Rapid progression to pulmonary arterial hypertension crisis associated with mixed connective tissue disease in an 11-year-old girl.

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Abstract

Mixed connective tissue disease (MCTD) is rare in pediatric rheumatic diseases. Pulmonary arterial hypertension (PAH) associated with MCTD usually progress gradually and is difficult to note at the asymptomatic phase. We report a 10-year-old girl with MCTD complicated with rapidly progressive PAH. Although PAH was not detected by echocardiogram or chest CT scan at the initial examination, it became apparent in 1 year and suddenly came to cardiac arrest during invasive

procedure. She was successfully treated with extracorporeal assist and both vasodilative and immunosuppressive medication. Combination of echocardiogram and plasma BNP levels could be a useful marker for the follow-up of such cases. *Conclusion* ; PAH could develop early in the course of pediatric MCTD and needs attention to unexpected acute exacerbation, especially under emotional stress.

Keywords

Mixed connective tissue disease, pulmonary arterial hypertension, pulmonary arterial hypertension crisis, pulmonary function test, B-type natriuretic peptide

Introduction

Mixed connective tissue disease (MCTD) is characterized by Raynaud phenomenon (RP) or swollen hands, overlapping clinical features of systemic lupus erythematosus, systemic sclerosis, and polymyositis/dermatomyositis in conjunction with the presence of anti-ribonucleoprotein (RNP) antibody. MCTD is rare in children and constitutes 0.6% of pediatric rheumatic diseases [3]. The poor prognosis is associated with the presence of interstitial lung diseases or pulmonary arterial hypertension (PAH). PAH is more severe in adult MCTD, however, tends to progresses gradually [1]. Here, we report an 11-year-old girl with rapidly progressive PAH associated with MCTD.

Case report

A 10-year-old Japanese girl was referred to our hospital because of RP since the age of nine

43 years. She also showed swollen fingers. Laboratory findings were as follows: white blood cell
44 count 4.1× 10^9 /L with normal differentiation, hemoglobin 118 g/L, platelet count 216 × 10^9 /L,
45 erythrocyte sedimentation rate 32 mm/h, C-reactive protein < 0.2 mg/L, C3 1.00 g/L, C4 0.17 g/L,
46 CH50 59.2 IU/ml, immunoglobulin (Ig) G 19.23 g/L, IgA 2.33 g/L, IgM 1.30 g/L, antinuclear antibody
47 titer > 1: 1,280, and anti-RNP antibodies 152.4 INDEX (normal range; <12.9). Anti-smith antibody,
48 anti-double-stranded DNA antibody, and anti-topoisomerase antibody were all negative. Pulmonary
49 function test (PFT) showed slightly decreased % diffusing capacity of carbon monoxide (%DLCO;
50 65.6%) and normal % vital capacity (%VC; 82%). There was no evidence of PAH or interstitial
51 pneumonia (IP) on either echocardiographic study or chest computed tomography (CT) scan. Plasma
52 B-type natriuretic peptide (BNP) level was 20.5 pg/ml (normal range; <18.4). The chest X-ray
53 showed normal cardiothoracic ratio (CTR) 50% (Fig. 1a). Four months later, she showed elevated
54 serum creatinine kinase, and thus, fulfilled the classification criteria of MCTD according to the
55 Ministry of Health, Labor, and Welfare of Japan. At the age of 11 years, she visited our hospital
56 because of fever, vomit, and general fatigue lasting for two days. She was alert but heavily sweated
57 with cold extremities. Biophysical monitoring showed: blood pressure 126/86 mmHg, body
58 temperature 37.1°C, and SpO_2 98% on room air. The chest X-ray showed cardiomegaly (CTR 68%),
59 but no apparent infiltrative shadows (Fig. 1b). Echocardiography demonstrated right ventricular
60 dilatation, paradoxical movement of the interventricular septum, and tricuspid regurgitation. These
61 findings suggested PAH rather than other causes of pulmonary hypertension such as interstitial lung
62 diseases. During insertions of catheters, electrocardiography showed wide-QRS bradycardia and
63 subsequently asystole. She needed percutaneous cardiopulmonary support for seven days followed by

extracorporeal membrane oxygenation for four days. On the 6th hospital day, systolic pulmonary arterial pressure assessed by right heart catheterization was 60 mmHg. Plasma BNP level was 1,146.3 pg/ml. PAH responded to the combination therapy with epoprostenol sodium, bosentan hydrate, and sildenafil citrate (Fig.2). Disseminated intravascular coagulation syndrome, pulmonary hemorrhage, and acute renal failure developed but were overcome by intensive care. During the course, she lost the distal phalanx of the left forefinger due to ischemic necrosis and suffered from paraplegia possibly due to infarct of the anterior spinal artery. Although mild ground-glass opacity suggesting IP or lung edema was observed on chest CT scan one month after her admission, it subsided following combination therapy with methylprednisolone pulse therapy (30 mg/kg/dose for consecutive three days) followed by high-dose prednisolone (PSL) (2 mg/kg/day) and three courses of monthly intravenous cyclophosphamide therapy (500 mg/m^2). She was finally discharged from the hospital after 10 months of hospitalization on daily PSL 10 mg/day, azathiopurin 50 mg/day, tadalafil 20 mg/day, bosentan 62.5 mg/day, and beraprost 300 μg/day. A follow-up echocardiography approximated a systolic pulmonary arterial pressure of 30-35 mmHg. BNP levels decreased and remained within normal range despite residual mild cardiomegaly (CTR 60%) (Fig. 1c).

Discussion

Although PAH is a life-threatening complication of MCTD, it is difficult to be noted at the asymptomatic phase, because early PAH symptoms mimic those of the underlying MCTD [8]. Heart catheterization is a gold standard for the diagnosis of PAH but is difficult to perform in critically ill cases like our patient. PFT is a noninvasive diagnostic test to detect obstructive or restrictive diseases.

Particularly, low and decreasing DLCO and %VC/%DLCO ratio≥1.4 are a valuable predictor of the PAH associated with connective tissue disease (CTD) [7,9]. Our case showed a low %VC/%DLCO ratio (1.25) and normal echocardiographic and chest CT scan findings at the initial examination. As well, BNP which is primarily produced by cardiomyocytes of the ventricles of the heart, a biochemical marker for impaired overall cardiac function, was initially near normal levels. These suggest that PAH progressed very rapidly within about one year after the initial examination. Thus, although annual screening of PAH by echocardiography, PFT, and BNP have been recommended in CTD [9], more frequent examinations should be considered.

Inflammation-mediated organizing vasculopathy are thought to be involved in the progression of CTD-associated PAH. Immunological and/or inflammatory endothelial damage initially leads to a vascular obliteration characterized by intimal proliferation, medial hyperplasia, and finally irreversible fibrosis of the small pulmonary arteriole walls [2,4]. This is supported by the fact that the survival rate of PAH has been improved by an early diagnosis and the prompt use of immunosuppressants in combination with modern PAH-specific vasodilative drugs such as prostanoid, PDE-5 inhibitors, and endothelin receptor antagonist [5,6]. Consistent with this, the response of PAH to the treatment with both immunosuppressants and vasodilative drugs suggests that the PAH in our case was, at least partially, still reversible. In addition to the slowly progressive inflammatory mechanisms, functional vasospasm due to sympathetic overactivity could be a cause of acute exacerbation of PAH. Invasive procedures could have triggered excessive vasospasms on the basis of underlying subclinically progressed PAH in our case.

Conclusion

Rapidly progressive PAH complicating MCTD was successfully treated with extracorporeal circulation and both vasodilative and immunosuppressive medication. PAH could develop early in the course of pediatric MCTD and needs attention to unexpected acute exacerbation, especially under emotional stress.

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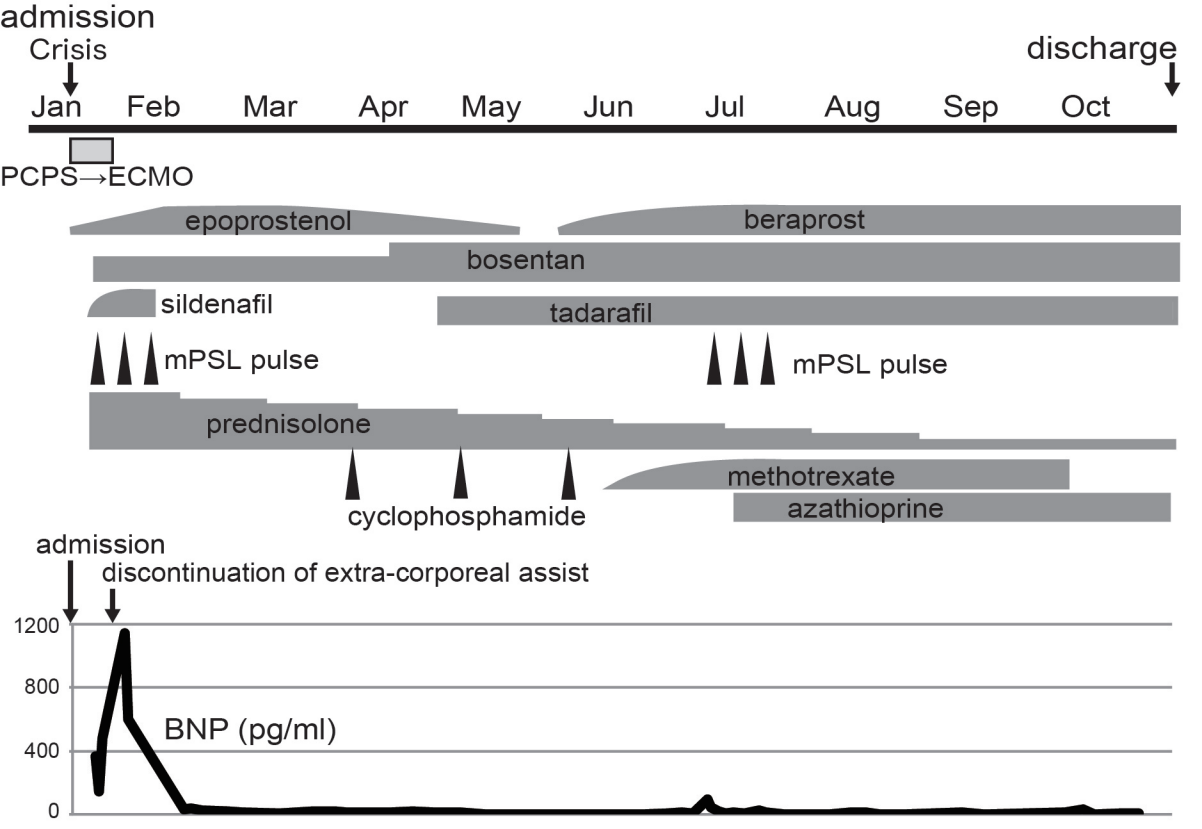
Figure legends

Fig. 1 Serial chest X-ray at the initial examination (a), acute deterioration (b), and discharge (c)

Fig. 2 Treatment and chronological changes in BNP levels. Extra-corporeal assist was performed for 11 days since her admission to our hospital. BNP level was first measured on the 5^{th} hospital day during extracorporeal assist. Soon after discontinuation of extra-corporeal assist, BNP level was 1146.3 pg/ml. Abbreviations; PCPS, percutaneous cardiopulmonary support; ECMO, extracorporeal membrane oxygenation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cyclophosphamide
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BNP (pg/ml)