MATTERS ARISING

Hepatic hypertrophic osteoarthropathy and liver transplantation

Hepatic hypertrophic osteoarthropathy (HOA) is a rare and disabling condition. It tends to respond poorly to conservative management such as analgesia or intra-articular injection of steroids. A recent article¹ highlighted the benefits of successful liver transplantation in producing remission of this painful arthritis. We report a case of HOA which developed nine years after orthotopic liver transplantation (OLT).

A 44 year old man presented in February 1993 with three week history of pain and swelling of his wrists, knees and ankles. He had no previous arthritic symptoms. In 1979, he had developed primary sclerosing cholangitis and had undergone liver transplantation in 1985. A Roux-en-Y procedure was performed in 1991 for biliary stasis. Contrast cholangiography later that year demonstrated good biliary drainage. No strictures were present, but abnormal tapering of the distal biliary tree was noted. Because of continuing cholestasis, a liver biopsy was performed in September 1992. This showed chronic active hepatitis but no evidence of rejection. There was no recurrence of his original disease.

Examination revealed toe but not finger clubbing and he was markedly icteric. There was synovitis affecting the wrists, knees, and ankles, with tenderness proximal to the joints. Synovial fluid was non-inflammatory. Radiographs of the relevant joints showed a marked periosteal reaction consistent with HOA (figure). Chest radiograph was normal. The knee effusions responded to intra-articular steroid injection and the arthritis symptoms have resolved. However, his liver tests have continued to deteriorate slowly and repeat transplantation is being considered.

The pathogenesis of HOA is unknown. Hormonal, circulatory, and neurogenic factors have been implicated. It is thought

that a growth factor mediated effect is probably involved² leading to elevation of the periosteum, new bone deposition and oedema of the surrounding tissues. This factor may accumulate as a result of impaired hepatic clearance or may be produced in excess by the liver as part of its response to disease. Hepatic HOA is rare.³ It is usually associated with cholestasis and is most commonly seen with primary biliary cirrhosis, chronic active hepatitis, and post-hepatic cirrhosis.

Liver transplantation, besides resulting in improved hepatic function, has also been shown to cause resolution of the joint symptoms of hepatic HOA.⁴ This may be because the stimulus for HOA, presumably resulting from the abnormal liver, has been removed. The syndrome can, however, occur de novo after liver transplantation, in those with chronic rejection,⁵ or with recurrence of the underlying disease.

This patient has had two separate liver diseases. It is interesting that HOA did not occur in association with sclerosing cholangitis, but developed later with active inflammation in the grafted liver. While a minority of patients respond poorly to conservative management, this man's symptoms resolved with intra-articular steroid administration and NSAIDs. If he undergoes repeat liver transplantation, it is possible that complete resolution of his HOA will be obtained.

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Cytokine therapy in rheumatoid arthritis

The leader by Giles Campion¹ has given a sure foundation on which to base our thoughts about cytokines, but is sparse on practical proposals.

For example, a recent *Lancet* article from Birmingham² emphasised the early onset of osteoporosis in patients with rheumatoid arthritis (RA). We know that interleukins (IL) 1 and 6 and tumour necrosis factor α (TNF α) all play their part in causing osteoporosis,³ and the indications are that IL-1 receptor antagonist production is relatively poor in RA.⁴

Hence one application that will require trial in several different or combined centres will be the administration of IL-1 receptor antagonist, to see if osteoporosis is ameliorated.

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AUTHOR'S REPLY: The scarcity of practical proposals, as Dr Wardle puts it, was more a function of editorial space than editorial license.

In fact, a large multicentre trial of recombinant human interleukin-1 receptor antagonist (IL-1ra) in rheumatoid arthritis (RA) is currently in progress and much care is being taken to document potential effects of this therapeutic approach on bone. Support for the existence of such an effect comes from the observation that IL-1 stimulates bone resorption *in vitro*¹ and *in vivo*² and promotes the development of osteoclast precursors.³ IL-1 bioactivity is increased in peripheral blood monocytes during the menopause⁴ and a further increase is seen in high turnover osteoporosis.⁵ This effect may actually be regulated by the production of IL-1ra.⁶ As Dr Wardle mentions, production of IL-1ra has been shown to be deficient in the rheumatoid synovium,⁷ so the administration of this cytokine may be an appropriate means to reverse IL-1 pathology, including juxta-articular osteoporosis and erosions.

Whether antagonising one cytokine is enough remains to be seen. In the ovariectomized rat, bone loss during the first month occurs as a result of activation of the mature osteoclast, whereas during the second month, bone loss occurs after proliferation and differentiation of osteoclast precursors.⁸

Radiograph of the knees, demonstrating marked periosteal reaction at the lower end of the femora.

Whereas IL-1ra can completely prevent the latter process,⁹ blocking activation of the mature osteoclast requires simultaneous inhibition of TNF and IL-1.¹⁰ It would therefore be logical to contemplate clinical trials in RA, inhibiting both of these cytokines and observing the effect on RA related osteoporosis as an end point.

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Antibodies to nuclear antigens in three patients with scleroderma and asthma

We read with interest the report of Martin *et al*¹ 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 up three female patients with scleroderma (two with localised 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 stress. Symptoms 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 son of the second patient also has asthma.

These cases cannot be included in the group of any 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 could find 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. Females also suffer from rosacea 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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AUTHOR'S REPLY: Dr Nikolov and his colleagues raise interesting questions. The three patients they describe had asthma diagnosed on clinical grounds and confirmed by spirometry. We also are not aware of any reports of asthma co-existing with scleroderma, but as asthma occurs in 4–6% of the population,¹ it is not surprising that the two diseases coexist. However, as Nikolov *et al* imply, a key question is whether scleroderma and asthma may have a common pathogenic basis.

In addition to the observations offered in their letter, it is interesting that scleroderma and asthma do share certain pathogenic features; for example increased dermal mast cells¹ and increased ability of mast cells to

release histamine² have been reported in scleroderma. Both these findings suggest that the pathogenesis of scleroderma may include a hypersensitive reaction similar to that described in asthma.¹ It is not clear if a similar process involving mast cells occurs in the lung in scleroderma, although circumstantial evidence suggests that it does.

Our report⁴ suggested that scleroderma patients with centromere and histone antibodies had more severe disease characterised by pulmonary and vascular involvement. It is not clear if the patients referred to by Nikolov *et al* had centromere antibodies, but two did have antibodies to histone H2a. Although review of our charts has not identified asthma as a clinical feature in our patients, based on the observations of Nikolov *et al*, in future studies it may be important to determine if there are clinical correlations between the two diseases.

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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.¹ The clinical manifestations of EDS are a result of abnormalities in collagen types 1 and 3, the major proteins of skin, ligaments, tendons, blood vessels, and internal viscera. Type 1 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 4} 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 was 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,