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Early diagnosis is crucial for successful treatment of pulmonary arterial hypertension: 2 cases of late diagnosis (RCD code: II-1A.1)

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Abstract

Pulmonary arterial hypertension is a rare disease of pulmonary circulation with poor prognosis if left untreated or diagnosed with delay. Active screening for the disease is not effective in the general population. However, in populations at increased risk for pulmonary arterial hypertension, all efforts should be taken to establish an early diagnosis. Here, we present 2 cases of late diagnosis. The first patient presented with a clear clinical picture, while the second case describes a patient in the at-risk population who received treatment too late to obtain satisfactory results. We discuss the pitfalls which led to delayed diagnosis that finally resulted in treatment failure. JRCD 2019; 4 (3): 47–50

Key words: rare disease, electrocardiography, echocardiography, cardiac catheterization, pulmonary functional test, specific therapy

Introduction

Pulmonary arterial hypertension (PAH) is a rare, progressive disorder, characterised by pulmonary small arteriolar remodelling which causes an increase in pulmonary vascular resistance, leading to progressive heart failure and death [1]. Prevalence of the disease in the general adult population has been reported in numerous registries to vary from 5.9 to 60 cases per million [2,3,4]. The most common presenting symptoms are exertional dyspnoea and fatigue. These symptoms, often subtle, are nonspecific and far more commonly observed in a variety of comorbidities [5]. Thus, there is frequently a long delay between patient-reported onset of symptoms and the diagnosis of PAH. Almost half of patients do not receive a diagnosis within 1 year of symptom onset and almost a third of patients wait over 2 years for a diagnosis [6]. In another analysis, there was nearly a 4-year delay from onset of symptoms to a diagnosis of PAH [7]. Echocardiography is crucial when PAH is suspected, although it must be supported by right heart catheterization (RHC), followed by a thorough differential diagnosis [8].

There are specific populations at increased risk for PAH such as scleroderma spectrum disorder patients, congenital heart disease patients, and drug-exposed individuals [8,9,10] in whom special attention is warranted in order not to miss the correct diagnosis. On the other hand, patients with left-heart diseases or chronic pulmonary disorders often present with echocardiographic signs of a high probability of pulmonary hypertension (PH) which should not be misclassified as PAH. In patients with chronic respiratory disorders presenting with dyspnoea, one may find individuals with PAH and only mild respiratory disease, which is mistakenly classified as the aetiology of their symptoms. All efforts should be taken to diagnose PAH early because advanced disease is less responsive to therapy [11]. Various studies and guidelines support a strategy of early treatment with PAH-specific drugs with therapy escalation based on risk-stratification of death [8].

Here, we report 2 cases. The first case describes a patient with recurrent admissions to the hospital treated without diagnosis, while the second case describes an individual with multiple outpatient visits diagnosed with chronic obstructive pulmonary disease (COPD) but not PH. These cases demonstrate the need for early and proper identification and immediate treatment of patients with PAH.

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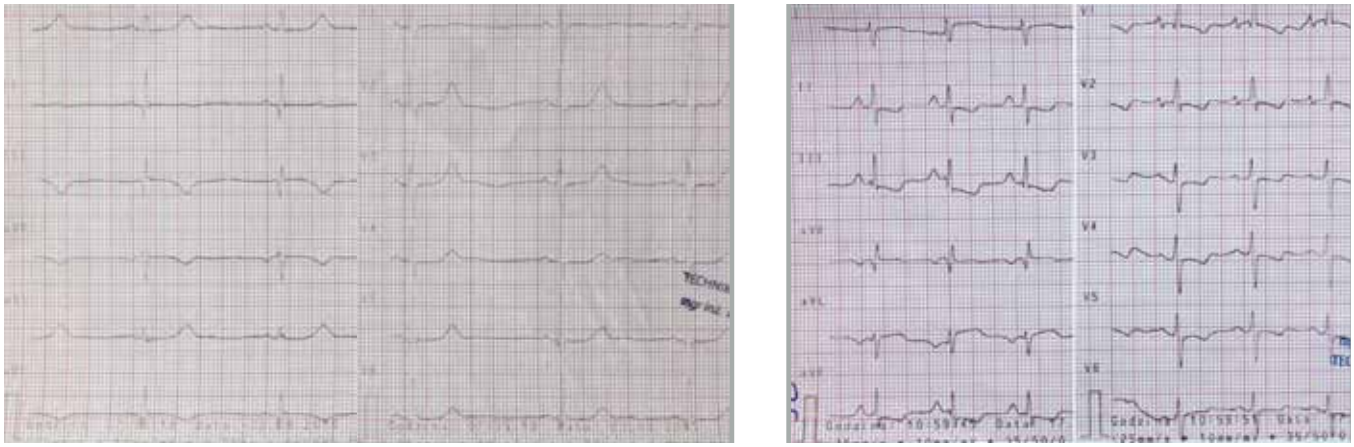

Figure 1. Two different patterns of ECG (2015 and 2018)

Table 1. Transthoracic echocardiograms performed in 2015 and 2018

	2015	2018
LVEDd (cm)	4,5	4,0
RVOT (cm)	3,1	4,8
LVEF (%)	50	60
Diastolic dysfunction	no	grade 1
RAAr (cm^2)	15	40
Tricuspid regurgitation	mild	severe
TR Vmax (m/s)	1,77	3,8
Pleural effusion	no	present

LVEDd – left ventricle end diastolic diameter, RVOT – right ventricle outflow tract, LVEF – left ventricle ejection fraction, RAAr – right atrium area, TR – tricuspid regurgitation

Case presentation

Case 1

In September 2015, a 49-year-old woman was hospitalised in our cardiology department due to acute coronary syndrome without ST elevation. Non-ST segment elevation myocardial infarction was diagnosed. The patient had multi-vessel coronary disease and complete percutaneous coronary revascularization was performed in a staged fashion without any complications. The underlying condition was chronic connective tissue disease, in her case, rheumatoid arthritis (RA). Comorbidities included hyperthyroidism and paroxysmal atrial fibrillation. At that time, no significant abnormalities in heart function were observed. Transthoracic echocardiogram (TTE) was unremarkable (Table 1) except for akinesis of the basal and medial inferior segments of the left ventricle. The patient was discharged without exertional symptoms with persistent signs of RA lesions.

The patient was then hospitalised on multiple occasions due to peripheral oedema over a span of 15 months. In May 2018, she was referred to our department (with a suspicion of PH) due to dyspnoea corresponding to functional class (FC) III according to the New York Heart Association/World Health Organisation (NYHA/WHO). Physical examination on admission revealed crepitations over the lungs, a grade 3 systolic heart murmur (on the Levine Scale), ascites, and peripheral oedema. In the electrocardiogram (ECG) there was a sinus rhythm of 65 bpm, dextrogram with signs of right ventricular (RV) hypertrophy and strain, right atrium enlargement, and pathologic Q waves over the inferior wall (Figure 1).

Laboratory findings were abnormal including an N-terminal-pro hormone of brain natriuretic peptide (NT-proBNP) value of 2672 pg/ml. Chest radiography revealed heart enlargement and interstitial opacifications of the lung fields. Total lung capacity (TLC) in body plethysmography was 88% of normal value, but diffusing capacity of the lung for carbon monoxide (DLCO) was below 50%. In the scintigraphy ventilation-perfusion (VQ) scan there were some perfusion defects in 3 segments with corresponding ventilation defects. We repeated the TTE, which confirmed the presence of severe tricuspid regurgitation (TR) and a high probability of PH (PASP 58 mm Hg, RV enlarged, compressing the left ventricle) (see Table 1 and Figure 2).

Using RHC, we confirmed precapillary PH (mean pulmonary arterial pressure [mPAP] 37 mm Hg at rest, pulmonary capillary wedge pressure [PCWP] 14 mm Hg, pulmonary vascular resistance [PVR] 7.61 Wood Units, right atrial pressure [RAP] 15 mm Hg and cardiac index [CI] as low as 1.83 l/min/m^2). The final diagnosis was precapillary PAH associated with connective tissue disease and the patient was assessed as WHO/NYHA FC III.

After establishing the diagnosis in May 2018, first line treatment for PAH was initiated (inhaled iloprost). This was due to concerns that sildenafil might lead to ineffective perfusion (ventilation/perfusion [VQ] mismatch). Concomitant medications included aspirin 75 mg, trandolapril 0.5 mg, nebivolol 2.5 mg, atorvastatin 40 mg, pantoprazole 20 mg, and propafenone 150 mg b.i.d. After 2 months, functional capacity did not improve and therapy was escalated by adding sildenafil 20 mg t.i.d. Furthermore, the patient did not consent to treatment with parenteral prostanoids. While receiving dual therapy with iloprost and sildenafil, the patient remained in WHO FC III, her 6-minute walking test (6MWT) result was only 231 m, and NT-proBNP level increased to 3768 pg/ml in September 2018.

Therapy with bosentan was initiated while sildenafil was discontinued due to a significant skin allergy.

In November 2018, our patient was admitted with dyspnoea at rest, fluid retention, paroxysmal atrial fibrillation, NT-proBNP level of 5542 pg/ml, hypertransaminasemia, and hyperbilirubinemia. Cardioversion led to cardiogenic shock which was treated with dobutamine and noradrenaline infusions. The high values of liver function tests persisted and bosentan treatment was interrupted. We added macitentan 10 mg daily on top of iloprost, and in January 2019 we added riociguat in order to provide triple antiproliferative therapy. However, the patient had another episode of atrial fibrillation, pneumonia with rapidly progressive cardiorespiratory failure requiring mechanical ventilation, and acute kidney injury following diuretic treatment (for fluid retention). The patient died from septic shock in early February 2019.

Case 2

A 69-year-old female with previously diagnosed moderate COPD was admitted to our cardiology department in September 2018 due to dyspnoea on minimal exertion and signs of fluid retention. Even though she had been complaining about shortness of breath, progressive fatigue, and swelling of the lower extremities since 2016, she had not been referred by her pulmonologist for any additional diagnostic tests. Moreover, COPD treatment introduced previously did not relieve the symptoms of fatigue and dyspnoea. On admission her blood pressure was 98/70 mm Hg, heart rate was 103/min., and rhythm was regular. Physical exam revealed severe oedema of the lower extremities. Laboratory findings were abnormal with an NT-proBNP value of 6431 pg/ml. ECG showed sinus tachycardia, right-axis deviation, right atrial hypertrophy, and RV hypertrophy with strain (Figure 3).

TTE revealed severe TR with peak velocity of 4 m/s, enlarged and hypokinetic RV with a 'D-shaped' left ventricle, RV outflow Doppler acceleration time of 81 msec, pulmonary artery diameter of 30 mm, right atrial area = 24 cm^2, and an inferior vena cava diameter of 20 mm with decreased inspiratory collapse <50% with a sniff. Pulmonary artery systolic pressure (PASP) was estimated to be 75mmHg, and because of this, PH was suspected.

High-resolution computer tomography (HRCT) of the lungs was performed and revealed signs of centrilobular emphysema located in the upper lung zones, ground-glass opacities and air trappings located in the lower lung zones, and a few fibrotic interstitial segments in the lower zone of the left lung together with thickened interlobular and centrilobular lung septa located at the lung apex (Figure 4). Since TLC measured by body plethysmography was found to be around 70% of predicated value, we classified the HRCT lung changes as moderate in intensity.

After several days of supportive treatment, the patient underwent RHC, which confirmed precapillary PH (mPAP: 52 mmHg, PCWP: 7 mmHg, CI: 2.36 L/min/m^2, PVR: 12.64 WU). Vasodilator testing was performed with inhaled iloprost and was negative for vasoreactivity. The final diagnosis was severe precapilliary PAH in a patient with mild to moderate combined pulmonary fibrosis and emphysema (CPFE).

As the patient's condition significantly deteriorated despite treatment with diuretics and digoxin, we decided to implement therapy

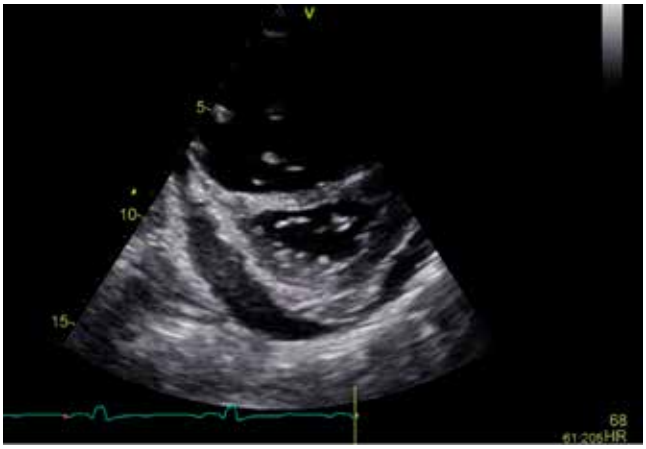

Figure 2. Short-axis echo view with massive enlargement of right ventricle, pericardial effusion and compressed left ventricle

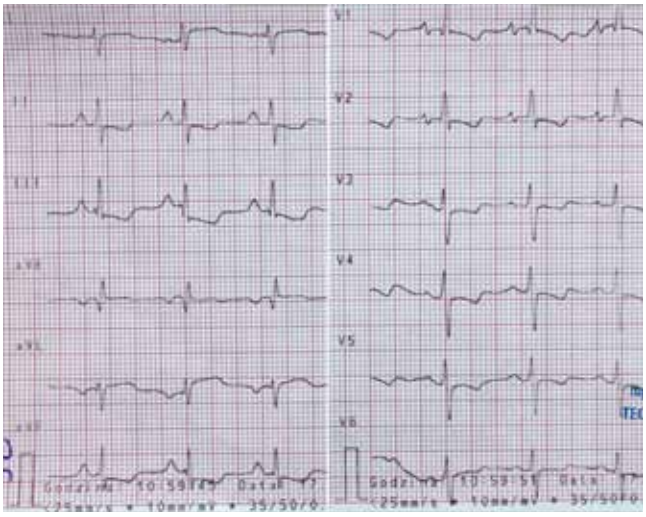

Figure 3. ECG showing right axis deviation with right ventricular hypertrophy and strain

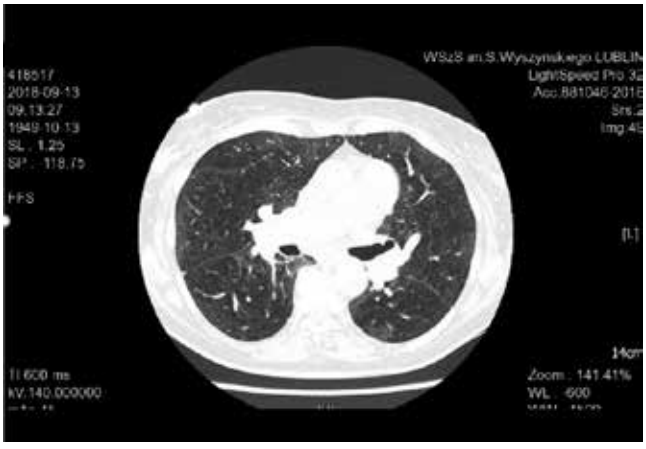

Figure 4. High resolution computed tomography of lungs showing moderate lung emphysema and fibrosis

with sildenafil and macitentan. The patient did not consent to treatment with epoprostenol or treprostinil. Unfortunately, progressive cardiorespiratory failure ensued and the patient died several weeks later from complications of pneumonia.

Discussion

Here, we describe 2 cases of PAH patients who were candidates for therapy much earlier in the course of the illness. Several factors contributed to the delay in diagnosis.

According to guidelines [8,9], patients with scleroderma spectrum disorders should have regular monitoring for the development of PAH. Although our patient with RA did not meet this criteria, the prevalence of PAH in patients with RA is still substantially higher than that of idiopathic PAH [12]. From this perspective, when hospitalised for a different reason, the patient should have been included in a frequent follow-up group dedicated to PAH identification. Unremarkable echocardiographic examination on first presentation (when hospitalised for acute coronary syndrome) did not rule out the need for close follow-up in this patient. Unfortunately, severe and recurrent symptoms of fluid retention due to right heart failure, which required the use of intravenous diuretics during numerous hospitalisations (in a secondary hospital), did not result in patient transfer to a reference hospital. It is expected that echocardiographic findings of right heart chamber dilatation would have been evident. Moreover, the patient was monitored by a rheumatologist, however, regular follow-up visits were not planned. Regular rheumatologic workup would have increased the probability of PAH diagnosis earlier. When finally transferred to a PAH centre, the patient presented with a whole spectrum of symptoms suggestive of severe chronic right heart failure. According to current data, there is a high risk of 1-year mortality in such a patient [8,13]. Furthermore, the response to therapy was poor, making the prognosis even worse.

Our second case described a patient with precapilliary PH and only mild to moderate chronic pulmonary disorder who had been treated for years as COPD. It is unclear whether the patient had PAH and concomitant respiratory pathology or if this was a case of "severe PH" in a patient with significant CPFE. When dual oral treatment for possible PAH was introduced as a rescue strategy in this severely compromised patient, we did not observe exacerbation of hypoxia, as one would expect if ineffective perfusion ('VQ mismatch') had occurred. Unfortunately, the patient died from severe hospital-acquired pneumonia.

There is often the difficult issue of differential diagnosis in such a case. PH due to chronic pulmonary diseases constitutes group 3 of the WHO PH classification [8] and does not require PAH-specific treatment according to current guidelines [14]. Although mPAP and PVR in group 3 PH is less elevated than in most of the other PH groups, this patient population has the worst prognosis of all PH groups [15]. Among PH group 3 patients, there are those with "severe PH" who meet at least 2 out of 3 criteria: mPAP > 35 mm Hg, mPAP ≥ 25mmHg, and CI <2.0L/min/m^2 or PVR>6WU [14]. The differential diagnosis in this group of patients should include PAH, as it suggests that a different pharmacological strategy should be introduced. Our second patient meets the criteria for allocation to the PAH group. These criteria, according to the Cologne Consensus Conference 2018, are as follows: normal or slightly decreased ventilatory function (forced expiratory volume in 1 s of 60% of the normal range for COPD and a vital capacity of 70% of normal range for idiopathic pulmonary fibrosis (IPF), absence of serious lung parenchymal changes on HRCT scans, and predominant circulatory limitation on physical exercise [14]. Although the second patient had regular outpatient follow-up visits with a pulmonologist, she did not respond to the prescribed therapy. In fact, the patient's condition slowly deteriorated and she was finally admitted to the hospital with breathlessness and signs of RV failure. Transfer to a PAH centre resulted in diagnosis of PAH, however, treatment was introduced too late and was unsuccessful.

The presented cases emphasize the importance of early PAH diagnosis. Although difficult to establish in the setting of many common comorbidities, this task is essential for treatment success and survival. Special attention should be taken when screening for the disease among high risk populations.

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