

Endobronchial tuberculosis: An unusual presentation of a common disease

Abstract

Endobronchial tuberculosis (EBTB) is an inflammation of the bronchial walls caused by tuberculous infection. The clinical, radiologic, and bronchoscopic presentation of EBTB is nonspecific and can be easily confused with other common pulmonary disorders. Its diagnosis requires isolation of *Mycobacterium tuberculosis* from bronchoscopic material. A high index of awareness of this entity and the early bronchoscopy in suspected patients are the cornerstones for establishing the diagnosis. The disease can occur in patients of all ages although it is more common in younger age group with a slight female preponderance. In recent years, a higher incidence has been reported in patients with human immunodeficiency virus infection.

Key words: Endobronchial tuberculosis, nonresolving pneumonia, tuberculosis

REVIEW OF LITERATURE

Endobronchial tuberculosis (EBTB) is defined as tuberculous infection of the tracheobronchial tree with a microbial and/or histopathological evidence.^[1] This definition inherently calls for bronchoscopic intervention for diagnosing this condition, and computed tomography (CT) scanning of the chest plays a supportive role.

Over the years, a uniform strategy of sputum analysis and chest radiographic evaluations has made the diagnosis of pulmonary tuberculosis easier, but the same cannot be said about EBTB. Until date, EBTB remains difficult to diagnose because of a multitude of reasons.

- It happens to be a less common type of pulmonary TB.
- Its clinical presentation may mimic bronchial asthma, bronchial adenoma or malignancy.
- Sputum smear microscopy is negative for acid-fast bacilli (AFB); with variable patterns of parenchymal involvement on chest radiograph.
- Contrast-enhanced CT of the chest can be supportive in the diagnosis, but its unavailability and cost often remain a deterrent to its use.
- Diagnostic bronchoscopy for microbiological confirmation in the broncho-alveolar lavage (BAL) and/or bronchial biopsy is essential but is not routinely performed in all pulmonary tuberculosis patients.

Epidemiology: Epidemiological data are highly variable as the threshold for bronchoscopy in sputum negative patients varies from between institutions and most of the studies in the available literature are passive retrospective studies. Furthermore, most sputum positive pulmonary tuberculosis cases do not undergo bronchoscopy, thereby contributing to gross underreporting of EBTB.

The incidence of EBTB in a retrospective analysis in pulmonary tuberculosis was 5.8% at National University Hospital, Seoul, Korea.^[2] According to Han *et al.*, prevalence of EBTB ranges from 10% to 40% in patients with active tuberculosis and 90% in patients with bronchial stenosis.^[3] Ozkaya *et al.* in a retrospective study had reported a 2.2% incidence of EBTB in previously diagnosed pulmonary tuberculosis cases.^[4] The occurrence of the disease in young adults with a female preponderance has been described.^[5] Seeding of the tracheobronchial tree with AFB in the swallowed sputum associated with cultural inhibitions in spitting out the sputum by females have been ascribed as probable cause for predisposition in females. Van den Brande *et al.* in 1990 described the clinical spectrum of EBTB in the geriatric population.^[6]

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PATHOGENESIS

Possible pathogenetic mechanisms for EBTB are direct implantation of tubercle bacilli into the bronchus from a contiguous pulmonary parenchymal lesion or infected mediastinal lymph node; hematogenous spread from erosion by an intra-parenchymal lymph node into the bronchus and the lymphatic extension to the peribronchial region by lymphatic drainage.

In a study by Kim *et al.* Transforming growth factor (TGF)-gamma and TGF-beta levels in the bronchial lavage fluids of patients with EBTB were found to be elevated.^[7] Lowered initial serum TGF-beta levels, and 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. More than one mechanism may be involved in the development of bronchostenosis in patients of EBTB. However, new methods are being tried to prevent bronchostenosis by use of inhaled TGF-beta-1 antibody therapy.^[8]

CLINICAL PRESENTATION

Endobronchial tuberculosis can be difficult to differentiate from other more common pulmonary illnesses. Patients usually present with fever with cough, hemoptysis and occasionally wheezing. Barking cough, which is persistent and nonresponsive to anti tussives should be investigated for EBTB.^[9,10] Hemoptysis is usually not massive. Bronchorrhea can also be a presenting feature.^[11] Rarely lithoptysis has been seen due to expectoration of caseous/calcific material from the extension of calcific nodes into the bronchi.

Chest examination may be normal. Rhonchi, decreased air entry or occasionally monophonic wheezing can be present. Often, it may be provisionally diagnosed and treated as bronchial asthma. In contrast to asthma, the wheeze is low-pitched, constant and always heard over the same area of the chest. Right middle lobe syndrome due to EBTB of the anatomically narrow orifice of right middle lobe bronchus has been described by Kim *et al.* in 22 cases.^[12] Poststenotic bronchial obstruction may manifest as loss of lung volume or recurrent/non-resolving pneumonias in a broncho-pulmonary segment.

Obstruction, atelectasis (with or without secondary infections) bronchiectasis and tracheal or bronchial stenosis are the complications encountered in EBTB. Constitutional symptoms such as weight loss, anorexia and fatigability may dominate the picture. Varying degrees of anemia may be seen. Chest pain due to lymph node rupture has been described.

Although 80-90% cases have X-ray evidence of PTB, 10-20% may have normal chest X-rays, as endobronchial lesions can exist without extensive parenchymal abnormalities. The most common finding in adults is upper lobe infiltrate and cavity, but segmental atelectasis may be the only finding often involving the right middle lobe and the anterior segment of the right upper lobe.

Extensive endobronchial TB can also be associated with bronchiectasis.

Investigations in a suspected case are aimed at histopathological and/or microbiologic confirmation of tuberculosis. The studies include acid-fast staining, culture for mycobacteria and polymerase chain reaction performed on sputum, BAL and bronchial biopsy.

In a study by Chung and Lee, sputum was positive for AFB in 53.3% patients and sputum culture for tuberculosis bacilli was positive in 73.6%.^[2] Sputum may be negative for AFB in 5-33% cases.^[13] Therefore, the sputum negativity does not exclude the diagnosis of EBTB.

We are presenting the case summaries of two patients from the department of medicine, SAIMS Medical College. Both subjects had negative sputum smear microscopy for AFB. Final diagnosis of EBTB could be reached only after bronchoscopic examination.

Patient no. 1: A 55-year-old male farmer, chronic heavy smoker, presented with low-grade fever for last 2 months. He had a cough with a mild mucoid expectoration for 1-month. He had noticed a weight loss of about 5-6 kg over last 2 months. He also had straining at urine, nocturnal frequency and urgency for 5-6 months, He had no history of diabetes, hypertension, heart disease, bronchial asthma or drug allergies. There was no family history of communicable diseases. On examination, he had average body habitus, was afebrile with mild pallor of the tongue and nails. The pulse was 96/min, regular, blood pressure was 100/60 mm of mercury; respiratory rate was 30/min. No icterus, cyanosis, clubbing, lymphadenopathy or edema was noted. Examination of the abdomen, cardiovascular and nervous system revealed no abnormality. Examination of the respiratory system showed bilaterally symmetrical chest, respiratory rate of 30/min with normal broncho-vesicular breath sounds all over.

INVESTIGATIONS

Hemoglobin-9 g%, total leukocyte count-5200 per cumm (neutrophils-71%, lymphocytes-23%, monocytes-10%), platelet count-3.11 lakhs/cu mm, erythrocyte sedimentation rate (ESR)-10 mm at 1 h, urine examination-normal, blood urea-33 mg/dl, serum creatinine-0.78 mg/dl, serum cholesterol-179 mg %, serum sodium-130 mEq/L, serum potassium-2.8 mEq, serum chlorides -100 mEq/L, serum bilirubin-0.30 mg/dl, serum glutamic-oxaloacetic transaminase (SGOT)-14 IU/L, serum glutamic-pyruvic transaminase (SGPT)-15 IU/L, HBsAg-negative, human immunodeficiency virus (HIV) I and II-negative, prostate specific antigen (PSA)-5 ng/ml (normal: 1-4 ng/ml). The sputum was negative for AFB, fungus, and malignant cells. Mantoux test was negative.

Ultrasound scanning of abdomen and pelvis showed an enlarged prostate with significant residual urine. Chest radiograph [Figure 1a] showed extensive fine military shadows in both the lung fields. High-resolution computed tomography chest [Figure 1b] showed generalized tiny centrilobular nodular opacities in both lungs with

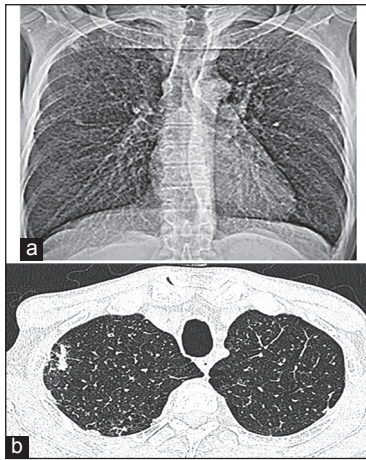


Figure 1: Patient 1 (a) Chest radiograph. (b) CT scan

patchy irregular area of fibro-atelectasis scarring seen in both upper lobes (left more than right) with cavitary changes.

DISCUSSION

The differential diagnosis of miliary pattern on chest radiography includes miliary tuberculosis (TB), histoplasmosis, sarcoidosis, pneumoconiosis, bronchoalveolar carcinoma, pulmonary siderosis, and hematogenous metastases from primary cancers of the thyroid, kidney, trophoblast, and some of the sarcomas. Primary lung cancer with hematogenous spread may cause miliary shadows.^[14,15]

In Indian scenario, the most likely diagnosis in such a presentation would be miliary tuberculosis, but interstitial lung disease, hypersensitivity pneumonitis, fungal infections and hematogenous spread from primary prostatic malignancy needed to be ruled out in view of his occupation, symptoms of prostatic enlargement and slightly high PSA.

Fiberoptic bronchoscopy showed mucosal inflammation of right lower lobe with purulent collection in the right main stem bronchus. BAL cytology showed respiratory epithelial cells, alveolar macrophages and occasional inflammatory cells. Bronchial brush cytology showed only red blood cells in a proteinaceous background. The Gram stain, Ziehl Nielsen stain showed no aerobic organisms, AFB or fungus and cultures were sterile.

Polymerase chain reaction for *Mycobacterium tuberculosis* was positive and histopathological examination of bronchoscopic biopsy revealed epithelioid granuloma with central caseating necrosis, which clinched the tissue diagnosis of tuberculosis.

Patient was discharged home on Directly Observed Treatment-Short (DOTS course) category I anti-tuberculosis treatment with 40 mg oral prednisolone. He showed improvement at 4 weeks follow-up.

Patient no. 2: A 65-year-old female patient was brought to the casualty on March 16, 2014 with complaints of extreme weakness, slurring of speech, drowsiness and profuse perspiration for

last 2-4 h. She had chronic type 2 diabetes and hypothyroidism and was taking oral hypoglycemic agents (metformin 500 mg, gliclazide 80 mg twice daily) and levothyroxine 100 µg once daily for last 4 years. She had poor appetite and low food intake for last 2-3 days, but had taken her medications. There was no other complaint. She was found to be hypoglycemic with a blood sugar level of 57 mg/dl. Her hypoglycemia took more than 24 h to respond to treatment but left no sequelae. In the 3rd week of January 2014 she had the fever, dry cough and nonexertional shortness of breath that was diagnosed and treated as Right lung pneumonia with ceftriaxone and amoxicillin with clavulanic acid for 3 weeks. As there was nonresolution of pneumonia on chest X-ray, she was being given oral levofloxacin 500 mg daily for last 3 weeks. On admission, she had no respiratory symptoms. On examination she weighed 74 kg, was afebrile with a regular heart rate of 112/min, blood pressure of 160/90 mm of Hg and had mild pedal edema.

Respiratory system examination revealed evidence of consolidation in the right infra-clavicular and mammary region with a dull percussion note, bronchovesicular breath sounds, rhonchi and crepitations. The rest of the systemic examination was normal.

INVESTIGATIONS

Haemoglobin-8.3 gram%, red cells were mildly microcytic, hypochromic; total leukocyte count-14700/cu mm (neutrophils-83%, lymphocytes-10%, monocytes-6%, eosinophils-1%), platelet count-4.83 lakhs/cu mm, ESR-40 mm at 1 h, urine examination-normal, blood urea-25 mg/dl, serum creatinine-0.68 mg/dl, serum cholesterol-105 mg %, serum sodium-125 mEq/L, serum potassium-3.32 mEq/L, serum chlorides-96 mEq/L, serum bilirubin-0.67 mg/dl, SGOT-34 IU/L, SGPT-25 IU/L, HBsAg-negative, serum proteins-5.01 gm/dl, serum albumin-2.20 gm/dl, serum globulin-2.81 gm/dl (A/G ratio-0.8), HIV I and II-negative, hemoglobin A1c-6.2%, thyroid stimulating hormone-0.485 i.u./ml, serum T3-0.554 ng/ml, serum T4-5.63 ug/dl. The Sputum was negative for AFB, fungus and malignant cells. Mantoux test was negative. Ultrasound of abdomen and pelvis showed grade I fatty liver. Chest radiograph showed extensive nonhomogeneous area of consolidation with multiple small cavitations surrounded by ground glass opacities in mid and part of the lower zones of the right lung [Figure 2a].

High resolution CT of the chest showed dense areas of consolidation, small cavitary lesions suggestive of a mild bronchiectasis with multiple centrilobular nodular opacities in the right lung segments [Figure 2b-d].

DISCUSSION

A consolidation lasting for more than 4-6 weeks is considered as nonresolving pneumonia and has various etiologies. Incorrect diagnosis, inadequate antibiotic therapy, impaired host defense, atypical organisms, resistant pathogens, noninfectious causes,

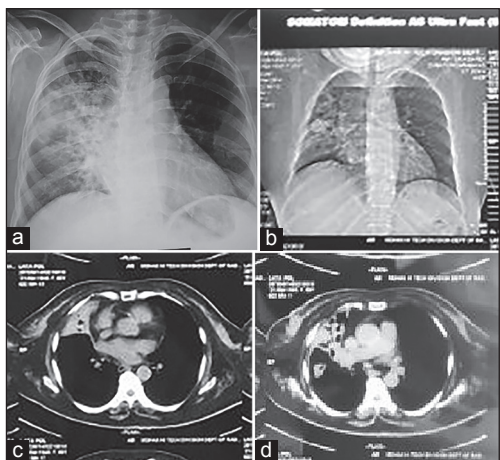


Figure 2 : Patient 2 (a) Chest radiograph. (b,c,d) CT scan

tuberculosis, endobronchial lesions, etc., are the common causes of nonresolving pneumonia or slowly resolving pneumonia.^[16-19]

Fiberoptic bronchoscopy showed right upper lobe endobronchial nodularity with irregular mucosa. BAL showed occasional pus cells, but no organisms on Gram stain and culture and had negative *M. tuberculosis* PCR. Bronchial biopsy showed chronic inflammatory cells mixed with Langerhans giant cells along with epithelioid cells in the subepithelial tissue indicative of EBTB. The patient was discharged on April 21, 2014 on DOTS category I antituberculosis drugs in addition to antidiabetic drugs, levothyroxine and supportive medications and has yet to report for first follow-up.

DISCUSSION

In a retrospective study by Ozkaya *et al.*, histopathologically confirmed cases of EBTB were evaluated for microbiologic confirmation.^[4] All cases were sputum negative for AFB. On BAL AFB, stain was positive in 26% of the total and 75% of granular subtypes. Culture positivity was present in 37% of the total cases and 75% of the granular subtypes, while the fibrostenotic variant had no positive results.^[4]

Bronchoscopic visualization of the tracheo-bronchial tree and sampling of lavage fluid brushed samples and biopsy remain the cornerstones for the histologic diagnosis of EBTB.

In the recent years, BAL fluid, TB PCR has also been recommended in the evaluation of EBTB.

A combination of BAL, AFB stain, culture and TB-PCR can greatly increase the sensitivity of microbiological diagnosis and permit sensitivity testing for antitubercular drugs.

Bronchial biopsy may be positive in 30-84% patients.^[20] Bronchial brushing has provided a high yield of 84.8%.^[13]

A classification of EBTB based on bronchoscopic findings by Chung and Lee has seven subtypes as shown in Figure 3 actively caseating, edematous-hyperemic, fibrostenotic, tumorous, granular, ulcerative, and nonspecific bronchitic.^[2]

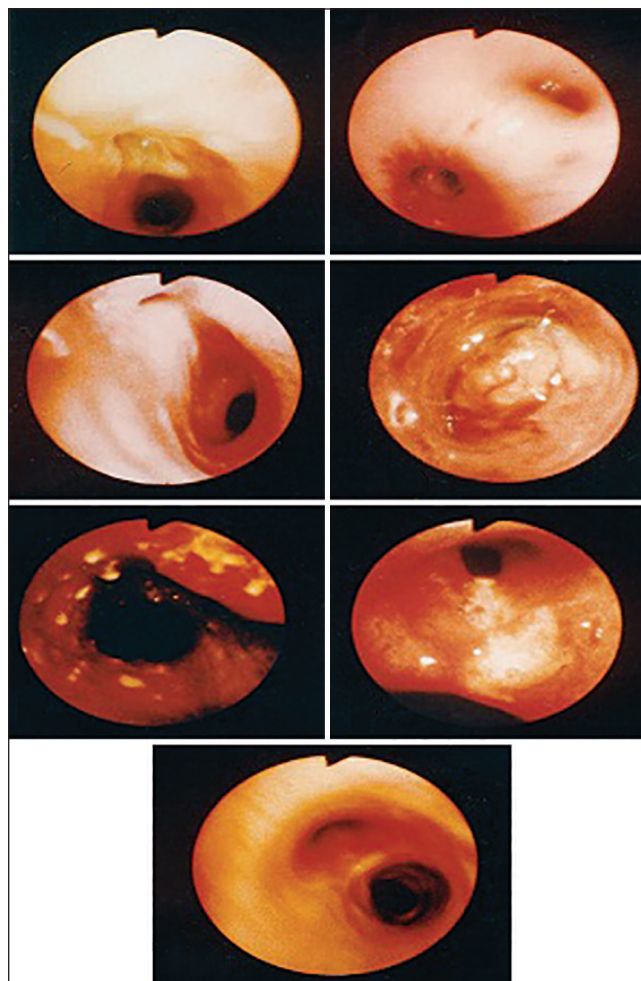


Figure 3: Chung et al.: Classification of endobronchial tuberculosis-actively caseating, edematous-hyperemic, fibrostenotic, tumorous, granular, ulcerative, and nonspecific bronchitic

Endobronchial tuberculosis is an unusual presentation of a common disease. It requires a high index of suspicion for the diagnosis, with the early bronchoscopy for diagnosis at an early stage to prevent serious sequelae like bronchostenosis. We have reported a couple of cases here with a view to increasing the early suspicion of EBTB. This is a small study, and larger series are required with early bronchoscopic studies to quantify the magnitude of the problem in our setting.

MANAGEMENT

The two most substantial treatment goals in EBTB are eradication of *M. tuberculosis* and prevention of tracheobronchial stenosis. To achieve these goals the diagnosis of EBTB must be established early and aggressive treatments instituted before the disease progresses too far.

Standard combination anti-tubercular therapy with intensive and continuation phases apply for EBTB as well. However, the treatment results are not uniformly promising. More than half of the actively caseating type and edematous-hyperemic types of EBTB evolve into fibrostenosis despite adequate antitubercular treatment. The prediction of clinical evolution has been particularly difficult in the tumorous subtype.

Inhalational steroids and streptomycin/isoniazid, intralesional steroids and oral steroids have provided variable results and needed systematic evaluation in preventing bronchostenosis.

CONCLUSION

Endobronchial tuberculosis is an unusual presentation of a very common disease in our high burden setting. It is unusually diagnosed due to the reasons mentioned in the discussion. It has permanent and serious sequelae such as bronchostenosis. It would be wise to develop a high index of suspicion for this disease and try to catch it as early as possible.

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