Pulmonary Arterial Hypertension Associated with Autoimmune Disease: A Single Medical Center Experience

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Abstract

Background: New drugs have significantly improved the prognosis and quality of life of patients with pulmonary arterial hypertension. However, PAH associated with autoimmune disease, particularly progressive sclerosis, remains a very serious problem.

Objectives: To evaluate whether the course of the disease and survival is significantly different in patients with PAH related to autoimmune disease as compared to other patients with PAH and to determine the prognostic factors in these patients.

Methods: We retrospectively compared 24 patients with PAH associated with autoimmune disease to 42 patients with other causes of PAH. We focused on the clinical and hemodynamic parameters and on the outcome.

Results: The early mortality rate was slightly higher in patients with PAH associated with autoimmune disease (13% after the first year, 25% after the fifth year). The prognostic factor was a shorter distance on the 6 minute walking distance test ($r = 0.2$, $P = 0.01$).

Conclusions: The early detection of PAH associated with autoimmune disease should encourage earlier and more aggressive treatment than in idiopathic PAH.

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Pulmonary arterial hypertension is a severe pulmonary vascular disease and the leading cause of mortality in patients with autoimmune disease. It has been reported in association with almost every type of autoimmune disease. Although its occurrence is rare in patients with rheumatoid arthritis or dermatomyositis, it is found in 5–10% of all patients with systemic lupus erythematosus and has a high incidence in patients with progressive sclerosis – CREST 50% (calcinosis, Raynaud’s phenomenon, esophageal dysfunction, sclerodactyly, telangiectasia) and diffuse scleroderma 15–30% [1].

Pulmonary hypertension associated with autoimmune disease may be associated with interstitial pulmonary fibrosis or may involve the small and medium-sized pulmonary arteries with pathologic findings similar to idiopathic pulmonary arterial hypertension (or it may be secondary to mechanical obstruction due to pulmonary embolism).

The introduction of new drugs has improved the outcome of patients with PAH [2–5]; however, PAH related to autoimmune disease remains a very severe disease with a high mortality rate and a poor response to treatment. This study was designed to evaluate whether the course of the disease and survival is significantly different in patients with PAH related to autoimmune disease from that in other patients with PAH and to determine the prognostic factors in these patients.

Patients and Methods

Patient selection

This retrospective study compared two groups: one with PAH and the other (the study group) with PAH associated with autoimmune disease. The patients were regularly followed at the Pulmonary Hypertension Clinic in the Rabin Medical Center during the years 1999–2004. The clinical data were collected and focused predominantly on the patients’ characteristics, illness course and survival.

The patients included in this study had a mean pulmonary arterial pressure > 25 mmHg with normal pulmonary wedge pressure, diagnosis of the autoimmune disease based on the American College of Rheumatology criteria (positive serology and standard clinical criteria), and New York Heart Association class II–IV. Patients with other causes of pulmonary hypertension, patients with Eisenmenger syndrome, or patients with significant interstitial lung disease (total lung capacity < 70% predicted) were excluded.

All patients underwent a right heart catheterization at diagnosis (routine hemodynamic assessment), a physical examination and clinical assessment every month, a 6 minute walking distance test, oxygen saturation pre- and post-exercise every 3 months, and an echocardiography every 3–6 months.

Patients’ characteristics

Our cohort comprised 24 patients with PAH associated with autoimmune disease (36% of the PAH patients) and 42 patients with PAH without autoimmune disease (64% of the PAH patients). The patients with PAH associated with autoimmune disease were younger (mean age 41 years vs 58 years, $P = 0.003$) and had a higher prevalence of Eisenmenger syndrome (38% vs 13%, $P = 0.03$).

PAH = pulmonary arterial hypertension
patients with other causes of PAH. Of patients with autoimmune disease, 15 had diffuse scleroderma, 5 had CREST, 3 had mixed connective tissue disease, and one had SLE. Of the patients with other causes of PAH, 37 patients had idiopathic PAH, 3 had portopulmonary hypertension, and 2 had chronic pulmonary thromboembolic disease.

In all patients with an autoimmune disease, the underlying disease was diagnosed years before the development of PAH. In only three patients was the pulmonary hypertension diagnosed during an acute respiratory episode that necessitated hospitalization. In most of them, the pulmonary hypertension was suspected on the basis of progressive dyspnea and confirmed by echocardiogram and right heart catheterization.

**Statistical analysis**

Patients were categorized into two groups: PAH associated with autoimmune disease, and other PAH patients. Pearson correlation coefficients (r) and the significance for it (P) were calculated between the variables (patients' characteristics, clinical and hemodynamic parameters). P values less or equal to 0.05 were considered statistically significant and P values of 0.10 were considered borderline significant. In order to analyze statistically significant differences between categorical variables, chi-square test or Fisher's exact test was used as appropriate. In order to analyze statistically significant differences in mean continuous parameters between two groups of patients Student's t-test was used.

**Results**

There were 20 females and 4 males, and their mean age was 50 ± 13 years. Patients with the autoimmune disease were slightly older than patients with primary PAH, their mean 6 minute walk distance was shorter (322 ± 134 meters) and their mean oxygen saturation was 94 ± 6%. There was no statistical difference in the NYHA class, the PAPm and the cardiac index between the two groups [Table 1].

All the patients were treated with anticoagulants. In the study group, 38% (8 patients) received prostacyclin therapy (intravenous epoprostenol or subcutaneous treprostinil), 45% (11 patients) received endothelin receptors antagonist (bosentan or sitaxentan, and 20% (5 patients) received sildenafil.

One year after diagnosis the overall mortality rate in the study group was 13% (25% after 5 years). In the comparison group, the mortality rate was 5% after 1 year (21% after 5 years) [Figure 1]. There were more deaths among patients with CREST than among the other autoimmune patients. All mortality cases were due to right heart deterioration.

After 5 years there was a statistically significant correlation between mortality and a shorter 6 minute walking distance (r = 0.2, P = 0.01) and a borderline correlation between mortality and NYHA class (r = 0.1, P = 0.13). We did not find a statistically significant correlation between higher mortality rate and elevated PAPm.

**Discussion**

PAH is one of the leading causes of mortality in patients with autoimmune disease and most of the reports show that the prognosis is poor in comparison with idiopathic PAH [6,7].

We observed a high prevalence of pulmonary hypertension associated with diffuse scleroderma (without interstitial lung disease). We also observed increased mortality in the study group in comparison to other PAH patients predominantly after the first year. We did not find a statistically significant correlation between mortality and elevated PAPm as it is described in some studies.

<table>
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<tr>
<th>Table 1. Patients' characteristics: comparison between the two groups</th>
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<tr>
<td><strong>Characteristics</strong></td>
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<td><strong>PAH with autoimmune disease (n=24)</strong></td>
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<tr>
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<td>CREST, 5</td>
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<td>MCTD, 3</td>
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<td><strong>Age (yrs)</strong></td>
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<td><strong>PAPm (mmHg)</strong></td>
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<td><strong>6 min walk (m)</strong></td>
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<td><strong>Oxygen saturation (%)</strong></td>
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CVD = collagen vascular disease, MCTD = mixed connective tissue disease, CPTE = chronic pulmonary thromboembolic disease.
2005;171:1292.


Conclusions

The diagnosis of PAH associated with autoimmune disease suggests a shorter life expectancy. The higher risk is in patients with elevated PAPm and during the first year. Early screening and detection of PAH will allow a more aggressive and early treatment and will give some hope to these patients.

References


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Earth is here so kind, that just tickle her with a hoe and she laughs with a harvest

Douglas W. Jerrold (1803-1857), British playwright and humorist

Capsule

Depression, serotonin, and p11

Serotonin is an important modulator in a large number of physiologic and pathologic brain states. Among the many different serotonin receptors, the 5-HT1B receptor plays a crucial role in regulating serotonin neurotransmission. Svenningsson and collaborators investigated the role of a protein, p11, which appears to interact with 5-HT1B receptors, in depression and antidepressant treatment. 5-HT1B receptor function depended on p11 expression, and p11 levels were low in depressive states both in animal models (transgenic overexpression and knockout lines), as well as in human postmortem brains from depressed patients. In contrast, p11 levels were increased by antidepressant drugs and electroconvulsive treatment.

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