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Case Report

Severe Pulmonary Arterial Hypertension and Exudative Pleural Effusion due to Limited Cutaneous Systemic Sclerosis: A Case Report

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Abstract

Systemic sclerosis (SSc) is a rare autoimmune disease characterized by small vessel vasculopathy, autoantibodies and fibrosis of skin and internal organs. Pulmonary arterial hypertension (PAH) secondary to SSc is devastating complication seen in advanced stages, which if untreated may proceed to right ventricular failure and death.

We present a case of a 67-year old Caucasian female who presented with a two-month history of pleuritic chest pain and was diagnosed with limited cutaneous SSc and PAH. Physical examination revealed sclerodactyly, telangiectasias, nailbed capillary changes, tachypnoea, irregular tachycardia, and peripheral edema. Pulmonary function tests showed low diffusion capacity of the lung for carbon monoxide to 57%, with normal lung volumes. An echocardiography on admission showed new right ventricular dysfunction and dilatation as well as an estimated pulmonary pressure of 81 mmHg. Pulmonary computed tomography-angiography and lung perfusion scintigraphy ruled-out pulmonary embolism and interstitial lung disease but showed pleural effusion. Analysis of autoantibodies in serum and pleural fluid identified anti-centromere and SSA-Ro/52 antibodies, a diagnosis of limited cutaneous SSc could be made. Right heart catheterization confirmed PAH. The patient was eligible for combination treatment with macitentan and sildenafil. Six weeks after RHC and initiation of PAH-directed therapy, the patient had improved functional capacity on the six-minute walk test, decrease in NT-proBNP, improved pulmonary hemodynamics and quality of life.

Both PAH and limited SSc may be misdiagnosed due to their non-specific and/or subtle symptoms. Our case highlights the difficulties regarding diagnosis and management of limited SSc and PAH the need to be aware of unusual presentations, like in our case which after many examinations led to the diagnosis of both limited SSc and PAH. Novel agents, in this case combination therapy with macitentan and sildenafil, have been proven to impact morbidity and mortality.

Keywords: *Case Report; Heart Catheterization; Macitentan; Pulmonary Arterial Hypertension; Sildenafil; Systemic Sclerosis*

Abbreviations

6MWT: Six-Minute Walk Test; ANA: Antinuclear Antibodies; ACR/EULAR: American College of Rheumatology/European League Against Rheumatism; CRP: C-reactive Protein; CT: Computed Tomography; D_{LCO}: Diffusion Capacity of the Lung for Carbon Monoxide; ERA: Endothelin Receptor Antagonist; NT-proBNP: N-Terminal-Pro Brain Natriuretic Peptide; PAH: Pulmonary Arterial Hypertension; PAP: Pulmonary Arterial Pressure; PDE-5i: Phosphodiesterase-5 Inhibitors; PVR: Pulmonary Vascular Resistance; RHC: Right Heart Catheterization; SSc: Systemic Sclerosis; WHO-FC: World Health Organization Functional Class

Introduction

Systemic sclerosis (SSc), is a rare autoimmune connective tissue disease characterized by small vessel vasculopathy, autoantibodies and fibrosis of skin and internal organs, subcategorized into diffuse SSc and limited SSc on the basis of skin involvement [1]. Although the disease can present at any age, the most common age at diagnosis is between 4th and 5th decade of life, being more common in females.

Because of its rarity of and the fact that presentation can vary greatly, the diagnosis remains challenging, however the new 2013 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria (Table 1) are more inclusive than ever [1]. Even though it was developed as inclusion criteria mainly for including SSc-patients in clinical studies, they are used in clinical practice for diagnosis [1]. Those classified as SSc are a subcategory of patients actually diagnosed with SSc, with diagnosis being more sensitive as it incorporates more signs and symptoms not mentioned in the classification criteria [1].

Items	Sub-items	Score
Skin thickening of the fingers of both hands extending proximal to the MCP joints (sufficient criterion)	-	9
Skin thickening of the fingers (only count the highest score)	Puffy fingers	2
	Sclerodactyly of the fingers (distal to MCP but proximal to the PIPs)	4
Finger tip lesions (only count the highest score)	Digital Tip Ulcers	2
	Finger Tip Pitting Scars	3
Telangiectasia	-	2
Abnormal nailfold capillaries	-	2
Pulmonary arterial hypertension (PAH) and/or Interstitial lung Disease (ILD) (maximum score is 2)	PAH	2
	ILD	2
Raynaud's phenomenon	-	3
Scleroderma related antibodies (any of anti-centromere, anti-Scl 70, anti-RNA polymerase III) (maximum score is 3)	Anti-centromere	3
	Anti-Scl 70	
	Anti-RNA polymerase III	

Table 1: *The 2013 ACR/EULAR classification criteria for systemic sclerosis [1]. Patients having a total score ≥ 9 are classified as having definite systemic sclerosis. The total score is determined by adding the maximum score from each category. Sensitivity is 91% and specificity is 92%. MCP: metacarpophalangeal; PIP: proximal interphalangeal.*

Pulmonary arterial hypertension (PAH) associated with SSc is a progressive devastating complication usually developed when the disease is advanced, which if untreated may proceed to right ventricular failure and death [2,3]. Diagnostic criteria for PAH are defined as mean pulmonary arterial pressure (PAP) ≥ 25 mmHg, mean pulmonary arterial wedge pressure ≤ 15 mmHg, and pulmonary vascular resistance > 3 Wood units as assessed by right heart catheterization (RHC) [4]. Here, we describe a patient with progressive PAH and limited SSc diagnosed simultaneously who presented with pleuritic chest pain and qualified for treatment with macitentan and sildenafil.

Case Presentation

A 67-year old Caucasian female presented to the emergency department with a two-month history of gradually worsening pleuritic chest pain, which was radiating to the left scapula and was aggravated with respiration and movement. The patient denied feeling of taught skin, chronic ulcers, urinary abnormalities, intestinal abnormalities, and sensitivity to light or sound. The patient had recently completed a 10-day regimen on prednisolone, however without improvement. She had no history of smoking.

Her medical history included Sjogren's syndrome, only sicca symptoms, and Raynaud's phenomenon in the past 30 years. Furthermore, she had esophageal strictures which had been dilated three times, dysphagia, gastroesophageal reflux, hypothyroidism, previous removal of vascular mass on the lower lip, previous pulmonary embolism, atrial fibrillation, aortic stenosis corrected with transcatheter aortic valve implantation followed by insertion of a pacemaker, and pulmonary hypertension assessed by echocardiography. Her father died at the age of 53 due to myocardial infarction and had suffered from systemic lupus erythematosus, multiple myocardial infarctions and stroke. The mother died at the age of 65, also due to myocardial infarction and had joint rheumatism and aortic stenosis. The patient's daily medications included dabigatran, digoxin, furosemide, bisoprolol, atorvastatin, omeprazole and Gaviscon™ (alginate acid, aluminum oxide, calcium carbonate, sodium bicarbonate).

Upon admission, cardiopulmonary examination was remarkable for tachypnea and irregular tachycardia. A peripheral edema was noted, especially in the lower extremities. The skin of the fingers (especially distally) was seemingly thicker, more taught and less elastic than the rest of the body (Figure 1). Several discrete telangiectasias could be seen on the lips, face and hands. Nailfold capillaroscopy demonstrated dilated vessels, splinter hemorrhages, and in some areas absence of vessels as seen in advanced SSc. There were no digital ulcers. There were neither signs of arthritis nor any complaints from the patient regarding joint pain. On admission erythrocyte sedimentation rate was 6 mm/h, C-reactive protein (CRP) 20 mg/l, D-dimer 0.19 mg/l and N-terminal-proBNP (NT-proBNP) 4,200 ng/l. Complete blood count demonstrated microcytic anemia and leukocytosis (125 mg/l and 15.3 x 10^9 cells/l, respectively). Level of transferrin was 2.33 g/l, transferrin saturation 5%, iron 3.0 µmol/l, and ferritin 50 µg/l. First and second cardiac troponin T was 18 and 19 ng/l (upper reference value 15 ng/l), respectively.

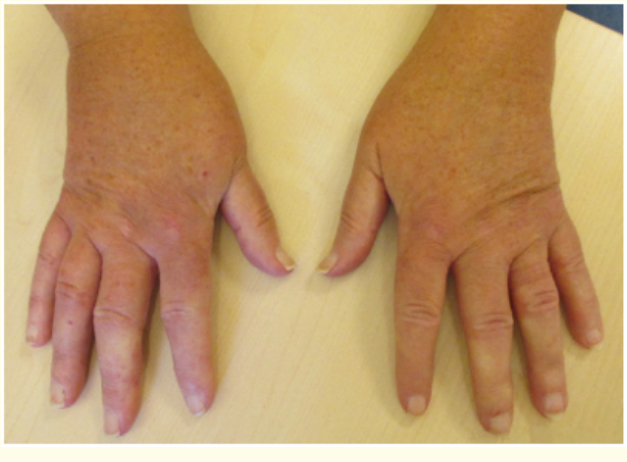

Figure 1: *Dorsal surface of the hands six weeks after vasodilator therapy; taught skin can be seen distally, as well as telangiectasias.*

The patient had previously performed pulmonary function tests which revealed lung capacities in the lower range of normal, without signs of restrictive disease. The diffusion capacity of the lung for carbon monoxide (D_{LCO}) was severely lowered to 57% (expected value 75%). Recently, the patient had performed a computed tomography (CT) with contrast twice which did not display any signs of pulmonary

embolism, restrictive- or interstitial lung disease, however there were minimal amount of pleural fluid. On admission a chest X-ray displayed pleural sinus effusion. An echocardiogram performed two months before admission displayed normal left and right ventricular function, mildly dilated left and right atria, normal location of the aortic valve with minimal leakage, mild mitral insufficiency, pronounced tricuspid insufficiency, and systolic pulmonary pressure of at least 50 mmHg. The same examination performed on admission displayed dilatation, moderate decrease in systolic function of the right ventricle (Figure 2) and a pulmonary pressure of at least 82 mmHg; however, the left ventricle was unaffected. A lung perfusion scintigraphy ruled out chronic thromboembolic pulmonary hypertension, which was considered a differential diagnosis. A diagnostic pleural tap showed mixed inflammatory cells and analysis of the pleural fluid was assessed as exudate according to Light's criteria. Antinuclear antibody (ANA) analysis (in serum and pleural fluid) was positive, confirming anti-centromere (CENP A and B) and SSA/Ro52 antibodies; this was also confirmed with immunoblot analysis. Anti-glomerular basement membrane, anti-neutrophilic cytoplasmic and anti-cardiolipin antibodies were negative in serum and pleural fluid.

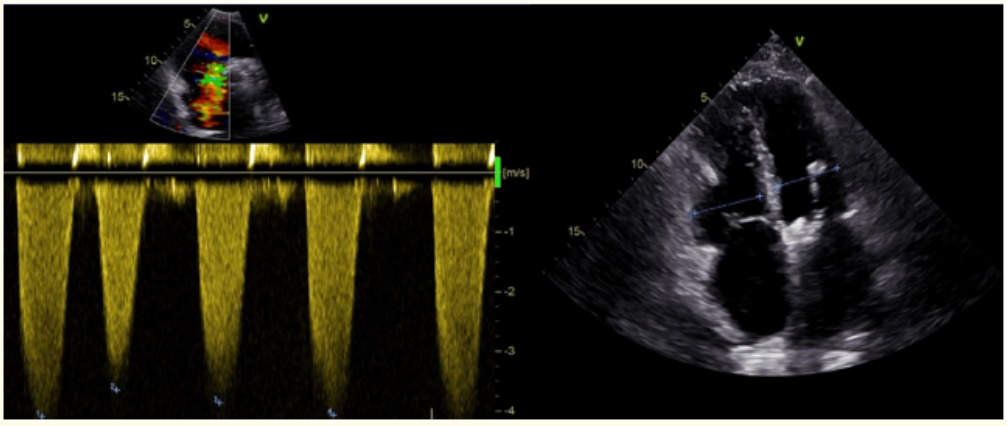

Figure 2: *Left, tricuspid regurgitation with Vmax 4.1 m/s. Right, echocardiography displaying dilatation of the right ventricle and atrium.*

During the hospitalization the patient became disoriented. Laboratory examination showed serum sodium 119 g/l, potassium 5.4 mmol/l, CRP 180 mg/l, and NT-proBNP 5,500 ng/l. Treatment with cefotaxime was initiated, urinary cultures were positive for *E. coli* while blood cultures were negative. The liver was affected with pathologic increase in gamma-glutamyl transferase, alanine transaminase, alkaline phosphatase, total bilirubin, activated partial thromboplastin time and prothrombin time. An abdominal ultrasonography displayed normal findings except for mildly dilated liver veins. Electrophoresis displayed moderate-severe inflammation, with normal levels of immunoglobulins and without monoclonal bands in plasma. Cortisol levels were normal. A cranial CT was performed that did not display any significant lesions. A new echocardiogram was performed with worsening right ventricular function and now also with decreased left ventricular function, the pulmonary pressure had increased. Sodium levels did not change significantly upon delivery of intravenous sodium. At this point, furosemide therapy was temporarily terminated because of hyponatremia. Plasma osmolality was decreased (257 mOsm/kg) and urinary sodium (< 20 mmol/l), potassium (22.6 mmol/l) and osmolality (351 mOsm/kg) were normal thus treatment according to hypervolemic hyponatremia was introduced. Spironolactone was introduced to inhibit the secondary hyperaldosteronism that had occurred because of the dilution hyponatremia and aggressive intravenous furosemide for diuresis. The sodium levels were normalized within two days. CRP decreased after administration of antibiotics.

A rheumatologist evaluated the patient and used the 2013 ACR/EULAR classification criteria for SSc and diagnosed limited cutaneous SSc. Immunosuppressive treatment would not be initiated as the disease had already progressed to irreversible fibrosis, thus the main focus was to treat the PAH.

The patient had during the two-week long hospitalization gained 13 kg of bodyweight, all of which she lost before performing the RHC. The increase in weight was mainly due to cor pulmonale and changes in medications, namely the fact that digoxin therapy was terminated due to high plasma concentration (1.4 nmol/l) and furosemide because of hyponatremia. Next, digoxin was reintroduced together with levosimendan, with subsequent improvement of right ventricular function. The suspicion of PAH was confirmed with RHC, results of which are summarized in Table 2. The patient was eligible for combination treatment with macitentan (10 mg daily) and sildenafil (60 mg daily).

	Baseline	After nitric oxide
sPAP/dPAP (systolic/diastolic pulmonary arterial pressure)	88/32 mmHg	73/22 mmHg
mPAP (mean pulmonary arterial pressure)	52 mmHg	41 mmHg
mPaWP (mean pulmonary arterial wedge pressure)	9 mmHg	14 mmHg
TPG (transpulmonary gradient)	43 mmHg	27 mmHg
DPG (diastolic pressure gradient)	23 mmHg	8 mmHg
PVR (pulmonary vascular resistance)	11.6 Wood units	6.8 Wood units
SVR (systemic vascular resistance)	23.2 Wood units	
mRAP (mean right atrial pressure)	9 mmHg	
RVESP (right ventricular end systolic pressure)	89 mmHg	
RVEDP (right ventricular end diastolic pressure)	10 mmHg	
$AV0_2$ (arteriovenous O_2 diffusion)	52 ml/l (aorta SO_2 87%, pulmonalis SO_2 52%)	44 ml/l
CO (cardiac output)	3.7 l/min^{THERMODILUTION}	4.0 l/min^{THERMODILUTION}

Table 2: *Hemodynamic results from right heart catheterization before and after vasoreactivity testing with nitric oxide. Precapillary pulmonary hypertension was diagnosed. Mild hypokinetic circulation with increased $AV0_2$ diffusion and hypoxia in rest (saturation 87-89%) could be noted.*

On a six-week follow up, the patient had improved functional capacity on the six-minute walk test (6MWT, see Table 3), lowered NT-proBNP (2,700 ng/l), and improved cardiopulmonary hemodynamics on echocardiography (estimated pulmonary pressure 40 mmHg).

	Before	After
Pulse (beats per minute)	72 - 180	75 - 138
Walking distance (m)	180	300
Stopped or paused walking before 6 minutes	No	No
Exertion Borg score (scale of 6 - 20)	16	12
Dyspnea Borg score (scale of 0 - 10)	4	3
SaO_2 (%)	90	86

Table 3: *A six-minute walk test comparing subjective feeling of exertion and dyspnea according to the Borg scale before and after vasodilator therapy at six-week follow up. The patient performed the test with a walker both times.*

Discussion

According to the 2013 ACR/EULAR classification criteria (Table 1), our patient gained points for nail bed capillary changes, Raynaud's phenomenon, telangiectasia, pulmonary arterial hypertension, anti-centromere antibodies and distal skin thickening in the fingers. In addition to this, she also had esophageal dysfunction, gastroesophageal reflux, and pleural effusion which are other symptoms seen in SSc [1]. Points for sclerodactyly in the fingers was given with uncertainty due to the patient being edematous, however the total amount of points even without those for sclerodactyly was enough for classifying the patient as having SSc, and together with the other symptoms, a rheumatologist could set the diagnosis of limited cutaneous SSc. Interestingly, our patient did not meet the old criteria for SSc published in 1980, which lacked sensitivity for early and limited SSc, maybe explaining why she had been undiagnosed for many years [1].

PAH is a leading cause of SSc related death with approximately 10 - 15% of patients developing this complication [5,6], which is also an independent risk factor of mortality in these patients [3]. SSc-PAH usually develops in those with long-standing limited SSc (especially in association with CREST syndrome), a low or progressive decline in D_{LCO} and high ratio of forced vital capacity/diffusion capacity of carbon monoxide ($FVC/D_{LCO} > 1.6$). Although PAH also occurs in patients with diffuse SSc, anti-centromere antibodies (as seen in the limited SSc) are associated with a higher likelihood of developing PAH, as well as the absence of anti-Scl 70 (as seen in diffuse SSc) antibodies [2]. In our patient all but one criterion (calcinosis) was found in the CREST phenotype, low D_{LCO}, FVC/D_{LCO} ratio > 1.6, presence of anti-centromere antibodies in serum and absence of anti-Scl 70 antibodies, putting her at high risk of developing PAH [7,8]. The severity of PAH directly correlates with mortality, however other predictive factors such as male gender, older age, pericardial effusions and low D_{LCO} have been identified as predictors of mortality and markers of PAH progression in SSc patients [8,9]. Although early PAH in SSc can be asymptomatic, exertional dyspnea is the most common initial symptom. Patients with SSc can also develop pleural effusion, however this is an uncommon complication with less than 10% being affected and often those affected are asymptomatic, but this differs with the etiology of the pleural effusion (for example pleuritis, heart failure, pneumonia, pericarditis) [10]. In our case this uncommon complication, a two month long pleuritic chest pain where other, more common causes had been ruled out, was the presenting symptom that lead to the diagnosis. Pleuritis associated with SSc is usually an exudative, lymphocytic effusion with no confirmed association with autoantibodies [11]. Our patient had disease antibodies in the pleural exudate, however it is unclear whether this was causative or not.

The therapeutic options currently on the market for PAH targets the prostacyclin, nitric oxide or endothelin pathway, all of which are intracellular pathways [12]. These agents consist of phosphodiesterase-5 inhibitors (PDE-5i; sildenafil, tadalafil), endothelin receptor antagonists (ERA; ambrisentan, bosentan, macitentan), prostanoids (epoprostenol, iloprost, treprostinil), soluble guanylate cyclase stimulators (riociguat) and IP (prostacyclin) receptor agonists (selexipag) [13].

A meta-analysis of randomized clinical trials of PAH-directed therapy showed that monotherapy could improve survival, exercise capacity, functional class, and hemodynamic status compared with placebo or conventional therapy [14]. Furthermore, combination therapy could further improve the above-mentioned parameters, however without any further improvement in survival and with more side-effects [14].

Sildenafil, a potent selective PDE-5i has generated promising results in clinical trials in patients with PAH by improving exercise capacity, pulmonary hemodynamics, and symptoms with mild adverse-effects that are mainly related to its vasodilatory action (such as headaches, dizziness, and flushing) [15,16].

In the SERAPHIN trial, macitentan, a dual endothelin receptor antagonist, was shown to significantly decrease morbidity and mortality in both treatment-naïve and pretreated patients (PDE-5i or non-parenteral prostanoids), proving that macitentan in sequential combination therapy could improve the latter mentioned effects [17,18]. However, the more recent COMPASS-2 trial failed to demonstrate a decrease in risk of morbidity and mortality by adding bosentan to patients pre-treated with sildenafil, results which could partly be explained by many limitations in the study design and execution but partly by drug-drug interactions such as bosentan significantly decreasing the plasma concentration of sildenafil when co-administered to patients with PAH [19,20]. Recently, an animal model study where macitentan was used for PAH demonstrated that not only does it improve pulmonary hemodynamics but also vascular remodeling and angiogenesis [21]. The main adverse-effects of endothelin-receptor antagonists are hepatotoxicity (bosentan), peripheral edema (bosentan and ambrisentan), and anemia (bosentan and macitentan) [22].

In the AMBITION trial, it was shown that upfront combination therapy with ambrisentan and tadalafil in treatment-naïve PAH patients led to a 50% decrease in clinical failure (defined as time from randomization to first occurrence of a composite of all cause death, hospitalization due to worsening of PAH, disease progression or unsatisfactory long-term clinical response), better performance of 6MWT and larger decrease of NT-proBNP as compared to monotherapy with either agent [23], indicating that combination therapy can be initiated directly when treatment commences.

Upfront combination therapy with ambrisentan and tadalafil is recommended in the current guidelines in those with World Health Organization functional class (WHO-FC) I and III (class of recommendation I/level of evidence B) and may be considered for those with WHO-FC IV (class of recommendation IIb/level of evidence C) [7]. As for combinations other than ambrisentan and tadalafil in the same classes, the guidelines state that one should consider using these combinations as upfront combination therapy in WHO-FC I and III (class of recommendation IIa/level of evidence C) and they may be considered in those with WHO-FC IV (class of recommendation IIb/level of evidence C) [7].

However, when it comes to sequential combination therapy with the ERA and PDE-5i class, the guidelines recommend macitentan added to sildenafil (class of recommendation I/level of evidence B) for WHO-FC II-III, and one should consider this combination in those with WHO-FC IV [7,18]. As of now, sequential is the most commonly utilized strategy of combination therapy, where one adds drugs in sequences in cases of inadequate results or in case of clinical worsening [7].

A meta-analysis showed that prognosis of SSc-PAH remains poor with a 3-year survival rate at 52% [3], however in the newer PHAROS trial 3-year survival rate was 75%, potentially reflecting improvements in diagnostics and novel PAH-directed therapy [8]. The REVEAL study showed that PAH associated with SSc have lower survival at 3-year compared to non-SSc-PAH (61% versus 81%) [24]. Current guidelines suggest clinical signs of right heart failure, progression of symptoms, syncope, WHO-FC, 6MWT, cardiopulmonary exercise testing, NT-proBNP, imaging (echocardiography and cardiac magnetic resonance imaging), and pulmonary hemodynamics for risk assessment of PAH and recommend regular follow-up to assess severity of PAH and clinical response to therapy [7].

Conclusion

Symptoms in early disease or in limited SSc may be non-specific and/or subtle, highlighting the need to have knowledge and a high clinical suspicion in order to detect the disease in early stages in order to impact outcome.

Using novel agents, in this case combination therapy with macitentan and sildenafil, have been proven to impact morbidity and mortality. A multidisciplinary approach is needed in these patients.

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the editor of this journal.

Conflict of Interest

The authors declare that they have no competing interests.

Authors' Contributions

RK: idea, design, data collection, major writing, patient management. GM: writing, critical revision, project management. JA: writing, critical revision, patient management. PM: design, writing, critical revision, project management. All authors read and approved the final manuscript.

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Bibliography

1. F van den Hoogen., *et al*. "2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative". *Annals of Rheumatic Diseases* 72.11 (2013): 1747-1755.

2. V Steen., *et al*. "Predictors of isolated pulmonary hypertension in patients with systemic sclerosis and limited cutaneous involvement". *Arthritis and Rheumatology* 48.2 (2003): 516-522.

3. G Lefèvre., *et al*. "Survival and prognostic factors in systemic sclerosis-associated pulmonary hypertension: a systematic review and meta-analysis". *Arthritis and Rheumatology* 65.9 (2013): 2412-2423.

4. MM Hoeper., *et al*. "Definitions and diagnosis of pulmonary hypertension". *Journal of the American College of Cardiology* 62.25 (2013): D42-D50.

5. C Muangchan., *et al*. "The 15 % rule in scleroderma: the frequency of severe organ complications in systemic sclerosis. A systematic review". *The Journal of Rheumatology* 40.9 (2013): 1545-1556.

6. X Yang., *et al*. "Prevalence of pulmonary arterial hypertension in patients with connective tissue diseases: a systematic review of the literature". *Clinical Rheumatology* 32.10 (2013): 1519-1531.

7. N Gailiè., *et al*. "2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension". *European Heart Journal* 37.1 (2016): 67-119.

8. L Chung., *et al*. "Survival and predictors of mortality in systemic sclerosis-associated pulmonary arterial hypertension: outcomes from the pulmonary hypertension assessment and recognition of outcomes in scleroderma registry". *Arthritis Care and Research* 66.3 (2014): 489-495.

9. C Mihai., *et al*. "Factors associated with disease progression in early-diagnosed pulmonary arterial hypertension associated with systemic sclerosis: longitudinal data from the DETECT cohort". *Annals of the Rheumatic Diseases* 77.1 (2018): 128-132.

10. AE Thompson., *et al*. "A study of the frequency of pericardial and pleural effusions in scleroderma". *British Journal of Rheumatology* 37.12 (1998): 1320-1323.

11. CL Gomez., *et al*. "Pulmonary manifestations of collagen diseases". *Archivos de Bronconeumología* 49.6 (2013): 249-260.

12. M Humbert., *et al*. "Treatment of pulmonary arterial hypertension". *The New England Journal of Medicine* 351.14 (2004): 1425-1436.

13. AC Lajoie., *et al*. "Combination therapy in pulmonary arterial hypertension: recent accomplishments and future challenges". *Pulmonary Circulation* 7.2 (2017): 312-325.

14. HL Liu., *et al*. "Efficacy and Safety of Pulmonary Arterial Hypertension-specific Therapy in Pulmonary Arterial Hypertension: A Meta-analysis of Randomized Controlled Trials". *Chest* 150.2 (2016): 353-366.

15. N Galiè., *et al*. "Sildenafil citrate therapy for pulmonary arterial hypertension". *The New England Journal of Medicine* 353.20 (2005): 2148-2157.

16. TP Singh., *et al*. "A randomized, placebo-controlled, double-blind, crossover study to evaluate the efficacy of oral sildenafil therapy in severe pulmonary artery hypertension". *American Heart Journal* 151.4 (2006): 851.e1-851.e5.

17. IS Hong., *et al*. "Macitentan for the treatment of pulmonary arterial hypertension". *Annals of Pharmacotherapy* 48.4 (2014): 538-547.

18. T Pulido., *et al*. "Macitentan and morbidity and mortality in pulmonary arterial hypertension". *The New England Journal of Medicine* 369.9 (2013): 809-818.

19. V McLaughlin., *et al*. "Bosentan added to sildenafil therapy in patients with pulmonary arterial hypertension". *European Respiratory Journal* 46.2 (2015): 405-413.

20. GA Paul., *et al*. "Bosentan decreases the plasma concentration of sildenafil when coprescribed in pulmonary hypertension". *British Journal of Clinical Pharmacology* 60.1 (2005): 107-112.

21. V Nadeau., *et al*. "Dual ETA/ETB blockade with macitentan improves both vascular remodeling and angiogenesis in pulmonary arterial hypertension". *Pulmonary Circulation* 8.1 (2018).

22. A Wei., *et al*. "Clinical Adverse Effects of Endothelin Receptor Antagonists: Insights From the Meta-Analysis of 4894 Patients From 24 Randomized Double-Blind Placebo-Controlled Clinical Trials". *Journal of the American Heart Association* 5.11 (2016): e003896.

23. N Galiè., *et al*. "Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension". *The New England Journal of Medicine* 373.9 (2015): 834-844.

24. L Chung., *et al*. "Unique predictors of mortality in patients with pulmonary arterial hypertension associated with systemic sclerosis in the REVEAL registry". *Chest* 146.6 (2014): 1494-1504.

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