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Focal segmental necrotizing glomerulonephritis in rheumatoid arthritis

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Summary

We report ten patients with rheumatoid arthritis (RA) who developed a focal segmental necrotizing glomerulonephritis (FSNGN) and extracapillary proliferation typical of vasculitic glomerulonephritis. Five patients also had extrarenal vasculitis. Renal presentation was with renal impairment ($n=9$) (median creatinine 726 µmol/l, range 230–1592 µmol/l), microscopic haematuria ($n=8$) and proteinuria ($n=10$). Nine patients were seropositive for rheumatoid factor and nine had bone erosions. Serum from four of five patients tested by indirect immunofluorescence was positive for anti-neutrophil cytoplasmic antibody (ANCA) with perinuclear staining. Only three patients had penicillamine or gold therapy. Treatment was with prednisolone and cyclophosphamide (six patients, two of whom were also plasma-exchanged), prednisolone and azathioprine (two patients) and prednisolone alone (two patients). There was a marked improvement in renal function in eight patients. Two patients with dialysis-dependent renal failure recovered renal function, although in one patient this was transient and she required further dialysis 4 months later. Two other patients progressed to dialysis at 3 months and 1 year respectively. Four patients died, one remains dialysis-dependent, and four continue to have good renal function at 5 year follow-up (median creatinine 148.5 µmol/l, range 120–193 µmol/l). One patient was lost to follow-up at 5 years. FSNGN should be considered in all patients with RA and renal impairment, proteinuria and/or microscopic haematuria. This diagnosis appears to be more likely in patients with clinical extrarenal vasculitis, bone erosions or who are seropositive. In these cases, an urgent renal biopsy is indicated.

Introduction

Renal vasculitis complicating RA appears to be rare, and there are few data on its presentation, treatment and outcome. Systemic rheumatoid vasculitis is a well recognized complication of RA, and the clinical features include nail-fold infarcts, skin ulceration, a purpuric rash and/or neurological involvement with mononeuritis multiplex. Data from one health district in the UK (Norwich Health Authority) suggests an overall incidence of systemic rheumatoid vasculitis of 12.5/million population[1].

Although renal disease is reported to be present in approximately one quarter of patients with systemic rheumatoid vasculitis,[2] there is little information available on renal histology in these patients. An autopsy study by Boers *et al.* of 132 patients with rheumatoid disease found a large-vessel renal vasculitis in eight out of a total of 18 cases with systemic vasculitis and in four patients there was an extracapillary proliferative glomerulonephritis.[3] There are a few case reports of a necrotizing and crescentic glomerulonephritis ascribed to patients with rheumatoid arthritis.[4–6] Similar glomerular lesions have also

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been reported in patients with rheumatoid arthritis and other disorders who were treated with D-penicillamine,[7–11] although the typical lesion associated with D-penicillamine is membranous nephropathy. We report data on ten patients with RA and FSNGN.

Methods

Between 1980 and 1994, 112 patients with RA and renal disease had a renal biopsy at our centre. We reviewed the renal histology on these patients and selected for further analysis those with FSNGN with or without extracapillary proliferation.

Patients

A total of ten patients were identified; five male and five female. All patients fulfilled the 1987 American Rheumatological Association criteria for RA. The diagnosis of a systemic rheumatoid vasculitis was based on the presence of a purpuric rash, deep skin ulceration, scleritis, mononeuritis multiplex and/or digital and nail-fold infarcts (as described by Scott and Bacon[2]).

Investigations

Renal biopsies were fixed in formol–saline, embedded in paraffin wax, and serially sectioned to give six to eight sections on each of ten numbered slides. Two slides at the end of the series were stained with haematoxylin and eosin, two adjacent slides with periodic acid–methenamine silver and two with haematoxylin–van Gieson and Congo red.

The others were stained as required. Extra sections were cut for immunoperoxidase staining for IgG, IgA, IgM and C3.[12] Acute vasculitic lesions were defined as areas of disruption of glomerular capillary loops with thrombosis and accumulation of cells in Bowman's space. Healed vasculitic lesions were defined as sharply outlined scarred areas in glomeruli affecting both the tuft and Bowman's space.[13,14] Vasculitis associated with IgA nephropathy, anti-glomerular-basement-membrane antibodies, systemic lupus erythematosus, infective endocarditis and cryoglobulinaemia were excluded by pathological, clinical and serological findings.

Bone erosions were defined by standard radiological criteria. Laboratory tests performed at the time of biopsy included serum creatinine and albumin. Rheumatoid factor (RF) was measured by the sheep red-cell agglutination test. Anti-nuclear antibody (ANA) was detected by indirect immunofluorescence and antibodies to double stranded (ds) DNA by a modified Farr assay. Anti-neutrophil cytoplasmic antibodies (ANCA) were detected by indirect immunofluoresence on ethanol-fixed neutrophils.

Treatment

Six patients were treated with oral prednisolone and cyclophosphamide, with the cyclophosphamide converted to azathioprine at 3 months. Two of these patients also received plasma exchange. Two patients were treated with prednisolone and azathioprine and two patients received prednisolone only.

Table 1 Clinical features

Patient	Age/sex	Duration of RA	Treatment prior to diagnosis	Erosions	Extra-renal features of vasculitis
1	54/M	1	Chloroquine	Y	Digital infarcts
2	63/M	2	NSAID	Y	Purpuric rash
3	59/F	25	NSAID Penicillamine Prednisolone	Y	Nil
4	69/F	16	Chloroquine Salazopyrine	Y	Scleritis, pulmonary Haemorrhage
5	64/F	2	NSAID	N	Cutaneous ulcer Nail-fold infarct Colonic vasculitis
6	64/M	22	NSAID	Y	Nil
7	69/F	20	NSAID	Y	Nil
8	57/M	15	Prednisolone Sulphasalazine Gold	Y	Nil
9	28/F	4	NSAID	Y	Nil
10	44/M	13	NSAID	Y	Purpuric rash

Results

Clinical features (Table 1)

The median age at diagnosis was 61 years (range 28–69 years) and the median duration of arthritis was 12 years (range 1–25 years). Nine patients had bone erosions and five patients had evidence of systemic rheumatoid vasculitis. One patient had received gold and two penicillamine in the three months prior to diagnosis. Eight patients were on a non-steroidal anti-inflammatory drug (NSAID), one on cyclophosphamide and prednisolone, and two each on steroids and salazopyrine at the time of diagnosis.

Renal presentation (Table 2)

All 10 patients had proteinuria and eight had microscopic haematuria. As measured by serum creatinine, nine patients had renal impairment, and of these two had dialysis-dependent renal failure. Median serum creatinine at presentation was 638 μmol/l (range 105–1592 μmol/l).

Table 2 Renal presentation

Patient	Creatinine (μmol/l)	Urinalysis (g/l)	Serum albumin (g/day)	Urine protein
1	425	MH/P	33	1.2
2	550	P	30	NA
3	1592	MH/P	28	NA
4	997	MH/P	NA	NA
5	1108	MH/P	25	1.1
6	852	MH/P	24	2.9
7	726	MH/P	25	0.6
8	105	P	42	0.64
9	367	MH/P	31	NA
10	230	MH/P	26	6.2

MH, microscopic haematuria; P, proteinuria; NA, not available.

Immunology (Table 3)

Nine patients had a positive rheumatoid factor and 6/9 patients tested had a positive ANA. No patient had anti-ds DNA antibodies. In one patient the serum C3 was low; C4 was normal in all patients tested. ANCA with a perinuclear staining pattern was present at a 1 : 25 serum dilution or greater in four of the five patients tested.

Pathology (Table 4)

Nine patients showed evidence of active vasculitic lesions within the glomeruli, seven of these patients had both acute and healed vasculitic lesions. Two patients had acute active vasculitis (patients 3, 7), one had mostly healed lesions (patient 1), three had a mixture of active vasculitis and chronic renal damage (patients 2, 5, 8), four patients had mainly chronic damage shown by a high proportion of globally sclerosed glomeruli with tubular atrophy and interstitial fibrosis (patients 4, 6, 9, 10). Three patients had glomerular abnormalities as well as vasculitis, namely, membranous nephropathy (patient 2), secondary or AA amyloid (patient 5) and mild diabetic glomerulopathy (patient 6).

Treatment and outcome (Table 5)

Treatment given to these patients after diagnosis of their renal lesion is summarized in Table 5. Renal function improved in seven of the nine patients who presented with impaired renal function. Two patients (3 and 5) were dialysis-dependent at the time of presentation. Both recovered renal function and

Table 3 Immunology

Patient	RF	ANA	anti-dsDNA	C3 (g/l)	C4 (g/l)	ANCA
1	1 : 512	− ve	− ve	1.2	0.23	NA
2	− ve	1 : 100	− ve	0.9	0.34	NA
3	1 : 32	1 : 400	− ve	0.68	0.34	NA
4	+ ve	− ve	− ve	0.99	0.46	pANCA Strong
5	1 : 256	1 : 40	− ve	0.85	0.42	NA
6	1 : 256	1 : 40	− ve	0.98	0.50	Weak + ve
7	1 : 128	1 : 25	− ve	1.35	0.43	− ve
8	1 : 256	1 : 40	− ve	1.15	0.39	Weak + ve
9	+ ve	NA	NA	NA	NA	NA
10	+ ve	− ve	− ve	1.0	0.29	1 : 400 pANCA

RF, rheumatoid factor; ANA, anti-nuclear antibody; Anti-dsDNA, anti-double stranded DNA antibodies; ANCA, anti-neutrophil autoantibodies; NA, not available.

Table 4 Renal biopsy findings

Patient	Number of glomeruli	Globally sclerosed glomeruli	Glomeruli with active vasculitic lesions	Glomeruli with healed vasculitic lesions	Tubular changes	Interstitial changes	Vascular changes	Summary of findings
1	14	1	1	5	Acute damage	Slight	Chronic arterial thickening	Mostly healed vasculitis, no chronic damage
2	44	15	7	3	Acute damage	Fibrosis	Chronic arterial thickening	Also has membranous nephropathy; mixture of active vasculitis and chronic damage
3	4	0	4	0	Acute damage	Slight	Slight	Acute vasculitis; repeat biopsy 2/12 later showed only healed lesions
4	16	12	2	2	Atrophy	Fibrosis	Slight	Mostly chronic damage
5	20	3	3	9	Acute damage	Fibrosis	Chronic arterial thickening	Also has AA amyloid; mixture of active vasculitis and chronic damage
6	42	24	2	3	Acute damage	Fibrosis	Fibrinoid necrosis	Also has mild diabetic glomerluronephropathy
7	1	0	1	0	Acute damage	Interstitial nephritis	Slight	Acute vasculitis
8	32	7	2	0	Mild atrophy	Slight	Chronic arterial thickening	Mild active vasculitis
9	52	15	5	22	Acute damage	Fibrosis	Chronic arterial thickening	Mostly chronic damage; repeat biopsies 3 m and 14 m later showed no active vasculitis
10	13	9	0	0	Atrophy	Fibrosis	Slight	Severe chronic damage

Table 5 Treatment and outcome

Patient	Initial creatinine (μmol/l)	Treatment	Creatinine (μmol/l)		
			3/12	1 year	5 years
1	425	P, C	200	167	120
2	550	P, A	190	210	550, died at 6 yrs
3	1592	P, C	199	210	193
4	997	P, C, PX	dialysis	died at 18/12	
5	1108	P, A	396	died at 15/12	
6	852	P, C, PX	209	186	NA
7	726	P, C	198	197	172
8	105	P	105	112	125
9	367	P, A	701	dialysis	
10	230	P, C	279	413	died at 18/12

P, prednisolone; C, cyclophosphamide, changed at 3 months to azathioprine; A, azathioprine; PX, plasma exchange.

came off dialysis with treatment. At 3 months the serum creatinine of patient 3 had fallen to 199 μmol/l, and this has remained stable over long-term follow-up. The serum creatinine in patient 5 fell to 396 μmol/l at 2 months; however her renal function then declined and four months after diagnosis she commenced maintenance dialysis. Her renal biopsy had shown a late vasculitic GN and amyloid. In two patients (cases 4 and 9) renal function continued to deteriorate despite treatment and both required maintenence dialysis at 3 and 12 months respectively. Their renal biopsies had showed severe chronic damage. Extra renal vasculitis in the five patients affected resolved with treatment and there have been no relapses of this.

Deaths

There were four deaths, two of which were caused by infection. Patient 2 died of septic shock 6 years after diagnosis. He had been maintained on prednisolone and azathioprine since diagnosis. Patient 10 died of a cerebral abscess 18 months after the diagnosis. He was on prednisolone 10 mg a day. Patient 4 died of a stroke. Patient 5 died suddenly following a pacemaker implant 15 months after diagnosis.

Discussion

All the patients in this study had typical RA as defined by the 1987 American College of Rheumatology criteria. Rheumatoid factor was present in the serum of nine patients and nine patients had bone erosions. Five patients had systemic vasculitis. Although six patients had a positive ANA these were mostly at low titre, and none had anti-ds DNA antibodies. These features indicate a diagnosis of rheumatoid arthritis and not systemic lupus erythematosus. Nine patients had a vasculitic glomerulonephritis with a segmental necrotizing and thrombosing glomerulonephritis and crescent formation, and one had healed vasculitic lesions. These features are typical of the vasculitic glomerulonephritis seen in ANCA-associated diseases such microscopic polyangiitis (polyarteritis) (MPA) and Wegener's granulomatosis (WG).[14] Although renal abnormalities are found in about 25% of patients with rheumatoid vasculitis,[2] there are few reports of renal vasculitis in these patients (Table 6). Kuznetsky *et al.*[4] reported four patients with RA and a segmental necrotizing GN of the vasculitic type. All four patients had a long history of RA with bone erosions, active synovitis and symptoms of lethargy and weight loss. Only one patient had a vasculitic rash. On renal biopsy all had immunoglobulin deposits which were focal and segmental, or in one case characteristic of membranous nephropathy. Renal function was significantly impaired in all four, two of whom were taking gold or penicillamine. Breedveld *et al.*[5] and Tebib *et al.*[6] report three patients with RA and a necrotizing glomerulonephritis who had not been treated with penicillamine. All three patients had long-standing rheumatoid disease and the onset of necrotizing glomerulonephritis was co-incidental with the development of systemic vasculitis. In all three patients, rheumatoid factor was strongly positive and lupus serology was negative. In the autopsy study of Boers *et al.*[3] 18/132 patients had a systemic vasculitis. Of these, eight had a large-vessel renal arteritis, four of which had an extra-capillary proliferative glomerulonephritis.

One patient in our study had glomerular deposits of amyloid as well as a vasculitic glomerulonephritis. There is one published report of this association and the authors speculate that destruction of the glomer-

Table 6 Previous case reports of FSNGN associated with RA

Author	Patient Age/sex	RA duration	Treatment at presentation	Renal presentation	Immunology	Histology immunostain	Treatment	Outcome
Kuznetsky[4]	34F	9 yrs	Pen	MH/Pr	RF 1 : 2560	Diff endocap GN/IgG IgM IgA C3	P, C	Reduced Cr at 4/12
	49F	17 yrs	Pen (stopped 1 yr prev)	MH/Pr CrCl 12	RF < 1 : 20 ANA −ve	FSNGN Scanty IgG IgM C3	P, C	HD at 1/12
	56F	5 yrs	Pen	MH/Pr CrCl 17	RF 1 : 160 ANA 1 : 100	FSNGN/memb IgG IgA Clq	P	Lost to FU
	72F	NA	nil	MH/Pr CrCl 21	RF 1 : 320	FSNGN/Ig −ve	P, C	Stable on FU
Tebib[6]	63M	1 yr	nil	CRF MH/Pr	RF 675iu/ml	Cresentic GN Ig −ve	P, C	Stable on FU
Breedveld[5]	52M	10 yrs	Chloroquine	CRF MH/Pr	RF 1 : 1024	Cresentic GN/ IgG IgA IgM C3	P, A	Reduced Cr 4/12
	74M	23 yrs	Pen (stopped 3 yrs prev)	CRF MH/Pr	RF 1 : 1024 ANA +ve	Cresentic GN/ NA	P, A	Died at 6/52

RA, rheumatoid arthritis; Pen, penicillamine; Cr, creatinine; MH, microscopic haematuria; Pr, proteinuria; CrCl, creatinine clearance (ml/min); CRF, renal impairment; RF, rheumatoid arthritis; ANA, anti-nuclear antibody; P, prednisolone; C, cyclophosphamide; A, azathioprine; FSNGN, focal segmental necrotizing glomerulonephritis; GN, glomerulonephritis; NA, not available.

ular tufts induced by amyloid deposition may be responsible for the crescent formation.[15] It is however, more likely that these two pathologies are coincidental, as renal amyloid is reported in up to 8–17% of cases of RA at autopsy.[16] In addition, one patient in our study had a membranous nephropathy and a further patient had evidence of an early diabetic nephropathy.

Nine of our ten patients had renal insufficiency at presentation and two were dialysis-dependent, indicating the severity of their renal disease. Eight patients had microscopic haematuria and proteinuria and two isolated proteinuria. This presentation is similar to other case reports. All of the patients reported by Kuznetsky *et al*. had renal impairment, three had microscopic haematuria and proteinuria and one isolated proteinuria.[4] The other three patients reported also all had renal impairment, microscopic haematuria and proteinuria.[5,6]

The pathogenesis of FSNGN in RA is unknown. In active RA, the presence of circulating immune complexes, RF and complement consumption would make immune complex-mediated glomerular damage an attractive mechanism for the vasculitic lesions. However, the renal biopsies in the patients in this study showed no significant immune deposits. Similarly, in the four patients reported by Kuznetsky, there was sparse glomerular deposition of immunoglobulin.[4] This 'pauci-immune' necrotizing glomerulonephritis is similar to that seen in MPA and WG, and the appearance is not that of an immune-complex-mediated lesion. None of these patients had a low C4 to indicate complement consumption.

It is possible that vasculitic glomerulonephritis in the two patients in this study who were treated with penicillamine was a complication of this drug. There are several reports of a necrotizing and crescentic glomerulonephritis in patients with RA, Wilson's disease and cystinuria who were treated with penicillamine.[8–11,17–18] In some cases there has been pulmonary haemorrhage as well as a cresentic nephritis, but without anti-glomerular basement membrane antibodies such as those seen in Goodpastures syndrome.[9] There is a single report of a necrotizing glomerulonephritis with pulmonary haemorrhage in a patient with rheumatoid arthritis treated with penicillamine who had antibodies to myeloperoxidase, which is an ANCA antigen.[19] Four of our patients had a positive pANCA, one of whom (patient 4) developed pulmonary haemorrhage, but the role of ANCA in the development of their vasculitis is unknown. One of our patients was on gold at the time of biopsy but there are no reports of FSNGN following its use. In addition, eight patients were using NSAIDs at the time of presentation. There are anecdotal reports of a vasculitis in patients treated with NSAIDs, but these are not particularly convincing, with the exception of one case report of generalized vasculitis associated with piroxicam, where the same clinical picture developed on re-challenge with the drug.[20] It is unlikely that these drugs were the cause of the FSNGN in our patients.

Prednisolone and cyclophosphamide are now established as effective treatment MPA, WG[21] and systemic rheumatoid vasculitis.[22] In our study, six patients received oral cyclophosphamide and prednisolone for 3 months, then maintenance prednisolone and azathioprine for a variable period. Four of these patients are alive with good renal function. This experience is supported by the experience of Kuznetsky *et al*.[4] Three of their patients were treated with cyclophosphamide and prednisolone. Renal function improved in two, and deteriorated in one, who required maintenance dialysis. Tebib *et al*.[6] treated their patient with pulse cyclophosphamide. Although renal function initially improved, it subsequently deteriorated such that dialysis was necessary. Of our four patients treated with prednisolone and azathioprine or prednisolone alone, renal function improved in two, stabilized in one and improved transiently in one. The two patients reported by Breedveld[5] were treated with methylprednisolone and azathioprine; one recovered renal function, the other died of systemic vasculitis. Our experience of treating systemic rheumatoid vasculitis and other systemic vasculitides[22,23] leads us to suggest that patients with rheumatoid arthritis and renal vasculitis should be treated with cyclophosphamide and prednisolone. The optimal regime (i.e. pulse or continuous) and duration of treatment remains unclear.

Six of our 10 patients have survived more than 2 years since diagnosis with no relapses of FSNGN or of extrarenal vasculitis. Patients who develop renal impairment and an abnormal urinary sediment should have an urgent renal biopsy. Although renal vasculitis is uncommon in RA, our data suggests that it can lead to significant renal impairment and also that it responds well to treatment with steroids and immunosuppressants. Although the presence of seropositivity, bone erosions and extra-articular vasculitis makes this disorder more likely, their absence does not exclude the diagnosis.

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