

Case Report

Endobronchial Tuberculosis: from Diagnosis to Management and Quality of Life- A Case Report

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Abstract

Despite rapid advances in diagnostic and treatment modalities, endobronchial tuberculosis (EBTB), the particular form of tuberculosis defined as infection of the tracheobronchial tree caused by *Mycobacterium tuberculosis*, continues to remain a challenge for clinicians. Non-specific respiratory symptoms as well as normal radiological appearance (10-20% of cases) can be invoked for the delay in diagnosis. The bacteriological examination of the sputum smear has a low diagnostic yield. The positivity of the sputum smear varies between 16 and 53%, so a negative result does not exclude the diagnosis. In such cases, high-resolution computed tomography (HRCT) functions as a more sensitive tool and demonstrates the involvement of the tracheobronchial tree classically described as "tree-in-bud" appearance. Bronchoscopic biopsy is considered the most reliable method of confirming the diagnosis with a yield of 30% to 84%. The evolution of the disease is unpredictable, with a frequent progression to bronchial stenosis, therefore it requires regular follow-up and early intervention. The quality of life of patients with EBTB is affected both because of the debilitating symptoms and the side effects of treatment. Tracheobronchial stenosis, a common complication, can turn patients into chronic sources of infection or cause serious pulmonary complications. In this context, we present the clinical case of a 40-year-old patient with persistent cough syndrome, diagnosed with endobronchial tuberculosis by bronchoscopy, later confirmed by positive cultures for *Mycobacterium tuberculosis*. Treatment included the standard treatment regimen, adjusted to manage adverse reactions. This case highlights the importance of early diagnosis and appropriate management to improve quality of life and reduce EBTB-associated morbidity.

Keywords: EBTB, high-resolution computed tomography (HRCT), pathogenesis, TGF-beta

Introduction

Tuberculosis continues to be a public health issue nowadays, being endemic in many parts of the world and among the top 10 causes of death worldwide, despite significant progress in the last decade [1,2]. Despite the significant progress made in recent years regarding the diagnosis, management and prevention of tuberculosis, the incidence of the disease is still increased, probably due to the negative impact of the development of drug-resistant strains, weaknesses in the prevention and treatment system, the increase in the prevalence of diabetes, the ageing of the population, poverty, migration and last but not least, the AIDS epidemic [3].

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Endobronchial tuberculosis (EBTB), the particular form of tuberculosis defined as infection of the tracheobronchial tree caused by *Mycobacterium tuberculosis*, is the main complication of pulmonary tuberculosis. According to the literature, 10-40% of patients with active pulmonary tuberculosis developed endobronchial involvement [3]. Endobronchial tuberculosis represents a major diagnostic challenge, both in terms of significant morbidity and potential mortality, as well as in terms of case management, the considerable risk of complications and the difficulty of complete eradication of the infection [4]. Regarding the prevalence by sex, it has been suggested that endobronchial tuberculosis is more common among females, because they have a longer exposure to bacilli because they expect less due to socio-cultural or aesthetic factors; none of the less, the anatomical structural differences play an essential role, given the fact that the bronchi are narrower, thus making them more susceptible to infection [3].

The pathogenesis of endobronchial tuberculosis is not fully understood [5], however it may involve different mechanisms, including involvement of the adjacent bronchus in pulmonary tuberculosis, either bronchogenic pathway from ulcerated lesions or by contiguity from an excavate parenchymal focus [6,7]. Also, bronchial damage can be secondary to a lymph node fistula, resulting from the reactivation of old lymph node lesions, especially in the context of a severe primary infection [7]. Erosion of lymph nodes in the adjacent bronchus is an important mechanism in the pathogenesis of endobronchial tuberculosis in pediatric patients, due to the small caliber and fragility of their bronchi [6]. Another mechanism involves direct seeding of the bronchus by pathogenic mycobacteria. Extension of the infection via the lymphatic and hematogenous route is also possible, but rarely encountered [6]. The most prone territories are the right upper lobe and the right primitive bronchus [8]. The initial bronchial lesion presents as a lymphocytic infiltrate followed by considerable congestion and perilesional edema [5,9]. Development of caseous necrosis with tuberculous granuloma formation can be found at the mucosal surface. Fibrotic modification of the lamina propria as well as healing of mucosal ulceration eventually progresses to bronchial stenosis [5,10]. In addition to local factors, various cytokines may play an important role in pathogenesis [5]. Increased levels of interferon gamma and TGF-beta in bronchial lavage fluids have been shown to be related to EBTB pathogenesis and progression. Initial low serum TGF-beta levels and changes in serum TGF-beta levels observed after treatment have been implicated in the development of bronchial stenosis during the course of the disease [11]. None of the less, it is evident that the complex interaction of multiple mechanisms is responsible for the development and progression of EBTB in adults [5].

The clinical presentation is heterogeneous and non-

specific, which can occur secondary to the condition itself, manifesting through persistent cough, most frequently with quantitatively reduced mucosal expectoration, chest pain, fever, fatigue and dyspnea, or it can be the result of complications of the disease, such as endobronchial stenosis (repeated post-obstructive pneumonia, bronchiectasis) [12,13,14]. The duration of symptoms and clinical features are variable and depend on the location, degree of involvement and stage of the disease [5]. General symptoms such as weight loss, loss of appetite, and night sweats may not be prominent in EBTB [15, 16]. Fever, if present, is usually low-grade at onset, but may become marked as the disease progresses [16]. Respiratory symptoms in EBTB are usually nonspecific and confusing. A cough syndrome that does not respond to common cough medications is the most common manifestation that progresses slowly over weeks or months [8]. Hemoptysis may occur occasionally, but it is rarely massive. With the rupture of the lymph nodes, chest pain can occur in the sternal or parasternal region is found in about 15% of patients [5]. Dyspnea is often associated with pulmonary atelectasis. And the presence of wheezing and stridor can be characteristics of bronchial stenosis [5,17]. Since these symptoms and signs are non-specific and mimic various lung diseases such as bronchial asthma [18], pneumonia [19], foreign body aspiration [20] and malignancy [21], it is very difficult to diagnose through the clinical picture and therefore frequently missed [5].

The bacteriological examination of the sputum smear is the most commonly used test for diagnosis, but it has a low diagnostic yield [22]. The positivity of sputum smear varies between 16-53%, a negative result does not exclude diagnosis [22,23,24]. Performing pulmonary function tests in patients with cough, dyspnea and wheezing, requires a differential diagnosis with bronchial asthma, a pathology with which it is frequently confused [5]. The dominant pattern in EBTB is usually restrictive (47%), followed by normal lung function, mixed or obstructive ventilatory dysfunction [25]. The predominance of restrictive ventilatory dysfunction could be explained by tracheobronchial tree obstruction or associated chronic inflammatory changes [5,26].

Computerized tomography (CT) and bronchoscopy are the most useful diagnostic tools for both confirming and evaluating tracheobronchial stenosis. Chest X-rays may be normal in approximately 10-20% of patients, except in cases where there is significant airway obstruction, leading to atelectasis of adjacent lung segments, or concomitant parenchymal or pleural pathology [22]. In a retrospective study conducted by Lee and Chung, 10% of patients diagnosed with endobronchial tuberculosis did not demonstrate any abnormalities on chest X-rays [25]. From an imaging point of view, computed tomography of the chest provides additional details, such as irregularities or stenosis of the airways and

other manifestations of tuberculosis in the chest, such as mediastinal lymphadenopathy, nodules, cavities and pleural effusions [27]. High-resolution computed tomography (HRCT) is more sensitive than conventional chest X-ray in demonstrating early endobronchial spread [5]. Studies using HRCT have shown a much higher prevalence of the disease, as endobronchial involvement can be accurately detected at an early stage as well [5]. Endobronchial involvement in pulmonary tuberculosis has been reported up to 95% and 97% with HRCT scanning in different studies [28, 29]. According to the literature, the earliest finding of bronchogenic dissemination are centrilobular nodules with a diameter of 2-4 mm containing caseous material in or around the terminal bronchus [28]. With extensive involvement, branched linear structures of similar caliber are noteworthy that arise from a stem that gives the "tree in bud" appearance [5]. In addition, nodules with poorly defined margins, lobular areas of consolidation, bronchial wall thickening, and interlobular septa also describe bronchogenic spread in some cases [5,29].

Bronchoscopy is a mandatory method of early diagnosis and an important tool in the exclusion of other subsidiary or concomitant diseases, such as malignancy. The yield of bronchial biopsies in diagnosing endobronchial tuberculosis is between 30% and 84% [17]. Based on bronchoscopic findings, EBTB is usually classified into seven subtypes with a specific appearance, namely caseos-ulcerative, edematous-hyperemic, fibrostenosis, tumor, granular, ulcerative and non-specific bronchitis [30]. Of these subtypes, the caseos-ulcerative type is reported as the most common form (43%). This classification of EBTB is closely related to the degree of progression of the disease [5].

The quality of life of patients diagnosed with endobronchial tuberculosis can be affected by the unpredictable clinical course of the disease, as well as by the frequent progression to complications, compared to patients diagnosed with pulmonary tuberculosis. The prognosis of caseos-ulcerative and edematous-hyperemic EBTB is the most unfavorable, leading to fibrostenosis in two-thirds of patients [5,22]. The prognosis is relatively better for granular, ulcerative and nonspecific bronchitis EBTB [5]. However, the clinical course of the tumor type is unpredictable, frequently leading to bronchial stenosis despite appropriate treatment [5,22]. Furthermore, this progression is not directed into a single dimension [5]. All subtypes of EBTB are located between the extreme ends of healing and bronhostenosis, and can develop into other subtypes during treatment [5,31]. But there is a critical point between these two ends, which is mainly determined by the extent of the progression of the disease and closely related to the formation of granulation tissue [5,31]. Bronchial stenosis is inevitable if the disease progresses beyond this critical point [5]. Bronchial stenosis and stricture are the most common complications and can develop in 60 to

95% of cases, despite appropriate antituberculosis therapy. If the stenosis involves the trachea, airway obstruction may develop [5]. Another common complication is bronchiectasis which frequently develops as a cicatricial process, secondary to lung destruction and fibrosis (traction bronchiectasis). Central bronhostenosis with distal bronchial dilation can also lead to the development of bronchiectasis. Hemoptysis is the most common presentation in symptomatic cases [5,32]. In order to make an early diagnosis, an increased level of awareness of this condition is essential, and bronchoscopy should be performed as soon as possible in suspected patients [4]. Patients with endobronchial tuberculosis may end up requiring pulmonary resections due to severe bronchial obstructions, extensive destruction of the lung parenchyma, infectious complications and reactivation of the infection, especially in cases of multidrug-resistant or extensive-drug-resistant tuberculosis [33,34,36]. Pulmonary resections are sometimes essential to eliminate outbreaks of infection that do not respond to drug treatment [33,35]. However, these surgeries have a profound impact on patients' quality of life [37]. Losing a significant portion of the lungs can reduce total respiratory capacity, causing dyspnea and limiting daily physical activities [37]. The post-operative recovery period often requires intensive pulmonary rehabilitation to optimize the remaining respiratory function, a process that can be long and demanding [37]. Patients also experience persistent post-operative pain and discomfort, and the risk of surgical complications such as infections and bleeding can worsen their overall health [33,37]. In addition to the physical impact, the need for major surgery and the diagnosis of severe tuberculosis can generate anxiety, depression and psychological stress, highlighting the need for continuous psychological support to help patients adapt to significant changes in their lives [37].

The treatment of EBTB is similar to the standard regimen of pulmonary tuberculosis. Four standard first-line drugs are used for the treatment of EBTB: isoniazid (INH), rifampin (RIF), ethambutol (EMB) and pyrazinamide (PZA). The duration of treatment is six months, consisting of INH, RIF and PZA for the first two months, followed by INH and RIF for the next 4 months daily [38]. However, it has been reported that bronchial stenosis can develop despite effective therapy [39]. Once the stenosis has developed, it is not possible to reverse it with chemotherapy or corticosteroids. Therefore, at this stage, airway permeability must be restored either by endobronchial interventions or by surgical means [40,41]. Corticosteroids have been used as adjuvant therapy, but the role of corticosteroids in the treatment of endobronchial tuberculosis is still controversial [42]. In adults, the therapeutic effects are interdependent on the stage of the disease. This therapeutic method proves its usefulness in the early stages by relieving inflammation and edema,

but the regression of irreversible fibrostenotic lesions is not possible [5,43]. Interventional bronchoscopy is an alternative treatment strategy in the management of endobronchial stenosis. There are various bronchoscopic techniques for relieving airway stenosis, including laser, cryosurgery, controlled heat application, balloon dilation and stent insertion [5]. If all these modalities fail, surgery is considered the method of choice because the surgical approach provides a permanent solution [5]. Surgical removal of a lung lobe complicated by atelectasis may be one of the surgical approaches. Other surgical methods include sleeve resection, carinal resection and end-to-end anastomosis [5,44]. None of the less, other surgical approach can be directed towards autografts, allografts, tracheal platforms performed through bioengineering and tracheal transplants [5]. Endobronchial tuberculosis remains a major public health problem because its diagnosis is frequently delayed, and airway stenosis, along with associated complications such as post-obstructive pneumonia, atelectasis, hemoptysis, wheezing, and dyspnea, may occur during treatment.

Case Report

We present the case of a 40-year-old patient, non-smoker, with no occupational or home exposure to respiratory toxic substances, an anamnestic positive for allergy to Ciprofloxacin. The patient presented in our clinic for a chronic cough syndrome, initially with an irritative character, later with purulent sputum, which started 3 months ago and progressively worsened until the moment of hospitalization, denying other manifestations. From the patient history we mention a hospitalization 10 years ago for dry cough and odynophagia, with a positive test for tuberculin intradermal reaction 16 mm. Radiologic findings were infiltrative-fibronodular lesions and calcareous lesions in the apical segment of the right upper lobe, highly suggestive of a

bacillary infection. In this context, it was necessary to perform a bronchoscopy with bronchoalveolar lavage (BAL). Both bronchial aspiration and sputum tests given during hospitalization at the time were negative for bacillary etiology. Following antibiotic treatment with quinolone antibiotics, for a period of 7 days, the infiltrative lesions were partially resorbed.

Currently, general physical examination revealed no significant sign of pallor, cyanosis, jaundice, clubbing or peripheral lymphadenopathy. On auscultation, vesicular breath sound was diminished with sibilant rales apically, requiring the continuation of complementary investigations. The biological examination reveals only a slight thrombocytosis, the rest of the hematological and biochemical parameters being within the limits of the reference values. Respiratory function, spirometry with bronchodilator test and body plethysmography shows a mild obstructive ventilatory dysfunction with maximum expiratory volume in the first normal second, with a significant bronchodilator response (pre-bronchodilator FEV1 3.16 L to post-bronchodilator FEV1 3.60 L; which shows an increase of FEV1 with 13.92% and 4410 mL), slightly decreased diffusing capacity with decreased transfer coefficient. In order to complete the imaging protocol, the native chest CT imaging evaluation is required, in which the presence of "tree in bud" pulmonary nodules and micronodules located in right upper lobe is objectified, associated with bilateral cylindrical bronchiectasis, with thin walls and calcifications included (Figure 1).

Given the fact that the patient had this cough syndrome for more than 3 months, it is considered appropriate to perform bronchoscopy with autofluorescence and BAL. The slim and ultra-slim (3.1 mm) bronchoscopes were used, which highlights whitish deposits, possibly necrotic, adhered to a mucosa with infiltrated and congestive appearance at the level

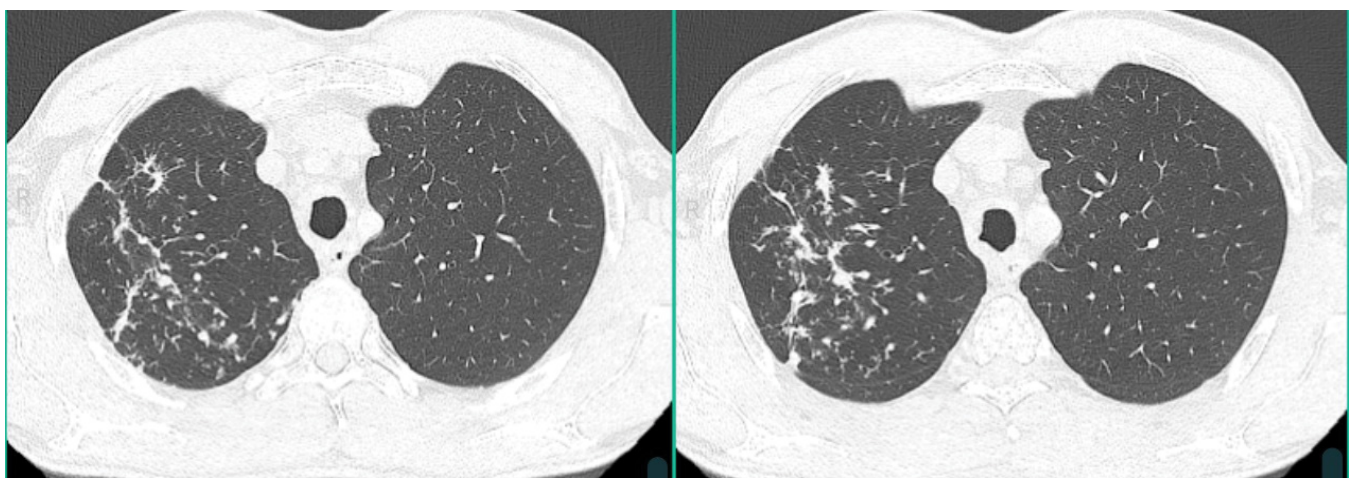


Figure 1: CT exam of the thorax highlights multiple micronodules and small juxacentimeter pulmonary nodules distributed predominantly in the right upper lobe described as “tree-in-bud” pattern.

of the trachea, starting from the first cartilage and continuing distally on the anterior, right lateral and posterior walls. They continue at the level of the right primary bronchus, up to the junction with the intermediate bronchus and at the level of the right upper lobe (RUL). RUL spurs have an infiltrated and congestive appearance, with partial erosion on the upper slope. RUL is almost completely stenosed, initially due to necrotic deposits and granulation tissue, continuing distally with a total obstruction of the dorsal segment of right upper lobe. From this level a multicentric biopsy was performed, with slight bleeding that stopped after bronchial toilet. Otherwise, bilateral diffuse bronchitis appearance, without changes in the bronchial tree. Mucosal changes seen on NBI examination in the mentioned areas. The cytological examination was performed, including bacteriology, mycology, Ziehl-Nielsen staining, culture in liquid medium and GeneXpert test.

Corroborating the anamnestic, clinical and paraclinical data, with a high endobronchial appearance suggestive of a caseum appearance, the suspicion of tracheobronchial tuberculosis is raised. The GeneXpert test that detected the high MTB complex, without resistance to Rifampicin, completed by the histopathological examination that revealed bronchial mucosa with denuded covering epithelium with marked predominantly acute inflammatory infiltrate, associating rare epithelioid histiocytes and marked fibrin-leukocyte deposits on the surface, being the one that confirms

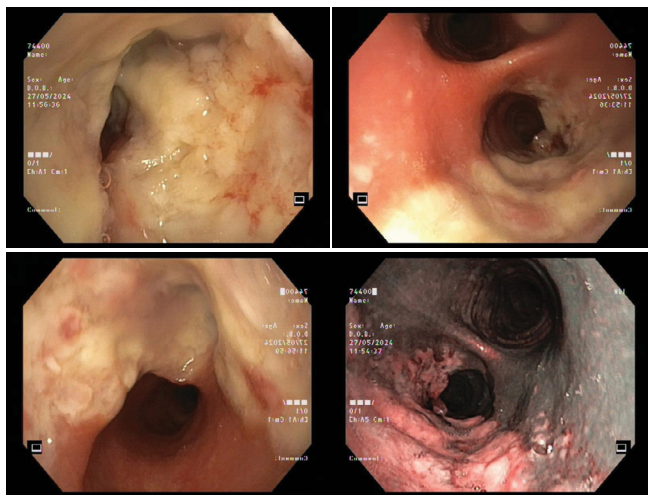


Figure 2: The bronchoscopy performed highlights white deposits, possibly necrotic, adherent, on the background of a mucous membrane with an infiltr-congestive appearance at the level of the trachea, starting from the first cartilage and continuing distally on the anterior, right lateral and posterior walls, then continuing at the level of the right primitive, until the junction with the bronchus intermediate and at the level of RUL. The right upper lobe spurs with infiltr-congestive appearance, with partial erosion on the upper slope. RUL is initially sub-totally stenosed by necrotic deposits and granulation tissue, continuing distally with total obstruction of the dorsal segmentation of the RUL.

the bacillary etiology. Following this result, the treatment scheme according to the National Program for Prevention, Surveillance and Control of Tuberculosis is initiated, per kilogram of body weight with Rifampicin 600 mg, Isoniazid 300 mg, Pyrazinamide 1500 mg, Ethambutol 1200 mg. During the initiation of the treatment, the patient developed an itchy erythematous reaction, mainly at the level of the upper limbs, bilaterally and flanks, which is why antihistamine treatment is also associated, with subsequent favorable evolution. The patient reported a gradual betterment in his condition within the next few weeks, but a radiological and bronchoscopic evaluation will be mandatory at 3 months of treatment, in order to evaluate the level of bronchostenosis and possible early complications.

Discussions

The case is an instructive one as it captures the non-specific aspect of first-intent imaging investigation, requiring a comprehensive and coordinated approach for correct diagnosis and appropriate patient management. Idiopathic cough is a chronic cough that persists for a period of eight weeks or more, which cannot be attributed to an obvious cause, despite an exhaustive medical evaluation. The estimated global prevalence of chronic cough is between 2% and 18%. Chronic cough is more common in women than men, with studies reporting that 66–73% of patients are women, likely due to hormonal differences that can influence cough reflex sensitivity and airway responsiveness [45]. This condition can be particularly frustrating for both the patient and the doctor, as standard therapies for chronic cough, caused by conditions such as asthma, gastroesophageal reflux disease, or respiratory infections, prove ineffective. Assessment of idiopathic cough usually involves a series of detailed investigations to rule out other potential causes, and treatment often focuses on managing symptoms and improving the patient's quality of life [46]. Although idiopathic cough and endobronchial tuberculosis are distinct conditions, there is a possibility that patients with endobronchial tuberculosis may develop a persistent chronic cough that may be difficult to differentiate from idiopathic cough, requiring a detailed and multidisciplinary medical evaluation. Awareness of the entity and consideration of EBTB as a differential diagnosis in difficult cases could be helpful for clinicians in planning a subsequent definitive diagnostic strategy.

Conclusion

Endobronchial tuberculosis (EBTB) is a distinct type of tuberculosis known for its high morbidity and potential for severe outcomes, associated with high impact on the quality of life of patients by the unpredictable clinical course of the disease, as well as the frequent progression to complications. Prompt diagnosis and the early initiation of antituberculosis therapy are crucial to managing EBTB effectively and

avoiding complications such as tracheobronchial stenosis. The use of corticosteroids in treatment remains debatable, though they may be beneficial in specific situations. For early and precise diagnosis, bronchoscopy should be the primary procedure performed in suspected cases. When medical therapy alone is insufficient, various interventional and surgical bronchoscopic techniques may be necessary to maintain lung function [47].

These interventions should be tailored to the disease stage as determined by bronchoscopic evaluation. Continuous follow-up and interventional care are vital to prevent severe, potentially irreversible complications. The optimal approach integrates the latest technologies with a commitment to research to enhance preventive, palliative, and therapeutic outcomes. Given the significant role of TGF- β in the development of bronchial stenosis, using neutralizing antibodies against TGF- β 1 could be effective in alleviating airway obstruction [48]. Nevertheless, a thorough understanding of the pathogenesis is essential to developing new therapeutic strategies that could improve patient outcomes.

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