DOI: 10.2169/internalmedicine.45.1407

Table 1. **Clinical Findings and Serological Data from 5 Patients with Palindromic Rheumatism**

	Age (yr)	Sex (M/F)	Affected joints	Disease Duration (M)	IgM-RF (IU/ml)	Anti-CCP Ab (U/ml)
Case 1	58	M	ankle, MTP	19	98.6	0.6
Case 2	51	F	wrist, shoulder, ankle, knee	64	<9.8	<0.6
Case 3	40	F	wrist, MCP, PIP	24	90.0	0.6
Case 4	68	M	wrist, elbow, ankle, knee	88	37.0	3.0
Case 5	63	M	wrist, elbow, ankle	22	28.0	<0.6
Case 6	52	M	shoulder, ankle, wrist	7	<9.8	72.0

IgM-RF was measured by latex-enhanced immunonephelometric assay (Dade Behring, Marburg, Germany, cut-off value=14 IU/ml). Anti-CCP Ab was measured by enzyme-linked immunosorbent assay (DIASTAT Anti-CCP, Axis-Shield, Dundee, UK, cut-off value=4.5 U/ml). IgM-RF was positive in cases 1, 3, 4 and 5, whereas anti-CCP Ab was positive in case 6.

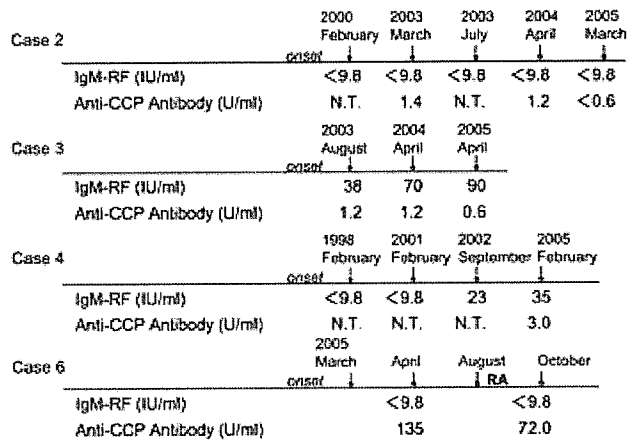

Figure 1. **Serial serological examinations of 4 patients with palindromic rheumatism. IgM-RF: IgM rheumatoid factor. Anti-CCP Ab: anti-cyclic citrullinated peptide antibody. N.T.: not tested. In case 2, the patient's condition developed into persistent arthritis in July 2003, whereas she did not fulfill the 1987 ACR classification criteria for RA. In addition, plain radiographs of the affected joints did not show any erosive change until now. In case 6, the patient was diagnosed as RA in August 2005; however, plain radiographs of the affected joints in October 2005 did not show any erosive change.**

(Fig. 1 and Table 1). Plain radiographs of the affected joints were examined serially (case 1 to case 6), but no erosive bone changes were not found in any of the patients (data not shown).

Discussion

Gonzalez-Lopez et al have reported that 28% of patients with palindromic rheumatism developed RA after a mean follow-up of 6 years (1). Previous investigations including that of Gonzalez-Lopez et al showed that seropositivity for IgM-RF could be one of the risk factors for subsequent development of RA (1-4). The present study includes 6 cases with a mean follow-up of 3.1 years. Among them, the one patient who developed RA later was seropositive for anti-CCP Ab and seronegative for IgM-RF. Thus, the presence of anti-CCP Ab might be a prognostic factor for future onset of RA. The involvement of proximal interphalangeal (PIP) joints, wrist joints and metacarpophalangeal (MCP) joints has been suggested to indicate future risk for RA in patients with palindromic rheumatism (1), and such involvement was observed in 5 out of 6 patients. Thus, further follow-up will be necessary to detect the onset of RA of our cases.

Van Gaalen et al recently revealed that the presence of anti-CCP Ab is the best predictor for the progression to RA in patients with undifferentiated arthritis (6). Anti-CCP Ab is reported to be found in 56.3% of patients with palindromic rheumatism in Spain (18 out of 32 patients); however, prediction of the future development of palindromic rheumatism to RA by anti-CCP Ab remains to be determined (5). Our prospective study of early-stage RA indicates that about 70% of the patients at baseline already show the seropositivity with anti-CCP Ab (7, 8); the difference in anti-CCP Ab seropositivity from that found by Salvador et al (5) in Spain may be due to arise from racial difference. Further study may answer question.

The present data are preliminary and limited; however, to our knowledge, this is the first prospective observation of Japanese patients with palindromic rheumatism regarding IgM-RF and anti-CCP Ab. Further clinical investigation, including a large number of patients will be necessary to clarify the significance of IgM-RF and anti-CCP Ab in the prediction of further onset of RA in Japanese palindromic rheumatism patients.

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

Abbreviations: ACR: American College of Rheumatology, anti-CCP Ab: anti-citrullinated peptide antibody, IgM-RF: IgM rheumatoid factor, MCP joint: metacarpophalangeal joint, MTP joint: metatarsophalangeal joint, PIP joint: proximal interphalangeal joint, RA: rheumatoid arthritis

References

1. Gonzalez-Lopez L, Gamez-Nava JI, Jhangri GS, Ramos-Remus C, Russell AS, Suarez-Almazor ME. Prognostic factors for the development of rheumatoid arthritis and other connective tissue diseases in patients with palindromic rheumatism. J Rheumatol **26**: 540-545, 1999.
2. Honnonen P, Mottonen T, Oka M. Palindromic rheumatism. A clinical survey of sixty patients. Scand J Rheumatol **16**: 413-420, 1987.

DOI: 10.2169/internalmedicine.45.1407

3. Williams MH, Sheldon PJ, Torrigiani G, Eisen V, Mattingly S. Palindromic rheumatism. Clinical and immunological studies. Ann Rheum Dis **30**: 375-380, 1971.
4. Youssef WA, Yan A, Russel AS. Palindromic rheumatism: A response to chloroquine. J Rheumatol **18**: 35-37, 1991.
5. Salvador G, Gomez A, Vinas O, et al. Prevalence and clinical significance of anti-cyclic citrullinated peptide and antikeratin antibodies in palindromic rheumatism. An abortive form of rheumatoid arthritis? Rheumatology **42**: 972-975, 2003.
6. van Gaalen FA, Linn-Rasker SP, van Venrooji WJ, et al. Autoantibodies to cyclic citrullinated peptides predict progression to rheumatoid arthritis in patients with undifferentiated arthritis: a prospective cohort study. Arthritis Rheum **50**: 709-715, 2004.
7. Tamai M, Kawakami A, Uetani M, et al. The presence of anti-cyclic citrullinated peptide antibody is associated with magnetic resonance imaging detection of bone marrow oedema in early-stage rheumatoid arthritis. Ann Rheum Dis **65**: 133-134, 2006.
8. Tamai M, Kawakami A, Uetani M, et al. Early prediction of rheumatoid arthritis by serologic variables and magnetic resonance imaging of the wrists and finger joints: results from prospective clinical examination. Ann Rheum Dis **65**: 134-135, 2006.

Patient 4

A 46-yr-old AA female with SLE for 12 yrs presented with serositis, fever, elevated creatinine, anaemia and thrombocytopenia. TTP was diagnosed on the basis of 4/5 clinical features and laboratory abnormalities. Daily plasmapharesis resulted in the recovery of her renal function, anaemia and thrombocytopenia after 24 cycles. She did not receive any cytotoxics and has been relapse free.

Patient 5

A 41-yr-old AA female with SLE for 4 yrs presented with renal insufficiency, fever, haemolytic anaemia and thrombocytopenia. A diagnosis of SLE flare-up and TTP was made because of 4/5 clinical features and numerous schistocytes. She was treated with daily plasmapharesis (14 cycles), IV cyclophosphamide and methylprednisolone with a haematological recovery. One week later, she had a relapse of TTP along with *Staphylococcus aureus* septicaemia, seizures and volume overload requiring haemodialysis. She required 11 additional cycles of plasmapharesis for a complete response, and is in remission and off dialysis currently.

Discussion

This case series highlights many issues relating to association of these two diseases, SLE and TTP. An exact frequency of the coexistence of these two disorders cannot be calculated, but it is probably higher than that currently indicated by the 60 reported cases and this series further adds to this information [5–10]. The onset of SLE precedes TTP in a majority of cases although TTP can antedate or occur simultaneously with SLE [5]. All the patients mentioned above were diagnosed with SLE prior to developing TTP, suggesting a possible temporal relationship. Activity of SLE and onset of TTP run a parallel course in some of these patients, which also holds true in this case series [5, 10].

This case series also confirms the significant morbidity associated with the occurrence of TTP in SLE. All of the patients had prolonged hospital stay, four required ICU care, two proceeded to ESRD, one developed renal insufficiency and one had sepsis. The role of cytotoxic therapy in this situation is unclear, but there is an indication that early use of these agents in a severe or refractory patient results in a better outcome [5]. All the patients received aggressive and prolonged plasmapharesis (>20, median = 26.8) and four were also treated also with cytotoxic agents early in the course of the illness. Although no conclusion can be drawn, multiple cycles of plasmapharesis and early use of cytotoxic agents may have affected the course and improved the outcome of this serious disease here, which is consistent with the previous series [5, 10].

These patients also present a diagnostic dilemma because these two diseases share many clinical features. Most of the patients in this series were diagnosed clinically, with a biopsy being feasible only in two patients due to severe thrombocytopenia and significant disease activity.

This series further suggests that TTP should always be considered in differential diagnosis of thrombocytopenia in SLE patients, and ruled out as it may carry significant prognostic and therapeutic implications.

The authors have declared no conflicts of interest.

V. Majithia, V. Harisdangkul

University of Mississippi, Medical Center, Division of Rheumatology, 2500 N. State Street, Jackson, MS-39216, USA
Accepted 23 May 2006
Correspondence to: V. Majithia.
E-mail: vmajithia@medicine.umsmed.edu

1. Ridolfi RL, Bell WR. Thrombotic thrombocytopenic purpura. Reports of 25 cases and review of the literature. Medicine 1981;60:413–28.
2. Fessler BJ. Thrombotic syndromes and autoimmune diseases. Rheum Dis Clin North Am 1997;23:461–79.
3. Rarick MU, Espina B, Mocharnuk R *et al.* Thrombotic thrombocytopenic purpura in patients with human immunodeficiency virus infection: a report of three cases and review of the literature. Am J Hematol 1992;40:103–9.
4. Doll DC, Weiss RB. Hemolytic anemia associated with antineoplastic agents. Cancer Treatment Rep 1985;69:777–82.
5. Hamasaki K, Mimura T, Kanda H, Kubo K. Systemic lupus erythematosus and thrombotic thrombocytopenic purpura: a case report and literature review. Clin Rheumatol 2003;22:355–8.
6. Guvenc B, Unsal C, Gurkan E. Systemic lupus erythematosus and thrombotic thrombocytopenic purpura: a case report. Transfus Apher Sci 2004;31:17–20.
7. Akaogi J, Akasaka N, Yamada H *et al.* Intravenous cyclophosphamide therapy in a case with refractory thrombotic microangiopathic hemolytic anemia and SLE. Clin Rheumatol 2004;23:541–3.
8. Kapoulas S, Liakos S, Karkavelas G, Ageloudi M, Grekas D, Giannoulis E. Thrombotic thrombocytopenic purpura associated with rapidly progressive lupus nephritis: report of two cases. Clin Nephrol 2005;63:297–301.
9. Starck M, Abedinpour F, Dendorfer U *et al.* Acquired thrombotic thrombocytopenic purpura as the presenting symptom of systemic lupus erythematosus. Successful treatment with plasma exchange and immunosuppression–report of two cases. Eur J Haematol 2005;75:436–40.
10. Vasoo S, Thumboo J, Fong KY. Thrombotic thrombocytopenic purpura in systemic lupus erythematosus: disease activity and the use of cytotoxic drugs. Lupus 2002;11:443–50.

Rheumatology 2006;45: 1171–1173
doi:10.1093/rheumatology/kel178
Advance Access publication 26 June 2006

Successful treatment using tacrolimus (FK506) in a patient with TNF receptor-associated periodic syndrome (TRAPS) complicated by monocytic fasciitis

Sir, Tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) is an autosomal-dominant inherited disease characterized by prolonged episodes of periodic fever and localized inflammation [1]. Although TRAPS was initially described in the pedigree of a large Irish/Scottish family with a periodic inflammatory condition, mutations in *TNFRSF1A* have now been found in many ethnic backgrounds, including Japanese, African Americans and Mediterranean populations [2]. The hypothetical pathogenesis of TRAPS is defective TNFRSF1A shedding from cell membranes in response to a stimulus including TNF-α. This mechanism has recently been shown to account for a minor population of TRAPS patients, and other mechanisms are thus needed to explain the disease [3]. Regarding the treatment of TRAPS, glucocorticoids can decrease the symptoms in most patients, but they do not decrease the frequency of attacks [1]. Clinical trials using etanercept, a TNFRSF1B receptor-immunoglobulin fusion protein, for TRAPS patients have

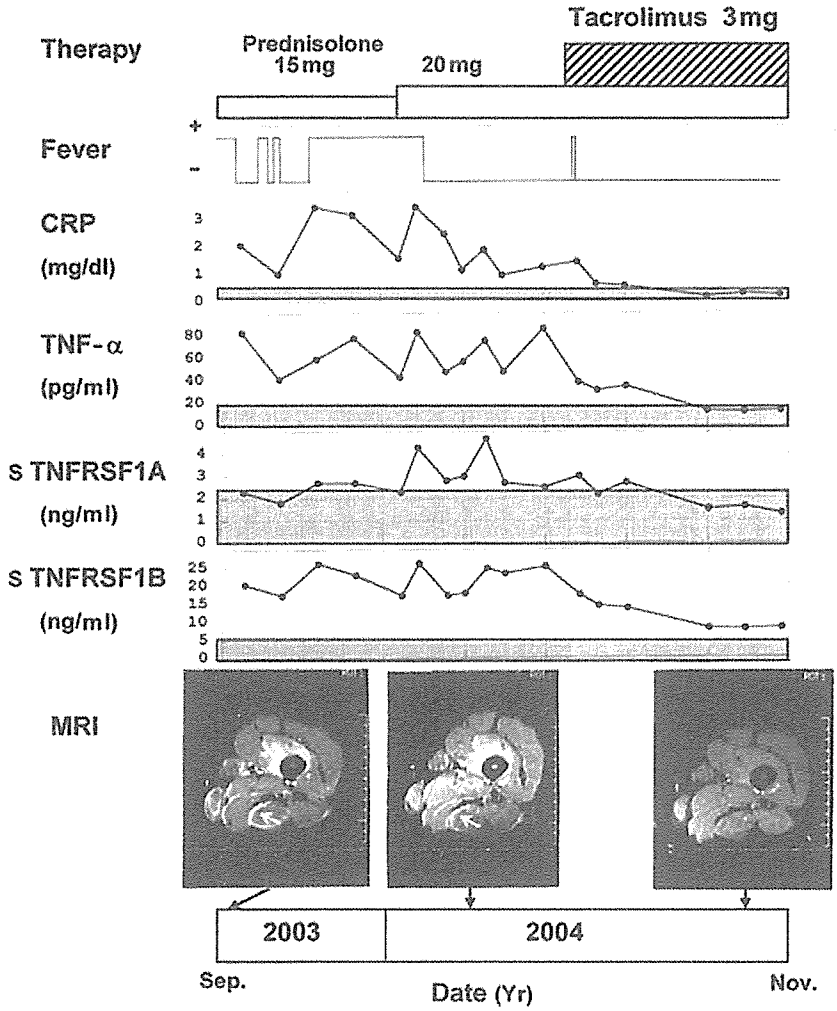

FIG. 1. Clinical course of the patient. Fever + means a fever over 38°C once a day. The clinical data include the serum levels of CRP, TNF-α, soluble TNFRSF1A and soluble TNFRSF1B. The normal range of CRP, TNF-α, soluble TNFRSF1A and soluble TNFRSF1B are <0.17 mg/dl, 10.5 ± 10.4 pg/ml ($n = 13$, average ± 2SD) 1.2 ± 1.1 ng/ml ($n = 13$, average ± 2SD), and 3.0 ± 1.3 ng/ml ($n = 13$, average ± 2SD), respectively, which are indicated by the shaded area in each column. Coronal views of the middle left thigh of a patient using STIR magnetic resonance imaging demonstrate high intensity signals in the fascia (white arrow) before the administration of tacrolimus.

shown that it can decrease both the attack frequency and the corticosteroid dose [4]. Etanercept may thus be useful as a treatment for TRAPS attacks; however, some patients do not respond to this drug [4, 5].

We previously reported a TRAPS patient associated with systemic lupus erythematosus (SLE) with a novel *TNFRSF1A* mutation (T61I) [6]. A family study and the known high prevalence in the general population (3%; nine healthy Japanese individuals out of 300 in our recent study) show that the T61I mutation has low penetrance, resembling the R92Q mutation [1, 6]. This patient was complicated by monocytic fasciitis in both thighs, which was confirmed by immunohistological studies (CD68-positive cells were seen to infiltrate the fascia) [6, 7]. Our previous data demonstrated that her TRAPS symptoms were not correlated with the serum level of TNF-α, because continuous elevation of serum TNF-α was observed for more than 3 yrs in spite of prednisolone administration. As TNF-α was mainly produced by monocytes, we speculated that her continuous high serum level of TNF-α was due to monocytic fasciitis in both thighs. This same Japanese female TRAPS patient, who is now 29 yrs old, was followed up at the First Department of Internal Medicine, Nagasaki University Hospital of Medicine and Dentistry, Japan. She was treated with prednisolone for a long time; however, continuous recurrent fever and inflammatory signs were observed. As high fever and increased, C-reactive protein (CRP) levels continued for more than 3 months in spite of the administration of 10 mg of prednisolone, and so we added another 5 mg of prednisolone, thus resulting in a total dosage of 15 mg of prednisolone on 14 January 2004 (Fig. 1). Thereafter, the high fever diminished and the serum level of CRP decreased; however, the serum level of TNF-α was still very high and high-intensity signals in the fascia remained clearly detected by short tan inversion recovery (STIR) magnetic resonance imaging (MRI) (Fig. 1).

Tacrolimus (FK506) is an immunosuppressive drug, which is widely used in transplantation, rheumatoid arthritis and atopic dermatitis. The immunosuppressive effects of tacrolimus have been reported by both us and other groups [8–10]. The action of this drug is mainly the suppression of activated T-cells via calcineurin inhibition [10]. The suppression of T-cell activation

leads to an inhibition of a subsequent production of inflammatory cytokines, such as TNF-α, IL-1β, IL-6, etc. [9, 10]. Further examinations will be needed for its direct effect in cytokine-producing cells. To inhibit the serum level of TNF-α in this TRAPS patient, we used 3 mg of tacrolimus in addition to 15 mg of prednisolone. Figure 1 shows that serum level of CRP, TNF-α, soluble TNFRSF1A and soluble TNFRSF1B were decreased after the administration of tacrolimus. Interestingly, after 4 months and 2 weeks of this tacrolimus treatment, the high-intensity signals in fascia were found to be almost undetectable by MRI. The proteinuria, which was thought to be the only SLE symptom observed at this time, decreased from 3.68 g/day (30 April 2004) to 1.40 g/day (27 September 2004) while the patient was being treated with tacrolimus, thus suggesting that this drug was also effective for lupus nephritis. Because continuous high-intensity signals detected by MRI had been observed nine times from November 2000, while, in addition, high serum levels of TNF-α continued [6], it is unlikely to assume that the spontaneous remission of TRAPS and monocytic fasciitis may have occurred during this period (after tacrolimus treatment). In this case, tacrolimus may prevent the TNF-α release from monocytes by inhibiting the inflammation of fascia in both thighs, thus demonstrating this to be a new strategy for targeting TNF-α-producing cells rather than neutralizing the serum TNF-α (i.e. etanercept). Tacrolimus might therefore be a potentially useful drug for TRAPS patients, especially in those complicated by monocytic fasciitis.

Rheumatology	Key message
	• This is the first report of a successful treatment using tacrolimus (FK506) in a TRAPS patient complicated by monocytic fasciitis.

The authors have declared no conflicts of interest.

H. Ida, T. Aramaki, K. Arima, T. Origuchi[1], A. Kawakami, K. Eguchi

First Department of Internal Medicine, Nagasaki University Hospital of Medicine and Dentistry, Graduate School of Biomedical Sciences, Nagasaki University and [1]Nagasaki University School of Health Sciences, Nagasaki, Japan
Accepted 18 April 2006
Correspondence to: Hiroaki Ida, MD, PhD, The First Department of Internal Medicine, Nagasaki University Hospital of Medicine and Dentistry, Graduate School of Biomedical Sciences, Nagasaki University, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan. E-mail: idah@net.nagasaki-u.ac.jp

1. Hull KM, Drewe E, Aksentijevich I *et al.* The TNF receptor-associated periodic syndrome (TRAPS): emerging concepts of an autoinflammatory disorder. Medicine 2002;81:349–68.
2. Grateau G. Clinical and genetic aspects of the hereditary periodic fever syndromes. Rheumatology 2004;43:410–5.
3. Aganna E, Hammond L, Hawkins PN *et al.* Heterogeneity among patients with tumor necrosis factor receptor-associated periodic syndrome phenotypes. Arthritis Rheum 2003;48:2632–44.
4. Drewe E, McDermott EM, Powell PT *et al.* Prospective study of anti-tumour necrosis factor receptor superfamily 1B fusion protein, and case study of anti-tumour necrosis factor receptor superfamily 1A fusion protein, in tumour necrosis factor receptor associated periodic syndrome (TRAPS): clinical and laboratory findings in a series of seven patients. Rheumatology 2003;42:235–9.
5. Nowlan ML, Drewe E, Bulsara H *et al.* Systemic cytokine levels and the effects of etanercept in TNF receptor-associated periodic syndrome (TRAPS) involving a C33Y mutation in TNFRSF1A. Rheumatology 2006;45:31–7.
6. Ida H, Kawasaki E, Miyashita T *et al.* A novel mutation (T61I) in the gene encoding tumour necrosis factor receptor superfamily 1A (TNFRSF1A) in a Japanese patient with tumour necrosis factor receptor-associated periodic syndrome (TRAPS) associated with systemic lupus erythematosus. Rheumatology 2004; 43:1292–9.
7. Hull KM, Wong K, Wood GM *et al.* Monocytic fasciitis: a newly recognized clinical feature of tumor necrosis factor receptor dysfunction. Arthritis Rheum 2002;46:2189–94.
8. Migita K, Eguchi K, Kawabe Y *et al.* FK506 augments activation-induced programmed cell death of T lymphocytes *in vivo*. J Clin Invest 1995;96:727–32.
9. Andersson J, Nagy S, Groth CG, Andersson U. Effects of FK506 and cyclosporin A on cytokine production studied *in vitro* at a single-cell level. Immunology 1992;75:136–42.
10. Miyata S, Ohkubo Y, Mutoh S. A review of the action of tacrolimus (FK506) on experimental models of rheumatoid arthritis. Inflamm Res 2005;54:1–9.

Rheumatology 2006;45: 1173–1174
doi:10.1093/rheumatology/kel209
Advance Access publication 29 June 2006

Anti-tuberculous therapy-induced crystal arthropathy

Case

Sir, We describe the case of a 76-yr-old Indian lady who presented with a 5-week history of neck pain and a positive Lhermitte's sign. Five years previously a diagnosis of cervical spondylosis had been made, and 40 yrs previously she underwent bilateral sympathectomies for profound Raynaud's syndrome. Physical examination revealed wasting of the small muscles of her hands associated with pyramidal tract signs. There was 4/5 weakness in the upper limbs of the extensors and up-going plantars. Blood laboratory investigations were normal apart from a mild normocytic anaemia. Her inflammatory markers were mildly elevated with an ESR of 60 mm/h and CRP of 28 g/dl. X-ray of the cervical spine showed severe degenerative disease. There was collapse of C6 with posterior displacement and kyphosis. An MRI scan of this region revealed a soft tissue mass with boney destruction consistent with tuberculosis. This diagnosis was confirmed and *Mycobacterium tuberculosis* (TB) chemotherapy initiated. The anti-tuberculous therapy consisted of rifampicin, ethambutol, isoniazid and pyrizinamide. Three weeks after the initiation of this therapy the patient developed an acute monoarthropathy of the right wrist. This was associated with a pyrexia of 38°. The wrist was swollen, erythematous, boggy and tender. Active movement was impaired secondary to pain and passive movement was limited to 30° extension and 40° flexion. X-ray of the wrist showed evidence of chondrocalcinosis (Fig. 1). CRP had risen to 60 g/dl, there was a leucocytosis and serum uric acid was elevated to 0.58 mM/l (normal on admission). From the joint 0.5 ml of 'creamy' pus was aspirated. Synovial fluid analysis revealed 50% neutrophils and 50% lymphocytes. The fluid was negative for Gram stain and acid-fast bacilli. Polarized light microscopy demonstrated urate and pyrophosphate crystals. The patient was treated with a 5-day course of diclofenac

LETTERS

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-diethylene-triamine 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 6] 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 T_1 weighted spin echo (repetition time 450, echo time 13) and short time inversion recovery (repetition time 3000, echo time 12, T_1 160) 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 3] 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, McGoogle 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.