

# Pulmonary involvement in patients presenting with extra-pulmonary tuberculosis: thinking beyond a normal chest x-ray

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## ABSTRACT

**INTRODUCTION:** Recognition of pulmonary involvement in extra-pulmonary tuberculosis (TB) may be an important public health issue, as smear-negative pulmonary TB is responsible for about 17% of new infections. Pulmonary TB can be present despite a normal chest x-ray (CXR), even in human immunodeficiency virus (HIV)–negative patients. In this retrospective clinical audit, we reviewed a case series of HIV-negative patients with extra-pulmonary tuberculosis to identify the proportion with concurrent pulmonary TB despite an unremarkable CXR.

**METHODS:** Clinical notes, microbiology results and CXR reports were reviewed from consecutive patients treated at Auckland City Hospital for extra-pulmonary TB from January 2007 to July 2010.

**RESULTS:** Of the sample of 103 patients with extra-pulmonary TB, the majority of patients were born in an Asian country (n=70; 68%). The commonest presentation of extra-pulmonary TB was lymphadenopathy (n=51; 50%), followed by pleural (n=24; 23%) and bone (n=6; 6%) disease. Extra-pulmonary TB was diagnosed by biopsy or excision of the extra-pulmonary site in the majority (n=74; 72%), and by sputum testing alone in 26 (25%). The majority had CXR abnormalities (n=76; 74%). In the group with a normal CXR (n=27), 55% (n=15) had sputum cultures performed. In total, 18% (n=5) of patients with extra-pulmonary TB and a normal CXR had pulmonary TB, of whom two were smear positive.

**DISCUSSION:** In patients with extra-pulmonary TB, sputum testing should be considered to detect concurrent pulmonary TB even if a CXR is normal, especially in immunosuppressed or symptomatic patients. This may aid diagnosis and determine infectivity and consequent public health action.

**KEYWORDS:** Chest x-ray; sputum; tuberculosis; tuberculosis, pulmonary

## Introduction

Extra-pulmonary tuberculosis is defined as tuberculosis (TB) occurring outside the lung parenchyma. This includes pleural, lymph node (LN), skeletal, abdominal, miliary TB, TB meningitis, and other rare forms of TB such as laryngeal, skin, and TB involving endocrine organs.<sup>1</sup>

In New Zealand from 2002 to 2007, extra-pulmonary TB was diagnosed in 33% of all patients with TB; 5% had coexisting pulmonary involvement.<sup>1</sup> The globally reported prevalence of

extra-pulmonary TB ranges from 17% to 52%,<sup>1–4</sup> with concurrent pulmonary involvement reported in up to 14%.<sup>2</sup>

Recognition of pulmonary involvement in patients presenting with an obvious extra-pulmonary source of TB is an important public health issue. While TB transmission occurs mainly from patients with smear-positive pulmonary TB, smear-negative patients are reported to have been responsible for about 17% of new infections.<sup>5,6</sup> Contact tracing is carried out only if the patient has confirmed pulmonary involvement and the 'urgency' pertaining to contact tracing and the

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need for respiratory isolation differs according to the 'infectivity' of the patient.<sup>7,8</sup>

It is standard practice at Auckland City Hospital to obtain a chest radiograph (CXR) during initial consultation for all patients with extra-pulmonary TB, with sputum examinations being discretionary in those without abnormal radiographic findings suggestive of pulmonary TB.<sup>1</sup>

The reported incidence of pulmonary TB in the presence of an unremarkable CXR was 22% to 32%<sup>9,10</sup> in the HIV-positive patient group, while the reported incidence in the HIV-negative group was 5%.<sup>10</sup>

Extra-pulmonary TB with concomitant pulmonary involvement, despite a normal CXR, was documented in 8% to 23% of the HIV-negative patients.<sup>11,12</sup>

The World Health Organization (WHO) guidelines on the treatment of extra-pulmonary TB recommend obtaining a sample for culture from the extra-pulmonary site and suggest examination of a CXR and sputum cultures to identify patients with simultaneous pulmonary involvement.<sup>13</sup>

The aim of this audit was to review a case series of HIV-negative patients with extra-pulmonary TB to identify the proportion with concurrent pulmonary TB, despite an unremarkable CXR.

## Methods

This is a retrospective clinical audit performed at the Auckland City Hospital (Auckland District Health Board [ADHB] facility), New Zealand. Ethics approval was obtained from The Northern Regional Ethics Committee (NTX/10/EXP175).

The Tuberculosis Service at ADHB is a dedicated tertiary referral centre for management of HIV-negative patients with TB.

The Tuberculosis Service maintains a separate record of all patients referred with clinical signs and symptoms consistent with extra-pulmonary TB by the referring doctor, who are treated at ADHB. Consecutive patient records from January 2007 to July 2010 were reviewed to collect data

in relation to demographics, clinical symptoms, CXR reports, and microbiology results. At the time of presentation, patients were not known to have pulmonary involvement.

At the initial consultation with the ADHB Tuberculosis Service, a respiratory physician assesses each new patient with extra-pulmonary TB with a CXR and makes a decision regarding sputum testing and further investigations. An abnormal CXR is defined as any detectable abnormality in the CXR, including parenchymal changes, cavitation, miliary pattern, effusions, mediastinal adenopathy, scarring or nodules indicative of pulmonary TB.<sup>1,14,15</sup> A radiologist at ADHB independently reports all CXRs. For the purposes of this audit, the final decision regarding the CXR was taken as the radiologist's report.

Extra-pulmonary TB was considered to be any form of TB occurring outside the lung parenchyma. If a sputum culture is positive, the patient is considered to have concurrent pulmonary involvement. Pulmonary TB is defined as TB of lung parenchyma alone.<sup>1</sup>

Acid Fast Bacilli (AFB) smear and culture are two separate tests performed together. Smear positivity indicates a sample that displays (AFB) with the Ziehl-Neelsen stain. A positive smear is graded from 4+ (>9/field AFB observed at 1000 magnification), indicative of high infectivity, to 1+ (1–9/100 fields AFB observed at 1000 magnification), indicative of lesser infectivity.<sup>16</sup> An AFB culture is incubated for up to six weeks to detect growth.

Data was analysed using the SAS version 9.1 statistical analysis software package.

## Results

The total sample size was 103 patients. The mean age was 41 years (range 16–98 years), with 53% (n=55) female patients. By country of birth, the majority of patients were Asian (n=70; 68%), followed by New Zealanders (16%) and Pacific Islanders (13%). All patients had a negative HIV test.

The commonest presentation with extra-pulmonary TB was in lymph nodes (LN; n=51; 50%),

Table 1. Characteristics of patients found to have coexisting pulmonary tuberculosis despite a normal chest x-ray (n=5)

Patients	Site of extra-pulmonary TB	Age/Sex	Country of birth	Sample used to diagnose TB	Method of sputum sampling	Reasons for testing sputum	Sputum smear	Sputum culture
1	Adrenal	58/M	New Zealand (Maori)	Sputum	Spontaneous	Productive cough and to obtain a diagnosis	2+	Positive
2	Bone	48/M	India	Sacroiliac bone biopsy	Induced	Rheumatoid arthritis Previously on immunosuppression	1+	Positive
3	Mediastinal lymph node	27/F	India	Mediastinal lymph node biopsy via EBUS*	Bronchial wash	Pyrexia of unknown origin	Negative	Positive
4	Bone	56/F	India	Base of skull bone biopsy	Induced	Performed during a ward admission	Negative	Positive
5	Cervical lymph node	37/M	India	Cervical lymph node biopsy	Induced	Cough	Negative	Positive

\* EBUS: Endo-bronchial ultrasound-guided biopsy

followed by pleural TB (n=24; 23%) and bone TB (n=6; 6%).

Almost all (n=100; 97%) had a culture obtained prior to treatment. TB was diagnosed by biopsy or excision of the extra-pulmonary site in the majority (n=74; 72%). Extensive effort was taken to obtain a culture, including biopsies obtained from the larynx, aorta, as well as the pericardium. However, in 25% (n=26) diagnosis of TB was made by sputum tests. Sputum samples were obtained by induced sputum in 52% (n=52), spontaneous sputum in 26% (n=27) and bronchial wash in 3% (n=3).

The majority had CXR abnormalities (n=76; 74%). In the group with a normal CXR (n=27), 55% (n=15) had sputum cultures performed. In all, 18% (n=5) of patients with extra-pulmonary TB and a normal CXR had concomitant pulmonary involvement, with two patients who were smear-positive graded at 1+ and 2+, demonstrating higher infectivity (Figure 1 and Table 1).

Of the 103 patients referred with extra-pulmonary TB, 50% (n=52) had concurrent pulmonary involvement. The sensitivity of the CXR in detecting pulmonary involvement was 90%, with a specificity of 32%.

In normal circumstances, no further testing would have been carried out when the CXR was unremarkable. However, 15 of the 27 patients

with a normal CXR had further sputum testing, with the primary aim of obtaining a culture prior to treatment (n=7; 46%) and not due to suspected pulmonary involvement (n=1; 7%). The other reasons for sputum testing carried out included: presence of a cough (n=2; 13%), pyrexia of unknown origin (n=2; 13%), suspected CXR abnormality by the respiratory physician (n=1; 7%), sputum test done by the primary referrer (n=1; 7%) and sputum testing performed during a ward admission as a routine (n=1; 7%).

Eight of the 76 patients with an abnormal CXR did not have a sputum sample taken for testing (Figure 1). In four patients, the CXR was thought to be normal during the initial clinic visit, with confirmation of the growth of *Mycobacterium tuberculosis* and the antibiotic sensitivity pattern being available from a culture obtained from the extra-pulmonary site. Three patients had relocated from out of the area and were already on established treatment. In one patient, the sputum culture was not pursued, as confirmation of the growth of *Mycobacterium tuberculosis* and antibiotic sensitivity was already available.

## Discussion

This case series demonstrates that in patients presenting with extra-pulmonary TB with a normal CXR, a noteworthy proportion of patients had coexisting pulmonary TB, in keeping with other published data.<sup>11,12</sup> This also highlights that in

identifying concomitant pulmonary TB in HIV-negative patients, a CXR is not 100% sensitive.<sup>11,17</sup>

It was surprising to find smear-positive patients demonstrating high infectivity while the CXR was completely normal. Of the two smear-positive patients, one had a productive cough and the other patient had previously used immunosuppressive agents for rheumatoid disease. These clinical factors could have raised 'red flags' to suspect concurrent pulmonary TB with higher infectivity, despite the normal CXR.<sup>17</sup>

A weakness of this audit is that not all patients had sputum cultures. Therefore, the true frequency of patients with extra-pulmonary TB having a normal CXR and concurrent pulmonary TB cannot be measured without a prospective study. As this study was a retrospective chart review, there was an inherent selection bias. Also, during the time of initial consultation, some patients may not have had a written radiology report; this mandates the respiratory physician interpreting the CXR and making a clinical decision on performing sputum testing as needed. In the majority of cases, both the respiratory physician and the radiologist had the same opinion regarding the CXR; there were five instances where the respiratory physician interpretation and the radiologist opinion differed, as seen in routine clinical practice.

It is of paramount importance to obtain a sample for culture prior to commencement of treatment, in order to identify the antibiotic sensitivity patterns and recognise drug resistance early. This is especially so where compelling re-treatment and in migrants from countries where TB is endemic. A survey in the European Union demonstrated culture availability to be 62.9% for pulmonary TB and 33.7% for extra-pulmonary TB,<sup>18</sup> while this audit found that the ADHB TB service greatly exceeded this, with 97% culture availability in patients presenting with extra-pulmonary TB.

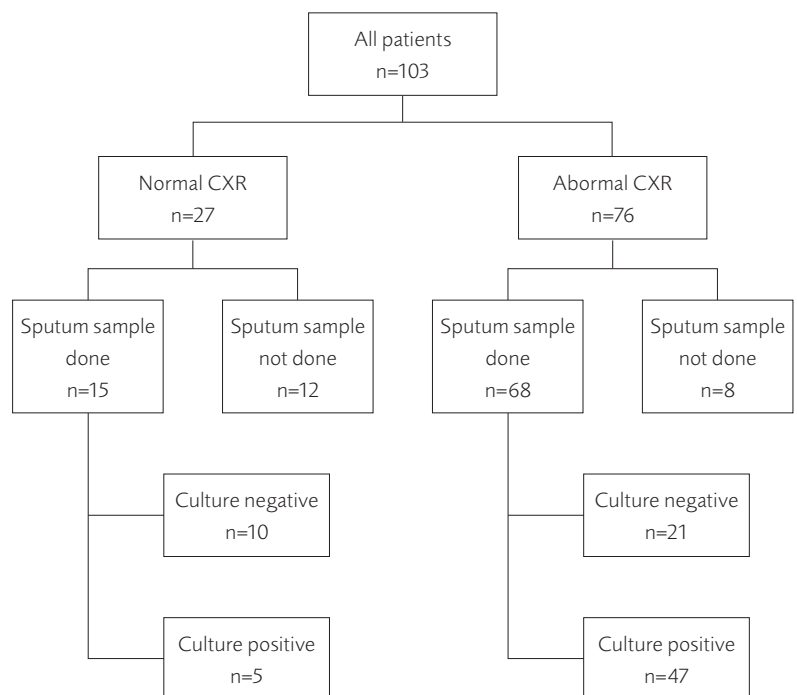
The majority of sputum samples obtained were induced with nebulized hypertonic saline. Sputum testing is a cheap and convenient means to obtain a sample for diagnosis of pulmonary involvement<sup>19</sup> and we suggest it should be used

## WHAT GAP THIS FILLS

**What we already know:** Pulmonary TB is a highly infectious airborne disease. Patients with abnormal CXR have a higher chance of pulmonary TB.

**What this study adds:** Patients presenting with extra-pulmonary TB may have culture-positive and sometimes smear-positive pulmonary TB, even when they have a normal CXR.

Figure 1. Outcome of the CXR findings and sputum sampling



in all patients with extra-pulmonary TB, so as not to miss a diagnosis of simultaneous pulmonary TB; a disease with high airborne infectivity and significant public health implications. This carries even greater importance in the face of emerging TB drug resistance.

The findings of our audit emphasise the utility and importance of performing sputum testing together with CXR in patients presenting with extra-pulmonary TB, as advocated by the World Health Organization Stop TB Initiative and other published studies, so as not to miss a diagnosis of concurrent pulmonary TB that may be infectious.<sup>10,12,13,17</sup>

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## COMPETING INTERESTS

None declared.