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EDITORIAL

Imaging of Inflammatory Sites in the 1990s: New Horizons

The anatomic localization of focal collections of inflammatory cells in the setting of acute or subacute infections or inflammatory states presents a major challenge to the clinician. The early and accurate detection of postsurgical infectious complications such as intra-abdominal absess, infection involving deep wounds suffered following major trauma and appendicitis would allow earlier therapy with antibiotics and surgical debridement. The availability of a rapid imaging technique for inflammatory cells would also aid in the diagnosis of skeletal infections, such as osteomyelitis, and in the evaluation of immunosuppressed patients who present with fever and subtle, but nonlocalizing signs of infection. Such a technique would also be very useful for diagnosing and assessing the response to therapy of inflammatory diseases such as ulcerative colitis, Crohn's disease, rheumatoid arthritis, systemic lupus erythematosus, the systemic vasculitidies and sacoidosis. Despite the fact that methods for imaging inflammatory and infectious lesions were developed as early as 1971 with ^{67}Ga scanning (*1*) and 1976 with the use of ^{111}In-labeled leukocytes (*2,3*), there as yet exists no widely available diagnostic test to clinicians for this purpose. This is particularly true in the detection of intra-abdominal sources of inflammation and infection.

The techniques currently in limited use for detecting inflammatory sites are:

1. Gallium-67 scanning.
2. Indium-111-labeled leukocytes.
3. Leukocytes labeled with ^{99m}Tc via phagocytic ingestion of colloid in the form of reducing agents such as stannous pyrophosphate, or via passive uptake by ^{99m}Tc-labeled lipophilic complexes.
4. Direct injection of ^{99m}Tc- or ^{111}In-labeled agents which localize at inflammatory sites such as anti-granulocyte antibodies, and polyclonal immunoglobulins.

Gallium-67-citrate was first noted to localize in inflammatory lesions in 1971 (*2,3*) and since that time has been useful in certain instances for the detection of infectious foci (*4*). The major problems with ^{67}Ga scanning are that at least 24 hr are required between injection and imaging, and that early bowel uptake precludes its use for evaluation of abdominal infections (*5–6*). Indium-111-labeled leukocyte scanning is recognized as a useful test for detecting inflammation and infection in vascular grafts, chronic pulmonary inflammation and certain abdominal afflictions including inflammatory bowel disease, pseudomembranous colitis, diverticulitis and bowel infarction (*7–10*). Although ^{111}In-labeled leukocytes do not normally localize in the bowel, false-positive images have been caused by gastrointestinal bleeding, swallowed leukocytes and multiple enemas (*9*). In a study of 312 scans from 271 patients with fever of unknown origin, 32 false-positive results of abdominal uptake were noted at 24 hr following injection due to gastrointestinal bleeding or swallowed leukocytes (*9*). Other disadvantages of ^{111}In-labeling are the expense and inconvenience of using ^{111}In and the radiation dose to the patient.

Various methods have been developed to label leukocytes with ^{99m}Tc instead of ^{111}In to improve image resolution and to decrease expense and radiation dose to the patient. Phagocytic uptake of ^{99m}Tc-labeled colloids or microspheres by neutrophils and monocytes has been used to this end (*11–13*). These methods require less blood from patients since no cell separation is required. Technetium-99m-albumin labeled colloid has been reported to localize appendiceal abscesses within 15 min to several hours depending on the clinical situation (*13*). The early activity (minutes) within the inflammatory site is due to the uptake of unphagocytized ^{99m}Tc-

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labeled colloid and not to localization of inflammatory cells. The problems with ^{99m}Tc-colloid labeled leukocytes include in vivo oxidation of the technetium to pertechnetate and obligate prior activation of the leukocytes from the phagocytic process leading to excessive early lung uptake.

In 1986, Peters et al. first described the use of ^{99m}Tc-hexamethylpropyleneamineoxime (HMPAO) to label leukocytes for imaging of abdominal inflammatory sites in six patients (*14*). All six patients showed positive scans, and most were positive within 30 min. HMPAO forms a lipid soluble complex with ^{99m}Tc which is passively taken up by leukocytes presumably by incorporation into the plasma membrane. For unknown reasons, the labeling of granulocytes is more stable than monocytes by this compound (*15*). The initial biodistribution of ^{99m}Tc-HMPAO labeled leukocytes is similar to ^{111}In-labeled cells except that activity is seen in the urine, occasionally the gall bladder, and consistently in the colon from 4 hr on (*15*). In a study of 100 patients with various types of inflammatory foci, 53 of which were referable to the abdominal cavity, the sensitivity of ^{99m}Tc-labeled leukocytes scanning was 100%, with a specificity of 95%, when measured 1–4 hr following injection (*16*). In a retrospective study of 43 consecutive patients, ^{99m}Tc-HMPAO-labeled leukocyte scanning gave an overall accuracy of 93.2%, a sensitivity of 92.8%, a specificity of 93.3% and a positive predictive value of 86% (*17*). These values were obtained 3–4 hr following injection of leukocytes. Imaging with ^{99m}Tc-HMPAO-leukocytes has been shown to be superior to gallium scanning (*18*), but not as specific as ^{111}In-labeled leukocytes for localizing intra-abdominal sepsis, due to the high number of false-positive scans noted at 24 hr secondary to physiologic bowel uptake (*19*).

In this issue of *The Journal of Nuclear Medicine*, Lantto and colleagues, in a systematic fashion, studied the efficacy of ^{99m}Tc-HMPAO-labeled leukocyte scanning at times ranging from 2 min to 4 hr in 80 patients (87 studies) with suspected intra-abdominal inflammation or infection. These investigators found that imaging within 2 hr from injection gave a sensitivity, specificity and accuracy of 95%, 85% and 92%. The 2-hr time point showed nonspecific bowel accumulation in 7% of the patients, but this was easily distinguishable from the pathologic activity. Imaging at 4 hr gave a higher specificity and accuracy than the 2-hr point, but was accompanied by physiologic bowel uptake in 28% of the patients. The mechanism of tracer accumulation at early time points was felt to be due to granulocyte localization rather than nonspecific blood-pool activity as assessed by injection of ^{99m}Tc-labeled RBCs. The preparation of labeled RBCs differed substantially from the WBC labeling insofar as less free ^{99m}Tc-HMPAO would be expected to be present in RBCs following density gradient centrifugation. These results will require confirmation using other methods. Nevertheless, this study clearly demonstrates that ^{99m}Tc-HMPAO-leukocyte scanning has high diagnostic value at 2 hr for imaging intra-abdominal sites of inflammation.

A major drawback still exists with the leukocyte labeling techniques in that blood must first be obtained from a patient, and skilled technical personnel must perform leukocyte separation prior to labeling. This requires more extensive facilities and specially trained personnel than is necessary for a prelabeled material which binds to leukocytes directly in vivo. Agents such as this include labeled monoclonal antibodies to granulocyte surface molecules (*20,21*), ^{111}In- and ^{99m}Tc-labeled polyclonal IgG (*22,23*), and the recently described ^{111}In-labeled chemotactic peptides (*24*). Studies with ^{99m}Tc-labeled monoclonal anti-granulocyte antibodies have been performed with imaging done between 2 and 6 hr following injection. One study of 34 patients using this type of agent showed a sensitivity of 95% but a reduced specificity of 85%, due predominantly to false-positive results obtained with postoperative hematomas (*21*).

During studies performed to evaluate the use of specific antibodies against bacteria to localize infections, it was found in control experiments that human polyclonal IgG labeled with ^{111}In also localized in areas of infection and inflammation (*22,23*). In a large study of 84 patients, a sensitivity of 92% and a specificity of 95% was obtained for imaging inflammatory foci (*23*). This tracer also localizes in primary and metastatic tumors. Imaging is done between 6 and 72 hr, and there is little nonspecific bowel uptake, making this scan useful for detection of intra-abdominal pathology. In addition, this scan has been efficacious for the detection of vascular graft infections (*25*). The mechanism of accumulation at inflammatory sites requires the Fc portion of the immunoglobulin molecule (*26*), but it has not been shown as yet to bind to leukocytes directly via Fc receptors. More experiments are needed to determine its mode of action. Studies have also been performed using ^{99m}Tc-polyclonal IgG, which have shown a similar specificity and sensitivity (*27*), although the two types of labeling procedures have not been compared in one study in the same patients.

Newer, potentially more specific avenues are being explored for imaging pathologic collections of inflammatory cells. Recent studies have shown that ^{111}In-labeled chemotactic peptide analogues are capable of imaging an experimentally induced infection in rats within 5 min (*24*). Safety testing of these agents is currently underway in primates. The ideal imaging agent for neutrophil or monocyte localization would be a high affinity antagonist which binds to a cell surface receptor (such as for chemotactic agents) of these phagocytes, but which does not activate the cells to produce untoward side effects. It may be possible in the future to diagnose particular types of inflammatory responses (granulomatous

versus neutrophilic versus eosinophilic) based on the specificity of the imaging agents used. The plethora of cytokines that act specifically on different cell types may be good candidates for such investigation.

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