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REVIEW ARTICLE

A Histopathological Study of Pulmonary Hypertension in Connective Tissue Disease

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ABSTRACT

Connective tissue diseases (CTD), such as systemic sclerosis (SSc), systemic lupus erythematosus (SLE), and mixed connective tissue disease (MCTD), develop pulmonary hypertension (PH). Generally all PH cases associated with any CTD are classified into the same PH group. However, histological examination shows both common and specific lesions for each disease. In patients with SLE, fibrosis is generally rare and mild. The findings of PH in SLE are similar to those in primary pulmonary hypertension. Many cases of SSc are accompanied by fibrosis. MCTD is rather close to SSc. Arterial and arteriolar lesions of MCTD are characterized by fibrous intimal thickening. In this review, we describe the pathological features of PH associated with each CTD.

KEY WORDS

autopsy, connective tissue disease, histopathology, mixed connective tissue disease, pulmonary hypertension

INTRODUCTION

Connective tissue diseases (CTD) demonstrate variable features and severity of lung involvement. Interstitial pneumonia and pulmonary hypertension (PH) are considered to be particularly serious complication of CTD, leading to death.[1,2] Currently, PH is classified according to the Dana Point classification,[3] which was a revision in 2008 of the classification proposed at the World Symposium on Pulmonary Arterial Hypertension in 2003.

The main CTD that develop PH are systemic sclerosis (SSc), systemic lupus erythematosus (SLE), and mixed connective tissue disease (MCTD). The incidence has been reported to be 2.6-12.3% in SSc patients, 0.9-10.5% in SLE patients, and 5-14% in MCTD patients.[4-7] Compared with the incidence of primary pulmonary hypertension (PPH), which is 1-3 per 1 million people, the incidence in CTD is extremely high. PH is a serious life-threatening complication in SSc, MCTD, and SLE.

Histopathological examination of cases with PH in SSc, MCTD, and SLE shows both common and specific lesions for each disease. However, all PH cases associated with any CTD are classified into the same PH group, and are currently treated based on a common concept. Plexogenic arteriopathy, often encountered in PPH can be seen in SLE, but is rarely observed in SSc and MCTD. In addition, fibrinoid vasculitis with deposition of immunoglobulins is often found in PH associated with SLE, but is rare in MCTD and is never seen in SSc. Therefore, this suggests that the pathogenesis of PH is somewhat different in each of these CTD. In this review, we describe the pathological features of each CTD from autopsy cases.

FEATURES AND SEVERITY OF PULMONARY VASCULAR LESIONS OF PH IN CTD

Figure 1 shows the results of the analysis of pulmonary lesions in 26 patients with SLE, 14 patients with SSc, 21 patients with polymyositis/dermatomyositis (PM/DM), and 15 patients with MCTD who were studied by the Research Committee for MCTD of the Ministry of Health, Labour and Welfare.[8] The vertical axis of each graph represents the grade of pulmonary fibrosis (PF) ranging (-)-(4+) and the horizontal axis indicates the grade of hypertensive pulmonary vascular disease (HPVD) ranging 0-6. Severe HPVD was encountered in 3 of 26 patients with SLE, but fibrosis was rare. In patients with SSc, 7 had grades of (2+)-(4+) and all patients had grades up to HPVD3. There-

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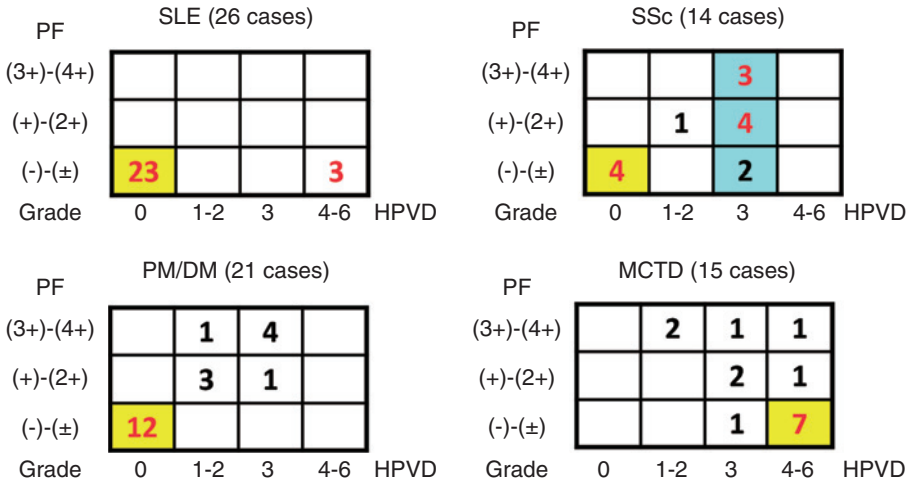


Fig. 1 HPVD and PF in CTD. These are all autopsy cases. In SLE, pulmonary findings are defined by acute DAD (23 cases) and vascular type (3 cases), not by fibrosis. From 14 SSc cases, 7 died of pulmonary fibrosis, not severe HPVD. From 15 MCTD cases, 9 died of HPVD and 4 died of PF. In PM/DM the pattern was rather similar to SSc. From above data the pulmonary findings of MCTD were characterized by vascular patterns that were different from those of SLE and SSc.

fore, fibrosis was relatively dominant in SSc. MCTD demonstrated characteristic features. The majority of patients, 9 of 15, had vascular lesions of HPVD.

FEATURES OF THE VARIOUS CTD

While CTD with PH show common findings, SLE, SSc, and MCTD with PH demonstrate individual characteristics, and cases with MCTD have findings common to both SLE and SSc, although the characteristics are slightly closer to SSc, as described above.

HISTOPATHOLOGICAL CHARACTERISTICS OF PH IN SLE

Pulmonary fibrosis is generally rare and if found in patients with SLE, the fibrosis is mild, based on autopsy findings. When patients with SLE die of respiratory failure, it is typically due to acute diffuse alveolar damage or hemorrhage, but fibrosis is rarely seen. Therefore, the incidence of PH is generally low. However, the findings of PH in SLE are similar to those in PPH, i.e., plexogenic arteriopathy or fibrinoid vasculitis (Fig. 2). Although the incidence of PH is low, the grade of PH is generally higher in SLE than in SSc.

HISTOPATHOLOGICAL CHARACTERISTICS OF PH IN SSc

Fibrinoid vasculitis or plexogenic arteriopathy is rarely seen in SSc. Characteristic findings in this disease are fibrous intimal thickening of medium-sized arteries and branching small vessels (Fig. 3a). Some cases also show luminal narrowing or obstruction throughout the peripheral vessels, which appear to impair gas exchange (Fig. 3b). Many cases of SSc are accompanied by fibrosis with impaired blood flow resulting in severe respiratory failure. Therefore, PH in SSc progresses and is more severe than that of SLE or ordinary MCTD, as described below.

HISTOPATHOLOGICAL CHARACTERISTICS OF PH IN MCTD

Although MCTD is considered to have intermediate or mixed characteristics between SLE and SSc, histologically it is rather close to SSc as regards skin, esophageal, and kidney lesions. Therefore, MCTD has been called 'undeveloped SSc'. However, arterial and arteriolar lesions of MCTD are characterized by fibrous intimal thickening but fibrinoid vasculitis or plexogenic arteriopathy are rare (Fig. 4). The incidence of mixed type of both vascular type and interstitial type is very low.

THE CHARACTERISTICS AND CAUSES OF PH IN MCTD

Among the CTD, MCTD shows a high incidence of PH with severe grade in pulmonary arteries. In MCTD, PH accounts for 16.7% of deaths.[9] Here, we would like to delineate the pathology of MCTD further. Figure 5 shows the relationship between HPVD and pulmonary fibrosis in 17 autopsy cases of MCTD.[10] The 10 cases indicated by the filled circles died of PH. PH encountered in MCTD consists of vascular type, interstitial type, and mixed type, which has features of both vascular and interstitial types. While the incidence of PH is very low in human dis-

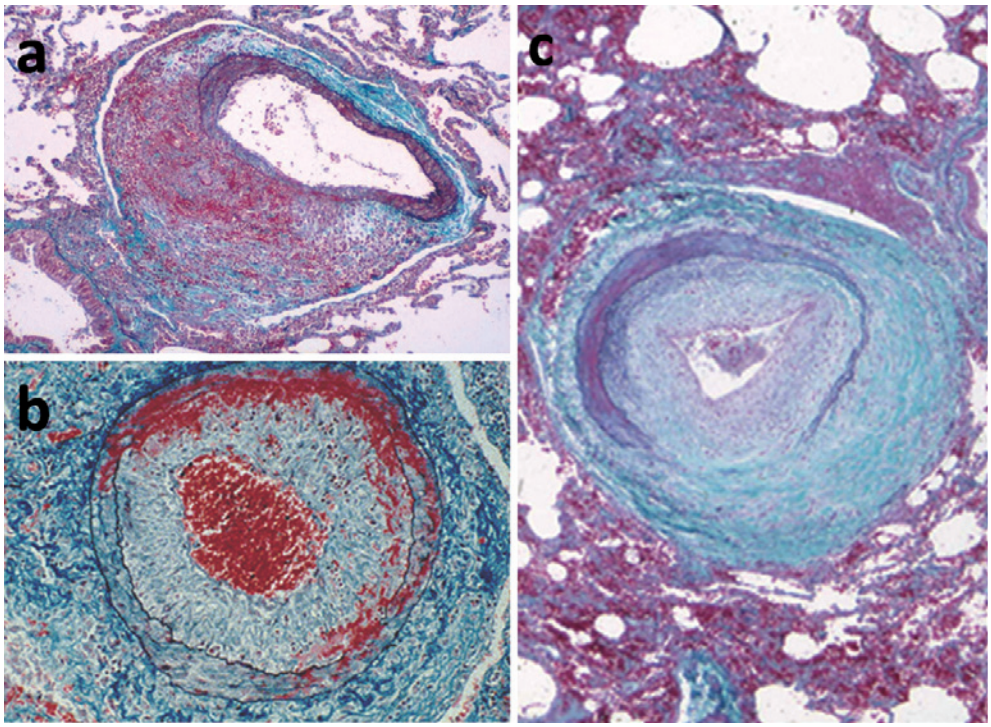


Fig. 2 Pulmonary vascular lesions in SLE. **a**) Vasculitis involving adventitia of artery in medium sized vessels (Elastica-Goldner stain). **b**) Fibrinoid arteritis of a medium sized artery with luminal narrowing (Elastica-Goldner stain). **c**) Vasculitis involving all layers of a medium sized artery with luminal narrowing (Elastica-Goldner stain). These are all different cases with no severe fibrosis. Generally in cases of SLE with severe PH, fibrosis is not so prominent, but diffuse alveolar damage (DAD) with hemorrhage is often seen accompanied by severe vascular lesion such as plexogenic arteriopathy and fibrinoid arteritis.

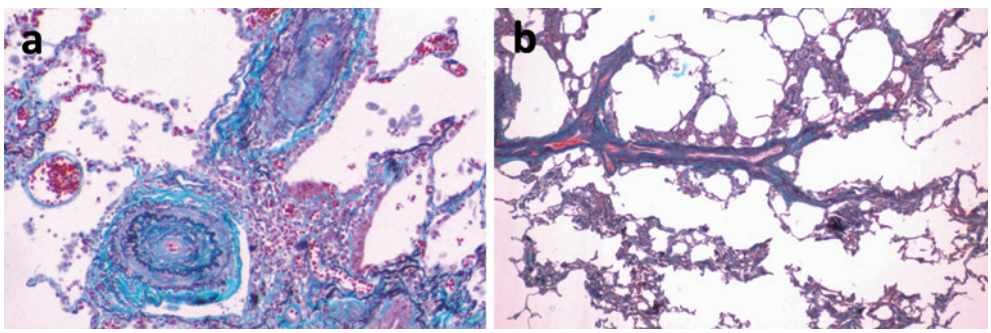


Fig. 3 Pulmonary vascular lesions in SSc. **a**) Fibrous occlusion or severe intimal thickening of medium to small sized arteries (Elastica-Goldner stein). **b**) Fibrous occlusion of medium sized arteries with collapse of small vessels impairing gas exchange in the alveolar region, or severe intimal thickening of small arteries that are partly occlusive (Elastica-Goldner stein). Above two figures, **a** and **b**, both belong to the vascular type without fibrosis. These pathologic findings are different from SLE, and SSc seldom show fibrinoid arteritis in the lung.

eases, it is fairly high in MCTD.

We examined histologically the autopsy cases where cause of death was PH associated with MCTD. Intimal thickening starting from the large vessels and spreading to the peripheral vessels is characteristic in severe PH cases. On the other hand, intimal thickening and thrombosis of the small blood vessels about 100 μm in diameter was also seen in the lungs of almost all patients who did not die of PH.[11] These findings suggest that slight endothelial damage progres-

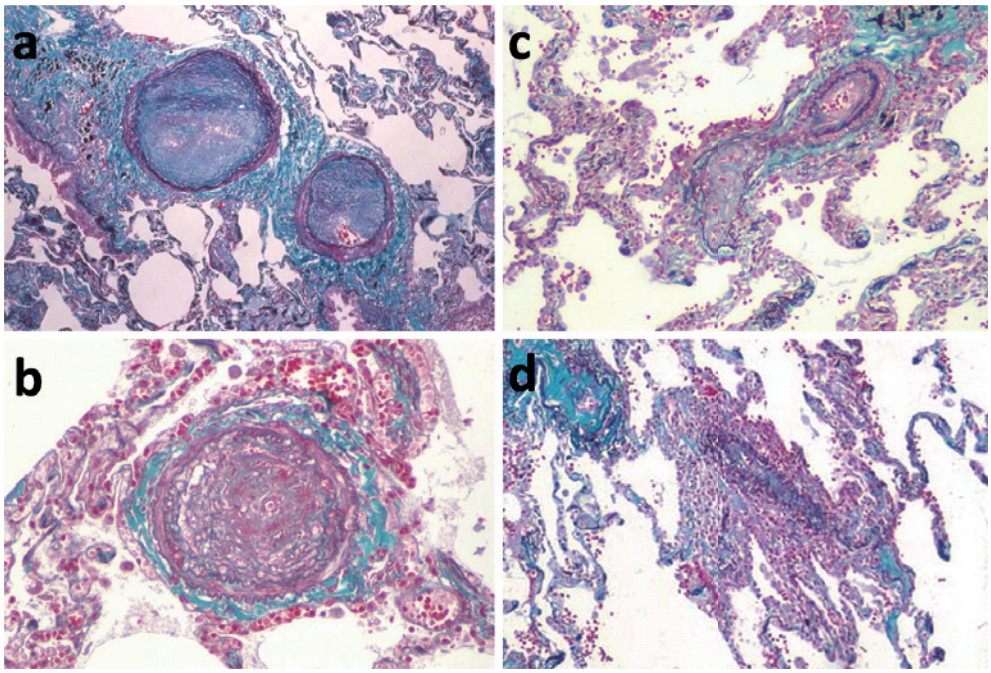


Fig. 4 Pulmonary vascular lesions in MCTD. **a**) Severe intimal fibrosis almost occluding the vascular lumen (Elasitica-Goldner stain). **b**) Organized thrombus in medium sized artery (Elasitica-Goldner stain). **c**) Plexogenic arteriopathy sometimes occured (Elasitica-Goldner stain). **d**) Vasculitis of small vessels with inflammatory infiltration around vessels almost composed of lymphocytes (Elastica-Goldner stain). MCTD cases with PH also show the interstitial type and vascular type and mixed type with both lesions; however the mixed type is very rare. Further, the vascular type of MCTD shows similar lesion to SSc such as fibrous thickening and to SLE such as plexogenic arteriopathy.

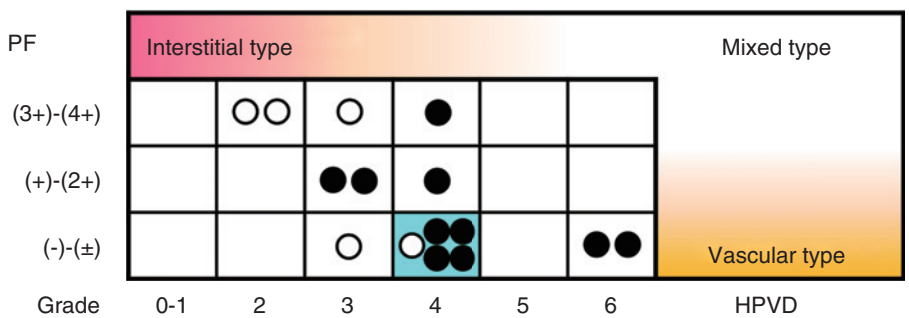


Fig. 5 Histopathological analysis of pulmonary vascular lesions in MCTD. The filled circle represents a patient with fetal PH, and the open circles represent patients who died of other causes besides PH such as respiratory insufficiency. We found that out of 15 autopsy cases with MCTD, 10 died of HPVD, more than 60% of the patients.

sively leads to severe vascular lesions (Fig. 6).

Based on the good correlation between pulmonary pressure and the grade of vascular lesions, the degree of luminal obstruction regarding the size of the pulmonary vessels was measured using a grading system of 1-4.[11] The results are shown as a schematic in Figure 7. It appears that endothelial injury firstly occurs in the small blood vessels in MCTD regardless of the presence or absence of PH clinically. Overt symptoms occur as a result of growth of small thrombi or intimal thickening. Therefore, we assume the existence of antibodies to endothelial cells of the small vessels, i.e., anti-endothelial cell antibodies (AECA).

The serum AECA levels in patients with MCTD were measured by flow cytometric analysis using human pulmonary microvascular endothelial cells. The results showed that AECA levels were higher in the

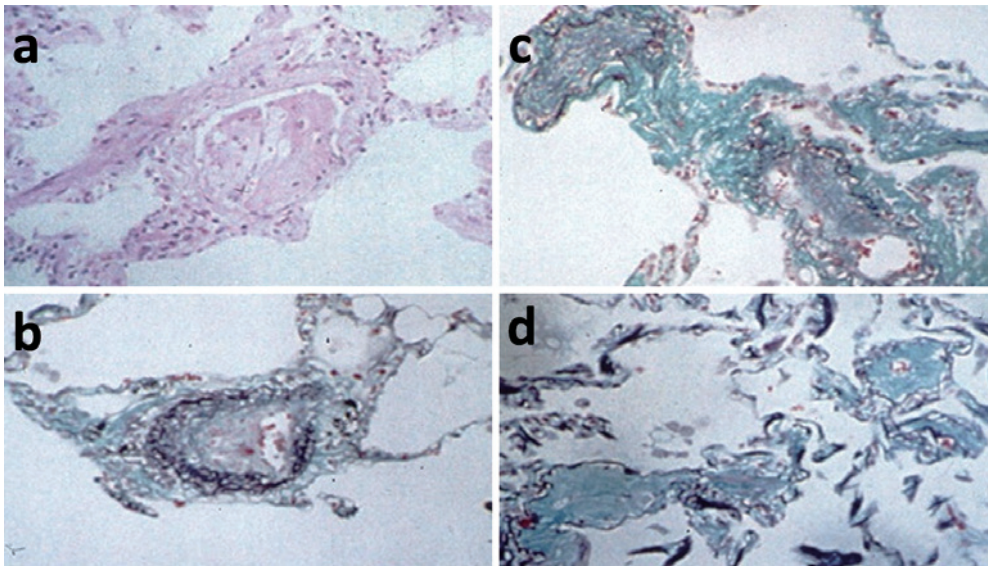
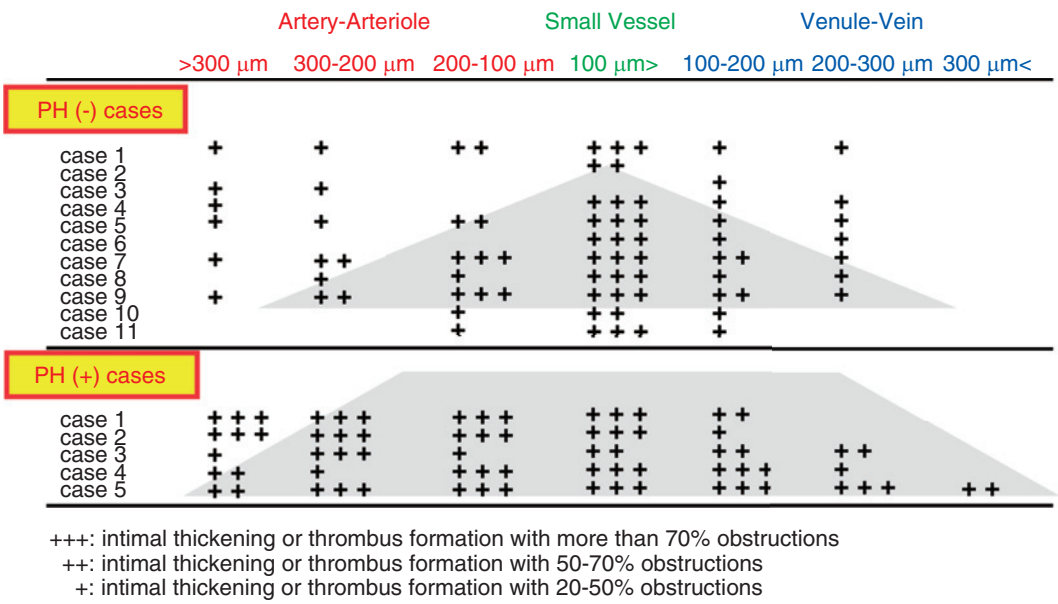


Fig. 6 Pulmonary vascular lesions in MCTD without PH. Organized thrombus or intimal thickening, resulting in partial obstruction of small vessels of less than 100 μm in size (**a**: Hematoxylin-Eosin stain, **b**, **c**, and **d**: Elastica-Goldner stain). Even in MCTD cases without complicating PH, vascular changes such as intimal thickening or organized thrombus occurs in small vessels. Whether intimal thickening or small thrombus is present or not, endothelial injury occurs in small vessels in MCTD, which may be the first step for severe vascular lesions seen in PH.



+++: intimal thickening or thrombus formation with more than 70% obstructions
++: intimal thickening or thrombus formation with 50-70% obstructions
+: intimal thickening or thrombus formation with 20-50% obstructions

Fig. 7 Grade and distribution of vascular lesions of pulmonary vessels in autopsy cases of MCTD. Cases with overt clinical PH show severe intimal thickening from artery to vein. Cases without clinical PH are characterized by involvement of small vessels. Our data suggest that vascular changes occur first in the small vessels in almost all cases, then some advance to PH with HPVD.

serum of patients with MCTD who presented with PH clinically (MCTD-PH) than in healthy people or in patients with MCTD without PH (MCTD-nonPH) (Fig. 8).[12]

SUMMARY OF PH ASSOCIATED WITH HISTOPATHOLOGICAL FINDINGS IN CTD

There are considered to be 2 possible causes of hypertension in the pulmonary circulation characterized

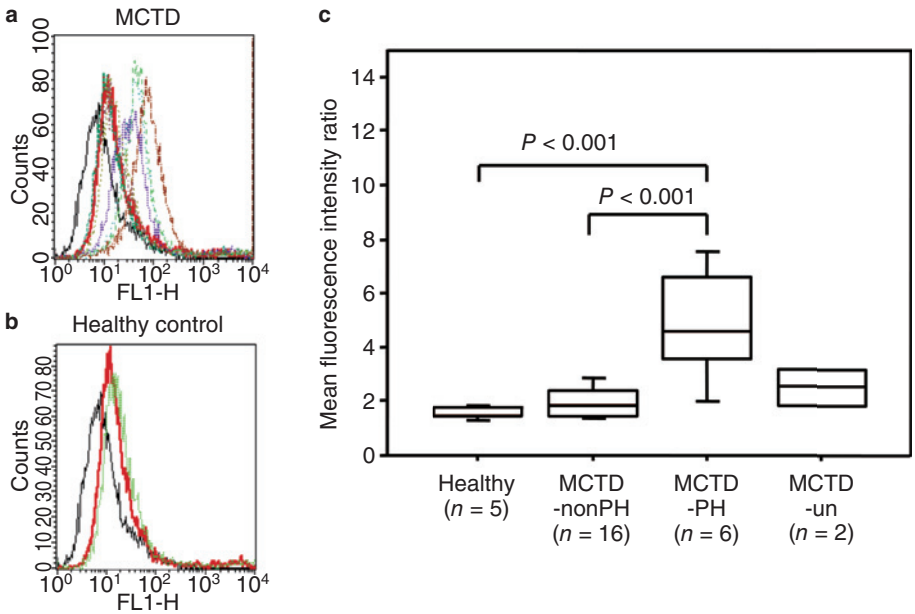


Fig. 8 Fluorescence intensity of flow cytometric analysis of serum levels of AECA against pulmonary microvascular endothelial cells in healthy controls and PH patients. MCTD cases demonstrate more intense pattern than healthy controls (red line) (**a, b**). Cases with PH show higher intensity than healthy controls and non-PH cases. MCTD-un indicates untreated patients in very early stage (**c**).

by a low pressure system. One is a functional mechanism, such as spasms of blood vessels due to hypoxia that was proven by many experimental studies.[13] Also, many individuals who live in high altitudes as in the Andes region of South America demonstrate PH. Some cases of PH associated with CTD are known as the functional type and these are believed to respond to drug and oxygen therapy better than the organic type described below. Because blood pressure (P) is calculated by following the formula: blood flow volume (V) x resistance (R), P increases as V increases. This phenomenon is usually seen in cases of left-to-right shunt with congenital heart diseases, such as ventricular septal defect, atrial septal defect, and patent ductus arteriosus. However, we will not deal with the pulmonary circular dynamism further here.

The other cause of PH is an organic change, which leads to an increase of vascular resistance (R) in the above formula. There are 2 major types of PH related to an elevation of R. One is the interstitial type that is accompanied by severe fibrosis of medium to small blood vessels, resulting in an increase of R. The arteries affected by fibrosis show secondary changes of severe intimal thickening called endarteritis. Many patients with this type of PH die of respiratory failure, rather than circulatory disturbance, before advance to severe PH.

The other type of PH is the primary vascular disease accompanied by severe fibrosis. This type is called vascular type of PH and is accompanied by plexogenic arteriopathy or severe fibrous intimal thickening, occasionally almost occlusive, which shows findings similar to PPH. This type generally has more severe vascular lesions compared with that of the interstitial type. Luminal occlusion of medium to small arteries induces the collapse of peripheral arteries resulting in impairment of gas exchange in spite of absence of severe fibrosis.

Immunological abnormalities have been considered as one of major pathogenic factors of PH in CTD. Even in PPH, immunological abnormalities are reported in 29% of the examined cases.[14] Because there are immunological abnormalities in PH associated with CTD, immunosuppressive therapy leads to a moderate improvement of the condition.[15,16]

Further, MCTD patients exhibit significantly higher AECA,[6] which is also found in other CTD.[17,18] AECA in the serum stimulates the production of endothelin that is related to vascular damage in patients with SLE.[19] We are now studying these pathways to elucidate the antigens that give rise to AECA. Such antigens may have applications in the treatment of PH.

Recently, several drugs have been developed for treatment of PH, particularly for PH associated with CTD. They targets of the drugs are biologically related to prostacyclin, endothelin, and phosphodiesterase type 5, which may be involved in vascular damage.[20] Further studies are needed to reveal their actual effects on the lesions.

CONFLICT OF INTEREST

No potential conflict of interest was disclosed.

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