

The Comparison of X-ray Finding in Pulmonary Tuberculosis with and without Diabetes Mellitus

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ABSTRACT

Diabetes Mellitus patients are considered as a high-risk population for the development of Pulmonary Tuberculosis (PTB) by about three-fold. Diabetes Mellitus sufferers by glycated haemoglobin A1C (HbA1C) level. The relative risk(RR) of Tuberculosis (TB) was 3,1 (95% CI 1.6-5.9) for those with HbA1C $\geq 7\%$. There are several contradictory opinions regarding the radiological appearance of TBC sufferers with genuine effect of DM. Chest X-ray remains the primary investigation for the assessment of PTB. Pulmonary Tuberculosis is found predominantly in the lung apices. It is not clear whether DM can affect the presentation of TB. Thus, whether diabetic subjects present atypical radiological presentation of PTB is still controversial. There have been several studies with contradictory results regarding the differences in the radiological appearance of PTB patients with and without DM. Clinical studies have shown ambiguous results. Any other risk factors maybe associated with age, sex, smoking status, and nutrition status.

Keywords: *Tuberculosis, pulmonary tuberculosis, diabetes mellitus, chest x-ray, lesion.*

INTRODUCTION

Tuberculosis is a chronic infection disease caused by bacteria belonging to the *Mycobacterium Tuberculosis* (MTb) which usually infects lung parenchyma.¹ Tuberculosis has been a significant public health problem worldwide for the last 2 decades. Globally, in 2021, there were an estimated 1.5 million deaths among TB infection. Furthermore, World Health Organization (WHO) estimated 9.6 million people fell ill with TB worldwide in 2021. Currently, Indonesia is the second largest contributor to TB cases in the world, after India. Diabetes Mellitus is an important risk factor for TB development. World Health Organization reported, DM was associated with an increased risk of PTB infection 3 times higher in patients than in those without DM.² Diabetes mellitus is known caused immune dysregulation, adversely affecting neutrophil chemotaxis, macrophage function and phagocytic responses, decrease T-helper cells (Th)-1 cytokine, tumor necrosis factor (TNF)- α and TNF- β , interleukin (IL) such as IL-1 and IL-6.^{3,4}

There are several contradictory opinions regarding the radiological appearance of TB sufferers with DM risk factors. Radiographic manifestations of PTB in patients with DM have previously been reported differently. Diabetes mellitus type 2 could increase the risk of advance lesion PTB as much as 5.25 times.⁵ Radiologically, co-existing DM and TB may induce an increase of pulmonary atypical manifestation, including lower lobe lung opacity, occurrence of more lung lesions, cavity, and extensive parenchymal involvement. Whereas non-DM patients usually had upper lobe infiltrates.⁶⁻⁹ However, the results reported by different researchers have not been consistent. Meanwhile, in several other studies, no differences were found in chest X-ray between PTB patients with and without DM. Two research from our hospital find no significant differences in the appearance of PTB lesions of DM compared to non-DM.¹⁰⁻¹³ Additional research by Morris JT and Weaver RA there was no cavitory lesions on PTB with DM patients.¹⁴⁻¹⁵

EPIDEMIOLOGY OF TBC AND DM

Globally, TB is one of the 10 leading causes of death and the top cause from a single infectious agent. The World Health Organization estimated the global burden of TB in 2017 at 10 million incident cases, which is 90% of cases are adults (aged ≥ 15 years).¹⁶ The higher MTb burden is associated with increasing number of DM cases.¹⁷ Active PTB will appear more often in insulin-dependent DM patients (insulin dependent diabetes mellitus/IDDM) compared with non-insulin dependent DM patients (non-insulin dependent DM/NIDDM). Diabetes Mellitus subject with baseline glycated hemoglobin A1C (HbA1C) levels $\geq 7\%$ higher prevalence of developing active PTB (adjusted hazard ratio [HR]: 3.11) with 95% confidence interval (CI) 1.6-5.9.¹⁸ Hyperglycemia was strongly associated with worsen pulmonary radiographic manifestation in TB patients.

RADIOLOGICAL FEATURES OF PTB

Chest x-ray constitutes the main diagnostic support to identifying suspected PTB. Chest x-ray examination is relatively simple but can describe the severity of PTB, the status of active PTB, and evaluate the extent of lung lesions/damage. Serial chest radiographs are also used to monitor PTB therapy.¹⁸ The location of the main lesion on chest radiograph was classified as typical and atypical lesion. Typical means the lesion is in the upper fields of the lung, while atypical means the lesion involves the lower fields of the lung. Primary TB parenchymal involvement can happen in any segment of the lung. Mostly, the lesions are in the apex area in accordance with bacterial predilection. *Mycobacterium Tuberculosis* is an aerobic bacterium and therefore proliferates higher oxygen tension and lower blood flow, i.e., a higher ventilation/perfusion (V/Q) ratio than the base lung fields.¹⁹⁻²⁰

The sensitivity and specificity of infiltrate-fibro infiltrate on chest X-ray to presumptive TB was 87.5% and 82.5%, while the combination >3 lesions was 87.5% and 77.2%. This means that existing chest X-ray abnormalities can significantly diagnose

patients with PTB. Specificity rates of 82.5% in fibro infiltrate and 77.18% in combined abnormalities means that not finding these lesions on a chest X-ray can significantly rule out the diagnosis of the patient not suffering from PTB.²¹⁻²²

The imaging appearances in PTB initially consists of cloud-like spots with unclear boundaries, then develop to various types of lesions. They can be grouped into lung parenchymal/infiltrate lesions (including consolidation, cavitation, miliary nodules, fibrosis, calcification, atelectasis), pleural lesions (including pleural effusion, pleurisy, pleural calcification), and mediastinal lesions (including hilar and mediastinal lymphadenopathy). The types of lesions in TB can imitate various other disease processes, furthermore TB is often called "the great imitator". For example, tuberculoma and consolidation as radiological finding in PTB is also often found in pneumonia, pulmonary mycosis, bronchial carcinoma, or metastatic carcinoma in the lung. Besides, a cavity picture is also present in lung abscesses.^{19,23}

The extent of disease was estimated based on the sum of all areas of abnormality in which a boundary of abnormal opacity could be drawn. Minimal lesions were defined as an area less than that above a horizontal line across the 2nd chondrosternal conjunction of one lung. Whereas PTB with extensive lesion includes moderately advanced lesion and far advanced lesion. Moderately advanced lesions were defined as an area greater in size than the minimal lesions but smaller than that of one entire lung. Far advanced lesions were defined as an area equivalent to or greater than one lung. The size of the largest cavity was dichotomized into small and large by the median diameter.²⁴

RADIOLOGICAL FEATURES IN PTB WITH DM

Diabetes Mellitus is also believed to affect radiological manifestations of PTB. It has been demonstrated in numerous studies that co-existing DM and TB conditions may induce an increased frequency of pulmonary atypical manifestation, including lower lobe lung opacity,

occurrence of more lung lesions, cavity and extensive parenchymal involvement. Impaired immune response in diabetic patients will increase bacterial load and inflammation, thus leading to necrosis and bacterial dissemination. The site of PTB lesions is generally present in the upper lobes. Compared with those without DM, PTB patients with DM were significantly more likely to have lesions over lower lung fields. In DM, there is an increase in alveolar ventilation and decrease in perfusion due to thickening of the lung alveolar epithelium. This condition resulting in an increase in alveolar oxygen pressure in the lower part of the lung which representative lesions in the lower lung fields.²⁵ The characteristics of atypical lesions in PTB sufferers with DM have been proven by many studies, such as those conducted by Qazi, et al, Perez-Gusman, and Shaikhet al.⁸⁻¹⁰

Several studies reported that TB patients with DM had worsen radiological finding. According to Layali et al (2019), diabetic PTB patients have a significantly 15-fold higher risk of multiple cavitary lesions and 6,29-fold higher risk of having an atypical lesion appearance compared with those without. In another study, Utomo and Margawati also reported that DM have increased the risk of advance lesion PTB as much as 5.25 times. Based on the area of the lesion, the degree of severity that most found was far advanced lesion (61.9%), followed by moderately advanced lesion (28.6%), and the least was minimal lesions (9.5%). In addition, Ramzi showed the chest X-rays of diabetic PTB are the most performed extensive lesions (60%).^{5,13,26} Thus, chest X-rays with extensive lesions was dominated by TB patients with DM.

Elevated levels of HbA1c can worsen infections caused by TB because HbA1c levels are directly proportional to blood glucose concentrations. Chronic hyperglycemia impairs the immune system, worsening the clinical appearance, and radiographic manifestations of PTB. This is in line with research by Chang JT et al, showed DM-TB patients with mean HbA1C $10.0 \pm 2.6\%$ results in more severe infections and higher mycobacterial loads. In fact, an increase of 1 unit in HbA1c indicates an

increased risk of 3 types of lung lesions (cavities, infiltrates, and fibroustracts) or ≥ 4 lung lesions in TB patients.^{27,28}

CONTRADICTIVE RADIOLOGICAL FEATURES OF TBC WITH AND WITHOUT DM

There had been much debate concerning the atypical radiographic findings of TB with DM. Some authors have reported no major differences while others have reported a higher involvement of the lower lung fields. Pérez-Guzman et al. reported that TB patients with DM had cavity disease more frequently than patients without DM. It is known that DM causes the dysfunction of polymorphonuclear leukocytes and reduces bactericidal activity. Thus, cavity development may be more progressive in DM patients with pulmonary TB. However, decreased immunity may also be related to the lower frequency of cavitation in DM patients, as discussed above. It remains controversial whether DM has a positive or negative impact on cavity disease.⁸

Similarly, research conducted by Alavi et al, showed that in PTB patients with DM, lesions were more common in the upper lobes of the lungs (59%).³⁰ Otherwise, Layali found a relationship between DM and the location of the lesion. TB subjects with DM had a 6.29 times risk of having atypical lesions compared to TB without DM ($P < 0.01$).²⁶ Diabetic PTB subjects who had HbA1c = 7-8.9% increased 14.25 times risk of having atypical lesions compared to those with HbA1c $< 7\%$ ($P = 0.024$). This is in accordance with previous research conducted by Bokam et al, who found that HbA1c levels with an average of 8.87 had 59% lesions in the lower lung fields.³¹ Further examination revealed that pulmonary TB lesions in the lower lung fields were more common in the group of TBC-DM subjects (24.11%) compared to TBC without DM (6.35%) ($P < 0.0001$).³² Likewise, research by Chiang et al, who found that TB with DM had a risk of having lesions in the lower part of the lungs 1.37 times compared to TB without DM (OR = 1.37; 95% CI = 1.04-1.81).¹⁵ In addition, Edwina examined the degree of severity which minimal lesions was found more common in PTB

non-DM (40%).³³ We conclude that the patients with PTB and DM are more likely to present atypical and extensive lesions in radiographic manifestation. Tuberculosis lesions in DM often occur in the lower lung fields because the VA/Q and PaO₂ ratios are high in the lower lung fields.⁸ The number of mature alveolar macrophages increased in PTB patients, but there was no significant difference in the number of T lymphocytes between PTB patients with and without DM. The lower proportion of mature alveolar macrophages in TB patients with DM may be responsible for the more severe expansion of lesions in the lung fields of pulmonary TB patients.¹⁰

FACTORS AFFECTING RADIOLOGICAL FINDING OF PTB

Besides the correlation with glycaemic index, other findings confirmed previous reports that age, sex, smoking, and nutritional status were associated with radiographic manifestation of pulmonary TB.

Age

The impact of age on the radiologic presentation of PTB is important because misinterpretation might delay appropriate diagnostic. Pulmonary Tuberculosis lesions in DM and elderly patients are often located in the lower lung fields. One possible explanation for this atypical presentation may be that in the elderly and diabetics increased alveolar oxygen pressure in the lower lobes promotes disease development in these areas. It is based on the concept that multiplication of MTb is favored by high oxygen tension. Aging leads to increased alveolar ventilation (VA) and reduced perfusion (Q), resulting in an increase in VA/Q mismatch and increases PaO₂ in the lower lung fields. Therefore, age-induced changes should favor multiplication of Mycobacterium tuberculosis in lower lung zones. Furthermore, Guzman et al, found that the frequency of upper lung field lesions (with or without lower lung field lesions) was similar at all ages, suggesting that aging does not alter conditions in the upper lobes.^{8,25,34} The proportion of patients with upper lung field

opacity did not differ by age group ($p=0.380$). Those aged ≥ 65 years were significantly more likely to have lower lung field opacity than those <65 years old (75.3% vs 68.6%, adjusted OR 1.42, 95% CI 1.09–1.85). In all age groups, the proportion of patients with upper lung field opacity was higher than those with lower lung field opacity. However, due to the increased proportion of patients with lower lung field opacity among those with DM in those aged <55 years old, the association between age group and lower lung field opacities was no longer statistically significant among DM ($p=0.550$). However, the frequency of cavitation in the TB group showed a negative correlation with age, from about 80% at age-periods 30–39 and 40–49, to less than 20% at age ≥ 80 ($p<0.05$). A higher proportion of both cavities and lower lung lesions was still observed in the diabetic group in all age categories (almost always more than 70%). Infiltrates were found to be the most common radiological finding in both younger (35.25%) and elderly (65.76%) patients.^{15,25,35,36} The elderly are more likely to have lower lung field lesions and less likely to have cavities as compared with younger patients

Cavitation with infiltration was significantly associated with the younger age group. Due to impaired T-cell function and poor immunological status, the elderly are less prone to cavity formation. The proportion of patients with cavitory lesions was highest among those aged 35–44 years and decreased progressively with age. Diabetes did not obscure but aggravated the differential risks of cavitory lesions between the elderly and younger patients. Diabetes increased the risk of cavitory lesions, especially among younger patients, likely through a mechanism that is different from the one causing increased lower lung field involvement, and the risk of cavity among diabetes patients is driven by glycemic control.^{25,35,36}

Sex

Radiographic manifestations of TB also differed by sex. Chiang reported males were significantly more likely to have any opacity on lung

parenchyma (male 99.3% vs female 97.6%, $p=0.019$), opacity over upper lung field (male 95.8% vs female 86.9%, $p<0.001$). Females were significantly more likely to have isolated lower lung field opacity (male 3.5% vs female 10.7%), with an adjusted odds ratio 2.5 (95% CI 1.4–4.5). Males were significantly more likely to have far advanced parenchymal lesions (male 23.0% vs female 14.5%, $p<0.001$), any cavitory lesion (male 46.3% vs female 31.5%, $p<0.001$) and cavitory lesions over upper lung fields (male 43.2% vs female 28.7%, $p<0.001$) but not cavitory lesions over lower lung fields (male 10.0% vs female 6.9%, $p=0.116$).¹⁵

Isolated lower lung field TB without upper lung field involvement deserves attention as diagnosis of lower lung field TB can be difficult. Aktogu reported that 6.2% of PTB patients had isolated lower lung field TB and the proportion of patients with isolated lower lung field TB was higher among females (11.8% of female vs 4.4% of males, $p<0.005$) and diabetes (11% of diabetic patients vs 5.3% non-diabetic patients). Chang reported that 5.1% of PTB patients had isolated lower lung field TB and the proportion of patients with isolated lower lung field TB was 16.3% among females and 3.1% among males ($p<0.005$). That a higher proportion of diabetic patients had isolated lower lung field TB than non-DM has also been reported by Pérez-Guzmán (19% among DM vs 7% among non-DM) and Marais (29% among DM vs 4.5% among non-DM).^{29,36,37,38} Our study confirmed that isolated lower lung field TB is more frequent among female than male but not more frequent among DM than non-DM.

Smoking

Although smoking and DM are both important risk factors for TB, it is unclear whether there is a differential influence of smoking on PTB between non-DM and DM patients. There is a significant relationship between smoking status and extensive PTB status. Research on the effects of nicotine has revealed that it may increase the risk of TB by reducing local TNF in the lungs. Tobacco smoke contains around 4,500 compounds that likely have active

biological effects. Anti- inflammatories and immunosuppressants were also found to be concentrated in the substance nicotine. An initial hypothesis was that nicotine is immunosuppressive because it activates hypothalamo pituitary adrenal axis (HPA axis) via nicotine receptors in the central nervous system. However, it was later discovered that the HPA axis was only important for the acute effects of nicotine, while the chronic anti-inflammatory effects persisted after adrenalectomy. The body's resistance, especially in the lungs, decreases, causing TB lesions that were initially not extensive to become extensive.^{24,39,40} By contrast, smoking reported was only associated with non-DM PTB patient. Smoking was increased frequency of bilateral lung parenchyma involvement (AdjOR 1.84, 95% CI 1.16-2.93) and far-advanced PTB (AdjOR 1.91, 95% CI 1.04-3.50) in non-DM PTB. Smoking was also significantly associated with an increased frequency of multiple, and large cavities in non-DM TB. However, smoking was not associated with cavitary lung parenchyma lesions in terms of the location, number, or size of cavitary lesions in DM TB patients.²⁴

Nutrition status

Tverdal et al showed overweight reduced risk of PTB. Obese were believed to have a high nutritional intake of protein to produce energy, which is immune function is not disturbed. It has been used, the more BMI of a DM patients decrease (underweight), had a correlation the wider active PTB lesion on the chest X-ray. Of note, Sahin et al, found in non-DM TB patients that a decrease in BMI was associated with elevated inflammatory markers as well as a more advanced radiological manifestation. It is a well-recognized fact that weight loss in TB is evidently related to the acute phase response.^{39,40}

CONCLUSION

Chest X-ray examination in PTB showed various forms (multiform). There are several contradictory opinions regarding the differences in the radiological appearance of PTB patients

with and without DM. Some research suggested either no difference between the appearance of the lesions or severity of PTB. The factors summarised included age, sex, smoking, and nutrition status. Abnormalities seen on chest X-ray may be suggestive of but are never diagnostic of TB.

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