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

Daniele Bendayan MD, David Shitrit MD and Mordechai R. Kramer MD

Pulmonary Institute, Rabin Medical Center (Beilinson Campus), Petah Tikva, Israel
Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

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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

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 trepostinil), 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.

Table 1. Patients' characteristics: comparison between the two groups

	PAP with autoimmune disease (PAH-CVD) (n=24)	Other PAP (n=42)
Characteristics	Diffuse scleroderma, 15 CREST, 5 MCTD, 3 SLE, 1	Idiopathic PAH, 37 Portopulmo PAH, 3 CPTE, 2
Age (yr)	50 ± 13	47 ± 16
Gender		
Male	4	12
Female	20	30
NYHA class		
II	11	24
III	12	18
IV	1	0
PAPm (mmHg)	59 ± 12	63 ±18
Cardiac Index (L/min/m²)	2.1 ± 0.4	2.3 ± 0.4
6 min walk (m)	322 ±134	340 ± 95
Oxygen saturation (%)	94 ± 3.8	93 ± 3.4

CVD = collagen vascular disease, MCTD = mixed connective tissue disease, CPTE = chronic pulmonary thromboembolic disease.

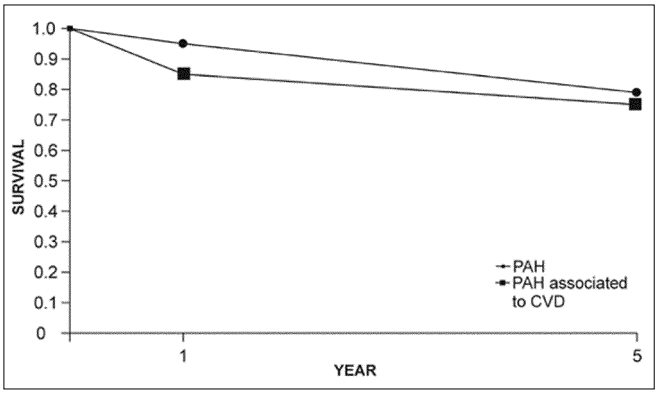

Figure 1. Survival curve of patients with PAH associated with autoimmune disease (PAH-CVD)

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

CREST = calcinosis, Raynaud's (phenomenon), esophageal (dysfunction), sclerodactyly, telangiectasia
SLE = systemic lupus erythematosus
NYHA = New York Heart Association
PAPm = mean pulmonary arterial pressure

[8,9]. Patients with autoimmune disease have a rapidly deterioration course and are less responsive to the treatment than other PAH patients. The prognostic factors for rapid deterioration and mortality were a short 6 minute walk distance and a high NYHA class.

The pathophysiology of PAH associated with autoimmune disease is not well understood. Endothelin plays an important role especially in progressive sclerosis [10]: the severity of the disease correlates with increased plasma levels of endothelin, with accumulation of endothelin in lung tissue, bronchoalveolar fluid and skin. Furthermore, endothelin is now recognized as having a fundamental role in the pathophysiology of PAH, and the introduction of endothelin receptor antagonist is a therapeutic option especially in this group of patients [11,12].

As in idiopathic PAH, it seems that the vascular injury can occur at the early stage of the disease before the appearance of dyspnea. Early detection of the disease remains the key to optimize the efficacy of the treatment, and it is now recommended that all patients with autoimmune diseases, particularly progressive sclerosis, undergo an annual echocardiography even in the absence of symptoms [12-15].

Conclusions

The diagnosis of PAH associated with immune diseases 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.

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Correspondence: Dr. M.R. Kramer, Pulmonary Institute, Rabin Medical Center (Beilinson Campus), Petah Tiqva 49100, Israel
Phone: (972-3) 937-7221
Fax: (972-3) 924-2091
email: kramerm@netvision.net.il