

## CLINICAL CASE

# Pulmonary arterial hypertension, a novelty in idiopathic inflammatory myopathies: insights and first experiences with vasoactive therapy

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**ABSTRACT**

To characterise the different types of pulmonary hypertension (PH) among idiopathic inflammatory myopathy (IIM). A retrospective case series with assessment of PH by right heart catheterisation, extent of interstitial lung disease (ILD) and outcome of vasoactive therapy. The group of patients with IIM with PH (n=9) showed a median age at PH diagnosis of 62 years (IQR 48–71 years; eight women), seven diagnosed with polymyositis and two with dermatomyositis; median disease duration of 5.7 years and five patients with a positive anti-Jo1 antibody. We found one patient to be classified in PH WHO group 2 (left heart disease), five patients in WHO group 3 (lung disease) and three patients in WHO group 1 (pulmonary arterial hypertension (PAH)). During median observed follow-up of 24 months, mortality for the total group was 44%. Surprisingly, we found a relevant group (33%) of patients with IIM who suffered from non-ILD-PH, which reflects the presence of PAH phenotype. This result should lead to more awareness among treating physicians that complaints of dyspnoea among patient with IIM could be related to PAH and not only ILD. The role of vasoactive therapy remains to be defined in patients with IIM suffering from PAH or PH-ILD.

**INTRODUCTION**

Pulmonary hypertension (PH) is a life-threatening condition presenting with symptoms like breathlessness, fatigue and syncope.<sup>1</sup> PH can occur as a complication of systemic autoimmune diseases.<sup>2–4</sup> The association with polymyositis (PM) and dermatomyositis (DM), together classified as idiopathic inflammatory myopathy (IIM), is not well known.<sup>5</sup> So far, only a few cases reported on PH in patients with IIM.<sup>6–11</sup> However, two recent cohort studies among antisynthetase patients revealed a prevalence of PH ranging from 7.9% to 14.8% with a worsened prognosis.<sup>12 13</sup> These study results reflect the clinical relevance of PH as a complication of IIM.

**Key messages****What is already known about this subject?**

► Pulmonary hypertension (PH) is a life-threatening condition and is associated with patients with idiopathic inflammatory myopathy (IIM). Although interstitial lung disease (ILD) is frequently found among patients with IIM patients, the question is whether this lung disease explains the presence of PH in all patients with IIM.

**What does this study add?**

► Surprisingly, we found a relevant group (33%) of patients with IIM who suffered from non-ILD-PH, which reflects the presence of pulmonary arterial hypertension (PAH) phenotype. The role of vasoactive therapy remains to be defined in patients with IIM suffering from PAH or PH-ILD.

**How might this impact on clinical practice?**

► This result should lead to more awareness among treating physicians that complaints of dyspnoea among patients with IIM could be related to PAH and not only ILD.

Patients with PH can be classified according to the WHO classification in pulmonary arterial hypertension (PAH) (group 1), PH associated to left heart disease (group 2), PH associated to lung disease (group 3), chronic thromboembolic PH (group 4) and PH with unclear mechanism (group 5).<sup>14</sup> The cause of PH in patients with IIM is however still unclear. Although interstitial lung disease (ILD) is frequently found among patients with IIM, occurring in up to 65% of the patients,<sup>15</sup> the question is whether this lung disease explains the presence of PH in all patients with IIM. In addition, data on long-term follow-up are scarce.

For this, we describe the clinical characteristics and follow-up of nine patients with IIM



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with PH and investigated the cause and effect of PH in these patients.

## METHODS

This is a retrospective case series which consisted of patients with IIM (n=9) with PH of two Dutch university hospitals (Radboud University Medical Center, Nijmegen) (n=4) and (VU University Medical Center, Amsterdam) (n=5) which are both expert centres for PH. According to Dutch law and regulations, the study was exempted from approval of a medical ethical committee and no informed consent was required since this was an observational, non-interventional study.

### Participants

All patients with IIM fulfilled at least the criteria for probable IIM according to the European Neuromuscular Centre (ENMC) classification criteria.<sup>16</sup> PH was defined as an increase in mean pulmonary arterial pressure (mPAP)  $\geq 25$  mm Hg assessed with right heart catheterisation (RHC).<sup>14</sup> All known patients with IIM and PH were included at both medical centres (VU University Medical Center, a registry of patients with PH; Radboud University Medical Center, Myositis Nijmegen cohort).

### Interstitial lung disease

Presence of extensive ILD was defined as signs of pulmonary fibrosis on high-resolution computed tomography (HRCT) scan with  $>10\%$  lung involvement. Limited ILD was defined as extent of lung parenchymal involvement  $\leq 10\%$  on HRCT which is a conservative cut-off in comparison with staging system of Goh *et al* ( $\leq 20\%$ ).<sup>17</sup> In remaining cases with an indeterminate extent on HRCT, an abnormal pulmonary function test (total lung capacity (TLC)  $<70\%$  predicted) was used to classify extensive ILD. A blinded pulmonologist (AV-N) retrospectively reviewed all available HRCT scans using the Wells method to score the presence and extent of ILD.<sup>18</sup>

### Haemodynamics RHC

Based on pulmonary capillary wedge pressure (PCWP), PH can be divided into precapillary PH (PCWP  $\leq 15$  mm Hg) and postcapillary PH (PCWP  $>15$  mm Hg), which can be related to different clinical causes.<sup>14</sup> Patients with precapillary PH and limited ILD were defined as non-ILD-PH (reflecting PAH), whereas patients with precapillary PH and extensive ILD as ILD-PH. Other parameters which were assessed by RHC were PCWP, cardiac output and pulmonary vascular resistance (PVR). Outcome of vasoactive therapy in patients with PH-IIM was evaluated by available information on mortality, hospital admissions, therapy adjustments and alterations of 6 min walking test (6MWT) or WHO functional class (WHO-FC).<sup>19</sup> The WHO-FC system grades severity of limitations due to PH on a scale of 1 (no limitations) to 4 (limitation of all exercise).

## CASE REPORT

### Patients

Our cohort consists of nine patients, of which seven patients were diagnosed with polymyositis and two with dermatomyositis. The median age at diagnosis of PH was 62 years (IQR 48–68 years; eight women). The median disease duration of IIM at diagnosis of PH was 5.7 years (IQR 3–10.3 years). In five patients, anti-Jo1 autoantibody was present (table 1).

### Interstitial lung disease

Signs of pulmonary fibrosis on HRCT scans were present in seven patients (88%), with scans performed in eight out of nine patients. All seven patients had a precapillary PH. A Wells score of 3, presenting dominance of a reticular pattern (ie, fibrosis) was present in three (38%) patients. The median lung involvement was 50% of the surface (range 0%–90%) with four patients  $\geq 70\%$  lung involvement on the scans. Three patients (37%) displayed none or limited lung involvement (surface  $\leq 10\%$ ) (table 1, patients 3, 5 and 9).

### PH characterisation

Eight patients presented with precapillary PH. Chronic thromboembolic PH and multifactorial PH causes were excluded. One patient was diagnosed with postcapillary PH caused by severe aorta valve stenosis, PH WHO group 2 (table 1).

Combining information on ILD with RHC data demonstrates that five out of eight precapillary patients with PH had a fair to severe lung fibrosis, while the other three patients had none to limited lung fibrosis. Those three patients were diagnosed with PAH associated to IIM, WHO group 1 (patients 3, 5 and 9). In these patients, pulmonary fibrosis was either absent or present in  $<10\%$  of the pulmonary surface (table 1). The remaining five patients with fair to severe pulmonary fibrosis were classified as PH caused by ILD (PH-ILD), WHO group 3.<sup>14</sup>

### Outcome

The total group of patients with IIM and PH revealed a mortality of four patients (44%) during a median observed follow-up of 16 months. Within 5 months of diagnosis of PH, two patients died (patients 4 and 5), one due to heart failure complicated by severe aorta valve stenosis. The other patients died as a result of respiratory failure complicated with pneumonia before vasoactive therapy could be started.

Vasoactive therapy was initiated in seven patients with precapillary PH (table 2). Therapy included the use of prostanoids, endothelin receptors antagonists and phosphodiesterase type-5 inhibitors. Follow-up information was unavailable in one patient due to transfer to another hospital (patient 8). After the start of therapy, two patients revealed an increase of walking distance (18% and 9%) during 6 min walking test after 2 and 12 months (patients 2 and 3). However, after initial improvement, one patient died 3 years later due to heart

**Table 1** Clinical and haemodynamic characteristics of each patient at PH diagnosis

| Characteristics                       | Patient   |           |           |                |           |           |           |           |           |
|---------------------------------------|-----------|-----------|-----------|----------------|-----------|-----------|-----------|-----------|-----------|
|                                       | Patient 1 | Patient 2 | Patient 3 | Patient 4      | Patient 5 | Patient 6 | Patient 7 | Patient 8 | Patient 9 |
| Clinical characteristics              | PM        | PM        | PM        | PM overlap SLE | DM        | DM        | PM        | PM        | PM        |
| ANA                                   | +         | +         | +         | +              | +         | -         | +         | +         | -         |
| Anti-Jo1                              | +         | +         | -         | -              | NA        | +         | +         | -         | +         |
| Raynaud's phenomenon                  | +         | +         | -         | -              | -         | +         | +         | +         | -         |
| Arthritis (history)                   | +         | +         | +         | -              | +         | +         | +         | +         | -         |
| Disease duration (years)              | 20.4      | 8.8       | 5.1       | 1.2            | 5.8       | 0.6       | 10        | 5.4       | 10.7      |
| WHO functional class                  | 2         | 3         | 2         | 4              | 4         | 3         | 2         | 3         | 3         |
| WHO PH group                          | 3         | 3         | 1         | 2              | 1         | 3         | 3         | 3         | 1         |
| HRCT scan                             |           |           |           |                |           |           |           |           |           |
| Lung fibrosis on HRCT                 | +         | +         | +         | NA             | -         | +         | +         | +         | +         |
| Wells score                           | 2         | 3         | 2         | NA             | 0         | 2         | 3         | 1         | 3         |
| Lung involvement (%)                  | 70        | 70        | 10        | NA             | 0         | 90        | 30        | 90        | 10        |
| Extent of ILD                         | Extensive | Extensive | Limited   | Extensive      | Limited   | Extensive | Extensive | Extensive | Limited   |
| Pulmonary function test               |           |           |           |                |           |           |           |           |           |
| TLC (% of predicted)                  | 66        | 80        | 64        | 57             | 51        | 87        | 65        | 50        | 105       |
| DLCO (% of predicted)                 | 66        | 53        | 68        | NA             | 39        | 67        | 69        | 62        | 42        |
| 6 Min walking test (m)                | NA        | 143       | 420       | NA             | NA        | NA        | 308       | 235       | 307       |
| RHC                                   |           |           |           |                |           |           |           |           |           |
| Mean PAP (mm Hg)                      | 45        | 40        | 66        | 41             | 60        | 32        | 25        | 33        | 52        |
| PCWP (mm Hg)                          | 12        | 5         | 7         | 35             | 1         | 14        | 11        | 14        | 14        |
| Cardiac index (L/min/m <sup>2</sup> ) | NA        | NA        | 2.3       | 1.4            | 2.2       | 2.6       | 2.5       | NA        | 2.1       |
| Cardiac output (L/min)                | NA        | 3.8       | 5.1       | 3.1            | 2.7       | 4.6       | 4.6       | 3.3       | 3.3       |
| PVR (dynes/s/cm <sup>5</sup> )        | NA        | 743       | 928       | 155            | 1749      | 315       | 242       | 461       | 109       |

ANA, antinuclear antibody; DLCO, diffusing capacity for carbon monoxide; DM, dermatomyositis; ILD, interstitial lung disease; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PM, polymyositis; PVR, pulmonary vascular resistance; RHC, right heart catheterisation; SLE, systemic lupus erythematosus; TLC, total lung capacity; NA, not available.

failure (patient 3). Stabilisation of walking distance after 6 months was observed in one patient. After 2 years, the patient died due to respiratory failure (patient 7). In one patient, pulmonary haemodynamics returned to normal after 1 year of therapy with bosentan (patient 6). The remaining two patients on PH therapy suffered from a slow progression on the WHO-FC (patients 1 and 9).

## DISCUSSION

In this clinical case series, we describe a group of nine patients with PH-IIM followed at two referral centres for

PH. We found one patient to be classified as PH, WHO group 2 (left heart disease), five patients in WHO group 3 (lung disease) and three patients in WHO group 1 (PAH). Our study confirms previous results, indicating that the majority of the PH in IIM can be classified as PH-ILD, WHO group 3.<sup>6-12</sup> However, PAH associated to IIM is a possibility, in this group occurring in 33% of the patients.

The pathogenesis of PAH in IIM is unknown; however, involvement of pulmonary vessels by diffuse infiltrative and inflammatory processes is likely to contribute.<sup>5</sup> An

**Table 2** Follow-up of vasoactive therapy effect

| Patient | Therapy at diagnosis | WHO-FC at PH diagnosis | Therapy adjustments                     | Observed follow-up (months) | Description outcome  | WHO-FC at end follow-up | Final outcome                                    |
|---------|----------------------|------------------------|---|-----------------------------|--|-------------------------|--|
| 1       | S                    | 2                      | S↑: 18 months<br>S↑: 36 months          | 36                          | Slow progression to WHO-FC 3   | 3                       | Alive  |
| 2       | S                    | 3                      | S + I: 12 months                        | 16                          | Remains at WHO-FC 3 after iloprost therapy   | 3                       | Alive  |
| 3       | B                    | 2                      | B + S: 7 months<br>B + S + T: 24 months | 36                          | Slow progression to WHO-FC 3<br>6-MWT at diagnosis 420 m, at 8 months 459 m, at 28 months 390m | 4                       | Death due to heart failure after 36 months       |
| 6       | B                    | 3                      | B↑: 48 months                           | 48                          | With bosentan no PH after 12 months, after 48 months progressive dyspnoea                      | NA                      | Alive  |
| 7       | S                    | 2                      | Stop S: 8 months                        | 24                          | Exacerbation of PM after 8 months, ↑ prednisone and start tacrolimus                           | 4                       | Death due to respiratory failure after 24 months |
| 8       | S                    | 3                      | NA                                      | 0                           | Unknown due to transfer to other hospital  | NA                      | NA   |
| 9       | A                    | 3                      | Diuretics: 2 months                     | 12                          | Short hospitalisation after 2 months due to heart failure, after 12 months stable in WHO-FC 3  | 3                       | Alive  |

A, ambrisentan; B, bosentan; I, iloprost inhalation; S, sildenafil; T, treprostinil; ↑, increase of dose; WHO-FC, WHO functional class; 6-MWT, 6 min walking test; PM, polymyositis; NA, not available.

autopsy study among patients with PM found suggestive changes for PAH by encroachment of the pulmonary blood vessel lumen with medial smooth muscle hyperplasia.<sup>20</sup> More recently, a Swedish study demonstrated that sera of anti-Jo1-positive patients with PM could activate endothelial cells in healthy lung tissue.<sup>21</sup> Altogether, these findings reinforce the hypothesis of specific pulmonary vascular involvement in the aetiology of PH among patients with IIM and the role of anti-tRNA synthetase autoantibodies such as anti-Jo1.<sup>5 12 20 21</sup>

Interestingly, two out of the three patients with PAH revealed the lowest diffusing capacity for carbon monoxide (DLCO) values in our study. This observation tends to suggest, conversely to PAH among patients with systemic sclerosis, that patients with IIM with PAH are associated with low DLCO values in pulmonary function test.<sup>22 23</sup>

Although small retrospective studies suggested that specific PAH therapy may be used in the presence of severe PH due to chronic lung disease, the benefit of this therapy still has to be demonstrated. In our cohort, initiation of PAH treatment was performed on the discretion

of the treating doctor, including six patients with ILD and one patient without ILD. Although our observations suggest that some of our patients seem to benefit from such an approach, the uncontrolled nature of this observational study does not allow to draw any conclusions on the effectiveness of such an approach in PAH.

A recent French observational study showed a 3-year survival of 58% in patients with PH antisynthetase.<sup>12</sup> The overall mortality in our study was 44% which suggests that the presence of PH was associated with a worse survival.

The strength of our study is the novelty of reporting cases of PAH among patients with IIM with complete RHC data.

A limitation of our study is that all patients were recruited from two tertiary referral PH expert centres, which could have led to a selection bias. However, to study an uncommon complication (PH) in a rare disease (IIM) inevitably leads to multicentre recruitment at tertiary centres. Furthermore, limited serology data were available by which proper classification of the presence of antisynthetase syndrome and further determination of antinuclear antibody positivity was not possible.

In conclusion, in this study, we found the presence of ILD-PH in the majority (55%) of the selected patients with IIM and PH. Surprisingly, a relevant group (33%) of patients with IIM suffered from non-ILD-PH, which reflects the presence of PAH phenotype on which connective tissue disease itself plays a role in the aetiology. Vasoactive therapy could play a role in the treatment of patients with IIM and PAH phenotype. Altogether, this result should lead to more awareness among treating physicians that complaints of dyspnoea among patients with IIM could be related to PAH and not only ILD. Given the rarity of PH-IIM, a joined international effort is required to obtain more insights in the different PH phenotypes and the optimal treatment strategy of this disease.

**Competing interests** None declared.

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