Profile of Patients With Tuberculous Pleural Effusion in Qatar: A Retrospective Study

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Abstract

Introduction

Tuberculosis (TB) remains one of the top 10 causes of death globally. Around 1.7 billion people are infected with mycobacterium TB worldwide, and almost 90% of cases each year are found in 30 high TB burden countries. Due to the influx of a large expatriate population mainly from the high TB burden countries, there is an increased number of pulmonary TB as well as tuberculous pleural effusion cases reported in Qatar.

Objectives

The demographic, clinical, laboratory, and histopathological parameters of patients with tuberculous pleural effusion were assessed.

Methods

A single-center study was conducted at Hamad General Hospital, Hamad Medical Corporation, Doha, Qatar. Adults diagnosed to have tuberculous pleural effusion were included, and those with clinical suspicion of tuberculous pleural effusion with positive sputum acid-fast bacillus (AFB) but negative AFB in pleural samples were excluded.

Results

A total of 106 patients were reviewed, of whom 100 were included for the final analysis, with 86% being men. Majority were from the Asian subcontinent, and the mean age was 33.8 years (SD ± 10.3). Main symptoms in decreasing order were cough (77%), fever (56%), and chest pain (54%). Of the patients, 72% had normal BMI, and rest were above the normal range. Anemia and hypoalbuminemia were found in 36.7% and 89.8% of the patients, respectively. Positive AFB culture was observed in pleural biopsy (79%), pleural fluid (13%), and sputum (16%). Positive AFB by polymerase chain reaction (PCR) was observed in pleural biopsy (57%), pleural fluid (3%), and sputum (2.2%), whereas AFB smear was positive in 2% of pleural biopsy samples. Caseating granuloma was seen in 80% of patients. All the three Light's criteria were met by 30% of the patients whereas 52% had two criteria fulfilled. No association between the number of Light's criteria and AFB yield was observed.

Conclusions

TPE was more common in healthy young adults. The AFB yield on pleural biopsy, PCR, and culture was significantly higher than that on all other samples. The number of positive Light's criteria did not have any association with positive AFB yield.

Categories: Internal Medicine, Infectious Disease
Keywords: tuberculosis, pleural effusion, bmi, lights criteria, tuberculous pleural effusion, acid-fast bacillus

Introduction

Tuberculosis (TB) remains one of the top 10 causes of death globally. According to the World Health Organization (WHO) 2019 report, around 1.7 billion people are infected with mycobacterium TB (MTB) globally, and almost 90% of cases each year are found in 30 high TB burden countries. The case rates vary from country to country, ranging from less than 50/million population/year to more than 5000/million population/year [1]. In 2018, there were 1.2 million deaths due to TB in human immunodeficiency virus (HIV) negative people. According to the WHO 2019 report, most cases are found in Southeast Asia (44%), Africa (24%), and the Western Pacific region (18%). Eight countries accounted for two-thirds of total global cases of TB, that is, India (27%), China (9%), Indonesia (8%), Philippines (6%), Pakistan (6%), Nigeria (4%), Bangladesh (4%), and South Africa (3%) [2].
Extrapulmonary TB is not an uncommon entity, especially in areas where TB is endemic. Tuberculous pleural effusion (TPE) is one of the most common extrapulmonary TB after TB lymph node. One study carried out in the eastern part of Kingdom of Saudi Arabia reported that 37% of pleural effusion were due to TB [3], whereas a study conducted in Qatar on 200 pleural effusion patients found that the most common cause of effusion was TB (32.5%), and majority of them were from the Asian subcontinent [4]. The incidence of pleural involvement varies from 3-5% in TB non-endemic areas to 30% in TB endemic areas [5,6].

The accumulation of fluid in TPE is multifactorial. The MTB antigen enters the pleural space following a rupture of subpleural caseous focus, which causes inflammatory response and results in increased capillary permeability. This also obstructs the lymphatic outflow, resulting in decreased clearance of pleural fluid [7-9]. TPE most commonly presents with fever (85%), cough (70%), and pleuritic chest pain (75%). Dyspnea (50%), night sweats (50%), and weight loss (25%) can also be there. TPE is commonly unilateral and the size of the effusion varies from patient to patient [10].

Even though Qatar is not listed in the high TB burden countries, a high number of pulmonary TB as well as TPE cases are reported due to the influx of a large expatriate population mainly from the high TB burden countries. In this single-center study, we sought to know the epidemiological, clinical, and biochemical profile of patients who were diagnosed with TPE.

Materials And Methods

Study design and setting
A retrospective observational study was carried out at the Hamad General Hospital, Hamad Medical Corporation, Doha, Qatar.

Study population
Patients older than 18 years of age who were admitted to the medical ward and diagnosed to have TPE between the period of January 2016 to December 2019 were included. The diagnosis of TPE was based on any of the following criteria: (1) positive acid-fast bacillus (AFB) by polymerase chain reaction (PCR)/smear or culture in the pleural fluid, (2) positive AFB by PCR/smear or culture in the pleural biopsy samples, and (3) caseating granuloma seen in pleural biopsy samples. Patients with clinical suspicion of TPE with positive sputum AFB but negative AFB in pleural samples were excluded.

Study procedures
Patient data were retrieved from the clinical information system using the health care number of study population. This included demographic features, body mass index (BMI), comorbid conditions, clinical symptom and signs, radiological data (chest X-ray, CT scan of the chest), blood investigations, pleural fluid analysis, and thoracoscopy/histopathology findings.

Ethical consideration
The study protocol was approved by the Ethics Committee of Medical Research Center of the institution.

Statistical analysis
Descriptive statistics were used to summarize and determine the sample characteristics and distribution of various considered parameters related to demographic and clinical features, biochemical parameters, and histopathological characteristics. The normally distributed data and results are reported with mean and standard deviation (SD). Categorical data are summarized using frequencies and percentages. Associations between two or more qualitative variables were examined and assessed using Pearson's chi-square test and Fisher's exact test as appropriate. Unpaired t-test and analysis of variance (ANOVA) were used to compare mean values of different quantitative parameters (such as age, BMI, white blood cell count, C-reactive protein (CRP), and other biochemical parameters) between two or more groups (such as AFB, histopathology, and treatment details). All statistical analyses were performed using statistical packages SPSS Version 24.0 (IBM Corp., Armonk, NY, USA) and Epi Info 2000 (Centers for Disease Control and Prevention, Atlanta, GA, USA).

Results

Basic demography
A total of 106 files were reviewed for inclusion, of which 100 patients fulfilled the criteria for analysis after exclusion (Incomplete data: 3; non-TB effusion: 3). Majority (86%) of the patients were men, and the mean age was 33.85 years (range: 18-84 years; SD: 10.26). Of the study patients, 60% were from the Asian subcontinent. Cough (77%), fever (56%), and chest pain (54%) were the most common presenting symptoms. Also, 72% had normal BMI (18.6-25). None of the patients was underweight (i.e., with BMI less than 18.5). The basic demographics and clinical features are summarized in Table 1.
| Characteristics                  | Number (%), n = 100 |
|----------------------------------|---------------------|
| **Gender**                       |                     |
| Male                             | 86 (86)             |
| Female                           | 14 (14)             |
| **Age (mean ± SD), years**       |                     |
| Mean age                         | 33.85 ± 10.26       |
| <30                              | 45 (45)             |
| 30-50                            | 50 (50)             |
| >50                              | 5 (5)               |
| **Length of stay (days ± SD)**   |                     |
| Mean length of stay              | 8.34 (±3.54)        |
| **Nationality**                  |                     |
| Qatar                            | 1 (1)               |
| Africa                           | 25 (25)             |
| India                            | 19 (19)             |
| Nepal                            | 28 (28)             |
| Sri Lanka                        | 2 (2)               |
| Bangladesh                       | 9 (9)               |
| Philippines                      | 13 (13)             |
| Indonesia                        | 1 (1)               |
| Pakistan                         | 2 (2)               |
| **Childhood TB**                 |                     |
| Yes                              | 3 (3.57)            |
| No                               | 84 (96.3)           |
| Missing data                     | 13                  |
| **Contact with open TB**         |                     |
| Yes                              | 10 (10.3)           |
| No                               | 87 (89.7)           |
| Missing data                     | 3                   |
| **Comorbidities**                |                     |
| Nil                              | 89                  |
| Diabetes                         | 6 (6)               |
| Hypertension                     | 2 (2)               |
| Asthma/COPD                      | 5 (5)               |
| Kidney Disease                   | 1 (1)               |
| HIV                              | 0                   |
| **Symptoms**                     |                     |
| Fever                            | 56 (56)             |
| Cough                            | 77 (77)             |
| Symptom                      | Count (Percentage) |
|------------------------------|--------------------|
| Weight loss                  | 25 (25)            |
| Night sweats                 | 29 (29)            |
| Chest pain                   | 54 (54)            |
| SOB                          | 34 (34)            |
| Anorexia                     | 15 (15)            |
| Others                       | 17 (17)            |

| Duration of symptoms (days)  | Count (Percentage) |
|------------------------------|--------------------|
| <7                           | 26 (26)            |
| 8 to 15                      | 34 (34)            |
| 16-30                        | 28 (28)            |
| >30                          | 12 (12)            |

| BMI                          | Count (Percentage) |
|------------------------------|--------------------|
| <18.5                        | 0                  |
| 18.6-25                      | 72 (72)            |
| 25.1-30                      | 26 (26)            |
| >30                          | 2 (2)              |

| PPD                          | Count (Percentage) |
|------------------------------|--------------------|
| <5 mm                        | 14 (34.1)          |
| 6-15 mm                      | 9 (22)             |
| >15 mm                       | 18 (43.9)          |
| Missing data                 | 59                 |

| QuantiFERON®                 | Count (Percentage) |
|------------------------------|--------------------|
| Positive                     | 37 (75.5)          |
| Negative                     | 12 (24.5)          |
| Missing data                 | 51                 |

| Other TB manifestation       | Count (Percentage) |
|------------------------------|--------------------|
| Parenchymal involvement      | 10 (10)            |
| Lymph nodes                  | 3 (3)              |
| Pott’s spine                 | 1 (1)              |
| Pericardial                  | 1 (1)              |
| Peritoneal                   | 3 (3)              |
| Disseminated                 | 1 (1)              |

| Drug resistance              | Count (Percentage) |
|------------------------------|--------------------|
| No                           | 95                 |
| INH                          | 3                  |
| Rifampicin                   | 2                  |
| MDR-TB                       | 2                  |
| Yes                          | 98                 |
### TABLE 1: Basic demographic characteristics and clinical profile

TB, tuberculosis; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; SOB, shortness of breath; PPD, purified protein derivative; INH, isoniazid; MDR-TB, multidrug-resistant tuberculosis

#### Laboratory parameters

Around 36.7% of the patients had anemia. In 44.9%, the platelet count was found to be high. Majority of the patients had hypoalbuminemia (89.8%). CRP was elevated in all patients except three, and 53.9% of patients had a CRP of more than 100 (Table 2).

| Variable                          | Number (%) | n = 100 |
|-----------------------------------|------------|---------|
| Hemoglobin                        |            |         |
| Normal                            | 62 (63.3)  |         |
| Anemia                            | 36 (36.7)  |         |
| Missing                           | 2          |         |
| White blood cell count (10^3/μL)  |            |         |
| 4,000-10,000                      | 89 (89.9)  |         |
| <4,000                            | 0          |         |
| >10,000                           | 10 (10.1)  |         |
| Missing data                      | 1          |         |
| Lymphocytes                       |            |         |
| Normal                            | 59 (60.2)  |         |
| Lymphopenia                       | 39 (39.8)  |         |
| Lymphocytosis                     | 0          |         |
| Missing data                      | 2          |         |
| Platelets (10^3/μL)               |            |         |
| 150-400                           | 52 (53.1)  |         |
| >400                              | 44 (44.9)  |         |
| <150                              | 2 (2)      |         |
| Missing data                      | 2          |         |
| C-reactive protein (mg/L)         |            |         |
| 0-5                               | 3 (3.4)    |         |
| 6-100                             | 38 (42.7)  |         |
| 101-200                           | 47 (52.8)  |         |
| >200                              | 1 (1.1)    |         |
| Missing data                      | 11         |         |
| Albumin (gm/L)                    |            |         |
| 35-52                             | 10 (10.2)  |         |
| <35                               | 88 (89.8)  |         |
| Missing data                      | 2          |         |
| CXR effusion                      |            |         |
| Right sided                       | 52 (52)    |         |
Radiological findings

Of the study patients, 52% had right-sided pleural effusion and 46% had left-sided effusion on their chest X-rays. Only two patients had bilateral pleural effusion on their chest X-ray. Parenchymal involvement in chest X-rays

|                      | 46 (46) |
|----------------------|---------|
| Left sided           |         |
| Bilateral            | 2 (2)   |
| CXR: parenchymal involvement |   |
| Yes                  | 10 (10) |
| Pleural fluid: lymphocytes |       |
| >50%                 | 87 (88.8) |
| <50%                 | 11 (11.2) |
| Pleural fluid: lymphocytes |       |
| Missing data         | 2       |
| Light’s criteria     | 97 (97) |
| Protein ratio > 0.5  |         |
| LDH ratio > 0.6      | 52 (52) |
| LDH > two-thirds of serum LDH | |
| Number of Light’s criteria fulfilled | |
| 1                    | 18 (18) |
| 2                    | 52 (52) |
| 3                    | 30 (30) |
| Therapeutic thoracocentesis | 19 (19) |
| Pleural biopsy: histopathology | |
| Caseating/necrotizing granuloma | 80 (80) |
| Noncaseating granuloma | 13 (13) |
| Others               | 7 (7)   |
| Thorascopic findings |         |
| Granuloma            | 11 (11.57) |
| Adhesions            | 42 (44.21) |
| Inflamed pleura      | 77 (81.05) |
| Sago-like nodules/nodules | 52 (4.74) |
| Incomplete data      | 5       |
| Complication of thoracoscopy | |
| Nil                  | 89 (89) |
| Pneumothorax         | 9 (9)   |
| Hydropneumothorax    | 2 (2)   |

**TABLE 2: Laboratory parameters and thoracoscopy findings**

CXR, chest X-ray; LDH, lactate dehydrogenase
X-ray was noted in 10% of the patients (Table 3).

**Pleural fluid analysis**
Overall, 87% of the patients had lymphocyte predominance (>50% lymphocytes) in the pleural fluid, and almost all except three had a pleural fluid/serum protein ratio of more than 0.5. On analyzing patients fulfilling the Light’s criteria, all three criteria were met by 30% of the patients, whereas 52% had two criteria fulfilled. The details of pleural fluid analysis are summarized in Table 2.

**Thoracoscopy and pleural biopsy findings**
All patients underwent thoracoscopy. Inflamed pleura (81%) and nodules (54.7%) were the most common findings observed in thoracoscopy. On histopathological examination of the biopsy sample, necrotizing/caseating granuloma was seen in 80% of the study patients. Eleven patients developed complications after thoracoscopy (pneumothorax in nine and hydropneumothorax in two) (Table 2).

**AFB yield by different specimens and different methods**
The yield of AFB by smear was low in all three samples (sputum: 0; pleural fluid: 0; and pleural biopsy: 2%). Even though the positivity of AFB by PCR technique in sputum and pleural fluid was low (2 and 3, respectively), it was significantly high in biopsy samples (57%). Similarly, AFB culture in biopsy specimen showed significantly higher positivity (79%) than sputum or pleural fluid culture (15% and 15%, respectively) (Table 3).

| Variable       | AFB yield |            |            |            |
|----------------|-----------|------------|------------|------------|
|                | Smear     | Positive   | Negative   | Missing data|
| Sputum         | 0         | 92         | 8          |            |
| PCR            | 2         | 87         | 11         |            |
| Culture        | 15        | 78         | 7          |            |
| Pleural fluid  | Smear     | 0          | 100        |            |
| PCR            | 3         | 97         |            |            |
| Culture        | 13        | 87         |            |            |
| Pleural biopsy | Smear     | 2          | 98         |            |
| PCR            | 57        | 43         |            |            |
| Culture        | 79        | 21         |            |            |

**TABLE 3: AFB yield from various sources**
P, polymerase chain reaction; AFB, acid-fast bacillus

**Sputum AFB positivity with normal chest X-ray**
In patients with no obvious parenchymal involvement on chest X-ray, sputum for AFB was positive by PCR and culture in 2.2% (2/90) and 11.1% (10/90), respectively.

**Comparison of parameters based on Light’s criteria**
We divided the patients into three groups based on the number of fulfilled Light’s criteria and compared the laboratory parameters, mainly the positive yield of AFB, using different methods. There was no significant difference in the positive yield of AFB by different techniques in samples from sputum, pleural fluid, and pleural biopsy, and the three Light’s criteria groups (Table 4).
| Blood: WBC count (10^3/uL) |  |  |  |  |  |
|----------------------------|---|---|---|---|---|
| Normal (4,000-10,000)      | 18 | 43 | 28 | 89 | 0.041 |
| More than 10,000           | 0  | 9  | 1  | 10 |     |
| Lymphocytes                |    |    |    |    | 0.627 |
| Normal                     | 12 | 30 | 17 | 59 |     |
| Lymphopenia                | 5  | 22 | 12 | 39 |     |
| CRP (mg/L)                 |    |    |    |    |     |
| 0-5                        | 0  | 3  | 0  | 3  |     |
| 6-100                      | 11 | 13 | 14 | 38 | 0.004 |
| 101-200                    | 3  | 32 | 12 | 47 |     |
| >200                       | 1  | 0  | 0  | 1  |     |
| Quanti-FERON               |    |    |    |    | 0.757 |
| Negative                   | 3  | 5  | 4  | 12 |     |
| Positive                   | 6  | 19 | 12 | 37 |     |
| Mantoux (PPD)              |    |    |    |    |     |
| <5 mm                      | 3  | 5  | 6  | 14 |     |
| 6-15 mm                    | 2  | 4  | 3  | 9  | 0.932 |
| >15 mm                     | 5  | 8  | 5  | 18 |     |
| Chest X-ray: parenchymal involvement |    |    |    |    |     |
| No                         | 13 | 47 | 30 | 90 | 0.008 |
| Yes                        | 5  | 5  | 0  | 10 |     |
| BMI                        |    |    |    |    |     |
| 18.5-25                    | 15 | 39 | 18 | 72 |     |
| 25.1-30                    | 2  | 13 | 11 | 26 | 0.178 |
| >30                        | 1  | 0  | 1  | 2  |     |
| Serum albumin (gm/L)       |    |    |    |    |     |
| Normal                     | 3  | 6  | 1  |    | 0.276 |
| Less than 35               | 14 | 46 | 28 |    |     |
| Pleural fluid: lymphocyte  |    |    |    |    |     |
| >50%                       | 17 | 43 | 27 | 87 | 0.099 |
| <50%                       | 0  | 9  | 2  | 11 |     |
| Pleural fluid AFB: smear   |    |    |    |    |     |
| Positive                   | 0  | 0  | 0  |    |     |
| Negative                   | 18 | 52 | 30 | 100|     |
| Pleural fluid AFB PCR      |    |    |    |    |     |
| Positive                   | 0  | 3  | 0  | 3  | 0.24 |
| Negative                   | 18 | 49 | 30 | 97 |     |
| Pleural fluid AFB culture  |    |    |    |    |     |
| Positive                   | 4  | 8  | 1  | 13 | 0.129 |
| Negative                   | 14 | 44 | 29 | 87 |     |
TABLE 4: Correlation of variables with Light's criteria

| Variable                  | Positive | Negative | P-value |
|---------------------------|----------|----------|---------|
| WBC, white blood cell; CRP, C-reactive protein; PPD, purified protein derivative; AFB, acid-fast bacillus; PCR, polymerase chain reaction; INH, isoniazid |           |          |         |
| Pleural biopsy: AFB smear | 2        | 16       | 0.01    |
| Positive                  | 2        | 0        | 0       | 2       | 0.01    |
| Negative                  | 16       | 52       | 30      | 98      |         |
| Pleural biopsy: AFB PCR   | 12       | 25       | 20      | 57      | 0.172   |
| Positive                  | 12       | 25       | 20      | 57      | 0.172   |
| Negative                  | 6        | 27       | 10      | 43      |         |
| Pleural biopsy: AFB culture| 15      | 37       | 27      | 79      | 0.115   |
| Positive                  | 15       | 37       | 27      | 79      | 0.115   |
| Negative                  | 3        | 15       | 3       | 21      |         |
| Drug resistance           | 15       | 50       | 30      | 95      |         |
| Nil                       | 15       | 50       | 30      | 95      |         |
| INH                       | 3        | 0        | 0       | 3       | 0.003   |
| Rifampicin                | 0        | 2        | 0       | 2       |         |
| Discussion                | 2020 Zahid et al. Cureus 12(12): e12391. DOI 10.7759/cureus.12391 |
Similar to pleural fluid, the yield of AFB smear in pleural biopsy was also low in our study (2%), whereas yield of PCR and culture of pleural biopsy samples were high, with culture (79%) showing a significantly higher positivity rate than PCR (57%). This is in contrast to the results of a past study that reported a diagnostic accuracy of 23.5% by smear or PCR or culture of biopsy sample [23]. Histopathological results in our study showed a very high percentage of the presence of granuloma in the study samples (80%), which is in contrast to the previously reported results of 41.2% [23]. Pleural biopsy has a sensitivity of 69%-97%, which is higher in HIV-positive patients [20,22]. The technique used for obtaining biopsy also has an effect on sensitivity. Medical thoracoscopy shown to have a sensitivity of up to 100% for TB pleuritis and increases the yield for culture and PCR [26,27], whereas ultrasound-guided biopsy has a diagnostic yield of 90% [28].

We also evaluated the sputum AFB positivity in patients with no obvious parenchymal involvement in chest X-ray. It was observed that sputum sample was bacteriologically positive (PCR or culture) in 15% (15/100) of patients with TPE, out of which 10% had no parenchymal involvement on chest X-ray. This has clinical significance in deciding the treatment regimen of the patient and also has epidemiological implications. In routine clinical practice, patients with TPE without obvious parenchymal involvement on chest X-ray are considered noninfectious. However, positive AFB in sputum in such patients renders them infectious, which needs isolation as well as contact tracing. In addition, the treatment regimen of such patients varies from that of TPE with negative sputum AFB. In comparison to our observation, previous studies have reported a higher percentage of positivity in sputum. Chaudhuri et al. evaluated the role of sputum examination for AFB in TPE patients without parenchymal involvement and reported that in 22.2% of their patients the sputum AFB was positive by smear and/or culture [29]. Conde et al. studied the yield of AFB smear and culture in induced sputum in TPE and found that bacteriological yield was 55% for sputum culture in patients with normal chest X-ray [30].

**Conclusions**

In the state of Qatar, TPE was more common in young healthy adults from high TB burden countries. None of the study patients was underweight, giving the assumption that low BMI is not a vulnerability factor for TPE. The AFB yield on pleural biopsy PCR and culture was significantly higher than that on all other samples. The number of positive Light’s criteria did not have any association with positive AFB yield. Finally, we recommend that sputum for AFB tests should be conducted in all patients with TPE even with no obvious parenchymal lesion on chest X-ray.

**Additional Information**

**Disclosures**

**Human subjects:** Consent was obtained by all participants in this study. Ethics Committee of Medical Research Center of HMC issued approval MRC 01-20-004. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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