RELAPSE RATE OF TUBERCULOUS PLEURAL EFFUSION AMONG PATIENTS WITH RESIDUAL PLEURAL THICKENING AFTER COMPLETING SHORT COURSE DIRECTLY OBSERVED TREATMENT

Itthiphat Arunsurat[1], Wipa Reechaipichitkul[1], Apichart So-ngern[2], Pailin Ratanawatkul[1] and Worawat Chumpangern[1]

1Division of Pulmonary, [2]Division of Sleep Medicine, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen Province, Thailand

Abstract. Residual pleural thickening (RPT) is a common residual after tuberculous pleural effusion (TPE) treatment but it is unclear what the tuberculosis (TB) relapse rate is among Thai patients with RPT. In this study we aimed to determine the TB relapsed rate among patients with RPT who had been treated by short course directly observed treatment (DOTS) and determine the prevalence, clinical characteristics, radiographic findings and pleural fluid analysis results of patients with RPT in order to inform TB control programs. We retrospectively reviewed the medical records of patients with TPE who presented to Srinagarind Hospital, Khon Kaen University, Thailand between 1 January 2014 and 30 November 2019, looking for evidence of relapse in these patients for at least 18 months after completing therapy for TPE. A total of 49 subjects were included in the study; 31 (63%) were male. Thirty-seven subjects (76%) developed RPT. The mean (±standard deviation (SD)) age of subjects with RPT was 53 (±17) years and subjects without RPT was 52 (±19). The common presenting symptoms among study subjects were: cough in 32 subjects (65%), fever in 25 subjects (51%), dyspnea in 21 subjects (43%) and pleuritic chest pain in 12 subjects (25%). The common underlying illnesses among subjects were: hypertension in 14 subjects (29%), diabetes mellitus in 8 subjects (16%) and chronic kidney disease in 6 subjects (12%). Thirty-four subjects (69%) were treated with the standard regimen of isoniazid, rifampicin, ethambutol and pyrazinamide for 2 months followed by isoniazid and rifampicin for 4 months (2IRZE/4IR). None of the TPE cases were treated with therapeutic thoracentesis or pleurodesis. There were no relapses of TB among patients with RPT. Our results suggest the current management of TPE cases using DOTS is adequate to prevent relapse of TB.

Keywords: tuberculous pleural effusion, residual pleural thickening, relapse rate, DOTS

Corresponding Author: Apichart So-ngern, Division of Sleep medicine, Department of Medicine, Faculty of Medicine, Khon Kaen university, Khon Kaen, 40002, Thailand
Tel: +66 (0) 4334 8360 Ext 3746, 3664; Fax: +66 (0) 4320 3767, +66 (0) 4334 8399
E-mail: apicso@kku.ac.th

INTRODUCTION

Tuberculosis (TB) is a major public health problem in many parts of the world. The World Health Organization (WHO) Global Tuberculosis report for 2019 estimated that world-wide TB incidence in 2018 was 10.0 million people (WHO, 2019). Southeast Asia had the largest number of TB cases in 2018, comprising 44% of the total cases world-wide (WHO, 2019). In 2018, Thailand was in the top 30 countries world-wide with the greatest proportion of the population with TB (WHO, 2019). The WHO estimated the incidence of TB in Thailand during 2018 was 153 cases per 100,000 population (WHO, 2019).

In 2018, pulmonary TB comprised 85% of the total TB cases (WHO, 2019). Tuberculous pleural effusion (TPE) is a common type of extrapulmonary TB, including in Thailand (Light, 2010; Wiwatworapan and Anantasetagoon, 2008). An old study from South Africa reported TPE occurred in 20% of TB cases among subjects who are HIV seronegative (Saks and Posner, 1992). An older study from Thailand reported 53.1% of TB cases had pulmonary TB and the rest had extrapulmonary TB and TPE was the second most common form of extrapulmonary TB following TB lymphadenitis (Wiwatworapan and Anantasetagoon, 2008).

Treatment regimen and duration of TPE is the same as pulmonary TB (Zhai *et al*, 2016). The effusion resolves on average 6-12 weeks after anti-TB treatment (Light, 2010; Zhai *et al*, 2016). After completion of TPE treatment, residual pleural thickening (RPT) occurs in approximately 26-73% (Barbas *et al*, 1991; Kwon *et al*, 2008; Lai *et al*, 2003; Soler *et al*, 1995). Therapy that has been tried and failed to prevent RPT including therapeutic thoracentesis, corticosteroid administration and pleural drainage (Bhuniya *et al*, 2012; Lai *et al*, 2003; Matchaba and Volmink, 2000). The TPE relapse rate among patients with RPT is unclear in the Thai population. The primary objective of this study was to determine the TB relapsed rate among patients with RPT who had been treated by short course directly observed treatment (DOTS) and secondary objective was to determine the prevalence, clinical characteristics, radiographic findings and pleural fluid analysis results of patients with RPT in order to inform TB control programs. The result of study would determine the efficacy of short course DOTS therapy for prevention relapse rate of TPE who had RPT at the end of treatment.

MATERIALS AND METHODS

Study subjects and data collection

This was a retrospective cohort study conducted by reviewing the charts of patients who presented to Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand between 1 January 2014 and 30 November 2019. Inclusion criteria for study subjects were being aged >18 years and having a diagnosis of TPE. The TPE patients were identified by searching all the patient charts using the International Classification of Diseases, 10th revision (ICD-10) codes associated with pleural effusion and tuberculosis (A15.6, A16.5) (WHO, 2016). Exclusion criteria for study subjects were having a malignant pleural effusion or a pleural effusion due to another cause. A

definite diagnosis of TPE was defined as identification of Mycobacterium tuberculosis by microbiological culture or molecular method from a pleural fluid specimen and/or sputum or histopathology of a pleural biopsy demonstrating epithelioid cell granulomas and/or caseating granulomas without evidence of other causes for granulomatous disease (Zhai *et al*, 2016). A presumptive diagnosis of TPE was made using the following criteria: exudative lymphocytic effusion, a pleural fluid adenosine deaminase (ADA) level >40 U/l, no evidence of malignancy on pleural fluid cytological examination and having clinical and radiological improvement with anti-TB drugs. The standard short course anti-TB regimen consisted of isoniazid (I), rifampicin (R), pyrazinamide (Z) and ethambutol (E) for 2 months followed by isoniazid and rifampicin for 4 months (2IRZE/4IR) (WHO, 2010). Among patients who were intolerant to the standard short course anti-TB regimen, alternative regimens used were as followings: 1) isoniazid, rifampicin and ethambutol for 2 months followed by isoniazid and rifampicin for 7 months (2IRE/7IR); 2) isoniazid, pyrazinamide, ethambutol and levofloxacin (L) for 2 months followed by isoniazid and levofloxacin for 16 months (2IZEL/16IL); 3) isoniazid, rifampicin and ethambutol for 9 months (9IRE); 4) isoniazid, rifampicin and ethambutol for 2 months followed by isoniazid and ofloxacin (O) for 10 months (2IRE/10IO); 5) isoniazid, rifampicin and ethambutol for 2 months followed by isoniazid and ethambutol for 10 months (2IRE/10IE); 6) isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months followed by isoniazid, ethambutol and ofloxacin for 10 months (2IRZE/10IEO) (Bureau of Tuberculosis of Thailand, 2015). Clinical response and chest radiography were conducted every 2 months until the end of TB treatment. The digital chest radiographs from Picture Archiving and Communication System (PACS) were independently reviewed and interpreted by blinded two pulmonologists. Pleural effusion size was classified as the maximum height of the effusion in fourths of a hemithorax as seen on chest radiography. RPT after completing treatment was defined as pleural thickness >2 mm. After completing treatment, all subjects with RPT were followed every 6 months for at least 18 months to evaluate for relapse. A case of relapsed TPE was defined as recurrence of clinical symptoms with an increase in pleural effusion size. The chart of each subject meeting inclusion criteria was reviewed and the clinical characteristics, pleural fluid results, other relevant laboratory findings and the treatment outcomes were recorded.

Statistical analysis

A minimum sample size was 42 subjects was calculated to be needed for this study based on a 2.8% relapse rate based on a previous study (Dhingra *et al*, 2004). This sample size would provide a power of 80% and a two-sided alpha level of 0.05. Statistical significance was set at a p-value <0.05. Categorical variables were expressed as percentages. Continuous variables were expressed as means or medians with interquartile ranges (IQR). The Student's t-test was used to assess differences among continuous variables. For continuous

variables that did not follow a normal distribution, the non-parametric Wilcoxon (Mann-Whitney) test was used. The Chi-square test was used for categorical variables. Statistical analysis was performed using Stata, version 10.1 (StataCorp, College Station, TX).

Ethical approval

This study was approved by the Human Research Ethics Committee, Khon Kaen University (approval no. HE621550).

RESULTS

A total of 49 subjects were included in the study; 31 (63%) males. Of these, 37 subjects (76%) had RPT whereas 12 subjects (24%) had no RPT. The mean (±standard deviation (SD)) age of subjects with RPT was 53 (±17) years and subjects without RPT was 52 (±19). The median (IQR) body mass index (BMI) of subjects with RPT was 20 (19-23) kg/m^2 and subjects without RPT was 21 (19-24) kg/m^2. Twenty-two subjects (45%) had definite TPE and 27 (55%) had presumptive TPE. Of those with definite TPE: 7 (14%) had a positive PCR TB test performed on the pleural fluid, 9 (18%) had a positive TB culture from pleural fluid, 1 (2%) had a positive TB culture from pleural tissue, 2 (4%) had granulomatous inflammation found on pleural histopathology, 4 (8%) had a positive PCR TB test from the sputum and 4 (8%) had a positive TB culture from the sputum. Of those with presumptive TPE: all had an ADA level >40 U/l and had clinical and chest radiography improvement with anti-TB therapy.

Table 1 showed the characteristics of study subjects. the All subjects had symptoms: the most common presenting symptoms were: cough in 32 subjects (65%), fever in 25 subjects (51%), dyspnea in 21 subjects (43%), weight loss in 18 subjects (37%) and pleuritic chest pain in 12 subjects (25%). Thirty-two subjects (65%) had a history of an underlying disease: hypertension in 14 subjects (29%), diabetes mellitus in 8 subjects (16%) and chronic kidney diseases in 6 subjects (12%). All subjects had HIV seronegative. Five subjects (10%) were taking immunosuppressive drugs: all were taking prednisolone (two were taking >15 mg per day). Eleven subjects (22%) had a history of a TB contact. Thirty-four subjects (69%) were treated with the standard anti-TB regimen, 10 subjects (20%) with 2IRE/7IR, 1 subject (2%) with 2IZEL/16IL, 1 subject (2%) with 9IRE, 1 subject (2%) with 2IRE/10IE, 1 subject (2%) with 2IRE/10IO and 1 subject (2%) with 2IRZE/10IEO. The median (IQR) treatment duration was 7 (6-9) months. None of the subjects were treated with pleural drainage or fibrinolysis. All the subjects had a good clinical response to treatment and the chest radiographs showed a decreased in pleural effusion in all subjects. Thirty-seven subjects (76%) had RPT after completing the anti-TB regimen.

Table 2 showed the chest radiographic results of study subjects. Unilateral pleural effusion was found in 45 subjects (92%). Right pleural effusion was found in 24 subjects (49%) and left pleural effusion was found in 21 subjects (43%). Bilateral pleural effusion was found in 4 subjects (8%). Twenty-five subjects (51%) had a pleural effusion involving <1/2 the hemithorax on chest radiography, 13 subjects (27%) had a pleural effusion involving >3/4 the

hemithorax and the remaining 11 subjects (22%) had a pleural effusion involving 1/2-3/4 the hemithorax. Nineteen subjects (39%) had parenchymal involvement on chest radiography comprised of a fibro-exudative infiltrate in 12 subjects (24%), a reticulonodular infiltrate in 6 subjects (12%), the presence of nodules in 4 subjects (8%), a patchy alveolar infiltrate in 2 subjects (4%), a miliary infiltrate in 1 subject (2%) and a cavitary lesion in 1 subject (2%) .

Table 1
Characteristics of study subjects

Characteristics	No RPT (*n*=12)	RPT (*n*=37)	*p*-value
Male, *n* (%)	6 (50)	25 (67)	0.27
Age in years, mean ± SD	52 ± 19	53 ± 17	0.56
BMI in kg/m^2, median (IQR)	21 (19-24)	20 (19-23)	0.99
Onset of symptoms in weeks, median (IQR)	2 (1-4)	3 (1-4)	0.56
Symptoms, *n* (%)			
Cough	8 (67)	24 (65)	0.90
Fever	5 (42)	20 (54)	0.45
Dyspnea	6 (50)	15 (40)	0.56
Weight loss	5 (42)	13 (35)	0.68
Pleuritic chest pain	5 (42)	7 (19)	0.11
Tuberculosis contact	3 (25)	8 (22)	0.80
Underlying disease, *n* (%)	8 (66)	24 (65)	0.90
Hypertension	6 (50)	8 (22)	0.05
Diabetes mellitus	3 (25)	5 (13)	0.35
Chronic kidney diseases	2 (17)	4 (11)	0.59
Chronic liver diseases	0 (0)	5 (13)	0.17
Cardiovascular diseases	1 (8)	4 (11)	0.80
Nephrotic syndrome	2 (17)	0 (0)	0.05
Autoimmune hemolytic anemia	0 (0)	1 (3)	0.56
Post-kidney transplant	0 (0)	1 (3)	0.56
Hematologic malignancy	0 (0)	1 (3)	0.56
On immunosuppressive drug, *n* (%)	2 (17)	3 (8)	0.58
Non-standard TB treatment regimen, *n* (%)	3 (25)	12 (32)	0.62

RPT: residual pleural thickening; SD: standard deviation; IQR: interquartile range; BMI: body mass index; TB: tuberculosis; kg/m^2: kilogram per square meter

Statistically significant at *p*-value <0.05

Table 2
Chest radiographic results of study subjects

Characteristics	No RPT (*n*=12)	RPT (*n*=37)	*p*-value
Location of pleural effusion, *n* (%)			
Right sided effusion	7 (58)	17 (46)	0.45
Left sided effusion	5 (42)	16 (43)	0.92
Bilateral effusion	0 (0)	4 (11)	0.56
Size of pleural effusion, *n* (%)			
<¼ hemithorax	3 (25)	4 (11)	0.34
¼ - ½ hemithorax	4 (33)	14 (38)	0.77
½ - ¾ hemithorax	4 (33)	7 (19)	0.29
>¾ hemithorax	1 (8)	12 (32)	0.10
Other radiographic findings, *n* (%)			
Fibroexudative infiltrate	2 (17)	10 (27)	0.46
Reticulonodular infiltrate	2 (17)	4 (11)	0.62
Nodule	1 (8)	3 (8)	0.98
Patchy alveolar infiltrate	1 (8)	1 (3)	0.43
Miliary infiltrate	0 (0)	1 (3)	0.57
Cavitary lesion	1 (8)	0 (0)	0.24

RPT: residual pleural thickening

Statistically significant at *p*-value <0.05

Table 3 showed laboratory results of study subjects. In 34 subjects (69%) the pleural fluid was straw-colored and in 15 subjects (30%) it was serosanguinous in color. The mean (+SD) pleural fluid ADA level was 48.8 ($\pm$19.1) U/l, the median (IQR) pleural fluid total protein level was 5.5 (5.0-5.8) g/dl, the median (IQR) pleural fluid lactate dehydrogenase (LDH) level was 336 (226-512) U/l and the median (IQR) pleural fluid glucose level was 113 (81-129) mg/dl. The median (IQR) pleural fluid protein/serum total protein level ratio was 0.75 (0.69-0.78), the median (IQR) pleural fluid LDH/serum LDH level ratio was 1.40 (0.82-2.27). The median (IQR) pleural fluid pH level was 7.42 (7.34-7.50). The median (IQR) pleural fluid white blood cell count was 2000 (1000-4575) cells/mm3, the median (IQR) percentage for pleural fluid lymphocytes was 82 (67-89) percent and the median (IQR) percentage of pleural fluid neutrophils was 3 (1-13) percent. Forty-one subjects (87%) had a pleural fluid specimen with predominantly lymphocytes and 5 subjects (11%) had a pleural fluid specimen with predominantly neutrophils 2 subjects (4%) had a pleural fluid specimen with >10% eosinophils.

Table 3
Laboratory results of study subjects

Characteristics	No RPT (n=12)	RPT (n=37)	p-value
Pleural fluid appearance, n (%)			
Straw color	9 (75)	24 (68)	0.67
Serosanguinous color	3 (25)	11 (32)	0.67
Pleural fluid profile			
ADA level in U/l, mean ± SD	49.1 ± 22.1	48.8 ± 18.2	0.48
Total protein in g/dl, median (IQR)	5.6 (5.1-5.9)	5.4 (5.0-5.7)	0.49
LDH level in U/l, median (IQR)	291 (206-631)	379 (253-512)	0.39
Glucose in mg/dl, median (IQR)	130 (107-147)	103 (75-127)	0.13
pH level, median (IQR)	7.41 (7.41-7.41)	7.42 (7.34-7.50)	0.75
WBC count in cell/mm^3, median (IQR)	1672 (1290-2725)	2050 (920-5000)	0.68
Differential count, n (%)			
Lymphocytes ≥50%	11 (100)	30 (86)	0.38
Neutrophils ≥50%	0	5 (14)	0.31
Eosinophils ≥10%	0	2 (6)	0.41

RPT: residual pleural thickening; SD: standard deviation; ADA: adenosine deaminase; IQR: interquartile range; LDH: lactate dehydrogenase; WBC: white blood cell

Statistically significant at p-value <0.05

The median (IQR) duration of subject follow-up after completing treatment was 33 (18-47) months. None of the TPE patients relapsed during the follow-up period even though 37 subjects (76%) had residual pleural thickening.

DISCUSSION

In our study, none of the TPE subjects with RPT relapsed during study period. The study of relapse TPE were still limited. The study from Spain with 103 TPE subjects and followed up period of 12 months revealed no case of relapse during study period (Macías *et al*, 2019). Another study from India included 36 TPE patients who completed follow up at least 18 months after treatment. There was 1 (2.8%) subject developed pulmonary TB during follow up period. However, this study did not mention the association between RPT and relapsed TB disease (Dhingra *et al*, 2004).

The prevalence of RPT in our study was 76%. This was similar to the previous reports (Barbas *et al*, 1991; Kwon *et al*, 2008; Lai *et al*, 2003; Soler *et al*, 1995). From our study, the pleural characteristics including total protein, glucose, or LDH level were not statistical significant difference between TPE subject with and without RPT. This finding was similar to previous studies. de Pablo *et al* (1997) conducted the study in Spain to determine pleural fluid parameters related to development of residual pleural thickening in TPE; they found the pleural protien, pH, gluose concentration were not statistically difference between the TPE subjects with or without RPT >2 mm. Another study from Brazil found no relationship between protein, glucose or LDH level in the pleural fluid and RPT (Barbas *et al*, 1991). Our study had some limitations. Firstly, the results cannot be applied to TPE patients infected with multidrug-resistant Mycobacterial tuberculosis. Secondly, this study was retrospective, some data were incomplete and confounding factors and selection bias could not be avoided. Thirdly, the sample size was small affecting the statistical power to determine the difference of clinical characteristic and pleural fluid parameters between the TPE with and without RPT.

In conclusion, the prevalence of RPT was frequent. There was no relapse TPE among subjects with RPT, the anti-TB drugs are able to stop when completed the course of treatment even though the patient had still RPT.

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REFERENCES

Barbas CS, Cukier A, de Varvalho CR, Barbas Filho JV, Light RW. The relationship between pleural fluid findings and the development of pleural thickening in patients with pleural tuberculosis. *Chest* 1991; 100: 1264-7.

Bhuniya S, Arunabha DC, Choudhury S, Saha I, Roy TS, Saha M. Role of therapeutic thoracentesis in tuberculous pleural effusion. *Ann Thorac Med* 2012; 7: 215-9.

Bureau of Tuberculosis of Thailand. Guideline for programmatic management of drug-resistant

tuberculosis, Thailand, 2015 [cited 2020 May 20]. Available from: URL: https://www.tbthailand.org/download/DR-TB%20Proof%2023%20FINAL.pdf [in Thai]

de Pablo A, Villena V, Echave-Sustaeta J, Encuentra AL. Are pleural fluid parameters related to the development of residual pleural thickening in tuberculosis? *Chest* 1997; 112: 1293-7.

Dhingra VK, Rajpal S, Aggarwal N, Aggarwal JK. Treatment of tuberculous pleural effusion patients and their satisfaction with DOTS - 1½ year follow up. *Indian J Tuberc* 2004; 51: 209-12.

Kwon JS, Cha SI, Jeon KN, *et al*. Factors influencing residual pleural opacity in tuberculous pleural effusion. *J Korean Med Sci* 2008; 23: 616-20.

Lai YF, Chao TY, Wang YH, Lin AS. Pigtail drainage in the treatment of tuberculous pleural effusions: a randomised study. *Thorax* 2003; 58: 149-51.

Light RW. Update on tuberculous pleural effusion. *Respirology* 2010; 15: 451-8.

Macías A, Sánchez-Montalvá A, Salvador F, *et al*. Epidemiology and diagnosis of pleural tuberculosis in a low incidence country with high rate of immigrant population: a retrospective study. *Int J Infect Dis* 2019; 78: 34-8.

Matchaba PT, Volmink J. Steroids for treating tuberculous pleurisy. *Cochrane Database Syst Rev* 2000: (2): CD001876.

Saks AM, Posner R. Tuberculosis in HIV positive patients in South Africa: a comparative radiological study with HIV negative patients. *Clin Radiol* 1992; 46: 387-90.

Soler JJ, Gil Suay V, Cordero P, Perpiñá M, Martínez E, Sanchis J. Pleural thickening in tuberculosis pleural effusion: the associated factors. *Arch Bronconeumol* 1995; 31: 157-61. [in Spanish]

Wiwatworapan T, Anantasetagoon T. Extra-pulmonary tuberculosis at a regional hospital in Thailand. *Southeast Asian J Trop Med Public Health* 2008; 39: 521-5.

World Health Organization (WHO). Global tuberculosis report 2019, 2019 [cited 2020 Mar 20]. Available from: URL: https://www.who.int/publications/i/item/global-tuberculosis-report-2019

World Health Organization (WHO). International statistical classification of diseases and related health problems, 10th revision, Fifth edition, 2016 [cited 2020 May 20]. Available from: URL: https://apps.who.int/iris/handle/10665/246208

World Health Organization (WHO). Treatment of tuberculosis: guidelines for national programmes, 2010 [cited 2020 May 20]. Available from: URL: https://www.who.int/tb/features_archive/new_treatment_guidelines_may2010/en/

Zhai K, Lu Y, Shi HZ. Tuberculous pleural effusion. *J Thorac Dis* 2016; 8: E486-94.