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Case Report

Vanishing Pulmonary Hypertension in Mixed Connective Tissue Disease

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Abstract: A 29-year-old woman with mixed connective tissue disease presented with signs of progressive pulmonary hypertension. After admission to the hospital her condition worsened rapidly and she developed a cardiac arrest resistant to cardiopulmonary resuscitation. Therefore, emergency extracorporeal assist was performed. No pulmonary embolism was found. Right heart catheterisation showed severe pulmonary hypertension, which was treated with nitric oxide ventilation. She was weaned from the extracorporeal assist with high doses of inotropic agents. Because of suspicion of exacerbation of her underlying disease, which led to pulmonary hypertension, immunosuppressive treatment was started with high doses of corticosteroids and plasma exchange. This resulted in slow recovery over the next four weeks. Control echocardiography showed complete normalisation of cardiac function without signs of pulmonary hypertension. Two months after admission she was discharged from the hospital in good condition.

Keywords: Mixed connective tissue disease; Nitric oxide ventilation; Plasmaexchange–plasmapheresis; Pulmonary hypertension

Introduction

Mixed connective tissue disease (MCTD) is a rheumatic syndrome characterised by overlapping clinical manifestations of systemic lupus erythematosus (SLE), progressive systemic sclerosis (PSS) and polymyositis (PM) and high titres of circulating antibodies to nuclear ribonucleo protein (RNP) [1]. Pulmonary hypertension (PHT) in patients with MCTD usually develops progressively. Occasionally severe and rapidly deteriorating PHT is seen in MCTD.

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Case Report

A 29-year-old woman was admitted because of exertional dyspnoea, asthenia and weight loss. She had a long-standing history of MCTD, including arthralgias, polymyositis, haemolytic anaemia, pericarditis and myocarditis. The serological profile revealed an antinuclear antibody titre of 1/320 with a speckled pattern, a high positive RNP titre, a positive titre for single-stranded DNA of 1/1280, and a hypergammaglobulinaemia. LE cell, anti-SM (smooth muscle) antibodies and antiphospholipid antibodies were absent, and serum complement was normal.

Clinical examination on admission revealed a cachectic woman with a sacral decubitus ulcer, normal body temperature, blood pressure of 120/80 mmHg and pulse rate of 200 bpm. She also showed a marked sclerodactyly with swollen fingers.

On electrocardiography, atrial flutter with a ventricular response of 200 bpm was seen. A chest radiograph revealed a normal heart and lung pattern, except for the prominent hili. Doppler echocardiography showed right ventricular dilatation with impaired left ventricular function. Mitral valve insufficiency (1/4) and tricuspid valve insufficiency (2/4) were also detected.

Treatment consisted of a slow intravenous bolus of 70 mg propafenone and 0.5 mg digoxin, this resulting in a conducting delay of the atrial flutter, rapidly changing to atrioventricular block without ventricular escape rhythm and (iatrogenic) cardiac arrest. Atropine administration (0.5 mg) resulted in ventricular fibrillation, which could be restored to sinus rhythm with electrical defibrillation. Cardiopulmonary resuscitation was started because of

Table 1. Haemodynamic parameters during NO ventilation

	Day						
	1	2	3	4	5	6	7
CI (l/min/m^2)	3.3	3.2	3.1	3.3	3.4	3.1	2.9
SVRI (dyne/s/cm^{-5}/m^2)	1552	2150	2374	2061	2118	2142	2345
PVRI (dyne/s/cm^{-5}/m^2)	509	400	490	436	424	361	342
MAP (mmHg)	70	94	100	96	100	93	96
HR (bpm)	96	111	110	107	107	115	99
CVP (mmHg)	6	8	8	11	10	10	9
MPAP (mmHg)	35	33	31	32	33	29	28
PAWP (mmHg)	8	12	12	14	15	14	13
Dopamine (μg/kg/min)	10	10	10	8	7	4	0
Dobutamine (μg/kg/min)	20	20	17	12	8	4	0
Norepinephrine (μg/kg/min)	5	3	1	0	0	0	0

NO, nitric oxide gas; CI, cardiac index; SVRI, system vascular resistance index; PVRI, pulmonary vascular resistance index; MAP, mean arterial blood pressure; HR, heart rate; CVP, ventral venous pressure; MPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure.

electromechanical dissociation, including manual chest compression and artificial ventilation. Control echocardiography showed severe dilatation of the right ventricle without tamponade and shifting of the intraventricular septum to the left side of the heart. Additionally severe hypoxaemia was noticed (pO_2 33 mmHg) making the diagnosis of massive pulmonary embolism very likely. A decision was made to perform emergency pulmonary embolectomy under extracorporeal cardiopulmonary assist. After sternotomy, manual open heart massage was continued. No major pulmonary embolism was found during the operation.

The patient could slowly be weaned from the extracorporeal assist, with the use of high doses of inotropic agents (dobutamine 20 μg/kg/min, dopamine 10 μg/kg/min, norepinephrine 5 μg/kg/min). Haemodynamic parameters derived from pulmonary artery catheterisation revealed severe PHT (Table 1). Because of a suspicion of exacerbation of her underlying disease, which led to PHT, immunosuppressive treatment was started with high doses of corticosteroids. Nitric oxide ventilation was started (10 ppm) in order to reduce PHT, and continued over the next 6 days.

Inotropic agents could be decreased gradually, but weaning from the ventilator took several weeks. There were no neurological or renal problems. After 1 week, plasma exchange sessions of 4 litres were started on an alternate day basis for five sessions and then reduced to a once a week session for 8 weeks.

One month after sternotomy, Doppler echocardiography showed completely normal heart function with no signs of PHT. Two months after admission she was discharged from hospital in good clinical condition with a weight gain of 13 kg. The immunological profile remained unchanged: positive ANA, a high positive RNP titre, a positive titre for single-stranded DNA, and a hypergammaglobulinaemia. Titre values went up and down in correlation with each session of plasmapheresis.

Disccussion

Our patient presented with acute severe PHT, as demonstrated by pulmonary artery measurements, leading to rapid haemodynamic deterioration. On echocardiography left ventricular function seemed seriously impaired, but because of severe tachycardia, it was impossible to perform quantitative ultrasound measurements. Propafenone was administered to reduce the heart rhythm, resulting in conduction delay and (iatrogenic) cardiac arrest. Previous reports have suggested that patients with MCTD may be at risk for developing conduction abnormalities, but their relationship with MCTD remains uncertain [1].

Emergency cardiopulmonary bypass was performed because of CPR resistant cardiac arrest [2,3] and the presumed diagnosis of massive pulmonary embolism. No embolism was found, which made the diagnosis of exacerbation of PHT due to concomitant worsening of MCTD more likely.

In MCTD two types of lung disease are found; interstitial lung disease and PHT [4]. PHT in patients with MCTD implicates a significantly worse prognosis [5]. Cor pulmonale is a major cause of death in these patients [6]. Several factors are responsible for the pathogenesis of PHT, including vasospasm, vascular thickening due to vasculitis and thromboembolism [7]. However, PHT in MCTD usually develops progressively and accelerated courses are rather occasional [8].

Pulmonary involvement has been considered to be easily treated with corticosteroids [4], but it has become apparent that PHT may not be responsive to corticoids or immunosuppressive treatment [9]. Nevertheless, early cytotoxic therapy may be beneficial [4]. Dahl et al. [7] described a 10-year survival in a woman with PHT and MCTD, who was successfully treated with cyclophosphamide during two relapses of PHT.

The pulmonary vascular reactivity to NO ventilation in MCTD has already been docuented elsewhere [9]. NO produced a moderate lowering of pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR) without any deleterious systemic effect. This vasodilator effect can also be reached with prostacycline or nifedipine, but systemic effects may produce severe complications [9]. In contrast, NO seems to be a selective vasodilator. The absence of systemic dilator effects is a result of rapid inactivation of inhaled NO by haemoglobin [10]. In our patient, PAP decreased within minutes after starting NO. Thereafter, PAP and PVR remained stable and no further decreases in PAP and PVR were noticed during NO inhalation.

In MCTD, increased concentrations of circulating immune complexes (CIC) may be detected, but this is not a common feature. In our patient, CIC were normal. The presence of high autoantibodies titres in MCTD correlates with associated diseases [11]. Plasma exchange has been demonstrated to be effective in the management of diseases mediated by autoantibodies and circulating immune complexes [12,13], probably because of the removal of immune complexes and maybe also other factors responsible for the disease. Removal of pathogenic autoantibodies or serum factors toxic to endothelial cells may have contributed to the improvement of our patient. Plasma exchange has been used in MCTD evolving to scleroderma with renal failure [12]. Fletchner et al. [13] described severe neuropsychiatric manifestations in MCTD responding dramatically to treatment with plasma exchange.

Conclusion

This case of MCTD with exceptionally fast progressive PHT was successfully treated with NO ventilation, plasma exchange and immunosuppressive medication.

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