"Eyeing" the Cause of Heart Failure: Visible Telltale Clues

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Fig. 1 *Pseudoxanthoma elasticum*. Clues to this patient's heart failure are the strikingly abnormal skin folds in her neck (Fig. 1A) and axilla (Fig. 1B)—changes characteristic of pseudoxanthoma elasticum, an autosomal recessive connective-tissue disease caused by mutations in the *ABBC6* gene.[1] The underlying pathophysiologic disturbance is degeneration and calcification of elastic fibers in the skin, eyes, and cardiovascular system. Its estimated prevalence is 1 in 50,000.

The cutaneous manifestations consist of yellow-orange macules or papules that coalesce to form plaques and redundant folds of skin in the neck and flexural areas—that is, the axillae, antecubital and popliteal fossae, and groin.

Ophthalmoscopic examination typically shows angioid streaks, which are breaks in the elastic lamina of the Bruch membrane beneath the retinae. These streaks appear as dark-red, brown, or gray bands that radiate from the optic disks independent of arteries and veins.

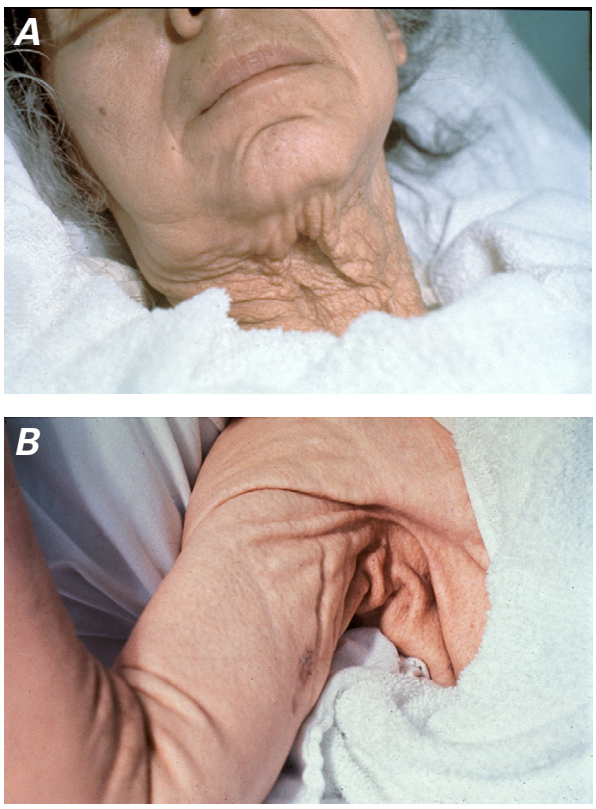

Fig. 1 *Pseudoxanthoma elasticum.*

Accelerated atherosclerosis at an early age is frequent and should suggest the diagnosis, especially when risk factors are absent. Cardiovascular complications result primarily from advanced atherosclerosis, which in turn leads to greatly diminished peripheral pulses, coronary artery occlusion and calcification, left ventricular dysfunction, and sometimes sudden death.[2]

The patient in the photograph looked much older than her 42 years. She had experienced long-standing angina pectoris, almost absent peripheral pulses, angioid streaks in both optic fundi, and radiographically detectable calcifications of her coronary arteries.

Fig. 2 *Hemochromatosis.* Alongside the leg of an intern are the legs of this patient. In addition to his telltale bronze-colored skin, the patient—a white man—had a history of long-standing diabetes mellitus, biopsy-proven hepatic cirrhosis with excessive iron deposition in the hepatocytes, and recently treated congestive heart failure. His father had died of liver failure.

In most cases, hemochromatosis is a genetic disease with autosomal recessive inheritance. The causative gene is close to the *HLA-A* locus on chromosome 6. Subsequently, scientists cloned the hemochromatosis gene (*HFE* gene for high iron [Fe]), which opened the door for additional genetic investigations.[3]

Clinical clues to this malady include hyperpigmented skin, diabetes mellitus, hepatomegaly, and unexplained heart failure. Changes in skin pigmentation are generally widespread, but the hue is often deeper in sun-exposed areas. The hue is typically bronze and results from melanin deposition, not iron. When iron deposition occurs, the hue becomes metallic gray.

Cardiac hemochromatosis has a wide range of manifestations.[3] It ordinarily causes dilated ventricles and reduced ejection fraction. Eventually, left ventricular failure occurs, followed by rapid clinical deterioration. Other occasional adverse effects include pericardial constriction or tamponade and various conduction defects.

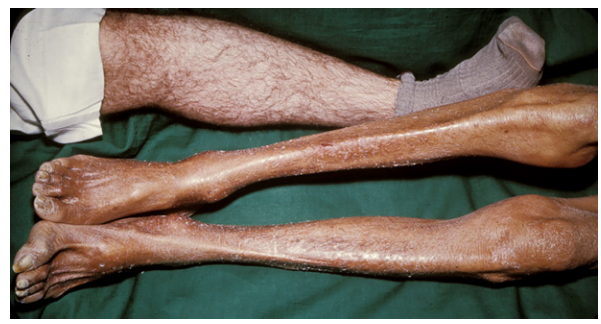

Fig. 2 *Hemochromatosis.*

Treatment involves removal of excess body iron by repeated phlebotomy, by use of chelating agents, or by erythrocytapheresis. Cardiac transplantation is an option for patients with severe congestive failure that is refractory to medical management.

Death usually results from heart failure, hepatocellular carcinoma, or complications of diabetes mellitus or portal hypertension.

Fig. 3 *Traumatic Arteriovenous Fistula.* The size and tortuosity of this neck vein should immediately suggest an arteriovenous (AV) fistula. Twenty years before seeking medical attention, the patient had sustained a stab wound to his neck. He recovered on his own and remained well until he presented with heart failure.

On physical examination, the vein had a palpable thrill and continuous murmur. Compressing the vein abolished the murmur and decreased the heart rate from 110 beats/min to 80 beats/min (Branham sign). An arteriogram showed a connection between the right external carotid artery and the right external jugular vein. Surgical closure of the fistula cured the patient's heart failure.

Although conventional angiography has been the gold standard for the diagnosis of traumatic AV fistulae, less invasive imaging techniques with comparable results are now available. These include Doppler ultrasonography, magnetic resonance angiography, and computed tomographic angiography.[4] Likewise, alternative surgical approaches include the use of endovascular stent-grafts.[5]

The important point is this: every patient with unexplained heart failure deserves a careful physical examination in pursuit of an AV fistula, which rarely is as obvious as the one displayed here. Once found, however, its surgical correction can eliminate the cardiac dysfunction.

Fig. 4 *Myotonic Dystrophy Type 1.* On careful inspection, this man has wasting of his facial muscles and no discernible neck or shoulder muscles. Not shown are his early frontal balding and the wasting of his temporal muscles. These findings are distinctive for myotonic dystrophy type 1—the most prevalent inherited form of muscular dystrophy affecting adults. It is an autosomal dominant disorder characterized by abnormally prolonged muscle contraction after active motion or mechanical stimulation. This patient's inability to relax his grip after a handshake sealed the diagnosis.

Cardiac involvement in this ailment includes a wide range of abnormalities: contraction disturbances, atrial and ventricular arrhythmias, left ventricular systolic dysfunction, heart failure, and sudden death.[6]

Fig. 5 *Fabry Disease.* Distributed all over this man's penis (Fig. 5A) and scrotum (Fig. 5B) are angiokeratomas—a telltale sign of Fabry disease. This is an X-linked lysosomal storage disorder caused by mutations in the *GLA* gene with resultant deficiency of the enzyme α-galactosidase A. The enzymatic defect leads to widespread deposition of glycosphingolipids, mainly globotriaosylceramide and galactosylceramide. Affected vessels become narrowed and the consequent tissue ischemia presumably accounts for many of the clinical features, including an array of cardiac abnormalities.[7,8]

Angiokeratomas are distended capillaries protruding into a hyperkeratotic epidermis. Detectable in childhood or adolescence, these lesions can appear anywhere on the body, but tend to cluster around the umbilicus and swimming-trunk areas. They often increase in size and number with age.

Additional manifestations include pain—usually in the extremities, often severe, and sometimes debilitating—and corneal dystrophy, lenticular opacities, and proteinuria. With time, cerebrovascular events, cardiac abnormalities, or renal problems predominate. Contrary to previous belief, women are frequently symptomatic, especially with arrhythmias. In the past, most victims died of renal failure. Now, most patients die of cardiovascular complications.[9]

The cardiac features warrant emphasis. More than half of all patients with Fabry disease have cardiac in-

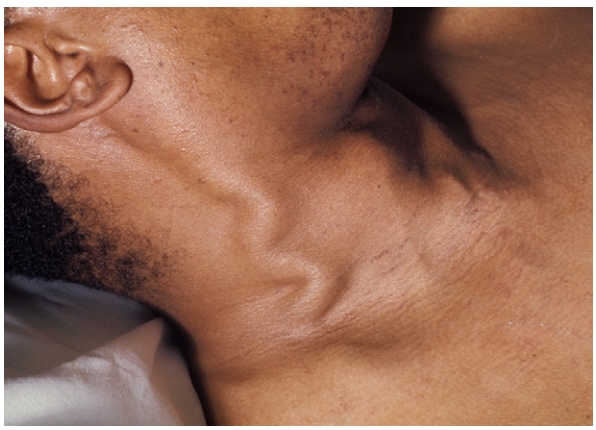

Fig. 3 *Traumatic arteriovenous fistula.*

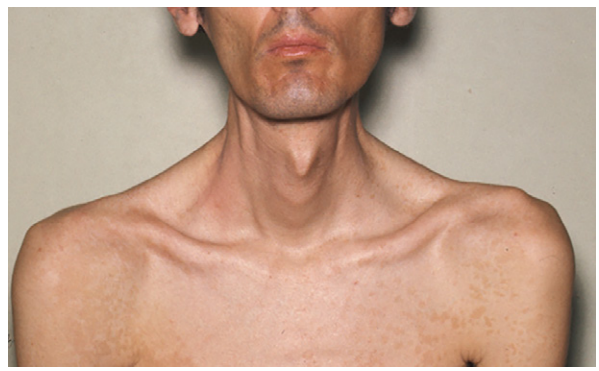

Fig. 4 *Myotonic dystrophy type 1.*

volvement.[10] Among many reported abnormalities are thickened and distorted valves; left ventricular hypertrophy; ischemic coronary artery disease leading to angina pectoris, myocardial infarction, or heart failure; a wide range of arrhythmias and conduction defects; and sudden cardiac death.[7,8,10]

Arousing suspicion of Fabry disease are unexplained episodes of pain with corneal lesions in children, and renal dysfunction, cardiomyopathy, or intracranial problems of unclear origin in adults. In either age group, however, the strongest clue is the angiokeratoma.

Diagnostic confirmation in men requires greatly deficient or absent α-galactosidase A activity in plasma or peripheral leukocytes, or gene sequencing. In women, gene sequencing is the preferred method.

The most effective therapy is prevention; hence, genetic counseling is essential. Enzyme-replacement or substrate-depletion strategies have provided some benefits, but more data are needed to document their long-term effects.

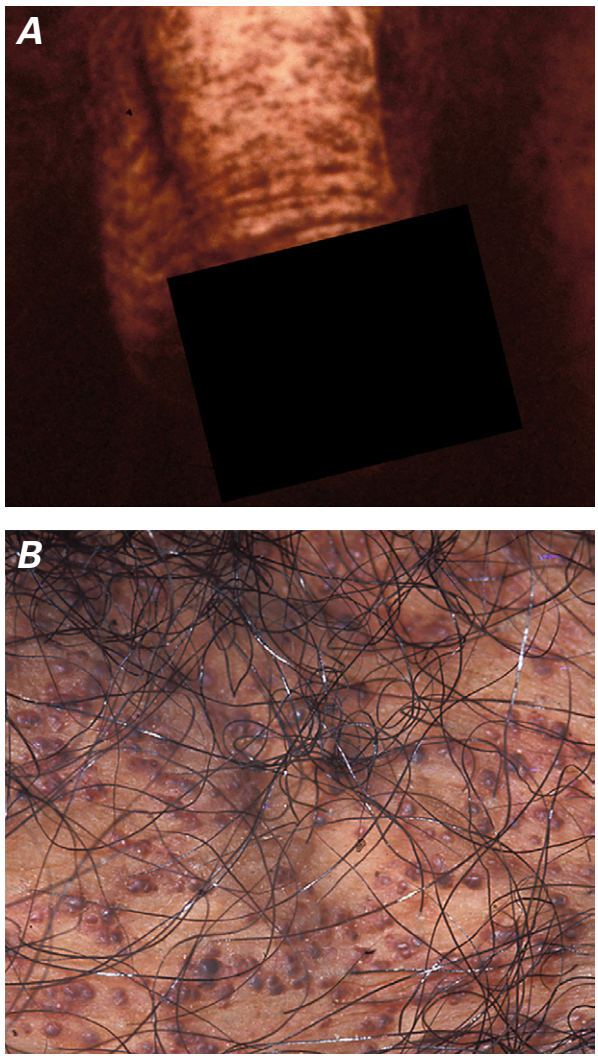

Fig. 5 *Fabry disease.*

Fig. 6 *Carcinoid Heart Disease.* In the presence of cardiac failure, purplish-red discoloration of the cheeks with underlying and surrounding telangiectases should immediately suggest carcinoid heart disease. This patient had a 4-month history of episodic wheezing and diarrhea, together with occasional bouts of asymptomatic facial flushing that occurred only during meals. After about an hour, the flush would subside.

On physical examination, he had an enlarged liver and striking murmurs of tricuspid regurgitation and pulmonic stenosis. A liver biopsy specimen showed findings indicative of a midgut carcinoid tumor.

Descriptions of the pathophysiology, work-up, and management of carcinoid heart disease are beyond the scope of this case presentation but are available elsewhere.[11-13] Here, we emphasize that facial flushing combined with right-sided cardiac valvular lesions essentially confirm the diagnosis of this disease. Moreover, with few exceptions, hepatic metastases have already occurred by the time flushing first appears. The flushes can vary considerably in color, frequency, duration, distribution, and symptoms, and eating sometimes provokes them.

Fig. 7 *Infective Endocarditis.* Finding conjunctival petechiae in someone with heart failure of uncertain cause should immediately raise suspicion of infective endocarditis. This patient was a heroin addict with acute staphylococcal infection of her tricuspid and mitral valves.

Before the antibiotic era, conjunctival petechiae were routinely sought and often found in patients suspected of having infective endocarditis.[14] Now, however, with so little emphasis on the physical examination, these

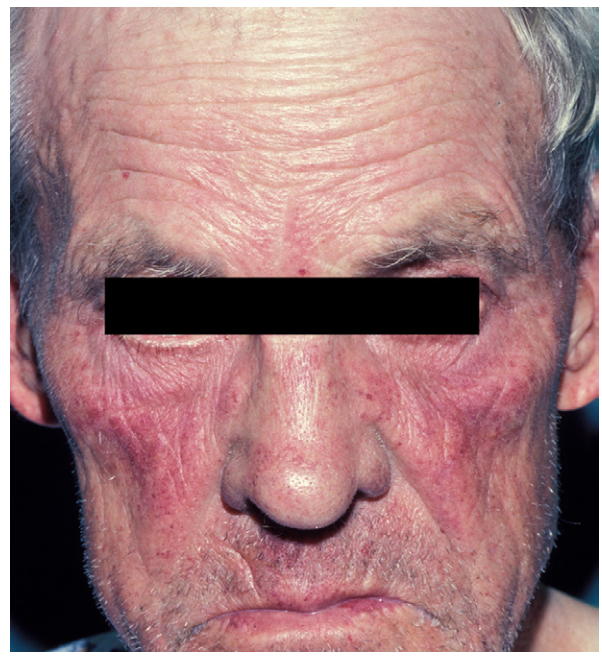

Fig. 6 *Carcinoid heart disease.*

lesions have lost much of the attention that they once commanded.[15]

Conjunctival petechiae can also be a sign of fat embolism,[16] cardiac bypass procedures,[17] and a host of primary infections and hematologic disorders. In all of these other conditions, however, heart failure is not an underlying feature.

Fig. 8 *Amyloidosis.* This woman's upper torso looked like that of a football player wearing shoulder pads. Such a "shoulder-pad" sign results from periarticular deposition of amyloid and is essentially pathognomonic of the disease.[18] The shoulders and surrounding structures, including the muscles, become markedly swollen and rubbery hard but not tender. This patient also had a distinctly enlarged tongue[18] and rapidly progressive heart failure,[19] both of which left no doubt about the diagnosis. Proof came at autopsy, which showed dense deposits of amyloid throughout her body, especially in her heart, kidneys, muscles, periarticular tissue, and vasculature.

Fig. 9 *Metastatic Melanoma.* Scattered about this patient's epigastrium and lower anterior part of the chest are numerous small subcutaneous and intracutaneous nodules, some of which have a black top. Note, too, that the skin itself has a reddish-purple hue. Together, these findings indicate the probability of metastatic melanoma, which is precisely what the patient had. Its origin was never established.

Melanoma is the neoplasm that most frequently metastasizes to the heart.[20] Ordinarily, cardiac metastases are clinically silent. When signs or symptoms do arise, pericardial effusion (with or without tamponade) and dysrhythmias are the usual causes. Cardiac failure, however, can be the initial sign, as it was in this patient. At his autopsy, the heart was extensively involved with black metastases, typical of what is called "charcoal heart."[20]

One additional point merits attention. The amount of tumor deposited in the heart of a patient with metastatic melanoma is far greater than that of any other cancer. In one case, for example, the melanoma-infiltrated heart weighed 2,450 g![21]

Fig. 10 *Acropachy and Pretibial Myxedema Accompanying Hyperthyroidism.* Painless swelling of the fingers (Fig. 10A) and bumpy swelling of the lower legs (Fig. 10B) are infrequent signs of hyperthyroidism. This patient also had bilateral exophthalmos and a diffusely enlarged thyroid gland.

Acropachy manifests itself as soft-tissue swelling of phalanges, clubbing of terminal phalanges, periosteal new bone formation, or any combination thereof. It is almost always associated with past or present hyperthyroidism, exophthalmos, and pretibial myxedema. It is typically painless, causes no disability, and requires no specific therapy.[22]

Localized myxedema—deposition of mucopolysaccharides in the skin—is nonpitting and firm. It typically involves the pretibial area, but can affect the hands, arms, face, ears, shoulders, back, or abdomen. The myxedema usually appears after the onset of thyrotoxicosis, but it occasionally develops before or with other clinical signs of hyperthyroidism. Treatment with plasmapheresis, cytotoxic agents, and topically applied steroids is

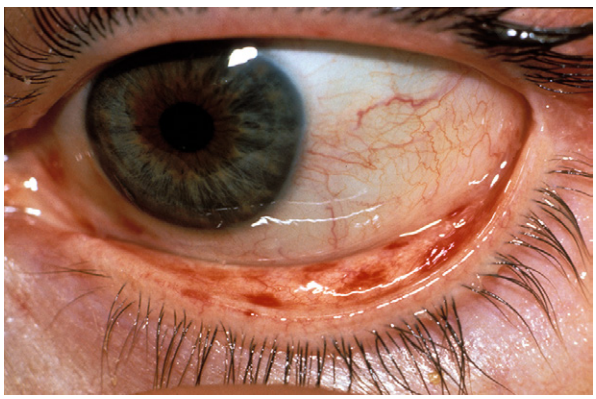

Fig. 7 *Infective endocarditis.*

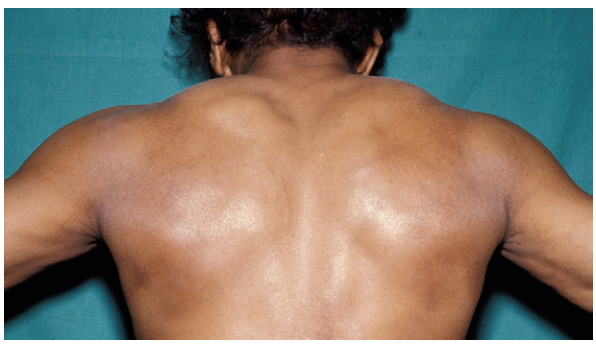

Fig. 8 *Amyloidosis.*

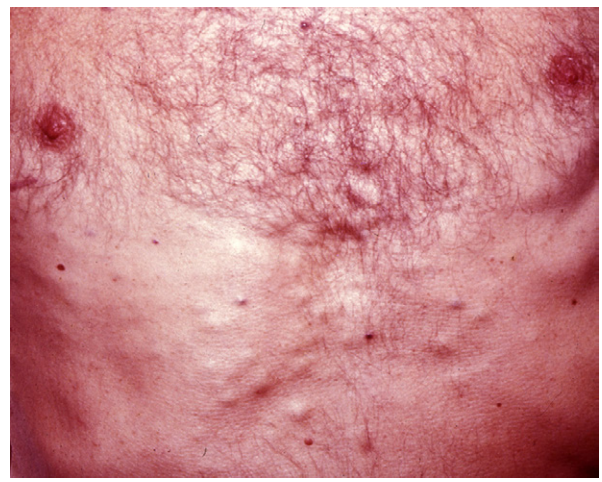

Fig. 9 *Metastatic melanoma.*

moderately effective, but complete remission occurs in only about 10% of cases.[22,23]

Heart failure in patients with hyperthyroidism is a complex problem with many facets.[24] Its mechanism and management are well described elsewhere.[24,25]

Fig. 11 *Systemic Sarcoidosis.* Tiny papules are evident at the inner canthus of each eye, on both cheeks, at the base of the nose, and on the left side of the chin (Fig. 11A). In addition, discrete nodules are evident on the anterior surface of each lower leg (Fig. 11B). These facial and leg lesions are classic signs of cutaneous sarcoidosis.[26] A biopsy specimen from one of the leg nodules showed noncaseating granulomas. The patient also had bilateral hilar and widespread peripheral adenopathy.

Cardiac involvement occurs in about 5% of patients with sarcoidosis and can be the presenting manifestation.[27] Depending on the location, extent, and activity of the granulomas, the main cardiac abnormalities are conduction defects; ventricular arrhythmias, including sudden death; and heart failure. Typically, these patients are highly symptomatic, and in about a third of them, the heart is the only organ involved. In patients with extracardiac sarcoidosis, the sensitivity, specificity, and cost-effectiveness of screening for silent cardiac involvement are not well established.

Currently, there are 2 recommended pathways to the diagnosis of cardiac sarcoidosis[28]:

1. Definite: presence of noncaseating granulomas on histologic examination of myocardial tissue with no alternative cause identified.
2. Probable: histologic evidence of extracardiac sarcoidosis together with a variety of unexplained cardiac abnormalities such as arrhythmias, heart block, and steroid-responsive cardiomyopathy.

Management of symptomatic cardiac sarcoidosis, including left ventricular dysfunction, should consist of all

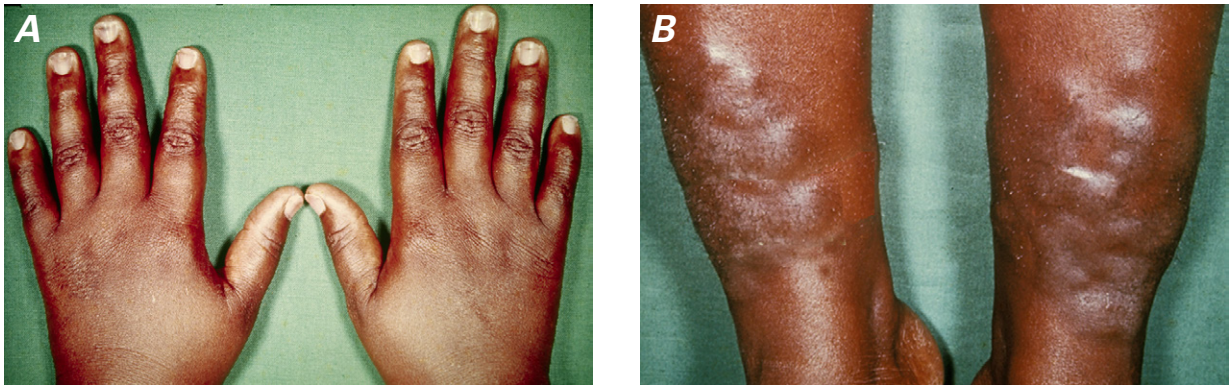

Fig. 10 *Acropachy and pretibial myxedema accompanying hyperthyroidism.*

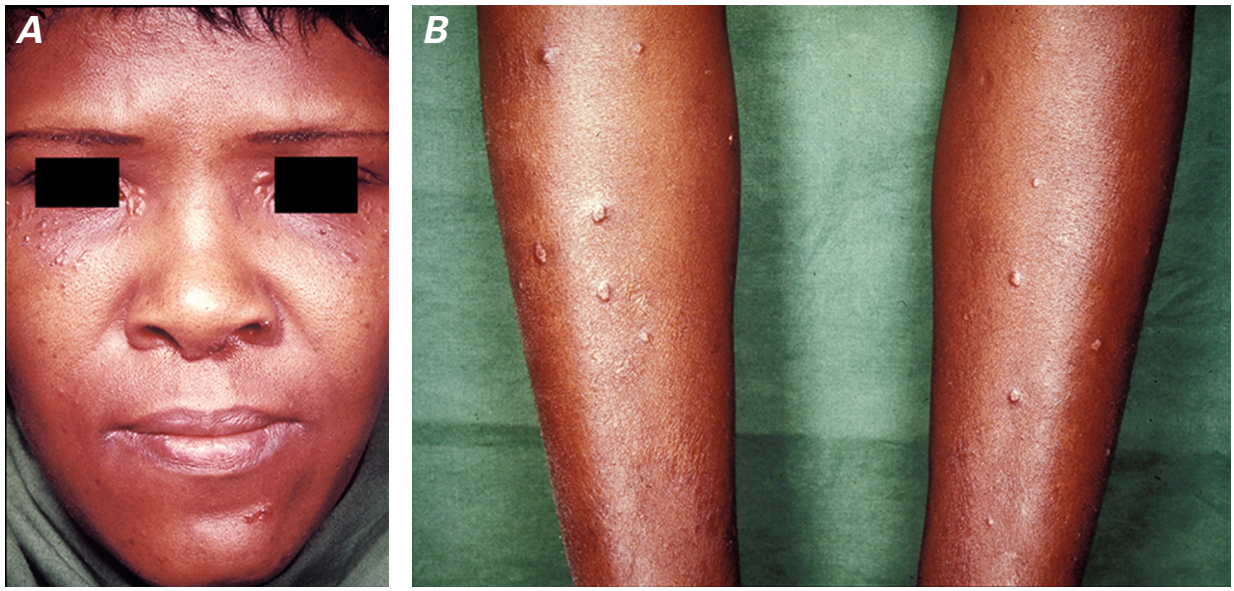

Fig. 11 *Systemic sarcoidosis.*

standard therapies for heart failure plus the use of support devices and heart transplantation when indicated.

Coda

In medicine today, few see because few look. If this report is successful, more might see because more will look.

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