The Primary Care Physician in the Early Diagnosis of Systemic Sclerosis: The Cornerstone of Recognition and Hope

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Abstract: Systemic sclerosis (SSc) is a disease of unknown causative factor that manifests as a heterogenous group of multiorgan system manifestations and is characterized by vasculopathy and fibrosis of the skin and internal organs, with mortality related to pulmonary, cardiac, renal or gastrointestinal involvement. The prevalence of SSc may be underestimated in the general population. Cases are often undiagnosed or misdiagnosed, particularly cases with mild or no skin manifestations. Because of late referrals to rheumatologic care, many moderate-to-severe cases progress to irreversible end-organ damage that might have been prevented by early diagnosis. Early diagnosis of SSc with initiation of appropriate treatment is essential, with great impact on morbidity and mortality. This review examines presenting features, ensuing complications and treatment providing a focus on SSc as a treatable disease. Primary care providers play a pivotal role in recognizing initial symptoms associated with SSc and securing early diagnosis through early referral to specialists.

Key Indexing Terms: Systemic sclerosis; Screening; Raynaud's; Scleroderma; Fibrosis; Early diagnosis and referral. **[Am J Med Sci 2014;347(1):54–63.]**

Systemic sclerosis (SSc), or scleroderma, is a complex multiorgan system group of diseases of unknown causative factor associated with increased mortality, complex morbidity, disability and reduced quality of life.[1–8] The striking clinical features of SSc have been poignantly described in art and literature. Paul Klee, the famous 20th century artist, suffered from SSc, and his work reflected the stages of his illness. As he became progressively disabled by his disease, his colorful, fine-line abstract paintings evolved into dark-colored masterpieces characterized by thick brush strokes and dark colors. His final self-portrait, Death and Fire (1940), depicts a dying figure whose face is ashen and near death (Figure 1). The brush strokes comprising his facial features spell out "Tod," which means death in German.[9] Sir Arthur Conan Doyle, the creator of Sherlock Holmes, chronicled a man suffering from localized scleroderma in his short story, "The Adventure of the Blanched Soldier."[10]

Characteristic features include vasculopathy and excessive collagen accumulation in skin and internal organs.[11,12] The classic clinical observation is induration or thickening of the skin (skleros, hard; derma, skin); however, skin findings may not be present or develop only after other signs and symptoms appear, such as Raynaud's phenomenon (RP). The earliest signs of SSc include RP, fatigue and arthralgia, which may include "puffy fingers" and worsening "heartburn."[13–16] Damage from SSc ensues from either vascular microangiopathy and obliteration (eg, kidneys), ischemic disease resulting in neural dysfunction and further fibrosis (eg, gastrointestinal [GI] dysmotility) or diffuse collagen deposition (eg, pulmonary fibrosis), which may be insidious, progressive and irreversible, involves the heart, lungs, kidneys, GI tract, muscles and periarticular structures and accounts for the major morbidity and mortality associated with the disease.

Prevalence estimates vary with the population studied and whether or not people with mild SSc-like illnesses are included.[17–22] Based on the most recent large scale epidemiologic studies in the Australia, Spain and the United States, prevalence rates are estimated to be 242 cases per million adults with an annual incidence of approximately 20 new cases per million adults per year.[17–22]

We present the following case histories of patients with SSc that could have benefited from early intervention, to illustrate the commonly observed initial clinical features of SSc and to assist primary care providers in identifying cases for referral for rheumatologic evaluation.

CASE VIGNETTES

1. A 53-year-old woman, with frequent visits to her internist for 9 months of patchy vitiligo and painful RP (initially attributed to hypothyroidism) and 6 months of diffuse body pains, develops worsening dyspnea and sudden "hysterical" coughing episodes over a 3-month period in addition to diffuse skin thickening on her hands, arms, legs, chest and face, such that she has difficulty opening her mouth. She now has claw-like deformities of her hands and her elbows are at 30° fixed flexion contractures bilaterally. This last visit, her internist realizes her symptoms are serious and referral to rheumatology is arranged. On workup, the patient is found to have lost greater than 50% of her expected lung volume with diffuse interstitial changes on chest imaging.
2. A 37-year-old male carpenter with a 3-year history of visits to his healthcare provider reports worsening stiff

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FIGURE 1. Paul Klee, Tod und Feuer (Death and Fire), 1940. Zentrum Paul Klee. Reproduced with permission from EUSTAR.[9]

joints and RP, assumed to be related to osteoarthritis and pneumatic drill use from when he was employed in construction 10 years ago, respectively. He is recently distressed by progressive loss of dexterity, extreme fatigue with activities, erectile dysfunction and palpitations. Several of his fingers have shortened. Ultimately, on rheumatologic referral, the patient is diagnosed with osteolysis and late functional class pulmonary hypertension related to SSc.

3. A 42-year-old woman visited her primary care physician with recurrent complaints of 2 years of cold blue fingers and increasing dyspnea over the past 3 months. Over the past 18 months, she has become increasingly less active and more tired and now is unable to walk from her house to her car without shortness of breath. The patient has a fainting spell secondary to hypoxia and is admitted to the ICU, intubated and diagnosed with interstitial pneumonitis and SSc. She dies in hospital of cardiopulmonary failure.

CLINICAL FORMS OF SCLERODERMA

Scleroderma is a heterogenousgroup of diseases divided into 2 general groups: localized and SSc. Localized scleroderma is considered nonlife-threatening but can be disfiguring. Localized scleroderma, which can occur in linear forms or as guttate morphea or morphea profunda, is very rarely a systemic disease and will not be elaborated on in this review.

SSc, conversely, is the most serious form of scleroderma and therefore the most important to identify early and is classified into limited cutaneous and diffuse cutaneous forms. It is important to recognize that these descriptors only apply to distribution of skin involvement and do not reflect potential of organ involvement, which occurs in both. Limited cutaneous SSc (lcSSc), formerly known as CREST syndrome for calcinosis, Raynaud's, esophageal dysmotility, sclerodactyly and telangiectasias, is typified by skin thickening limited to the distal extremities, face and upper neck. It was originally considered to be a more benign form of the disease but is now recognized for its life-threatening effects on multiple organ systems with lcSSc patients experiencing some of the most severe GI effects. Specifically, lcSSc carries with it a high prevalence of pulmonary arterial hypertension (PAH) which, if untreated, is uniformly fatal within 5 to 10 years.[2,23,24] It is also important to note that patients with lcSSc may experience severe pulmonary fibrosis.

Diffuse cutaneous SSc (dcSSc) is generally characterized by a rapidly progressive skin thickening proximal to the elbows and/or knees. Progressive and diffuse skin involvement is correlated with a higher incidence of internal organ involvement—with fibrosis of heart and lung and renal crisis ensuing within the first 5 years of illness—and death,[6,7] although patients with lcSSC may have a higher incidence of PAH.

The following discussions pertain to both dcSSc and lcSSc; although some findings may be more prevalent in one form over another, both forms of SSc share all of the concerns and clinical/pathologic aspects discussed later. Following a brief overview of the current understanding of the pathogenesis of this heterogenous disease, we will review organ system involvement so that primary care and specialty physicians may be better equipped to identify clinical features that herald disease onset. Although SSc is not a curable disease, it is a treatable disease in the early stages. Because early diagnosis and treatment may prevent or delay significant morbidity and mortality, international collaborative efforts are underway to identify patients very early in the course of SSc[13–15,23,25–28] by immediate referral of patients with RP to a rheumatologist at a recognized SSc center.

PATHOGENESIS

The causative factor and pathogenesis of SSc, despite tremendous recent developments by dedicated translational scientists,[29–43] remains largely an unknown phenomenon. The evidence and characterization of these pathological events[11,12,44,45] are considerable and beyond the scope of this article; but, a basic overview is important to understand the importance of early diagnosis, complications and treatment of SSc.

Fibrosis, although the hallmark of SSc, appears to be a late event in a complex web of potentially hundreds of layered, cascading and coincident processes, whereby the deposition of collagen and other components ultimately replace the normal architecture of blood vessels, internal organs and skin.[11,12,15,34,37,44] The initial catalyst inciting the events that lead to fibrosis is presumed to reside at the vascular level, that is, vascular injury from exposure, either chemical or microbial, or from immunologic insult or both.

This catalyst injury, however, is thought to occur in an already dysfunctional vascular system in which all layers of the vessel are potentially vasculopathic. In SSc, vascular repair processes appear to be inherently dysregulated by impaired recruitment and integration of endothelial cells in vasculo-/angiogenesis—despite high levels of circulating proangiogenic factors such as vascular endothelial growth factor and endothelial cell apoptosis.[29–35,44] Injury results in the recruitment and overexpression of an inflammatory surge of poorly regulated interactions in cell-to-cell communications in a wide array of repair, immune, epithelial and endothelial cells.[29–35,44]

This elaborate series of inflammatory and immune events comprise what is considered an upstream phase of fibrosis; this prefibrosis/inflammation/immune phase is potentially the optimal time for efficacious intervention or at least very close observation.[6,7,13–16,25,27]

Aberrant cytokines such as transforming growth factor-beta are thought to induce fibroblast production and deposition of extracellular matrix constituents such as collagen that result