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CASE REPORT

Primary Laryngeal Amyloidosis: A Discussion of 10 Cases with a Review of the Literature

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ABSTRACT

Primary laryngeal amyloidosis is rare, accounting for 0.2 to 1.2 % of its benign tumors. However, it is the most common site in the upper aerodigestive tract for isolated primary amyloidosis. The most common symptom is hoarseness of voice, and depending on the extent of involvement, it may present with varying degrees of breathlessness. Diagnosis requires accurate histopathology using special staining by Congo red stain which demonstrates the typical apple-green birefringence when seen under polarized light. Diagnosis is often missed in the absence of special stains. Treatment requires as complete an excision as possible preferably with a laser. Periodic follow-ups are needed for the detection of recurrences.

We present a series of 10 patients with primary laryngeal amyloidosis attending the voice clinic from March 2011 to February 2018, with a discussion of their management and a review of literature.

Keywords: Benign laryngeal tumor, Larngeal amyloidosis, Primary amyloidosis

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INTRODUCTION

Amyloidosis is a group of heterogeneous disorders characterized by extracellular deposition of amyloid protein in various organs of the body. The word amyloidosis is derived from the Greek word amylon, meaning starch and ideos , meaning resemblance.[1] In 1938 Mathias Schleiden des a German botanist used the term for the first time to describe the amylaceous deposit of plants[1]. The term was coined by Virchow because of the starch like reaction of the protein on treatment with iodine and sulfuric acid.[1,2] Von Rokitansky first discovered amyloid deposits in the liver and spleen in 1842.[3,4] Amyloid proteins are deposits of an amorphous, eosinophilic, acellular, homogeneous material in the subepithelial space (Fig. 1), which shows apple green birefringence under the polarized light when stained with Congo red stain (Fig 2). Electron microscopy has shown the fibrillar nature of amylaceous deposits.[5]

Amyloidosis can be localized or systemic. Primary amyloidosis of the larynx is rare accounting to 0.2 to 1.2% of the benign tumors.[1,4] However, it is the most typical site in the upper aerodigestive tract to be affected by primary amyloidosis. The most common symptom is hoarseness of voice. The symptoms depend on the extent of involvement. Extensive deposition of the proteins causing airway narrowing and eventual stridor has been reported.[6] The commonest presentation mimics laryngeal neoplasm or polyps, and hence a high degree of suspicion is necessary to diagnose this condition.[7] As the disease is present submucosally, a deep biopsy is essential for a representative biopsy.[8]

We present 10 cases of isolated laryngeal amyloidosis that presented to the voice clinic from March 2011 to February 2018 with a discussion of their management.

CASE REPORTS

Case 1

A 74-year-old gentleman presented to the voice clinic with gradually progressing hoarseness of voice since the past one year. He also complained of dyspnoea on exertion

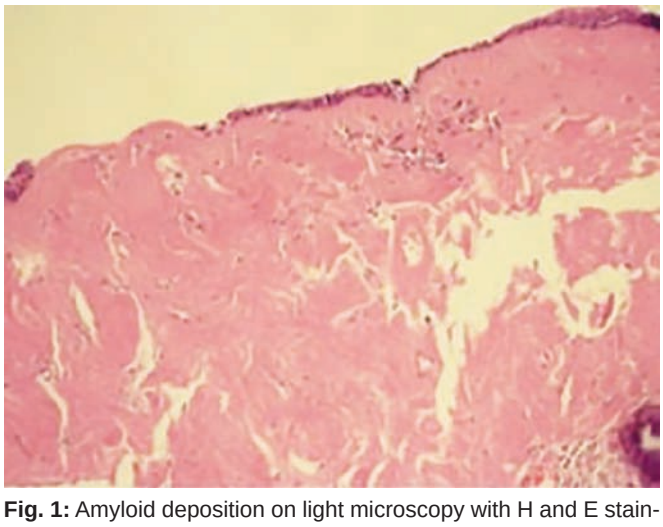

Fig. 1: Amyloid deposition on light microscopy with H and E staining showing sub epithelial deposition of amorphous, homogenous, eosinophilic material

(*Source*: Jaypee Brothers Medical Publishers, Atlas of Phonomicrosurgery, Ed.1, Nupur K Nerurkar, Amyloidosis, Chapter 16, 2018)

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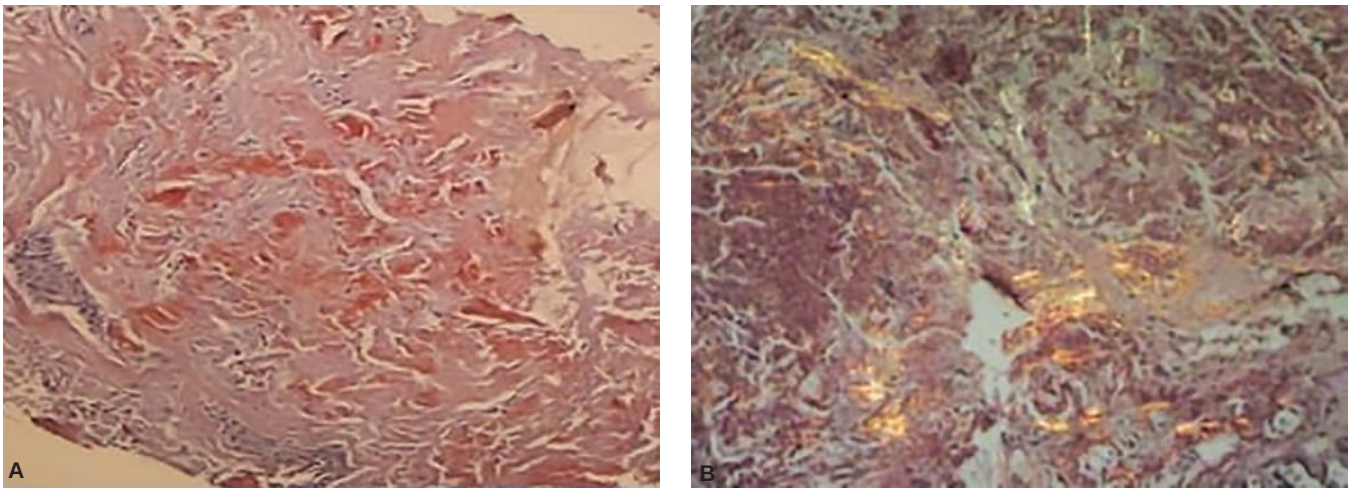


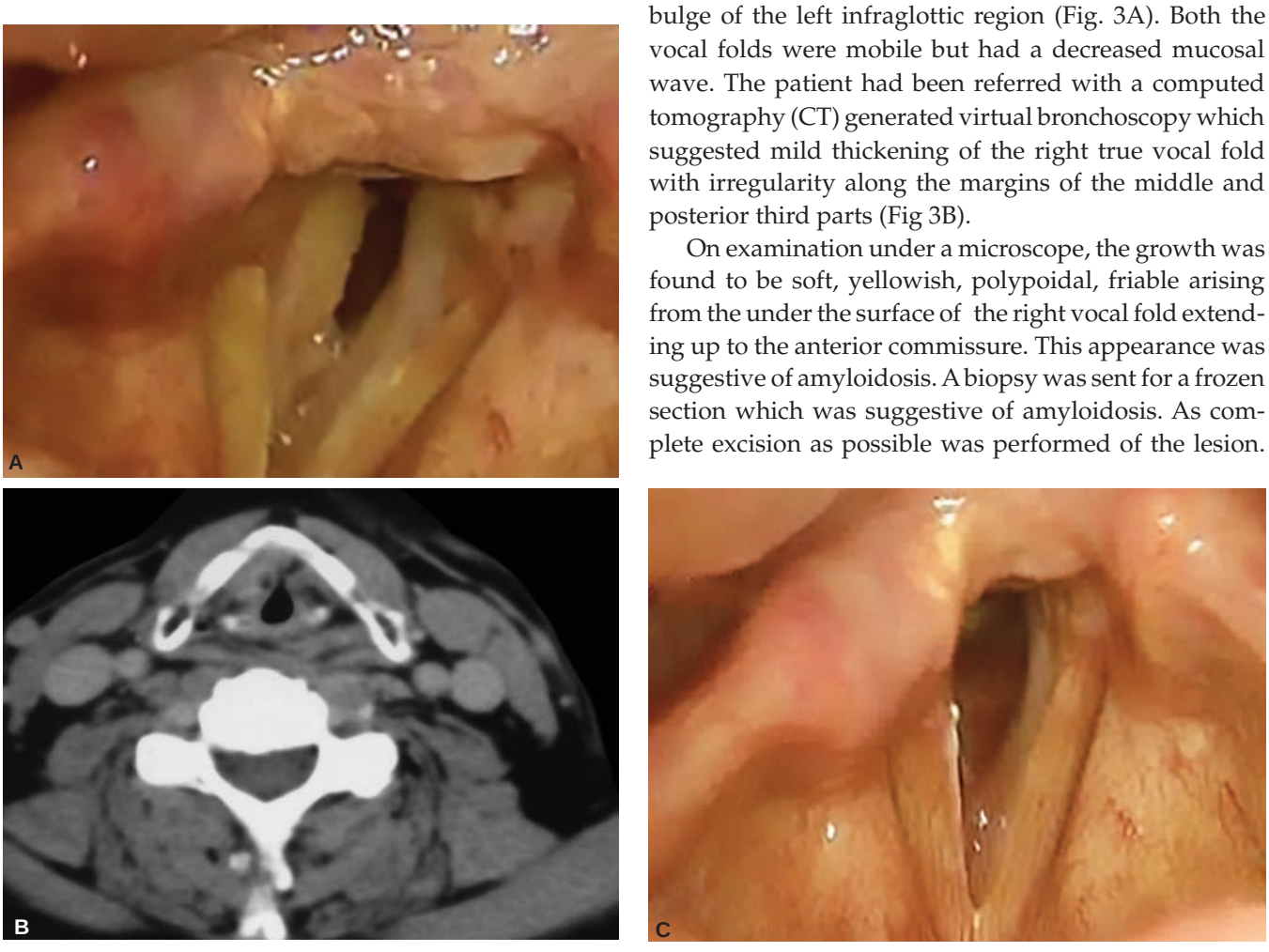
Figs 2A and B: (A) Congo red staining of the amyloid tissue; (B) Apple green birefringence seen under polarised light of the congo red stained amyloid

(*Source*: Jaypee Brothers Medical Publishers, Atlas of Phonomicrosurgery, Ed.1, Nupur K Nerurkar, Amyloidosis, Chapter 16, 2018)

for one month. He was a non-smoker, nondiabetic and non-hypertensive patient. He gave the history of tracheostomy 15 years ago following difficulty in re-intubation after he went into bronchospasm during extubation when he underwent submandibular lymph node biopsy under general anaesthetic (GA). He had an uneventful decannulation four days after tracheostomy.

A stroboscopy was performed and he was found to have a subepithelial bulge in the right infraglottic region extending up to the anterior commissure and a mild bulge of the left infraglottic region (Fig. 3A). Both the vocal folds were mobile but had a decreased mucosal wave. The patient had been referred with a computed tomography (CT) generated virtual bronchoscopy which suggested mild thickening of the right true vocal fold with irregularity along the margins of the middle and posterior third parts (Fig 3B).

On examination under a microscope, the growth was found to be soft, yellowish, polypoidal, friable arising from the under the surface of the right vocal fold extending up to the anterior commissure. This appearance was suggestive of amyloidosis. A biopsy was sent for a frozen section which was suggestive of amyloidosis. As complete excision as possible was performed of the lesion.



Figs 3A to C: (A) Case 1 Amyloid growth seen circumferrentially in infraglottic region giving a pseudosulcus appearance; (B) Computed Tomography scan of case 1 showing subglottic growth; (C) One month post operativestroboscopy of case 1 showing well healed vocal folds

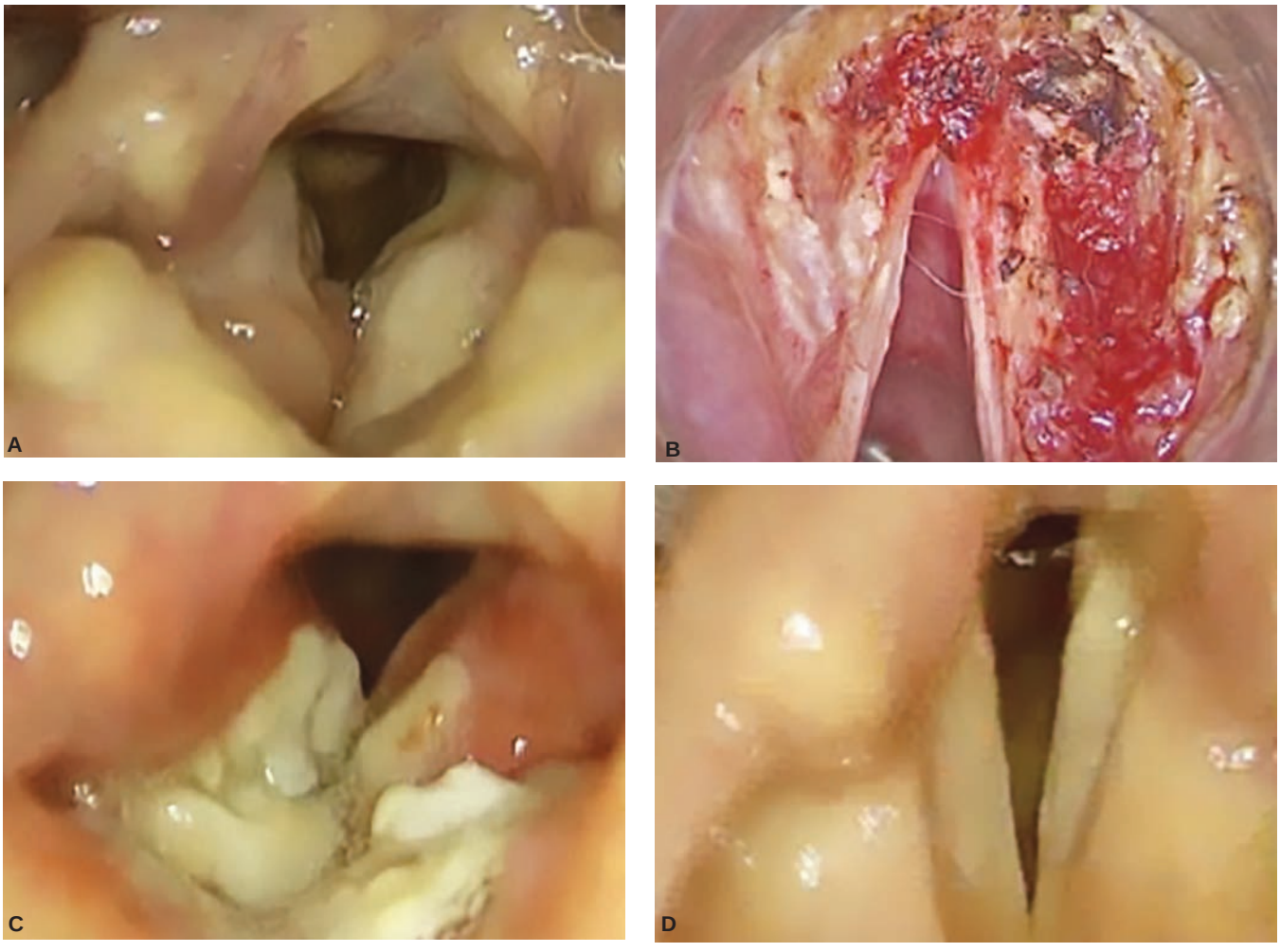
(*Source*: Jaypee Brothers Medical Publishers, Atlas of Phonomicrosurgery, Ed.1, Nupur K Nerurkar, Amyloidosis, Chapter 16, 2018)

The final histopathology report with Congo red staining confirmed amyloidosis. A complete workup for systemic amyloidosis was performed with serum and urine electrophoresis for light chain and immunoglobulin detection which was negative. The patient was followed up a week after surgery and then after a month and remains under follow-up. The voice has improved considerably, and the patient finds it normal with no complaints of dyspnoea on exertion (Fig. 3C).

Case 2

A 54-year-old lady presented to the voice clinic with hoarseness of voice for six to eight months. There was no history of breathlessness. She gave a history of 3 surgeries done by cold steel in the past 2 to 3 years for the same complaint in her hometown with no improvement in voice. The histopathology reports of prior surgeries revealed a benign lesion without any specific diagnosis. She was not a diabetic or a hypertensive patient. The stroboscopy was suggestive of smooth yellowish growth involving bilateral false folds, bilateral ventricles, anterior commissure and a laryngeal surface of the epiglottis (Fig. 4A). Both the right folds were mobile with a decreased amplitude of the waves, possibly a result of the bulky supraglottis. The clinical appearance was highly suggestive of amyloidosis.

Examination under the microscope under GA showed a typical smooth, yellowish appearing growth suggestive of amyloidosis on the left side, while the right side was more granular looking and vascular. The growth was excised as completely as possible using a CO_2 laser (Fig. 4B) and was sent for histopathology examination which revealed amyloidosis on special staining with Congo red. Since the anterior commissure disease was also removed entirely at one go there was slough formation (Fig. 4C) which was cleaned at 3 weeks under general anesthesia. Systemic amyloidosis was ruled out by doing the gamut of investigations which was negative for any deposits elsewhere. The patient was followed up at one week, one month, three months and remains under follow-up (Fig. 4D). The voice has improved very much, and there were no fresh deposits to date.



Figs 4A to D: (A) Case 2 - amyloid deposits seen on the laryngeal surface of epiglottis, bilateral false folds, bilateral ventricles and true folds; (B) Post laser excision performed in both false folds and ventricles and superior surface of right vocal fold. (C) Post operative slough present 3 weeks later on laryngoscopy. (D) Laryngoscopy showing well healed vocal folds after 7 months

(*Source*: Jaypee Brothers Medical Publishers, Atlas of Phonomicrosurgery, Ed.1, Nupur K Nerurkar, Amyloidosis, Chapter 16, 2018)

Case 3

A 38-year-old lady presented with the complaints of hoarseness of voice for one year. She also complained of breathlessness on exertion since the past six months. She did not have any other comorbidities.

A stroboscopy was done which revealed a growth over the supraglottic area extending into the false folds and both the ventricles.

Evaluation under the microscope (Fig. 5) confirmed the above findings and showed the typical yellowish appearance of amyloidosis. A CO_2 laser excision was performed to excise as much of the lesion as possible, and histopathology confirmed amyloidosis after special staining. A complete evaluation for systemic amyloidosis was negative. Postoperative follow-up showed proper healing with no fresh deposits in six years with considerable voice improvement.

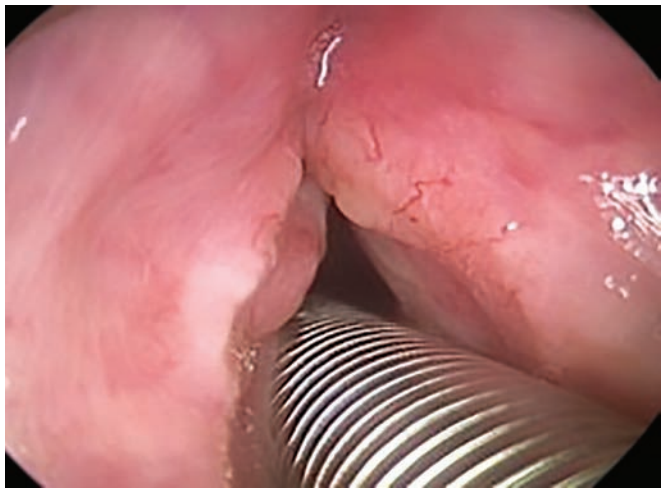


Fig. 5: Case 3 - microlaryngoscopic picture showing amyloid deposits involving bilateral false folds and both ventricles

Case 4

A 42-year-old male patient presented with a history of progressive hoarseness of voice for 8 months with dyspnoea on exertion for 3 months.

Examination revealed pedunculated, firm looking masses of both the vocal folds (Fig. 6A) with a reduced mucosal wave on the right and no mucosal wave on the left.

Microlaryngoscopic CO_2 laser excision was done under GA and histopathology with special staining confirmed amyloidosis. Systemic evaluation for amyloidosis was negative. A clean up was required at 3 weeks for slough removal to minimize chances of web formation. Postoperative examination showed a small polyp at 4 months (Fig. 6B), but since the patient had a very serviceable voice, he decided to wait and observe and is under follow up with no recurrent lesions till date.

Case 5

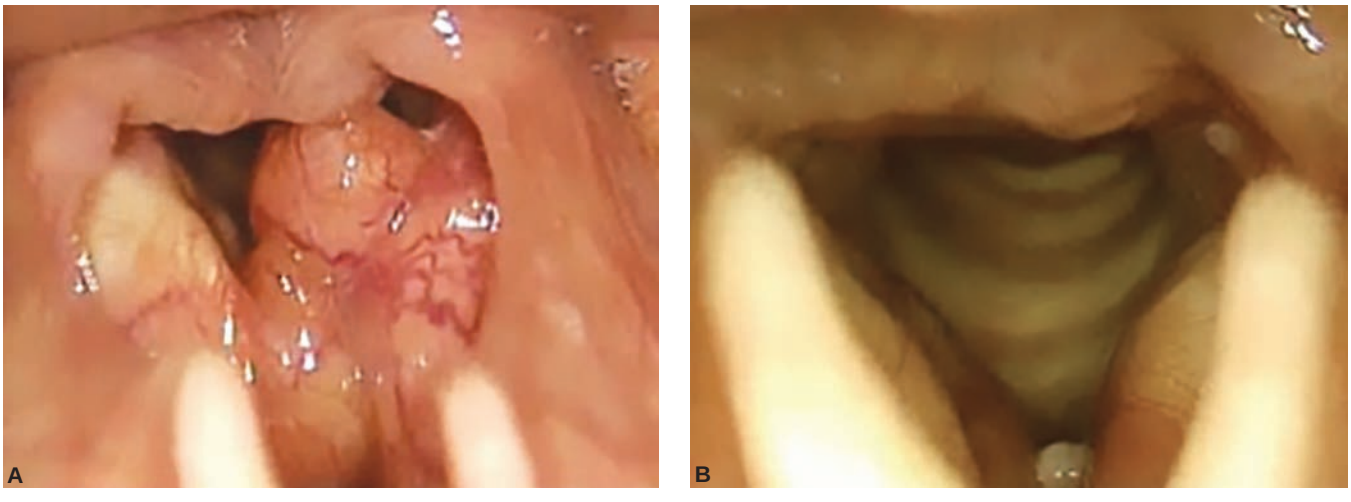
An adult male was referred to the voice clinic with persistent and progressive hoarseness for a year. On examination, the right false vocal fold revealed a swelling which was clinically suggestive of a subepithelial lesion (Fig. 7). The true vocal folds were normal.

Microlaryngoscopic CO_2 laser excision was done, and histopathology with special stains confirmed amyloidosis and further evaluation for systemic amyloidosis was negative. Postoperatively he healed well, and the vocal outcome was good. The patient remains under follow-up.

Case 6

An adult male patient was referred to the voice clinic with complaints of hoarseness of voice for 5 months. Stroboscopy revealed a left false vocal fold bulge with normal true folds.

On evaluation under the microscope, the lesion was seen involving the left false vocal fold and ventricle (Fig. 8A).



Figs. 6A and B: (A) Case 4- laryngoscopy revealing pedunculated firm looking masses of both vocal folds; (B) Laryngoscopy at 4 months follow up revealed a small anterior polypoidal lesion

(*Source*: Jaypee Brothers Medical Publishers, Atlas of Phonomicrosurgery, Ed.1, Nupur K Nerurkar, Amyloidosis, Chapter 16, 2018)

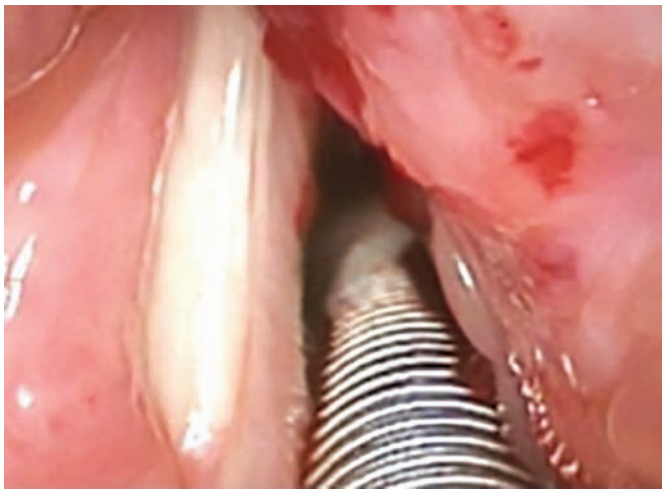


Fig. 7: Case 5- microlaryngoscopic image showing right vocal fold and ventricle bulging suggestive of subepithelial deposits

(*Source*: Jaypee Brothers Medical Publishers, Atlas of Phonomicrosurgery, Ed.1, Nupur K Nerurkar, Amyloidosis, Chapter 16, 2018)

A CO_2 laser excision was performed (Fig. 8B) and histopathology with special stains confirmed amyloidosis. Systemic evaluation for amyloidosis was negative. The postoperative vocal outcome was good, and the patient remains under follow-up.

Case 7

An adult female patient came with complaints of hoarseness of voice for 6 weeks. Stroboscopy revealed a small lesion at the left vocal fold near the anterior commissure which was clinically diagnosed as a subepithelial cyst.

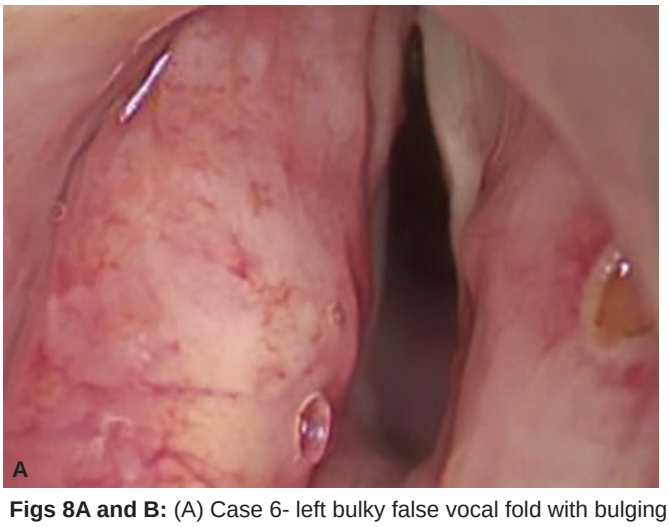
During microlaryngoscopic laser excision the lesion was excised in toto (Fig. 9). Histopathology with special staining revealed the definitive diagnosis as amyloidosis. Workup to rule out systemic amyloidosis was performed and was negative and 10 years post surgery the patient retains a good voice and is under follow-up.

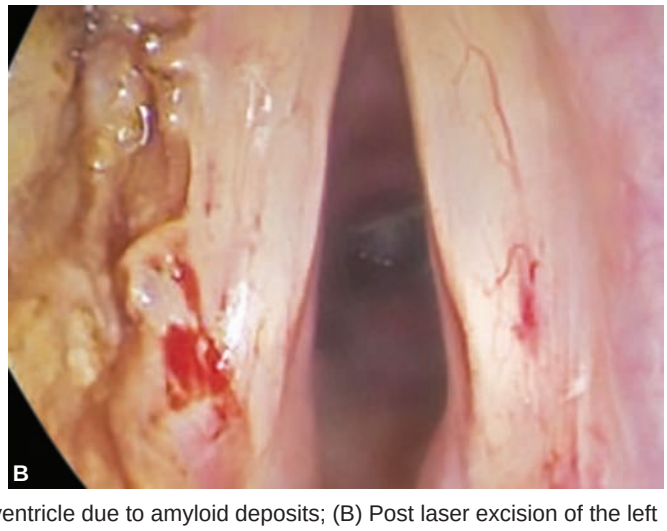
Case 8

A 73-year-old gentleman, known asthmatic, presented with complaints of hoarseness of voice for 2 months. On stroboscopy, he was found to have a ventricular pattern of phonation with bilateral apparently normal vocal folds with a moderate amplitude of the mucosal waves. He was advised voice therapy, and a regular follow up. However, the patient followed up after 4 years with complaints of a gradual increase in hoarseness and a sensation of constriction in his voice as well as airways. The stroboscopy at this stage revealed an oedematous lesion over the superior surface of right vocal fold and ventricle, with a decreased mucosal wave (Fig. 10A). Both the false vocal folds appeared slightly bulky with right slightly bigger than the left. During surgery, both the false vocal folds did not appear firm on palpation and the edematous lesion on the superior surface of the right vocal fold was excised. The final histopathology with special stain revealed a plasma cell neoplasm with amyloidosis. Immunohistochemistry confirmed amyloidosis with local lambda restricted plasma cells. A CT scan performed after the surgery documented an ill-defined mass in the right false vocal fold abutting the right, true vocal fold suggestive of the residual lesion (Fig. 10B). A workup to rule out systemic amyloidosis including serum and urine electrophoresis, a whole body positron emission tomography (PET) scan and bone marrow testing was negative. The patient has been recommended radiation therapy targeted to the vocal folds in a bid to eliminate the residual plasma cells and amyloidosis.

Case 9

A 24-year-old young female presented to the voice clinic with complaints of hoarseness of voice for 1 year . Stro-





Figs 8A and B: (A) Case 6- left bulky false vocal fold with bulging ventricle due to amyloid deposits; (B) Post laser excision of the left false vocal fold and ventricle lesion

(*Source*: Jaypee Brothers Medical Publishers, Atlas of Phonomicrosurgery, Ed.1, Nupur K Nerurkar, Amyloidosis, Chapter 16, 2018)

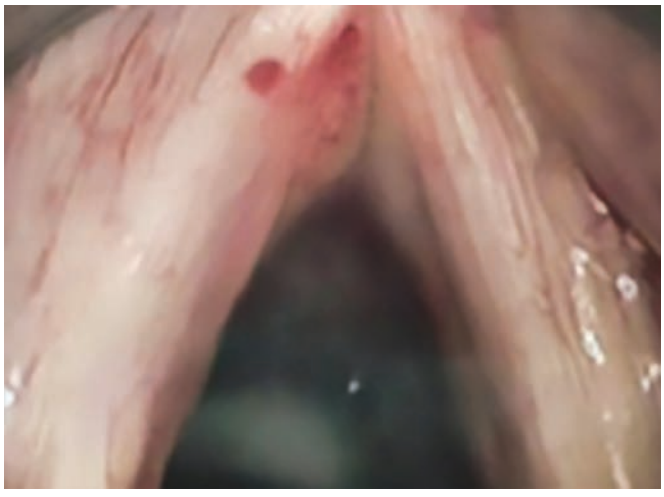


Fig. 9: Case 7- Intra operative image showing a left anterior commissure lesion which gave the appearance of a subepithelial cyst (*Source*: Jaypee Brothers Medical Publishers, Atlas of Phonomicrosurgery, Ed.1, Nupur K Nerurkar, Amyloidosis, Chapter 16, 2018)

boscopy revealed a yellowish growth involving the right false vocal fold, ventricle, true vocal folds laryngeal surface of epiglottis. Microlaryngoscopic CO_2 laser excision was performed with as complete excision as possible. Histopathology with special staining confirmed amyloidosis. Workup to rule out systemic amyloidosis was performed and was negative. The postoperative voice was good for a year.

However, she had a gradual worsening of voice after a year and came to us 3 years after her primary surgery with complaints of hoarseness again. Stroboscopy and examination under the microscope once again revealed a smooth yellowish growth involving the right false vocal fold, ventricle, true vocal fold going on to the anterior commissure, suggestive of recurrence of amyloidosis (Fig. 11A). Microlaryngoscopic CO_2 laser excision (Fig. 11B) was performed and she remains under follow-up.

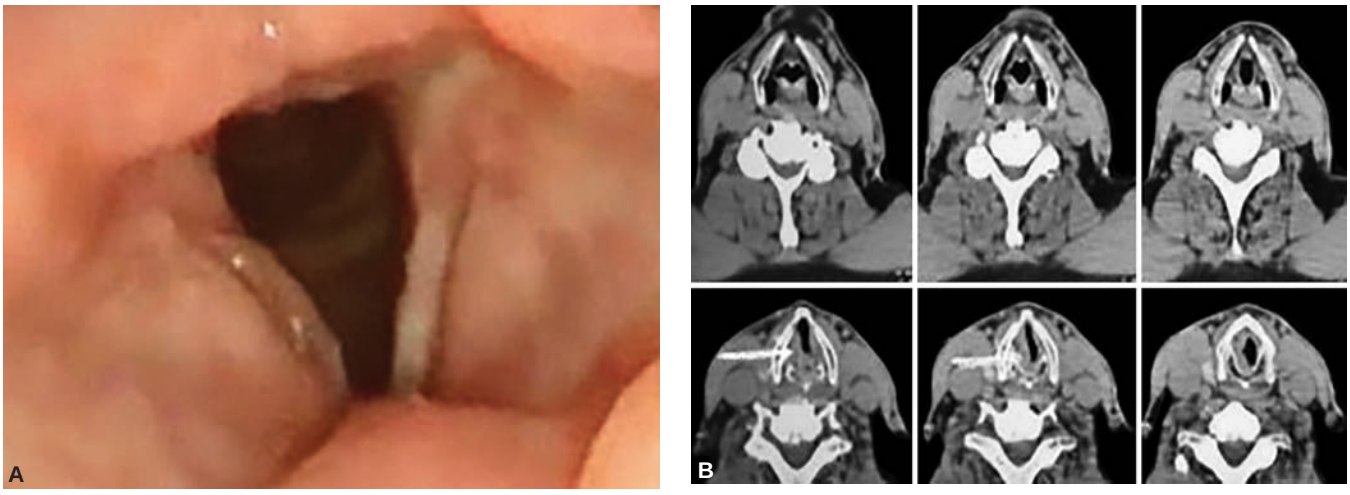
Case 10

An adult male patient came with hoarseness of voice for 1 year. Stroboscopy and examination under the microscope revealed a smooth growth involving the right false vocal fold, ventricle, true vocal fold, anterior commissure and going on to the left ventricle (Fig. 12A). He gave the history of microlaryngoscopic biopsy of the lesion outside a month prior, with the histopathology revealing a benign lesion without any specific diagnosis.

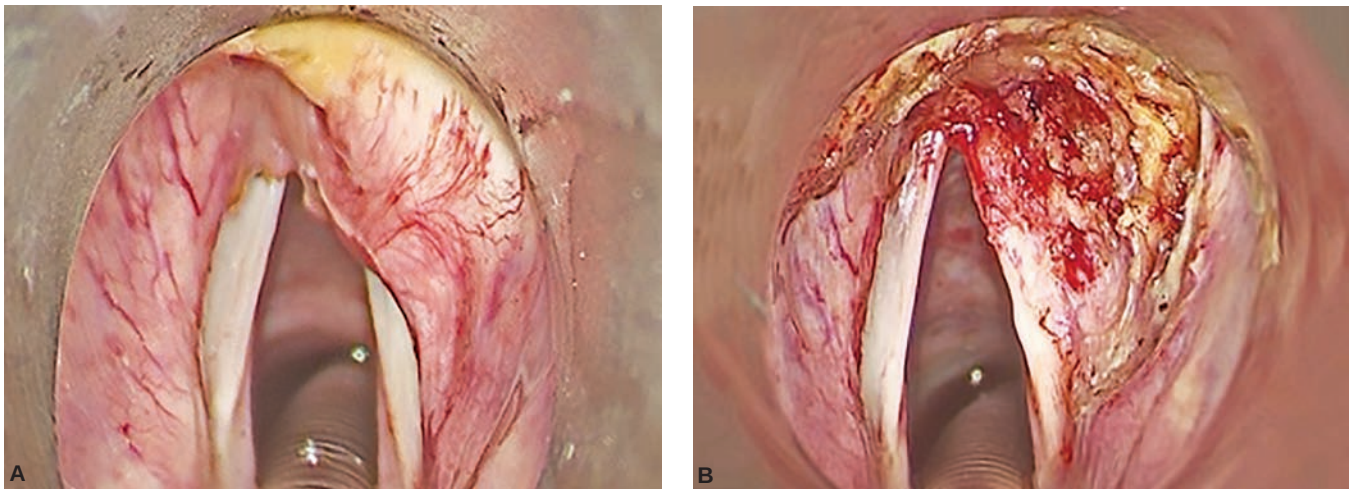
Microlaryngoscopy with CO_2 laser excision was performed. A small lesion at the anterior commissure was left behind to prevent circumferential scarring and web formation (Figs 12B and C). Histopathology with special stains revealed amyloidosis and the systemic workup for the same was negative. The postoperative vocal outcome was good, and the dyspnoea was relieved. Since the patient was comfortable, we have not performed a second stage surgery for the residual anterior commissure lesion, and he remains under follow-up (Fig 12D).

DISCUSSION

Amyloidosis is a rare, slowly growing, benign disease. It can be classified in various ways. Etiologically it can be classified as hereditary, idiopathic or primary and reactive or secondary. Secondary amyloidosis is usually associated with coexisting infectious or chronic inflammatory diseases. Primary can be further classified as localized and systemic. Recent classification gives almost 15 types based on the type of protein deposited in the tissues. However, most common types are AL[9,10] which is derived from plasma cells containing kappa or lambda light chains in association with myelomas, AA which is a familial non-immunoglobulin mediated chronic inflammatory disease also found in reactive amyloidosis, AB with beta-2 microglobulin deposits in the fibrils and hemodialysis-associated amyloidosis.[6,7,9]



Figs 10A and B: (A) Case 8- preoperative image revealing an oedematous area over the right vocal fold and ventricle; (B) Computed Tomography scan showing an ill defined contrast enhancing mass in the right false vocal fold upto the thyroid cartilage suggestive of amyloidosis

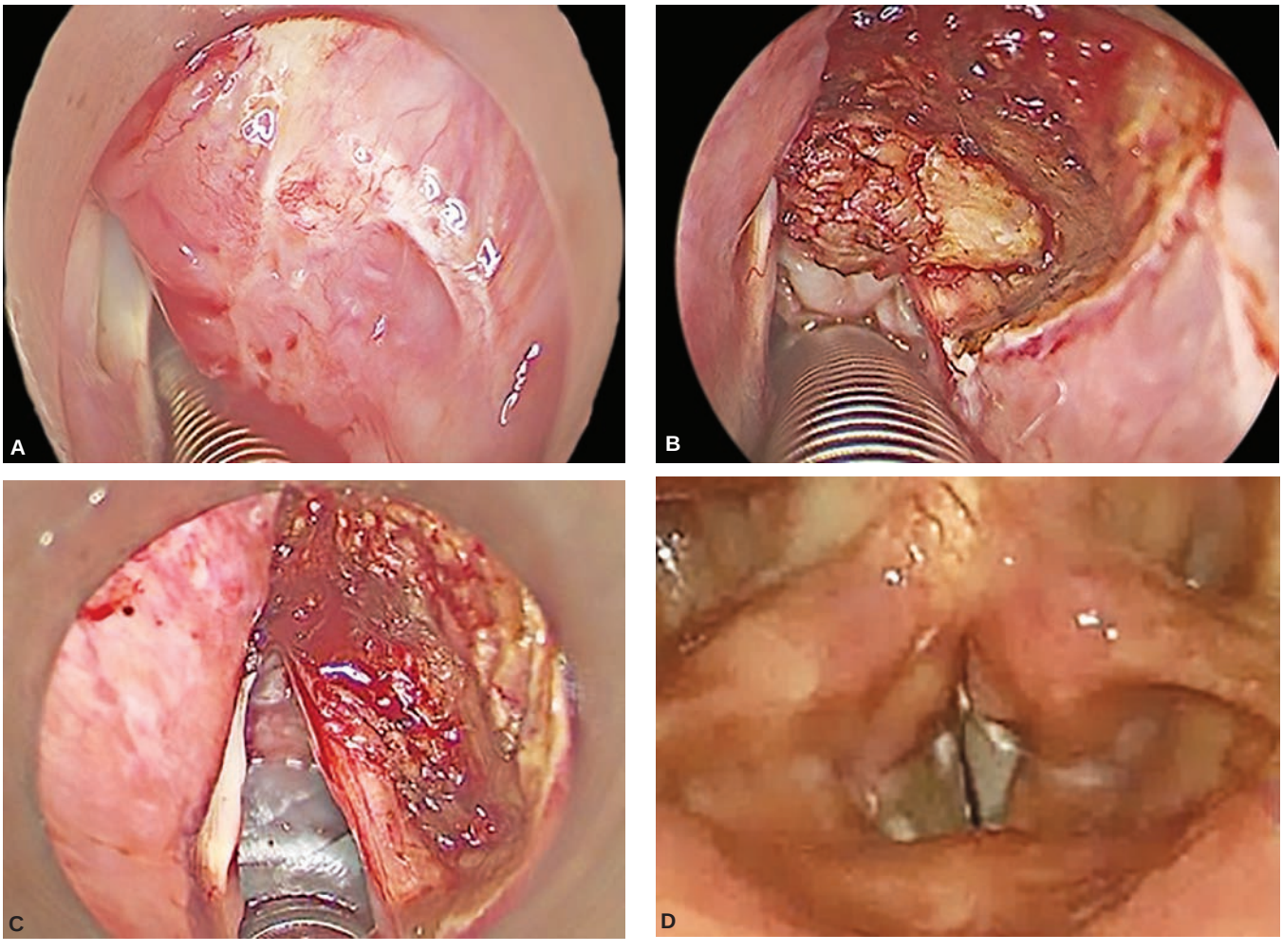


Figs 11A and B: (A) Case 9-growth involving right false fold, ventricle going on to the left anterior commissure; (B) Immediate post operative image after excision of growth

The most common sites of involvement in systemic amyloidosis are the kidneys and heart. Also, most patients have cutaneous manifestations too. The prognosis is not very good and depends on the extent of involvement. Patients usually die of cardiac or renal failure.

The common sites of localized amyloidosis are larynx, the tracheobronchial tree, paranasal sinuses, nose, eye, and orbits, etc. Localized amyloidosis usually has a good prognosis.

Etiopathogenesis of localized amyloidosis is still poorly understood. It is an immunoglobulin-mediated deposition though its source is as yet not certain. It is usually of the AL type. One hypothesis suggests that there is a production of abnormal light chain proteins locally



Figs 12A to D: (A) Case 10- Growth involving right false vocal fold (B) Glottic growth seen after excision of the growth over the false vocal fold and ventricle (C) Immediate post operative image after complete excision of growth (D) Three months after surgery

by the plasma cells, which gets deposited as amyloid proteins. Thus it can be considered as a form of localized plasma cell dyscrasia. A second theory proposes deposition of a circulating precursor protein after a breach in the vasculature and inability of the mucosal related lymphoid tissue to clear it.[1,9]

Though laryngeal amyloidosis usually presents more frequently in men than women in a ratio of 3:1,[1,2] in our series of 10 patients 60% were male giving a 3:2 ratio.

In 1919, New suggested two types of laryngeal involvement in amyloidosis, one as a discrete tumor nodule and other as diffuse subepithelial deposits.[11] The most common site in the larynx which is affected is the ventricles (55%), followed by the false vocal folds (36%), subglottis (36%), true vocal folds (27%), the arytenoids (23%) and the anterior commissure (14%).[12] In our series one patient presented a discrete tumor nodule which was glottic (10%) and within the remaining nine cases of diffuse disease, seven cases presented with supraglottic with glottic involvement, one case as only supraglottic disease and one case as only subglottic disease.

Depending on the site of involvement the symptoms vary from hoarseness of voice to dyspnoea. In our series, all ten patients had hoarseness of voice, and three patients had dyspnoea on exertion as well. The average duration of symptoms at presentation was 8 months.

Laryngeal evaluation usually shows the presence of a smooth yellowish, greyish colored growth but sometimes it may mimic the appearance of malignancy. In 60% of our patients, we were able to accurately make a clinical diagnosis of amyloidosis after stroboscopy and in 20% after the evaluation under the microscope. In case seven and eight we had not been able to suspect amyloidosis until we received the pathology. Of these two patients, one was thought to be a subepithelial fibrotic cyst (case 7), and the other had appeared as edematous lesion during stroboscopy, however on palpation was a little firm and was thus suspected to be possibly dysplastic or malignant (case 8).

Final diagnosis requires a biopsy or excision and demonstration of the typical apple-green birefringence under polarized light with Congo red stain. Hematoxylin and eosin staining show amorphous homogenous protein deposition. Without special staining, the diagnosis can be missed as happened in two of our patients who previously had been operated at another center (cases 2 and 10).

Treatment of amyloidosis is microlaryngoscopy with as complete a surgical excision as possible, preferably using a CO_2 laser.[8] The aim is to stay lateral to the lesion and cut through normal tissue; however, this is not always possible due to the diffuse nature of the disease and the absence of any encapsulation of the disease. The aim of surgery is the preservation of voice, maintenance of the airway eight and minimal surgical procedures. Repeated surgical excisions may be required in some patients due to reappearance of lesions or an increase in disease left behind. In case of involvement of the anterior commissure, a cleanup of the slough becomes necessary after 2 to 3 weeks to reduce the chances of webbing as done in two of our cases. A staged procedure after 4 to 6 weeks is an alternative in such cases.

Once the diagnosis of amyloidosis is established by histopathology a complete workup must be performed to rule out systemic amyloidosis. A complete haemogram, liver function tests, renal function tests, ECG, serum immunoglobulin assay, serum and urine electrophoresis CT scan of the larynx to see the contrast enhancement within the larynx was the protocol followed by us. Previously abdominal fat, renal or rectal biopsy was done to rule out systemic amyloidosis but is not used anymore.[3] In case any systemic involvement is seen then it should be managed accordingly. Most of the laryngeal amyloidosis is localized and of the AL type.[10] None of our patients had systemic amyloidosis. However, one patient had a plasma cell neoplasm along with the amyloidosis.

Most of the cases respond very well to surgical removal. All of our patients had a very serviceable voice postoperatively. Regular followup is a must to rule out recurrence. One of our patients (10%) required a second surgery (case 9), and another (case 2) had three previous excisions at different hospitals before she came to us.

Keeping in mind that laryngeal amyloidosis is almost always localized and a rare, slow-growing benign lesion it is important for an ear, nose, and throat (ENT) surgeon to diagnose it at the earliest to give a good and serviceable voice outcome.

CONCLUSION

Laryngeal amyloidosis is rare and requires a high index of suspicion. In our 10 patients seen over 7 years, six were females. The patients presented with their complaints at an average of 8 months. The most common site of involvement was the supraglottis (80%). Microlaryngoscopy using CO_2 laser with as complete excision as possible was the standard treatment followed in all our patients of isolated laryngeal Amyloidosis.The patient with associated plasma cell neoplasm received a low dose radiation therapy.

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