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

S Sangle, D P D’Cruz, M A Khamashta, 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 58). Seventeen had systemic lupus erythematosus (SLE) as classified by the ACR criteria. 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. 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 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. Recently, metatarsal fracture has been reported in patients with rheumatoid arthritis and chronic bronchitis. 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
rheumatoid arthritis and one with polymyalgia rheumatica who developed stress insufficiency fractures. All were treated with corticosteroids and had low bone mineral density.

Here we describe 19 patients with SLE who had metatarsal fractures, six of which were bilateral. Only one had any history of trivial injury five years previously. Interestingly, 13 of our patients had normal bone mineral density values on DEXA scanning, one had osteopenia, and five others had osteoporosis as defined by World Health Organisation criteria. This finding goes against the hypothesis that osteoporosis was the sole cause of metatarsal fractures in these patients. Furthermore, six of the patients had bilateral metatarsal fractures without any obvious history of preceding trauma, and only one of these had osteoporosis, arguing against the concept of repeated trauma leading to metatarsal fractures, as seen in military personnel and sports injuries.

One patient had diabetes mellitus type 1 with secondary antiphospholipid syndrome and was well controlled on insulin; her DEXA scan showed normal bone mineral density. Her metabolic profile was normal. Clearly other factors may have been important in explaining the metatarsal fractures in this patient.

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.

Thirteen patients with antiphospholipid syndrome were anticoagulated with warfarin, with a target INR of 3.0 to 4.0. This raises the possibility that warfarin may have played a role in the fractures. Two recent papers have studied the association between long term warfarin, a vitamin K antagonist, and osteoporosis. The results were contradictory, one showing an association between warfarin and osteoporosis while the other (involving 6000 postmenopausal women on warfarin) found no increased risk of osteoporosis. In our cohort, two patients with secondary antiphospholipid syndrome were on long term warfarin (for more than one year) and had received steroids (more than 15 mg/day). Both had osteoporosis. It therefore remains unclear whether warfarin played a role in the development of metatarsal fractures in our patients.

An increased frequency of non-traumatic metatarsal fractures in the patients with SLE has not been reported before. In general, it would be easy to blame osteoporosis caused by the disease or by steroid treatment, and indeed five of our patients showed evidence of osteoporosis. However, other factors are certainly important in the pathogenesis of these fractures. Thus, while 10 patients had received steroids in their disease course, eight had been on low doses (<7.5 mg/day), which makes it less likely that this was the major cause of the metatarsal fractures. None of these patients had experienced undue physical stress or repetitive or overuse injuries.

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 (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>1.3</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>SLE and aPL+ (n = 12)</td>
<td>11</td>
<td>4</td>
<td>11</td>
<td>1 (DM)</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>Nil.</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 submaximal stress or vasculopathy of the vessels supplying the bones, and osteoporosis. Antiphospholipid syndrome (Hughes syndrome) is characterised by arterio-venous thrombosis.\(^9\) 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 microinfarcts 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.\(^11\) 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.\(^13\) Asherson described osteonecrosis of bone as an unusual manifestation of antiphospholipid syndrome.\(^14\) Another study showed a correlation between anticardiolipin antibodies and recurrent venous thrombosis, thrombocytopenia, 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.\(^15\) 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.\(^16\) These intriguing findings give further support to the view that microinfarcts 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 antiphospholip 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.

**Authors’ affiliations**

S Sangle, D P D’Cruz, M A Khamashta, G R V Hughes, The Lupus Research Unit, The Rayne Institute, Lambeth Wing, St Thomas’ Hospital, London, UK.

**REFERENCES**

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

S Sangle, D P D'Cruz, M A Khamashta and G R V Hughes

Ann Rheum Dis 2004 63: 1241-1243
doi: 10.1136/ard.2003.016105

Updated information and services can be found at:
http://ard.bmj.com/content/63/10/1241

These include:

References
This article cites 15 articles, 3 of which you can access for free at:
http://ard.bmj.com/content/63/10/1241#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Calcium and bone (725)
- Musculoskeletal syndromes (4951)
- Osteoporosis (137)
- Immunology (including allergy) (5144)
- Connective tissue disease (4253)
- Systemic lupus erythematosus (571)
- Pain (neurology) (883)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/