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Original Article

Isolated Tuberculous Myositis: A Systematic Review and Multicenter Cases

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Objective: To investigate the clinical features and associated underlying conditions of isolated tuberculous myositis (ITBM), a rare extrapulmonary tuberculosis (TB).

Methods: A systematic literature search and a multicenter survey were performed using a triangulation strategy. Data from the identified ITBM cases were extracted and analyzed to determine the underlying conditions, clinical presentations, treatments, and outcomes.

Results: Based on the systematic review, we identified 58 ITBM, including 9 pediatric, cases in the literature published from 1981 to 2021: 25 (43.1%) immunocompromised and 33 (56.9%) non-immunocompromised patients. Immunocompromised cases had a significant shorter symptom duration (median 30.0 vs. 75.0 days) and a higher prevalence of multilocular involvement (20.8% vs. 0%). Among 24 immunocompromised adult patients, dermatomyositis/polymyositis (DM/PM; n=10, 41.7%) were the most common underlying diseases in adults with ITBM identified in the systematic review. Over the past 20 years, 11 Korean adults with ITBM were identified in the multicenter survey. Of 7 immunocompromised cases, two (28.6%) were DM/PM patients. TB death rate of immunocompromised patients was 0.0% and 5/23 (21.7%) in the pediatric and adult ITBM cases identified in the systematic review, respectively, and 3/7 (42.9%) in survey-identified ITBM cases.

Conclusion: ITBM has a unique clinical presentation including fever, tenderness, local swelling, overlying erythema, abscess formation and was associated with a grave outcome, especially in immunocompromised hosts. DM/PM was a highly prevalent underlying disease in both systematic review-identified and survey-identified immunocompromised ITBM patients.

Keywords: Mycobacterium tuberculosis, Infectious myositis, Dermatomyositis, Polymyositis

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INTRODUCTION

Tuberculosis (TB) has remained a major global and public health burden and a leading cause of deaths worldwide [1]. The global TB incidence in 2018 increased by 11%, compared to the incidence in 2008. The World Health Organization (WHO) launched the End TB Strategy in 2014 to target a 95% and 90% reduction in the number of TB deaths and new cases, respectively, during 2015~2035 [2]. However, from 2015 to 2019, the rates of decline in TB deaths and TB incidence were only 14% and 9%, respectively.

Although *Mycobacterium tuberculosis* infection mainly manifests as pulmonary TB (PTB), TB can affect any organ or tissue. Extrapulmonary TB (EPTB) accounts for approximately 15% of new TB cases, and the EPTB incidence increased by 33% from 2013 to 2019 [2]. Musculoskeletal EPTB is uncommon (1%~3% of all TB cases), and spondylitis, arthritis, and osteomyelitis are responsible for most EPTB cases [3]. TB myositis has been sporadically reported, and can occur through contiguous infection or hematogenous spread; muscle involvement is generally secondary to disseminated TB or adjacent skeletal EPTB. However, TB of only the skeletal muscle, which is known as isolated TB myositis (ITBM), is very rare. Therefore, since 1886 when the involvement of lower leg muscle was first described [4], there has been little information on the clinical features of ITBM and its associated conditions. Until now, three separate reviews on TB myositis have been published [5-7]. However, these studies included TB myositis cases with concurrent other organ involvement, not ITBM.

Therefore, we conducted a systematic review of ITBM and retrospectively collected ITBM cases through a multicenter survey. To improve our clinical understanding of ITBM, we investigated clinical characteristics and underlying comorbidities in patients with ITBM.

MATERIALS AND METHODS

In the present study, a triangulation strategy was used with regard to the data and the methodology: 1) a systematic literature review from the electronic database was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations to generate research-based evidence, and 2) a multicenter survey was undertaken to obtain real-world data from clinical practice in South Korea.

Inclusion criteria for ITBM patients

The inclusion criteria were: 1) bacteriologically confirmed TB infection defined as positive result for acid-fast bacillus stain, TB culture, or TB polymerase chain reaction (PCR) in muscle biopsy or aspiration. And clinically diagnosed TB was defined by a physician based on histology and clinical improvement with anti-TB medications [8]. 2) We included TB myositis cases only involving limb extremities including the shoulder and hip girdles as ITBM. We excluded cases with TB involving axial muscles alone or patients with concurrent symptomatic involvement of other organs (including neighboring bones and joints).

Literature search strategy and study selection

The search strategy was designed to identify reports of ITBM cases published between January 1981 and February 2021. The search terms "myositis" and "tuberculosis" were used in combination to identify all articles with the key words. We searched MEDLINE/PubMed, EMBASE, Cochrane Library, and Scopus and identified additional cases by manually searching the reference lists of the retrieved articles. The search strategy is described in the supplementary information (Supplementary Table 1).

After the exclusion of duplicated or non-English papers, two authors (JHK and JSL) independently scanned the abstracts of the selected papers and reviewed the full text of all potentially eligible papers. This systematic review was performed in accordance with the PRISMA guidelines (Figure 1, Supplementary Table 2). Any disagreements between the authors were resolved by consensus through a discussion with both the authors and the principal investigator (YJL). The quality of each individual article was assessed by National Heart, Lung and Blood Institute (NHLBI) at National health institute (NIH) Quality Assessment Tool for Case Series Studies [9]. The quality assessment was independently performed by the two authors for the internal validity of all the studies. The quality score was calculated as the number of "yes" response to each item in the NIH tool. An overall quality was assessed using as good (score ≥6 of the maximum possible 9 points), fair (score 3 to 5), or poor (score <3, Supplementary Table 3).

Multicenter survey for Korean cases with ITBM

In South Korea, the annual EPTB incidence is 9.8/100,000

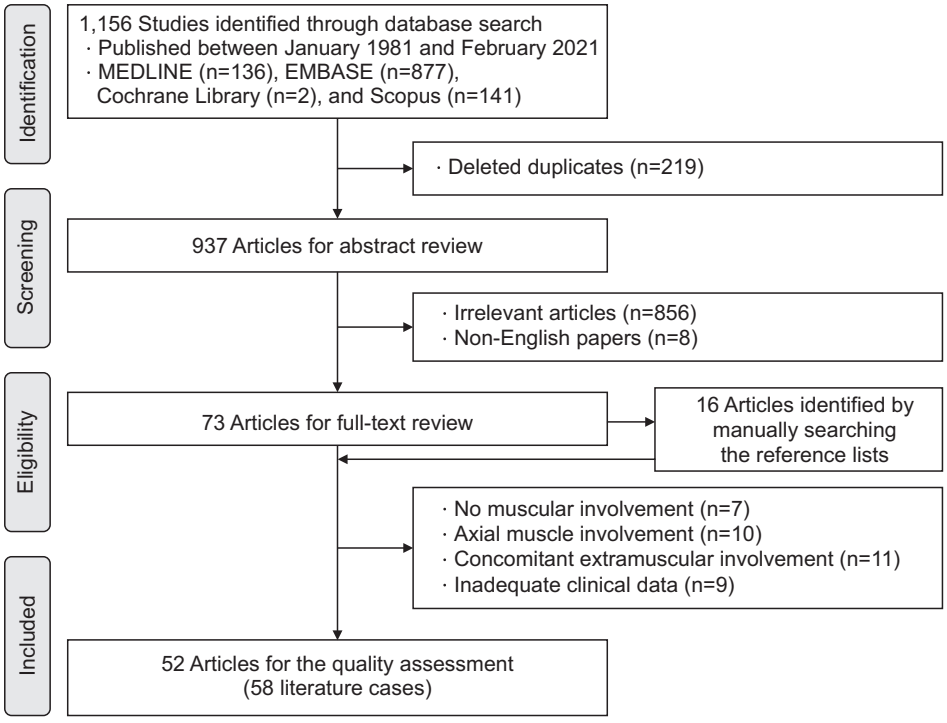

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of study selection.

and nearly 6.5% of incidental cases have osteoarticular TB [10]. A survey questionnaire for TB myositis was e-mailed to rheumatologists or infectious disease specialists in 30 referral hospitals, and all of the centers responded. Thirteen cases, which was diagnosed between 1999 and 2018, were recorded from seven (23.3%) centers and all cases were from replies from rheumatologists. However, two of these cases were excluded from the final analysis based on the selection criteria as follows: TB osteomyelitis (n=1) and only lumbar muscle structure involvement (n=1). This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB No. B-1712/435-107) and the requirement of informed consent was waived because the data were anonymized and retrospectively analyzed.

Data collection

We extracted the following data: 1) demographics (age, sex, and nationality/region); 2) underlying clinical conditions (TB history, comorbidities, and concomitant medications); 3) TB-related variables (symptoms, symptom duration, involved regions, the presence of multidrug-resistant [MDR] TB, and treatments); and 4) outcomes and cause of death. The topographic regions were defined as the right/left shoulder and upper arm, forearm, buttock and thigh, or low leg area.

The conditions inducing immunocompromise included human immunodeficiency virus (HIV) infection, active malignancy, chronic renal insufficiency (serum creatinine >3.0 mg/dL), chronic alcohol abuse, or use of immunosuppressants, including glucocorticoids. Furthermore, we stratified patients who were taking glucocorticoids into low-risk and high-risk (prednisone equivalent ≥15 mg/day) subgroups [11]. Intramuscular abscess formation was defined based on imaging evidence or the presence of pus on aspiration. Local treatments included needle aspiration, incision and drainage, or excision. Standard combination treatment was defined as anti-TB treatment using ≥3 agents, including isoniazid, rifampicin, ethambutol, or pyrazinamide, for ≥6 months. TB death was defined as the incidence of death before or during the treatment [10]. Treatment success was defined as the completion of TB treatment and the disappearance of TB symptoms [10]. An unevaluated outcome was the one in which a treatment outcome was not assigned.

Statistical analysis

We carried out a qualitative analysis because all the identified cases were from case reports or series and the sample size was limited. Continuous variables are expressed as median with 25th~75th interquartile range (IQR) and were compared using the Mann–Whitney U-test. Categorical variables were compared

using the chi-square test or Fisher's exact test. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 21 (IBM Co., Armonk, NY, USA).

RESULTS

There were no limitations for the study design during data extraction of systematic literature review. However, unfortunately, no cohort studies or experimental researches have been performed yet, there were only some case reports. We analyzed data from 58 literature cases identified from the systematic review and 11 survey cases identified from the multicenter study. Through a systematic literature search that was guided by the PRISMA guideline, we identified 52 articles (58 cases; Figure 1); six articles were case-series, and the rest were all case reports [7,12-62]. The quality assessment tool presented good correlation. Among all of the articles evaluated, 84.6% and 90.4% that

Table 1. Characteristics of cases with isolated tuberculous (TB) myositis

Variable	Literature cases (n=58)		Adult survey cases (n=11)
	Pediatrics (n=9)	Adults (n=49)	
Male	6 (66.7)	22 (44.9)	2 (18.2)
Age (yr)	11.0 (8.0~13.0)	45.0 (30.0~55.5)	58.0 (44.0~67.0)
≥45 yr		25 (51.0)	8 (72.7)
Country			
India	6 (66.7)	14 (28.6)	
United States of America	1 (11.1)	6 (12.2)	
Taiwan	1 (11.1)	5 (10.2)	
Thailand	0 (0.0)	3 (6.1)	
Greece	0 (0.0)	3 (6.0)	
United Kingdom	0 (0.0)	3 (6.1)	
Others*	1 (11.1)	15 (30.6)	
Tuberculosis history	0 (0.0)	4 (8.2)	3 (27.3)
Suspicion of direct trauma	0 (0.0)	1 (2.0)	1 (9.1)
Symptom duration (d)	60.0 (33.0~105.0)	43.5 (20.8~90.0)	54.0 (29.0~61.0)
Immunocompromised	1 (11.1)	24 (49.0)	7 (63.6)
Immunosuppressant use	0 (0.0)	19 (38.8)	5 (45.5)
AIDS	0 (0.0)	2 (4.1)	1 (9.1)
Leukemia	1 (11.1)	2 (4.1)	0 (0.0)
Others†	0 (0.0)	1 (2.0)	1 (9.1)
Systemic rheumatic diseases	0 (0.0)	18 (36.7)	3 (27.3)
DM/PM	0 (0.0)	10 (20.4)	2 (18.2)
SLE	0 (0.0)	4 (8.2)	0 (0.0)
Rheumatoid arthritis	0 (0.0)	1 (2.0)	1 (9.1)
Others‡	0 (0.0)	3 (6.1)	0 (0.0)
Local treatment	8 (88.9)	35 (71.4)	4 (36.4)
Treatment success	9 (100)	42/47 (89.4)	7 (63.6)
TB deaths	0 (0.0)	5/47 (10.6)	4 (36.4)

Values are presented as number (%) or median (25th to 75th interquartile range). AIDS: acquired immune deficiency syndrome, DM/PM: dermatomyositis/polymyositis, SLE: systemic lupus erythematosus. *Included Brazil (n=2), Tunisia (n=2), Turkey (n=2), Australia (n=1), Canada (n=1), China (n=1), Japan (n=1), Jordan (n=1), South Korea (n=1), Nepal (n=1), Romania (n=1), Singapore (n=1), and Spain (n=1); †Included chronic kidney disease (n=1) and chronic alcohol abuse (n=1); ‡Included systemic sclerosis (n=1), Sjögren's syndrome (n=1), and polymyalgia rheumatica (n=1).

were rated by the rater 1 and 2, respectively, demonstrated good quality on assessment, and no articles were rated as being poor in quality (Supplementary Table 3). The summary of individual cases is shown in Supplementary Table 4.

Baseline characteristics of literature cases with ITBM

Among the 58 literature cases with ITBM, 9 (15.5%) involved patients who were younger than 18 years. As none of pediatric cases received glucocorticoid treatment or had systemic rheumatic disease, we summarized the characteristics of pediatric ITBM cases separately (Table 1). The median age was 11.0 (8.0~13.0) years and 45.0 (30.0~55.5) years in pediatric and adult ITBM cases, respectively. There was a slight male predominance (66.7%) in the pediatric group, whereas the ratio of male-to-female patients was similar (44.9% vs. 55.1%) in the adult group. Moreover, 26 ITBM cases (44.8%; 6 and 20 in pediatric and adult groups, respectively) were from the 30 high TB burden countries that was defined by the WHO in 2021 [2]. The commonest country of origin was India (n=20, 34.5%), followed by the United States (n=7, 12.1%) and Taiwan (n=6, 10.3%). Only four adult patients (8.2%) had a history of TB, and a direct inoculation through a penetrating muscle injury was suspected in a single case.

There were 25 (43.1%; 1 child and 24 adults) immunocompromised patients; among them, 19 patients (76.0%) received immunosuppressants. Moreover, 18 (36.7%) adult patients had a history of glucocorticoid therapy, and 11 (73.3%) of 15 adults with available data on daily glucocorticoid dose were high-risk glucocorticoid users. Only one was administered anti-tumor necrosis factor-α monoclonal antibodies (infliximab). Interestingly, dermatomyositis/polymyositis (DM/PM; n=10, 41.6%) was the most prevalent disease in 24 immunocompromised adult patients, and they all received chronic glucocorticoid therapy (Figure 2A). Comorbid rheumatic diseases included systemic lupus erythematosus (n=4), rheumatoid arthritis (RA; n=1), Sjögren's syndrome (n=1), systemic sclerosis (n=1), and polymyalgia rheumatica (n=1). Other causes of immunocompromise included leukemia (n=3), HIV infection (n=2), and renal transplantation (n=2). None of the patients included in this study had MDR-TB.

Clinical presentation of literature cases with ITBM

Among all of the literature cases with ITBM, the lower extremities were more commonly involved than the upper extremities (64.6% vs. 35.4%), and the buttock and thigh (44/80 involved regions, 54.4%) was the most frequently involved anatomical region (Figure 3A). The regional distribution did not differ significantly between pediatric and adult ITBM patients. Most ITBM cases showed a unilocular lesion, and 3 pediatric (33.3%) and 5 adult (10.2%) ITBM patients showed multilocular involvement. The prevalence of main symptoms and signs did not differ significantly different between pediatric and adult ITBM patients: fever, pain/tenderness, swelling, overlying skin erythema, and local intramuscular abscess were seen in 22.2%, 44.4%, 100%, 0.0%, and 88.9% of pediatric ITBM patients and in 50.0%, 77.1%, 93.8%, 32.9%, and 79.6% of adult ITBM patients, respectively (Figure 3B). Four pediatric patients had presentations similar to cold abscess.

When comparing between patients in high TB burden countries and those in non-high TB burden countries, cases in high TB burden countries showed a significantly lower prevalence of fever (30.0% vs. 64.3%, p=0.009), pain (65.0% vs. 85.7%, p=0.029), and erythema (10.0% vs. 32.1%, p=0.043) than those in non-high TB burden countries. In addition, the former had

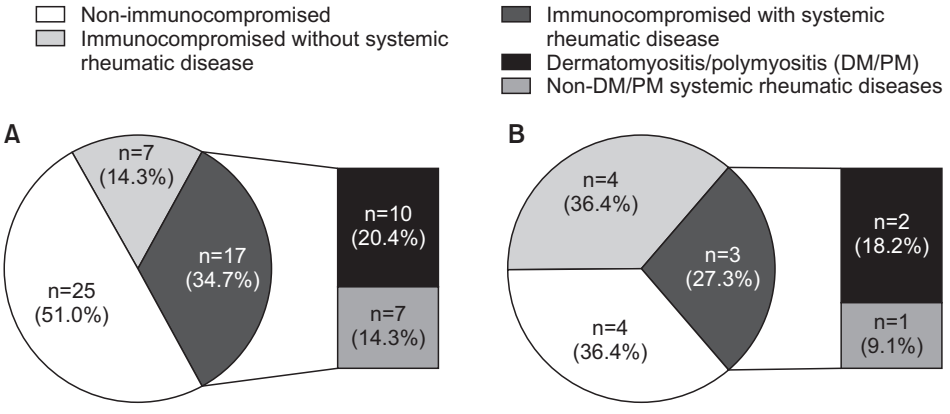

Figure 2. The prevalence of underlying immunocompromised conditions in both systematic review-identified ITBM (A) and survey-identified ITBM (B) cases. ITBM: isolated tuberculous myositis.

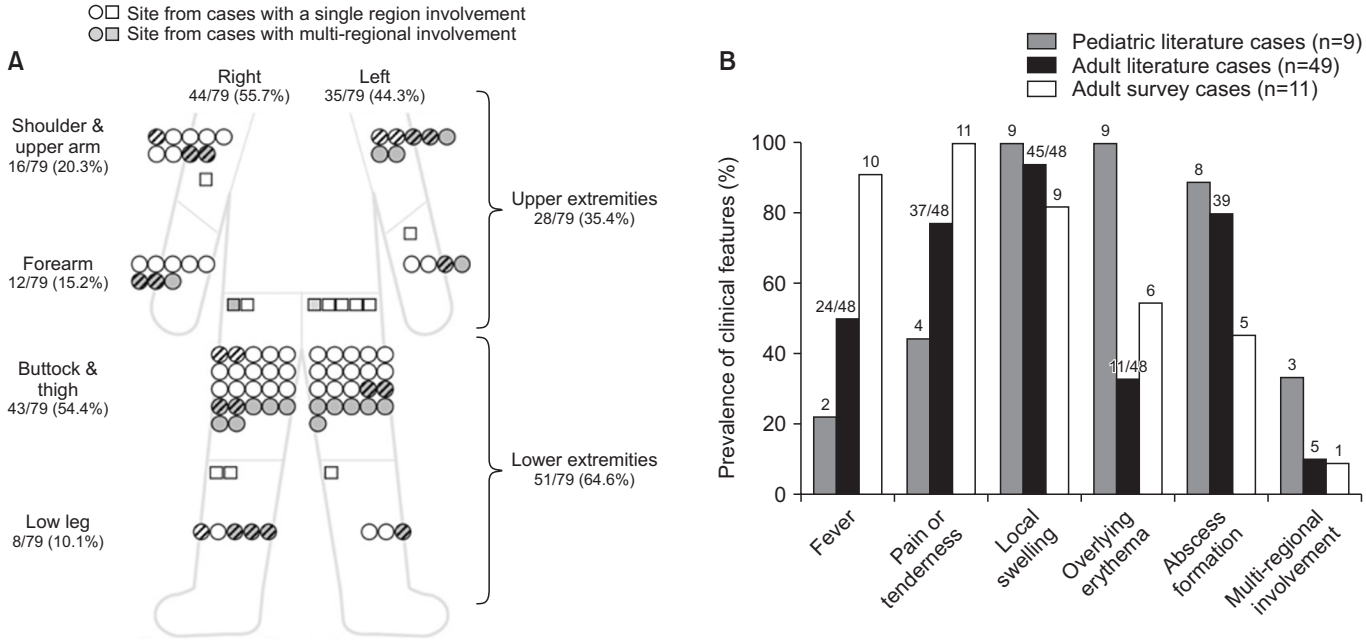

Figure 3. Clinical features of isolated tuberculous myositis (ITBM). (A) The regional distribution of muscle involvement in both systematic review-identified ITBM and survey-identified ITBM cases. The percentage of involvement of each region was calculated from the systematic review-based data of the cases. Circles represent cases identified from the literature search and squares indicate cases identified from the multicenter survey. Hatched circles indicate systematic review-identified pediatric ITBM cases. (B) The prevalence of symptoms in both systematic review-identified ITBM (pediatric and adults) and survey-identified ITBM patients. The figures above the bars are the number of cases.

a lower prevalence of lower extremity involvement (55.0% vs. 86.2%, p=0.004).

A comparison of immunocompromised with non-immunocompromised adult ITBM patients showed that immunocompromised had a shorter duration of symptom (median 30.0 (14.0~45.0) vs. 75.0 (42.0~120.0) days, p=0.003) and also tended to have multilocular involvement (20.8% vs. 0%, p=0.022). Additionally, the prevalence of fever (83.3% vs. 16.7%, $p=7.262\times10^{-6}$), pain/tenderness (95.8% vs. 58.3%, p=0.004), or overlying erythema (39.1% vs. 8.0%, p=0.016) was significantly higher in the immunocompromised patients than in the non-immunocompromised patients. Moreover, the 11 high-risk glucocorticoid users showed a significantly lower prevalence of local intramuscular abscess (54.5% vs. 88.6%, p=0.025) and a significantly higher frequency of fever (90.9% vs. 32.4%, p=0.001) and multilocular involvement (45.5% vs. 0.0%, $p=3.370\times10^{-4}$) than the ITBM patients without high-risk glucocorticoid use.

Treatment and outcomes of literature cases with ITBM

All 58 literature cases with ITBM received standard combination treatment for TB, and 44 (74.1%, including 35 of 49 adults and 8 of 9 children) underwent additional local treatment as needle aspiration, incision and drainage, and excision. The treatment outcome was unevaluated in two adult ITBM patients, and treatment success was observed in 42/47 (89.4%) adult and 9/9 (100%) pediatric ITBM patients. The all-cause mortality rate was 7/47 (14.9%) in adults, of which TB death was 5/47 (10.6%); two patients died of hematologic malignancy after the completion of TB treatment. The causes of TB death included septic shock/multiorgan failure (n=2), acute respiratory distress syndrome (n=1), fulminant hepatic failure (n=1), and cerebral hemorrhage (n=1).

In immunocompromised ITBM patients, the TB death rate was 5/23 (21.7%). These five ITBM patients with TB death were significantly older than survivors (median 55.0 [47.5~65.0] vs. 42.0 [29.3~50.5] years, p=0.041). In addition, ITBM patients with TB death had shorter symptom durations (14.0 [7.0~40.0] vs. 58.0 [23.3~112.5] days, p=0.035) and had a higher prevalence of fever (100% vs. 46.3%, p=0.050) compared to survivors. Among the ten DM/PM patients, two cases (20%) died due to ITBM. The other underlying diseases in literature cases with TB death were Sjögren's syndrome (n=1), leukemia (n=1), and

chronic renal insufficiency (n=1).

Multicenter survey cases with ITBM

In the 11 survey cases, there were no pediatric cases, and female patients were predominant (n=9, 81.8%). In only one case, direct inoculation via a contaminated acupuncture was suspected. And 1 patient showed multilocular involvement and the prevalence of multilocular involvement was not different between literature- and survey-identified cases. Seven (63.6%) patients were immunocompromised and 3 patients (27.3%) had systemic rheumatic diseases. Among the immunocompromised, 2 patients were inflammatory myositis such as DM/PM (n=2, 18.2%) (Figure 2B). The other underlying diseases included RA (n=1), HIV infection (n=1), renal transplantation (n=1), and chronic alcohol abuse (n=1). Additionally, the regional distribution was comparable between the literature and survey ITBM cases (Figure 3A). Nine ITBM patients received the standard combination treatment for TB; one patient died before initiating anti-TB drugs. TB related death occurred in 4 survey cases with ITBM, with the following underlying conditions: DM/PM (n=2), chronic alcohol abuse (n=1), and congestive heart failure (n=1; Table 2). The causes of TB related death were multiorgan failure (n=2), acute respiratory distress syndrome (n=1), and sudden cardiac death (n=1).

DISCUSSION

We identified 58 cases with ITBM from literature published over the past 30 years and 11 survey cases with ITBM diagnosed over the past 20 years in an intermediate TB-risk country. Worldwide, 1.1 million (16% of 7.1 million new and relapsed cases) individuals were newly diagnosed with EPTB in 2019 [2]. Thus, we infer that ITBM is a rare musculoskeletal EPTB although the true incidence is unknown.

With regard to the clinical features, ITBM showed both similarities or dissimilarities with classical bacterial pyomyositis (tropical myositis). In this study, the most common affected area was the proximal lower extremities, which is similar to the affected areas in spontaneous bacterial pyomyositis [63,64]. Swelling, pain/tenderness, and intra-muscular abscess in the limb were frequently observed in ITBM cases. Comparing survey-identified cases with literature-identified cases, the results showed a similar regional distribution of ITBM. In addition, although there were differences in rates, patients with ITBM showed fever (90.9% in literature cases vs. 51.0% in survey cases), overlying erythema (54.5% in literature cases vs. 22.4% in survey cases), and local intramuscular abscess (45.5% in survey cases vs. 80.0% in survey cases) as common clinical manifestations.

Patients often did not have overlying erythema because TB infection occurs deep within the muscle, as in spontaneous

Table 2. Related factors for tuberculosis (TB) death in adult patients with isolated tuberculous myositis

Variable	Literature cases (n=47)†			Survey cases (n=11)		
	TB death (–) (n=42)	TB death (+) (n=5)	p-value‡	TB death (–) (n=7)	TB death (+) (n=4)	p-value‡
Age (yr)	42.0 (29.3~50.5)	55.0 (47.5~65.0)	0.041*	52.0 (38.0~65.0)	68.0 (53.5~70.5)	0.073
≥ 45 yr	19 (45.2)	5 (100)	0.050	4 (57.1)	4 (100)	0.236
Symptom duration (d)	58.0 (23.3~112.5)	14.0 (7.0~40.0)	0.035*	56.0 (29.0~61.0)	52.5 (30.0~75.8)	0.927
Immunocompromised	18 (42.9)	5 (100)	0.022*	4 (57.1)	3 (75.0)	1.000
Immunosuppressants	16 (38.1)	3 (60.0)	0.381	3 (42.9)	2 (50.0)	1.000
High-risk glucocorticoids§	8/39 (20.5)	3 (60.0)	0.091	1/6 (16.7)	2 (50.0)	0.500
Systemic rheumatic disease	15 (35.7)	3 (60.0)	0.357	1 (14.3)	2 (50.0)	0.491
DM/PM	8 (19.0)	2 (40.0)	0.285	0 (0.0)	2 (50.0)	0.109
Fever	19/41 (46.3)	5 (100)	0.050	6 (85.7)	4 (100)	1.000
Local abscess formation	34 (81.0)	3 (60.0)	0.285	5 (71.4)	0 (0.0)	0.061
Multiregional involvement	3 (7.1)	2 (40.0)	0.081	0 (0.0)	1 (25.0)	0.364

Values are presented as median (25th to 75th interquartile range) or number (%). DM/PM: dermatomyositis/polymyositis. *p<0.05. †Two were cases with unevaluated outcomes; ‡Calculated by the Mann–Whitney U-test, chi-square test, or the Fisher's exact test; §Prednisolone equivalent dose ≥15 mg/day.

bacterial pyomyositis [64]. Whereas bacterial pyomyositis is endemic to tropical countries and is more common in children and young adults [63], ITBM was reported worldwide and in all age groups. Although bacterial myositis could develop in some immunocompromised patients, including HIV-infected patients in temperate regions [64], half of the adult ITBM patients in the present study were immunocompromised (49.0% and 63.6% in the literature and survey cases with ITBM, respectively). Additionally, patients with ITBM presented with a more slowly progressive course (median symptom duration: 44 and 54 days in the literature and survey cases with ITBM, respectively) than those with tropical pyomyositis, wherein the suppurative stage with high spiky fever occurs by 10~21 days [64].

The overall mortality rate of bacterial pyomyositis is 0.5%~4% and the mortality rate of spinal TB, the commonest musculoskeletal EPTB, is 0%~5.3% [63-66]. In our study, although there was no TB death in the pediatric ITBM cases, the TB death rate was 10.6% and 36.4 % in the adult ITBM cases identified from the systematic review and survey, respectively. TB is the leading cause of death among HIV-infected persons [67]. The TB death rate (13.4%, 9/67) of the overall study population in the present study was similar to the previously reported overall mortality (13.3%~14.7%) of HIV-infected EPTB patients [68,69]. Additionally, the TB death rate of immunocompromised patients was 5/23 (21.7%) in the adult literature cases with ITBM and 3/7 (42.9%) in the survey cases with ITBM. These findings suggest that ITBM patients have a poorer outcome than those with bacterial pyomyositis and spinal TB. Therefore, ITBM should always be included in the differential diagnosis of infectious myositis involved the proximal lower extremities, especially in immunocompromised patients.

The onset of TB is often insidious because *M. tuberculosis* grows more slowly than most bacteria. However, the immunocompromised literature cases with ITBM had a shorter symptom duration than immunocompetent patients. Furthermore, these patients more frequently had a multiregional lesion pattern and constitutional symptoms, such as fever. These findings could indicate that the innate alarm system is triggered only after a large burden of *M. tuberculosis* is achieved in the muscle of the immunocompromised hosts. In fact, glucocorticoids inhibit necrotic death of *M. tuberculosis*-infected cells [70]. Moreover, patients with TB deaths had a significantly shorter symptom duration than those with non-TB deaths in the adult literature cases with ITBM. Therefore, physicians should remember that the immunocompromised can have atypical ITBM features. Additionally, based on these findings, we infer that more aggressive diagnostic and therapeutic approaches are warranted in immunocompromised hosts due to the more rapid progression of ITBM-indicative symptoms and signs.

Of note, in the present study, DM/PM was the most prevalent underlying comorbid disease in the systematic literature review-identified and survey-identified ITBM cases. Opportunistic infections, including TB, are a significant problem in immunocompromised patients or patients who are receiving immunosuppressive therapy. One third of DM/PM patients undergo multiple episodes of severe infection [71]. Additionally, the overall infectious burden is significantly higher in DM/PM patients than in the general hospitalized population [72]. Furthermore, there was a higher incidence of opportunistic infections in DM/PM patients than in patients with other rheumatic diseases and a high risk of TB (rate ratio; RR=6.6~8.0) [73,74]. In our literature cases with ITBM, 49.0% of the adults were immunocompromised and 41.7% of the immunocompromised patients had DM/PM. Similarly, in the survey cases with ITBM, 63.6% were immunocompromised and 28.6% among the patients had DM/PM. Moreover, the TB death rate in ITBM patients with underlying DM/PM reached 20% in the literature cases and 100% in the survey cases.

The musculature is believed to be resistant to infection because of the abundant blood supply, lactate production, or lack of reticuloendothelial tissue [4]. Even on direct inoculation or after Staphylococcus aureus bacteremia, intramuscular abscess is rarely observed [63]. However, in damaged muscle, hematogenous bacterial invasion could result in pyomyositis [63]. A history of muscle damage was reported in 30%~50% of bacterial pyomyositis cases [63,64]. Skeletal muscle contains 10%~15% of the total body iron and a post-traumatic increase in the muscular iron can lead to bacterial persistence and growth [63,75]. Additionally, iron increases *M. tuberculosis* growth, whereas an iron-chelating agent inhibits the viability of this bacterium [76,77]. Therefore, the interesting association of ITBM with DM/PM might be mediated by the DM/PM-related muscle injury as well as the host immune dysfunction. Moreover, immunosuppressants, including glucocorticoids, could pose a further risk for developing TB. Glucocorticoids are a well-known risk factor for TB reactivation. In a study conducted in Taiwan, the current (RR 2.76), recent (RR 1.99), and chronic (RR 1.58) use of glucocorticoids as well as past (RR 1.17) or ever (RR 1.60) use

of glucocorticoids increased the risk of TB [78].

Our study had some limitations. First, various variables were not captured and some were missed because this study was based on a systematic review of the literature as well as retrospectively collected data. Second the issue of heterogeneity could not be explored because the systematic review was based on narrative case reports or small case series. Third, survey-identified cases were collected through responses from rheumatologists alone. Nevertheless, to our knowledge, this study represents the largest sample of ITBM cases to date. Additionally, we believe that our attempts to take a complementary approach for the methodology and dataset generation provides a robust understanding of ITBM, which is a rare form of EPTB, through an analysis of both literature-based and real-world data.

CONCLUSION

In conclusions, the results of this study demonstrated that ITBM has several unique clinical features, is associated with a high mortality rate, and can be distinguished from spontaneous bacterial pyomyositis. In addition, approximately half of the ITBM patients were immunocompromised and their clinical presentation could be considered atypical. Furthermore, DM/PM was the most prevalent underlying disease among the immunocompromised ITBM patients. Therefore, clinicians should consider a diagnosis of ITBM in immunocompromised subjects, especially in DM/PM patients, when having clinical findings suspicious of mono- or multilocular myositis even without pulmonary or miliary TB.

SUPPLEMENTARY DATA

Supplementary data can be found with this article online at https://doi.org/10.4078/jrd.22.0014.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

YJL and YWS conceived the study concept and framework. JSL, WHH, and YJL designed the study. JHK, WHH, and YJL analyzed the data. BYC, Y-HC S-JY, JHJ, KS, ESK, H-JB, WP, YWS, and YJL participated in data acquisition and interpretation. JHK and JSL wrote the manuscript. BYC, Y-HC S-JY, JHJ, KS, ESK, H-JB, and WP edited and contributed the figures that are included with the manuscript. All authors revised the manuscript critically and approved the final version of the manuscript.

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