

**CASE REPORT****Case report of atypical seronegative scleroderma**

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*Department of Geriatric Medicine, Nepean Blue Mountains Hospital, NSW, Australia***Received on: 30 December 2019; Revised on: 20 January 2020; Accepted on: 01 February 2020****ABSTRACT**

Scleroderma is a rare, systemic, and clinically heterogeneous connective tissue disorder associated with anti-Scl70 antibodies and anti-centromere antibodies. We present a case of systemic sclerosis with typical clinical features but negative serology. It is important to consider seronegative scleroderma when patients presented features of scleroderma with multiorgan involvement even in the absence of specific antibodies to allow early diagnosis and regular follow-up.

**Keywords:** Atypical, Scleroderma, Seronegative, Systemic sclerosis**INTRODUCTION**

Scleroderma is a rare, systemic, and clinically heterogeneous connective tissue disorder. It is accompanied by various degrees of tissue fibrosis and chronic inflammatory infiltration in numerous visceral organs, prominent fibroproliferative vasculopathy, and humoral and cellular immune alterations. Virtually, all organs can be affected in scleroderma, particularly lungs, heart, kidneys, and gastrointestinal tract, which are clearly shown in our patient who had pulmonary fibrosis, liver fibrosis, and pericardial effusion probably due to scleroderma.

**Case**

A 73-year-old woman presented with recurrent presyncope, worsening dysphagia, and dyspnea on exertion with general examination highly suggestive of scleroderma in the absence of specific antibodies such as anti-Scl70 antibodies, anti-centromere antibodies, and anti-RNA polymerase III antibodies. Further, investigations

with imaging revealed the involvement of other organs, including the heart, lungs, and gastrointestinal tract.

**Significance**

This case highlights the importance to consider seronegative scleroderma when patients presented features of scleroderma with multiorgan involvement even in the absence of specific antibodies to allow early diagnosis and regular follow-up.

**CASE REPORT**

A 73-year-old Asian woman was admitted to our geriatric department in February 2018 with presyncope on a background of recent hospital admission for small subdural hematoma from fall a month ago, which was treated conservatively. She had been suffering ongoing lightheadedness and loss of balance since her previous admission. She has a background history of pulmonary fibrosis, liver fibrosis, asthma, and GORD. Her regular medications were terbutaline, Symbicort, and pantoprazole. She was previously on prednisone for her pulmonary fibrosis, but prednisone was

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ceased recently. She has never smoked and denies alcohol use.

General examination revealed bilateral pitting edema of lower limbs, skin thickening and tightening over fingers, chest, and mouth with decreased oral aperture, as well as facial telangiectasia. The neurological examination was unremarkable. On further exploration of history, she also reported positive Raynaud's phenomenon and worsening of shortness of breath on exertion. Her BSL was found to be 2.7mmol/L on admission. Her hypoglycemia was treated with an IV 50% dextrose solution in the emergency department.

Blood tests revealed hypokalemia and hyponatremia. Repeated CT brain showed the previously documented subdural hematoma that had nearly completely resolved and no evidence of new intracranial hemorrhage was found. The patient was admitted for monitoring of BSL, correction of electrolytes imbalance, and further investigations for clinical features that were highly suggestive of scleroderma.

During admission, she had further episodes of hypoglycemia that was treated with hypokit and IV dextrose solution. Investigations for causes of recurrent hypoglycemia such as insulinoma and adrenal insufficiency were negative, with C-peptide of 0.61nmol/L and morning serum cortisol of 381. Her hypokalemia resolved with increased oral intake and regular potassium tablets. Further investigations revealed that her hyponatremia was secondary to SIADH. Her serum osmolality was 274, urine sodium was 75 mmol, and urine osmolality was 361. Her SIADH resolved with a fluid restriction of 1.2L daily.

Further investigations to confirm the diagnosis of scleroderma were carried out. Blood tests showed that ANA was positive with a titer of >1:2560 and speckled pattern detected, positive anti-Ro60 antibodies, positive anti-Ro52 antibodies, raised ESR, and gradually lowering of normocytic anemia; but anti-Scl70 antibodies, anti-centromere antibodies, and anti-RNA polymerase III antibodies were negative. Rheumatoid factor, anti-CCP, and anti-RNP antibodies were also negative. The vasculitic screen was unremarkable.

Investigations for hepatic fibrosis found a positive AMA suggesting an autoimmune etiology. The

hepatitis panel was negative, and iron studies were normal.

With respect to her pulmonary fibrosis, a high-resolution computed tomography of her chest found ground-glass opacities and traction bronchiectasis in multiple lobes indicative of predominantly interstitial pneumonitis pattern. It also revealed that a large pericardial effusion and extensive mediastinal lymphadenopathy were found. Transthoracic echocardiogram showed fibrinous pericardial effusion with no signs of cardiac tamponade. Pericardiocentesis was not performed as the effusion was not large enough. CT chest abdomen pelvis with contrast was done and confirmed extensive mediastinal lymphadenopathy. However, no solid organ tumor was found.

The patient was started on 500 µg of colchicine BD. Repeat transthoracic echocardiogram after a week showed that the effusion size was stable. She was discharged home on colchicine.

High-resolution chest computed tomography, axial slices, showing bilateral lower lobe consolidations (right larger than left) on the background of bibasal honeycombing (left more than right), traction bronchiectasis, and ground-glass change in multiple lobes [Figures 1 and 2]. Figure 2 also shows significant large pericardial effusion.

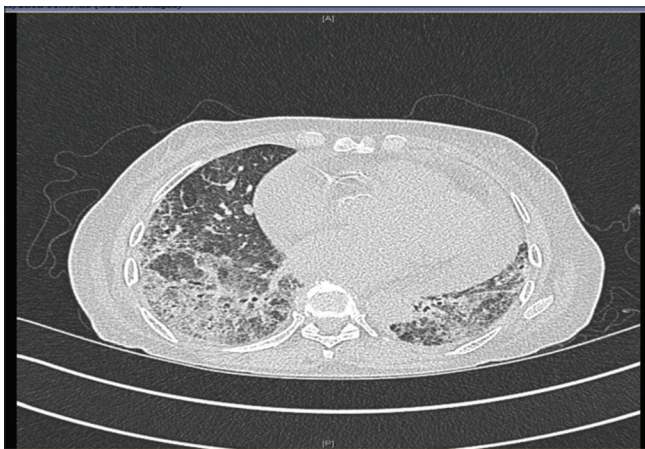
Figures 3 and 4 are transthoracic echocardiogram showing small global pericardial effusion without echocardiographic evidence of cardiac tamponade.

## DISCUSSION

We report a case with clinical features highly suggestive of scleroderma with multiorgan involvement. Scleroderma is a rare, systemic, and clinically heterogeneous connective tissue disorder. It is accompanied by various degrees of tissue fibrosis and chronic inflammatory infiltration in numerous visceral organs, prominent fibroproliferative vasculopathy, and humoral and cellular immune alterations.<sup>[1,2]</sup> Virtually, all organs can be affected in scleroderma, particularly lungs, heart, kidneys, and gastrointestinal tract, which are clearly shown in our patients who had pulmonary fibrosis, liver fibrosis, and pericardial effusion probably due to scleroderma.



**Figure 1:** High resolution CT chest, axial view

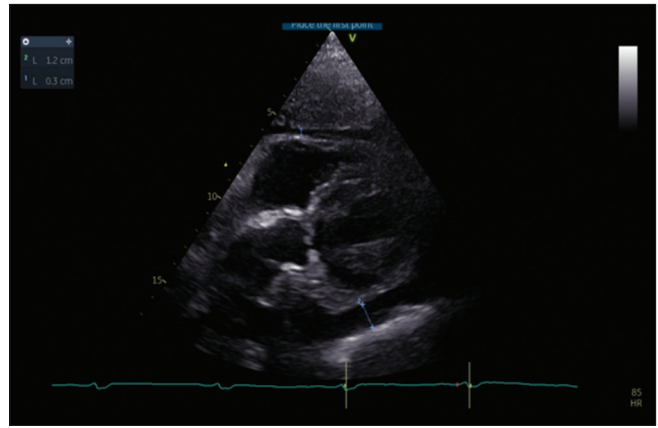


**Figure 2:** High resolution CT chest, axial view

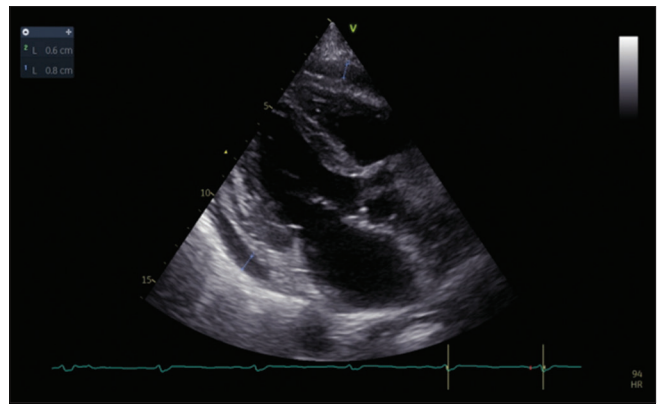
Serum autoantibodies are present in >95% of patients and are helpful biomarkers for establishing an early diagnosis.<sup>[3]</sup> However, the highly specific antibodies, including anti-topoisomerase I (anti-scl-70), anti-centromere antibody, and anti-RNA polymerase III antibody, are not sensitive as these antibodies are negative in 20–50% of reported scleroderma cases.<sup>[4-6]</sup> Anti-RO antibodies that were positive in our case, on the other hand, can often be found in scleroderma patients with a specificity of 50%.<sup>[7,8]</sup>

Studies that look at the clinical relevance of anti-RO antibodies in scleroderma also noted an association between anti-RO antibodies and interstitial lung disease. Anti-RO52 antibodies are independently associated with poor survival in patients with scleroderma in the presence of interstitial lung disease.<sup>[9-12]</sup>

Gastrointestinal involvement, in particularly abnormal esophageal motility, is present in almost



**Figure 3:** Transthoracic echocardiography, subcostal view



**Figure 4:** Transthoracic echocardiography, parasternal long axis

all patients with scleroderma. The decreased oral intake and dysphagia described in our case that contributed to recurrent hypoglycemia are secondary from esophageal dysmotility.

Cardiac involvement is one of the most serious visceral organ complication of scleroderma due to its associated high mortality rate.<sup>[13]</sup> According to the large European league against rheumatism European scleroderma trials and research database, 33 (26%) out of 128 scleroderma-related deaths were of cardiac origin.<sup>[13]</sup>

Cardiac involvement may be due to either the primary sclerosing process of the heart or secondary to involvement from the disease of the lungs or kidneys.<sup>[2]</sup> The manifestation of cardiac complications of scleroderma can involve all structures of the heart and may present in the form of myocardial fibrosis, ischemia, pericarditis, pericardial effusion/tamponade, arrhythmias, and systolic and diastolic dysfunction. Cardiac

involvement is reported in at least 15% of scleroderma patients, but up to 70% of patients were found to have myocardial involvement after autopsy.<sup>[14,15]</sup> Necropsy studies report 33–72% of patients with scleroderma had pericardial involvement, only 7–20% of patients reported symptoms of pericarditis or pericardial effusion.<sup>[16,17]</sup> Pericardial involvement in scleroderma has been described to present with two clinical variants, which are acute pericarditis and chronic pericardial effusion. The presence of pericardial effusion and congestive heart failure has been described to be associated with renal failure in the majority of the patients with scleroderma.<sup>[18]</sup> Although clinical presentations of pericardial involvement in patients with scleroderma can vary from asymptomatic to right-sided heart failure and cardiac tamponade, most pericardial involvement in patients with scleroderma is subclinical. Pericardial effusion can only be detected with an echocardiogram in 41% of patients.<sup>[19]</sup> Pericardial effusion in the majority of patients with scleroderma is small and often happens after manifestations of the other systemic clinical features of scleroderma. Moderate pericardial effusion is the most commonly detected pericardial manifestations in scleroderma patients, whereas large pericardial effusion that usually led to cardiac tamponade is very rare.<sup>[20]</sup> The use of glucocorticoid is avoided in our case due to concern of the scleroderma renal crisis. A retrospective case–control study of 110 patients with scleroderma renal crisis suggested the use of glucocorticoid that was associated with markedly increased risk.<sup>[21]</sup> Multiple studies also suggested that 60% of patients with scleroderma renal crisis have had prior recent exposure to glucocorticoids.

## CONCLUSION

We are describing a case with clinical features that are highly suggestive of scleroderma. Although the initial presenting symptoms are non-specific symptoms with multiorgan involvement, it is important to think of seronegative scleroderma to allow early diagnosis of the disease. Positive ANA and positive anti-RO antibodies are suggestive of scleroderma, even though the highly specific antibodies were negative.

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