Pulmonary Hypertension Complicating Mixed Connective Tissue Disease

Mixed connective tissue disease (MCTD) has a combination of clinical features similar to those of systemic lupus erythematosus (SLE), progressive systemic sclerosis (PSS) and polymyositis (PM) with a high titer of antibodies against ribonucleoproteins (RNP) (1). Raynaud’s phenomenon and swollen hands are the two major clinical findings of the disease. The disease is usually sensitive to glucocorticoid treatment with good prognosis. However, MCTD patients with pulmonary hypertension (PH) are refractory to conventional treatment and show a poor prognosis. Kasukawa et al (2) have reported that the mean period from the diagnosis of MCTD to PH is 5.43 years and that from the diagnosis of PH to death is 1.34 years on average. Major causes of death are sudden death presumably due to ventricular arrhythmia, and right heart failure (3). A very recent report by Sawai et al (4) on 32 autopsy cases of MCTD also confirmed above findings.

PH can be caused by various disorders, i.e. mitral stenosis, left ventricular failure, diffuse lung diseases such as pulmonary emphysema and pulmonary fibrosis, congenital heart diseases and obstructive pulmonary vascular diseases. The histopathological findings of PH seen in MCTD are similar to those in primary pulmonary hypertension (PPH), which are characterized by intimal thickening and plexiform lesions in the small pulmonary arteries (3, 4). These proliferative changes in the vasculature result in increased pulmonary arterial resistance. Little or no interstitial changes of the lung are observed. In contrast, pulmonary fibrosis is the major contributing factor for PH in PSS.

See also p 421.

The Research Committee for MCTD of the Ministry of Health and Welfare, Japan has established diagnostic criteria for PH complicated in MCTD (5). This criteria contains six clinico-laboratory findings: i.e. 1) exertional dyspnea, 2) left parasternal pulsation on inspection, 3) accentuated second pulmonary sound, 4) dilatation of the pulmonary artery segment on chest roentgenogram, 5) right ventricular hypertrophy on electrocardiogram (ECG), and 6) right ventricular enlargement on echocardiogram. PH can be diagnosed if 4 out of 6 findings are fulfilled. This diagnostic criteria is calculated to have the sensitivity of 92% and the specificity of 100%. A mean pulmonary pressure of over 25 mmHg in cardiac catheterization is helpful to substantiate the diagnosis of PH but echocardiogram can be an alternative method for diagnosis with less invasion. Classification tree criteria of PH in MCTD has recently developed by the same Committee (6). This criteria is constructed with two criteria, i.e. dilatation of the pulmonary artery segment evident on chest roentgenography (or an accentuated pulmonary sound as a surrogate) and shortness of breath on exertion, which demonstrates a sensitivity of 96% and a specificity of 99%.

So far, there is no definite clinical hallmark for this fatal complication of MCTD. Raynaud’s phenomenon might be related to the pathogenesis of PH but is not specifically observed in patients with PH. There is no correlation found between the occurrence of PH and laboratory findings such as the titer for anti-RNP antibodies in MCTD. Various autoantibodies including those against cardiolipin and vascular endothelial cells can induce the damage of pulmonary vascular endothelial cells. However, these antibodies are not always detected in MCTD as shown in the case reported by Itoh et al (7). Overexpression of endothelin-1, a potent vasoconstrictive substance with growth factor activity for vascular smooth muscle cells, is speculated to be involved in the pathogenesis of PPH (8). However, serum endothelin-1 levels were also within normal limits in Itoh’s case (7).

Once pulmonary hypertension is established, there is no effective treatment. Vasodilators including calcium channel blockers and prostaglandin E1, prostaglandin I2 are generally used to reduce pulmonary vascular tone with less efficacy. It is therefore essential to elucidate the pathogenesis of this fatal complication.

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References

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