CASE REPORT

Systemic sclerosis: severe pulmonary arterial hypertension and pericardial effusion at diagnosis

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SUMMARY

A 51-year-old female patient with a recent hospital admission reported to the emergency room (ER) with progressive worsening of fatigue, dyspnoea and chest discomfort. She had been recently admitted and discharged with the diagnosis of pericarditis and medicated with non-steroidal anti-inflammatory drugs and diuretics. She returned to the ER with persisting symptoms. Echocardiography was repeated and showed signs of elevated right ventricular systolic pressure and a slightly increased moderate/severe pericardial effusion without signs of cardiac tamponade. The patient was admitted and further evaluation confirmed an underlying case of advanced systemic sclerosis with skin, vascular, pulmonary and cardiac involvement. The patient was referred to specialised consults in autoimmune pathology and pulmonary arterial hypertension. She was started on bosentan and corticosteroids, presenting a favourable clinical evolution although symptoms of exertional dyspnoea persist.

BACKGROUND

Systemic sclerosis (SS) is a chronic multisystem autoimmune disease, characterised by excessive fibrosis and vascular endothelial dysfunction, associated with significant mortality, morbidity and impaired quality of life, most frequently affecting women.^{1 2} Cardiac, pulmonary, renal and oesophageal involvement are the most common.³ Vascular manifestations such as Raynaud phenomenon (RP) occur in up to 98% of cases and are usually the first symptom of underlying disease.⁴ Underlying cardiac involvement is frequently underestimated. However, pericardial tamponade or constrictive pericarditis are uncommon.⁵ Pulmonary arterial hypertension (PAH) is a frequent finding, and consequently, all patients with SS should undergo screening.⁶

CASE PRESENTATION

A 51-year-old female smoker with a history of arterial hypertension and depression presented to the Emergency Room (ER) with complaints of fatigue for the past 1 month. She also mentioned a respiratory tract infection characterised by rhinorrhoea, non-productive cough and myalgia, weeks before the present clinical picture. Physical examination revealed high blood pressure (blood pressure 171/116 mm Hg) with peripheral capillary oxygen saturation of 94% and a systolic heart murmur. The ECG showed sinus rhythm, a left anterior fascicular

block, Q waves in lead III and avF and negative T waves in V1–V3. A thoracic CT angiography excluded pulmonary embolism but revealed significant pericardial effusion and pulmonary findings of fibrosis and emphysema. Transthoracic echocardiogram showed a circumferential pericardial effusion (20 mm) without signs of cardiac tamponade and estimated systolic pulmonary artery pressure (SPAP) of 73 mm Hg. The patient was admitted to the cardiology ward where diuretics and non-steroidal anti-inflammatory drugs (NSAIDs) were started. She evolved favourably and was thus discharged with the diagnosis of acute pericarditis.

Ten days later, the patient returned to the ER because of aggravated dyspnoea, fatigue and chest discomfort. Physical examination was similar to previously documented findings. Blood workup excluded elevation of cardiac enzymes or of inflammatory markers and the ECG showed no signs of acute ischaemia. Chest radiograph revealed pulmonary hyperinflation, diffuse bilateral hypotransparency of the inferior lobes and diaphragmatic flattening (figure 1). A transthoracic echocardiogram revealed dilatation of right heart chambers, signs of right-sided overload, large circumferential pericardial effusion (16–22 mm) without associated cardiac tamponade, estimated SPAP of 98 mm Hg and severe tricuspid valve regurgitation.

The patient was admitted for further investigation and treatment. The persistence of severe pericardial effusion in a middle-aged woman despite medication aimed at pericarditis suggested an overlooked alternative aetiology. The patient presented a history of sporadic discolouration of the tips of both hands and feet that worsened on exposure to cold (figure 2). She had previously been discharged from a hospital consult, maintaining follow-up with her family practitioner.

Considering the clinical findings suggestive of RP and severe pulmonary hypertension, the authors suspected an eventual autoimmune disease, namely, SS and systemic erythematous lupus (SLE) as the most probable diagnostic hypotheses.

INVESTIGATIONS

Various diagnostic hypotheses for underlying aetiologies of severe pericardial effusion were considered. To exclude a neoplastic context in an active smoking middle-aged woman, abdominal, pelvic and mammary echographic studies were realised which did not demonstrate pathological findings. Thyroid function tests were normal.

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Figure 1 Chest radiograph at admission revealed an enlarged cardiac silhouette, signs of pulmonary hyperinflation and diaphragmatic flattening, findings suggestive of pericardial effusion and pulmonary emphysema, respectively. Bilateral diffuse hypotransparency was also evident.

A thoracic angio-CT excluded pulmonary embolism and revealed significant bilateral pulmonary fibrosis of the bases (figure 3). Venous Doppler imaging of the inferior extremities excluded deep venous thrombosis.

To adequately characterise the findings of SPAP, right heart catheterisation was realised and confirmed severe PAH with a partial responsive criteria to inhaled nitric oxide (mean pulmonary artery pressure decrease of 40 mm Hg, with an absolute decrease less than 10 mm Hg) and a wedge pressure of 10 mm Hg.

Blood workup revealed a high titre of antinuclear antibodies (ANA) with a nucleolar pattern and mildly positive anti-Ro-52 antibodies. The findings of bronchofibroscopy and bronchoalveolar lavage specimens (direct examination, culture and immunophenotyping) were normal.

Given the presence of significant pericardial effusion without analytical or clinical evidence of pericarditis in a middle-aged woman without apparent underlying neoplastic disease or pulmonary embolism as the cause of pulmonary hypertension, but with interstitial pulmonary disease, vascular alterations suggesting RP and elevated ANA titer, the authors maintained the main hypotheses of autoimmune disease. The patient was submitted to nail-fold capillaroscopy (NFC) that confirmed findings compatible with late-phase scleroderma (figure 4).

TREATMENT

Calcium channel blockers were initiated (diltiazem) and previously prescribed beta blockers were withdrawn considering

Figure 2 Skin thickening, telangiectasia and discolouration of the fingers and toes. Clinical signs of discolouration were more evident on exposure to cold.

Figure 3 Thoracic CT revealed extensive subpleural fibrosis of the pulmonary bases with a posterior predominance and also anteriorly at the mid-level of both lungs. Coexistence of bilateral paraseptal emphysematous findings at the pulmonary apex.

right heart catheterisation findings and the patient's persistently low-normal blood pressure profile. NSAIDs were discontinued due to lack of evidence of pericarditis. Smoking cessation was encouraged.

OUTCOME AND FOLLOW-UP

The patient was discharged and referred to a pulmonary hypertension consult where she was started on the endothelin receptor antagonist bosentan and has maintained regular follow-up with transthoracic echocardiography and 6 min walking tests. Three years later, transthoracic echocardiography demonstrates regular PSAP. Additional follow-up in internal medicine and autoimmune disease consults has been conducted and no additional hospital admissions were necessary since discharge. The patient is currently undergoing treatment with the following medication: bosentan 125 mg twice daily, deflazacorte 6 mg qd, nifedipine 30 mg qd, alprazolam 1 mg qd, venlafaxine 75 mg qd. She remains capable of realising daily life activities with mild exertional dyspnoea and presents more evident skin thickening, namely of the face and extremities.

DISCUSSION

The presented clinical case focuses on a middle-aged woman with two consecutive hospital admissions due to exertional

Figure 4 Images of the patient's nail-fold capillaroscopy. Findings consisted of severely reduced cutaneous transparency, cutaneous thickening and pericapillary oedema, moderately altered capillary architecture with significant loss of organisation, avascular areas with neoangiogenesis phenomena, one of various telangiectasia of the hands corresponding to grand-scale neoangiogenesis and greatly reduced number of capillaries.

dyspnoea in the context of a large pericardial effusion and severe pulmonary arterial hypertension (PAH). The patient's medical history and physical examination suggested a long-standing RP that had previously been diagnosed as a primary case. The clinical context and progressively increased pericardial effusion despite therapy with NSAIDs suggested an overlooked underlying systemic disease.

SS is an autoimmune disease, characterised by vascular alterations and fibrosis of multisystem distribution, with significant associated mortality and morbidity compromising quality of life.^{1,2} Women have a significantly higher risk than men (ratio range 3:1 to 14:1).³ The most frequently affected organs consist of the lungs, heart and digestive tract, with cardiopulmonary complications constituting the main cause of death. Data support the conclusion that vasculopathy is a significant component of the disease's pathophysiology, with consequent tissue injury via mechanisms of ischaemia-reperfusion and the triggering of progressive fibrosis. This fibrosis reduces vessel lumens, provoking a hypoxic effect on affected tissues.²

Pericardial disease is one of the primary causes of cardiac involvement in SS.⁵ Usually clinically silent, pericardial disease can be symptomatic in 5%–16%.⁷ Common identified causes include infections (15%–30%), cancer (10%–25%), iatrogenic (15%–20%) and connective tissue disease (CTD) (5%–15%).⁸ Clinical features of SS other than cardiac disease usually precede the detection of pericardial effusions, especially cutaneous manifestations. Underlying SS should be considered in the differential diagnosis of pericardial effusions of undetermined aetiology.⁵

PAH associated with CTD is quite common, especially in cases of SS, occurring in approximately 10%. In these patients, PAH can be linked to interstitial lung disease or pulmonary vascular disease.^{6,9} The elevated prevalence of PAH encourages active screening in patients with SS. Vasoreactive patients should initiate therapy with calcium-channel blockers.⁹ Various studies suggest that PAH associated with CTD usually responds less to this therapy. However, primary endpoints such as the 6 min walk distance can be influenced by musculoskeletal disease and patients' age.⁶ Pericardial effusion is considered a major poor prognostic factor of SS-PAH.¹

RP is extremely frequent in patients with SS, occurring in up to 98%.⁴ Its importance in SS is highlighted in the 2013 recent classification criteria, distinguishing it as a feature to confirm the diagnosis of scleroderma.¹⁰ The differential diagnosis of RP includes the following: rheumatic disease (SLE, SS, dermatomyositis, Sjogren's syndrome), haematological disorders (cryoglobulins, cold agglutinin, paraneoplastic disorder), hypothyroidism, obstructive vascular disease, carpal tunnel syndrome, frostbite and drug-related disorders. Patients who initially present with suggestive clinical features and progress to secondary disease usually have a CTD, namely SS.¹¹ In fact, RP commonly precedes other clinical features by years, suggesting that peripheral vasculature could be the initial target of SS pathophysiology.⁴

RP is the most important indication for NFC, a non-invasive examination of microcirculation, whose findings related to SS are currently the best described. In fact, the European League Against Rheumatism (EULAR) 2013 criteria have included the SS NFC pattern as a major diagnostic criterion. In more than 95% of patients with SS, microangiopathy exhibits a typical pattern that can classify disease in its 'early', 'active' and 'late' phases.¹² In our patient, NFC confirmed abnormalities compatible with late SS. The NFC's associated high negative predictive value has great clinical importance in the exclusion of SS.¹³ NFC results suggestive of SS can be found in other connective tissue disorders, such as dermatomyositis

and mixed CTD (MCTD).¹² However, given the global clinical picture and the specific NFC findings in our patient, these other possibilities were excluded. Our patient's capillaroscopy was realised by a highly trained rheumatologist dedicated to this diagnostic technique.

Pulmonary hypertension, RP, interstitial lung disease and pericardial effusion could suggest an underlying case of MCTD. However, the absence of anti-nRNP antibodies, the *sine qua non* for the diagnosis of MCTD, excluded this possibility.

Serum autoantibodies are helpful biomarkers both for an early and accurate diagnosis. Highly specific autoantibodies for SS include antitopoisomerase 1, anticentromere, anti-RNA polymerase III. However, various others can be detected, including anti-SS-A (Ro52, Ro60), anti-PM/Scl, anti-Ku, anti-U1-RNP, anti-NOR. Anti-Ro52 antibodies can be found in up to 20% of patients with SS.¹⁴

The American College of Rheumatology/EULAR 2013 classification criteria have incorporated three main features: fibrosis, vasculopathy and autoantibodies. The creation of revised criteria aimed to increase sensitivity for disease definition since the 1980 criteria excluded many patients with SS, namely, early and long-lasting disease and limited or no skin involvement.^{2,15} The presence of classic scleroderma-related antibodies is not obligatory for diagnosis. These criteria should only be applied to patients with a high suspicion of SS.¹⁵

This clinical case report demonstrates a peculiar and severe presentation of scleroderma. Even though the clinical history and presentation provided important clues to the underlying aetiology, diagnosis was delayed and achieved at a late onset.

Learning points

- ▶ Pericardial effusion should encourage the exclusion of underlying systemic disease.
- ▶ Pulmonary arterial hypertension is commonly associated with connective tissue disease and screening should be realised in patients with systemic sclerosis.
- ▶ Raynaud's phenomenon of secondary origin usually precedes other clinical manifestations.
- ▶ Nail-fold capillaroscopy is a non-invasive and safe diagnostic method used to differentiate primary from secondary Raynaud's phenomenon.
- ▶ Capillaroscopy is a recognised systemic sclerosis classification criterion.

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REFERENCES

- 1 Desbois AC, Cacoub P. Systemic sclerosis: an update in 2016. *Autoimmun Rev* 2016;15:417–26.
- 2 Barsotti S, Bellando Randone S, Guiducci S, et al. Systemic sclerosis: a critical digest of the recent literature. *Clin Exp Rheumatol* 2014;32(6 Suppl 86):S194–205.

- 3 Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. *N Engl J Med Overseas Ed* 2009;360:1989–2003.
- 4 Cappelli L, Wigley FM. Management of Raynaud phenomenon and digital ulcers in scleroderma. *Rheum Dis Clin North Am* 2015;41:419–38.
- 5 Lambova S. Cardiac manifestations in systemic sclerosis. *World J Cardiol* 2014;6:993–1005.
- 6 Condliffe R, Howard LS. Connective tissue disease-associated pulmonary arterial hypertension. *F1000Prime Rep* 2015;7:06.
- 7 Champion HC. The heart in scleroderma. *Rheum Dis Clin North Am* 2008;34:181–90.
- 8 Adler Y, Charron P, Imazio M, et al. 2015 ESC guidelines for the diagnosis and management of pericardial diseases. *Eur Heart J* 2015;36:2921–64.
- 9 Galiè N, Humbert M, Vachiery J-L, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2016;37:67–119.
- 10 van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheum* 2013;65:2737–47.
- 11 Wigley FM, Flavahan NA. Raynaud's phenomenon. *N Engl J Med* 2016;375:556–65.
- 12 Chojnowski MM, Felis-Giemza A, Olesińska M. Capillaroscopy – a role in modern rheumatology. *Reumatologia* 2016;54:67–72.
- 13 Bissell LA, Abignano G, Emery P, et al. Absence of scleroderma pattern at nail fold capillaroscopy valuable in the exclusion of scleroderma in unselected patients with Raynaud's phenomenon. *BMC Musculoskelet Disord* 2016;17:342.
- 14 Kayser C, Fritzler MJ. Autoantibodies in systemic sclerosis: unanswered questions. *Front Immunol* 2015;6:167.
- 15 Pope JE, Johnson SR. New classification criteria for systemic sclerosis (Scleroderma). *Rheum Dis Clin North Am* 2015;41:383–98.

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