Pseudohemarthrosis: a new manifestation of Osler-Resende-Weber disease

Sirs: Haemarthrosis is usually associated with trauma. It can occur either spontaneously or in association with minor trauma in patients receiving anticoagulants, with bleeding disorders or vascular tumours. A few cases of haemarthrosis have been reported in multiple myeloma and Glanzmann’s thrombasthenia. We report here a case of an acute painful shoulder due to spontaneous periarticular bleeding, mimicking haemarthrosis, in a patient with Osler-Resende-Weber disease. A 73 year old man was admitted to our hospital in 1982 because of clauding of consciousness and gait unsteadiness. He had been diagnosed as having chronic subdural haematoma, Osler-Resende-Weber syndrome, and pulmonary arteriovenous fistula. He had a history of childhood tuberculosis as well as frequent gingival bleeding and epistaxis. There was a familial history of recurrent mucosal bleeding and subarachnoid haemorrhage. He was readmitted to hospital in 1988 because of right shoulder pain with swelling and functional loss for one month previously. He denied fever, previous trauma, or pain in any other joint. Examination disclosed multiple purpuric lesions that disappeared under unusual pressure disseminated over the face, tongue, and lips. There was swelling and decreased range of motion of the right shoulder. Arteriography yielded 40 ml of grossly bloody fluid, negative for crystals and micro-organisms. There was no evidence of coagulation disorders and a radiograph of the shoulder was normal. Computed tomography showed an image of high density over the anterior aspect of the glenohumeral joint secondary to arteriovenous fistula (figure A) and a deep bloody effusion surrounding the joint (figure B). During his admission several punctures were performed with great clinical improvement and without recurrence of bleeding. On discharge there was only a minimal limitation of the shoulder mobility. The patient had no more problems up to now.

Hereditary haemorrhagic telangiectasia (Osler-Resende-Weber disease) is an autosomal dominant disorder characterised by a systemic fibrovascular dysplasia, which affects capillaries, arteries, and veins. Three types of dysplasia are distinguished: telangiectasias, arteriovenous malformations, and aneurysms. The fragility and easy bleeding of these abnormalities, as well as the formation of arteriovenous shunts, may contribute to the clinical manifestations in this entity. Several organs may be affected: (a) central nervous system, where arteriovenous malformations, focal neoplasms, and abscesses can occur; (b) skin and mucosal surfaces with epistaxis, gingival haemorrhage, haematuria, and gastrointestinal bleeding; (c) lung, resulting in haemoptysis and pulmonary shunt with hypoxia; (d) liver, with portal hypertension and encephalopathy secondary to porto-systemic shunts. Furthermore, a hyperdynamic state may develop owing to systemic arteriovenous shunts, leading to heart failure. To the best of our knowledge joint symptoms have never been associated with hereditary haemorrhagic telangiectasia. This case reinforces the suggestion that Resende-Weber disease is a systemic disorder that may affect any system in the organism.

JAIME CALVO-ALLEN
BRANDON LOZA
JOSE L ALONSO
VICENTE RODRIGUEZ-VALVERDE
Rheumatology Division
Hospital Universitario Marques de Valdecilla
Sanander
Spain

Correspondence to: Dr J Calvo-Allen, Hospital Universitario Marques de Valdecilla, Rheumatology Division, Avenida Valdecilla s/n, 39008 Santander (Cantabria, Spain).


Lupus anticoagulant activity and anticardiolipin antibody titre in patients with systemic lupus erythematosus

Sirs: We read the article by Out et al., describing a prospective study of fluctuations of lupus anticoagulant activity and anticardiolipin antibody titre in patients with systemic lupus erythematosus, with interest. We support the views expressed by these authors that IgG anticardiolipin antibodies may be a marker of disease activity but would strongly recommend that the relatively simple global score used by the authors be replaced by systems such as the BILAG instrument, which defines far more precisely which organs or systems are affected at the time of the blood test.

We also support their suggestion that lupus patients should not be classified as being antiphospholipid antibody positive or negative simply on the basis of one test sample. We were disappointed, however, that these authors did not acknowledge the study that we and our colleagues published several years ago. In this study 42 lupus patients attending a lupus clinic at least four times between August 1983 and 1984 were assessed prospectively. IgG and IgM anticardiolipin antibodies were measured by a sensitive radioimmunoassay. Using the UCH/Middlesbrough criteria then available, we showed in an analysis of the whole group that IgM anticardiolipin antibody levels were useful in distinguishing inactive or mild disease from moderate or severe disease in patients whose musculoskeletal system was affected. Levels of both IgG and IgM anticardiolipin antibodies distinguished patients with severely active renal disease from those with less active forms, and patients with moderately or severely affected cardiovascular respiratory system from those with inactive or mild disease. Finally, in studies of seven patients who had become severely ill during the course of the one year study, IgM or IgG concentrations, or both, reflected disease activity very clearly in three. Thus measurement of anticardiolipin antibody levels as a means of helping to assess activity in lupus patients may be useful in some cases.

D A ISENBERG
C B COLACO
Bloombergh Rheumatology
Arthur Stanley House
40-50 Tottenham Street
London W1P 9NQ


Authors’ Reply Des Isenberg and Colaco comment on the use of the disease activity score and suggest that we should have used a more precise instrument such as the BILAG score. We acknowledge the fact that more precise and extensive activity scores, such as the systemic lupus erythematosus disease activity score (SLE-DAI), the systemic lupus activity measure (SLAM), or the BILAG are available, but we wonder whether the use of other scores would greatly alter our results. The score we used has been validated, as mentioned in the paper, which is in our opinion the most important feature of any activity score.
We are glad that Drs Ibench and Galaco agree on the need to use more than one sample before determining the antiphospholipid antibody status of a lupus patient. Their paper in *Medicine* was referenced by us in our initial article on fluctuations of anticoagulation antibody titres. The authors suggest that there may well be significant use in measuring anticoagulant antibody levels as a means of helping to assess activity in lupus patients. We found a significant relation between IgG anticoagulant antibodies and disease activity in whole group analysis. Individually, however, in only 11 of 33 patients was a correlation with lupus activity seen for IgG anticoagulant antibodies and in only four of 53 for IgM. Therefore, in our opinion the significance of these findings is that positive anticoagulant antibody results will increase clinical awareness in patients whose lupus activity is high rather than providing a new tool for assessing disease activity.

H J OUTF H W M DERKSEN
Department of Internal Medicine
University Hospital Utrecht
PO Box 85000
3508 GA Utrecht
The Netherlands


### Failure of cold pressor testing to induce changes in plasma renin activity or renal duplex sonography in patients with systemic sclerosis

Sir: The pathogenetic mechanism(s) of Raynaud's phenomenon in autoimmune disease has yet to be determined. There has been a lot of debate about the presence of this phenomenon in various internal organs, such as heart, lungs, and kidneys. In scleroderma, Kovalchik et al have shown that a cold stimulus triggers patients with characteristic scleroderma renal histology to secrete more renin than patients with mild or no lesions in renal biopsies. Despite that, no reliable predictive factors of the development of scleroderma renal crisis levels are yet available. This prompted us to study the response of the renal vasculature in eight patients with scleroderma of relatively short duration (ranging from five months to two years from the onset of their first symptoms) to the cold pressor test using a duplex Doppler technique (ATL UM 8 system, Advanced Technology laboratories, Bothell, USA). Duplex Doppler sonography has been proved to be a sensitive means of studying small vessels in other conditions.

Eight patients with scleroderma and Raynaud's phenomenon (six women, two men) and six subjects with osteoarthritis (four women, two men) matched for age were studied. The mean age of the patients with scleroderma was 49 years (range 34-69). All patients with scleroderma met the American Rheumatism Association diagnostic criteria,

and none had signs of visceral organ disease—that is, all had normal cardiac, lung, and renal function. All had normal blood pressure and no coronary vessel disease. All drugs, including non-steroidal anti-inflammatory drugs, were stopped one week before the study and patients and controls received a standard sodium diet of 100 mmol/day. Patients with scleroderma and controls had their hand immersed in ice cold water in the supine position. Digital Raynaud's phenomenon occurred within one minute in all patients with scleroderma. Venous blood samples were taken before and within two minutes after the appearance of Raynaud's phenomenon. Doppler signals were studied from the interlobar arteries at the upper or lower pole of the kidney. The pulsatility index was calculated by averaging three subsequent measurements; the pulsatility index is the peak systolic frequency shift of the Doppler spectrum minus the end diastolic frequency shift, divided by the mean frequency shift. Thus the pulsatility index measures resistance to flow—that is, the higher the pulsatility index, the higher the resistance to blood flow. The table shows the mean blood pressure, pulsatility index, and plasma renin activity in the two groups at baseline and after cold pressor testing. The blood pressure increased significantly in response to cold pressor test in both groups. In addition, the pulsatility index and the plasma renin activity increased in patients with scleroderma, whereas these parameters decreased in controls; the differences were not statistically significant, however. Only one patient with scleroderma responded with a large rise in plasma renin activity from 230 to 750 fmol/l, and a significant rise in pulsatility index (from 0.94 to 1.71). Overall, these patients with scleroderma and healthy subjects showed similar rises in mean arterial blood pressure during cold pressor testing—that is, the peripheral vascular bed of patients with early scleroderma does not show an aberrant response to a strong reflexogenic sympathetic stimulus. Although a trend towards stimulation of the renin-angiotensin system and corresponding renal vasconstrictor function was found in the group with scleroderma, there was no conclusive evidence to support the earlier data of Kovalchik et al.

Their data and ours should be interpreted cautiously, however, because only a small group of patients was studied in each case. Therefore, the possibility that some patients with scleroderma do show a systemic vascular hypersensitivity to cooling cannot be precluded. Furthermore, other agents than plasma renin—for example, endothelins, may play a part in the pathogenesis of Raynaud's phenomenon in patients with scleroderma or be the missing link in the complex network of vascular pathology, Raynaud's phenomenon, and the excessive deposition of collagen fibres in scleroderma. Identification of the changes in the intra-arteral pressure during immersion of the hand in ice-cold water. Circulation 1955; 12: 963-73.


### Inactive αt antiprotein in rheumatoid synovial fluid: oxidation, proteolysis, or complex formation?

Sir: We read with considerable interest the paper in the *Annals* by Chickwell and colleagues on the inactivation of elastase by antibodies in fresh samples of rheumatoid synovial fluid. Have the authors considered that the effect they are observing might be attributable to the consumption of the antiprotease as a result of its complex covalent binding with IgA within the joints of rheumatoid patients? Because we have previously reported, such a complex is present in high concentrations in rheumatoid synovial fluids; in contrast with fluids from patients with osteoarthritis, in which significant inactivation of αt antiprotein does not seem to have occurred. Moreover, from our experience in the development of an enzyme linked immunosorbent assay (ELISA) procedure for the immunological estimation of IgA-αt antiprotein complex, such a covalent coupling...
immunoglobulin does not impair the capacity of the antiprotease to react with antibodies directed against digests of the free antiprotease molecule. This could explain, therefore, why Dr Chidwick and his colleagues found that the elastase inhibitory activity of rheumatoid synovial fluids appeared to be disproportionately depressed relative to the concentrations of α1 antiproteinase determined immunochemically.

As we have suggested elsewhere, a substantial degree of inactivation of α1 antiproteinase might be expected to occur within the joints of rheumatoid patients owing to a high proportion (that is, as much as a third) being lost in this way. Furthermore, as we have shown from in vitro studies the resultant IgA–α1 antiproteinase complex is itself capable of eliciting further protease release from macrophages.

DENIS R STANWORTH
Rheumatology and Allergy Research Unit
Department of Immunology
University of Birmingham
Birmingham B15 2TT

PETER T DAWES
Staffordshire Rheumatology Centre
Haywood Hospital
Burton
Stock on Trent ST6 7AG


AUTHORS’ REPLY
Dr S Stanworth and Dawes put forward the intriguing suggestion that the presence of inactive α1 antiproteinase in fresh synovial fluid samples from patients with rheumatoid arthritis might be explained by the covalent complexing of α1 antiproteinase with IgA. We agree that this process might be the cause of the inactivation of a proportion of the α1 antiproteinase in rheumatoid synovial fluid. Having said this, we should point out that it is unlikely that the presence of IgA–α1 antiproteinase complexes accounts for all the inactivation seen as there is experimental evidence for other types of α1 antiproteinase inactivation. This includes demonstration of the presence in rheumatoid synovial fluid of (a) proteolytically processed fragments of α1 antiproteinase, (b) α1 antiproteinase containing a C-terminal methionyl sequence—although this study was performed on a single, stored synovial fluid sample, and complexes between α1 antiproteinase and a molecule such as a protease inhibitor which this type of complex usually presents a very small proportion of the total α1 antiproteinase in rheumatoid synovial fluid. As mentioned in our recent paper, a scan of 41% of the α1 antiproteinase in rheumatoid synovial fluid samples is seen. Subsequent analysis of further data from this study has also shown that the extent of inactivation of synovial fluid α1 antiproteinase varies with the serum C reactive protein levels. Hence, the role of proteolysis in fresh synovial fluid α1 antiproteinase inactivation was examined by gel electrophoresis followed by western blotting. We found that α1 antiproteinase cleavage was more pronounced in the elastase inhibitory activity of fresh synovial fluid than in osteoarthritic synovial fluid or normal serum, based on the intensity of staining of the cleaved α1 antiproteinase band (50 kilodaltons) relative to the intensity of the intact α1 antiproteinase band (54 kilodaltons). In an attempt to quantify this observation, western blots were scanned, and for each sample the intensity of the 50 kilodalton band was expressed as a fraction of the 54 kilodalton band intensity. In rheumatoid synovial fluids the mean value for this ratio was 0.6. If it is assumed that equal amounts of the 50 kilodalton fragment and the 54 kilodalton intact protein give the same staining intensity it can be cautiously suggested that about 23% of the total α1 antiproteinase in fresh rheumatoid synovial fluid is proteolytically cleaved.

Taken together, the above values for the proportion of inactive α1 antiproteinase and the proportion of cleaved α1 antiproteinase suggest that not more than about 60% of the inactivation in rheumatoid synovial fluid can be accounted for by proteolysis. Of course, this percentage value may be much lower than this because oxidised or complexed α1 antiproteinase might be subsequently fragmented by proteolysis. Furthermore, proteolysis has been excluded as the source of exercise induced inactivation of α1 antiproteinase in rheumatoid synovial fluid. Thus covalent complexing with IgA, with the formation of a disulphide bridge between one of the cysteine residues in the penultimate positions of the IgA heavy chains and the single cysteine residue (in position 232) of the α1 antiproteinase polypeptide chain, may be one of several causes of inactivation of α1 antiproteinase.

Although we carried out the above mentioned gel electrophoresis—western blotting study of rheumatoid synovial fluid samples, we presently have no information on whether an α1 antiproteinase-containing band with a molecular weight corresponding to IgA–α1 antiproteinase is present as our gels were run under denaturing and reducing conditions which would result in cleavage of the disulphide bridge between α1 antiproteinase and IgA.

The hypothesis of Drs Stanworth and Dawes could be tested in vitro, however, by measuring the elastase inhibitory capacity of the de novo generated complex of α1 antiproteinase with IgA, to ascertain whether such complexing results in a loss of α1 antiproteinase activity. If this were the case it would be of great interest to measure the IgA–α1 antiproteinase complex concentration, together with the concentration of inactive α1 antiproteinase, in rheumatoid synovial fluids.

We have recently shown that the inactivation of α1 antiproteinase in rheumatoid synovial fluid may be particularly significant because active α1 antiproteinase inhibits superoxide anion radical production by stimulated human peripheral blood neutrophils.

PAUL G WINYARD
CORMAC D BLEE
KEITH CHIDWICK
ZHI ZHANG
Inflammation Research Group
Bore and Joint Research Unit
London Hospital Medical College
Whitechapel, London
United Kingdom

Correspondence to: Dr Paul G Winyard, Inflammation Research Group, Bone and Joint Research Unit, London Hospital Medical College, 25–29 Ashfield Street, London E1 1AD, United Kingdom.


HLA-D region genes and rheumatoid arthritis

SIR: The recent article by Singal et al concludes, among other things, that HLA-DR1 may be associated with mild rheumatoid arthritis (RA). The classification of mild and severe RA was based largely on whether or not non-steroidal anti-inflammatory drugs were deemed adequate to control symptoms. We divided a group of 234 patients with classical and definite RA into patients whose disease was controlled by NSAIDs (the ‘mild’ group) and those felt to need second line agents (the ‘severe’ group). Table 1 shows that this was successful in producing significantly higher scores for those given second line drugs on a clinical disease severity scale (the spread/ severity index), the Stanford Health Assessment Questionnaire score, and a modified Larsen x ray grading. When we looked at the

### Table 1: Measures of rheumatoid arthritis disease severity and demographic variables in the groups receiving non-steroidal anti-inflammatory drugs (NSAIDs) and second line drugs. Results are means (SD)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Treatment group</th>
<th>p Value^1</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs only</td>
<td>(n=86)</td>
<td></td>
</tr>
<tr>
<td>Mean SS index score</td>
<td>15.1 (7.5)</td>
<td></td>
</tr>
<tr>
<td>Mean HAQ score</td>
<td>1.5 (0.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean modified Larsen index score</td>
<td>19.3 (11.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>57.4 (10.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>No (% of women)</td>
<td>65 (76)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean disease duration (years)</td>
<td>9.6 (9.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Second line drugs</td>
<td>(n=148)</td>
<td></td>
</tr>
<tr>
<td>Mean SS index score</td>
<td>21.3 (9.8)</td>
<td></td>
</tr>
<tr>
<td>Mean HAQ score</td>
<td>2.2 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Mean modified Larsen index score</td>
<td>25.4 (9.6)</td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>57.2 (10.7)</td>
<td></td>
</tr>
<tr>
<td>No (% of women)</td>
<td>69 (80)</td>
<td></td>
</tr>
<tr>
<td>Mean disease duration (years)</td>
<td>12.9 (11.0)</td>
<td></td>
</tr>
</tbody>
</table>

SS=spread/ severity index; HAQ=Health Assessment Questionnaire.

^1 p Values calculated using the Mann-Whitney U test.
distribution of available HLA-DR types (using the microlymphocytotoxicity assay on separated B lymphocytes) the 'mild' group had a higher prevalence of HLA-DR1 positivity, and an HLA-DR1/non-DR4 phenotype (table 2). These differences were not statistically significant, but showed trends in a similar direction to those demonstrated by Singal et al.1

However, before agreeing with the possibility that HLA-DR1 is associated with more mild RA, we feel that it is appropriate that like should be compared with like, otherwise demographic variables such as disease duration might account for differences in disease status, and not immunogenetic factors. As Table 1 shows, the 'severe group' were of similar age and sex distribution, but had a significantly longer disease duration. This raises the possibility that members of the 'mild' group may enter the 'severe' group, given time. A subsequent follow up study might then show that HLA-DR1 was not associated with milder RA.

The area of HLA and RA disease expression is important, but more reproducible measures of disease severity are needed than the arbitrary decision to introduce second line agents in management of the patient's disease. Unless prospective studies are conducted which measure a variety of disease severity indicators, or cross sectional studies demonstrate that potential confounding demographic variables have been controlled, it is difficult to conclude that HLA-DR1 predicts milder RA.

C M DEIGHTON
D J WALKER
Department of Rheumatology
Royal Victoria Infirmary
Newcastle-upon-Tyne NE1 4LP
United Kingdom


Liver toxicity with sulphasalazine

Sir: I was most interested to read the report of two patients who developed liver toxicity with sulphasalazine.1 I would like to bring to the authors’ and readers’ attention that in an multicentre pilot study of sulphasalazine in juvenile chronic arthritis2 we reported one child with systemic onset disease who as part of a generalised reaction to sulphasalazine had a grossly abnormal liver function while in two other children liver function was transiently abnormal. Thus the report of Caspi et al was not the first report of disturbed liver function in juvenile chronic arthritis.

W N DODDS
St Luke’s Hospital
Bradford
West Yorkshire BD9 5NA
United Kingdom

*On behalf of the multicentre study group of sulphasalazine in juvenile chronic arthritis.


AUTHOR’S REPLY We were pleased to note that Drs Deighton and Walker of the Royal Victoria Infirmary, Newcastle-upon-Tyne, England, had confirmed our findings of a high prevalence of HLA-DR1 in ‘mild’ seropositive rheumatoid arthritis.1 We entirely agree that the results must be interpreted with caution, and that further properly designed prospective studies are indicated. It is possible, as Deighton and Walker have suggested, that disease duration may account for differences in disease status, though this was not apparent in our studies. It might also be possible that the immunological response—that is, titre of rheumatoid factor, which has been shown in many studies to be an important determinant in prognosis, may be determined by HLA-DR genes. Thus those with DR1 may develop only low titres of rheumatoid factor, whereas those with DR4-DQw7 have high titres. There is evidence from our own studies that antibodies to Ro and La in Sjögren’s syndrome are associated with the DR3 phenotype.

The answer to the question whether DR1 and DR4-DQw7 haplotypes are related to outcome in rheumatoid arthritis is not just academic. If patients with disease could be identified who were likely to have a poor prognosis then early institution of second line treatment would be indicated, and vice versa, if patients could be identified who were likely to have a good prognosis then these drugs might not be started.

W WATSON BUCHANAN
D P SINGAL
McMaster University
Hamilton, Ontario
Canada L8N 3S5