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Pre-XDR spinal tuberculosis and 360° approach in two surgical times: a case report

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ABSTRACT:

— ***Background:*** *Spinal tuberculosis (STB), or Pott's disease, is a relatively frequent form of extrapulmonary involvement representing 50% of bone tuberculosis. Its diagnosis continues to be challenging due to the insidious presentation of the condition and is essential because it can cause disability due to late diagnosis or inadequate management.*

— ***Case report:*** The objective of this study is to report a case of Pott's disease due to multidrug-resistant bacilli in a pediatric patient who required surgical management with pharmacological support in a tertiary care pediatric hospital. The management of these deformities is surgical; however, with new technologies and techniques in spinal surgery, the best approach for this type of patient has been discussed, whether it should be anterior, posterior, or mixed. In our case, a 360° approach was necessary due to the magnitude of the deformity with a favorable postoperative period with good tolerance to antituberculosis drugs without additional neurological deficit.

— ***Conclusions:*** *Pott's disease due to multidrug-resistant bacilli continues to be a challenge thanks to the insidious presentation of the condition. However, there is no consensus regarding the best surgical approach for patients with the presented characteristics.*

— ***Keywords:*** *Pott's disease, Spinal tuberculosis, XDR-TB.*

INTRODUCTION

Tuberculosis (TB) is one of the oldest infections on record. In recent years, it has been possible to trace its existence to approximately 150 million years by molecular tests. As for spinal tuberculosis, it has coexisted with man since its first records; lesions were reported in Egyptian mummies and the pre-Columbian era[1].

TB continues to be a public health challenge and an important cause of morbidity and mortality since, in some countries, it is still considered an endemic pathology[2]. Furthermore, its prevalence varies according to the specific geographical area. In 2015, 10.4 million new tuberculosis cases were registered worldwide, with 11% occurring in HIV-positive patients, and 1.8 million people died from the disease[3]. In the United States, it was present in 2.96 cases per 100,000 inhabitants[4]. According to statistics from the National Institute of Health (INS) of Colombia, during the year 2018, 13,032 new cases were reported, representing an incidence of 26.9 cases per 100,000 inhabitants for all forms of tuberculosis, translated into a mortality of 2 cases per 100,000[5].

Musculoskeletal TB has an underlying pulmonary or lymphatic disease, either active or quiescent. Spinal tuberculosis (STB), or Pott's disease, is a relatively frequent form of extrapulmonary involvement, representing 50% of bone tuberculosis, the latter being 1-2% of extrapulmonary tuberculosis[6]. It is characterized by

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an insidious clinic presentation, characterized by predominantly nocturnal fever, weight loss, and back pain, which often delay diagnosis[7] and subsequently contribute to the morbidity and mortality of the pathology. However, since early diagnosis allows rapid therapeutic intervention, it positively impacts the prevention of possible complications[8].

TB treatment involves regular anti-tubercular medications, and surgical procedures may be required to eliminate collections and perform correction of residual deformities due to alteration of the spinal anatomy, especially in severe kyphosis, which requires spinal decompression[9].

Multidrug-resistant tuberculosis (MDR-TB) is defined as an infection by a strain in which the *bacillus* is resistant to Isoniazid and Rifampicin, and the suffix XDR (Extremely Resistant) is added when additional resistance to injectable drugs and quinolones is present[10]. MDR-TB is considered to be one of the main obstacles to eliminating the disease[11]. Up to 2,040 cases of STB per year have been reported[7], mainly in the adult population. Patients have less effective options and often have poor outcomes[12] despite the lengthy treatment time involved, since XDR-TB is resistant to the most effective drugs for treatment.

There are multiple opinions[13] regarding the duration of the treatment for spinal tuberculosis caused by MDR-TB; therefore, there is no consensus well stablished. This is caused by factors such as antibiotic multiresistant mycobacteria, anatomic location preventing pharmacologic availability, and insufficient data about the pharmacological security in pediatric population[14].

Center for Disease Control and Prevention (CDC) guidelines recommend a two-phase treatment for MDR-TB; the first phase comprehends a period of 5-7 months of treatment with 5 drugs and continuing with the second phase of 15-21 months of 4 drugs after a negative test for cases of MDR-TB[15]. CDC guidelines have a similar approach to the one proposed by the World Health Organization (WHO)[14], but the WHO has an individualized duration treatment according to the clinical and radiological patient's status. Therefore, it can be concluded that the treatment should be prolonged until a minimum duration of 18 months[16-18]. However, some studies[19] have obtained similar results with a shorter treatment.

Failure of an antituberculosis regimen with second-line drugs (one injectable + one fluoroquinolone) and close contact with an individual with documented XDR-TB or who has been failing with a scheme of second-line drugs, are two risk factors strongly associated with XDR-TB[20].

Medical literature has a broad description of firts line antituberculosis drug's bone tissue penetration and other pharmacocinetic parameters[21] but few data about the second line treatment, in particular about the new anti-tuberculous drugs. Bone tissue has intrinsic desadvantages regarding biodisponibility of the drug due to its poor vascularization[22].

There are no publications that evaluate the penetration of Bedaquiline or Delamanid into bone, although one study by Alghamdi et al[23] suggests that a weight adjustment should be made for the treatment of spinal MDR-TB. Quinolones are well absorbed into bone tissue[24] and other drugs, such as Linezolid[25] or Clofazimine[26], may have a relatively favorable profile of absorption due to their wide volume of distribution and their penetration in bone and bone marrow.

Also, there are no clinical trials evaluating the efficacy of the new anti-tuberculous drugs for the treatment of spinal tuberculosis. However, its use could be beneficial in these cases of tubercular infections, as suggested by a recent case report[27]. More studies are required to evaluate the efficacy of the new antituberculosis drugs[27,28].

The objective of this study is to report clinical and surgical management of a patient with spinal tuberculosis (STB) due to multidrug-resistant *bacilli* in a tertiary care pediatric hospital.

CASE REPORT

An 8-year-old female patient who had 6-month history of symptoms consisting of a granulomatous lesion with a fistula in the middle region of the back (Figure 1), associated with decreased strength in the lower limbs, loss of sphincter control, and subjective progression of spinal deformity. She was from an indigenous community with previous diagnosis of STB and had history of house cohabitants with pulmonary TB with no medical follow-up nor administration of anti-tubercular treatment (Isoniazid, Rifampicin, Ethambutol and Pyrazinamide). During the initial diagnosis, biological samples were sent to the National Institute of Health; however, due to sample contamination, it was not possible to perform typification and sensitivity.

Initially, ELISA test of HIV, surface antigen for Hepatitis B, IgG and IgM for *Brucella sp*, flow cytometry for lymphocytes, complement study of immunoglobulins, and 1, 2, 3 Dihydrorhodamine were performed, and all the results were negative. Due to clinical history and origin from a highly endemic region, a Mantoux test was not requested. Regarding the diagnostic images, a Magnetic Resonance Imaging (MRI) of the spine was

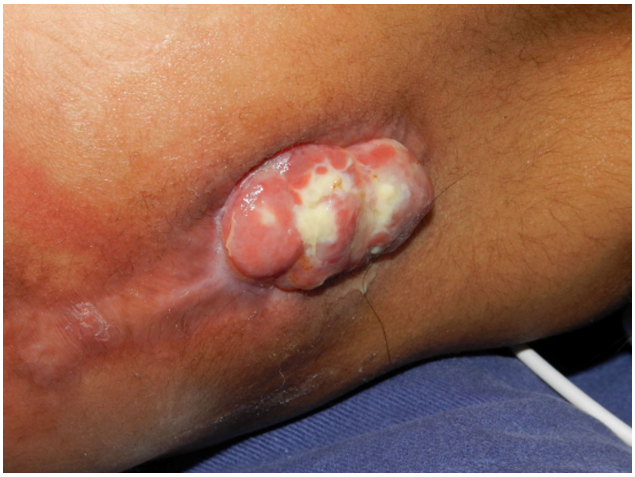

Figure 1. There is evidence of a granulomatous lesion associated with a fistula in the dorsal region of the back.

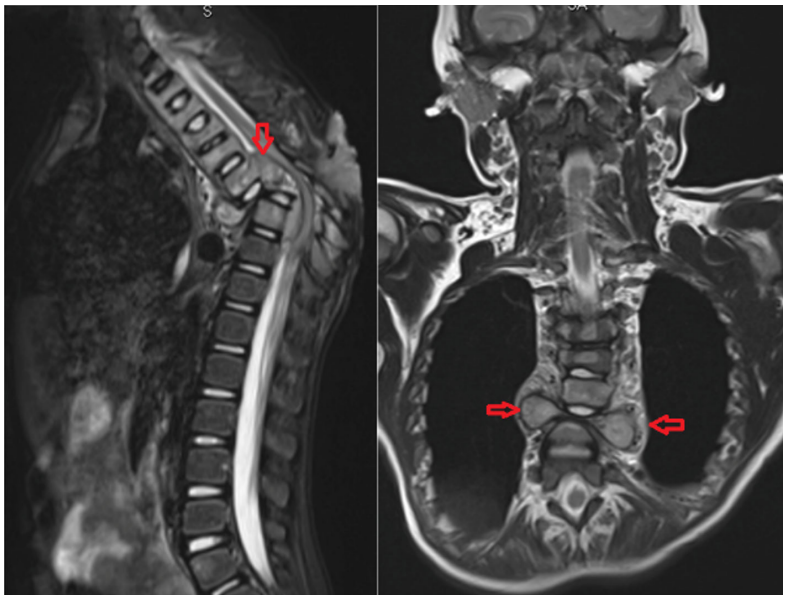

Figure 2. Magnetic resonance imaging of the spine in T2 sequence. Red arrows indicate paravertebral abscesses at the level of T7 with the destruction of the vertebral body.

requested, which revealed lesions compatible with spinal tuberculosis associated with the destruction of the T7 vertebral body and fracture-dislocation in kyphosis at this level with the spinal cord section (Figure 2).

Given the findings, it was decided to take the patient to a surgical procedure of lavage and curettage of lesions, with sampling for molecular biology, culture, and pathology studies. Additionally, stabilization using temporary bone cement replacing the destroyed vertebral body was performed (Figure 3). On the other hand, smear microscopy was performed on gastric juice, bronchoalveolar lavage, and polymerase chain reaction (PCR) on cerebrospinal fluid (CSF), and therapy with Rifampicin and Isoniazid was subsequently continued.

The bone biopsy showed massive necrosis due to a granulomatous process with the presence of Langhans cells, PAS, Gömöry trichrome, and Ziehl-Neelsen staining negative for acid-fast *bacillus* (AFB). Smear microscopy and CSF PCR were negative. The PCR performed on bronchoalveolar lavage, soft tissue, and bone (vertebral) was positive for *Mycobacterium tuberculosis* resistant to Isoniazid, Rifampicin, and injectable drugs, maintaining sensitivity to quinolones**,** so it was considered to be a case of pre-XDR tuberculosis and therapy with Isoniazid and Rifampicin was discontinued. The case was treated as difficult-to-manage tuberculosis, where the antituberculosis treatment was readjusted with Moxifloxacin, Cycloserine, Ethionamide, Pyrazinamide, Ethambutol, and Isoniazid.

The scheme with the six drugs was proposed for 6 months as an "intensive phase", to then continue with a "maintenance phase" of 18 months with all drugs, except Isoniazid. The sensitivity studies for the antituberculosis medication of the samples taken during the readmission to the institution were processed again at the INS.

The result for the soft tissue sample (not bone) was positive for *Mycobacterium tuberculosis* resistant to Isoniazid, Rifampicin, and Pyrazinamide, while maintaining sensitivity to Quinolones, injectable drugs, and Ethambutol. Therefore, with these new findings, it was decided to continue the same established management scheme despite the resistance to Pyrazinamide of said isolation in soft tissue during the two phases of treatment, and the addition of management with injectable drugs was ruled out.

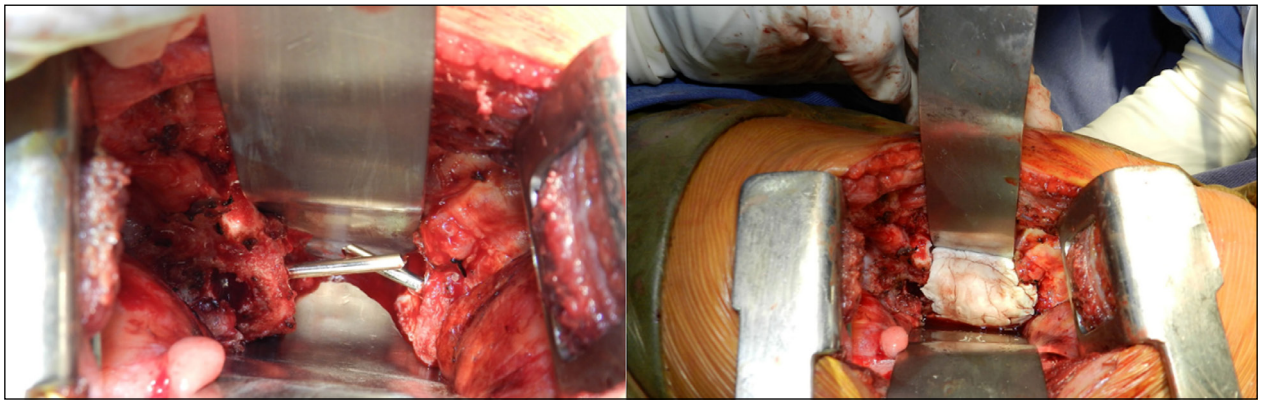

Figure 3. Exposure of the surgical field is seen using an anterior approach for stabilization with pins and bone cement.

Figure 4. Images with anterior, left lateral and posterior views prior to hospital discharge.

Regarding surgical management, once the patient was stabilized, she underwent a first surgical stage through an anterior approach in which the provisional cement was removed, and anterior fixation was performed by placing plates and tibia allograft. Eight (8) days later, the second surgical stage was performed through a posterior approach, in which the definitive fixation was performed.

The patient presented a favorable postoperative period with good tolerance to antituberculosis drugs, so 15 days after the second intervention, she was discharged with outpatient orders for periodic follow-up. The clinical and radiological results are shown in Figures 4 and 5, respectively. No additional neurological deterioration was documented after discharge.

DISCUSSION

STB is the most common form of bone tuberculosis and one of the main manifestations of extrapulmonary tuberculosis[7]; however, most cases are due to infection by *bacilli* sensitive to first-line drugs. Few case series[17,29] record the unusual presentation of STB associated with a resistant *bacillus*. Pawar et al[17], in their work, show one of the most vital records of the cases related with MDR-TB in the literature, with 25 patients in an Asian country[17]. Mohan et al[29] present three cases of the same pathology associated with XDR *bacilli*[29], the most extensive report in the literature.

In addition to the low frequency of infection by resistant *bacilli*, it should be noted that STB is mainly a

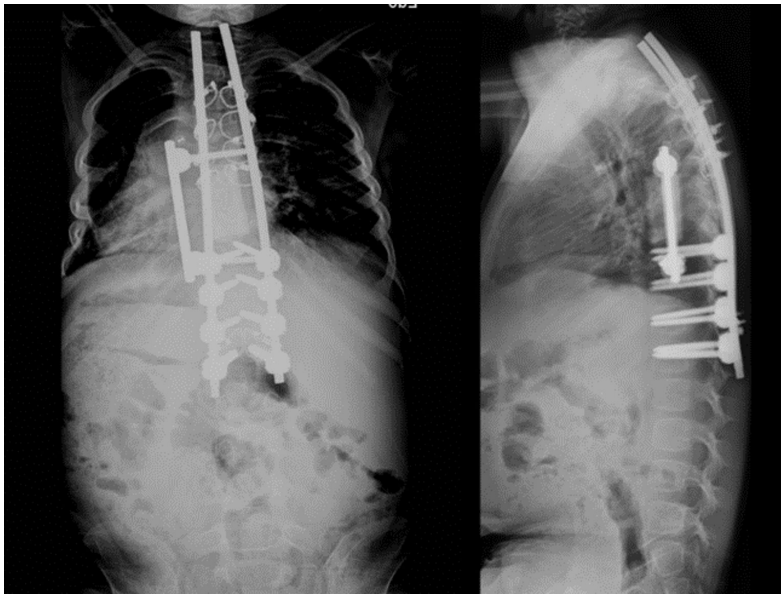

Figure 5. Panoramic radiograph of the AP and lateral spine showing the result after two-stage surgical management with autologous tibial graft and posterior transpedicular instrumentation in a posterior approach.

pathology of male adults, with an average age at diagnosis of 43.4 years[7]. Factors such as poverty, overcrowding, illiteracy, malnutrition, alcoholism, drug abuse, diabetes mellitus, immunosuppressive treatment, and HIV infection have been described as predisposing factors to the disease[30]. However, few cases have been described in the pediatric population. In the work of Cui et al[31] published in 2016, the average age of patients with STB who required surgical management for their deformity was 38 years old[31]. In their 70 cases, Jain et al[32] show that, all patients were older than 15 years old[32]. Although its prevalence in endemic countries may be high, its presentation in children is exotic. According to the literature review, our report is the first to document an STB associated with a Pre-XDR *bacillus* in a pediatric patient.

The natural history of the disease in STB leads to a severe kyphotic deformity with the collapse of the vertebral bodies and neurological deficit due to spinal cord compression or section[33]. However, in a large percentage, due to the difficulty of early diagnosis and the establishment of late treatments, patients often present at admission with some deformity with surgical indications and an already established neurological deficit[31]. Spinal deformity, mechanical instability, and a neurological deficit that does not respond to chemotherapy are the most common complications of STB that require surgery[34].

Management of STB cases associated with resistant *bacilli* follows the guidelines for managing its pulmonary counterpart. They generally include injectable drugs and the addition of aminoglycosides or quinolones, depending on the resistance profile detected[10].

Due to the social conditions surrounding the reported case, the use of oral drugs available in the National Health System, which was easily accessible, was prioritized. Following CDC guidelines, drugs from steps 1, 3, 5, and 6 were used[15]. Additionally, when the treatment started, there was no access to Bedaquiline or Linezolid orally. We had special consideration in the use of ethambutol due to its alert for use in the pediatric population[35]. However, there were no oral alternatives, and the benefit of preventing therapeutic failure was greater than the risk of developing adverse events.

Although the gold standard for diagnosing tuberculosis is culture, it presents some difficulties in practice, such as its low sensitivity, the need for second-level laboratories, and the time for the growth of the *bacillus*. Therefore, molecular biology tests, especially PCR-based, have gained importance in the clinical setting. Not only because of their outstanding results, but also because of the possibility of establishing resistance patterns without waiting for the antibiogram, thus avoiding complications due to late diagnosis or effective treatment in patients[36].

The management of these deformities is surgical; however, with new technologies and techniques in spinal surgery, the best approach for this type of patient has been discussed, whether it should be anterior, posterior, or mixed. In general, the anterior approaches have a disadvantage by presenting more significant pulmonary and cardiovascular morbidity, greater risk of injury to vascular structures, and a more extended postoperative period. On the other hand, it allows better exposure of the vertebral body and the intervertebral disc. Posterior approaches, for their part, lack these complications but are technically more demanding and may present a greater risk of spinal cord injury. In the work carried out by Wang et al[37], the correction through the posterior approach shows better outcomes with a lower incidence of perioperative complications and in the follow-up of patients[37]. In our case, a 360° approach was necessary due to the deformity and the application of the bone autograft; additionally, anterior fixation helps avoiding proximal kyphosis, as in this patient due to poor bone quality and potential for recurrent disease.

CONCLUSIONS

Spinal tuberculosis is a relatively frequent diagnosis in regions with a high incidence of tuberculosis, such as our country. However, its presence in the pediatric population associated with the MDR phenotype is rare. Its diagnosis continues to be a challenge due to the insidious presentation of the condition. There is no consensus regarding the best surgical approach for patients with the characteristics presented. There are three scenarios, single anterior/posterior or mixed approaches in two surgical times.

Authors' Contribution:
Carlos Segundo Montero Silva, Fernando Alvarado Gómez, Frank Mario Herrera Mendez, Fredi Giovanni Soto Guzmán: Revising the manuscript critically for important intellectual content. Take responsibility for the completeness and accuracy of the content. Approval of the submitted and final versions. Nahala Fahed Aborashed Amador, Alexander Tristancho, Maria Camila Giraldo Bernal: Contribution to the conception, design, data analysis, and interpretation of data. Drafting the manuscript. Take responsibility for the completeness and accuracy of the content. Approval of the submitted and final versions.

Conflict of interest:
The authors have no competing interests to declare that are relevant to the content of this article.

Informed Consent:
Informed consent was obtained from the parents of the patient.

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