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ENDGAMES

PICTURE QUIZ

A woman with raised alkaline phosphatase and forearm deformity

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A 71 year old Chinese woman was referred from the general outpatient clinic to our endocrine clinic for evaluation of raised serum alkaline phosphatase (ALP), which had been measured as part of a routine check-up. Apart from a history of hypertension and gout, she was well. For the past two years her blood tests had shown a raised ALP (183-277 U/L; reference range 47-124). Liver enzymes, renal function tests, thyroid function tests, and adjusted calcium and phosphate concentrations were all within normal ranges.

Examinations of the abdomen, cardiovascular system, and respiratory system were normal. She was noted to have a deformity of the right forearm (fig 1). She denied a history of trauma or fracture. The deformity had been present for three years, but she had not sought medical advice because it did not affect her hand function and was not painful. A radiograph of the right forearm was taken (fig 2).

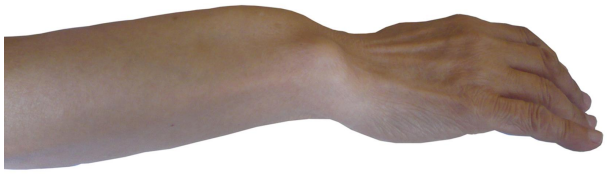

Fig 1 Deformity of the right forearm

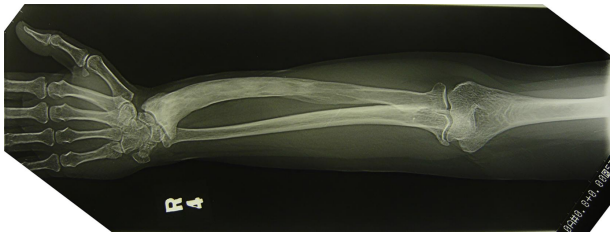

Fig 2 Radiograph of the right forearm

Questions

1 What is the diagnosis?

2 Describe the radiological abnormalities that confirm the diagnosis

3 How would you treat this condition?

Answers

1 What is the diagnosis?

Short answer

The diagnosis is Paget's disease of bone.

Long answer

Paget's disease of bone was first described by James Paget, who named this skeletal condition "osteitis deformans" in 1877.[1] It is a disease of bone remodelling and is characterised by excessive bone resorption at affected skeletal sites, followed by disorganised bone formation. The overproduced bone is sclerotic and of poor quality, and it is susceptible to deformity and fracture.[2] Paget's disease of bone is the second most common metabolic bone disease in European countries. The prevalence of Paget's disease in the United Kingdom has been estimated at 5% in people over 55 years of age.[3] Paget's disease, however, is rare in Chinese people. The prevalence of Paget's disease in non-white populations is not known because few case reports and case series are found in the literature.[4 5] Pagetic lesions are usually found in the pelvis, spine, skull, and long bones of the lower extremities. Paget's disease of the radius is rarely reported.[6] Most patients with Paget's disease are asymptomatic. Around 5% of patients have symptoms including bone pain, bowing of long bones, skull deformities, fractures, and nerve entrapment syndromes.[7]

The diagnosis is usually made using plain radiographs (see below). Plain radiographs are also useful in the diagnosis of

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secondary complications such as contiguous arthritis and fractures. Radionuclide bone scan using a radiolabelled bisphosphonate is highly sensitive in assessing the extent of skeletal involvement.[8] However, it is not specific to Paget's disease—focal uptake or "hot spots" can also be seen in fractures, infections, and even metastases. Any increased uptake in bone scan should be followed by targeted radiographs.

Serum alkaline phosphatase is a sensitive marker of bone formation, and concentrations are increased in 85% of patients with Paget's disease of bone.[9] In patients with monostotic disease (only one bone affected; about 15% of cases) or underlying liver derangement, bone specific alkaline phosphatase may be more useful.[10] Bone formation markers, such as procollagen type 1 N-terminal propeptide (P1NP), and bone resorption markers, such as urinary pyridinoline, are usually raised, but they are not widely available and are seldom used for diagnosis or monitoring of disease activity.[11]

Bone biopsy is rarely needed for the diagnosis, but it might help exclude osteosarcoma or bone metastases. Histological analysis typically shows an increase in bone resorption, with large multinucleated osteoclasts and increased bone marrow fibrosis surrounding bone trabeculae.

2 Describe the radiological abnormalities that confirm the diagnosis

Short answer

This radiograph shows cortical thickening of the radius and ulnar with a coarse trabecular pattern and bowing of the radius. Sclerosis of the distal radius is also seen, as well as lytic lesions in the shaft of the radius (fig 3).

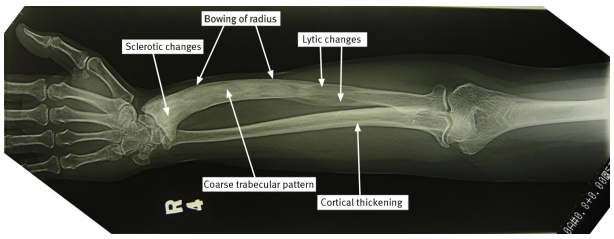

Fig 3 Radiograph of the right forearm showing sclerosis of the distal radius and lytic lesions in the shaft of the radius

Long answer

Paget's disease is usually diagnosed with the use of plain radiographs. The characteristic radiological findings are most prominent in the skull and long bones. Initially, osteolysis of the skull causes "osteoporosis circumscripta," which is seen as radiolucent areas on radiographs. This is followed by excessive formation of new bone, which leads to cortical thickening, "cotton wool" appearance as a result of localised sclerosis, and skull enlargement. The long bones typically show cortical thickening and enlargement, mixed areas of sclerotic and lytic lesions, and bowing deformities. If the vertebral body is affected a characteristic "picture frame" appearance is seen, as a result of enlargement of the vertebral body.[10]

3 How would you treat this condition?

Short answer

Bisphosphonates are the gold standard treatment. The aim is to decrease the abnormal bone turnover caused by osteoclastic bone resorption.

Long answer

Treatment is not warranted in asymptomatic patients who have normal serum alkaline phosphatase or a normal bone scan.

Indications for treatment include symptoms that are caused by metabolically active Paget's disease, such as bone pain, joint pain, headache (when the skull is affected), or neurological symptoms; planned surgery at a metabolically active pagetic site (treatment can decrease intraoperative bleeding); the presence of immobilisation hypercalcaemia; serum alkaline phosphatase concentration more than 1.5 times the upper limit of normal; and prevention of disease progression or future complications.[12]

Around 5% of patients with Paget's disease of bone experience bone pain.[7] They may benefit from simple analgesics, low dose tricyclic antidepressants, and physical methods, including transcutaneous electric nerve stimulation.[13] Surgery may be warranted if pain is caused by osteoarthritis or nerve compression.[13]

Bisphosphonates are the mainstay of medical treatment in Paget's disease of bone, which aims to suppress the abnormal bone turnover.[13] Five bisphosphonates are currently indicated for the treatment of Paget's disease of bone:

- Zoledronic acid (5 mg infusion)[14 15]
- Pamidronate (30 mg or 60 mg infusion every three months)[16]
- Risedronate (30 mg daily for two months)[15 17]
- Etidronate (5 mg/kg daily for six months, or 10 mg/kg daily for three months)[18]
- Tiludronic acid (400 mg daily for three months).[19]

The first two come as intravenous preparations, whereas the last three are oral preparations. They are associated with a 50-80% reduction in plasma concentrations of alkaline phosphatase, and an improvement in bone pain and appearance on radionuclide scanning.

Serum creatinine, calcium, and vitamin D concentrations should be measured before using intravenous bisphosphonates, because severe hypocalcaemia can occur with pre-existing vitamin D deficiency. Consider reducing the dosage and infusion rate in patients with mild renal impairment. Intravenous bisphosphonates are generally well tolerated, although some patients may experience febrile reactions, especially after the first infusion. Febrile reactions are self limiting and easily managed with paracetamol.

Oral bisphosphonates, on the other hand, are poorly absorbed from the gastrointestinal tract and associated with gastrointestinal side effects. It is recommended that oral bisphosphonates are taken with a full glass of water on an empty stomach and that patients wait for at least half an hour before eating or drinking. Adequate intake of calcium (1000-1500 mg daily) and vitamin D (800-1000 IU daily) is recommended before and after treatment with bisphosphonates. Ocular side effects including conjunctivitis and uveitis have been reported with bisphosphonates, but these complications are rare.

Serum alkaline phosphatase concentrations usually fall within 7-10 days of starting bisphosphonates, but the nadir occurs three to six months later. Pain relief and normalisation of serum alkaline phosphatase are the goals of treatment. Serum alkaline phosphatase should be monitored every three months for the first six months of treatment, and at six monthly intervals months thereafter. Retreatment with bisphosphonates may be considered in patients with recurrence of bone pain or biochemical relapse,

defined as an increase in alkaline phosphatase of 25% above the nadir.[13]

Patient outcome

A radionuclide bone scan showed intense tracer uptake over L3 and the right radius, with a patchy increase in uptake over the skull (fig 4). Radiography of the lumbar spine showed a heterogeneous increase in density of the L3 vertebral body, with bony expansion (fig 5). She was treated with a single infusion of 60 mg pamidronate and had a mild febrile illness for a few days after treatment. Her ALP fell from 277 U/L to 110 U/L in three months.

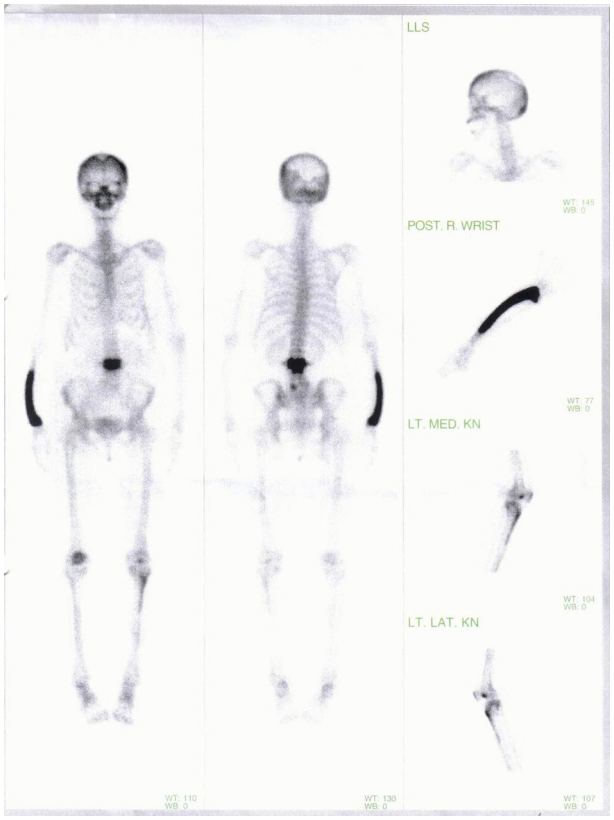

Fig 4 Radionuclide bone scan showing intense tracer uptake over L3 and the right radius, with a patchy increase in uptake over the skull

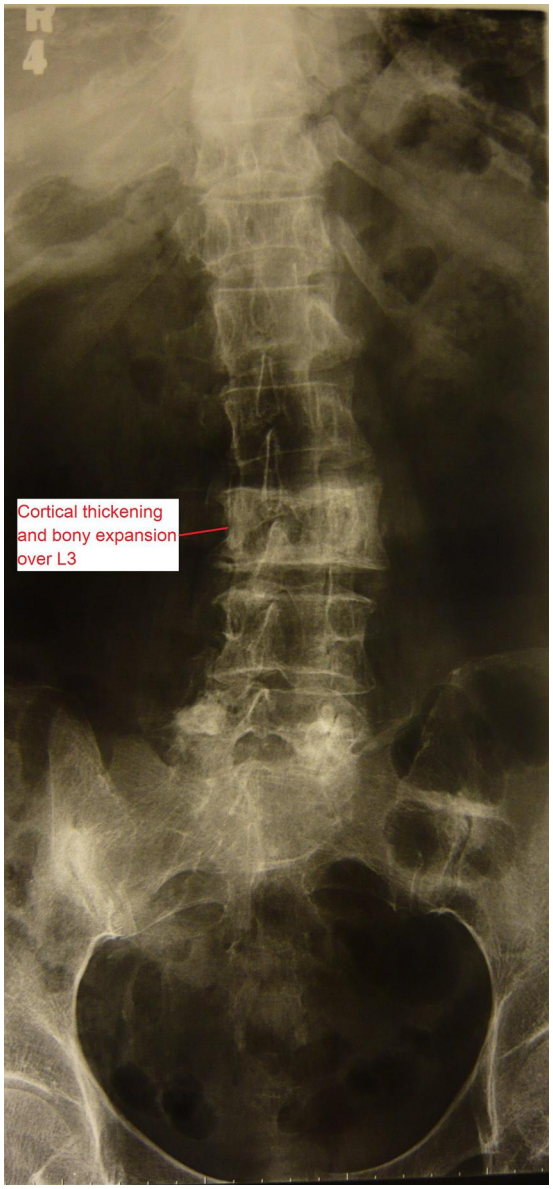

Fig 5 Radiography of the lumbar spine showing a heterogeneous increase in density of the L3 vertebral body and bony expansion

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Patient consent obtained.

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