Richter and Kerr. J Geriatr Med Gerontol 2016, 2:008
Volume 2 | Issue 1
ISSN: 2469-5858

Journal of
Geriatric Medicine and Gerontology

Review Article: Open Access

Late-onset Diffuse Systemic Sclerosis: A Presentation of Five Cases

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Abstract

Diffuse systemic sclerosis typically presents in persons aged 30-50 years. Although it is not uncommon to encounter the limited form of the disease in persons over the age of 65, diffuse disease in this age group is considered to be uncommon. Thus it is not considered as a diagnostic possibility in older adults who develop respiratory or gastrointestinal complaints.

In contrast to this perception, we describe our recent experience over the past 18 months in which we diagnosed diffuse systemic sclerosis in 5 patients all of whom presented with symptom onset after the age of 65. All five had typical physical signs and symptoms including proximal skin thickening, and upon further investigation four of the patients had some evidence of pulmonary hypertension or interstitial lung disease.

These findings highlight the importance of recognizing the early signs of diffuse systemic sclerosis in older adults and reaffirm some of the unique disease features previously reported in this demographic.

Keywords

Systemic sclerosis, Scleroderma, Raynaud's, Interstitial lung disease

Introduction

Systemic Sclerosis (SSc) is an autoimmune disease characterized by fibrosis of the skin and internal organs and obliterative vasculopathy. The disease is more common in women and has a peak age of onset between 40 and 50 years, though a significant proportion of patients develop the disease later in life [1]. In a cohort of over 2,000 patients with SSc, 9.5% had an age of onset after 65, and 1.7% had an age of onset after 75 [2,3]. While advanced age has been associated with a poorer prognosis, it is unclear whether this is due to differences in their disease course or delayed recognition due to other factors that accompany aging [4,5].

SSc is one of two major categories of scleroderma; the other is localized scleroderma that only affects the skin. SSc is further divided into either a limited or diffuse form. Limited SSc typically presents as CREST syndrome (Calcinosis, Raynaud's phenomenon, Esophageal involvement, Sclerodactyly, and Telangiectasias) and is associated with a milder course with less organ involvement, while diffuse SSc has acral and truncal skin thickening and extensive organ involvement earlier in the disease course. Diffuse SSc is also associated with a higher morbidity and mortality [6]. The main cause of death is pulmonary involvement, which can present as pulmonary hypertension and/or interstitial lung disease [7]. While older adults with new onset SSc more often present with the limited subtype, there are reports of these patients presenting with pulmonary manifestations [6,8,9]. This study will examine five cases of late-onset diffuse SSc, four of which presented with some evidence of lung disease.

Methods

Subjects

Between January 2013 and October 2015, three patients with new-onset SSc presented to the geriatric rheumatology clinic at Mount Sinai Medical Center. Two additional patients were seen as part of the rheumatology inpatient consult service between July 2015 and September 2015. Diagnosis was made based on the 2013 American College of Rheumatology classification criteria for systemic sclerosis, and patients were categorized as having diffuse disease if they had evidence of internal organ involvement or skin thickening extending proximal to the elbows [10]. Secondary causes of SSc including industrial exposures and certain medications were ruled out with patient histories. Pulmonary hypertension was diagnosed by echocardiography and defined as a resting mean pulmonary arterial pressure of greater the 25 mmHg, though this did not suffice as evidence of organ involvement. To be classified as late-onset scleroderma, patients needed to confirm that their first non-Raynaud's symptom began after the age of 65 [6].

Data

A retrospective chart review was conducted which included details on demographics, clinical features, autoantibodies, comorbidities, and results from chest imaging and pulmonary function tests (PFTs). Internal organ involvement was established through evidence of fibrosis on computed tomography (CT) or a restrictive pattern on pulmonary function testing, defined as a decrease in both forced expiratory volume in one second (FEV1) and forced vital capacity (FVC), and a FEV1/FCV ratio greater than 80%. Severe gastrointestinal involvement presenting as pseudo-obstruction also served as evidence of diffuse disease.

Results

The clinical features seen during the patients' initial presentations are presented in Table 1. All five patients were female and were

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Citation: Richter MD, Kerr LD (2016) Late-onset Diffuse Systemic Sclerosis: A Presentation of Five Cases. J Geriatr Med Gerontol 2:008

Received: November 25, 2015: **Accepted:** January 14, 2016: **Published:** January 18, 2016

Table 1: Clinical features upon initial presentation

	1	2	3	4	5
Age/Sex	72F	81F	77F	68F	72F
Diagnosis	SSc (diffuse)	SSc (diffuse)	SSc (diffuse)	SSc (diffuse)	SSc (diffuse)
Presenting complaint	Shortness of breath	Pseudo-obstruction	Shortness of breath	Pseudo-obstruction	Toe ulceration
Raynaud's (duration)	-	+ (1 years)	+ (20 years)	+ (unknown)	+ (3 years)
Esophageal involvment	+	+	+	+	-
Proximal Skin involvement	+	+	+	+	+
Scleroderma facies	+	+	+	+	+
Telangiectasias	-	-	+	-	-
Synovitis	-	-	-	-	-
ANA	1:640	1:640	1:640	1:10,240	Not collected
Anti-centromere B	-	-	+ (87)	-	+ (155)
Anti-Scl-70	-	-	-	-	Not collected
Comorbidities	CAD	Pituiatary adenoma	CAD	Renel cell carcinoma	PAD
	DM type II	Hypothyroidism	HTN	DM type II	DM type II
	Osteopenia	HTN	Cervical spinal fusion	CHF	HTN
	BPPV	Osteopenia		Asthama	

ANA: antinuclear antibody; CAD: coronary artery diseases; DM: diabetes mellitus; BPPV: benign paroxysmal positional vertigo; HTN: hypertension; CHF: congestive heart failure.

Table 2: Evaluation of possible pulmonary disease

	1	2	3	4	5
Transthoracic Echocardiography	Mild pulmonary hypertension	No evidence of pulmonary hypertension	Moderate pulmonary hypertension, severly reduced RV function	Mild pulmonary hypertension	Moderate pulmonary hypertension
CT Chest	Honycombing and reticular changes consistent with mild interstitial lung disease	Enlarged pulmonary arteries, no interstitial changes	Ground glass opacities and diffuse interstitial markings, consistent with fibrotic changes	No interstitial changes	-
Pulmonary Function Tests	Mild restriction without air trapping FEV1/FVC 83% DLCO 80%	-	Severe gas transfer defect FEV1/FVC 83% DLCO 45%	-	-

CT: computed tomography; FEV: forced expiratory volume; FVC: forced vital capacity; DLCO: diffusion capacity for carbon monoxide.

diagnosed with SSc after the age of 65. In 4 cases the presenting complaint was a manifestation of their internal organ involvement: 2 patients presented with dyspnea due to interstitial lung disease and another 2 had intestinal pseudo-obstruction. All five patients had diffuse proximal skin thickening.

Raynaud's phenomenon was present in all but one patient and in each case preceded the onset of their disease. Proximal skin thickening, sclerodactyly and scleroderma facies were present in all five patients. Four out of five patients had some degree of esophageal involvement, typically presenting as persistent gastroesophageal reflux disease (GERD). No patients had any sign of active joint inflammation, and only one presented with telangiectasias, which were diffuse over both palms. Serum antinuclear antibodies (ANA) were positive in four patients, though this test was not conducted for patient 5. Anticentromere antibodies were positive in only two patients, while no patients had antibodies to topoisomerase I.

Each patient underwent some degree of evaluation for possible pulmonary disease (Table 2). Interstitial lung disease was diagnosed in patients 1 and 3 through PFTs that showed a decreased diffusion capacity. Chest CTs of these patients were also remarkable for changes characteristic of pulmonary fibrosis. Patient 5 did not undergo these testing modalities but was shown to have moderate pulmonary hypertension on transthoracic echocardiography (TTE). In total, four out of five patients had some evidence of pulmonary hypertension on TTE.

Discussion

While not routinely seen in general practice, SSc is a potentially life threatening disease that can present in the geriatric population, and should therefore be recognizable to general practitioners. The diagnosis is most often made clinically which highlights the importance of recognizing the early features of the disease. This can be particularly challenging in older patients with multiple comorbidities and subtle findings such as skin changes or worsening GERD, and diagnosis is often delayed [6,8,11]. As shown in our study these patients were referred to a rheumatologist only after a significant disease burden, which made it difficult to determine precisely when their first symptom occurred.

Many patients who develop SSc have a prior history of Raynaud's phenomenon, which can serve as a useful clinical warning sign. While the condition can present in isolation, primary Raynaud's disease predominantly affects young women and is rare among elderly patients, who will most often go on to develop some type of connective tissue disease, usually SSc [12,13]. Other causes of Raynaud's to consider include various connective tissue disorders, vascular diseases, medication side effects, and thyroid disease. Diagnosing Raynaud's from the patient's history can be challenging, particularly because older adults have a lower tolerance to cold temperature at baseline [14]. However, eliciting a history of characteristic color changes in response to cold or stress, distinct from simply increased sensitivity, can be diagnostic of Raynaud's without any further testing [6].

Testing for autoantibodies in SSc has a limited diagnostic utility. Anti-nuclear antibodies have a low specificity but are present in about 90% of cases and can be helpful if the clinical diagnosis is uncertain. Anticentromere antibodies are typically associated with the CREST variant of SSc (96-98% specific), though most patients even with limited disease do not test positive [15]. Patient 3 in our study is a rare example of a patient with diffuse disease who tested positive for anticentromere antibodies. Anti-Scl-70, also called anti-topoisomerase I, is mainly seen in diffuse SSc but again is absent in the majority of these patients [16]. None of the patients in our study with diffuse disease were positive for Anti-Scl-70. While they can sometimes be useful in diagnosis and prognostication, testing for

autoantibodies is only indicated for patients with clear clinical signs of systemic sclerosis [17].

There is contradictory evidence regarding the differences in clinical presentation between early and late-onset SSc. Traditionally it was thought that older patients tended to have a milder disease course, and a recent study that included 191 patients over the age of 60 concluded that the standardized mortality ratio was lower in older patients when controlling for the population effects of age and sex [3,9]. However, other studies have suggested that age is associated with an increased risk of internal organ manifestations, particularly pulmonary hypertension [3,18,19]. One study comparing older to younger patients showed that this risk is twofold for patients presenting after the age of 60 [20].

While there is currently no consensus regarding screening for pulmonary disease in SSc patients, it is generally recommended that patients undergo echocardiography and PFTs every 6 months to 1 year [21]. There are several immunosuppressive therapies that have proven useful in SSc interstitial lung disease, though their potential benefit in older patients must be balanced with the increased risk for infections, side effects, and drug interactions. Pulmonary hypertension can also be treated pharmacologically, though the response of patients with SSc tends to be poorer than those with pulmonary hypertension secondary to other causes [21]. There is currently no set of unique guidelines for the diagnosis or treatment of SSc in the geriatric population, and the effects of aging and comorbidities are still only partially understood. Despite these limitations, earlier recognition of systemic sclerosis could lead to better clinical outcomes and less irreversible organ damage.

Acknowledgments

We gratefully acknowledge the referrals from the Geriatric Practice, Martha Stewart Living Center at Mount Sinai Medical Center.

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