Progression, Treatment and Follow-Up of Laryngeal Amyloidosis: A Report of 4 Cases

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Abstract

Background: Laryngeal amyloidosis is rare, representing 1% of benign tumors of the larynx. It is usually a localized amyloid light-chain (AL) amyloidosis. The most common symptom is dysphonia hoarseness.

Aim of Study: To report the four cases who presented with laryngeal amyloidosis and to describe their outcomes during a long-term follow-up. Each patient underwent at least one surgical procedure for this condition. The entire amyloid tissue was completely excised in only one case without recurrence. In the three other cases, the lesion increased slowly in the larynx. An extension into the trachea was observed in one case. In conclusion, laryngeal amyloidosis is a benign disease, but its location within the larynx may be associated with functional impairment in terms of phonation, swallowing and breathing. To improve function, the treatment of this evolutive disease may involve surgical removal (complete or incomplete), radiation therapy or simple follow-up.

Conclusions: Laryngeal amyloidosis is difficult to cure while preserving laryngeal function. Regular laryngoscopic follow-up is justified due to the potential of recurrence. Multiple surgical procedures may be required and may be combined with other therapeutic modalities, including new radiation therapy techniques. However, long-term follow-up for at least 10 years is fundamental not only because of the recurrence but also because of the possible development of systemic disease.

Key Words: Laryngeal amyloidosis – Case report.

Introduction

AMYLOIDOSIS is a disease that is characterized by the presence of extracellular deposits of insoluble protein in tissues [1]. There are systemic and localized forms. They are classified into primary, which develops spontaneously or secondary to chronic inflammatory diseases [2]. The affected organs can be the kidney, heart, gastrointestinal tract, liver, skin, peripheral nerve, eye, almost all the sensory organs, and eventually almost all tissues [3,4].

The classification of amyloidosis is based on the clinical signs and the biochemical structure of the amyloid protein present in the deposits. The most common types of amyloidosis are AA (inflammatory), AL (immunoglobulin), and ATTR (transthyretin). Amyloidosis is usually localized and AL type and results from pathological deposits of fibril protein composed of an immunoglobulin light chain (L) produced by monoclonal lymphoplasmacytic proliferation [1].

The diagnosis of amyloidosis is made histologically [8]. The specificity of the amyloidosis is the apple-green birefringence under polarized light after Congo red staining [1]. Amyloidosis is a benign disease, but its development can be severe according to the affected organ. Because it interferes with the normal structures, the amyloidosis can therefore affect the normal functioning of that organ [5].

Laryngeal amyloidosis is a rare entity and constitutes only 1% of benign localized laryngeal tumors. It is usually a localized amyloid light-chain (AL) amyloidosis. However, laryngeal involvement will hinder the functions of phonation, swallowing and breathing. The prognosis is also functional and vital. The most common clinical presentation is changes in the voice, most often becoming raspy. Other clinical signs include dysphagia, dyspnea, and stridor [6].

We aim to report the cases of four patients who presented with laryngeal amyloidosis and to describe their outcomes during a long-term follow-up.
Case Reports

Case 1:

This patient was treated for laryngeal amyloidosis in 1998 when she was 11 years old. The first symptom was dysphonia, beginning 2 years before. The laryngostroboscopy revealed a swelling of the right false vocal fold with an infiltration in the area of the intersection of the three folds (pharyngoepiglottic, aryepiglottic and glossoepiglottic). The right arythenoid was almost fixed. An MRI and a CT scan of the larynx revealed a right paralaryngeal mass next to the vestibular fold, extended upward inside the aryepiglottic fold toward the pre-epiglottic space remaining under the vallecula and extended down to the vocal fold. Under general anesthesia, biopsies were performed, leading to the diagnosis of AL amyloidosis.

A complementary assessment was performed with rectal and skin biopsies, echocardiography, abdominal and renal ultrasounds, sinus X-rays, immunoassays (immunoglobulins, protein electrophoresis), and renal test searching for hematuria and proteinuria. The results were all negative.

The treatment was by complete surgical excision of the lesion by an external approach. The procedure consisted of an excision of a tissue flap at the expense of the right vestibular fold. The dissection was extended from the intersection of the three folds up to the perichondrium of the thyroid cartilage externally and down to the vocal fold, preserving the vocal muscle. This procedure allowed a full resection of the lesion, which appeared as yellowish and irregular. The entire sample was histologically infiltrated with amyloid deposits.

Subsequently, the patient presented a granuloma at the anterior part of the vocal fold, which was treated with laser vaporization.

Two years after the surgery, the laryngostroboscopy found a right fixed hemilarynx and scar replacing the missing vocal fold (Fig. 1). The left hemilarynx was normal and mobile, and the closure in phonation was complete.

For 5 years, the patient remained stable with persistent hoarse voice (hoarseness) and without respiratory distress or a swallowing disorder. Six years after the surgery, the dysphonia worsened, related to a vocal fold cyst on the left side. The excision of the cyst was performed by microsurgery associated with fat injection in the right side with the goal of stabilizing her voice. During this operation, which was performed 7 years after the original surgery, the absence of recurrence of amyloid lesions was confirmed. This patient, who initially underwent a complete tumoral resection, is now 24 years old and has maintained a stable outcome with no evidence of recurrence.

Case 2:

A 61-year old man was seen in 2005 because of hoarseness that had progressed for 2 years. He had no complaint of dysphagia or dyspnea but described the sensation of intermittent gastroesophageal reflux.

He had multiple comorbidities with hypertension and diabetes, and his previous history included a thyroid surgery, myocardiac infarction with stents, and inferior limb arteriopathy with a right iliofemoral bypass. This patient had never presented alcohol or tobacco intoxication.

At the examination, there was an inflammation of the upper part of the larynx, hypertrophy of the base of the tongue, an aspect of edema of the vocal folds and a cyst-like aspect inside the right ventricle. The patient was advised first to perform voice therapy to treat the signs of muscle tension dysphonia. His voice outcomes were very limited, and a new examination revealed a growth of the lesion localized inside the right ventricle and the appearance of the same type of lesion on the left ventricle. These lesions appeared to interfere with the vibrations of the vocal folds.

A laryngeal CT scan and an examination under general anesthesia were then performed. The CT scan confirmed the existence of a tissue process in the right vestibular fold and the anterior third of the left ventricle. The examination under general anesthesia found mainly swelling that had developed in the middle and anterior right ventricle, infiltrating the vestibular fold and reaching the anterior commissure above the glottic plane. The biopsies found that the mucous connective tissue contained small eosinophilic acellular deposits appearing congophilic and birefringent with Congo red staining, confirming the diagnosis of amyloidosis. The general assessment eliminated systemic amyloidosis (echocardiography, abdominal ultrasound, rectal biopsy, liver function test, renal function test, and immunoassay). The management decision was to follow-up the patient and the bulging appearance of the two ventricles every 3 to 6 months.

Three years after the beginning of the management, worsening dysphonia was associated with an increased volume of the lesions, leading to the decision to perform a surgical resection. This resection consisted of a CO\textsubscript{2} laser resection with
excision of the lesion of both vestibular folds. The samples were fully infiltrated by amyloid deposits. The postoperative clinical exam showed persistent lesions on the residue of the right vestibular fold and inside the left aryepiglottic fold.

Six months after the first surgery, the patient complained of a recent change in his voice. The laryngoscopy revealed, in addition to the persistence of the lesion observed in the post-op examination, an anterior synechia. A new surgical procedure was then performed with a CO$_2$ laser excision of the lesion of the third front of the right vestibular fold. The anterior synechia remained.

One year after the second procedure, the patient had no specific complaints, but an examination revealed a recurrence of the injury in the area of the left vestibular fold and persistence of the synechia (Fig. 2).

A CT scan was performed and did not detect a new infiltration. The patient then underwent microsurgery, enabling the resection of the lesion in the left vestibular fold and the opening of the anterior synechia. However, the resection could not be completed.

After the microsurgery, his voice remained hoarse, and an examination revealed abnormalities in the anterior commissure and a smaller synechia (Fig. 3), which remained stable until the last examination performed on October 2010.

Thus, the follow-up period of 6 years showed that the amyloidosis, which had never been completely resected, had grown slowly. The surgical indications remained not aggressive due to the good functional tolerance.

**Case 3:**

A 49-year old man was seen in 2007. His complaint was a recent dysphonia with a hoarse voice. He had no particular history and no treatment. The first ENT examination favored a nodule of the left vocal fold, and a microsurgery was performed, removing the mucosa and also part of the vocal ligament because of the discovery of an infiltrating lesion during the operation.

The pathological examination revealed leucokeratosis. Despite this procedure, his dysphonia worsened, and 6 months later, a new examination revealed a normal appearance of the right vocal fold but with reduced mucosal waves and an increased volume of the left vocal fold with dehiscence on the posterior third, which may be related to the previous surgery. An exploration under general anesthesia with a laryngeal fat injection to reduce the lack of glottis closure was proposed. Under microsurgery, a yellowish infiltration involving the right vocal fold in the posterior third was observed.

The same type of infiltration was noted in the entire contralateral vocal fold. Biopsies and a fat injection in the posterior third of the left vocal fold were performed and revealed AL amyloidosis. A full assessment was then performed and was normal.

The patient was regularly monitored throughout 2009. An important dysphonia remained, but the increasing volume of the left vocal fold justified a new sample on that side, which revealed the amyloid tissue. The treatment was completed in April 2010 by a remodeling of the left vocal fold with the aim of improving his voice, without any outcome. The follow-up decision was to not surgically treat the amyloidosis due to the significant risk of sequelae on the voice.

The endolaryngeal amyloid lesions remained stable with the persistence of reduced vibrations of both vocal folds (Fig. 4). A CT scan revealed an infiltration with a bilateral glottic extension up to the tissue of the paraglottic space (Fig. 5).

This patient raised the issue of a debilitating laryngeal amyloidosis with severe dysphonia and lesions that cannot be completely resected without risking further deterioration of his voice. The therapeutic approach remains unmodified because the surgical risk of the resection is higher than the current functional impairment.

**Case 4:**

This woman was 53 years old when she presented with dysphonia, justifying her first examination in 1985. She had no previous medical history and did not smoke or consume alcohol. The laryngoscopic examination showed an anterior subglottic stenosis. She was treated with CO$_2$ laser microsurgery, and the analysis of the samples led to the diagnosis of laryngeal amyloidosis. Then, she was lost to follow-up for 10 years.

She consulted our department again in 1995 for dysphonia and dyspnea limiting her physical activities. The review found a descending circumferential subglottic lesion of 3cm, which reduced the space by 50%. The swelling was yellow, firm, striated by vessels, and developed from both vocal folds. The same lesions were visualized in the anterior commissure and at the interarytenoid area. Biopsies were performed and revealed amyloid material. The resection of these lesions was performed by CO$_2$ laser 3 months later.
Fifteen days after the surgery, we found that the larynx was healing with only a grainy lower edge of the right vocal fold. A general assessment revealed no abnormalities. Her follow-up examinations were stable until 1998, and then the patient was again lost until 2010. She returned due to worsening of the dyspnea. The examination showed a development of the amyloidosis, which extended upwards to the anterior commissure, the foot of the epiglottis, and two third of the vestibular folds, thickening the vocal process posteriorly with a possible forward subglottic extension (Fig. 6).

A CT scan (Fig. 7) revealed that this extension reduced the glottis laryngeal sector by 50% as well as the trachea, making complete resection impossible or disproportionate to the functional consequences of this benign disease. Reducing the volume of the lesion to unblock the trachea and glottis laryngeal sector was considered, but the patient wished for a simple follow-up. She presented a worsening of functional impairment for which a surgical tracheal dilatation was done for here after which was complicated by a tracheal stenosis for this reason a tracheotomy was performed for here.

She was then treated by a low dose of radiation (24 Gy) for the remaining tracheal and laryngeal lesions. By the end of this treatment weaning of tracheostomy was realized without difficulties. And the patient maintained a stable condition.

Table (1): Description of cases.

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Site</th>
<th>Amylose type</th>
<th>Management</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>Right paralaryngeal region</td>
<td>Localized AL</td>
<td>Complete surgical excision</td>
<td>Complete cure</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>Laryngeal ventricles, bilaterally</td>
<td>Localized AL</td>
<td>Complete surgical excision</td>
<td>Slowly progressive</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>Vocal cordes, bilaterally</td>
<td>Localized AL</td>
<td>Partial surgical excision</td>
<td>Slowly progressive, disabeling</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>Glottic, paraglottic regions bilaterally, trachea</td>
<td>Localized AL</td>
<td>Surgery and Radiotherapy</td>
<td>Extensive, very debilitating</td>
</tr>
</tbody>
</table>

Fig. (1): Laryngoscopic view of the larynx of case 1, showing right immobile hemilarynx scar and normal left vocal cord.

Fig. (2): Laryngoscopic view of the larynx of case 2, showing anterior synechia and a small lesion of the left vestibular fold.

Fig. (3): View of the larynx of case 2 after the last surgery, showing anterior synechia without a visible lesion at the left vestibular fold.

Fig. (4): Laryngoscopic view of case 3, showing symmetric vocal folds with a yellowish aspect visible on the third part of the right vocal fold.
Fig. (5): Computed tomography scan. axial (A) and coronal (B) reconstruction. Laryngeal tissue infiltration affecting the two vocal cords, ventricular folds predominantly to the left side and the anterior commissure with the para-glottic spaces are affected predominantly in the right side.

Fig. (6): Laryngoscopic view of case 4: Extension to two-thirds of the vestibular folds, a thickened vocal process and a yellowish subglottic injury.

Fig. (7): Computed tomography scan of case 4 (axial and sagittal reconstruction), showing laryngeal tissue infiltration affecting the two vocal cords, the anterior commissure, the ventricular folds and the paraglottic spaces predominantly to left side. Sub-glottic extension is also noted in the sagittal reconstruction.
Discussion

In our series and in the literature, laryngeal amyloidosis is typically primary and AL type [6,8,10,11]. As previously described, these four cases illustrated that amyloidosis could affect both genders and individuals of any age. The disease occurs most often in the 5th and 6th decades [2] and preferentially affects males [8].

Yiotakis et al., [6] described the youngest case of laryngeal amyloidosis in the literature, involving a child of 11 years old. Our case 1 was 9 years old at the beginning of her symptoms and was treated at the age of 11. This case provides evidence that the disease may possibly begin before 10 years of age. The symptoms most frequently reported in cases of laryngeal amyloidosis are hoarseness and dyspnea. Other symptoms reported in the literature, but absent in our cases, were dysphagia and hemoptysis [6,8,12].

The diagnosis of localized amyloidosis requires a systematic search of other sites for better therapeutic management. This assessment includes an interview, physical examination, laboratory tests generally examining serum electrolytes, urinary test for proteinuria and hematuria, liver test, echocardiogram, electrocardiogram, protein electrophoresis, and a biopsy of at least one other site [7]. Some authors also discuss the indication for an abdominal ultrasound, bone marrow biopsy, or other tests guided by the physical examination [5,8]. A 123I-SAP scintigraphy appears to be helpful but is rarely used [8,9]. In our four cases, the assessment performed favored the diagnosis of localized amyloidosis, and the follow-up examinations confirmed this diagnosis. However, the patients should be followed-up for at least 10 years due to the possibility of developing systemic disease [6,8,10,12].

The prognosis for patients with localized laryngeal amyloidosis is excellent if the lesions can be removed entirely. However, as emphasized by Piazza et al., [14], “complete regression of disease after endoscopic and/or open neck surgery is possible, but occurs rarely and should be therefore considered the exception instead of the rule”.

The first line of treatment is usually surgical excision by CO2 laser, cold resection or some other endoscopic technique [2,5,6,10,12]. Occasionally, the resection can be performed by thyrotomy. Rarely, a total laryngectomy has been indicated because of extensive pharyngolaryngeal or laryngotracheal amyloidosis [10]. Radiation therapy is not recommended, as a first line treatment for localized laryngeal amyloidosis. Because of the difficulty of complete excision, Neuner et al., [15] recommend a combination of surgery and radiation therapy to cure this disease. Medical treatment (local or systemic cortico steroids, colchicines, melphalan and chemotherapy) may be the treatment of choice for certain types of systemic amyloidosis [1,3,5,11,16].

In summary, the tendency of the lesions to recur justifies the repeated use of endoscopic resection as long as possible, along with conservative management to preserve laryngeal function [17]. We emphasize a long-term follow-up with regular laryngoscopic examinations for recurrence. Further studies are needed to determine the efficacy of radiation therapy, that is, whether a radiation dose response relationship for controlling localized laryngeal amyloidosis exists [13]. This option combined with surgery appears to be a solution to cure the disease when the extension becomes difficult to control.

In conclusion, laryngeal amyloidosis is a rare benign entity and is difficult to cure while preserving laryngeal function. Regular laryngoscopic follow-up is justified due to the potential of recurrence. Multiple surgical procedures may be required and may be combined with other therapeutic modalities, including new radiation therapy techniques. However, long-term follow-up for at least 10 years is fundamental not only because of recurrence but also because of the possible development of systemic disease.

References


