Nuclear Medicine Imaging of Spinal Infection

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Contents

Abstract

Spinal infection can be challenging to diagnose accurately, as symptoms can be insidious and nonspecific. Advanced radiological imaging procedures can be very useful to aid diagnosis. Nuclear medicine imaging can provide significant information, in addition to more conventional imaging techniques such as radiography and MRI. Nuclear medicine imaging (SPECT and PET) have shown high sensitivity and accuracy with regard to spinal

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infection diagnosis, especially when used in combination with conventional radiological investigations such as CT and MRI. By providing additional functional information, nuclear medicine imaging helps to identify possible sites for biopsy, monitor treatment responses, and guide the duration of antimicrobial treatment. Expert consensus guidelines have been published, addressing the use and implementation of nuclear medicine imaging techniques in spinal infection.

Abbreviations

[^{18}F] FDG	Fluorine-18 2′-deoxy-2-fluoro-D-glucose
^{67}Ga	Gallium-67
^{99m}Tc	Technetium-99m
CT	Computed tomography
MRI	Magnetic resonance imaging
PET	Positron emission tomography
SPECT	Single photon emission computed tomography

1 Introduction

Spinal infection includes vertebral osteomyelitis, discitis, and spondylodiscitis and may also involve the posterior elements, epidural space, and paraspinal soft tissues. The usual routes of infections are hematogeneous spread, direct inoculation from interventional procedures or penetrating trauma, and extension from contiguous infection (Raghavan et al. 2018). The majority of spinal infection are pyogenic in origin, most commonly caused by *Staphylococcus aureus* (60%), followed by *Enterobacter* species (30%), and less commonly by non-pyogenic agents such *Mycobacterium tuberculosis*, *Brucella*, fungi, and parasites. Disease involvement is mostly single spinal segment (65%), followed by multilevel contiguous (20%), and noncontiguous infection (10%) (Prodi et al. 2016; Raghavan et al. 2018). Clinical features such as back pain and variable presence of fever are generally nonspecific, and manifestations of neurological deficits are present in only a minority of patients. Therefore, spinal infection can be confused with degenerative process, leading to delayed diagnosis and significant morbidity and mortality (Mylona et al. 2009).

Laboratory findings also vary, depending on the grade, causative agent, the type of spinal infection, and associated pathology. Elevation of erythrocyte sedimentation rate (ESR) is mostly consistent, and white blood cell count and C-reactive protein (CRP) plasma levels are variable. The most definitive diagnosis is identification of the pathogen from biopsy of the bone lesion or the wound, by histopathological analysis or indirectly from blood cultures. As the biopsy specimens and blood cultures can remain negative, noninvasive imaging becomes paramount in diagnosis and assessing response to treatment of spinal infection (Gemmel et al. 2006).

Among the morphological imaging techniques, radiographs are usually the first imaging modality performed, despite their low sensitivity and specificity. Signs are not usually seen radiographically till the bone destruction exceeds 30% and until 2–8 weeks after the initial symptoms (Khoo et al. 2003). Computed tomography (CT) is the best modality for detection of bony abnormalities and detects small areas of destruction earlier than radiographs. Currently, CT is mostly used for percutaneous needle biopsy and percutaneous drainage of abscesses (Lazzeri et al. 2019). Magnetic resonance imaging (MRI) is the reference standard for imaging of spinal infection because of its high sensitivity, specificity, and accuracy. Other advantages are its high-contrast resolution, multiplanar imaging capability, high sensitivity for soft tissue and bone marrow abnormalities, and absence of ionizing radiation. Some of the disadvantages of MRI are overestimation of infected tissue, its inherent limitations in the postoperative setting, and difficulty in differentiating reparative process and therapy failure. Consequently, radionuclide or functional imaging studies are often performed to increase diagnostic accuracy, particularly in postsurgical infections or to complement equivocal MRI findings (Hong et al. 2009; Ohtori et al. 2010; Seifen et al. 2012; Saha et al. 2013).

2 Conventional Nuclear Medicine

Single-photon emitting radiopharmaceuticals used for musculoskeletal infections are labeled diphosphonates (such as Technetium-99m methylene diphosphonate/hydroxymethylene diphosphonate [^{99m}Tc MDP/HDP]), ^{67}Ga citrate, labeled autologous leukocytes and novel radiotracers. Individual centers use different radiotracers, depending upon their availability, technical capability, and their own experience and expertise. Mechanisms of accumulation of these tracers at the site of infection are different (Thang et al. 2014).

2.1 Bone Scintigraphy

^{99m}Tc-labeled diphosphonate bone scintigraphy is widely available worldwide and easily performed. These radiopharmaceuticals bind to the inorganic mineral hydroxyapatite crystalline matrix of the bone. The uptake depends on multiple factors including blood supply, capillary permeability, quantity of mineralized bone, and rate of bone turnover. For clinical suspicion of osteomyelitis, triphasic bone scan is routinely performed in angiographic, blood pool, and delayed bone phases. Soft tissue infection manifests as increased radionuclide accumulation in the angiographic and blood pool phases, with no increased bony tracer activity in the delayed phase. Osteomyelitis shows increased tracer activity in all the three phases due to focal hyperperfusion, hyperemia, and increased bony uptake (Thang et al. 2014; Raghavan et al. 2018).

Bone scintigraphy is sensitive in diagnosing osteomyelitis, but the specificity decreases in the settings of pre-existing conditions such as degenerative changes, fractures, and prosthesis. A meta-analysis of 30 original articles published between 1984 and 2004 regarding the use of different types of radionuclide imaging of spinal infection showed that bone scans had a sensitivity of 81.4% and specificity of 40.7% (Prandini et al. 2006) (Fig. 1). In a prospective study conducted in 30 patients who had vertebral osteomyelitis, the sensitivity of the bone scintigraphy was reported to be 86%, but the target-to-background ratio did not correlate with histological grade and severity of the osteomyelitis. The triphasic bone scan was positive with severe infection but not in individuals with mild or moderate infection (Gratz et al. 2000).

In a retrospective study conducted in 22 patients, planar imaging was found to be 73% sensitive, 31% specific, and 50% accurate for diagnosing infection, and triphasic bone scan improved the specificity to 92% and diagnostic accuracy to 67% (Love et al. 2000). Due to its specific bone affinity, bone scintigraphy is of limited use in the evaluation of associated paraspinal infection in spondylodiscitis. Lisbona et al. (1993) retrospectively reviewed bone scintigraphy in 21 patients with infectious spondylitis (14 nontuberculous and 6 tuberculous). The scan was abnormal in 16 of 17 sites of nontuberculous infection and 6 of 9 sites of tuberculous infection of vertebrae, but none of the 8 paraspinal infections (6 nontuberculous and 2 tuberculous) was detected (Lisbona et al. 1993; Gemmel et al. 2006).

2.2 Gallium-67 (^{67}Ga) Citrate Scintigraphy

^{67}Ga citrate was one of the preferred radiotracers for musculoskeletal infections from the early 1970s till the mid-1980s. Several mechanisms have been proposed for the increased uptake of ^{67}Ga citrate at the sites of infection, namely, (1) about 90% of circulating tracer is bound to transferrin and because of increased blood flow and vascular permeability; it is delivered and accumulated more in the sites of infection; (2) it dissociates from transferrin and binds to lactoferrin which is present in high concentrations at the infection sites; and (3) direct bacterial uptake through siderophores and leukocyte transport. Imaging is usually delayed, performed from 18 to 72 h after injection. The main disadvantages are poor image quality compared to ^{99m}Tc MDP, excretion through the gastrointestinal tract obscuring the infection sites in the abdominopelvic region (requiring the use of laxatives prior to imaging), higher radiation burden,

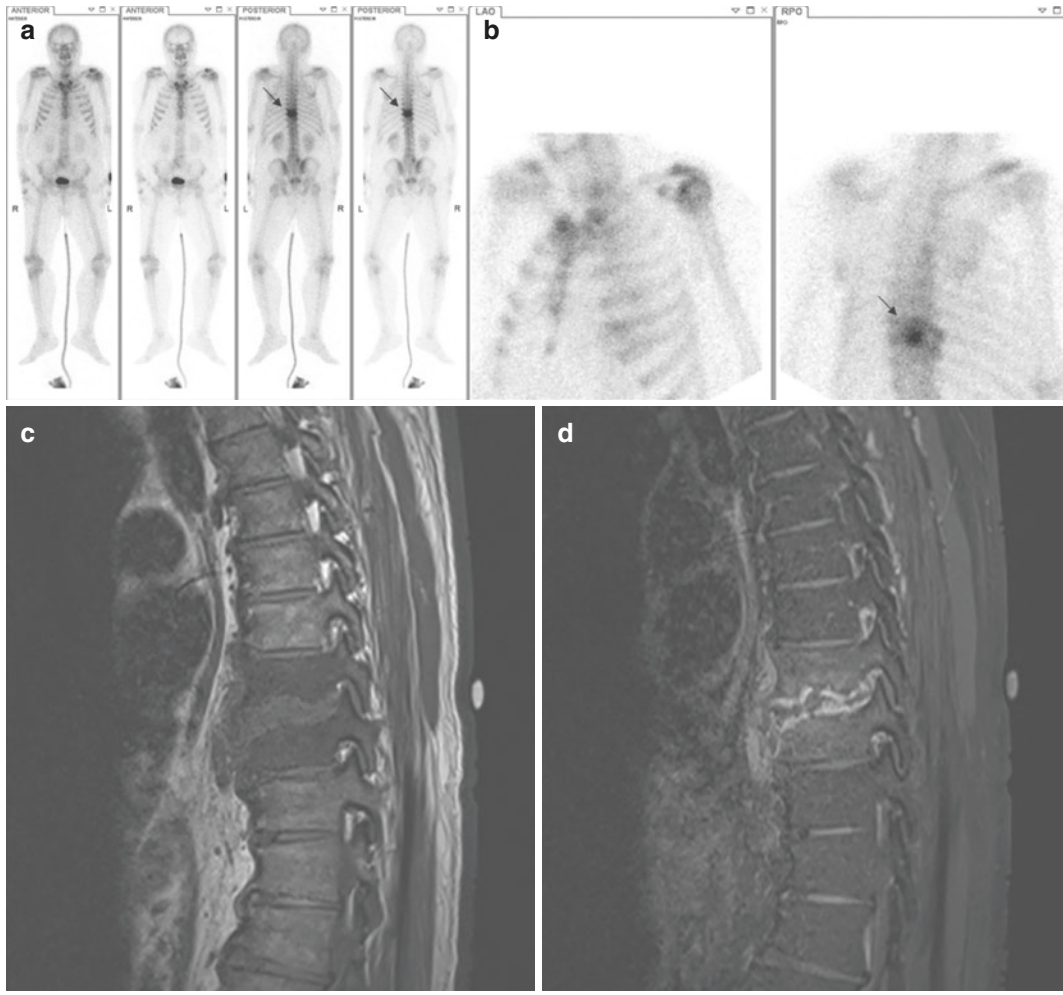


Fig. 1 Whole-body ^{99m}Tc MDP bone scan shows (**a**) intense tracer uptake at T8/T9 vertebrae (black arrows) which is better seen in the (**b**) local views. These findings correlated with spondylodiscitis seen on MRI. Sagittal (**c**) T1-W MR image shows hypointense vertebral marrow signal, and (**d**) contrast-enhanced FS T1-W MR image shows corresponding enhancement pattern typical of T8/T9 infective spondylodiscitis

and nonspecificity for infection versus inflammation (Gemmel et al. 2006; Thang et al. 2014; Raghavan et al. 2018; Lazzeri et al. 2019).

Despite its shortcomings, ^{67}Ga citrate scintigraphy is more useful than bone scintigraphy in the diagnosis of spinal infection due to its high specificity, even though their sensitivity is comparable (Fig. 2). In a retrospective study of 21 patients with infectious spondylitis involving 26 sites of infection, Lisbona et al. (1993) reported that ^{67}Ga citrate scintigraphy identified all 17 sites of nontuberculous infection and 9 sites of tuberculous infection and disclosed 6 sites of paraspinal infection, with the detection rate better than that of bone scintigraphy. Gratz et al. (2000) reported sensitivity, specificity, and diagnostic accuracy of 73%, 61%, and 80%, respectively, for ^{67}Ga planar and SPECT/CT imaging, in a prospective study of 30 patients with suspected diagnosis of spondylodiscitis. Love et al. (2000) retrospectively reviewed the results of ^{67}Ga imaging performed on 22 patients with suspected spondylodiscitis and showed that planar ^{67}Ga imaging had sensitivity, specificity, and accuracy of 82%, 77%, and 79%, respectively, which is better than bone scintigraphy.

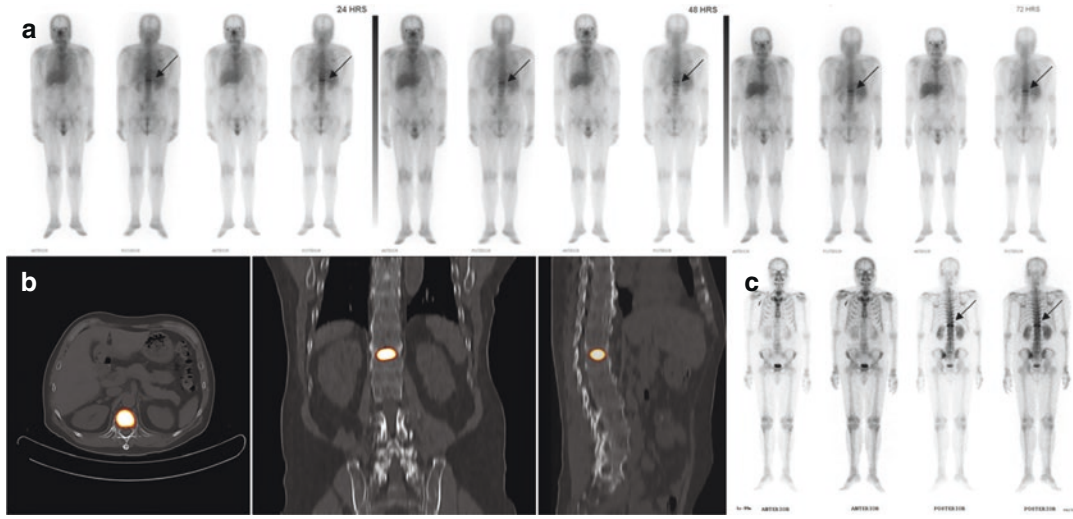


Fig. 2 (**a**) Gallium-67 citrate whole-body images show persistent tracer uptake at the T12 vertebra (black arrows). (**b**) SPECT/CT images localize the intense tracer activity to T12 vertebral body nearer to the upper end plate, suspicious for spondylodiscitis. (**c**) Correlative whole-body ^{99m}Tc MDP bone scan also shows congruent increased tracer uptake at the T11/T12 vertebral junction (black arrows) which is compatible with spondylodiscitis

A combination of bone scintigraphy and ^{67}Ga imaging can be done to increase the diagnostic accuracy, especially in the patients having post-surgical infections and to complement doubtful MRI findings. When performed together with bone scintigraphy, ^{67}Ga imaging improves the specificity, may detect the infection site earlier, and identifies the soft tissue infections which are otherwise undetected (Love and Palestro 2016; Lazzeri et al. 2019). In a prospective study conducted in 34 patients, combined bone scintigraphy and ^{67}Ga imaging were correctly interpreted as positive (true-positive) for spondylitis in 14 of 18 patients and correctly interpreted as negative (true-negative) in 13 of 16 patients. The sensitivity and specificity of the combined imaging were 78% and 81%, respectively, with an overall accuracy of 79%. If the equivocal pattern was considered positive, the sensitivity raised to 100%, but the specificity dropped to 50% (Fuster et al. 2012). Conversely, a retrospective study conducted by Love et al. (2000) concluded that ^{67}Ga SPECT was sufficient to diagnose spondylodiscitis, and bone scintigraphy was not necessary, as the results of combined bone scintigraphy, ^{67}Ga SPECT, and ^{67}Ga SPECT were identical with 91% sensitivity, 92% specificity, and 92% accuracy.

2.3 Radiolabeled Leukocyte Imaging

Labeling of autologous white blood cells (WBC) can be performed with Indium-111 (^{111}In) and Technetium-99m hexamethylpropylene amine oxime (^{99m}Tc HMPAO), with the half-life of Indium-111 being longer than that of Technetium-99m. Labeled leukocytes accumulate at the site of infection as part of the inflammatory process. The uptake depends upon intact chemotaxis, number and types of cells labeled, cellular response, and initiation of antimicrobial therapy, with the scan being most sensitive for detecting acute neutrophil-mediated infections. A combination with ^{99m}Tc sulfur colloid marrow imaging is useful to improve the diagnostic accuracy, since the physiological uptake of leukocytes by the bone marrow may complicate the interpretation of the study (Thang et al. 2014; Raghavan et al. 2018) (Fig. 3).

Unfortunately, radiolabeled leukocyte imaging is not very useful in diagnosing spondylodiscitis. In about 50% of the patients, leukocyte scintigraphy fails to detect vertebral osteomyelitis, and the site of infection appears often "cold" due to decreased or absent activity (Palestro et al.

1991). The explanations for this photopenia are not clearly known, and suggested probable causes are occlusion of the microcirculation of the involved bone, infection-induced death of reticulo-endothelial cells and normal marrow uptake by the viable bone. Patients who are symptomatic for less than 1 month usually show increased tracer uptake, while patients who are symptomatic for more than a month demonstrate decreased tracer uptake. Besides, several noninfectious conditions, such as treated spondylodiscitis, tumor, infection, compression fracture, hemangioma, and Paget disease, may also present with photopenia. This limitation of radiolabeled leukocyte imaging for spinal infection has also been reported with anti-granulocyte antibody imaging (Palestro et al. 1991; Gemmel et al. 2006; Palestro and Love 2007; Raghavan et al. 2018).

2.4 Other Types of Radiotracers

2.4.1 ^{99m}Tc Ciprofloxacin (Infection)

Ciprofloxacin is a fluoroquinolone, and its activity is mediated by inactivation of bacterial DNA gyrase and topoisomerase IV. ^{99m}Tc ciprofloxacin is the radiolabeled antibiotic developed for the diagnosis of infection, based on the fact that it would be incorporated and metabolized by bacteria at the site of infection. In a study conducted in 48 patients with suspected spondylodiscitis, planar and SPECT imaging was performed after injection of ^{99m}Tc ciprofloxacin. A relatively high number of false-positive results were reported in that study, with an explanation being that the patients had undergone surgery recently and had spinal implants at the time of scanning. Subsequent investigations revealed poor specificity and the enthusiasm for radiolabeled antibiotics subsequently faded (Yapar et al. 2001; De Winter et al. 2004; Palestro 2016).

2.4.2 Streptavidin/^{111}In-Biotin

Biotin or vitamin B7 plays a key role in glucose metabolism, and it is also a bacterial growth factor. Streptavidin, a 65-kDa protein, accumulates at the site of infection due to increased capillary permeability. ^{111}In-biotin, given subsequently, binds to streptavidin at the site of infection due to the abovementioned factors (Lazzeri et al. 1999). Lazzeri et al. (2004) evaluated this tracer complex in 55 consecutive patients with suspected spondylodiscitis in a multicenter study and

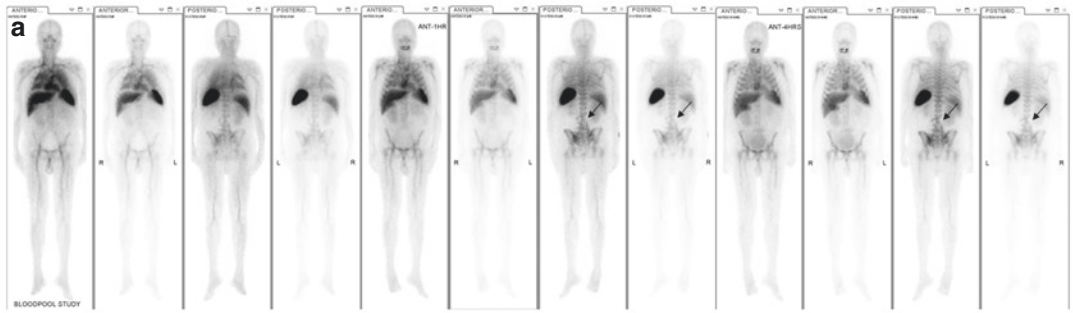
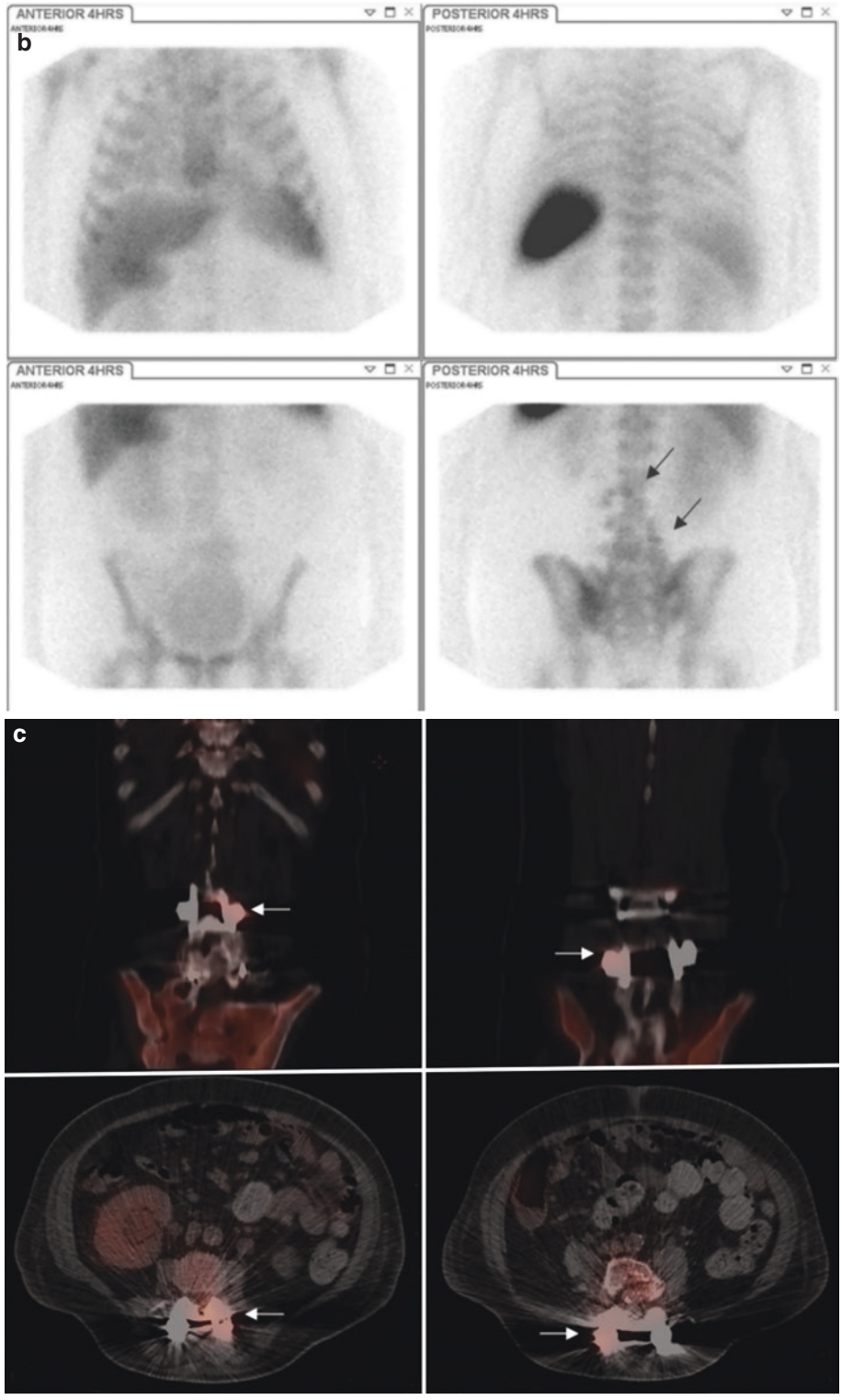


Fig. 3 (**a**) Radiolabeled WBC whole-body planar images show tracer accumulation of degree similar to that of the background marrow noted around the left L3 vertebra pedicle screw, around the L3 posterior elements and right L5 pedicle screw (black arrows). (**b**) Local views of the WBC scan show a close-up of the WBC accumulation in the pedicle screws (black arrows). (**c**) SPECT/CT images clearly demarcate the tracer activity in the L3 pedicle screw (white arrows, left facing) and the L5 pedicle screw (white arrows, right facing). (**d**) Sulfur colloid bone marrow planar images and (**e**) SPECT/CT image show no definite Tc-99m sulfur colloid uptake seen corresponding to the foci of radiolabeled WBC accumulation at the pedicle screws. Tracer accumulation in the posterior elements of L3 vertebra seen on the planar images (black arrows) appear to correspond to the findings seen in the radiolabeled WBC scan and hence unlikely to represent infection. Overall findings are suggestive of the pedicle screws as a source of infection



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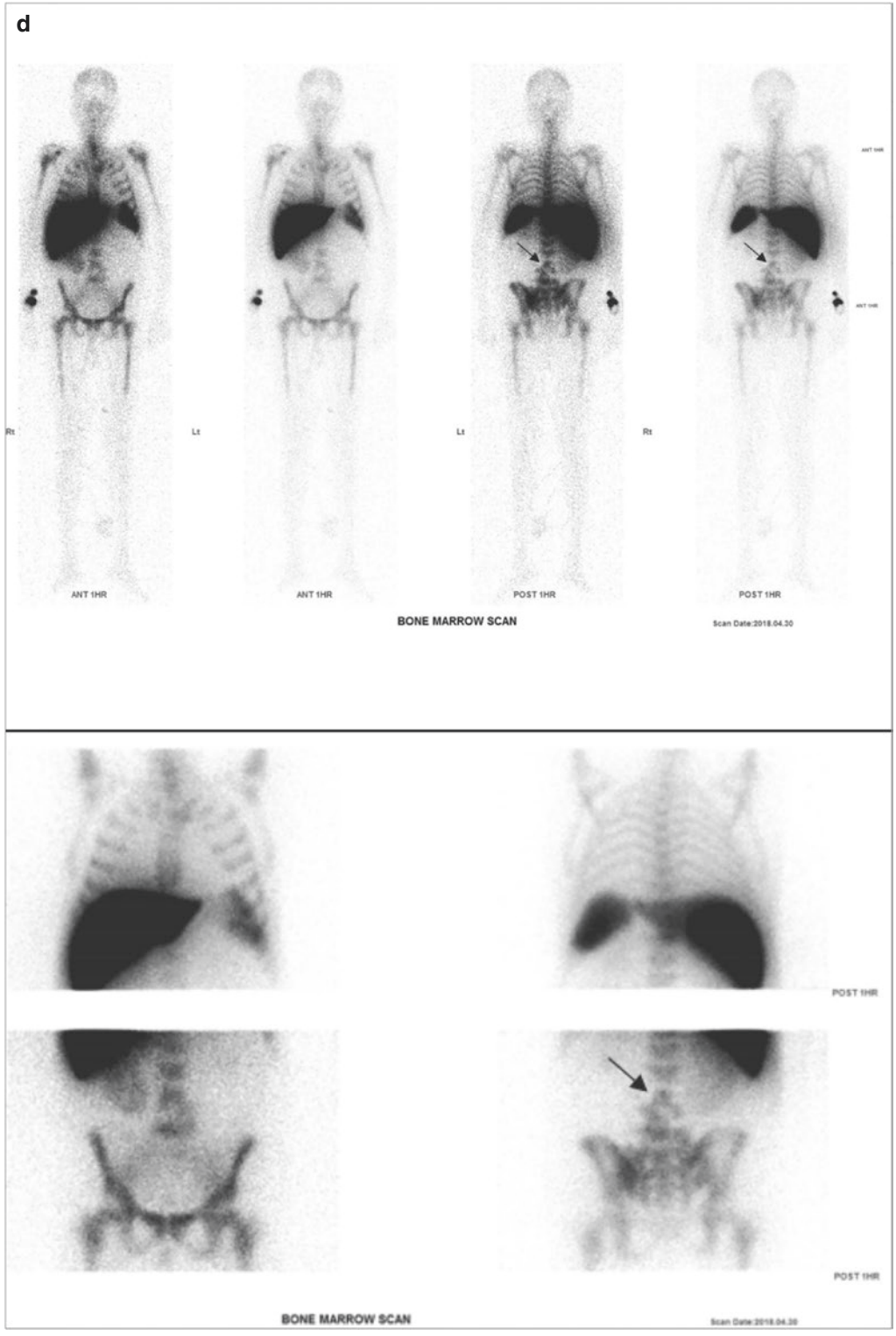

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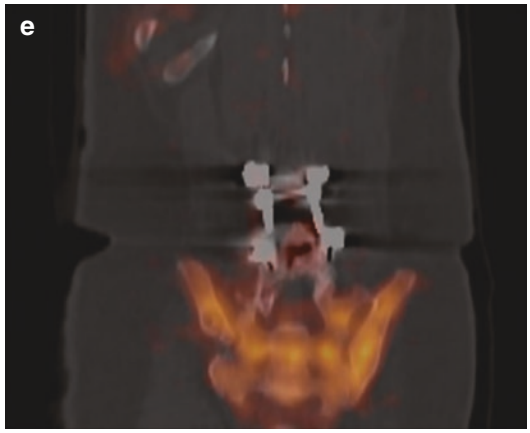

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reported that the sensitivity, specificity, and accuracy were 94%, 95%, and 94%, respectively. The advantages of this tracer are same-day imaging (within 6 h), faint bone marrow uptake, relatively low radiation burden, and whole-body imaging capability. The antibiotic treatment did not affect the sensitivity. However, the important disadvantage is the potential for immunogenic reactions to the subsequent administration of the drug which can lead to altered tracer distribution (Lazzeri et al. 2004).

2.4.3 Radiolabeled Antimicrobial Peptides

Antimicrobial peptides are small, cationic and amphipathic, and part of the natural defense mechanism and interact with pathogens by multiple mechanisms. Their therapeutic and diagnostic potentials against a broad spectrum of pathogens are being investigated. One example is ^{99m}Tc-labelled ethambutol or isoniazid for tuberculous infection. Radiolabeled synthetic fragments of ubiquicidine, which is present in murine macrophages, have been investigated for infection-specific imaging. Both ^{99m}Tc- and ^{68}Ga-labeled ubiquicidine successfully detects spinal infection (Palestro et al. 2013; Palestro 2016). Dillmann-Arroyo et al. (2011) evaluated the role of ^{99m}Tc ubiquicidine in 27 patients suspected to have spinal infection and reported that the test was 100% sensitive and 87.5% specific for spondylodiscitis.

3 Single-Photon Emission Computed Tomography/Computed Tomography (SPECT/CT)

The development of hybrid imaging techniques, especially SPECT/CT, has revolutionized nuclear medicine imaging by improving the diagnostic accuracy. The CT data is used for both anatomical correlation and attenuation correction. The differentiation between bone and soft tissue is often very difficult with planar imaging alone and may lead to false-positive results in spinal infection. The introduction of SPECT/CT has improved the localization of spinal infection compared to planar scintigraphy in bone scintigraphy, ^{67}Ga scintigraphy, and radiolabeled leukocyte imaging (Erba and Israel 2014; Thang et al. 2014). Bone scintigraphy has high sensitivity and moderate specificity for diagnosing osteomyelitis in non-violated bones. But the specificity decreases significantly from over 50% to 35% in the presence of previous trauma and surgical intervention. In these clinical situations, SPECT/CT improves the specificity of bone scintigraphy by reducing the number of false-positives and equivocal findings (Erba and Israel 2014).

In a prospective study conducted in 82 patients, Bar-Shalom et al. (2006) evaluated the role of additional SPECT/CT to planar imaging of ^{67}Ga scintigraphy and ^{111}In-labeled WBC scintigraphy. They found that SPECT/CT provided additional contribution to diagnosis in 48% of patients who underwent ^{67}Ga scintigraphy and 55% of patients who underwent ^{111}In-labeled WBC scintigraphy. The study revealed that SPECT/CT enables more precise anatomical localization and accurate delineation of the extent of infection (Fig. 4). However, SPECT/CT did not significantly contribute, if planar imaging was negative (Bar-shalom et al. 2006). Similarly, Lazzeri et al. (2010) also concluded that SPECT/CT imaging provides accurate evaluation of spinal infection by differentiating vertebral and adjacent soft tissue involvement in a study which investigated ^{111}In-biotin SPECT/CT in patients with suspected spinal infection. The authors demonstrated that the diagnostic accuracy of

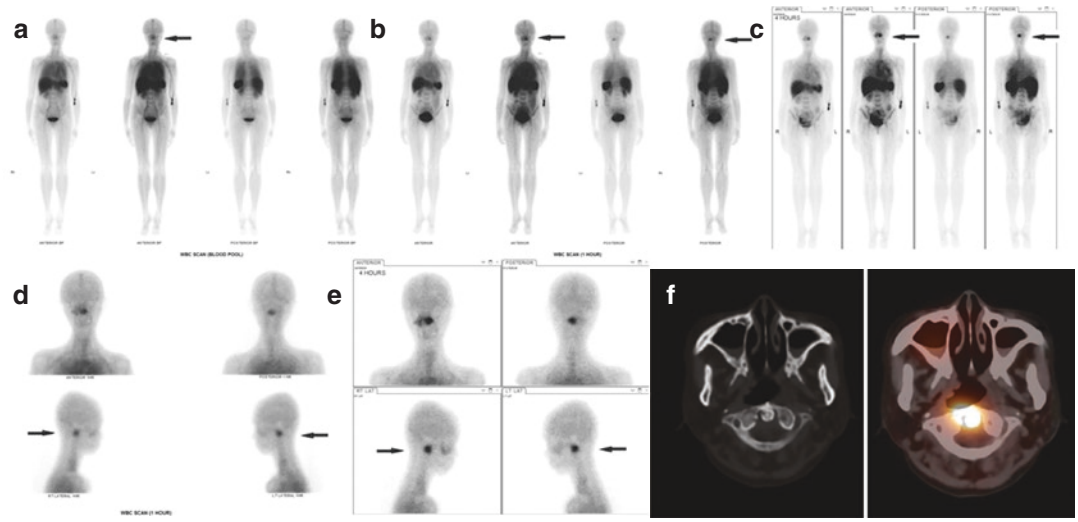

Fig. 4 Radiolabeled WBC whole-body planar images obtained at (**a**) blood pool phase, (**b**) 1 h, and (**c**) 4 h show increasing tracer activity (black arrows) in the midline of the head which appears to be at the upper cervical spine and best appreciated in the local views obtained at (**d**) 1 h and (**e**) 4 h. (**f**) SPECT/CT images localize the tagged WBC accumulation to be centered at the right anterior arch of the C1 vertebra and the medial atlantoaxial joint, suspicious for osteomyelitis with contiguous involvement of the atlantoaxial joint

SPECT/CT (93%) was higher than planar scintigraphy (76.3%) and stand-alone SPECT (90.3%) (Lazzeri et al. 2010).

4 Positron Emission Tomography/Computed Tomography (PET/CT)

Proton-rich unstable nuclei such as fluorine-18 (^{18}F) and gallium-68 (^{68}Ga) decay by electron capture or positron emission. The emitted positron travels a short distance from its origin site, loses energy, annihilates with a resident electron, and emits two 511 keV gamma photons in opposite directions. Hybrid PET/CT scanners identify the annihilation event and localizes it in the cross-sectional images with aid of coincidental detection and computer image reconstruction algorithms. Positron-emitting radiopharmaceuticals have intrinsic high spatial resolution and facilitate the precise localization of uptake in PET/CT, compared to single-photon-emitting isotopes. They have the added advantage of providing widely acceptable semiquantitative analysis, which is helpful in differentiating infectious and noninfectious conditions, monitoring treatment response, and diagnosing relapsed infections during follow-up (Kannivelu et al. 2014; Raghavan et al. 2018).

4.1 Fluorine-18-2′-Deoxy-2-Fluoro-D-Glucose ([^{18}F] FDG)

[^{18}F] FDG is the most commonly used tracer in PET/CT imaging for spinal infection. [^{18}F] FDG is a fluorinated structural analog of glucose and is transported into the cell by glut-1 transporters and initially phosphorylated by the same mechanism, namely, hexokinase. But the phosphorylated [^{18}F] FDG cannot be further metabolized as phosphorylated glucose and gets trapped within the cell in proportion to the rate of glucose uptake. Several factors influence the increased [^{18}F] FDG uptake at the infection sites. Because of hyperemia, more [^{18}F] FDG is distributed to the region of infection. The activated inflammatory cells such as neutrophils, lymphocytes, monocytes, and macrophages are present in increased numbers at the infection zones. They express more glucose transporters in their cell

membranes, resulting in increased affinity and uptake of [^{18}F] FDG. Furthermore, the normal bone marrow physiological uptake of [^{18}F] FDG is low. All these factors, together with its widespread availability, make [^{18}F] FDG an effective tracer and excellent alternative to conventional radionuclide imaging for diagnosis of spinal infection (Gemmel et al. 2006; Palestro 2013).

[^{18}F] FDG PET shows increased tracer uptake in both acute and chronic osteomyelitis, corresponding to the areas of inflammatory cell filtration, neutrophils in the acute phase and macrophages in the chronic phase. In a study conducted in acute and chronic osteomyelitis in 21 patients, [^{18}F] FDG PET yielded true-positive results in all seven patients who had spondylitis (Kälicke et al. 2000). Guhlmann et al. (1998) studied the usefulness of [^{18}F] FDG PET in 15 patients with suspected chronic osteomyelitis, compared it with radiolabeled anti-granulocyte antibody imaging, and concluded that [^{18}F] FDG PET had a higher diagnostic accuracy. Similarly, in evaluation of [^{18}F] FDG PET in 16 consecutive patients with suspected spondylodiscitis, the investigators showed that [^{18}F] FDG PET was true positive in all 12 patients of infection and true negative in 3 of 4 patients without infection. They also demonstrated the advantage of PET in delineation of the involvement of paravertebral soft tissue (Schmitz et al. 2001). In general, [^{18}F] FDG PET/CT performs better than bone scintigraphy and ^{67}Ga scintigraphy in identification of paraspinal soft tissue infection, and differentiation of degenerative arthritis from infection, providing higher diagnostic accuracy (Gratz et al. 2002; Gemmel et al. 2010; Fuster et al. 2012) (Fig. 5). A recent systematic review and bivariate meta-analysis, based on 12 selected studies among 26 articles, for the effectiveness of [^{18}F] FDG PET/CT in patients with suspected spondylitis showed sensitivity of 94.8% and specificity of 91.4% overall (Treglia et al. 2020).

In the presence of severe degenerative changes of the vertebral end plates and intervertebral disks, [^{18}F] FDG PET appears to be superior in differentiation of infection from degeneration, compared to ^{67}Ga scintigraphy and MRI (Gratz et al. 2000; Schmitz et al. 2001; Gemmel et al. 2010) (Fig. 6). In a prospective study of 30 patients with substantial vertebral end-plate

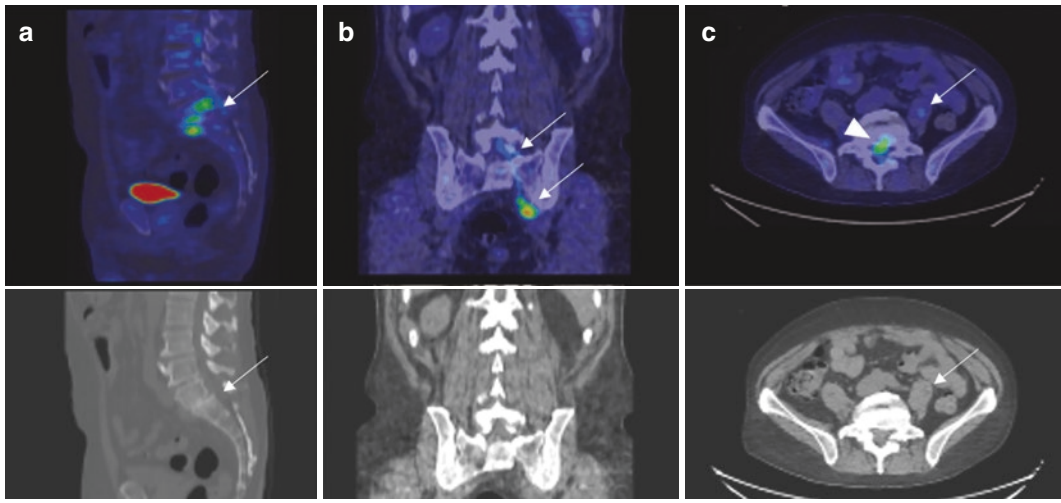

Fig. 5 [18F] FDG PET/CT. (**a**) Sagittal images show a Grade 1 anterolisthesis of L5 on S1 vertebral segments with moderately diffuse FDG uptake at the L5 and S1 vertebrae with epidural extension (white arrows). (**b**) Coronal images show increased FDG avidity along the left S1 nerve (white arrows). (**c**) Axial images also show a hypermetabolic soft tissue lesion in the left psoas muscle (white arrow). The hypermetabolic epidural extension can also be appreciated (white arrowhead). Overall findings are suggestive of L5/S1 spondylodiscitis with epidural extension and a left psoas abscess

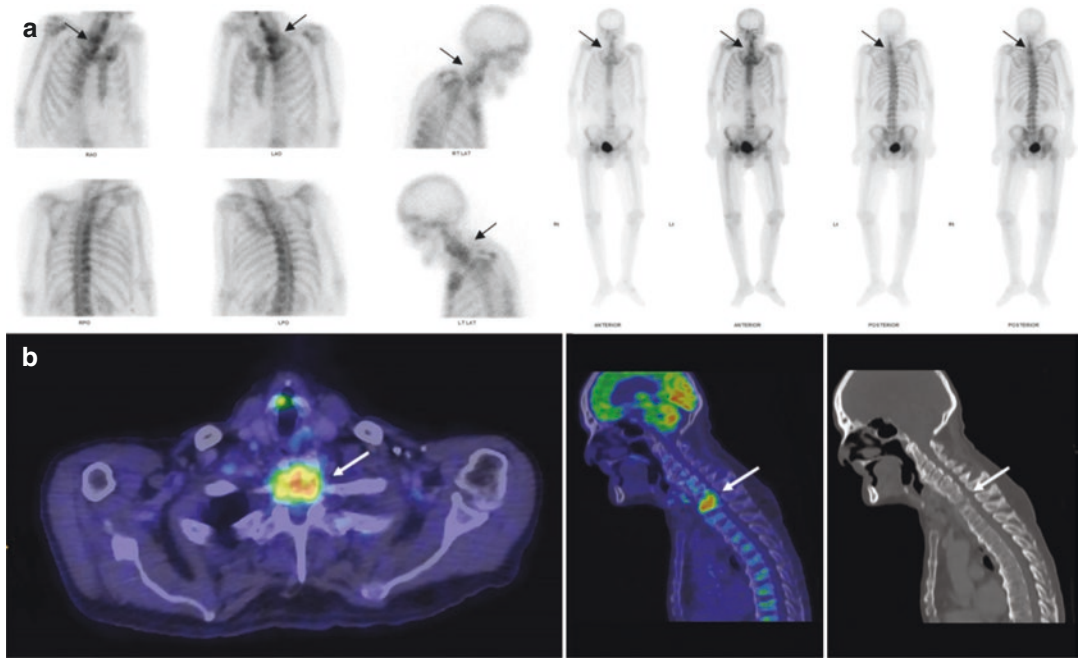

Fig. 6 (**a**) Whole-body ^{99m}Tc MDP bone scan with local views show moderately increased radiotracer uptake in the C7/T1 region (black arrows) suspicious for spondylodiscitis in the background of degenerative changes of the cervical spine. (**b**) Correlative FDG PET/CT images show increased metabolic activity at the C7/T1 level centered on the intervertebral disk with destructive changes at the adjacent vertebral end plates (white arrows), compatible with spondylodiscitis

abnormalities, [^{18}F] FDG PET was true-positive in all 5 foci of infection and true-negative in all 33 uninfected sites with 100% sensitivity and 100% specificity, compared to 50% sensitivity and 96% specificity for MRI (Stumpe et al. 2002). However, Rosen et al. (2006) concluded differently that significant focal [^{18}F] FDG uptake of varying degrees was seen in more than half of patients with degenerative spinal disease, primarily in the lumbosacral spine. Similarly, a few studies conducted to evaluate the potential of [^{18}F] FDG PET to differentiate tuberculous from pyogenic spinal infections contributed variable results. Kim et al. (2008) performed dual time point [^{18}F] FDG PET imaging in 22 consecutive patients with high suspicion of spondylitis at 1 h and 2 h after injection of [18F] FDG. They observed that the SUVmax at 1 h was significantly higher for tuberculous infection than nontuberculous infection. However, at 2 h, the differences were not significant and not useful for differentiating tuberculous and nontuberculous infections. Gunes et al. (2016) investigated the usefulness of [^{18}F] FDG PET/CT in 32 patients with spondylodiscitis. Images were acquired at 90 min and 2 h after injection of [^{18}F] FDG, and they observed no significant differences between pyogenic and tuberculous spondylitis in early and delayed imaging. It would be safe to conclude that neither visual nor semiquantitative analysis, using dual point imaging, could reliably differentiate pyogenic and tuberculous spinal infections (Kim et al. 2008; Gunes et al. 2016).

The diagnosis of spinal infection in the presence of previous trauma and hardware is a great challenge in all available imaging modalities, including [^{18}F] FDG PET/CT. Even in the absence of infection, there can be increased [^{18}F] FDG uptake at the location of instrumentation due to foreign body immune response, aseptic loosening, bone remodeling, and peri-prosthetic fracture. Hungenbach et al. (2013) performed [^{18}F] FDG PET for 42 patients with spondylodiscitis, including 13 who underwent prior surgery. They

evaluated for the intensity and patterns of [^{18}F] FDG uptake and found that the test was 86% sensitive and 95% specific. Hartmann et al. (2007) investigated the diagnostic value of [^{18}F] FDG PET/CT in patients with trauma and suspected chronic osteomyelitis in the axial and appendicular skeleton, including patients with metallic implants. For the subgroup of nine spinal region infections, [^{18}F] FDG PET/CT was true positive in all seven patients with spondylodiscitis and true negative in the two patients without infection (100% diagnostic accuracy). The added value of anatomical localization provided by the CT component in PET/CT imaging to identify the extent of infection and soft tissue involvement for better clinical management was emphasized by these investigators (Hartmann et al. 2007) (Fig. 7).

In the largest prospective series to date, De Winter et al. (2003) evaluated the role of [^{18}F] FDG PET in patients with postoperative spine, including 16 patients in the control group (hematogeneous spondylitis) and 57 patients in the investigation group (30 patients without spinal implants and 27 patients with spinal implants). Using optimal cut-off values, the overall sensitivity, specificity, diagnostic accuracy, positive predictive value, and negative predictive value were 100%, 81%, 86%, 65%, and 100%, respectively. Among the 30 patients without spinal implants, there were two false-positive studies;

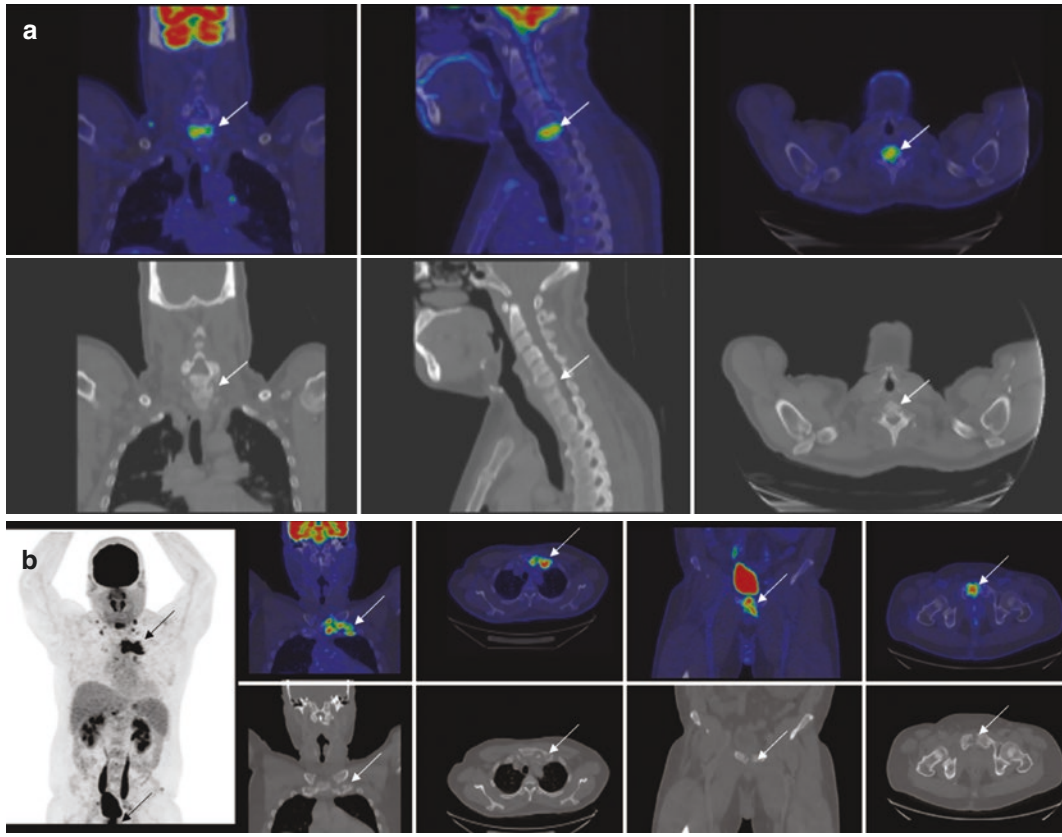

Fig. 7 FDG PET/CT (**a**) coronal, sagittal, and axial images show intense FDG avidity in the C6/C7 vertebrae with bony destruction (white arrows), suspicious for spondylodiscitis. (**b**) MIP image (far left) shows hypermetabolic lesions in the left sternoclavicular junction and the pubic symphysis (black arrows) which correspond to the areas of intense FDG uptake and bony destruction on the coronal and axial FDG PET/CT images (white arrows). The CT component provides accurate anatomical localization. These raise the suspicion for multiple sites of septic arthritis

and among the 27 patients with spinal implants, there were 6 false-positive studies. The specificity was 65% in the group with spinal implants, compared to 92% in the group without spinal implants. The authors concluded that chronic postoperative spinal infection can be excluded in negative [^{18}F] FDG PET studies; however, positive studies must be interpreted cautiously (De Winter et al. 2003).

MRI and [^{18}F] FDG PET/CT are complementary to each other in the diagnosis of spinal infection, especially in the patients in which they are not individually conclusive. There are many comparative studies between MRI and [^{18}F] FDG PET/CT to assess their effectiveness and limitations. Even with their limited resolution, [18F] FDG PET was found to be superior to MRI in detecting low-grade spondylitis and discitis (Gratz et al. 2002). In the presence of degenerative vertebral end-plate changes, [^{18}F] FDG appears to better at diagnosing or ruling out spondylodiscitis (Stumpe et al. 2002; Ohtori et al. 2010). In a prospective study, Fuster et al. (2012) compared [^{18}F] FDG PET/CT and MRI in 26 patients with clinical symptoms of spondylodiscitis. The diagnostic accuracies of MRI and [^{18}F] FDG PET/CT were fairly similar, being 84% and 81%, respectively. They concluded that [^{18}F] FDG PET/CT had a higher specificity than MRI. However, MRI was superior for detecting soft tissue involvement. The combination of [^{18}F] FDG PET/CT and MRI detected spondylodiscitis in all the patients who had infection (Fuster et al. 2012). Comparison studies conducted by various investigators provided comparable but conflicting sensitivity and specificity values for [^{18}F] FDG PET/CT and MRI in diagnosing spinal infection, but all agree that [^{18}F] FDG PET/CT is a useful adjunct to MRI and can be used when MRI is inconclusive and cannot be performed (Seifen et al. 2012; Skanjeti et al. 2012; Palestro 2013; Raghavan et al. 2018).

[^{18}F] FDG PET/CT is very useful during follow-up for monitoring treatment response and detecting relapse. Nanni et al. (2012) evaluated the potential of [^{18}F] FDG PET/CT in the early assessment of treatment response to antibiotics in 34 patients with hematogeneous spondylodiscitis. The SUVmax of the baseline study (SUV1) and SUVmax of the second study (SUV2) which was performed 2–4 weeks after the start of treatment were compared. They found that in responders, SUV2 was significantly less than SUV 1. By using delta-SUVmax {(SUVmax baseline − SUVmax response)/SUVmax baseline}, higher sensitivity and specificity were achieved (Nanni et al. 2012). In addition to the quantification, the tracer uptake pattern in the follow-up scans is also helpful for differentiating active infection and patients without active infection. In active infection, the [^{18}F] FDG uptake is usually seen in the bone and soft tissue, whereas the uptake confined to the margins of destroyed disks after treatment is not indicative of infection (Riccio et al. 2015). In a study conducted in 21 patients with 24 sites of disease, Skanjeti et al. (2012) found that [^{18}F] FDG PET/CT was more accurate than MRI in assessing treatment response. Dauchy et al. (2016) prospectively investigated for relapsed infection in 30 patients, including 19 with spinal hardware who had previously confirmed spondylodiscitis. In a comparison between [^{18}F] FDG PET/CT and MRI using a combination of visual and semiquantitative analysis, the results of [^{18}F] FDG PET/CT were better than those of MRI, though the differences were not significant (Dauchy et al. 2016).

[^{18}F] FDG PET/CT is a promising alternative to conventional nuclear imaging and is becoming a frontline investigation together with MRI for investigation of spinal infection. The disadvantage of limited anatomical information of PET has now been overcome by co-registration with in-line CT in hybrid PET/CT scanners. Still, we should be mindful that the uptake of [^{18}F] FDG is nonspecific and can be seen in infection, inflammation, and tumor. Even though [^{18}F] FDG PET/CT is more effective than other imaging choices in diagnosing spinal infection in the presence of degenerative changes and previous trauma, it is important to note that the specificity is moderately reduced in patients with spinal instrumentation. Other disadvantages of [^{18}F] FDG PET/CT are scarce availability, radiation burden, and relatively higher costs (Gemmel et al. 2010; Lazzeri et al. 2019).

4.2 Gallium-68 (^{68}Ga) and Other Radiotracers

^{68}Ga is a positron-emitting isotope with physical half-life of 68 min, which is shorter than 78-h half-life of ^{67}Ga. The uptake of ^{68}Ga citrate at the sites of inflammation and infection are nonspecific and similar to ^{67}Ga. ^{68}Ga offers superior quality imaging as it is a positron emitter, and imaging should be performed within a few hours after injection because of its short half-life. Little data are available on the role of ^{68}Ga citrate imaging in spinal infection. Nanni et al. (2010) performed ^{68}Ga PET/CT scans on 31 patients with suspected spondylodiscitis, and of these, 23 cases were positive. They reported sensitivity, specificity, and accuracy of 100%, 76%, and 90%, respectively (Nanni et al. 2010). Similar to ^{111}In-biotin, efforts were made to develop a specific infection imaging agent, by complexing biocytin with ^{68}Ga. ^{68}Ga-DOTA-biocytin was stable over 3 h and may prove useful for diagnosing infection (Asti et al. 2012; Raghavan et al. 2018).

^{18}F sodium-fluoride (NaF) is a bone-specific positron-emitting isotope, and NaF PET/CT has been used for the diagnosis of various bone and joint diseases. Recently, this isotope was evaluated for diagnosing bone infection, including spinal infection and postsurgical interventions. A dual-phase NaF PET/CT imaging protocol was introduced to detect infection and inflammation, with early-phase PET imaging performed within 10 min after tracer injection and standard bone phase PET/CT imaging performed 30–90 min after tracer injection (Freesmeyer et al. 2014). In a recent study, Lee et al. (2019) evaluated the role of NaF PET/CT in diagnosing surgical site infection of the 23 patients, and they reported that the sensitivity, specificity, and accuracy of dual-phase NaF bone PET/CT were 92.9%, 100%, and 95.7%, respectively. Based on these results, the authors suggested that NaF PET/CT can be an alternative nuclear medicine imaging modality for detecting orthopedic infections, especially spinal infection (Lee et al. 2019).

5 Positron Emission Tomography/Magnetic Resonance Imaging (PET/MRI)

Hybrid PET/MRI scanners have become increasingly common, after integration was made possible by newer technical advances such as avalanche photodiodes and new MR Dixon sequence (Kannivelu et al. 2012). The combination of the strengths of [^{18}F] FDG PET and MRI offers highly sensitive metabolic and high-resolution anatomical imaging with excellent soft tissue contrast, hence overcoming their individual limitations. The scientific literature and available data are still limited for the role of PET/MRI in the diagnosis of spinal infection. Fahnert et al. (2016) conducted a prospective study in patients with suspected spondylodiscitis with previous inconclusive MRI results. Image datasets of 28 patients (a total of 29 regions) were evaluated. When the PET component was added, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of PET/MRI improved to 100%, 88%, 86%, and 100%, respectively, compared to the sensitivity, specificity, PPV, and NPV of MRI alone which were 50%, 71%, 54%, and 67% respectively. Among the 8 of 29 inconclusive regions of MRI alone, the added PET information changed the diagnosis to spondylodiscitis in 5 regions and to absence of spondylodiscitis in 3 regions. There were no false-negative results using combined PET/MRI. The investigators concluded that the use of [^{18}F] FDG PET/MRI significantly increases the diagnostic certainty of the detection of spinal infection, especially in patients with inconclusive clinical or MRI findings. They concluded that [^{18}F] FDG PET/MRI can become the one-stop-shop approach for earlier initiation of proper treatment to patients with spinal infection (Fahnert et al. 2016).

6 Consensus Guidelines

An expert specialist team, comprising nuclear medicine physicians appointed by the European Association of Nuclear Medicine (EANM),

neuroradiologists appointed by the European Society of Neuroradiology (ESNR), and infectious diseases specialists appointed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), reviewed the literature from January 2006 to December 2015 and published guidelines for the diagnosis of spinal infection (spondylodiscitis) in adults. They issued 20 consensus statements which were graded by level of evidence based on the 2011 Oxford Centre of Evidence Based Medicine criteria (Lazzeri et al. 2019). Among them, the issued guidelines (statements) regarding nuclear medicine imaging are summarized below:

- In primary and postsurgical spondylodiscitis, if MRI is contraindicated, the imaging modality of choice is [^{18}F] FDG-PET/CT (Level 2).
- In postsurgical spondylodiscitis, with or without spinal hardware, [^{18}F] FDG-PET/CT can detect both spinal infection and soft tissue infection (Level 2).
- In patients with suspected spinal infection and elevated ESR and/or CRP and doubtful MRI, [^{18}F] FDG-PET/CT should be performed (Level 1).
- In patients with suspected spinal infection, elevated ESR and/or CRP, doubtful or unperformable MRI, and doubtful or unperformable [^{18}F] FDG-PET/CT, a CT scan should be performed with an image-guided biopsy (Level 2).
- The role of hybrid PET/MRI, although promising, needs to be evaluated (Level 5).
- In case of negative MRI or negative [^{18}F] FDG-PET/CT, the diagnosis of spondylodiscitis should be excluded (Level 5).

7 Conclusion

There has been much advance in diagnostic imaging of spinal infection since the advent of CT and MRI which provide exquisite spatial resolution but limited functional data. As clearly illustrated in this chapter, nuclear medicine functional techniques for spinal infection imaging have also come to the forefront, especially with the use of hybrid SPECT/CT, PET/CT, and PET/MRI, which provide traditionally high sensitivity and superior functional information afforded by nuclear imaging and the superior spatial resolution and anatomical detail from CT and MRI. A myriad of radiotracers is available to nuclear medicine physicians in this respect, ranging from SPECT tracers based on SPECT isotopes such as ^{99m}Tc and ^{67}Ga radionuclides, to PET tracers based on PET isotopes such as ^{18}F-fluorine- and ^{68}Ga-labelled positron emitters.

Advantages of hybrid nuclear imaging in spinal infection include their usefulness in patients who had prior spinal instrumentation where conventional anatomical imaging is difficult or cannot detect the source of infection, providing more information to directing targeted biopsy for tissue cultures, and helping to determine treatment response and the efficacy of antimicrobial therapy. Improved specificity with high negative predictive values of FDG PET/CT in this setting has led to it being the preferred noninvasive nuclear medicine diagnostic imaging modality of choice in the diagnosis, management, and clinical decision-making process in spinal infection.

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