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Serum immune complexes containing IgA appear to predict erosive arthritis in a longitudinal study in rheumatoid arthritis*

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SUMMARY Fifty seven patients with rheumatoid arthritis (RA) were studied longitudinally, and the presence of rheumatoid factor (RF) and various types of immune complexes (IC) was correlated with joint activity and the presence of extra-articular features (EAF). In a cross sectional study it was found that the levels of circulating IC and RF correlated significantly with joint disease activity and the presence of EAF. Longitudinally, levels of IC measured by the C1q binding activity and IC containing IgG and IgM correlated significantly with fluctuations in joint disease activity, whereas IC containing IgG and IgA correlated with the occurrence of EAF. RF and IC levels, however, did not predict the clinical course of the disease. IC containing C3 and C4 were found infrequently and were only present in patients with active rheumatoid vasculitis (RV). The continuous presence of these IC appeared to be linked to the recurrence of vasculitis, irrespective of treatment. Significantly more erosions of hands and feet were found after one year follow up in those RA patients who presented early (disease duration less than one year) who initially had a raised serum IgA IC level ($r=0{\cdot}72$; $p<0{\cdot}005$).

Key words: prognostic value, articular activity, extra-articular disease, erosions.

During the last decade many reports have been published on numerous immune complex assays used to investigate the serum or synovial fluid (SF), or both, in autoimmune disease such as rheumatoid arthritis (RA). The presence of immune complexes (IC) has been implicated in the pathogenesis of RA.[1] Some cross sectional studies have shown that raised levels of IC in serum and synovial fluid (SF) are associated with an active joint disease[2–4] or with the presence of extra-articular features (EAF),[5–7] whereas other authors found only a weak association or none at all between IC and disease parameters.[7–9] This discrepancy might be partially due to differences in the sensitivity of various assays for various types of IC.[10] With the development of specific methods for the detection of circulating IC containing not only IgG but also IgA, IgM, and complement (C3 or C4) it is now possible to investigate the occurrence and significance of various classes of circulating IC.[11 12]

In a recent cross sectional study we found a positive association between the levels of C1q binding activity (C1qBA), IC containing IgG and IgA (IgG IC, IgA IC) and both joint severity (i.e., the Ritchie index) and the presence of rheumatoid vasculitis (RV).[13] Relatively little is known about the relevance of longitudinal measurements of circulating IC and rheumatoid factor (RF) as indicators of disease activity within individual RA patients. Some studies have shown that a decrease of IC levels and the amount of RF are associated with a reduction of joint inflammation[14 15] or diminished activity of a systemic disease, e.g., RV,[16 17] when patients are treated with a remission inducing drug. Few prospective studies have been published concerning the value of RF and IC for the

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prediction of disease activity.[18–20] Most of the methods used for the determination of IC in these studies were based on the detection of complement or IgG within the IC. Other components of IC have seldom been investigated.

The aim of the present study was to determine whether changes in disease activity correlated with fluctuations of the class specific IC and RF titres and whether any of these assays can predict joint disease activity or development of EAF. In addition, possible correlations were sought between measurements of circulating IC at the initial clinical assessment of patients with RA who present early and the development of erosions one year later.

Patients and methods

PATIENTS

Fifty seven of the original 60 seropositive patients with definite or classical RA[21] described elsewhere[13] were followed up for at least one year. Three patients were lost to follow up; one refused further evaluation, one died of septicaemia, and the other died with severe RV. The patients entered this prospective study over a period of 12 months, and after 30 months the study was closed. On entry thirty two patients had a disease duration of less than one year (early RA) and 25 patients had established RA with a disease duration of at least two years. Of the patients with established RA, seven had signs of RV at entry. Vasculitis was defined by the presence of one or more of the following features: deep ulcers, severe nailedge thrombi, digital gangrene, palpable purpura, or neuropathy. In six of seven patients this was histologically proved by biopsies of skin, muscle, or kidney at the initial assessment. One patient in the early RA group developed RV after one year of the study with skin eruptions. The involved skin had leucocytoclastic vasculitis. All clinical measurements were performed by the same physician (MLW) at six month intervals with special attention to the signs of EAF such as nodules, pleuritis, pericarditis, episcleritis, neuropathy, Felty's syndrome, or vasculitis. Joint disease activity was scored not only as joint tenderness according to the Ritchie articular index[22] but also as the total number of swollen joints. Hand, wrist, and forefoot radiographs of the patients with early RA were taken at entry and one year later. At the end of the study the radiographs of each patient were assessed blindly by one of us (AC) according to the *Atlas of Standard Radiographics*.[23] Erosions were scored according to a five point scale: no abnormalities (0), dubious (1), mild but definite (2), moderate erosions (3), and severe destructive lesions or ankylosis, or both (4). The total number of joints in the hands, wrists, and feet with radiographic scores of grade 2 or more was recorded (maximum of 42 joints for each patient).

LABORATORY ASSESSMENT

At the time of physical examination (mid-morning) blood was collected for laboratory analysis. Serum was stored at −70°C before testing. RF were detected by the Waaler-Rose agglutination test[24] and the latex fixation test.[25] IC were measured by the ^{125}I-C1q binding assay (C1qBA)[26 27] and radioimmune polyethylene glycol 6000 (PEG) precipitation assays (for IC containing IgM, IgG, IgA, C3, and C4),[11 12 28] using 3½% PEG.

STATISTICAL ANALYSIS

Spearman's rank correlation coefficient was used to detect associations between laboratory values and clinical parameters for disease activity at the time of examination and also six months later. Patients with RA were divided into two groups, one showing EAF at more than 50% of all clinical evaluations and the other with EAF at less than 50% of the hospital visits. The differences in RF titres of IC levels between these two groups were assessed by the Wilcoxon two sample test (see Table 2). Possible relationships between the results of IC assays and RF tests and increases of the number of radiographic erosions were assessed by the Spearman's rank correlation coefficient for each patient separately. The associations between the individual parameters were assessed with Student's t test to examine the hypothesis that the (weighted) mean of the correlation coefficient was equal to zero.[19] The relation within patients between fluctuations in the occurrence of EAF and RF titres or IC levels was studied by computing for each patient the mean test value during the periods when the patient did and did not show EAF. The sign test was then used to establish whether the difference between these two mean levels was significantly more often positive than negative.

Results

JOINT DISEASE ACTIVITY, SERUM IC LEVELS, AND RF TITRES

Correlation analysis between the levels of IC and RF titres and clinical parameters at successive times of assessment (Table 1) showed that IC measured by the C1qBA and IgM IC had the most significant correlations. In most instances, however, a significant correlation was also observed between disease activity and the other laboratory parameters. At the initial assessment RF titres did not correlate with either the number of swollen joints or the Ritchie

Table 1 *Correlation between indices of joint activity and laboratory parameters in the present study*

Time of assessment after entry (months)		*Correlation coefficient*					
		Latex	*Waaler-Rose*	*C1qBA*	*IgG IC*	*IgA IC*	*IgM IC*
0 (n=57)†	Swollen joints	0·18	0·15	0·45***	0·39**	0·29*	0·41**
	Articular index	0·11	0·19	0·44**	0·42**	0·35**	0·52***
6 (n=57)	Swollen joints	0·43**	0·44**	0·47***	0·43**	0·26	0·14
	Articular index	0·42**	0·33*	0·37**	0·36**	0·31*	0·43**
12 (n=57)	Swollen joints	0·40**	0·41**	0·42**	0·42**	0·37**	0·38**
	Articular index	0·42**	0·38*	0·42**	0·44**	0·40**	0·39**
18 (n=36)	Swollen joints	0·40**	0·23	0·29*	0·34*	0·46**	0·39**
	Articular index	0·41**	0·28	0·36*	0·27	0·32*	0·56***
24 (n=36)	Swollen joints	0·48**	0·53**	0·40*	0·31	0·29	0·42*
	Articular index	0·41*	0·35	0·21	0·28	0·36	0·28

*p<0·05; **p<0·01; ***p<0·001.
†n=number of patients.

index for the total group of 57 patients, whereas a significant correlation was found during the follow up period. This difference occurred because of the lack of association between RF titres and joint activity parameters (number of swollen joints or articular index) of the 32 patients with early disease. In contrast, IC levels were similar in patients with longstanding RA and in those with early disease (data not shown). No association was found between the presence of C3 IC or C4 IC and the activity parameters.

ASSOCIATION BETWEEN MEAN SERUM IC LEVELS AND RF TITRES AND THE INCIDENCE OF EAF

There was an association between the occurrence of EAF and the mean level of IC and titre of RF. Nine patients who showed no EAF had a mean C1qBA level of 31 μmol/ml, 18 patients who had signs of EAF at half or less of all their physical examinations had a mean level of 42 μmol/ml, 13 patients who had EAF at more than 50% of all examinations had a mean IC level of 84 μmol/ml, and 17 patients who had signs of EAF throughout the study had a mean IC level of 203 μmol/ml. Similar differences in mean levels of IC containing IgG, IgA, and IgM were found for these groups of patients (data not shown).

As shown in Table 2 raised levels of IC containing C1qBA, IgG, IgA, and IgM were associated with EAF. When patients with vasculitis were excluded, however, the association held only for C1qBA IC and IgM IC.

Table 2 *Association between raised mean values of circulating IC or RF and an increased incidence of EAF (<50%) during the follow up study (n=57)*

Test	*p Value**
Latex	NS
Waaler-Rose	NS
C1qBA	<0·001
IgG IC	<0·05
IgA IC	<0·005
IgM IC	<0·005
C4 IC	=0·05
C3 IC	NS

*p Values were calculated with Wilcoxon's two sample test.

RELATION OF RF TITRES AND IC LEVELS TO DISEASE ACTIVITY AND THE OCCURRENCE OF EAF

To investigate the possible relation between clinical and laboratory parameters within individual patients in a longitudinal study correlation coefficients were computed for each patient. The analysis was based on between three and six observations for each patient. To compensate for the unequal numbers of observations taken into account these correlation coefficients were normalised by multiplying them by $\sqrt{(n-1)}$ (i.e., the approximate standard error), n being the number of observations of the patients. Student's one sample *t* test was then used to examine whether the mean correlation coefficient differed significantly from zero.[19] Table 3 shows the results of these analyses. The fluctuation of RF titre, C1qBA IC, and IgM IC correlated significantly with the disease activity (number of swollen joints or articular index, or both) IgG IC correlated significantly only with the articular index, and IgA IC did not correlate with either parameter of joint disease activity.

Only 30 patients showed fluctuations of EAF during this longitudinal study. Nine patients showed

Table 3 *Correlation of RF and IC levels with joint disease activity during the course of the disease in individual patients†*

Assays	*No of patients‡*	*Mean (SD) of normalised Spearman's rank correlation coefficients ($r\sqrt{n-1}$) for:*	
		Swollen joints	*Articular index*
Latex	50	0·65 (0·93)***	0·43 (0·98)**
Waaler-Rose	55	0·46 (1·08)**	0·51 (1·05)***
C1qBA	54	0·51 (0·87)***	0·76 (0·92)***
IgG IC	54	0·28 (1·13)	0·39 (1·02)*
IgA IC	44	0·32 (1·06)	0·20 (1·09)
IgM IC	57	0·47 (0·94)***	0·39 (0·98)**

*p<0·01; **p<0·005; ***p<0·001.
†Significance of the deviation of the mean correlation coefficient (r) from zero assessed by Student's one sample *t* test.
‡Correlation coefficients could not be calculated for all patients.

no signs of EAF during the entire study period, and 18 patients always had EAF when examined. In the group of 30 patients differences between the RF titre or IC level during the stage when EAF were present or absent were computed (Table 4). Application of the sign test showed that the levels of IgG IC and IgA IC in each patient were significantly higher in the presence of EAF. Complement C3 IC and C4 IC were found infrequently and were not related to joint disease parameters during this longitudinal study. They were always present in sera of three patients with recurrent active vasculitis. In four other patients the C3 IC and C4 IC became undetectable at the same time as signs of vasculitis disappeared after treatment with corticosteroids or cytostatics, or both.

VALUE OF IC AND RF FOR PREDICTION OF JOINT ACTIVITY AND OCCURRENCE OF EAF

When RF titres or IC levels of individual patients were compared with disease activity parameters measured six months later significant correlation coefficients were not found (data not shown). Thus these tests were in no way predictive of joint disease activity. Furthermore, RF titres and IC levels did not predict the development of EAF.

Table 4 *Association between fluctuation in the occurrence of EAF and laboratory parameters in individual patients in the follow up study (p values calculated with the sign test)*

Assays	*No of patients*	*Significance (p)*
Latex	30	NS
Waaler-Rose	30	NS
C1qBA	29	NS
IgG IC	30	<0·01
IgA IC	29	<0·05
IgM IC	29	NS
C4 IC	29	NS
C3 IC	29	NS

VALUE OF CIRCULATING RF AND IC FOR THE PREDICTION OF AN INCREASE IN JOINT EROSIONS

To investigate the relation between laboratory parameters and the development of radiological abnormalities radiographs were taken of each patient with early disease at entry to the study (n=32) and again after approximately one year. Of the various RF and IC tests, only the level of IgA IC at the initial assessment was predictive of an increase of radiological lesions after one year (r=0·72; p<0·001). Furthermore, a significant association (p<0·001) was found between the increase of the total number of joints with erosions (grade 2 or more) in each patient and the presence of IgA IC (Fig. 1). All six patients who had raised IgA IC levels showed a significant increase in the number of joints with erosions. This suggests that this test could serve as a specific indicator for the development of erosive arthritis in early RA.

Discussion

In an early cross sectional study we found that patients with active joint disease, as measured by the Ritchie articular index, have raised circulating IC levels and higher mean levels of IC more frequently than patients with inactive disease.[13]

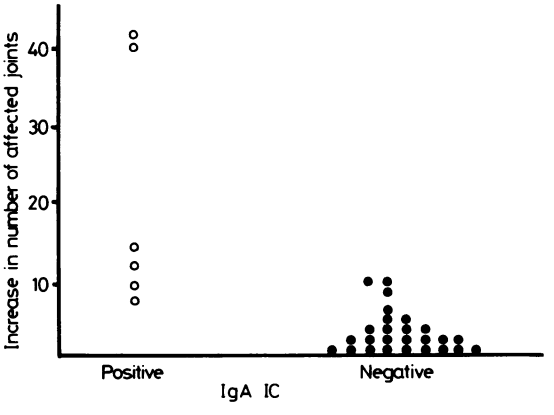

Fig. 1 *Increase in the number of joints with radiological erosive disease after one year of observation of patients with (○) or without (●) circulating IgA IC at the start of the study. (p<0·001, Wilcoxon's rank sum two sample test).*

Circulating IC were also associated with the presence of EAF, including RV. The results of the present longitudinal study made at initial assessment, and also at almost all subsequent assessments, confirm the earlier findings.

The absolute values of the IC and RF were found to correlate significantly with disease activity as assessed by either the Ritchie index or the number of swollen joints (Table 1), though the correlation coefficients were not high. Similar correlations were found between high mean levels of IC and the presence of EAF during our study (Table 2). When signs of clinical RV were excluded from this patient group, however, only IC containing C1qBA and IgM correlated significantly with EAF. This is explained by the fact that IgA IC, IgG IC, C3 IC, and C4 IC were associated predominantly with RV. IgM IC alone may not cause RV, since in one study signs of vessel inflammation were absent in biopsy specimens of clinically uninvolved skin even though IgM deposits were present in the vessel wall.[29] IC levels determined by the C1qBA test correlated significantly with the presence of IgM deposits in the skin.[30]

An overall correlation between the level of circulating IC and various measurements of disease activity (joint activity, extra-articular features, or erythrocyte sedimentation rate (ESR)) had been found in a large number of clinical studies, though published values differ considerably.[2–7] This relationship has been substantiated by one of the most extensive cross sectional studies.[31] According to these authors none of the tests used to detect IC offered diagnostic advantages over other established laboratory tests. This report raised several questions. Are IC determinations clinically useful for the monitoring of disease activity in individual patients? Can they predict the course of inflammatory parameters of joint disease, the occurrence of EAF, or the development of erosions?

The data from the present longitudinal study indicate that RF and some IC tests (C1qBA and IgM IC) correlate significantly with clinical indices for joint activity (Table 3). Of all these tests, we found the C1qBA to be associated most significantly with fluctuations in Ritchie articular index, and this laboratory parameter might be useful for monitoring rheumatoid joint disease. Our data indicate, however, that the RF and IC tests have no value as prognostic indicators of disease activity (joint activity or EAF). Only a few reports are available concerning serial studies on RF and circulating IC in relation to articular manifestations.[14–19 32 33] In general, our data confirm the results reported by these authors, though most of the studies reported previously were based on a small number of observations in each patient, or the period covered was relatively short. Our results concerning the lack of predictive value of IC and RF for joint disease activity during the course of the disease are compatible with recent reports,[20 33] which suggest that the circulating IC are epiphenomena and not pathogenic. If so, the IC and RF would not be more clinically specific for joint destruction than, for example, the ESR.

The occurrence of IgA IC in RA, and particularly in patients with EAF, is of interest.[13] In our patients only changes in IgA IC and IgG IC paralleled changes in EAF (Table 4), and IC did not predict the occurrence of EAF. IC containing C3 and C4 were found so infrequently that statistical tests were not applicable, but it was obvious that they occurred only in patients with recurrent vasculitis. In two patients only slightly increased IC levels were detected at the first clinical evaluation, but a few weeks later active vasculitis developed, and the IC levels were strongly raised, showing the lack of predictive value in circulating IC measurement.

Few studies have been published on serial determinations of circulating IC in patients with RV treated with remission inducing drugs.[16 17] In these studies concentrations of IC and RF decreased with the disappearance of vasculitis, and one author suggested that IC containing IgG RF might be responsible for the development of vasculitis.[17] Special tests to assess class specific immunoglobulins containing IC were performed in only one study, and in agreement with our observations these investigators found an association between the occurrence of EAF and the demonstration of IgA IC in RA patients.[34]

Although levels of IgA IC did not significantly coincide with changes in joint disease activity in our study, they did correlate significantly with the appearance of EAF. The established associations between IgA IC and EAF,[13 34 35] between EAF and the development of erosive disease,[36 37] and between IgA IC and marked erosive changes in early RA, found in the present study, suggest that IgA IC may be a good marker of the development of erosive disease. It has been suggested that IgA RF is less easily cleared from the joints than IgG RF and IgM RF and can spill over into the peripheral circulation.[19] Whether the same applies to IgA IC is uncertain, but venous blood from limbs with actively inflamed joints has a higher content of IgA IC than arterial blood from the same limb.[38] Involvement of IgA in the pathogenesis of the rheumatoid disease seems likely, especially since serum IgA levels are frequently raised in RA patients and a fall in the IgA level coincided with improvement of RA in patients treated with disease modifying drugs.[39] Moreover,

the presence of IgA IC in early RA appears to be associated with an unfavourable course of RA, as already found for IgA RF.[18 19]

In summary, determination of RF and class specific IC did not yield more information about the clinical state or the prognosis of disease activity in RA patients than physical examination or other common laboratory tests. The same conclusion was drawn from a follow up study in patients with SLE.[40] It is known that not all IC are functionally similar, however, and studies on IC combined with functional tests to assess phagocytosis and clearance of IC might yield more information about the role of IC in the pathogenesis of the often erratic course of RA and contribute to the understanding of this disease.[41] Because IgA IC may precede the development of erosive arthritis further studies on the presence of these IC in early arthritis are warranted.

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