

Received: 2014.09.22
Accepted: 2014.12.11
Published: 2015.04.24

Unusual Clinical Presentation of Thoracic Tuberculosis: The Need for a Better Knowledge of Illness

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCDEF 1 **Sandra Manca**
BCDF 1 **Alessandro Giuseppe Fois**
BCD 1 **Luigi Santoru**
BCD 2 **Rocco Trisolini**
BCD 1 **Maria Francesca Polo**
BCD 1 **Salvatore Otera**
BCD 2 **Marco Patelli**
ABCDEF 1 **Pietro Pirina**

1 Department of Respiratory Disease, University of Sassari, Sassari, Italy
2 Thoracic Endoscopy and Pulmonology Unit, Maggiore Hospital, Bologna, Italy

Corresponding Author: Pietro Pirina, e-mail: pirina@uniss.it
Conflict of interest: None declared

Patient: Male, 73
Final Diagnosis: Bronchoesophageal fistula in endobronchial tuberculosis and mediastinal lymphadenopathy
Symptoms: Nonproductive cough • weight loss
Medication: Isoniazid • rifampin • pyrazinamide • ethambutol
Clinical Procedure: Laser treatment
Specialty: Pulmonology





Objective: Unusual clinical course
Background: Pulmonary tuberculosis (TB), a highly contagious infectious disease, is a significant public health problem all over the world and remains an important cause of preventable death in the adult population. Endobronchial TB is an unusual form of thoracic TB that may be complicated by tracheobronchial stenosis, and bronchoesophageal fistula formation is a very rare complication. Tubercular lymphadenitis can also lead to fistula formation through a process of caseum necrosis and opening of a fistula between the bronchus and oesophagus.

Case Report: We report an uncommon case of thoracic TB in an immunocompetent 73-year-old Caucasian man who presented several problems: bronchoesophageal fistula, endobronchial TB, and mediastinal lymphadenopathy in the absence of contemporary parenchymal consolidation. Furthermore, he presented a normal chest radiograph and mostly unclear and non-specific symptoms at onset.

Conclusions: We emphasize the need for a better knowledge of this illness and awareness that it may have an unusual presentation. In these cases, diagnosis and proper treatment can be delayed, with severe complications for the patient. Pulmonary TB remains a real diagnostic challenge: a normal chest radiograph and nonspecific symptoms do not allow us to exclude this persistent infectious disease.

MeSH Keywords: Bronchial Fistula • Tuberculosis, Lymph Node • Tuberculosis, Pulmonary

Full-text PDF: <http://www.amjcaserep.com/abstract/index/idArt/892546>

 1897   4  18



Background

Tuberculosis is one of the most common systemic infectious disease, and a major public health problem all over the world. It has several forms of presentation and clinical manifestations and remains an important cause of preventable death in the adult population. An uncommon form of pulmonary tuberculosis is endobronchial tuberculosis, which accounts for about 10–40% of the cases of active tuberculosis [1,2]. It may be complicated by tracheobronchial stenosis, and fistula formation is an unusual complication, mainly in the region of the pleura and less frequently in the oesophagus (BEF). Increased risk of acquiring these rare complications occurs largely in immunocompromised people (e.g., HIV, malignancies, and patients undergoing immunosuppressive therapy). In these cases, the diagnosis is often missed or delayed.

Tubercular lymphadenitis can also lead to fistula formation through a process of caseum necrosis and opening of a fistula between the bronchus and oesophagus.

The purpose of this article is to discuss a case report of thoracic tuberculosis that showed an unusual presentation, emphasizing the importance of an early diagnosis in order to reduce both the risk of mortality and prevent the spread of infection to the community.

Case Report

An immunocompetent 73-year-old Caucasian man who is an ex-smoker of 42 pack-years, presented in the past 6 months with a history of accessional nonproductive cough that appeared during meals, especially after ingestion of liquids, and a significant weight loss of 10 kg in a year. He had no fever, dyspnea, night sweats, chest pain, or hemoptysis. There was no family history of tuberculosis or previous contact with a TB patient. He had no significant past medical or surgical history and prior to the onset of coughing during meals, remarkable respiratory symptoms were not reported.

During the first 6 months, on the basis of a clinical suspicion of gastroesophageal reflux, he was initially, treated by a general practitioner, with a standard dose of proton pump inhibitors (PPI) therapy. Due to the lack of a treatment response, in June 2013, he underwent a barium contrast swallow test. The chest X-ray examination performed with a barium contrast showed the presence of a fistula extending from the lower tract of the esophagus to the right main bronchus (Figure 1), without evidence of active parenchymal lung infiltrates or pleural involvement.



Figure 1. Fistula demonstrated by barium contrast swallow from the middle third and lower third of the esophagus to the right main bronchus.

He was then endoscopically treated by application of metal clips in the esophagus for fistula closure. No chest CT scan was performed in this first phase of the diagnostic process.

For persistence of cough, on July 2013 the patient was sent to our Clinic where, after chest CT scan, he underwent a flexible fiberoptic bronchoscopy in an outpatient setting.

Routine blood investigation results were normal; only an increase of PCR (3.45 mg/dl) was found. Serum QuantiFERON testing was positive (2.41 IU/mL). The remaining systemic examination revealed no abnormality.

The chest CT scan “with contrast” showed a significant enlargement of mediastinal lymph nodes (Figure 2A) that caused tracheal compression with deflection to the right side and reduction of its lumen for presence of an endoluminal vegetating lesion. Several other enlarged lymph nodes were seen in the right supraclavicular and axillary area, but there was no associated parenchymal infiltrates.

Bronchoscopy revealed a mild inflammation of the bronchial mucosa and the presence of different vegetating lesions in the carina, on the medial wall of the main bronchi, and on the lateral wall of the intermedius bronchus (Figure 3).

Histopathology revealed moderate chronic granulomatous inflammation characterized by the presence of lymphocytes,

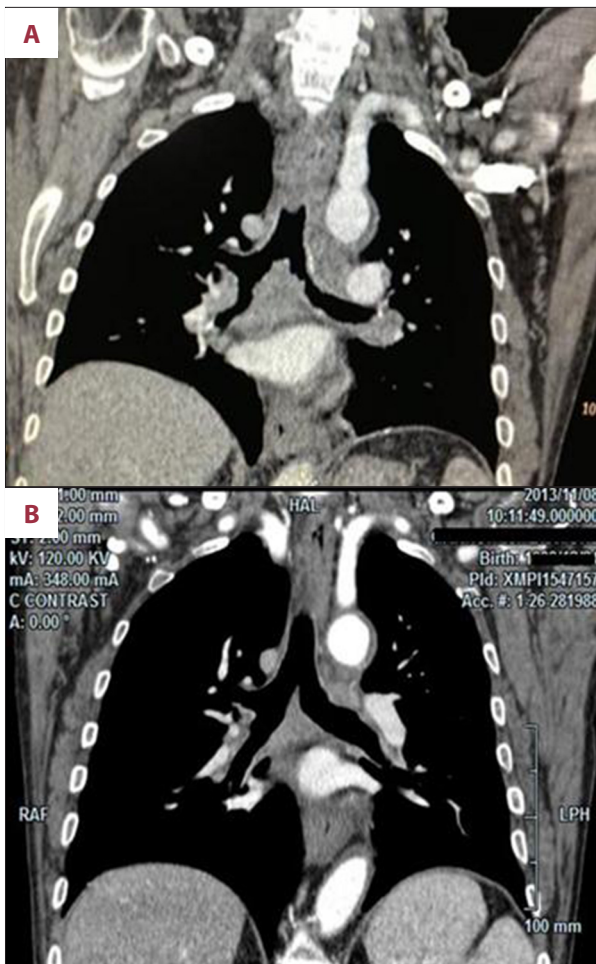


Figure 2. (A) CT scan of chest (coronal view) pre-antituberculosis treatment showing a mediastinal lesions. (B) CT scan of chest (coronal view) during antituberculosis treatment showing regression of mediastinal lesions.

histiocytes, and Langhans-type giant cells. Bronchial aspirate test results for routine culture, fungal, and AFB (acid-fast bacilli) were negative.

The patient was re-evaluated after a week by esophagoscopy and bronchoscopy, mainly for worsening symptoms and for the re-evaluation of the fistula. The first reconfirmed the persistence of bronchoesophageal fistula, so further endo-clips were placed. The bronchoscopy control showed that the vegetating lesions had increased in size, so a laser treatment was performed with lumen desobstruction. Bronchial aspirate testing confirmed the presence of a marked lymphocytic and histiocytic inflammatory infiltrate with giant cells and granulomatous component without central necrosis. Results of a microscopic examination and molecular test (PCR) for Koch's bacillus were negative.

Based on the pathological pattern, we decided to start a standard antitubercular treatment with isoniazid 300 mg daily,



Figure 3. Bronchoscopic view showing a vegetating lesions.

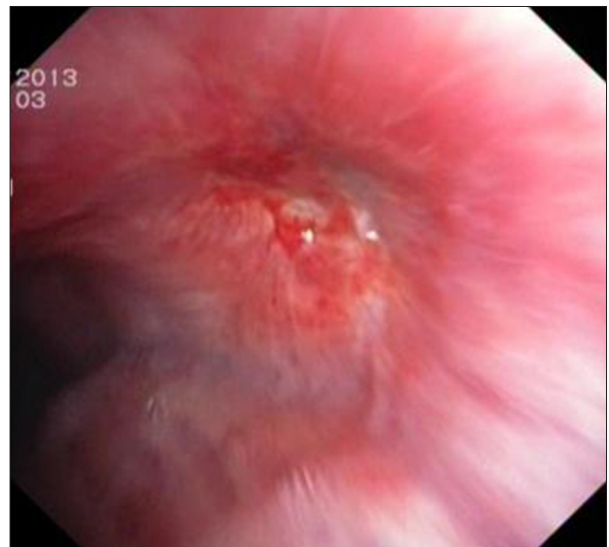


Figure 4. Bronchoscopic view: scar tissue of the fistula.

rifampin 600 mg daily, pyrazinamide 1500 daily, and ethambutol 1200 mg daily. The patient was placed in isolation with negative pressure inside the room.

After 40 days, the culture of the first bronchoscopic biopsy demonstrated the growth of *Mycobacterium tuberculosis* (Lowenstein-Jensen medium and Bactec Mycobacteria Growth Indicator Tube (MGIT) 960 TB System). The drug susceptibility test did not show any resistance to the first-line drugs. Our patient continued anti-tuberculous treatment for 2 months, followed by rifampicin and isoniazid treatment for the following 4 months.

During antitubercular treatment, symptoms progressively improved. CT and bronchoscopy performed 2 months later showed regression of lymph node enlargement (Figure 2B) and the disappearance of intraluminal lesions in the tracheobronchial tree. Bronchoscopy also showed the bronchoesophageal fistula closure (Figure 4).

At 6-month and 1-year follow-up, physical and bronchoscopy examinations did not show evidence of recurrence, a chest CT scan at 1 year demonstrated no evidence of mediastinal lymphadenopathy, and symptoms of patient were resolved. The final diagnosis was “bronchoesophageal fistula in endobronchial tuberculosis and mediastinal lymphadenopathy”.

Discussion

Bronchoesophageal or tracheoesophageal fistula is extremely rare in adults. It is more frequently a congenital condition; otherwise, the acquired forms, are usually secondary to primary neoplasm (benign, malignant, or metastatic), infectious diseases (tuberculosis, histoplasmosis, actinomycosis, and syphilis), traumatic events (sequels of surgical procedures), and connective tissue diseases. Broncho-esophageal fistula (BEF) in adults is commonly due to malignancy, mainly oesophagus carcinoma and, less frequently, lymphoma, carcinoma of the lungs or trachea. Benign BEF is a rare condition [3]. The fistula has a short course and usually the communication is pervious, permitting the passage of air in the stomach and liquids in the airways. The clinical symptoms and signs that occur as a result of attempted oral feeding are closely related to the size of the fistula and are characterized by chest pain, dyspnea, barking cough, cyanosis, hemoptysis, and sputum production; in some cases episodes of pneumonia and other respiratory infections can occur through a mechanism of “aspiration” [4,5].

Endobronchial tuberculosis (EBTB), defined as “tuberculous infection of the tracheobronchial tree with microbial and histopathological evidence”, is a particular form of TB [1]. Described for the first time by Mortem in 1698, represents about 10–40% of cases of active TB [1,2]. It's more common in young adults, with a female predominance, and only 15% in elderly patients [6–8]. Often dangerous for its consequences (trachea and bronchostenosis, recurrent pneumonia, atelectasis and respiratory failure) is potentially an important source of infection spread in the community [9,10]. Its pathogenesis remains unclear; however, different mechanisms have been suggested and the more plausible are: direct implantation of *Mycobacterium tuberculosis* (Mt) in the bronchus after their inhalation, or direct extension of infection from parenchymal lesions or erosion and infiltration from adjacent mediastinal lymph nodes into the bronchus [11].

The mediastinal tuberculous lymphadenitis is rare in the absence of simultaneous lung involvement in immunocompetent adults [12], while it may be observed more frequently in HIV-positive patients and in developing countries with high rates of TB just as it is in sub-Saharan Africa [13].

During primary TB, tubercle bacillus reaches the mediastinal or hilar lymph nodes causing lymph node enlargement

but the parenchymal infiltrate in an immunocompetent subject may resolve without sequels at conventional radiography. *Mycobacterium tuberculosis* may stay inactive (dormant) for many years inside the lymph nodes and becomes active again during decreased immune status, as for example in the elderly.

Our clinical case was characterized by several criticisms:

- The considerable delay with which the patient has been subject to a chest CT scan and bronchoscopy. Bronchoscopy should be done promptly in the case of a fistula suspicion. The cough during meals would suggest the presence of a bronchoesophageal fistula and this suspicion involves the assessment of the cause.
- Usually, it is thought that microbiological examination of bronchial aspirate and BAL are positive for *Mycobacterium tuberculosis* in patients with EBTB, and that examination provides a good diagnostic yield [14]. A study conducted by Ozkaya et al. highlights the difficulty of the bacteriological diagnosis of EBTB based on BAL analysis, bronchial aspirate, or sputum analysis, and showed that a high diagnostic yield was obtained through the histopathologic examinations of bronchial biopsies, confirmed in our clinical case [15].
- Chest x-ray, performed on our patient in the first instance, did not pose a suspicion of TB. There were no direct signs such as parenchymal consolidation, or pneumonia and/or excessive gastric and intestinal gasification as expression of communication between the oesophagus and airway, specific lesions of active TB or inactive as scarring; complications of endobronchial TB (recurrent pneumonia or atelectasis) or mediastinum lymph node enlargement. In fact, up to 20% of patients with EBTB have a normal chest radiograph [11].
- The presence of non-specific symptoms such as cough, only present during meals, simulated a gastro-esophageal reflux disease. In fact, despite the bronchial obstruction, the patient didn't have any symptoms of endobronchial tuberculosis. EBTB, may sometimes present with a very insidious onset and, in some cases, it may simulate other pathological conditions such as bronchogenic carcinoma or bronchial asthma. This symptom can mimic many diseases, misleading the doctor for a proper diagnosis. Moreover, several studies showed that, in the elderly, the classic signs and symptoms of TB, such as fever, weight loss, night sweats, and hemoptysis and sputum production are sometimes absent compared to young adult [16].
- Pathogenesis of bronchoesophageal fistula in this specific case report remains difficult to interpret. It may be secondary to endobronchial tuberculosis, through a mechanism of erosion of the bronchial wall, involvement of mediastinal lymph nodes and then fistula formation into the esophagus. However, the absence of parenchymal involvement, makes unlikely this mechanism. Much more probable, was a reactivation of a primary infection in peritracheal and

peribronchial lymph nodes, as a consequence of an immunodepression state, subsequent lymph node erosion into oesophagus and bronchus and fistulization with a consequent implantation of Mt in the bronchial mucosa and secondary endobronchial TB onset. Similar studies show that both mechanisms are uncommon or rare complications of thoracic tuberculosis [1,2,17,18]. As far as we know, no cases have been reported in the literature with simultaneous combination of bronchoesophageal fistula, endobronchial tuberculosis without parenchymal involvement, mediastinal tuberculous lymphadenitis in the elderly.

Despite the delay and the mismanagement, the patient has responded optimally to a standard treatment with isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months, followed by isoniazid and rifampicin for a further 4 months. The 1-year follow-up showed healing of tuberculosis, without evidence of recurrence.

References:

1. Hoheisel G, Chan BK, Chan CH et al: Endobronchial tuberculosis: Diagnostic features and therapeutic outcome. *Respir Med*, 1994; 88: 593-97
2. Rikimaru T: Endobronchial tuberculosis. *Expert Rev Anti Infect Ther*, 2004; 2: 245-51
3. Jayakumar T, Chandramohan P, Babu B, Babu A: Benign broncho-esophageal fistula in adult – two case reports. *IJTCVS*, 2006; 22(4): 230-32
4. Grillo HC: Surgery of the Trachea and Bronchi: Chapter 12 Acquired Tracheoesophageal and Bronchoesophageal Fistula. 2004 BC Decker Inc Hamilton London, 341-55
5. D'Auria V, Solazzo A, Leonessa F et al: Diagnostica radiologica delle fistole tracheo-esofagee post-traumatiche *Giornale Ateneo* 2011 Seconda Università degli studi di Napoli [in Italian]
6. Nemati A, Safavi E, Ghasemi Esfe M et al: Fistula formation between the right and left main bronchus caused by endobronchial tuberculosis. *Am J Med Sci*, 2012; 343(4): 330-31
7. Ip MS, So SY, Lam WK, Mok CK: Endobronchial tuberculosis revisited. *Chest*, 1986; 89: 727-30
8. Lee JH, Park SS, Lee DH et al; Endobronchial tuberculosis: Clinical and bronchoscopic features in 121 cases. *Chest*, 1992; 102: 990-94
9. Brande PM Vanden, Mierop FV, Verbeken EK, Demedts M: Clinical spectrum of endobronchial tuberculosis in elderly patients. *Arch Intern Med*, 1990; 150: 2105-8
10. EPICENTRO: Il portale dell'epidemiologia per la sanità pubblica a cura del Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute www.epicentro.iss.it [in Italian]
11. Kashyap S, Mohapatra PR, Saini V: Endobronchial tuberculosis. *Indian J Chest Dis Allied Sci*, 2003; 45: 247-56
12. Lee KS, Song KS, Lim TH et al: Adult-Onset Pulmonary Tuberculosis: Findings on Chest Radiographs and CT Scans. *Am J Roentgenol*, 1993; 160(4): 753-58
13. Pirina P, Spada V, Santoru L et al: Chest tuberculosis with mediastinal asymptomatic lymphadenitis without lung involvement in an immunocompetent patient. *J Infect Dev Ctries*, 2013; 7(3): 280-85
14. Soto A, Salazar D, Acurio V et al: Evaluation of the diagnostic utility of fiberoptic bronchoscopy for smear-negative pulmonary tuberculosis in routine clinical practice. *J Bras Pneumol*, 2012; 38(6): 757-60
15. Ozkaya S, Bilgin S, Findik S et al: Endobronchial tuberculosis: histopathological subsets and microbiological results. *Multidiscip Respir Med*, 2012; 7(1): 34
16. Alvarez S, Shell C: Pulmonary tuberculosis in elderly men. *Am J Med*, 1987; 82(3 Spec No): 602-6
17. Nanaware SK, Gothi D, Joshi JM: Tuberculous broncho-esophageal fistula managed conservatively. *Lung India*, 2005; 22: 65-67
18. Liao LY, Wu H, Zhang NF et al: Bronchoesophageal fistula secondary to mediastinal lymph node tuberculosis: a case report and review of the literature. *Zhonghua Jie He He Hu Xi Za Zhi*, 2013; 36(11): 829-932

Conclusions

Bronchoesophageal fistula is a rare manifestation of a common disease such as tuberculosis.

We know that early diagnosis and proper treatment may modify the natural course of this disease and increase the rate of healing. Therefore, if not treated, severe complications may occur, endangering the patient's life.

The difficulty of this case report, associated with the low level of knowledge of the illness and its serious complications, caused a diagnostic delay, deferring the start of an effective antitubercular treatment.

We cannot forget that a normal chest radiograph and the presence of nonspecific symptoms do not exclude the diagnosis of tuberculosis, but even the best early detection is of no use if subsequent treatment is inadequate, or downright wrong.