Sarcoidosis-associated pulmonary hypertension treated with sildenafil

The authors declare no financial disclosure

Abstract

Development of sarcoidosis-associated pulmonary hypertension (SAPH) significantly worsens prognosis in sarcoidosis patients. Unfortunately, there is no treatment of proven benefit for this condition. Medications used for treatment of pulmonary arterial hypertension are of great interest in this respect. Here, we report a case of a patient with severe SAPH treated with sildenafil. A significant, but only temporary improvement in functional status was observed, and the patient died of gradually progressing heart and respiratory failure while awaiting for lung transplantation.

Key words: sarcoidosis, pulmonary hypertension, treatment, sildenafil

Introduction

Sarcoidosis is a multisystem inflammatory disease of unknown aetiology that manifests as noncaseating granulomas in affected tissues, predominantly in the lungs and intrathoracic lymph nodes. It is a very heterogeneous condition in respect of clinical picture and prognosis [1]. One of the possible complications of sarcoidosis is pulmonary hypertension (PH). In the general sarcoidosis population, PH prevalence is estimated to be around 6%, but it rises up to 74% in an advanced fibrotic pulmonary sarcoidosis [2–4]. The severity of sarcoidosis-associated PH (SAPH), in contrast to its prevalence, does not correlate with the extent of pulmonary abnormalities on radiological studies or body plethysmography [5]. Pulmonary hypertension worsens symptoms and negatively influences survival in sarcoidosis [5–7]; unfortunately, there is no treatment of proven benefit for SAPH [8]. Because of poor prognosis related to this complication, there is a constant search for an effective treatment. Below, we report a case of a patient with severe SAPH who was treated with sildenafil.

Case report

A 53-year-old Caucasian woman was diagnosed with stage IV sarcoidosis (chest x-ray showed in Fig. 1) in 2010. She presented with Löfgren’s syndrome, and the diagnosis was confirmed with pathologic examination of the mediastinal lymph node. The initial computed
tomography (CT) of the chest (Fig. 2) revealed mediastinal and hilar lymphadenopathy, massive lung fibrosis, small nodular opacification, areas of ground-glass opacifications, and thickened interlobular septa. Features of PH were also seen: dilated central pulmonary arteries and tapered peripheral vessels, enlarged right atrium (RA) and right ventricle (RV) of the heart. Pulmonary thromboembolic disease was excluded. Transthoracic echocardiography (TTE) was compatible with high probability of PH: tricuspid valve regurgitation pressure gradient (TVPG) of 50 mm Hg, shortened acceleration time of RV ejection into the PA (AcT Pa) — 74 ms (N ≥ 120 ms), abnormal function of the interventricular septum (IVS), borderline size of RA, RV and pulmonary artery (PA). The diameter of the inferior vena cava (IVC) and its collapsibility index were normal. Systolic PA pressure (PAPs), estimated from TVPG and IVC, was 55 mm Hg. The chambers and valves of the left heart were normal, there were no signs of congenital heart disease. Pulmonary function testing (PFT) revealed moderately restrictive pattern with total lung capacity (TLC) 62 % of predicted (pred.) and severe impairment of diffusing capacity of the lungs for carbon monoxide (DLCO) — 31% pred. In six-minute walk test (6MWT), the patient covered the distance of 408 m, desaturation from

Figure 1. Chest x-ray showing diffuse nodular and linear opacifications dominating in upper and middle fields of the lungs as well as enlarged heart silhouette

Figure 2. Chest CT study: A,B,C — lung window scans showing massive lung fibrosis with areas of nodular and ground-glass opacifications as well as thickened interlobular septa; D — mediastinal window scans showing dilated PA (30 mm) and proximal pulmonary arteries, narrow and winding peripheral pulmonary arteries, and enlarged mediastinal lymph nodes.
93% to 74% was observed, dyspnoea on exertion was moderate according to the Borg scale. Serum concentration of N-terminal pro-brain natriuretic peptide (NT-proBNP) was 49 pg/ml (N < 125 pg/ml). Due to extensive interstitial lung disease, restrictive pattern on PFT with low DLCO and deep desaturation on exertion, prednisone 0.7 mg/kg body weight (40 mg daily) was commenced. Six months later subjective improvement was noted. The 6MWT distance increased by 160 m. Chest x-ray, TTE, PFT indices and exertional desaturation were, however, comparable to those from the baseline. In addition, the patient’s body weight increased by 10 kg. Because of unsatisfactory therapeutic outcome and the presence of side-effects, the dose of prednisone was reduced to 20 mg per day, and methotrexate at a dose of 15 mg once a week was added. In the next months, an improvement on chest CT scans was noted with significant regression of hilar and mediastinal lymphadenopathy, resolution of ground-glass and nodular opacifications. Massive fibrotic conglomerates persisted. TLC increased to 89% pred., but there was no significant change in DLCO. For another 2 years the patient’s condition remained stable. The doses of prednisone and methotrexate were meanwhile gradually lowered to 7.5 mg/d and 12.5 mg/week, respectively. In 6MWT, performed with oxygen supplementation, the patient covered the distance of 318 m with desaturation from 95% to 71%. NT-proBNP serum concentration decreased to 351 pg/ml. DLCO remained low — 20% pred. At this point the patient was referred to a lung transplant centre, and soon she got enrolled on a waiting list. The positive response to sildenafil did not persist, and nine months after the drug commencement, marked progression of PH and RV failure was seen. NT-proBNP serum concentration reached 7179 pg/ml. After seventeen months of sildenafil treatment and six years after initial presentation with SAPH, the patient died of gradually progressing heart and respiratory failure. An autopsy was not performed.

**Discussion**

Sarcoidosis-associated PH was suspected in our patient in 2010, based on the results of TTE examination. The presence of sPAP 55 mm Hg, shortened AvcT and abnormal movement of interventricular septum indicate high probability of PH, according to the latest ESC/ERS guidelines [8]. SAPH belongs to group 5 of clinical classification of PH, i.e. group including PH with

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Year</th>
<th>PAPs/d/m [mm Hg]</th>
<th>RAP [mm Hg]</th>
<th>PAWP [mm Hg]</th>
<th>CI [l/min·m²]</th>
<th>PVR [Wood units]</th>
<th>SaO₂mv [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>49/19/31</td>
<td>3</td>
<td>6</td>
<td>2.95</td>
<td>4.96</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>54/28/38</td>
<td>3</td>
<td>9</td>
<td>2.50</td>
<td>7.02</td>
<td>65</td>
<td></td>
</tr>
</tbody>
</table>

PAPs/d/m — pulmonary artery pressure systolic/diastolic/mean; RAP — right atrium pressure; PAWP — pulmonary artery wedge pressure; CI — cardiac index; PVR — pulmonary vascular resistance; SaO₂mv — mixed venous blood oxygenation
unclear and/or multifactorial mechanisms [8]. Mechanisms involved in development of SAPH are: fibrotic lung disease with destruction of pulmonary vessels, extrinsic compression of pulmonary vessels by lymphadenopathy or fibrosing mediastinitis, granulomatous pulmonary arteriopathy and venopathy, systemic vasculitis with pulmonary vascular involvement, LV systolic or diastolic dysfunction, portal hypertension [9]. In the presented patient, the most probable cause of PH was interstitial granulomatous and fibrotic lung disease that caused restrictive pattern of PFT. Left-heart failure, extrinsic compression of pulmonary vessels and portal hypertension were excluded. RHC was not incorporated in the initial assessment, as PH guidelines recommended it in patients with chronic lung diseases only in the following cases: evaluation for lung transplant was deemed necessary, clinical worsening and progressive exercise limitation was disproportionate to ventilatory impairment, progressive gas exchange abnormalities were disproportionate to ventilatory impairment, or there was a suspicion of left ventricular dysfunction [10]. Initial therapy, including glucocorticosteroid (GC) and later added methotrexate, resulted only in partial regression of interstitial lung disease. Despite TLC normalisation, the gas exchange impairment persisted. Moreover, the immunosuppressive therapy had no influence on PH assessed by echocardiography. The knowledge about the impact of GCs and other immunosuppressive agents on SAPH is limited, but improvement in PH was achieved in some of patients [5, 11], while the therapy was not successful in others, mainly in those in whom lung fibrosis was advanced [5, 11, 12].

In our patient, significant decline in exercise capacity and DLCO, with profound desaturation on exertion was observed during follow-up. Increase in estimated sPAP to 70 mm Hg was noted on TTE, while lung volumes on PFT and lung infiltrates on chest CT remained stable. At this point, RHC was performed and confirmed precapillary PH with mPAP 31 mm Hg. The oxygen therapy was started due to hypoxaemic respiratory failure. The most probable cause of PH progression at that time was intrinsic granulomatous pulmonary vasculopathy. Granulomatous involvement of the pulmonary vessel wall is very common in sarcoidosis, reaching up to 100% of cases according to pathological studies [5, 13]. One year later, further deterioration was seen with signs of right heart insufficiency. The second RHC confirmed the progression of PH. According to the recommendations from the Fifth World Symposium on Pulmonary Hypertension, PAH (pulmonary arterial hypertension)-specific treatment may be considered by the expert centres as an off-label therapy for severe PH due to lung disease [10], thus sildenafil 75 mg/day was commenced. A significant functional improvement was observed after three months of the therapy, with marked NT-proBNP serum concentration decrease. The publications on PAH-specific treatment in sarcoidosis are mostly case series, and the results are difficult to interpret [14–18]. Nevertheless, a haemodynamic improvement thanks to drugs such as epoprostenol, iloprost, sildenafil, and bosentan was reported in all of them. Improvement of exercise capacity was less common. In 2013, Dobarro et al. [19] performed a meta-analysis of the published reports indexed in MEDLINE. Overall, the improvement in haemodynamics was substantial, with mean reduction in mPAP of 8.03 mm Hg, increase in cardiac output of 0.97 L/min, and a decrease in PVR of 4.24 Wood units. There was also a tendency towards 6MWT distance improvement by a mean of 30.6 m. In 2014, Baughman et al. [20] published results of the only randomised clinical trial of either bosentan or placebo in SAPH patients. They documented significant improvement in mPAP and PVR, but not 6MWT, in the patients treated with bosentan [20]. These findings suggest that SAPH treatment with PAH-specific drugs may be effective. Table 2 contains a list of currently available studies on PAH-specific treatment in patients with SAPH.

The most troublesome side-effect of PAH-specific therapy in SAPH may be the worsening of blood oxygenation resulting from an increase in ventilation-perfusion mismatch. Such effect was noted during treatment with epoprostenol [17] and bosentan [20], but not with sildenafil [14]. Sildenafil did not cause a need for escalation of oxygen supplementation in the described patient either.

One of the most valuable PH predictors in our patient was NT-proBNP serum concentration. Its high values were present at the times of significant clinical deterioration and reached 7000 pg/ml in the end-stage disease. On the other hand, a decrease in NT-proBNP blood concentration was noted at the time of clinical improvement during the first months of sildenafil therapy. The role of NT-proBNP in SAPH diagnosing and monitoring is still under debate [25], but papers published lately documented high NT-proBNP serum concentration in patients with severe PH in the course of other ILD [26, 27] and a significant decrease of the marker in the course of PAH-specific treatment [22].
Table 2. Currently available studies on PAH-specific treatment in patients with SAPH

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Type</th>
<th>Treatment</th>
<th>N</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preston et al. [21]</td>
<td>2001</td>
<td>prospective open-label</td>
<td>inhaled nitric oxide, i.v. epoprostenol</td>
<td>5</td>
<td>Improvement in 6MWD and hemodynamics</td>
</tr>
<tr>
<td>Fisher et al. [17]</td>
<td>2006</td>
<td>retrospective</td>
<td>i.v. epoprostenol</td>
<td>5</td>
<td>Improvement in WHO FC</td>
</tr>
<tr>
<td>Milman et al. [14]</td>
<td>2008</td>
<td>retrospective</td>
<td>p.o. sildenafil</td>
<td>9</td>
<td>Improvement in hemodynamics, No benefit in 6MWD</td>
</tr>
<tr>
<td>Baughman et al. [16]</td>
<td>2009</td>
<td>prospective open-label</td>
<td>inhaled iloprost</td>
<td>15</td>
<td>Decrease in PVR ≤ 20% in 6 pts, increase in 6MWD ≥ 30m in 3 pts, Improvement in qol</td>
</tr>
<tr>
<td>Barnett et al. [15]</td>
<td>2009</td>
<td>retrospective</td>
<td>i.v. epoprostenol, p.o. sildenafil, p.o. bosentan</td>
<td>22</td>
<td>Improvement in 6MWD, WHO FC and hemodynamics</td>
</tr>
<tr>
<td>Judson et al. [22]</td>
<td>2011</td>
<td>prospective open-label</td>
<td>p.o. ambrisentan</td>
<td>10</td>
<td>No benefit in 6MWD, WHO FC, or qol</td>
</tr>
<tr>
<td>Dobarro et al. [19]</td>
<td>2013</td>
<td>retrospective</td>
<td>p.o. sildenafil, p.o. bosentan</td>
<td>8</td>
<td>Improvement in 6MTO and serum NT-proBNP</td>
</tr>
<tr>
<td>Baughman et al. [20]</td>
<td>2014</td>
<td>RCT</td>
<td>p.o. bosentan</td>
<td>35</td>
<td>Improvement in hemodynamics, no benefit in 6MWD</td>
</tr>
<tr>
<td>Keir et al. [23]</td>
<td>2014</td>
<td>retrospective</td>
<td>p.o. sildenafil, p.o. bosentan</td>
<td>25</td>
<td>Improvement in 6MWD, serum BNP, and TAPSE</td>
</tr>
<tr>
<td>Bonham et al. [15]</td>
<td>2015</td>
<td>retrospective</td>
<td>i.v. epoprostenol, s.c. treprostinil</td>
<td>13</td>
<td>Improvement in hemodynamics, NT-proBNP, and WHO FC</td>
</tr>
<tr>
<td>Ford et al. [24]</td>
<td>2016</td>
<td>prospective open-label</td>
<td>p.o. tadalafil</td>
<td>12</td>
<td>no benefit in 6MWD or QoL</td>
</tr>
</tbody>
</table>

i.v. — intravenous; p.o. — per os; s.c. — subcutaneous; 6MWD — six-minute walking distance; WHO FC — World Health Organisation Functional Class; PVR — pulmonary vascular resistance; QoL — quality of life; NT-proBNP — N-terminal pro-brain natriuretic peptide; BNP — brain natriuretic peptide; TAPSE — tricuspid annular plane systolic excursion

Pulmonary hypertension, even if not severe in most cases, increases mortality in sarcoidosis [5, 6]. Our patient survived 6 years from diagnosis of SAPH. In the literature, median survivals in SAPH patients were 4.2 and 5.3 years [7, 19], and factors associated with worse prognosis were WHO FC IV and moderate/severe pulmonary fibrosis [5, 6, 19] — both present in our patient.

Given the mortality rate of patients with SAPH, evaluation for lung transplantation should be considered early.

Conflict of interest

The authors declare no conflict of interest.

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