LETTERS TO THE EDITOR

Systemic sclerosis and porphyria cutanea tarda

Sir: The appearance of sclerodermoid changes in porphyria cutanea tarda is well known¹; cases of porphyria cutanea tarda associated with systemic sclerosis have rarely been described, however.^{2,3} A further case of this association is reported here. Repeated phlebotomy led to a slight improvement in the cutaneous sclerosis, but visceral involvement remained unchanged.

A 48 year old man was admitted for study of generalised cutaneous thickening. He was a heavy smoker and drinker. He had received no drugs and had not been in contact with toxic products. Outbreaks of vesicular lesions on the back of his hands, face, soles of the feet and intermittent dark urine had been evident for the past three years. Generalised skin thickening, particularly on his hands, and Raynaud's phenomenon had developed nine months before admission. Other clinical data included constitutional symptoms, pyrosis, impotence coeundi of six months' duration, and diffuse cutaneous hyperpigmentation lasting for three months' before admission.

Physical examination showed erosions, crusts, scars, and milium cysts in areas exposed to the sun and on the soles of his feet. There was diffuse hyperpigmentation with vitiligo-like patches. Skin thickening on the chest, back, abdomen, face, and arms made pinching impossible and greatly limited articular function. The legs were relatively unaffected. The finger tip showed pitting scars. There were no telangiectasias or subcutaneous calcifications. The remainder of the physical examination, blood and urine analysis were unremarkable. α Fetoprotein, carcinoembryonic antigen, cortisol, and adrenocorticotrophic hormone were normal; iron 10 μ mol/l (normal 10-28 μ mol/l), transferrin 1.7 g/l (normal 1.6-2.7 g/l), saturation index 22% (normal 20-40%), ferritin 350 μ g/l (normal 18-300 μ g/l), the urinary uroporphyrin level was 640 nmol/24 h (normal <48 nmol/24 h) with presence of faecal isocoproporphyrins; antinuclear antibody titre was 1/160 homogeneous pattern and 1/10 240 speckled pattern; and Scl-70 and other antitissue antibodies were negative.

A chest radiograph showed slight emphysema. Functional respiratory tests showed slight restrictive ventilatory disturbance, with impairment of both the transfer factor of the lung for carbon monoxide and the transfer coefficient. Pulmonary gammagraphy with gallium-67 was normal. A hand radiograph disclosed lysis of the distal phalanges. Nailfold capillaroscopy showed capillary dilatation in several fingers. Abdominal echography showed slight liver enlargement. Liver biopsy showed moderate hepatic siderosis, but no needle-like inclusions in the hepatocyte cytoplasm were seen under polarised light microscope. Skin biopsy disclosed epidermal hyperpigmentation of the basal layer, a thickened basement membrane positive for periodic acid-Schiff reagent, superficial perivascular hyalinisation, and an increase in dermal collagen. Oesophageal manometry showed hypotension of the lower oesophageal sphincter and severe

hypomotility of the distal two thirds of the oesophagus.

The patient was diagnosed as having porphyria cutanea tarda and systemic sclerosis. Alcohol abstinence was recommended and treatment with repeated phlebotomy (300 ml every two weeks) was started. At six weeks of treatment urinary porphyrins were normal and a slight decrease in both pigmentation and cutaneous sclerosis was seen over several months. Oesophageal manometry results after six and 24 months of treatment remained unchanged, however.

Our patient had porphyria cutanea tarda before the clinical onset of systemic sclerosis. We wonder whether this was a chance co-existence of two admittedly different pathogenic entities or whether there is a causal relation between them.

Sclerodermoid lesions may develop in 18 to 27% of patients with porphyria cutanea tarda.^{1,2} They are usually late lesions, which appear in patients with untreated porphyria cutanea tarda of several years' duration and tend to have a characteristic appearance and location.⁴ The face may take on a systemic sclerosis-like appearance and the fingers may show sclerodactyly not usually associated with Raynaud's phenomenon.⁵

Experimental studies have shown that uroporphyrin I increases collagen synthesis in human skin fibroblasts with or without ultraviolet radiation.⁶ Although in most cases sclerodermoid changes in porphyria cutanea tarda are confined to the skin, some cases with visceral involvement suggestive of true systemic sclerosis have been reported.^{2,3} Friedman and Doyle believe that although it is reasonable to think that porphyria cutanea tarda may be associated with systemic sclerosis as with other connective tissue diseases, improvement in most cases of sclerodermoid changes with normalisation of uroporphyrin concentrations suggests more than simple coexistence.⁷ In this case only a slight improvement in cutaneous sclerosis, but not in visceral involvement, was achieved with treatment. We believe that when systemic sclerosis is associated with porphyria cutanea tarda, treatment of the latter does not modify the former, at least not the visceral involvement. In view of the small number of reported cases there is for the moment no answer to the question posed earlier.

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Increased concentrations of soluble interleukin-2 receptor in the serum of patients with systemic sclerosis

Sir: The extent to which the immune system is important in the pathogenesis of systemic sclerosis is still poorly understood. In a recent issue of the *Annals* Gustafsson and colleagues showed the presence of increased numbers of HLA-DR positive T lymphocytes in the peripheral blood of patients with systemic sclerosis compared with those in healthy controls.¹ Expression of HLA-DR antigens as well as of the interleukin-2 receptor on a cellular surface is acquired by T cells after stimulation by antigens or mitogens.

It has been reported that a soluble form of interleukin-2 receptor is released in culture supernatants by activated lymphocytes,² derived mostly from T cells,³ and that it can be measured in the sera of patients with various clinical disorders in which the immune system is activated. Therefore, the soluble form of interleukin-2 receptor has been regarded as a new marker of T cell activation: increased concentrations have been noted in the sera of patients with systemic autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, and Sjögren's syndrome.⁴⁻¹⁰

We evaluated the concentration of the soluble form of interleukin-2 receptor in the sera of patients with systemic sclerosis by an enzyme linked immunosorbent assay (ELISA) based on the sandwich principle (Cellfree, T Cell Science, Cambridge, MA).² Results are expressed in units/ml relative to a set of standards supplied with the test kits.

Twenty eight patients (27 women, one man; median age 52 years) were studied. All patients met the American Rheumatism Association preliminary criteria for the classification of systemic sclerosis¹¹: 21 had typical sclerodermatous skin changes proximal to the metacarpophalangeal joints (anti-Scl-70 was present in nine of them and antientromere in three); sclerodactyly and at least three of the other four signs of the CREST syndrome (calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, and telangiectasia) were present in the other seven patients (six of them were antientromere positive).

Serum concentrations of the soluble form of interleukin-2 receptor were markedly higher in patients with systemic sclerosis than in 19 controls matched for age and sex (mean (SD) 846 (387) U/ml v 301 (90); $p < 0.005$, Wilcoxon's test). Twenty four of 28 patients (86%) had concentrations of the soluble form of interleukin-2 receptor more than 3 SD above the mean concentration of the controls. Patients with the CREST syndrome had nonsignificantly lower concentrations than those with diffuse scleroderma (679 (148) U/ml v 902 (427)). Our data agree with those of previous studies showing the presence of activated lymphocytes in systemic sclerosis.^{1,12} They are at variance with the findings of Gustafsson *et al*,¹ however, as we did not note a significant inverse correlation between disease duration and the marker of T cell activation ($R = -0.14$; Spearman's test).

Further studies are needed to clarify the biological significance of the soluble form of interleukin-2 receptor in systemic sclerosis and, by longitudinal follow up of several patients, its possible use for monitoring the progression of the disease.

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Nature of the ossicular joints and their involvement in rheumatoid arthritis

Sir: I read with interest the paper published recently in the *Annals*¹ but must disagree with the description of the ossicular joints as synovial with cartilaginous articular discs. I note the use of the paper by Reiter *et al*² as a reference for this statement, but examination of his paper shows that his assertion is not based on referenced histological or anatomical fact. In 1981 the ossicular joints were described by Anson as 'diarthrodial joints surrounded by a thin capsular ligament. From the inner surface of the capsular ligament a wedge-shaped circular rim projects into the joint cavity and incompletely divides it'.³ There was no mention of synovium or a cartilaginous disc. Modern understanding of the physiology

of sound conduction through the middle ear emphasises the importance of the ossicles acting only as a piston without significant rotation about the joints.⁴ In man the incudo-malleal joint seems to have no function apart from binding the two bones together as there is no movement at the joint. Indeed in many rodents there is no joint and the malleus and incus are one bone. The most important factor changing the low pressure, high displacement vibrations of air into high force, low displacement vibrations suitable for driving cochlear fluids is the ratio of the areas of the tympanic membrane and the stapes footplate.

Therefore, the presumption that these joints should participate in the rheumatoid process seems far less likely. Interestingly, however, this study and those of Reiter² and Moffat⁵ all showed altered stiffness of the middle ear conducting mechanism. Goodwill, who examined the ossicles removed at necropsy from three rheumatoid patients, did not find nodules or erosive joint changes but instead fibrous tissue replacement of the long process of the incus.⁶ This finding is not uncommon in chronic otitis media and is thought to result from the fact that the long process of the incus has the most tenuous blood supply of all the ossicular elements and thus is most at risk from endarteritis obliterans secondary to infection with subsequent resorption of bone and replacement by fibrosis. Probably, the middle ear changes in rheumatoid arthritis are secondary to the associated vasculitis, which is already known to account for most of the other extra-articular manifestations.

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Ankylosing spondylitis and selective IgA deficiency

Sir: We read with interest the account from Dr Herrero-Beaumont and colleagues of a patient with selective IgA deficiency and severe spondyloarthropathy.¹ We report a further case of IgA deficiency in ankylosing spondylitis. The patient, a 38 year old white woman, first noted inflammatory low back pain and stiffness at the age of 27. Over the following years she also experienced intermittent knee and ankle synovitis, each episode resolving without intervention or sequelae. Ankylosing spondylitis was diagnosed at 33, after referral to a rheumatologist. Sacroiliac radiographs showed bilateral marginal sclerosis

and erosions, and she was HLA-B27 positive. There was no past or family history of uveitis, psoriasis, or other associated disease, and serological tests for antinuclear antibodies and rheumatoid factor were consistently negative. Treatment consisted of non-steroidal anti-inflammatory drugs, analgesics, and exercise.

The course of her disease was unremarkable and did not feature the destructive peripheral arthropathy noted in the previous reports. At her last assessment her disease activity was subjectively moderate, with no morning stiffness and with lower back pain rated as 26% of maximum on a visual analogue scale. The modified Schober index² was 5 cm, chest expansion 2 cm, and she had no peripheral synovitis or enthesitis. Erythrocyte sedimentation rate was 43 mm/1st h, C reactive protein 27 mg/l (normal <10).

The patient was otherwise healthy, and IgA deficiency was not suspected on clinical grounds. During serological studies of a sample of patients with ankylosing spondylitis (to be reported separately) she was noted to have barely detectable concentrations of specific IgA antibodies. Serum total IgA concentration was <0.2 g/l (normal range 0.8-3.9) by laser nephelometry, and <50 mg/l by enzyme linked immunosorbent assay (ELISA). By contrast, her serum IgM was normal at 1.3 g/l (0.5-3.5), and IgG slightly raised at 17.1 g/l (7.2-16.2). Bone marrow examination was not indicated.

Although selective IgA deficiency has been associated with recurrent mucosal infection and allergy, and with an increased incidence of several autoimmune disorders, most patients are asymptomatic.³ IgA deficiency affects about 0.2% of the adult white population,³ and ankylosing spondylitis up to 1%.⁴ By chance alone the two disorders will therefore occur together in 0.002% (one in 50 000 people), suggesting that there are around 1000 such patients in the United Kingdom. Unlike the four previously reported cases¹ our patient did not have 'severe' ankylosing spondylitis, and we argue against interpreting IgA deficiency as a poor prognostic factor in ankylosing spondylitis until more evidence has been accumulated.

At a mechanistic level the existence of such cases indicates that an intact IgA response is not essential to the pathogenesis of ankylosing spondylitis.

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