Antiphospholipid antibodies, systemic lupus erythematosus, and non-traumatic metatarsal fractures

S Sangle, D P D’Cruz, M A Khamash, G R V Hughes

Background: Stress fractures are common in military recruits and athletes and are thought to be secondary to stress and overuse. Less often they are associated with metabolic disorders such as osteoporosis, hypophosphataemia, and diabetes mellitus.

Objective: Analysis of 19 patients with systemic lupus erythematosus and antiphospholipid antibodies presenting consecutively with foot pain. All had metatarsal fractures (six bilateral) without any obvious history of trauma.

Results: 13 of the 19 patients had antiphospholipid syndrome. Among the whole group, 13 had normal bone mineral density, one had osteopenia, and five others had osteoporosis as defined by WHO criteria; 10 had received steroids, mostly in low dosage; 13 were receiving warfarin. There was no evidence that a metabolic bone abnormality was a unifying factor in the pathogenesis.

Conclusions: Atraumatic metatarsal stress fractures may occur in SLE, particularly in association with the antiphospholipid syndrome. The pathogenesis of these fractures remains uncertain but microinfarcts in the metatarsal bones are a possible cause.

METHODS

We describe 19 patients with SLE with or without antiphospholipid syndrome, who subsequently developed metatarsal fractures. All were regular outpatients at the Louise Coote Lupus Unit at St Thomas’ Hospital. The patients were seen over the previous year and represent consecutive patients presenting to the clinic with foot pain. Our cohort of 2500 patients with connective tissue disease was not specifically screened for patients with foot pain.

All patients were female, with a mean age of 42 years (range 24 to 85). Seventeen had systemic lupus erythematosus (SLE) as classified by the ACR criteria.13 Thirteen of these 17 SLE patients had antiphospholipid syndrome and two were positive for aPL. Two had primary antiphospholipid syndrome. Thus 17 of 19 patients had positive aPL and 13 of these patients fulfilled the Sapporo classification criteria for antiphospholipid syndrome.14 Thirteen of these patients with antiphospholipid syndrome were anticoagulated with warfarin, with a target INR of 3.0–4.0. Five patients had previously received prednisolone (>15 mg) for more than six months. Only one had a history of a trivial foot injury associated with the fracture. One patient had type 1 diabetes in addition to SLE and antiphospholipid syndrome. All the patients were assessed for the duration of their autoimmune disease, steroid dose, menopausal status, bone mineral density, chronic metabolic diseases, haemoglobinopathies, and myeloma. The location and characteristics of the metatarsal fractures were determined by radiology and in some cases by radionuclide bone scan.

RESULTS

Of the 19 patients with metatarsal fractures, six had bilateral fractures (figs 1 and 2). One patient had diabetes mellitus, but her metabolic bone profile and bone mineral density were normal. Five patients had osteoporosis and one had osteopenia, while the other 13 had normal bone mineral density (table 1). One patient with primary antiphospholipid syndrome had avascular necrosis of the second and third metatarsal heads. A further patient with SLE and antiphospholipid syndrome on prednisolone had bilateral avascular necrosis of the femoral head as well as metatarsal fractures. One of the two patients with primary antiphospholipid syndrome, who had never received steroids, had bilateral metatarsal fractures. Apart from the one patient with type 1 diabetes mellitus, none had any chronic metabolic disease, malignancies, or haemoglobinopathies. All patients had normal serum calcium, alkaline phosphate, and phosphate levels.

DISCUSSION

Metatarsal fractures (fatigue fractures) are common in military personnel. They are also seen in athletes, but much less so in civilian practice. Metatarsal fractures are described in metabolic disorders such as osteoporosis, hypophosphataemia, osteoporosis, and diabetes mellitus. There is a correlation between metatarsal fractures and low bone mineral density in both sexes, confirmed by the low DEXA scan findings.15 Recently, metatarsal fracture has been reported in patients with rheumatoid arthritis and chronic bronchitis.16 Elkayam et al described eight patients with...

Abbreviations: aPL, antiphospholipid antibodies; DEXA, dual energy x-ray absorptiometry; INR, international normalised ratio; SLE, systemic lupus erythematosus
corticosteroids and had low bone mineral density.7

All patients were screened for metabolic disorders, endocrine disorders, and malignancies including multiple myeloma. Five of the patients had osteoporosis and one had diabetes mellitus, while one had SLE nephritis with antiphospholipid syndrome and was on high doses of steroids (>15 mg/day). This latter patient had avascular necrosis of the hips, and her bone mineral density was in the osteoporotic range. It is possible that in this patient three or more factors were responsible for the metatarsal fractures. However, the other 14 patients (including the one with diabetes mellitus) did not have any metabolic bone abnormality. This further reduces the possibility that metabolic disorders alone were the main cause of metatarsal fractures in these patients.

Table 1 Metatarsal fractures in patients with systemic lupus erythematosus and antiphospholipid syndrome

<table>
<thead>
<tr>
<th>Patients</th>
<th>Unilateral fractures</th>
<th>Bilateral fractures</th>
<th>Osteoporosis (mean T and Z scores)</th>
<th>Normal BMD (no osteoporosis, n = 14)</th>
<th>Chronic metabolic disease</th>
<th>Serum calcium*; normal range, 2.20–2.60 mmol/l</th>
<th>Serum alkaline phosphatase; normal range, 31–116 IU/l</th>
<th>Serum phosphate; normal range, 0.8–1.15 mmol/l</th>
<th>Prednisolone &gt;15 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary APS (n = 2)</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>Nil</td>
<td>2.26</td>
<td>84</td>
<td>1</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>SLE and aPL+ (n = 12)</td>
<td>11</td>
<td>4</td>
<td>4</td>
<td>11</td>
<td>2.34</td>
<td>78</td>
<td>1.4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>SLE and aPL– (n = 2)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2.35</td>
<td>113</td>
<td>1.1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*Corrected for albumin.

APS, antiphospholipid syndrome; BMD, bone mineral density; DM, diabetes mellitus; SLE, systemic lupus erythematosus.
The precise pathogenesis of metatarsal fractures in our patients with SLE and antiphospholipid syndrome remains unclear. The possible contributory factors include sub-maximal stress or vasculopathy supplying the bones, and osteoporosis. Antiphospholipid syndrome (Hughes syndrome) is characterised by arterial-venous thrombosis. Strikingly, 13 of our 19 patients had antiphospholipid antibodies associated with thrombosis. Four patients had raised anticardiolipin antibodies (IgG) and others were positive for lupus anticoagulants. Two aPL positive patients did not fulfil the Sapporo criteria for antiphospholipid syndrome. It is therefore possible that bone microinfracts may lead to bone damage and to long bone fractures in the feet.

Avascular necrosis of the hips is well described in patients with sickle cell disease and results from bone infarction in the femoral head. Asherson et al reported that avascular necrosis of the hip was twice as common in lupus patients with antiphospholipid syndrome as in those without antiphospholipid syndrome. However, Houssiau et al failed to show an increased prevalence of avascular necrosis in patients with aPL. Recently, Tektonidou et al found asymptomatic avascular necrosis of femoral heads in almost 20% of patients with antiphospholipid syndrome. Asherson described osteonecrosis of bone as an unusual manifestation of antiphospholipid syndrome. Another study showed a correlation between anticardiolipin antibodies and recurrent venous thrombosis, thrombocytopaenia, haemolytic anaemia, recurrent fetal loss, cutaneous ulcers, transverse myelitis, and pulmonary hypertension, but no correlation between anticardiolipin antibodies and migraine, transient ischaemic attacks, psychosis, or avascular necrosis of bone. In our series, only four patients had raised anticardiolipin antibodies in significant titre and the rest were positive for lupus anticoagulant. Recently, Jones et al described the high incidence of osteonecrosis in patients with coagulopathies including anticardiolipin antibodies. These intriguing findings give further support to the view that microinfracts in the metatarsal bones could result in fractures in patients with antiphospholipid syndrome and antiphospholipid antibodies, who may already have experienced previous thrombotic events. There was a strong correlation between antiphospholipid antibodies and the metatarsal fractures in our series. However, the role of anticoagulation with warfarin in the pathogenesis of these fractures remains unclear.

Our unit is a referral centre for both SLE and antiphospholipid syndrome and it is possible that referral bias may have influenced our observations. Furthermore this was a case series of consecutive patients attending our clinics with foot pain who on investigation were found to have metatarsal fractures. To ascertain the true prevalence of these fractures and their relation to aPL, a prospective study is clearly needed, screening both symptomatic and asymptomatic patients with SLE and aPL positivity, and comparing them with aPL negative patients.

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**REFERENCES**