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The role of nuclear medicine in the diagnosis of spondylodiscitis

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Abstract. – *Background:* **The diagnosis of spondylodiscitis can be difficult, because the patients history, subjective symptoms and physical findings are often inconclusive, particularly in the early stages.**

Aim: **To perform an overview on the role of nuclear medicine procedures with single photon emission tomography (SPET) and positron emission tomography (PET) tracers in the diagnosis of spondylodiscitis.**

Materials and Methods: **A literature review about bone scintigraphy, Gallium-67-citrate scintigraphy, labeled leukocytes scintigraphy and PET was performed. Main findings of the literature were reported.**

Results: **Bone scintigraphy is a sensitive and widely available nuclear medicine technique, but it is characterized by low specificity. Gallium-67-citrate scintigraphy is often used as a complement to bone scintigraphy to enhance the specificity of the study and to detect extra-osseous sites of infection. Labeled leukocytes scintigraphy is not a useful method in the diagnosis of spondylodiscitis. Fluorine-18-fluorodeoxyglucose positron emission tomography is a sensitive method and could potentially be useful in the diagnosis of spondylodiscitis and in the evaluation of treatment response. Nevertheless, scientific literature about this topic is still limited.**

Conclusions: **Overall, nuclear medicine procedures play a useful role in the diagnosis of spondylodiscitis identifying functional abnormalities which precede morphological changes. Therefore, nuclear medicine procedures may complement or integrate morphological imaging findings in patients with suspected spondylodiscitis.**

Key words:

Nuclear medicine, Spondylodiscitis, Scintigraphy, Positron Emission Tomography.

Introduction

The diagnosis of spondylodiscitis (SP) can be difficult, because the patients history, subjective symptoms and physical findings are often inconclusive, particularly in the early stages[1,2]. Nuclear medicine procedures, which identify pathophysiological reactions preceding morphological changes, can play a useful role in the diagnosis of SP; several studies have investigated about the utility of nuclear medicine techniques with single photon emission tomography (SPET) and positron emission tomography (PET) tracers in the early diagnosis, staging and post-treatment evaluation in patients with SP[3].

Role of nuclear medicine techniques with SPET tracers in patients with spondylodiscitis

Conventional nuclear medicine techniques such as bone scintigraphy with Technetium-99m-diphosphonates, scintigraphy with autologous radiolabeled leukocytes and scintigraphy with Gallium-67-citrate are to date performed in the diagnostic management of patients with bone infections, even though the wider availability of magnetic resonance (MRI) has considerably narrowed their application fields.

Bone scintigraphy with Technetium-99m-diphosphonates

Bone scan with Technetium-99m-diphosphonates allows to detect sites of bone remodeling, which can be determined by either an infectious condition or any other pathological process of the spine characterized by accelerated bone turnover (rheumatic and degenerative osteo-articular diseases, osteoporosis fractures, pseudo-arthrosis, neoplastic involvement)[4-6]. Bone scintigraphy for the diagnosis of bone infection is usually performed with a three-phase modality: a dynamic "angiographic sequence" for the study of hyperemia; a "blood-pool image" to detect inflammatory involvement of soft tissues; a "later (or bone) image" (after at least 2-3 hours) to investi-

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gate bone turnover[4-6]. In SP, the radiopharmaceutical uptake is centered about the disk space and adjacent vertebral bodies and has a vertical orientation. Early SP typically shows increased tracer uptake on bone scintigraphy despite normal findings on radiographs (Figure 1)[5].

Performing an hybrid tomographic single photon emission tomography/computed tomography (SPECT/CT) acquisition provides a higher specificity than planar scans; in fact, the improved anatomical localization of sites of abnormal radiopharmaceutical uptake in different vertebral components is useful to distinguish between different spinal diseases which follow certain predictable patterns[7,8].

Overall, bone scintigraphy with Technetium-99m-diphosphonates is well known for its high sensitivity, ranging from 80 to 95%, much greater than conventional x-ray in the early diagnosis of SP: in fact, alterations in local blood supply and in bone turnover detected by bone scan occur far before anatomical changes[9-13]. Furthermore, if antibiotic therapy is initiated in early stage, radiological abnormalities could not be apparent[9-13]. Thanks to its high sensitivity, a normal bone scintigraphy provides very reliable evidence for the absence of bone inflammation; on the contrary, an increased uptake in all phases is suggestive. Besides, the scanning of the entire body allows the detection of eventual clinically silent infectious focuses, whether in the spine and in other bone segments. Since an intact vasculature in the affected bone is needed to allow an adequate accumulation of the radiopharmaceutical, false negative results may be the consequence of inadequate blood supply (vasospasm, thrombosis of vessels, oedema), lytic lesions with loss of osseous tissue or subperiosteal abscesses[9-13]. Nevertheless, abnormalities seen on bone scintigraphy do not reflect infection specifically, hence specificity is low, especially in the setting of previous vertebral surgery (e.g. prosthetic implants) or injuries[9-13].

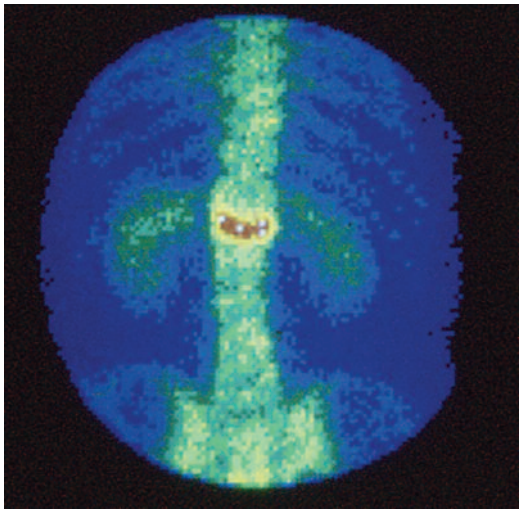

Figure 1. Bone scintigraphy with Technetium-99m-diphosphonates planar image (*posterior view*) in a 44 year-old female patient with spondylodiscitis showing increased tracer uptake between D12 and L1.

Scintigraphy with autologous radiolabeled leukocytes

Leukocytes, and particularly neutrophils, significantly accumulate in the site of infection to take part in the inflammatory response against the microbial agent. Therefore, scintigraphy with autologous radiolabeled leukocytes is a potentially useful diagnostic tool in patients with spine infection. Leukocytes labeling is obtained with Technetium-99m-hexamethylpropylene amine oxime (^{99m}Tc-HMPAO) or Indium-111-oxine, even if the latter method has become obsolete for most indications because of poor image resolution[14]. However, disregarding the biological risk related to the manipulation of infected blood, the physiological uptake of leukocytes by the hematopoietically active bone marrow (which can be found in the axial bone segments such as the skull, clavicles, sternum, scapulae, ribs, vertebrae and pelvis) is the major drawback which reduces the sensitivity of this method in the diagnosis of SP[15]. Palestro et al[16] reported a low sensitivity (39%) of scintigraphy with labeled leukocytes in patients with SP when increased vertebral labeled leukocytes uptake was considered, while specificity was very high (98%). Photopenic lesions at scintigraphy with labeled leukocytes are shown in about 50% of patients affected by SP, probably due to encapsulation of the infected site and therefore reduced migration of leukocytes[16,17]; nevertheless, this pattern is nonspecific for infection.

Scintigraphy with Gallium-67-citrate

Infectious foci usually show high concentrations of Gallium-67-citrate. Several mechanisms have been proposed: binding to transferrin resulting in deposit to the sites of increased vascular membrane permeability; binding to lactoferrin, a globular glycoprotein with antimicrobial activity,

produced by innate immunitary system and abundant in the site of infection; direct uptake by certain bacteria through siderophores[18,19]. The major drawback of Gallium-67-citrate scintigraphy is that only a small amount of the injected dose is retained by the bone, whereas a great amount is retained by the liver, bone marrow and soft tissues at 48 h and the 25% is physiologically excreted through the urinary system and the colon within the first 24 h[20]. Furthermore, poor image quality, high bowel uptake in the early images requiring delayed images (up to 48-72 h) to reduce intestinal activity, nonspecific tumor and nodal uptake and an unfavourable physical half-life reduce the diagnostic yield of this method[20,21]. Nevertheless, chronic infections of the spine are correctly identified by Gallium-67-citrate scintigraphy[22-24] (Figure 2). Moreover, Gallium-67-citrate scintigraphy should be performed regardless of the findings of a contemporaneous bone scan: in fact, it improves the sensitivity and the specificity of bone scan and detects soft tissue involvement especially if performed with SPECT/CT modality[22-24]. Love et al[24] found that Gallium-67-citrate SPECT is more accurate than bone scintigraphy with Technetium-99m-diphosphonates (92% vs 71%), as sensitive as MRI (91%) and slightly more specific than MRI (92% vs 77%). These Authors suggested that Gallium-67-citrate SPECT should be considered as a reliable alternative to MRI in case of diagnostic uncertainty and/or unfeasibility. Unfortunately, as Lin et al[25] described, postoperative uptake of Gallium-67-citrate at the site of surgical incision should be considered. Therefore, foci of Gallium-67-citrate uptake in an immediately post-surgical setting must be critically regarded. Despite its own limitations, scintigraphy with Gallium-67-citrate is less subjected to the interference of bone remodeling than bone scintigraphy with Technetium-99m-diphosphonates, being therefore more sensitive than bone scan in the follow-up evaluation of SP and in monitoring treatment response[26].

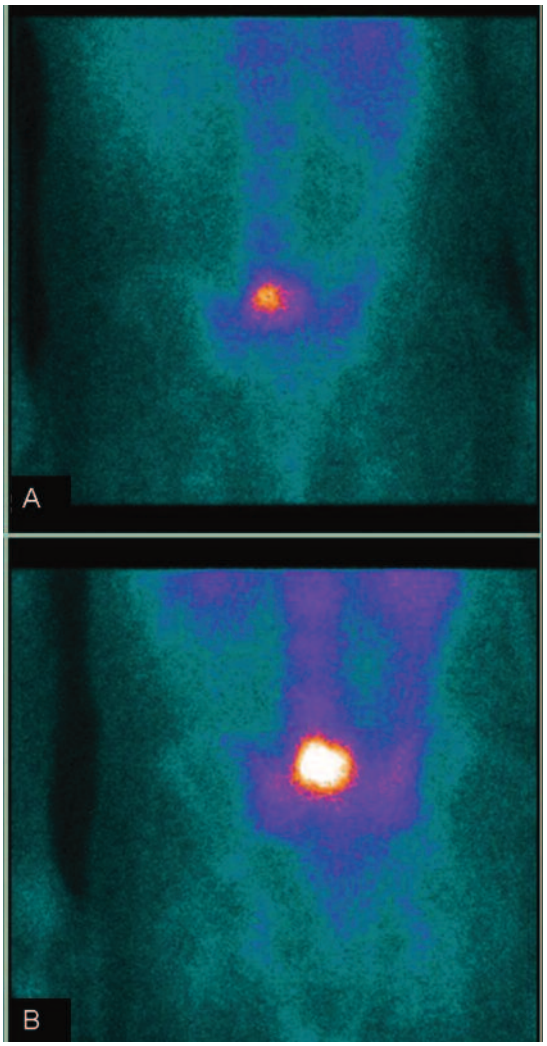

Figure 2. Scintigraphy with Gallium-67-citrate planar image (*posterior view*) in a 45 year-old male patient with spondylodiscitis showing increased tracer uptake corresponding to L5 both at 6 hours (*A*) and at 24 hours (*B*) after radiopharmaceutical injection.

Role of PET in patients with spondylodiscitis

Fluorine-18-fluorodeoxyglucose positron emission tomography (FDG-PET) plays an important role in the diagnosis, staging and monitoring of malignant tumors[27]. Not only tumors but also infections show an increased uptake of FDG (a glucose analogue), due to the increased glucose metabolism in activated inflammatory cells such as leukocytes[28,29]. Therefore, in the last years, the role of FDG-PET and PET/CT in infectious and inflammatory diseases, beside oncologic field, is growing[28]. Nevertheless, to date, scientific literature about this nuclear medicine technique in the field of SP is limited[30-37].

FDG-PET is a very sensitive imaging procedure in the detection of SP (Figure 3). Compared to other nuclear medicine procedures, PET enables a rapid imaging with acceptable radiation dose and high spatial resolution[30,31]. The sensitiv-

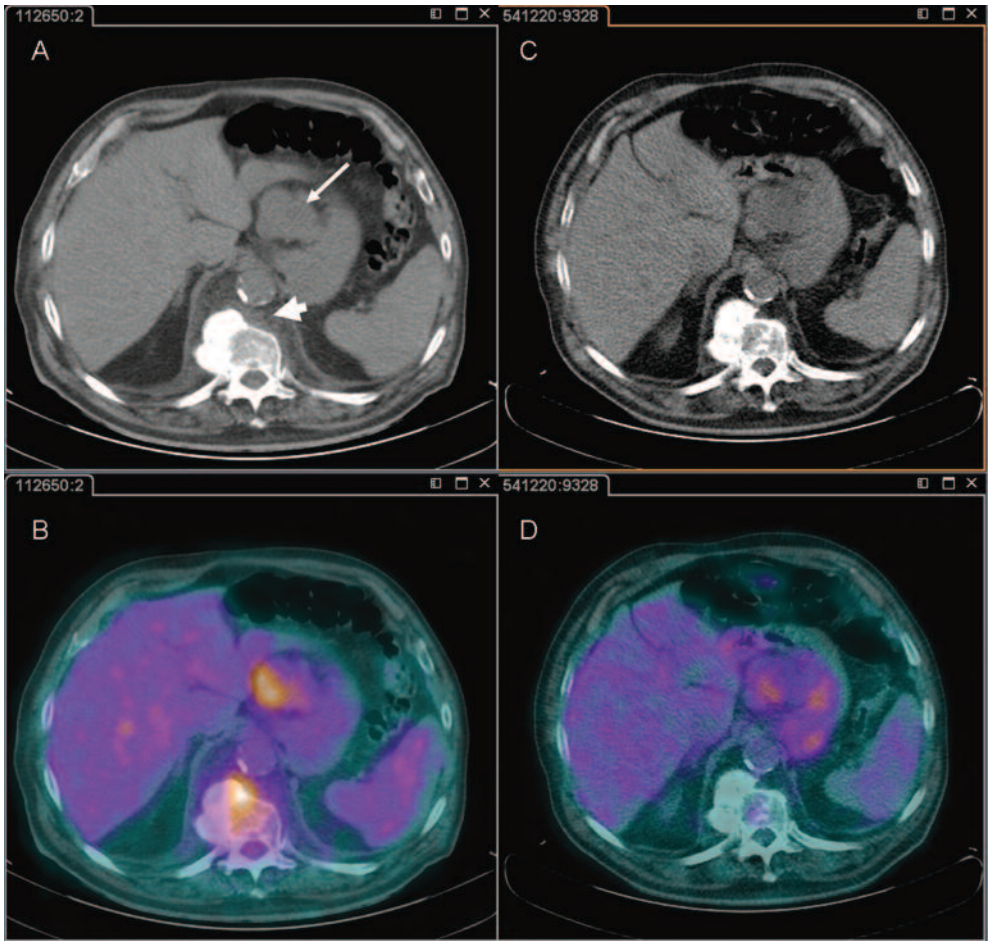

Figure 3. Transaxial CT (A,C) and Fluorine 18-fluorodeoxyglucose (FDG) PET/CT (*B*, *D*) images in a 50 year-old female patient with concomitant gastrointestinal stromal tumor (*arrow head*) and spondylodiscitis (*arrow*). There was an increased unspecific uptake of FDG both in tumor and in inflammatory lesion at diagnosis (*A*, *B*). After anti-neoplastic therapy with Imatinib and antibiotic therapy both lesions showed a decrease of FDG uptake (*C*, *D*), demonstrating a good metabolic treatment response.

ity and specificity in detecting SP infection is very high if FDG-PET is used in addition to conventional tests and imaging. Furthermore, FDG-PET is recommended for distinguishing between common Modic change at radiological imaging and spinal infection[32,33].

Gratz et al[34] reported that FDG-PET was superior to MRI, scintigraphy with Gallium-67-citrate and Technetium-99m-diphosphonates, especially in patients with low-grade spondylitis (as compared with MRI), adjacent soft tissue infections (as compared with scintigraphy with Gallium-67-citrate) and advanced bone degeneration (as compared with scintigraphy with Technetium-99m-diphosphonates).

It is possible to clearly differentiate between infections of vertebrae and adjacent soft tissue infections by using hybrid FDG-PET/CT. Furthermore, this modality is also capable of demonstrating the extent of the infection. This may be helpful in assessing the paravertebral abscess in SP. Hybrid PET/CT systems offer an excellent anatomic localization of the actual site of uptake, minimizing misinterpretation of localization from areas of arthritic bony disease and infection, such as demonstrating the uptake to be associated with an arthritic facet joint rather than with the vertebral body or interspace[30,35].

Furthermore, FDG-PET allows quantification of inflammatory activity: in fact, a decreased FDG uptake generally corresponds to a clinical improvement. Therefore, the quantification of inflammatory activity might be useful for treatment monitoring[31]. Kim et al[36] reported that FDG-PET is useful for the discrimination between residual and non-residual spine infections after therapy.

Overall, FDG-PET is a very promising alternative to conventional nuclear medicine procedures, appearing to be superior in the detection of spinal infections and in the differentiation of degenerative from infectious end-plate abnormalities. The advantages of PET are obvious: the study is sensitive, is completed in a single session, and image resolution is superior to that obtained with conventional nuclear medicine procedures. As with Gallium-67 scintigraphy, however, specificity remains an issue. While FDG uptake in uninfected fractures may normalize more rapidly than gallium or diphosphonate uptake, differentiating infection from tumor may still be problematic. Moreover, inflammatory reactions incited by spinal implants also may adversely affect specificity. Nevertheless, there is an expanding body of evidence that supports the use of FDG-PET and PET/CT for diagnosing spinal infections, especially in patients with MRI contraindications and in the postoperative spine[30-36]. In fact, morphological imaging techniques rely on structural changes to make diagnosis but when normal anatomy is distorted by post-surgical changes or scarring or in the presence of implants, these techniques are less reliable. Functional imaging studies are performed to improve diagnostic accuracy showing high negative predictive value, especially in these cases[30-36]. Nevertheless, several examinations are required to strengthen any diagnosis of SP; the use of FDG-PET alone is not recommended.

Recently, Nanni et al[37] reported promising results of Gallium-68-citrate PET/CT in a population of patients with suspected bone infections, including nine patients with SP. Although preliminary, these data confirm a possible role for Gallium-68-citrate as a PET tracer in the diagnosis of SP, especially in consideration of its favorable characteristics[37].

In conclusion, more studies are necessary to validate the usefulness of PET imaging with different tracers (FDG or Gallium-68) in patients with SP.

Conclusions

Overall, nuclear medicine procedures play a useful role in the diagnosis of spondylodiscitis identifying functional abnormalities which precede morphological changes. Therefore, nuclear medicine procedures may complement or integrate morphological imaging findings in patients with suspected SP.

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