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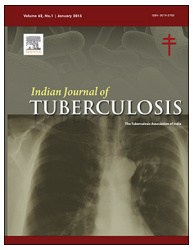

Review article

Smear microscopy as a diagnostic tool of tuberculosis: Review of smear negative cases, frequency, risk factors, and prevention criteria

Tarig M.S. Alnour [a,b]

[a] *Assistant Professor, Faculty of Applied Medical Sciences, Department of Medical Laboratory Technology, University of Tabuk, Saudi Arabia*
[b] *Faculty of Medical Laboratory Sciences, Department of Microbiology and Immunology, AlZaiem AlAzhari University, Sudan*

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ABSTRACT

Tuberculosis is one of the global health problems, the estimated deaths due to TB was around 2 million in the year 2013. Failure in early diagnosis and providing suitable treatment leads to increase the prognosis of the disease. Smear microscopy is used in many countries as a primary diagnosis of TB especially in the district poor facility laboratories, where smear negative frequency is high. This review aimed to reflects the importance of smear negative tuberculosis as a source of infection and poor prognosis of TB treatment and prevention. In addition to, discuss the possible causes and suggests solutions to improve the yields of smear microscopy.

1. Introduction

Tuberculosis (TB) is still a public health problem with estimated one third of world population have been infected. According to the global tuberculosis report issued on 13 October 2016, the WHO announced that In 2015, 10.4 million people fell ill with TB and 1.8 million died from the disease (including 0.4 million among people with HIV).[1] The causative agents of this disease is the slow grower, acid fast bacteria, *Mycobacterium tuberculosis* complex (MTBC) which comprises 7 closely related *Mycobacterium* species (*M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microti*, *M. canetti*, *M. pinnipedii*, and *M. caprae*).[2,3] The gold standard method for diagnosis of pulmonary TB is mycobacterium culture but this method is very slow, expensive and requires well equipped specialized laboratory.[4,5] Acid fast staining techniques such as Ziehl Neelsen (ZN) stain or Auramine O – Rhodamine stain remain the easiest and cheapest methods, although they are less sensitive and not specific for diagnosis of MTBC.[6] Its estimated that up to 50% of Ziehl Neelsen staining smear were negative, although the samples showed the presence of MTBC by other methods including culture.[6] This review aimed to highlight the smear negative pulmonary tuberculosis (SNPT), how it occurs? What's the reasons to have SNPT?, and suggests some solutions to avoid SNPT and increase the outcome of smear microscopy. Most publication and clinical practice have not tend to distinguish between smear negative pulmonary tuberculosis and smear positive although it's obvious that patients with SNPT have poor prognosis, could be infectious and tend to spread the disease in the community.

E-mail address: telnour@ut.edu.sa.
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2. What's smear negative pulmonary tuberculosis (SNPT)?

Smear-negative pulmonary tuberculosis (SNPT) is defined, according to the WHO (2010), as a clinical suspect with at least two negative acid fast bacilli (AFB) smears and a positive culture for TB in either solid or liquid media. Another way to classify the patient as SNPT is to have two negative smears, radiographical abnormalities consistent with active pulmonary TB and No improvement with a course of broad-spectrum antibiotic (if HIV-negative), in addition to physician decision to treat the patient as TB suspects. Also, HIV-positive patients with radiological abnormalities similar to TB granuloma is treated as smear negative PTB patient.[7–9]

3. Factors influencing to have smear negative pulmonary tuberculosis?

Several factors attributed to have smear negative culture positive cases; this might be categorized into laboratory errors, patient's status or habits, and presence of other infectious diseases (mainly HIV).

3.1. *Laboratory errors*

A well-equipped tuberculosis laboratory with well-trained personnel has few frequency of SNPT.[10,11] Laboratory personnel, specimens quality, numbers of provided samples, types of the stains used and to somehow types of microscope used may considered also as a laboratory errors to have smear negative PTB.[12,13] Lack or deficiency in the training of tuberculosis laboratory technologist plays a major role in laboratory errors to have false negative staining results. Many laboratories in low-income countries could not obtained such facilities especially that located in rural areas.[14] Other mentioned factors may also linked to laboratory errors for having false negative sputum smears.

3.2. *Patient's status or habits*

Age of the patient is one of the important factors contributed to SNPT. Children who are unable to produce quality sputum samples are the main reason to have smear negative PTB.[15,16] In one study, Smear-negative tuberculosis was more common in older than younger patients in a country with low prevalence of HIV infection.[17] Diabetes and smoking habits were investigated as risk factors for smear negative but No proved correlation were founded.[18–20]

3.3. *Presence of infectious diseases*

Human immunodeficiency virus (HIV) is the main reasons to have SNPT. Many investigators correlated the HIV infection with smear negative pulmonary tuberculosis.[18,21–34] The WHO announce that any HIV with pulmonary lesion typical to TB lesion not responding to antibacterial treatment should be treated as smear negative PTB.[1]

The main reason of having smear negative among patient with AIDS is lack of immunity which leads to disappearance of cavitation and TB associated granuloma and high possibility of extra-pulmonary spreading of the disease.[21] This might be associated with normal or atypical chest radiography.

4. Frequency of smear negative tuberculosis

Smear negative account for 30–60% of tuberculosis patients[6,17,18]; Extreme studies conducted in Pakistan (4 years retrospective study) by Ahmed et al.,[35] in Guatemala by Samayoa-Peláez et al.[36] and in Ethiopian prisons by Biadglegne et al.[37] They found low frequency of smear negative pulmonary tuberculosis (SNPT), 15.63%, 14% and 8%, respectively. In western pacific region, the WHO case notification rates in the year 2012 showed an average frequency of 50.7%, the lowest frequencies were in Tonga and Papua New Guinea (9.1% for both), while the highest 59.3% was scored in China.[38]

5. Risk factors of have smear negative pulmonary tuberculosis

5.1. *Infectivity*

The first question which come to your mind when any person talk about smear negative pulmonary tuberculosis is does Smear Negative Pulmonary Tuberculosis patient able to transmit the disease? In the past, many investigators thought that SNPT patients are not infectious or weakly infectious, but recently several investigators described the possibility of TB transmission from SNPT. Tostmann et al. showed that smear negative (culture positive) pulmonary tuberculosis responsible for 13% of tuberculosis transmission in a large cohort study done in Netherlands.[39] Thapa estimated that smear negative tuberculosis responsible for 13–41% of disease transmission.[40] In San Francisco, smear negative culture positive responsible for 17% of tuberculosis transmission.[41] High risk of possibility of transmission was noted by Hernández-Garduño et al. in the Greater Vancouver regional district, they stated that 41% of pulmonary and extrapulmonary smear negative cases appear responsible for TB transmission.[42]

5.2. *Possibility to spread multidrug resistant* Mycobacterium tuberculosis *MDR – MTB*

One of the most important problem in Tuberculosis is the development of multidrug resistant strains (MDR-MTB), this might be due to delay in diagnosis and irregular uptake of antituberculosis drugs without final judgment of having TB. Liu et al. estimated the percentage of MDR – MTB strains among smear negative pulmonary tuberculosis was 26.5% in Beijing, China, which might increase the possibility of spreading MDR strains and affects the outcome of controlling these organisms.[43]

5.3. *Treatment outcome*

Treatment outcome may be affected by smear negative tuberculosis cases. In one study done by Mukherjee et al.,

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