Familial primary localized laryngeal amyloidosis in two sisters

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Laryngeal amyloidosis is rare, accounting for less than 1% of all benign laryngeal tumors. Although familial primary localized amyloidosis has been reported in other parts of the body, no familial cases have been reported in the larynx. Primary localized laryngeal amyloidosis was detected in two sisters whose ages were 35 years and 38 years, respectively. In the elder patient, a previous endolaryngeal biopsy for symptoms of dysphonia yielded no pathologic findings. Laryngoscopic examination of the patient showed a significant submucosal accumulation at the level of ventricles and vocal folds. The younger sister had a complaint of hoarseness for five years. The results of endolaryngeal biopsies performed in both patients were reported as amyloidosis. Further evaluations were negative for systemic amyloidosis. No surgical intervention was considered. The patients were monitored for more than two years without any other coexisting disease.

Key Words: Amyloidosis, familial; biopsy; laryngeal diseases/diagnosis; larynx/pathology.

Amyloidosis is a benign idiopathic disorder characterized by the extracellular accumulation of normally soluble proteins in an abnormal fibrillar form, leading to tissue damage and disease. Amyloidosis comprises a family of disorders. Modern classification of amyloidosis is based on biochemical characterization. Amyloidoses are referred with a capital A to denote amyloid and additional abbreviations for the fibril proteins. Twenty different fibril proteins and consequently 20 types of human amyloidoses have been identified. Amyloidoses are classified by the following three parameters: (i) The fibrillar protein making up the amyloid deposit; (ii) The precursor protein from which the amyloid...
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was derived; (iii) The clinical description of the disease process.

Amyloid deposition may be either localized or systemic and either primary or secondary.\(^2\)

Tumor-like, organ-limited amyloidosis is a relatively rare, but well recognized condition. It is usually not accompanied by plasma-cell dyscrasia and not followed by systemic disease. The common sites of involvement include the respiratory tract,\(^4\) skin,\(^5\) and the urinary bladder.\(^6\)

In this report, two non-smoker sisters with laryngeal amyloidosis were presented.

**CASE REPORT**

The two sisters were at the age of 35 years and 38 years, respectively. The elder patient had symptoms of dysphonia for nearly 10 years and had a history of an endolaryngeal biopsy under general anesthesia, whose record was unavailable. She was told that the biopsy was “negative” and “clean”. She described a two-year period of decreased symptoms after biopsy; however, she always had a hoarse and breathy voice for years. Videolaryngostroboscopic examination of the patient showed a significant submucosal accumulation at the level of ventricular folds, ventricles, and vocal folds (Fig. 1). Mucosal waves were significantly decreased and even nearly absent in both vocal cords. Computed tomographic images did not show specific changes except for submucosal thickening in the abovementioned areas. An endolaryngeal biopsy under local anesthesia was reported as amyloidosis.

The younger sister had had a hoarse voice for nearly five years. She never had a biopsy before. She was given drugs for upper respiratory tract infections twice by a general practitioner for dysphonia. An endolaryngeal biopsy was performed under local anesthesia and histopathologic examination was reported as amyloidosis (Fig. 2). In both patients, further evaluations were negative for systemic amyloidosis. They did not have any other symptoms except dysphonia. Both patients were followed-up without any surgical intervention for more than two years.

**DISCUSSION**

In the head and neck, localized amyloidosis is most common in the larynx. Other sites include the salivary glands, oral cavity, pharynx, nasopharynx, sinonasal cavities, larynx, trachea, bronchi and lungs, and lymph nodes.

Laryngeal amyloidosis is usually a primary and localized disease and is classified as AL/kappa/primary or AL/lambda/primary. Multifocal disease is present in up to 15% of patients. Amyloidosis of the larynx is rare, accounting for less than 1% of all benign laryngeal tumors.

Laryngeal amyloidosis may affect individuals at the age of 11 to 80 years, with a peak incidence in the fifth decade.\(^7\) Male to female ratio is usually equal, but different ratios between 1:1 and 3:1 were reported.\(^8\) The etiology of amyloidosis remains unknown. There is no direct relation with vocal abuse, recurrent infections, or smoking. Most authors defined laryngeal amyloidosis as isolated, without systemic

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**Fig. 1.** Videolaryngoscopic image showing subepithelial amyloid deposits especially in the left vocal fold.

**Fig. 2.** Videolaryngoscopic image showing subepithelial amyloid deposits in both vocal folds.
involvement. However, systemic involvement was reported in 7% of 177 patients with laryngeal amyloidosis. Although rare, systemic evaluation should be considered because the disorder may occur in association with an underlying lymphoid neoplasm like multiple myeloma or extramedullary plasmacytoma. Amyloidosis of the larynx may also be of the secondary type, i.e. related to tuberculosis, malignant tumors, osteomyelitis, myocarditis, or rheumatoid arthritis. This possibility has to be excluded, as well.

Clinical presentation varies depending on site of involvement. Fibril accumulation causes progressive disruption of the structure and function of involved tissues and organs. Within the larynx, the ventricles and false vocal cords are most frequently affected. Amyloid may involve the hypopharynx and mimic a post-cricoid tumor. Hoarseness is the main symptom; however, dysphagia and cough may be the presenting symptoms, as well. The speed of progression is unpredictable. A patient with 17 years of non-growing amyloid was reported. Rare cases presenting with an acute onset of airway obstruction have also been reported. Although localized amyloidosis of the larynx is usually described as a non-bleeding lesion, mortality due to hemorrhage secondary to localized laryngeal amyloidosis has also been reported. Computed tomography or magnetic resonance imaging may be helpful in showing the extent of the disease. Extralaryngeal respiratory involvement is reported in 15 to 40%, emphasizing the need for a complete endoscopic examination to rule out coexisting lesions.

Localized laryngeal amyloidosis might be classified into two main categories, the nodular and diffuse infiltrative types. The nodular type consists of discrete masses of amyloid deposits in the larynx, usually in the vestibule, less frequently in the ventricular and vocal folds, or subglottis. It may be sessile or pedunculated, and is often multiple. It is more dangerous because of the potential risk for causing acute respiratory obstruction. In the diffuse infiltrative type, extensive subepithelial deposits of amyloid are seen in the larynx, starting usually at the glottis and extending downward by contiguity to the tracheobronchial tree for a variable extent. It may result in progressive stenosis of the airways. Both types may occur in all regions of the respiratory tract and many cases have been described in which both types were present.

A detailed family history and physical examination are required. Complete blood cell count, liver and renal function tests, urine laboratory tests to rule out Bence Jones proteinuria, chest radiography, technetium pyrophosphate cardiac imaging, and directed biopsies may be warranted. Areas to be biopsied may include the rectum, abdominal fat, lip, kidney, liver, bone marrow, and skin. Abdominal fat fine-needle aspiration biopsy is now the method of choice for tissue confirmation of systemic amyloidosis, with a positive predictive value of 100% and a negative predictive value of 85%. Rectal biopsy is also preferred to demonstrate generalized amyloidosis, as it is positive in 84% of the cases. A bone marrow biopsy may be performed to rule out multiple myeloma. Hematologic consultation is usually recommended for systemic involvement in all cases of upper aerodigestive tract involvement.

Familial primary localized amyloidosis is an extremely rare disease, reported in cases of endocrine, senile, cutaneous, and corneal amyloidosis. Although the larynx is the most frequently affected site in primary localized amyloidosis, no familial cases have been reported in the larynx.

Amyloidosis of the upper aerodigestive tract can not be diagnosed by visual inspection alone, because the clinical appearance mimics other lesions. On laryngoscopy, amyloid appears as a yellow, gray, or red subepithelial mass and may be mistaken for a benign vocal polyp or laryngcele. Computed tomography or magnetic resonance imaging may be helpful in mapping lesions, which may be more extensive than they are seen during laryngoscopy. Amyloid has also been imaged with radiolabeled serum amyloid P component. Nonetheless, a biopsy is required for pathologic review and definitive diagnosis.

The most effective treatment currently available for organ-limited laryngeal amyloidosis is microlaryngoscopic excision. Multiple surgeries are required commonly to remove residual or recurrent amyloid deposits. Staged excisions often preserve laryngeal function and are usually preferable to radical surgical extirpation compromising postoperative voice and swallowing functions. Use of the CO2 laser has increased in recent years. The goal of the treatment is to provide a stable airway while maintaining stable voice quality. In severe cases, a tracheotomy is required for airway stabilization. Adjuvant therapies such as irradiation, chemotherapy, or steroids have no
proven benefit in the treatment of the disorder.\textsuperscript{16,19} Recurrence of laryngeal amyloidosis is common and expected, with some occurrences up to 14 years after initial presentation and treatment.\textsuperscript{16} Regular follow-up, with frequent laryngeal examinations and periodic imaging studies, is required to detect recurrence at an early stage. Recurrences may present as an ongoing amyloid deposition or residual disease secondary to incomplete removal of extensive, multifocal, submucosal amyloid deposits.\textsuperscript{16}

REFERENCES