Successful Use of High Dose Intravenous Immunoglobulin in Rapidly Progressive Crescentic Glomerulonephritis with Vasculitis

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Rapidly progressive glomerulonephritis is a clinical entity characterized by extensive crescent formation and rapid deterioration of renal functions. In general, the prognosis is poor unless treatment is instituted early in the course of the disease (before serum creatinine has risen above 8 mg/ml). Steroids and cyclophosphamide are well accepted for the treatment of RPGN. Other modalities including trimethoprim-sulphametoxazol, intravenous immunoglobulin and cyclosporin have also been tried. Intravenous immunoglobulin contains anti-idiotypic antibodies to anti-neutrophil cytoplasmic antibodies, which may reduce ANCA activity. ANCA has been pathogenically implicated in activation of neutrophils and their degranulation.

We describe a patient who presented with RPGN accompanied by rapidly declining renal functions. Oral cyclophosphomide and prednisone treatment failed to reverse this condition. In spite of an initial poor prognosis of the disease, IVIG caused a dramatic improvement in the patient's renal function. The patient is under continuous follow-up by our department and her renal function has remained stable for 3 years.

Patient Description

A 68 year old previously healthy woman was admitted for investigation because of weakness, weight loss and anemia. Physical examination was normal.

Laboratory results on admission were as follows: urea 160 mg/dl, creatinine 5 mg/dl, urinary sediment with few red blood cells and no red blood cell casts; mild proteinuria (400 mg/dl), hemoglobin concentration 7.7–8.2 g/dl; complement levels were normal; C-ANCA was negative and P-ANCA was positive. Serology for hepatitis B and C viruses was negative; serum protein electrophoresis and bone marrow biopsy were normal. Computerized tomography of paranasal sinuses was normal. Ultrasonography showed relatively small kidneys (8.5–9 cm) with good differentiation of cortex and medulla.

Necrotizing crescentic glomerulonephritis was diagnosed by kidney biopsy, with total sclerosis of 5 glomeruli and crescent formation in 13 glomeruli, 6 of which disclosed fibrinoid necrosis and acute inflammation. The biopsy also revealed necrotizing vasculitis (artheriolythis) with severe inflammation of interstitium and focal atrophy of tubules. Immunofluorescence for immunoglobulins (IgG and IgA) was weakly positive with granular C3 deposits. Electron microscopy showed immune complexes in the mesangium of the glomeruli and a focus of necrotizing vasculitis (arteriolitis). Rapid deterioration of kidney function was observed with creatinine rising to 7.2 mg/dl.

Daily oral cyclophosphamide (3 mg/kg/day) and high dose steroid therapy was started, with improvement of renal functions (creatinine decreased from 7.2 to 4.0 mg/dl during the first 2 weeks of therapy), but during the next month creatinine levels rose, reaching 5.2–6.0 mg/dl. A 4 day course of high dose IVIG (Omr-IgG-am5%IV) of 0.5 g/kg/day was instituted, followed by improvement and stabilization of renal function (creatinine levels 3.8–3.9 mg/dl). Proteinuria remained mild. P-ANCA results after treatment were negative. Cyclophosphamide was continued for the next 6 months and then switched to azathioprine in order to reduce the risk of malignancy. The patient's follow-up was continued for the next 3 years and stable renal functions (creatinine levels 3.8–3.9 mg/dl) were recorded during this period.

Comment

Rapidly progressive glomerulonephritis is a well-known clinical syndrome associated with rapid and progressive decline in renal functions, and without treatment usually results in end-stage renal failure within weeks or months. The disease is characterized by crescent formation. The prognosis for RPGN is usually poor unless the treatment is initiated in the early course of the disease. Poor prognosis is observed with circumferential crescents in more than

ANCA = anti-neutrophil cytoplasmic antibodies
RPGN = rapidly progressive glomerulonephritis
IVIG = intravenous immunoglobulin

C-ANCA = cytoplasmic ANCA
P-ANCA = perinuclear ANCA

80% of the glomeruli together with extensive tubular atrophy. Steroids and cyclophosphamide are widely used for the treatment of crescentic glomerulonephritis; plasmapheresis may provide benefit mostly in type 3 RPGN (pauci-immune, ANCA-positive). Several studies on this issue failed to exhibit any particular advantages of plasmapheresis as compared to steroid therapy plus cyclophosphamide or azathioprine [1]. Only about half of the patients who responded favorably to treatment maintained stable renal functions. Other modalities have been tried, including trimethoprim-sulphametoxasol, methotrexate, intravenous immunoglobulin, monoclonal anti-T cell antibodies and cyclosporin.

High dose IVIG was used for the treatment of ANCA-associated systemic vasculitis (Wegener's granulomatosis, Churg-Straus vasculitis) by Richter et al. [2,3], with improvement of skin findings, but no amelioration of nephritis, pericarditis, conjunctivitis or scleritis. Other authors described dramatic improvement of ANCA-positive systemic vasculitis with glomerulonephritis after IVIG was used with concomitant reduction of serum ANCA titer [4].

Recently the role of antineutrophilic cytoplasmic autoantibody has been implicated as a pathogenic antibody associated with neutrophil degranulation and release of lytic enzymes [5]. IVIG contains anti-idiotypic antibodies to ANCA, which may diminish ANCA activity [2]. Antiproteinase-3 activity of high dose intravenous immunoglobulin *in vitro* was demonstrated by adding F(AB)2 fragments of IVIG to sera of patients with inhibition of antiproteinase-3 activity by 25%–70% [2]. However, the *in vitro* effect was not always accompanied by clinical improvement.

We present a patient with rapidly progressive crescentic glomerulonephritis accompanied by clinical and pathological findings suggesting a poor prognosis. Cyclophosphamide and high dose steroid therapy provided only temporary improvement, with subsequent rise in creatinine levels and deterioration of renal function. Owing to this regression in kidney efficiency, high dose intravenous globulin was introduced as rescue therapy and provided a prolonged stabilization in renal function despite the original poor prognosis when first presented.

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