THE INVESTIGATION OF PULMONARY ABNORMALITIES IN PATIENTS WITH MIXED CONNECTIVE TISSUE DISEASE

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I. INTRODUCTION

Mixed connective tissue disease (MCTD) is an autoimmune disease, which is characterized by chronic inflammation causing damage to multiple organs. MCTD was diagnosed on the basis of Alarcon-Segovia and Villareal criterion symptoms which includes:

1. Raynaud's phenomenon
2. Swelling of the back of the hand, accompanied by the fusiform thickening of the fingers
3. Sclerodactylia
4. Polyarthritis, polyarthralgia
5. Myositis, verified by electromyography (EMG) and/or biopsy
6. The presence of anti-U1-RNP antibodies in the serum.

If 4 out of 5 clinical symptoms, and additionally, the anti-U1RNP antibodies are present, the diagnosis of MCTD may be confirmed.

When MCTD was first described in 1972, no respiratory symptoms were observed during the short-term follow up of the patients. In the early 1980-ies, it became evident that the respiratory alterations affect the patients' quality of life and survival. From 20 to 85% of patients with MCTD had respiratory organ symptoms, based on the data from various immunological centers. The most common forms of pulmonary symptoms in patients with MCTD are the interstitial lung disease (ILD) and the pulmonary arterial hypertension (PAH).

If PAH developed in patients with MCTD it was a rapid and progressively worsening form, causing death in most of the cases.

The mortality of MCTD varies between 5 and 15% during a follow up period of 6-15 years and the primary cause of death is PAH, which is accounted for 50% of the total mortality in patients with MCTD.

OBLITERATIVE VASCULOPATHY

The pathomorphological feature of MCTD is the obliterative vasculopathy. In 1977, Singsen et al. were the first to detect and describe proliferative vascular arteriopathy in patients died of MCTD. The alterations observed were characterized by thickening of the intima, media hypertrophy and rarely arteritis of the small arteries of the lungs. Plexiform lesions resembling the alterations in pulmonary arterial hypertension were found at the origin of the small pulmonary arteries.

The obliterative vascular disease affected all organs, including the kidneys, the coronary arteries of the heart, the large vessels and the abdominal aorta. However, the alterations in the lungs had the key role regarding the clinical symptoms and the prognosis. Initially, the analyses of the samples derived from patients suffered sudden death, PAH was verified as the underlying cause. Obliterative vasculopathy causes the dysfunction of several organs, including the kidneys and the skeletal muscles. Furthermore, it affects the pulmonary arteries causing arterial hypertension and cardiac complications.

INTERSTITIAL LUNG DISEASE

Interstitial lung disease (ILD) that causes damage to the pulmonary parenchyma often starts with mild symptoms. The interstitial infiltration seen on the chest X-ray image is initially alveolar type, then it spreads to the interstitium and fibrosis may develop at a later stage. Inflammation can be detected by HRCT (High Resolution Computed Tomography) at an early stage. The characteristic alteration of ILD detected by HRCT is the milk-glass-like opacity. Compared to systemic sclerosis (SSc), the occurrence of severe fibrosis accompanied by honeycomb pattern is rare in patients with MCTD.

The diagnosis of ILD in patients with MCTD is based upon the clinical symptoms and the abnormalities revealed by the respiratory function tests and the various imaging techniques.

If the diagnosis of ILD is uncertain by HRCT, lung biopsy must be performed. The histological classification of the samples taken from patients with MCTD is the same as the classification of interstitial pneumonias as defined and modified in 2002 by the American Thoracic Society. This classification is also used in patients with other polysystemic autoimmune diseases.

ILD indicates active alveolar and interstitial inflammation i.e. the activity MCTD, and it necessitates the employment of corticosteroids (CS) and/or cytostatics.

The factors triggering pulmonary fibrosis and the detailed development of the alteration is still unknown in MCTD. The alveolo-capillary membrane suffers damage in ILD and the deposition of IgG and complement C3 in the walls of the alveoli was observed, which implies the possible pathogenic role of circulation immunocomplexes. The presence of chemokines and proinflammatory, fibrosis-enhancing cytokines (IL-8, TNF-α, IL-1, TGF-β, PDGF) in the broncho-alveolar lavage fluid indicates active inflammation. Endothelin-1 (ET-1) and TGF-β are fibrosis-inducing mediators, cytokines.

PULMONARY ARTERIAL HYPERTENSION

PAH is one of the most severe and life-threatening complication of MCTD. In the beginning, several cases of sudden death drew attention to this, then from the mid 1980-ies, after following up a growing number of patients with MCTD, it became evident that PAH is responsible for almost 50% of the mortality in patients with MCTD. According to Nishimaki et al, the mean survival in MCTD accompanied by PAH is 4.4 years from the onset of the disease.

PAH is not caused by interstitial lung disease in patients with MCTD, as endothelial cell proliferation in the pulmonary vessels and obliterative vasculopathy are responsible for the increasing pressure in the pulmonary arteries. The incidence of PAH is less frequent than

ILD in patients with MCTD, as it is present in 23-50% of the patients and it usually develops after several years from the first onset of the disease.

Low pressure and low vascular resistance may be measured in the branches of the pulmonary arteries of healthy individuals, furthermore, the increase in pressure is not significant even during physical stress. The diagnosis of pulmonary arterial hypertension is verified if the resting systolic pressure in the pulmonary artery is greater than 25 mmHg and increases above 30 mmHg during physical stress. If the underlying cause of the increased pressure is unknown, then it is classified as primary-idiopathic form (IPAH). This abnormality is often accompanies other diseases, therefore polysystemic autoimmune diseases (quite often SSc, MCTD, systemic lupus erythematosus [SLE], less often rheumatoid arthritis [RA], ploymyositis/dermatomyositis [PM/DM], Sjogren's syndrome) portal hypertension, HIV infection, various storage diseases, or toxic effects may be the underlying causes in these cases. The incidence of PAH is 1-2 new cases per 1000000 per year.

PAH accompanying polysytemic autoimmune diseases has the same clinical, haemodynamical and pathomorphological characteristics as the idiopathic form.

The major clinical symptoms of PAH resemble those of pulmonary embolism. The "gold standard" of detecting increased pulmonary arterial pressure is still the right heart catheterization, but recently, transthoracic Doppler echocardiography – being a non-invasive method – is gaining an increasingly important role in the early recognition of PAH and the evaluation of the course of the disease and the effectiveness of the therapy employed. Several studies confirmed that the values measured using echocardiography and right heart catheterization, were nearly the same, if the systolic pulmonary pressure was above 45 mmHg.

The vasculature of the lungs undergoes morphological changes, called as "vascular remodelling". This is induced and maintained by factors, which are still not appropriately

known and detailed. The inducing factors may equally be hypoxia causing vasoconstriction of the pulmonary arteries, mechanical or other biochemical factors (free radicals, drugs, infection [HIV], immunological processes). As a consequence of endothelial cell dysfunction, the factors/processes regulating vasoconstriction (endothelin-1, thromboxane A, serotonin, angiotensin converting enzyme) and vasodilation (NO, prostacyclin) become unbalanced i.e. the proinflammatory, mitogenic and thrombogenic mechanism are becoming dominant. Subequently, the main pathomorphological features of PAH develop, including plexiform lesion, intima hyperplasia, endothelial cell proliferation and media hypertrophy. Local thrombus formation is a characteristic abnormality, which is induced by the release of thrombogenic factors and the subsequent platelet activation, furthermore the presence of antiphospholipid antibodies might have a role. The complete pathophysiological mechanism is still unknown, however, the presence of antinuclear antibodies, rheumatoid factor, immunoglobulins and complement deposits in the wall of the pulmonary vessels, the elevated serum IL-6 level and the presence of anti-endothelial cell antibodies imply immunological mechanisms as the trigger of the process leading to PAH.

We do not have therapeutic recommendations regarding PAH accompanying MCTD yet, however, we employ the treatment used in patients with idiopathic PAH. CS and immunosuppressant drugs have a major role in the therapy since patients with MCTD accompanied by PAH have active immunological abnormalities.

Several case reports described successful treatment, which verifies that early recognition has a crucial role to maintain the reversibility of the processes inducing PAH. Nowadays, the more and more extensive studies are aimed at the detection of signs and symptoms of pulmonary pressure increase in the earliest stage possible with the available methods, in addition to the better understanding of the pathomechanism of PAH.

II. OBJECTIVES

1. During our investigation, we examined the incidence of respiratory organ alterations in our patients with MCTD and analyzed their effect on the course of the disease and the survival.

2. We made our best effort to diagnose ILD and PAH at an early stage and to use the adequate diagnostic methods for this purpose.

3. We analyzed the immunological features of the two most common respiratory organ complications in MCTD, namely ILD and PAH.

4. We compared the clinical and immunoserological parameters of patients with MCTD accompanied by PAH and MCTD patients without PAH.

5. We examined the alterations in the serum implying endothelial damage/activation and tried to reveal correlation between the presence of the latter and the developed vascular damage.

6. We tried to analyze the role of immunological processes in the pathomechanism of PAH.

7. We were eager to reveal whether MCTD – as a chronic disease – has an effect on myocardial function, furthermore, we evaluated the extent of the residual damage to the right heart as a consequence of the pulmonary arterial pressure increase.

8. We investigated the effectiveness of therapy in MCTD patients with ILD and PAH and we made efforts to develop a consistent therapeutic protocol.

III. PATIENTS AND METHODS

1. Patients

We analyzed patient data of 179 patients with MCTD, diagnosed and treated between 1979 and 2002 in the 3rd Department of Internal Medicine of the University of Debrecen Medical and Health Science Center.

MCTD was diagnosed on the basis of Alarcon-Segovia and Villareal criterion symptoms.

The control group for evaluating myocardial function was consisting of patients, who attended at the Outpatient Care Unit of the 3rd Department of Internal Medicine due to locomotive organ symptoms and whose examinations verified spondylosis. The members of the control group had no cardiovascular abnormalities.

2. Methods

Patients with MCTD were followed-up in every 4 months in our Outpatient Clinic of Autimmune Diseases. We performed chest X-ray imaging, respiratory function tests, Doppler echocardiography and high resolution CT (HRCT) imaging of the patients, once a year. In addition to recording the physical status, we determined the erythrocyte sedimentation rate, the CBC, the renal and liver function tests and the immunoserological parameters.

At the onset of ILD we re-performed the HRCT, the respiratory function tests (FEV1, TLC, DLCO), the chest X-ray imaging and the ECG, a./ during the acute phase of ILD, b./ 6 months after the therapy, and c./ 4 years after the onset of the acute phase.

When PAH was diagnosed, we determined the arterial blood gas, performed transthoracic echocardiography, pulmonary function tests, measured the diffusing capacity of the lungs (DLCO) and determined the immunoserological parameters. In order to rule out pulmonary embolism in MCTD patients with PAH, ventilation/perfusion lung scintigraphy

was performed, furthermore HRCT was also performed in order to rule out interstitial lung disease.

The patients' blood samples were stored at -70^{o}C until use.

Total damage-index was determined according to the recommendations of the American College of Rheumatology (ACR).

Echocardiographic examinations included not only the measurement of usual parameters (such as heart chamber size, left ventricular systolic function, valves, wall-movement abnormalities), but that of the diastolic and global ventricular functions as well. As a diagnostic tool, Doppler echocardiograpy is sensitive and non-invasive, but unfortunately, under certain circumstances – such as changes in pre- and afterload, and in the case of arrhythmias – its reliability to evaluate systolic and diastolic ventricular dysfunction is limited. In contrast, another, increasingly wide-spread method is being used. It is the so called tissue Doppler ultrasound, which is based on the measurement of myocardial wall-movement velocity, and is therefore eligible to evaluate both global and segmental ventricular function. Global ventricular function is best estimated using the myocardial performance index (MPI), first described by Tei. MPI is calculated from ventricular in- and outflow and is used to characterize systolic and diastolic function. The greatest advantage of the method resides in the fact that it is independent from changes in the heart rate and from those in the pre- and afterload.

We determined the Tei-index of both ventricles by adding the isovolumetric relaxation time (IVRT) and the isovolumetric contraction time (IVCT), then dividing the sum by the ejection fraction (ET) [(IVRT+IVCT)/ET]. To determine diastolic function, early (Ee) and late (Aa) diastolic velocity of mitral and tricuspidal annuli, Ee/Aa quotient, and deceleration time (DT) was used.

Lung biopsy was performed on 5 patients, whose diagnosis of ILD was not unambiguous on the basis of the HRCT results. Histological classification of samples was based on the classification of interstitial pneumonias defined by the American Thoracic Society, last modified in 2002.

Immunoserological tests

Antinuclear antibodies (ANA) were shown on HEp2 cell lines, using indirect immunofluorescence. *Autoantibodies* (anti-ENA, anti-RNP, anti-Sm, anti-SSA, anti-SSB, anti-Jo1, anti-scl70, anti DNA, anti-cardiolipin [anti-CL] antibodies) were determined using an ELISA method (Pharmacia & Upjohn, Diagnostic GmbH, Freiburg, Germany and Cogent Diagnostics, Edinburgh, UK).

Von Willebrand Factor Antigen (vWFAg) levels were determined from platelet-poor plasma using immunoturbidimetry.

Anti-Endothelial Cell Antibodies (AECA) were tested on human umbilical cord endothelial cells, using the method previously described by our workgroup.

Serum thrombomodulin (TM) levels were measured using enzyme immunoassays (Diagnostica Stago France).

Serum IL-6 cytokine levels were measured using an ELISA method (OptEIA™ system, Pharmingen, San Diego, CA, USA).

Statistical analysis

Evaluation of the measurement data was performed using SAS™ for Windows™ 6.11 software. The data was analyzed using descriptive analysis (case number, average value, standard deviation :SD). Groups were compared using t-test, Fischer's Exact test, and

ANOVA. Survival was determined using the Kaplan-Meier method; with a significance level of $p<0.05$.

IV. RESULTS, NEW CONCLUSIONS

ILD was diagnosed in 96 out of 179 (53,6%) MCTD patients. ILD developed in the 5-8th year from the onset of MCTD; in those cases where ILD was present already in the early stages of MCTD, relapse tendency was higher.

PAH was found in 25 cases out of 179 MCTD patients (13,9%) during the course of the disease. Anamnestic data revealed no PAH before the diagnose of MCTD. PAH was most likely to develop between the 6-10th year of the MCTD.

> Based on a long-term follow-up of a large group of MCTD patients, our results prove that during the course of the disease, lungs become affected in more than half of the patients.
>
> ILD developed in 53.6% , PAH in 13.9% of our patients. These respiratory alterations develop after 5 years from the onset of MCTD.

HCRT performed in the acute phase of MCTD revealed fine-spotted opacities in 75 out of the 96 (78.2%) ILD patients, while 21 patients (21.8%) showed clear signs of incipient fibrosis in addition to alveolitis. Six months after the treatment, the above mentioned abnormalities regressed in 67 patient (69.8%); 15 (15.6%) patients showed the signs of incipient fibrosis, while manifest fibrosis remained in 13 of them (13.5%). Parenchymal degradation called honeycomb lung was observed in only one patient (1.6%). Follow-up HCRT was performed four years after the first alveolar phase, which showed fine spotted opacities only in 27 patients (28,1%), regardless of the relapses.

Among respiratory function tests (forced expiratory volume-FEV1, total lung capacity-TLC, vital capacity VC, diffusing capacity of the lung for carbon monoxide-DLCO), *DLCO* had the highest sensitivity for diffusion disturbances.

Lung biopsy performed in five patients revealed the typical histological signs of interstitial pneumonitis. Interalveolar septa showed lymphocytic and plasmocytic infiltration of variable intensity, furthermore, IgM and C3 complement deposits were detected in the alveolar epithelial cells.

HCRT is a reliable method in the early recognition and diagnosis of alveolitis. Should there be any doubt about the definite diagnosis, lung-biopsy must be carried out. Among lung-function tests, DLCO showed the highest sensitivity for diffusion disturbances.

In those cases, where the clinical picture of MCTD was *complicated by ILD*, serum concentrations of anti-U1RNP were pathologically high, but could be significantly reduced employing a 6-month treatment. After treatment, there were no significant differences in anti-U1RNP serum levels between MCTD patients with and without ILD.

After being diagnosed with ILD, our MCTD-ILD patient received iv. methylprednisolone in a dose of 2 mg/kg/day. Two weeks after the introduction of CS therapy, 51 of our patients developed fever, repose dyspnea and increased erythrocyte sedimentation rate, as a sign of non-response, so their therapy was supplemented with cyclophosphamide (2 mg/kg/day orally or 15 mg/kg iv, 6 times) from the 3rd week on.

Following CS and *immunosuppressant therapy*, previously high pathological immune complex concentrations showed marked decrease, while total haemolytic complement activity increased, and C3 complement concentrations returned to normal.

In those cases, where MCTD is complicated by ILD, the combination of CS and cytostatic treatment is recommened. If this combined therapy was introduced at

an early stage, the prognosis of MCTD-ILD was fairly favorable; only 1 out of 4 patients developed moderate-degree fibrosis in the bases.

The incidence of polyarthritis, Raynaud's phenomenon, myositis, glomerulonephritis and esophagus dysmotility was the same in MCTD patients with or without PAH. Serositis, skin symptoms, erythema, photosensitivity, hypo/hyperpigmentation, and teleangiectasy occurred more often in MCTD patients with PAH, than in those without it. Antiphospholipid-syndrome with arterial or venous thrombosis affected MCTD-PAH patients (24%)more often, than those without PAH (17%), however, the difference was not statistically significant.

In those cases, where MCTD is complicated by PAH, diffuse organic anomalies occurred more frequently and were more severe than in those without PAH.

Right heart catheterization was completed in 11 out of 25 PAH patients. The pressure values measured by the catheter-technique were the same as those with *Doppler-echocardiography*, which made the latter method suitable for long-term follow-up as well, in order to keep track of the response to the therapy. At the time of the recognition of PAH, systolic pulmonary arterial blood pressure was significantly higher in patients who died later on. ($p<0,001$).
As soon as we had a *definite diagnose of PAH*, we introduced pulse corticosteroid therapy. All five patients, who later passed away, previously received methylprednisolone in a dose of 100-200 mg/day, the other 20 patients - living even today - received 500 mg/day iv. for 3 successive days. Doses were gradually decreased in the next 2 months, until we reached a maintenance dose of 16 mg/day. Parallel to the pulse corticosteroid therapy, patients received 15 mg/kg cyclophosphamide in infusions, combined with vasodilator drugs, furthermore, to avoid local thrombus formation, the treatment was completed with low molecular weight heparin and prolonged acenocoumarol therapy.

In the 8th week of the therapy, we could detect a significant decrease of the pulmonary arterial pressure in those 20 patients, who are still alive.

Echocardiography has a major role in the care of MCTD patients, in the early diagnosis of PAH and during monitoring the treatment.

With the early recognition and treatment (CS, cytostatics, vasodilators and anticoagulants) of PAH complicating MCTD, we may be able to stop the consequent pulmonary damage, reduce pulmonary pressure and preserve patients in a fairly good physical condition.

MCTD-PAH patients had higher serum concentrations of U1RNP autoantibodies, and the presence of AECA was more frequent, furthermore, many of them had higher levels of TM and vWFAg as well, compared to MCTD patients without PAH. The average serum concentrations of AECA, TM and vWFAg was significantly higher in MCTD-PAH patients than in those without PAH ($p<0.001$).

Sera of MCTD-PAH patients were more likely to contain anti-CL IgM antibodies and the level of IL-6 - indicating acute inflammation - was also higher, compared to patients without PAH ($p<0.001$).

We discovered a positive correlation between the serum levels of anti-endothelial cell antibodies and vWFAg ($r=0.550$), and between anti-endothelial cell antibodies and TM serum concentrations ($r=0.446$).

The correlation between the serum levels of anti-endothelial cell antibodies and vWFAg , and between anti-endothelial cell antibodies and TM serum

concentrations arise the possibility that the presence of anti-endothelial cell antibodies has an important role in the pathomechanism of PAH.

4 of our female patients developed both ILD and PAH during their course of disease. In all 4 cases, ILD was the first to appear in the 2-4th year from the onset of MCTD. Lung-biopsies were performed in two of these patients; histological analysis revealed the typical features of interstitial pneumonitis. In all 4 patients, PAH developed within 1-2 years from the onset of ILD. The symptoms of PAH – featuring tachycardia, cardiac insufficiency, and elevated (44-83 mmHg) pulmonary arterial pressure – developed rapidly. No evidence supported the theory that PAH could have been induced by an already existing pulmonary fibrosis. HCRT revealed moderate-degree basal fibrosis in only one patient. For the treatment of PAH, we employed immunosuppressant drugs (CS and cyclophosphamide), prostacyclin analogues, NO, LMWH, and on the long-term, acenocoumarol. Our treatment proved to be effective, considering that all 4 patients mentioned above are still alive.

The interstitium and the pulmonary vasculature may suffer damage simultaneously, but as long as ILB is not followed by fibrosis, the treatment of PAH stands a good chance to be successful.

12 (6.7%) out of the 179 MCTD patients died, the prognosed 5-year-survival of the others is 96.4%, the 10-year-survival is 93.9%, while their 15-year-survival is 89.6%.
In 5 out of the 12 patients who died, PAH was identified as the cause of death.
20 out of 25 patients affected by PAH are still alive. The prognosed 5-year-survival of MCTD-PAH patients is 86.74%, while their 10-year-survival is 73.39%. Differences clearly show that PAH patients have significantly slimmer survival chances than non-PAH patients ($p<0.001$).

The most common cause of death among MCTD patients is PAH. If MCTD is complicated by PAH, the probability of long-term survival decreases.

All patients in our study (51 MCTD and 30 normal, healthy controls) had well preserved, sufficient left ventricular systolic function (EF).

Left ventricular diastolic dysfunction could be detected in all three groups (MCTD-PAH, MCTD without PAH, and control), but it was markedly of higher degree in the two MCTD groups than in the control group.

Left ventricular *Tei-index* was significantly higher (as a sign of global ventricular dysfunction) in the MCTD group than in the control, furthermore, MCTD patients with PAH had significantly higher index values than those without it.

Compared to normal, the Ee/Aa velocity quotient of the tricuspid lateral annulus and the deceleration time (DT) indicated significant *right ventricular diastolic dysfunction* in MCTD-PAH patients. A slight right ventricular diastolic dysfunction could be detected in MCTD patients without PAH as well, however, this could not be declared as significant compared to the results of the control group.

The increase in Tei-index indicating global right ventricular dysfunction was of significant degree in the MCTD-PAH group in comparison with the other two groups.

Our study demonstrates that those MCTD patients who suffered from PAH exhibit significant right and left ventricular diastolic dysfunction, which lasts for a prolonged period, even later, in the inactive phase, furthermore it can be detected using the tissue Doppler-technique in patients without clinical symptoms.

Significant left ventricle diastolic dysfunction develops even in those MCTD patients, who remain free of respiratory complications, which implies that it is a result of the primary disease, namely the MCTD, itself.

According to our data, regular echocardiographic follow-up of MCTD patient is by all means necessary, with special regard to those, who developed pulmonary arterial hypertension during the course of disease.

Examination and treatment of MCTD patients can only be carried out in the form of complex health care, under appropriate, high-quality diagnostic and therapeutic conditions.

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