KTP Laser in Laryngeal Amyloidosis: Five Cases with Review of Literature

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Abstract To study the clinical presentation and review the options in the management of laryngeal amyloidosis. To study the efficacy of KTP 532 laser in the excision of laryngeal amyloidosis. Study was conducted in our department in a tertiary care hospital between Jan 2001 and Feb 2010. We report five patients who presented with hoarseness of voice and localized laryngeal lesions. The biopsy proven laryngeal amyloidosis lesions were excised microendoscopically using KTP 532 laser in three patients and other two patients were kept only on follow-up as they refused further surgery. The patients were evaluated for systemic amyloidosis. The average duration of follow up was 2.6 years (3 months–6 years). All the five patients in our study were asymptomatic with no evidence of recurrence at their last follow up. In our small case series, KTP 532 laser excision of the laryngeal amyloidosis had a favorable outcome. Long term follow up is required to rule out recurrence and systemic involvement.

Keywords Amyloidosis · Larynx · KTP 532 laser

Introduction

Amyloidosis was first proposed by Rokitansky in 1842 [1]. Virchow, who gave amyloid its name, found that it stained violet with iodine and sulphuric acid and he attributed this to its starch like nature [2]. Amyloidosis refers to a disturbance in the metabolism with a pathological deposit of extra cellular

homogenous eosinophilic proteinaceous filaments in the form of well defined β pleated sheets. On hematoxylin and eosin stained sections, groups of homogenous pink tissues are found in the stroma and in the walls of blood vessels. Congo red staining shows apple green birefringence under a polarized light microscope [3]. Amyloidosis can be hereditary or acquired, systemic or localized [4]. Larynx is the commonest site of involvement in the head and neck [5]. Laryngeal amyloidosis amounts for 0.2–0.5% of benign laryngeal tumors. Amyloidosis of the larynx was first reported by Burow and Neumann in 1875 [6]. Since then more than 300 cases have been reported in the literature.

Localized amyloidosis in the head and neck is a rare and benign process. Familial transthyretin amyloidosis (ATTR) is a hereditary degenerative disease. It is associated with single amino acid substitutions found in plasma protein transthyretin. A definitive diagnosis of familial transthyretin amyloidosis relies on the detection and identification of transthyretin variants by using immunoprecipitation, electrospray ionization mass spectrometry and matrix assisted laser desorption/ionization [7]. The systemic type can be classified into primary, when associated with plasma cell dyscrasia and secondary, when associated with chronic inflammation such as tuberculosis. In a study, primary amyloidosis of the larynx showed significant increase in serum β 2 microglobulin. It was also the main component of the tissue, as shown by indirect immunofluorescence. However the clinical condition associated with this elevation was unclear. Hence it could be part of the structure of either primary or secondary amyloidosis [8].

The cause of amyloidosis is not known. Some investigators believe that amyloid deposition stems from a derangement in immunoregulation after protracted antigenic challenge that results in an immunoglobulin precursor protein that polymerizes in the extracellular space,

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producing amyloid [9]. Some authors believe that amyloid deposition stems from isolated clones of plasma cells, producers of immunoglobulin light chains that through enzyme degradation form amyloid fibrils in connective tissues [10]. Others have suggested that localized amyloidosis may arise from burnt out extramedullary plasmacytomas [11]. Evidence suggests an immunoglobulin origin of at least some cases of amyloid localized to the larynx. It is theorized that the secretion of a monoclonal plasmacytic infiltrates of the larynx are metabolized into immunoglobulin light chain fragments by adjacent histocytes and deposited extracellularly as amyloid [12].

There are many biochemical forms of amyloidosis. The commonest three are, (a) AL (light chain) primary amyloidosis is derived from plasma cells and contains kappa or lambda immunoglobulin light chains. It may be localized or systemic associated with myeloma, (b) AA (amyloid-associated) amyloidosis is a unique non-immunoglobulin protein synthesized by liver. It is a reactive systemic amyloidosis associated with acquired or hereditary chronic inflammatory diseases, (c) AB amyloidosis presents as cerebrovascular and intracerebral plaque amyloid in Alzheimer's disease and occasional familial cases [5].

Case Reports

There were five patients of localized laryngeal amyloidosis treated between Jan 2001 and March 2010 in the Department of Otolaryngology of our tertiary referral hospital.

Case Report 1

A 74 year old woman presented with 5 months history of hoarseness and dyspnoea of 1 month. Routine indirect laryngoscopy showed bilateral edematous ventricular bands partly obscuring the view of the true vocal cords. Rest of her larynx and hypopharynx were normal. On microlaryngoscopy, under jet ventilation, a smooth, raised lesion was seen in both the ventricles with normal vocal cords and subglottis. A biopsy of the lesion was done. Histopathological examination showed tissue lined by respiratory epithelium with some areas of squamous metaplasia and focal hyperplasia overlying amorphous homogenous eosinophilic material surrounded by lymphocytes, plasma cells and congested capillaries showing deposition of amorphous material in thin wall (Fig. 1). Special stains namely PAS and Congo red were positive confirming amyloidosis. A complete excision of the lesion was performed under microendoscopic vision using KTP 532 laser. The patient was evaluated for systemic amyloidosis and multiple myeloma. X-ray chest, ultrasonography of the neck and abdomen were normal. Patient's complete blood picture, coagulation profile, renal and liver

Fig. 1 Photomicrograph illustrating amorphous homogenous material surrounded by lymphocytes, plasma cells (*thick arrow*) and congested capillaries showing deposition of amorphous material in thin wall (*thin arrow*) [Haematoxylin and Eosin stain; $\times 40$]

function tests were normal. Urine Bence Jones protein was negative. Serum IgA, IgG were low and IgM was raised. Patient was on regular follow up for 6 years and asymptomatic on the last follow up with no evidence of recurrence on rigid telescopic evaluation.

Case Report 2

A 37 year old woman presented with change in voice of 8 months duration. The patient had no other symptoms. Rigid telescopic showed fullness of the right ventricular band obscuring the anterior two-third of the right vocal cord, both the vocal cords were mobile. Microlaryngoscopy done under general anaesthesia revealed a firm lesion involving the right ventricular band, right ventricle and anterior commissure (Fig. 2a). Biopsy of the lesion was done. Histopathological examination showed ciliated columnar epithelium with amorphous deposit of eosinophilic material suggesting amyloid surrounded by histocytes, giant cells, lymphocytes and plasma cells. Congo red staining confirmed the diagnosis. The patient was investigated for systemic involvement with a complete hemogram, urine routine, liver function test, renal function test, chest x-ray and ECG. All the investigations were found to be within the normal limits. Bence Jones protein was absent in the urine. Subsequently, patient underwent KTP 532 laser assisted excision of the lesion under microendoscopic vision under general anaesthesia. Patient was asymptomatic on four and a half years of follow up with no recurrence of the laryngeal lesion (Fig. 2b).

Case Report 3

A 68 year old man presented with change in voice of one and half months duration. Patient was a known

Fig. 2 Microlaryngoscopy showing a firm lesion involving the right ventricular band, right ventricle and anterior commissure (a), follow up showing no recurrence of the laryngeal lesion (b)

hypertensive on treatment. Indirect laryngoscopy showed fullness of the right ventricular band with a reddish, polypoidal mass arising from the right ventricle obscuring the view of middle third of the right vocal cord. Both the vocal cords were mobile. A microlaryngoscopy was performed and biopsy was reported as a benign vocal cord polyp. On follow up, the patient had persistent voice change and right ventricular band fullness. CT scan of the larynx showed thickening in the region of right ventricular band (Fig. 3).

Under general anaesthesia, microlaryngoscopic examination and KTP 532 laser assisted excision of the right ventricular band and the cystic lesion in the right ventricle was performed. Histopathology of the cyst specimen showed amyloidosis (PAS and Congo red positive). The patient's complete blood picture, coagulation profile, renal function tests, serum electrolytes, liver function tests, random blood sugar and protein electrophoresis were all

within normal limits. Urine Bence Jones protein was negative. Bone marrow study showed normal cellularity, maturation and cell morphology, with no evidence of multiple myeloma. In the subsequent follow ups for the last one and a half years, the patient had improvement in his voice. Clinically there was no evidence of recurrent disease in the larynx.

Case Report 4

A 52 year old woman presented with change in voice for 4 months. Patient had no other symptoms. Indirect laryngoscopy showed smooth bulge of left ventricular band obscuring view of left anterior two-third of vocal cord, anterior commissure and anterior one-third of the right vocal cord. Both the arytenoids were mobile. Microlaryngoscopic excision biopsy was performed and histopathology was reported as amyloidosis (Congo red positive). The patient's complete blood picture, coagulation profile, renal function tests, serum electrolytes, random blood sugar and protein electrophoresis were all within normal limits. Urine Bence Jones protein was negative. Patient refused further evaluation and laser excision of minimal residual laryngeal lesion. In the last 6 months, the patient was reviewed three times in our out patient department with no fresh complaints and no evidence of increase in the extent of the laryngeal lesion on rigid telescopic evaluation.

Case Report 5

A 50 year old woman presented with change in voice for 1 year. She had associated voice fatigue and dry cough for 2 months. Patient had no history of vocal abuse, hemoptysis or fever. Rigid telescopic evaluation showed congested, edematous and thickened right vocal cord. Bilateral vocal cords were mobile and rest of the larynx was normal. Microlaryngoscopy and biopsy was performed. Histopathology was reported as amyloidosis (Congo red positive).

Fig. 3 CT scan of the larynx showing thickening in the region of the right ventricular band

The patient's complete blood picture, coagulation profile, renal function tests, liver function test, serum electrolytes, random blood sugar and protein electrophoresis were all within normal limits. Urine Bence Jones protein was negative. Patient reported improvement in the voice in 3 months of follow up.

Discussion

Approximately 9–15% of amyloidosis lesions are localized [10, 11]. Most common site for localized amyloidosis in the upper respiratory tract is the larynx [5]. Most common area of laryngeal involvement is vestibule, followed by the false cords, the aryepiglottic folds and subglottic region [12, 13]. However, Finn and Farmer found the true vocal cord to be the most common site [14].

The maximum incidence of amyloidosis is in the 5th decade [15]. Two pediatric cases were reported by Naraghi et al. [16]. The youngest reported case of localized laryngeal amyloidosis is that of an 8 year old female [13]. The male to female ratio is 3:1 [10, 15, 17].

Hoarseness is the most common symptom [4, 5, 16, 18]. All the three patients in our study presented with hoarseness. Dyspnoea on exertion is occasionally reported. Stridor, hemoptysis, dysphagia, fullness in the throat and sudden airway obstruction are rare symptoms [17, 19–21]. Localized tracheobronchial amyloidosis presenting as hemoptysis is reported in the literature [22]. Lewis JE et al. [6] reported a patient of laryngeal amyloidosis who died due to development of progressive tracheobronchial amyloidosis without systemic amyloidosis.

Fullness in the ventricular band is the commonest sign [4]. In our clinical experience, ventricular band fullness is the commonest clinical sign on indirect laryngoscopy. Subglottic lesion can present as a polypoid granulation [19] or irregular lesion [20]. In the aryepiglottic fold, it can present as a smooth, well rounded submucosal mass [21] and in the epiglottis as a smooth, firm, yellowish mass [23]. The laryngeal involvement could be either a diffuse subepithelial deposition or a discrete nodule [24]. A case of laryngeal amyloidosis associated with a laryngocele has been reported [25]. Clinically, differential diagnosis for laryngeal amyloidosis includes hyalinized myomatous polyps, malignancy, granulomatous conditions like tuberculosis and scleroma of the larynx.

The appearance of the laryngeal amyloidosis on Computed Tomography (CT) scan is nonspecific. The lesion looks like a relatively well defined, submucosal, homogeneous mass. Contrast enhancement is absent or minimal. Although bone erosion has been described in skull base and spine lesions [26], head and neck amyloidomas rarely produce osteolysis. The presence of areas of localized

calcifications within the mass is not uncommon; it was reported in all cases of head and neck amyloidomas in one series [9], but was not present in laryngeal amyloidosis in another series [27]. Focal and multiple calcifications of laryngeal amyloidomas have also been reported [23]. However, the presence of focal calcifications within a laryngeal mass has been considered by several authors as highly suggestive or even pathognomonic of chondrosarcoma [28]. The presence of calcification has also been reported in chronic inflammatory disease of the larynx, i.e. in tuberculosis [29].

MRI (Magnetic Resonance Imaging) could play an important role in the differential diagnosis of laryngeal calcified masses, specifically between amyloidomas and cartilaginous tumors. The MR signal characteristic of amyloidoma reveals intensity equal to that of surrounding muscles on T1 weighted images and remains isointense or slightly hyperintense on T2 weighted images [26]. MR signal of laryngeal chondrosarcoma is hypointense or isointense relative to muscle on T1 weighted and proton density-weighted images and is definitely hyperintense on T2 weighted images, which parallels the appearance of mature hyaline cartilage [28]. Therefore, T2 signal characteristics might help differentiate calcified amyloidoma from calcified chondrosarcoma of the larynx. On MRI, amyloidosis has the same signal as skeletal muscle. This is an important differentiating point because the muscle is an easy reference frame and tumors do not appear in this manner in MRI [9].

Many authors have suggested various investigations to rule out systemic amyloidosis. They include full blood counts, erythrocyte sedimentation rate, electrolyte, chest x-ray, renal function test, liver function test, thyroid function test, electrocardiogram, echo cardiography, serum and urine electrophoresis, urine Bence Jones protein, serum immunoglobulin level, β 2 microglobulin level, bronchoscopy, chest CT [4, 20]. Some authors have suggested work up for assessment of collagen vascular diseases, tuberculosis, multiple myeloma, extramedullary plasmacytoma, rheumatoid factor, anti-nuclear antibody, purified protein derivatives, associated familial syndromes and endocrinopathies [17]. Fine needle aspiration of abdominal fat has been shown to be a simple and effective procedure to rule out systemic amyloidosis [5, 18]. Biopsies of the lip, gingiva, abdominal fat, rectum and bone marrow have been suggested [5, 12, 13, 15, 17, 18]. As these biopsies have low yield in cases of localized laryngeal amyloidosis, these invasive investigations have very limited diagnostic benefit in patients with clinically localized disease [16]. However there have been documented cases of laryngeal amyloidosis with systemic involvement (primarily in the upper respiratory tract and stomach) [18]. Hence, indications for such invasive investigation are limited to patients with

laryngeal amyloidosis who have manifestations of other system involvement such as impaired renal function [4].

Treatment of localized laryngeal amyloidosis varies from simple observation of the lesion to partial laryngectomy. Treatment with local corticosteroid injections and localized radiotherapy were found to be ineffective [5, 13]. Systemic steroids and chemotherapy are also ineffective [5, 18]. Use of an experimental small molecule drug called R-1-[6-[R-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid (CPHPC) that depletes serum amyloid P component (SAP) was described for the treatment of amyloidosis [30]. SAP typically binds to amyloid fibrils and makes them resistant to degradation. CPHPC interferes with SAP binding to amyloid fibrils and leads to rapid clearance of SAP by the liver [18]. The role of this drug in the treatment of localized amyloidosis and its safety are yet to be proven for use in routine treatment.

Management of localized laryngeal amyloidosis should be limited to local excision of laryngeal lesions when symptomatic, otherwise observation is the best treatment in asymptomatic patients [4]. Localized tumour like lesion may be completely removed endoscopically [31]. Endoscopic excision with cold knife may be adequate [32]. Microlaryngoscopy and carbon dioxide laser excision is advised as the modality of surgical management in the literature by many authors [16, 19, 20]. The clinical advantages of laser over conventional surgery in larynx are accuracy, reduced bleeding, reduced reaction (both short and long term) with faster healing and less scarring as it induces less inflammatory changes in the mucosa and submucosa. Two or more resections may be necessary to effect a complete removal of tracheobronchial [22, 33], and pulmonary amyloidosis [34]. We have used KTP 532 laser with good result. None of these three patients required repeat laser excision in an average of 4 years (1.5–6 years) of follow up. Extensive lesions compromising airway may be treated either endoscopically or by an external approach. Tracheostomy for airway obstruction by laryngeal amyloidosis has been reported [20, 21]. One of these patients underwent laryngofissure and excision of the smooth supraglottic mass which had produced sudden airway obstruction [21]. There are reports of patients requiring multiple endoscopic excisions of the laryngeal lesions for symptomatic recurrences. The authors believe that laser reduces the scarring of the laryngeal airway and subsequent stenosis in these patients. These authors also suggested that the local recurrence cases that were asymptomatic may be managed with regular follow up [4, 19, 20, 23].

Localized amyloidosis has an excellent prognosis in comparison to the systemic type [17]. There is still no cure for systemic amyloidosis. The major cause of death from systemic amyloidosis is renal and cardiac failure [1].

Conclusion

Laryngeal amyloidosis should be considered as one of the differential diagnosis in a case of long standing hoarseness with only smooth bulge of ventricular band or similar benign lesion in the larynx. Extensive investigations are not required for patients with localized laryngeal lesions in the absence of systemic symptoms as the disease rarely progresses to systemic amyloidosis. Surgical excision is better done with the use of laser for its precision and reduced scar formation. KTP 532 laser is an equally effective and efficient alternative to carbon dioxide laser. Long term follow up is advisable.

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