

Pulse dose steroids in severe pulmonary arterial hypertension secondary to systemic lupus erythematosus

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Abstract

Objective: The pulmonary vascular targeted treatment for systemic lupus erythematosus-associated pulmonary arterial hypertension is similar to other connective tissue disease-associated pulmonary arterial hypertension. In addition, there also appears to be a role for immunosuppression in the overall management. However, the optimal immunosuppressive regimen and what patients will respond to treatments are currently not clearly elucidated given the lack of randomized controlled trials on the subject. Our objective is to highlight the importance of early immunosuppression in systemic lupus erythematosus-associated pulmonary arterial hypertension and the role of pulse dose steroids in management.

Methods: This case describes a 23-year-old woman who presented with pulmonary arterial hypertension diagnosed by right heart catheterization with mean pulmonary artery pressure of 74 mmHg, pulmonary capillary wedge pressure of 12 mmHg, and a pulmonary vascular resistance of 1908 dyne s cm⁻⁵. Due to the aggressive nature of her disease, she declined despite management with epoprostenol and sildenafil. Because of coexisting systemic lupus erythematosus with hemolytic anemia and worsening pulmonary arterial hypertension, intensive immunosuppressive therapy with pulse dose steroids was initiated.

Results: Shortly after initiation of pulse dose steroids and maintenance immunosuppression, she had a dramatic symptomatic and hemodynamic response with a decrease in her pulmonary vascular resistance from 1908 to 136 dyne sec cm⁻⁵ and improvement in her mean pulmonary artery pressure from 74 to 27 mmHg on repeat right heart catheterization.

Conclusion: Early immunosuppression is important to consider in those with systemic lupus erythematosus-associated pulmonary arterial hypertension. Limited studies are available, but most have focused on the use of cyclophosphamide. Pulse dose steroids may be a potentially less toxic but equally effective manner to aid in the treatment of systemic lupus erythematosus–pulmonary arterial hypertension when intensive immunosuppression is being considered.

Keywords

Rheumatology/clinical immunology, respiratory medicine, cardiovascular, connective tissue disease, lupus

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Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disorder that can affect multiple organ systems. In particular, pulmonary arterial hypertension (PAH) is a rare complication of SLE that historically affects 0.5%–17.5% of the SLE population.¹ Treatments for SLE-associated PAH (SLE-PAH) are similar to those of other idiopathic and connective tissue disease (CTD)-associated PAH (CTD-PAH). However, there are also important differences in these groups. Specifically, there appears to be a role for immunosuppression. This has been seen in prior case reports and series showing immunosuppressive therapy both with and without typical PAH therapy can significantly improve

pulmonary hemodynamics in these patients. While other CTDs such as mixed connective tissue disease (MCTD) can respond to immunosuppression as well, both SLE and

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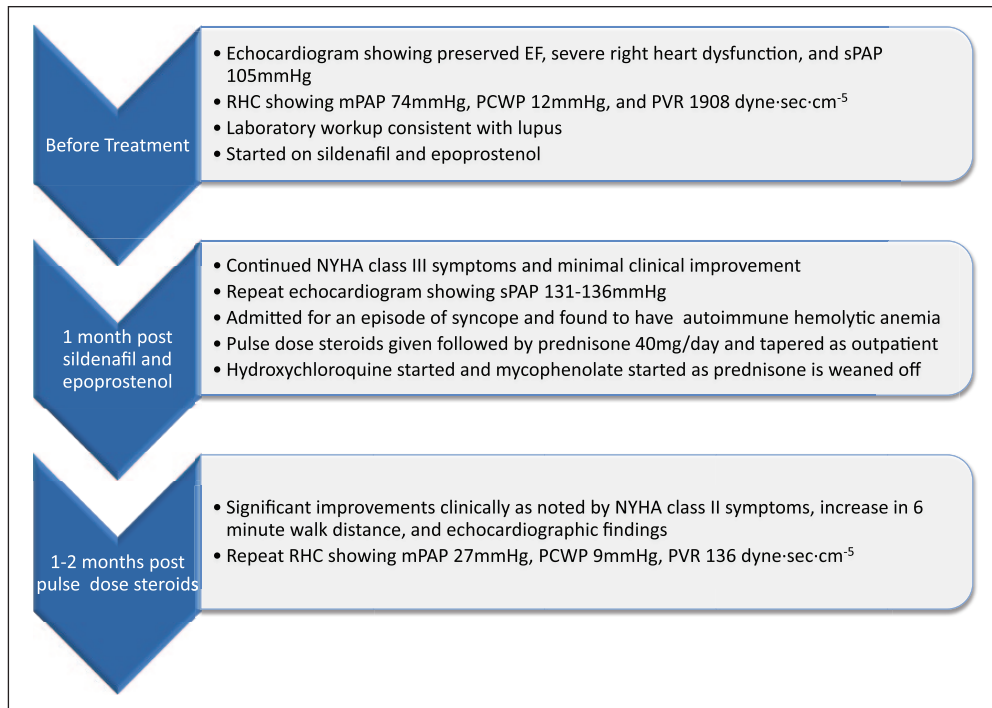
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Table 1. Echocardiographic data.

	Before immunosuppression	1 month after sildenafil and epoprostenol	1 month after pulse dose steroids and immunosuppression
Ejection fraction	75%	65%–70%	60%–65%
RV enlargement	Severe	Severe	None
RV systolic dysfunction	Severely reduced	Severely reduced	None
SPAP (mmHg)	105	131–136	55

RV: right ventricle; SPAP: systolic pulmonary artery pressure.

**Figure 1.** Timeline of events.

EF: ejection fraction; SPAP: systolic pulmonary artery pressure; RHC: right heart catheterization; mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; NYHA: New York Heart Association.

MCTD patients are in sharp contrast to those with systemic sclerosis where immunosuppression has no role. We describe a unique case of PAH as the sole presenting symptom of SLE where therapy with sildenafil and epoprostenol had failed with worsening echocardiographic findings and clinical symptoms. Improvement was noted only after intensive immunosuppressive therapy was started with pulse dose steroids.

Case report

A 23-year-old African American woman with a history of hypertension, childhood asthma, and recent small pulmonary embolism treated with warfarin presented to PAH clinic for 1 month of progressive dry cough and dyspnea on exertion. Prior workup was notable for an echocardiogram transthoracic echocardiogram (TTE) showing an ejection fraction of 75%, severely dilated right ventricle (RV),

severely reduced RV function, and estimated systolic pulmonary artery pressures of 105 mmHg (Table 1). In addition, a computed tomography (CT) of the chest was done showing no evidence of interstitial lung disease, and pulmonary function tests revealed an forced vital capacity (FVC) of 3.12 (96% predicted), forced expiratory volume in one second (FEV1)/FVC ratio of 84%, diffusing capacity of carbon monoxide (DLCO) of 19.79 (77% predicted), and an FVC/DLCO ratio of 1.09. During the visit, she endorsed New York Heart Association (NYHA) class III symptoms and the decision was made to admit her for expedited workup of her PAH and initiation of targeted PAH therapy (Figure 1).

On admission, testing was notable for a repeat TTE showing an ejection fraction of 60%–65%, severely dilated RV, severely reduced RV function, and estimated systolic pulmonary artery pressures of 117 mmHg. An extensive laboratory workup was completed, but notable positive findings included

Table 2. Right heart catheterization and 6-min walk data.

	Before immunosuppressive therapy	2 months after immunosuppressive therapy
RAP (mmHg)	12	2
PAP (mmHg)	110/54	41/15
mPAP (mmHg)	74	27
PCWP (mmHg)	12	9
Cardiac output (L min ⁻¹)	2.6	8.8
PVR (dyne s cm ⁻⁵)	1908	136
6-min walk distance (m)	280.42	388.62

RAP: right atrial pressure; PAP: pulmonary artery pressure; mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance.

Table 3. Laboratory data.

Labs	Value	Normal range
ESR	33	0–29 mm h ⁻¹
Creatine kinase	161	30–223 U L ⁻¹
ANA and pattern	1:160 homogeneous	1:40
Double-stranded DNA	40	0–9 IU mL ⁻¹
C3 complement	72	87–200 mg dL ⁻¹
C4 complement	<8	19–52 mg dL ⁻¹
SCL-70 antibody	Negative	Negative
SM antibody	Negative	Negative
SM/RNP antibody	Positive	Negative
SSA/SSB	Negative	Negative
Anti Jo-1	Negative	Negative
Rheumatoid factor	<5	<10 IU mL ⁻¹
HIV	Non-reactive	Non-reactive
Anticardiolipin IgA	Negative	Negative
Anticardiolipin IgG	Negative	Negative
Anticardiolipin IgM	Negative	Negative
Lupus anticoagulant	Negative	Negative
Beta-2 glycoprotein I IgG	<9	0–20 GPI IgG units
Beta-2 glycoprotein I IgM	<9	0–32 GPI IgM units
Beta-2 glycoprotein I IgA	<9	0–25 GPI IgA units
NT-proBNP before methylprednisolone	3826	<450 pg mL ⁻¹ (age < 50)
NT-proBNP after methylprednisolone	110	<450 pg mL ⁻¹ (age < 50)
Hemoglobin (baseline before hemolytic anemia)	12.3	11.7–15.5 g dL ⁻¹
Hemoglobin (admission with hemolytic anemia)	7.7	11.7–15.5 g dL ⁻¹
Hemoglobin (on discharge after hemolytic anemia)	10.6	11.7–15.5 g dL ⁻¹

an antinuclear antibody (ANA) (1:160 and homogeneous pattern), elevated double-stranded DNA, elevated N-terminal Pro-Brain Natriuretic Peptide (NT-proBNP), and low complement levels (Table 3). Notable negative studies include a urine drug screen, antiphospholipid antibodies, and HIV. Her right heart catheterization (RHC) showed a right atrial pressure of 12 mmHg, pulmonary artery pressure of 110/54 mmHg (mean 74 mmHg), pulmonary capillary wedge pressure of 12 mmHg, cardiac output of 2.6 L min⁻¹, and a pulmonary vascular resistance (PVR) of 1908 dyne s cm⁻⁵ (Table 2). A ventilation-perfusion (VQ) scan was done showing no signs of chronic thromboembolic disease and was without persistent perfusion defects. Based on this, she was diagnosed

with World Health Organization group 1 PAH secondary to SLE. For PAH, she was started on sildenafil 20 mg three times daily and epoprostenol for which she was increased to 7 ng kg⁻¹ min⁻¹ by discharge with continued up titration as an outpatient with her final dose being 20 ng kg⁻¹ min⁻¹. As for her SLE, no immunosuppression was started per the rheumatology team consulted given no other systemic involvement beyond PAH and concerns with starting hydroxychloroquine given her low G6PD.

One month after starting sildenafil and epoprostenol, she had minimal improvement with continued NYHA class III symptoms. A repeat TTE showed worsening pulmonary artery pressures and right heart failure (Table 1). Two weeks

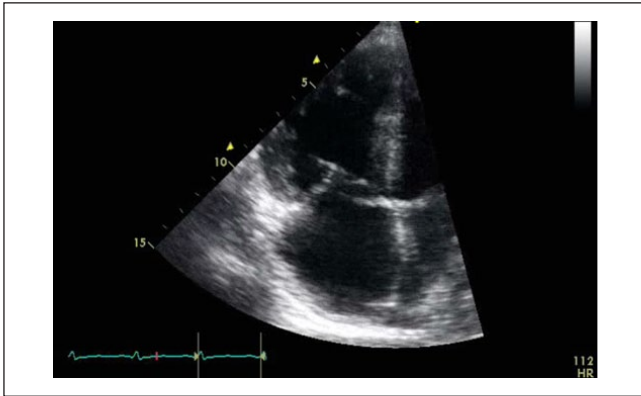


Figure 2. Echocardiogram with four-chamber view before PAH therapy.

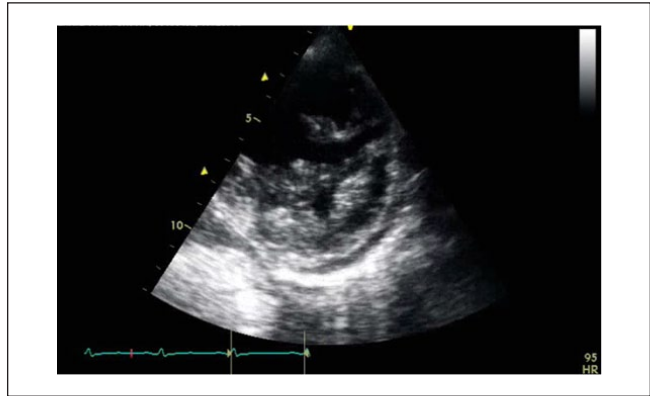


Figure 4. Echocardiogram showing systolic interventricular flattening of the ventricular septum before PAH therapy.

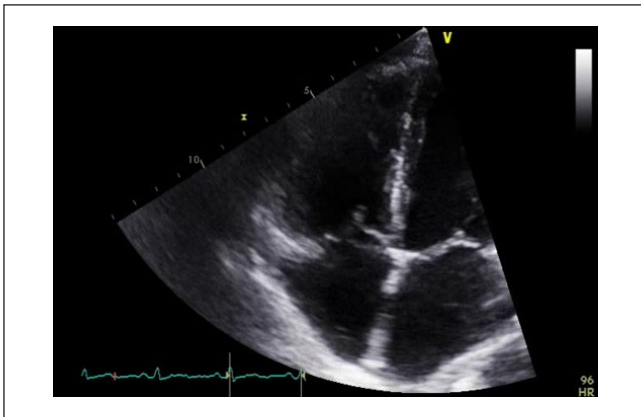


Figure 3. Echocardiogram with four-chamber view after pulse dose steroids.

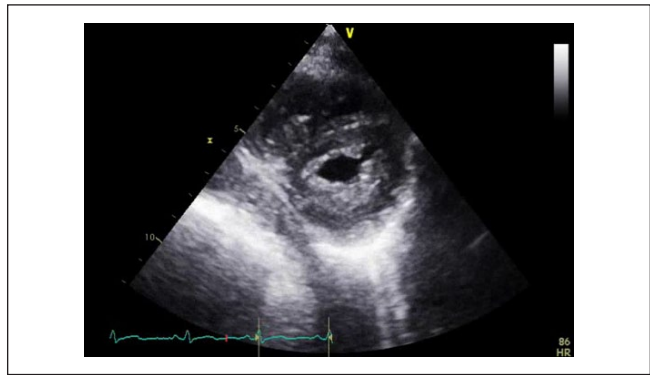


Figure 5. Echocardiogram showing improvement in systolic interventricular flattening of the ventricular septum after pulse dose steroids.

later, her symptoms had progressed to NYHA class IV with an episode of syncope. Beyond syncope, she began to have signs of an active SLE flare with an episode of autoimmune hemolytic anemia (Table 3). The decision was then made to start hydroxychloroquine 200 mg twice a day and pulse dose steroids with 1 g intravenous methylprednisolone daily for 3 days, followed by oral prednisone 1 mg kg⁻¹ daily with a slow taper as an outpatient. For her PAH, she was continued on epoprostenol at 20 ng kg⁻¹ min⁻¹ and sildenafil. Her hemolytic anemia quickly resolved and 1 month after starting pulse dose steroids and maintenance immunomodulation, she had dramatic improvement in her clinical symptoms as well as TTE findings (Figures 2–5). Symptomatically, she improved to NYHA functional class II and had significant improvements in her 6-min walk distance as well as NT-BNP (Tables 2 and 3). At that point, she was also started on mycophenolate 500 mg twice daily. Two months after pulse dose steroids, a repeat RHC was completed showing a right atrial pressure of 2 mmHg, pulmonary artery pressures of 41/15 mmHg (mean, 27 mmHg), pulmonary capillary wedge pressure of 9 mmHg, cardiac output of 8.8 L min⁻¹, and a PVR of 136 dyne s cm⁻⁵ (Table 2). This response was maintained for the 1 year we

followed the patient and no further intensive immunosuppression such as cyclophosphamide or further pulse dose steroids were required. She was weaned off prednisone and her final immunosuppressive regimen consisted of mycophenolate and hydroxychloroquine.

Discussion

The patient presented for discussion shows a severe case of SLE-PAH with PAH as the primary initial manifestation of her SLE. This case highlights the effect of pulse dose steroids and the role immunosuppression can play in the management of SLE-PAH. The prevalence of SLE-PAH historically is approximately 0.5%–1.5%, with newer studies having it in the range of 2%–8%.^{2–5} Treatment for SLE-PAH is similar to that of other CTD-PAH and involves phosphodiesterase inhibitors, prostanoids, and endothelin receptor antagonists. Each of these agents has been shown to be effective in clinical trials; however, there is a paucity of data that focuses primarily on SLE-PAH. Given that nearly 75% of CTD-PAH is due to systemic sclerosis, SLE patients are grouped together under the category of CTD-PAH in major trials often making

it difficult to extrapolate results. While there is certainly overlap between the pathophysiology of SLE-PAH and other CTD-PAH, important distinctions remain.

One such distinction is the role of immunosuppression. Immunosuppressive therapy has been shown in prior studies to improve SLE-PAH.^{6–10} One potential explanation for this lies in prior research which has shown that in SLE patients, there is deposition of complement and IgG in the pulmonary artery walls as well as elevated pro-inflammatory cytokines and overexpression of growth factors.¹¹ This suggests that an immune complex deposition is involved in some patients. However, not all PAH in SLE improves with immunomodulation and the majority of prior case reports and series have only reported the effects of therapies such as cyclophosphamide followed by maintenance immunosuppression, leaving limited information on the utility of pulse dose steroids. Given the varied response to immune-mediated therapies, it is possible there may be multiple different subsets of disease each with a distinct underlying process. A recent article by Johnson et al. proposed that those with SLE-PAH were classified into three distinct subsets. One such subset was felt to be an immune-mediated process leading to a pulmonary vasculitis which could potentially respond to immunosuppression. This would correlate well with our patient as well as others who have responded to immunotherapy.^{12,13} Another study by Jais et al.⁶ used monthly pulses of cyclophosphamide 600 mg m⁻² for 6 months as well as oral prednisone 0.5–1 mg kg⁻¹ day⁻¹ for 4 weeks with slow tapering of prednisone after. Those who responded to treatment had less severe PAH characteristics and lower NYHA functional class at baseline. Yet, while some patients noted significant improvement, the improvement was noted only after 6 months of cyclophosphamide.

The rapidity of improvement in this patient was striking and not something that is typically seen with PAH or cyclophosphamide therapy alone. One of the more significant impacts on pulmonary hemodynamics occurred in a recent retrospective study showing reductions in pulmonary artery pressures by 30% and PVR by 60% over a period of 4 months with upfront triple therapy.¹⁴ However, this patient's hemodynamic response exceeds expectations even with the most aggressive pulmonary vascular therapy. Within 1 month of pulse dose steroids, she had near-complete resolution of her TTE findings and significant improvements in her clinical symptoms, 6-min walk distance, NT-proBNP, and NYHA functional class. Repeat RHC showed a decrease in pulmonary artery pressures by 64% and PVR by over 90%. Similar rapid improvements were noted in a report by Huang et al.¹³ adding further potential evidence to the theory that in those with a more immune-mediated process leading to their PAH, intensive immunotherapy should be considered as part of the treatment.

In conclusion, SLE-PAH while sharing some commonality between other CTD-PAH differs vastly from others such as systemic sclerosis given the response in some patients to

immunosuppression. In our particular case, improvement was only seen after starting pulse dose steroids and maintenance immunosuppression. Although prior studies have shown improvement with cyclophosphamide, pulse dose steroids alone could be a potential less toxic but equally effective manner to aid in the treatment of SLE-PAH when intensive immunosuppression is being considered. Nonetheless, while there is a role for immunosuppressive therapy, that exact role remains undefined and will need larger randomized controlled trials to fully evaluate.

Declaration of conflicting interests

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Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

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Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

References

1. Dhala A. Pulmonary arterial hypertension in systemic lupus erythematosus: current status and future direction. *Clin Dev Immunol* 2012; 2012: 854941.
2. Condliffe R, Kiely DG, Peacock AJ, et al. Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. *Am J Respir Crit Care Med* 2009; 179(2): 151–157.
3. Humbert M, Sitbon O, Chataat A, et al. Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med* 2006; 173(9): 1023–1030.
4. Li M, Wang Q, Zhao J, et al. Chinese SLE Treatment and Research group (CSTAR) registry: II. Prevalence and risk factors of pulmonary arterial hypertension in Chinese patients with systemic lupus erythematosus. *Lupus* 2014; 23(10): 1085–1091.
5. Ruiz-irastorza G, Garmendia M, Villar I, et al. Pulmonary hypertension in systemic lupus erythematosus: prevalence, predictors and diagnostic strategy. *Autoimmun Rev* 2013; 12(3): 410–415.
6. Jais X, Launay D, Yaici A, et al. Immunosuppressive therapy in lupus- and mixed connective tissue disease-associated pulmonary arterial hypertension: a retrospective analysis of twenty-three cases. *Arthritis Rheum* 2008; 58(2): 521–531.
7. Sanchez O, Sitbon O, Jais X, et al. Immunosuppressive therapy in connective tissue diseases-associated pulmonary arterial hypertension. *Chest* 2006; 130(1): 182–189.
8. Gonzalez-lopez L, Cardona-muñoz EG, Celis A, et al. Therapy with intermittent pulse cyclophosphamide for pulmonary

- hypertension associated with systemic lupus erythematosus. *Lupus* 2004; 13(2): 105–112.
9. Kommireddy S, Bhyravavajhala S, Kurimeti K, et al. Pulmonary arterial hypertension in systemic lupus erythematosus may benefit by addition of immunosuppression to vasodilator therapy: an observational study. *Rheumatology* 2015; 54(9): 1673–1679.
 10. Kato M, Kataoka H, Odani T, et al. The short-term role of corticosteroid therapy for pulmonary arterial hypertension associated with connective tissue diseases: report of five cases and a literature review. *Lupus* 2011; 20(10): 1047–1056.
 11. Quismorio FP, Sharma O, Koss M, et al. Immunopathologic and clinical studies in pulmonary hypertension associated with systemic lupus erythematosus. *Semin Arthritis Rheum* 1984; 13(4): 349–359.
 12. Johnson SR and Granton JT. Pulmonary hypertension in systemic sclerosis and systemic lupus erythematosus. *Eur Respir Rev* 2011; 20(122): 277–286.
 13. Huang C, Zhang S, Tian Z, et al. Could pulmonary arterial hypertension be an active index of systemic lupus erythematosus? A successful case of SLE-PAH cured by methylprednisolone pulse therapy. *Lupus* 2014; 23(14): 1533–1536.
 14. Sitbon O, Jaïs X, Savale L, et al. Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study. *Eur Respir J* 2014; 43(6): 1691–1697.