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Research Article

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Primary Tuberculous Pleural Effusion: A Retrospective Study of 32 Patients from Tripoli-Libya

Mahdia Buargub[1@], Ishraq Elshamli[2], Mohanid Alazabi[1], Milad Algmizi[1], Moiied Elazzabi[1], Ahmed Elshatewi[1], Masoud Azzabi[2] and Ahmed Ballouz[3]

[1]Tripoli Central Hospital, [2]Tripoli Medical Center,[3]Abusetta Chest Hospital, Tripoli, Libya
[4]Department of Medicine, Faculty of Medicine, University of Tripoli, Libya

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ABSTRACT

Involvement of the pleura is one of the most common sites of extra-pulmonary tuberculosis. In the absence of lung parenchymal lesions, tuberculous pleural effusion (TBE) can present a diagnostic challenge, especially in developing countries. Our objective was to describe the characteristics of a series of 32 Libyan patients who presented with isolated pleural effusion and were diagnosed with primary type tuberculous pleural effusion (TPE).
A retrospective study of 32 patients recruited from three respiratory clinics in Tripoli (Abusetta Hospital, Tripoli Central Hospital and Tripoli Medical Center) during the period from January 2007 to December 2009.
The patients presented acutely with fever, non-productive cough, chest pain, shortness of breath and unilateral pleural effusion without radiological evidence of lung parenchymal lesions. They failed to respond to empirical antibiotic therapy (Amoxicillin plus Clarithromycin). They had no past history of TB, their tuberculin skin test readings were highly positive and pleural aspiration showedan exudative lymphocytic fluid. The diagnosis of TPE was based ondetection of acid fast bacilli (AFB) in the pleural fluid. When the latter was negative, blind pleural biopsy using Abraham' needle was underaken and the diagnosis was based on detection of caseating granuloma in the biopsy specimens. Data was analyzed by using statistical package for social sciences (SPSS) version 16.
The mean age of the patients was 40.4 years and there was an almost equal representation of males and females. The mean duration of clinical symptoms was 14 days. They all presented with fever, dry cough, chest pain and shortness of breath. The mean values of peripheral white blood cells, the C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were 14,000 cells/mm^3, 180 mg/L, and 118 mm/hr. respectively. Their chest radiography showed unilateral pleural effusions with no apparent lung paryncymal lesions. Pleural fluid analysis showed exudative lymphocytic pleural effusions, and tuberculin skin test readings were positive (≥ 15 mm induration). Pleural fluid smear was positive for AFB in 11 patients (34.4%). Histopathologic examination of pleural biopsy specimens from the 21 patients who had pleural fluid AFB negative results confirmed the presence of tuberculous caseating granuloma. Five of the 32 studied patients (15.6%) were doctors from Tripoli Central Hospital working at the medical and emergency department.
The studied patients had a classic acute presentation of primary TPE. Compared with reports from other developing countries, they were older and both genders were equally affected. The diagnostic yield of pleural fluid AFB was high (34.4%) and caseating granuloma was detected in all of the patients who underwent blind pleural biopsy. The significant number of hospital doctors involved suggested that TB infection control measures need to be revised in our hospitals.

Keywords-*Pleural effusion; Primary; Tuberculosis; Developing counties.*

INTRODUCTION

Tuberculous pleural effusion (TPE) is second only to lymphatic involvement as a site of extra-pulmonary tuberculosis (TB), and is a common cause of pleural effusion in developing countries.[1,2] Pleural involvement can be seen in up to 38% cases of primary TB and up to 18% cases of reactivation TB.[3] The latter is more common in developed countries and patients are of older age and have a more insidious onset.[4] TBE usually presents as an acute illness. The most frequent symptoms are non-productive cough, pleuritic chest pain and fever without a significant elevation in the peripheral white blood cell count.[2] Night sweats, chills, dyspnea and weight loss are also frequently reported.[2]

Although TBE can resolve spontaneously, 65% of untreated cases can develop active TB, hence rapid and accurate diagnosis with early treatment is necessary.[2,5] Chest radiography of TPE typically reveals small to moderate unilateral pleural effusion. Co-existing parenchymal diseae is seen in approximately 20% of

@ Author to whom correspondence should be addressed. Dr Mahdia Buargub*; Tel.+21892 0913759301;* E-mail: mahdiabuargub @hotmail.com

cases, though this proportion increases up to 80% when CTchest is performed.[6] The definitive diagnosis of TBE depends on demonstration of acid-fast bacilli (AFB) in the sputum, pleural fluid, or pleural biopsy specimens.[7] There are numerous difficulties involved in reaching a definitive diagnosis, such as low test yields, long waiting time for culture results and invasiveness of the pleural biopsy.[7,8] In developed countries, due to recent advances in the field of molecular biology assays, the diagnosis can be made in few hours or days when other investigations are not helpful.[9,10]The objective of this study was to describe the characteristics of a series of 32 Libyan patients who were diagnosed with isolated primary type TPE.

MATERIALS AND METHODS

A retrospective study of a series of 32 Libyan patients recruited from three respiratory clinics in Tripoli (Abusetta, Tripoli Central Hospital and Tripoli Medical Center) over the period from January 2007 to December 2009. The patients presented acutely with fever, non-productive cough, chest pain, dyspnea and unilateral pleural effusion with no radiological evidence of lung parenchymal lesions, and failed to respond to empirical antibiotic therapy (Amoxicillin plus Clarithromycin). They had highly positive tuberculin skin tests and thoracocentesis revealed exudative lymphocytic fluid. The diagnosis of tuberculous origin was based on either detection of pleural fluid AFB (using the conventional Ziehl- Neelsen stain) or when the pleural fluid was negative for AFB by detection of caseating granuloma in blind biopsy specimensobtained using Abraham's needle.

Clinical laboratory and radiological details of the 32 patients were extracted from their case records and analyzed. Statistical analysis was performed using statistical package for social sciences (SPSS 16). Continous data were expressed as mean ± standard deviation (SD) and the categorial variables as numbers or percentage. *T-test* was applied for continuous variables and *Chi-square* analysis for categorial variables. The cut off value for statistical significance was considered to be $P<0.05$.

RESULTS

The results of the 32 studied patients (Table 1) revealed the number of male and female patients was comparable 17 and 15 respectively. There was a wide range of age (25-65 years) and the mean age was 40.4 years. The distribution of the patients by age and gender. The mean duration of clinical symptoms prior to presentation was 14 days (ranged from 10 to 21 days). They were prescribed empirical antibiotics for community acquired pneumonia before their referral to the chest clinic. They had fever that ranged from 38°C to 39.5°C (mean of 38.6°C), chest pain and shortness of breath. The symptoms were described as severe in 17 patients (53.1%). They complained of recent weight loss in the range from 6-16 kg (mean of 10.3 kg+/-2.3). None of them had a past history of TB, diabetes, or chronic obstructive airway disease, and none tested positive for HIV. Two patients had stable chronic kidney disease (6.25%) and 6 patients (18.8%) had mild asthma treated occasionally with short courses of steroids. Five patients (15.6%) worked as doctors in the general medical and emergency deparment at Tripoli Central Hospital.

Their peripheral white blood cell (WBC) counts were moderately elevated and ranged from 11,000 to 17,000 cells / mm^3 (mean of 14,000 cells / mm^3), the C- reactive protein (CRP) titer ranged from 110 to 230 mg/L (mean of 180), and erythrocyte sedimentation rate (ESR) values ranged from 90 to 160 mm/hr. (mean of 118).

Chest radiography showed unilateral small to medium sided pleural effusion (equally located on the right and left sides) with no apparent lung parynchymal lesion on postero-anterior and lateral views. On pleural fluid analysis, they all had exudative pleural effusion by one of Light's criteria (effusion protein/serum protein ratio greater than 0.5). Effusion lactate dehydrogenase (LDH), pH and adenosine deaminase (ADA) were not performed. Tuberculin skin test readings were positive ≥ 15 mm of in duration. Pleural fluid smear for AFB was positive in 11 patients (34.4%) who were presumed to have TPE and started on anti-TB chemotherapy.

The other 21 patients with pleural fluid AFB negative results underwent closed pleural biopsy using Abraham's needle. No serious complications were documented. Histopathologic examination of all the biopsy specimens confirmed the presence of caseating granuloma. The 32 studied patients were referred to the TB Center to complete their anti-TB therapy. Statistical analysis showed significant associations between right sided pleural effusion and each of the following: duration of illness (*P*.009), degree of weight loss (*P*.002) (Figure 1), CRP titer (*P*.035) and ESR level (*P*.031), and between duration of clinical symptoms and pleural fluid positivity for AFB (*P*.041) (Table 2).

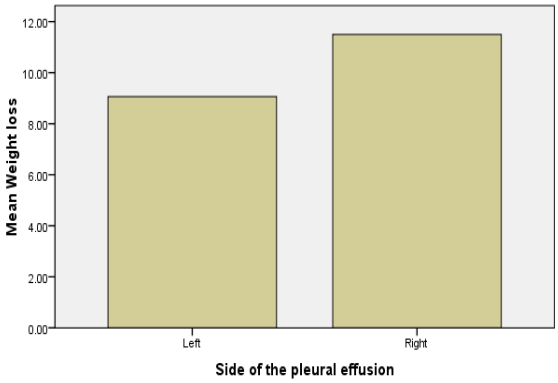

Figure 1 : Weight loss by the side of the pleural effusion

Table 1: Clinical characteristics of the 32 studied patients (n=32)

Characteristic	Mean or percentage
Age (years)	40.4±10
Gender (male)	17(53.1%)
Co-morbidity Asthma Chronic Kidney disease	 6 (18.8%) 2 (6.25%)
Duration of illness (days)	14 ± 3.4
Fever	38.6 ± 0.4 ^{O}C
Weight loss	10.3 kg ± 2.3)
Laterality of effusion	50% right, 50% left
Tuberculin test reading (mm)	15-17
WBC (cells / mm^3)	14,000 ± 1200
CRP titer (mg/L)	180 ± 74
ESR (mm/hr)	118 ± 33
Pleural fluid (PF)	
TLC (cells / mm^3)	1240 ±2410
Lymphocytes (%)	75.5 ±22
PF /serum protein	0.62 ± 0.12
Glucose (mg/dL)	80.5±34
Z-N stain	11 (34.4%)
Pleural biopsy performed and diagnostic	21/21 (100%)

Results either as percentage, mean values ± SD, or range.

Table 2: Statistical significance of studied parameters

Parameters	*P*-value
Age and gender	.317
Pleural fluid positivity and fever (higher with positive)	.191
Pleural fluid positivity and weight loss	.175
Pleural fluid positivity and duration of illness	.041
Pleural fluid positivity and age	.116
Pleural fluid positivity and gender	.529
Right side of pleural effusion and duration of illness	.009
Right side of pleural effusion and weight loss	.002
Right side of pleural effusion and CRP titer	.035
Right side of pleural effusion and ESR level	.031

T-test for continuous vaiables, and Chi-square analysis for categorial variables.

DISCUSSION

The acute presentation of the 32 studied patients with fever, dry cough, and shortness of breath, in the absence of markedly elevated peripheral leukocyte count and poor response to empirical antibiotics were all suggestive of TPE.[11,12] Absence of past history of TB and lung parenchymal lesion was going with a primary type of disease.[2, 4] The mean age of 40 years was oldercompared with that reported from other developing countires (32 to 34 years)[13], and only 53.1% of our study were men while TPE usually predominates in men. The pleural effusions were unilateral, mild to moderate in size, and equally distributed (50% left and 50% right sided). We had no clear reason for the statistical associations with the right side pleural effusion in this study.

The reported sensitivity and specificity of tuberculin skin test in BCG-vaccinated TB endemic areas has been reported as 47% and 86% respectively.[15] In developing countries stated that a reading more than 10 mm is considered positive for diagnosis of TB.[16] All of our patients were BCG vaccinated and had a highly postive skin test readings of ≥ 15 mm in duration. Our patients had dry cough and so sputum was not sent for AFB.

Traditionally, the yield of sputum smear stains and cultures has been low in TPE patients with no radiologic evidence of pulmonary TB (< 10%).[5] However, this test is probably underutilized in the diagnosis of TBE.[2] Conde *et al* (2003)[17] has reported a 52% culture yield with induced sputum.

In 90% of TBE cases, pleural fluid was an exudative with lymphocytic predominance[2], while low pH and glucose level were more characteristic of chronic tuberculous empyema.[19] LDH and pH levels were not performed in our study. Pleural fluid cell count in TPE usually reveals WBC count between 1,000 and 6,000 cells /mm^3 with

lymphocyte predominance (defined as >75% lymphocytes, and/or lymphocyte to neutrophil ratio ≥ 0.75).[20]

The yield of pleural fluid examination by Ziehl- Neelsen stain is reported to be low, while mycobacterial culture has a low sensitivity (30%) and is limited by the lenghty delays of up to 8 weeks in obtaining results when conventional culture media are used.[5] In this study, the pleural fluid smear yield for AFB was high (34.4%). This high result could be due to the high selectivity of the study patients. Pleural fluid biomarkers, such as ADA, could help distinguish TPEs from other causes of pleural effusion. The test is cheap and has a high diagnostic accuracy.

In patients with a typical clinical presentation, a combined pleural fluid ADA level > 70 U/L and lymphocyte/ neutrophil ratio ≥ 0.75 is considered diagnostic of TPE.[2,5,9] However, this test was not available. When the clinical suspicion of TPE is high despite negative results, pleural biopsy should be performed.[18] With the advent of medical thoracoscopy, closed pleural biopsy has fallen out of favor, though it continues to have a role in the diagnosis of TPE, especially in developing countries.[19,20] Granulolma was seen in 50-97% of cases[21] and considered adequate for diagnostic of TBE.[2] The 21 patients with AFB negative pleural fluid underwent closed pleural biopsy specimens and caseating granuloma was detected in all of them.

Five of the 32 studied cases; (15.6%) were hospital doctors at the Medical and Emergency department. Occupational TB among healthcare workers occurs at an alarming proportion in the low-and middle-income countries due to both increased exposure and lack of preventive measures. The risk is reported to be the highest among workers in TB in-patient facilities, laboratories, general medicine and emergency rooms. The application of the World Health Organization (WHO) guidelines for prevention of TB transmission in healthcare facilities need to be examined and strongly implemented in our hospitals.

The high number of affected doctors could also reflect a rising incidence of TB in our country. The prevalence of TB is one of the costs of immigration and we have a large number of immigrants who come from TB endemic regions, such as South East Asia and Africa.

Study limitations:

This is a retrospective study with several limitations. An analysis of the serum and pleural LDH and pleural ADA were not performed. Induced sputum smear and culture were not sent and pleural mycobacterial cultures were not documented as well.

CONCLUSION

The 32 studied patients had a classic acute presentation of primary TPE. Compared with reports from other developing countries, the patients were older and both genders were equally affected. The pleural fluid yield of AFB was high (34.4%) and caseating granuloma was detected in all of the patients who underwent blind pleural biopsy.

RECOMMENDATIONS

The significant number of hospital doctors among the studied cases suggested that TB infection control guidelines need to be revised in our hospitals.

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