Primary Sjögren’s syndrome and aplastic anaemia

Primary Sjögren’s syndrome (SS) is an autoimmune disease characterised by the presence of xerostomia and xerophthalmia without evidence of another systemic autoimmune disease. It has a wide clinical spectrum, extending from exocrinopathy to systemic autoimmune disease and to B cell lymphoma. The association of SS with aplastic anaemia (AA) has rarely been reported and only in patients with lymphoma. We report here an exceptional case of primary SS and severe AA without evidence of another systemic autoimmune disease. We believe this to be an exceptional case of “idiopathic” AA.

A 28-year-old white man was referred in February 1990 for lymphadenopathies and pancytopenia. He complained of xerostomia and ocular burning. Xerophthalmia was confirmed by an abnormal Schirmer’s test (right eye 2 mm, left eye 1 mm after 10 min) and a punctate keratitis on slit lamp examination after Rose-Bengal staining was observed. Labial salivary gland biopsy examination showed features of SS (grade 4 according to Chisholm’s focus score). A polyclonal hypergammaglobulinaemia with a low level of IgA was present and fluorescent antinuclear antibodies were positive in a titre of 1: 640 with a speckled pattern. Rheumatoid factor and anti-DNA antibody test were negative. HLA typing was A3,B8,B27,DR3,DR28.

The blood cell count showed pancytopenia with 3.3 × 10^9 leucocytes composed of 14% neutrophils, 76% lymphocytes, and 9% monocytes; haemoglobin: 7.4 g/dl with a mean corpuscular volume of 92 µl; red cell count: 3.1 × 10^12/l; and platelet: 54 × 10^9/l. Ninety four per cent of the patient’s peripheral blood lymphocytes were CD3+, CD4- , and 76% were γ-δ TCR (5 TCS1+) with a non-clonal pattern observed when Vβ1δ1 amplification was performed. Direct Coombs antiglobulin test was positive for IgG and C3d without signs of haemolysis. Antineutrophil antibodies were detected in the serum with an autologous immunological assay.

A bone marrow aspirate and trephine biopsy examination showed a hypoplastic marrow (cellularity of 15%) composed of 60% mature lymphocytes and 3% erythroblasts. No abnormal cell or myeloblasts was seen. Cytogenetic analysis of blood, bone marrow, and skin cells of the patient showed a reciprocal translocation involving the chromosomes 14 and 20, (t14;20) (q24;p13) within all analysed cells. Ham test, sucrase lysis test, serological tests for HIV, HTLV1, EBV, CMV, and type B and type C hepatitis were negative, serum β2 globulin was normal. Lymph node biopsy examination showed a follicular lymphoid hyperplasia without light chain restriction. Thorax and abdominal computed tomography showed no adenopathies, or feature of lymphomatous involvement. Pancytopenia gradually worsened over three months, the patient required red cells transfusion every 10 days, platelet count was 6 × 10^9/l, absolute neutrophil count was 0.3 × 10^9/l. A five day course of high dose (400 mg/kg/d) intravenous polyvalent gammaglobulins (Biotransfusion, Lille, France) was unsuccessful. Then, the patient received a seven day course of antilymphocyte antibodies (Onkoger, Lyon, France; 20 mg/kg/d) with objective improvement. Neutrophil and platelet counts reached respectively 1.2 × 10^9/l and 107 × 10^9/l, three weeks after the onset of the treatment while the transfusion requirement decreased.

Two months later the AA relapsed. A haematopoietic progenitor cell analysis was performed and a pronounced decrease of bone marrow mononuclear cells (50% of normal range) and colony forming unit for granulocyte-monocyte (CFU-GM) (4% of normal range) was observed. CFU-GM colony and cluster counts at day 8 were increased by 10-fold when bone marrow mononuclear cells were pre-incubated with antilymphocytic antibodies. Precipitations with the patient’s serum or peripheral blood mononuclear cells did not influence the colony formation. A familial allogeneic bone marrow transplantation was performed. The conditioning regimen associated cyclophosphamide (200 mg/kg) and busulphan (12 mg/kg). A graft rejection occurred and the patient died two months after the transplantation of pulmonary aspergillosis.

Pancytopenia complicating primary SS is rare and AA was first described in primary SS associated with lymphoma. We did not find an inhibition of mononuclear cells to the haemopoietic progenitors as reported by Seki in a case of pancytopenia and primary SS.

Our patient fulfilled criteria for primary SS and had no evidence of associated lymphoma. We suggest that an underlying primary SS can be found in the setting of ‘idiopathic’ AA.

The translocation t(14;20) (q24;p13) within all analysed cells. CFU-GM colony and cluster counts at day 8 were increased by 10-fold when bone marrow mononuclear cells were pre-incubated with antilymphocytic antibodies. Precipitations with the patient’s serum or peripheral blood mononuclear cells did not influence the colony formation. A familial allogeneic bone marrow transplantation was performed. The conditioning regimen associated cyclophosphamide (200 mg/kg) and busulphan (12 mg/kg). A graft rejection occurred and the patient died two months after the transplantation of pulmonary aspergillosis.

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The translocation t(14;20) (q24;p13), present in our patient has not been described before in SS. Interestingly,14q24 and 20p12-13 are two methotrexate and aphidicolin induced fragile sites: their prevalence in subjects with constitutional and acquired chromosomal instability. Am J Med Genet 1987;27:471-82.


they suggest that this 16% means that underlaying mechanisms may be common for CTS and FM.

We cannot agree with this suggestion. Our study was not controlled, but no statistically significant differences could be appreciated in a group of patients with FM and CTS, who had all been referred to a rheumatology unit. FM prevalence was 14.1% (95/668), while patients with CTS were 17.0% (11 of 65). The prevalence of associated musculoskeletal conditions was 35.0% (65/191) from our series with that in general population of Dutch women (10.2%).

In conclusion, at the present time, it is clear that CTS is often overlooked or misdiagnosed in patients showing atypical clinical features mimicking inflammatory conditions. In addition, in another abstract, for clinical examination, and 93 of 182 (51.1%) agreed to be visited. One would expect that patients with both conditions would be more frequent in patients referred to rheumatology units than the 2.4% previously reported in a retrospective series. 5


Authors’ reply

Perez-Ruiz and colleagues raise several interesting points on the relation between fibromyalgia (FM) and carpal tunnel syndrome (CTS). The first point is that in their original paper no significant difference in the prevalence of CTS was found between Spanish women with FM (15.1%) and a general population of Dutch women (10.2%).

However, we feel that comparing populations from different geographical areas may be misleading because environmental and social differences may modulate perception of pain. In fact, data from the US 1988 National Health Interview Survey report a prevalence of self diagnosed CTS of 1.55%. To verify the null hypothesis on the association between CTS and FM, a well conducted epidemiological study should be performed in the general population of a single geographical area.

Our previous study was not specifically devised to consider this point. It acknowledged that the insufficient response to the questionnaire could have biased the results toward an over-representation of the association. But, as the original questionnaire we used was developed to identify patients with rheumatoid arthritis. We were surprised to find that a considerable proportion of the group of patients answered positively to this questionnaire were in fact affected by a combination of FM and CTS. 5 Also Perez-Ruiz et al noted that patients attending a rheumatology clinic occasionally show multiple manifestations mimicking inflammatory conditions. In addition, in another abstract, Perez-Ruiz et al report that 19% of patients with CTS have FM and that CTS is more severe in this subgroup. This finding would further support the idea of a common pathogenetic link between the two conditions.

Finally, we agree with Perez-Ruiz et al that patients with FM commonly report paresthesia and pain in the area innervated by the median nerve but also present pain and numbness elicited by specific maneuvers. However, results of the diagnostic studies are often negative in FM. A possible explanation is that the median nerve may be involved in FM in a milder degree than in classic CTS. In this setting, electrodagnostic tests may show a poor sensitivity.

Measurement of IgAα1-antitrypsin complex in rheumatoid arthritis: A question of specificity?

We feel we should comment on a recent article by Iwana et al on the clinical value of measuring circulating IgAα1-antitrypsin (IgA-AT) complex concentrations in patients with rheumatoid arthritis (RA) using a prototype ELISA kit. We are concerned about the specificity of the monoclonal antibody used as the capture monoclonal ELISA plates. The authors say that the antibody recognises specific epitopes on the IgA-AT complex. However no direct proof of this is provided here or in previous reports where this particular antibody has been used. 6 Recently, in response to another study using this assay we provided data to show that the antibody recognises the complement regulatory protein, factor H. 7

We have shown that replacing the ‘complex specific’ antibody with other monoclonal antibodies to factor H (OX23 and OX24) in the ELISA essentially makes no difference to measurement of ‘complex’ values. We have also shown that the ‘IgA-AT’ antibody recognises different epitope on factor H to that recognised by OX23 and OX24, and feel that it would be surprising if monoclonals directed against three different regions of factor H all showed cross reactivity with IgA-AT.

Our studies pose the question as to what is actually being measured in the IgA-AT ELISA. The specificity of the coating antibody for factor H might suggest that some form of factor H-IgA complex is being measured. However, a crucial factor in the use of this particular ELISA is the lack of any blocking step (for example, with bovine
serum albumin or gelatin) between antibody coating and addition of standards and samples. This may allow IgA (and other serum proteins) to bind non-specifically to free binding sites on the plate. We have run exactly the same ELISA using a blocking step with 1% serum albumin before addition of samples and found that this obliterates most of the binding of the standards and the samples. This suggests that the monoclonal antibody on the plate is irrelevant and that most of the IgA detected by the secondary antibody is bound to unblocked sites. Clearly the IgA would have to compete with other serum proteins for these binding sites. Thus, the assay seems to be measuring the ratio of IgA and IgA associated proteins to all other serum proteins. If this is the case then their results are not that surprising as a number of studies have shown IgA values to be increased in RA patients.

We have recently developed a new assay for measuring IgA-AT complexes based on a sandwich ELISA with a monoclonal antibody to \( a_1 \)-antitrypsin as the capture antibody and a secondary antihuman IgA peroxidase antibody for detection of the complexes. Using this assay we have shown that IgA-AT complexes are significantly higher in the serum of RA patients than in those with reactive arthritis. In addition we have shown that serum concentrations are higher than synovial fluid concentrations in both RA and ReA, suggesting that such complexes are produced systemically rather than locally within the joint. We were unable to find any association with the concentrations of acute phase reactants and no association with joint inflammation in itself.

IgA-AT complex values may be useful for monitoring the effectiveness of second line drugs because values have been shown to fall during treatment with D-penicillamine, gold, and sulphasalazine. However these studies used a two-dimensional immunoelectrophoresis method unsuitable for screening large numbers of specimens. An ELISA method is clearly more desirable but one needs to be confident that it is only IgA-AT complex values that are being measured. We are doubtful whether this is the case for the assay used by Iwana et al. It would be interesting to use our assay to measure IgA-AT complex values in their RA patients and reactive arthritis specimens to see if similar correlations were found with the clinical findings.

Correspondence to: Dr D L Mattey.


5 Davis MJ, PT, Dawes PT, Bresnick E, Lewin IV, Stanworth DR. The relationship between the complex of immunoglobulin A and \( a_1 \)-antitrypsin, its constituent components and the acute phase response as measured by \( C \) reactive protein in rheumatoid arthritis treated with infliximab. Br J Rheumatol 1987;26:351–3.


8 Scott LJ, Dawes PT, Mattey DL. Comparison of IgA-\( a_1 \)-antitrypsin levels in RA and reactive arthritis. Immunology 1996;89(suppl 1):93.


Authors’ reply

We appreciate the comments of Dr D L Mattey and colleagues regarding our article.

As the prototype kit used in our study for detecting IgA-\( a_1 \)-antitrypsin (IgA-AT) complex was a generous gift from Professor D R Stanworth, we were not informed about the detailed specificity of the monoclonal antibodies reacting with the specific epitopes on the IgA-AT complex. Therefore, Dr Stanworth is in a better position than ourselves to comment on this issue.

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1 Treatment with calcitonin for osteoporosis

I would like the opportunity to correct, or possibly update, a number of the facts concerning calcitonin contained in Dr Patel’s comprehensive review article on drug treatments for osteoporosis.

He states that nasal preparations of calcitonin are licensed for use in osteoporosis in ‘some European countries and Japan’, whereas in fact the nasal spray formulation of salmon calcitonin developed at Sandoz (now Novartis) is currently approved in more than 70 countries worldwide, including the USA and almost all the countries of Europe, Japan, on the other hand, has not yet granted marketing approval.

Further, it is claimed that calcitonin has ‘significant’ side effects and is unlikely to gain widespread acceptance in osteoporosis, the evidence accumulated as a result of this extensive use does not bear this out. Neither the incidence nor the severity of side effects reported with the nasal spray can be described as significant, while in our experience its acceptance has been excellent—by both patients and physicians.

On the issue of cost, while I agree that calcitonin is much more expensive than standard analogics, these are not without their disadvantages in terms of side effects, habituation potential, and tachyphylaxis. Where pain is associated with bone disease, salmon calcitonin has certainly proved extremely beneficial, and pain relief in contrast with established osteoporosis is an important secondary indication for the preparation of the hormone.

It is perhaps also fair to add that, purely as a treatment for osteoporosis, calcitonin is hardly more expensive than alendronate, at least in the USA.

MOISE AZRIA
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Comments by Professor Stanworth

I should welcome an opportunity to reply to the comments of Mattey and associates as the assay in question was developed in my laboratory in Birmingham.

Since making the assay available to Professor Iwana in the National Medical Centre of Japan, we have been made aware by Dr Mattey that the anticomplex antibody used within the assay may cross react with complement factor \( H \). This, however, does not negate the finding reported by Iwana and his associates as they used a secondary anti-IgA antibody within the assay. This antibody is specific for IgA, and IgA containing complexes, and does not cross react with factor \( H \). Indeed this assay format did not detect factor \( H \). Moreover, the assay was checked to ensure that free IgA was not detected; thus precluding the possibility of non-specific binding to the plate as suggested by Dr Mattey.

DENIS R STANWORTH
Birmingham

Letter, Matters arising


Author’s reply

I thank Dr Azria for pointing out that nasal calcitonin is not licensed in Japan. In addition he is probably correct in stating that nasal calcitonin has few side effects and is acceptable, although this probably reflects lower bioavailability and potentially limited efficacy. As I indicated, there do not seem to be any long term side effects from calcitonin and this is in its favour. Certainly there will be a number of patients who may be intolerant to other compounds and for whom calcitonin, if available, should be considered.

With respect to pain relief, it makes common sense to use simple analogics, such as
paracetamol or paracetamol/codeine mixtures in the first instance, before consideration of salmon calcitonin. This, in my opinion would be good medical practice, particularly because salmon calcitonin would have to be given by a parenteral route. On the issue of cost, physicians will have to judge the suitability of drugs for osteoporosis depending on their interpretation of efficacy and local price for the individual compounds.

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Intra-articular hyaluronan treatment for osteoarthritis

We wish to comment on the article by Stefan Lohmander in which the results of a placebo controlled study with intra-articular hyaluronan in osteoarthritis of the knee were presented. It was suggested that aged patients with a high disease severity might be the best ‘responders’ to such a treatment. We felt that it was worthwhile to reanalyse the data of the patients of our German multicentre study with hyaluronan to see whether this somewhat unexpected but clinically extremely important hypothesis could be supported. The results of our subgroup analysis clearly seem to indicate again that the patient sample over the age of 60 years and with a high baseline score of >10 Lequesne points is the most likely subgroup to benefit from the treatment (table 1).

Stratified analyses of other methodologically comparable studies or preplanned trials in severe osteoarthritis could contribute to a validated identification of such patients who will probably respond best to an intra-articular treatment with hyaluronan in osteoarthritis of the knee.

Table 1 Lequesne score (ISK) improvements (mean values)

<table>
<thead>
<tr>
<th>Evaluation time</th>
<th>All patients (40–75 years, ISK baseline 2.0–18.5)</th>
<th>Subgroup (&gt;60 years, ISK baseline &gt;10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Verum (n=95)</td>
<td>Control (n=100)</td>
</tr>
<tr>
<td></td>
<td>Verum (n=28)</td>
<td>Control (n=26)</td>
</tr>
<tr>
<td>1 week after last injection</td>
<td>3.5 (n=95)</td>
<td>2.6 (n=100)</td>
</tr>
<tr>
<td>Follow up after 1 month</td>
<td>3.8 (n=95)</td>
<td>2.7 (n=100)</td>
</tr>
<tr>
<td>Follow up after 2 months</td>
<td>4.4 (n=95)</td>
<td>2.8 (n=100)</td>
</tr>
</tbody>
</table>

Treatment with calcitonin for osteoporosis

MOÏSE AZRIA

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