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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
years. She also showed swollen fingers. Laboratory findings were as follows: white blood cell count $4.1 \times 10^9 / \text{L}$ with normal differentiation, hemoglobin 118 g/L, platelet count $216 \times 10^9 / \text{L}$, erythrocyte sedimentation rate 32 mm/h, C-reactive protein $< 0.2 \text{ mg/L}$, C3 1.00 g/L, C4 0.17 g/L, CH50 59.2 IU/ml, immunoglobulin (Ig) G 19.23 g/L, IgA 2.33 g/L, IgM 1.30 g/L, antinuclear antibody titer $> 1:1,280$, and anti-RNP antibodies 152.4 INDEX (normal range; $<12.9$). Anti-smith antibody, anti-double-stranded DNA antibody, and anti-topoisomerase antibody were all negative. Pulmonary function test (PFT) showed slightly decreased % diffusing capacity of carbon monoxide (%DLCO; 65.6%) and normal % vital capacity (%VC; 82%). There was no evidence of PAH or interstitial pneumonia (IP) on either echocardiographic study or chest computed tomography (CT) scan. Plasma B-type natriuretic peptide (BNP) level was 20.5 pg/ml (normal range; $<18.4$). The chest X-ray showed normal cardiothoracic ratio (CTR) 50% (Fig. 1a). Four months later, she showed elevated serum creatinine kinase, and thus, fulfilled the classification criteria of MCTD according to the Ministry of Health, Labor, and Welfare of Japan.

At the age of 11 years, she visited our hospital because of fever, vomit, and general fatigue lasting for two days. She was alert but heavily sweated with cold extremities. Biophysical monitoring showed: blood pressure 126/86 mmHg, body temperature 37.1°C, and SpO₂ 98% on room air. The chest X-ray showed cardiomegaly (CTR 68%), but no apparent infiltrative shadows (Fig. 1b). Echocardiography demonstrated right ventricular dilatation, paradoxical movement of the interventricular septum, and tricuspid regurgitation. These findings suggested PAH rather than other causes of pulmonary hypertension such as interstitial lung diseases. During insertions of catheters, electrocardiography showed wide-QRS bradycardia and 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/m²). 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,
obsentan 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 $\geq 1.4$ 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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References


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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 5th 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
admission
Crisis

Jan  Feb  Mar  Apr  May  Jun  Jul  Aug  Sep  Oct
discharge

PCPS → ECMO

epoprostenol  →  bosentan  →  sildenafil  →  tadalafil

prednisolone
mPSL pulse
mPSL pulse

BM

cyclophosphamide
methotrexate
azathioprine

admission
discontinuation of extra-corporeal assist

BNP (pg/ml)