

Radionuclide Infection Imaging: Conventional to Hybrid

Muhammad Umar Khan and Muhammad Sharjeel Usmani

*Departments of Nuclear Medicine/PET Al-Jahra Hospital & Kuwait Cancer Control Centre,
Kuwait*

1. Introduction

Radionuclide imaging has been frequently used for detection and localization of infectious and inflammatory diseases for over five decades. Although there are many infection seeking agents available and currently being used but there is a general consensus that none of them is ideal. No clear cut guidelines exist to recommend a particular radionuclide imaging procedure for a particular clinical indication, however, in some instances the literature does provide us with ample evidence for the choice of the infection specific agent whereas one may have to depend upon the routine management protocols to decide which radionuclide imaging procedure to perform in a particular situation. In fact, presently, the clinical utility of radionuclide infection imaging varies under different circumstances and clinical scenarios; but with the incorporation of hybrid imaging systems, the fusion of functional and anatomical data in form of SPECT-CT and PET-CT has certainly improved the sensitivity and specificity of detecting and localizing an infectious process. Ga-67 citrate, bone seeking radiotracers, radiolabelled leukocytes, antibody and antibody fragments labelled white cells are used in different clinical situations such as osteomyelitis, diabetic foot, infected vascular grafts, infected hip or knee prostheses, intra-abdominal infections including acute appendicitis, cardiovascular, pulmonary infections, malignant otitis externa with variable sensitivity and specificity. Similarly, the ability of F-18 FDG PET to detect infection, inflammation and granulomatous diseases due to their increased glycolytic activity has provided us with another effective agent especially in cases of fever of unknown origin, vasculitis, chronic osteomyelitis, sarcoidosis, inflammatory bowel disease and assessing response to therapy. New advances in the form of SPECT-CT have now also incremented the diagnostic capability of conventional scintigraphic procedures to localize infection. Finally, many investigational new infection seeking agents are in the process of being developed in search of an ideal. These include Tc-99m ubiquickidin, Tc-99m labelled Interleukin-8, N-formyl products, chemotactic cytokines etc. Therefore, with on going research in development of infection specific agents and the advent of hybrid imaging the future offers definite hope for better infection detection and localization in our patients.

2. Gallium scintigraphy

2.1 Gallium-67 citrate: Pharmacological and physiochemical characteristics

Ga-67 citrate has been used since 1971 to detect and localize infectious and inflammatory process. The exact mechanism of uptake has been studied extensively and various factors

are thought to govern the tracer accumulation at the infection site. Most of the circulating Ga-67 is in the plasma and nearly all of it complexes with transferrin. Due to the increased blood flow and vascular membrane permeability the Ga-67/transferrin complex is delivered to the inflammatory sites or foci. Ga-67 is also thought to bind to lactoferrin which is present in high concentrations in the inflammatory foci. Direct bacterial uptake and accumulation as well as Ga-67 transportation bound to the leukocytes is also another factor studied. Bacteria and some fungi produce low molecular weight chelates called siderophores present on their cell surfaces and these have a high affinity for Ga-67. The Ga-67/siderophore complex facilitates the transport of Ga-67 within the cell itself. This mechanism of Ga-67 uptake may be attributable to the accumulation of Ga-67 within an abscess in neutropenic patients.

Ga-67 is a cyclotron produced radioisotope and emits principle gamma rays (93, 184, 296, 394 KeV). These are suitable for imaging. The dosage of Ga-67 typically used is 185-370 MBq for infection imaging, however, in our personal experience even a lesser dose did produce adequate images worth interpretation. Around 15-25% of the injected dose is excreted via the kidneys by 24 hours. After 24 hours the principle route of excretion is the colon. At 48 hours 75% of the injected dose remains in the body and is equally distributed among the liver, bone, bone marrow and soft tissues. The physical half-life of Ga-67 is 78 hours while the biological half-life of around 25 days gives ample opportunity to take delayed images even after days post injection.

2.2 Gallium-67: Imaging protocols and pre-requisites

Ga-67 imaging is usually performed 18-72 hours post injection, however, we also routinely image the patients at 6 hours post injection particularly if the suspected focus of infection is in the abdomen. This we have found to be helpful in a number of cases. Limited spot views or whole body imaging can be done depending upon the clinical indication and the use of a medium energy collimator is a standard. Patients' preparation with laxatives and enemas has been considered by some but the effectiveness of such preparation seems limited. Recent Gadolinium exposure as in an MR contrast study or multiple blood transfusions resulting in excess ferric ion may alter the Ga-67 biodistribution by saturation of the protein-binding sites. This needs to be sorted out in history while preparing the patient for injection and imaging.

2.3 Gallium-67: Clinical utilities and applications

Ga-67 citrate has been extensively used in the past four decades in clinical practice for several pathological conditions particularly whenever infection or inflammation has been in question. Ga-67 has demonstrated high sensitivity for both acute and chronic infectious process as well as non-infectious inflammation. Moreover, the Ga-67 tracer activity parallels acute inflammation, returning to normal as the disease process resolves.

The most common of the clinical scenarios where Ga-67 has been and is still utilized include fever of unknown origin (FUO), sarcoidosis, pulmonary infections like pneumocystis carinii pneumonia (PCP), drug-induced pulmonary toxicity as is seen with bleomycin or amiodarone, and in cases of malignant otitis externa. Further Ga-67 has been successfully utilized in spinal discitis and vertebral osteomyelitis. Mediastinal infections in immunocompromised patients have been detected by Ga-67.

In patients with the clinical diagnosis of FUO, anatomical imaging is less helpful as functional changes occur prior to anatomical alteration at a suspected site resulting in

normal anatomical imaging. FUO has numerous causes and neoplasms including lymphoma account for up to 25% of these cases. Although PET/CT and labelled leukocytes are more frequently employed for FUO but Ga-67 can still be helpful with good detection rates where these formal are not available (Figure 1).

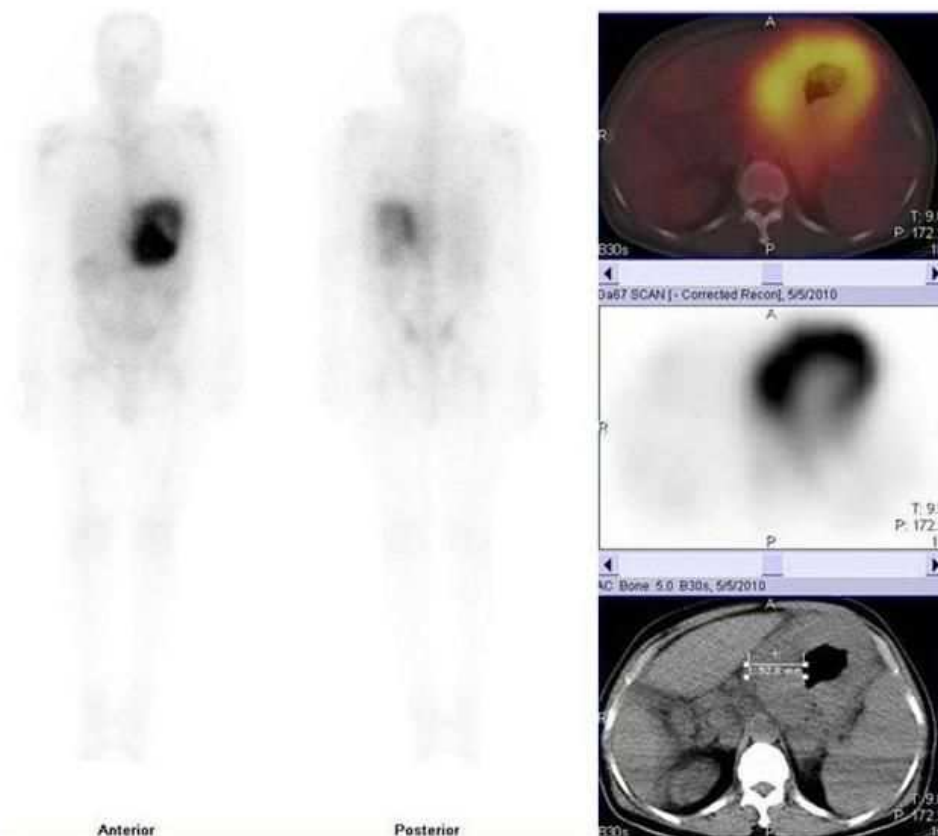


Fig. 1. A 40-year-old male with FUO. Ga-67 scintigraphy shows intense tracer accumulation in the left side of abdomen. SPECT/CT images localize the abnormal uptake to the thickened gastric wall measuring over 50mm. SPECT/CT report raised the suspicion of lymphoma and suggested subsequent endoscopic biopsy; the report of which showed findings consistent with gastric lymphoma.

Sarcoidosis is a systemic disorder that involves the lungs in up to 90% of the cases. Hilar lymph nodal involvement is evident in over 80% of the cases. Pulmonary accumulation of Ga-67 in these patients parallels active disease and there exists a good concordance between the Ga-67 intensity of uptake and the disease severity. Ga-67 scintigraphy has a sensitivity of 70% for detecting pulmonary parenchymal disease and a 95% for hilar adenopathy. The overall sensitivity is about 90%. If these patients are further subjected to a Thallium scintigraphic exam, it is usually negative. A characteristic Ga-67 scintigraphic pattern seen in patients with sarcoidosis is termed as the "Panda sign" (due to typically increased and

more prominent lacrimal, parotid and nasopharyngeal activity). This can be seen in up to 80% of patients with stage I disease. Moreover the pre-tracheal and bilateral hilar adenopathy gives rise to an inverted “Y” which is termed as a “Lambda sign” (Figure 2). It is important, however, to remember that the panda sign can be seen in cases of Mikulicz syndrome (uveoparotid fever), lymphoma, Sjogren’s syndrome and HIV. Some Pulmonologist believe that a panda sign on Ga-67 scintigraphy even without a lambda sign, but with hilar adenopathy on CXR or CT is still suggestive of sarcoidosis and do not opt for a biopsy.

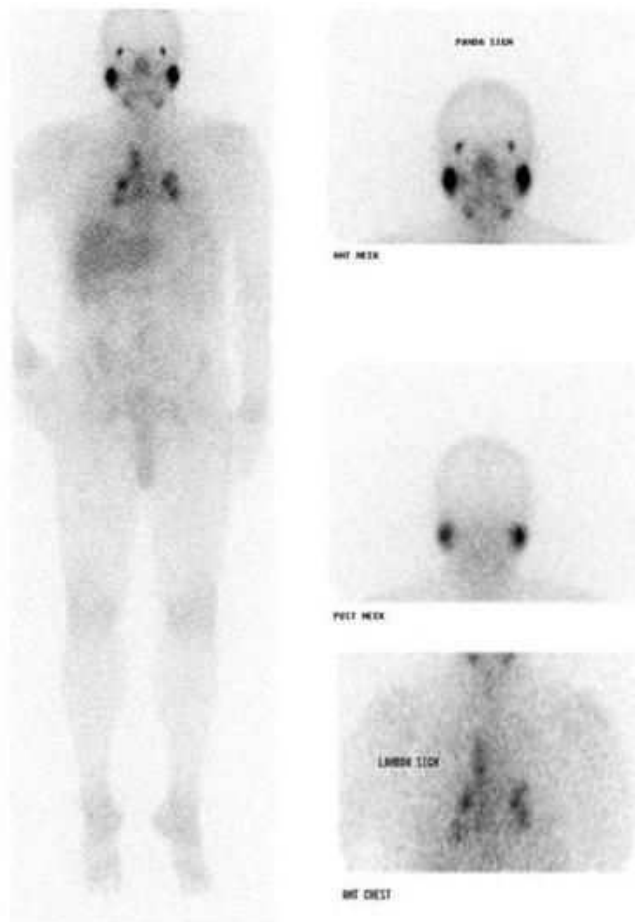


Fig. 2. A 28-year-old male with suspicion of sarcoidosis. Ga-67 scintigraphy shows typical “Panda” and “Lambda” signs.

The sensitivity of Ga-67 scintigraphy for PCP in HIV patients has been reported to be as high as 90-95%. The scintigraphic pattern is that of diffuse increased pulmonary uptake which is disproportionate to the clinical and radiological findings. However, due to a long

list of differentials that can give rise to a similar scintigraphic picture the specificity can be increased by considering the intensity and distribution of the tracer as well as the comparison of activity either with the liver uptake or the sternum. Diffuse heterogeneous pulmonary activity which is more intense than the liver has specificity for PCP between 95-100%.

In cases of drug-induced pulmonary toxicity (Bleomycin, Cyclophosphamide, Methotrexate, Nitrofurantoin, Amiodarone) radiologically the abnormalities are not evident at early stages of the toxicity. In such a scenario, Ga-67 provides early detection with usually moderate increased uptake seen in the lungs on the scan. More recently, Ga-67 scintigraphy (Figure 3) as well as PET/CT has been used to evaluate malignant otitis externa. These modalities are also used to evaluate the response to therapy in such cases. Vertebral osteomyelitis has been detected and evaluated by Ga-67, however, the specificity can be increased if the interpretation is done in conjunction with the bone scan. An accepted criterion in such a clinical scenario is to have Ga-67 uptake greater than uptake seen on the bone scan with incongruent tracer distribution. Labelled leukocytes, however, are more accurate for the evaluation of vertebral osteomyelitis.

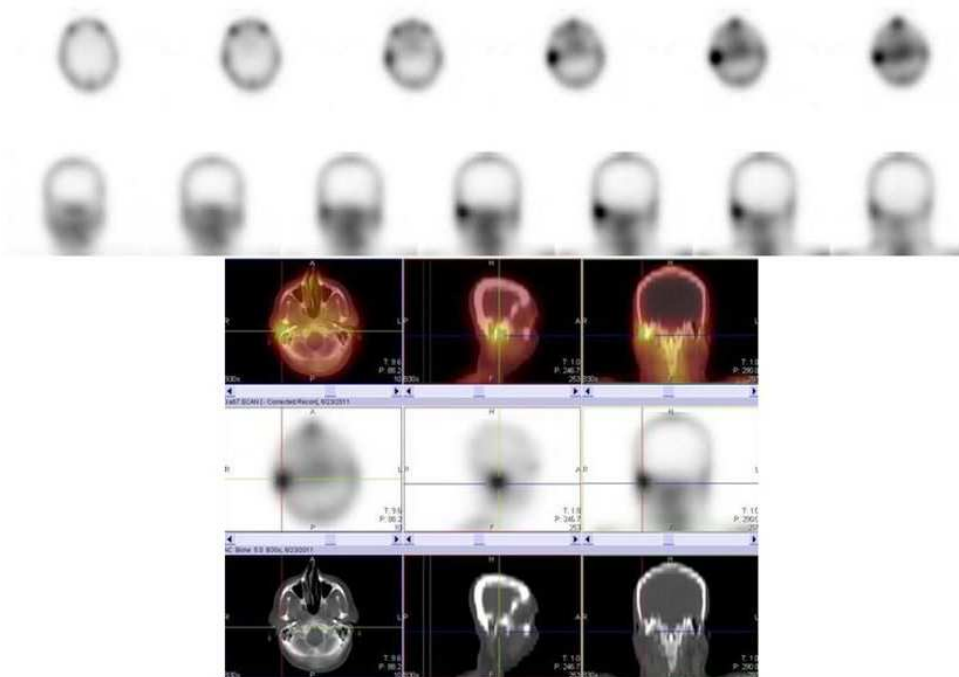


Fig. 3. A 46-year-old female with clinical diagnosis of right malignant otitis externa referred for Ga-67 scintigraphy. Transverse and coronal SPECT images show intense tracer uptake in the right auricular region. SPECT/CT images localize the abnormal uptake to right external auditory meatus without evidence of any underlying bony cortical breach.

2.4 Gallium-67: Hybrid SPECT/CT imaging

Ga-67 scintigraphy is primarily characterized by poor spatial resolution and low specificity due to paucity of anatomical and morphological information. (Bar-Shalom et al., 2006) studied patients with multiple infectious conditions including FOU and concluded that SPECT/CT was found to be beneficial in determining the precise anatomical sites of infection in 85% of discordant studies. In particular, substantial benefits were observed in scans of the chest and abdomen. In our own experience the addition of SPECT/CT to Ga-67 scintigraphy has a definite incremental value that helps resolve many difficult clinical scenarios (Figure 4).

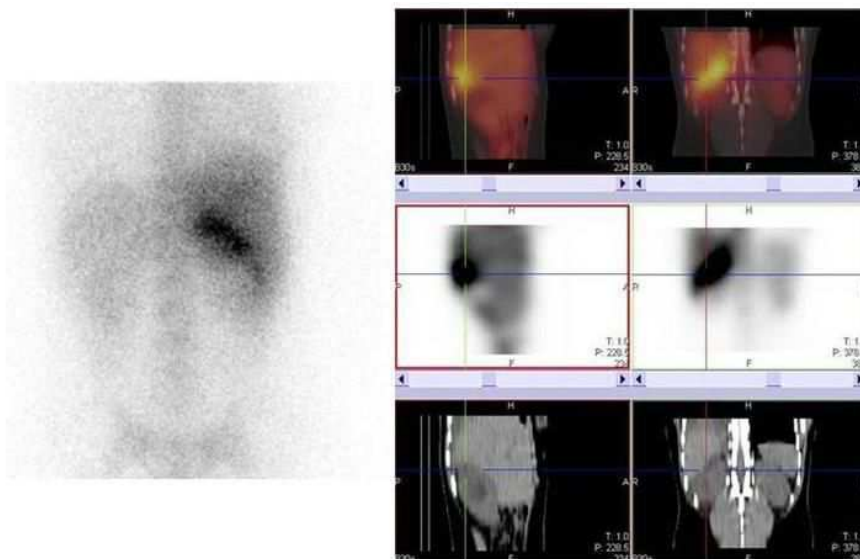


Fig. 4. A 21-year-old female with history of polycystic kidney disease referred for Ga-67 scintigraphy to evaluate suspected infected right renal cyst. Ga-67 scintigraphy shows linear intense tracer accumulation in the infra-hepatic region. SPECT/CT images localize the abnormal uptake to an area in the upper pole of right kidney just above a hypodensity (renal cyst) that shows photopenia on SPECT images. Subsequent guided biopsy drained abscess just beneath the renal capsule.

3. Bone scintigraphy

3.1 Tc-99m MDP: Pharmacological and physiochemical characteristics

Tc-99m Methylene-Diphosphonate (MDP) has been extensively used in the work up of osteomyelitis. The mechanism of uptake of diphosphonates has not been completely elucidated but the general presumption is that they are adsorbed to the mineral phase of bone with relatively lesser binding to the organic phase. Some also have postulated chemo-adsorption to the hydroxyl-apatite mineral component of the osseous matrix itself. Tc-99m (Technetium 99m) is a generator produced radioisotope with the principle gamma photon of 140 KeV optimal for imaging with low energy high resolution parallel-hole collimator. The physical half-life of Tc-99m is 6 hours making possible delayed imaging with good target to

background ratio. Approximately 50% of the injected dose is localized to the bone. The tracer uptake is dependent upon the blood flow and the rate of new bone formation.

3.2 Tc-99m MDP: Imaging protocols and pre-requisites

When bone scintigraphy is performed for the evaluation of osteomyelitis, the study is done in three phases. These include a dynamic sequence termed as the flow or perfusion phase, followed by immediate static image of the area of interest termed as the blood-pool phase or soft tissue phase. The third phase is the static delayed imaging of the area of interest usually acquired 2-4 hours post injection. Some also perform a fourth phase at 24 hours which is usually a static spot view of the region of interest. The usual adult dosage is 740-925 MBq. Patients are instructed to be well hydrated and void frequently after the injection.

3.3 Tc-99m MDP: Clinical utilities and applications

Three-phase bone scintigraphy is the radionuclide procedure of choice for diagnosing osteomyelitis in non-violated bone i.e. bone that is not affected by underlying conditions. It is highly sensitive for diagnosing osteomyelitis and can detect the process 7-14 days before the manifestation of radiological changes. The reported sensitivity of 90-100% and specificity of 70-95% for identification of osteomyelitis is in non-violated bone. In adults a negative bone scan essentially rules out infection. Focal hyperperfusion, focal hyperemia, and focally increased bony uptake on delayed images are the characteristic scintigraphic findings for osteomyelitis. Many times due to some underlying bone conditions the specificity of the bone scan for osteomyelitis is further compromised. In such situations, the additional images at 24 hours (4th - phase) may improve specificity. This is due to the fact that uptake in woven or immature bone present in osteomyelitis continues for several more hours than normal bone. The accuracy of 4-phase bone scan that is more specific but less sensitive than a 3-phase bone scan is approximately 85%. Further the specificity of bone scan can also be improved by addition of Ga-67 scintigraphy. The overall accuracy of bone scan/Ga-67 scintigraphy is approximately 65-80%.

3.4 Tc-99m MDP: Hybrid SPECT/CT imaging

Three-phase bone scintigraphy and MRI are considered the modalities of choice for diagnosing osteomyelitis. Moreover, MRI can assess the associated soft tissue complications. MRI has its limitations as well. The replacement of marrow fat with edema and exudate results in a decreased signal on T1 and an increased signal on T2-weighted images. Such findings are not specific for osteomyelitis and can be seen with acute infarction, fracture or even tumour. Therefore the overall sensitivity and specificity of MRI for detection of acute osteomyelitis ranges from 92-100% and 89-100% respectively. CT is more sensitive to detect cortical destruction. On site-based analysis by (Bar-Shalom et al., 2006) scintigraphy (planar & SPECT) and SPECT/CT showed concordant results for diagnosis and localization of 50% of infection sites. SPECT/CT defined the precise anatomical localization of 44% of infectious sites that were erroneous or equivocal on scintigraphy in this study. In another preliminary report, (Horger et al., 2003) found that SPECT/CT improved the diagnostic performance of three-phase bone scan for osteomyelitis avoiding false-positive or equivocal results. In our own experience SPECT/CT has always had an incremental value to routine planar imaging and in many clinical situations in particular further characterizing the abnormalities to reach definitive imaging diagnosis (Figure 5).

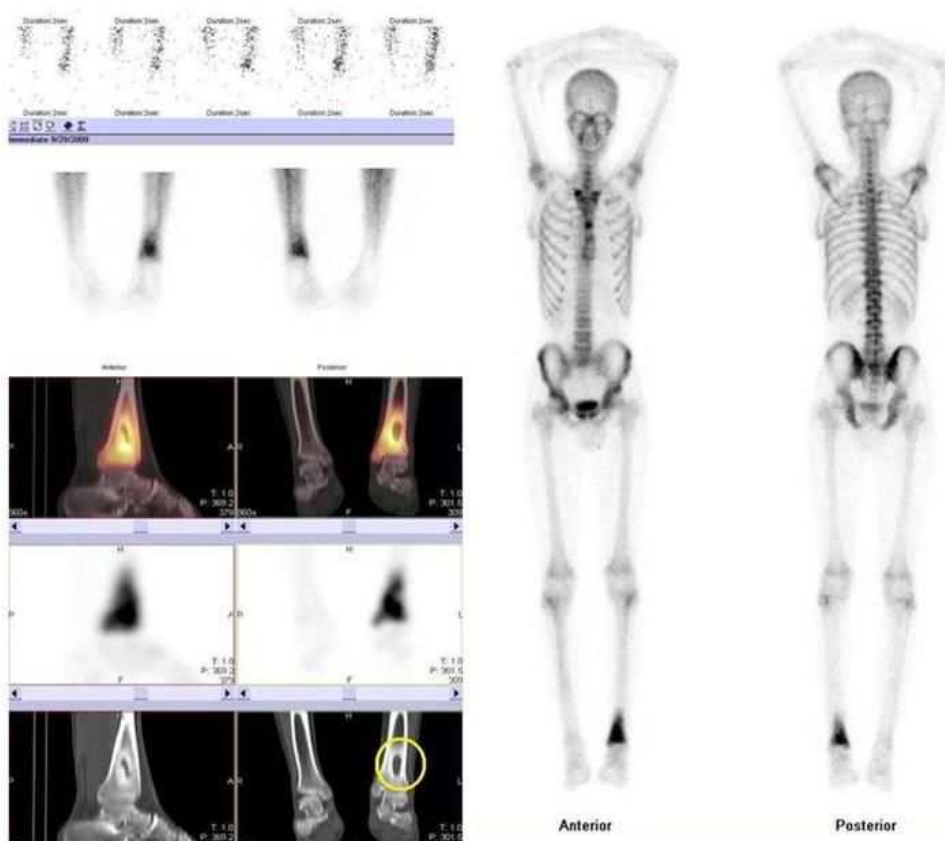


Fig. 5. A 19-year old male referred for evaluation of pain left lower limb. Tc-99m MDP images show hyperaemia, increased pool activity and intense increase tracer uptake in the distal end of left tibia. SPECT/CT images show a well-defined low attenuation metaphyseal lesion with central radiolucent area surrounded by peripheral bone sclerosis clearly confined to within the bone itself sparing the joint cavity. Findings consistent with diagnosis of osteomyelitis with features typical of a Brodie's Abscess.

4. Radiolabelled leukocytes scintigraphy

4.1 Radiolabelled leukocytes: Pharmacological and physiochemical characteristics

These days radiolabelled leukocytes are the most commonly used method to detect and localize infection. The leukocytes can be labelled using either Indium-111 (In-111) oxyquinoline or Tc-99m hexamethylpropylene amine oxime (HMPAO). In-111 oxine is a highly lipophilic ligand which diffuses across leukocyte membranes. Once inside the cell, it dissociates into oxine (8-hydroxyquinoline, which diffuses out of the cell) while In-111 is retained within the cytoplasm as a result of binding with intracellular proteins. In-111 labelled leukocytes localize at sites of infection through diapedesis, chemotaxis, and enhanced vascular permeability. In-111 has a physical half-life of 67 hours. It decays by

electron capture with gamma emissions of 173 and 247 KeV. In-111 labelled leukocytes are normally distributed to the liver, spleen, and bone marrow. Intense pulmonary activity is seen soon after injection, which clears rapidly, and it is probably due to leukocyte activation during labelling, which impedes their movement through the pulmonary vascular bed, prolonging their passage through the lungs.

Tc-99m HMPAO is a lipophilic agent that readily crosses the cell membrane of leukocytes. Once inside the cell the compound becomes hydrophilic and remains trapped. It is subsequently bound to intracellular organelles, primarily the nucleus and mitochondria. The bond to granulocytes is more stable than to monocytes and the tag elutes from these cells five times more rapidly. The normal biodistribution of Tc-99m HMPAO labeled leukocytes is more variable. In addition to the reticuloendothelial system, activity is also normally present in the genitourinary tract, large bowel, blood pool, and occasionally the gallbladder. Physiologic bowel excretion limits the usefulness of this agent for imaging abdominal infections.

4.2 Radiolabelled leukocytes: Labeling technique

There are a number of methods for labelling leukocytes, however, the basic principles and technique remains uniform. Approximately 40 ml of blood is withdrawn from the patient into a syringe that contains anticoagulant. This syringe containing blood is then kept in an upright position for about 1-2 hours to promote gravity erythrocyte sedimentation, a process that is facilitated by the addition of hydroxyethyl starch. The process can be accelerated by using hypotonic lysis of the red cells instead of gravity sedimentation as well. After the erythrocytes have been separated, the leukocytes must be separated from platelets. The leukocyte-rich plasma is centrifuged, and the leukocyte "pellet" that forms at the bottom of the tube is removed, incubated with the radiolabel, washed, and re-injected into the patient. The usual dose of In-111 labelled leukocytes is 10-18.5 MBq; while the routine dose of Tc-99m HMPAO labelled leukocytes is 185-370 MBq. The majority of leukocytes labelled are neutrophils, and hence the procedure is most useful for identifying neutrophil-mediated inflammatory processes, such as bacterial infections. The procedure is less useful in conditions where the predominant cellular response is other than neutrophilic such as tuberculosis.

A total white count of at least 2000/mm³ is needed to obtain satisfactory images. ABO compatible donor WBC's may be used in neutropenic patients (i.e. White cell count less than 2000/mm³). Radiolabelled leukocytes should be administered within 1-2 hours of cell labelling. Labelled cells stored longer than 3 hours have a significant loss of cell viability. Temperatures higher than 70°F tend to increase cell damage and should be avoided. Cell labelling should be performed by trained laboratory personnel in a laminar flow hood using sterile procedures. Care must be taken to ensure correct identification of patients and blood products. All patients and laboratory procedures should have an appropriate quality control program.

4.3 Radiolabelled leukocytes: Imaging protocols and pre-requisites

In-111 labelled leukocyte is usually performed 18-24 hours post injection because early imaging at 4 hours usually misses out on two-thirds of the lesions detected on later images. However, it is critical to obtain early (1-4 hour) images when evaluating patients for inflammatory bowel disease or those suspected of possible ischemic bowel disease.

Occasionally, 48 hour delayed images may be necessary due to prolonged circulation of labelled cells in about 10% of cases. Limited spot views or whole body imaging can be acquired depending upon the clinical indication. Images should be acquired with a medium-energy parallel-hole collimator. Energy discrimination is accomplished by using a 15% window centered on the 173 KeV photopeak and a 20% window centered on the 247 KeV photopeak. Simultaneous In-111 leukocyte/Tc-99m MDP bone images can be obtained using a gamma camera that can acquire and discriminate the 140 KeV Tc-99m photons from the In-111 photons. Each In-111 leukocyte/Tc-99m bone image is acquired using a medium energy collimator for 50K counts in the In-111 window or for 15 minutes, 4 hours and/or 16-30 hours post injection of In-111 leukocytes. Tc-99m Sulphur colloid imaging can also be performed after or simultaneously with In-111 leukocyte imaging if bone marrow distribution is in question.

The interval between injection of Tc-99m HMPAO labeled leukocytes and imaging varies with the indication; in general, imaging is usually performed 3-4 hours post injection. Some centers perform only 2 hours post injection images and occasionally 24 hour delayed images may be necessary due to prolonged circulation of labelled cells.

4.4 Radiolabelled leukocytes: Clinical utilities and applications

Labelled leukocytes have been used for the diagnosis of complicated osteomyelitis after fractures and surgery i.e. violated bone, vascular graft infections, and various soft-tissue insults. In-111 labelled leukocytes are probably the preferable agent for imaging suspected sites of infection in the abdomen, while Ga-67 is preferable for detecting pulmonary pathology in the setting of FUO. There are advantages as well as certain disadvantages associated with both In-111 and Tc-99m labelled leukocytes. Advantages of the In-111 label are those of virtually constant normal distribution of activity that is limited to the liver, spleen, and bone marrow and its more stable in-vivo characteristics. Further In-111 labelled leukocytes can be used in simultaneous dual-isotope acquisitions. On the contrary, the drawbacks of the In-111 label include a low photon flux due to less than ideal photon energies. When compared to the Tc-99m label, the latter has a high photon flux and somewhat ideal photon energies; with relatively more radioactivity injected, the ability to detect abnormalities within a few hours post injection is a plus for Tc-99m label. Disadvantages of Tc-99m labelled leukocytes include genitourinary tract activity, which appears shortly after injection, and colonic activity, that appears by 4 hours post injection thereby obscuring potential foci of infections at these sites.

Labelled leukocytes have been studied by many to be an accurate technique for the diagnosis of osteomyelitis in the setting of violated bones as well as in diabetic foot infection. The overall sensitivity and specificity of Tc-99m HMPAO labelled leukocytes is 88% and 91%, respectively, for osteomyelitis in previously violated bones. However, Tc-99m HMPAO labelled leukocytes imaging is performed only after a positive finding on a three phase bone imaging, because the latter is highly sensitive but significantly less expensive, making it more appropriate as a first-line screening procedure. (Devillers et al., 2000) reported an overall sensitivity, specificity, and accuracy of 93%, 100%, and 96%, respectively, for Tc-99m HMPAO labelled leukocytes and 100%, 17%, and 53.3%, respectively, for Tc-99m MDP bone imaging. In our own experience combined Tc-99m HMPAO/Tc-99m MDP imaging proved useful in diagnosing osteomyelitis. The specificity of Tc-99m MDP bone scanning improved from 30% to 78% with the addition of Tc-99m HMPAO labelled leukocytes (Figure 6).

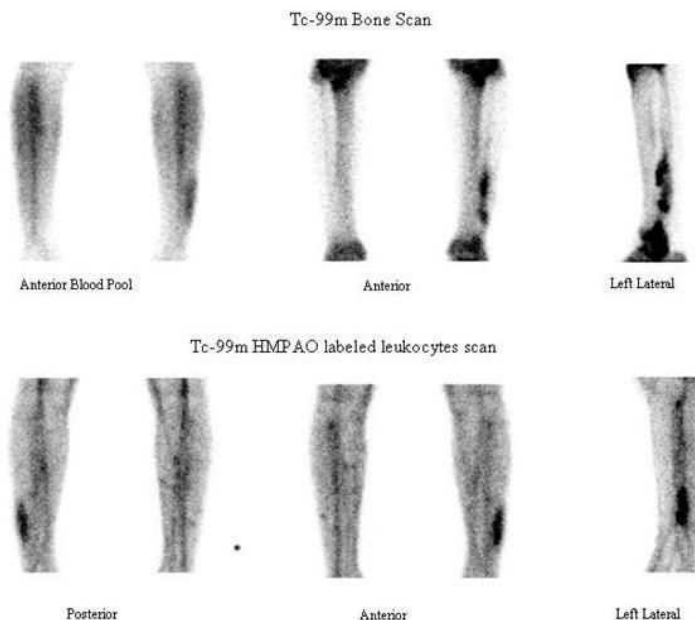


Fig. 6. A 30-year old female with chronic left leg pain, presented with tenderness and swelling at left lower leg. Tc-99m MDP bone scan show increased pool activity and increase tracer accumulation at the distal $\frac{1}{2}$ of left fibula on delayed images. Tc-99m HMPAO labelled leukocytes scan showed increase tracer uptake in the distal left fibula corresponding to the site seen on bone scan, findings consistent with scintigraphic evidence of osteomyelitis.

Labelled leukocytes imaging have been used in the diagnosis of orthopaedic implant infection after positive findings on three phase bone scanning. False positive scans can occur due to dystrophic ossification, peri-prosthetic granulomas, altered distribution of red marrow, and damage to the polyethelene surface of the prosthesis and metallosis. Combined leukocyte-marrow imaging can overcome many of the problems created by variable marrow distribution post-operatively. (Palestro et al., 1990) reported good results with combined In-111 labelled leukocytes/bone marrow imaging, with 86–100% sensitivity and 97–100% specificity in hip and knee prosthesis infections. (Joseph et al., 2001) also noted the ability of added sulphur colloid scanning to eliminate the false positive results. Our own experience suggest Tc-99m HMPAO labelled leukocytes scan appears significantly valuable in detecting osteomyelitis in patients with prosthetic implants (Figure 7).

Labelled leukocyte imaging is the procedure of choice for the evaluation of patients with diabetic foot. Sensitivity and specificity of In-111 labelled leukocytes for diabetic foot osteomyelitis is between 72%–100% and between 67%–100%, respectively. Sensitivity of Tc-99m HMPAO labelled leukocytes has been reported to be 90% and 93% while the specificity has been observed to be 86% and 100% by various groups. Interestingly, the combination of Tc-99m HMPAO labelled leukocytes scan with Tc-99m three phase bone scan has yielded both high sensitivity and high specificity (92.6% and 97.6%, respectively), moreover this combination is of benefit in patients with Charcot osteoarthopathy. The reported sensitivity



Fig. 7. A 70-year old female with history of left total knee replacement three years ago, presented with pain and swelling in the left knee prosthesis. Tc99m MDP bone scan show increased pool activity and intense increase tracer accumulation around left knee prosthesis. Tc-99m HMPAO labelled leukocytes scan showed increase tracer localization with rings of tracer uptake at the femoral component of left knee prosthesis suggesting prosthetic infection.

of 92.6% and a specificity of 97.6% by (Poirier et al., 2002) for Tc-99m HMPAO/Tc-99m MDP bone imaging for the diagnosis of osteomyelitis in diabetic foot ulcers appear promising and it is believed that neuroarthropathy does not affect the performance of this scan. In our own institutional experience this combination for diabetic foot ulcers proved to be useful in diagnosing underlying osteomyelitis (Figure 8).



Fig. 8. A 50-year old male with history of diabetic right big toe amputation done 3 years ago, now presented with discharge from the right foot. Tc-99m HMPAO labelled leukocytes scan showed features consistent with osteomyelitis at right 3rd metatarsal bone with overlying soft tissue infection in the right distal foot.

Leukocyte labelled imaging is not as sensitive for infection of the spine as it is for other musculoskeletal infections and may be falsely negative in up to 80% of cases. The difficulty in interpretation may be related to the large percentage of spinal osteomyelitis which produces a cold, rather than a hot lesion (marrow uptake in the spine may be higher than in

the adjacent inflammatory site which may mask the abnormality or cause the appearance of a cold defect). MRI is presumably the modality of choice when evaluating patients for suspected vertebral osteomyelitis.

In-111 labelled leukocytes scans are superior to Ga-67 for evaluation of suspected abscess in abdomen and pelvis due to the lack of a normal bowel excretory pathway. Some abscesses accumulate In-111 labelled leukocytes very slowly, and 48 hour delayed imaging may be necessary to identify these lesions. In appendicitis a focal area of increased activity in the right lower quadrant may be identified. Labelled leukocyte can be used to assess for disease activity and distribution of inflammatory bowel disease and excellent correlation is found between endoscopy, histology, and scintigraphic findings for disease extent and activity. (Annovazzi et al., 2005) reported in a meta-analysis that leukocytes labelled with In-111 oxine or Tc-99m HMPAO should be considered as the procedures of choice in acute phases of disease, since endoscopic and barium studies are contraindicated.

Labelled leukocyte imaging has been successfully utilized to detect both cardiovascular and central nervous system infections with limited clinical consequences. Leukocyte scintigraphy provides valuable information about contrast-enhancing brain lesions seen on radiological imaging. Positive findings indicate that the origin of the brain lesion is almost assuredly infectious; a negative result rules out infection with a high degree of certainty. However, false positive results can be seen in brain tumours, and false-negative results in patients receiving high-dose steroids. Labelled leukocyte imaging is the radionuclide procedure of choice for diagnosis of graft infection, with a sensitivity of more than 90%; neither duration of symptoms nor pre-treatment with antibiotics adversely affects the study. The specificity of labelled leukocyte imaging is more variable, ranging from 53% to 100%. Causes of false-positive results include peri-graft hematomas, bleeding, graft thrombosis, pseudoaneurysms, and graft endothelialisation, which occur within the first 1-2 weeks after placement.

4.5 Radiolabelled leukocytes: Hybrid SPECT/CT imaging

SPECT/CT has incremental value for interpretation of labelled leukocytes imaging for an array of clinical indications in different regions of the body, by distinguishing normal physiologic distribution from accumulation due to underlying infectious process. Benefit has been observed when characterizing foci of labelled leukocytes accumulation near the major vessels. The hybrid technology helps in discriminating blood-pool activity from infectious sites, particularly in evaluation of suspected vascular graft infection and fever of unknown origin. Moreover, SPECT/CT with Tc-99m HMPAO labelled leukocytes is useful to image bone and joint infections, providing accurate localization especially some cases where planar images alone are not able to distinguish soft tissue from bone and to precisely define the extent of infection, thus modifying clinical patient management and therapeutic approaches in several cases. In particular those with diabetic foot infection, it helps support treatment planning and avoiding more invasive procedures. (Filippi & Schillaci, 2006) more recently reported that SPECT/CT avoided unnecessary bone amputation in significant numbers of patients.

(Filippi & Schillaci, 2006) have evaluated the usefulness of SPECT/CT for interpreting Tc-99m HMPAO labelled leukocytes in bone and joint infection. SPECT/CT fusion correctly characterized and localized the site of abnormal uptakes in all patients with osteomyelitis, having a substantial impact on the clinical management. Moreover, those patients with a suspicion of infection post orthopaedic implants, SPECT/CT offered a more accurate

anatomic localization of the site of infection than SPECT alone allowing differentiation between prosthesis and soft-tissue uptake. Similarly, (Bar-Shalom et al., 2006) observed that using In-111 labelled leukocyte SPECT/CT contributed to accurate identification of infection in 55% of patients suspected to have osteomyelitis and 67% of those suspected to have a vascular graft infection.

5. Tc-99m labelled Anti-granulocyte antibody scintigraphy

5.1 Tc-99m labelled Anti-granulocyte antibody: Pharmacological and physiochemical characteristics

Three anti-granulocyte antibodies have been used including anti-NCA-95 immunoglobulin IgG, fanelosomab (a monoclonal murine M class immunoglobulin), sulesomab (a murine monoclonal antibody fragment anti-NCA-90 Fab) and anti-CD15. Presently most routinely sulesomab (Leukoscan®) is used in clinical practice.

Leukoscan consists of a small murine monoclonal antibody fragment, sulesomab, labelled with Tc-99m. The radiolabelled antibody fragment (Fab) reacts with the normal cross reacting antigen (NCA-90) present on the surface of virtually all neutrophils. Therefore areas where neutrophils have accumulated can be detected and this proves useful in determining the location and extent of infection and inflammation. Uptake at sites of infection is therefore related to migration of antibody labelled circulating granulocytes and non-specific non-antigen related uptake of free antibody. The use of radiolabelled monoclonal antibodies against surface antigens as present on granulocytes has the advantage that labelling procedures are easier and do not require handling of potentially contaminated blood. Since the leukocytes are not removed from the patient, it is considered as in-vivo labelling process. Mounting of an immune response and production of human anti-mouse antibodies (HAMA) may pose a concern; however, in our experience and available published data the level of adverse events and probability of HAMA response are both low.

5.2 Tc-99m labelled Anti-granulocyte antibody: Imaging protocols and pre-requisites

Tc-99m Sulesomab is presented as a lyophilised powder (0.31 mg per vial) to be reconstituted with sodium chloride. Approximately 555-925 MBq is injected intravenously. Imaging should be performed 1-8 hours post injection. We usually perform imaging at 10 minutes and 2-4 hours post injection with occasional 24 hour delayed imaging in certain situations to have better target to background ratio for better delineation of lesions.

5.3 Tc-99m labelled Anti-granulocyte antibody: Clinical utilities and applications

Tc-99m Sulesomab is commonly indicated as an adjunctive diagnostic imaging of infection/inflammation in patients with suspected osteomyelitis, including patients with diabetic foot ulcers. As Tc-99m MDP bone scan has a low specificity, Tc-99m Sulesomab imaging as a follow-up test reduces the false-positive rate of Tc-99m MDP imaging. The overall sensitivity and specificity for the diagnosis of infections is 86% and 72%, respectively. In patients with diabetic foot ulcers, the diagnostic accuracy of Tc-99m Sulesomab compared with In-111 and Tc-99m HMPAO labelled leukocytes scanning was observed not to be significantly different (81 and 75%, respectively). However, Tc-99m Sulesomab imaging has a significantly higher sensitivity. In our own experience Tc-99m Sulesomab imaging has an incremental diagnostic value in the detection and ruling out osteomyelitis especially when used subsequent to Tc-99m MDP imaging (Figure 9).

Tc-99m fanolesomab has been used for diagnosis of acute appendicitis. It has a good overall accuracy with a positive predictive value (PPV) of 74-87% and a negative predictive value (NPV) between 95-100%. A high NPV is helpful for the patients to avoid unnecessary surgery, however, a number of false positives have been an issue with this radiopharmaceutical.

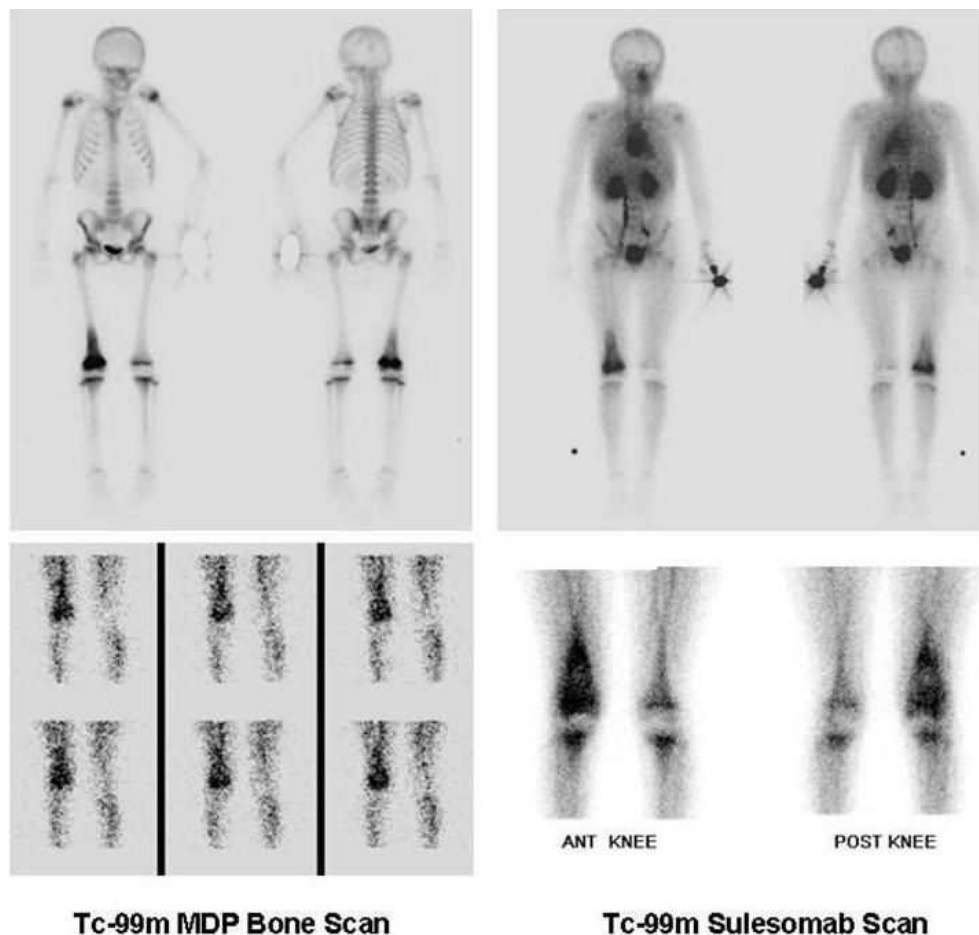


Fig. 9. A 10-year old girl, presented with tenderness and swelling at right distal femur. Tc-99m MDP bone scan show hyperperfusion and increases tracer accumulation at the distal 1/3rd of right femur. Tc-99m Sulesomab imaging show increased tracer uptake at distal right femur corresponding to the site seen on bone scan, confirming osteomyelitis.

5.4 Tc-99m labelled Anti-granulocyte antibody: Hybrid SPECT/CT imaging

(Horger et al., 2003) showed that SPECT/CT changed the interpretation of radioimmunoscinigraphy with Tc-99m labelled anti-granulocyte antibodies in 28% of suggestive foci evaluated in 27 patients in whom relapsing post-traumatic osteomyelitis was

suspected. In another recent study (Graute V et al., 2010) concluded that SPECT/CT substantially improves the utility of imaging with Tc-99m labelled anti-granulocyte antibodies for diagnosis and localization of suspected joint infections and provide information on the extent of the infection. We have found that SPECT/CT imaging not only helps anatomical localization of the infectious site but also provides lesion characterization and extent of involvement of the infectious process (Figure 10).

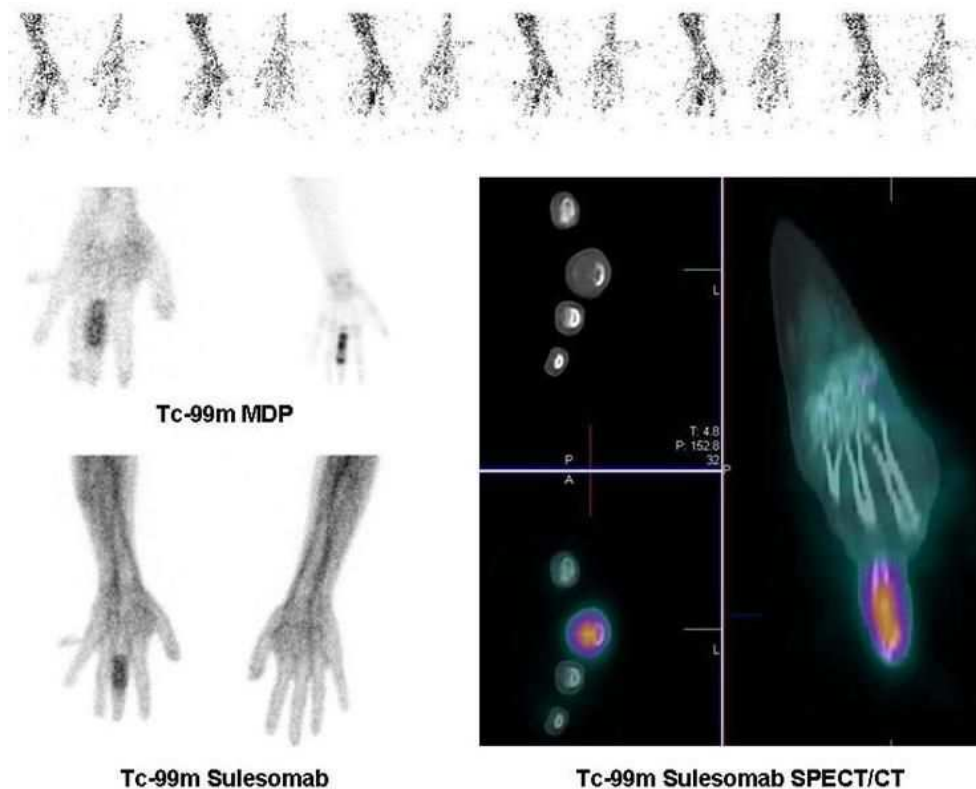


Fig. 10. A 25-year old female referred for evaluation of osteomyelitis in the left middle finger. Tc-99m MDP bone scan show hyperaemia, increased pool activity and intense linear increased tracer uptake in the left 3rd proximal phalanx extending up to the mid of middle phalanx. Tc-99m Sulesomab images show increased uptake at the same site confirming osteomyelitis. Further correlative SPECT/CT images show evident cortical distortion with low attenuation changes.

6. F-18 fluorodeoxyglucose positron emission tomography

6.1 F-18 FDG: Pharmacological and physiochemical characteristics

Fluorine 18 (F-18) Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) has been extensively used for imaging malignant processes, however, it is also now an established agent for imaging benign processes such as infection, inflammation and

granulomatous disease. Increased F-18 FDG uptake in these tissues is attributed to the increased glucose consumption through the hexose monophosphate shunt, which is the main energy source in chemotaxis and phagocytosis. The respiratory burst or the phagocytes activation results in increased F-18 FDG uptake. Marked F-18 FDG uptake is seen in neutrophils during acute phase of inflammation while during the chronic phase it is the macrophages and polymorphonuclear leukocytes that take up the tracer. Therefore, in cases of sterile inflammation it is mainly the neutrophils and macrophages that take up F-18 FDG. The mechanism of F-18 FDG uptake in infectious and inflammatory process is the same as in malignancy with metabolic trapping of the F-18 FDG-6-phosphate that cannot be further metabolised as it is not a substrate for the glucose 6-phosphatase isomerase enzyme. However, as the level of glucose 6-phosphatase remains the same in inflammatory cells as opposed to tumour cells where they are decreased, the F-18 FDG washes out from the inflammatory cells in due course. Further the numbers of GLUT (glucose transporter receptors) are less in inflammatory cells when compared with tumour cells.

The normal distribution of F-18 FDG includes the brain, myocardium, and the genitourinary system with variable uptake seen in the stomach, bowel and the bone marrow. Increase F-18 FDG activity can be seen in the spleen in patients with infection and presumably reflects the increased glucose usage by spleen in the setting of an infectious process.

6.2 F-18 FDG PET: Imaging protocols and pre-requisites

The patients are advised to fast for several hours before imaging. This reduces the F-18 FDG uptake in normal tissues. Moreover, it reduces the competition for glucose transporters. The physical activity of the patient is limited prior to injection and this reduces the F-18 FDG uptake in the striated muscles. Some centers also administer benzodiazepines 30-60 minutes prior to injection to reduce the brown fat and muscle uptake. Patient is routinely injected 370-550 MBq of F-18 FDG intravenously and laid to rest in a comfortable bed. Imaging is usually done at 60 minutes post injection, however, some centers may extend the uptake period to 90 minutes or may acquire images twice at different times (dual point) particularly in cases of granulomatous processes such as tuberculosis. Whole body imaging is preferred in cases where a focus of infection is to be investigated. F-18 is cyclotron produced radioisotope. The physical half-life of F-18 is 110 minutes. The principal gamma photons produced are of 511 KeV energy generated by positron emission.

6.3 F-18 FDG PET: Clinical utilities and applications

The indications for F-18 FDG PET for imaging infection are not different from those discussed previously, however, in particular investigation for the site of infection or ascertaining the cause in FOU, vasculitis, HIV-AIDS, infected prostheses, as well as osteomyelitis, diabetic foot infections, sarcoidosis and tuberculosis have been studied.

In case of FOU, the sensitivity and specificity of F-18 FDG PET has been observed to be 84-93% and 86-90% respectively. In most studies, it has helped in the management of about 35-37% cases. The reported PPV is 87% and the NPV 95%. Negative F-18 FDG PET makes it very unlikely that a morphologic origin of the fever will be identified. Infective endocarditis that can be a source of FOU has also been studied with F-18 FDG PET.

F-18 FDG accumulation has been observed in certain conditions resulting in vasculitis. These include giant cell arteritis, Takayasu arteritis, polymyalgia rheumatica, aortitis/peri-aortitis, infectious vasculitis and unspecified large vessel vasculitis. Inflammation of the

vessel walls cannot be detected in the early phase on conventional anatomical imaging. F-18 FDG assists in early diagnosis, assessing the extent of the disease and has also been found superior to MRI in depicting disease activity and treatment response. High brain uptake, relatively high skin background and the smaller diameter of the vessels lower the sensitivity of F-18 FDG PET in temporal arteritis. Giant cell arteritis in arteries greater than 4mm in diameter is nicely demonstrated by F-18 FDG PET. It is important to remember that vasculitis can be one of the causes of FUO as we have observed in some of our referred patients (Figure 11). Assessment for this is done by observing both non-attenuation corrected and attenuation corrected PET images.

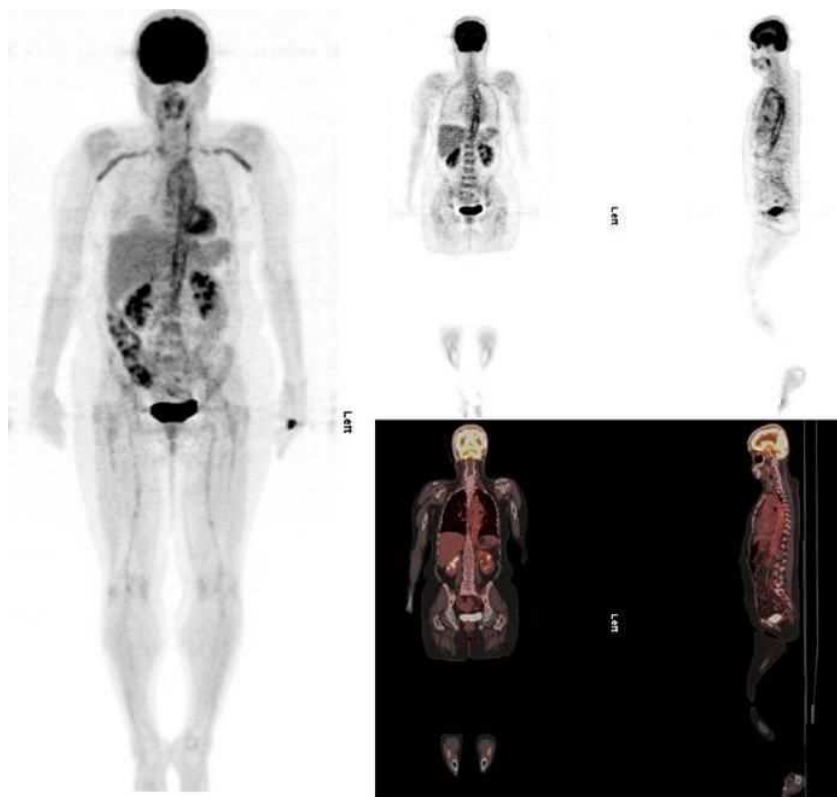


Fig. 11. A 56-year old female with FUO referred for detecting potential site(s) of infection. F-18 FDG PET/CT scan show diffuse increased FDG uptake evident in major blood vessels including the carotids, brachiocephalics, aortic arch, descending thoracic aorta extending up to the renal level. Findings consistent with the inflammatory etiology of vasculitis.

In patients with HIV-AIDS, there is increased likelihood of opportunistic infections as well as malignancy. (O'Doherty et al., 1997) reported that F-18 FDG PET has a sensitivity of 92% and specificity of 94% in localizing abnormalities that required treatment in these patients; however, they also concluded that it is not possible to clearly distinguish infectious from a malignant process in these patients. Toxoplasmosis is the commonest of the opportunistic

infections in AIDS patients. Most commonly the central nervous system is affected. F-18 FDG has been reported to be superior and more accurate than MRI in differentiating CNS lymphoma from conditions such as toxoplasmosis, progressive multi-focal leukoencephalopathy and syphilis. Further on quantitative assessment it has been shown that the standardized uptake values of toxoplasmosis are significantly lower than lymphoma with virtually no overlap.

F-18 FDG PET has been used extensively to evaluate painful lower limb joint prostheses. It has a limited significance especially when distinguishing infected joint prosthesis from aseptic prosthetic loosening. As inflammation is part of both the conditions, there is increased F-18 FDG peri-prosthetic accumulation observed in both. F-18 FDG PET is considered highly sensitive for evaluation of chronic osteomyelitis. Unlike bone scintigraphy F-18 FDG uptake normalizes in less than 2-3 months following treatment, thereby, reducing the false positive scans seen when osteomyelitis is suspected in complicated fractures. F-18 FDG PET has also been used with variable utility in diabetic foot infections, sarcoidosis, tuberculosis, organ transplantation and inflammatory bowel disease. In case of sarcoidosis the imaging findings are similar to those seen and discussed with Ga-67 scintigraphy. Further F-18 FDG PET can detect metastatic infectious foci with high sensitivity even if other imaging is negative.

6.4 F-18 FDG PET: Hybrid PET/CT imaging

Hybrid PET/CT systems in fact gained more popularity than the SPECT/CT systems and PET imaging is synonymously used for PET/CT imaging. The incorporation of anatomical data fused with the functional PET images results in accurate localization of the abnormalities and moreover detailed characterization of the lesions can be ascertained. In our experience PET/CT imaging for infectious process has limited utility, primarily in cases of FUO, vasculitis, malignant otitis externa and assessment of chronic osteomyelitis. However, as more evidence based data surface, this modality may prove to be an important method in detection and management of a number of infective conditions.

7. Brief considerations and limitations regarding anatomic imaging modalities

Radiograph or plain films are almost always the initial imaging study for diagnosing and assessing osteomyelitis. Finding on plain films to suggest or support infectious process include periosteal elevation or thickening, cortical thickening, irregularity with loss of trabecular architecture, sclerosis, osteolysis, and new bone formation. It is however important to note that these changes may not be evident at least until 5-7 days in children and 10-14 days in adults. Plain films show lytic changes only after at least 50%-75% of the bone matrix is destroyed.

Ultra-sonography is mostly utilized in evaluation and diagnosing of fluid collections, involvement of the periosteum, along with assessing surrounding soft tissue abnormalities. It may provide guidance for diagnostic or therapeutic aspirations, subsequent drainage and/or tissue biopsy.

Anatomic imaging modalities including CT and MR imaging provide excellent structural resolution for the detection and characterization of infectious or inflammatory conditions. These provide a high-quality assessment of infection related structural abnormalities. However, the limitation is that these techniques rely solely on structural changes and,

therefore, differentiation between active and structural but indolent alterations following surgery or other interventions is difficult to differentiate and these modalities are generally of limited value in detecting early disease regardless of the cause. In evaluation of infectious process CT scans may assist in the assessment of disruption of the bony cortex and soft-tissue involvement. Furthermore, CT may also reveal edema, intra-osseous fistula and cortical defects that lead to soft tissue sinus tracts.

CT is better suited for an evaluation of cortical bone, whereas MR imaging is more useful for the evaluation of internal architecture of structures such as the bone marrow, muscles, tendons, ligaments, cartilage etc. MR imaging has high accuracy in the acute osteomyelitis evaluation and detection primarily delineating adjacent soft tissue infection; particularly when no prior alterations in osseous or soft structure are present. However, in patients who have undergone previous surgical intervention, MR imaging may not be able to clearly distinguish signal abnormality secondary to bone marrow edema or enhancement related to a reactive phenomenon and that related to infection. Similarly, the diagnostic accuracies of both CT and MR imaging to evaluate osteomyelitis generally decrease in the presence of metallic implants due to streak and susceptibility artefacts.

MR imaging has a higher sensitivity and specificity than plain films and CT. Further findings become positive earlier in the disease process with MR than with plain films. MR imaging is particularly better at depicting bone marrow abnormalities with sensitivity of 82%-100% and specificity of 75%-95%. Vertebral osteomyelitis is one condition where MR has a characteristic pattern of confluent vertebral body and disk involvement; the diagnostic accuracy in such cases amount to 90%. MR imaging findings in osteomyelitis usually are related to the replacement of marrow fat with water secondary to edema, exudate, hyperemia, and bone ischemia. Findings include the following: decreased signal intensity in the involved bone on T1-weighted images, increased signal intensity in the involved bone on T2-weighted image, and increased signal intensity in the involved bone on short-tau inversion recovery (STIR) images. A decreased intensity on T1-weighted images with no change on T2-weighted images may indicate surgical or post-traumatic scarring of bone marrow. The MR imaging limitations are primarily due to the reason that findings of osteomyelitis are nonspecific, and similar changes may occur as a result of fractures, tumours, and a number of various intramedullary or juxtamedullary processes that result in bone marrow edema.

8. Future prospects and novel agents

The future for infection imaging looks promising with the search for an ideal agent still on. There has been a progression in the development of leukocytes labelled in-vitro by F-18 FDG. Moreover, leukocytes labelled with Copper-64 (Cu-64) are being studied. Radiolabelled antibiotics are also in vogue. The theoretical reasoning for radiolabelled antibiotics would be that such would incorporate into and metabolized by bacteria, thereby, making it possible to localize the site of infection. Tc-99m Ciprofloxacin has been studied, some results published with regards to its use in post-operative infections, however, this did not go into routine clinical practice due to conflicting data. Tc-99m labelled anti-microbial peptides are also being studied including Tc-99m labelled recombinant human beta-defensin-3 that exerts bactericidal effects on gram positive and gram negative bacteria as well as some yeasts, and Tc-99m ubiquicidin whose uptake is related to number of viable bacteria. Most recently (Lupetti et al., 2011) in a review have mentioned radiolabelled

antimicrobial peptides, fluconazole and chitin targeting agents that have been studied to image fungal infection in mice. There is a limitation of difficulty in differentiating bacterial and fungal infections. However, radiolabelled fluconazole has the ability to distinguish *Candida albicans* infection from bacterial infections/sterile inflammation.

Tc-99m ubiquickidin (Tc-99m UBI29-41), Tc-99m labelled lactoferrin (hLF1-11), Tc-99m fluconazole and I-123 labelled chitinase are being further studied at the moment. Tc-99m UBI29-41 was clinically tested in trial setting as human infection imaging agent (Akhtar et al., 2005) with promising results. They suggested an optimal imaging time of 30 minutes post injection for this agent. Another team (Salber et al., 2008) assessed and compared Tc-99m ubiquickidin and F-18 ubiquickidin autoradiography to anti-*Staphylococcus aureus* immunofluorescence in rat muscles abscesses. However, most recently, (Assadi et al., 2011) assessed the diagnostic accuracy of Tc-99m UBI29-41 scintigraphy for osteomyelitis making a comparison to Tc-99m MDP Bone scan and MR imaging. The authors concluded that for fast imaging with high accuracy, Tc-99m UBI29-41 is suitable for detection of osteomyelitis. In this most recent study the accuracy for Tc-99m UBI29-41 for detection of infection was observed to be 100% as compared to 90% for Tc-99m MDP bone scan. MR imaging was done in more than half of these cases and showed an accuracy of 75% for detecting osteomyelitis. Further in another most recent preliminary study by (Nazari et al., 2011) evaluated the role and ability of Tc-99m UBI29-41 to assess response to antibiotic therapy in orthopedic infections with quantitative analysis. With these recent encouraging reports, Tc-99m UBI29-41 seems a novel agent of the future for infection imaging.

N-formyl products (fMLF or fMLP) labelled with Tc-99m are also being studied in rabbits for localization of infection. Tc-99m labelled Interleukin-8 (IL-8) seems another promising agent for the future as after initial animal model experiments it has been tried in humans with promising initial results.

9. Conclusion

Radionuclide imaging plays a significant role in infection detection and localization. Currently the selection of infection imaging agent depends upon the availability and local expertise especially in cases of labelling leukocytes which require time consuming labelling procedures. SPECT-CT provides essential anatomical localization especially in cases of vertebral osteomyelitis, diabetic foot, and infected prosthesis, cardiovascular, abdominal and pulmonary infections. Gallium scintigraphy can be replaced with FDG PET where available. FDG PET is a preferred procedure of choice for pyrexia of unknown origin, vasculitis, sarcoidosis, infected grafts and inflammatory bowel disease, moreover quantitative FDG PET analysis appears another promising further advance. Finally, with the progress in hybrid imaging the diagnostic power of conventional scintigraphy in detection and localization of infection has greatly augmented and the development of newer infection seeking agents pave the way for improved patient management in future.

10. Acknowledgment

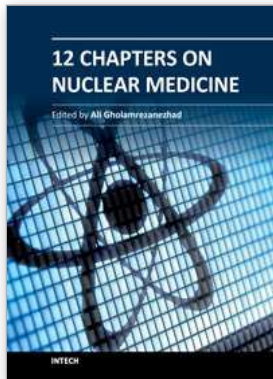
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12 Chapters on Nuclear Medicine

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The development of nuclear medicine as a medical specialty has resulted in the large-scale application of its effective imaging methods in everyday practice as a primary method of diagnosis. The introduction of positron-emitting tracers (PET) has represented another fundamental leap forward in the ability of nuclear medicine to exert a profound impact on patient management, while the ability to produce radioisotopes of different elements initiated a variety of tracer studies in biology and medicine, facilitating enhanced interactions of nuclear medicine specialists and specialists in other disciplines. At present, nuclear medicine is an essential part of diagnosis of many diseases, particularly in cardiologic, nephrologic and oncologic applications and it is well-established in its therapeutic approaches, notably in the treatment of thyroid cancers. Data from official sources of different countries confirm that more than 10-15 percent of expenditures on clinical imaging studies are spent on nuclear medicine procedures.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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