Antibodies to nuclear antigens in three patients with scleroderma and asthma

We read with interest the report of Martin et al1 regarding autoantibodies to centromere and histone in patients with scleroderma and severe pulmonary and vascular disease. During the past two years we have been following the clinical course of five female patients with scleroderma (two with localized scleroderma and one with diffuse scleroderma) and asthma, aged 40, 48, and 77, respectively. The onset of scleroderma had been preceded by asthma in each of them. The first two patients were atopic. Accompanying diseases were acne rosacea (first patient), thyroid adenoma (second), and diabetes mellitus type II (third patient). The diabetes in the last patient had begun 30 years ago after he had suffered a heart attack. Typical of asthma and radiographic evidence of pulmonary emphysema were found in all patients; none had symptoms suggestive of Sjögren’s syndrome. The serum IgE values were increased in the first two patients. All patients had positive antinuclear antibodies (ANA) detected by indirect immunofluorescence on HEp-2 cells in titre 1:80 with a speckled pattern of immunofluorescence. The second patient had positive DNA antibodies (enzyme linked immunosorbent assay (ELISA)), and the second and third patients positive antibodies to histone 2A (ELISA). None of the three had Ro(SS-A) or La(SS-B) antibodies. The two patients, therefore, may be included in the group of overlap syndromes. The question is whether asthma is a manifestation of fibrosis, or the two diseases are independent entities. The scleroderma involves only the skin in two of the patients. Spirometry showed an obstructive defect of ventilation in all three patients. The increase in IgE in the sera of two patients suggests involvement of reaginic type reactions. The ANA positivity suggests type II and III immune reactions.

We found no published reports of a combination of scleroderma, asthma, and positive ANA. The presence of two diseases—scleroderma and asthma—raises the following issues:

(1) The role of scleroderma as a cause for the development of asthma in these patients. The pulmonary involvement in scleroderma is very common. It is of a restrictive type, while in asthma, obstruction of the airways is a characteristic feature. Our data support the notion of an independent development of asthma.

(2) The role of the endocrine system in the development of scleroderma. It is well known that rheumatic diseases are more frequent in females. Asthma also may suffer from resorptions more often and the appearance of the disease may be linked to the climacteric. It is notable that two of our patients had accompanying endocrine diseases, thyroid adenoma and diabetes. The combination of asthma with scleroderma and endocrine disorders in our three patients warrants further investigation of this association.

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LETTERS TO THE EDITOR

Ehlers Danlos syndrome and osteoporosis

Ehlers Danlos syndrome (EDS) is a group of inherited connective tissue disorders with extreme genetic and clinical variability. The clinical manifestations of EDS are a result of abnormalities in collagen types 1 and 3, the main protein components of skin, ligaments, tendons, blood vessels, and internal viscera. Type I collagen is also the main protein constituent of the bone matrix and its abnormalities form the molecular basis of osteogenesis imperfecta (OI).2 EDS is therefore quite closely linked to OI and the two conditions are known to coexist.3 In spite of this there are no detailed studies available on bone mineral content in patients with EDS.

In the past three years we have seen seven patients with EDS and assessed bone densities in the lumbar spine and hip using dual energy x-ray absorptiometry. A 65 year old lady referred from the orthopaedic department for investigations of a wedge fracture of the L2 vertebra. She did not have any obvious precipitating causes for osteoporosis in her past medical, menstrual, and obstetric history. She was a very active woman and had never had a bone fracture. Her bone density was decreased and osteoporosis was diagnosed. The patient had a daughter who also had osteoporosis.

A 56 year old lady with Ehlers Danlos type IV referred from a dermatology department. She had a history of bruising easily and frequent surgeries prevented a definitive diagnosis of her condition. A decreased bone density was found.

A 36 year old lady with Ehlers Danlos type IV referred from a dermatology department. Her skin was easily bruised and she had multiple surgical scars. A decreased bone density was found.

A 50 year old lady with Ehlers Danlos type II referred from a dermatology department. Her skin was very fragile and she had multiple surgical scars. A decreased bone density was found.

A 45 year old lady with Ehlers Danlos type IV referred from a dermatology department. Her skin was easily bruised and she had multiple surgical scars. A decreased bone density was found.

A 36 year old lady with Ehlers Danlos type IV referred from a dermatology department. Her skin was very fragile and she had multiple surgical scars. A decreased bone density was found.

A 35 year old lady with Ehlers Danlos type IV referred from a dermatology department. Her skin was easily bruised and she had multiple surgical scars. A decreased bone density was found.

A 32 year old lady with Ehlers Danlos type IV referred from a dermatology department. Her skin was very fragile and she had multiple surgical scars. A decreased bone density was found.

In conclusion, Ehlers Danlos syndrome is not as rare as has been previously described. It is very important to diagnose Ehlers Danlos syndrome in a patient who presents with bone fragility. A detailed family history and an assessment of bone density are necessary in any patient with Ehlers Danlos syndrome.
or dietary history. She was adopted as a child and had no known family. On general examination, she had lax skin, blue sclera, and paper thin scars on forehead and shins. She was hypomobile and had bilateral pes planus. On questioning she said that she bruised easily, was double jointed and suffered from rectal prolapse. She was tender on the lumbar spine and the neurological examination in the lower limb was normal. Haematological and radiological investigations excluded myeloma or other malignant deposits.

A diagnosis of EDS type 2 was made. She underwent bone densitometry examination by dual energy x ray absorptiometry which revealed Z scores of −1.21 (T score = −2.69) in the lumbar spine and −1.88 (T score = −3.55) in the femoral neck. She was treated with analgesics and hydrotherapy and commenced hormone replacement therapy (HRT). Over the next four years, she consistently gained bone density at the lumbar spine, though after the initial gains HRT failed to maintain the bone mineral density (BMD) at the femoral neck (fig. 4). Her backbone has remained under control and she has had no new fractures.

In the past three years we have seen six other patients with EDS: four females aged 16–62 and two males aged 55 and 70. None of them was known to have EDS; they were referred by their general practitioner for assessment of bone densitometry at their request. Detailed history failed to identify any predisposing factors for osteoporosis and diagnoses of EDS were made for the first time as a result of clinical characteristics. All the patients had low BMD in either the lumbar spine or the femoral neck (table). For the seven patients taken together, the average Z score was −1.4 (T score = −2.26) at the lumbar spine and −1.83 (T score = −3.2) at the femoral neck.

The genetic defects in the most common forms of EDS (types 1, 2, and 3) are as yet unknown, but in some forms of EDS the exact molecular pathology has been identified and includes hydroxylysine deficiency in type 6, defect in the synthesis and processing of types 1 and 3 collagens in EDS types 7 and 4. Theories of mineralisation of the organic matrix of bone suggest that normal quality collagen is required to form normally mineralised bone. Histophenometric and electron microscope studies support this theory and have shown that the defective collagen fibrils in OI may be non-mineralised or may contain crystals of hydroxyapatite that are irregularly arranged.

We hypothesise that abnormality of the collagen framework in EDS leads to faulty deposition of bone mineral, with resultant decreased bone mass.

In a period of four years, the patient with EDS who received HRT showed improved spinal BMD, but lost BMD in the femoral neck. We previously found that HRT was not effective in maintaining bone mass in the lumbar spine in two of three postmenopausal female patients with OI. With so few subjects, it is impossible to draw any conclusions as to the effective therapy for treating osteoporosis in patients with heritable connective tissue diseases. Our preliminary observation is that monitoring by regular bone densitometry is invaluable in the assessment of therapy in these patients.

Ehlers Danlos Syndrome should be considered in any patients for presumed postmenopausal osteoporosis. The disorder may be missed earlier and present for the first time in later life as "osteoporotic fractures." The response to osteoporosis therapy in heritable connective tissue diseases can be unpredictable because of underlying collagen abnormalities and these patients therefore need careful monitoring.

Remission of nephrotic syndrome in a patient with renal amyloidosis associated with Takayasu’s arteritis after treatment with dimethylsulphoxide

Amyloidosis is a chronic infiltrative disorder characterised by the presence of extracellular deposits of insoluble protein of unknown nature. Renal involvement generally carries a poor prognosis in patients with secondary amyloidosis, who usually display severe proteinuria, nephrotic syndrome and progressive renal failure; uremia is the major cause of death in this group.1 There is as yet no accepted treatment for amyloidosis and the patient’s life expectancy is short.2 We present a patient with renal amyloidosis associated with Takayasu’s arteritis (TA) (aortitis syndrome) who demonstrated a favourable clinical course.

This 29 year old woman was admitted to our hospital in April 1981 with nephrotic syndrome. Her history revealed that, seven years earlier, she had presented with fever, vertigo, and systolic hypertension. Stenosis of the abdominal aorta was noted. TA was diagnosed; the patient had received prednisolone 5 mg daily since that time. There was no family hereditary disease including amyloidosis.

At admission in 1981, physical examination revealed a systolic heart murmur and murmurs in the neck, subclavicular area, and abdomen. Blood pressures taken in the right arm, left arm, right leg, and left leg were 158/40, 164/40, 110/40 and 104/40 mm Hg, respectively. Laboratory data revealed massive proteinuria of 8-0 g/day. There was no haematuria and renal function was normal, with creatinine 0.56 mg/dl, blood urea nitrogen 6.0 mg/dl, and glomerular filtration rate 123-4 ml/min. Serum albumin concentration was 2.3 g/dl and renal cholesterol concentration 289 mg/dl. C reactive protein concentration was >1 mg/dl and serum gamma globulin concentration 1-69 g/dl. The erythrocyte sedimentation rate (ESR) was 160 mm.

Examination of tissue obtained at renal biopsy revealed varying degrees of amyloid deposition in the mesangial areas of all glomeruli. A few arterioles showed mild focal deposits of amyloid. The glomeruli and the interlobular arteries were positively stained with Congo red and antibody to amyloid-A protein. Electron microscopy showed amyloid fibrils in the glomerular mesangium and sub-epithelial region. Deposition of amyloid was

1Patient described in text. PM = postmenopausal; ND = hip scan not done.