Nuclear Medicine imaging of vertebral infections
Lazzeri, Elena

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Chapter 1

Introduction

Spine infections include vertebral osteomyelitis (infection of the vertebral body), discitis (infection of the intervertebral disk) and spondylodiscitis (infection of two adjacent vertebral bodies and their intervertebral disk). The exact anatomical location of the infective process allows to classify Spondylodiscitis (SD) in anterior, posterior, spinal canal or bone graft site (1). The infectious process may extends into adjacent soft tissues; posterior extension can result in epidural, subdural abscess or in meningitis, while anterior or lateral extension can result in paravertebral, retrofaringeal, mediastinic or retroperitoneal abscess.

The prevailing etiology of SDs is bacterial, mycobacterium or, more rarely, micotic infection. Many pathologies, like diabetes mellitus, immuno deficiency syndromes i.e. AIDS, chronic renal failure and alcoholism represent predisposing factors. The most frequent site of vertebral infection is the lumbar spine (45%) followed by the dorsal (35%) and the cervical tract (20%) (2).

SDs are clinically classified as primary or secondary being the latter most frequently consecutive to surgical procedures or associated with other pathological conditions. Men are affected more frequently than women (1.5:3.1).

Primary SD (bacterial or micotic etiology) represents 2-4% of all osteomyelitis. S. aureus is the most frequently isolated bacterium (55-80%), followed by coagulase...
negative staphylococcus and by enterobacter (Salmonella spp., E. coli, Klebsiella spp., Serratia spp.). Pseudomonas aeruginosa is frequently isolated in drug addicted individuals, while miceti lievitiformi like Candida spp., are responsible of infection in drug addicted and in patients with vascular devices (3-7). Acquired Immune Deficit Syndrome (AIDS) and decompensated diabetes represent predisposing condition. SD may occur at any age even if the incidence of primitive SD is higher in patients older than 50 years. The symptom constantly present during spondilodiscitis is back pain. Motor deficits (70%), elevated levels of C-reactive protein (CRP) and increased erythrocyte sedimentation rate (ESR) (64%) may be also present as do fever and spinal tenderness in variable percentage (3, 8).

In adults, spinal infections are initially localised in the anterior part of the vertebral body which presents more vascular structures (9-10), thus extending into the adjacent tissues (intervertebral disc and adjacent vertebrae).

Micobacterium tuberculosis SD (vertebral tuberculosis or Pott disease) begins in the anterior part of the vertebral body and usually involves the subcondral region, diffusing subsequently to the cortical bone and to the adjacent disk. The diffusion of Tubercular infection frequently involves soft paravertebreal tissues. Pain accompanied by raise ESR, elevated CRP with normal or moderate increase white blood cells counts represent the most common symptoms. (11-12). Multi organ pathology is often present with high frequency of pulmonary localization that can sometimes mask other symptoms (13).

**Secondary SDs** are caused by direct contamination of microorganisms in the surgical field following spinal anesthesia, local infiltration of analgesics and, above all, surgical procedures for slipped disk, spondyloysis and spondylolistesisis (2, 9-10, 14-15).

The bacteria more frequently isolated in this type of SD are St. Aureus, St. Epidermidis and Coagulase-negative St. Gram negative bacteria (E. coli, Enterobacter spp., Serratia spp., Pseudomonas aeruginosa, Acinetobacter spp.) are more often responsible of vertebral infection in AIDS and drug addicted patients (1). The incidence of secondary SD changes according to the type of surgical procedure: less than 1% risk of infection is observed after discectomy rising to 1-5% in spinal fusion without instrumentation (15), 2.6-4.4% in spinal fusion with instrumentation (16-17) and 6.9% in cases of surgery for scoliosis (18-21). When the infection is associated with a spinal implant, intraoperative cultures typically yield low-virulent microorganisms that hamper the cultural diagnosis, making necessary to extend the culture for more than one week (21). In fact, the presence of pus around spinal implants may be related to foreign body reaction consisting of non-infectious granulomatosis due to metallic debris produced by micromotion around the fiches of the implant. Intraoperative findings of such condition confirm the presence of an
extensive glycocalyx surrounding the entire spinal hardware without evidence of bacteria growth just as in aseptic loosening of joint prosthesis (22). Spine involvement may be present in different infective conditions as i.e. distant emboli in endocarditis. Those kind of SD are undervalued because of the clinical importance of the main disease. Clinical manifestations of secondary SDs are pain, motor deficits and fever accompanied by raised ESR, CPR and white blood cells counts. The course of SD, both primitive and secondary, is strongly affected by the time of diagnosis and early antibiotic treatment initiation (23). The diagnosis of SD is based on clinical symptoms, laboratory finding and microorganism isolation. Pathogens are directly characterized by intra-operative cultures of wound, bone or spinal implants and indirectly by blood cultures (24). Unfortunately, in every direct sampling the risk of non pathogens contamination leading to uncorrect diagnosis may be taken into account (25) as well as the possibility of a negative blood culture despite the presence of bacterial infection (26). Bacterial culture from specimens obtained by CT-guided biopsy has an high diagnostic specificity, but its sensitivity has been reported to range between 58% and 91% (2, 27). Thus, this invasive procedure is not routinely used.

**Diagnostic Morphological Imaging**

Magnetic Resonance Imaging (MRI) is currently considered the modality of choice for the evaluation of suspected spinal infections (28). MRI sensitivity and specificity in the early phase of primary SD are considerable and the high spatial resolution allows a brilliantly delineation of the infection extent (29). Nevertheless, this technique suffers from several limitations in differentiating vertebral benign pathologies from infection (30-32), for patients follow-up during antibiotic therapy and for the diagnosis of secondary SDs. In fact, this method is often inadequate to distinguish postsurgical changes from infective process (33-34) and in postoperative infections MRI cannot distinguish between septic and aseptic SD, especially in the early post surgical period (35).

**Diagnostic Functional Imaging**

Nowadays the gold standard imaging technique for infection is represented by autologous labelled leukocytes scintigraphy. Radiolabelled leukocytes presented high sensitivity (95%) and specificity in many infectious processes (90%) (36-37), but not in the case of vertebral infection. In fact, in case of SD labelled leukocytes scan presents a photopenic area of uptake in the corresponding vertebral body which is not specific for infection. The cold spot is caused by the failure of labelled leukocytes to localized into the infected bone because of vascular compression due to the development of infarction and albeit septic, that may hinder white cells migration trough vertebral vessels (38).
Rarely, an increased uptake of labelled leukocytes in site of vertebral infection has been described and correlated to some extent with the duration of symptoms: less than 25% of patients who were symptomatic for more than 2 weeks presented such finding (38).

Many other pathologies like vertebral crush, Paget's disease or tumors show a decrease of leukocytes uptake in nuclear medicine imaging (37-46) making the presence of a cold area aspecific for vertebral infection diagnosis. Most radiopharmaceuticals proposed to complement the diagnostic value of MRI, such as bone scintigraphy with $^{99m}$Tc-MDP or with $^{67}$Ga-citrate (47-48) and $^{18}$F-FDG PET (49-56) have shown high sensitivity but variable specificity (ranging from 35.8% to 87.9%). Furthermore, they suffer from some limitations as non-negligible radiation burden, long acquisition time and high costs.

Some new labelled infection tracers like PEG-lyposomes and IL-8 (61-62) showed high potential value for diagnosing infection, but they need further evaluation in the clinical setting. Radiolabelled antimicrobial peptides (63-64), have been proposed only in experimental animal models, therefore their potential to distinguish infection from sterile inflammation is very exciting, but it remains to be further validated in patients with SD.

Indeed, infection imaging radiopharmaceuticals, such as $^{99m}$Tc-ciprofloxacin, used originally in peripheral bone infection (57-58) have shown discordant results with high sensitivity but quite low specificity for spine infections especially when evaluating recently operated patients (59). To better understand the mechanism of action of labelled antibiotics we have evaluated, based of published papers the amount of bacteria-associated radiopharmaceuticals in the site of infection (Chapter
It has been possible to calculate the number of bounded molecules of radiopharmaceutical per single bacteria at site of infection and the results suggested that, the majority of radioactivity at site of infection is non-specifically bound to bacteria and it is due to presence of plasma leakage from capillaries. Streptavidin/biotin system is based on aspecific depot of streptavidin in infection site due to altered capillary permeability and on the strong leakage between biotin and streptavidin. Two-step Streptavidin/$^{111}$In-Biotin scintigraphy have demonstrated high accuracy in patients with osteomyelitis and spinal infections (Chapter 4 and 5), but the possible development of human anti-streptavidin antibodies and the non specific uptake of streptavidin at site of infection have limited its use.

Biotin, also called vitamin H, is a water-soluble vitamin of the B-complex group of vitamins. Biotin (molecular weight about 224 d) is a growth factor for human cells and also for bacteria. In particular, pyruvate carboxylase, a key metabolic pathway for producing energy by ATP cleavage, is biotin-dependent and bacterial Acetyl-coA carboxylase is a biotin-dependent enzyme implied in the first step of fatty acid synthesis (66-67).

Since the described limitation of the Streptavidin/Biotin approach and the specificity of biotin as bacterial growth factor, I explore the capability of $^{111}$In-Biotin alone to detect early vertebral infection in a large consecutive series of patients (Chapter 6) and then to study the add value of SPECT/CT acquisition of $^{111}$In-Biotin scintigraphy in the diagnosis of osteomyelitis of the skeleton (Chapter 7).

In conclusions, in clinical setting the diagnosis of SD is based on clinical findings and imaging modalities that are often chosen on the basis of local availability rather than on a validated (evidence-based) diagnostic algorithm. This situation motivated me and collegues to publish first Italian guide lines (Chapter 3) and then European guide lines (in progress) about diagnostic nuclear imaging algorithms for infective diseases included those of osteomyelitis and SD.
References


60. Can we produce an image of bacteria with radiopharmaceuticals? Signore A., D’Alessandria C., Lazzere E., Dierckx R. EJNMMI 2008


