

The presence of anti-cyclic citrullinated peptide antibody is associated with magnetic resonance imaging detection of bone marrow oedema in early stage rheumatoid arthritis

M Tamai, A Kawakami, M Uetani, S Takao, F Tanaka, H Nakamura, N Iwanaga, Y Izumi, K Arima, K Aratake, M Kamachi, M Huang, T Origuchi, H Ida, K Aoyagi, K Eguchi

Ann Rheum Dis 2006;**65**:133–134. doi: 10.1136/ard.2005.04138

Early prediction of erosive joint damage is very important in rheumatoid arthritis (RA) because significant articular damage in patients is evident radiologically within the first few years of the disease.¹ This study was designed to confirm whether anti-cyclic citrullinated peptide antibodies (anti-CCP Ab) define the subset of patients with early stage RA who have bone marrow oedema, observed by magnetic resonance imaging (MRI).

Patients were referred from the Early Arthritis Clinic, started in 2001 at the First Department of Internal Medicine, Graduate School of Biomedical Sciences, Nagasaki University. After prospective follow up, diagnosis of RA was made by the 1987 criteria for RA of the American College of Rheumatology.² Eighty patients who gave their informed consent to the protocol that was approved by the Institutional Review Board of Nagasaki University were enrolled in the study.

The disease duration of 80 patients with RA at the entry was <24 months (mean disease duration 4.8 months), and thus these patients had early stage RA. Serological variables at entry were as follows: mean (SD) C reactive protein 1.6 (2.5) mg/ml, matrix metalloproteinase 3 (MMP-3) positivity 46.3%, anti-CCP Ab positivity 67.5%, and IgM rheumatoid factor (IgM-RF) positivity 67.5%. The mean modified Genant-Sharp score of plain radiographs of both hands at entry was 0.41.

Magnetic resonance images of both wrists and finger joints were taken simultaneously using the 1.5 T system (Sigma, GE Medical Systems, Milwaukee, WI). Images were evaluated for the presence or absence of bone marrow oedema and synovitis in 15 joints of each finger and wrist—that is, the distal radioulnar joint, radiocarpal joint, mid-carpal joint, 1st carpometacarpal joint, 2nd–5th carpometacarpal joints (together), 1st–5th metacarpophalangeal joints separately, and the 1st–5th proximal interphalangeal joints separately (total 30 joints from both hands).

The severity of synovitis was assessed by the number of joints with synovitis and the rate of enhancement (E-rate), on a dynamic study by injection of gadolinium-diethylenetriamine pentaacetic acid. The E-rate means the vascularity,^{3–4} by plotting the signal intensity against time in a selected region of interest (about 2–3 mm in diameter) of the site of maximum enhancement in the above-mentioned 15 joints. Determination of bone marrow oedema was also carried out^{5–7} by two experienced radiologists (MU and ST), and decisions were reached by consensus.

We examined simply and automatically the wrists and finger joints, including proximal interphalangeal joints, by MRI, using the above-mentioned variables instead of the OMERACT 5 RA-MRI scoring system.^{6,7} We divided the 80 patients with early stage RA according to the presence or absence of anti-CCP Ab (table 1).

The proportion of patients with bone marrow oedema was significantly higher in the anti-CCP Ab+ group than in the anti-CCP Ab- group. In contrast, there were no differences between the two groups for the other variables (for example, CRP, MMP-3 positivity, number of joints with synovitis, and mean E-rate of 30 joints).

Division of patients according to the presence or absence of IgM-RF also showed a higher proportion of patients with bone marrow oedema in those who were anti-CCP Ab positive than in those negative for the antibody, but the difference was not significant (table 2). However, because 81.5% of anti-CCP Ab+ patients also possessed IgM-RF (44/54 patients), anti-CCP Ab and IgM-RF are not independent factors for bone marrow oedema. Bone marrow oedema is a forerunner of bone erosion on plain radiography,⁸ and thus our present data show the additional importance of the

Table 1 Comparison of anti-CCP Ab+ and anti-CCP Ab- patients

Variables	Anti-CCP Ab+ (n = 54)	Anti-CCP Ab- (n = 26)	p Value
CRP (mg/ml)	1.3 (2.0)	2.2 (3.3)	0.39*
MMP-3 (%)	50.0	38.5	0.33†
Number of joints with synovitis	12.2 (6.4)	10.3 (6.4)	0.30*
Mean E-rate of 30 joints	7.7 (3.0)	7.4 (2.9)	0.67*
Bone marrow oedema			
%	64.8	38.5	0.03†
No	2.8 (3.5)	1.1 (2.3)	0.01*

Data are mean (SD) unless stated otherwise. The proportion of patients with bone marrow oedema was significantly higher in the anti-CCP Ab+ group than in the anti-CCP Ab- group: *by Mann-Whitney U test; †by χ^2 test.

Table 2 Comparison of IgM-RF+ and IgM-RF- patients

Variables	IgM-RF+ (n = 54)	IgM-RF- (n = 26)	p Value
CRP (mg/ml)	1.5 (2.1)	2.0 (3.3)	0.96*
MMP-3 (%)	51.9	34.6	0.23**
Number of joints with synovitis	12.1 (5.6)	10.6 (7.8)	0.22*
Mean E-rate of 30 joints	7.6 (3.2)	7.6 (2.3)	0.58*
Bone marrow oedema			
%	63.0	42.3	0.08**
No	2.7 (3.5)	1.4 (2.7)	0.07*

Data are mean (SD) unless stated otherwise. Division of patients by IgM-RF seropositivity showed a higher proportion of patients with bone marrow oedema compared with those negative for the antibody, but the difference was not significant: *by Mann-Whitney U test; †by χ^2 test.

presence of anti-CCP Ab at baseline as an indication of future bone erosion in early stage RA.⁹

We thank Misses Maiko Kubo, Youko Uchiyama, Nobuko Fukuda, and Kouko Munechika for their technical assistance.

This study was supported by a grant from The Ministry of Health, Labour and Welfare, Japan.

Authors' affiliations

M Tamai, A Kawakami, F Tanaka, H Nakamura, N Iwanaga, Y Izumi, K Arima, K Aratake, M Kamachi, M Huang, H Ida, K Eguchi, First Department of Internal Medicine, Graduate School of Biomedical Sciences, Nagasaki University, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan

M Uetani, S Takao, Department of Radiology and Radiation Research, Graduate School of Biomedical Sciences, Nagasaki University, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan

K Aoyagi, Department of Public Health, Graduate School of Biomedical Sciences, Nagasaki University, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan

T Origuchi, Nagasaki University School of Health Sciences, Nagasaki University, 1-7-1 Sakamoto, Nagasaki 852-8520, Japan

MT and AK contributed equally to this work.

Correspondence to: Professor K Eguchi, eguchi@net.nagasaki-u.ac.jp

Accepted 2 June 2005

REFERENCES

- 1 **Fuchs HA,** Kaye JJ, Callahan LF, Nance EP, Pincus T. Evidence of significant radiographic damage in rheumatoid arthritis within the first 2 years of disease. *J Rheumatol* 1989;**16**:585-91.
- 2 **Arnett EC,** Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, *et al.* The American Rheumatology Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;**31**:315-24.
- 3 **Graffney K,** Cookson J, Blades S, Coumbe A, Blake D. Quantitative assessment of the rheumatoid synovial microvascular bed by gadolinium-DTPA enhanced magnetic resonance imaging. *Ann Rheum Dis* 1998;**57**:152-7.
- 4 **Reece RJ,** Kraan MC, Radjenovic A, Veale DJ, O'Connor PJ, Ridgway JP, *et al.* Comparative assessment of leflunomide and methotrexate for the treatment of rheumatoid arthritis, by dynamic enhanced magnetic resonance imaging. *Arthritis Rheum* 2002;**46**:366-72.
- 5 **McQueen FM.** Magnetic resonance imaging in early inflammatory arthritis: what is its role? *Rheumatology (Oxford)* 2000;**39**:700-6.
- 6 **Lassere M,** McQueen F, Ostergaard M, Conaghan P, Shnier R, Peterfy C, *et al.* OMERACT rheumatoid arthritis magnetic resonance imaging studies. Exercise 3: An international multicenter reliability study using the RA-MRI score. *J Rheumatol* 2003;**30**:1366-75.
- 7 **Conaghan P,** Lassere M, Ostergaard M, Peterfy C, McQueen F, O'Connor P, *et al.* OMERACT rheumatoid arthritis magnetic resonance imaging studies. Exercise 4: An international multicenter longitudinal study using the RA-MRI score. *J Rheumatol* 2003;**30**:1376-9.
- 8 **McQueen FM,** Benton N, Perry D, Crabbe J, Robinson E, Yeoman S, *et al.* Bone edema scored on magnetic resonance imaging scans of the dominant carpus at presentation predicts radiographic joint damage of the hands and feet six years later in patients with rheumatoid arthritis. *Arthritis Rheum* 2003;**48**:1814-27.
- 9 **van Gaalen FA,** Linn-Rasker SP, van Venrooij WJ, de Jong BA, Breedveld FC, Verweij CL, *et al.* Autoantibodies to cyclic citrullinated peptides predict progression to rheumatoid arthritis in patients with undifferentiated arthritis: a prospective cohort study. *Arthritis Rheum* 2004;**50**:709-15.

Early prediction of rheumatoid arthritis by serological variables and magnetic resonance imaging of the wrists and finger joints: results from prospective clinical examination

M Tamai*, A Kawakami*, M Uetani, S Takao, H Rashid, F Tanaka, K Fujikawa, T Aramaki, H Nakamura, N Iwanaga, Y Izumi, K Arima, K Aratake, M Kamachi, M Huang, T Origuchi, H Ida, K Aoyagi, K Eguchi

Ann Rheum Dis 2006;**65**:134-135. doi: 10.1136/ard.2005.043075

We aimed at characterising the serological variables and magnetic resonance imaging (MRI) early changes in the wrists and finger joints which would differentiate rheumatoid arthritis (RA) from rheumatic diseases other than RA (non-RA) at the earliest stage.

Patients were referred from the Early Arthritis Clinic, started in 2001 at the First Department of Internal Medicine, Graduate School of Biomedical Sciences, Nagasaki University. After prospective follow up, a diagnosis was made according to international classification criteria, and in particular, RA was defined by 1987 criteria of the American College of Rheumatology for RA.¹ Informed consent was obtained from all the patients, and the protocol was approved by the Institutional Review Board of Nagasaki University.

Eighty consecutive patients with RA and 33 non-RA patients were studied and a diagnosis evaluated 12 months after entry, by March 2005. The mean disease duration of the 80 patients with RA at entry was 4.8 months, and thus they were described as early stage RA.

MR images of both wrists and finger joints were acquired with a 1.5 T system (Sigma, GE Medical Systems, Milwaukee, WI, USA) with the use of an extremity coil. Coronal T₁ weighted spin echo (repetition time 450, echo

time 13) and short time inversion recovery (repetition time 3000, echo time 12, T₁ 160) images were acquired. The images were evaluated for the presence or absence of bone marrow oedema, bone erosion, and synovitis in 15 joints in each finger and wrist—namely, distal radioulnar joint, radiocarpal joint, mid-carpal joint, 1st carpometacarpal joint, 2nd–5th carpometacarpal joints (together), 1st–5th metacarpophalangeal joints separately, and 1st–5th proximal interphalangeal joints separately (total 30 joints from both hands). The extent of synovitis, bone marrow oedema, and bone erosion was determined, as previously described,²⁻⁵ by two experienced radiologists (MU and ST), and decisions were reached by consensus.

Symmetric arthritis is a characteristic feature of RA.¹ The presence of symmetric synovitis on MRI was defined as bilateral involvement of wrist sites, metacarpophalangeal joints, or proximal interphalangeal joints without absolute symmetry. Because we focused on the presence or absence of early joint changes on MRI for the differentiation, we did not use the OMERACT 5 RA-MRI scoring system.^{4,5} As expected, the positivity of matrix metalloproteinase 3 (MMP-3; measured by enzyme linked immunosorbent assay (ELISA; Daiichi Pure Chemicals, Fukuoka, Japan) (46.3% v 12.1%),

Table 1 Serological variables and MRI findings for the discrimination between early stage RA and non-RA

Variables	Odds ratio	Coefficient	SE	p Value	Weighted score
Anti-CCP antibody and/or IgM RF	7.42	2.00	0.57	0.0005	1
MMP-3	2.87	1.05	0.72	0.14	0
Symmetric synovitis	4.37	1.47	0.57	0.009	1
Bone marrow oedema and/or bone erosion	5.48	1.70	0.63	0.007	1

Logistic regression analysis identified the presence of anti-CCP antibody and/or IgM RF, symmetric synovitis on MRI, and bone marrow oedema and/or bone erosion on MRI as significant and independent measures for discrimination between early stage RA and non-RA. The weighted score was calculated based on the regression coefficient for each variable as described in the text.

Table 2 Evaluation of the prediction score (≥ 2) in early stage RA at the first visit

Total score	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)
≥ 1	96.3	30.3			
≥ 2	82.5	84.8	93.0	66.7	83.2
3	50.0	96.9			

We calculated the sensitivity and specificity of our scoring system for the prediction of early stage RA according to the sum of weighted scores described in table 1.

Sensitivity and specificity are shown for patients classified as early stage RA according to the total score (sum of weighted score 1–3).

We evaluated the statistical character of prediction score (≥ 2) for the present 113 patients for the prediction of RA at entry.

anti-cyclic citrullinated peptide antibody (anti-CCP antibody; measured by ELISA; DIASTAT Anti-CCP, Axis-Shield, Dundee, UK) (67.5% v 12.1%), and IgM rheumatoid factor (IgM RF; measured by latex-enhanced immunonephelometric assay; Dade Behring, Marburg, Germany) (67.5% v 30.3%) as well as the frequency of symmetric synovitis (81.3% v 36.4%), bone marrow oedema (56.3% v 12.1%), and bone erosion (45.0% v 9.1%) were higher in early stage RA than in non-RA.

Logistic regression analysis using the statistical analysis system software demonstrated that the presence of anti-CCP antibody and/or IgM RF, symmetric synovitis and bone marrow oedema and/or bone erosion at entry could discriminate between patients with RA and non-RA patients (table 1).

At the first visit, a total score of two or more of the three objective measures (anti-CCP antibody and/or IgM-RF: 1, symmetric synovitis on MRI: 1, bone marrow oedema and/or bone erosion on MRI: 1) allowed the prediction of RA with 82.5% sensitivity and 84.8% specificity, respectively (table 2). (Statistical weights of the variables were calculated based on the regression coefficient for each variable, standardised by dividing by the coefficient for symmetric synovitis; values were rounded off to yield integers.)

Our present data may indicate that the prediction of autoantibodies as well as MRI detection of early joint changes contribute to the accurate diagnosis of early stage RA.

We thank Misses Maiko Kubo, Nobuko Fukuda, Kouko Munechika, and Junko Matsushita for their technical assistance. This study was supported by a grant from the Ministry of Health, Labour and Welfare, Japan

Authors' affiliations

M Tamai, A Kawakami, F Tanaka, K Fujikawa, T Aramaki, H Nakamura, N Iwanaga, Y Izumi, K Arima, K Aratake, M Kamachi, M Huang, H Ida, K Eguchi, First Department of Internal Medicine, Graduate School of Biomedical Sciences, Nagasaki University, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan
M Uetani, S Takao, H Rashid, Department of Radiology and Radiation Research, Nagasaki University, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan
T Origuchi, Nagasaki University School of Health Sciences, Nagasaki University, 1-7-1 Sakamoto, Nagasaki 852-8520, Japan
K Aoyagi, Department of Public Health, Graduate School of Biomedical Sciences, Nagasaki University, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan

*MT and AK contributed equally to this work.

Correspondence to: Professor K Eguchi, eguchi@net.nagasaki-u.ac.jp

Accepted 2 October 2005

REFERENCES

- 1 **Arnett EC**, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, *et al*. The American Rheumatology Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;**31**:315–24.
- 2 **McQueen FM**. Magnetic resonance imaging in early inflammatory arthritis: what is its role? *Rheumatology (Oxford)* 2000;**39**:700–6.
- 3 **Conaghan PG**, O'Connor P, McGoogale D, Astin P, Wakefield RJ, Gibbon WW, *et al*. Elucidation of the relationship between synovitis and bone damage: a randomized magnetic resonance imaging study of individual joints in patients with early rheumatoid arthritis. *Arthritis Rheum* 2003;**48**:64–71.
- 4 **Lassere M**, McQueen F, Ostergaard M, Conaghan P, Shnier R, Peterfy C, *et al*. OMERACT rheumatoid arthritis magnetic resonance imaging studies. Exercise 3: An international multicenter reliability study using the RA-MRI score. *J Rheumatol* 2003;**30**:1366–75.
- 5 **Conaghan P**, Lassere M, Ostergaard M, Peterfy C, McQueen F, O'Connor P, *et al*. OMERACT rheumatoid arthritis magnetic resonance imaging studies. Exercise 4: An international multicenter longitudinal study using the RA-MRI score. *J Rheumatol* 2003;**30**:1376–9.

Brain natriuretic peptide is a potentially useful screening tool for the detection of cardiovascular disease in patients with rheumatoid arthritis

S M J Harney, J Timperley, C Daly, A Harin, T James, M A Brown, A P Banning, K Fox, S Donnelly, B P Wordsworth

Ann Rheum Dis 2006;**65**:136. doi: 10.1136/ard.2005.040634

Patients with rheumatoid arthritis (RA) have a significantly higher risk of coronary heart disease, despite being less likely to report symptoms of angina, and are more likely to experience unrecognised myocardial infarction and sudden cardiac death than non-RA controls.¹ Furthermore, left ventricular diastolic dysfunction has been described in up to 40% of patients with RA.²

Traditional risk factors partially account for this increased risk, and primary prevention is important in this high risk group. Electrocardiography (with or without stress testing) and echocardiography are commonly requested investigations to detect underlying cardiac disease, but access, particularly to echocardiography, is mostly limited to those who are symptomatic. Brain natriuretic peptide (BNP) is a new cardiac biomarker, which is increased in ventricular dysfunction, both systolic and diastolic, and also left ventricular hypertrophy. Measurement of serum BNP levels has become a powerful adjunct to diagnosis and prognostic stratification of patients with suspected ventricular dysfunction in recent years.

This study aimed at investigating the extent to which appropriate primary preventative measures were being used in a group of patients with RA, and investigating the potential use of measurements of serum BNP levels in screening patients with RA for occult cardiac disease.

One hundred and twenty consecutive outpatients fulfilling the 1987 American College of Rheumatology criteria for RA were recruited over a 12 week period. Demographic data, age of onset, and duration of RA, current/past drugs, disease activity, and cardiovascular risk factors were recorded using structured questionnaires (available on request). Blood was taken to determine C reactive protein, erythrocyte sedimentation rate, BNP, thyroid function, and random lipid and glucose profiles. A one way analysis of variance test was used for all normally distributed data and the Mann-Whitney test was used for non-parametric data. Results are presented as mean (SD) unless otherwise stated. Table 1 summarises the clinical characteristics of the 120 patients.

Twenty six patients with RA from the initial group, selected specifically for the absence of a previous physician diagnosis of hypertension or ischaemic heart disease or symptoms of cardiac disease were studied further by Doppler echocardiography and compared with 32 healthy controls. The mean (SD) age of this subgroup was 63 (9.4) years, and 50% were female. Systolic dysfunction (ejection fraction <50%) was evident in 7 (27%) and diastolic dysfunction in 11 (42%) patients. Left ventricular hypertrophy was present in 14 (54%; mean (SD) mass 212 (66) g). BNP levels were significantly higher in patients with RA (mean 9.2 pmol/l, range 0.6–52.6) than in controls (mean 2.5 pmol/l range 0.6–10.4) ($p = 0.004$). BNP levels correlated with end diastolic volume ($r^2 = 0.83$, $p = 3 \times 10^{-7}$), end systolic volume ($r^2 = 0.62$, $p < 0.0001$), and left ventricular mass ($r^2 = 0.4$, $p = 0.0009$). Although the patients were older (mean age 63) than the controls (mean age 50), the correlations with BNP remained highly significant after adjustment for age and other covariates (including sex, full blood count, C reactive

Table 1 Summary of clinical characteristics of the 120 patients (74 female, 46 male) in the initial study

Age, mean (range)	63 (35–81)
Breathlessness and/or chest pain on exertion (%)	17 (14)
Random cholesterol measurements >5 mmol/l	
No (%)	25 (21)*
Range (mmol/l)	5.1–8.1
Statin usage in the hypercholesterolaemic group*,	2/25 (8)
No (%)	
Receiving aspirin and/or ACE inhibitors, No (%)	5 (4)

ACE, angiotensin converting enzyme.
*Random cholesterol measurements >5 mmol/l.

protein, erythrocyte sedimentation rate, and renal function), by logistic regression. Using a cut off point of 5 pmol/l, the sensitivity and specificity of BNP for detection of systolic dysfunction was 70% and 64% and of diastolic dysfunction 60% and 69%.

In this study, occult cardiac dysfunction was present in a worrying proportion of asymptomatic patients with RA. BNP has the potential to be a useful marker of occult cardiac disease in this population, despite potential confounding by age, sex, and subclinical renal disease. The cost of this assay is about one-tenth the cost of an echocardiogram, and so it would be a cost effective initial screening test in patients with RA. Larger studies are needed to confirm this finding, with longitudinal follow up to ascertain its prognostic usefulness.

Authors' affiliations

S M J Harney, A Harin, M A Brown, B P Wordsworth, University of Oxford Institute of Musculoskeletal Sciences, Botnar Research Centre, Oxford, UK

J Timperley, A P Banning, Department of Cardiology, John Radcliffe Hospital, Oxford, UK

C Daly, K Fox, Kim Fox Research Department, Royal Brompton Hospital, London, UK

T James, Department of Biochemistry, John Radcliffe Hospital, Oxford, UK

S Donnelly, Department of Rheumatology, St George's Hospital, London UK

Correspondence to: Dr S M J Harney, Institute of Musculoskeletal Sciences, University of Oxford, Botnar Research Centre, Nuffield Orthopaedic Centre, Windmill Road, Headington, Oxford OX3 7LD, UK; sinead@well.ox.ac.uk

Accepted 11 May 2005

REFERENCES

- 1 Maradit-Kremers H, Crowson CS, Nicola PJ, Ballman KV, Roger VL, Jacobsen SJ, *et al*. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. *Arthritis Rheum* 2005;**52**:402–11.
- 2 Sagnella GA. Measurement and significance of circulating natriuretic peptides in cardiovascular disease. *Clin Sci (Lond)* 1998;**95**:519–29.

Severe relapse of Wegener's granulomatosis during the early postpartum period

A Woywodt, K de Groot, S Bahte, A Schwarz, H Haller, M Haubitz

Ann Rheum Dis 2006;**65**:137. doi: 10.1136/ard.2005.037598

Pregnancy in Wegener's granulomatosis (WG) has been rare, but increasing numbers of pregnancies are now being reported, not least because of the use of less toxic drug regimens. New onset disease during or after pregnancy has been noted previously, but postpartum relapse has not been reported so far. Here, we report a severe postpartum relapse of WG after longstanding remission.

A 27 year old woman was first diagnosed with WG of the upper and lower respiratory tract, central nervous system, eye, and skin in 1995. Treatment with methylprednisolone (500 mg/day for 5 days), oral cyclophosphamide (3 mg/kg), intravenous immunoglobulins, and co-trimoxazole induced remission. Cyclophosphamide was stopped in 1996. Prednisolone and co-trimoxazole were stopped in August 1997 and June 1999, respectively, while the patient continued to be in full remission.

The patient subsequently became pregnant, with an uneventful delivery in September 2000 and a normal postpartum period. In 2004, the patient became pregnant again after she had been counselled about the risk of relapse. When seen in our clinic in August 2004, she was in good health; the C reactive protein (CRP) was normal and antinuclear cytoplasmic antibodies (ANCA) were negative. At that time, proteinuria was 0.29 g/day and urine examination showed no dysmorphic erythrocytes. The patient subsequently had another uneventful delivery on 20 September 2004.

On 27 September, the patient presented with urinary tract infection, which was treated appropriately. On 7 October, she developed an abscess of the left mamma requiring incision and drainage. In mid-October 2004, the patient developed maxillary pain, dry cough, and fever that did not respond to antibiotic treatment. On 18 October, she was first seen in our clinic after she had received treatment elsewhere during pregnancy. Computed tomography showed sinusitis and pulmonary infiltrates as well as nodules, and bronchoscopy demonstrated bronchitis. Bronchoalveolar lavage showed neutrophil and eosinophil alveolitis with no growth in culture. The CRP peaked at 439 mg/l with normal procalcitonin. Urine examination disclosed dysmorphic erythrocytes, and proteinuria increased to 0.85 g/day. Serum creatinine level and clearance were normal. The ANCA became positive at a titre of 1/32. A relapse was diagnosed with involvement of upper respiratory tract, lung, and kidney. Methylprednisolone (500 mg/day) and pulsed intravenous cyclophosphamide were started, with good response, and CRP values declined. As of January 2005, the patient is well with steroids and monthly cyclophosphamide.

The number of pregnancies in patients with WG is currently increasing, but effects of the disease on pregnancy and vice versa remain ill defined.¹ New onset WG during pregnancy or during the postpartum period has been reviewed elsewhere.² Some 26 pregnancies in patients with WG have been reported, and we describe the first in which relapse occurred post partum. Relapse during pregnancy has been noted previously and it has been estimated that among women with WG who conceive in remission, about one in four relapse.³ Lima and colleagues described two relapses during pregnancy.⁴ Active disease at the onset of pregnancy

appears to be correlated with poor outcome,³ and maternal mortality has been reported.⁵ It has been noted that other small vessel vasculitides occur in association with pregnancy as well.^{6,7}

We report the first case of relapse during the early postpartum period. We were surprised to see widespread disease develop so quickly after pregnancy, especially after 7 years of remission. The preceding infections may also have triggered the relapse. Our patient underlines the observation that length of remission does not predict an uncomplicated course during and after pregnancy.² Moreover, our patient confirms the impression that uneventful previous pregnancies do not exclude a relapse with subsequent pregnancies. Finally, our report refutes the assumption that persistently negative ANCA titres indicate a low likelihood of peripartum relapse.² Treatment of active WG in pregnancy has been reviewed elsewhere.³

In conclusion, we report the first case of relapse of WG post partum. We fear that vasculitis in conjunction with pregnancy may occur more often than expected and propose meticulous reporting of such cases. We speculate that immune events associated with pregnancy may trigger disease, as in lupus.⁸ We emphasise the need for pregnancy counselling in female patients of childbearing age with vasculitis and recommend close surveillance during pregnancy and post partum.

Drs Woywodt and Haubitz are supported by a grant from the Deutsche Forschungsgemeinschaft (grant Wo 907/1-1)

Authors' affiliations

A Woywodt, K de Groot, S Bahte, A Schwarz, H Haller, M Haubitz, Division of Nephrology, Department of Medicine, Hannover Medical School, Hannover, Germany

Correspondence to: Dr A Woywodt, Division of Nephrology, Department of Medicine, Hannover Medical School, Carl-Neuberg-Strasse 1, 30625 Hannover, Germany; Woywodt.Alexander@MH-Hannover.de

Accepted 29 May 2005

REFERENCES

- 1 Doria A, Iaccarino L, Ghirardello A, Briani C, Zampieri S, Tarricone E, *et al.* Pregnancy in rare autoimmune rheumatic diseases: UCTD, MCTD, myositis, systemic vasculitis and Behçet disease. *Lupus* 2004;**13**:690–5.
- 2 Auzary C, Huong DT, Wechsler B, Vauthier-Brouzes D, Piette JC. Pregnancy in patients with Wegener's granulomatosis: report of five cases in three women. *Ann Rheum Dis* 2000;**59**:800–4.
- 3 Langford CA, Kerr GS. Pregnancy in vasculitis. *Curr Opin Rheumatol* 2002;**14**:36–41.
- 4 Lima F, Buchanan N, Froes L, Kerslake S, Khamashta MA, Hughes GR. Pregnancy in granulomatous vasculitis. *Ann Rheum Dis* 1995;**54**:604–6.
- 5 Milford CA, Bellini M. Wegener's granulomatosis arising in pregnancy. *J Laryngol Otol* 1986;**100**:475–6.
- 6 Milne KL, Stanley KP, Temple RC, Barker TH, Ross CN. Microscopic polyangiitis: first report of a case with onset during pregnancy. *Nephrol Dial Transplant* 2004;**19**:234–7.
- 7 Hiyama J, Shiota Y, Marukawa M, Horita N, Kanehisa Y, Ono T, *et al.* Churg-Strauss syndrome associated with pregnancy. *Intern Med* 2000;**39**:985–90.
- 8 Doria A, Ghirardello A, Iaccarino L, Zampieri S, Punzi L, Tarricone E, *et al.* Pregnancy, cytokines, and disease activity in systemic lupus erythematosus. *Arthritis Rheum* 2004;**51**:989–95.

HLA-DR11 and HLA-DR2 are negatively associated with autoantibody production in chronic hepatitis C

C-Y Hu*, C-S Wu*, C-S Lee, C-H Wu, H-F Tsai, P-J Chen, P-N Hsu

Ann Rheum Dis 2006;65:138–139. doi: 10.1136/ard.2005.039982

Chronic hepatitis C virus (HCV) infection is associated with immunological abnormality, including circulating immune complexes, production of autoantibodies, and concurrent autoimmune disorders.^{1,2} Both viral and host factors may contribute to the development of autoantibodies and rheumatological manifestations. In this study we investigated the production of autoantibodies in patients with HCV in order to determine a possible link between the polymorphic HLA-DRB1 allele(s) and autoantibody production in chronic HCV infection.

We analysed HLA-DR polymorphisms in 288 HCV infected subjects in the Department of Internal Medicine, National Taiwan University Hospital. All patients were assayed for their serum autoantibodies with detection of antinuclear antibodies (ANA), rheumatoid factor (RF), antithyroid antibodies (antithyroglobulin (ATG) and antimicrosomal (AMG) antibodies), and antineutrophil cytoplasmic antibodies (ANCA). The HLA-DR polymorphisms were genotyped by polymerase chain reaction and sequence-specific oligonucleotide probe hybridisation as previously described.³ The allelic distribution of the DRB1 gene of the HCV infected subjects was compared with that of a control group of 238 unrelated healthy adults. The results showed that 125/288 (43.4%) subjects had at least one of the autoantibodies, with ANA being the most prevalent (23.2%). RF was also detectable in 52/288 (18.1%) subjects. The antithyroid (ATG: 4.9%, AMC: 8.3%) and antineutrophil (proteinase 3-ANCA: 4.9%, myeloperoxidase-ANCA: 5.2%) antibodies were less common.

The presence of autoantibodies did not correlate significantly with the presence of clinical rheumatological

manifestations. In the HLA-DR study we found no significant difference in the DRB1 allelic distribution between the HCV infected subjects and the non-infected control group. The genotypic frequency of HLA-DR11 was significantly decreased in patients with chronic hepatitis C with ANA (odds ratio (OR)=0.2, $p \leq 0.001$) or ATG (OR=0.2, $p \leq 0.0408$) (table 1). The genotypic frequency of HLA-DRB11 was also significantly lower among subjects with at least one autoantibody than among those without any serum autoantibodies (OR=0.5, $p \leq 0.0357$). HLA-DR2 was more prevalent in HCV infected patients in whom RF was absent (OR=0.4, $p \leq 0.0133$). These results indicate that HLA-DR11 and HLA-DR2 are negatively associated with autoantibody production in Taiwanese patients with chronic hepatitis C.

In our study we found that serum autoantibodies were commonly found in patients with HCV infection. Forty three per cent of the subjects had at least one detectable autoantibody in their sera. ANA and RF were the predominant autoantibodies in HCV infected patients. Recent genetic studies have indicated that HLA class II genotypes strongly influence the outcome of HCV infection.^{4,5} HCV infection has been frequently detected in patients with immune complex mediated disease such as mixed cryoglobulinaemia, Sjögren's syndrome, and glomerulonephritis.^{6,7} It has been reported that HLA-DR11 is significantly more common in patients with HCV associated type II cryoglobulinaemia (mixed cryoglobulinaemia (MC)); whereas, HLA-DR7 is less common in HCV infected patients with MC.⁸

It has also been reported that HLA-DR4 is positively associated with autoantibody production, whereas HLA-DR3 subjects are predisposed to cryoglobulinaemia.⁹

Table 1 HLA-DRB1 genotypic frequencies and seropositivity of autoantibodies among the 288 patients with chronic hepatitis C

DRB1 type	Antibody	No/ subtotal	OR G	95% CI p ≤	Antibody	No/ subtotal	OR G	95% CI p ≤	Antibody	No/ subtotal	OR G	95% CI p ≤
DR11	ANA(+)	2/67	0.2	0.05 to 0.7	ATG(+)	0/14	0.2	0 to 3.5	AutoAb ¹ (+)	11/125	0.5	0.2 to 1.0
	ANA(-)	37/221	10.746	0.001	ATG(-)	39/274	4.185	0.0408	AutoAb ¹ (-)	28/163	4.409	0.0357
DR2	RF(+)	10/52	0.4	0.2 to 0.9	MPO(+)	2/12	0.3	0.1 to 1.2	AutoAb ² (+)	16/82	0.4	0.2 to 0.7
	RF(-)	86/236	6.128	0.0133	MPO(-)	101/273	4.02	0.045	AutoAb ² (-)	80/206	10.47	0.0012
	ATG(+)	2/14	0.4	NS	AMC(+)	4/24	0.4	0.1 to 1.2				
	ATG(-)	94/274			AMC(-)	92/264	3.651	0.056				
DR12	AutoAb ² (+)	29/82	2.1	1.2 to 3.6	RF(+)	17/52	1.6	NS	AMC(+)	10/24	2.4	1.0 to 5.4
	AutoAb ² (-)	43/206	6.298	0.0121	RF(-)	55/236			AMC(-)	62/264	3.507	0.0611
DRB1*0403	ATG(+)	3/14	6.4	1.7 to 24.0	AMC(+)	4/24	5.4	1.6 to 17.6				
	ATG(-)	12/274	4.76	0.0291	AMC(-)	11/264	5.323	0.021				
DRB1*1401	RF(+)	10/22	2.7	1.1 to 7.0	ATG(+)	0/14	0.43	NS	AMC(+)	0/24	0.24	0.0 to 4.25
	RF(-)	29/236	3.539	0.066	ATG(-)	20/274			AMC(-)	20/264	3.163	0.0573
DRB1*1405	PR3(+)	2/14	6.3	1.4 to 27.8	MPO(+)	3/15	6.4	1.7 to 24.0				
	PR3(-)	11/274	4.777	0.0228	MPO(-)	11/273	4.76	0.0291				

Single allele found in HLA-DR11 type (DRB1*1101), HLA-DR12 type consists of several alleles.

AutoAb¹, seropositive for any one of the autoantibodies tested; AutoAb², seropositive for any one of the autoantibodies tested other than antinuclear antibodies; OR, odds ratio; 95% CI, 95% confidence interval of the OR; G, log likelihood ratio; NS, non-significant.

The differences in the immunological abnormalities and HLA-DR genotype may be related to the genetic background in different ethnic groups. In this report we clearly observed a protective effect conferred by HLA-DRB1*11 against autoantibody production in chronic hepatitis C. Our results also demonstrated that HLA-DR2 was more prevalent in HCV infected patients without RF. These findings support the hypothesis that specific HLA-DR alleles have an important role in the immunological abnormalities in chronic hepatitis C, and our results present clear evidence for a relationship between HCV infection and immunological abnormalities.

Investigation of the molecular mechanism of HLA-DR11 and HLA-DR2 involvement in protecting subjects from autoantibody production in chronic HCV infection awaits further investigation. In conclusion, our results suggest that the existence of HLA-DR linked protection genes (DR11 or DR2) prevents the production of serum autoantibodies in Taiwanese patients with chronic hepatitis C.

Authors' affiliations

C-Y Hu, Department of Clinical Laboratory Sciences and Medical Biotechnology, College of Medicine, National Taiwan University, Taipei, Taiwan

C-S Wu, C-H Wu, P-J Chen, P-N Hsu, Department of Internal Medicine, National Taiwan University Hospital, Taiwan

C-S Lee, Department of Internal Medicine, McKay Memorial Hospital and MacKay Medicine, Nursing and Management College, Taiwan, and Taipei Medical University, Taipei, Taiwan

H-F Tsai, Department of Internal Medicine, Taipei City Hospital, Ho-Ping Branch, Taipei, Taiwan

P-N Hsu, Graduate Institute of Immunology, College of Medicine, National Taiwan University, Taipei, Taiwan

Supported by grants from the National Science Council (NSC 91-2320B-002, and NSC91-2314-B-002-278)

*C-Y Hu and C-S Wu contributed equally to this work.

Correspondence to: Professor P-N Hsu, Graduate Institute of Immunology, College of Medicine, National Taiwan University, No 1, Sec. 1, Jen-Ai Rd, Taipei, Taiwan, Republic of China; pnsu@ha.mc.ntu.edu.tw

Accepted 14 June 2005

REFERENCES

- 1 **Buskila DM**. Hepatitis C-associated arthritis. *Curr Opin Rheumatol* 2000;**12**:295-9.
- 2 **Wener MH**, Johnson RJ, Sasso EH, Gretch DR. Hepatitis C virus and rheumatic disease. *J Rheumatol* 1996;**23**:953-9.
- 3 **Hu C**, Hsu PN, Lin RH, Hsieh KH, Chua KY. HLA DPB1*0201 allele is negatively associated with immunoglobulin E responsiveness specific for house dust mite allergens in Taiwan. *Clin Exp Allergy* 2000;**30**:538-45.
- 4 **Vejbaesya S**, Songsivilai S, Tanwandee T, Rachabun S, Chantangpol R, Dharakul T. HLA association with hepatitis C virus infection. *Human Immunol* 2000;**61**:348-53.
- 5 **Yenigun A**, Durupinar B. Decreased frequency of the HLA-DRB1*11 allele in patients with chronic hepatitis C virus infection. *J Virol* 2002;**76**:1787-9.
- 6 **Zein NN**, Persing DH, Czaja AJ. Viral genotypes as determinants of autoimmune expression in chronic hepatitis C. *Mayo Clin Proc* 1999;**74**:454-60.
- 7 **Pawlotsky JM**, Roudot-Thoraval F, Simmonds P, Mellor J, Ben Yahia MB, Andre C, et al. Extrahepatic immunologic manifestations in chronic hepatitis C and hepatitis C virus serotypes. *Ann Intern Med* 1995;**122**:169-73.
- 8 **Cacoub P**, Renou C, Kerr G, Hue S, Rosenthal E, Cohen P, et al. Influence of HLA-DR phenotype on the risk of hepatitis C virus-associated mixed cryoglobulinemia. *Arthritis Rheum* 2001;**44**:2118-24.
- 9 **Hwang SJ**, Chu CW, Huang DF, Lan KH, Chang FY, Lee SD. Genetic predispositions for the presence of cryoglobulinemia and serum autoantibodies in Chinese patients with chronic hepatitis C. *Tissue Antigens* 2002;**59**:31-7.