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Case report

Pulmonary arterial hypertension secondary to adult-onset Still's disease: Response to cyclosporine and sildenafil over 15 years of follow-up

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ABSTRACT

Adult onset Still's disease (AOSD) is an autoimmune disease characterized by systemic inflammation and is a rarely reported cause of pulmonary arterial hypertension (PAH). We describe the clinical course of a 40-year-old woman who presented with PAH 19 months after a diagnosis of AOSD. Sildenafil and immunosuppressive therapy with cyclosporine resulted in clinical and hemodynamic improvement with long-term survival 15 years after her initial presentation of AOSD. We review the literature for published cases of PAH due to AOSD and discuss the potential mechanisms relating inflammatory diseases and PAH.

1. Introduction

Adult-onset Still's disease (AOSD) is a rare inflammatory autoimmune disease of unknown etiology characterized by fever, arthritis, evanescent maculopapular rash, lymphadenopathy, hepatosplenomegaly, elevated liver enzymes, leukocytosis, hyperferritinemia, negative antinuclear antibodies (ANA) and a negative rheumatoid factor (RF) [1]. In a significant minority of patients, there is an associated macrophage activation syndrome present. Pulmonary arterial hypertension (PAH) is a disease of the pulmonary arterioles resulting in progressive elevation in pulmonary arterial pressure and pulmonary vascular resistance, which can lead to right heart failure and death [2]. PAH is frequently associated with autoimmune and connective tissue diseases (CTD) such as systemic sclerosis, systemic lupus erythematosus (SLE) and mixed CTD but has only rarely been associated with AOSD [3]. Perivascular inflammation, dysregulated immune cells and elevated cytokine levels have been implicated in the pathogenesis of PAH and may be a mechanism by which autoimmune diseases, including AOSD, result in PAH [4]. We present a case of PAH associated with AOSD with an excellent long-term response to cyclosporine and sildenafil over 15 years of follow-up.

2. Case presentation

A 40-year-old woman from Korea presented in 2001 with recurrent fevers, arthralgia of her ankles and knees, and a salmon coloured rash on her arms and trunk. Laboratory investigations were consistent with AOSD: erythrocyte sedimentation rate of 81 mm/h, ferritin level of 422 μg/L, alkaline phosphatase 400 U/L, alanine aminotransferase 475 U/L and splenomegaly on ultrasound. Hepatitis C antibodies, ANA, RF and anti-double stranded DNA antibodies were not detected. Bone marrow aspiration and biopsy showed a hypercellular marrow, with an increased number of histiocytes, but only minimal evidence of hemophagocytosis. Shortly after the diagnosis of AOSD in October 2001, an echocardiogram was performed showing normal cardiac function and right ventricular systolic pressure (RVSP) in the normal range at

Abbreviations: AOSD, adult onset Still's disease; PAH, pulmonary arterial hypertension; ANA, antinuclear antibody; RF, rheumatoid factor; SLE, systemic lupus erythematosus; RVSP, right ventricular systolic pressure; IL, interleukin; WHO, World Health Organization; RHC, right heart catheterization; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; 6MWD, 6-minute walk distance; PH, pulmonary hypertension; NFAT, nuclear factor of activated T cells.

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27 mm Hg. She was treated with prednisone and non-steroidal anti-inflammatory agents for 4 months but experienced persistent fevers, arthralgia and fatigue. She was then started on the interleukin (IL)-1 receptor antagonist, anakinra, with improvement but incomplete resolution in symptoms of AOSD. In July of 2003 she presented with progressive dyspnea, rated as World Health Organization (WHO) function class III, pedal edema and hypoxemia. At that time her treatment consisted of prednisone 15 mg/d and anakinra 100 mg injections subcutaneously daily.

Her physical examination revealed a Cushingoid appearance, blood pressure 130/70 mm Hg, heart rate 80 beats per minute, respiratory rate 20/min, and oxygen saturation 93% with 2 L/min supplemental oxygen. Her jugular venous pulsation was seen near the earlobe when sitting at 90°. There was a parasternal heave, wide splitting of the second heart sound with a loud pulmonic component, and a murmur consistent with tricuspid regurgitation. Her lungs were clear to auscultation. Peripheral leg edema was present and a palpable spleen tip was noted on abdominal examination.

Investigations revealed a low probability ventilation perfusion scan, no evidence of interstitial or parenchymal lung disease on a computed tomography scan of the chest, and splenomegaly on abdominal ultrasound without hepatic enlargement. Human immunodeficiency virus serology was negative. Pulmonary function testing revealed normal spirometry and lung volumes with an isolated low diffusion capacity for carbon monoxide of 39% predicted. A right heart catheterization (RHC) was then performed, which confirmed pre-capillary PAH: mean pulmonary artery pressure (mPAP) 39 mm Hg, pulmonary artery wedge pressure (PAWP) 7 mm Hg, cardiac output 4.8 L/min, pulmonary vascular resistance (PVR) 532 dynes·sec·cm^{-5}. There was no significant hemodynamic response to inhaled nitric oxide at 40 parts per million. Her baseline 6-minute walk distance (6MWD) was 104 m.

Anakinra was discontinued and she was treated with intravenous furosemide and bosentan 62.5 mg B.I.D, which was titrated to 125 mg B.I.D. after 4 weeks. In May of 2004 she presented with decompensated right heart failure, a pericardial effusion and clinical evidence of a flare of AOSD. Prednisone and cyclosporine 150 mg B.I.D were initiated in hospital. Due to the interaction between bosentan and cyclosporine, bosentan was discontinued. In September of 2004, with immunosuppression alone, her 6MWD improved to 190 m (see Fig. 1), at which point sildenafil 75 mg Q.I.D. was added. She continued with cyclosporine, oral furosemide and 4 L/min oxygen. By January 2005, she had experienced marked clinical improvement to WHO functional class II, had decreasing oxygen requirements to 2 L/min and further increase in her 6MWD to 340 m. Between 2005 and 2015 she remained clinically stable with no further hospitalizations for PAH or right heart failure. She currently has mild exercise intolerance (WHO functional class II), improved mPAP, cardiac index and PVR from baseline (Table 1) and requires oxygen only for nocturnal hypoxemia. She has remained on sildenafil 75 mg Q.I.D and the dose of cyclosporine was gradually reduced to 50 mg twice daily with clinical and laboratory remission of AOSD and sustained improvement in 6MWD (Fig. 1).

3. Discussion

We have described a patient who developed PAH 19 months after the diagnosis of AOSD and experienced long-term survival with sustained clinical and hemodynamic responses to cyclosporine and sildenafil. Other potential causes of pulmonary hypertension (PH) including left heart disease, chronic thromboembolic pulmonary hypertension, and interstitial lung disease, were excluded at the time of PAH diagnosis. Her manifestations of AOSD subsequently flared necessitating initiation of immunosuppression with prednisone and cyclosporine, which resulted in clinical improvement. The addition of high-dose sildenafil (75 mg Q.I.D.) to cyclosporine 4 months later resulted in improved functional status and 6MWD, which have been sustained over a 13-year period (Fig. 1). Hemodynamic reassessments in 2005 and 2007 demonstrated mild increases in mPAP, which was predominantly post-capillary in nature and improved cardiac index (Table 1). She had several echocardiograms and a cardiac magnetic resonance study showing no significant left sided dysfunction or valve disease. Possible explanations for the elevated PAWP at follow-up include left ventricular diastolic dysfunction secondary to interventricular septal shift from the elevated right ventricular end-diastolic pressure, or fluid overload from cyclosporine-induced sodium retention. The most recent RHC in 2015 showed hemodynamic improvement compared to all previous measurements. This is the first reported case of AOSD associated PAH demonstrating long-term survival and clinical response to a combination of a PAH-specific pulmonary vasodilator and immunosuppression.

The association of PAH with rheumatic disease and CTD such as

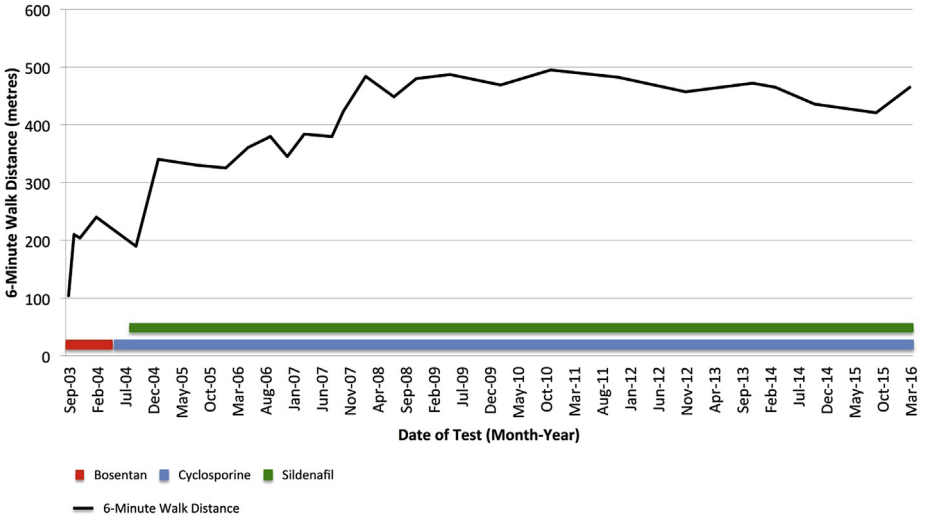

Fig. 1. Change in 6-minute walk distance and treatment regimen.