Management of tracheobronchial amyloidosis: a review of the literature

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Shareable abstract (@ERSpublications)
This systematic review shows that there is great heterogeneity in the management of tracheobronchial amyloidosis patients. Deciding on the best treatment approach can be challenging and is still based on expert opinion due to the lack of treatment guidelines. https://bit.ly/3MqTmRu

Cite this article as: Smesseim I, Cobussen P, Thakrar R, *et al*. Management of tracheobronchial amyloidosis: a review of the literature. *ERJ Open Res* 2024; 10: 00540-2023 [DOI: 10.1183/23120541.00540-2023].

Received: 26 July 2023
Accepted: 29 Oct 2023

Abstract

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

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

Results 77 studies consisting of 300 patients were included. We found a great heterogeneity in the management of tracheobronchial amyloidosis 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 Sjögren syndrome (n=5, 1.7%) and tracheobronchial amyloidosis compared to the normal population (0.5–1.0%).

Conclusions There is a great heterogeneity in the management of tracheobronchial amyloidosis 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.

Introduction

Tracheobronchial amyloidosis is a rare idiopathic disorder characterised by extracellular deposition of misfolded protein fibrils in the tracheobronchial tree [1, 2], which accounts for ~1% of benign tumours in the tracheobronchial tree [3]. Immunoglobulin light chain amyloidosis has an incidence of 8–12 persons per million per year [4] and its localised form accounts for only ~10% of cases [5]. The most common symptoms are nonspecific and include dyspnoea, cough, haemoptysis 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 polarised light microscopy [7, 8].

There are no guidelines or randomised controlled trials in this area, and data are scant on individual treatment modalities, so deciding on the best treatment approach can be challenging [1]. Furthermore, 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.

Methods

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. 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 1 January 1990 through 1 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.

Study selection

The screening of eligible publications was carried out independently by two reviewers (I. Smesseim and Tejas Ingle (University College London Hospitals, London, UK)). First, the titles and abstracts of all citations were reviewed. After removal of duplicates, the full text of potentially relevant articles was reviewed. Cases were included if they concerned adult patients (aged >18 years) with histology-proven tracheobronchial amyloidosis. Discrepancies were resolved by consensus.

Data selection and quality assessment

Data were extracted by two reviewers (I. Smesseim and T. Ingle) on patient characteristics (age, sex, background), symptoms, distribution in the tracheobronchial tree, management and prognosis.

Data synthesis and analysis

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

Role of the funding source

There was no funding source for this study.

Results

Search results

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 two publications reporting cases in which no clinical characteristics were described (only radiological diagnosis) and seven 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 three retrospective cohort studies reporting a combined 139 cases [81–83] (figure 1).

Characteristics of patients

A total of 77 studies consisting of 300 patients were included. There were 159 (53.0%) men and 123 women (41.0%); the gender of 18 patients was not mentioned. The median (IQR) age was 52.0 (49.0–60.0) years. 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 dyspnoea (n=134; 44.7%), cough (n=112; 37.3%) and haemoptysis (n=42; 14.0%). Other presenting symptoms are reported in table 1. Distribution of tracheobronchial amyloidosis varied between the trachea, main bronchi, lobar bronchi and entire tracheobronchial tree. The trachea was the most affected area (33.3%). Tracheobronchial amyloidosis in the

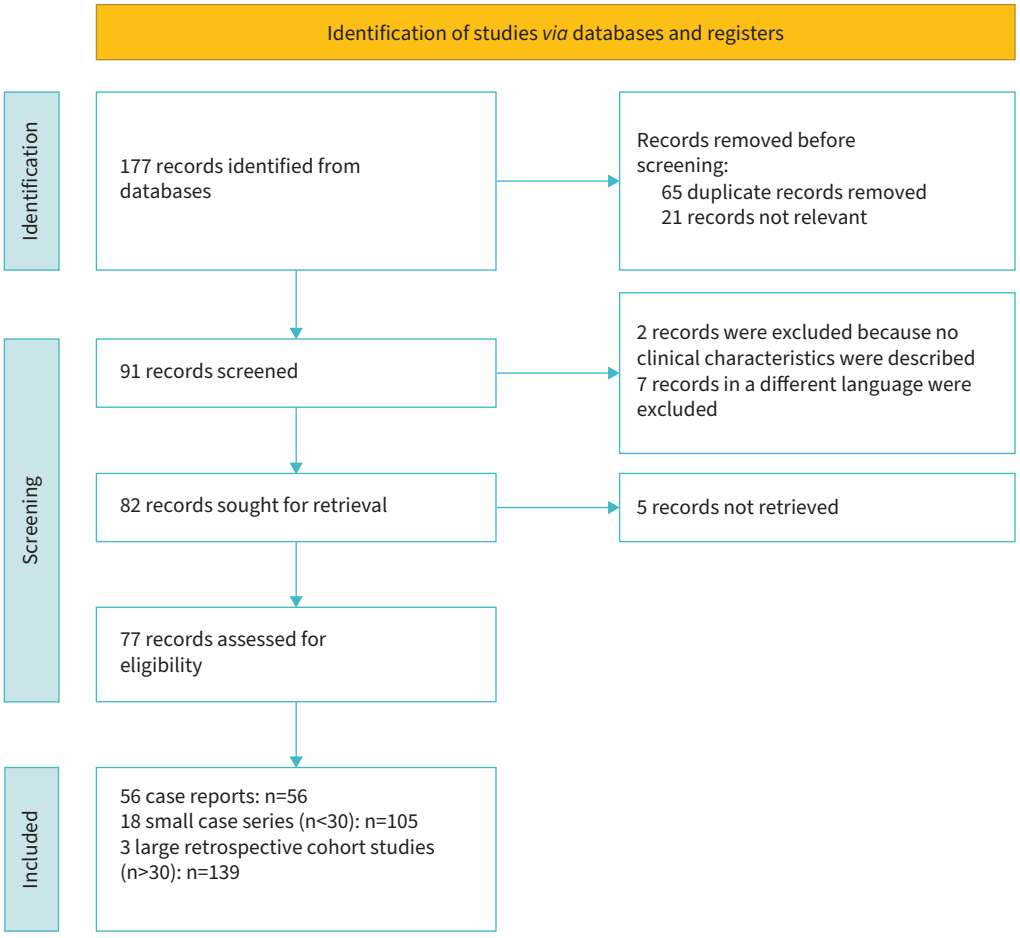

FIGURE 1 Study selection flow diagram.

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.

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 (table 2). 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%). 12 (4%) patients underwent surgery, with lobectomy performed in two (0.7%) cases and tracheostomy in 10 (3.3%) cases due to respiratory failure caused by tracheobronchial amyloidosis. Some patients (n=46; 15.3%) received multiple treatments from the main categories.

Outcome

During follow-up, 37 (22.7%) out of 163 patients died. Information about mortality and the stage of tracheobronchial amyloidosis was missing for 137 (45.7%) out of 300 patients. The death rate observed for the main treatment categories were: observation nine (13.8%) out of 65, external beam radiotherapy 15 (22.7%) out of 66, therapeutic bronchoscopy 13 (14.3%) out of 91, medication six (18.8%) out of 32 and surgery seven (58.3%) out of 12 (table 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 (67.7%) out of 300 patients, the follow-up duration time was missing. Common side-effects of external beam radiotherapy were fatigue, cough and

TABLE 1 Patient characteristics

Total patients	300
Age years	52.0 (49.0–60.0)
Sex	
Male	159 (53.0)
Female	123 (41.0)
Missing	18 (6.0)
Comorbidities	
Blanco	35 (11.7)
Other	15 (5.0)
Cardiovascular disease	10 (3.3)
Asthma	8 (2.7)
Recurrent respiratory infections	7 (2.3)
Diabetes mellitus	6 (2.0)
Morbus Sjögren	5 (1.7)
Lung emphysema	3 (1.0)
Pulmonary tuberculosis	2 (0.7)
Lung cancer	1 (0.3)
Missing	224 (74.7)
Symptoms	
Dyspnoea	134 (44.7)
Cough	112 (37.3)
Haemoptysis	42 (14.0)
Hoarseness	23 (7.7)
Wheezing	18 (6.0)
Other	18 (6.0)
Fever	7 (2.3)
Stridor	3 (1.0)
Missing	92 (30.7)
Distribution in tracheobronchial tree	
Trachea	100 (33.3)
Right main bronchus	48 (16.0)
Left main bronchus	45 (15.0)
Lobar bronchi	38 (12.7)
Entire tracheobronchial tree	12 (4.0)
Missing	152 (50.7)

Data are presented as n, median (interquartile range) or n (%). Patients could have multiple comorbidities, symptoms and affected parts of the tracheobronchial tree.

TABLE 2 Management of patients with tracheobronchial amyloidosis

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

Data are presented as n (%). Patients could have received multiple different treatments (as many as three different types).

TABLE 3 Summary of follow-up time and death rate

	Follow-up time months	Deaths
Observation	6.0 (0.0–72.0)	9/65 (13.8)
External beam radiotherapy	48.0 (9.0–48.0)	15/66 (22.7)
Therapeutic bronchoscopy	10.5 (3.0–34.5)	13/91 (14.3)
Immunosuppressive medication	19.0 (12.0–22.3)	6/32 (18.8)
Surgery	10.0 (10.0–10.0)	7/12 (58.3)

Data are presented as median (interquartile range) or n (%). Some patients who died received multiple treatments.

dyspnoea. 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 were very limited.

Discussion

In the 77 studies we included, with a total of 300 patients, we found a great heterogeneity in the management of tracheobronchial amyloidosis 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 dyspnoea, recurrent cough and wheezing are also common with asthma, we believe that most patients with tracheobronchial amyloidosis and asthma may be misdiagnosed and that the prevalence (2.7%) of asthma was probably lower than reported.

Different medications were used to treat tracheobronchial amyloidosis 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 tumour necrosis factor -α-induced NF-κB pathway attenuating the inflammatory response [84]. Colchicine can inhibit the deposition of amyloid fibrils in organs, as has been demonstrated in mouse models [85]. Patients treated with external beam radiotherapy had the longest median (IQR) follow-up with 48.0 (9.0–48.0) months; 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. Furthermore, it was not possible to draw conclusions about how to treat the patient with tracheobronchial amyloidosis 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 tracheobronchial amyloidosis compared to the normal population (0.5–1.0%) [10]. Although the exact pathogenesis of tracheobronchial amyloidosis 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]. Conversely, 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 tracheobronchial amyloidosis and Sjögren syndrome remains unclear, further research is needed to understand if and how morbus Sjögren and tracheobronchial amyloidosis 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. Additionally, the sample sizes were 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. Moreover, 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 than efficacy. 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 tracheobronchial amyloidosis.

Conclusion

Our review shows that patients with tracheobronchial amyloidosis present with nonspecific 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 randomised 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 tracheobronchial amyloidosis patients.

Provenance: Submitted article, peer reviewed.

Acknowledgements: We thank all colleagues for their collaboration, in particular Tejas Ingle (University College London Hospitals, London, UK) for reviewing the articles.

Conflict of interest: The authors have nothing to disclose.

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