An Unusual Presentation of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis

Discrepancy Between Histopathology and Clinical Presentation

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A 60-year-old man was admitted to our clinic with dyspnea, hemoptesis, anuria, nephritic syndrome, and a positive myeloperoxidase antineutrophil cytoplasmic antibody titer. He was diagnosed with antineutrophil cytoplasmic antibody-associated vasculitis due to Wegener granulomatosis, microscopic polyangiitis, or drug induction. Unexpectedly, histopathologic examination of the kidney biopsy specimen revealed the diagnosis of noncrescentic and nonnecrotizing glomerulonephritis. We report this case because of the unusual histologic type of renal involvement.

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INTRODUCTION

Rapidly progressive glomerulonephritis (RPGN) is a clinical syndrome manifested by features of glomerular disease in the urine and progressive loss of kidney function over a relatively short period of time (days, weeks, or months). The classic pathologic correlate of RPGN is crescent formation involving most glomeruli.[1] This histological finding is common in the elderly acute nephritis.[2] The severity of the disease is partly related to the degree of crescent formation; patients with circumferential crescents in more than 80% of the glomeruli tend to present with severe kidney failure that may not respond well to therapy. By comparison, patients with noncircumferential crescents in less than 50% of the glomeruli follow a more indolent course.[3] Rapidly progressive glomerulonephritis or crescentic glomerulonephritis is usually due to one of 4 disorders including anti-glomerular basement membrane, immune complex, pauci-immune, and double–antibody-positive diseases. Pauci-immune RPGN is characterized morphologically by necrotizing glomerulonephritis, which contains few or no immune deposits by immunofluorescence or electron microscopy. The majority of patients with renal-limited vasculitis are positive for antineutrophil cytoplasmic antibody (ANCA) (75% to 80% having positive myeloperoxidase [MPO]-ANCA), and many have or will develop the systemic symptoms of a vasculitis.[4,5] We describe a patient with nephritic syndrome, advanced kidney failure, hemoptesis, and positive MPO-ANCA who developed nonnecrotizing pauci-immune glomerulonephritis without crescent formation.

CASE REPORT

A 60-year-old man presented to the emergency department with a 2-week history of progressive dyspnea followed by bloody sputum and purple skin lesions in the lower extremities. He also noted a marked reduction in urine output and low-grade fever for 10 days. The patient had a history of gout, urinary calculus, and benign prostatic hypertrophy for the previous 3 years and smoking half a pack of cigarettes daily for 40 years. He had been informed of the presence of hematuria, proteinuria, and a positive MPO-ANCA titer 4 months earlier. He was receiving allopurinol (during the past 1 year), tamsulosin, captopril, prednisolone, and azathioprine (the 2 latter drugs for 1 week). The patient was a baker and his family history was notable for his daughter's having the scleroderma and her sister's having rheumatoid arthritis.

On physical examination, vital signs were normal, except for mild tachypnea (18 breaths per minute). Ecchymosis and palpable purpura were found

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in the skin of the lower extremities with edema. Examination of other organs was unremarkable. Laboratory tests revealed leukocytosis; elevated serum creatinine; nephritic urine sediment (dysmorphic erythrocytes, subnephrotic proteinuria, and leukocytoria); negative urine culture; and positive antinuclear antibody (ANA) and MPO-ANCA titers. No infectious disease was detected. Laboratory test results are shown in the Table.

Chest radiography showed right middle lobe opacity, and high-resolution computerized tomography of the lungs revealed diffuse grand glass appearance in the right lingula, middle lobe, and bilateral inferior lobes (Figure 1). Pulmonary function tests were normal. Computerized tomography of the sinuses indicated involvement of the right maxillary and bilateral anterior ethmoidal sinuses. Ultrasonography of the kidneys showed increased size of the right kidney (13.7 cm), normal size of the left kidney (12 cm), and parenchymal hyperechogenicity of the right kidneys. Urinary output was 60 mL during the first hour of care in the emergency department and did not change considerably after cautious fluid challenge test.

Because of anuria and presence of mild confusion, urgent hemodialysis was started, and with regard to clinical syndromes of acute kidney failure, glomerulonephritis, palpable purpura, and hemoptesis (pulmonary-renal syndrome), intravenous steroid pulses (3 days) were administered after a diagnosis of pauci-immune RPGN was made. In addition, kidney and skin biopsies were performed to confirm the diagnosis. Kidney biopsy revealed focal and segmental glomerulosclerosis with obsolescence of about 30% of the total (n = 30) glomeruli. The rest of the glomeruli showed enlargement with generally preserved tuft architecture and minimal mesangial expansion with clustering of the mesangial cells. There were no crescent, spikes, double contour, or abundant inflammatory cells (except for a small number of mononuclear cells). Moderate atrophy in about 20% of the cortical tubules with hyaline casts and rare granular casts and moderate fibrosis in 25% of the cortical interstitial area were seen. Immunofluorescent studies showed no immune deposits (Figure 2). Skin biopsy indicated non-necrotizing vasculitis (Figure 3). The patient's urine output was established after 3 days and the

Laboratory Studies*

Parameters	Value	Reference Range
Serum creatinine, mg/dL	10.9	< 1.5
Serum urea, mg/dL	271	20 to 40
Serum sodium, mEq/L	131	135 to 145
Serum potassium, mEq/L	4.8	3.5 to 5.0
Serum uric acid, mg/dL	6.8	2.5 to 8.0
Serum total protein, g/dL	7	5.5 to 8.0
Serum albumin, g/dL	5	3.5 to 5.5
Serum triglyceride, mg/dL	180	< 160
Serum cholesterol, mg/dL	200	< 200
Prothrombin time, sec	12	11 to 13
PTT, sec	30	22 to 35
ESR, mm/h	25	0 to 20
Hemoglobin, g/dL	12	13.5 to 17.5
Arterial blood gas		
pH	7.3	
Bicarbonate, mEq/L	16.2	
PCO_2, mm Hg	31.3	
Blood leukocyte count, $\times 10^9$/L	16800	4.5 to 11.0
Platelet count, $\times 10^9$/L	180000	150 to 350
Antineutrophil antibody	1/40	< 1/80
MPO-ANCA	100	Negative < 5
PR3-ANCA	2.4	Negative < 5
Urine protein, mg/24 h	150mg/80ml	< 150
Hepatitis B virus antigen	Negative serology	…
Hepatitis C virus antibody	Negative serology	…
Urine sediment	Dysmorphic erythrocytes, leukocytes, granular and red cell casts	…
Urine culture	Negative	…
Complements	Within normal limits	…
Anti-double-stranded-DNA	Negative	…
Rheumatoid factor	Negative	…
Liver enzymes	Within normal limits	…

*PTT indicates partial thromboplastin time; ESR, erythrocyte sedimentation rate; PCO_2, bicarbonate pressure; MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibody; and PR3-ANCA, proteinase 3-antineutrophil cytoplasmic antibody.

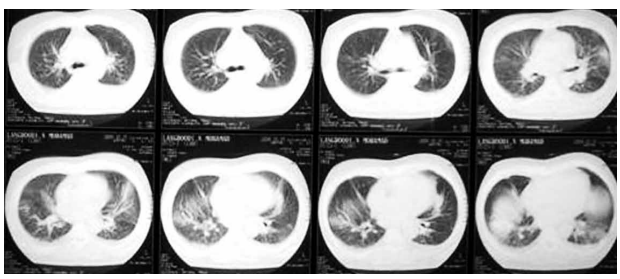

Figure 1. Computerized tomography of lungs shows diffuse grand glass appearance.

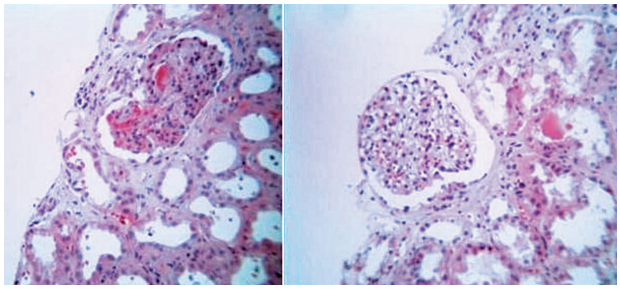

Figure 2. Kidney biopsy (low resolution) shows focal and segmental glomerulosclerosis, moderate tubulointerstitial atrophy, and scanty mononuclear cell infiltration.

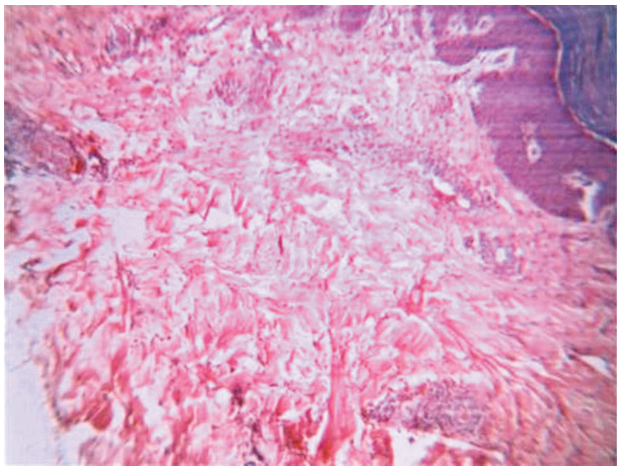

Figure 3. Skin biopsy shows vasculitis.

serum creatinine declined to 2.6 mg/dL during a 2-week admission due to appropriate medical management. On follow-up examination after 4 months, the patient had a bland urine sediment and a serum creatinine of 1.2 mg/dL.

DISCUSSION

Crescent formation represents a nonspecific response to severe injury to the glomerular capillary wall.[3] The active inflammation stage is often followed by the development of fibrocellular and fibrous crescents, which do not respond to immunosuppressive therapy.[6,7] Presence of ANCA are associated with many cases of pauci-immune glomerulonephritis including Wegener granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome, renal-limited vasculitis, and certain drug-induced vasculitis syndromes.[4,8] In these conditions, ANCA consistently have specificities for either proteinase 3 (PR3-ANCA) or MPO-ANCA, but almost never for both. Essentially, all patients with Wegener granulomatosis present with upper airway or pulmonary involvement, and the majority have both. Renal involvement can be manifested by acute kidney failure with dysmorphic erythrocytes, urinary casts, proteinuria, and segmental necrotizing glomerulonephritis with few or no immune deposits.[9,10] The glomerular involvement is often accompanied by mononuclear tubulointerstitial infiltrates with or without granuloma formation.[10,11] The American College of Rheumatology proposed 4 clinical criteria for the classification of Wegener granulomatosis in 1990, before the availability of ANCA testing. The four clinical criteria are nasal or oral inflammation (ulcers or bloody nasal discharge); abnormal chest radiography showing nodules, fixed infiltrates, or cavities; abnormal urinary sediment (microscopic hematuria with or without erythrocyte casts); and granulomatous inflammation on biopsy of an artery or perivascular area.[12] The presence of 2 or more of these criteria yielded a sensitivity of 88% and a specificity of 92%. At present, the diagnosis of Wegener granulomatosis is suggested from the clinical and laboratory findings and from the presence of PR3-ANCA (in 80% to 90% of cases).[4] However, ANCA alone does not appear to be sufficiently accurate to preclude the need for tissue biopsy. A typical finding on upper respiratory tract biopsies is acute and chronic inflammation, often with granulomatous features. Biopsy of the skin reveals a leukocytoclastic vasculitis with little or no immune deposits. Kidney biopsy typically shows a segmental necrotizing glomerulonephritis that is usually pauci-immune.[13] Some patients have vasculitic lesions resembling to Wegener granulomatosis, but, at presentation, do not have symptomatic or histologic respiratory involvement; such individuals have microscopic polyangiitis which is closely related to Wegener granulomatosis. This disorder is thought by some investigators to represent part of a clinical spectrum that includes Wegener granulomatosis, since both are associated with the presence of ANCA and similar histologic changes outside the respiratory tract.[5] The usual histopathologic lesion is pauci-immune focal segmental necrotizing and crescentic glomerulonephritis.[5]

Approximately 70% of patients with MPA are ANCA positive (versus 90% to 95% in Wegener granulomatosis) with MPO-ANCA predominance.[4] The presenting case had 2 clinical criteria of

Wegener granulomatosis with positive MPO-ANCA titers and can be classified as MPA- Wegener granulomatosis clinical spectrum who presented with RPGN. However, there are some discrepancies between clinical and histopathologic presentations. As mentioned above, pauci-immune segmental necrotizing glomerulonephritis is the usual histologic feature of MPA- Wegener granulomatosis in kidney specimen biopsy, which should be accompanied with crescent formation if Wegener granulomatosis presents as RPGN. On the contrary, crescent formation, inflammatory cells infiltration and necrotizing vasculitis were absent in patient's kidney biopsy. Indeed, unexpected histopathologic findings in patient's kidney biopsy indicate a good outcome, despite, severe clinical disease. On the other hand, certain medications may induce ANCA-associated vasculitis (mostly MPO-ANCA in high titers).[4] This vasculitis is usually associated with constitutional and joint symptoms, and cutaneous lesions. However, crescentic glomerulonephritis and alveolar hemorrhage can also occur. The patient had gout and has been receiving allopurinol for 1 year that could induce ANCA-associated vasculitis. If allopurinol had induced pauci-immune vasculitis and RPGN, crescent formation and necrotizing vasculitis should be present in renal biopsy.[14] However, allopurinol may induce proliferative glomerulonephritis associated with vasculitis which is comparatively consistent with histopathologic findings in this case. As a result, allopurinol was discontinued. In addition, histopathologic findings associated with absence of PR3-ANCA persuaded us to propound probable role of immunosuppressive therapy, with azathioprine and prednisolone for joint symptoms one week before admission, in diminishing of renal injury severity.

In conclusion, this case may be a representative of reversible pauci-immune drug induced vasculitis associated with glomerulonephritis that has improved with supportive therapy and drug discontinuation which indicates a favorable outcome, however, necessitates regular periodic follow up examinations.

CONFLICT OF INTEREST

None declared.

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