Systemic Lupus Erythematosus and ANCA-Associated Vasculitis Overlap Syndrome: A Case Report

Jaclyn Khil, Thuy M. Nguyen, Megan L. Troxell, and Sijie Zheng

Concomitant lupus nephritis and antineutrophil cytoplasmic antibody-positive crescentic glomerulonephritis is rare, and there is little guidance on the management and outcomes of these patients. A Hispanic woman in her early 40s with no contributory medical history presented with 3 weeks of cough, shortness of breath, fever, and malaise. Laboratory test results were notable for serum creatinine level of 17.4 mg/dL (previously normal), urinalysis with a high hemoglobin level, >182 red blood cell count, and urinary protein-creatinine ratio of 5.72 g/g. Serologies showed elevated dsDNA, ribonucleoprotein antibody, Smith antibody, myeloperoxidase antibody, positive antinuclear antibody, and low complement levels. She was urgently started on hemodialysis and solumedrol 1 g for 3 days. On day 2, she had a kidney biopsy, which showed necrotizing crescentic glomerulonephritis and immunofluorescence with “full house” pattern, immune complex deposits, and strong antinuclear antibody staining of nuclei. She developed diffuse alveolar hemorrhage and was initiated on plasmapheresis and cyclophosphamide. She improved and was discharged without needing further dialysis. Clinicians should consider systemic lupus erythematosus and antineutrophil cytoplasmic antibody disease overlap syndrome when a young, female patient presents with new kidney failure and alveolar hemorrhage. Early biopsy and aggressive treatment are essential in preserving kidney function, and plasmapheresis should be considered in severe cases. This is a severe case with a positive outcome.

INTRODUCTION

The rare concomitant presentation of both systemic lupus erythematosus (SLE) and antineutrophil cytoplasmic antibody (ANCA) vasculitis is termed overlap syndrome. Lupus nephritis is a complication of SLE seen in 30%–40% of lupus cases, often developing early in the disease course and disproportionately affecting young women and children.1,4 Lupus nephritis is an immune complex glomerulonephritis (GN) that should be suspected in patients with lupus, presenting with abnormal kidney function, hematuria, proteinuria, elevated autoantibodies (ie, antinuclear antibody [ANA] and dsDNA), and low complement levels and may coincide with a clinical flare. Furthermore, lupus nephritis is strongly associated with higher morbidity and mortality in patients with SLE.4 ANCA-associated vasculitis is a necrotizing vasculitis that affects small vessels of many organs, with >75% of patients having kidney involvement.5 Kidney involvement typically encompasses pauci-immune crescentic GN and/or necrotizing vasculitis. Patients with ANCA disease often report systemic symptoms, including fever, fatigue, and weight loss.6 For clinicians, unexplained hemoptysis should always raise concern for ANCA disease or other pulmonary kidney syndromes, including antiglomerular basement membrane disease. Patients who meet diagnostic criteria for both SLE and ANCA disease are considered to have an overlap syndrome.7,8 Currently, there are no treatment guidelines, and often, management decisions are left up to clinicians based on the predominant features of either ANCA disease or lupus nephritis on presentation. Here, we report a woman in her early 40s with a severe presentation of dialysis-dependent acute kidney injury and diffuse alveolar hemorrhage treated aggressively initially as ANCA disease with good results and later treated as lupus nephritis in the outpatient setting.

CASE REPORT

A Hispanic woman in her early 40s with a history of prediabetes and total hysterectomy for fibroids presented to our hospital with 3 weeks of cough, shortness of breath, fever, malaise, and arthralgias in knees and elbows. She was tachycardic, hypertensive (165/102 mm Hg), and hypoxic, requiring 2 L of supplemental oxygen. Her laboratory studies were significant for hemoglobin of 6.3 g/dL, white blood cell count of 13.9 K/μL, and serum creatinine level of 17.4 mg/dL, which was previously normal at 0.7 mg/dL (estimated glomerular filtration rate >60 mL/min/1.73 m²) 1.5 years ago. Urinalysis demonstrated large hemoglobin and >182 red blood cells with urinary protein-creatinine ratio of 5.72 g/g. Autoimmune work-up was significant for dsDNA 22 IU/mL (normal range, <9 IU/mL), ribonucleoprotein antibody >8 (normal range, <0.9), Smith antibody >8 (normal range, <0.9), ANA serum qualitative positive, erythrocyte sedimentation rate of >140 mm/h (normal range, 0–20 mm/h), C-reactive protein level was 8.7 mg/dL (normal range, <0.5 mg/dL), C3 of 29 mg/dL (normal range, 83–180 mg/dL), C4 of <8 mg/dL (>10 mg/dL), myeloperoxidase of >8 (normal range, <0.9), and proteinase 3 was <0.2 (normal range, ≤0.9). Kidney ultrasound showed increased echogenicity and no hydronephrosis.
Transthoracic echocardiogram finding was unremarkable. She was urgently started on hemodialysis and high-dose steroids (solumedrol 1 g for 3 days then prednisone 60 mg daily). On day 2 of admission, a kidney biopsy was performed. The initial diagnostic consideration was lupus nephritis given the age and sex of the patient and high anti-ribonucleoprotein antibody, anti-Smith antibody, dsDNA, and ANA as well as low complement levels. On day 3, she developed hemoptysis, and subsequent bronchoscopy with bronchoalveolar lavage demonstrated diffuse alveolar hemorrhage. The decision was made to start plasmapheresis on day 4.

Biopsy results demonstrated necrotizing crescentic GN with only segmental glomerular proliferation on light microscopy (Fig 1). Large cellular or fibrocellular crescents involved 9 of 15 open glomeruli, with 1 globally sclerotic glomerulus. Segmental endocapillary hypercellularity involved only 2 glomeruli; leukocytes were present in rare capillary loops. Immunofluorescence staining showed “full house” glomerular immune deposits (Fig 1). IgG dominant with relatively weak segmental deposits for C3, C1q, and IgM, with IgA negative. There was fibrinoid necrosis in 4 and cellular crescents in 9 of 12 glomeruli sampled for immunofluorescence. There was also strong IgG and light chain staining of nuclei, resulting from high ANA levels in the patient’s serum. Electron microscopy demonstrated correlative small mesangial, paramesangial, and rare subepithelial deposits, again in the setting of large crescents and fibrin tactoids. Endothelial tubuloreticular structures were identified, as are fairly typical of lupus nephritis. Given the biopsy results and serology, there was high suspicion for lupus nephritis and ANCA GN overlap. The patient was started on cyclophosphamide (750 mg). The patient completed 7 sessions of daily plasmapheresis, with kidney function improving to serum creatinine level of 11.7 mg/dL. (Fig 2). She was discharged home on
prednisone 1 mg/kg and atovaquone for pneumocystis jiroveci pneumonia prophylaxis. She did not need dialysis on discharge. She completed 5 cycles of monthly cyclophosphamide with tapering steroid daily doses. Unfortunately, her posthospitalization course was complicated by diverticulitis, herpetic dendritic keratitis, and pneumocystis pneumonia despite atovaquone prophylaxis. Eventually she was switched to mycophenolic acid and low-dose prednisone. Her disease is presently controlled with serum creatinine level nadired at 1.1 mg/dL at 4 months posthospitalization, with normalization of C3 and autoantibody titers.

**DISCUSSION**

Although SLE and ANCA disease overlap syndrome is a rare entity, this case demonstrates the importance of rapid performance of kidney biopsy and immunosuppressive therapy when a young woman presents with new kidney failure. This patient was started on steroids and scheduled for kidney biopsy within 2 days of admission. Expedited biopsy and treatment initiation is crucial in preserving kidney function.

The biopsy findings, in correlation with the serologic data, helped to establish the diagnosis and guide aggressive therapy. The biopsy findings of ANCA vasculitis and lupus nephritis are usually distinct. ANCA vasculitis most commonly presents as rapidly progressive GN with a pauci-immune (no or few deposits) necrotizing crescentic GN on kidney biopsy. In contrast, biopsy findings in lupus nephritis classically show “full house” immune complex deposits with glomerular proliferation, often including endocapillary and extracapillary proliferation (crescents) and bulky deposits. In the setting of lupus nephritis with a disproportionate abundance of crescents, it is important to consider ANCA serologies and the possibility of an overlap syndrome, as in this patient.

After establishing the likely diagnosis of overlap syndrome, we chose to use cyclophosphamide instead of rituximab because of comparable efficacy in treating ANCA vasculitis and lack of data on rituximab for patients with pulmonary hemorrhage. Plasma exchange should also be considered in those patients with severe presentation, including diffuse alveolar hemorrhage, especially if there is a lack of response to pulse steroids. This patient completed 7 sessions (daily for 7 days) and showed clinical improvement resulting in being discharged without requiring further dialysis. A review of the literature describing 39 cases of overlap syndrome described patients as mostly women, with an aggressive kidney presentation and both ANA and anti-myeloperoxidase antibodies, like our patient. Of these 39 cases, outcome data were available for 8 patients. Two of 8 patients had SLE and ANCA disease occurring simultaneously, similar to our patient. One patient died at month 7 of hepatocellular carcinoma, and the other patient achieved remission at month 6 after induction with corticosteroids and cyclophosphamide. In 2008, Nasr et al described a cohort of 10 patients with SLE, ANCA positivity, and kidney biopsy findings of lupus nephritis and ANCA-associated GN, all of which were treated with cyclophosphamide and prednisone. Three patients died of infectious complications in the first 6 months and 5 patients achieved near complete or complete remission.

There are no treatment trials for the rare SLE–ANCA overlap syndrome. Plasmapheresis has been studied in the setting of ANCA vasculitis. The Plasma Exchange and Glucocorticoid Dosing in the Treatment of Anti-Neutrophil Cytoplasm Antibody Associated Vasculitis: An International Randomized Controlled Trial (PEXIVAS) concluded that plasma exchange in patients with severe ANCA-associated vasculitis did not reduce the incidence of death or end-stage kidney disease. However, the median serum creatinine level in the study was 3.72 mg/dL (interquartile range, 2.34–5.6 mg/dL) and only 8% had severe pulmonary hemorrhage. It is also important to factor in the lack of kidney biopsies in the PEXIVAS study. In contrast, the Plasma Exchange for Renal Vasculitis study included patients who presented with serum creatinine level of >5.8 mg/dL. In the Plasma Exchange for Renal...
Vasculitis study, the plasma exchange arm was associated with improved mortality and improved kidney function (43% vs 19% risk of progression to end-stage kidney disease at 1 year), and many patients in the plasmapheresis arm were able to come off dialysis. In subgroup analyses of the PEXIVAS study, plasma exchange was shown to trend toward benefit in patients with more severe kidney disease, including dialysis-dependent patients (hazard ratio, 0.77; 95% confidence interval, 0.53-1.11) versus in patients with diffuse alveolar hemorrhage versus in patients without.

This case is an example of a severe presentation of overlap syndrome with a good outcome that likely benefited from rapid diagnosis and early initiation of aggressive therapy. Our patient was discharged off dialysis and with continued kidney recovery, despite infectious complications. Because the literature for SLE and ANCA disease overlap is largely limited to case reports, relatively little is known about outcomes. This case demonstrates the complex nature of lupus nephritis and ANCA-associated vasculitis and the importance of treating patients aggressively in severe cases. Furthermore, the question of which disease entity is more prominent at presentation and which entity may recur after remission has not been answered. The challenge of treating an overlap syndrome requires a keen clinical eye and very close monitoring.

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