CASE PRESENTATION

A 79-year-old man with a past medical history of mild hypertension presented to his primary care physician with a complaint of 2 weeks of cough productive of blood-tinged sputum and progressively worsening dyspnea and was admitted to the hospital. He had completed a 7-day course of levofloxacin for similar complaints 1 week prior to presentation, but the symptoms persisted. The patient also noted that he had generalized fatigue and weakness for the previous 10 days, mild left-sided pleuritic chest pain of 3 days’ duration, and a decline in urine volume over the past 24 hours. He had no sinus or nasal symptoms.

Medications included a multivitamin, aspirin (81 mg/d), metoprolol (25 mg/d), and the recently prescribed levofloxacin (200 mg twice daily). Social history was unremarkable for alcohol or illicit drug abuse, but the patient smoked 1 pack of cigarettes per day (50-pack-year history). He lived alone at home. Family history was positive for hypertension and coronary artery disease.

Physical examination revealed a thin male with mild dyspnea at rest, blood pressure of 150/92 mm Hg, pulse of 100 bpm, respirations of 26 breaths/min, and temperature of 99.1°F. Head and neck examination revealed pale conjunctiva, anicteric sclera, and no otorrhoea. There were no palpable lymph nodes, carotid bruises, or thyromegaly. Jugular venous pulsations were present in the sitting position. Lungs had crackles at both bases and in the lower one third of the left lung field. Heart rate and rhythm were regular without murmur or rub. Abdominal examination was benign. Lower extremities had trace edema without rash, and the neurologic examination was physiologic.

Notable results on the complete blood count were as follows: leukocyte count, 12.5 × 10^3/µL; hemoglobin, 8.1 g/dL; hematocrit, 25%; and platelet count, 228 × 10^3/µL. The patient had a normal eosinophil count. Electrolytes were within normal limits, while blood urea nitrogen (BUN) was 85 mg/dL and serum creatinine (SCR) was 3.9 mg/dL. Chest radiograph revealed infiltrates in both bases and in the lower left lung field. Urinalysis showed a specific gravity of 1.015, pH of 6.0, positive blood (2+), positive leukocyte esterase (1+), and positive protein (2+). The urine sediment revealed dysmorphic erythrocytes, scattered leukocytes, erythrocyte casts, and granular casts. A spot urine test for protein and creatinine revealed a protein/creatinine ratio of 2.1 (equivalent to 2.1 g of protein in a 24-h urine collection).

The patient had ongoing hemoptysis with lung infiltrates and acute renal failure characterized by hematuria (erythrocyte casts) and proteinuria. Nephrology and pulmonary consultants recommended kidney biopsy. Percutaneous kidney biopsy was performed under computed tomography scan guidance. A light microscopy view of the renal histology is shown in Figure 1 and Figure 2. Immunofluorescence and electron microscopy were negative for staining and dense deposit deposition, respectively.

The patient was treated with high-dose intravenous methylprednisolone (1 g/d for 3 days) and was then continued on oral prednisone 60 mg/d. Oral cyclophosphamide was also initiated at 2 mg/kg/d (125 mg/d). Subsequent serologic testing revealed an antinuclear antibody (ANA) titer of 1:640, was negative for anti–glomerular basement membrane (GBM) antibody and perinuclear-antineutrophil cytoplasmic antibody (p-ANCA), and was positive for cytoplasmic-ANCA (c-ANCA). Testing for anti-myeloperoxidase antibody was negative, while testing for anti-proteinase 3 antibody was positive at 12 (normal, < 6).

Despite therapy, the patient continued to decline and required intubation and mechanical ventilation for respiratory failure and hemodialysis for severe oliguric acute renal failure (BUN, 124 mg/dL; SCr, 7.1 mg/dL). On hospital day 6, the patient experienced cardiac arrest and could not be resuscitated.

Dr. Brewster is an assistant professor of medicine, and Dr. Perazella is an associate professor of medicine, Section of Nephrology, director of the Renal Fellowship Program, and director of acute dialysis services. Both are at the Yale University School of Medicine, New Haven, CT.

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WHAT IS THE ETIOLOGY OF PULMONARY–RENAL SYNDROME IN THIS PATIENT?

(A) Goodpasture’s syndrome (anti-GBM disease)
(B) Systemic lupus erythematosus (SLE) with pulmonary hemorrhage and lupus nephritis
(C) Wegener’s granulomatosis
(D) Necrotizing bacterial lung infection with proliferative glomerulonephritis

The correct answer is (C) Wegener’s granulomatosis. Based on the clinical history, laboratory data, and, most importantly, the renal pathology, the patient was determined to have Wegener’s granulomatosis. Renal histopathology demonstrated segmental necrosis in the glomerulus (Figures 1 and 2), granulomatous vasculitis (Figure 3), interstitial nephritis (Figure 1) with scarring (Figure 2), and fibrinoid crescents (Figure 4). As will be discussed, Wegener’s granulomatosis is a form of pauci-immune vasculitis that causes pulmonary–renal syndrome, and it must be distinguished from the other potential causes of this syndrome.
PULMONARY–RENAL DISEASE

Pulmonary–renal syndrome is a morbid syndrome that has multiple etiologies but is most commonly caused by 3 categories of disease (Table). It is easiest to think of the classic causes of pulmonary–renal syndrome as one of the following:

1. Direct antibody mediated (Goodpasture’s syndrome)
2. Pauci-immune vasculitis (Wegener’s granulomatosis, microscopic PAN)
3. Immune-complex disease (SLE, cryoglobulinemia)

Thus, the initial differential diagnosis in this patient should include these 3 disease states. Other less common causes of the pulmonary–renal syndrome can be considered if the clinical, laboratory, and histopathologic data do not support any of the 3 categories. Therapy of these disease states will not be discussed.

Epidemiology

Epidemiologic clues that may point toward the correct diagnosis include age and sex. Anti-GBM disease is uncommon, with an annual incidence of 1 to 2 cases per million population per year. Anti-GBM disease has 2 peaks of disease incidence. Young males in the third decade of life often present with pulmonary and renal manifestations. The second peak occurs at about 60 years of age and has an equal distribution of men and women who present with primarily kidney disease. Immune-complex disease from SLE more often occurs in young or middle-aged women. Most often, lupus nephritis develops after SLE already has been diagnosed. However, severe kidney disease and pulmonary hemorrhage can rarely be the presenting symptom of SLE in a young woman. Pauci-immune disease, associated with either Wegener’s granulomatosis or microscopic PAN, occurs most commonly in older patients (middle-aged and elderly) and more often causes pulmonary–renal syndrome in the elderly than does either anti-GBM disease or immune-complex disease.

Clinical Features

Clinical manifestations may also suggest the cause of the pulmonary–renal syndrome. The history, physical examination, and laboratory data must be synthesized to develop an appropriate differential diagnosis and highlight likely causes of the underlying process. A serologic work-up is often conducted with a focus on ANCA. ANCA can stain with either a perinuclear or cytoplasmic pattern. The p-ANCA is directed against myeloperoxidase and the c-ANCA is directed against proteinase 3.

Both of these tests, particularly p-ANCA, can be positive in multiple disease states, including vasculitis, inflammatory bowel disease, cystic fibrosis, and rheumatoid arthritis; therefore, the results must be interpreted with caution and in the proper clinical context.

Anti-GBM disease from Goodpasture’s syndrome is characterized by pulmonary hemorrhage (with or without obvious hemoptysis) and kidney disease. Patients commonly have dyspnea, cough, and cyanosis. Pulmonary symptoms often precede renal manifestations. Pulmonary rales and pale conjunctiva are present on physical examination. A chest radiograph with patchy or diffuse infiltrates in the central lung fields supports the diagnosis of anti-GBM disease. Anemia is prominent on the complete blood count, while hypoxemia is noted on the arterial blood gas analysis. BUN and SCr concentrations are often elevated, reflecting acute renal failure. Urine studies reveal hematuria (± erythrocyte casts) and proteinuria. Circulating anti-GBM antibodies are detected by enzyme-linked immunosorbent assay approximately 50% of the time. Patients with anti-GBM disease may have a positive p-ANCA test 33% of the time, which demonstrates the need for renal biopsy to make a definitive diagnosis.

Immune-complex disease due to SLE often has multiorgan involvement when pulmonary–renal syndrome develops. For example, patients may also have evidence of cerebritis, skin rash, and arthralgias from systemic disease activity. Pulmonary hemorrhage may be obvious or may be evident only on chest radiograph with patchy infiltrates and effusion. Hematuria, proteinuria, and acute renal failure are typically present. ANA is positive with a high titer as are other serologic markers of SLE.
Patients with pauci-immune vasculitis from Wegener’s granulomatosis commonly have constitutional symptoms, including fever, night sweats, anorexia, and fatigue. Sinus symptoms and upper respiratory manifestations (otitis media, rhinorrhea, epistaxis) may be prominent. Pulmonary symptoms include cough with or without hemoptysis. Chest radiograph may reveal patchy or diffuse infiltrates or solitary or multiple nodules (that may have cavities) in various lung fields. Renal failure as well as an active urinary sediment with hematuria, erythrocyte casts, and proteinuria occur. Eosinophilia may or may not occur. In the setting of active disease, the c-ANCA test has a sensitivity of 90% and a specificity of 98%; however, the sensitivity falls to 63% when disease is quiescent or in those patients without classic symptoms of the disease. The c-ANCA test is positive in more than 90% of patients with classic Wegener’s granulomatosis (upper and lower respiratory tract involvement and kidney disease). It is important to note, however, that the ANCA test is insufficient to clinch a diagnosis of Wegener’s granulomatosis. A tissue diagnosis is mandatory prior to initiation of long-term cytotoxic therapy. Most but not all patients with microscopic polyangiitis are p-ANCA positive.

Histopathology

Ultimately, evaluation of a tissue sample is required to make a firm diagnosis of the cause of pulmonary–renal syndrome and facilitate proper therapy. This point is particularly important because use of incorrect therapy of these diseases is associated with significant morbidity and high mortality. Also, treatment of these diseases is toxic and fraught with numerous potentially lethal complications. Choosing the tissue to sample is the first step. In most cases of pulmonary–renal syndrome, the biopsy choices are either lung or kidney. Occasionally, patients with Wegener’s granulomatosis and sinus symptoms may undergo a sinus biopsy searching for necrotizing granulomas. However, the findings are often negative, thus requiring biopsy of another site. Kidney biopsy (with light, immunofluorescence, and electron microscopy) is less invasive and has equal or higher yield than lung biopsy.

In anti-GBM disease, examination of the kidney biopsy specimen using light microscopy often demonstrates segmental areas of necrosis in the glomeruli with crescent formation (proliferation of parietal epithelial cells of Bowman’s space). Immunofluorescence microscopy reveals linear deposition of IgG in the glomerular basement membrane. Electron microscopy does not show electron dense deposits (excluding immune-complex disease). When lung tissue is obtained, alveoli filled with erythrocytes and hemosiderin-stained macrophages are seen, while the pulmonary basement membrane demonstrates similar linear deposition of IgG.

The renal histopathology of immune-complex disease from SLE in the setting of pulmonary–renal syndrome often demonstrates segmental or diffuse areas of necrosis in the glomerulus under light microscopy. Wire loops (thickened capillary loops) and crescents are commonly found in glomeruli with necrosis. Examination with immunofluorescence microscopy shows deposition of multiple immunoglobulins and complement in the mesangial and capillary loops. The glomerulus has electron dense deposits in the mesangium as well as the subendothelial and subepithelial spaces on electron microscopy.

Wegener’s granulomatosis can be diagnosed with nasopharynx biopsy if necrotizing granulomatous vasculitis is seen. Pathologic examination of renal tissue provides a higher diagnostic yield. Light microscopy demonstrates focal and segmental necrosis of the glomeruli, epithelial crescents, and active tubulointerstitial nephritis. In this case, segmental necrosis of collapsed glomeruli is clearly seen on hematoxylin-eosin staining and on periodic acid-Schiff staining (Figures 1 and 2). An interstitial infiltrate with eosinophils is seen as well (Figure 3). Perhaps most remarkable is the direct invasion of a blood vessel by a granuloma with associated inflammation (Figure 3). Immunofluorescence staining of fibrin highlights the epithelial crescent surrounding a glomerulus (Figure 4). Antibody and GBM staining are negative on immunofluorescence and electron microscopy, which excludes both anti-GBM disease and immune-complex disease. Examination of lung tissue would likely show necrotizing granulomatous vasculitis, but the procedure is low yield and high risk.

CONCLUSION

Diagnosis of the patient with Wegener’s granulomatosis requires synthesis of the clinical, laboratory, and histopathologic data collected from the patient. The initial differential diagnosis of the patient with pulmonary–renal syndrome includes anti-GBM disease, immune-complex disease, and pauci-immune disease. The most important piece of data required to secure the correct diagnosis is tissue from the appropriate organ. In most cases, the kidney is the most accessible organ and has the highest diagnostic yield. Utilizing all aspects of microscopy—light, immunofluorescence, and electron—will guarantee correct diagnosis in the
vast majority of cases, allowing the patient to undergo the appropriate, albeit toxic, therapy.

REFERENCES


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