

## Case report

# Role of immune complexes in rheumatoid polyarteritis

JAMES B. FARRELL,<sup>1</sup> DONALD A. PERSON,<sup>2</sup> ROGER D. ROSSEN,<sup>3</sup>  
AND MARTIN D. LIDSKY<sup>1</sup>

From the Departments of <sup>1</sup>Internal Medicine, <sup>2</sup>Virology and Epidemiology, Pediatrics, and Microbiology and Immunology, Baylor College of Medicine, Texas Medical Center, and the <sup>3</sup>Laboratory for Immunological Research at the Veterans Administration Hospital, Houston, Texas 77211, USA

**SUMMARY** Serial clinical and serological observations were made on a patient with necrotising polyarteritis associated with rheumatoid arthritis. Significant levels of circulating immune complexes as determined by a C1q binding assay, were observed up to 2 years before the clinical manifestations of polyarteritis but rose abruptly immediately before and concurrently with the onset of polyarteritis. Concomitant serial determinations of C3, latex fixation titres for anti-immunoglobulin, and patterns of fluorescence of antinuclear antibody afforded insight into the nature of these complexes, as did clinical and serological response to glucocorticoid and cytotoxic therapy. Our data suggest that the antibody involved in the complex was of the IgG class and capable of complement fixation.

Necrotising polyarteritis complicating rheumatoid arthritis (RA) is an infrequent but potentially lethal extra-articular manifestation of the disease. Patients who develop this complication have immunological abnormalities, including high titres of serum anti-immunoglobulin G (IgG) antibody (rheumatoid factor), antinuclear antibodies (ANA), and reduced levels of complement (Morgan *et al.*, 1969). Here we report the case of a patient with long standing seropositive RA who developed necrotising polyarteritis. Serial serological observations made before, during, and after the development of the arteritis indicated that the onset of vasculitis was associated with high levels of circulating immune complexes and low levels of circulating complement. The clearance kinetics of the complexes from his circulation after the institution of adrenocorticosteroid therapy suggested that the antibody responsible for the arteritis-inducing complex was of the IgG class.

### Materials and methods

The C1q binding activity (C1qBA) was determined using a modified radioimmunoassay (Zubler *et al.*,

1976, Rossen *et al.*, 1977). Serum anti-IgG antibody was measured by the latex agglutination method (Singer and Plotz, 1956). Radial immunodiffusion was used to measure the third component (C3) (Immuno-plate III Radial immunodiffusion test, human complement C3 Test, Hyland, Div. Traveno Laboratories, Inc., Costa Mesa, CA 91676). Serum ANA were determined with cryostat sections of mouse liver as substrate and rabbit antihuman IgG conjugated with fluorescein isothiocyanate in an indirect immunofluorescence assay (Person *et al.*, 1974). Serum cryoglobulins were tested for by using microcapillary tubes. An indirect immunofluorescence procedure utilising a dipteran trypanosome, *Crithidia luciliae*, as substrate was used to detect antibody to native DNA (Person *et al.*, 1975). Regression analysis was performed on a programmable calculator.

### Case report

A 58-year-old man with seropositive RA was admitted in January 1977 to the Houston Veterans Administration Hospital for evaluation of purpura and dysaesthesias of the lower extremities. The patient had been followed up by us since 1969 for definite RA. His illness began in 1965 with recurrent polyarthralgias of the proximal interphalangeal (PIP) joints, shoulders, and wrists. A severe exacerbation

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Correspondence to Martin D. Lidsky, MD, Department of Medicine, Baylor College of Medicine, Texas Medical Center, Houston, Texas 77030, USA.

of the polyarthritis involving the metacarpophalangeal (MCP) and PIP joints, shoulders, and wrists occurred in 1968. Systemic adrenocorticosteroids were administered at that time for a period of 5 months. Gold sodium thiomalate, 50 mg weekly, was given from March to May 1969 without apparent clinical response. The patient first came to us in May 1969 and was admitted to the hospital for evaluation of polyarthritis. He had effusions of the right third and fourth PIP joints, both elbows and knees, and flexion contractures of the elbows and knees. Haemogram and urine analysis were normal at that time. The serum anti-IgG antibody titre was 1:5120. His serum ANA was positive at a 1:4 dilution with a diffuse and nucleolar pattern.

The patient responded initially to physical therapy, bed rest, and salicylates. His disease was stable until April 1972, when the polyarthritis flared. Chrysotherapy was begun with 25 mg of gold sodium thiomalate weekly. The chrysotherapy was discontinued in October 1975 because of the lack of clinical response. In November 1975 D-penicillamine, 250 mg twice daily, was begun together with indomethacin 25 mg 3 times a day. The patient failed to respond clinically, and the D-penicillamine was stopped after 8 months of therapy.

In January 1977 he was admitted for evaluation of a purpuric, raised, macular eruption initially noted over the dorsum of the feet, forearms, and thighs which had been present for 2 weeks. Dysaesthesias of the feet developed at the same time. Raynaud's phenomenon was observed shortly after the onset of purpura. On admission, nailfold infarctions (Fig. 1), diffuse lymphadenopathy, and a palpable spleen were present. Diminished sensation to pin prick in a symmetrical stocking distribution of both feet was detected. There was weakness of dorsiflexion of the left great toe. Multiple joint

deformities and rheumatoid nodules on a number of extensor surfaces were present. After admission pain and cyanosis of the fifth digit on the left hand developed. On admission haemogram, urine analysis, fasting blood glucose, blood urea nitrogen, serum creatinine, serum alkaline phosphatase, serum glutamic oxaloacetic transaminase, and serum electrolytes were normal. Biopsy of a skin lesion revealed acute perivascular inflammation, with extensive dermal necrobiosis and necrosis of the overlying epidermis.

Prednisone 40 mg daily was begun on the third day in hospital and continued for 5½ weeks, when the dose was slowly tapered to a level of 17.5 mg daily. During this period the dermal lesions and peripheral neuropathy resolved. Eight days later multiple nailfold infarcts reappeared, and cyclophosphamide 150 mg daily was started. The patient was maintained on 15 mg of prednisone and 150 mg of cyclophosphamide daily through January 1978 without recurrence of polyarteritis.

### Results

During almost the entire course of this patient's illness his serum bound abnormally large amounts of C1q, indicative of a low-grade immune complexaemia (Fig. 2). A striking finding was the further increased binding of C1q (82–87%) which occurred coincidentally with the development of necrotising polyarteritis and a depression in circulating complement. The increase in serum C1qBA and the fall in C3 were accompanied by rising ANA and latex fixing anti-IgG antibody titres (Table 1).

Glucocorticoid treatment caused a rapid reversal of these serological abnormalities (Fig. 2 and Table

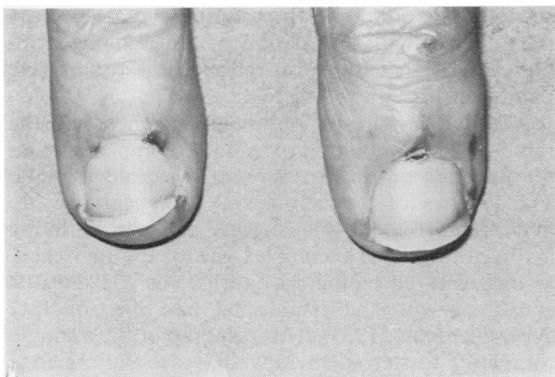


Fig. 1 Several nailfold infarcts are clearly visible.

Table 1 Time course of anti-IgG and antinuclear antibodies

Date	Anti-IgG antibody (reciprocal titre)	Antinuclear antibody (reciprocal titre pattern)
12 May 1969	1280	4 diffuse, nucleolar
6 May 1970	1280	4 diffuse, nucleolar
26 May 1971	2560	4 diffuse, nucleolar
14 April 1972	2560	16 diffuse, nucleolar
25 April 1973	2560	8 diffuse, nucleolar
24 April 1974	2560	32 diffuse
23 April 1975	2560	∞ 64 diffuse
21 April 1976	5120	∞ 64 diffuse
21 January 1977*	10240	∞ 64 diffuse
28 February 1977	2560	16 diffuse, nucleolar
14 March 1977	2560	32 diffuse, speckled
14 April 1977	2560	32 diffuse, speckled
9 May 1977†	10240	∞ 64 diffuse, speckled
23 May 1977	20480	32 diffuse, speckled
23 June 1977	10240	16 diffuse, speckled

\*Steroid therapy initiated. †Cyclophosphamide therapy added.

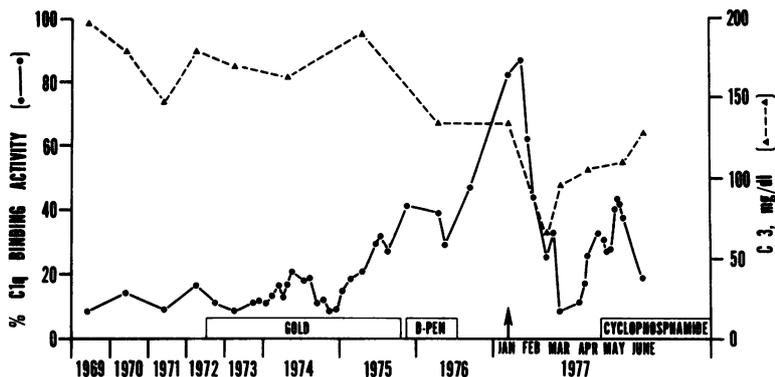


Fig. 2 Time course of C1qBA and circulating C3 level. Arrow indicates the initiation of corticosteroid therapy.

1), as well as marked clinical improvement. Immune complexes decreased linearly with a half life of 31 days (Fig. 3), only to rebound somewhat in April 1977 when the steroid dose was tapered (Fig. 2). Despite the cytotoxic drug, serum C1q binding

continued to rise, but more slowly. The patient's C3 had begun to return to more normal levels.

Finally, during the 8-year period of observation we did not detect cryoglobulins or hepatitis B surface antigen (HBsAg), nor did we find anti-DNA antibodies.

### Comment

The progressive increase in binding activity which peaked simultaneously with the development of clinical polyarteritis was the noteworthy observation. The lowered serum complement associated with the high C1qBA suggested that the immune complexes fixed complement. Although these observations do not prove that the identified immune complexes were responsible for the arteritis, the temporal association is highly suggestive. The results obtained here are similar to those seen in the animal model for 'one shot' serum sickness (Germuth, 1953). The ANA (an antibody of the IgG class by virtue of the test performed in our laboratory) and anti-IgG antibody (an antibody of the IgM class) tended to parallel the C1qBA. We do not suggest that either of these antibodies necessarily participated in the formation of the immune complexes, only that they also reflected the progressive nature of the patient's disease.

Another important observation concerned the rapid, linear elimination of immune complexes from the patient's serum in response to steroid therapy. The kinetics of the complexes' disappearance are first order (Fig. 3) and suggest that the antibody involved in the toxic complex was of the IgG class, as the observed biological half life (i.e., 31 days) is consistent with the established half life for IgG (Volweiler *et al.*, 1955). This response of the immune complexes to steroid therapy supports the previous observations demonstrating the selective suppression of IgG synthesis by methylprednisolone (Butler and

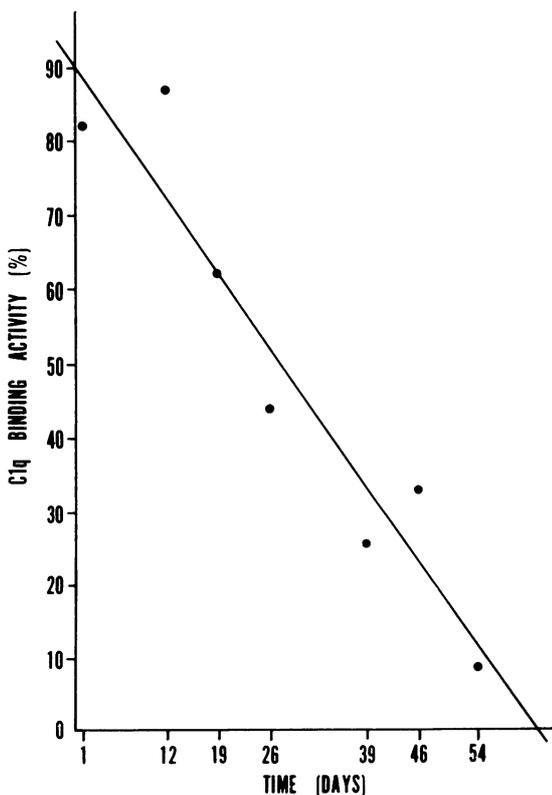


Fig. 3 Linear regression of C1qBA versus time after steroid therapy was begun. The regression line is  $y = 90.06 - 1.46x$  and  $r = 0.95$  ( $P < 0.001$ ).

Rossen, 1973). The data are compatible with the antibody involved being of the IgG class and capable of fixing complement.

We know much less about the putative antigen. Several possibilities known to be sometimes associated with immune complex disease have been ruled out. These would include cold reactive IgM anti-IgG seen in mixed cryoglobulinaemia (negative cryoglobulins); HB<sub>s</sub> antigenaemia-associated polyarteritis nodosa (negative HB<sub>s</sub>AG); and, at least by inference, DNA-anti-DNA as seen in systemic lupus erythematosus (negative anti-DNA antibody). We are currently analysing the patient's sera for other possible antigens. The changing antinuclear antibody pattern bears mention in this regard (Table 1). The loss of antinucleolar reactivity in the serum from April 1974 and its reappearance in February 1977 after 5 weeks of glucocorticoid therapy might suggest that RNA was involved in the complex. Antinucleolar antibody is thought to be specific for antibody to RNA or an RNA precursor (Pinna *et al.*, 1973), and its absence during that period might suggest that circulating RNA and antibody to RNA were complexed in equilibrium. Other materials, such as low molecular weight IgM or IgG rheumatoid factor, could conceivably participate in the toxic complex.

Finally, when the steroid dose was reduced, the arteritis was no longer suppressed and the patient's condition was exacerbated both clinically and serologically. Suppression of the vasculitis was eventually achieved with the use of cyclophosphamide.

We believe that the serial analysis of immunological events in this case has provided greater insight into the immunopathological events which occur during the development of rheumatoid vasculitis.

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