

## FATAL CONSEQUENCES OF THERAPEUTIC THORACENTESIS IN PATIENTS WITH SYSTEMIC SCLEROSIS

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**ABSTRACT.** Systemic sclerosis (SSc) is a systemic autoimmune disease, characterized by systemic fibrosis and involvement of visceral organs. Pulmonary complications are common and a leading cause of death. Pleural effusions, however, are rare. Thoracentesis is a common procedure, performed to reveal the cause of pleural effusion or to drain it and relieve dyspnea. Although generally considered a low-risk intervention, complications of thoracentesis can lead to increased morbidity and mortality. We describe three patients with SSc and symptomatic pleural effusion who required thoracentesis. All patients deteriorated shortly after the procedure and died. We assume that patients with SSc are at high-risk to develop complications after thoracentesis, most likely due to the low compliant lungs and the low elastance of the pleura. In this population, thoracentesis should be done with high caution, while measuring the pleural pressure – invasively, or with noninvasive surrogates. Further studies are required to determine mechanisms of the complication. (*Sarcoidosis Vasc Diffuse Lung Dis* 2020; 37 (3): e2020006)

**KEY WORDS:** systemic sclerosis, pleural effusion, thoracentesis, pleural pressure monitoring, pulmonary hypertension

### INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune disease of unknown etiology, characterized by microvascular changes of intimal proliferation and dysregulated neoangiogenesis, systemic fibrosis, and involvement of visceral organs, including lungs, heart, gastrointestinal tract and kidneys (1). Pulmonary complications are common and are a leading cause of death (2-3). However, pleural effusions are rare, described in 7% of SSc patients, especially in the context of heart failure secondary to pulmonary

hypertension (4-5). Pleural effusions in patients with SSc have been related to comorbidities, including concurrent infection or malignancy (6-7).

We present a case series of patients with SSc and symptomatic pleural effusion that required thoracentesis. All cases deteriorated shortly following the procedure and had fatal outcomes. Our goal is to raise awareness of thoracentesis as a potentially hazardous procedure among SSc patients.

### CASE SERIES

We describe three patients with diffuse SSc who were under routine follow-up in our department. They developed pleural effusions that contributed to respiratory deterioration, leading to hospital admission. None of the patients had pericardial effusion.

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Patients' characteristics at admission are presented in Table 1. All three had undergone right-sided thoracentesis during hospitalization, while patient no. 2 also required pleurodesis for recurrent, intractable effusion. The patients died shortly after the pleural interventions.

### CASE 1

A 40-year-old male with SSc was admitted due to progressive dyspnea and anasarca. SSc was diagnosed 6 years earlier, when he presented with muscle weakness, Raynaud's phenomenon, sclerodactyly, and positive antinuclear and anti-Scl-70 antibodies. He developed pulmonary arterial hypertension (PAH), progressive interstitial lung disease (ILD), esophageal injury and right heart failure. Regular medications were carvedilol, furosemide, losartan, acetylsalicylic acid, mycophenolate mofetil, esomeprazole and macitentan. He required long-term, ambulatory oxygen therapy.

On admission, the patient was tachypneic, with signs of anasarca including ascites, limbs and abdominal wall edema. Bilateral pleural effusions, greater on the right, were identified on chest X-ray. Echocardiography showed a dilated, akinetic right ventricle due to severe pulmonary hypertension, with preserved left ventricular (LV) function. He was treated with intravenous furosemide and metolazone without significant improvement. A therapeutic thoracentesis was performed to improved dyspnea, with drainage of 1.2 liter from the right hemithorax. A few hours after thoracentesis he developed acute respiratory distress, with CO<sub>2</sub> accumulation and cardiovascular collapse necessitating intubation, mechanical ventilation and vasopressor therapy. After hemodynamic stabilization was achieved, he was treated with continuous intravenous infusion of epoprostanol. A right thoracic drain was inserted for continuous drainage over several days, but the patient continued to deteriorate, with multiorgan failure resulting in death. There were no signs of infection.

**Table 1.** Patients' characteristics

Characteristic	Patient No.		
	1	2	3
Sex	Male	Male	Female
Age at diagnosis, years	34	46	58
Duration of disease, years	6	13	3
Organs involved	Raynaud's Lungs (ILD+PAH) Skin (diffuse) Esophagus Myopathy	Raynaud's Lungs (PAH) Skin (diffuse) Esophagus Heart	Kidneys (SRC) Arthritis Skin (diffuse) Myositis Heart
Pulmonary hypertension	Yes	Yes	No
Pulmonary fibrosis	Yes	No	No
Pericardial effusion	No	No	No
Antibody status	ANA>1:640 fine speckled Anti-Scl-70	ANA>1:1000 fine speckled Anti-Scl-70	ANA>1:1280 Homogenous + nucleolar Anti-Scl-70
Pleural effusion characteristics, fluid/blood (ratio)			
Total protein (g/dL)	3.6/7.4 (0.48)	2.5/7 (0.35)	
Albumin (g/dL)		1.1/3 (0.36)	2.6/3.5 (0.74)
LDH (U/L)	336/532 (0.63)	227/369 (0.62)	313/407 (0.76)
ILD, interstitial lung disease; PAH, pulmonary arterial hypertension; SRC, scleroderma renal crisis; ANA, antinuclear antibodies; LDH, lactic dehydrogenase			

## CASE 2

The patient was diagnosed with SSc at the age of 46, when he presented with Raynaud's phenomenon, which progressed to finger necrosis. He was treated with intravenous iloprost for several years and was positive for ANA and anti-Scl-70 antibodies. Over time, he developed PAH and esophageal injury, and complete AV block that required a pacemaker. He was maintained on iloprost, omeprazole, bosentan, nifedipine, and captopril.

Thirteen years after initial diagnosis, he was admitted with dyspnea related to bilateral pleural effusions, right larger than left, treated with repeated therapeutic thoracenteses of about 1 liter. Due to refractory right pleural effusion, he underwent right thoroscopic pleurodesis under general anesthesia. A day after the procedure the patient deteriorated hemodynamically and developed respiratory distress. Echocardiography showed signs of severe pulmonary hypertension and a failing right ventricle, with preserved LV function. Chest imaging showed bilateral consolidations consistent with pulmonary edema, more pronounced at the right side. The patient refused endotracheal intubation and mechanical ventilation and continued to deteriorate until he succumbed.

## CASE 3

A 61-year-old female with SSc was admitted due to progressive dyspnea. SSc was diagnosed 3 years earlier, when she presented with myositis and arthritis that were treated with tocilizumab. She tested positive for ANA and anti Scl-70 antibodies. Two years later, she developed a scleroderma-related renal crisis, that was treated with high doses of captopril until hemodynamic stabilization was achieved. However, progressive renal failure ultimately required hemodialysis. Cardiac injury resulted in chronic left heart failure. An implantable cardioverter defibrillator (ICD) was installed for secondary prevention after an episode of ventricular tachycardia, a year prior to the current admission.

On admission, the known right pleural effusion was enlarged. At thoracentesis, 1 liter of fluid was drained. Immediately following the procedure, she became unresponsive with hemodynamic and respiratory collapse. Cardiopulmonary resuscitation was

unsuccessful. ICD read did not show arrhythmia. A postmortem examination was declined by her family.

## DISCUSSION

We describe three patients with SSc and clinically significant pleural effusions requiring therapeutic thoracentesis. They had advanced heart failure secondary to SSc complications. One patient had PAH and ILD, the second had PAH, and the third had left heart failure, secondary to a hypertensive scleroderma renal crisis.

Pulmonary complications are a common visceral involvement in SSc and the leading cause of death (2-3). The two most significant forms are ILD and PAH (1). Other less common pulmonary manifestations are aspiration pneumonitis complicated by chronic gastroesophageal reflux, pulmonary hemorrhage, spontaneous pneumothorax and, uncommonly, pleural disease (8). Evidence of ILD can be found in up to 90% of patients with SSc at autopsy and in up to 85% with thin-section, high resolution computed tomography. Clinically significant ILD is less common, developing in 16–43%, and may remain asymptomatic until advanced (1, 9-10). Pulmonary hypertension develops in approximately 15% of patients with SSc, with several possible etiologies, including association with ILD, secondary to left heart disease, PAH, chronic thromboembolic disease, or multifactorial (11).

The prognosis of SSc-associated PAH is worse and treatment response poorer, than in idiopathic PAH. In many patients, it follows a downhill course with development of right heart failure. The median survival of SSc patients with untreated PAH is 1 year (2-3). In light of the poor prognosis of untreated PAH, all SSc patients should be screened for its presence at initial evaluation, and yearly echocardiographic screening for PAH is recommended.

Pleural effusions are a common presentation of heart failure. In connective tissue diseases (CTD), they may result from left heart failure or cor pulmonale mainly secondary to pulmonary hypertension, or may reflect direct pleural involvement by the disease as inflammatory serositis or pleural fibrosis. Previous studies reported higher rates of pleural effusions in patients with PAH associated with CTD, than in patients with idiopathic or familial PAH,

since some effusions might be due to the CTD itself (4), and reported a prevalence of 20-50% in patients with rheumatoid arthritis or systemic lupus erythematosus (6-7, 12). In SSc, however, pleural effusions are uncommon, and data regarding this association is surprisingly scarce. In a study which systematically evaluated patients with SSc for pleural and pericardial effusions, 4/58 had pleural effusion (7%) on chest X-ray (5). Another study compared X-ray findings in patients with "pure" SSc to patients with SSc-overlap syndromes. There were no pleural effusions in any of the 44 cases of "pure" SSc, while there were 3 cases of effusions in the 20 patients with SSc-overlap syndromes (15%) (13). In more contemporary studies using CT of the chest, pleural effusions were identified in 4/40 patients (10%) (10), 5/28 patients (17.9%) (14), and 0/25 patients with SSc (15), but thoracentesis was not required in any case. Thus, the prevalence of pleural effusions in SSc is low, most effusions may be clinically insignificant, and some cases are probably related to comorbidities. Unlike pericardial effusions which are typically exudative reflecting active serositis (16-17), many cases of pleural effusions in SSc are transudates, and arise from heart failure and/or pulmonary hypertension, like in our subjects.

Thoracentesis is performed to reveal the cause of pleural effusion or to drain the effusion and relieve dyspnea. Although generally considered a low-risk intervention, complications, including pneumothorax, bleeding (puncture site bleeding, chest wall hematoma, hemothorax), and re-expansion pulmonary edema (REPE), can lead to increased morbidity, mortality, and healthcare costs (18). The use of ultrasonography to guide pleural procedures has been associated with fewer complications (19).

REPE is a rare complication of thoracentesis (0.01-0.5%) (20-21). It is characterized by the development of hypoxemia and new alveolar infiltrates, usually within several hours after pleural drainage. Symptoms consist of chest discomfort, persistent cough, dyspnea, and may progress to respiratory failure and hemodynamic instability. Management of these patients is supportive; diuresis, steroids, inotropic agents, and continuous positive airway pressure have all been suggested. It is believed that increased hydrostatic forces in the re-expanding lung, as well as direct injury to the alveolar-capillary barrier may contribute to REPE pathogenesis (22).

Older studies have shown that removal of large volumes of fluid are associated with the risk of REPE and cessation of fluid removal after drainage of 1-1.5 liters was advocated. However, current evidence suggests REPE is related to intrapleural pressure, rather than to the volume of fluid removed (20). In some centers, pleural pressure monitoring is available and experts recommend halting further fluid removal if end-expiratory pleural pressure drops below 20cm-H<sub>2</sub>O. Pleural pressure can be directly measured during fluid removal with a manometer. Data suggest that the development of chest discomfort correlates with marked decreases in pleural pressure (23). In their recent study, Ault *et al.* used symptoms, including chest tightness, cough, and pain referred to the upper chest or neck, as a signal to halt fluid removal. This supports the efficacy of monitoring noninvasive, easily obtainable clinical surrogates for excessive negative pleural pressure (24).

Chowdhary *et al.* described REPE after thoracentesis in patients with left heart failure and suggested that the mechanism may be the rapid redistribution of fluid into the pulmonary extravascular space after pleural drainage, in the presence of a non-compliant LV. They postulated that significant fluid shift in the re-expanded lung (due to pulmonary edema) critically reduces the ventricular filling volume with poor LV reserve and leads to rapid cardiovascular collapse (25).

We believe that patients with SSc are prone to develop complications after thoracentesis, especially REPE, most likely due to non-compliant lungs and the low elastance of the pleura. Patients who have advanced heart failure are at high-risk for developing complications. Thoracentesis may also cause excessive vaso-vagal tone, resulting in bradycardia and hypotension that cannot be compensated for in patients with advanced cardiac failure.

## CONCLUSIONS

Pleural effusion is not a rare complication in patients with SSc, especially in patients with advanced heart failure, and should be suspected in patients with respiratory deterioration. We assume that patients with SSc are at high-risk for developing complications post-thoracentesis, due to several possible mechanisms. In this population, therapeutic thora-

centesis should be performed very cautiously, while measuring pleural pressure, either invasively or with noninvasive surrogates. Prospective studies should be conducted to confirm this hypothesis.

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