

## Persistent rash on the face and lips

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**A** 52-year-old man was referred to the dermatology clinic for a persistent rash on his face and lips of 5 months' duration, despite the use of a mild steroid cream prescribed by his primary care physician. He noted that the rash had "seemed to spread" and was now on his hands as well. In addition, he had hard nodules on his fingers that had become noticeable in the previous 2 weeks. He reported a history of long-standing gastroesophageal reflux disease that was well controlled with proton pump inhibitors. Physical examination revealed matlike telangiectasias on the patient's face, lips, and hands (*Figure 1*), hard subcutaneous nodules on fingers that appeared edematous and tight (*Figures 2 and 3*), and a loud P<sub>2</sub> component on cardiac auscultation. Upon further questioning, he reported a long history of cold intolerance, with cold weather causing aching hands that "turn blue."



**Figure 1.** Matlike telangiectasias on the face and lips.



**Figure 2.** Nonpitting edema of hands and fingers with matlike telangiectasias. The skin is waxy and tight with no hair on the dorsum of the hands. (File photo of another patient with the same disorder.)



**Figure 3.** Subcutaneous calcium hydroxyapatite nodules in the fingertips.

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**DIAGNOSIS:** CREST syndrome.

## DISCUSSION

Originally known as Thibierge-Weissenbach syndrome, in honor of the French physicians who first described the condition in 1910, CREST syndrome was renamed by Winterbauer in 1964 as an acronym for its prominent features (calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias) (1, 2). CREST syndrome is the mildest form of a spectrum of diseases under the broad heading of scleroderma. Scleroderma is a descriptive term in its own right, from *skleros*, meaning hard, and *derma*, meaning skin (3). Scleroderma has 2 major forms; 40% of patients have diffuse systemic scleroderma, and 60% have limited systemic scleroderma, of which CREST syndrome is a subtype (4). The 2 major differences between the categories are the location of skin involvement and the degree of internal organ involvement. First, the skin involvement in diffuse scleroderma can occur anywhere, whereas in limited scleroderma the telangiectasias involve only the face, feet, forearms, and hands, with skin thickening limited to the face and hands (4, 5). Second, internal organ involvement seen in diffuse scleroderma, a more rapidly progressing disease, can lead to renal failure, malignant hypertension, pericarditis, and pulmonary fibrosis, none of which occur in the limited disease. Scleroderma has an average age of onset in the third through fifth decades of life, and the ratio of females to males is 4:1 (3, 4). There is no known genetic predisposition (3).

The central pathogenesis of CREST syndrome remains a mystery. Multiple studies have evaluated such hypotheses as a primary injury to blood vessel endothelial cells, dysregulation of fibroblasts, viral infection leading to increased susceptibility, various forms of autoimmunity (including a graft-vs-host disease from retained maternal fetal lymphocytes), and silica exposure. Though a single, central dysfunction has not been found, both a primary vasculopathy and fibroblast dysregulation play key roles. First, a vasculopathy with primary endothelial cell damage results in telangiectasias. Here, the primary process is a "proliferative, obliterative" vasculopathy that has a preference for small arteries, arterioles, and capillaries (3). Over time, the vasculopathy leads to a decrease in the numbers of cutaneous capillaries. The remaining vessels then proliferate and dilate, causing visible, matlike telangiectasias in affected areas. Loss of capillaries also leads to loss of hair follicles and eccrine glands, causing hair loss and anhidrosis.

The primary cause of skin thickening and esophageal dysmotility is dysregulation of fibroblasts, which leads to an overproduction of collagen (4). Though not part of the CREST acronym, skin thickening and tightening is an important symptom of the syndrome. Early in the disease, the skin of the face and hands may become inflamed and have notable nonpitting edema with tightening of the skin. Then, activated fibroblasts thicken the dermis by depositing collagen in the tissue, which, over time, leads to progression of the tightening and loss of flexibility, giving the characteristic "masklike facies." Next comes a fibrotic state in which the skin becomes even thicker and the dry surface causes intense pruritus. The final atrophic stage occurs when the skin becomes "atrophic and thinned with tethering secondary to fibrotic tissue binding to underlying structures" (3).

Vasculopathy and fibrosis also occur in the gastrointestinal tract, leading to esophageal dysmotility, another prominent feature of CREST syndrome. Decreased peristalsis in the esophagus results in both dysphagia and reflux esophagitis (4). The small intestine may also be affected, where dysmotility leads to malabsorption from bacterial overgrowth, bloating, and irregular bowel habits.

The first symptom to appear in CREST syndrome is typically Raynaud's phenomenon (3). Brought on by cold temperatures or emotional stress, pallor followed by cyanosis of the fingers results from spasm and closure of the muscular digital arteries and arterioles. Once the stimulus is removed, the vasospasm resolves in 10 to 15 minutes, sometimes resulting in the skin flushing or blushing. Raynaud's phenomenon affects as many as 90% of patients with scleroderma, but it may also be seen in the general population at a rate of 4% to 15%. Over time, repeated bouts of Raynaud's phenomenon, in addition to the aforementioned pathologic features of CREST, lead to tissue fibrosis causing characteristic sclerodactyly (loss of the digital pad) or may lead to digital ulceration descriptively termed "rat bite necrosis." Sclerodactyly has been described as "Madonna" fingers that are tapered at the ends and covered with shiny, hardened, waxy skin. An aggravating factor in the above processes is vascular occlusive disease resulting from activated platelets responding to the abnormal vascular endothelium. A very late result can be resorption of the bone, leading to shortening of the digits.

Another prominent feature of CREST is calcinosis. Calcinosis cutis is the deposition of amorphous calcium hydroxyapatite, forming subcutaneous nodules. These nodules can lead to ulceration of the skin or can cause recurrent inflammation that is often mistaken for local infection.

Complications from organ involvement are seldom seen in CREST syndrome. CREST has been associated with 3 main complications. First, digital gangrene can occur from the results of Raynaud's phenomenon and secondary infection. Second, there has been an association with biliary cirrhosis. Finally, up to 50% of patients with CREST syndrome develop primary isolated pulmonary hypertension (2, 3).

Diagnosis is made by physical examination and autoantibody studies. Ninety percent of patients with either type of scleroderma have a positive test for antinuclear antibodies, 30% have a positive test for rheumatoid factor, and patients' erythrocyte sedimentation rate is typically elevated. Identification of autoantibodies helps to differentiate the types of scleroderma. Anticentromere antibodies are seen in 50% (1) to 71% (4) of patients with CREST but in only 21% of patients with diffuse systemic scleroderma. Anti-Scl70 and anti-RNA polymerase III results are positive in 20% to 30% of patients with diffuse scleroderma but are seldom positive in those with CREST syndrome. In addition, laboratory studies may uncover a mild hemolytic anemia secondary to damage of erythrocytes in diseased capillaries (5).

Until recently, the goal of treatment was symptom control alone. Patients with Raynaud's phenomenon were instructed to avoid exacerbating factors such as smoking and cold weather. Wearing warm gloves (and bundling up the rest of the body) and undergoing biofeedback training have been the mainstays of treatment. More recently, however, the disorder has been treated with long-acting calcium channel blockers such as nifedipine or

losartan. Success has also been noted with intravenous treatment of digital ulcers using the prostacyclin analog iloprost because it leads to vasodilation and platelet inhibition, counteracting the vasospasm and local hypercoagulability of Raynaud's phenomenon. The ulcerations themselves can be treated with wet soaks and with oral antibiotics against staphylococcus when necessary. Occasionally, surgical debridement or amputation may be required. The gastrointestinal symptoms of CREST are usually well controlled with medications. Proton pump inhibitors and reflux precautions are very useful in preventing the symptoms and sequelae of gastroesophageal reflux disease. Tetracycline is used to treat the bacterial overgrowth that leads to malabsorption, though some patients require supplementation of fat-soluble vitamins and calcium (5). Penicillamine is also used in systemic sclerosis to inhibit collagen cross-linking and thus improve skin thickening and 5-year survival (3). Skin thickening is also treated with moisturizers and avoidance of excessive bathing. While calcinosis cannot be prevented, the inflammation resulting from the nodules is often treated successfully with colchicine.

A significant challenge in treating CREST syndrome has been the problem of isolated pulmonary hypertension, which carries a poor prognosis and has proven difficult to treat. Multiple recent studies have associated the overexpression of endothelin in the pulmonary vasculature with primary pulmonary arterial hypertension (6). Two uncontrolled studies and one randomized trial have shown significant improvement in pulmonary artery pressures with intravenous infusion of epoprostenol (prostacyclin) (7). Recent trials using sildenafil for pulmonary hypertension have also shown benefit. Sildenafil is a phosphodiesterase type 5 inhibitor that causes relaxation of smooth muscle by a nitric oxide-dependent mechanism and is relatively specific for pulmonary vasculature. Recent case reports also show that adding sildenafil, as high as 200 mg/day (divided into 4 to 6 doses), to intravenous prostacycline gives added benefit and reduces mean pulmonary artery pressure even further (8). Unlike chronic obstructive pulmonary disease, mortality in primary pulmonary hypertension is not affected by the administration of oxygen (3). As a last resort, a combined heart and lung transplant remains an option.

The prognosis for patients with uncomplicated CREST syndrome is very good. The course is highly variable, though typically one of continued progression, with a 10-year survival rate of >70% (3). Spontaneous remissions are not uncommon and, if they occur, are typically permanent (3). The subset of patients who develop pulmonary hypertension face a difficult prognosis: this complication is typically a very late event, but the 2-year mortality is as high as 50% (2). Most of these patients die from arrhythmias due to hypoxia, in situ pulmonary arterial thrombosis, or cor pulmonale due to respiratory insufficiency (3).

Much remains to be learned about the pathogenesis and treatment of scleroderma and CREST syndrome. Clinical trials have been difficult to perform because of the relative rarity of the disease. In addition, the variable course, dotted with spontaneous remissions, makes therapeutic studies difficult to perform and interpret. Despite these challenges, ongoing studies continue to examine and evaluate the intricacies of this disease.

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