Virchows Arch [Pathol Anat] (1984) 404:335–340

Virchows Archiv A

Mixed connective tissue disease with fatal pulmonary hypertension and a review of literature

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Summary. The paper presents an autopsy case of mixed connective tissue disease (MCTD) with pulmonary hypertension (PH) and a review of literature. A 33-year-old woman with Raynaud's phenomenon and dyspnea of one year duration was diagnosed as having MCTD on the basis of a higher titer (1:163,840) of serum antibodies to the ribonucleoprotein (RNP). Cardiac catheterization showed complicating PH, confirmed an autopsy by the findings of concentric intimal cellular proliferation and typical plexiform lesions in the small arteries and arterioles of the lung, suggesting primary PH. Fatal PH with MCTD has been reported only 6 cases in literature including our case. All were young females, with histopathological findings consistent with plexogenic pulmonary arteriopathy in 5 cases and with recurrent pulmonary thromboembolism in the other. The aetiology of PH is still unknown, but it may be due to vasoconstriction evoked by the hyper-reactivity of the vessels.

Key words: Mixed connective tissue disease (MCTD) – Pulmonary hypertension (PH) – Ribonucleoprotein (RNP) – Raynaud's phenomenon

Among the rheumatic diseases, the diagnosis of well-established rheumatoid arthritis, progressive systemic sclerosis (PSS), dermatomyositis-polymyositis (DM-PM) and systemic lupus erythematosus (SLE) is usually clear cut, although some cases show the characteristic of more than one rheumatic disease and are referred to as "overlap" syndromes. Most of these have the features of 2 to 3 rheumatic diseases, such as SLE, PSS and PM or DM. Sharp et al. (1972) described an overlap syndrome of SLE, generalized scleroderma (GSD) and PM, which they considered to be a new category of a "rheumatic disease syndrome different from the overlap syndromes" and termed it "Mixed Connective Tissue Disease (MCTD)". The distinct

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feature of this concept was defined by a high titer of antibodies to a saline extractable nuclear antigen (ENA), which were separated into ribonucleoprotein (RNP) and Sm antibodies by Mattioli (1977). The former was found in a small number of patients with classical PSS and SLE. Notman et al. (1975) has shown that the Sm-antibodies are restricted to patients with SLE. Patients with MCTD show a favorable response to corticosteroid therapy and a benign course. Although immune-complex glomerulonephritis with MCTD has often been reported, there have been only a few cases of fatal pulmonary hypertension (PH) with MCTD.

This paper presents an autopsy case of MCTD in a patient who succumbed to fatal pulmonary hypertension, together with a review of the literature.

Case report

A 33 year old Japanese female noted that she had oedema of the face in May, 1980 and thrombophlebitis in the left leg in June, 1981. Following this, she visited a physician because of extensive weight loss and general fatigue. The oedema subsequently spread to the extremities and there were palpitation, bloody sputum and Raynaud's phenomenon. She was first admitted to the hospital in Jan., 1982. Although the symptoms were relieved by use of diuretics, cardiac failure followed and she coughed up sputum and became hoarse. She was transferred to the Kobe University Hospital in February 1982. A physical examination showed drowsy consciousness, erythema of face, cyanosis of extremities, atrophic and shiny finger tips with clubbing of fingers, pigmentation of left foot and Raynaud's phenomenon. Percussion showed cardiac enlargement. The following values were obtained from laboratory tests: WBC 10,900/mm^3, RBC 553×10^4/mm^3, Hb 17.8 g/dl, Ht 53.3%, platelet 9×10^4/mm^3, blood gas pH 7.455, P_{O_2} 64.1 mmHg, P_{CO_2} 32.2 mmHg, O_2 Sat 90.5% HCO_3^- 22.9 mEq/l and BE 0.4 mEq/l, total serum protein 9.6 g/dl, albumin 38.7%, α_1-globulin 2.7%, α_2-globulin 4.6%, β-globulin 10.9%, γ-globulin 43.1%, IgA 600 mg/dl, IgG 700 mg/dl, IgM 100 mg/dl. Urinalysis revealed microhematuria.

The chest roentogenogram showed a 67% cardiothracic ratio. Intracardiac catheterization showed the pulmonary artery pressure to be 100/44 mmHg. Her case was diagnosed as pulmonary hypertension.

Serological studies indicated a high titer (1:163,840) of antibodies to RNP and negative Sm-antibodies. RA, RAHA, CRP and microsome tests were all negative. The LE test was positive, although LE cells were not detected. The following additional data were obtained: DNA test 1:320; ANA 1:40; Coombs' test direct +, indirect −; C_3 83.7 mg/dl; C_4 12.2 mg/dl; CH_{50} 40.8 U/ml.

Although she was treated with corticosteroids, diuretics, digitalis and O_2 inhalation, her condition gradually deteriorated. There was a sudden onset of apnoea and cardiac arrest in May, 1982 and resulting in her death.

Gross findings

The autopsy was performed 4 h following her death. An erythematous rash was evident on upper extremities. The finger-tips were sclerotic and slightly atrophic. There was a fibrous adhesion in left pleura and no pleural effusion was visible. The fibrous pericardial fluid measured 50 ml in volume. The heart weighed 510 g and the right ventricle was hypertrophied and markedly dilated. There was no gross evidence of stenosis of pulmonary valves, congenital heart disease. The right lung weighed 550 g, and the left, 470 g, The lungs were congested although there was no evidence of fibrosis. The liver weighed 1210 g and showed a slight fatty degeneration with congestion. The spleen weighed 120 g and was remarkably congested. The right and left kidneys weighed 170 g and 180 g and were also congested. The capsule could be easily stripped and the cortical surface was smooth.

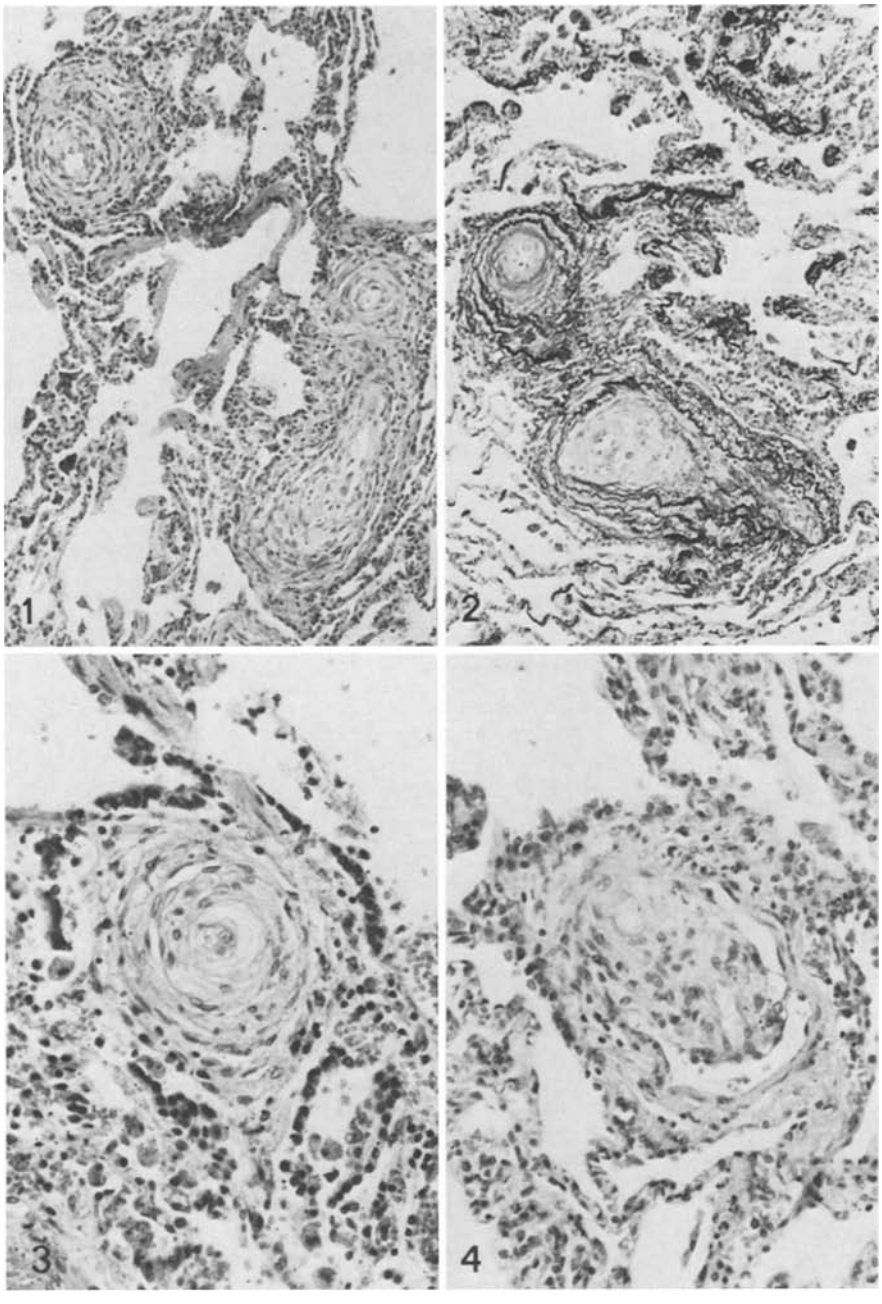

Fig. 1. Pulmonary muscular arteries showing hypertrophy of media and severe intimal proliferation with narrowing of the lumen. (H & E ×120)

Fig. 2. Pulmonary muscular arteries showing severe intimal fibroelastosis and elastic lamina being grossly thickened. Elastica-van Gieson. ×450

Fig. 3. Concentric laminar intimal proliferation (onion-skin like appearance) with obstruction of the lumen in pulmonary muscular artery. (H & E ×450)

Fig. 4. Certain arteriole showing eccentric intimal proliferation. (H & E ×450)

Microscopic findings

Heart. Pericarditis with lymphoid cell infiltration and fibrin was recognized. There was no inflammatory change, necrosis, or fibrosis in the myocardium. Both ventricles showed muscular hypertrophy.
Lung: The small arteries and arterioles showed concentric fibroelastic intimal proliferation with marked luminal narrowing, and were the most remarkable histological findings (Figs. 1–3). Typical plexiform-like lesions were most commonly observed at the sites where small arteries branched from the parent arteries. Thrombus was not observed in these vessels. In some parts, eccentric intimal proliferation indicating organized thrombi was observed (Fig. 4). Furthermore, medium-sized muscular arteries with medial hypertrophy and narrowed lumina were observed and dilatated venous like vessels surrounded them. According to the Heath-Edwards classification, this case was diagnosed as grade 4. Arteritis, shown by fibrinoid necrosis and inflammatory change, was not present. Alveolar septa had not thickened by fibrosis but the alveolar capillaries were congested. Immunohistochemical studies for IgG, IgA, IgM and C_3 revealed negative staining. Electron microscopic examination showed no dense deposits in the basement membrane of the capillaries, arteries and arterioles. The site of intimal proliferation was composed of many smooth muscle cells, elastic fibers and collagen fibers.

Liver. The central zones of the hepatic lobules were congested and necrosis of the liver cells was observed. Some liver cells in peripheral zones showed slight fatty degeneration.

Spleen. The spleen had undergone remarkable congestive changes. Onion-skin lesions and arterial change were not found.

Kidney. Congestion was remarkable, particularly in the renal medulla. There was moderate proliferation of mesangeal cells in some glomeruli. No definite "wire-loop" lesions were present. PAM stain showed no thickening of the basement membrane. According to immunohistochemical studies, only the IgG-stain was positive, as a linear pattern, although the result was different from the pattern in typical membranous glomerulonephritis. Electron microscopic findings showed no dense deposits in the basement membrane of the glomeruli.

Oesophagus. The muscularis mucosae was atrophic with intramuscular fibrosis. Marked lymphoid cell infiltration in the submucosal layer was noted.

Skin. Skin sections from the abdominal wall exhibited remarkable dermal atrophy. There was no inflammatory change in dermal as well as vascular tissues of the skin.

Discussion

Since "rheumatic diseases" have been clearly characterized, Sharp et al. (1972) consider that MCTD can be distinguished from certain classical collagen diseases and have pointed out the following characteristics of MCTD: (1) the clinical characteristics of the patients included features similar to those of SLE, PSS and PM and (2) serologically it is characterized by a high titer of antibodies to RNP and abscence of Sm antibody. In 1980, Sharp and Anderson indicated that MCTD may be characterized in terms of RNP antibody elevation and functional disturbances in oesophageal motility, gas exchange in the lung and in major joint mobility. Furthermore, the incidence of MCTD is higher than that of SLE and less than that of DM. Most of the patients have been female ranging in age from 5 to 80 years. The clinical and pathological findings in our patient clearly indicated MCTD. In addition, a microscopic examination of the patient's lungs showed concentric intimal cellular proliferation accompanied by extensive luminal narrowing of small arteries and arterioles. Typical plexiform lesions were observed in the arteries although no thrombus could be detected.

Table 1. Reported autopsy cases of MCTD with fatal pulmonary hypertension

Authors	Age	Sex	Histopathology						Serological data	
			MH	ICP	PL	Ar	Thr	IEP	RNP	Sm
Jones et al. (1978)	16	F	−	−	−	−	+	ND	100,000	−
Manthorpe et al. (1980) (case 1)	32	F	ND	+	ND	+	ND	ND	1,000,000	+
Wiener-Kronish et al. (1981)*1 (case 1)	21	F	+	+	+	+	ND	ND	500,000	−
Eulderink et al. (1981)	23	F	+	+	+	+	+	+	positive	−
Kobayashi et al. (1982)	34	F	+	+	+	−	+	ND	160,000	−
Ueda et al.*2,3 (present case)	33	F	+	+	+	−	−	+	163,800	−

MH; Medial hypertrophy, ICP; Intimal concentric proliferation, PL; Plexiform lesion, Ar; Arteritis, Thr; Thrombus, IEP; Intimal eccentric proliferation, RNP; Antibodies to ribonucleoprotein, Sm; antibodies to Sm antigen, ND; not described

*1; Immunofluorescent stains for IgG, IgA, IgM, IgE, C_3, Clq, and fibrinogen showed positive granular staining for IgG in the blood vessels of the lung
*2; Immunofluorescent stains for IgG, IgA, IgM, and C_3 showed negative in the lung
*3; Electron microscopic findings showed no dense deposits in the basement membrane of the capillaries, arterioles, and arteries in the lungs

According to Sharp's report (1975), pulmonary changes resulting from MCTD occurred in more than 60% of patients. PH in either classical or overlap collagen diseases is usually secondarily evoked and histopathological studies in these cases indicate interstitial fibrosis of the lung as a cause of PH (Silver et al. 1976). In PH with MCTD, several cases similar histological findings to primary PH have also been reported. To our knowledge, only 6 cases of fatal PH with MCTD including present case have been reported and are summarized in Table 1. The patients, all female, ranged in age from 16 to 34 years. Jones et al. (1978) considered that PH could be due to recurrent thromboembolic process inducing obliterative changes in small muscular pulmonary arteries and arterioles. However, it is not clear whether thrombi are embolic or develop locally in the pulmonary microvasculature. Wiener-Kronish's case showed plexogenic pulmonary angiopathy and positive immunofluorescent staining for IgG, C_3 and Clq in the lung (1981). Although there was no remarkable change in interstitial lung or alveolar walls, arteritis with fibrinoid necrosis and thrombi were often detected in medium-sized arteries and arterioles. Other cases (Manthorpe et al. 1980; Eulderink and Cats 1981; Kobayashi et al. 1982) showed concentric and eccentric intimal proliferation of arteries without description of thrombus and immunohistochemical studies.

In the present case, reactive medial hypertrophy was a striking feature

but there was no evidence of pulmonary arteritis, veno-occlusive disease or gross pulmonary embolism. The lesions of intimal proliferation showed myxoid change and lack of necrosis. There was no positive immunofluorescent staining of the vessels and alveolar walls.

Although the aetiology of plexogenic pulmonary arteriopathy is unknown, most evidences indicate a vasospastic origin of the disease (Wagenvoort CA and Wagenvoort N 1970). It is of interest that digital vasospasm has been reported in 7–30% of patients with plexogenic PH (Wagenvoort CA and Wagenvoort N 1970; Walcott et al. 1970) probably resulting from the prolonged pulmonary arterial vasoconstriction due to individual hyperreactivity of vessels toward various stimuli (Wagenvoort CA and Wagenvoort N 1970). Our case had plexogenic PH with Raynaud's phenomenon, although a direct relationship between MCTD and PH in studies of histology, immunohistochemistry and electron microscopy could not be found. We postulated vasoconstriction may be considered to play an important role in PH. Confirmation of such a relationship will require additional information from cases similar to the present.

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Accepted August 8, 1984