

Original article

Systemic sclerosis without antinuclear antibodies or Raynaud's phenomenon: a multicentre study in the prospective EULAR Scleroderma Trials and Research (EUSTAR) database**Daniel Schneeberger¹, Alan Tyndall¹, Jonathan Kay², Klaus H. Søndergaard³, Patricia E. Carreira⁴, Ewa Morgiel⁵, Katrin Deuschle⁶, Chris T. Derk⁷, Malgorzata Widuchowska⁸ and Ulrich A. Walker¹****Abstract****Objective.** To assess patients with SSc who present without circulating ANAs or RP.**Methods.** Five thousand three hundred and ninety patients who fulfilled the ACR criteria for SSc and were enrolled in the EULAR Scleroderma Trials and Research (EUSTAR) database were screened for the absence of both RP and circulating ANA. To differentiate SSc from its mimics, additional information was gathered using a standardized questionnaire.**Results.** Five thousand three hundred and seventy-eight (99.8%) of the 5390 SSc patients in the EUSTAR database had either detectable ANA or a history of RP. Twelve (0.2%) patients lacked both circulating ANA and RP. Details of the medical history could be obtained for seven patients. Three cases were compatible with ANA-negative and RP-negative SSc and were not typical of any known SSc mimic. Four patients had a malignancy: two had breast cancer, one had multiple myeloma with possible scleromyxoedema and one had bladder carcinoma. There was no temporal relationship between the onset of skin fibrosis and that of the tumour. Although no patient with confirmed nephrogenic systemic fibrosis was identified among the cases of ANA-negative and RP-negative SSc, the presentation of one patient could be compatible with that of nephrogenic systemic fibrosis other than for the absence of chronic kidney disease or of known prior gadolinium exposure.**Conclusion.** We have identified a very small subgroup of SSc patients who lack both circulating ANA and RP, none of whom fulfils the diagnostic criteria for any known SSc mimic. Prospective studies are needed to elucidate the clinical presentation, evolution and outcome of such patients.**Key words:** systemic sclerosis, scleroderma, nephrogenic systemic fibrosis, scleromyxoedema, eosinophilic fasciitis, ANA, Raynaud's phenomenon, digital ulcers, differential diagnosis.

¹Department of Rheumatology, Basel University, Felix Platter Spital, Basel, Switzerland, ²Division of Rheumatology, Department of Medicine, University of Massachusetts School of Medicine, Worcester, MA, USA, ³Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, ⁴Servicio de Reumatología, Hospital Universitario 12 de Octubre, Madrid, Spain, ⁵Department of Rheumatology and Internal Medicine, Wrocław Medical University, Wrocław, Poland, ⁶Department of Rheumatology and Clinical Immunology, Charité, Berlin, Germany, ⁷Division of Rheumatology, University of Pennsylvania, Philadelphia, PA, USA and ⁸Department of Internal Medicine and Rheumatology, Medical University of Silesia, Katowice, Poland.

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Correspondence to: Ulrich A. Walker, Department of Rheumatology, Basel University, Felix Platter Spital, Burgfelderstr. 101, 4012 Basel, Switzerland. E-mail: ulrich.walker@fps-basel.ch

Introduction

SSc is an autoimmune disease in which vascular and immunological processes lead to progressive organ fibrosis [1]. Prominent early features of the disease include circulating ANAs as a marker of immunological abnormalities and RP, which often results in digital ulceration, as a sign of vascular dysfunction. Circulating ANAs are detected in more than 90% of SSc cases [2], and the prevalence of RP has been as high as 98% in some studies [3]. There is a single report of a patient with SSc, but without RP or circulating ANA [4]. However, it has not yet been determined whether this individual might epitomize a subgroup

of patients with SSc who lack both RP and circulating ANA.

The presence of cutaneous fibrosis without RP or circulating ANA should always prompt the search for an alternative diagnosis. The differential diagnosis of hardened and thickened skin includes several SSc mimics, among which are nephrogenic systemic fibrosis (NSF), scleromyxoedema, eosinophilic fasciitis, pansclerotic morphea and scleroedema adutorum (of Buschke) [5, 6]. Differentiation among these entities is facilitated by assessment of physical findings, laboratory testing, skin biopsy and nail-fold capillaroscopy (Table 1). Despite these additional investigations, some patients with sclerotic skin may still be misclassified as having SSc, even by expert rheumatologists. This is exemplified by NSF, a newly evolved disease that produces an SSc phenotype [7, 8]. The objective of this study was to assess the prevalence of SSc mimics in a large cohort of patients fulfilling the ACR criteria for SSc [9], but lacking both RP and circulating ANA.

Patients and methods

We conducted this study in the multicentre prospective cohort of the EULAR Scleroderma Trials and Research (EUSTAR) group. The structure of the EUSTAR database has been published [10]. As per EUSTAR requirements, every patient followed in the EUSTAR must have a signed consent form and each centre must have obtained local ethics committee approval. Adult patients registered in the EUSTAR database as of December 2007 and fulfilling the ACR criteria for SSc [9] were analysed. Subjects were included in this subcohort if they never had RP and if they also tested negative for ANA at any of the annual visits. Because none of the scleroderma mimics typically is associated with digital ulcers (DUs), the presence of a DU at any of the annual visits excluded a subject from this subcohort.

Centres that had patients meeting these criteria were invited to complete a standardized questionnaire in which they were asked to confirm the presence of SSc and the absence of RP and ANA, and to provide additional information on clinical details not regularly captured in the EUSTAR database (e.g. the temporal onset of skin changes, the distribution of skin involvement and findings on nail-fold capillaroscopy). In particular, we also tried to identify patients who might have NSF by enquiring about the presence of chronic kidney disease and any exposure to gadolinium-containing contrast agents (GCCAs) in relation to disease onset [7, 11]. Because of the association with scleromyxoedema, we also inquired about paraproteinaemia and the presence of mucin in skin histology (Table 1). The questionnaire also asked about any history of cancer, medical treatment, response to treatment and clinical outcome.

Results

At the date of census in December 2007, 5390 adult patients who met the ACR criteria for SSc were enrolled in EUSTAR. Of these, 5378 (99.8%) patients had either

detectable circulating ANA or a history of RP; 12 (0.2%) of the 5390 patients had neither RP nor ANA. Although we had specified that subjects would be excluded from the subcohort if they had a DU, no patient with the absence of both ANA and RP had any digital ulceration.

Completed questionnaires provided additional medical information about 7 of the 12 patients without either RP or circulating ANA, but no additional information could be obtained from the remaining 5 cases. We were unable to obtain consent from one female patient who was lost to follow-up, therefore her detailed medical data have not been included. Demographic characteristics of the seven patients are presented in Table 2. Eight (66.7%) of the 12 patients without RP or ANA presented with a phenotype compatible with diffuse SSc, as compared with only 38% of the patients in the remaining EUSTAR population. There was a trend towards shorter disease duration and higher modified Rodnan skin score (mRSS) among the patients without RP or ANA, but this was not statistically significant.

Although 5 of the 12 patients without RP or ANA had been lost to follow-up, we were able to obtain limited medical information about them. All had serum creatinine levels within the normal range and none had been diagnosed with chronic kidney disease. Only one of these five patients had undergone a GCCA-enhanced MRI examination. We present the individual cases of the six patients without RP or ANA for whom data were available and consent was provided, and their differential diagnoses are discussed.

Case 1

A 63-year-old white woman had a mastectomy at the age of 47 to treat breast cancer, without subsequent recurrence after local irradiation. At the age of 57, she noticed a small pruritic morphea plaque on the abdomen and visited a dermatologist. Local treatment with a betamethasone was begun. Four months later she developed sclerodactyly, as well as tightness and non-pruritic induration of the forearms and the perioral skin, characteristic of SSc. She had never been exposed to gadolinium or environmental toxins known to cause skin fibrosis, including chemotherapeutic agents [12]. Within 2 months of the onset of skin changes, her mRSS progressed from 15 to 27. She exhibited facial involvement with microstomia, moderate skin thickening on her forearms and hands with sclerodactyly, mild skin thickening on her upper arms and distal thighs and severe skin thickening on her legs and feet. The skin on her hands, distal forearms and feet was oedematous and there was polyarticular joint swelling. She had NYHA (New York Heart Association) stage II dyspnoea due to mild interstitial lung disease with ground glass opacifications and there also was thickening of her oesophageal wall. She had mild peripheral blood eosinophilia (along with mild elevations of other peripheral blood leucocytes, including neutrophils, lymphocytes and monocytes). Nail-fold capillaroscopy was normal (Fig. 1a). Biopsy of the involved abdominal skin demonstrated severe dermal fibrosis, thickened s.c.

TABLE 1 Differential diagnosis of skin fibrosis [5, 25]

Clinical feature	SSc	NSF	Scleromyxoedema	Eosinophilic fasciitis	Scleroedema adultorum (of Buschke)	Generalized morphea
Skin thickening	Yes	Yes (cobblestone)never face	Yes (lichenoid papules)	Yes (woody induration)	Yes (doughy induration)	Yes
Sclerodactyly	Yes	Yes	Yes	No	No	No
Facial involvement	Frequent	No	Typical	Usually spared	Typical	Possible but rare
DUs	Possible	No	No	No	No	No
RP	Almost universal	No	Rarely	No	No	No
ANAs	Yes	No	No	No	No	Possible, but rare
Paraproteinaemia	No	No	83% (mostly IgG λ)	No	Rarely	No
Oesophageal involvement	Yes	No	Yes	No	No	None or subclinical
Lung fibrosis	Yes	Possible	Yes	No	No	None or subclinical
Nail-fold capillaroscopy	Abnormal	Normal	Normal	Normal	Normal	Normal
Cellular skin infiltration	Stage dependent	Sparse inflammatory cells, increased dermal fibroblasts, CD34 ⁺ dermal fibrocytes	Lymphocytic	Eosinophilic	None	Stage dependent
Cutaneous mucin deposit	No	Yes	Yes	No	Yes	No
Special features	Telangiectasia, calcifications	Yellow scleral plaques	Myopathy and neuropathy	Distal extremities spared	Neuropathy (seizures, dementia, coma)	
Clinical associations		Chronic kidney disease, prior gadolinium exposure	Monoclonal gammopathy	Immune-mediated cytopenia, malignancies	Infection, para-proteinaemia, diabetes mellitus	

Table was compiled from Boin et al. [5] and Walker et al. [25].

TABLE 2 Clinical characteristics of the study population

Clinical feature	Negative for all of RP, ANA and DU		Remaining SSc patients (n = 5378), %
	Analysed (n = 7), %	Additional data not retrievable (n = 5), %	
ACR criteria positive	100.0	100.0	100
RP positive	0.0	0.0	96.3
ANA positive	0.0	0.0	92.3
DU positive	0.0	0.0	35.0
Age, mean (s.d.), years	48.8 (12.9)	66.8 (11.3)	57.8 (13.7)
SSc duration, mean (s.d.), months	67.0 (60.5)	76.1 (43.9)	175.1 (133.1)
mRSS, mean (s.d.)	23.8 (9.1)	21.2 (5.2)	11.8 (9.2)
DSSc	71.4	60.0	38.0
LSSc	28.6	40.0	57.5
ACA positive	0.0	0.0	30.4
Scl-70 positive	0.0	0.0	36.4
Elevated acute phase reactants	28.6	80.0	32.4
Proteinuria	14.3	0.0	6.2
Active disease	42.9	20.0	34.0
Synovitis	14.3	0.0	17.0
Joint contractures	71.4	20.0	34.3
Oesophageal involvement	42.9	20.0	68.6
Lung fibrosis (by chest X-ray)	14.3	20.0	22.6
Dyspnoea	14.3	0.0	37.9
Lung fibrosis	28.6	40.0	35.7
Arterial hypertension	14.3	0.0	18.9
Pulmonary hypertension	14.3	40.0	21.6

septae and sparse perivascular lymphocytic inflammation without eosinophils or mucin deposition (Fig. 1b and c).

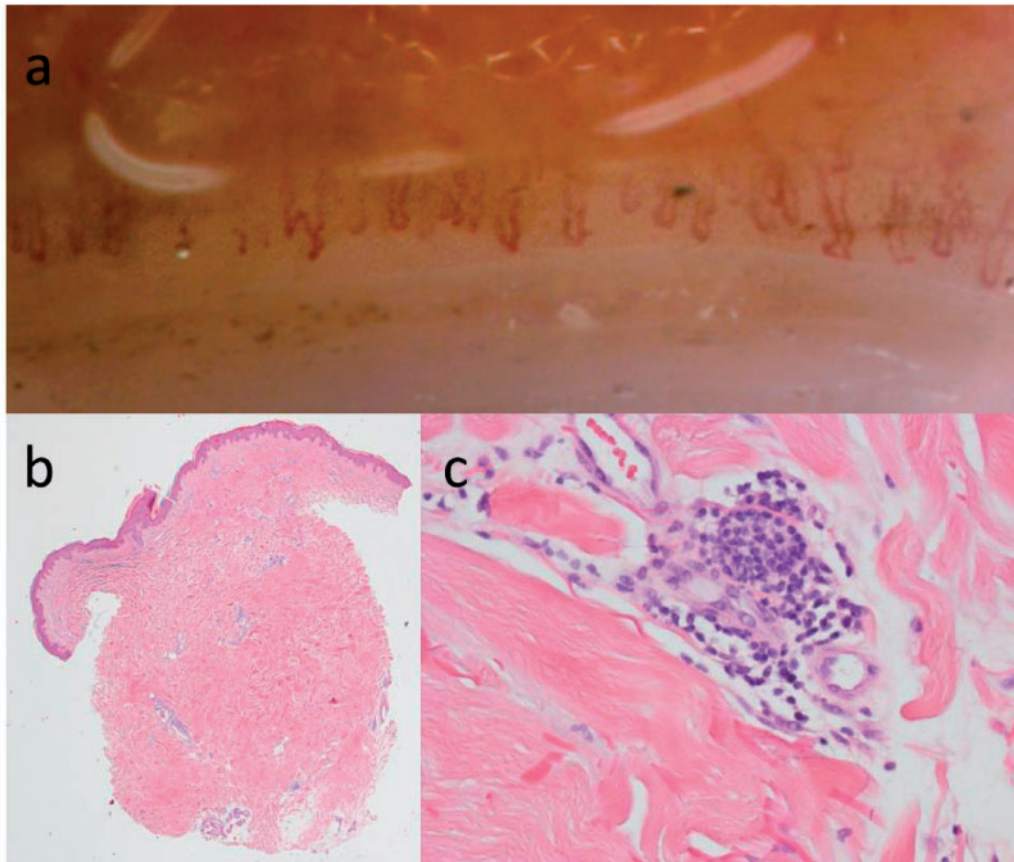
Five months after the onset of skin changes, treatment was initiated with low-dose daily oral prednisolone and monthly i.v. pulses of CYC. With treatment, her mRSS decreased from 27 to 12 and her forced vital capacity (FVC) improved from 80 to 90% of predicted; however, the DL_{CO} (diffusion capacity of the lung for carbon monoxide) remained within normal limits (93%). Prednisolone was tapered and discontinued. Weekly oral MTX treatment was initiated and, 4 years after the onset of skin changes, her mRSS decreased to 3. Her dyspnoea resolved and she was able to dance for hours. Because she experienced arthralgias after each dose, MTX was subsequently tapered and discontinued. Six months after stopping MTX, a relapse of polyarthritis was treated with SSZ and low-dose prednisolone. At age 62 years, her mRSS remained at 3 and the 6-minute walk test (6 MWT) was 558 m without oxygen desaturation. Nail-fold capillaroscopy revealed no scleroderma pattern.

The primary diagnostic considerations in this patient had been eosinophilic fasciitis, a paraneoplastic syndrome and nephrogenic systemic fibrosis. She had peripheral blood eosinophilia; however, the absence of an eosinophilic infiltrate in her skin biopsy and the presence of interstitial lung disease go against a diagnosis of eosinophilic fasciitis. Also, there were no signs of recurrent malignancy. The absence of skin changes on her face and of mucin deposition in her skin biopsy is inconsistent with

scleromyxoedema or scleroedema adutorum. Without prior gadolinium exposure, NSF would be unlikely; however, patients can be unaware of imaging studies during which GCCA is administered. This patient most likely represents a true case of ANA-negative and RP-negative SSc or of another systemic autoimmune disease with SSc overlap [4].

Case 2

A 53-year-old white woman noted the onset of skin thickening on her trunk. She also experienced joint pain and contractures, episodic swelling of her hands and muscle weakness and atrophy. Concurrently with the onset of skin thickening, she observed a tumour in her right breast and underwent a mastectomy for ductal carcinoma. She denied exposure to any toxins. Her skin sclerosis was itchy, symmetrical and involved most parts of her body, but spared her hands and feet (Fig. 2). The skin of the abdomen, thighs and upper arms had a peau d'orange appearance. Over time she developed severe contractions. Her mRSS was 17. Nail-fold capillaroscopy revealed avascular areas. There was no peripheral blood eosinophilia or paraproteinaemia. A skin biopsy from her left forearm showed increased melanin in the stratum germinativum with a discrete diffuse lymphocytic infiltrate in the dermis and extensive collagen fibres without mucin deposition. *Borrelia burgdorferi* infection was excluded by serologic testing.

Fig. 1 Nail-fold capillaroscopy and skin biopsy from case 1.

(a) A representative area from a technically difficult nail-fold capillaroscopy demonstrating the absence of a typical scleroderma pattern in case 1. (b) Haematoxylin and eosin stain of a punch biopsy specimen from the abdominal skin of case 1, showing severe dermal fibrosis and s.c. septae. Dermal capillaries are slightly hypotrophic and the s.c. fat is diminished in the vicinity of the adnexae. (c) A higher magnification reveals a sparse perivascular lymphocytic inflammatory infiltrate without eosinophils.

Three years after the onset of skin thickening she developed pulmonary fibrosis that was treated with daily oral ciclosporin and monthly i.v. pulses of CYC. Although her FVC improved from 41% to 56%, 3 years later she continued to experience dyspnoea. At her most recent visit, 6 years after the onset of skin changes, there had been no recurrence of her breast cancer. This patient's presentation is also compatible with ANA-negative and RP-negative SSc, although a paraneoplastic syndrome must be considered.

Case 3

A 25-year-old white female with a history of palpitations and FM noted thickening of the skin on her face and sclerodactyly and was diagnosed as having limited SSc. No cobblestone or peau d'orange changes were seen. She never developed RP, pulmonary arterial hypertension or pulmonary fibrosis, but she experienced oesophageal reflux and dysphagia. She never suffered from pruritus and denied any exposure to environmental toxins.

Nail-fold capillaroscopy showed an early SSc pattern [13] but, over a period of 7 years, ANA testing has been repeatedly negative. She has had no peripheral blood eosinophilia or paraproteinaemia and had not undergone any GCCA-enhanced MRI studies. A skin biopsy was not performed. Her initial mRSS was 5, at which time treatment with MTX and oral CSs was initiated and continued for the next 2 years. After 7 years of follow-up her skin changes have remained stable. This patient's presentation is also compatible with ANA-negative and RP-negative SSc.

Case 4

A 41-year-old white man experienced the onset of skin thickening with symmetrical involvement of his arms and legs and on his face and trunk. He did not suffer from pruritus and denied toxin exposure. Five years later his mRSS was 31. He exhibited severe flexion contractures of his elbows, but he had normal renal function and reported no prior gadolinium exposure. He experienced

Fig. 2 Symmetrical skin thickening involving all parts of the body, sparing only the hands and feet (case 2).



dysphagia, but he had no pulmonary fibrosis. Neither nail-fold capillaroscopy nor skin biopsy was performed. He had an IgG paraproteinaemia and was diagnosed with multiple myeloma. He was treated with autologous stem cell transplantation. Unfortunately he was subsequently lost to follow-up. The development of cutaneous fibrosis in the setting of paraproteinaemia makes scleromyxoedema the most likely diagnosis.

Case 5

A 51-year-old white woman with a history of urothelial bladder carcinoma, treated exclusively with surgery 4 years earlier, experienced the onset of sclerodactyly and thickening of the skin on her face. Her skin sclerosis progressed rapidly within a few months to also involve her hands, feet, arms, legs and trunk. Her maximum mRSS at that time was 37. On physical examination her skin was thickened, hard to palpation and tightly adhered to deeper tissues. The skin surface was uniform and without peau d'orange or cobblestone appearance. Although she resides in a cold climate, she never experienced RP. She denied pruritus and had no known toxin exposure. Nail-fold capillaroscopy was normal on two occasions. At presentation she had peripheral blood eosinophilia (800/ μ l, 10%) and elevation of her ESR to 37 mm/h.

Biopsy of skin from her forearm revealed no mucin, but suggested eosinophilic fasciitis.

Because of symmetric pain and severe stiffness in her hands, knees and feet that was most pronounced in the morning but not accompanied by joint swelling, she was treated with oral prednisone 10 mg daily, oral MTX up to 20 mg weekly and oral HCQ 400 mg daily. Her joint symptoms improved markedly with medical treatment and her mRSS decreased to 18.

One year later she experienced a relapse of her bladder carcinoma and treatment with MTX, prednisone and HCQ was discontinued. Within 2 months of stopping these medications, her skin sclerosis worsened, at which time her mRSS was 31, and she again experienced arthralgias and morning stiffness. After surgery to treat her recurrent bladder carcinoma, she was treated with oral *D*-Pen 500 mg daily and prednisone therapy was reinitiated. Because she did not note any improvement in her skin or joint symptoms, MTX was restarted 6 months after surgery. Her articular symptoms improved and her mRSS decreased to 15.

Five years after her initial presentation there is still no evidence of visceral involvement. Her mRSS has decreased further to 10 and she experiences only mild arthralgias and morning stiffness. Although some features of this case are compatible with eosinophilic fasciitis [6], the presence of sclerodactyly and facial involvement are

not consistent with that diagnosis. Thus another paraneoplastic syndrome must be considered.

Case 6

A 62-year-old white man with coronary artery disease, hypertension and diabetes mellitus presented with cutaneous non-pruritic sclerosis and mRSS 17. Unfortunately his medical records did not provide a more detailed description of his skin changes or the exact date of onset of his skin changes. There was no history of toxin exposure. He also experienced dysphagia and dyspnoea due to pulmonary fibrosis and pulmonary hypertension. Neither a skin biopsy nor nail-fold capillaroscopy was performed; his specific diagnosis remains unknown. He subsequently was not seen by a rheumatologist and he died 3 years after his initial evaluation for the EUSTAR database. The presence of pulmonary fibrosis and dysphagia are compatible with SSc, but not with either scleromyxoedema or scleroedema adutorum of Buschke, which might be considered in the setting of his diabetes mellitus.

Discussion

In this study, 12 (0.2%) of 5390 patients in the EUSTAR database who fulfilled the ACR criteria for SSc had neither RP nor circulating ANA. Assuming the prevalence of RP to be 98% [3] and that of circulating ANA to be 90%, based on data from other SSc cohorts [2], our result corresponds well with the calculated theoretical prevalence of RP-negative and ANA-negative SSc $[(1-0.98) \times (1-0.90) = 0.2\%]$.

Although all seven patients for whom detailed information was available fulfilled the ACR criteria for SSc, an unequivocal diagnosis of SSc could not be made in four cases. The other three (cases 1–3) were compatible with ANA-negative and RP-negative SSc and were not typical of most known SSc mimics. We are aware of only one other report of ANA-negative and RP-negative SSc [4] occurring in the absence of malignancy. Our study has identified additional cases of ANA-negative and RP-negative SSc, but additional investigation is needed to further characterize the clinical presentation, evolution and outcome of this subset of SSc patients and to ascertain whether this entity represents a discrete clinical syndrome.

The diagnosis of a paraneoplastic syndrome must also be considered when SSc presents without RP or circulating ANA; this is difficult to exclude completely in a retrospective analysis of a large database of patients who have been enrolled at many different centres. The characterization of SSc as a paraneoplastic syndrome is still not well defined; it is questionable as to whether an association between SSc and cancer truly exists. One report described skin fibrosis without associated RP that developed in five patients with solid tumours: three with lung cancer, one with breast cancer and one with undifferentiated head and neck cancer [14]. Circulating ANAs were detected in only two of the five patients. Serum basic fibroblast growth factor (bFGF) levels were elevated in these five patients with paraneoplastic SSc as compared

with both SSc patients and healthy controls; bFGF expression was up-regulated in the fibroblasts of affected skin [14]. In the present study, four of the seven patients for whom detailed information was available had a malignancy (cases 1, 2, 4 and 5): two had breast cancer, one had multiple myeloma and one had bladder carcinoma. A fifth patient (case 6) died 3 years after his initial visit without a recorded cause of death; thus he might also have had a malignancy. In most cases where SSc develops in the setting of malignancy, there is a close temporal relationship between the onset of SSc and the diagnosis of cancer [14, 15]. Because case 1 developed breast cancer 10 years before the onset of her SSc and her cancer had not reoccurred within 6 years after the onset of her cutaneous and pulmonary fibrosis, it is unlikely that her systemic fibrosis represented a true paraneoplastic process.

Several studies have reported that breast, pulmonary, urogenital, haematological, gastrointestinal and head and neck malignancies occur more frequently in patients with SSc as compared with the general population. Thus SSc might be considered as a risk factor for the development of cancer [14–23]. However, unlike our analysis, these studies did not attempt to differentiate SSc from its mimics and classified patients with skin fibrosis using only the ACR criteria for SSc [15–17].

Our findings highlight the importance of conducting a thorough clinical evaluation when SSc is suspected in the absence of circulating ANA and RP. This assessment should include a detailed history (including toxin exposure) and a thorough clinical examination to assess the anatomic distribution of skin sclerosis and the precise appearance of the skin (Table 1). The history should include toxin exposure in terms of gadolinium, cleaning products, organic solvents, formaldehyde, epoxy resins and silica dusts [12]. We also suggest that nail-fold capillaroscopy, serum immunoelectrophoresis, skin biopsy and CT of the chest be performed as part of the routine evaluation of these patients.

NSF is a relatively recently described fibrosing disorder that may be underdiagnosed [24]. Although no case of definite NSF was identified among the cases of ANA-negative and RP-negative SSc in the EUSTAR database, the clinical presentation of the 54-year-old woman with multiple myeloma who underwent GCCA-enhanced MRI about 4 weeks before the onset of skin changes could be compatible with that of NSF, other than for the absence of chronic kidney disease. Since the physicians contributing cases to the EUSTAR database are experts in fibrosing diseases, they may have been aware of NSF as a distinct SSc mimic and not entered those cases into the EUSTAR database.

Among the small number of patients who present with cutaneous fibrosis in the absence of RP and circulating ANA, some have ANA-negative and RP-negative SSc, whereas others have atypical presentations of conditions that are known to mimic SSc. The presence or the subsequent development of a malignancy must be considered as a serious possibility in these patients;

however, some cases ultimately cannot be classified into known diagnostic entities.

Rheumatology key messages

- Some patients with an SSc phenotype lack ANAs and RP.
- Unusual presentations of SSc require a thorough differential diagnosis.
- Other causes of skin sclerosis must be strongly considered in patients who have skin fibrosis but lack ANA and RP.

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