Case Report

Paradoxical reaction during treatment of spinal tuberculosis in an immunocompetent individual

Reação paradoxal durante o tratamento de tuberculose vertebral em um indivíduo imunocompetente

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ABSTRACT

Paradoxical reactions to the treatment of spinal tuberculosis in HIV-uninfected individuals, with clinical and radiological worsening, are rarely described in the literature. We report the case of a 26-year-old woman complaining of pain in the thoracic spine who had a previous history of coughing, night sweats, and weight loss. Magnetic resonance imaging of the thoracic spine showed discitis and incipient spinal cord compression. Despite the negative results of the etiological investigation, empirical treatment for tuberculosis was initiated based on clinical and radiological criteria. Despite adequate medication, the patient developed alterations in physical examination suggestive of spinal cord compression, which was also observed on new imaging findings of worsening bone involvement, deformity of the vertebral bodies, and increased adjacent fluid collections. Consequently, a surgical approach with resection of the posterior vertebral element and arthrodesis was necessary, and the diagnosis was confirmed by a rapid test for tuberculosis using a sample taken intraoperatively. The patient progressed satisfactorily without sequelae during the drug treatment period, which did not include corticosteroids.

Headings: Spinal tuberculosis; Discitis; Antituberculosis agents; Case report.

RESUMO

A reação paradoxal com piora clínica e radiológica da tuberculose vertebral em indivíduos não infectados pelo HIV é raramente descrita na literatura. Nós reportamos o caso de uma jovem de 26 anos com queixa álgica em coluna torácica e história prévia de tosse, sudorese noturna e perda de peso. Ressonância magnética de coluna torácica evidenciou espondilodiscite e compressão medular incipiente. Apesar dos resultados negativos da investigação etiológica, optou-se por iniciar tratamento empírico de tuberculose a partir de critérios clínicos e radiológicos. Mesmo com o uso correto da medicação, no entanto, a paciente evoluiu com alterações no exame físico sugestivas de compressão medular evidenciada por novas imagens que demonstraram acentuação do comprometimento ósseo, deformidade dos corpos vertebrais e aumento das coleções adjacentes. Fez-se necessária uma abordagem cirúrgica com ressecção de elemento vertebral posterior e artrodese, confirmando-se o diagnóstico pelo teste rápido molecular de tuberculose a partir de amostra coletada no intraoperatório. A paciente evoluiu de forma satisfatória e sem sequelas com a manutenção do tratamento medicamentoso, sem o uso de corticoides.

Descritores: Tuberculose da coluna vertebral; Espondilodiscite; Medicamentos antituberculose; Relato de Caso.

INTRODUCTION

Clinical and/or imaging worsening during tuberculosis treatment can occur due to drug malabsorption, drug resistance, differential diagnoses, or paradoxical reactions[1,2]. Paradoxical reactions are characterized by the worsening of pre-existing lesions or the appearance of new lesions,

despite adequate medication. People living with HIV/AIDS are at a higher risk of developing this condition; however, a paradoxical reaction can occur in HIV-uninfected individuals, with a prevalence varying between 6% and 30%[2,3].

This case report describes an example of spinal tuberculosis in a young woman without HIV who developed clinical and radiological signs compatible with spinal cord compression after 3 months of adequate use of the standard treatment regimen, ultimately requiring surgery. This is a clinical condition that has rarely been described in the literature and whose report highlights the importance of continuing treatment to ensure favorable outcomes in the face of a high potential for sequelae.

CASE REPORT

A 26-year-old women from Maranhao who had lived in Sao Paulo for 7 years visited the outpatient orthopedic clinic with the complaining of increasing nonradiating pain in the thoracic spine for 4 months. She reported that she also had a daily cough, an intermittent fever, night sweats, and had lost 4 kg; however, she did not remember exactly when the symptoms had begun. She denied diabetes or any previous illnesses, as well as alcohol use or smoking. She also denied a history of tuberculosis or close contact with the disease. The patient was in good general condition, eupneic, hydrated, normal colored, alert and oriented, and hemodynamically stable. The cardiovascular and pulmonary physical examination was normal, as was the initial orthopedic and neurological assessment, with preserved strength in the arms and legs and no difficulty walking. The blood count on admission showed no anemia and normal leukocyte count; however, there was a slight serum elevation in the levels of non-specific inflammatory parameters, namely erythrocyte sedimentation rate of 15 mm/h (reference value in women is up to 10 mm/h) and C-reactive protein of 5.7 mg/dL (normal value is <1 mg/dL). The main serologies for infectious diseases were nonreactive, including HIV. The first magnetic resonance images (MRI) of the spine showed discitis with a fluid collection permeating the disk space and the vertebral bodies at T9 and T10 (Figure 1, frames A and C) that projected into the anterior paravertebral space and deformed the ventral face of the dural sac posteriorly, with signs of incipient compressive myelopathy. The patient underwent a percutaneous biopsy of the thoracic spine, the result of which showed fibroconnective and skeletal muscle tissue with an intense chronic inflammatory process and suppurative foci associated with histiocytic reaction and necrosis, with no signs of malignancy. The rapid test to detect

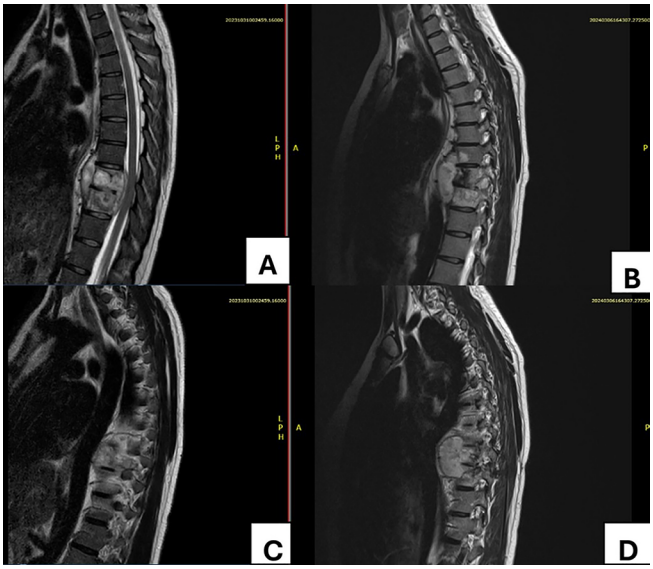

Figure 1. Longitudinal T2-weighted MRI slices of the thoracic spine. A and C: Before the start of tuberculosis treatment, showing spondylodiscitis with a fluid collection adjacent to the T9 and T10 vertebral bodies, deforming the dural sac, and suggesting signs of incipient myelopathy. B and D: After 3 months of treatment, there was an increase in the fluid collection with a change in the spinal cord signal, characterizing compressive myelopathy.

Mycobacterium tuberculosis in the biopsied tissue was negative. To look for other infectious foci, a chest CT scan was performed that showed only noncalcified nodules at the apex of the left lung (Figure 2). Despite the absence of a definitive diagnosis of tuberculosis, we decided to start specific empirical treatment with the standard regimen (rifampicin, isoniazid, pyrazinamide, and ethambutol) based on the clinical and radiological criteria available. The late results of the cultures of aerobic and anaerobic bacteria, fungi, and mycobacteria of the biopsied samples were all negative.

Figure 2. Chest CT scan showing noncalcified nodules in the left lung apex, with no other changes in the parenchyma.

After 3 months of regular drug treatment, the patient returned for an outpatient visit reporting pain improvement and weight gain. The subsequent physical examination, showed patellar hyperreflexia with positive clonus of both legs. A second MRI showed marked bone involvement, deformity of the vertebral bodies, and an increase in adjacent fluid collections, including the one in the epidural space, with compression and a slight change in the spinal cord signal, now indicating compressive myelopathy (Figures 1B and 1D). A surgical approach was indicated for resection of the posterior vertebral element, decompression of T9–T10, and thoracic–lumbar–sacral arthrodesis, which was promptly performed by the orthopedic team (Figure 3). This time, the rapid test for *M. tuberculosis* of the intraoperative sample came back positive, with sensitivity to rifampicin. Therefore, this clinical worsening was considered a paradoxical reaction, and it was decided to maintain the tuberculosis treatment regimen, which was already in the maintenance phase with rifampicin and isoniazid, without corticosteroids. The hospital stay lasted for 17 days because of hospital-acquired pneumonia and the use of intravenous antibiotics, and there were no other postoperative complications. There was a complete neurological recovery; the patient is still being followed-up as an outpatient and is progressing without complaints and without complications or sequelae, about to complete 12 months of specific treatment.

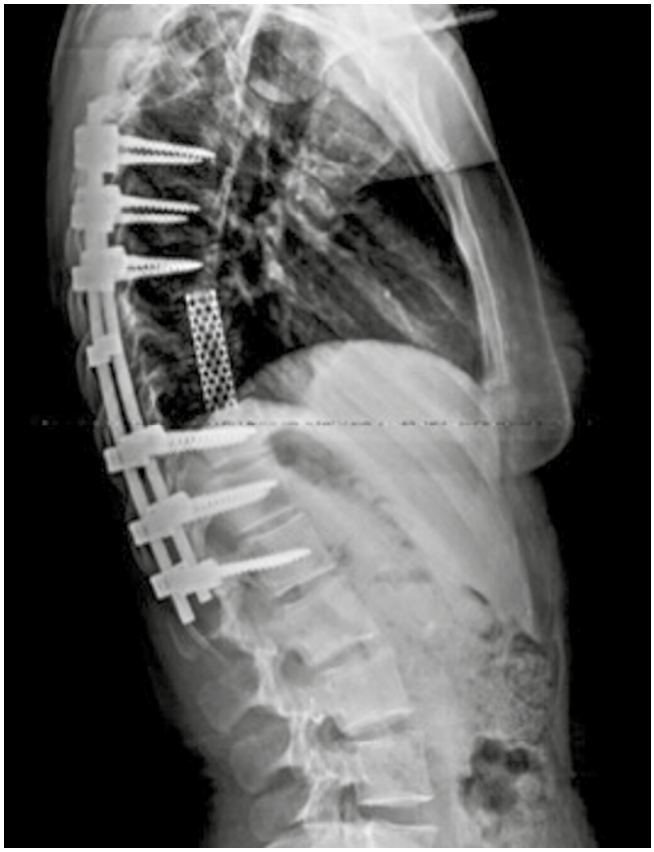

Figure 3. Control X-ray after the thoracic–lumbo–sacral arthrodesis procedure using a fixation system with pedicle screws, metal rods, and a vertebral prosthesis.

DISCUSSION

MRI is the imaging exam of choice for investigating spinal infections, and it helps to differentiate between tuberculous and pyogenic discitis[4,5]. A meta-analysis of 32 studies showed that the involvement of two or more vertebral bodies, epidural extension, paravertebral collection, subligamentous spread, abscesses with thin and regular walls, vertebral collapse, and kyphosis are more suggestive of tuberculosis[5-7]. In addition, tuberculous spondylodiscitis affects the thoracic spine more often than the lumbar spine, unlike pyogenic spondylodiscitis[5]. This pattern may be related to the proximity to the primary pulmonary focus and to the hematogenous spread to highly vascularized vertebral areas. The infection usually begins in the anterior subchondral region of the vertebral body and progresses to below the anterior longitudinal ligament, where the vascular anatomy favors the accumulation of septic emboli and the formation of abscesses[5]. Unlike the pyogenic form, which is restricted to the endplate, tuberculous spondylitis affects the vertebral bodies extensively, often leads to the loss of more than half their height and resulting in collapse, as was shown in our patient's MRI.

Around 40% of patients with osteoarticular tuberculosis have concomitant pulmonary involvement[8], which justifies a targeted investigation to look for specific etiological confirmation at other sites. In the present case, the chest CT scan showed only the presence of nodules at the apex of the lung, without much evidence of active pulmonary tuberculosis but consistent with the hypothesis of a primary infectious focus. In the absence of a definitive diagnosis, the decision to start empirical treatment must take into account clinical, imaging, and laboratory factors, as well as epidemiological issues related to public health[9,10]. This case report highlights the importance of clinical judgment and reinforces the need for outpatient follow-up with serial imaging tests to monitor the response to therapy. Although the patient was asymptomatic, a specialized physical examination revealed new clinical signs suggestive of spinal cord compression, prompting a second MRI. Thus, the paradoxical reaction hypothesis was based on the regular use of the medication and the reported improvement in pain and weight gain. In addition, all the cultures of the previously biopsied samples were

negative, which reduced the likelihood of there being other untreated conditions and confirmed the decision to maintain exclusively the treatment regimen for tuberculosis.

The paradoxical reaction is well described in patients with tuberculosis of the central nervous system, especially in the meningeal form[11]; however, there are few reports documenting this phenomenon in tuberculous spondylitis. Im et al.[1] described four cases of paradoxical worsening between two and 12 weeks after the start of adequate treatment in patients without HIV. Their symptoms included worsening of low back pain, weakness in the legs, and increased vertebral enhancement on MRI images, all leading to the need for surgical decompression. Immune reconstitution inflammatory syndrome (IRIS) in patients coinfected with HIV and tuberculosis shares clinical similarities with paradoxical reaction; although, they represent distinct conditions[12]. In patients with IRIS developed after the introduction of antiretroviral therapy, there is activation of inflammatory pathways through inflammasomes associated with the expansion of a deregulated antigen-specific T-cell response[12]. These pathways have not been fully studied in people without HIV infection. Therefore, their pathogenesis is not yet well understood in patients with paradoxical reactions. Analysis of the cytokine profile in individuals without known immunosuppression showed an increase in the expression of IL-6 and TNF-α after starting the medication[13]. Bell et al. hypothesized that the two conditions share a baseline immune impairment related to host factors or to a potential pre-existing lymphopenia caused by tuberculosis itself, which, when associated with a high bacillary load, is confronted with the restoration of immunity after treatment initiation[14]. Some studies suggest that other factors, such as anemia and hypoalbuminemia, increase the risk of developing paradoxical worsening;[11,15] however, this is not what we observed in the reported case. In a retrospective analysis of 80 HIV-negative patients with spinal tuberculosis in India, 6 patients showed growth of spinal lesions after 3 months of therapy, despite reporting overall clinical improvement with increased appetite and weight gain, similar to our patient[16].

The benefit of corticosteroids in the treatment of paradoxical reaction in tuberculous spondylitis is controversial. Some studies indicate that using corticosteroids in this context does not significantly reduce the risk of neurological sequelae[1,17]. In contrast, a meta-analysis of 10 studies showed that corticosteroids were the main strategy to manage paradoxical reactions, and their use was reported in 40%–100% of HIV-negative children with different forms of tuberculosis[12]. However, there are no controlled clinical trials evaluating its therapeutic use in HIV-negative patients who develop paradoxical worsening.

In a recent Brazilian series of 30 patients with confirmed osteoarticular tuberculosis, surgical debridement and arthrodesis of the spine was indicated in 64.71% of cases[8]. Although the treatment of vertebral tuberculosis is primarily pharmaceutical, surgery should be considered not only in the presence of installed spinal cord compression but also as a preventive measure against the imminent risk of vertebral collapse[18]. The posterior surgical route is most commonly used because it leads to less morbidity; however, it can result in the incomplete removal of the infectious focus. The anterior route allows direct access to the lesion with better visualization and debridement; however, it has a higher risk of complications, such as graft failure and pulmonary complications. The combined approach, which is more invasive, is indicated for extensive and unstable lesions[18]. Complications, such as hemothorax and surgical site infection, are reported in all approaches, and patients undergoing surgical intervention usually have a longer hospital stay than those treated only clinically[8].

So far, our patient has not only had a good therapeutic response but has also progressed without sequelae, which is not the most common outcome. Around 60% of patients develop some degree of functional limitation or motor deficit, possibly due to late diagnosis and irreversible neurological impairment[8].

CONCLUSION

This report reinforces the importance of considering a paradoxical reaction as a possible complication of spinal tuberculosis treatment, even in patients uninfected with HIV. Clinical and imaging surveillance together with adequate adherence to and continuity of treatment were essential in indicating an early and successful surgical approach, which, in addition to confirming the definitive diagnosis, allowed for a positive outcome of a form of extrapulmonary tuberculosis with a high potential for sequelae.

"This case report deserved an official declaration of acknowledgement and ethical approval by its institution of origin and was peer-reviewed before publication, whilst the authors declare no fundings nor any conflicts of interest concerning this paper. It is noteworthy that case reports provide a valuable learning resource for the scientific community but should not be used in isolation to guide diagnostic or treatment choices in practical care or health policies.

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