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Interstitial lung disease in South Africans with systemic sclerosis

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Abstract
To investigate the frequency, severity and predictors of interstitial lung disease (ILD) in a cohort of South Africans with systemic sclerosis (SSc). Retrospective record review of SSc patients attending a tertiary Connective Tissue Diseases Clinic. Patients with ILD, defined by a combination of clinical findings, imaging, and lung function tests were compared to patients without ILD in terms of demographics, clinical features and autoantibodies. The majority (86.8%) of the 151 patients included were of Black ethnicity, 40% had ILD, of whom 39% had moderate–severe lung disease. Univariate predictors of ILD included: disease duration (OR 1.08, 95% CI 1.01–1.15); cough (OR 2.93, 95% CI 1.37–6.29); dyspnoea (OR 2.44, 95% CI 1.23–4.87); bibasal crackles (OR 7.58, 95% CI 3.31–17.37); diffuse cutaneous SSc (dcSSc) (OR 4.55, 95% CI 2.10–9.86) and a speckled anti-nuclear antibody (ANA) pattern (OR 2.47, 95% CI 1.25–4.90). Conversely, limited cutaneous disease (OR 0.22, 95% CI 0.09–0.50) and anti-centromere antibody (ACA) (OR 0.12, 95% CI 0.02–0.97) were protective. Independent predictors of ILD on multivariate analysis were bibasal crackles (OR 9.43, 95% CI 3.25–27.39), disease duration (OR 1.19, 95% CI 1.09–1.30) and speckled ANA (OR 2.95, 95% CI 1.22–7.15). Almost all (86.4%) patients received immunosuppressive treatment and the leading cause of death was related to ILD itself (44.4%). In this cohort of predominantly Black South Africans, SSc ILD was common and carried a poor prognosis. ILD occurred mainly, but not exclusively, in patients with dcSSc, especially those with a speckled ANA pattern. Conversely, the presence of ACA was protective against ILD.

Keywords Systemic sclerosis · Interstitial lung disease · Sub-Saharan Africa

Introduction

Systemic sclerosis (SSc) is a rare multisystem connective tissue disease that has a markedly poorer survival compared to the general population, with interstitial lung disease (ILD) being a leading cause of death [1]. The prevalence of ILD in SSc ranges between 16 and 96% [2, 3], depending on diagnostic method as well as the population studied. In the European League Against Rheumatism Scleroderma Trials and Research Group (EUSTAR) database of predominantly Caucasian patients with limited cutaneous SSc (lcSSc), ILD was diagnosed by pulmonary function tests (PFTs) in 32% of cases, 40% by chest X-ray (CXR) and 52% by high-resolution computed tomography (HRCT) [4].

Risk factors for ILD in SSc include male gender [5, 6], silica exposure in gold miners [7–9], diffuse cutaneous SSc (dcSSc), reflected by higher modified Rodnan skin scores [10, 11], and the presence of anti-topoisomerase I antibodies (ATA) [5, 12–15]. Conversely, the presence of anti-centromere antibodies (ACA) has been found to be protective [2, 12, 13, 16]. Moreover, African American SSc patients have a higher rate of ILD [13, 14], more severe ILD [13, 14], and a higher mortality rate compared to matched Caucasian patients [14, 17, 18]. There is no such data published in Black African patients.

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In patients who have ILD, several factors appear to predict severity. These include male gender [6], cigarette smoking [19], dcSSc [6], cough [20], higher dyspnoea scores [17], bibasal crackles on physical examination [17], and baseline C-reactive protein (CRP) > 8 mg/l [21]. Additionally, both dyspnoea and bibasal crackles are predictors of lung function decline [22].

In previous South African studies, ILD diagnosed on CXR findings alone was found in 56% of SSc patients generally [16], but in up to 96% of gold miners with SSc patients [7–9]. To date, there have been no studies in sub-Saharan Africa that have focused specifically on severity and predictors of ILD and outcome in SSc. Therefore, this study was undertaken to determine the frequency and characteristics of ILD and to compare findings between ILD and non-ILD SSc patients. Ethical approval was granted by the Human Research Ethics Committee (Medical), University of the Witwatersrand (approval no. M120966, 2012-09-28).

Patients and methods

This was a single-centre retrospective review of SSc patient records at the Connective Tissue Diseases Clinic at Chris Hani Baragwanath Academic Hospital from 1 January 1992 until 31 May 2012. Inclusion criteria were: age ≥ 18 years; classification criteria met according to the American College of Rheumatology (ACR) preliminary classification criteria for SSc [23]; and adequate clinical records including history, examination findings, and laboratory results.

The diagnosis of ILD was based on clinical findings, CXR, restrictive PFTs, and compatible features on HRCT scans of the chest (groundglass opacification, interlobular septal thickening, fibrosis, and honeycombing) as judged by a pulmonologist or radiologist. Restrictive lung disease was defined by PFTs as a forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio ≥ 80% and impaired if FVC < 70% of predicted and/or diffusing capacity for carbon monoxide (DLCO) < 70% of predicted, as per Goh et al. [24]. Patients were further subclassified at ILD diagnosis into severity groups: mild if FVC ≥ 70% predicted; moderate if FVC 50–69% of predicted; and severe if FVC < 50% predicted. As there were only three patients with severe ILD, the moderate and severe groups were combined for statistical analysis. Pulmonary hypertension (PHT) was defined as estimated right ventricular pressure ≥ 40 mmHg on echocardiogram. None of the patients had confirmatory right heart catheterisation.

Disease duration was defined as time from onset of first non-Raynaud's symptom until date of last contact. Smoking history was considered to be positive if the patient smoked either previously or currently. Digital lesions (digital ulcers, pitting scars, or gangrene) were grouped together as indicative of cutaneous vasculopathy. Nailfold changes were documented as dilated capillary loops, haemorrhages, or capillary drop out. Disease subsets were based on descriptions by LeRoy et al. [25]. The anti-nuclear antibody (ANA) test was done by indirect immunofluorescence using Hep2 cells as substrate and titres ≥ 1:160 judged to be positive. The staining patterns were classified as either nucleolar, speckled, centromere and homogenous. The Western blot was used to detect ATA. Immunosuppressive therapy received during the course of follow-up was recorded. Outcomes were documented where known as alive or demised. The cause of death was categorised into: infection, malignancy, ILD related, cardiovascular related, or unknown.

Statistical methods

Appropriate descriptive analyses were performed on all patients with SSc. Comparisons were made between ILD and non-ILD groups using the two-tailed Fisher's exact test or one-way ANOVA as appropriate. The two-tailed unpaired Student's *t* test was used for quantitative data comparisons. A $p < 0.05$ was considered statistically significant. Odds ratios (OR) were calculated using a binary logistical option at a 95% confidence interval (CI) for all OR. An estimated OR was calculated using the + 1 rule for the zero ACA frequency in the ILD group. Multivariate logistic regression analysis was applied using the ENTER method [26] with all variables pre-determined from significance. The entry point was at $p = 0.05$ and the exit point was at $p = 0.10$.

Results

Of 177 patient records reviewed, 151 met inclusion criteria. Twenty-six records were excluded due to inadequate clinical information or the patients failed to meet the classification criteria. The overall findings are shown in Table 1. The majority of patients were female (87.4%) and of Black ethnicity (86.8%). Caucasians represented 2.7%, Indians 3.3% and mixed race 7.2%. The mean age (SD) at diagnosis was 44.1 (13.0) years. The commonest clinical features were Raynaud's phenomenon (82.8%), and nailfold capillary changes (70.2%) and the majority had dcSSc (62.2%). The ANA was positive in 88.1% of cases, the commonest ANA patterns being speckled (40.6%), nucleolar (31.6%) and only 7.5% had a positive ACA. Nineteen percent of patients were ATA positive.

Sixty patients were diagnosed with ILD. In most cases (63%), ILD was diagnosed in the same year as their SSc diagnosis, and 73.3% within the first 3 years. In all but eight patients, was ILD diagnosed without confirmatory HRCT. In the 46 ILD patients who had echocardiography performed, 34.8% had evidence of PHT. Forty-three

Table 1 Clinical and laboratory features of all SSc patients

Demographics	Overall ($n=151$)	ILD ($n=60$)	Non ILD ($n=91$)	p
Female	132 (87.4)	50 (83.3)	82 (90.1)	0.32
Mean age at diagnosis in years (SD)	44.1 (13.0)	42.7 (12.1)	45.0 (13.4)	0.14
Median duration in years (IQR)	4.0 (1–7.0)	6.1 (1–9.3)	4.0 (0–5.0)	0.009**
Black ethnicity	131 (86.8)	53 (88.3)	78 (85.7)	0.82
History at presentation				
Gold mining history	6 (4.0)	5 (8.3)	1 (1.1)	0.026*
Smoking history ($n=130$)	20 (15.4)	9 (17.6) ($n=51$)	11 (13.8) ($n=80$)	0.60
Raynaud's phenomenon	125 (82.8)	50 (83.3)	74 (81.3)	0.56
Reflux	85 (56.3)	33 (55.0)	51 (56.0)	0.94
Dyspnoea	52 (34.4)	27 (45.0)	24 (26.4)	0.010*
Cough	37 (24.5)	21 (35.0)	15 (16.5)	0.005**
Examination at presentation				
Digital lesions	66 (43.7)	24 (40.0)	42 (46.2)	0.46
Nailfold capillary changes	106 (70.2)	39 (65.0)	66 (72.5)	0.44
Telangiectasia	19 (12.6)	6 (10.0)	13 (14.3)	0.44
Calcinosis	13 (8.6)	7 (11.7)	5 (5.5)	0.09
Tendon friction rubs	15 (9.9)	4 (6.7)	11 (12.0)	0.28
Bibasal crackles	39 (25.8)	28 (46.7)	10 (11.0)	< 0.0001***
Disease subtype				
dcSSc	94 (62.2)	49 (81.7)	45 (48.9)	< 0.001***
lcSSc	46 (30.5)	8 (13.3)	38 (41.3)	< 0.001***
Unclassified systemic sclerosis	11 (7.3)	3 (5.0)	8 (8.7)	0.38
Laboratory features				
HIV seropositivity	9 (6.0)	4 (6.8)	5 (5.5)	1.00
CRP > 8 mg/l (SD)	61 (40.4)	26 (49.1) ($n=53$)	35 (44.3) ($n=79$)	0.60
ESR > 20 mm/h (SD)	83 (55.0)	34 (57.6) ($n=59$)	47 (54.7) ($n=86$)	0.74
Anti-nuclear antibodies				
Positive ANA	133 (88.1)	57 (95.0)	76 (83.5)	0.07
Speckled ANA pattern	54 (40.6)	29 (50.9)	25 (32.9)	0.010**
Homogenous ANA pattern	4 (3.0)	3 (5.3)	1 (1.3)	0.30
Nucleolar ANA pattern	42 (31.6)	13 (22.8)	29 (38.2)	0.17
Anti-centromere antibody	10 (7.5)	0 (0.0)	10 (13.2)	0.006**
Anti-topoisomerase I antibody	25 (18.8)	13 (22.8)	12 (15.8)	0.17

All values are given as number (%), unless otherwise specified

SSc systemic sclerosis, *ILD* interstitial lung disease, *SD* standard deviation, *IQR* interquartile range, *dcSSc* diffuse cutaneous systemic sclerosis, *lcSSc* limited cutaneous systemic sclerosis, *HIV* human immunodeficiency virus, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *ANA* anti-nuclear antibody

*$p<0.05$; **$p<0.01$; ***$p<0.001$

ILD patients had barium swallow studies, of whom 53.4% had dysmotility and 81.4% had gastro-oesophageal reflux. Only a minority of nine ILD patients reported a smoking history and all but one of the six patients with a history of underground gold mining had evidence of ILD.

Associations and predictors of interstitial lung disease

On univariate analysis comparing ILD and non-ILD groups (Table 1), those with ILD had a longer disease duration (6.1 vs. 4.0 years; OR 1.08, 95% CI 1.01–1.15, $p=0.009$), dyspnoea (OR 2.44, 95% CI 1.23–4.87, $p=0.010$), cough (OR 2.93, 95% CI 1.37–6.29, $p=0.005$), and the presence of bibasal crackles on clinical examination (OR 7.58, 95% CI 3.31–17.37, $p<0.0001$). The dcSSc disease subtype was associated with ILD ($p<0.001$), whereas lcSSc was protective ($p<0.001$). A speckled ANA pattern was more common in the ILD group (OR 2.47, 95% CI 1.25–4.90, $p=0.010$). In contrast, ACA was protective for ILD where none of the patients with ACA had ILD (OR 0.12, 95% CI 0.02–0.97, $p=0.006$).

Table 2 Multivariate analysis for predictors of ILD at first presentation

Variable	OR (95% confidence intervals)	*p*
Bibasal crackles	9.43 (3.25–27.39)	< 0.0001***
Disease duration	1.19 (1.09–1.30)	< 0.0001***
Speckled ANA	2.95 (1.22–7.15)	0.017*
Gold mining history	5.90 (0.49–70.78)	0.14
Dyspnoea	1.05 (0.38–2.86)	0.90
Cough	2.60 (0.86–7.87)	0.16
Diffuse cutaneous disease	4.36 (0.79–24.23)	0.31
Limited cutaneous disease	0.86 (0.14–5.26)	0.62

ILD interstitial lung disease, *OR* odds ratio, *ANA* anti-nuclear antibody; r^2 0.499

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

The results of the multivariate logistic regression analysis are shown in Table 2. Only disease duration, bibasal crackles, and speckled ANA were independently associated with ILD.

With respect to the relationship of SSc subsets, patients with a gold mining history had predominantly dcSSc (83.3%), and had a significantly higher frequency of ILD compared to those without a history of gold mining (OR 8.18, 95% CI 0.93–71.88, $p = 0.026$). As shown above, ILD was associated with dcSSc, and ATA were associated with dcSSc (OR 6.32, 95% CI 1.42–28.30, $p = 0.007$), but there was no significant association of ATA with ILD. In the case of lcSSC, ILD was only observed in the absence of ACA.

Severity of interstitial lung disease

In the 59 patients who were able to perform PFTs, the mean (SD) overall FVC % predicted at SSc ILD diagnosis was 78.4 (22.1) and the mean (SD) DLCO % predicted was 65.2 (24.2) ($n = 53$). Most patients, 36 (61%) had mild ILD and 23 (39%) had moderate–severe disease. The DLCO in the moderate–severe group was significantly lower than in the mild group [mean (SD) DLCO 53.4 (16.0) vs. 73.3 (25.4), respectively, $p = 0.001$]. In the mild group, 52.8% of patients were diagnosed in the same year as their SSc diagnosis compared to 73.9% in the moderate–severe group ($p = 0.013$). A higher proportion of gold miners had moderate–severe disease (OR 7.37, 95% CI 0.77–70.71, $p = 0.066$) and dyspnoea was more common in the moderate–severe ILD group (OR 5.19, 95% CI 1.67–16.19, $p = 0.008$).

Treatment of interstitial lung disease

The median (IQR) time from SSc ILD diagnosis to immunosuppressive therapy was 1 (0–3) months. As shown in Table 3, 86.4% of the ILD patients received immunosuppressive therapy. Prior to the introduction of cyclophosphamide, D-penicillamine was used in ten ILD patients. Corticosteroids were used in conjunction with cyclophosphamide as an induction therapy followed by maintenance with either azathioprine or mycophenolate mofetil in 59.3% of ILD patients. Response to therapy is beyond the scope of this study.

Treatment-related complications occurred in only seven patients and were not related to the severity of ILD. Four developed pulmonary tuberculosis; two developed haemorrhagic cystitis from cyclophosphamide; and one developed pneumonia (other than tuberculosis).

Outcome of interstitial lung disease patients

At last contact, the outcome of 90 patients was known, 24.4% of whom had died. The proportion of deaths in the ILD group and non-ILD group were similar, the causes of death differed. In the case of the ILD group, ILD was a common cause of death (44.4%), followed by infection (22.2%) and in one-third of cases the exact cause of death was unknown. In contrast, deaths in the non-ILD group were mainly cardiovascular related and infection (each 30.8%), malignancy (15.4%) and unknown cause of death (23.1%).

Discussion

In this study of SSc ILD in a sub-Saharan African population, ILD was common (40%), often complicated by PHT, and was a frequent cause of death. Interstitial lung disease was associated with the following features: longer duration of disease, history of occupational gold mining exposure, cough, dyspnoea, dcSSc disease subtype, bibasal crackles

Table 3 Immunosuppressive treatment given in mild ILD and moderate–severe ILD groups

Treatment	Mild ILD ($n = 36$)	Moderate–severe ILD ($n = 23$)	*p*
Intravenous cyclophosphamide	20 (55.6)	15 (65.2)	0.76
D-Penicillamine	6 (27.8)	4 (17.4)	0.61
Azathioprine	11 (30.6)	5 (21.7)	0.44
MMF	6 (27.8)	3 (13.0)	0.79
Methotrexate	4 (11.1)	6 (26.1)	0.11
Corticosteroids (> 10 mg/day)	26 (72.2)	18 (78.3)	0.89
No treatment	6 (27.8)	2 (8.7)	0.32

All values are given as number (%)

ILD interstitial lung disease, *MMF* mycophenolate mofetil

and speckled ANA pattern. Limited cutaneous SSc and ACA were protective.

Interstitial lung disease has been described to occur in the majority of patients within the first 3 years of SSc diagnosis [5], whereas in our study most patients were diagnosed with ILD within the same year as their SSc diagnosis. This may be related to late presentation of our patients.

With respect to association with clinical subsets and autoantibodies, we found a significant association of ILD with dcSSc but not with ATA, which has been shown in previous studies [5, 12–15]. This lack of association of ILD with ATA is probably related to the relatively small sample size in the present study. Conversely, we found ACA positivity to be protective against ILD, a finding that has been observed in several studies [2, 12, 13, 16].

The three independent predictors of ILD, namely disease duration, bibasal crackles and a speckled ANA pattern, predicted only about 50% of ILD. Indeed, fewer than 50% of all ILD patients had clinical findings such as cough, dyspnoea and bibasal crackles. This emphasises the importance of screening all newly diagnosed SSc patients for ILD irrespective of clinical findings [24]. Those patients with suggestive signs should have investigations expedited, particularly in the case of dyspnoea which was found to be significantly associated with more severe ILD and occurred in almost 70% of patients in this subgroup.

The severity of ILD in this study was comparable to the spectrum of ILD seen in other studies [5], however, notably more patients here with moderate–severe ILD were diagnosed with ILD in the same year as their SSc diagnosis. This may again be a function of late presentation, as well as those with more severe symptoms being expedited for HRCT and PFTs.

Some of the limitations of this study relate to the relatively small sample size as compared to larger databases such as the EUSTAR and Pittsburgh, albeit the largest in the region. The retrospective method meant that there were missing data, for example, we were unable to correlate Rodnan skin scores with ILD. Another major limitation of this study is the lack of more accurate confirmation of PHT by right heart catheterisation due to scarce resources. However, considering limited resources, the majority of patients had a rapid diagnosis of ILD using PFTs and HRCT, and received appropriate treatment soon after diagnosis.

In summary, the strength of this study is that it is the largest from sub-Saharan Africa to describe SSc ILD patients in terms of severity, predictors of disease, therapy and outcome. In our cohort of patients, the dcSSc subtype is a significant driver behind the development of ILD, rather than the presence of specific autoantibodies such as ATA. Indeed, the lack of ACA and its protective effect in these patients contributed to ILD. Contributions from genetic factors remain unknown, which is an important aspect to be incorporated into anticipated prospective studies.

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Author contributions PA, MT, CI: Study conception and design. PA, MW: Acquisition of data. PA, MT, CI: Analysis and interpretation of data. PA, CI: Drafting of article. PA, MT, MW, CI: Critical revision of article. MT, CI: Supervision. PA, MT, MW, CI: Approval of version to be published.

Compliance with ethical standards

Funding This was an unfunded study.

Conflict of interest Philippa Ashmore, Mohammed Tikly, Michelle Wong, Claudia Ickinger declare that they have no conflict of interest.

Ethics approval The study was approved by the Human Research Ethics Committee (Medical), University of the Witwatersrand (approval no. M120966, 2012-09-28), with waive of informed consent as this was a retrospective chart review. All procedures performed in studies involving participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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