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Pulmonary arterial hypertension among Filipino patients with connective tissue diseases

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Abstract We describe the clinical features, therapies, and clinical course of pulmonary arterial hypertension (PAH) in a group of Filipinos with connective tissue diseases (CTDs). We retrospectively reviewed the records of patients diagnosed with PAH by a two-dimensional echocardiogram as a tricuspid regurgitant jet of more than 25 mmHg. All patients had underlying CTDs, defined by the American College of Rheumatology criteria, and were seen at the rheumatology clinics of the University of Santo Tomas Hospital and the St. Luke's Medical Center, Philippines. Of the 33 patients (32 women) included in the analysis, there were 14 patients with systemic lupus erythematosus (SLE), 12 with scleroderma, 5 with mixed connective tissue disease (MCTD), 1 with primary antiphospholipid syndrome (APS), and 1 with dermatomyositis. The average age at PAH diagnosis was 38 ± 14 years (mean ± SD), and the mean duration of illness from CTD to PAH diagnosis was 53 ± 52 months. Twelve patients had died at the time of this report, with a median duration of 15 months (range 1–57 months) from PAH diagnosis to mortality: six of these had scleroderma, five with SLE, and one with APS. The following therapies were used in this group of patients: low molecular weight heparin, warfarin, calcium-channel blockers, aspirin, cyclophosphamide, bosentan, iloprost, and sildenafil. We have described the clinical profile of PAH in a group of Filipino patients with CTDs, most commonly SLE. Various forms of pharmacologic therapies were used among these patients. Mortality remains high, particularly among those with underlying scleroderma. Early recognition and treatment are crucial in order to provide a better outcome for these patients.

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Introduction

Pulmonary arterial hypertension (PAH) is a condition that occurs as a consequence of chronic obstruction of small pulmonary arteries caused by endothelial cell, vascular smooth muscle cell, and fibroblast dysfunction and proliferation.[1–3]

In 1998, the World Health Organization (WHO) developed a classification system on the basis of the clinical features of patients with pulmonary hypertension.[4] This is apart from the New York Heart Association classification using the functional status of the patient.[4] The WHO classification makes it possible to classify patients according to the underlying disease etiology, thus clearly identifying the underlying cause and contributing factors that can lead to an effective therapeutic strategy. This is in line with the recommendation by the American College of Chest Physicians (ACCP) Medical Therapy for PAH.[5] Data among Asian countries, specifically from Japan and India, were included in the guidelines. The data reported on the natural history, the prognostic factors, and the prediction of life.

Pulmonary complications can occur in patients with connective tissue disease (CTD). They may occur as a result of underlying primary pathology or as a complication of its treatment. Although interstitial lung disease (ILD) is the most common pulmonary complication of CTD, pulmonary vascular involvement may occur as alveolar hemorrhage or as pulmonary hypertension. PAH may accompany ILD or may be the only pulmonary problem.[6]

A study previously presented the clinical features and disease course of Filipinos with systemic lupus erythematosus (SLE) patients and pulmonary hypertension.[7] This present study aims at describing the clinical features, treatment regimens, and outcomes among Filipino patients with PAH secondary to CTD.

Table 1. Characteristics of 33 Filipino patients with pulmonary arterial hypertension (PAH) secondary to connective tissue disease (CTD)

	All patients $n = 33$	SLE $n = 14$ (42%)	Scleroderma $n = 12$ (36%)	MCTD $n = 5$ (15%)	APS $n = 1$ (3%)	Dermatomyositis $n = 1$ (3%)
Demographic characteristics						
Age in years, mean ± SD	43 ± 14	35 ± 11	50 ± 13	42 ± 12	35	66
Age at the diagnosis of CTD in years, mean ± SD	34 ± 14	26 ± 11	41 ± 13	33 ± 19	28	59
Age at the diagnosis of PAH in years, mean ± SD	38 ± 14	30 ± 10	45 ± 13	40 ± 12	28	66
Duration of CTD at the diagnosis of PAH in months, mean ± SD	53 ± 52 (1–224)	50 ± 33 (1–92)	47 ± 50 (1–146)	79 ± 97 (1–224)	0	74
Pulmonary arterial pressure (mmHg) by tricuspid regurgitant jet, mean ± SD	65 ± 29	65 ± 28	51 ± 10	51 ± 16	128	110
Clinical manifestations						
Dyspnea, *n* (%)	20 (55.56)	7 (58)	6 (66.67)	3 (75)	1	1
Accentuated P2,*n* (%)	14 (38.89)	4 (33.33)	5 (55.56)	2 (50)	1	1
Cardiomegaly, *n* (%)	12 (33.33)	5 (41.76)	3 (33.33)	2 (50)	0	0
Nephritis, *n* (%)	11 (30.56)	5 (41.67)	4 (44.44)	2 (50)	0	0
Serositis, *n* (%)	9 (25)	5 (41.67)	3 (33.33)	1 (25)	0	0
Raynaud's, *n* (%)	8 (22.22)	3 (25)	3 (33.33)	1 (25)	0	0
Interstitial lungdisease, *n* (%)	8 (22.22)	4 (33.33)	1 (11.11)	1 (25)	0	1
Parasternal heave, *n* (%)	5 (13.89)	1 (8.33)	2 (22.22)	1 (25)	1	1
Cough, *n* (%),	3 (8.33)	3 (25)	0	0	0	0
Raised JVP, *n* (%)	2 (5.56)	1 (8.33)	1 (11.11)	0	0	1

PAH, pulmonary arterial hypertension; CTD, connective tissue disease; SLE, systemic connective tissue disease; MCTD, mixed connective tissue disease; APS, antiphospholipid syndrome; JVP, jugular venous pressure; SD, standard deviation

Materials and methods

A retrospective case series was conducted among patients with underlying CTD who presented with PAH. To classify the patients' CTD, the classification criteria for the respective CTD, published by the American College of Rheumatology, were used.[8] These patients were seen at the University of Santo Tomas, Section of Rheumatology, Clinical Immunology, and Osteoporosis and at St. Luke's Medical Center (SLMC), Section of Rheumatology, Allergy, and Immunology, from 2000 to 2005. In the selection of patients, those with pulmonary arterial pressure by tricuspid regurgitant jets more than 25 mmHg at rest were included. Data were gathered from medical records and diagnostic results, including interviews with the patients. The collected data were verified and double-checked for accuracy and veracity by a separate investigator. Only patients with underlying CTD that occurred prior to the diagnosis of PAH were included.

Descriptive statistics were used for the demographic and clinical features. Data on mortality were analyzed on the basis of the number of months from diagnosis to mortality. NCSS 2004 and PASS 2005 software were used for statistical computation.

Results

A total of 33 patients were included in the case series. Table 1 shows the characteristics of 33 Filipino patients with PAH. Of the total 33 patients, there were 32 women, and 1 man. The mean age of the patients was 43 ± 14 years. The mean age at PAH diagnosis was 38 ± 14 years (mean ± SD) and the mean duration of CTD to PAH diagnosis was 53 ± 52 months. The most common underlying CTD was SLE followed by scleroderma, mixed connective tissue disease (MCTD), antiphospholipid syndrome (APS), and dermatomyositis. Common clinical manifestations (in descending order) at diagnosis of PAH for all patients were mostly cardiac, pulmonary, and renal in origin, represented by dyspnea, accentuated pulmonic sound (P2), cardiomegaly, nephritis, and serositis. Other clinical manifestations were as follows: Raynaud's, ILD, cough, parasternal heave, and raised jugular venous pressure (JVP).

Table 2. Treatments used among 33 Filipino patients with CTD and PAH

Treatment	No.
Calcium-channel blocker	13
Warfarin	12
Iloprost	8
Low molecular weight heparin	7
Sildenafil	5
Bosentan	4
Low-dose aspirin	4
Beraprost	2

Treatment

In addition to the treatment of the underlying CTD with steroids and cytotoxic drugs such as cyclophosphamide, medications directed to PAH were low molecular weight heparin, warfarin, calcium-channel blockers (CCB), aspirin, bosentan, intravenous or inhaled iloprost, beraprost, and sildenafil (Table 2).

Table 3. Mortality data of 12 Filipinos with PAH secondary to CTD

Characteristics	All patients ($N = 12$)	Scleroderma ($n = 6$)	SLE ($n = 5$)	APS ($n = 1$)
Age in years, mean ± SD	44 ± 15	50 ± 18	37 ± 6	35
Age at the diagnosis of CTD in years, mean ± SD	33 ± 14	38 ± 17	26 ± 6	28
Age at the diagnosis of PAH in years, mean ± SD	38 ± 14	44 ± 16	30 ± 7	28
Duration of CTD at diagnosis of PAH in months, mean ± SD	58 ± 49	72 ± 58	51 ± 29	0
Duration of PAH from diagnosis to mortality in months, median (range)	15 (1–57)	2 (1–16)	42 (15–57)	34

PAH, pulmonary arterial hypertension; CTD, connective tissue disease; SLE, systemic lupus erythematosus; APS, antiphospholipid syndrome; SD, standard deviation

Mortality and associated connective tissue disease

Twelve patients had died at the time of this report (Table 3), with a median duration of 15 months and a range of 1–57 months from PAH diagnosis to mortality. Individual analysis from PAH diagnosis to mortality showed that there were variations among the different CTDs: scleroderma with a median duration of 2 months and a range of 1–16 months from PAH diagnosis to mortality, SLE with a median duration of 42 months and a range of 15–57 months, and APS (the only case) showed a duration of 34 months. Among the CTDs, six had scleroderma, five had SLE, and one had APS. Patients with scleroderma tend to have a higher mortality than those with SLE. Survival data among scleroderma patients appear to be worse than for those with SLE.

Discussion

Reviewing the records from 1992 to 2005, we were able to gather patients from two institutions. This article presents the clinical characteristics of PAH among Filipino patients with CTDs.

Most patients diagnosed with PAH represent the productive age group of the population. It should be noted that once a diagnosis of CTD is made, the primary care physician should routinely examine the patient to look for signs and symptoms of PAH, especially when the underlying CTDs are scleroderma, SLE and MCTD. In our series, the duration of CTD to PAH diagnosis ranged from as early as 1 month to as late as 18 years, reinforcing the need for vigilance in the recognition of this complication.

Scleroderma, SLE, and MCTD were among the CTDs mentioned in the series. As previously described, PAH is a common complication among these CTDs.[9] APS and dermatomyositis were also mentioned in the series. Rare reports on PAH resulting from either recurrent pulmonary emboli or in situ thrombosis can be found.[10,11] The occurrence of PAH has been reported in association with every known type of CTD. However, the frequency varies significantly with regard to the different CTDs. PAH is a common complication of scleroderma, MCTD, and SLE.[9] Eleven studies of patients with scleroderma reported a prevalence of PAH, ranging from 4.9%[12] to 38%[13] with a mean from several studies of 16%.[12,14–16] In MCTD, one long-term follow-up study found that PAH was the most common cause of death, occurring in 38% of patients.[17] PAH occurs less frequently in SLE. Four studies[18–21] of patients with SLE reported a prevalence of PAH that ranged from 4.3% to 43% with a mean of 7%.[18–21] Our study population showed more patients with SLE in contrast to the aforementioned studies; it may be that there is a relatively larger population of SLE in the Philippines compared with other countries.

In general, patients with PAH present with progressively worsening dyspnea, dry cough, fatigue, and palpitations.[22] Physical findings include accentuated P2, parasternal heave, pedal edema, ascites, and an elevated JVP.[23,24] Raynaud's phenomenon has been described in up to 60% of the patients.[22] Chest radiographs may show cardiomegaly with prominent pulmonary artery segments and oligemic lung fields. The manifestations mentioned in the literature were almost similar to those in our patients except that there were fewer manifestations of Raynaud's phenomenon, which maybe explained by the difference in the number of underlying CTDs.

Dyspnea, accentuated P2, and cardiomegaly were among the most common manifestations in our patients, for which conditions careful examinations should be conducted. These conditions are easily detected during routine check-up and can be further verified by a chest radiograph and an echocardiogram. ACCP has included the chest radiograph and the echocardiogram as part of the patient's evaluation if there is a reason to suspect PAH.[24] The chest radiograph is obtained to reveal features supportive of a diagnosis of PAH and to lead to the diagnosis of the underlying disease, whereas echocardiogram is performed as a noninvasive screening test that can detect PAH, although it may be imprecise in the determination of the actual pressures when compared with the invasive evaluation in a group of patients.[24] The recommendation carries a corresponding strength of evidence as stated by the ACCP committee.[25]

The treatment guidelines for PAH associated with CTD recommend vasoreactivity testing, although the level of evidence is only an expert opinion.[5] This is done to determine the patients' response to vasodilator therapy. In a setting where vasoreactivity testing is not available, considering that this is an invasive procedure, this was not done to the patients in the series.

Calcium-channel blockers and warfarin are the two most common drugs used in the series. These drugs are part of

the treatment recommendation with corresponding levels of evidence and benefit.[5] New drugs such as prostacyclin (iloprost and beraprost), bosentan, and sildenafil were likewise given to the patients who did not respond to CCB therapy. Prostacyclin, a potent vasodilator, has been found to be deficient among patients with PAH.[26] Furthermore, there was evidence of decreased expression of prostacyclin synthase in the lungs from patients with severe PAH.[27] Bosentan, on the other hand, is an endothelin receptor antagonist that utilizes the pathogenic role of endothelin-1.[28,29] Even with medical therapy, mortality remains high for CTD patients developing PAH, with a median duration from diagnosis to mortality of 15.5 months with a range of 1–57 months. PAH with scleroderma appears to have a higher incidence of mortality and shorter duration from diagnosis to mortality when compared with other CTDs.

In conclusion, we have described the clinical profile of PAH in a group of Filipino patients with CTD, most commonly SLE. Various forms of pharmacologic therapies were used among these patients. Mortality remains high, particularly among those with underlying scleroderma. Early recognition and treatment are crucial in order to provide a better outcome for these patients.

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