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Brucellosis – Granulomatous Spine Infection

Ana M. Cerván, Miguel Hirschfeld, Miguel Rodriguez and Enrique Guerado

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Abstract

Brucellosis mainly affects the musculoskeletal system, with the spine as the most common location. Diagnosis is based on clinical symptoms, but in some cases, they may be lacking. Laboratory diagnosis is mainly made on the combination of high erythrocyte sedimentation rate (ESR) together with high levels of C-reactive protein (CRP) and leukocytosis. Blood culture is a very cost-effective investigation; plain radiographs may be useful, but magnetic resonance images (MRI) with gadolinium enhancement is the choice for diagnosing osteoarticular and spinal complications of human brucellosis. MRI diffusion-weighted imaging fast sequence is the most sensitive for differentiating acute and chronic forms of spondylodiscitis. The basis for treatment is usually the medical management. The indications for surgical treatment (endoscopy or open) are when: no microorganism has been isolated, spinal cord or dural compression is seen in MRI, or there's spinal instability or severe deformity. Open surgery is the standard: the anterior approach allows for anterior disc and bone debridement. If there is an epidural abscess or posterior elements are involved it's indicated as a posterior approach. To prevent relapses and reduce the rate of sequelae, it's necessary to have an appropriate duration of antimicrobial therapy and a timely indication to perform surgery.

Keywords: Brucellosis, spine brucellosis, spondylodiscitis, granulomatous infection, surgical treatment

1. Introduction

Spondylodiscitis refers to an infection affecting the intervertebral disk, the vertebral body, or the posterior arch of the vertebra. Aetiologically, spinal infection can be classified as pyogenic, granulomatous (tuberculosis, brucellosis, or fungal infection), or parasitic. Brucellosis mainly affects the musculoskeletal system, with the spine as the most common location.

Epidemiology. Brucella, one of the world's major zoonotic pathogens, is responsible for huge economic losses, as well as significant human morbidity in endemic areas [1]. It is caused by an aerobic, Gram-negative rods of the genus Brucella, discovered by David Bruce in 1887 [2]. In humans, this disease is also called Maltese fever, Bang's disease, undulant fever, or Mediterranean fever [3]. Human brucellosis involves an important public health problem in most developing countries including those of the Mediterranean, Balkans, the Middle East, Central Asia, and Central and South America. New foci of human brucellosis have emerged, particularly in Central Asia [4].

Pathogenic. Brucellosis is a systemic disease and many organ systems (nervous system, heart, skeletal system, bone marrow, etc.) may become involved following hematogenous dissemination. However, osteoarticular involvement is the most common complication of brucellosis, being reported in 10%–85% in most series [5]. The sacroiliac joint and arthritis are generally affected in the acute form. However the spine is usually affected in the subacute and chronic forms of this disease. The sacroiliac joint involvement and arthritis occur in patients under 30 years old, whereas the spine affectation is characteristic of older patients [6]. In the musculoskeletal system the spine is the most often affected location [7, 8]. The incidence of spinal involvement can be quite different, from 2%–54%, it depends on the type of population you study [9]. The radiographic changes will appear between the third to the twelfth week of the start of clinical symptoms [10]. The L4-L5 and L5-S1 junctions are the most frequent locations affected [11].

Clinical syndrome. Brucellosis is an acute (25%–77%), subacute (12.5%–59%), or chronic (5%–27.5%) illness that presents with a spectrum of nonspecific signs and symptoms. The disease is severely disabling with fever, sweating, fatigue, weight loss, headache, and joint pain that can persist for weeks to months. Spinal manifestations tend to occur during chronic infections [12, 13]. Clinical presentation varies widely [14] and approximately one-third of the patients have a more fulminant illness with acute onset of systemic toxicity [15]. The earliest sign of spondylitis is localized spine pain [16], since some degree of neurologic compromise may occur between 10%–43% of those with spondylitis [17], and in 10%–20% a paraspinal abscess develops. In a multicenter prospective study of 593 patients with brucellosis [18], 9.7% had spondylitis; neurologic deficits occurred in five (71%) of the patients with cervical spondylitis, two (11%) of the patients presented thoracic involvement, and nine (21%) developed lumbar disease. Paraspinal and epidural abscesses were more frequent in patients with cervical and thoracic disease; the worst prognosis was for those having cervical spine involvement. Complications of spinal brucellosis, with affectation of neighboring vertebrae with paraspinal, psoas, or epidural abscesses, with or without neurological affectation is uncommon; however, several series have published cases of complicated spinal brucellosis [19–22], although possible multilevel involvement may occur [23].

Diagnosis. It is not always easy. Suspected diagnosis of spondylodiscitis is based on clinical symptoms (pain, fever, and deformity), although, in some cases, they may be lacking. Patients complaining of back pain, particularly in endemic areas, should be accurately investigated. Laboratory diagnosis is mainly made in the presence of combination of high erythrocyte sedimentation rate (ESR) together with high levels of C-reactive protein (CRP) and, less useful,

leukocytosis. Blood cultures are positive in less than half the cases overall but indeed in 70% of patients with acute B. melitensis infection. An agglutination reaction with a Brucella antibody titer of 1 : 160 or greater is presumptive evidence of infection, but an increasing titer is a more helpful sign of active infection [16, 17].

The diagnostic confirmation of spinal spondylitic granulomatous can be done by the polymerase chain reaction (PCR). If we have a case of prior antibiotic used or the presence of fastidious microorganisms, the molecular diagnostic can be done using broad-range 16S rDNA PCR [24]. By amplification of the mec A gene, doing species-specific PCR, especially targeting the Staphylococcus aureus, the sensitivity can increase, providing methicillin susceptibility [25]. But these methods are not completely unerring by themselves; in fact, nowadays, they are considered as an important complementary to standard cultures particularly those harvested through image-guided surgery [25]. Blood culture is a very cost-effective investigation. Plain radiographs may be useful; however, even large destructive spondylodiscitis may go undetected on X-rays as changes take several months to appear. Furthermore, usually in more aged patients, it may be difficult to distinguish between infection destruction and degenerative changes. The first radiological sign that we will find is osteoporosis of the affected vertebral body and erosion of the anterior-superior endplate, so-called Pons' sign, also a vacuum phenomenon may be observed in the anterior part of the disc (accumulation of gas with the crevices of the intervertebral or adjacent discs). The appearance of destructive changes on plain radiographs appears from the third month of the disease.

Radionuclide tests are currently less used. If magnetic resonance images (MRI) cannot distinguish among degenerative changes and infection, the fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) can be useful [26].The most useful image test, with the higher sensitivity and specificity for the diagnosis of spondylodiscitis, is MRI with gadolinium enhancement, which also provides information on anatomy [27]. CT-scan is useful in assessing the bone destruction and also for surgical planning, as well as contributes greatly in the CT-guided needle percutaneous biopsy [28]. MRI is the method of choice for diagnosing osteoarticular and spinal human brucellosis and its complications, especially during the early phase [29, 30]. It has been published [31] that diffusion-weighted imaging fast sequence is the most sensitive diagnosis tool for differentiating between acute and chronic forms of spondylodiscitis.

Sometimes diagnosis of brucellar spondylodiscitis becomes a major task as clinical findings are usually nonspecific and radiological features may mimic those of other bacterial, fungical, inflammatory, and neoplastic diseases. Likewise, it is very common to confuse spinal brucellosis with tuberculosis.

Differential diagnosis must be performed with tuberculous spondylitis, salmonella spondylitis, pyogenic spondylitis, disc herniation, and metastatic lesions [32–34]. The radiologic findings for tuberculous and brucellar spondylodiscitis are similar, so serologic testing for brucellosis is necessary in such cases [11]; and also the MRI findings are different as tuberculosis produces more severe changes with more deformity and abscess formation [35]. There are also differences regarding the involvement of the intervertebral disc spaces, whereas in brucellar spondylodiscitis intervertebral discs are narrowed, in metastatic diseases or in

tuberculous spondylitis intervertebral discs are rarely affected. However, in brucellar spondylodiscitis the affectation of the posterior elements is very uncommon, while it may be frequently encountered in metastatic disease and tuberculosis spondylodiscitis. Paravertebral and epidural abscess formation and spinal cord and root compression are considered very rare findings in brucellar spondylodiscitis and are generally considered to be findings for tuberculosis and pyogenic spondylodiscitis.

Findings characteristic of MRI for brucellar spondylitis [36] are: vertebral body signal changes without morphologic changes, marked signal increase in the intervertebral disc on T2-weighted and contrast-enhanced sequences, vertebral endplate defects mimicking Schmorl's nodules, obliteration of muscle fat borders, moderate amount of paraspinal granulation tissue, and gas accumulation in the disc space and facet joint involvement. Nevertheless, some of these signs, such as the presence of gas, can also be present in pyogenic infections. In any case, the most useful method for detecting the presence and extension of brucellar spondylitis is the MRI, particularly using the fat-suppression technique with contrast. Even in extensive cases, vertebral collapse and gibbus deformity are rare findings, and the vertebral body is usually morphologically intact (Figures 1, 2, 3).

Biopsy is necessary to confirm the diagnosis in only 5% of the cases, in contrast to pyogenic and tuberculosis spondylitis [37].
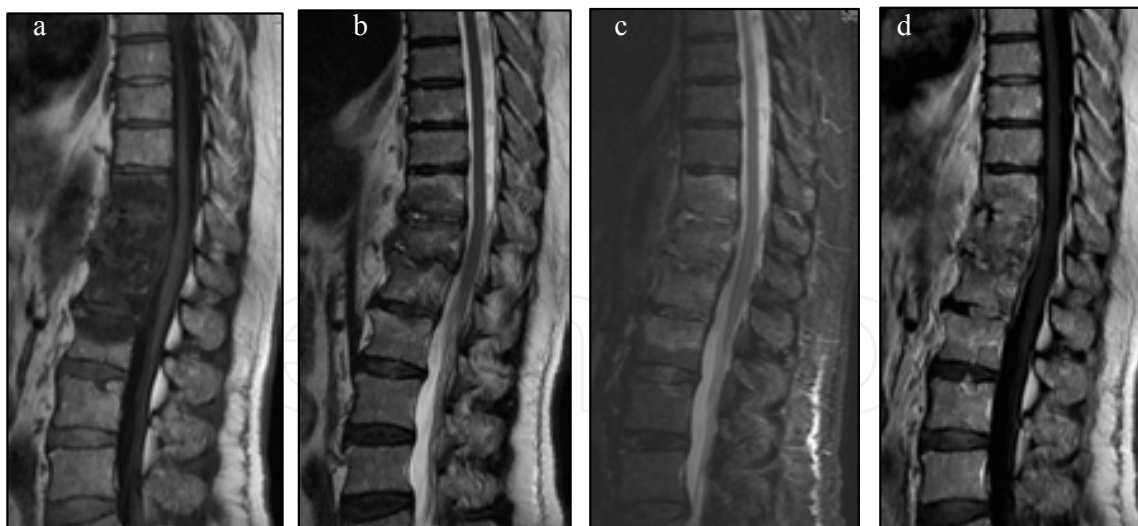

figure_1a-d Sagital magnetic resonance images from a 62 years old man with brucellar spondylodiscitis. a. T1-weighted image showing irregularity and destruction of vertebral end plates and hypointensity at T11 to L2. b. T2 weighted image showing increase signal intensity of the disc and loss of intervertebral disc height. c. Saggital STIR image shows hyper intense lesions vertebral contiguous. d. Contrast enhanced T1 weighted sagittal image shows involvement of intervertebral disc space between T11-L2 vertebral levels, vertebral bodies and vertebral end plate.

Figure 1. Sagital magnetic resonance images from a 62-year-old man with brucellar spondylodiscitis. a. T1-weighted image showing irregularity and destruction of vertebral endplates and hypointensity at T11 to L2. b. T2-weighted image showing increase signal intensity of the disc and loss of intervertebral disc height. c. Sagittal STIR image showing hyperintense lesions vertebral contiguous. d. Contrast-enhanced T1-weighted sagittal image shows involvement of intervertebral disc space between T11-L2 vertebral levels, vertebral bodies, and vertebral endplate.
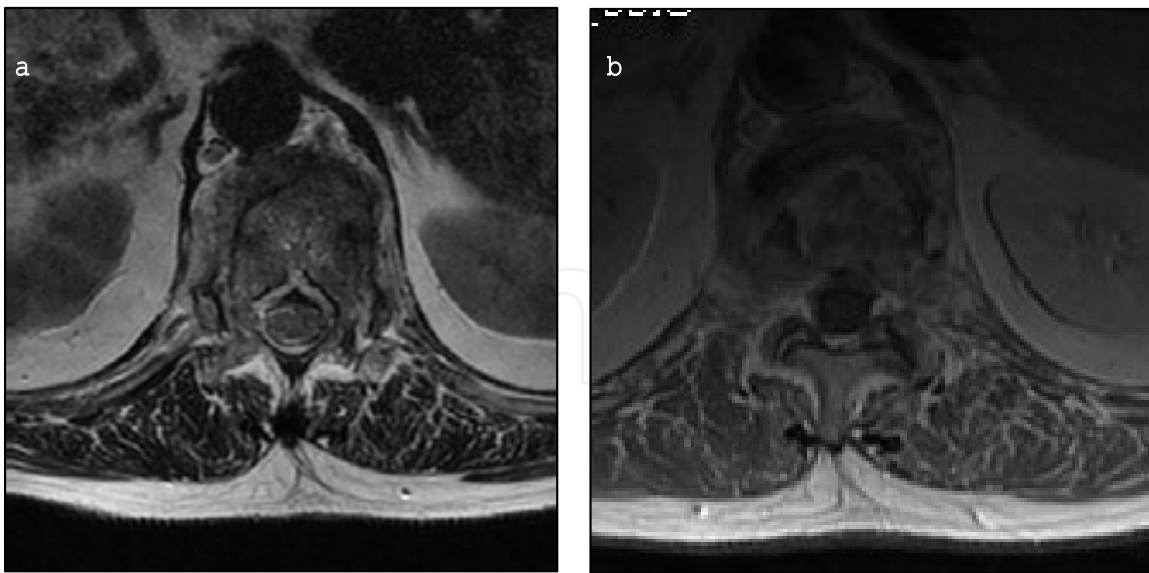
Figure 2. a. Axial T2-weighted image reveals a paravertebral abscess. b. Contrast enhanced T1-weighted axial image shows enhancement in affected vertebra and paravertebral soft tissue.

2. Treatment

The treatment of spinal brucellosis is mainly medical. The surgical intervention is reserved for biopsy, severe neurological impairment, and rarely for spinal stabilization.

The combination of tetracycline (tetracycline, 500 mg every 6 hours given orally or doxycycline, 100 mg every 12 hours) for 6 weeks together with an aminoglycoside (preferably streptomycin, 1 g/day intramuscularly for 2–3 weeks or gentamicin 5 mg/kg/day intravenously or intramuscularly for 7–10 days) is the current first-line therapy for brucellosis as recommended by the World Health Organization. The combination of rifampicine (600–900 mg/day orally administrated) and doxycycline (100 mg every 12 hours orally administrated) for 6 weeks is suggested as the principal alternative therapy. In spinal brucellosis it is noted that the same regimens can be given, but the duration of therapy should be longer. A combination of doxycycline (200 mg/day, for at least 12 weeks) with streptomycin (1 g/day, for 2 or 3 weeks) is still the first-line antimicrobial regimen in spinal brucellosis. For a long time Doxycycline + rifampin or co-trimoxazole + rifampin or ciprofloxacin + rifampin or ciprofloxacin + streptomycin could be used as an alternative when adverse reactions or contraindications (ototoxicity, nephrotoxicity, pregnancy, lactation, etc.) are present [38]. The combination of doxycycline and streptomycin has been used for a long time for complications and severe disease [39]. However, therapeutic failure and relapse are still reported with this regimen [40]. Response to treatment is monitored with repeated agglutination tests. Lifeso and colleagues [17] recommend continuing antibiotic therapy until the agglutination test titer is equal or less than 1 : 160 and there is clinical and radiographic evidence of disease resolution. Relapses seldom
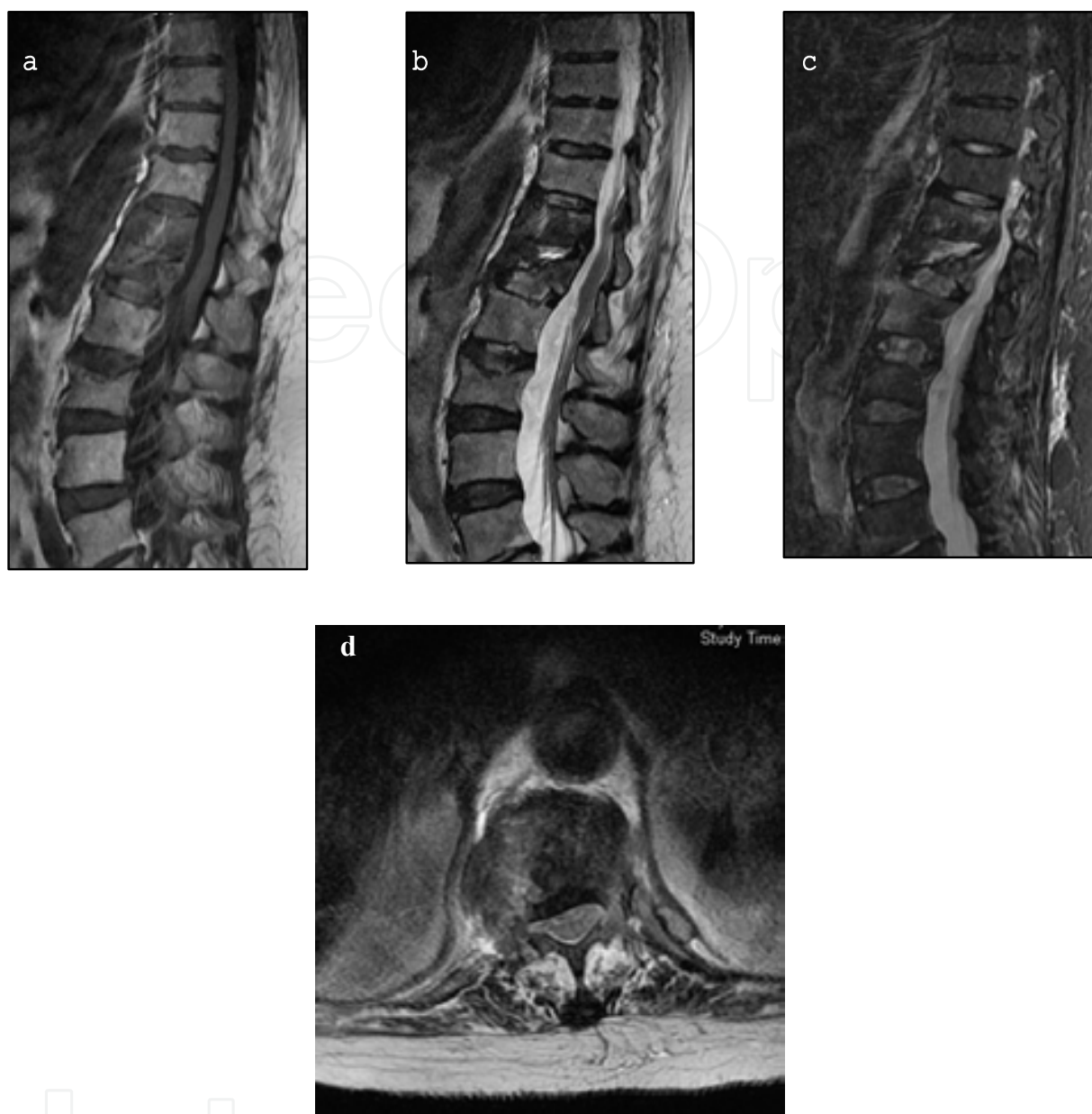
Figure 3. Sagittal magnetic resonance images from an 69-year-old woman with brucellar spondylodiscitis a. The T1-weighted image reveals complete signal loss at the T12 and L1 vertebrae bodies. b. The T2-weighted image reveals high signal intensity at T12-L1, medullar compression by the T12 pedicle. c. Sagittal STIR image shows hyperintense lesions at T12-L1. d. Axial T2-weighted image shows paravertebral and muscle abscesses. A medullar compression by T12 right pedicle is observed.

occur in patients who do not receive appropriate treatment and are usually perifocal suppurative complications such as spondylitis.

Conservative treatment is indicated in patients without spinal instability or neurological deficits and with high surgical risk [41]. The doubt may arise in case of minor neurological deficits, for that some authors [42] prefer conservative treatment if there is no spinal instability as neurological symptoms will be improved with antibiotics. It is of para-

mount importance to achieve proper immobilization of the affected spinal segment; orthoses could be used for that purpose and in same instances, protected bed rest, although home confinement now is being abandoned [43].

If after 4 to 6 weeks of conservative treatment there are signs of spine instability, progressive deformity, or no clinical improvement, surgical treatment must be the choice.

On the other hand, early surgical treatment should be performed in the presence of sepsis or neurological deficits. Patients with spinal epidural abscess have high rates of morbidity and mortality, therefore, in these urgent surgical cases surgical treatment is essential [44].

Surgery is indicated in the presence of spinal instability, cord compression or radiculopathy [45]. Whenever a root, spinal cord, or dura mater compression is seen on MRI (epidural abscess with an anterior longitudinal ligament bulge), the patient must be taken to the theatre [46]. A clear indication for surgical treatment is spinal instability due to a great deformity or due to bone destruction. In case of an anterior abscess larger than 2.5 cm, a surgical evacuation must be carried out. Also, if there is concomitant vertebral body destruction, bone debridement with subsequent anterior body reconstruction must done, too. There are other indications for surgery such as: unsuccessful medical treatment, negative biopsy or lingering pain [47]. The main role for surgery is to perform a debridement and biopsy for culture, and also if there is biomechanical instability a stabilizing surgery will be performed at this moment or at another time [48].

Nowadays, there are two different surgical treatment options: less invasive or classic open surgery.

Less invasive techniques can facilitate debridement [49] (e.g., endoscopy, CT-scan percutane-ous-guided surgery) and reconstruction (posterior percutaneous instrumentation is already regularly used in patients undergoing a double approach) [50] (Figure 4). Thoracoscopy has very much changed the philosophy of the current surgical treatment for the spondylodiscitic thoracic spine.

Open surgery can use any standard approach (anterior, posterior, or combined). The choice will depend on the location of the infection, the degree of bone destruction, and the presence of neurological deficits.

Thus, open surgery can be either anterior, posterior, or a combination of both, performed either in one or two stages. Usually, open surgery consists of an anterior approach and a secondary posterior approach. During the anterior approach, full disc and affected vertebral bone sequestra must be performed, followed by inserting a tricortical bone graft piece in between the above and below vertebral bodies for anterior vertebral bodies bridging. Ostheosynthesis through the combined posterior approach (in epidural abscess, important kyphosis and/or instability) with pedicular instrumentation is advisable to complement anterior debridement and fusion.

The anterior approach is the standard for anterior vertebral body debridement and stabiliza-tion. Most authors agree with the conclusion of the Medical Research Council that the Hong Kong procedure [51] of anterior radical debridement and reconstruction of the large anterior
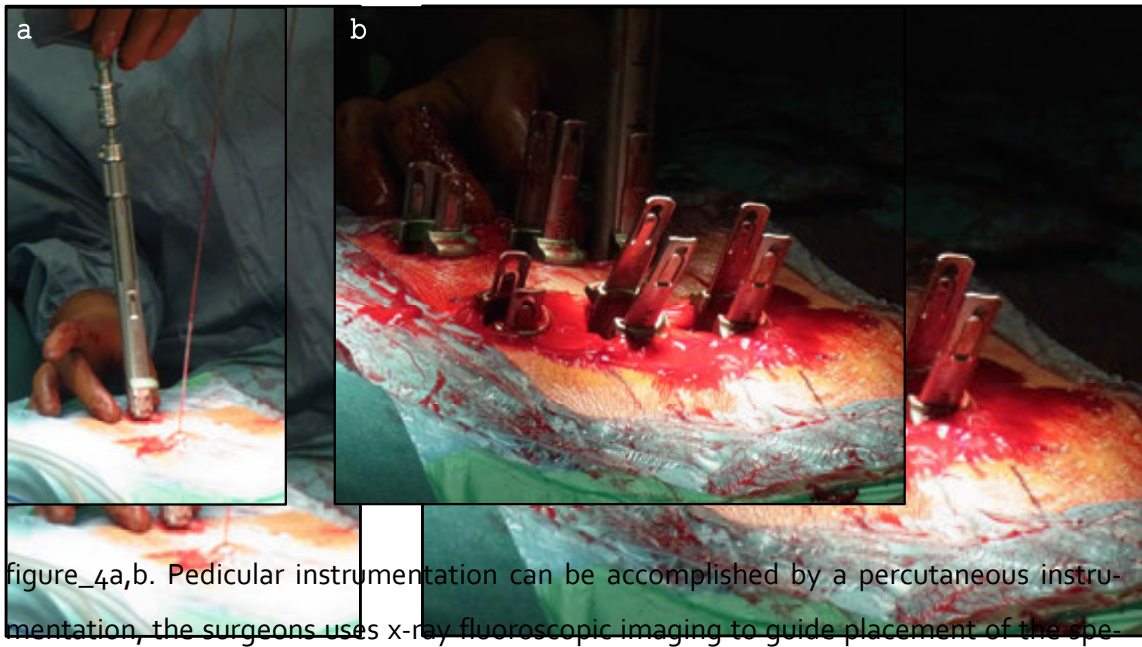
figure_4a,b. Pedicular instrumentation can be accomplished by a percutaneous instrumentation, the surgeons uses x-ray fluoroscopic imaging to guide placement of the special cannulated screws into the vertebrae. This is a minimally invasive procedure, us do not splits and aretracts the muscle off the spine through a much larger incision, have more benerfitt.

Figure 4. Pedicular instrumentation can be accomplished by percutaneous instrumentation where the surgeons use x-ray fluoroscopic imaging to guide placement of the special cannulated screws into the vertebrae. This is a minimally invasive procedure, it does not split and retract the muscle off the spine through a much larger incision and has more benefits.

figure_5 a. Large debridement (disc and vertebrae bodies) was performed by an anterior approach. b. Autologous graft insertion and a plate was carried out for anterior stabilization.
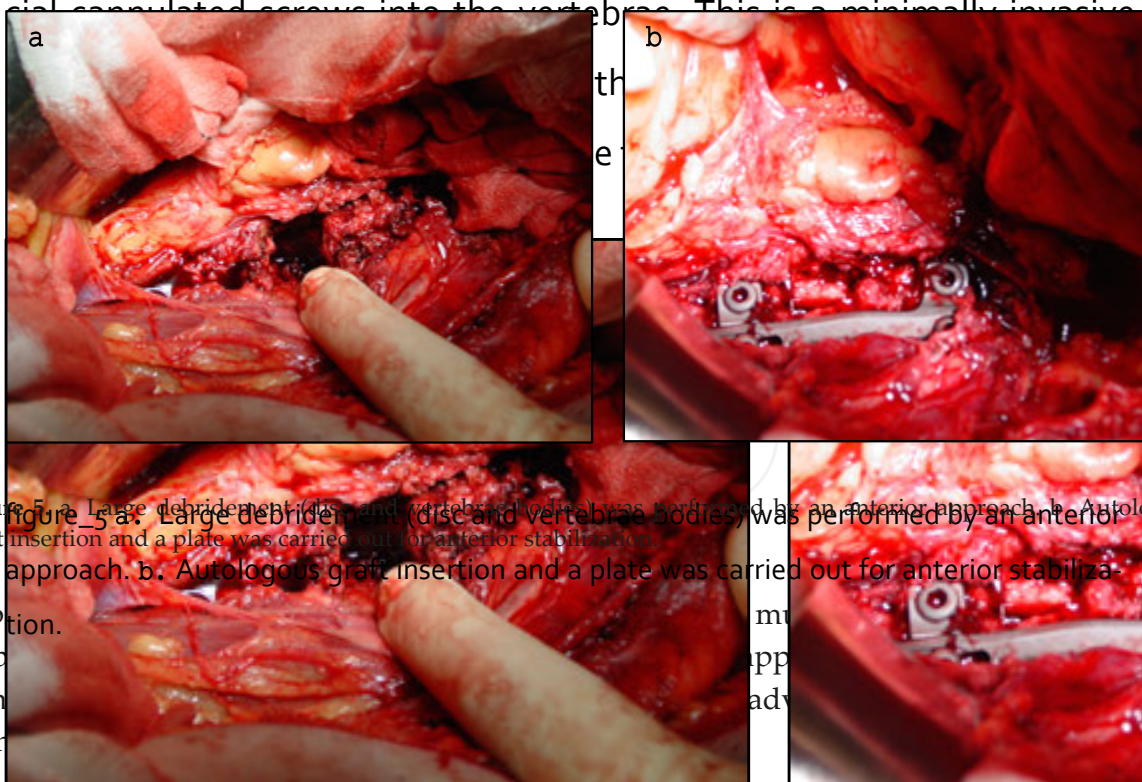
Figure 5. a. Large debridement (disc and vertebrae bodies) was performed by an anterior approach. b. Autologous graft insertion and a plate was carried out for anterior stabilization.

In many series, radical debridement and anterior insertion is followed by the insertion of a titanium cage, filled with autogenous bone graft, together with a posterior less invasive approach for pedicle screw fixation in order to eliminate posterior soft tissue injury, preserve

blood supply, and reduce surgical time, blood loss, and surgical complications [54]. Interbody cages have the function of providing an anterior support to compression forces, without the morbidity of tricortical harvesting [55]. Though, if we do a literature review, it seems that interbody cages have not completely resolved the complications and problems of interbody spinal fusions [56, 57].

The posterior approach is the first choice in cases of epidural abscess at the lumbar level in order to perform proper drainage, followed by pedicular instrumentation. If only one level is approached, instrumentation can be avoided. Large multilevel laminectomies without instrumentation are contraindicated, as it increases instability that already exists, provoked by the destruction of the anterior spine; it therefore, may result in paraplegia. Thus, in cases of substantial anterior destruction, collapse, spinal deformity, and when great debridement is recommended, an anterior approach must be the choice [58, 59]. A two-stage (posterior and anterior) surgical treatment for pyogenic or granulomatous spondylitis (first, the placement of posterior instrumentation and then anterior debridement and bone graft) provided satisfactory results; however, should kyphosis exists, changes in sagittal alignment may be difficult to be corrected [60].

In smaller defects, autograft is usually harvested from the iliac crest and ribs, and for larger bone deficits the choice is fibular graft [61]. In severe cases, only fibular grafts can allow a buttressing support, with a tension band principle if a concurrent pedicular instrumentation is also performed [62]. Louw [63] reported high fusion rates with vascularized rib grafts for stabilization and also good results with fibular graft for large defects used with stabilization by a posterior instrumentation. The use of BMPs combined with structural bone graft for spinal fusion has been claimed to provide good results and improve posterior fusion rates in pyogenic vertebral osteomyelitis after a 11–30 months follow up [64], though more studies are needed with longer follow-up.

According to the level of infection, surgical planning will be different. To the cervical spine, upper C1-C2 spine can be approached by a transpolar access; a posterior approach for occiput-C2 fusion may be necessary whenever a major instability is observed. The C3-C7 segment can be approached either anteriorly, posteriorly, or both, depending on abscess localization, instability, and fusion technique for this segment. Usually an anterior approach is recommended for debridement, decompression (eventual corpectomy), and fusion with bone graft associated with anterior plate stabilization (Figure 6). If it is a multilevel intervention, this must be complemented with pedicular instrumentation [65].

The thoracic spine can be approached either through an anterior transthoracic, posterior costotransversectomy, or an extra pleural anterolateral approach. Transthoracic approach give better results than lateral costotrasversectomy, for debridement, fusion rates, and mortality. At this spine level, it is recommended to use autograft and pedicular instrumentation.

The lumbar spine retroperitoneal approach is very useful, but opening the peritoneum must be avoided as intraperitoneal complications can occur. Debridement, abscesses drainage, and anterior instrumentation are easily performed by this approach.

Figure 6. An anterior approach is the technique of choice for disc and vertebrae debridement at the C3-C7 segment.

Despite a properly treatment, sequelae, such as back pain or residual neurological symptoms, will persist due to degenerative changes secondary to destruction and instability caused by the infectious process.

In order to prevent relapses and reduce the rate of sequelae, it is necessary that an appropriate duration of antimicrobial therapy (antimicrobial treatment should be prolonged in complicated spinal forms of brucellosis [65]) and a timely indication to perform surgery, if necessary.

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