**Lower Gastrointestinal Tract Involvement** Impaired intestinal motility may result in malabsorption and chronic diarrhea secondary to bacterial overgrowth. Fat and protein malabsorption and vitamin $B_{12}$ and vitamin D deficiency ensue, sometimes culminating in severe malnutrition. Disturbed intestinal motor function can also cause intestinal pseudoobstruction, with symptoms of nausea and abdominal distension that are indistinguishable from those of delayed gastric emptying. Patients present with recurrent episodes of acute abdominal pain, nausea, and vomiting. Radiographic studies show acute intestinal obstruction, and the major diagnostic challenge is to differentiate pseudoobstruction, which responds to supportive care and intravenous nutritional supplementation, from mechanical obstruction.

Colonic involvement may cause severe constipation, fecal incontinence, gastrointestinal bleeding from telangiectasia, and rectal prolapse. In late-stage SSc, wide-mouth sacculations or diverticula occur in the colon, occasionally causing perforation and bleeding. An occasional radiologic finding is pneumatosis cystoides intestinalis due to air trapping in the bowel wall that may rarely rupture and cause benign pneumoperitoneum. Although the liver is rarely affected, primary biliary cirrhosis may coexist with SSc.



### RENAL INVOLVEMENT: SCLERODERMA RENAL CRISIS

Scleroderma renal crisis occurs in 10–15% of patients and generally within 4 years of the onset of the disease. Prior to the advent of angiotensin-converting enzyme (ACE) inhibitors, short-term survival in scleroderma renal crisis was <10%. The pathogenesis involves obliterative vasculopathy and luminal narrowing of the renal arcuate and interlobular arteries. Progressive reduction in renal blood flow, aggravated by vasospasm, leads to juxtaglomerular hyperplasia, increased renin secretion, and activation of angiotensin, with further renal vasoconstriction resulting in a vicious cycle that culminates in accelerated hypertension. Risk factors for scleroderma renal crisis include African-American race, male gender, and dcSSc with extensive and progressive skin involvement. Up to 50% of patients with scleroderma renal crisis have anti-RNA polymerase III antibodies. Palpable tendon friction rubs, pericardial effusion, new unexplained anemia, and thrombocytopenia may be harbingers of impending scleroderma renal crisis. High-risk patients with early SSc should be counseled to check their blood pressure daily. Patients with lcSSc or anticentromere antibodies rarely develop scleroderma renal crisis. Because there is an association between glucocorticoid use and scleroderma renal crisis, prednisone should be used in high-risk SSc patients only when absolutely required and at low doses (<10 mg/d).

Patients characteristically present with accelerated hypertension and progressive oliguric renal insufficiency. However, approximately 10% of patients with scleroderma renal crisis present with normal blood pressure. Normotensive renal crisis is generally associated with a poor outcome. Headache, blurred vision, and congestive heart failure may accompany elevation of blood pressure. Urinalysis typically shows mild proteinuria, granular casts, and microscopic hematuria; thrombocytopenia and microangiopathic hemolysis with fragmented red blood cells can be seen. Progressive oliguric renal failure over several days generally follows. In some cases, scleroderma renal crisis is misdiagnosed as thrombotic thrombocytopenic purpura or other forms of thrombotic microangiopathy. In these cases, a renal biopsy may be of some benefit. In addition, biopsy findings of vascular thrombosis and glomerular ischemic collapse predict poor renal outcomes. Oliguria or a creatinine >3 mg/dL at presentation predicts poor outcome, with permanent hemodialysis and high mortality. Rarely, crescentic glomerulonephritis occurs in the setting of SSc and may be associated with myeloperoxidase-specific antineutrophil cytoplasmic antibodies. Membranous glomerulonephritis may occur in patients treated with D-penicillamine. Asymptomatic renal function impairment occurs in up to half of SSc patients. Such subclinical renal involvement is associated with other vascular manifestations of SSc and rarely progresses.

### CARDIAC INVOLVEMENT

Although it is often silent, cardiac involvement in SSc is frequently detected when patients are screened with sensitive diagnostic tools. Clinically evident cardiac involvement is associated with poor outcomes. Cardiac disease in SSc may be primary or secondary to PAH, ILD, or renal involvement. It occurs more frequently in patients with dcSSc than in those with lcSSc and generally develops within 3 years of the onset of skin thickening. Clinically evident cardiac involvement in SSc is a poor prognostic factor. The endocardium, myocardium, and pericardium may each be affected separately or together. Manifestations of pericardial involvement include acute pericarditis, pericardial effusions, constrictive pericarditis, and cardiac tamponade. Conduction system fibrosis occurs commonly and may be silent or manifested by atrial and ventricular tachycardias or heart block. Recurrent vasospasm and ischemia-reperfusion injury contribute to myocardial fibrosis, resulting in asymptomatic systolic or diastolic left ventricular dysfunction that may progress to overt heart failure. Systemic and pulmonary hypertension and lung and renal involvement may also impact on the heart. Despite the presence of widespread obliterative vasculopathy, the frequency of clinical or pathologic epicardial coronary artery disease in SSc is not increased. While conventional echocardiography has low sensitivity for detecting SSc preclinical heart involvement, newer modalities such as tissue Doppler echocardiography (TDE), cardiac magnetic resonance imaging (cMRI), thallium perfusion, and nuclear imaging (single photon emission CT [SPECT]) reveal a high prevalence of abnormal myocardial function or perfusion in SSc patients. The serum level of N-terminal pro-BNP, a ventricular hormone, is a marker for PAH in SSc, but may also have utility as a marker of primary cardiac involvement.

### MUSCULOSKELETAL COMPLICATIONS

Carpal tunnel syndrome occurs frequently and may be a presenting manifestation. Generalized arthralgia and stiffness are prominent in early disease. Mobility of small and large joints is progressively impaired, especially in dcSSc. Most commonly affected are the hands. Contractures develop at the proximal interphalangeal joints and wrists. Large joint contractures can be accompanied by tendon friction rubs, characterized by leathery crepitation that can be heard or palpated upon passive movement, that are due to extensive fibrosis and adhesion of the tendon sheaths and fascial planes at the affected joint. Presence of tendon friction rubs is associated with increased risk for renal and cardiac complications and reduced survival. True joint inflammation is uncommon; however, occasional patients develop erosive polyarthritis in the hands. Muscle weakness is common and may indicate deconditioning, disuse atrophy, and malnutrition. Less commonly, inflammatory myositis indistinguishable from idiopathic polymyositis may occur. A chronic noninflammatory myopathy characterized by atrophy and fibrosis in the absence of elevated muscle enzyme levels can be seen in late-stage SSc. Bone resorption occurs most commonly in the terminal phalanges, where it causes loss of the distal tufts (acro-osteolysis) (Fig. 382-5). Resorption of the mandibular condyles can lead to bite difficulties. Osteolysis can also affect the ribs and distal clavicles.

### OTHER DISEASE MANIFESTATIONS

Many SSc patients develop dry eyes and dry mouth (sicca complex). Biopsy of the minor salivary glands shows fibrosis rather than focal lymphocytic infiltration characteristic of primary Sjögren's syndrome (Chap. 383). Hypothyroidism is common and generally due to fibrosis of the thyroid gland. The frequency of macrovascular involvement, including peripheral vascular and coronary artery disease, may be increased. Whereas the central nervous system is generally spared, sensory trigeminal neuropathy due to fibrosis or vasculopathy can occur, presenting with gradual onset of pain and numbness. Pregnancy in women with SSc may be associated with an increased rate of adverse fetal outcomes. Furthermore, cardiopulmonary involvement may worsen during pregnancy, and new onset of scleroderma renal crisis has been described. Erectile dysfunction is frequent in men with SSc and may be the initial disease manifestation. Inability to attain or maintain penile erection is due to vascular insufficiency and fibrosis.

**Malignancy in SSc** Epidemiologic studies indicate an increased risk of cancer in SSc. Lung cancer and esophageal adenocarcinoma typically occur in the setting of long-standing ILD or gastroesophageal reflux disease and may be caused by chronic inflammation and repair. In contrast,