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Research Article

Serial Changes in Pulmonary Function Testing in A Patient with Tracheobronchial Amyloidosis: Relevance for Early Diagnosis

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ABSTRACT

Amyloidosis is a disease of abnormal extracellular deposition of proteins within tissues, commonly affecting solid organs such as the heart, liver, and kidneys. Less commonly, amyloidosis may affect the proximal tracheobronchial tree. Clinical symptoms are vague and may include shortness of breath, stridor, hoarseness. Pulmonary function testing at the time of diagnosis usually reveals an obstructive pattern. Diagnosis is difficult, and patients with tracheobronchial amyloidosis are frequently misdiagnosed with asthma or chronic obstructive pulmonary disease. Early changes in pulmonary function testing in patients with tracheobronchial amyloidosis have not been described.

We present a case of a firefighter who with obstructive symptomatology who was subsequently diagnosed with proximal tracheobronchial amyloidosis. As a component of his occupational health surveillance, yearly examinations and pulmonary function testing had been performed. Serial pulmonary function testing dating back fourteen years prior to diagnosis reveal an early decrease in peak expiratory flow. Over time and in retrospect, progressive blunting of the expiratory limb of his flow-volume loops is identified beginning ten years prior to presentation. These changes significantly predated his clinical symptomatology and may be useful for early identification of patients with tracheobronchial amyloidosis. The relationship between chronic smoke inhalation and the development of tracheobronchial amyloidosis is unclear.

Introduction

Amyloidosis is a disease of extracellular deposition of amyloid proteins within tissues and organs including the liver, kidneys, and heart. Less commonly, localized amyloidosis of the lungs and proximal tracheobronchial tree has been described [1, 2]. Patients affected with tracheobronchial amyloidosis frequently present with dyspnea on exertion, stridor or hoarseness of insidious origin, making early diagnosis difficult. Pulmonary function testing at the time of presentation typically reveals an obstructive pattern, and patients with proximal tracheobronchial amyloid deposition may exhibit a pattern of proximal respiratory obstruction. Early detection and recognition of tracheobronchial amyloidosis is difficult, however, and is frequently misdiagnosed as asthma or chronic obstructive pulmonary disease. We describe a patient with proximal tracheal amyloidosis in whom serial lung function testing was obtained as a component of his occupational health screening who demonstrated progressive and eventually severe proximal obstructive disease. These early changes in pulmonary function testing may be useful for the prompt recognition of tracheobronchial amyloidosis prior to clinical symptoms.

Case Report

Our patient is a 39-year-old previously healthy male firefighter referred to the Pulmonary Medicine clinic from his employer with increasing dyspnea on exertion. He had noticed that for the past several years his

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activity level had progressively decreased due to shortness of breath. He was asymptomatic at rest and denied fevers, chills, sputum production, or history of recent lung infection. He had no significant past medical history and was a non-smoker. Environmental exposures included smoke and chemical inhalation during his fourteen-year employment as a firefighter. Physical exam was unremarkable. As a requirement of his employer, the patient underwent yearly pulmonary function testing. He was diagnosed at an outside facility with asthma several years prior to his current presentation and was treated symptomatically with inhalers. Due to progression of symptoms, as well as changes in his pulmonary function testing, he was referred to the Pulmonology Clinic.

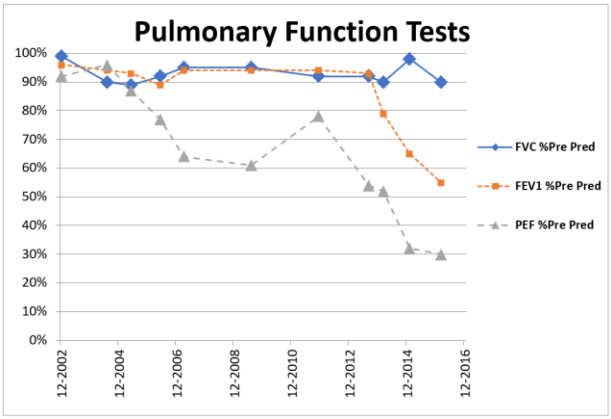

Figure 1: FEV1, FVC, and PEF over time. PEF is noted to decrease first, followed by a decrease in FEV1, with a stable FVC

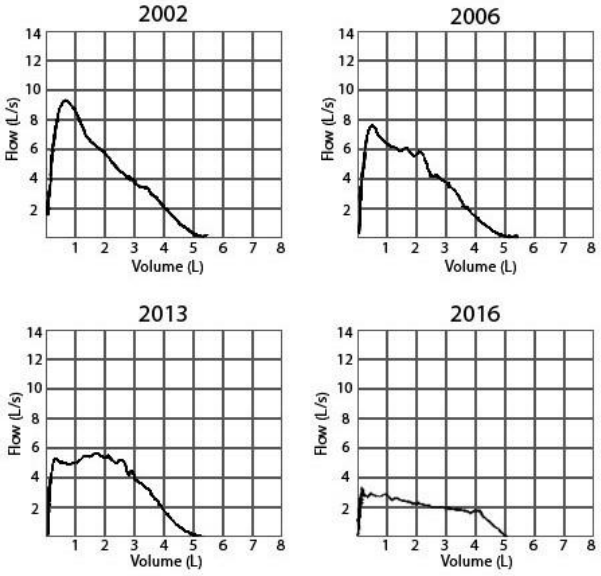

Figure 2: Isolated expiratory limbs of flow volume loops show progressive blunting over time

Complete pulmonary function testing was performed and compared with previous studies. Evidence of proximal obstructive disease was demonstrated. Additionally, when compared with prior studies, significant changes over time were noted (Figure 1). The first significant change in pulmonary function testing noted was a decrease in the previously stable percent predicted peak expiratory flow from 87% to 77%, occurring ten years prior to his diagnosis. Over the course of fourteen years, the patient showed a progressive blunting of the expiratory limb of the flow volume loops. In 2002 he had a near-normal expiratory limb, and within four years, a significant change was noted (Figure 2). By 2016, the loop was significantly blunted. These changes are indicative of a progressive variable intrathoracic obstructive process, consistent with the patient's diagnosis of primary tracheobronchial amyloidosis. In addition to flow volume loop changes, the patient had a progressive decrease in his forced expiratory volume in one second (FEV1) with preservation of his forced vital capacity (FVC). Notably, however, these changes occurred later in the patient's course, and only three years prior to his diagnosis. Changes in the expiratory limb of the flow volume loops predated changes in his FEV1 and forced expiratory volume in one second/forced vital capacity ratio (FEV1/FVC) by seven years. Inspection of the flow-volume loops also revealed a steady decrease in his peak expiratory flow (PEF) and corresponding dampening of the expiratory portion of his flow volume loop that had been previously unappreciated (Figure 1, 2).

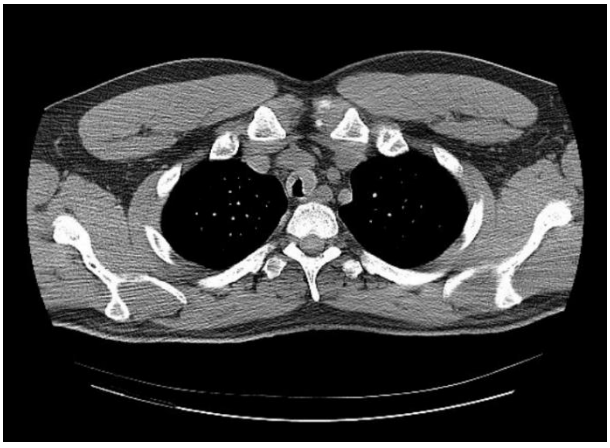

Figure 3: CT chest at presentation with circumferential thickening of the trachea

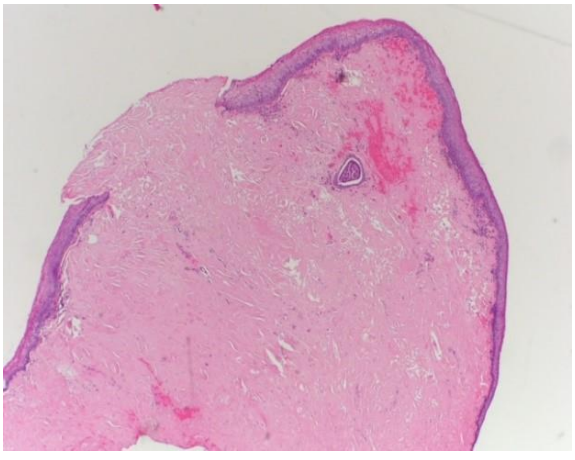

Figure 4: Tracheal biopsy with H&E stain courtesy of Greg Asmus, MD, Sanford Health Fargo, ND Pathology Department

Radiographic imaging was obtained. Chest x-ray showed a small amount of narrowing of the trachea when compared to a chest x-ray fourteen months prior but was otherwise normal. Chest CT demonstrated up to 9 mm of lobulated mural thickening of the trachea extending from the lower pole of the thyroid to the aortic arch without enlarged surrounding lymph nodes concerning for inflammation or neoplasm (Figure 3). While non-specific, this is consistent with previous case reports for tracheobronchial amyloidosis [3, 4]. He was referred for diagnostic biopsy of the trachea and was taken to the operating room for

direct laryngoscopy, flexible and rigid bronchoscopy. Upon direct examination, he was found to have an overgrowth of erythematous tissue on his cartilaginous trachea. Pathological examination of multiple tracheal biopsy sites showed amorphous material that was Congo Red positive with apple-green birefringence consistent with amyloidosis (Figure 4). Further analysis identified it as AL-type amyloid deposition. Clinically the patient recovered uneventfully from his biopsy. His respiratory symptoms persist despite elimination of environmental exposure.

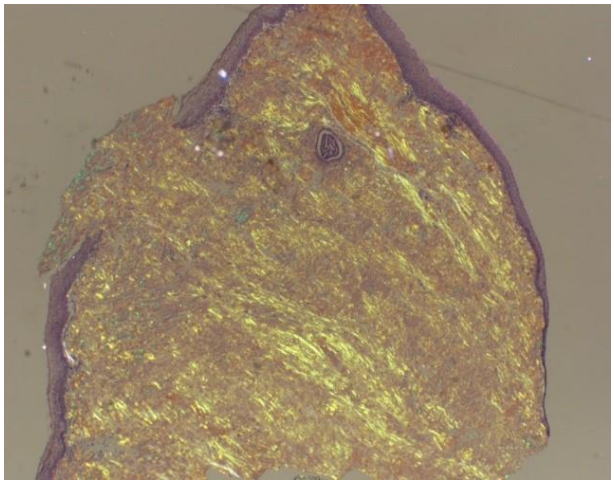

Figure 5: Tracheal biopsy with amyloid stain courtesy of Greg Asmus, MD, Sanford Health Fargo, ND Pathology Department

Discussion

Amyloidosis is caused by the overexpression of genes that code for proteins which deposit in the body in the form of sheets of fibers, with the potential to cause organ dysfunction. In systemic amyloidosis, this process is frequently found in the heart, liver, and kidneys. The etiology of amyloidosis is unclear. Localized light chain (AL) amyloidosis has been suggested to be associated with foci of monoclonal B cells that secrete immunoglobulin chains, similar to the pathogenesis of monoclonal gammopathy of undetermined significance (MGUS) or multiple myeloma [3, 5]. The most common type of amyloidosis is AL type, which can be systemic or localized. Amyloid type A protein (AA) amyloidosis is a secondary systemic amyloidosis due to its association with chronic inflammatory conditions and is not typically associated with primary tracheobronchial amyloidosis. In both systemic and localized AL amyloidosis, circulating plasma cells produce monoclonal immunoglobulin light chains that are found on protein analysis of amyloid deposits. These plasma cells are also associated with myeloma-associated amyloid and ruling-out plasma cell dyscrasias is an essential part of the evaluation of tracheobronchial amyloidosis.

Pulmonary amyloidosis can be difficult to diagnosis and is usually classified as tracheobronchial amyloidosis, nodular parenchymal amyloidosis, and diffuse parenchymal amyloidosis. Tracheobronchial amyloidosis accounts for nearly one half of the cases of pulmonary amyloidosis, either systemic or localized [6, 7]. Tracheobronchial amyloidosis has been found to be only 0.5% of symptomatic tracheobronchial lesions, and amyloidosis restricted to the respiratory tract has been reported less than 250 times in the literature [2, 3, 8]. Due to its rarity, patients with this disorder are frequently treated for more benign lung conditions including pneumonia, asthma, COPD, or bronchiectasis. Our patient had previously been diagnosed and treated for asthma and presented with worsening dyspnea on exertion and exercise intolerance. Symptoms for patients with tracheobronchial amyloidosis are varied and include shortness of breath, cough, chest tightness, progressive dyspnea, and rarely, hemoptysis [9]. Severity of symptoms depends primarily on the location of the disease and degree of airway compromise. Symptoms typically progress slowly, worsening over many years. Similar to our patient, this often leads to an incorrect diagnosis and ineffective treatment.

This case report highlights the importance of pulmonary function testing in the diagnosis of proximal obstructive airway disease. Early recognition of obstructive patterns allows a more timely diagnosis of pathologies including tracheobronchial amyloidosis. Our patient's occupation as a firefighter who underwent routine pulmonary function testing is unique and allows for the identification of early changes in his expiratory flow pattern consistent with proximal obstructive airway disease which predates his clinical symptomatology. While other case reports have included pulmonary function testing at the time of presentation, serial testing and changes over years has not been previously reported. Case reports have reported limited expiratory function, with a decreased FEV1, and one case described normal FEV1 and FVC, with a significantly decreased PEF and expiratory plateau on flow volume loop, indicating an intrathoracic process [3, 10]. The pulmonary function test findings in our case are consistent with a proximal airway obstructive disease process confirmed to be advanced tracheobronchial amyloidosis with additional testing.

Unlike other reports, we have identified early and progressive changes in expiratory flow-volume loops which predate clinical symptoms in a patient with tracheobronchial amyloidosis. This change prompted investigation into causative obstructive processes, leading to early diagnosis of this patient's rare disease. Decreases in FEV1 and FEV1/FVC ratio are later signs of the disease. FVC remained normal despite advanced and symptomatic disease. In our patient, the FEV1 began to decrease only with the onset and progression of his symptoms, occurring three years prior to his diagnosis and treatment. Retrospective analysis of our patient's pulmonary function testing revealed that changes in his peak expiratory flow were evident ten years prior to his diagnosis and progressively worsened over time. We submit that any patient with progressively deteriorating peak expiratory flow on serial pulmonary function testing merits prompt examination into respiratory pathologies through radiographic imaging, bronchoscopy and biopsy.

Our patient was a firefighter with regular exposure to smoke and chemical inhalants. It is unclear whether inhalation injury from biomass smoke may contribute to the pathogenesis of tracheobronchial amyloidosis, but it is plausible. Firefighters have been shown to have increased infiltration of neutrophils, eosinophils, and lymphocytes within bronchoalveolar lavage fluid that correlates to years of service [11]. Chronic biomass smoke inhalation also appears to confer a high risk of the development of chronic obstructive pulmonary disease due to chronic leukocytic infiltration and development of chronic airway sensitization [12]. Previous reviews have suggested there is no correlation between tobacco use and the development of tracheobronchial amyloidosis, with less than 50% of patients reporting a smoking history [4]. Significant differences exist between exposure to tobacco and biomass smoke, however. The pathogenesis of inflammation and injury due to biomass smoke inhalation is due to its

biphasic composition, a combination of a superheated gaseous phase and the particulate phase. It is of general consensus that the superheated gaseous phase leads to damage to the upper airways through thermal injury. Chemical irritants found within the particulate phase cause injury to the tracheobronchial system and lead to reactive bronchoconstriction and neutrophilic infiltration of the airway mucosa [13]. Of particular interest is the increased presence of lymphocytes within the airways after chronic biomass smoke exposure, as AL amyloidosis appears to be the result of excessive light chain protein extrusion from plasma cells into local tissues. Serum amyloid A levels also increase after exposure to biomass smoke in otherwise healthy individuals [14]. How the effects of chronic biomass smoke inhalation in a firefighter, such as our patient, may affect levels of serum amyloid A and the development of the AA type amyloidosis is not known.

A history of biomass smoke inhalation may also lead to a delay in the diagnosis of tracheobronchial amyloidosis given the association of smoke inhalation with more common causes of obstructive disease such as COPD or asthma and highlight the importance of accurate interpretation of pulmonary function testing. Our finding that changes in the expiratory flow-volume loop predate clinical symptomatology imply that persons chronically exposed to biomass smoke (such as firefighters) should undergo frequent and routine pulmonary function testing, with careful analysis of the flow-volume loops. Certainly, a high index of suspicion should be held for patients with a history of chronic biomass smoke exposure who present with obstructive symptoms that are difficult to treat.

Conclusions

Tracheobronchial amyloidosis is a rare condition characterized by proximal obstructive airway disease usually noted when patients present with dyspnea on exertion. Decreases in FEV1 and PEF have previously been reported in symptomatic patients with tracheobronchial amyloidosis and are rather late findings in the disease. Our patient with over a decade of serial pulmonary function testing, demonstrates that a proximal obstructive pattern in airflow is detectable before clinical symptoms occur and before decreases in FEV1 and PEF. Whether biomass smoke exposure increases the risk of tracheobronchial amyloidosis remains unclear but is possible. Those exposed to biomass smoke, including firefighters, are already at increased risk for respiratory disease and in our opinion would benefit from regular pulmonary function testing and careful interpretation, with particular attention to the expiratory limb of the flow volume loops. Early and regular pulmonary function testing may lead to earlier diagnosis and allow for changes in behavior or occupation in an effort to avoid or slow disease progression.

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