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CASE REPORT OPEN ACCESS

Spinal Osteoarticular Multidrug-resistant Tuberculosis (MDR/RR-TB) in a Child: A Case Report

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Abstract:

Introduction: We report a case of a young child with multidrug-resistant tuberculosis (MDR/RR-TB) of the thoracic spine, complicated by myelopathy.

Case Report: Clinical assessment revealed a lower thoracic gibbus and neurological features of upper motor neuron syndrome conforming to myelopathy. Radiological evaluation revealed a marked kyphosis, contiguous T10-T11 vertebral destruction, paraspinal soft tissue collection, and intraspinal compression with cord signal changes, suggestive of spinal TB. Rapid molecular testing expedited the diagnosis of MDR/RR-TB and guided prompt treatment initiation. Although second-line drugs are the mainstay of treatment, surgery was undertaken due to marked kyphosis, spinal instability, and neurological complications in the growing spine.

Conclusion: Although the case seems interesting, it, unfortunately, highlights multiple health system failures in developing countries, resulting in premature termination of MDR/RR-TB treatment and loss of kyphosis correction with subsequent recurrence of the kyphotic deformity.

Keywords: Osteoarticular TB, Multi-drug resistant TB, Spinal TB, Tuberculosis, Gibbus, Kyphosis.

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1. INTRODUCTION

Tuberculosis (TB) in children is common in high TB burden countries, such as South Africa [1]. The World Health Organisation (WHO) highlights the problem of TB and Human Immunodeficiency Virus (HIV) co-infection, with up to 70% of adult cases reported [2]. Extra-pulmonary TB accounts for 15–20% of all TB cases, and of these, 10% are skeletal TB [3]. Spinal TB accounts for 50% of the skeletal TB cases [3]. TB in children contributes to approximately 20% of all TB cases in South Africa [4].

Drug-resistant TB (DR-TB) continues to be a global public health crisis, as declared by the WHO in 1993 [5]. According to the WHO drug resistance surveillance data, an estimated 230,000 people died globally from DR-TB in 2017 [6]. DR-TB can occur where previously drug-susceptible organisms develop resistance within one human host. Alternatively, resistance can be transmitted where already resistant mycobacteria are transmitted to a new host. Children usually have transmitted resistance, making acquired resistance less likely [7]. The paucibacillary nature of paediatric DR-TB makes its diagnosis challenging, particularly in those with HIV co-infection. As a result, the initiation of effective therapy is often delayed [8].

Patients with DR-TB are categorised by the resistance pattern of Mycobacterium tuberculosis (M. Tuberculosis) strains isolated in the specimen. Multidrug resistance (MDR) refers to resistance to both isoniazid (INH) and

rifampicin (RIF) [9]. Thomas *et al*. [10] highlighted the risk of developing MDR-TB disease among children and estimated it to be higher than among adults, given the high rates of ongoing community-level transmission and young children's unique vulnerability to progression from infection to disease.

In the global and South African paediatric literature, there are few publications concerning DR-TB and even fewer regarding DR-TB of the spine. The few paediatric DR-TB of the spine case series published reported a frequent delay in the diagnosis of DR-TB of the spine in children ranging from six months to five years. Despite this delay, reports suggest that once DR-TB of the spine is identified, children tolerate therapy well and are successfully treated [11].

This case report represents a case of spine MDR/RR-TB out of 26 paediatric patients surgically treated for spine TB in a South African tertiary hospital between 2012 and 2019.

2. CASE PRESENTATION

A 21-month-old boy was referred from a regional hospital in December, 2017, with a collateral history from his maternal grandmother. The child presented with a month-long history of progressive loss of ability to stand and walk, associated with painful spinal deformity. Perinatal history revealed a term, vaginal-delivered infant with low APGAR scores, resulting in in-hospital care for a month. The mother was unemployed, 32 years old, HIV infected, and on antiretroviral treatment. The child's HIV-1 polymerase chain reaction (PCR) testing done at 9 months of age was negative. His immunisation card was up to date.

Developmental history was normal until one month before admission when progressive milestones regression was observed. Family and social history revealed that the child lived with his mother, maternal grandparents, and other relatives. The grandfather, who worked at the referring hospital at the time, had been receiving anti-tuberculosis treatment (ATT) for pulmonary TB but unfortunately passed away when the baby was five months old. Although exposed to TB, both the grandmother and the mother subsequently had their sputum screened for pulmonary TB and were found to be negative. There was no indication that the child was also screened.

On examination, the child was the appropriate size for his age, well-hydrated, and without dysmorphic features. He had a tender gibbus in the lower thoracic region. Neurologically, he was intact. He was able to sit and crawl but could not stand or walk. He had good truncal and upper limb control. Deep tendon reflexes in biceps, triceps and both knees were normal. He had bilateral sustained ankle clonus. We could not reliably assess sensation considering the child's age.

There was the destruction of T10-T11 vertebral bodies with 40°kyphotic angulation, according to Konstam [12] measurement methods and spinal column sagittal translation of the lower thoracic spine on X-rays. The retropulsion of the diseased vertebra is considered evidence of spinal instability as per Rajasekaran's spine at "risk signs". The chest X-rays (CXR) showed no evidence of active lung disease.

Magnetic resonance imaging (MRI) of the thoracolumbar spine confirmed features conforming to lower thoracic spine TB, as evidenced by T10 to T11 vertebral body destruction, associated with marked kyphosis, paraspinal soft tissue mass and collection, extending into the spinal canal and causing extradural compression, spanning between T6-T11, as well as associated spinal cord signal. The extrinsic and intrinsic spinal cord changes were conforming to his clinical presentation (Fig. **1**).

Given the clinical and radiological findings, a provisional diagnosis of TB of the thoracic spine was made, and as a result, empiric paediatric ATT was initiated while preparing for surgery.

In this case, neurological complications, as well as marked kyphotic deformity and spinal instability, were the main indications for a two-stage anterior and posterior spinal surgery. The first stage consisted of anterior decompression as described by Hodgson *et al*. [13, 14], and fusion using fibula autograft, followed by a second-stage un-instrumented posterior fusion with autograft from left 7th rib after subperiosteal exposure of posterior spinal elements two weeks later (Figs. **2** and **3**).

The real-time PCR for M. tuberculosis (Xpert® MTB/RIF Ultra–Cepheid, Sunnyvale, California, USA) detected rifampin-resistant MTB-complex strains (molecular). The TB culture result, at an 11-day incubation period, was positive for the M. tuberculosis complex. No standard drug susceptibility testing (DST) was performed. The molecular resistance testing was performed on cultured isolate for first-line drugs by line probe assay, using the GenoType MTBDRplus Ver 2.0 (Hain Lifescience GmbH. Hardwiesenstraße 1, 72147 Nehren, Germany) for RIF and INH, and confirmed mono-resistance to RIF. No mutations were detected on subsequent use of the GenoType MTBDRsl Ver 2.0 Kit for second-line agents (fluoroquinolones and second-line injectable agents) (Hain Lifescience GmbH. Hardwiesenstraße 1, 72147 Nehren, Germany).

Given the diagnosis of MDR/RR-TB, in consultation with the Paediatric Infectious Disease unit, a second line ATT was initiated, consisting of INH (10-15mg/kg), Levofloxacin (10mg/kg), Pyrazinamide (30-40mg/kg), Terizidone (10-20mg/kg), and Ethionamide (20mg/kg) [15]. This second line ATT did not include an injectable.

A supportive post-operative thoracolumbar sacral orthosis (TLSO) brace was custom-made and fitted to assist with external stabilisation of the spine until complete fusion. There was no indication that the brace was ever used as prescribed.

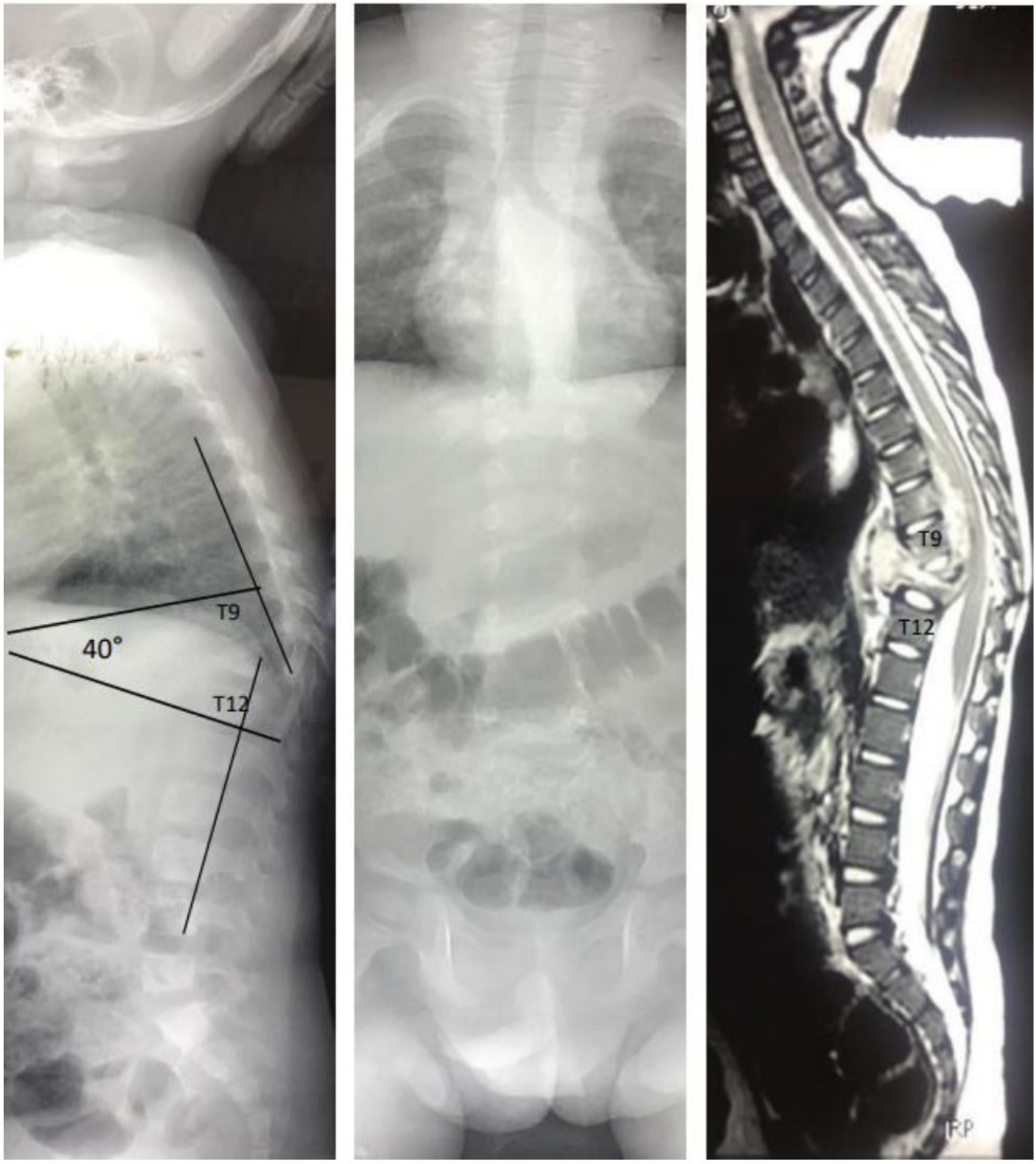

Fig. (1). (**A** and **B**) Thoracolumbar spine X-rays (Lateral and AP) show evidence of destruction of T10-T11 vertebral bodies, 40° kyphotic angulation lower thoracic region and spinal column sagittal translation. (**C**) MRI shows anterior cold abscess and intraspinal extradural soft tissue granulation spanning T6-T11 with cord signal.

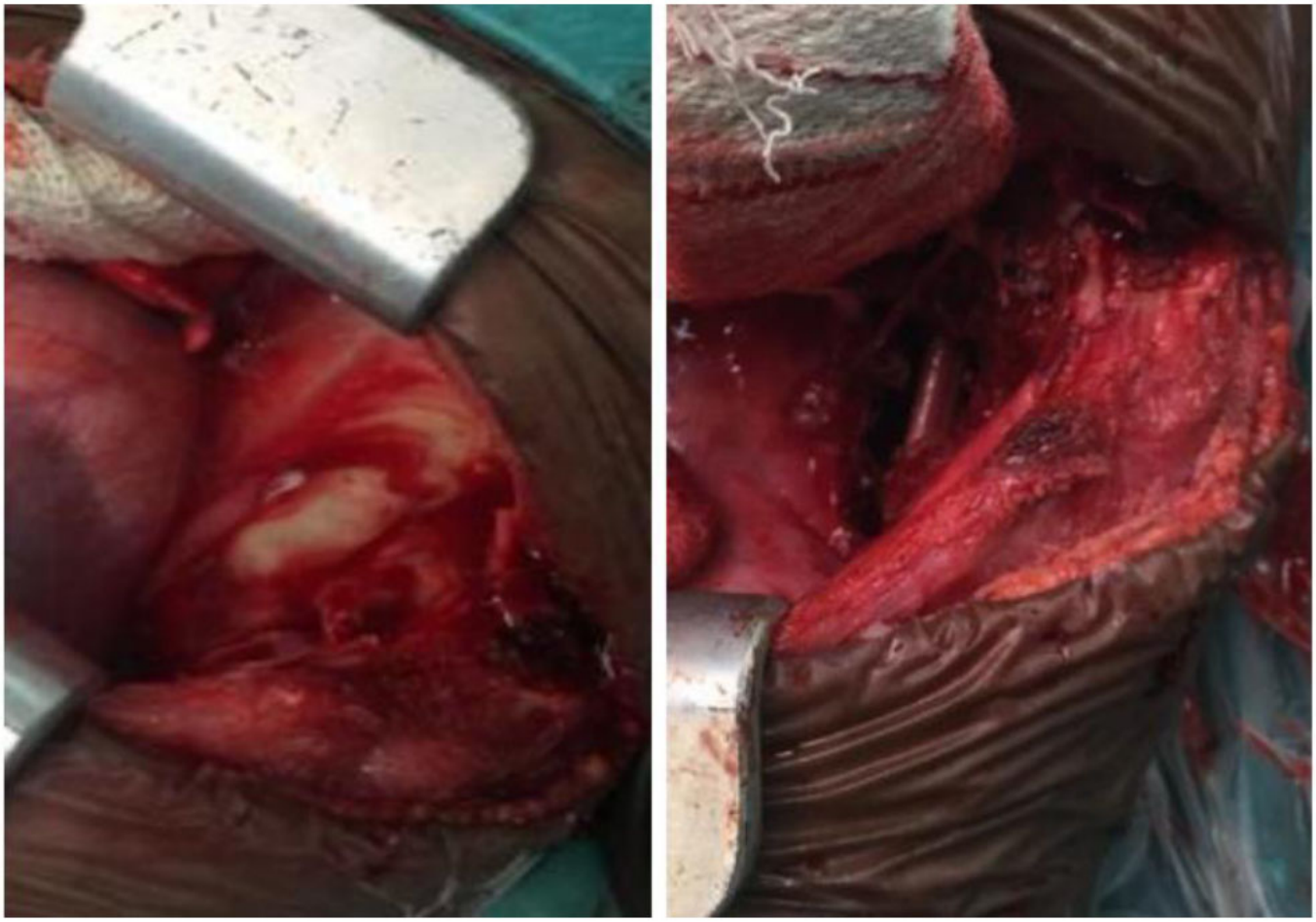

Fig. (2). (**A** and **B**) show evidence of copious amounts of pus and anterior decompression and fusion *in situ* (fibula graft) through a left trans-thoracic approach.

The child was then hospitalised at a regional Infectious Disease Hospital (SIZWE) for MDR/RR-TB medical treatment. He was discharged home four months later to continue supervised outpatient treatment until 18 months. There was no indication that on discharge, the patient continued treatment at the local Public Health Centre (PHC) or followed up by the MDR unit. If this is true, it will represent a serious public health system failure.

After multiple calls to the mother and grandmother, the child only arrived for a post-op surgical follow-up visit 21 months later. The shocking discovery was that the treatment had been terminated at six months without any explanations provided. There was a suspicion that the mother might have absconded from the healthcare facility, representing a health system failure. Nonetheless, clinically, the child looked clinically well and neurological intact as per the American Spinal Cord Injury Association Impairment scale (ASIA E) [16]. There was a notable residual kyphotic deformity. The child appeared to have tolerated the second-line ATT well and showed no adverse events (Fig. **4**).

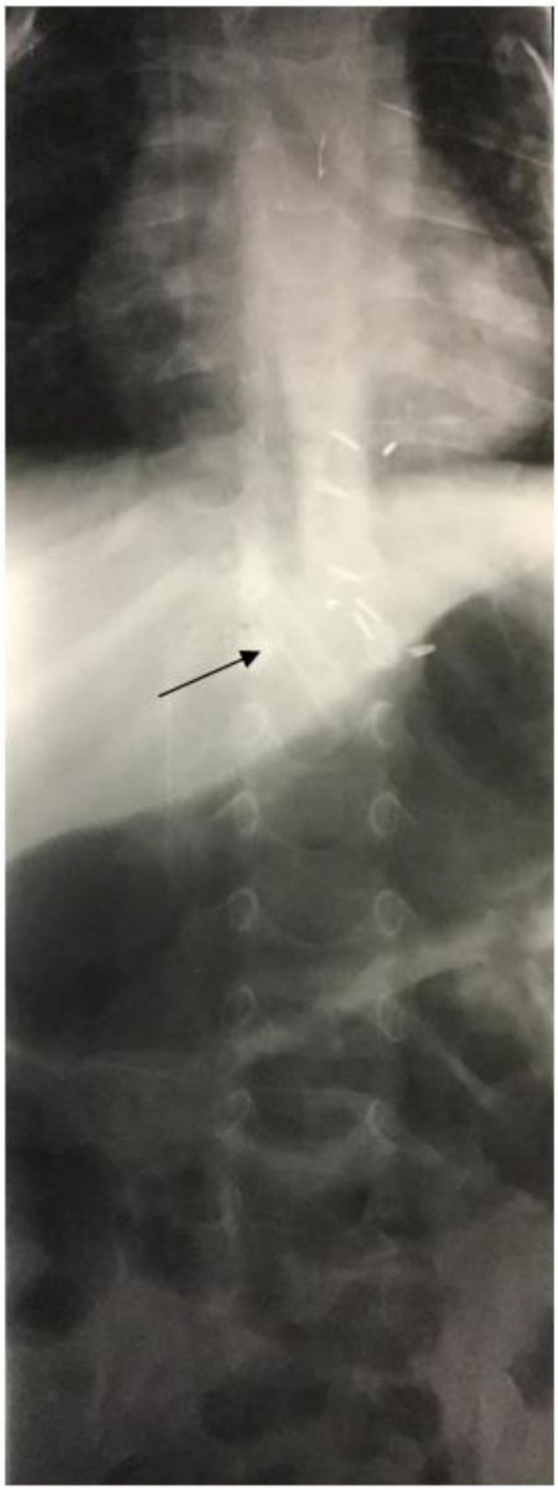

Fig. (3). Post-operative thoracolumbar spine X-rays AP view shows evidence of a well-aligned spine with an angulated fibula graft used for anterior column reconstruction.

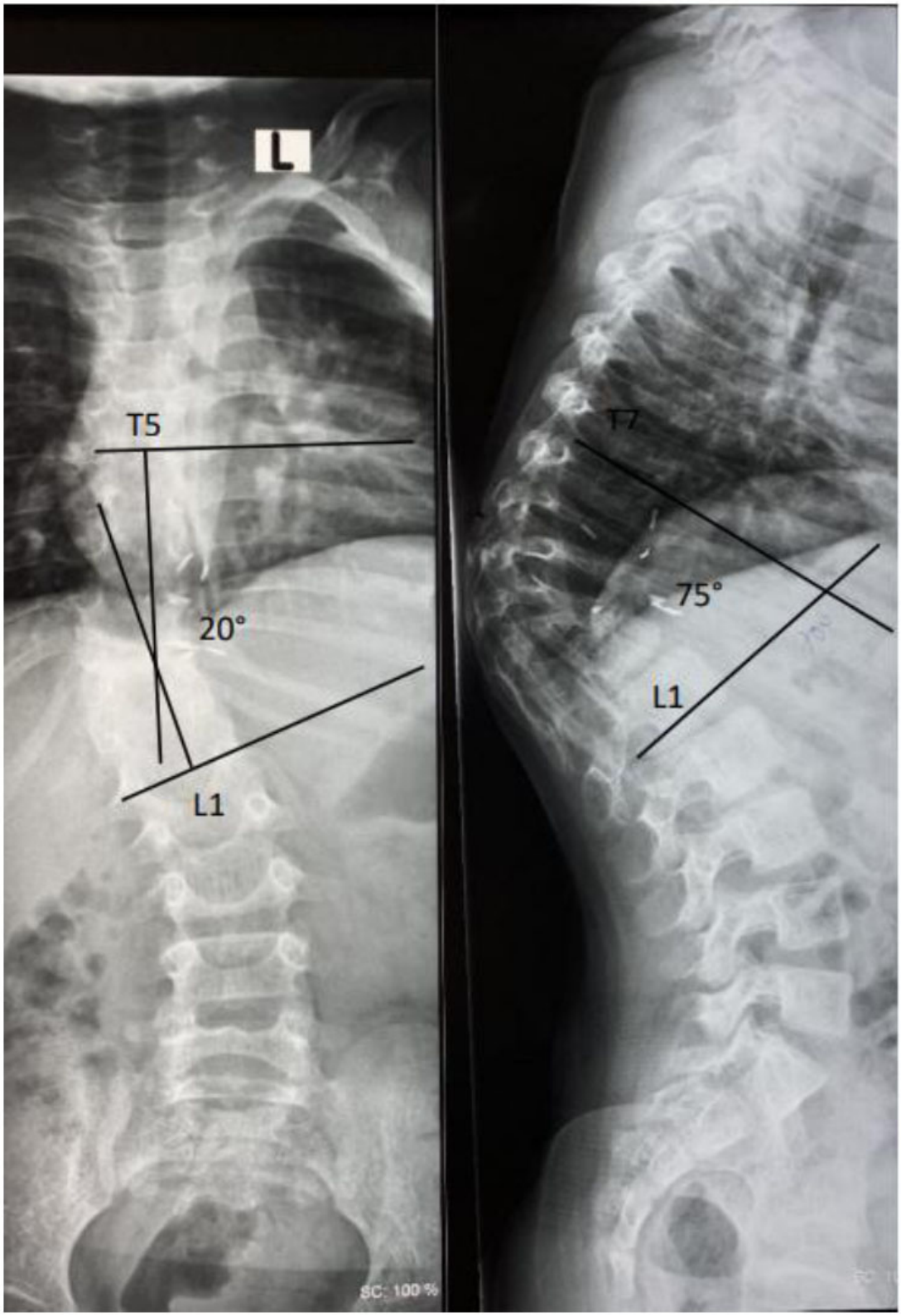

Fig. (4). (**A** and **B**) show radiological evidence of healthy-looking bones of a well-nourished child with a residual healed post-TB kypho-scoliotic deformity.

3. DISCUSSION

Medical management is the mainstay of treatment, but drugs alone may not adequately address bone destruction, neurological compromise, or mechanical instability that may occur with spinal TB. Studies on the adult population have shown that as an adjunct to chemotherapy, surgery can achieve a cure [9, 17]. Therefore, clinicians must remain vigilant of those who require adjunct surgical intervention [11].

In this case, neurological complications marked by kyphotic deformity and sagittal spinal instability were the main indications for surgery, consisting of anterior spinal decompression and fusion, followed by posterior spinal fusion [18]. In our setting, the surgical procedure of choice is one-stage anterior surgery for debridement and bone strut (fibula autograft or allograft) and posterior surgery for posterior fusion. Posterior instrumentation is reserved for thoracolumbar and cervico-thoracic regions due to their distinctive biomechanics [19]. It is also advised in cases where more than 3 vertebrae are involved or in the event of early anterior graft failures.

The commonest reported surgical complication is loss of kyphosis correction due to the poor graft quality, lack of instrumentation and an inherent biomechanical instability in this spinal region. In this case, it was multifactorial, such as premature termination of medical therapy and loss to surgical follow-up. Furthermore, there is no indication that the supportive post-operative brace was used.

On mitigation against the loss of correction, Govender *et al*. [20] reported 100% arthrodesis at six months with fresh-frozen allografts. Moon *et al*. [21] performed a single or two-stage anterior and posterior surgery using instrumentation in the form of Hartshill and sublaminar wires to correct and prevent kyphosis deterioration. The main concerns with Hartshill are wire breakage and loosening, implant prominence, and unnecessary fusion of a large number of segments in a growing spine [21].

Although the child has shown loss of correction resulting in a recurrence of thoracic kyphosis, corrective surgery is still an option at a later stage. However, close surgical follow-up needs to be maintained to assess deformity progression.

Studies have highlighted the need for laboratory confirmation of TB, especially when radiological features are atypical or when the patient is unresponsive to conventional medical therapy [3, 7, 22]. The detection of spinal MDR/RR-TB requires bacteriological confirmation and testing for drug resistance using rapid molecular tests, culture methods or sequencing technologies [23]. In this child, RR-TB was detected from specimens taken during anterior radical debridement on GeneXpert, day one post-surgery. After 11 days of incubation, the culture confirmed TB, and sequencing of cultured results detected RR-TB. In South Africa, the wide use of rapid diagnostics that can speed up the diagnosis of resistance among patients has accelerated treatment initiation and decreased the number of pre-treatment patients lost to follow-up [24].

A history of TB contact is critical in the evaluation and management of suspected or asymptomatic child contact. Fox *et al*. [25] reported that contacts of TB patients are a high-risk group for developing TB, particularly within the first year, especially when children are younger than 5 years and living with HIV. In this case report, there was a TB contact from the deceased grandfather, who was on ATT and whose drug sensitivity pattern was unknown. Although exposed to TB, both the grandmother and the mother were screened for pulmonary TB and were found to be negative. Furthermore, WHO recommends clinical evaluation and follow-up of high-risk MDR-TB contacts for two years but does not recommend chemoprophylaxis [25]. However, according to Loveday *et al*. [26], unknown exposure to DR-TB is common in this high-burden setting. Unfortunately, the fact that the child was never screened made this a major health system failure, according to the national and WHO guidelines [15, 27].

Given the diagnosis of MDR/RR-TB, in accordance with WHO and national guidelines, treatment requires a course of second-line drugs for at least 9 months and up to 20 months, supported by counselling and monitoring for adverse events [15, 27]. More recently, WHO has recommended expanded access to all-oral regimens, like those used in this case [23]. According to Al-Dabbagh *et al*. [28], treatment duration depends on the extent and context of the DR-TB disease.

The child has shown clinical and neurological recovery with healed residual post-TB kyphosis and without any drug side effects [7]. Erythrocyte Sedimentation Rate (ESR) to assess spinal TB activity was normal. No tissue biopsy was warranted, as deemed not clinically relevant. Al-Dabbagh *et al*. [28] and Loveday *et al*. [26] cautioned against the use of laboratory diagnosis alone in the absence of a consistent clinical picture, considering the increased risks and cost of unnecessary treatment [26].

Although there was no credible explanation for defaulting treatment and loss to follow-up, the most likely assumption is that the caregiver absconded from the TB hospital. This is not unusual in high-burden DR-TB countries, such as South Africa. Hirasen *et al*. reported that 17% of patients were lost to follow-up within a year after initiation of MDR/RR TB treatment [29]. Furthermore, decentralised and deinstitutionalised MDR-TB treatment from the old policy management of centralised treatment in specialised units has resulted in early initiation of therapy and increased treatment compliance by decreasing stigma, hence better treatment outcomes. Most importantly, the reported decrease in the economic burden on the caregiver and family is not to be underestimated [28].

The limitations of this case report reside in the fact that the patient was not optimally treated due to multiple health system failures that started when the maternal grandfather was diagnosed with pulmonary TB. It was evident that the child was at high risk of contracting TB with such close contact. Singh *et al*. indicated that an atypical presentation of TB often leads to delayed diagnosis [30]. Commonly cited risk factors for these

atypical manifestations are low socioeconomic status and inadequate nutrition [30]. The lack of tracking and tracing, when the child and mother disappeared from the infectious disease hospital, resulted in early termination of treatment and subsequent loss to surgical follow-up.

CONCLUSION

We described a case of MDR/RR-TB of the lower thoracic spine associated with a marked kyphotic deformity complicated by myelopathy. The patient was managed medically with second-line TB drugs reserved for MDR-TB. An adjunctive two-stage anterior and posterior surgery was undertaken to protect the spinal cord and restore spinal alignment and stability.

AUTHORS' CONTRIBUTIONS

FU formulated the research aims and objectives, collected the data, and prepared the draft of the manuscript. MC contributed to inpatient management, data collection, case summary, and manuscript preparation.

LIST OF ABBREVIATIONS

ATT	=	Anti-tuberculosis Treatment
CXR	=	Chest X-rays
DR-TB	=	Drug-resistant TB
DST	=	Drug Susceptibility Testing
INH	=	Isoniazid
HIv	=	Human Immunodeficiency Virus
MDR	=	Multidrug Resistant
MDR/RR-TB	=	Multidrug Resistant or Rifampicin Resistant Tuberculosis
M. tuberculosis	=	Mycobacterium Tuberculosis
RIF	=	Rifampicin
MRI	=	Magnetic Resonance Imaging
PHC	=	Public Health Centre
TB	=	Tuberculosis
TLSO	=	Thoracolumbar Sacral Orthosis
WHO	=	World Health Organisation
XDR	=	Extensive Drug Resistant

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Informed consent was taken from the parent.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available within the article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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