniques used have had some limitations. These limitations include: (a) the inability to distinguish the noninfectious inflammation from infection (*13*); (b) the false-negatives in osteomyelitic osteonecrosis or in chronic osteomyelitis with mainly lymphocytes and monocytes in the exudate (*14,15*) identified by the scintigraphy as cold lesions; (c) the false-positives due to increased bone-marrow uptake found in some inflammatory processes and prosthetic implants (*16–19*). These last cases, however, could be resolved by using ^{99m}Tc nanocolloid and ^{99m}Tc leukocytes (*19–21*) together, even if this method has a bias due to the difficulty in evaluating a match or a no match between scintigraphic results of radioleukocytes and those obtained from a scan with radiocolloids. Other limitations are the time-consuming method of labeling the leukocytes, the dosimetry and the cost.

The background history of the use of Hig for detecting inflammatory process is scanty and papers are less numerous than those relative to the other radiopharmaceuticals (*22,23*). Some studies have been performed using ^{99m}Tc-Hig and ^{111}In-Hig with favorable and encouraging results in comparison to

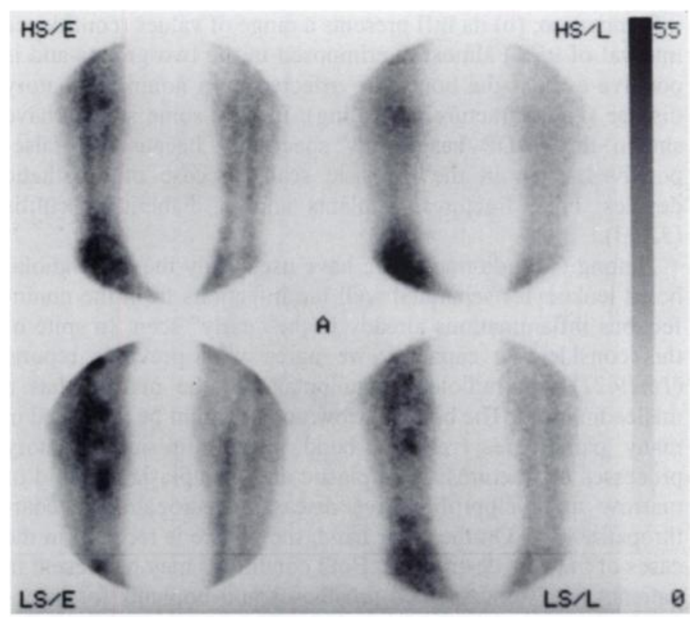

FIGURE 5. Right tibia osteomyelitis as a complication of an exposed fracture in a 19-yr-old patient. The radiolabeled leukocyte scintigraphy showed multiple foci of activity along the medium segment of the tibia, whereas a diffuse distribution pattern with a single focus of uptake was observed in the Hig study. The activity remained elevated in the "late" scan of both the examinations. HS/E = "early" Hig scintigraphy; HS/L = "late" Hig scintigraphy; LS/E = "early" leukocyte scintigraphy; LS/L = "late" leukocyte scintigraphy.

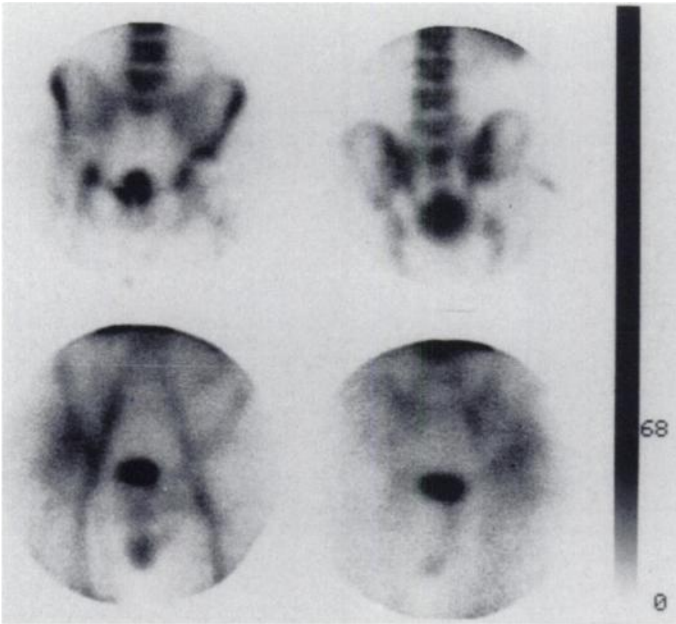

FIGURE 6. Scintigraphy in a 43-yr-old patient with an infective lesion of the right hip joint after an ileopsoas abscess caused by *Staphilococcus aureus*. Both the Hig and leukocyte studies were true positives. The soft tissue inflammation was best mapped by Hig scintigraphy. Hig did not concentrate on bone marrow, as shown in the picture. Top views: "early" leukocytes scintigraphy; bottom views: "early" Hig scintigraphy; anterior views on the left; posterior views on the right.

other radiotracers in orthopedic inflammatory processes (*24–27*). In addition, the ^{99m}Tc-Hig has been successfully used for assessing the grade of psoriatic and rheumatoid arthritis (*28–31*). But, a comparative analysis between ^{99m}Tc-Hig, ^{99m}Tc leukocytes and ^{99m}Tc-MDP in the diagnosis of musculoskeletal inflammation has never been perfomed on the same patient.

Our data have confirmed that: (a) the MDP scan has a low discriminatory capacity between infection and noninfectious inflammation; (b) its InfI presents a range of values (confidence interval of 95%) almost overimposed in the two groups and is positive even if the bones are affected by a noninflammatory disease (i.e., a fracture in healing). In fact, some studies have shown that MDP has a low specificity because of false-positives, even in the triphasic scan, in case of prosthetic devices, bone fractures, implants and in diabetic vasculitis (*32,33*).

Among the radiotracers we have used, only the InfI radiolabeled leukocytes separated well the infections from the noninfectious inflammations already in the "early" scan. In spite of this considerable capacity, we agree with previous reports (*16,19,21*) that radioleukocyte uptake in the marrow has a misleading role. The bone marrow uptake might be increased in many pathologies: reactive bone marrow in inflammatory processes or fractures; hyperplastic and metaplasia myeloid of marrow in myeloproliferative diseases; neuropathic osteoarthropathy (*34*). On the other hand, the uptake is reduced in the cases of marrow destruction. Both conditions may be present in patients with noncemented prostheses and implants for osteosynthesis.

In two of our cases, leukocytes were false-positive. There was no clear explanation for the patient with neurodysthrophy of the hip. One hypothesis is the presence of a slight, but calculable, difference in the marrow perfusion between the two femoral epiphysises. In the second case, the patient suffered from myelofibrosis. In this disease there are often isles of hyperplastic marrow in omeral and femoral diaphysis to justify the false-positive result.

On the contrary, Hig does not concentrate in the unaffected bone marrow. By the acquisition of the "late" Hig images, we obtained a InfI value that strongly differentiated the infections from the noninfectious inflammations that had significantly lower values. The comparative statistical analysis between "early" radioleukocytes studies and "late" Hig studies verified an analogous behavior, but a larger confidence interval, for the Hig. Moreover, we observed that the InfI value usually rises from "early" to "late" scan in both acute and chronic infections, whereas in the noninfectious inflammations it may decrease or remain almost unchanged (Fig. 2).

These variations of the InfI value are less evident in radioleukocyte studies. One of the causes may be the uptake in normal bone marrow so that the ratio between the lesion area and the controlateral area, presumed normal, is reduced.

The eventual decrement of the Hig InfI in the noninfectious inflammations may be explained by the data obtained in animal experiments (*35,36*). One method of Hig uptake is the increase of vascular permeability. The Hig binding to fragment c (Fc) leukoreceptors or to Fc receptors of the microbial agents (the method that has been criticized after the experiments of Morrel, Oyen and Juweid) probably does not happen or it occurs poorly (*37*). In agreement with Corstens and Claessens (*5*), it is likely that the concentration relates to the expansion of fluid space available for macromolecules, and it is proportional to the grade of the infection or the simple noninfectious inflammation. In the last case, it is possible that a more moderate interstitial fluid space dilation occurs and that a portion of the exuded Hig is removed through lymphatic circulation. Hig behaves as a blood-pool marker with both quick washin and washout in noninfectious inflammation (*38,39*). This behavior as a blood-pool radioindicator has been described by others in cases of uncomplicated inflammatory arthropathy (*28,29,40*).

Hig reveals infection by binding with Fc receptors or by a different unknown method of Ab trapping. Its accumulation in musculoskeletal infection is progressive with time.

CONCLUSION

We have confirmed the important role of radioleukocytes in the study of orthopedic inflammatory pathologies. It seems likely that with our InfI, the "early" radioleukocytes scintigraphy (2–4 hr) allows us to separate the infections from the noninfectious inflammations rather well.

In contrast, the same result can be obtained only with the "late" scan in Hig studies. Nevertheless, the physiological lack of uptake in the bone marrow, the negligible incidence of false-positives, the high sensitivity reached in the "late" acquisition, in addition to good availability, simple preparation and use, low dosimetry and low cost, have led us to consider that ^{99m}Tc-Hig is the most favorable alternative tracer in detecting musculoskeletal inflammation. Finally, as previously recognized, MDP shows an excessively low specificity, particularly for soft tissue infections or complicated pathologies.

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