Medicine®

OPEN

Clinical and radiologic characteristics of radiologically missed miliary tuberculosis
Characteristics of missed miliary TB

Jooae Choe, MD, PhD[a], Kyung Hwa Jung, MD[b], Joung-Ha Park, MD[c], Sung-Han Kim, MD, PhD[c], Mi Young Kim, MD, PhD[a,*]

Abstract

While chest CT provides important clue for diagnosis of miliary tuberculosis (TB), patients are occasionally missed on initial CT, which might delay the diagnosis. This study was to evaluate the clinical and radiological characteristics of radiologically missed miliary TB.

Total 117 adult patients with microbiologically confirmed miliary TB in an intermediate TB-burden country were included. 'Missed miliary TB' were defined as the case in which miliary TB was not mentioned as a differential diagnosis in the initial CT reading. Clinical characteristics and radiologic findings including the predominant nodule size, demarcation of miliary nodules and disease extent on CT were retrospectively evaluated. Findings were compared between the missed and non-missed miliary TB groups. Multivariable analyses were performed to determine independent risk factors of missed miliary TB.

Of 117 patients with miliary TB, 13 (11.1%) were classified as missed miliary TB; these patients were significantly older than those with non-missed miliary TB (median age, 71 vs 57 years, $P = .024$). There was a significant diagnostic delay in the missed miliary TB group ($P < .001$). On chest CT, patients with missed miliary TB had a higher prevalence of ill-defined nodules (84.6% vs 14.4%; $P < .001$), miliary nodule less than 2 mm showing granular appearance (69.2% vs 12.5%; $P < .001$), and subtle disease extent (less than 25% of whole lung field, 46.2% vs 8.7%; $P < .001$). Multivariable analysis revealed that only CT findings including ill-defined nodule (Odd ratios [OR], 15.64; $P = .002$) and miliary nodule less than 2 mm (OR, 10.08; $P = .007$) were independently associated with missed miliary TB.

Approximately 10% of miliary TB could be missed on initial chest CT, resulting in a delayed diagnosis and treatment. Caution is required in patients with less typical CT findings showing ill-defined miliary nodules less than 2 mm showing granular appearance and follow-up CT might have a benefit.

Abbreviations: TB = tuberculosis, CT = computed tomography, GGO = ground glass opacities, HRCT = high-resolution computed tomography, HIV = human immunodeficiency virus, AIDS = acquired immune deficiency syndrome, AFB = acid fast bacilli, BAL = bronchoalveolar lavage, M. tuberculosis = Mycobacterium tuberculosis, MIP = maximum intensity projection, PCR = polymerase chain reaction, ICD = international classification of diseases, OR = odds ratio, CI = confidence interval, IQR = interquartile range.

Keywords: lung disease, tuberculosis, infection, tomography, X-ray computed

1. Introduction

Miliary tuberculosis (TB) is a potentially lethal form of TB resulting from intense systemic dissemination from the rupture of a *Mycobacterium tuberculosis*-laden focus into a vascular channel.[1] Rapid diagnosis of miliary TB requires chest computed tomography (CT) to evaluate disease extent and allow differential diagnosis due to high resolution and lack of image overlapping compared with chest radiographs.[2–5] However, the classic miliary pattern may be evident in up to only 50% of patients with miliary TB.[5] In immunocompromised hosts, such as those with human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS), or those receiving immunosuppressive therapy after transplantation, the host immune response to *M. tuberculosis* may be affected, which can alter the clinical manifestations and radiographic features, making it difficult to diagnose miliary TB.[6–8]

Identification of *M. tuberculosis* in respiratory specimens by microbiological culture is the gold standard for establishing a diagnosis of pulmonary TB, but it usually takes 2 to 8 weeks to acquire positive results from mycobacterial culture.[9] However,

in cases of miliary TB, the sensitivity of acid fast bacilli (AFB) staining is 20% to 40% and polymerase chain reaction (PCR) is 60% to 80%, which is lower than that of pulmonary TB.[10] Therefore, CT imaging is crucial for the early diagnosis of miliary TB. However, miliary TB may occasionally be missed or misinterpreted on chest CT, and the diagnosis and treatment can therefore be delayed, which may contribute to increased disease severity and mortality.[11,12] The current study aimed to evaluate the clinical and radiological characteristics of radiologically missed miliary TB.

2. Materials and methods

2.1. Study population

This retrospective study was performed at a tertiary hospital in an intermediate TB burden country (annual TB incidence in 2016, 77 per 100,000 population).[13] Data from patients treated between January 2008 and December 2018 were reviewed. All adult patients (aged ≥18 years) who had a 2019 international classification of diseases (ICD)-10 diagnosis code of A19 for miliary TB were initially screened. The criteria for a diagnosis of miliary TB was the presence of a miliary pattern on a CT image and/or evidence of multiorgan involvement, along with microbiological evidence: positive *M. tuberculosis* culture or PCR results from a respiratory or extrapulmonary TB biopsy specimen, and/or histopathologically confirmed TB. Patients who had no available high-resolution chest CT at the time of symptom onset were excluded (Fig. 1).

The study protocol was approved by the institutional review board (IRB number 2018-0441), and the requirement for informed patient consent was waived due to the retrospective study design.

2.2. Study design and definitions

The clinical and radiologic characteristics of patients in the radiologically 'missed' and 'non-missed miliary TB' groups were compared. 'Missed miliary TB' was defined after retrospective review of initial CT scans, where miliary TB as well as TB related diagnosis were not mentioned as a differential diagnosis in initial formal CT reports. The remaining patients comprised the 'non-missed miliary TB' group, where TB had been suggested as a diagnosis or as a differential diagnosis. Immunocompromised patients were defined as patients with predisposing factors for TB, such as HIV infection, malignancy, liver cirrhosis, chronic renal failure, and transplantation status, or those who were receiving immunosuppressive treatment.[14–19]

Clinical information of the enrolled patients was collected via electronic medical records. We collected demographic variables, previous history of TB, comorbidities and survival outcome. The information about the diagnosis and treatment of TB was included, such as the presence of symptoms and signs that suggested infection or inflammation of a specific site, anatomic site of infection, date and result of laboratory, microbiologic and radiologic tests.

2.3. CT evaluation

Patients underwent either non-enhanced CT (n=41) or contrast-enhanced chest CT (n=76) with high-resolution CT (HRCT)
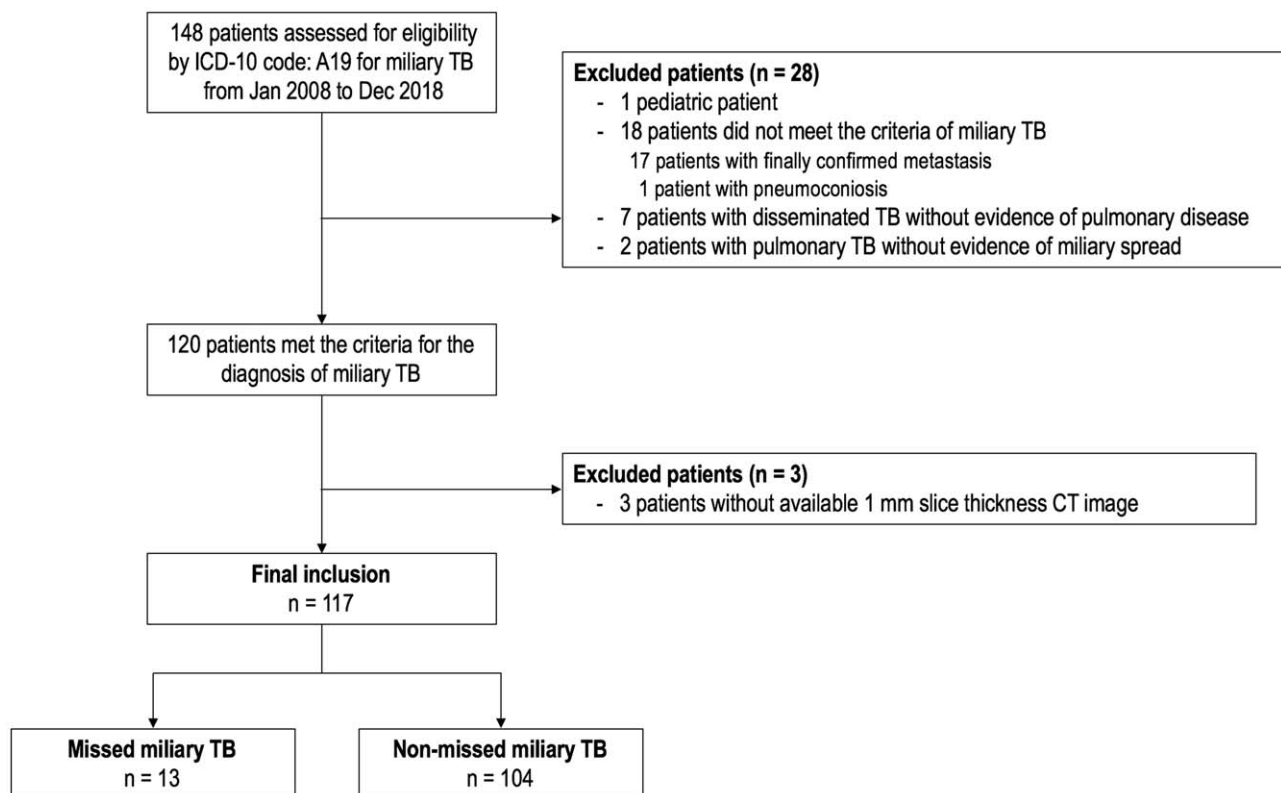

Figure 1. Flow chart of the study inclusion. ICD-10 = 2019 international classification of diseases-10 diagnosis code; TB = tuberculosis; CT = computed tomography.

images at the time of symptom onset and initial admission to hospital as a part of routine clinical evaluation. In the conventional CT scanning, CT scans were reconstructed into axial images with 3 mm slice thickness at 3 mm intervals without gaps (n = 110) or 5 mm slice thickness at 5 mm intervals (n = 7), and coronal images with 5 mm slice thickness. For HRCT scans, axial and coronal images with 1 mm slice thickness at 5 mm intervals and a bone algorithm were obtained.

CT scans obtained before the administration of anti-TB medication were retrospectively reviewed in consensus by 2 chest radiologists (J.C. and M.Y.K., with 3 years and 22 years of experience in thoracic radiology, respectively). The predominant nodule size, demarcation, and distribution (axial and cranio-caudal) of miliary nodules were evaluated.[20] The "classic" miliary nodule was defined as a well-defined nodules (2−4 mm) with random and widespread in distribution. A "non-classic" miliary nodule was defined when micro-nodules could not be clearly discernible with ill-defined margin and/or smaller size (less than 2 mm) showing coarse and granular appearance (Fig. 2). Other ancillary findings of miliary TB were evaluated, including the presence of interlobular septal thickening, ground glass opacities (GGO), intrathoracic lymphadenopathy (short-axis diameter ≥1 cm and/or central necrosis), and pleural effusion.[21,22] The extent of GGO was categorized as 4 categories; none < 25%, 25% to 50%, ≥ 50% of whole lung field.[20,23] The presence and dominant location of secondary TB features (including clustered centrilobular nodules with or without tree-in-bud appearance, macronodule measuring > 10 mm, focal bronchial wall thickening, and focal consolidation) were also evaluated, suggesting bronchogenic spread of the TB focus. The total disease extent was evaluated in a 4 point scale: subtle (< 25%), mild (25%−50%), moderate (50%−75%), and severe (> 75%) of whole lung field. The presence of significant respiratory motion artifacts on CT was also evaluated.

2.4. Statistical analysis

Categorical variables were compared using the χ^2 or Fisher exact test, and continuous variables were compared using the Student t test or the Mann–Whitney U test, as appropriate. Risk factors associated with missed miliary TB were investigated in univariable and multivariable analysis using logistic regression models. Variables with $P \leq .20$ in univariable analysis were included in the final multivariable model. In addition, clinically important risk factors (such as immunocompromised host) and radiologically important features were included despite having nonsignificant P values in univariable analysis. All tests of significance were 2-tailed and a $P < .05$ was considered statistically significant. Calculations were performed using SPSS for Windows, version 21.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Patient characteristics

A total of 117 patients met the criteria for the diagnosis of miliary TB and were included in the analysis (mean age, 57.7 ± 18.6; 53 males and 64 females); 74 patients (63.2%) initially showed sputum smears negative for AFB stain. Of the total patient cohort, 13 (11%) were classified into the missed miliary TB group (Fig. 1).

The baseline characteristics and clinical outcomes are summarized in Table 1. Patients with missed miliary TB were significantly older than patients with non-missed miliary TB (median age, 71 vs 57 years, respectively; $P = .024$). There was no significant difference between the initial clinical symptoms, the number of immunocompromised patients, and the sites of extrapulmonary TB between the 2 groups. The median duration from the chest CT to anti-TB medication was significantly longer in patients with missed miliary TB (median, 11.0 days; IQR, 6.5 − 30.5) than in patients with non-missed miliary TB (median 1.0 day, IQR 0.0 − 2.0), demonstrating a significant delay in diagnosis and treatment ($P < .001$). There was no statistically significant difference in the in-hospital mortality rate between the missed and non-missed groups (7.7% vs 6.7%, respectively; $P = .897$; Table 1).

3.2. CT features associated with missed miliary TB and non-missed miliary TB

The CT findings of miliary TB in missed and non-missed miliary TB are summarized in Table 2. Among the 117 patients, 90
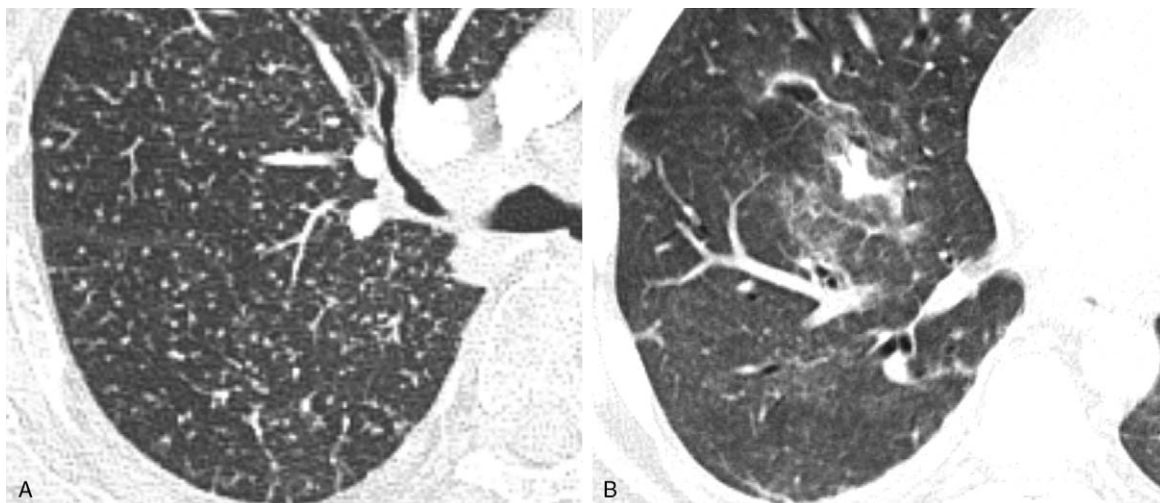

Figure 2. Example of CT interpretation of miliary nodules. (a) Miliary nodule with well-defined nodules measuring 2−4 mm and showing random distribution on axial high-resolution CT. (b) Miliary nodule with ill-defined miliary nodules measuring less than 2 mm showing coarse and granular appearance on axial high-resolution CT.

Baseline clinical characteristics and outcomes of the 117 patients with missed miliary TB and non-missed miliary TB.

Variables	Missed miliary TB (n=13)	Non-missed miliary TB (n=104)	*P* value
Age, median (IQR), years	71.0 (61.0–77.5)	57.0 (43.3–73.8)	.024
Male	4 (30.8)	49 (47.1)	.264
Initial clinical symptom or sign			
Fever or febrile sense	8 (61.5)	63 (60.6)	.947
Cough or sputum	4 (30.8)	31 (29.8)	.943
Dyspnea	1 (7.7)	21 (20.2)	.277
Other symptoms	4 (30.8)	57 (54.8)	.102
Underlying disease			
HIV	1 (7.7)	7 (6.7)	.897
Solid tumor	1 (7.7)	8 (7.7)	1.000
Chronic kidney disease	1 (7.7)	15 (14.4)	.505
Liver cirrhosis	1 (7.7)	6 (5.8)	.783
Diabetes mellitus	2 (15.4)	25 (24.0)	.485
Underlying condition			
Steroid use[a]	2 (15.4)	14 (13.5)	.849
Immunosuppressant use[b]	1 (7.7)	16 (15.4)	.458
Immunocompromised host[c]	6 (46.2)	54 (51.9)	.695
Previous history of tuberculosis treatment	0 (0)	15 (14.4)	.143
Positive sputum AFB smear	4/11[d] (36.4)	39/102 (38.2)	.903
Positive sputum culture	7/11 (63.6)	76/102 (74.5)	.438
Positive bronchial aspirate or BAL AFB smear	0 /4 (0)	10/43 (23.3)	.277
Positive bronchial aspirate or BAL culture	1/4 (25.0)	28/43 (65.1)	.114
Positive M. tuberculosis PCR[e]	4/10 (40.0)	40/80 (50.0)	.551
Pathologic confirmed	7/8 (87.5)	31/41 (75.6)	.461
Patient with concurrent extrapulmonary TB	7 (53.8)	58 (55.8)	.895
Lymph node	0 (0)	8 (7.7)	.300
Pleural	0 (0)	3 (2.9)	.535
Pericardial	0 (0)	1 (1.0)	.723
Intra-abdominal	1 (7.7)	8 (7.7)	1.000
Genitourinary	0 (0)	1 (1.0)	.723
Skeletal	1 (7.7)	5 (4.8)	.657
Central nervous system	1 (7.7)	11 (10.6)	.747
Bone marrow	0 (0)	3 (2.9)	.535
Skin and soft tissue	0 (0)	2 (1.9)	.614
Larynx	0 (0)	1 (1.0)	.723
Disseminated	4 (30.8)	16 (15.4)	.165
Interval from CT to anti-TB medication (IQR), days	11.0 (6.5–30.5)	1.0 (0.0–2.0)	<.001
Outcome			
In-hospital mortality	1 (7.7)	7 (6.7)	.897
7 day mortality	0 (0)	1 (1.0)	.723
30 day mortality	1 (7.7)	6 (5.8)	.783
60 day mortality	1 (7.7)	7 (6.7)	.897
90 day mortality	1 (7.7)	8 (7.7)	1.000

[a] Corticosteroid use is defined as the use of corticosteroids at a mean minimum dose of 0.3 mg/kg/d of prednisolone equivalent for ≥3 weeks.

[b] Treatment with immunosuppressants (e.g., tacrolimus, cyclosporine, sirolimus, azathioprine, or mycophenolate mofetil) during the previous 90 days.

[c] Immunocompromised host is defined as patients with underlying diseases such as human immunodeficiency virus infection, malignancy, liver cirrhosis, and chronic renal failure, or those receiving immunosuppressive treatment.

[d] Number of patients with a positive test result/number of patients tested.

[e] Positive M. tuberculosis PCR is defined as positive M. tuberculosis PCR and/or Xpert TB/RFP PCR.

Data are presented as number (%) unless otherwise indicated. IQR = interquartile range; HIV = human immunodeficiency virus; AFB = acid fast bacilli; BAL = bronchoalveolar lavage; M. Tuberculosis = Mycobacterium tuberculosis; PCR = polymerase chain reaction; TB = tuberculosis; CT = computed tomography.

(76.9%) showed secondary TB features on CT, which was most frequently seen in typical locations of TB, i.e., both upper lobes and the superior segment of both lower lobes in both study groups. The demarcation of miliary nodules were more frequently ill-defined and smaller (<2 mm, with a granular appearance) on CT in patients with missed miliary TB than in patients with non-missed miliary TB (*P* < .001 for both). There was no significant difference in the prevalence of TB scars, presence and extent of GGO, interlobular septal thickening, and secondary TB features. However, the location of secondary TB features was less frequently seen in the typical location of pulmonary TB in the patients with missed miliary TB compared with those with non-missed miliary TB (*P* = .021). In the patients with missed miliary TB, the distribution of disease was more frequently seen to be in a central (*P* = .012) rather than an even distribution, and a higher proportion of patients showed a subtle disease extent (46.2% vs 8.7%; *P* < .001) compared with patients with non-missed miliary TB. Among the 13 patients with missed miliary TB, CT findings were reported as a negative, with the exception of nonspecific inflammatory nodules in 3 patients, viral

Table 2

Chest computed tomography features of the 117 patients with missed miliary TB and non-missed miliary TB.

Characteristics	Missed miliary TB (n = 13)	Non-missed miliary TB (n = 104)	P value
Underlying emphysema or small airway disease	2 (15.4)	7 (6.7)	.270
TB scar	6 (46.2)	32 (30.8)	.264
Demarcation of miliary nodule			
Ill-defined	11 (84.6)	15 (14.4)	<.001
Well-defined	2 (15.4)	89 (85.6)	<.001
Size of dominant miliary nodule			
<2 mm, granular	9 (69.2)	13 (12.5)	<.001
≥2 mm	4 (30.8)	91 (87.5)	<.001
CT pattern of miliary nodule[a]			
Classic miliary nodule	9 (69.2)	13 (12.5)	<.001
Non-classic miliary nodule	4 (30.8)	91 (87.5)	<.001
Ground glass opacity			.578
None	9 (69.2)	64 (61.5)	
<25%	0 (0)	13 (12.5)	
25%–50%	2 (15.4)	11 (10.6)	
≥50%	2 (15.4)	16 (15.4)	
Interlobular thickening	1 (7.7)	21 (20.2)	.277
Secondary TB feature			
Centrilobular nodule	9 (69.2)	76 (73.1)	.769
Tree-in-bud	7 (53.8)	63 (60.6)	.641
Macronodule >10 mm	5 (38.5)	46 (44.2)	.692
Focal bronchial wall thickening	7 (53.8)	60 (57.7)	.792
Focal consolidation	3 (23.1)	41 (39.4)	.251
Location of secondary TB[b]			
Typical[c]	7/9 (77.8)	78/81 (96.3)	.021
Atypical[c]	2/9 (22.2)	3/81 (3.7)	.021
Lymphadenopathy	3 (23.1)	51 (49.0)	.077
Necrosis[d]	1/4 (25.0)	19/66 (28.8)	.871
Pleural effusion			
Unilateral	2 (15.4)	24 (23.1)	.529
Bilateral	1 (7.7)	33 (31.7)	.072
Distribution			
Cranio-caudal			
Upper lung	3 (23.1)	36 (34.6)	.405
Middle lung	0 (0)	0 (0)	–
Lower lung	0 (0)	1 (1.0)	.723
Whole lung	10 (76.9)	67 (64.4)	.370
Axial			
Central	2 (15.4)	2 (1.9)	.012
Peripheral	0 (0)	0 (0)	–
Even	11 (84.6)	102 (98.1)	.012
Disease extent			
Subtle <25%	6 (46.2)	9 (8.7)	<.001
Mild 25−50%	5 (38.5)	40 (38.5)	1.000
Moderate 50−75%	2 (15.4)	40 (38.5)	.102
Severe >75%	0 (0)	15 (14.4)	.143

[a] CT pattern of classic miliary nodule refers to well-defined and small nodules (2–4 mm) with random distribution and non-classic miliary nodule was defined when micro-nodules could not be clearly discernible with poorly-defined margin and/or smaller size (less than 2 mm) showing coarse and granular appearance.

[b] Location of secondary TB feature was evaluated in the subgroup of patients who showed secondary TB features described above (n=89).

[c] Typical location of secondary TB feature includes both upper lobes and both lower lobe superior segments. Atypical location of secondary TB feature refers to the other lung areas, including right middle lobe, left upper lobe lingular division, and both lower lobe basal segments.

[d] Presence of necrosis in lymph nodes was evaluated in the subgroup of patients who showed secondary lymphadenopathy and underwent contrast-enhanced CT (n=70).

Data are presented as number (%) unless otherwise indicated. TB = tuberculosis.

pneumonia in 5 patients, drug reaction in 1 patient, metastasis of either lung cancer or other unknown primary tumor in 4 patients, lymphoproliferative disease in 1 patient, and fungal infection in 1 patient (Figs. 3 and 4). Of these patients, 5 underwent follow-up CT scans within 2 months (median, 29 days; range, 15−55 days), and all patients showed aggravation of disease with a CT pattern of classic miliary nodule. Respiratory motion artifacts on CT were present in 23 patients (3 patients [23.1%] in the missed miliary TB group and 20 patients [19.2%] in the non-missed miliary TB group; P=.740). Contrast-enhancement can hamper to detect subtle disease on CT but the proportion of CT scans with contrast-enhancement was similar between the 2 groups (missed vs non-missed miliary TB, 84.6% vs 62.5%; P=.117). In terms of slice thickness of CT scan, 7 patients were reconstructed with thick (5 mm) slice thickness but in these patients, no patients were missed and all included in the non-missed miliary TB group.
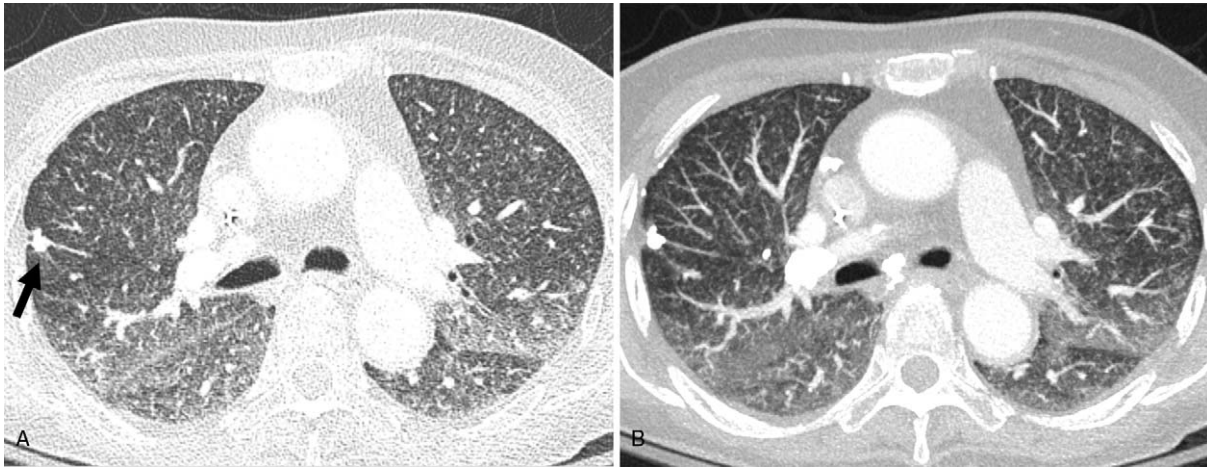
Figure 3. 73-year-old woman with missed miliary TB. (a) Miliary TB in a 73-year-old woman admitted to hospital with persistent fever and underlying diffuse large B-cell lymphoma with ongoing chemotherapy. A lung window of an axial CT (1.0 mm section thickness) shows fine, ill-defined nodules predominantly < 2 mm in size and showing a coarse, granular appearance distributed throughout both lungs, with ill-defined, patchy ground glass opacities. A calcified granuloma is shown in right upper lobe, possible a sequelae of previous tuberculosis (arrow). Miliary TB was missed on the initial CT reading at symptom onset. The CT was interpreted as an atypical pathogen pneumonia, such as viral pneumonia or a drug reaction. (b) 8-mm axial maximum intensity projection (MIP) slab shows non-classic miliary nodules superimposed on same level of image, which is more conspicuous on MIP slab.

3.3. Independent risk factors associated with missed miliary TB

The clinical and radiologic risk factors associated with missed miliary TB are shown in Table 3. In the univariable analysis, older age (odds radio [OR], 1.05; 95% confidence interval [CI], 1.01−1.10; $P = .027$) was a significant clinical risk factor. Among the radiologic variables, ill-defined miliary nodules (OR, 32.63; 95% CI, 6.57−162.10; $P < .001$), miliary nodule size less than 2 mm showing granular appearance (OR, 15.80; 95% CI, 4.24−58.57; $P < .001$), central distribution (OR, 9.27; 95% CI, 1.19−72.48; $P = .034$) and subtle disease extent (OR, 9.05; 95% CI, 2.50−32.77; $P = .001$) were significant risk factors. Multivariable analysis revealed that ill-defined miliary nodules

(OR, 15.64; 95% CI, 2.73−89.77; $P = .002$) and miliary nodule size less than 2 mm (OR, 10.08; 95% CI, 1.87−54.50; $P = .007$) were independent predictors for missed miliary TB. Age remained marginally significant ($P = .061$) in multivariable analyses.

4. Discussion

Miliary TB is a potentially lethal disease and early diagnosis remains challenging even for experienced clinicians. The current study shows that a substantial number of patients with miliary TB can be missed on initial chest CT (11.1%) in the tertiary hospital of intermediate TB burden country, resulting in delayed diagnosis and treatment. Missed miliary TB was more frequent in the elderly, and ill-defined and smaller-sized miliary nodules showing
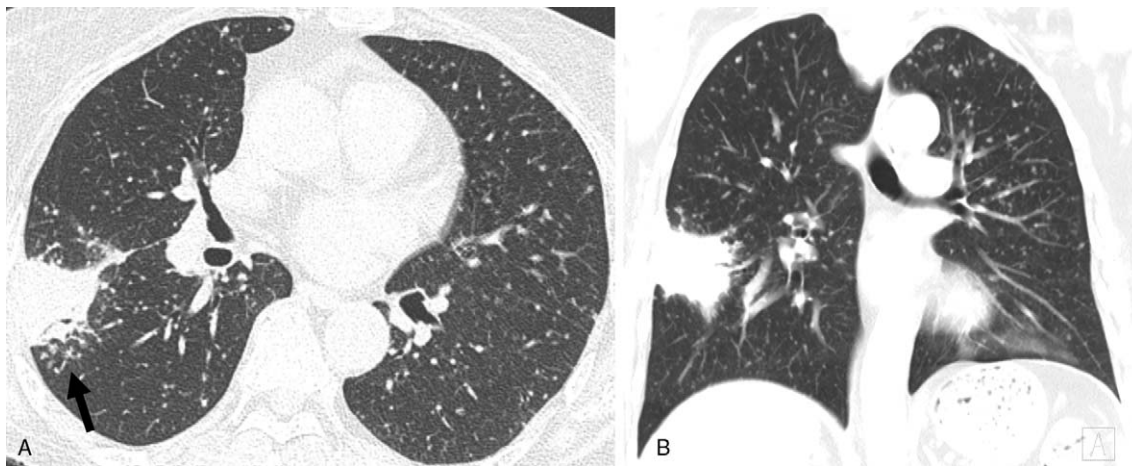

Figure 4. 67-year-old woman with missed miliary TB. Miliary TB in a 67-year-old woman who was admitted to hospital with persistent fever. (a) A lung window of an axial CT (1.0 mm section thickness) shows irregular mass-like consolidation in the right lower lobe superior segment and surrounding centrilobular nodules with branching opacities, showing tree-in-bud appearance (arrow). (b) A lung window of a coronal CT (5 mm section thickness) shows multiple well-defined randomly distributed micronodules, predominantly 2−4 mm in size, in both lungs. Miliary TB was missed on the initial CT reading at symptom onset. Mass-like consolidation in the right lower lobe was misinterpreted as a primary lung cancer, and miliary nodules were interpreted as metastasis. Centrilobular nodules with tree-in-bud appearance located in locations typical of secondary TB were neglected and not interpreted appropriately.

Table 3

Univariable and multivariable analysis to identify the clinical and radiological risk factors of missed miliary TB.

	Univariable analysis		Multivariable analysis	
	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Clinical characteristics				
Age, years	1.05 (1.01 − 1.10)	.027	1.05 (1.00 − 1.11)	.061
Immunocompromised host	0.79 (0.25 − 2.52)	.695		
Disseminated tuberculosis	2.44 (0.67 − 8.90)	.175		
CT characteristics				
Miliary nodule				
Nodule demarcation, ill-defined	32.63 (6.57 − 162.10)	<.001	15.64 (2.73 − 89.77)	.002
Dominant nodule size, < 2 mm (granular)	15.80 (4.24 − 58.57)	<.001	10.08 (1.87 − 54.50)	.007
Extent of ground glass opacity ≥ 50%	1.27 (0.36 − 4.45)	.712		
Interlobular thickening	0.33 (0.04 − 2.68)	.300		
Secondary TB feature				
Atypical location[a]	7.43 (1.06 − 52.17)	.044		
Central distribution	9.27 (1.19 − 72.48)	.034		
Subtle disease extent (disease extent < 25%)	9.05 (2.50 − 32.77)	.001		

[a] Typical location of secondary TB feature includes both upper lobes and both lower lobe superior segments. Atypical location of secondary TB feature refers to the other lung areas, including right middle lobe, left upper lobe lingular division, and both lower lobe basal segments.
OR = odds ratio; CI = confidence interval; TB = tuberculosis.

coarse and granular appearance were seen to be significant independent risk factors associated with missed miliary TB.

The median duration from chest CT to anti-TB medication was 11 days in the missed TB group, which was ten times longer than that seen in the non-missed group. As a result, appropriate administration of anti-TB medication was delayed, and the transmission of TB to other patients or the deterioration of the prognosis during the period of diagnostic delay is a matter of concern.[11] Clinical factors (such as the patients' underlying disease and immune status) were not associated with missed miliary TB. Therefore, it is important to understand that approximately 10% of patients with miliary TB can present showing less typical CT findings ("non-classic" miliary nodules) and subtle disease extent, which may be helpful for the diagnosis and treatment of miliary TB.

With global population ageing, TB in the elderly is an increasingly challenging clinical and epidemiological problem. In our study, old age was the only significant clinical risk factor associated with missed miliary TB which remained marginally significant (*P* = .061) in multivariate analyses. It can be associated with that older patients might have lower threshold to seek medical care and presenting earlier in the course of the disease showing less typical imaging findings and subtle disease extent. Old age is also known to be associated with poor prognosis in patients with miliary TB.[24] Therefore, it is important for clinician to have a suspicion for miliary TB when patient presents regardless of uncertain clinical and imaging features and more detailed surveillance of miliary TB should be undertaken in elderly patients.

In previous studies, the typical chest CT findings of miliary TB were randomly distributed miliary nodules (2−4 mm) with GGO, reticular opacity, and interlobular septal thickening.[2,5,25] These typical features ("classic" miliary nodule) are consistent with the chest CT findings of the non-missed miliary TB population in the current study. However, we found that in cases of missed miliary TB, these typical CT findings were presented in only a small number of patients (2/13, 15.4%), and the majority of patients with missed miliary TB showed less typical and non-classic features. The differential diagnoses for these atypical CT findings can include viral pneumonia (such as cytomegalovirus pneumonia), hypersensitivity pneumonitis or drug reaction, miliary metastasis, and lymphoproliferative disease. The observation of non-classic miliary nodules may be due to the patient being in the early stages of disease or due to decreased immune response, with premature or more unstructured granulomas demonstrating less-defined and smaller-sized miliary nodules.[26,27] It is known that the arrival of TB-specific T-cells in the lungs coincides with the arrest of bacterial proliferation 14 to 21 days after initiation of infection, although the defense and immune response to TB infection depends on the patients balance of T-cells and tumor necrosis factor-α (TNFα) production.[27–29] Five patients in the missed miliary TB group underwent follow-up CT scans within 2 months and all showed aggravation of disease with classic miliary nodule. Therefore, in cases of patients with a clinical presentation that cannot rule out miliary TB, it is important to consider the possibility of TB, and short-term follow-up chest CT might be beneficial.

The current study also showed that among the 117 study patients, 76.9% of patients showed combined secondary TB features on CT, which were most frequently seen in typical locations, i.e., both upper lobes and the superior segment of both lower lobes in both groups. This suggests that the primary focus of infection may be the lung in a high proportion of patients. In the missed TB group, atypical location of secondary TB features were more frequent compared to non-missed group which were more easily neglected. Therefore, carefully identifying secondary TB features will be important clues to aid differential diagnosis. In the previous study of Lee J et al,[12] miliary TB patients with an extent of GGO > 50% had less discernible miliary nodule on CT and had a greater potential for delayed diagnosis, however, no significant difference was found in proportion of GGO extent ≥ 50% between missed and non-missed TB group in our study.

In our study, there were no significant differences in mortality between missed and non-missed miliary patients although there was a significant difference regarding the diagnostic delay between 2 groups. This could be resulted from the small number of patients in missed miliary group as well as a small number of event (death) in the study cohort.

The efficacy of the mycobacterial culture or PCR of miliary TB is lower compared with that for pulmonary TB, despite of extensive lung involvement in miliary TB. It is known that only 30% to 65% of cases of miliary TB are positively diagnosed on the basis of sputum culture.[30] In this context, miliary TB is usually classified as pauci-bacillary TB, despite the high mycobacterial antigenic burden. Our previous studies demonstrated that the sensitivity of Xpert TB/RIF, even in the bronchoalveolar lavage fluid from patients with very low pauci-bacillary pulmonary TB, was only 31%.[31,32] Rapid diagnostic tests such as AFB smear and *M. tuberculosis* PCR revealed low sensitivity (38% and 49%, respectively), and *M. tuberculosis* culture that required 2 to 6 weeks' incubation also exhibited suboptimal sensitivity (73%).[32–35] Therefore, early diagnosis of miliary TB relies heavily on CT findings.

Our study has several limitations. First, it was a retrospective study with a small sample size that limits the generalizability of findings and raises the possibility of selection bias. The small number of patient with missed miliary TB may have reduced statistical power. Patients with less typical chest CT findings may be underestimated because some missed TB patients may remain undiagnosed or have a different diagnostic code who cannot be included in the cohort. Second, culture of *M. tuberculosis* and rapid molecular tests were not performed in all patients. In our hospital, the Xpert TB/RIF PCR test was introduced in August 2014, and this test has been conducted in selected patients with suspected TB due to the national insurance coverage criteria for this test (i.e., suspected multidrug-resistant TB, life-threatening TB, and exposure to multidrug-resistant TB patients). Nevertheless, our findings reflect real clinical practice regarding suspicion of TB and delayed diagnosis in an intermediate TB burden country. Third, only 1 patient with HIV was included in our study population. Therefore, our conclusions might be hard to apply in countries with a high prevalence of HIV. Finally, among the patients, CT scan protocols were variable in terms of slice thickness and use of contrast agent. However, there was no significant difference in proportion of missed TB with different CT protocols. For the image reconstruction, maximum intensity projection (MIP) images were not evaluated in this study because in our hospital MIP reconstruction was not routinely used. MIP were known to improve the detection of pulmonary nodules.[36] Therefore, it might help to detect subtle disease and less discernible nodule in case of non-classic miliary nodule but it could also exaggerate the GGO components which make more difficult the interpret the CT findings.

In conclusion, approximately 10% of miliary TB could be missed on initial chest CT, resulting in a delayed diagnosis and treatment. Caution is required in patients with ill-defined and smaller sized miliary nodules showing granular appearance and follow-up chest CT might have a benefit.

Author contributions

Conceptualization: Mi Young Kim.
Data curation: Jooae Choe, Kyung Hwa Jung, Joung-Ha Park.
Formal analysis: Jooae Choe, Kyung Hwa Jung.
Supervision: Sung-Han Kim, Mi Young Kim.
Writing – original draft: Jooae Choe, Kyung Hwa Jung.
Writing – review & editing: Jooae Choe, Kyung Hwa Jung, Mi Young Kim.

References

[1] Sharma SK, Mohan A, Sharma A, et al. Miliary tuberculosis: new insights into an old disease. Lancet Infect Dis 2005;5:415–30.
[2] Oh YW, Kim YH, Lee NJ, et al. High-resolution CT appearance of miliary tuberculosis. J Comput Assist Tomogr 1994;18:862–6.
[3] Optican RJ, Ost A, Ravin CE. High-resolution computed tomography in the diagnosis of miliary tuberculosis. Chest 1992;102:941–3.
[4] Hauser H, Gurret JP. Miliary tuberculosis associated with adrenal enlargement: CT appearance. J Comput Assist Tomogr 1986;10:254–6.
[5] McGuinness G, Naidich DP, Jagirdar J, et al. High resolution CT findings in miliary lung disease. J Comput Assist Tomogr 1992;16:384–90.
[6] van Crevel R, Ottenhoff TH, van der Meer JW. Innate immunity to Mycobacterium tuberculosis. Clin Microbiol Rev 2002;15:294–309.
[7] Jones BE, Ryu R, Yang Z, et al. Chest radiographic findings in patients with tuberculosis with recent or remote infection. Am J Respir Crit Care Med 1997;156:1270–3.
[8] Geng E, Kreiswirth B, Burzynski J, et al. Clinical and radiographic correlates of primary and reactivation tuberculosis: a molecular epidemiology study. JAMA 2005;293:2740–5.
[9] Siddiqi K, Lambert ML, Walley J. Clinical diagnosis of smear-negative pulmonary tuberculosis in low-income countries: the current evidence. Lancet Infect Dis 2003;3:288–96.
[10] Schlossberg D. Tuberculosis and Nontuberculous Mycobacterial Infections (Seventh Edition). 2017 American Society of Microbiology.
[11] Virenfeldt J, Rudolf F, Camara C, et al. Treatment delay affects clinical severity of tuberculosis: a longitudinal cohort study. BMJ Open 2014;4:e004818.
[12] Lee J, Lim JK, Seo H, et al. Clinical relevance of ground glass opacity in 105 patients with miliary tuberculosis. Respir Med 2014;108:924–30.
[13] Cho KS. Tuberculosis control in the Re public of Korea. Epidemiol Health 2018;40:e2018036–2018030.
[14] Johnson JL, Vjecha MJ, Okwera A, et al. Impact of human immunodeficiency virus type-1 infection on the initial bacteriologic and radiographic manifestations of pulmonary tuberculosis in Uganda. Makerere University-Case Western Reserve University Research Collaboration. Int J Tuberc Lung Dis 1998;2:397–404.
[15] Kiyan E, Kilicaslan Z, Gurgan M, et al. Clinical and radiographic features of pulmonary tuberculosis in non-AIDS immunocompromised patients. Int J Tuberc Lung Dis 2003;7:764–70.
[16] Munoz P, Rodriguez C, Bouza E. Mycobacterium tuberculosis infection in recipients of solid organ transplants. Clin Infect Dis 2005;40:581–7.
[17] Kamboj M, Sepkowitz KA. The risk of tuberculosis in patients with cancer. Clin Infect Dis 2006;42:1592–5.
[18] Cho YJ, Lee SM, Yoo CG, et al. Clinical characteristics of tuberculosis in patients with liver cirrhosis. Respirology 2007;12:401–5.
[19] Kim SH, Song KH, Choi SJ, et al. Diagnostic usefulness of a T-cell-based assay for extrapulmonary tuberculosis in immunocompromised patients. Am J Med 2009;122:189–95.
[20] Nachiappan AC, Rahbar K, Shi X, et al. Pulmonary tuberculosis: role of radiology in diagnosis and management. Radio Graphics 2017;37:52–72.
[21] Burrill J, Williams CJ, Bain G, et al. A radiologic review. Radio Graphics 2007;27:1255–73.
[22] Kim JY, Jeong YJ, Kim KI, et al. Miliary tuberculosis: a comparison of CT findings in HIV-seropositive and HIV-seronegative patients. Br J Radiol 2010;83:206–11.
[23] Hong SH, Im JG, Lee JS, et al. High resolution CT findings of miliary tuberculosis. J Comput Assist Tomogr 1998;22:220–4.
[24] Wakamatsu K, Nagata N, Kumazoe H, et al. Prognostic factors in patients with miliary tuberculosis. J Clin Tuberculosis Mycobacterial Dis 2018;12:66–72.
[25] Lee KS, Song KS, Lim TH, et al. Adult-onset pulmonary tuberculosis: findings on chest radiographs and CT scans. AJR Am J Roentgenol 1993;160:753–8.
[26] de Noronha AL, Bafica A, Nogueira L, et al. Lung granulomas from Mycobacterium tuberculosis/HIV-1 co-infected patients display decreased in situ TNF production. Pathol Res Pract 2008;204:155–61.
[27] Miyoshi S, Takasaki J, Mine S, et al. Fatal unusual miliary tuberculosis in which a patient developed acute respiratory distress syndrome induced by infliximab: an autopsy case report. Intern Med 2017;56:1079–83.
[28] Ndlovu H, Marakalala MJ. Granulomas and inflammation: host-directed therapies for tuberculosis. Front Immunol 2016;7:434.

[29] Cooper AM. Cell-mediated immune responses in tuberculosis. Annu Rev Immunol 2009;27:393–422.

[30] Sharma SK, Mohan A, Sharma A. Challenges in the diagnosis & treatment of miliary tuberculosis. Indian J Med Res 2012;135: 703–30.

[31] Hong J, Lee SH, Ryu BH, et al. Diagnostic usefulness of bronchoalveolar lavage fluid xpert MTB/RIF in pauci-bacillary pulmonary tuberculosis. Infect Dis (Lond) 2018;50:725–7.

[32] Park JH, Choe J, Bae M, et al. Clinical characteristics and radiologic features of immunocompromised patients with pauci-bacillary pulmonary tuberculosis receiving delayed diagnosis and treatment. Open Forum Infect Dis 2019;6:ofz002.

[33] Kim JH, Langston AA, Gallis HA. Miliary tuberculosis: epidemiology, clinical manifestations, diagnosis, and outcome. Rev Infect Dis 1990; 12:583–90.

[34] ATS adopts diagnostic standards for tuberculosis. American Thoracic Society. Am Fam Physician 2001;63:979–80.

[35] Steingart KR, Schiller I, Horne DJ, et al. Xpert(R) MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev 2014;Cd009593.

[36] Kawel N, Seifert B, Luetolf M, et al. Effect of slab thickness on the CT detection of pulmonary nodules: use of sliding thin-slab maximum intensity projection and volume rendering. Am J Roentgenol 2009; 192:1324–9.