



Mycobacterium xenopi related spine infections: A case report and systematic literature review

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ARTICLE INFO

Keywords:

Mycobacterium xenopi
Spine infections
Predisposing factors
Treatment

ABSTRACT

Background and purpose: Nontuberculous mycobacteria (NTM) disease is an important infection disease throughout the world. *Mycobacterium xenopi* (*M. xenopi*) is a common NTM. Extrapulmonary infections due to *M. xenopi*, particularly spine infections, are a rare occurrence, but lack of research is cited as a constraint for implementing NTM control in such patients. The purposes of this paper are to describe a case of spondylodiscitis, to review the published literature on cases of *M. xenopi* spine infections, and to summarize the predisposing factors, diagnosis, and treatment of infection.

Methods: A case of spondylodiscitis was caused by *M. xenopi* in a patient with systemic lupus erythematosus (SLE). Research was conducted using the PubMed, ScienceDirect, Embase, Wiley Online Library, and Scopus databases using the following search terms: “*Mycobacterium xenopi*”, “vertebral”, “spinal”, “spondylodiscitis”, “infection”, and “osteomyelitis”.

Results: We retrieved 14 cases published before August 2022. The risk factors for infection were iatrogenic infections (3/14, 21.43%), SLE (4/14, 28.57%), AIDS (4/14, 28.57%), and immunocompetence without any comorbidities (3/14, 21.43%). The most common sites of infection were thoracic vertebrae (10/14, 71.43%) and lumbar vertebrae (4/14, 28.57%). A total of 14 cases were isolated and identified as *M. xenopi* from a toad by mycobacterial culture. The identification time was 55.00 ± 7.55 days (the present report identification time of metagenomic next generation sequencing (mNGS) was only 2 days). All patients were treated with antibiotic therapy, and the duration of treatment was 13.18 ± 2.13 months. Clarithromycin-based therapy showed a higher improvement rate (5/6, 83.33%). Surgical intervention was performed in 5 patients. Only 1 patient did not show any improvement after surgical treatment.

Conclusion: *M. xenopi* spine infection in humans presents with atypical clinical symptoms. mNGS identification may be a good choice. *M. xenopi* may be considered in immunocompromised patients with spinal infection. We recommend a clarithromycin-containing regimen and prolonging the duration of treatment to ensure effectiveness.

1. Introduction

Mycobacterium xenopi (*M. xenopi*) is a slow-growing, non-photochromogenic, nontuberculous mycobacterium [1]. It was isolated from the South African toad for the first time in 1959, and then it was found in the natural waters and hospital's hot water system. It was thought that patients were mainly infected by exposure to contaminated soil or water, or by infectious aerosols [2]. Data of species identification

of nontuberculous mycobacteria (NTM) from clinical specimens in 14 countries, including Europe and Asia, have shown an increasing trend of the isolation rate of *M. xenopi* [3]. Pneumonia is the most common infection caused by *M. xenopi*. Extrapulmonary localizations, particularly spine infections, are a rare occurrence [4]. The clinical characteristics and iconography of *M. xenopi* infection are similar to those of *Mycobacterium tuberculosis*. The identification of *M. xenopi* is difficult, and it can be easily overlooked. In this study, we report a case of spine

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<https://doi.org/10.1016/j.oneht.2023.100502>

Received 10 October 2022; Received in revised form 5 February 2023; Accepted 5 February 2023

Available online 11 February 2023

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infection caused by *M. xenopi* and review the published literature on cases of spine infections caused by *M. xenopi*, with a focus on the predisposing factors, diagnostic and therapeutic difficulties to assist future research on this priority disease.

2. Case description

In January 2021, a 32-year-old woman was referred to our hospital because of fever since six days and rash since five days. The patient had a history of systemic lupus erythematosus (SLE) for about 15 years, and it was being treated with prednisolone 10–15 mg daily. In December 2019, the patient was diagnosed with *M. tuberculosis*-related spine infection at another center, and she was treated with quadruple anti-tuberculosis treatment (isoniazid, rifampicin, pyrazinamide, and ethambutol) for 1 year without any improvement. Skin testing revealed anergy to tuberculin. On examination, she was found to be febrile with a body temperature of 39.4 °C. Assessment of her spine showed tenderness in the L2–4 lumbar vertebrae, and a full neurologic assessment revealed no abnormality. The basic laboratory indices showed the following findings: White blood cell (WBC) count $1.77 \times 10^9/L$, erythrocyte sedimentation rate (ESR) 26 mm/h, C-reactive protein (CRP) 67.80 mg/L, and Interferon- γ assays <1.0 (negative). Magnetic resonance imaging (MRI) of the spinal column revealed destruction of the L2–4 discs, with associated abnormal paravertebral soft tissue (Fig. 1a). On the 9th day of

hospitalization, piperacillin/tazobactam therapy was added to the patient's regimen on the basis of quadruple anti-tuberculosis treatment. After the procedures, her fever and rash improved. But the pain was not reduced. On the 13th day of hospitalization, the patient underwent abscess drainage. The result of metagenome next-generation sequencing (mNGS) of the tissue specimen showed *M. xenopi* two days later. Based on the above results, treatment was initiated with a combination of amikacin (0.4 g ivgtt q12 h), rifampicin (0.6 g po Qd), ethambutol (0.75 g po Qd), and clarithromycin (0.5 g po Bid). After 1 month, amikacin therapy was discontinued by the patient herself. Nonetheless, 5 months after the initiation of treatment, the cultures were negative, and the patient's condition had greatly improved. But MRI of the spinal column revealed that the abscess had increased in size. The patient's drug regimen was subsequently modified to rifampicin (0.6 g po Qd), ethambutol (0.75 g po Qd), clarithromycin (0.5 g po Bid), and levofloxacin (0.5 g po qd). After 1 month, MRI of the spinal column still showed that the abscess had further slightly increased in size further. Linezolid (0.6 g po q12 h) was added to the original drug regimen. After 4 months, linezolid therapy was discontinued because of numbness in both lower limbs and chills. After another 7 months, MRI of the spinal column revealed that the abscess had significantly reduced in size, and the degree of enhancement of vertebral lesions was significantly lower than that on the earlier MRI (Fig. 1b). Her pain was also markedly improved. We plan to continue a 2-year course of antimycobacterial

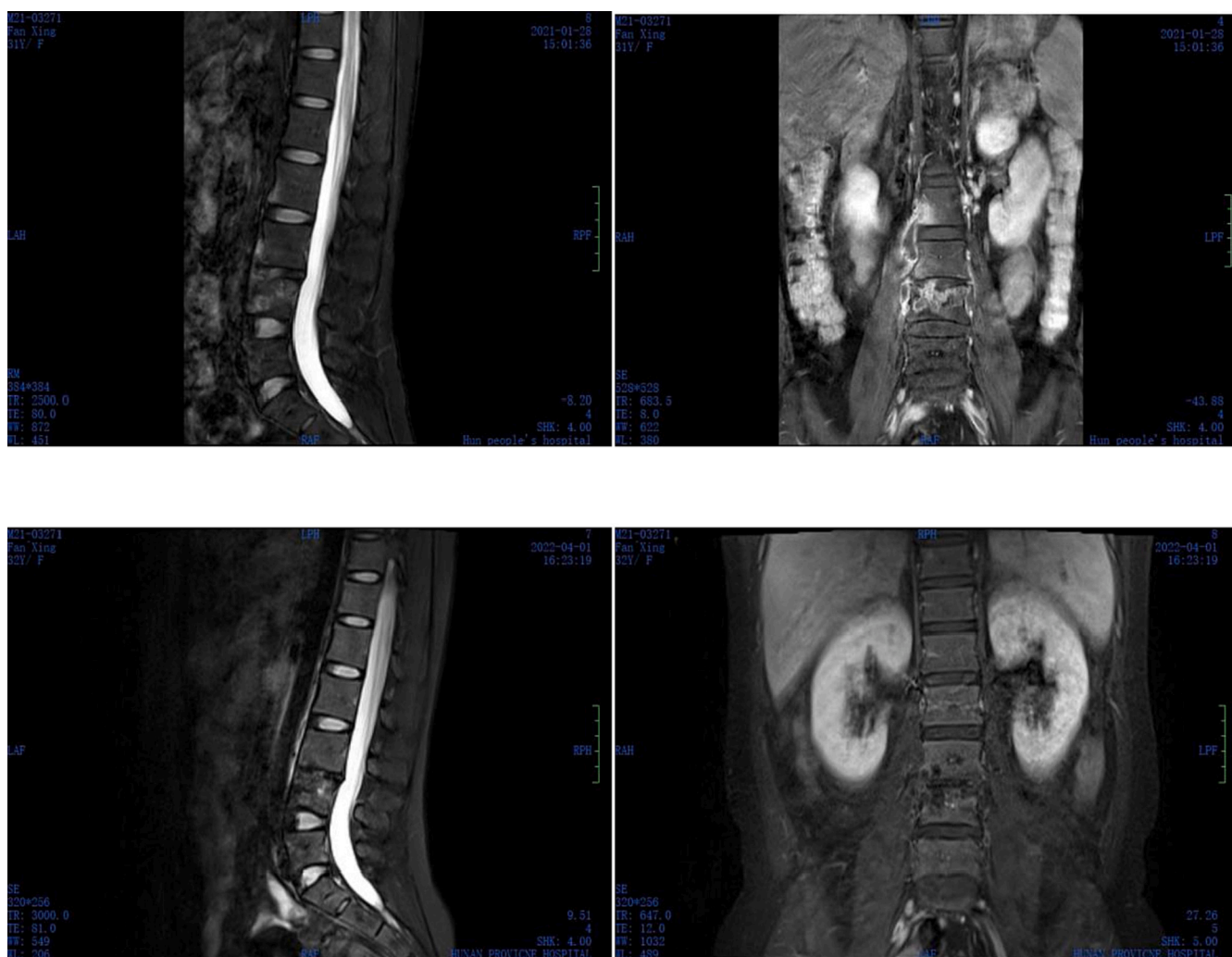


Fig. 1. A T2-weighted sagittal and coronal magnetic resonance image of the lumbar spine.

a: At admission: Image showing L2, L3, and L4 bone destruction and a paravertebral soft tissue mass.

b: After anti-*M. xenopi* treatment: Image showing a significantly reduced degree of enhancement in L2, L3, and L4 vertebrae and abscess shrinkage.

therapy, and then to monitor the relapse risk in the patient.

3. Materials and methods

We conducted a review of case reports and case series published before August 2022. No restrictions based on the language or year of publication were applied.

3.1. Search strategy

The following databases were searched for relevant studies: PubMed, ScienceDirect, Embase, Wiley Online Library, and Scopus using the following search terms: “*Mycobacterium xenopi*”, “vertebral”, “spinal”, “spondylodiscitis”, “infection”, and “osteomyelitis”. The study flow is described in Fig. 2.

3.2. Inclusion and exclusion criteria

Inclusion criteria: all case reports of adult patients diagnosed with spine infections caused by *M. xenopi* for whom the treatment and outcome were specified. Exclusion criteria: (1) A case report on other sites of infection (pulmonary or extrapulmonary); (2) Lack of clinical data of individual patients; (3) Unpublished reports, book paragraph, and meeting abstracts.

3.3. Data collection

Clinical data and medication were entered into a pre-designed Excel file. The following information was extracted from each paper: (1) Characteristics of patients (sex and age); (2) Infection characteristics, site of infection, predisposing factors, underlying diseases, symptoms, and laboratory examination results; (3) Treatment; (4) Outcome after treatment.

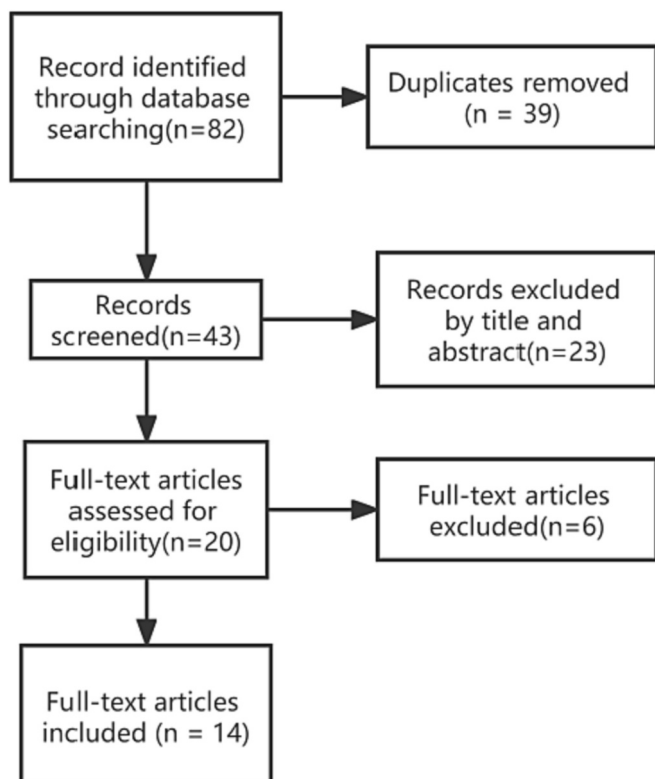


Fig. 2. Study flow chart.

4. Results

As shown in Fig. 2, a total of 14 articles were included in the study, accounting for 14 patients (Table 1). Both sexes were equally affected, with 7 females (including 4 patients with SLE) and 7 males (including 4 HIV patients). The mean patient age was 50.57 years. A total of 10 cases of infection in the thoracic vertebrae were identified. All patients had clinical symptoms. A total of 7 cases had purified protein derivative (PPD) skin test records, and only 1 case was positive. The results of pathological examination were recorded in 11 cases, and 10 cases showed granulomatous inflammatory changes. The results of staining smear examination were recorded in 8 cases, and acid-fast bacilli (AFB) were found in 3 cases. All 14 cases were identified as *M. xenopi* by microbial culture, and the identification time was 55.00 ± 7.55 days. All patients were treated with drug combinations (i.e., at least two antibiotics), but the regimens varied widely (Table 1). A rifamycin (rifampin) regimen was used in 13 patients; and ethambutol was used in 13 cases, isoniazid was used in 9 cases, pyrazinamide was used in 6 cases, clarithromycin was used in 6 cases, fluoroquinolones were used in 5 cases (ciprofloxacin, moxifloxacin, pefloxacin, and levofloxacin), and azithromycin was used in 1 case. A total of 11 cases showed improvement in clinical symptoms and/or imaging, of which 1 case recurred and was cured by surgery combined with drug therapy. Among the cases treated with clarithromycin-based regimen, 5 cases improved and 1 case did not improve. Among them, One case each including isoniazid or quinolones was improved. In the non-clarithromycin or azithromycin treatment, the combination of isoniazid and rifampicin was mainly used; with 6 cases showing improvement and 3 cases not showing any improvement. A total of 5 cases received surgical treatment. The duration of treatment was 13.18 ± 2.13 months. The results are shown in Tables 1 and 2.

5. Discussion

NTM are ubiquitous in the environment. *NTM* infections are rarely transmissible between humans and epidemic cases [19], and they are often associated with contaminated water, soil, or aerosols [2]. It is postulated that susceptible individuals acquire disseminated infections through respiratory and digestive tract colonization [19]. *M. xenopi* is the third most common *NTM* isolated from pulmonary samples in Europe, and it is less commonly isolated in Asia, USA, and Australia [20]. *M. xenopi* is widely isolated from environmental sources, such as water, soil, and tap water systems. The most common clinical manifestation of *M. xenopi* infection is lung disease. However, spine infection caused by *M. xenopi* is a rare occurrence [21–23]. The pathogenic factors underlying *NTM* disease have not been fully understood. Current studies indicate that patients, and environmental and bacteriological factors interact to create a ‘susceptible host’ [24]. Immunodeficiency is a non-negligible risk factor, especially in female SLE patients and HIV patients [25,26]. Immunocompetent patients usually acquire infection by direct penetration of the pathogen as a result of a penetrating injury or contamination during surgical procedures [27,28]. In the present study, there were 11 (78.57%) cases of SLE, HIV, and surgical contamination. In addition, the mean age of immunocompetent patients (non-surgical contamination) was 74.00 ± 1.70 years. It should be noted that increasing age may be an independent risk factor for spinal infection in elderly patients [8].

This study suggested that the most common sites of *M. xenopi* infection are the thoracic and lumbar vertebrae. Walid Osman proposed that tuberculosis of the spine occurs by hematogenous spread of infection from a pulmonary or extrapulmonary site. The infection may begin in the subchondral bone and spread slowly to the intervertebral disc space and adjacent vertebral bodies, usually in the lower dorsal and upper lumbar spines in the absence of pulmonary infection [29,30]. The most common site of infection for spinal tuberculosis is also the thoracolumbar spine. Therefore, it is considered that *M. xenopi* may have a similar infection pathway as *M. tuberculosis*.

Table 1
Features of the 14 reported cases of *M. xenopi* spinal infections.

Ref	Age (y)/sex	Site of infection	Predisposing factors	Underlying diseases	Presenting symptoms	biomarker	MT	QFT	Histopathologic	Acid-fast staining	Time to species identification	Medical therapy (duration in months)	surgery	Outcome
[5]	44/M	T9/10	HIV, Kaposi's sarcoma (not on HAART)	coronary artery bypass graf	Chest pain and notalgia(1d)	/	/	-	/	/	/	CCR, R, E, MXF	No	unkown
[6]	55/F	L3	systemic lupus erythematosus (15y,prednisolone 5 mg daily.)	None	left loin pain, nausea and weight loss. 1y)	ESR:55 mm/h	-	/	Granuloma	-	4 m	1. E(2 m), R, I (16 m) 2. S, I, R, P(2 m)	No	1. Persistence of infection 2. Clinical and radiographic improvement
[7]	28/M	T10	HIV	None	back pain(10y), nocturnal awakening, sweating, weight loss, fever (3y)	CRP:38 mg/L, WBC:13.7/nL, ESR:40 mm/h, CD4T-cell:400cells/mm ³ CD4/CD8:0.5	/	/	Granuloma	-	/	Rfb, I, E, CCR (6 m)	Yes	Clinical and radiographic improvement
[8]	75/F	T6/7	None	None	back pain and night sweats. (6w)	ESR:79 mm/h	-	/	Granuloma	+	8w	1. R, P, I, E (2 m) 2. R, E(22 m)	Yes	1.Clinical improvement 2.Clinical and radiographic improvement Clinical and radiographic improvement
[9]	33/M	T11/12	HIV, CD4 count was 20 cells/mm ³	primary Pneumocystis carinii pneumonia	back pain and night sweats(2 m)	WBC:14.86*10 ⁹ /L; NE:11.56*10 ⁹ /L; ESR:18 mm/h; CD4:490cells/mm ³	/	/	Granuloma	+	/	R, E, I(6 m)	No	Clinical and radiographic improvement
[10]	56/F	T8/9	SLE(20y);low-dose corticosteroids and azathio prine.	/	Left shoulder pain and notalgia(2 m)	ESR:31 mm/h	/	/	without granuloma	/	7 W	I, CCR, C(9 m)	No	Clinical and radiographic improvement
[11]	70/F	T3/4	/	Hypertensie cardiovascular disease; II diabetes mellitus; Radical left mastectomy	Back pain; weakness of both legs(6w)	WBC:5700/mm	-	/	Granuloma	-	/	1. R, P, I(4 m) 2. R, P, I, CCR, E(4 m) 3. P, I, CCR, E (4 m) 4. Continue the 3 program for a total of 2 years.	Yes	1. Radiographic improvement 2. No clinical change 3. Radiographic improvement4. no record
[12]	46//F	T8/9	SLE(15); prednisolone (10 mg daily)	pyelonephritis of the right kidney, mitral valve insufficiency and aphasia	Skelasthenia, walking disorder and notalgia(10 m)	ESR: 27 mm/h; CRP:49.7 mg/L	/	-	Granuloma	-	37d	E, Rfb, A(5 m)	Yes	Clinical and radiographic improvement
[13]	77/F	L1/2	Her husband had tuberculosis 40 years previously.	hypertension	lower back pain radiating to the right buttock. (5y)	ESR:54 mm/h	/	/	/	-	2 m	1. R, I, P和E(2 m); 2. R, I, P, E, C (1y, it's planned to continue	No	1. Clinical improvement; 2. Clinical improvement

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Table 1 (continued)

Ref	Age (y)/sex	Site of infection	Predisposing factors	Underlying diseases	Presenting symptoms	biomarker	MT	QFT	Histopathologic	Acid-fast staining	Time to species identification	Medical therapy (duration in months)	surgery	Outcome
[14]	42/M	T7/8	HIV	Pneumocystis carinii pneumonia	flaccid paralysis of both legs(2w)	CD4:41/mm ³	-	/	without granuloma	-	6w	these for 2 years. 1. R, I, P, E(2 m) ; 2. I, E, CCR, Rfb (unkown)	No	1. Clinical and radiographic improvement 2. Unknown
[15]	61/M	L3/4	a history of L3-L4 and L4-L5 percutaneous nucleotomy performed 15 years earlier (in 1992)	None	pain in the low back and left buttock. (6 m)	Normal	-	/	Granuloma	+	8w	1. CCR, R, E(4 m)。 2. CCR, R(14 m)。	No	1.Clinical and radiographic improvement 2. Recovery
[16]	28/M	L4/5	percutaneous nucleotomy as treatment of sciatica at the L5 level due to a herniated disk at the L4-L5 level before a month	None	lumbar spine pain	ESR:32 mm/h CRP:10 mg/L WBC:7500/mm	+	/	Granuloma	/	2 m	1. R, E, I, P(2 m) 2. Pe, CCR, E (18 m)	No	1.Persistence of infection ; 2.Recovery
[17]	30/F	T10/11	SLE(15);prednisone (15 mg daily)	None	Back pain	ESR:30 mm/h	+	/	/	+	4w	I, R, E, P(18 m)	Yes	1.Clinical and radiographic improvement ; 2. relapsed after 9 mo off treatment; Clinical improvementwith debridement and antituberculous medication. Persistence of infection ;
[18]	63/M	T12/L1	A needle biopsywas performed at T12-L1 before 10 years	T12-L1nondisplaced fracture; myocardial infarction.	back pain (20y)	/	-	/	without ganuloma	/	6w	Le, R, E, CCR (10.5 m)	Yes	Persistence of infection ;

Note:clarithromycin(CCR), rifabutin(Rfb), rifampicin(R), isoniazid(I), ethambutol(E), pyrazinamide(P), streptomycin(S), ciprofloxacin(C), pefloxacin(Pe), moxifloxacin(MXF), levofloxacin(Le), azithromycin(A).

MT: Mantoux test; QFT:Quantiferon test for TB.

-: Negative; +: positive; /:no record.

d: day; m: month; y:year.

Table 2
Characteristics of the 14 cases of spine infection due to *M. xenopi*.

Parameter		Total	immunocompetent	Cases with iatrogenic infections	Cases with SLE	Cases with HIV
Sex	Male	7	0	3	0	4
	Female	7	3	0	4	0
Age(y)		50.57 ± 4.45	74.00 ± 1.70	50.67 ± 9.27	46.75 ± 5.21	36.75 ± 3.27
Site of infection	Thoracic vertebra	10	2	1	3	4
	Lumbar vertebra	4	1	2	1	0
Pre-treatment biomarkers (↑/normal/no record)	WBC	1/7/6	0/2/1	0/2/1	0/2/2	1/1/2
	ESR	6/2/5	2/0/1	1/1/1	3/0/1	0/1/3
	CRP	1/1/12	0/0/3	0/1/2	1/0/3	0/0/4
Biomarkers after treatment (↓/normal/no record)	WBC	1/7/6	0/2/1	0/2/1	0/2/2	1/1/2
	ESR	6/2/5	2/0/1	1/1/1	3/0/1	0/1/3
	CRP	1/1/12	0/0/3	0/1/2	1/0/3	0/0/4
Tuberculosis test (+/-/no record)	MT	4/4/6	2/1/0	1/1/1	0/2/2	1/0/3
	QFT	0/2/12	0/0/3	0/0/3	0/1/3	0/1/3
Histopathologic	Granuloma	11	2	2	2	3
	without granuloma	2	0	1	1	0
	no record	2	1	0	1	1
microorganism	Acid-fast staining(+/-/no record)	3/5/6	0/1/2	1/0/2	1/2/1	1/2/1
	Identification time(m)	55.00 ± 7.55	58 ± 2	58.50 ± 4.46	36.28 ± 18.14	42
treatment	Antibiotic	9	1	3	2	3
	Antibiotic+surgery	5	2	0	2	1
outcome	Improvement	4/7	1/2	1/1	2/1	0/3
	Relapse	2	/	1	1	/
	Unkown	1	/	/	/	1

Previous reports have indicated that the ESR or CRP level is increased in spinal tuberculosis and it tends to decrease after initiation of treatment, and that patients with poor prognosis tend to have a higher ESR during treatment than those with good prognosis [31]. Among the cases with recorded biomarkers in this study, mainly ESR, most of the biomarker levels were increased and decreased significantly after treatment. It can be considered that the inflammatory state caused by *NTM* infection may be similar to that of *M. tuberculosis*, and the level of inflammation is affected by the disease, although a study found a significant difference in the CRP and procalcitonin (PCT) levels between SLE patients and SLE patients with an infection [32]. Nevertheless, some studies do not support the widespread use of ESR, CRP, or PCT to diagnose infection in SLE inpatients due to the increased risk of heterogeneity and bias [33,34], which requires further investigation.

This study showed that it should be carefully considered whether PPD skin test results can be used as exclusion criteria for *M. xenopi* spinal infection, with a positive to negative ratio of 1:1 in PPD skin test results. The microbial culture and identification time of *M. xenopi* is long, with an average time period of 55.00 ± 7.55 days; thus, the best treatment time can be easily delayed. Metagenome next-generation sequencing analysis of BALF samples has high accuracy in the differential diagnosis of MTB and *NTM* [35]. According to the mNGS results interpretation guidelines [36], high-grade pathogenic agents, such as *M. tuberculosis* and *cryptococcus neoformans*, may be pathogens in most types of samples. This article reported that mNGS identification of *M. xenopi* only took only two days and was accurate. Therefore, on the basis of absence of microbial culture results, mNGS may be a good choice for timely and effective treatment of patients.

The treatment plan for spinal infection caused by *M. xenopi* mainly refers to pulmonary infection, and the best treatment regimen and duration have not yet been determined. An in vitro drug susceptibility test showed that clarithromycin and moxifloxacin had the lowest MIC values and ethambutol/rifampicin combined with clarithromycin or moxifloxacin had significant bactericidal activity against *M. xenopi*.

[37,38]. Nevertheless, the response of this organism to treatment is variable and not always well correlated with the results of in vitro susceptibility. Amikacin-containing regimens are most effective in rat models of *M. xenopi* infection [39]. The guidelines [40] pointed out that reasonable treatment options may include isoniazid, rifabutin or rifampicin, ethambutol, and clarithromycin. Streptomycin may or may not be added in the initial regimen. The duration of treatment is 12

months after a negative culture. But the recurrence rate is high, even if a regimen containing macrolides is used. Experts also supported the claim that [41] reasonable treatment options include amikacin (the first three months of treatment), clarithromycin/azithromycin, rifabutin/rifampicin, moxifloxacin/linezolid, and ethambutol. The duration of treatment lasts at least 1 year after a negative culture. The difference between the two options is the recommendation of amikacin, isoniazid, and linezolid. The latter is recommended based on in vitro susceptibility. The vast majority of *M. xenopi* pathogens are sensitive to rifabutin, macrolides, moxifloxacin, and linezolid, and they are moderately sensitive to isoflurane, rifampicin, ethambutol, and ciprofloxacin [42–44].

Previous studies have suggested that *M. xenopi* pulmonary infection can achieve good results after standard treatment [45,46]. In this study, most of the cases of spinal infection were significantly improved after treatment, but the combination of drugs and the duration of treatment were quite different. The improvement rate of clarithromycin-based treatment was 83.33%, while the success rate of non-clarithromycin-based treatment was 66.67% (excluding azithromycin). It can be suggested that the success rate of clarithromycin treatment for spinal infection caused by *M. xenopi* may be higher. The efficacy gap was not obvious for the regimen included isoniazid or quinolones. Infection in the case reported in this article was aggravated by the quadruple anti-tuberculosis regimen. The abscess continued to increase in size after isoniazid was replaced with clarithromycin, but infection was improved after clarithromycin was combined with levofloxacin. This confirms the treatment variability of spinal infection caused by *M. xenopi*. The evaluation and adjustment of clinical treatment are based on the actual treatment effect. In addition, some cases with poor drug treatment achieved cure or improvement after surgical treatment and post-operative anti-*NTM* treatment; thus, suggesting that surgical debridement may also be an important factor in the success of treatment.

In conclusion, spinal infections caused by *M. xenopi* are still a challenging issue due to the rarity of occurrence and complexity of treatment. We have summarized and updated the predisposing factors, diagnosis, and treatment of 14 cases of *M. xenopi* spinal infection through a systematic review. We have suggested that prolonged antibiotic therapy (≥ 12 months, according to the efficacy can be extended to 24 months, possibly including clarithromycin-based combination with rifampicin/rifabutin, ethambutol, isoniazid, or quinolones) is indicated for the treatment of *M. xenopi* spinal infections. Nevertheless, this study has several shortcomings. The first limitation is the small

number of cases, especially long-term follow-up cases. Secondly, there may be some differences in the collected information of different case reports. Although there are some limitations, this study has a certain reference value for the clinicians to help identify, diagnose, and treat spinal infection caused by *M. xenopi*.

Ethics statement

Consent was provided by the patient and her parents to enable anonymized reporting of the results of this study.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

CRediT authorship contribution statement

Min Peng: Conceptualization, Software, Validation, Investigation, Resources, Writing – original draft. **Wei Li:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – review & editing, Supervision. **Fengyi Li:** Methodology. **Bo Tang:** Methodology, Software. **Yinhua Deng:** Validation. **Shuai Peng:** Resources. **Li Chen:** Visualization. **Yingchun Dai:** Visualization.

Declaration of Competing Interest

None.

Data availability

Data will be made available on request.

Acknowledgments

None to declare.

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