Letters to the Editor

An uncommon association: Sjögren’s syndrome and autoimmune myelofibrosis

Str, Haematological disorders are common in Sjögren’s syndrome (SS) and may be due to dysfunction of both cell and humoral immunity [1]. SS has therefore been reported to be associated with autoimmune cytopenia, aplastic anaemia and lymphoid malignancies [2, 3]. We recently observed a case of particular interest, where a patient with SS developed an autoimmune myelofibrosis.

A 30-yr-old woman presented in September 1997 with a 1-month history of asthenia. In April 1997, the diagnosis of SS was performed on the basis of a 5 month history of both xerostomia and xerophthalmia, an abnormal Schirmer test, positive Rose Bengal staining, and salivary gland histology showing grade 3 salivary gland damage according to Chisholm’s classification, with interlobular and intralobular infiltrates composed of mononuclear cells. Full blood count was normal, i.e. haemoglobin 7.9 mmol/l, white blood count (WBC) 8.1 × 10⁹/l, platelets 410 × 10⁹/l. Autoantibody screening was positive only for ANA 1/1000e with a speckled pattern and anti-Ro (SS-A) antibodies. The patient had no other connective tissue disorders and no history of exposure to both toxics and drugs. On admission, the patient was pale and physical examination revealed xerostomia and keratoconjunctivitis sicca. General examination was otherwise normal, and in particular hepatosplenomegaly, lymphadenopathy and parotid gland enlargement were absent. Full blood count showed: anaemia (haemoglobin 3.8 mmol/l, mean corpuscular volume 89 μm³) with reticulocytes 74 × 10⁹/l, leucopenia (WBC 3.1 × 10⁹/l, neutrophils 1.54 × 10⁹/l, lymphocytes 1.47 × 10⁹/l) and thrombocytopenia 80 × 10⁹/l. Renal and liver tests, serum folic acid, vitamin B12 and ferritin levels were within normal limits. ESR was 30 mm/h and CRP 10 mg/l. Blood electrophoresis revealed a polyclonal gammopathy with elevated IgG at 32 g/l. Blood and urinary immunoelectrophoresis, serum lactic dehydrogenase and β₂ microglobulin were normal. Blood cultures and viral serologies [cytomegalovirus, Epstein–Barr virus, parvovirus B₁₉, human immunodeficiency virus (HIV), coxsackie, echovirus, hepatitis, HTLV] were all negative. Autoantibody screening was positive for RF, ANA 1/1000e with a speckled pattern and anti-Ro antibodies 85 IU/ml (normal <5); the direct Coombs test, anticiardiolipin and antiphospholipid antibodies, anti-native DNA antibody, lupus-like anticoagulant and cryoglobulin were negative. Investigations including thoracic and abdominal CT were normal. The sternal bone marrow aspirate, which was carried out because of pancytopenia, was repeatedly unsuccessful. Bone marrow biopsy specimens of the right posterior iliac crest revealed hypocellular bone marrow with fibroblast proliferation, collagen and dense reticulin fibrosis (Figs 1 and 2); there were no abnormal cells or dysplastic change in erythroid, myeloid or megakaryocyte lineages, and bacterial cultures of bone marrow were negative. The diagnosis of autoimmune myelofibrosis in a patient with SS was made. The patient was treated with methylprednisolone pulses (500 mg i.v. × 3 days), followed by oral administration of prednisone 1 mg/kg daily (i.e. 70 mg). In the following month, peripheral haematological abnormalities returned to a normal range (haemoglobin 7.8 mmol/l, reticulocytes 140 × 10⁹/l, WBC 5.7 × 10⁹/l, platelets 170 × 10⁹/l). In September 1998, the patient continues to remain asymptomatic and the full blood count is also normal with a 15 mg/day prednisone regimen.

Myelofibrosis is characterized by an increased deposition of collagen, fibronectin and laminin within the bone marrow [4]. It is often associated with various conditions, including malignant diseases and chronic infections, especially HIV and tuberculosis [4–6]. Myelofibrosis has more rarely been described in association with autoimmune diseases, i.e. SLE and systemic sclerosis [5–8]. However, in a series of 73 patients with
Letters to the Editor


Bone mineral density in scleroderma

Sir, Recent data suggest that the mortality from scleroderma may not be as high as was previously estimated [1], and consequently, with increased life expectancy, patients with scleroderma may be more at risk for the disorders of aging in general, including osteoporotic fractures. Previous data have suggested that Caucasian subjects with scleroderma have lower bone mineral density (BMD) of the spine, radius and whole body compared with controls using bone densitometry [2, 3]. We conducted a study to determine the effects of scleroderma on BMD of the hip and spine in African Americans and Caucasians with scleroderma, selecting controls matched on age, race, menopausal status and oestrogen use.

Fifteen female subjects (10 Caucasian, five African American) with scleroderma (nine with diffuse, six with limited disease) (average duration of disease 9.87 yr) and 15 healthy female controls matched on age, race, menopausal status and use of exogenous oestrogens were recruited for this study. Subjects and controls were excluded if they had any history of a medical disorder known to affect bone metabolism or were on any medication that could affect BMD. Dual energy X-ray absorptiometry (DXA) of the anterior/posterior (AP) lumbar spine and right femur was performed using a Hologic QDR 4500A by trained and certified DXA technicians. Positioning and analyses of subjects to determine BMD were according to the Fracture De´partement de Me ´decine Interne, Centre Hospitalier Intervention Trial protocol [4]. In our laboratory, the in vitro precision of DXA is 0.38% for the lumbar spine and 0.44% for the hip. The in vivo precision at the lumbar spine and hip is <1.0%.

There were no statistically significant differences between scleroderma subjects and controls with respect to height, weight, age, body mass index, tobacco use, calcium intake, and family history of osteoporosis (P > 0.05). Reproductive indices, including age at menarche and menopause and oestrogen usage, were also not significantly different between the scleroderma subjects and controls (P > 0.05). Physical activity was assessed by self-report concerning leisure time and activities of daily living. Subjects with scleroderma reported significantly less physical activity than did controls (P = 0.008). Multivariate regression analysis was then used to control for the effects of exercise on BMD differences.

Table 1 presents the differences in BMD, T and Z scores of the total hip, femoral neck, trochanter and lumbar spine (L2–L4) between scleroderma subjects and controls. There were differences in mean absolute BMD in g/cm² for scleroderma subjects compared to controls.

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Table 1. Bone mineral density (g/cm²), T and Z scores (mean ± s.d.) of the hip and spine in scleroderma vs controls

<table>
<thead>
<tr>
<th>Skeletal site</th>
<th>Scleroderma (n = 15)</th>
<th>Control (n = 15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total hip</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMD</td>
<td>0.745 ± 0.15</td>
<td>0.907 ± 0.12</td>
<td>0.0032</td>
</tr>
<tr>
<td>T score</td>
<td>-1.890 ± 1.22</td>
<td>-0.540 ± 0.98</td>
<td>0.0032</td>
</tr>
<tr>
<td>Z score</td>
<td>-1.062 ± 1.27</td>
<td>0.220 ± 1.02</td>
<td>0.0056</td>
</tr>
<tr>
<td>Femoral neck</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMD</td>
<td>-0.671 ± 0.13</td>
<td>0.820 ± 0.14</td>
<td>0.0103</td>
</tr>
<tr>
<td>T score</td>
<td>-2.183 ± 1.31</td>
<td>-0.706 ± 1.34</td>
<td>0.0084</td>
</tr>
<tr>
<td>Z score</td>
<td>-0.923 ± 1.45</td>
<td>0.469 ± 1.32</td>
<td>0.0181</td>
</tr>
<tr>
<td>Trochanter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMD</td>
<td>0.580 ± 0.12</td>
<td>0.720 ± 0.09</td>
<td>0.0020</td>
</tr>
<tr>
<td>T score</td>
<td>-1.595 ± 1.34</td>
<td>-0.121 ± 1.02</td>
<td>0.0020</td>
</tr>
<tr>
<td>Z score</td>
<td>-0.812 ± 1.41</td>
<td>0.605 ± 1.11</td>
<td>0.0026</td>
</tr>
<tr>
<td>Spine (L2–L4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMD</td>
<td>0.98 ± 0.15</td>
<td>1.047 ± 0.19</td>
<td>0.7269</td>
</tr>
<tr>
<td>T score</td>
<td>0.870 ± 1.35</td>
<td>0.320 ± 1.74</td>
<td>0.3894</td>
</tr>
<tr>
<td>Z score</td>
<td>0.243 ± 1.30</td>
<td>0.718 ± 1.85</td>
<td>0.4212</td>
</tr>
</tbody>
</table>

at the level of the total hip (0.75 ± 0.15 vs 0.91 ± 0.12 vs 0.72 ± 0.09, P = 0.002). No significant differences were noted between scleroderma subjects and controls at the lumbar spine (L2–L4) (0.98 ± 0.15 vs 1.047 ± 0.19, P = 0.277). These results did not change when comparisons were made between the study groups adjusted for physical activity levels. The corresponding T and Z scores were also significantly reduced at the level of the total hip, femoral neck and trochanter, with no significant differences present at the lumbar spine in subjects with scleroderma compared with controls.

This cross-sectional study is the first to demonstrate lower BMD at the hip in both African American and Caucasian females with scleroderma compared with controls. While other studies have reported lower levels of BMD at the radius, total body and lumbar spine in scleroderma subjects compared with controls [2, 3], this may have been due to differences in other co-morbid factors, including menopausal status. In our study, we believe that the differences in BMD were due to the disease of scleroderma itself, possibly secondary to an inflammatory process. Elevated sedimentation rates and active myositis, indicators of inflammation, have been noted in scleroderma [5], and increased secretion of the cytokine interleukin-1 alpha, a known stimulant of bone resorption [6], has been reported to occur in scleroderma [7]. However, other factors including occult malabsorption, decreased sunlight exposure or decreased activity levels in scleroderma subjects may have contributed to the lower BMD noted.

In our study, we found lower BMD of the hip in both African American and Caucasian subjects with scleroderma. This is of some importance, because the incidence of scleroderma in African Americans compared with Caucasians is increased, and African Americans with scleroderma are more likely to have severe disease and reduced survival compared with Caucasians [5].

Important limitations of our study include small sample size with the possibility for type 2 error and potential selection bias. However, we did find a reduction in density at the critically important area of the hip in scleroderma subjects. A 9.4% lower BMD in our subjects with scleroderma compared to controls translates into almost 1 s.d. difference between the two groups. Prospective studies have shown that such a decrease in BMD results in a 2.6-fold increased risk of fracture [8]. Therefore, measurements of BMD should be considered in scleroderma and preventive measures undertaken to reduce osteoporosis.

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Does parenteral oestrogen therapy flare up disease activity in patients with systemic lupus erythematosus complicated by haemorrhagic cystitis?

Sir, Haemorrhagic cystitis is a rare, but most serious complication of systemic cyclophosphamide therapy [1]. It is associated with significant morbidity and occasionally may lead to death [2]. Successful treatment of patients with cyclophosphamide-induced haemorrhagic cystitis with conjugated oestrogen has been reported by Liu et al. [3], but the use of sex hormones in patients with systemic lupus erythematosus (SLE) is controversial [4, 5]. We present a patient with SLE who developed haemorrhagic cystitis after cyclophosphamide therapy and died of disease activity shortly after oestrogen therapy.

Letters to the Editor
This 14-yr-old female patient was diagnosed as having SLE with ARA criteria of malar rash, arthritis, heavy proteinuria, positive antinuclear antibody (titre 1:2560, homogeneous type), and low C3 (16 mg/dl, normal: 80–115 mg/dl) and C4 (<5.1 mg/dl, normal: 13–37 mg/dl). Laboratory findings were normal except hypoalbuminaemia (2.7 g/dl, normal: 3.1–5.3 g/dl) and hyperlipidaemia (cholesterol 478 mg/dl, triglyceride 286 mg/dl). Urinalysis showed RBC 11–20/high-power field (HPF); WBC 11–20/HPF. Twenty-four hour urine protein was 5.29 g/day and urine creatinine clearance was 57.8 ml/min/1.73 m². Autoantibody assay showed elevated anti-double-stranded DNA titre (640 IU/ml, normal: <7 IU/ml) and positive anti-SSA antibody. Renal biopsy was compatible with class IV lupus nephritis. Owing to high lupus activity and renal involvement, methylprednisolone (20 mg/kg/day) and i.v. cyclophosphamide (2 mg/kg/day) were prescribed for 5 days. Then oral prednisolone (40 mg/day) and cyclophosphamide (2 mg/kg/day) were introduced continuously. One month later, the CH₅₀ haemolytic assay was 22 U/ml (normal: >25 U/ml) and urinalysis was normal. Prednisolone was tapered to 20 mg/day and oral cyclophosphamide was decreased to 1 mg/kg/day. After being treated with these medications for another 2 months, the patient developed an acute episode of gross haematuria. SLE activity at that time was mild: CH₅₀ haemolytic assay 22 U/ml, C3 86 mg/dl, C4 12.2 mg/dl. Abnormal laboratory findings were Hgb 5.0 g/dl, WBC 12,200/mm³ and platelet count 132,000/mm³. The blood clotting time was mildly prolonged: prothrombin time, INR 1.18, 13.5 s (control 11.5 s), APTT, 36.5 s (control 30.4 s). Urinalysis showed RBC 3+/HPF, WBC 11–20/HPF and protein 30 mg/ml. Cystoscopy revealed mucosal oedema, telangiectasia and multiple haemorrhagic points, which are compatible with haemorrhagic cystitis. The family refused aggressive therapies, such as intravesical formalin instillation. Because of frequent blood transfusion and urinary retention caused by a blood clot, i.v. premarine (25 mg per 6 h) was used to control the bleeding. The urine cleared dramatically 3 days after the treatment, but 2 days later the patient developed seizure and severe pulmonary haemorrhage. Lupus activity was rechecked and showed low C3 and C4 (C3 50 mg/dl, C4 10.2 mg/dl). CT scan of the brain and blood culture were negative. The impression was of a flare in her lupus disease with diffuse vasculitis. Premarine was tapered within 3 days and methylprednisolone was used to control the disease. The patient developed pancytopenia and acute renal failure. Haemodialysis and high-dose i.v. immunoglobulin (2 g/kg) were given, but in vain. She died of acute respiratory distress syndrome and renal failure 2 weeks later.

SLE is a challenging disease with high mortality and morbidity, especially in those with class IV lupus nephritis. In the past 10 yr, aggressive use of immuno-suppressive regimens, such as cyclophosphamide and cyclosporin, have improved the quality of life and survival rate in children with SLE [6], but for the use of cyclophosphamide, the most serious concern is haemorrhagic cystitis, which may occur even while being prevented with fluids. Mesna may be used to avoid this complication, but the oral form is not available in our hospital. Haemorrhagic cystitis may be treated with aggressive therapy, such as i.v. instillation of formalin solution, hyperoxygenation therapy or application of Helmstein hydrostatic balloon, but this may cause other complications [7]. Parenteral conjugated oestrogen was reported to be effective in treating haemorrhagic cystitis caused by cyclophosphamide [3]. It may work through decreasing the vascular fragility. Oestrogen usage in lupus patients is quite controversial. Until now, there has been no definite proof that oral contraceptives actually precipitate or exacerbate lupus, except that some may be more likely to have adverse effects. Some papers suggest that oestrogens could be used in lupus with great caution [5]. The reasons why we chose hormone therapy were that the family refused other aggressive therapies and the bleeding could not be controlled with conservative treatment. We saw the disease flare up shortly after the oestrogen therapy. We suggest that oestrogen should be used with special caution in adolescent SLE patients. Disease flare-up and side-effects have to be considered and monitored. If possible, other treatments, such as intravesical formalin instillation, should be chosen instead of conjugated oestrogen therapy in lupus patients.

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Seronegative oligoarthritis in the course of refractory anaemia with excess blasts

SIR. The myelodysplastic syndromes (MDS) are a het-erogeneous group of poorly understood refractory anaem-
mias resulting from a clonal abnormality in the pluripotential stem cell. The onset of the condition is asymptomatic until gradually progressive cytopenia and cell line dysfunction eventually manifest as fatigue, dyspnoea, recurrent infection, and/or bleeding problems. Rheumatic manifestations in MDS have been reported infrequently, although in a study 10% of patients suffered several rheumatic complaints [1]. Here, we describe the case of a patient with a seronegative asymmetrical oligoarthritis beginning 3 months after the diagnosis of refractory anaemia with excess blasts (RAEB).

In November 1996, a 48-yr-old man was diagnosed as having RAEB, and treated with supportive measures. His past medical history revealed moderate well-controlled arterial hypertension and long-standing insulin-dependent diabetes mellitus. In February 1997, he was admitted to hospital because of asthenia, anorexia, vasculitis and lupus-like syndrome that constituted with moderate improvement. Ten days after being discharged, he returned to the emergency room because of an accidental fall at home and died as a consequence of cranial trauma.

The MDS are acquired clonal diseases characterized by proliferation of bone marrow-derived stem cells, that causes ineffective haematopoiesis with cytopenia(s) and a pre-leukaemic state. These diseases are insidious in onset, usually occurring in the elderly, but affecting any age category. Immunological disturbances have been known for some time. Abnormalities in natural killer cells, diminished T-helper cells, and generalized impairments in T-cell, B-cell and polymorphonuclear cell function have been shown. Haemolytic anaemia, cutaneous vasculitis and lupus-like syndrome have been described [2]. Castro et al. [1] identified rheumatic manifestations in 10% of patients with MDS, appearing early after diagnosis and sometimes preceding the disease. The majority of these patients were from the RAEB class.

The mechanisms leading to the rheumatic manifestations in patients with MDS are unknown, but the co-occurrence implies a role for the bone marrow in the development of these manifestations. As in rheumatoid arthritis (RA), the aetiopathogenesis of autoimmune diseases lies in a primary defect of bone marrow stem cells which induces T-cell dysfunctions [3]. Killer effector cells (CD8-S6F1), producing cytotoxic T-cell joint disease and a non-macrophage myeloid cell population (FH4+) have been identified in the bone marrow from RA patients compared with bone marrow from control subjects, supporting a potential bone marrow-derived mechanism of joint destruction [4, 5].

In our patient, the initial monoarthritis of the ankle, together with fever and a cloudy synovial fluid, led us to treat it as an infective arthritis. The presence 3 days later of a new synovitis made the septic origin of the arthritis unlikely. Other rheumatic diseases were excluded. No infiltration was evidenced in the bone marrow aspiration and no malignant cells were found in the cytological examination of the synovial fluid. As in other patients, NSAIDs did not control the symptoms, but a prompt response was achieved with prednisone. Prompt recognition of the disease avoids expensive and laborious diagnostic procedures, and facilitates the adequate treatment regimen, especially in patients with potentially serious adverse effects.
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5. Ochi T, Hakomori S, Adachi M et al. The presence of a myeloid cell population showing strong reactivity with monoclonal antibody directed to difucosyl type 2 chain in epiphyseal bone marrow adjacent to joints affected with rheumatoid arthritis (RA) and its absence in the corresponding normal and non-RA bone marrow. J Rheumatol 1988;15:1609–15.

Hypertrophic osteoarthropathy associated with bacterial endocarditis

Sir, A 40-yr-old man suffering from Marfan’s syndrome was admitted with Streptococcus mitis endocarditis. His fever responded within 10 days of starting i.v. benzyl penicillin and netilmicin therapy. Four weeks later, while still on the same treatment, he developed low-grade continuous fever. He was noted to have finger clubbing, and painful swollen wrists and ankles (Fig. 1). He also had effusions of his ankle and knee joints. Repeat blood cultures were negative. His C-reactive protein, which was gradually settling, started rising again. Since there was no apparent reason for the recurrence of fever, his wrist joint was aspirated and the fluid was sterile. However, radiographs of his ankles and wrists revealed marked periosteal new bone formation around the distal parts of the radius, ulna, tibia and fibula (Figs 2 and 3). These findings, along with finger clubbing, were consistent with the diagnosis of hypertrophic osteoarthropathy. The Rose Waaler test became positive during the course of illness, but the rest of his autoimmune profile, viral serology, repeat chest radiographs and abdominal ultrasound were negative. Since repeated blood cultures were all persistently negative, the antibiotics were stopped and the patient was started on 10 mg of oral prednisolone. His response to them was quite dramatic. The pain and swelling subsided considerably, fever settled, clubbing regressed and the inflammatory markers fell to normal. He was discharged on the same treatment, and has made a good recovery; he is presently taking 5 mg of prednisolone per day and is symptom free. His present blood profile reveals a normal white cell count and a C-reactive protein of two. His repeat Rose Waaler test has become negative.

The combination of finger clubbing, painful tender swelling of bones and joints, and the radiological periostitis form the characteristic presentation of hypertrophic osteoarthropathy [1]. Hypertrophic osteoarthropathy is mostly secondary, but can also be primary, which is very rare. The differential diagnosis of hypertrophic osteoarthropathy includes thyroid acropachy. Although over 90% of cases of hypertrophic osteoarthropathy are secondary to lung cancer, there are also other causes, which are listed in Table 1. In some rare instances, it may be confined to the lower limbs alone. These conditions include patent ductus arteriosus with reversal of flow, and infected aortic grafts [2].

Periostitis typically presents with symptoms and signs of inflammation at the ends of the long bones, which is characteristically periarticular. The adjoining joints, especially the large ones, may have signs of mild syno-
Radionuclide bone imaging is a highly sensitive method in defining the presence and the extent of periostitis [4]. Since most cases of hypertrophic osteoarthropathy may have a serious and a potentially treatable cause, it should always be investigated.

Two different theories have been forwarded to explain the pathophysiology of hypertrophic osteoarthropathy. The neurogenic theory associates it closely with the autonomic nervous system. The humoral theory, on the other hand, tries to explain it on the basis of circulating factors in the venous circulation, which are usually removed or inactivated by the lungs. Recent hypotheses working on the same theory postulate that this factor may be the platelet-derived growth factor (PDGF). These factors are normally produced by the clumping and peripheral fragmentation of megakaryocytes, but are trapped by the pulmonary capillary bed [5]. This theory also helps to explain why patients with infected aortic grafts have hypertrophic osteoarthropathy confined to the lower limbs alone. This chronic infection leads to the formation of platelet clumps with secondary release of PDGF in the distal arterial circulation. Venous blood, however, is cleared of the PDGF while going through the lungs or the periphery, thereby preventing similar changes from appearing in the arms. It is, therefore, not difficult to explain why a systemic infection like sub-acute bacterial endocarditis will give rise to a more generalized hypertrophic osteoarthropathy, as found in our case.

It is interesting to note that all these changes of formation around the distal ends of the tibia and fibula hypertrophic osteoarthropathy may diminish or even disappear after appropriate treatment [6, 7]. Symptoms can be controlled with non-steroidal anti-inflammatory drugs. Colchicine has been reported to have an ameliorating effect [8]. In our case, once the bacterial endocarditis was cleared, the swelling and the changes of hypertrophic osteoarthropathy responded dramatically to low-dose oral steroids, as did the inflammatory markers.

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7. Ho A, Williams DM, Zeleznick GB, Braunshtstein EM. Unilateral

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**Fig. 3.** Radiograph of the ankle showing periostal new bone formation around the distal ends of the tibia and fibula.

**Table 1.** Associations of hypertrophic osteoarthropathy

<table>
<thead>
<tr>
<th>Common causes</th>
<th>Uncommon causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer</td>
<td>Chronic osteomyelitis</td>
</tr>
<tr>
<td>Intra-thoracic chronic supplicative infection</td>
<td>Syphilis</td>
</tr>
<tr>
<td>Cyanotic congenital heart disease</td>
<td>Yaws</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>Chronic venous stasis</td>
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<tr>
<td>Crohn’s disease</td>
<td>Polyaerteritis nodosa</td>
</tr>
<tr>
<td>Biliary cirrhosis</td>
<td>Diverticular disease of the colon</td>
</tr>
<tr>
<td>Nasopharyngeal carcinoma</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Oesophageal carcinoma</td>
<td>Human immunodeficiency virus infection</td>
</tr>
<tr>
<td>Familial Mediterranean fever</td>
<td>Prostaglandin administration in neonates</td>
</tr>
</tbody>
</table>

vitis and effusion. The joint involvement is, however, typically non-erosive [3].

The laboratory inflammatory markers are usually raised, depending on the amount of inflammatory response generated. Their serial monitoring may be helpful in disease monitoring. Rheumatoid factor is negative, as is the rest of the autoimmune profile. Joint fluid is sterile with low cell count. Radiology characteristically reveals periostal new bone formation. CT and MRI scanning may be helpful in demonstrating early changes and ruling out an underlying osteomyelitis.

Cutaneous necrotizing vasculitis, erythema nodosum and ankylosing spondylitis

Sir, Vasculitis in patients with ankylosing spondylitis (AS) is uncommon with most reported cases also having IgA nephropathy. We describe a patient with longstanding AS who developed necrotizing vasculitis of the lower limbs, erythema nodosum and Escherichia coli bacteraemia.

A 53-yr-old Caucasian woman with AS since the age of 14 yr gave a history of a 6 month illness beginning with an episode of cellulitis over her left thigh spreading down to her left knee. This responded to a course of co-amoxiclav prescribed by her general practitioner. The following month, a black nodule had appeared on the back of her left leg, which soon ulcerated. Subsequently, she developed ulcers over her right ankle and left shin, each starting as a black nodule. Multiple, red, painful nodules had recently appeared over her trunk, upper limbs and left thigh. She complained of malaise, lethargy and night sweats. She denied any disturbance of bowel habit or micturition. Her regular medication, which had not altered recently, was piroxicam 20 mg daily and ranitidine 150 mg twice daily. There were no known allergies.

On examination, there were typical features of AS with global restriction of spinal movements and chest expansion. There was an ulcer over the left shin and healing ulcers over the right ankle. In addition, there were multiple erythematous, tender nodules over her trunk, upper limbs, buttocks and left thigh, suggestive of erythema nodosum. She had a low-grade pyrexia of 37.5 °C. Examination of the cardiovascular and respiratory systems was unremarkable.

Urine dipstick testing was normal and mid-stream urine specimen culture was negative. A full blood count showed a haemoglobin of 12.9 g/dl with normal white cell and platelet counts. The ESR was 18 mm in the first hour. Biochemical profile including urea and electrolytes, liver function tests and serum calcium were within normal limits. Rheumatoid factor, ANA and ANCA were negative. Serum immunoglobulins and angiotensin-converting enzyme levels were normal. Antistreptolysin O (ASO) titres were slightly elevated at $320 \times 10^3$ U/l (normal upper limit $250 \times 10^3$ U/l). A chest X-ray showed no pulmonary lesion. Two separate blood cultures grew *E. coli* and in view of this an abdominal ultrasound scan, followed by an abdominal CT, were arranged. These showed no organ abnormality and no abscess collection. An echocardiogram showed no endocardial vegetations. Skin biopsies were taken from the edge of the ulcer on the left shin and from one of the nodules on the same limb. The former showed an acute necrotizing vasculitis with fibrinoid necrosis in the dermis and s.c. fat (Fig. 1). The nodule biopsy revealed characteristic features of erythema nodosum, namely septal and lobular acute and chronic panniculitis with epithelioid granuloma formation.

Treatment with i.v. cefotaxime was commenced when the results of the blood cultures were available. After 48 h, this was substituted for oral co-amoxiclav, which was continued for 6 weeks. The patient felt much better after 72 h of antibiotic treatment. With the results of the skin biopsies, prednisolone was added at a dose of 20 mg daily. Further immunosuppression was avoided in view of the *E. coli* bacteraemia and apparent confinement of the vasculitis to the skin. She was discharged 2 weeks following admission. On review in clinic 3 weeks later, she was feeling much better, with no further vasculitic lesions. There was an episode of fresh rectal bleeding, but a flexible sigmoidoscopy and rectal biopsy showed no evidence of colitis. Over the subsequent 3 months, there was a gradual healing of the leg ulcers and fading of the erythema nodosum. The steroid dose was reduced slowly and finally stopped after 4 months.

![Fig. 1. Acute vasculitis with dense inflammatory infiltrate in and around blood vessel walls, and fibrinoid necrosis of the dermis and s.c. fat.](Image)
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of treatment. There has been no relapse in the subsequent 9 months of follow-up.

The occurrence of non-cardiac vasculitis is uncommon in patients with AS. There are case reports of systemic vasculitis in the literature [1, 2], although one of these described a patient with co-existing rheumatoid arthritis [2]. Many more cases of cutaneous vasculitis have been described in AS patients with IgA nephropathy [3–5]. Those cases whose skin biopsies were examined with immunofluorescence showed IgA deposition [4, 5]. Our patient, however, had no overt evidence of IgA nephropathy and her serum IgA levels were within normal limits.

The aetiology of the erythema nodosum remains obscure, although the raised ASO titre suggests a streptococcal infection and the initial cellulitis was a possible focus. There is evidence for a causal link between streptococcal infection and systemic vasculitis [6], and this may have been a factor in this case. The E. coli bacteremia would appear to have contributed to the patient’s illness, as evidenced by the improvement in well-being with antibiotic treatment. The lack of significant leucocytosis or raised inflammatory markers to suggest infection was surprising, however. Thorough investigation failed to find an infective source, although the leg ulcers would be a strong possibility. It would be interesting to speculate whether prolonged antibiotic treatment alone would have resulted in the same clinical outcome, but our feeling is that oral steroids were required to control the patient's vasculitis at the time.

In conclusion, we have reported a case of cutaneous vasculitis in a patient with long-standing AS. However, it is difficult to say whether this is a true association or merely a coincidental finding.

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Predominant ankle arthropathy in hereditary haemochromatosis

Sir, Since the first description of arthropathy as a manifestation of haemochromatosis by Schumacher [1], several reports have described the spectrum of possible skeletal manifestations of this hereditary iron storage disease. Involvement of the ankle joint seems to be rare. Clinically or radiologically diagnosed ankle arthropathy has so far been described in only a few case reports or small series [2–6].

We report here a 45-yr-old male Caucasian who presented at our out-patient clinic with symmetrical pain of the ankles. Over the last 2 yr, both ankles had developed pronounced swelling. Only recently, symmetrical arthralgies of metacarpophalangeal joints II and III had begun. Patient history was normal; there was no evidence of trauma, particularly to the ankles, in the past.

Physical examination demonstrated prominent hard and tender swelling of both ankles (Fig. 1), resulting in moderate restriction of movement. A small, hard and painless swelling was also demonstrated at the right ankle. Over the last 2 yr, both ankles had developed pronounced swelling. Only recently, symmetrical arthralgies of metacarpophalangeal joints II and III had begun. Patient history was normal; there was no evidence of trauma, particularly to the ankles, in the past.

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Fig. 1. Dorsal view of both ankles demonstrating prominent swelling and deformation.
bilateral significant joint space narrowing, osteophytes and sclerosis of metacarpophalangeal joints II–III on both sides were found.

Electrocardiography and echocardiography were normal. Ultrasonography of the abdomen demonstrated hepatomegaly with an increased homogeneous signal pattern. The patient refused liver biopsy, but agreed to a synovial biopsy of the right ankle, which revealed a hyperplastic synovitis with markedly increased iron storage in the synovial lining cell layers without evidence of crystal deposition.

The diagnosis of hereditary haemochromatosis with concomitant severe arthropathy of the ankles and diabetes mellitus was established, based on enhanced serum iron overload and the radiological changes of affected joints. The diagnosis was confirmed by synovial biopsy and by molecular genetic analysis of blood cell DNA.

Predominant ankle arthropathy as the initial manifestation of hereditary haemochromatosis is probably a rare clinical event, even though it may be more common in cases with involvement of several joint areas. Osteoarthritic alterations and cyst formation are characteristic radiological changes of joint manifestation of haemochromatosis [3, 4]. In our patient, radiography and MRI showed symmetrical severe osteoarthritic degenerative changes of both ankles and formation of subchondral cystic lesions in the right ankle. Chondrocalcinosis, which is not unusual in haemochromatosis [8], was not observed. However, in the absence of a history of trauma and with regard to histological signs of increased synovial proliferation with enhanced iron deposition, arthropathy in our case was considered as being most likely due to haemochromatosis. The demonstration of increased iron deposition, intimal cell hyperplasia and villous formation in synovial tissue of affected joints has been reported in haemochromatosis [3], although these histological features did not relate to clinical or radiological evidence of arthropathy [9]. Biopsy examination of liver tissue, which is generally used to demonstrate the hepatic iron index and to judge the degree of tissue damage, was not possible in our case.

In further support of the diagnosis of haemochromatosis arthropathy, the metacarpophalangeal joints showed a classical bilateral pattern with predominant changes in MCP joints II–III. MRI failed to demonstrate intra-articular iron deposits in the ankle joint. However, lack of a reliable correlation between intra-articular iron deposition, serum ferritin and degenerative changes on MRI has been reported [10].

The identification of a characteristic mutation in the HLA-H locus of our patient and his daughter supported the clinical and histological diagnosis of haemochromatosis. Molecular analysis of the HLA-H locus, dispensable if the diagnosis of haemochromatosis has already been otherwise established, is compatible with the diagnosis in cases where biopsy cannot be obtained.

In conclusion, the case reported here demonstrates that arthropathy, particularly of unusual sites, should lead to consideration of haemochromatosis in the differential diagnosis of joint disease, and consequently to further diagnostic procedures, including serological tests of iron metabolism, radiology and liver or synovial biopsy.

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A case of systemic sclerosis that developed under dexfenfluramine use

Sir, There are several reports on the association of appetite-suppressant drugs such as fenfluramine and dexfenfluramine with pulmonary hypertension and valvular heart disease [1, 2]. It has also been claimed that fenfluramine leads to the development of systemic sclerosis [3]. We report a patient who used dexfenfluramine and developed systemic sclerosis shortly after starting the drug.

An 18-yr-old female patient started to use 30 mg/day of dexfenfluramine (Isomeride) because of obesity. She started to complain of Raynaud’s phenomenon and puffy fingers during her second month of treatment. She stopped using the drug after 2.5 months and realized that there was a generalized thickening of the skin all over her body. She was diagnosed as having scleroderma by her local physician and was started on 40 mg/day of fluocortolone that was tapered to 10 mg/day in 1 month.
She was seen in our out-patient department in August 1996 with the findings of generalized skin thickness, microstomia, flexion contractures in her hands and elbows. Laboratory examinations revealed a haematocrit (htc) of 17%; reticulocytes: 8%; haaptoglobulin: 40 mg/dl (NR: 50–320 mg/dl); LDH: 2763 U/l (NR: 200–450 U/l); platelets: 47 000/mm³; Coombs test (−); normal C3, C4 levels. There were many fragmented erythrocytes in her peripheral blood smear. The serum creatinine was 3.1 mg/dl. There was 2+ proteinuria in her urine and her glomerular filtration rate was 3 ml/min. A urinary sediment revealed 3–4 erythrocytes and leucocytes/high-power field, and granular casts. Echocardiography revealed a minimal pericardial effusion. She was diagnosed as having a scleroderma renal crisis with normal blood pressure and died in spite of the administration of ACE inhibitors and haemodialysis.

The patient was diagnosed as having systemic sclerosis because she had developed Raynaud’s phenomenon, puffy fingers and widespread cutaneous sclerosis 3 months after starting the drug, and had a positive ANA test and the typical nail-fold capillaroscopic changes by the fifteenth month.

Scleroderma-like changes have been found in patients with carcinoid syndrome who have elevated blood levels of serotonin [4]. Fenfluramine promotes the rapid release of serotonin, inhibits its re-uptake, and may have receptor-agonist activity [5]. The d-isomer of fenfluramine, dexfenfluramine, appears to be relatively selective for the central serotoninergic system. There have been previous reports on the relationship between appetite suppressants and the long-term utilization of fenfluramine and scleroderma [3, 6].

We did not, however, come across any reports in the literature concerning the association of dexfenfluramine, a closely related compound, with scleroderma. We think that the use of dexfenfluramine in our patient could have started or provoked the onset of scleroderma.

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Enhanced frequency of autoimmune congenital heart block in female offspring

Sir. The vast majority of congenital heart block (CHB) is characteristically associated with maternal autoantibodies against the autoantigens 52 kDa Ro(SS-A) and La(SS-B). While the coincidence of persistent maternal autoantibodies and CHB appears to be of pathogenic importance and has been shown to inhibit the calcium channel type L [1], the relative recurrence rate for CHB has been calculated in the range 8–18% [2, 3]. This suggests that other factors have to be essentially involved in the establishment of CHB. To the best of our knowledge, and in contrast to this range of recurrence, we have followed a mother with a striking history of repetitive CHB pregnancies. After she had given birth to a healthy girl in 1981, a subsequent pregnancy led to the first development of CHB in a girl in 1984. Although our patient has been repeatedly informed about the increased risk for CHB in a subsequent pregnancy, she had another pregnancy with a girl with CHB in 1988 who died 8 months after birth. Six years later, a fourth pregnancy with a healthy boy did not exhibit any complication. In 1997, the patient was again referred to our hospital because a fetal echocardiogram revealed a complete atrioventricular heart block of the fifth pregnancy (atrial frequency 150 b.p.m., ventricular frequency 55 b.p.m.) in the 21st week of gestation. Combined therapy with dexamethasone (4 mg/day) and plasmapheresis did not improve the fetal heart block. A girl was delivered by Caesarean section in the 38th week of gestation (APGAR score 5/8/7). The CHB coincided with a dysplasia and insufficiency of the tricuspid valve, as well as a stenotic aortic valve, leading to rapid progressive heart failure and death 38 h after birth. During this follow-up, the mother exhibited no signs or symptoms of a systemic autoimmune or other disease, but was ANA positive (1:2560, speckled pattern) with anti-52 kDa Ro(SS-A) antibodies. The follow-up of the presented case indicates that the recurrence rate for pregnancies complicated by CHB can be higher in individual cases and, therefore, greater than previously noted.

Such a series of pregnancies with girls affected by CHB has not been reported so far. In particular, the healthy boy who was born within a series of affected girls raised the question whether gender can influence...
the development of CHB as an independent factor. Subsequently, an in-depth analysis tested the hypothesis that gender is related to the susceptibility to acquire CHB in a cohort of 25 mothers with altogether 27 CHB pregnancies (group I) that we have monitored since 1984. As summarized in Table 1, there was no preference to affect offspring born in a first, second or third pregnancy, respectively, by CHB in mothers with several pregnancies. After the delivery of a child with CHB, 18 mothers with one CHB child (13 girls/5 boys) and seven women with several pregnancies (six girls with CHB and three boys with CHB) did not have any further pregnancy. One mother (RC; Table I) gave birth to a girl with CHB before she delivered a healthy girl. Most notably, an overall predominance of affected girls with CHB (n = 19) in contrast to boys with CHB (n = 8) gave further indications that a genetic and gender-related predisposition enhances CHB susceptibility for girls remarkably.

To assess further the influence of gender for the development of CHB, the female/male ratio of two additional cohorts was compared with those of our CHB group (Table 2). First, a previously characterized group of newborns [4] with a variety of cardiac conduction abnormalities (14 female/18 male) without maternal autoantibodies (group II) and secondly a group of healthy offspring who were born to SLE patients (group III; 22 female/23 male). Whereas there was no difference in the female/male ratio between these two control groups as well as between the group of CHB children and the healthy offspring of SLE patients (group III), comparison of the CHB group with the children suffering from cardiac conduction defects without autoimmune findings (group II) revealed a significant preference for girls to acquire a CHB (odds ratio 3.054; 95% confidence interval, P < 0.04).

This comparative analysis suggests that gender or gender-related factors and/or genes appear to influence CHB susceptibility. Although the female to male ratio in neonatal lupus erythematosus has been determined to be 3:1 [3, 5], there are different reports in the literature about this relationship in CHB. Whereas a recent study using information for a Research Registry for Neonatal Lupus [5] collected retrospectively 56 boys and 57 girls, earlier studies reported a clear predominance of affected girls [4, 6, 7]. Thus, Chameides et al. [6] described five girls and one boy with CHB and, moreover, another study [7] reported 28 girls suffering from CHB and 16 boys with CHB. These data are consistent with previous findings that CHB is significantly more frequent in girls than incomplete atioventricular conduction defects [4]. It is conceivable that genetic and/or hormonal factors can influence the initiation of antibody-related pathogenicity in the fetal tissues [1–3]. In this context, it has been demonstrated that 17β-oestradiol [8] at concentrations of 10^-8–10^-7 mol/l induced a 5-fold surface expression of the 52 and 60 kDa Ro(SS-A) antigens on human keratinocytes obtained from neonates in comparison to untreated cells. Therefore, hormonal differences might influence the accessibility of the target antigens, resulting in significant tissue damage, and subsequently the development of CHB. Together, factors modulating the pathogenic effect of maternal autoantibodies in CHB appear to be enhanced in female offspring. Prospective studies are needed to evaluate the relative risk for CHB in male and female infants, respectively, as well as to identify the molecular nature of different gender-related susceptibilities for CHB.

**Table 1.** Occurrence and gender of CHB cases in mothers with several pregnancies*

<table>
<thead>
<tr>
<th>Mother</th>
<th>Child 1</th>
<th>Child 2</th>
<th>Child 3</th>
<th>Child 4</th>
<th>Child 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZM</td>
<td>Female</td>
<td>Female/CHB</td>
<td>Female/CHB</td>
<td>Male</td>
<td>Female/CHB</td>
</tr>
<tr>
<td>RC</td>
<td>Miscarriage*</td>
<td>Female/CHB</td>
<td>Female/CHB</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>PAS</td>
<td>Female</td>
<td>Male/CHB</td>
<td>Male/CHB</td>
<td>Female/CHB</td>
<td></td>
</tr>
<tr>
<td>FK</td>
<td>Female</td>
<td>Male/CHB</td>
<td>Male/CHB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HB</td>
<td>Male</td>
<td>Female</td>
<td>Female/CHB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JP</td>
<td>Male</td>
<td>Female</td>
<td>Female/CHB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PU</td>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Cases in bold represent offspring affected by CHB. *The cause of the miscarriage in the 12th week of gestation could not be determined.

**Table 2.** Comparison of the female/male ratio in the three groups of infants

<table>
<thead>
<tr>
<th>Group</th>
<th>Female (n)</th>
<th>Male (n)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. CHB infants</td>
<td>19</td>
<td>8</td>
<td>2.38*</td>
</tr>
<tr>
<td>II. Heart rhythm disorders without autoimmune findings</td>
<td>14</td>
<td>18</td>
<td>0.77*</td>
</tr>
<tr>
<td>III. Unaffected children from SLE patients</td>
<td>22</td>
<td>23</td>
<td>0.96</td>
</tr>
</tbody>
</table>

*Odds ratio 3.054 (95% confidence interval, P < 0.04).


Oral methotrexate: the hazard of different tablet strengths

Sir, Methotrexate is probably the most commonly prescribed disease-modifying drug for the treatment of rheumatoid arthritis (RA) [1], and is now being used for a number of other rheumatological conditions including psoriatic arthritis, systemic lupus erythematosus and myositis. The adverse effects include bone marrow suppression, pneumonitis and cumulative dose-related hepatotoxicity [2].

Methotrexate (Maxtrex) is currently available in 2.5 and 10 mg tablets (Pharmacia), which are difficult to distinguish from one another (Fig. 1). We report a case of a patient with RA who received a potentially toxic dose of methotrexate due to confusion between the 2.5 and 10 mg tablets.

A 56-yr-old woman with seropositive RA was taking 7.5 mg methotrexate (3 × 2.5 mg tablets) weekly, with folate the following day for several years. Drug monitoring and prescribing were shared with her general practitioner so that changes in drug dosage were advised by hospital rheumatologists. Dispensing was usually undertaken by retail pharmacies. In August 1997, due to a flare in disease activity, the dose of methotrexate was increased to 10 mg weekly (4 × 2.5 mg tablets). Ten milligram tablets were dispensed, but the patient’s attention was not drawn to the change in tablet strength. Believing these to be 2.5 mg tablets, she began taking four (40 mg) once weekly. During regular clinic reviews, the alanine transaminase (ALT) was noted to have risen, climbing from 40 to 98 IU/l (normal range 5–55 IU/l) over a 6 month period. Alkaline phosphatase and bilirubin remained normal, and there was no evidence of bone marrow suppression.

It was presumed that she was taking the prescribed dose of 10 mg of methotrexate, but in view of the abnormal ALT, the dose of methotrexate was reduced to 7.5 mg. It was only when collecting her new prescription that the patient realized the original error, and reported it to us. By this time, the ALT had climbed to 137 IU/l and the methotrexate was stopped. Within 1 month, the ALT returned to normal (22 IU/l). She was subsequently restarted on 7.5 mg weekly, and her ALT has remained stable.

This is not an isolated incident. One author (CH) has seen three patients in the London area within the last year who have been given 10 mg methotrexate tablets in bottles labelled as containing 2.5 mg tablets. Each of these patients received their tablets from a different pharmacy. Only the vigilance of the patients in noticing this error prevented them from taking 30, 40 and 50 mg of methotrexate per week, respectively.

We believe that urgent action should be taken to make 2.5 and 10 mg methotrexate tablets more easily distinguishable from one another, and we have written to the manufacturers, the Royal Pharmaceutical Society, and the UK Committee on Safety of Medicines (CSM). The Royal Pharmaceutical Society was sufficiently concerned following our report that they have published a Law and Ethics Bulletin concerning this problem [3]. Doctors involved in the prescribing and dispensing of methotrexate should be aware of this potentially life-threatening problem.


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