



Scleroderma Overview and Causes

Introduction

Scleroderma is an autoimmune disease which means that it is a condition in which the body's immune system attacks its own tissues. The normal role of the immune system is to provide protection from outside invaders such as bacteria and viruses. In autoimmune disorders, this ability to distinguish foreign from self is compromised. As immune cells attack the body's own tissue, inflammation and damage result. Scleroderma (the name means "hard skin") can vary a great deal in terms of severity. For some, it is a mild condition; for others it can be life-threatening. Although there are medications to slow down disease progression and help with symptoms, right now there is no cure for scleroderma.

TYPES OF SCLERODERMA

There are two main forms of scleroderma: systemic (systemic sclerosis, SSc) that usually affects the internal organs or internal systems of the body as well as the skin, and localized that affects a local area of skin either in patches (morphea) or in a line down an arm or leg (linear scleroderma), or as a line down the forehead (scleroderma en coup de sabre). It is very unusual for localized scleroderma to develop into the systemic form.

SYSTEMIC SCLEROSIS (SSc)

To make matters more confusing, there are two major types of systemic sclerosis or SSc: limited cutaneous SSc and diffuse cutaneous SSc. The difference between limited cutaneous and diffuse cutaneous SSc is the extent of skin involvement. In limited SSc, skin thickening only involves the hands and forearms, lower legs and feet. In diffuse cutaneous disease, the hands, forearms,

upper arms, thighs, or trunk are affected.

The face can be affected in both forms. The importance of making the distinction between limited and diffuse disease is that the extent of skin involvement tends to reflect the degree of internal organ involvement.

Systemic Sclerosis sine (without) skin thickening refers to the unusual occurrence (only about 5% of all cases) in which there is evidence of internal organ complications of SSc but no skin thickening.

Several clinical features occur in both limited and diffuse cutaneous SSc. Raynaud phenomenon, for example, occurs in both. Raynaud phenomenon is a condition in which the fingers turn pale or blue upon cold exposure, and then become ruddy or red upon warming up usually associated with a numb or tingling sensation in the fingers. These episodes are caused by a spasm of the small blood vessels in the fingers. As time goes on, these small blood vessels become damaged to the point that they may become totally blocked. This can lead to ulcerations of the fingertips. Raynaud phenomenon occurs in almost all (95%) SSc patients with either limited or diffuse disease, and painful finger ulcers can also be seen in both forms.

The esophagus is also affected in almost all SSc patients with loss of the usual movement. As a result, food can "hang up" in the esophagus, and stomach acid can reflux back up into the esophagus, causing heartburn.

Telangiectasias are small red spots that appear on the hands, arms, face, and/or trunk. These are tiny blood vessels in the skin that have widened. They are usually not dangerous in themselves, but are cosmetically unpleasing, particularly

if they occur on the face. Some people have telangiectasias in the esophagus, stomach, and bowel that can be a source of bleeding.

People with the diffuse form of SSc are at a greater risk of developing pulmonary fibrosis (scar tissue in the lungs that interferes with breathing, also called interstitial lung disease), kidney disease, and bowel disease.

All patients with SSc should have periodic pulmonary function tests to monitor for the development of pulmonary fibrosis. Symptoms of pulmonary disease include a dry cough and shortness of breath. However, in the early stages there may not be any symptoms at all.

Kidney involvement occurs more frequently in the diffuse than in the limited form of SSc, especially in the first five years after disease onset, and typically takes the form of a sudden increase in blood pressure. As is the case with usual high blood pressure, there are no symptoms at first. However, if undetected and untreated, this high blood pressure can damage the kidneys in a matter of weeks, which is why it is called scleroderma renal crisis. The key to management and prevention of permanent kidney damage is early detection and treatment of high blood pressure with a class of medications called ACE inhibitors.

The risk of extensive gut involvement, with slowing of the movement or motility of the stomach and bowel, is higher in those with diffuse rather than limited SSc. Symptoms include feeling bloated after eating, diarrhea, or alternating diarrhea and constipation.

Calcinosis refers to the presence of calcium deposits in, or just under, the skin. This takes the form of firm nodules or lumps that tend to occur on the fingers or forearms, but can occur anywhere on the body. These calcium deposits can sometimes break out to the skin surface and drain whitish material (described as having the consistency of toothpaste).

Pulmonary hypertension (PH) is high blood pressure in the blood vessels of the lungs. It is totally independent of the usual blood pressure that is taken in the arm. This tends to develop in patients with limited SSc after several years of disease. The most common symptom is shortness of breath on exertion. However,

several tests need to be done to determine if PH is the real culprit. If the ultrasound of the heart, called an echocardiogram, is abnormal, then a right heart catheterization should be done to actually measure the pressure in the lung blood vessel (pulmonary artery) and to test for other abnormalities that can cause PH. Because there are now many medications to treat PH, the earlier it is detected and treated, the better the result will be.

LOCALIZED SCLERODERMA

Localized scleroderma is almost always a purely skin condition, and is virtually never associated with the severe and potentially life threatening complications of SSc.

Morphea

Morphea consists of patches of thickened skin that can vary from half an inch to six inches or more in diameter. Some people have only one or a few such patches, while others have multiple ones all over the body. The patches can be lighter or darker than the surrounding skin and thus tend to stand out. Also there is usually a loss of the fatty layer underneath the morphea spots. Morphea, as well as the other forms of localized scleroderma, does not affect internal organs.

Linear scleroderma

Linear scleroderma consists of a line of thickened skin down an arm or leg on one side. The fatty layer under the skin can be lost, so the affected limb is thinner than the other one. In growing children, the affected arm or leg can be shorter than the other.

Scleroderma en coup de sabre

Scleroderma en coup de sabre is a form of linear scleroderma in which the line of skin thickening occurs on the forehead or elsewhere on the face. In growing children, both linear scleroderma and en coup de sabre can result in distortion of the growing limb or lack of symmetry of both sides of the face.

WHAT CAUSES SCLERODERMA?

The cause of scleroderma is unknown. However, we do understand a great deal about the biological processes involved. In localized

scleroderma, the underlying problem is the overproduction of collagen (scar tissue) in the involved areas of skin. In systemic sclerosis, there are three processes at work: blood vessel abnormalities, fibrosis (which is overproduction of collagen) and immune system dysfunction, or autoimmunity.

In systemic sclerosis, the small blood vessels are damaged and become narrowed. This is what is responsible for Raynaud phenomenon and the painful ulcers that can occur on the fingers. This vascular damage also occurs in the internal organs and is responsible for scleroderma renal crisis and PH.

The small arteries are normally capable of constricting (narrowing) or dilating (relaxing) to adjust blood flow to the needs of the body. For example, in very cold weather the blood vessels to the hands and feet narrow in order to maintain central body warmth. However, in SSc the blood vessel loses its normal method of relaxation, becoming prone to episodes of vasospasm (contraction of the muscle wall that closes the vessel). The vessels become overly sensitive to cold temperatures and other stimuli like emotional stress, which results in Raynaud attacks.

The thickened skin in scleroderma is caused by overproduction of collagen, which is the basic component of scar tissue. Abnormal accumulation of collagen is called fibrosis. Collagen is a normal part of skin and many organs. However, in scleroderma the balance of collagen formation and collagen breakdown is altered so that too much collagen builds up.

In localized scleroderma this process is confined to some areas of the skin. In SSc, excess collagen can cause fibrosis in the heart, lungs, and the muscles that line the GI tract.

Collagen is made by fibroblasts (a type of cell that is part of almost every tissue in the body) which can be provoked or activated to make more collagen. Under normal circumstances, the production of a scar is the last step in healing following an injury or an infection, for example, the production of a scar following a cut in the skin. Fibroblasts are activated by the immune system to produce collagen as part of the normal healing process. However, in SSc fibroblasts are activated for no apparent reason. The resulting

scar causes tissue damage, decreased flexibility, and malfunction of the organ involved.

The third problem in SSc is the dysregulation of the immune system resulting in an immune attack on the body's own tissues. In patients with early disease, immune cells such as B cells, T cells and macrophages appear to be activated and poised to attack the patient's own tissues. This might be particularly prominent in the skin and the lungs. In addition, the body generates self-directed antibodies called autoantibodies. Some of these autoantibodies are found in several autoimmune diseases, while others are highly specific for scleroderma.

One way to detect activation of the immune system is to find antibodies (proteins made by immune cells, the bullets of our immune army) in the blood that targets the body's own tissue (autoantibodies). A very specific set of autoantibodies is found in scleroderma. These autoantibodies can be thought of as footprints of the scleroderma disease process because they are only made under very specific conditions. At this point, it is still not clear what role, if any, these autoantibodies play in damaging the blood vessels or stimulating collagen overproduction in SSc.

WHO GETS SCLERODERMA?

There are many clues that define susceptibility to develop scleroderma. A genetic basis for the disease has been suggested by the fact that SSc is more common among patients whose family members have other autoimmune diseases (such as lupus). In rare cases, SSc runs in families, although for most patients there are no other family members affected. Scleroderma may affect some Native Americans and African Americans more severely than Caucasians.

Women are more likely to get SSc.

Environmental factors may trigger the disease in the susceptible host. For example, silica exposure (as in coal mining or sand blasting) has been associated with systemic scleroderma and certain drugs can cause scleroderma-like reactions. Localized scleroderma is more common in children, whereas SSc is more common in adults. However, both can occur at any age.

PUTTING IT ALL TOGETHER?

Research suggests that the susceptible host for scleroderma is someone with a genetic predisposition to injury from some external agent, such as a viral or bacterial infection or a substance in the environment. In localized scleroderma, the resulting damage is confined to the skin. In SSc, the process causes injury to blood vessels, or indirectly perturbs the blood vessels by activating the immune system. Fibroblasts are activated as part of the response to tissue injury. Interacting networks of immune inflammation and injury from inadequate blood supply drive the process, so it becomes chronic. Collagen made in excess interferes with normal organ function, sometimes leading to organ failure. In many cases, the process goes into remission after some years of activity. Research continues to assemble the pieces of the scleroderma puzzle to identify the susceptibility genes, to find the external triggers and cellular proteins driving fibrosis, and to interrupt the networks that perpetuate the disease.

Please note that this brochure is provided for educational purposes only. It is not intended to substitute for informed medical advice.

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