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Contents

Thrice Monthly Volume 11 Number 12 April 26, 2023

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Cohort Study

Retrospective Study

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 12 April 26, 2023

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 12 April 26, 2023

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 12 April 26, 2023

Contents

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CASE REPORT

Cardiac amyloidosis presenting as pulmonary arterial hypertension: A case report

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Abstract

BACKGROUND

Pulmonary hypertension is a rare cardiopulmonary disease, with an insidious onset that usually worsens rapidly. Amyloid light chain (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 who presented with progressively worsening dyspnea. Transthoracic echocardiography indicated severe pulmonary hypertension. Twenty-seven months after first admission, the patient returned with symptoms of progressive heart failure. A myocardial tissue sample stained with Congo red was positive, and 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; Case report

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 amyloid light chain (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.

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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]. Amyloid light chain (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 is considered a disease in the field of cardiology. Cardiac amyloidosis is confirmed by 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 to hospital due to dyspnea, occurring over a 1-mo period.

Physical examination

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

Laboratory examinations

Plasma N-terminal brain natriuretic peptide (NT-proBNP) was elevated to 3780 pg/mL (normal range 0-125 pg/mL).

Imaging examinations

Electrocardiography (ECG) demonstrated a sinus rhythm with a heart rate of 65 bpm, 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 27 mm, a left ventricular cavity of normal diameter, an end diastolic chamber size of 42 mm and preserved systolic function, as well as an ejection fraction of 64%. The left atrium (42 mm) and right atrium (48 mm × 48 mm) were both enlarged. Transmitral Doppler flow was consistent with restrictive physiology. The left ventricle was revealed to have impaired diastolic dysfunction (mitral E wave velocity = 0.99 m/s, A wave (1.28 m/s, medial E/e' > 15). Transthoracic echocardiography 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 pulmonary capillary wedge pressure < 15 mmHg and pulmonary vascular resistance > 3 Wood Units as assessed by right heart catheterization[6]. The criterion for 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 > 35 mmHg or mean > 25 mmHg at rest or mean > 30 mmHg when exercising[7]. Color

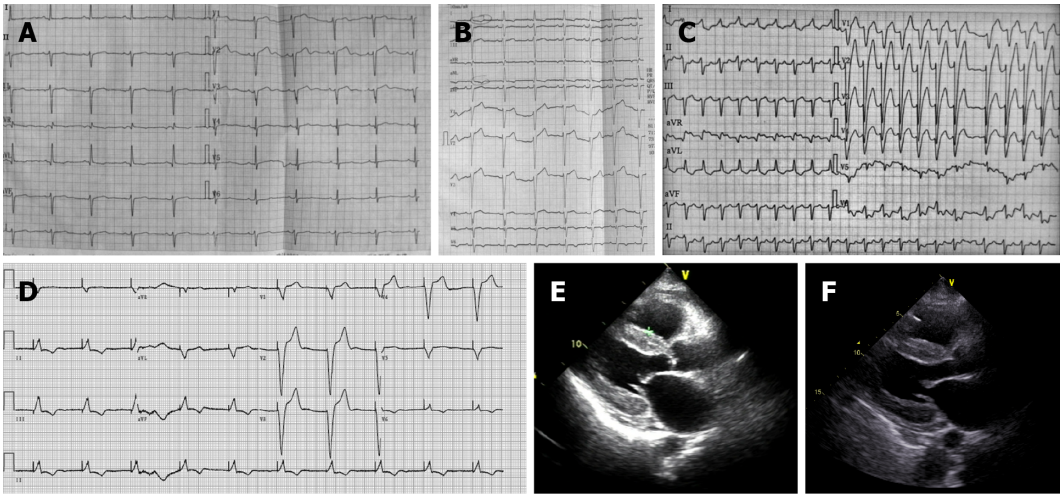

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Figure 1 Serial changes on electrocardiography and echocardiography. A: Electrocardiography (ECG) demonstrated a left anterior fascicular block, poor R-wave progression in leads V1-V3, and a non-specific T wave and ST-segment; B: 11 mo later, ECG demonstrated a new left bundle branch block, ST-segment depression in leads I and augmented unipolar limb lead (AVL) and T wave inversion in leads I, AVL, and V4-V6; C: 21 mo later, ECG demonstrated atrial fibrillation, left bundle branch block with wider QRS wave group, ST segment elevation in leads V1-V3, and T wave inversion in leads I, AVL and V4-V6; D: Echocardiography revealed characteristic sparkling and a granular texture in the ventricle wall; E: Pacing ECG was showed; F: Echocardiography revealed atrial enlargements and worsening systolic dysfunction (ejection fraction 48%).

Doppler showed mild regurgitation at the mitral and pulmonary valves. Furthermore, 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 showed serologic test results that were negative for human immunodeficiency virus, 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 3780 pg/mL to 7910 pg/mL

(normal range 0-125 pg/mL). ECG demonstrated a left anterior fascicular block, a new left bundle branch block, ST-segment depression in leads I and augmented unipolar limb lead (AVL) and T wave inversion in leads I, AVL, and V4-V6 (Figure 1B).

Ten months later (21 mo after first admission), the patient's respiratory condition continued to deteriorate. The patient was admitted due to new appearance of orthopnea and worsening edema in the lower extremities. NT-proBNP was again elevated at 11600 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). Furthermore, 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 wave group, ST segment elevation in leads V1-V3, and T wave inversion in leads I, AVL and V4-V6.

Six month later (27 mo after 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 Atrioventricular block, and premature ventricular contraction on 24-h dynamic electrocardiography. Echocardiography revealed progressive atrial enlargement (the left atrial diameter was 51 mm, and the right atrial diameter was 52 mm × 62 mm). The patient also had worsening systolic dysfunction (ejection fraction 48%). The ventricle wall had a characteristic sparkling apperance, with a granular texture (Figure 1D). Immunohistochemistry of amyloid deposits was used to distinguish transthyretin from other proteins that may cause amyloidosis. Immunoglobulin light chain was associated with AL amyloidosis. Serum free light-chain analysis showed lambda light-chain was increased at 378 mg/L (normal range 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 tissue 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-d course, and dexamethasone (20 mg/day) was administered on days 1, 2, 8, 9, 15, 16, 21, and 22. Unfortunately, 1 d 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 the pacing electrocardiogram is shown in Figure 1E. Echocardiography revealed atrial enlargements and worsening systolic dysfunction (ejection fraction 48%) (Figure 1F).

It was 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 amyloidosis is a rare disease, and patients frequently experience significant delays between the onset of non-specific symptoms and a confirmed amyloidosis 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 amyloidosis (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 for diagnosing 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. Based on criteria from the National Institutes of Health, a mean pulmonary artery pressure ≥ 25 mmHg at rest (> 30 mmHg with exercise) is the standard for the diagnosis of pulmonary hypertension[9].

Table 1 Previous reports of cases of pulmonary hypertension with amyloidosis

Case	Ref.	Age (year)/sex	Biopsy site	Type of amyloid	MPAP (mmHg)	MM	Treatment	Time to death (mo)
1	Chapman *et al* [19], 1999	91/F	Lung, heart	AL	NI	(-)	NI	NI
2	Cirulis *et al*[4], 2016	53/F	Lung, heart	IgGκ AL	46	(+)	Bortezomib-thalidomide-dexamethasone, sildenafil	Survival
3	D'Aloia *et al*[20], 2008	75/M	Fat, heart	AL	NI	(-)	NI	NI
4	Dingli *et al*[10], 2001	61/F	BM, fat	IgGκ AL	58	(+)	Diuretics, melphalan, prednisone, cyclophosphamide, vincristine doxorubicin, dexamethasone	1
5	Dingli *et al*[10], 2001	64/F	BM	IgGλ AL	NI	(+)	Diuretics, vincristine, BCNU, Melphalan, cyclophosphamide, prednisone	29
6	Dingli *et al*[10], 2001	82/M	BM	IgGλ AL	NI	(-)	Diuretics, digoxin, calcium channel blocker	32
7	Dingli *et al*[10], 2001	54/F	Lung	IgGκ AL	48	(-)	Diuretics, calcium channel blocker, aspirin	2
8	Dingli *et al*[10], 2001	48/F	Liver	Amyloid A AL	62	(-)	Calcium channel blocker, colchicine	2
9	Eder *et al*[8], 2007	73/F	BM	AL	90	(+)	Prednisone, chlorambucil, dexamethasone, cyclophosphamide	8
10	Hashimoto *et al* [21], 2015	85/F	BM	IgGκ AL	60	(+)	Melphalan-prednisolone, Lenalidomide-dexamethasone, bortezomib, cyclophosphamide, vincristine, and dacarbazine	29
11	Kruczak *et al* [22], 2013	67/F	Lung, colon mucosa	Transthyretin AL	95	(-)	Methylprednisolone, melphalan and cyclophosphamide	1
12	Lehtonen and Kettunen[23], 2007	48/M	BM, fat	AL	46	(+)	Sildenafil, melphalan, prednison	NI
13	Lutz *et al*[24], 1995	61/F	Heart, lung	β2M AL	75	(-)	Antihypertensive medication	12
14	Shiue and McNally[25], 1988	65/F	BM, lung, rectal	AL	39	(+)	Melphalan, prednisolone, diuretics	1
15	Sullivan and Schwarz[26], 1994	72/F	BM, lung	AL	56	(+)	NI	6
16	Krishnan *et al* [27], 2015	69/F	BM, heart, renal	AL	41	(+)	Sildenafil, bumetadine, warfarin, metoprolol succinate, ambrisentan	NI
17	Present case, 2019	51/F	BM, heart, fat	IgGλ AL	51	(-)	Sildenafil, cyclophosphamide, bortezomib, dexamethasone	60

F: Female; M: Male; BM: Bone morrow; MPAP: Mean pulmonary artery pressure; MM: Multiple Myeloma; AL: Light chain amyloid; NI: No information; β 2M: Beta-2 microglobulin.

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

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. Phosphodiesterase type 5 inhibitors, such as Sildenafil, are a class of drugs used to prolong the physiological effects of Nitric oxide–cyclic guanosine monophosphate (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, and 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 accordance with those in previous studies. However, it was difficult to determine whether the clinical deterioration was related to the use of sildenafil in our patient. Such an event, underscores the importance of a treatment strategy that addresses the underlying etiology in order to effectively improve pulmonary hypertension. Therapeutic interventions for AL amyloidosis are controversial. Definitive management involves stopping production of the paraprotein responsible for amyloid formation. The combination of CyBorD, as a first-line treatment, has shown signs of early promise, with high rates of hematologic responses in many patients[18]. Unfortunately, our patient suffered cardiac arrests during CyBorD chemotherapy. Therefore, the patient declined further CyBorD treatment and we did not observed any changes in pulmonary hypertension following treatment of the underlying process driving 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.

FOOTNOTES

Author contributions: Gao M completed the clinical data collection and the manuscript draft; Chen LP and Yang N improved later revision of the article; Zhang WH and Tong Q participated in the treatment decisions; Zhang ZG, Zhang WH and Tong Q revised the manuscript critically to ensure the authenticity and practicability; All authors read and approved the final manuscript.

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