

Case Report

Pulmonary arterial hypertension as the initial pulmonary manifestation in a patient with primary antiphospholipid antibody syndrome: a case report

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Abstract: Pulmonary thrombosis and secondary pulmonary hypertension (thrombosis pulmonary hypertension) are among the most frequent pulmonary complications of primary antiphospholipid syndrome (PAPS). However, non-thrombosis pulmonary hypertension without any thromboembolic symptoms for a long time is rare. A 38-year-old female first visited the former hospital for 5-month progressive exertional dyspnea and irritable cough. Echocardiography showed bilateral atrial and right ventricular enlargement, with tricuspid valve incompetence and severe pulmonary arterial hypertension (PAH). No obvious abnormalities were apparent in the routine blood sample tests or her clinical presentations other than a decreased platelet count, increased ESR and positive anticardiolipin antibody immunoglobulin G (IgG aCL), which were collectively diagnosed with undifferentiated connective tissue disease (UCTD) and related PAH. Then PAPS was diagnosed at our hospital based on her history of recurrent miscarriage, positive IgG aCL, pulmonary embolism (PE) and subsequent hepatic infarction. After treatment with anticoagulant, supplement of platelet and plasma, high-dose gamma globulin shock therapy, dyspnea and cough disappeared and no complications occurred during 3-month follow-up. Herein, we report a case for the first time in whom the initial symptom was PAH, with progressive disease. Two types of PH (non-thrombosis pulmonary hypertension and thrombosis pulmonary hypertension) coexisted in a 38-year-old woman who was ultimately diagnosed with primary antiphospholipid antibody syndrome (PAPS).

Keywords: Non-thrombosis pulmonary hypertension, primary antiphospholipid antibody syndrome, pulmonary embolism, case report

Introduction

Primary antiphospholipid antibody syndrome (PAPS) is characterized by distinct clinical features, which include thrombocytopenia, recurrent vascular thrombosis and spontaneous abortion [1]. The interaction of antiphospholipid antibodies such as anticardiolipin antibodies (aCL), lupus anticoagulant (LA), and anti-beta 2GPI antibodies (a-β2GPI) with various coagulation proteins, platelets or endothelial cells may contribute to the diagnosis of disease. Additionally, APS also is accompanied by many clinical complications, such as cardiac valvular disease, nephropathy, thrombocytopenia, livedo reticularis, and Coombs' positive hemolytic anemia [2]. Its manifestations vary both between individuals and over time in a single patient.

The most serious consequences can even include death; thus, it is critical to diagnose this disease prospectively and correctly at an early stage. Currently, APS has often been reported associated with pulmonary arterial hypertension (PAH) or pulmonary embolism (PE). However, it is important to note that PAH has previously rarely been reported as an initial pulmonary presentation in PAPS. We present an uncommon case of PAPS with PAH who initially showed no evidence of PE, followed by a demonstration of CTEPH several months later.

Case report

A 38-year-old woman was first admitted to a hospital with a 5-month history of exertional dyspnea and irritable cough. An echocardi-

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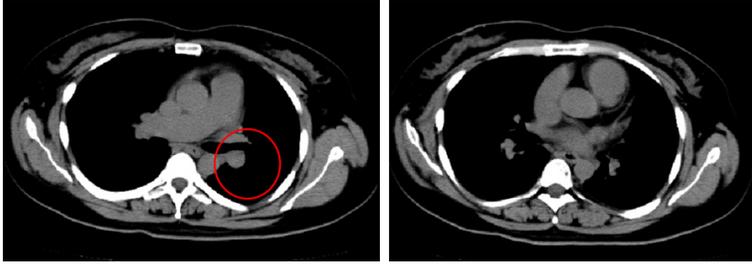


Figure 1. In the former hospital, CT plain scan revealed a small amount of pericardial effusion, along with right atrial and ventricular enlargement, and there was no filling defects in the subsegmental pulmonary arteries. Combined her clinical symptoms and normal plasma D-dimer level, thrombosis PAH did not considered.

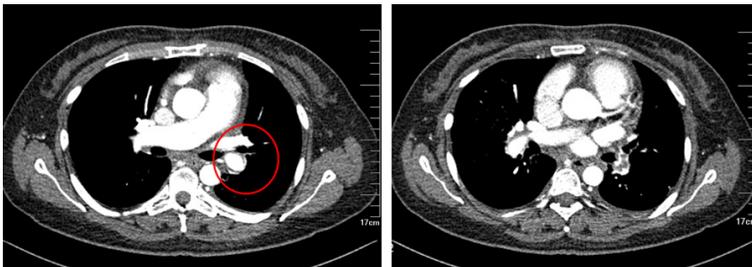


Figure 2. Four months later in our hospital, computed tomographic of the thorax showed filling defects in the subsegmental pulmonary arteries of the left lower lobe, along with right atrial and ventricular enlargement, confirming the diagnosis of pulmonary embolism and CTEPH. And there were also small pleural effusion and pericardial effusion.

gram revealed moderate to severe PAH and her pulmonary artery systolic pressure (PASP) was elevated at 83 mmHg. Additionally, enlargement of the right atrium and right ventricle were obvious (RA: 40 mm, RV: 21 mm). Chest computed tomography also revealed a small amount of pericardial effusion, along with right atrial and ventricular enlargement. The reason for PH was unknown, and further workup was initiated to confirm the diagnosis.

She had no history of arterial or vein thrombosis, and showed no symptoms of systemic venous thromboembolism (VTE), no evidence of arterial or vein thrombosis in chest CT (**Figure 1**), and had normal levels of plasma D-dimer (113 ng/ml, normal range: 68-494 ng/ml). The possibility of thrombosis pulmonary hypertension was not considered. Laboratory examination at presentation showed a low platelet count ($60 \times 10^9/L$), high titer (1608 pg/ml) of N-terminal pro brain natriuretic peptide (NT pro-BNP), positive anticardiolipin antibody immunoglobulin G (IgG aCL) and negative immu-

noglobulin M, anti-nuclear antibody (ANA), anti-SS-A, anti-SS-B, anti-Sm, anti-RNP, anti-Scl-70, Anti-J_o-1 and Lupus anticoagulant (LA). There was no apparent evidence of connective tissue diseases (including pleural effusion, ulcerations in the oral cavity, characteristic hematological and immunological abnormalities or the presence of antinuclear antibodies); thus, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and other connective tissue diseases were also excluded. A diagnosis of undifferentiated connective tissue disease (UCTD) and related pulmonary hypertension was made. After discharge, she was maintained on sildenafil citrate (25 mg, tid), beraprost sodium tablet (40 μ g, tid) and Singulair (10 mg, qd) and remained relatively well until her second admission to our hospital 5 months later.

On the second admission, she presented with symptoms of severe dyspnea after activities, chest congestion and palpitations that had lasted for 11 months, and facial and lower limb edema that had lasted for 4 months. Additional details about her medical history were sought, and an interview revealed that she had a history of two fetal losses 10 years ago, and she had terminated gestation for stillbirth followed by septic shock, after which she was found to have severely low platelet counts (Thrombocytopenia). Laboratory examinations showed the following: platelets were decreased to $12 \times 10^9/L$ and the activated partial thromboplastin time (APTT) were markedly prolonged at 58.2 seconds. The plasma D-dimer was 1683 ng/ml (normal range: 68-494 ng/ml). IgG aCL was positive and increased to more than 300 GPL/ml (normal range: 0-18). We suspected that she had APS based on her history of recurrent fetal loss and quite low platelets. Further examinations were performed for diagnosis and treatment.

PAH as the initial pulmonary manifestation in a patient with PAPS

Table 1. Summary of lab tests at diagnosis and after treatment

	First admission	Second admission	After treatment
Plasma D-dimer (ng/ml)	113	1530	114
APTT (s)	52.9	58.2	47.6
Platelet count ($\times 10^9/L$)	60	12	128
NT pro-BNP (pg/ml)	1608	5693	77.34
IgG aCL	+	+	-
ANA	-	-	-
Anti-SS-A	-	-	-
Anti-SS-B	-	-	-
Anti-Sm	-	-	-
Anti-RNP	-	-	-
Anti-Scl-70	-	-	-
Anti-J _o -1	-	-	-
LA	-	-	-

Chest CT presented multiple pulmonary thromboembolisms of the left lobe with coexisting pulmonary hypertension (**Figure 2**). Abdominal CT also indicated the possibility of hepatic embolism. The lower limb vascular ultrasound was normal, which excluded deep vein thrombosis (DVT). Moderate to severe PH (PASP: 76 mmHg), enlargement of both the right atrium and ventricle (RA: 48 mm, RV: 26 mm), and moderate tricuspid regurgitation were demonstrated on echocardiography. Then, she underwent right heart catheterization (RHC) which showed the following significant hemodynamic parameters: mean pulmonary artery pressure (mPAP) increased to 31 mmHg (62/13 mmHg), continuous cardiac output (CCO) of 7 L/min, and a pulmonary vascular resistance index (PVRI) of 400 dyne/s/cm⁵, which provided direct evidence for a diagnosis of PAH. Ultimately, a diagnosis of PAPS coexisting with PE, hepatic embolism and thrombocytopenia was made. Additionally, mild PAH related to CTD and aggravated with PE was considered, as well as chronic pulmonary heart disease at decompensation stage.

Platelet transfusion was prescribed because of her extremely low platelet count. Intravenous immunoglobulin (IVIG) and prednisolone (20 mg/day) were used to treat for her high titers of aCL. Warfarin (1.25 mg/day) was added for the thromboembolism and hepatic embolism. At the 3 month follow up, repeated echocardiography showed that both the right atrium and ven-

tricle were smaller than before (RA: 36 mm vs 48 mm, RV: 16 mm vs 26 mm), and there was moderate pulmonary hypertension (65 mmHg). APTT was 47.6 s. IgG aCL was negative (**Table 1**).

Discussion

Syndromes can occur in isolation, termed primary antiphospholipid syndrome (PAPS), or in association with either SLE or other connective tissue diseases, which is referred to as secondary antiphospholipid syndrome (SAPS) [3]. As it is a multisystem disease, PAPS has been reported to affect many organs and tissues that include the heart, kidneys, lung, nerves, intestines, pancreas, skin and blood vessels [4-8]. Pulmonary complications in PAPS are relatively rare compared to the other clinical signs of this disease.

Non-thrombosis PAH is a rare initial presentation in PAPS. According to a lot of many studies, the most common pulmonary complication is pulmonary thromboembolism [9]. Approximately 40% of patients with APS suffer from PE in the course of the disease, and PE is often the first clinical complication of APS, which is different from our present case. Additionally, another decade-long study of 128 cases of PAPS claimed that the most common initial APS manifestations were DVT (33%), pregnancy loss (23%), and stroke (13%) [10].

It is difficult to identify cases in which two types of PAH coexist. A PubMed search for articles published to date was conducted using the following keywords: primary antiphospholipid syndrome and pulmonary hypertension. This returned 64 relevant publications, and only 1 study reported case who manifested PAH with no evidence of PE [11]. We also used the keywords "primary antiphospholipid syndrome" and "primary antiphospholipid syndrome OR CTEPH" to search in PubMed, there are 8 publications, and none that were complicated with non-thrombosis PAH. In addition to the non-thrombosis pulmonary hypertension mentioned in the study of Nagai, our case also confirmed CTEPH several months later, which indicates thrombosis pulmonary hypertension exacerbated previous non-thrombosis pulmonary hypertension. To the best of our knowledge, our case is the first report about this subject to be published.

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Both PAH and APS are severe and progressive conditions associated with significant morbidity and mortality. Patients with PAH and APS usually have a fetal outcome [12-14]. Several researchers have found that CTD related with PAH is associated with a worse prognosis and poor response to therapy than idiopathic pulmonary hypertension (IPAH). The mortality of CTD-PAH is approximately 4 times higher, with a median survival in untreated patients who is as low as 12 months [15-17]. Making a timely and initiating early accurate diagnosis and treatment can markedly improve the quality of life of a patient.

Patients with non-special clinical presentations often suffer from a delayed diagnosis until more typical symptoms develop [18]. Taking an entire medical history was crucial to avoid misdiagnosis and delayed diagnosis of atypical PAPS. Additionally, it will be helpful to elect the optimal therapy if we can distinguish patients with PH due to pulmonary arterial hypertension, left heart disease, pulmonary chronic lung disease, hypoxia, CTEPH and unclear multifactorial mechanisms [19]. In our present case, non-thrombosis PAH was non-special manifestation and the patient was initially diagnosed with "pulmonary hypertension correlated with UCTD". The initial hospital did not consider PAPS, because they ignored the patient history of two fetal losses. When she readmitted to our hospital four months later, the complication of PE occurred, and an accurate diagnosis of PAPS was made.

After arriving at a correct diagnosis of PAPS, prompt therapy is needed. Generally, it is recommended that, unless there is a particular contraindication, permanent anti-coagulation therapy should be added to patients with APS [20]. Moreover, although there is no evidence of PE at the early stage, it is hard to say whether any chronic microthromboembolism had existed but was difficult to detect. Currently, whether preventive anti-coagulation therapy would reduce the risk of thrombosis in patients with PAPS complicated by non-thrombosis PAH is currently unclear [21]. Accordingly, it is necessary to engage in long-term monitoring to patients with non-thrombosis PAH and PAPS.

In conclusion, although it is uncommon, the possibility of the coexistence of CTEPH should be considered in patients with PAPS who pres-

ent with non-thrombosis PAH. Although this case showed PAH without evidence of PE at its early stage, it is not certain that there was no microthromboembolism. Thus, we should still conduct long-term assessments of coagulation function in cases of the emergence of PE. Only by arriving at a timely diagnosis and administering correct therapy, in addition to the collaboration of patients and physicians, can patients with PAPS and/or PAH be stabilized in good condition.

Acknowledgements

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Disclosure of conflict of interest

None.

Abbreviations

Acl, anticardiolipin antibodies; ANA, anti-nuclear antibody; APS, antiphospholipid antibody syndrome; APTT, activated partial thromboplastin time; CT, computer tomography; CTDs, connective tissue diseases; CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; IgG, immunoglobulin G; IgM, immunoglobulin M; IPAH, idiopathic pulmonary hypertension; IVIG, intravenous immunoglobulin; LA, lupus anticoagulant; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; PAPS, primary antiphospholipid antibody syndrome; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; PE, pulmonary embolism; PFT, pulmonary function test; PH, pulmonary hypertension; RA, rheumatoid arthritis; RHC, right heart catheterization; SAPS, secondary antiphospholipid syndrome; SLE, systemic lupus erythematosus; UCTD, undifferentiated connective tissue disease; VTE, venous thromboembolism.

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