Systemic Sclerosis in an Afro-Caribbean Population

A Review of Demographic and Clinical Features

C Flower, C Nwankwo

ABSTRACT

Objective: *To assess the clinical and selected demographic features of patients with systemic sclerosis (SS) seen over a 10-year period at the Rheumatology service of the Queen Elizabeth Hospital, Barbados. To compare these data with what is known to obtain in other ethnic populations.*
Design and Methods*: A chart review involving all patients who were found to have SS based on the American College of Rheumatology clinical criteria was conducted between 1996 and 2006.*
Results: *Twenty-seven patients with SS were identified in this predominantly Afro-Caribbean population. The prevalent and incident cases numbered 10 and 17 respectively. Twenty-six of these patients were female and the mean age at diagnosis was 37.3 years. Diffuse cutaneous involvement was seen in 63% of cases and limited cutaneous involvement in 37%. The most common clinical features in descending order of frequency were Raynaud's phenomenon, gastroesophageal reflux, pigmentary skin changes, digital pitting/ulceration, telangiectasia and pulmonary disease.*
Conclusion: *In a predominantly Afro-Caribbean population, SS was uncommonly seen, had a marked female preponderance and an earlier age of onset than that seen in Caucasian populations. As expected, diffuse disease was the more common subtype and digital pitting, pigmentary skin changes, and pulmonary disease were amongst the most frequent clinical features. Telangiectasia were found more frequently than the literature suggests is typical for patients of African descent.*

Esclerosis Sistémica en la Población Afrocaribeña

Un Estudio de las Características Demográficas y Clínicas

C Flower, C Nwankwo

RESUMEN

Objetivo: *Evaluar los rasgos clínicos y las características demográficas seleccionadas de pacientes con esclerosis sistémica (ES) atendidos por un periodo de 10 años en el Servicio de Reumatolog?ía del Hospital Queen Elizabeth Hospital, Barbados. Comparar estos datos con lo que se conoce que existe en otras poblaciones étnicas.*
Diseño y Métodos: *Entre 1996 y 2006, se llevó a cabo una revisión de historias clínicas, la cual abarcó a todos los pacientes a quienes se les diagnosticó ES, sobre la base de los criterios clínicos del Colegio Americano de Reumatología.*
Resultados*: Se identificaron veintisiete pacientes con ES en esta población predominantemente afrocaribeña. Los casos prevalentes e incidentes ascendieron a 10 y 17 respectivamente. Veintiséis de estos pacientes fueron hembras y la edad promedio en el momento del diagnóstico fue 37.3 años. En 63% de los casos se observó compromiso cutáneo difuso, en tanto que en el 37% se observó compromiso cutáneo limitado. Los rasgos clínicos más comunes en orden descendente de frecuencia fueron el fenómeno de Raynaud, el reflujo gastroesofágico, cambios de pigmentación de la piel, ulceración digital, telangiectasia y enfermedad pulmonar.*

West Indian Med J 2008; 57 (2): 118

From: School of Clinical Medicine and Research, The University of the West Indies, Queen Elizabeth Hospital, Bridgetown, Barbados

Correspondence: Dr C Flower, School of Clinical Medicine and Research, The University of the West Indies, Queen Elizabeth Hospital, Martindale's Road, Bridgetown, Barbados. E-mail: cflower@caribsurf.com

INTRODUCTION

Systemic sclerosis (SS), an autoimmune disorder of connective tissue characterized by fibrosis of the skin and internal organs, has well documented racial and ethnic variations. Patients of African descent are thought to be affected twice as frequently as Caucasians and additionally have an earlier age of onset, a higher frequency of diffuse disease, more severe pulmonary disease and overall poorer prognosis (1).

Information on SS in persons of Afro-Caribbean origin is limited. Afro-Caribbean patients have been found to have a relatively high prevalence of anti U3-RNP (anti-fibrillarin) antibodies and a strong association of these antibodies with diffuse disease (2).

The Queen Elizabeth Hospital, the only government-sponsored tertiary healthcare facility on the island of Barbados, serves a population of 270 000 (2000 census) of whom over 90% are of African descent. Selected demographic and clinical features of patients with SS seen over a 10-year period by the rheumatology service of the Queen Elizabeth Hospital are reviewed.

METHODS

We reviewed the charts of all patients diagnosed with SS in accordance with the American College of Rheumatology Criteria (Table 1) and presenting to the Rheumatology service between 1996 and 2006 (3). We recorded demographic and clinical data for these cases. Patients with systemic sclerosis *sine* scleroderma, overlap connective tissue diseases and localized scleroderma were excluded.

RESULTS

Twenty-seven patients with SS were identified, consisting of 10 prevalent and 17 incident cases, with 96% being of African origin. There were 26 females and 1 male, varying in age from 15 to 64 years, with a mean age of 37.3 years at diagnosis. Seventeen patients (63%) had diffuse disease (scleroderma skin changes extending proximal to the elbows and knees) while 10 patients (37%) had limited disease (scleroderma skin changes in the distal limbs with or without facial and neck involvement). The clinical features are listed in Table 2. In addition to skin thickening and tightening inherent in the diagnosis, the most common clinical features in descending order of frequency were Raynaud's phenomenon, gastroesophageal reflux, pigmentary skin changes (vitiligo and hyperpigmentation) and digital pitting/ulceration. These features were also noted to predominate in patients with diffuse disease.

Table 1: American College of Rheumatology diagnostic criteria for systemic sclerosis

Major Criterion	Minor criteria
Proximal sclerodermatous skin changes (proximal to the metacarpophalangeal joints)	1. Sclerodactyly
	2. Digital pitting scars of fingertips or loss of the distal finger pad
	3. Bibasilar pulmonary fibrosis

Gastroesophageal reflux was diagnosed based on clinical symptoms and was responsive to proton-pump inhibitors without causing protracted morbidity. Only one patient had an additional significant gastrointestinal complication, that of small bowel overgrowth.

Fibrosis was the most frequent pulmonary complication seen, occurring in 8 of the 11 patients identified on Chest X-ray and echocardiography as having varying degrees of alveolar and pulmonary vascular disease. Five of the eight patients were asymptomatic and were not prescribed immunosuppressive therapy.

Clinically and echocardiographically significant pericardial effusions were seen in three patients, with one patient requiring pericardiocentesis for impending cardiac tamponade. One patient had a cardiomyopathy.

Table 2: Clinical features of 27 patients with diffuse and limited systemic sclerosis seen over a 10-year period

Clinical feature	Diffuse % n = 17	Limited % n = 10
Raynaud's phenomenon	100	80
Gastroesophageal reflux	94	80
Pigmentary changes	94	70
Digital pitting/ulcers	88	40
Telangiectasia	41	60
Pulmonary disease	35	50
Cardiac disease	18	10
Myositis	12	10
Renal crisis	18	0
Calcinosis	12	0

Myositis and scleroderma renal crisis each occurred in three patients while calcinosis was documented in two patients. One patient developed a malignancy, multiple myeloma, during the review period. Two deaths were recorded during the follow-up period. One patient died of a pulmonary embolus within the first year of diagnosis and another patient died of a ruptured cerebral aneurysm three years after diagnosis of SS.

Table 3 compares data from the three US ethnic groups comprising the 'Genetic versus Environment in Scleroderma outcome study group' (GENISOS study group) with the Barbados cohort. Our cohort had a significantly earlier age of diagnosis and a high percentage of patients with diffuse disease, pigmentary changes, digital pitting and pulmonary disease as is typically described in patients of African descent. Additionally, telangiectasia was more commonly seen in the patients in Barbados that previously recognized in other reviews of patients of African origin.

Table 3: Comparison of clinical data from 3 US ethnic groups with systemic sclerosis and the Afro-Caribbean cohort

Clinical feature	Caucasian n = 79	*GENISOS Hispanic n = 54	Black n = 28	Afro-Caribbean n = 27
Gender % female	82	93	100	96
Mean age at diagnosis/years	51.4	48.5	46.8	37.3
Diffuse cutaneous %	46	61	62	63
Raynaud's phenomenon %	86	93	96	93
Gastroesophageal reflux %	62	63	71	89
Digital pits/ulcers %	49	61	82	70
Pigmentary changes %	51	59	82	85
Telangiectasia %	53	52	14	48
Calcinosis %	15	22	18	11
Pulmonary fibrosis %	14	22	32	30
Pulmonary hypertension %	3	6	4	11
Myositis %	9	15	11	11

*Genetics versus environment in systemic sclerosis outcome study group
Semin Arthritis Rheum 2001; **30:** 332–46.

DISCUSSION

Scleroderma, derived from the Greek words meaning 'hard skin', was first described in 1753 in a 17-year-old woman from Naples. It was, however, not until 1945 that visceral involvement became an accepted complication (4) and Systemic Sclerosis became a more appropriate term. This chronic disease characterized by increased deposition of collagen and extra-cellular matrix in the skin and internal organs results in fibrosis and destruction of the micro-vasculature. Newer insights into the pathogenesis of SS suggests that an antigen may activate T cells resulting in infiltration of tissues and the production of profibrotic cytokines such as interleukin 4, transforming growth factor beta and platelet-derived growth factor. B cells are also thought to contribute to the fibrotic process (5).

Recent epidemiologic data from a large US cohort in Detroit reports a prevalence rate of 242 cases per million and an annual incidence rate of 19.3 per million (6). The female to male ratio was 4.6 and similar to our patients; 60% of the patients of African descent had diffuse disease (compared to only 27% of those not of African descent). This small cohort in Barbados with a single tertiary care referral centre suggests that the disease is rare in our setting, though admittedly cases of limited cutaneous systemic sclerosis could conceivably go unrecognized and escape referral.

In the predominantly Caucasian Detroit cohort, the mean age at time of diagnosis of SS was 10 years older than that seen in the present study, supportive of the known earlier age of onset of SS in persons of African descent. Other ethnic differences noted were the observed higher rates of digital ulcers, digital pitting and impaired lung function in persons of African descent when compared to Caucasians (7).

In another review of racial and ethnic differences, African-Americans were found more likely to have pigmentary skin changes and be associated with anti-U1 and anti-U3 ribonucleoprotein antibodies while Caucasians were more likely to have telangiectasia and an association with anti-centromere antibodies (8). Indeed, pigmentary skin changes were seen in 85% of index patients making this the most common cutaneous manifestation after sclerodermatous skin involvement itself. Specific autoantibody analysis was not available in our patients.

Secondary Raynaud's phenomenon, the recurrent, reversible vasospasm of arterioles and digital arteries in systemic sclerosis is an almost universal feature and occurred in all of the patients with diffuse disease in this study. It is associated with ischaemia and reperfusion injuries which are thought to be important in the pathogenesis of sclerosis (9).

Raynaud's phenomenon, though an important early feature of SS, may also occur as a primary phenomenon in otherwise healthy individuals. To distinguish between the two and to aid in predicting which patients with Raynaud's phenomenon are likely to develop SS, a thermography study, the 'distal-dorsal difference' may be applied. A difference of greater than 1°C between the fingertips and the dorsum of the hand is suggestive of the structural vascular disease that is typical of SS (10).

Gastroesophageal reflux, the most common gastrointestinal complication of SS, can cause local complications such as oesophageal erosions and strictures as well as extra-intestinal conditions such as aspiration pneumonia (11). As therapeutic options for this complication have expanded, the resultant morbidity has been minimized.

Digital pitting and ulceration, a frequent clinical feature in our patients is most strongly associated with diffuse disease, is the result of ischaemia, repetitive micro-trauma and delayed healing. Ischaemia is thought to be associated with vasospasm, intimal fibro-proliferation and microthrombosis (12).

Telangiectasia, most typically associated with limited disease, ultrastructurally are dilated post-capillary venules located in the papillary and superficial reticular dermis (13). Recognition of these lesions in heavily pigmented skin may be challenging, with the potential for underestimation. Calcinosis, though infrequently seen, represents one of a decreasing number of complications of SS for which no standard treatment regimen has evolved. Newer treatment options with reported success in individual cases include extracorporeal shock wave lithotripsy (14) and carbon dioxide laser vaporization (15).

For SS, the influence of race on disease susceptibility and disease expression has been outlined and differences may be explained in part by genetic factors. It is known that certain polymorphisms of the Cytotoxic T Lymphocyte associated Antigen 4 (CTLA 4) gene are associated with SS in African-Americans but not Caucasians (16), and Afro-Caribbean individuals share a common West African ancestry with African-Americans.

This review establishes the baseline characteristics of SS in the Barbadian population and we hope to complement the further inventory of cases with serologic data.

REFERENCES

1. Reveille JD. Ethnicity and race and systemic sclerosis: how it affects susceptibility, severity, antibody genetics and clinical manifestations. Curr Rheumatol Rep 2003; **5:** 160–7.
2. Tormey VJ, Bunn CC, Denton CP, Black CM. Anti-fibrillarin antibodies in systemic sclerosis. Rheumatology 2001; **40:** 1157–62.
3. Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum. 1980; **23:** 581–90.
4. Rodnan GP, Benedek TG. An historical account of the study of progressive systemic sclerosis (diffuse scleroderma) Ann Intern Med 1962; **57:** 305–19.
5. Sakkas LI. New developments in the pathogenesis of systemic sclerosis. Autoimmunity 2005; **38:** 113–6.
6. Mayes MD, Lacey JV Jr, Beebe-Dimmer J, Gillespie BW, Cooper B, Laing TJ et al. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. Arthritis Rheum 2003; **48:** 2246–55.
7. Nietert PJ, Mitchell HC, Bolster MB, Shaftman SR, Tilley BC, Silver RM. Racial variation in clinical and immunological manifestations of systemic sclerosis. J Rheumatol 2006; **33:** 263–8.
8. Reveille JD, Fischbach M, McNearney T, Friedman AW, Aguilar MB, Lisse J et al. Systemic sclerosis in 3 US ethnic groups: a comparison of clinical, sociodemographic, serologic, and immunogenetic determinants. Semin Arthritis Rheum. 2001; **30:** 332–46.
9. Sunderkotter C, Riemekasten G. Pathophysiology and clinical consequences of Raynaud's phenomenon related to systemic sclerosis. Rheumatol 2006; **45:** S3 33–5.
10. Anderson ME, Moore TL, Lunt M, Herrick AL. The 'distal-dorsal difference': a thermographic parameter by which to differentiate between primary and secondary Raynaud's phenomenon. Rheumatol 2007; **46:** 533–8.
11. Ntoumazios SK, Voulgari PV, Potsis K, Koutis E, Tsifetaki N, Assimakopoulos DA. Esophageal involvement in scleroderma: Gastroesophageal reflux the common problem. Semin Arthritis Rheum 2006; **36:** 173–81.
12. Chung L, Fiorentino D. Digital ulcers in patients with systemic sclerosis. Autoimmun Rev 2006; **5:** 125–8.
13. Walker JG, Sterling J, Beroukas D. Histopathological and ultrastructural features of dermal telangiectasia in systemic sclerosis. Pathology 2005; **37:** 220–5.
14. Sparsa A, Lesaux N, Kessler E, Bonnetblanc JM, Blaise S, Lebrun-Ly V et al. Treatment of cutaneous calcinosis in CREST syndrome by extracorporeal shock wave lithotripsy. J Am Acad Dermatol 2005; **53:** S263–5.
15. Chamberlain AJ, Walker NP. Successful palliation and significant remission of cutaneous calcinosis in CREST syndrome with carbon dioxide laser. Dermatol Surg. 2003; **29:** 968–70.
16. Mayes MD. Race, scleroderma, and survival: Why is there a difference. J Rheumatol 2005; **32:** 1873–4.