

Editorial: What Is the Best Method For Imaging Focal Infections?

In a series of publications from the Massachusetts General Hospital (MGH) (1-4), a new agent was proposed for the scintigraphic detection of foci of infection. Human nonspecific polyclonal immunoglobulin (hIgG) (prepared commercially for intravenous therapeutic use and conjugated with diethylenetriamine pentaacetic acid (DTPA) carboxycarbonic anhydride) was labeled with indium-111 (^{111}In) and administered intravenously (1.75 mg protein, 1.5 mCi ^{111}In) (4). Gamma camera images at 6, 24, and 48 hr successfully demonstrated various foci of infection. In a series of 128 patients, there were 58 true-positives, including 12 skeletal infections, 5 false-negatives and no false-positives. However, in 16 other patients with cancer but without infection, focal localization occurred in 13. These workers found this agent effective in demonstrating vascular graft infections (3). Because there was no normal gastrointestinal excretion, it also was useful for delineating inflammatory bowel disease. Adverse reactions even from continued therapeutic use of intravenous immunoglobulin, human (Sandoglobulin) occur in < 1% of patients who are not immunodeficient, according to the manufacturer. Reactions from minute doses of 1-2 mg, therefore, should be extremely rare.

In this issue, Oyen et al. (5), found that imaging with hIgG was a valuable supplement to technetium-99m (^{99m}Tc) MDP imaging for inflammatory bone lesions, particularly in chronic osteomyelitis. The hIgG was conjugated with the cyclic dianhydride of DTPA for labeling with ^{111}In . These authors emphasized the progressive accumulation of this agent in the lesions up to 48 hr. They observed uptake in sterile inflammatory arthritis, hematoma, and recent fractures, as well as in infectious bone or joint disease.

Oyen et al. (5), stated that the mechanism of IgG uptake at the inflammatory site has not been fully elucidated as yet. In 16 of their patients, they observed a higher degree of uptake with ^{111}In nonspecific IgG than with ^{111}In -white blood cells. In a rat model of focal deep soft-tissue infections induced with gram-negative bacteria, the investigators at MGH (1) observed good localization of intact nonspecific IgG and Fc fragments, but minimal localization of Fab fragments. Consequently, they postulated that nonspecific IgG may bind to the Fc receptors of circulating leukocytes and macrophages. There is enhanced expression of Fc receptors in the presence of focal inflammation. Nonetheless, it is possible that the low uptake of the Fab fragments could have been due to their rapid clearance by the kidneys. Moreover, the relative competition of the labeled IgG and the large quantities of endogenous glob-

ulin in the circulation for the Fc receptors of leukocytes and platelets is not known. In this rat model, these investigators observed also that the lesion localization of nonspecific IgG was superior to that of ^{99m}Tc -human serum albumin (HSA) and ^{67}Ga -citrate (2). The localization of ^{125}I -labeled nonspecific IgG was slightly less than that of ^{111}In -labeled material at 3 and 24 hr. It would be interesting to study the distribution of activity in the plasma and various blood cellular components after the administration of ^{111}In nonspecific IgG in both animals and patients.

As yet, there is little additional information on the merits of nonspecific IgG relative to other agents. The localization of ^{111}In -IgG, ^{131}I -albumin, and ^{99m}Tc -leukocytes was studied in a sterile inflammatory reaction in rabbit muscle (6). At 18 hr, the inflamed-to-normal muscle ratio by direct tissue radioassay was only slightly better with IgG than albumin (1.6 versus 1.4), and best with leukocytes (2.7). These results, however, might have been different in infectious inflammatory lesions as opposed to a sterile inflammatory reaction. Buscombe et al. (7) compared images at 1, 4, and 20 hours with ^{99m}Tc -labeled hIgG and ^{111}In -oxine labeled leukocytes in patients with intraabdominal sepsis or inflammatory bowel disease. Images were positive with both agents in eight patients, but in a ninth patient, only the labeled leukocyte study was positive. The disadvantages of the ^{99m}Tc agent were the presence of some unbound ^{99m}Tc activity in the kidney and bladder, precluding the detection of urinary infections, and the prolonged retention of the bound activity in the blood resulting in high background surrounding the lesions.

With ^{111}In -oxine or tropolone-labeled leukocytes, the sensitivity of detection of osteomyelitis has varied from 50%–95% in different reports (9). One frequently quoted series of 32 patients (10) with suspected musculoskeletal low-grade sepsis included 30 with the diagnosis established after surgery by histology and bacteriology. In the remaining 12 patients, surgery was not needed. Sequential Tc-Ga imaging had a sensitivity of detection of 56% and a specificity of 78%. The criteria of a positive test were spatially incongruent images or a more intense uptake with gallium than with technetium. In contrast, imaging with ^{111}In -tropolone labeled leukocytes had a sensitivity of 83% and a specificity of 94%. Here, the criterion of a positive test was a higher uptake within the bony lesion than in the surrounding bone.

In another series of 50 patients with suspected infected prostheses (9), there were 22 true-positives and 1 false-negative with ^{111}In -oxine leukocytes, or a sensi-

tivity of 95%. There were 18 false-positives, however, due to aseptic chronic inflammation, osteonecrosis, loosening of prostheses, rheumatoid arthritis, nonunion fractures, osteosarcoma, Paget's disease, and even some metastatic carcinomas and lymphomas. Kim et al. (11) cautioned that patients with suspected osteomyelitis complicating fracture may have mild to moderate uptake of labeled leukocytes in many types of lesions. Intense focal uptake was the most reliable indication of osteomyelitis. In another study (12), the combination of ^{99m}Tc -MDP and ^{111}In -leukocyte images was the best means of detecting osteomyelitis complicating nonunion fractures, compared with ^{67}Ga . The best criterion of positivity was the localization of ^{111}In within the bone at the fracture site.

When the regulatory barriers are cleared in the U.S., other agents used in Europe and elsewhere will be useful alternatives in certain types of clinically suspected sepsis. The best ^{99m}Tc -leukocyte labeling agent to date is probably, *d*,1-hexamethylpropyleneamine oxime (HM-PAO), originally developed for brain imaging. In an experimental comparison with ^{111}In -oxine labeled leukocytes in dogs with *E. coli* soft-tissue abscesses (13), images of some animals with HM-PAO leukocytes showed excellent localization whereas others were poor or negative, probably due to batch variations. The mean abscess concentration of technetium by tissue radioassay at 24 hr was only approximately one-third of that obtained with indium. Mock et al. (14), studied leukocytes labeled with Tc-HM-PAO and ^{111}In -tropolone in dogs with induced tibial osteomyelitis at 2 and 4 wk. In some experiments, the results of the two agents were comparable, but in others, the recovery of technetium in the blood was lower, probably due to a variation in the radiopharmaceutical from batch to batch. The percent administered dose in the bone lesion measured by gamma camera imaging in comparison with an external standard was ~30%–40% lower with technetium than with indium.

Technetium-99m-HM-PAO-labeled leukocytes as well as ^{111}In -tropolone labeled cells had a high sensitivity in the diagnosis of osteomyelitis imaged at 4 and 20 hr in a clinical study at the Hammersmith Hospital (15). These workers routinely performed colloid imaging as well. Thus, when the intensity on the leukocyte image was greater than the intensity in the colloid image, the study was considered positive for osteomyelitis. The manufacturers of the HM-PAO kit found that 0.4 mg sodium iodide added to pertechnetate eluate immediately after elution before adding to the kit greatly delayed the spontaneous conversion of the lipophilic complex to pertechnetate in vitro, at least for 1 hr (16). It is possible that this step may improve the reliability of leukocyte labeling with this agent.

A very small particle ^{99m}Tc -labeled colloid of HSA [Nanocoll, Solco, Basel, Switzerland] localizes well in

the hematopoietic bone marrow. Approximately 86% of these particles are 30 nm in diameter or smaller and the remainder between 30–80 nm (17). In animals, it demonstrated abscesses better than microcolloids of serum albumin with a larger particle size [0.2–0.3 μm]. The rationale for its efficacy in foci of infection is merely increased capillary permeability permitting diffusion of the small colloidal particles similar to macromolecules. Unlike macromolecules, however, the blood clearance is faster so that imaging may be completed within 4 hr. Thereafter, activity may appear in the gastrointestinal tract probably from spontaneous oxidation to pertechnetate. It has been claimed (18) that the sensitivity for detection of osteomyelitis in the extremities with nanocolloid at least equals that of labeled leukocytes. In another study (19), 30-min nanocolloid images were compared with delayed ^{67}Ga images in 39 patients with suspected bone or joint infections. A higher sensitivity and specificity were found with the nanocolloid. This was the agent which provided the quickest answer, but could not differentiate between sterile and septic inflammatory lesions.

An antigranulocyte IgG₁ monoclonal antibody designated BW 250/183 produced by Behringwerke, Marburg, FRG, binds to an antigen NCA-95, a 95kD surface glycoprotein present on almost all human granulocytes and is not cytotoxic after cell binding. It is an anti-carcinoembryonic antigen [anti-CEA] MAb, which was originally developed by Mach's Group and designated MAb 047 (20). In clinical studies (21), 75–150 μg MAb labeled with 8 mCi ^{99m}Tc were directly injected intravenously. The half-time of disappearance from the blood was ~6 hr. The initial uptake in the lungs cleared by 4 hr. Approximately 10% of the injected dose remained in the spleen, and 17% remained in the liver. Activity in the marrow also was visible on the images. Approximately 26% of the circulating activity was granulocyte-bound. Unlike ^{99m}Tc -HM-PAO, there was no activity normally in the GI tract. Many abscesses were detected in images at 4–6 hr. If these images were negative, however, they were repeated at 24 hr. The localization of this MAb in abscesses could be due, at least in part, to binding of free circulating MAb to viable or damaged granulocytes already localized at the abscess site.

In another series of 54 patients with suspected bone infection (22), ^{99m}Tc -HM-PAO labeled leukocytes were compared with the ^{99m}Tc -antigranulocyte MAb, and ^{99m}Tc -nanocolloid studies were performed in 15 of these patients. There was no great difference in the results between these three agents. However, the sensitivity was relatively low (68%) because of false-negatives in infectious spondylitis compared with infections of the extremities. The specificity also was low (63%), due to long-standing lesions undergoing remodelling.

In spontaneous osteomyelitis unassociated with

trauma or previous surgery and including the acute hematogenous form in childhood, the diagnosis is usually evident on three-phase diphosphonate images alone. However, infection complicating fractures, previous surgery, prostheses or diabetes often requires imaging with other agents and other modalities besides radiography and scintigraphy. In a series of 22 patients with suspected osteomyelitis after previous surgery or fracture (23), magnetic resonance imaging (MRI) was compared with ^{111}In -tropolone labeled leukocyte images. An additional 15 patients with suspected acute osteomyelitis or soft-tissue infection had MRI without labeled leukocyte images. The overall sensitivity of MRI was 92%, and soft-tissue lesions were better demonstrated than by radiography or CT. In patients with previous surgery or fracture, it was difficult to differentiate those with and without infection by MRI. In these patients, ^{111}In -leukocyte images were more specific.

In later publications on MRI in osteomyelitis, increased signal in the lesion was noted on T_2 -weighted, short T_1 , inversion recovery (STIR) or gradient-echo fast low-angle short (FLASH) images, as well as decreased signal with T_1 -weighted images (24). The advantages of MRI are its ability to differentiate actual marrow involvement from inflammation in adjacent soft tissue and its demonstration of sinus tracts and sequestra (24) because of its superior spatial resolution compared to scintigraphy with MDP. Some authors (24) found that neither MDP nor MRI could consistently distinguish healing fractures or neoplasms from osteomyelitis, whereas others believed that infection complicating previous trauma could be discerned by increased signal on T_2 -weighted images (25). MRI was recommended in evaluating the feet of diabetic patients because the incidence of false-positive diagnoses of osteomyelitis is high on MDP images, due to cellulitis, chronic ulcers, trauma, or neuroarthropathy (26).

In a series of dogs with one-day-old *E. coli*-induced gluteal abscesses in our laboratories in Syracuse (as yet unpublished), detecting small abscesses with unenhanced CT proved difficult, but this was improved in contrast-enhanced images. In T_1 -weighted MR images performed on a two-tesla CSI Unit, the lesions seen as decreased signal were more obvious than by CT, but it was difficult to distinguish abscess from surrounding edema. This differentiation was greatly improved by repeat T_1 -weighted imaging after gadolinium-DTPA (Magnevist, Berlex Imaging) thereby showing the lesion as increased signal. On T_2 -weighted images, the abscess and surrounding edema could be distinguished by a brighter signal in the abscess itself. The contrast between abscess and normal surrounding muscle tissue however was higher on planar ^{111}In -oxine leukocyte images, and even higher yet on SPECT images.

CONCLUSIONS

Detecting foci of infection remains important for clinical management despite the proliferation of new antibiotics. Long ago, experimental pathologists found that many dye indicators localize in these foci due to increased capillary permeability. Many substances labeled with radioactivity will do likewise, and the search for better agents continues.

The most suitable agent for inflammatory foci may vary under different clinical conditions and in different institutions. At present, ^{111}In -labeled leukocytes reach the highest known concentrations in these foci, but the techniques of harvesting and labeling these cells are time-consuming and must be carried out meticulously by experienced personnel to preserve cell viability. The best test of viability is to periodically measure the recovery of the radioactivity in the circulation, and the cellular and plasma distribution on centrifugation of a sample of blood 1–4 hr after the injection of the labeled cells. When the "ex vivo" time interval between blood withdrawal and cell reinjection exceeds 3 hr, the results are poor. There may be no agent worse than dead-labeled leukocytes for imaging these foci. The 24-hr interval before optimal visualization of the lesions is another disadvantage. With the Tc-99m agents summarized above, this elapsed time is shorter. We should not limit ourselves to any one agent or any fixed combination. I believe that the eventual role of labeled non-specific human globulin, HM-PAO labeled leukocytes, nanocolloid, or MAbs can be defined only after more comparative studies.

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