CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 24-2018: A 71-Year-Old Man with Acute Renal Failure and Hematuria

Ronald J. Falk, M.D., Jad S. Husseini, M.D., Andrew Z. Fenves, M.D., and Ivy A. Rosales, M.D.

From the Department of Medicine, University of North Carolina School of Medicine, Chapel Hill (R.J.F.); and the Departments of Radiology (J.S.H.), Medicine (A.Z.F.), and Pathology (I.A.R.), Massachusetts General Hospital, and the Departments of Radiology (J.S.H.), Medicine (A.Z.F.), and Pathology (I.A.R.), Harvard Medical School — both in Boston.

N Engl J Med 2018;379:568-78.
DOI: 10.1056/NEJMcpc1802829

PRESENTATION OF CASE

Dr. Joshua Z. Drago (Medicine): A 71-year-old man was transferred to this hospital because of worsening renal function and hematuria.

Three weeks before this admission, the patient's wife became ill with chills, fatigue, and myalgias, and she thought she had influenza. A few days later, the patient reportedly had a subjective fever, with intermittent shaking chills, fatigue, malaise, anorexia, and mild diffuse myalgias. He noted that he had reduced his fluid intake and that his urine had become darker. His symptoms were temporarily relieved with the administration of acetaminophen.

Approximately 10 days before this admission, the patient was evaluated by his primary care physician, who thought the patient was dehydrated. Laboratory tests were performed, and the results came back later that day, revealing a serum creatinine level of 4.9 mg per deciliter (433 μmol per liter; reference range, 0.6 to 1.4 mg per deciliter [53 to 124 μmol per liter]); the creatinine level had been 0.8 mg per deciliter (71 μmol per liter) 2 months earlier. He was referred to the emergency department of another hospital.

On evaluation at the other hospital, the patient reported persistent constitutional symptoms, intermittent lower abdominal cramping, and increased darkening of the urine, which had become the color of cola. The temperature was 36.9°C, the heart rate 87 beats per minute, the blood pressure 153/82 mm Hg, and the oxygen saturation 98% while he was breathing ambient air. The weight was 103.2 kg, and the mucous membranes were moist. The remainder of the examination was normal. Testing of a nasopharyngeal swab for influenza A and B viruses was negative, and a urine culture was obtained; other laboratory test results are shown in Table 1. Imaging studies were obtained.

A chest radiograph was reportedly normal. Computed tomography (CT) of the abdomen and pelvis, performed without the intravenous administration of contrast material, reportedly revealed bilateral renal cysts without evidence of hydronephrosis, diverticulosis without evidence of diverticulitis, cholelithiasis without evidence

of cholecystitis, and vascular calcifications of the abdominal aorta, with an abdominal aortic aneurysm (3.9 cm in diameter).

Intravenous normal saline was administered, and the patient was admitted to the other hospital. His outpatient medications were aspirin, atorvastatin, amlodipine with benazepril, metformin, cholecalciferol, and n–3 fatty acids, as well as ibuprofen every other day for knee pain. Ibuprofen, aspirin, benazepril, and metformin were discontinued on admission.

Renal ultrasonography revealed normal-sized kidneys (13.3 cm on the right and 11.8 cm on the left), with bilateral cysts (≤5.5 cm in diameter), including one with a thin septation, and no evidence of hydronephrosis. A nephrology consultation was obtained; additional test results are shown in Table 1. On hospital day 4, the creatinine level decreased to 3.2 mg per deciliter (283 μmol per liter), but over the next 2 days, hematuria occurred and the creatinine level increased to 3.9 mg per deciliter (345 μmol per liter). Examination of the urinary sediment revealed red cells, red-cell casts, and white-cell casts. Empirical treatment with intravenous methylprednisolone was started, and a plan was made for kidney biopsy.

Because the patient had temperatures of up to 37.7°C and persistent leukocytosis, two sets of blood cultures were obtained. Two days later, gram-negative rods grew in the two anaerobic bottles. Treatment with intravenous ceftriaxone was started, and methylprednisolone was discontinued. Repeat cultures of the blood and urine were obtained, ceftriaxone was discontinued, and treatment with cefepime and aztreonam was started.

Repeat CT of the abdomen and pelvis, performed without the intravenous administration of contrast material, revealed an increased amount of perinephric fluid without evidence of a discrete abscess. It also revealed a hyperintense renal cyst (0.9 cm in diameter) in the right upper pole, new evidence of presacral fat stranding, and trace bilateral pleural effusions. An echocardiogram showed normal ventricular function and no valvular calcifications. On hospital day 11, the creatinine level was 3.0 mg per deciliter (265 μmol per liter), and the patient requested transfer to this hospital.

On evaluation at this hospital, a review of systems was notable for gross hematuria with brown urine, fatigue, low-grade fevers, anorexia, and intermittent cough. The patient reported diffuse crampy abdominal pain that he rated at 3 on a scale ranging from 0 (no pain) to 10 (the most severe pain). He reported that he had no dysuria, increase in urinary frequency, flank pain, nausea, vomiting, pharyngitis, dyspnea, rash, headache, or neurologic symptoms.

The patient had a history of impaired glucose tolerance, hypertension, hyperlipidemia, abdominal aortic aneurysm, eczema, benign colonic polyps, diverticulosis, and osteoarthritis of the knees, shoulders, and lumbar spine. He had undergone right inguinal hernia repair, as well as radical prostatectomy for the treatment of prostate cancer 16 years previously. He had had no adverse reactions to medications. Several of his five young grandchildren had been ill during the month before this admission. He had retired 1 year earlier from a job in sales, which had involved travel to Europe and most recently to Mexico. He had drunk 3 or 4 beers daily since he had retired. He had smoked a half pack of cigarettes daily for 50 years but had most recently smoked a few cigarettes per day. His father had had lung cancer and his mother had had diabetes, but there was no family history of autoimmune or renal disease.

On physical examination, the temperature was 37.4°C, the heart rate 84 beats per minute, the blood pressure 159/90 mm Hg, the respiratory rate 18 breaths per minute, and the oxygen saturation 94% while the patient was breathing ambient air. The weight was 103.6 kg, the height 175 cm, and the body-mass index (the weight in kilograms divided by the square of the height in meters) 33.8. The patient appeared comfortable. Dentition was poor, but there were no oropharyngeal lesions. Auscultation of the chest revealed an early-peaking systolic murmur (grade 2/6) at the left base and bibasilar crackles. The abdomen was soft, nontender, and nondistended, and there was no tenderness at the costovertebral angle. A left inguinal hernia was present. There were no septic lesions on the nails and no rashes. Voided urine was rose-colored, without clots. The rest of the examination was normal.

Cultures of the urine and blood were obtained. Blood levels of magnesium, phosphorus, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and bilirubin were normal. Other laboratory test results are shown in Table 1. Examination of the urinary sediment

Table 1. Laboratory Data.*

Variable	Reference Range, Adults, Other Hospital	On Presentation, Other Hospital	Hospital Day 3, Other Hospital	Reference Range, Adults, This Hospital†	On Presentation, This Hospital
Blood					
Hemoglobin (g/dl)	12.0–17.0	13.5	11.0	12.0–16.0	10.8
Hematocrit (%)	35.0–50.0	39.8	33.6	36.0–46.0	32.1
White-cell count (per mm^3)	4500–11,000	16,500	11,600	4500–11,000	16,580
Differential count (%)					
Neutrophils		76.1	71.5	40–70	
Lymphocytes		12.6	14.5	22–44	
Monocytes		9.2	10.2	4–11	
Eosinophils		0.6	0.7	0–8	
Basophils		0.3	0.3	0–3	
Immature granulocytes		1.2	2.8	0–0.9	
Platelet count (per mm^3)	150,000–400,000	388,000	461,000	150,000–400,000	300,000
Sodium (mmol/liter)	137–146	140	144	135–145	143
Potassium (mmol/liter)	3.5–5.3	4.1	4.0	3.4–5.0	3.5
Chloride (mmol/liter)	98–107	100	109	100–108	107
Carbon dioxide (mmol/liter)	23–32	26	23	23–32	23
Urea nitrogen (mg/dl)	5–25	72	58	8–25	50
Creatinine (mg/dl)	0.6–1.4	4.6	3.9	0.60–1.50	2.78
Glucose (mg/dl)	70–100	101	93	70–110	99
Calcium (mg/dl)	8.6–10.3		8.8	8.5–10.5	7.9
Total protein (g/dl)	6.4–8.3		6.6	6.0–8.3	5.1
Albumin (g/dl)	4.0–5.0		3.0	3.3–5.0	2.4
Glycated hemoglobin (%)	4.3–5.9		5.9		
Erythrocyte sedimentation rate (mm/hr)	0–20		82		
Antinuclear antibody	Negative		Negative	Negative at 1:40 and 1:160	Positive at 1:40; negative at 1:80 and 1:160
Antiproteinase 3 antineutrophil cytoplasmic antibody	<0.2 U		<0.2 U	Negative	Negative
Antimyeloperoxidase antineutrophil cytoplasmic antibody	<0.4 U		<0.2 U	Negative	Negative
C3 (mg/dl)	75–175		153	81–157	114
C4 (mg/dl)	14–40		30	12–39	21
Anti–double-stranded DNA				Negative at 1:10	Negative at 1:10
Rheumatoid factor (U/ml)				0–30	31
Hepatitis B surface antigen				Negative	Negative
Hepatitis B surface antibody				Negative	Negative
Hepatitis B core antibody				Negative	Negative
Hepatitis C antibody				Negative	Negative
Antitreponemal antibody				Negative	Negative
Prostate-specific antigen (ng/dl)				0–4.0	<0.10
Kappa light chain (mg/liter)				3.3–19.4	32.4
Lambda light chain (mg/liter)				5.7–26.3	30.9

Table 1. (Continued.)

Variable	Reference Range, Adults, Other Hospital	On Presentation, Other Hospital	Hospital Day 3, Other Hospital	Reference Range, Adults, This Hospital†	On Presentation, This Hospital
Iron (μg/dl)				45–160	25
Iron-binding capacity (μg/dl)				230–404	146
Ferritin (μg/liter)				20–300	603
Transferrin (mg/dl)				200–360	121
Urine					
Color	Yellow	Yellow	Yellow	Yellow	Rose
Clarity	Clear	Clear	Clear	Clear	Slightly cloudy
pH	5.0–8.0	5.0	5.0	5.0–9.0	6.0
Specific gravity	1.003–1.030	1.010	1.009	1.001–1.035	1.008
Protein	Negative	100 mg/dl	100 mg/dl	Negative	2+
Glucose	Negative	Negative	Negative	Negative	Negative
Ketones	Negative	Negative	Negative	Negative	Negative
Blood	Negative	Large	Negative	Negative	3+
Bilirubin	Negative	Negative	Negative	Negative	Negative
Nitrite	Negative	Negative	Negative	Negative	Negative
Leukocyte esterase	Negative	Negative	Negative	Negative	Negative
Red cells (per high-power field)	0–2	111	35	0–2	>100
Leukocytes (per high-power field)	0–5	15	11	0–2	10–20
Eosinophils (%)	0		2		
Bacteria	Negative		Few	Negative	1+
Sodium (mmol/liter)		<20			43
Creatinine (mg/dl)	39.0–259.0	101.0	85.0		57
Total protein (mg/dl)			198.3	0–13.5	325.3
Microalbumin (mg/dl)				0–2.0	194.5
Ratio of total protein (in mg) to creatinine (in mg)	<0.2		2.3	<0.15	5.71
Ratio of microalbumin (in mg) to creatinine (in g)				<30.0	3412.3

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for serum creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for iron and iron-binding capacity to micromoles per liter, multiply by 0.1791.
† 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.

revealed nondysmorphic red cells that were "too numerous to count," a few granular casts, and no cellular casts. Results of serum protein electrophoresis were normal, and a urine test for Bence Jones protein was negative.

Dr. Jad S. Husseini: CT of the abdomen and pelvis was performed without the intravenous administration of contrast material (Fig. 1). There was mild bilateral perinephric stranding with no hydronephrosis. The kidneys contained multiple, bilateral simple renal cortical cysts. There was colonic diverticulosis, predominantly involving the sigmoid colon, with fat stranding and multiple prominent lymph nodes in the sigmoid mesentery. These findings were compatible with acute sigmoid diverticulitis. The peritoneum contained a trace amount of free fluid and no free air. There were vascular calcifications involving the abdominal aorta and its major branches, with an infrarenal abdominal aortic aneurysm (3.9 cm in diameter). The lung bases were clear. There were trace bilateral pleural effusions.

Dr. Drago: Intravenous ceftazidime and metronidazole were administered. On hospital day 2,

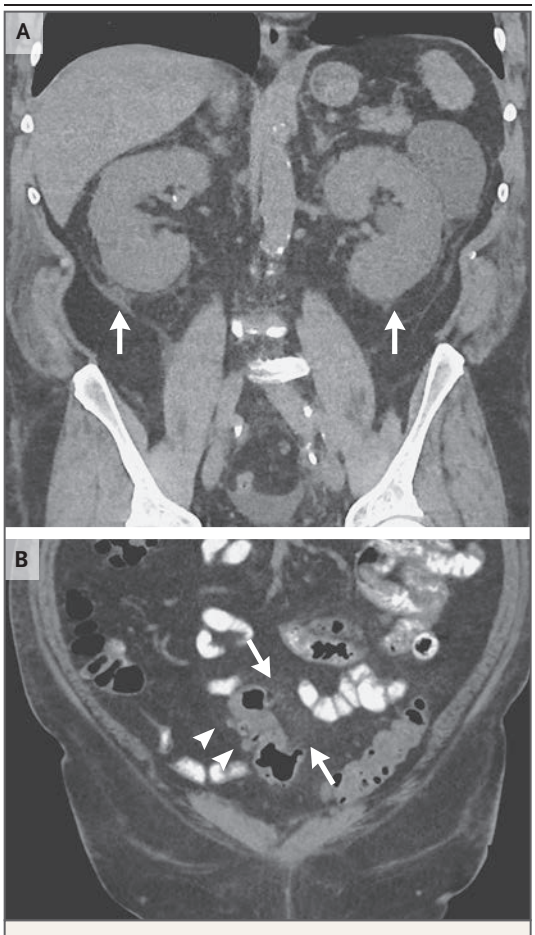

Figure 1. CT Scan of the Abdomen and Pelvis.

A CT scan of the abdomen and pelvis was obtained without the intravenous administration of contrast material. Coronal images show mild bilateral perinephric stranding (Panel A, arrows) without evidence of hydronephrosis, multiple diverticula in the sigmoid colon (Panel B, arrowheads), and fat stranding in the sigmoid mesentery (Panel B, arrows).

crampy abdominal and suprapubic pain occurred and the urine appeared darker red. Diagnostic tests were performed.

DIFFERENTIAL DIAGNOSIS

Dr. Ronald J. Falk: This 71-year-old man presented with rapidly declining kidney function and hematuria. His serum creatinine level rose over a period of 2 months, from 0.8 to 4.9 mg per deciliter. In constructing a differential diagnosis, the first step is to determine whether this patient's declining kidney function is due to an obstructive uropathy, a prerenal condition, or intrinsic kidney disease.

The patient had few symptoms involving the urinary tract and had no evidence of hydronephrosis on renal ultrasonography, making obstructive uropathy an unlikely diagnosis in this case. A prerenal insult such as intravascular volume depletion would be unlikely to cause the degree of acute kidney injury seen in this patient in the absence of considerable preexisting kidney disease. Furthermore, the administration of intravenous saline did not result in a marked improvement in renal function, which also makes intravascular volume depletion an unlikely explanation for this patient's presentation. Medications that could alter the glomerular filtration rate, including nonsteroidal antiinflammatory drugs (NSAIDs) and angiotensin-converting–enzyme inhibitors, had been discontinued. Therefore, the disease process is most likely intrinsic to the kidney.

EXAMINATION OF THE URINARY SEDIMENT

Much can be gleaned from descriptions of the urinary sediment. On initial presentation, the urine was described as the color of cola, and examination of the urinary sediment revealed red cells, red-cell casts, and white-cell casts, findings suggesting glomerulonephritis.[1] The results of urinalysis and the deteriorating kidney function raised concerns, and treatment with intravenous methylprednisolone was started.

The presence of white-cell casts raises the possibility of interstitial nephritis. Although interstitial nephritis may be caused by facultative gram-negative anaerobes (e.g., yersinia) that are acquired during foreign travel,[2] interstitial nephritis rarely causes macroscopic hematuria. Given the degree of hematuria seen in this patient, interstitial nephritis would be unlikely and other common causes of hematuria should be considered.

A subsequent examination of the urinary sediment revealed nondysmorphic red cells and no cellular casts, findings suggesting a source of bleeding in the urinary tract. Renal ultrasonography and CT without contrast enhancement revealed simple kidney cysts and one minimally complex cystic mass (Bosniak 2 classification) of little clinical significance, along with a contracted bladder. Although a source of bleeding in the urinary tract cannot be ruled out, it would be

an unlikely cause of rapidly declining kidney function in this patient.

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

Rapidly progressive glomerulonephritis is the most likely diagnosis in this patient, and the workup would need to proceed quickly to prevent glomerular and interstitial scarring. Evaluation of the serum complement (C3 and C4) levels is very helpful in narrowing the differential diagnosis. Activation of the classic complement pathway, which reduces both the C4 level and the C3 level, suggests glomerular disease due to a process such as systemic lupus erythematosus or cryoglobulinemia. Activation of the alternative complement pathway, which results in a low C3 level and a normal C4 level, raises the possibility of a variety of infectious diseases and membranoproliferative glomerulonephritis. In this case, the C3 and C4 levels were normal, suggesting that the declining kidney function was due to a process such as IgA nephropathy, antineutrophil cytoplasmic antibody (ANCA)–positive glomerulonephritis, or anti–glomerular basement membrane (GBM) disease (Goodpasture's syndrome).

This patient had several negative serologic tests, including tests specific for hepatitis B and C viruses, findings that decrease the likelihood of viral glomerulonephritis. A negative anti–double-stranded DNA test makes the diagnosis of systemic lupus erythematosus unlikely, and negative tests for antiproteinase 3 and antimyeloperoxidase antibodies, on two separate occasions, decrease the likelihood that ANCAs were driving the disease pathogenesis. There is no mention of serologic testing for anti-GBM antibodies.

With any diagnosis of glomerulonephritis, two separate yet intertwined questions should be asked. First, is the inflammatory condition limited to the kidney, or is it part of a systemic disease process? The presence of extrarenal manifestations aids in narrowing the differential diagnosis. For example, a patient could have a pulmonary–renal syndrome (e.g., ANCA-positive glomerulonephritis or anti-GBM disease) or crampy abdominal pain associated with IgA vasculitis of the bowel. In this case, crampy abdominal pain is the only extrarenal clue. Second, do extrarenal manifestations provide clues to the pathogenesis of the disease? In this case, the intersection of infection and kidney disease sharpens the focus.

INFECTION AND KIDNEY DISEASE

Some infections (e.g., hepatitis B or C virus infection, human immunodeficiency virus infection, syphilis, and staphylococcal infection) may cause kidney disease, and some may aggravate existing kidney conditions, such as IgA nephropathy or anti-GBM disease, or may drive the cause of kidney disease. This case contains many clues. Could the patient have received an infection from his wife or grandchildren or during his recent travel to Mexico? The list of possible transmissions is long. Since the patient was known to have diverticular disease, his intermittent lower abdominal cramping and discomfort were most likely due to colitis or diverticulitis. He began to receive antibiotic therapy, which was broadened to provide coverage of the gram-negative anaerobes that grew in the blood culture. There are over two dozen genera of gram-negative anaerobic bacilli, and *Bacteroides fragilis* and *Fusobacterium nucleatum* lead the list of possibilities in this case. An endovascular infection of the aortic aneurysm or a cardiac valve is possible but unlikely, given the absence of vegetations on echocardiography and the relatively normal periaortic region on CT.

GRAM-NEGATIVE BACTEREMIA AND GLOMERULONEPHRITIS

Could the gram-negative bacteremia have contributed to the immunopathogenesis of this patient's glomerulonephritis? IgA nephropathy is caused by defects of mucosal immunity, and the interplay between this glomerular disease and intestinal disorders is well documented.[3] Flares of IgA nephropathy may occur synchronously with gastrointestinal infections. Patients with IgA vasculitis (Henoch–Schönlein purpura) may present with crampy abdominal pain. That said, rapidly progressive IgA nephropathy would be a highly unusual new diagnosis in a 71-year-old patient with no previous episodes of macroscopic hematuria. It is possible that he had an ANCA-negative necrotizing and crescentic glomerulonephritis that mimicked ANCA-positive glomerulonephritis.[4] Both IgA nephropathy and ANCA-negative glomerulonephritis must remain in the differential diagnosis.

The most likely diagnosis in this patient is

anti-GBM disease — a cause of rapidly progressive glomerulonephritis in both the young and the old. Anti-GBM disease may cause pulmonary bleeding, but this patient had no evidence of such bleeding. Anti-GBM disease does not affect abdominal organs. Do the crampy abdominal pain and gram-negative anaerobic bacteremia provide insight into the disease process in this patient?

Autoimmune diseases occur as a consequence of multiple factors and not a single "hit." The patient must lose immunologic tolerance to the autoantigen; specifically, patients with anti-GBM disease lose immunologic tolerance to a remarkably restricted epitope on the noncollagenous domain of the alpha-3 chain of type IV collagen, known as alpha-3(IV)NC1 or Goodpasture's antigen.[5,6] This antigen is normally hidden from immune surveillance and must undergo a structural change or "autoantigen conformopathy" to permit its interaction with circulating anti-GBM antibodies.[7]

Genetic predisposition and environmental factors play a role in autoantibody formation and autoantigen availability. Anti-GBM disease is marked by "spatial and temporal clustering,"[8] indicating the importance of genetic and environmental factors. Genetic predisposition is based on a very strong HLA association.[9] Environmental risks are numerous and include cigarette smoking and infection. Ernest Goodpasture's original case (which may actually have been a case of ANCA-positive glomerulonephritis) was associated with the influenza outbreak of 1918.[10] The occurrence of seasonal variations of disease in spring and early summer suggests infectious triggers. In a recent study,[11] 67% of patients with anti-GBM disease had prodromal fever and bacterial infections due to a variety of gram-negative bacteria.

The immunopathogenic potential of microbes in anti-GBM disease has been tested in several ways. An important human B-cell epitope of alpha-3(IV)NC1 overlaps with a T-cell epitope of murine anti-GBM disease, suggesting that a critical amino acid motif is responsible for autoimmunity in anti-GBM disease. When this amino acid motif was screened against microbial protein databases, seven microbe-derived peptides based on this motif were found. Circulating antibodies to these bacteria were discovered in the circulation of patients with anti-GBM disease.[12] Three of these microbial peptides were from bacteroides species.

This patient's anti-GBM disease may be an example of molecular mimicry induced by a gram-negative anaerobe such as bacteroides or other gram-negative bacteria that contribute to diverticulitis. There are two other mechanisms by which infection may have exacerbated the disease. First, anti-GBM antibodies can be found in the circulation for months or years before the manifestation of disease,[13] and it is possible that a bacteroides infection revved up the production of anti-GBM antibodies. Second, the critical alpha-3(IV)NC1 epitope must undergo autoantigen conformopathy,[14] and it is possible that an infectious milieu exposed the hidden antigen.

There is another diagnostic consideration in this case. This patient had much more marked proteinuria than would be expected in a patient with anti-GBM disease. A protein:creatinine ratio of 5.71 would most likely result from perturbation of podocytes induced by another glomerular disease. For example, the patient could have had concurrent membranous nephropathy associated with cancer caused by years of cigarette smoking. However, this man, who had obesity and glucose intolerance and was receiving metformin, most likely had mild concurrent diabetic nephropathy. In North America, there is an epidemic of diabetes and diabetic nephropathy that can coexist with any glomerular disease.[15] To establish the diagnosis of anti-GBM disease in this patient, I would perform a kidney biopsy.

Dr. David M. Dudzinski (Cardiology): Dr. Fenves, what was your clinical impression when you evaluated this patient?

Dr. Andrew Z. Fenves: This 71-year-old patient had a rapid decline in renal function and active urinary sediment with red cells and red-cell casts. He had some response to intravenous methylprednisolone. All these findings point to a rapidly progressive (crescentic) glomerulonephritis. Our differential diagnosis included ANCA-positive pauci-immune glomerulonephritis, anti-GBM disease, IgA nephropathy (supported by his episodes of gross hematuria), and the least likely possibility of systemic lupus erythematosus–associated nephritis. The presence of proteinuria in the nephrotic range raised the possibility of NSAID-induced membranous glomerulonephritis or diabetic nephropathy.

CLINICAL DIAGNOSIS

Rapidly progressive (crescentic) glomerulonephritis.

DR. RONALD J. FALK'S DIAGNOSES

Anti–glomerular basement membrane disease causing a crescentic glomerulonephritis.

Diverticulitis due to *Bacteroides fragilis* and other gram-negative anaerobic bacteria.

Podocytopathy, possibly due to mild diabetic nephropathy.

PATHOLOGICAL DISCUSSION

Dr. Ivy A. Rosales: The diagnostic procedures in this case were a core needle biopsy of the kidney, a serum enzyme-linked immunosorbent assay (ELISA), and Western blot analysis. Examination of the biopsy specimen revealed 21 glomeruli, of which 19% were globally sclerosed and 38% were cellular crescents (Fig. 2A and 2B). Segmental necrosis was present in some glomeruli. Red-cell casts (Fig. 2C), reabsorption droplets, and tubular injuries of varying degrees of severity were also present. Approximately 30% of the cortex showed interstitial fibrosis and tubular atrophy. The blood vessels showed mild intimal fibrosis in arteries and arteriolar hyalinosis. Altogether, these findings show evidence of a necrotizing and crescentic glomerulonephritis.

On immunofluorescence microscopy of the glomeruli, the GBM showed bright, global, linear (4+) staining for IgG (Fig. 2D) and a similar pattern and intensity of staining for kappa and lambda. Crescents were positive for fibrin. The GBM showed 3+ to 4+ staining for IgG4, 2+ to 3+ staining for IgG1, and 1+ staining for IgG2. Staining for IgG3 was negative. On electron microscopy, endothelium was reactive. There was global effacement of podocyte foot processes, a finding that accounted for the patient's proteinuria. There were no electron-dense deposits (Fig. 2E). There was no evidence of diabetic nephropathy.

Serum ELISA for the detection and quantitation of antibodies to alpha-3(IV)NC1 was negative at less than 2 reference units per milliliter (positive result, ≥20). Western blot analysis for the detection of antibodies to alpha-3(IV)NC1 was positive.

The findings are diagnostic of anti-GBM disease but with several unusual features. First, the crescents and necrosis were not as prominent as they would be in a classic case of anti-GBM disease, in which the crescents are diffuse, global, and circumferential, typically involving approximately 75% of glomeruli.[16,17] In this case, the crescents involved less than half the glomeruli and were small, suggesting subacute or transient disease.

Second, serum ELISA was negative for anti-GBM antibodies, whereas the more sensitive Western blot analysis was positive. False negative tests occur in 2 to 3% of cases of anti-GBM disease.[18] In this case, the negative ELISA suggests that the antibody titer was too low for detection.

Finally, this case showed an IgG4-dominant subclass distribution. IgG4 is considered to be inert and has a limited capacity to fix complement and Fc receptors. IgG4 dominance may have accounted for the lesser severity and extent of the glomerular lesions. IgG4 antibodies to alpha-3(IV)NC1 can cause a false negative ELISA.[19,20] In anti-GBM disease, IgG subclass distribution may be associated with disease severity.[21]

In summary, necrotizing and crescentic glomerulonephritis associated with a positive Western blot analysis for antibodies to alpha-3(IV)NC1 is diagnostic of anti-GBM disease. The relatively modest extent and severity of glomerular lesions and the negative serum ELISA for anti-GBM antibodies are features that have been described in unusual presentations of anti-GBM disease.[18,22]

DISCUSSION OF MANAGEMENT

Dr. Fenves: Once the diagnosis of anti-GBM disease was established, we treated this patient with intravenous methylprednisolone for 3 consecutive days and oral cyclophosphamide daily for 5 days, followed by a taper. There was no evidence of pulmonary hemorrhage, but this possibility prompted us to proceed with five sessions of plasmapheresis during the 10 days after the kidney biopsy.

Anaerobic blood cultures from the other hospital grew three organisms: *B. fragilis*, *F. necropho-*

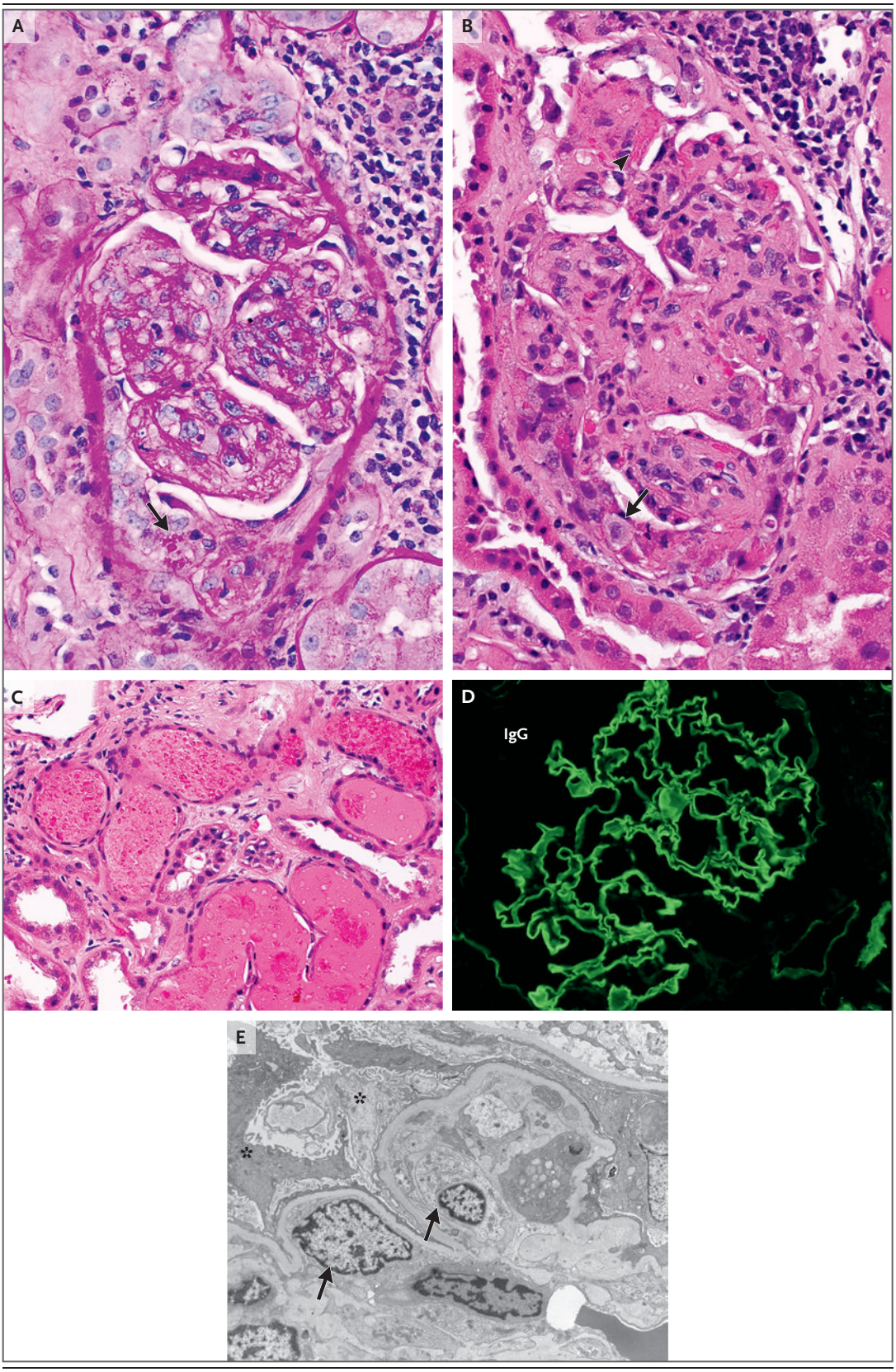

Figure 2 (facing page). Renal-Biopsy Specimen.
Periodic acid–Schiff staining and hematoxylin and eosin staining (Panels A and B, respectively) show hypercellular glomeruli with cellular crescents (arrows) and segmental necrosis (arrowhead). Additional hematoxylin and eosin staining (Panel C) shows red-cell casts and tubular injury. Direct immunofluorescence microscopy (Panel D) shows bright, linear (4+) staining for IgG along the glomerular capillary wall. Electron microscopy (Panel E) shows reactive podocytes (asterisks), with effacement of foot processes, and reactive endothelial cells (arrows). There are no electron-dense deposits.

rum, and *Peptoniphilus indolicus*. The bacterial infections were successfully treated with intravenous ceftazidime and metronidazole. Subsequent blood cultures were negative.

Five days after the kidney biopsy, severe abdominal pain developed, along with a leukocyte count of more than 40,000 per cubic millimeter. CT of the abdomen revealed evidence of diverticulitis with a small colonic perforation. The patient initially received conservative treatment but ultimately underwent a sigmoid colectomy and a colostomy. His immunosuppressive medications were withheld for 3 days during the perioperative period. Bilateral deep venous thrombosis developed postoperatively and was treated with intravenous heparin.

During the 2 weeks after kidney biopsy, the patient had fluctuating renal function, with a serum creatinine level ranging from 2.3 to 3.2 mg per deciliter (203 to 283 μmol per liter). He never needed to undergo renal-replacement therapy.

The patient's hospitalization lasted for more than 6 weeks. During that time, he had two episodes of wound dehiscence. The wounds were probably aggravated by ongoing glucocorticoid therapy, and they eventually healed by second intention. There was never any evidence of a pulmonary hemorrhage, a dreaded potential feature of anti-GBM disease that can lead to severe complications and occasionally to death. Toward the end of his hospital course, the patient received intravenous rituximab. His serum creatinine level at discharge was 2.0 mg per deciliter (177 μmol per liter).

Three months after discharge, the patient received a second dose of intravenous rituximab. Cyclophosphamide was stopped after 3 months, and prednisone was tapered over a 5-month period and then discontinued. The patient had a successful reversal of the colostomy 1 year later. Now, 16 months after he received the diagnosis of anti-GBM disease, he is doing well, with a serum creatinine level of 1.5 mg per deciliter (133 μmol per liter), and he is currently receiving no immunosuppressive medications.

ANATOMICAL DIAGNOSIS

Anti–glomerular basement membrane disease.

This case was presented at the Medicine Grand Rounds.

Supported in part by the Case Records of the Massachusetts General Hospital McNeely Visiting Professor Series.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Drs. Charles Jennette, David Van Duin, William Hyslop, and Manish Saha for their help in preparing for the conference and for providing a critical review of a previous draft of the manuscript; Bernard Collins for his assistance with and input on the enzyme-linked immunosorbent assay and Western blot analysis; Drs. Rex Neal Smith and Robert Colvin for their input on the pathological discussion; and Dr. Frank Cortazar for helpful suggestions regarding the treatment of this patient.

REFERENCES

1. Charles Jennette J, Falk RJ. Glomerular clinicopathologic syndromes. In: Gilbert SJ, Weiner DE, eds. Primer on kidney diseases. 7th ed. Philadelphia: Elsevier, 2018:162-74.
2. Raghavan R, Eknoyan G. Acute interstitial nephritis: a reappraisal and update. Clin Nephrol 2014;82:149-62.
3. Coppo R. The intestine-renal connection in IgA nephropathy. Nephrol Dial Transplant 2015;30:360-6.
4. Falk RJ, Jennette JC. ANCA disease: where is this field heading? J Am Soc Nephrol 2010;21:745-52.
5. Butkowski RJ, Langeveld JP, Wieslander J, Hamilton J, Hudson BG. Localization of the Goodpasture epitope to a novel chain of basement membrane collagen. J Biol Chem 1987;262:7874-7.
6. Wieslander J, Kataja M, Hudson BG. Characterization of the human Goodpasture antigen. Clin Exp Immunol 1987;69:332-40.
7. Hudson BG, Tryggvason K, Sundaramoorthy M, Neilson EG. Alport's syndrome, Goodpasture's syndrome, and type IV collagen. N Engl J Med 2003;348:2543-56.
8. Canney M, O'Hara PV, McEvoy CM, et al. Spatial and temporal clustering of anti-glomerular basement membrane disease. Clin J Am Soc Nephrol 2016;11:1392-9.
9. Fisher M, Pusey CD, Vaughan RW, Rees AJ. Susceptibility to anti-glomerular basement membrane disease is strongly associated with HLA-DRB1 genes. Kidney Int 1997;51:222-9.
10. Wilson CB, Smith RC. Goodpasture's syndrome associated with influenza A2 virus infection. Ann Intern Med 1972;76:91-4.
11. Gu QH, Xie LJ, Jia XY, et al. Fever and prodromal infections in anti-glomerular basement membrane disease. Nephrology (Carlton) 2018;23:476-82.
12. Li JN, Jia X, Wang Y, et al. Plasma from patients with anti-glomerular basement membrane disease could recognize

microbial peptides. PLoS One 2017;12(4):e0174553.
13. Olson SW, Arbogast CB, Baker TP, et al. Asymptomatic autoantibodies associate with future anti-glomerular basement membrane disease. J Am Soc Nephrol 2011;22:1946-52.
14. Pedchenko V, Bondar O, Fogo AB, et al. Molecular architecture of the Goodpasture autoantigen in anti-GBM nephritis. N Engl J Med 2010;363:343-54.
15. O'Shaughnessy MM, Hogan SL, Poulton CJ, et al. Temporal and demographic trends in glomerular disease epidemiology in the southeastern United States, 1986-2015. Clin J Am Soc Nephrol 2017;12:614-23.
16. Jennette JC. Rapidly progressive crescentic glomerulonephritis. Kidney Int 2003;63:1164-77.
17. McAdoo SP, Pusey CD. Anti-glomerular basement membrane disease. Clin J Am Soc Nephrol 2017;12:1162-72.
18. Ohlsson S, Herlitz H, Lundberg S, et al. Circulating anti-glomerular basement membrane antibodies with predominance of subclass IgG4 and false-negative immunoassay test results in anti-glomerular basement membrane disease. Am J Kidney Dis 2014;63:289-93.
19. Rosales IA, Colvin RB. Glomerular disease with idiopathic linear immunoglobulin deposition: a rose by any other name would be atypical. Kidney Int 2016;89:750-2.
20. Nasr SH, Collins AB, Alexander MP, et al. The clinicopathologic characteristics and outcome of atypical anti-glomerular basement membrane nephritis. Kidney Int 2016;89:897-908.
21. Zhao J, Yan Y, Cui Z, Yang R, Zhao MH. The immunoglobulin G subclass distribution of anti-GBM autoantibodies against rHalpha3(IV)NC1 is associated with disease severity. Hum Immunol 2009;70:425-9.
22. Salama AD, Dougan T, Levy JB, et al. Goodpasture's disease in the absence of circulating anti-glomerular basement membrane antibodies as detected by standard techniques. Am J Kidney Dis 2002;39:1162-7.