Clinico-Radiological characteristics of patients with Pleural Tuberculosis and misuse of Antibiotics prior to diagnosis

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TA conceived idea, TA AN drafted the study, TA collected data, TA AN did statistical analysis & interpretation of data, TA AN critical reviewed manuscript, Both approved final version to be published

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The Authors declares that there is no conflict of interest.

Abstract

Background: Pleural tuberculosis is one of the commonest causes of pleural effusion in regions endemic for tuberculosis including Pakistan.

Objective: To study the types of clinico-radiological presentations of pleural tuberculosis and analyze misuse of antibiotics prior to its diagnosis.

Methodology: Prospective analysis of clinico-radiological features and misuse of antibiotics among 58 patients with pleural tuberculosis, over 24 months (May 2015 to May 2017), presenting at the department of pulmonology, Shaikh Zayed Hospital, FPGMI Lahore, Pakistan.

Results: The study included 58 patients including 37 males (64%) and 21 females (36%), having ages in the range of 14 to 72 years. Thirty three (56.9%) were indoor and 25 (43.1%) were OPD patients; 38 (48.3%) had left sided pleural effusion, 38 (48.3%) with right pleurisy & 2 (3.4%) had bilateral pleural effusions. Small sized pleural effusions on chest radiographs were seen in 6 (10.34%), moderate effusions in 22 (37.93%), larger effusions in 25 (43.10%) and massive effusions in 5 (8.62%) patients with 50% having septations on ultrasound chest examination. Diagnosis of pleural TB was made on the basis of either positive pleural biopsy (caseating granulomatous inflammation) with lymphocytic (51.72%) or neutrophilic (5.17%) exudative effusions or exudative lymphocytic effusion alone (43.10%). Duration of illness prior to hospital visit was ≤ 2 weeks in 24 (41.4%), 2-3 weeks in 14 (24.1%) and ≥ 4 weeks in 20 (34.5%) patients. Majority (63.2%) of the patients had intermediate to high grade continuous or intermittent pyrexia while 24 (41.4%) had low grade continuous fever with 24 (41.4%) subjects experiencing night sweats. Forty (69%) patients had cough and 13 (22.4%) had mild sputum production. Forty three (74.1%) patients also had dyspnea. Chest pain was present in 32 (55%) and 25 (43.1%) had pain of pleuritic nature. Wheeze and hemoptysis were the least frequent symptoms in 9 (15.5%) and 2 (3.4%) individuals respectively. Forty nine (84.5%) patients had visited physicians prior to presenting to the hospital and misuse of antibiotics was reported by 42 (72.4%) patients. Association of age with duration of illness prior to hospital visit showed statistical significance as majority (56.2%) of patients having ≤ 30 years of age had ≤ 2 weeks duration of illness compared to only 3 patients in 31-50 years of age group and 3 subjects having ages > 50 years (p-value = 0.048). Association of young age ≤ 30 years with other parameters including fever grade (p-value = 0.004), wheeze (p-value=0.050), physicians' visits (p-value = 0.075) and antibiotics misuse (p-value = 0.026) also revealed significant associations.

Conclusion: Tuberculous pleural effusions appear moderate to large on chest radiographs, and presents in an acute manner, and should be investigated earlier to avoid diagnostic delay and prevent misuse of antibiotics.

Key words: Antibiotics; Clinical characteristics; Radiological; Tuberculosis.

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Introduction

Tuberculous pleural effusion (TPE) is the second most common form of extra pulmonary TB (after lymph node disease) and is the most frequent cause of infective pleural disease in regions endemic for tuberculosis.[1,2] The mycobacterial infection within the pleural space is paucibacillary and development of TPE typically occurs due to delayed hypersensitivity reaction to mycobacterial antigens in the pleural space.[3] TPE sometimes may develop when a subpleural focus of pulmonary parenchymal disease ruptures into the pleural space.[4] TPE can occur in association with reactivation disease (mostly adults) or primary tuberculosis(mostly children/adolescents).

Methodology

A case series including fifty eight (58) patients with TPE, enrolled during May 2015 to May 2017, presenting at the department of pulmonology, Shaikh Zayed Hospital, FPGMI Lahore, Pakistan. The aim of this study was to prospectively evaluate the types of clinico-radiological presentations of patients with TPE and analyze the misuse of antibiotics prior to its diagnosis. Data were collected on a specifically designed study proforma recording the following details including patients' demographics [name, age (date of birth), gender] contact number, address, and modality for diagnosis of TPE (exudative lymphocytic effusion with caseating granulomatous pleural tissue biopsy, exudative neutrophilic effusion with granulomatous pleural biopsy or exudative lymphocytic effusion alone). Further recorded details included the size and site of effusion on chest radiograph posteroanterior (PA) projection, presence of loculations in the pleural space utilizing bedside thoracic ultrasound (TUS); duration of illness prior to presentation in the hospital; fever grade, duration and night sweats; respiratory symptoms including presence of cough, sputum, chest pain, dyspnea (MMRC grade), hemoptysis and wheeze; number of physicians' visits prior to diagnosis as well as number and misuse of antibiotics before presentation to the hospital.

Low-grade fever was defined as oral body temperature ranging from 99 F-101 F; 102 oF was taken as intermediate grade & high-grade fever was fever ≥ 103 oF. Size of pleural effusion on chest radiograph was considered small if it obliterated diaphragmatic shadow; moderate if it occupied 50% of hemithorax volume (at the level of hilum); large if it exceeded >50% of hemithorax (above the hilum) and massive if effusion caused diffuse opacification of hemithorax.

In patients suspected of having loculations /septations, bedside departmental TUS was carried out, and in doubtful cases radiology services were requested. All patients underwent diagnostic pleurocentesis and those with symptomatic large or massive effusions also had therapeutic pleurocentesis (up to 1.5 liters). Pleural fluid analysis included biochemistry (protein, glucose, LDH and albumin) and microbiology [TLC, DLC and Ziehl-Neelsen (ZN) staining]. Among all patients who had pleurocentesis, those consenting also had Abrams' closed pleural biopsy. Those not consenting for pleural biopsy were closely followed up during the course of their treatment to document the clinico-radiological resolution of their pleural disease compatible with the clinical diagnosis. Patients who were lost to follow up and those who had exudative lymphocytic effusion alone and showed no response to anti-tuberculous chemotherapy and/or were found to have an alternative diagnosis were also excluded from the study. Tuberculous empyemas were also excluded from the study.

Data were analyzed using IBM SPSS statistics.[20] Frequencies and percentages were recorded for all variables including age, gender, modality for diagnosis, size and site of effusion, presence of loculations, fever and its grade, night sweats, cough, sputum, chest pain, dyspnea (MMRC grade), hemoptysis and wheeze; number of physicians' visits and number and use of antibiotics before presentation to the hospital (Table 1). Data for relationship of age with duration of illness prior to presentation to the hospital, fever grade, wheeze, and physicians' visits prior to presentation and use of antibiotics was presented by cross table and analyzed by using chi-square likelihood ratio test (Table 2). P value ≤ 0.005 was considered statistically significant. Graphical presentation was used for modality of diagnosis (Figure 1) and size of pleural effusion (Figure 2).

Results

The study included 58 consenting patients with TPE including 37 males (64%) and 21 females (36%), having ages between 14-72 years (mean age 35.6 years). Majority (32, 55.2%) of the subjects were ≤ 30 years of age, 11 (19%) were 31-50 and 15 (25.9%) patients were ≥ 50 years old. Thirty three (56.9%) subjects were enrolled from indoor ward and 25 (43.1%) were pulmonology OPD patients.

Twenty eight (48.3%) individuals had right sided pleural effusion and a similar number (48.3%) had left sided pleurisy while only 2 patients (3.4%) had bilateral pleural effusions. Small sized pleural effusions were seen in 6 (10.34%), moderate effusions in 22 (37.93%), larger effusions in 25 (43.10%) and

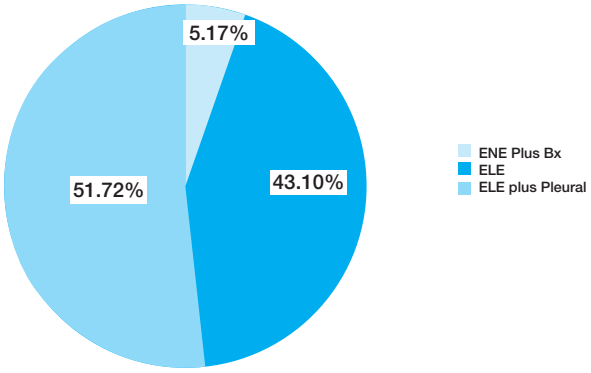

Figure 1: Modalities for diagnosis of pleural tuberculosis (ENE exudative neutrophilic effusion, ELE exudative lymphocytic effusion, Bx biopsy)

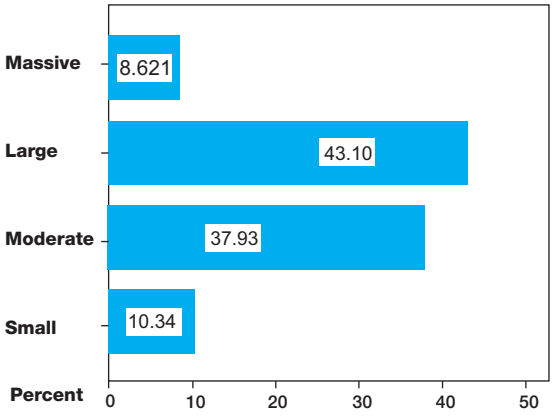

Figure 2: Size of pleural effusion on chest radiograph

massive effusions only in 5 (8.62%) patients. Half (50%) of the patients with pleural effusions showed some septations/loculations seen on TUS performed at bedside. Twenty one (36%) patients had also evidence of coexisting parenchymal disease (pulmonary TB). All patients (100%) underwent diagnostic ± therapeutic pleurocentesis and 33 (57%) consenting individuals (for pleural biopsy) had Abrams' closed pleural biopsy; 28 (85%) had necrotizing granulomatous inflammation and remaining 5 (15%) had chronic non specific inflammation. All patients had ZN staining of their pleural fluid and only two (3.44%) out of 58 patients had Acid Fast Bacilli (AFB) smear positive in fluid besides exudative biochemistry and granulomatous pleural biopsy. Diagnosis of TPE in 30 (51.72%) patients was made on the basis of positive pleural biopsy (caseating granulomatous inflammation) in the presence of exudative lymphocytic effusion or positive pleural biopsy in the presence of exudative neutrophilic effusion in 3 (5.17%) individuals or exudative lymphocytic effusion alone in 25 (43.10%) patients who did not consent for pleural biopsy and had clinico-radiological features consistent with TPE and showed response to anti-tuberculous chemotherapy.

Duration of illness prior to hospital visit was ≤ 2 weeks in 24 (41.4%), 2-3 weeks in 14 (24.1%) and ≥ 4 weeks in 20 (34.5%) patients. Association of age with duration of illness prior to hospital visit (in days) showed statistical significance as majority (56.2%) of patients ≤ 30 years of age had duration of illness ≤ 2 weeks compared to only 3 patients in 31-50 years of age and three subjects > 50 years old (p-value = 0.048). All patients except one had history of fever at the time of presentation. Majority (63.2%) of the patients had intermediate to high grade continuous or intermittent pyrexia while 24 (41.4%) had low grade continuous fever during the course of illness. Twenty four (41.4%) patients had associated night sweats. Association of age with grade of fever also showed statistical significance as majority (81.2%) of patients ≤ 30 years of age had grade of fever which was intermediate (102 oF) to high (≥ 103 oF) compared to 5 patients in 31-50 years of age and five > 50 years old (p-value = 0.004). Forty (69%) patients also had cough accompanying their illness and in most (88%) patients it was dry in

Table 1: Clinico-Radiological characteristics of patients with pleural tuberculosis

Variables		n	%
Indoor		33	56.9
Age	< 30	32	55.2
	31-50	11	19.0
	>50	15	25.9
Males		37	63.8
CXR-PR site of pleurai effusion	Left	28	48.3
	Right	28	48.3
	Bilateral	2	3.4
Pleural septations/loculations		29	50.0
Duration of illness prior to hospital visit (days)	<14	24	41.4
	15-28	14	24.1
	>28	20	34.5
Intermediate to high grade fever		36	63.2
Night Sweating		24	41.4
Cough		40	69.0
Dyspnea		43	74.1
MMRC grade	Grade 1	5	11.6
	Grade 2	29	67.4
	Grade 3	9	20.9
Chest pain	Pleuritic	25	43.1
	Non Pleuritic	7	12.1
	None	26	44.8
Wheeze		9	15.5
Hemoptysis		2	3.4
Sputum		13	22.4
Doctor visits before diagnosis	None	9	15.5
	One	19	32.8
	Two	14	24.1
	Three	8	13.8
	Four	8	13.8
Antibiotics misuse		42	72.4
Number of antibiotics	None	17	29.3
	One	12	20.7
	Two	20	34.5
	Three	9	15.5

nature and only 13 (22.4%) reported mild sputum production. Forty three (74.1%) patients also had dyspnea; grade 1 Modified Medical Research Council (MMRC) was found in 5 (11.6%), grade 2 in 29 (67.4%) and grade 3 in 9 (20.9%) individuals and none had grade 4 dyspnea. Chest pain was present in 32 (55%) and among these 25 (43.1%) had pleuritic chest pain ipsilateral to the side of effusion and only 7 (12.1%)

complained of diffuse chest pain. Wheeze and hemoptysis were the least frequent symptoms in 9 (15.5%) and 2 (3.4%) individuals respectively. Association of age with wheeze also showed statistical significance in terms of 7 (21.9%) patients ≤ 30 years of age in which wheezing was present compared to only 2 (18.2%) patients in 31-50 years of age and none > 50 years old (p-value = 0.050).

Forty nine (84.5%) patients had visited their primary care or general/pulmonary physicians prior to presenting to the hospital. Nineteen (32.8%) had history of visiting a single physician, 14 (24.1%) had visited two doctors, 8 (13.8%) visited three and remaining 8 (13.8%) had consulted four doctors before their presentation to the hospital. The distribution of doctors' visits showed borderline statistical significance in younger individuals of ≤ 30 years of age who visited one to four doctors before their presentation to the hospital compared to individuals 31-50 years of age and those > 50 years old (p-value = 0.075). Misuse of antibiotics was reported by 42 (72.4%) patients and majority (34.5%) had used a combination of antibiotics prescribed. Single antibiotic use was revealed by 12 (20.7%) patients and 3 antibiotics during their illness were prescribed to 9 (15.5%) individuals. The misuse of antibiotics had statistical significance in younger individuals of ≤ 30 years of age as 25 patients in this age group had used antibiotics prior to their diagnosis compared to 10 subjects in 31-50 years of age and 7 of more than 50 years old (p-value = 0.026).

Table 2: Association of age with duration, symptoms, doctors' visits and antibiotic misuse among pleural tuberculosis patients

Variables		Age									
		<30		31-50		>50		Total		Chi-sq	p-value
		n	%	n	%	n	%	n	%		
Duration of illness prior to hospital visit (days)	<14	18	56.2	3	27.3	3	20.0	24	41.4	9.58	0.048
	15-28	8	25.0	2	18.2	4	26.7	14	24.1		
	>28	6	18.8	6	54.5	8	53.3	20	34.5		
Fever grade	low	6	18.8	5	50.0	10	66.7	21	36.8	11.18	0.004
	Intermediate to high	26	81.2	5	50.0	5	33.3	36	63.2		
Wheeze	Present	7	21.9	2	18.2	0	0.0	9	15.5	6.01	0.050
	Absent	25	78.1	9	81.8	15	100.0	49	84.5		
Physicians' visits before diagnosis	None	3	9.4	1	9.1	5	33.3	9	15.5	14.26	0.050
	One	10	31.2	6	54.5	3	20.0	19	32.8		
	Two	8	25.0	4	36.4	2	13.3	14	24.1		
	Three	6	18.8	0	0.0	2	13.3	8	13.8		
	Four	5	15.6	0	0.0	3	20.0	8	13.8		
Antibiotic misuse	Yes	25	78.1	10	90.9	7	46.7	42	72.4	7.27	0.026
	No	7	21.9	1	9.1	8	53.3	16	27.6		

Discussion

On a global scale, tuberculosis remains one of the most frequent causes of pleural effusions.6 Approximately 95% of TB cases occur in developing countries mostly in young adults and predominantly males due to frequent community exposures.[7] The same demographic pattern was observed in the present study. In a similar Indian study, TPEs were usually unilateral, and were small to moderate in size.[8] In another Spanish study, TPE occurred slightly more frequently on the right side than left (55 versus 45

percent) and occupied less than one-third of the hemithorax in 82 percent of cases.[9] The results of our study were different as the frequency of side of pleural effusion was equally distributed and majority of patients (43%) had larger effusions occupying more than 50% of the hemithorax. In another Pakistani study, the distribution of side of pleural effusion was also equal among 50 patients with TPE.[10] Five younger (8.6%) patients from our study also had massive effusions causing opaque hemithorax, requiring frequent therapeutic aspirations and all of them had lymphocytic exudates in the presence of caseating granulomatous pleural tissue histology. One of them was a 17 year-old-male who had 4.5 liters of fluid drained in three aspirations. Massive size (opaque hemithorax) is not a frequent feature of TPE, this is probably attributable to intense hypersensitivity reaction in the pleural space in young immune competent individuals.[9] Our population may have genetic differences as we also reported a similar case of pleuro-pulmonary tuberculosis from our centre having larger multiloculated TPE.[11] A case of massive TPE from India was also reported in a patient with chest wall tuberculous involvement.[12]

Half (50%) of the current study patients with pleural effusions showed some septations seen on TUS, which in academic centers has become a standard practice to localize pleural fluid septations.[13] Ten (34.4%) patients had history of pleurocentesis before the TUS which could be responsible for adhesions in the pleural space. Studies have shown that like parapneumonic effusions, TPE can also develop loculations.[11,14] TUS appearance of TPEs range from anechoic to homogeneously echogenic to non-septated or complex septated effsuions.[15] In a larger old study, chest radiography demonstrated parenchymal disease in association with pleural effusion in up to 50 percent of patients with TPE.[16] In comparison, only 36% of our patients had coexisting parenchymal TB, ipsilateral to the side of effusion.

Besides pleural fluid basic biochemical (protein, glucose, albumin, LDH) and microbiological (TLC, DLC) work up, multiple investigations (having variable yield) can be utilized for the diagnosis of TPE including pleural fluid AFB smear and culture, adenosine deaminase (ADA) level, nucleic acid amplification test (NAAT), pleural tissue histology and mycobacterial culture.[8,17] We selected pleural fluid biochemistry, TLC, DLC, AFB smear and pleural tissue histology because of the cost constraints. AFB smear in pleural fluid was positive in only two (3.44%) out of 58 patients. The reported yield is also < 10% in pleural fluid because the effusion is due to delayed hypersensitivity response to mycobacterial antigens in the pleural space.[18,19] Majority (51.72%) of our patients were diagnosed to have TPE on the basis of caseating granulomatous pleural tissue histology in the presence of exudative lymphocytic effusion; only 3 (5.17%) individuals had exudative neutrophilic effusion with positive pleural biopsy and remaining had exudative lymphocytic effusion alone. The patients who had neutrophilic exudate in our study had their pleural fluid analysis and pleural biopsy within the first week of their presentation to the hospital. These findings are similar to some other studies which revealed lymphocytic predominance in 60 to 90 percent of TPE cases and neutrophil predominance in the remaining cases, with neutrophils predominating in the first few (4-7) days following onset of pleural inflammation.[8,16,20]

In the current study, the yield of pleural tissue histology (caseating granulomatous inflammation) was 85% which is comparable to 60- 95% sensitivity reported in some studies.[17,21,22] The presence of caseating granulomas containing AFB on histological examination of the pleural surface is diagnostic of TB pleuritic.[8] The demonstration of AFB is not an absolute requirement; the presence of caseating granulomas in high burden settings is considered adequate for the diagnosis of pleural tuberculosis.[23] Clinically, in contrast to parenchymal pulmonary TB, most TPE effusions present as an acute febrile illness, with nonproductive cough (94 percent) and pleuritic chest pain (78 percent).[24] Approximately one-third of patients with TPE are symptomatic for less than 1 week and two thirds for less than 1 month. Night sweats, chills, weakness, dyspnea, and weight loss can also occur in many patients.[8] In the present study, duration of illness prior to hospital visit was ≤ 2 weeks in 41.4%, 2-3 weeks in 24.1% and ≥ 4 weeks in 34.5% patients. Similar to above mentioned studies, majority (41.4%) of our patients had acute presentation with duration of illness that was ≤ 2 weeks before presentation to the hospital and short duration of illness was more evident in younger individuals < 30 years of age. The distribution of acute respiratory symptoms and fever were also more pronounced in individuals with younger age group. Majority (63.2%) of patients presented with short duration of illness (< 2 weeks) and younger patients (< 30 years of age) had intermediate to high grade fever compared to individuals > 31-50 and those >50 years old, most of those presented with low grade pyrexia. The minimal duration of illness was 3 days in an 18 year old male having large left TPE. Compared to the study of Berger and Mejia, who reported cough in 94% of their patients, 69% of our patients had cough, majority

(88%) with dry cough and remaining producing scanty sputum.[24] Similar to the above mentioned studies, 8,16,19,24 most (74.1%) of our patients also had accompanying dyspnea, majority with grade 2 (MMRC); pleuritic chest pain in 43.1% with wheeze and hemoptysis being the least frequent symptoms in minority of patients were again more frequent among younger patients.

Majority (84.5%) of this study patients' (mostly from younger age group) had visited their primary care, general or pulmonary physicians prior to presentation at the hospital and were prescribed antibiotics. This is suggestive of younger people from productive ages seeking earlier medical attention, compared to late presentation in individuals >50 years old. There was probably more parental influence in many younger patients who were brought to the hospital by their parents. The study also reflects of lack of general knowledge of working physicians about the acute presentation of TPEs and therefore prescribing antibiotics. Misuse of antibiotics was reported by majority (72.4%) of patients and 34.5% had used a combination of antibiotics prescribed. Combination usually consisted of oral/IV second or third generation cepahalosporin e.g cefepime, cefuroxime or co-amoxiclav in combination with a macrolide like clarithromycin or fluoroquinolones like moxifloxacin and levofloxacin. Many studies have shown that majority of empirical antibiotics are prescribed by primary care physicians leading to delays in the diagnosis and treatment, increase antibiotics resistance and poor prognosis especially in TB patients prescribed fluoroquinolones before the appropriate diagnosis was established.[25,26]

The limitations of this study include the small sample size and relying on plain chest radiographs to pick up the parenchymal lung and pleural disease. Although not recommended routinely, CT thorax is more sensitive than chest radiography as it can demonstrate parenchymal disease in over 80 percent of cases.[27] In addition, we didn't utilize ADA, pleural fluid and tissue AFB cultures and NAAT because of cost limitedness.

Conclusion

TPE especially in young adults are moderate to large in size, may show septations and present in an acute fashion resembling a pneumonic illness. TPE should be suspected as a prime diagnosis in patients presenting with acute pleurisy, as early diagnosis will prevent misuse of antibiotics thus reducing cost of treatment and possibly reduction in rising state of antibiotics resistance.

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