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Does pleural tuberculosis disease pattern differ among developed and developing countries

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Summary *Background*: A number of reports from developed countries have documented a rising age at which pleural tuberculosis occurs and increase in the frequency of reactivation disease being as the main cause of pleural involvement.

Objective: To determine the age at which pleural tuberculosis occurs, study its clinical pattern, and to determine whether pleural tuberculosis is a result of reactivation of pulmonary tuberculosis or it is a primary one comparing our findings with results from developed countries.

Method: Retrospective study of 100 cases discharged from Hamad General Hospital with the diagnosis of pleural tuberculosis from January 1996 to December 2002.

Results: Pleural tuberculosis tends to affect younger age groups (84% are below the age of 45 years, with mean age of 31.5). The disease tends to be mostly a primary infection. Fever is the most common symptom (90%) and the disease is usually an acute or sub acute one. Weight loss precedes other symptoms. Exudative pleural effusion with predominant lymphocytosis is characteristic. Majority of patients have no predisposing conditions for the disease.

Conclusion: In contrast to what has been reported in some developed countries, Pleural tuberculosis tends to be a primary disease in the present study. Younger age groups are particularly affected.

Introduction

Tuberculosis still a leading cause of death worldwide, especially in sub-Saharan Africa where

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infection with HIV virus has caused a large excess in incidence and mortality from active tuberculosis.[1] Pleural involvement remains the most common extra pulmonary manifestation of tuberculous infection.[2,3] Pleural tuberculosis is still considered in developed countries as a disease of older population.[4] Pleural tuberculosis is usually an acute febrile illness, it is thought to result from a delayed hypersensitivity reaction to mycobacterial antigen in the pleural space, these antigens may enter from a parenchymal lung focus.

Since the introduction of anti-tuberculous chemotherapy and control measures there has been a marked reduction in the incidence of tuberculosis in the developed world. This has lead to the result that pleural tuberculosis being more commonly due to reactivation than primary infection in developed countries and complicates about 7% of cases of active pulmonary tuberculosis.[5]

A study from Edinburgh[2,6] for the years 1980–1991 noting reactivation as a cause of tuberculous effusions in 40.3% while in 22.5% of cases the effusion was primary. Another study from Los Angeles[7] showed that 46% of cases of pleural tuberculosis were due to reactivation disease. Pleural tuberculosis is still a difficult disease to diagnose; Pleural biopsy remains the gold standard for the diagnosis of pleural tuberculosis.[2,8]

The peninsula of Qatar lies half way along the west coast of the Arabian Gulf. The population of Qatar is around 769,152 (July 2001 estimate), 80% are foreign workers, majority of these expatriates are Asians (Indians, Bangladeshi, Nepali, and Arabs). Africans, Europeans and Americans constitute a minor proportion. Hamad Medical Corporation is the main health care provider in the state of Qatar with Hamad General hospital and Rumailah hospital being the main teaching hospitals.

The objective of the present study was to determine the age at which pleural tuberculosis occurs in HIV negative and HIV positive patients, study the demographic, clinical pattern and risk factors of pleural tuberculosis, and to determine whether pleural tuberculosis is a result of reactivation of pulmonary disease or it is a primary disease, comparing the situation in developed and developing countries.

Methods

A retrospective study of cases admitted to Hamad General hospital during the period from 1996 to 2002 and diagnosed with certainty as pleural TB was conducted.

Table 1 Socio-demographic, past history and disease detail of the patients.

	$N = 100$ n(%)
Gender	
Male	94(94.0)
Female	6(6.0)
Nationality	
Qatari	4(4.0)
Non-Qatari	96(96.0)
Age group	
<35 years	56(56.0)
35–45 years	29(29.0)
>45 years	15(15.0)
Past history of TB	
Yes	1(1.0)
No	99(99.0)
History of contact with TB patient	
Yes	9(9.0)
No	91(91.0)
Diabetes mellitus	
Yes	5(5.0)
No	95(95.0)
HIV	
Yes	1(1.0)
No	99(99.0)
Asthma	
Yes	0(0.0)
No	100(100.0)
COPD	
Yes	0(0.0)
No	100(0.0)
Use of immunosuppressant drug	
Yes	9(9.0)
No	91(91.0)
Smoking habits	
Smoker	26(26.0)
Non-smoker	74(74.0)

Inclusion criteria

The diagnosis should be based on: Presence of pleural effusion in a patient with one of the following criteria:

1. Histological findings of caseating granuloma.
2. Histological findings of non-caseating granuloma with clinical picture consistent with pleural tuberculosis &/or positive sputum for AFB &/or Positive PPD.

Table 2 Frequency of Symptoms and duration of symptoms among patients by age group.

	$N = 104n(\%)$	Duration of symptoms in days*					
		<35 years			⩾35 years		
		Median	Mean ± SD	95% CI	Median	Mean ± SD	95% CI
Fever	93(89.4)	15.00	29.39 ± 35.8	18.75–40.03	12.00	20.49 ± 31.8	9.57–31.40
Cough	90(86.5)	21.00	38.86 ± 50.7	24.31–53.41	14.00	25.58 ± 35.7	12.50–38.66
Sputum	42(40.4)	14.0	25.84 ± 26.3	13.17–38.51	13.00	29.31 ± 45.6	5.00–53.63
Hemoptysis	5(4.8)	22.00	27.25 ± 24.2	−11.19–65.69	—	—	—
Weight loss	59(56.7)	60.0	71.00 ± 53.4	48.95–93.05	30.00	68.93 ± 68.5	29.37–108.49
Shortness of breath†	33(31.7)	15.00	27.07 ± 30.0	10.45–43.68	8.00	10.54 ± 7.4	6.07–15.00
Pleuratic pain	61(58.7)	15.00	31.46 ± 38.0	16.12–46.81	14.00	36.96 ± 51.1	15.86–58.06
Night sweating	60(57.7)	21.00	35.22 ± 35.1	21.32–49.13	10.00	25.90 ± 41.6	6.42–45.38

*Mann–Whitney test was used to compare duration of symptoms among the two age groups.
†$P = 0.044$.

3. Positive pleural fluid, &/or pleural biopsy for AFB.

Criteria for diagnosing reactivation pleural tuberculosis

We depend on the same criteria used by authors from developed countries[4,6,10,11] to diagnose pleural tuberculosis secondary to reactivation which are:

1. Absence of any parenchymal lung disease.
2. Absence of past history of pulmonary tuberculosis.

A total of 104 cases were found to be discharged with the diagnosis of pleural tuberculosis during the period from January 1996 to December 2002. Out of this number 4 cases were excluded from the study as they did not fulfill our criteria of diagnosis mentioned above. The remaining 100 cases were included as they fulfill the criteria. Various points in the history, clinical examination, radiological, laboratory, Microbiological, Histopathological were investigated and recorded in a sheet. Adenosine deaminase of the pleural fluid was not done in any of the cases because it was not available in Hamad general hospital during that period.

Various data were obtained from the medical records of the patients including hospital number, age, sex, past history of tuberculosis, history of diabetes, HIV infection, COPD, asthma, history of contact with tuberculosis case, drug history like immunosuppressants, steroids, antituberculous drugs, smoking history, different symptoms and duration for each, radiological findings, biochemical parameters in the blood, PPD readings, result of sputum direct smear and culture for AFB, characteristics of pleural fluid and the result of fluid direct smear and culture for AFB, the histopathological and microbiological result of pleural biopsy, whether the biopsy was complicated by pneumothorax, and the various drug sensitivities of the AFB.

Data analysis

The Statistical Package for Social Sciences[9] (SPSS) was used for statistical analysis. Data are expressed as mean and standard deviation (SD) unless otherwise stated. Student's t test was used to ascertain the significance of differences between mean values of two continuous variables and the Mann–Whitney test performed for nonparametric test. χ^2 analysis was performed to test for differences in proportions of categorical variables between two or more groups. The cut-off value for significance was considered to be $P < 0.05$.

Results

Table 1 shows the demographic features of pleural tuberculosis. As can be seen from the table, Pleural tuberculosis tends to affect younger age groups (85.0% are below the age of 46 years). The mean age of the study subjects was 31.7 ± 7.1. This is different from what was thought to be in the past.[4] Only one patient in our study is HIV positive (his age at presentation was 66 years). The presence of complications like diabetes, asthma, COPD and use

Table 3 Laboratory findings among the patients.

	Age <35, $N=56$ n(%)	Age $\geqslant 35$, $N=44$ n(%)	Total
CXR findings			
Right effusion	33(58.9)	25(56.8)	58(58.0)
Left effusion	27(48.2)	20(45.5)	47(47.0)
Bilateral pleural effusion	4(7.1)	1(2.3)	5(5.0)
Consolidation	9(16.1)	5(11.4)	14(14.0)
Fibrosis	1(1.8)	5(11.4)	6(6.0)
Cavitation	0(0.0)	4(9.1)	4(4.0)
Haemoglobin (g/dl)			
$\leqslant 12$	18(32.1)	12(27.3)	30(30.0)
>12	38(67.9)	32(72.7)	70(70.0)
WBC (10^9/l)			
4–10	52(92.9)	38(86.4)	90(90.0)
>10	4(7.1)	6(13.6)	10(10.0)
Neutrophils (%)			
45–74%	38(67.9)	30(68.2)	68(68.0)
$>74\%$	18(32.1)	14(31.8)	32(32.0)
Lymphocytes (%)			
$<16\%$	25(44.6)	21(47.7)	46(46.0)
16–45%	31(55.4)	23(52.3)	54(54.0)
ESR (mm/h)			
<20	5(8.9)	3(6.8)	8(8.0)
20–40	14(25.0)	10(22.7)	24(24.0)
>40	37(66.1)	31(70.5)	68(68.0)
PPD mm (mean $\pm$ SD)*	20.06 $\pm$ 5.5	17.33 $\pm$ 4.6	0.042
Platelets (10^9/l)			
150–400	32(57.1)	23(52.3)	55(55.0)
401–500	17(30.4)	13(29.5)	30(30.0)
>500	7(12.5)	8(18.2)	15(15.0)
Serum albumin(g/l)			
25–35	37(66.1)	29(65.9)	66(66.0)
36–55	19(33.9)	15(34.1)	34(34.0)
Sputum for AFB (direct smear)			
Positive	2(3.6)	4(9.1)	6(6.0)
Negative	54(96.4)	40(90.9)	94(94.0)
Sputum for AFB (culture)			
Positive	10(17.9)	13(29.5)	23(23.0)
Negative	46(82.1)	31(70.5)	77(77.0)

*$P=0.042$.

of immunosuppressant drug was uncommon among the study subjects. (5.0%, 0%, 0%, 9%, respectively). In total, 26.0% of the subjects were smokers.

Table 2 shows the symptoms in order of frequency and their durations. Fever is the most common presenting symptom (90.0%) followed by cough (86.0%), Pleuratic pain (60%) and night sweats (57.0%). The disease tends to be an acute illness rather than a chronic one as the duration of symptoms are less than 30 days at presentation (in 71.4–83.9% of cases) except for weight loss, indicting that weight loss is the earliest symptom to occur. The duration of symptoms showed a high deviation and interestingly duration of shortness of breath was significantly higher the younger group (age <35 years), $P=0.044$.

Table 3 shows the chest X-ray and laboratory findings. The disease is mostly a primary infection rather than a reactivation of co-existing pulmonary

Table 4 Pleural fluid analysis by age group.

	Age <35, $N=56$ n(%)	Age $\geqslant 35$, $N=44$ n(%)	Total
Fluid color			
Straw	52(92.9)	38(86.4)	90(90.0)
Hemorrhagic	4(7.1)	5(11.3)	9(9.0)
Purulent	0(0.0)	1(2.3)	1(1.0)
Pleural pH			
$\leqslant 7.2$	4(7.1)	1(2.3)	5(5.0)
>7.2	52(92.9)	43(97.7)	95(95.0)
Protein g/l			
<30	0(0.0)	1(2.3)	1(1.0)
$\geqslant 30$	56(100.0)	43(97.7)	99(99.0)
Fluid protein/serum protein ratio			
<0.5	1(1.8)	0(0.0)	1(1.0)
>0.5	55(98.2)	44(100.0)	99(99.0)
Fluid glucose (mmol/l)**			
<3.5	28(50.0)	9(20.5)	37(35.6)
>3.5	28(50.0)	35(79.5)	63(63.0)
Fluid LDH level u/l			
<350	2(3.6)	1(2.3)	3(3.0)
>350	54(96.4)	43(97.7)	97(97.0)
The predominant cells			
Predominant lymphocytes	54(96.4)	39(88.6)	93(93.0)
Predominant neutrophil	2(3.6)	5(11.4)	7(7.0)
Fluid AFB (culture)			
Positive	10(17.9)	13(29.5)	23(23.0)
Negative	46(82.1)	31(70.5)	77(77.0)
Caseating granuloma			
Yes	41(73.2)	32(72.7)	73(73.0)
No	15(26.8)	12(27.3)	27(27.0)
Non-caseating granuloma			
Yes	12(21.4)	10(22.7)	22(22.0)
No	44(78.6)	34(77.3)	78(78.0)
Pleural biopsy of AFB direct smear			
Yes	5(8.9)	4(9.1)	9(9.0)
No	51(91.1)	40(90.9)	91(91.0)
Pleural biopsy of AFB culture sensitivity			
Yes	29(51.8)	25(56.8)	54(54.0)
No	27(48.2)	19(43.2)	46(46.0)
Pneumothorax as complication			
Yes	8(14.3)	5(11.4)	13(13.0)
No	48(85.7)	39(88.6)	87(87.0)

** $P=0.002$.

tuberculosis (Past history of tuberculosis is absent in 99% of cases, evidence of parenchymal lung lesions are absent in 78% of cases). Right pleural effusion is slightly more common than left (58% compared to 47%). Up to 5% of cases may have bilateral pleural effusion. In total, 30.0% of patients are Anemic at presentation. ESR is elevated in majority of cases (above 40 mm/h in 68%). PPD was significantly higher among younger age group (<35 years) (20.06 ± 5.5 vs. 17.33 ± 4.6,

$P = 0.042$). Pleural biopsies were performed among 83(83.0%) of the cases.

Table 4 shows pleural fluid analysis results. Almost all patients have exudative effusion with fluid protein more than 30 g/l and LDH level more than 350 μm/l 99.0%.

Sputum culture gives a better positive yield than direct smear examination (23.0% compared to 6.0%). While pleural fluid direct smear is negative in all cases, pleural fluid culture for mycobacteria is positive in 23.0%. Predominant lymphocytes were higher among the younger subjects (<35 years) 96.4% vs. 88.6%).

Looking at drug sensitivity of mycobacteria towards anti-TB drugs INH resistance is seen in 6.3% of cases, while Rifampicin resistance is seen in 2.1% of cases.

Fig. 1 shows the histogram of PPD readings and Table 5 shows the trend of active and pleural TB cases during the years 1996–2002. Also, in Table 5, the percentage of pleural TB from active TB is shown.

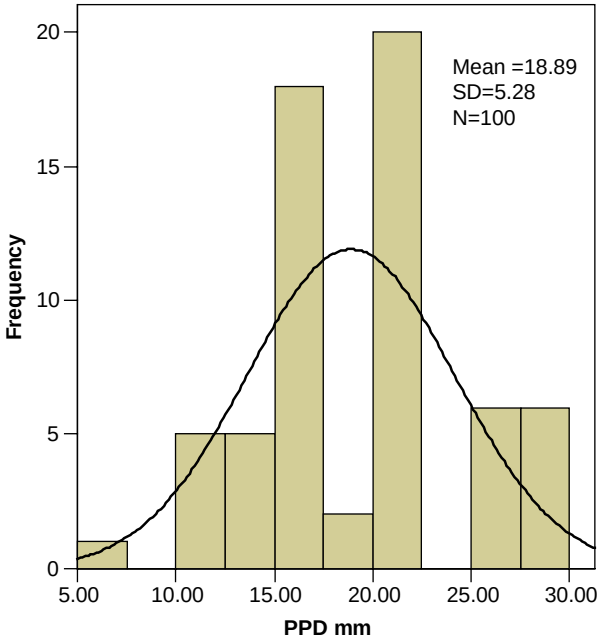

Figure 1 The histogram of PPD readings ($N = 100$).

The diagnosis of pleural tuberculosis is based on clinical findings, chest radiography, PPD testing, and pleural fluid analysis. Pleural biopsy remains the gold-standard for the diagnosis (Table 6). Pleural biopsy was done in our study on the 83(83.0%) cases.

Discussion

Reports from some developed countries documented that pleural tuberculosis is more frequent in older age group suggesting that it may be due to reactivation disease.[4,6,10,11] However, the situation in developing countries is not clear. In our study, we found that the disease is mainly a primary one rather than a reactivation of previous parenchymal lung tuberculosis.

Table 7 shows examples of the situation in some developed and developing countries. In addition we found that pleural tuberculosis tends to affect younger age groups (84% are below the age of 45 years and 56% are below the age of 35 years).

These findings may be explained partly by the reduction in incidence of tuberculosis in developed world.[2] Therefore, with fewer new infections, pleural disease now more commonly accompanies reactivation than primary infection in developed countries.

The mean age in our study was 34.8 years; however, most of the foreigners in the Gulf area are in the working age group, therefore this can be misleading.

The unilateral tuberculous effusion reported in our study confirmed previous findings of right-sided predominance.[6,12]

One recent study from Spain [13] describing pleural tuberculosis in children showed that history of contact with a tuberculous case was positive in

Table 5 Incidence of active and pleural TB cases in Qatar.

Year	Population	Active TB	Pleural TB	Pleural TB (%) from active TB (%)
1996	510070	257	5	1.9
1997	526427	212	22	10.4
1998	543315	253	10	4.0
1999	560746	258	14	5.4
2000	578470	279	31	11.1
2001	595321	281	5	1.8
2002	616138	278	13	4.7

Table 6 Diagnostic yield for pleural tuberculosis.*

Series	No. of cases	Fluid culture positive (%)	Biopsy histology positive (%)	Biopsy culture positive (%)
Sibley (1950)	74	**28**	**NS**	**NS**
Roper (1955)	99	51	**NS**	**NS**
Scharer(1968)	40	23	63**	55
Levine(1970)	21	48	71**	76
Berger(1973)	49	24	69†	65
Epstein(1987)	23	35	56†	39
Antoniskis(1990)	59	77	58†	52
Maartens(1991)	62	47	84†	71
Chan(1991)	83	23	51**	40
Seibert(1991)	70	58	84†	67
Moudgil(1994)	62	54	60**	NS
Batungwanayo(1993)	90	46	52†	50
Relkin(1994)	70	86	80†	66
Kirsch(1997)	30	NS	80†	60
Ibrahim et al. (2004)	100	25.3	83**	54.2

NS = not specified.
*Richard S Morehead; Tuberculosis of the pleura; *Southern Medical Journal;1998; 91; 630–637.*
**Caseating granuloma
†Caseating or non-caseating granulomas &/or positive AFB Smear.

Table 7 Percentage of Primary and Reactivation Pleural TB.

Author	Year	Primary (%)	Reactivation (%)	Country
Antoniskis et al.[7]	1990	54	46	USA
Moudgil et al.[6]	1994	22.5	40.3	UK
Arriero et al.[14]	1998	76	24	Spain
Liam et al.[15]	1999	63.7	36.3	Malaysia
Ibrahim et al. (Present study)	2004	78	22	Qatar

25.7% of patients, however, in our study we found only 9.0% of our patients had such history, indicating that contact with tuberculous cases seems to be less evident in adults.

Sputum direct microscopy for AFB seems to be of no use in diagnosing primary pleural tuberculosis.

Conclusion

We conclude that, in contrast to what has been reported in some developed countries, pleural tuberculosis tends to be a primary disease rather than a reactivation of parenchymal disease, younger age groups are particularly affected. We suggest that further prospective studies are needed to confirm these findings and to find an explanation for the differences particularly in regard to social and nutritional status and pathogenesis of disease.

References

1. Sudre P, Dam GT, Kochi A. Tuberculosis, a global overview of the situation today. *Bull WHO* 1992;**70**:149–59.
2. Richard SM. Tuberculosis of the pleura. *Southern Med J* 1998;**91**:630–7.
3. Mehta J, Dutt A, Harvill L, Mathews KM. Epidemiology of extrapulmonary tuberculosis. *Chest* 1991;**99**:1134–8.
4. Epstein DM, Kline LR, Albelda SM, Miller WT. Tuberculous pleural effusion. *Chest* 1987;**91**:106–9.
5. Aktogu S, Yorgancioglu A, Cirak K, Kose T, Dereli SM. Clinical spectrum of pulmonary and pleural tuberculosis, a report of 5480 cases. *Eur Resp J* 1996;**9**:2031–5.
6. Moudgil H, Sridhar G, Leitch A. Reactivation disease: the commonest form of tuberculous pleural effusion in Edinburgh, 19980–1991. *Resp Med* 1994;**88**:301–4.
7. Antoniskis D, Amin K, Barnes PF. Pleuritis as a manifestation of reactivation tuberculosis. *Am J Med* 1990;**89**(4): 447–50.
8. Chan CH, Arnold M, Chan CY, Mark TW, Hoheisel GB. Clinical and pathological features of tuberculous pleural effusion and its long term consequences. *Respiration* 1991;**58**(3–4): 171–5.

9. Norusis MJ. *SPSS/PC+ for windows: base system and advanced statistics user's guide*. *Release version # 11*. Chicago: SPSS Inc.; 1998.
10. Seibert A, Haynes J, Middleton R, Bass Jr. JB. Tuberculous pleural effusion, twenty years experience. *Chest* 1991;**99**: 883–6.
11. Dutt AK, Mores D, Stead WW. Tuberculous pleural effusion, 6-month therapy with isoniazid and Rifampin. *Am Rev Resp Dis* 1992;**145**:1429–32.
12. Sibley JC. A study of 200 cases of tuberculous pleurisy with effusion. *Am Rev Tuberc* 1950;**62**:314–24.
13. Merino JM, Carpintero I, Alvarez T, Rodrigo J, Sanchez J, Coello JM. Tuberculous pleural effusion in children. *Chest* 1999;**115**:26–30.
14. Arriero JM, et al. Tuberculous pleurisy with or without radiographic evidence of pulmonary disease, is there any difference? *Int J Tuuberc Lung Dis* 1998;**2**(6):513–7.
15. Liam CK, Lim KH, Wong CM. Tuberculous pleurisy as a manifestation of primary and reactivation disease in a region with a high prevalence of tuberculosis. *Int J Tuberc Lung Dis* 1999;**3**(9):816–22.