



Management of scleroderma in a New Zealand tertiary rheumatology centre: emphasis on pulmonary complications

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Abstract

Aims To determine the current local practice of managing scleroderma (SSc) patients, in particular screening of SSc-related lung disease in a tertiary rheumatology centre.

Methods SSc patients were identified from our inpatient (July 1999 till June 2004) and outpatient (January 2002 till June 2004) databases. Patient demographics and relevant investigations performed to monitor for pulmonary, renal, and cardiac complications related to SSc were sought from computerised clinical and laboratory records.

Results Nine of the 39 (23%) limited SSc (lcSSc) patients and 5 of the 10 (50%) diffuse SSc (dcSSc) patients had lung involvement. A higher proportion of diffuse SSc patients had investigations for SSc lung disease compared to the lcSSc group (90% vs 67% had pulmonary function tests and 70% vs 56% had high resolution chest CT scans respectively). About half of the patients in both groups had echocardiographs (50% lcSSc vs 46% dcSSc) for assessment of pulmonary arterial hypertension.

Conclusion SSc lung disease has been generally poorly screened in our cohort of patients with SSc. Limited SSc patients were not screened as rigorously as dcSSc patients for SSc lung disease. In large part, this was because of the lack of availability of treatments in New Zealand when the lung disease was identified. The generation of a standardised screening and monitoring protocol may help identify patients with progressive lung disease so that early treatment could be considered as this becomes more readily available.

Systemic scleroderma (SSc) is a rare autoimmune rheumatic disease with the potential for multiorgan system involvement. It can be categorised to two major groups, limited (lcSSc) and diffuse (dcSSc) cutaneous SSc, depending on the extent of skin involvement. A recent meta-analysis has found that the involvement of gastrointestinal, lung and renal organ systems are important predictors of mortality.¹

Lung disease occurs in more than 70% of SSc patients and is the second most frequent organ system involved. The two main clinical manifestations of lung disease in SSc patients are interstitial lung disease (SSc-ILD) and pulmonary vascular disease leading to pulmonary arterial hypertension (PAH).

Lung disease is now the leading cause of death in patients with SSc.² The prognosis of these patients is poor with a 70% mortality at nine years.³ The prevalence of PAH in SSc varies from 10-40%^{4,5} and is more common in lcSSc. PAH is an independent poor prognostic marker in dcSSc regardless of the presence of SSc-ILD.⁶

A large proportion of SSc patients have sub-clinical pathology, and symptoms are often an unreliable marker in determining the presence of pulmonary disease.

Pulmonary function tests (PFT), chest X-ray (CXR), and high resolution computed tomography (HRCT) chest scans are routine investigations used to diagnose and monitor lung disease in SSc patients. PFT, in particular diffusing capacity for carbon monoxide (DLCO) is the most sensitive test to detect a functional decline in SSc patients.⁷

A reduction in DLCO in ILD (< than 65% normal) is usually associated with a restrictive pattern on PFT. However, PFT and CXR are relatively crude tests to detect SSc-ILD. HRCT chest is useful to identify early lung disease and to distinguish reversible ground- glass opacification and irreversible fibrotic disease.

Bronchoalveolar lavage (BAL) has shown to be of prognostic value in several studies^{8,9} but there is a wide variability in technique and reporting of BAL differential cell counts depending on the training of local personnel.¹⁰ Specialised SSc units generally recommend that PFT and HRCT chest be done at baseline and PFT to be repeated periodically, at more frequent intervals in early disease, and this can be extended to yearly if results are normal and the patient is asymptomatic.

Echocardiograph remains the primary screening tool for PAH, especially if the DLCO is extremely low with near normal forced vital capacity (FVC).¹¹ However, the sensitivity and specificity of this test is variable depending on the patient population studied and the definition of a “positive” echocardiography result.¹² Right heart catheterisation remains the gold standard to diagnose PAH. Annual echocardiography is recommended as a routine systematic screen for PAH in SSc patients.¹³

The early diagnosis of SSc-related pulmonary involvement is essential for prompt treatment before irreversible damage occurs especially with recent major pharmacotherapeutic advances in the treatment of PAH.¹²

This audit was undertaken to determine the local practice of managing scleroderma patients at Middlemore Hospital, Auckland with emphasis on the screening strategies used to detect pulmonary, renal and cardiac organ involvement. We also discuss the relevance of available evidence based practice for the management of patients with SSc lung disease in New Zealand.

Methods

Middlemore Hospital is a tertiary rheumatology referral centre for the South Auckland population in New Zealand. The SSc patients were identified from our outpatient rheumatology database at Middlemore Hospital from January 2002 till June 2004. The rheumatology outpatient database included all patients with the read code “collagen tissue not otherwise specified”. We also identified patients from the inpatient admission database from July 1999 till June 2004. Patients with overlap syndromes, Sjogrens disease, undifferentiated connective tissue disease, and myositis were excluded from analysis.

Patients who were known to our local rheumatology service were identified. Patient demographics; and tests performed by the attending clinician for the presence and extent of lung, cardiac, and renal organ involvement; were retrospectively sought from computerised clinic records and laboratory data. Disease duration and the use of disease modifying anti rheumatic drugs (DMARDs) were noted.

Results

Seventy-four patients with the diagnosis of SSc were identified. The majority of patients (72%) had lcSSc (Table 1).

Table 1. Types of SSc disease

Systemic sclerosis	Patient numbers
Limited	53
Diffuse	11
Localised	3
Not specified	7

As expected, most of the patients were females (88%) and of European ethnicity (Table 2).

Table 2. Patient ethnic groups

Ethnicity	Patient (%)
European	80
Asian	11
Pacific*	3
Māori	1
Other	5

*Mostly of Samoan, Tongan, Niuean, or Cook Islands origin.

Of the 53 lcSSc patients, 39 were followed up regularly at our rheumatology service. Ten of the 11 dcSSc patients were known to our service. The other SSc patients who were not known to our service were primarily admitted under the inpatient care of the plastic surgical or vascular services for surgical management of ischaemic digits.

The mean age at last review of the lcSSc patients was 61 years compared to 44 years in the dcSSc group.

We analysed the following data from the SSc patients who were known to our service (39 lcSSc and 10 dcSSc patients).

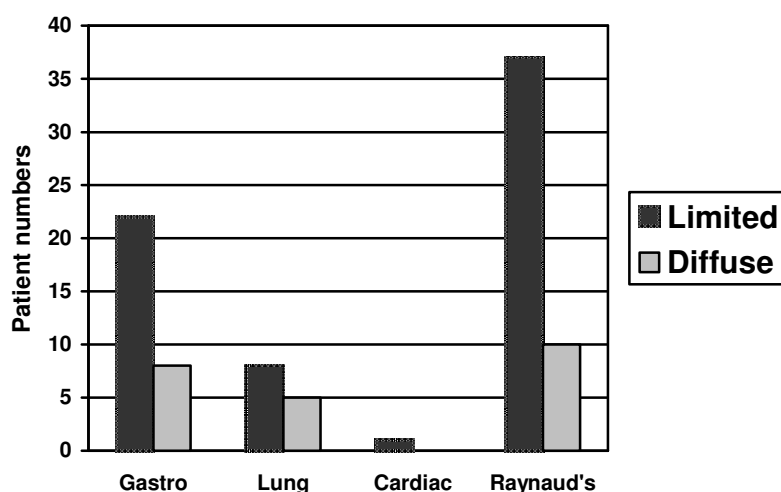
The majority of dcSSc patients (80%), and slightly more than half (58%) of the lcSSc patients, had the disease for more than 5 years. There were only two diffuse SSc patients with disease duration of less than 5 year—one patient was asymptomatic for lung disease but both patients had the same lung screening tests except one did not proceed to have an echocardiography.

Raynaud's phenomenon was the most frequent clinical feature observed followed by gastrointestinal and lung organ involvement in both groups (Figure 1).

Nine of the 39 (23%) lcSSc patients and 5 of the 10(50%) dcSSc patients had lung involvement. Approximately half of these patients (54% lcSSc and 60% dcSSc) had no respiratory symptoms. Of the patients who were symptomatic, the majority (92%) complained of dyspnoea or a dry cough (26%).

All patients with lung involvement had abnormal PFT with an obstructive or restrictive ventilatory defect, decreased DLCO, or a combination of both abnormalities. The types of lung disease observed are ILD (non specific interstitial pneumonitis), bronchiectasis and PAH.

Figure 1. Frequency of major organ involvement



Of the 9 lcSSc patients with pulmonary involvement, 5 (56%) had PAH; 1 patient also had pulmonary embolic disease. Only 1 of the 5 dcSSc lung patients had PAH associated with ILD. None of the patients with underlying SSc-ILD and PAH had specific drug treatments for their lung disease, because treatment was not available at that time. No patients in either the lcSSc or dcSSc groups developed renal crisis. Three lcSSc patients have died. The causes of death were pulmonary hypertension complicated with right heart failure, peritonitis and metastatic oesophageal carcinoma.

Table 3 shows the frequency of patients who have had investigations for their respective organ involvement. In general, a higher proportion of dcSSc patients had investigations for pulmonary (except for BAL), renal, and cardiac involvement compared to the lcSSc group. The majority of the investigations were instigated by the attending physician only when the patient was symptomatic.

Table 3. Frequency of investigations performed for respective organ systems

Investigation	Limited (%); n=39	Diffuse (%); n=10
<i>Pulmonary</i>		
Lung functions	26 (67)	9 (90)
CXR	26 (67)	8 (80)
HRCT chest scan	22 (56)	7 (70)
BAL*	2 (5)	None
<i>Cardiac</i>		
ECG†	6 (15)	2 (20)
Echocardiograph	18 (46)	5 (50)

<i>Renal</i>		
BP‡	30 (77)	9 (90)
Dipstick urine analysis	13 (33)	7 (70)
Electrolytes	25 (64)	10 (100)

*BAL: bronchoalveolar lavage; †ECG: electrocardiograph; ‡BP: blood pressure.

Nail fold capillaroscopy examination was frequently not performed or documented in the clinic letters (67% lcSSc and 70% dcSSc).

The prevalence of common autoantibodies associated with SSc in each group is outlined in Table 4.

Table 4 Frequency of SSc auto antibodies

Auto antibody profile	Limited (n=27) (%) §	Diffuse (n=7) (%)
Anti centromere antibody positive	22 (81)	None
Scl 70 positive	2 (7)	5 (71)

§No records in 12 patients; ||No records in 3 patients

Table 5 lists the various DMARDs used. The majority of patients were on calcium channels blockers for Raynaud's phenomena (22/39 lcSSc patients and 6/10 dcSSc patients).

Table 5 Disease modifying anti rheumatic drugs (DMARDs) used

DMARDs	Limited (n=39)	Diffuse (n=10)
Penicillamine	1	2
Methotrexate	1	2
Azathioprine	1 [¶]	1

[¶] For autoimmune hepatitis.

Discussion

This audit reviews our local practice of screening and diagnosing pulmonary, renal and cardiac related diseases in patients with SSc. A review of SSc patients in Auckland 25 years ago showed that the involvement of renal and cardiac organ systems were main adverse prognostic factors associated with a poor survival rate.¹⁴ This has changed over the years with the advent of angiotensin–converting enzyme inhibitors. Scleroderma renal crisis now only accounts for 8% of scleroderma related deaths.¹² This is reflected in this audit where no deaths were related to scleroderma renal crisis.

This audit shows that lcSSc patients were not screened as rigorously as the dcSSc patients for lung disease, although visceral lung involvement can occur in both groups. A higher proportion of dcSSc patients had the relevant tests to monitor for pulmonary, renal, and cardiac SSc-related diseases.

The initial standard respiratory tests used at our centre are PFT and CXR. Some of these patients proceeded to HRCT chest and BAL (in a minority of patients, n=2) if there was a strong clinical indication of SSc-ILD, although BAL was not routinely performed.

We found no consistency in the frequency of PFT request. Although it is recommended that PFT and HRCT chest be repeated at periodic intervals, there has been no Cochrane or published systematic review addressing this aspect of management in patients with SSc.

None of the patients with underlying SSc-ILD in this audit received cyclophosphamide as previously, the evidence for this potentially toxic immunosuppressive has mainly been based on uncontrolled retrospective studies.

The Scleroderma Lung Study group has recently demonstrated that oral cyclophosphamide has a modest benefit in SSc-ILD in a controlled trial.¹⁵ One would need to balance the potential toxicity of cyclophosphamide versus benefit when initiating cyclophosphamide therapy in SSc-ILD. We recommend the generation of a standardised protocol for regular interval respiratory investigations which may help identify patients with progressive lung disease so that early treatment could be considered.

Most of the patients in this audit did not have the recommended annual screening echocardiography. In the majority of cases, an echocardiography was requested only when patients were symptomatic. However, it is important to identify “early” PAH patients for early intervention as the disease can be irreversible when patients become symptomatic. The optimal screening method is yet to be determined. A recent prospective study showed that an algorithm based on dyspnoea, echocardiograph and right heart catheterisation can detect mild PAH at an early stage.¹⁶

In the last 5 years, there have been major advances in the treatment of PAH. Prostacyclin analogues (epoprostenol, treprostinil, and iloprost) can have short term benefits in improving the New York Heart Association function and cardiopulmonary haemodynamics.¹⁷ Endothelin receptor antagonists (bosentan, sitaxsentan) can improve exercise capacity and cardiopulmonary haemodynamics in PAH.¹⁸ Recent studies suggest that these agents may also improve survival in PAH associated connective tissue diseases.^{19, 20} Sildenafil (phosphodiesterase inhibitor) may be of benefit in reducing pulmonary vascular resistance.²¹ A recent study has confirmed that sildenafil improves the exercise capacity and haemodynamics of symptomatic PAH patients.²²

Treatment options for pulmonary hypertension in New Zealand are currently very limited. Most of the agents mentioned above are currently not funded in New Zealand and the difficulties of obtaining these agents were highlighted in a recent review.²³ This probably has an impact on our practice as highlighted in this audit where only half of the patients with lcSSc and dcSSc had echocardiographs performed. Thus, the recommended annual echocardiography screen for an early diagnosis of PAH in SSc may not be applicable in New Zealand. Another advantage in performing annual echocardiography screening is for the detection of primary cardiac involvement related to SSc.

Significant cardiac abnormalities have been found in more than half of SSc patients at autopsy suggesting the sub clinical nature of SSc-related cardiac disease.²⁴ The cost-effectiveness of routine screening with more expensive investigations such as HRCT and echocardiography also needs to be taken into account.

This audit highlighted that nailfold capillaroscopy examination was infrequently performed. Abnormalities in nailfold capillaroscopy may be an early finding in SSc-ILD. One study showed that severe nailfold capillaroscopy changes have a sensitivity of 100% for ground-glass opacities on HRCT in patients with disease duration of less than 5 years.²⁵ This abnormality should be looked for to identify patients needing more intensive investigations for the presence of SSc-ILD.

The overall treatment of patients with SSc is generally lacking. Initial studies suggested that D- penicillamine was effective for the skin and possibly lowers the incidence of systemic involvement.²⁶ Since then, a double blind randomised trial has shown that there is no benefit of high dose penicillamine compared to low-dose penicillamine.²⁷ It is still unclear if low dose penicillamine has any beneficial effect. There were only three SSc patients in our audit who were on penicillamine.

Interestingly, the demographic results from this audit suggest a low prevalence of SSc in the Māori and Pacific population (4%) in comparison to a higher prevalence rate of systemic lupus erythematosus in similar ethnic groups.²⁸

In conclusion, this audit has reviewed the current local practice of screening SSc patients in a tertiary rheumatology centre in New Zealand. The generation of a local screening and monitoring protocol may improve the management of SSc-ILD in light of the recent Scleroderma Lung Study findings. The access to new therapeutic agents for PAH associated with SSc remains an ongoing issue in New Zealand which has implications on the practice of early detection of pulmonary hypertension in SSc patients.

Competing interests: None.

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