

Predictors of pulmonary involvement in patients with extra-pulmonary tuberculosis

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ABSTRACT

Objectives: The aim of this study is to assess the value of chest radiographs (CXRs) and sputum examinations in detecting pulmonary involvement of tuberculosis (TB) in patients with extra-pulmonary tuberculosis (EPTB). **Materials and Methods:** A retrospective analysis was performed among 248 EPTB patients with culture-proven diagnosis of tuberculosis seen between January 2001 and December 2007 at a tertiary teaching hospital, Riyadh, Saudi Arabia. Demographics, clinical, laboratory and radiological findings were reviewed and assessed. This study was approved by the hospital ethics and research committee. **Results:** One hundred twenty five of 233 EPTB patients (53.6%) had abnormal CXR findings. There was a significant difference in the occurrence of positive sputum culture results between patients with abnormal CXR findings (30/57) and those with normal CXR findings (4/17) ($P = 0.04$). Of 17 HIV-negative/unknown HIV-status EPTB patients with normal CXR results, 4 patients (23.5%) had positive sputum culture results. Intrathoracic lymphadenopathy ($P < 0.001$), pleural TB ($P < 0.001$) and disseminated TB ($P = 0.004$) were associated with an increased risk of abnormal CXR findings. Patients with cough (52.9%), weight loss (41.2%) and night sweats (26.5%) are more likely to have positive sputum culture results. **Conclusion:** CXR findings are predictive of positive sputum culture results. However, the rate of normal CXR among EPTB patients with positive sputum culture results was relatively high. Therefore, respiratory specimen cultures should be obtained in TB suspects with a normal CXR to identify potentially infectious cases of TB.

Key Words: Predictors, pulmonary, extra-pulmonary tuberculosis, radiology, chest radiographs

INTRODUCTION

Tuberculosis (TB) is a major cause of human mortality and morbidity, affecting almost one third of the world's population.^[1] Mycobacterial infections have been shown to be increasing in number worldwide, mainly due to a global increase in developing countries, the increased number of patients with HIV infection, an increasing number of elderly patients and the emergence of multi-drug resistant tuberculosis. Extra-pulmonary tuberculosis mainly results from reactivation of a tuberculosis focus after haematogenous dissemination or lymphogenous

spread from a primary, usually pulmonary focus. In low income countries with a high TB burden, sputum culture for mycobacteria is not routinely available.^[2] Therefore, active TB is usually excluded by clinical symptoms, sputum smear, and response to empiric antimicrobials treatment.^[3,4] Whereas smear-positive tuberculosis is considered infectious, patients with smear-negative but culture-positive pulmonary disease and those with non-pulmonary disease are considered to be non-infectious. However, previous reports and genotypic molecular studies have shown that patients with smear-negative pulmonary TB could transmit TB to others.^[5-7] The infectiousness of patients with extra-pulmonary tuberculosis (EPTB) has previously been reported.^[5] In the PTB suspect with negative sputum smears, the diagnosis is usually dependent on chest radiograph appearances. Although, chest radiograph (CXR) is commonly requested for patients with EPTB, sputum examinations are usually limited to those with abnormal radiographic or clinical findings suggestive of pulmonary TB. Many reports have studied the yield of sputum examination and CXR in patients with PTB. However,

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the value of sputum examinations and CXRs in detecting pulmonary involvement in EPTB patients has not been studied in detail. The aim of this study was to determine the usefulness of CXR, sputum examinations and clinical predictors of pulmonary involvement in patients with EPTB.

MATERIALS AND METHODS

Data collection

A retrospective study was conducted among 248 patients with EPTB who attended King Khalid University Hospital (KKUH), between January 2001 and December 2007. Our hospital is a tertiary care teaching hospital serving the region of Riyadh, the capital city of Saudi Arabia. The total population served by the hospital is about 1.5 million inhabitants. The definition of EPTB disease follows the international classification.^[8] EPTB is defined as TB of organs other than the lungs, such as pleura, lymph nodes, abdomen, genito-urinary tract, skin, joints, bones, tubercular meningitis, tuberculoma of the brain, etc. In this study all EPTB patients with culture positive for *M. tuberculosis* reported from the microbiology laboratory were included. The results were collected from the computerized database maintained by the microbiology laboratory and Division of TB control. In all patients the demographic and clinical characteristics including age, sex, place of birth, HIV status, physical examination, symptoms on presentation (fever, cough, sputum production, hemoptysis, shortness of breath, chest pain, malaise and night sweats), medical conditions (diabetes mellitus, renal failure, hemodialysis, chronic liver disease, malignancy, and chronic obstructive pulmonary disease [COPD]) were obtained by medical record review.

CXRs and sputum examinations

The first CXR obtained in the TB evaluation was used for the analysis. All CXRs were reviewed by a radiologist as part of routine clinical care along with written reports. The criteria used to define a normal CXR included any of the following written reports: normal, no evidence of active lung disease, no evidence of TB. The criteria for an abnormal CXR included reports of hilar adenopathy, mediastinal lymphadenopathy, calcified hilar lymph nodes, pleural effusion, apical scarring, pericardial effusion, old healed TB, interstitial densities, para tracheal density or scarring. Sputum smears and cultures were performed by the mycobacteriology laboratory at KKUH. Sputum collection usually follows the policy at KKUH. Three consecutive early morning sputum samples were obtained from TB suspect patients. One sputum induction is usually attempted in patients who did not spontaneously produce sputum. All sputum samples were examined by auramine-rhodamine and Ziehl-Neelsen staining for acid-fast bacilli.

Smears were read quantitatively under a fluorescent microscope, and the results were reported according to the American Thoracic Society guidelines.^[9] A new sputum smear-positive is a positive ZN stained smear of well collected sputum sample from a TB suspect who has been seen for the first time. Solid media (Lowenstein-Jensen) and Bactec Middlebrook 7H12 liquid media (BD Diagnostics, Sparks, MD, USA) were used for cultures.

Statistical analysis

Categorical variables were compared using the χ^2 and the Fisher's exact tests. The *P* values were determined using two tailed analysis. A value of <0.05 was considered to be statistically significant. Analysis of symptoms and sputum culture results associated with normal and abnormal CXR appearance was performed using a software package (SPSS).

RESULTS

During a 7-year study period, 248 EPTB patients with culture positive *M. tuberculosis* were diagnosed at KKUH. The male to female ratio was 0.94 (120/128). The mean age was 43.5 years (range, 1 to 101 years). The majority of patients (89.5%) were from the Middle East region, mostly Saudi patients (83.5%). Nearly 5.3% of the patients were Indonesian and Filipino, 4% were Asians and 1.2% were Africans. HIV serology results were available for 107 patients (43.2%); 2 of 107 patients (1.8%) were HIV positive. Both were middle aged male patients with extrapulmonary disease (abdominal TB). Among the two HIV-infected patients, one patient presented to treatment due to symptoms of cough, fever, weight loss and abdominal distention. He had a positive culture result from a bone-marrow aspirate specimen, but not from any other specimens, which permitted diagnosis and susceptibility testing. His CXR showed military TB. The other HIV-infected patient had pancreatic abscess and demonstrated pleural thickening on CXR. His sputum smear and culture results were positive for TB. The most common EPTB site was the Lymph nodes (105 patients; 42.3%). Seventy six of 105 lymphadenitis cases were extra thoracic.

Two hundred and thirty three patients had a CXR at the time of diagnosis that was interpreted by both the radiologist and the TB consultant. The CXR was obtained within 1 month after the diagnosis of EPTB for all patients. One-hundred and twenty five (53.6%) had abnormal CXR findings. The most common CXR findings were pleural effusion and intra thoracic lymphadenopathy. Patients having intra thoracic lymphadenopathy, pleural TB and disseminated TB are more likely to have abnormal CXR findings (*P* < 0.05). On the other hand, patients with extra thoracic TB, bone and joint TB and cold abscesses are more likely to have normal

CXR findings ($P < 0.05$) [Table 1]. Of the 233 patients for which CXRs were obtained, sputum smear and culture results were available for 74 patients. Of those, nine patients (12.1%) had sputum smears that were positive for TB, and 35 patients (47.3%) had sputum cultures that were positive for TB [Table 2]. The proportion of sputum-culture positive patients with abnormal CXR findings is higher than that for patients with normal CXR findings, the difference was statistically significant (30 of 57 patients (52.6%) vs. 4 of 17 patients (23.5%), respectively; $P = 0.04$ [Figure 1].

The association between sputum culture for *Mycobacterium tuberculosis* and clinical symptoms is shown in Table 3. Patients reporting cough (52.9%), weight loss (41.2) and night sweats (26.3) were more likely to have a positive sputum culture results compared with patients having negative sputum culture. However, the difference between the two groups was not statistically significant.

DISCUSSION

Screening of EPTB patients for pulmonary involvement usually based on clinical symptoms, sputum examination and radiographic findings. This study describes the chest

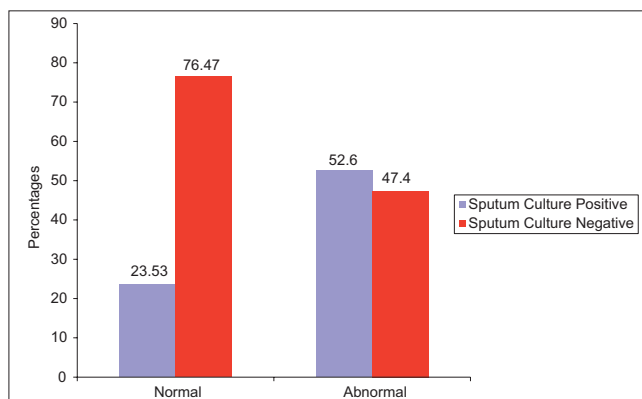


Figure 1: The proportion of sputum culture and chest radiographs findings for 74 patients with extra-pulmonary tuberculosis

Table 1: Chest radiographic findings among 233 extra-pulmonary tuberculosis patients

Site of the infection (N = 248)	Chest radiographs (N = 233)		P value
	Normal (N = 108)	Abnormal (N = 125)	
Lymph nodes (N = 105)			
Extra-thoracic (76)	49 (45.4)	19 (15.2)	<0.001
Intra-thoracic (29)	0 (0.0)	28 (22.4)	<0.001
Pleura (N = 30)	0 (0.0)	29 (23.2)	<0.001
Abdominal (N = 33)	13 (12.0)	17 (13.6)	0.72
Bone and joint (N = 40)	25 (23.1)	15 (12.0)	0.02
Disseminated (N = 10)	0 (0.0)	9 (7.2)	0.004
Abscess (N = 13)	12 (11.1)	1 (0.01)	0.001
CNS (N = 8)	5 (4.6)	2 (1.6)	0.25
Genitourinary (N = 4)	3 (2.8)	1 (0.01)	0.34
Renal (N = 4)	1 (0.01)	3 (2.4)	0.63
Skin (N = 1)	0 (0.0)	1 (0.01)	1.0

CNS = central nervous system

Table 2: Sputum examinations and chest radiographic appearances of 74 extra-pulmonary tuberculosis patients based on the site of infection

Site of infection	Sputum culture-positive (N = 35)*		Sputum culture-negative (N = 42)**	
	Normal CXR (N = 4)	Abnormal CXR (N = 30)	Normal CXR (N = 13)	Abnormal CXR (N = 27)
Lymph nodes (N = 30)				
Extra-thoracic	3	1	7	7
Intra-thoracic	-	7	-	5
Pleura (N = 18)	-	9	-	9
Abdominal (N = 8)	-	4	1	3
Bone and joint (N = 7)	1	4	2	-
Disseminated (N = 4)	-	4	-	-
CNS (N = 2)	-	-	1	1
Abscess (N = 2)	-	-	1	1
Renal (N = 2)	-	1	-	1
GU (N = 1)	-	-	1	-

CXR = chest x-ray, CNS = central nervous system, GU = genitourinary system * = CXR was not done for one patient; ** = CXR was not done for two patients

Table 3: The association between sputum culture for *Mycobacterium tuberculosis*, chest radiographic findings and clinical symptoms

Symptoms	Culture negative	Culture positive	P value
	(N = 40) (54.1%)	(N = 34) (45.9%)	
Respiratory symptoms			
Cough	(14) 35%	(18) 52.9%	0.12
Shortness of breath	(13) 32.5%	(8) 23.5%	0.39
Chest pain	(11) 27.5%	(9) 26.5%	0.92
Constitutional symptoms			
Fever	(17) 42.5%	(16) 47.1%	0.69
Weakness/malaise	(2) 5%	(2) 5.9%	1.0
Weight loss	(11) 27.5%	(14) 41.2%	0.22
Night sweat	(4) 10%	(9) 26.5%	0.10

radiographic findings and sputum examinations of 74 EPTB patients. The main objective was to assess the value of CXRs and sputum examinations for identification of EPTB patients with pulmonary involvement who could be potentially infectious. Clinical predictors of culture positive sputum among EPTB patients were also evaluated.

In contrast to other studies (10), our results suggest that CXR is predictive of EPTB patients with pulmonary involvement. However, an important finding in this study was the high rate (23.5%) of normal CXR among patients with culture confirmed PTB.^[10,11] Interestingly, this rate was among non-HIV infected individuals with culture-positive TB. These results suggest that although CXR is predictive of positive sputum culture, it might not detect all EPTB patients with pulmonary involvement and highlight the importance of obtaining respiratory specimen cultures in the evaluation of persons with suspected TB, even those with normal CXRs. A recent observational cohort study^[10] has reported that of 601 respiratory culture-positive TB cases, 53 (9%) had normal CXRs. Twenty-two percent of them were HIV-infected patients. In another study^[11] conducted among patients with solely EPTB, the rate of normal CXR with positive-sputum culture was (19%). Although it appears that HIV infection may be a significant factor contributing to the incidence of pulmonary TB with a normal CXR, our study findings suggest that other factors may exist.

The reliability of CXRs in the diagnosis of TB is questionable.^[12,13] However, in the presence of cavities, the sensitivity and specificity of CXR becomes higher.^[12] The performance of CXR expressed as sensitivity and specificity in the diagnosis of culture positive TB cases is influenced by many factors. Abnormal, particularly apical radiographic abnormalities associated with TB are more expected in patients without underlying immunosuppression including HIV-infected patients and patients with renal disease.^[10,14-16] The interpretation of CXRs by radiologist is another

important factor. The radiologist usually has little or no information about the patient and may have the tendency to under-read or over-read the chest radiographs. In one study using radiography found that 20% of the cases of active TB were reported as normal.^[17] Moreover, quality control in the interpretation of CXR is hardly practiced. In a large study^[12] conducted in Nairobi, Kenya involving 998 patients, the specificity of CXR was low (67%). The number of patients labeled as having TB using CXR with a negative culture that were placed treatment was high (22%) among all TB suspects.

In our study we found that 9 of 74 EPTB patients (12.1%) had sputum smears that were positive for acid-fast bacilli. This rate is relatively higher than previous report.^[11] Although it is assumed that smear-negative TB patients are not infectious, the transmission of TB from smear-negative, culture-positive patients has been documented in many studies.^[8,17-19] In one molecular epidemiological study among 1574 patients with pulmonary tuberculosis in San Francisco, patients with smear-negative culture-positive tuberculosis were responsible for 17% of tuberculosis transmission. In another similar study done by Hernandez-Garduo,^[5] patients with extra-pulmonary disease were included and represent 27% of the clustered cases in the Greater Vancouver regional district. Higher estimates of transmission were found when patients with EPTB alone were included (25-41%) than in patients with pulmonary disease suggesting the infective potential of patients with EPTB. In a recent molecular study done by Tostmann A^[20] including both pulmonary and extra-pulmonary TB cases, 13% of the secondary cases were attributable to transmission from patients with smear-negative TB.

Pulmonary tuberculosis patients including those having normal chest radiograph are usually symptomatic with cough/sputum being reported most commonly.^[13,20] In other series weight loss was found as a strong predictor of pulmonary and extra-pulmonary TB.^[10,12] In a recent study done by Wang, *et al*, weight loss and fever were significantly

found to be predictive of smear-positive TB patients^[21] In our study, although not statistically significant, night sweat, cough and weight loss were predictive clinical factors for positive sputum culture results in EPTB patients. Our findings suggest that sputum for *M. tuberculosis* smear and culture should be obtained in those patients to enable prompt recognition of EPTB patients with pulmonary involvement.

In conclusion, in this studied population of patients, CXR results are predictive of positive sputum culture results. However, it is important to obtain respiratory specimen culture in the diagnosis of EPTB patients particularly in the presence of a relatively high rate of positive sputum culture and normal CXR findings. This may improve detection rates and lead to improved patients outcomes and reduced transmission of *M. tuberculosis*.

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