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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 etiology that manifests as a heterogeneous group of multi-organ 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. Due to 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.

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Conflicts of Interest

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Dedication

This manuscript is dedicated to our patients who exemplify grace and bravery in the face of a catastrophic and disabling illness and to the selfless dedication of many SSc researchers for their tireless, and very often voluntary efforts, to improve the lives of patients with SSc.

Keywords

systemic sclerosis; screening; Raynaud's; scleroderma; fibrosis; early diagnosis and referral

Introduction

Systemic sclerosis (SSc), or scleroderma, is a complex multi-organ system group of diseases of unknown etiology associated with increased mortality, complex morbidity, disability and reduced quality of life.^{1–8} The striking clinical features of systemic sclerosis have been poignantly described in art and literature. Paul Klee, the famous 20th century artist, suffered from systemic sclerosis, 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 (e.g. kidneys), ischemic disease resulting in neural dysfunction and further fibrosis (e.g. GI dysmotility), or diffuse collagen deposition (e.g. pulmonary fibrosis) which may be insidious, progressive and irreversible, involves the heart, lungs, kidneys, gastrointestinal (GI) tract, muscles and peri-articular 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, in order 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 Raynaud's phenomenon (initially attributed to hypothyroidism) and 6 months of diffuse body pains, develops worsening dyspnea and sudden ‘hysterical’ coughing episodes over a 3-month period as well as 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. Upon work-up,

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 joints and Raynaud's phenomenon, 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, upon 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 heterogeneous group of diseases divided into 2 general groups: localized and systemic sclerosis. Localized scleroderma is considered non-life-threatening but can be disfiguring. Localised 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.

Systemic sclerosis, on the other hand, is the most serious form of scleroderma and therefore the most important to identify early, 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 5–10 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 as well as 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 diffuse and limited cutaneous systemic sclerosis; although some findings may be more prevalent in one form over another, both forms of systemic sclerosis share all of the concerns and clinical/pathologic aspects discussed below. Following a brief overview of the current understanding of the pathogenesis of this heterogeneous 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. While 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 etiology 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 in order to understand the importance of early diagnosis, complications and treatment of SSc.

Fibrosis, while 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 i.e. 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 pro-angiogenic factors such as VEG-F as well as endothelial cell apoptosis^{29–35,44}. Injury results in the recruitment and over-expression 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 pre-fibrosis / 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 (ECM) constituents such as collagen that result in fibrosis whereby ECM itself is antigenic thus contributing to the perpetuation of pathogenic phases^{40–43}. These sequential and inter-related vascular, immunologic and fibrotic phases of the disease reflect the varied clinical manifestations that often also occur in similar sequence e.g. RP (vascular changes), puffy painful fingers (inflammation) as earlier signs with skin thickening or contractures (fibrosis) as later findings^{13–16,46,47}.

Manifestations and Complications

Raynaud's Phenomenon

RP (Figure 2) is overwhelmingly the first specific symptom of SSc articulated by patients, making it the most accessible portal to an early diagnosis of SSc^{13–16,25–28}. Patients often describe painful stinging fingers in response to cold or stress with associated colour changes from white (blanching due to lack of circulation) to blue (hypoxia) and finally to red (reperfusion). Many people with RP may never develop a connective tissue disease (CTD). However, secondary RP signals an underlying vasculopathy and is present in >95% of SSc patients and identifying patients who are at risk of developing a CTD may improve health outcomes and survival in CTD patients^{13–15,25–28,45,48–51}. Primary care physicians play an integral role in identifying RP and orchestrating an efficient work-up and referral. Accurate classification of RP can be accomplished through a combination of strategies optimally performed by an experienced rheumatologist with established expertise in SSc a)

examination with nailfold capillaroscopy (Figure 3); b) obtainment of an appropriate antibody profile; c) meticulous review of systems and physical examination to detect often overlooked findings that are consistent with rheumatologic disease^{13–16,25–28,49–57}.

Nailfold capillaroscopy, in which the examiner places a drop of immersion oil at the base of the patient's nailbed for microscopic visualization of the nailfold capillaries is an essential component in the assessment of a patient with RP^{25,26,52}. In primary RP the capillaries will appear normal, while in CTDs capillaries are likely to appear abnormally dilated with lost or "dropped-out" capillaries often evident (Figure 3). The presence of either positive antibodies or abnormal capillaroscopy findings is highly predictive for a CTD^{13–15,25–28}. The role of diagnostic auto-antibodies in SSc is discussed following a systematic review of organ system involvement.

Constitutional

Fatigue can be one of the most troubling symptoms experienced by patients with SSc, and patients often describe fatigue early in disease. It is a major contributor of disability in SSc, paralleling that of patients with cancer undergoing chemotherapy^{58,59}.

Weight loss can happen in SSc for many reasons: dysphagia, PAH- or ILD-related dyspnea, malabsorption syndrome, pain or mechanical difficulty with chewing due to oral anatomical changes, arthritis or osteolysis of the mandible, painful digital ulcers making it difficult to feed oneself or cachexia of systemic inflammation. Patients with rapidly progressive diffuse SSc can quickly lose muscle mass and become malnourished. Weight loss is indicative of a poor prognosis in SSc.

Digital Ischemia

RP in SSc is associated with vasospasm and fibrosis, both with the potential to cause hypoxia in surrounding tissue. Severe RP can rapidly develop into painful and disabling ischemia, resulting in digital ulcerations (DU)⁴⁸. DUs are the cause of significant morbidity with pain, resultant disability and decreased quality of life. Often difficult to heal due to skin thickening and calcinosis, DUs may progress to gangrene (Figure 4), osteomyelitis and amputation and are exacerbated by the vasoconstrictive effects of smoking, -making smoking cessation counseling a vital component at every primary care and specialist visit.

Skin Findings

Skin findings include skin thickening, telangiectases, hypo- and hyper-pigmentation due to skin thickening or associated vitiligo and atrophy in addition to digital pitting and ulceration. Telangiectasias - a more prominent skin manifestation of lcSSc -, are rhomboid-shaped dilated capillary clusters that are typically found on the face, oral mucosa, lips, fingers and palms (Figure 5). Telangiectasias are often unrecognized by non-specialists and are an important diagnostic clue as well as a prognostic feature of SSc is associated with vasculopathy and predictive for the presence of occult or potential development of PAH as well as heart involvement^{60, 61}. These rhomboid-shaped lesions are distinguished from the more common spider-like configurations associated with solar damage.

Skin thickening generally develops after the onset of RP and is associated with internal organ involvement, making it crucial to establish rheumatologic care before skin involvement rapidly progresses. Skin thickening is preceded by edema or a doughy appearance of the skin beginning distally and then, in dcSSc, ascending proximally beyond to the elbows and/or knees. Skin involvement may progress rapidly resulting in a woody appearance of involved skin and joint contractures occurring secondary to overlying skin, fascial and muscle involvement. Hypo- and hyperpigmentation and skin atrophy appear later

in the disease process. Over time, the classical skin induration may soften and abate. Despite the improvement that may be observed in skin over time, internal organ involvement requires constant vigilance, with lung (leading cause of death) and GI involvement progressing independently of skin involvement. Potentially effective treatment for the skin manifestations of SSc may exist in the future but is unlikely to reverse damage that has already occurred.

Musculoskeletal

Musculoskeletal manifestations typically present early in the course of SSc and may predominate in initial phases of SSc. Symptoms may seem vague with body pain, hand pain and swelling resulting in dismissal of symptoms or treatment with diuretics^{78,13–16}. Inflammatory arthritis and tendon involvement, often diagnosed by the presence of tendon friction rubs, with joint contractures are common and associated with significant disability in SSc^{8,46,47,79,80}. They are associated with rapidly diffuse systemic disease, internal organ involvement and mortality^{6,7,46,47}. Prior to diagnosis patients often describe puffy, doughy and often uncomfortable painful swelling of digits.

Myopathy is very common in SSc and may be the result of inflammation, fibrosis, necrosis or unidentifiable cause. The majority of involvement is identified upon physical examination with very few patients reporting symptoms - possibly due to the other overwhelming effects of SSc. Atrophy, myalgia, and weakness are common with the presence of myopathy warranting biopsy to guide treatment. Myopathy is also associated with internal organ involvement with a very prominent association with cardiac abnormalities in SSc^{65–67,81–83}. Assessment of muscle strength and ambulation is an important aspect of the musculoskeletal evaluation in patients with SSc. Finally, osteoporosis has a higher prevalence amongst patients with SSc⁸⁴.

Pulmonary Involvement

A complaint of dyspnea in a patient with SSc should always be taken very seriously as it may be a manifestation of potentially life-threatening cardio-pulmonary involvement. Patients with early SSc often present with new onset RP and dyspnea. ILD and PAH are the most common and two of the most dreaded complications of SSc. ILD is now the leading cause of death for patients with SSc followed by PAH and both result in cardiopulmonary failure.^{2,6,7,15,23,24,62,63} Both cause significant disability with potential for rapid demise if untreated. PAH, in particular, is often asymptomatic in early stages. Imperative initial screening with subsequent interval screening is essential in SSc with , pulmonary function testing assessing forced vital capacity, total lung capacity and diffusion capacity of the lung for carbon monoxide (DLCO); chest imaging and echocardiograms. Abnormalities on the echocardiogram, including right ventricular systolic pressure >40mmHg, suggest the presence of pulmonary disease and warrant the aggressive investigation with right heart catheterization.^{23,24,64} However, echocardiogram is an imperfect instrument in the assessment of possible PAH with a high frequency of mis correlations with pulmonary artery pressures. Declining DLCO may be an important clue in detecting PH. Unexplained new onset fatigue, dyspnea or palpitations with a normal echo, should prompt consideration for right heart catheterization⁶⁴. Again, smoking cessation cannot be over-emphasised.

Cardiac Involvement

Cardiac manifestations are a major contribution to mortality in SSc,^{2,6,7} and may include carditis, pericardial effusion and tamponade, myocardial fibrosis with resultant diastolic dysfunction, cardiac arrhythmia and pulmonary hypertension^{64–67}. Heart failure not due to coronary arterial disease or restrictive cardiomyopathy demands careful attention in SSc

with several potential causes that may require urgent intervention. A careful cardiac examination including physical examination, ECG and echocardiogram should be part of the comprehensive evaluation of potential cardiac symptoms.

Renal Involvement

Scleroderma renal crisis (SRC) is a microangiopathic disease (Figure 6) that most commonly occurs early in dcSSc heralded by an acute rise in blood pressure followed by acute renal failure. Before early detection and prompt treatment with ACE inhibitors, mortality due to SRC surpassed ILD and PAH in patients with SSc.^{63,68} Steroids, commonly used to treat symptoms of other CTDs, have limited efficacy in SSc and may precipitate of SRC.^{68,69} Blood pressure should be carefully monitored at frequent intervals in all patients with SSc.

Gastrointestinal Involvement

Gastrointestinal involvement is common, contributes significantly to morbidity and mortality, and may result in death with severe chronic disease requiring palliative interventions and contributing greatly to diminished quality of life⁷⁰. Any part of the GI tract can be affected, from the mouth to the anus, with any site of involvement capable of contributing to the severe impairment of quality of life with pervasive manifestations such as pain, nausea, malnutrition, food intolerance, diarrhea, colonic inertia and fecal incontinence.

Gastroesophageal reflux is one of the most common early clinical manifestations of SSc. Gastroesophageal reflux (GER) and aspiration may result from esophageal dysmotility (Figure 7) dysphagia and delayed gastric emptying. In later stage disease, severe esophageal involvement is proportional to interstitial lung disease, suggesting that aspiration from dysphagia or GER may exacerbate ILD^{71,72}.

GI dysmotility represents a key dysfunction creating severe chronic complications in SSc. Neural effects from vascular ischemia and to a much lesser extent fibrosis within the GI tract interferes with normal gut motility, anywhere from the esophagus to the anus, causing decreased digestion, emptying, absorption and peristalsis, with resultant dilation which may result in pseudo-obstruction or malabsorption syndrome.

Vascular ectasia of the GI tract may be an early manifestation of scleroderma and can result in either acute catastrophic hemorrhage or chronic bleeding with iron-deficient anemia⁷⁰. Gastric antrum vascular ectasia (GAVE) (Figure 8) is also known as watermelon stomach due to the typical appearance of the endoscopy of exposed vessels creating linear projections extending from the pylorus into the antrum. The colon can also be involved with vascular ectasia.

Malabsorption in SSc can result in malnutrition, weight loss, diarrhea and fecal incontinence. Malabsorption can involve the gastric mucosa, small intestine or colon. Vasculopathy of the GI mucosa may contribute to the poor absorption of micronutrients from the GI lumen. Fibrosis interfering with motility may be the most significant underlying cause of malabsorption, resulting in bacterial overgrowth with diarrhea, bloating and incontinence, and is difficult to treat in late stage SSc.

Sexual Function

SSc in men is related to a high incidence of erectile dysfunction thought to be related to fibrosis of the corpus cavernosae^{73–75}. In women, fibrosis of the vaginal canal with consequently decreased introitus size and dryness results in ~60% experiencing dyspareunia, which impairs sexual function.^{3,76–77}

Antibodies in SSc

The role of antibodies in the pathogenesis of SSc is unclear though antibodies to at least one of several antigens may be detected in >90% of patients with SSc^{13–15,26,34,42,51,53–57}. Identification of specific antibodies is not necessary for a diagnosis of SSc. Though antibodies have been identified in affected organs, their utility beyond diagnosis and prognostication as well as exact role in pathogenesis remains to be elucidated.

Despite our lack of understanding of the pathogenesis of SSc, the presence of particular antibodies is associated with specific organ targets and distribution of involvement. As there are more than 25 different antibodies that have been identified in association with SSc, an extended discussion is beyond the purview of this article. The most prevalent antibodies specific to SSc are Scl-70 extractable nuclear antigen (an antibody to topoisomerase-I) and the anti-centromere antibody. Scl-70 is highly specific for SSc, predicts severe disease and correlates with rapidly progressive diffuse disease, portends a poorer prognosis and more extensive organ involvement, especially interstitial lung disease^{2,6,7,47,55,85}. Anti-centromere antibodies correlate with a presentation of limited skin involvement and portend high risk for development of vascular complications such as PAH^{23,55,85}. It is of great importance to note that newer methods of anti-nuclear antigen testing by means of immuno-absorbent bead complexing yields a high rate of *false negatives* whilst for Scl-70 has demonstrated a high rate of false *positives* - it is important that laboratory method is adherent to immune-fluorescence assays in patients being evaluated for SSc.

Diagnosis

Diagnosis of SSc can be elusive and the criteria for diagnosis are continually being challenged as strategies for earlier diagnosis are continually refined^{13,14,26,27,86}. In the absence of extracutaneous manifestations as described above, the most predictive and specific finding is nailfold capillary abnormalities followed by antibody presence (see RP section)^{13,14,26,27,49,51}. Recognition of presenting signs and symptoms of SSc as outlined above, can greatly expedite diagnosis for patients with SSc which can ultimately translate into improved outcomes^{13,15,23,26}.

Treatment

Patients with SSc should be referred to SSc specialists for concurrent care because recognition and management of coincident complications requires specialized expertise and is highly likely to improve health outcomes and to prevent and postpone permanent damage and death^{13–15}. A rheumatologist experienced in treating the complex heterogeneous manifestations of SSc will work in concert with the patient's primary care provider to ensure optimal and comprehensive care for this complicated disease.

Treatment of SSc typically requires both systemic and organ-based approaches^{87,88}. Highly effective systemic treatments for SSc - for which therapeutic responsiveness may be influenced by delayed time to diagnosis remain elusive, but many researchers are actively involved in the pursuit of effective disease modifying agents for SSc such as the Scleroderma Clinical Trials Consortium and EUSTAR which are international collaborative bodies of investigators. Early detection and referral may also increase participation in clinical trials which are vital to identifying potential therapies for this rare disease. Systemic treatment currently involves the use of immunosuppressive agents with the avoidance of steroids wherever possible as the latter can precipitate an SSc renal crisis⁶⁸. Cyclophosphamide, mycophenolate mofetil, rituximab, tocilizumab, imatinib mesylate, serotonin 2B receptor inhibitors and stem cell transplantation are currently being used in the clinical setting or under investigation^{87–97}. Adjuvant therapies, such as glitazones,

angiotensin modulation, statins and SSRIs as potential antifibrotics, are being explored.^{87,88}. Some of the agents traditionally used in rheumatoid arthritis such as methotrexate and hydroxychloroquine can help manage arthritis in SSc.

PAH, digital ulcers, osteolysis, calcinosis and RP comprise the overt vascular complications of SSc. Symptoms of RP and digital ischemic pain are often treated with long-acting calcium channel blockers, ACE modulators, phosphodiesterase inhibitors (PDE), topical nitroglycerin, topical lidocaine and digital nerve blocks must include total smoking cessation^{48,87,88,98–101}. Preventive strategies that maintain warmth with gloves and hand warmers should be emphasized at every visit. Use of beta-blocking agents can worsen digital ischemia. The more refractory digital ulcers and PAH, can be treated with many of the same therapeutics: PDEs, endothelin receptor agonists, and prostacyclins alone or in combination^{48,87,88,98–101}. Ulcers require aggressive evaluation by an SSc wound care team along with the debridement of necrotic or infectious lesions as well as the removal of eschars to disclose and prevent infection. Hyperbaric treatment and digital sympathectomy have reported efficacy in the treatment of ischemia and ischemic wounds in SSc.^{100–102}

Occupational, physical, speech and dental specialists are integral in the global treatment of SSc. An SSc specialty center would have inter-disciplinary care with faculty knowledgeable and experienced in the complexity of SSc. Physical, occupational and or speech therapy are pivotal in patients' efforts to optimize and maintain function. Patients are often provided interventions and durable supplies specific to the needs of SSc-related contractures, range of motion, pain, diminishing mouth apertures and enigmatic loss of strength. Dental and endodontic care can be crucial as SSc results a complex array of complicated and difficult to diagnose manifestations such as drastic anatomical and physiological changes in the oral cavity resulting in difficulty chewing and tooth loss; osteolysis and calcinosis of the jaw or invasive cervical absorption of teeth,

Renal crisis must be identified early and managed with aggressive use of ACE inhibitors. Pulmonary fibrosis, may require immunosuppression with cyclophosphamide, mycophenolate mofetil, rituximab^{87–90,103} or with stem cell or lung transplantation. GI manifestations are treated promptly to avoid severe complications. Proton pump inhibitors (PPIs) and preventive strategies are used to manage gastric reflux. Prokinetics for hypomotility are a poor choice in patients with SSc and if employed should be used with great caution as they increase pressure on the lower esophageal sphincter and cause cardiac arrhythmias. Oxygen use has also been reported to enhance mobility in colonic inertia; with surgical resection as a last resort after extensive conservative intervention.¹⁰⁴ Bacterial overgrowth is difficult to eradicate and early treatment with antibiotics may impact the course of manifestation. GAVE with bleeding requires endoscopic ablation and possibly transfusion support.

Conclusion

In summary, SSc is a rare and life-threatening disease of unknown etiology with clinical manifestations involving almost every organ system. Its prevalence is likely underestimated as it may sometimes remain undiagnosed, particularly in its milder forms. Continued registry data collections coupled with thorough occupational and environmental history-taking may one day provide clues to this enigmatic rare disease. Scleroderma is a treatable disease.¹⁰⁵ Increased vigilance and knowledge on the part of primary care physicians is the cornerstone for improving outcomes. Early detection and referral to a rheumatologist with SSc expertise may prolong survival, preserve optimal function and substantially improve quality of life for patients with SSc.

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Appendix A: Resources for Physicians and Patients

European League Against Rheumatism, Scleroderma Trials and Research Group (EUSTAR). www.eustar.org This organization maintains an online resource of international scleroderma centers for patient care, physician education, and an ongoing international scleroderma registry as well as information on available clinical trials.

International Scleroderma Network: www.sclero.org A multilingual comprehensive educational resource with networking ability for patients and families that also supports international research.

Louisiana State University Scleroderma and Sarcoidosis Patient Care and Research Center. New Orleans. Provides comprehensive care to patients with SSc with hotline for referral and further information for patients, their families and physicians regarding diagnosis and care for people with SSc. 1-504-568-4498 www.medschool.lsuhsu.edu/rheumatology

Pulmonary Hypertension Association: <http://www.phassociation.org> Promotes patient support, education and research in pulmonary hypertension. Physicians can find on-line courses and other education resources in PH.

Raynaud's Association: www.raynauds.org Provides support and education to patients who suffer from RP.

Scleroderma Clinical Trials Consortium (SCTC): <http://www.sctc-online.org> Provides information on clinical research in scleroderma for clinical investigators and patients.

Scleroderma Foundation: www.scleroderma.org Provides patients, families and physicians with current advocacy and education information. Physicians can find on-line courses in SSc.

Scleroderma Research Foundation: www.srfcure.org A resource for information about scleroderma and scleroderma research for clinical investigators, physicians and patients.

Figure 1.
Paul Klee, *Tod und Feuer (Death and Fire)*, 1940. Zentrum Paul Klee. Reproduced from Hans-Jurg Suter, *Paul Klee and His Illness: Bowed but Not Broken by Suffering and Adversity* (Basel: S Karger, 2010), 191.

Figure 2. Patient with SSc and Raynaud's phenomenon: image shows blanching due to lack of circulation;. Courtesy of EUSTAR, French National Scleroderma Center, University of Lille, Lille, France.

Figure 3.

Capillaroscopy images. Early panel shows tortuosity and dilatation; active panel begins to show the drop out of capillaries with hemorrhages (darker areas in top right corner). Late panel shows severe disease with avascular areas and neoangiogenesis. Normal capillaroscopy included for comparison in upper left. Courtesy of EUSTAR, University of Genoa, Liguria, Italy.

Figure 4. Dry gangrene after severe digital ischemia. Courtesy of the Scleroderma and Sarcoidosis Patient Care and Research Center, Louisiana State University Health Science Center, Louisiana State University, New Orleans, Louisiana, USA.

Figure 5. Telangiectasias seen on hands of patient with SSc. Courtesy of Daniela Opris, Clinica de Medicina Interna si Reumatologie Spitalul Sf Maria-UMF Carol Davila, Bucuresti, Romania.

Figure 6. Scleroderma renal crisis. Arteriogram of kidneys: left: normal kidney; right: a kidney of a patient with scleroderma renal crisis. Courtesy of EUSTAR, University of Florence, Florence, Italy.

Figure 7. Esophageal dilatation on barium swallow causing severe heartburn and dysphagia. Courtesy of EUSTAR; University of Florence, Florence, Italy.

Figure 8.
Watermelon stomach (gastric ectasia) in a patient with persistent fatigue and anemia.
Courtesy of EUSTAR; University School of Medicine at Cochin Hospital, Paris, France.