Original articles

Vasculitis and rapidly progressive glomerulonephritis in the elderly

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Summary

The proportion of patients with vasculitis and rapidly progressive nephritis aged 70 years or over has risen from about 10% in the 1980s to over 30% in series reported in the 1990s. This study was undertaken to examine the presentation and outcome of such older patients. Seventeen of 56 patients (30%) who presented at two renal units were aged 70 years or over. Mean creatinine level at presentation was 530 $\mu\text{mol/l}$, and five patients received dialysis at presentation. Outcome was dependent on three factors, namely co-morbid pathology, response to immunosuppressive therapy, and the occurrence in three cases of temporary spontaneous partial remission. Overall patient survival at one and two years was 62.5% and 50%, respectively, and 90% and 100% of surviving patients were independent of dialysis at one and two years, respectively. Response to chemotherapy was excellent, with full rehabilitation in many cases and no deaths directly attributable to adverse effects of immunosuppressive therapy. We conclude that diagnosis of vasculitis and rapidly progressive glomerulonephritis by renal biopsy and the subsequent administration of chemotherapy (including cyclophosphamide in many cases) resulted in a worthwhile benefit in these elderly patients.

Keywords: vasculitis, glomerulonephritis, cyclophosphamide, elderly patients

It is increasingly recognised that rapidly progressive glomerulonephritis with vasculitis occurs in elderly patients. In three British series published in the mid 1980s, only 15 of 132 patients (11%) were aged over 70 years,^{1–3} and in some series no patient was aged over 70 years.^{4,5} However, in three recently published series of patients suffering from Wegener's granulomatosis or rapidly progressive glomerulonephritis, 28 out of 86 patients (33%) were aged over 70 years.^{6–8} In a survey of patients with Wegener's granulomatosis and polyarteritis performed by the European Dialysis and Transplant Association in 1991, over 20% of patients were aged over 65 years.⁹

It has not been shown, however, whether or not the increased frequency of diagnosis of

these conditions in elderly patients is associated with a worthwhile outcome. Significantly worse survival in older patients has been reported by several groups,^{3,7,10} and in one series there was a mortality of 41% in patients aged over 50.³ More recently a mortality of 36% in patients aged over 70 years was reported in one series,⁷ and of 56% in another.⁸

The aim of this study was to describe the presentation and outcome of vasculitis and rapidly progressive glomerulonephritis in elderly patients, with particular attention to the risks and benefits of immunosuppressive therapy.

Patients and methods

Patients presenting to the Renal Units at King's College Hospital (Dulwich) and at the Withington Hospital between January 1991 and December 1993 inclusive were included if there were systemic vasculitis or a proliferative glomerulonephritis with crescents. Patients with anti-glomerular basement membrane disease were excluded, although those with vasculitis associated with both anti-glomerular basement membrane antibodies and anti-neutrophil cytoplasmic antibodies (ANCA) were included. One patient (case 17) will be the subject of a separate publication.

Data were recorded retrospectively on a standard data acquisition sheet in both centres. ANCA were measured in both centres by standard indirect immunofluorescence techniques. Cytoplasmic (cANCA) and perinuclear (pANCA) antibodies were distinguished according to immunofluorescent staining patterns, and the presence of pANCA confirmed by ELISA if strongly positive antinuclear antibodies (ANA) were present.

Prednisolone was given in both centres at a dose of 40–60 mg/day, tapering to 10 mg/day by three months. Cyclophosphamide was given as 3–4 weekly intravenous pulses at the Withington Hospital, and at King's College from mid-1993. The dosage was 0.8 g/m², reduced to 0.5 g/m² if there was renal failure (plasma creatinine > 250 $\mu\text{mol/l}$). These dosages were halved in frail patients over 65 years. Prior to this date at King's College, cyclophosphamide was given by mouth at a dose of 2–2.5 mg/kg daily. The doses of oral and pulse intravenous cyclophosphamide were adjusted according to the total peripheral white cell count. In three cases at King's College,

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induction immunosuppression was given using azathioprine at a daily dosage of 1.5–2 mg/kg. Prednisolone and either cyclophosphamide or azathioprine were administered by mouth as maintenance therapy after the induction phase in both centres.

Results

Of 56 patients fulfilling the inclusion criteria, 17 (30%) were aged 70 years or more. There were no systematic differences between the two centres in presentation or outcome. Six of 19 patients (32%) at King’s College were aged 70 years or over, compared with 11 of 37 (30%) at the Withington Hospital. Presenting features are shown in the box. All had multisystem disease. Over half the cases had evidence of pulmonary involvement, with fibrosis in two cases and haemorrhage in seven cases. The mean creatinine level on presentation was 530 (range 114–971) $\mu\text{mol/l}$.

INVESTIGATIONS

These are shown in table 1. Twelve patients (71%) were ANCA-positive (seven cANCA; four pANCA; one not characterised). Case 10 did not have a crescentic or necrotising glomerulonephritis on renal biopsy. However, there was a mesangial proliferative glomerulonephritis and the patient also presented with pulmonary haemorrhage, a vasculitic skin rash and a strongly positive cANCA. The clinical diagnosis was Wegener’s granulomatosis, and although there was minimal renal involvement this case fell within the inclusion criteria for this study.

TREATMENT AND OUTCOME

Table 2 shows induction immunosuppression given in the first three months, together with outcome at three months and latest follow-up. Actual patient survival is shown in the figure.

Three patients (18%) had a spontaneous partial remission with improvement in renal

Presenting features of patients (n = 17)	
Mean age (years)	74.4 (range 70–81)
Male:female	9:8
Haematuria (%)	100
Elevated creatinine (%)	94
Creatinine > 500 $\mu\text{mol/l}$ (%)	47
Organ systems involved (%)	
respiratory tract	53
joints	53
skin	35
gastrointestinal tract	13
nervous system	12

function before chemotherapy was given, compared with only one such case in the 39 cases (3%) aged less than 70 years seen in our units in the same time period. The plasma creatinine levels fell from 347 to 280 $\mu\text{mol/l}$ (case 3); from 880 to 550 $\mu\text{mol/l}$ (case 11); and from 738 to 601 $\mu\text{mol/l}$ (case 13). However, in all three cases the plasma creatinine rose over the next year of follow-up, to 350, 697 and 1060 $\mu\text{mol/l}$, respectively, despite the administration of prednisolone and azathioprine to case 3. The case in the younger age group with a spontaneous partial remission also experienced a steady decline in renal function after an initial improvement, and became dialysis dependent within two years of presentation.

RENAL BIOPSIES

Biopsy findings are summarised in table 1. The proportion of glomeruli that were sclerosed was a good predictor of outcome of renal function, with active disease (cellular crescents and necrotising glomerulonephritis) being poor predictors of outcome. Of the six patients with greater than 33% glomerulosclerosis on biopsy, four (67%) developed end stage renal failure within nine months, compared with one of the 11 (9%) patients with 33% glomerulosclerosis or less.

Table 1 Results of immunological testing and renal biopsy

Case number	Presenting creatinine ($\mu\text{mol/l}$)	ANCA	GBM	ANA	Glomeruli (%)					Immunofluorescence	Vasculitis
					Sclerosed	Crescentic	Necrotising				
1	618	–	–	–	12	0	3		–		+
2	369	cANCA	–	+	50	39	–		IgG, IgM, C3		–
3	347	cANCA	–	+	17	6	17		–		–
4	528	–	–	+	17	17	10		IgG, IgM C3		+
5	840	cANCA	–	–	61	30	21		C3		–
6	460	pANCA	–	–	38	25	25		IgG, IgM, C1q, Fib		–
7	184	cANCA	+	+	50	56	56		–		–
8	432	pANCA	–	–	20	30	95		IgM, C3, C1q, Fib		–
9	971	pANCA	–	–	70	8	0		IgG, IgM, C3, C1q		–
10	114	ANCA	ND	–	0	0	0		–		–
11	880	–	–	+	33	6	0		IgM, C3		–
12	318	–	–	–	6	0	0		IgA, C3		+
13	738	cANCA	–	–	17	+	0		IgM, C3, C1q		–
14	232	ND	ND	ND	10	10	100		ND		+
15	866	cANCA	–		6	17	+		–		+
16	750	pANCA	–	+	64	21	+		–		–
17	360	cANCA	+	+	16	52	+		ND		+

ND = not done; vasculitis = extraglomerular arterial vasculitis seen on histopathological examination of the kidney; GBM = glomerular basement membrane

Figure Actual patient survival. Number on follow-up at 12 months = 16; number at 24 months = 10

Immunofluorescence showed that six patients had a ‘pauci-immune’ glomerulonephritis, and there was a variety of patterns of immunoglobulin and complement deposition in the other biopsies (table 1).

Discussion

The increased proportion of elderly patients with crescentic glomerulonephritis and progressive renal failure compared with reports from the 1980s could reflect either a higher incidence of disease or an increased rate of diagnosis, we suspect the latter. This may be due to an increased referral rate of elderly patients to renal units, and also to the wider availability of the ANCA test to screen patients with renal failure for vasculitis.¹¹

PRESENTATION

These elderly patients had evidence of multi-system vasculitis in the majority of cases, and the majority also had a positive ANCA test. Both these features were similar to the younger cases in this series, and to previous reports in the literature.^{1,3,12,13} Screening for the presence

of multisystem vasculitis can be performed simply by testing the urine for blood (all patients in this series were dipstick positive for blood in the urine), measuring renal function and testing for ANCA. However, it should be noted that ANCA are not always present, even in patients with active multisystem or pulmonary disease. There was a high incidence of pulmonary vasculitis in these elderly patients, with either pulmonary haemorrhage or fibrosis. The possibility of vasculitis should therefore be addressed carefully in any patient with haemoptysis or unexplained abnormality in the lungs.

CO-MORBID DISEASE AND OUTCOME

Co-morbid disease caused more deaths than vasculitis in this series, although in many cases this was because co-morbid disease determined a patient’s suitability for renal replacement therapy. It should be remembered when assessing such patients that some apparently co-morbid conditions (such as arthritis, breathlessness or cerebrovascular disease) could be due to multisystem vasculitis, and thus potentially respond well to treatment.

SPONTANEOUS PARTIAL REMISSION

It is increasingly recognised that most cases of systemic vasculitis with renal involvement run a chronic course, and relapse with worsening of renal failure may occur even after many years of follow-up.¹⁴ However, we observed three cases in this series with a spontaneous improvement

Differential diagnoses in acute kidney failure

- rapidly progressive glomerulonephritis
- acute tubular necrosis with associated sepsis
- bacterial endocarditis
- acute interstitial nephritis
- multiple myeloma
- cholesterol embolisation

Table 2 Treatment and outcome of patients aged 70 years or over with vasculitis and rapidly progressive glomerulonephritis

Case number	Induction immunosuppression				At 3 months		Latest follow-up	Cause of death
	Pred	Aza	Cyclo	PE	dialysed	outcome		
1	+	+	–	–	–	dead		stroke
2	+	+	–	–	+	dialysis	died at 23 months	diverticular disease
3	+	+	–	–	–	Cr = 171	Cr = 174 at 18 months	
4	+	–	+	–	+	Cr = 217	died at 18 months	heart failure
5	+	–	+	–	+	Cr = 340	Cr = 487 at 28 months	
6	+	–	+	–	–	Cr = 164	died at 24 months	myocardial infarction
7	+	–	+	+	–	Cr = 140	died at 5 months	multisystem vasculitis
8	+	–	+	–	–	Cr = 277	Cr = 190 at 25 months	
9	+	–	+	+	–	dead		dementia (not dialysed)
10	+	–	+	+	–	Cr = 120	Cr = 139 at 27 months	
11	–	–	–	–	–	Cr = 550	on dialysis at 41 months	
12	+	–	–	–	+	dead		gastrointestinal bleed
13	–	–	–	–	–	Cr = 601	died at 9 months	frailty (not dialysed)
14	–	–	–	–	–	dead		carcinoma lung
15	+	–	+	–	+	Cr = 320	Cr = 174 at 12 months	
16	+	–	–	–	–	dead		arthritis (not dialysed)
17	+	–	+	–	–	Cr = 256	Cr = 250 at 18 months	

Cr = creatinine (μmol/l); Pred = prednisolone; Aza = azathioprine; cyclo = cyclophosphamide; PE = plasma exchange

in renal function, associated with renal biopsy appearances of an inactive or 'burnt out' crescentic glomerulonephritis. This occurred more often in the elderly patients in this series than in those aged less than 70 years (three out of 17 compared with one out of 39, respectively). Whether this is due to a tendency for autoimmune disease to be less aggressive in elderly patients, or whether milder disease was diagnosed more frequently in these elderly patients is not clear from our data.

Importantly, all four patients with a spontaneous partial remission subsequently experienced a decline in renal function, with two reaching end-stage renal failure. This may have been due to low-grade disease activity, or to progressive tubular atrophy in scarred kidneys. Long-term follow-up is therefore essential in patients who have apparently improved spontaneously, with continual monitoring of disease activity and renal function.

IMMUNOSUPPRESSIVE TREATMENT

The response to induction immunosuppression in these patients was excellent, with good medium-term preservation of renal function in surviving patients (table 2). Furthermore, there were no serious side-effects from immunosuppressive therapy, although the steroid dosage was tapered more rapidly than is our normal practice in younger patients. Furthermore the course of pulse intravenous cyclophosphamide was shorter and given at a lower dose than in younger patients.

Although there may be reservations about the use of powerful cytotoxic drugs in the elderly, it has clearly been shown that prednisolone alone is generally ineffective in the treatment of Wegener's granulomatosis with renal failure, and the same probably applies for other types of systemic vasculitis with necrotising or crescentic glomerulonephritis.^{13,15} Therefore we believe that cyclophosphamide should be used in patients with active renal involvement, whatever their age.

Although a diagnosis of vasculitis with renal failure may be probable on clinical grounds, it is our practice to perform renal biopsy in all

Summary/learning points

- 30% of renal vasculitis cases are over 70 years
- renal biopsy is required for diagnosis
- treatment response may be excellent, even in the elderly
- rapid diagnosis improves outcome

cases before giving cyclophosphamide. Thus we can confirm the diagnosis and determine the degree of scarring in the kidney and hence the likely benefit from intensive immunosuppressive therapy. It has previously been suggested that patients presenting with advanced renal failure have a particularly poor outcome.^{7,16} However, in this series the renal biopsy appearances provided a better indication of prognosis than the presenting creatinine level.

DIALYSIS

In this series nine of the 17 elderly patients developed renal failure to a degree such that dialysis was necessary for relief of symptoms. Only three cases were unsuitable for dialysis because of co-morbid pathology. In the other six cases, three patients required dialysis at presentation but later recovered renal function, and two patients were successfully treated with outpatient maintenance dialyses. One patient who required dialyses at presentation died soon after from acute gastrointestinal haemorrhage.

We conclude that, even in elderly patients, dialysis may result in a successful outcome and patients should be referred to a specialised unit for assessment when renal failure is present.

Summary

In conclusion, it seems that the improvement in outcome for patients with systemic vasculitis first noted in the 1980s for younger patients¹⁰ can now be applied to the elderly. Intensive treatment including renal biopsy, dialysis and cyclophosphamide treatment can be used successfully in many such cases.

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