Pulmonary amyloidosis with tracheobronchial presentation: clinical case report

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ABSTRACT: Introduction: Amyloidosis is the term used to describe diseases that cause extracellular deposition of pathological amyloid proteins in organs and tissues, which can be systemic or restricted to a single organ. The clinical manifestations are diverse and include cardiomyopathy, renal failure, splenomegaly, intestinal problems, neuropathies, lung problems, among others. Objective: to report a clinical case of a patient with pulmonary amyloidosis. Methodology: bibliographic review and comparison to the case report, which was described based on data collected from the patient’s record and complementary exams. Clinical case: a seventy-year-old female patient sought medical assistance due to back pain, also presenting wheezing, dry cough, paroxysmal nocturnal dyspnea and orthopnea. Diagnostic investigation was carried out during hospitalization, and the biopsy of the tracheobronchial mucosa and alveolar lavage were positive for the Congo Red test, which confirmed the diagnosis of amyloidosis. The patient was then referred for laser ablation therapy. Conclusion: in a patient with a nonspecific clinical presentation and diagnostic suspicion of pulmonary amyloidosis, it is essential to investigate and rule out differential diagnoses such as malignancy or plasma cell dyscrasia. Therefore, it is necessary to perform high precision analysis of imaging exams to suggest this diagnosis, which should be confirmed through fiberoptic bronchoscopy and biopsy bronchial tissue biopsy with Congo Red staining, which will show the presence of an amorphous and birefringent material, compatible with amyloid.

Keywords: Amyloidosis; Immunoglobulin light-chain Amyloidosis; Pulmonary atelectasis; Airway obstruction.

RESUMO: Introdução: Amyloidose é o termo utilizado para designar doenças que fazem deposição extracelular de proteínas fibrilares patológicas em órgãos e tecidos, podendo ser sistêmica ou restrita a um único órgão. As manifestações clínicas são diversas, como cardiomiopatia, falência renal, esplenomegalia, problemas intestinais, neuropatias, problemas pulmonares, entre outros. Objetivo: relatar um caso clínico de paciente com amyloidose traqueobrônquica. Metodologia: revisão de bibliografias em comparação ao relato de caso, o qual foi descrito a partir de dados retirados do prontuário e de exames complementares da paciente. Caso clínico: paciente do sexo feminino, 70 anos, procurou assistência médica por dor lombar, apresentando também chiado, tosse seca, dispneia paroxística noturna e ortopneia. Realizou-se investigação diagnóstica durante a internação, na qual biópsia da mucoosa traqueobrônquica e coleta de lavado alveolar foram positivas para o teste Vermelho Congo, o que confirmou o diagnóstico de amyloidose. A paciente, então, foi encaminhada para terapia de ablação a laser. Conclusão: portanto, diante de um paciente com quadro clínico inspecífico e suspeita diagnóstica principal de amyloidose pulmonar, é imprescindível investigar e descartar diagnósticos diferenciais como neoplasia ou discrasia de células plasmáticas. Para isso, é necessário que haja alta precisão na análise dos exames de imagem, de modo a sugerir esse diagnóstico, o qual deve ser confirmado através da fibrobroncoscopia com biópsia de tecido brônquico, que através da coloração Vermelho do Congo, evidenciará presença de substância amorfa e birrefringente, compatível com substância amiloide.

Palavras-chave: Amyloidose; Amyloidose de cadeia leve de imunoglobulina; Atelectasia pulmonar; Obstrução das vias respiratórias

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INTRODUCTION

Amyloidosis is the term used to name the extracellular deposition of pathological amyloid proteins in a specific anatomical site. This disease can be divided into two large groups: localized (only one organ is affected) or systemic (more than one organ is affected), which is the most common.

Lung involvement in amyloidosis is a rare occurrence that is classified into four variants, depending on the location and degree of involvement: localized or diffuse tracheobronchial amyloidosis and nodular or diffuse parenchymal amyloidosis. This disease goes from a mere accidental finding to a serious condition that can lead to death.

Based on the rarity of this pathology, the objective of this study is to report the case of a patient in her seventh decade of life with localized tracheobronchial amyloidosis, diagnosed by fiberoptic bronchoscopy and a biopsy that demonstrated, through Congo Red staining, the presence of an amorphous and birefringent material compatible with amyloid.

CASE REPORT

A female 70-year-old patient, pardu, single, retired, born in Marau (RS) and from Passo Fundo (RS) was admitted to Hospital São Vicente de Paulo (HSVP) with a nonspecific complaint of back pain. However, the anamnesis revealed that her main symptom was dyspnea on mild exertion, accompanied by wheezing, which had started 3 years prior to the consultation and was attenuated with inhaled medications and aggravated by changes in temperature. In addition, she reported dry cough, paroxysmal nocturnal dyspnea, and orthopnea.

The patient had a previous history of bronchial asthma, chronic sinusitis, systemic arterial hypertension and dyslipidemia and was also a former smoker (1.8 pack-years). She was using Losartan, Hydrochlorothiazide, Simvastatin, Omeprazole, Formoterol + Budesonide (on demand) and Budesonide. She reported that her mother died from lung disease at age 37. The physical examination of the lungs showed inspiratory whoop in the right lung base, with no other alteration in the respiratory system or other systems.

The patient had undergone several tests before admission, including: a chest X-ray, which showed parenchymal opacities in the left lower lobe, associated with signs of atelectasis (which may be associated with an inflammatory or infectious process), cardiomegaly and aortic elongation with parietal calcifications; a spirometry, which revealed a mild obstructive ventilatory defect and post-bronchodilator change; an echocardiogram, which showed diastolic dysfunction, left ventricular remodeling and left atrial enlargement; and a chest tomography, which showed residual linear atelectasis in the lower lobes, residual lingula and middle lobe, sparse ground-glass opacity in both lung fields, predominantly in the lower lobes, probably residual, mild bronchiectasis in the lower lobes, calcification of the aorta, signs of cardiomegaly and a solid partially calcified nodular mass of ill-defined limits, located in the segmental bronchi in the lower lobe of the left lung, determining partial atelectasis of the adjacent lung segments, with bronchiectasis in between.

As soon as the patient was admitted, a control chest CT was requested for a new assessment of the lung manifestations, but the request was denied by the Hospital. On the 2nd day after admission, a fiberoptic bronchoscopy with biopsy of the tracheobronchial mucosa (right lower lobe, tracheal carina and left main bronchus) was performed and bronchoalveolar lavage was collected, which revealed localized tracheobronchial amyloidosis. During hospitalization, a series of laboratory tests were performed, most of them without particularities, including cultures for Koch’s bacillus and negative AFB tests, as well as culture and direct search for negative fungi. However, hypokalemia (K⁺ = 3.1 mEq/L) was found on the day of admission, and hypophosphatemia (P³⁻ = 4.9 mg/dL) on the following day, which can be explained by the previous use of hydrochlorothiazide, as well as positive bacterial culture for Antimicrobial susceptibility of viridans group streptococci and bacterioscopy with rare polymorphonuclear leukocytes in the bronchial lavage after 2 days of hospitalization. After eight days of hospitalization, hyperuricemia (7.6 mg/dL) was detected, which can also be explained by the chronic use of hydrochlorothiazide. The next day, other tests were performed, which included Beta 2 microglobulin 1.62, urine Kappa (light chain) 0.680 and immunoelctrophoresis of blood and urine proteins, both of which showed absence of monoclonal protein, ruling out one of the differential diagnoses of amyloidosis, plasma cell dyscrasias, including multiple myeloma.

Twelve days after admission, a new computed tomography (CT) of the chest showed, among other findings, the following: presence of an apparently hypoattenuating endobronchial nodular mass near the left pulmonary hilum, with irregular calcifications, measuring 1.9 x 1.3 cm and extending caudally to the segmental bronchiolar branches in the left lower lobe. The mass was of indeterminate nature and was suggestive of localized tracheobronchial amyloidosis. The imaging exam also detected that this nodule caused obstruction of the left lower segmental bronchus, causing ectasia in the bronchioles at the distal level, especially in the anterior and lateral basal segments of the left lower lobe, in addiction to atelectasis in these bronchioles (Figures 1 and 2).
The tomographic finding of distal bronchial obstruction due to the presence of an intraluminal nodule, associated with consequent segmental pulmonary collapse and bronchiectasis, corroborates the clinical picture of obstructive ventilatory disorder, explaining the patient’s chronic dyspnea. These manifestations are nonspecific and common to other diseases, but the constant presence of dyspnea reported by the patient suggests a constant obstruction rather than an intermittent event. Thus, the clinical picture can be better explained by the radiological finding of bronchial obstruction than by the patient’s previous history of asthma or chronic sinusitis.

Twenty-three days after admission, the results of the biopsy collected through fiberoptic bronchoscopy on the second day of hospitalization came out. The biopsy (Figures 3 and 4) showed, through Congo Red staining (Figures 5 and 6), the presence of an amorphous and birefringent material, compatible with amyloid, in the tracheal carina and left main bronchus and the absence of neoplasia.

Subsequently, immunohistochemical tests were performed and showed negative results for the following antibodies: anti-human cytokeratin monoclonal antibody (AE1-3), common leukocyte monoclonal antibody (LCA), anti NK cell monoclonal antibody (CD56), anti-cytokeratin 7 monoclonal antibody (CK7) and anti-thyroid transcription

Figures 1 and 2 – Chest computed tomography showing the presence of an apparently hypoattenuating endobronchial nodular mass near the left pulmonary hilum, which caused an obstruction in the bronchioles at the distal

Figures 3 and 4 – Anatomopathological study obtained through biopsy of the tracheobronchial mucosa

Figures 5 and 6 – Anatomopathological study with Congo Red staining, showing presence of an amorphous and birefringent material, compatible with amyloid, in the tracheal carina and left main bronchus
factor 1 monoclonal antibody (TTF-1), excluding the possibility of diagnosing a primary neoplasm or metastases that could be affecting the lung. However, the analysis revealed a positive result for Anti-Kappa and Anti-Lambda antibodies, related to the deposition of immunoglobulin light chains in the biopsied tissue. With these results, the diagnosis of amyloidosis in the collected material was concluded.

The determination of the type of fibril through immunohistochemistry was not performed due to unavailability at the Hospital and refusal of the health system to send the sample to another center for analysis. However, the determination of the type of fibril by immunohistochemistry would not change the medical conduct and therapeutic choices for the patient, as the lesion was single and easily accessible and the possibility of systemic involvement or gammopathy was excluded due to the absence of monoclonal proteins in the immunoelectrophoresis of blood and urine proteins.

After the confirmation of the diagnosis of localized tracheobronchial amyloidosis, the following were provided: prescription of continuous medication, schedule of outpatient visit, guidance on warning signs and referral for laser ablation therapy at the Hospital de Clinicas de Porto Alegre. At the time this report was written, laser ablation therapy of the lesion had already been successfully performed.

**DISCUSSION**

Amyloidosis is not a single disease but a term for diseases that share a common feature: the extracellular deposition of pathologic insoluble fibrillar proteins, known as amyloid, in organs and tissues. The term amyloid is a histological description that encompasses a wide variety of fibrillar proteins that exhibit similar tinctorial, ultrastructural and x-ray diffraction properties. In short, several molecular mechanisms make soluble proteins prone to undergo an irreversible transition from their native conformation into highly ordered aggregates. The aggregation of these amyloids in the extracellular space of organs and tissues causes functional damage of the structures involved, determining a rare and underdiagnosed chronic disease, amyloidosis.

Despite of the different predisposing conditions, including plasma cell dyscrasias [immunoglobulin (AL) light chain amyloidosis], chronic inflammation [reactive amyloidosis (AA)] or mutations (hereditary amyloidosis), the clinical manifestations visibly overlap and mimic more prevalent conditions, complicating and often delaying the recognition of these rare and complex diseases.

Reactive amyloidosis (AA) is associated with heredity and chronic infectious processes and rarely presents as a respiratory disease; idiopathic (AL) or primary amyloidosis is the most common form of amyloidosis, with monoclonal immunoglobulin light chain κ or λ as the amyloidogenic precursors. There are several clinical manifestations, such as cardiomyopathy, nephrotic syndrome, renal failure, hepatomegaly, splenomegaly, orthostatic hypotension, diarrhea, intestinal pseudo-obstruction, peripheral neuropathy, autonomic neuropathy, arthropathy, carpal tunnel syndrome, hemorrhage, adrenal dysfunction, gout, lung problems, weight loss, fatigue, malaise and macroglossia. ATTR amyloidosis is related to transthyretin and associated with senile systemic amyloidosis, with predominant cardiac involvement, polynuropathy, or kidney involvement.

Amyloidosis can be systemic or localized, acquired or hereditary. Its incidence is estimated to be around 10 cases per million people/year. Tracheobronchial amyloidosis is the least common form of pulmonary amyloidosis, with approximately 100 cases reported in the literature. Three patterns of involvement have been described: proximal, mid, and distal airway disease. It most often presents as multifocal submucosal plaques in the tracheobronchial tree and it is an organ-limited type of amyloidosis that is generally not associated with detectable systemic lymphoplasmacytic clonal proliferation. Most cases represent AL amyloidosis, and the pulmonary parenchyma is not involved. The mean age of patients is between 50 and 60 years, with no sex predilection.

Patients with tracheobronchial amyloidosis are usually symptomatic, due to the stenosis resulting from the amyloid deposits in the trachea and large bronchi. Narrowing of airways and organ dysfunction cause patients to present with cough, wheezing, hoarseness, distal atelectasis, recurrent pneumonia, lobar collapse, and hemoptysis, which can occasionally be abundant. Bronchoscopy with transbronchial biopsy is most useful for establishing the diagnosis of tracheobronchial amyloidosis, whereas the CT scan is very helpful for determining the extent of the disease. On pulmonary function tests, patients with proximal airway disease have decreased airflows, whereas patients with distal airway disease have normal airflows.

Differential diagnosis is limited and includes diffuse tracheal diseases, such as tracheobronchopathia osteochondroplastica (TPO), relapsing polychondritis, granulomatosis with polyangiitis, sarcoidosis, inflammatory bowel disease, tracheobronchitis, tracheal paracoccidioidomycosis and tuberculosis.

The diagnostic gold standard for amyloidosis is histological confirmation by Congo red staining, which show apple-green birefringence under polarized light. Positive histological results for amyloidosis should be followed up with immunohistochemical analysis to determine the type of fibril. All amyloid fibrils share a common ultrastructure, regardless of the precursor.
proteins, as demonstrated by X-ray diffraction studies. The highly ordered morphology of the antiparallel strands perpendicular to the fibril axis is responsible for the organized binding of Congo Red, resulting in green birefringence under polarized light. This technique is the gold standard for identifying amyloid in histological sections. There are also other methods of staining amyloid, such as the use of thioflavin T and metachromatic dyes, such as crystal violet.

As the clinical characteristics of the different forms of amyloidosis are similar, the chemical identification of the amyloidogenic protein should be unequivocally determined by analyzing its sequence if possible, as it helps to define the treatment and prognosis. There are several techniques for identifying amyloidogenic protein, such as immunohistochemistry with electron microscopy and mass spectrometry. All international protocols recommend, for patients with suspected amyloidosis, diagnosis by tissue biopsy and Congo red staining with characteristic green birefringence under polarized light, as well as electron immunomicroscopy, which is useful for confirmation in some scenarios, characterization chemistry and differential diagnosis and is more specific than Congo red light microscopy.

Although amyloidosis is a benign lesion, it can be fatal if it results in airway obstruction or respiratory failure. A regression of the pathology has been systematically demonstrated in patients with AA amyloidosis after intensive anti-inflammatory therapy, in patients with AL amyloidosis after chemotherapy, and in patients with familial amyloid polyneuropathy and amyloidosis, with significant decrease in liver and kidney transplantation. High-dose melphalan followed by autologous stem cell transplantation (ASCT) in eligible patients showed considerable benefits in patients with AL amyloidosis. Laser ablation therapy was initially described as effective for controlling localized tracheobronchial amyloidosis, however, it only has a palliative effect in the diffuse form. Stents also play a role if occlusion is complete. Colchicine and systemic steroids were not effective.

The prognosis is variable: in some patients the disease may remain stable for long periods while in others it may progress and lead to death. In this sense, the deterioration of pulmonary function seems to be an important marker. Follow-up with observation of new respiratory symptoms, bronchoscopy, and pulmonary function tests helps in further management once the diagnosis is established.

CONCLUSION

Therefore, it is important that all chest X-ray assessments in patients who already have pulmonary pathologies are thorough, in order to reduce the possibility of missing the diagnosis of a more complex condition. It is important to highlight that patients with tracheobronchial amyloidosis may present a range of nonspecific symptoms and specific findings on imaging exams. Tomographic findings showing involvement of the tracheal membrane and calcification are common in patients with tracheobronchial amyloidosis, but not specific, and it is important to rule out the differential diagnoses of tracheobronchial amyloidosis, such as neoplasia and plasma cell dyscrasia. The imaging studies and laboratory and pathological investigation of the patient in this report ruled out neoplasia, and laboratory tests ruled out plasma cell dyscrasia. The diagnosis of tracheobronchial amyloidosis was confirmed by fiberoptic bronchoscopy and a biopsy of bronchial tissue that demonstrated, through Congo Red staining, the presence of an amorphous and birefringent material compatible with amyloid. Patients with significant airway obstruction need invasive therapies, such as laser ablation - which was our patient’s case. Finally, it is essential that these patients continue to follow up with specialized professionals.

Conflict of interest: there are no conflicts of interest among the authors.


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