MATTERS ARISING

Similar anti-*Proteus mirabilis* titres in P₁ positive and P₁ negative individuals with rheumatoid arthritis

During recent years there have been several reports showing increased antibody levels against *Proteus mirabilis* in patients with rheumatoid arthritis (RA).¹⁻³ *P. mirabilis* is a well known cause of urinary tract infection, and adhesion to the epithelium in the urinary tract seems to be essential in the pathogenesis of urinary tract infections. The blood group antigen P₁ is expressed on the epithelium of the urinary tract, and this molecule is assumed to act as a receptor for P fimbriae expressed on *P. mirabilis*.⁴ These facts led Deighton and colleagues to study the relationship between expression of the P₁ antigen and antiproteus titres³ in 140 RA patients and in their 114 healthy siblings. They found that P₁ negative RA patients had significantly higher antiproteus titres than the P₁ positive patients ($p < 0.04$).

We have measured the antiproteus titres in 50 RA patients who participated in a controlled clinical trial of fasting and a one year vegetarian diet,⁵ and in 28 age and sex matched controls by an indirect immunofluorescence technique.⁶ Antibody titres were expressed in arbitrary units (AU) which were defined as log₂ dilution units (1:10 = 1 AU; 1:20 = 2 AU; 1:40 = 3 AU, and so forth). The P blood group status of these patients and controls was also determined by means of a standard microtyping system (DiaMed AG, Murten, Switzerland). All samples were examined under code. In agreement with previous reports, we found that the mean antiproteus titre was significantly higher in the RA patients than in the controls (mean (SD): 3.5 (1.3) AU *v* 2.2 (0.7) AU; $p < 0.0001$, Mann-Whitney *U* test), and that RA patients with a high disease activity (C reactive protein >10 mg/l) had a significantly higher mean titre than patients with low disease activity (mean (SD): 4.6 (1.3) AU *v* 3.0 (1.0) AU; $p < 0.0001$). The mean antiproteus titre was slightly higher in the P₁ negative than in the P₁ positive subjects (mean (SD): 3.5 (1.6) AU *v* 3.0 (1.3) AU)—RA patients and healthy controls (figure). This difference, however, was not significant ($p < 0.27$, Mann-Whitney *U* test). Furthermore, the antiproteus titres did not differ significantly between P₁ negative and P₁ positive individuals when RA patients and healthy controls were analysed separately ($p < 0.25$ and $p < 0.14$). In the group of RA patients, the P blood group status was not significantly associated with rheumatoid factor status, disease activity, disease duration, or whether or not the patients had a beneficial effect of dietary therapy.

Deighton and colleagues examined a much larger number of patients than we did, and it is possible that the difference between their and our results is attributable to differences in the power of the statistical analyses.

Anti-*Proteus mirabilis* titres in RA patients (●) and healthy controls (○) positive (+ve) and negative (-ve) for the P₁ antigen. Antibody titres expressed in arbitrary units (AU) defined as log₂ dilution units (1:10 = 1 AU; 1:20 = 2 AU; 1:40 = 3 AU, etc). No significant differences between P₁ negative and positive groups.

However, despite the large number of subjects who were examined, they only found marginally significant differences between P₁ negative and P₁ positive individuals ($p < 0.04$). Therefore, we do not believe that the P₁ antigen plays an important role in the pathogenesis of RA.

J KJELDSEN-KRAGH
Red Cross and National Hospital Blood Centre,
Oslo, Norway

T RASHID
A EBRINGER
Division of Biomolecular Sciences,
King's College London,
United Kingdom

Correspondence to: Dr Jens Kjeldsen-Kragh, Red Cross and National Hospital Blood Centre, PO Box 6739, St Olavs Plass, N-0130 Oslo, Norway.

- 1 Ebringer A, Ptaszynska T, Corbett M, *et al*. Antibodies to *Proteus* in rheumatoid arthritis. *Lancet* 1985; 2: 305-7.
- 2 Rogers P, Hassan J, Bresnihan B, Feighery C, Whelan A. Antibodies to *Proteus* in rheumatoid arthritis. *Br J Rheumatol* 1988; 27 (suppl 2): 90-4.
- 3 Deighton C M, Gray J, Roberts D F, Bint A J, Walker D J. P blood group phenotype, proteus antibody titres and rheumatoid arthritis. *Ann Rheum Dis* 1992; 52: 1242-4.
- 4 Eden C S, Leffler H. Glycosphingolipids of human urinary tract epithelial cells as possible receptors for adhering *Escherichia coli* bacteria. *Scand J Infect Dis Suppl* 1980; 24: 144-7.
- 5 Kjeldsen-Kragh J, Haugen M, Borchgrevink C F, *et al*. Controlled trial of fasting and one-year vegetarian diet in rheumatoid arthritis. *Lancet* 1991; 338: 899-902.
- 6 Kjeldsen-Kragh J, Rashid T, Dybwad A, *et al*. Decrease in anti-*Proteus mirabilis* but not anti-*Escherichia coli* antibody levels in rheumatoid arthritis patients treated with fasting and a one-year vegetarian diet. *Ann Rheum Dis* 1995; 54: 221-4.

LETTERS TO THE EDITOR

Early development of Hodgkin's lymphoma in association with the use of methotrexate for the treatment of dermatomyositis

It is widely accepted that dermatomyositis is associated with cancer. This time-honoured perception has recently gained additional endorsement from a meta-analysis by Zantos *et al*, based upon four controlled studies.¹ These authors confirmed the association between the two conditions and suggested that dermatomyositis can be regarded as a paraneoplastic phenomenon.¹ The link between cancer and dermatomyositis in children is less obvious, yet well documented.

Immunosuppressive agents commonly used to treat rheumatic diseases, including dermatomyositis, are reportedly oncogenic. Furthermore, methotrexate, the most widely used disease modifying antirheumatic drug in the USA, has recently been implicated in a similar way.²⁻⁸ We report here a patient who developed Hodgkin's lymphoma after six months of methotrexate therapy for newly diagnosed dermatomyositis.

An 18 year old white male with spastic triplegia secondary to cerebral palsy and a history of multiple corrective orthopaedic procedures developed persistent malaise, followed by an erythematous rash affecting his face and extensor surfaces of the elbows, wrists, knuckles, knees, and feet. On examination, a typical dermatomyositic rash was noted and symmetrical muscular weakness documented in his shoulders, hips, and neck flexors.

Laboratory evaluation revealed a normal peripheral blood count, a sedimentation rate of 13 mm/1st h, borderline positive antinuclear antibody (ANA) at 1:50, negative double stranded (ds)DNA antibodies, and normal muscular enzymes. An electromyogram demonstrated both myopathic and denervation potentials. A muscle biopsy specimen was non-diagnostic and a biopsy specimen of uninvolved skin revealed perivascular lymphocytic infiltrate.

Prednisone (80 mg/day) and hydroxychloroquine (200 mg/day) were prescribed, with excellent clinical response, but the hydroxychloroquine was soon discontinued because of persistent headaches. Attempts to decrease the dose of prednisone over the ensuing weeks were frustrated by worsening of the rash and systemic symptoms. At the seventh month, oral methotrexate (15 mg/week) was initiated, with virtual resolution of the cutaneous and muscular symptoms over the next four weeks. The dose of prednisone was successfully decreased to nothing over an eight week period.

At 13 months (six months of exposure to methotrexate), the patient was entirely asymptomatic, but a right supraclavicular mass was detected on examination. The pathological report on an excisional biopsy specimen revealed Hodgkin's lymphoma

Observed malignancies among nine reported patients with rheumatoid arthritis (RA) or dermatomyositis (DM) receiving methotrexate (MTX)

	Patient No								
	1	2	3	4	5	6	7	8	9
Age (yr)/Sex	51F	55F	44M	48M	62M	86M	65F	83F	30F
Rheumatological diagnosis	RA	RA	RA	RA	RA	RA	DM	RA	RA
Duration of MTX (weeks)	33	456	116	104	52	156	60	156	40
Tumour	NHL	NHL	NHL	NHL	AC	NHL	HL	NLL	NHL
Reference	8	7	6	6	5	4	4	2	3

AC = Adenocarcinoma; HL = Hodgkin's lymphoma; NHL = non-Hodgkin's lymphoma; NLL = non-lymphocytic leukaemia.

(nodular sclerosis). Further investigations established that his tumour was stage II A. Accordingly, methotrexate was discontinued and a full course of radiation therapy delivered immediately. After six months of follow up the patient had no evidence of disease relapse.

The table summarises nine reported patients²⁻⁸ who developed malignancies while receiving methotrexate therapy. Patient 7⁴ shows striking similarities to ours, in that both developed nodular sclerosis Hodgkin's lymphoma after presenting with dermatomyositis. However, causality in the first case was well established, given the regression of the tumour observed after methotrexate discontinuation.

It is unclear if our patient's dermatomyositis was an early manifestation of Hodgkin's lymphoma or a consequence of methotrexate therapy. In support of the latter, our patient showed: a short interval between development of the rash and of the tumour; a tumour which is relatively uncommon among patients with dermatomyositis and malignancy; and clinical and histological similarities with another reported patient in whom the relationship between tumour development and methotrexate use was proven.⁴

We propose that careful examination of the lymph nodes, using sensitive techniques, should be undertaken in adolescents with dermatomyositis who are about to receive low dose methotrexate therapy.

BASSAM F BITTAR
CARLOS D ROSE
Division of Rheumatology,
Alfred I duPont Institute,
Wilmington, USA

Correspondence to: Dr C D Rose, Division of Rheumatology, Department of Paediatrics, The Alfred I duPont Institute, 1600 Rockland Road, Wilmington, DE 19899, USA.

- Zantos D, Zhang Y, Felson D. The overall and temporal association of cancer with PM and DM. *J Rheumatol* 1994; 21: 1855-9.
- Pointud P, Prudat M, Peron J. Acute leukemia after low-dose methotrexate therapy in a patient with rheumatoid arthritis. *J Rheumatol* 1993; 20: 1215-6.
- Taillan B, Garnier G, Castanet J, Ferrari E, Pesce A, Dujardin P. Lymphoma developing in a patient with rheumatoid arthritis taking methotrexate. *Clin Rheumatol* 1993; 12: 93-4.
- Kamel O, Van de Rijn M, Weiss L M, et al. Reversible lymphomas associated with EBV occurring during methotrexate therapy for rheumatoid arthritis and dermatomyositis. *N Engl J Med* 1993; 328: 1317-21.
- Sanders K M. Low dose methotrexate and cholangiocarcinoma of the common hepatic duct. *Arthritis Rheum* 1991; 34: 498.
- Kingsmore S, Hall B, Allen N, Rice J, Caldwell D. Association of methotrexate rheumatoid arthritis and lymphoma: Reports of 2 cases and literature review. *J Rheumatol* 1992; 19: 1462-5.
- Cobeta-Garcia J, Ruiz-Jimeno M, Fontova-Garrote R. Non-Hodgkin's lymphoma, rheumatoid arthritis and methotrexate. *J Rheumatol* 1993; 20: 200-2.

- Elman M, Hurwitz H, Thomas C, Kozloff M. Lymphoma developing in a patient with rheumatoid arthritis taking low-dose weekly methotrexate. *J Rheumatol* 1991; 18: 1741-3.

Serum myosin light chain determinations in patients with inflammatory myopathy—a preliminary report

The determination of serum myosin light chain (MLC) has been used to detect myocardial infarction and to assess the extent of myocardial damage in a variety of myocardial disorders.¹⁻⁴ This technique has improved diagnostic sensitivity and has provided a better correlation with left ventricular function compared with the routine serum creatine kinase (CK) determination. The technique has not previously been evaluated for the assessment of disease activity in the inflammatory myopathies.

Twenty seven measurements of both serum CK and MLC were made in 19 patients with established myositis. In five patients, two or more measurements at different times were available. All patients fulfilled at least three of the diagnostic criteria set by Bohan and Peter,⁵ and 17 had an inflammatory myopathy confirmed by biopsy. The table lists the patients' clinical characteristics. Patients were considered to have active disease if they exhibited progressive muscle weakness for the three months preceding the test, an increased CK concentration, or both; they were considered to have inactive disease if they exhibited stable muscle power for the three months preceding the test associated with a normal CK level. Muscle power was assessed by the modified sphygmomanometer technique;⁶ none of the patients had joint pain which could influence the assessment. The CK determination was performed by the routine biochemistry laboratory; normal values were <130 U/l for women and <160 U/l for men.

Clinical features of patients with myositis

Demographic details (n = 19)	
White	15
Oriental	3
Native Indian	1
Age (yr)	53.3 (28-83)
Sex (F/M)	13/6
Diagnoses	
Polymyositis	6
Dermatomyositis	6
Polymyositis/overlap	4
Systemic lupus erythematosus	2
Progressive systemic sclerosis	1
Mixed connective tissue disease	1
No with inclusion body myositis	3
Disease duration (yr)	5.4 (0.1-18)

Absolute values or mean (range)

Serum MLC concentrations were determined by a liquid phase competitive radioimmunoassay using a mouse monoclonal antibody against MLC and an iodine-125 radiolabelled synthetic polypeptide as described by Nicol *et al.*⁷ Normal values were determined in 70 healthy individuals: the upper limit of normal (mean + 3 SD) was found to be 1 ng/ml. Variance in the assay was 17.3%. Statistical significance was calculated by Fischer exact test and Mann-Whitney U test.

Serum MLC concentrations in patients with active disease (median 31 ng/ml) were significantly greater than those in the patients with inactive disease (median 0.32 ng/ml) ($p = 0.0002$) (figure). In particular, all 17 measurements in patients exhibiting active disease were increased. Among these patients, serum MLC values were increased in three patients who were considered to have active disease (as defined above), despite normal CK concentrations; two of these three were not treated with corticosteroids and one was treated with prednisone 10 mg/day. In two patients, muscle biopsy confirmed an active inflammatory process. In nine patients with inactive disease, three of 10 measurements were elevated (>1 ng/ml). Further studies are needed to clarify the significance of these findings.

The relationship between serum MLC concentration and disease activity over time was examined in five patients. A marked reduction in serum MLC was noted when the disease became inactive (as defined above). In patients with active disease the median serum MLC concentration was 68.8 ng/ml, compared with 3.7 ng/ml in patients with inactive disease. In four patients, however, MLC values remained increased three months after normalisation of the CK concentration—at a time when the patients were considered clinically to have inactive disease. Further studies involving serial muscle biopsies from patients in this group will clarify the significance of this finding.

Our preliminary data in patients with inflammatory myopathies demonstrate increased serum MLC concentrations which correlate strongly with disease activity. Our results suggest that measurement of MLC concentrations may be advantageous in diagnosis and the evaluation of response to treatment. In myositis the response to treatment is particularly difficult to monitor because of the rapid normalisation of the electromyogram and CK levels. Whether

MLC concentrations in patients with active or inactive disease. x = Median values for each group.