Thymic neoplasms patients complicated with bronchiectasis: Case series in a Chinese hospital and literature review

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Bronchiectasis; diffuse panbronchiolitis; Good syndrome; thymic neoplasm.

Abstract

Background: Bronchiectasis is a rare complication in patients with thymic neoplasm. The aim of this study was to investigate the clinical and radiological manifestations, laboratory tests, pathologic features, and outcome of treatment of bronchiectasis in patients with thymic neoplasm.

Methods: From January 2000 to January 2018, 20 patients with a diagnosis of thymic neoplasm and bronchiectasis were hospitalized at the Peking Union Medical College Hospital. Clinical data was retrospectively analyzed.

Results: The prevalence of bronchiectasis in thymic neoplasms in our cohort was 1.56% (20/1279). Eighteen patients were diagnosed with thymoma, while two patients were diagnosed with thymic carcinoma. The duration from diagnosis of thymic neoplasm to bronchiectasis varied. Distributions of bronchiectasis were bilateral in 17 patients and unilateral in three patients. Four patients were previously diagnosed with diffuse panbronchiolitis and another two were suspected with diffuse panbronchiolitis. Twelve patients had various parathymic syndromes, including Good syndrome, myasthenia gravis, and aplastic anemia. Thymectomy was performed in all of these patients. Macrolide antibiotics were administered to 10 patients, and the symptoms improved in 8.

Conclusion: Bronchiectasis is a complication in thymic neoplasms, although prevalence is low. There may be multifactorial etiologies for bronchiectasis in patients with thymic neoplasms. Comprehensive treatment should be carried out to ensure optimal outcomes.

Introduction

Thymic neoplasms are rare heterogeneous neoplasms of the anterior mediastinum, requiring complex multidisciplinary management. Patients with thymic neoplasms might be clinically indolent or present with thoracic symptoms. A wide range of autoimmune parathymic syndromes associated with thymic neoplasms has been reported. Myasthenia gravis is the most common parathymic syndrome in thymic neoplasm patients, followed by pure red cell aplasia and adult-onset hypogammaglobulinemia. Although bronchiectasis has seldom been reported as a parathymic syndrome in patients with thymic neoplasm, it could be associated with thymic neoplasms, resulting in recurrent pulmonary infection and progressively worsening dyspnea.

Bronchiectasis is a morphologic term used to describe abnormal, irreversibly dilated and thick-walled bronchi,
which is a pathological endpoint that results from many diseases. It was reported that 63.4% of bronchiectasis patients in a cohort in the United Kingdom had at least one coexisting comorbid illness associated with bronchiectasis, including asthma, chronic obstructive pulmonary disease (COPD), HIV infection, rheumatoid arthritis and connective tissue disorders, inflammatory bowel disease, or allergic bronchopulmonary aspergillosis (ABPA). Pulmonary infection is the most common cause of bronchiectasis, but there are a variety of possible causes, particularly for diffuse bronchiectasis. Diffuse bronchiectasis might be secondary to systemic inflammatory disorders or immune deficiency disorders, such as hypogammaglobulinemia and HIV infection.

Thymic neoplasm with adult onset hypogammaglobulinemia is defined as Good syndrome, which is reported as an unusual cause of bronchiectasis. Patients with Good syndrome are more susceptible to recurrent sino-pulmonary infections, which might be the leading cause of bronchiectasis in such patients. However, in our clinical practice we found that bronchiectasis could develop in thymic neoplasm patients with or without Good syndrome. Very few cases of bronchiectasis without hypogammaglobulinemia in thymoma patients have been reported to date.

We reviewed the records of 20 thymic neoplasm patients with bronchiectasis and summarized the related cases reported in the literature to provide a systemic investigation of the clinical and radiological manifestations, serological testing profiles, response to treatment, and prognosis in this cohort of patients.

Methods

Patients

We performed a retrospective review of the medical records of patients with a diagnosis of bronchiectasis and thymic neoplasm at Peking Union Medical College Hospital (PUMCH) from January 2000 to January 2018. Among the 1279 patients diagnosed with thymic neoplasms, 20 patients also had bronchiectasis and were enrolled in this study. The diagnosis of thymic neoplasm was based on pathological confirmation and is established radiographically by the presence of airway dilatation on chest computed tomography (CT), especially on high-resolution images. The diagnostic criteria of Good syndrome were employed: “classic Good syndrome:” patients with a combination of a thymoma and hypogammaglobulinemia; and “probable Good syndrome:” patients with thymoma or thymic carcinoma and any unclassified immune deficiency that does not meet the criteria for classic Good syndrome.

Methods

Using standardized forms, two authors extracted medical information. Medical records were reviewed for the following clinical factors: age, gender, clinical symptoms, duration from diagnosis of thymic neoplasm to bronchiectasis, history of infection, comorbidity of thymic neoplasms, histologic type of thymic neoplasm, laboratory findings, radiological features, and treatment. Laboratory findings were reviewed, including serum immunoglobulin concentrations, lymphocyte subset counts, and pulmonary function testing. A chest CT scan was conducted on all patients, and the radiographic investigation mainly focused on pulmonary manifestations. Thymic neoplasm-related therapies (surgery, chemotherapy, targeted therapy, and radiotherapy), bronchiectasis-related therapies, and responses to therapies were reviewed. The PUMCH Institutional Review Board approved this study.

We performed a PubMed search of all relevant articles in English language, in Japanese language with an English abstract, and in Chinese language with an English abstract, published from 1990 to December 2017, using the key words: “bronchiectasis” or “panbronchiolitis” and “thymoma” or “thymic neoplasm” or “thymic tumor.” We also searched the China National Knowledge Infrastructure (CNKI) database for relevant Chinese articles. Two authors screened these citations without blinding by title and abstract to identify the relevant studies. We excluded case series in which individual patient data were not reported and case reports without detailed disease data. The citations were reviewed in detail and the full text of each citation was obtained if available. Two authors extracted medical information from enrolled literature using standardized forms.

Statistical analysis

All statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Continuous data were described by median and range.

Results

Clinical characteristics

The prevalence of bronchiectasis in thymic neoplasms in our cohort was 1.56% (20/1279). The clinical characteristics of the 20 patients (10 women, 10 men) are shown in Tables 1 and 2. The patients’ median age was 54.5 (range: 22–72) years. Thymectomy was performed on all of these patients. Eighteen patients were diagnosed with thymoma, while two patients were diagnosed with thymic carcinoid.
The duration from diagnosis of thymic neoplasm to bronchiectasis varied. Six patients suffered from a cough and purulent expectoration for 2 to 40 years before thymic neoplasms were diagnosed; four patients acquired a cough and purulent expectoration 5–9 years after thymectomy; and 10 patients were diagnosed with a mediastinal mass and bronchiectasis concurrently. The presenting pulmonary symptoms of these 20 patients included: cough (18 patients), purulent expectoration (17 patients), dyspnea (9 patients), and hemoptysis (4 patients). The respiratory tract was the most common site of infection, including pulmonary infection (16 patients) and sinusitis (4 patients). The identified infection pathogens included *Pseudomonas aeruginosa* (4 patients), *Haemophilus influenza* (3 patients), *Acinetobacter baumannii* (2 patients), invasive pulmonary aspergillosis (1 patient), and tuberculosis (1 patient).

**Radiological features**

Bronchiectasis was evident on chest CT in all 20 patients (Fig 1). Distributions of bronchiectasis were bilateral in 17 patients and unilateral in 3 patients. Centrilobular nodules were also evident in nine patients. We found over a series of CT scans that centrilobular nodules gradually progressed to bronchiectasis in several patients.

**Laboratory tests**

Serum immunoglobulin (Ig)G, IgA, and IgM concentrations were measured in 10 patients, and all were decreased in three patients. Slightly lower selective IgM was noted in another two patients, and slightly lower selective IgA in one patient. Lymphocyte subset counting was performed in seven patients. B cells were not detected in the three hypogammaglobulinemia patients, B cells were 27/μL (normal reference range: 180–324/μL) in patients with normal serum Ig, and the B cell number was normal in the remaining three patients.

Pulmonary function testing, which was performed in 16 patients, revealed that seven patients had an obstructive ventilatory defect and three patients had a restricted ventilatory defect.

**Comorbidity**

Four of the 20 bronchiectasis patients had previously been diagnosed with diffuse panbronchiolitis (DPB) and another two were suspected with DPB according to chest CT.
findings and/or pathology results. DPB in these six patients was accompanied by diffuse bronchiectasis or diffuse centrilobular nodules that gradually progressed to bronchiectasis.

Twelve patients with bronchiectasis also had various parathyroid syndromes, including Good syndrome (6 patients), myasthenia gravis (5 patients), aplastic anemia (2 patients), hypophosphatemic osteomalacia (1 patient), and rheumatoid arthritis (1 patient).

Pathology

Nine patients underwent wedge resection of the lung at the same time as thymectomy. The pathology of pulmonary samples demonstrated larger airway wall destruction as well as bronchial dilation in five patients, and small airway wall inflammation in six patients. Chronic inflammation with an accumulation of histiocytosis, plasma cells, and lymphocytes in the walls of respiratory bronchioles, adjacent alveolar ducts, and alveoli was found in three lung samples, which was consistent with a diagnosis of DPB. Ciliary dyskinesia was noted by transmission electron microscopy in one patient.

Treatment and outcome of bronchiectasis

Thymectomy was performed in all 20 patients. Macrolide antibiotics, such as azithromycin, roxithromycin, clarithromycin, and erythromycin, were administered to 10 patients, together with bronchodilators. The symptoms improved in eight patients, one patient died from severe recurrent pulmonary infection and one patient was lost to follow-up. Three patients with Good syndrome received periodic intravenous immunoglobulin (IVIg) (2 of them received macrolide antibiotics) and achieved good infection control. One patient was administered IVIg and pyridostigmine treatment for myasthenia gravis, and the symptoms markedly improved after thymectomy. One patient died from perioperative complications after thymectomy. Seven patients were lost to follow-up.

Literature review

To date, 11 case reports on PubMed and two case reports on CNKI have been published, with a total of 14 thymic neoplasm patients with bronchiectasis (7 women and 7 men). Among these reports, eight were in English, three in Japanese, and two in Chinese. A summary of the literature is shown in Table 3. The patients’ median age was 50.8 (range: 22–71) years. Seven patients began experiencing cough and purulent expectoration 0.75 to 12 years after thymectomy, and six patients were diagnosed concurrently with a mediastinal mass and bronchiectasis. Six patients had Good syndrome and two patients without hypogammaglobulinemia were suspected of probable Good syndrome. Five patients were diagnosed with DPB and two patients were thought to have pulmonary lesions similar to DPB. Eight patients had improved symptoms after macrolide antibiotic treatment, two patients with Good syndrome had improved symptoms after IVIg treatment, one patient had improved symptoms after thymectomy, and one patient died of recurrent infection.

Discussion

To the best of our knowledge, this study presents the largest series of bronchiectasis in thymic neoplasm patients. We reveal several interesting findings: (1) thymic neoplasms may be complicated by bronchiectasis (the prevalence of bronchiectasis in our cohort was 1.56%, 20/1279); (2) the duration from diagnosis of thymic neoplasm to bronchiectasis varied; (3) six bronchiectasis patients (6/20, 30%) in our cohort and six (6/14, 42.9%) in the literature had Good syndrome, while four patients (4/20, 20%) in
| Study          | Gender | Age | Histologic classification of thymic neoplasms | Treatment of thymoma                          | Complication of thymoma                       | Duration (year) | Symptoms of pulmonary disease                  | Chest CT                    | DPB | Treatment                             | Outcome                  |
|---------------|--------|-----|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------|-----------------------------------------------|----------------------------|-----|---------------------------------------|--------------------------|
| Pu et al. 10  | M      | 37  | Type AB thymoma                               | Thymectomy, adjuvant radiotherapy             | Good syndrome                                 | 2               | Cough and purulent expectoration              | Bronchiectasis             | N   | IVIg                                   | Improved                 |
| Maekawa et al. 11 | M    | 55  | Type B3 thymoma                               | Thymectomy, radiation therapy                | Myasthenia gravis, alopecia, Dysgeusa, myositis, and cholangitis | 12              | Cough, dyspnea                                | Diffuse centrilobular opacities, bronchiectasis | Y   | Corticosteroid and tacrolimus            | Died                     |
| Hunt 6        | F      | 22  | Type B2 thymoma                               | Thymectomy                                    | Good syndrome                                 | 0               | Dyspnea                                       | Bronchiectasis             | N   | No                                     | Improved                 |
| Ogoshi et al. 14 | M    | 45  | Type B2 thymoma                               | Thymectomy, 1 cycle chemotherapy, thymectomy | Pure red cell aplasia, myasthenia gravis, Good syndrome | 0.75            | Cough, purulent expectoration, dyspnea       | Diffuse panbronchiolitis, centrilobular small nodular | S   | Clarithromycin and azithromycin          | Improved                 |
| Ishiguro et al. 12 | M    | 53  | Thymoma                                       | Thymectomy                                    | No                                            | 0               | Cough, dyspnea                                | Mild bronchiectasis, centrilobular nodules | N   | Clarithromycin                          | Improved                 |
| Zhang et al. 13 | F    | 41  | Thymoma                                       | Thymectomy                                    | No                                            | 3               | Cough, purulent expectoration, dyspnea       | Centrilobular nodules     | Y   | Erythromycin                           | Improved                 |
| Tsuburai et al. 15 | F    | 65  | Thymoma                                       | Surgical treatment, irradiation therapy       | Good syndrome                                 | NA              | Cough, purulent expectoration, dyspnea       | Centrilobular nodules     | S   | Erythromycin                           | Improved                 |
| Arend et al. 16 | F    | 59  | Benign thymoma                                | Thymectomy                                    | Good syndrome                                 | 0               | Cough, purulent expectoration, dyspnea       | Bronchiectasis with peribronchial inflammation | N   | IVIg, antibiotics                      | Improve                  |
| Fox et al. 17  | F      | 71  | Spindle-cell thymoma                          | No                                            | Anemia, Good syndrome                          | 0               | Cough, dyspnea                                | Bronchiectasis             | N   | NA                                    | NA                       |
| Okano et al. 18 | F    | 58  | Malignant thymoma                             | Thymectomy                                    | Sjogren’s syndrome, pseudolymphoma            | 0               | Cough, purulent expectoration, dyspnea       | Diffuse reticulonodular shadows | Y   | NA                                    | NA                       |
| Jin et al. 19  | M      | 27  | Thymoma, type B3, partially type B2, UK       | Thymectomy                                    | Myasthenia gravis                             | 0               | Cough, purulent expectoration, dyspnea       | Small centrilobular and branching nodules | Y   | Roxithromycin                          | Improved                 |
| Li et al. 20  | F      | 62  | Thymoma                                       | Thymectomy                                    | Probable Good syndrome                        | 0.75            | Cough, purulent expectoration, dyspnea       | Diffuse panbronchiolitis and bronchiectasis | N   | Azithromycin                          | Improved                 |
| M             | M      | 46  | Malignant thymoma                             | Thymectomy                                    | Probable Good syndrome                        | 9               | Cough, purulent expectoration, dyspnea       | Diffuse panbronchiolitis, bronchiectasis | N   | Azithromycin                          | Improved                 |
our cohort and five (5/14, 35.7%) in the literature were diagnosed with DPB; (4) Comprehensive treatment might be beneficial to improve the pulmonary symptoms in these patients.

Approximately 1–8% of adults with bronchiectasis have humoral immune deficiency. Common variable immune deficiency (CVID) and X-linked agammaglobulinemia (XIA) are the most common immune deficiency diseases causing bronchiectasis. Hypogammaglobulinemia in almost 6–11% of thymoma patients is called Good syndrome, which is similar to CVID. Recurrent pulmonary infections caused by hypogammaglobulinemia have been recognized as the cause of bronchiectasis in patients with thymic neoplasm. However, only six patients (6/20, 30%) in our cohort and six patients (6/14, 42.9%) in the literature had Good syndrome. The literature indicates that neither bronchiectasis nor DPB is a typical manifestation or complication of Good syndrome. Sun et al. evaluated 12 Good syndrome patients with infection in our hospital, but only one patient had bronchiectasis. Therefore, we suggest that recurrent pulmonary infection caused by Good syndrome is an important etiology for bronchiectasis, but is not the only reason.

In the literature review (Table 3), five patients (5/14, 35.7%) were diagnosed with DPB and two patients were suspected with DPB. In our cohort, four patients (4/20, 20%) were diagnosed with DPB and two patients were suspected with DPB. The clinical features of some of the patients in our study, such as a cough, purulent sputum, and breathlessness with exertion, were similar to those of DPB patients. CT findings of diffused bronchiectasis in patients complicated with thymic neoplasms were sometimes similar to DPB. Most notably, pathology of three lung biopsy samples in our study and four cases in the literature review were consistent with the distinctive pathological features of DPB. The pathogenesis of DPB is not clear. Apart from genetic factors, environmental and systemic factors appear to contribute to DPB development. The prominence of lymphocytes in and around the bronchioles indicates the potential role of lymphocytes in the pathogenesis of DPB. The DPB-like pathological features suggest that bronchiectasis and DPB-like manifestations might be the result of an abnormal immune attack of parathympic phenomena. This theory is derived from studies of parathympic phenomena in thymoma, where lymphocytes or autoantibodies directly or indirectly damage target cells or organs, leading to many autoimmune manifestations. Bronchia, respiratory bronchioles, or airway epithelium are potential target tissues and cells of parathympic phenomena. Pathology of pulmonary samples in our cohort showed the chronic inflammation of small airways in six patients and ciliary dyskinesia in one patient. Lymphocyte infiltration in small airway walls, adjacent alveolar ducts, and alveoli

| Study | Gender | Age | Duration (year) | Complication of thymoma | Treatment of thymoma | Treatment of DPB | CT findings | Symptoms of pulmonary disease | Histologic classification of thymic neoplasms | Outcome |
|-------|--------|-----|-----------------|-------------------------|----------------------|------------------|-------------|--------------------------|--------------------------------|---------|
| Zhai et al. | M | 70 | 5 | No | Thymectomy | No, similar to DPB | Diffuse bronchiolitis, centrallobular nodules, bronchiectasis | Cough, purulent expectoration, dyspnea | Type AB thymoma | Improved |
| Y. Liu et al. | F | 65 | 3 | No | Thymectomy | No, similar to DPB | Diffuse panbronchiolitis, bronchiectasis | Cough, purulent expectoration, dyspnea | Type AB thymoma | Improved |
| Freier et al. | M | 80 | 7 | No | Thymectomy | No, similar to DPB | Diffuse bronchiolitis, centrallobular nodules, bronchiectasis | Cough, purulent expectoration, dyspnea | Type AB thymoma | Improved |

CT, computed tomography; DPB, diffuse panbronchiolitis; IVIg, intravenous immunoglobulin; N, No; NA, not applicable; S, similar to DPB; UK, unknown; Y, yes.
might lead to small airway wall thickening and irreversible bronchial dilatation, as well as decreased cilium movement, which might be another cause of bronchiectasis. Dys-expectoration caused by myasthenia gravis may be an additional factor for bronchiectasis.

We conducted this study to summarize the etiology of bronchiectasis in patients with thymic neoplasm. First, recurrent pulmonary infection caused by hypogammaglobulinemia (Good syndrome) is one of the main causes. Second, patients with thymic neoplasm might have immunologic abnormalities, and bronchia and respiratory bronchioles might be the targets of abnormal immune attack, as in DPB. Third, patients with myasthenia gravis in thymic neoplasms were prone to pulmonary infections as a result of poor expectoration.

Another interesting question is: When does bronchiectasis occur in the whole stage of thymic neoplasms? We noted that bronchiectasis could occur at any stage of thymic neoplasm. Six patients had suffered from bronchiectasis-related symptoms (cough and purulent expectoration) for several years before thymic neoplasms were diagnosed, and in 10 patients, thymic neoplasms were revealed during the diagnostic workup for bronchiectasis. The symptoms improved in some patients after thymectomy and bronchiectasis related treatment; however, bronchiectasis developed after thymectomy in four patients, which suggests that the abnormal immune status caused by thymic neoplasms might not resume after thymectomy. The gradual changes in several patients’ CT scans (from centrilobular nodules to bronchiectasis) indicated that DPB-like manifestation gradually developed into bronchiectasis. The slow process of evolution indicates that bronchiectasis development might be a long-term underlying consequence of thymic neoplasms.

Understanding the potential etiologies of bronchiectasis in thymic neoplasms helps the management of these patients. Thymectomy should be considered for all patients in order to relieve parathymic phenomena. For patients with Good syndrome, Ig replacement is recommended to maintain appropriate serum IgG concentration, in order to reduce recurrent respiratory infections. For patients with myasthenia gravis, pyridostigmine might improve respiratory muscle powers for expectoration. Macrolide antibiotic treatment was administered to half of our cohort and those in the literature. The macrolide treatment, derived from DPB-related treatment, resulted in a dramatic improvement in these patients. The mechanisms of the beneficial effect of macrolide antibiotics in DPB are thought to be the result of immunomodulation rather than antibiotics. 25–27 The reduced effect of macrolide antibiotics on the proinflamatory response may be beneficial to the abnormal immune status of the small airway wall in patients with thymic neoplasm. Meanwhile, a general approach to bronchiectasis management should be considered, including airway clearance, bronchodilation, antibiotic therapy, and management of complications.

In conclusion, bronchiectasis is a rare but significant comorbidity of thymic neoplasms. Multifactorial etiology of bronchiectasis in patients with thymic neoplasm may exist, including hypogammaglobulinemia, abnormal immune attack of parathymic phenomena, and dys-expectoration. Apart from thymectomy, macrolide antibiotics might be useful to treat bronchiectasis in these patients, and IVIg should be used to treat patients with Good syndrome.

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Disclosure

No authors report any conflict of interest.

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