

## **Systemic Sclerosis / Scleroderma (SScl)**

### **Introduction:**

While it is called by many names and comes in different varieties, SScl is characterized by one basic problem: over-production of collagen. Collagen is an important protein in the body that is a component of scar tissue, which allows injuries to heal. When too much collagen is deposited, however, a number of problems can arise, and this is the basic obstacle that must be faced in patients with SScl.

The excess collagen seen in SScl is triggered by inflammation, which appears to simulate the cells in the body that make collagen. While the results of this process are most easily seen in the skin ("scleroderma" is literally translated "hard skin"), many other parts of the body can become involved. When this takes place, life-threatening complications may ensue.

SScl affects roughly 1 in 7,000 individuals in the United States, begins most commonly between 30 and 50 years of age, and affects women nearly 4 times as often as men. Depending on the type of skin involvement present and the organs that are affected, between 20-30% of patients will die from complications within the first 7 years of disease onset. These figures indicate that SScl is over twice as lethal as systemic lupus erythematosus (SLE).

### **Features of SScl:**

There are two different categories that patients with SScl fall into: limited SScl and diffuse SScl. Limited SScl is sometimes also called "CREST syndrome." While both subsets of patients may have involvement of the skin over the face and neck, those with limited disease demonstrate skin thickening that is restricted to the areas below the elbows and/or knees, while those with diffuse disease also experience skin thickening of the upper arms and/or legs or the trunk.

The appearance of the skin in such patients is initially "puffy" but in time become hardened and "leathery." Changes in skin pigment, loss of wrinkles, and contractures of fingers or limbs may occur. Skin thickening of the face typically results in diminished opening of the mouth. These changes develop at different rates in different patients, and many with limited SScl may only have subtle thickening over the fingers. Generally speaking, the extent of the skin thickening tends to correlate with the severity of involvement in other organs.

Dilated blood vessels, known as telangiectasias, often occur on the cheeks, lips, or fingers of SScl patients. These lesions appear as small red spots that blanch out when pressure is applied. Calcium deposits known as calcinosis may occur under the skin around the elbows, knuckles, and other locations. Occasionally, these deposits may appear as larger lumps or may drain a chalky white material.

Just as in SLE, isolated forms of skin involvement may occur that do not involve other organs. Morphea is a plaque-like area of skin thickening that commonly involves the trunk or limbs, and linear scleroderma is a potentially disfiguring process that causes streaks or "dents" to appear in the skin. Neither of these conditions, however, typically results in the more serious manifestations of SScl that will be discussed below.

Raynaud's phenomenon is present in over 90% of patients with SScl and may begin even before the onset of skin thickening or other signs of the disease. This condition is characterized by spasm of the blood vessels in the fingers or toes with cold exposure, resulting in white, blue, and/or red color changes. About 5% of the general population can describe a similar pattern of symptoms, but in patients with SScl, the loss of circulation is more severe and can lead to loss of tissue on the tips of the fingers if left untreated.

Lung disease is the number one cause of death in SScl. When present, lung impairment can take the form of interstitial fibrosis, where scar tissue builds up in the lungs, or pulmonary hypertension, where blood vessels leading to the lung become narrowed and place a strain on the right side of the heart. Most commonly, patients with diffuse SScl develop fibrosis of the lungs, while a minority of patients with SScl develops pulmonary hyper-tension.

Involvement of the esophagus may result in difficulty swallowing food or heartburn symptoms. Patients with diffuse SScl may also develop impairment of function in the lower part of the intestinal tract. This complication often results in difficulty in digesting food or obstructs the flow of gut contents, requiring nutritional support.

Other complications that occur almost exclusively in diffuse SScl include renal crisis, resulting in severe rises in blood pressure

and progressing to kidney failure; and heart involvement, resulting in either rhythm disturbances or inflammation of the lining of the heart known as pericarditis. At times, SScl may also overlap with other rheumatic diseases, such as SLE, Sjögren's syndrome (SS), or myositis (see related sections).

### **Diagnosis:**

The finding of skin thickening on physical examination is generally necessary in order to diagnose SScl. Rare skin diseases, exposure to various chemicals, and other rheumatic diseases may at times be difficult to distinguish from SScl. Uncommonly, a biopsy of affected skin can help to confirm the diagnosis, but this is usually not necessary if typical features of SScl are present elsewhere. When coupled with Raynaud's phenomenon and/or other findings consistent with SScl (lung disease, esophageal disease, etc.), the diagnosis is further strengthened.

The antinuclear antibody (ANA) is positive in at least 90% of patients with SScl. This antibody is also found in SLE, SS, and in some individuals who have no obvious rheumatic disease, but some subsets of this antibody are more typical for SScl and may aid in the diagnosis. For example, anti-centromere antibodies tend to be seen in patients with limited SScl, and anti-Scl-70 antibodies are associated with diffuse SScl.

Often, the biggest challenge is not making the diagnosis of SScl, but assessing the extent of involvement of the disease in other organs. Lung function studies are a good screening test to detect complications early. If abnormal, computerized tomographic (CT) scans or other procedures such as biopsy may be indicated to confirm the presence of lung involvement. An echocardiogram can be useful to detect abnormalities of heart function as well as findings suggesting pulmonary hypertension. Barium procedures performed in the x-ray department can detect SScl involvement of the esophagus or intestines. Frequent monitoring of blood pressure, especially in patients with diffuse SScl, is prudent to detect early renal crisis.

### **Treatment:**

Therapy for SScl is generally less successful than that of rheumatoid arthritis or SLE. Nonetheless, advances are being made that are resulting in improved outcomes, particularly for those with some of the more severe complications.

Treatment of skin thickening in SScl is not necessary for every patient, especially those with limited SScl, who are usually not significantly impaired by their skin changes. Patients with progressive skin thickening can logically be treated, but the results of studies attempting various medical therapies have been disappointing. Notably, studies of this type are very difficult to interpret due to the fact that patients with SScl typically experience a loosening of their skin a few years after the onset of their disease, raising the question of whether the drug or the natural course of the disease is responsible for such changes.

D-penicillamine has been a traditional choice among physicians due to its effects on cells producing collagen. Unfortunately, trials of this medication in SScl have yielded unimpressive results. A number of other medications that suppress the immune system have been attempted, including methotrexate and azathioprine, both of which failed to demonstrate benefit. Early results suggest that cyclosporine may be useful in treating the skin thickening of SScl, but further confirmation is needed. In summary, there are no guidelines for treating the skin component of SScl. An experienced physician, in conjunction with the patient, should carefully weigh the risks and benefits of these therapies before making treatment decisions.

Raynaud's phenomenon is treated by avoidance of cold temperatures, wearing protective clothing, and if still bothersome by medications. Drugs that dilate blood vessels, ordinarily used to treat high blood pressure, are preferred by most physicians (nifedipine and diltiazem, e.g.). Recent reports also suggest that fluoxetine (Prozac) has beneficial effects on circulation in Raynaud's phenomenon. More aggressive measures, such as intravenous medications (see treatment of pulmonary hypertension below) and surgery to reduce the spasm of the blood vessels, are sometimes necessary when fingertips lose blood supply and become ulcerated. Lung fibrosis has been treated with a number of different medications over the years. Recently, many physicians in the field of rheumatology have considered cyclophosphamide, a medication that powerfully suppresses the immune system, as the treatment of choice to address this complication.

Studies seem to indicate that this medication stabilizes or improves respiratory function in SScl patients with active inflammation in their lungs. Other medications such as cyclosporine and methotrexate have also been suggested as medications to treat lung fibrosis in SScl, but well-done studies have not been performed. Pulmonary hypertension is a serious complication of SScl with high mortality rates and few effective treatments until recent years. When severe, this complication can be treated with medications that must be infused intravenously on a continuous basis (epoprostenol, e.g.) but which appear to improve quality of life and survival. Because this option is difficult to manage, a new oral medication known as bosentan (Tracleer) has been devel-



oped. This medication seems to have similar effects on reducing pressures in the arteries leading to the lungs and possibly improving survival. Strangely enough, sildenafil (Viagra) also appears to be a promising therapy for pulmonary hypertension. Prompt recognition and the sound judgment of an experienced team of physicians are the best measures to most effectively treat this challenging problem. Esophageal disease may be treated with medications that reduce acid production in the stomach. Renal crisis is best treated with a class of blood pressure medications known as ACE inhibitors (captopril, lisinopril, e.g.). Before the introduction of these drugs, this complication was the top cause of death in SScl patients. Now, if medications are started early enough, the kidney function is often preserved. Moreover, about 1/2 of patients whose kidneys fail and require dialysis will be able to come off dialysis if staying on these drugs.

Heart-related complications in SScl are treated by correcting the rhythm abnormality if possible and giving medications to reduce inflammation when pericarditis is present. SScl is challenging to treat, although not nearly so challenging at times as it is to live with the complications the disease may cause. Because it is a relatively uncommon disorder, a qualified specialist or team of physicians working in conjunction with the primary care doctor is often needed to provide the best possible outcomes. As we discover more about this potentially devastating illness, it is hoped that more effective therapies will be developed to treat its various manifestations and enhance both the quality and the duration of patients' lives.