Original Article

Laryngotracheobronchial Amyloidosis: Patterns of Presentation and Management

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Abstract

Objective: To evaluate the pattern of presentation and management of laryngotracheobronchial amyloidosis at a tertiary care academic center over a 27 year period.

Methods: In a retrospective review, the electronic medical record at a tertiary care academic center was queried for encounters with 3 laryngologists between 1996 and 2019 which included the ICD-9 or ICD-10 diagnosis of amyloidosis. Demographics, clinical presentation, referral diagnoses, medical history, family history, laboratory values, radiology studies, and treatment modalities of subjects were collated. Results were analyzed using standard univariate descriptive statistics.

Results: Seventeen subjects were identified with an average age at diagnosis of 58 years (range 26-76 years). The most common amyloid type on biopsy was immunoglobulin light chain (AL) subtype. The most common location of laryngeal amyloid at diagnosis was the glottis and disease was more likely to be bilateral at the time of diagnosis in this location. Supraglottic disease more often had a unilateral presentation and had a tendency to spread to additional laryngeal subsites. Nearly 25% of subjects had associated systemic disease, including multiple myeloma, auto-immune disease, and familial ATTR mutation.

Conclusions: The overall rate of associated systemic disease was low in our study cohort; however, it is higher than typically referenced in extant literature. Our cohort demonstrates that while laryngeal amyloidosis is a chronic condition, the behavior is generally indolent with a low treatment burden.

Keywords

amyloidosis, laryngotracheobronchial, larynx, trachea, systemic disease

Introduction

Amyloidosis is a heterogeneous collection of protein-folding diseases which can affect multiple organs, including the larynx and large airways. It is characterized by extracellular deposition within tissues of amorphous insoluble fibrils that are composed of aggregates of soluble precursor proteins. Definitive diagnosis relies on tissue biopsy demonstrating the characteristic finding of apple green birefringence under polarizing light microscopy with Congo red stain, then identification of the precursor protein using liquid chromatography-tandem mass spectrometry on samples of the congophilic material isolated by microdissection.[1,2] Amyloidosis can be a localized or systemic disease process and is classified into subtypes based on the dominant amyloid precursor protein. The most common types of amyloidosis include primary (AL type, precursor is usually immunoglobulin light chain from a clonal plasma cell or B-cell disorder), secondary (AA type, precursor is serum amyloid A from a systemic inflammatory disorder), hereditary (most common precursor is mutant ATTR), and wild-type ATTR/Senile. In localized amyloidosis, amyloidogenic proteins are secreted locally and disease remains confined to the affected organ. In systemic amyloidosis, abnormal amyloid protein is secreted into the bloodstream and can aggregate and deposit within multiple organ systems.[3,4]

The most commonly affected site of amyloidosis in the head and neck is the larynx.[5-9] The first case of laryngeal amyloidosis was described in 1873, yet much of the disease process and natural history of laryngeal amyloidosis remains to be elucidated.[10] Laryngeal amyloidosis is

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considered a benign process which carries an excellent prognosis.[9,11] It is classically thought of as a localized disease process and is considered to be rarely associated with systemic disease.[9,12,13] In a recent retrospective review of 103 cases of laryngeal amyloidosis in England, zero patients were found to progress to systemic amyloid.[14]

Given that laryngeal amyloidosis accounts for less than 1% of benign laryngeal tumors, much of the extant literature is based on case reports and small cohort studies.[7,15-21] This study sought to evaluate the pattern of clinical presentation, characteristics of disease, and management of laryngotracheobronchial amyloidosis at a tertiary care academic medical center over a 27 year period.

Table 1. Initial Presentation.

Sex (%)		Average age	Range
Female	53	56	40-71
Male	47	60	25-76
Race (%)		Site at diagnosis (%)	
Caucasian	94	Supraglottis	35
Asian	6	Glottis	76
Referral diagnosis (%)		Subglottis	24
Dysphonia	82	Trachea	6
Dyspnea	12	Bronchi	6
Dysphagia	6	Multisite	41
Cough	6		
Incidental	12		

Material and Methods

In a retrospective review, the electronic medical record of Michigan Medicine, a tertiary care academic medical center, was queried for encounters with 3 laryngologists between 1996 and 2019 which included the International Classification of Diseases Ninth Revision (ICD-9) or Tenth Revision (ICD-10) diagnosis of amyloidosis. The medical records of potential subjects were reviewed to verify a diagnosis of amyloidosis involving the larynx with or without tracheobronchial involvement. Demographics, clinical presentation, referral diagnoses, medical history, family history, laboratory values, radiology studies, and data on treatment modalities and treatment outcome over time were collated on the subjects identified as carrying a diagnosis of laryngeal amyloidosis. Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Michigan.[22,23] Results were analyzed using standard univariate descriptive statistics.

This study was deemed exempt from full committee review by the University of Michigan Institutional Review Board (HUM00168939).

Results

A total of 17 subjects with laryngeal amyloidosis with or without distal airway involvement were identified. A total of 53% were female and the average age at diagnosis was 58 years (range 26-76 years). The mean longitudinal follow-up was 48 months (range 2-156 months), with 5 subjects followed for greater than 5 years. Over half of the subjects were misdiagnosed or lacked a clarifying diagnosis prior to laryngology referral. The most common referring diagnosis was laryngopharyngeal reflux. The most common presenting symptoms were dysphonia (83%), dyspnea (12%), and dysphagia or cough (6%). Dysphonia was the chief complaint of most patients, regardless of location of amyloid. The most common laryngeal location of amyloid at diagnosis was the glottis (77%) followed by the supraglottis (35%) (Table 1). Glottic disease was more likely to be bilateral at diagnosis (62%), while supraglottic disease was almost exclusively unilateral (92%). Bilateral glottic disease had a unique presentation, most often extending into the anterior infraglottis (Figure 1E–H). Unilateral supraglottic disease most often involved the anterior false vocal fold, though often extended into the ventricle or paraglottic space (Figure 1D). Only 2 patients in the cohort had distal airway involvement (11.7%). All individuals underwent biopsy to confirm the diagnosis of amyloidosis and approximately 65% of the cohort underwent amyloid subtype testing. Several patients who were referred with a previous tissue diagnosis of amyloid did not undergo repeat biopsy for subtype testing. Upon biopsy subtype testing, light chain (AL) was the most commonly identified amyloid subtype (Table 2).

The most common treatment modality was suspension microlaryngoscopy with carbon dioxide (CO2) laser excision. This was often done at the time of initial biopsy following frozen section evaluation that was supportive of diagnosis of amyloidosis. The maximum number of procedures required was two. Repeat procedures were performed in 3 subjects to further reduce amyloid bulk due to persistent dysphonia that was felt amenable to surgical treatment. An informed approach to surgical treatment of this disease recognizes that complete excision is not possible in almost all cases of glottic amyloid because disease is incorporated within vital voice structures. Careful analysis of stroboscopic and intraoperative findings guides judicious reduction of disease that is causing geometrical abnormalities resulting in functional impairment, while balancing knowledge that overzealous reduction can significantly impair vocal function. Excision was therefore customized to the location and burden of amyloid while honoring applicable principles of phonomicrosurgery including: preservation of normal epithelium and the superficial lamina propria of the membranous vocal fold where possible, avoiding contralateral raw surfaces adjacent the anterior commissure, and pursuit of a normal glottic contour. Exophytic depositions, particularly depositions extending into the supraglottis or infraglottis, were often directly excised. Subepithelial

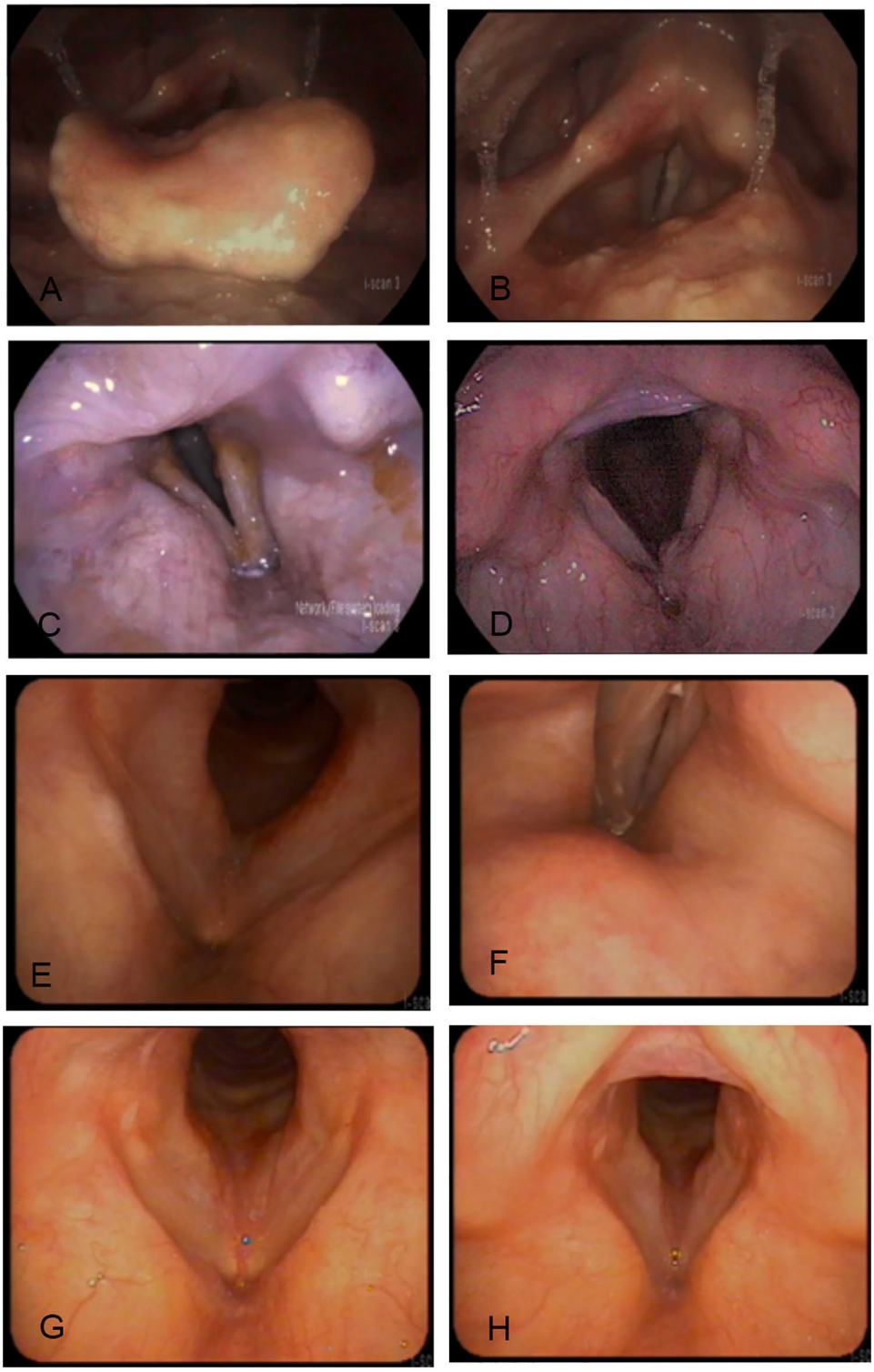

Figure 1. Representative images of laryngeal amyloidosis. (A and B) Left supraglottic disease (laryngeal surface of epiglottis and false vocal fold). (C) Diffuse laryngeal infiltration. (D) Left supraglottic disease (false vocal fold and ventricle). (E–H) Bilateral glottic disease.

Table 2. Biopsy and Testing Results.

Lab				Imaging			
	Patients tested (%)	Normal results (%)	Abnormal result (%)		Patients tested (%)	Normal results (%)	Abnormal result (%)
CBC	100	94	6	CT	59	10	90
CMP	100	94	6	PET	6	100	0
ESR	18	66	33	XR	18	100	0
ANA	12	100	0	TTE	53	78	22
ANCA	12	100	0	Other			
RF	6	6	0	BMBx	35	67	33
ENA	12	6	6	FPBx	18	100	0
Calcium	88	100	0	Amyloid biopsy			
SPEP	88	87	13	Light chain (AL)		59	
IFE	76	92	8	Untested		35	
UA	47	88	12	Auto-immune (AA)		6	
UPEP	59	90	10				
BJP	59	90	10				

Abbreviations: ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; BJP, Bence Jones protein assay; BMBx, bone marrow biopsy; Ca, calcium (serum or ionized); CBC, complete blood count; CMP, comprehensive metabolic panel; CT, computed tomography; ENA, extractable nuclear antibodies; ESR, erythrocyte sedimentation rate; FPBx, fat pad biopsy; IFE, immunofixation electrophoresis; PET, positron emission tomography; RF, rheumatoid factor; SPEP, serum protein electrophoresis; TTE, transthoracic echocardiogram; UA, urinalysis; UPEP, urine protein electrophoresis; XR, X-ray skeletal survey.

deposits, particularly deposits within the substance of the membranous vocal fold, were treated with cordotomy, subepithelial dissection, and ablation of amyloid. Concurrent steroid injection, most commonly betamethasone 6 mg/mL, was often performed at the time of excision, particularly if glottic intervention was performed.

All subjects identified underwent evaluation for systemic disease under direction of a hematologist and/or rheumatologist. Routine chemistry and hematologic laboratory testing were frequently normal in these patients (94%). Autoimmune markers were normal in all subjects with the exception of extractible nuclear antigen antibodies which were positive in 2 subjects. Computed tomography (CT) studies (59%), echocardiograms (53%), and bone marrow biopsies (35%) were more commonly obtained during clinical workup, while MRI (0%), PET (6%), and skeletal surveys (18%) were not often ordered (Table 2). CT scans of the neck were often ordered prior to laryngology referral to investigate the etiology of symptoms. For several patients, CT scans of the neck were ordered by the laryngologist due to concern for submucosal neoplasm, given the appearance of the larynx on in-office laryngoscopy prior to definitive diagnosis. Approximately 25% of subjects had associated systemic disease, including multiple myeloma, auto-immune disease, and familial ATTR mutation. Medical treatment was rarely necessary for these cases; however, when medical treatment was performed, this included external beam radiation (6%) or chemotherapy (12%) (Table 3). Illustrative images of laryngeal amyloidosis are shown in Figure 1.

Table 3. Final Diagnoses and Treatment Modalities.

Final diagnosis (%)	
Localized amyloidosis	76
Multiple myeloma	6
Auto-immune disease	6
Chronic lymphocytic leukemia	6
Transthyretin (ATTR) genetic mutation	6
Surgical treatment (%)	
Laser excision	69
Cold excision	6
Other	6
Adjunctive treatment (%)	
Steroid injection	38
Balloon dilation	6
Medical treatment (%)	
Chemotherapy	12
External beam	6

Discussion

This study provides an updated review of the patterns of presentation and management of laryngotracheobronchial amyloidosis from a tertiary care academic medical center over a 20 year period. Over half of the subjects in our cohort had a non-clarifying diagnosis at the time of referral. While the most commonly presenting symptom, dysphonia, can be attributed to many processes, examination and clinical workup by a laryngologist was essential in many subjects to identify, and treat laryngeal amyloidosis. Amyloid may

present subtly and evaluation including stroboscopy by a laryngologist is often needed to recognize these cases. Our experience as a tertiary care referral center may be biased, however our case series highlights the value of subspecialty laryngology consultation for this rare disease process.

The most common laryngeal subsite involved on presentation was the glottis, which correlates with the most common presenting symptom of dysphonia. Supraglottic disease more often had a unilateral presentation and had a tendency to spread to additional laryngeal subsites over time. Our cohort demonstrates that while laryngeal amyloidosis is a chronic condition, the behavior is generally indolent with a low treatment burden over time. The majority of patients were successfully treated with surgical excision and only one operative intervention was necessary to satisfactorily relieve symptoms. One subject did receive external beam radiation due to concurrent tracheobronchial amyloidosis. The decision to proceed with radiation was made based on desire to prevent progression of dyspnea. Treatment response to radiation not well understood with respect to laryngotracheobronchial amyloidosis given the rarity of the condition. This patient continues to have no evidence of recurrence of her laryngeal amyloidosis after completion of radiation and her dysphonia has continued to improve at each interval evaluation. Isolated laryngeal recurrences can be managed with recurrent surgery, however surgical debulking of more diffuse tracheobronchial disease, as seen with this patient, is more challenging.[24]

Laryngeal amyloid is commonly thought of as an isolated, single-organ process.[9,12,13] However, other studies have demonstrated up to an 18% incidence of additional organ involvement.[25] While the overall rate of associated systemic disease was low in our study cohort, it is higher than typically referenced in the literature.[9,12-14,25]

Cases of systemic disease in our cohort included autoimmune disease, multiple myeloma, and familial ATTR mutation. In all cases, systemic disease was identified in the subsequent work up following diagnosis of laryngeal amyloidosis. Further evaluation and management of systemic amyloidosis is done in collaboration with various specialties, including hematology/oncology, cardiology, rheumatology, neurology, gastroenterology and nephrology. The correct referral is chosen based on a review of the patient's symptoms, physical exam, and amyloid typing. Labs screening organ function (complete blood count with differential, comprehensive metabolic panel, troponin T, BNP or NT-proBNP) and screening for plasma cell disorders (serum protein electrophoresis and immunofixation, serum free light chain assay) are also helpful on initial assessment following diagnosis of amyloidosis as amyloid typing can take several weeks. Patients with signs of systemic amyloid should initially be referred based on symptoms, exam, and labs. For example, patients with abnormalities in the labs for plasma cell disorders should be referred to hematology/oncology; patients with dyspnea, swelling, high troponin or BNP should be referred to cardiology; edema and/or low albumin could indicate renal involvement (nephrotic syndrome), or gastroenterologic involvement (malabsorption). Following completion of amyloid typing, AL amyloid should be referred to a hematologist/oncologist, AA amyloid to a rheumatologist, and all others to the appropriate specialty for their apparent organ involvement. When available, referral to an amyloidosis center is beneficial and, given that AL amyloid is the most common type, involvement of a hematologist/oncologist is reasonable when beginning assessment.

While many cases did not require additional systemic treatment, subjects with plasma cell malignancy did all undergo systemic chemotherapy. In cases requiring chemotherapy for systemic disease, the patients' laryngeal symptoms remained stable throughout treatment and did not improve beyond initial surgical debulking. From our limited patient experiences, surgical debulking of amyloid deposits at the glottic level provides improvement in voice which is not further augmented by systemic therapy. The prevalence of systemic disease identified in our study highlights the need for collaboration with hematology and other subspecialties to screen for systemic amyloidosis

This study is limited by the anticipated challenges of a retrospective review. While the sample size is small, laryngeal amyloidosis is an uncommon disease and much of the available literature consists of single case reports. For some patients, we have short follow up time which limits our ability to conclude that there is low treatment burden over time. Nevertheless, in many cases the initial surgical treatment is both diagnostic and therapeutic. Patients may be counseled that we balance benefits of surgical reduction with the negative effects and scarring of overly aggressive surgery. Surgeon judgment intraoperatively determines how much disease to remove at the time of surgery. In some cases, the surgeon ultimately decides after definitive diagnosis and healing post initial surgery that more reduction is indicated. This clinical decision requires balancing benefit and harm for the patient. In our study, only 2 individuals required more than 1 procedure to address their disease. Our study adds data from over 20 years of experience at a tertiary academic center, contributing to the existing literature in an attempt to further elucidate this rare disease process.

Conclusion

This study identifies the patterns of presentation of laryngotracheobronchial amyloidosis and describes the most commonly performed systemic workup for patients with confirmed disease. Notably, we found that the rate of associated systemic disease was higher than that typically referenced. It is our hope that these insights from patterns of disease activity can be applied to patient counseling for evaluation and treatment of laryngotracheobronchial amyloidosis.

Author's Note

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Author Contributions

Dr. Morrison had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of data analysis. *Study concept and design*: Kupfer, Hogikyan, Morrison. *Acquisition of data/research methods*: Dermody, Morrison. *Analysis and interpretation of data*: Dermody, Campagnaro, Kupfer, Hogikyan, Morrison. *Drafting of the manuscript*: Dermody. *Critical revision of the manuscript*: Campagnaro, Kupfer, Hogikyan, Morrison. All named authors reviewed and revised the manuscript and approved the manuscript as submitted.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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