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CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

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Case 6-2008: A 46-Year-Old Woman with Renal Failure and Stiffness of the Joints and Skin

Jonathan Kay, M.D., Hasan Bazari, M.D., Laura L. Avery, M.D.,
and Aashiyana F. Koreishi, M.D.

PRESENTATION OF CASE

Dr. Nancy Cibotti-Granof (Medicine): A 46-year-old woman with end-stage renal disease was seen by a rheumatology consultant because of stiffness of her joints and skin.

The patient had been well except for mild asthma until 7 years earlier, when group A streptococcal pneumonia developed, complicated by septic shock, with acute respiratory distress syndrome; septic emboli to the lungs, brain, and kidney; renal failure requiring dialysis; flaccid quadriplegia; and coma. On the 25th day after initial admission to another hospital, she was transferred to this hospital while she was receiving mechanical ventilation.

As part of the evaluation during admission, computed tomography (CT) of the thorax, abdomen, and pelvis with intravenous contrast revealed cavitory lesions in the right lower lobe of the lung, with diffuse bilateral ground-glass opacities, small bilateral pleural effusions, and multiple prominent mediastinal lymph nodes. CT of the head revealed regions of cortical mineralization in the left posterior frontal lobe and the right parietal lobe, with surrounding hypodensity consistent with edema and minimal enhancement consistent with cerebritis. Magnetic resonance imaging (MRI) of the brain with gadolinium revealed regions of cortical enhancement with surrounding edema in the left posterior frontal lobe and right parietal lobe consistent with cerebritis and vasculitis, as well as a small infarct in the right corona radiata (Fig. 1A).

Follow-up CT scans with contrast enhancement and MRI studies with gadolinium enhancement revealed regions of cerebritis and small infarcts, with no drainable abscesses. Transthoracic and transesophageal echocardiography showed a patent foramen ovale, normal left ventricular function, and no valvular vegetations. A filter was placed in the inferior vena cava.

During the hospital stay, the blood pressure stabilized; the patient regained consciousness and recovered speech and motor strength, with residual right-sided weakness. Kidney function improved, and hemodialysis was discontinued. Weakness, sensory loss, and pain in both feet persisted, and treatment with gabapentin (300 mg twice daily) was begun. The patient was discharged on the 53rd hospital day, first to a rehabilitation facility for 2 months, and then to home. Follow-up MRI

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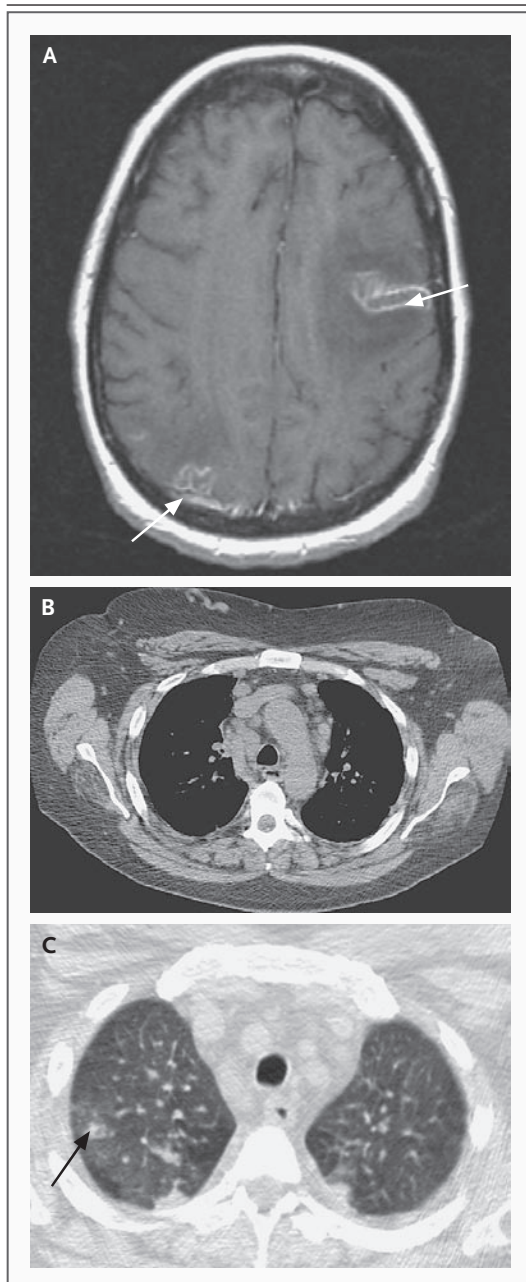


Figure 1. Radiology Imaging Studies.

An axial T₁-weighted image of the patient's brain (Panel A) from magnetic resonance imaging performed on her first admission, with gadolinium contrast, demonstrates regions of gyriform enhancement with surrounding edema in the right parietal lobe and posterior left frontal lobe (arrows). The appearance is consistent with cerebritis. Computed tomographic scanning of the chest without contrast (Panel B), performed 22 months before the patient's admission, shows enlarged lymph nodes present on soft-tissue windows. There has been interval development of patchy opacities (Panel C, arrow) superimposed on ground-glass opacification of the lung parenchyma.

of the brain with gadolinium enhancement revealed abnormalities consistent with previous cerebritis.

During the course of the next 2 years, the patient resumed most activities. Mild right-sided weakness and painful neuropathy persisted, which were managed with gabapentin and acetaminophen with codeine. Chronic kidney disease persisted, with serum creatinine levels ranging from 2.4 to 3.5 mg per deciliter (212.2 to 309.4 μ mol per liter). The renal failure was associated with edema of both feet and legs, which was treated with diuretics, and anemia, which was treated intermittently with recombinant erythropoietin (epoetin alfa). She was admitted to the hospital on several occasions because of respiratory distress; these episodes were thought to be exacerbations of asthma. Several episodes of atrial fibrillation occurred. Chest radiography, performed on admission for shortness of breath 4.5 years before the current admission, revealed fullness of the right paratracheal area, and CT of the chest showed enlarged mediastinal and hilar lymph nodes, hazy ground-glass opacities in both lungs, and scarring or atelectasis in both upper lobes, the lingula, and the right middle lobe. Four years before admission, dryness of the skin of the hands and feet developed, as did pain and stiffness in the hands, elbows, and knees that was worse in the morning.

Twenty-two months before admission, she reported worsening shortness of breath over the past 6 months and having to rest after walking 50 ft. On evaluation, oxygen saturations of 82 to 84% were noted after exertion while she was breathing ambient air. Chest CT revealed a marked increase in the size and number of mediastinal lymph nodes and stable ground-glass opacities. Treatment was begun at home with 40 mg of prednisone daily and supplemental oxygen; her symptoms improved slightly, and bronchoscopy and mediastinoscopy were scheduled. Results of laboratory tests are shown in Table 1. On the day of the scheduled bronchoscopy, she reported increased shortness of breath, with more frequent use of home oxygen and nebulizers; the procedure was canceled and she was admitted to the hospital.

The pulse was 100 beats per minute and the respiratory rate 24 breaths per minute; oxygen saturation was 93% while the patient was breathing oxygen at 3 liters per minute by nasal cannula, and there was pitting edema (2+) of the feet

Table 1. Results of Laboratory Tests.*

Test	Reference Range, Adults†	22 Mo before Admission	18 Mo before Admission	17 Mo before Admission	On Admission
Rheumatoid factor (IU/ml)	<30	<30			
Autoantibodies					
Antinuclear antibody	Negative at 1:40 dilution	Positive at 1:320 dilution, speckled pattern			
Anti-double-stranded (native) DNA	Negative	Negative			
Anti-Ro (SSA) antibody	Negative	Negative			
Anti-La (SSB) antibody	Negative	Negative			
Anti-Smith antibody	Negative	Negative			
Anti-RNP antibody	Negative	Negative			
Anti-Scl-70 antibody	Negative				Negative
Antineutrophil cytoplasmic antibody	Negative		Negative		
Anticardiolipin IgM (MPL units)	0–15	33.7	41.0		
Anticardiolipin IgG (GPL units)	0–15	4.7	3.5		
Partial-thromboplastin time–lupus anticoagulant	Negative	Negative			
Goodpasture's antigen	Negative		Negative		
Heparin–PF4 antibody				Positive for heparin-induced thrombocytopenia (type 2)	
Serum protein electrophoresis					Normal pattern
Immunofixation					No M component detected
IgG (mg/dl)	614–1295				1190
IgA (mg/dl)	69–309				268
IgM (mg/dl)	53–334				301

* GPL denotes IgG phospholipid, and MPL IgM phospholipid.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and who do not have medical conditions that could affect the results. Therefore, they may not be appropriate for all patients.

and legs. Intravenous furosemide was administered. Repeated CT of the chest (Fig. 1B and 1C) revealed progression of diffuse ground-glass changes with new soft-tissue opacities in both lungs and stable diffuse mediastinal and hilar lymphadenopathy. Pulmonary-function tests revealed a forced expiratory volume in 1 second (FEV₁) of 0.44 liter (15% of the predicted value) and a forced vital capacity (FVC) of 0.77 liter (22% of the predicted value), findings that were consistent with a severe combined obstructive and restrictive defect. The pathological examination of specimens of lung and paratracheal lymph nodes obtained on a subsequent biopsy revealed pulmonary hemosiderosis; dendriform ossification; extensive fibrosis of the lymph nodes with scattered giant cells, histiocytes, and poorly formed gran-

ulomas; and no evidence of cancer. The findings were thought to be caused by sarcoidosis, and thus the dosage of prednisone was increased to 60 mg daily. Her symptoms improved and she was discharged on the 10th day to continue prednisone on a tapering dose, along with supplemental oxygen at home.

Eighteen months before the current admission, her weight had increased by 7 kg; dyspnea and pedal edema increased, and the woman was readmitted to this hospital. Chest radiography showed small bilateral pleural effusions. Atrial fibrillation followed by transient asystole occurred; a diagnosis of the sick sinus syndrome was made and a pacemaker was placed. Laboratory test results are shown in Table 1. The patient was evaluated for possible lung and renal

transplantation. Magnetic resonance angiography with gadolinium enhancement revealed small renal arteries without significant stenosis. Cardiac catheterization demonstrated cardiac output of 8.4 liters per minute by thermodilution and severely elevated right heart pressures with a high wedge pressure (30 mm Hg). After diuresis, her weight returned to baseline; her symptoms resolved, and she was discharged. Two weeks later, pathological examination of an endomyocardial biopsy specimen showed active and organizing fibrosis; no amyloid, iron, or organisms were seen on special stains.

Fifteen months before the current evaluation, the serum urea nitrogen level was 78 mg per deciliter (27.8 mmol per liter) and the creatinine level 3.2 mg per deciliter (282.9 μ mol per liter). An arteriovenous fistula was created in the arm, and hemodialysis was begun. In the following month, the fistula clotted, and a right internal jugular catheter was placed. Subsequent attempts to place a peritoneal catheter failed because of infections. During the next 14 months, the patient was admitted on numerous occasions because of episodes of dyspnea, fluid overload, and peripheral edema, and also with infections associated with dialysis.

Two weeks before the current evaluation, she saw a neurologist for an evaluation of her chronic pain. On examination, her skin appeared taut and glassy, with focal ulcerations and abrasions; there was sensory loss in the lower legs, with decreased position and vibratory sense in the toes. Consultation with a rheumatologist was suggested. Ten days later, the patient was readmitted to this hospital because of fever due to an infection at the site of the hemodialysis catheter; the catheter was removed, and she received antibiotic treatment. The infection resolved, and the catheter was replaced on the third day. The same day, she was seen by the rheumatology service.

The patient reported that the skin of her hands and feet had become dry and tight approximately 4 years earlier, with pruritus and scratching that resulted in excoriation. The skin did not change color in the cold, although the symptoms were worse in the cold. Pain and stiffness in her joints had begun at the same time and involved her shoulders, elbows, knees, and interphalangeal joints. The pain and stiffness were worse on awakening, improved during the day, and were

not associated with redness or warmth. The arthralgias and skin changes had worsened during the past 3 years. She did not have heartburn or difficulty swallowing.

The patient had had asthma since childhood; a diagnosis of obstructive sleep apnea had been made 5½ years earlier, and she had subsequently received treatment with continuous positive airway pressure; since her illness 7 years earlier, she had had depression and emotional lability. A diagnosis of lumbar spinal stenosis had been made 3 years earlier. She lived with her husband and two children, who were healthy. She did not smoke, drink alcohol, or use illicit drugs. Her father had had lymphoma; her mother had had colon cancer at 55 years of age, and one of her grandparents had had a stroke. She had a history of heparin-induced thrombocytopenia and allergies to penicillin, oxycodone-acetaminophen, and verapamil. Her medications included warfarin, montelukast sodium, ipratropium bromide by inhaler, furosemide, gabapentin, sertraline, a multivitamin, and sevelamer hydrochloride.

On examination, the patient was obese and appeared chronically ill. The vital signs were normal and the oxygen saturation was 94% while she was breathing 2 liters of oxygen by nasal cannula. Breath sounds were decreased in both lungs, without wheezing. There were abdominal scars, 3+ edema of both legs, and a clotted arteriovenous graft in the left arm. The skin was hyperpigmented, tight, hard, and dry on both arms and legs to the elbows and knees. There were flexion contractures on the hands, worse on the right than on the left. Shoulder abduction was limited by pain, more on the left than on the right; elbow extension was normal bilaterally, and extension at the knees was slightly decreased. The remainder of the examination was normal. The plasma level of creatinine was 3.1 mg per deciliter (274.0 μ mol per liter; normal, <132.6 μ mol per liter) and of urea nitrogen was 48 mg per deciliter (17.1 mmol per liter; normal range, 3.6 to 7.1 mmol per liter). Results of other tests are shown in Table 1.

A diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Hasan Bazari: I cared for this patient and am aware of the diagnosis. This 46-year-old woman

lived through a severe illness characterized by sepsis, the acute respiratory distress syndrome, and septic emboli to multiple organs — including the brain and the kidney. The renal injury was probably related to sepsis, embolic disease, exposure to contrast media, and nephrotoxicity from antibiotics. Immune-complex glomerulonephritis can occur in the setting of widespread infection, with the classic example being endocarditis. Nonetheless, she recovered from the illness with remarkable renal and neurologic function and was able to function independently. She then had a gradual decline over many years. We confronted the question of whether her decline was related to the sequelae of the previous illness or to the emergence of a new disease entity.

PERIPHERAL NEUROPATHY

This patient's initial illness was followed by persistent painful neuropathy. The differential diagnosis of neuropathy is broad, and some causes are summarized in Table 2. Diabetes mellitus, toxins, and vitamin deficiencies were ruled out. There was no evidence of vasculitis, cryoglobulinemia, or Sjögren's syndrome.¹⁻³ Paraproteinemia, in which monoclonal proteins may be directed against myelin-associated glycoprotein,^{4,5} was not found. Medications were not implicated.⁶ Finally, renal failure itself can be associated with axonal neuropathy,⁷ paresthesias, reduction in deep-tendon reflexes, impaired vibration sense, muscle wasting and weakness, as well as with autonomic neuropathy.⁸

The cause of this patient's neuropathy was never clear, but we believed it was an unusual sequela of her episode of septic shock and her chronic kidney disease.

RESPIRATORY FAILURE

The need for supplemental oxygen slowly developed in this patient. The considerations to explain this requirement included the progression of obstructive sleep apnea, congestive heart failure in the setting of both anemia and chronic kidney disease, and a primary pulmonary process such as idiopathic pulmonary fibrosis. In cases of idiopathic pulmonary fibrosis, the course is usually more relentlessly progressive. Secondary causes such as Goodpasture's syndrome, collagen vascular diseases such as scleroderma and lupus, and asbestosis resulting from occupational exposures

should be ruled out. It was also possible that this problem was due to recurrent or progressive fluid overload. The patient did not have clear signs of a systemic disease such as lupus. She did have antiphospholipid antibodies, which can be associated with acute pulmonary capillaritis. Chronic pulmonary emboli could be related to her hypercoagulable state, but she was receiving adequate anticoagulant treatment.

The oxygen saturation values fell when the patient was walking, which raised the worrisome possibility of an interstitial lung disease. The presence of mediastinal and hilar lymphadenopathy, together with the ground-glass opacities, made us suspect a primary pulmonary process. A search for a treatable cause led to a lung biopsy, which showed pulmonary hemosiderosis and fibrosis of the lymph nodes, with scattered giant cells and poorly formed granulomas.

GRANULOMATOUS PULMONARY DISEASE

Was the clinical diagnosis of sarcoidosis justified? The presence of granulomas supported the diagnosis,⁹ but granulomatous disease in the lung can be caused by a wide variety of illnesses including tuberculosis, nontuberculous mycobacterial infections, fungi, other granulomatous in-

Table 2. Causes of Peripheral Neuropathy.*

Category	Example
Metabolic disorders	Diabetes mellitus
Toxins	Ethanol
Vitamin deficiencies	B ₁₂ , folate
Vasculitis and autoimmune diseases	Cryoglobulinemia, the Churg–Strauss syndrome, Sjögren's syndrome
Amyloidosis	AL, AA, transthyretin, beta ₂ -microglobulin
Paraproteinemia-associated neuropathy	POEMS syndrome, CIDP
Paraneoplastic syndromes	Anti-Hu-antibody-related neuropathy
Familial	Hereditary sensory neuropathy, Charcot-Marie-Tooth disease
Immune-mediated disorders	Guillain-Barré syndrome, CIDP
Medications	Thalidomide, pyridoxine, leflunomide
Renal failure	—
Infections	Syphilis, leprosy

* CIDP denotes chronic inflammatory demyelinating polyradiculoneuropathy, and POEMS polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.

fections including those caused by bacteria and dirofilariasis, as well as noninfectious causes including sarcoidosis, berylliosis, talcosis, Wegener's granulomatosis, the Churg–Strauss syndrome, necrotizing sarcoid granulomatosis, bronchocentric granulomatosis, aspiration pneumonia, and rheumatoid nodules.¹⁰ With no support for these diagnoses, a tentative diagnosis of sarcoidosis was made, and the patient received treatment with 60 mg of prednisone daily, with some improvement in her symptoms.

CONGESTIVE HEART FAILURE

Congestive heart failure developed in the setting of atrial fibrillation and the sick sinus syndrome. The development of disease of the conduction system in a young person suggests an infiltrative process. Sarcoidosis of the heart can involve the conduction system, and it can lead to a restrictive cardiomyopathy with diastolic dysfunction. Indeed, right heart catheterization confirmed the presence of high pulmonary-artery wedge pressure. This could have been related to fluid overload or anemia, but it suggests that there must have been some diastolic dysfunction. The detection of granulomas on cardiac biopsy has a relatively low sensitivity (20 to 30%), so the negative results from the endomyocardial biopsy do not rule out this diagnosis.¹¹ Although a diagnosis of sarcoidosis could explain the pulmonary and cardiac disease, peripheral-nerve involvement is unusual in sarcoidosis.¹²

AMYLOIDOSIS

Systemic amyloidosis¹³ can cause a restrictive cardiomyopathy, disease of the conduction system, and peripheral neuropathy. AL amyloidosis related to immunoglobulin light chains is typically associated with a clonal plasma-cell disorder, with or without overt myeloma or lymphoma. AA amyloidosis can be seen in chronic infections such as osteomyelitis or tuberculosis as well as chronic inflammatory diseases. This patient's initial infection was successfully treated, and there was no evidence of a chronic smoldering infection. Beta₂-microglobulin amyloidosis can develop in patients with end-stage renal disease who are undergoing dialysis.¹⁴ This form of amyloidosis has a propensity for deposition in joints and bones, leading to cyst formation, as well as carpal tunnel syndrome. Clinically significant cardiac

involvement is very unusual. All types of amyloidosis were ruled out by the right heart biopsy, which also ruled out unlikely diagnoses such as hemochromatosis and glycogen storage diseases.

The POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) can be associated with neuropathy, skin thickening, and lymphadenopathy.¹⁵ However, the lymph-node biopsy did not show evidence of osteosclerotic myeloma, a monoclonal (M) component, or an endocrinopathy. Castleman's disease was also ruled out by the findings on the same biopsy. The cardiac biopsy showed fibrosis. An earlier episode of myocarditis with residual fibrosis is a consideration in this setting, as is ischemic injury to the myocardium. Uremic pericarditis could have led to constrictive pericarditis, but this condition was not detected in the right heart catheterization and seemed highly improbable.

For those who cared for this patient, it was difficult to explain the subsequent deterioration in her condition. Occam's razor would mandate that all the clinical features be drawn together to a unifying diagnosis. We were unable to recognize the common thread. Increasing skin thickening and joint contractures developed with time, which eventually led to consultation with the rheumatology department.

Dr. Jonathan Kay: I participated in this patient's care and am aware of the diagnosis. Three years after her initial hospitalization, this patient observed dryness and tightening of the skin on her distal arms and legs, with pruritus. Simultaneously, she began to have pain and stiffness in her shoulders, elbows, and knees, as well as in the interphalangeal joints of her fingers. She did not have Raynaud's phenomenon, dysphagia, or heartburn. This constellation of findings gives rise to a differential diagnosis of fibrosing disorders.

FIBROSING DISORDERS

Skin tightening and joint stiffness are features of systemic fibrosing disorders (Table 3). Chronic kidney disease may develop in patients with scleroderma as a result of scleroderma renal crisis, but it is unusual for scleroderma to develop in patients with preexisting chronic kidney disease. The absence of Raynaud's phenomenon, dysphagia, heartburn, and facial involvement is inconsistent with a diagnosis of scleroderma. Many patients with

Table 3. Fibrosing Disorders.

Disorder	Associated Features
Localized idiopathic cutaneous fibrosing disorders	
Morphea (localized scleroderma)	Circumscribed sclerotic plaques
Linear scleroderma (localized scleroderma)	Circumscribed linear sclerotic plaques
Scleredema diabeticorum	Neck, shoulders, and upper back affected, not the extremities; diabetes mellitus
Lipodermatosclerosis	Painful, brownish tightening of the skin of the lower legs — does not affect the arms; chronic venous insufficiency
Systemic idiopathic fibrosing disorders	
Diffuse systemic sclerosis (scleroderma)	Raynaud's phenomenon, dysphagia, heartburn, facial involvement Circulating antinuclear antibodies, including anti-topoisomerase I (anti-Scl-70) antibodies
Scleromyxedema	Facial involvement; circulating monoclonal paraprotein (usually IgG lambda)
Eosinophilic fasciitis	Joint stiffness, peripheral eosinophilia (intermittent)
Fibrosing disorders with identified causes	
Spanish toxic oil syndrome ¹⁶	Caused by olive oil adulterated with rapeseed oil
Eosinophilia-myalgia syndrome ¹⁷	Caused by contamination of L-tryptophan with 1,1-ethyldenebis [L-tryptophan]
Graft-versus-host disease	Previous bone marrow transplantation
Nephrogenic systemic fibrosis	Exposure to gadolinium-containing contrast agents in the setting of chronic kidney disease

scleroderma present with circulating antinuclear antibodies, some of which have specificity for topoisomerase I (anti-Scl-70 antibodies). This patient had IgM anticardiolipin antibodies, which may have explained her positive result in tests for antinuclear antibodies (Table 1); after examining her, we requested testing for antibodies to topoisomerase I, which was negative. The absence of facial involvement is also inconsistent with a diagnosis of scleromyxedema, and the continued progression of her skin changes despite corticosteroid therapy is inconsistent with eosinophilic fasciitis.

Localized cutaneous fibrosing disorders such as morphea, scleredema diabeticorum, and lipodermatosclerosis can be ruled out because the appearance and distribution of skin changes typical of these conditions differ from those observed in this patient.

BETA₂-MICROGLOBULIN AMYLOIDOSIS

This patient presented with flexion contractures of her hands and limited shoulder movement, both of which may be clinical features of beta₂-

microglobulin amyloidosis, a form of amyloidosis that occurs exclusively in patients with chronic kidney disease.¹⁸ Because the hand flexion contractures of beta₂-microglobulin amyloidosis result from amyloid infiltration, causing the finger flexor tendons to adhere to one another, patients with this condition present with prominent subcutaneous soft-tissue masses on their palms. This patient's flexion contractures were caused by tightening of the overlying skin, and she did not have soft-tissue masses on her palms.

NEPHROGENIC SYSTEMIC FIBROSIS

This patient's clinical presentation is most consistent with nephrogenic systemic fibrosis, previously known as nephrogenic fibrosing dermopathy. This condition is manifested by progressive, painful tightening of the skin, with tethering to underlying fascia, usually beginning on the hands and feet and extending proximally; it is associated with woody induration, brawny hyperpigmentation, and peau d'orange changes of affected skin.¹⁹ Because of the cutaneous fibrosis, contractures of the elbow, finger, knee, and ankle joints

develop, which significantly limit physical function. Although involvement of the trunk may occasionally occur, facial involvement has not been described, other than characteristic yellow scleral plaques. Raynaud's phenomenon and circulating autoantibodies are not features of nephrogenic systemic fibrosis.

First observed in 1997, nephrogenic systemic fibrosis has been described only in patients with kidney disease, typically those receiving dialysis treatment but also those who have undergone successful renal transplantation or have had an episode of acute renal failure. As many as 13% of patients with stage 5 chronic kidney disease have the skin changes that are now recognized as signs of nephrogenic systemic fibrosis, and these changes are associated with an increase in mortality that is three to five times greater than that among patients without these skin changes.²⁰ Extracutaneous fibrosis involving the heart, lungs, diaphragm, skeletal muscle, liver, genitourinary tract, and central nervous system has been reported.²¹⁻²⁵ Thus, this patient's pulmonary and cardiac disease could also be explained by a diagnosis of nephrogenic systemic fibrosis.

In 2006, Grobner²⁶ suggested a possible association between exposure to gadodiamide during magnetic resonance angiography and the development of nephrogenic systemic fibrosis, and the condition has subsequently been shown to be strongly associated with exposure to gadolinium-containing contrast media (e.g., gadodiamide and gadopentetate dimeglumine) among patients with stage 4 and stage 5 chronic kidney disease.^{22,27,28} Gadolinium is a trivalent cation that binds strongly to many tissues when it dissociates from its chelating agent. Although it is not known how gadolinium might induce fibrosis, the detection of gadolinium in skin-biopsy specimens from several patients with nephrogenic systemic fibrosis suggests a potential causal relationship.^{28,29} This patient underwent multiple gadolinium-enhanced magnetic resonance studies, with a total dose before our consultation of 158 ml of gadopentetate dimeglumine.

We recommended a biopsy of the skin to confirm the diagnosis.

DR. JONATHAN KAY'S DIAGNOSIS

Nephrogenic systemic fibrosis.

PATHOLOGICAL DISCUSSION

Dr. Aashiyana F. Koreishi: A skin-punch biopsy of the left lateral thigh showed fibrosis of the deep dermis, with fibrous septa extending into the subcutaneous tissue (Fig. 2A). Collagen bundles were surrounded by clefts, and an increased number of nuclei were present (Fig. 2B). Many CD34+ spindle cells were seen on immunohistochemical staining (Fig. 2B, inset). These findings are consistent with early nephrogenic systemic fibrosis. The presence of CD34+ spindle cells that coexpress procollagen-I and CD45RO is highly characteristic of nephrogenic systemic fibrosis.^{22,30,31} Dermal mucin deposition, fragmented and elongated elastic fibers, osseous metaplasia, osteoclast-like giant cells, and calciphylaxis may also be seen. The histologic differential diagnosis includes scleroderma and scleromyxedema, and diagnostic features may not be present on skin-biopsy specimens in all cases.

In light of the diagnosis of nephrogenic systemic fibrosis, the specimens obtained from the lymph node, lung, and cardiac biopsies were reviewed (Fig. 2C and 2D). In retrospect, the findings were consistent with nephrogenic systemic fibrosis. Thus, in this patient there is evidence of nephrogenic systemic fibrosis with cutaneous and systemic involvement.

DISCUSSION OF MANAGEMENT

Dr. Kay: In almost all cases, nephrogenic systemic fibrosis progresses relentlessly. Only two cases have been reported in which patients had spontaneous improvement with resolution of acute renal failure.³² Mildly decreased skin thickening and improved joint mobility have been reported in seven patients treated with extracorporeal photopheresis,³³⁻³⁵ and slight reversal of skin changes was observed in one other patient, who received treatment with pentoxifylline.²⁸ However, other therapeutic approaches, such as topical and oral steroids, immunosuppressive drugs, intravenous gamma globulin, and plasmapheresis, have failed to improve the skin changes associated with nephrogenic systemic fibrosis. When I first saw this patient, I did not recommend specific treatment. One year later, physical examination revealed progression of her skin disease, including thickening of the skin and tethering to underlying

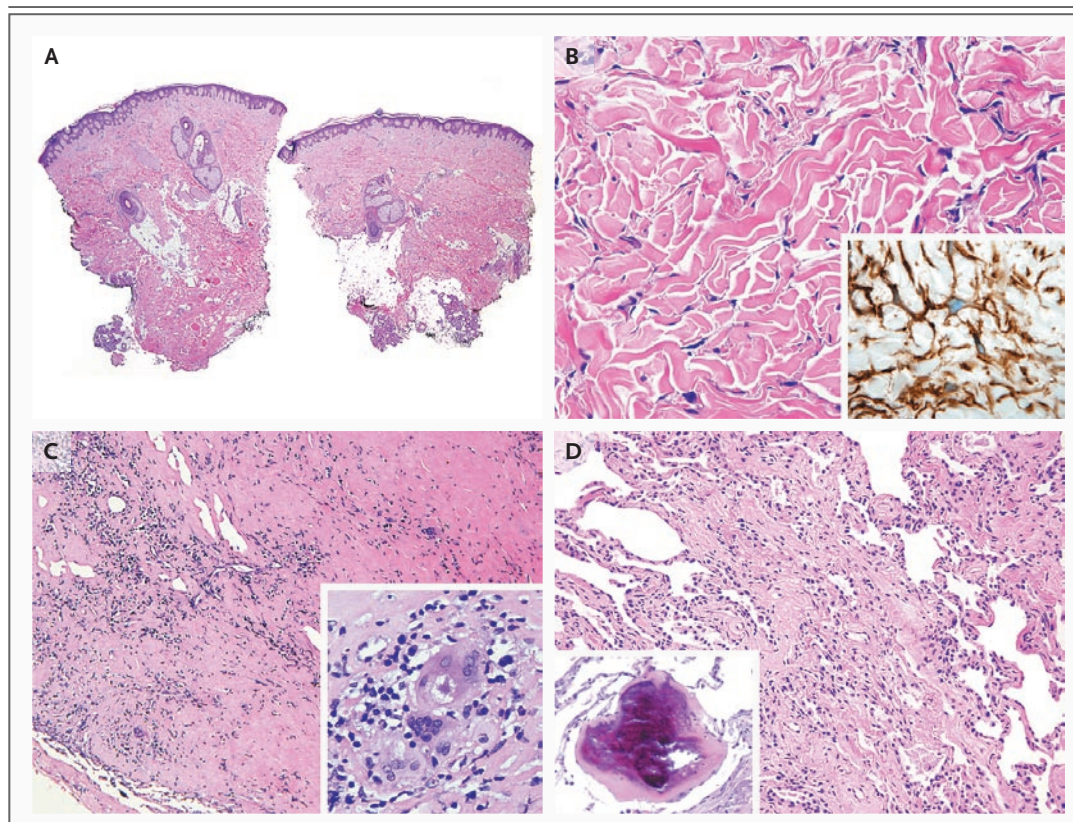


Figure 2. Biopsy Specimens.

A specimen from a skin-punch biopsy from the left lateral thigh (Panel A, hematoxylin and eosin) shows fibroblastic expansion of dermis and fibrous septa extending into the subcutaneous tissue. Prominent collagen bundles with surrounding clefts and increased numbers of nuclei are seen within the dermis (Panel B, hematoxylin and eosin). An immunohistochemical stain (inset) reveals dermal spindle cells expressing CD34, a characteristic feature of nephrogenic systemic fibrosis. The paratracheal lymph-node specimen obtained from a biopsy 22 months earlier (Panel C, hematoxylin and eosin) shows extensive regional fibrosis, with poorly formed granulomas containing scattered multinucleated giant cells (inset, hematoxylin and eosin). The lung-biopsy specimen from the same procedure (Panel D, hematoxylin and eosin) shows focal interstitial fibrosis with fibrous thickening of alveolar septa and focal ossification (inset). The findings in the lymph node and lung are consistent with nephrogenic systemic fibrosis.

ing fascia, worsening flexion contractures of the elbows and knees, and fixed contractures of her fingers. Because I had observed improvement of skin changes in two patients with nephrogenic systemic fibrosis treated with imatinib mesylate,³⁶ I recommended that our patient try this agent; however, she was unable to obtain it.

Because no treatment has yet been proven to be consistently effective in reversing nephrogenic systemic fibrosis, the most effective strategy is to prevent its development.

Dr. Laura L. Avery: Incidents of the development of nephrogenic systemic fibrosis have been reported after use of each of the five available formula-

tions of gadolinium. As recommended recently by the Food and Drug Administration (www.fda.gov/Cder/drug/infopage/gcca/default.htm), we in the Radiology Department at this hospital calculate the estimated glomerular filtration rate from the serum creatinine level of all patients for whom contrast-enhanced MRI is requested. If the glomerular filtration rate is less than 30 ml per minute per 1.73 m² of body-surface area, a gadolinium contrast agent will not be used unless there is an urgent medical need, and it will be used in consultation with a nephrologist and after obtaining written informed consent. Patients receiving dialysis should not receive a gadolinium

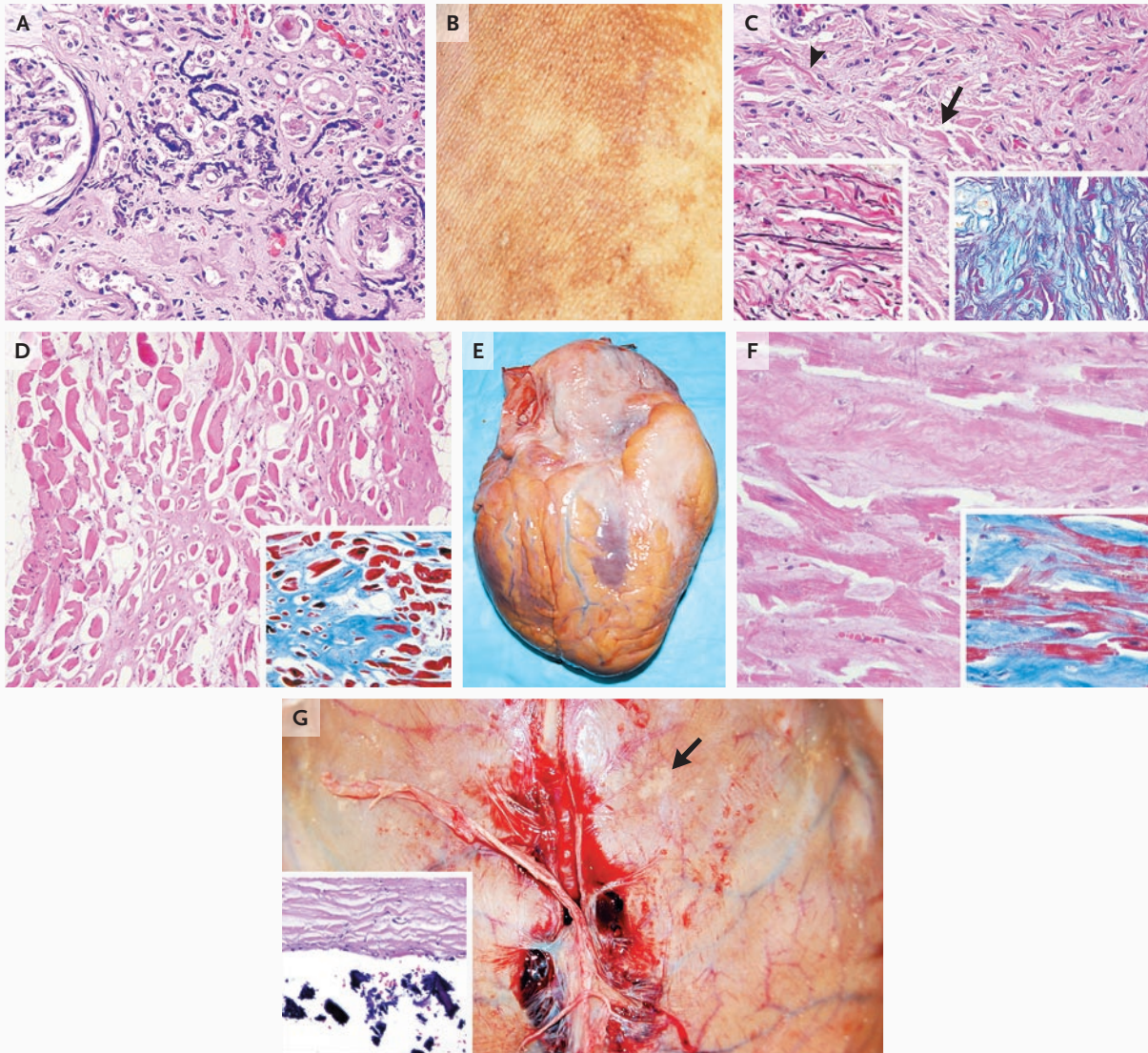


Figure 3. Autopsy Findings of Nephrogenic Systemic Fibrosis.

Examination of a histologic section obtained from the kidneys at autopsy (Panel A, hematoxylin and eosin) shows nephrocalcinosis with basophilic deposits within tubular basement membranes and interstitial fibrosis. Gross examination of the skin on the right upper leg (Panel B) shows prominent brawny induration, hyperpigmentation, and skin tightening. Histologic sections of the skin (Panel C, hematoxylin and eosin) reveal dense dermal fibrosis with extension into subcutaneous tissue and prominent collagen fibrils with surrounding clefts (arrow), elastic fibers (arrowhead), and increased numbers of nuclei. Verhoeff elastic-tissue staining of the dermis (Panel C, inset on left) shows fragmented as well as elongated black elastic fibers within the dermis. Colloidal-iron staining of the dermis (Panel C, inset on right) shows blue-green connective-tissue mucin deposition within the dermis. A section of the psoas muscle (Panel D, hematoxylin and eosin) shows the accumulation of fibrous tissue between and around muscle cells, as well as muscle-cell atrophy. The extent of fibrosis is highlighted with a trichrome stain (inset). A gross external photograph of the heart (Panel E) shows patchy white areas of epicardial fibrosis. A histologic section of the heart (Panel F, hematoxylin and eosin) shows fibrous tissue between cardiac myocytes (inset, trichrome stain). Gross and microscopical photographs of the dura (Panel G) show deposits of tan-yellow firm material on the dura (arrow), corresponding to focal dural thickening and calcification (inset, hematoxylin and eosin).

contrast agent unless the radiologist and referring physician concur that the benefit to the patient outweighs the risk; hemodialysis immediately after the examination should be considered on an individual basis, although it has not been proven to be of benefit.

Dr. Cibotti-Granof: During the 15 months after the rheumatology evaluation, the patient was hospitalized several times for catheter sepsis and peritonitis related to dialysis. Her final admission was for peritonitis, which was complicated by pneumonia, sepsis, and sigmoid perforation. Hypotension and multiorgan failure developed, and after discussion with the family, aggressive measures were withdrawn and the patient died.

PATHOLOGICAL DISCUSSION

Dr. Koreishi: An autopsy was performed. Bronchopneumonia was the immediate cause of death. Interstitial pulmonary fibrosis was also present, consistent with nephrogenic systemic fibrosis. There was end-stage renal disease with atrophy, focal glomerulosclerosis, interstitial fibrosis, and tubular atrophy. Nephrocalcinosis was prominent (Fig. 3A). Gross examination of the skin revealed brawny induration and hyperpigmentation involving predominantly the arms and legs (Fig. 3B). Microscopical examination disclosed dense fibrosis involving the superficial and deep dermis with extension into the subcutaneous tissue (Fig. 3C). Staining of the elastic tissue highlights both fragmented and elongated elastic fibers (Fig. 3C, inset left). There was prominent connective-tissue mucin deposition within the dermis (Fig. 3C, inset right). Immunohistochemical staining again showed an increased number of CD34+ spindle cells throughout the dermis, as well as scattered CD68+ and factor XIIIa+ cells. There were fibrosis and atrophy of the diaphragm, psoas muscle (Fig. 3D), epicardium (Fig. 3E), and myocardium (Fig. 3F). There were focal areas of dural thickening and calcification (Fig. 3G).

This patient, like others who have been de-

Table 4. Gadolinium Content in Autopsy Tissue.

Site	Mass (mg)	Gadolinium (parts per million)
Skin, left lateral thigh	1.2	29.5
Right kidney plus adrenal gland	6.31	488.2
Left kidney plus adrenal gland	10.17	585.4
Skin, right thigh	6.31	130.2
Skin, left thigh	4.72	36.7
Lymph node	5.96	184.5
Left thyroid plus liver	9.11	56.3
Lung, right middle lobe	4.22	145.5
Heart, left ventricle	9.66	544.7

scribed,^{24,37,38} had extensive systemic involvement by nephrogenic systemic fibrosis. Tissue blocks from the autopsy were sent to Dr. Whitney A. High's laboratory at the University of Colorado Health Sciences Center for gadolinium detection and quantification.^{30,31,39,40} Gadolinium was detected in all the tissue samples that were analyzed (Table 4).

Dr. Nancy Lee Harris (Pathology): Are there any comments or questions?

Dr. Robert B. Colvin (Pathology): Although the basophilic material seen in the kidneys is interpreted as calcium, it could also conceivably represent gadolinium deposition.

ANATOMICAL DIAGNOSIS

Nephrogenic systemic fibrosis, involving the skin, heart, lungs, diaphragm and psoas muscles, dura, and possibly the kidney.

End-stage renal disease with nephrocalcinosis.

Acute and organizing bronchopneumonia.

No potential conflict of interest relevant to this article was reported.

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