



Elbow nodules

The nodules on the patient's elbow prompted her visit. The fact that she also had frequent heartburn provided an important diagnostic clue.

A 42-YEAR-OLD WOMAN came to our clinic to have lumps on her right elbow removed. She said the lumps did not bother her, but on further questioning, admitted that her fingers turned white when they were exposed to the cold. She had frequent heartburn, but denied fatigue, weight loss, dysphagia, diarrhea, dyspnea, chest pain, palpitations, muscle weakness, or digital pain.

On physical exam, there were multiple small, firm subcutaneous nodules—some with a white surface protruding through the skin of

her right elbow (FIGURE 1A). The nodules were slightly tender to palpation. On further examination we noted tight, smooth skin on her fingers (FIGURE 1B). Her right thumb was fixed in an extended position (FIGURE 2). There were also small blood vessels on her hands and pitted scars on her fingertips.

- WHAT IS YOUR DIAGNOSIS?
- HOW WOULD YOU TREAT THIS PATIENT?

Lucia Diaz, MD;
Richard P. Usatine, MD

University of Texas Health
Center at San Antonio

Diazl3@uthscsa.edu

DEPARTMENT EDITOR

Richard P. Usatine, MD
University of Texas Health
Center at San Antonio

*The authors reported
no potential conflict of interest
relevant to this article.*

FIGURE 1

Elbow nodules and clubbing of the fingers



IMAGES COURTESY OF: RICHARD P. USATINE, MD

The 42-year-old patient sought care at the clinic to have slightly tender nodules removed from her right elbow. The patient also had tight skin and clubbing of the fingers.

Diagnosis: CREST syndrome

Our patient had CREST syndrome, a variant of limited systemic scleroderma. CREST syndrome is characterized by Calcinosis cutis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly, and Telangiectasias.

Systemic scleroderma is a chronic autoimmune disease involving sclerotic, vascular, and inflammatory changes of the skin and internal organs. There are 19 new cases per million adults per year, with an estimated annual prevalence of 276 cases per million adults in the United States.¹ Scleroderma occurs in women 4.6 times more often than in men; the mean age at diagnosis is 45 years.¹ Although the pathogenesis of scleroderma remains unclear, interactions among leukocytes, endothelial cells, and fibroblasts are likely to be central in this disease.²

According to the 1980 American College of Rheumatology (ACR) guidelines,³ a diagnosis of systemic scleroderma can be made with either 1 major criterion or 2 minor criteria present. The major criterion is symmetric thickening, tightening, and induration of the skin proximal to the metatarsal-phalangeal or metacarpal-phalangeal joints. This may affect the whole extremity, trunk, neck, and face. The minor criteria include sclerodactyly, digital pitting scars or a loss of substance from the finger pads, and bibasilar pulmonary fibrosis.

■ **Two forms of scleroderma.** To improve sensitivity for milder forms of disease, the condition is often divided into diffuse systemic scleroderma (dSSc) or limited systemic scleroderma (lSSc) (TABLE 1), with CREST syndrome being a variant of the limited form.⁴ Patients with dSSc usually have a rapid diffuse involvement of the trunk, hands, feet, and face with early internal organ involvement. Patients with lSSc, however, usually have slow skin involvement limited to hands, feet, and face, and delayed systemic involvement, if any.

If CREST syndrome is suspected, it is important to look for its cardinal features. Cutaneous calcinosis usually presents over the bony prominences of knees, elbows, spine, and iliac crests, and may be painful. Patients may complain of Raynaud's phenomenon

FIGURE 2

Thumb fixed in an extended position



The patient had tight skin on her fingers and a pitted scar on her thumb, which was fixed in an extended position.

with triphasic color changes, ie, pallor, cyanosis, and rubor, occurring months to years before sclerosis. Ulcerations at fingertips from Raynaud's may be evident as pitted scars on physical exam. There is also a nonpitting edema of hands and feet that later progresses into sclerodactyly with tapering of fingers (our patient actually had clubbing). Patients may complain of stiffness of the hands and feet as the sclerosis progresses.

As a result of the edema and fibrosis of the face, patients may lose facial lines and comment that they look younger. Often, they will indicate that they have noticed the appearance of small blood vessels on their face, mouth, or hands. Patients may also complain of gastrointestinal problems such as esophageal reflux, diarrhea, or dysphagia.

Differential includes morphea and scleromyxedema

A thorough history, physical exam, lab work, and possibly biopsy will help differentiate systemic scleroderma from the possible diagnoses with sclerosis listed below:

- **Morphea** features a localized, patchy distribution of skin fibrosis. There is no systemic involvement or Raynaud's phenomenon.
- **Mixed connective tissue disease** has features of other autoimmune diseases, along with those of scleroderma.

➤ Although the pathogenesis of scleroderma is unclear, interactions among leukocytes, endothelial cells, and fibroblasts are likely to be central in this disease.

TABLE 1

Characteristics of systemic sclerosis⁴⁻⁶

	Diffuse systemic sclerosis	Limited systemic sclerosis (Includes CREST syndrome)
Constitutional	Fatigue and weight loss or gain	None
Vascular	Mild to moderate Raynaud's phenomenon	Moderate to severe Raynaud's phenomenon
Cutaneous	Sclerosis to trunk, arms, and face; rapid progression	Sclerosis to hands or toes and face; slow progression; calcinosis is prominent
Musculoskeletal	Arthralgias and deformities, muscle weakness, and tendon friction rubs	Arthralgias
Gastrointestinal	GERD, esophageal dysmotility, and malabsorption are common; all may be severe	Mild to moderate GERD and esophageal dysmotility are common; malabsorption is less common
Renal	Severe hypertension, and renal infarcts in renal crisis are common	Rare
Pulmonary	Pulmonary hypertension and interstitial lung disease are common	Uncommon
Cardiac	Cardiomyopathy, heart failure, and arrhythmias are common	Uncommon

GERD, gastroesophageal reflux disease.

- **Eosinophilic fasciitis** involves the fascia and muscle on biopsy. There is sparing of the hands.
- **Scleromyxedema** represents the skin thickening seen in patients with a gammopathy. Raynaud's phenomenon may also be present.
- **Scleredema** is associated with diabetes. Skin changes are found mostly on the neck, shoulders, and upper arms. On rare occasions, there is visceral involvement. Raynaud's phenomenon is not present.

In addition, the differential includes chronic graft-vs-host disease; lichen sclerosis et atrophicans; amyloidosis; porphyria cutanea et tarda; primary Raynaud's phenomenon; and polyvinyl chloride, bleomycin, or pentazocine exposure.

Nailfold capillary abnormalities help with the diagnosis

As noted earlier, diagnosing systemic sclerosis hinges on taking a good history, doing

a thorough physical exam, applying the ACR diagnostic criteria, and ordering lab work. The sensitivity of the ACR criteria increases from 67% to 99% with the addition of nailfold capillary abnormalities (telangiectasias), identified using a dermatoscope.⁵

The initial lab work that you should consider includes an antinuclear antibody (ANA) test, complete blood count, and erythrocyte sedimentation rate. If the ANA is positive, anticentromere antibody (ACA) and DNA topoisomerase I (Scl-70) antibody tests should be ordered to see if sclerosis is likely limited or diffuse. ACA will be present in 21% of dSSc and 71% of ISSc cases, whereas Scl-70 will be present in 33% of dSSc and 18% of ISSc cases.⁶

If the diagnosis is still unclear, do a punch biopsy. Histology in the early phase will show mild cellular infiltrates around dermal blood vessels and at the dermal subcutaneous interface, while the later phase will show thickening of dermis with broadening of collagen fibers and hyalinization of blood vessel walls.⁶ If lung, kidney, heart, or gastrointestinal involvement is



Initial lab work for CREST syndrome includes an antinuclear antibody test, complete blood count, and erythrocyte sedimentation rate.

➤
Pharmacologic therapy is focused on symptoms and organ-specific problems.

TABLE 2

Medical treatment of systemic sclerosis⁵⁻⁹

Organ-specific problem/symptom	Treatment
Raynaud's phenomenon	Nifedipine, verapamil, losartan, iloprost, prazosin, bosentan*
Pulmonary hypertension	Bosentan,* iloprost, captopril, enalapril, sildenafil
Interstitial lung disease	Cyclophosphamide, prednisone
Cardiomyopathy or arrhythmias	Antiarrhythmics, diuretics, digoxin, pacemaker, transplant
Renal failure or crisis	Captopril, kidney dialysis, transplant
Skin fibrosis	Methotrexate, cyclosporine, D-penicillamine
Arthralgias	Ibuprofen, acetaminophen
GERD, gastroparesis, diarrhea	H ₂ blockers, proton pump inhibitors, prokinetics, antibiotics
Pruritus	Antihistamines, low-dose topical steroids

GERD, gastroesophageal reflux disease.

*Restricted access in the United States.

suspected based on symptoms or physical exam, you'll need to do an organ function work-up.

Treatment focuses on organ-specific problems

Currently, there are no guidelines for the treatment of scleroderma, given that the exact pathogenesis remains unclear and the disease course varies from patient to patient. Pharmacologic therapy is focused on symptoms and organ-specific problems (TABLE 2). Prazosin 1 to 3 mg TID is moderately effective in treating Raynaud's phenomenon secondary to scleroderma⁷ (SOR: A). Losartan has been reported to reduce the frequency and severity of Raynaud's phenomenon compared with a low dose of nifedepine,⁸ in a nonblinded randomized controlled trial (SOR: B). For interstitial lung disease, cyclophosphamide has been found to modestly reduce dyspnea while improving lung function, but it requires close monitoring⁹ (SOR: A). Bosentan is approved for symptomatic pulmonary hypertension and has been shown to decrease the occurrence of digital ulcers secondary to Raynaud's phenomenon¹⁰ (SOR: A). (Bosentan is available in the United States under a special restricted distribution program called the Tracleer Access Program.)

Nonpharmacologic treatments should also be considered in the management of scleroderma. Advise patients that Raynaud's phenomenon may be improved by avoiding exposure to the cold and by not smoking (SOR: C). Cutaneous ulcers can be protected with an occlusive dressing and treated with antibiotics if infected (SOR: C). To remove painful calcinotic nodules or release contractures secondary to sclerosis that may limit movement, you may want to consider surgery for your patient¹¹ (SOR: C). If aesthetically unappealing, telangiectasias may be removed with electrosurgery or laser therapy (SOR: C).

Prognosis for scleroderma varies, depending on whether it is diffuse or limited. One large study found that patients with lSSc had a 10-year survival rate of 71%, compared with 21% for patients with dSSc (SOR: B).⁴ Patients with systemic sclerosis should be monitored for interstitial lung disease, pulmonary hypertension, renal failure, and cardiomyopathy (SOR: C). Prognosis worsens with renal, pulmonary, or cardiac involvement; pulmonary disease is the leading cause of death in dSSc.¹

Our patient has a change of heart

Our patient had all the cardinal features of CREST syndrome on history and physical

exam. She had an ANA of 1:640 with speckled pattern and ACA and Scl-70 were negative, demonstrating that diagnosis must be made in clinical context and not just based on lab markers. We treated her GERD with lifestyle changes and a proton pump inhibitor. We explained the risks and benefits of cutting out her calcinosis nodules and she chose not to have surgery.

JFP

CORRESPONDENCE

Lucia Diaz, MD, 7703 Floyd Curl Drive, Mail #7816, San Antonio, TX 78229; DiazL3@uthscsa.edu

Strength of recommendation (SOR)

- A** Good-quality patient-oriented evidence
- B** Inconsistent or limited-quality patient-oriented evidence
- C** Consensus, usual practice, opinion, disease-oriented evidence, case series

References

- Mayes MD, Lacey JV Jr, Beebe-Deemer J, et al. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in large US population. *Arthritis Rheum.* 2003;48:2246-2255.
- Hasegawa M, Sato S. The roles of chemokines in leukocyte recruitment in systemic sclerosis. *Front Biosci.* 2008;13:3637-3647.
- Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. *Arthritis Rheum.* 1980;23:581-590.
- Barnett AJ, Miller MH, Littlejohn GO. A survival study of patients with scleroderma diagnosed over 30 years (1953-1983): the value of a simple cutaneous classification in the early stages of disease. *J Rheumatol.* 1988;15:276-283.
- Hudson M, Taillerfer S, Steele R, et al. Improving sensitivity of the American College of Rheumatology classification criteria for systemic sclerosis. *Clin Exp Rheumatol.* 2007;25:754-757.
- Wolff K, Johnson RA, Suurmond D. *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology.* 5th ed. New York, NY: McGraw-Hill; 2005.
- Harding SE, Tingey PC, Pope J, et al. Prazosin for Raynaud's phenomenon in progressive systemic sclerosis. *Cochrane Database Syst Rev.* 1998;(2):CD000956.
- Dziadzio M, Denton CP, Smith R, et al. Losartan therapy for Raynaud's phenomenon and scleroderma. *Arthritis Rheum.* 1999;42:2646-2655.
- Tashkin DP, Elashoff R, Clements P, et al, for the Scleroderma Lung Study Research Group. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med.* 2006;354:2655-2666.
- Korn JH, Mayes M, Matucci Cerinic M, et al. Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelial receptor antagonist. *Arthritis Rheum.* 2004;50:3884-3995.
- Melone CP Jr, McLoughlin JC, Beldner S. Surgical management of the hand in scleroderma. *Curr Opin Rheumatol.* 1999;11:514-520.

» Irritable Bowel Syndrome With Constipation (IBS-C): Improving Primary Care Assessment and Management

FREE
1.5 CME/CE
CREDITS

Irritable bowel syndrome with constipation (IBS-C) and its symptoms account for 12% to 14% of primary care visits. However, IBS-C often goes undiagnosed because of a lack of clinician awareness and poor patient-clinician communication. This publication seeks to raise awareness about the prevalence of IBS-C and provide practical tools to assess and manage the condition.

Faculty

- William D. Chey, MD, FACP (Chair)
- Richard H. Davis, Jr, PA-C
- Margaret M. Heitkemper, PhD, RN, FAAN

Click on CME/Supplements/Newsletters at jfponline.com. Or, visit <http://www.jfponline.com/supplements.asp?id=7581>

This activity was submitted by DIME and the Duke University School of Medicine and supported by an independent educational grant from Sucampo Pharmaceuticals, Inc., and Takeda Pharmaceuticals North America, Inc.