Main Article

# Primary Laryngeal Amyloidosis and $CO_2$ Laser as the Treatment Modality

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**ABSTRACT**

***Introduction***

*Amyloidosis is brought about by intracellular and/or extracellular accumulation of insoluble abnormal amyloid fibrils that alters the normal function of the tissues. Localized laryngeal amyloidosis is a rare disease which lacks long-term follow-up studies. It is prone to recurrence; hence meticulous excision is required. We are doing this study to analyse clinical features of primary laryngeal amyloidosis, the subsites commonly found in, and the effectiveness of $CO_2$ laser as treatment modality.*

***Materials and Methods***

*It is a retrospective study of 13 patients diagnosed as Primary Laryngeal Amyloidosis in between 2005 to 2018, where clinical features, histologic and immuno-histochemical patterns of the patients were evaluated. Systemic amyloidosis was ruled out by the non-appearance of Bence-Jones proteins in urine and serum electrophoresis examination. Systemic workups were pursued during the follow-up. The patients were followed up 3 monthly for the first year, then 6 monthly after that, for 3 years. The last patient who underwent the surgery was in the 2018 and had just finished his 2nd follow up, while the rest have been followed up for 3 years.*

***Results***

*Hoarseness was the most common complaint in all the patients. The subsites most common for amyloid deposition were seen in the true vocal cords followed by supraglottis, anterior commissure, ventricle and the subglottis. Microscopically, the amyloid was deposited within the submucosa surrounded by lymphoplamocytic infiltration. All cases were treated with microlaryngoscopic $CO_2$ Laser excision. With the exception of one patient, the rest had no recurrence.*

***Conclusion***

*Primary Laryngeal Amyloidosis is an uncommon benign disease that has a predisposition for recurrence. With use of $CO_2$ laser as the primary treatment modality, the percentage of recurrence has drastically reduced. Systemic involvement should be ruled out. A frequent follow-up of the patients is desirable for early detection of recurrences. Laser is a novel treatment of laryngeal amyloidosis.*

***Keywords***

*Laryngeal Diseases; Hoarseness; Amyloidosis; Laser, Carbon dioxide*

Amyloidosis is the abnormal extracellular deposition of the fibrillar aggregates of monoclonal immunoglobulin light chains (amyloid) in vital organs.

Clinically amyloidosis is divided into primary and secondary. It is said to be primary when there is no evidence of preceding or coexisting disease. Primary amyloidosis is an idiopathic condition (56%), while the secondary one is related to chronic inflammatory or infectious process (5%).[1] Laryngeal amyloidosis has a recurrent/persistent process and its recurrence is the norm rather than the exception.[2]

Laryngeal amyloidosis is an uncommon benign disease ranging between 0.2 and 1.2% of all benign lesions of larynx. Reports of laryngeal amyloidosis have been recorded as early as 1875 by Burrow and Neuman.[2,3]

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In the head and neck region, larynx is a common site for amyloid deposition.[2] Within the larynx, the vocal cords, followed by the aryepiglottic folds, and then subglottis, are commonly affected sites.

The condition is chronic and slowly progressive, mostly primary but occasionally correlated with a generalised systemic form.[3] Presenting symptoms include progressive hoarseness, sometimes associated with cough. Stridor and dyspnoea could develop in patients with extensive involvement.[1,2]

Histologically, amyloid can be established with Congo Red staining which shows classic bright green birefringence when seen under polarizing light microscopy as well as immunohistochemical stains.[1]

Treatment aims to provide consistent or improvise the voice quality, to support laryngeal airway, and prevent recurrences. Treatment can be medical or surgical. Medically, therapy with the proteasome inhibitor bortezomib along with corticosteroids has been proved effective.[4] Surgically microlaryngoscopy with excision in the treatment of choice. As the recurrence is common in laryngeal amyloidosis it has to be followed up regularly for longer periods.

The $CO_2$ laser is the most reliable of laryngologic lasers.[4,5] A $CO_2$ laser runs on a wavelength of 10.6 μm and is well absorbed by tissues containing water and can therefore be used to dissect, vaporise and ablate tissue.[6]

This study aimed to analyse the clinical features of primary laryngeal amyloidosis diagnosed in a tertiary care hospital, the subsites commonly involved and the effectiveness of $CO_2$ laser as treatment modality.

## Materials and Methods

It is a retrospective study of 13 patients diagnosed with Primary Laryngeal Amyloidosis who were admitted in the Dept. of ENT and Head & Neck surgery of Deenanath Mangeshkar Hospital, Pune, in between the years, from 2005 to 2018.

Most patients had presented with hoarseness and some with associated dyspnea.

Of the 13 patients, 9 were male and 4 were females. The age of presentation was between 35 and 70 years of age with the mean age being 40 years. Diagnostic flexible laryngoscopy was done for all cases. Lesions are presented in an array of variations, from papillomatous to polypoid, lobulated, or granulomatous. The most common sites of involvement were the true vocal cords and supraglottis.

Systemic workups were done before the surgery for all the cases like Complete blood counts, Erythrocyte sedimentation rates, serology, Liver function test, Renal function test, etc. as protocol.

A $CO_2$ laser was used in all cases with robotic laser microsurgery system (AcuPulse DUO, Lumenis, Yokneam, Israel) under general anesthesia using jet ventilation to perform the procedures. Prior to the surgery, a laser safety was checked, eg., laser fibre and settings, smoke evacuation system, closed doors, blinded windows, microlaryngoscopy instruments, damp gauges, etc. Surgeons, OT staff and patients are provided with laser safety glasses.

The diagnosis was confirmed by doing histopathology and immunohistochemical tests of specimens collected during microlaryngoscopic excision with $CO_2$ laser. Systemic amyloidosis was ruled out in all cases, by doing urine and serum protein electrophoresis for Bence Jones proteins post operatively.

All cases were followed up using flexible laryngoscopy, on 3 monthly bases for the first year, then 6 monthly after that for three years. The last patient who underwent the surgery in 2018 has just finished his 2nd follow up. Details of all the patients were recorded.

## Results

Results (Table I) of the 13 patients 9 were men and 4 were women with the male: female ratio of 2.25:1.

Ages ranged from 35 to 70 years, mean age being 40 years.

Progressive hoarseness/ husky voice was the chief complaint of most the patients (84.6%) while 23% of the patients also complained of dysphagia. No patients had airway obstruction or acute respiratory symptoms.

The most common gross appearance of amyloidosis was polypoidal 46.2% (6). The sizes range from 1.0 to 3.0 cm. The most common sites of the lesion were in

**Table I: Overview of 13 patients with Primary Laryngeal Amyloidosis**

| SL. NO. | AGE IN YEARS | SEX | SITE OF INVOLVEMENT | APPEARANCE |
|---|---|---|---|---|
| 1 | 41 | M | Supraglottis, True vocal cords. | Polypoid |
| 2 | 44 | F | True vocal cords, Supraglottis. | Lobulated |
| 3 | 69 | M | Right false vocal cord, Right ventricle. | Polypoid |
| 4 | 35 | M | Supraglottis, Trachea. | Granulomatous |
| 5 | 40 | F | True vocal cords. | Polypoid |
| 6 | 50 | M | False vocal cords, Aryeppiglotic folds. | Lobulated |
| 7 | 38 | F | Supraglottis, True vocal cords. | Granulomatous |
| 8 | 42 | M | True vocal cords, Ventricles. | Lobulated |
| 9 | 39 | M | Supraglottis, Trachea. | Lobulated |
| 10 | 56 | F | True vocal cords, Subglottis. | Granulomatous |
| 11 | 44 | M | True vocal cords. | Polypoid |
| 12 | 36 | M | True vocal cords. | Polypoid |
| 13 | 41 | M | True vocal cords, Supraglottis | Polypoid |

true vocal cords 84.6% (11), supraglottis 38.5% (5), the ventricles and subglottic 15.4% (2) and aryepglottic folds 7.7% (1). (Figs. 1,2,3) In one case (7.7%) it was extending into the trachea.

In all cases, microlaryngoscopy with CO2 laser excision of lesions was done and the specimen was collected for histopathological examination. Pathologic findings: Grossly, the specimens consisted of numerous friable, grey to brown soft tissue fragments. Histologically they gave the appearance of scattered submucosal round accumulation of acellular, eosinophillic, amorphous matter on hematoxylin-eosin stained slides, presenting with scanty chronic inflammatory infiltrates, consisting principally of mature plasma cells and lymphocytes, at the periphery of the amyloid deposits. (Figs. 4,5,6) Under polarized light, staining with Congo red showed apple-green birefringent material.

All patients were followed up at the regular interval

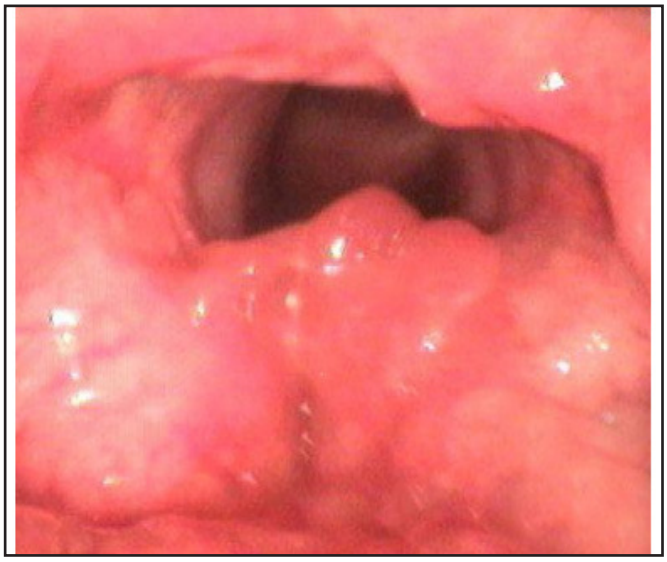

**Fig. 1. Irregular lobulated yellowish submucosal, firm and non-ulcerated lesions in the anterior commissure (Amyloidosis)**

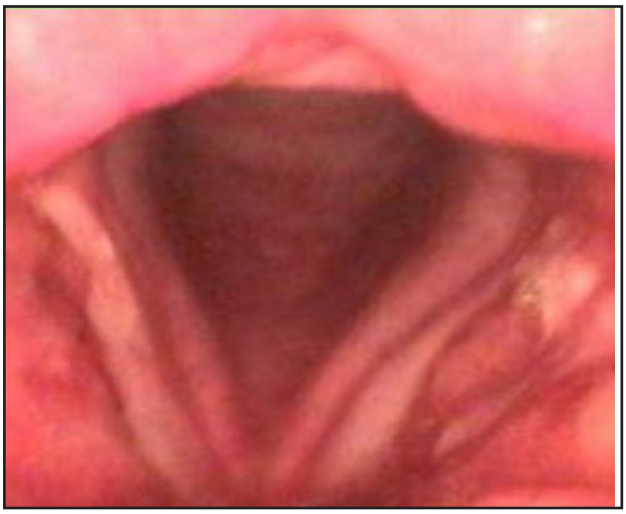

**Fig.2. Lesions in the B/L false cords (Amyloidosis)**

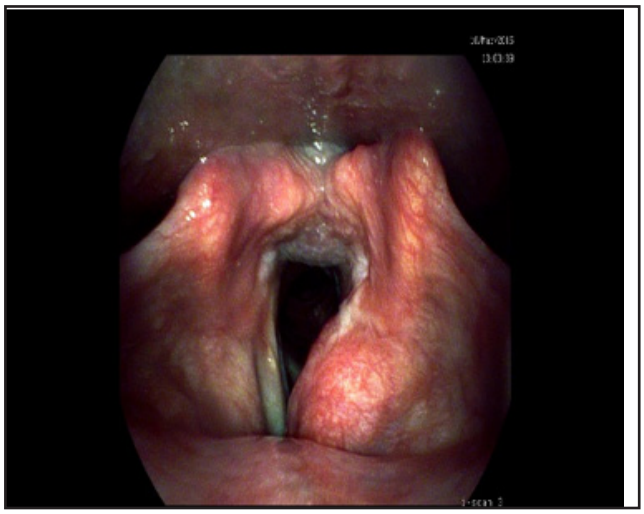

**Fig. 3. Lesion in the left supraglottis region, affecting the false cord (Amyloidosis)**

and only one patient (7.7%) has had recurrence and a repeat laser surgery was done for him.

## Discussion

Amyloidosis is a very uncommon disorder caused by extracellular deposition of insoluble, amorphous, acellular, eosinophilic matter with occasional histiocytes and giant cells which are peripherally present around the amyloid or are enclosed within it, altering the function of the tissues as they become stiff and plastic, having a hyaline-like appearance.[7] Amyloid deposits can be attained from any one of a diverse, unrelated group of plasma precursor proteins. These proteins, through an unknown mechanism, misfold and auto-aggregate to become fibrillar structure in the extracellular space.[7]

Amyloidosis can be primary or secondary.[1,7] Primary type of amyloidosis is usually idiopathic (56 %), whereas the secondary form is often associated with an infectious process or chronic inflammatory (5%).[1]

Amyloidosis can be local or systemic. The larynx is hardly ever the first location of systemic amyloidosis; but due to its potentially ominous prognosis, the latter should be taken into consideration.[2,3,4,7] Apart from one case in two sisters, familial primary localized

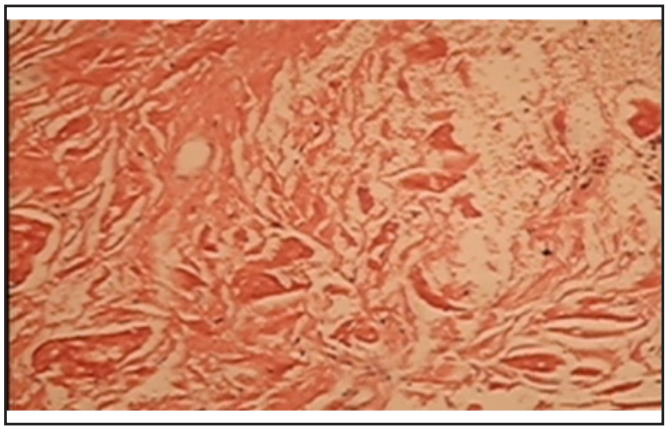

**Fig. 4. Amyloidosis: diffuse submucosal globular amorphous, acellular, eosinophilic material (H&E, 40X)**

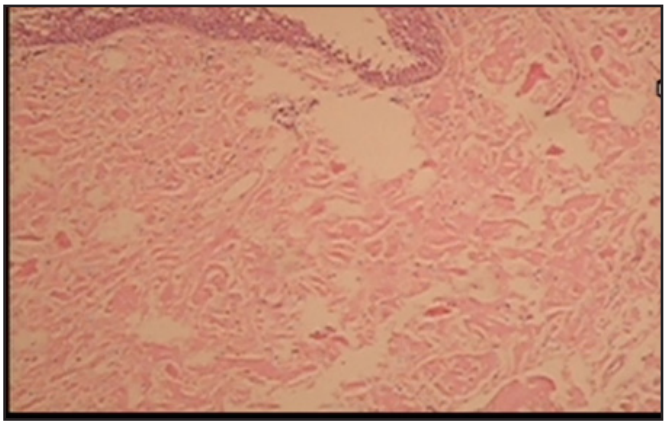

**Fig. 5. Diffuse submucosal deposition of eosinophilic material in amyloidosis (H&E, 4X)**

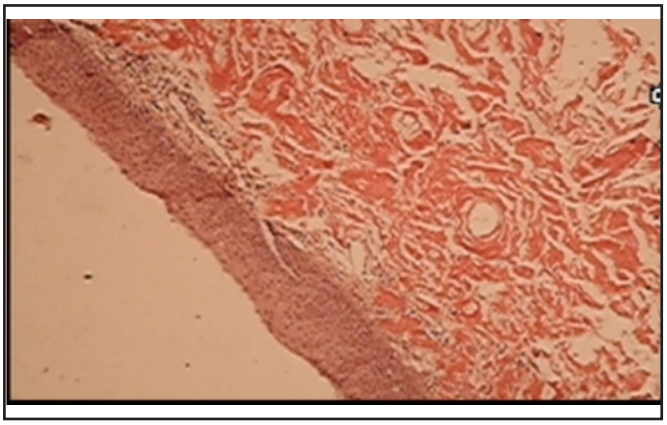

**Fig. 6. Diffuse submucosal globular deposition of eosinophillic acellular materials in amyloidosis (H&E, 10X)**

amyloidosis of the larynx has not yet been reported elsewhere.[8]

In the head and neck region, larynx is the most commonly found site of amyloidosis[2,3,7] and accounts for 0.2 - 1.5% of benign laryngeal tumours.[2,3,7] The ventricles and the vocal cords are the most prevalent sites for localized amyloidosis in the airway.[4] It is a rare benign disease with chronic slow progression and presents with hoarseness, cough, dyspnoea, and less commonly stridor and sleep apnoea.[2]

On laryngoscopic examination, appearance varies from diffuse[2,4,7] to discrete, yellowish submucosal thickening, non-ulcerated granulomatous, polypoid or nodular.[4,7] In our study, we observed that the most common type was polypoid (46.2%), and the predominant sub sites were the true vocal folds (84.6%) and supraglottis (38.5%).

True vocal cord was found to be the most common site according to Finn and Farmer[3] while ventricles and vestibular folds were recorded as the commonest in the one done by Fernandes et al.[5] Michael described false cord as the most prevalent,[9] while Mittrani and Biller cite the ventricle and false cords as the most common sites.[10]

Amyloidosis is often seen in more than one subsite, as well as supraglottic amyloid deposits may form an anterior glottic growth, obscuring the vocal cords, hence advisable for full endoscopic assessment.[3,9] Amyloidosis of vocal cords interferes with vibratory movements leading to hoarseness.

The disease is mostly seen in adults, but a few have been reported in paediatric patients as well.[11] In adults, affection seen commonly in the 50-70 years' age group, with male to female predominance of 3:1.2,[4] In our study, age ranged from 35 to 70 years, mostly seen in the fourth decade, and sex predilection towards male by 2.25:1 ratio.

Accurate diagnosis is often delayed up to a year or more. Diagnosis begins with clinical suspicion and confirmed by histologic examination of tissue. The 'gold standard' for diagnosis is tissue biopsy demonstrating characteristic amorphous eosinophilic appearance by hematoxylin and eosin changes and apple-green birefringence with Congo red.[2,4,7] They have a fibrillar appearance on electron micrography. They are visible as Beta- pleated sheets by X-ray diffraction pattern.

MRI scan is the radiological investigation of choice since amyloid gives an intermediate T1 signal and low T2 signal.[12,13] The appearance of amyloid on CT imaging is non-specific and similar to any inflammatory tissue.[15]

To exclude systemic amyloidosis, urine, and serum protein electrophoresis is done but other invasive procedures like aspiration of abdominal fat, bone marrow, and rectal biopsy have been reported.[7] Mittrani et al. reported that corticosteroids and radiotherapy are ineffective in treating laryngeal amyloidosis.[10]

Surgical intervention using microlaryngoscopic methods is the most preferred method. Repeated surgeries are often necessary as recurrences are common, thus treatment has to be directed at complete removal of amyloid with minimum trauma to neighbouring tissues, especially near the vocal cords as scarring is a dreadful sequel.

In recent years, the use of carbon dioxide laser in treating both localised and widespread laryngeal amyloidosis has been recommended.[3,7] $CO_2$ laser excision is better as compared to the cold knife as it has the advantage of clear operation field visualization[15] giving accuracy allowing minimal tissue manipulation and a longer working distance[16] reduced intraoperative bleeding,[15] reduced inflammatory reaction and neighbouring tissue damage[15] with faster healing and less scarring as it induces inflammatory changes in

the mucosa and submucosa.[16] Endoscopic $CO_2$ laser excision has been to show good control of the disease and marked reduction in postoperative swelling.[5,7,17,18]

In our study, out of 13 patients, only one patient had recurrence. Long-term follow-up is important because reported recurrence rates are as high as 50%.[19] O'Halloran and Lusk recently reported a relatively rapid recurrence of laryngeal amyloidosis after laryngofissure.[20] Hence regular endoscopic examinations are strongly recommended.[7,21]

## Conclusion

Primary laryngeal amyloidosis is a rare and benign clinical disorder due to deposition of abnormal insoluble amyloid fibrils extracellularly in the various subsites of the larynx that alter the voice quality, breathing, and sometimes swallowing. The best method of diagnosing is by conducting a tissue biopsy demonstrating typical amorphous eosinophillic appearance in hematoxylin and eosin changes and green apple birefringence with Congo red under polarized light.

In our study, there is a male predominance by 2.25:1 to females and age predilection of 35-70 years of age, with mean age of 40 years.

Management should be least aggressive as can be. Our study showed microlaryngoscopic $CO_2$ laser treatment had given excellent results as it has the advantage of precise application with fewer postoperative complications. A regular follow-up should be done in all the cases for a longer period as the disease tends to recur. Localized amyloidosis has an excellent prognosis compared to the systemic type.

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