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Review

Bronchoscopy procedures in diagnostics and treatment of endobronchial tuberculosis

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Abstract

Endobronchial tuberculosis is a rare form of tuberculosis that is characterized by the presence of tuberculous granuloma within the respiratory tract, usually in the trachea or main bronchi. Multiple key notes regarding this form make it difficult to detect and treat, which can lead to prolonged, lifelong even, problems that lead to a significant loss in quality of life. Even if the conventional treatment for tuberculosis is started on time, endobronchial tuberculosis can still develop. In those cases, a bronchoscopy should be performed to objectify the type of endobronchial tuberculosis and treat it in order to prevent permanent airway stenosis. In this paper, we will note the main characteristics of endobronchial tuberculosis, as well as bronchoscopy procedures used for its treatment such as balloon dilatation, laser, argon plasma coagulation, cryotherapy, and implementation of the stent. The main goal is to raise awareness of endobronchial tuberculosis to reduce the risk of complications of its mistreatment.

Key words: Tuberculosis; trachea; bronchi; bronchoscopy.

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Introduction

Tuberculosis (TB) remains one of the leading global health issues, especially in the third world and developing countries. Despite TB being a preventable disease, it is estimated that around 10 million people globally fall ill from tuberculosis [1]. Due to its high prevalence, in 2015 the World Health Organization (WHO), and in 2018 the United Nations, have both created programs whose goals were to reduce the incidence, mortality, and financial cost for both treatment and prevention [2,3]. However, in the latest report by the WHO on TB, it was noted that in 2022 TB was the second leading cause of death from a single infectious agent in 2022 [4], after COVID-19. Considering such high incidence and mortality, one should be familiar with all forms of TB, both pulmonary (one of which is endobronchial tuberculosis) and extrapulmonary, to be able to properly treat it, and prevent potential lethal outcomes.

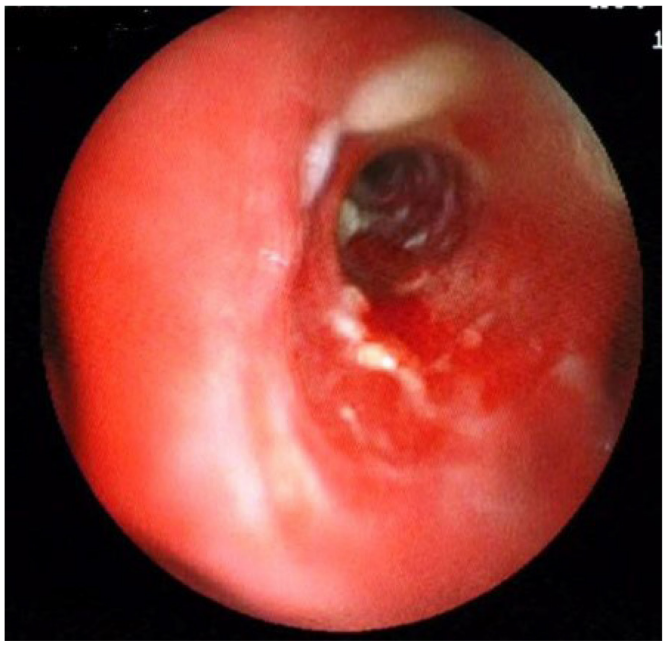
Pathogenesis and risk factors

Endobronchial tuberculosis (EBTB) is a form of pulmonary tuberculosis where the primary pathological process is in the tracheobronchial tree. The presence of *M. tuberculosis* in respiratory tree can lead to nonspecific inflammation in the tree itself, manifesting in hyperemia and oedema. If left untreated, nonspecific inflammation will further develop into necrotizing granuloma located anywhere between mucosa, submucosa, or even in muscular layer or cartilage. Because of the destruction of the layers of the wall, macroscopically, patients can develop ulcers or fistulas, or, if destroyed structures are repaired and replaced with fibrine, stenosis [5]. The degree of destruction and further evolution of granuloma largely depends on the quantity of *M. tuberculosis* present, the state of the immune system of the host, and previous structural abnormalities of the tracheobronchial tree. *M. tuberculosis* can be present in the tracheobronchial tree via multiple ways: directly from nearby infected tissue, hematogenic, or lymphogenic. Since *M. tuberculosis* can be present in multiple parts of the tracheobronchial tree simultaneously, EBTB can be classified as single, if present only in one place or multiple, if present in multiple parts; the second classification can be on central and peripheral, depending on whether it afflicts

the proximal or distal part of the bronchus. Using both classifications, clinicians can determine the severity of the disease and can plan the treatment accordingly.

Stenosis of the bronchus can be the end-stage state of the previous EBTB. The stenosis is irreversible and remains even after the eradication of *M. tuberculosis*, and can cause further complications, such as atelectasis or susceptibility to infections due to the difficulty of sputum elimination. There are multiple risk factors for the development of EBTB and many more are still unknown [6]. Any state that reduces the elimination of the infected sputum, such as anatomic variations of the airway (narrower left main bronchus compared to right main bronchus; narrower female bronchi vs male bronchi) or hyperviscosity of the sputum itself (cystic fibrosis, chronic obstructive pulmonary disease), increases the risk for EBTB. Even though smoking is a risk factor for the development of TB, paradoxically, studies have shown that it has a protective effect on the development of EBTB [7]. The risk for EBTB rises with the length of untreated *M. tuberculosis* infection. Suppression of the coughing, either by the usage of medicine, or voluntarily due to social norms, leads to the prolonged presence of *M. tuberculosis* in the tracheobronchial tree, which is another risk factor for EBTB. The main obstacle to identifying all the risk factors for EBTB is that EBTB is usually undiagnosed and underdiagnosed, and most data available is from retrospective studies.

Figure 1. Nonspecific endobronchial tuberculosis.



Clinical presentation and diagnostics

Clinical presentation in the early stages of EBTB is unspecific and consists of coughing, chest discomfort, hemoptysis, and dyspnea, of which coughing is the most common one. If left untreated, and stenosis is developed, the patient can have wheezing. Systemic symptoms, such as fever, fatigue, loss of weight, night sweats, and loss of appetite, usually present in TB, are uncommon in EBTB, which further complicates the diagnostics. Again, if stenosis is developed, the patient can have an increase in lower respiratory tract infections. It should be noted that stenosis can lead to complete obstruction of the airway, however, patients usually do not present with signs and symptoms present in acute foreign body asphyxiation, as time is required for the development of stenosis. During physical examination, one could find reduced breathing sound, isolated wheezing, and/or crackles. Sputum examination for mycobacterial presence is important, as it is a noninvasive diagnostic procedure, and should always be performed. In case of EBTB, compared to TB, direct microscopy, rapid PCR tests, and sputum cultures are more frequently negative, however, this does not exclude the diagnosis of EBTB. Chest X-ray should be performed; however, it can be normal in up to 20% of all cases and is more commonly found if central EBTB is present, considering that the central structures can hide the EBTB. The most common pathological finding is patchy parenchymal infiltrates in the affected lobe, similar to tracheobronchitis or bronchiolitis, depending on whether EBTB is proximal or distal, respectfully. Other findings, such as atelectasis, obstructive pneumonia, and mucoid impactions, are present only if stenosis is present. Peribronchial calcifications can be present if EBTB is untreated for a prolonged time. It is possible to find radiological signs of both EBTB and TB in the same patient, as well as only signs of TB. A CT scan is a more sensitive radiological procedure for detecting EBTB, with a sensitivity of up to 97% [8]. EBTB in its initial stages is shown as unilateral nodes, located primarily in the wall of the afflicted airway. If there is a dominant bronchial spread, "tree-in-bud" can also be seen. Despite the relatively high sensitivity of CT scans, bronchoscopy should be performed for definitive diagnosis of EBTB.

Bronchoscopy

Bronchoscopy is the most valuable tool in both diagnostics as well as treatment of EBTB and can be performed in any and all stages of the disease. Besides the direct observation of the airway mucosae, while

performing bronchoscopy biopsy, brushing, bronchoalveolar lavage, and/or bronchoscopic ultrasound can be performed to both diagnose EBTB and exclude other diseases that can mimic it, such as malignancies or other granulomatous diseases. Biopsy is one of the most important diagnostics procedures, as it can give the correct diagnosis in up to 83%. Endoscopic examination of EBTB has enabled researchers to give several subtypes, depending on the stage of pathological process (biopsy should be performed, due to similarity to other diseases):

1. Nonspecific bronchitis: tracheobronchial mucosa has nonspecific inflammation and mild edema; however, it has no similarity with granulomatous inflammation; *M. tuberculosis* is rarely isolated from this sample. The prognosis is good and does not require bronchial treatment (Figure 1).
2. Edematous-hyperemic: tracheobronchial mucosa still has nonspecific inflammation; however, the predominant finding is severe edema and hyperemia. The airway is narrowed due to the severity of edema. If left untreated, it will progress to caseating and fibrostenotic form (Figure 2).
3. Granular: tracheobronchial mucosa has on its surface nodules. The prognosis is usually good.
4. Caseating: tracheobronchial mucosa is inflamed and covered with a cheese-like substance (necrotic debris); this is the most common form of the disease. The airway is narrowed, not only due to inflammation, but due to necrotic debris. If left untreated, this form also does not have a good prognosis, as it leads to a fibrostenotic form.
5. Ulcerative: ulcers are present in tracheobronchial mucosa. Despite ulcers developing, in their reparation scars that remain do not obstruct the airway, so the prognosis is positive.
6. Tumorous: caused by endoluminal growth of granuloma, and can mimic endobronchial cancer. The prognosis is variable, as this form can be recurring, even after treatment. If recurring, it can leave scarring and further stenosis. (Figure 3).

Figure 3. Tumorous endobronchial tuberculosis.

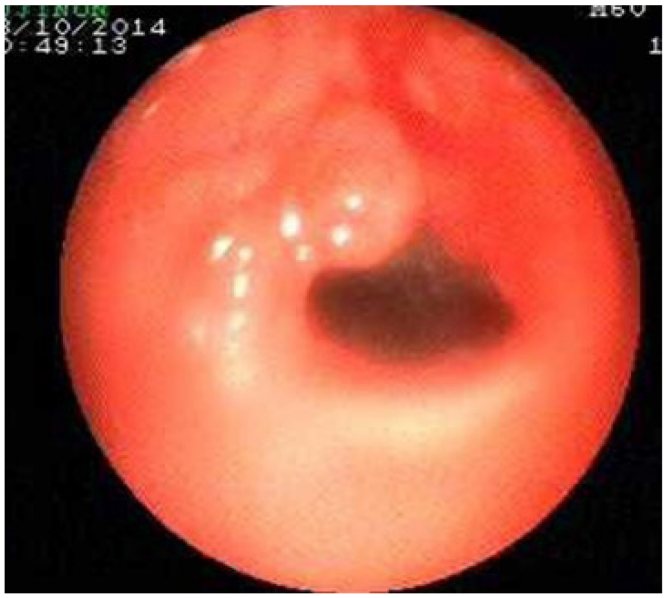


Figure 2. Edematous endobronchial tuberculosis.

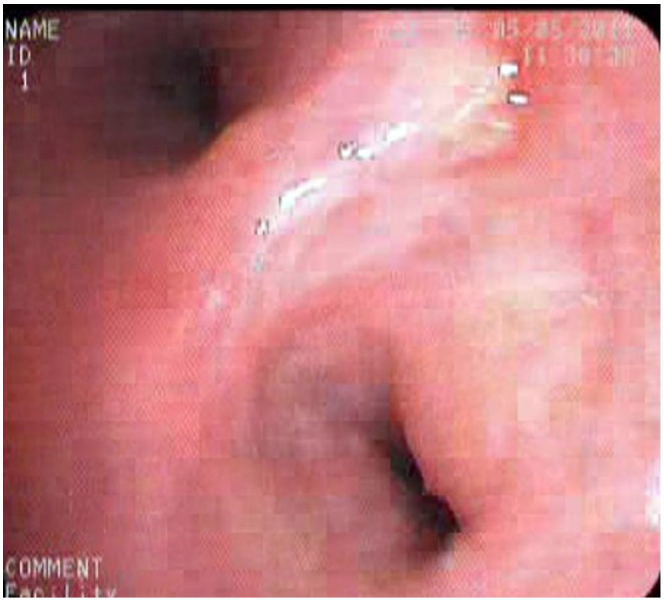
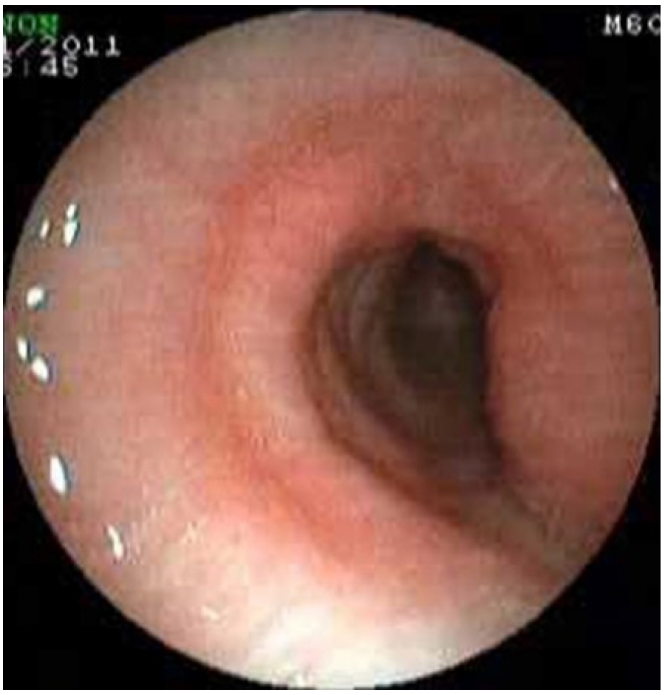


Figure 4. Fibrostenotic endobronchial tuberculosis.



7. Fibrostenotic: narrowing of the airway, usually nonconcentric strictures; *M. tuberculosis* is rarely isolated from this sample. The form with the worst prognosis, as it is made of scarring tissue, and the changes are irreversible [9] (Figure 4).

It should be noted that when performing a biopsy, the zone of inflammation should be sampled, as zones with caseosa will only show cellular debris with or without detectable bacteria, and fibrostenotic zones will not show any specific cellular components, and cannot be differentiated from other fibrotic diseases.

The subtypes correspond to the pathophysiological evolution of the disease. Initial nonspecific bronchitis is caused by the activation of the innate immune system of the mucosa with further lymphocytic infiltration, and cannot be differentiated from other bronchitis. The inflammation is unresolved (edematous-hyperemic), due to specifics of *M. tuberculosis*, and specific tuberculoma are developed (granular). As tuberculomas are developed on the surface of the mucosa, EBTB enters its granular phase, when it is most commonly diagnosed. With the destruction of the granuloma, the necrotic tissue whiting is released (caseating), and when multiple granulomas are connected the ulcerative phase is found. If the granuloma does not perforate, the patient will not have the ulcerative phase, and the granuloma will grow both within the mucosa and toward the airway and create tumor-like structures (tumorous). If the inflammation continues, the fibrotic tissue will proliferate, which leads to the fibrostenotic phase. In this phase, it could be difficult to give the correct diagnosis, as the fibrosis is not specific, and the pathogen cannot be detected. It should be noted that different stages can be seen in the same patient during the same procedure; the knowledge of this subtype can significantly help in determining the length of the disease, as well as its prognosis.

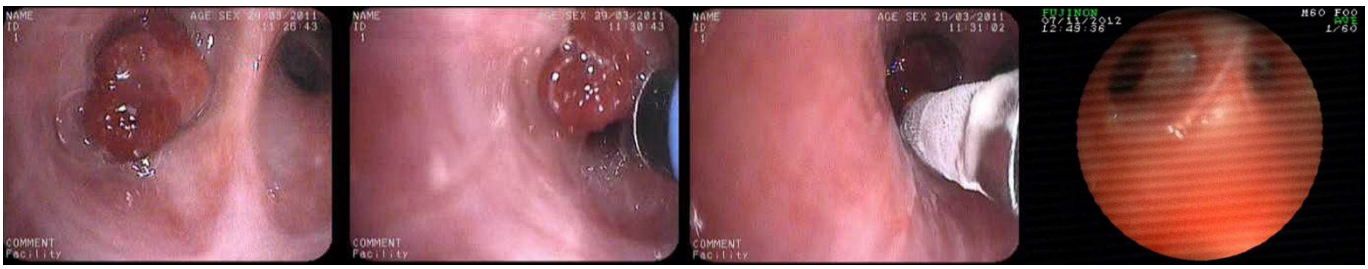
Treatment

Treatment of EBTB consists of a combination of drugs and bronchoscopic procedures. There are two main goals in the management of EBTB: the eradication of M. tuberculosis in as shortest time possible and the prevention of complications, primary stenosis.

Drugs used in EBTB are no different than drugs used in TB, first-line antituberculosis drugs (ATD): rifampin, isoniazid, ethambutol, and pyrazinamide with/without streptomycin are used, for between 6 to 9 months, the same protocol as for treatment of TB. The use of corticosteroids remains controversial. Certain studies have shown the benefit of early-stage low-dosage corticosteroids to prevent stenosis [10]. Rikimaru had shown benefits in intralesional administration of a combination of corticosteroids and ATD, showing accelerated healing and reducing stenosis [11]. Further prospective studies are still required to provide concrete benefits and a standardized approach to the administration of corticosteroids in EBTB.

The most important complication of EBTB is stenosis since when it occurs, there is no medicinal treatment that can reverse it. Bronchoscopic procedures used in the treatment of stenosis are balloon dilatation, laser, argon coagulation, and cryotherapy. These procedures can be repeated in case of recurring stenosis, however in those cases, the application of bronchial stent should be considered. Balloon dilatation is a minimally invasive procedure in which a balloon is placed in the middle of the stricture and, when inflated, it mechanically causes a dilatation, however, a certain degree of stenosis remains. Balloon dilatation can be repeated, is best used in circular stenosis, and should be avoided in cases with active inflammation, or when structures whiting the wall (cartilage) are damaged. Laser treatment is suggested to be performed in cases of stenosis on large airways, such as trachea or main bronchi; argon coagulation can be used in the treatment of both stenotic and tumorous EBTB. Cryotherapy has shown the highest safety in the treatment of stenosis, compared to laser and argon coagulation, as well as a quicker time to recovery compared to those procedures (Figure 5). Possible complications of all these procedures are rupture of the wall, hemorrhage (low in cryotherapy), and recurrence of the initial changes. It

Figure 5. Criobiopsy in treatment of EBTB- before and after.



should be noted that, besides balloon dilatation, other procedures are still relatively new in the treatment of EBTB, and currently published studies are conducted on a relatively small sample [12,13]. Currently, topical administration of mitomycin-C, a cytostatic with antifibrotic properties, is under research, as it has shown benefits in post-operational stenosis [14]. If the stenosis is recurring after previously mentioned interventions, temporary placement of the stent is possible [15]. Both metallic and silicone stents can be placed, however silicone stents have an advantage, since they can be removed if needed, and the degree of surrounding tissue reaction is less, compared to metallic ones. In severe cases, with large central stenosis, or with significant hemoptysis, surgical procedures such as lobectomy or even pneumonectomy can be performed.

Conclusions

EBTB is a rare form of tuberculosis, which if left untreated, can lead to serious complications, primarily in the form of stenosis of the major airways. For definitive diagnosis and for assisting in therapy, a bronchoscopy is required. Development of intralesional and topical drugs for EBTB will only lead to further need for bronchoscopy, to prevent possibly life-threatening stenosis.

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Conflict of interests

No conflict of interests is declared.

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