LETTER TO THE EDITOR

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^{1,2} and only in patients with lymphoma. We report here an exceptional case of primary SS and severe AA without lymphoma who had cytogenetic and immunological abnormalities, which might give clues to the pathogenesis 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 mn) 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 score³).

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.

A blood cell count showed pancytopenia with $3.3 \times 10^9/l$ leucocytes composed of 14% neutrophils, 76% lymphocytes, and 9% monocytes; haemoglobin: 7.4 g/dl with a mean corpuscular volume of 92 μ^3 ; reticulocytes, $2 \times 10^9/l$; and platelets: $84 \times 10^9/l$. Ninety four per cent of the patient's peripheral blood lymphocytes were CD3 +, and 76% were $\gamma\delta$ TCR (δ TCS1) + with a non-clonal pattern observed when Vd1-Jd1 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.⁴ A bone marrow aspirate and trephine biopsy examination showed a hypoplastic marrow (cellularity of 15%) composed of 60% mature lymphocytes and 8% erythroblasts. No abnormal cell or myelofibrosis was seen. Cytogenetic analysis of blood, bone marrow, and skin cells of the patient showed a reciprocal translocation involving the chromosomes 14 and 20, t(14;20) (q24;p13) within all analysed cells. Ham test, sucrose lysis test, serological tests for HIV, HTLV1, EBV, CMV, and type B and type C hepatitis were negative, serum β_2 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 $6 \times 10^9/l$, absolute neutrophil count was $0.3 \times 10^9/l$. 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 globulin (Merieux, Lyon, France; 20 mg/kg/d) with objective improvement. Neutrophil and platelet counts reached respectively $1.2 \times 10^9/l$ and $107 \times 10^9/l$, 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) cells (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 antilymphocyte globulin. Preincubations 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.^{1,2} Our patient fulfilled criteria for primary SS and had no evidence of associated lymphoma.

We did not find an inhibition of mononuclear cells to the haematopoietic progenitors as reported by Seki in a case of pancytopenia and primary SS.⁵ However, antilymphocyte globulin, which may act in AA through a cytotoxic effect on immunocompetent cells, yielded a transient and partial improvement.

The concentration of $\gamma\delta$ TCR+ cells in our patient was higher than those previously reported in SS.⁶ The cultured $\gamma\delta$ TCR+ lymphocytes demonstrated cytotoxic function *in vitro*.⁷ This suggests a possible involvement of $\gamma\delta$ TCR+ cells in the pathogenesis of AA.

The strong correlation between SS and HLA B8 DR3 suggests that genetic factors may play a part in the development of some subgroups of SS.⁸ 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 common fragile sites observed in at least 40% of humans, but also in patients with Fanconi anaemia.⁹ The gene for transforming growth factor β has also been located in 14q24^{10,11} and this gene is a haematopoietic-suppressor lymphokine. So, the presence of a genetic abnormality in 14q24 in our patient as in patients with Fanconi anaemia might lead to an abnormal expression of transforming growth factor β and hence to the suppression of haematopoiesis.

In conclusion, this uncommon finding suggests that an underlying primary SS can be found in the setting of 'idiopathic' AA. Moreover, a high concentration of $\gamma\delta$ TCR+ cells as well as genetic abnormalities in 14 q24 might have contributed to the occurrence of AA.

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MATTERS ARISING

Fibromyalgia and carpal tunnel syndrome

Recently, Cimmino *et al*¹ reported an epidemiological survey on the prevalence of carpal tunnel syndrome (CTS) in patients with fibromyalgia syndrome (FM). These authors found that 9.7% of 93 patients studied after mailing a questionnaire had both CTS and FM, suggesting an association between them and that there were possible similarities in the aetiopathological mechanisms.

Cimmino *et al* referred to our previous report on CTS and FM² in which we observed 33 patients with CTS in a group of 206 consecutive FM patients (16%), and

they suggest that this 16% means that underlying 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 the prevalence of CTS in FM women (29 of 191) from our series with that in general population women reported by de Krom *et al* (35 of 340).³ On the other hand, we noticed that CTS had been overlooked in 27 of 191 (14.1%) women with FM in our series despite mean duration of CTS symptoms of 8.1 years (range 6 months to 15 years)² while only 23 of 340 (6.7%) women with CTS did not have a previous diagnosis of CTS in the series of de Krom *et al*.³

Both studies are probably biased. In our study, patients with FM and CTS would complain about more severe symptoms and were referred to a rheumatology unit, and thus CTS prevalence could be overestimated in this sample. As pain and paresthesia in the hands are common complaints in patients with FM, CTS was overlooked before rheumatological consultation. Recently, we have carried out studies that may highlight these points: firstly, we have observed that patients referred for rheumatological consultation often have multiple diagnosis at discharge (38%) that explain the musculoskeletal symptoms of the patient.⁴ Patients with both CTS and FM had never had a diagnostic suspicion of both diseases previous to rheumatological consultation. In another study of the clinical characteristics of 173 patients with idiopathic CTS (diagnosis was based on neurophysiological studies in all cases),⁵ CTS was commonly bilateral and severe, and most patients had been referred with a diagnosis of 'arthritis'. Again, the prevalence of FM and CTS was high (19%) and patients with FM had significantly more severe CTS than patients without FM. Presence of associated musculoskeletal conditions in a given patient or bilateral CTS involvement seem to act as confounding symptoms for correct diagnosis before rheumatological consultation.

In the study of Cimmino *et al*, 2440 of 4456 (54%) of the subjects returned the questionnaire, 182 of 2440 (7.2%) met criteria for clinical examination, and 93 of 182 (51.1%) agreed to be visited. One would expect that patients with both conditions would be more prone to answer the questionnaire and accept consultation.

In conclusion, at the present time, it cannot be stated that CTS is more frequent in patients with FM than in the general population, and common pathogenic mechanisms should not be proposed. Nevertheless, it is clear that CTS is often overlooked or misdiagnosed in patients showing atypical symptoms such as bilateral, severe CTS, or associated FM before rheumatological consultation. In addition, we feel that rheumatologists should be alert to the possibility of associated CTS and FM, which is probably more frequent in patients referred to rheumatology units than the 2.4% previously reported in a retrospective series.⁶

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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 paper¹ 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%).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%.³ 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 FM-CTS.¹ The postal questionnaire we used was developed to identify patients with rheumatoid arthritis. We were surprised to find that a considerable proportion of the patients who answered positively to this questionnaire were in fact affected by a combination of FM and CTS.⁴ 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 hypothesis 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 their hands. In our experience, FM patients not only often describe paresthesia and pain in the area innervated by the median nerve but also present pain and numbness elicited by specific manoeuvres.

However, results of electrodiagnostic 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, electrodiagnostic tests may show a poor sensitivity.

These similarities between FM and CTS give the impression of an association of these conditions. To elucidate whether FM and CTS are really associated, we are presently comparing the electrodiagnostic findings as well as the appearance of the median nerve and of the carpal tunnel by ultrasonography and dedicated extremity magnetic resonance in patients with pure CTS or with the presumptive association FM-CTS.

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Measurement of IgA- α_1 -antitrypsin complex in rheumatoid arthritis: A question of specificity?

We feel we should comment on a recent article by Iwana *et al*¹ on the clinical value of measuring circulating IgA- α_1 -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 reagent on their 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.²⁻⁶ 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 a 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 on 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% bovine 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 largely 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 α_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.⁸ 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.^{9,10} 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 and osteoarthritis specimens to see if similar correlations were found with the clinical findings.

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Authors' reply

We appreciate the comments of Dr D L Matthey and colleagues regarding our article.¹

As the prototype kit used in our study for detecting IgA- α_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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Comments by Professor Stanworth

I should welcome an opportunity to reply to the comments of Matthey 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 Matthey that the anticomplex antibody used within the assay may cross react with complement factor H. This, however, does not negate the findings 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 Matthey.

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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.¹

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!

Regarding his claim 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 analgesics, 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 patients 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.

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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 analgesics, 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.¹ 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

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

Evaluation time	All patients (40–75 years, ISK baseline 2.0–18.5)			Subgroup (>60 years, ISK baseline >10)		
	Verum (n=95)	Control (n=100)	Intergroup difference	Verum (n=28)	Control (n=26)	Intergroup difference
1 week after last injection	3.5	2.6	0.9	4.6	3.2	1.4
Follow up after 1 month	3.8	2.7	1.1	5.7	3.3	2.4
Follow up after 2 months	4.4	2.8	1.6	6.5	3.6	2.9

data of the patients of our German multicentre study with hyaluronan² 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.

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