RadioGraphics

Combined Labeled Leukocyte and Technetium 99m Sulfur Colloid Bone Marrow Imaging for Diagnosing Musculoskeletal Infection[1]

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TEACHING POINTS
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The use of labeled leukocyte (white blood cell [WBC]) studies in the diagnosis of osteomyelitis can be problematic. A combined study consisting of WBC imaging and complementary bone marrow imaging performed with technetium 99m (^{99m}Tc) sulfur colloid is approximately 90% accurate and is especially useful for diagnosing osteomyelitis in situations involving altered marrow distribution. There are limitations and pitfalls associated with a combined study. If there is no labeled WBC activity in the region of interest, marrow imaging is not useful. The sulfur colloid image becomes photopenic within about 1 week after the onset of infection, so that the study should be interpreted cautiously in the acute setting. Labeled WBC accumulation in lymph nodes can also confound image interpretation, although nodal activity can usually be recognized because it is typically round, discrete, multifocal, linear in distribution, and often bilateral. Furthermore, ^{99m}Tc–sulfur colloid that is improperly prepared or is more than about 2 hours old degrades image quality, potentially causing erroneous conclusions. Nevertheless, WBC-marrow imaging is a very accurate technique for diagnosing osteomyelitis. Knowledge of the criteria for image interpretation and of the aforementioned limitations and pitfalls, combined with careful attention to imaging technique, will maximize the value of this study.

Abbreviation: WBC = white blood cell

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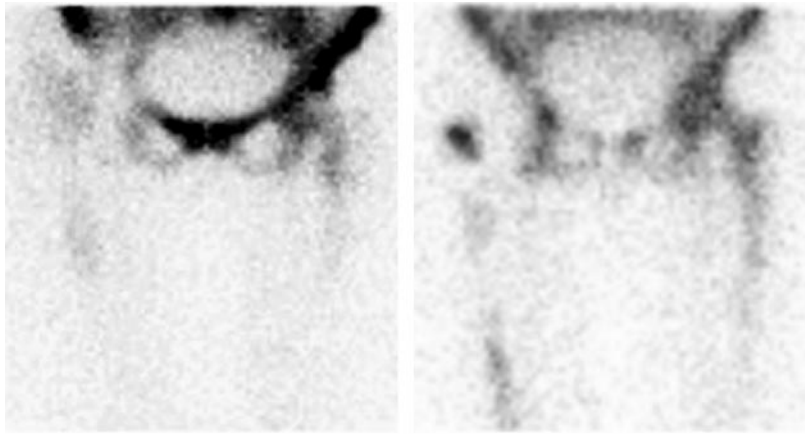
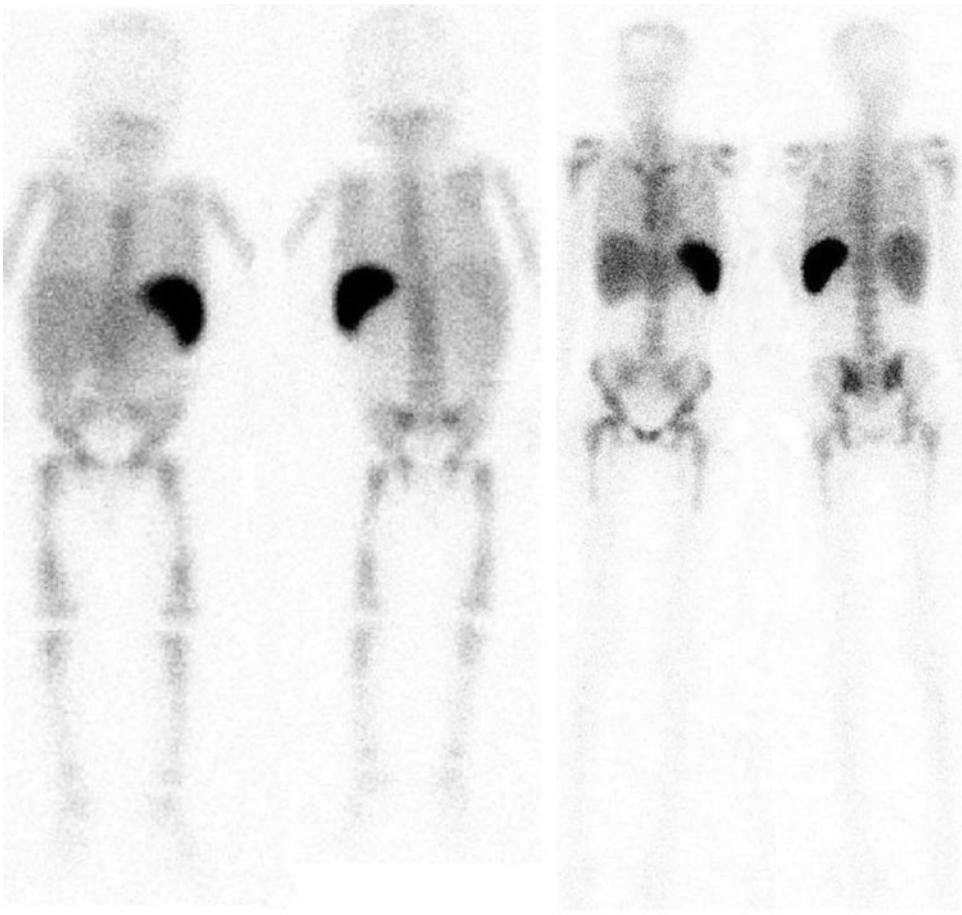


Figure 1. **(a)** Infected right hip replacement. WBC image shows mild, diffuse activity around a right hip prosthesis. This activity is less intense than that in the left hip and femur. **(b)** Aseptically loosened right hip replacement. WBC image shows irregularly increased activity around a right hip prosthesis. Proximally, this activity is more intense than both adjacent activity and activity in the left hip and femur. The intensity of periprosthetic activity on WBC images is not a reliable criterion for determining the presence of infection.

Introduction

Leukocytes (white blood cells [WBCs]) usually do not accumulate at sites of increased bone mineral turnover in the absence of infection. In theory, labeled WBC scintigraphy should be extremely useful for diagnosing osteomyelitis (1,2); however, reported results have varied widely. Some investigators have reported that the test lacks sensitivity, whereas others have reported poor specificity. Poor sensitivity is often attributed to chronicity of the infection; poor specificity is ascribed to nonspecific inflammation (3–9). Chronicity and nonspecific inflammation are undoubtedly part of the explanation for inconsistent results; however, another more fundamental problem with WBC imaging is related to the interpretation of the images themselves. The standard practice for interpreting WBC images is to compare activity in the region of interest with activity at some presumably normal reference point. Thus, WBC studies are interpreted as positive for osteomyelitis when *(a)* uptake in the region of interest exceeds that at the predetermined reference point, or *(b)* activity outside the normal areas of distribution of the radiotracer is observed (2). Unfortunately, both the intensity of uptake in a focus of infection and the normal distribution of labeled WBCs are variable. In one study of painful hip prostheses (10), investigators reported that the sensitivity and specificity of WBC imaging for diagnosing infection varied with the criteria used for image interpretation. When any periprosthetic activity was considered positive for infection, the test was 100% sensitive but only 23% specific. When only activity more intense than activity in the corresponding contralateral site was considered positive for infection, specificity rose to 61% but sensitivity fell to 65% (Fig 1) (10). These investigators observed similar changes when the same criteria were applied to knee replacements (11).

The normal biodistribution of labeled WBCs includes the bone marrow, one of the largest and most widely distributed organs in the human body. The bone marrow is the site of hematopoiesis in the fetus as early as the 20th week of gestation. At birth, virtually all medullary cavities are filled with hematopoietic cells; hence, the marrow appears red. With advancing age, these hematopoietic cells are gradually replaced with adipose tissue, giving rise to "yellow" or fatty marrow. Approximately one-half of the hematopoietic cells in the tibia and femur are replaced by fatty material after the 1st decade of life, and by young adulthood, hematopoietically active marrow is confined to the cavities of bones that are centrally located—that is, the axial skeleton, which includes the skull, clavicles, sternum, scapulae, ribs, vertebrae, and pelvis (12,13). Hematopoietically active marrow is also usually present in the proximal 25%–30% of the femurs and humeri (Fig 2). However, there is considerable intra- and interindividual variability in the distribution of hematopoietically active marrow (13). Generalized mar-



a. b.

Figure 2. **(a)** Anterior (left) and posterior (right) WBC images of a 15-month-old infant show normal findings. In healthy infants and very young children, virtually all of the medullary cavities contain hematopoietically active marrow; thus, labeled WBC activity will be present throughout much of the skeleton. **(b)** Anterior (left) and posterior (right) WBC images of an adult show normal findings. As a person ages, hematopoietically active marrow recedes and is replaced by fatty marrow. By young adulthood, hematopoietically active marrow is confined to the axial skeleton, proximal femurs, and proximal humeri.

row expansion may be either transient or permanent and is a response to a systemic process, such as various anemias, tumors, and other myelophthisic states. In severe cases, generalized marrow expansion may progress to extramedullary hematopoiesis (14). Localized marrow expansion, in contrast, is usually transient and is a response to a local stimulus, such as fracture, inflammation, orthopedic hardware, the neuropathic joint, or even calvarial hyperostosis (2,15–18).

Currently available radionuclide agents, including labeled WBCs, accumulate in the bone marrow as a result of phagocytosis by the reticuloendothelial cells in the marrow. The distribution of the reticuloendothelial component of the bone marrow closely parallels that of the hematopoietic component in most conditions; therefore, alterations in the distribution of the hematopoietic component are accompanied by similar alterations in the distribution of the reticuloendothelial component (13,14).

Teaching Point

Consequently, generalized and localized expansion of hematopoietically active marrow may produce unusual, even bizarre patterns of activity, in terms of both intensity and distribution, on WBC images. These alterations in marrow distribution complicate the interpretation of WBC images because it is difficult to determine whether WBC activity represents infection or merely hematopoietically active marrow in an unexpected location (Fig 3) (2). Because labeled WBCs normally accumulate in bone marrow and the distribution of marrow can vary so dramatically from one individual to another, a logical method for distinguishing infection from marrow is to combine WBC imaging with bone marrow scintigraphy. This technique is reliable—assuming, of course, that both radiotracers accumulate in marrow, whereas only WBCs accumulate in infection.

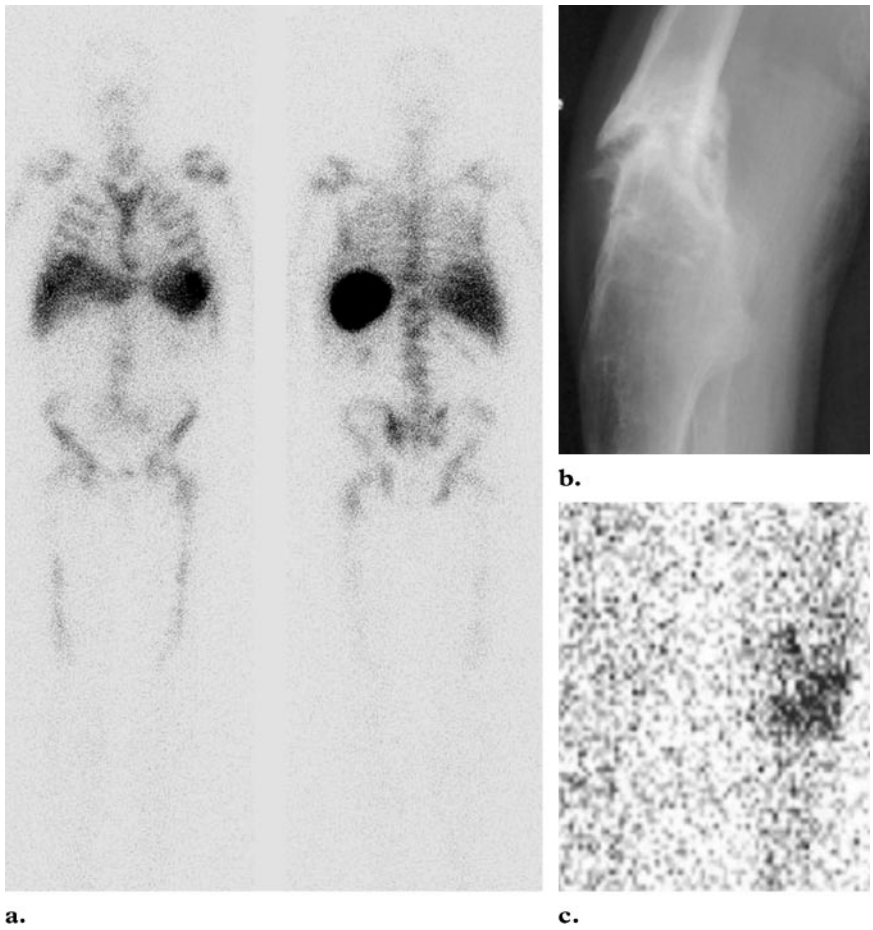


Figure 3. **(a)** Generalized marrow expansion. Anterior (left) and posterior (right) WBC images obtained in a patient with metastatic prostate carcinoma show diffuse, irregular activity extending into the distal humeri and femurs. The photopenic regions correspond to areas in which marrow has been replaced by tumor. Sites of apparently increased activity, such as the left sacroiliac region, represent areas of functioning marrow, not infection. **(b, c)** Localized marrow expansion. **(b)** Radiograph demonstrates a left femoral fracture. **(c)** WBC image shows focally increased WBC activity in the uninfected fracture.

In this article, we review the use of combined labeled WBC–marrow imaging in the diagnosis of musculoskeletal infection in terms of principles, technique, indications (prosthetic joint infection, fractures, neuropathic joint, systemic diseases, miscellaneous conditions), and limitations and pitfalls (concerning absent WBC response, duration of infection, lymph node activity, and sulfur colloid preparation). All of the WBC images shown in this article were obtained with indium 111 (^{111}In)–oxine.

Principles of Combined WBC-Marrow Imaging

Some years before the concept of WBC-marrow scintigraphy was described, investigators found that the development of osteomyelitis in regions of hematopoietically active marrow produced photopenic defects at marrow scintigraphy (19). Other investigators studying the use of WBC imaging and bone marrow scintigraphy in noninfectious conditions observed that the patterns of distribution of the two radiotracers, regardless of alterations in marrow distribution, were nearly identical (20). Still other investigators found that, in the setting of infection, the distributions of the two radiotracers were different (21). The end result of these isolated observations was the development of WBC-marrow imaging. The basis for this combined test is the fact that both WBCs and sulfur colloid accumulate in marrow regardless of its location, whereas WBCs accumulate in infection but sulfur colloid does not. The distribution of activity on WBC and marrow images in healthy individuals is similar to that in persons with underlying abnormalities; in other words, the images are spatially congruent. The one exception is osteomyelitis, which stimulates uptake of WBCs and suppresses uptake of sulfur colloid. The WBC-marrow study is positive for infection when there is activity on the WBC image without corresponding activity on the marrow image; in other words, the images are spatially incongruent. When any other pattern is present, the study is negative for infection (Figs 4, 5) (2). The reported accuracy of combined WBC-marrow imaging over the years has been excellent, ranging from 88% to 98% (10,11,15,16,21–26).

Teaching Point

The discordant manifestation of osteomyelitis on WBC images versus marrow images is related

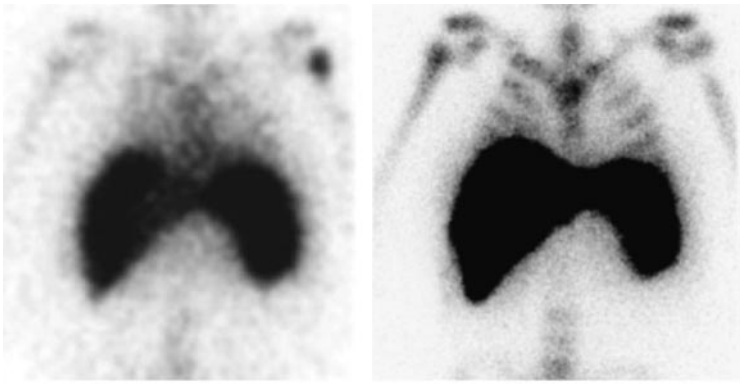


Figure 4. Osteomyelitis of the left humerus. **(a)** WBC image shows focally increased activity in the proximal left humerus. **(b)** Marrow image reveals a photopenic defect in the same region.

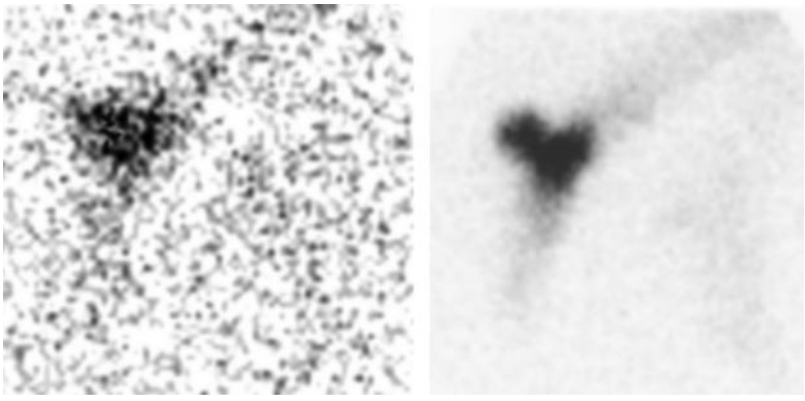


Figure 5. Localized marrow expansion. WBC **(a)** and marrow **(b)** images show increased activity in the right hindfoot. There was no obvious reason for this localized marrow expansion.

to the evolution of the disease itself. Micro-organisms localize in the bone by means of hematogenous seeding, direct inoculation, or extension from a contiguous focus of infection. Once in the bone, the bacteria proliferate and cause an influx of inflammatory cells, predominantly neutrophils initially, which accounts for the presence of increased activity on WBC images. Within 48 hours of bacterial seeding, entrapped bone begins to undergo necrosis and abscess formation. Simultaneously, marrow edema and vascular congestion develop, producing increased intraosseous pressure, small vessel thrombosis, reduced oxygen tension, and low pH (27). The combination of low oxygen tension, acidic pH, vascular insufficiency, and elevated intraosseous pressure suppresses or destroys the bone marrow phagocytes; consequently, uptake of sulfur colloid does not occur (28).

Imaging Technique

There are a variety of ways to perform combined WBC-marrow imaging. The precise method used depends on, among other factors, available equipment and may vary from one institution to another. Thus, the protocols that follow are offered as general suggestions, albeit ones that, in our experience, have yielded very satisfactory results over the years (29). Patients should be injected with 10 mCi (370 MBq) of freshly prepared technetium 99m (^{99m}Tc) sulfur colloid. Using preparations more than 2 hours old may result in persistent blood pool and urinary bladder activity, both of which degrade image quality. The interval between injection and imaging should be at least 30 minutes to maximize radiotracer clearance from the circulation. Ten-minute images of the region of interest are acquired with a gamma camera having a large field of view with use of a 128×128 matrix.

^{111}In-labeled WBC imaging is a 2-day procedure. The cells are labeled and reinjected on the 1st day, and images are acquired about 24 hours later. Marrow imaging can be performed either at the time of WBC labeling or immediately after completion of WBC imaging. If marrow imaging is performed prior to the injection of ^{111}In-labeled WBCs, a low-energy, high-resolution parallel-hole collimator and a 15%–20% window centered on 140 keV should be used. If marrow imaging is performed after WBC imaging, a 10% window centered on 140 keV should be used; the rest of the acquisition parameters can remain unchanged. Alternatively, simultaneous dual isotope imaging

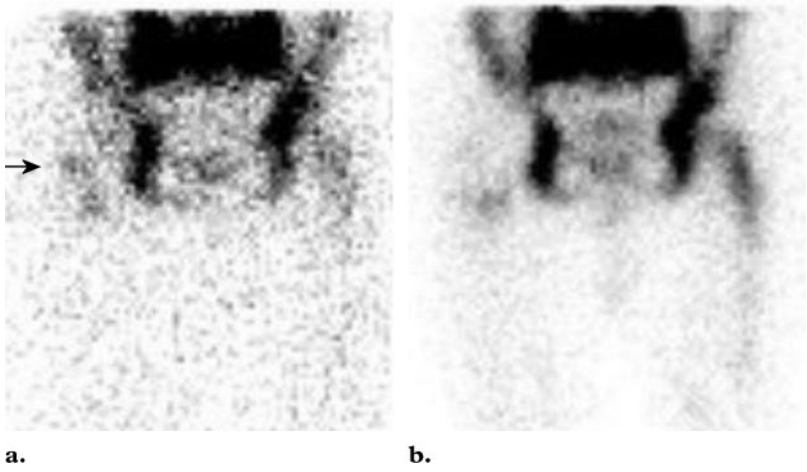


Figure 6. Infected left hip replacement. **(a)** Posterior WBC image shows minimal periprosthetic activity in the intertrochanteric region of a left hip prosthesis (arrow), a finding that would be interpreted as normal. **(b)** Marrow image shows no corresponding activity in the intertrochanteric region; consequently, the combined study is positive for infection. (Fig 6 reprinted, with permission, from reference 30.)

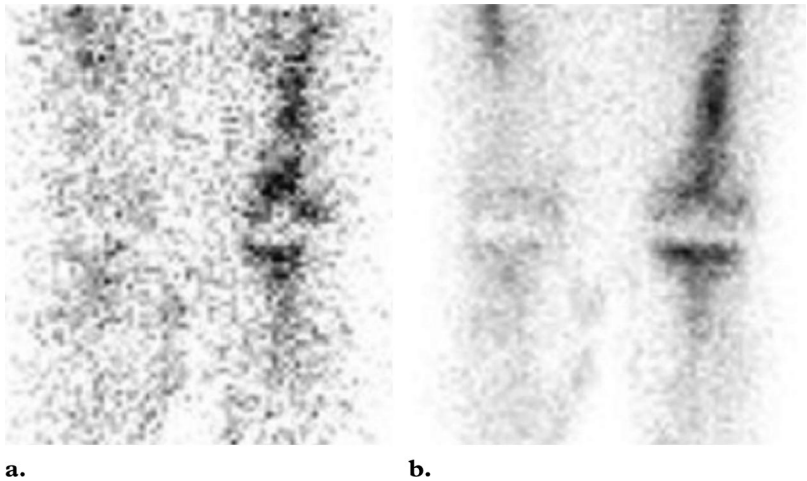


Figure 7. Aseptically loosened left knee replacement. WBC **(a)** and marrow **(b)** images show intensely increased activity around the femoral and tibial components of a left knee prosthesis. The combined study is negative for infection.

can be performed. A medium-energy parallel-hole collimator is used, with a 10% window centered on 140 keV, a 5% window centered on 174 keV, and a 15% window centered on 247 keV. Again, images should be acquired at 10 minutes per view with a 128 × 128 matrix.

Although the accuracy of the test remains largely unchanged regardless of when marrow imaging is performed, there are advantages to performing marrow imaging after WBC imaging. First, if there is no activity in the region of interest on WBC images, marrow imaging need not be performed. In addition, simultaneous dual isotope imaging can be performed, allowing more precise comparison of WBC images and marrow images as well as image fusion, thereby facilitating study interpretation.

The use of ^{99m}Tc-labeled WBCs rather than ^{111}In-labeled WBCs necessitates some modifications of the procedure. Persistent and potentially confounding activity on both WBC images and marrow images can be observed up to 48 hours after injection. Therefore, when ^{99m}Tc-labeled WBCs are used, WBC imaging and marrow imaging should be performed at least 48 hours, and preferably 72 hours, apart.

Indications

Prosthetic Joint Infection

Exactly why hematopoietically active marrow develops around joint prostheses is uncertain. This phenomenon may be due, in part, to displacement of the marrow during the implantation process. Perhaps the intramedullary component of the prosthesis stimulates the conversion of fatty marrow into hematopoietically active marrow. Aseptic loosening is frequently accompanied by an intense inflammatory reaction, which may also stimulate the conversion of fatty marrow into hematopoietically active marrow (18,30). Regardless of the explanation, insertion of a joint prosthesis can produce alterations in the normal distribution of the bone marrow (31). WBC-marrow imaging allows this problem to be overcome and permits the accurate assessment of whether infection is present (10,11,21,26). When interpreting

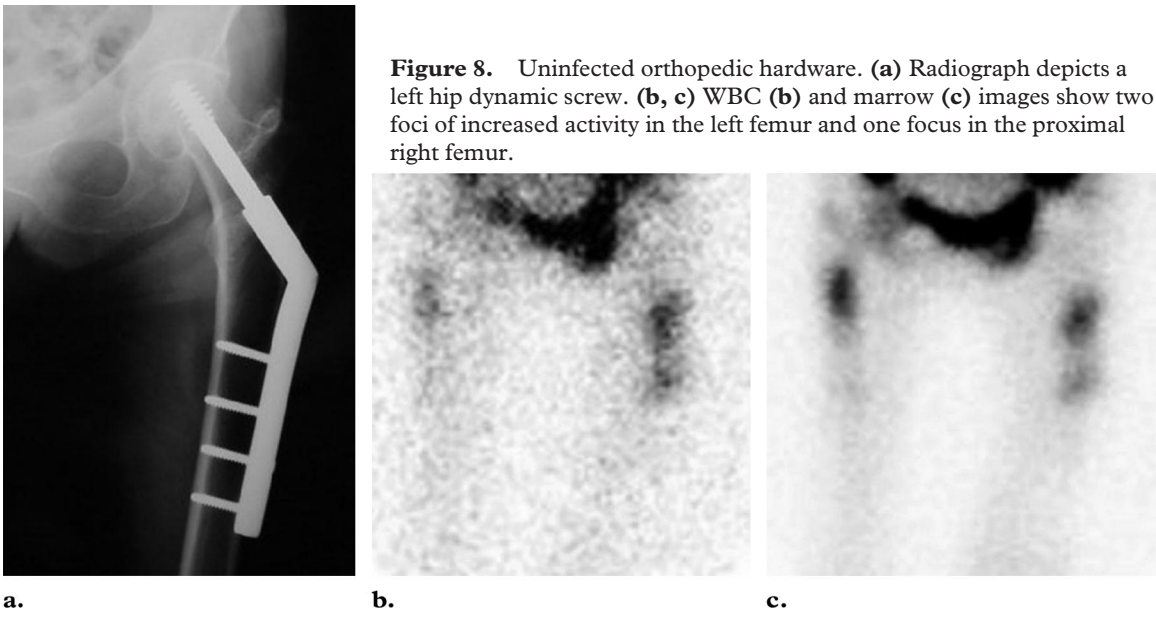


Figure 8. Uninfected orthopedic hardware. **(a)** Radiograph depicts a left hip dynamic screw. **(b, c)** WBC **(b)** and marrow **(c)** images show two foci of increased activity in the left femur and one focus in the proximal right femur.

a. **b.** **c.**

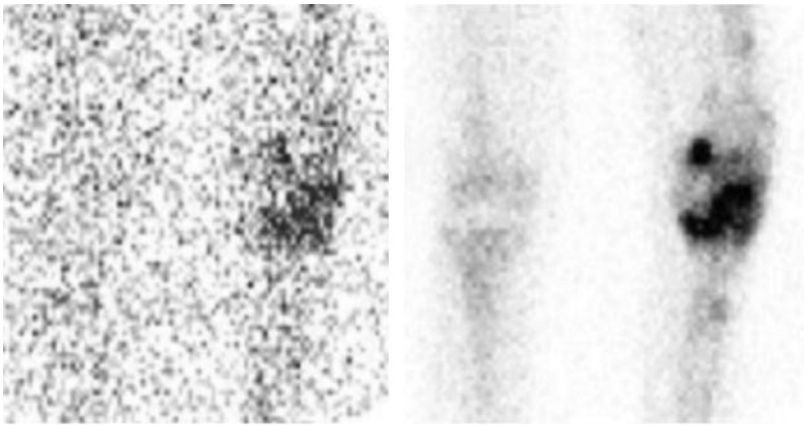


Figure 9. Uninfected fracture of the distal left femur in the same patient as in Figure 3b and 3c. WBC **(a)** and marrow **(b)** images show increased activity at the site of the fracture. Labeled WBC uptake in uninfected fractures is probably due, at least in part, to the presence of hematopoietically active marrow, which is part of the reparative process.

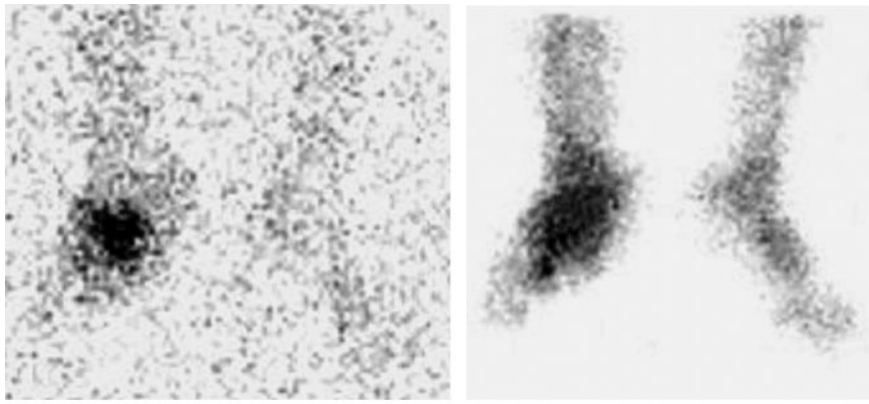
a. **b.**

these studies, it is important to recognize that the spatially incongruent zone is almost always located in or around the joint space and that the intensity of periprosthetic labeled WBC activity should not be considered. Only studies that demonstrate activity on the WBC image without corresponding activity on the marrow image should be interpreted as positive for infection (Figs 6, 7).

Although uptake of labeled WBCs around uninfected prostheses is now well recognized, this phenomenon has also been described in association with other types of orthopedic hardware, and WBC-marrow imaging can allow differentiation between infection and marrow in these situations as well (Fig 8) (16,22,23).

Fractures

Labeled WBC accumulation in uninfected fractures has been described and has often been attributed to inflammation (32). However, the inflammatory response that accompanies a fracture is polymorphonuclear only in its earliest phase (33). The poor sensitivity of WBC imaging for detecting inflammatory and infectious conditions in which the cellular response is other than neutrophilic is well documented; thus, it is unlikely that labeled WBC accumulation in uninfected fractures is due solely to inflammation. The sequence of events in new bone formation includes *(a)* cartilage formation and maturation, *(b)* invasion of the newly formed cartilage by blood vessels and marrow precursors, and, eventually, *(c)* the formation of bone and bone marrow. Bone marrow is intimately involved in fracture repair (13,33). Thus, labeled WBC accumulation in uninfected fractures is probably due, at least in part, to the presence of hematopoietically active marrow (Fig 9).



a. b.

Figure 10. Uninfected neuropathic joint in a diabetic patient. WBC **(a)** and marrow **(b)** images show increased activity in the right midfoot.

Neuropathic Joint

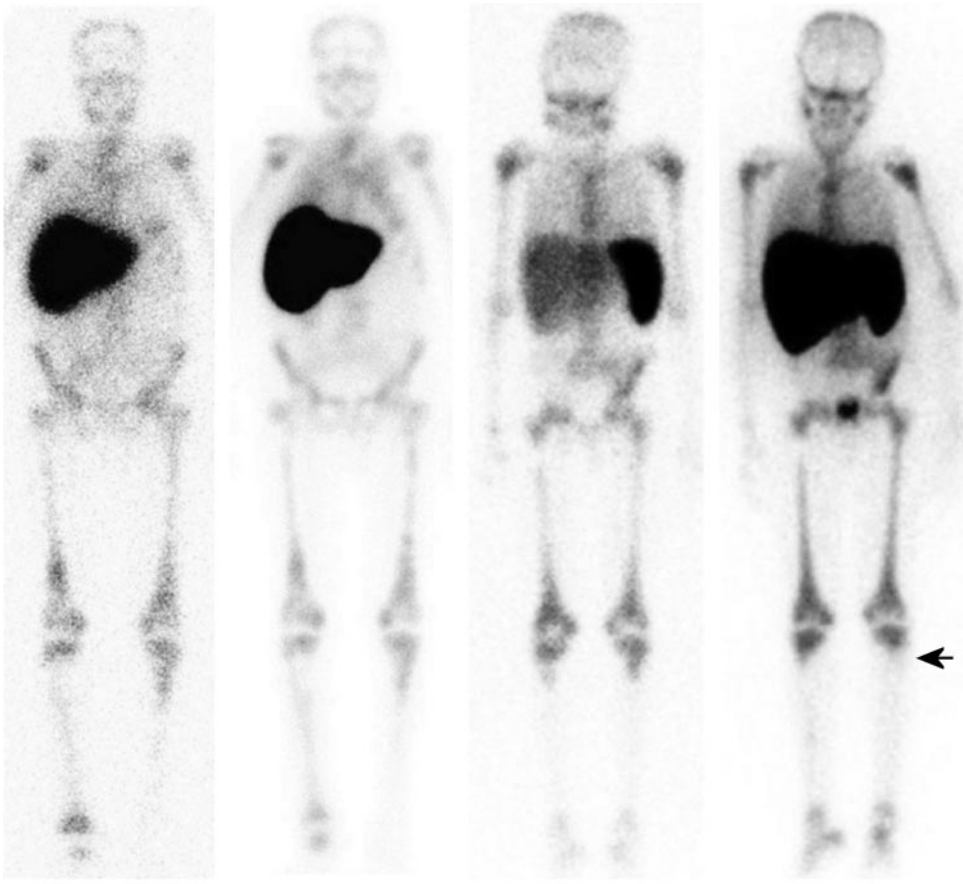
The neuropathic (Charcot) joint is most often associated with diabetes mellitus. At least 35% of all diabetic patients develop a neuropathy, and approximately 5% will eventually develop a neuropathic joint, usually between the 5th and 7th decades of life. The foot is the most common site. The tarsal and metatarsal (Lisfranc) joints are affected in about 60% of cases, the metatarsal phalangeal joints in about 30%, and the tibiotalar joint in about 10%. Repetitive stress on an insensitive foot leads to bone and joint disruptions, valgus or varus deformities, and joint instability, which in turn lead to joint degeneration, subluxation, and, eventually, destruction. The endless cycle of injury, destruction, and incomplete healing results in a grossly deformed foot. Pain is often absent, and when present it is typically not proportional to the appearance of the foot at gross examination. Synovial effusions are generally noninflammatory or hemorrhagic and are composed predominantly of mononuclear cells (34).

At one time, labeled WBC accumulation in the uninfected neuropathic joint was attributed to the inflammation, fractures, and reparative process that are part of the disease process itself. However, the synovial effusions present in the Charcot joint are not usually inflammatory; moreover, the cells present in these effusions are predominantly mononuclear. As mentioned earlier, the inflammatory response that accompanies fractures is polymorphonuclear only in its earliest phase (33).

There are data that suggest that labeled WBC accumulation in the uninfected Charcot joint is related to the presence of hematopoietically active marrow (15). Exactly why functioning marrow is present in such an unusual location is unclear. Perhaps the development of hematopoietically active marrow is part of the arthropathy itself. The conversion of fatty marrow into hematopoietically active marrow in induced arthritis of the lower extremities has been observed in animals, possibly as a result of increased cytokine activity (18). A similar process may occur in the Charcot joint. Fractures are an integral part of the neuropathic joint, and the bone marrow is intimately involved in fracture repair (33), which may also account for the presence of marrow in the neuropathic joint. Regardless of the explanation, it is important to recognize that labeled WBC accumulation in the uninfected neuropathic joint does occur and that this uptake is related to the presence of hematopoietically active marrow (Fig 10).

Systemic Diseases

Generalized marrow expansion is a response to a systemic process and can be seen in anemias such as sickle cell disease and end-stage renal disease, tumors, and other myelophthisic states such as Gaucher disease. The extensive, and often irregular, marrow expansion that is associated with



11a. 11b. 12a. 12b.

Figures 11, 12. **(11)** Gaucher disease in a patient who had previously undergone splenectomy. **(a)** WBC image shows asymmetric activity in the lower extremities. It would be difficult to exclude osteomyelitis of the proximal left tibia and right ankle. **(b)** Marrow image demonstrates virtually identical findings. The abnormalities in this case are the areas of decreased activity, which are due to marrow infiltration by Gaucher cells. **(12)** Bone infarctions and osteomyelitis in a patient with sickle cell disease. **(a)** On a WBC image, the most obvious abnormalities are areas of decreased activity in the right hemipelvis, proximal right femur, and proximal right tibia, all of which findings are consistent with infarctions. **(b)** Marrow image demonstrates similar findings in the right side of the pelvis and the right femur and tibia. Note, however, the absence of activity in the proximal left tibia (arrow). If the marrow image had not been obtained, the proximal left tibial focus of osteomyelitis could easily have gone unrecognized on the WBC image.

these conditions can cause difficulties in the interpretation of labeled WBC images obtained in patients with suspected musculoskeletal infection (Figs 11, 12) (2,16).

Miscellaneous Conditions

A variety of conditions are associated with an atypical distribution of hematopoietically active marrow, which potentially can confound the interpretation of WBC images. For example, in hyperostosis frontalis interna, there is an increase in the diploic space that is accompanied by an increase in marrow, which probably accounts for the increased calvarial activity that has been observed on WBC images. The symmetric appearance of this increased activity is useful for distinguishing hyperostosis from infection. However, not all cases of hyperostosis are symmetric,

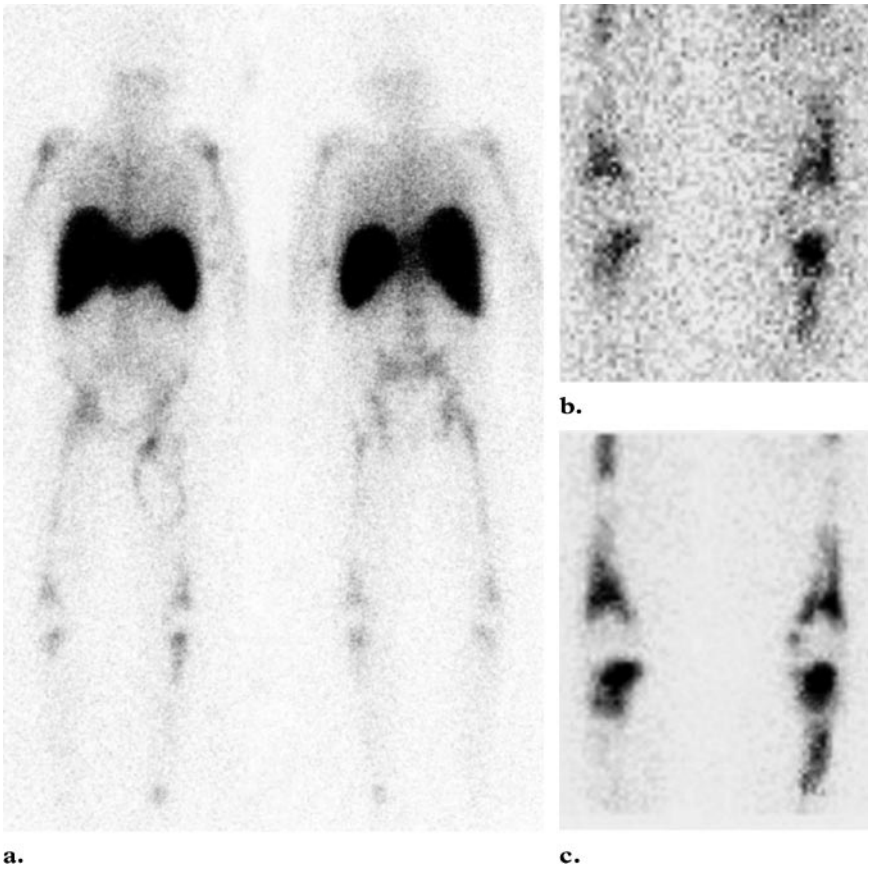


Figure 13. Infected vascular graft in a hemodialysis patient. **(a)** Anterior (left) and posterior (right) WBC images show increased activity in an infected left femoral vascular graft. Generalized marrow expansion is also present. Note the asymmetric activity in the long bones of the lower extremities. **(b, c)** WBC **(b)** and marrow **(c)** images show a virtually identical distribution of activity in the distal femurs and proximal tibias. The distal distributions of the two radiotracers were also identical.

and in these cases, marrow imaging is useful (17). Other conditions in which marrow may be present include myositis ossificans progressiva, traumatic myositis ossificans, and neurogenic heterotopic ossification, collectively referred to as heterotopic ossification (35). WBC-marrow imaging has numerous applications and can be used anytime there is doubt about the significance of osseous activity on WBC images (Fig 13).

Limitations and Pitfalls

WBC-marrow imaging has proved to be a very reliable test for diagnosing osteomyelitis. Nevertheless, there are certain limitations and pitfalls of which individuals responsible for interpreting the test should be aware.

Absent WBC Response

Teaching Point

If WBCs do not migrate to the site of infection, marrow imaging will not contribute any additional information. This is especially true in the spine, where osteomyelitis frequently manifests as an area of photopenia on labeled WBC images (36).

Duration of Infection

Animal study data suggest that the marrow image becomes photopenic within about 1 week after the onset of infection (19). Although this has not proved to be a problem in the evaluation of joint prostheses or the neuropathic joint, there are no human study data that indicate how soon after the onset of osteomyelitis photopenia appears on the marrow image. Consequently, these studies should be interpreted cautiously in the acute setting.

Lymph Node Activity

Teaching Point

Labeled WBC accumulation in lymph nodes, especially in the groin region, can confound image interpretation by producing incongruent WBC-marrow images. However, careful examination of the images usually reveals that the incongruent areas are round, discrete, multiple, linear in distribution, and frequently bilateral (Fig 14).

Sulfur Colloid Preparation

Teaching Point

The importance of sulfur colloid preparation to the accuracy of combined WBC-marrow imaging cannot be overemphasized. Sulfur colloid that has been improperly prepared or is more than about 2 hours old can degrade image quality and may lead to erroneous conclusions.

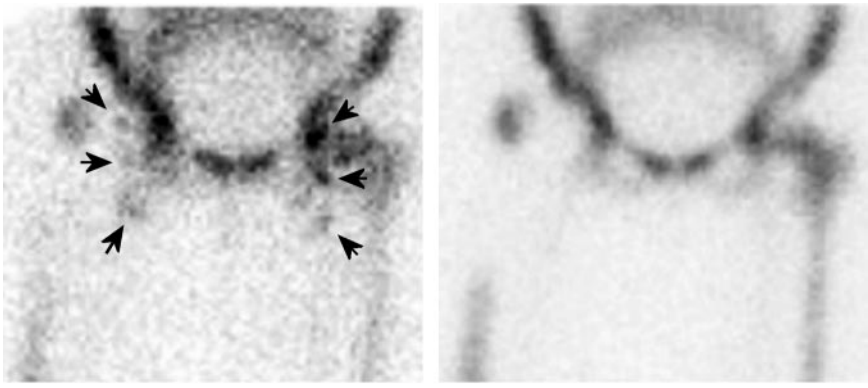


Figure 14. Nodal uptake of labeled WBCs. **(a)** WBC image shows multiple small, punctate foci in a linear distribution along the medial aspects of both hips (arrows). **(b)** Marrow image shows no corresponding foci, and the combined study could erroneously be interpreted as consistent with infection. An aseptically loosened right hip replacement was revised. There was no evidence of infection.

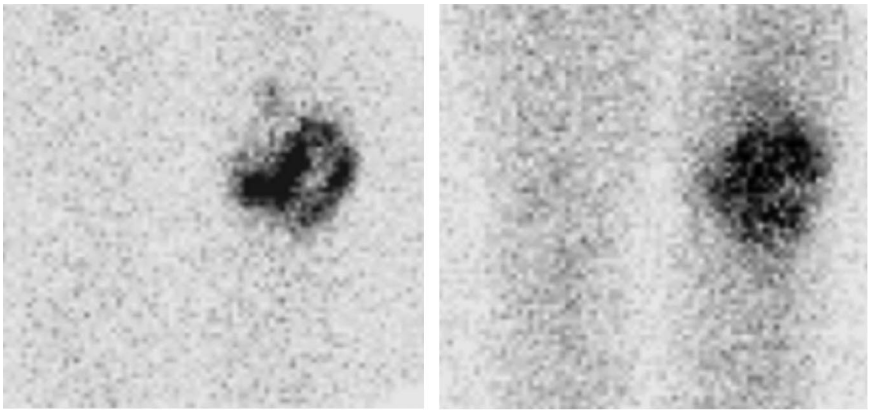


Figure 15. Septic arthritis. **(a, b)** WBC **(a)** and marrow **(b)** images show diffusely increased activity in the left knee. The study could be interpreted as negative for infection. **(c)** Pelvic marrow image shows considerable bladder activity, which indicates presence of unbound pertechnetate, rendering **b** uninterpretable. Use of bladder imaging with the routine marrow imaging protocol is a simple quality control procedure.

In addition to using freshly prepared sulfur colloid, routinely obtaining a 5-minute image of the pelvis, including the urinary bladder, is a useful quality control measure (Fig 15).

Conclusions

Combined WBC-marrow imaging is a very accurate technique for diagnosing osteomyelitis. Although most published work has focused on the prosthetic joint, the indications for WBC-marrow imaging are far more diverse. A thorough knowledge of the criteria for image interpretation and of the limitations and pitfalls of WBC-marrow imaging, combined with careful attention to the method used, will maximize the value of this technique.

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Combined Labeled Leukocyte and Technetium 99m Sulfur Colloid Bone Marrow Imaging for Diagnosing Musculoskeletal Infection

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Consequently, generalized and localized expansion of hematopoietically active marrow may produce unusual, even bizarre patterns of activity, in terms of both intensity and distribution, on WBC images. These alterations in marrow distribution complicate the interpretation of WBC images because it is difficult to determine whether WBC activity represents infection or merely hematopoietically active marrow in an unexpected location (Fig 3) (2).

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The WBC-marrow study is positive for infection when there is activity on the WBC image without corresponding activity on the marrow image; in other words, the images are spatially incongruent. When any other pattern is present, the study is negative for infection (Figs 4, 5) (2).

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If WBCs do not migrate to the site of infection, marrow imaging will not contribute any additional information.

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Labeled WBC accumulation in lymph nodes, especially in the groin region, can confound image interpretation by producing incongruent WBC-marrow images.

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Sulfur colloid that has been improperly prepared or is more than about 2 hours old can degrade image quality and may lead to erroneous conclusions.