Endobronchial tuberculosis—a review

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Abstract: Endobronchial tuberculosis (EBTB) is a tuberculous infection of the tracheobronchial tree with microbial and histopathological evidence. Patients may present with symptoms secondary to disease itself or from the complication of disease like endobronchial obstruction. Diagnosis requires a high index of suspicion. Computed tomography (CT) and bronchoscopy along with microbiological investigations are the most useful diagnostic tools for the confirmation as well as for the evaluation of the tracheobronchial stenosis. The goals of treatment are eradication of tubercle bacilli with anti-tubercular medications and the prevention of airway stenosis. Interventional Bronchoscopic techniques and surgery is required for those patients who develop severe tracheobronchial stenosis that causing significant symptoms including dyspnea, repeated post obstructive pneumonia or bronchiectasis.

Keywords: Endobronchial tuberculosis (EBTB); bronchoscopy; complications; radiology; endobronchial obstruction

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Introduction

Tuberculosis (TB) is a major global health problem. It affects millions of people each year and ranks alongside the human immunodeficiency virus (HIV) as a leading cause of death worldwide. In 2014, there were an estimated 9.6 million new TB cases and 1.5 million deaths worldwide according to WHO (1). Endobronchial tuberculosis (EBTB) or tracheobronchial TB is a special form of TB and is defined as tuberculous infection of the tracheobronchial tree with microbial and histopathological evidence (2). Involvement of trachea and bronchi by TB was first described by Richard Morton, an English physician in 1698 (3). This form of TB is difficult to diagnose because the lesion is not evident in the chest radiograph frequently and thus delaying treatment. Further investigations like computed tomography (CT) scan of chest and bronchoscopy are often needed to diagnose and evaluate bronchial lesions such as stenosis or obstruction. The evolution and prognosis

of EBTB is variable, going from complete resolution to residual severe tracheobronchial stenosis (4). The most important goal of treatment in active EBTB is eradication of tubercle bacilli. The second most important goal is prevention of bronchial stenosis. Because of its increasing incidence, significant morbidity and potential mortality, early diagnosis and treatment is necessary to prevent complications. This article has reviewed the latest updates about the pathogenesis, signs, symptoms, diagnostic tools, treatment and prognosis of this disease entity.

Epidemiology

Exact incidence of EBTB is not known as bronchoscopy was not routinely performed in all cases of pulmonary TB. Prior to era of antituberculous therapy, endobronchial TB was relatively more common (5,6). In 1943 a study done in a TB sanatorium, EBTB were observed in 15% of cases via rigid bronchoscopy and in 40% of cases at autopsy (5). Since the availability of antituberculous therapy, the reported incidence of EBTB in pulmonary TB patients varies greatly, ranging from 6% to 54% in various studies (7-11).

EBTB has been proposed to be more common in females (7,11,12). Exact phenomenon is not well known but the possible causes include a longer exposure to tubercle bacilli, as female patients have less expectorated sputum containing bacilli due to sociocultural and aesthetic factors. Second also a structural difference may play a role as female bronchi are narrower than those of males, which may make females more susceptible to EBTB (11-14).

Majority of patients with EBTB usually presents in second or third decade (12,13). The second peak is also described in old age (13,15). The possible mechanism is likely due to diminished immune response and complicating comorbid illnesses resulting in reactivation or reinfection by exogenous MTB and increasing bronchoscopies in elderly patients (11).

Pathology and pathogenesis

EBTB may affect any part of the bronchial tree. Primary bronchi, bilateral superior lobar bronchi and right middle lobar bronchus are the commonly affected sites. Jung *et al.* classified EBTB by the number of involved levels (11). Single-level EBTB was defined when only one site of trachea, main bronchus or lobar bronchus was involved. EBTB that involved two or more bronchial levels was defined as multiple-level EBTB, while that occurred proximal to the lobar bronchi was defined as central EBTB which had a potential to develop symptomatic stenosis (11).

Pathologically EBTB may affect any layer of the tracheobronchial wall including lamina muscularis and cartilage (16). Pathological changes mainly include mucosal and submucosal tuberculous infiltration, ulcer, granuloma, fibroplasias and tracheobronchial stenosis. Initially mucosal and submucosal hyperemia is present secondary to infiltration of inflammatory cells, mainly lymphocytes. Later tubercular nodules are formed in the diseased region followed by caseous necrosis in the nodules and mucosal ulceration (7,17). This ulcer may progress into the tracheobronchial wall and become deep-part ulcer, or may become inflammatory hyperplastic polyps protruding the tracheobronchial lumen like tumor. In advanced stages, fibrous hyperplasia and contracture develop and cause tracheobronchial stenosis (7,17,18), whose incidence may reach up to 68% in the initial 4-6 months and rises further with elongating course of the disease (12).

The exact pathogenesis of EBTB is not yet fully understood, the five proposed mechanisms of infection described in literature include (I) direct extension from an adjacent parenchymal focus; (II) implantation of organisms from the infected sputum; (III) haematogenous dissemination; (IV) lymph node erosion into a bronchus; and (V) spread of infection via the lymphatics (7,13,19).

The development and progression of EBTB is a complex phenomenon and various cytokines may also play an important role in pathogenesis in addition to local factors. Elevated levels of interferon gamma and TGF-beta in bronchial lavage fluids may be related to pathogenesis and progression of EBTB (13,20). Changes in the levels of TGF-beta observed in the serum after treatment have been implicated in the development of bronchial stenosis during the course of the disease (20).

Clinical features

The clinical manifestations of EBTB vary widely according to the site, extent of involvement, or stage of the disease, and may be acute or insidious in onset. Symptoms may be secondary to disease itself or from the complication of disease like endobronchial obstruction.

Systemic symptoms of TB like anorexia, generalized weakness and weight loss are usually reported in more than 50% of the patients (12,21). Cough is the most common symptom and present in 70-80% of the patient (12,21,22). Cough could be dry or with bronchorrea especially when EBTB is a part of cavitory TB (23). Fever is usually low grade but may become marked with advanced cavitory disease (12,22). Hemoptysis may occur in 15-40% of the patient but is usually mild but sometime massive hemoptysis may occur (22). Chest pain of variable intensity may be present in 15-25% of patients (9,24). Localized wheezing and decreased breath sounds if there is a stenosing effect by the endobronchial lesion (25,26). However, these symptoms and signs are nondistinctive as EBTB can simulate other diseases like malignancy (27), bronchial asthma (28), foreign bodies, and recurrent pneumonia (12,15,25).

Diagnosis

Early diagnosis leads to appropriate management that favorably changes the course of EBTB. The diagnosis of EBTB is more difficult as compared to pulmonary TB because of variable and nondistinctive clinical manifestations. Although sputum examination is the essential and first step towards the diagnosis of EBTB, bronchoscopy and CT are the methods of choice for

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accurate diagnosis of bronchial involvement and its complications (7,11,12).

Sputum examination

Bacteriological examination of sputum smear like acid-fast bacilli (AFB) staining is the most important and commonly used test to diagnose EBTB; however the diagnostic yield is low. Freshly expectorated sputum should be taken for acidfast bacilli staining in order to increase diagnostic success (13). Positivity of sputum AFB smear in EBTB is variable in different studies ranging from 16% and 53% but a negative sputum smear does not exclude the diagnosis of EBTB (8,13,29). One of the possible reasons suggested for this low yield is mucus entrapment by proximal bronchial granulation tissue. EBTB with ulceration and mucosal involvement has a higher yield of sputum smear and culture positivity (8,12,13).

Newer nuclear amplification tests like Xpert MTB/RIF assay and line probe assay (Geno Type MTBDR Plus) shows better results than sputum AFB smear and are recommended in suspected cases but still very limited data is available in utility of these tests in EBTB (30).

Bronchoscopy

Bronchoscopy is the most valuable method to establishing early diagnosis and assessing prognosis in EBTB. Bronchoscopic procedures such as biopsy, brushings, needle aspiration, bronchoalveolar lavage (BAL) and endobronchial ultrasonography can be used to establish diagnosis (8,11,30,31). Bronchoscopy is also important to exclude any other underlying or concomitant disease like malignancy.

The bronchoscopic appearance of EBTB is closely related to the pathological changes and has been classified into seven subtypes by Chung et al. (7) but none is exclusive enough to establish the diagnosis by appearance alone: (I) nonspecific bronchitic (tracheobronchial mucosa only is mildly swollen and/or hyperemia); (II) edematous-hyperemic (tracheobronchial mucosa is severely swollen and hyperemic); (III) actively caseating (tracheobronchial mucosa is swollen, hyperemic and covered with a large amount of whitish cheese-like material); (IV) granular (tracheobronchial mucosa appears severely inflammatory and is scattered by rice-like nodules); (V) ulcerative (tracheobronchial mucosa ulcerate); (VI) tumorous (hyperplastic focal tissue shapes, intraluminal mass like tumor); and (VII) fibrostenotic (tracheobronchial lumen narrows due to fibrous hyperplasia and contracture). Each subtype of EBTB has its own characteristic appearance

and has been proposed to be closely related to the extent of disease progression. The prominent lymph nodes are seen during bronchoscopy as grayish-yellow masses through the bronchial mucosa; while hemorrhage, granulation tissue fistula formation and caseous material draining into bronchus may also be seen.

Bronchoscopic biopsy is the most validated method for confirming the diagnosis. The yield of bronchial biopsies to diagnose EBTB is 30% to 84% of patients in various studies (13,32).

The AFB smears and culture yield in BAL is high then the sputum examination. A study done by Ozkaya *et al.* showed that microbiologic and smear examination of BAL fluid was positive for AFB in 26% of the patients with the highest rates found in granular-type cases (75%) while the cultures of BAL fluids for Mycobacterium TB were positive in 39.1% of patients, and the positivity was highest in granular-type cases (75%) in histologically proven sputum smear negative cases (8).

Chest radiograph

Chest radiograph may be normal in about 10–20% of patients with EBTB (7,25). Any chest radiographic findings are not specific for the diagnosis of EPTB. The most common abnormality on chest X-ray is the patchy parenchymal infiltrates in the affected lobe. The other chest X-ray findings are depending on the severity of bronchostenosis and may present as persistent segmental or lobar collapse, lobar hyperinflation, obstructive pneumonia and mucoid impaction. (25,33). Erosion of calcified hilar nodes into adjacent bronchi, known as broncholithiasis, may also result in segmental collapse or over inflation. Other radiological findings include fibrotic and calcific focus, cavity, bronchiectasis, intrathoracic lymphadenitis and pleural effusion. Different radiological signs are often seen in the same patient (7,25,34).

CT scan

In recent years, because of high resolution power and minimal partial volume effect, high resolution computed tomography (HRCT) has been found to be superior to conventional chest radiography and standard CT in the localization of disease in the pulmonary lobule and in the evaluation of pulmonary parenchymal disease. Endobronchial involvement in pulmonary TB has been reported as high as 95% and 97% with HRCT scanning in various studies (35,36). Early findings include centrilobular nodules or linear structures which are well defined lesions 1–4 mm thick, separated by more than 2 mm from the pleural surface or interlobular septa. Later multiple branching linear structures of similar caliber originating from a single "stalk" (the "tree-in-bud" appearance) were commonly seen in patients with extensive bronchogenic spread (36). Other CT findings include segmental bronchial narrowing with concentric wall thickening, complete endobronchial obstruction, extrinsic obstruction by adjacent adenopathy and scarring (13,32,36). Even with a highly suspected CT chest, bronchoscopy with a histopathological or microbiological confirmation is still required for a definite diagnosis of EBTB (7).

Complications

The most common complications of EBTB are bronchial stenosis and stricture formation that may develop in more than two third of patients despite of adequate medical management. Patients can also develop severe airway obstruction and respiratory failure if the larger airways are involved. Another common complication is post obstructive bronchiectasis that leads to frequent pneumonia and hemoptysis (13,29). A group of patient also developed persistent obstructive airway disease as a sequel of EBTB.

Treatment

The main goals of EBTB treatment are eradication of MTB infection and prevent tracheobronchial stenosis. The course and prognosis is mainly related to the degree, the extent and the duration of lesions before treatment. So, early diagnosis and adequate treatment is necessary to prevent complications.

The treatment of EBTB is similar to pulmonary TB. Five standard first line drugs are used for the treatment of EBTB which includes Isoniazid (H), Rifampicin (R), Ethambutol (E), Pyrazinamide (Z) and Streptomycin (S).

Local antituberculosis medications have also been used in the treatment of EBTB with variable results. These include the inhalation of nebulized antituberculosis drugs, the diseased region lavage with antituberculosis drugs and the submucous injection of antituberculosis drugs. The common locally used anti-tuberculosis drugs include isoniazid or streptomycin (16).

Corticosteroids have been used as an adjunct therapy in treatment of EBTB but their role is still controversial. Corticosteroids may be useful in the earlier stages of EBTB when hypersensitivity is the predominant mechanism but in later stages they have less likely to be helpful rather may cause detrimental effects. Corticosteroids have shown improvement in clinical outcomes when used in children (13,37). The beneficial role in children might be contributed by anti-inflammatory response thereby preventing bronchial compression resulting from erosion of lymph nodes into bronchial lumen however this has not been shown to prevent bronchostenosis in adults (25,38).

Corticosteroids have also been tried locally. Rikimaru showed that the healing time of ulcerous lesions was shorter and bronchial stenosis was less severe, in patients treated with aerosol therapy, consisting of streptomycin 100 mg, dexamethasone 0.5 mg and naphazoline 0.1 mg administered twice-daily along with conventional oral therapy (39). In another study submucosal methylprednisolone injection also demonstrated resolution of EBTB (25,40). The role of corticosteroids needs to be further evaluated in larger prospective trials before its regular use in adult patients.

The development of bronchial stenosis or strictures is the most common sequel and usually irreversible despite adequate antituberculous therapy and therefore requires airway patency to be restored either with bronchoscopic or surgical interventions (41). There are various bronchoscopic interventions to relieve airway stenosis including balloon dilatation, stent insertion, laser and cryosurgery (42). Fibrostenosis is the indication of balloon dilatation which can be achieved via a rigid or flexible bronchoscope. Bronchial wall rupture is one of the complications of balloon dilatation and should avoid excessive inflation (42). Persistent airway stenosis following balloon dilatation has been described especially if active inflammation, calcification and malacia are evident. The incidence of restenosis is about 37.5% a month after balloon dilatation (43).

Patients who require more than one session of balloon dilatation need stenting or ablative procedures (44). Both metal and removable silicon have been used but the removable stents are preferable to avoid long term stent-related complications. Both types of stent have complications like migration, stent fractures, retained secretions, colonization of stent material, and development of granulation tissue and need regular followups (44).

In the setting of alleviating central airway obstruction, laser resection, electro cautery, and argon plasma coagulation can provide immediate relief (45). Laser resection is the application of laser energy delivered via rigid and/or flexible bronchoscopes in order to manage different endobronchial lesions. The neodymium: yttrium aluminum garnet (Nd-YAG) equipment is the most widely used for bronchoscopic Interventions. The main indication for laser

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bronchoscopy comprises obstructive lesions of the trachea, main bronchi and the lobar orifices that compromise ventilation and produce severe symptoms including dyspnea, stridor, intractable cough, and hemoptysis (13,45).

Cryosurgery is another option and it is safer than balloon dilatation or laser. There is a less chances of bronchial wall perforation is with cryosurgery as compared to other procedures but it requires repeated procedure and time consuming (13,46).

Severe tracheobronchial stenosis, which causes severe bronchiectasis, lung collapse, repeated pulmonary infection or frequent hemoptysis may require thoracic surgery like pneumonectomy or lobectomy (47). Newer surgical techniques are also emerging to restore air way patency in endobronchial stenosis.

Conclusions

EBTB is a special form of TB which is associated with significant morbidity and potential mortality. Early diagnosis and aggressive treatment with antituberculous chemotherapy is necessary in the management of EBTB to prevent complications like tracheobronchial stenosis. The role of corticosteroids is still controversial but can be used in selected patients. For early and accurate diagnosis, bronchoscopy should be performed initially in suspected cases. If medical treatment is not sufficient in the management, then various bronchoscopic and surgical techniques should be utilized to preserve lung function. Future research is required to know the exact pathogenesis and the course of disease. Additionally, efforts should be undertaken to control the transmission of this disease entity by infection control measures.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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