CASE REPORTS/CLINICAL VIGNETTES

Pulmonary Hypertension and Amyloidosis—an Uncommon Association: A Case Report and Review of the Literature

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Only a limited number of patients with amyloidosis and pulmonary hypertension have been reported in the literature. We report a 73-year-old female with AL type amyloidosis who developed respiratory insufficiency and right heart failure because of severe pulmonary hypertension. There were no signs of cardiac involvement with amyloid or findings consistent with interstitial lung disease. Previous reports of pulmonary hypertension without an apparent parenchymal lung or myocardial involvement with amyloidosis are summarized. Pulmonary hypertension due to deposition of amyloid in the pulmonary vasculature is an uncommon finding; however, it should be considered in cases of unexplained pulmonary hypertension in patients with amyloidosis.

KEY WORDS: pulmonary amyloidosis; cardiac amyloidosis.
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INTRODUCTION

Amyloidosis is the term for diseases that share a common feature of extracellular deposition of pathologic insoluble fibrillar proteins in organs and tissues.[1] The classification of amyloidosis is based on the nature of precursor plasma proteins that form the fibril deposits.[2] The most common form is primary amyloidosis, also known as light chain amyloidosis. The structural subunits of amyloid proteins in light chain (AL) amyloidosis are made up of fragments of monoclonal immunoglobulin heavy chains or light chains.[3] The extracellular deposits interfere with organ function and may lead to premature death. The most common presentations are unexplained nephrotic syndrome, cardiomyopathy, hepatomegaly, and peripheral neuropathy.[4] Clinically significant pulmonary amyloidosis is uncommon despite the fact that amyloid deposition in the lung parenchyma is a common histological finding in this condition.[6] Isolated amyloid deposition in the pulmonary vasculature, without clinically significant parenchymal involvement, is a histological finding that occurs to some extent in all systemic forms.[7] However, pulmonary hypertension is rarely reported in these cases.

The subject of this report is a patient with amyloidosis AL type who presented with severe pulmonary hypertension without an apparent cardiac or parenchymal lung involvement. Previous reports of pulmonary hypertension in amyloidosis are summarized and discussed.

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CASE REPORT

A 73-year-old woman presented with a 2-month history of progressive exertional dyspnea, increasing leg edema, and abdominal distention. Three days earlier, purpuric lesions appeared spontaneously around her eyes. She reported no chest pain, orthopnea, or paroxysmal nocturnal dyspnea.

Two years before admission, the patient presented with symptomatic anemia and was diagnosed as having AL type amyloidosis. Echocardiography and pulmonary function test were not performed at that time. She received 1 course of chemotherapy with prednisone and chlorambucil, which were stopped because of severe pancytopenia without any additional chemotherapeutic treatments thereafter. The patient did not have any other significant medical condition.

At presentation, the patient was tachypneic (respiratory rate of 25/minute) and tachycardic (120 beats/minute). Her blood pressure was 110/70 mmHg. Easily detectable purpuric rash was noted around her eyes. Elevated jugular venous pressure of 11 cm, prominent ascites, and leg edema grade 3 were also noted. Auscultation of the heart revealed an accentuated pulmonic component of the second heart sound and a grade 3/6 systolic murmur over the left sternal border. Inspiratory rales were detected at the lower third of both lung fields. The rest of the physical examination was unremarkable. Arterial blood gas analysis on room air revealed a PO_2 of 58 mmHg, PCO_2 of 30 mmHg, and pH=7.5.

Further laboratory workup revealed normocytic anemia (Hb=10 gr/dL), thrombocytopenia of 60,000/mm^3, white blood cells (WBC) of 9,500/mm^3, mild impairment of renal functions (creatinine=1.1 mg/dL, urea=60 mg/dL), albumin=3.5 gr/dL, globulin=3 gr/dL, hypercalcemia of 11.5 mg/dL, and a high lactate dehydrogenase of 607 U/L (normal value <480 U/L). Serum protein electrophoresis showed a 16.3 g/L monoclonal spike in the gamma fraction and serum immunoelectrophoresis demonstrated increased IgG level with monoclonal Lambda chain peak. Urine test for Bence Johns proteins was positive. Bone marrow biopsy confirmed a diagnosis of multiple myeloma

with plasma cells comprising 70% of the marrow elements. Electrocardiogram showed sinus tachycardia with right bundle branch block and prominent R waves in the right anterior leads (V_{1-3}).

Additional tests were ordered to investigate the respiratory symptoms. A chest roentgenogram showed slightly increased pulmonary markings. A transthoracic echocardiogram revealed severe pulmonary hypertension with an estimated systolic pulmonary arterial pressure of 90 mmHg and moderate tricuspid regurgitation, but good left ventricular function (ejection fraction=66%). No signs of left to right shunt and no echocardiographic signs of restrictive cardiomyopathy or cardiac amyloidosis were found.

Investigation of pulmonary hypertension was undertaken and included ventilation–perfusion lung scan which revealed nonhomogenous perfusion without segmental perfusion defects that was interpreted as low probability of pulmonary embolism. A high resolution computed tomography (CT) [high-resolution computed tomography (HRCT)] angiogram of the chest did not demonstrate evidence of pulmonary embolism or signs of interstitial or other lung diseases. Lung functions are summarized in Table 2 and were interpreted as normal spirometry with decreased diffusing capacity of the lung for carbon monoxide (DLCO). Serologic testing for HIV was negative and no clinical findings or laboratory markers suggesting collagen vascular disease were detected. Doppler ultrasound of the portal vein and liver scan did not show signs of portal hypertension or chronic liver disease. The patient refused catheterization of the right heart. Based on the absence of significant pulmonary parenchymal lung findings in HRCT, and findings in pulmonary function tests that are consistent with pulmonary hypertension, and the risk of lung biopsy in severe pulmonary hypertension, we decided to avoid this procedure.

In light of the patient's refusal to undergo right heart catheterization, the diagnosis of pulmonary hypertension was based on echocardiographic findings. Because of the absence of a secondary condition causing pulmonary hypertension, the most likely cause was deposition of amyloid in the pulmonary vasculature. It should be noted, however, that this was merely a diagnosis of exclusion. The patient was treated with nifedipine and diuretics with subsequent clinical improvement in signs and symptoms of right heart failure and slight lowering of the pulmonary hypertension, with an estimated pulmonary artery pressure of 84 mmHg in echocardiogram. She was discharged with supplemental oxygen treatment. During the subsequent 4 months, she received 10 additional courses of prednisone and chlorambucil which were replaced by dexamethasone and cyclophosphamide. However, the respiratory condition continued to deteriorate.

Six months after the first admission, the patient presented with worsening dyspnea, cough, and leg edema. Chest roentgenogram revealed an infiltrate in the left lower lung. Based on a presumptive diagnosis of pneumonia, treatment with antibiotics, supplemental oxygen and diuretics were initiated. She died because of progressive respiratory failure refractory to treatment and died on the seventh hospital day. A postmortem examination was declined by her family.

DISCUSSION

Only 8 cases of amyloidosis with pulmonary hypertension have thus far been reported. We present a case of AL type amyloidosis in association with severe pulmonary hypertension, which raises two issues: the relationship of pulmonary hypertension to pulmonary amyloidosis and the role of amyloid deposition and vascular dysfunctions.

Systemic light-chain deposition due to plasma cell dyscrasias usually causes restrictive cardiomyopathy due to cardiac amyloidosis and manifests by signs and symptoms of diastolic ventricular dysfunction. Restrictive cardiomyopathy can be difficult to detect. Doppler evaluation of ventricular function is essential to rule out cardiac amyloidosis and the absence of characteristic findings of cardiac amyloidosis in echocardiography, as in the present case, has a negative predictive value of 88%.[5] Hence, the possibility of cardiac amyloidosis as a main cause of right heart failure in this case is low.

Pulmonary amyloidosis rarely causes symptoms despite the fact that it is commonly found in autopsy.[6] Various classifications of pulmonary amyloidosis have been proposed based upon the site of amyloid deposition. It is classified as tracheobronchial or parenchymal, the latter being further classified radiographically either as solitary/multiple nodules or as a diffuse

Table 1. Features of Patients with Pulmonary Hypertension and Amyloidosis

	Age	Sex	Type of pulmonary amyloidosis*	Cardiac amyloidosis†	Symptoms	Type	Age at diagnosis of amyloidosis	Age at diagnosis of PHTN	Estimated PAP (mmHg)	Multiple Myeloma	Time to death (d)
1	91	F	Alveolar septal	N	HF	AL	91	91	–	N	
2	65	F	Partial alveolar septal	N	D, HF	AL	65	65.5	39	Y	41
3	61	F	–	N	D, HF	AL	61	66.5	58	Y	19
4	64	F	–	N	D, HF	AL	64	64	–	Y	892
5	82	M	–	N	D, HF	AL	82	82	–	N	1,036
6	54	F	Alveolar septal	N	D, HF	AL	54	54	48	N	73
7	48	F	–	N	D, CP, HF	AA–FMF	48	48	62	N	61
8						Ab2M				N	
Current case-9	73	F	–	N	D, HF	Al	71	73	90	Y	240

CP Chest pain, D dyspnea, HF heart failure, N no, PHTN pulmonary hypertension, Y yes.

**Diagnosis was made by lung biopsy or by autopsy in cases 1–2, 6–7.*

†Cardiac amyloidosis was ruled out by echocardiography in cases 2–5 and 9 and by autopsy histological examination in cases 1, 6, and 7.

alveolar septal pattern.[6,7] Amyloid involvement of the pulmonary vasculature is a histological finding that occurs at least, to some extent, in all systemic forms[8]; however, pulmonary hypertension is only rarely reported.

Pulmonary arterial hypertension is defined as sustained elevation of the pulmonary arterial pressure to more than 25 mmHg at rest or to more than 30 mmHg with exercise, with left ventricular end-diastolic pressure of less than 15 mmHg.[9] Pulmonary arterial hypertension encompasses idiopathic pulmonary hypertension, pulmonary arterial hypertension in the setting of collagen vascular disease, portal hypertension, congenital left-to-right intracardiac shunts, and infection with human immunodeficiency virus (HIV).[10]

Our patient was diagnosed as having multiple myeloma (MM) with amyloidosis. The association between MM and pulmonary hypertension has been rarely reported in the literature. All reported cases were related to thalidomide treatment,[11–13] which is irrelevant to our case. As mentioned previously, deposition of amyloid in the pulmonary vasculature is a common histological finding. Amyloid deposition in blood vessel walls can result in endothelial dysfunction and eventually lead to pulmonary arterial hypertension. The pathologic mechanisms that cause pulmonary arterial hypertension probably involve vasoconstriction, smooth muscle cell and endothelial cell proliferation, and thrombosis. This suggests the presence of perturbations in the normal relationships between vasodilators and vasoconstrictors, growth inhibitors and mitogenic factors, and antithrombotic and prothrombotic determinants. These homeostatic imbalances are probably consequences of pulmonary endothelial cell dysfunction or injury.[14]

Vasculopathy secondary to amyloid deposition can result in flow abnormalities and ischemia. Vascular involvement has been described in 88–90% of patients with AL amyloidosis.[15,16] Despite the frequent histological vascular involvement, clinical expression secondary to amyloid vasculopathy is infrequent. Suwaidi et al. described an abnormal response of endothelial-dependent vasodilatation in the coronary arteries to acetylcholine infusion in patients with amyloidosis.[17] In addition, β2-amyloid was shown to enhance the vasoconstriction induced in aortic rings by phenylephrine and endothelin.[18] Hence, amyloid deposition in blood vessel walls can result in systemic endothelial dysfunction. It is possible that similar mechanisms operate in the pulmonary circulation causing pulmonary hypertension. To the best of our knowledge, data that support this suggestion are unavailable.

Until now, 8 patients with pulmonary hypertension and amyloidosis without cardiac or parenchymal lung involvement have been reported in the literature.[19–23] The main clinical and laboratory findings in these reports and those of our patient are summarized in Table 1. The details of one case with β2 microglobulin amyloidosis[23] could not be obtained. The median age of the patients at diagnosis of amyloidosis was 67 ± 13, while the median age at the diagnosis of pulmonary hypertension was 1 year higher (68 ± 13). All patients had exertional dyspnea and signs of right heart failure upon physical examination. Seven patients had AL amyloidosis, 1 patient had AA type amyloidosis secondary to untreated familial Mediterranean fever, and 1 patient had β2 microglobulin amyloidosis secondary to hemodialysis treatment. From the available echocardiographic data (6 out of 9 patients), no evidence of cardiac amyloidosis was found. The median left ventricular ejection fraction was 66%, while all patients had right ventricular dilatation with depressed function. Four patients underwent invasive pulmonary artery pressure (PAP) measurements. The mean PAP was 51 mmHg. The diagnosis of pulmonary hypertension secondary to deposition of amyloid in the pulmonary vasculature was confirmed by a lung biopsy in 5 cases. Follow-up data shows rapid clinical deterioration in most of the patients, with a median time until death of 73 days after the diagnosis of pulmonary hypertension. In comparison, the mean survival of patients with primary pulmonary hypertension without therapy is 2–3 years,[24] while that of patients with AL amyloidosis is 12 months.[1]

Table 2. Results of Pulmonary Function Tests

	Actual	Predicted	Percent (%) Act/ Pre
FEV1 (L)	1.34	1.78	75.4
FVC (L)	1.68	2.17	77.6
FEV1/FVC (%)	79	75	
DLCO	3.73	6.53	57.1

In summary, we present a woman with amyloidosis who developed dyspnea and right heart failure and was diagnosed with pulmonary hypertension, most probably secondary to pulmonary vascular involvement by amyloid fibrils. Dyspnea and right heart failure are not uncommon in patients with amyloidosis and are usually the consequence of cardiac and pulmonary amyloidosis. Pulmonary hypertension due to deposition of amyloid in the pulmonary vasculature is uncommon; nevertheless, it should be considered as a possibility in unexplained pulmonary hypertension in patients with amyloidosis.

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