

# Primary amyloidosis of the larynx

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## ABSTRACT

Laryngeal amyloidosis is a rare condition accounting for less than 1% of all benign laryngeal tumors. With slightly of male preponderance, the incidence is more common in fifth to seventh decade of life. We report a case of primary laryngeal amyloidosis presented in a 40-year-old Malay lady, who presented with chronic hoarseness. The lesion was completely excised with endoscopic laser treatment.

**Keywords:** Amyloidosis, immunoglobulin light chain, larynx

## INTRODUCTION

Amyloidosis of the larynx is rare, accounting for between 0.2 and 1.2% of all benign tumours of the larynx. The incidence increases with age but occasionally young adults are affected. <sup>1</sup> The presentation is usually with local symptoms. However it also may be a part of systemic disease, the result of a familial condition, a primary disorder, or secondary to an underlying disease or tumour proliferation. <sup>2</sup>

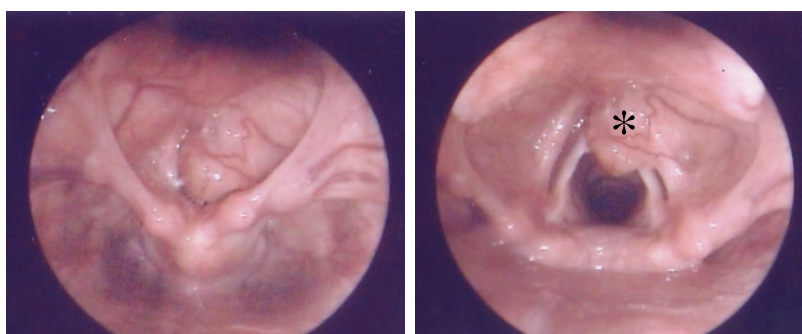
In amyloidosis of the larynx, there is a predilection for supraglottic involvement (54.1%), with the ventricle and false cords being the most common subsites, followed by involvement of the glottis (18.9%), transglottic (16.2%) and tracheal (10.8%). <sup>3</sup>

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## CASE REPORT

A 40-year-old Malay lady presented with complaint of hoarseness for the previous 10 years. The hoarseness remained static during this period, sometimes worsened by underlying upper respiratory tract infection or with frequent throat clearing. Apart from this, there was no significant history of odynophagia, dysphagia or reflux. There was no dyspnoea or noisy breathing. There was no history of previous neck trauma or instrumentation such as endotracheal intubation. She had history of asthma and mild dyspepsia relieved with treatment; salbutamol inhaler and oral ranitidine, taken on intermittent basis.

On examination, she was well and good built. There was hoarseness, but without any vocal fatigue and breathlessness. She was comfortable at rest without any respiratory distress or stridor. The laryngeal framework was normal and the laryngeal crepitus

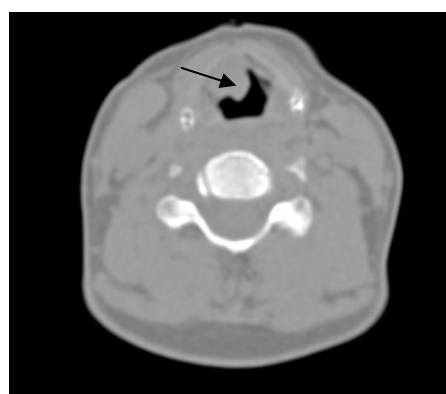


**Figs. 1: a) A mass (\*) was seen obscuring both glottis during phonation, and limited to the right false cord with suspicious of anterior commissure involvement on inspiration**

was present. There was no palpable neck lymph nodes. Thorough oral and nasal endoscopic findings were unremarkable. On a 70 degree rigid endoscopy, there was a smooth mass arising from the right false cord, extending partly into the left false cord anteriorly and further occluding the anterior commissure (Figure 1). Both the vocal cords were mobile and symmetrically placed. The arytenoids were normal bilaterally.

Blood investigations including full blood count and renal function test were normal. Chest radiograph and electrocardiogram was normal. A contrast computed tomography (CT) scan of the neck showed a well-defined supraglottic mass originating from the right anteromedial wall, protruding into the laryngeal ventricle. It measured 1.3cm x 1.2cm x 0.7cm with slight narrowing of the laryngeal ventricle (Figure 2). Otherwise, the airway was patent.

The patient was counselled for surgery and proceeded to a laser-assisted endoscopic laryngeal micro surgery. Intraoperatively, the mass was noted to involve the anterior two-thirds of the right false cord sparing the left false cord. The anterior commis-



**Figure 2: The mass was benign looking, originated from right supraglottic level (Arrow).**

sure was spared. The mass was excised in toto using carbon dioxide laser.

Histopathological examination of the mass revealed an extracellular amorphous eosinophilic substance deposited within the stroma (Figures 3). The substance stained positive for Congo-red and exhibited an apple-green birefringence under polarised light confirming the diagnosis of amyloidosis.

The patient was discharged on the second post-operative day. Her voice had normalised when seen two weeks later. Currently at four months post-excision, she remained

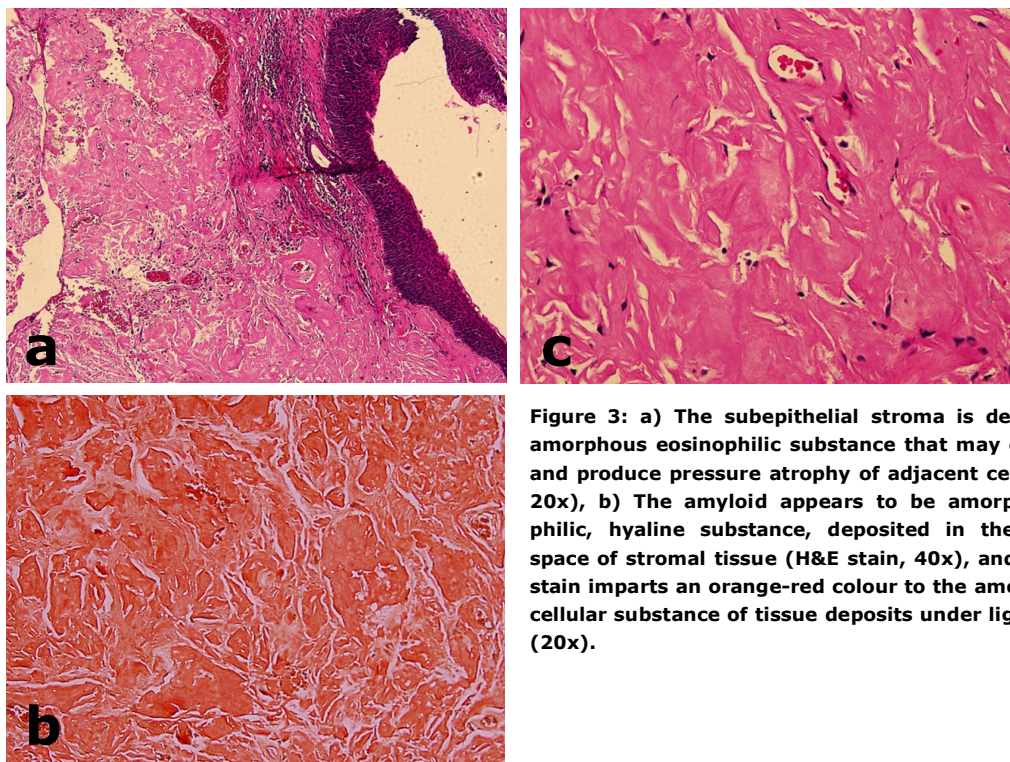


Figure 3: a) The subepithelial stroma is deposited by an amorphous eosinophilic substance that may encroaches on and produce pressure atrophy of adjacent cells (H&E stain, 20x), b) The amyloid appears to be amorphous, eosinophilic, hyaline substance, deposited in the extracellular space of stromal tissue (H&E stain, 40x), and c) Congo-red stain imparts an orange-red colour to the amorphous extracellular substance of tissue deposits under light microscopy (20x).

well with no evidence of recurrence (Figure 4).

## DISCUSSION

Amyloid is a pathologic proteinaceous substance that is deposited in the extracellular space in various tissue and organs in a wide variety of clinical settings. Ultra-structurally, it is made up largely of continuous, non-branching fibrils that wound around one another with regular space that bind with the Congo red dye. <sup>4</sup> Amyloidosis is a benign and results from abnormal folding of proteins which are deposited as fibrils in extracellular tissues and disrupt normal function.<sup>4</sup>

Amyloid may be systemic (generalised) when it is involved several organ system or localised when deposits are limited to a single organ, such as the heart.

On clinical grounds, the systemic type is further sub-classified into primary and secondary amyloidosis. <sup>5</sup> The hereditary or familial amyloidosis constitutes a separate and heterogeneous group. <sup>4</sup>

Biochemically, the three most common amyloid proteins are AL (amyloid light chain, derived from Ig light chains produced in plasma cells), AA (amyloid associated, non-



Figure 4: Laryngoscopic appearance at four months post surgery showing no recurrence.

Ig protein synthesised by the liver) and A $\beta$  (from  $\beta$  amyloid precursor protein found in Alzheimer disease).<sup>4</sup> The primary amyloidosis is associated with some immunocyte disorder, thus the AL-amyloid immunoglobulin light chain predominates,<sup>6</sup> whereas secondary amyloidosis occurs as a complication of chronic inflammatory disorders and is represented by amyloid A protein (AA).<sup>5</sup> The familial and senile systemic amyloidosis are represented by wild type and mutant transthyretin molecules.<sup>7</sup> To differentiate between AA and the other forms of amyloidosis, it requires potassium permanganate sensitivity of which AL and familial amyloidosis are resistant.<sup>7</sup>

Typical sites affected by localised amyloidosis without systemic involvement are the skin, brain, bladder, ureter, urethra and renal pelvis. Other sites include the conjunctiva, larynx and tracheobronchial tree.<sup>8</sup> At least in some cases, the amyloid consists of AL protein and may therefore represent a localised form of immunocyte-derived amyloid.<sup>4</sup> Most of the laryngeal amyloidosis are of AL type.<sup>6</sup> Our patient also fits in into the criteria of laryngeal amyloidosis of AL type. It may not be necessary to perform a battery of investigations such as submucosal gingival biopsy, rectal biopsy and bone marrow biopsy to rule out systemic disease.<sup>2</sup>

The diagnosis is based on the finding of amorphous eosinophilic, hyaline, extracellular substance with hematoxylin and eosin stains and Congo-red stains imparts a pink or red colour under an ordinary light microscope. When observed under polarising microscopy, the Congo-red stained amyloid shows an apple green birefringence. Electron microscopic

examination shows a continuous nonbranching fibrils. X-ray crystallography and infrared spectroscopy demonstrate a characteristic cross- $\beta$ -pleated sheet conformation.<sup>4</sup>

Congo-red staining may be falsely negative if the tissue sections are less than 5  $\mu$ m thick.<sup>9</sup> In our patient the mass was excised en-bloc and measured 22 mm in aggregate diameter. The deposits of amyloid, proteinaceous aggregates have a high fluid content and can occur as a diffuse submucosal process or as small subepithelial masses. In our patient, the presentation was of small mass involving one of the supraglottic subsites, the right false cord.

Our patient has suffered from laryngeal manifestation for many years without any other systemic manifestation. Biochemical tests on other vital organs in systemic amyloidosis presentation such as the kidney, liver and heart were normal. If left untreated, it can cause local obstruction. Local primary lesions rarely progress into systemic amyloidosis. In amyloidosis of the larynx, hoarseness is the main presenting symptom. Other symptoms which include dysphonia, dyspnoea, haemoptysis and dysphagia may be present in such similar cases.<sup>5</sup> The type and severity of presentations depend on the site of the lesion. The sites which are commonly involved are the ventricles, false cords, vocal cords, aryepiglottic folds and the subglottic.<sup>5</sup> There is no preponderance to a specific location in the larynx that is more frequently affected by amyloidosis, instead all parts of the larynx can be affected.<sup>2</sup>

Other diseases that can mimic or be associated with amyloid in the larynx includes

small cell carcinoma of the larynx or medullary carcinoma of the thyroid that has invaded the larynx.<sup>2</sup> It is imperative to exclude these adjacent structural pathology. Besides clinical and radiological appearances, this diagnostic differential usually can be assessed with the application of immunohistochemical antibodies for keratin, chromogranin, calcitonin, or other neuroendocrine markers on the biopsied material after confirmation of amyloidosis.

As for imaging assessment, amyloidosis appears as marked thickening in the laryngeal soft tissue on CT scan whereas on MRI it appears as the same signal of skeletal muscle.<sup>5</sup> This is rather useful in differentiating a case of amyloidosis and malignancy, as malignancy does not appear in this manner on MRI. If there is a high index of suspicion it is wise to obtain an MRI. However in this case the presentation and clinical assessment are more towards a benign laryngeal lesion.

In order to preserve voice quality and maintain the airway patency, the treatment of choice in such a localised amyloidosis as in our patient is either via cold endoscopic excision method or using carbon dioxide laser. Corticosteroids have no effect on management of laryngeal amyloidosis.<sup>10</sup> As the patient has localised AL, systemic treatment is not indicated and the patient was managed by localised treatment.<sup>9</sup>

Supraglottic amyloidosis present as larger deposits and are diffuse, thus making carbon dioxide laser a helpful tool in removing the lesion. The aim of excising the mass via carbon dioxide laser is to maintain the airway and also minimise further procedures on the patient as each potential procedure can lead

to further scarring and intralaryngeal webbing. If in a case of glottic amyloidosis, in which small deposits are located at the critical anatomical sites, it is preferably to use cold endoscopic excision. Our patient was doing well in her follow up, with good recovery of voice and no recurrence noted. However, being a supraglottic amyloidosis, it is stated that the underlying clonal plasma cell population is often diffuse and thus sometimes if not excised in total, patients may require a repeat removal of the amyloid deposits.<sup>6</sup>

On conclusion, localized amyloidosis of the larynx is a rare condition and also has rare progression into systemic amyloidosis. It is a slow progressive disease and should be treated accordingly to the underlying complaint. Invasive investigations should be limited to those who present with systemic manifestation otherwise in a case of localised laryngeal deposits only require routine investigations such as full blood count, renal function test and liver function test. Mainstay of treatment is excision, with carbon dioxide laser being more superior followed by observation. Long term follow up is essential due to the slow progressive nature of the disease.

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