FREQUENCY OF ACTIVE AND LATENT PULMONARY TUBERCULOSIS IN APPARENTLY HEALTHY ASYMPTOMATIC YOUNG PATIENTS HAVING SUBTLE NON-SPECIFIC X RAY CHEST ABNORMALITIES

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ABSTRACT

Objective: To determine the frequency of active and latent pulmonary tuberculosis in apparently healthy young patients having subtle nonspecific x-ray chest abnormalities picked up during medical fitness for foreign assignment.

Study Design: Cross-sectional study.

Place and Duration of Study: Pulmonology department, Pak Emirates Military Hospital Rawalpindi, from Mar 2018 to Sep 2018.

Methodology: A total of 85 healthy young patients having subtle nonspecific x-ray chest findings and no previous history of tuberculosis treatment or exposure were selected. All these patients underwent qualitative C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and Mantoux testing followed by high-resolution computed tomography (HRCT) chest. An induration >10mm was considered positive test. An erythrocyte sedimentation rate greater than 20mm fall after one hour was considered abnormal. Lastly bronchoscopy with endobronchial washings was carried out in all study participants and samples sent for MTB Gene X-pert, Acid-Fast Bacillus (AFB) stain and Mycobacterial Tuberculosis culture and sensitivity.

Results: Mean age of the participants was 35.81 with SD ± 4.5 (age range 27-54). Most common finding reported on chest x-ray was apical pleural thickening which was observed in 44.7% (38 cases). The most common high-resolution computed tomography scan chest finding was also apical pleural thickening reported in 75.3% (64) of the participants. Microbiological evidence of tuberculosis was found in 9.4% (8/85 cases). Only 5 had abnormal erythrocyte sedimentation rate but none of them were found were positive for tuberculosis. Mantoux was positive in 23 of participants and 17 were labelled to be suffering from latent tuberculosis infection (LTBI). Presence of soft-tissue nodules on high-resolution computed tomography was the only statistically significant finding associated with detection of tuberculosis (p-value <0.05).

Conclusion: The prevalence of active and latent tuberculosis infection in healthy asymptomatic patients having subtle x-ray abnormalities is quite high.

Keywords: Apical pleural thickening, Blunt costophrenic angle, Diaphragmatic tenting, Endobronchial washings, Military personnel, MTB GeneXpert, Mantoux test.

INTRODUCTION

Tuberculosis (TB) is a global health problem, a leading cause of death after HIV among infectious diseases. In 2014, an estimated 9.6 million people suffered from TB whereas 1.5 million died from the disease[1]. It is shown that 80% of current TB cases are residing in 22 high burden countries. Among 22 countries, Pakistan ranked 5th in terms of absolute numbers of TB cases where incidence rate is estimated to be 231/100,000 and prevalence rate 364/100,000 population[2] respectively. Nevertheless, this is not the true representation of disease burden as many cases are not reported to National TB Control Program in Pakistan. It is estimated in a recent study that 27% cases of TB are not reported at all[3]. A more detailed study later on found out that, the prevalence of smear positive and culture positive TB in Pakistan was respectively 270.3 (95% CI 217.3–323.3) and 397.9 (95% CI 333.2–462.6) per 100,000 population[4]. The population carrying a latent TB infection (LTBI) is commonly quoted as

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"one-third" of the global population, a reservoir of approximately 2.3 billion individual[5]. However, recently a worldwide survey estimated its prevalence to be just under a quarter of the global population i.e 1.5 billion which is 23% of world population[6]. X-ray chest is one of most important screening test for pulmonary Tuber-culosis. Recently chest x-ray has been promoted as a useful tool that can be placed early in screening and triaging because of numerous national TB prevalence surveys have demonstrated that CXR is the most sensitive screening tool for pulmonary TB[7]. An abnormal CXR is always an indication for full diagnostic evaluation[8]. CXR can also identify populations at highest risk of developing TB disease: those who have inactive TB or fibrotic lesions without a history of TB treatment. Therefore, once active TB has been excluded, patients with fibrotic lesions should be followed-up, given their high risk for developing active disease[9]. Every year hundreds of healthy soldiers are sent on foreign assignments after beings declared fit in pre departure medical examination. As per fitness guidelines, even a subtle abnormality on CXR is enough to render an individual unfit although many abnormalities seen on a CXR turn out to be artefacts or benign problems. Pakistanis seeking employment in Gulf countries and Saudi Arabia have to undertake a prerequisite medical examination at any of the accredited medical clinics in Pakistan. Similar type of examination is conducted for intending immigrants to UK, USA, Canada, Australia, and New Zealand. During the medical examinations, every candidate is in routine subjected to CXR in accordance with the laid down criteria, even if no other medical indication exists. The purpose of this study was to find out TB either active or latent tuberculosis infection (LTBI) in candidates only having very nonspecific subtle CXR abnormalities not having predilection for any chest disease. Certain abnormalities on CXR like upper lobe infiltrates or consolidation, cavity formation, a round density in lung parenchyma, pleural effusion and bilateral hilar lymphadenopathy are highly suggestive of active TB[10] hence, declared unfit and excluded from our study. Similarly the discrete nodules and fibrotic scars being marker of inactive or healed TB were also not selected and excluded from study. Subtle abnormalities like apical pleural thickening (capping), diaphragmatic tenting, blunting of costophrenic angles (CP angles) and calcified nodules are usually not suggestive of active tuberculous[10] but can be found in LTBI. Therefore apparently healthy soldiers demonstrating such subtle x-ray findings were selected to further find out smear/culture positive active TB as well as LTBI. As a first step of evaluation erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were checked and for study purpose a value of ESR >20mm fall after one hour was considered abnormal. This value was selected in accordance with age by a universally accepted formula[11]. Later on, Tuberculin skin testing (TST) (Mantoux) was carried out and a value of induration >10mm was considered positive. A TST >10mm is considered 90% sensitive to pick LTBI. High-resolution computed tomography (HRCT) chest was carried out to find the affected bronchopulmonary segment from which endobronchial washings for further testing were taken. No study on subtle x-ray chest abnormality has been carried out in Pakistan yet and our study may be the pioneer one in this regard.

METHODOLOGY

Study was carried out in Pulmonology department, Pak Emirates Military Hospital Rawalpindi, from April 2018 to September 2018. Permission from hospital ethical committee was sought first. A written informed consent was taken from all participants. Sample size was calculated by using WHO Sample Size Calculator and making following entries; Confidence level-95%, anticipated Population Proportion –5.8% (p=0.058), Absolute Precision Required –5% (D=0.05). Sample size came to be 83. Therefore a total of 85 healthy young personnel referred for medical fitness having subtle nonspecific x-ray chest findings and no previous history of tuberculosis treatment or exposure were selected by non-probability consecutive sampling from

April 2018 to September 2018. Nonspecific subtle findings included Apical capping (thickening), Diaphragmatic tenting (Juxtaphrenic peak sign), Blunting of costophrenic angle and Solitary calcified nodules or granuloma with in lung, hila or mediastinum. All these soldiers underwent qualitative CRP and ESR testing. CRP was measured byBionic kit and levels more than 6 mg/L was considered positive. Similarly an ESR greater than "20 mm fall after one hour" was considered abnormal. Mantoux testing (TST) was also carried out followed by HRCT chest. For Mantoux testing, 0.1ml (5 Tuberculin units) of tuberculin material was injected intradermally on inner surface of forearm and after 72 hours the transverse diameter of induration (not erythema) was recorded in millimeters. An induration >10 mm was considered positive test. After mapping out the affected bronchopulmonary segment on HRCT chest, bronchoscopy with endobronchial washings were carried out from all study partici-pants and samples sent for MTB GeneXpert, acid-fast bacillus (AFB) stain and Mycobacterial TB culture and sensitivity. Active pulmonary tuberculosis was defined as a person who is found positive for any one of the following tests; MTB GeneXpert, AFB stain, MTB culture carried out on bronchial washings. Latent Tuberculosis infection (LTBI) was defined as a person having subtle x-ray abnormalities and positive Mantoux test. The remaining subjects in whom there were only subtle x-ray chest abnor-malities and all tests were negative were consi-dered healthy and fit. Finally, the variables were defined qualitatively and quantitatively and frequencies, percentages, means and standard deviations were calculated. All the data were analyzed using SPSS-23. Chi-square/ Fischer exact test was done for cateogorical data and percentages comparison and *p*-value ≤0.05 was considered significant.

RESULTS

A total of 85 participants were included in the study. Mean age of the participants was 35.81 years with SD ± 4.5 (age range 27-54 years). Nine (11%) had history of smoking. Most common finding repor-ted on chest x-ray was apical pleural thickening which was observed in 38 (44.7%). Other chest x-ray findings included calcified nodules or lymph nodes 21 (24.7%), CP angle blunting 17 (20.0%), reticulonodular opacities 13 (15.3%) and tenting of hemi-diaphragm in 10 (11.8%). Calcified nodules were most commonly seen in right upper zone of lung. All calcified nodules were smaller than 10mm. Reticulostriate opacities/shadows were most commonly seen in Right upper zone 61.5% (8/13) and left upper zone 23.1% (3/13).

The most common HRCT scan chest finding was also apical pleural thickening, reported in 64 (75.3%) of the participants, followed by the presence of fibrotic or atelectatic pleuroparen-

Table: Comparison of HRCT scans chest findings in cases with microbiological evidence of tuberculosis and no evidence of tuberculosis.

HRCT Findings	Tuberculosis Detected	No Tuberculosis	*p*-value
Total	8 (9.40%)	77 (90.6%)	
Apical Thickening	6 (75.0%)	57(74.0%)	1.00
Fibrotic bands	4 (50.0%)	45 (58.4%)	0.717
Sub-centimeter lymph nodes	7 (87.50%)	41 (53.20%)	0.13
Calcified nodules	-	19 (24.70%)	0.19
Bronchiectasis	3 (37.50%)	14 (18.20%)	0.34
Soft tissue nodules	6 (75.0%)	8 (10.40%)	0.0001
Ground-glass consolidation	2 (25.0%)	4 (5.20%)	0.096
Tree-in-bud appearance	2 (25.0%)	4 (5.20%)	0.96
Sub-pleural/Parenchymal cyst	2 (25.0%)	3 (3.90%)	0.68
Prominent lymph nodes	1 (12.5%)	3 (3.9%)	0.33
Bronchoceles	1 (12.50%)	2 (2.60%)	0.25

chymal bands in 49 (57.6%) of cases. These were most commonly seen in right apical and/or apicoposterior segments in right upper lobe (RUL) and medial segment of right middle lobe (RML), whereas in left lung they were commonly seen in apicoposterior segments and inferior lingular segments of left upper lobe (LUL). Calcified nodules and granulomas were seen mostly in apical and anterior segments of RUL. Although sub centimeter mediastinal/hilar lymph node enlargement/lymphadenopathy was seen in 48 (56.5%), only 4 (4.7%) had prominent i.e. more than 1 cm enlarged lymph nodes.

All patients had normal bronchoscopy i.e no structural abnormalities such as endobronchial lesions were reported. Microbiological evidence of tuberculosis was found in 9.4% (8/85 cases). In 3.5% (3/85) cases endobronchial washings AFB smear was positive, 5 (5.8%) had positive GeneXpert, 6 (7.05%) cases had Mycobacterium tuberculosis cultures positive and 2 (2.3%) had Non-Tuberculous Mycobacteria growth on MGIT cultures. Mantoux testing was positive in 27.05% (23/85) of participants and 26.08% (6/23) among them were detected with Tuberculosis whereas remaining were labelled to be suffering from LTBI. Out of 8 TB positive cases Mantoux testing was negative in 37.5% (2/8) and positive in 62.5% (6/8). Mantoux testing was found positive in 22% (17/77) AFB/ culture/MTB Gene Xpert negative cases hence labelled LTBI. All participants had negative CRP levels. Only 5 (5.8%) had abnormal ESR but none of them were found positive for TB. Mean ESR levels were 9.96 SD ± 4.08. HRCT findings more commonly seen in patients with tuberculosis were soft tissue nodules, Tree-in-Bud appearance, Sub centimetric lymph nodes, Ground glass haze and Bronchiectasis. Presence of soft-tissue nodules was the only statistically significant finding on HRCT associated with detection of tuberculosis (p-value <0.001), However, 4 cases with the classic tree- in- bud appearance on HRCT scan did not show any microbiological evidence of tuberculosis. Similarly, calcified nodules and apical pleural thickness were also not associated with Tuberculosis. Findings summarized in table-I.

DISCUSSION

Although apical thickening is considered more common in older ages[11-13], we did not find any significant association between apical thickening or diagnosis of tuberculosis with age in our study. Considering the stringent criteria for fitness, disclosure of TB contact was possibly with held by some participants. Calcified granulomas in 26% of subjects, were the most commonly seen abnormality in a screening study done in Pakistan, blunting of CP angle was seen in 23% and Apical thickening in 12.72% cases[14], in another study[15] calcified granulomas, lymph nodes, or both; were also the most common finding with 92/152 (57.9%) cases, and 25 (15.7%) cases of apical pleural thickening; 16 (10%) of fibrous scarring; and 31 (19.5%) cases of noncalcified nodules. In contrast, Apical pleural thickening was the most common chest-xray finding in our study. Some 7.3% asymptomatic military members had signs of previous PTB in form of either fibro cavitary changes, granulomas, calcified lymph nodes or a combination of these on their chest x-rays in a study done in South Africa[16].

Findings of HRCT scan in AFB/culture positive TB in our study were consistent with various international studies[17,18], in literature. CT scan is more sensitive than chest x-ray in detection of subtle and localized disease[19]. In a study done by Drusty *et al* in India[18] calcified nodules were not found in any case with tuberculosis whereas they were seen in 21.4% of disease negative cases which is in agreement with absence of calcified nodules in TB cases in our study, soft tissue nodules were the most common finding[18], however the tree-in-bud appearance was relatively more common in these studies although it is a sensitive finding but it is not specific[19].

In a study done by Moosavi *et al*[20], in Iran, the prevalence of active tuberculosis in patients with fibrotic changes in CT scan was 15% (6/40)

as compared to 9.4% of our study, the differences exist due to different study populations and radiographic protocols/techniques. In a mass radiographic screening program in military recruits in Taiwan[21], minimal apical or subapical lesions were detected in 120/237 (51%) patients with abnormal radiographs, Only one of these patients had a sputum culture positive for M. Tuberculosis and none were sputum smear-positive for AFB, in our study 2/30 with isolated apical thickening on chest x-ray were diagnosed with tuberculosis, however none of the cases with isolated apical thickening on HRCT scan i.e. in absence of fibrotic bands/ bronchiectasis /nodules tested positive for tuberculosis. Upto 6% cases of PTB in one study had normal chest x-rays[22].

Various studies recommend against the use of chest x-ray as a pre-employment screening tool citing cost-effectiveness,radiation, low-resources, low-yield and false positive results[14,23,24], whereas some studies[16,20,25], such as one by Mor *et al*, recommend chest x-ray as a beneficial tool in detection of old healed tb cases which are at higher risk of developing active PTB[25].

Mantoux testing was positive in 27% of studied population (23/85) out of which 6 were found AFB/culture/MTB GeneXpert positive TB cases (26%) and 17/77 (22%) had LTBI. A study on UK immigrants mainly coming from subcontinent including Pakistan found that prevalence of LTBI was 20% but in contrary to our study, the method used was interferon Gamma assay. Prevalence of LTBI in our study was also compatible with a large study which estimated the global burden of LTBI6. Although CRP has been proposed as a candidate biomarker for active infection with Mycobacterium Tuberculosis, in our study inflammatory markers like ESR and CRP were unable to differentiate between healthy and infected population. One of the reasons could be the fact that qualitative CRP is less sensitive, to pick early inflammation as do in our study population. Secondly, our study population did not include individuals with typical X ray findings of TB. Nevertheless more studies are required to confirm this finding.

A chest x-ray in our setup costs around 6 dollars (600 rupees), together with the cost of HRCT scan, bronchoscopy and microbiological testing of Bronchial washings, the total cost of finding one case of active tuberculosis in this study was 250 dollars (25,000 Pakistani Rupees). Lastly there were few limitations of our study. Our study was exclusive for male young and apparently healthy individuals; hence results can't be applied to general population. Radiologists were not selected or blinded for reporting of radiographs hence the reports were subject to interobserver variability due to differences in experience and interpretation of radiologist, uniform protocols for chest x-ray and CT scan were also not pre-defined, only those referred to Pulmonology department were part of the study, resulting in a smaller sample size. We only measured qualitative CRP which is less informative and a quantitative estimation might help differentiating tuberculous from non-tuberculous infections as well as extent of infection.

CONCLUSION

The prevalence of active and latent tuberculosis infection in healthy asymptomatic patients having subtle x-ray abnormalities is quite high.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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