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Laryngeal Amyloidosis: Case Series of an Unusual Cause of Hoarseness.

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ABSTRACT

Background: Amyloid can be defined as in in-vivo deposited amorphous material which on electron microscopy is fibrillar in appearance and gives apple-green birefringence on Congo-red staining. Beta-pleated sheet structure observed on X-Ray Diffraction is the characteristic finding. Deposition of this amyloid material in the human body interfering in the normal physiological functions of the body is called amyloidosis. Amyloidosis can be divided into localized or systemic form depending upon whether it is arising from proteins expressed by cells at the local site or they get deposited at different organs after production at a local site. Though amyloidosis can affect any organ of the body the most commonly affected organs include kidneys, heart and liver. In head and neck region macroglossia is the most common manifestation of amyloidosis. Laryngotracheal system is also one of the commonly affected site for localized amyloidosis. It usually appears as nodule or polypoid lesion in the larynx and constitute 1% of all benign laryngeal lesions. We present here a case series of 6 cases of laryngeal amyloidosis who presented to ENT department of our medical college and a leading ENT hospital in an urban area. Aims: To study the clinical presentation, examination findings, management and outcome of patients with laryngeal amyloidosis. **Methods:** This is a case series of 6 patients who presented to us with gradual change in voice. Detailed history was noted and clinical examination was done. Laryngoscopy was done in all cases. Later microlaryngoscopy and CO2 laser excision of polypoidal masses was performed under general anesthesia. Diagnosis was made on haematoxylin and eosin stain while confirmation was done by Congo red stain. Patient was discharged post-operative day 2 with broad spectrum antibiotics, analgesics and oral methylprednisolone for one week and was advised to take voice rest for five days. All patients were followed on seventh day, 1month, 3 months and 6months interval and thereafter yearly. **Results:** Patients included 4 females and 2 males with female to male ratio 2:1 their ages ranged from 40 to 70 years with mean age at presentation of 55 yrs. The most common age group involved was found to be 50-60 years. In majority of the cases (5/6) a single lesion was found while in 1 patient the lesions were multiple involving larynx and epiglottis also. In majority of the patients (50%) the duration of hoarseness was 1-2 years. successful microlaryngoscopy and CO2 laser excision was done in all the cases. All the patients were followed up regularly for a period of 5years. One patient showed recurrence after 3 years after first surgery the patient who developed recurrent disease had polypoidal and diffuse amyloid deposits. **Conclusion:** Laryngeal amyloidosis is a rare benign condition affecting larynx and should be suspected in any patient presenting with gradually increasing hoarseness of voice. It is diagnosed by characteristic birefringence under polarized light. It can be effectively treated by laser excision. Follow up is essential due to chances of recurrence

Keywords: Laryngeal Amyloidosis, Hoarseness of voice, Laser excision, recurrence.

INTRODUCTION

Amyloid can be defined as in in-vivo deposition of amorphous material which on electron microscopy is fibrillar in appearance and gives apple-green birefringence on Congo-red staining. X-Ray Diffraction characteristically shows beta-pleated sheet structure.[1] Deposition of this amyloid material in the human body interferes with the normal physiological functions of the body.[2] The common site where amyloidosis occurs are kidney, heart, liver, CNS and GIT. Majority of the amyloid material consist of misfolded proteins.[3] Various other constituents of amyloid material include glycosaminoglycan (GAG), apolipoproteins-E and serum amyloid P-component. Amyloidosis is classified as localized or systemic depending upon whether it is deposited at the same site where it is produced or it is precipitated systemically after production at a remote site.[4] The mechanism

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responsible for development of amyloidosis is thought to be due to mutations causing changes in thermodynamic or kinetic properties. Other etiopathogenetic mechanisms involved in amyloidosis are thought to be due to infections (prion disease), gene mutations, transcription errors and defects in post-translational modifications of the proteins.[5] Systemic amyloidosis may occur in various inflammatory conditions including infection and neoplastic diseases. Some of the significant medical conditions associated with amyloidosis are Rheumatoid arthritis, Alzheimer disease, juvenile idiopathic arthritis, ankylosing spondylitis, psoriasis and Bechets syndrome.[6]

Primary laryngeal amyloidosis is a rare condition representing approximately 1% of all benign laryngeal lesions.[7] The exact cause of localized laryngeal amyloidosis is not well known but it is thought to be due to local synthesis and deposition of amyloid material in the larynx.[8] In 1872 Borow et al described first case of amyloidosis of head and neck following which many authors have described various cases of pharyngeal and laryngeal amyloidosis.[9] Laryngeal amyloidosis is usually seen in patients in fifth or sixth decade of their life. The most common clinical feature is gradually increasing hoarseness of voice. Other symptoms, though uncommon, may include dysphagia and dyspnea. The usual approach include physical examination followed by indirect laryngoscopy. CECT neck is routinely done before proceeding with excision biopsy. Endoscopy with flexible endoscope and microlaryngoscopy and removal or biopsy of mass under general anesthesia is usually done. The diagnosis of laryngeal amyloidosis can be confirmed by immunohistochemical stains and Congo red staining by viewing it under polarized light microscopy. Alternatively electron microscopy can also confirm the diagnosis of amyloidosis in patients. Systemic amyloidosis should be ruled out by rectal biopsy and other relevant examinations. Conditions which may be associated with amyloidosis like rheumatoid arthritis, Bechets syndrome, psoriasis and multiple myeloma etc. should be ruled out by appropriate investigations.[10]

MATERIALS AND METHODS

This was a multi-centric prospective study conducted at a medical college and a well-known ENT hospital situated in an urban area. We studied 6 cases of laryngeal amyloidosis over a period of 2 yrs. All the 6 patients presented with history of long-term change in voice with gradually increasing hoarseness of voice. Detail history taking and clinical examination was done, there was no history of dysphagia, dyspnea, stridor or odynophagia. All the patients were submitted to 70" laryngoscopy in OPD to confirm nature of lesion. In all 6 patients there was a granular polypoidal mass lesions on false cords and ventricles of larynx. Routine blood investigations, x-ray chest, USG abdomen and CECT neck were done to rule out systemic focus of amyloidosis.

Microlaryngoscopy and CO2 laser excision of polypoidal masses was performed under general anesthesia and patients were discharged post-operative day 2 with broad spectrum antibiotics, analgesics and oral methylprednisolone for one week and was advised to take voice rest for 1 week. In all cases diagnosis was made on haematoxylin and eosin stain while confirmation was done by Congo red stain.

All patients were followed on seventh day, 1 month, 3 months, and 6 months interval and thereafter yearly to know recurrence. One patient had recurrence of lesions at same site after 3 years of first surgery, which was again treated by microlaryngoscopy and laser ablation and kept under regular followup.

RESULTS

Out of the studied cases there were 4 (66.66%) females and 2 (33.33%) males with a male to female ratio 1:2.

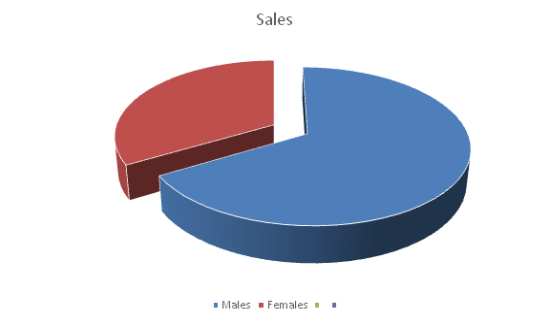

Figure 1: Gender Distribution of the studied cases

The analysis of age distribution of the patients revealed that the most common age at presentation was between 50-60 years (50%) followed by 40-50 (33.33) years and 60-70 years (16.67%).

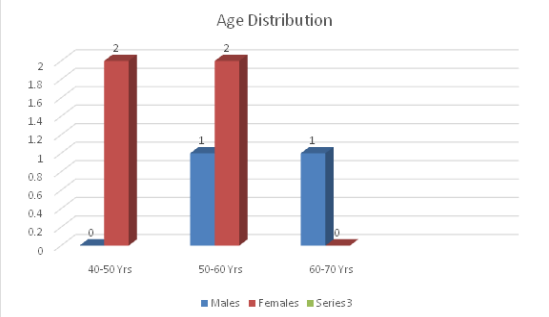

Figure 2: Age distribution of the cases with laryngeal amyloidosis.

The most common signs and symptoms present in the studied cases included hoarseness of voice, feeling of lump in the neck, cough, and hemoptysis.

Other symptoms like dyspnea, dysphagia, stridor or odynophagia was not present in any of the patients.

Table 1: Presenting complaints in the studied cases.

Signs/Symptoms	No of cases	Percentage
Hoarsness of voice	6	100%
Feeling of lump in neck	2	33.33%
cough	2	33.33%
hemoptysis	1	16.66
Dysphagia,odynophagia or stridor	0	0

The most common presenting complaint was found to be hoarseness of voice. The analysis of duration of hoarseness revealed that the majority of the patients (50%) had gradually increasing hoarseness of voice since 1-2 years while in 2 patients (33.33%) the hoarseness was present since 2-3 years. 1 patient (16.66%) had history of hoarseness since less than 1 year.

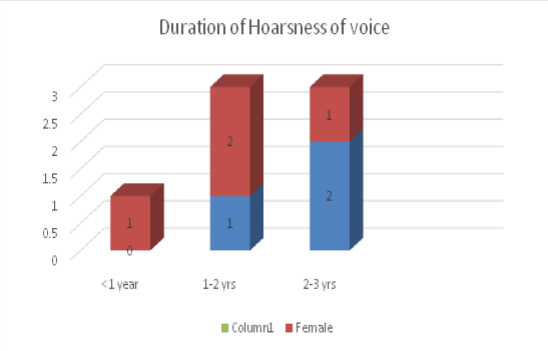

Figure 3: Duration of hoarseness of voice

No patient had airway obstruction or acute presentation. 4 patients had lesions on false cords and ventricle of larynx, while 2 patients showed involvement of true vocal cords. 1 patient had evidence of multifocal disease in larynx involving epiglottis as well. In our series two patient showed bilateral involvement & no patient showed impaired vocal cord mobility. All patients had negative systemic workup and did not show evidence of systemic disease.

Figure 4: Pre-operative 70 degree laryngoscopy showing polypoidal masses in bilateral ventricles (Left). Post- operative laryngoscopic view showing raw area after excision with laser and normal vocal cords (Right)

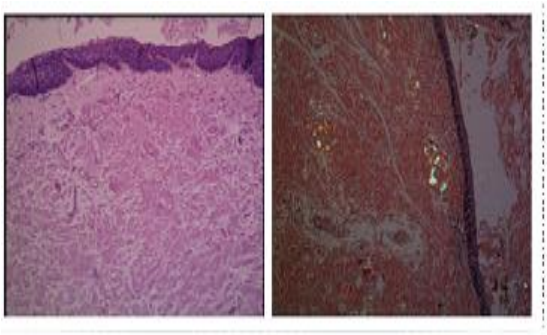

Figure 5: H & E staining showing polypoidal mass lined by respiratory epithelium and extensive subepithilial nodular, amorphous eosinophilic acellular deposits of amyloid (Left).Amyloidosis confirmed with Congo-Red staining (Right).

Table 2: Distribution of the lesion in the studied cases.

No. Of Lesions	No. Of Patients Observed	Site Of Lesions	No Of Patients Observed
Singel Lesion	5	False Cord	6
		Ventricle	6
Multiple Lesion	1	True Cord	2
		Epiglottis	1
		Subglottis	0

All patients were treated with microlaryngoscopy and CO2 laser excision of amyloid mass. Excision of mass was done in 1 patient who had recurrence. While doing excision attention was given to preserve vocal cord epithelium for favorable voice outcome. No adjunctive therapy was used for any of the patient. All the patients were followed regularly over period of 5yrs with minimum follow up of 1yr. one patient showed recurrence 3 years after first surgery the patient who developed recurrent disease had polypoidal and diffuse amyloid deposits. Lesions were smooth to bossilated, polypoid no surface ulceration was noted the masses ranged in size from 0.6 to 3cm in max dimension. False cord masses were large as compare to that of true vocal cord. No patient had any associated systemic disease like multiple myeloma, rheumatoid arthritis, Bechets syndrome or reiters arthritis.

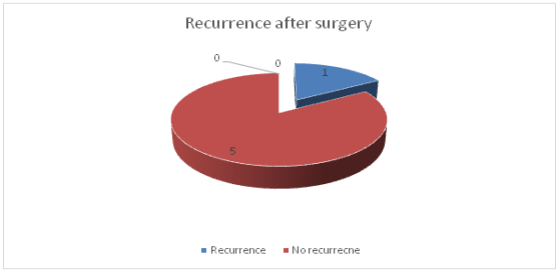

Figure 6: Outcome after successful surgery.

Amyloid presented as subepithilial extracellular,acellular, amorphous eosinophilic material. In none of our cases was amyloid difficult to be identified. It was dispersed randomly throughout lamina-propria sparing overlying epithelium it showed perivascular and periglandular

deposits, sometimes completely obliterating seromucus glands. There was sparse inflammatory infiltrate of lymphocytes and plasma cells with occasional histiocytes and few giant cells. The foreignbody type giant cells were seen arranged focally around amyloid deposits. Amyloid was confirmed with histochemical technique (Congo red, methyl violate) apple-green birefringence under polarized light with Congo red proved to be the most reliable and easy to interpret technique.

DISCUSSION & CONCLUSION

The literature supports that most cases of amyloidosis of larynx are composed of proteins that is immunologically identical to the variable lesion of the light chain fragment of immunoglobulins and is classified as a fibril type, similar, if not identical, to that of primary amyloid.[11] The widely accepted theory about etiopathogenesis of laryngeal amyloidosis states that the localized amyloidosis in the larynx is secondary to occurrence of plasma cell reaction to inflammatory antigens. This theory is supported by presence of polyclonal plasma cells within the amyloid substance.

Imaging like MRI may show intermediate T1-weghted signal intensity and low T2-weighted signal intensity and help in suspecting the diagnosis of amyloidosis.[12] Although immunophenotyping has become universally available, the "gold standard" for the diagnosis of the amyloid, tissue biopsy demonstrating characteristic H&E changes, Congo red birefringence or metachromatic staining with methyl violate are confirmatory.[13] Almost all patients experience voice changes depending on size and location of lesion. It usually presents in adults, though none of our cases were children, pediatric cases have been documented.[14] Average age of presentation in our series was 55 yrs. Amyloidosis can affect all the parts of larynx and may present usually as single localized lesion or multifocal in few cases. Literature also supports multifocal or systemic involvement in patients of laryngeal amyloidosis.[15]

A wide variety of studies have suggested different behavior of laryngeal amyloid. Clinical and laboratory assessment including a search for lymphadenopathy, radiographic imaging, urinary and digestive tract evaluation, ECG and blood count has been suggested to ascertain the true nature of the disease and rule out systemic disease.[16]

Other diseases can also be associated with amyloid with larynx including small cell carcinoma of larynx or medullary carcinoma of thyroid.[17] Laryngeal amyloidosis seems to be running an indolent course with patients living a long time with evidence of recurrent disease.[18] Treatment of localized laryngeal amyloidosis consist of simple observation if the lesion is small and is not causing much discomfort or hoarseness.[19] In severe cases laser ablation, excision or even partial laryngectomy may be required. Surgical resection using CO2 laser is very effective in removing the diseased tissue. Other treatment options may include corticosteroids, colchicine and melphalan.[20] Regular follow up with laryngoscopy is a must for early diagnosis and management of recurrence.

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