RADIOLOGY

Functional imaging in orthopaedic infections—Update on immunoscintigraphy

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Summary
This article highlights the role of radionuclide imaging including isotope bone scanning, radiolabelled white cell scanning and newer imaging techniques such as monoclonal antibodies in orthopaedic infection.

Introduction
The diagnosis of orthopaedic infection is based on clinical examination, laboratory investigations, musculoskeletal imaging and tissue culture. Nuclear medicine plays an important role in the evaluation of patients with suspected musculoskeletal infection (osteomyelitis and septic arthritis). This is especially so in joint prostheses or patients with metallic implants, where complementary imaging with Ultrasonography (USG), Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) may not be helpful.

Imaging in orthopaedic infection

Plain radiographs
Plain radiographs are usually the first investigations in the diagnosis of orthopaedic infections. Although crucial, they are often inconclusive, non-specific and sometimes misleading. Changes do not occur until 1 to several weeks after the onset of infectious disease allowing bone or joint destruction if diagnosis is delayed.

USG, CT and MRI
When infection is established, USG, CT and MRI all have individual value in diagnosis including guiding biopsy and in therapy.

USG offers a non-invasive, operator-dependant evaluation of musculoskeletal infection especially in septic arthritis and is free of radiation. However, the uses of ultrasound in the diagnosis of osteomyelitis are limited to the detection of the soft tissue abnormalities around the bone because the sonic beam does not cross the bone cortex and identify a bone marrow discontinuity.

CT scanning provides an excellent assessment of bone and soft tissue structures. Cross-sectional images are created with the benefit of high density, high contrast and spatial resolution. The procedure involves significant radiation exposure.

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MRI gives a greater contrast resolution and higher anatomical detail than plain radiographs and CT, and does not involve radiation exposure. It is a useful procedure for the detection and determination of the extent of infection. However, because of imaging interference, MRI and CT scans are often not helpful in patients with metallic implants, aneurysm clips, pacemakers or prosthetic joints.3

Nuclear medicine in infection imaging

Nuclear medicine is a powerful diagnostic modality in the assessment of musculoskeletal abnormalities. Nuclear medicine applications in infection are most useful when complementary imaging is not helpful. Scintigraphic detection is based on physiochemical changes and hence provides a functional evaluation of bone pathology.

Basis

Radionuclide imaging uses applied tracer physiology in which the tracers are radionuclide compounds (radio pharmaceuticals). When the radio pharmaceutical is administered to the patient and it localises in the sites of abnormality, it emits gamma-rays, which are detected by scintillation crystals in a gamma camera. The crystal emits tiny scintillations of light, which reproduces the pattern of isotope distribution in the patient.4 Dealing with patients with presumed or established infective disorders, nuclear medicine techniques can answer the common clinical questions.

Mechanism of action

(1) Localisation in sites of enhanced vascular permeability.
(2) Localisation in sites of leucocytes accumulated in infective foci by diapedesis and chemotaxis.

Traditional bone scintigraphy in orthopaedic infection

Bone scans rely on the property of orthopaedic lesions to excite a local osteoblastic response and increase in vascularity. This results in an accumulation of radiotracer and will be seen on the bone scan as a ‘hot spot’. The introduction of 99mTc-labelled phosphates for skeletal imaging in 1971/72 has provided a non-invasive technique to detect and localise sites of osseous infection and became a reliable method for evaluating patients with suspected inflammatory bone disease and metastatic bone disease.5

A three-phase bone scan is the basic examination which detects sites of increased bone turnover with high sensitivity of more than 90%.6 Typically the scintigraphic appearance of osteomyelitis is associated with increase in uptake in all three phases (blood flow/angiographic, blood pool and delayed phases), especially the third. A normal 99mTc-diphosphonate bone scan excludes chronic osteomyelitis with a very high certainty of more than 90%.7 However, if any other cause of bone remodelling, complicating the diagnosis of infection is present, the sensitivity remains high but the specificity reduces markedly.8 Because of the low specificity of the isotope bone scan, more specific scintigraphic techniques are required when the bone scan is abnormal (Table 1).

67Gallium citrate increases specificity for imaging infections, but has an accuracy rate of less than 70%.6,9 67Gallium citrate has been replaced by white blood cell scans labelled with either 111indium oxime or 99mTc hexamethyl propylene amine oxime. The accuracy of diagnosing bone infection is increased by 111indium-WBC imaging and is still recommended as a gold standard for skeletal infection imaging by many authors.2,9,10 However, both leukocyte procedures require in vitro granulocyte isolation and labelling, which are time consuming and involve biohazard risk to medical personnel and potential for misadministration of blood products to the wrong patient. The search is still on for the ideal (Table 2) and newer infection imaging radio pharmaceuticals (Table 3).

Immunoscintigraphy (antibody imaging)

Scientific basis

Immunoscintigraphy is an imaging procedure using antibodies labelled with radiopharmaceuticals. The antigen reacting Fab’ fragment of an immunoglobulin can be tagged with a radiopharmaceutical and thus be available for infection imaging. Antibody imaging can be both

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**Table 1** Features of traditional agents commonly used for infection imaging.

<table>
<thead>
<tr>
<th>Radio pharmaceutical</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>99mTc-MDP</td>
<td>Readily available</td>
<td>Low specificity</td>
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<tr>
<td></td>
<td>Inexpensive</td>
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<td></td>
<td>High sensitivity</td>
<td></td>
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<tr>
<td>67Gallium</td>
<td>Easy to prepare</td>
<td>Time consuming, delayed imaging</td>
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<tr>
<td></td>
<td>Low toxicity</td>
<td>High radiation dose</td>
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<tr>
<td></td>
<td>Detects low grade infection</td>
<td>Low specificity</td>
</tr>
<tr>
<td>111In-WBC</td>
<td>High target to background ratio</td>
<td>Time-consuming preparation</td>
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<tr>
<td></td>
<td></td>
<td>Complex and expensive radiolabelling</td>
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<tr>
<td></td>
<td></td>
<td>In vitro labelling required</td>
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<td></td>
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<td>Poor availability</td>
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antibody (HAMA) response needs to be monitored.

antibodies, allergic reactions such as the human anti-mouse cyte monoclonal antibody/antibody fragments.

Advantages of immunoscintigraphy

non-specific, e.g polyclonal human immunoglobulin G (99mTc-HIG) and specific, e.g antigen binding anti-granulocyte monoclonal antibody/antibody fragments.

Since immunoscintigraphy involves use of cloned murine antibodies, allergic reactions such as the human anti-mouse antibody (HAMA) response needs to be monitored.

Advantages of immunoscintigraphy

- Unlike autologous leukocyte techniques in the imaging of infection, immunoscintigraphy does not require isolation of white blood cells ex vivo for tagging.
- In-vivo tagging avoids chances of misadministration and contamination of healthcare professionals.
- Available in a readymade kit, easier to prepare, simpler to use.
- The antibodies can be tagged with either with 111indium or 99mTc, however, because of low radiation dose, better quality images and availability, 99mTc is preferred.

99mTc-Sulesomab scintigraphy

99mTc-Sulesomab is 99mTc-labelled Fab’ fragment of IMMUNOMN3, an immunoglobulin G1 murine monoclonal antibody produced from a hybridoma developed by fusion of murine myeloma (SP2/0) cells with spleen lymphocytes obtained from a mouse immunised with carcinoembryonic antigen. The antibody reacts strongly with non-specific cross-reacting antigen (NCA-90) present on human granulocytes.11

Mechanism

99mTc-Sulesomab uptake at the site of infection is explained by the migration of circulating antibody-labelled granulocytes to the site of infection.

Advantages of 99mTc-Sulesomab scintigraphy

- 99mTc-Sulesomab is labelled with 99mtechnetium. 99mTc technetium is less expensive, readily available and gives superior quality images compared to 111indium.
- 99mTc-Sulesomab preparation is a simple 5 min, one-step process, thus eliminating the 2h delay, technically demanding cell isolation procedure and its concomitant biohazard risks to medical personnel and blood product misadministration risk to patients.
- 99mTc-Sulesomab images are obtained the same day (within hours) in contrast to the 18–24h delay with 111indium WBC scan.
- With 99mTc-Sulesomab, the granulocytes can be specifically tagged in situ by the circulating radiolabelled anti-granulocyte antibody. In contrast, WBC labelling is an in vitro process labelling lymphocytes and granulocytes present in 30–50ml of withdrawn blood. Thus 99mTc-Sulesomab is capable of tagging considerably more granulocytes than 111indium WBC scan.
- Chances of allergic reaction, especially the HAMA response are reduced with use of monoclonal antibody fragments instead of whole antibodies.
- Rapid clearance of radiotracer, since 99mTc-Sulesomab imaging involves antibody Fab’ fragments rather than whole antibody.

Present clinical experience

Hakki et al., in a total of 74 evaluable patients with a heterogeneous group of bone and joint infections including long bones, diabetic feet and prosthetic joints found that 99mTc-Sulesomab had a sensitivity of 93%, a specificity of 91%, an accuracy of 92%, a positive predictive value of 86% and a negative predictive value of 96% compared to 111indium. In contrast, WBC scans done concurrently in the same patients1 (Figs. 1 and 2).

In the other trial with 99mTc-Sulesomab, Becker et al. found a sensitivity of 90%, a specificity of 84.6% and a diagnostic accuracy of 87.9%, again in a heterogeneous group of patients with suspected musculoskeletal infections.12
Experience at our institution reveals a sensitivity of 96.7%, specificity of 85.1% and an accuracy of 89.5%, along with a significant negative predictive value of 98.2% including those of long bones, joints and diabetic feet. This emphasises the emerging role of $^{99m}$Tc-Sulesomab imaging in the evaluation of variety of orthopaedic infections.

The accuracy of $^{99m}$Tc-Sulesomab in the evaluation of suspected prosthetic joint infections was 81.5% with a sensitivity of 91%. With a high negative predictive value of 96%, $^{99m}$Tc-Sulesomab seems to be useful in excluding infection rather than confirming it in patients with suspected infection of prosthetic joints. This needs further evaluation.

**Practice points**

- Nuclear medicine imaging plays an important role in early and accurate diagnosis of orthopaedic infection
- WBC imaging presently is considered gold standard
- Immunoscintigraphy has an emerging role
- $^{99m}$Tc-Sulesomab imaging is rapid, simpler and safer to use with negligible HAMA response rate and accuracy comparable to WBC scanning but with better quality images
- Immunoscintigraphy has the potential to replace WBC scans for infection imaging

**Research directions**

- Continuing and further evaluation of clinical safety especially regarding HAMA response and implications to long-term prognosis after undergoing the test
- Cost effectiveness in the context of manpower and ease of use
- Collaboration across centres would help the immunoscintigraphy results to be evaluated in a wider perspective (maybe with multi-centre trials)

**References**