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Clinical and serological features of severe vasculitis in rheumatoid arthritis: prognostic implications

ARNI J GEIRSSON,[1] GUNNAR STURFELT,[1] AND LENNART TRUEDSSON[2]

From the [1]Department of Rheumatology, and the [2]Department of Medical Microbiology, University Hospital, Lund, Sweden

SUMMARY Sixteen patients with classic rheumatoid arthritis (RA) complicated by severe vasculitis were studied and compared with a matched control group of 16 RA patients without vasculitis. Seven of the patients with vasculitis died within 4 to 120 months (median 32 months) after developing vasculitic symptoms. Gangrene of digits and extremities, bowel ulcers or bowel perforation, or both, and cardiac involvement were more common among the patients who died than among those with a more favourable course. The present data suggest that large vessel vasculitis in RA is associated with high frequency of arteriosclerotic vascular disease. The serum concentrations of complement components C3 and C4 were lower, and concentrations of IgM rheumatoid factor, complement activating rheumatoid factor, and C1q binding immune complexes (C1q solid and C1q fluid phase assay) were significantly higher among vasculitic patients than in the control group. Laboratory data provided little prognostic information with regard to rheumatoid vasculitis, with the exception that IgM and IgG rheumatoid factors were significantly higher among patients with fatal course of disease than in those who achieved remission.

Key words: extra-articular features, complement, complement activating rheumatoid factors.

Rheumatoid vasculitis is a disorder with heterogeneous clinical presentation.[1] Extra-articular vasculitic manifestations range from benign cutaneous lesions to gangrene of extremities and visceral organs associated with considerable mortality.[2]

The aim of this study was to identify clinical and laboratory variables characteristic of severe rheumatoid vasculitis and predictive for the outcome of the disease. We studied patients with rheumatoid vasculitis seen at the department of rheumatology in Lund over a 10 year period in comparison with a matched control group with classic RA without signs of extra-articular vasculitis.

Patients and methods

PATIENTS

We studied 16 consecutive patients with classic rheumatoid arthritis (RA) according to the American Rheumatism Association criteria.[3 4] They all had various extra-articular vasculitic manifestations interpreted as part of the rheumatic disease. Demographic data are given in Table 1. Selection of patients was based on signs of systemic vasculitis. Patients with mononeuritis multiplex, gangrene of extremities, or inner organ vasculitis were included in the study. Patients with purely cutaneous manifestations such as palpable purpura, rash, ulcers, and nail fold infarcts were not included. The interval between onset of RA and vasculitic symptoms varied between 0·5 and 36 years, median 7·5 years (Table 1). Whenever possible, biopsies were done for microscopic verifications of vasculitis in cutaneous and internal organ lesions.

When vasculitic symptoms appeared the patients were treated as follows: non-steroidal anti-inflammatory drugs (NSAIDs) (16 patients); antimalarial drugs (10 patients); prednisolone 5–30 mg (six patients); corticotrophin (ACTH) injections (two patients); penicillamine (six patients); gold salts (five patients); and podophyllotoxin derivatives (two patients).

CONTROLS

Sixteen controls (10 male, six female), all with

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Correspondence to Dr Gunnar Sturfelt, Department of Rheumatology, University Hospital, S-221 85 Lund, Sweden.

Table 1 *Age at onset of RA and at inclusion in the study of patients with rheumatoid vasculitis and of controls*

	Sex	*Age (years)*		*Age at onset of RA (years)*		*Disease duration (years)*	
		Median	*Range*	*Median*	*Range*	*Median*	*Range*
Patients (n=16)	M (n=10)	69·0	44–79	50·5	21–75	7·5	0·5–26
	F (n=6)	64·0	59–82	49·0	28–75	8	0·5–36
RA controls (n=16)	M (n=10)	69·0	44–77	46·0	26–75	14	2–29
	F (n=6)	63·5	58–76	52·5	23–69	15	5–22

classic or definite RA (Table 1), were chosen from among patients at the department of rheumatology, Lund. They were matched for age, sex, duration of disease, and presence of rheumatoid factor (Waaler-Rose test). Patients who had presented clinical manifestations clearly related to systemic vasculitis were excluded. One of the control patients died of poorly differentiated carcinoma of unknown origin four months after inclusion in the study. No control developed severe vasculitic manifestations within a follow up of one year after inclusion in the study.

At inclusion in the study the controls were being treated according to the following alternatives: NSAIDs (15 patients); prednisolone (nine patients); cytotoxic drugs (azathioprine, chlorambucil) (four patients); penicillamine (two patients); antimalarial drugs (two patients); and sulphasalazine (one patient). The two patients treated with chlorambucil had verified renal amyloidosis.

BLOOD SAMPLING

Serum and ethylenediaminetetra-acetate (EDTA) plasma were serially sampled from the patients with vasculitis and once from the control patients. Coagulation was allowed to proceed at room temperature for two hours. The samples were frozen at −80°C until use.

RHEUMATOID FACTORS

The Waaler-Rose test was performed according to standard procedures.[5] A haemolysis in gel assay was used for measuring complement activating rheumatoid factors (RF).[6] The concentrations of complement activating RF were expressed in arbitrary units (AU) referring to a RF reference calibrated against an RA serum supplied by the WHO laboratory for biological standards, Copenhagen,[7] which was said to contain 1·000 AU/ml. IgG RF, IgA RF, and IgM RF were measured by enzyme linked immunosorbent assay (ELISA),[6] values being given in arbitrary units (AU), with a RF reference containing 1·000 AU/ml of IgG RF, IgA RF, and IgM RF.[6]

COMPLEMENT FACTORS

The complement components, C1q,[8] C4, C3, and factor B,[9] were measured by electroimmunoassay. Values were given as percentages of the concentration in a reference serum or EDTA plasma pool said to contain each component at 100%. C3d/dg fragments were measured by double decker, rocket immunoelectrophoresis.[10] C3d/dg values were given as percentages of the C3d in a normal serum pool treated with inulin (100 mg/ml, 37°C, 120 min).

CIRCULATING IMMUNE COMPLEXES

Circulating immune complexes (CIC) were measured by a fluid phase C1q binding assay (C1qBA)[11] and by a solid phase C1q binding assay (C1qSP).[12] The values were given as equivalents of aggregated IgG in micrograms per millilitre. Control sera yielded values <100 μg/ml in C1qBA and <10 μg/ml in C1qSP.

OTHER ASSAYS

C reactive protein (CRP) was measured by electroimmunoassay.[13] Antinuclear antibodies (ANA) were determined by indirect immunofluorescence technique.[14]

STATISTICS

The Fisher exact probability test (two tailed) was used for comparing clinical symptoms and outcome of the 16 rheumatoid vasculitis patients, the Mann-Whitney U test (two tailed) for comparing laboratory variables in the two groups of patients, and the Spearman rank test for calculating correlations between groups.[15]

Results

CLINICAL FINDINGS

Ten of the patients (62·5%) with vasculitis had rheumatoid nodules, as compared with six of the controls. Two patients with vasculitis had Sjögren's syndrome, and one had Felty's syndrome. Among the controls three patients had Sjögren's syndrome

and none Felty's syndrome. There was no significant difference in the number of swollen joints between the two groups; 0–20 (median 7) in the vasculitis group and 0–14 (median 5) in the control group. The most common feature of vasculitis was neuropathy, sensory polyneuropathy being seen in 13 patients (81%) and motor neuropathy in 12 (75%). Bilateral lesion of n. peroneus communis occurred in seven patients (44%). Cutaneous manifestations were present in 12 patients (75%), including ulcers in 10 (62·5%), petechiae or purpura in six patients (37·5%), and dermal infarcts in two patients (12·5%). Gangrene of extremities was seen in six patients (37·5%) (Table 2).

Gastrointestinal involvement occurred in six patients (37·5%), three of whom had painful bleeding gastric ulcers. One patient had pyloric ulcer with a biopsy showing vasculitis. Another patient with perforated prepyloric ulcer had a rectal biopsy showing vasculitis. One patient with bowel perforation and peritonitis died having refused surgical treatment, and the relatives declined postmortem examination (Table 2).

Cardiac involvement during vasculitic flare was seen in five patients, of whom four had perimyocarditis, two congestive heart failure, and one myocardial infarction. Pulmonary involvement was seen in four patients with pleuritis (Table 2). Two of the controls had previously had pleuritis, one perimyocarditis, and one of the controls had pulmonary fibrosis.

Two patients had scleritis. Cerebral symptoms occurred in three patients, of whom one had syncopal attacks, one had epileptiform convulsions, and the third had transient ischaemic attacks with dysarthria. No patient had clinical renal involvement, though one had intermittent microscopic haematuria without other evidence of kidney disease; this patient's glomerular filtration rate was normal and he had no proteinuria; kidney biopsy

Table 2 *Clinical symptoms in 16 patients with severe rheumatoid vasculitis related to clinical outcome*

Symptoms	*All patients (n=16) No (%)*	*Fatal course (n=7) No (%)*	*Remission (n=9) No (%)*
Mononeuritis multiplex	12 (75)	7 (100)	5 (56)
Polyneuropathy	13 (81)	6 (86)	7 (78)
Cutaneous ulcers/ infarcts	10 (62)	4 (57)	6 (67)
Gangrene digits/ extremities	6 (38)	5 (71)*	1 (11)
Bowel ulcers/ perforation	6 (38)	5 (71)*	1 (11)
Pleuritis	4 (25)	3 (43)	1 (11)
Cardiac involvement†	5 (31)	5 (71)**	0
Cerebral involvement‡	3 (19)	3 (43)	0
Purpura/petechiae	6 (38)	3 (43)	3 (33)
Scleritis	2 (12)	2 (29)	0
Haematuria	1 (6)	1 (14)	0

*p<0·025 (Fischer exact probability test); **p=0·005.
†Perimyocarditis (four patients); congestive heart failure (two patients); myocardial infarction (one patient).
‡Convulsions, syncopal attacks, transient ischaemic attack.

Table 3 *Comparison of some immunological variables in patients with rheumatoid arthritis (RA) with vasculitis and in RA patients with uncomplicated disease*

	RA vasculitis			*RA control*			*p Value**
	n	*Median*	*Range*	*n*	*Median*	*Range*	
Waaler-Rose test (titre)	16	256·0	32–1024	16	32·0	8–256	<0·002
IgM RF (AU)	16	235·0	60–1480	16	135·0	20–1460	<0·05
IgG RF (AU)	16	80·0	20–670	16	75	15–380	NS
IgA RF (AU)	15	360	60–4570	16	180·0	20–3360	NS
Complement activating RF (AU)	16	1775·0	80–12 500	16	155·5	2–1316	<0·002
C3d/dg (% of normal, ref area<6%)	13	9·0	6–17	12	10·2	7–14	NS
C1q (% of normal, ref area 78–130%)	16	125·0	78–191	16	113·0	73–157	NS
C3 (% of normal, ref area 70–136%)	16	120·5	66–167	16	159	86–340	<0·002
C4 (% of normal, ref area 53–207%)	16	87·0	25–158	16	150·5	65–302	<0·02
Factor B (% of normal, ref area 59–154%)	16	137·5	88–220	16	131	92–171	NS
C1qBA† (<100 μg/ml)	16	1612·5	590–2000	16	197·5	100–1360	<0·002
C1qSP‡ (<10 μg/ml)	15	34	8–821	16	11·5	8–93	<0·05
CRP (<12 mg/l)	16	95·0	12–224	16	26·0	12–132	<0·05
ANF (titre)	11	50	10–600	12	30	10–200	NS

*Calculated using the Mann-Whitney U test.
†Circulating immune complexes in C1qBA.
‡Circulating immune complexes in C1qSP.
AU=arbitrary units; C1qBA=C1q binding assay; C1qSP=solid phase C1q binding assay; CRP=C reactive protein; ANF=antinuclear factor.

was not performed. Cutaneous or visceral biopsies were done in seven patients, all showing necrotising vasculitis. None of the patients with vasculitis but two of the controls had verified secondary amyloidosis.

Nine of the 16 patients had symptoms of cardiovascular 'disease before the development of vasculitis. Five of these nine patients had congestive heart failure, four had angina pectoris, three myocardial infarction, and three atrial fibrillation. Three patients within this group also had diabetes mellitus. In contrast, only three of the controls had evidence of cardiovascular disease at inclusion in the study, a difference that was significant ($p<0.05$).

Of 16 patients in the vasculitis group, seven (four men, three women) died on average within 17·8 months after onset of vasculitic symptoms, which gives a mortality of 43%. Cardiac involvement ($p<0.005$), gangrene of digits and extremities ($p<0.025$), and ischaemic bowel lesions ($p<0.025$) were all significantly more common among patients with a fatal course of rheumatoid vasculitis than among those who achieved remission. All of those who died had mononeuritis multiplex. The causes of death were: gangrene and terminal septicaemia in three patients, pulmonary thrombosis/emboli in one patient, peritonitis after bowel perforation in one patient, congestive heart failure in one patient, and multiple myeloma in one patient. The last patient had a vasculitis (gastrointestinal and cutaneous)

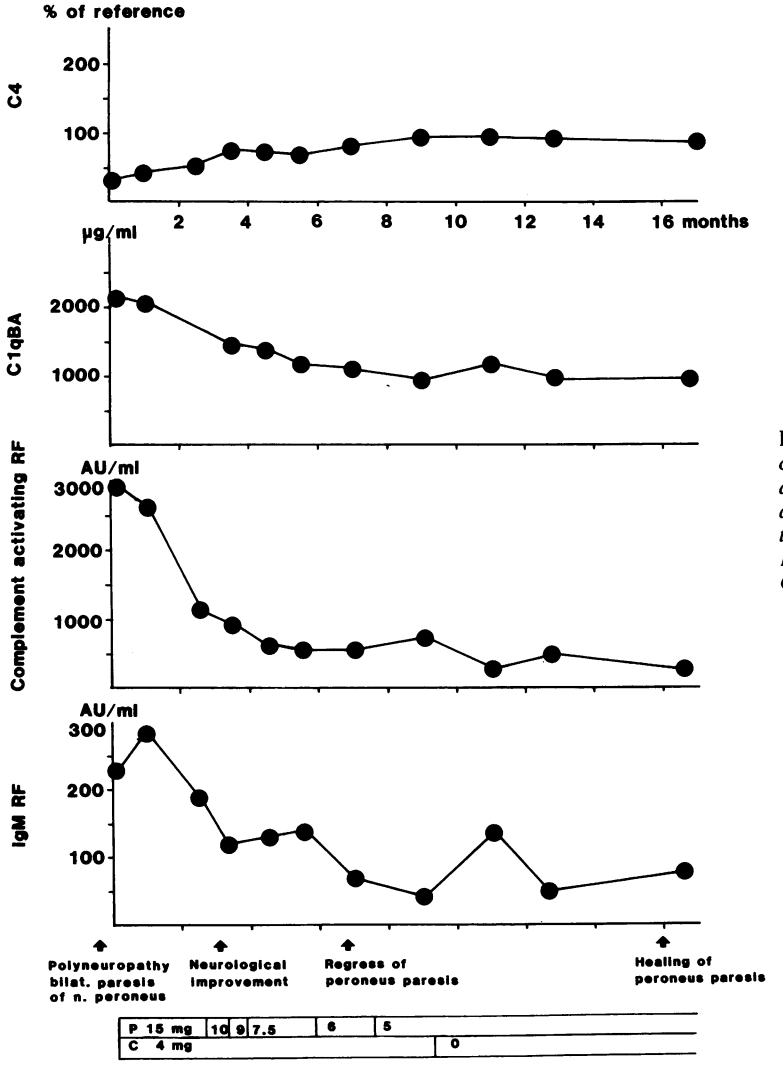

Fig. 1 *Temporal relation between clinical and laboratory findings in a patient with rheumatoid vasculitis achieving remission during treatment with chlorambucil. P=prednisolone; C=chlorambucil.*

verified by biopsy, and there was no indication that hyperviscosity caused the vascular symptoms. A summary of the main clinical symptoms within the vasculitis group in relation to clinical course is given in Table 2.

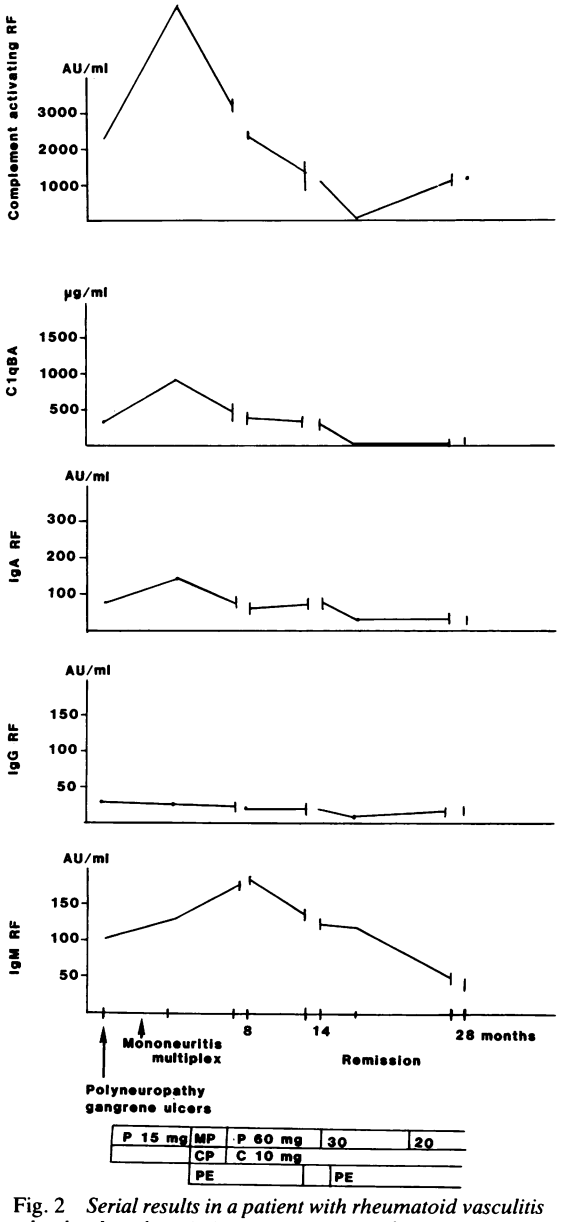

Fig. 2 *Serial results in a patient with rheumatoid vasculitis who developed remission on treatment with cyclophosphamide and methylprednisolone, both given as intermittent bolus injection, followed by oral prednisolone and chlorambucil. P=prednisolone; MP=methylprednisolone; CP=cyclophosphamide; C=chlorambucil; PE=plasma exchange.*

The patients who died were treated as follows: prednisolone 5–40 mg (seven patients); cytotoxic drugs (chlorambucil, azathioprine) (four patients); penicillamine (two patients); plasmapheresis (one patient). The patients with vasculitis who achieved sustained remission were treated as follows: prednisolone 5–40 mg (eight patients); penicillamine (two patients); cytotoxic drugs (cyclophosphamide, chlorambucil, or azathioprine) (eight patients—three of these eight patients were treated with methylprednisolone 1 g intravenously (IV) and cyclophosphamide 15 mg/kg IV, as described by Scott and Bacon[16]). As an adjunct to treatment with cytotoxic drugs, two patients were treated with plasmapheresis. When vasculitis and control patients were compared no relation was seen between dosage and duration of treatment with corticosteroids before development of vasculitis.

LABORATORY FINDINGS

The Waaler-Rose titres were significantly higher in the vasculitis group than in the control group ($p<0.002$), as were serum concentrations of IgM RF ($p<0.05$). Concentrations of complement activating RF were significantly higher in patients with RA vasculitis ($p<0.002$) than in controls (Table 3). No significant difference was observed between the two groups for concentrations of IgG RF and IgA RF. The patients in the vasculitis group who died, however, had, at onset of vasculitic symptoms, significantly higher serum levels of IgM RF ($p<0.05$) and IgG RF than had those who achieved remission ($p<0.05$).

The patients with RA vasculitis had at onset of clinical symptoms significantly lower serum concentrations of C3 ($p<0.002$) and C4 ($p<0.02$) than had the RA controls. Although C1q and factor B levels were normal in both groups, increased concentrations of C3d/dg fragments were found in all patients, without significant difference with regard to the presence of vasculitis. Circulating immune complexes were significantly higher in the vasculitis group than in the control patients, measured both by C1qBA ($p<0.002$) and C1qSP ($p<0.05$) (Table 3).

In the vasculitis group an inverse correlation was found between C4 and complement activating RF ($r=-0.579$, $p<0.05$), and also between C4 and CIC measured by C1qBA ($r=-0.508$, $p<0.05$). A significant correlation was found between concentrations of C3d/dg and immune complexes measured by C1qBA ($r=0.677$, $p<0.02$) and by C1qSP ($r=0.581$, $p<0.05$).

The serum concentrations of CRP were significantly higher in the vasculitis group than among

controls ($p<0.05$) (Table 3). The difference was not explained by more active joint symptoms among patients with vasculitis.

ANA titres were increased in both groups (Table 3).

The relation between course of disease and laboratory findings is illustrated by the course of two patients who went into remission with treatment (Figs 1 and 2). Both patients had polyneuropathy and mononeuritis multiplex, and one of them had gangrene and skin ulcers as well. Treatment resulted in the disappearance of these symptoms and concomitant decrease in the titres of rheumatoid factors and circulating immune complexes and rise in complement levels.

Discussion

Severe rheumatoid vasculitis is a rare disorder probably occurring in less than 1% of patients with rheumatoid arthritis.[17] Estimations of the incidence of the disease are often unreliable owing to the heterogeneous clinical manifestations.[1] Although rheumatoid arthritis is more common among women than among men severe forms of rheumatoid vasculitis are more often seen in men,[2 18] and thus the female:male ratio in our sample was 1:1·67.

We found that the presence of gangrene of digits and extremities, the development of intestinal lesions with bleeding or perforation, cardiac involvement, and probably mononeuritis multiplex indicate extensive vasculitis and are associated with a poor prognosis. These results support previous reports.[18 19] In patients with these symptoms aggressive immunosuppressive therapy is probably justified, as outlined by Scott *et al*,[2] Abel *et al*,[20] and Winkelstein *et al*.[21] In contrast, cutaneous ulcers and pure sensory polyneuropathy are obviously manifestations associated with favourable prognosis. In the present study the prevalence of extra-articular manifestations other than vasculitis was similar among patients with vasculitis and RA controls. Two of the RA controls but none of the patients with vasculitis had secondary amyloidosis.

The high mortality rate in severe vasculitis found in the present study is in accordance with previous reports.[20 22–25] The causes of death were related to severe vasculitic lesions in internal organs and terminal infections.

The present study indicates that cardiovascular disease is common among patients with rheumatoid vasculitis. It may be that common pathogenetic factors are operating in atherosclerosis and systemic vasculitis.[26] Whether arteriosclerosis and cardiovascular disease predispose to development of large vessel vasculitis in the rheumatic patient could not be readily addressed in the present study. Clinical manifestations of arteriosclerosis are more common in men than in women in the relevant age group,[27 28] which may explain why severe rheumatoid vasculitis is more prevalent in men than in women.

Kemper *et al* have claimed that treatment with corticosteroids predisposes to necrotising vasculitis.[29] We were unable to record any apparent relationship between prior corticosteroid treatment and the development of vasculitis.

Concentrations of IgG RF and IgM RF were higher in the group of patients with vasculitis that died than in those who achieved remission. Thus it is suggested that high levels of IgG RF and IgM RF may be associated with poor prognosis in rheumatoid vasculitis. We could not confirm the observation by Scott *et al* that serum levels of IgG RF are more closely related to the course of rheumatoid vasculitis than IgM RF.[30] One possible explanation could be methodological differences. In the present study the ELISA technique was used for the measurement both of IgG RF and IgM RF. The serum concentrations of IgA RF were similar in patients with vasculitis and in controls. Thus the results did not support a major role for IgA RF in the pathogenesis of RA vasculitis.

The increased concentrations of C1q binding immune complexes and complement activating RF in the vasculitis group, as compared with the RA control group, suggest a pathogenetic role for RF containing immune complexes in rheumatoid vasculitis.[30]

The CRP levels were high in the vasculitic group, indicating a pronounced acute phase reaction, and thus the synthesis of complement factors C3 and C4 would also be expected to increase.[31] The levels of C3 and C4 were moderately low in the vasculitic patients, however, indicating complement consumption, despite similar concentrations of C3d/dg in the two groups. The latter finding might be explained by localised complement consumption associated with vasculitic lesions not reflected by the serum and plasma levels of complement fragments. The serum concentrations of C1q were fairly high in the vasculitic group, probably indicating the presence of free circulating C1q in these patients, which could be of pathophysiological importance in RA vasculitis.[32]

In conclusion, the results of the present study are consonant with a pathogenetic role for RF containing immune complexes in RA vasculitis. A prolonged prospective study should give more conclusive information on the relation between complement activating rheumatoid factors and prognosis in the disease.

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