Case report

Pulmonary arterial hypertension occurrence after liver transplant in systemic sclerosis: a report of 2 cases sustainably treated by Sildenafil

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ABSTRACT

We present the unusual cases of 2 systemic sclerosis patients with a history of liver transplant, who developed pulmonary hypertension in the course of their diseases. Sildenafil was the preferred pulmonary arterial hypertension drug because of its safety within this context. Clinical and functional responses were good, with a follow-up of more than 2 years.

Introduction

Pulmonary arterial hypertension (PAH) occurs in 8-12% of systemic sclerosis (SSc) (1, 2), and together with pulmonary fibrosis represents the first cause of death in patients with this disease. This explains the increasing interest in early detection and treatment of PAH related to connective tissue diseases (CTD). Based on the recent progress in the understanding of the pathogenesis of CTD-PAH that includes a vasoconstriction phenomenon, coagulation abnormalities and remodelling of the pulmonary vessel, several treatments have now been developed (3).

These include prostacyclin therapy, the more recent endothelin antagonists (4, 5) and phosphodiesterase inhibitors (6, 7). We describe herein the cases of 2 SSc patients, who had previously undergone a liver transplant for hepatic failure. A few years later, whilst there was no complication of the transplant itself, these patients developed pre-capillary PAH. Because of their history of liver transplant and the risk of endothelin antagonist-induced hepatotoxicity, sildenafil was the preferred treatment option. We report the course of PAH after 2 years of follow-up.

Case 1

In 1991, a 43-year-old woman with Raynaud's phenomenon since 1980, was diagnosed with limited cutaneous SSc. She presented with skin sclerosis limited to the face and hands, calcinosis, and an episode of digital tip ulcer. Antinuclear antibodies were positive, with anti-centromere specificity. Her presentation also included liver enzymes abnormalities and anti-mitochondrial antibody positivity, leading to the associated diagnosis of primary biliary cirrhosis (PBC). In 1999, she underwent a liver transplant because of liver failure, and has received since then the immunosuppressive drugs mycophenolate mofetil and tacrolimus. In 2006, while the transplant was doing well and treatment was unchanged, she described exertional dyspnea (class II NYHA). Lung diffusing capacity for carbon monoxide normalised for alveolar volume (DLCO/VA) was decreased at 50% of predicted value, in the absence of pulmonary fibrosis. The echocardiographic estimate of systolic pulmonary artery pressure (sPAP) was 46 mmHg, controlled at 63 mmHg a few months later, with NT-pro brain natriuretic peptide (NT-proBNP) at 558 pg/ml. Pre-capillary PAH was demonstrated by right heart catheterisation in March 2007 (mean PAP [mPAP] =26mmHg). Because of concerns about liver function, the antiphosphodiesterase inhibitor sildenafil was chosen and introduced at 20mg 3 times a day. Since then, the patient describes an improvement of respiratory symptoms for daily activities and remains in class II dyspnea. With now a follow-up of more than 2 years since treatment introduction, the dyspnea has not worsened, lung function parameters did not show any marked deterioration at the latest assessment in November 2009: NT-proBNP=710pg/ml, echocardiographic sPAP=50mmHg without

abnormal right ventricular contractility, and DLCO/VA=44%. Tolerance of sildenafil has been excellent so far.

Case 2

In 1978, a 32-year-old woman was diagnosed with limited cutaneous SSc. She presented with Raynaud's phenomenon, acral skin involvement, calcinosis, and a digital ulceration. Anti-centromere antibodies were positive. She also suffered from Sjögren's syndrome, confirmed by a salivary gland biopsy showing grade 3 Chisholm sialadenitis.

In 1994, she underwent an emergency liver transplant for a fulminant hepatitis of unclear origin. She has received immunosuppressive therapy (tacrolimus) since that time. The cause of this hepatitis remains uncertain despite intensive searches. Nevertheless, the absence of viral infection or toxic exposure including any drugs, suggested that the cause could be of autoimmune origin. Indeed PBC is found in approximately 3% of SSc patients (8). Between 2000 and 2007, the patient gradually experienced the onset of a class II NYHA dyspnea. PAPs was normal on several echocardiographies. However, in 2007, echocardiographic sPAP was elevated, at 42 mmHg, and DLCO/VA was decreased, at 40%, in the absence of pulmonary fibrosis. NT-proBNP value was 273 pg/ml. Cardiac catheterisation confirmed pre-capillary PAH in December 2007 (mPAP=30 mmHg). For the same reason as for patient 1, sildenafil was initiated at 20 mg 3 per day. The patient describes an improvement in dyspnea leading to stage her in class I dyspnea since October 2008, and has been stable with a follow-up of more than 2 years now. Her last test results showed a NT-proBNP value of 193 pg/ml, sPAP of 49 mmHg on Doppler-echocardiography, and DLCO/VA of 52%. Tolerance is excellent.

Discussion

These cases focus on the management of SSc-PAH in the very specific context of liver transplant. The association of SSc with CBP is not exceptional, as recently confirmed in two large European cohorts (8), however the occurrence in SSc of both liver transplantation and PAH is very rare. PAH is very severe in SSc and survival was recently reported at 47% after 3 years (9). PAH may also be observed in the case of portopulmonary hypertension and cirrhosis. In these 2 cases, the association of liver involvement with PAH may suggest portopulmonary hypertension, which is present in approximately 8.5% of patients undergoing a liver transplant. However, no portal hypertension was documented in our patients. After more than a 2-year follow-up of each patient, the clinical response is encouraging. This may be explained by the early diagnosis as both patients were on class II dyspnea at the time of diagnosis. Right heart catheterisation was not repeated in these patients although it may be indicated for accurate follow-up of PAH. Indeed, because of the severe comorbidities of our patients together with excellent clinical and biological response, catheterisation was not performed in the follow-up. Therapeutic strategies for PAH include prostacyclin analogues, endothelin receptor antagonists, and 5-phosphodiesterase inhibitors. Several data support that early diagnosis and early treatment are critical in PAH. The benefit of early treatment of PAH was suggested in a recent trial in which bosentan treatment was associated with improvements in haemodynamics and seemed to prevent clinical deterioration in patients with mildly symptomatic PAH (10). Nevertheless, too few CTD patients were included to draw conclusions in this sub-group of PAH patients. Our cases also illustrate good outcomes following sildenafil therapy (11). Sildenafil was preferred over other treatment options because patients were in dyspnea class II and for safety issues as endothelin receptor antagonists may induce toxic hepatitis (12). Furthermore, it is remarkable that these patients developed PAH despite longstanding treatment with immunosuppressive drugs. This raises the point of pathogenesis in CTD-PAH and the hypothesis of the role of inflammation and immunity in vascular remodelling within this context. These cases do not support the hypothesis of a leading role of immunity in SSc-PAH but no firm conclusion can be drawn from these 2 observations.

In conclusion, these cases illustrate the severe condition that is SSc, and the good outcome of PAH at more than 2 years with sildenafil as a single therapy within the context of liver transplant. They support the need for accurate follow-up of SSc patients and early detection of PAH. They also raise the point of the occurrence of PAH despite intensive immunosuppressive therapies.

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