SYSTEMIC SCLEROSIS, A RARE CASE

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Abstract

Systemic sclerosis (SS) is a rare severe autoimmune disease involving the connective tissue. The pathophysiology is not clearly understood. It is characterized by a remarkable clinical heterogeneity, and virtually all organs can be affected. Concerning diagnosis, the presence of antinuclear antibodies (ANA) can be found in more than 90% of patients, but the diagnosis is made gathering clinical manifestations, autoimmune panel, nailfold capillaroscopy and in some cases biopsy of the organ involved. The disease course is also weakly understood, although some serological patterns can be distinguished. Current therapeutic options target few aspects of pathologic mechanism and clinical management remains a challenge.

The authors presented a rare case of a SS ANA negative, which demonstrates the diagnostic challenge of this disease.

Keywords: Systemic sclerosis; Antinuclear Antibodies; Myopericarditis.

Introdution

Systemic sclerosis is a rare, severe autoimmune disease involving the connective tissue of the skin and internal organs[1].

The pathophysiology is not totally understood, although it seems that there are abnormalities in at least three types of cells: fibroblasts, cells of the immune system (T and B lymphocytes) and endothelial cells[2]. The disease hallmark is an overproduction and accumulation of collagen and other extracellular matrix proteins, resulting in thickening of skin and fibrosis of affected organs (gastrointestinal tract, lung, heart and kidney)[3]. Reflecting current concepts, on a given heterogeneous genetic background (involving, in particular, genes of immune system and the connective tissue), one or several unknown factors induce an inflammatory response, which spreads and induces an activation of the immune and vascular system. Profibrotic signals cooperatively activate fibroblasts of the affected tissues, which under repeated hypoxic stress and the influence of fibrogenic mediators lose their original organ-derived phenotype and transdifferentiate in the direction of a bone/cartilage like differentiation. Increased deposition of altered proteins contributes to perpetuation of the hypoxic state[3].

SS is a rare disease and epidemiologic data varies greatly according to geographic location and disease definition[4], with estimated annual prevalence between 3 and 24 per 100000 inhabitants, higher in North America and Australia compared to Europe and Japan[1]. SS occurs more frequently in women than men (4:1), although this ratio is more pronounced in younger patients than in patients over 50 years[4]. The type of SS, as well as autoantibodies markers varies by geographic region and racial group, giving a strong indication that host and environmental factors (exposure to silica, organic solvents and heavy metals) play a role in pathogenesis and expression[1,4,5].

The ten-year cumulative survival has improved significantly from 54% in the 1970s to over 70% in the 2000s, and pulmonary fibrosis and pulmonary arterial hypertension are the two main causes of death[1]. Concerning the risk factors which influence mortality, diffuse cutaneous form, cardiac, pulmonary or renal involvements are considered independent risk factors[1].

Case Report

Female patient, 39 years old, working in frozen-food industry, with familiar history of rheumatoid arthritis (sister), who initiated 3 months before cutaneous thickness, digital edema with Raynaud s

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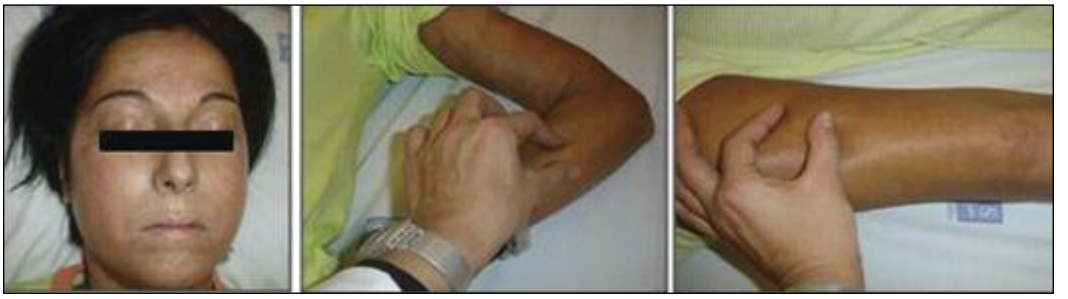

Figure 1. Skin thickness: face and limbs.

phenomena, complicated by digital ulcer of the third finger of her right hand (aggravated by her job). She also referred symmetrical inflammatory polyarthralgias, namely in the wrists, hands, knees and ankles. At physical examination, she had diffuse cutaneous thickness (Figure 1) in the face, trunk and on upper and lower limbs (both proximal and distal); there was no sign of active arthritis and a scar was observed in third finger (right hand). In initial study there was no evidence of systemic inflammatory syndrome and the immunological study [namely ANA by enzyme immunoassay (EIA), anti-Scl 70, anti-centromere, anti-Jo, anti-dsDNA] was negative. The chest X-ray was normal, but pulmonary function tests showed reduced diffusing capacity for CO (78% of predicted DLCO). The high resolution CT scan was normal. The nailfold capillaroscopy was inconclusive due to severe Raynaud s phenomena in all fingers (granular flow and one enlarged capillary). Concluding, this patient had a suggestive clinical picture of systemic sclerosis, without characteristic serologic or capillaroscopic markers, and so without a clear diagnose. She maintained in follow up, with symptomatic treatment (namely calcium channel antagonist, acetylsalicylic acid and physical precautions).

About 10 months later, she started with fever (maximum 38°C) and non-productive cough during 48h and was treated with acetaminophen. This auto-limited clinical presentation evoluted with progressive dyspnea, orthopnea and generalized oedema. She was admitted in the Emergency Department with acute heart failure (HF) presenting ansarca, increased jugular venous pressure, hypotension, pulmonary sounds suggesting bilateral pleural effusion and pulmonary congestion, and digital ischemia signs (Figure 2). In complementary exams we found: elevation of specific myocardial biomarkers as well as elevated liver enzymes; low-voltage QRS complexes in EKG (the previous was normal); echocardiogram showed concentrically hypertrophy of left ventricle with infiltrative aspect of epicardium, pericardial effusion with thickness of visceral layer, as well as severe decrease function, no signs suggesting pulmonary hypertension; and, chest CT reveled bilateral pleural effusion, discrete hepatomegaly (congestive aspect), no signs of pulmonary hypertension or embolism. The patient progressed to cardiogenic shock, with multiorgan failure. The presence of acute left HF without pulmonary hypertension in a female patient with cutaneous thickness but no serologic autoimmune abnormalities was a diagnostic challenge. Two hypothesis were considered: infectious cardiac disease and cardiac involvement by autoimmune seronegative disease. In fact, the analytic study for main agents associated with myopericarditis (Table I) was negative, as well as new immunological study (Table II). Aggressive measures were taken, covering both hypothesis: steroids (1mg/kg/day of prednisone, associated with renin-angiotensin-aldosterone inhibitor for renal protection), hypocoagulation and HF therapeutic including dobutamine. Forty-eight hours later, there was sustained clinical improvement with complete resolution of HF signs. All echocardiographic changes disappeared within

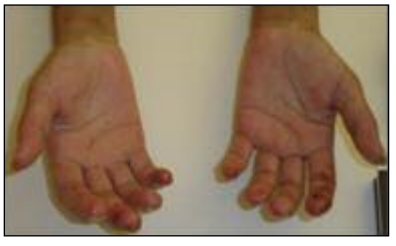

Figure 2. Skin thickness and digital ischemia, suggesting vasculopathy

Table I. Virology study

Human immunodeficiency virus	negative
Hepatitis C virus	negative
Hepatitis B virus	negative
Adenovírus IgM	negative
Adenovírus IgG	weak positive
Echovírus	negative
Parvovírus B19	negative
Coxsackievirus A	negative
Coxsackievirus B IgM	negative
Coxsackievirus B IgG	weak positive

Table II. Immunologic study

ANA (U/mL)	negative
Anti-ds DNA Ab (U/mL)	negative
Anti RNP Ab (U/mL)	negative
Anti SCL 70 Ab (U/mL)	negative
Anti Centromere Ab (U/mL)	negative
Anti Jo Ab (U/mL)	negative
Anti- β2glycoprotein Ab IgG/IgM	negative
Anti-Cardiolipin Ab (U/mL)	negative
Immunoglobulinne (A,D,G,M)	normal

the first month, so to clarify cardiac involvement a MRI was performed and did not show abnormalities in myocardial structure. The diagnosis accepted was probable myopericarditis in a patient with suspected SS, and she was discharged with steroid therapy (at decreasing doses) and treatment for Raynaud s phenomena. Concerning digital ischemic signs, low molecular weight heparin in therapeutic dose was continued until full recovery. In outpatient clinic, a skin biopsy (Figure 3) was performed, which confirmed the systemic sclerosis diagnose. All HF therapeutic approach was suspended without symptomatic complains, as well as hypocoagulation.

After steroid suspension, she developed joint complaints with functional disability and methotrexate was initiated. There was a clear improvement regarding joint complaints and also ameliorated skin thickness, including limbs, trunk and face (Figure 4). To demonstrate the improvement during treatment the 17 sites Modified Rodnan Skin test was preformed, with a total score of 45 (out of 51) in admission to an up to date present total score of 31 (out of 51). During one year follow up, the immunological study was once again negative, the gastrointestinal study was normal, there was normalization of DLCO and the echocardiogram was normal. Repeated nailfold capillaroscopy revealed an early sclerodermic pattern. Currently, she maintains outclinic follow up, with symptomatic therapy for Raynaud s phenomena (calcium blocker antagonists, anti-oxidants and transdermal nitrates), methotrexate (20mg/week) and antiplatelet therapy.

Discussion

Systemic sclerosis is characterized by a remarkable heterogeneity of the disease course and affected organs in the individual patient[3]. It is usually subclassified as limited or diffuse depending on the extent of skin involvement. The distinction between this two forms varies, although most authorities concur that diffuse SS has truncal and acral involvement, while changes distal to metacarpophalangeal and metatarsophalangeal joints are consistent with limited SS. Typically, patients with

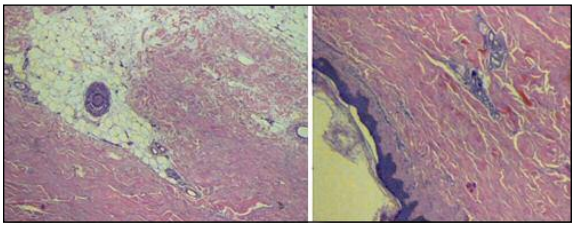

Figure 3. Normal epidermis, dermis markedly thickened by deposition of collagen, markedly sclera-hyaline particularly involving hypodermic adipose tissue. Rare glandular annexes. No vacuities or amyloid deposition

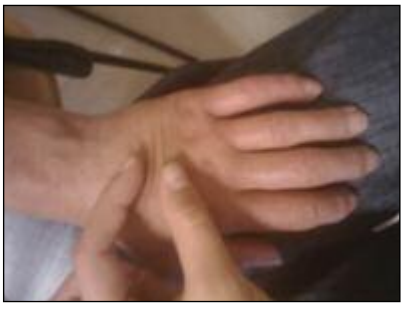

Figure 4. Skin thickness improved after MTX introduction

limited SS have more insidious disease onset, describing Raynaud s phenomenon for some years prior to onset of sclerodactyly. In the diffuse form the skin thickening tends to more closely coincide with the onset of Raynaud s phenomenon and there is a more acute course involving internal organs within 5 years[4]. In this case, the clinical picture was consistent with the diffuse form, as the symptoms evolutes only during one year, first with Raynaud and then cutaneous thickness.

Virtually all organs can be affected. The lung involvement, particularly important in mortality risk, can develop as interstitial lung disease or vascular pulmonary disease (pulmonary hypertension). Although less frequent, with the introduction of angiotensin-converting enzyme inhibitor, the scleroderma renal crisis is still a threat when corticosteroids are used. Gastrointestinal involvement with dysmotility, is frequent and indolent. Cardiac involvement may occur in less than 50% of the patients; the most common cardiac manifestations are those secondary to pulmonary hypertension, but it can include primary cardiac tissue involvement by myocardial fibrosis and contraction band necrosis, which can lead to cardiomyopathy with heart failure as well as varying degrees of heart block or rhythm abnormalities[6]. The heterogeneity plays an extraordinary challenge to the diagnostic and management of these patients. This case is an example. When the patient was admitted, there was no doubt about skin, digital vasculophathy and joint involvement. The issue was on cardiac versus pulmonary involvement. In this case, there was a life threatening situation which justifies the clinical options covering all diagnostic hypothesis.

Concerning diagnosis, the presence of ANA can be found in more than 90% of patients[4,6,7,8]. Anti-centromere antibodies (ACA) and anti-topoisomerase I antibodies (anti-topo I, formerly Scl-70) are the classic autoantibodies associated with SS. ACA are associated with limited SS involvement and isolated pulmonary hypertension as well as a favorable prognosis. Anti-topo I are associated with diffuse skin involvement and pulmonary fibrosis, correlated with a poor prognosis and SS-related mortality. Additionally, anti-RNA polymerase antibodies are associated with diffuse cutaneous disease and renal involvement. Anti-nucleolar antibodies define multiple subgroups of patients with SS, and of these, anti-Th/To antibodies and anti-PM-Scl antibodies are associated with limited cutaneous SS, whereas anti-U3RNP antibodies are associated with diffuse cutaneous SS. In addition, anti-Th/To and anti-U3RNP can be predictors for a less favorable prognosis. Other autoantibodies are less frequently reported: anti-Ku antibodies, anti-U1RNP antibodies, anti-human upstream-binding factor, and anti-U11/U12 antibodies[7]. Although a battery of laboratory tests are available for ANA detection, indirect immunofluorescence antinuclear antibody test (IF-ANA) and EIA/enzyme linked immunosorbent assay (ELISA) are commonly used in day-to-day practice. IF-ANA, with high sensitivity and specificity, detects ANA by adhere to reagent test cells (substrate), forming distinct fluorescence patterns that are associated with certain autoimmune diseases (reporting three parameters: pattern of fluorescence, substrate used and the titer of a positive test). There are two types of EIA or ELISA methods currently used for ANA testing (one called generic assay which detects ANA of broad specificity similar to IF-ANA and other is antigen specific assay that detects ANA and reacts with a single autoantigen); these tests, both highly specific and sensitive, became the most widely used method not only for routine screening but also for detection of specific ANA[12]. The method used in this case report was EIA, with a sensitivity and specificity estimated by the manufacturer of 96%.

Nailfold video-capillaroscopy (NVC) shows a variety of morphological changes, including enlarged capillaries, bushy capillary formations, microhaemorrhages and a variable loss of capillaries with or without avascular areas[6]. The diagnosis is made gathering clinical manifestation, autoimmune panel, NVC, and in some cases, biopsy of the organ involved. SS differential diagnosis was based on the exclusion of diseases showing similar changes namely: physical trauma, chemical exposure (vinyl chrolide, silica, organic solvents), drugs (arsenic, toxic oil syndrome, bleomicin), other autoimmune diseases (cryoglobulinemia, lupus, rheumatoid arthritis), eosinophilic syndromes (eosinophilic fasciitis, eosinophilia myalgia syndrome), metabolic disorders (scleromyxedema, diabetes related scleroderma, paraproteinemias and amyloidosis) or paraneoplasic syndromes[5,6]. This clinical case belongs to the rare group of patients without serologic autoimmune markers, namely ANA. This fact became the diagnosis approach more difficult and the skin biopsy the key exam.

Several treatments have been proposed over the past decades, and so far, no single effective SS treat-

ment exists[9]. Mehtotrexate, cyclophosphamide, calcium channel blockers, angiotensin converting enzyme inhibitors, prostacyclin analogues, D-penicillamine are the most widely study treatments[9]. The European League Against Rheumatism guidelines recommend assessing the patient for organ systems involved and, on this basis, suggest using cyclophosphamide for lung disease and either cyclophosphamide or methotrexate for skin disease[10,11]. More recently, the approach with endothelin receptor antagonists and phosphodiesterase-5 inhibitors for pulmonary arterial hypertension and peripherical vascular disease was introduced. Waiting for solid data are stem cell transplantation, intravenous gamma globulins, mycophenolate mophetil, fluoxetine, pirfenidone, relaxin, halofunginone, anti-TNF antibodies and tyrosine kinase inhibitors. Current therapeutic options target few aspects of pathologic mechanism, but clinical management remains a challenge[9]. In this clinical case, MTX was started with very good results particularly in skin thickness, joint complains and pulmonary changes.

Conclusion

Diffuse systemic sclerosis is a rare disease. Serum negative ANA is even a more rare case. This clinical case is part of this particular group of patients, and exemplifies the diagnostic challenge as well as treatment management.

Acknowledgments
We thank: Dr. Álvaro Ferreira, Unidade de Cuidados Intermédios, Centro Hospitalar de Entre Douro e Vouga, Unidade de Santa Maria da Feira; Dra. Raquel Mota Garcia, Serviço de Cardiologia, Centro Hospitalar de Entre Douro e Vouga, Unidade de Santa Maria da Feira; Dra. Isabel Almeida, Unidade de Imunologia Clínica, Hospital de Santo António, Centro Hospitalar do Porto; Dr. António Marinho, Unidade de Imunologia Clínica, Hospital de Santo António, Centro Hospitalar do Porto.

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