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Case 30-2011: A 62-Year-Old Woman with Renal Failure

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PRESENTATION OF CASE

Dr. Kyle Staller (Medicine): A 62-year-old woman was admitted to this hospital because of renal failure.

The patient had an autoimmune overlap syndrome with polymyositis, treated with prednisone and mycophenolate mofetil, but had been in her usual health until 6 weeks before admission, when she noted increasing skin tightness around her mouth, dry mouth, difficulty swallowing, worsening gastroesophageal reflux, hair loss, and discoloration of her fingers, which were ash-colored, painful, and cool. Prednisone was increased from 10 to 20 mg daily, without improvement. Four days before admission, the patient was found on the floor of her bathroom, confused and minimally conversant, and was taken to another hospital.

The day before admission to the other hospital, the patient had reported some weakness and no other symptoms. On examination, the temperature was 35.9°C, the blood pressure 175/99 mm Hg, the pulse 84 beats per minute, and the respiratory rate 17 breaths per minute. The patient was awake, with slow responses, and oriented to person only. The skin around the mouth and on the fingers was tight, and there was muscle wasting of the neck. On neurologic examination, she followed simple commands inconsistently, with psychomotor slowing, a decreased ability to name objects, and an inability to read or to repeat words spoken to her. Her face was symmetric, with possible mild weakness on the right side. Muscle strength was 4 out of 5 or better (with 5 indicating normal strength), with mild asterixis bilaterally.

Levels of vitamin B_{12}, folate, and glycated hemoglobin were normal, as were tests of coagulation and thyroid function; other laboratory-test results are shown in Table 1. Urinalysis revealed yellow, cloudy urine with a pH of 5.5 and a specific gravity of 1.016; a screening dipstick test showed a large amount of blood, 15 mg of ketones per deciliter, 300 mg of protein per deciliter, and 0.2 mg of urobilinogen per deciliter. Microscopical examination of the urine revealed 1 to 2 hyaline casts per low-power field, as well as 37 white cells and no red cells per high-power field.

A chest radiograph reportedly showed basilar consolidation in the right lung, a small pleural effusion on the right side, and increased interstitial markings bilaterally, which were thought to be chronic. Computed tomography (CT) of the head without the administration of contrast material revealed hyperdensities adjacent

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Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	26 Mo before Admission	10–11 Mo before Admission, Outpatient	On Admission, Other Hospital	4th Day	On Admission, This Hospital	2nd Day
Hematocrit (%)	36.0–46.0 (women)	39.0	40.0	34.2	23.2	26.3	25.7
Hemoglobin (g/dl)	12.0–16.0 (women)	12.7	13.3	10.9	7.9	8.3	8.2
White-cell count (per mm^3)	4500–11,000	5200	8000	14,800	16,300	20,000	17,200
Differential count (%)							
Neutrophils	40–70		92	95	95	97	97
Lymphocytes	22–44		6	2	2	1	2
Monocytes	4–11		2	2	2	1	1
Eosinophils	0–8		0	1	1	1	0
Platelet count (per mm^3)	150,000–400,000	328,000	312,000	297,000	128,000	144,000	137,000
Peripheral-blood smear				2+ anisocytosis	2+ anisocytosis, 2+ schistocytosis	1+ microcytosis, 2+ anisocytosis, 2+ hypochromasia	1+ microcytosis, 2+ anisocytosis, 2+ hypochromasia
Erythrocyte sedimentation rate (mm/hr)	1–17 (women)		16		74 (ref 0–30)		70
Sodium (mmol/liter)	135–145		141	140	140	139	141
Potassium (mmol/liter)	3.4–4.8		4.4	6.0	3.8	4.1	4.0
Chloride (mmol/liter)	100–108		102	106	97	94	96
Carbon dioxide (mmol/liter)	23.0–31.9		30.6	12.3	26.5	24.4	25.2
Urea nitrogen (mg/dl)	8–25		18	140	127	122	123
Creatinine (mg/dl)	0.60–1.50		0.74	6.60	6.30	6.64	6.79
Estimated glomerular filtration rate (ml/min/1.73 m^2)	>60 (if patient is black, multiply results by 1.21)		>60	6	7	7	7
Glucose (mg/dl)	70–110		152	128	154	158	142
Protein (g/dl)							
Total	6.0–8.3		7.2	7.4	5.2		6.0
Albumin	3.3–5.0		4.4	4.1	2.8		3.1
Phosphorus (mg/dl)	2.6–4.5				6.6 (ref 2.4–4.7)		6.4
Calcium (mg/dl)	8.5–10.5			9.3	6.5		6.7
Alkaline phosphatase (U/liter)	30–100		54	133 (ref 38–126)	93		116
Alanine aminotransferase (U/liter)	7–30		29	48	38		44
Aspartate aminotransferase (U/liter)	9–32		31	38	66		78
Lactate dehydrogenase (U/liter)	110–210		264		720 (ref 98–192)	1129	
Creatine kinase (U/liter)	40–150 (women)		274	914 (ref 38–234)	2337	2930	2918

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Creatine kinase MB isoenzymes (ng/ml)				49.79 (ref 0.18–5.0)		
Troponin I (ng/ml)				0.86 (ref <0.04)		
Immunoglobulins (mg/dl)						
IgA	69–309	139	145			96
IgG	614–1295	1535	928			802
IgM	53–334	53	63			33
Serum protein electrophoresis and immunofixation	Normal pattern	Abnormal pattern; banding present; 0.29 g/dl of IgG lambda M component present	Abnormal pattern; banding present; 0.16 g/dl of IgG lambda M component present			Abnormal pattern; banding present; 0.36 g/dl of IgG lambda M component present
Homocysteine (μmol/liter)					47.7 (ref 5.0–14.0)	
Cholesterol (mg/dl)					237 (ref 0–200)	
High-density lipoprotein cholesterol (mg/dl)					40 (ref 35–85)	
Triglycerides (mg/dl)					396 (ref 0–150)	
Low-density lipoprotein cholesterol (mg/dl)					118 (ref <100)	
C-reactive protein (mg/liter)	<8.0					113.2
Antinuclear antibodies	No nuclear staining					Positive cytoplasmic staining at 1:40 dilution, filamentous and granular staining
As detected with immunofluorescence assay	Negative at 1:40 and 1:160 dilutions	Positive at 1:40 and 1:160 dilutions, speckled pattern				Negative at 1:40 and 1:160 dilutions
Antibodies to smooth muscle	Negative at 1:20 dilution	Positive at 1:80 dilution				Positive at 1:20 dilution
Antimitochondrial antibodies	Negative at 1:20 dilution	Negative at 1:20 dilution				
Aldolase (U/liter)	<7.7					18.7
D-Dimer (ng/ml)	<500					4774
Fibrinogen (mg/dl)	150–400					547

* Ref denotes the reference range at the other hospital. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the value for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the value for creatinine to micromoles per liter, multiply by 88.4. To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the value for phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.

† 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 do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

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to the frontal horn of the left lateral ventricle in the vicinity of the caudate head and in the left basal ganglia, findings that were thought to be consistent with a small hemorrhagic infarct. The CT scan also showed prominent ventricles and sulci.

The patient was admitted to the intensive care unit; intravenous fluids, furosemide, chlorothiazide, methylprednisolone, nicardipine drip, ceftriaxone, atenolol, nitroglycerin paste, mycophenolate mofetil, and famotidine were administered. The next morning, magnetic resonance imaging (MRI) of the head revealed high T_2-weighted signal intensity in a lesion in the left basal ganglia and in a lesion in the left thalamus (suggestive of an acute infarction in the basal ganglia and a subacute infarction in the left thalamus), a diffusion abnormality in the left caudate head with high signal intensity on sagittal T_1-weighted images, brain atrophy, and small-vessel ischemic changes; there was no mass effect or midline shift. Renal ultrasonography revealed kidneys (9.1 cm and 9.8 cm in the longest axis) with increased echogenicity and no nephrolithiasis or hydronephrosis. Echocardiography revealed left ventricular hypertrophy, with an ejection fraction of 63%. Serum levels of complement (C3 and C4) and antibodies to double-stranded DNA and glomerular basement membrane were normal. Other test results are shown in Table 1. An electroencephalogram showed abnormalities consistent with toxic metabolic encephalopathy. A urine culture was sterile. On the fourth day, the patient was transferred to this hospital.

A diagnosis of autoimmune overlap syndrome had been made 17 months earlier, after an 18-month progressive illness, including increasing limb weakness and head drop. Approximately 2.5 years before admission, pathological examination of a bone marrow–biopsy specimen reportedly showed slightly hypocellular bone marrow with relative erythroid hyperplasia and a mild increase in the number of mononuclear cells with plasmacytoid features. Results of laboratory testing performed 26 months before admission are shown in Table 1. A diagnosis of monoclonal gammopathy of undetermined significance (MGUS) was made. Approximately 2 years before admission, the creatine kinase level, measured at another hospital, was reportedly 3800 U per liter; electromyography revealed findings suggestive of myopathy. Twenty months before admission, pathological examination of a biopsy specimen of the sternocleidomastoid muscle showed marked variation in fiber size, with hypertrophic and round atrophic fibers, marked endomysial fibrosis, phagocytosis, and a small focus of inflammation surrounding individual muscle cells. Results of testing for dystrophin and other sarcolemmal proteins were normal, as was the result of electron microscopy. The administration of prednisone (60 mg per day) was begun, with partial improvement in strength. Tests for other autoimmune antibodies were negative; levels of free kappa light chains were low, and levels of lambda light chains, angiotensin-converting enzyme, nonmaternal alpha-fetoprotein, CA 19-9, CA-125, C-reactive protein, carcinoembryonic antigen, and β_2-microglobulin were normal. Prednisone was gradually tapered to 10 mg daily.

Approximately 11 months before admission, urine collection revealed 102 mg of protein per 24 hours (170 mg per liter); no Bence Jones protein was detected in a urine specimen concentrated 50 times. Other test results are shown in Table 1. Seven months before admission, while the patient was taking prednisone (10 mg), she had persistent, severe weakness and atrophy in the neck muscles with head drop. The patient's muscle strength was rated 2 to 3– on the Medical Research Council (MRC) scale, which ranges from 0 (paralysis) to 5 (normal strength). She also had moderately severe weakness in the muscles of the shoulder girdle and pelvic girdle (MRC score, 3+ to 4–), with well-preserved distal muscles, tendon reflexes, and sensation. Ambulation and balance were normal. A follow-up electromyogram (EMG) continued to show an active myopathy. Five months before admission, the administration of mycophenolate mofetil (1000 mg twice weekly) was begun; strength in the neck muscles improved, but limb weakness continued and fatigue worsened. Two weeks before admission, the patient fell at home, injuring her back, and thereafter took naproxen daily for pain.

The patient's medical history included hypertension, osteoporosis, depression, and multinodular nontoxic goiter. A thyroid-biopsy specimen showed no abnormalities. She was allergic to azithromycin and cephalexin. She was single, lived alone, and was a retired office worker. She drank alcohol occasionally and did not smoke or use illicit drugs. Her mother had had breast cancer and Alzheimer's disease and died at 81 years

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of age, her father died of myocardial infarction at the age of 65 years, a sister died of systemic lupus erythematosus at the age of 27 years, and two other siblings were healthy.

On examination, the patient was alert and conversant and afebrile. The blood pressure was 173/76 mm Hg, the pulse 75 beats per minute, the respiratory rate 16 breaths per minute, and the oxygen saturation 96% while she was breathing ambient air. There was marked thickening and puckering of the skin around the mouth, and the oral mucosa was dry. The neck was supple and showed evidence of muscle wasting; the jugular venous pressure was normal. There were fine crackles at the lung bases bilaterally. Telangiectasias were evident over the patient's face and upper chest. On neurologic examination, she was slow to respond to questions but eventually provided clear, cogent answers. Motor strength in the hip flexors was less than 3 out of 5, bilaterally; she was unable to lift her legs off the bed. The results of the remainder of the lower-extremity motor and sensory examination and the general examination were normal.

Levels of total and direct bilirubin, globulin, magnesium, and haptoglobin were normal, as were tests of coagulation; other test results are shown in Table 1. Urinalysis showed cloudy, yellow urine with a specific gravity of 1.008 and a pH of 6.0, with 3+ occult blood, 2+ albumin, 0 to 2 red cells and white cells per high-power field, and very few transitional cells. An electrocardiogram was normal. A chest radiograph showed bilateral pleural effusions and basilar atelectasis, with no evidence of pulmonary edema. CT of the head without contrast material was unchanged. Normal saline and furosemide were administered intravenously; urine output was approximately 30 ml overnight. On the second day, levels of C3 and C4 were normal and tests for anticardiolipin antibodies, antineuronal nuclear antibodies, and antibodies to Ro, La, and Scl-70 were negative, as was a test for lupus anticoagulant; additional results are shown in Table 1, and other results were pending. A 24-hour urine collection and electrophoresis revealed 1160 mg of protein per liter (reference range, 0 to 135), moderate albumin and alpha, beta and probably intact immunoglobulin, and a low level of IgG lambda M component in the same region as the serum IgG lambda M component; no Bence Jones protein was detected in urine that was concentrated 50 times. The administration of ceftriaxone and atenolol was stopped, and captopril was begun. Prednisone (20 mg daily) and mycophenolate mofetil were continued. Oliguria persisted.

On the third day, a diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

Dr. John Cunningham: This patient has a complex medical history, culminating in the development of hypertension, advanced renal failure, and an acute brain disturbance. May we review the imaging studies?

Dr. Mukesh G. Harisinghani: A chest radiograph obtained at the time of admission to this hospital was normal. CT of the chest was performed after the administration of intravenous and oral contrast material. Images through the lower neck showed an enlarged right lobe of the thyroid, with a nonspecific finding of low-density nodules (Fig. 1A). The esophagus was dilated, and an air–liquid level was seen in the upper thoracic segment (Fig. 1B and 1C). No mass lesion was identified at the gastroesophageal junction. Scattered small and slightly enlarged mediastinal lymph nodes were also seen (Fig. 1D).

A CT scan of the brain showed dilatation of the left frontal horn. An ill-defined area of hyperdensity in the left caudate nucleus was suggestive of chronic ischemic changes.

A renal ultrasonogram showed normal-size kidneys. Doppler evaluation of the renal arteries showed no abnormalities.

Dr. Cunningham: My initial differential diagnosis will focus on the renal disturbance (Table 2). Many features of this case are consistent with a polymyositis–systemic sclerosis overlap syndrome characterized by rapidly progressive features of diffuse cutaneous systemic sclerosis and progression to a renal crisis. Other potential causes of acute renal failure in this patient are accelerated-phase hypertension unrelated to systemic sclerosis, nephropathy due to the nonsteroidal antiinflammatory drug (NSAID), cast nephropathy due to progression of the dysproteinemia, rhabdomyolysis due to ongoing polymyositis, and the hemolytic–uremic syndrome or thrombotic thrombocytopenic purpura. Renal failure due to other parenchymal nephropathies (e.g., acute glomerulonephritis, renal or systemic vasculitis, anti–glomerular basement membrane disease [Good-

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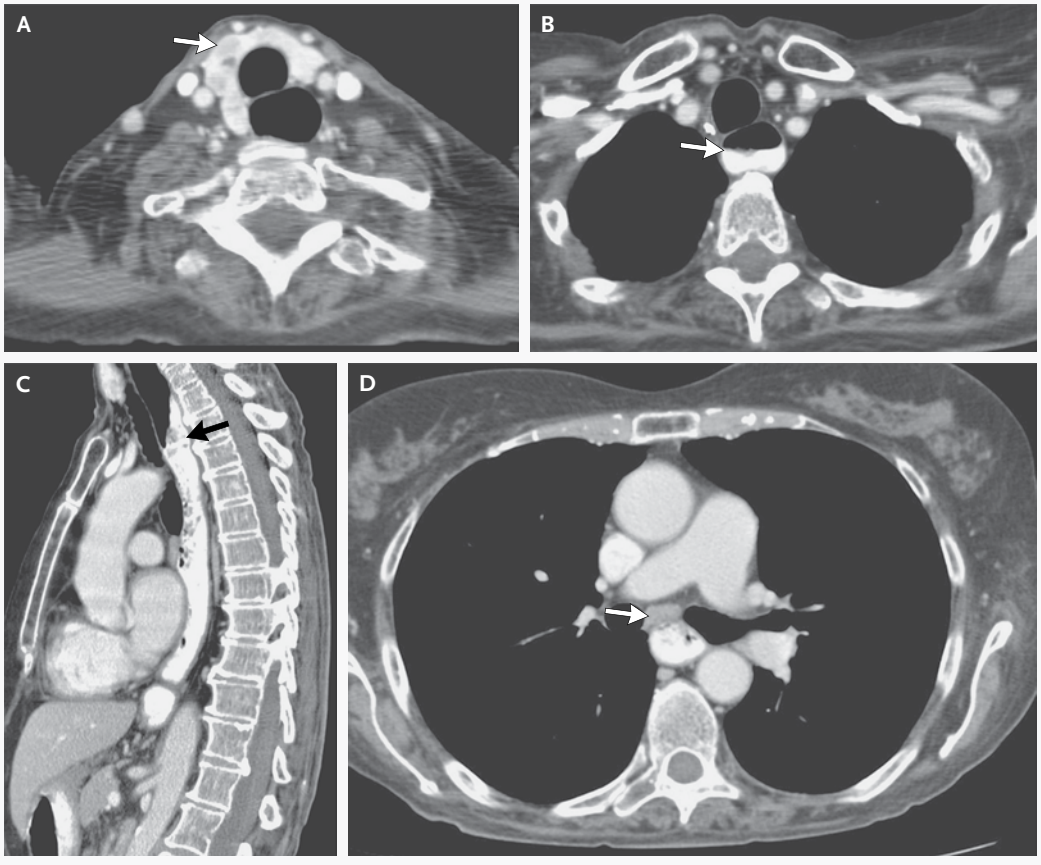

Figure 1. CT Scans of the Chest Obtained after the Administration of Oral and Intravenous Contrast Material.
An axial image of the lower neck shows an enlarged lobe in the right thyroid, with low-density nodules (Panel A, arrow). Dilatation of the esophagus and an air–liquid level are shown in an axial reformatted image (Panel B, arrow) and in a coronal reformatted image (Panel C, arrow). A slightly enlarged subcarinal lymph node is shown in Panel D (arrow).

pasture's syndrome], acute tubulointerstitial disease, renal vascular disease, and acute renal failure due to obstruction of the urinary tract) must be considered and ruled out, even though none of these disorders fit comfortably with the clinical and laboratory findings in this patient. Severe sepsis, endocarditis, and other infections such as legionella and leptospira are also unlikely but must be ruled out.

INFLAMMATORY MYOSITIS

We were told that the patient initially presented with proximal muscle weakness and that an inflammatory myositis was ultimately diagnosed. Of relevance in this case is the positive test for cytoplasmic antibodies in a filamentous and granular pattern. This raises the possibility of the antisynthetase syndrome, which includes myositis, Raynaud's phenomenon, arthralgia, fever, skin changes ("mechanic's hands"), and interstitial pneumonitis.[1] Of several autoantibodies to cytoplasmic aminoacyl–transfer RNA (tRNA) synthetases, the most common is Jo-1, which is directed against histidyl–tRNA synthetase. We were not told whether Jo-1 antibodies were assessed in this patient, but the characteristic cytoplasmic staining raises the possibility that she initially presented with polymyositis associated with Jo-1 or another aminoacyl–tRNA synthetase.

SCLERODERMA

Systemic sclerosis or scleroderma[2-6] is more common in females than in males and typically presents between the ages of 30 and 60 years. It is

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associated with sclerodactyly, Raynaud's phenomenon, telangiectasia, xerostomia, the sicca syndrome, and dysphagia, all of which this patient had. Patients with systemic sclerosis have autoantibodies to various specific cellular components that correlate with distinct clinical subsets of the disease. These antibodies often have a relatively high specificity, but their sensitivity is moderate at best. Clinical features are likely to predominate in the diagnostic process, with the antibody profiles providing additional support only in some cases.

If this patient has scleroderma, is the renal disturbance the result of a scleroderma renal crisis? Renal crisis is a dangerous development in a patient with scleroderma. In the era before treatment with inhibitors of the renin–angiotensin–aldosterone system was available, the 1-year mortality rate approached 100%. More recent series show early survival rates of 70 to 80%.[7,8] A number of important early and late signs warning of scleroderma renal crisis have emerged.[7,9] Early warning signs include the onset of the diffuse-skin-disease subtype of scleroderma within the past 4 years, rapidly progressive skin disease, the presence of RNA-polymerase antibodies,[7,9] and the recent intensification of glucocorticoid therapy (to doses of prednisone >15 mg daily).[10] Late warning signs of renal crisis include new or worsening hypertension, encephalopathy, a substantial reduction in the glomerular filtration rate, and a recent finding of proteinuria or urinary red cells (or both). At presentation, patients with scleroderma renal crisis usually have grade 3 or 4 hypertensive retinopathy and evidence of microangiopathic hemolytic anemia. The patient under discussion has many of these features; therefore, the clinical scenario is consistent with a diagnosis of diffuse cutaneous systemic sclerosis progressing to a renal crisis. Although test results for RNA-polymerase antibodies were not specifically reported, the positive test for antinuclear antibodies with a speckled pattern is consistent with the presence of RNA-polymerase antibodies. The prevalence of RNA-polymerase antibodies in patients whose disease is progressing to renal crisis is at least five times as high as the prevalence in patients without disease progression,[9] a difference precisely matched by the relative prevalence of antinuclear antibodies with a speckled pattern in these two groups of patients. Conversely, the presence of anti–Scl-70 antibodies does not seem to have an effect on disease outcome.

Table 2. Initial Differential Diagnosis of the Patient's Renal Disturbance.

Polymyositis–systemic sclerosis overlap progressing to renal crisis
Accelerated-phase hypertension unrelated to systemic sclerosis
Nephrotoxic effects of the nonsteroidal antiinflammatory drug
Cast nephropathy due to monoclonal gammopathy of undetermined significance, with progression to myeloma
Rhabdomyolysis due to ongoing polymyositis
Hemolytic–uremic syndrome or thrombotic thrombocytopenic purpura
Antiphospholipid antibody syndrome
Renal failure due to other parenchymal disease
Acute glomerulonephritis
Acute interstitial nephritis
Other multisystem diseases
Systemic lupus erythematosus
Goodpasture's syndrome
Vasculitis
Renal vascular disease or renal-artery stenosis
Sepsis with or without endocarditis, legionella, or leptospirosis
Acute renal failure due to obstruction of the urinary tract

Scleroderma renal crisis is a likely diagnosis in this patient.

MONOCLONAL GAMMOPATHY

The patient has received a diagnosis of MGUS. By the time she was admitted to this hospital, the serum level of IgG lambda paraprotein had risen, pointing to progression of the dysproteinemia. Also important in the differential diagnosis is the coexistence of dysproteinemia and the clinical phenotype of scleroderma, which is found in several conditions, such as the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes), scleredema, scleromyxedema, and AL amyloidosis.

In this case, the features are most consistent with the presence of a connective tissue disease overlap syndrome. The MGUS is probably an incidental finding and is unlikely to explain the patient's renal disease.

ACUTE-ON-CHRONIC KIDNEY DISEASE

Advanced age and preexisting chronic kidney disease strongly predispose the kidneys to further injury in the event of a superimposed acute insult (acute-on-chronic disease).[11] Although this patient's serum creatinine level is within the reference range, it is likely that the polymyositis has

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resulted in a low muscle mass. The patient's creatinine level would most likely have been much lower if her renal function had been normal; thus, the calculation of the estimated glomerular filtration rate that was based on the serum creatinine level was probably erroneously high. Approximately 70% of patients with diffuse cutaneous systemic sclerosis have renal involvement, even in the absence of renal crisis.[12] This patient also had marked hypertension with left ventricular hypertrophy. Therefore, I think her kidneys are vulnerable to acute insults. In this context, the possibility of a toxin-related or ischemia-related acute renal injury is important to consider.

Pigment-Cast Nephropathy

Pigment-cast nephropathy (characterized by pigment derived from myoglobin or hemoglobin) is part of the differential diagnosis. The screening dipstick test showed a large amount of blood, but microscopical examination of the urine revealed no red cells. These findings point to either hemolyzed blood in the urine or to myoglobinuria (myoglobin registers in the same way as hemoglobin on most routine dipstick-type urinalyses). The marked hyperphosphatemia and hypocalcemia seen in this patient are features that would be consistent with a diagnosis of rhabdomyolysis, although the peak creatine kinase level was 2900 U per liter, which is not as high as the level usually associated with rhabdomyolysis-induced acute renal failure. The absence of myoglobin in the urine also argues against this diagnosis. The normal serum haptoglobin level tells us that intravascular hemolysis, if present, was not severe enough to cause acute kidney injury. I conclude, therefore, that hemoglobin or myoglobin cast nephropathy is unlikely.

Nephrotoxic Effects of NSAIDs

The patient's use of naproxen for 2 weeks before admission is potentially important. Nephrotoxic effects of NSAIDs take at least three discrete forms: acute tubulointerstitial nephritis, an acute ischemic kidney injury resulting from inhibition of the intrarenal synthesis of vasodilatory prostaglandins, and, on rare occasions, glomerular injury with heavy proteinuria.[13] Renal injury caused by NSAIDs is unusual in patients with normal, unperturbed kidneys and is much more likely in patients with preexisting renal disease or concomitant renal insults such as volume contraction, hypotension, or simultaneous exposure to other nephrotoxins. It is therefore very likely that the NSAID was an important contributor to the acute renal failure in this patient, although I do not believe it was the principal cause.

Acute Glomerulonephritis

The possibility of an acute glomerulonephritis is not supported by the facts in this case. Urinalysis was bland, with protein and white cells only and no red cells or cellular casts. Furthermore, tests for antibodies to double-stranded DNA, antibodies to glomerular basement membrane, and ANCA were all negative and the serum complement level was normal, making systemic lupus erythematosus, anti–glomerular basement membrane disease, and ANCA-positive systemic vasculitis unlikely.

THE HEMOLYTIC–UREMIC SYNDROME AND THROMBOTIC THROMBOCYTOPENIC PURPURA

Could this patient have the hemolytic–uremic syndrome, thrombotic thrombocytopenic purpura, or the antiphospholipid syndrome? Some features are consistent with these possibilities, although none are strongly supportive. Schistocytes seen on the blood film are suggestive of a microangiopathic hemolytic anemia, but in the presence of a normal serum haptoglobin level, this must be of only moderate severity, if present at all. The lactate dehydrogenase level was elevated, but we see parallel elevations of the creatine kinase, aldolase, and aminotransferase levels, suggesting that much of the lactate dehydrogenase originated from muscle. The patient has moderate and progressive thrombocytopenia, but it is less severe than is usually seen in cases of the hemolytic–uremic syndrome or thrombotic thrombocytopenic purpura. Negative tests for anticardiolipin antibodies and lupus anticoagulant argue against the antiphospholipid antibody syndrome.

SUMMARY

In synthesizing the features of this case, I propose the following sequence of events. This patient's initial presentation with a possibly Jo-1–positive polymyositis evolved into a diffuse cutaneous scleroderma–polymyositis overlap syndrome. Active polymyositis and rapid progression of a phenotype of diffuse cutaneous scleroderma 6 weeks before admission prompted the patient's physicians to increase the dose of prednisone to 20 mg daily, and the patient subsequently presented with acute renal failure, hypertension, encephalopathy, and possibly

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a seizure. I believe that the diagnostic procedure performed was a kidney biopsy and that the specimen showed features consistent with a scleroderma renal crisis, including mucoid intimal thickening of the interlobular arteries and fibrinoid necrosis affecting the arterioles. I also believe that there is a strong possibility of a concomitant acute tubular injury attributable to NSAID (naproxen) use.

Dr. Eric S. Rosenberg (Pathology): Dr. Staller, what was your clinical impression when you initially evaluated this patient?

Dr. Staller: In this patient with acute kidney injury in combination with worsening symptoms of scleroderma, new-onset hypertension, bland urine sediment, and evidence of microangiopathic hemolytic anemia, we thought the most likely diagnosis was scleroderma renal crisis. The diagnostic procedure was a renal biopsy.

CLINICAL DIAGNOSIS

Scleroderma renal crisis.

DR. JOHN CUNNINGHAM'S DIAGNOSIS

Scleroderma renal crisis.

PATHOLOGICAL DISCUSSION

Dr. Diana Taheri: The renal-biopsy specimen consisted of two cores of renal cortex and medulla, with 11 glomeruli and 7 small arteries. Foci of acute cortical necrosis involved both cores and approximately 40% of the sample (Fig. 2A). All glomeruli showed varying degrees of acute ischemic changes (Fig. 2B), including swollen endothelial cells, mesangiolysis, and frank necrosis. All small arteries had acute changes, including mucoid intimal thickening (Fig. 2C), trapping of erythrocytes, fibrin deposition in the intima, and fibrin thrombi (Fig. 2D). The interstitium was edematous but not particularly inflamed. There was acute tubular injury in areas not affected by frank necrosis.

Immunofluorescence staining showed occasional fibrin thrombi in the glomerular capillaries (Fig. 2E) and arterial intima, but there was no staining for IgG, IgM, IgA, kappa and lambda light chains, C3, C4d, C1q, or albumin. Electron microscopy (Fig. 2F) showed widespread endothelial loss and injury and wrinkling of the glomerular basement membrane. There was segmental duplication of the glomerular basement membrane and extensive loss of podocyte foot processes.

These findings are not specific and can be seen in various forms of severe thrombotic microangiopathy, including arteriolar nephrosclerosis due to malignant hypertension, the hemolytic–uremic syndrome, thrombotic thrombocytopenic purpura, radiation nephropathy, drugs, the antiphospholipid-antibody syndrome, and systemic scleroderma (scleroderma renal crisis).[14] In this patient with scleroderma, these histologic changes are indicative of scleroderma renal crisis.

The renal-biopsy specimens not only can confirm the diagnosis of scleroderma renal crisis but also can predict the long-term outcome.[9,15,16] The histologic changes showing the most severe acute vascular injury (e.g., vascular thrombosis, glomerular ischemic collapse, and to a lesser degree, acute tubular injury) correlate with an increased risk of failure to recover renal function.[16] In addition, deposition of C4d (a product of classic complement degradation) in the peritubular capillary may be an unfavorable prognostic finding. In this case, there were no C4d deposits in the peritubular capillary, but the biopsy specimen showed other histologic features that indicated severe vascular injury.

Dr. Rosenberg: Dr. Thomas, what happened with the patient?

Dr. Lynette E. Thomas (Nephrology): Despite aggressive increases in the dose of captopril, the patient remained markedly hypertensive, and the serum creatinine level continued to increase. She continued to have oligoanuria, with increasing volume overload; hemodialysis was initiated. By the 16th day, the patient remained anuric, with no evidence of renal recovery. She underwent six sessions of hemodialysis, without complications, and her symptoms improved; the blood pressure returned to normal, and the angiotensin-converting–enzyme inhibitor was continued. On the 17th day, she was discharged to a rehabilitation facility to continue hemodialysis. Records from the rehabilitation facility indicate that the patient had one hemodialysis session with no complications but that a subsequent hemodialysis session 2 days later was complicated by severe hypotension. Her clinical status worsened rapidly, and after a conference with the patient's health care proxy, comfort measures only were instituted. The patient died on her eighth day at the rehabilitation facility.

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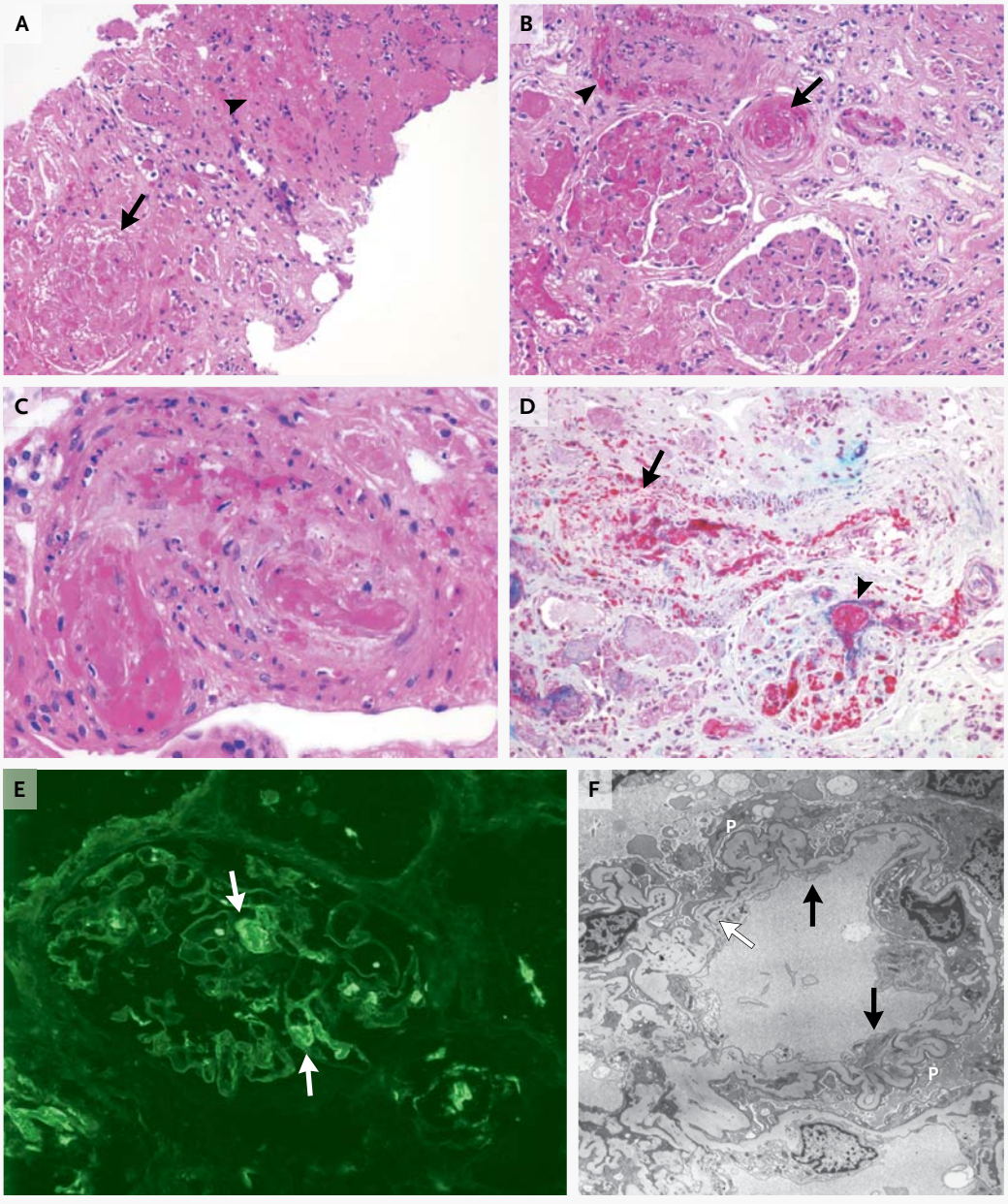

Figure 2. Renal-Biopsy Specimen.

In Panel A (hematoxylin and eosin), a specimen from a core biopsy of the right kidney shows foci of acute cortical necrosis involving 40% of the specimen; a necrotic glomerulus is seen at the lower left (arrow) and necrotic tubules at the upper right (arrowhead). Two glomeruli are shown (Panel B, hematoxylin and eosin), which have swollen endothelial cells, loss of cellularity, and mesangiolysis. One arteriole is occluded by fibrin thrombi (arrow), and one small artery has fibrinoid necrosis of the medial layer (arrowhead). An interlobular artery (Panel C, hematoxylin and eosin) has mucoid intimal thickening with fibrinoid necrosis and fibrin thrombi. Panel D (Masson's trichrome) shows an artery with fibrinoid necrosis, red-cell entrapment, and fragmentation (arrow); an arteriole (arrowhead) contains luminal thrombus, which continues into the hilar region of a glomerulus. Immunofluorescence staining of a frozen section of the renal-biopsy specimen (Panel E) shows positive staining for fibrin in some glomerular capillaries (arrows). Electron microscopy (Panel F) shows loss of endothelial-cell fenestrations (black arrows), with wrinkling of the glomerular basement membrane. There is segmental duplication of the glomerular basement membrane (white arrow) and extensive effacement of the podocyte foot processes (P).

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A Physician: How do you explain the apparent stroke the patient had at the time of presentation?

Dr. Cunningham: I considered the possibility that thrombotic thrombocytopenic purpura caused the stroke, but I think hypertensive encephalopathy is more likely and that the changes seen on CT are probably chronic.

A Physician: In patients with end-stage renal disease due to scleroderma renal crisis, is kidney transplantation an option?

Dr. Cunningham: It has been performed, but the results are not as good as in other patient groups, and the results of dialysis are not as good either. These results partly reflect practical issues, such as vascular access for dialysis in a patient with scleroderma, as well as the circulatory legacy from the catastrophic cardiovascular insult that constitutes the renal crisis.

ANATOMICAL DIAGNOSIS

Renal thrombotic microangiopathy with arteriopathy and cortical necrosis, consistent with scleroderma renal crisis.

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