Rapid progressive idiopathic pulmonary arterial hypertension (RCD code: II-1A.1)

Leszek Drabik*, Grzegorz Kopeć, Piotr Podolec

John Paul II Hospital, Department of Cardiac and Vascular Diseases of the Jagiellonian University, Medical College, Krakow, Poland

Abstract

A 48-year-old woman was admitted to our centre with symptoms of right heart failure. Pulmonary arterial hypertension (PAH) was diagnosed. The patient's general condition deteriorated despite initiation of sequential PAH specific therapy and hemodynamic support. Coexisting fungal mural endocarditis led to devastating consequences. Infection presented in a deceptive manner. The patient was afebrile, inflammatory markers were low, blood cultures were negative for bacteria, echocardiography revealed only an increased trabeculation of the right ventricle.

The authors discuss management of decompensated right ventricular failure secondary to chronic pulmonary hypertension. The literature on fungal mural endocarditis is also reviewed. JRCD 2013; 1 (2): 69–74

Key words: progressive idiopathic pulmonary arterial hypertension, right ventricular failure, fungal mural endocarditis, sibutramine

Background

Data from registries confirm that the prevalence of pulmonary arterial hypertension (PAH) is in the range of 15 to 50 cases per million [1,2]. Current clinical classification distinguishes several forms of PAH, namely, idiopathic PAH, heritable, induced by drugs and toxins, associated with other disorders (e.g. connective tissue diseases, HIV infection, portal hypertension, congenital heart disease), and persistent pulmonary hypertension of the newborn [3].

Several anorectic drugs, such as aminorex, fenfluramine, dexfenfluramine, and benfluorex have been shown to be directly related to the development of PAH. Some other drugs and toxins are also suspected to participate in its development, especially those disturbing noradrenergic and serotonergic systems, including selective serotonin uptake inhibitors, cocaine, and methamphetamines [4]. Sibutramine is a serotonin and noradrenaline reuptake inhibitor used in patients with obesity to facilitate weight loss. Short-term observations from several clinical trials did not show an increased risk of pulmonary hypertension in patients taking sibutramine. [5]. However, postmarketing data have shown at least 1 case of pulmonary hypertension that may be attributed to this drug [6].

Case presentation

A 48-year-old woman was admitted to the Center for Rare Cardiovascular Diseases, Krakow, Poland, on June 18, 2010, with a 2-month history of breathlessness and fatigue at rest (New York Heart Association functional class IV on admission). The patient reported milder symptoms for several months prior to admission. Proximal deep vein thrombosis of the left leg was recognized 2 months before admission. Anticoagulation therapy with heparin intravenously was initiated and subsequently converted to warfarin.

In the past (July and August 2009), the patient had a short episode of sibutramine use to reduce weight. A family history was negative for pulmonary hypertension.
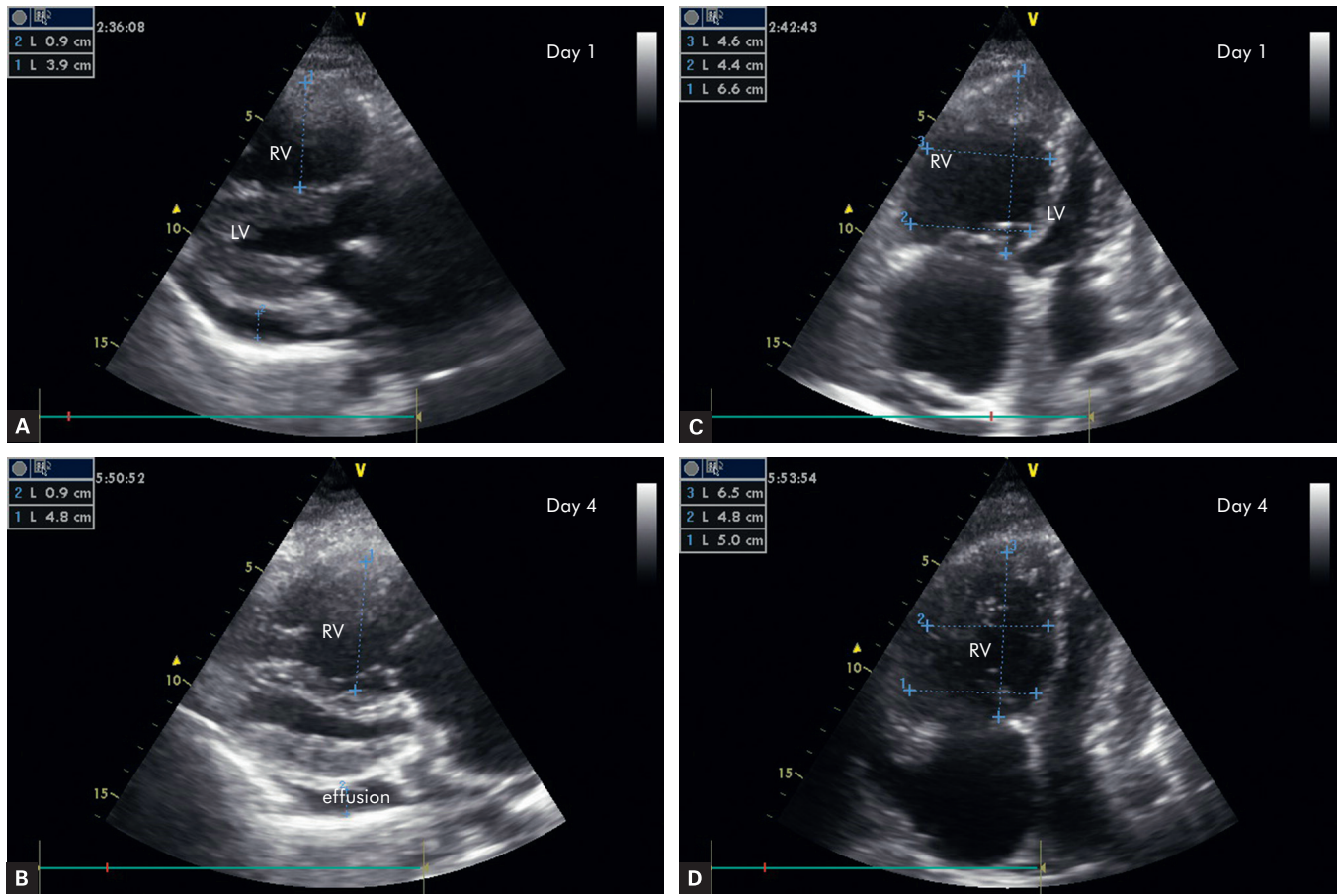
On admission, the patient was in a bad general condition. The signs and symptoms of advanced heart failure were observed. A physical examination revealed low blood pressure (96/58 mm Hg), regular heart rate 88 beats/min, accentuated pulmonary component of the second heart sound, high-pitched pansystolic murmur, most prominent in the fourth intercostal space in the left parasternal region, jugular vein distension, decreased breath sounds at the lung bases, hepatomegaly, central cyanosis,
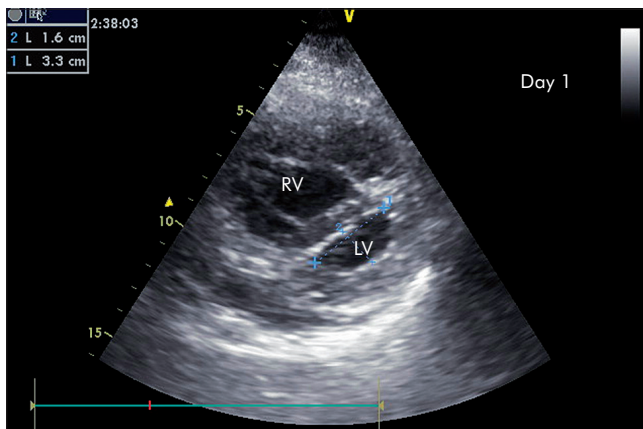
Figure 1. Transthoracic echocardiography. A, B. Parasternal long-axis view. C, D. Apical four-chamber view. Dynamic progression of right chambers dilatation between day 1 (A,C) and day 4 (B,D) of hospitalization. Main abnormalities include enlarged right ventricle (RV), small left ventricle (LV), pericardial effusion. A,B. RV end-diastolic diameter measured at proximal portion of RV outflow tract: day 1 – 39 mm, day 4 – 48 mm. C,D. RV end-diastolic inflow tract diameter: day 1 – 44 mm, day 4 – 48 mm; RV long-axis: day 1 – 66 mm, day 4 – 65 mm; RV end-diastolic area: day 1 – 24.4 cm2, day 4 – 30.9 cm^2
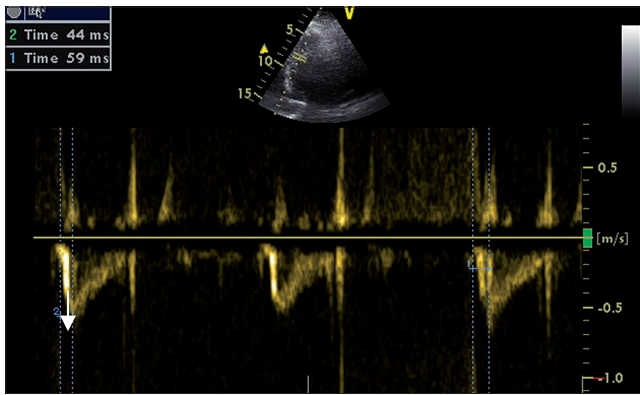

Figure 2. Transthoracic echocardiography. Parasternal short-axis view at the mid-ventricular level. Day 1 enlarged right ventricle (RV); small left ventricle (LV). The interventricular septum is shifted toward the LV cavity. The LV eccentricity index above 1 suggests RV pressure overload (LV eccentricity index = LV anteroposterior diameter / LV septolateral diameter = 33 mm / 16 mm = 2.06)
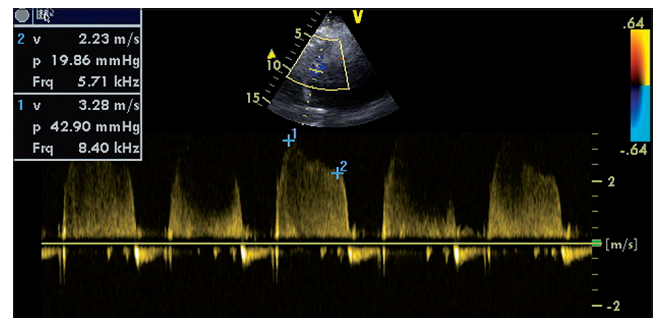
Figure 3. Transthoracic echocardiography. Continuous-wave Doppler. Pulmonary regurgitation flow pattern. Increased peak early-diastolic pulmonary regurgitation gradient (43 mm Hg)

massive peripheral edema, ascites, and obesity (body mass index, 32.8 kg/m^2). Pulse oximetry showed low SpO$_2$ of 86%. Routine laboratory tests revealed polycythemia (red blood cells, 5.6×10^3/μL; hemoglobin 16.7 g/dL, and hematocrit, 50.7%), elevated levels of brain natriuretic peptide (2871 pg/mL; N <100 pg/mL), troponin I (0.16 ng/mL; N <0.1 ng/mL), C-reactive protein (7.6 mg/mL), international normalized ratio of 2.26, and normal levels of D-dimers (<300 ng/mL). HIV and antinuclear and anticentromere antibod-

Figure 4. Transthoracic echocardiography. Pulsed-wave Doppler. Pulmonary flow pattern with short acceleration time of 52 ms (arrow)

Figure 5. Transthoracic echocardiography. A. Pulsed-wave Doppler. Mitral flow pattern. E/A = 0.42. B. Pulsed tissue Doppler of mitral annulus. E′ = 6 cm/s

Tabela 1. Hemodynamic data at baseline and after 5 minutes of nitric oxide (20 ppm) inhalation

Pressure [mm Hg]	Baseline	After NO
right atrium	26/21/19	—
pulmonary artery	111/47/69	110/46/72
left ventricle	104/10/16	100/5/9
aorta	102/75/85	–
Saturation [%]		
superior vena cava	43.1	–
interior vena cava	40.7	–
pulmonary artery	36.2	28
aorta	87	83
cardiac output [L/min]	1.78	1.64
cardiac index [L/min/m^2]	1.0	0.9
ratio of pulmonary to systemic flow	1:1	1:1
pulmonary vascular resistance [dyne × s × cm^{-5}]	3095	3071

performed due to dyspnea at rest. Venous ultrasound examination excluded the recurrence of deep-vein thrombosis.

Transthoracic echocardiography revealed numerous abnormalities (fig. 1–5):

– right ventricular (RV) and right atrial enlargement: RV end-diastolic area was 26 cm^2 (N <25 cm^2); right atrial area at ventricular end-systole was 23 cm^2 (N <18 cm^2)

– small left ventricle (left ventricular [LV] end-diastolic diameter, 27 mm; LV eccentricity index, 2.06)

– impaired RV systolic function: RV fractional area change was 23% (N >35%); tricuspid annular plane systolic excursion was 10 mm (N >16 mm)

– paradoxical septal motion

– preserved LV ejection fraction of 70%

– impaired LV diastolic function

– increased trabeculation of the right ventricle

– moderate-to-severe tricuspid regurgitation due to RV and tricuspid annular dilatation: vena contracta width was 6 mm, tricuspid E-wave velocity was 0.7 m/s, and effective regurgitant orifice area was 0.35 cm^2

– dilated inferior vena cava of 28 mm without any collapse with a sniff

– increased RV systolic pressure estimated at 91 mm Hg as a sum of tricuspid regurgitation peak gradient (76 mm Hg; V_{max} 4.3m/s) and right atrial pressure (15 mm Hg)

– increased mean pulmonary artery pressure estimated at 58 mm Hg as a sum of early-diastolic pulmonary regurgitation gradient (43 mm Hg; V_{max} 3.3 m/s) and right atrial pressure

– dilated pulmonary trunk and branches

– short acceleration time of pulmonary arterial flow (52 ms)

– mild pulmonary regurgitation

ies were negative, and so were the blood cultures for bacteria and fungi. Arterial oxygen and carbon dioxide tensions were decreased (PaO$_2$, 56 mm Hg; PaCO$_2$, 25 mm Hg). A resting electrocardiogram showed right axis deviation and low-voltage R waves in the limb and precordial leads. A Holter examination revealed increased heart rate (mean, 88/min) and single premature ventricular beats. A chest X-ray showed an enlarged cardiac silhouette, mild prominence of the main pulmonary artery, redistribution of pulmonary blood flow, and moderate pleural effusion in the right pleural cavity. Pulmonary function tests and 6-minute walking test could not be

Table 2. Etiology of acute right ventricular failure in pulmonary hypertension [40]

– Myocardial ischemia
– Sepsis
– Infective endocarditis
– Pulmonary embolism
– Atrial and ventricular tachyarrhythmias
– Iatrogenic causes:
  – acute withdrawal of PAH-specific therapy
  – use of
    – negative inotropic agents (β-blockers, calcium channel blockers)
    – sedatives
    – vasodilators (nitroprusside, milrinone)
    – mechanical ventilation with high plateau and high positive end-expiratory pressures

Table 3. Recommendations for pulmonary arterial hypertension – targeted therapy in patients at functional class IV [7]

	class* level#
Epoprostenol i.v.	I/A
Ambrisentan, Bosentan, Sildenafil, Tadalafil, Iloprost inhaled, i.v., Treprostinil s.c., i.v., inhaled	IIa/C
Sequential combination therapy ERA ±PDE-5I ±prostanoids	IIa/B
Initial combination therapy ERA ±PDE-5I ±prostanoids	IIa/C

* Class of recommendation
# Level of evidence
ERA – endothelin receptor antagonist; PDE-5I – phosphodiesterase type-5 inhibitor

Table 4. Recommendations for supportive therapy in pulmonary arterial hypertension [7]

	class* level#
Diuretic treatment in patients with the signs of RV failure and fluid retention	I/C
Continuous long-term O2 therapy if arterial blood O2 pressure is consistently less than 8 kPa (60 mm Hg)	I/C
Oral anticoagulant treatment in patients with idiopathic PAH, heritable PAH, and PAH caused by anorexigens	IIa/C
Oral anticoagulant treatment in patients with PAH due to the use of anorexigens	IIb/C
Digoxin in patients who develop atrial tachyarrhythmias to slow ventricular rate	IIb/C

* Class of recommendation
# Level of evidence
PAH – pulmonary arterial hypertension, RV – right ventricular

– ratio of pulmonary-to-systemic flow of 1:1
– moderate pericardial effusion without features of tamponade

Contrast computed tomography (CT) angiography of the pulmonary artery did not reveal pulmonary embolism. High-resolution CT excluded interstitial lung disease and emphysema but confirmed the presence of pleural effusion with a 5-cm layer in the right pleural cavity and pericardial effusion (8 mm). Using right-sided thoracentesis, we were able to evacuate 200 mL of transudate.

Coronary angiography revealed no critical lesions in the coronary arteries. Right heart catheterization showed severe pulmonary hypertension (mean pulmonary artery pressure, 69 mm Hg), increased pulmonary vascular resistance (PVR, 3095 dyne $\times$ s $\times$ cm^{-5}; 38.7 Wood units), borderline pulmonary capillary wedge pressure (15 mm Hg), and very low cardiac output – 1.78 L/min (1.0 L/min/m^2). The results of a vasoreactivity test with inhaled nitric oxide were negative (Table 1).

The patient's general condition deteriorated despite the initiation of sequential PAH-specific therapy (iloprost, 5 mcg 6 times/day; subsequently, combination therapy with sildenafil, 20 mg t.i.d,) and supportive treatment (warfarin, digoxin, diuretics, inotropic agents, oxygen supplementation). Intravenous epoprostenol was not available at that time. Transthoracic echocardiography revealed progression of ventricular enlargement and dysfunction (fig. 1). The patient died 4 days after admission due to low-output heart failure. A histological examination of specimens obtained during autopsy revealed primary pulmonary arteriopathy and fungal mural endocarditis.

Discussion

Overall 5-year survival for idiopathic PAH has increased from approximately 30% in the 1980s to approximately 60% at present. This is mainly associated with the introduction of PAH-specific therapy to clinical practice. RV failure is the leading cause of death in PAH [7]. The management of decompensated RV failure secondary to pulmonary hypertension requires treatment of the underlying cause and hemodynamic support (Table 2–4). The RV function can improve significantly in patients with myocardial infarction who underwent revascularization or in unstable patients with acute pulmonary embolism after thrombolytic therapy or embolectomy [8,9]. Thromboendarterectomy is a treatment option for patients with chronic thromboembolic pulmonary hypertension and RV failure [10]. Treating the reversible underlying cause of the disorder improves prognosis. The effect of hemodynamic support on long-term survival is not clear. Hemodynamic support includes oxygen, intravenous fluids, inotropic agents, pulmonary vasodilators, mechanical assist devices, and surgery. The effect of volume loading on ventricular hemodynamics depends on the degree of RV afterload and volume status. Low preload restricts cardiac output. Fluid administration may improve the condition of patients without increased right-sided preload and LV failure. On the other hand, volume overload may lead to overdistension of the RV, increased wall tension, decreased contractility, interventricular septal shift, and compression of the LV that results in decreased LV filling and reduced systemic cardiac output [11]. Patients with severe RV dysfunction often have high RV filling pressure, and aggressive fluid resuscitation can worsen

Table 5. Recommendations for surgical treatment of right-sided infective endocarditis [35]

	class* level#
Microorganisms difficult to eradicate (e.g., persistent fungi) or bacteremia for >7 days (e.g., *S. aureus, P. aeruginosa*) despite adequate antimicrobial therapy	IIa/C
Persistent tricuspid valve vegetations >20 mm after recurrent pulmonary emboli with or without concomitant right heart failure	IIa/C
Right heart failure secondary to severe tricuspid regurgitation with poor response to diuretic therapy	IIa/C

* Class of recommendation
# Level of evidence

their condition [12]. Diuretic therapy and restriction of fluid and sodium intake reduces ventricular filling pressures. Intravenous loop diuretics are most efficient in patients with severe congestion and hypoperfusion. Typically, they are used in combination with other diuretics. Hemofiltration is an option if volume overload and renal dysfunction are present [13].

Inotropic agents, such as dobutamine, milrinone, or levosimendan, improve biventricular function but may cause vasodilation and systemic hypotension [14,15]. Combined treatment with inotropes and vasopressors may increase cardiac output without causing hypotension and hyperfusion, but it is associated with an increased risk of proarrhythmic events. In normotensive patients with decreased cardiac output, therapy may be started with inotropic agents. Vasopressors should be added if hypotension develops. In hypotensive patients, vasopressors should be instituted followed by inotropes if cardiac output remains low [16]. The choice of vasopressors and inotropes should be individualized and based on a patient's response and effects on PVR and cardiac output. Adverse effects limit the use of drugs of both classes. Dobutamine in moderate doses (above 5 µg/kg/min) may cause tachycardia and systemic hypotension [17]. Norepinephrine increases PVR and worsens PAH. Beneficial effects include a decrease in the ratio of pulmonary arterial pressure to systemic blood pressure [18]. Dopamine and epinephrine increase PVR and have high proarrhythmic potential [19]. Vasopressin, owing to nonadrenergic mechanism of action, may help avoid exacerbation of tachycardia but, at high doses, may increase PVR [20]. Digoxin may produce a small increase in cardiac output and is useful for controlling heart rate [21].

Vasodilators may improve RV output by reducing afterload. Systemic vasodilators, such as nitroglycerine and nitroprusside, reduce right ventricular preload and afterload at the cost of decreased systemic vascular resistance, which may cause hypotension, worsen ischemia, and reduce right-sided cardiac output [22]. Pulmonary vasodilators can significantly reduce pulmonary artery pressure, improve ventilation/perfusion matching, and arterial oxygenation. Inhalation route of administration and a short half-life prevents systemic vasodilation [23]. Inhaled nitric oxide improves cardiac output in patients with pulmonary hypertension of varied origin, for example, acute respiratory distress syndrome, pulmonary embolism, and chronic obstructive pulmonary disease [24].

Rapid interruption of nitric oxide administration causes rebound pulmonary hypertension and rapid clinical deterioration. A gradual discontinuation prevents rebound effect [25]. Inhaled iloprost, a prostacyclin analog, appears to induce greater hemodynamic improvement [26]. Other prostacyclin analogs, such as subcutaneous or intravenous treprostinil and intravenous alprostadil, have relatively long half-lives and higher risk of hypotension [27]. Epoprostenol has the highest recommendation (1/A) in the treatment of PAH in the World Health Organization class IV [7]. Pulmonary vasodilators can also increase capillary wedge pressure in patients with concomitant severe LV dysfunction leading to pulmonary edema. Other PAH-specific drugs, including phosphodiesterase-5 inhibitors and endothelin receptor antagonist, are usually introduced after an episode of acute right heart failure (Table 3). Sildenafil, a phosphodiesterase-5 inhibitor, can be used to minimize rebound pulmonary hypertension after inhaled nitric oxide discontinuation [28]. Data on endothelin receptor antagonist use in the setting of acute RV failure are limited. A combination of pulmonary vasodilators and milrinone, a new inotropic and vasodilator agent, has additive effect on pulmonary vasodilation and RV contractility [29].

In selected patients, intraaortic balloon pump may increase coronary artery perfusion and reduce ischemia. RV assist devices and extracorporeal membrane oxygenation may be an option for patients with potentially reversible acute pulmonary hypertension [30]. Other surgical options include atrial septostomy and lung or heart and lung transplantation. However, they are associated with high morbidity and mortality in critically ill patients [31]. Patients with respiratory failure may require mechanical ventilation. A strategy based on reduction of transpulmonary pressure (low tidal volumes) and end-expiratory pressure limits the negative effect of mechanical ventilation on PVR [32]. Treatment with 100% oxygen reduces PVR in patients with PAH [33].

Patients without the signs of RV volume overload should be treated with fluids and, subsequently, with pulmonary vasodilators. Patients with RV volume overload should receive vasopressors, inotropic agents, and pulmonary vasodilators. If unsuccessful, mechanical assist devices, balloon atrial septostomy, and transplantation should be considered. Invasive hemodynamic monitoring may be helpful in guiding management [8,11,13].

Fungi are responsible for 1% to 6% of the cases of infective endocarditis (IE). The incidence of fungal endocarditis in patients with PAH is unknown. Pierrotti et al.,[34] analyzed 152 cases of fungal endocarditis reported in English-language literature between 1995 and 2000. The most common predisposing conditions included underlying anatomical cardiac conditions, prosthetic cardiac devices, central venous catheters, and previous antibiotic use. *Candida* and *Aspergillus* species were identified in 95 and 28 patients, respectively. Patients with Candida IE had positive blood culture more often than patients with *Aspergillus* IE (81.2% vs. 30.8%). Transthoracic echocardiography demonstrated vegetations or myocardial abscess in 81% and 5.9% of the cases, respectively. The overall mortality rate was 56.6%. The mortality rate among patients with *Aspergillus* IE exceeded 90% [34]. Amphotericin B remains the drug of choice for antifungal therapy. Successful monotherapy with caspofungin has also been reported. Valve replacement may improve prognosis in selected patients (Table 3) [35,36].

Nonvalvular mural endocarditis is an uncommon condition. Kearney et al. [37] described 52 patients with mural endocarditis in 3 autopsy studies. The majority of these infections were caused by bacteria [37]. The most common symptoms of fungal mural endocarditis include fever, chills, and peripheral embolization. Transthoracic echocardiography or magnetic resonance imaging may reveal nonvalvular mural mass intertwined within the ventricular trabeculae [38,39]. In patients with fungal mural endocarditis, blood cultures are rarely positive (7%–16%). The prognosis for fungal mural endocarditis is poor. IE may exacerbate RV failure in chronic pulmonary hypertension [40]. The death of our patient might have been, at least partially, related to IE.

Management strategy

Our patient suffered from 2 rare disorders: PAH and fungal mural endocarditis. The examinations suggested that the symptoms of RV failure could be attributed to PAH. Fungal mural endocarditis was diagnosed postmortem. It presented in a subtle and unremarkable manner: the patient was afebrile, inflammatory markers were low, blood cultures were negative, and echocardiography revealed only increased trabeculation of the RV. A rapid deterioration of the patient's condition limited the time of diagnosis. Clinical diagnosis of PAH was confirmed by autopsy. The association between PAH and exposure to sibutramine cannot be excluded.

We observed insufficient response to PAH-specific drugs (sildenafil and iloprost) and supportive treatment (warfarin, digoxin, diuretics, inotropic agents, O_2 therapy). We suspect that IE contributed to this poor response.

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