

Use Skin Changes to Sort Out Scleroderma Mimics

BY PATRICE WENDLING

CHICAGO — Few rheumatologists would be fooled nowadays by gadolinium-induced nephrogenic systemic fibrosis, but there are other diseases that can masquerade as scleroderma.

The precise diagnosis of scleroderma-like illnesses is important because even though many of them are called scleroderma, they differ from systemic sclerosis in both treatment and outcome, Dr. Virginia Steen said at a symposium sponsored by the American College of Rheumatology.

The diagnosis is most often based on the distribution and clinical characteristics of skin findings, as biopsies don't always differentiate types of scleroderma. Rheumatologists would do well to keep in mind the following scleroderma mimics to avoid misdiagnosis:

► **Lipodermatosclerosis** is one condition that physicians often fail to think of as a scleroderma mimic. Also known as hypodermatitis sclerodermaformis, it refers to localized chronic inflammation and fibrosis of the skin and subcutaneous tissues of the lower leg. In the acute stage, the leg is inflamed and warm, the skin is very tight, and cellulitis may be present. The ankle and toes are not involved.

In its chronic stage, there is induration, contraction of the skin and subcutaneous tissues, and irregular depressions that can look almost identical to lower-leg scleroderma, she said. The leg even-

tually resembles an inverted champagne bottle, in which the upper half remains edematous and has a much greater circumference than does the lower sclerotic portion.

Lipodermatosclerosis is a sign of severe end-stage venous insufficiency, and should be differentiated from scleroderma, cellulitis, superficial thrombophlebitis, and erythema nodosum. The diagnosis is made from clinical observation, but direct immunofluorescence of early and late lesions has been used to show dermal pericapillary fibrin deposits.

If left untreated, lipodermatosclerosis can progress to ulceration, atrophy blanche, or shortening of the Achilles tendon. Treatment involves weight loss, controlling the underlying disease, and consistent wearing of support stockings that may need to be specially made, said Dr. Steen, professor of medicine and director of the rheumatology fellowship program at Georgetown University in Washington. Topical steroids are useful if the skin is inflamed, and antibiotics are recommended for cellulitis.

► **Scleredema** tends to target the upper body without affecting the lower extremities. Thickening occurs on the skin of the neck and face; severely affected patients are unable to wrinkle their foreheads or open their mouths. In most patients, the shawl sign is present, with skin involvement over the chest and arms, according to Dr. Steen.

Pathological features include swollen



Lipodermatosclerosis exhibits an inverted champagne bottle trait.

COURTESY, KENNETH E. GREER, MD

collagen with clear spaces and accumulation of hyaluronic acid and glycosaminoglycans. Although scleredema is commonly associated with diabetes, it can also occur after a viral illness. The treatment emphasis is on better diabetes control, but spontaneous resolution of symptoms is possible after infection.

► **Eosinophilic fasciitis** is a rare disorder characterized by symmetrical and painful inflammation and swelling of the extremities, leading to induration and the characteristic peau d'orange configura-

tion. The palms may be involved, but typically the fingers and toes are spared. Contractures demonstrating the groove sign commonly evolve as a result of induration.

Eosinophilic fasciitis is slightly more common in middle-aged men, but can occur in women and children. It was initially distinguished from systemic sclerosis by the absence of Raynaud's phenomenon, autoantibodies, and visceral involvement, and—unlike systemic sclerosis—it responds to corticosteroids.

Histologically, there are marked eosinophilia and inflammatory infiltrates in the fascia. The extent of the histologic changes depends on the stage of the disease, and thus is not a consistent component of the disease. Aside from marked peripheral eosinophilia, other laboratory features to watch for include an increased erythrocyte sedimentation rate, increased gamma globulin, and an increased aldolase, with a normal creatinine phosphokinase.

Physical therapy is a key component of treatment, because this and most scleroderma mimics discussed here can cause joint contractures.

In eosinophilic fasciitis, low- to moderate-dose prednisone (20-30 mg)—and, if needed, methotrexate as a steroid-sparing agent—can be given. There is also some anecdotal evidence to suggest that rituximab (Rituxan), mycophenolate mofetil (CellCept), or tumor necrosis factor inhibitors may be useful, said Dr. Steen, who disclosed no conflicts of interest. ■

Interferon-Alpha Blockade Is in Testing for Some Myopathies

BY DIANA MAHONEY

DESTIN, FLA. — A safety and efficacy trial is underway of an agent designed to treat dermatomyositis or polymyositis in adults via the novel approach of blocking interferon-alpha or its receptor.

Dr. Steven A. Greenberg reported that he and his colleagues are currently assessing the safety and tolerability of multidose, intravenously administered MEDI-545 (a fully human anti-interferon-alpha monoclonal antibody) in adult patients with dermatomyositis or polymyositis. The agent is being tested in study MICP151, a phase IB clinical trial sponsored by the drug manufacturer, MedImmune Inc.

"This is a true personalized-medicine trial, in that patients have to have a pattern of type I interferon-inducible gene activation in their blood by microarray studies to be enrolled," said Dr. Greenberg, a neurologist at Brigham and Women's Hospital in Boston. He noted that in a rank-order listing of blood gene expression of patients with active disease who are enrolled in the study thus far, 90% of the genes are type I interferon transcripts, confirming that "these are biomarkers of active disease."

Microarray and protein studies are identifying long-overlooked immune system cell types and processes that are involved in muscle damage in these diseases; such findings open channels for more targeted drug development and clinical trials of existing drugs that act on these immune pathways.

For example, dermatomyositis is characterized by progressive proximal muscle inflammation and weakness, as well as associated skin changes. "The way peo-

ple have thought about this disease for a couple of decades is that the muscle injury is an end product of capillary injury," said Dr. Greenberg at the Congress of Clinical Rheumatology. "It has largely been believed that dermatomyositis is a disease in which antibodies are binding to an endothelial cell antigen, causing complement-mediated injury in capillaries, and that the capillary injury eventually causes ischemia to muscle. According to this model, the characteristic perifascicular atrophy is thought to simply be a result of lack of blood supply to muscle."

There are a number of problems with this theoretical model, Dr. Greenberg explained. "Importantly, no antigens or antibodies have been demonstrated and, in experimental models of ischemia, perifascicular atrophy doesn't occur. Experimental ischemic myopathy actually affects the central portions of fascicles, not the peripheral portions," he said. "Nor does one ever see perifascicular atrophy in vasculitis, the one disease in which we do know there is muscular ischemia."

Plasmacytoid dendritic cells, which produce alpha and beta interferons, have recently been identified in the muscle and skin of patients with dermatomyositis. Gene-expression profiling of these cells shows significant up-regulation of type I interferon-alpha/-beta-inducible genes that correlates with disease activity. These findings suggest a different mechanistic model, said Dr. Greenberg. "One potential way to think about this disease is that the overproduction of type I interferon—usable proteins, regardless of the mechanism, may be separately injuring both capillaries and the perifascicular muscle fibers," he said.

"There are muscle fibers that appear to be dying for

no apparent reason. There are no immunoglobulin molecules; there are no T cells touching them," said Dr. Greenberg. "The question that arises is whether the production of some interferon-inducible transcript or protein within myofibers themselves could injure the muscle fibers," he said.

"Is this an autoimmune disease in which tissue injury results from the intracellular proteins of the innate immune system, rather than by-products of the adaptive immune system, either in the immunoglobulin molecules secreted by plasma cells or effector cytotoxic molecules secreted by CD8 plasma T cells?"

Given this possibility, "it is very reasonable to try blocking interferon-alpha or its receptor for the treatment of dermatomyositis," said Dr. Greenberg. The paradigm for muscle injury in inclusion body myositis (IBM) and polymyositis should also be revisited in light of recent "surprises," according to Dr. Greenberg. Both diseases have long been considered "classic intramuscular CD8 T-cell-mediated diseases." However, recent research has demonstrated an abundance of both myeloid dendritic cells (which are implicated in triggering the adaptive immune system) and differentiated B cells (in the form of CD138+ plasma cells) in the inflamed muscle tissue of patients with either IBM or polymyositis.

These findings, taken together, broaden the pool of potential therapeutic agents. "There are at least 15 [Food and Drug Administration]-approved drugs targeting these molecules of interest," said Dr. Greenberg.

He disclosed having a sponsored-research agreement with MedImmune for support of his research laboratory, but noted that all data discussed in this presentation were obtained prior to this agreement. ■