Original Article

Decreasing Rate of Unknown Bronchiectasis Etiology: Evaluation of 319 Adult Patients with Bronchiectasis

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Abstract

OBJECTIVE: Bronchiectasis can have several causes, but there are only a limited number of studies about the prevalence of these causes. Most of the studies in adults are from previous years. This study aimed to identify etiologies in adult patients with bronchiectasis.

MATERIAL AND METHODS: Between January 1996 and June 2015, data from 319 patients admitted to a specialized bronchiectasis clinic were analyzed. Diagnoses were confirmed using high-resolution or multislice computed tomography and were retrospectively evaluated.

RESULTS: Of the 319 patients, 187 (58.6%) were women and 132 (41.4%) were men. The mean age was 49.0±17.4 (range 15–83) years. The mean duration of illness was 19.5±14.9 years. There were several common etiologies: (1) post-infections (215; 67.5%, 70 of the 215 patients had tuberculosis); (2) obstructive lung diseases (28, 8.8%); (3) defects in mucociliary clearance (13, 4.2%); (4) connective tissue diseases (8, 2.4%); (5) immunodeficiency (5, 1.5%); (6) structural lung conditions (1, 0.3%); and (7) obstruction of a single bronchus (1, 0.3%). No causes could be established in 41 (12.9%) patients.

CONCLUSION: Despite developments in antibiotic therapy and vaccination programs, the most common etiology for bronchiectasis is post-infectious conditions as observed in previous years. However, with improvements in diagnostic tests and procedures, the rate of unknown etiologies has dropped from ≥50% to 12.9%.

KEYWORDS: Bronchiectasis, etiology, infections

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INTRODUCTION

Bronchiectasis is defined as permanently dilated airways owing to chronic bronchial inflammation caused by inappropriate clearance of mucus and infectious agents [1-3]. It was first described by Rene Theophile Laënnec in 1819 [4]. This description is general and describes many lung diseases; therefore, bronchiectasis etiologies can include various causes, and an underlying cause can only be clearly identified in 50% of all patients [5-7]. There are a few studies on the etiology of bronchiectasis in adult patients, and only a minority of these studies were conducted in the recent years [8-12]. This study aimed to identify etiologies of bronchiectasis in adult patients.

MATERIAL AND METHODS

Data from 319 patients who were admitted to a specialized bronchiectasis clinic between 1996 and 2015 and who had been diagnosed using high-resolution or multislice computed tomography (HRCT or CT, respectively) were retrospectively evaluated. The study was performed according to the principles of the Helsinki Declaration. The study protocol was approved by the local ethics board (approval #83045809/863). As it was a retrospective study, informed consent was not required.

Study Design
The patients who were diagnosed with bronchiectasis via radiologic evaluations in the general polyclinic and who were referred to a specialized bronchiectasis clinic were included in this study. In this clinic, the patients were regularly followed according to a protocol. During the first visit, a detailed evaluation was performed to determine the bronchiectasis etiology. For the first year, the patients came to the clinic every 3 months and later on every 6 months. In this study, the data of these patients were retrospectively evaluated.

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Clinical Evaluation

A detailed medical history was taken from each patient. Age, sex, duration of disease, and starting time of the disease were evaluated. If a patient had symptoms such as purulent sputum that strongly suggested bronchiectasis, the starting time of the symptom was accepted as the starting time of the disease. If a patient had no symptoms, the first time that the diagnostic radiological test showed bronchiectasis was accepted as the starting time of the disease. Patients were considered to be smokers if they smoked daily at least for 1 year. The level of smoking was expressed in package-years. If patients quit smoking at least 1 year before the study, they were accepted as ex-smokers.

Laboratory Tests

Complete blood counts, erythrocyte sedimentation rates, and C-reactive protein levels were routinely analyzed. Other laboratory tests were conducted in patients whose symptoms started in childhood, including serum immunoglobulins (Ig); IgG, IgA, IgM, and IgG subclasses; serum protein electrophoresis; and alpha1-antitrypsin (A1AT) levels. If atopic complaints were present, total IgE levels were studied, and a prick test was performed. The sweat test was performed in patients with cystic bronchiectasis with recurrent pulmonary infections, recurrent sinusitis/pansinusitis, nasal polyposis, gastrointestinal problems such as hepatic steatosis and biliary cirrhosis, endocrine problems (diabetes mellitus), and urogenital systems such as azoospermia and infertility.

Radiological Evaluation

All patients underwent HRCT or multislice CT and were evaluated according to the presence of cystic, varicose, or cylindrical bronchiectasis. The total number of lobes with bronchiectasis was also documented [13]. HRCT or multislice CT imaging of patients was accepted after interpretation by a radiologist who specialized in thoracic radiology.

Spirometric Evaluation

All patients underwent spirometric evaluation during the stable phase using a Sensor Medics Vmax device (SensorMedics Series 22, USA). Spirometry was performed according to the criteria of American Thoracic Society/European Respiratory Society guidelines [14].

Bronchoscopy

Bronchoscopy was performed to determine if radiologically localized bronchiectasis, unusual features, or suspicion of malignancy were present.

MAIN POINTS

- Despite developments in antibiotic therapy and vaccination programs, the most common etiology for bronchiectasis is post-infectious conditions.

- Detailed systematic approach is necessary to find bronchiectasis etiologies with a standard follow-up protocol.

- With improvements in diagnostic tests and procedures, the rate of unknown etiologies has dropped from ≥50% to 12.9%.

Determination of Etiology

All patients were evaluated, and idiopathic bronchiectasis was diagnosed if the etiology was not found to be related to clinical and laboratory findings.

Post-infectious bronchiectasis

The term post-infectious bronchiectasis is used to describe bronchiectasis because of pneumonia, tuberculosis, measles, pertussis, or other respiratory infections. It was identified according to either 1 of the 2 criteria: (1) If the patients were informed that they had a type of infection known to be causative for bronchiectasis in childhood or during a previous time of their life, and the beginning of symptoms was after these infections or if the patients were informed that they had an unknown type of pulmonary infection in childhood or at a previous time during their life, and the beginning of symptoms was after these infections, then both of these conditions were accepted as an etiological factor for bronchiectasis; or (2) tuberculosis (TB) was accepted as an etiological factor if it was known that patients had normal radiological findings during the course of TB, and if bronchiectasis was diagnosed later or when the etiology was not found in patients with bronchiectasis and radiologically bronchiectasis was present in areas, including local fibrosis and calcification, which strongly supported the sequela of primary TB.

Bronchiectasis secondary to obstructive airway disease

Chronic obstructive pulmonary disease (COPD) was accepted as an etiological factor when patients had long histories of verified asthma or COPD, and the symptoms of bronchiectasis started after a COPD or asthma diagnosis with the absence of any other possible etiological factors for bronchiectasis. A1AT level was examined in patients with predominantly lower lobe emphysema or family history of A1AT deficiency and a clinical prediction of A1AT.

Bronchiectasis secondary to defects of mucociliary clearance

Kartagener syndrome was diagnosed in the presence of bronchiectasis, chronic sinusitis, and situs inversus. If there was any suspicion of abnormal ciliary function, ciliary function tests were performed. The patient underwent nasal brushing or nasal mucosa biopsy. Samples were analyzed for cilia beat frequency and beat pattern under light microscopy, and cilia ultrastructure was studied by electron microscopy [15, 16]. Upon suspicion of cystic fibrosis (CF), a sweat test was initially conducted. If the result was positive (sweet chloride >60 mmol/L) or borderline (40–59 mmol/L) or there were some other findings (such as upper lobe bronchiectasis or a family history) suggesting a CF diagnosis, CF genotyping was performed [17].

Bronchiectasis in connective tissue diseases

Connective tissue diseases were accepted as an etiological factor when the patients had a history of verified connective tissue diseases and when any other possible etiologic factor was not present.

Bronchiectasis secondary to immunodeficiency

In patients whose symptoms had started in childhood or who had frequent infections, serum Ig, and IgG, IgA, IgM, and IgG subclasses were studied. Common variable immune deficiencies of IgA, IgM, and IgG were diagnosed according to reference values and in combination with clinical findings.

Bronchiectasis secondary to obstruction of single airway
In patients who had localized bronchiectasis and/or history of aspiration and/or supportive radiological findings for foreign body aspiration, bronchoscopy was performed to show foreign body aspiration.

Bronchiectasis secondary to structural lung conditions
Structural lung conditions such as McLeod syndrome were accepted as etiological factors after excluding other possible causes.

Others
Yellow nail syndrome was diagnosed in the presence of bronchiectasis, lymphedema, and characteristic nail appearance. Secondary amyloidosis, familial Mediterranean fever, toxic gas inhalation, gastroesophageal reflux disease, and radiotherapy were accepted as etiological factors after excluding all other possible causes; these findings were accepted in combination with radiological findings of bronchiectasis after diagnoses of these conditions if the patient had previous normal radiological findings.

Statistical Analysis
Statistical analysis was performed using the Statistical Package for Social Sciences software version 20.0 (IBM SPSS Corp.; Armonk, NY, USA). Continuous variables were listed as mean±standard deviation or median when necessary, and all categorical variables were shown as number and percent of cases. Continuous variables were compared using Student's *t* test or Mann-Whitney *U* test, depending on the distribution of data. The Chi-square test was used for the comparison of categorical data between groups; $p < 0.05$ was accepted as significant.

RESULTS

A total of 319 patients were included in this study. The patient characteristics are shown in Table 1. The mean number of radiologically involved lobes was 2.5±1.4 (median 2) for all patients with bronchiectasis. Per radiological evaluations, the most common type of bronchiectasis was the cylindrical type (n=190; 59.7%), and the most common involved lobe was the right and/or left lower lobe (n=229; 71.8%). The types of bronchiectasis and the lobe involvement are listed in Table 2.

Etiologies for bronchiectasis were identified in 278 (87.1%) patients; however, no cause could be identified in 41 (12.9%) patients. The etiologies of bronchiectasis in the 319 patients are shown in Table 3. At least 1 symptom was present in 276 (86.5%) of 319 patients. The predominant symptoms were chronic cough (n=276; 86.5%), sputum (n=258; 80.9%), dyspnea (n=189; 59.2%), and hemoptysis (n=90; 28.2%). Of the 90 patients with hemoptysis, 16 (21.1%) had massive (described as blood expectoration of more than half a glass at a time) hemoptysis, but there was no mortality owing to hemoptysis.

The age at disease onset was significantly younger in patients with post-infectious etiology for bronchiectasis (p=0.034) or in patients with hemoptysis (p=0.02). It was found that among female patients, the probability of bronchiectasis because of pneumonia was significantly higher than in male patients (p=0.04).

The mean number of radiologically involved lobes was significantly higher in patients with immunodeficiency as an etiology for bronchiectasis (3.7±0.5, p=0.03) and significantly lower in patients with connective tissue diseases as an etiology for bronchiectasis (1.7±0.6, p=0.001).

The possibility of cystic bronchiectasis was significantly higher in patients with pneumonia as an etiological factor for bronchiectasis (p=0.003) and significantly lower in patients with tuberculosis as an etiology (p=0.015). The upper lobe involvement was significantly higher in patients with tuberculosis as an etiology (p<0.001). Middle lobe lingula (p=0.01) and lower lobe involvement (p>0.001) were significantly lower. However, the middle lobe lingula involvement was significantly higher in patients with pneumonia as an etiology (p=0.035) and significantly lower in patients with connective tissue diseases as an etiology (p=0.016).

There was no relationship between the etiologies of bronchiectasis and the presence of hemoptysis (p>0.05). Hemoptysis was more frequently observed in patients with right or left upper lobe involvement (p<0.001); however, it was significantly lower in patients with cystic bronchiectasis (p=0.015).

Table 1. Baseline characteristics of 319 patients

Characteristics	Values
Total patients (n)	319
Sex (F/M)	187/132
Age (years), mean±SD (range)	49.0±17.4 (15-83)
Duration of illness (year), mean±SD (median)	19.5±14.9 (17.0)
Age at disease onset (year), mean±SD (median)	26.7±21.9 (25)
Smoking history, n (%)	
- Smoker	35 (11.0%)
- Nonsmoker	210 (65.8%)
- Ex-smoker	74 (23.2%)
Amount of smoking (packet-years), mean±SD (median)	28.8±28.9 (20.0)

F/M: female/male; SD: standard deviation

Table 2. Types of bronchiectasis and the lobe involvement (because ≥1 type of bronchiectasis or multiple lobe involvement may be present in same patients; the sum of the ratios is >100%)

Future	n (%)
• Types of bronchiectasis	
- Cystic	126 (39.5)
- Varicose	69 (21.6)
- Cylindrical	190 (59.7)
• Lobe involvement	
- Right and/or left upper lobes	157 (49.2)
- Middle lobe and lingula	167 (52.4)
- Right and/or left lower lobes	229 (71.8)

It was found that among patients with asthma as an etiological factor for bronchiectasis, their age at disease onset was significantly younger (p=0.001), dyspnea was more common (p=0.001), and right lower lobe involvement was more frequent (p=0.009).

Among patients with TB as an etiological factor for bronchiectasis, cigarette smoking was significantly higher (p=0.029), but cough (p<0.001), sputum (p=0.003), and dyspnea

(p=0.002) were significantly lower than in other patients. However, among patients with pneumonia as an etiological factor for bronchiectasis, the amount of cigarette smoking was significantly lower (p=0.011), and sputum (p=0.029) and dyspnea (p=0.027) were significantly higher than in other patients.

DISCUSSION

We evaluated 319 patients with bronchiectasis diagnosed by HRCT or multislice CT. We found that the rate of unknown etiologies was 12.9%, and the most common etiology for bronchiectasis was post-infectious conditions. The ratio of 12.9% for no identifiable cause is lower than the ratio found in other studies of the etiologies of bronchiectasis [9-12]. This is probably because of the advanced diagnostic methods used compared with past techniques and also a detailed systematic approach to find bronchiectasis etiologies in a specified reference clinic with a standard follow-up protocol. For example, in the study published by Qi et al. [12] in 2015, they reported that the ratio of idiopathic bronchiectasis was 66%, but they excluded patients with asthma and COPD. They did not address the patients' symptoms that suggested bronchiectasis, and they also did not screen for atypical CF. This suggested that the 66% ratio for idiopathic bronchiectasis was actually higher than the real ratio.

In our study, the most common cause of bronchiectasis was childhood or adulthood infections (215, 67.5%). This was similar to the studies by Pasteur et al. (44, 29%) [6] and Shoemark et al. (52, 32%) [9]. A number of childhood respiratory infections were blamed for bronchiectasis etiology, including measles, pertussis, and tuberculosis [8]. Li et al. have reported that post-infective cases were decreasing in the pediatric population with non-CF bronchiectasis, and they attributed this to the widespread use of antibiotics and vaccination programs [3]. In contrast to these findings, Karadağ et al. [18] have reported in the same year that post-infectious cases were the most common infections in the pediatric population with non-CF bronchiectasis. Parallel to the finding of Karadağ study, from 1819 to present, several scientists have reported that infections are the most common cause of bronchiectasis [2, 4, 8, 10-12, 19]. This shows that despite vaccination programs and antibiotic strategies, post-infectious conditions are still the most common cause of bronchiectasis in developing countries. In addition, TB is an important health problem in developing countries such as Turkey; and in this study, it was 1 of the most noticeable and preventable etiologies among the post-infection group. It is necessary to develop new approaches, including vaccination, early diagnosis, and medical treatments for patients with bronchiectasis.

In our study, the second-most common cause of bronchiectasis was obstructive airway diseases (28, 8.8%), including asthma (20, 6.3%), COPD (6, 1.9%), and A1AT deficiency (2, 0.6%). This high ratio may be owing to the evaluation of patients with asthma and COPD for the presence of bronchiectasis in our clinic. There are studies that address the presence of bronchiectasis in patients with asthma showing that the prevalence of bronchiectasis in these patients varies between 17.5% and 40% [20-28]. It is now considered that asthma is

Table 3. Bronchiectasis etiologies in 319 patients

Etiology of bronchiectasis	n (%)
Post-infectious	215 (67.5)
Pneumonia	94 (29.5)
Tuberculosis	70 (22.0)
Measles	25 (7.8)
Pertussis	3 (1.0)
Other respiratory infections	23 (7.2)
Obstructive airway disease	28 (8.8)
Asthma	20 (6.3)
COPD	6 (1.9)
Alpha-1 antitrypsin deficiency	2 (0.6)
Defects of mucociliary clearance	13 (4.2)
Cystic fibrosis:	5 (1.6)
Kartagener syndrome	5 (1.6)
Primary ciliary dyskinesia-	3 (1.0)
Bronchiectasis in connective tissue diseases	8 (2.4)
Rheumatoid arthritis	5 (1.6)
Systemic lupus erythematosus	1 (0.3)
Behçet's disease	1 (0.3)
Sjogren's syndrome	1 (0.3)
Immunodeficiency	5 (1.5)
Common variable immune deficiency	1 (0.3)
IgA deficiency	2 (0.6)
IgA and IgM deficiency	1 (0.3)
IgG deficiency	1 (0.3)
Obstruction of single airway	1 (0.3)
Foreign body aspiration	1 (0.3)
Structural lung conditions	1 (0.3)
McLeod syndrome	1 (0.3)
Others	7 (2.1)
Secondary amyloidosis	1 (0.3)
Yellow nail disease	1 (0.3)
Familial Mediterranean fever	1 (0.3)
Toxic gas inhalation	2 (0.6)
Gastroesophageal reflux disease	1 (0.3)
Radiotherapy	1 (0.3)
Idiopathic	41 (12.9)
Total	319

COPD: chronic obstructive pulmonary disease; IgA: immunoglobulin A; IgM: immunoglobulin M; IgG: immunoglobulin G

an etiological factor for bronchiectasis [9]. However, multiple studies that evaluated patients with asthma did not find bronchiectasis, and more studies are needed to evaluate patients with bronchiectasis to determine asthma as an etiology. In this study, we also found that the age at disease onset was significantly younger, and dyspnea was more common in patients with asthma as an etiology for bronchiectasis. Therefore, patients with asthma who have chronic symptoms such as sputum, cough, and dyspnea should be examined for the presence of bronchiectasis.

Furthermore, there is no doubt that bronchiectasis is present in patients with COPD, but it is difficult to entirely blame COPD as the cause of bronchiectasis [29, 30]. King [31] listed COPD among the etiological factors associated with bronchiectasis. Patel et al. [29] reported that the prevalence of bronchiectasis in patients with moderate-to-severe COPD was 50%. Tulek et al. [30] showed that characterization of COPD phenotypes according to different HRCT findings, including bronchiectasis, was useful in the management and prognosis of patients with COPD. Similar to these studies, the results from our study supported the hypothesis that both asthma and COPD may be important causes of bronchiectasis and must be considered in the management of patients with bronchiectasis. More studies are needed to evaluate groups of patients with bronchiectasis to determine COPD as an etiological factor.

Mucociliary clearance defects, including CF and Kartagener syndrome can cause bronchiectasis [5, 6, 8, 9, 32-34]. In our study, mucociliary clearance defects were present in 13 (4.2%) patients; 5 had CF, 5 had Kartagener syndrome, and 3 had primary ciliary dyskinesia. All the patients with CF had been followed by the department of pediatrics before the age of 15, and all of them were diagnosed by genotyping.

Connective tissue diseases were found to be an etiological factor for bronchiectasis in 8 (2.4%) patients in our study; this was not an unexpected result. Recently, Qi et al. have reported that this ratio is 4.4%, Shoemark et al. have reported that it is 2%, and Pasteur et al. reported that it is 3%. [6, 9, 12]. Rheumatoid arthritis was also shown to be an etiological factor in patients with bronchiectasis [9-12]. Despaux et al. [35] have reported that the incidence of bronchiectasis in patients with rheumatoid arthritis was as high as 41%, with a significant number of them being asymptomatic. Except for rheumatoid arthritis, associations between bronchiectasis and systemic lupus erythematosus and other connective tissue diseases were reported in a small case series [36-38]. Connective tissue diseases should be kept in mind in the management of patients with bronchiectasis.

The number of women was high in our study (women/men=187/132). This was similar to the results from other studies [6, 9]. Interestingly, in our study it was found that among female patients, pneumonia as an etiological factor for bronchiectasis was significantly higher than in male patients (p=0.04). This may be because of women having low socioeconomic status, a heavy workload, and family responsibilities in developing countries such as Turkey. Thus, women take less care of their health and go to the doctor in only the late stages of an illness.

New preventive approaches should be taken to protect the health of women in developing countries. It is not surprising that upper lobe involvement is higher in patients with TB as an etiological factor for bronchiectasis. This is supported by the result of Qi et al. [12]. However, the symptoms, including cough, sputum, and dyspnea were lower in patients with TB as an etiological factor for bronchiectasis. It was found that the number of lobes with bronchiectasis is higher in patients with immunodeficiency as an etiological factor for bronchiectasis. Recurrent pulmonary infections may cause increased numbers of lobe involvement in this group of patients. We found that the amount of cigarette consumption was significantly higher in patients with TB as an etiological factor for bronchiectasis compared with other patients. This finding supported the idea that the risk of developing bronchiectasis may be higher in patients with TB who are smokers, and this group of patients should be followed up carefully. Some studies reported that the probability of pulmonary TB was higher in smokers [39, 40]. In addition to these findings, our results also demonstrated a relationship between cigarette smoking and bronchiectasis in patients with TB. The highlights of our study were the large study population and longer follow-up periods in a specified reference bronchiectasis unit established in 1996. This unit accepts patients with bronchiectasis as a special group of patients who are followed up by a specific reference clinic with a specific follow-up protocol.

The limitation of this study was its retrospective design.

In conclusion, despite developments in antibiotic therapy and vaccination programs, the most common etiology for bronchiectasis is post-infectious conditions as has been observed in previous years. However, with the advances in diagnostic tests and procedures, the rate of unknown etiology has dropped from ≥50% to 12.9%.

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