Infection imaging in nuclear medicine

Nuclear medicine has a role to play in investigating patients with suspected infection.

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Although there are many imaging agents, only a few are important in routine clinical practice. Understanding the role and place of each of them is important for cost-effective clinical use.

Introduction

Regardless of advances in medicine, infection continues to play a major role in patients' morbidity and mortality. Nuclear medicine techniques have an important role in the evaluation of patients suspected of harbouring infection. Many different agents may be used in an attempt to image infection. There are, however, a number of important limitations in clinical practice. Labelled leukocytes, regarded as the gold standard imaging agent, require at first a laborious preparation procedure. Then the requirement for complementary scintigraphic imaging adds a dimension of complexity that may inconvenience patients and also increase the cost of the investigation. However, the development of *in vivo* leukocyte-labelling methods and the introduction of fusion imaging with anatomical examinations may assist in reducing those limitations and in increasing diagnostic accuracy.

Agents

The clinician searching for a site of infection in a patient has a considerable number of choices, which continue to increase with the advances in medicine. However, in clinical practice, the properties of an ideal agent should be understood: easy preparation, wide availability, low cost, low toxicity, absence of an immune response, and high specificity.

Gallium-67 (Ga-67)

This grandfather of infection imaging continues to play a role in the following: pyrexia of unknown origin (PUO), immunocompromised patients with fever, suspected osteomyelitis in the spine, chronic osteomyelitis, and certain lung infections.

Labelled leukocytes

The basis for using labelled leukocytes in nuclear medicine is that infection imaging relies on the ability to image inflammatory cells at the sites of infection. Two isotopes are generally used to label leukocytes – indium-111 (In-111) and technetium-99m (Tc-99m). Whenever clinicians request infection imaging with these agents, they should understand the following:

- labelling of leukocytes is a laborious process that takes about 3 hours
- approximately 40 - 60 ml of a patient's blood is needed for the labelling process
- imaging may require up to 24 hours for Tc-99m or up to 72 hours for In-111 before study completion.

Clinicians should be aware that most of the labelled cells are neutrophils, thus making the procedure more useful for the identification of a neutrophil-mediated inflammatory process, such as bacterial infections.[1] It is known that lymphocytes are sensitive to radiation and fail to re-circulate normally after labelling. Therefore, labelled leukocyte imaging is less useful in disease in which the cellular response is not predominantly from neutrophils, such as in tuberculosis.[1] Leukocytes labelled with Tc-99m-hexamethylpropyleneamine oxime (Tc-99m-HMPAO) are better used for the diagnosis of acute musculoskeletal infections and also suited for children because of the lower radiation dose. In-111 is the preferred agent in labelling leukocytes for the diagnosis of gastrointestinal and genitourinary infections.

Fluorine-18 fluorodeoxyglucose positron emission tomography (F-18 FDG PET)

This is an analogue of glucose and is used in a range of clinical applications, including infection. The high-resolution tomographic images and rapid completion of the examinations have made F-18 FDG PET an appealing imaging modality.[2]

Inflammatory cells have an increased positive expression of glucose transporters and growth factors, which affect the affinity of these transporters for deoxyglucose. The net result is seen as a high accumulation of F-18 FDG in areas of infection because it is carried into cells by the glucose transporters.[3] Although F-18 FDG has been used in a variety of infections, it can play an important role in the central nervous system for differentiating lymphoma from toxoplasmosis, and its role has become increasingly significant in the evaluation of patients with PUO.[3,4]

Technetium-99m methylene-diphosphonate (Tc-99m MDP)

This bone-seeking agent, primarily not used for infection, plays an important role in the diagnosis of osteomyelitis. When it is appropriately used in a 3-phase imaging acquisition, a Tc-99mm MDP bone scan may be enough for the diagnosis of an acute osteomyelitis, particularly in children without previous trauma to their skeleton.[2,5]

Indications for the use of nuclear medicine

Osteomyelitis

This clinical entity may be imaged by one, or a combination of, the following procedures: a 3-phase bone scan, Ga-67 imaging and labelled leukocyte scintigraphy. In previously intact skeleton, it is preferable to use 3-phase bone scanning as the imaging modality of choice for osteomyelitis. It classically presents as a focal area of sequential increased perfusion, hyperaemia and late bone uptake (Fig. 1).[6] Because the increased uptake indicates the rate of new bone formation, the technique is less useful in the presence of fractures, in orthopaedic hardware, or in a neuropathic joint. In these conditions, specificity can be improved by adding Ga-67 imaging.[6] Combined bone/Ga-67 imaging may be positive (Fig. 2), negative (Fig. 3), or equivocal (Fig. 4). The overall accuracy of this combination

is about 65 - 80%. However, the technique requires multiple imaging sessions over several days.[6]

For the diagnosis of spinal osteomyelitis, magnetic resonance imaging (MRI) is the procedure of choice, with an accuracy of about 90%.[2] However, in situations in which MRI is difficult to perform or is not diagnostic, nuclear medicine imaging may be used. The technique of choice for vertebral osteomyelitis is combined bone/G-67 a scintigraphy.

When labelled leukocytes are used for the diagnosis of osteomyelitis, images may be difficult to interpret because it is difficult to distinguish uptake in infection from the normal uptake in bone marrow. Therefore, bone marrow imaging with Tc-99m colloid is combined with labelled leukocyte scans. The overall accuracy of combined leukocyte/marrow imaging for infection is approximately 90% (Fig. 5).[6] This imaging combination is used mainly in diabetes and joint prostheses.

With the worldwide prevalence of diabetes exceeding 200 million, an estimated quarter of this population will be at risk of developing a forefoot pedal ulcer, with a high risk of subsequent amputation.[7] The current standard approach to imaging a diabetic foot for infection is a bone scan and/or labelled leukocyte imaging. However, labelled leukocyte imaging alone does not provide the anatomical detail provided by a complementary bone scan. This anatomical detail is necessary to distinguish soft-tissue infection from bone infection. However, currently, labelled leukocyte imaging alone is the main procedure for evaluating diabetic foot infection. The technique has an overall accuracy of about 80 - 85%, regardless of the agent used.[7] Mid- and/or hind-foot complications in diabetics are usually due to a neuropathic joint or a Charcot's joint. Complementary marrow imaging may be required to determine the presence of superimposed infection in these joints. In most clinical cases of diabetic foot, a bone scan is not required, while the introduction of single photon emission computed tomography combined with anatomical computed tomography (SPECT-CT) should improve diagnostic accuracy, especially in the mid- and hind-foot.[7]

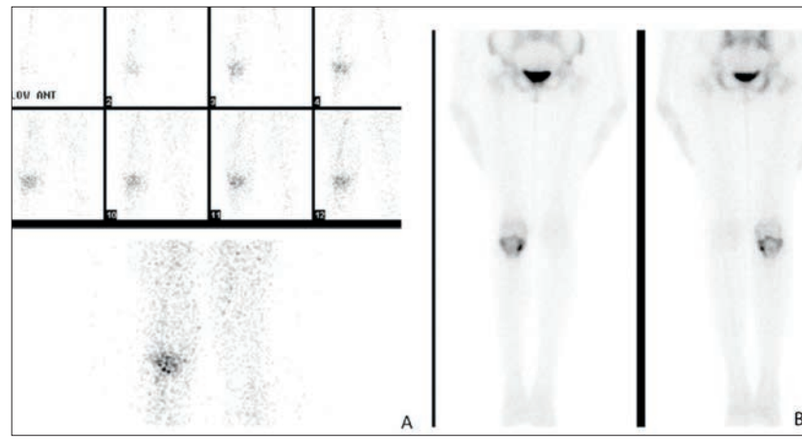

Fig. 1. A 26-year-old female patient with positive retroviral disease and a history of sudden swelling in the proximal right leg just below the knee. A 3-phase Tc-99m MDP bone scan shows evidence of increased perfusion and blood-pool activity (A) and increased delayed (2 hours) uptake (B) that are suspicious of infection.

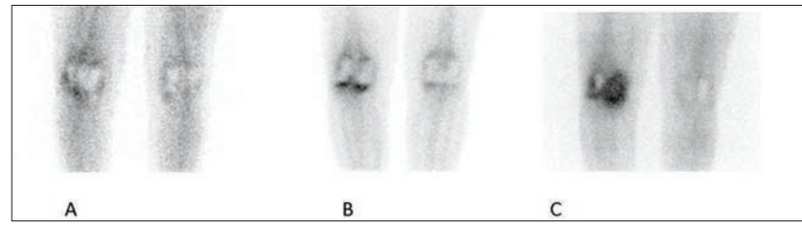

Fig. 2. A 72-year-old female patient with bilateral knee replacement. The left knee, replaced 12 years ago (2001), was painful for 3 months and is now swollen. The patient walks with difficulty. Tc-99m MDP posterior images (A and B) show increased blood-pool activity and delayed (2 hours) uptake. Forty-eight hours' Ga-67 imaging (C) shows increased activity that is congruent but more intense than the uptake in the bone scan, and is therefore positive for infection.

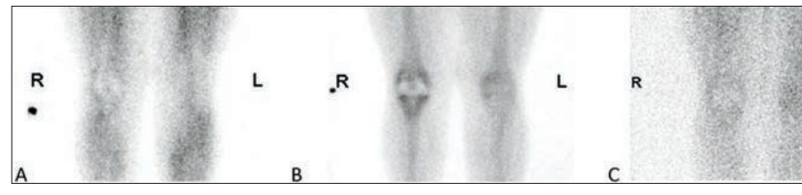

Fig. 3. A 76-year-old female patient with a painful right knee prosthesis inserted 18 months before. Moderate increased blood-pool activity (A) and late bone uptake (B) are noted on a Tc-99m MDP bone scan. No increased Ga-67 activity was seen on the 48 hours' imaging (C), thus excluding the possibility of infection.

Because of their clinical and histopathological similarities, it is difficult to distinguish between a loose and an infected joint prosthesis. This distinction is important because the treatment differs. Combined leukocyte/marrow imaging, which has an accuracy above 90%, is the imaging procedure of choice in determining whether or not infection is present.[8,9]

Pyrexia of unknown origin

It is often difficult to identify the source of PUO. Anatomical imaging (such as X-rays, and ultrasound) should be the first line in the work-up of PUO. If no diagnosis can be made, nuclear medicine imaging should be used. Labelled leukocyte imaging will be more sensitive in the early course of disease, while Ga-67 imaging will be more sensitive later in the illness.[10]

However, in the past decade, F-18 FDG PET has been increasingly used in patients with PUO. Because the most common causes of PUO are known to be from infections, neoplasms and inflammatory processes, it

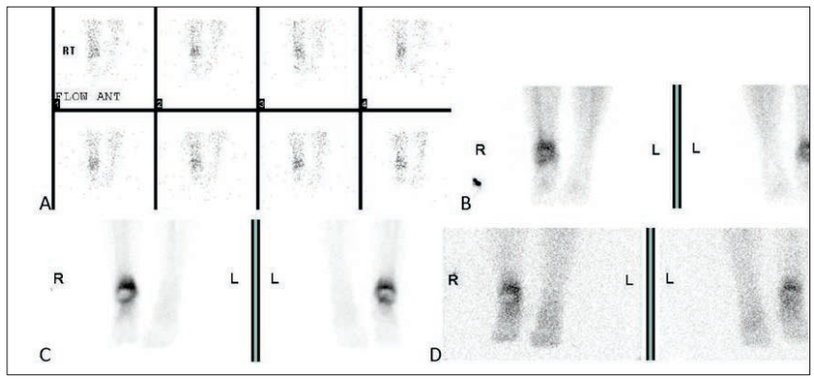

Fig. 4. A 31-year-old male patient who sustained a traumatic fracture in the right ankle in 2003. Due to continuous pain and reduced mobility, a prosthesis was inserted in 2012. He recently presented with severe pain. Increased perfusion (A), blood-pool activity (B) and late bone uptake (C) are noted on Tc-99m MDP bone scans. Similar activity was noted on a 48 hours' Ga-67 scan (D).

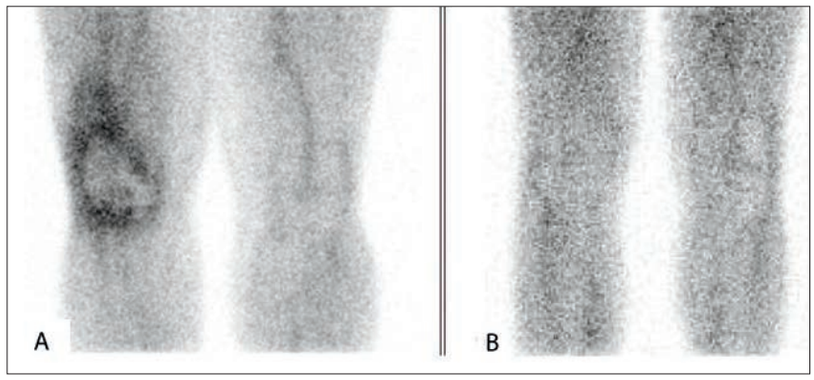

Fig. 5. A 48-year-old male patient with a swollen and painful right knee prosthesis. Increased activity is noted on in vivo *labelled leukocyte (A), but the Tc-99m colloid scan (B) is normal, confirming sepsis in the replaced knee.*

makes sense to use F-18 FDG PET to search for the aetiology. Studies have shown a negative predictive value (NPV) of 90% or more.[11,12] The practical implication of this high NPV is that in the presence of a negative F-18 FDG PET study, the cause of PUO is unlikely to be found with any further investigations or imaging studies. Because of its high sensitivity, F-18 FDG PET may become the first investigation for PUO.[2]

Immunocompromised conditions

Immunodeficient patients have an increased susceptibility to numerous infections. Ga-67 imaging is the procedure of choice in this group of patients.[13] Normal Ga-67 studies of the chest exclude infection with a high degree of certainty.[2] Focal uptake usually indicates bacterial pneumonia, whereas diffuse pulmonary uptake of Ga-67 is associated with *Pneumocystis jiroveci*. Leukocyte imaging is superior to Ga-67 for the detection of sinusitis and bowel infections.[13]

Postoperative infection

The diagnoses of infection in the postoperative patient may be challenging. When anatomical modalities (ultrasound, CT, MRI) fail to diagnose infection, labelled leukocyte scintigraphy is the preferred study.

Conclusion

Nuclear medicine imaging has a role in the diagnosis of patients suspected to harbour infections. All tracers described here are available in South Africa and may be used alone or in combination with others. The availability of F-18 FDG PET is still relatively limited but this should not be the primary reason to exclude the use of this modality. The success in the selection for an ideal and cost-effective study depends on the information provided from the referring clinicians.

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Summary

- Labelled leukocytes are more useful for the identification of bacterial infections.
- Tc-99m HMPAO is better suited for acute musculoskeletal infections.
- Combined bone/gallium imaging requires several days of scanning.
- The procedure of choice in the evaluation of the diabetic foot is labelled leukocyte imaging.
- The accuracy of leukocyte/marrow imaging in detecting prosthesis infection surpasses 90%.
- Both labelled leukocytes and Ga-67 have a place in the diagnosis of the cause of PUO.
- A normal Ga-67 scan of the chest of an immunodeficient patient excludes infection with a high degree of certainty.