

Systemic sclerosis – metamorphosis of a life

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ABSTRACT

Systemic sclerosis is a complex autoimmune disorder marked by heterogeneous clinical manifestations and variable disease course.

We present the case of a patient with diffuse cutaneous systemic sclerosis with anti-PM/Scl antibodies and associated calcinosis cutis. Currently, there is no uniformly effective therapy for calcinosis, but in the present case study combined therapy (calcium channel blocker, colchicine, bisphosphonate and minocycline) showed a good outcome with significant clinical improvement.

Calcinosis in patients with systemic sclerosis is relatively common and it represents a challenge that requires appropriate management.

Keywords: systemic sclerosis, calcinosis cutis, anti-PM/Scl antibodies, romilkimab, minocycline

INTRODUCTION

Systemic sclerosis (SSc) is a connective tissue disease characterized by immune dysregulation and endothelial cell dysfunction followed by defective vascular repair and neovascularisation resulting in progressive tissue fibrosis of the skin and organs. This complex autoimmune disorder is marked by heterogeneous clinical manifestations and variable disease course (1).

CASE PRESENTATION

We present the case of a 40-year-old female evaluated in the rheumatology department of Saint Mary Clinical Hospital in Bucharest for diffuse cutaneous SSc with articular and pulmonary involvement and associated calcinosis cutis.

The disease onset occurred in 2013 consisting of Raynaud phenomenon followed by digital ulcerations. At that time, antinuclear antibodies (ANA) were positive and a nailfold capillaroscopy was performed. Thus, using the Very Early Diagnosis of SSc (VEDOSS) criteria, the diagnosis of early systemic sclerosis was established and treatment with antiplatelet agent and peripheral vasodilator was initiated.

In the period 2014-2015, the patient interrupts the treatment on her own initiative during pregnancy and lactation.

In August 2015, she was evaluated for the first time in the rheumatology department of Saint Mary Clinical Hospital, presenting polyarthralgia, severe Raynaud's phenomenon, digital ulcers and pitting scars, but also rapidly progressive skin thickening (modified Rodnan skin score - mRSS - 28) associated with small periarticular subcutaneous calcified plaques (elbows, knees). Also, the patient mentioned decreased exercise tolerance.

Several paraclinical investigations were performed: ANA profile-positive anti-PM/Scl antibodies, nailfold capillaroscopy showing active scleroderma pattern (Figure 1), pulmonary function tests (PFTs) revealing moderate restrictive impairment - forced vital capacity (FVC) 67% of predicted with decreased diffusion capacity for carbon monoxide (DLco) - 68% of predicted and a chest computed tomography (CT) showing ground glass opacities (Figure 2). The echocardiography revealed normal left and right ventricle systolic function and low probability of pulmonary hypertension.

Considering the clinical and paraclinical aspects, the diagnosis of diffuse cutaneous SSc (dcSSc) with articular and pulmonary (fibrosing alveolitis) in-

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Article History:

Received: 31 August 2021

Accepted: 4 September 2021



FIGURE 1. Nailfold capillaroscopy: mild loss of capillaries, frequent giant capillaries, frequent capillary hemorrhages, mild disorganization of the capillary architecture



FIGURE 2. Chest Computed Tomography: bilateral ground glass opacities

involvement was established. Given the rapidly progressive skin involvement and the interstitial lung disease (ILD), immunosuppressive therapy with cyclophosphamide (CYC) was initiated (intravenous pulses 800 mg monthly for 6 months followed by 800 mg every 2 months for another 12 months). The patient also received an oral endothelin-1 receptor antagonist - bosentan, an antiplatelet agent and a low dose of glucocorticoids.

Following the administered treatment, the patient had a favorable outcome with a significant improvement of the mRSS, no recurrent digital ulcers and no significant changes in the PFTs (Table 1). So, in 2017 the maintenance treatment was started with azathioprine (AZA) 50 mg daily, but after a four weeks the patient presented elevated transaminase levels that required treatment cessation. After that, maintenance therapy with mycophenolate mofetil (MMF) 1g daily was attempted, but after one week the patient developed acute pyelonephritis and she did not agree to resume treatment afterwards. Six months later, in 2018, PFTs remained constant, but the skin involvement and the subcutaneous calcifications continued to progress (table 1).

Fortunately, a phase IIa clinical trial with romilkimab - an engineered humanised immunoglobulin (Ig) G4 antibody that binds and neutralizes interleukin (IL) 4 and IL-13 - was underway in our rheumatology department. The patient was eligible for the study and after 6 months of treatment, in December 2018, the evolution was favorable: a significant improvement of PFTs and mRSS (table 1).

Considering the favorable evolution, after the end of the study, it is decided to temporarily interrupt immunosuppressive treatment. Thus, at the next evaluation in May 2019, there is a significant increase in both mRSS and the number and size of subcutaneous calcifications.

Between June 2019 and January 2021, due to the pandemic, the patient was not constantly evaluated, but there were numerous attempts to resume therapy with MMF.

Also, taking into account the progression of subcutaneous calcifications, colchicine, bisphosphonate - risedronate and calcium channel blocker (CCB) - diltiazem were added to the treatment.

It is worth mentioning that in November 2020 the patient developed a mild form of Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) infection (myalgias, arthralgias and fever associated with leukopenia with lymphopenia and elevated inflammatory markers levels). Fortunately, the patient did not require hospitalization and she was

TABLE 1. Patient evaluations between 2015 and 2019

	August 2015	February 2016	August 2016	March 2017	November 2017	March 2018	December 2018
FVC % predicted	67%	70%		72%	69%	70%	78%
DLco % predicted	68%	64%		59%	60%	64%	72%
Modified Rodnanskinscore	28	22	16	15	18	22	15
Digital ulcerations	+++	-	-	-	-	-	-
Calcifications	+	+	+	++	++	++	++



FIGURE 3. Sclerodactyly and pitting scars



FIGURE 4. Areas of skin hyperpigmentation and hypopigmentation (salt-and-pepper appearance)



FIGURE 5. Calcified subcutaneous plaques

treated with antipyretics, antiplatelet agent and azithromycin.

In January 2021, the patient was hospitalized for an extensive evaluation. Clinical examination revealed sclerodactyly, pitting scars, but no digital ulcers (Figure 3), areas of skin hyperpigmentation and



FIGURE 6. Knee ultrasound - periarticular hyperechoic deposits that produce an acoustic shadow



FIGURE 7. Periarticular calcification with numerous areas of skin fistulization

hypopigmentation (salt-and-pepper appearance) (Figure 4), large subcutaneous calcified plaques in the right prepatellar area and in the right elbow extension area (Figure 5). The mRSS was 15. The PFTs remained stationary.

The knee ultrasound showed periarticular hyperechoic deposits that produce an acoustic shadow—suggestive aspect for periarticular calcifications (Figure 6).

In April 2021, the patient had a swollen knee with impaired function and significant local inflammation with numerous areas of skin fistulization with chalky, yellow discharge (Figure 7).

Blood tests revealed significantly increased inflammatory markers and *Staphylococcus aureus* was detected in the cultures from the suppurative lesion.

A knee radiograph was performed showing large prepatellar calcifications with infrapatellar and suprapatellar extension (Figure 8).

Also, a magnetic resonance imaging (MRI) scan was performed describing a diffusely delimited



FIGURE 8. Knee radiography – large prepatellar calcifications with infrapatellar and suprapatellar extension



FIGURE 9. Knee MRI – diffusely delimited plaque in the subcutaneous adipose tissue consisting of a central liquid component and a peripheral component with tissue edema and hemorrhage

plaque by a central liquid component and a peripheral component consisting of tissue edema and hemorrhage localized in the subcutaneous adipose tissue (Figure 9).

Antibiotic therapy was initiated – intravenous ciprofloxacin 2 weeks followed by oral cefuroxime for another 2 weeks. Treatment for calcinosis also included minocycline for 8 weeks, colchicine, diltiazem and ibandronic acid instead of risedronate. The patient continued treatment with mycophenolate mofetil, antiplatelet agent and bosentan.

Three months later, there was a significant clinical improvement (Figure 10) and both the elbow and knee calcifications decreased in size.

DISCUSSIONS

This case has many particularities: a patient with dcSSc and negative SSc-specific autoantibodies with positive anti PM/Scl antibodies associated with large subcutaneous calcifications, rapidly progressive dis-



FIGURE 10. Prepatellar calcification after three months of treatment

ease in the postpartum and participation in a clinical study with romilkimab with favorable outcome. Also, a considerable aspect is the mild SARS-CoV-2 infection in a patient with pre-existing ILD.

In the present case, a postpartum worsening of disease with rapid and significant progression of skin involvement was noticed. The consensus of several studies is that, generally, pregnancy does not impact on SSc course (2,3,5). A prospective study including 59 women showed that the disease was stable during pregnancy in 60% of them and 20% noted improvement, particularly of Raynaud's phenomenon (4). Most women did not experience worsening of symptoms after delivery. However, 33% of patients reported an increase in the severity of some symptoms: Raynaud's phenomenon, arthritis, skin thickening (4) – similar to our patient.

A recent study that included 110 pregnant patients revealed that SSc pregnancies have generally a favorable outcome despite a higher risk of gestational hypertension, pre-eclampsia, fetal growth restriction, prematurity and delivery of small for gestational age newborns (5). Our patient had a good gestational and neonatal outcome without any complications.

Autoantibodies, markers of immune dysregulation, are detected in >90% of patients with SSc. Anti-topoisomerase antibodies, anticentromere antibodies and anti-RNA polymerase antibodies, first described in the 1970–1990s, are the classical disease-specific antibodies and may be relevant to the different clinical manifestations of SSc, such as dif-

fuse/limited cutaneous subtypes and ILD (6). However, our patient had negative SSc-specific antibodies and positive anti-PM/Scl antibodies. These are anti-nucleolar antibodies against components of the exosome, known also as the polymyositis/scleroderma (PM/Scl) complex (7). They are found in various systemic autoimmune diseases such as polymyositis, dermatomyositis, SSc and more frequently in overlap syndromes. According to literature they are detected in about 2% of patients with SSc (8). A recently published article presenting results from the EUSTAR cohort described the phenotype of SSc patients with positive anti-PM/Scl antibodies consisting of muscle involvement, cutaneous dermatomyositis, calcinosis and ILD characterized by a good functional outcome. Scleroderma renal crisis and malignancies do not seem to be part of this clinical subset (9). Consistent with the phenotype described in this study, our patient had ILD with persistent satisfactory PFTs and calcinosis cutis.

Calcinosis in SSc is present in one quarter of patients with long-standing disease. Small studies have related SSc-calcinosis with several disease features: male gender, digital ulcers, acro-osteolysis, telangiectasias, anti-centromer antibodies and anti-PM/Scl antibodies (10). A cohort study revealed a strong association of calcinosis with osteoporosis (11).

The pathophysiology of calcinosis cutis is not fully understood, but there are two mechanisms of calcification in soft tissues: metastatic and dystrophic calcification – the latter being the most common presentation of calcinosis occurring in association with SSc. Chronic inflammation and ischemia seem to play a role in the tissue damage resulting in deposition of calcified material (10).

There are no specific recommendations for the treatment of SSc-calcinosis. General measures include improvement of blood flow to the extremities - avoiding trauma, smoking and cold exposure and the medical treatment of Raynaud phenomenon and digital ulcerations. Also, a very important aspect is the supportive therapy consisting of pain and anti-inflammatory medication, treatment of infection and wound care. Appropriate empirical treatment of a superinfected lesion should cover streptococci and staphylococci. If the lesion becomes ulcerated, the area should be cleaned with hydrogen peroxide 3% and a polyurethane hydrocolloid film should be applied as a barrier against bacteria and further injury (10).

The pharmacologic agents used in the treatment of calcinosis cutis have not received regulatory approval as the majority of evidence comes from case reports or small open-balel studies (10).

In our patient we opted for combined therapy – CCB, bisphosphonate, colchicine and minocycline.

CCB reduce the intracellular calcium influx in the tissues and macrophages. The most frequently CCB used for the treatment of calcinosis is diltiazem (12). Several case reports have shown favorable results with diltiazem from 240 to 480 mg/day for 1 to 12 years for SSc-calcinosis (10).

Bisphosphonates may be effective in reversing the calcification process by reducing the calcium turnover and the production of proinflammatory cytokines. Several reports regarding the effect of bisphosphonates on calcinosis have been published revealing conflicting results - some case reports showed functional improvement and partial regression of lesions and other showed little success with clinical and radiologic progression of calcinosis (10).

Warfarin inhibits the production of gamma-carboxyglutamic acid, which has calcium-binding properties, and has been found to be increased in patients with calcinosis. However, the efficacy of warfarin in calcinosis remains unclear (10).

Minocycline has anti-inflammatory and calcium-binding properties. A study including 9 patients with SSc-calcinosis showed promising results with a reduction in inflammation and ulceration associated with calcinosis, but also a decrease in the size of the deposits. These results are consistent with the favorable evolution of our patient. The authors recommend cyclic long-term use of minocycline (13).

Colchicine seems to be more effective in reducing the inflammation associated with calcinosis than the size of the deposits (12). Some authors propose colchicine as a second choice for calcinosis treatment after CCB (10).

There are several case reports that revealed mixed results on the efficacy of other pharmacological agents: ceftriaxone, probenecid and aluminum hydroxide (10).

Rituximab may be a promising therapy for calcinosis in patients with SSc. A case series reported that three out of six patients with SSc-calcinosis had clinical improvement as early as 6 months after the first cycle (14). Other biologic agents - tumor necrosis factor α inhibitor infliximab and abatacept - showed mixed results (15).

In some cases, interventional procedures like extracorporeal shock wave lithotripsy or surgical excision maybe useful (10).

Regarding SARS-CoV-2 infection, our patient had mild-moderate disease with favorable evolution despite pre-existing ILD. In a recent study including 59 patients with SSc, course of COVID-19 was mild-moderate in 65% of them and severe course was observed in 35%. The mortality rate was 20%. Among the deceased patients, only one patient with SSc had not had ILD and more than half had been treated with rituximab (16).

It is worth mentioning the favorable evolution that the patient had after treatment with romilkimab regarding both skin and lung involvement - improvement of PFTs and decreased mRSS. Romilkimab is a humanised, bispecific IgG4 antibody that binds and neutralizes IL-4/IL-13. The patient was included in a phase IIa study which evaluated the efficacy of romilkimab in early dcSSc. The primary endpoint of the study was met - romilkimab resulted in a statistically significant decrease in mRSS versus placebo. The secondary outcomes regarding improvement of FVC and DLco were not achieved, although romilkimab was associated with a smaller decline in FVC than placebo (17).

Conflict of interest: none declared

Financial support: none declared

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CONCLUSIONS

Systemic sclerosis is a complex, multifaceted autoimmune disease characterized by extensive patient-to-patient variability. Calcinosis cutis is frequently encountered in patients with SSc and may be associated with both functional impairment and complications such as ulceration and superinfection. Concerning treatment, no medication has shown an unequivocal beneficial effect.

For the clinician, the striking heterogeneity of clinical presentation, natural history, complications and medication responsiveness in SSc means that it remains as challenging to manage as it is fascinating to study.