CASE REPORTS

D-Penicillamine–Induced ANCA-Associated Crescentic Glomerulonephritis in Wilson Disease

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Several drugs, including hydralazine and propylthiouracil, can induce antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. D-Penicillamine was implicated in a few patients with rheumatoid arthritis or systemic sclerosis, but in patients with both diseases, ANCA-associated vasculitides were described in the absence of the drug. Therefore, the role of D-penicillamine treatment could not be established. We report the first case of antimyeloperoxidase antibody–associated vasculitis in a patient treated with D-penicillamine for Wilson disease. Because Wilson disease was never associated with ANCA-related nephritis, this case strongly supports that D-penicillamine can induce ANCA-vasculitis. The presentation and rapidly progressive and potentially severe outcome of this complication dramatically contrast with those of membranous and minimal change glomerulopathy, also induced by the sulfhydryl compound.

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Drug-induced antineutrophil cytoplasmic antibody (ANCA)-associated small-vessel vasculitis with renal involvement is well documented for hydralazine and thionamide antithyroid drugs.[1] D-Penicillamine is a sulfhydryl compound used for the treatment of patients with Wilson disease and other illnesses, including rheumatoid arthritis and systemic sclerosis. As many as 7% of patients receiving prolonged D-penicillamine therapy develop such renal side effects as membranous nephropathy and minimal change disease.[2,3] D-Penicillamine withdrawal usually induces remission of the renal disease, although this may take years. ANCA-associated vasculitides occasionally were reported in patients with rheumatoid arthritis or systemic sclerosis treated with D-penicillamine. However, they also were reported in patients with these diseases in the absence of D-penicillamine therapy. Therefore, the relationship between ANCA-associated vasculitis and D-penicillamine treatment is questionable.[4,5] Here, we report the first fully documented case of ANCA-associated small-vessel vasculitis with renal involvement in a patient with Wilson disease treated with D-penicillamine.

CASE REPORT

A 19-year-old woman was referred to our nephrology department for acute renal failure, nephrotic-range proteinuria, and hematuria. Two years earlier, Wilson disease was diagnosed based on clinical neurological examination abnormalities, Kayser-Fleischer rings, cirrhosis, and excessive copper content in liver tissue. D-Penicillamine was administered as copper chelator at 900 mg/d and was well tolerated. It dramatically improved the patient's neurological symptoms during a 2-year period. At that time, renal function was normal, with serum creatinine level of 0.8 mg/dL (67 μmol/L) and estimated glomerular filtration rate using the Modification of Diet in Renal Disease Study equation of 101 mL/min/1.73 m^2 (1.68 mL/s/1.73 m^2), without proteinuria (protein $<$ 0.02 g/L) or hematuria.

Between July and November 2003, the patient lost 20 kg and developed microcytic anemia and alopecia without photosensitivity. In December 2003, laboratory findings showed a moderate decrease in kidney function, nephrotic syndrome, and microscopic hematuria. When she was referred to our department, blood pressure was 150/85 mm Hg and temperature was 38.6°C. She was eupneic with 96% oxygen saturation measured by using pulse oximetry in ambient air. Physical examination showed bilateral pleural effusion. Neurological examination showed unmodified changes related to Wilson disease. There was no sinonasal

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disease or hearing loss. There was no other abnormal clinical finding.

Serum creatinine level was 1.9 mg/dL (146 μmol/L), with estimated glomerular filtration rate of 42 mL/min/1.73 m^2 (0.70 mL/s/1.73 m^2). The patient had hypoalbuminemia (albumin, 2.32 g/dL [23.2 g/L]), a urine protein-creatinine ratio of 906 mg/mmol, and microscopic hematuria (200 red blood cells/μL), but no leukocyturia. Hemogram showed microcytic anemia with hemoglobin level of 8.5 g/dL (85 g/L) and increased white blood cell count ($12 \times 10^3/\mu$L [12×10^9/L]) with neutrophils at $9.4 \times 10^3/\mu$L (9.4×10^9/L). Platelet count and hepatic test results were unremarkable.

ANCA testing by means of immunofluorescence was positive (titer, 1/20; normal, $<$1/10) for perinuclear ANCA that were antimyeloperoxidase (anti-MPO)–specific immunoglobulin G (IgG) by means of enzyme-linked immunosorbent assay (33 U/mL; positive, $>$20 U/mL). Antinuclear factors also were positive (titer, 1/1000). Testing for other autoantibodies, including anti–glomerular basement membrane antibodies and cryoglobulinemia, was negative. Complement components were normal. There was no evidence for hemolysis. All bacteriological and virological tests on blood, urine, and bronchoalveolar fluid had negative results.

Chest radiography showed bilateral pleural effusion, which was noninflammatory after analysis of drained fluid. Cardiac ultrasound showed a mild noncompressive pericardial effusion. Kidneys were normal by means of ultrasound. Bronchoscopy results were unremarkable. Computed tomography and alveolar cytological test results were consistent with intra-alveolar hemorrhage. Bronchoalveolar lavage fluid contained almost exclusively red blood cells, with a small contingent of alveolar macrophages that were all Perls positive siderophages.

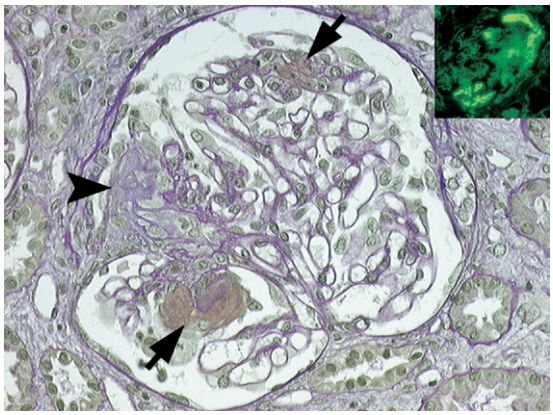

Figure 1. Necrotizing and crescentic glomerular lesions. By means of light microscopy, percutaneous renal biopsy specimen shows typical features of pauci-immune necrotizing glomerulonephritis: focal fibrinoid necrosis of the floculus (arrow) and crescentic cell proliferation (arrowhead) were seen in 50% of glomeruli. Fibrin deposition was seen by means of immunofluorescence (inset). (Masson trichrome stain; original magnification $\times$400; insert: antifibrin antibody.)

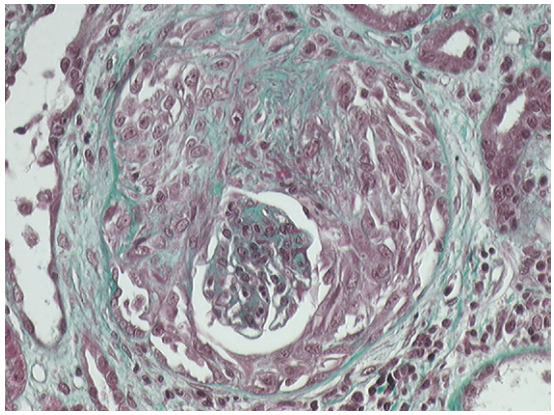

Figure 2. Large crescentic glomerular lesions. The figure shows a more severely injured glomerulus than in Fig 1, with a large crescentic cell proliferation. (Masson trichrome stain; original magnification $\times$400.)

Standard staining of the kidney biopsy specimen showed typical figures of extracapillary proliferation with segmental (Fig 1) or global crescents (Fig 2) and fibrinoid necrosis (Fig 1) in 50% of glomeruli. Cortical interstitium showed mild diffuse fibrosis with a mild mononucleated cell infiltrate and no significant vascular lesion. Endocapillary or mesangial proliferation was not reported. By means of immunofluorescence, antifibrin antibody showed segmental deposit in Bowman space (Fig 1 insert). There was weak mesangial IgA and C3 deposits, but no significant IgM, IgG, or C1q deposit (data not shown).

The patient therefore was given a diagnosis of ANCA-associated vasculitis, crescentic glomerulonephritis, and intra-alveolar hemorrhage that we attributed to prolonged D-penicillamine treatment.

Shortly after admission, the patient's condition worsened, with acute respiratory distress, high fever reaching 40ºC, and rapidly progressive renal failure (creatinine level to 2.4 mg/dL [210 μmol/L]). Oral zinc therapy was immediately substituted for D-penicillamine to control copper levels, and immunosuppression was started. The patient was administered 3 methylprednisolone daily pulses (500 mg/d), followed by 1 mg/kg/d of methylprednisolone orally, and a total of 7 monthly cyclophosphamide pulses (0.5 g/m^2). Ramipril, co-trimoxazole, vitamin D, and bisphosphonate therapies were started at the same time. The patient's condition rapidly improved, with apyrexia and normalization of respiratory condition within 48 hours of steroid treatment. Pleural and pericardial effusions resolved within 2 weeks. Weight progressively increased. Renal function normalized within 3 weeks (serum creatinine, 0.6 mg/dL [51 μmol/L]), hematuria disappeared within 4 months, and albuminuria decreased to albumin less than 1 g/d at 5 months and finally disappeared. Anemia corrected slowly with iron and folic acid supplementation after inflammation resolved. ANCAs remained positive for 3 months, and then definitively disappeared. Full remission was achieved after 6 months, and maintenance immunosuppressive therapy was started with mycophenolate mofetil. The steroid dosage was slowly de-