Coincidence of asymptomatic avascular necrosis and fracture of the femoral neck: a rare combination of glucocorticoid induced side effects

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Glucocorticoids have profound anti-inflammatory and immunosuppressive actions when used therapeutically. Unfortunately, these drugs have adverse effects—for example, on bone metabolism. Osteoporosis is well known to be a common side effect, whereas a glucocorticoid associated avascular osteonecrosis is rarely diagnosed. However, as far as we know, the coincidence of manifest osteoporosis with fracture and avascular osteonecrosis in the same area is unique.

CASE REPORT
We present the case of a 47 year old postmenopausal woman who had had mixed connective tissue disease (MCTD) for more than 20 years. The MCTD was complicated by progressive vasculitis, and had required immunosuppressive treatment with prednisolone (maximum dose 500 mg/day (pulse therapy; average dose 15 mg/day) for 20 years and azathioprine (75 mg/day). In 1995, she complained for the first time of severe back pain and noticed a height loss of 10 cm within two years. There was no history of previous fractures.

Glucocorticoid induced osteoporosis was suspected. Indeed, bone densitometry (DXA-LUNAR) showed decreased bone mineral density (BMD) of the lumbar spine (L2–4) and left femoral neck (table 1). An x ray examination demonstrated osteoporotic changes—for example, end plate fractures, osteopenia. Treatment with fluorides, vitamin D, and calcium was started. One year later the BMD of the lumbar spine had increased, whereas the BMD of the femoral neck and back pain remained unchanged. Consequently, the treatment was changed to bisphosphonates (alendronate) supplemented by calcium and vitamin D. Another year later her back pain was reduced. The BMD of lumbar spine had become stable while decreasing by 30% at the femoral neck (table 1). No evidence of fluorosis, secondary hyperparathyroidism, or abnormal vitamin D metabolism was found.

Shortly after this visit the patient was admitted to hospital for alprostadil treatment of her Raynaud’s phenomenon associated with the MCTD. She complained of sudden severe pain in her left hip during a forest walk. Surprisingly, an x ray examination showed left femoral head fracture and avascular necrosis (early radiological Ficat stage IV) (fig 1). After successful hip replacement, the patient was able to walk without pain.

DISCUSSION
This patient with MCTD demonstrates typical side effects of long term glucocorticoid treatment, but several points are of particular interest:

(1) Osteoporosis treatment had been started at a time when the BMD was already decreased. Other risk factors were early menopause without hormone replacement therapy and inflammatory rheumatic disease (cytokines can affect bone turnover). Official guidelines for the prevention of glucocorticoid induced osteoporosis were published by the American

| Table 1 Bone mineral density of lumbar spine and femoral neck over the course of three years |
|-----------------------------------------------|----------|----------|----------|
| Lumbar spine (mg/cm³) | 0.800    | 0.875    | 0.874    |
| Lumbar spine (t score) | −3.33    | −2.71    | −2.83    |
| Femoral neck (mg/cm³)  | 0.538    | 0.549    | 0.381    |
| Femoral neck (t score) | −3.68    | −3.68    | −4.99    |

Figure 1 An x ray image of the left hip showing femur head necrosis (early radiological Ficat stage IV) and fracture of the left femoral neck.
College of Rheumatology in 1996. Today it is clear that early prophylaxis can prevent manifest osteoporosis. Potent drugs for the prevention and treatment of osteoporosis are bisphosphonates and substitution of calcium and vitamin D.

(2) Another important aspect is osteoporosis with intercurrent avascular osteonecrosis of the left femoral head. The absence of pain in this condition is uncommon. To the best of our knowledge, unilateral osteonecrosis of the hip at an advanced stage without pain has not been previously reported. Only early stage forms or one hip without pain in bilateral osteonecrosis have been described. Avascular necrosis is not a specific disease entity. Predisposing factors are trauma, glucocorticoids, alcohol abuse, and connective tissue disorders. It may also be idiopathic. Avascular necrosis is a rare side effect of glucocorticoid treatment and is normally painful. In autoimmune diseases a correlation has been shown between glucocorticoids and bone death, which appears to be due to blood stasis and ischaemia in the trabecular bone. Theories of thrombotic formation or fat embolism have proved to be invalid. A further suspected mechanism could be the increase of osteocyte apoptosis owing to microdamage in the bone. Ischaemic vasculopathy as part of the underlying disease may also have a role. However, if these mechanisms are correct, then the association reported here should occur more often than it does. Active vasculitis or mechanical orthopaedic factors were excluded in our case. The absence of pain might be the result of peripheral nerve dysfunction secondary to polynoeyopathy caused by previous MCTD associated vasculitis. Glucocorticoid treatment might also have decreased the pain by reducing femoral head synovialitis.

(3) The simultaneous occurrence of osteonecrosis and atraumatic fracture of the femoral neck was even more surprising than the rare occurrence of severe, yet asymptomatic, osteonecrosis. Revascularisation of dead bone begins shortly after interruption of the blood supply. It promotes removal of necrotic bone by osteoclasts while inducing osteoblasts to synthesise new bone, thus creating more stability. The combination of osteonecrosis and fracture in the same region is therefore extremely rare.

In conclusion, osteoporosis is a common side effect of glucocorticoid treatment, and early prevention and treatment are necessary. Osteonecrosis and osteoporosis with a fracture in the same area as the side effects of glucocorticoid treatment is extremely rare. Only imaging techniques will allow differentiation.

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