Management of tracheobronchial amyloidosis: a review of the literature

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2510 words

Abstract
Introduction

Tracheobronchial amyloidosis (TBA) is a rare idiopathic disorder characterized by extracellular deposition of misfolded protein fibrils in the tracheobronchial tree. It presents with non-specific symptoms. Deciding on the best treatment approach can be challenging due to the lack of a treatment guideline. We undertook a review to review the therapeutic options for tracheobronchial amyloidosis and to highlight gaps within the existing evidence.

Methods

We performed a literature search from 1st January 1990 until 1st March 2022 to identify relevant literature regarding patient characteristics, symptoms, management and prognosis for patients with TBA.

Results

A total of 77 studies consisting of 300 patients were included. We found a great heterogeneity in the management of TBA patients. Although a fifth of the reported patients were managed with a wait and see approach many different treatments were used as a single intervention or multiple treatments were combined. An interesting finding is the slightly higher percentage of patients with Morbus Sjögren (n=5, 1.7%) and TBA compared to the normal population (0.5% to 1.0%).

Conclusions

There is a great heterogeneity in the management of TBA patients. The treatment is still based on expert opinion due to the lack of a treatment guideline. Various treatment approaches include a wait and see approach, external beam radiotherapy, therapeutic bronchoscopy, immunosuppressive treatment and surgery.

1. Introduction
Tracheobronchial amyloidosis (TBA) is a rare idiopathic disorder characterized by extracellular deposition of misfolded protein fibrils in the tracheobronchial tree [1, 2], which accounts for about 1% of benign tumors in the tracheobronchial tree. [3] Immunoglobulin light chain amyloidosis (AL) has an incidence of 8–12 persons per million per year [4] and its localised form accounts for only around 10% of cases. [5] The most common symptoms are nonspecific and include: dyspnea, cough, hemoptysis and wheezing [6], which often leads to diagnostic delay and treatment for suspected diseases with similar symptoms such as asthma or bronchitis [1]. Pulmonary function abnormalities may occur depending on the disease location and degree of airway obstruction in the tracheobronchial tree. Histopathological biopsy is the gold standard for diagnosis, which typically demonstrates amyloid deposits in the tracheobronchial subepithelial interstitial tissue associated with an inflammatory cell infiltrate, and the diagnosis is confirmed by birefringence of Congo red-stained tissue under polarized light microscopy. [7, 8] There are no guidelines or randomised controlled trials in this area, and data is scant on individual treatment modalities, so deciding on the best treatment approach can be challenging. [1] Further, disease progression can be slow, so careful evaluation is needed to assess whether treatment is needed at all. Nonetheless, observation, mechanical debulking, laser ablation, balloon dilatation, stent placement, radiotherapy and immunosuppressive treatment are the current mainstays of treatment. Local excision often proves to improve symptoms only temporarily with multiple local recurrences. [9] We undertook a review to review the therapeutic options for tracheobronchial amyloidosis and to highlight gaps within the existing evidence.

2. Methods

2.1 Data sources and searches

We performed a literature search on treatment of patients with tracheobronchial amyloidosis. This review was performed and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). Studies were eligible if they included adult patients with histology-proven tracheobronchial amyloidosis [10]. Medline, Google Scholar, Scopus, Embase, Web of Science,
PubMed, PubMed Central, UpToDate and The Cochrane Library were searched for articles, with an English-language restriction, from 1st January 1990 through 1st March 2022. The following search terms were used: tracheobronchial amyloidosis, tracheal amyloidosis, trachea, amyloid, amyloidosis, laryngeal tracheobronchial amyloidosis, endobronchial. References of included articles were assessed manually and included when relevant.

2.2 Study selection

The screening of eligible publications was carried out independently by two reviewers (IS and TI). First the titles and abstracts of all citations were reviewed. After duplicate removal the full text of potentially relevant articles was reviewed. Cases were included if they concerned adult patients (>18 years) with histology-proven tracheobronchial amyloidosis. Discrepancies were resolved by consensus.

2.3 Data selection and quality assessment

Data was extracted by two reviewers (IS and TI) on patient characteristics (age, sex, background), symptoms, distribution in the tracheobronchial tree, management and prognosis.

2.4 Data synthesis and analysis

Data was summarized using descriptive statistics, with median and interquartile range (IQR) for continuous variables and frequencies and percentages for dichotomous variables.

2.5. Role of the funding source

There was no funding source for this study.

3. Results

3.1 Search results

A total of 177 unique citations were initially retrieved through database searching. After removal of duplicates and articles without full text availability we identified 91 citations as potentially relevant and reviewed the full publication. We excluded 2 publications reporting cases in which no clinical characteristics were described (only
radiological diagnosis) and 7 different language articles. Five publications were not retrievable. A total of 77 articles were identified as eligible for inclusion: 56 case reports [3, 9, 11-64], 18 small case series (n<30) reporting a combined 105 cases [1, 8, 65-80] and 3 retrospective cohort studies reporting on a combined 139 cases [81-83].
3.2 Characteristics of patients
A total of 77 studies consisting of 300 patients were included. There were 159 men (53.0%) and 123 (41.0%) women, the gender of 18 patients was not mentioned. The median age was 52.0 years (IQR: 49.0-60.0). The comorbidities were missing for 224 patients. Common comorbidities described in this population were cardiovascular disease (3.3%), asthma (2.7%) and recurrent respiratory infections (2.3%). Some patients (n=13; 4.3%) had multiple comorbidities. Five patients were co-diagnosed with Morbus Sjögren. The most common presenting symptoms were dyspnea (n=134; 44.7%), cough (n=112; 37.3%) and hemoptysis (n=42; 14.0%).

Other presenting symptoms are reported in Table 1. Distribution of TBA varied between the trachea, main bronchi, lobar bronchi and entire tracheobronchial tree. The trachea was the most affected area (33.3%). TBA in the entire tracheobronchial tree was present in 4.0% of the patients. Systemic amyloidosis, defined as amyloid fibril deposition in various organs and tissues, was described in only seven patients.

3.3 Management
Several treatments have been attempted for patients diagnosed with tracheobronchial amyloidosis. The included patients were exposed to different management strategies. The main categories of treatment include a wait and see approach, external beam radiotherapy, therapeutic bronchoscopy, immunosuppression and surgery. The most commonly performed treatments were therapeutic bronchoscopy (30.3%), external beam radiotherapy (22.0%) and a significant proportion of patients were managed with a wait and see approach (21.7%). Additionally, some individuals received systemic treatment including corticosteroids (9.0%), colchicine (5.0%), melphalan (2.0%) and rituximab (0.3%). Twelve patients (4%) underwent surgery, with lobectomy performed in two cases (0.7%) and tracheostomy in 10 cases (3.3%) due to respiratory failure caused by tracheobronchial amyloidosis. Some patients (n=46; 15.3%) received multiple treatments from the main categories.
3.4 Outcome

During follow-up 37/163 (22.7%) patients died. Information about mortality and the stage of TBA was missing for 137/300 patients (45.7%). The death rate observed for the main treatment categories were: observation n=9/65 (13.8%), external beam radiotherapy (EBRT) n=15/66 (22.7%), therapeutic bronchoscopy n=13/91 (14.3%), medication n=6/32 (18.8%) and surgery n=7/12 (58.3%). Some of these patients received multiple different treatments. No studies comparing different treatment modalities on disease outcomes were found. The most common cause of death was respiratory failure (n=25; 67.6%). In 203/300 (67.7%) patients the follow-up duration time was missing. Common side effects of external beam radiotherapy were fatigue, cough and dyspnea. The most common side effect of bronchoscopic Nd YAG laser irradiation was cough post-procedure and hypoxia that developed during the procedure. Unfortunately data on symptoms and lung function tests before and after treatment was very limited.

Table 4 | Summary of follow up time and death rate

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Follow up time (months, IQR)</th>
<th>Death (number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Observation</td>
<td>6.0 (0.0-72.0)</td>
<td>9/65 (13.8%)</td>
</tr>
<tr>
<td>2. External beam radiotherapy</td>
<td>48.0 (9.0-48.0)</td>
<td>15/66 (22.7%)</td>
</tr>
<tr>
<td>3. Therapeutic bronchoscopy</td>
<td>10.5 (3.0-34.5)</td>
<td>13/91 (14.3%)</td>
</tr>
<tr>
<td>4. Immunosuppressive medication</td>
<td>19.0 (12.0-22.3)</td>
<td>6/32 (18.8%)</td>
</tr>
<tr>
<td>5. Surgery</td>
<td>10.0 (10.0-10.0)</td>
<td>7/12 (58.3%)</td>
</tr>
</tbody>
</table>
Some patients who have died received multiple treatments

4. Discussion

In the 77 studies we included with a total of 300 patients we found a great heterogeneity in the management of TBA patients. Although a fifth of the reported patients were managed with a wait and see approach many different treatments were used as a single intervention or multiple treatments were combined. Because symptoms of dyspnea, recurrent cough and wheezing are also common with asthma, we believe that most patients with TBA and asthma may be misdiagnosed and that the prevalence (2.7%) of asthma was likely lower than reported. Different medications were used to treat TBA and more cases have been reported recently of patients that were treated with oral or intravenous drugs such as corticosteroids, colchicine, rituximab and melphalan. Colchicine is a tricyclic, lipid-soluble alkaloid that interferes with several inflammatory pathways including adhesion and recruitment of neutrophils and the tumor necrosis factor alpha (TNF-α) -induced nuclear factor κB (NF-κB) pathway attenuating the inflammatory response. [84] Colchicine can inhibit the deposition of amyloid fibrils in organs, as has been demonstrated in mice models. [85]. Patients treated with EBRT had the longest median follow up with 48.0 months (IQR: 9.0-48.0), however it is not possible to calculate a reliable overall survival because the initial staging, time until progression and death was missing for most of the patients. It is impossible to draw conclusions about efficacy of treatments because there were no comparative studies, small sample sizes, limited follow-up and because different interventions were combined in various ways. It was also not possible to draw conclusions about how to treat the patient with TBA in the entire tracheobronchial tree as these patients (n=12) were treated differently. An interesting finding is the slightly higher percentage of patients with Morbus Sjögren (n=5, 1.7%) and TBA compared to the normal population (0.5% to 1.0%) [10]. Although the exact pathogenesis of TBA remains unclear, there are some hypotheses. Borie et al [17] were the first to demonstrate the presence of a local B-cell clone in tracheobronchial amyloidosis and the efficacy of B-cell-targeted therapy with rituximab, an anti-CD20 monoclonal antibody. Other reports suggest a local production of amyloidogenic light chains by subtle local clones of
lymphoplasmocytes. [86, 87] On the other hand, pulmonary involvement may occur in 9-70% of patients with Sjögren syndrome and the most common pulmonary abnormalities are bronchiolitis and interstitial lung disease. [88, 89] Although the pathophysiology associated with TBA and Sjögren syndrome remains unclear, further research is needed to understand if and how Morbus Sjögren and TBA are associated.

A strength of this review was that it used a comprehensive search strategy, particularly for treatment options including endobronchial or surgical intervention, radiotherapy and pharmacological therapy. To our knowledge, we are reporting the largest and most comprehensive review of case reports and case series of patients with tracheobronchial amyloidosis. Another strength that distinguishes our work from previous published literature reviews is that we yielded more studies focusing on the treatment options and outcome.

There are several limitations that deserve to be mentioned. One of the limitations is that only retrospective data exists for this subgroup of disease and its management. In some of these studies different treatments were combined which making individual effect hard to describe. Furthermore, in certain published studies, the follow-up survival data or long-term side effects were not reported. Another limitation is publication bias as many cases of tracheobronchial amyloidosis may go unpublished. This may significantly affect the results such as reported frequencies of findings and outcome. Our findings are also limited by the quality of the data in the reports, which was not consistent or uniform. Information about the medical background and follow up of patients was missing in multiple case reports. The rationale for a treatment choice was also missing in most cases. The sample sizes were also small, follow-up was limited and different interventions were combined in various ways. Because symptoms prior to and after treatment and lung function results were not always reported it is unknown what outcome parameter is most suitable to follow-up this disease with. Also bronchoscopy surveillance was not reported for most patients. The reported death rates should be interpreted with caution. The death rate is more probably a reflection of disease stage then efficacy. And this is an important ‘knowledge gap’. The current retrospective literature does not allow for any conclusions about efficacy and safety of the different treatment
modalities. Due to these limitations, we are unable to formulate a treatment guideline for TBA.

5. Conclusion
Our review shows that patients with TBA present with non-specific respiratory symptoms. Various treatment approaches include (a combination of) a wait and see approach, external beam radiotherapy, therapeutic bronchoscopy, immunosuppressive treatment and surgery. Deciding on the best treatment approach can be challenging and is still based on expert opinion due to the lack of a treatment guideline. Unfortunately no randomized controlled trials are available comparing the different treatment options. Future research is needed to identify useful outcome parameters for this disease to assess outcome of treatment and compare different treatments. We suggest that an international registry could be of great help to collect information concerning demographic details, different treatments and prognosis of TBA patients.
References


78. Ren, S., External beam radiation therapy is safe and effective in treating primary pulmonary amyloidosis. Respiratory Medicine, 2012(106): p. 1063-1069.


Figure 1 | Study selection flow diagram

Identification of studies via databases and registers

Identification

177 Records identified from databases

Records removed before screening:
65 Duplicate records removed
21 Records not relevant

Screening

91 Records screened

2 Records were excluded because no clinical characteristics were described
7 Records in a different language were excluded

82 Records sought for retrieval

5 Records not retrieved

77 Records assessed for eligibility

56 Case reports: n=56
18 Small case series (n<30): n=105
3 Large retrospective cohort studies (n>30) n=139

Included
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total patients n=300 (n, percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age in years (IQR)</strong></td>
<td>52.0 years (IQR: 49.0-60.0)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>159 (53.0%)</td>
</tr>
<tr>
<td>Female</td>
<td>123 (41.0%)</td>
</tr>
<tr>
<td>Missing</td>
<td>18 (6.0%)</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
</tr>
<tr>
<td>Blanco</td>
<td>35 (11.7%)</td>
</tr>
<tr>
<td>Other</td>
<td>15 (5.0%)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>10 (3.3%)</td>
</tr>
<tr>
<td>Asthma</td>
<td>8 (2.7%)</td>
</tr>
<tr>
<td>Recurrent respiratory infections</td>
<td>7 (2.3%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (2.0%)</td>
</tr>
<tr>
<td>Morbus Sjögren</td>
<td>5 (1.7%)</td>
</tr>
<tr>
<td>Lung emphysema</td>
<td>3 (1.0%)</td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Missing</td>
<td>224 (74.7%)</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>134 (44.7%)</td>
</tr>
<tr>
<td>Cough</td>
<td>112 (37.3%)</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>42 (14.0%)</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>23 (7.7%)</td>
</tr>
<tr>
<td>Wheezing</td>
<td>18 (6.0%)</td>
</tr>
<tr>
<td>Other</td>
<td>18 (6.0%)</td>
</tr>
<tr>
<td>Fever</td>
<td>7 (2.3%)</td>
</tr>
<tr>
<td>Stridor</td>
<td>3 (1.0%)</td>
</tr>
<tr>
<td>Missing</td>
<td>92 (30.7%)</td>
</tr>
<tr>
<td><strong>Distribution in tracheobronchial tree</strong></td>
<td></td>
</tr>
<tr>
<td>Part of the Tracheobronchial Tree</td>
<td>Count (Percentage)</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Trachea</td>
<td>100 (33.3%)</td>
</tr>
<tr>
<td>Right main bronchus</td>
<td>48 (16.0%)</td>
</tr>
<tr>
<td>Left main bronchus</td>
<td>45 (15.0%)</td>
</tr>
<tr>
<td>Lobar bronchi</td>
<td>38 (12.7%)</td>
</tr>
<tr>
<td>Entire tracheobronchial tree</td>
<td>12 (4.0%)</td>
</tr>
<tr>
<td>Missing</td>
<td>152 (50.7%)</td>
</tr>
</tbody>
</table>

*Patients could have multiple comorbidities, symptoms and affected parts of the tracheobronchial tree.*
Table 3 | Management of patients with tracheobronchial amyloidosis

<table>
<thead>
<tr>
<th>Management</th>
<th>Patients (n,%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wait and see</td>
<td>65 (21.7%)</td>
</tr>
<tr>
<td>External beam radiotherapy</td>
<td>66 (22.0%)</td>
</tr>
<tr>
<td>Therapeutic bronchoscopy</td>
<td>91 (30.3%)</td>
</tr>
<tr>
<td>Bronchoscopic Nd YAG laser irradiation</td>
<td>79 (26.3%)</td>
</tr>
<tr>
<td>Mechanical debulking</td>
<td>24 (8.0%)</td>
</tr>
<tr>
<td>Argon plasma therapy</td>
<td>11 (3.7%)</td>
</tr>
<tr>
<td>Stent placement</td>
<td>5 (1.7%)</td>
</tr>
<tr>
<td>Balloon dilatation</td>
<td>5 (1.7%)</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>4 (1.3%)</td>
</tr>
<tr>
<td>Intermittent microwave ablation</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>Immunosuppression/immunosuppressive medication</td>
<td>32 (10.7%)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>27 (9.0%)</td>
</tr>
<tr>
<td>Colchicine</td>
<td>15 (5.0%)</td>
</tr>
<tr>
<td>Melphalan</td>
<td>6 (2.0%)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Surgery</td>
<td>12 (4.0%)</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>10 (3.3%)</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>2 (0.7%)</td>
</tr>
</tbody>
</table>

Patients could have received multiple different treatments, even up to 3 different types.