Diagnosis of tuberculosis pleurisy with three endoscopic features *via* pleuroscopy

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Abstract

Background: Tuberculosis (TB) is a constant threat even with a worldwide active public health campaign. Diagnosis of TB pleurisy is challenging in the case of pleural effusion of unknown origin after aspiration analysis. The study was designed to demonstrate a simple image interpretation technique to differentiate TB pleurisy from non-TB pleurisy using semi-rigid pleuroscopy.

Methods: The study retrospectively enrolled 117 patients who underwent semi-rigid pleuroscopy from April 2016 to August 2018 in a tertiary hospital. We analyzed the possibility of TB pleurisy using three simple pleuroscopic images *via* semi-rigid pleuroscopy.

Results: Among 117 patients, 28 patients (23.9%) were diagnosed with TB pleurisy. Sago-like nodules/micronodules, adhesion, and discrete distribution were noted in 20 (71.4%), 20 (71.4%), and 19 (67.9%) patients with TB pleurisy, respectively. Sago-like nodules/micronodules, adhesion, and discrete distribution were noted in six (6.7%), 37 (41.6%), and no (0.0%) patients with non-TB pleurisy, respectively. The positive and negative predictive values of any two out of three pleuroscopic patterns for TB pleurisy were 100.0% and 93.7%, respectively.

Conclusions: A high positive predictive value for TB pleurisy was demonstrated by the presence of any two out of the three characteristic features. Absence of all three features had an excellent negative predictive value for TB pleurisy. Our diagnostic criteria reconfirm that pleuroscopic images can be used as predictors for TB pleurisy in patients with undiagnosed pleural effusion.

The reviews of this paper are available via the supplementary material section.

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Introduction

Despite the aggressive public health strategy and effective treatments against tuberculosis (TB), it remains a major infectious cause of death worldwide, with 9 million new cases and nearly 2 million deaths annually.[1] Tuberculous pleural effusion is a common manifestation of extra-pulmonary TB and is the leading cause of pleural effusion in some geographical areas.[2–5] The incidence of TB pleurisy as a manifestation of extrapulmonary TB is 23–66%.[6] In contrast, TB accounts for 25–44% of all cases of pleural effusion.[3]

The early diagnosis of TB pleurisy is crucial for a favorable clinical outcome. A previous study reported that prognosis was worse if effective anti-TB treatment was delayed even by a duration of 2 weeks after the first visit.[7] A time-consuming diagnostic process is the major cause of delay in effective anti-TB treatment in the early stage of the disease. Conventional diagnostic tests include microscopic examination of the pleural fluid for acid-fast bacilli (AFB); mycobacterial culture of the pleural fluid, sputum, or pleural tissue; and pathological examination of the pleural tissue for granulomatous inflammation. Microscopic examination of the pleural fluid is positive for AFB in less than 5% of cases due to the paucibacillary nature of the disease,[8,9] while mycobacterial culture of the pleural fluid is time-consuming and has low sensitivity

(24–58%).[9,10] Biopsy of the pleural tissue for combined histological examination and mycobacterial culture of the pleural fluid and tissue is the most sensitive method among currently available methods.[11] The levels of adenosine deaminase (ADA) in pleural fluid have high sensitivity and specificity in the diagnosis of TB pleurisy.[12,13] However, the use of ADA may not be widely available in developing countries.

In clinical practice, undiagnosed pleural effusion is frequently encountered even after thoracentesis and closed tube biopsy. The possible causes for undiagnosed pleural effusion include malignancy, TB, infection and inflammation.[14] Therefore, invasive procedures for biopsy under direct visualization *via* pleuroscope are employed to reach the diagnosis. Recent evidence suggests that a semi-rigid pleuroscope is an effective diagnostic tool for undiagnosed pleural effusion.[14] Semi-rigid pleuroscopy is conducted by a non-surgical pulmonologist in the endoscopy suite, with patients under local anesthesia and conscious sedation. The diagnostic yield of closed tube biopsy ranges from 50% to 60%.[11] Pleuroscopy has been demonstrated to improve the diagnostic accuracy of TB pleurisy[15] in undiagnosed pleural effusion. The improved diagnostic yield of semi-rigid pleuroscopy is mostly due to examination of the pleural lesion and guides the biopsy of abnormal pleural lesions. Apart from its role in improving the diagnostic yield of TB pleural disease, abnormal pleural lesions can be observed directly under the pleuroscope. Several characteristic patterns could be observed in the pleuroscopic examination.[16] By identifying the characteristic features of TB pleurisy, precise biopsy of the targeted lesion may increase the diagnostic yield rate and reduce the duration of the procedure. In addition, tissue culture for mycobacterial detection and drug sensitivity test can be performed using this procedure. The aim of the present study was to investigate the sensitivity and sensitivity of three characteristic features observed under semi-rigid pleuroscopy for the diagnosis of TB pleural effusion.

Methods

Patients
The present study was approved by the Institutional Review Board (IRB) of Chang Gung Memorial Foundation (IRB no.: 201902075B0). We retrospectively recruited 120 patients from April 2016 to August 2018 at Linkou Chang Gung Memorial Hospital, Taiwan, which is a tertiary referral medical center. Consecutive patients who underwent semi-rigid pleuroscopy within the study period were identified from the database and their demographic characteristics were recorded. Among the 120 patients who received pleuroscopy, three patients were excluded due to failure in biopsy. The causes for failure of biopsy were severe adhesion without enough explored view ($n = 1$), the presence of bronchopleural fistula ($n = 1$), and severe cough during the pleuroscopy procedure ($n = 1$). Therefore, a total 117 patients were recruited for final analysis.

Diagnostic criteria of TB pleurisy
Patients with TB pleurisy were defined according to a previous study. They included patients with confirmed as well as probable TB pleurisy.[17] A patient with confirmed TB pleurisy was defined as a patient with a pleural fluid sample that was culture-positive for *Mycobacterium tuberculosis* and/or a histopathological finding consistent with TB on pleural biopsy. A patient with probable TB pleurisy was defined as a patient with at least one of the following characteristics: (a) sputum specimen that was culture-positive for *M. tuberculosis*; (b) other biological specimens that were culture-positive for *M. tuberculosis*; (c) raised pleural lymphocytes and protein levels; and (d) a positive response to anti-TB medication with the absence of other possible causes of pleural effusion. According to previous studies,[9,10] patients with positive *M. tuberculosis* culture results represent a relatively small portion of all cases of TB pleurisy. The present study employed a combination of pleural *M. tuberculosis* culture, pleural pathological analysis, and clinical diagnosis as the reference method for diagnosing TB pleurisy. To confirm the diagnosis of TB pleurisy, two senior physicians independently reviewed each patient's clinical and laboratory records.

Procedure and equipment
All patients underwent pleuroscopy performed by an experienced operator and two trained assistants. All patients received moderate sedation with fentanyl and midazolam with or without propofol during the procedure. Before starting the examination, chest ultrasound was performed to identify the optimal entry site with the patients in the decubitus position. After local administration
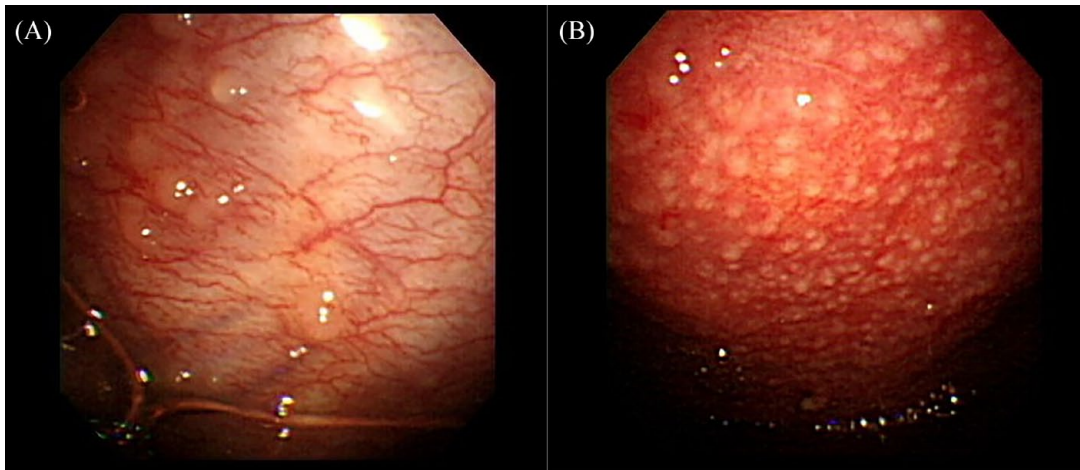
Figure 1. A representative case of tuberculosis pleurisy.
The pleuroscopic image shows sago-like nodules (A) and micronodules (B).

of 2% lidocaine for anesthesia, a 1.0-cm incision was made followed by thoracotomy with an 8-mm flexible trocar (MAJ-1058, Olympus Medical Systems Corp., Japan). A semi-rigid thoracoscope (LTF-240; Olympus, Tokyo, Japan) was initially used for draining the effusion and for exploring the pleural cavity. Cryoprobe or a pair of forceps (FB-15C-1; Olympus, Tokyo, Japan) were used for biopsy through the working channel of the semi-rigid thoracoscope. A 1.9 or 2.4-mm flexible cryoprobe (Erbokryo CA, Erbe, Germany) was used to perform cryobiopsy with carbon dioxide as the cryogen. The cooling time of each cryobiopsy was approximately 3 s and the temperature of the probe tip reached approximately −70°C. At least three biopsies were considered the standard procedure in each patient. The biopsy area was restricted in parietal pleura. For histopathological analyses, all biopsy samples were transported in separate formalin containers. The biopsy samples were processed according to standard protocols for histopathological and immunohistochemical staining. After completing the biopsies, a drainage tube with a 16 Fr pigtail catheter (BT-PDS-1630-W-NK1; Bioteq, Taipei, Taiwan) was placed to monitor and drain the pleural effusion. The timing of catheter removal was decided by clinicians' judgment based on the amount of pleural effusion (less than 50 ml) and the clinical condition.

Specimen processing
The pleural and sputum specimens were processed according to the procedure described in a previous report.[18] Briefly, pleural fluid and sputum specimens were stained with Ziehl–Neelsen stain for microscopic examination. Decontamination was performed using *N*-acetyl-L-cysteine-sodium hydroxide (BBL MycoPrep; Becton Dickinson, Cockeysville, MD, USA). The samples were cultured in BACTEC 12B vials (radiometric BACTEC 460TB system; Becton Dickinson, Franklin Lakes, NJ, USA) and Lowenstein–Jensen medium (Bio-Rad, Marnesla-Coquette, France).

Image analysis
Each pleuroscopy image was evaluated for three features, namely the character of nodules, adhesion, and the distribution of the lesions. Three characteristic features were adopted for differentiating TB pleurisy from non-TB pleurisy: (a) lesions with sago-like nodules (Figure 1A) or micronodules (Figure 1B); (b) the presence or absence of adhesion (Figure 2); and (c) the distribution of the lesions (discrete or fused together) (Figure 3). To define the absence or the presence of these three features among subjects, it took 10–15 min to make a conclusion between two senior pulmonologists. They evaluated the clinical course and discussed each pleuroscopy image to arrive at a consensus.

Statistical analysis
Data were expressed as mean ± standard error of the mean. Student's *t*-test was used for the comparison of continuous variables between patients with TB pleurisy and those with non-TB pleurisy, while the Mann–Whitney U-test was used for
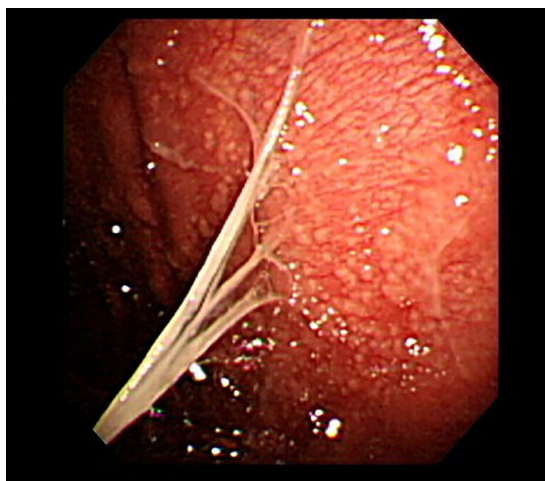
Figure 2. A representative case of adhesion.
The pleuroscopic image shows the presence of fibrous bands between the visceral and the parietal pleura.
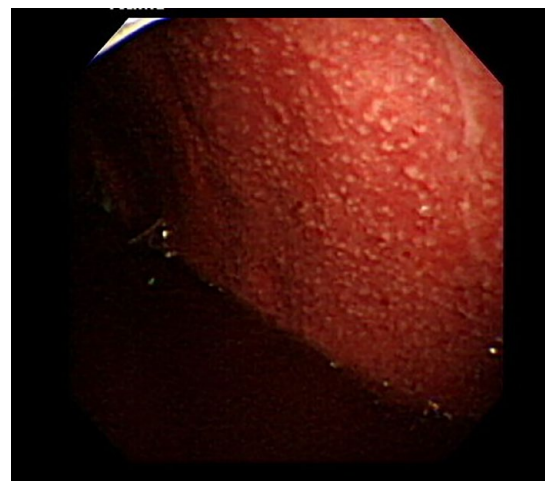

Figure 3. A representative case of discrete distribution of lesions.
The pleuroscopic image shows diffusely distributed lesions of similar size.

non-normal distributions. Categorical variables were compared with the chi-squared test or Fisher's exact test. Univariate logistic regression analysis with odds ratios and 95% confidence intervals (CIs) were used to assess the difference in diagnostic yields between the groups. The sensitivity, specificity, positive predictive value, and negative predictive value were expressed as 95% CIs. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using SPSS version 13.0 (SPSS Inc.; Chicago, IL, USA).

Results

Diagnoses of pleural effusion
Among 117 patients, 28 had TB pleurisy and 89 had non-TB pleurisy. The causes for non-TB pleurisy included adenocarcinoma ($n = 39$), squamous cell carcinoma ($n = 2$), metastatic carcinoma ($n = 6$), lymphoma ($n = 1$), mesothelioma ($n = 1$), mesothelial cell hyperplasia ($n = 2$), reactive mesothelial changes ($n = 1$), fibrinous pleuritis ($n = 24$), empyema ($n = 5$), Wegener's granulomatosis ($n = 1$), and undiagnosed ($n = 7$) (Table 1).

The characteristic patterns of pleuroscopy images
Sago-like nodules or micronodules (the 'A pattern') in the pleuroscopy images were noted in 20 patients (71.4%) with TB pleurisy and in six patients (6.7%) with non-TB pleurisy ($p < 0.001$)

(Table 2). Adhesion (the 'B pattern') in the pleuroscopy image was observed in 20 patients (71.4%) with TB pleurisy and in 37 patients (41.6%) with non-TB pleurisy ($p = 0.006$). Discrete distribution (the 'C pattern') was observed in the pleuroscopy images of 19 patients (67.9%) with TB pleurisy and in none of the patients (0%) with non-TB pleurisy. The presence of sago-like nodules or micronodules was found in the non-TB group with a diagnosis of adenocarcinoma ($n = 1$), methothelioma ($n = 0$), and fibrous pleuritis ($n = 3$). The adhesion was noted in the non-TB group with a diagnosis of adenocarcinoma ($n = 15$), methothelioma ($n = 0$), and fibrous pleuritis ($n = 13$). The presence of A + B features were observed in 13 patients (46.4%), A + C features were observed in 16 patients (57.1%), and B + C features were observed in 11 patients (39.3%) with TB pleurisy. Among patients with non-TB pleurisy, no patient presented with two concomitant features. The presence of any two characteristic features (A + B, A + C, or B + C) was noted in 22 patients (78.6%) with TB pleurisy and in none of the patients with non-TB pleurisy. The presence of all three pleuroscopic features was noted in nine patients (32.1%) with TB pleurisy. The presence of all three features was observed in none of the patients with non-TB pleurisy. In contrast, the absence of all three pleuroscopic features was observed in none of the patients with TB pleurisy, but it was observed in 46 patients (51.7%) with non-TB pleurisy.

Table 1. Diagnosis and causes of pleural effusion in 117 patients.

Diagnosis	Number (%)
TB pleurisy	28 (23.9)
Non-TB pleurisy	
Adenocarcinoma	39 (33.3)
Squamous cell carcinoma	2 (1.7)
Metastatic carcinoma	6 (5.1)
Lymphoma	1 (0.9)
Mesothelioma	1 (0.9)
Mesothelial cell hyperplasia	2 (1.7)
Reactive mesothelial changes	1 (0.9)
Fibrinous pleuritis	24 (20.5)
Empyema	5 (4.3)
Wegener's granulomatosis	1 (0.9)
Undiagnosed	7 (6.0)

Data are presented as number (percentage).
TB, Tuberculosis.

Predictive values of pleuroscopic features for TB pleurisy

The predictive values were initially measured based on each feature alone. Adhesion had the highest sensitivity for the diagnosis of TB pleurisy (71.4%). However, it had the lowest specificity (58.4%). In contrast, discrete distribution had the highest specificity (100.0%) and the lowest sensitivity (67.9%). The sensitivity (71.4%) of sago-like nodules/micronodules was the same as the sensitivity of adhesion. The specificity of sago-like nodules/micronodules (93.3%) was intermediate. The positive predictive value of all three pleuroscopic features for TB pleurisy was 100.0%. The negative predictive value of a lesion with none of the three pleuroscopic features for the diagnosis of TB pleurisy was 100.0%. The positive and the negative predictive values of any two out of three pleuroscopic features for TB pleurisy were 100.0% and 93.7%, respectively (Table 3).

Discussion

The present study showed that with three simplified image features, namely sago-like nodules or micronodules, adhesion, and discrete distribution, pleuroscopy might be a useful tool for differentiating TB pleurisy from non-TB lesions. The presence of any single feature yields a positive predictive value of 39.4% for malignancy. The likelihood of TB pleurisy rises to 100% when the lesion exhibits any two of the specific features. A lesion with all three features is almost certain to indicate TB pleurisy. In contrast, the absence of any of these features is extremely likely to exclude the diagnosis of TB pleurisy.

Conventional diagnostic tests for TB pleurisy include microscopic examination of the pleural fluid for AFB; mycobacterial culture of the pleural fluid, sputum, or pleural tissue; and pathological examination of the pleural tissue for granulomatous inflammation.[8] Mycobacterial culture is a time-consuming process. Hence, sputum AFB smear, pleural effusion AFB smear, and pleural biopsy can provide clinical evidence for the early diagnosis of TB pleurisy. Due to the low prevalence of pleural effusion AFB smear positivity, pleural biopsy is the major contributor to the rapid diagnosis of TB pleurisy. Rapid diagnosis and treatment have long been considered a crucial factor for better outcome in TB patients.[7] Pleural biopsy *via* pleuroscopy has been widely used due to the higher diagnostic yield when compared with conventional closed tube

Table 2. Prediction of tuberculosis pleurisy based on pleuroscopy image features.

Features	TB pleurisy (*n* = 28)	Non-TB pleurisy (*n* = 89)	OR	95% CI	*p* Value
Sago-like nodules or micronodules	20 (71.4)	6 (6.7)	34.6	10.8–110.9	<0.001
Adhesion	20 (71.4)	37 (41.6)	3.5	1.4–8.8	0.006
Discrete distribution	19 (67.9)	0 (0.0)	–	–	–

Values are presented as number (percentage).
CI, confidence interval; OR, odds ratio; TB, tuberculosis.

Table 3. Predictive values pleuroscopic features for tuberculosis pleurisy.

Features	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Likelihood ratio
A alone	71.4	93.3	76.9	91.2	46.500
B alone	71.4	58.4	35.1	86.7	7.776
C alone	67.9	100.0	100.0	90.8	68.642
A or B or C	100.0	51.7	39.4	100.0	33.534
A and B and C	32.1	100.0	100.0	82.4	28.294
A and B	46.4	100.0	100.0	85.6	42.953
A and C	57.1	100.0	100.0	88.1	55.129
B and C	39.3	100.0	100.0	84.0	35.425
AB or AC or BC	78.6	100.0	100.0	93.7	84.010

A, Sago-like nodules or micronodules; B, adhesion; C, discrete distribution.

biopsy. In addition, pleuroscopy could provide larger sized specimens for pathological examination and tissue culture for *M. tuberculosis*. Cultures of pleural biopsies were positive in 63% of cases, while the positive culture rate of pleural fluid was 5–15%.[15] Drug resistance is a common problem in developing countries.[19] With drug sensitivity results from the culture, aggressive treatment may be administered to improve the outcome while avoiding drug resistance. If any two out of the three characteristic features could be observed in pleuroscopy, the operator should obtain specimens from multiple sites for tissue culture as well as for pathological examination.

Rupture of the sub-pleural caseous focus in the lungs into the pleural space is considered the initial event in the pathogenesis of primary TB pleural effusion. The release of mycobacterial antigens into the pleural space is followed by a delayed hypersensitivity reaction.[20] After cell injury, granulomatous inflammation, which is a histological pattern of tissue reaction, may result from *M. tuberculosis* infection. It usually consists of necrotizing granulomas. These granulomatous lesions may grossly present as sago-like lesions in the pleura. A recent study demonstrated that a sago-like nodule is the most common gross pleuroscopic finding in TB pleural effusion.[21] Our results were consistent with this finding and showed that a sago-like nodule was observed in more than 70% of the patients with TB pleurisy.

Fibrous tissue formation and adhesions between two different tissues are important reactions during the healing process, especially after inflammation. Adhesion of the pleural cavity may be due to chronic inflammation caused by TB pleurisy. Fibrin is abundant in exudative pleural effusion and may form concentrated deposits. Fibrin might give rise to pleural adhesions, fibrotic septa, and even chronic loculation. In addition, some of the patients with TB pleurisy who have undergone thoracentesis for drainage have more potential for coagulation and adhesion formation. Over two-thirds of the cases with TB pleurisy showed adhesions on thoracoscopy in previous reports.[16,22] We also observed that the most common appearance of a pleural lesion in TB pleurisy was adhesion with fibrotic septa on pleuroscopic examination.

In contrast to the discrete distribution pattern of a benign disease, malignant pleural lesions were likely to appear as fused and bulging nodules of various sizes on pleuroscopic examination.[23] The rapid growth of cancer cells and central necrosis pattern may result in the appearance of these lesions. Considering the pathophysiology of TB pleurisy with rupture of antigens into the pleural cavity causing diffuse hypersensitivity reaction, discrete distribution of lesions is a reasonable presentation for TB pleurisy. Therefore, our study suggested that discrete and non-bulging lesions might be the characteristic features for TB pleurisy. The present study showed that 67.9% of

the patients with TB pleurisy presented with discrete distribution of lesions. The study by Kong *et al.* also reported that 64.5% of the TB pleurisy cases showed diffuse miliary lesions on medical pleuroscopic examination.[16]

The principal limitation of the present study is its retrospective nature, which might have resulted in an underestimation of the incidence of TB pleurisy and bias in patient selection. Moreover, the sample size of the study was small. Therefore, the results of the present study should be interpreted with caution. Prospective studies with a larger sample size are warranted to confirm the application of these specific features in pleuroscopic examination of undiagnosed pleural effusion. Finally, the study did not measure ADA in pleural fluid. Given the high sensitivity and specificity of ADA,[12,13] it is widely used in the diagnosis of TB pleurisy. Nonetheless, the use of ADA measurement in pleural fluid may be limited in terms of availability in developing countries. Due to the requirement for an invasive procedure for pleuroscopy to look for features in patients suspected of TB *versus* non-TB pleurisy, the results of the study may only be applied in certain countries and hospitals.

Conclusion

In conclusion, a simple classification of pleuroscopic images may prove to be a useful tool for differentiating TB pleurisy from other pleural lesions. A high positive predictive value for TB pleurisy was demonstrated by the presence of any two out of the three characteristic features. The absence of all three features had an excellent negative predictive value for TB pleurisy. Our diagnostic criteria reconfirm that pleuroscopic images can be used as predictors for TB pleurisy in patients with undiagnosed pleural effusion.

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Supplemental material

The reviews of this paper are available via the supplemental material section.

References

1. Dye C, Scheele S, Dolin P, *et al.* Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. *JAMA* 1999; 282: 677–686.

2. Valdes L, Pose A, San Jose E, *et al.* Tuberculous pleural effusions. *Eur J Intern Med* 2003; 14: 77–88.

3. Liam CK, Lim KH and Wong CM. Causes of pleural exudates in a region with a high incidence of tuberculosis. *Respirology* 2000; 5: 33–38.

4. Valdes L, Alvarez D, Valle JM, *et al.* The etiology of pleural effusions in an area with high incidence of tuberculosis. *Chest* 1996; 109: 158–162.

5. Metry MA, Al Salmi I, Al-Abri S, *et al.* Epidemiology and outcome of tuberculosis in

immunocompromised patients. *Saudi J Kidney Dis Transpl* 2017; 28: 806–817.

6. Ozvaran MK, Baran R, Tor M, *et al.* Extrapulmonary tuberculosis in non-human immunodeficiency virus-infected adults in an endemic region. *Ann Thorac Med* 2007; 2: 118–121.

7. Lin MT, Wang JY, Yu CJ, *et al.* Mycobacterium tuberculosis and polymorphonuclear pleural effusion: incidence and clinical pointers. *Respir Med* 2009; 103: 820–826.

8. Light RW. Useful tests on the pleural fluid in the management of patients with pleural effusions. *Curr Opin Pulm Med* 1999; 5: 245–249.

9. Escudero Bueno C, Garcia Clemente M, Cuesta Castro B, *et al.* Cytologic and bacteriologic analysis of fluid and pleural biopsy specimens with Cope's needle. Study of 414 patients. *Arch Intern Med* 1990; 150: 1190–1194.

10. Seibert AF, Haynes J Jr, Middleton R, *et al.* Tuberculous pleural effusion. Twenty-year experience. *Chest* 1991; 99: 883–886.

11. Lin CM, Lin SM, Chung FT, *et al.* Amplified *Mycobacterium tuberculosis* direct test for diagnosing tuberculous pleurisy – a diagnostic accuracy study. *PLoS One* 2012; 7: e44842.

12. Burgess LJ, Maritz FJ, Le Roux I, *et al.* Combined use of pleural adenosine deaminase with lymphocyte/neutrophil ratio. Increased specificity for the diagnosis of tuberculous pleuritis. *Chest* 1996; 109: 414–419.

13. Neves DD, Dias RM and Cunha AJ. Predictive model for the diagnosis of tuberculous pleural effusion. *Braz J Infect Dis* 2007; 11: 83–88.

14. Lee CS, Li SH, Chang CH, *et al.* Comparison of diagnostic yield and safety between semirigid pleuroscopic cryobiopsy and forceps biopsy for undiagnosed pleural effusion. *Can Respir J* 2019; 2019: 5490896.

15. Casalini AG, Mori PA, Majori M, *et al.* Pleural tuberculosis: medical thoracoscopy greatly increases the diagnostic accuracy. *ERJ Open Res* 2018; 4: 00046–2017.

16. Kong XL, Zeng HH, Chen Y, *et al.* The visual diagnosis of tuberculous pleuritis under medical thoracoscopy: a retrospective series of 91 cases. *Eur Rev Med Pharmacol Sci* 2014; 18: 1487–1495.

17. Moon JW, Chang YS, Kim SK, *et al.* The clinical utility of polymerase chain reaction for the diagnosis of pleural tuberculosis. *Clin Infect Dis* 2005; 41: 660–666.

18. Lin SM, Ni YL, Kuo CH, *et al.* Endobronchial ultrasound increases the diagnostic yields of polymerase chain reaction and smear for pulmonary tuberculosis. *J Thorac Cardiovasc Surg* 2010; 139: 1554–1560.

19. Wang TY, Lin SM, Shie SS, *et al.* Clinical characteristics and treatment outcomes of patients with low- and high-concentration isoniazid-monoresistant tuberculosis. *PLoS One* 2014; 9: e86316.

20. Barnes PF, Mistry SD, Cooper CL, *et al.* Compartmentalization of a CD4+ T lymphocyte subpopulation in tuberculous pleuritis. *J Immunol* 1989; 142: 1114–1119.

21. Thomas M, Ibrahim WH, Raza T, *et al.* Medical thoracoscopy for exudative pleural effusion: an eight-year experience from a country with a young population. *BMC Pulm Med* 2017; 17: 151.

22. Wang Z, Xu LL, Wu YB, *et al.* Diagnostic value and safety of medical thoracoscopy in tuberculous pleural effusion. *Respir Med* 2015; 109: 1188–1192.

23. Ceruti P, Lonni S, Baglivo F, *et al.* Endoscopic diagnosis and management of pleural effusion in malignant pleural mesothelioma. *J Thorac Dis* 2018; 10: S269–S275.