In this Journal feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors’ commentary follows.

A 57-year-old man presented to the emergency department with a 2-week history of progressive dyspnea with exertion, edema of the upper and lower legs, a nonproductive cough, and scant hemoptysis. He also reported the occasional passage of bright red blood from his rectum and intermittent nausea and vomiting during the previous 4 days. He reported no recent upper respiratory tract infection, fever, weight loss, abdominal pain, hematuria, chest pain, or hematemesis.

This seemingly unrelated array of symptoms cannot be readily explained by a single diagnosis, but their simultaneous development tempts the clinician to find a unifying cause. The combination of dyspnea with hemoptysis and peripheral edema occurring over a relatively short period raises a concern about possible venous thromboembolic disease. In this circumstance, peripheral edema could predispose the patient to venous thromboembolism or could be the result of pulmonary hypertension and right ventricular failure. In the absence of evidence of vigorous upper gastrointestinal bleeding, passage of bright red blood from the rectum suggests a lower intestinal source, possibly hemorrhoids or angiodysplasia.

The patient’s medical history included hypertension, type 2 diabetes mellitus diagnosed 20 years earlier, hyperlipidemia, and gastroesophageal reflux with Barrett’s esophagus; the most recent endoscopic examination, performed 2 years earlier, showed no evidence of neoplasia. He began insulin therapy 2 years earlier, when he was already being treated with glipizide. His other medications included metoprolol, losartan, aspirin, omeprazole, and simvastatin. He was a heavy smoker and reported occasional marijuana use and a history of excessive drinking, but he said he did not currently drink alcohol or use intravenous drugs. He had worked with paint solvents approximately 2 weeks before coming to the hospital but reported no previous exposure to hydrocarbons.

On admission, the temperature was 37.9°C, the heart rate 84 beats per minute, the respiratory rate 24 breaths per minute, the blood pressure 158/84 mm Hg, and the oxygen saturation 91% while the patient was breathing ambient air. There was conjunctival pallor and dried blood in the oropharynx. Crackles were heard at both lung bases. The cardiac examination revealed an early systolic murmur, grade 1 out of 6, at the left upper sternal border. The jugular venous pressure was normal. The patient’s abdomen was not tender and there was no organomegaly or ascites. A rectal examination revealed external hemorrhoids, and a guaiac test of a stool specimen was negative. There was 3+ pitting edema up to the sacral region. The patient’s skin was warm and dry, without evidence of nodules, rash, or petechiae. There was no joint
swelling or tenderness and no lymphadenopathy. The neurologic examination was normal.

The patient has tachypnea, and his oxygen saturation is mildly depressed; these findings, along with the presence of bibasilar crackles on examination of the chest, suggest a pulmonary parenchymal process at the level of the interstitium or the alveolar spaces. Bibasilar crackles are not characteristic of pulmonary embolism and therefore suggest some other pulmonary disorder. His conjunctival pallor raises the possibility of anemia, but since there was no objective evidence of ongoing gastrointestinal bleeding on stool examination, causes of anemia other than bleeding from the rectum must be considered. For example, the combination of hemoptysis, dried blood in the oropharynx, and bibasilar crackles on chest examination could reflect pulmonary hemorrhage, as occurs with Goodpasture’s syndrome and other pulmonary–renal syndromes. Of note is the patient’s history of heavy smoking and also his exposure to paint solvents, each of which has been associated with pulmonary hemorrhage in patients with anti–glomerular basement membrane antibodies.

The patient’s peripheral edema extends to the sacrum. Although a possible cause is right ventricular failure, either alone or in combination with left ventricular failure, the patient’s normal jugular venous pressure suggests that the edema cannot be explained by heart failure. Alternatively, the edema might be due to hypoalbuminemia, which could be the result of renal loss or decreased hepatic synthesis of albumin. Although Goodpasture’s syndrome would link the pulmonary and renal disease, it is associated with a nephritic rather than a nephrotic presentation, and the latter would be a more likely pattern for renal disease with this degree of edema. Systemic lupus erythematosus, on the other hand, is a potential cause of pulmonary hemorrhage as well as renal disease with a nephrotic presentation. I would want to know whether there were other clinical features suggesting underlying lupus.

The white-cell count was 15,000 per cubic millimeter, with 84% polymorphonuclear cells and 8% lymphocytes; the hematocrit 17%, with a mean corpuscular volume of 79.4 fl; and the platelet count 515,000 per cubic millimeter. The serum sodium level was 139 mmol per liter; potassium, 4.2 mmol per liter; chloride, 108 mmol per liter; bicarbonate, 23 mmol per liter; blood urea nitrogen, 73 mg per deciliter (26 mmol per liter); and creatinine, 4.9 mg per deciliter (433 μmol per liter); 6 months earlier, the creatinine level had been 0.8 mg per deciliter (70.7 μmol per liter). The baseline hematocrit was 45%. Levels of liver enzymes were normal. The albumin level was 2.2 g per deciliter, and the international normalized ratio (INR) was 1.2. A urinalysis revealed 3+ protein and 3+ blood with abundant red cells, some of which were dysmorphic, 11 to 20 granular casts, oval fat bodies, and muddy brown casts. No red-cell casts were observed. Urinalyses performed 18 months and 6 months before admission showed microalbuminuria and 1+ protein, respectively. A chest radiograph showed bilateral pulmonary opacities (Fig. 1).

The most striking abnormalities on the initial diagnostic workup include severe anemia (with microcytosis), renal insufficiency, relatively recent clinically significant proteinuria, lipiduria, and marked hypoalbuminemia — the latter three findings are consistent with the nephrotic syndrome. The chest radiograph is diffusely abnormal, with a pattern of alveolar filling; in a patient with microcytic anemia and a history of hemoptysis and guaiac-negative stools, opacification on the radiograph is likely to represent intraalveolar hemorrhage. The combination of pulmonary hemorrhage and renal disease suggests that this patient has

![Figure 1. Posteroanterior Chest Radiograph.](image) Bilateral patchy pulmonary opacities are present, with relative sparing of the lung apexes.
one of the so-called pulmonary–renal syndromes, which include Goodpasture’s syndrome, systemic lupus erythematosus, Wegener’s granulomatosis, and microscopic polyangiitis. Although the patient has a leukocytosis and a mild fever, the chest radiograph and the overall clinical picture do not suggest a bacterial pneumonia, and I would not treat him with antibiotics at this point.

The patient was admitted to the medical service and given an empirical regimen of intravenous ceftriaxone and azithromycin for possible community-acquired pneumonia. After he received packed red cells, his hematocrit rose to 28%; however, his blood urea nitrogen and creatinine levels rose to 94 and 5.7 mg per deciliter (34 mmol per liter and 504 μmol per liter), respectively, in the first 36 hours after admission. A renal ultrasonogram revealed mild enlargement of both kidneys, with normal echogenicity and no hydronephrosis, stones, or scarring. A transthoracic echocardiogram revealed normal size and functioning of the right and left ventricles, mild aortic sclerosis without stenosis, and mild mitral regurgitation.

Computed tomography (CT) of the chest showed bilateral alveolar filling, a finding that is consistent with alveolar hemorrhage. Despite the indeterminate result of the test for anti–glomerular basement membrane antibodies, I would favor Goodpasture’s syndrome as the diagnosis most likely to explain the constellation of findings. However, because the nephrotic syndrome is an unusual feature in patients with Goodpasture’s syndrome, I wonder whether the patient’s history of diabetes may have complicated the renal presentation, being either the primary cause of or a factor contributing to his proteinuria. Given the confusing presentation of his renal disease, I would favor proceeding with a renal biopsy. However, empirical institution of therapy for Goodpasture’s syndrome is appropriate if a biopsy cannot be performed immediately.

A renal biopsy was performed, and examination of the biopsy specimen revealed florid epithelial crescents, with signs of early organization in approximately 85 to 90% of the glomeruli — findings that are consistent with rapidly progressive glomerulonephritis. Also present were Kimmel-
stiel–Wilson nodules, which are characteristic of diabetic nephropathy (Fig. 3B). Immunofluorescence revealed linear staining of glomerular capillary walls for IgG, indicative of anti–glomerular basement membrane antibody disease (Fig. 3C). On repeat ELISA, the level of anti–glomerular basement membrane antibodies was 53 U per milliliter.

Treatment with oral cyclophosphamide was initiated, and intravenous corticosteroid therapy and daily plasmapheresis were continued. However, the patient had persistent nausea and vomiting. Hemodialysis with ultrafiltration was started and performed three times weekly, without signs of recovery of renal function; the urine output declined to less than 240 ml per day. Levels of anti–glomerular basement membrane antibodies fell to 7 U per milliliter after 10 days of plasmapheresis, but hemoptysis persisted, so the patient continued to receive plasmapheresis four times a week.

The renal-biopsy findings indicate that both diabetic nephropathy and anti–glomerular basement membrane antibody disease underlie the patient’s renal disease. His initial treatment with plasmapheresis, oral cyclophosphamide, and corticosteroids was appropriate. Unfortunately, however, the high percentage of glomeruli with crescents, the elevated creatinine level with oliguria, and the need for dialysis suggest a poor prognosis for recovery of renal function.

After 4 weeks, the hemoptysis resolved, and plasmapheresis was discontinued. The patient’s oxygen saturation remained greater than 95% while he was breathing ambient air. For further evaluation of the passage of bright red blood from his rectum and to rule out another cause of anemia, he underwent colonoscopy, which revealed nonbleeding internal hemorrhoids and a hyperplastic polyp, and upper endoscopy, which confirmed the diagnosis of Barrett’s esophagus. The patient was discharged to a skilled nursing facility after prolonged hospitalization. Seven months after discharge, he continues to receive hemodialysis three times a week, oral cyclophosphamide, and prednisone.

COMMENTARY

During the 1918–1919 influenza pandemic, the pathologist Ernest Goodpasture (1866–1960) reported two patients with a rapidly progressive and ultimately fatal syndrome characterized by hemoptysis, anemia, and renal failure. Similar cases were subsequently described and attributed to the clinical entity that now bears his name. Today, the terms “Goodpasture’s syndrome,” “Goodpasture’s disease,” and “anti–glomerular basement membrane antibody disease” are often used interchangeably to describe the triad of pulmonary hemorrhage, glomerulonephritis, and anti–glomerular basement membrane antibodies, the last of which underlies the pathogenesis of this disease process. However, some use the term “Goodpasture’s syndrome” more broadly to describe the combination of glomerulonephritis and lung hemorrhage in the absence of another specific cause (e.g., Wegener’s granulomatosis), whether or not there are circulating anti–glomerular basement membrane antibodies.

Manifestations of the disease are caused by autoantibodies to the noncollagenous-1 domain of the α3 chain of type IV collagen in the basement membrane of glomerular and alveolar tissue; the antibodies form when cryptic antigens are exposed through injury or infection.

The patient reported two environmental triggers that have been associated with the development of Goodpasture’s syndrome: cigarette smoking and exposure to solvents. Exposure to cigarette smoke is strongly correlated with the development of pulmonary hemorrhage in patients with Goodpasture’s syndrome. Data in humans and animals suggest a causal link between hydrocarbon exposure and the development of anti–glomerular basement membrane antibody disease.

As the discussant notes, the differential diag-
nosis of renal diseases that present with both a nephritic urinary sediment and nephrotic-range proteinuria is limited (primarily membranoproliferative glomerulonephritis, Wegener’s granulomatosis, lupus, and IgA nephropathy). The discussant recognized that Goodpasture’s syndrome is the most likely diagnosis on the basis of the clinical findings, despite the presence of the nephrotic syndrome, and ultimately, the evaluation revealed underlying diabetic nephropathy that probably contributed to the patient’s presentation. Previous reports have described the occurrence of Goodpasture’s syndrome concomitantly with other diseases associated with the nephrotic syndrome (membranous nephropathy, diabetic nephropathy, Wegener’s granulomatosis, lupus, and IgA nephropathy).

Edema of the legs, often seen with nephrotic-range proteinuria, has also been reported in patients with Goodpasture’s syndrome; in this case, it was probably related to both hypoalbuminemia and renal failure. The hematochezia was most likely due to hemorrhoids and was not associated with gastrointestinal hemorrhage. Cases of gastrointestinal involvement have been described in patients with systemic vasculitis. Notably, one of the index cases described by Goodpasture involved splenic and small intestinal infarcts that were probably due to vasculitis rather than anti–glomerular basement membrane antibody disease.

The discussant emphasized that a renal biopsy was warranted, especially given the indeterminate level of anti–glomerular basement membrane antibodies and the atypical features of this case. In one small case series, involving patients with biopsy-proven anti–glomerular basement membrane antibody disease with alveolar hemorrhage, only 64% of the patients had circulating anti–glomerular basement membrane antibodies. The negative antibody tests in patients with documented disease may be attributable to laboratory variations in detection and reduced assay sensitivity in instances of early-stage and milder disease. Furthermore, immunosuppressive therapy may reduce levels of circulating anti–glomerular basement membrane antibodies, and antibody titers do not correlate directly with disease progression. In the case described, treatment with prednisone and plasmapheresis was initiated for the indeterminate level of anti–glomerular basement membrane antibodies before the renal biopsy was performed, given the high clinical suspicion of Goodpasture’s syndrome. Ultimately, the biopsy (as well as a subsequent antibody titer) confirmed the diagnosis. Early diagnosis and combined treatment with

Figure 3. Pathological Findings.
Hemosiderin-laden macrophages are present in a bronchoalveolar-lavage specimen (Panel A, arrows; Papanicolaou’s stain). In a renal-biopsy specimen, an epithelial crescent (Panel B, arrow) shows signs of early organization in a glomerulus with mesangial sclerosis and a characteristic Kimmelstiel–Wilson nodule (arrowhead; silver stain with hematoxylin-and-eosin counterstain). Glomerular capillary basement membranes are shown with linear immunofluorescence staining for IgG (Panel C).
corticosteroids, cyclophosphamide, and plasmapheresis improve the outcomes for patients with this once universally fatal disease. Prompt diagnosis is important, since outcomes correlate with the creatinine level at the time of diagnosis. In one observational study, 1-year rates of overall survival and dialysis-free survival were 100% and 95%, respectively, for patients with a creatinine level of 5.7 mg per deciliter (503.9 μmol per liter) or less at diagnosis. In contrast, these rates were 83% and 82%, respectively, for patients with higher creatinine levels who did not yet require dialysis, and 65% and 8%, respectively, for those who did require dialysis. Patients who had crescentic changes involving all glomeruli on initial biopsy and required dialysis were more likely to remain dialysis-dependent at 1 year. Unfortunately, despite early initiation of plasmapheresis and immunosuppressive therapy, our patient required hemodialysis beginning early in his course and has not recovered.

In summary, this case of multiorgan disease has classic themes with interesting variations—a pulmonary–renal syndrome with nephritic-range proteinuria and gastrointestinal bleeding. A good clinical history with rigorous analysis enabled the discussant to deduce combined diagnoses. A definitive diagnosis should be sought early in patients with the combination of renal disease and pulmonary hemorrhage to identify potentially treatable causes.

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REFERENCES