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). 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 fimbiae expressed on P. mirabilis.4 These facts led Deighton and colleagues to study the relationship between the expression of the P1 antigen and antiproteus titres 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, and in 28 age and sex matched controls by an indirect immuno-fluorescence technique. Antibody titres were expressed in arbitrary units (AU) which were defined as log, 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 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): 4.0 (1.4) AU v 2.0 (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.

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 rheumatoid arthritis, including methotrexate, 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 3 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 dermatomyositis 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 anti-nuclear antibody (ANA) at 1:50, negative double stranded (ds)DNA antibody, and normal muscle 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.

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

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.1,2 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 been previously 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,3 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;4 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

<table>
<thead>
<tr>
<th>Demographic details (n = 19)</th>
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<tbody>
<tr>
<td>White</td>
<td>15</td>
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<tr>
<td>Oriental</td>
<td>3</td>
</tr>
<tr>
<td>Native Indian</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>53-3 (28-83)</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>13/6</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Diagnosis</th>
<th></th>
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<tbody>
<tr>
<td>Polymyositis</td>
<td>6</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>6</td>
</tr>
<tr>
<td>Polymyositis/overlap</td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>2</td>
</tr>
<tr>
<td>Progressive systemic sclerosis</td>
<td>1</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>3</td>
</tr>
<tr>
<td>No with inclusion body myositis</td>
<td>3</td>
</tr>
<tr>
<td>Disease duration (yr)</td>
<td>5-4 (0-1-18)</td>
</tr>
</tbody>
</table>

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.1 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 Fisher 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 elevated for 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
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B Bittar and C D Rose

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