

## Case Report

# Coexistence of pulmonary tuberculosis and small cell lung carcinoma: A significant problem in tuberculosis-endemic country?

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## Abstract

Pulmonary tuberculosis and lung cancer are public health problems, causing significant morbidity and mortality worldwide. The coexistence of the two diseases has rarely been reported while their causative association has been noticed leading to diagnosis delayed and prognosis worsening. In this case report, we present the case of a patient with coexistence of pulmonary tuberculosis and small cell lung carcinoma. A 54-year-old male was presented with the complained of lower left chest pain for six months, which was getting worse four days before admission to the hospital. The patient also complained of cough and decreased appetite and weight loss. Initial chest X-ray revealed an infiltrate and cavity in the upper right lung and inhomogeneous consolidation in the left paracardial. After the patient was diagnosed with pulmonary tuberculosis and was given anti-tuberculosis drugs for two months, the cavity and consolidation decreased with no clinically significant improvement. We performed a bronchoscopy with suspicion of lung cancer and a forcep biopsy in which small cell carcinoma was confirmed. The patient received two cycles of chemotherapy and anti-tuberculosis was continued for four months. During the observation in the fourth month, there was a reduction in the tumor size. This case highlights that similarity of clinical symptoms between pulmonary tuberculosis and lung cancer often lead to misdiagnosis of both. Therefore, in the absence of complete clinical and radiological improvement in pulmonary tuberculosis patients, the coexistence of lung cancer should be considered. This also highlights that early diagnosis is critical for the favorable outcome.

**Keywords:** Tuberculosis, pulmonary TB, lung cancer, small cell carcinoma, coexistence

## Introduction

Lung cancer is the primary cause of death from cancers and it is estimated that the number new cases reached 2.2 million with 1.8 million deaths in 2020 [1, 2]. Tuberculosis (TB) is the principal cause of death from infection in the world, with approximately 1.6 million deaths in 2021 [3, 4]. It is known that TB increases the risk of lung cancer and affects its prognosis [5, 6]. The patient with lung cancer and TB will have higher mortality than the one without TB [7]. TB and lung cancer coexistence is rarely described in literature, but the incidence of the coexistence is approximately 2% [8]. It is reported that the risk of lung cancer increased 1.7-fold in people with TB [9].



There are some hypotheses that explain the mechanism, but it is suspected that the main cause is related to the chronic inflammation of the lung [10]. Long-term TB creates an old scar that could lead to metaplasia of lung epithelium [11]. Other than that, it is also related to the immune system of which *Mycobacterium tuberculosis* infection could weaken the immune system [7, 12, 13]. An epidemiologically based case-control study showed an association between TB and lung cancer with an odds ratio of 2.1 after adjusting for socioeconomic factors and smoking habits [5]. Smoking habits is one of the risks of lung cancer and along with TB simultaneously cause damage to the lungs [6].

Clinicians need to consider TB when treating lung cancer, or vice versa [14]. The clinical and radiological features of lung TB and lung cancer are often similar, which can lead to misdiagnosis, and missed or late diagnosis. Here we present the case of a patient who was initially diagnosed with pulmonary TB; however, later diagnosed as pulmonary tuberculosis and confirmed small cell lung carcinoma during the course of treatment.

## Case

In August 2022, a 54-year-old male was referred to Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia with chief complaints of left chest pain for six months and became worse four days before the admission. The patient complained of tired quickly with strenuous activities and had decreased appetite for one month, accompanied by weight loss. The patient worked as a motorcycle mechanic and was a smoker with a high Brinkman index (800). At the previous hospital, Dr. Fauziah Birueun Hospital, Aceh, Indonesia, the patient was diagnosed with bacteriologic confirmed pulmonary TB through chest X-ray examination (**Figure 1A**) and GeneXpert MTB/RIF. The patient was then given an anti-tuberculosis drug, 3 tablets of 4 fixed dose combination (FDC) each day since May 2022. The tablet consisted 75 mg isoniazid (H), 150 mg rifampicin (R), 400 mg pyrazinamide (Z), and 275 ethambutol (E). After almost two months of pulmonary TB therapy, the acid-fast bacilli sputum for follow-up yielded negative result; however, the patient did not feel total clinical improvement and the chest pain was getting worse.

A physical examination of the lungs showed abnormalities in the left lung with weakened stem fremitus, dullness in the lower chest, and decreased breath sounds followed by additional breath sounds. After two months of TB treatment at Dr. Fauziah Birueun Hospital, the patient got another chest X-ray, and there was a slight improvement of infiltrates in the upper right lung with inhomogeneous consolidation. The cavity was slightly reduced compared to the first chest X-ray (**Figure 1B**). Because there was a suspicion of lung cancer, the thorax CT-scan was requested, which revealed a malignant mass on the lower lobe of the left lung with an amorphous form suggestive of lung carcinoma, with a size of 5.4 x 3.7 x 5 cm (**Figure 1C and 1D**).

At Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia a bronchoscopy and forceps biopsy (**Figure 1E and 1F**) examination was performed as a diagnostic before starting the chemotherapy, which showed an infiltrative mass in the lingula, and a forceps biopsy was performed on the mass. It revealed anaplastic proliferative tissue with round nuclei, spindles, and coarse chromatin, diffusely arranged in accordance with the description of small-cell lung carcinoma.

The patient was diagnosed to have small-cell lung carcinoma with coexisting pulmonary TB. Subsequently, the patient decided to receive chemotherapy with carboplatin (671 mg/21 days) and etoposide (173 mg/21 days) and to continue anti-tuberculosis treatment for four months.

After four months of TB treatment and two cycles of chemotherapy at Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia, clinical and radiological improvement was observed, characterized by a reduction in the tumor size. The size changed to 5.1 x 3.1 x 1.8 cm with the results of stable disease resistance (**Figure 1G and 1H**). The patient was planning to continue four cycles of chemotherapy every 21 days and TB treatment for 6 months. Since the patient's condition was stable, the patient is continuing the treatment at Dr. Fauziah Birueun Hospital, Aceh, Indonesia.

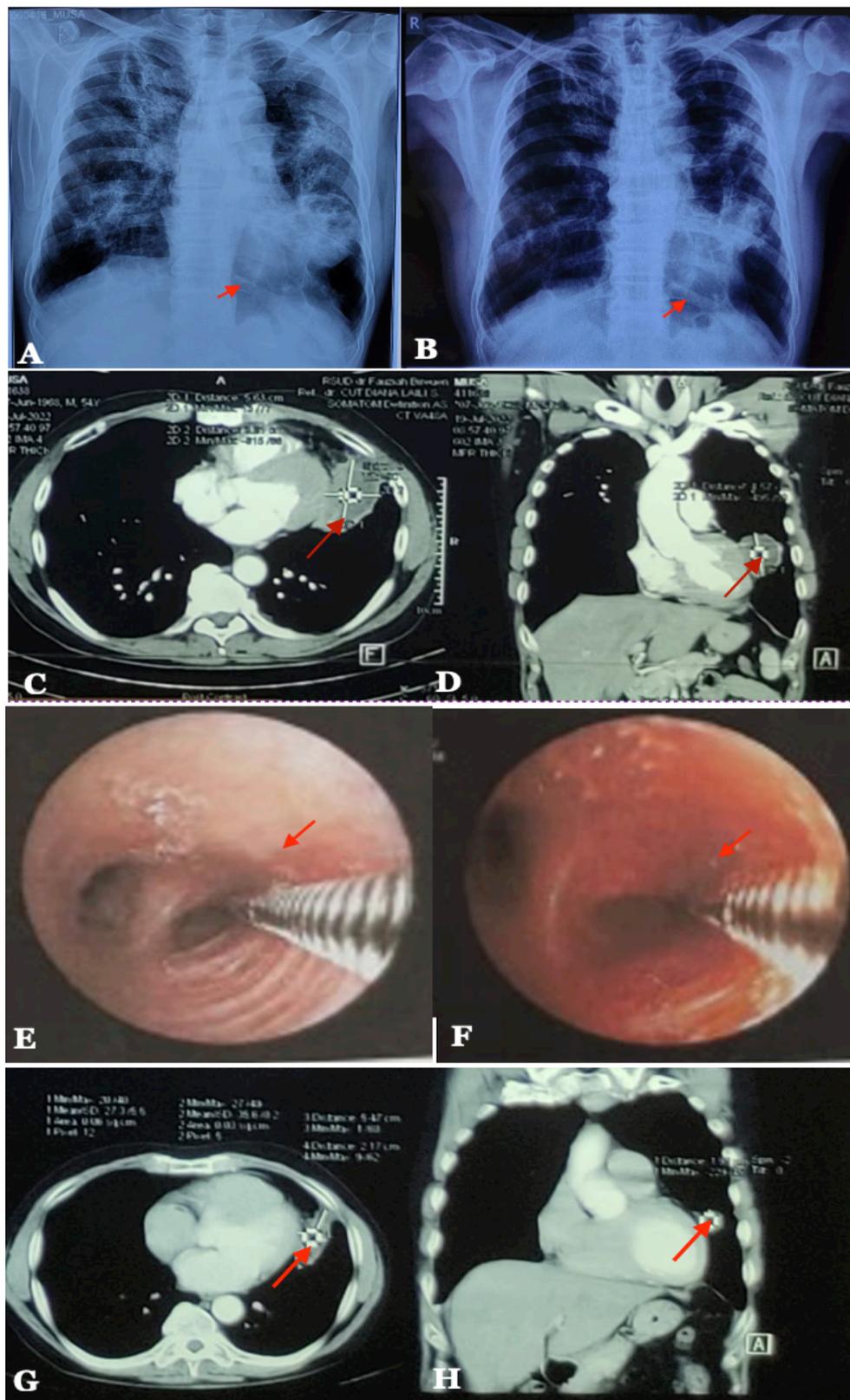


Figure 1. Imaging and bronchoscopy examinations of the patient. (A) Chest X-ray examination before and (B) after two months of anti-tuberculosis (TB) therapy. The red arrow indicates suspected mass on the lower lobe of the left lung. (C) and (D) Chest CT scan after two months of TB treatment at Dr. Fauziah Birueun Hospital. The red arrow indicates a mass on the left lung approximately 5.4 x 3.7 x 5 cm. (E) Bronchoscopy examination and when the forceps biopsy is performed (F). The red arrow indicates the infiltrative mass in the lingula. (G) and (H) Chest CT scan after four months of TB treatment and two cycles of chemotherapy. The red arrow indicates a shrink lung mass after two cycles chemotherapy, approximately 5.1 x 3.1 x 1.8 cm.

## Discussion

Lung cancer and TB are currently public health problems and epidemiological data show a causal relation between the occurrence of TB and lung cancer [9] of which pulmonary TB patients have a high risk of evolving lung cancer [15]. A cohort study also found that the incidence of lung cancer in TB patients was 269 per 100,000 people per year, which was higher than in the normal population (153 per 100,000 people per year [5]).

Several factors are found to be the relation between TB and lung cancer, including smoking habits, age, gender, and chronic inflammation due to *M. tuberculosis* infection [10, 13, 15]. Based on American Thoracic Society (ATS) data, the age with a high risk of lung cancer is around 50 years, while TB can occur at any age [16]. This is consistent with our patient, a 54-year-old male who was a smoker and diagnosed with TB. However, there was study found that TB is an essential factor in the occurrence of lung cancer which can occur at any age [17].

Smoking is a strong risk factor for both lung cancer and TB [6,10]. During smoking, formation of the polycyclic aromatic hydrocarbon-DNA complex leads to generating G-T transversion in TP53 gene which causes DNA mutations [18]. G-T transversion at codon 157 of TP53 gene is common in smokers' lung cancer but not in non-smokers [18]. The overall relative risk of developing lung cancer was 2.45, which is 2.64 for unfiltered cigarette smokers and 2.23 for filtered cigarette smokers [19]. Smokers have a 10-fold increased risk of lung cancer, and heavy smokers (more than 20 cigarettes a day) have a 20-fold increased risk [20]. Our patient was a smoker with a high Brinkman index diagnosed with TB and developed lung cancer. This case is in accordance with research conducted by Silva et al. that, generally, patients with the coexistence of pulmonary TB and lung cancer are men with a history of being a smoker or ex-smoker [21].

TB is a chronic infectious disease whose infection process is accompanied by lung tissue remodelling that can lead to pulmonary fibrosis and scarring [6]. The specific pathological hallmark of this process is the generation of granulomas centred on mycobacteria, surrounded by lymphocytes and myeloid cells [22]. Antigen-specific T lymphocytes originate interferon- $\gamma$  and other cytokines [23, 24]. The increased production of inflammatory cytokines, reactive oxygen species and nitrogen, prostaglandins, and proteases to eliminate bacteria is due to activated macrophages [22, 24]. Eliminating *M. tuberculosis* causes extensive damage to lung tissue, and it is like a double-edged sword process [22]. Repetitive inflammatory injury and the ensuing repair process of lung epithelial cells in the following stage cause fibroblast aggregation and abnormal growth factor activation, along with the hyperplasia and metaplasia of lung epithelial cells [22]. The theory is in line with our patient that there is a diffuse proliferation of lung tissue that matches the description of small-cell lung carcinoma.

A systematic review and meta-analysis showed that active pulmonary TB had a relative risk of small cell carcinoma of 2.1 (95%CI: 1.544–2.905) compared to other types of lung cancer [25]. Another study found the hazard ratio for small cell carcinoma in men with TB was 3.65 (95%CI: 1.97–6.80). This figure is smaller than the hazard ratio for small cell carcinoma accompanied by other lung diseases (asthma or chronic obstructive pulmonary disease) [26]. Our case is also in line with the study which showed a significant relationship between male smokers with pulmonary TB with squamous cell carcinoma and small cell carcinoma [27].

According to the time, the diagnosis of TB and lung cancer can be classified into two: (1) simultaneous, when the diagnosis of TB and lung cancer match or the time between the two diagnoses is no longer than two months; and (2) sequential either lung cancer is diagnosed first, then TB is diagnosed within 12 months of completion of cancer treatment or tuberculosis is diagnosed first, and then lung cancer is diagnosed two months later [11, 21]. Our patient was included in simultaneous because it was diagnosed two months before, so it can be considered that pulmonary TB and lung cancer were diagnosed together [28].

A study showed that the most common type of lung cancer in TB patients was adenocarcinoma and followed by epidermoid carcinoma [21]. However, case series in Ankara, Turkey, reported that squamous cell carcinoma was the most common type of lung cancers in with pulmonary TB patients [24]. The study from 1986–2005 also reported that squamous cell carcinoma (25.4%) was the most common type of lung cancer, followed respectively by small

cell carcinoma (14.0%) and adenocarcinoma (8.3%) [6]. In our case, the patient was diagnosed with small cell carcinoma, which is less common than the two types of lung cancer above.

There are some limitations that need to be discussed. The patient has not completed the chemotherapy cycles when the case was reported and therefore it was difficult to conclude the final outcome of therapy. Nevertheless, the patient was stable in the first cycle of chemotherapy. The coexistence of TB and lung cancer has not been widely described and therefore it was quite challenging to deal with this case. We encourage clinicians to pay attention to the possibility of this coexistence because the symptoms of TB and lung cancer are often the same or almost similar.

## Conclusion

Diagnosis and treatment of the coexistence of pulmonary TB and lung cancer is still a challenge in TB-endemic countries. The symptoms of pulmonary TB often resemble lung cancer and vice versa. Early detection is needed before the disease reaches an advanced stage. In case of TB treatment does not achieve the clinical or radiological improvements after five weeks, it is advisable to initiate the lung cancer coexistence screening.

## Ethics approval

Not applicable for case report.

## Patient's consent

Informed consent was directly obtained from the patient for the publication of this report and any accompanying images.

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## Conflict of interest

Authors declare no conflict of interest.

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