Systemic Sclerosis 2nd Edition

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Chapter 23:

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Introduction

Facing an illness like scleroderma is often seen as a crisis, yet the overall impact of the disease can be positively influenced by the input, education and compassion provided by the patient's medical team. Knowledge about their illness empowers patients to become advocates for their health and informed partners in treatment. The manner in which the patient is approached and the style of subsequent interactions are critical components of patient care. Although scleroderma is often mild in its expression, the patient must deal with the complex concept of living with a rare, chronic disease that is incompletely understood by the medical profession. Newly diagnosed patients frequently state: "My physician says I have a serious, life-threatening disease that he does not see very often. He also says that there is no treatment and does not know what else to do for me." Obviously, these statements will leave the patient confused, anxious and frightened. Although scleroderma can cause pain and disability, fear and misunderstanding may create more distress than the disease itself. In fact, studies find that mood and quality of life in scleroderma are affected more by personality traits and social support than the severity of the disease (1,2).

In this chapter, we present a conceptual framework that we use when attempting to explain the complexities of scleroderma to patients. During the actual encounter, we individualize the degree and amount of detail based on the current manifestations of the

disease, the patient's educational level, and the complexity of diagnostic and treatment program. We frequently employ drawings to solidify and simplify the concepts of pathogenesis and treatment. A holistic approach is emphasized with attention given not only to the biology of the disease but also to the social and psychological aspects of patient care. We feel that a clear understanding of current concepts of the disease and up-to-date information about the state of the art of the management of scleroderma is critical to good patient care.

In order to accomplish effective patient education, it is recommended that the following approach be taken (Fig. 23a.1):

- New patients need to be seen in a comfortable setting without the usual hassles of a busy clinical practice. Ample time (usually 2 hours) should be allowed for the evaluation and discussion.
- Patients should be encouraged to bring all medical records, but also be prepared to ask questions and to learn about scleroderma.
- Patients should be encouraged to bring family members or friends to participate in their care.
- Note taking or tape recording of the session is also encouraged. We often use written material and drawings that are created during the medical discussions to help the patient visualize and understand difficult concepts. A copy of the material is given to the patient with an outline of planned diagnostic testing and treatment.
- Clear lines of communication are established with instruction of who to call when. Phone numbers and e-mail addresses are exchanged. A timetable of events and follow-up is planned.

We recommend that the educational session begin after the history and physical examination is completed and the physician examines all available data. A discussion about scleroderma and broad concepts about the disease should start the educational process. We do this before the specifics about the individual's care are outlined. Removing some of the mystery about scleroderma and telling the patient that much is known about the biology and natural history of the disease and how to manage it can improve the ability to cope with the disease. Emphasizing the need for the patient to actively participate in overall good health behavior is most important. The patient needs to know that expert care is available and that treatments exist that can prevent problems, reduce distress and maintain a good quality of life.

Although a positive approach to the patient is very important, the information presented must be realistic. The patient does not need a "cheerleader" who inappropriately ignores the severity of the situation. They need a sensitive expert who is confident, knowledgeable and readily available for advice and consultation. The physician needs to be confident in his/her approach and should provide a positive message that clearly outlines all the expectations and options of treatment to the patient. There are several basic concepts that need to be emphasized to every patient and their families from the very beginning of the management process:

- While scleroderma means "hard skin", not all patients have progressive or severe skin changes.
- In fact, different types of scleroderma exist. One type has very limited or no skin changes. The other major type (diffuse scleroderma) has more extensive skin disease.
- Scleroderma is highly variable in its expression and more often is a manageable,

non-life-threatening disease.

- Individual patients will express the disease in their own unique way and therefore each patient must be evaluated and treated as an individual with a treatment formula that works for them.
- Serious internal organ disease does not occur in every patient and treatment *does* exist to prevent and treat many of the problems associated with scleroderma.
- Scleroderma almost always goes into remission with spontaneous improvement in skin changes and body function.
- Scleroderma can be a very serious disease with life threatening internal organ disease. Therefore, it is critical to establish a well-designed and comprehensive health care program. This includes proper diet, balanced rest and exercise, and control of environmental (e.g. cold temperature) and emotional stress.

After establishing these basic concepts, we recommend beginning a more detailed discussion about the disease pathogenesis that is tailored to the patient's education level by answering these questions:

- What does it mean that scleroderma is a chronic disease?
- How does one get scleroderma?
- What do we think is causing scleroderma?

The text that follows is an example of how these questions can be explained to the patient.

Conceptual Framework

Systemic sclerosis (scleroderma), like other chronic diseases, is the consequence of a disruption of normal body functions. The human body works by an incredibly

complex array of biological interactions that are delicately balanced and closely linked. Similar to a healthy and functional society, the human body is dependent on each biological system to work properly and cooperate. Interaction among systems must work for the whole to operate normally. A disease occurs when one or more of these biological systems are damaged or not fully functional.

The symptoms of scleroderma are the manifestation of the disruption of specific biological pathways that are unique to this disease. The mystery of the complex disease process causing scleroderma is rapidly being unraveled.

THE SPARK

We know that a small spark from the strike of a match can ignite a huge and devastating forest fire. In order for the spark to start the fire there must be a unique set of circumstances that allows the propagation of the fire: the presence of dry leaves and shrubs, a certain degree of humidity, just the right wind, and so forth. When all these things are in place the spark causes trouble and an uncontrollable forest fire results.

Similarly, we know that there is a “spark” or biological event that initiates the scleroderma disease process. The exact cause of scleroderma is unknown. Therefore, we still do not know the nature of the initiating event that starts the scleroderma disease process. Obviously, if we knew the trigger for scleroderma we could design a treatment to prevent it. There are many theories on the nature of this spark, based on our current understanding of the biology and clinical features of the disease, but none is yet proven. One theory suggests that scleroderma is caused by a virus or other infection. For example, a common virus called CMV (cytomegalovirus) is known to infect cells (endothelial cells) that line our blood vessels, which we know are diseased in scleroderma (3). This CMV infection could cause our normal immune system (see below) to attack the

infected blood vessels to rid the body of the infection. As a consequence of this invasion by our own immune system, we could "spark" a sequence of events that starts the scleroderma "forest fire". For example, the resulting damage to the blood vessels could cause Raynaud's phenomenon by disrupting the normal responses to temperature in the blood vessels of the skin. Although the theory that an infectious agent causes scleroderma is attractive, there is no evidence that scleroderma is contagious. There are many other common environmental substances that are now implicated in triggering scleroderma including silica, chemicals and some medications (4, 5). More than likely, we will discover that several environmental or common infectious agents can insult the body and potentially spark the disease. If this is the case then why doesn't everybody who is exposed to these common agents get scleroderma? Why isn't there an epidemic of scleroderma? Remember the forest fire analogy: a whole series of other circumstances have to be in place for the fire to spread.

In the normal host, an infection is usually contained; we rapidly rid ourselves of the virus and we return to normal good health. However, if our immune system is defective or if the infection alters the tissues it can change the body's normal equilibrium; if this happens then propagation of disease could result. An abnormal response only occurs if the body's systems allow it to happen. In medicine, we use the term the *susceptible host* to describe an individual who could develop scleroderma if the right trigger or spark occurs in the wrong circumstances.

Discovering the factors that make an individual a susceptible host for scleroderma is a very active area of research. The first clues come from clinical observations. Scleroderma is more common in women than men (3-6 to 1) and usually starts after the age of 30 (average age of onset, 40-50 years). This suggests that gender related factors

(e.g. estrogen) and age somehow make a patient more likely to contract scleroderma. Family clustering of scleroderma is uncommon but it can occur (6, 7) suggesting that there is a gene(s) that is passed through family members making one susceptible to scleroderma. It is rare, however, for more than one family member to have scleroderma. It is more common to find other family members who have other autoimmune diseases, such as thyroid disease, lupus or rheumatoid arthritis. Although scleroderma affects all races, there are distinct differences in the clinical course and potential problems that occur when comparing racial groups. For example, African Americans and Native American are more likely to have diffuse skin disease with lung involvement (8, 9). These observations suggest that here are several genes or genetic factors that can affect not only the occurrence of the disease but also the severity of scleroderma. We now know that every human biological function is under direct or indirect genetic control. Genes are biological units that function to produce molecules and proteins that are the essence of life. Most scientists believe that scleroderma has several genes that influence the expression and susceptibility to the disease. In other words, scleroderma is a complex genetic disease, unlikely to be explained by one “bad” gene.

THE FIRE

We understand that during our life we will encounter various acute health problems. A pulled muscle heals over several days of rest, a cold is usually over in a week or a bacterial pneumonia can be cured within days of starting the appropriate antibiotic. Scleroderma is a chronic disease. This means that once it is initiated it continues to be active over some extended period of time. Like a forest fire, once the disease process starts, it appears to fuel itself, propagating the disease. The course of the disease, however, is highly variable and in some cases may rapidly go into complete

remission. What are the components of the chronic scleroderma disease process? How can we try to stop this process from damaging tissues?

There are four components that are thought to allow disease propagation in scleroderma

- Inflammation,
- Autoimmunity (immune cells acting against one's own body tissues),
- Vascular (blood vessels) disease
- Tissue fibrosis (scarring).

The end result is organ malfunction and the related clinical symptoms. There is extensive clinical (what the doctor sees) and biological (what the scientist can measure) evidence that these four elements are active in scleroderma. It is also clear that although these common biological events are active, they are woven together in a unique way to cause the disease we call scleroderma. Attempting to control these events is the foundation to our current approach to treatment.

Inflammation

Inflammation is a common term in medicine that means a process that is characterized by redness, pain, heat and swelling. These four classic features of inflammation can be seen when they involve visible areas like the skin or joints; inflammation in internal organs (i.e. heart, lung, stomach) cannot be seen and special techniques are needed to measure the disease activity. In scleroderma, we know that inflammation is present when the disease is active because we can see red, swollen skin or warm, painful joints and we can measure the markers of inflammation in the blood and other body fluids. For example, a bronchoalveolar lavage (BAL; washing of the lung by bronchoscopy) can reveal inflammatory cells in the air sacs (alveoli). Traditional anti-

inflammatory drugs [non-steroidal anti-inflammatory drugs (NSAIDs), e.g., ibuprofen] or corticosteroids (e.g., prednisone) are used to control some forms of inflammation associated with scleroderma, but they do not fully control the disease. These drugs reduce joint pain and can control muscle inflammation, but they do not seem to control the skin disease or the underlying inflammatory process that is fundamental to scleroderma.

Autoimmunity

Scleroderma is thought to belong to the family of autoimmune diseases. The main evidence for this notion is the fact that patients with scleroderma make autoantibodies, and these "autoreactive" immune cells can be found in the diseased tissues. We know that our immune system is an army of circulating cells that are trained and programmed to fight invaders (nonself) that may enter our body. The immune army is divided into a front-line defense (the innate system) and a reserve system (the inducible system) that expands to fight the specific battle of the day. Through evolution, the immune system has been programmed to detect and engage both self and invader. Self-reacting cells are either eliminated or suppressed from activation, while cells programmed for invaders circulate or wait in specialized tissues (lymph nodes) looking for trouble. When the immune system attacks an invader, a very complex biological warfare is set into action to kill the invader. Antibodies are produced that identify the invader and signals (cytokines) are sent out to communicate with other members of the immune system and trigger the weapons needed to kill the invader. The activity of the normal immune process creates inflammation (heat, redness and swelling), which is responsible for some of the clinical features of active disease (fever, pain or tissue damage). With most infections we win the battle, the inflammation rapidly subsides and we return to normal health. In an autoimmune process, the inflammation continues, and if not controlled it becomes a

chronic rather than acute disease process.

In autoimmune disease, the immune invasion is triggered by self-proteins (autoantigens) rather than proteins or antigens from the invader. How and why a self-reaction occurs is another very active area of research. One popular theory suggests that, in scleroderma, there is a viral infection or other environmental stimulus that induces a normal immune response and tissue damage. The damaged tissue can then appear to the immune system like a new invader and thus trigger an autoimmune attack on self. For example, there is evidence that when the CMV virus infects the endothelial cells of blood vessels, the immune cells also recognize a normal cell component. The recognition of this normal cell component triggers a self-sustaining autoimmune reaction, local inflammation, and further tissue damage. The evidence supports the concept that an autoimmune response either drives the disease activity or amplifies the scleroderma process. In other words, the immune system is the fire that burns and damages tissues. It triggers other biological events that lead to tissue fibrosis (scar), damage, and organ malfunction.

Blood Vessels

One of the principal targets in scleroderma appears to be medium and small blood vessels called *arteries* (Fig.23a.2). These arteries are in the terminal part of the vascular tree and are responsible for blood flow, nutrition, and oxygen supply of various tissues (skin, lung, heart, kidneys). The arteries have several layers, including an inner lining called the *endothelial layer*, a middle layer called the *intima* and an outer layer of smooth muscle. Each layer has distinct and interactive functions. The endothelial layer produces chemicals and molecules that perform many of its functions, including: prevention of

blood clotting, control of the movement of inflammatory cells from the blood into tissues, and regulation of vessel dilation and contraction. The smooth muscle contracts and narrows the lumen of the vessel when stimulated by chemical mediators released by the nervous system or other cells. Malfunctions at the level of the blood vessel can affect the surrounding tissues leading to fibrosis and organ damage.

The vascular disease of scleroderma is characterized by perturbation of each of the layers of the arteries. The endothelial layer appears to be damaged or activated, the intimal layer thickens owing to production of excess collagen and connective tissue (fibrosis), and the smooth muscle is over-sensitive to stimulation by the nervous system input, such as epinephrine (adrenaline). The vessel becomes less functional and the lumen narrowed to the point that normal blood flow is compromised. The clinical consequences of this vascular disease are decreased blood flow, reduced nutrition, and low oxygen supply to the involved tissue. For example, Raynaud's phenomenon occurs because the distal arteries of the limbs are affected and patients present with cold-sensitive fingers, ischemic digital ulcers, or even digital amputation. The skin of the digits becomes avascular and thickened (sclerodactyly). A similar mechanism of tissue injury is postulated to occur in the other organs and tissues that are diseased in scleroderma, including the kidney, lung, heart, and gastrointestinal tract. Treating the vascular disease is considered fundamental to the success of controlling the scleroderma disease process.

So what causes this vascular injury? The answer is still unknown, but evidence suggest that the autoimmune process plays a major role and is either the principle cause of vascular injury or amplifies the vascular disease caused by an infection or other environmental insult. The end result is damage to tissue, fibrosis, and organ malfunction.

Fibrosis

Fibrosis (scarring) is an end product of several different types of insult to the involved tissue (Fig. 23a.3). Inflammation, an active autoimmune process, and low oxygen content secondary to low blood flow are all present in scleroderma and can each activate the process of tissue fibrosis. The tissue fibroblast is a factory for the production of collagen and other components of connective tissue. These cells are abnormally activated in scleroderma and overproduce collagen into the involved tissues. The most dramatic example of this is seen in the skin disease of the diffuse cutaneous form of scleroderma. These patients present with signs of skin inflammation (erythema, pain, pruritis and edema) that then transforms into progressive fibrosis (scarring). This process continues over several months, resulting in thickened (fibrosed) skin and damaged internal organs. The thickened skin has excess collagen and other connective tissue elements produced by the skin fibroblast. Any management program must attempt to directly or indirectly control tissue fibrosis.

SUMMARY

The scleroderma fire is triggered by some yet unknown factor or event that occurs in a susceptible host. The spark initiates a sequence of biological events that interact to stimulate a persistent chronic process. The biological consequences are a unique vascular disease, autoimmunity, and tissue fibrosis. The genetic makeup of the individual not only defines his or her susceptibility to scleroderma but probably also dictates the specific course the disease will follow and the degree and type of organ involvement that will occur.

Principles of Managing Scleroderma

After the discussion about the disease process, we then move to a general discussion about the principles of management, before we initiate a discussion about the patient's specific treatment options. There are five basic principles to guide the physician managing scleroderma:

- Subsets of disease exist with unique clinical phenotypes.
- Scleroderma is highly variable in its expression.
- Scleroderma has different stages of activity and it can go into spontaneous remission.
- Scleroderma is a systemic disease and not just a skin disease.
- Not every health problem in the patient is secondary to scleroderma.

SUBSETS OF SCLERODERMA EXIST WITH UNIQUE CLINICAL PHENOTYPES

The physician must be aware of the fact that unique subsets of patients exist and patients need to realize that *their* disease process, and therefore management is unique. Each patient has a different disease expression; this variability needs to be recognized and care must be customized for each patient. Several years ago a panel of experts established a classification that defined two main groups of patients with scleroderma, based on the extent of skin involvement (10) (Fig. 23a.1). Patients with "limited scleroderma" have minimal skin involvement that does not extend beyond the knees and elbows or face, whereas patients with "diffuse scleroderma" have more extensive skin fibrosis. In this classification system, the CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia), with skin involvement mainly limited to face or fingers, is considered to be a form of limited scleroderma. Approximately 5% of patients will have scleroderma without skin

involvement (systemic sclerosis sine scleroderma). Classifying the patient into one of these subgroups is useful because the degree of skin involvement predicts distinct patterns of organ involvement, disease severity, and survival.

Patients with limited scleroderma generally have a good prognosis and minimal or no internal organ involvement. Raynaud's phenomenon and gastrointestinal reflux disease (heartburn) are usually the first symptoms of limited scleroderma that predates other clinical problems by years. Recognizing the subtype of scleroderma helps define the specific treatment approach. There is no indication that medications will change the course of limited scleroderma, but they are effective in general at managing the symptoms. Managing specific vital organ involvement, particularly peripheral vascular disease (Raynaud's phenomenon), the gastrointestinal tract, and the pulmonary circulation, is the key approach to therapy in limited scleroderma.

Diffuse cutaneous scleroderma (involving larger areas of skin) *may* have significant internal organ disease (heart, lung, kidney and gastrointestinal) and the prognosis of these patients is worse than in the group with limited disease. In the early stage of diffuse cutaneous scleroderma, there is an impressive inflammatory appearance that rapidly extends over the extremities, face, or trunk. It is during this early phase that progressive internal organ involvement may occur. Early intervention can theoretically stop inflammation, reduce the autoimmune response, and control the overproduction of collagen and other extracellular matrix components before mature fibrosis is established. However, just as in limited scleroderma, organ-specific therapy is still the mainstay of treatment and can be particularly effective; internal organ-directed therapy that may prevent vital organ failure should take precedence over "skin only" therapy.

It is also recognized that within the current patient grouping there are very specific disease expressions that cluster together. For example, in the group of patients with limited disease, the most common situation is mild disease and a good prognosis. However, in a subset of limited patients (10%), pulmonary hypertension (high blood pressure in the blood vessels of the lung) develops, usually without significant lung fibrosis. Another subset of limited patients will have severe Raynaud's phenomenon with larger vessel disease and recurrent deep ulcers or even digital amputation. Patients with limited disease are also more likely to have features of another autoimmune disease process such as sicca syndrome (dry eyes and mouth), polyarthritis, autoimmune liver disease (primary biliary cirrhosis), or autoimmune mediated hypothyroidism (a form of underactive thyroid disease known as *Hashimoto's thyroiditis*). Similar subgroups are seen among patients with diffuse cutaneous scleroderma. For example, patients can present with severe, rapidly progressive skin disease without significant internal organ involvement. Another common pattern is development of interstitial lung disease without signs of any other serious organ involvement. Gastrointestinal involvement of the small and large bowel can dominate the clinical problem in another subgroup of patients with diffuse skin disease. Interestingly, there are unique associations with autoantibodies that coexist with an individual clinical phenotype. For example, the presence of antibody against topoisomerase is associated with interstitial lung disease, whereas antibodies against centromeres are associated with the CREST syndrome.

It is most important that a treatment plan is designed that recognizes the specific subset of disease and pattern of organ involvement.

SCLERODERMA IS HIGHLY VARIABLE IN ITS EXPRESSION

The degree of skin involvement can be measured by pinching the skin. On average, the thickened areas of skin generally progress and reach a maximum severity after 15-20 months from the onset of the first symptoms of the disease (11) (Fig. 23a.4).

After the peak skin involvement is reached, there is spontaneous softening of the skin that occurs over several months in most patients. The degree of cutaneous manifestations of scleroderma varies so greatly among patients that the treating physician must follow the course in short intervals to determine the individual pattern. The fingers and hands usually have the most intense skin thickening. In these areas, the skin first thickens then atrophies (thins). Unfortunately, deep contractures (areas that will not move) around joints can develop. It appears that new, serious internal organ involvement is *uncommon* after the skin has reached its maximum severity (12). Lung (fibrosing alveolitis), gastrointestinal, and kidney disease (scleroderma renal crisis) all generally occur early in the course of diffuse scleroderma while clinical evidence of cardiac disease can present in some patients as a late manifestation.

Although there are some definite predictable patterns of disease, the management of the scleroderma *must* be designed to fit each patient's unique situation. Patients with limited scleroderma do not need medications to stop progressive skin disease because severe skin thickening does not occur. In the patients with diffuse skin disease, the course of scleroderma is highly variable, with some patients manifesting very mild skin disease without serious internal organ involvement, and others presenting with widespread and progressive skin and other organ fibrosis.

SCLERODERMA HAS DIFFERENT STAGES OF ACTIVITY AND IT CAN GO INTO SPONTANEOUS REMISSION

In the early stage of diffuse cutaneous scleroderma, there is an impressive inflammatory appearance that rapidly extends over proximal parts of the extremities, face or trunk. The skin is edematous (fluid filled) and reddened and it feels thickened. The patient complains of discomfort in the involved areas, and pruritus (itching) is often intense. It is during this inflammatory phase that overproduction of collagen and other extracellular matrix components is active and potentially could be stopped with medications. This inflammatory phase continues for several weeks, during which the skin becomes more fibrotic and thicker, with less flexibility. The surface of the skin undergoes various pigment changes. Both hyperpigmentation (increased pigment) and hypopigmantation (loss of pigment) are seen as manifestations of skin inflammation. Lack of motion of fingers, wrist, and other joints is caused both by abnormal thickened skin and by the thickening that forms in the deeper tissues. This deeper fibrosis can trap tendons and affect muscle function. Contractures of the fingers, wrist, elbow, shoulder, hip girdle, knee and ankle/foot will sometimes result from local tissue fibrosis and atrophy of tissues.

The “activity” of this process is measured by identifying signs of inflammation on direct examination of the patient. As the activity of the inflammatory process spontaneously slows or comes under control from medication, the discomfort significantly improves and itching subsides. Any pain and disability at this time is usually related to damaged tissue. New areas of skin involvement do not appear and the old involved areas go through an evolutionary process of skin remodeling. The disease process at the level of the skin appears to be monophasic (one wave of activity), although

repeat flares of activity can rarely occur (5 % of patients with diffuse disease).

The physician must recognize the different stages of disease activity. Obviously, treatment options are different if the disease is in an active inflammatory stage as opposed to a mature, inactive fibrotic stage. Anti-inflammatory or immunosuppressive medication may work during the inflammatory phase but cannot dissolve established, mature collagen. The concept of active disease versus established organ damage or inactive disease is not limited to the skin but is applicable to every organ involved in scleroderma. The degree of involvement, the duration of the "active" phase, and the severity of damage vary a great deal from patient to patient. One of the challenges of managing scleroderma is to carefully define disease activity and recognize that a natural remission occurs frequently that can stabilize the disease or, in the case of the skin, lead to remodeling and natural repair.

SCLERODERMA IS A SYSTEMIC DISEASE AND NOT JUST A SKIN DISEASE

Scleroderma literally means "hard skin". Skin disease is the most dramatic aspect of scleroderma because it is visible, disfiguring, and immediately distressing. However, scleroderma is a systemic disease and internal organs can be affected. The principal targets of disease are the circulation, gastrointestinal tract, lung, kidney, heart, joints and muscles. *Not every patient* will have all or any organ involved and the natural course of the internal organ involvement differs from the skin disease. The main principal is that the physician must be sensitive to the possibility of internal organ disease; he or she must carefully and periodically redefine the level of active disease in any organ.

NOT EVERYTHING THAT GOES WRONG IS SECONDARY TO SCLERODERMA

It is very common for patients with scleroderma and their health care providers to blame every new health issue on scleroderma. Every ache or pain, fatigue, or acute or chronic symptom needs to be individually evaluated and appropriately treated. Patients with scleroderma can have other health problems that are related or unrelated to the disease. For example, there is thought to be an increased chance of development of lung cancer, hypothyroidism, and the sicca complex (dry eye and dry moth) among patients with scleroderma. Care must be taken to look for these problems if new, suggestive symptoms occur. Medications used for scleroderma can cause their own health problems, including direct toxicity or allergic reactions. Multiple drugs increase the chances of drug interactions and potential side effects. Immunosuppressive medications increase the likelihood of common or unusual infections. Common medical conditions, such as diabetes, abnormal cholesterol levels, high blood pressure, gallbladder disease, coronary artery disease, osteoporosis, and so forth, can occur in scleroderma patients like any other person. Therefore, it is very important that every scleroderma patient follow the usual health care guidelines recommended for their age and sex. Obviously, specific scleroderma-related preventive and maintenance care is added to these routine health care measures.

SUMMARY

These five principles provide guidelines that help the physician, but the key to excellent care is a well designed comprehensive program that is customized to the individual patient and their circumstances. In limited skin disease, management of Raynaud's phenomenon and specific internal organ care is the major focus because the skin disease is not severe. In diffuse scleroderma, a disease-modifying agent has the

potential to alter the natural course of the disease. The opportunity to prevent tissue fibrosis and irreversible disease in scleroderma presents itself during the early, inflammatory phase of the disease. Efforts should be made to classify the subtype of scleroderma, the stage of the disease process, the degree and activity of organ involvement, and the severity or degree of irreversible tissue damage before a specific therapy is started. Although there are still no drugs or treatment regimens that convincingly control the scleroderma disease process, there are many treatment options that improve quality of life, prevent progressive organ damage, and likely prolong survival.

Specific Management Options

Once patients have an overall appreciation for the disease process, it is important to emphasize where each patient "fits" in the spectrum of scleroderma (Fig. 23a.1). Before a detailed discussion about a tailored management program begins, patients should understand:

- What subtype of disease that they have
- Which organs appear to be involved
- What is the current stage of disease or activity level

In the following section, we discuss management for each potentially involved organ system. The direction of the discussion needs to be modified for each patient and should address the subjective symptoms the patient is currently experiencing and any potential organ involvement suggested by objective data (i.e., pulmonary function testing, echocardiogram).

An overall disease-modifying agent that cures scleroderma has not yet been discovered. Current therapy is designed using medications that are reasonably safe,

available, and make sense given our understanding of the pathogenesis of the disease. The four main features of the disease that focus the treatment include drugs that treat inflammation, autoimmunity, vascular disease, and tissue fibrosis. Our current understanding of the pathogenesis of scleroderma links all these aspects of the disease (e.g., autoimmunity causes inflammation, which causes vascular disease and tissue fibrosis), and one can imagine that one drug might stop the whole process by interrupting the cascade of biological events causing the disease. This is not yet the case in scleroderma. Although the most common approach to disease therapy is to have one drug that is the "magic bullet" that controls the disease, in scleroderma a multidrug approach makes more sense.

In general, if the disease is active, there are three major options to offer the patient:

1. *Do not use any disease-modifying drug, but provide other good medical care and watch the natural course of the disease.*

   In patients with limited scleroderma, this approach is reasonable. It may also be reasonable in patients with early diffuse disease who have no internal organ involvement and have not demonstrated that the skin disease will be widespread or intense. However, the more skin disease that is detected, the more likely the disease will involve internal organs and be more severe.

2. *Use currently available (on the market) medications that have evidence of benefit.*

   The most popular approach is to use drugs that have the potential to control inflammation, the immune response, and tissue fibrosis. Drugs that help the vascular disease are also available. These current medications will be discussed in

the sections below.

3. *Treat the patient with active disease in a research protocol with therapy that has promise but is not yet available or proven to have benefit.*

This approach is particularly attractive in patients with rapidly progressive skin disease or active internal organ involvement who have not yet been treated. Patients who have unresponsive skin or internal organ involvement after conventional therapy are also candidates for research protocols. Unfortunately, referral to a research center is often delayed until the disease has advanced to irreversible damage, by which time drug therapy may not be able to change the outcome. This should be avoided by early recognition of the disease and appropriate referral in the early phase of scleroderma. There are many agents that are being tested that have the potential of reversing the scleroderma disease process. Only through well designed cooperative studies will we discover if they are beneficial in scleroderma.

ANTI-INFLAMMATORY MEDICATIONS

Many medications are thought to directly or indirectly affect inflammation. In scleroderma, there are two major types of inflammation that are related to the disease process. The first is a more conventional type that can cause arthritis (inflammation in the joints), myositis (inflammation in the muscles), or serositis [inflammation in the lining of the heart (pericarditis) or lining of the lung (pleuritis)]. This type of inflammation responds to traditional anti-inflammatory drugs: NSAIDs (e.g. ibuprofen) or corticosteroids (e.g. prednisone). The duration of therapy and the dose of medication are dictated by the specific situation. Some patients will need chronic administration and

others will recover after a limited course of therapy.

The other type of inflammation relates to the skin and other tissue injury caused by the scleroderma process. This phase of the disease does not appear to respond to NSAIDs or corticosteroids, although the exact role of corticosteroids is not fully studied. There are risks associated with the use of these agents, including gastrointestinal disease, fluid retention, and renal toxicity. Corticosteroid use is also associated with an increased risk of scleroderma renal crisis. Therefore, it is recommended that the use of NSAIDs and corticosteroids be limited to inflammatory states that demonstrate responsiveness.

IMMUNOSUPPRESSIVE THERAPY

The most popular approach to controlling the inflammatory phase of scleroderma is the use of immunosuppressive therapy. The rationale is that an autoimmune process is causing the inflammation and the downstream result is tissue damage and fibrosis. In this model, the fibrosis is an “innocent bystander” that is driven by the cytokines (chemical messengers) produced by the immune system. There are several drugs that are being used, but only a few well designed studies have been performed. These immunosuppressing drugs include methotrexate, cyclosporine, antithymocyte globulin, mycophenolate mofetil and cyclophosphamide. A recent study suggested that methotrexate did not significantly alter the skin score (a measure of skin thickening) compared with placebo (no treatment). Cyclosporine is not completely studied due to reports of renal toxicity. The most promising drugs are mycophenolate mofetil or cyclophosphamide with or without antithymocyte globulin. Unfortunately, there is no placebo-controlled study (i.e., half the patients get the medication and half get a sugar pill) to define their exact role in treating scleroderma, but if used during the active inflammatory phase of the disease, they appear to work.

A major area of current research is the use of aggressive immunosuppressive therapy either with very-high-dose cyclophosphamide or with autologous bone marrow transplantation. Because these aggressive forms of immunosuppressive therapy have potential risks, they should be used in severe cases of scleroderma and administered as part of a research protocol.

DRUG THERAPY OF VASCULAR DISEASE

The vascular disease in scleroderma is widespread and affects medium and small arteries. It is manifest clinically as Raynaud's phenomenon in the skin, and there is evidence that repeated episodes of ischemia (low-oxygen state) occur in other tissues. Low blood flow into the skin and tissues is thought not only to damage tissue by the lack of nutrition and oxygen but to activate fibroblasts and promote tissue fibrosis. Therefore, treatment of the vascular disease is now considered crucial to controlling the disease as a whole as well as preventing specific organ damage. There are three major features of the vascular disease that potentially need treatment: vasospasm (spasm of blood vessels), a proliferative vasculopathy (thickening of blood vessels), and thrombosis (blood clots) or structural occlusion of the vessel lumen (blockage of blood vessels).

Vasospasm is best treated with vasodilator therapy (drugs that open blood vessels). The most effective and popular vasodilator therapy continues to be the calcium channel blockers (e.g., nifedipine). Studies demonstrate that the calcium channel blockers can reduce the frequency of Raynaud's phenomenon attacks and reduce the occurrence of digital ulcers. It is now known that the microcirculation of each organ has a unique mechanism for controlling its own blood supply. The skin blood flow is regulated by the sympathetic nervous system; the kidney blood flow by locally produced hormones such

as renin; and the circulation in the lung by endothelin, prostaglandins and nitric oxide. There are very specific agents to counteract the negative influence of the scleroderma vascular disease on each involved organ. For example, the calcium channel blockers are reported to help blood flow to the skin and heart; angiotensin converting enzyme inhibitors (ACE) inhibitors reverse the vasospasm of the scleroderma renal crisis; and bosentan (a new endothelin-1 receptor inhibitor) or epoprostenol (prostacyclin) improve blood flow in the lung.

Although there are several vasoactive drugs on the market that are being used to treat vascular disease, there is no agent that is known to reverse the intimal proliferation (thickening of the inner layer of the blood vessel) that is part of the scleroderma vascular disease. Drugs that reverse vasospasm (calcium channel blockers, bosentan, prostacyclin, or nitric oxide) all have the potential to modify the course of the disease. There is evidence that these vasodilators may also directly affect the tissue fibrosis. For example, bosentan may be of benefit because it inhibits endothelin-1, a molecule produced by blood vessels that can also directly activate tissue fibroblasts to make collagen.

The final outcome of untreated scleroderma vascular disease is occlusion of the vessels by either thrombus formation or advanced fibrosis of the intima. Therefore, anti-platelet therapy in the form of low-dose aspirin is recommended. Good studies to determine if antiplatelet or anticoagulation therapy is helpful do not exist. In an acute digital ischemic crisis (sudden development of threatened loss of a digit), anti-coagulation (use of blood-thinning medications) is often used for a short period.

ANTI-FIBROTIC AGENTS

It has been known for years that, in scleroderma, excess collagen is being produced in the skin and other organs. Several drugs are used that have *in vitro* (in the tissue culture) ability to reduce collagen production or to destabilize tissue collagen. The older medications in this category include colchicine, para-aminobenzoic acid (PABA), dimethyl sulfoxide, and D-penicillamine. Although there is evidence for and against the use of these agents, most experts are disappointed with them and believe that the benefit either does not exist or the drug is not potent enough to warrant its use. D-penicillamine remains a popular alternative for some experts, despite a controlled trial demonstrating no difference between low and high doses of the drug.

The search for new drugs that alter the fibrotic reaction is probably one of the most active areas of scleroderma research. Strategies include directly suppressing the fibroblast and its ability to make collagen, inhibiting the cytokines that activate the fibroblast, and the use of agents that might break down collagen faster and promote tissue remodeling.

COMPREHENSIVE CARE

Specific therapies exist and are usually efficacious in the treatment of the organ-specific manifestations of scleroderma, and can greatly improve symptoms and reduce morbidity and perhaps mortality. A focused discussion of these organ-specific therapies

should be individualized to each patient. A review of the details of these treatments is beyond the scope of this chapter, but is covered in detail elsewhere in this book.

Patients who have scleroderma should be seen by a rheumatologist for consultation. It is important to recognize that scleroderma is a chronic systemic disease that has both a physical and emotional impact on the patient. A comprehensive history and physical examination will define the type of scleroderma, the potential organ involvement and give insight into the level of disease activity. The type of laboratory testing that is needed is dictated by the history and physical findings. The initial evaluation needs to focus on the specific organ involvement and pertinent non-scleroderma-associated medical and social problems. It is most important that the physician understand the full impact the disease has on the quality of life and to use a team approach to management. This team effort should include the patient, family, appropriate friends, non-physician medical staff and whatever other medical specialist that are needed. It must be appreciated that scleroderma is a rare disease without a proven curative therapy. Many current treatments are potent and complex medications. Referral to a scleroderma center is recommended both to take advantage of the expertise of a "scleroderma specialist"; but also to participate in novel therapy and new research initiatives.

At each visit, the physician should assess the level of skin involvement by performing a skin score. This is done by palpation of the skin to determine the degree of thickening. Seventeen areas (fingers, hands, forearms, upper arms, face, chest, abdomen, upper leg, lower leg and feet) are scored from normal (zero) to severe (3) thickness. The

maximum score is 51. The skin score provides a semi-quantitative method to characterize the degree of skin involvement and classify the patient as having limited or diffuse scleroderma. Palpation of the skin can also stage the disease and give some sense of disease activity. Active disease is associated with inflammatory signs (e.g. edematous skin) while inactive skin disease is manifest by thickened sclerotic skin typical of mature scar tissue. Usually, physical features can determine the subgroup of scleroderma at first visit. However, if the patient has new onset disease then serial observations at short intervals (approximately once per month) are necessary to fully appreciate the disease type. The degree of skin disease and the level of disease activity provide clues about the risk for internal organ involvement. The higher the skin score, the worse the prognosis and there is a higher the risk for internal organ involvement. Active skin disease correlates with active disease in other organs (e.g. fibrosing alveolitis or renal crisis). Thus a very simple beside examination of the skin will give information about both severity and activity of the disease.

Patients with scleroderma should monitor their blood pressure regularly. Particularly in patients with early diffuse scleroderma, this should be done frequently (daily) using a well-calibrated home blood pressure device. It is this subset of patients who are at greater risk for kidney disease (known as *scleroderma renal crisis*). Scleroderma kidney disease usually presents as new systemic hypertension that may be asymptomatic. Evidence suggests that renal blood vessels suddenly constrict (Raynaud's phenomenon of the kidney), dropping blood flow to the body or cortex of the kidney. Left untreated, the low blood flow leads to tissue damage and kidney failure. This

reversible problem was the leading cause of death in scleroderma before new treatment was discovered. Rarely, renal failure secondary to scleroderma vascular disease occurs in the absence of hypertension. Patients with hypertension should be treated as a medical emergency with rapid assessment of renal function (urinalysis and blood testing) and control of any blood pressure elevation with an angiotensin converting enzyme (ACE) inhibitor. Patients with evidence of renal crisis often need to be hospitalized to order to monitor blood pressure and renal function closely and to titrate medications.

Lung tissue and the blood vessels in the lung can be affected by the scleroderma disease process. Therefore, the lung and heart need to be carefully evaluated in every patient both at the onset of the disease and periodically thereafter. A full set of pulmonary function testing (spirometry, lung volumes and diffusing capacity) should be obtained on the first encounter and, if results are abnormal, carefully evaluated. Scleroderma causes a restrictive ventilatory defect (small lungs) secondary to an inflammatory process in the lung alveoli (air sacs). This process, left untreated, leads to fibrosis of the lung tissue (a fibrosing alveolitis) that interferes with normal gas exchange from the air to the blood.

It is challenging to detect lung involvement in scleroderma because active disease may be present in the absence of symptoms. The physical examination and traditional chest x-ray are insensitive methods to detect early lung disease. Pulmonary function testing is very sensitive and reliable but defines function of the lung and not the activity of the disease. Serial pulmonary function testing can define activity, but several months must pass before changes occur. If the pulmonary function tests are abnormal, then a high-resolution computed tomography (CT) scan can detect early lung fibrosis and inflammatory changes. If the lung function test results are normal, it is recommended that they be repeated every 4 to 6 months in patients with early diffuse scleroderma. Patients

with worsening lung function by pulmonary function testing or abnormalities on high resolution CT scan should undergo a bronchoalveolar lavage (BAL). This investigation obtains fluid and cells directly from the lung. Cell counts, determination of cell types and other special studies can define disease activity with precision. A patient with abnormal results on the BAL study suggestive of active lung disease should be treated with immunosuppressive or other therapy.

The right heart pumps blood into the lung to get oxygen to the body. Usually, this is a very low-pressure system because the lung and its blood vessel are a system with very low resistance. If the blood vessels or lung tissue becomes diseased, then the pressure in the pulmonary circulation and the right heart rises (pulmonary hypertension). Pulmonary hypertension generally occurs late in scleroderma. The rapid onset of severe pulmonary hypertension presents primarily in patients with limited scleroderma after years of relatively mild disease (e.g. sclerodactyly, GERD and Raynaud's phenomenon alone). A 2D-echocardiography (ultrasound test of the heart) study is a simple, non-invasive method of assessing heart function and estimating right ventricular systolic pressure (an indirect method of estimating pulmonary artery pressure). Patients with signs or symptoms of right heart failure who have abnormal right ventricular systolic pressure may need a right heart catheterization to determine the exact pressure and the need for therapy. Severe pulmonary hypertension can shorten the patient's life. Early detection is important because new medications are now available to treat this disorder. Therefore a 2D-echocardiogram should be done on a yearly basis on every patient with scleroderma.

Although most patients do not have serious heart disease, care must be taken to discover heart disease. Heart disease in scleroderma is usually asymptomatic until the late stages of disease. Periodic monitoring with careful bedside examination, periodic 2D-

echocardiography and electrocardiography are most important. The heart may be affected by scleroderma microvascular disease, tissue fibrosis, pericardial disease and inflammation of the heart muscle (myocarditis). Although scleroderma may cause heart disease, non-scleroderma causes of heart disease are more frequent and need to be detected and prevented when possible. The traditional risk factors (e.g. family history, hyperlipidemia, smoking) also exist in the scleroderma patient and care must be taken to practice good internal medicine in these patients. Therefore, a lipid profile should be obtained on every patient with scleroderma.

Evidence suggests that the involuntary muscle of the gastrointestinal tract (smooth muscle) can be affected in scleroderma. When this muscle is involved, abnormal motor function of the esophagus, stomach, small or large bowel results. Difficulty with swallowing, dyspepsia, heartburn, early stomach filling/delayed emptying, constipation and diarrhea – all or some of these symptoms can result. Minor gastrointestinal symptoms are more common then severe problems. Typical (heartburn) or atypical (chest pain, gagging, dry cough) gastrointestinal reflux symptoms are almost universal among both limited and diffuse scleroderma patients. If untreated, inflammation of the esophagus, esophageal stricture, gastrointestinal bleeding or poor quality of life may result. Special testing may be necessary, particularly if the patient does not respond to routine therapy (e.g. a proton pump inhibitor). Endoscopy, motility studies or swallowing studies are used to fully appreciate the severity and complications of the gastrointestinal disease. The timing of these studies is dictated by symptoms and response to therapy. Several medications now exist that can effectively treat the gastrointestinal manifestations of scleroderma, including medications to treat acid reflux and motility problems.

In general the liver and biliary system is not affected by scleroderma. However, autoimmune hepatitis and primary biliary cirrhosis are associated with the limited form of scleroderma. Therefore, liver function test should be obtained in every patient.

Dry membranes of the mouth and eye are very common complaints. Dysfunction of tear or salivary glands secondary to an autoimmune process or tissue fibrosis is thought to be the cause. Tooth decay and periodontal disease need to be prevented. These problems are due to a decrease in normal saliva and difficulties performing dental care, particularly in patients with a decreased oral aperture. Identifying this problem is very important and instructing the patient to have frequent dental care is essential

Musculoskeletal complaints are common in the rheumatic diseases and scleroderma is no exception. Arthritis can be detected by physical examination but muscle disease may be asymptomatic until weakness occurs. Muscle weakness, secondary to an autoimmune mediated inflammatory myositis or a non-inflammatory fibrotic myopathy, can be detected by measuring muscle enzymes (CPK, aldolase and transaminases). If the enzymes are abnormal, then further specialized testing (EMG or muscle biopsy) may be necessary. It is equally important to carefully determine if other causes of muscle weakness exist. These include fibrosis of the muscle secondary to the scleroderma process, weakness from disuse or wasting from deconditioning and malnutrition. Patients also can have a non-scleroderma cause of muscle weakness including metabolic disease (e.g. hypothyroidism), side effects from medications (e.g. lipid lowering agents and corticosteroids can induce myopathy) or another disease process (e.g. tumor associated myopathy). When weakness is present, all of these causes must be considered and investigated. Once a cause is determined, effective therapy can be instituted.

Raynaud's phenomenon and cold intolerance are seen in almost every patient with scleroderma. Patients often feel worse in winter months and complications from Raynaud's phenomenon such as digital ulcerations are more likely to occur in the cold winter months. In addition to management with vasodilator therapy, patients must be taught about cold temperature avoidance and stress control. Careful examination for larger vessel disease is important. For example, patients with limited scleroderma and severe Raynaud's phenomenon with digital amputation often have evidence of macrovascular disease such as ulnar artery occlusion. In addition, care must be taken to detect other causes of vascular disease including diabetes, atherosclerosis, emboli or a hypercoagulable state. A comprehensive care plan to manage the vascular disease of scleroderma is usually warranted.

When the disease is in the active phase, constitutional symptoms of fatigue and low energy are common. These are often coupled with inability to sleep normally. Sleep is disrupted by fear of the illness, depression, pain, skin itching and/or specific internal organ dysfunction (e.g. heartburn from gastrointestinal reflux or shortness of breath from heart or lung failure). The lack of sleep amplifies daytime symptoms; especially diffuse soft tissue pain and fatigue. Disordered sleep is treated by both non-drug and drug therapies.

Scleroderma does not appear to cause central nervous system dysfunction. It is, however, associated with mood disorders (depression), altered self-image and sexual dysfunction. The cause of these problems is likely multifactorial, but should be addressed in each patient. Fear of the disease (anxiety/panic) and depression are often not revealed by the patient because of the embarrassment of discovering an emotional illness or the fear of appearing psychiatrically ill. The physician must allow time to specifically

explore this aspect of the patient's health and he or she should provide the opportunity for the patient to get the appropriate therapy. Recent studies show that pain is a major cause of depression in scleroderma. If pain is left untreated, the patent's level of distress escalates and his or her quality of life declines. One of the most intense sources of pain in scleroderma is the deep tissue fibrosis that causes joint contractures and tendon friction rubs in patients with the diffuse form of the disease. The traditional anti-inflammatory medications (NSAID and corticosteroids) are not particularly effective and low dose narcotics may be necessary.

Self-image is a complex concept that is often not mentioned by the patient or addressed by the physician. Scleroderma can be disfiguring and almost always affects the face and hands, two areas that are important cosmetically. Patients can be more distressed by facial telangiectasia and deformed hands than occult lung or heart dysfunction. Although the management of self-image problems in scleroderma is not well studied, the emotional impact of this aspect of the disease needs to be recognized and treated.

Every person has an important social role in life. Scleroderma can disrupt one's ability to perform their usual role as mother or husband or good student or superb tennis player, etc. Often the individual becomes a "scleroderma patient" both in the physician's office and at home. It is most important that every effort is made to have the patient maintain their social role in the family and elsewhere. For example, the physician must recognize that individuals are comfortable when they are in control of their daily activities. A chronic illness like scleroderma takes that control away and adds an element of fear of the unknown. In managing the person with scleroderma, the physician must recognize this and engage the patient in his or her own health care. The patient should have easy access to the physician and be part of the "team" providing care. The family

needs to understand and appropriately adjust, but at the same time allow the patient to be an individual who continues his or her proper role in the family.

Sexual function is often impaired in scleroderma, yet rarely discussed or managed. In fact, there are few studies that define the magnitude of the problem or provide clear guidelines for treatment. Erectile dysfunction is common among males with scleroderma and is thought to be secondary to abnormal microvascular function and local tissue fibrosis of the corpus cavernosum. All males with erectile dysfunction should be carefully evaluated and treated appropriately (e.g. sildenafil). Sexual dysfunction among women with scleroderma is not well studied. Open discussion about sexual relationships and the need to design an intervention is most important. Professional counseling, and treatment of pain, dry membranes and anxiety or depression can be helpful.

Recognizing the physical, emotional and social impact of scleroderma can enhance quality of life. Patients can be consumed by the disease to the point that their usual life activities are diverted to health care issues only. Health care needs to be blended into a formula that allows the patient to be in control and to enjoy usual aspects of daily living. Surprisingly, the impact of scleroderma on the quality of life does not necessarily correlate with the severity of the disease. Patients with relatively mild disease can be devastated because they know they have scleroderma. Sometimes this response is dictated by the personality traits of the affected individual but it is almost always strongly influenced by how the patient is handled by their physician(s) and the availability of various types of social support. Misconceptions about scleroderma are the most common cause of distress. Often patients with mild disease have the concept that they have an untreatable fatal disease. The lack of a cure is translated into “no treatment is available”. Education, expert care, and institution of comprehensive medical management improve

quality of life.

The most important intervention that a physician can perform for patients with scleroderma is educating them about the disease process and emphasizing that sustained contact with their physician is vital. Regular physician visits, routine screening procedures and prompt attention in the time of an acute crisis are crucial in the management of scleroderma.

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