INVITED COMMENTARY

Imaging Infection in Patients with Agranulocytosis

Agranulocytosis is a relatively uncommon disease, with an incidence of approximately 3.3 per one million population (*1*). The causes of granulocytopenia can be divided into 3 broad categories: peripheral destruction of polymorphonuclear cells, overwhelming sepsis, and generalized bone marrow failure from a hematologic cause (*2*). The most common specific cause is drug-induced antibodies that destroy autologous granulocytes (*2*). Analgesics; sedatives; antidepressants; anticonvulsants; antibiotics; and antipsychotic, antithyroid, and cardiovascular drugs are among the broad classification of pharmaceuticals that have been associated with agranulocytosis (*2*).

Clinically, 70% of granulocytopenic patients present with fever (*3*). The clinical signs of infection are often minimal. Wade et al. (*4*) estimated that in 20%–40% of febrile granulocytopenic patients, the fever is caused by drugs or a paraneoplastic reaction and not by infection. The usual treatment of agranulocytosis is to stop the offending drug and support the patient with antibiotic therapy and granulocyte–macrophage colony-stimulating factor when necessary. Agranulocytosis has 2 possible outcomes: The patient either recovers or succumbs to overwhelming sepsis. The time to recovery is variable but is usually from 3 to 56 d, with a mean of 12 d (*5*).

As imaging specialists, we are asked to evaluate and localize suspected infections in granulocytopenic patients. The first imaging technique is often an anatomic technique such as CT, MRI, or sonography. However, if an anatomic technique fails to detect the source of infection, the next imaging approach should be a physiologic technique such as ^{111}In-leukocytes or ^{67}Ga instead of a second anatomic imaging technique (*6*). Labeled leukocytes are generally considered the best physiologic agent for the evaluation of suspected infection; however, granulocytopenic patients have so few granulocytes that one would need to withdraw an impracticably large quantity of blood.

A second approach might be to use ^{67}Ga instead of ^{111}In-leukocytes. Most ^{67}Ga studies in immunosuppressed patients have been in AIDS patients. There seems to be general agreement that, in the thorax, ^{67}Ga provides excellent results (*7–9*). In a direct comparison of ^{111}In-labeled leukocytes and ^{67}Ga in febrile AIDS patients, Fineman et al. (*10*) found that ^{67}Ga was more accurate in the evaluation of infections of the thorax but that ^{111}In-labeled leukocytes were superior for infection outside the thorax because ^{67}Ga had a lower sensitivity there. Thus, a strong case can be made for the use of ^{67}Ga in immunocompromised patients. Palestro and Torres (*11*) stated in a recent review article, "In the immunocompromised population, typified by the AIDS patient, gallium scintigraphy is the radionuclide of choice for diagnosing opportunistic diseases."

Alternatively, one might consider monoclonal antibodies or chemotactic peptides, both of which are experimental in the United States, although antigranulocyte monoclonal antibodies are available in most of the rest of the world. Prvulovich et al. (*12*) studied the use of ^{99m}Tc-labeled antigranulocyte monoclonal antibody in 23 AIDS patients and found that 4 of 21 studies were true-positive for infection, all in patients with colitis, and that 2 of 2 studies were true-negative for infection. This result gave a sensitivity of only 24%. If one examines the 17 false-negative studies, one finds that 8 were of infection within the thorax, including 6 patients with *Pneumocystis carinii* pneumonia, 4 with bacteremia, and 5 with miscellaneous infections (*12*). Prvulovich et al. concluded that ^{99m}Tc-antigranulocyte antibody is not a good agent for studying suspected infection in these patients.

McDougall et al. (*13*) briefly mentioned a fourth approach, the use of ^{111}In-labeled donor leukocytes to evaluate infection in patients with granulocytopenia. McDougall et al. were studying ^{111}In-leukocytes in infection in general rather than in granulocytopenic patients in particular and described 1 study with true-positive results, 1 study with positive results but with the patient refusing further workup, and 2 studies with negative results not characterized further (*13*). More recent studies of donor or heterologous labeled leukocytes have contained between 5 and 14 patients. Thus, calculations of sensitivity and specificity are not meaningful; however, good results were reported for most of the studies (*14–18*).

In this issue of *The Journal of Nuclear Medicine,* Gratz et al. (*19*) report their well-designed study comparing autologous and heterologous ^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO)–labeled granulocytes in rabbits with *E. coli* infection. Autologous labeled granulocytes gave superior results to heterologous labeled granulocytes from a noninfected rabbit donor. In addition, heterologous labeled granu-

Received Jan. 9, 2002; revision accepted Feb. 9, 2002.

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locytes from an infected donor gave results identical to those of autologous labeled granulocytes. Gratz et al. speculate that "biologically active factors" may be present in the blood of infected patients, improving migration of the exposed granulocytes.

Gratz et al. (*19*) state that the use of radiolabeled donor leukocytes presents problems. They characterize the results reported in the literature as "suboptimal" and "mediocre" compared with imaging using labeled autologous leukocytes in human patients (*14–17*). Dutcher et al. (*14*) examined 14 granulocytopenic patients with known sites of infection and found localization of the donor leukocytes at all 14 sites. In addition, no false-positive areas of uptake were apparent in any patient (*14*). Schell-Frederick et al. (*15*) used ^{111}In-labeled leukocytes to study suspected infection in 117 cancer patients, including 5 imaged with donor leukocytes. In all 5 of the patients imaged with donor leukocytes, the correct result was obtained: true-positive in 2, true-negative in 1, and correct but not further characterized in the remaining 2. Anstall and Coleman (*16*) used donor leukocytes to examine 8 severely leukopenic patients and found 3 true-positive and 5 true-negative results. O'Doherty et al. (*17*) used donor leukocytes to examine 4 patients with AIDS and 7 other neutropenic patients. Three results were true-positive and 1 was true-negative in the AIDS patients, whereas 2 results were true-positive and 5 were negative but not clarified further in the neutropenic patients (*17*). Thus, combining these results gives 33 correct results in 33 patients and 5 negative results not clarified further, for an apparent accuracy of 100%.

In addition to the articles cited by Gratz et al. (*19*), the article by McDougall et al. (*13*) and another by Alavi et al. (*18*) have described the clinical use of labeled donor leukocytes. The latter study used labeled donor leukocytes to localize infection in 7 neutropenic patients and found good visualization for 2 patients, fair localization for 1 patient of 5 with proven infection, presumably true-negative results for 2 patients, and false-negative results for 2 patients (*18*). Alavi et al. separated the donor granulocytes using filtration leukapheresis, which they believed might have decreased the migratory ability of the granulocytes and thereby decreased the true-positive results (*18*). For 1 patient with negative study findings, the findings became positive when imaging was repeated using leukocytes derived from a different donor (*18*). The presence of "biologically active factors," as described by Gratz et al. (*19*), may explain why the second injection of donor leukocytes showed the infection whereas the original injection did not. Of course, the hypothesis of Alavi et al.—that decreased migration is caused by filtration leukapheresis—is equally plausible.

Combining the results of these 5 studies using donor leukocytes gives a total of 29 proven positive cases, 27 of which had positive results for labeled donor leukocytes (*14–18*). In the 14 patients studied by Dutcher et al. (*14*), the location of the infection was known before the study began, possibly biasing the results. If those 14 were excluded, the sensitivity would still be 13 of 15, or approximately 87%. Both false-negative results came from the study by Alavi et al. (*18*), who also reported problems with decreased migration caused by filtration leukapheresis, which was used to separate the granulocytes before labeling. Considering the exclusion of the 14 true-positive results of Dutcher et al. and the possible problem of false-negative results caused by filtration leukapheresis (*18*), the 87% sensitivity would seem to be a conservative estimate of the true sensitivity of labeled donor leukocytes.

How do the above results for labeled donor leukocytes compare with results for autologous labeled leukocytes? Using ^{99m}Tc-HMPAO–labeled leukocytes simultaneously with ^{111}In-tropolonate–labeled leukocytes, Weldon et al. (*20*) prospectively studied 50 patients with suspected intraabdominal abscess and found a sensitivity of 76% (13/17) and a specificity of 100% for each agent, with both giving identical results in all patients. The 4 false-negative results from both labeled leukocyte studies occurred in patients with "nonpurulent" liver abscesses (*20*). Using ^{111}In-labeled leukocytes, Knochel et al. (*6*) retrospectively studied 136 patients with suspected abdominal abscesses and found a sensitivity of 30 of 35, or 86%, and a specificity of 96 of 101, or 95%. Carter et al. (*21*) retrospectively studied 45 patients with suspected intraabdominal sepsis but without localizing signs. With the use of ^{111}In-oxine–labeled mixed leukocytes, sensitivity was 21 of 22 (95%) and specificity was 21 of 23 (91%) (*21*).

Although the analysis of labeled donor leukocytes in granulocytopenic patients is superficial and the numbers are small, these results appear similar to what one might expect with autologous labeled leukocytes. On the other hand, Gratz et al. (*19*) clearly show that, in rabbits, autologous labeled granulocytes gave better results than did heterologous labeled granulocytes from noninfected donors. Two explanations for this apparent discrepancy are plausible. The first is that the results of Gratz et al. are predictive of what may happen in humans. However, too few studies using labeled donor leukocytes in humans have been published to show the decreased sensitivity that is so obvious in the study of Gratz et al. on rabbits. Unfortunately, because the use of labeled donor leukocytes is uncommon, it is unlikely that a large, definitive prospective study on humans will ever be performed.

The other possible explanation is that the rabbit model is not totally analogous to the human model. The results of animal studies, although typically predictive of what we see when we perform similar studies on human beings, occasionally lead us astray. An example is ^{99m}Tc-3,4-dimethoxyphenylethylamine (DMPE), which seemed to be the first promising ^{99m}Tc-labeled cardiac perfusion agent when studied in mice and especially in dogs (*22–24*). In humans, however, ^{99m}Tc-DMPE proved inferior to ^{201}Tl; therefore, de-

velopment of ^{99m}Tc-DMPE was abandoned (*25–27*). In an attempt to better understand the development of a predictable ^{99m}Tc-labeled myocardial perfusion agent, Deutsch et al. (*28*) conducted the "Noah's Ark experiment." They looked at ^{99m}Tc-DMPE and a related compound in 10 different animal species to determine which species or combination of species would best approximate the experience in humans. They attempted to minimize loss of animal life without losing the ability to accurately predict human results. Unfortunately, no animal species or combination of animal species could successfully predict the results in humans.

Thus, the current literature on human donor leukocytes seems too limited to establish whether the sensitivity of donor leukocytes in detecting infection is decreased in granulocytopenic patients. Regardless, the results of Gratz et al. (*19*) contribute to a better understanding of the biokinetic mechanism of granulocyte migration. It seems so intuitive that the in vivo environment of leukocytes before migration may play a major role in their migratory capacity.

Where do we go from here? First, a larger prospective study of labeled donor leukocytes from humans would help determine whether the results are indeed inferior to those from labeled autologous granulocytes. Unfortunately, such a study may not be possible, because these patients are so rarely seen in routine clinical practice. Second, it would seem unwise to harvest donor granulocytes from a patient with known infection to give to a granulocytopenic patient. Further identification is needed of the "biologically active factors," which might be incubated with the donor blood to improve the migratory capacity of the donor granulocytes.

In conclusion, Gratz et al. (*19*) have produced a well-designed, thought-provoking study. Confirmation of their findings by further studies will lead to improved detection of infection in granulocytopenic patients through the use of labeled donor leukocytes. Such studies may also lead to a better understanding of the factors involved in attracting granulocytes to a site of infection.

ACKNOWLEDGMENTS

The author thanks Mark Green, PhD, for his guidance on misleading animal models and Kathy Carlson and Bonnie Ridenour for their help with production of the manuscript.

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