Underestimated Aetiology Of Tracheobronchomalacia In Adults In China

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Research Article

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Abstract

Background: Tracheobronchomalacia (TBM) is an infrequent airway disease, but frequently unrecognized or misdiagnosed with other respiratory diseases, and its etiology remains unclear in China.

Methods: Anthropometric information, smoking history, medical history, symptoms, signs, etiology, diagnosis, treatment and prognosis of ten patients were retrospectively analyzed. Etiologies were summarized from previous reports of Western countries.

Results: The median onset age of the ten patients was 55 years. Patients presented productive cough, chest distress, and inspiratory wheezing. Etiologies of TBM included chronic obstructive pulmonary disease (COPD), tracheobronchial tuberculosis, relapsing polychondritis, and chronic bronchitis, the first two of which were dominated, accounting for 40%. Obstructive ventilation disturbance was found in the lung function test, and the flow-volume curve displayed main airway obstruction. Seven patients were worried about the side-effect of stenting, so they refused stenting. During follow-up (3-120 months), all patients survived.

Conclusions: In China, main etiologies of TBM may be COPD and tracheobronchial tuberculosis, which are different from those of Western countries and seriously underestimated.

Introduction

Tracheobronchomalacia is defined as the loss of cartilaginous support of the trachea or major bronchus, leading to complete or near-complete collapse of the airway lumen during respiration [1]. TBM can be diagnosed primarily through bronchoscopy or multidetector computed tomography (CT) [2]. Bronchoscopy has been regarded as the main and traditional diagnostic modality for evaluating presence and severity of TBM [3]. Multidetector CT with 3-dimensional imaging is also a highly accurate preoperative noninvasive imaging modality for evaluating TBM and providing anatomic information consistent with and complementary to bronchoscopy [4]. However, TBM is frequently unrecognized or misdiagnosed with other respiratory conditions [5, 6]. A survey indicated that due to deficiency of awareness, TBM can be identified by only 29% of pulmonologists on bronchoscopy and only 39% of them on CT [7]. TBM is usually confused with airway obstructive disease, and it can be diagnosed through pulmonary function test after ruling out other diseases [8–10].

Secondary TBM is the main type of TBM in adults. TBM occurs in the normally developed trachea due to mechanical causes (tracheal surgery, closed chest trauma, tracheostomy, *etc.*), chronic airway inflammation [chronic obstructive pulmonary disease (COPD), uncontrol asthma, recurrent infections, relapsing polychondritis, tuberculosis, malignant airway obstruction, *etc.*), and congenital causes (Mounier-Kuhn syndrome) [11–23]. Symptoms, signs, onset age, disease severity and prognosis of TBM are considerably different due to different etiologies. The more common etiologies are COPD, asthma, Mounier-Kuhn syndrome and relapsing polychondritis according to previous reports of Western countries.

After searching the PubMed database for published articles on TBM, however, few case reports of TBM in China were found.

In this paper, it was hypothesized that the TBM etiologies in mainland Chinese patients differ from those of Western countries. Through some cases with TBM, the etiologies and clinical characteristics of TBM were determined and compared with literature reports.

Materials And Methods

Patients

The diagnosis and treatment course of ten 32-75-year-old patients diagnosed with TBM and consecutively hospitalized from outpatient respiratory clinics in Shanghai Pulmonary Hospital from December 2008 and December 2020 were retrospectively analyzed, specifically including general and anthropometric information (*i.e.* age and sex), smoking history, medical history, onset of symptoms, course of disease, symptoms (*e.g.* cough, sputum, chest distress, hemoptysis and chest pain), signs, etiology, diagnosis, malacia position, treatment and prognosis. Written informed consent was obtained from all participants through letters. The study protocol was approved by the Ethics Committee of Shanghai Pulmonary Hospital (K21-302; Shanghai, China), and was conducted in accordance with the amended Declaration of Helsinki.

Diagnostic criteria for TBM

There are no uniform diagnostic criteria for TBM. Bronchoscopy and multidetector CT with 3-dimensional imaging have been regarded as the main diagnostic modality for evaluating presence and severity of TBM [2–4]. TBM in adults is a disease defined as a stenosis of more than 50% of the airway lumen during expiration [21]. In this study, TBM was diagnosed based on bronchoscopy and multidetector CT with 3-dimensional imaging.

Main etiologies of TBM

To date, the etiology of TBM remains unclear yet. Etiologies of TBM in adults were summarized aspects follows: congenital cartilage dysplasia (Mounier-Kuhn syndrome), autoimmune disease (relapsing polychondritis), external pressure factors (surgical intervention for a vascular ring, post-thyroidectomy and post-pneumonectomy), chronic airway obstructive disease (COPD and asthma), airway trauma (tracheal intubation), tracheal and bronchial cancer, and other pulmonary diseases (interstitial lung disease and pulmonary tuberculosis) (Table 1).

Table 1
Summarized the main aetiologies of TBM

Aetiology	Methods	References
Polychondritis	Bronchoscopy Chest CT History inquiry	10
Mounier-Kuhn Syndrome	Bronchoscopy Chest CT	11, 20
Chronic Obstructive Pulmonary Disease	History inquiry Pulmonary Function Tests Bronchoscopy	12, 20
Bronchial cancer	Bronchoscopy Chest CT	13
Pulmonary tuberculosis	History inquiry Bronchoscopy Chest CT	13
Surgical intervention for a vascular ring	History inquiry Bronchoscopy Chest CT	14
Post-thyroidectomy	History inquiry Chest CT	15
Intubation	History inquiry Chest CT	16
Pulmonary emphysema	History inquiry Chest CT	17
Asthma	History inquiry Pulmonary Function Tests Bronchoscopy	18, 20

CT: computed tomography.

Aetiology	Methods	References
Post-pneumonectomy	History inquiry Bronchoscopy Chest CT	19
Interstitial lung disease	Bronchoscopy Chest CT	20
CT: computed tomography.		

Results

The median onset age of the ten patients was 55 years (32–74 years), 57.8 years (32–75 years) at the time of diagnosis. The course of disease ranged from 3 months to 120 months. Three patients had a history of smoking and COPD, two patients had a history of tracheobronchial tuberculosis, and one patient had a history of asthma and bronchiectasis (Table 2). Eight patients were misdiagnosed in other hospitals (asthma in 3 cases; COPD in 3 cases; chronic bronchitis in 2 cases).

Table 2
Demographic data of ten patients

Patient no.	Age	Sex	Onset age	Course of disease	Smoke	Other disease history
1	38	F	37	13 months	No	No
2	71	M	62	117 months	Yes	COPD
3	59	F	59	25 months	No	tracheobronchial tuberculosis
4	32	M	32	3 months	No	tracheobronchial tuberculosis
5	75	F	74	14 months	No	Right hand injury
6	54	M	54	2 months	No	COPD
7	52	F	52	4 months	No	No
8	73	M	72	12 months	No	No
9	55	F	54	12 months	No	Asthma and bronchiectasis
10	69	M	59	120 months	yes	COPD
COPD: Chronic Obstructive Pulmonary Disease.						

Chest distress was the most common clinical symptom, accounting for 90% (9/10). Seven patients complained of productive cough, while two patients complained of dry cough. Chest pain occurred in two patients, and hemoptysis in one patient. In examination, inspiratory wheezing rale was heard in auscultation, and two patients had tachypnea (Table 3).

Table 3
Symptoms and signs of ten patients

Patient no.	Symptoms					Signs	
	Cough	Sputum	Chest distress	Chest pain	Hemoptysis	Tachypnea	Inspiratory phase wheezing sound
1	√	√	√	√		√	√
2	√	√	√				√
3	√	√	√		√	√	√
4	√		√				√
5	√	√	√				√
6	√	√	√	√	√	√	√
7	√		√				
8			√			√	
9	√	√	√			√	√
10	√	√				√	

Every patient was diagnosed through dynamic bronchoscopy and multidetector CT with 3-dimensional imaging in Table 4(Table 4) according to the diagnostic criteria proposed by Ngerncham M *et al* [2]. Case 1 diagnosed with relapsing polychondritis and Case 6 diagnosed with COPD were affected both left and right main bronchi. The trachea was affected in Case 2 who had a history of smoking and COPD, and was treated with tracheal stenting. Both trachea and right main bronchus were affected in Case 3 and 4 who had a history of tracheobronchial tuberculosis and affected in Case 10 who had a history of COPD. Right main bronchus was affected in Case 5 who had a history of chronic bronchitis. Left main bronchus was affected in Case 7 who had no history of other diseases. Case 9 diagnosed with asthma and bronchiectasis and Case 8 were affected in trachea and both main bronchi.

Table 4
Diagnosis methods, aetiology and prognosis of ten patients

Patient no.	Methods of diagnosis	position	Aetiology	Therapy	Current clinical status (Duration of survival)
1	Bronchoscopy 3D-CT	BM	Polychondritis	symptomatic therapy	Survived (74 months)
2	Bronchoscopy 3D-CT	Trachea	COPD	Trachea stent	Survived (70 months)
3	Bronchoscopy 3D-CT	Trachea and RM	tracheobronchial tuberculosis	symptomatic therapy	Survived (27months)
4	Bronchoscopy 3D-CT	Trachea and RM	tracheobronchial tuberculosis	symptomatic therapy	Survived (12 months)
5	Bronchoscopy 3D-CT	RM	Chronic bronchitis	symptomatic therapy	Survived (3 months)
6	Bronchoscopy 3D-CT	BM	COPD	Trachea stent	Survived (2 months)
7	Bronchoscopy 3D-CT	LM	No	symptomatic therapy	Survived (4 months)
8	Bronchoscopy 3D-CT	Trachea and BM	No	symptomatic therapy	Survived (12 months)
9	Bronchoscopy 3D-CT	Trachea and BM	Asthma and bronchiectasis	Trachea stent	Survived (12 months)
10	Bronchoscopy 3D-CT	Trachea and RM	COPD	symptomatic therapy	Survived (120 months)

3D-CT: three-dimensional computed tomography; BM: both main bronchi; RM: right main bronchus. LM: Left main bronchus.

Eight patients were worried about the side-effect of stenting, so they refused stenting. These patients' symptoms could be improved by bronchodilators to some extent. Tracheal stent was placed in three patients. During follow-up (3-120 months), all patients survived.

Lung function tests were conducted on 7 out of 10 patients. Five patients had obstructive ventilation function disturbance, one patient had mixed ventilation dysfunction and the remaining one had no impaired lung function (**Table 5**). Among the seven patients receiving lung function tests, forced

expiratory volume in 1 second (FEV_1) % predicted and FEV_1/forced vital capacity (FVC) declined, while residual volume (RV)% predicted and airway resistance rose in 6 patients. Flow-volume curve displayed main airway obstruction.

Table 5
Pulmonary function of seven patients

Patient no.	FVC%	FEV1%	FEV1/FVC	RV%	RV/TLC%	DLCO%	R%
1	58.2	21.8	35.2	379.8	77.59	79.2	293.7
2	87.3	46.4	51.8	176.4	55.9	78.2	187.4
3	79.3	39.0	40.39	180.3	60.0	83.2	313.5
4	95.7	43.5	38.03	157.8	39.49	103.6	188.4
5	71.8	64	71.37	185.8	59.55	61.7	264.3
7	96.9	97.0	98.3	101.3	94.0		158.9
8	75.4	25.3	26.17				

FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; RV: residual volume; TLC: total lung capacity. DLCO: carbon monoxide diffusing capacity; R: airway resistance

Discussion

Adult TBM frequently occurs in middle-aged and elderly patients [8], consistent with the results in this paper. The course of adult TBM varies widely (from several months to more than ten years). The different courses of disease may be related to different etiologies. TBM has a wide range of etiologies. Congenital TBM results from abnormalities of airway maturation, most seen in children born with esophageal atresia and esophageal tracheal fistula [24, 25]. Adult TBM occurs in the normally developed trachea due to chronic airway inflammation, mechanical causes and congenital causes [12-21]. In this study, the etiologies of TBM included COPD, tracheobronchial tuberculosis, bronchiectasis, relapsing polychondritis, and chronic bronchitis. However, the main etiologies in our hospital were COPD and tracheobronchial tuberculosis, which differed from those in Western countries.

COPD is one of the main causes of TBM in adults in some countries, but COPD and TBM are likely to be confused with each other because of similar symptoms and pulmonary function [8]. A study demonstrated evidence of TBM on expiratory phase CT scan in 53% of patients with COPD [13]. Smoking and chronic airway inflammation can lead to structural changes in the airway and result in bronchial cartilage deficiency [26]. Pathogenesis of TBM from chronic bronchitis is like that of COPD. In China, the overall prevalence of spirometry-defined COPD is 13.7% in a national cross-sectional study by Chen-Wang [27], indicating that there are approximately 100 million patients with COPD in China. The possible

reason is that there are a considerable number of patients with TBM secondary to COPD. However, there are few case reports about TBM secondary to COPD in China due to insufficient attention. TBM should be suspected if the patient with COPD has poor or no response to rational bronchodilators and glucocorticoids. More attention should be paid to dynamic multidetector CT with 3-dimensional imaging and flow-volume curve. If the patient is in good condition, bronchoscopy can be performed to assist diagnosis.

Tracheobronchial tuberculosis was another main cause of TBM in this study. The two patients had no history of other diseases [28], except tracheobronchial tuberculosis, one of the most common concurrent diseases in China. When *Mycobacterium tuberculosis* directly involves the bronchial wall, bronchial cartilage will be destroyed and the bronchial wall will become thickened [29]. Tracheobronchial tuberculosis can be divided into active type and fibrous type [27], but its exact cause remains unclear, which may be related to the location of the lesion in the tracheobronchial tract, the range and depth of the lesion, missed diagnosis and delayed treatment. Finally, destruction of bronchial cartilage and fibrosis of the bronchial wall led to TBM. Tuberculosis cases in eight countries account for two thirds of the total globally , and the top three are India (26%), Indonesia (8.5%) and China (8.4%) [30]. The number of tuberculosis cases reported in China has shown a continuous downward trend, but there are nearly 800,000 new cases of tuberculosis every year in China with a large population base [30]. Tracheobronchial tuberculosis is present in 10-40% of patients with active pulmonary tuberculosis [31]. It is surmised that there are an abundant number of patients with TBM secondary to tracheobronchial tuberculosis. However, the morbidity of TBM secondary to tracheobronchial tuberculosis is substantially undervalued due to pulmonologists' insufficient recognition of TBM in China. Therefore, a long-term prospective multicenter study on the morbidity of TBM secondary to tracheobronchial tuberculosis is needed.

Relapsing polychondritis is a rare systemic disease of unknown etiology, characterized by recurrent episodes of inflammation with the systemic destruction of cartilage tissues [11]. In a study involving 337 cases of relapsing polychondritis, Kent *et al* [11] found that 55% of them have respiratory tract symptoms. Case 1 was diagnosed with relapsing polychondritis according to the criteria proposed by Diamiani and Levine [28].

Etiologies of TBM in Western countries were summarized in previous reports, mainly including COPD, asthma, Mounier-Kuhn syndrome, and relapsing polychondritis. In China, COPD and tracheobronchial tuberculosis are the major etiologies of TBM. The morbidity of TBM is substantially undervalued due to insufficient recognition and epidemiological survey results.

Chest distress and cough are the main symptoms of patients with TBM [32], consistent with our findings, and they are common in obstructive airway disease, leading to misdiagnosis of TBM as COPD or asthma. Although chest distress and cough are not the specific clinical symptoms of TBM, they may be indications of TBM. In clinical practice, therefore, it is needed to consider whether patients with chest

distress and cough as the main clinical manifestations suffer from COPD or asthma, and to pay attention to TBM.

The diagnosis of symptomatic TBM can be complex. The clinical presentation of TBM is nonspecific and like that of other common respiratory diseases. It is important to have a high degree of clinical suspicion especially when the symptoms are caused by COPD and asthma or conventional treatment fails. For TBM, pulmonary function test is neither sensitive nor specific, and main airway obstruction shown in flow-volume curve may be a hint of TBM. Multidetector CT with 3-dimensional imaging is a noninvasive method for the diagnosis of TBM, and bronchoscopy is regarded as the golden standard for diagnosis [4, 33]. Therefore, TBM is mainly diagnosed by bronchoscopy or dynamic multidetector CT with 3-dimensional imaging. Chest distress and cough, inspiratory wheezing rale in auscultation and flow-volume curve are beneficial supplement and hint for the diagnosis of large airway obstruction.

Therapeutic methods of TBM mainly include medical management, stent insertion and surgical treatment. Airway collapse impairs airway clearance [34, 35]. Chest physiotherapy, gastroesophageal control, and nebulization of normal saline or hypertonic saline are effective management means in a clearance regimen [36], and almost all patients with mild to severe TBM will benefit from airway clearance of mucus [37]. Corticosteroids, regardless of routine, active or continuous type, should be avoided because of the risks of cartilage degradation and progressive tracheomalacia [36]. Patients may not benefit from the use of bronchodilators, because bronchodilator can relax airway smooth muscle, resulting in aggravation of airway collapse [38, 39]. Continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BIPAP) are helpful for patients with TBM-induced decreased lung compliance and airway obstruction [40]. However, noninvasive ventilation is generally not considered a therapeutic method, but a "bridge" to surgical intervention, or the last treatment for patients who cannot tolerate long-term airway stents [23]. Tracheobronchial stenting can improve dyspnea, lung function, and quality of life in patients with airway obstruction, which, however, are associated with a higher risk of granulation tissue formation as well as stent fatigue and fracture, migration or blockage [23, 41]. Therefore, tracheobronchial stents should only be used when tracheobronchoplasty is not feasible or is contraindicated [23, 42, 43]. Surgical stabilization of the airway is the definitive treatment for patients with TBM. Thoracoscopic aortopexy, and anterior and posterior tracheobronchopexy are successful surgical treatments [36, 44]. In our study, all patients were given symptomatic treatment, and their symptoms were improved to some extent. Some patients chose conservative treatment, and three patients were inserted with tracheal stents. Despite severe symptoms, some patients refused tracheobronchial stenting because of worry about the side effects. None of the 10 patients received surgical treatment.

Almost all symptoms of patients can be improved after relaxing airway, tracheobronchial stenting or tracheobronchoplasty. There are diverse etiologies of TBM in adults. Different primary diseases have different outcome and survival time. A report by Hong G *et al* [11] indicated that the 5-year overall survival rate of a group patients with relapsing polychondritis is 75%. The long-term outcomes of TBM in adults with different etiologies are absent.

The main limitation of this study is that the number of cases was only ten, and some etiologies were not summarized. However, Shanghai is a large city in eastern China with a population of more than 20 million and is representative of East Asia. Patients in Shanghai, in addition to residents, are from everywhere of Chinese mainland. The etiologies of TBM in this study included COPD (Case 2, 6 and 10), tracheobronchial tuberculosis (Case 3 and 4) and relapsing polychondritis (Case 1). China has a large population and the incidence of COPD and tracheobronchial tuberculosis is higher, indicating that the number of patients with COPD and tracheobronchial tuberculosis are large. The results of this study still have considerable clinical value. Large-scale epidemiological investigation about TBM remains to be conducted in the future.

Conclusions

Ten patients were retrospectively analyzed in this study, and the etiologies of TBM included COPD, tracheobronchial tuberculosis, chronic bronchitis, asthma, bronchiectasis and relapsing polychondritis. In China, main etiologies of TBM may be COPD and tracheobronchial tuberculosis, which are different from those of Western countries and seriously underestimated.

Abbreviations

TBM: Tracheobronchomalacia; COPD: chronic obstructive pulmonary disease; CT: computed tomography; 3D-CT: three-dimensional computed tomography; BM: both main bronchi; RM: right main bronchus; LM: Left main bronchus; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; RV residual volume; TLC: total lung capacity; DLCO: carbon monoxide diffusing capacity; R: airway resistance.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from all participants through letters. The study protocol was approved by the Ethics Committee of Shanghai Pulmonary Hospital (K21-302; Shanghai, China) and was conducted in accordance with the amended Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study has been included in this article, and was available public.

Competing Interests

The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The authors declare that they have no conflicts of interest.

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Authors' Contributions

ZC and JWB: conceptualization and collecting the data and writing original draft. SL, HWL, YG and JFX: review and editing. All authors contributed to the article and approved the submitted version.

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