Research article

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The value of Gene Xpert MTB/RIF of bronchial lavage fluid in diagnosis of sputum AFB negative pulmonary tuberculosis

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Abstract

Objective: To describe the characteristics of pulmonary tuberculosis patients with acid-fast bacilli (AFB) negative sputum and determine the value of Gene Xpert MTB/RIF of bronchial lavage fluid in diagnosis of sputum AFB-negative pulmonary tuberculosis.

Method: This cross-sectional study was conducted on 120 patients who were admitted to the Respiratory Department of Thong Nhat Hospital from July 2022 to August 2023 suspected of pulmonary tuberculosis with AFB-negative sputum.

Results: There were 67.9% male and 32.1% female. Mean age was 57.8 ± 20.1 years and the body mass index was 21.4 ± 1.8 kg/m^2. Common comorbidities included hypertension (41.1%), type 2 diabetes (30.4%), and chronic lung disease (5.4%). There were 48.2% of patients who had injuries in more than 1 location on X-ray. Characteristics of X-ray injuries were in right lung (46.4%), left lung (28.6%), upper lobe (51.8%), lower lobe (17.8%). Infiltrative injury on X-ray accounted for 64.3%, followed by consolidation (21.4%) pleural effusion (10.7%), cavity (8.9%), and nodular (5.4%). Gene Xpert MTB/RIF of bronchial lavage fluid had tuberculosis bacteria in 40.8% of cases. The positive rate of Mycobacteria growth indicator tube culture (MGIT) of bronchial lavage fluid was 46.7%. The sensitivity of Gene Xpert MTB/RIF compared to MGIT was 85.7% and the specificity was 98.4%. The positive predictive value was 97.9% and the negative predictive value was 88.7%. Rifampicin resistance rate was 4.1%.

Conclusion: Pulmonary tuberculosis patients with AFB-negative sputum have diverse clinical and radiological characteristics. Gene Xpert MTB/RIF of bronchial lavage fluid had high sensitivity and specificity in diagnosis of AFB-negative pulmonary tuberculosis. Rifampicin resistance rate was at a low rate.

Keywords: Pulmonary tuberculosis, negative-AFB tuberculosis, Gene Xpert MTB/RIF.

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1. INTRODUCTION

Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis. Tuberculosis can be found in all parts of the body, of which pulmonary tuberculosis is the most common form (accounting for 80 - 85% of total cases) and is the main source of infection to surrounding people through droplets from the air. There were 10 million people with tuberculosis worldwide in 2018 with 130 new cases per 100,000 people. In 2018, there were about 0.5 million new cases of rifampicin resistance [1-3]. In 2021, the World Health Organization (WHO) estimated that about 10.6 million people will be infected with tuberculosis, an increase of 4.5% compared to 2020 [1,4]. Every year, Vietnam has approximately 170,000 new cases of tuberculosis, of which pulmonary tuberculosis accounts for 81%. Besides, 23% of cases are pulmonary tuberculosis in which no tuberculosis bacteria

are found in sputum by direct examination, also known as acid-fast bacilli (AFB) negative pulmonary tuberculosis [1-4].

Flexible bronchoscopy is a minimally invasive procedure that is very useful in obtaining bronchial lavage fluid, especially for patients with no sputum or poor sputum production [5,6]. The Gene Xpert MTB/RIF testing system has been available since 2009 and has been recommended by WHO for use in the initial diagnosis of suspected pulmonary tuberculosis in adults. In 2019, the National Tuberculosis Program began using the Gene Xpert MTB/RIF test for all cases of lung injury suspected of tuberculosis [6,7]. To increase the accuracy in diagnosing pulmonary tuberculosis with AFB-negative sputum, we conducted this study with the following goals: (1) Describe the characteristics of pulmonary tuberculosis patients with AFB-negative sputum and (2) Determine the value of Gene Xpert MTB/RIF test in diagnosis of AFB-negative pulmonary tuberculosis at Thong Nhat hospital.

2. METHODS

2.1. Study design and participants

A cross-sectional study was conducted at Department of Respiratory in Thong Nhat Hospital, which is one of the most advanced hospitals in Ho Chi Minh City. There were 120 participants enrolled in the study from July 2022 to August 2023.

Participant's selection criteria included (1) adult patients (≥ 18 years old) with clinical symptoms and/or injuries suggestive of tuberculosis on X-ray and (2) ≥ 2 AFB-negative sputum samples taken on the first day of admission (AFB sputum test was performed at the Microbiology Department of Thong Nhat Hospital.

Exclusion criteria was (1) severe patients, or (2) not agreeing to participate in the study, or (3) not providing qualified sputum samples

2.2. Procedures

- Participants were collected personal information, paying special attention to medical history (age, gender, smoking, alcohol, tuberculosis, and comorbidities), and a full clinical examination was performed.

- Chest X-ray, complete blood count, liver and kidney function, prothrombin time, and activated partial thromboplastin time test were done.

- Flexible bronchoscopy was performed to collect bronchial lavage fluid samples to perform Mycobacteria growth indicator tube culture (MGIT) and Gene Xpert MTB/RIF. Absolute contraindications of flexible bronchoscopy include acute respiratory failure (unless intubated and mechanically ventilated), severe tracheal obstruction, inability to provide enough oxygen to the patient during the procedure, and the arrhythmia cannot be treated or is life-threatening. Relative contraindications: recent myocardial infarction, uncooperative patient, uncorrected coagulation disorders.

- Gene Xpert was performed on a Gene Xpert Cepheid machine (USA) with Xpert MTB/RIF cartridge model GX IV-R2. Fast results after 2 hours, determine whether the specimen has tuberculosis bacteria and is resistant to rifampicin or not.

2.3. Statistical analysis

Data was processed with SPSS 20.0 for Windows software. Continuous variables were presented as mean ± standard deviation (SD) for normally distributed data. Categorical variables were presented as frequencies (%). Chi-square or Fisher's exact test was used to compare proportions, T-test for continuous variables with normal distribution. Statistical significance was accepted at p-value < 0.05.

2.4. Ethics issues

Patients were informed and agreed to the study. Information was guaranteed to be secure and private. The study contributed to the diagnosis of AFB-negative sputum pulmonary tuberculosis and rifampicin-resistant pulmonary tuberculosis more quickly and accurately, thereby helping to provide timely and correct treatment. The study did not delay or change patient diagnosis or treatment with the approval of the Board of Directors and the Scientific Research Council of Thong Nhat Hospital.

3. RESULTS

During the study period, there were 120 patients with suspected pulmonary tuberculosis but had AFB-negative sputum. Only 56 patients had MGIT of bronchoalveolar lavage detecting tuberculosis with a mean age was 57.8 ± 20.1 and the body mass index (BMI) was 21.4 ± 1.8 kg/m^2 (Table 1).

Table 1. Characteristics of participants with AFB-negative sputum but MGIT-positive bronchoalveolar lavage fluid

Characteristics	Frequency (n = 56)	Percentage
Sex		
Male	38	67.9
Female	18	32.1
Symptoms and signs		
Sputum cough	47	83.9
Fever	30	53.6
Weight loss	22	39.3
Shortness of breath	13	23.2
Chest pain	10	17.9
Crackles	25	44.6
Comorbidities		
Hypertension	23	41.1
Type 2 diabetes	17	30.4
Chronic lung disease	3	5.4
Smoking	9	16.1

There were 67.9% of males and 32.1% of females (male/female ratio was 2.1). Common clinical symptoms included cough with sputum (83.9%), followed by fever (53.6%), crackles (44.6%), weight loss (39.3%), shortness of breath (23.2%), and chest pain (17.9%). Frequent comorbidities were hypertension (41.1%), type 2 diabetes (30.4%), and chronic lung disease (5.4%). The smoking rate accounted for 16.1% of participants (Table 1).

Table 2. Chest X-ray characteristics of participants with AFB-negative sputum but MGIT-positive bronchoalveolar lavage fluid

Characteristics	Frequency (n = 56)	Percentage
Location		
> 1 location	27	48.2
Right lung	26	46.4
Left lung	16	28.6
Upper lobe	29	51.8
Lower lobe	10	17.8
Kind of injury		
Infiltration	36	64.3
Solidification	12	21.4
Pleural effusion	6	10.7
Cavity	5	8.9
Nodular	3	5.4

There were 48.2% of patients who had injuries in more than one location. The right lung injury rate was more common than the left side (46.4% vs. 28.6%) and the upper lobe injury rate was more than the lower side (51.8% vs. 17.8%). Characteristics of injuries on X-ray included infiltration (64.3%), solidification (21.4%), pleural effusion (10.7%), cavity (8.9%), and nodular (5.4%) (Table 2).

Table 3. Gene Xpert MTB/RIF compared with MGIT results of bronchial lavage fluid

	MGIT positive	MGIT negative	Total
Gene Xpert MTB/RIF positive	48 (40.0)	1 (0.8)	49 (40.8)
Gene Xpert MTB/RIF negative	8 (6.7)	63 (52.5)	71 (59.2)
Total	56 (46.7)	64 (53.3)	120 (100)

Data are shown as frequency (percentages). MGIT Mycobacteria growth indicator tube culture.

Gene Xpert MTB/RIF of bronchial lavage fluid had tuberculosis bacteria in 40.8% while MGIT-positive rate was 46.7%. The sensitivity of Gene Xpert MTB/RIF compared to MGIT was 85.7%, and the specificity was 98.4%. The positive predictive value was 97.9% and the negative predictive value was 88.7% (Table 3).

Table 4. Rifampicin resistance results in Gene Xpert MTB/RIF

Characteristics	Frequency (n = 49)	Percentage
Resistance to rifampicin	2	4.1
Not resistant to rifampicin	39	79.6
Unidentified resistance	8	16.3
Total	49	100

Among 49 patients with Gene Xpert MTB/RIF results to detect tuberculosis, the rate of resistance to rifampicin was only 4.1% (Table 4).

4. DISCUSSION

The study recruited 120 patients with suspected pulmonary tuberculosis but had AFB-negative sputum results. There were 56 patients with MGIT-positive of bronchoalveolar lavage samples whose mean age was 57.8 ± 20.1 and BMI was 21.4 ± 1.8 kg/m2 (Table 1). According to data from the Vietnam Tuberculosis Control Program in 2015, the rate of tuberculosis in men accounted for 65% of the total number of patients. Some types of tuberculosis such as AFB-positive pulmonary tuberculosis had a male/female ratio of 3/1. This result was equivalent to the results of some other studies [4,10,11,14]. Common comorbidities included hypertension (41.1%), followed by type 2 diabetes (30.4%), and chronic lung disease (5.4%). History of smoking accounted for 16.1%, similar to the results of two previous studies [11,12].

Common clinical symptoms included cough with sputum (83.9%), followed by fever (53.6%), crackles (44.6%), weight loss (39.3%), shortness of breath (23.2%), and chest pain (17.9%). In research by Le Hoan et al., the rate of sputum cough was 81.7%, chest pain (21.5%), shortness of breath (20.5%), fever (11%), and weight loss (6.6%) [10]. Cuong et al. studies showed that the sputum cough rate was 76.4%, dry cough (23.6%), and hemoptysis (17.1%) [9,12]. Besides, Phuong et al. demonstrated that sputum cough rate was 72.3%, hemoptysis (31.9%), chest tightness (44.7%), shortness of breath (48.9%), fatigue (70.2%), and fever (38.3%) [13]. A study by Hang et al. represented that the cough rate was 79.3% and mainly cough lasting more than 2 weeks, fever (42.8%), crackles (38.1%), and hemoptysis (22.3%) [14].

In this study, 48.2% of patients had injuries in more than one location on chest X-ray and 64.3% of patients had infiltration (Table 2). Some previous research results showed that 25.9% of participants had bilateral diffuse injuries, multiple lobes on one side (11.9%), upper lobe (60.7%), middle lobe (34.8%), and lower lobe (19.4%) [9,12]. Characteristics of injuries on X-ray included infiltration (64.3%), solidification (21.4%), pleural effusion (10.7%), cavity (8.9%), and nodular (5.4%) (Table 2). Meanwhile, research by Cuong et al. demonstrated that nodular accounted for 82.9%, followed by infiltration (68.3%), cavities (26.8%), and fibrosis (37.8%) [9]. The results of another study showed that 74.7% of the injuries were infiltration, followed by mediastinal lymph node (51.6%), solidification (22.9%), cavity (7.6%), and pleural effusion (6.3%) [10]. Results of Hang et al. showed that the most common injury is infiltration, accounting for 63.5% [14]. The new appearing cavity in patients with suspected AFB-negative tuberculosis accounted for 30.2% [15].

The positive rate of Gene Xpert MTB/RIF test in bronchial lavage fluid of this study was 40.8%, in line with Phuong et al. (36.2%), and Hang et al. (47.6%) [13, 14]. Therefore, bronchoscopy is a useful procedure to obtain bronchial lavage fluid for Gene Xpert MTB/RIF testing to achieve a higher value in diagnosing difficult-to-diagnose cases of pulmonary tuberculosis [13].

In this study, the sensitivity of Gene Xpert MTB/RIF compared to MGIT was 85.7%,

and the specificity was 98.4%. The positive predictive value was 97.9% and the negative predictive value was 88.7%. (Table 3). According to Lee et al., the sensitivity and specificity of Gene Xpert MTB/RIF in bronchial lavage fluid were 81.6% and 100% compared to culture in diagnosing tuberculosis [16]. Le Palud's study showed that bronchoscopy to obtain bronchial lavage fluid or biopsy in patients with suspected tuberculosis showed that Gene Xpert MTB/RIF and culture had nearly equivalent sensitivity (60% versus 66.7%) [17]. According to Phuong et al., the positive rate of Gene Xpert MTB/RIF test in bronchoalveolar lavage fluid was 24.5%. In cases of MGIT-positive pulmonary tuberculosis patients, Gene Xpert MTB/RIF has a sensitivity and specificity up to 92.1% and 85.1%, respectively [6]. Meanwhile, Ha et al. showed that the MGIT test had a sensitivity of 64.3% (45.7-88.0%), a specificity of 82.4% (55.8-100.0%), positive predictive value of 85.7% (61-100.0%), and negative predictive value of 58.3% (39.5-83.1%) when compared to the Gene Xpert MTB/RIF [8]. Results of other studies when performing Gene Xpert MTB/RIF in sputum showed that 7.6% detected tuberculosis bacteria [10], and the sensitivity and specificity of Xpert MTB/RIF were 83.3%, and 95.7%, respectively [9]. Besides, Binh et al. showed that the sensitivity of Gene Xpert MTB/RIF sputum in diagnosing new pulmonary tuberculosis with negative AFB was 72.3% [14]. Therefore, Gene Xpert MTB/RIF bronchial lavage fluid has a high value in diagnosing pulmonary tuberculosis due to its high sensitivity and specificity [6].

Among 49 patients with Gene Xpert MTB/RIF results of bronchial lavage fluid detecting tuberculosis bacteria, the rifampicin resistance rate was 4.1%, unknown resistance was 16.3%, and non-resistant accounted for the majority of 79.6% (Table 4). Different from the research results of author Hang et el., Gene Xpert MTB/RIF bronchial lavage fluid did not record resistance to rifampicin [14]. However, the rate of rifampicin resistance when performing Gene Xpert MTB/RIF in other studies was from 3.2% to 4.3%, in line with this study [9,11].

4. CONCLUSIONS

Pulmonary tuberculosis patients with AFB-negative sputum have diverse clinical and radiological characteristics. Gene Xpert MTB/RIF of bronchial lavage fluid had high sensitivity and specificity in diagnosis of AFB-negative pulmonary tuberculosis. Rifampicin resistance rate was at a low rate.

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