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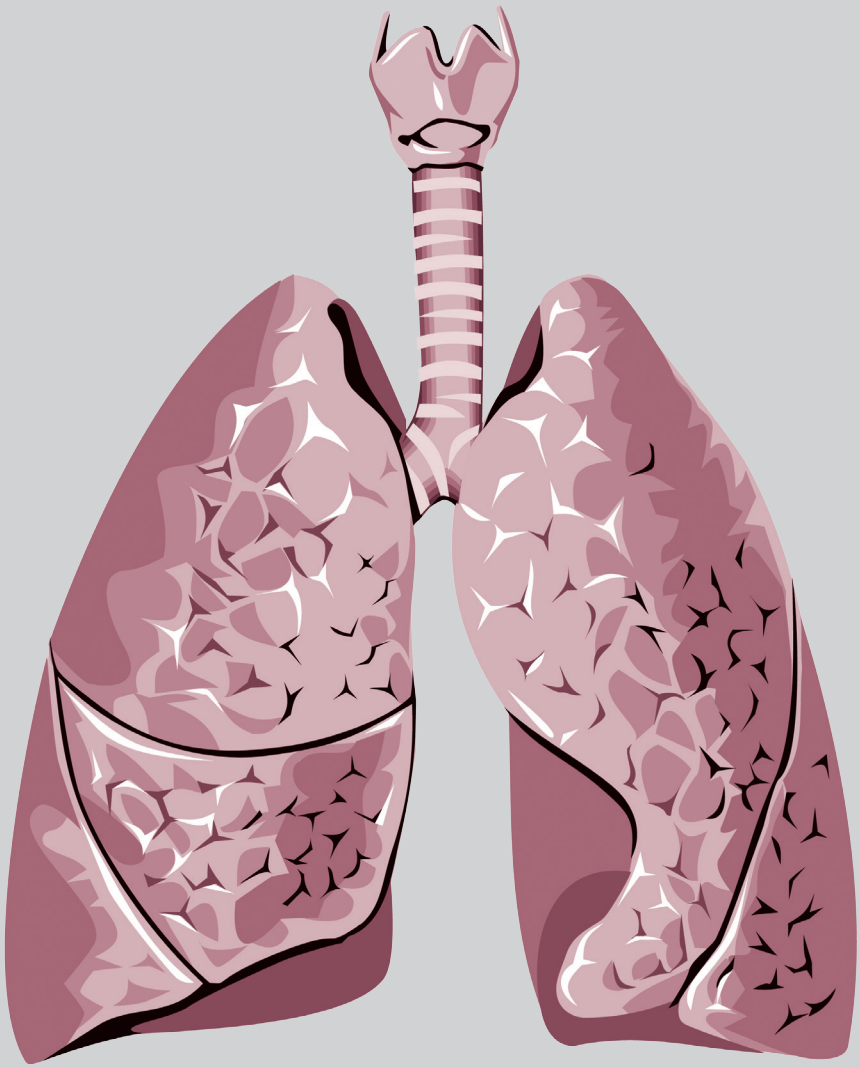

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CONTENTS

Predictors and Effects of Treatment Consistency on Recurrence of Tuberculosis: A Population-based Cohort Study in Taiwan

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Introduction: Recurrence of tuberculosis (TB) is not uncommon in active TB patients after completion of anti-TB treatment. Several disease-related and host-related factors have been reported to increase the risk of recurrence of TB. The impact of treatment consistency on TB recurrence has rarely been evaluated.

Methods: Patients with active TB were identified retrospectively from the National Health Insurance Research Database from 2006 to 2014 in Taiwan. Treatment consistency was determined on the basis of the number of days with anti-TB drugs during the intensive and continuous phases. The 2-year TB recurrence rates were analyzed and compared between patients with treatment consistency ≥80% and those with <80%. The factors associated with 2-year TB recurrence and treatment consistency were also analyzed.

Results: Among the 54,803 active TB patients included for analysis, 17,029 (32.4%) had treatment consistency <80%. The 2-year TB recurrence rate was 0.95% in the ≥80% consistency group and 1.36% in the <80% consistency group ($P < 0.001$). In multivariate analysis, treatment consistency <80% remained an independent factor for 2-year TB recurrence, with a hazard ratio of 1.49 (95% CI = 1.19–1.87). We found that individuals who were older, had extrapulmonary involvement, were male, rural area residents, and had comorbidities were more likely to have treatment consistency <80%.

Conclusion: Treatment consistency <80% was not rare in TB patients and was associated with an increased risk of TB recurrence. ***(Thorac Med 2021; 36: 147-160)***

Key words: adherence, directly observed therapy, recurrence, tuberculosis, treatment consistency

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Introduction

Global efforts to control tuberculosis (TB) currently are focused on detection, diagnosis, cure, and preventive care, but the issue of recurrence does not receive much attention. Recurrence rates after the standard 6-month treatment regimen range from 1% to 2% within 1 year and 3.4% within 5 years, depending on the region [1-2]. TB recurrence is also an integral part of the assessment of the efficacy of anti-TB regimens, which indicates the crucial role of recurrence in controlling TB [3-4].

The risk factors for TB recurrence can be classified into 3 categories: disease-related, host-related, and treatment-related. Disease-related and host-related factors, such as cavitary lesions in chest radiography, smoking, low-socioeconomic status, and comorbidities, are established facts [5-8]. Treatment-related factors, including anti-TB regimens, treatment duration, and treatment adherence also have vital roles in TB recurrence [3-4, 9-10]. Nevertheless, whether patients with treatment interruption during the intensive phase or the continuation phase would have a higher recurrence rate remains unclear.

In this study, we hypothesized that patients with interrupted treatment for any reason, during either the intensive or the continuation phase, would have an increased risk of TB recurrence. Taiwan is a TB endemic area, with an incidence of 41.4 cases per 100,000 population in 2017 [11]. The directly observed therapy strategy (DOTS) program was initiated in Taiwan in April 2006 with the intent of improving the treatment of TB patients. To prove our hypothesis, we conducted a retrospective population-based cohort study that enrolled TB patients treated after DOTS program implementation.

Methods

Study source

The National Health Insurance (NHI) program in Taiwan was initiated in 1995. This compulsory insurance system offers comprehensive health services and affordable costs, and currently covers >99% of the 23 million people in Taiwan [12]. We analyzed data from the National Health Insurance Research Database (NHIRD). The details are described in the supplementary information section. The NHIRD is a suitable database for research on long-term outcomes of diseases. This study was approved by the Institutional Review Board of Taipei City Hospital (TCHIRB-10704109-W).

Study subjects

We identified subjects who had been newly diagnosed with TB between April 2006 (the year the DOTS program was implemented in Taiwan) and December 2014 [13]. Patients who had an anti-TB treatment period of between 167 and 284 days were eligible for enrollment. Patients who had treatment for <167 days, which was 2 weeks less than the standard 180-day treatment period and implied that they had defaulted, died, or transferred out, were excluded because of inadequate treatment duration. Those who had treatment >284 days, which meant a treatment period that extended 2 weeks beyond 270 days, were not included because of the high likelihood of drug-resistant TB that usually requires a prolonged treatment period. Patients with a previous TB diagnosis were not selected because repeated recurrence is beyond the scope of our evaluation. We also excluded patients with incomplete demographic

profiles and those who were dropped from the NHI program in ≤60 days because of mortality or being transferred out. The study subjects were followed up for 2 years after TB treatment completion, or until TB recurrence, death, dropping out from the NHI program, or December 31, 2016.

Case definition and treatment consistency determination

Active TB was defined by at least 2 ambulatory visits or 1 inpatient record with a compatible diagnosis (ICD-9-CM code 011-018), plus the prescription of 3 or more anti-TB drugs at least once and prescription of at least 2 anti-TB drugs simultaneously for >120 days within 180 days [9]. During anti-TB therapy, the first 2 months were defined as the intensive phase, and the following 4 months were considered to be the continuation phase [14]. Treatment consistency was determined on the basis of the number of days that anti-TB drugs were taken during the intensive and continuation phases. The number of days were calculated according to defined daily dose. Patients who were prescribed isoniazid (H), rifampicin (R), and pyrazinamide (Z) for ≥48 days in the intensive phase, and took H and R for ≥144 days in the first 6 months, were defined as the high consistency group (≥80% treatment consistency) [9]. Patients who failed to meet the above criteria were classified as the low consistency group (<80% treatment consistency).

Variables and outcomes

The variables were age, sex, sociodemographic data, and comorbidities. The sociodemographic variables included income level and urbanization. The income level was calculated from the average monthly income of the insured person and categorized into 3 levels: low [≤610.20 United States Dollars (USD)], intermediate (610.20 USD to <1271.24 USD), and high (≥1271.24 USD). The urbanization level of the patients' residences was categorized as urban, suburban, and rural [15].

Comorbidities were confirmed if the diagnosis was established within 1 year before TB according to ICD-9-CM codes (Supplementary) [16]. Corticosteroid exposure was defined as taking a daily dose ≥7.5 mg for >3 months during the year before TB diagnosis [17]. Two-month culture positivity was determined by having undergone a drug susceptibility test (DST) after 2 months of anti-TB treatment, because the DST was done only for those with a positive culture [9].

The main outcome was the 2-year TB recurrence rate. We defined TB recurrence as a recurrent TB episode that fulfilled the definition of TB as described above, after completion of anti-TB treatment. The TB recurrence rate was based on the person-time of follow-up. Patients who withdrew from the NHI system contributed to person-time until the last follow-up date in the NHI records.

Statistical analysis

Continuous variables were presented as means ± standard deviations (SD) and compared with independent t tests for intergroup differences. Categorical variables were expressed as absolute numbers and percentages (%). Pearson χ^2 tests were performed for categorical variable comparisons where appropriate.

We used Cox proportional hazards regression analysis to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) of the co-variables, to identify independent risk factors for TB recurrence within ≤2 years. We

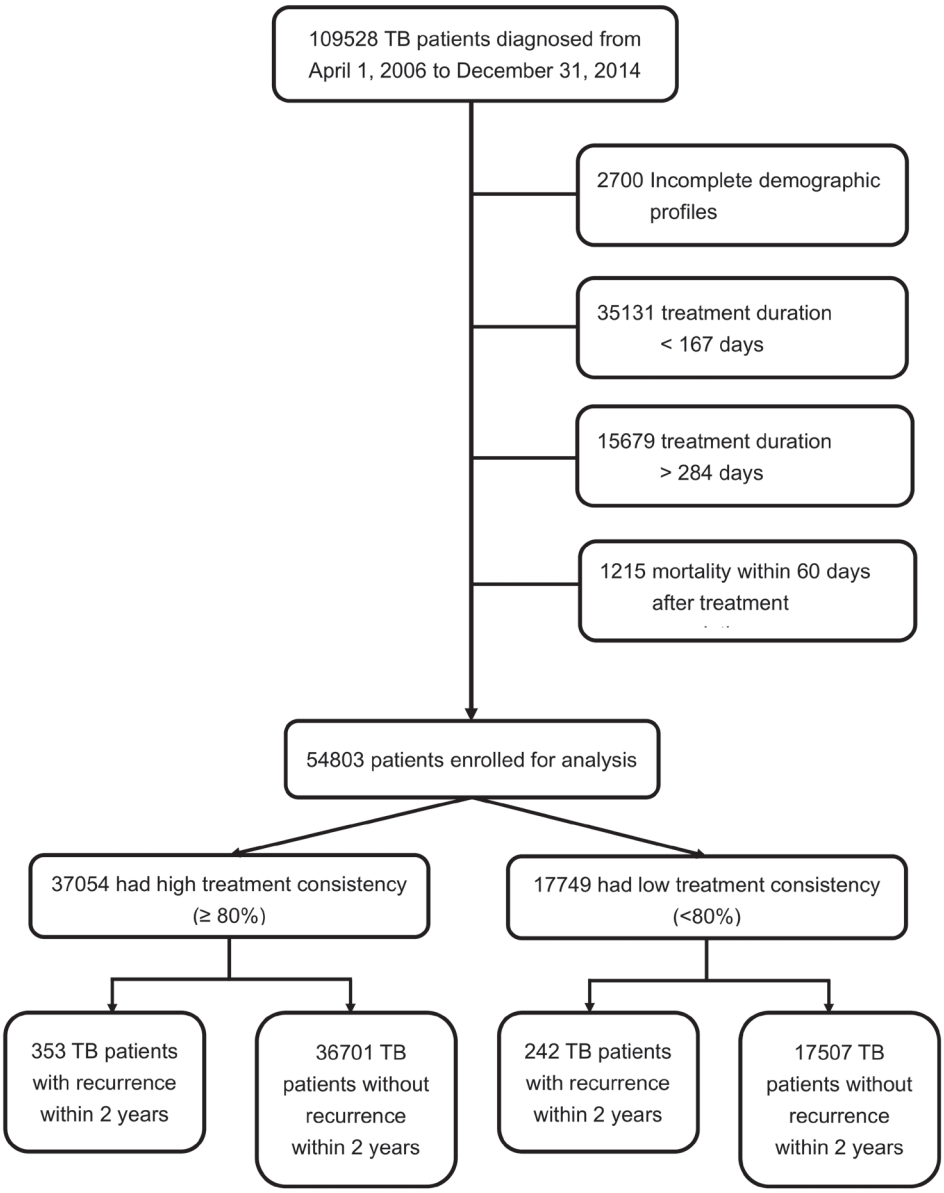

Fig. 1. Flow diagram of the study cohort. Acronym: TB, tuberculosis.

used the multivariate logistic regression model to calculate the odds ratios (OR) and 95% CIs to identify independent risk factors for low treatment consistency. Two-tailed *P* values of <0.05 were considered statistically significant. The Kaplan–Meier method was used to estimate the cumulative rate of TB recurrence. We accounted for the competing risk of death using the cumulative incidence competing risk method. The log rank test was used to compare the TB recurrence rate between the different subgroups (consistency: 100%, 80%–99%, and <80%).

We performed subgroup analysis after stratifying the study subjects by age, sex, income level, TB type, urbanization, and comorbidities,

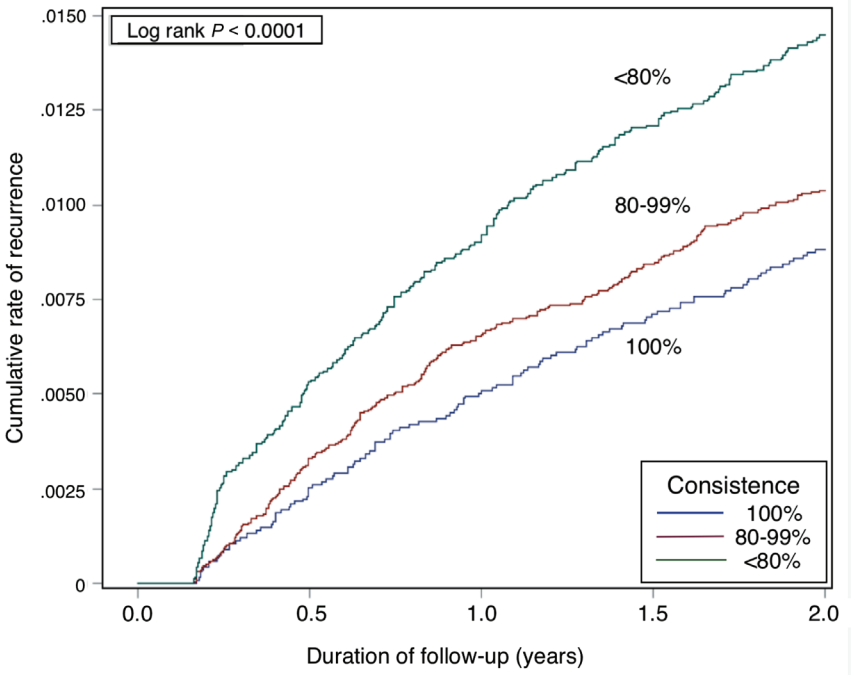

Fig. 2. Kaplan–Meier curves of the probability of recurrence within 2 years of completion of anti-TB treatment. The cumulative rate of 2-year TB recurrence was significantly higher in the <80% consistency group ($P < 0.001$ by log-rank test). Acronym: TB, tuberculosis.

as per the sample size of each subgroup. All analyses were performed using SAS version 9.4 (SAS Institute Inc).

Results

From April 1, 2006 to December 31, 2014, 109,528 patients were identified as having TB and were eligible for enrollment. After excluding those with incomplete demographic profiles (n=2700) and treatment duration <167 days (n=35,131) and >284 days (n=15,679), and those who had died with ≤60 days of treatment completion (n=1215), 54,803 patients were included for further analysis. The flow diagram for patient selection is presented in Figure 1. The study population characteristics are presented in Table 1. Among these enrollees, 37,054 (67.6%) had high treatment consistency (≥ 80%). The mean age of individuals with high consistency was 52.25 years (SD, 18.41 years), which was younger than those with low consistency (<80%). The low consistency group had significantly more male patients, more extrapulmonary TB, lower income levels, more rural-region residents, more comorbidities (diabetes mellitus (DM), alcoholism, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), human immunodeficiency virus (HIV), liver cirrhosis), and more cases with corticosteroid exposure. There was no significant difference in the proportions of 2-month culture conversion between the 2 groups (12.79% vs. 12.46%, $P = 0.5167$) (Table 1).

The 2-year recurrence rate in the high and low consistency groups was 0.95% (353/37054) and 1.36% (242/17749), respectively ($P < 0.001$). The annual recurrence rates in the first

Table 1. Demographic Characteristics of TB Patients with High and Low Treatment Consistency*

Characteristics	Treatment consistency		*P-value*
	High+, N = 37,054	**Low+, N = 17,749**	
Mean age (SD)	52.25 (18.41)	55.84 (19.10)	<0.0001
TB Type			<0.0001
Pulmonary TB	34,687 (93.61%)	16,347 (92.10%)	
Extrapulmonary TB	2367 (6.39%)	1402 (7.90%)	
Gender			<0.0001
Female	13,022 (35.14%)	5,713 (32.19%)	
Male	24,032 (64.86%)	12,036 (67.81%)	
Income level			<0.0001
Low	8,918 (24.07%)	5,225 (29.44%)	
Intermediate	18,169 (49.03%)	8,623 (48.58%)	
High	9,967 (26.90%)	3,901 (21.98%)	
Urbanization			<0.0001
Urban	19,926 (53.78%)	8,670 (48.85%)	
Suburban	12,765 (34.45%)	6,390 (36.00%)	
Rural	4,363 (11.77%)	2,689 (15.15%)	
Comorbidity			
DM	7,196 (19.42%)	4,261 (24.01%)	<0.0001
Alcoholism	527 (1.42%)	407 (2.29%)	<0.0001
COPD	8,053 (21.73%)	4,332 (24.41%)	<0.0001
CKD	1,927 (5.20%)	1,353 (7.62%)	<0.0001
Cancer	4,605 (12.43%)	2,291 (12.91%)	0.1129
HIV	74 (0.20%)	71 (0.40%)	<0.0001
Corticosteroid exposure	2,890 (7.80%)	2,200 (12.40%)	<0.0001
Liver cirrhosis	796 (2.15%)	619 (3.49%)	<0.0001
2-month culture conversion	1,826 (12.79%)	821 (12.46%)	0.5167
Treatment duration, days (SD)	210.26 (36.03)	219.96 (36.01)	<0.0001
2-year relapse rate (%)	353 (0.95%)	242 (1.36%)	<0.0001

* Data are presented as mean ± SD or n (%) unless otherwise stated

+ High consistency: prescription of isoniazid, rifampicin, and pyrazinamide for >48 days in the first 2 months, plus prescription of isoniazid and rifampicin for >144 days in the first 6 months of anti-TB treatment. Low consistency: the aforementioned criteria were not fulfilled.

Acronyms: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HIV, human immunodeficiency virus; SD, standard deviation; TB, tuberculosis

Table 2. Univariate and Multivariate Analysis of Risk Factors for TB Recurrence Within 2 years

Characteristics	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)*	*P*-value	HR (95% CI)	*P*-value
Age				
<65 years	1.00		1.00	
≥65 years	0.89 (0.74–1.07)	0.2058	0.77 (0.63–0.95)	0.0152
TB type				
Pulmonary	1.00		1.00	
Extra-pulmonary	1.38 (1.05–1.83)	0.0215	1.41 (1.07–1.87)	0.016
Gender				
Female	1.00		1.00	
Male	1.09 (0.92–1.30)	0.3225	1.06 (0.89–1.27)	0.5076
Income Level				
Low	1.00		1.00	
Intermediate	0.85 (0.71–1.03)	0.0936	0.86 (0.71–1.04)	0.1178
High	0.78 (0.62–0.98)	0.0312	0.77 (0.60–0.97)	0.0267
Urbanization				
Urban	1.00		1.00	
Suburban	1.02 (0.86–1.22)	0.7849	1.03 (0.86–1.23)	0.7656
Rural	1.12 (0.88–1.43)	0.3396	1.09 (0.84–1.41)	0.5021
DM	1.27 (1.05–1.52)	0.0126	1.28 (1.06–1.55)	0.012
COPD	1.03 (0.86–1.25)	0.7257	1.04 (0.85–1.27)	0.7131
CKD	0.83 (0.58–1.20)	0.3306	0.75 (0.51–1.09)	0.1278
Cancer	1.03 (0.81–1.31)	0.7866	1.03 (0.80–1.31)	0.8258
HIV	3.24 (1.34–7.80)	0.0089	2.69 (1.11–6.50)	0.0279
Alcoholism	1.81 (1.13–2.89)	0.0134	1.43 (0.90–2.28)	0.134
Corticosteroid exposure	1.54 (1.22–1.95)	0.0003	1.49 (1.17–1.89)	0.0012
Liver cirrhosis	1.59 (1.06–2.39)	0.0259	1.33 (0.88–2.01)	0.1797
2-month culture positivity	0.67 (0.43–1.05)	0.082	0.67 (0.43–1.06)	0.0853
Treatment consistency				
100% consistency	1.00		1.00	
99-80% consistency	1.17 (0.93–1.46)	0.176	1.14 (0.91–1.43)	0.2498
<80% consistency	1.59 (1.27–1.98)	<0.0001	1.49 (1.19–1.87)	0.0005

* HR and 95% CI were derived from Cox regression analysis.

Acronyms: CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HIV, human immunodeficiency virus; HR, hazard ratio; TB, tuberculosis

and second year after treatment completion were 908.7 and 555.6 cases per 100,000 person-years in the low consistency group, and 601.4 and 384.3 cases per 100,000 person-years in the high consistency group (Supplementary Table 1).

We further categorized the patients into 3 subgroups according to their treatment consistency (100%, 80%–99%, and <80%). The Kaplan–Meier analysis results of the 2-year recurrence rates for the TB patient subgroups are shown in Figure 2. The <80% group had a significantly higher TB recurrence rate ($P < 0.001$; log-rank test).

Independent risk factors associated with TB recurrence

We identified independent risk factors for TB recurrence using Cox proportional hazards analysis (Table 2). After adjusting for potential confounders, low treatment consistency remained an independent factor (HR = 1.49, 95% CI = 1.19–1.87, $P = 0.0005$; Table 2). Other variables independently associated with recurrence of TB included age <65 years old, extrapulmonary TB, DM, HIV, and corticosteroid exposure. Subjects with high incomes were less likely to have TB recurrence. Two-month culture positivity was not an independent predictor of 2-year TB recurrence.

A forest plot of the subgroup analysis for the correlation between treatment consistency and 2-year TB recurrence is shown in Figure 3. After adjusting for other variables, low consistency remained an independent risk factor associated with 2-year TB recurrence in those of any gender, with any TB type, aged <65 years, with an intermediate to high-income level, urban residents, and in those without comorbidities.

Factors associated with low treatment consistency

Using a multivariate logistic regression model, we found that individuals aged >65 years, males, rural area residents, extrapulmonary TB patients, and those with alcoholism, DM, CKD, HIV, corticosteroid exposure, or liver cirrhosis were associated with <80% treatment consistency (Table 3). Compared to those in the low-income group, individuals with intermediate and high income had a lower risk of low treatment consistency.

We analyzed the medical behaviors among the enrollees (Supplementary Table 2). Patients with low treatment consistency were more likely to receive blood tests and have more OPD visits both before and after TB diagnosis ($P < 0.001$). During the anti-TB treatment period, patients with low treatment consistency had more TB-related admissions (71.66% vs. 31.86%, $P < 0.001$) and longer hospital stays (11.72 ± 11.12 days vs. 3.39 ± 6.14 days, $P < 0.001$) than the high treatment consistency group. We found that the low consistency group received more medical care than the high consistency group.

Discussions

This is the first population-based cohort study to have analyzed the impact of treatment consistency on TB recurrence. Our results showed that low treatment consistency (<80%) was not uncommon among our TB patients and was an independent factor associated with 2-year recurrence. The risk factors for low treatment consistency among the TB patients were age >65 years, extrapulmonary TB, male, low-income level, living in a rural region, and having comorbidities. We also found that TB patients with low treatment consistency had

Table 3. Univariate and Multivariate Analysis of Clinical Factors Associated with Low Treatment Consistency (<80%).

Characteristics	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)*	*P*-value	OR (95% CI)	*P*-value
Age				
<65 years	1.00		1.00	
≥65 years	1.41 (1.35–1.46)	<0.0001	1.22 (1.16–1.27)	<0.0001
TB type				
Pulmonary	1.00		1.00	
Extrapulmonary	1.26 (1.17–1.35)	<0.0001	1.28 (1.19–1.37)	<0.0001
Gender				
Female	1.00		1.00	
Male	1.14 (1.10–1.19)	<0.0001	1.06 (1.02–1.10)	0.0031
Income Level				
Low	1.00		1.00	
Intermediate	0.81 (0.78–0.85)	0.625	0.82 (0.78–0.85)	0.0002
High	0.67 (0.64–0.70)	<0.0001	0.77 (0.73–0.81)	<0.0001
Urbanization				
Urban	1.00		1.00	
Suburban	1.15 (1.11–1.20)	<0.0001	1.09 (1.05–1.14)	0.0001
Rural	1.42 (1.34–1.50)	<0.0001	1.29 (1.22–1.36)	<0.0001
Alcoholism	1.63 (1.43–1.85)	<0.0001	1.48 (1.30–1.70)	<0.0001
DM	1.31 (1.26–1.37)	<0.0001	1.23 (1.18–1.29)	<0.0001
COPD	1.16 (1.11–1.21)	<0.0001	1.00 (0.96–1.05)	0.859
CKD	1.50 (1.40–1.62)	<0.0001	1.30 (1.21–1.40)	<0.0001
Cancer	1.04 (0.99–1.10)	0.1109	0.95 (0.90–1.00)	0.0521
HIV	2.01 (1.45–2.78)	<0.0001	2.05 (1.47–2.85)	<0.0001
Corticosteroid exposure	1.67 (1.58–1.77)	<0.0001	1.55 (1.46–1.65)	<0.0001
Liver cirrhosis	1.65 (1.48–1.83)	<0.0001	1.42 (1.27–1.59)	<0.0001

* OR and 95% CI were derived from logistic regression analysis

Acronyms: CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HIV, human immunodeficiency virus; OR, odds ratio; TB, tuberculosis

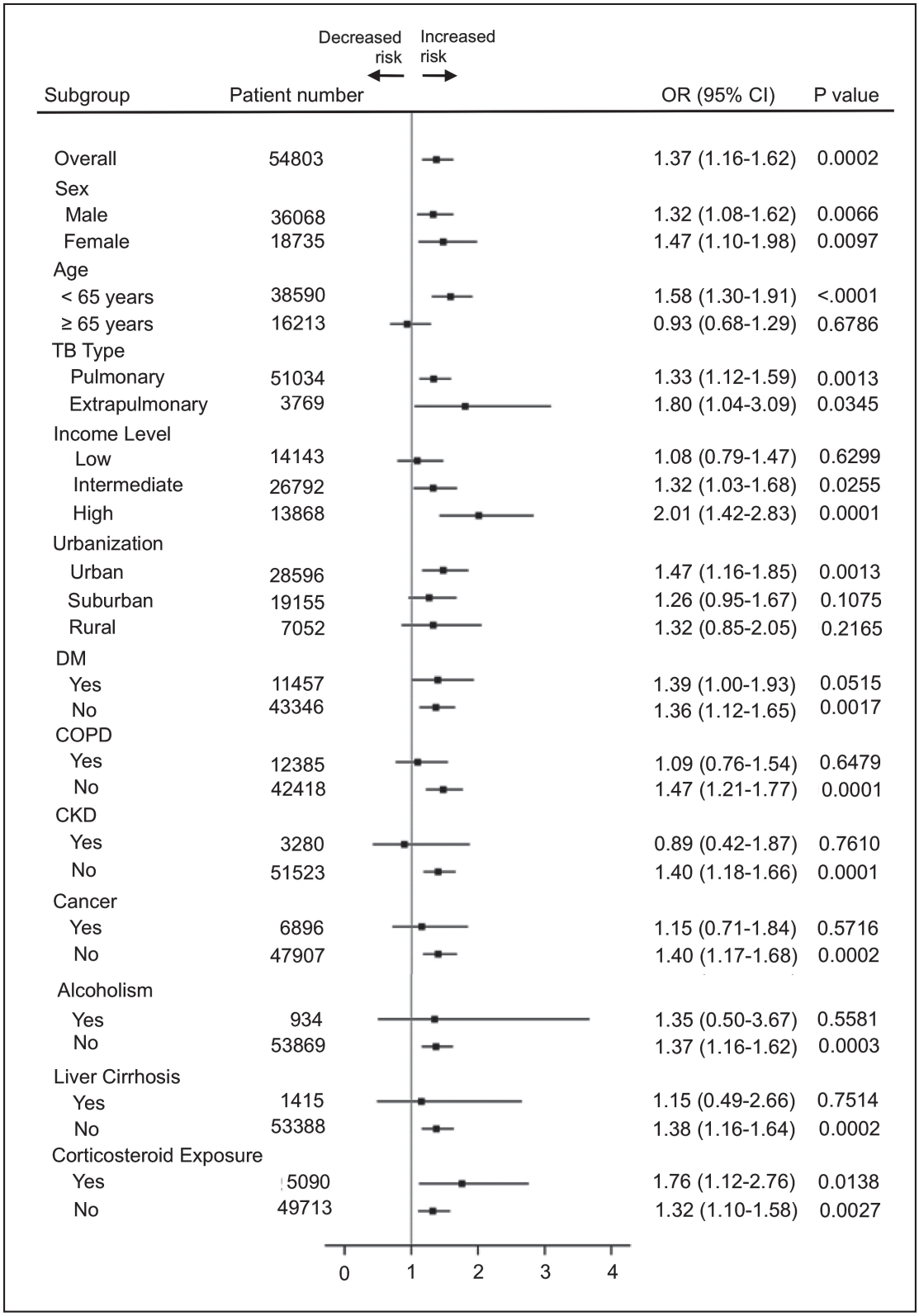

Fig. 3. Forest plot of subgroup analysis for the association between 2-year TB recurrence and low treatment consistency (<80%). Acronyms: CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; OR, odds ratio; TB, tuberculosis.

more blood tests, clinic visits, and hospital admissions during treatment than those with high treatment consistency.

Non-adherence is always an issue in anti-TB treatment. Using various definitions, the non-adherence rate has ranged from 11.5% to 29.8% [18-22]. The definitions of non-adherence have included: not taking anti-TB drugs daily for 8 months, missing >20% of total prescribed doses, missing >10% of total prescribed doses, missing a scheduled DOTS visit, and taking <95% of prescribed doses [18-22]. Some of the treatment adherence information has been self-reported or obtained from questionnaires [20, 23]. Recall bias may confound the results and lead to overestimated compliance. In this study, the low consistency rate was 32.4%. We obtained the patients' drug histories from the payment and reimbursement dataset in our NIHRD, which is pretty reliable. This information also highlighted the difficulties in maintaining good treatment quality for TB patients, even in an area with high medical accessibility and DOTS program implementation.

Few case-control studies have explored the relationship between non-adherence and TB recurrence [24-25]. Anaam *et al*. reported an overall 5.4% relapse rate within 1 year of treatment completion. The adjusted OR for taking <80% of prescribed doses in the continuation phase was 25.7 [24]. Bestrashniy et al. reported a 5.7% recurrence rate during a median follow-up period of 1,111 days, and the median time to relapse was 12 months [25]. The OR for incomplete treatment adherence, which was not defined, was 2.0. In our study, the overall 2-year recurrence rate was 1.09% and the HR for treatment consistency <80% was 1.49. Our sensitivity analysis revealed that the effect of low treatment consistency on recurrence was similar among most patient subgroups, indicating that <80% treatment consistency in the first 6 months of anti-TB treatment would compromise the patient's long-term outcome. It is worth mentioning that the low consistency and the 2-year TB recurrence rate actually shared some risk factors: extrapulmonary TB, DM, HIV, and corticosteroid exposure. The results suggested that clinicians should pay more attention to these populations so as to both improve consistency and reduce the TB recurrence rate.

Two systematic reviews found that lack of knowledge, barriers to medical accessibility, and the burden of medication costs are the major causes of non-adherence [26-27]. The outcomes of non-adherence among TB patients included the development of drug resistance TB and a higher risk of death [28-29]. In Taiwan, with NHI coverage and assistance from public health care staff, medical costs related to TB treatment are very low. Moreover, all of our patients were enrolled after the nationwide implementation of the DOTS program, which has a coverage rate >90% [30]. Therefore, problems related to the aforementioned barriers would be a minor issue in Taiwan. Our study investigated the clinical characteristics of TB patients with low consistency, and found that elderly patients, males, patients with extrapulmonary TB, low income, and comorbidities, and rural area residents were more likely to have <80% treatment consistency. The low consistency group had more blood tests, OPD visits, hospital admission, and longer hospital stays during the anti-TB treatment period.

However, non-adherence is not equal to low-consistency in this study. Actually, the low-consistency group in the present study had good adherence to the DOTS program, as the numbers of their medical visits were not less

than those of the high-consistency group. Given the intensified healthcare needs we observed in cases with low treatment consistency, the complications of TB per se or the adverse reactions related to anti-TB treatment should be taken into consideration. Although without direct information of adverse reactions in our database, we speculated that the main causes of low treatment consistency in our patients were the occurrence of adverse reactions to anti-TB medication and TB-related complications in older patients and those with multiple comorbidities.

Our study has several limitations. This was a retrospective cohort study, so the cause–effect relationship could not be established. Nevertheless, considering the overall low recurrence rate, studies evaluating factors associated with recurrence can only be conducted in such a population-based cohort. Second, the details of drug sensitivity could not be obtained in this database, so those with multidrug-resistant TB (MDR-TB) and extensive drug-resistant TB (XDR-TB) may have been enrolled. Since the treatment duration of MDR-TB and XDR-TB is mostly >9 months, we attempted to minimize selection bias by excluding patients taking anti-TB drugs for >284 days. Third, we could not distinguish reinfection from relapse, since information about the genotypes was not available in the NHIRD dataset. Since we evaluated recurrence that occurred within ≤2 years, which is a relatively short period, we believe that most of these TB recurrences were due to endogenous reactivation. Fourth, information regarding educational levels, adherence to the DOTS program, and adverse effects cannot be readily analyzed in our dataset. Instead, we collected information about the medical behaviors of patients who had more OPD visits and in-hospital days, suggesting that complications and adverse reactions were probably the major causes of low treatment consistency.

Our study highlights the clinical importance of treatment consistency to outcomes of active TB. Low treatment consistency in the initial 6 months of anti-TB treatment is not uncommon in active TB patients, and was found to be an independent factor associated with an increased risk of 2-year recurrence. In Taiwan, the reason for low consistency may be related to complications of active TB and adverse drug reactions related to anti-TB treatment, rather than barriers to medical accessibility or medical costs. Clinical physicians should recognize and manage complications and adverse drug reactions without delay and work on these problems aggressively to keep treatment consistency and improve long-term outcomes of TB patients.

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Uniportal Thoracoscopic Lung Tumor Resection With or Without Needlescopic Assistance: A Prospective Randomized Study

Huan-Jang Ko[1], Shun-Mao Yang[1,2], Ming-Chi Yang[1]

Introduction: The use of uniportal video-assisted thoracoscopic surgery (VATS) for lung tumors has gained widespread popularity. Its feasibility and safety have been verified in numerous case series; however, evidence of its superiority over multiportal VATS remains controversial. This prospective, randomized study investigated whether adding needlescopic ports to the existing uniportal VATS for pulmonary resection affects postoperative outcomes.

Methods: A total of 110 patients were randomly and equally divided into 2 groups: a standard uniportal VATS group (uniportal group) and a needlescopic-assisted uniportal VATS group (needle-assisted group). The primary outcome measures were postoperative pain, opioid analgesic dosage, and incidence of chronic pain. The secondary outcome measures were surgical duration, length of postoperative hospital stay, postoperative complications, and operative or 30-day mortality.

Results: The clinico-demographic parameters (age, sex, and comorbidities), procedure types, and pathological variables of the 2 groups were comparable. The operative results, including operation time, duration of drainage (4.5 ± 1.7 vs. 4.4 ± 1.8 days; p = 0.709), and hospital stay (4.9 ± 2.1 vs. 4.5 ± 2.1 days; p = 0.281), were comparable for both groups, and no significant differences were noted in acute pain scores. The chronic neuralgia results at postoperative 1 and 3 months were comparable in both groups.

Conclusion: The addition of needlescopic ports to conventional uniportal VATS did not negatively affect the short-term outcomes. ***(Thorac Med 2021; 36: 161-172)***

Key words: lung tumor, needlescopic, neuralgia, video-assisted thoracoscopic surgery

Introduction

Compared with thoracotomy, video-assisted thoracoscopic surgery (VATS) significantly reduces pain, hastens recovery, and improves the quality of life of patients with lung tumor [1]. Different types of VATS approaches have evolved in parallel with technological advances in surgical devices and quality of imaging systems [2]. The use of uniportal VATS has gained

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widespread popularity recently because of internet-based videos and hands-on courses that offer guidance and highlight ways to master these techniques that are promoted by experts in the field of uniportal VATS [3, 4]. Although the feasibility and safety of uniportal VATS have been verified in numerous case series, evidence of its superiority over multiportal VATS remains controversial [5], especially in terms of reduction of postoperative pain and chronic intercostal neuralgia, which are the most common reasons for performing uniportal VATS.

Our institute initiated minimally invasive thoracic surgery with conventional 3-port VATS and started performing uniportal VATS in 2015. After 1 year of practicing uniportal VATS, we incorporated additional needlescopic ports and instruments into our uniportal VATS system to improve surgical assistance and cooperation [6], with the aim of continuing to achieve the favorable postoperative outcomes associated with uniportal VATS. A retrospective analysis of our initial experience showed that the uniportal VATS system with additional needlescopic-assisted ports had short-term postoperative outcomes comparable to uniportal VATS for anatomical resection [7]. There have been just 2 randomized trials with small sample sizes that compared uniportal and multiportal VATS, and the results have been inconclusive [8, 9]. Furthermore, in 2 case series, 2–3-cm mini-thoracostomy incisions or conventional trocar ports ranging from 5–12 mm in diameter were used to constitute the multiportal VATS system [3, 5]. There is a lack of adequate evidence for needlescopic-based multiportal systems; thus, this prospective randomized trial investigated whether additional needlescopic ports in the existing uniportal VATS setting affected postoperative outcomes, including pain and incidence of intercostal neuralgia.

Patients and Methods

Study design and patients

This prospective, open-label, parallel-group, randomized trial was performed between February 21, 2018, and April 30, 2019 (patient recruitment ended December 12, 2018), at National Taiwan University Hospital, Hsinchu Branch, Taiwan. Patients were consecutively recruited by their primary physicians. The study was approved by the research ethics committee at National Taiwan University Hospital, Hsinchu Branch, Hsinchu City, Taiwan (#106-067-F). Inclusion criteria were age between 20 and 90 years and computed tomography-detected pulmonary lesions that required unilateral thoracoscopic resections. Patients were excluded if they had an underlying pulmonary parenchymal disease, or a history of ipsilateral thoracic surgery, coagulopathy, or other serious medical disorders.

Randomization

Patients were randomly assigned (1:1) by a study nurse (who was blinded to the patients' characteristics) to standard uniportal VATS (the uniportal group) (Figure 1A) or needlescopic-assisted uniportal VATS (the needle-assisted group) (Figure 1B). Randomization was performed using a block size of 4 in sequentially numbered, sealed envelopes. The nurse opened the randomization envelopes and performed randomization after the patient had been sent to the operation room.

Study interventions

Uniportal VATS

A 3–4 cm incision was made in the fifth

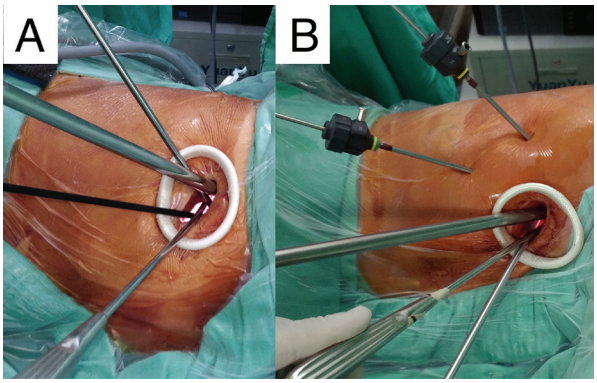

Fig. 1. Surgical setup for standard uniportal and needlescopic-assisted VATS. (A) Uniportal VATS (B) Needlescopic-assisted uniportal VATS.

or sixth intercostal space, and a wound protector was routinely used. For wedge resections, an endoscopic stapler was used to resect the target lesion. For anatomical resections, we used curved or angled dissectors to dissect the pulmonary vessels and bronchus, and used endoscopic staplers to divide them. Staging mediastinal lymph node dissections were performed for patients with primary lung cancer. After completing the procedure, intercostal nerve blockade with a needle injection of 0.5% bupivacaine was administered under thoracoscopy, and a chest tube was routinely placed through the incision.

Needlescopic-assisted uniportal VATS

The technical details have been described previously,6,7 and the surgical principle for the lung lesions was the same as that for the uniportal group. Once the uniportal system was prepared, additional needlescopic ports were created using the stab method for the needlescopic instruments (Minilaparoscopy; Karl Storz SE & Co. KG, Tuttlingen, Germany, or BJ needle, Niti-On Co., Chiba, Japan). The intercostal spaces for the needle ports were chosen after assessment under thoracoscopy. With an assistant standing on the contralateral side, the entire surgical uniportal VATS technique could be facilitated using assistant-operated needlescopic instruments. Intercostal nerve blockage and chest tube placement were performed as for the uniportal group.

Postoperative care

In general, the same protocol was used to manage both groups postoperatively. Postoperative patient-controlled analgesia (PCA) included intravenous morphine (1 mg/mL). Additional analgesics, including oral nonsteroidal analgesic agents and acetaminophen, were administered once the patients had resumed oral intake 2–4 h following surgery. The chest tube was removed in both groups if there were no air leaks and drainage was <200 mL within a 24-h period. Prolonged air leaks were defined as those that lasted >5 days. Postoperative follow-up included patient visits and X-rays.

Study outcomes

The primary outcome measures were as follows: (i) Acute pain in the early postoperative stage assessed using a visual analog scale (VAS); the median patient-reported pain score was recorded postoperatively. (ii) Total opioid analgesic dosage during the postoperative course. (iii) Incidence of chronic residual pain at 1 and 3 months post-operation. Symptoms of chronic pain were assessed using the validated painDETECT questionnaire (PD-Q), which has been used to evaluate post-thoracotomy pain [10]. Each pain characteristic could be scored from 0 to 5 (never = 0, hardly noticed = 1, slightly = 2; moderately = 3, strongly = 4, very strongly = 5), and the total score was calculated for each patient. The pain location at the operated site also was recorded for each patient. Surgical duration

and length of postoperative hospital stay, postoperative complications, and operative or 30-day mortality were secondary outcomes.

Sample size

We hypothesized that the additional needlescopic ports with instruments would be minimally damaging and less invasive to the intercostal space, compared with the conventional ports or utility incisions used in multiportal VATS. This study was designed as a non-inferiority trial to demonstrate that additional needlescopic-assistance would not compromise the favorable outcomes of a lower incidence of intercostal neuralgia using uniportal VATS. In a previous comparative study of uniportal and conventional multiportal VATS, the incidence of neuropathic wound pain was approximately 15% and 35%, respectively [11]. Considering a unilateral type I error of 5% and a type II error of 20%, the estimated number of patients for each group was 55, with a total sample size of 110 patients.

Statistical analysis

Patient demographics, hospital stay, chest drainage duration, complications, and surgical results were prospectively collected. Demographic data are reported as mean ± standard deviations for continuous variables and frequencies with percentages for categorical variables. The independent t test or Fisher's exact test was used to compare intergroup differences, as appropriate. The Wilcoxon rank-sum test was used to assess intergroup differences in pain scores. Multivariable linear regression was used to assess the associations between the total dosage of PCA and potentially explicable covariates, including age, sex, body mass index (BMI), smoking status, needlescopic-assistance, middle/lingual lobe lesion, operation time, anatomical/complex resection, and malignancy. Statistical analyses were performed using SPSS version 22 (SPSS Inc., Chicago, USA).

Results

A total of 110 patients were included in this trial and underwent thoracoscopic pulmonary resection at our institution. They were randomized and equally divided into those receiving uniportal VATS (uniportal group; n = 55) and those undergoing other needlescopic-assisted uniportal VATS techniques (needle-assisted group; n = 55) (Figure 2). Both groups were comparable in terms of age, sex, mean BMI, tumor location, and comorbidities. The needle-assisted group showed better results on pulmonary function tests in terms of forced vital capacity (101.3 ± 17.1% vs 108.3 ± 18.3%, p = 0.042) and forced expiratory volume in 1 s (99.7 ± 19.6% vs 108.2 ± 18.4%, $p = 0.021$) (Table 1).

Thirty-four patients in the uniportal group and 31 in the needle-assisted group received single or multiple wedge resections as the final procedure. Anatomical lung resections,

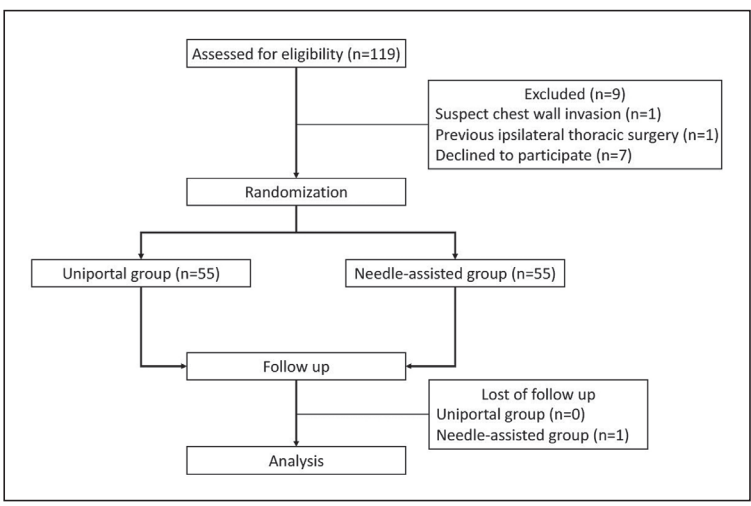

Fig. 2. Study flow chart.

Table 1. Patient Demographics and Baseline Characteristics

	Uniportal (n = 55)	Needle-assisted (n = 55)	*p-value*
Age, y	58.8 ± 11.6	56.0 ± 12.3	0.234
Sex (female)	31 (56.4%)	28 (50.9%)	0.215
Height, cm	160.3 ± 8.6	162.8 ± 9.7	0.159
Weight, kg	62.9 ± 11.2	62.7 ± 12.9	0.958
BMI, kg/m^2	24.4 ± 4.0	23.9 ± 3.8	0.481
Smoking	10 (18.2%)	19 (34.5%)	0.051
FVC (% of prediction)	101.3 ± 17.1	108.3 ± 18.3	0.042
FEV_1 (% of prediction)	99.7 ± 19.6	108.2 ± 18.4	0.021
Tumor location			0.854
Right upper	16 (24.6%)	13 (21.6%)	
Right middle	7 (10.8%)	7 (11.7%)	
Right lower	13 (20.0%)	10 (16.7%)	
Left upper	16 (24.6%)	20 (33.3%)	
Left lower	13 (20.0%)	10 (16.7%)	
Diagnosis			0.948
Primary lung cancer	33 (60.0%)	34 (61.8%)	
Metastatic tumor	6 (10.9%)	5 (9.1%)	
Benign disease	16 (29.1%)	16 (29.1%)	
Comorbidity			
Extrathoracic malignancy	14 (25.5%)	15 (27.3%)	1.000
Hypertension	17 (30.9%)	9 (16.4%)	0.116
Diabetes mellitus	5 (9.1%)	3 (5.5%)	0.716
Cardiac diseases	3 (5.5%)	2 (3.6%)	1.000
Neoadjuvant therapy	0 (0.0%)	1 (1.8%)	1.000
ASA class			0.692
I	5 (9.1%)	3 (5.5%)	
II	31 (56.4%)	30 (54.5%)	
III	19 (34.5%)	22 (40.0%)	

BMI: body mass index; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s;
ASA: American Society of Anesthesiologists.

including lobectomy and segmentectomy, were performed for 16 patients in the uniportal group and 19 in the needle-assisted group. Five patients in each group required complex procedures defined as anatomical resections performed separately (for example, segments 6 and 8) or a single anatomical resection with additional wedge resections. Operation time for wedge resection (80.3 ± 23.0 vs. 79.8 ± 21.0 min; $p = 0.916$) and anatomical resection (138.9 ± 31.3 vs. 149.7 ± 34.7 min; $p = 0.343$) was comparable for both groups. One patient (1.8%) in the uniportal group had surgical conversion to multiportal VATS because of tumor adhesion to the pericardium. Two patients (3.6%) in the needle-assisted group had conversion to thora-

cotomy due to major pulmonary artery bleeding and chemotherapy-related adhesion in the hilar area. Two patients (3.6%) in the uniportal group and 1 (1.8%) in the needle-assisted group had prolonged air leaks. One patient in the uniportal group had postoperative pneumonia and received a prolonged course of antibiotic treatment. Another patient, who underwent neoadjuvant chemotherapy in the needle-assisted group, had postoperative pulmonary arterial lobar ischemia due to inadvertent division of the common basal branch of the pulmonary artery when performing right middle lobectomy; this was followed by re-exploration and completion bilobectomy on postoperative day 3. There were no differences between the uniportal and needle-assisted groups in mean postoperative intensive care unit stay, mean hospital stay, or mean duration of an indwelling chest drainage tube (Table 2). Ninety-four patients (uniportal: 50, needle-assisted: 44) received postoperative intravenous PCA with morphine. Multivariable linear regression model analysis indicated that the total PCA dose was positively associated with operation time ($p = 0.018$) and lesions located at the middle/lingual lobe ($p = 0.011$) (Table 3).

No significant differences were observed in acute pain scores between the uniportal and needle-assisted groups during the postoperative

Table 2. Operative Results

	Uniportal (n = 55)	**Needle-assisted (n = 55)**	***p-value***
Procedure type			0.287
Wedge resection	34 (61.8%)	31 (56.4%)	
Anatomical resection	16 (29.1%)	19 (36.5%)	
Segmentectomy	7 (12.7%)	10 (18.2%)	
Lobectomy	9 (16.3%)	9 (16.3%)	
Complex resection*	5 (9.1%)	5 (9.1%)	
Operation time (min)			
Wedge resection	80.3 ± 23.0	79.8 ± 21.0	0.916
Anatomical resection	138.9 ± 31.3	149.7 ± 34.7	0.343
Surgical conversion	1 (1.8%)	2 (3.6%)	1.000
Postoperative complication			
Prolonged air leak	2 (3.6%)	1 (1.8%)	1.000
Pneumonia	1 (1.8%)	0 (0%)	1.000
Pulmonary lobar ischemia	0 (0%)	1 (1.8%)	1.000
Patient-controlled analgesia	51 (92.7%)	45 (81.8%)	0.151
Postoperative chest drainage (day)	4.5 ± 1.8	4.3 ± 1.7	0.544
Postoperative ICU stay (day)	0.8 ± 1.5	1.7 ± 7.0	0.362
Postoperative hospital stay (day)	5.4 ± 4.3	5.8 ± 10.1	0.798

*Complex resection: single anatomical resection plus additional wedge resections or ≥2 anatomical resections performed separately; ICU: intensive care unit

Table 3. Total PCA Dose-multivariate Analysis (N = 94)

	95% CI	*p-value*
Age	-0.368–0.442	0.858
Sex	-8.219–12.221	0.702
BMI	-0.645–1.638	0.396
Smoking	-15.780–8.767	0.577
Needle-assistance	-11.553–6.768	0.610
Middle/lingual lobe lesion	3.834–27.001	0.011
Operation time	0.029–0.331	0.022
Anatomical/complex resection	-14.840–11.304	0.792
Malignancy	-15.966–6.976	0.445

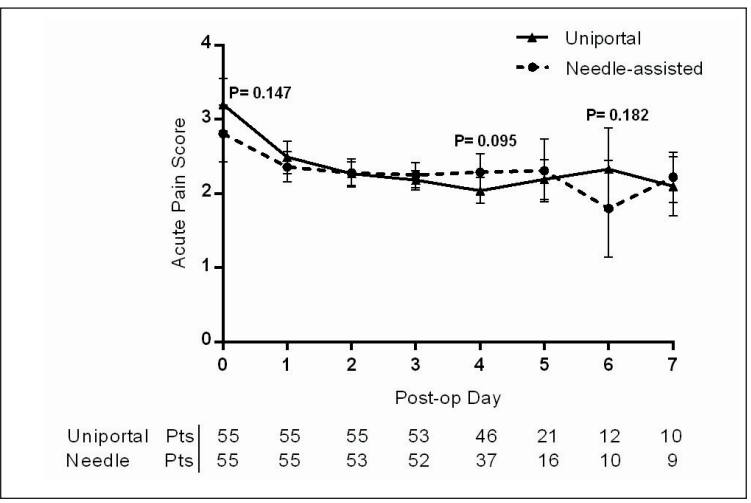

Fig. 3. Acute pain evaluated with the Visual Analog Scale (VAS) during the entire postoperative course.

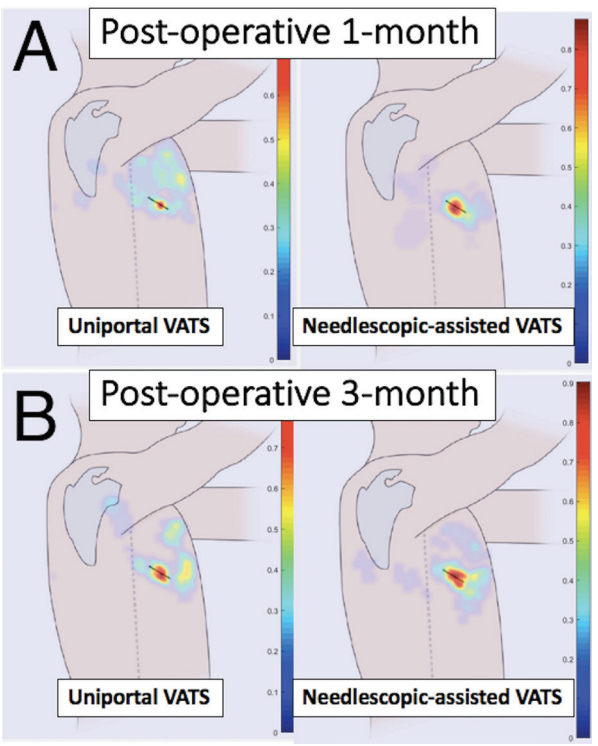

Fig. 4. Frequency plot: Locations of residual neuralgia. (A) Postoperative 1 month (B) Postoperative 3 months.

course (Figure 3). The uniportal pain course decreased slightly but non-significantly on post-operative day 4 (p = 0.095). Chronic pain surveys (PD-Q) at postoperative 1 and 3 months (Table 4) were completed for 109 patients in follow-up calls (55 uniportal, and 54 needle-assisted). The most common pain characteristic was pain evoked by mild pressure (1 month: 41.8% [23/55] uniportal, 42.6% [23/54] needle-assisted; 3 months: 40.0% [22/55] uniportal, 37.0% [20/54] needle-assisted). No significant difference was seen in the incidence of different pain characteristics between the 2 groups. The total painDETECT scores for both groups were comparable, and >90% of patients had a score ≤12, which was interpreted as unlikely neuropathic pain. Figure 4 shows the frequency plot of the pain location recorded at postoperative 1 and 3 months.

Table 4. Chronic Pain

	Uniportal (n = 55)	Needle-assisted (n = 54)	*p-value*
Postoperative 1 month			
Pain character			
Burning	7 (12.7%)	7 (12.9%)	1.000
Tingling or prickling	16 (29.1%)	18 (33.3%)	0.786
Light touching	16 (29.1%)	15 (27.7%)	1.000
Electric shock or shooting	7 (12.7%)	8 (14.8%)	0.970
Evoked by heat or cold	5 (9.1%)	10 (18.5%)	0.250
Numbness	12 (21.8%)	10 (18.5%)	0.849
Evoked by mild pressure	23 (41.8%)	23 (42.6%)	1.000
Scoring of painDETECT (0–35)			
≤12 (Unlikely neuropathic pain)	52 (94.5%)	51 (94.4%)	
13–18 (Possible neuropathic pain)	1 (1.8%)	3 (5.5%)	
≥19 (Likely neuropathic pain)	2 (3.6%)	0 (0%)	
Total score	2.98	3.3	
Postoperative 3 months			
Pain character			
Burning	8 (14.5%)	8 (14.8%)	1.000
Tingling or prickling	13 (23.6%)	18 (33.3%)	0.363
Light touching	11 (20.0%)	14 (25.9%)	0.612
Electric shock or shooting	3 (5.4%)	8 (14.8%)	0.192
Evoked by heat or cold	4 (7.3%)	9 (16.6%)	0.223
Numbness	11 (20.0%)	14 (25.9%)	0.612
Evoked by mild pressure	22 (40.0%)	20 (37.0%)	0.904
Scoring of painDETECT (0–35)			
≤12 (Unlikely neuropathic pain)	55 (100%)	51 (94.4%)	
13–18 (Possible neuropathic pain)	0 (0%)	3 (5.5%)	
≥19 (Likely neuropathic pain)	0 (0%)	0 (0%)	
Total score	2.05	3.3	

Discussions

Although long-term outcomes have not been reported, uniportal VATS, characterized by a single incision with a minimized incidence of intercostal neuralgia caused by the creation of thoracic ports, has prevailed in the field of thoracic surgery over the past decade. Most current retrospective clinical reports favored uniportal VATS in terms of several short-term outcomes, including postoperative pain, drainage time, and hospital stay [12]. However, there are only 2 prospective randomized trials, and both have reached different conclusions regarding the su-

periority of uniportal to multiportal VATS [9, 13], making it difficult to compare the 2 minimally invasive approaches, especially in terms of minor outcomes such as pain scores, which were already reported to be very low. Other than acute postoperative pain, chronic residual neuralgia is more relevant to long-term functional outcomes and quality of life, but clinical series reporting on residual pain are few [11, 14-16].

In current studies comparing uniportal and multiportal VATS, multiportal VATS data included different sizes of working ports, ranging from 5-mm ports to 40-mm thoracic incisions. Among the 11 published studies that used 5-mm instruments [9,13,15, 17-24], 7 suggested that uniportal VATS reduced acute pain scores. In addition, 3 of the 4 studies that used 10-mm instruments [11, 25-27] also reported similar results for acute pain. However, no recent study has compared multiportal VATS with a needlescopic system to uniportal VATS. In the field of general surgery, needlescopic surgery, similar to mini-laparoscopic surgery, proved to result in less postoperative pain and better cosmetic results than conventional laparoscopic surgery using 5–12-mm trocar ports [28-29]. These studies suggested the potential benefit of using thinner needlescopic instruments, but similar comparative studies in the field of thoracic surgery are rare. The diameter of thoracoscopic ports would be even more critical in terms of postoperative pain and residual neuralgia, because the size of the intercostal space might be even smaller than that of the regular trocar port, and the thinner 2–3-mm ports could be of tremendous benefit. As the trend in VATS quickly shifted from multiportal to uniportal approaches, the advantage of using needlescopic instruments in the multiportal VATS system could not be validated.

In the present study, acute pain was evaluated using the VAS score and PCA dose. The use of additional needlescopic ports neither significantly changed the VAS score over the entire postoperative course nor had a significant effect on the total PCA dose. One factor that did have a significant impact on the total PCA dose was surgical procedure duration, which implies that longer surgery is associated with more acute postoperative pain. In our cohort, we routinely applied a wound protector because utility incisions were performed up to the end of the intrathoracic procedure; thus, the duration of the application of the wound protector would strongly correlate with surgical duration, PCA dose, and associated acute postoperative pain. There are concerns that the wound protector might induce wound pain and intercostal neuralgia if the wound were tightly expanded by the wound protector, thus placing direct pressure on the intercostal space. This might explain the correlation between surgical duration and total PCA dose. Another factor significantly associated with a higher total PCA dose was the middle/lingual lobe lesion. In our surgical experience, to access the area of the right middle lobe and lingual segment from an anterior uniportal incision, the thoracoscope and instruments might often be placed toward the ventral side at an angle close to 90° between the ribs. This could exert a mechanical force on the intercostal region and the periosteum of the rib, causing subsequent pain and the need for an increased PCA dose.

In the largest reported population of thoracic surgery patients subjected to a chronic pain survey on discharge, the most common pain reported was that evoked by light touch and numbness [10]. In our study, the most common pain reported was that evoked by mild pres-

sure, which was not listed in the previous study [10], although it is a form of pain listed in the standard painDETECT form. We hypothesized that this type of pain could be associated with the pain evoked by light touch, as reported in the previous study; however, many of our patients might not have been able to differentiate "mild pressure" from "light touch" during the pain survey. In contrast to the previous study, we scored each pain component from 0–5 and summed a total score; most patients had a total score of <12, which was considered as unlikely neuropathic pain in the painDETECT system [30]. Another critical issue was the location of the pain, which was recorded for all patients experiencing residual pain and was summarized using a frequency plot (Fig. 4). The most frequent location of residual pain was around the anterior incision. The incidence of posterior residual pain was lower than expected, and was commonly observed around the inferior scapular border. However, residual chest wall pain might not be located exactly around the incision site, given the synergistic pain effect and the complexity of nerve innervation, and this could make identification of the source of pain difficult.

There are limitations in this study. First, the patients recruited for this trial underwent different pulmonary resection procedures, including wedge resection, segmentectomy, and lobectomy, all of which varied in terms of technical demand and procedural time required; thus, the impact of additional needlescopic ports on different types of procedures requires further clarification. Second, 2 types of needlescopic instruments, with a diameter of either 2.1 mm or 3.5 mm, were used in this trial; thus, the influence of different diameters of needlescopic instruments could not be measured in this study. Third, the number of additional needlescopic ports varied from 1 to 3, with 2 additional ports usually being used, which may also have caused bias.

Conclusion

This prospective randomized trial demonstrated that the addition of needlescopic ports to the conventional uniportal VATS setup does not negatively affect short-term outcomes, including postoperative pain, chest drainage, and hospital stay. Furthermore, the incidence of residual neuralgia did not increase, despite adding these thinner ports.

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Pleuroscopy for diagnosis of tuberculous pleurisy: Experience-sharing from Changhua Christian Hospital

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Introduction: This retrospective study evaluated the usefulness of medical thoracoscopy, also called pleuroscopy, in confirming the diagnosis of tuberculous pleurisy. We also assessed pleuroscopic findings of tuberculous pleurisy and compared them with those from surgical biopsy. Pleural effusion removed through thoracentesis, and sputum sample stain and culture were also evaluated.

Methods: Fifty-nine patients with exudative pleural effusion underwent pleuroscopy; 14 were diagnosed as having tuberculous pleurisy. We assessed clinical manifestations, routine and biochemical tests of pleural fluid, and cultures of pleural fluid, sputum, and pleural biopsy for M. tuberculosis and pathological findings.

Results: In all, 28%, 35%, and 64% of sputum, pleural fluid, and pleural biopsy cultures, respectively, were positive for M. tuberculosis. Furthermore, 92% of patients with tuberculous pleurisy had high adenosine deaminase (ADA) levels in their pleural fluid (>40 U/L). In 1 patient with low ADA levels, culture of pleuroscopy-obtained tissue revealed M. tuberculosis. Pathology reports revealed granulomatous inflammation in 86% of the patients with tuberculosis (TB).

Conclusion: Pleuroscopy is useful for identifying tuberculous pleurisy. Anesthesia is not absolutely required for pleuroscopy, resulting in a shorter intervention time and better procedure tolerance than with surgical biopsy. The diagnosis of TB based on ADA levels alone precludes culture, leading to a lack of antibiotic sensitivity testing; consequently, any drug resistance is identified only after anti-TB treatment failure. ***(Thorac Med 2021; 36: 173-177)***

Key words: Adenosine deaminase, thoracoscopy, pleuroscopy, tuberculous pleurisy

Introduction

Pleuroscopy or medical thoracoscopy is performed to diagnose lesions in the pleural space, including tuberculous pleurisy. Regardless of which organs it affects, tuberculosis (TB) causes considerable morbidity and mortality [1-2]. A particular form of extrapulmonary TB, tuberculous pleurisy, results from the presence of mycobacteria in the pleural cavity [3-4], and

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poses a diagnostic challenge [5]. It has been suggested that Mycobacterium tuberculosis (M. tuberculosis) can be detected in the pleural fluid or pleural biopsy samples by smear, culture, or histopathology. Findings such as lymphocyte-predominant exudates and, in particular, high adenosine deaminase (ADA) levels in the pleural fluid are useful for the diagnosis of tuberculous pleurisy [6]. An ADA level of >40 U/L in lymphocyte-predominant pleural fluid, with a sensitivity and specificity of 92% and 90%, respectively, is considered to indicate tuberculous pleurisy [4]. However, the value of using ADA levels to diagnose tuberculous pleurisy in areas in which it is not epidemic has been debated [4,7].

Although ADA levels can help in the diagnosis of TB or malignancy, tissue culture-grown TB, obtained using pleuroscopy biopsy, enables antimicrobial sensitivity testing. This retrospective study evaluated both the value of pleuroscopy for patients with suspected tuberculous pleurisy and the percentage of positive M. tuberculosis culture findings.

Methods

We evaluated 59 patients with exudative pleural effusion who underwent pleuroscopy. Fourteen of the 59 patients were diagnosed as having tuberculous pleurisy. We evaluated their ADA level, cultures of their pleural fluid, sputum, and pleural biopsy, as well as histopathological findings for the detection of M. tuberculosis. TB was diagnosed when a positive culture of M. tuberculosis was detected in the pleural, sputum, or bronchial specimens, or upon the detection of caseous granulomas in pleural biopsy samples.

Results

In all, 28%, 35%, and 64% of sputum, pleural fluid, and pleural biopsy cultures, respectively, were positive for M. tuberculosis in patients with TB (Table 1, Figure 2). Moreover, 92% of these patients had high pleural fluid ADA levels (>40 U/L). In 1 patient with low ADA levels, culture of pleuroscopy-obtained tissue

Table 1. ???????

All patient ifformation	Range (mean±SD) or n (%)
Age (years)	23-90(±12)
Gender (male/female)	35/24
previous TB history	0
Sputum positive for AFB	2
Sputum positive for TB culture	4
PLE positive for AFB	0
PLE positive for TB culture	5
ADA>40	13
Tissue positive for AFB	2
Tissue positive for TB culture	9
Granulomatous inflammation	12

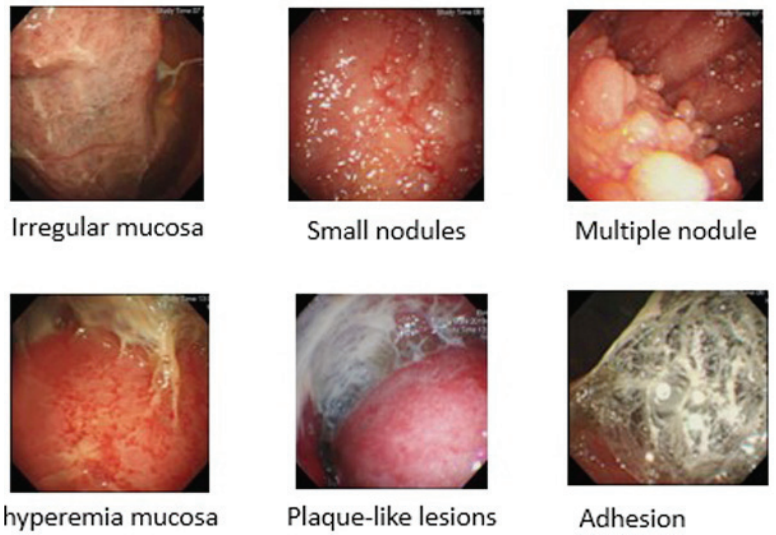

Fig. 1. Pleural lesions visualized using pleuroscopy

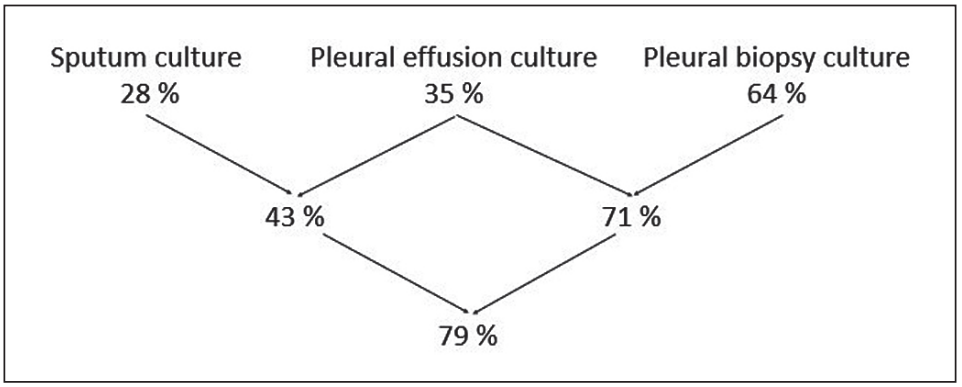

Fig. 2. Detection of tuberculosis through cultures of different samples

revealed M. tuberculosis. Under pleuroscopy, we observed pleural nodules, pleural adhesion, hyperemia, and plaque-like lesions with tuberculous pleurisy (Figure 1). No severe adverse events were noted, and the most common minor complication was mild chest pain from the indwelling chest tube. Pathology reports revealed granulomatous inflammation in 86% of the patients with TB. All TB-positive cultures were subjected to antimicrobial sensitivity testing.

Discussions

Medical thoracoscopy or pleuroscopy can be performed under local anesthesia; however, surgical thoracoscopy can be performed only under general anesthesia in the operating room. Unilateral lymphocytic pleural effusions can have multiple causes, and in Taiwan, tuberculous pleurisy should be excluded in patients due to the high prevalence of TB. We therefore evaluated the use of pleuroscopy for diagnosing

tuberculous pleurisy and presented our findings.

A case series from Qatar [8], where the mean age of 100 patients with tuberculous pleurisy was 31.5 years old, found that male sex, young age (<34 years old), and 1-sided pleural effusions were associated with tuberculous pleurisy. The pleural fluid and sputum smears were positive for acid-fast bacilli in only 2.5% and 3.7% of patients, respectively, whereas sputum, pleural fluid, and pleural biopsy cultures were positive for M. tuberculosis in 12.5%, 19.2%, and 41.9% of patients, respectively. Thus, an assessment of biopsied tissues through pleuroscopy improved the detectability of tuberculous pleurisy. Furthermore, the efficacy and safety of pleuroscopy in diagnosing tuberculous pleurisy have been reported [9-10]. Pleuroscopy is a minimally invasive procedure completed under local anesthesia that can be performed outside the operating room.

Tuberculous pleural effusions are identified by the formation of tuberculous granulomas [11-12]. In the current study, granulomas were identified in pleural biopsy specimens obtained from 63.3% of the patients. Specifically, 77.0% of patients aged 18–34 years were found to have granuloma in their biopsy specimens, compared with 37.9% of patients >60 years old. The pleural biopsy culture was significantly more likely to be positive for M. tuberculosis in patients with granulomas (48.1%) than in those without (29.5%). One study identified granulomas in pleural needle biopsy specimens obtained from 80% of patients with tuberculous pleurisy aged 34.1 ± 18.1 years [13].

In the current study, 83.3%, 72.8%, 51.2%, and 34.7% of patients who were <18, 18–34, 35–59, and >60 years old, respectively, had high ADA levels (>40 U/L) in the pleural fluid. A high ADA level is considered a diagnostic criterion of tuberculous pleurisy [6]. Abrao et al. [14] reported that the pleural fluid ADA level in patients with tuberculous pleurisy was low and correlated with age [15]. These findings may be supported by weak T-cell-mediated immune responses in older patients. Taken together, these findings indicate that in older patients, pleural fluid ADA levels ≤40 U/L do not rule out tuberculous pleurisy. In the current study, the number of positive pleural fluid and biopsy cultures and the percentage of granulomas in biopsy samples were considerably higher in the high ADA group than in the low ADA group.

However, the current study has some limitations. First, this was a single-center retrospective study; multicenter prospective studies are required to confirm our results. Second, the T-cell enzyme-linked immunospot test for TB (T-SPOT) was not used in this study. This is a relatively new test developed for TB diagnosis [16]. Xu et al. [5] reported that the area under the receiver operating characteristic curve of the T-SPOT test for diagnosing tuberculous pleurisy in pleural fluid was 0.918.

In summary, pleuroscopy is helpful in diagnosing tuberculous pleurisy by increasing the detection rate compared with sputum and pleural effusion studies. Patients with tuberculous pleurisy have an increased likelihood of granulomas in pleural biopsy specimens, and younger patients tend to have higher pleural fluid ADA levels. Although high ADA levels have high sensitivity and specificity for TB diagnosis, pleuroscopy-obtained tissue in 1 patient with a low ADA level was observed to be TB-positive on culture in the present study. If a TB diagnosis is based on the ADA level, then no drug sensitivity and resistance report will be available. Thus, pleuroscopy is effective for diagnosing tuberculous pleurisy.

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Identification of Risk Factors Predicting Respiratory Failure in Adult Patients With Positive Rapid Influenza Diagnostic Tests in Taiwan

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Background: Severe influenza is associated with a greater likelihood of respiratory failure and mortality. Early identification of patients who are potentially critically ill is important. The aim of this study was to determine the predictors of respiratory failure in severe influenza patients.

Methods: In this retrospective case-control study, we enrolled 3635 adult patients with influenza infection from a regional teaching hospital in Kaohsiung between 1 January 2017 and 31 December 2019. All patients with positive rapid influenza diagnostic tests were separated into 2 groups: a respiratory failure group and a non-respiratory failure group. We evaluated predictors, including age, gender, body mass index ≧27 kg/m2, diabetes, chronic heart disease, chronic lung disease, acute kidney injury, C-reactive protein >2 mg/dL, thrombocytopenia, leukopenia, albumin <3.5 g/dL, and a quick Sequential Organ Failure Assessment (qSOFA) score ≧2, and examined whether these factors correlated to respiratory failure.

Results: The incidence of influenza-related respiratory failure was 0.8 percent in this study. Multiple logistic regression analysis showed that significant predictors of influenza complicated by respiratory failure were age (OR=1.093, *P*=0.001), diabetes (OR=1.884, *P*=0.001), chronic lung disease (OR=1.854, *P*=0.004), chronic heart disease (OR=1.256, *P*=0.005), a qSOFA score ≧2 (OR=2.541, *P*=0.026), and acute kidney injury (OR=1.872, *P*=0.001).

Conclusion: This study revealed the predictors of severe influenza complicated by respiratory failure. The results of this study could provide a reference for physicians to identify risk factors early, so as to prevent the development of influenza complicated by respiratory failure. ***(Thorac Med 2021; 36: 178-186)***

Key words: predictor, respiratory failure, influenza, Taiwan

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Introduction

Influenza is a highly contagious respiratory illness caused by influenza viruses. Most people who develop influenza will recover within a few days to less than 2 weeks. However, influenza can sometimes cause severe illness. Serious outcomes of influenza can result in hospitalization or even death.

The World Health Organization announced the first pandemic of the 21st century in 2009 [1-2]. While most pandemic H1N1 infections were mild or subclinical, the case fatality rate was 0.1-0.7% [3]. Early reports suggested a case hospitalization rate of 2-8% [4]. In Taiwan, during the post-pandemic period (31 March 2011), there were 1751 cases of influenza with severe complications; 50.1% reported underlying diseases. Among the reported cases, 128 deaths were associated with influenza [5]. Influenza causes significant morbidity and mortality in adults, and numerous patients require intensive care unit (ICU) admission. Of the patients with influenza-related disease in ICUs, 20.3% had acute respiratory failure, and for those admitted for acute respiratory failure, the mortality rate was 11.8% [6]. Some studies have identified pregnancy, obesity and diabetes as potential risk factors for severe disease [7-9]. Another study found that an abnormal chest x-ray or a raised C-reactive protein (CRP) level, especially in patients who were recorded as obese or who had pulmonary conditions other than asthma or chronic obstructive pulmonary disease (COPD), indicated a potentially serious outcome [10].

Although certain clinical risk factors have been identified, few studies have reported and discussed the complication of respiratory failure in patients on or during admission to the ICU due to influenza infection. Furthermore, many studies have evaluated only the individual predictors of mortality. In this case-control study, we aimed to report these predictors together in 1 model. We attempted to identify the risk factors based on demographic data, clinical conditions and chronic comorbidities, to predict respiratory failure in patients with influenza infection. Understanding the risk factors for progression to respiratory failure and death is important for determining triage, and can help physicians make decisions about further management algorithms.

Methods

Design and sample

Patients

This study, using a retrospective case-control design, was conducted at Kaohsiung Municipal United Hospital (a regional teaching hospital) in southern Taiwan. Using a retrospective review, this study enrolled 3635 adult patients with influenza infection in Kaohsiung between 1 January 2017 and 31 December 2019. Nasal and throat viral swabs were obtained from all suspected patients. All cases of influenza infection were identified using rapid influenza diagnostic tests (RIDTs). RIDTs are immunoassays that can identify the presence of influenza A and B viral nucleoprotein antigens in respiratory specimens, and display the result in a qualitative way (positive vs. negative) [11]. We included all adult patients (>18 years) who visited the emergency department and who had positive RIDTs. Cases of respiratory failure that were attributed to influenza should have occurred after positive RIDTs results. Patients who had respiratory failure at the diagnosis of influenza were excluded. Treatment with oselta-

mivir was initiated for all patients. Routine serial hematologic, biochemical testing and chest radiographs were performed.

Patients with positive RIDTs were separated into 2 groups: a respiratory failure group and a non-respiratory failure group. Those with respiratory failure were referred to the medical ICU. Influenza infection-related respiratory failure was defined as having to use either invasive or non-invasive ventilator support after obtaining positive RIDTs results. During the 3-year period of the study, 3635 patients with positive RIDTs were included and 32 patients with the complication of respiratory failure were admitted to the medical ICU. Demographic data, medical history, clinical findings, results of laboratory tests and patient outcomes were obtained from medical records, including physicians` records, nursing charts, and computer databases.

Variables measured

The following variables were recorded for all study patients at admission: age, gender, BMI ≧27 kg/m^2, diabetes, chronic heart disease, chronic lung disease, acute kidney injury (AKI), CRP level, thrombocytopenia, leukopenia, albumin, and qSOFA score. Patients who did not have the above complete data were excluded. The missing data included 238 patients` BMI, 43 patients` blood cell counts, 184 patients` CRP levels, and 312 patients` albumin, for a total of 427 patients. The researchers reviewed the complete data of each patient. The study was performed with the approval of the hospital ethics committee.

Definitions

Obesity was an identified risk factor for a fatal pandemic 2009 influenza infection [12]. Obesity was defined as a BMI ≧27 kg/m2 according to the criteria of the Department of Health in Taiwan. Chronic heart disease was defined as having a history of coronary artery disease, arrhythmia, heart failure, vascular heart disease and cardiomyopathy. Chronic lung disease was defined as having a history of persistent lung disorder, including COPD, asthma, bronchiectasis, and interstitial lung disease. According to the Acute Kidney Injury Network (AKIN) classification [13], AKI is defined as a sudden decrease (within 48 hours) in renal function, or by an increase in absolute serum creatinine (SCr) of at least 0.3 mg/d L or by a percentage increase in SCr ≧50%, or by a decrease in urine output (documented oliguria < 0.5 mL/Kg/h for more than 6 hours). We compared the SCr level at the emergency department with the patient's previous SCr record or with the SCr during admission. If the patient's absolute SCr increased 0.3 mg/dl, then the patient would meet the criteria for AKI. If the patients were admitted to the ICU, then we could monitor the urine output. Those patients that did not meet the above conditions would fall into the non-AKI group. All blood cell counts were checked at the emergency department. CRP and albumin were checked at the emergency department or during admission.

CRP has been reported as both a sensitive and a specific marker for bacterial infection in patients presenting with influenza-like illness [14]. In this study, we used the same cutoff value of CRP >2 mg/dL to determine a secondary bacterial infection complication of influenza infection. A survey from China reported that 21.4% of patients had leukopenia [15]. Leukopenia in our study was defined as a fall in the number of blood leukocytes to under 4000 white cells per cubic millimeter of blood. This may correlate with an immune system over-

reaction to the viral infection, leading to a so-called cytokine storm, which triggers inflammation and lung damage that can lead to multiple organ failure and death [16]. The platelet counts may be predictors of mortality. Patients with thrombocytopenia showed a lower in-hospital survival rate [17]. In this study, we used a platelet count < 150,000/μL in the adult population as a predictor of mortality.

The qSOFA score ranges from 0 to 3, with 1 point for each of the following 3 components: respiratory rate ≧22 breaths per minute, altered mental status, and systolic blood pressure less than 100 mmHg. An altered mental status was defined as a Glasgow Coma Scale (GCS score) < 15. A positive qSOFA score was defined as a score of 2 or higher [18].

Data analysis

Data were analyzed using SPSS/PC software Version 20.0. Descriptive statistics were used to describe the overall patients. Respiratory failure was the primary outcome measure. For univariate analysis, a chi-square test was performed to investigate relationships between characteristics variables. All *P* values were 2-tailed and a *P* value < 0.05 was considered to be statistically significant. All significant characteristics variables were entered into multivariate analysis using a multiple logistic regression model to identify independent risk factors for respiratory failure. The reference category was "non-respiratory failure". All characteristics from the multiple logistic regression analysis with a p value < 0.05 were used to construct the logistic regression model.

Results

Demographic, clinical and laboratory parameters

We categorized the patients into 2 groups: (1) an influenza infection-related respiratory failure group after positive RIDTs results (n=32) and (2), an influenza infection-related non-respiratory failure group after positive RIDTs results (n=3603). The days of occurrence of respiratory failure with either invasive or non-invasive ventilator support after obtaining positive RIDTs varied from 0 to 8, with a mean of 2.4 days (Table 1). The incidence of respiratory failure after obtaining positive RIDTs

Table 1. Days of Occurrence of Respiratory Failure Uusing Either Invasive or Non-invasive Ventilator Support After Positive RIDTs

Days of occurrence of respiratory failure after positive RIDTs* (days)	Patient numbers
0	4
1	8
2	6
3	7
4	3
5	1
6	2
7	0
8	1
Mean : 2.4	Total: 32

results was 0.8% (Table 2). The significance differences between the 2 groups were: age >75 (P<0.001), diabetes (P=0.002), chronic lung disease (P=0.01), chronic heart disease (P=0.049), qSOFA score ≧2 (P=0.001), and AKI (P=0.034).

These results infer that influenza infection complicated with respiratory failure was more common in patients at an older age, with underlying diseases like diabetes, chronic lung disease, and chronic heart disease, or in patients presenting with an increase of more than 2 points in the qSOFA score, or with AKI. There were no significant differences in sex, albumin level, BMI, elevated CRP, leukopenia and thrombocytopenia between the 2 groups.

Table 2. Bivariate analysis of Respiratory Failure Among Patients with Positive Rapid Influenza Diagnostic Tests Using patient Demographics and Underlying Diseases

		Respiratory failure (n=32)	Non-respiratory failure (n=3603)	*P* value
		Number (%)	Number (%)	
Age	≧75	18(56.3)	978(27.1)	<.001
	＜75	14(43.8)	2616(72.6)	
Sex	Female	15(46.9)	1741(48.3)	.227
	Male	17(53.1)	1862(51.7)	
Albumin <3.5g/dL	Yes	24(75.0)	901(25.0)	.4857
	No	8(25.0)	2702(75.0)	
BMI ≧27 kg/m^2	Yes	19(59.4)	873(24.2)	.066
	No	13(40.6)	2730(75.8)	
Diabetes mellitus	Yes	20(62.5)	1210(33.6)	.002
	No	12(37.5)	2393(66.4)	
CRP* >2 mg/dL	Yes	26(81.3)	2421(67.2)	.095
	No	6(18.8)	1182(32.8)	
Chronic lung disease	Yes	18(56.3)	1978(54.9)	.001
	No	14(43.8)	1625(45.1)	
Chronic heart disease	Yes	19(59.4)	2007(55.7)	.049
	No	13(40.6)	1596(44.3)	
Leucopenia	Yes	18(56.3)	1940(53.8)	.079
	No	14(43.8)	1663(46.2)	
Thrombocytopenia	Yes	20(62.5)	1596(44.3)	.088
	No	12(37.5)	2007(55.3)	
qSOFA** ≧2	Yes	22(68.8)	2967(82.3)	0.01
	No	10(31.3)	636(17.6)	
Acute kidney injury	Yes	18(56.3)	1661(46.1)	.034
	No	14(43.8)	1942(53.9)	

*CRP: C-reactive protein

** qSOFA: quick Sequential (sepsis-related) Organ Failure Assessments score

As shown in Table 3, the odds ratios (ORs) of the risk factors that could lead to influenza infection-related respiratory failure after obtaining positive RIDTs results were age (OR=1.093, *P*=0.001), diabetes (OR=1.884, *P*=0.001), chronic lung disease (OR=1.854, *P*=0.004), chronic heart disease (OR=1.256, *P*=0.005), a qSOFA score ≧2 (OR=2.541, *P*=0.026), and AKI (OR=1.872, *P*=0.001). A qSOFA score ≧2 seemed to be the most important risk factor, as it increased the risk of respiratory failure with influenza infection 2.5 times.

Discussions

The results of this study confirmed that older age, having the co-morbidities of diabetes, or chronic heart or lung disease, or findings consistent with AKI or a qSOFA score ≧2 at the time of presentation to the emergency department were associated with a higher risk of respiratory failure. Of these variables, a qSOFA

Table 3. Odds Ratios of Respiratory Failure Among Patients with Positive Rapid Influenza Diagnostic Tests Using Patient Demographics and Underlying Diseases

Determinants		**Adjusted OR**	***P* value**
Age	≧75	1.093	
	＜75	1	0.001
Sex	Female	0.754	
	Male	1	0.577
Albumin <3.5g/dL	Yes	1.691	
	No	1	0.871
BMI ≧27 kg/m^2	Yes	0.576	
	No	1	1.271
Diabetes mellitus	Yes	1.884	
	No	1	0.001
CRP* >2 mg/dL	Yes	0.975	
	No	1	0.687
Chronic lung disease	Yes	1.854	
	No	1	0.004
Chronic heart disease	Yes	1.226	
	No	1	0.005
Leukopenia	Yes	0.621	
	No	1	1.605
Thrombocytopenia	Yes	0.652	
	No	1	1.224
qSOFA** ≧2	Yes	2.541	
	No	1	0.026
Acute kidney injury	Yes	1.872	
	No	1	0.001

*CRP: C-reactive protein ** qSOFA: quick Sequential (sepsis-related) Organ Failure Assessments score

score ≧2 was found to be the best predictor of subsequent respiratory failure and the need for mechanical ventilation. Although some studies found that the qSOFA score may not be an adequate screening tool in the emergency department due to its poor sensitivity [19-21], the qSOFA score in this study seemed to be a useful predictor for severe influenza infection.

Zimmerman *et al*. found that serum CRP levels in patients presenting with pandemic H1N1 influenza A infection could serve as a useful gauge for predicting disease course [22]. However, in this study, we found no significant difference between the 2 groups in terms of serum CRP levels as a risk factor. The reason for this finding might be related to the "cut-off value". In the Zimmerman et al. study, 19% of patients with a serum CRP level ≧7 mg/dL needed to be admitted to the ICU, and 8% required mechanical ventilation [22]. But in our view, if the cut-off value of the CRP level is lowered to 2 mg/dL, the prediction of severe influenza infection would achieve higher sensitivity but lower specificity.

The same condition was also found with the albumin parameter. Wi YM, *et al*., in their study, found that serum albumin levels on admission were a predictor of the need for intensive respiratory or vasopressor support in adult patients with H1N1. The cut-off value in this study was 2.7 g/dL, with a specificity of 85.7% [23]. However, the specificity would decrease if the cut-off value were increased to 3.5 g/dL.

Obesity has been previously identified in many reports as an independent risk factor for severe pandemic H1N1 infection [24-25]. In our study, those with a BMI ≧27 vs <27 amounted to 59.4% vs 40.6% of the influenza infection-related respiratory failure group. (P=0.06) The P value nearly achieved a significant difference with this predictor. However, this may be related to the smaller sample size.

During the 2016 winter season, an influenza outbreak occurred in Taiwan. In total, 1735 subjects were admitted to ICUs due to severe complicated influenza, according to data from the Centers for Disease Control of Taiwan [26]. During this outbreak, some patients with pandemic influenza infection suffered extremely rapid progression. Critically ill influenza patients could progress to hypoxic respiratory failure within 24 hours. Also, the mean time from positive RIDTs to intubation or non-invasive ventilator support in this study was 2.4 days. Therefore, we hope that the use of these early predictors could help physicians make timely decisions and provide prompt intensive care for patients with potentially fatal outcomes, particularly in resource-limited hospitals.

In Taiwan, patients with severe symptoms or multiple comorbidities may tend to visit referral hospitals, especially medical centers. However, these conditions rarely occur in patients with influenza. The reasons for this might be as follows. First, patients with the first signs of influenza infection might consider it a common cold and just visit the nearest hospital for convenience. Second, medical expenses in public regional hospitals are lower than in medical centers, so patients with influenza tend to visit public regional hospitals for economic reasons. Research supports these statements, in that self-rated health and willingness to pay are influencing factors in health-seeking behavior [27]. Third, if the patients suffered from a severe and complicated influenza infection, then the conditions would be so fulminant and rapidly progressive that the patients would not have the opportunity to choose their favorite hospitals. However, under this circumstance, the role of

physicians at emergency departments is very important. They need to make wise judgements based on the risk factors, ICU capacity and hospital treatment ability, and decide whether to transfer the patient or arrange their hospital admission.

Limitations

The limitations of this study should be considered. First, all participants in this study were recruited from a regional teaching hospital in southern Taiwan, which might limit the generalizability of the study. Further studies are needed to evaluate larger populations from different hospital levels or other areas of Taiwan. Second, this study collected objective data only, and did not include subjective data, such as the time interval between symptom onset and performing the rapid influenza test. Further studies are needed to explore subjective risk factors predicting respiratory failure in adult patients with influenza. Finally, 427 patients did not have complete data and were excluded from the study. The missing data might have influenced the results of this stud.

Conclusion

In the current sample of influenza infection patients with positive RIDTs results, older age, co-morbidities including diabetes, chronic heart or lung disease, AKI and qSOFA were found to be significantly correlated to disease severity, especially the complication of respiratory failure. These prognostic predictors might serve as useful tools to identify potentially critically ill patients and help make adequate therapeutic decisions for patient management.

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Pulmonary Alveolar Microlithiasis: A Case Report and Literature Review

Shr-Hau Dai[1], Yao-Min Ting[1], Herng-Sheng Lee[2], Lin Lee[1]

Pulmonary alveolar microlithiasis (PAM) is an uncommon genetic lung disease characterized by the deposition of calcium phosphate within the alveoli. Mutations in the SLC34A2 gene, which encodes a sodium/phosphate co-transporter, are responsible for this disease. Dysfunction of this transporter leads to local aggregation of phosphate in the alveolar airspaces and formation of microliths. The long-term prognosis is poor and no known effective treatment is available to date. We describe the case of a 47-year-old woman who was referred to our hospital for eye surgery, but chest radiography incidentally revealed extensive interstitial lung disease. Shortness of breath and lip cyanosis gradually developed in the following half-year. A computed tomography-guided biopsy was performed that confirmed the PAM diagnosis. The patient died 6 months after the initial chest image finding. It was concluded that the disease was discovered late in this patient and progressed rapidly. ***(Thorac Med 2021; 36: 187-192)***

Key words: pulmonary alveolar microlithiasis; SLC34A2 gene; sodium-phosphate co-transporter

Introduction

Pulmonary alveolar microlithiasis (PAM) is an uncommon autosomal recessive disease characterized by the widespread deposition of calcium phosphate microliths within the alveoli. It is caused by inactivating mutations in the SLC34A2 gene that encode a sodium-dependent phosphate co-transporter [1]. This co-transporter is responsible for the uptake of phosphate released from the phospholipids in the outdated surfactant. The inability to clear phosphate from the alveolar space leads to its local aggregation in the alveoli and the formation of microliths.

The disease was first described in 1686, and was given its current name in 1933. Up to 2014, more than 1,000 cases of PAM have been described in the literature worldwide [2]. Most of the patients with PAM are asymptomatic at the time of diagnosis and the disease is usually identified incidentally by chest radiography undertaken for other purposes. The typical chest radiographic presentation of PAM is a fine, sand-like micronodular pattern, termed a "sandstorm" appearance [3]. While disagreement between the clinical and radiological findings is possible due to a paucity of symptoms, dramatic imaging findings can enable an accurate

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diagnosis. However, as the disease progresses, symptoms such as dyspnea on exertion and dry cough may develop. PAM is usually diagnosed based on a typical radiological pattern. However, in doubtful cases, bronchoalveolar lavage may help confirm the diagnosis when microliths with a typical lamellar structure are observed [4]. Many authors argue that the presence of a typical "sandstorm" pattern precludes the need for a lung biopsy in most cases. However, lung biopsy was still performed for diagnosis in about 46.9% of cases in the literature [5], most likely because the disease is unfamiliar to many physicians.

The clinical traits of PAM are heterogeneous, ranging from a completely lack of symptoms to respiratory failure [2]. The disease remains stationary in a few patients, while it progresses at different speeds in most other patients. The long-term prognosis of PAM is poor and effective treatment is not yet available. Most PAM patients have a follow-up period of >10 years after the initial diagnosis, and some patients have survived >20 years [2]. Herein, we report a patient who died approximately 6 months after the initial chest radiograph finding.

Case Description

A 47-year-old female, who was abandoned by her natural parents after birth, had an intellectual disability. Her foster parents found out that the patient had mental retardation years after she was adopted. She needed assistance in daily activities and her parents had difficulty in taking her out. She was referred to our respiratory team for an abnormal chest radiograph appearance on 2018/04/09. Chest imaging incidentally discovered diffused nodular and interstitial infiltration in the bilateral lungs (Figure 1A) during her pre-operative examination for ophthalmic surgery on 2017/10/24. Interstitial lung diseases or lymphatic metastasis was suspected. Referral to a respiratory physician was suggested by an ophthalmologist, but the patient did not follow through. The patient then visited the Department of Respiratory Medi-

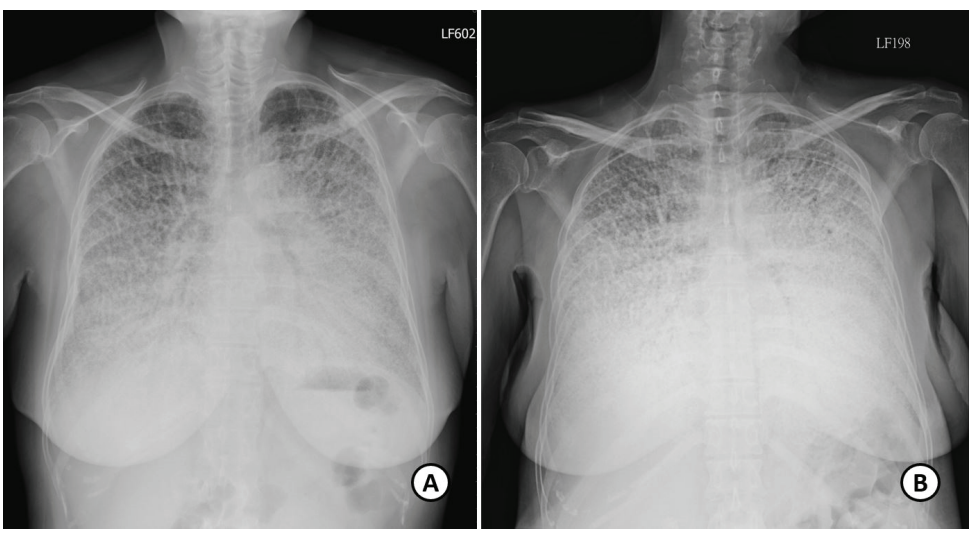

Fig. 1. (A) Chest radiograph with a posteroanterior view incidentally detected diffused nodular and interstitial infiltration in the bilateral lungs in October 2017. (B) Follow-up chest radiograph 6 months later revealed progressive change, compared with the previous study with an anteroposterior view.

cine, Kaohsiung Veterans General Hospital, for progressive shortness of breath with lip cyanosis on 2018/04/09. The patient could not communicate with others and thus her parents did not realize that the exertional dyspnea had presented before. The patient was a non-smoker but had a history of diabetes and hypertension without medical control. There is no available information regarding her natural parents and thus her family history is unknown.

Upon admission, her physical examination revealed marked inspiratory crackles and lip cyanosis. Her total leukocyte count was 6,500/mm3, with a differential cell count of 65.3% neutrophils, 22.6% lymphocytes, 7.6% monocytes, and 3.6% eosinophils. Her hemoglobin level was 15.3 g/dL, but hyperbilirubinemia (total bilirubin 2.0 mg/dL, direct bilirubin 0.9 mg/dL) was noted with negative urine bilirubin and elevated urine urobilinogen, suggesting possible hemolysis. There were no skin rashes or arthralgia on examination and her antinuclear antibody (ANA) and erythrocyte sedimentation rate (ESR) tests were all negative. Other investigations, including serum electrolytes, renal function, and liver function tests, were all within normal limits. Chest radiograph (Figure 1B), which was obtained on 2018/04/18, showed a progressive change with increased opacities in the bilateral lungs. High-resolution computed tomography (HRCT) (Figure 2) revealed diffused interlobular hyperdense septal thickening with ground-glass opacities and a crazy-paving appearance in both lung fields. Pulmonary alveolar microlithiasis was first considered. There was no fever or leukocytosis during the 17 days of the hospital course. Her serum procalcitonin level was <0.05 ng/ml at admission, suggesting that bacterial infection was unlikely. Antibiotic was not prescribed due to the lack of evidence for infection. The patient was not able to cooperate with the registered nurses, and we were

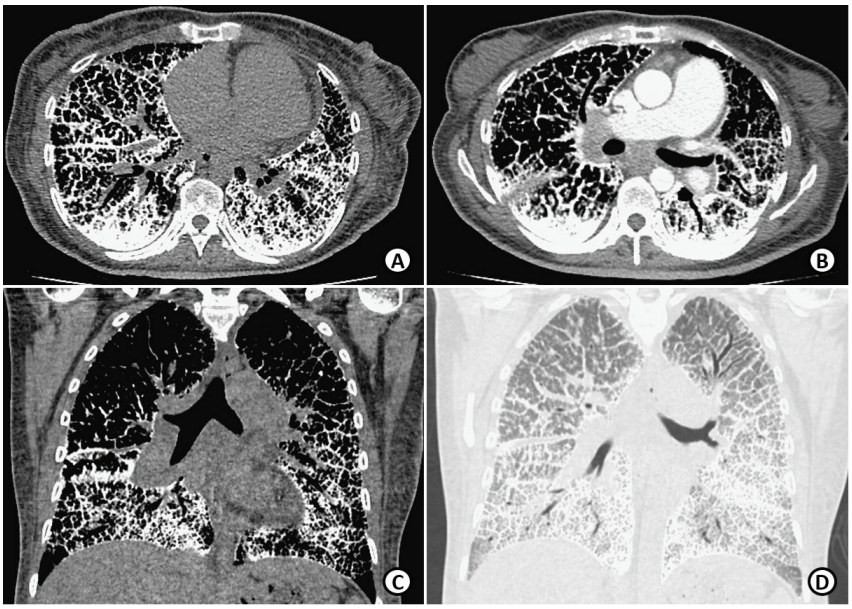

Fig. 2. High resolution computed tomography (HRCT) of the chest revealing (A) diffused interlobular hyperdense septal thickening with (D) ground-glass opacities and (C) a lower zone predilection associated with (B) bulky subcarinal and hilar lymphadenopathy.

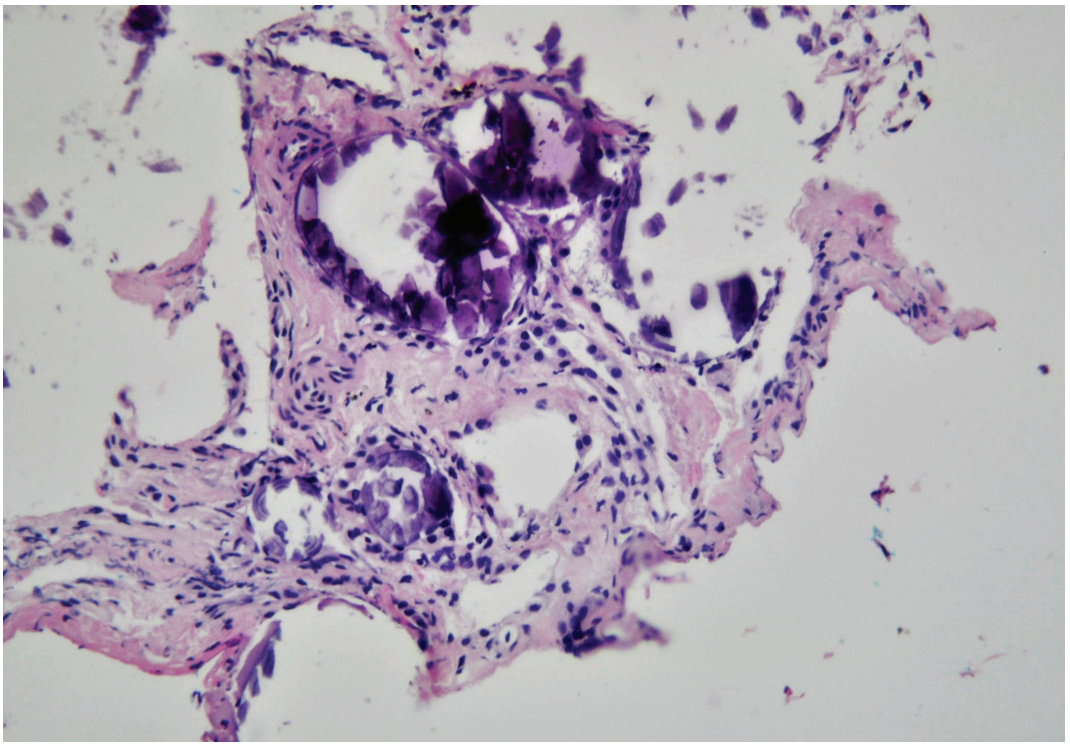

Fig. 3. A lung section from the CT-guided biopsy showing lung tissue admixed with multiple spherical calcifications (H&E staining, 200 × magnification).

unable to collect sputum specimens for bacterial culture or cytology examination.

However, we were still concerned about the possibility of pulmonary alveolar proteinosis or lymphangitic carcinomatosis due to unknown malignancy. Her respiratory condition worsened and a non-rebreathing mask was used on 2018/04/20. Serum tumor markers were evaluated, and the values were all within normal limits. We discussed with her parents the use of CT-guided lung biopsy, because bronchoscopy was not possible in case there was a high oxygen demand. CT-guided lung biopsy was performed on 2018/04/27, and revealed multiple spherical calcifications with an onion skin feature in the alveoli (Figure 3), confirming the diagnosis of PAM. There was no evidence of atypia or malignancy. However, the patient passed away due to respiratory failure on 2018/05/04.

Discussion

PAM is a rare autosomal recessive genetic lung disease characterized by widespread sand-like intra-alveolar calcifications. The disease has been reported in every country, with no particular geographic or racial distribution. However, Asia, followed by Europe, is the most prevalent area [2]. According to the genetic hypothesis, PAM is caused by inactivating mutations in the SLC34A2 gene, which is located on 4p15 and comprises 13 exons [6]. More than a dozen different mutations have been described in PAM patients. The SLC34A2 gene is primarily expressed in alveolar type II cells, and encodes a sodium phosphate co-transporter that plays an essential role in the clearance of phospholipids released by the outdated surfactant [7]. Therefore, dysfunction of the SLC34A2 protein

may lead to the accumulation of intra-alveolar microliths formed by phosphate-chelating calcium. Both sporadic and familial cases of PAM have been reported. The incidence of familial occurrence of PAM was reported to range from 32% to 61% in a previous study [8]. In this case, we did not know whether the family members of the patient had experienced any type of respiratory illness, since she was adopted.

A PAM diagnosis can usually be established radiographically, if a classic "sandstorm" appearance of diffusely scattered micronodules is present. Chest HRCT typically reveals widespread, tiny microcalcifications throughout the lungs with a subpleural and peribronchial distribution [9]. Additional accompanying HRCT features include calcified interlobular septa, diffused ground-glass opacities, and crazy-paving pattern. Although bronchoscopy is usually not needed for a PAM diagnosis, bronchoalveolar lavage demonstrating microliths with a typical lamellar structure can be helpful if the diagnosis is uncertain. Lung biopsy appears to have a reasonable outcome and safety profile; however, it should be reserved for cases in which uncertainty persists even after the use of more conservative diagnostic methods [10]. When diffused calcified pulmonary densities are observed on chest CT, the differential diagnoses may include tuberculosis, mycosis, sarcoidosis, hemosiderosis, pneumoconiosis, amyloidosis, metastatic pulmonary calcification, and pulmonary ossification. PAM can be differentiated from metastatic pulmonary calcification by CT images, which have a predilection for lung bases distribution in PAM, but a strong upper lung zone predilection in metastatic pulmonary calcification. Chest CT of our patient showed pulmonary calcifications with a lower zone predilection, and we also evaluated the serum calcium and intact parathyroid hormone level to exclude metastatic pulmonary calcification. Her serum calcium and intact parathyroid hormone levels were all in the normal range. It was difficult to decide whether to perform lung biopsy for this patient since she had severe oxygen desaturation and a non-rebreather mask was needed. Her parents agreed to her undergoing lung biopsy due to the prolonged hospitalization with no definitive diagnosis. A PAM diagnosis was confirmed after the procedure and no CT-guided biopsy complication was identified after 1 week of hospital observation.

PAM has been described in subjects of all ages ranging from infants to the elderly, but it is usually diagnosed around the second and third decade of life [2]. Some authors have reported cases of PAM with a normal chest radiograph years before diagnosis, suggesting that the disease can be acquired over a lifetime. The clinical course of PAM is variable, ranging from a stationary course for decades to a rapid onset with progression to mortality within a few years. The long-term prognosis of PAM is poor and most patients eventually progress to respiratory failure, lung fibrosis, or cor pulmonale. PAM usually progresses through a 10-20-year follow-up period after the initial diagnosis [5]. In our patient, however, the disease progressed from the initial onset of symptoms to death in only 6 months. There were also corresponding chest X-ray findings of deteriorated bilateral lung opacities during this period. We attempted to find possible exacerbating and correctable factors for her respiratory failure. However, the bacterial culture, including a mycobacterial culture, from the CT-guided biopsy showed no growth. To the best of our knowledge, there is no proven treatment that can reduce disease progression. Systemic corticosteroids, calcium-

chelating agents, and whole lung bronchoalveolar lavage have no demonstrated benefits and are used only as palliative treatments [11]. The use of diphosphonates has also been proposed to reduce calcium phosphate precipitation in PAM. However, this therapy remains controversial given the limited number of reports in the literature [12]. Lung transplantation has been beneficial in patients with severe respiratory failure [13]. To date, no recurrence of PAM after lung transplantation has been reported. Therefore, PAM patients should be referred to a lung transplantation team before the development of severe right ventricular dysfunction.

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Diffuse High-Attenuation Pulmonary Reticular Abnormalities: Idiopathic Diffuse Dendriform Pulmonary Ossification

Yen Chin[1], Herng-Sheng Lee[2], Ruay-Sheng Lai[1,3]

Dendriform pulmonary ossification is a rare pulmonary entity, and the diagnosis has usually been established on postmortem examination. Histologically, it is characterized by widespread ectopic fine branching osseous fragment formation in the lung parenchyma. On chest radiographs, it mimics other interstitial lung diseases, and may present as diffuse high-attenuation nodular and/or branching abnormalities on high-resolution computed tomography. At chronic stages, the disease presents without remarkable clinical manifestations, and the majority of cases are found in the middle-aged to older male population. Here we present the case of a young female adult with idiopathic dendriform pulmonary ossification confirmed via video-assisted thoracoscopy surgery biopsy. ***(Thorac Med 2021; 36: 193-197)***

Key words: pulmonary alveolar microlithiasis; SLC34A2 gene; sodium-phosphate co-transporter

Introduction

Dendriform pulmonary ossification (DPO) is characterized by widespread ectopic fine branching osseous fragments in the alveoli or interstitium of the lung, either localized or disseminated throughout the lung parenchyma [1]. It is rarely seen and can be idiopathic or associated with a pre-existing chronic pulmonary or cardiac disorder, such as idiopathic pulmonary fibrosis or heart failure [2]. Patients are usually asymptomatic, and the presence of pulmonary ossification is often not apparent on chest radiograph, but can usually be identified on high-resolution computed tomography (CT) [3]. A careful examination can help in reaching a timely diagnosis and in providing appropriate treatment for associated cardiopulmonary diseases, and also enables a better understanding of the natural course of this rare disease entity. Here, we report the case of a 31-year-old female who was diagnosed as having idiopathic diffuse DPO due to the accidental findings of an abnormality on chest X-ray. Her diagnosis was confirmed via video-assisted thoracoscopy surgical (VATS) biopsy. We also review related

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case reports and imaging findings in the literature to provide a comparison of differences between pulmonary parenchymal ossification and calcification.

Case Description

A 31-year-old female visited our chest clinic due to abnormal chest radiographic findings during a routine health check-up. She was a non-smoker and denied any exposure to noxious environmental particles. Her medical history was significant for allergic rhinitis, which was controlled by steroid-containing nasal sprays. She had no fever, chronic cough, chest tightness, exertional dyspnea, or exercise intolerance. On physical examination, vital signs appeared normal. Her breathing sounded clear on auscultation. Laboratory investigations, including complete blood count, serum chemistry, thyroid hormones, parathyroid hormone, and biomarkers for autoimmune disorders, were all within normal limits. Electrocardiogram showed normal sinus rhythm. Peripheral oxygen saturation was 97% at rest, while breathing ambient air. The pulmonary function test revealed normal ventilation and gas exchange function (FEV1 86%, FVC 83%, FEV1/FVC 80% and a gas transfer factor of 82% of the predicted value). Chest radiograph showed predominant bilateral fine reticulonodular infiltrates in the lower lung (Figure 1A). Chest CT revealed diffuse numeral calcified and non-calcified tiny nodules mixed with linear branching opacities in the interstitial septum, mainly in the subpleural area. There was an absence of lymphadenopathy, bronchiectasis, or honeycomb appearance (Figure 1B). Under the presumptive diagnosis of pulmonary sarcoidosis, the patient underwent surgical lung biopsy by VATS. Pathology findings revealed mature bony trabeculae with bone marrow elements surrounded by collagen fiber bundles, with peri-terminal bronchioles and an alveolar distribution. (Figure 2) The alveolar structures among the lesions were mostly unremarkable. Honeycomb and fibroblast foci were absent. There was no evidence of malignancy or granuloma formation. A final diagnosis of

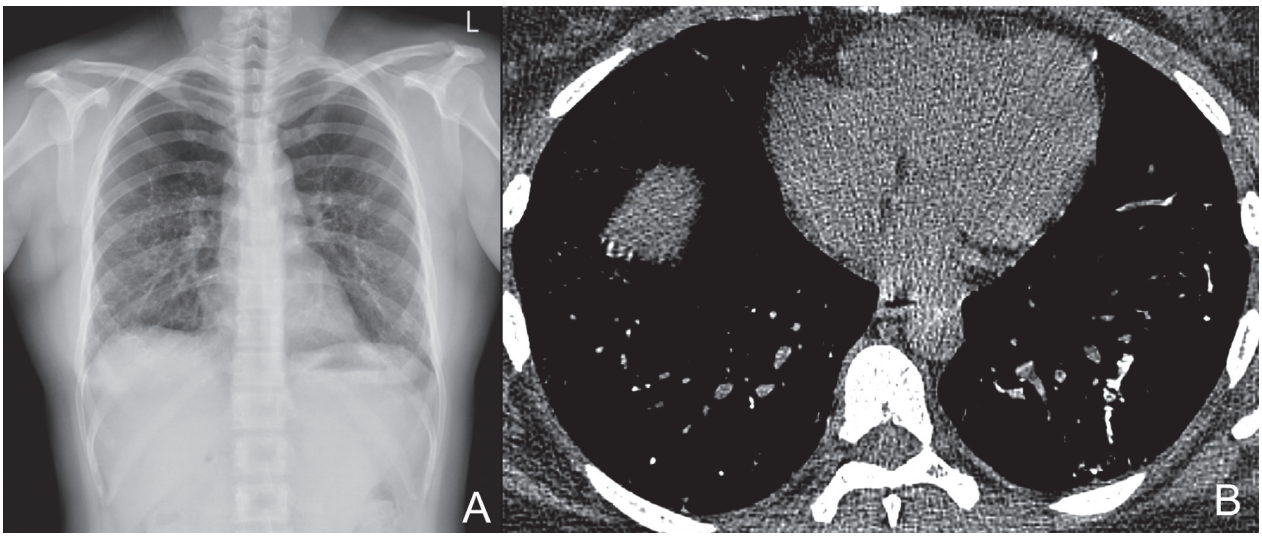

Fig. 1. (1A) Chest radiograph showed predominant bilateral fine reticulonodular infiltrates in the lower lung fields. (1B) Bone window thoracic CT revealed high-attenuation of the pulmonary parenchyma with a fine, linear pattern of calcification.

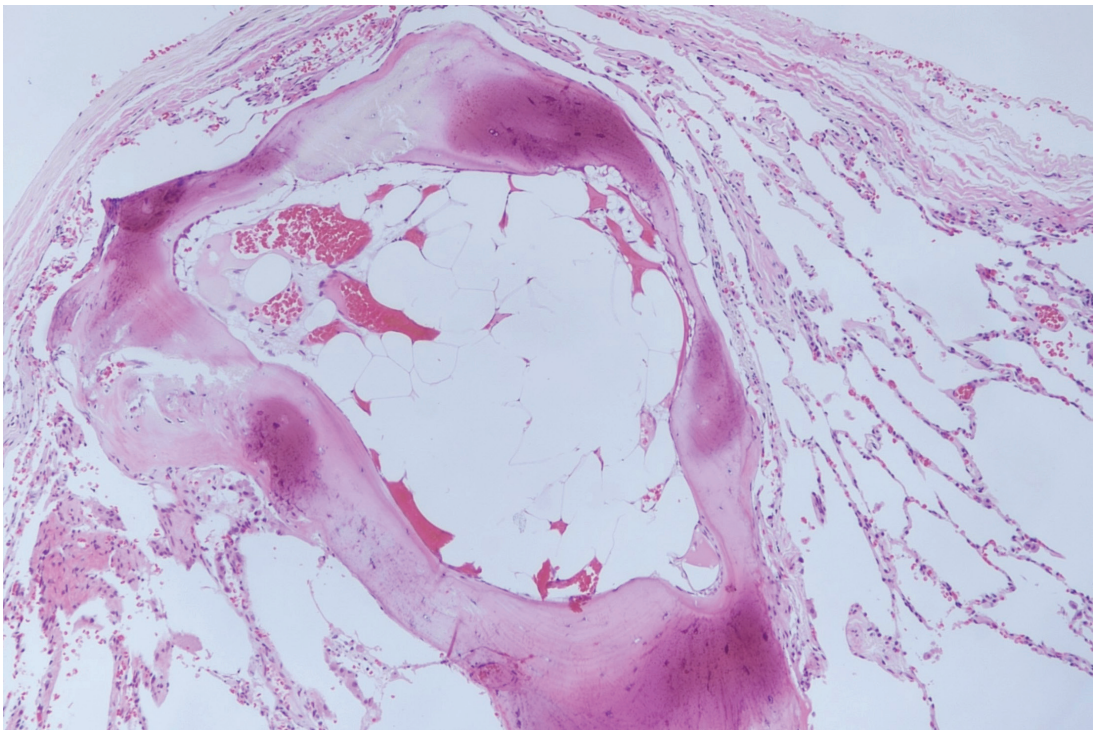

Fig. 2. Bone marrow (center) with bone trabeculae adjacent to lung alveoli (hematoxylin and eosin stain × 400).

pulmonary ossification, dendriform type, was established.

Discussion

On chest imaging, diffuse pulmonary parenchymal calcifications are common findings, and may present in a wide variety of pulmonary conditions. Diffuse pulmonary ossification is defined as widespread ectopic bone formation in the interstitium or alveolar space [4-5], and such ossification is usually undetected on chest radiographs. Both pulmonary parenchymal calcification and pulmonary ossification may present as diffuse high-attenuation abnormalities on high-resolution CT (Table 1). Therefore, it may be difficult to differentiate them from one another on imaging studies, especially in diffuse small calcified nodule or linear patterns [6].

Pulmonary parenchymal calcification refers to the deposition of calcium salt in the lung parenchyma, and may occur in a wide variety of diseases. Pulmonary parenchymal calcification can be divided into metastatic and dystrophic calcification. Metastatic calcification is mainly related to a mineral ion imbalance with hypercalcemia. The major etiologies include primary or secondary hyperparathyroidism, chronic renal insufficiency under hemodialysis, and malignant neoplasm (e.g., multiple myeloma and sarcoma). Pulmonary dystrophic calcification occurs under conditions of previous lung injury, such as infectious (tuberculosis, viral, parasitic), granulomatous (sarcoidosis), occupational (silicosis, coal worker pneumoconiosis), metabolic (amyloidosis, pulmonary alveolar microlithiasis), and pulmonary vascular (pulmonary hypertension) disorders [2].

Table 1. Comparison of Differences Between Pulmonary Parenchymal Calcification and Ossification

	Calcification		Ossification	
	Metastatic	**Dystrophic**	**NPO**	**DPO**
Pathology	deposition of calcium salt in normal lung tissue	deposition of calcium salt in previously injured lung tissue	bone tissue +/- marrow elements	
			ectopic bone formation in alveolar space	ectopic bone spicules with marrow elements in lung interstitium
Pathogenesis	serum calcium, phosphate, alkaline phosphatase activity, pH, PTH, Vit. D	follows caseation, necrosis, fibrosis, infection	uncertain, but may be associated with angiogenesis, chronic venous congestion, lung fibrosis, growth factors (TGF-ß, VEGF, IL-1, IL-4…)	
Etiology	chronic renal insufficiency, secondary hyperparathyroidism, under hemodialysis	granulomatous diseases, occupational, infectious disease (TB, viral, parasitic infection), amyloidosis, etc.	pulmonary venous congestion such as mitral valve stenosis, chronic heart failure	chronic inflammatory lung diseases such as UIP (usual interstitial pneumonia)
HRCT	upper lobe predominant, fluffy ground-glass opacities, containing foci of calcification	variable	round with smooth contours; lobulated	fine linear branching opacities in the interstitium, mostly in bibasilar subpleural area, best seen in an osteoporosis window setting

Data from references 2,3,7,9,10,11.

Pulmonary ossification, in contrast, has normal serum calcium and phosphate levels and presents with discernible bony trabeculae as a mineralized focus, as seen on histology. Diffuse pulmonary ossification is uncommon. The pathogenesis of pulmonary ossification still remains unclear, with an incidence of 1.63 cases/1000 autopsies. Studies have also revealed a male predominance and a predilection toward having underlying pulmonary disease [7,13]. There are 2 forms of pulmonary ossification: nodular pulmonary ossification (NPO) and DPO. On imaging, NPO is represented by densely calcified round nodules. Histologically, it presents as an ectopic bone formation that is seen as round calcified nodules in the alveolar space [5]. NPO may result from intra-alveolar exudate organization, without a marrow element, and is often linked to conditions with pulmonary venous congestion, such as mitral valve stenosis and chronic heart failure. In contrast, DPO is characterized by bone spicules with a marrow element in the lung interstitium [5], It may be associated with a chronic inflammatory lung disease such as usual interstitial pneumonia (UIP) [8,12]. On high-resolution chest CT, DPO manifests as dendritic, fine branching linear opacities in the alveolar interstitium, more prominent in the basal lung field. Such a characteristic radiographic appearance is too subtle

and can only be recognized on chest CT; it is best seen on the bone window setting, which may distinguish it from other forms of pulmonary calcification [3]. Some studies have reported that the increased prevalence rate of DPO in patients with UIP was not found in patients with nonspecific interstitial pneumonia (NSIP). This finding should be helpful in differentiating UIP from NSIP in clinical practice [8].

In conclusion, DPO has an insidious and nonspecific clinical manifestation and the process is indolent. When high-resolution CT shows extensive high-attenuation of the pulmonary parenchyma with diffuse small calcified nodules in a linear pattern, DPO should be considered as a differential diagnosis.

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Primary Small Cell Carcinoma of the Trachea-- a Case Report

Ko-Yun Chang[1], Shuo-Hsiu Hsu[2], Shang-Heng Wu[2], Jeng-Sen Tseng[1,3,4], Gee-Chen Chang[1,3,4]

Primary small cell carcinoma of the trachea is extremely rare. The diagnosis is usually delayed because the symptoms may mimic other airway diseases. The incidence, treatment, and outcome of this disease remain poorly investigated. We present the case of a 66-year-old man with progressive shortness of breath and cough. Bronchoscopy revealed a tumor mass in the trachea, and the diagnosis of small cell carcinoma was made by tumor debulking. The patient underwent concurrent chemoradiation after operation, and the disease relapsed 6 months after treatment. Atezolizumab in combination with carboplatin and etoposide were prescribed and an objective response was achieved. As of this writing, the patient is still alive, with a good performance status. Herein, we provide information about the treatment of primary tracheal small cell carcinoma, including protective tracheostomy, surgical debulking, chemotherapy, immunotherapy, and consolidative radiotherapy. ***(Thorac Med 2021; 36: 198-202)***

Key words: small cell carcinoma, tracheal tumor, trachea

Introduction

Tumors that originate in the trachea are rare, and the majority are malignant [1]. Since the clinical symptoms, such as cough, dyspnea and wheezing, can mimic those of airway diseases, diagnosis is often delayed. According to an epidemiological study that analyzed data from the Surveillance, Epidemiology, and End Results program (SEER) database, squamous cell carcinoma (45%) and adenoid cystic carcinoma (16.3%) comprised the majority of

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primary tracheal tumors [2]. Primary small cell carcinoma of the trachea is a rare condition. It remains unclear whether the treatment should be the same as that for small cell lung carcinoma. Herein, we report the case of a 66-year-old man with primary tracheal small cell carcinoma and discuss the clinical presentations, treatments, and outcome.

Case Description

A 66-year-old man with shortness of breath and cough was initially diagnosed with chronic obstructive pulmonary disease and was treated at a pulmonology clinic. He had a history of cigarette smoking (more than 80 pack-years). After 3 months of treatment, he presented to the emergency department because of progression of symptoms. The patient also described the feeling of choking, a foreign body sensation in the throat, and difficulty expectorating sputum. He had no fever, no hemoptysis, no significant weight loss, and no chest pain.

On presentation to the emergency department, the patient's body temperature was 36.7℃, blood pressure 159/129 mmHg, heart rate 133 beats per minute, respiratory rate 26 breaths per minute, and oxygen saturation 95% while breathing ambient air. Physical examination revealed tachypnea and inspiratory stridor. There was neither acid-base imbalance nor significant hypercapnia or hypoxemia in the arterial blood gas analysis. Other laboratory findings and chest X-ray were unremarkable. The patient's clinical condition did not improve with bronchodilator and systemic steroid therapy.

During hospitalization, bronchoscopy was arranged due to a suspicion of upper airway obstruction. A tracheal mass lesion was noted beneath the subglottis, which occupied around half of the tracheal lumen (Figure 1A). Biopsy was not performed because of respiratory distress and a high risk of worsening the airway obstruction if bleeding occurred. Emergency surgery including protective tracheostomy and surgical debulking of the tracheal tumor was carried out by an otolaryngologist. The pathology report revealed small blue round tumor cells with hyperchromatic nuclei (Figure 1B) and positive immunohistochemical staining for AE1/AE3, thyroid transcription factor-1 (TTF-1) (Figure 1C), and synaptophysin (Figure 1D), which supported the diagnosis of small cell carcinoma. A series of staging studies including computed tomography (CT) of the chest, whole body bone scan, abdominal sonography, and brain magnetic resonance imaging (MRI) were performed, and revealed no evidence of metastasis. Limited stage primary tracheal small cell carcinoma was then diagnosed. The patient's Eastern Cooperative Oncology Group (ECOG) performance status was 1 at that time.

Three weeks after surgery, the patient underwent systemic chemotherapy with cisplatin plus etoposide. Concurrent radiotherapy, which covered the tracheal tumor bed and the mediastinum, was also prescribed. He then received 5 cycles of chemotherapy and radiotherapy with a total dose of 6400 cGy in 32 fractions. After completion of concurrent chemoradiation, CT of the chest showed no evidence of tumor recurrence. The tracheostomy tube was then removed and the patient exhibited normal breathing and vocal function.

An enlarged lymph node in the right neck was noted 6 months later. Ultrasound-guided fine needle aspiration disclosed small cell carcinoma, which suggested disease recurrence. Positron emission tomography (PET)/CT scan showed increased 18F-FDG uptake at the right

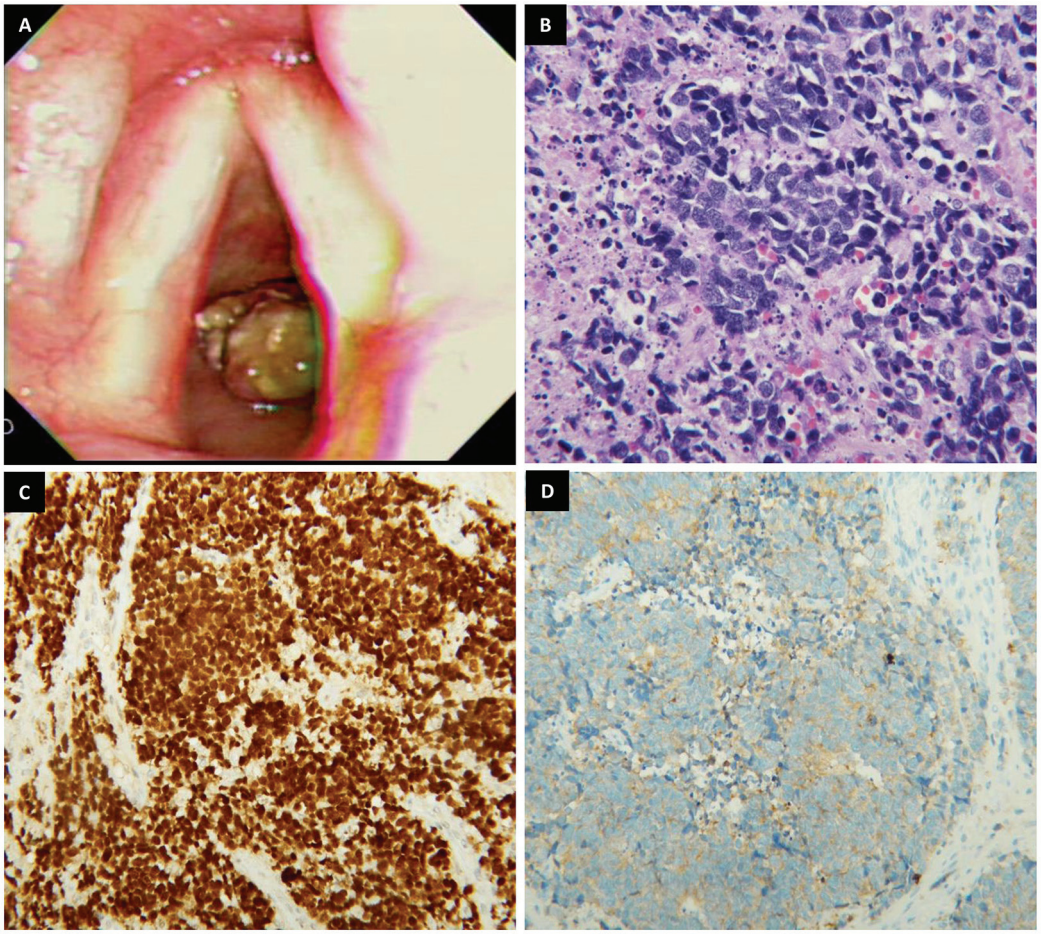

Fig. 1. (A) Bronchoscopy showed a tumor mass in the trachea. (B) Pathology revealed small blue round tumor cells with hyperchromatic nuclei (hematoxylin and eosin stain). Immunohistochemical stain was positive for both thyroid transcription factor-1 (TTF-1) (C) and synaptophysin (D)

neck (SUVmax 9.8) (Figure 2A); otherwise, no significant metastatic lesion was found. Brain MRI was also unremarkable. Under the diagnosis of recurrent small cell carcinoma with right neck lymph node metastasis, the patient received atezolizumab plus carboplatin and etoposide. Follow-up CT of the neck after 3 cycles of treatment revealed a partial response (Figure 2B). The patient then received 6 cycles of atezolizumab plus chemotherapy. Consolidative radiotherapy with a total dose of 6600 cGy in 33 fractions was also prescribed. The patient was then kept on atezolizumab therapy. At the time of this writing, he is still alive with a good performance status. To date, he has received 10 cycles of atezolizumab maintenance. The progression-free survival (PFS) with atezolizumab plus chemotherapy is 14.0 months, and the survival time calculated from the diagnosis of primary tracheal small cell carcinoma is 24.7 months.

Discussion

Primary tracheal malignant tumor is uncommon, accounting for just 0.1% to 0.4% of

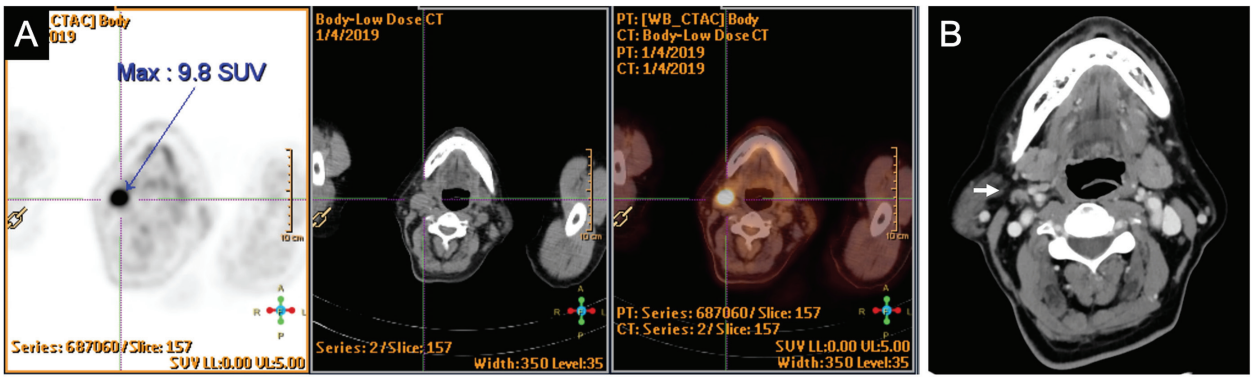

Fig. 2. (A) PET/CT scan revealed increased 18F-FDG uptake at the right neck. (B) CT of the neck after treatment revealed shrinkage of the right neck lymphadenopathy (arrow)

all newly diagnosed cancers [2]. Because of the rarity of these tumors, clinical suspicion is low, resulting in a delayed diagnosis. Moreover, it is difficult to investigate the treatment and outcome of these patients. Among all types of tracheal tumors, squamous cell carcinoma and adenoid cystic carcinoma are the most common histological types. An analysis of the SEER database by Urdaneta et al. revealed that neuroendocrine tumors comprised 9.7% of primary tracheal carcinomas [2]. However, this category included carcinoid, atypical carcinoid, and other neuroendocrine carcinomas. We suggest that the incidence of primary small cell carcinoma of the trachea may be much lower.

Regarding the treatment of tracheal tumors, there are no prospective controlled trials to suggest a consensus. Surgery remains the most effective treatment whenever the lesion is resectable [1, 3]. Available data suggest that postoperative chemoradiation may improve the survival of patients at higher risk of recurrence, particularly those with surgical margin involvement. Other risk factors suggesting adjuvant therapy include advanced tumor stage (T3, T4), extracapsular extension, perineural invasion, and lymphovascular invasion [1]. For patients with unresectable tumors or with contraindications for surgery, endoscopic laser therapy, stent implantation, and palliative radiotherapy could be considered for management of the airway obstruction symptoms. The prognosis of tracheal tumors depends on the resectability and the histological types [1]. Previous studies suggested that patients with adenoid cystic carcinoma have a higher 5-year survival rate than those with squamous cell carcinoma [1, 3]. To date, no clinical trials have defined the optimal regimens for patients with unresectable or metastatic tracheal tumors of different histological types. Further research is still needed.

Chemotherapy with platinum plus etoposide is the main treatment for small cell carcinoma of the lung, and around 50% of patients can achieve an objective response to the regimen [4]. Among patients with extensive disease, the expected PFS and overall survival are 5 and 10 months, respectively [5]. It is difficult to evaluate the response to systemic chemotherapy among patients with primary tracheal carcinoma because the measurement of the intra-airway lesion may not be accurate, and most of these patients will undergo local tumor treatment simultaneously. There are currently few

case reports of primary small cell carcinoma of the trachea in the literature and most of these primarily discuss the role of radiotherapy [6]. The efficacy of chemotherapy is seldom mentioned. In the present case, the PFS of first-line concurrent chemoradiation was 9.7 months.

Small cell carcinoma of the lung carries a high recurrence rate. If the disease relapses more than 6 months after first-line chemotherapy, treatment with the original regimen is recommended by the current guidelines [4]. The IMpower133 study recently found that atezolizumab in combination with chemotherapy can result in significantly longer PFS and overall survival than traditional platinum doublet chemotherapy among patients with treatment-naïve extensive stage small cell lung carcinoma [5]. Whether the regimen can work in patients with relapsed disease remains unclear. Our patient underwent atezolizumab plus carboplatin and etoposide treatment after disease recurrence. He achieved a partial response and experienced a long survival time. Further studies are needed to clarify the role of combined immunotherapy and chemotherapy in patients with relapsed small cell carcinoma.

Airway obstruction, which may lead to life-threatening hypoxemia, is a major complication of primary tracheal tumors. It can result from tumor growth and may be aggravated by tumor bleeding. Qiu et al. reported a patient that died of massive hemoptysis [6]. In the treatment of patients with tracheal tumors, clinicians should be especially mindful of the importance of airway protection. Since the tumor in our patient was located near the subglottis, there was an opportunity to perform a protective tracheostomy before tumor debulking, which lowered the risk of airway compromise. After treatment, the tracheostomy tube was removed successfully and the patient's vocal function was preserved.

Although chemotherapy remains the mainstay of treatment for extensive stage small cell lung carcinoma, consolidative thoracic radiotherapy is beneficial for selected patients with a good response to chemotherapy [4].

Since our patient experienced disease recurrence and neck lymph node metastasis after initial concurrent chemoradiation, the tumor stage was upgraded from limited to extensive disease. His outcome seems to be better than that typically seen in extensive stage small cell lung carcinoma. This may be explained, at least in part, by his low tumor burden, which allowed us to prescribe consolidative radiotherapy. Further research on the epidemiology and treatment of primary small cell carcinoma of the trachea is still needed.

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Diaphragmatic Repair with Talc Pleurodesis for Refractory Hepatic Hydrothorax Before Liver Transplantation

Hsiu-Ping Chou[1], Pei-Yi Chu[1], Hung Chang[1], Tsai-Wang Huang[1]

Hepatic hydrothorax is pleural effusion that has accumulated in cirrhosis patients, without concomitant cardiopulmonary disease. The estimated prevalence of hepatic hydrothorax is 10-15%, and the incidence is 5-11%. It is a rare complication of cirrhosis. Some patients with hepatic hydrothorax can be asymptomatic. However, hepatic hydrothorax can lead to respiratory conditions, such as cough, shortness of breath, hypoxemia or respiratory failure, in some patients. We present the case of a hepatic hydrothorax patient with respiratory syndrome who was not successfully treated with medication. There are many therapeutic strategies for the treatment of hepatic hydrothorax. However, there is a high rate of recurrence of post-treatment pleural effusion. In addition, complications frequently occur with each treatment. In our case, we successfully diagnosed the reason for the hydrothorax and treated the patient with talc-pleurodesis and diaphragm repair under video-assisted thoracoscopy. No recurrence was noted in the following outpatient department visits. ***(Thorac Med 2021; 36: 203-206)***

Key words: hepatic hydrothorax; talc; diaphragm repair

Introduction

Hepatic hydrothorax is pleural effusion that has accumulated in cirrhosis patients, without concomitant cardiopulmonary disease. The estimated prevalence of hepatic hydrothorax is about 5-15% [1-2], and the incidence is 5-11% [2-3]. It is a rare complication of cirrhosis. Some patients with hepatic hydrothorax are asymptomatic, but other patients may develop respiratory conditions, such as cough, shortness of breath, hypoxemia or respiratory failure [4]. Moreover, sepsis may derive from a spontaneous bacterial infection, and may bring about the patient's death. The origin of hepatic hydrothorax is still debated. The most acceptable explanation is that massive ascites pass through a defect in the diaphragm and remain in the pleural space due to intra-abdominal pressure. There are several ways to treat symptomatic hepatic hydrothorax, from medication to surgery. Here, we describe a case of dyspnea that was

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diagnosed as hepatic hydrothorax.

Case Report

A 61-year-old male, a hepatitis B carrier, had a history of hepatic tumor status post-radiofrequency ablation in 2014. He had liver cirrhosis with ascites and had been treated for 5 years. This time, he was admitted to the ward for a recurrent tumor in the liver. During hospitalization, deteriorating dyspnea was found. The physical examination showed that he had a respiratory rate of 26/min, with decreased breathing sounds at the right lower lung region. No specific finding was revealed via the hemogram. The chest X-ray film confirmed the right hydrothorax (Figure 1). The contrast-enhanced computed tomography scan of the chest disclosed cirrhosis with massive ascites. In addition, a defect in the right hemidiaphragm was found that had formed an abdominal-pleural fistula (Figure 2).

The patient was treated with diuretics and fluid restriction. Pleural drainage via a pigtail catheter was also performed. The dyspnea improved somewhat, but the daily amount of pleural drainage showed no decrease. Hence, he underwent video-assisted thoracoscopic surgery with diaphragmatic repair using an absorbable suture reinforcement felt and chemical pleurodesis with talc. The postoperative course went well. There was no recurrence of the hydrothorax during the subsequent 1 month (Figure 3).

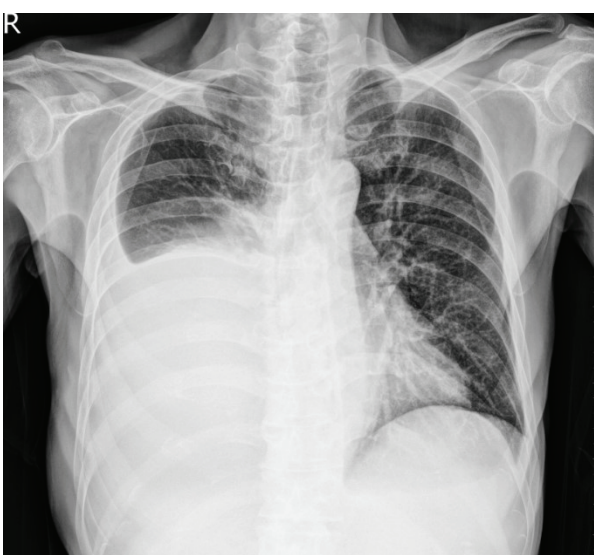

Fig. 1. Chest X-ray with a posteroanterior view. An elevated diaphragm with pleural effusion was found at the right thoracic cage.

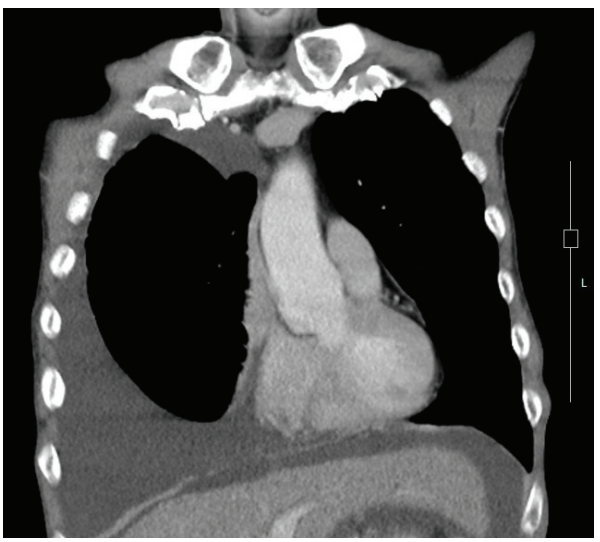

Fig. 2. Cirrhosis with massive ascites was revealed via a contrast-enhanced computed tomography scan of the chest. An abdominal-pleural fistula with a defect at the right hemidiaphragm was seen.

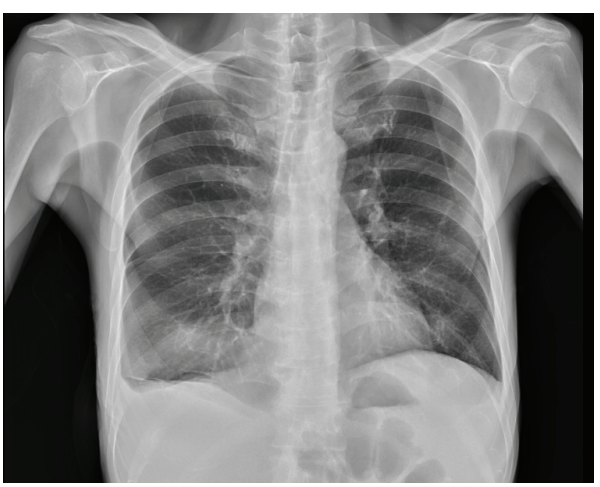

Fig. 3. Postoperative chest film with a posteroanterior view. There was no recurrence of the hydrothorax, and no elevated right diaphragm.

Discussion

The estimated prevalence of hepatic hydrothorax is about 5-15%, and the incidence is 5-11% (1-3). It is an erratic complication in cirrhosis patients who have no other reason for pleural effusion accumulation, such as cardiogenic and pulmonary problems, or pleural disease. Right-sided pleural effusion is the most common [5], and it can be asymptomatic. However, when there is fluid accumulation of more than 500 mL, respiratory conditions, such as cough, shortness of breath, and respiratory failure can occur.

Massive and unilateral pleural effusion may occur when there is a defect at the diaphragm allowing communication between the pleural and abdominal space. There is no obvious reason for this defect formation, and there is still debate as to whether it is of congenital or traumatic origin. The most acceptable explanation is that the small defect is of congenital origin and that it was dilated by the tension between the ascites and the negative pressure of the pleural cavities [6].

Image study and thoracentesis with fluid testing are the basis of diagnosis [4]. A frontal chest radiograph can show pleural effusion and a lateral view helps to reveal small effusions. Advanced imaging, like a computed tomography scan, can help to evaluate the anatomical problem. Fluid analysis will show: (a) A cell count less than 500 cells/mm3, PMN <250 cells/mm3 and a negative culture. (b) A total protein concentration <2.5 g/dL or a total protein ratio of pleural fluid-to-serum <0.5. (c) A lactate dehydrogenase pleural fluid-to-serum ratio <0.6. (d) A serum-to-pleural fluid albumin gradient >1.1 g/dL. (e) An amylase concentration: serum >pleural fluid. (f) A pH value: 7.4-7.55. (g) A pleural glucose level similar to the serum level. Meanwhile, alternative causes of the effusion, such as cardiogenic pleural effusion or parapneumonic pleural effusion, should be ruled out.

The definite treatment for hepatic hydrothorax is liver transplantation [4]. An untreated hepatic hydrothorax can develop into empyema or further lethal disease [7]. However, the availability of liver for transplantation is limited: liver recipient candidates must wait a long time. Before transplantation, the essential treatment for symptomatic patients is medication, diuretics and fluid restriction, all of which decrease ascites production. The success rate of these patients is around 84% [8]. Others in this group may fail to recover from the massive hepatic pleural effusion. Thus, refractory hepatic hydrothorax appears after the medications fail. To treat refractory hepatic hydrothorax, adequate drainage through therapeutic thoracentesis, pleural drainage catheter, and transjugular intrahepatic portosystemic shunt are alternate choices. Frequent thoracentesis is needed due to the massive creation of pleural effusion that brings inconvenience to the patients [9]. As for pleural drainage catheter indwelling, many complications may occur, including infection, and sepsis, which might be fatal for the patient. One study reported that the infection rate with a pleural drainage catheter was about 16% [10]. Continuous body fluid loss can lead to malnutrition [11]. Another advanced alternative is adequate chest drainage, followed by diaphragmatic repair using absorbable suture reinforcement felt and chemical pleurodesis with talc, especially in patients with an obvious diaphragm defect.

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