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Scleroderma autoantibodies are associated with very specific demographic, clinical, organ system, and survival features. The use of scleroderma autoantibodies may be very helpful in determining the prognosis, as well as monitoring and treatment of scleroderma patients. There are many faces of scleroderma that seem to be closely associated with scleroderma autoantibodies. These antibodies should be used in performing clinical trials and in doing genetic and basic research. Hopefully, these scleroderma antibodies will lead to a better understanding of the pathogenesis of scleroderma.

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It currently is believed that scleroderma is a complex polygenic disease that occurs in genetically predisposed individuals who have encountered specific environment exposures and/or other stochastic factors. The nature of these genetic determinants and how they interact with environmental factors are areas of active investigation. This article discusses the evidence that supports a strong genetic link to scleroderma. These studies implicate potential pathogenetic mechanisms involved in scleroderma, which, it is hoped, may translate into clinical utility, including determination of disease risk, diagnosis, prognosis, and novel therapeutics.

The Pathology of Scleroderma Vascular Disease

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Jo Nadine Fleming and Stephen Mark Schwartz

Systemic sclerosis is characterized by three distinct pathologic processes: fibrosis, cellular/humoral autoimmunity, and specific vascular changes. Although a mild vasculitis may sometimes be present, the vascular pathology of scleroderma is not necessarily inflammatory and is best characterized as a vasculopathy. In this article, the authors propose that SSc vasculopathy is the result of an early event involving vascular injury that eventuates in a vicious cycle mediated in part by the immune process. The subsequent vascular malformation and rarefaction may be a function of systemic angiogenic dysregulation, with over expression of vascular endothelial growth factor but a lack of proper interactions with smooth muscle cells needed to stabilize and organize blood vessels.

Vascular Disease in Scleroderma: Mechanisms of Vascular Injury

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Bashar Kahaleh

Vascular endothelial injury in systemic sclerosis (SSc) includes a spectrum of changes that involve predominantly the microcirculation and arterioles. The pathologic changes in the blood vessels adversely impact the physiology of many organ systems, with a reduction in the size of microvascular beds leading to decreased organ blood flow and ultimately to a state of chronic ischemia. Current hypotheses in SSc vascular disease suggest a possible chemical or infectious trigger.

Vascular Disease in Scleroderma: Angiogenesis and Vascular Repair

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Mary Jo Mulligan-Kehoe and Michael Simons

Vascular abnormalities are one of the primary pathologic components of scleroderma. An early vascular indicator is aberrant nail fold capillaries that appear to undergo a switch from a pro- to anti-angiogenic process. Later in the disease process, ineffective and aberrant wound healing becomes apparent with frequent and widespread fibrosis. Pulmonary hypertension, largely due to the loss of pulmonary arterial vasculature, is frequently observed in late stages of the disease. The common theme of all these processes is abnormal regeneration of the vasculature and ongoing vascular losses due to defective maintenance of the vasculature. Although most aspects of vascular injury in scleroderma are poorly understood, certain biologic themes are beginning to emerge that are important in understanding scleroderma-related vascular disease.

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Because of the role of the RhoA/Rho kinase (ROCK) pathway in regulating numerous pathologic processes including vasoconstriction, vascular remodeling, and fibrosis, ROCK inhibitors may be especially beneficial in treating Raynaud's phenomenon and scleroderma.

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Ariane Herrick	

The manifestations of peripheral vascular disease in patients who have systemic sclerosis (SSc) range from episodic Raynaud's phenomenon to irreversible tissue injury with ulceration and gangrene. Structural and functional changes may occur in the microvessels, digital arteries, and sometimes more proximal vessels. This article discusses the assessment of patients who have Raynaud's phenomenon in whom an underlying scleroderma-spectrum disorder is suspected and patients who have SSc with critical digital ischemia/ulceration. Different imaging techniques, including capillaroscopy and angiography, complement the history and examination, and developments in vascular imaging should facilitate future studies of pathogenesis and treatment response. New vasoactive treatments are currently being researched and older treatments revisited; therefore new approaches to therapy will likely be developed over the next 5 to 10 years.

Fibrosis in Systemic Sclerosis	115
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This article reviews current understanding of the pathophysiology of fibrosis in systemic sclerosis. It highlights recent discoveries, insights, and emerging research, and potential opportunities for the development of targeted antifibrotic therapies.

Novel Treatment Approaches to Fibrosis in Scleroderma	145
Jörg Distler and Oliver Distler	

The molecular mechanisms leading to tissue fibrosis were only poorly understood in the past, and even today the cause or trigger of systemic sclerosis is still unknown. Remarkable breakthrough findings have been obtained regarding the identification of key molecules, key cellular mechanisms, and key intracellular signaling cascades, which mediate the perpetuation of fibrosis rather than

trigger it. These findings have true translational implications, because modifiers of these key mediators and key mechanisms are often in clinical use in other disease indications, such as cancer. This article summarizes the clinical and preclinical evidence of examples of these novel antifibrotic treatment approaches in systemic sclerosis, including stem cell transplantation, modifiers of transforming growth factor- β 1 signaling, intravenous immunoglobulins, tyrosine kinase inhibitors, and histone deacetylase inhibitors.

Current Approaches to the Management of Early Active Diffuse Scleroderma Skin Disease

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Svetlana I. Nihtyanova and Christopher P. Denton

Skin sclerosis is a clinical hallmark of systemic sclerosis (SSc) and provides a means to classify and evaluate patients. In the diffuse cutaneous subset, skin involvement is often extensive and warrants direct therapy. Currently, broad spectrum immunosuppressive strategies are used, but more targeted specific approaches are now emerging. This article reviews the evidence for efficacy of current treatment approaches and future developments for managing skin disease in early diffuse cutaneous SSc.

The Heart in Scleroderma

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Hunter C. Champion

The heart is one of the major organs involved in scleroderma, the involvement of which can be manifested by myocardial disease, conduction system abnormalities, arrhythmias, or pericardial disease. Additionally, scleroderma renal crisis and pulmonary hypertension lead to significant cardiac dysfunction secondary to damage in the kidney and lung. This article summarizes the types and mechanism of abnormalities in the heart in scleroderma. The concept of cardiac dysfunction in scleroderma and other rheumatologic conditions has received new interest with the advent of newer noninvasive imaging techniques, as well as the interest in detecting subclinical disease. With this increased interest in cardiac manifestations in scleroderma comes the realization that long-term studies are needed to better assess the appropriate screening and treatment in this patient population.

Treatment of Pulmonary Arterial Hypertension Due to Scleroderma: Challenges for the Future

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Lewis J. Rubin

Although progress has been made in treatment of pulmonary arterial hypertension, serious challenges remain. This article provides an overview of the challenges faced in treatment of PAH caused by scleroderma. It also provides a glimpse into the future, based on recent developments in the field that hold promise for enhancing the treatment of this disease.

Scleroderma-like Fibrosing Disorders
Francesco Boin and Laura K. Hummers

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Many conditions presenting with clinical hard skin and tissue fibrosis can be confused with systemic sclerosis (scleroderma). These disorders have very diverse etiologies and often an unclear pathogenetic mechanism. Distinct clinical characteristics, skin histology, and disease associations may allow one to distinguish these conditions from scleroderma and from each other. A prompt diagnosis is important to spare patients from ineffective treatments and inadequate management. This article highlights nephrogenic systemic fibrosis (nephrogenic fibrosing dermatopathy), eosinophilic fasciitis (Shulman's syndrome), scleromyxedema, and scleredema. These often are detected in the primary care setting and referred to rheumatologists for further evaluation. Rheumatologists must be able to promptly recognize them to provide valuable prognostic information and appropriate treatment options for affected patients.

Often Forgotten Manifestations of Systemic Sclerosis
Ami A. Shah and Fredrick M. Wigley

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Many clinical manifestations of systemic sclerosis (scleroderma) often go unrecognized; yet they can cause significant morbidity and are challenging to manage. This article discusses osteolysis, avascular necrosis of the wrist, oral manifestations, erectile dysfunction, pharyngeal weakness, fecal incontinence, nonscleroderma renal disease, liver disease, thyroid disease, and neurological disease in the scleroderma patient.

Systemic Sclerosis and Localized Scleroderma in Childhood
Francesco Zulian

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Juvenile scleroderma syndromes, including the systemic and the localized varieties, represent the third most frequent chronic rheumatic conditions in pediatric rheumatology practice. In children, systemic sclerosis shows a significantly less frequent involvement of all organs, a higher prevalence of arthritis and myositis, and a better outcome than in adults. Recently, new classification criteria were proposed, which help improve patient care by enabling earlier, more definite diagnoses and by standardizing the conduct of clinical trials. Localized scleroderma is the more frequent subtype of scleroderma in childhood. It comprises a group of distinct conditions that involve mainly the skin and subcutaneous tissues. They range from small plaques of fibrosis involving only the skin to diseases causing significant functional deformity with various extracutaneous features.

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