Imaging with Tc-99m MDP and Ga-67 Citrate in Patients with Rheumatoid Arthritis and Suspected Septic Arthritis: Concise Communication

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Fifteen patients with rheumatoid arthritis and suspected septic arthritis had joint aspiration and imaging with Tc-99m MDP and Ga-67 citrate. Joint-to-bone ratios for Tc-99m and Ga-67 were obtained from regions of interest over each joint and an area of bone proximal to the joint. Eight patients had septic arthritis with *Staphylococcus aureus*, and the cultures from the other seven gave no growth. Although the mean joint-to-bone ratios were higher for the culture-positive patients with both Tc-99m and Ga-67, there was no level that separated culture-positive from culture-negative patients.

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It is often difficult to make the diagnosis of septic arthritis or osteomyelitis quickly in a patient with a chronic underlying joint disease such as rheumatoid arthritis (RA) because these patients might be expected to have clinical evidence of inflammation in their joints, including exacerbations and remissions, as part of the primary disease process. Furthermore, they may be more susceptible to infection than normal because of their potentially altered immune status (*1*,*2*) or because of therapy involving steroids or immunosuppressive drugs (*3*). On occasion, a joint markedly inflamed out of proportion to other affected areas, or overt signs or symptoms of infection, make the diagnosis of infectious arthritis easy and it is readily confirmed by arthrocentesis and an appropriate microbiological study. Frequently, however, the clinician is faced with an arthritis patient with flaring in one or more joints but without the classical spectrum of septic manifestations. As infectious arthritis is clearly possible in such a clinical setting, it is important that the diagnosis be established or ruled out as rapidly as possible.

In early septic arthritis, or in periarticular osteomyelitis that has not yet spread to the joint space, the joint fluid may yield negative gram stain and cultures, and the leukocytosis in the synovial fluid may be inaccurately attributed to the chronic disease process. Thus, it would be desirable to have rapid and reliable alternative diagnostic tests to use in this setting. Others such as synovial fluid glucose (*4*) or lactate (*5*) levels have been suggested without great general benefit. Such a role has also been advocated for radionuclide imaging (*6*). Joint and bone imaging using Tc-99m phosphate complexes and Ga-67 citrate has proved sensitive for detecting the changes of septic arthritis and osteomyelitis before radiographic changes (*7*). In addition, noninfectious inflammatory joint disease has shown to be significantly sensitive to these techniques (*8*).

In an attempt to clarify the role of radionuclide bone and soft-tissue imaging in septic arthritis and/or osteomyelitis in patients with underlying inflammatory joint disease, we have performed quantitative joint measurements of Tc-99m methylene disphosphonate and Ga-67 citrate in RA patients with and without infectious arthritis demonstrated by culture.

METHODS

Fifteen patients with either classical or definite rheumatoid arthritis according to American Rheumatism Association criteria (*9*) and with suspected septic

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TABLE 1. RHEUMATOID ARTHRITIS WITH SUSPECTED INFECTIOUS ARTHRITIS

Patient	Age	Sex	Years RA	Joint involved	Joint score	Synovial-fluid culture	WBC	PMNs	Joint-to-bone Tc-99m	Joint-to-bone Ga-67	Ga-67 ratio Tc-99m ratio
1	60	F	20	Right knee	9	*S. aureus*	NA*	NA	5.4	1.9	0.35
2	69	M	20	Right knee	4	*S. aureus*	NA	NA	3.9	2.1	0.54
3	58	F	15	Left knee	5	*S. aureus*	NA	NA	1.0	1.0	1.0
4	72	F	8	Left tibiotalar	9	*S. aureus*	NA	NA	3.2	7.5	2.3
5	59	M	5	Left tibiotalar	8	*S. aureus*	56,250	96%	4.5	5.4	1.2
6	67	F	30	Right tibiotalar	5	*S. aureus*	NA	NA	6.3	3.5	0.56
7	52	M	20	Right knee	7	*S. aureus*	87,000	98%	2.1	1.4	0.67
8	56	M	27	Right knee	6	*S. aureus*	3,500	10%	1.3	1.1	0.85
9	67	M	30	Right 2nd MCP	3	Neg	6,000	95%	6.0	3.7	0.62
10	60	F	9	Right knee	5	Neg	9,900	63%	2.6	1.8	0.69
11	79	F	5	Right knee	6	Neg	5,500	75%	2.4	1.7	0.71
12	67	F	4	Left knee	9	Neg	1,000	28%	1.4	1.0	0.71
13	64	M	5	Right shoulder	6	Neg	46,000	88%	1.4	1.0	0.71
14	63	F	50	Left knee	3	Neg	10,250	9%	1.4	1.1	0.79
15	60	M	15	Left knee	5	Neg	NA	NA	1.7	1.5	0.88

* Not available.

arthritis were studied (Table 1). Their ages ranged from 52 to 79 (mean 64) and all had had RA for several years. Eight were female and seven male. The criteria for suspicion of septic arthritis were the following: (a) high index of clinical suspicion (*1–3*), (b) fever and/or other symptoms of sepsis, (c) an inflamed joint out of proportion to other affected joints, (d) suspected portal of entry such as infection elsewhere, and (e) peripheral blood leukocytosis with left shift. The patients' medications were not changed during the study, and antibiotics were administered only after the imaging studies and arthrocenteses were performed. In addition to a complete physical examination and appropriate laboratory studies, involved joints were specifically evaluated for pain on motion, tenderness, and swelling, using a scale that rated the joint from 0 (no abnormality) to 3 (severely involved) on each parameter. A total score for each joint was obtained by adding the scores for the three symptoms, with a maximum score of 9. After completing the imaging studies, the suspected infected joints were aspirated and the synovial fluids cultured. Concurrent synovial-fluid leukocyte and differential counts were also obtained on nine patients. Some patients had more than one involved joint, but only the single most inflamed joint was included in the study for each patient.

The patients were injected with 20 mCi of Tc-99m methylene diphosphonate (MDP). Images of the joints were started 2.5 hr after the administration of the radiopharmaceutical. The same imaging protocol was used for each patient, so that the joints were always imaged in the same order and for approximately the same time. The gamma camera was interfaced to a laboratory computer. The next day, 4 mCi of Ga-67 citrate were administered, and the joint images were obtained 24 hr later. In addition to the analog images, joint accumulation for both the Tc-99m MDP and Ga-67 was quantified by analyzing regions of interest over the joint and the bone proximal to the joint (Fig. 1). The average counts per pixel were obtained, and a joint-to-bone ratio was calculated.

RESULTS

Eight patients had synovial-fluid cultures positive for *Staphylococcus aureus*, whereas the other seven patients with suspected infectious arthritis had negative cultures. Three septic patients had involvement of the tibiotalar joint, two each had infection of the knee or metatarsophalangeal joints, and one patient had an involved proximal interphalangeal joint of a finger. While synovial fluid, white cell, and differential counts were not

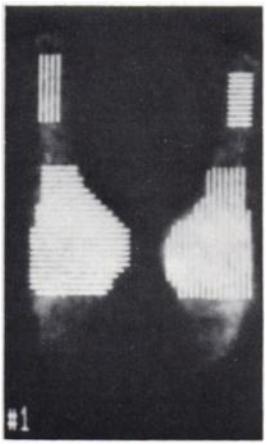

FIG. 1. Anterior Tc-99m MDP knee images from computer, demonstrating four regions of interest, two over the knee joints and two over the femurs proximal to the knee joints.

available in all patients, they were of possible predictive value in two of three patients with positive cultures and were potentially suggestive of infection in two of six patients with negative cultures if the criterion of >85% polymorphonuclear leukocytes on the differential count is used to suggest infection (Table 1).

The joint-to-bone ratios of activity for Tc-99m MDP and Ga-67 demonstrate a wide range of values for both tracers (Table 1) in culture-negative as well as culture-positive patients. If one assumes that bone-to-joint ratios greater than 1.8 are abnormal (*13*), then in culture-positive patients, six of eight have elevated Tc-99m MDP levels and five of eight have increased Ga-67 values. By contrast, three of seven culture-negative patients have increased Tc-99m MDP levels and two of seven have abnormal Ga-67 ratios. When the joint-to-bone ratio for Ga-67 is divided by the ratio for Tc-99m, three of the eight patients with septic joints have values of 1 or greater, and the seven patients with negative cultures have values less than 1. While mean joint-to-bone ratios are higher for both Tc-99m MDP and Ga-67 in culture-positive patients (Table 2), near-baseline values are obtained in two studies in this group.

Whereas all of the suspected infectious joints had some evidence of clinical inflammation, the joint scores do not segregate in a clearly predictable fashion with the synovial-fluid leukocyte values or the joint-to-bone imaging results in either culture-positive or culture-negative patients.

DISCUSSION

The localization of bone-seeking radiopharmaceuticals to the region of an inflamed joint results primarily from increased blood flow to this area (*10*). As with the spread of infection itself, the concentration of radionuclides may depend upon the circulation in the periarticular area, which varies with age (*11*). In the adult, the synovium and the epiphyseal-metaphyseal bone adjacent to the joint share a common blood supply. Thus, inflammatory processes that increase blood flow to the synovium might also enhance the circulation to adjacent bone (*12*). As increased blood flow is characteristic of all joint inflammation, including infection, there will be associated increased radiopharmaceutical accumulation as well. It follows that abnormal increases in bone-seeking radionuclide levels per se will not differentiate between the various types of inflammatory joint disease, including infection.

Park and associates (*13*) quantitated Tc-99m HEDP joint uptake using a collimated thyroid-uptake probe for the elbows, ankles, and knees and a gamma camera fitted with a variable-sized lead template to image the small hand joints. In addition to counting the elbows, ankles, and knees, they obtained probe counts of the forearms, thighs, and legs as reference points for the corresponding joints. An image of the opposite forearm was obtained as a reference for the small hand joint counts. Following intravenous administration, serial probe counts, corrected for injected activity, demonstrated two components for both normal and RA knee joints. The RA joints had a faster first component than normal joints ($t_{1/2}$ = 6.5 vs. 16.6 min), but slower second components ($t_{1/2}$ = 11.3 vs. 5.8 hr). The probe counts corrected for injected activity reached a plateau between 2 and 3 hr following administration, but the joint-to-bone ratios for both the inflamed and normal knee joints continued to rise during the 5-hr study. Using counts obtained at the fourth hour, they found a 95% accuracy in separating normal joints from RA joints using an arbitrary joint-to-bone ratio of 1.8. In our Tc-99m MDP study, several joints with joint-to-bone ratios less than 1.8 at approximately 2.5 hr after injection were clinically involved with RA, and some had abnormal ratios with minimal abnormalities on examination. Thus the 1.8 joint-to-bone ratio was not as reliable for separating joints normal on physical examination from those with active rheumatoid involvement. Perhaps a different normal ratio is needed for the various joints. The discrepancy between our observations and those of Park et al. (*13*) may involve several factors. They did not define "active RA joints" or normal joints, they used a different tracer (Tc-99m HEDP), and their counting or imaging postinjection time was 4 hr after administration instead of the 2½-hr delay used in our study. Previous studies comparing MDP and HEDP for detecting skeletal lesions have not shown one to be significantly better than the other (*14–16*). However, Fogelman et al. (*15*) demonstrated a significant increase in the bone-to-soft-tissue and tumor-to-bone ratios with Tc-99m MDP imaged at 4 hr compared with 2 hr, but neither of these ratios was significantly different from the ratio using Tc-99m HEDP and imaging at 4 hr.

TABLE 2. SUMMARY OF CLINICAL AND IMAGING RESULTS

Culture	Number	Joint score	Joint-to-bone ratio		Ga-67 ratio
			Tc-99m	Ga-67	Tc-99m ratio
Positive	8	6.6 (1.9)*	3.5 (1.9)	3.0 (2.3)	0.93 (0.61)
Negative	7	5.3 (2.1)	2.4 (1.7)	1.7 (0.9)	0.73 (0.08)

* Mean (s.d.).

Thus, it is unlikely that either the tracer or imaging time after administration could explain the discrepancy between our results and those of Park et al. (*13*).

Gallium-67 citrate imaging has been used to increase the specificity of an abnormal radionuclide bone study in a patient with suspected osteomyelitis or septic arthritis (*17,18*). However, accumulation of Ga-67 in a bone or joint does not necessarily reflect infection (*19*), since Ga-67 can accumulate in areas of increased bone metabolism secondary to other disorders such as trauma. Rosenthall et al. (*19*) have demonstrated that incongruence of Ga-67 accumulation as compared with Tc-99m MDP is more likely to represent osteomyelitis following total hip prosthesis insertion than if the patterns are congruent. Gallium-67 accumulation in noninfected inflamed joints has been reported in reactive bursae after surgery and in inflamed synovium from various causes including RA (*19,20*).

In our small group of RA patients, we did not find that the joint-to-bone ratios for Tc-99m MDP allowed separation of culture-positive patients from those with negative cultures, nor did these data provide segregation of suspected infectious joints from those thought to be inflamed only from the rheumatoid process. Whereas two of the culture-positive patients had Ga-67 joint-to-bone ratios clearly above those of the culture-negative patients, the majority were not distinguishable. Three of the eight patients with positive culture had a Ga-67 joint-to-bone ratio greater than that for Tc-99m, whereas none of the patients with negative cultures had a higher ratio with Ga-67 than with Tc-99m. We did not find a relationship between the joint's score on physical examination and the joint-to-bone ratio with Tc-99m MDP or Ga-67 citrate. The number of joint-fluid leukocyte studies was too small to be helpful but did show exceptions to usually reported findings in infectious and noninfectious arthritis.

The roles for radionuclide joint imaging remain to be fully defined. While these studies may be useful adjuncts to traditional clinical approaches to the difficult problems of joint inflammation, they appear to have no utility in the identification of septic arthritis in patients with RA, since they lack both sensitivity and specificity. If infectious arthritis is suspected in the rheumatoid patient, expeditious arthrocentesis, followed by appropriate microbiologic studies and antimicrobial treatment, remains the approach of choice.

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