Pediatr Nephrol (2003) 18:696–699
DOI 10.1007/s00467-003-1114-4

BRIEF REPORT

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Successful renal transplantation in a child with ANCA-associated microscopic polyangiitis

Received: 12 June 2002 / Revised: 11 December 2002 / Accepted: 17 December 2002 / Published online: 13 May 2003

Abstract Crescentic glomerulonephritis (CGN) is a clinicopathologic entity which is characterized by severe renal dysfunction of rapid onset with glomerular crescents. Type III CGN is associated with the absence of glomerular immune complex deposition (pauci-immune) and is associated with antineutrophil cytoplasmic antibody (ANCA). Microscopic polyangiitis and idiopathic pauci-immune necrotizing glomerulonephritis (NCGN) are strongly associated with ANCA directed against myeloperoxidase (anti-MPO). We describe here an unusual pediatric patient with MPO-ANCA-associated rapidly progressive glomerulonephritis (RPGN), emphasizing the management and outcome of the disease.

Keywords Rapidly progressive glomerulonephritis · Crescentic glomerulonephritis · Antineutrophil cytoplasmic antibody (ANCA) · Management · Renal transplantation

Introduction

Crescentic glomerulonephritis (CGN) is a clinicopathologic entity which is characterized by severe renal dysfunction of rapid onset with glomerular crescents. CGN may be a primary renal disease, termed idiopathic, or occur secondary to a wide variety of etiologic events and pathogenetic mechanisms. Primary forms of CGN have several pathogenetic subtypes. Type I is associated with anti-GBM autoantibodies. Type II is characterized by extensive immune complex deposition in the mesangium and capillary walls. These patients usually do not have anti-GBM antibodies or antineutrophil cytoplasmic antibody (ANCA). Type III is associated with the absence of glomerular immune complex deposition (pauci-immune) and is associated with ANCA. ANCA is positive in 80–90% of patients with primary pauci-immune crescentic glomerulonephritis [1, 2, 3, 4]. ANCA-associated small vessel vasculitides include Wegener granulomatosis, microscopic polyangiitis, renal-limiting microscopic polyangiitis, and Churg-Strauss syndrome. In patients with primary pauci-immune CGN, the presence of a necrotizing glomerular lesion, the demonstration of ANCA and the response to immunosuppressive agents suggest that this is a renal-limited form of microscopic polyangiitis even though patients often have constitutional symptoms [2, 3, 4].

We describe here an unusual pediatric patient with MPO-ANCA-associated RPGN, emphasizing the management and outcome of the disease.

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Case report

A 12-year-old girl was admitted to Hacettepe Children's Hospital with complaints of weakness, periumbilical abdominal pain, loss of appetite, nausea, vomiting, pallor and decreased urine output with hematuria. Her previous and family histories were uneventful, without consanguinity between parents. In her physical examination, the temperature was 37°C and blood pressure 110/60 mmHg. The skin was pale. The rest of her physical examination was normal. Laboratory findings were as follows: hemoglobin, 7.8 g/dl; white blood cell count, 7,300/mm^3; platelets, 240,000/mm^3; erythrocyte sedimentation rate, 120 mm/h. Urinanalysis showed 4+ proteinuria and 7 red blood cells/high-power field. Abnormal findings in the blood biochemistry were as follows: blood urea nitrogen (BUN), 51 mg/dl; creatinine, 5.84 mg/dl;

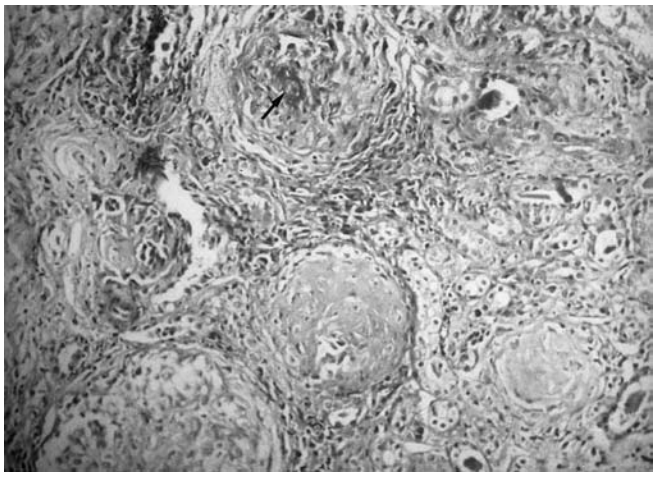

Fig. 1 One of the glomeruli is showing extensive crescent formation along with fibrinoid necrosis (*arrow*). The neighboring two glomeruli are progressing to global sclerosis. Periglomerular and interstitial mononuclear infiltration are also noted. Trichrome light green, ×100

uric acid, 5.9 mg/dl; total protein, 7.3 g/dl; albumin, 3.2 g/dl. Urinary protein loss was 87.5 mg/m^2/h. Creatinine clearance was 18 ml/min/1.73 m^2. Complement and quantitative immunoglobulin levels were all within normal limits. Cryoglobulin was negative. Microbiologic investigation was unremarkable. Serological studies for hepatitis B, C, other viruses, ANA, and anti ds-DNA were negative as well. Strong p-ANCA was obtained with indirect immunofluorescence (IIF) and was also confirmed by the high level of MPO-ANCA on ELISA (250 EU/ml, normal <20 EU/ml). c-ANCA was negative. Anti-GBM antibody was positive. Alpha-1 antitrypsin activity was normal. Chest X-ray was normal. Renal ultrasonography demonstrated normal-sized kidneys with increased echogenicity.

The clinical diagnosis before biopsy was rapidly progressive glomerulonephritis due to microscopic polyangiitis or Goodpasture syndrome. A renal biopsy was performed.

Renal biopsy findings

Renal biopsy included 17 glomeruli representing both cortex and corticomedullary junction. Glomeruli showed focal and segmental tuft necrosis and cellular or fibrocellular crescents (14/17) without any endocapillary proliferation. Some glomeruli demonstrated partial or global sclerosis with adhesions to Bowman's capsule. Tubules revealed hydropic changes with numerous red blood cells and hyaline casts. Edema and mild mononuclear inflammatory infiltration were noted in the interstitium. Immunofluorescence microscopy exhibited only fibrin deposits within necrotic areas and crescents (Fig. 1).

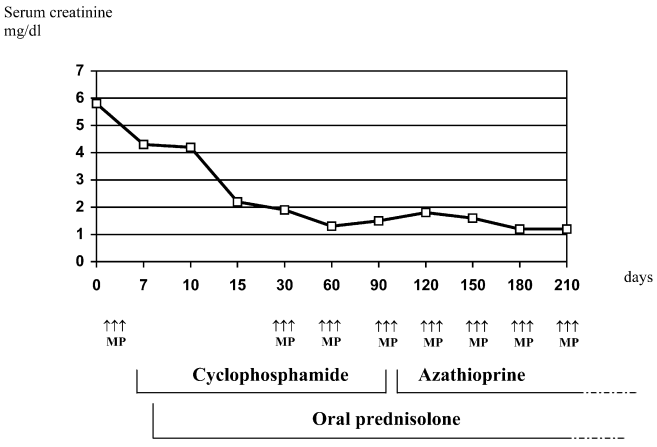

Fig. 2 Serum creatinine levels of the patient show progressive decrease parallel to the treatment

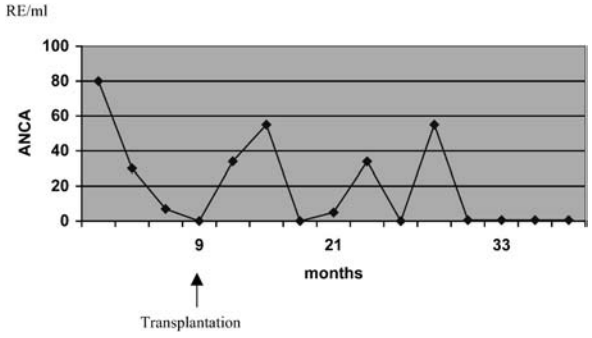

Fig. 3 ANCA levels of the patient after end stage renal failure (point 0 is for the initiation of hemodialysis)

Clinical course

After biopsy results were obtained, she was treated with pulse methyl prednisolone (1 g/day, for 3 days) and cyclophosphamide (2 mg/kg, p.o.). Prednisolone (45 mg/m^2, p.o.) was added 3 days later. Urine output was increased while serum creatinine levels decreased gradually (Fig. 2). She was discharged from the hospital on the 15th day. When she was admitted to our clinic 1 month later for the second course of pulse steroid, she complained of chest pain. Gallium-67 scintigraphy showed diffuse increased accumulation of gallium in the right lung compatible with diffuse inflammation. In addition, the visualization of the kidneys at the 48th hour after ^{67}Ga ingestion suggested bilateral renal inflammation. After infection was excluded with microbiologic and serologic investigations, the second pulse of methyl prednisolone (i.v. for

Table 1 Immunosuppressive regimen given for transplantation

Drug	Dose	Time	
Basiliximab (Simulect)	12 mg/m^2 (i.v.)	2 h before transplantation 4th day after transplantation	
Methyl prednisolone	500 mg (i.v.)	Intraoperative	
Prednisolone (Deltacortril)	80 mg (p.o.)	Postoperative	Tapered 10 mg/day for 2 months
Azathioprine (Imuran)	150 mg (i.v.)	Preoperative	
Mycophenolate mofetil (Cell-Cept)	1500 mg/day (p.o.)	Postoperative	
Cyclosporin A (Sandimmune)	2.5 mg/kg (i.v.)	Preoperative	
5 mg/kg (p.o.)	Postoperative		

3 days) followed by prednisolone (p.o) and cyclophosphamide (p.o.) was given. Three months later, cyclophosphamide was switched to azathioprine for 2 years with monthly pulse methyl prednisolone for 1 year. In her follow-up, anti-GBM antibody was negative. However, ANCA was usually positive and high in titer (Fig. 3). After azathioprine was stopped, serum creatinine rose gradually and hemodialysis treatment was started 6 years after the initial symptoms. Nine months later, she was transplanted successfully from a living related donor (father) while ANCA was negative. The immunosuppression protocol employed is given in Table 1. ANCA was negative for 3 years and recurrence of the disease in the graft was not seen.

Discussion

Small vessel vasculitides include microscopic polyangiitis (MPA), Wegener granulomatosis (WG) and Churg-Strauss syndrome [5]. The latter is very rare in childhood. The characteristic pathological lesion of both MPA and WG is idiopathic pauci-immune necrotizing glomerulonephritis (NCGN). The presented child was classified as having microscopic polyangiitis because of the clinical features and strong association with ANCA directed against myeloperoxidase (anti-MPO) as well as the lack of granulomatous inflammation during the long course and lack of upper respiratory tract involvement.

Experimental data suggest that ANCA and/or ANCA antigen related autoimmune responses are implicated in the pathophysiology of these vasculitic disorders. Neutrophils are important effector cells of tissue damage in ANCA-associated vasculitis and necrotizing crescentic glomerulonephritis [1]. Among those with a clinical presentation of rapidly progressive glomerulonephritis and a positive MPO-ANCA serology, the positive predictive value of finding a pauci-immune crescentic glomerulonephritis on renal biopsy was at least 98% in all age groups [2, 3]. Patients with small vessel vasculitis have a high frequency of ANCA that reacts with cytoplasmic constituents of neutrophils and monocytes. The predictive value of ANCA varied markedly depending upon the age and degree of renal disease at presentation. In microscopic polyangiitis, positive p-ANCA/MPO ANCA is seen in approximately 40–80% [4]. In Wegener granulomatosis one would expect a c-ANCA pattern and reaction against PR-3; however, a negative result does not exclude this diagnosis. In WG c-ANCA is present in 65% of the patients whereas p-ANCA was detected in up to 20% [6]. On the other hand in MPA, approximately 40–80% of patients have a positive p-ANCA/MPO-ANCA. Those with MPA and IIF ANCA staining but without anti-MPO antibodies most commonly have c-ANCA/PR3-ANCA [4]. WG was excluded in our patient not only due to lack of c-ANCA and the high level of MPO-ANCA but also because of the clinical features.

Idiopathic pauci-immune necrotizing glomerulonephritis was also not considered in the differential diagnosis due to the pulmonary involvement. In one series, 50% of patients with ANCA-positive glomerulonephritis had pulmonary disease ranging from severe life-threatening pulmonary hemorrhage to alveolar infiltrates [7]. Guillevin et al. have reported pulmonary disease in 24.7% of their vasculitis patients [4]. In our published series, 4 patients (15%) had pulmonary involvement in 26 patients with polyangiitis [3, 8].

Our patient also had anti-GBM antibodies. These antibodies have been found in 10–15% of patients with ANCA, almost all in the subgroup with antibodies to MPO [9]. It has been suggested that the anti-GBM response in these vasculitis patients may be secondary to damage to the GBM [9].

Most induction regimens still use oral prednisolone (1 mg/kg) and cyclophosphamide (2–3 mg/kg) depending on age, renal function and bone marrow reserve. In patients with rapidly progressive glomerulonephritis, pulse methyl prednisolone of 7–15 mg/kg daily for 3 days results in recovery of renal function even in those who are dialysis dependent. Pulse methyl prednisolone is also effective in the treatment of pulmonary hemorrhage. Pulse cyclophosphamide probably has no advantage over oral administration in the induction phase of aggressive disease [10, 11]. Mortality is increased in patients who present late, who have pulmonary hemorrhage or c-ANCA-associated disease or who are treated with corticosteroid alone [12]. In our patient we have used pulse and oral steroids along with oral cyclophosphamide that was switched to azathioprine after 3 months. We have tried to monitor the disease with the ANCA titers. The value of using ANCA assay to monitor the natural outcome of renal vasculitis and help in the early diagnosis of clinical relapses is controversial [13]. In most patients the titers decrease during effective immunosuppressive treatment, although in 22–55% who achieve remission, ANCA positivity persists at a low to intermediate titer [14]. Patients with a persistently elevated ANCA titer at clinical remission tend to have higher relapse rates [15]. In our patient, the ANCA titer correlated with clinical activity. The adverse renal outcome of this patient may be associated with the very high fibrous crescent formation of the initial biopsy.

Transplantation is a safe alternative therapy for children with MPA who enter ESRD. Results of kidney transplantation in patients with vasculitis are as good as in other patients [16]. The rate of relapse of vasculitis for patients on chronic dialysis and after transplantation was 0.09 and 0.02/patient/year, respectively [17]. Our patient is another example of successful transplantation in these children. It is possible that the immunosuppressive regimen employed for transplantation prevents recurrence of the disease. This patient has presented with a typical "adult" type microscopic polyangiitis. We suggest that for patients who develop ESRD in spite of treatment, transplantation is an effective alternative.

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