

Sonographic septation: a predictor of sequela of tuberculous pleurisy after treatment

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Running head: Predicting TB pleurisy sequela by sonography

ABSTRACT

Background: Findings in the literature have been quite conflicting with respect to predicting residual pleural thickening (RPT) for tuberculous pleurisy (TP). The aim of this study was to determine which sonographic feature of TP might help in predicting the development of RPT.

Methods: Eighty-seven patients with TP were enrolled prospectively. The initial sonographic features were classified as anechoic, homogeneously echogenic, complex non-septated, and complex septated. RPT level was measured 12 months after the start of anti-TB treatment. Spirometry was performed at the 6th and 12th months after the start of anti-TB treatment.

Results: A higher odds of RPT level > 10 mm was found in patients with positive TB bacillus culture in pleural fluid (OR, 20.9; 95% CI, 2.2-198.0) and complex septated sonographic pattern (OR, 145.0; 95% CI, 22.3-942.3). Complex septated sonographic pattern can predict RPT with a sensitivity of 80%, specificity of 96%, positive predict value of 84%, and negative predict value of 94%. Patients with RPT level > 10 mm had a lower force vital capacity than those without (75.4 ± 9.2 % predicted vs. 83.2 ± 9.5 % predicted, $p < 0.01$)

Conclusion: Complex septated sonographic pattern is a useful sign to predict RPT level > 10 mm one year after the start of anti-TB treatment. RPT level > 10 mm is associated with a high probability of decreased lung volumes. Therefore, the initial sonographic feature is beneficial in predicting the sequelae of TP after treatment.

KEYWORDS

sonographic septation, tuberculous pleurisy, residual pleural thickening, lung volume.

Abbreviations: LDH, lactate dehydrogenase; RPT, residual pleural thickening; TB, tuberculosis; TP, tuberculous pleurisy.

INTRODUCTION

The incidence rate of tuberculosis (TB) in Taiwan was 67.38 per 100,000 people in 2006.[1] Although the prevalence and mortality rates have decreased with time owing to the effective drug therapy, this infectious disease remains a serious public health issue because of its detrimental complications. Tuberculous pleurisy (TP) is one of TB manifestations and represents 10% of all causes of TB in Taiwan.[2] Although updated therapeutic regimens can effectively control this infectious disease and minimize its sequela, residual pleural thickening (RPT) has been found in about half of the patients.[3-5] We have previously shown that approximately 26% of patients with TP after treatment complicated with RPT levels > 10 mm.[6] RPT may result in a decreased lung volume and then have important clinical repercussions. It is therefore important to identify the clinical and functional impairment resulting from RPT in TP patients receiving anti-TB treatment. Thus, the aim of this prospective study was to investigate if the sonographic feature can serve as a predictor of patient outcomes 12 months after the start of anti-TB drugs treatment. To the best of our knowledge, limited studies have been published regarding the evaluation of RPT and the associated impairment in treated TP patients by using the initial sonographic parameters.

METHODS

Patients

Between February 2004 and January 2007, all patients aged 17 years and older with the initial presentation of pleural effusion not treated elsewhere were eligible for this prospective study. Following a thoracic sonography, all patients received a needle pleural biopsy and a diagnostic thoracentesis on the first day of hospitalization for pleural effusion. Informed consents were obtained from all patients prior to the study. TP was confirmed by the presence of caseating granulomas either with or without acid-fast bacilli on histological examination. Other diseases such as sarcoidosis, rheumatoid arthritis, and fungal or nocardial infection which may produce granulomatous pleurisy were excluded.

Standard anti-TB treatment including isoniazid (300 mg/day), rifampin (450 mg/day in patients < 50 kg body weight; 600 mg/day in patients \geq 50 kg body weight), ethambutol (800mg/day) and pyrazinamide (1500 mg/day) were given to the patients thereafter. With the exception of pyrazinamide which was administered during the initial two months only, all anti-TB drugs were administered for a total of six months. No patient had received pleural fluid drainage during the study period.

Chest x-rays

Standard posterior-anterior and lateral chest radiographs of each patient were taken on admission and on a two monthly basis during the outpatient follow-up period up to six

months after completion of the full treatment course. At initial presentation, the amount of pleural effusion on chest x-ray was recorded as small (less than 1/3 of one hemithorax), moderate (between 1/3 and 2/3 of one hemithorax), or large (more than 2/3 of one hemithorax). Significant RPT was defined as the maximal pleural thickness in excess of 10 mm on posterior-anterior and lateral chest radiographs. Measurements were made by two independent observers and concurrence was evaluated by using the Kappa index.

Pulmonary function tests

Standard spirometric tests were performed at the 6th and 12th months after the beginning of anti-TB treatment (Vitalograph, Spirotrac III., Vitalograph Inc. U.S.A.). All pulmonary function measurements were performed in accordance with the American Thoracic Society guidelines.[7]

Sonography

All patients were examined with a linear, convex and sector ultrasound transducer with the frequency of 3.5-5.0 MHz (model SSD 63, Aloka, Tokyo, Japan). According to the internal echogenicity, pleural effusions have been categorized into 4 types: anechoic, homogeneously echogenic, complex non-septated, and complex septated. Effusions induced by TB were subclassified as anechoic, complex non-septated, or complex septated since homogeneously echogenic type had not been observed among patients with TP.[8] Effusion was defined as anechogenic if totally echo-free spaces were present between the visceral and parietal pleura (Fig 1A). Effusion was defined as complex if echogenic materials were present inside the effusion, and then subclassified to non-septated or septated according to the absence or presence of septums inside the effusions (Fig1 B&C).

Statistical analysis

Data normality was assessed by using the Shapiro-Wilk test. Normally distributed numerical variables are presented as mean \pm SD, while median values with interquartile range (IQR; 25% and 75%) were expressed for the skewed data. Between-groups comparisons for continuous data were performed using the Student's *t* test or Wilcoxon rank-sum test as appropriate. Independent proportions were compared by using the Fisher exact or Chi-square test. We then performed a multiple logistic regression analysis by using a forward stepwise selection procedure to study the independent influences of these variables on the risk of RPT. Results of the logistic regression model were presented as the odds ratio (OR) and 95% CI. *p* values < 0.05 were considered statistically significant. Statistical analyses were performed by using commercially available software (SPSS version 12.0; SPSS Inc, Chicago, Illinois, USA).

RESULTS

During the 3-year period, 92 consecutive patients with TP were diagnosed. Five were excluded because of non-adherence to the treatment or loss of follow-up. Among the 87 remaining patients, 61 were male, with a mean age of 64.2 ± 18.2 years. Two experienced readers, who were blinded to the clinical history, assessed the initial size of pleural effusion and the initial and final pleural thickenings 12 months after start of anti-TB treatment. The inter-observer Kappa index was 0.95, with the strength of agreement being considered very well when $k = 0.8-1.0$.

The patient characteristics are shown in Table 1. No pleural thickening was observed in the initial radiographic and sonographic studies. Men were found to be more likely to develop RPT level > 10 mm after anti-TB treatment. The pleural fluid analytic variables are listed in Table 2. There was no significant difference in the pleural fluid analysis between 2 groups except for a higher lactate dehydrogenase (LDH) level in patient with RPT levels > 10 mm. Table 3 shows the initial sonographic features of all TP patients. No patient presented the feature of homogeneously echogenic pattern. Table 4 demonstrates the initial sonographic features in pure TP patients (i.e. TP patients without pulmonary TB). Anechoic pattern on sonography is associated with RPT levels ≤ 10 mm while complex septated pattern is associated with RPT levels > 10 mm. In univariate analysis, a higher odd ratio of RPT was found in male patients, positive TB bacillus in pleural fluid culture, higher pleural LDH and complex septated echogenic pattern. Results of multivariate logistic regression analysis are presented in Table 5. The association of RPT levels > 10 mm with positive TB bacillus in pleural fluid culture, and that with complex septated echogenic pattern remained. In 16 of 20 patients with RPT levels > 10 mm sonographic examination revealed a complex septated pattern. On the other hand, only 3 of 67 patients with RPT levels ≤ 10 mm had a complex septated pattern during the initial sonographic exam. Complex septated echogenic pattern can predict RPT levels > 10 mm after 12 months of the start of anti-TB therapy with a sensitivity of 80%, a specificity of 96%, a positive predict value of 84%, and a negative predict value of 94%. For patients with pure TP only, complex septated echogenic pattern also can predict RPT levels > 10 mm after 12 months of the start of anti-TB therapy with a sensitivity of 79%, a specificity of 96%, a positive predict value of 85%, and a negative predict value of 94%.

After 6 months of anti-TB drugs treatment, all patients were cured according to the clinical response and the improvement of serial chest radiograms. Modification of anti-TB treatment due to drug resistance was not observed. No patient received tube drainage or surgical intervention during the treatment course. At 6 and 12 months after the start of anti-TB treatment, patients with RPT levels > 10 mm had a lower force vital capacity than those without (73.6 ± 9.7 % predicted vs. 81.4 ± 9.6 % predicted, $p < 0.01$ and 75.4 ± 9.2 % predicted vs. 83.2 ± 9.5 % predicted, $p < 0.01$, respectively). In patients with pure TP, force vital capacity was also lower in those with RPT levels > 10 mm at 6 and 12 months after the

start of anti-TB treatment (74.3 ± 9.9 % predicted vs. 80.8 ± 9.3 % predicted, $p < 0.05$ and 75.4 ± 9.9 % predicted vs. 84.0 ± 18.4 % predicted, $p < 0.05$, respectively).

DISCUSSION

In the present study, we demonstrated the usefulness of sonography in predicting the sequelae of TP after anti-TB treatment. The complex septated pattern shown on the initial sonographic study appears to be a predicting feature for RPT in association with a decreased forced vital capacity.

Dutt et al. reported a good efficacy of the 6-month regimen of rifampin and isoniazid for TP in 1992 and this regimen has been widely used ever since.[9] Despite effective anti-TB chemotherapy, RPT is considered to be a common radiographic sequela in patients with TP after treatment.[3-5] The incidence of RPT levels > 10 mm one year after the start of anti-TB treatment is about 23% in the present study. RPT may reduce static and dynamic lung volumes and thus have important clinical repercussions. Therefore, clinical and functional impairments induced by RPT are not uncommon in TP patients treated with standard anti-TB drugs.

Regarding the development of RPT after anti-TB treatment, most of the studies measured RPT right at the termination of medication (i.e. six months after the beginning of anti-TB medication). However, further resolutions of RPT after discontinuance of treatment have been reported.[10-11] Radiographic improvements of RPT can occur even at six months after the completion of anti-TB chemotherapy.[10-11] Chan et al. conducted a retrospective study which assessed 83 patients with TP, and 22 patients of which had been medically treated two years previously.[10] None of them had significant RPT and their pulmonary function tests did not show any significant impairment when compared to the matched control subjects. Han et al. reported that the incidence of RPT decreased from 50.6% at 6 months to 27.1 % at 12 months after the start of medication.[11] These studies indicate that RPT is a common complication of TP and may regress with time. It is possible that RPT at the initial phase is composed of inflammatory tissues which can be diminished by anti-TB treatment. The local inflammatory hypersensitivity response within TP is mediated in part by a number of pro-inflammatory mediators such as complement-degrading products, interferon gamma and cytokines which are abundant in the pleural effusion.[10-12] As the inflammatory activity mitigated with treatment, the fibrous tissue within pleural effusion forms RPT which barely changes with time.

In this study we took 12 months after the start of anti-TB chemotherapy as the evaluating point to determine the possible risk factors. Along with demographic and clinical features, serum and pleural fluid analysis, and initial chest radiographic patterns, the initial sonographic features of TP were used to identify who were more likely to develop persistent RPT. Findings in the published literature have been quite controversial with respect to the

prediction of RPT.[3, 12] While Barbas et al. could not find any association between RPT and demographic or pleural fluid analyses including pleural LDH and glucose levels at the time of initial thoracentesis,[3] De Palbo and colleagues found that lower glucose concentration and pH level in the pleural fluid were associated with RPT.[5] In the present study the development of RPT does not appear to be well correlated to the initial pleural fluid biochemical analyses except the level of pleural LDH. Regarding gender difference in RPT, Ruit et al. found RPT to be more common in males with TP.[13] By univariate analysis, we demonstrated a male predominance of RPT. However, this finding appears to be insignificant by multivariate analysis. By multiple logistic regression analysis, we could only identify TB bacillus in pleural fluid culture and septate complex echo as significant predictors of RPT levels > 10 mm.

The value of sonography for evaluation of pleural disease has been well documented.[14-15] The presence of septation in the pleural fluid revealed by sonography has been shown to be related to the cellular debris in empyema and to clots in the hemothorax.[13, 16, 17] Sonographic septation is also a useful prognostic indicator of acute thoracic empyema.[16] Since TP may be a chronic inflammation followed by a pleural fibrosing process which may result in RPT, patients with complex septated echo patterns were more likely to benefit from intrapleural fibrinolytic therapy.[16] In the present study, 16 of 20 patients with RPT levels > 10 mm had a septated complex pattern in the initial sonography. On the other hand, there were only 3 in 67 patients with RPT levels \leq 10 mm had the septated complex sonographic patterns. The sensitivity of predicting RPT levels > 10 mm for a complex septated sonographic pattern is 84%, with a specificity of 96%, positive predict value of 84%, and negative predict value of 94%. In patients with pure TB, sonographic septation had similar predict value. Therefore, sonographic septation can serve as a useful predictor for the development of RPT after anti-TB treatment.

Akham et al. studied 20 TP patients with ultrasonography, and septations with a lattice-like appearance were found in 6 (30%) patients.[17] In 1989 Martinez et al. reported that winding bands were seen with sonography in 8 out of 21 (38%) patients with TP.[18] In the present study we showed that 17 out of 87 (21.8%) patients had septation revealed by thoracic sonography. In a recent study it was shown that early effective drainage with streptokinase for TP may reduce occurrence of RPT.[19] Therefore, predicting which patients with TP will develop RPT in the long run is crucial. Then effective drainage with fibrinolytic therapy in addition to standard anti-TB drug treatment should be introduced for such patients.

In the present study, we also showed that patients with RPT levels > 10 mm had a lower force vital capacity than those without. Although Candela et al. showed a weak correlation between the force vital capacity and the degree of radiographic pleural thickening at the end of follow-up, only 6% of patients had RPT levels > 10 mm in their study, which is much lower than in our series (26%).[20]

There were some limitations for this study. First, we were unable to test pulmonary function prior to the initial presentation of TP. It is possible that the difference of forced vital capacity between the 2 groups existed before the development of TP. However, it is not feasible to gather patients' pulmonary function before infected with TB. Furthermore, since patients with TP have the potential to be with pulmonary TB and performing pulmonary function tests might raise the concern in spreading this infectious disease, we did not check lung function at the very beginning. Another limitation is that pleural thickness was not evaluated at initial presentation of these patients, which may make the correlation of complex TP and RPT weak. However, no obvious pleural thickness had been observed in the initial radiographic studies. In addition, the patients had no previous pleural disease or other major pulmonary disease by history taking.

In conclusion, the results of the present study suggest that severe TP shares some common features with thoracic empyema. Sonographic septated complex echo pattern but not the pleural fluid biochemical analysis is a useful feature to predict RPT levels > 10 mm one year after the start of anti-TB drug treatment in patients with TP. An RPT level > 10 mm was associated with a higher probability of a decreased lung volumes.

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Figure Legend

Figure 1. Three representative sonographic patterns of tuberculous pleural effusion. A, anechoic; B complex non-septated. C, complex septated. D = diaphragm; E = effusion; L = lung; S = septum.

Table 1 Patient characteristics with residual pleural thickening (RPT) > 10 mm and RPT ≤ 10 mm

Characteristics	RPT > 10 mm (N = 20)	RPT ≤ 10 mm (N = 67)	p value
Male gender (%)	90.0	64.2	0.029
Age (years ± SD)	61.2 ± 20.3	65.1 ± 17.6	0.345
Symptoms to treatment days	11 (7-30)	10 (7-14)	0.620
Smokers (%)	55.0	34.3	0.096
Alcohol abuse (%)	15.0	9.0	0.424
Diabetes mellitus (%)	20.0	20.9	0.931
Pulmonary TB (%)	30.0	23.9	0.581
Initially large amount of pleural effusion (%)	65.0	40.3	0.148
Loculated pleural effusion (%)	20.0	16.4	0.740
Positive pleural biopsy culture (%)	25.0	31.3	0.782
Positive pleural fluid culture (%)	20.0	4.5	0.046
Sputum positive AFB (%)	25.0	16.4	0.511

AFB, acid-fast bacillus; RPT, residual pleural thickening; TB, tuberculosis.

Table 2 Pleural fluid findings of patients with RPT > 10 mm and RPT ≤ 10 mm

Pleural fluid analyses	RPT > 10 mm (N = 20)	RPT ≤ 10 mm (N = 67)	p value
Lymphocyte (%)	89.5 (76.5-93.5)	88.0 (74.0-93.0)	0.956
Neutrophil (%)	10.0 (5.0-17.0)	8.0 (3.0-18.0)	0.479
Leukocytes (cells/mm)	1732 (890-2647)	1960 (1000-3520)	0.139
LDH (U/L)	584 (290-682)	183 (127-399)	0.001
Protein (g/dL)	4.75 (4.25-5.45)	5.0 (4.40-5.40)	0.495
Glucose (mg/dL)	93 (43-132)	95 (78-114)	0.684
pH	7.20 (7.18-7.24)	7.21 (7.18-7.29)	0.126
CEA (ng/mL)	3.0 (2.0-3.7)	3.1 (2.4-3.5)	0.571

Data are expressed as median (25%-75% range).

CEA, carcinoembryonic antigen; LDH, lactate dehydrogenase.

Table 3 Initial sonographic findings of TP patients with RPT > 10 mm and RPT ≤ 10 mm

Sonographic features	RPT > 10 mm (N = 20)	RPT ≤ 10 mm (N = 67)	p value
Anechoic (%)	5.0	68.7	<0.001
Complex non-septated echoic (%)	15.0	26.8	0.276
Complex septated echoic (%)	80.0	4.5	<0.001

Table 4 Initial sonographic findings of pure TP patients with RPT > 10 mm and RPT ≤ 10 mm

Sonographic features	RPT > 10 mm (N = 14)	RPT ≤ 10 mm (N = 51)	p value
Anechoic (%)	7.1	72.5	<0.001
Complex non-septated echoic (%)	21.4	21.6	1.0
Complex septated echoic (%)	71.5	5.9	<0.001

Table 5 Odds ratio of developing RPT > 10 mm assessed by multivariate logistic regression analysis

Characteristics	Odds ratio (95% CI)	p value
Positive pleural fluid AFB	20.9 (2.2-198.0)	0.008
Complex septated echoic	145.0 (22.3-942.3)	<0.001

AFB, acid-fast bacillus; CI, confidence interval.

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