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Original Article

Characteristics of *Talaromyces marneffei* with bone destruction in Guangxi Province, China: a retrospective study

Yiguang Bai[1,2*], Deshuang Xi[3*], Qiaoling Chen[4*], Zhuohua Shi[1], Bocheng Wen[1], Qiong Zhang[5], Quan Zhou[6,7], Yanan Zhang[6], Haibin Nong[1], Gaofeng Zeng[5], Shaohui Zong[1,8]

[1]Department of Spine Osteopathia, The First Affiliated Hospital of Guangxi Medical University, Guangxi Medical University, Nanning, Guangxi, China; [2]Department of Orthopaedics, Nanchong Central Hospital, The Second Clinical Institute of North Sichuan Medical College, Nanchong, Sichuan, China; [3]Department of Spine Surgery, Liuzhou Worker Hospital, The Forth Affiliated Hospital of Guangxi Medical University, Liuzhou, China; [4]Department of Oncology, Nanchong Central Hospital, The Second Clinical Institute of North Sichuan Medical College, Nanchong, Sichuan, China; [5]College of Public Hygiene of Guangxi Medical University, Guangxi Medical University, Nanning, Guangxi, China; [6]Collaborative Innovation Center of Guangxi Biological Medicine, Guangxi Medical University, Nanning, Guangxi, China; [7]Department of Emergency, The Hongqi Hospital Affiliated to Mudanjiang Medical University, Mudanjiang, Heilongjiang, China; [8]Research Centre for Regenerative Medicine and Guangxi Key Laboratory of Regenerative Medicine, Guangxi Medical University, Nanning, Guangxi, China. [*]Equal contributors.

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Abstract: Background and objective: This study retrospectively analyzed the clinical and imaging features of TM mycosis complicated with bone destruction with the aim to improve understanding, diagnosis, and treatment. Methods: Data of hospitalized TM-infected patients with bone destruction from October 2012 to May 2019 were collected. The clinical and imaging features of the disease were comprehensively analyzed. Results: All 35 patients were non-HIV infected, but some had underlying co-morbid illnesses. The duration of the disease was 1-36 months (median: 5 months). Fever, anemia, weight loss, and respiratory symptoms were the main clinical manifestations of the patients. There were 18 patients (51.4%) who had bone pain. Peripheral blood leukocyte count increased significantly in 27 patients (77.1%). The neutrophil count increased in 28 patients (80%). C-reactive protein (CRP) and immunoglobulin G levels increased in 93.3% (14/15) and 82.1% (23/28) patients, respectively. The imaging examination showed osteolytic lesions, which were multiple in several bony areas. Conclusion: Young and middle-aged patients with non-AIDS TM complicated with underlying diseases should be especially cautious in case of occurrence of bone destruction. The main clinical manifestations of patients with TM complicated with bone destruction were pulmonary symptoms and bone and joint pain, which could be accompanied by progressive consumptive diseases.

Keywords: Talaromyces marneffei, osteolytic lesion, retrospective study

Introduction

Talaromyces marneffei (TM) causes a type of mycosis that is prevalent in Southern China and Southeast Asia [1-3]. TM mycosis can involve the skin, respiratory system, digestive system, and reticuloendothelial system, resulting in local or disseminated infection [4]. Animal studies have shown that rats were infected with TM by inhaling atomized conidia in the environment. The respiratory system is often the first to be invaded by the fungus [5-8].

In 1984, Thais first reported bone destruction in patients with TM disease [9]. Chan et al. in 1990 and Deng in Guangxi in 1994 also reported bone destruction [10, 11]. Jing et al. reported 14 patients with disseminated TM infection complicated with bone disease, suggested that the bone lesions of patients with HIV-negative TM disease were often ignored. In clinical practice, we found that TM disease can sometimes be associated with bone pain. Imaging examination can detect bone destruction in the spine and ribs. It is still not clear why TM infections

cause bone destruction. Clinical features that can identify bone destruction, other than imaging examination, is also unclear. It is very important for orthopedic doctors to determine bone destruction in patients in a timely fashion and prevent the occurrence of pathological fractures, to reduce the disability rate associated with TM infection and improve the overall quality of life of patients.

In clinical practice, TM infection is often misdiagnosed as tuberculous disease. Due to the untimely diagnosis and treatment, TM disease is often progressive, which leads to a series of fatal conditions such as respiratory complications [5, 7, 8], that greatly reduce the survival rate of patients. In this study, we retrospectively analyzed patients with TM with bone destruction who were hospitalized at the First Affiliated Hospital of Guangxi Medical University from October 2012 to May 2019. Descriptive analysis of the clinical, laboratory examinations, imaging, and characteristic features were performed.

Clinical data and methods

Study participants and research methods

Inclusion criteria: patients were clinically diagnosed of TM (fungal culture TM positive, or pathological diagnosis, and polymerase chain reaction [PCR], next-generation sequencing technology [NGS] and other molecular diagnosis of TM infection); patients whose CT, ECT or PET-CT, and other imaging data showed bone destruction.

Exclusion criteria: patients without etiological evidence of TM infection; patients complicated with other bone-destruction diseases; patients with incomplete clinical data.

Diagnostic criteria of TM: (i) Pathogens were isolated and cultured from clinical samples (peripheral blood, bone marrow, lymph nodes, sputum, bronchoalveolar lavage fluid, skin lesions, and lung biopsy) during hospitalization. Positive results were identified by Microbiology Department of the First Affiliated Hospital of Guangxi Medical University. (ii) TM were isolated and cultured from clinical samples obtained from patients.

Diagnostic criteria of TM with bone destruction: (i) Diagnosed with TM infection; and (ii) disseminated TM infection (involving more than two systems), with ECT, CT, and other imaging examination showing bone damage, after ruling out other osteolytic diseases such as tuberculosis, tumors, hematopathy, and other fungal infections like African histoplasmosis, cysticercosis, and cryptococcosis [4].

The electronic medical record system of our hospital searched to identify patients diagnosed with TM, from May 2012 to June 2019. After eliminating duplicates and incomplete medical records, the remaining medical records were screened according to the inclusion criteria and exclusion criteria. Finally, 35 cases of TM complicated with bone destruction were selected. For patients with multiple hospitalization records, the data at first diagnosis was considered. Included patients' data were retrospectively analyzed. The clinical baseline data of the patients, including demography (age distribution and sex ratio) were collated. The patients' symptoms (fever, bone pain, cough, and dyspnea), clinical signs (site of enlarged lymph nodes, weight changes, pleural effusion, and ascites) and the proportion of underlying disease were collated and analyzed. We collated and analyzed the laboratory examination results of patients, including blood and urine routine examination, liver and kidney functions and blood electrolytes examination, inflammatory indicators, and immune function. The CT, ECT, and PET/CT images were collected to understand the pulmonary manifestations and the distribution of bone destruction in the whole body. The positive rate of TM bacterial spores in the lesions was investigated by referring to the pathological reports. Medical records and telephone follow-up were collected to evaluate the treatment and prognosis of the patients.

Statistical analysis

Normal distributed continuous variables were expressed as mean ± standard deviation. Non-normal distributed data were expressed as median and interquartile range. Categorical data were expressed as frequency (percentage). U-test was used to compare non-normal distributed data between groups. R language software (3.6.1) was used for all statistical analyses. The elegant and versatile R package ggplot2 and ggpubr were involved in this study. When compared, the non-normal distributed data, methods are specified as "two-sided test" and "unpaired data".

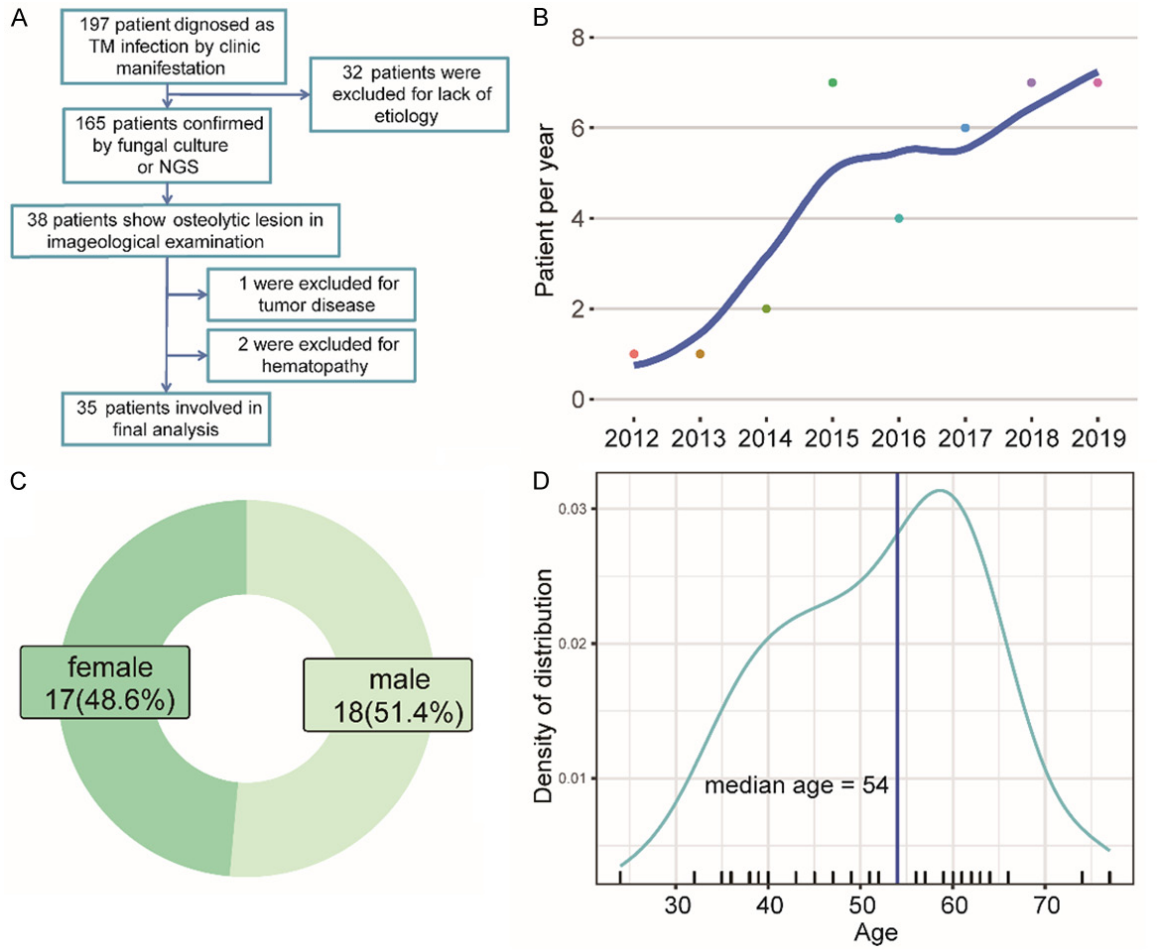

Figure 1. Case selection and clinical base line. A. Flow chart of case screening; B. The figure shows that the number of cases of TM disease with osteoclast increased per year; C. Circle diagram showed the sex ratio of TM patients with bone destruction; D. The median age of the patients is 54 years. The carpet icon below shows the actual age distribution.

Results

Clinical baseline data

According to the inclusion and exclusion criteria, 165 patients were diagnosed with TM in the First Affiliated Hospital of Guangxi Medical University from May 2012 to June 2019. Upon reviewing the clinical and imaging data of the patients, 38 patients showed bone destruction. Three patients were excluded (2 had leukemia and one had tumor recurrence). A total of 35 patients were included in the final analysis. The patient screening process is shown in **Figure 1**.

From 2012 to 2019, 35 cases of TM disease with bone destruction were diagnosed in our hospital. The number of new diagnoses increased year by year, with an average of 4.3 new cases per year. Male patients accounted for 51.4% (18/35), with a median age of 54 years old (range: 24-77 years old) (shown in **Figure 1**).

The mean time from onset of clinical symptoms to diagnosis of TM was 7 months (range: 1-36 months; median: 5 [3-9]). In the study population, some of the people had a history of smoking and drinking and associated underlying comorbid diseases, as shown in **Figure 2**. All the patients in this study were HIV negative.

Main symptoms and signs

With respect to clinical symptoms, 10 (28.6%) had varying degrees of fever, mainly moderate fever (38.1-39°C), 16 (45.7%) had cough and

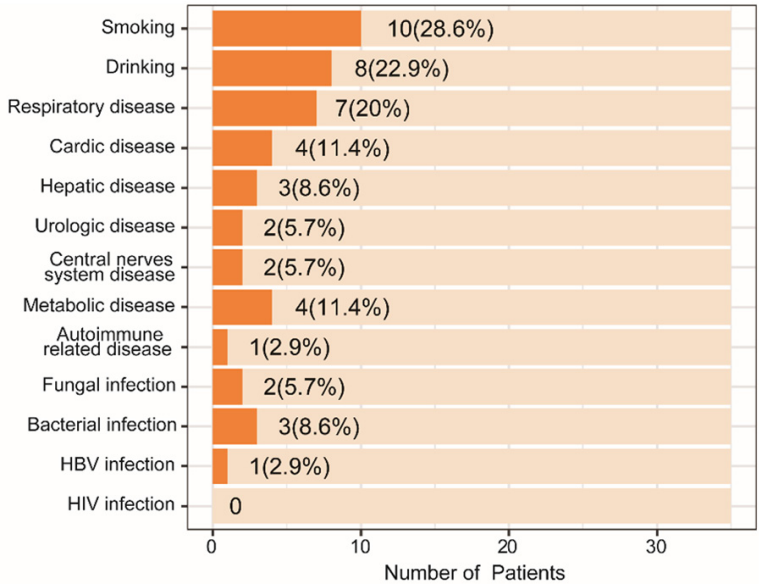

Figure 2. Demographic data and distribution of underlying disease.

Table 1. Symptoms of TM-infected patients with bone destruction

	Total population (n=35)	
	Number of patients	Percent (%)
Fever Grade		
Hyperpyrexia	3	8.6
Moderate pyrexia	6	17.1
Low pyrexia	1	2.9
Bone pain	18	51.4
Cough and expectoration	16	45.7
Dyspnea	6	17.1
Chest pain	7	20.0
Hemoptysis	1	2.9
Abdominal pain	1	2.9
Diarrhea	1	2.9
Weight loss	24	68.6
Anemia	31	88.6

expectoration, and six (17.1%) had dyspnea. Seven patients (20.0%) had chest pain and one patient (3.2%) had hemoptysis. Weight loss was common and observed in 18 (58.1%) of 31 patients (**Table 1**).

Bone pain is a characteristic manifestation of patients with bone destruction. Eighteen patients (51.4%) in this study had bone pain; 31 patients (88.6%) had varying degrees of anemia, with most of them being moderately anemic (60 g/L<Hg<90 g/L); and eight patients (25.8%) developed skin lesions such as rashes or skin ulcers. More than half of the patients with bone destruction had superficial lymph node enlargement. The frequency of occurrence was cervical lymph node enlargement (n=17, 48.6%); axillary lymph node enlargement (n=11, 31.4%); supraclavicular lymph node enlargement (n=8, 22.9%), and inguinal lymph node enlargement (n=8, 22.9%) as shown in (**Table 2**).

Deep lymph node enlargement was mainly seen in the hilar and mediastinal lymph nodes (n=17, 48.6%) and abdominal lymph nodes (n=2, 5.7%). Pleural effusion may have occurred in some patients (n=12, 34.3%), but only one patient had ascites. Splenomegaly occurred in four patients and hepatomegaly in one (**Table 2**).

Laboratory examination

Blood routine examination showed that 25 (71.4%) patients with TM disease complicated with bone destruction showed an increase in white blood cell count (WBC>10×10^9/L) (mean: $21.1\pm6.6\times10^9$/L). Accordingly, The neutrophil count in these patients also increased (mean: $17.4\pm6.7\times10^9$/L). Thirty-one patients (88.6%) had decreased hemoglobin (male <115 g/L, female <110 g/L) (mean: 77.4±11.2 g/L). Other blood routine and biochemical examinations are shown in **Tables 3** and **4**.

Overall, 33/34 (97%) patients had elevated erythrocyte sedimentation rate (ESR) and 14/15 (93.3%) had elevated CRP and hypersensitive CRP tests. In terms of immune function, IgA, IgG, and IgM increased in nine (32.1%), 23 (82.1%), and nine (32.1%) patients respectively, among the 28 patients who underwent three immune protein tests (**Table 5**).

Table 2. Clinical signs of TM-infected patients with bone destruction

	Total population (n=35)	
	Number of patients	Percent (%)
Skin lesions	12	34.3
Superficial lymphadenopathy	22	62.9
Cervical lymphadenopathy	17	48.6
Axillary lymphadenopathy	11	31.4
Supraclavicular lymphadenopathy	8	22.9
Inguinal lymphadenopathy	8	22.9
Abdominal lymphadenopathy	2	5.7
Hilar and mediastinal lymphadenopathy	17	48.6
Pleural effusion	12	34.3
Ascites	1	2.9
Hepatomegaly	1	2.9
Splenomegaly	4	11.4

Table 3. Blood and urine routine examination

Parameter	Count	Percent
White blood cell count >10×10^9/L	27	77.1%
Hemoglobin <90 g/L	20	57.1%
Platelet count >300×10^9/L	25	71.4%
Absolute neutrophil count >6.3×10^9/L	28	80%
Absolute lymphocyte count <1.1×10^9/L	6	17.1%
Monocytes Absolute >0.6×10^9/L	23	65.7%
Absolute eosinophils >0.52×10^9/L	18	51.4%
Absolute basophils >0.06×10^9/L	13	37.1%
Weak positive or positive urine occult blood	10	28.5%
Weak positive and positive urine protein	3	8.5%

Table 4. Liver and kidney functions and blood electrolytes examination

Parameter	Count	Percent
Total bilirubin >21 μmol/L	4	11.4%
Albumin <40 g/L	34	97.1%
Globulin >40 g/L	23	65.7%
Albumin/Globulin >1	7	20%
Aspartate aminotransferase >45 U/L	1	2.8%
Alanine aminotransferase >45 U/L	3	8.5%
ALP >125 U/L	22	62.8%
Creatinine >104 μmol/L	3	8.5%
Endogenous creatinine clearance <85	21	60%
Creatine kinase >174 mL/min	1	2.8%
Creatine kinase isoenzyme MB >25U/L	1	2.8%
Lactate dehydrogenase >245 U/L	7	20%
A-hydroxybutyrate dehydrogenase >182 U/L	5	14.2%
K^+<3.5 mmol/L	12	34.2%
Ca^{2+}<2.08 mmol/L	14	40%

Chest imaging findings

All 35 patients were examined by chest CT. The main manifestations of chest CT are shown in **Table 6** and **Figure 3A**.

Anatomical distribution of bone lesions

In 35 patients, bone destruction by TM involved multiple sites of the bone. The anatomical distribution of bone destruction site and percentage were shown in **Table 7**.

Imaging findings of bone destruction

In this study, the diagnosis of bone destruction was based on imaging data. ECT (n=28, 80.0%), other imaging data of bone destruction included chest CT (n=5, 14.3%), abdominal CT (n=2, 5.7%), craniocerebral CT (n=1, 2.9%), MRI (n=2, 5.7%), radiography (n=5, 14.3%), and PET/CT (n=2, 5.7%) (**Figure 3B-D**).

Comparison of diagnosis time between patients with and without bone destruction

In TM patients with bone destruction, the median time from onset to diagnosis was 5 (3, 9) months. In TM patients without bone destruction, the median time from onset to diagnosis was 2 (1, 4) months. The diagnosis time of TM patients with bone destruction was significantly longer than that of TM patients without bone destruction ($P<0.05$) as shown in **Figure 4A**.

Clinical outcome of patients

The main treatment plan is systemic application of antifungal drugs. In all, 32 patients

Table 5. Inflammatory indicators and immune function

Parameter	Count	Percent
Fibrinogen >5 g/dL	17	48.5%
High-sensitivity C-reactive protein >5 mg/L	14	93.3% (14/15)
C-reactive protein >10 mg/L	14	93.3% (14/15)
ESR >15 mm	33	97% (33/34)
Immunoglobulin M >1.32 g/L	9	32.1% (9/28)
Immunoglobulin G >18 g/L	23	82.1% (23/28)
Immunoglobulin A >2.69 g/L	9	32.1% (9/28)
Immunoglobulin E >100 IU/mL	7	100% (7/7)

Table 6. Lung CT findings

	Total population (n=35)	
	Number of patients	Percent (%)
Multiple Texture	5	14.3
Spot	28	80.0
Nodule	12	34.3
Cord	25	71.4
Cavity	1	2.9
Intrapulmonary calcification	5	14.3
Ground-glass changes	1	2.9
Enlarged mediastinal lymph nodes	17	48.6
Pleural effusion	16	45.7
Pleural thickening	11	31.4

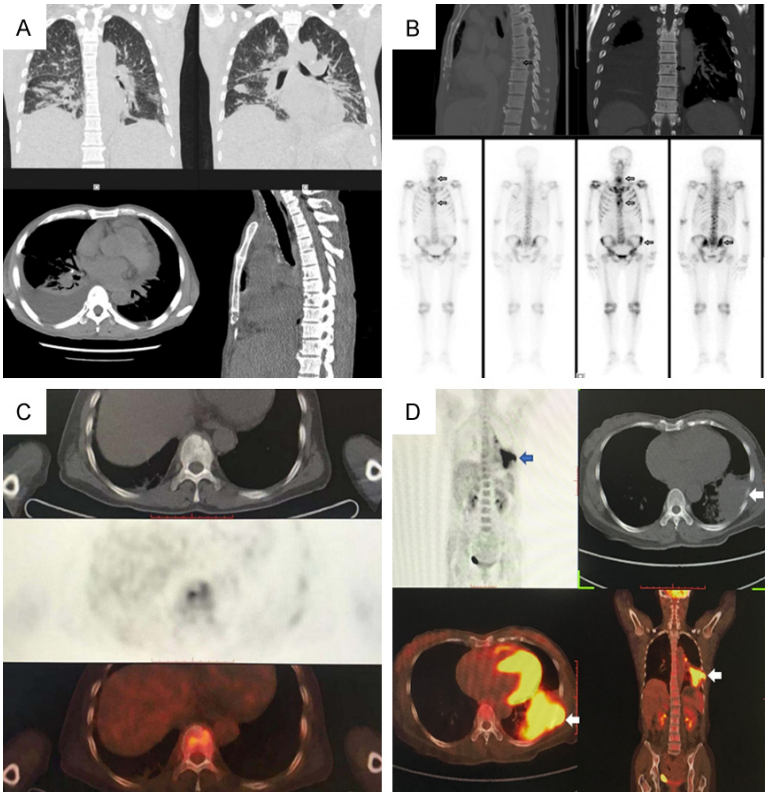

Figure 3. Imaging findings of TM patients with bone destruction. A. Chest computed tomography of TM-infected patient with bone destruction. Chest CT showed multiple lobar, nodular, and striped hyperdense shadows in both lungs with blurred boundary. Pleural effusion can be seen on the right side. B. CT and ECT images of TM-infected patients with bone destruction. CT examination showed multiple osteolytic lesions of the spine. The bone mineral density of the lesion was decreased, and osteolytic bone destruction was found. ECT images showed multiple radionuclide concentrations in the cervical and thoracic segments of the spine, bilateral ilium, and bilateral sacroiliac joints. C. PET-CT showed osteolytic destruction of thoracic vertebrae. D. PET-CT showed pathological fracture of ribs.

were treated with fluconazole or amphotericin B; after discharge, they took itraconazole orally for 6 months to 1 year. Patients showed good tolerance to the drug, and had no recurrence. Two patients died within 2 weeks after diagnosis, due to liver and kidney failure. One patient discontinued treatment because of critical illness and financial difficulties. Fungal spores were found in one patient's sacroiliac joint lesion biopsy (**Figure 4B** and **4C**). The bone pain and chest pain disappeared within one week after effective treatment, and the osteolytic lesions were absorbed in 2 months. One case of pathological rib fracture was treated with a chest girdle and vest external fixation. The other patients did not need surgical debridement or drainage.

Discussion

Talaromyces Marneffei, a temperature-dependent biphasic fungus, is prevalent in South-

Table 7. Anatomical distribution of bone destruction site

Site	Frequency	Percent (%)
Skull	14	45.2
Upper limb bone and pectoral girdle		
Shoulder joint	7	22.6
Clavicle	4	12.9
Scapula	3	9.7
Wrist joint	2	6.5
Humerus	2	6.5
Phalanges	2	6.5
Hand Joint	1	3.2
Trunk		
Rib	16	51.6
Lumbar vertebra	7	22.6
Thoracic spine	6	19.4
Sacrum	3	9.7
Sternoclavicular joint	2	6.5
Cervical	2	6.5
Sternum	1	3.2
Lower Extremity		
Iliac bone	8	25.8
Femur	7	22.6
Knee joint	5	16.1
Sacroiliac joint	3	9.7
Tibia	2	6.5
Ankle joint	1	3.2
Hip joint	1	3.2

ern China and Southeast Asia. The bamboo mouse is the natural host of TM. In 1956, a Vietnamese study was the first to isolate and report TM from the liver of bamboo mice [12]. In the Guangxi province of China, 19% of HIV-positive patients have TM-infection. TM was the HIV related opportunistic pathogen next to Mycobacterium tuberculosis [13]. In the past, it was generally believed that TM infection was related to AIDS [14]. With the use of antiretroviral drugs, the prevalence of HIV has been partially controlled. The incidence of HIV-related TM infection has decreased significantly [15]. At present, an increasing number of studies have reported TM infection in HIV-negative patients [15]. The patients with HIV-negative TM still had a higher recurrence rate and poorer prognosis [1, 4, 6, 16].

TM infection spreads through the blood circulation, often involving the reticuloendothelial system, skin, and lungs [17, 18]. Osteolytic lesions are rare [19] and are often ignored in clinical practice. Previous studies have shown that TM mainly invades the host monocyte-macrophage system after invading the body through the respiratory system. Bone marrow is the main site of pathogen invasion [17]. Bone destruction mainly occurs in HIV-negative individuals. There is no report of bone destruction in HIV-positive individuals [20]. Not all patients with HIV-negative TM disease will have bone destruction. How TM infection causes bone destruction is still not well understood.

In this study, we reviewed 165 patients with TM disease, of which 80 were HIV negative. Thirty-five patients with osteolytic lesions were all HIV negative. The incidence of osteolytic lesions in HIV-negative patients was 43.8%, accounting for 21.2% in patients with TM disease, which was like the previously reported results [4]. TM infection complicated with osteolytic lesions was mainly observed in HIV-negative patients, which were consistent with previous reports [4, 10]. Although these patients did not have AIDS, most of them had complications due to underlying diseases, which may have led to the decline of patients' immunity and created conditions for pathogen invasion. Previously, some studies reported the difference between HIV and non-HIV patients in TM [21-23]. In both cases, the patient's immunity is suppressed, but the mechanism of immunosuppression may be different in the two cases [24]. HIV-negative patients with TM disease had significantly higher WBCs and stronger neutrophil function than HIV-positive patients [19, 25]. The course of TM infection in patients with bone destruction is generally longer than that in patients without bone destruction. This is mainly because patients with bone destruction are mainly HIV-negative. In addition, the diagnosis of TM disease needs etiological evidence. HIV-negative patients have a strong ability to resist pathogens. The positive rate of peripheral blood culture is not high, and often, repeated clinical samples are required for mycological culture. Bone destruction can occur in patients with tuberculosis or non-tuberculosis mycobacterium and other fungal infections. Patients with HIV-negative TM disease are often misdiag-

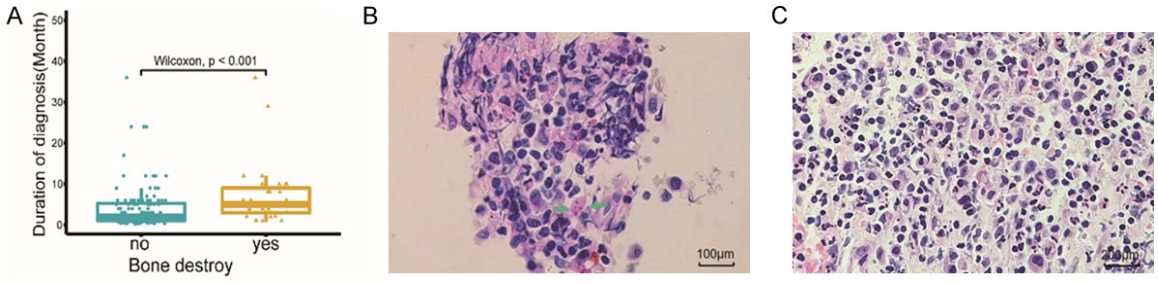

Figure 4. Comparison of duration of diagnosis and histopathological results of bone destruction sites. A. The time to diagnosis for TM patients with bone destruction is longer than that of TM patients without bone destruction; B. D-PAS staining, 400×, Bar =100 μm: The arrow shows several PAS-D-positive spores in the macrophages. C. HE, 200×, Bar =200 μm: Pathology shows mixed chronic active osteomyelitis composed of mixed lymphocytes, plasma cells, histiocytes (macrophages), and neutrophils.

nosed with tuberculosis, resulting in delayed diagnosis.

It is generally believed that TM infection is rare in HIV-negative individuals, so the diagnosis of TM disease in HIV-negative patients is typically delayed. In our study, the average time of diagnosis in patients with bone destruction was significantly longer than that in patients without bone destruction, with a median of 8.5 months. The positive rate of blood culture in patients with bone destruction was lower than in those without bone destruction. The positive rate of fungal culture in skin lesions or superficial tissue biopsies was higher. Delayed diagnosis and untimely treatment can cause pathogens to multiply in large numbers in the body, trigger a strong immune response, and further strengthen bone destruction. In severe cases, it can cause pathological fractures [4]. Some studies have reported that the imaging manifestations of TM disease usually appear several weeks or even months after the clinical manifestations. Bone destruction caused by TM infection has a variety of imaging manifestations. Similar lesions can occur in osteomyelitis caused by tuberculosis, non-tuberculosis mycobacterial tumors, and other osteomyelitis such as African histoplasmosis, blastomycosis, cryptococcosis, and coccidioidomycosis [26-28]. Osteolytic damage is more common in HIV-negative patients with TM infection, but it is also easy to be ignored by clinical workers [4]. Some researchers have proposed that infection of TM should be included in the differential diagnosis of fungal osteomyelitis [4]. Considering clinical symptoms and signs, TM osteomyelitis can be diagnosed by its radiological features, typical clinical features, histopathological examination, and etiological culture, especially from bone, bone marrow, and skin lesions. In our study, we showed mixed chronic active osteomyelitis composed of mixed lymphocytes, plasma cells, histiocytes (macrophages), and neutrophils in bone marrow samples (**Figure 4C**). Several D-PAS staining positive spores of TM were also found in the macrophages (**Figure 4B**).

At present, there is still a lack of understanding of this regional disease. This study cannot fully summarize the clinical characteristics of TM disease. It does have a certain reference value for medical workers in Southern China and Southeast Asia.

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Disclosure of conflict of interest

None.

Address correspondence to: Shaohui Zong, Department of Spine Osteopathia, The First Affiliated Hospital of Guangxi Medical University, 22 Shuangyong Road, Nanning 530021, Guangxi, China. Tel: +86-15289669819; E-mail: xiaohui3008@126.com; Gaofeng Zeng, College of Public Hygiene of Guangxi Medical University, 22 Shuangyong Road, Nanning 530021, Guangxi Zhuang Autonomous Region, China. Tel: +86-18275799833; E-mail: 1685858372@qq.com

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