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CASE REPORT

Isolated Laryngo-tracheal Amyloidosis Presenting as a Refractory Asthma and Longstanding Hoarseness

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Respiratory tract amyloidosis is characterized by deposition of amyloid fibril protein at any site along the respiratory tract ranging from the larynx to the pulmonary parenchyma. Usually, it is not associated with primary systemic amyloidosis. We report a case with isolated laryngo-tracheal amyloidosis, which is relatively a rare condition, together with a history of refractory asthma accompanied with longstanding hoarseness.

Keywords amyloidosis, larynx, trachea, hoarseness, asthma

CASE

A 41-year-old woman was referred to our clinic with dyspnea and hoarseness. She had been diagnosed with allergic rhinitis and asthma 15 years ago. She had used inhaled corticosteroid and long-acting beta₂ agonist. She was successfully treated with this therapy until the past 2 years. Two years ago, she felt a difference in her voice followed by hoarseness. Ears, nose, throat (ENT) examination did not show any pathology explaining her hoarseness. Furthermore, her dyspnea increased progressively despite regular inhaler therapy. During the last 6 weeks, her dyspnea was not responding to high dose inhaler therapy, not even to oral corticosteroid. On admission to our clinic, her respiratory rate was 16 breaths/minutes. Chest auscultation showed diffuse wheeze. Her past medical history was otherwise unremarkable. She was a lifetime nonsmoker and denied fever, weight loss, fatigue, or other symptoms. Palpation revealed no abdominal organomegaly. All other findings were within the normal limits. Arterial blood gas analysis revealed a PaO₂ of 99 mmHg, PaCO₂ of 37 mmHg. Complete blood count and sedimentation rate were normal. The chest radiograph was normal. Spirometry was indicative of obstructive airway disease with a FEV₁ of 1.710 L (62% of predicted), FVC of 3.80 L (97% of predicted), and an FEV₁/FVC ratio of 68%. Flow-volume loop showed a plateau on the expiratory phase indicating an intrathoracic upper airway obstruction (Figure 1). Thorax computed tomography (CT) demonstrated thickening at the posterior wall of the proximal trachea (Figure 2). Virtual bronchoscopy showed nodular lesions on the posterior tracheal wall (Figure 3). Flexible bronchoscopy showed red and yellowish diffuse nodular thickenings on the posterior wall of the proximal trachea (Figure 4). Forceps biopsies showed extracellular protein deposits staining positive with Congo red dye and exhibiting apple-green birefringence by polarized microscopy; a finding characteristic

of amyloid. Histopathologic diagnosis was amyloid light-chain (AL) nodular amyloidosis. Direct laryngoscopic examination revealed an accumulated material, possibly amyloid, starting from the subglottic area and approaching the anterior commissura, inhibiting the closure of the cords (Figure 5). To exclude systemic amyloidosis, other systems and tissues were investigated. Serum and urine protein electrophoresis and the serum free light chain ratio were normal. Electrocardiography, cardiac and abdomen magnetic resonance imaging (MRI), and technetium 99m methylene diphosphonate bone scintigraphy were negative for systemic amyloidosis. An abdominal fat pad biopsy did not reveal amyloid. She refused bone marrow aspiration biopsy and rectal biopsy. The patient was diagnosed as having isolated laryngo-tracheal AL amyloidosis.

DISCUSSION

Respiratory tract amyloidosis (RTA) is characterized by deposition of amyloid at any site along the respiratory tract ranging from the larynx to the pulmonary parenchyma (1). It is usually not associated with primary systemic amyloidosis (2). RTA is generally classified as laryngeal, tracheobronchial, and parenchymal amyloidosis. Most of the cases in the literature have tracheobronchial amyloidosis (TBA) and were often discovered as an incidental finding on chest radiography. Conversely, isolated RTA is relatively rare (2).

Respiratory symptoms may vary according to the anatomic deposition of amyloid (2). Patients with upper tracheal or proximal airway disease develop varying degrees of airway obstruction. They have worse prognosis than those with distal airway involvement (3). Common presenting symptoms are dyspnea, cough, and wheezing. These symptoms are not specific and may mimic different pathologies, such as asthma, chronic bronchitis, and endobronchial tumor. Those with distal tracheal and bronchial disease may have atelectasis, recurrent pneumonias, or bronchiectasis (4). Severe obstruction of the main bronchi may cause respiratory failure. The tumor-like variant of TBA is frequently confused with bronchogenic carcinoma. The parenchymal form is very rare and

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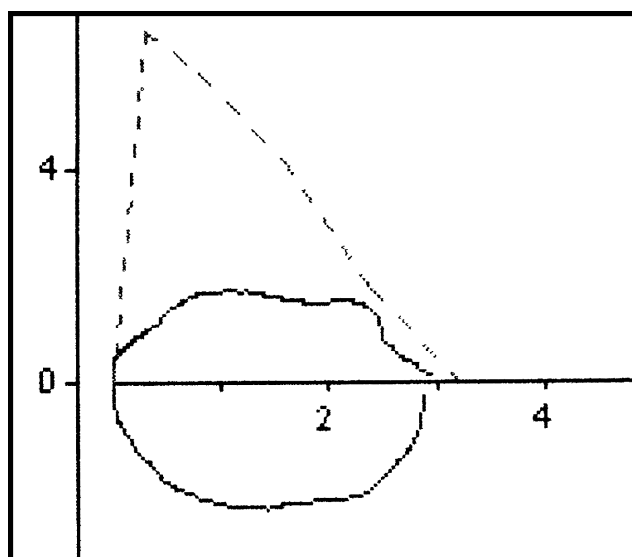


FIGURE 1.—Spirometry and flow-volume loop revealing a plateau on the expiratory phase.

usually presents with multiple, or less commonly, a single nodule or mass. Patients are usually asymptomatic and are often discovered incidentally on chest radiography. Diffuse parenchymal type of amyloidosis is the least common form, and the most common presenting symptom in this form is progressive dyspnea. Patients with this form are more likely to die of respiratory failure.

As in our case, TBA is usually associated with larynx amyloidosis (5). Laryngeal amyloid deposits occur most commonly in the supraglottic larynx and usually present with

hoarseness or stridor and may cause dyspnea on exertion (2). A diffuse infiltrative pattern with an intact mucosa is more common than nodular laryngeal amyloid deposition (2). Laryngotracheal amyloidosis can cause hoarseness, dysphonia, stridor, and dyspnea.

Spirometry allows an objective assessment of airway obstruction. Follow-up tests are necessary to evaluate disease progression. If there is a significant change in the spirometry, radiological control with CT scanning is necessary (6).

Chest radiographs may be normal or may reveal atelectasis or pneumonic consolidation due to endobronchial obstructing lesions (4, 7). The CT may demonstrate mucosal thickening or irregularities and luminal narrowing at various levels of the respiratory tract (8). Although the CT findings of TBA are relatively specific, other trachea-bronchial diseases should be considered, such as tracheobronchopathia osteochondroplastica, relapsing polychondritis, and tracheobronchial tuberculosis (9). In tracheobronchopathia osteochondroplastica, CT shows thickening of the tracheal wall that spares the posterior tracheal membrane, with irregular calcifications protruding into the lumen, and these findings are pathognomonic. Relapsing polychondritis is a systemic disease that affects cartilage in many anatomic sites of the body, including the nose, joints, ear lobes, ribs, or tracheobronchial airway. Also Wegener's granulomatosis, laryngotracheobronchial papillomatosis, idiopathic laryngotracheal stenosis, sarcoidosis, or tracheobronchitis with ulcerative colitis may radiologically mimic TBA. Idiopathic laryngotracheal stenosis is characterized by narrowing of the larynx and the subglottic trachea. It commonly affects middle-age women, and there is no history of intubation. Laryngotracheal papillomatosis is an HPV-associated viral disease and has a risk for malignant transformation to squamous cell carcinoma.



FIGURE 2.—Thorax CT demonstrating thickening at the posterior wall of the proximal trachea.

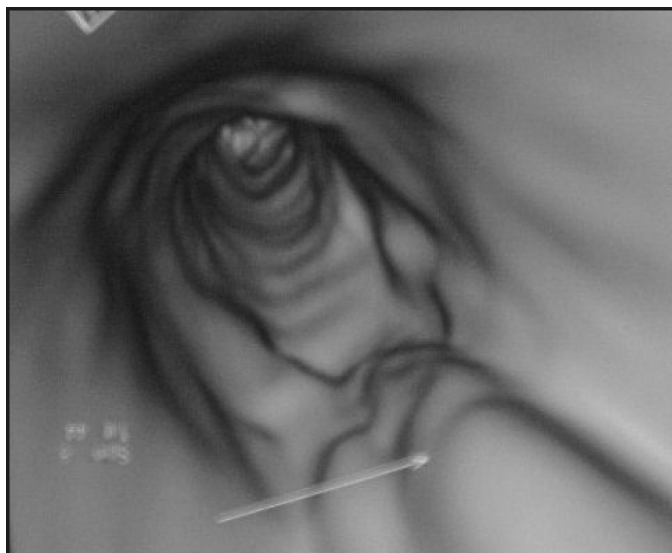


FIGURE 3.—Virtual bronchoscopy showing nodular lesions on the posterior tracheal wall.

Since symptoms and chest radiographs are not specific for laryngo-tracheal amyloidosis (LTA), patients' conditions are often misdiagnosed as bronchitis, asthma, or a tumor (10, 11). Therefore, the diagnosis of LTA is frequently delayed. Our patient had a history of asthma. Owing to progressive dyspnea and hoarseness unresponsive to medical treatment, she was diagnosed with refractory asthma without the need for further evaluation except ENT examinations. Unfortunately, several ENT examinations did not reveal any pathology explaining her hoarseness.

Laryngoscopy or bronchoscopy with tissue biopsy is necessary for the definitive diagnosis of LTA (2). Endoscopic appearances of amyloid deposits on trachea are submucosal plaques or nodules, tumor-like or polypoid appearance, circumferential wall thickening, superficial yellow lesions, cobblestone infiltration, erythematous elevations, or longitudinal



FIGURE 4.—Flexible bronchoscopy showing red and yellowish diffuse nodular thickenings on the posterior wall of the proximal trachea.



FIGURE 5.—Laryngoscopic examination showing an accumulated material.

fold. Biopsy specimen staining with Congo red dye and exhibiting green birefringence under polarized microscopy is diagnostic for amyloid deposition. The amyloid deposition in RTA may be either AL or amyloid A (AA), although AL deposition accounts for 63% to 80% of cases (4, 12). Isolated AL amyloidosis is most often identified in the respiratory, urogenital and gastrointestinal tracts, the skin, and the orbit. The diagnosis of isolated RTA requires the absence of systemic amyloidosis (13). Our case had the diagnosis of AL type isolated LTA with negative clinical and laboratory evidence of systemic amyloidosis.

Unfortunately, LTA has no universally accepted treatment. The management is dependent on symptoms. Treatment options are bronchoscopic approaches, surgery, radiation, and observation. Therapy may not be required for asymptomatic patients. Cases with proximal airway obstruction are difficult to manage. Bronchoscopic methods are mechanical debulking, endobronchial laser ablation, and stent or balloon dilatation in selected patients with stenosis. These methods are preferable and safer than surgery. However, such methods may be ineffective and repeated procedures may be required (2, 6). Bleeding is a common complication of these procedures. Sometimes external beam radiation or surgical resection is necessary (14–16). Since endoscopic examination of our case did not show significant obstruction, we found it appropriate for the patient to receive follow-up.

In summary, isolated LTA is an uncommon disease and the diagnosis is usually confused and delayed because of non-specific symptoms and normal chest radiography.

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