Diffuse systemic sclerosis with pulmonary involvement and scleroderma renal crisis: report of a rare clinical association

João Matos-Costa*[a], Sofia C. Jorge**[b], José Barbas**[b], M. Martins Prata**[b], Nelson Rodrigues*[a]

Abstract

INTRODUCTION: Systemic sclerosis (SSc), an immunological disorder of unknown etiology, is characterized by progressive localized or diffuse tissue fibrosis.

The diffuse sub-type and prolonged course of the disease are associated with increased risk of visceral involvement, mainly of the lungs and kidneys. Pulmonary hypertension (PHT) and scleroderma renal crisis (SRC) are not mutually exclusive, but are associated in rare cases; however, both are important causes of death in these patients. Mortality in SSs is four times that of the general population, particularly in the first 3-5 years, and the overall survival rate at 15 years is around 50%.

We report a case of this rare association and present a brief review of the pathophysiology and therapeutics.

CASE REPORT: The case is presented of a 56 year-old Caucasian female, diagnosed with SSc 3.5 years previously, treated with vasodilators, oral anticoagulation (due to recurrent deep vein thrombosis) and corticosteroids (she had fibrosing alveolitis, and was previously treated with 13 pulses of cyclophosphamide, with a favorable response).

She was admitted with fever, arterial hypertension, periorbital edema and deterioration in renal function. A bilateral pleural effusion was diagnosed, without alveolitis, and with characteristics of transudation. ANA and anti-Scl-70 were positive, while ANCA and antiphospholipid were negative. The echocardiogram revealed PHT and a pericardial effusion, without hemodynamic compromise. Ultrasound of the kidneys was normal. Edema and blood pressure improved with captopryl; however renal function rapidly worsened with oliguria, so a renal biopsy (RB) was carried out, and the patient began hemodialysis due to uremia and fluid overload. RB histology was typical of SRC. Renal function showed no improvement under dialysis. On the 29th day of hospitalization, patient showed typical signs of pulmonary embolism, and treatment began with IV heparin; later, a cardiorespiratory arrest with asystole ensued, which did not respond to cardiopulmonary resuscitation.

DISCUSSION: SRC is more frequently associated with diffuse SSc and anti-Scl-70. Its hallmark is an abrupt onset of severe arterial hypertension and rapidly progressive renal failure with hyperreninemia.

It may coexist with microangiopathic hemolytic anemia similar to hemolytic-uremic syndrome.

Therapy with angiotensin converting enzyme inhibitors improved survival and prognosis, reducing the need for dialysis, and in some cases, allowing suspension of the renal replacement therapy.

Overlap syndrome/renal vasculitis were considered a possibility, due to polyserositis and recurrent deep venous thromboses. Corticosteroid therapy appears to be associated with the onset of SRC.

There have been reports linking SRC with the onset of PHT in SSc. Some authors believe there is a common pathophysiology, namely, the coexistence of renal and pulmonary thrombotic microangiopathy with myocardial dysfunction.

Key words: scleroderma renal crisis, pulmonary hypertension, hyperreninemia, microangiopathy.

Introduction

SS is an autoimmune disease which is characterized by progressive tissue fibrosis, with extremely variable manifestations.[1,2] The principal manifestation of the disease is Raynaud's phenomenon.[3] Visceral involvement is the result of conjunctive tissue fibrosis and vascular obliteration in the digestive tract, lungs, heart and kidneys.[4]

There is no basic treatment that induces remis-

(a) Medicine Service III, Hospital Distrital de Santarém

(b) Nephrology and Transplantation Service, Hospital de Santa Maria, Lisbon

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sion, and the use of immunosuppressants has shown variable results. Therapy is based on the clinical manifestations and their severity. In order to plan the treatment, it is important to define the clinical subtype and evolution timeline, establish the risk of visceral involvement, and treat these complications. A good understanding of the differences between the natural history of localized and diffuse SSc enables the physician to treat existing problems and anticipate future ones more efficiently.[2,3]

In diffuse SSc, there is rapid emergence of Raynaud's phenomenon and manifestations of early visceral involvement in the first three years, with sclerosis of the organs as early as the first year. Involvement of the internal organs occurs earlier, and with higher frequency, than in the localized type, after which the risk of visceral involvement decreases. While cutaneous sclerosis tends to worsen in the initial years and stabilize or improve later, internal organ lesions seldom decrease, and may even evolve in a small percentage of patients. However, if organ lesions already exist, these can worsen despite the improvement in cutaneous sclerosis. Patients with diffuse SSc have a much more acute onset of systemic disease, and may also have subtle cutaneous involvement.[1,2,3]

Case report

Patient born on 17 January 1949 in Torres Novas, Caucasian, residing in Chamusca, office assistant, divorced. Followed up by the Internal Medicine external consultancy since 27/12/2001, when she was referred for cutaneous sclerosis and Raynaud's phenomenon with rapid evolution in the three previous months. She presented, at that time, skin edema of the face and fingers, periungal ischemia and microstomia, without morphea lesions of the skin tegument. Initially, spirometry (RFT) was normal. She presented positive auto-antibodies ANA, anti-RNP, anti-SSa, anti-SSb, anti-Sm; and negative anti-Scl-70. Capillaroscopy showed rapid movement patterns. Manometry showed the body of the esophagus without peristalsis. It was concluded that she had diffuse systemic sclerosis with cutaneous and esophageal involvement. She was medicated for 12 months, with D-penicillamine.

During 2002, she reported tiredness but with slight alterations in RFT, and chest CT revealed incipient fibrosis. Bronchofibroscopy (BFC) with bronchoalveolar lavage (BAL) confirmed granulocytic alveolitis, and she was medicated with 12 monthly cyclophosphamide pulses (1000mg), terminating at the end of 2003 with clinical and laboratory improvement.

Patient had deep vein thrombosis (DVT) in 2002, and the assay for possible thrombophilia was negative. She was treated with anticoagulant drugs in association with warfarin. Under this treatment regime, but with sub-therapeutic values for INR, she had two more DVTs.

During 2004 she was kept under monitoring, with no clinical or laboratory signs of pulmonary, vascular or interstitial deterioration. She was diagnosed positive for Anti-Scl-70.

In the same year, she showed worsening of the perfusion of the fingers, with skin ulcers, although there was no significant deterioration in the capillaroscopy, and symptomatic improvement was observed with the use of pentoxyphiline alone, without the need for Iloprost. At the end of 2004 worsening of the RFT occurred, after a period of improvement and posterior clinical stability, therefore cyclophosphamide was reintroduced; she received one 500mg pulse of cyclophosphamide, with a quarterly pulse schedule from that date onwards. The peripheral component did not suffer any deterioration, and the echocardiogram (Echo-CG) findings showed only slight tricuspid regurgitation (pulmonary artery systolic blood pressure [PASP] = 31mmHg), with no other alterations.

On 18 February 2005, the patient was medicated with amoxicillin/ clavulanic acid for respiratory infection. Hospital admission was proposed, in order to initiate endovenous antibiotic therapy due to a state of esophagic atonia and probable intestinal involvement of the disease, which raised doubts as to the absorption of the antibiotics. However, the patient refused admission.

On 1 March 2005 she was admitted to the emergency unit due to persistent fever, vomiting, and worsening of clinical condition. The fever and erythrocyturia were treated, and there were no previous renal alterations or hypertension; she was medicated with nifedipine CR 30mg/d, warfarin, pantoprazole 40mg/d, deflazacort 30mg/d, calcium + vitamin D3 and amoxicillin/clavulanic acid 875/125mg bid. She presented some ronchi on auscultation, but no other adventitious breath sounds, slight periorbital edemas; axillary Temp. =38.2ºC, BP=156/97mmHg (values above normal levels), digital hypocratism "again".

Chest X-Ray showed left pleural effusion and an increase in cardiothoracic index (CTI), neither of these symptoms being present on 18 February 2005. Despite the absence of significant laboratory alterations in renal function, (Urea=43.5mg/dL, Creatinine=1.5mg/dL, Hemoglobin=12.2g/dL, Reactive Protein C (RPC)=5.08mg/dL), we decided to admit the patient for monitoring, due to a suspected emerging renal crisis *versus* recurring pulmonary involvement. We also suspected the infectious condition was not being controlled, due to deficient absorption of antibiotics. An echo-CG was carried out in the emergency unit, which revealed good global systolic function (GSF) with no dilatation of cavities and PASP=45mmHg. Renal and vesicular echography did not show any renal alterations or vesicular vegetation. Simple X-Ray of the abdomen, with the patient standing, showed the presence of intraluminal gas without hydroaerial levels.

Patient was immediately medicated with captopryl 6.25mg q6h titrated up to 50mg q8h with subsequent addition of losartan 50mg, maintaining the nifedipine. Microbiological tests were requested (expectoration, blood, urine) and antibiotic therapy was initiated with piperacillin/tazobactam 4.5g q6h + ciprofloxacin 400mg q8h (200mg q8h after 72h) maintaining 25mg/d of prednisolone. A significant improvement in the fever was observed, but which began to worsen again between the 4th and 8th days. From a hemodynamic point of view, she tolerated the increase in captopryl, with improvement of the periorbital edemas. The microbiological tests were negative.

High resolution chest CT revealed the existence of pericardiac effusion and passive atelectasis of the lower lobe of the left lung due to bilateral pleural effusion, without alveolitis, which led us to believe that there was no benefit in carrying out BFC. Thoracentesis and pleural biopsy were carried out. The citrine yellow liquid is a transudate, pH = 8.1, protein = 2.0 mg/dL, glucose = 96.8 mg/dL, LDH = 11UI/L, 660 cells with predominance of lymphocytes, ADA = 7.9UI/L.

Another Echo-CG was carried out, which was similar to that taken on admission, with an increase in facial effusion compared to previous serial studies, but with no sign of hemodynamic impairment.

From the 8th day on, worsening of renal function was observed (Urea=55.7mg/dl, Creatinine=2.3mg/dl) without proteinuria, increase in PCR (7.36mg/dl) and the emergence of anemia (Hemoglobin=9.1g/dl) with no apparent hematic losses.

TABLE I

Results of pending exams on date of transfer

Pleural Biopsy: non-specific inflammatory infiltrate, no neoplasic cells.
Proteinuria of 0.48g/d + microalbuminuria of 155.1mg/d (clearance=12ml/min)
Negative bacteriologies, only C.albicans isolated in expectoration.
Immunological assay with no other findings than those already known: ANA + (1/160, mottled pattern, negative anti-DNA, negative anti-Ssa, negative anti-SSB, negative anti-Sm, positive anti-Scl-70 126 U/ml (N< 40), negative ANCA-PR3, ANCA-MPO and anti-GBM, as well as lupic, anticardiolipin and antiphospholipid anticoagulant.

The case was discussed with the Nephrology Dept., who agreed with the hypothesis of SRC and with the medical treatment prescribed, which should be reassessed if renal biopsy (RB) or hemodialysis (HD) became necessary, should the patient did not respond to medical treatment, with an increase in creatinine and/or reduction in urinary output. It was jointly decided to maintain the corticoid therapy, due to the presence of polyserositis with an increase in PCR, without rejecting the coexistence of overlap syndrome or vasculitis.

On the 15th day (15 March 2005), the patient presented oligoanuria (50cc/h), sediment with proteinuria 1+ and progressive worsening of renal function (Urea=93.2mg/dL, Creatinine=3.24mg/dL); prednisolone 50mg ev q8h was introduced and furosemide was increased from 40mg po/d to 20mg ev q8h, with disappearance of the fever, restoration of diuresis (3300cc/24h) and apparent clinical improvement.

Patient was transferred to the Hospital Santa Maria (HSM) on 17 March 2005 for a RB and possible HD; with the following therapy: hydric balance, protein restricted diet (10.6mg/kg/d), metoclopramide SOS 10mg ev q8h, prednisolone 20mg ev q8h, losartan 50mg id, captopryl 50mg q8h, hydroxyzine 25mg id, domperidone 10mg q8h, pentoxyphiline 400mg q8h, omeprazole 20mg q12h, and nadroparine 0.3cc q12h. She was awaiting the results of the pleural histology, proteinuria and a new immunological assay, which were requested to document any alterations to the previous immunological pattern *(Table I)*.

After suspending the anticoagulation therapy, a percutaneous RB was carried out on day 2 after admission, in the Nephrology Service of the HSM, which occurred without complications. The renal echography and echocardiogram were repeated, with similar results to those carried out at the HDS.

Anticoagulation therapy was reinstituted on 24 March 2005, with enoxaparin given in a prophylactic dose (40 mg sc/day). Treatment with captopryl and losartan was maintained, which controlled the blood pressure, but a progressive deterioration in renal function was observed (increase of urea and Creatinine to 225 mg/dl and 4.8 mg/dl, with potassium of 5.3mEq/L), oliguria (despite diuretic therapy: furosemide 60 mg oral/d). The anticoagulation therapy was suspended, and a venous catheter placed in the right femoral vein, through which urgent dialysis was performed on 25 March 2005, due to hydric overload and uremia. A state of dialysis-dependant renal insufficiency continued. For this reason, right humeral-cephalic arterial-venous fistula was scheduled for 30 March 2005, and the anticoagulation treatment remained suspended.

On 24 March 2005 we obtained the result of the renal biopsy: "a kidney fragment of 8 mm in length (cortex), with a total of 18 glomerulus with ischemic alterations. Slight interstitial fibrosis. Marked intimal mucinoid thickening of the interlobular arteries and arteriole walls, with a marked reduction of lumen. In one of the arteries there was a focus of fibrinoid necrosis, and the presence of fragmented erythrocytes in the wall. Absence of immunofluorescence deposits. The aspects described are compatible with acute renal crisis of scleroderma".

On 30 March 2005, the patient reported an episode of oppressive retrosternal pain, with sudden appearance during rest (at about 4 a.m.), accompanied by dyspnea and tachycardia. Analytically, an increase in LDH (723 UI/L) was observed, with no alteration to the remaining cardiac enzymes; hypoxemia and hypocapnia in the arterial gasometry (pH: 7.356, pCO2: 38.6mmHg, pO2: 71.9mmHg, lactates: 36.3 mg/dL). ECG: sinusal rhythm with 65 ppm, blockage of the right branch and semi-blockage of the anterior left branch, with left electrical axis deviation. The hypothesis of pulmonary thromboembolism was confirmed, with initiation of heparin perfusion (1000 U/h).

About one hour after the start of this treatment, the patient's breathing difficulty worsened, with an episode of supraventricular tachycardia and hypotension; reversion of sinusal rhythm was observed under treatment with amiodarone IV, and correction of hypotension using dopamine. Thoracic Echo-CG was carried out at the patient's bedside, revealing small anterior and posterior pericardiac effusion without hemodynamic impairment, and left ventricle with good global systolic and segmental function. About 2 h after the start of therapy with heparin, a cardio-respiratory arrest in asystole was observed. Patient was submitted to resuscitation maneuvers, which failed, and she died.

Discussion

The clinical case presented illustrates the complexity and difficulties associated with patients with PSS. SRC is one of the extremes of the spectrum of renal involvement in scleroderma, and is frequently associated with anti-Scl-70, an auto-antibody which became positive in this patient about three years after the onset of the first symptoms of the disease. Positivity for anti-Scl-70 should be a warning sign for the risk of SRC, data that identifies a group of patients with a predisposition for renal involvement and a worse prognosis:[1,3] 75% of SRC cases have early onset, during the first three to four years after the initial manifestation of PSS in 10% of all cases of PSS and in 25% of cases of diffuse SSc; [1,4,5] as in our case.

Renal involvement in PSS was first described in 1863, by Aupitz.[4,5] It manifests clinically in 8.3% to 47% of sclerodermas, but its frequency in necroptic studies is around 60% to 80%.[4,6] Slow progression renal disease is rare[5] and the most common characteristic is SRC, of which the case presented here is a dramatic example, with rapidly progressive renal failure (RPRF), arterial hypertension (AHT) and anemia. AHT may be malignant, with encephalopathy/retinopathy, and anemia may be hemolytic microangiopathic; there may also be proteinuria with pathological sediment[3], although this was not observed in the case reported here.

Corticosteroid therapy may be one of the main triggering factors,[3,4,5] as it has a renal vasoconstriction effect which is associated with the reduction in prostacyclin[7], with inhibition of the physiological pathway of the inhibitors angiotensin-converting enzyme (IACE).[5,8] In the case reported here, SRC may also have been triggered by a respiratory infection,

exposure to cold, use of calcium channel blockers, dehydration caused by vomiting, [4,5] and hidden hematic losses related to gastrointestinal malformations with consequent nitrogenated overload.[9] The association is also reported between SRC and the use of non-steroid anti-inflammatory drugs, cyclosporine A, pregnancy, post-partum [4,5] and nephropathy by calcium oxalate crystals due to hyperoxaluria associated with poor intestinal absorption.[10]

According to the literature reviewed, warning signs of SRC include the existence of recent anemia, pericardiac effusion and/or congestive cardiac insufficiency and a history of fibrosing alveolitis.[5,8,11] Anemia is a sign of microangiopathy and SRC, since it is not part of the general scenario of PSS, contrary to what is seen in other auto-immune diseases;[5] it can also precipitate fibrosis myocardial dysfunction by local Raynaud's phenomenon.[1,4] Patients with SRC frequently show alterations in pulmonary microvascularization, and can develop posterior or simultaneous pulmonary arterial hypertension, with the possibility that the common mechanism could be generalized thrombotic microangiopathy.[4,12] Pericardiac effusion is an early sign of volume overload (which can be difficult to notice) which may be associated with myocardial stress, aggravated by the AHT, with consequent cardiac insufficiency, arrhythmias and arrest.[5] Previous existence of fibrosing alveolitis, although associated anti-Scl-70 and a more aggressive stage of the disease, may not be an independent predictive factor for SRC, since it is related to the use of corticosteroids for its treatment.[8,4,13]

The typical histopathology of SRC is the intimal proliferation indistinct of the malignant AHT,[3] and it was first characterized by Moore and Sheenan in 1952.[5] However, AHT appears to be an aggravating factor and a consequence, but not the cause of SRC. The sclerodermic kidney has a lesion chronology: there is local vascular Raynaud's phenomenon with reduction of renal vasodilatation and acellular mucoid intimal infiltration, with a reduction in the vascular lumen; the glomerular lesion is non-specific and may be present in the absence of clinical development,[4,5] differing from that of malign AHT, which shows thrombosis and fibrinoid necrosis. However, in the terminal state corresponding to SRC, the histopathological condition is identical to other thrombotic microangiopathies, and renal biopsy per se is not enough to establish a definitive diagnosis.[4,5,8]

In the case presented here, the rapid onset of RPRF, associated with erythrocyturia, was sufficient for a diagnosis of SRC.[3] The condition may initially involve recurrent vomiting which is often neglected, since these patients also have regurgitation due to the digestive tube involvement caused by the disease,[7] with consequent dehydration which contributes to a worsening of a vicious cycle of renal ischemia and vasoconstriction, with permanent activation of the renine-angiotensin-aldosterone system.[6] Ten percent of SRC cases are normotensive, particularly where was previous corticosteroid therapy,[1,8,14] as in the case reported here. However, thrombocytopenia and hemolysis are normally present, therefore a diagnosis of SRC should be considered,[4,5,7] even when urinary sediment is normal,[3] in patients without AHT, but with higher than normal blood pressure values, and treatment with IACE[1,8] should be initiated immediately.

In the case reported here, we also considered the probability of renal vasculitis ANCA-positive[3,7] or overlap syndrome, as the observed that the patient initially (in 2002) had positive anti-Sm[15] and anti-RNP;[4,8,13] although this was not confirmed later *(Table I)*. Despite its rarity, and the fact that it was previously described with Asian patients,[16] its occurrence has now also been reported among European patients,[17,18,19] and should be excluded when there is a state of fever and polyserositis, due to the treatment implications; this hypothesis led us to maintain corticosteroid therapy, which may have decisively contributed to the SRC. Given the history of fibrosing alveolitis and prior treatment with D-penicillamine, the hypothesis of sclerodermic renal pulmonary syndrome (association of acute renal insufficiency and alveolar hemorrhage) was excluded.[11]

Until 1979, when IACE was introduced to the treatment of SRC, the disease was normally fatal for 90% of patients.[5,12] Nowadays, patients have a five-year survival rate of around 65%. IACE should be started early, before creatinine levels reach 3 mg/dl and even when AHT is not present. Starting the treatment late leads to a worse prognosis, which occurs when the AHT cannot be controlled within 3 days. 55% of patients may continue progressing to RPRF, even when using IACE, and may require hemodialysis (HD). The degradation of the renal function should not be attributed to IACE, since suspending its use never leads to an improvement in renal function, and the

use of IACE should be continued even after the start of HD, as it enables later suspension of HD.[5,20]

The evolution of patients undergoing HD is similar to that of other groups, with identical complication rates.[5,20] The group with earlier death rates has shown higher rates of myocardial, digestive, and pulmonary diseases, infections, and problems related to HD, than those who survive. 70% of patients have vascular access via a central venous catheter, with the rate of access thrombosis being similar to that of other patients undergoing HD.[20] Our patient belonged to this higher mortality group, since she had confirmed pulmonary and digestive diseases; as well as recurring episodes of venous thrombosis. However, the suspension of anticoagulants, on two occasions, was indispensable for carrying out the renal biopsy and placing the central venous catheter for hemodialysis.

Sometimes survivors show recovery of diuresis, when the predominant phenomenon is the renal vasoconstriction and not the thrombosis of glomerules.[4] Recovery of renal function is seen in 50% of patients[20] and occurs mainly in the 18 first months. Patients who recover renal function after HD have a survival rate which is similar to that of patients with PSS who did not develop SRC. After suspension of HD, only 4% of patients present a recurrence of SRC.[20]

Angiotensin-II receptor Antagonists (ARA-II) still do not have a definitive indication of SRC and PSS. Although there is data pointing to the specific role of losartan as an antifibrotic in the modulation of the principal underlying disease,[21,22] these data are still not consistent. Similarly, they should not be used as substitutes for IACE in the prevention of nephropathy or treatment of SRC, where they do not seem to be very efficient in the absence of association with IACE.[5,23] They are associated with higher mortality when used in isolation in SRC, and with higher rates of recurrence of SRC in patients who have undergone transplantation.[6]

Although renal transplant is therapeutic, the worst results are in the first 18 months after SRC,[6,24,25] for which reason it would not be immediately considered in this patient, even had she survived.

Conclusion

SSc is the systemic auto-immune disease with the highest specific mortality rate.[26] Even patients with lower risk deserve the same degree of nephropathy/SRC monitoring, and the same prophylactic measures.[20]

A complete urological and immunological assessment should be carried out, to exclude and treat infections. Although SRC is the most prevalent RPRF in SS, an extensive assessment of the causes that can condition other treatment options should always be carried out, since 20% of cases of SS show overlapping[26] characteristics, regardless of which treatment with IACE should be started immediately.

Careful prophylaxis against thrombotic events is necessary.

The evolution of these patients in dialysis is better than initially expected. [20] The patient's survival appears to depend more on aspects related to the way in which the terminal renal disease is managed, and its common complications in dialysis patients, than to the activity of the principal underlying disease. ■

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