The complexity of managing systemic sclerosis: screening and diagnosis

M. Matucci-Cerinic1, V. Steen2, P. Nash3 and E. Hachulla4

The difficulties inherent in diagnosing, screening and treating SSc are reflected by the complex pathology of the disease, which involves the development of severe organ-based complications that reduce both quality of life and overall survival. Early detection and prompt treatment of such complications depend upon a successful and timely screening strategy, which, in turn, requires cooperation between disciplines and good collaborative links at all stages of the disease. Establishment of a disease registry for SSc may also be of benefit, as such registries facilitate longitudinal observation of trends in disease presentation, management and outcome. They may also help to determine potential risk factors and identify those patient subgroups that face the highest risk of developing disease. In patients with known or suspected SSc, a panel of disease-specific markers—such as autoantibodies, cell activation markers and markers of organ involvement—may help to establish the diagnosis and assess prognosis; however, changes in serum levels of such markers throughout the course of SSc should be interpreted with caution, as they may not always correlate with disease activity. Nail-fold capillaroscopy is a promising tool for SSc assessment and may provide useful diagnostic and prognostic information, although further research is required to clarify its role in evaluating disease evolution.

**KEY WORDS:** SSc, Early diagnosis, Capillaroscopy, Cross-disciplinary communication.

Introduction

SSc is a chronic connective tissue disease of unknown aetiology, with an estimated prevalence of ~1 in 10 000. As this uncommon but severe disorder is characterized by a high level of clinical heterogeneity, an unpredictable course, high mortality and resistance to therapy [1], it has long represented one of the greatest challenges in the management of autoimmune rheumatic diseases. Diagnostic and therapeutic standards vary widely across the global clinical community, and no consensus has been reached on the optimum approach to screening and diagnosis.

The complexity of SSc

The difficulties inherent in diagnosing, screening and treating SSc are due to the complex pathology of the disease, which involves interplay between the immune system, vasculature and components of connective tissue [2]. These interactions contribute towards the development of severe organ-based complications, including digital ulceration [DU; often secondary to RP], renal disease, cardiac or gastrointestinal (GI) manifestations of SSc and pulmonary disease. In turn, organ-based complications produce the high case-specific mortality rate observed among patients with SSc [1, 2]. Data from the Royal Free Hospital in London show that over two-thirds of deaths attributable to SSc between the years 1990 and 2002 were caused by internal-organ complications, and that pulmonary complications carry the worst prognosis.

A total of 302 deaths attributed to SSc in this cohort, the deaths of 128 patients (42%) were attributed to pulmonary manifestations. Early detection of such problems and prompt initiation of treatment is therefore of paramount importance in improving outcome.

**Digital ulceration**

The most common and most visible manifestation of the widespread vascular pathology observed in SSc is RP, which is almost universal among patients with the disease [3]. RP is characterized by excessive vasoconstrictive responses to cold stimuli, leading to pallor and cyanosis of the distal extremities, infarction and DU. DU affects approximately half of the patients with SSc, and an estimated 75% of the affected patients experience their first episode within 5 yrs of their first non-RP symptom [4]. Occurring in ~30% of the SSc patients each year [3], DU is a major clinical problem; not only does it cause severe pain and functional impairment, but it may also result in significant disfiguration and infection that can lead to gangrene, osteomyelitis and eventual amputation [3–5].

**Renal complications**

Despite the use of angiotensin-converting enzyme inhibitors to prevent scleroderma renal crisis (SRC), it occurs in ~6% of all patients with SSc, and in 10–15% of those with diffuse SSc. The outcome remains inadequate for many patients. Up to half of them will require dialysis and the early mortality rate approaches 10% [2].

The course of SRC is characterized by rapidly progressive renal impairment, hyperreninaemia, new-onset accelerated phase hypertension and acute renal failure with vascular lesions that may occur without hypertension at presentation [6]. Early diagnosis and treatment may thus be crucial in improving outcomes. Fortunately, the following factors can be used to identify those SSc patients who have a high risk of developing SRC: (i) early diffuse SSc in which skin thickening is rapidly progressing; (ii) recent onset of SSc without evidence of RP; (iii) presence of tendon friction rubs; and (iv) RNA polI/III antibodies.

**Cardiac manifestations**

Cardiac manifestations of SSc include pericardial effusion, myocardial inflammation, conduction abnormalities and, eventually, cardiac failure. Such complications are usually under-diagnosed. Autopsy studies suggest that subclinical cardiac involvement is very common, but *in vivo* evaluation is inherently limited.
problematic: biopsies can be hazardous and might not sample affected tissue. Gated cardiac MRI has shown some promise as a research tool, but other diagnostic approaches—including nuclear studies and detailed electrophysiological investigation of SSc patients—have yielded inconsistent results [2].

GI manifestations

Complications involving the GI tract are common among patients with SSc. Reflux and difficulty with swallowing are two of the main features of GI involvement, though other problems may include malabsorption, weight loss, bleeding, diarrhoea/constipation, colonic perforation, bowel pseudo-obstruction, faecal incontinence, early satiety and bloating. Affected patients often have a very poor quality of life.

Pulmonary disease

Pulmonary complications are among the most common and deadly manifestations of SSc and most often comprise fibrosis or interstitial lung disease and pulmonary vascular disease leading to pulmonary arterial hypertension (PAH) [7]. Interstitial lung disease in SSc may account for 16% of the deaths, [8] and during post-mortem examination, evidence of pulmonary fibrosis is detectable in most SSc patients [9]. The clinical significance of lung fibrosis in SSc is best defined by high-resolution CT, and can be monitored optimally using pulmonary function testing [10].

PAH is a devastating life-threatening condition that signals advanced stages of disease in the pulmonary vasculature, parenchyma and airways [11]. PAH is defined as a mean pulmonary arterial pressure of $\geq 25$ mmHg at rest or $\geq 30$ mmHg during exercise, with a normal pulmonary capillary wedge pressure ($<15$ mmHg) [12]. Currently, identification of PAH often occurs late in the course of SSc, with up to 81% of the patients categorized as New York Heart Association (NYHA) Class III or IV at the time of PAH diagnosis [13]. Unsurprisingly, PAH and lung disease without PAH have a dramatic effect on survival in patients with SSc (Fig. 1) [14]. Screening for pulmonary complications may therefore enable earlier diagnoses, and treatment initiated earlier may modify the course of disease.

The importance of cross-disciplinary collaboration

In order to illustrate the importance of cross-disciplinary collaboration in the management of patients with SSc, we consider the potential impact of PAH in patients with SSc—a key area in which strong collaborative links are crucial for optimal screening and diagnosis.

Screening and diagnosis of PAH in SSc

Between 12% and 16% of SSc patients have PAH [15], and untreated mortality rates remain high (Fig. 1). In view of these unfavourable observations, it becomes evident that screening of SSc patients is essential to permit early detection of PAH and timely therapeutic intervention. International and European guidelines recommend the systematic screening of SSc patients with annual Doppler echocardiography [16, 17], a pivotal tool for PAH screening.

Of course, a screening programme that involves echocardiography necessitates the involvement of a cardiopulmonary specialist. Engaging the services of a cardiologist can be difficult, and it is often necessary to convince him/her that optimal investigation and management is justified in this patient population. It is important to highlight any suspicion of PAH and to emphasize the need to focus on the right side of the heart, as most echocardiographers only deal routinely with the left side. Crucially, the cardiopulmonary specialist should be provided with specific details of the clinical picture, including details of functional capacity and any symptoms or signs that are suggestive of PAH or right heart failure. Finally, the goal of cross-disciplinary collaboration should be the development of a combined clinic in which specialists from different areas work together towards optimal detection and treatment of SSc-associated PAH.

Limitations of echocardiographic assessment of PAH

Doppler echocardiography is a simple, reliable and non-invasive method for estimating pulmonary arterial pressures and detecting pulmonary hypertension. However, its use is associated with a number of limitations, foremost among which is a tendency to over- or underestimate the prevalence of PH. In one study by Arcasoy and colleagues [11], Doppler echocardiography was more likely to overestimate systolic pulmonary artery pressure (sPAP) in patients without PH, yet was just as likely to overestimate or underestimate sPAP in patients with evidence of PH (Fig. 2). The use of echocardiography alone for the diagnosis of PAH may result in a misleading diagnosis in almost 10% of the cases [12]. These findings suggest that, while Doppler echocardiography represents a convenient tool for screening and identifying those SSc patients who face a high risk of developing PAH, it may be imprecise in determining actual pressures. Therefore, it should not be used alone to diagnose PAH.

Right heart catheterization in PAH

PAH is primarily a disease of pulmonary vascular resistance (PVR) caused by proliferation and contraction of vascular smooth muscle cells. In order to diagnose PAH, it is therefore necessary to establish whether or not the patient has an elevated PVR. Currently, the only available method for detecting and assessing PVR and other important haemodynamic parameters (i.e. cardiac output) is right heart catheterization (RHC). RHC should be
performed in all cases in which PAH is suspected following Doppler echocardiography: it not only confirms the presence of PH and enables a specific diagnosis of PAH to be established, but it also aids the diagnostic process by eliminating other cardiac aetiologies and by assessing the degree of right heart dysfunction.

**Screening for PAH: evidence of benefit**

The importance of establishing a screening programme for PAH is highlighted by data from the Royal Free Hospital, which has a 10-yr history of screening SSc patients. At this centre, early identification of PAH through screening is followed by prompt initiation of therapy with endothelin receptor antagonists (ERAs), with resulting improvements in survival rates. With the recent introduction of combination therapy, such as ERAs plus phosphodiesterase 5 inhibitors, 1-yr survival data appear to be even more favourable (Table 1).

These data suggest that screening procedures can be effective and can allow the clinical outcome of PAH to be altered. If the disease is identified early in its course, treatment can be introduced as soon as possible and the survival profile of affected patients can be improved.

Another benefit provided by screening programmes is the occasional identification of danger signals that require emergency treatment. It is therefore important that all clinicians involved in a screening programme, including the cardiologist and the echocardiographer, are in agreement regarding the clinical criteria that constitute a medical emergency. At the Royal Free Hospital, SSc patients with PAH are considered to require immediate treatment if echocardiography reveals a very high tricuspid gradient (>4 m/s), right ventricular dilation, pericardial effusion or an enlarged right atrium (>27 cm²). Such patients are catheterized within 2 weeks of finding these features on an echocardiography scan.

**Screening algorithm for PAH**

An algorithm for screening patients with SSc has been proposed. It involves the conduct of pulmonary function tests, echocardiography and catheterization of any patient who raises concern (Fig. 3a). Once screened, a patient is referred and, at this point, cross-disciplinary collaboration must be intensified—a practice made much easier by the establishment of combined clinics. After referral and initial telephone contact with the patient, it is necessary to decide whether the case is urgent; if so, appropriate treatment is administered within 2 weeks. If the case is not urgent, the system will run its 3-month course from referral to diagnosis (Fig. 3b). The time from referral to diagnosis must therefore be managed, and a team should be established to ensure that this happens on a continuous basis.

**Early diagnosis of PAH: a national programme for early detection**

An alternative screening algorithm for SSc-related PAH based on symptoms, Doppler echocardiography and RHC has recently been proposed by Hachulla et al. [12]. By this method, SSc patients without severe pulmonary function abnormalities underwent Doppler echocardiography, and all patients with a peak velocity of tricuspid regurgitation of >3 m/s or 2.5–3 m/s with unexplained dyspnoea underwent RHC to confirm diagnosis [12].

Of the 599 patients analysed, 29 had known PAH [12]. A further 33 had suspected PAH (based on Doppler echocardiography) and underwent RHC; of these 33 patients, 18 had a diagnosis of PAH confirmed [12]. Newly diagnosed cases of PAH were mild when compared with known cases, as measured by RHC [12]. The estimated prevalence of PAH was 7.85% (95% CI 5.7, 10.0).

The algorithm reported by Hachulla et al. [12] is considered to enable early detection of PAH at a mild-to-moderate stage of severity, and should be applicable in routine practice. It remains...
Setting standards of care: establishing a disease registry

Why are disease registries important?

The importance of disease registries when evaluating a rare disease, such as SSc, lies in their ability to aid the longitudinal observation of trends in disease presentation, management and outcome. They can help to identify both potential risk factors of disease and the patient sub-groups that face the highest risk of disease; importantly, they can also be used to determine long-term outcomes, establish ‘real life’ natural history and treatment trends, quantify disease burden and facilitate research. As a result, disease registries have gained widespread acceptance by the scientific community, and their use can assist in all aspects of the diagnosis and management of rare diseases.

Objectives, patient populations and outcome measures

The most important issue when establishing a registry is the determination of objectives. The purpose of the registry may be to collect data on the natural history of a disease, or on the incidence or prevalence of the features of that disease. Alternatively, the aim may be to capture data on risk factors or treatment outcomes. Whatever the goal, it is important to ensure that the objectives are specific and well-defined if the registry is to be of maximum utility.

Similarly, the type of patients to be included in the registry must be identified and defined at the outset. All patients with the same disease may be recruited and analysed, or they may be divided into disease subsets (e.g. ethnicity, organs affected). Inclusion criteria may specify that only patients with certain aspects of disease, or only those treated with specific therapies, should be included. Whichever way inclusion criteria are determined, a well-defined patient population is crucial.

Finally, the outcome measures must be established. Specific measures assessed by disease registries—which may include patient-derived outcomes, laboratory studies, disease-related events or survival—should all be defined, standardized and validated.

Logistics and data analysis

A disease registry can take the form of a traditional (paper-based) or internet-based database, both of which are associated with advantages and disadvantages. Data submission to a traditional database typically comprises case report forms submitted to a clinical research centre; the processing of which can be expensive. In addition, the monitoring of data and provision of access to data by research personnel are time-consuming processes. In contrast, an internet database enables electronic data capture and submission, and facilitates access to data and data analysis by authorized research staff. However, there are high, short-term, development costs associated with this approach, and security risks are increased in comparison with traditional databases. Whichever format is chosen, physician case report forms and patient questionnaires must be prepared, recruitment and enrolment strategies described, and guidelines for the protocol, patient recruitment and data entry developed.

In addition to basic logistics, methods of data analysis should be defined from the start. The sample size for preliminary data should be determined, and any specific composite measures or calculations for specific variables should be prepared. It is important to ensure that data can be transferred easily to the planned data analysis programme, and that strategies are in place to manage the data and to deal with any queries or missing data.

Limitations of data registries

Loss to follow-up. The major challenge of disease registries is to collect follow-up data on every study subject recruited. Patients lost to follow-up are a major source of bias, as these participants do not necessarily have the same outcomes or experience as those who remain under observation. Multiple sources of information can be used to obtain complete follow-up information; however, it may be better to have high follow-up on a limited number of patients than poor follow-up on many. If many data (e.g. >20%) are lost to follow-up, the validity of the study results may be compromised; even if loss to follow-up is low (e.g. 10%), major problems with data interpretation may still occur. For instance, if the incidence of a particular finding is very low in the population yet relatively high among patients lost to follow-up, the observed point estimate may be severely biased.

Data lost to follow-up must therefore be kept to an absolute minimum by using vigorous tracking techniques at patient entry and employing people-finding methods where necessary. Statistical methods to handle losses to follow-up should be applied, and other biases should be limited.

Types of bias. There are several types of bias that may be encountered commonly in cohort studies involving disease registries [18]. One of these is information bias, which can be minimized by standardizing measurement instruments and administering instruments in the same way to all patients. Strict guidelines for data collection should be established, and observers and/or interviewers should be trained to obtain data in the same manner. The use of multiple sources of information may also help to reduce bias.

Missing data. All studies and registries have some missing information; to maintain the validity of the results, it is essential to include rigorous methods for imputing missing data. Such methods include the following: linear extrapolation for patients missing a value; use of appropriate imputation techniques for patients with other types of missing data; and use of sensitivity analyses to explore the effect of missing data.

Biological markers in SSc

In patients with known or suspected SSc, a panel of diseasespecific markers may help to establish the diagnosis and assess prognosis. Such markers include autoantibodies, cell activation markers and markers of organ involvement (Table 2).

Autoantibodies

The detection and quantification of autoantibodies has become an important component in the diagnosis and management of SSc, as specific autoantibodies have been shown to correlate closely with various clinical and laboratory manifestations of the disease (Table 3).

However, measurement of autoantibodies is not considered to be a ‘gold standard’ diagnostic test for SSc; autoantibodies are no more than markers of disease with significant limitations, and are best used as part of a diagnostic panel.

Cell activation markers

Numerous markers of cell activation have been correlated with clinical features of SSc (Table 4).

Several studies have evaluated the effects of treatment on the levels of various cell activation markers in patients with SSc. In one study, 13 patients with early diffuse SSc were treated with oral cyclophosphamide (2–2.5 mg/kg/day) and methylprednisolone (30 mg/kg every other day) for 1 yr, and followed up for clinical and laboratory parameters. After 1 yr of treatment, patients showed evidence of clinical improvement; concentrations of the...
Several diagnostic and prognostic tools are available in SSc, such as circulating autoantibodies and cellular activation markers 

<table>
<thead>
<tr>
<th>Autoantibodies</th>
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<tbody>
<tr>
<td>ANAs</td>
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<tr>
<td>Anti-DNA topoisomerase I, anti-centromere, anti-RNA polymerase I–III, anti-SSA RNP, anti-Th, anti-PM-Scl,</td>
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<tr>
<td>Anti-endothelial cell antibodies</td>
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<tr>
<td>Anti-fibroblast antibodies</td>
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<tr>
<td>Anti-PDGFβ antibodies</td>
</tr>
<tr>
<td>ANCA</td>
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<tr>
<td>Anti-PDGFr antibodies</td>
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<tr>
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<tr>
<td>Anti-fibroblast antibodies</td>
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<td>Anti-endothelial cell antibodies</td>
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</table>

Cell activation markers

Endothelial cells

- ET-1, E-selectin, vWFAg, ICAM-1, VCAM-1, ACE
- T-B lymphocytes, monocytes
- sII-2r, IL-4, IL-6, IL-13, IL-17, BAFF, TGF-β, CD30, MCP-1, TNF-α
- Fibroblasts
- Procollagen III-N propeptide, CTGF, TIMP 1, YKL-40
- Platelets
- B-thrombomodulin, PF-4

Markers of internal organ involvement

Plasma renin activity

(Pro)BNP

Surfactant proteins A, D, KL-6, CC16, CK19, SLX

Vitamin B12, folate, ferritinaemia

ACE: angiotensin converting enzyme; BAFF: B cell activating factor; CTGF: connective tissue growth factor; ICAM: intercellular adhesion molecule; MCP-1: monocyte chemoattractant protein; PDGFβ: platelet-derived growth factor receptor; PF: platelet factor; sII-2r: soluble IL-2 receptor; TGF-β: transforming growth factor; TIMP: tissue inhibitor of metalloproteinases; VCAM: vascular cell adhesion molecule; vWFAg: von Willebrand factor antigen; YKL-40: chitinase 3-like protein 1. Adapted from [19–21].

Table 2. Biological markers in SSc

<table>
<thead>
<tr>
<th>Autoantibodies</th>
<th>Clinical correlate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-DNA topoisomerase I</td>
<td>dsSSc, pulmonary fibrosis, disease severity (total skin score [22])</td>
</tr>
<tr>
<td>Anti-centromere</td>
<td>lcSSc, favourable prognosis</td>
</tr>
<tr>
<td>Anti-RNA polymerase I–III</td>
<td>lcSSc, renal involvement [23]</td>
</tr>
<tr>
<td>Anti-Ig RNP</td>
<td>dsSSc, males, African-American race, pulmonary hypertension [24]</td>
</tr>
<tr>
<td>Anti-Th</td>
<td>lcSSc, intestinal involvement [25]</td>
</tr>
<tr>
<td>Anti-PM-Scl</td>
<td>lcSSc, overlap with myositis [26]</td>
</tr>
<tr>
<td>Anti-fibroblast</td>
<td>Pro-adhesive and pro-inflammatory phenotype in fibroblasts [27]</td>
</tr>
<tr>
<td>Anti-endothelial cell</td>
<td>Induction of apoptosis and fibrin 1 expression in dermal endothelial cells [28]</td>
</tr>
</tbody>
</table>

Table 3. Marker autoantibody specificities in patients with SSc

<table>
<thead>
<tr>
<th>Circulating activity marker</th>
<th>Clinical correlate</th>
</tr>
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<tbody>
<tr>
<td>IL-10</td>
<td>Total skin thickness score</td>
</tr>
<tr>
<td>sIL-2r and IL-8</td>
<td>Raynaud’s phenomenon</td>
</tr>
<tr>
<td>sII-2r</td>
<td>Renal crisis</td>
</tr>
<tr>
<td>ICAM-1</td>
<td>‘Ground glass’ on HRCT*</td>
</tr>
<tr>
<td>Oncostatin M</td>
<td>Swollen joint count</td>
</tr>
<tr>
<td>vIL-6, IL-10, VEGF, sIL-2r</td>
<td>Cardiomegaly</td>
</tr>
<tr>
<td>BAFF</td>
<td>Total skin thickness score</td>
</tr>
</tbody>
</table>

Table 4. Correlations between clinical and laboratory measures of disease activity in SSc

Table 5. markers of internal organ involvement

<table>
<thead>
<tr>
<th>Markers of internal organ involvement</th>
<th>Clinical correlate</th>
</tr>
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<tbody>
<tr>
<td>(Pro)BNP</td>
<td></td>
</tr>
<tr>
<td>Surfactant proteins</td>
<td></td>
</tr>
<tr>
<td>Vitamin B12, folate, ferritinaemia</td>
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</table>

Acute vasculitis

- Raynaud’s phenomenon
- Immunosuppressants
- Cyclophosphamide
- Antifibroblast antibodies

Biomarkers for PAH

Several prognostic markers are also available for predicting the risk of organ involvement in SSc (Table 2). Of particular utility when assessing the haemodynamics of SSc patients is (pro)BNP, which has been found to correlate significantly with mean pulmonary arterial pressure (r = 0.53), right ventricular end diastolic pressure (r = 0.59) and PVR (r = 0.49) [32]. These data are extended by a more recent study in which proBNP levels were significantly higher in SSc patients with PAH (n = 68) than in those without PAH (n = 41; P = 0.0002) [33]. ProBNP was also found to be predictive of survival: for every order of magnitude increase in proBNP levels among patients with PAH, there was a 4-fold increase in the risk of death (P = 0.002 for baseline proBNP levels; P = 0.006 for proBNP levels after 10 months’ follow-up) [33]. Assessment of proBNP levels in SSc-related PAH may therefore represent a potentially valuable diagnostic and prognostic tool.

Assessment of microvascular damage: capillaroscopy

Microvascular lesions are a principal feature of SSc and may play a central pathogenic role [34]. Microangiopathy appears to be the best evaluator of SSc development, and may precede manifestation of symptoms and involvement of the internal organs by many years [34]. Therefore, the activity and severity of digital vascular disease in patients presenting with PAH—often the earliest clinical sign of vascular involvement in SSc—must be measured and monitored [35]. Several methods of assessment can be used, but capillaroscopy is currently viewed as the standard procedure for evaluating the microcirculation.

Nail-fold capillaroscopy

Nail-fold capillaroscopy is a non-invasive, safe and inexpensive imaging method that allows the in vivo assessment of the cutaneous microvasculature. It is widely regarded as one of the most useful diagnostic and prognostic tools in the early stages of isolated RP [36], as any patient with RP and abnormal capillaries is likely to have or develop underlying connective tissue disease, such as SSc [32, 36]. On widefield capillaroscopy, characteristic nail-fold capillary abnormalities are observed in patients with SSc, including capillary dilatation and loop dropout.

Capillaroscopic patterns in SSc

SSc microangiopathy has been graded into three distinct capillaroscopic patterns (early, active and late) using nail-fold videocapillaroscopy (NVC) [34, 37, 38]. The early appearance of giant capillaries and haemorrhages (‘early’ stage) is of great relevance for the early diagnosis of SSc, and allows differentiation between primary and secondary RP [34]. The microangiopathic changes observed in the early pattern are more evident in the ‘active’ phase. With severe loss of capillaries, evidence of vascular architectural disorganization and the presence of ramified or bushy capillaries, the ‘late’ stage represents the clearest aspect of SSc microvascular damage [34]. These three distinct patterns seem to reflect the evolution of SSc pathology—a hypothesis supported by observations of longer disease duration in patients with the late NVC pattern than in those with early or active patterns [34]. However, longitudinal studies are needed to confirm this assumption.

*Refers to a hazy opacity that does not obscure the associated pulmonary vessels. This appearance results from parenchymal abnormalities that are below the spatial resolution of HRCT. Ground-glass opacity can be seen with alveolar wall inflammation or thickening, with partial airspace filling, or with a combination of the two. HRCT: high-resolution CT; ICAM: intercellular adhesion molecule; sII-2r: soluble IL-2 receptor; vIL-6: viral IL-6; VEGF: vascular endothelial growth factor. Adapted from [29] with permission from the Journal of Clinical and Experimental Rheumatology.

by significant changes in the levels of most cellular activation markers assessed [31]. These findings suggest that, although cellular activation markers might be useful in monitoring the progress or regression of a disease, they may not always correlate directly with disease activity. Any changes in serum levels of such markers following treatment for SSc should therefore be interpreted with caution.
Conclusions

Heightened vigilance towards early detection of SSc and its many organ-based complications may help to improve clinical outcomes. An integrated, methodological and strategic approach to screening and detection is required—an approach that also necessitates cross-disciplinary cooperation and good collaborative links at every stage of the disease. As SSc is a rare condition, its diagnosis and management may benefit from the establishment of a disease registry that allows assessment of longitudinal patterns in presentation, treatment and outcomes. Currently, physicians can rely on some disease-specific biological markers to aid the diagnosis and assessment of SSc, with proBNP showing particular promise as a diagnostic and prognostic tool in patients with pulmonary complications. However, until biological markers are validated as outcome measures, it is important that they are used as part of a diagnostic panel rather than as definitive indicators of disease or prognosis. Finally, patients at risk of SSc may be identified using methods to assess early microangiopathic changes. NVC has enormous potential in this area, and the identification of distinct NVC patterns might be useful in assessing and following microvascular involvement in SSc. However, long-term longitudinal studies are necessary to further assess the correlation between NVC patterns and clinical manifestations of disease.

Rheumatology key messages

- Patients with SSc are at high risk of developing severe, organ-based complications that reduce quality of life and survival.
- Early detection and prompt treatment of such complications is critical, and requires vigilance during management.

Acknowledgements

The authors received editorial assistance from Elements Communications, supported by an educational grant from Actelion Pharmaceuticals Limited (Allschwil, Switzerland).

Supplement: This paper forms part of the supplement entitled ‘Ten years of partnership: translating ideas into progress in systemic sclerosis’. This supplement was supported by an unrestricted grant from Actelion Pharmaceuticals Ltd.

Disclosure statement: E.H. has received honoraria from and is a consultant for Actelion, Roche, GlaxoSmithKline, United Therapeutics, LFB and Pfizer. M.M.-C. has a consultancy relationship with Actelion Pharmaceuticals. All other authors have declared no conflicts of interest.

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