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**Original Article**

# Pulmonary arterial hypertension in autoimmune diseases: an analysis of 19 cases from a medical center in northern Taiwan

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**Background and Purpose:** Pulmonary arterial hypertension (PAH), a serious complication of autoimmune diseases, has rarely been reported in Taiwan.

**Methods:** Nineteen patients with various autoimmune diseases diagnosed with PAH at Taipei Veterans General Hospital from 2002 to 2004 were enrolled; the underlying autoimmune diseases included systemic lupus erythematosus (n = 6), primary Sjögren's syndrome (n = 5), systemic sclerosis (n = 4), adult-onset Still's disease (n = 2), and mixed connective tissue disease (n = 2). The characteristic manifestations of underlying autoimmune diseases and the clinical features of PAH were analyzed.

**Results:** There were 16 female and 3 male patients. The median age at onset of PAH was 44 years and the mean right ventricular systolic pressure (RVSP) was 67.9 mm Hg. Patients without pneumonitis had a significantly higher RVSP value than those with pneumonitis (77.5 ± 24.3 vs 54.8 ± 18.4 mm Hg, $p$=0.041). Four out of 7 patients (57.1%) with RVSP ≥80 mm Hg and 1 out of 12 patients (8.3%) with RVSP <80 mm Hg died. In all of the 19 patients, the severity of RVSP was significantly correlated with serum uric acid (UA) level (r = 0.686, $p$=0.001). Among the PAH patients without pneumonitis, the severity of RVSP inversely correlated with the diffusion capacity of the lung for carbon monoxide ($D_{LCO}$) [r = –0.856, $p$=0.003]. The characteristic manifestations of underlying autoimmune diseases included a high incidence of Raynaud's phenomenon (15/19, 78.9%), a high titer of antinuclear antibody (13/17, 76.5%), positive anti-ribonucleoprotein antibody (8/15, 53.3%), hypergammaglobulinemia (15/19, 78.9%), hyperuricemia (13/19, 68.4%), and less renal involvement.

**Conclusions:** PAH in autoimmune diseases could be potentially fatal with characteristic manifestations. Moreover, RVSP correlated directly with serum UA level and inversely with $D_{LCO}$.

**Key words:** Autoimmune diseases, pulmonary diffusion capacity, pulmonary hypertension, Taiwan, uric acid

## Introduction

Pulmonary arterial hypertension (PAH) is a potentially fatal disease and is characterized by elevated right ventricular systolic pressure (RVSP) and increased pulmonary vascular resistance. Without adequate treatment, it can result in heart failure, pulmonary edema, arrhythmia and sudden death. The causes of PAH are diverse. PAH can be primary with an unknown etiology or secondary to some underlying diseases, such as heart, lung, or collagen vascular diseases [1]. The underlying diseases reported included left ventricular dysfunction, mitral valve disease, congenital heart disorder, pulmonary fibrosis, chronic obstructive pulmonary disease, pulmonary thromboemblism, chronic hypoxia and various autoimmune diseases such as systemic sclerosis (SSc) [2], CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia) [3], systemic lupus erythematosus (SLE) [4], mixed connective tissue disease (MCTD) [5] and Sjögren's syndrome (SS) [6].

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PAH as a complication in autoimmune diseases is not frequently reported. This disorder occurs most often in SSc (ranging from 4.9% to 38%) and CREST syndrome (up to 50%), but less frequently in SLE (3-5%), primary SS or adult-onset Still's disease (AOSD) [2,7-9]. PAH is one of the severe complications in collagen vascular diseases. Patients with PAH always have poor life quality, such as impaired exercise tolerance, exertional dyspnea, easy fatigue, and a high mortality rate [9,10]. Therefore, it is very important to understand this disorder and its relationship with underlying diseases. In this study, we sought to discover the characteristic manifestations and laboratory features in patients with PAH associated with autoimmune diseases.

## Methods

Nineteen PAH patients with various underlying autoimmune diseases who had been regularly followed up at the outpatient department (OPD) of the Division of Allergy, Immunology, and Rheumatology, Department of Medicine, Taipei Veterans General Hospital from May 2002 to August 2004 were enrolled. All patients had complete surveys for symptoms and signs of connective tissue disease in our OPD. Those patients with symptoms and signs suggesting cardiopulmonary diseases, such as exertional dyspnea, cardiomegaly, congestive heart failure and palpitation, were surveyed for PAH by echocardiogram. PAH was defined by the criteria of the National Institutes of Health Registry on Primary Pulmonary Hypertension [10]. Resting RVSP or mean pulmonary arterial pressure (mPAP) ≥25 mm Hg, as revealed by either echocardiography or heart catheterization, were considered as PAH.

The demographic data are shown in Table 1. Among the 19 PAH patients with underlying autoimmune diseases, the female-to-male ratio was 16/3 (84.2% vs 15.8%). The median age at onset of the underlying autoimmune diseases was 41 years (range, 13 to 67); the median age at onset of PAH was 44 years (range, 23 to 68). The mean duration of PAH was 1.7 years (range, 0.5 to 3). The underlying autoimmune diseases were SLE (n = 6), primary SS (n = 5), SSc (n = 4), AOSD (n = 2), and MCTD (n = 2).

The classification criteria used for these various autoimmune diseases were: 1997 American College of Rheumatology (ACR) criteria for SLE [11]; 2002 American-European Consensus criteria for primary SS [12]; 1980 ACR criteria for SSc [13]; Alarcon-Segovia's criteria for MCTD [14]; and Yamaguchi's criteria for AOSD [15].

**Table 1**. Demographic data of 19 pulmonary arterial hypertension (PAH) patients with underlying autoimmune diseases

| No. | Gender | Age (years) | Autoimmune disease | Age onset of autoimmune disease (years) | Age onset of PAH (years) | Duration of PAH (years) | RVSP (mm Hg) | Outcome |
|---|---|---|---|---|---|---|---|---|
| 1 | F | 55 | MCTD | 51 | 52 | 3 | 52 | Survival |
| 2 | F | 51 | MCTD | 50 | 50 | 0.5 | 100 | Death |
| 3 | F | 41 | AOSD | 34 | 32 | 2 | 105 | Survival |
| 4 | F | 27 | AOSD | 22 | 25 | 2 | 102 | Survival |
| 5 | F | 44 | SSc | 40 | 43 | 1 | 35 | Survival |
| 6 | F | 46 | SSc | 42 | 44 | 2 | 88 | Death |
| 7 | F | 53 | SSc | 49 | 51 | 2 | 69 | Survival |
| 8 | M | 70 | SSc | 67 | 68 | 2 | 42 | Survival |
| 9 | F | 38 | Primary SS | 28 | 36 | 2 | 39 | Survival |
| 10 | F | 61 | Primary SS | 59 | 59 | 2 | 40 | Survival |
| 11 | M | 65 | Primary SS | 62 | 63 | 2 | 48 | Survival |
| 12 | F | 42 | Primary SS | 41 | 41 | 0.5 | 85 | Death |
| 13 | F | 60 | Primary SS | 58 | 59 | 1 | 43 | Death |
| 14 | F | 25 | SLE | 13 | 23 | 2 | 78 | Survival |
| 15 | F | 33 | SLE | 18 | 32 | 1 | 91 | Survival |
| 16 | F | 30 | SLE | 23 | 27 | 3 | 91 | Death |
| 17 | M | 29 | SLE | 23 | 26 | 3 | 69 | Survival |
| 18 | F | 51 | SLE | 36 | 50 | 1 | 44 | Survival |
| 19 | F | 54 | SLE | 52 | 53 | 1 | 69 | Survival |

Abbreviations: RVSP = right ventricular systolic pressure; F = female; M = male; MCTD = mixed connective tissue disease; AOSD = adult-onset Still's disease; SSc = systemic sclerosis; SS = Sjögren's syndrome; SLE = systemic lupus erythematosus

 

**Table 2**. Clinical features and laboratory findings of 19 patients with pulmonary arterial hypertension

| No. | Autoimmune disease | Lung | | | Kidney | | CNS involvement | Raynaud's phenomenon |
|---|---|---|---|---|---|---|---|---|
| | | DOE | Pneumonitis | $D_{LCO}$ (%) | Cr | Proteinuria | | |
| 1 | MCTD | + | – | 93 | 0.8 | – | – | + |
| 2 | MCTD | + | – | 72 | 0.9 | – | – | + |
| 3 | AOSD | + | – | 43 | 0.8 | – | – | + |
| 4 | AOSD | + | – | 54 | 1 | – | – | + |
| 5 | SSc | + | Mild | 92 | 0.9 | – | – | + |
| 6 | SSc | + | Moderate | 72 | 0.6 | – | – | + |
| 7 | SSc | + | Mild | 82 | 0.8 | – | – | + |
| 8 | SSc | + | Mild | 62 | 1 | – | – | + |
| 9 | Primary SS | + | – | 105 | 0.7 | – | – | + |
| 10 | Primary SS | + | – | ND | 1.3 | + | – | + |
| 11 | Primary SS | + | Mild | 51 | 1 | – | + | + |
| 12 | Primary SS | + | – | 68 | 0.9 | – | – | – |
| 13 | Primary SS | + | Moderate | 57 | 0.6 | – | – | – |
| 14 | SLE | + | – | 67 | 0.8 | + | + | – |
| 15 | SLE | + | – | 82 | 0.9 | + | – | + |
| 16 | SLE | + | – | 76 | 0.9 | – | – | + |
| 17 | SLE | + | – | ND | 1 | – | + | + |
| 18 | SLE | + | Mild | 64 | 0.8 | – | – | – |
| 19 | SLE | + | Mild | ND | 0.9 | – | – | + |

Abbreviations: DOE = dyspnea on exertion; $D_{LCO}$ = diffusion capacity of the lung for carbon monoxide; Cr = creatinine; CNS = central nervous disease; AOSD = adult-onset Still's disease; SSc = systemic sclerosis; SS = Sjögren's syndrome; SLE = systemic lupus erythematosus;

Medical charts were reviewed and data were collected, including demographic data, clinical features (major symptoms/signs and organ involvement), laboratory findings (complete blood count, serum chemistry and uric acid [UA]), immunologic profiles (antinuclear antibody [ANA], anti-SSA antibody, anti-ribonucleoprotein [anti-RNP] antibody and serum immunoglobulin G [IgG], immunoglobulin A [IgA], immunoglobulin M [IgM], etc.), urinalysis, chest radiological findings (chest X-ray and high-resolution computed tomography [HRCT]), and pulmonary function tests (diffusion capacity of the lung for carbon monoxide [$D_{LCO}$]).

To compare the severity of RVSP between those patients with and without pneumonitis, HRCT was used to define whether pneumonitis was present or not. The presence of ground-glass, reticular opacity, or honeycombing changes as revealed in the chest HRCT study defined the presence of pneumonitis. All of the features which might have contributed to false-positive pneumonitis in HRCT, such as infection or congestive heart failure, were excluded after extensive studies. Eleven out of 19 patients (57.9%) did not have pneumonitis, including 2 MCTD patients, 2 AOSD patients, 3 primary SS patients and 4 SLE patients. The remaining 8 patients (42.1%) had mild to moderate pneumonitis, including 4 SSc patients, 2 primary SS patients and 2 SLE patients (Table 2). Correlation between the severity of RVSP and clinical parameters was also analyzed in these 2 groups.

### Statistical analysis

Student's *t* test and Pearson correlation coefficient were used to analyze the data. A difference was considered significant if the *p* value was ≤0.05.

## Results

### Clinical features and laboratory findings

The clinical features and laboratory findings are presented in Table 2. Raynaud's phenomenon was present in 78.9% of patients (15/19). All the patients with MCTD, AOSD or SSc had Raynaud's phenomenon, but only 60% of primary SS patients (3/5) and 66.7% of SLE patients (4/6) had this change. Central nervous system involvement occurred in 3 patients, in which seizure/psychosis was noted in 1 SLE patient and cerebral infarction in 1 primary SS patient and 1 SLE patient. Serum creatinine was within normal limits in all 19 patients. Proteinuria (>0.5 g/day) was found in only 3 patients, including 1 primary SS patient and 2 SLE patients.

Because AOSD is defined by negative ANA and other autoantibodies, it was not included in the immunological profile analysis. High titer of ANA (>1:640) was

| ANA titer | Anti-RNP | RF | Anti-SSA | aCL | Hyper-gammaglobulinemia | Serum complement | Uric acid (mg/dL) |
|---|---|---|---|---|---|---|---|
| 2560 | + | – | + | + | + | – | 5.8 |
| 2560 | + | + | + | ND | + | ↓ | 14.6 |
| – | – | – | – | ND | – | – | 6.4 |
| – | – | – | – | – | + | – | 19 |
| 2560 | + | – | ND | – | – | ↓ | 6.9 |
| 160 | – | – | – | ND | + | ↓ | 10.5 |
| 640 | – | – | + | – | + | ↓ | 7.1 |
| 640 | – | + | + | ND | + | – | 4.7 |
| 160 | ND | – | – | ND | + | – | 4.9 |
| 2560 | + | + | ND | – | + | – | 7.1 |
| 1280 | – | – | – | – | + | – | 6.2 |
| 2560 | + | + | + | – | + | ↓ | 9.2 |
| 640 | – | – | + | – | + | ↓ | 8.5 |
| 2560 | – | – | + | + | + | ↓ | 9.6 |
| 320 | ND | – | ND | + | – | ↓ | 9.5 |
| 2560 | + | ND | ND | + | + | ↓ | 11 |
| 320 | – | – | + | – | – | ↓ | 8.4 |
| 2560 | + | + | – | + | + | ↓ | 7.1 |
| 2560 | + | + | + | ND | + | ↓ | 10.1 |

system; ANA = antinuclear antibody; RNP = ribonucleoprotein; RF = rheumatoid factor; aCL = anticardiolipin; MCTD = mixed connective tissue
+ = positive; – = negative; ND = not determined; ↓ = low

noted in 76.5% of patients (13/17). Anti-RNP antibody was present in 53.3% of patients (8/15), including 100% of MCTD patients (2/2), 25% of SSc patients (1/4), 50% of primary SS patients (2/4) and 60% of SLE patients (3/5). Rheumatoid factor (RF) was present in 37.5% of patients (6/16), including 50% of MCTD patients (1/2), 40% of primary SS patients (2/5) and 40% of SLE patients (2/5). Anti-SSA antibody was shown in 69.2% of patients (9/13), including 100% of MCTD patients (2/2), 66.7% of SSc patients (2/3), 50% of primary SS patients (2/4) and 75% of SLE patients (3/4). Anticardiolipin (aCL) antibody IgG was found in 5 patients, including 1 MCTD patient and 80% of SLE patients (4/5).

In this study, the normal ranges of serum IgG, IgA and IgM were 751-1560, 82-453 and 46-304 mg/dL, respectively. Hypergammaglobulinemia is defined as a level 10% above the upper limit of the normal range of any immunoglobulin on 2 different occasions. Hypergammaglobulinemia was found in 15 patients, including 100% of MCTD patients (2/2), 50% of AOSD patients (1/2), 75% of SSc patients (3/4), 100% of primary SS patients, and 66.7% of SLE patients (4/6). Low serum complement C3 or C4 level was noted in 12 patients, including 50% of MCTD patients (1/2), 75% of SSc patients (3/4), 40% of primary SS patients (2/5), and 100% of SLE patients (6/6).

The characteristic manifestations of the underlying autoimmune diseases observed included a high incidence of Raynaud's phenomenon, high-titer ANA (31:640), positive anti-RNP antibody, hypergammaglobulinemia, hyperuricemia, and less renal involvement.

## Correlation between RVSP, pneumonitis, and laboratory profiles

The RVSP in these 19 patients was 67.9 ± 24.3 mm Hg (range, 35 to 105). RVSP in PAH patients without pneumonitis was significantly higher than in those with pneumonitis (77.5 ± 24.3 vs 54.8 ± 18.4 mm Hg, $p$=0.041). RVSP inversely correlated with DLCO among PAH patients without pneumonitis (r = -0.856, $p$=0.003), but not in the total group of patients (r = –0.337, $p$=0.202) or in those with pneumonits (r = 0.141, $p$=0.763) [Table 3]. The mean serum UA level for these 19 patients was 8.8 ± 3.5 mg/dL (range, 4.7 to 19). In addition, RVSP significantly correlated with the serum UA level (r = 0.686, $p$=0.001) [Table 3].

## Outcome

Up to March 2005, 5 patients (26.3%) had died, as shown in Table 4. The mortality rate was 57.1% for those with RVSP ≥80 mm Hg and 8.3% for those with RVSP <80 mm Hg. One patient (RVSP = 43 mm Hg)

**Table 3**. Correlation between right ventricular systolic pressure (RVSP) values and clinical parameters in 19 patients with pulmonary arterial hypertension (PAH)

| | No. | DLCO | | Serum UA level | |
|---|---|---|---|---|---|
| | | r | *p* | r | *p* |
| RVSP in total patients | 19 | –0.337 | 0.202 | 0.686 | 0.001 |
| RVSP in PAH with pneumonitis | 8 | 0.141 | 0.763 | 0.715 | 0.046 |
| RVSP in PAH without penumonitis | 11 | –0.856 | 0.033 | 0.651 | 0.030 |

Abbreviations: r = Pearson correlation coefficient; DLCO = diffusion capacity of the lung for carbon monoxide; UA = uric acid

died of pneumonia. The other patients experienced sudden death, most likely related to PAH.

## Discussion

PAH has a highly fatality rate in patients with underlying autoimmune diseases — 26.3% of our patients have died. This study has shown that various kinds of collagen vascular diseases, including SLE, primary SS, SSc, MCTD and AOSD could be complicated with PAH. The great majority of our patients were female, which is consistent with the observations of other authors.

PAH may result from pulmonary interstitial fibrosis or proliferative vascular lesions. However, previous studies have shown that pulmonary vasculopathy had a closer association with PAH than fibrosis abnormality [2,5]. Our data revealed that PAH patients without pneumonitis had significantly higher RVSP than those with pneumonitis. Also, higher RVSP may result in higher mortality. Pulmonary proliferative vasculopathy was likely to be the major cause of PAH, and the characteristic features of vasculopathy included medial hypertrophy, endothelial cell dysfunction/proliferation, and the formation of plexiform lesions [1,6]. These changes can result in progressive pulmonary artery obliteration and an elevation of pulmonary arterial pressure [16]. We thought that a pathological process confined primarily to the pulmonary vessels (i.e., the patients without pneumonitis) could result in more severe PAH.

Reduction of DLCO was found in the majority of our patients. Although DLCO did not correlate inversely with RVSP among the total group of patients, it did correlate inversely with RVSP in those without pneumonitis. This suggested that pulmonary vasculopathy could be reflected in the reduction of DLCO. Steen and Medsger reported that a decreasing DLCO is a good predictor of the subsequent development of PAH in SSc [17].

Hyperuricemia (>7 mg/dL) was found in 68.4% of our patients; in addition, a significant correlation between the serum UA level and RVSP was observed. Some reports have shown a positive correlation between pulmonary arterial pressure and the serum UA level [18, 19]. Bendayan et al also found that the serum UA level is increased in severe PAH [20]. Serum UA increased in proportion to hypoxic status, such as in those with congestive heart failure or obstructive lung disease [21-23]. PAH may result in right-side heart failure, subsequently causing low cardiac output and tissue hypoperfusion, and finally leading to an overproduction of UA. Moreover, heart failure itself can cause renal hypoperfusion, resulting in increased reabsorption and decreased excretion of UA in the renal tubules [24]. Both overproduction and underexcretion may have contributed to the hyperuricemia in patients with PAH, although further studies are needed to elucidate the true mechanisms.

Raynaud's phenomenon has been reported to be strongly associated with the occurrence of PAH [25] and was present in 78.9% of our patients. Serum creatinine levels were all within normal limits in our patients and proteinuria was noted in only 3 patients. This suggested that severe renal involvement, such as diffuse proliferative glomerulonephritis, may be rare in SLE patients with PAH. When PAH patients do

**Table 4**. Correlation between outcome and right ventricular systolic pressure (RVSP) value in 19 patients with pulmonary arterial hypertension

| Group | Mortality rate (n [%]) | Pneumonitis (n) | Death (n) |
|---|---|---|---|
| RVSP <80 mm Hg (n = 12) | 1/12 (8.3%) | With (7) | 1 |
| | | Without (5) | 0 |
| RVSP ≥80 mm Hg (n = 7) | 4/7 (57.1%) | With (1) | 1 |
| | | Without (6) | 3 |

develop renal damage, it may be mild and take the form of a membranous glomerulopathy with nephrotic features, the type of renal change frequently encountered in MCTD patients [26,27].

Sacks et al showed that SSc patients with anti-U3RNP antibody may develop more severe PAH [28]. By definition, anti-U1RNP antibody comprises a substantial portion of the immune response in MCTD [29]. Anti-RNP antibody was positive in half of our patients, and may be involved in the pathogenesis of PAH. Also, a high positive rate of anti-SSA antibody was noted in our patients with autoimmune diseases. However, reports of anti-SSA antibody as a predisposing factor for pulmonary vasculopathy are limited and deserve further investigation. Five of our patients were positive for aCL, including 1 non-SLE patient and 4 SLE patients. The presence of aCL and thrombin formation may be one of the factors that precipitate PAH [30], especially in those patients with SLE.

High-titer ANA and hypergammaglobulinemia were observed in this study. Immunofluorescent studies in PAH patients have shown immunoglobulin and complement deposits in the pulmonary arterial walls [4,6,31]. In the report of Quismorio et al, immunoglobulin eluted from the lung of SLE patients with PAH contained RF and anti-DNA antibody [4]. These results suggested that B cell activation and immune complex deposition may also contribute to the pathogenesis of PAH.

In conclusion, PAH can be a severe complication attracting a high excess mortality in autoimmune diseases. The characteristic clinical features and laboratory findings of the underlying autoimmune diseases include Raynaud's phenomenon, less renal involvement, high-titer ANA, positive anti-RNP antibody and hypergammaglobulinemia. As compared to PAH patients with pneumonitis, PAH patients without pneumonitis tend to have higher pulmonary arterial pressure and a higher mortality rate. On the other hand, reduction of $D_{LCO}$ and elevation of the serum UA level can be an indicator of the severity of PAH.

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