

Iron therapy as a novel treatment of scleroderma-related pulmonary hypertension: A case report and literature review

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Abstract

Pulmonary arterial hypertension (PAH) is the leading cause of death in patients with systemic sclerosis (SSc), with a 3-year mortality of 40%–50% despite optimal therapy. Treatment mirrors that of idiopathic PAH and is often ineffective. This is a case report of a patient with SSc evaluated for progressive dyspnoea with exertion and found to have elevated pulmonary artery systolic pressures (PASP). She received ferritin-targeted iron infusions as a novel treatment of suspected SSc-associated PAH, with subsequent resolution of respiratory symptoms and PASPs that normalized. We review PAH especially associated with SSc, its treatment and identify a possible novel therapeutic approach for those with PAH-SSc.

KEYWORDS

iron therapy, pulmonary arterial hypertension, pulmonary hypertension, scleroderma, systemic sclerosis

INTRODUCTION

In this case report, we review pulmonary arterial hypertension (PAH) especially associated with systemic sclerosis (SSc), its treatment and identify a possible novel therapeutic approach for those with PAH-SSc.

CASE REPORT

Our patient is a 72-year old woman, never smoker, with a history of scleroderma. Her SSc presented with Raynaud's phenomenon, sclerodactyly, telangiectasias and oesophageal dysmotility in 1997. In 2018, she came to our clinic for evaluation of progressive dyspnoea on exertion over several months. At the time of her initial visit, her exercise tolerance was limited to two city blocks before needing to rest and recover. She had normal vital signs and her physical examination was significant for mucosal telangiectasia and tightening of the skin around the mouth and fingers. Pulmonary function tests including diffusing capacity were normal but showed significant post-bronchodilator reversibility. An echocardiogram done 3 years prior showed normal pulmonary artery pressures (PAPs) as a means for assessing pulmonary hypertension (PH). She underwent a stress echocardiogram, which showed elevated PAPs. Her pre-exercise

pulmonary artery systolic pressure (PASP) was 40 mmHg with a mean PAP (mPAP) of 28 mmHg. Post exercise, her PASP was 60 mmHg with an estimated mPAP of 40 mmHg.

Laboratory values at this time were significant for a ferritin level of 23 ng/ml (her level in 2015 was 30 ng/ml) and haemoglobin level of 12.9 g/dl with prior baseline values between 13 and 13.2 g/dl. The patient had a history of chronic gastro esophageal reflux disease, likely due to her SSc, for which she was on H2 blockers. She had esophagogastroduodenoscopy and colonoscopies, and there were no lesions found that would be implicated as aetiology for iron deficiency (ID). She was not on any immunosuppressive agents. During the evaluation for PAH, the patient found literature noting that ID may have some involvement with worsening of PH. At the time of her evaluation, iron stores were low, consistent with ID despite normal haemoglobin values. In light of these data, she established care with a haematologist who treated her deficient iron stores hoping to improve her exercise tolerance.

Over the period of approximately 1 year, the patient underwent two series of ferrous gluconate infusions using a ferritin level of approximately 80 ng/ml and an iron saturation of >25% as a guide to repeat dosing (Figure 1A). The target ferritin was used by the patient's haematologist, likely representing a 'normal' level. Her haemoglobin during this time

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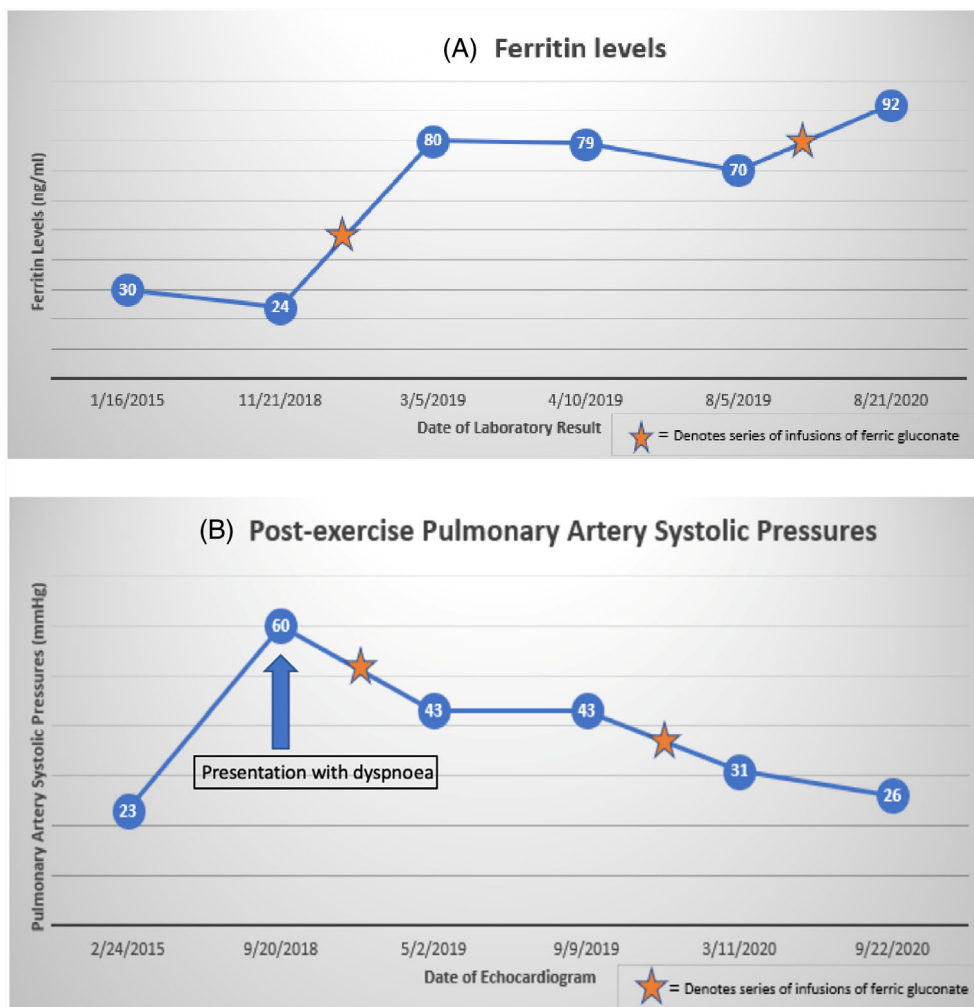


FIGURE 1 (A) Ferritin levels plotted against the date of result. The stars on the graph denote a series of infusions of sodium ferric gluconate dosed at 12.5 mg/kg. The patient received the first series of six infusions from November 2018 to February 2019 and the second series of five infusions during November 2019. (B) Pulmonary artery systolic pressure obtained via transthoracic echocardiogram plotted against the date of the test. As shown in (A), stars denote when the series of infusions of sodium ferric gluconate were given to the patient. During this time, the patient's haemoglobin varied between 12.9 g/dl (16 January 2015) and 13.9 g/dl (21 August 2020). There was little correlation of the ferritin level with the haemoglobin; for example, on 21 November 2018, the haemoglobin was 12.6 g/dl with ferritin of 24 ng/ml and on 5 August 2019 the haemoglobin was 12.8 g/dl with ferritin of 70 ng/ml. In the absence of repeated right heart catheterization, the mechanism underlying the surprising improvement in pulmonary pressures cannot be defined

varied between 12.9 and 13.9 g/dl. Serial echocardiograms were performed as a means for assessing PH after the initiation of treatment which demonstrated normalization of the PASPs (Figure 1B). No right heart catheterizations were performed due to patient preference. Repeat pulmonary function testing was significant for an increase in diffusing capacity from 95% to 110% after adjusted for the rise in haemoglobin. Approximately 1 year after her last iron infusion, she continues without shortness of breath, and repeat echocardiogram measurements continue to show normal PASPs with maintenance of serum ferritin and iron saturation as described above.

DISCUSSION

SSc is a complex connective tissue disease characterized by excess collagen production, endothelial dysfunction, chronic

inflammation and abnormalities of the immune system leading to progressive fibrosis of the skin and internal organs (affecting the lungs, gastrointestinal tract, heart, kidneys, muscles and joints).¹ Pulmonary involvement is seen in more than 80% of the patients and is manifested primarily as PAH and/or interstitial lung disease. PAH is often progressive, can develop any time in the disease course and is the leading cause of death in SSc patients with a 3-year survival of 56% despite optimal therapy.² Although the exact pathogenesis of PAH in SSc patients is unknown, many believe that pulmonary artery endothelial cell dysfunction plays a role. Diseased endothelium has difficulty producing vasodilators (such as nitric oxide and prostacyclin), while overexpressing vasoconstrictors (such as endothelin-1), which results in increased vascular tone.³

Most conventional therapy for PAH-SSc is identical to that for idiopathic PAH (iPAH) with the exception of

high-dose calcium channel blockade, as vasodilator-responsive PAH is very rare in SSc patients. Combining therapies from two different classes is often done, and each drug is introduced individually. Agents used for treatment include endothelin receptor antagonists, phosphodiesterase type 5 inhibitors and soluble guanylate cyclase stimulators (nitric oxide pathway), prostacyclin agonists/analogues and tyrosine kinase inhibitors, which are all therapies for iPAH. Despite these therapies, mortality in these patients remains high. Finally, lung transplantation is a remaining option for those with PAH-SSc non-responsive to medical therapy.

Iron therapy is not included in the standard of care for patients with PAH, and our literature search produced no reported cases utilizing iron therapy in PAH-SSc patients. There is, however, ample evidence that iron plays a pivotal role in pulmonary vascular homeostasis and possible pathogenesis of PAH. We performed a PubMed literature search and found several articles regarding iron and PAH. The important interplay between iron and oxygen is well known and essential to aerobic life. PAH patients are often found with mitochondrial dysfunction, and iron is vital to many mitochondrial enzymes.⁴ Ramakrishnan et al. explored the importance of iron homeostasis disruption and its link to the development of PAH.⁵ In vitro rat model studies showed that ID led to profound pulmonary vascular remodelling with prominent muscularization, medial hypertrophy and perivascular inflammatory cell infiltration, and was associated with raised PAPs and right ventricular hypertrophy.⁶

Although we found no data utilizing iron supplementation as a treatment for PAH-SSc, a literature search provided many articles about the use of iron therapy in the treatment of PAH from other causes. In a retrospective study of 98 patients with iPAH, 63% had ID, which was associated with increased disease severity and poor clinical outcomes.⁷ The study demonstrated an inverse relationship between transferrin levels and disease severity and outcomes. They showed that iron therapy could be a helpful intervention in iPAH. Soon et al. found that those with iPAH had lower serum iron and transferrin saturation, which correlated with higher levels of the inflammatory cytokine IL-6 ($r = -0.6$, $p = 0.006$ for iron and $r = 0.68$, $p = 0.001$ for transferrin saturation); high IL-6 correlated with higher mortality.⁸ The study recommended screening for ID in patients with iPAH and proposed iron replacement as a possible intervention that may impact symptoms and/or survival. Viethen et al. studied 20 ID patients with PAH and found a significant improvement in 6-min walk test (6MWT) and quality of life in those patients repleted with iron compared to the non-treated group.⁹ Ruitter et al. used iron replacement therapy in 15 ID patients with iPAH.¹⁰ After 12 weeks, although 6MWT was unchanged, exercise endurance time and aerobic capacity increased. The latest ESC/ERS guidelines now recommend monitoring iron levels in PAH patients. Based on preliminary data that ID may be associated with reduced exercise capacity and higher mortality, iron supplementation likely optimizes overall patient care prior to embarking on pulmonary vasodilator treatment.

Although our patient's haemoglobin increased from 12.8 to 13.9 g/dl, as her ferritin levels increased from 24 to 92 ng/ml, at times there was no correlation between her haemoglobin and ferritin levels (Figure 1). However, the measured echocardiographic PASPs did show an inverse relationship to the ferritin levels (Figure 1) and also iron saturation which is not shown. PASPs are used rather than mPAP as, specifically in SSc patients, abnormal delta PASPs (the difference between rest PASP and post-exercise PASP) could indicate sub-clinical PAH.¹¹ The mechanisms explaining the improvement in clinical outcomes with iron supplementation in ID patients with PAH are unclear but likely involve direct effects on iron-dependent pathways in the pulmonary vascular bed.¹² This is supported by a study that demonstrated that intravenous (IV) iron administration immediately before a hypoxaemic event blunted rise in PAPs even before haemoglobin increased.¹³

It should be noted that not all studies support the role of iron in PAH. For example, in the SIPHON (Supplementation of Iron in Pulmonary Hypertension) study, a multicentre, double-blind, randomized, controlled, crossover clinical trial, Howard et al. explored IV iron supplementation in 40 ID patients with iPAH.¹⁴ The results showed no significant change in endurance time or other secondary endpoints. However, this trial used a fixed dose of supplemented iron (either 1 g or 15 mg/kg depending on weight) without a targeted ferritin level or iron saturation. The SIPHON study also observed outcomes at 12 weeks, which may not be a sufficient amount of time to measure full response to iron supplementation. Our patient showed response over a 6–7-month period—so designing a randomized control study over a longer period of time than 12 weeks may yield more relevant results.

In summary, there are some existing studies that show benefit from iron therapy in patients with iPAH. We believe that our patient, with suspected PAH-SSc, had marked clinical improvement and normalization of PASPs as a direct result of iron therapy without any other vasodilator therapy administered. The patient remains with normal PASPs measured by echocardiogram with maintenance of ferritin levels at 80 ng/ml and iron saturation of >25%. In the absence of repeated right heart catheterization, the mechanism underlying the surprising improvement in pulmonary pressures cannot be defined.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

Dr. Melissa Neumann, MD, was the main author who wrote the initial draft (Abstract, Introduction and Discussion) of the manuscript, performed the literature review and edited the manuscript. Dr. Karen A. Wong, MD, was the second author, who edited the manuscript and prepared the figures. Dr. Kevin Lazo, DO, was the third author, who wrote the Case Report section and reviewed the manuscript and edited the manuscript. Dr. Diane Stover, MD, reviewed each draft

of the manuscript, reviewed the literature, wrote portions of the Case Report section and edited the manuscript in detail.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

ETHICS STATEMENT

The authors declared that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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