

Post COVID-19 endobronchial tuberculosis misdiagnosed as asthma

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Abstract

Chronic cough is a common symptom with a diversity of underlying respiratory causes. The COVID-19 pandemic has added complexity to the identification of the etiology of chronic cough, as persistent cough has been frequently reported among

COVID-19 survivors. We present a case of a 21-year-old woman, with prolonged cough and wheezing following a mild COVID-19 infection. Despite multiple attempts to recognize the cause and manage her cough, her symptoms did not improve. A careful examination revealed monophonic wheezing and purulent sputum, raising suspicion for Endobronchial Tuberculosis (EBTB). Chest computed tomography scan showed a tree-in-bud pattern and narrowed the bronchial lumen. Acid-fast *bacillus* smear and genXpert MTB/RIF test further confirmed the presence of *Mycobacterium tuberculosis*. This case highlights the importance of considering EBTB as a potential diagnosis for chronic cough, particularly in COVID-19 survivors in tuberculosis-endemic areas.

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Introduction

Chronic cough is a prevalent symptom, causing adults to seek outpatient care. It has a wide-ranging impact on health status, including incontinence, cough syncope, social isolation, and depression.¹ Its common causes with normal Chest X-Ray (CXR) include post-nasal drips, asthma, gastroesophageal reflux, smoker's cough, and non-asthmatic eosinophilic bronchitis.² Despite being less common, Endobronchial Tuberculosis (EBTB) should be considered as a potential etiology for chronic cough, particularly in endemic regions of tuberculosis, like Southeast Asia. EBTB represents a distinct form of tuberculosis, affecting the tracheo-bronchial tree. In cases where CXR shows no or subtle parenchymal abnormality, defining EBTB can be challenging.³ This situation is further complicated in the post COVID-19 pandemic era, where coughing is more frequently reported in association with post COVID-19 syndrome. Here, we presented a case of a 21-year-old female patient, whose cough persisted for months after recovering from COVID-19 infection. She was diagnosed with post COVID-19 cough, pharyngitis, and asthma previously, but all treatment showed no improvement, finally confirmed the presence of EBTB.

Case Report

A 21-year-old female patient visited our outpatient clinic with chronic cough. She is a non-smoker and has shellfish allergy. Her body mass index is 25.4 kg/m². Her past history included a mild COVID-19 infection, 9 months prior, which was managed with oral methylprednisolone 16 mg once daily, and amoxicillin/clavulanic 875/125 mg twice daily, for one week. Although her viral infection symptoms, including fever and fatigue, had quickly improved, she continued to have occasional wheezing and a lingering cough with whitish sputum for three months. She then sought help at a long COVID-19 clinic. The complete blood count, liver, and renal function were normal. Her CXR revealed no parenchymal abnormality (Figure 1). The patient was diagnosed

with post-COVID-19 prolonged cough, and was prescribed desloratadine 5 mg once daily, montelukast 10 mg once daily, and neocodion twice daily for 7 days.

Upon completing the prescribed treatment, the patient reported no alleviation, and her cough developed yellow sputum. She visited an otolaryngologist, a repeated CXR still with no abnormality, and a diagnosis of acute pharyngitis was given. The treatment included a course of cefixime and ciprofloxacin, which resulted in some improvement. Nevertheless, hoarseness and sputum recurred after antibiotic discontinuation. She then sought medical attention at our clinic. On the physical examination, the patient presented normal vital signs, and wheezing was heard bilateral lung fields. The pulmonary function test showed no sign of restrictive or obstructive pattern, with Forced Vital Capacity (FVC) of 3.81 L (110% predicted), Forced Expiratory Volume in One Second (FEV₁) of 3.42 L (113% predicted), and the negative result of the bronchodilator test (post-test FEV₁ of 3.45 L). The fraction of exhaled nitric oxide was 21 parts per billion. Diagnosis of asthma could not be ruled out and she was prescribed a trial with formoterol-budesonide two inhalations twice daily for a month, but without improvement. At the next clinical appointment, we noticed wheezing with monophonic characteristic and the loudest volume at the central region of the lung. Suspecting EBTB, the chest Computed Tomography (CT) scan undertaken revealed a tree-in-bud pattern in the lower left lung, along with left bronchial lumen narrowing (Figure 2). Sputum for acid-fast bacillus smear and genXpert MTB/RIF test were all positive with no resistance to rifampycin. Consequently, she was prescribed the anti-tuberculous regimen including isoniazid, rifampin, pyrazinamide, and ethamb-

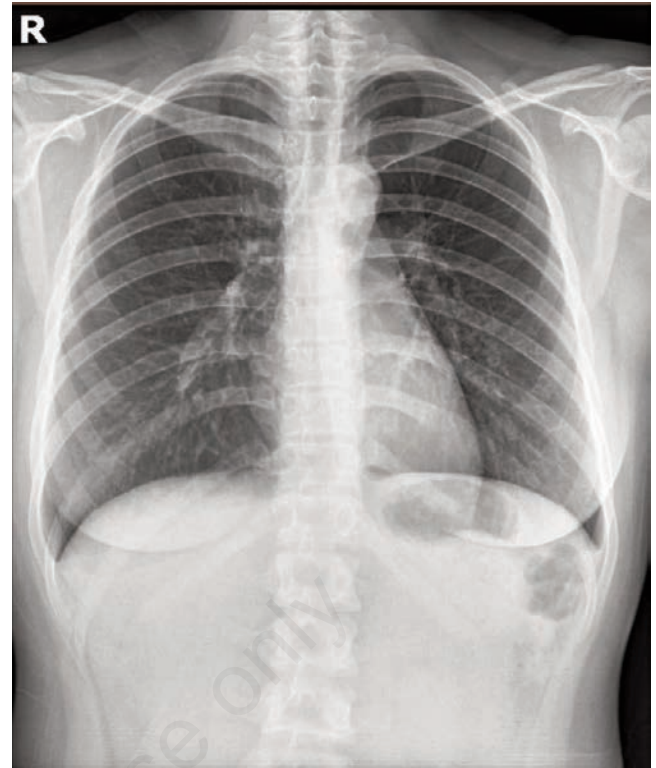


Figure 1. Chest X-ray 3 months after COVID-19 infection revealed no parenchymal abnormality.

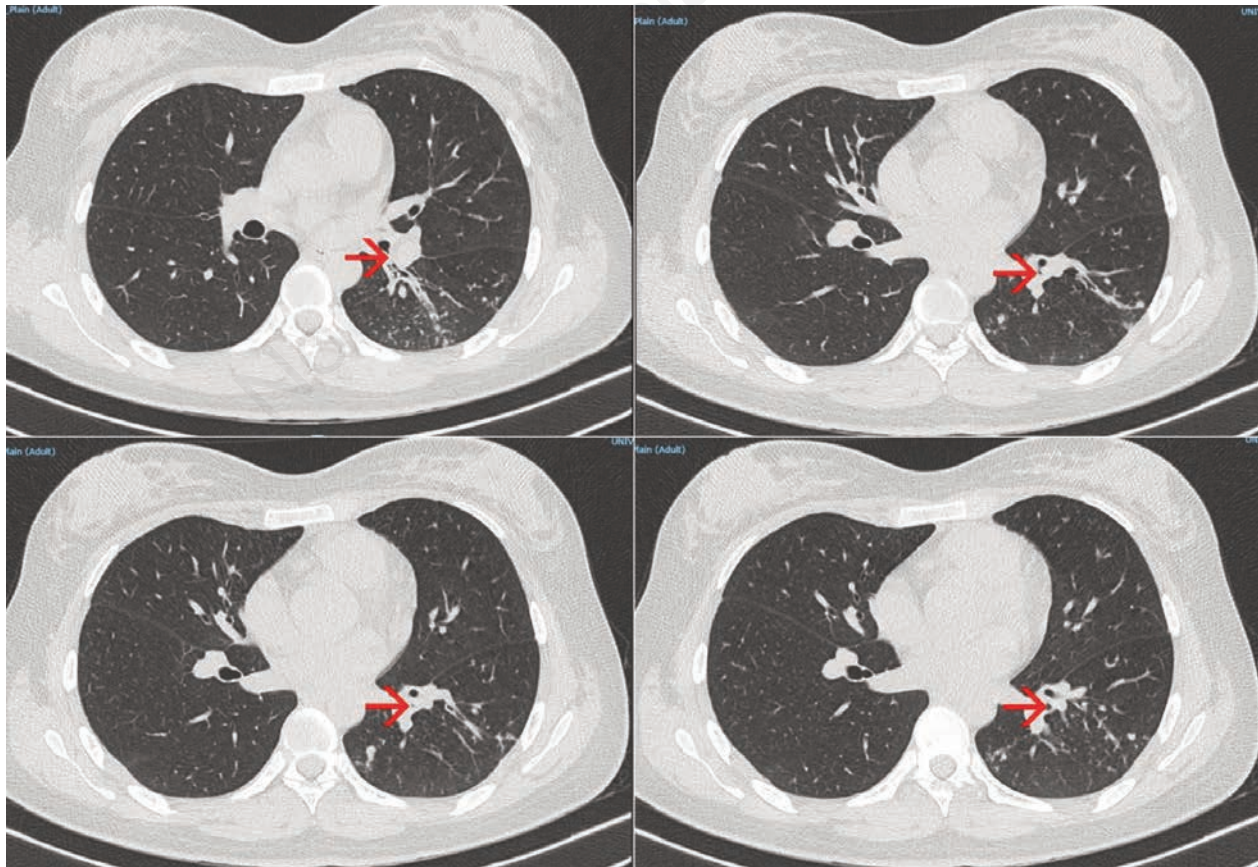


Figure 2. Chest computed tomography scan showed “tree-in-bud” pattern in the superior segment of the left lower lobe. Narrowing of the left lower lobe segmental bronchi is also indicated (red arrows).

utol for 2 months, followed by isoniazid and rifampin for an additional 4 months. The patient demonstrated a reduction in cough within 4 weeks after treatment.

Discussion

Cough is a sudden reflex to expel mucus, irritants, and pathogens from the airway and the lungs. When it persists for over 8 weeks, it is classified as a chronic cough.² Chronic cough can have a disruptive impact on the quality of life, comparable to that experienced by patients with chronic obstructive pulmonary disease.⁴ The major impacts of chronic cough are urinary incontinence, dysphonia, and depression.⁵ The process of identifying its etiology, already challenging, has become even more complicated since the COVID-19 pandemic, as potential causes now extend beyond the previous ones. Cough is among the most prevalent symptoms observed in COVID-19 patients, not only during the acute stage but also the convalescent stage. Studies have reported rates of cough 2 months after COVID-19 infection, ranging from 7% to 34%.⁶⁻⁸ Post COVID-19 cough can result from hypersensitivity in the cough pathways,⁹ triggered by pre-existing lung diseases, or secondary infections such as bacterial or fungal pathogens. The chronic cough induced by EBTB in our case was misdiagnosed with post COVID-19 cough, pharyngitis, and asthma. EBTB, a special form of tuberculosis in which tuberculous infection affecting the tracheobronchial tree, poses challenges in its diagnosis. The development of bronchial stenosis can cause wheezing, mimicking obstructive lung disease like asthma. A normal CXR does not preclude its diagnosis, particularly in EBTB cases with little or no involvement of parenchymal abnormality.³ Previously published cases have shown that 10-20% of EBTB patients exhibit normal CXR.¹⁰ Sputum Acid-Fast *Bacillus* (AFB) smear, although widely available, has a low yield for detecting EBTB.^{11,12} Fortunately, our case showed the normal CXR, but sputum smear was positive for AFB, and genXpert MTB/RIF test further confirmed the presence of *M. tuberculosis*.

COVID-19 can impair cellular immunity to create an opportunity to develop tuberculosis disease. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) does not activate *M. tuberculosis*-specific CD4⁺ T cells, indicating that acute SARS-CoV-2 infection may not immediately lead to the progression of latent tuberculosis infection to active disease. However, there was a significant drop in the number of *M. tuberculosis*-specific CD4⁺ T cells compared to healthy participants. As an intact T cell response is a crucial element in *M. tuberculosis* control, this could imply the host cellular immunity against tuberculosis weakens with SARS-CoV2 infection.¹³ The administration of immunosuppressive agents during management of COVID-19 is also a risk factor for tuberculosis reactivation, as it may lead to a suppression of cellular immunity.¹⁴ From the epidemiological perspective, the COVID-19 pandemic has adversely affected the pursuit of tuberculosis eradication. All the progress in tracking and management of tuberculosis worldwide has somewhat stalled during the times of the pandemic, with the foremost impact of the pandemic being the significant reduction in the number of newly diagnosed TB. The number peaked in 2019 at 7.1 million, but then dropped to 5.8 million in 2020, representing an 18% decline. The number improved slightly in 2021 with 6.4 million.¹⁵ The decline in the number of tuberculosis detections suggests that more people would be undiagnosed and untreated. These would lead to higher rates of transmission in the community, and in time, there will be an increase in the number of people with new tuberculosis, as well as higher mortality. The clinician should therefore increase suspicion

for undiagnosed tuberculosis among individuals experiencing persistent respiratory symptoms following COVID-19 infection.

Meticulous evaluation and high suspicion index for EBTB as an etiology for prolonged cough is always required, particularly in endemic regions of tuberculosis such as Southeast Asia. The first clue in our case was the characteristic of the sputum. Mucopurulent or purulent sputum is a characteristic of infectious disease rather than asthma.¹⁶ Wheezing in EBTB patients is usually more pronounced centrally and monophonic, as it is caused by the intraluminal obstruction due to the secretion, proliferative tubercule, or stricture after healing tubercular focus, or extra compression from tubercular lymphadenopathy. Further investigations, including bronchoscopy, chest CT scan, and nucleic acid amplification tests are required when tuberculosis is suspected. Alteration in bronchovascular structures can be detected in 95% of pulmonary tuberculosis cases through high resolution CT.¹⁷ Bronchoscopic biopsy stands as the most validated method for confirming the diagnosis of EBTB. The yield of bronchial biopsies in diagnosing EBTB ranges from 30% to 84% of patients.^{18,19}

Conclusions

Our case highlights the importance of considering EBTB as a potential cause of chronic cough in recovered COVID-19 patients. The overlapping symptoms and diagnostic challenges require a high index of clinical suspicion among healthcare professionals, especially in endemic regions.

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