CASE REPORT

Recurrent atraumatic metatarsal, rib and sacral insufficiency fractures in a woman with the antiphospholipid syndrome

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SUMMARY

Antiphospholipid syndrome (APS) is characterised by recurrent arterial and/or venous thromboses and recurrent late miscarriages in the presence of antiphospholipid antibodies, and can be a hugely debilitating disorder. While the commonest thrombotic manifestations of this condition such as deep vein thrombosis and stroke are well documented, there has been increasing recognition of numerous less common complications in most organ systems. We present a female patient with APS and a lupus-like illness who had atraumatic sacral fractures as well as multiple spontaneous fractures affecting her ribs and the metatarsals in both her feet.

BACKGROUND

The antiphospholipid syndrome (APS) is an autoimmune prothrombotic disorder first characterised by Hughes.¹ In this seminal paper he described the occurrence of recurrent arterial and venous thrombosis and recurrent miscarriages in patients with systemic lupus erythematosus (SLE) or a lupus-like illness who had antiphospholipid antibodies. These antibodies are not a single entity but a heterogeneous group and include lupus anticoagulant, anticardiolipin antibodies and anti- β_2 glycoprotein I antibodies. The diagnosis of this rare but potentially debilitating disorder is currently based on the 2006 Sydney Classification Criteria which states that the diagnosis can be made in patients with objectively validated vascular thrombosis and/or obstetric morbidity in the presence of persistently elevated levels of antiphospholipid antibodies.

In 2004, Sangle *et al*² reported the rare occurrence of atraumatic metatarsal fractures in 19 patients with a diagnosis of primary APS or APS in the presence of SLE. In this case report we present a 54-year-old woman with a diagnosis of APS and a lupus-like illness who presented with atraumatic sacral insufficiency fractures in addition to multiple rib and metatarsal fractures.

CASE PRESENTATION

A 54-year-old Caucasian woman was referred to our service in 2007 with a history of arthralgia, fatigue, sicca symptoms and Raynaud's phenomenon. There was a history of three miscarriages and a deep venous thrombosis and pulmonary embolism (PE) in the third trimester of her only successful pregnancy, a year prior to referral. The lupus anticoagulant assay was positive on three occasions,

at least 3 months apart, but neither anticardiolipin or β_2 -glycoprotein I antibodies were detected. She also had a positive antinuclear antibody at a titre of 1:160, with a speckled staining pattern. However, the extractable nuclear antigen screen was negative and anti-double-stranded DNA antibodies were not detected.

She was unable to tolerate initial treatment with hydroxychloroquine due to diplopia, headaches and abdominal pain. Aspirin lead to exacerbation of her pre-existing asthma, so she was switched to clopidogrel 75 mg daily.

In 2008 headaches and poor short-term memory became more prominent. An MRI scan of the brain was normal at that stage. Later that year she developed a right femoral vein thrombosis and a further PE, and lifelong treatment with warfarin was started, with an initial target international normalised ratio (INR) of between 2 and 3. Treatment with prednisolone 10 mg daily and azathioprine was added in 2009 due to persistent symptoms from her lupus-like illness. A dual-energy X-ray absorptiometry (DEXA) scan in 2009 showed osteopenia in the lumbar spine, with a T score of -2.1 and Z score -1.3. The respective scores in the left hip were -0.8 and -0.3. Weekly oral alendronate together with calcium/vitamin D supplements were used for bone protection.

In 2010, she was admitted with a sudden onset of severe headache associated with nausea and vomiting. The headache increased in severity on lying flat. MRI of the brain revealed a third ventricle colloid cyst with possible mild hydrocephalus. Anticoagulation with warfarin was reversed using vitamin K and fresh frozen plasma and treatment switched temporarily to dalteparin. She underwent an exploratory craniotomy through a transcortical frontal incision. Although the ventricles were tight, excision of the colloid cyst was not required. There was no hydrocephalus. No further severe or postural headaches have recurred during follow-up. She was anticoagulated again with warfarin, aiming for a target INR of between 3.5 and 4 on the advice of a tertiary centre.

In 2011, she was referred for an orthopaedic opinion because of persistent severe pain in her right forefoot. Examination revealed exquisite tenderness over her second metatarsal but was otherwise normal. A plain radiograph of her right foot revealed a displaced fracture of her second metatarsal. Radiographs also suggested she had already sustained a distal fibula fracture on the same side.

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She strongly denied any prior trauma or repetitive actions such as running long distances. A further DEXA scan that year showed stable bone density in the lumbar spine (T score -2.1) but a deterioration in the femoral neck (T score -1.4).

In 2012, she developed lower back, buttock pain and left groin pain with difficulty weight bearing. On examination she had a good range of movement in her spine but irritability of her left hip. There was only minimal tenderness on compression of her pelvis. As she was immunosuppressed and anticoagulated there was initial concern that she may have developed a psoas abscess or haematoma. The addition of methotrexate as a steroid-sparing drug prior to this had been associated with a significant increase in INR. An urgent CT was therefore requested, revealing insufficiency fractures in the left sacral wing, right superior pubic ramus and left ischium. The patient was started on intravenous pamidronate three monthly, with cessation of oral alendronate. A plain radiograph taken a few weeks later confirmed the presence of a left pubic ramus fracture, but Flamingo views of the pelvis revealed no pelvic instability.

Later in 2012, she developed further pain and tenderness over her right forefoot. An examination revealed exquisite tenderness over the third metatarsal. There was no history of trauma. Plain radiographs revealed a fracture of the third metatarsal. An isotope bone scan showed multiple fractures with increased uptake in the right middle ribs, L4/5 vertebrae and bilaterally in the sacrum. In addition there was increased uptake in the medial aspect of the left acetabulum, in the left ankle and the forefeet (figure 1).

DIFFERENTIAL DIAGNOSIS

Atraumatic fractures are a recognised complication of APS, notably affecting the metatarsals. However, there are several metabolic disorders also associated with atraumatic fractures, which include osteoporosis, osteomalacia, hypophosphataemia, diabetes mellitus and hyperthyroidism. Pharmacological therapy is another significant risk for atraumatic fractures, notably glucocorticoids and bisphosphonates.

OUTCOME AND FOLLOW-UP

At her latest review in the clinic she reported with worsened arthralgia and fatigue and an additional fracture of the fourth metatarsal in her right foot was diagnosed, once more in the absence of any trauma (figure 2).

DISCUSSION

The patient we report had multiple atraumatic insufficiency fractures. Screening for the underlying cause had consistently found normal serum calcium and phosphate levels as well as normal alkaline phosphatase activity. She was also found to have normal thyroid function and serum glucose levels. Further, protein electrophoresis was normal. She was still menstruating, had been a life-long non-smoker and abstained from alcohol. Her DEXA scan had revealed she was osteopenic rather than truly osteoporotic according to WHO definitions. For a very short period in 2010 she received low molecular weight heparin but was promptly switched to warfarin. Long-term warfarin therapy has

Figure 1 Technetium isotope bone scan showing focal uptake in right midlateral ribs, lower lumbar spine, sacrum and medial left acetabulum. There are also signs of fractures in the left distal fibula and forefeet.

Figure 2 Multiple atraumatic metatarsal fractures at various stages of healing.

been shown to increase the risk of fractures in the setting of osteoporosis, but this was only apparent in men.³

Bisphosphonate therapy had been used in this lady from 2009 until a switch to a parenteral agent in 2012, following a number of atraumatic fractures. The American Society for Bone and Mineral Research commissioned a task force in 2010 to address a number of concerns regarding long-term bisphosphonate therapy and atypical femoral fractures.⁴ The prevailing theory is that bisphosphonates lead to the so-called 'frozen bone syndrome' where microfractures accumulate on the background of reduced bone remodelling. Reviewing the literature it has been observed that predominantly long bones, particularly in the lower limbs, are at risk of atypical fractures. This observation would support current opinion of microfracture accumulation and the biomechanics that affects long bones. However, in the presented case many of the fractures were in short bones and pelvic skeletal elements, hence suggesting it unlikely that bisphosphonate therapy is the main factor in these fractures.

A significant confounding factor in this case is the utilisation of glucocorticoids. The patient had been started on prednisolone 10 mg daily in 2008 and continued that dose up to the present

day. Every effort has been made to reduce the dose and stop altogether but rapid worsening of her symptoms quickly follows, even in the presence of therapeutic doses of steroid-sparing immunosuppressives such as azathioprine. The effects of glucocorticoids on bone physiology are numerous. Weinstein *et al*⁵ showed that glucocorticoids inhibit osteoblastogenesis and promote apoptosis in osteoblasts and osteocytes, therefore having a deleterious affect on bone density. In addition Jia *et al*⁶ have shown that glucocorticoids directly act on osteoclasts promoting their survival and increasing bone resorption. Another intriguing mode of action is its affect on vascular physiology. Little attention is given to the viscoelastic effect of water but adequate hydration of bone reduces stresses during loading and produces a 2.5-fold increase in ultimate strength.⁷

Mature osteoblasts and osteocytes play a vital role in the mechanosensory system that directs osteogenesis to areas of stress. The hydraulic elements of the canalicular system are derived from the blood supply, which in addition supports the health of the osteoblasts and osteocytes. Excess glucocorticoids reduce the expression of hypoxia-inducible factor-1 α therefore reducing growth factors, in particular vascular endothelial growth factor, which are essential for the formation of new blood vessels.⁸ The net effect is reduced water content of bone and reduced osteoblast and osteocyte viability. This culminates in reduced osteogenesis and derangement of the mechanosensory system, which could potentially lead to excess regional forces and collapse of the trabecular network.

It is again the pattern of the presented fractures, which is highlighting our attention to an additional element that would fully explain the clinical picture. Glucocorticoid-related fractures generally occur in the long bones, usually with a degree of trauma or with osteonecrosis of the head of long bones. The presented fractures do not conform to this pattern and there is objective evidence that she is not osteoporotic as shown by her recent DEXA results.

Evidence in support of a role for APS can be gleaned from the clinical picture. It is interesting to note that her symptoms generally deteriorated around the time when her fractures occurred, which coincided with objective evidence of suboptimal anticoagulation (figure 3). It could therefore be conjectured that microthrombi, as stated by Sangle *et al*² are forming during periods of suboptimal anticoagulation. Microfractures may be developing secondary to micro-osteonecrosis. Tektonidou *et al*⁹ showed that up to 20% of patients with APS had asymptomatic avascular necrosis of the femoral head. This again could be supported by the explanation postulated by Sangle *et al*.²

Another interesting observation is that Sangle *et al*² reported that a majority of their patients (15 of 19) were positive for lupus anticoagulant. Our patient was positive for lupus anticoagulant, rather than anticardiolipin antibodies. This raises further questions: Does lupus anticoagulant really carry an additional risk of osteonecrosis and if it is the case as the presented data suggest then what is the underlying pathophysiological mechanism for this extended effect? Clinically, should we be anticoagulating these patients at higher INRs than those with anticardiolipin antibodies and anti- β_2 glycoprotein I antibodies?

We are very much aware that it is difficult to assign a direct causative relationship between these fractures and APS, however, there does appear to be some association. What is apparent from this case is that patients with a diagnosis of APS need to be consistently anticoagulated. Warfarin is far from ideal with complicated pharmacokinetics and drug interactions, and there is a need for careful INR monitoring, but newer oral anticoagulants are currently being investigated and may yield more reliable therapeutic options.

Figure 3 Relationship between fracture occurrence (blue arrows) and suboptimal anticoagulation with warfarin, as measured by international normalised ratio (INR).

Learning points

- ▶ Antiphospholipid syndrome (APS) is a rare but important cause of atraumatic fractures.
- ▶ Glucocorticoids are an important therapy for APS but long-term usage will impact on bone health and increase the likelihood of fragility fractures.
- ▶ Consistent anticoagulation is needed to prevent the thrombotic complications of APS, which at times can be difficult with the complex pharmacokinetics of warfarin.

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Competing interests None.

Patient consent Obtained.

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REFERENCES

- 1 Hughes GR. Thrombosis, abortion, cerebral disease, and the lupus anticoagulant. *BMJ* 1983;287:1088–9.
- 2 Sangle S, D'Cruz DP, Khamashta MA, *et al.* Antiphospholipid antibodies, systemic lupus erythematosus, and non-traumatic metatarsal fractures. *Ann Rheum Dis* 2004;63:1241–3.
- 3 Gage BF, Birman-Deych E, Radford MJ, *et al.* Risk of osteoporotic fracture in elderly patients taking warfarin: results from the National Registry of Atrial Fibrillation 2. *Arch Intern Med* 2006;166:241–6.
- 4 Shane E, Burr D, Ebeling PR, *et al.* Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 2010;25:2267–94.
- 5 Weinstein RS, Jilka RL, Parfitt AM, *et al.* Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids: potential mechanisms of the deleterious effects on bone. *J Clin Invest* 1998;102:274–82.
- 6 Jia D, O'Brien CA, Stewart SA, *et al.* Glucocorticoids act directly on osteoclasts to increase their lifespan and reduce bone density. *Endocrinology* 2006;147:5592–9.
- 7 Weinstein RS. Glucocorticoids, osteocytes and skeletal fragility: the role of the bone vascularity. *Bone* 2010;48:564–70.
- 8 Whang Y, Wan C, Deny L, *et al.* The hypoxia inducible factor alpha pathway couples angiogenesis to osteogenesis during skeletal development. *J Clin Invest* 2007;117:1616–26.
- 9 Tektonidou MG, Malagari K, Vlachoyiannopoulos PG, *et al.* Asymptomatic avascular necrosis in patients with primary antiphospholipid syndrome in the absence of corticosteroid use: a prospective study by magnetic resonance imaging. *Arthritis Rheum* 2003;48:732–6.

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