Pediatr Radiol (2011) 41:803–810
DOI 10.1007/s00247-011-2013-7

REVIEW

Functional imaging of infection: conventional nuclear medicine agents and the expanding role of ^{18}F-FDG PET

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Received: 28 January 2011 / Accepted: 1 February 2011 / Published online: 24 May 2011
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Abstract A growing body of literature suggests that 18-fluorine fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET), particularly when combined with CT, is a useful tool for the detection of infectious and inflammatory disease processes. This article will briefly review the data to date on the use of FDG PET in diagnosing musculoskeletal infections and fever of unknown origin, comparing it to conventional scintigraphic techniques in both adults and, when available, in children.

Keywords Infection · FDG PET/CT · Radionuclide imaging · Children

Introduction

Nuclear medicine plays a vital role in evaluating infection and inflammatory conditions. Procedures commonly utilized for this purpose include: (1) either a 2- or 3-phase bone scan using technetium-99m methylene diphosphonate (Tc-99m MDP) for distinguishing acute and chronic osteomyelitis from septic arthritis or cellulitis; (2) gallium (Ga-67) citrate scanning for uncomplicated and spinal osteomyelitis, chronic infections, fever of unknown origin (FUO), and in the immunocompromised patient, and (3) technetium hexamethyl-propylene-amine oxime labeled white cells (Tc-99m HMPAO WBC) for acute, chronic or complicated osteomyelitis, a variety of lung infections, inflammatory bowel disease, complicated appendicitis or other intra-abdominal infections. Indium (In-111)-oxine autologous leukocytes, whose use in identifying infectious and inflammatory processes is prevalent in adults, is not recommended for children due to its high radiation burden [1]. The use of radiolabeled monoclonal antibodies (^{99m}Technetium-fanolesomab) and other potential inflammatory agents such as antibody fragments and radiolabeled peptides, has seen little application in the pediatric population.

Most of the conventional radionuclide imaging modalities suffer from relatively poor spatial resolution, and low specificity in the detection of chronic infections. Gallium 67 citrate, the archetypical agent for inflammation and infection imaging, not only lacks specificity but has the additional disadvantages of long imaging time (24–72 hours), low resolution, high physiological uptake in liver, kidneys and bowel which decreases its sensitivity in detecting suspected intra-abdominal or pelvic infections, and high patient radiation dose [2]. Disadvantages of in-vitro labeled white cell imaging include an expensive and labor-intensive labeling procedure, lack of availability, risk to health care workers involved with the handling of blood products, the possibility that severely neutropenic patients may not have sufficient leukocytes for adequate labeling, and limited success in some chronic infections [3]. Moreover, the large quantity of blood (50 ml) needed for the procedure limits its use in neonates and small children.

In recent years, growing evidence, primarily in adult patients, suggests that 18-fluorine fluorodeoxyglucose positron emission tomography (FDG PET), either alone or in combination with computed tomography (FDG PET/CT), has an important role to play in the diagnosis of a variety of infectious processes, including fever of unknown origin (FUO). FDG accumulates in a variety of infections,

Disclaimer The supplement this article is part of is not sponsored by the industry. Dr. Parisi has no financial interests, investigational or off-label uses to disclose.

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including abdominal, brain, lung, renal and tubo-ovarian abscesses, pneumonia, osteomyelitis, tuberculosis, *Mycobacterium avium-intracellulare* infection, mastitis, acute enterocolitis and infectious mononucleosis [4]. According to Basu [5] and others [3, 4, 6–10] in a series of review articles, the conditions in which FDG PET has demonstrated its greatest utility in the adult population include chronic osteomyelitis, complicated lower limb prostheses, complicated diabetic foot, fever of unknown origin, acquired immunodeficiency syndrome, and vascular graft infection and fistula.

The literature regarding the use of FDG PET/CT for identifying infection and inflammation in children is relatively sparse, although increasing. In children, FDG PET uptake has been reported in infectious processes, including osteomyelitis [11], inflammatory bowel disease [12–14], chronic granulomatous disease [15] and in evaluating fever of unknown origin in general [16, 17], and when encountered in the pre-liver transplant patient [18]. Figures 1 and 2 demonstrate abnormal FDG PET studies in two children, one with serological and biopsy-confirmed histoplasmosis and the other with infectious pneumonitis.

The use of FDG in PET is based on the observation of the increased glycolytic rate of cancer cells compared to that of normal cells. FDG, like glucose, is initially carried into the cell by the endothelial glucose transport system and is then converted to FDG-6-phosphate. However, unlike glucose, FDG is then trapped within the cell where it accumulates at a rate proportionate to glucose utilization [19]. Similar to malignant cells, activated inflammatory cells use glucose as a source of energy resulting in high FDG accumulation at sites of inflammation and infection. On the molecular level, overexpression of glucose transporter 1 (GLUT1) receptors in stimulated macrophages, neutrophils and lymphocytes has been proposed as the most likely explanation for FDG uptake in inflammatory cells [20, 21].

FDG PET and, particularly, PET/CT have several advantages over conventional nuclear medicine techniques including high spatial and contrast resolution, high sensitivity for chronic infections, minimal labor intensity, short imaging times resulting in the ability to quickly obtain results, high interobserver agreement and, when compared to Ga-67 or labeled white cell scanning, lower dose [5]. FDG PET is limited by its inability to reliably distinguish infectious from noninfectious inflammation or malignancy, limited availability, relatively high cost and, in young children, the need for sedation [5].

This article will briefly review the data to date on the use of FDG PET in diagnosing musculoskeletal infections and fever of unknown origin, comparing it to conventional scintigraphic techniques, in both adults and, when available, in children.

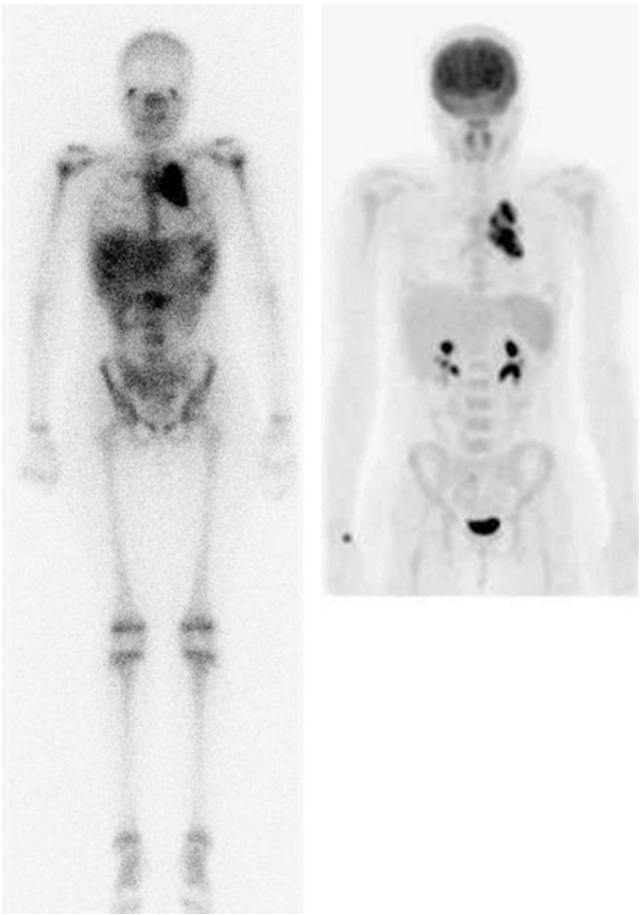

Fig. 1 An 11-year-old girl presents with fever, night sweats and weight loss. Anterior view from a whole-body Ga-67 scan (*left*) and a corresponding coronal FDG image (*right*) from a whole-body FDG PET/CT both reveal abnormal uptake in the left anterior mediastinum, worrisome for lymphoma. Biopsy demonstrated histoplasmosis, also confirmed with serological testing. Not only does FDG PET have superior spatial resolution compared to Gallium 67, but results can be obtained quickly, within 1.5–2 hours, compared with the prolonged time (24–72 hours) required for completion of a gallium scan. (Images courtesy of Dr. Barry Shulkin)

Musculoskeletal infections

The diagnosis of musculoskeletal infection presents an ongoing challenge, particularly in children where early recognition may be difficult or confused with other pathologies, including trauma or tumors.

Osteomyelitis, defined as any form of inflammation involving bone and/or bone marrow, is most commonly due to infection [22]. Unlike in adults where osteomyelitis commonly arises from open fractures, diabetic foot infections or surgical treatment of closed injuries, osteomyelitis in children is due to hematogenous spread of bacterial infection [23]. *Staphylococcus aureus* is responsible for 70-90% of cases in children [22].

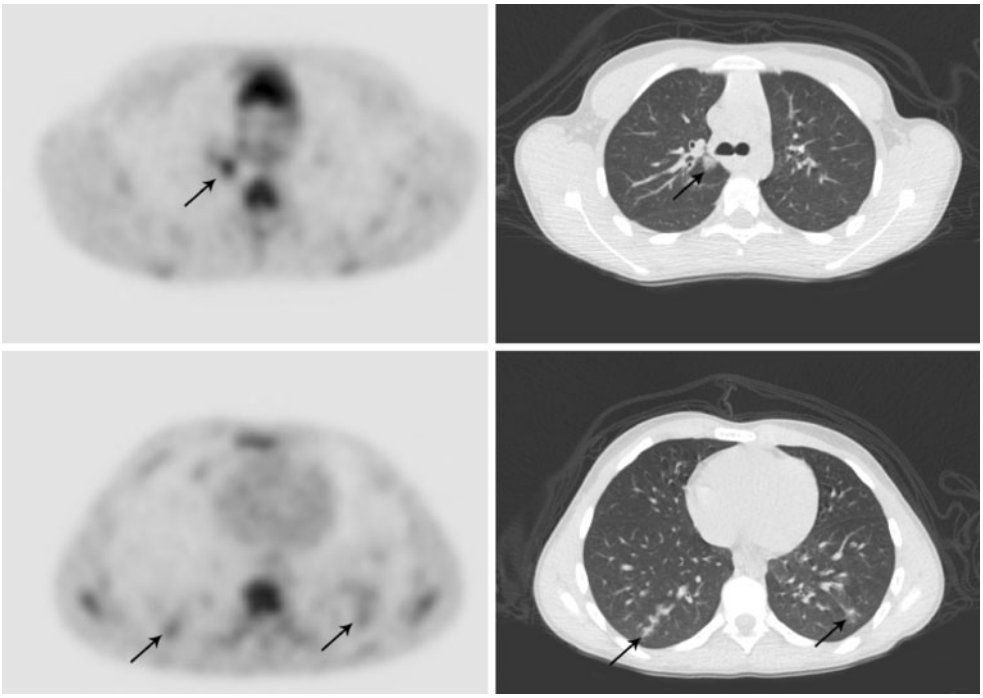

Fig. 2 A 14-year-old boy, 13-months S/P completion of therapy for Hodgkin disease, undergoes surveillance imaging with whole-body FDG PET/CT. At the time of imaging, the patient had intercurrent upper respiratory symptoms with intermittent fever, nasal congestion, sore throat and cough. Axial FDG (*left*) and corresponding low-dose CT (*right*) images reveal abnormal FDG-uptake corresponding to multiple nodules (*arrows*) with indistinct borders in a centrilobular (tree-in-bud) distribution throughout both lungs, most consistent with an infectious pneumonitis. No organisms were isolated. The child responded to antibiotic therapy with complete resolution of symptoms. Interestingly, diagnostic noncontrast chest CT obtained 5 days prior to the FDG PET/CT (*not shown*) was normal

In a series of review articles, authors discuss the relative merits and limitations of the anatomical and nuclear medicine imaging studies in osteomyelitis, the content of which is summarized below [23–30]. Plain films, while notoriously insensitive in the detection of acute osteomyelitis, are used to exclude other diagnostic possibilities, such as trauma or tumor, or to provide clues for underlying pathological conditions. While soft tissue swelling may be noted on plain radiographs shortly after the onset of symptoms, osseous changes are rarely seen before 7–10 days. Visualization of bony changes may be further delayed when disease involves the spine or the pelvis. The major role of computed tomography (CT) in osteomyelitis is in the detection of sequestra in cases of chronic osteomyelitis; it is also valuable in cases of vertebral osteomyelitis. Ultrasound (US) has multiple advantages: it is readily available, can be performed quickly and relatively inexpensively with little patient discomfort, and is useful in regions complicated by orthopedic hardware and for those in whom MRI is contraindicated [30]. US can detect acute osteomyelitis earlier than plain films and can be used to evaluate involvement of adjacent soft tissues in chronic osteomyelitis. Like MRI, US has the distinct advantage of eliminating patient exposure to ionizing radiation, which is so important in the pediatric population.

Of the available imaging modalities, MR is considered to have the highest sensitivity for detecting acute osteomyelitis, including associated soft tissue involvement, typically within 3–5 days after the onset of infection [23, 24, 29, 30]. When acute osteomyelitis is suspected, MR imaging may supplant inconclusive plain films, although scintigraphy is usually preferred as it is readily available, inexpensive and does not typically require sedation [23]. Finally, although anatomical imaging modalities are frequently used in assessing osteomyelitis, they are limited by lack of specificity, difficulty in distinguishing active infection from postoperative change and, particularly for CT and MRI, are limited in the presence of metallic implants.

Since their introduction in the 1970's, polyphosphates and phosphonates revolutionized the field of nuclear bone imaging. The 3-phase Tc-99m MDP bone scan, which includes an initial flow phase (acquired at 2 seconds per frame for 2 min), followed by blood pool images approximately 5–10 min following radiotracer injection, and delayed imaging 3 hours later, is the initial radionuclide procedure of choice for diagnosing acute osteomyelitis in children without underlying structural bone changes. Abnormal findings indicative of osteomyelitis on radionuclide bone scan include increased flow and blood pool activity as well as focal radiotracer accumulation in the area

of interest on delayed imaging. In neonates and infants, localizing signs are generally poor or nonspecific; young children are often unable or unwilling to accurately verbalize or localize sites of pain. For these reasons, it is essential to image the entire axial and appendicular skeleton when performing radionuclide bone scans in all children.

Tc-99m MDP has a high sensitivity (82-95%) and accuracy (90%) for detecting acute, uncomplicated osteomyelitis, becoming positive within 28–48 hours after the onset of symptoms. It can reliably differentiate cellulitis (which is only positive on flow and blood pool phases) from osteomyelitis. Compared with anatomic modalities, the radionuclide bone scan has the further advantage of detecting multiple foci of disease which can be present in 7% of children and 22% of neonates. The specificity of bone scans in osteomyelitis ranges from 38-82%. Single photon emission CT (SPECT) imaging is essential in pediatric scintigraphy, allowing for improved image contrast and diagnostic accuracy [28]. On the other hand, while bone scan may detect concomitant soft tissue involvement in those with osteomyelitis, it is not accurate in fully defining local extension. Other limitations of bone scan due to its lack of specificity include the potential for false-positive and false-negative results. Bone scintigraphy can remain positive for a protracted period – even years– following a fracture or placement of orthopedic hardware and, as a result, is of limited use in evaluating osteomyelitis in these settings. Rapidly progressive or "cold osteomyelitis" in which there is relative ischemia from vascular compression and thrombosis may be difficult to appreciate on bone scan, leading to false-negative results. Figure 3 demonstrates classic bone scan findings of osteomyelitis.

While purportedly more specific than the three-phase bone scan for osteomyelitis, gallium suffers from poor image quality, long scanning time and significantly higher patient radiation dose. Gallium scans may be particularly helpful in cases of cold osteomyelitis on bone scan. Reported sensitivities for gallium range from 25% to 80% with a specificity of 67% [23]. Prior antibiotic therapy may decrease its sensitivity. As a consequence, gallium is rarely performed.

The primary advantage of using in-vitro labeled leukocytes is increased specificity – up to 80–90% – compared to bone scans, particularly when complicating conditions such as fracture, presence of metallic orthopedic hardware or neuropathic joint disease are superimposed. Unfortunately, as previously stated, their performance requires the withdrawal of a large amount of blood (50 cc). It is also costly, labor intensive and has the inherent limitations related to personnel safety, including the risks of infection and cross-contamination from handling blood products. Moreover, they have very poor spatial resolution as demonstrated in Fig. 4.

Like radiolabeled white blood cell imaging, FDG PET images are not adversely affected by the presence of metallic hardware. Another advantage of FDG PET is that it rapidly normalizes following traumatic or surgical fractures as fibroblasts predominate during normal healing; likewise, FDG accumulation quickly subsides within 3–4 months following surgery [10].

Sensitivities of 98% and specificities ranging from 75% to 99% have been reported for FDG PET in acute and subacute bone and soft tissue infections in adults [6]. For osteomyelitis alone, diagnostic sensitivities and specificities were 100% and between 83% and 96% respectively. Despite these high sensitivities and specificities, as well as its other advantages, FDG PET/CT has limited value in diagnosing uncomplicated osteomyelitis compared with the combination of physical examination, evaluation of biochemical marker alteration and 3-phase bone scan or MRI [5]. This is particularly true in children given the increased need for sedation and high patient radiation dose of FDG PET/CT compared to Tc-99m MDP bone scan.

In contradistinction, in adults, FDG PET and PET/CT appear to be the imaging procedures of choice in chronic osteomyelitis where accurate diagnosis is often difficult. Not only are FDG PET and PET/CT highly effective and highly sensitive in the diagnosis of chronic osteomyelitis, but they also have a greater specificity than Ga-67, radiolabeled leukocyte or bone scintigraphy, and MRI [5]. Guhlman and colleagues were among the first to report the utility of FDG PET in chronic osteomyelitis [31]. Chacko et al. [7], evaluating a series of 56 patients with chronic osteomyelitis, reported the sensitivity, specificity and overall accuracy of FDG PET to be 91%. Meller et al. [32], in a prospective study of 30 patients, concluded that FDG PET was superior to In-111 WBC imaging for diagnosing chronic osteomyelitis in the central skeleton. deWinter et al. [33], in a series of 60 patients in whom infection was confirmed with either histopathology or microbiology, reported overall sensitivity, specificity and accuracy of FDG PET for diagnosis of chronic osteomyelitis was 100%, 88% and 93% respectively.

Fever of unknown origin

Fever of unknown origin in adults was originally defined by Petersdorf and Beeson as an illness lasting more than 3 weeks with fever >38.3 degrees Celsius on several occasions and with no diagnosis after at least 1 week of inpatient investigation [34]. Recent updated versions substitute a week of intensive outpatient evaluation, including performance of an abdominal CT, in lieu of the inpatient hospitalization [35, 36]. The definition of FUO varies even more widely in children, in whom fever is one

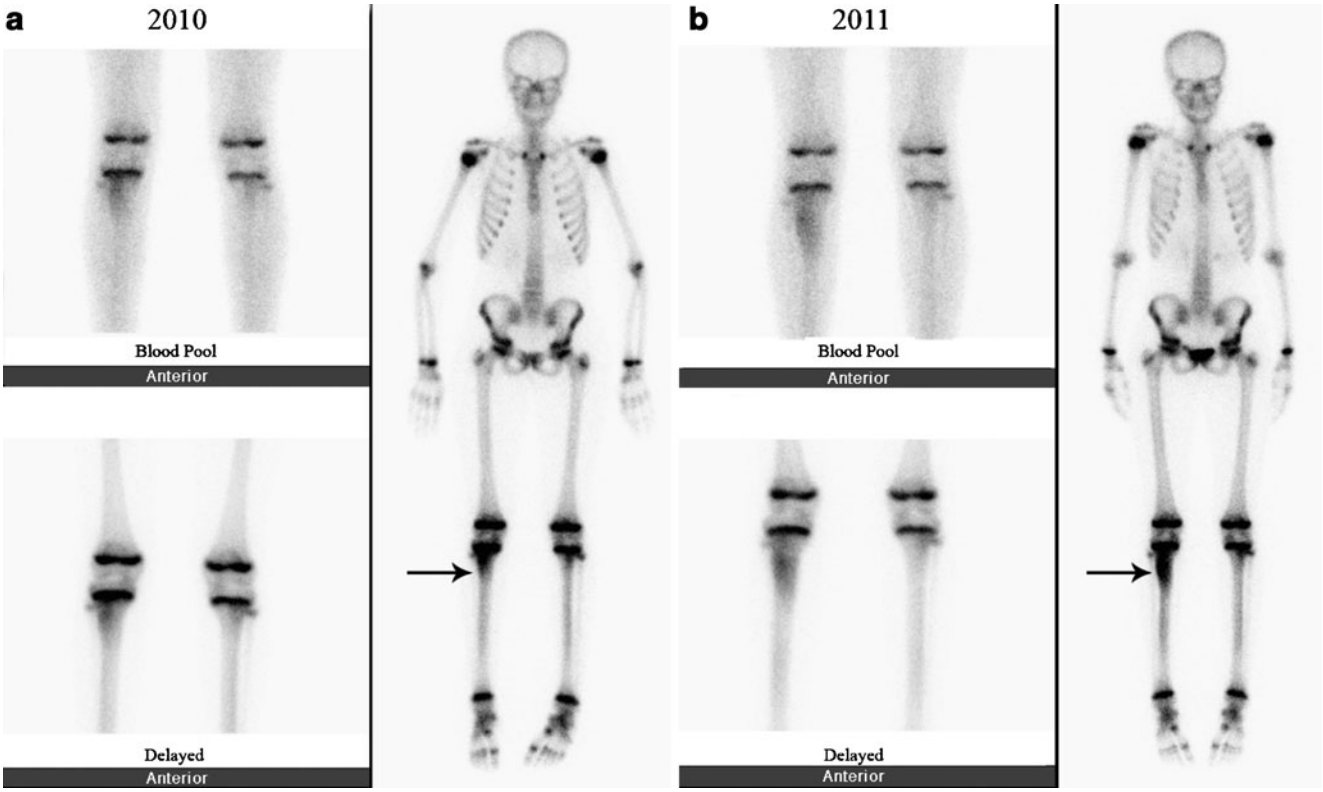

Fig. 3 Two-phase bone scans performed 1 year apart in an 11-year-old girl, who initially presented with a 2-month history of right knee pain in the absence of fever or trauma. On the initial study (a), left, 2010), anterior blood pool (*top left*), delayed static (*bottom left*) and whole body (*right*) scintiphotos demonstrate increased uptake in the proximal right tibia, findings compatible with osteomyelitis, possibly chronic, confirmed pathologically and on anatomical imaging. No organism was isolated. Appropriate antibiotic therapy ensued, but worsening pain nearly 1 year post-treatment prompted a second bone scan. Subsequent bone scan 1 year later (b), *right*, 2011), demonstrates progression, with more marked uptake in the proximal right tibia on both phases of the examination, again consistent with osteomyelitis, either representing chronic active osteomyelitis or, more likely in view of clinical course, a variant of chronic recurrent multifocal osteomyelitis (CRMO)

of the most common presenting complaints, accounting for 25% of emergency department visits [37]. Mourad et al. estimate the prevalence of FUO at 2.9% of hospitalized patients [38]. Early identification of the etiology of FUO will prevent the performance of unnecessary invasive procedures and prolonged antibiotic use.

According to Tolan, most children with FUO will have a discernible cause and, although the proportion of diagnoses varies from study to study, approximately 30–35% will have an infection; 20% will have a rheumatological, autoimmune, inflammatory or granulomatous condition, 10% will have a neoplasm, 5% will have a rare condition, and 30% will remain undiagnosed (most resolving before a diagnosis can be made) [39]. These broad etiological categories and their relative incidences are remarkably similar to findings in adults.

Although the approach to the febrile child varies widely, a careful and thorough history, followed by a meticulous physical examination are invaluable in the assessment of the febrile child [39, 40]. All prior laboratory testing, including biopsies and imaging studies, should be reviewed. Reasonable screening evaluations, if not already performed, should include complete blood count, erythrocyte sedimentation rate, comprehensive metabolic profile, C-reactive protein, urinalysis with culture, blood cultures with prolonged fever, tuberculin test, urine *Histoplasma* antigen and other studies as appropriate for endemic pathogens, selected serologies, serum immunoglobulins including an antinuclear antibody titer, stool for blood, leukocytes, ova and parasites if symptomatic, and a chest radiograph [39].

MRI, radionuclide examinations and more invasive procedures are considered most helpful only when available information suggests pathology to be characterized [39]. Evidence of the disappointing results of imaging is documented in an early study by Steele et al. in which 109 children with FUO were evaluated [41]. Confirmed diagnoses were achieved in only 33%. Imaging included abdominal ultrasonography, abdominal CT, Tc-99m MDP bone, In-111 WBC and Ga-67 scans, upper GI and cranial CT. In 16 instances, bone marrow aspiration was performed.

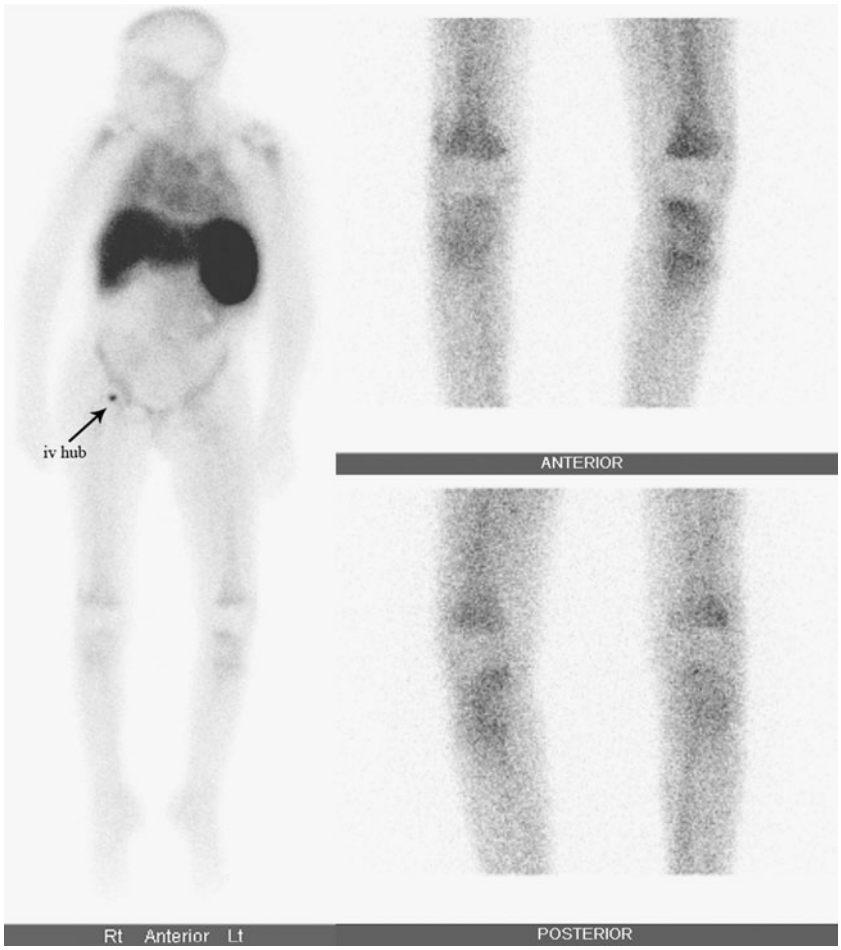

Fig. 4 An 18-year-old medically complex patient with end-stage renal disease and restrictive cardiomyopathy presents with fever, pain and hypotension 4 months following the performance of bilateral proximal tibial osteotomies for genu valgum deformity. Anterior whole-body (*left*) and focal spot images of the knees (*right*) from a Tc-99m HMPAO WBC scan demonstrate mildly abnormal uptake in the region of both proximal tibias, most marked on the left, findings consistent with surgical diagnosis of deep soft tissue abscess on the right and left osteomyelitis. Note the poor spatial resolution and difficulty in distinguishing soft tissue from osseous involvement

A total of 123 procedures were performed with positive results obtained in 22 (17%), most commonly utilizing abdominal ultrasound.

Buonomo and Treves evaluated the role of gallium scanning in 30 children with FUO [42]. Four patients had positive scans; 1/25 patients who presented with systemic signs and symptoms in addition to fever and 3/5 patients with more focal complaints which had remained occult despite imaging with other modalities. They concluded that gallium scanning is rarely useful in children with FUO and systemic complaints alone.

In more recent studies of adults with infection, Seshadri et al. found the overall sensitivity of In-111 leukocyte scintigraphy was 60%, with a specificity of 71% and positive and negative predictive values of 55% and 75% respectively [43]. Bar-Shalom et al. demonstrated an incremental contribution of SPECT/CT in gallium and labeled white cell studies for infection, providing additional information for diagnosis, localization and extent of disease in 48% [44].

FDG PET is increasingly being recognized as having utility in FUO. An early prospective study by Meller et al. compared the role of FDG PET with Ga-67 SPECT in 20 consecutive patients with FUO, reporting a sensitivity of 81% and a sensitivity of 86% for FDG PET compared to 67% and 78% respectively for Ga-67 SPECT [45]. Not only does FDG PET provide more sensitive results compared with Ga-67 or In-111 WBC, but does so within a few hours with little labor intensity.

Ferda et al., in evaluating 48 patients with FUO (mean age 57.6 years; range 15–89 years), reported that FDG PET/CT identified the cause of FUO in 44/48 patients, with findings confirmed objectively [46]. There were two cases of erroneous PET interpretation. Authors concluded that FDG PET/CT had a sensitivity of 97% and specificity of 75% in those with FUO.

Simons et al. evaluated 35 FDG PET/CT scans in 33 ventilated ICU patients (median age 58 years; range 1 month–72 years), including 5 children, suspected of having infection [16]. Twenty-four FDG PET/CT scans were abnormal; 21 were true positive; 3 were false-positive (specificity 79%), and 11 were true negative (sensitivity 100%) resulting in an overall accuracy of 91%. In five cases, the results of the PET/CT scan had direct therapeutic consequences. Simons et al. concluded that FDG PET/CT was of additional value in the evaluation of suspected infection in critically ill patients in whom conventional

diagnostics did not lead to a diagnosis. A normal FDG PET/CT, with its high negative predictive value, can exclude clinically important infections requiring prolonged antibiotic therapy and can help prevent the performance of unnecessary invasive procedures.

In the first large series evaluating children, Jasper et al. retrospectively evaluated 47 FDG PET and 30 PET/CT scans obtained in 69 pediatric patients presenting with FUO (44 scans) or unexplained signs of inflammation without fever (33 scans) [17]. They found that a final diagnosis could be established in 54% of their patients. Of all the scans, 82% were abnormal, but only 45% were considered helpful by either excluding or allowing further targeted investigations. When a scan was helpful, a final diagnosis could be established in 77%. Conversely, among those 54% of patients with a final diagnosis, scans were found to have been contributory in 73%.

Finally, in a series of 11 children with biliary cirrhosis awaiting liver transplant, FDG PET was focally positive within the liver in five [18]. These FDG-positive focal lesions were confirmed either structurally or histologically to represent local infections, including infectious necrosis, focal abscess or microabscesses or suppurative cholangitis [18]. In the remaining 6 cases, where no abnormal FDG uptake was identified, no infections were detected in the liver.

Conclusion

In conclusion, FDG PET and FDG PET/CT, with its increased specificity compared to FDG PET alone, appear to be sensitive techniques for detecting various types of musculoskeletal infections and evaluating patients with FUO. However, more data is clearly needed, particularly in children, to adequately determine not only the diagnostic utility but the cost-efficacy of FDG PET/CT compared to CT, MRI, US and conventional radionuclide studies in the evaluation of infection and noninfectious inflammatory diseases.

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