



# Isolated Amyloidosis of the Larynx: A Case Report of an Atypical Presentation of Amyloidosis

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## Abstract

Isolated laryngeal amyloidosis is a rare presentation of amyloid deposition. In this case report, we present a 50-year-old male with 6 months of progressive hoarseness found to have a supraglottic mass. Excision of the mass was achieved through Potassium Titanyl Phosphate (KTP) laser assisted ablation. Final pathology by Congo red stain and characterization by mass spectrometry confirmed AL amyloidosis. This article provides a case presentation including work-up of the patient followed by a literature review of laryngeal amyloidosis.

## Introduction

Amyloidosis is a disease process occurring from the deposition of a non-soluble fibrillar protein, amyloid, in the extracellular spaces of organs leading to progressive organ dysfunction [1-3]. Common locations of amyloid deposition include the kidneys, heart, liver, nerves, and spleen [4]. Furthermore, amyloidosis can be systemic or isolated to a specific organ and is further clinically classified based on the specific type of precursor amyloid protein [3,4]. Overall, it is a rare process with an estimated 5-10 cases per million per year [2]. Estimates show that up to 20% of amyloidosis cases involve the head and neck, however, localized laryngeal amyloidosis is a rare finding and compromises only 0.2% to 1.2% of all benign laryngeal growths [2,5,6]. Amyloidosis of the larynx was first described in 1875 by Burrow and Neumann [7,8]. It commonly presents with isolated hoarseness in adults in the age range of 40 to 60 [2]. This case report provides a description, our evaluation and treatment approach, and review of isolated laryngeal amyloidosis.

## Case Presentation

The patient is a 50-year-old male referred for a 6-month history of progressive hoarseness. At presentation, he denied any associated symptoms including difficulty breathing or dysphagia. Biopsy from the laryngeal mass, obtained from an outside hospital, was consistent with laryngeal amyloid based on positive Congo red staining (Figure 1). The patient had no known autoimmune diseases, chronic inflammatory conditions, or known malignancy. Voice was severely hoarse and strained. Flexible laryngoscopy revealed a firm submucosal right supraglottic mass extending to the glottic level with reduced mucosal wave on stroboscopy (Figure 2 and 3).

Given this concern for systemic amyloid, the patient underwent a comprehensive medical work-up. Bone marrow biopsy and aspirate did not show any light-chain restricted plasma cell population with negative Congo red staining. Serum Protein Electrophoresis (SPEP), Urine Protein Electrophoresis (UPEP) did not show any monoclonal protein, and the serum kappa/lambda ratio was normal. Magnetic Resonance Imaging (MRI) of the heart showed no cardiac amyloid present, and liver size and function were normal suggesting lack of systemic involvement by AL amyloidosis. Investigations into underlying chronic inflammatory and/or rheumatologic conditions also proved unremarkable.

To treat the patient's dysphonia and to obtain further biopsies to allow for amyloid sub typing, the patient was brought to the operating room. He underwent micro-direct laryngoscopy with laser ablation using the subtotal Potassium Titanyl Phosphate (KTP) laser. The amyloid was found to push the vocal cord medially. Only a very small area of amyloid around the recurrent laryngeal nerve entry point into the larynx was left untreated to avoid nerve damage and vocal cord paralysis.

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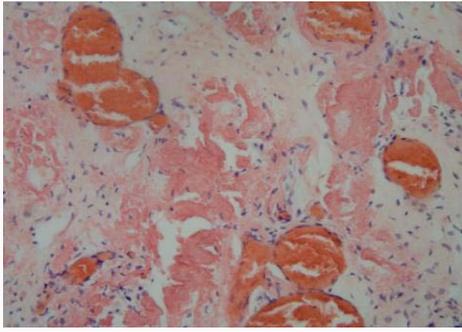
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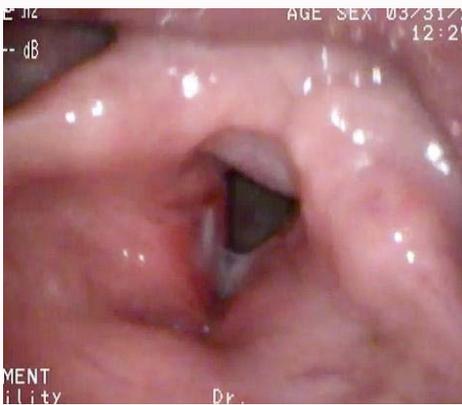
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**Figure 1:** Congo red staining binding to amyloid protein of the right laryngeal lesion specimen. Deposits seen at the vessel walls (20x magnification).



**Figure 2:** Flexible laryngoscopy showing fullness of the right supraglottis representing the submucosal amyloid deposit.



**Figure 3:** Flexible laryngoscopy showing a right supraglottic mass causing effacement of the ventricle and pushing the vocal cord medially.

amyloidosis, due to AA, is a process secondary to an underlying chronic inflammatory process or hereditary predisposition for precipitation of certain type of proteins [10]. AA is a hepatically derived acute phase reactant presenting in patients with chronic diseases including but not limited to Rheumatoid Arthritis, Inflammatory Bowel Disease, and Familial Mediterranean Fever [3,7]. Lastly, AB amyloid is the protein form seen in cerebrovascular and intracerebral plaques of Alzheimer's disease [10].

Amyloid can deposit in virtually any tissue in the body, and up to 20% of amyloidosis can involve the head and neck region of which the larynx is the most common site [2]. Laryngeal amyloidosis is rare and comprises 0.2% to 1.2% of all benign laryngeal growths [2,5,6]. Primary lesions of amyloid in the larynx were first reported in 1875 by Burrow and Neumann and since then there have been more than 300 cases reported in literature [7,8]. Laryngeal amyloidosis is more prevalent in males with a 3:1 ratio and primarily affects persons ages 40-60 with peak incidence in the 5<sup>th</sup> decade [2]. Localized amyloidosis of the larynx is characterized by monoclonal deposits of AL and rarely associated with a systemic presentation of amyloidosis [2,7]. The most common presenting symptom is hoarseness while progressive dyspnea, dysphagia, cough, hemoptysis, and stridor can also be prominent [2,8]. Within the larynx, amyloid deposits may be present in one solitary location or found in multiple sites [7]. Deposits can occur in any region within the larynx, however the most common sites include the ventricles, false vocal cords, true vocal cords, and the supraglottic larynx [5,7]. While a benign process, local laryngeal amyloidosis is often progressive with the most concerning complication being airway compromise. Intervention is necessitated to mitigate progression of local amyloidosis.

A reasonable differential diagnosis for a patient presenting with progressive hoarseness includes benign vocal cord nodules, malignancy, HPV laryngeal papillomatosis, laryngeal amyloidosis, and granulomatous conditions [5,8]. However, amyloidosis is typically a submucosal process, thus a refined differential for suspected laryngeal amyloidosis should also include malignancy, plasmocytoma, and mixed tissue tumors. Initial investigation should include laryngoscopy during which fullness on ventricular bands is a typical finding for laryngeal amyloidosis [8]. To confirm a diagnosis of suspected laryngeal amyloidosis, a tissue biopsy must be obtained and be positive on Congo red stain [1]. Amyloid fibrils exhibit affinity for Congo red stain with either green, yellow, or orange birefringence under polarized light [1]. Biopsy results providing amyloid subtype

Within 3 months, the patient's voice had normalized almost to baseline with no other laryngeal complaints. Further analysis by Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) of the repeat biopsies revealed the nature of amyloid deposition as Lambda light chain.

## Discussion

Amyloidosis is a spectrum of clinical manifestations that can occur from the deposition of a non-soluble fibrillar protein, amyloid, in the extracellular spaces of organs [1-3]. It is a rare process with an estimated 5-10 cases per million per year [2]. The onset of amyloidosis is often silent and insidious, but overtime continued progression of the deposition of amyloid may lead to organ dysfunction, be increasingly difficult to treat, and possibly lead to death [1].

Amyloidosis is categorized as AL and non-AL based on the nature of precipitated protein, as well as localized or systemic, based on distribution pattern of involved tissue. There are currently 36 types of human amyloid protein that have been identified based on the main fibril protein [1]. The three most common forms of amyloid are AL (light chain), AA (amyloid associated), and AB. AL amyloidosis can be systemic or localized and preferentially impacts the cardiovascular, renal, and hepatic systems [3]. Systemic AL amyloidosis is attributed to plasma cells dyscrasia in the bone marrow leading to the release of immunoglobulin light (kappa, lambda) or heavy chain protein that is able to spread systemically and deposit throughout the body [2,9]. On biopsy of involved tissue in the localized form of AL amyloidosis, rare clonal plasma cells can often be detected providing support to the plasma cell etiology of localized AL amyloidosis [3]. Non-AL

should be used to guide further workup regarding evaluation of systemic vs. localized processes. Imaging, if available, can be useful for further clinical assessment of a suspected laryngeal amyloid mass. Computed Tomography (CT) is not recommended as an amyloid mass will appear as a non-specific, submucosal, homogenous mass with minimal contrast enhancement [8]. MRI is more clinically impactful as an amyloid MR signal is similar to that of skeletal muscle serving as a reliable reference frame; malignant lesions have signals distinct from muscle on MRI [10].

Despite localized laryngeal amyloidosis rarely being associated with a systemic process, it is important to rule out evidence of systemic amyloidosis given the silent nature of progression and potential for end organ dysfunction. To rule out underlying hematologic malignancy, serum and urine protein electrophoresis is recommended [3,7]. Another method to rule out systemic amyloidosis is fine needle aspiration of abdominal adipose for its ease and efficacy [8].

In cases of systemic amyloidosis, therapy is based on the "precursor-product" approach which focuses on eliminating the precursors to the amyloid protein as the main avenue of mitigating growth of amyloid deposits [3]. Systemic AA amyloidosis is treated by decreasing levels of Serum Amyloid A (SAA) protein through treatment of the underlying chronic inflammatory process (i.e. controlling Rheumatoid Arthritis via methotrexate) [3]. The strategy employed in treating systemic AL amyloidosis is to eradicate plasma cells dyscrasia through various chemotherapy regimens which are still being studied for overall efficacy. A regimen that has been shown to have benefit is high-dose Melphalan, used to target plasma cells in Multiple Myeloma, followed by autologous hematopoietic stem cell transplantation [3]. Research endeavors are underway to identify pharmacological interventions that may stabilize the precursor proteins, prevent deposition, or promote removal [3,4]. In addition, management of systemic amyloidosis involves subduing the effects of organ dysfunction of involved systems. This may include preventing symptoms of right-heart failure, minimizing effects of nephrotic syndrome through salt restrictions and diuretics, or controlling neuropathic pain caused by nerve involvement [4]. Prognosis for untreated systemic amyloidosis is multifactorial and dismal with median survival of <1 year for AL type and 2-4 years for AA type, but adequate and early treatment can drastically improve survival [3,4]. Management of systemic amyloidosis has distinct challenges compared to localized amyloidosis and does not readily cross over to treatment for localized laryngeal amyloidosis.

The ultimate goals of treatment of localized laryngeal amyloidosis are to prevent inevitable progression, maintain airway patency, and improve voice. Due to the low overall incidence of laryngeal amyloidosis, preferred treatment stratification based on lesion size is not well reported. In a report of 16 cases by Wierzbicka et al. [11] sizes of lesions ranged from 3 mm to 4 cm. Rather treatments is aimed at maximizing preservation of function through a surgical approach. Non-surgical interventions including local corticosteroid injections, local radiotherapy, systemic steroids, and chemotherapy have been found to be ineffective [8]. Close observation is an acceptable option for patients who are asymptomatic given the possibility that progression may be slow or stalled over time [2,8,10]. The definitive treatment for the majority of localized laryngeal lesions is endoscopic surgical excision either by cold knife, laser, or a combination of the two [8]. An extensive lesion that has the imminent possibility of causing airway obstruction may require a more aggressive external

approach [10]. Recurrence of amyloid is not unusual and an overly aggressive approach to accomplish complete amyloid removal can lead to loss of laryngeal function and therefore may not be the best option. Risks and benefits for mass excision versus debulking need to be weighed appropriately. Debulking should be considered as the primary surgical approach if disease is extensive and full resection would destroy normal architecture of vocal cords resulting in long-lasting impairment of laryngeal function. Debulking procedures, although not definitive, can be followed up by repeat procedures involving further resection or laser ablation in order to maintain voice and airway [11]. Historically, laser treatment has been through a Carbon Dioxide (CO<sub>2</sub>) laser and is preferred over cold knife because of increased accuracy, decreased blood loss, faster healing, and decreased scarring [8]. Intuitively, the angiolytic KTP laser may not be the instrument of choice, as amyloid is an acellular protein deposit without blood vessels, however, if the appropriate settings are chosen the KTP laser is very effective in ablating amyloid. Further, the ablative characteristics of the KTP laser allow the surgeon to identify the interface between amyloid and normal tissue to assist in maximizing preservation of normal tissue along critical areas, which is extremely important around the superficial lamina propria of vocal cord. In the author's experience, KTP laser is an effective tool to manage laryngeal amyloid safely allowing for repeated laryngeal amyloid excision without unnecessarily jeopardizing vocal cord tissue and voice. In 2013, Deviprasad et al. [8] published results supporting the use of KTP laser excision as an equally effective and efficient alternative to CO<sub>2</sub> laser excision for the treatment of laryngeal amyloidosis. Given the low incidence of laryngeal amyloidosis, there is no definitive data in the literature on optimal excision approaches; however, surgical removal is necessary due to the progressive nature of amyloidosis.

Overall, localized amyloidosis has a better prognosis compared to systemic amyloidosis. However, local recurrence is a concern that must be monitored. Localized recurrence is common in laryngeal AL amyloidosis after first-line therapy and occurred in all patients treated surgically (18/18) of which 2/3 required revision surgery in a cohort studied by Hazenberg et al. [9]. Recurrence tends to occur within the first 5 years after treatment, thus patients should be followed up every 3-6 months for the first 5 years and yearly thereafter [12]. In Hazenberg's cohort, disease progression stopped 7 years after surgery in all but one patient; the proposed theory is that recurrence slows over time due to exhaustion of underlying clonal plasma cells [9]. Systemic recurrence is uncommon and has not been reported upon [7,9].

## Conclusion

Localized laryngeal AL amyloidosis is a rare etiology of persistent hoarseness. Given the progressive nature of amyloidosis, it is important to keep laryngeal amyloidosis in the differential for a patient presenting with hoarseness. With small cohorts available to guide treatment and long-term evaluation, diagnosis through positive biopsy and thorough evaluation of systemic disease is essential followed by excision of the lesion. Historically, CO<sub>2</sub> laser excision has been preferred for management, but recent case reports and our experience show that KTP laser is an effective alternative modality in managing laryngeal amyloid. Patients should be followed for at least 5 years given the high reported rates of localized recurrence.

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