Glomerulonephritis associated with antibodies to neutrophil cytoplasm and glomerular basement membrane

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Summary: The prognosis for recovery of renal function of oligoanuric patients with anti-glomerular basement membrane disease is generally regarded as poor. Five patients are reported with dialysis-dependent renal failure in whom antibodies were present simultaneously both to neutrophil cytoplasm and glomerular basement membrane all of whom responded, at least initially, to immunosuppressive therapy and plasma exchange. Two of the 5 remain in clinical and immunological remission at 25 and 51 months of follow-up. We suggest that reversal of dialysis-dependent renal failure may be possible in some patients who display this dual antibody positivity.

Introduction

A number of patients have been identified in whom rapidly progressive renal failure secondary to crescentic glomerulonephritis is associated with antibodies to glomerular basement membrane and antibodies to neutrophil cytoplasmic antigens.^{1,2} It is unknown whether patients with this dual antibody positivity represent a subgroup of anti-glomerular basement membrane disease with a different pathogenesis and clinical outcome. We report 5 patients with dialysis-dependent renal failure in whom antibodies to glomerular basement membrane and neutrophil cytoplasm were present simultaneously.

Patients, methods and results

Clinical information is given in Table I. The patients (3 female, 2 male) ranged from 20 to 80 years of age. One of these patients (MP) has previously been reported by us.³ All 5 had oligoanuric renal failure which required dialysis within 5 days of referral to the Regional Nephrology Unit. Anti-glomerular basement membrane antibody titres were determined by radioimmunoassay and anti-neutrophil cytoplasmic antibodies detected by indirect immunofluorescence.⁴ In each case a cytoplasmic (cANCA) pattern of immunofluorescence was observed. Percutaneous renal biopsies were performed in 4 patients and crescentic glomerulo-

nephritis (defined as greater than 50% crescents) was demonstrated histologically in each case (Table II). In 3 of the 4, immunofluorescence showed linear IgG along the glomerular basement membrane. There was no evidence of granulomata on any biopsy neither were vasculitic lesions seen on histology (Table II).

Initial treatment consisted of immunosuppression (cyclophosphamide 3 mg/kg, prednisolone 1 mg/kg) and plasma exchange in all cases. One patient (80 year old male), withdrew voluntarily from active treatment and died from acute renal failure 2 weeks after referral. The remaining 4 patients all recovered self-supporting renal function accompanied by a return of anti-glomerular basement membrane and anti-neutrophil cytoplasmic antibodies to the normal range. At follow-up (24–51 months, mean 31 months), 2 patients remain well with creatinine clearances of 66 ml/min and 27 ml/min, respectively. The remaining 2 patients were intolerant of cyclophosphamide because of bone marrow suppression and this resulted in a suboptimal dosage for immunosuppression; both patients progressed to end stage renal disease within 5 months (in one, TM, associated with a recrudescence of antibody to glomerular basement membrane) and are now receiving maintenance haemodialysis. Subsequent auto-antibody serology in all 4 patients has been persistently negative.

Discussion

The prognosis for recovery of renal function in oligoanuric patients with anti-glomerular base-

Table I

			<i>Creatinine ($\mu\text{mol/l}$)</i>	<i>Current</i>	<i>Duration</i>	
<i>Patient</i>	<i>Age</i>	<i>Symptoms</i>	<i>Presentation</i>	<i>(lowest)</i>	<i>of dialysis</i>	<i>Outcome</i>
MP	37	Renal	435	105	4 weeks	Reversal of ARF
NC	80	Renal	688	–	–	Death from ARF
		Respiratory				
TM	45	Renal	1,460	(350)	6 weeks	Progression to HD within 5 months
		Skin				
MM	20	Renal	1,590	(463)	3 weeks	Progression to HD within 3 months
		Respiratory				
EM	57	Renal	638	250	5 weeks	Reversal of ARF
		Respiratory				

ARF = Acute renal failure; HD = haemodialysis.

Table II

<i>Patient</i>	<i>ANCA*</i>	<i>GBM† (%)</i>	<i>Renal biopsy (% crescents)</i>	<i>Histopathology</i>	<i>Immunofluorescence (IgG)</i>
MP	1/640	84	55	'Exploding' crescents, interstitial inflammation, patchy tubular necrosis	Strongly positive linear staining along GBM
NC	1/160	70	No biopsy	—	—
TC	1/80	155	95	Diffuse cellular crescents, interstitial inflammation, tubular necrosis	Strongly positive linear staining along GBM
MM	1/640	57	100	Half crescents cellular, half fibrous, intense interstitial inflammation, patchy tubular injury	No definite linear IgG but much glomerular destruction
EM	1/640	40	90	Diffuse crescentic GN, many fibrous, patchy interstitial infiltrate, no tubular necrosis	Very weak linear staining along GBM

*ANCA = Anti-neutrophil cytoplasmic antibody titre at presentation; †GBM = anti-glomerular basement membrane antibody titre at presentation; GN = glomerulonephritis; GBM = glomerular basement membrane.

ment membrane disease is generally regarded as poor.⁵ Anti-neutrophil cytoplasmic antibodies are described as a serological marker of systemic vasculitis⁶⁻⁸ and their presence in patients with anti-glomerular basement membrane disease may point to coincidental vasculitis contributing to the pathogenesis of renal impairment. Although only one of our patients had clinical evidence of disease outside the renal and pulmonary systems, in a recent review of antibodies to glomerular basement membrane and neutrophil cytoplasm in rapidly progressive glomerulonephritis, 12 of 20 (60%) patients had extra renal/pulmonary disease.² Only 3 of 11 patients in this latter study who were

initially dialysis-dependent recovered self-supporting although impaired renal function, while 4 of the 11 succumbed to the disease. In our experience subjects with rapidly progressive glomerulonephritis who have antibodies to both neutrophil cytoplasm and glomerular basement membrane form a subgroup of dialysis-dependent patients who respond, at least initially, to immunosuppression and plasma exchange. Recovery of renal function in the dialysis-dependent patients described here was considered possible as biopsy appearances indicated some potentially viable glomeruli and tubulo-interstitial scarring was not established.

Intolerance of cytotoxic therapy with failure to maintain disease suppression may have contributed to the subsequent loss of renal function in 2 of the 5 patients reported.

We suggest that reversal of dialysis-dependent renal failure is possible in some patients with crescentic glomerulonephritis in whom antibodies are present to both neutrophil cytoplasm and glomerular basement membrane.

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