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Cardiac Amyloidosis Presenting as Pulmonary Arterial Hypertension: A Case Report and Review of Literature

Cardiac Amyloidosis Presenting as Pulmonary Arterial Hypertension

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Abstract

BACKGROUND

Pulmonary hypertension is a rare cardiopulmonary disease, with an insidious onset that usually worsens rapidly. AL amyloidosis is a rare systemic disease caused by extracellular deposition of pathologic, insoluble, and proteinaceous fibrils in organs and tissues; however, it is difficult to diagnose given its varied and nonspecific symptoms. To date, rare cases of amyloidosis with pulmonary hypertension have been reported. Of note, the optimal treatments for cardiac amyloidosis complicated with pulmonary hypertension remain unclear.

CASE SUMMARY

We report a case of a 51-year-old woman presented with progressively worsening dyspnea. Transthoracic echocardiogram findings indicated severe pulmonary hypertension. Twenty-seven months after the first admission, the patient returned with symptoms of progressive heart failure. A myocardial sample stained with Congo red was positive, ant the patient was ultimately diagnosed with AL amyloidosis with cardiac involvement.

CONCLUSION

Although pulmonary hypertension may be idiopathic, it is frequently associated with other conditions. In rare cases, pulmonary hypertension can be a complication of AL amyloidosis, which should be seriously considered in any adult presenting with nonspecific signs or symptoms of cardiac distress.

Key Words: cardiac amyloidosis; heart involvement; pulmonary hypertension

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Core Tip: Symptomatic pulmonary hypertension is only rarely described and, when present, is typically associated with progressive disease, such as elevated filling pressures secondary to cardiac amyloid. In this case, the patient initially presented with pulmonary hypertension, she was found, 2 years later, to have AL amyloidosis with cardiac involvement. We highlight the diagnostic difficulties presented by pulmonary hypertension in a patient with AL amyloidosis, and illustrate the complicated progression of the disease, as well as the poor efficacy of current palliative medicine.

INTRODUCTION

Pulmonary hypertension is a rare cardiopulmonary disease with an insidious onset that usually worsens rapidly, and, if left untreated, has a median survival of 2–3 years [1]. Although pulmonary hypertension may be idiopathic, it is frequently associated with other conditions. The most common clinical disorders that cause pulmonary hypertension include primary cardiac abnormalities, chronic pulmonary embolism, pulmonary parenchymal problems, obstructive sleep apnea, connective tissue disorders, cirrhosis with portal hypertension, and use of appetite suppressants [2]. AL amyloidosis is a rare systemic disease caused by extracellular deposition of pathologic, insoluble, and proteinaceous fibrils in organs and tissues[3]. Group I pulmonary hypertension is a rare complication of AL amyloidosis [4]. In addition to AL amyloidosis, transthyretin-related amyloidosis (ATTR) has been considered a disease in the field of cardiology. Cardiac amyloidosis was confirmed according to results of endomyocardial biopsy, with Congo red staining, nuclear scintigraphy and immunohistochemistry to determine the amyloid type[5]. To date, only a few, rare cases of amyloidosis with pulmonary hypertension have been reported. We present the following article in accordance with the CARE reporting checklist.

In this report, we highlight the diagnostic difficulties presented by pulmonary hypertension in a patient with AL amyloidosis, and illustrate the complicated progression of the disease, as well as the poor efficacy of current treatment strategies.

CASE PRESENTATION

Chief complaints

A 51-year-old woman was admitted for dyspnea, occurring over a 1-month period.

History of present illness

The patient had no significant medical history.

History of past illness

The patient had no significant medical history.

Personal and family history

No notable personal or family history.

Physical examination

Physical examination revealed blood pressure of 101/55mmHg, heart rate of 65 beats/min.

Laboratory examinations

Plasma N-terminal brain natriuretic peptide (NT-proBNP) was elevated to 3,780 pg/mL (normal 0-125 pg/mL).

Imaging examinations

Electrocardiography (ECG) demonstrated a sinus rhythm with a heart rate of 65 beats/min, a left anterior fascicular block, poor R-wave progression in leads V1-V3, and a non-specific T wave and ST-segment (*Figure 1A*). A 2-dimensional transthoracic echocardiogram revealed right ventricular enlargement, with a chamber diameter of 27mm, a left ventricular cavity of normal diameter, an end diastolic chamber size of 42mm and preserved systolic function, as well as an ejection fraction of 64%. The left atria (42 mm) and right atria (48*48 mm) were both enlarged. Transmitral Doppler flow

was consistent with restrictive physiology. The left ventricle was interpreted to have impaired diastolic dysfunction (mitral E wave velocity = 0.99 m/s, A wave (1.28 m/s, medial E/e' >15). Transthoracic echocardiogram findings indicated severe pulmonary hypertension on the basis of the estimated right ventricular systolic pressures (the pulmonary arterial pressure was 51 mmHg). Pulmonary arterial hypertension is defined as the pulmonary capillary wedge pressure <15 mmHg and pulmonary vascular resistance >3 Wood Units as assessed by right heart catheterization [6]. The criterion of clinically significant pulmonary hypertension when detected by Doppler echocardiography is not precisely defined. Commonly used definitions of pulmonary hypertension are a pulmonary artery systolic pressure >35mmHg or mean >25mmHg at rest or mean >30mmHg when exercise[7]. Color Doppler showed mild regurgitation at the mitral and pulmonic valves. Further, moderate tricuspid valve regurgitation was observed (the tricuspid regurgitation area was 7.8 cm^2).

When pulmonary hypertension was identified, the patient was further evaluated for an underlying etiology. A high resolution computed tomography angiogram of the chest did not show evidence of pulmonary embolism or signs of interstitial or other lung disease. The patient had negative findings upon spirometry, and denied a family history of pulmonary hypertension, sleep apnea, and premature death. No laboratory markers or clinical symptoms that suggested collagen vascular disease were detected in the patient. Furthermore, a doppler ultrasound of the portal vein and liver scan did not show signs of portal hypertension. The patient also had serologic test results that were negative for HIV, and the patient refused right heart catheterization.

FINAL DIAGNOSIS

The patient was diagnosed with pulmonary hypertension based on echocardiographic finding. Pulmonary hypertension in heart failure with preserved ejection fraction represents the most complex situation. We cannot make a clear distinction between idiopathic pulmonary arterial hypertension (group 1 pulmonary hypertension) and pulmonary hypertension secondary to left heart disease (group 2

pulmonary hypertension) without right heart catheterization, Idiopathic pulmonary arterial hypertension was considered in our case who had an early indication of left ventricle diastolic dysfunction (E/e' >15 and enlarged left atria), but severe pulmonary hypertension.

TREATMENT

The patient was treated with a phosphodiesterase 5 inhibitor (sildenafil, 20 mg, three times a day) and diuretics (furosemide, 20 mg, twice a day and spironolactone, 20 mg, three times a day), and showed subsequent improvement in signs and symptoms of right heart failure, in addition to a slight lowering of pulmonary hypertension.

OUTCOME AND FOLLOW-UP

However, the patient returned 11 mo after her first admission and presented with worsening dyspnea, paroxysmal nocturnal dyspnea, and complaints of an inability to lie flat on her back. Echocardiography showed newly-presenting left ventricular hypertrophy (the septal and left posterior wall thicknesses were 12 mm and 12 mm, respectively). NT-proBNP was elevated from 3,780 pg/mL to 7,910 pg/mL (normal 0-125 pg/mL). ECG demonstrated a left anterior fascicular block, a new left bundle branch block, ST-segment depression in leads I and AVL and T wave inversion in leads I, AVL, and V4-V6 (*Figure 1B*).

Ten months later (21 mo after the first admission), the patient's respiratory condition continued to deteriorate. The patient was admitted for new appearance of orthopnea and worsening edema in the lower extremities. NT-proBNP was elevated to 11,600 pg/mL (normal 0-125 pg/mL). Transthoracic echocardiography showed worsening systolic dysfunction, and echocardiography revealed progressive left ventricular hypertrophy (the septal and left posterior wall thicknesses were 14 mm and 13 mm, respectively). Further, severe tricuspid regurgitation (13.2 cm^2) and higher pulmonary artery pressure (58 mmHg) were also observed. ECG demonstrated atrial

fibrillation, left bundle branch block with wider QRS complex, ST segment elevation in Leads V1-V3, and T wave inversion in leads I, AVL and V4-V6.

Then, 6 mo later (27 mo after the first admission), the patient returned again with symptoms of New York Heart Association class III heart failure. ECG showed atrial fibrillation with rapid ventricular response, left bundle branch block (*Figure 1C*), first degree atrioventricular block, Mobitz type I second-degree AV block, and premature ventricular contraction in 24-hour dynamic electrocardiogram. Echocardiography revealed progressive atrial enlargement (the left atrial diameter was 51 mm, and the right atrial diameter was 52×62 mm). The patient also had worsening systolic dysfunction (ejection fraction 48%). The ventricle wall was characteristic sparkling, with a granular texture (*Figure 1E*). Immunohistochemistry of amyloid deposits is used to distinguish TTR from other proteins that may cause amyloidosis. Immunoglobulin light chain associated with light chain (AL) amyloidosis. Serum free light-chain analysis showed lambda light-chain was increased at 378 mg/L (normal 8.3-27 mg/L), with an altered kappa/Lambda of 22/378. The lambda and kappa light-chain were not detected in the urine. Cardiac magnetic resonance imaging showed suspected delayed subendocardial gadolinium enhancement. The patient underwent endomyocardial biopsy at another hospital. Amyloid deposits were detected by Congo red staining. Myocardial sample was positive, but periumbilical fat aspirates, as well as samples from the tongue, gums and bone marrow were all negative. The patient was ultimately diagnosed with stage III AL amyloidosis with cardiac involvement, per the Mayo 2012 staging system. In this patient, the most likely cause of pulmonary hypertension was deposition of amyloid in the pulmonary vasculature.

The patient's therapeutic plan was to receive three cycles of therapy consisting of cyclophosphamide/bortezomib/dexamethasone (CyBorD). Bortezomib (1.3 mg/sqm/day) and cyclophosphamide (300 mg/day) were administered on the 1st, 5th, 15th, and 22nd day of each 35-day course, and dexamethasone (20mg/day) was administered on days 1, 2, 8, 9, 15, 16, 21, and 22. Unfortunately, 1 day after the first cycle of therapy, the patient experienced an episode of cardiopulmonary arrest due to

cardiac arrest, with a quick return of spontaneous circulation after a brief cardiopulmonary resuscitation. The next day, the patient experienced cardiac arrest 4 times, returning to spontaneous circulation after cardiopulmonary resuscitation in each case. A pacemaker was implanted to address the recurrent cardiac arrests and pacing electrocardiogram was showed in *Figure 1D*. Echocardiography revealed atrial enlargements and worsening systolic dysfunction (ejection fraction 48%) (*Figure 1F*).

It remained unclear whether there was a causal relationship between CyBorD and cardiac arrest. However, the patient refused CyBorD chemotherapy for cardiac amyloidosis. The patient died 5 years after the first admission and 3 years after the diagnosis of cardiac amyloidosis.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient.

DISCUSSION

Cardiac amyloid is a rare disease, and patients frequently experience significant delays between the onset of non-specific symptoms and a confirmed amyloid diagnosis. Symptomatic pulmonary hypertension is only rarely described and, when present, is typically associated with progressive disease, such as elevated filling pressures secondary to cardiac amyloid (*Table 1*)[4, 8]. Although our patient initially presented with pulmonary hypertension, she was found, 2 years later, to have AL amyloidosis with cardiac involvement. This report further emphasizes the insidious nature of amyloidosis that makes it difficult to diagnose. Multiple underlying factors and a long term follow-up must be considered for patients with pulmonary hypertension in order to reduce the time to diagnosis.

Doppler echocardiography is a commonly used method to diagnose pulmonary hypertension [9]. Echocardiography provides an estimate of the systolic pressure in the pulmonary artery. However, a definitive diagnosis of pulmonary hypertension requires

a direct pulmonary arterial pressure measurement *via* right heart catheterization. Generally pressures obtained *via* echocardiography are similar to those obtained by catheterization, if they are in the lower pressure ranges (below mmHg). Based on criteria from the National Institutes of Health, a mean pulmonary artery pressure ≥25mmHg at rest (>30mmHg with exercise) is the standard for the diagnosis of pulmonary hypertension [9].

Because of etiologic uncertainty and several possible contributing factors, further diagnostic evaluation was pursued in our patient. However, the underlying disease causing pulmonary hypertension remained unclear at the time of the initial presentation. Two years later, our patient was finally diagnosed with amyloidosis following presentation of progressively worsening symptoms and echocardiographic evidence indicating ventricle wall with characteristic sparkling and granular texture.

In patients with AL amyloidosis, the most common etiologies of pulmonary hypertension are left-side restrictive cardiomyopathy from amyloid deposition or diffuse lung disease [8, 10]. Pulmonary amyloidosis rarely causes symptoms despite the fact that it is commonly found in bronchoscopic lung biopsy [11]. The main patterns of pulmonary involvement are tracheobronchial or parenchymal, the latter being further classified radiographically, either as solitary/multiple nodular parenchymal, or as a diffuse alveolar septal pattern [12]. A tracheobronchial pattern is a common form of respiratory amyloidosis, in which amyloid is found in the subepithelial interstitial tissue and often surrounds tracheobronchial ducts and acini. Nodular parenchymal amyloidosis is rare and amyloid is often present only in the alveolar interstitium at nodule peripheries. A diffuse parenchymal pattern is the least common form of respiratory amyloidosis, in which amyloid is present in the media of small blood vessels and in the parenchymal interstitium. In all reported cases, vascular obstructions due to amyloid deposits are considered the cause of increased pulmonary vascular resistance [13]. Amyloid deposition in blood vessel walls can result in endothelial dysfunction. The abnormal endothelial cells express lower levels of nitric oxide synthase and cyclooxygenase, as well as increased levels of endothelia, and promote the onset of

vasoconstriction and smooth muscle proliferation. It is possible that similar mechanisms operate in the pulmonary condition, lead to vasoconstriction and pulmonary hypertension, even in the absence of severe intra-vascular amyloid deposits. An increase in pulmonary vascular resistance requires a higher pulmonary arterial pressure to maintain the same right ventricular output, which eventually leads to pulmonary arterial hypertension.

Treating pulmonary hypertension in patients with amyloidosis can be a challenging. Despite a paucity of data, diuretics and vasodilators, with calcium channel blockers, are often appropriate therapies used to treat patients with pulmonary hypertension [14]. However, patients with amyloidosis often have orthostatic hypotension and cannot tolerate the high doses required for successful treatment. The pulmonary hypertension-specific drugs that have emerged over the past 2 decades have largely focused on targeting the underlying complex etiology *via* the endothelial, prostacyclin, and nitric oxide pathways. PDE type 5 inhibitors, such as Sildenafil, are class of drugs used to prolong the physiological effects of NO/cGMP signaling by inhibiting cGMP degradation [15]. Sildenafil is approved for treatment of pulmonary hypertension as a class I indication in World Health Organization-Functional Class (WHO-FC) II and III, and as a class IIa indication in WHO-FC IV patients [16]. However, pulmonary hypertension-specific drugs are not recommended treatments for patients with pulmonary hypertension related to left heart disease [17]. Since 2013, several randomized controlled trials have been completed in patients with pulmonary hypertension related to left heart disease, no effect was observed on the primary end-point of mean pulmonary artery pressure . The principle of the treatment applied is always related to the underlying disease. Our patient was first treated with sildenafil; however, her symptoms continued to gradually progress which is in accord with those of previous studies. But it is difficult to determine whether the clinical deterioration was related to the use of sildenafil from our case study. Such an event, underscores the importance of using a treatment strategy that address the underlying etiology in order to effectively improve pulmonary hypertension. Therapeutic interventions for AL

amyloidosis remain controversial. Definitive management involves stopping production of the paraprotein responsible for amyloid formation. The treatment combination of CyBorD has shown signs of early promise, with high rates of hematologic responses as a first line treatment in a many patients[18]. Unfortunately, our patient suffered cardiac arrests during CyBorD chemotherapy. Therefore, the patient declined further CyBorD treatment and we could not observed any changes in pulmonary hypertension following treatment of the underlying process driving the amyloid deposition.

CONCLUSION

Although pulmonary hypertension may be idiopathic, it is frequently associated with other conditions. Pulmonary hypertension is a rare complication of AL amyloidosis, which is associated with a poor prognosis and significant mortality. Further studies are required to develop targeted therapies to effectively improve outcomes among patients with pulmonary hypertension, and in those with other comorbidities due to AL amyloidosis.

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