LETTERS TO THE EDITOR

Lack of involvement of the Fas system in ankylosing spondylitis

Apoptosis or programmed cell death is one of the regulation mechanisms of cell homeostasis.

Fas is a transmembrane receptor protein which transmits a cell death signal when cross linked with an antibody or with its physiological ligand—Fas ligand (Fas L).¹ Fas and Fas L have a pivotal role in regulating lymphocyte apoptosis and maintaining lymphocyte homeostasis.

Soluble forms of Fas and Fas L may be detectable and measured in the serum,² and may reflect the activation of this pathway. Moreover, soluble forms of Fas regulate Fas/Fas L mediated apoptosis.³ Raised levels of soluble Fas (sFas) have been shown in various chronic inflammatory rheumatic diseases, systemic lupus erythematosus, Sjögren's syndrome,^{4,5} and in the synovial fluid of rheumatoid arthritis.⁶ These diseases are autoimmune diseases with lymphocyte involvement.

Ankylosing spondylitis (AS) is another chronic inflammatory rheumatic disorder, with less autoimmune background or lymphocyte involvement. Involvement of apoptosis in the pathogenesis of AS has not been discounted.

This preliminary study aimed at evaluating the apoptotic Fas/Fas L system in AS by measuring the amount of the soluble forms of these proteins in the serum of patients with AS compared with controls.

Forty nine consecutive inpatients and outpatients with AS according to the revised New York criteria were included.⁷ Forty healthy subjects without any inflammatory or autoimmune disease, with the same age and sex distribution, were used as controls.

For the patients with AS the disease activity was assessed by clinical variables (Bath Ankylosing Spondylitis Disease Activity Index (BASDAI))⁸ and biological variables (erythrocyte sedimentation rate (ESR), serum C reactive protein (CRP) levels).

Soluble Fas (sFas) and soluble Fas Ligand (sFas L) levels were measured twice in the serum of the patients and controls using a sandwich enzyme linked immunosorbent

assay (ELISA) (sFas ELISA kit and sFas L ELISA kit; Medical and Biological Laboratories Co, Ltd, Nagoya Japan). Statistical analysis was by Student's *t* test.

Of the 49 patients (34 men, 15 women), with a mean (SD) disease duration of 8.6 (7.2) years, 40 (82%) were HLA-B27 positive. The mean BASDAI index was 5.34 (1.97), mean ESR 24.9 (22.7) mm/1st h, and mean CRP 16.0 (18.8) mg/l.

There were no differences in the serum levels of sFas and sFas L between patients with AS and controls (table 1).

Moreover, no differences were found in the sFas and sFas L serum levels between patients with active and inactive AS (table 2). For 26 patients the BASDAI was >5.3 and for 23 patients <5.2. Similarly, 19 patients had an ESR >25 mm/1st h and in 30 patients the ESR was <25 mm/1st h. CRP was >16 mg/l in 17 patients and <16 mg/l in 32. The split between the groups was defined by the mean of the values.

This study failed to show any modification in serum levels of sFas and sFas L in patients with AS compared with controls. There were no differences between patients with clinically or biologically active and inactive AS, and so there was no correlation with disease activity.

These results are in contrast with the results found with other chronic inflammatory autoimmune rheumatic diseases.^{1,4,5} However, Fas levels do not seem to correlate with the clinical diagnosis of autoimmune disease, or laboratory abnormalities.⁹ AS differs from these conditions as there is no lymphocyte activation,¹⁰ but involvement of polymorphonuclear cells and intracellular chronic infection. These mechanisms do not seem to interfere with apoptosis. For example, it has been shown that clearance of *Chlamydia trachomatis* (a micro-organism implicated in some spondyloarthropathies) from the genital mucosa does not require Fas mediated apoptosis.¹¹

Our results suggest that there is no involvement of apoptosis via a Fas/Fas L pathway in AS.

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Table 1 Details of patients and controls

	Patients	Controls	p Value
Number	49	40	
Age	38.7	35.6	
M/F	34/15	25/15	
sFas (ng/ml)	2.16 (0.55)	2.16 (0.37)	NS
sFas L (ng/ml)	0.025 (0.021)	0.026 (0.029)	NS

Table 2 Values of soluble Fas (sFas) and soluble Fas ligand (sFas L) in patients with active and inactive ankylosing spondylitis

	BASDAI* >5.2	BASDAI <5.2	ESR* >25 mm/1st h	ESR <25 mm/1st h	CRP* >16 mg/l	CRP <16 mg/l
Mean (SD)	6.61 (1.02)	3.52 (1.59)	47.58 (20.58)	10.76 (6.36)	34.92 (20.84)	5.95 (4.48)
sFas (ng/ml)	2.08 (0.54)	2.15 (0.52)	2.07 (0.42)	2.22 (0.62)	2.01 (0.35)	2.24 (0.62)
sFas L (ng/ml)	0.021 (0.020)	0.031 (0.021)	0.023 (0.021)	0.025 (0.021)	0.023 (0.020)	0.025 (0.021)

*BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; ESR = erythrocyte sedimentation rate; CRP = C reactive protein.

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HLA-DRB1*04 may be a marker of severity in giant cell arteritis

Salvarani *et al* recently studied 39 patients with giant cell arteritis (GCA) and found no association with HLA-DRB1*04.¹ In contrast, previous immunogenetic studies did show an association between HLA-DRB1*04 and GCA.^{2,3} Rauzy *et al*, also, reported a significant increase in DRB1*04 frequency in GCA. HLA-DRB1*04 was present in 20 of their 41 patients with GCA (49%) compared with a prevalence of 20% in the control group.⁴

Likewise, in a series of 53 patients with GCA from north west Spain, we found a significant increase in DRB1*04 frequency (44% *v* 26% in the controls).⁵ Although Rauzy did not find a correlation between HLA markers and the initial severity of the vasculitis, there are several similarities between their results and ours. Those authors described a relation between HLA-DRB1*04 and corticosteroid resistance. In our series HLA-DRB1*04 was particularly pronounced in those patients with severe visual complications.⁵ Both higher corticosteroid requirement and severe ischaemic complications imply a worse outcome of the GCA. This supports the idea put forward by Rauzy *et al* that HLA-DRB1*04 in GCA may be a genetic marker of severity for this form of vasculitis.

In contrast, although Combe *et al* described an increased frequency of DRB1*04 in their series of 42 patients with GCA, they did not find a significant relation between markers of disease severity and activity of GCA and HLA-DRB1 genes.⁶ These discrepancies may be related to the different

ethnic backgrounds of the groups investigated. The importance of HLA-DRB1*04 in the development of more severe GCA needs to be confirmed by further studies of a greater number of patients. An examination of the importance of other class II and non-class II molecules as markers of severity in GCA is also required.

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Acute oedematous dermatomyositis

There are many published reports of limb oedema occurring in various rheumatic diseases.¹ It may be present in patients with dermatomyositis oedema, especially where the subcutaneous tissue is loose, such as the upper eyelids.²

A 27 year old woman presented with an eight week history of a progressive increase in girth of both forearms and tightening of the overlying skin. Four weeks from onset she had developed a triad of cutaneous features: a periorbital heliotrope rash, an erythematous malar rash affecting the nasolabial folds, and a 'V' sign rash on her neck. Two weeks later proximal muscle weakness developed. Physical examination showed markedly oedematous forearms, the overlying skin was tense, and elbow extension limited. Nailfold capillary microscopy was abnormal showing disorganisation and dilatation. Neurological assessment showed grade 4 muscle power in hip flexors and shoulder abductors; other systems were normal.

Figure 1 Magnetic resonance scan of the forearm showing fluid in the subcutaneous space adjacent to extensor and flexor muscles (arrow A) and increased signal in the extensor digitorum muscles (arrow B).

Investigations included a normal full blood picture, differential white cell count, C reactive protein, and erythrocyte sedimentation rate. Muscle enzymes were raised: creatinine kinase 1454 U/l (normal 0-195), serum aspartate aminotransferase 106 IU/l (7-40), serum alanine aminotransferase 77 IU/l (10-60), aldolase 6.1 U/l (0.5-3.1). Thyroid function was normal. Antinuclear antibody was negative, as were antibodies to extractable nuclear antigens and Jo-1. Virology for coxsackievirus, Epstein-Barr virus, cytomegalovirus, picornavirus, echovirus, parvovirus-19, influenza, and rubella and serology for trichinella and toxoplasma were all negative. Chest radiograph, electrocardiography, pulmonary function tests (lung volumes and transfer factor) were normal. An ultrasound scan of the abdomen and pelvis was normal. Tumour markers CEA and CA-125 were within normal limits. Electromyography of the right deltoid and biceps muscles showed a myopathic abnormality. A forearm muscle biopsy specimen showed perivascular inflammation, and a second full thickness biopsy specimen showed only patchy inflammation, with the deep fascia unaffected. A magnetic resonance (MR) scan of the forearm was performed on the arm that was not biopsied (fig 1). A T-2 weighted inversion recovery scan showed an extensive collection of fluid lying in the subcutaneous space adjacent to both extensor and flexor muscles (arrow A) with increased signal in the extensor digitorum muscles in keeping with myositis (arrow B).

The diagnosis of dermatomyositis, suggested initially by the cutaneous stigmata and proximal myopathy, was confirmed by raised muscle enzymes, classical histological findings on muscle biopsy, and myopathic features on electromyography. Investigations to exclude other causes of an inflammatory myopathy or any associated malignancy were normal. There was a dramatic clinical response after the start of treatment with daily prednisolone (1 mg/kg) and azathioprine (2 mg/kg). Within 48 hours muscle power was completely restored and muscle enzymes returned to normal. Within 10 days both arms were normal in size and had a normal skin texture. Steroid treatment was cautiously reduced and discontinued six months from presentation; one month

later azathioprine was stopped. This patient remains under review and has not had further symptoms at two years' follow up.

Gross peripheral oedema represents an unusual presenting feature of dermatomyositis. Indeed the atypia of this additional physical sign in a case of otherwise classical dermatomyositis made the authors consider and exclude eosinophilic fasciitis as part of the differential diagnosis.

Recently, the use of MR imaging has proved to be a useful adjunctive test for assessing disease activity, guiding therapeutic decisions, and aiding the selection of a site for muscle biopsy in inflammatory myopathies.³ In this case MR imaging provided radiological evidence as to the cause of the increase in forearm girth. The aetiopathogenesis of the free fluid seen is likely to be due to an increase in capillary permeability, a result of the intense inflammatory process in the underlying muscle. In acute polymyositis and dermatomyositis, MR imaging is known to show focally or inhomogeneously increased signal intensities on T-2 weighted images in affected muscles, which has been shown to correlate with disease activity, and returns to normal after successful treatment.³⁻⁶ Additionally, perimuscular oedema, which probably represents oedema of the fascia or adjacent tissue, and increased signal intensity in a reticular distribution in the subcutaneous fat, have been described.⁷

Early diagnosis of polymyositis and dermatomyositis is often missed. This case thus illustrates a possible early clinical sign and furthermore, shows the use of MR imaging in this condition.

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