Total-Hip Arthroplasty: Periprosthetic Indium-111-Labeled Leukocyte Activity and Complementary Technetium-99m-Sulfur Colloid Imaging in Suspected Infection

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Indium-111-labeled leukocyte images of 92 cemented total-hip arthroplasties were correlated with final diagnoses. Prostheses were divided into four zones: head (including acetabulum), trochanter, shaft, and tip. The presence (or absence) and intensity of activity in each zone was noted, and compared to the corresponding contralateral zone. Though present in all 23 infected arthroplasties, periprosthetic activity was also present in 77% of uninfected arthroplasties, and was greater than the contralateral zone 51% of the time. When analyzed by zone, head zone activity was the best criterion for infection (87% sensitivity, 94% specificity, 92% accuracy). Fifty of the arthroplasties were studied with combined labeled leukocyte/sulfur colloid imaging. Using incongruence of images as the criterion for infection, the sensitivity, specificity, and accuracy of the study were 100%, 97%, and 98%, respectively. While variable periprosthetic activity makes labeled leukocyte imaging alone unreliable for diagnosing hip arthroplasty infection, the addition of sulfur colloid imaging results in a highly accurate diagnostic procedure.

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The noninvasive diagnosis of orthopedic implant infection is challenging. Radionuclide procedures used include technetium-99m (^{99m}Tc) bone, gallium-67-(^{67}Ga) citrate, and indium-111-(^{111}In) labeled leukocyte (WBC) scintigraphy (*1–23*).

Our initial experiences using ^{111}In-labeled leukocyte scintigraphy for diagnosis of this entity were unsatisfactory. While absence of periprosthetic leukocyte activity was seen only in uninfected prostheses, periprosthetic activity was present in infected and uninfected prostheses. Neither pattern nor intensity of periprosthetic activity reliably separated infected from uninfected arthroplasties. Because the physiologic distributions of ^{99m}Tc-sulfur colloid and labeled leukocytes in marrow are similar (*24*), and because osteomyelitis typically stimulates leukocyte accumulation and inhibits sulfur colloid accumulation (*25*), combined labeled leukocyte/sulfur colloid imaging was performed in an effort to differentiate physiologic marrow accumulation from infectious accumulation of labeled leukocytes.

We report the patterns of periprosthetic labeled leukocyte activity in 92 cemented total-hip arthroplasties, as well as the results of combined ^{111}In-labeled leukocyte/^{99m}Tc-sulfur colloid imaging of 50 of these arthroplasties.

MATERIALS AND METHODS

Patient Population

Seventy-two consecutive patients with 92 (68 primary, 24 revision) cemented total-hip arthroplasties were retrospectively reviewed. Fifty-two patients had unilateral arthroplasties and 20 had bilateral arthroplasties. There were 26 males and 46 females with a mean age of 62 yr (range: 20–87 yr). The mean time between arthroplasty and scintigraphy was 4.6 yr (range: 1 wk–17 yr).

Arthroplasties were considered infected if operative cultures grew out organisms (n=19) or if gross purulence was evident at surgery (n=4). Arthroplasties were considered uninfected if operative smears revealed no leukocytes and intraoperative cultures were reported as no growth (n=33). Arthroplasties not operated on were considered uninfected if: (a) they were the asymptomatic arthroplasty in a patient whose contralateral hip arthroplasty was symptomatic (n=20), or (b) they were the asymptomatic arthroplasty in a patient undergoing leukocyte imaging for reasons unrelated to that arthroplasty (n=10), or (c) they were a painful arthroplasty that responded to conservative (anti-inflammatory, but not antibiotic) therapy (n=6). No patients with clinically uninfected arthroplasties developed symptoms referable to their arthroplasties during a minimum follow-up period of 6 mo after imaging.

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Scintigraphy

Leukocyte scintigraphy was performed 24 hr after injection of ~18.5 MBq (500 μCi) of autologous mixed leukocytes labeled with ^{111}In-oxine, according to the method of Thakur et al. (*26*). Six-minute anterior and posterior images of the arthroplasties were obtained on a large field of view gamma camera equipped with a medium-energy parallel-hole collimator using 20% windows centered over the 174 keV and 246 keV photopeaks of ^{111}In.

The last 50 arthroplasties were studied with ^{99m}Tc-sulfur colloid imaging immediately after the labeled leukocyte study. Patients were injected with 370 MBq (10 mCi) of ^{99m}Tc-sulfur colloid, and 6 min anterior and posterior static images were obtained 1–2 hr later on a gamma camera equipped with a low-energy, high-resolution, parallel-hole collimator, using a 10% window centered on the 140 keV photopeak of ^{99m}Tc. Prior to ^{99m}Tc-sulfur colloid injection, to confirm that the contribution of ^{111}In photons to the ^{99m}Tc image was minimal, a 6-min anterior view of the region of interest was obtained using a 10% window centered around the 140 keV photopeak of ^{99m}Tc, and the standard intensity setting for routine sulfur colloid marrow imaging. Because no discernible contribution of ^{111}In photons to the ^{99m}Tc image was seen in any of the 20 arthroplasties so studied, this is no longer routinely performed.

Image Evaluation and Diagnostic Criteria

Each arthroplasty was divided into four zones: head (including acetabulum), trochanter, shaft, and tip (Fig. 1). The presence or absence of labeled leukocyte activity in each zone was noted. When present, the intensity of this activity was compared to the intensity of activity in the corresponding contralateral zone. The pattern of periprosthetic labeled leukocyte activity around each arthroplasty was also noted. Chi-square statistics were used to analyze the significance of the relationship between periprosthetic labeled leukocyte activity (n=76) by zone and the presence or absence of infection.

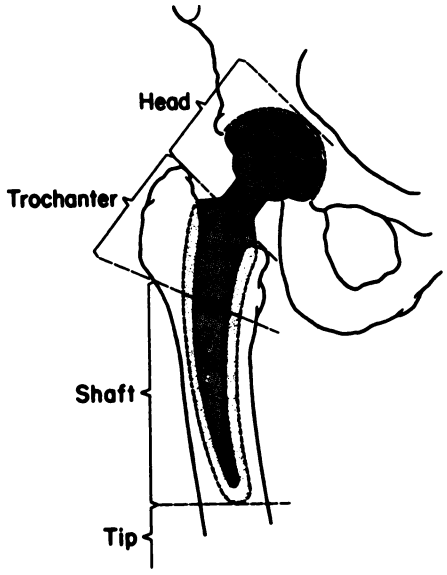

FIGURE 1
Diagrammatic representation of the four zones into which each arthroplasty was divided.

For the 50 arthroplasties studies with labeled leukocytes and sulfur colloid, images were classified as congruent if the distribution of the two radiotracers was spatially identical, and incongruent if labeled leukocyte activity was observed without corresponding activity on the sulfur colloid images. Four criteria for diagnosing infection were selected and compared:

Criterion 1: Any periprosthetic activity.
Criterion 2: Periprosthetic activity greater than the contralateral side.
Criterion 3: Labeled leukocyte activity in the head zone, regardless of activity in any other zone. (Retrospective analysis of activity by zone indicated that this was the best criterion for diagnosing infection with labeled leukocyte imaging alone).
Criterion 4: Incongruent labeled leukocyte/sulfur colloid images.

The results reported represent the consensus of independent, blinded, random readings by two experienced nuclear physicians, who had no knowledge of the final diagnoses.

RESULTS

Twenty-three arthroplasties were infected, all operatively confirmed. Thirteen different organisms were identified: 6 gram-positive, 6 gram-negative and 1 fungal. Sixty-nine were uninfected, 33 operatively confirmed, and 36 by one of the previously described clinical criteria. Eleven different patterns of periprosthetic leukocyte activity ranging from no uptake in any zone to uptake in all four zones were identified (Fig. 2).

Sixteen (17%) arthroplasties demonstrated no periprosthetic labeled leukocyte activity: none of these were infected.

Seventy-six (83%) arthroplasties demonstrated varying degrees of periprosthetic labeled leukocyte activity: all 23 infected and 53 uninfected arthroplasties. Peri-

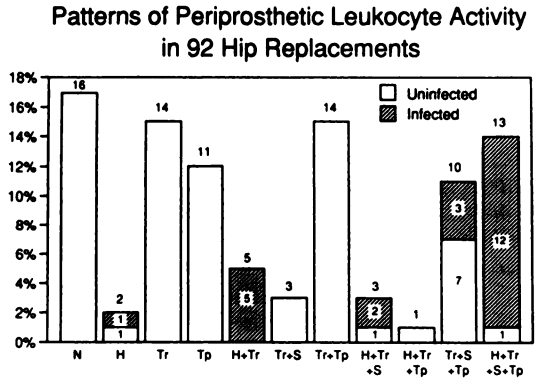

FIGURE 2
Eleven patterns of periprosthetic labeled leukocyte activity were identified among the 92 arthroplasties reviewed. N = no periprosthetic activity, H = head and acetabulum, Tr = trochanter, S = shaft, and Tp = tip.

TABLE 1
Comparison of Criteria for Diagnosis of the Infected Hip Arthroplasty

Presence of	Infected	Uninfected	Sensitivity	Specificity	Accuracy
Any activity	23/23	53/69	100%	23%	42%
Activity > contralateral zone	15/23	27/69	65%	61%	62%
Head zone activity	20/23	4/69	87%	94%	92%
Incongruent leukocyte/sulfur colloid	10/10	1/40	100%	97%	98%

prosthetic activity was greater than corresponding contralateral zone activity in 15 infected and 27 uninfected prostheses.

The most significant finding observed following analysis by zone, of 76 arthroplasties with periprosthetic leukocyte activity, was that infection was infrequently found in the absence of head zone activity (3/49), while 20 of 24 arthroplasties with head zone activity were infected. The difference was highly significant (x^2=43.2, $p \ll 0.001$). When 16 arthroplasties without any uptake are included, Criterion 3 yielded a sensitivity and specificity of 87% and 94%, respectively.

Of 50 arthroplasties studied with labeled leukocyte/sulfur colloid imaging there were 10 infected and 40 uninfected prostheses. Images were incongruent in all 10 infected prostheses and 1 uninfected prosthesis. Images were congruent in 39 uninfected arthroplasties.

A comparison of the four criteria for diagnosis of hip arthroplasty infection is summarized in Table 1.

DISCUSSION

Pain occurs in ~20% of hip arthroplasties, and is usually secondary to loosening with or without infection (*27*). While infection occurs in 1%-4% of primary hip arthroplasties (*28–31*), infection rates of 32%–38% following revision arthroplasty have been reported (*31, 32*). Therefore, accurate preoperative diagnosis and treatment of an occult infection is essential for a successful revision arthroplasty.

Criteria used to diagnose the infected orthopedic prosthesis, including clinical history, physical examination, erythrocyte sedimentation rate, peripheral leukocyte count, aspiration and culture, and plain radiography, are insensitive or nonspecific or both, and their usefulness is limited (*21,22,33*).

Technetium-99m bone scintigraphy, sensitive for detecting osseous inflammation, suffers from a lack of specificity. It is especially unreliable in the assessment of hip prostheses during the first 12 mo after implantation (*1,4,5,9,12,17,22,34,35*). Sequential ^{99m}Tc bone and ^{67}Ga scintigraphy has been used to improve the accuracy of diagnosing prosthetic infection. Gallium, however, localizes in septic and aseptic inflammation, and in any region of increased osseous activity. The overall accuracy of sequential bone/gallium imaging for orthopedic implant infection has been reported to be between 60–80% (*8,12,15,20,36*).

Indium-111-labeled leukocyte scintigraphy has also been evaluated, alone, and in combination with other radiotracers and has been compared to ^{99m}Tc bone and ^{67}Ga scintigraphy, with a wide range of results reported (*10–23*).

Generally, when used alone, interpretation of this study has been based upon either the intensity of periprosthetic labeled leukocyte activity in comparison to various reference points (*12,15,17–20*) or a grading system of periprosthetic uptake (*14,16,22*). The reported sensitivity of the procedure using these criteria has ranged from 50% to 100%, and the specificity, from 45% to 100% (Table 2). The low specificity is especially critical because of the low prevalence of arthroplasty infection in general.

In our own series, with the exception of head zone activity, neither the presence of periprosthetic activity nor the intensity of such activity accurately identified

TABLE 2
Diagnosis of Orthopedic Implant Infection with Labeled Leukocyte Imaging Alone

Group/Reference	Criteria	No. of implants	Sensitivity	Specificity
Reference 16*	1	50	100%	90%
Reference 14*	1	40	100%	92%
Palestro et al†	1	92	100%	23%
Reference 12	2	16	86%	100%
Reference 19	2	24	100%	45%
Reference 20	2	40	95%	90%
Reference 21	2	29	100%	50%
Reference 15	3	50	73%	95%
Palestro et al†	3	92	65%	61%
Reference 18	3, 4	38	88%	93%
Reference 22	5	98	88%	73%
Reference 11	6	16	50%	100%
Palestro et al†	7	92	87%	94%

Criteria: (1) Any periprosthetic activity; (2) Periprosthetic activity > surrounding bone activity; (3) Periprosthetic activity > contralateral side; (4) Periprosthetic activity > symphysis pubis on anterior view or > sacroiliac joint on posterior view; (5) Periprosthetic activity > normal marrow activity; (6) Criteria not specified; (7) Head zone activity.

* Studies performed with ^{111}In-labeled granulocytes.

† Current series.

TABLE 3
Diagnosis of Orthopedic Implant Infection by Dual-Tracer Imaging

Group/ Reference	Tracers	Criteria	No. of implants	Sensitivity	Specificity
Reference 19	A	1	24	85%	85%
Reference 21	A	1	29	88%	95%
Reference 10	B	2	30	92%	100%
Reference 23	B	2	54	100%	93%
Palestro et al*	B	2	50	100%	97%

A: labeled leukocyte and bone imaging; B: labeled leukocyte and sulfur colloid imaging; 1: incongruent bone and leukocyte images; 2: incongruent sulfur colloid and leukocyte images.
*Current series.

the infected arthroplasty (Figs. 3–4) (Table 2). We attribute this to the variable patterns of periprosthetic labeled leukocyte activity encountered in both infected and uninfected arthroplasties. Although the normal distribution of marrow in adults up to 70 yr old generally includes the axial skeleton, humeral heads, femoral trochanters, and frequently the femoral shafts, there is considerable individual variation. The implantation of a prosthetic device may produce additional variations. Changes in the normal distribution of marrow through surgical manipulation have, in fact, been demonstrated in animals (*37,38*).

Improved accuracy for diagnosing osseous infection using labeled leukocyte plus ^{99m}Tc-bone imaging (*13, 19,21*), and labeled leukocyte plus ^{99m}Tc-sulfur colloid marrow imaging (*10,23*) has been observed (Table 3). The reported sensitivity and specificity of leukocyte/bone imaging have ranged from 70% to 88%, and 75% to 95%, respectively.

Using combined labeled leukocyte/sulfur colloid imaging, Mulamba et al. (*10*) reported a sensitivity of 92%, and a specificity of 100%, while Fink-Bennett et al. (*23*) reported a sensitivity of 100%, and a specificity of 93%. Using this technique we obtained a sensitivity of 100% and a specificity of 97%, which are in close accord with the results of these two investigators. Combining the results of these two series with our data, the sensitivity, specificity, and accuracy of the procedure are 96%, 97%, and 97%, respectively, superior to labeled leukocyte imaging alone or in combination with routine bone scintigraphy.

This superiority is, we believe, related to the distributions of each of these tracers. Technetium-99m-MDP accumulates in bone, while labeled leukocytes and sulfur colloid accumulate in marrow. Conditions that affect bone may or may not exert similar effects on marrow, and vice versa. Therefore incongruent bone and marrow, i.e., labeled leukocyte, images could result even in the absence of infection. Oswald et al. (*39*) reported that labeled leukocyte and bone images were incongruent 15% of the time, even in the absence of infection.

Both labeled leukocyte and sulfur colloid images reflect radiotracer accumulation in the reticuloendothelial cells of the marrow, although it is unclear whether marrow activity present on leukocyte images reflects labeled leukocytes alone or in combination with free ^{111}In. Alterations in the distribution of marrow (which is otherwise normal) produce similar, or congruent, images on both of these studies (*24*). Infection, however, may actually exert opposite effects on leukocytes and sulfur colloid. While stimulating leukocyte accumulation infection of bone has been reported to decrease sulfur colloid accumulation (*25*). These inverse effects result in incongruent images, and permit discrimination of infection from unusual, but not abnormal, periprosthetic marrow distribution.

In contrast to previous reports (*10,23*), we performed sulfur colloid imaging after, rather than before, the

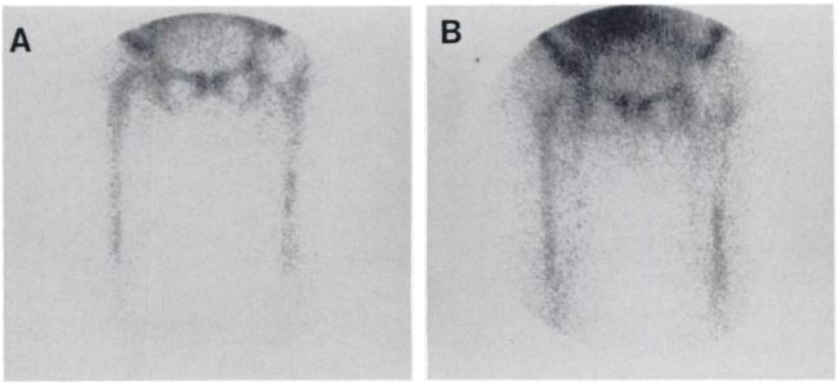

FIGURE 3
A 60-yr-old female with a left total-hip arthroplasty implanted 6 yr prior to imaging. (A) Anterior 24-hr labeled leukocyte image demonstrates periprosthetic leukocyte activity in the trochanteric, shaft, and tip regions. Although slightly heterogeneous, this activity is approximately the same intensity as the surrounding marrow activity, and less intense then marrow activity on the contralateral side. (B) Anterior sulfur colloid image performed approximately 1 hr after (A) reveals nearly absent marrow activity in the trochanteric and shaft regions. The study was interpreted as incongruent leukocyte/sulfur colloid images, consistent with infection. An infected arthroplasty was removed at surgery.

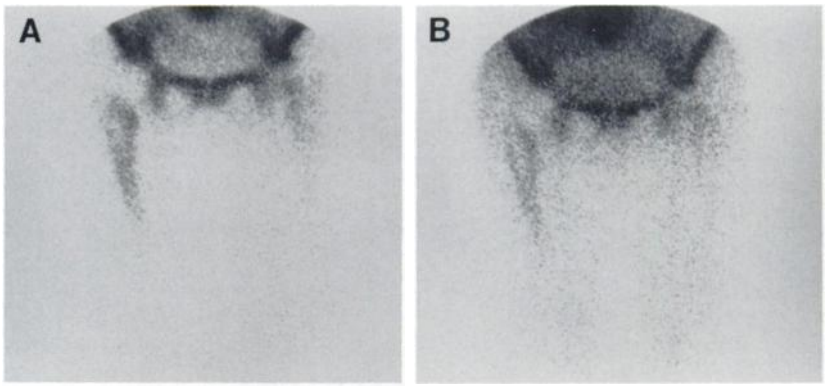

FIGURE 4
An 81-yr-old female with a right total-hip arthroplasty inserted 15 yr prior to imaging. (A) Anterior 24-hr labeled leukocyte image demonstrates intense periprosthetic activity surrounding the trochanteric, shaft, and tip zones. This activity is more intense than the corresponding contralateral region. (B) Sulfur colloid image reveals distribution of radiotracer similar to that in (A). This study was interpreted as congruent leukocyte/sulfur colloid images, without evidence of infection. A loose, but uninfected prosthesis was removed.

labeled leukocyte study. The advantage of this is that those arthroplasties which demonstrate no periprosthetic labeled leukocyte activity (17% in our series) need not be studied with sulfur colloid imaging.

One false-positive labeled leukocyte/sulfur colloid study occurred. While we have no definite explanation for this occurrence, it is possible that overlying soft tissue inflammation was the cause.

In conclusion, periprosthetic activity on labeled leukocyte images is extremely variable, both in pattern of distribution and intensity of uptake, frequently making interpretation of these images by themselves difficult (Fig. 5). Although recognition of a significant relation between the presence of activity in the head zone and arthroplasty infection improves the accuracy of the labeled leukocyte study when interpreted alone, the addition of sulfur colloid imaging improves discrimination of physiologic labeled leukocyte accumulation in marrow from accumulation due to infection, resulting in a superior (98% accuracy in our series) test for the diagnosis of the infected hip arthroplasty.

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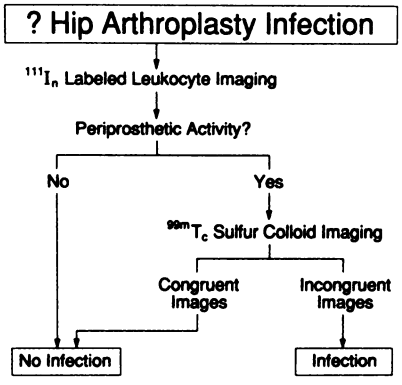

FIGURE 5
Interpretative algorithm for labeled leukocyte imaging in the diagnosis of the infected hip arthroplasty.

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Editorial
Diagnosing Prosthetic Joint Infection

For the past 17 years, we have been studying the problem of how to best diagnose infection in a prosthetic joint by nuclear imaging. We have studied prosthetic joints with various combinations of technetium bone scans, gallium, indium leukocytes, indium chloride, and newer infection imaging formulations including indium-labeled gamma globulin and ^{99m}Tc-HMPAO. Palestro et al. in this issue of *JNM* presents the case for the combination of ^{111}In-labeled leukocytes and ^{99m}Tc-colloid bone marrow imaging. To better understand why this has been so problematic a clinical diagnostic imaging challenge, we need to review our past history in imaging infected prosthetic joints, including the hows and whys of the various radiopharmaceuticals used.

Between 1973 and 1979, Reing et al. and Bauer et al. (*1,2*) reported results of trials of bone scans and gallium scans in patients suspected of having infection or loosening of prostheses. Conclusions often stated that a normal bone scan excluded the possibility of need for surgical

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