

Circulating immune complexes, serum immunoglobulins, and acute phase proteins in psoriasis and psoriatic arthritis

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SUMMARY Raised levels of circulating immune complexes were found in the plasma of 47% of patients with psoriasis and in 58% of those with psoriatic arthritis. The mean levels were significantly raised when compared with normals, but there was no difference between the 2 patient groups. The levels of acute phase proteins (C-reactive protein, fibrinogen, alpha-1-antitrypsin, and the 9th component of complement) were normal in those patients with psoriasis but were significantly raised in patients with psoriatic arthritis. Serum immunoglobulin G and A levels were equally raised in both patient groups, immunoglobulin M being normal. C-reactive protein and fibrinogen gave the best correlation with the clinical index of disease activity.

Psoriatic arthritis occurs in about 7% of patients with psoriasis,¹ the reason for the development of an arthritis being unknown. In rheumatoid arthritis immune complexes have been demonstrated in serum and synovial fluid and may play a role in its pathogenesis.^{2,3} Immunoglobulin G complexes have been found in eluates from the synovium in psoriatic arthritis,⁴ and it is possible that immune complexes may play a role in the pathogenesis of the arthritis.

In this study we measured circulating immune complexes using the solid phase C1q radioimmunoassay to determine whether they were present in patients with psoriatic arthritis but absent in those with psoriasis alone. Koskello *et al.*⁵ have shown serum caeruloplasmin levels to be normal in psoriasis but raised in severe psoriatic arthritis. Serum copper levels were raised in both groups, so it is possible that the caeruloplasmin levels were raised because it can also act as an acute phase protein. This difference between the 2 patient groups could be due to a difference in type or severity of the inflammatory response. We therefore measured C-reactive protein, fibrinogen, alpha-1-antitrypsin, and the 9th component of complement to determine whether there was a difference between the 2 patient groups with respect to these acute phase proteins.

Patients and methods

The patient groups consisted of 15 patients in hospital with severe psoriasis and 29 with psoriatic arthritis, whose skin involvement varied from mild to severe. They were compared with 21 age matched controls. The psoriatic arthritis patients conformed to the rheumatoid-like pattern as described by Moll and Wright⁶ and were all IgM rheumatoid factor negative.

Clinical assessment of disease activity consisted of early morning stiffness measured in minutes, Ritchie index,⁷ and the number of active joints. An active joint was defined as one with synovial thickening, with or without an effusion. All these measurements were then scored on a 0-4 scale and then summated for each patient to give a clinical activity index. At the time of the study the psoriasis patients were receiving only topical corticosteroids and those with arthritis nonsteroidal anti-inflammatory drugs.

Serum samples were stored in aliquots at -70°C and thawed only once. Purified human C1q was prepared by the method of Reid *et al.*⁸

Immune complexes were measured by the modified solid phase C1q radioimmunoassay of Hay *et al.*⁹ 1 ml quantities of human C1q solution (10 mg/l) in phosphate buffered saline (PBS) pH 7.4 were incubated in polystyrene tubes (LP3, Luckham, Ltd, Sussex) for 72 hours at 4°C. The tubes were then washed 3 times with PBS. 50 µl of test serum were

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added to 100 μ l of 0.2 M EDTA (adjusted to pH 7.5 with NaOH) and incubated for 30 minutes at 37°C. The mixture was then transferred to an ice bath.² Duplicate 50 μ l samples were placed in the coated plastic tubes together with 950 μ l of PBS containing 0.05% Tween 20 (PBS-Tween). Coated tubes containing 1 ml PBS-Tween were used as background controls. The tubes were incubated for 1 hour at 37°C and for 30 minutes at 4°C. Unbound proteins were then removed by washing 3 times with cold PBS. Immune complexes bound to the C1q-coated tubes were detected by incubating the tubes with 1 μ g of purified radiolabelled anti-IgG in 1 ml PBS-Tween at 37°C for 1 hour and then at 4°C for 30 minutes. Unbound labelled reagent was removed by 3 washes with cold PBS. The tubes were then counted in a gamma-ray spectrometer, the amount of radioactivity bound being a measure of the immune complexes in the patient's serum.

The acute phase proteins, C-reactive protein, fibrinogen, 9th component of complement, alpha-1-antitrypsin, and the immunoglobulins G, A, and M were measured by single radial immunodiffusion in agar, with monospecific antisera (Behring).¹⁰

Statistical evaluation was by Student's *t* test and multiple regression analysis.

Results

Levels of circulating immune complexes were greater than the normal mean plus 2 standard deviations in 47% of patients with psoriasis and in 58% of those with psoriatic arthritis (Fig. 1). There was no significant difference between the mean levels of the 2 patient groups (psoriasis mean \pm SD, 2.6 \pm 1.9 mg/l serum anti-IgG bound; psoriatic arthritis, 3.0 \pm 2.3) but when compared with the normal controls (mean \pm SD, 1.1 \pm 0.7) the values for both patient groups were significantly raised ($P < 0.01$). There was no correlation between circulating immune complex levels and serum immunoglobulin G or C-reactive protein. The level of immune complexes in patients with arthritis did not show any correlation with the clinical index of disease activity, age of onset, or disease duration.

Table 1 shows the mean acute phase protein levels. Those patients with psoriasis alone had levels that were not significantly different from normals, whereas those with psoriatic arthritis had significantly raised levels of erythrocyte sedimentation rate (ESR), C-reactive protein, fibrinogen, 9th component of complement ($P < 0.01$), and alpha-1-antitrypsin ($P < 0.05$). The patients with arthritis had raised levels of ESR, C-reactive protein, and 9th component of complement ($P < 0.05$) when compared with those with psoriasis alone.

The acute phase proteins were compared with the clinical index of disease activity in those patients with psoriatic arthritis, and the results are shown in Table 2. C-reactive protein and fibrinogen correlated significantly with clinical disease activity ($P < 0.01$), ESR

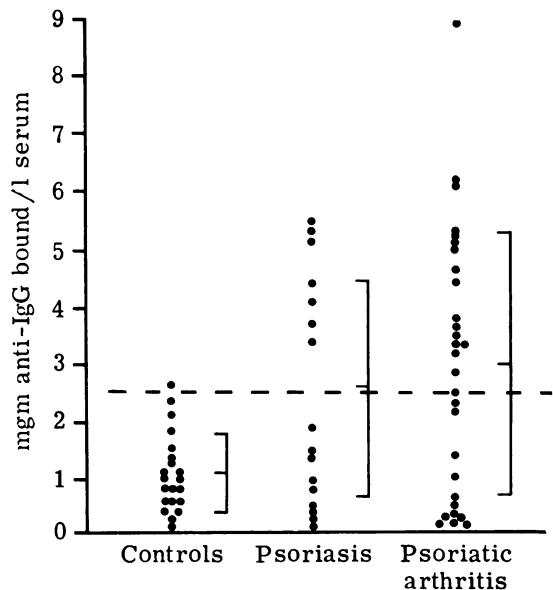


Fig. 1 Solid phase C1q binding in patients with psoriasis alone and psoriatic arthritis compared with normal controls. The vertical bars indicate mean \pm standard deviation, and the dotted horizontal line is the upper limit of normal (95% confidence limit).

Table 1 Acute phase protein levels in normal controls and patients with psoriasis and psoriatic arthritis

	Controls* (1)	Psoriasis* (2)	Psoriatic arthritis* (Mean \pm SD) (3)	P 2 vs. 1	P 3 vs. 1	P 2 vs. 3
ESR mm/h	8.1 \pm 4.5	12.9 \pm 10.4	33.3 \pm 25.4	NS	0.01	0.01
C-reactive protein (mg/100 ml)	0.4 \pm 0.2	0.7 \pm 0.3	2.23 \pm 2.01	NS	0.01	0.01
Fibrinogen (mg/100 ml)	363 \pm 50	398 \pm 75	448 \pm 88	NS	0.01	NS
Complement 9 (% normal)	102 \pm 50	120 \pm 55	165 \pm 60	NS	0.01	0.05
Alpha-1-antitrypsin (mg/100 ml)	278 \pm 60	296 \pm 72	330 \pm 60	NS	0.05	NS

*Mean \pm standard deviation. NS = Not significant. (SI conversion: g/l = mg/100 ml \times 0.01.)

Table 2 *Correlation between clinical assessment of disease activity, acute phase proteins, and serum immunoglobulins*

Clinical disease activity		
Correlated with:	C-reactive protein	P=0.01
	Fibrinogen	P=0.01
	ESR	P=0.05
	Complement 9	P=0.05
Did not correlate with:	Alpha-1-antitrypsin	
	Immunoglobulins G, A, M	

Table 3 *Serum immunoglobulin levels in normal controls and patients with psoriasis and psoriatic arthritis.*

	Controls* (1)	Psoriasis* (2)	Psoriatic arthritis* (3)	P 2 vs. 1	P 3 vs. 1	P 2 vs. 3
IgG (IU/ml)	116±24	158±56	171±65	0.01	0.001	NS
IgA (IU/ml)	125±58	221±76	245±91	0.01	0.001	NS
IgM (IU/ml)	113±58	107±63	120±67	NS	NS	NS

*Mean ± standard deviation. NS = Not significant.

and 9th component of complement were marginally significant ($P < 0.05$), and the alpha-1-antitrypsin and immunoglobulin G, A, and M levels did not correlate with clinical activity.

In Table 3 mean immunoglobulin levels for IgG, A and M are shown. IgG and IgA levels were significantly raised for both groups (psoriasis $P < 0.01$; psoriatic arthritis $P < 0.001$). Although the mean levels present in the psoriatic arthritis group were higher than those with psoriasis alone, they did not reach statistical significance. IgM levels were normal for both groups. The ratio of IgA to IgG was measured to determine their relative increases, our normal ratio being 1.08 ± 0.18 (mean ± SD). Patients with psoriasis had a ratio of 1.40 ± 0.32 (mean ± SD) and psoriatic arthritis 1.43 ± 0.28 (mean ± SD), these ratios being significantly raised in comparison with the normals ($P < 0.01$) and also with those of rheumatoid arthritis patients (1.06 ± 0.5 , mean ± SD, $P < 0.01$) (Highton, personal communication).

Discussion

Circulating immune complex (CIC) levels, as measured by the C1q solid phase radioimmunoassay, were equally raised in both psoriasis and psoriatic arthritis. In the patients with psoriasis immune complex levels did not correlate with clinical measurements of disease activity. Karsh *et al.*¹¹ using the C1q deviation test, found raised levels of CIC in both patient groups. There was no difference between the 2 groups or correlation with

disease activity. They were unable to detect CIC using a modified Raji cell assay measuring only IgG complexes and concluded that the complexes measured probably contained IgM rather than IgG. The method we used measures IgG complexes, and the reason for the discrepancy may be due to the assay used. It is often difficult to interpret immune complex results, because the type of complex detected varies depending on the method used. Braun-Falco *et al.*,¹² using the C1q deviation test in psoriasis found CIC in 70% of patients. Therefore raised levels of CIC are present in psoriasis and psoriatic arthritis and do not appear to be specific for psoriasis.

The role of circulating immune complexes in psoriasis and psoriatic arthritis is unknown, but it is an interesting possibility that it could be related to the abnormal blood vessel morphology in this disease. Nail fold capillaries in patients with psoriatic arthritis have been shown to be meandering with tight terminal convolutions,¹³ an abnormality also present in psoriatic skin capillaries.¹⁴ Histologically a large number of endothelial gaps in the walls of postcapillary venules of both involved and uninvolved skin have been demonstrated.¹⁵ It is therefore possible that circulating immune complexes could pass through these gaps in the vessel walls and become deposited in the skin, thus initiating the pathological process. These blood vessel defects have not been demonstrated in psoriatic synovium, but Lawrence¹⁶ has postulated that, if present, they could contribute to the arthritis. The complexes we measured had IgG as the antibody, but in view of the high IgA levels it would be interesting to see whether IgA-containing complexes were present and to determine their relationship to the arthritis.

The acute phase protein levels were significantly raised only in those with arthritis. Even in the patients with severe psoriasis alone these levels were not significantly elevated. These differences could be due to 2 factors. First, they may reflect the severe inflammation present in the arthritis group; or, secondly, the arthritis is a different inflammatory process, producing the appropriate stimuli for the acute phase protein response. The ESR has been shown to be raised in psoriatic arthritis and to correlate with clinical disease activity.¹⁷ In this study C-reactive protein and fibrinogen gave a better correlation with disease activity than the ESR.

The raised levels of immunoglobulin A and G are in agreement with previous reports.^{18,19} The mean levels were slightly higher in those patients with arthritis but did not correlate with disease activity. It is interesting that the ratio of IgA to IgG in psoriasis and psoriatic arthritis is higher than that in rheumatoid arthritis, showing relatively greater

increase in IgA production. There is evidence for defective function of a T cell subset,^{20 21} and it has been postulated that this could be a suppressor cell which, when absent, allows increased production of IgA. Another possibility is that the causative antigen for psoriasis may enter through the gastrointestinal tract. However, the exact reason for this disproportionate elevation of IgA levels is unknown.

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