REVIEW ARTICLE

Multiagent imaging of inflammation and infection with radionuclides

Christopher J. Palestro · Andor W. J. M. Glaudemans · Rudi A. J. O. Dierckx

Abstract Molecular imaging with single photon- and positron-emitting tracers plays an important role in the evaluation of inflammation and infection. Although supplanted by labeled leukocyte imaging for most indications, gallium-67 remains useful for opportunistic infections, pulmonary inflammation and interstitial nephritis and, when [18F]FDG is not available, spinal infection and fever of unknown origin. In vitro labeled leukocyte imaging is the radionuclide procedure of choice for most infections in immunocompetent patients. When performed for musculoskeletal infection, complementary bone marrow imaging usually is necessary. Recent data suggest that dual time point imaging might be an alternative to marrow imaging. Several methods of labeling leukocytes in vivo, with agents including antigranulocyte antibodies and antibody fragments, peptides and cytokines, have been investigated, with variable results. These agents are not widely available and none of them are available in the USA. Radiolabeled antibiotics have been investigated as "infection-specific" tracers, but the results to date have been disappointing. Conversely, radiolabeled antimicrobial peptides do hold promise as infection-specific tracers. The use of positron-emitting tracers for diagnosing inflammation and infection has generated considerable interest. [18F]FDG is useful in fever of unknown origin, spinal osteomyelitis, vasculitis and sarcoidosis. Other positron-emitting tracers that have been investigated include [18F]FDG-labeled leukocytes, copper-64-labeled leukocytes, gallium-68 citrate and iodine-124 FIAU. Although radiolabeled tracers are used primarily for diagnosis, they also offer objective biomarkers for assessing response to therapeutic interventions in inflammatory diseases. They could also potentially be used to target cells and molecules with specific receptor expression for histological characterization, select patients for receptor-targeted therapy and predict response to treatment.

Keywords Gallium citrate · Labeled leukocytes · Biotin · Antimicrobial peptides · [18F]FDG · PET

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Introduction

Despite significant advances in our understanding of microorganisms and the pathogenesis of inflammation and infection, infection remains a major cause of patient morbidity and mortality. Although signs and symptoms such as fever, pain, general malaise and abnormal laboratory results may suggest the presence of infection, the diagnosis can be elusive and imaging tests often are used for confirmation and localization. There are two principal

categories of imaging tests: anatomical or morphological, and molecular. Anatomical imaging tests, such as radiographs, ultrasound and computed tomography (CT) reveal structural alterations in tissues and organs caused by microbial invasion and the inflammatory response of the host. Prototypical molecular imaging tests use agents such as gallium-68 citrate, labeled leukocytes and fluorine-18 fluorodeoxyglucose ([^{18}F]FDG). These agents, which reflect the physiological changes that are part of the inflammatory process, are taken up directly by cells, tissues and organs, or are attached to native substances that subsequently migrate to an inflammatory focus. Because they provide different types of information, anatomical and molecular imaging studies are complementary to each another. There are certain situations, however, in which molecular imaging tests are especially valuable: postoperative infections and infections associated with orthopedic hardware, notably prosthetic joint infection. Postoperative infections are a significant cause of morbidity and mortality. Ultrasound, CT and magnetic resonance imaging (MRI) cannot consistently separate abscesses from other fluid collections and, on occasion, even from normal postoperative changes. The distorted anatomy, metallic sutures and the surgical incision itself further complicate study interpretation. Molecular imaging studies, however, demonstrate physiological processes, which often precede anatomical changes, and can help distinguish normal postoperative inflammation from infection. In suspected orthopedic hardware infection, plain radiographs are neither sensitive nor specific and cross-sectional imaging modalities, such as CT and MRI, are limited by hardware-induced artifacts. Radionuclide imaging is not affected by metallic hardware and is the current imaging modality of choice for diagnosing orthopedic hardware infection.

This article reviews the various radiolabeled molecular imaging agents used for detecting and localizing inflammation and infection as well as the potential role of these agents in guiding selection of therapeutic agents and monitoring treatment response.

Single photon-emitting (SPECT) tracers

Non-specific agents

Gallium-67 citrate

Several factors contribute to gallium-67 citrate (^{67}Ga-citrate) uptake in inflammation and infection. About 90 % of circulating Ga ions are bound to transferrin in the plasma. Increased blood flow and vascular membrane permeability result in increased ^{67}Ga delivery and accumulation at the inflammatory foci. ^{67}Ga also binds

to lactoferrin, which is present in high concentrations in inflammatory foci. Direct bacterial uptake, complexing with siderophores and leukocyte transport also contribute to ^{67}Ga uptake in inflammation and infection. Imaging usually is performed 18–72 h after injection. The normal distribution of ^{67}Ga, which is variable, includes bone, marrow, liver, gastrointestinal and urinary tracts, and soft tissues [1].

Replaced by labeled leukocyte imaging for most indications, ^{67}Ga remains useful in select circumstances. Opportunistic infections affect the lungs, and a normal scan of the chest excludes infection with a high degree of certainty. In HIV-positive patients, lymph node uptake is associated with mycobacterial infection and lymphoma. Focal, or localized, pulmonary parenchymal uptake usually is associated with bacterial pneumonia. Diffuse pulmonary uptake, especially when intense, suggests *Pneumocystis jirovecii* pneumonia [1].

^{67}Ga is a sensitive indicator of pulmonary inflammation and accumulates in interstitial pneumonitis, drug reactions, collagen vascular disease, pneumoconioses and sarcoidosis. In patients with sarcoidosis, uptake correlates with disease activity and response to therapy [1].

^{67}Ga can help differentiate interstitial nephritis from acute tubular necrosis in patients with acute renal failure. Interstitial nephritis is characterized by renal uptake that is more intense than lumbar spine uptake. Acute tubular necrosis is characterized by little or no renal uptake [1] (Fig. 1).
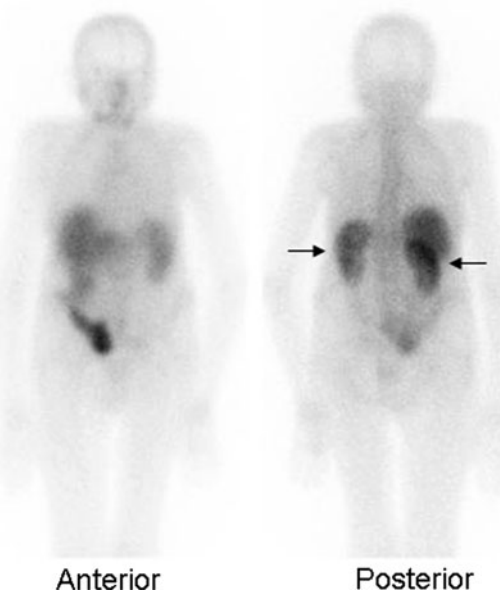
Fig. 1 Interstitial nephritis. On images acquired approximately 48 h after injection, renal activity (*arrows*) is more intense than adjacent lumbar spine activity. This is the characteristic presentation of interstitial nephritis on gallium imaging

Although [18F]fluorodeoxyglucose ([18F]FDG) PET is the radionuclide test of choice for fever of unknown origin and spinal osteomyelitis, ^{67}Ga is an acceptable alternative when this agent is not available [1].

Labeled leukocytes

In vitro labeled leukocytes In vitro leukocyte (WBC) labeling usually is performed with ^{111}In-oxyquinolone (^{111}In) or ^{99m}Tc-exametazime (^{99m}Tc-HMPAO). Uptake depends on intact chemotaxis, number and types of cells labeled and cellular response in a particular condition. A circulating WBC count of at least 2,000/μL is needed for satisfactory images. Although a mixed population of WBCs is labeled, the majority of WBCs labeled are usually neutrophils and the procedure is most sensitive for identifying neutrophil-mediated infectious processes [2]. It is possible to selectively label granulocytes. To do so, however, requires the use of a gradient separation process, further lengthening an already labor-intensive process. Published results, in general, have shown no real advantage of radiolabeled granulocytes over radiolabeled leukocytes for routine clinical use [3].

Images obtained shortly after injection of labeled WBCs are characterized by intense pulmonary activity, which clears rapidly. This phenomenon probably results from WBC activation during labeling, which impedes cell movement through the pulmonary vascular bed and prolongs transit through the lungs [2].

The advantages of In-WBCs include label stability, a normal distribution limited to liver, spleen and bone marrow and the possibility of performing delayed imaging. Complementary bone marrow imaging can be performed during cell labeling, as a simultaneous dual isotope acquisition, or after ^{111}In-WBC imaging. Disadvantages include low counts, low-resolution images and the 16–30 h interval between injection and imaging [2].

The normal distribution of ^{99m}Tc-HMPAO-WBCs is more variable than that of ^{111}In-WBCs. In addition to the reticuloendothelial system, activity is normally present in the urinary tract, large bowel (within 4 h of injection) and occasionally gallbladder. The advantages of ^{99m}Tc-HMPAO-WBCs include high-resolution images and the capacity of the technique to detect abnormalities within a few hours of injection. Disadvantages include label instability and the short half-life of ^{99m}Tc, which limits the possibility of performing delayed imaging. When performing bone marrow imaging, an interval of 48–72 h is required between the two imaging procedures [2].

In the brain, MRI can, in most cases, differentiate tumors from abscesses. When MRI cannot be performed or is not diagnostic, WBC imaging is a useful alternative, being both sensitive and specific. WBC uptake has been observed in some tumors, but usually is less intense than that observed in abscesses. High- or medium-dose steroid treatment may decrease sensitivity [4–6].

Pneumonia is easily and accurately diagnosed with morphological imaging tests and consequently molecular imaging rarely is needed to diagnose pulmonary infection. Focal pulmonary activity on WBC images that is segmental or lobar in appearance indicates a high likelihood of pyogenic infection. Diffuse, bilateral pulmonary uptake is associated with numerous conditions including opportunistic infection, pulmonary drug toxicity and acute respiratory distress syndrome (ARDS), but almost never with bacterial pneumonia [7].

Radionuclide imaging, traditionally, has played a limited role in diagnosing bacterial endocarditis; recent data suggest, however, that ^{99m}Tc-HMPAO-WBC SPECT/CT contributes useful information in patients suspected of having this condition [8]. The value of WBC imaging for diagnosing complications of bacterial endocarditis, such as myocardial abscesses and mycotic aneurysms, is already well established [2, 9]. WBC imaging is also useful for diagnosing prosthetic vascular graft infection. The reported sensitivity, which in most series exceeds 90 %, is not affected by antibiotic therapy or duration of symptoms. Specificity ranges from 50 to 100 %. False-positive results are associated with lymphoceles, perigraft hematomas, thrombosed grafts, bleeding, pseudoaneurysms and uninfected grafts <1-month-old [2].

In the postoperative patient, morphological imaging techniques cannot consistently separate abscesses from other fluid collections, or even from normal postoperative changes. WBC imaging provides physiological information and is complementary to these techniques [10].

^{99m}Tc-HMPAO-WBC imaging, the radionuclide study of choice for inflammatory bowel disease (IBD), is very sensitive and can be used as a screening test. In patients thought to have ulcerative, or indeterminate, colitis, skip areas of activity in the colon, or the presence of small bowel activity, support the diagnosis of Crohn's disease. The test is useful in patients who cannot or will not undergo endoscopy or contrast radiography can be used to monitor response to therapy and can impact on patient management by differentiating active inflammation from scarring. Imaging at multiple time points and SPECT both increase sensitivity. ^{99m}Tc-HMPAO-WBC is more sensitive for lower than for upper gastrointestinal tract disease. Its sensitivity may be affected adversely by concomitant corticosteroid administration [11].

WBC imaging of diabetic pedal osteomyelitis has been extensively investigated. The sensitivity of ^{111}In-WBC in diabetic foot infections ranges from 72 to 100 % and the specificity from 67 to 100 %. The sensitivity and specificity of ^{99m}Tc-HMPAO-WBC range from 86 to 93 % and from 80

Fig. 2 Soft tissue infection, right great toe. There is focally increased activity (*arrows*) in the right great toe on the dorsal and plantar images (**a**) obtained approximately 6 h after injection of ^{99m}Tc-exametazime-labeled autologous leukocytes. It is not possible to determine whether the infection involves bone. The SPECT/CT (**b**) confirms that the infection (*arrows*) is confined to the soft tissues
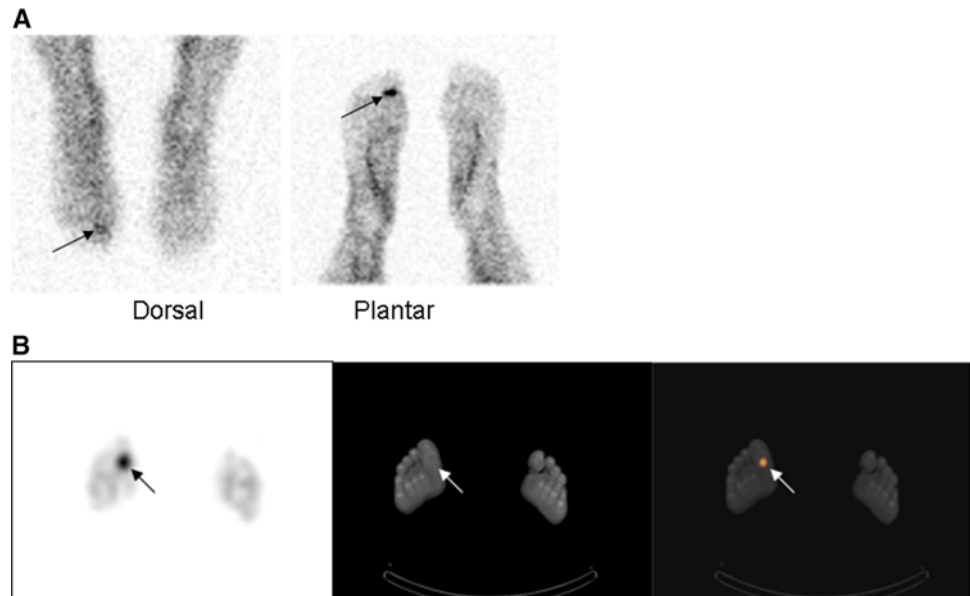
to 98 %, respectively. SPECT/CT improves test accuracy [12–15] (Fig. 2). In a recent investigation, ^{99m}Tc-HMPAO-WBC imaging was found to be more accurate than [^{18}F]FDG PET/CT for diagnosing pedal osteomyelitis in diabetics [16].

WBC imaging is not useful for diagnosing spinal osteomyelitis; 50 % or more of these cases present as non-specific areas of decreased or absent activity. [^{18}F]FDG PET, or alternatively ^{67}Ga-citrate scintigraphy, is the preferred nuclear medicine test for this indication [17].

WBC imaging, the procedure of choice for diagnosing complicating osteomyelitis, is frequently performed together with colloid bone marrow imaging. The reason for this is that WBCs accumulate not only in sites of infection, but also in the bone marrow. The normal distribution of hematopoietically active bone marrow in adults is variable. Systemic diseases such as sickle cell and Gaucher disease produce generalized alterations in marrow distribution; fractures, orthopedic hardware and neuropathic joints cause localized alterations. The normal distribution of hematopoietically active marrow in children varies with age. Consequently, it may not be possible to determine whether an area of activity on a WBC image represents infection or marrow. Performing ^{99m}Tc-colloid bone marrow imaging overcomes this problem. Both WBCs and colloid accumulate in marrow; WBCs also accumulate in infection, but colloid does not. The combined study is positive for infection when activity is present on the WBC image without corresponding activity on the marrow image. Any other pattern is negative for infection. The combined study has been most extensively investigated in prosthetic joint infections, but is valuable in any condition that affects marrow distribution, showing an overall accuracy of approximately 90 % [18] (Fig. 3).
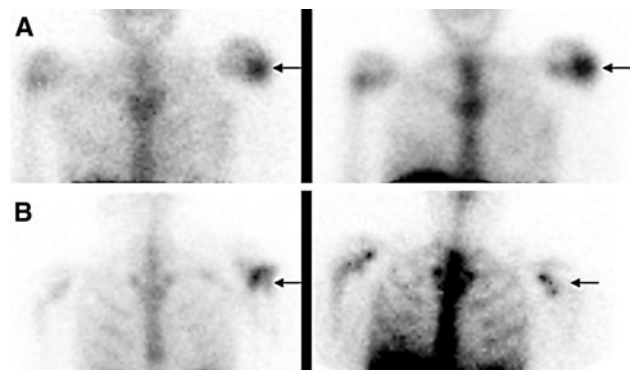
Fig. 3 a Hypercellular bone marrow. On the ^{111}In-labeled leukocyte image (*left*), acquired 24 h after injection of autologous labeled leukocytes, there is focally increased activity in the left shoulder of a patient with sickle cell disease, who presented with fever and left shoulder pain. The distribution of activity is virtually identical on the bone marrow image (*right*), which was performed immediately after the labeled leukocyte imaging, and 1 h after injection of ^{99m}Tc-sulfur colloid and hence the test is negative for osteomyelitis. The increased activity in the left shoulder is the result of localized marrow hyperplasia. **b** Osteomyelitis, left shoulder. On the ^{99m}Tc-exametazime image (*left*), acquired approximately 16 h after injection of labeled autologous leukocytes, there is focally increased activity in the left shoulder (*arrow*) of a patient who presented with shoulder pain, fever and positive blood cultures. On the bone marrow image (*right*), which was performed 1 h after injection of ^{99m}Tc-sulfur colloid and 2 days after the labeled leukocyte study, the left shoulder is photopenic (*arrow*) and the test is positive for osteomyelitis

As an alternative to marrow imaging, dual time point imaging (delayed images obtained 3–4 h after reinjection and late images 20–24 h after reinjection), with acquisition times corrected for ^{99m}Tc decay, has been suggested. Decay-corrected images avoid operator bias and the fact of using the same count scale in all images facilitates

image interpretation. Increasing uptake, either in size or over time, is considered positive for infection; lack of uptake or decreasing uptake over time is classified as negative for infection. Dual time point imaging with decay-corrected acquisition times may decrease the need for complementary bone marrow imaging, thereby reducing costs as well as radiation exposure to both patients and personnel [19].

In vivo labeled leukocytes Besilesomab (Scintimun®), a 150 kDa murine monoclonal antibody of the IgG$_1$ kappa isotype, binds to non-specific cross-reacting antigen-95 (NCA-95), an epitope expressed on cell membranes of granulocytes and granulocyte precursors. About 10 % of injected activity is neutrophil bound by 45 min, while 20 % circulates freely and presumably localizes in inflammatory foci through non-specific mechanisms. Studies usually become positive within 6 h of injection; next-day imaging increases the sensitivity of the test [20].

In one investigation, ^{99m}Tc-besilesomab was more sensitive (75 vs 59 %), but less specific (72 vs 80 %) than ^{99m}Tc-HMPAO-WBC for diagnosing appendicular osteomyelitis [21]. ^{99m}Tc-besilesomab has a level of accuracy similar to that of in vitro labeled WBC imaging for diagnosing diabetic pedal osteomyelitis. Results in suspected prosthetic joint infection have been variable. Combining the test with bone scintigraphy, performing semiquantitative analysis and incorporating SPECT/CT into the imaging protocol may improve the accuracy [2, 22, 23].

^{99m}Tc-besilesomab accurately diagnoses appendicitis, contributes useful information in patients with pyrexia of unknown origin and may be a useful screening test for acute myocarditis. It is less accurate than ^{99m}Tc-WBC in inflammatory bowel disease [24–26].

A significant disadvantage of ^{99m}Tc-besilesomab is the incidence of human antimurine antibody (HAMA) response, which ranges from <5 % in patients receiving a single dose of 125 μg of antibody to more than 30 % in patients receiving repeated injections [20]. To minimize potential problems, patients should be prescreened for HAMA, a maximum of 250 μg antibody should be injected and repeated administrations should be avoided.

Fanolesomab (LeuTech®, NeutroSpec®) is a 900 kDa M class immunoglobulin that exhibits a high affinity for 3-fucosyl-*N*-acetyl lactosamine contained in the CD15 antigen expressed on human leukocytes. Accumulation in infection is via binding to circulating neutrophils that subsequently migrate to infection and bind to neutrophils and neutrophil debris already sequestered in an infection. ^{99m}Tc-fanolesomab accurately diagnoses atypical appendicitis as well as musculoskeletal and prosthetic vascular graft infections. Following reports of serious and life-threatening cardiopulmonary events, including two fatalities shortly after administration, ^{99m}Tc-fanolesomab was withdrawn from the market [2].

Sulesomab (Leukoscan®) is a 50 kDa fragment antigen binding (Fab′) portion of an IgG$_1$ class murine monoclonal antibody that binds to normal cross-reactive antigen-90 (NCA-90) present on leukocytes. Approximately, 3–6 % of the injected activity is associated with circulating neutrophils; at 24 h after injection, about 35 % of the remaining activity is in the bone marrow. Initial investigations suggested that sulesomab binds to circulating neutrophils that migrate to foci of infection and to leukocytes already present at the site of infection. Recent data, however, suggest that the accumulation in infection is non-specific [2].

Most investigations have found that ^{99m}Tc-sulesomab is sensitive for diagnosing musculoskeletal infection. Specificity is variable, especially in suspected prosthetic joint infection. ^{99m}Tc-sulesomab is comparable to in vitro labeled WBC imaging for diagnosing pedal osteomyelitis in diabetics (Fig. 4). The test is reasonably accurate for diagnosing soft tissue infections and pyrexia of unknown origin, but is less useful for inflammatory bowel disease [2]. ^{99m}Tc-sulesomab may have a role in implanted deep brain stimulation device infections. Imaging results correlate well with the presence and extent of infection, thereby facilitating patient management [27].

Most techniques for labeling leukocytes in vivo use antigranulocyte antibodies or antibody fragments. Cytokines, low molecular weight proteins that interact with specific cell-surface receptors on specific cell populations, also have been investigated.

Interleukin 8 (IL-8) is a member of the CXC subfamily of chemotactic cytokines that binds with high affinity to the CXC type I (IL-8 type A) and CXC type II (IL-8 type B) receptors expressed on neutrophils and monocytes. The agent is well tolerated, rapidly accumulates at sites of infection and clears rapidly from the blood pool and non-target tissues. In a rabbit model of acute osteomyelitis, ^{99m}Tc-IL-8 clearly showed the area of osteomyelitis [28–30].

Although the majority of investigations have focused on labeling granulocytes for infection localization, some investigators have used labeled lymphocytes to study inflammatory conditions. Interleukin 2 (IL-2) is synthesized and secreted by T lymphocytes and binds with high affinity to IL-2 receptors expressed by activated lymphocytes during inflammation. Radioabeled IL-2 allows visualization of both lymphocytic infiltration and T cell lymphocyte activation and has been used in several inflammatory diseases characterized by chronic lymphocytic infiltration, such as Takayasu's arteritis, diabetes mellitus, celiac disease, Crohn's disease, autoimmune thyroid diseases and atherosclerosis [31].
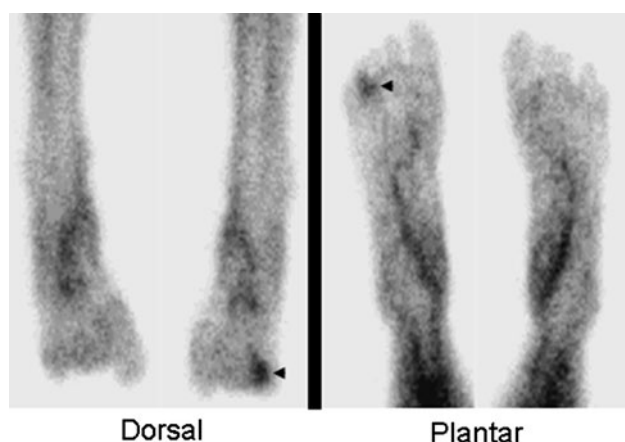
Fig. 4 Diabetic pedal osteomyelitis. There is focally increased radionuclide uptake in the right fourth toe (*arrowheads*) on images acquired approximately 1 h after injection of ^{99m}Tc-sulesomab. Published data suggest that the accuracy of ^{99m}Tc-sulesomab for diagnosing pedal osteomyelitis in diabetics is similar to that of in vitro labeled leukocytes

Infection-specific agents

Radiolabeled antibiotics

None of the clinically available agents is truly specific for infection, and the search continues for such an agent. Radiolabeled antibiotics have been investigated as "infection-specific" tracers. Presumably, the labeled antibiotic is incorporated into, and metabolized by, bacteria and assuming that uptake is proportional to the number of microorganisms present, the measured radioactivity would accurately and specifically localize infection. The most extensively investigated radiolabeled antibiotic, ^{99m}Tc-ciprofloxacin, was initially reported to be both sensitive and specific for infection [32, 33]. Subsequent investigations, however, raised serious doubts about this agent as an infection-specific tracer and much of the original enthusiasm for radiolabeled antibiotics as diagnostic tools has waned [34–36].

[111]In-Biotin

Biotin is necessary for cell growth, fatty acid production and metabolism of fats and amino acids, and it serves as a growth factor for certain bacteria. ^{111}In-Biotin, alone or in combination with streptavidin, accurately diagnoses spinal infections and may be a useful alternative to [^{18}F]FDG PET and ^{67}Ga-citrate imaging. ^{111}In-Biotin does not accumulate in normal bone or marrow, so there are no anatomical landmarks, and SPECT/CT is especially helpful for correctly localizing foci of ^{111}In-Biotin accumulation and guiding the selection of therapy [37, 38].

Radiolabeled antimicrobial peptides

Antimicrobial peptides are critical to the biological defenses of multicellular organisms. They are produced by various cells, including phagocytes, and endothelial and epithelial cells, and bind to the bacterial cell membrane. Their expression may be constant or induced on contact with microbes; they may also be transported to sites of infection by leukocytes [39].

Radiolabeled synthetic fragments of ubiquicidin (UBI), a naturally occurring human antimicrobial peptide that targets bacteria, possess the ability to differentiate infection from sterile inflammation [40]. ^{99m}Tc-UBI 29–41 may be useful for monitoring the efficacy of antibacterial agents in infections caused by *Staphylococcus aureus* [41, 42]. In an animal model of prosthetic joint infection, all six infected devices were positive on day 9, but only four of the six were positive on day 20. The decreased sensitivity over time may have been related to effects of the protective glycocalyx secreted by the bacteria [43].

Available human data are encouraging. In six children with suspected osteomyelitis, tracer cleared rapidly from the circulation with a mean residence time of about 30 min. Approximately, 85 % of the injected activity was eliminated by renal clearance within 24 h. There was minimal accumulation in non-target tissues with an average target/non-target ratio of 2.18 ± 0.74 in positive lesions at 2 h [39]. The sensitivity, specificity and accuracy of ^{99m}Tc-UBI 29–41 in 18 patients suspected of having various infections were 100, 80 and 94.4 %, respectively. Optimal visualization of abnormalities occurred about 30 min after injection [44]. ^{99m}Tc-UBI 29–41 detected five out of six cases of mediastinitis among 13 patients who had recently undergone cardiac surgery [45]. A recent meta-analysis reported that the pooled sensitivity, specificity and accuracy of ^{99m}Tc-ubiqicidin were 94.5, 92.7 and 93.7 % [46].

[99m]Tc-labeled recombinant human beta-defensin-3 (HBD-3) that exerts bactericidal effects on Gram-positive and Gram-negative bacteria has also been investigated. By 3 h after injection, tracer uptake in a *Staphylococcus aureus* infection model was significantly higher than that in sterile inflammation [47].

Positron-emitting (PET) tracers

In general, positron emission tomography (PET) offers several advantages over SPECT imaging. PET provides three-dimensional images of the whole body with superior resolution and facilitates [especially, when combined with CT (PET/CT)] precise localization of abnormal uptake. Furthermore, semiquantitative analysis is more readily available and could be helpful for differentiating between
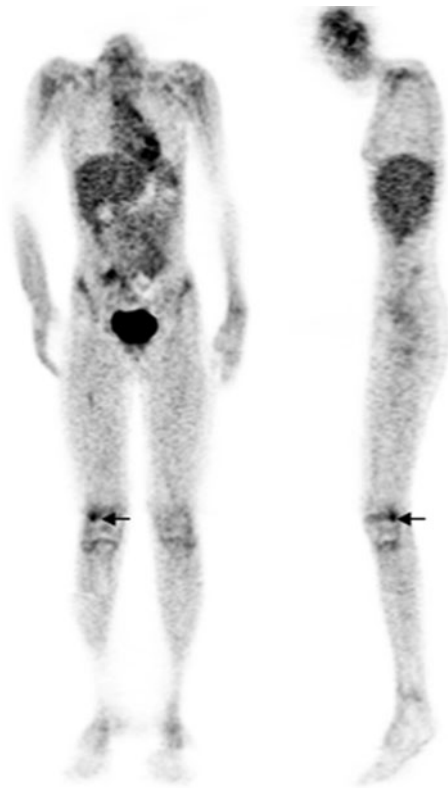
Fig. 5 Right femur osteomyelitis. There is focal hypermetabolism (*arrows*) in the lateral condyle of the distal right femur on the coronal and sagittal [18F]FDG PET images of a 12-year-old leukopenic patient with *Staphylococcus aureus* bacteremia and right knee pain. Imaging was performed approximately 1 h after [18F]FDG injection

infections and other causes of uptake, as well for monitoring response to therapy.

Non-specific agents

[18F]Fluorodeoxyglucose

[18F]FDG, a well-established tool in oncology, has been an increasing focus of attention in the field of infection and inflammation imaging over the past decade, since [18F]FDG also accumulates in activated leukocytes, which use glucose as an energy source only after activation during their metabolic burst [31]. Transport of [18F]FDG across the cell membrane is mediated by glucose transporter proteins (GLUT). Intracellular [18F]FDG is phosphorylated by the enzyme hexokinase and trapped in the cell. With the exception of a few organs, physiological uptake of [18F]FDG is low and clearance from non-target tissue is rapid, resulting in relatively high target-to-background ratios. With the new hybrid PET/CT systems, diagnostic evaluation can be completed in a single visit in just 1–2 h (including the waiting time, after injection, necessary for sufficient tracer uptake). Compared with many other
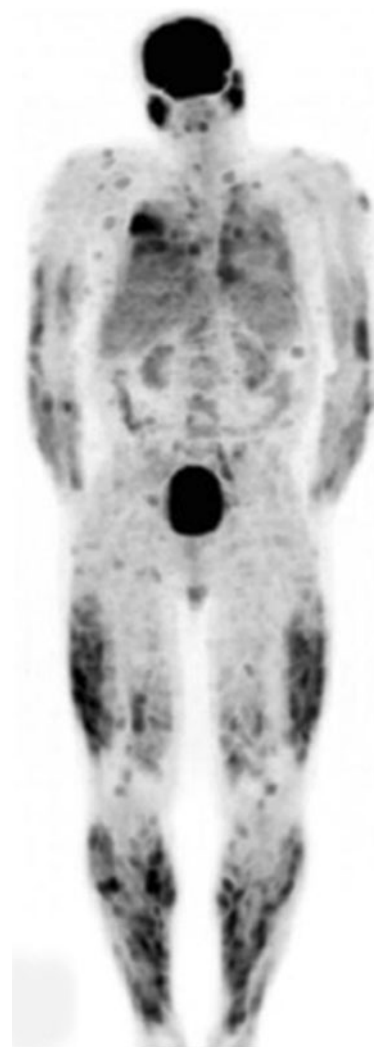

Fig. 6 Sarcoidosis. Anterior maximum intensity projection image (MIP) acquired approximately 1 h after [18F]FDG injection demonstrates innumerable pulmonary and cutaneous foci of hypermetabolism in a patient with disseminated active sarcoidosis

radiopharmaceuticals, [18F]FDG has a very favorable dosimetry. It is very sensitive and in most situations has a high negative predictive value. There are, however, limitations to this agent, notably its specificity. [18F]FDG PET merely detects enhanced glucose metabolism and is therefore unable to discriminate reliably between infection/inflammation, malignancy and any other hypermetabolic state. [18F]FDG also cannot distinguish between different inflammatory pathways, which can be relevant in some clinical situations [31].

Combined EANM/SNMMI guidelines for the use of [18F]FDG in infection and inflammation have been published. Major indications are peripheral bone osteomyelitis (non-postoperative, non-diabetic foot) (Fig. 5), sarcoidosis (Fig. 6), suspected spinal infection (Fig. 7), evaluation of fever of unknown origin (FUO), evaluation of metastatic

Fig. 7 Spinal osteomyelitis/infected spinal hardware. On the sagittal images from the PET/CT scan, performed approximately 1 h after [^{18}F]FDG injection, there is spinal hypermetabolism extending from approximately T11 to L3 (*arrows*), with a maximum SUV of 9.3 (color figure online)
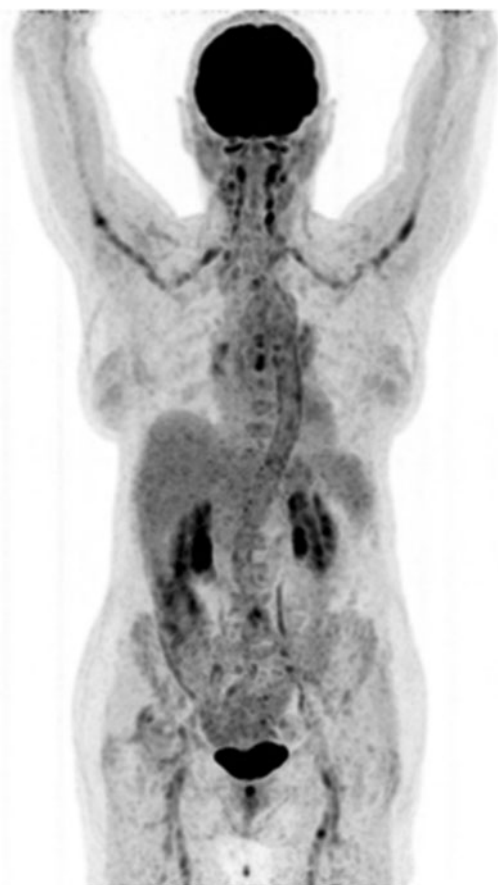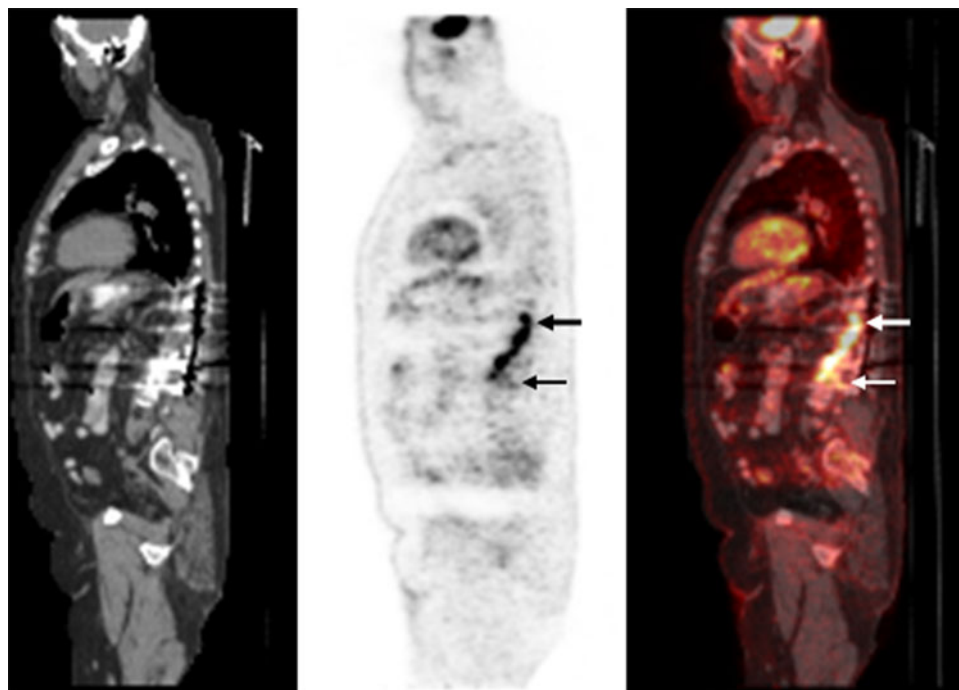
infection and high-risk patients with bacteremia, and primary evaluation of suspected vasculitis (Fig. 8) [48].

[^{18}F]FDG may be useful for diagnosing infected hepatic and renal cysts, infected intravascular devices and AIDS-associated opportunistic infections and for assessing tuberculous lesions. Sufficient evidence-based data for these indications, however, are currently lacking [48].

While specificity is usually the limiting factor in [^{18}F]FDG imaging, there are some situations in which the limitation is low sensitivity, e.g., in prosthetic joint infections, diabetic foot infections and in the evaluation of medium- and small-vessel vasculitis [49].

[^{18}F]FDG-labeled leukocytes

Leukocytes have been labeled in vitro with [^{18}F]FDG in an attempt to develop a more specific PET tracer. Whole-body and organ dosimetry are comparable to those of conventional doses of ^{111}In-WBCs [50]. Initial results were encouraging [51, 52]. However, the labeling efficiency is low and may be affected by blood glucose levels [53]. In some indolent infections, labeled leukocyte accumulation is slow and imaging at later time points (e.g., 24 h) may be necessary to detect the abnormality. Given the short half-life of ^{18}F (110 min), it is technically not feasible to perform imaging much later than 4–5 h after injection. Although there are some data indicating different distribution patterns between [^{18}F]FDG and [^{18}F]FDG-labeled leukocytes (suggesting improved specificity of the coupled tracer), well-designed clinical trials demonstrating an

Fig. 8 Giant cell arteritis. Note the intense, relatively homogeneous [^{18}F]FDG accumulation in the carotid and subclavian arteries, as well as in the aortic arch, thoracic and abdominal aorta, and the iliac and femoral arteries. Imaging was performed about 1 h after injection of tracer

added value of [18F]FDG-labeled leukocytes versus [18F]FDG are lacking [54, 55].

Copper-64-labeled agents

Copper-64 (64Cu), theoretically, is one of the more suitable PET isotopes for imaging purposes. Its physical half-life of 12.7 h makes it a suitable tracer for imaging infectious and inflammatory diseases. In ten volunteers, leukocytes were labeled in vitro with 64Cu, In and [18F]FDG. 64Cu-WBC labeling efficiency and viability were comparable or superior to those of 111In-WBC and significantly higher than those of [18F]FDG-WBC. 64Cu was retained inside the cells without evident toxicity. These data suggest that 64Cu-labeled leukocytes may potentially be useful for imaging inflammation and infection and further investigation is warranted [56].

However, the shortage of appropriate chelating agents has, to date, limited the wider application of 64Cu [57]. New developments in 64Cu imaging focus primarily on cancer research. 64Cu-labeled natriuretic peptide is a potential tracer for the in vivo imaging of atherosclerotic plaques [58]. Mice with induced colitis, compared with control groups, were found to show higher uptake of a 64Cu-labeled anti-β7 integrin antibody [59]. Recently, in an in vitro investigation, chitosan-coated magnetic 64Cu nanoparticles were found to be taken up by granuloctyes through phagocytosis, and showed a high stability (of up to 80 %) of retained activity after 24 h of incubation [60].

Gallium-68 citrate

The imaging characteristics of the positron emitter gallium-68 (68Ga) are superior to those of 67Ga by virtue of the higher spatial resolution and quantitative features of PET in comparison with single-photon imaging. 68Ga-citrate has suitable radiophysical and radiopharmaceutical properties: high positron yield and a half-life of 68 min, and thus, showing rapid blood clearance, quick diffusion and target localization, is able to match the pharmacokinetics of many peptides and other small molecules [61]. In addition, this agent can be generator produced, and several generators are commercially available.

68Ga-citrate is produced with high radiochemical yield and purity and can be used in the detection of inflammatory and infectious diseases [62]. However, large clinical trials are still lacking. The largest series to date consisted of 31 patients with suspected osteomyelitis or discitis who underwent a total of 40 68Ga-citrate PET/CT scans. An overall accuracy of 90 % was found, and the authors stated that the possible role of 68Ga-citrate in the diagnosis of bone infections was confirmed [63]. While 68Ga-citrate may be superior to 67Ga-citrate, to adequately assess its value as an inflammation/infection imaging agent it must be compared to [18F]FDG, which, when available, has replaced 67Ga.

It is likely that if 68Ga-citrate is to be useful in inflammation/infection imaging, it will need to be complexed with other agents. Some molecules have, in fact, been complexed with 68Ga for this purpose. 68Ga-apo-transferrin, for example, detected *Staphylococcus aureus* infection in a rat model within an hour of injection [64]. The specific detection of *Aspergillus fumigatus* infection in rodent models using 68Ga-labeled siderophores has also been described [65, 66].

Infection-specific agents

124I-FIAU

The radioiodinated thymidine analog fialuridine (FIAU) is a tracer that has been developed for reporter genes, for cells that were transfected with herpes simplex virus thymidine kinase (HSV-TK). FIAU, because of the homology between viral and bacterial TK, is also a specific substrate of bacterial TK [67]. Localized infections caused by five genera of bacteria have been imaged successfully with 125I-FIAU [68]. Data also suggest that this tracer can be used to monitor the efficacy of antimicrobial therapy, because in a preclinical model of lung infection 125I-FIAU signal intensity was proportional to the bacterial load. It was suggested that imaging with FIAU could potentially be used to evaluate the efficacy of newly developed antibiotics [69]. The feasibility of using 124I-FIAU for diagnosing infection in humans was demonstrated in an investigation of nine subjects, including eight with suspected musculoskeletal infection and one healthy control. All patients with proven musculoskeletal infections demonstrated 124I-FIAU accumulation at the site of infection by 2 h after injection. There was no abnormal tracer uptake in the one control and there were no adverse reactions among any of the subjects [70]. The role of 124I-FIAU as a diagnostic imaging agent for diagnosing prosthetic joint infection is under investigation.

Therapy

As is evident from this review, SPECT and PET tracers play an important role in the diagnosis of inflammation and infection. Though less extensively investigated, molecular imaging also has the potential to guide therapeutic management and to assess response to therapy. Imaging with the radiolabeled anti-tumor necrosis factor alpha (anti-TNFα) monoclonal antibodies infliximab and adalimumab, for example, has been shown to be of value both for

identifying patients with Crohn's disease and rheumatoid arthritis who would benefit from anti-TNFα therapy, and for monitoring response to treatment [71, 72].

The ability of receptor-based molecular imaging agents to target molecules and cells involved in inflammation and infection has the potential to facilitate the selection of patients for receptor-targeted therapy, and, by monitoring changes in intensity of uptake during and after therapy, to predict response as well as relapse.

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