

Received: 2025.10.17
Accepted: 2026.02.09
Available online: 2026.03.09
Published: 2026.04.22

e-ISSN 1941-5923
© Am J Case Rep, 2026; 27: e951840
DOI: 10.12659/AJCR.951840

Spinal Tuberculosis Diagnosed by Metagenomics Capture (MetaCAP) in a Patient Undergoing Maintenance Hemodialysis: A Case Report

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Financial support: Kunming Municipal "Non-Ten-Hundred-Thousand" Health Research Project (2023-03-05-012)
Conflict of interest: None declared

Patient: Female, 64-year-old
Final Diagnosis: Spinal tuberculosis
Symptoms: Low back pain
Clinical Procedure: —
Specialty: Laboratory Diagnostics
Objective: Unusual clinical course
Background: Spinal tuberculosis is difficult to diagnose in patients undergoing maintenance hemodialysis (MHD) because of immunosuppression, atypical clinical manifestations, and the limited sensitivity of conventional microbiological assays. Rapid and accurate pathogen identification is essential to distinguish spinal tuberculosis from other causes of vertebral destruction, including metastatic malignancy and bacterial spondylitis. This report aims to illustrate the diagnostic value of capture-based targeted sequencing for detecting *Mycobacterium tuberculosis* in extrapulmonary infection when routine tests and metagenomic next-generation sequencing (mNGS) yield inconclusive or misleading results.
Case Report: A 64-year-old woman with end-stage renal disease secondary to IgA nephropathy, receiving long-term MHD, presented with progressive low back pain. Imaging revealed multilevel vertebral involvement with pathological fractures, raising suspicion of metastatic disease or infectious spondylitis. Histopathological examination demonstrated granulomatous inflammation, while acid-fast staining and routine cultures were negative. Initial mNGS of spinal tissue identified *Staphylococcus aureus*, leading to targeted antibacterial therapy. Although inflammatory markers declined, the patient's symptoms worsened and pancytopenia developed. Subsequent analysis of spinal pus using metagenomic capture (MetaCAP)-based targeted sequencing detected the *Mycobacterium tuberculosis* complex with high confidence. Anti-tuberculosis therapy was promptly initiated, resulting in rapid clinical improvement and radiological resolution.
Conclusions: This case shows the limitations of conventional microbiological methods and unbiased mNGS in diagnosing extrapulmonary tuberculosis in immunocompromised patients. Capture-based targeted sequencing offers enhanced sensitivity for *Mycobacterium tuberculosis* detection and may facilitate timely diagnosis and appropriate treatment of spinal tuberculosis in patients undergoing MHD.
Keywords: Tuberculosis, Spinal • Renal Dialysis • Metagenomics
Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/951840>

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Introduction

Patients with end-stage renal disease (ESRD) frequently are immunocompromised, which markedly increases their susceptibility to tuberculosis (TB) [1-3]. According to a recent meta-analysis, the incidence of TB among dialysis patients worldwide is 5611 per 100 000 individuals, an almost 20-fold increase compared with rates reported for the general population in the World Health Organization Southeast Asia Region [4-6]. TB is traditionally classified as pulmonary or extrapulmonary [7]. In extrapulmonary TB, osteoarticular involvement is particularly common; spinal TB constitutes roughly half of these cases, most often affecting the lumbar vertebrae [8,9]. Spinal TB in patients with ESRD often presents with non-specific clinical features; coupled with the low sensitivity of conventional microbiological tests, this considerably complicates pathogen identification. In this report, we present a case of spinal TB in a patient undergoing maintenance hemodialysis (MHD) in whom the diagnosis was established by metagenomic capture (MetaCAP) technology. This method is based on probe hybridization capture combined with high-throughput sequencing and bioinformatic analysis, allowing precise pathogen identification within 24 h while offering exceptionally high sensitivity and an unbiased detection profile, which translates into timely and reliable diagnostic outcomes.

Case Report

A 64-year-old woman with ESRD secondary to IgA nephropathy was receiving MHD 3 times a week. She was admitted to our hospital on March 7, 2024, after experiencing lumbar pain following a fall. The complete process of diagnosis and treatment is presented in **Figure 1**.

She had multiple comorbid conditions, including grade 3 hypertension, inactive hepatitis B virus carriage, and a previous diagnosis of clear cell renal cell carcinoma, for which she underwent right nephrectomy and adrenalectomy in January 2020. The pathological staging was pT2N0M0, Fuhrman grade II, and no adjuvant therapy was administered; there had been no evidence of recurrence. She also had a history of hysterectomy. Before admission, her medications included levofloxacin (0.5 g administered intravenously on dialysis days for a total of 17 days), metoprolol tartrate, and erythropoietin. She had no history of immunosuppressive therapy, no known exposure to TB, and no history of smoking or alcohol consumption. Her family history was unremarkable for TB or autoimmune diseases.

On admission, her vital signs were stable. Physical examination revealed localized tenderness on palpation over the lumbar spinous processes, while spinal alignment, range of motion, and overlying skin appeared normal. The straight leg

raise test was negative bilaterally. Motor strength, muscle tone, and sensory function in the lower extremities were intact. Deep and superficial tendon reflexes were symmetric and within normal limits, and no pathological reflexes, including Hoffmann or Babinski signs, were elicited. Initial laboratory tests revealed anemia and hypoalbuminemia, accompanied by markedly elevated inflammatory markers, including procalcitonin (PCT), high-sensitivity C-reactive protein (hs-CRP), and erythrocyte sedimentation rate (ESR). In contrast, the white blood cell count, platelet count, liver function tests, and coagulation parameters were within normal ranges (**Table 1**). A repeat complete blood count on March 11 demonstrated concomitant increases in total leukocyte and neutrophil counts along with rising hs-CRP levels, whereas lymphocyte counts, PCT, and ESR had declined (**Table 1**). Magnetic resonance imaging (MRI) of the thoracic and lumbosacral spine revealed abnormal signal intensities involving the left spinal canal at T9 and the T11 vertebral body, raising suspicion for metastatic disease. Additional findings included a pathological compression fracture of the L2 vertebral body, wedge deformity of L5, disc bulging from L2/3 to L4/5, and spinal canal narrowing at the L2 level (**Figure 1A, 1B**).

The patient underwent L2 vertebral body puncture biopsy under C-arm-guided fluoroscopy. Microscopic histological evaluation demonstrated fragmented bone tissue with fibrous proliferation between trabeculae, accompanied by epithelioid cell hyperplasia and infiltration of plasma cells, lymphocytes, and neutrophils. Occasional aggregates of multinucleated giant cells forming granulomatous nodules were observed, consistent with granulomatous inflammation (**Figure 1C, 1D**). Immunohistochemical analysis showed no evidence of malignancy. Special stains failed to identify any specific pathogens, and bacterial cultures and acid-fast bacilli (AFB) staining were negative. Initial untargeted metagenomic next-generation sequencing (mNGS) of the biopsy specimen detected *Staphylococcus aureus* and hepatitis B virus (**Table 2**). In view of the patient's symptoms, physical findings, laboratory abnormalities, imaging features, and mNGS results, we suspected she had *Staphylococcus aureus* spinal osteomyelitis. Accordingly, targeted antimicrobial therapy was initiated with cefoperazone-sulbactam (3.0 g intravenous glucose tolerance test [IVGTT]) combined with vancomycin (0.5 g IVGTT on hemodialysis days), in addition to supportive therapy with erythropoietin and albumin.

Despite 30 days of continuous therapy and a documented decline in inflammatory markers (**Figure 2B**), her clinical condition continued to deteriorate, accompanied by the development of pancytopenia (**Figure 2A**). Given this discordance between laboratory improvement and clinical progression, she was referred to another institution on April 24, 2024, for advanced spinal imaging and multidisciplinary evaluation. MetaCAP analysis

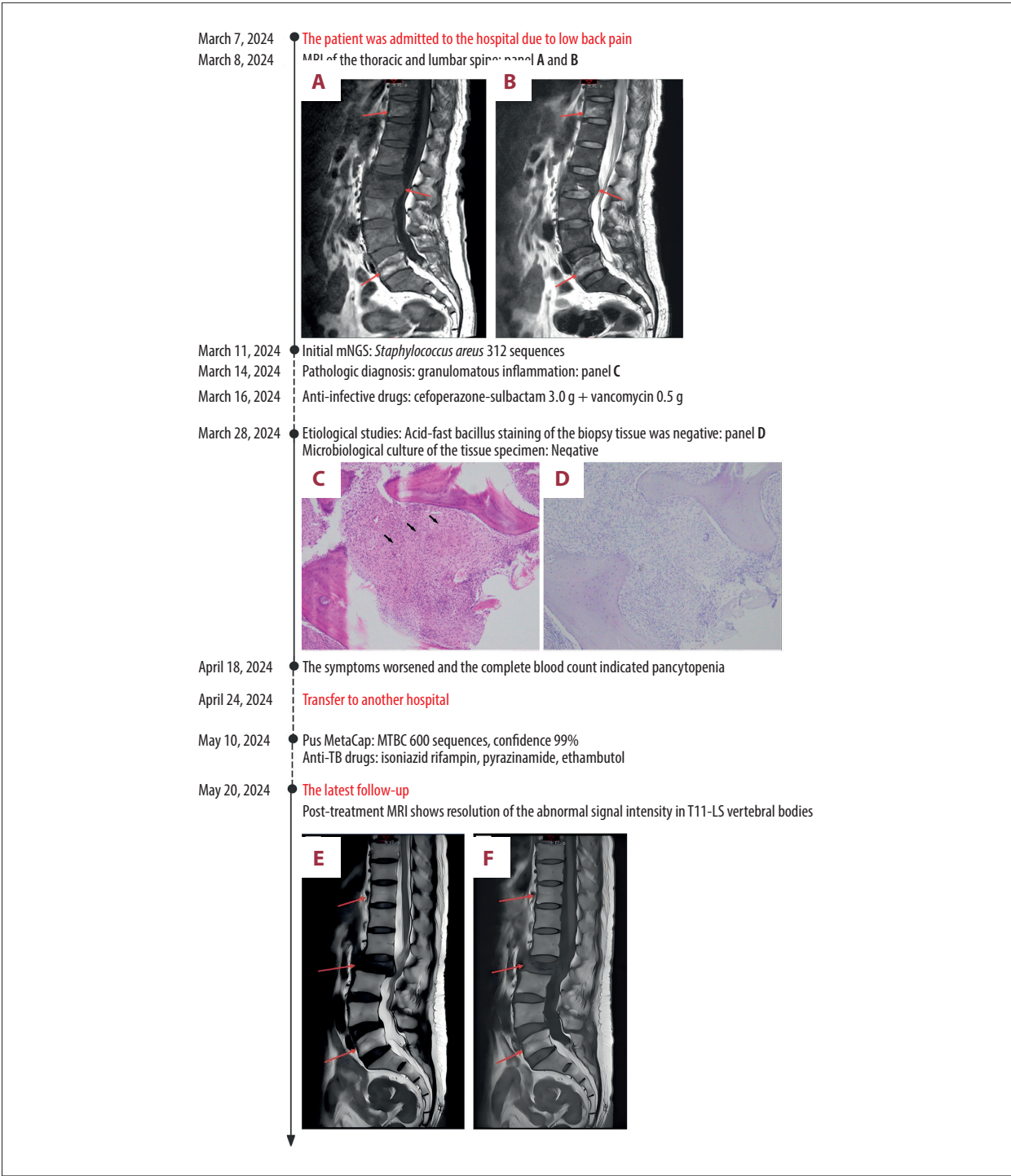


Figure 1. Timeline of the diagnosis and treatment process. (A) Before treatment, T1WI shows hyper-intensity in T11-L5 vertebral bodies (red arrow); hypo-intensity in the L2 vertebral body (red arrow). (B) Before treatment, T2WI shows hyper-intensity in T11, L2, and L5 vertebral bodies (red arrow); mild flattening of the L2 vertebral body (red arrow). (C) L2 vertebral body biopsy pathology: fibrous and epithelial cell hyperplasia with mixed inflammatory infiltration and occasional multinucleated giant cells forming granulomas (black arrow). (D) Acid-fast staining of pathological tissue was negative. (E) After treatment, T2WI shows resolution of the prior hyper-intensity (red arrow). The hypo-intensity in the L2 vertebral body (red arrow) indicates reparative calcification. (F) After treatment, MRI shows resolution of the abnormal signal intensity in T11-L5 vertebral bodies (red arrow). The hypo-intensity in L2 (red arrow) is reparative calcification.

Table 1. Laboratory examination results of the patient.

	Normal range	Mar 7	Mar 11	Mar 23	Apr 18
WBC ($\times 10^9/L$)	3.50-9.50	9.3	18.79	8.93	2.85
NEU ($\times 10^9/L$)	1.80-6.30	6.5	16.59	6.37	1.80
LYM ($\times 10^9/L$)	1.10-3.20	1	0.79	1.14	0.62
PLT ($\times 10^9/L$)	125-350	172	112	106	65
RBC ($\times 10^9/L$)	4.30-5.80	3.34	3.29	2.48	2.08
Hb (g/L)	130-175	101	99	72	66
hs-CRP (mg/L)	0-5	87.9	124.9	51.7	15.9
PCT (ng/mL)	0.000-0.046	4.070	2.870	1.490	0.57
ESR (mm/h)	<21	60	47	-	-
ALB (g/L)	35-55	29.00	28.21	-	-

WBC – white blood cell; NEU – neutrophil; LYM – lymphocyte; PLT – platelet; RBC – red blood cell; Hb – hemoglobin; hs-CRP – high-sensitivity C-reactive protein; PCT – procalcitonin; ESR – erythrocyte sedimentation rate; ALB – serum albumin; ‘-’ – none.

Table 2. mNGS result of spinal surgical specimen.

Genus	Species				
Name	Sequence number	Relative abundance	Name	Sequence number	Relative abundance
<i>Staphylococcus</i>	1823	5.02%	<i>Staphylococcus aureus</i>	312	0.96%
Orthohepadnavirus	1	-	Hepatitis B virus	1	-

‘-’ – none.

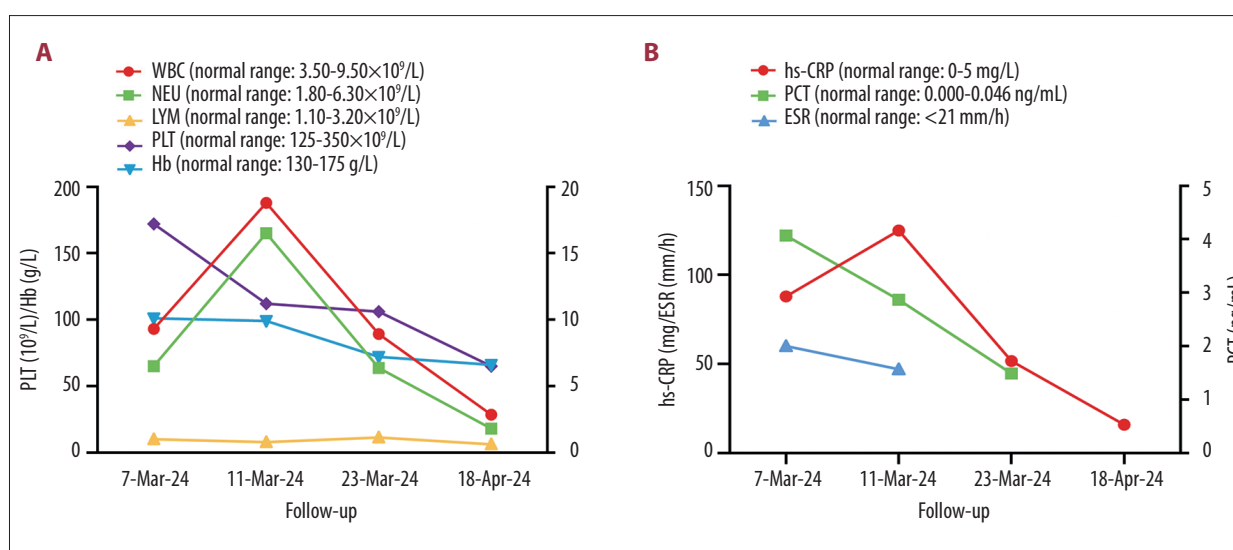


Figure 2. (A, B) Changes in clinical indicators during treatment with anti-infective drugs. WBC – white blood cell; NEU – neutrophil; LYM – lymphocyte; PLT – platelet; RBC – red blood cell; Hb – hemoglobin; hs-CRP – high-sensitivity C-reactive protein; PCT – procalcitonin; ESR – erythrocyte sedimentation rate.

Table 3. MetaCAP result of spinal pus specimens.

Name	Sequence number	Confidence coefficient
Torque teno virus	26	99%
<i>Mycobacterium tuberculosis</i> complex	600	99%

of spinal pus specimens identified 600 sequence reads corresponding to the *Mycobacterium tuberculosis* complex (MTBC), with a confidence coefficient of 99% (Table 3). On this basis, she was diagnosed with spinal TB, and the antimicrobial regimen was immediately revised to anti-TB therapy. Doses were adjusted for her ESRD (estimated glomerular filtration rate <10 mL/min/1.73 m²): isoniazid 200 mg daily, rifampin 450 mg daily, pyrazinamide 1.0 g 3 times weekly, and ethambutol 750 mg 3 times weekly, all administered after hemodialysis. Vitamin B6 25 mg daily was co-administered to ameliorate the adverse effects of the anti-TB drugs.

Following the initiation of anti-tuberculous therapy, the patient demonstrated substantial clinical improvement. Serial imaging showed a marked reduction in lesion size without evidence of progressive spinal deformity (Figure 1E, 1F), thereby reinforcing the diagnosis of TB. Although radiographic evidence of vertebral damage was present, surgical intervention was initially deferred because there was no progression of neurological deficits and she had a favorable early response to medical treatment. During the 6-month follow-up period, she experienced complete pain relief and regained independent ambulation. Subsequent neurological examinations confirmed normal muscle strength, tone, and sensory function in the lower extremities. Deep tendon reflexes remained intact, and no pathological reflexes, including Hoffmann or Babinski signs, were elicited.

Discussion

Spinal TB frequently presents insidiously, with non-specific imaging and laboratory findings that complicate timely and accurate diagnosis; this diagnostic ambiguity commonly leads to misdiagnosis or inappropriate management [10]. In our case, the patient had been receiving long-term MHD and had a history of right renal clear cell carcinoma, yet presented solely with lower back pain and without classical systemic or neurological symptoms. For most clinicians, metastatic bone disease, osteoporotic vertebral fractures, and spinal infections would be the primary considerations within the broad differential diagnosis. Moreover, spinal MRI revealed multilevel vertebral involvement accompanied by disc bulging (Figure 1A, 1B). Although these features are compatible with spinal TB, they

substantially overlap with the imaging characteristics of metastatic disease, indicating that imaging studies alone cannot establish a definitive diagnosis.

Currently, established diagnostic strategies for TB primarily include *Mycobacterium tuberculosis* (MTB) culture, histopathological examination, tuberculin skin testing (TST), AFB smear microscopy, and related phenotypic assays [11]. Although MTB culture remains the standard diagnostic method, its prolonged turnaround time of 4 to 8 weeks and limited sensitivity substantially restrict its value in time-sensitive clinical settings. Histopathological findings may reveal granulomatous inflammation without caseous necrosis, a pattern that lacks sufficient specificity for definitive TB diagnosis. Immunological and microscopic methods are similarly constrained. TST, while simple to perform, is prone to false-positive and false-negative results due to host and environmental factors [12]. AFB smear microscopy is rapid and cost-effective but has low sensitivity and cannot distinguish viable from nonviable organisms; its performance is further diminished in extrapulmonary, pediatric, and HIV-associated TB [13]. Although T-SPOT testing improves sensitivity compared with acid-fast staining, its limited specificity and inability to differentiate active from latent infection reduce its diagnostic reliability [14].

Molecular assays have partially addressed these shortcomings. Polymerase chain reaction (PCR)-based methods are an important advance but require predefined targets, limiting their capacity to detect rare pathogens or mixed infections. Similarly, Xpert MTB/RIF provides rapid and automated detection of MTB and rifampicin resistance, but its diagnostic sensitivity varies considerably depending on the type of extrapulmonary specimen analyzed [15]. These constraints are persistent challenges in accurately diagnosing extrapulmonary TB using conventional diagnostic modalities alone.

To overcome the limited sensitivity and diagnostic uncertainty associated with conventional assays, high-throughput sequencing-based approaches for pathogen detection have emerged, most notably mNGS and targeted next-generation sequencing (tNGS). Among these, MetaCAP is a tNGS-based strategy that utilizes pathogen-specific probe hybridization to enrich target nucleic acids prior to high-throughput sequencing [16].

The mNGS directly sequences all nucleic acids present in clinical specimens without prior selection, allowing comprehensive detection of both known and previously unrecognized pathogens [8]. The standard workflow includes nucleic acid extraction, library preparation, high-throughput sequencing, and extensive bioinformatic analysis. The principal advantage of mNGS is its hypothesis-free detection, obviating the need to predefine suspected pathogens. As a result, mNGS can identify a wide array of pathogens – bacterial, viral, fungal,

and parasitic – within a single specimen [17], offering particular utility in cases of rare or clinically non-specific infections. Moreover, mNGS is especially advantageous in immunocompromised individuals, who are prone to infections by a diverse range of organisms. In comparison, traditional culture techniques generally take 2 to 3 days to produce results, while mNGS can deliver findings in an average of 48 h [18]. Accordingly, mNGS has been successfully applied in the etiological diagnosis of respiratory [9,19], central nervous system [20], bloodstream [21], and osteoarticular infections [22], with good potential for clinical application in infectious disease diagnosis and management [23,24].

Despite these advantages, mNGS exhibited notable limitations in the present case. A major challenge arises from the overwhelming host nucleic acid background. In blood or tissue specimens, host sequences frequently account for more than 95% of the total nucleic acid pool, causing pathogen sequences to be heavily diluted, reducing sensitivity and increasing the risk of false-negative results. In addition, result interpretation remains intrinsically complex. Detected sequences may derive from pathogens, colonizing organisms, or environmental contaminants, making it challenging to differentiate between colonization and active infection. Consequently, diagnostic conclusions based on mNGS are highly dependent on clinical correlation and expert judgment [8,25,26].

tNGS differs from mNGS by focusing high-throughput sequencing on predefined genomic regions, thereby improving sensitivity for pathogen detection. MetaCAP is a representative tNGS platform that integrates probe-based hybrid capture with next-generation sequencing and offers several distinct advantages. Its primary innovation lies in workflow optimization: following nucleic acid extraction, sequencing is not performed in a random manner. Instead, a large panel of pathogen-specific probes is employed to hybridize with target nucleic acids in the sample, enabling forward enrichment of pathogen sequences. The captured targets are subsequently subjected to high-throughput sequencing and bioinformatic analysis [27].

Compared with mNGS, MetaCAP achieves bidirectional pathogen enrichment and supports whole-genome capture, including resistance-associated and independent functional genes, which markedly reduces interference from host-derived background sequences. In addition, the platform allows simultaneous detection of both DNA and RNA, further enhancing diagnostic sensitivity [28]. Owing to its targeted design, MetaCAP substantially reduces sequencing data volume, resulting in lower costs and shorter turnaround times, while improving the accuracy and efficiency of pathogen identification. The clinical utility of tNGS has been demonstrated in infectious disease surveillance and genomic typing during the COVID-19

pandemic [29]. Notably, studies have reported a diagnostic positivity rate of up to 95.6% for tNGS in patients with acute lower respiratory tract infections [30]. Beyond common pathogens, tNGS has also shown robust performance in the detection of rare and atypical organisms, including *Legionella pneumophila*, *Chlamydia* species, *Tropheryma whipplei*, *Scedosporium*, and *Cryptococcus neoformans* [31-33].

Within this methodological context, the diagnostic course observed in our patient becomes more readily interpretable. The initial mNGS analysis failed to detect *MTB*, likely owing to a low pathogen burden and overwhelming host-derived nucleic acid background. In contrast, MetaCAP achieved efficient enrichment of pathogen-derived sequences and successfully identified the *MTBC*, enabling the timely initiation of anti-tuberculous therapy.

Conclusions

This case illustrates that spinal TB exhibits atypical presentations in immunocompromised patients, and that traditional diagnostic methods have limited sensitivity. MetaCAP significantly enhances diagnostic yield through efficient bidirectional pathogen enrichment, providing a valuable tool for early etiological diagnosis of extrapulmonary TB, particularly in cases with negative results using traditional methods. Clinicians can adopt an integrated approach that combines imaging, microbiological detection, and pathomorphology, which serves as a novel diagnostic strategy.

Acknowledgments

The authors thank the patient for providing informed consent for publication of this case. We are grateful to the clinical staff of the Department of Nephrology and the Department of Orthopedics for their dedicated patient care and assistance in data collection. We also thank the laboratory team for their technical support in metagenomic and capture-based sequencing analyses. Their contributions were essential to the completion of this work.

Institution Where Work Was Done

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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