CASE REPORT

Two siblings with Paget's disease of bone

Dukhabandhu Naik,[1] Hesargatta Shyamsunder Asha,[2] Suma Susan Mathews,[3] Thomas Vizhalil Paul[2]

[1]Department of Endocrinology & Diabetes, Christian Medical College, Vellore, Tamil Nadu, India
[2]Christian Medical College, Vellore, Tamil Nadu, India
[3]Department of ENT, Christian Medical College, Vellore, Tamil Nadu, India

Correspondence to
Professor Thomas Vizhalil Paul, thomasvpaul@yahoo.com

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SUMMARY

Paget's disease of bone (PDB) is a chronic disorder characterised by focal areas of excessive osteoclastic bone resorption with a secondary increase in osteoblastic bone formation. First-degree relatives of patients with PDB are at seven times higher risk of developing this disorder, with a tendency towards earlier age at onset. We report two siblings who presented with features of polyostotic Paget's disease. They presented with features of non-inflammatory back pain. Biochemical evaluation was unremarkable except for elevated serum alkaline phosphatase. Subsequently, radiology and bone scans were diagnostic of polyostotic PDB. They were treated with bisphosphonates with which they improved.

BACKGROUND

Paget's disease of the bone (PDB) can run in members of the same family. These two cases (sister and younger brother) presented with features of polyostotic Paget's disease, highlighting the fact that family members should be screened for Paget's disease when they present with skeletal symptoms such as back pain to make an early diagnosis and initiate treatment to prevent complications.

CASE PRESENTATION

A 64-year-old postmenopausal woman and a 57-year-old man (both were siblings) presented to the medicine outpatient clinic with low back pain of non-inflammatory nature with no history of trauma. The woman had back pain for the past 5 years and on examination was found to have a head circumference of 68 cm (macrocephaly) and moderate hearing loss in both ears. Systemic examination was normal and she had no bone tenderness. Her brother had a similar history of back pain for the past 2 years and examinations revealed an enlarged head with a circumference of 62 cm. He also had moderate sensorineural hearing loss in both ears. The rest of the examinations were unremarkable. No other members of the family were affected.

INVESTIGATIONS

The woman's corrected serum calcium was 8.8 mg % (8.3–10.4 mg%), phosphorus 4.1 mg% (2.5–4.6 mg%) and serum creatinine 0.8 mg% (0.5–1.4 mg%), total alkaline phosphatase 238 U/L (reference interval 40–125 U/L), serum parathyroid hormone 52 pg/mL (normal range 8–72 pg/mL) and 25 hydroxyvitamin D 23.3 ng/mL (normal range 30–75 ng/mL). Her X-ray showed characteristic sclerotic and lytic lesions in the skull and pelvic bones, suggestive of PDB (figure 1). A technetium pyrophosphate bone scan showed intense increase in tracer uptake in the skull, right shoulder, L4, S1 vertebra, left pelvic bone and right acetabulum (figure 2).

Biochemical evaluation of her brother revealed a corrected serum calcium of 9 mg%, phosphorus 4.2 mg%, serum creatinine 1 mg%, 25 hydroxyvitamin D 26.2 ng/ml and parathyroid hormone 62 pg/mL along with a grossly elevated total alkaline phosphatase 1003 U/L. His prostate specific antigen was 2 ng/mL. He had radiological findings similar to his sister (figure 3). Bone scan showed an increased uptake of tracer in the skull, L5, sacral vertebrae, bilateral pelvic bones and upper half of femur on both sides, suggestive of Paget's disease (figure 4).

DIFFERENTIAL DIAGNOSIS

The clinical features, radiology and bone scan features in these siblings were diagnostic of PDB.

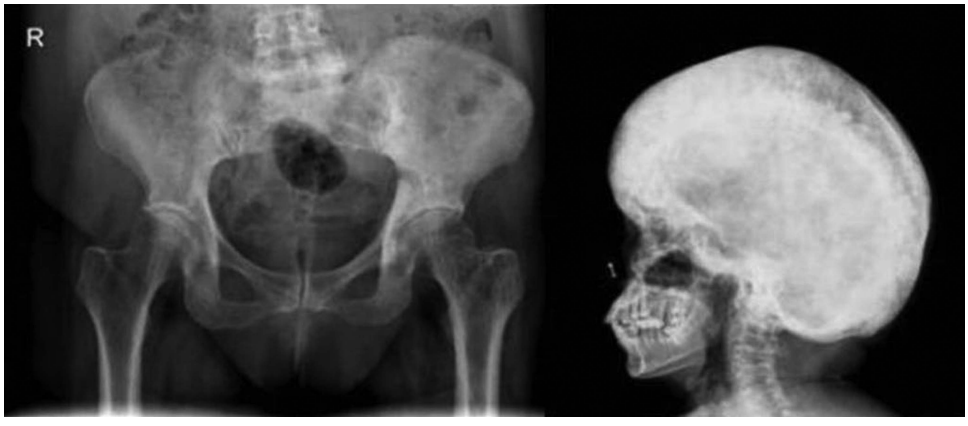

Figure 1 X-ray of the pelvis and skull showing osteosclerotic and lytic lesions in the index case (female).

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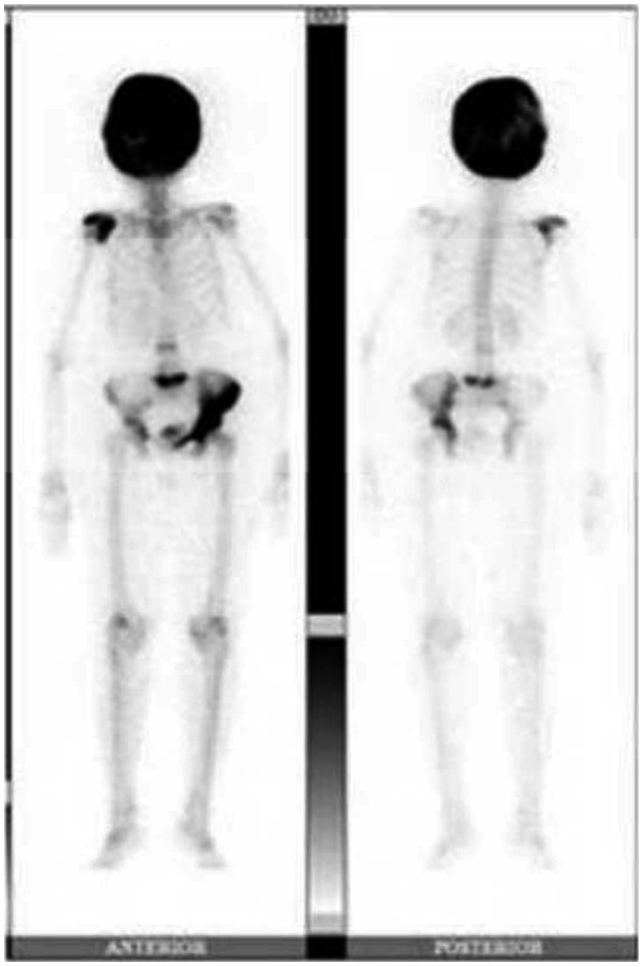

Figure 2 Technetium pyrophosphate bone scan showing intense increase in tracer uptake in the skull, right shoulder L4, S1 vertebra, left pelvic bone and right acetabulum (female).

TREATMENT

Both patients were initiated on bisphosphonates (alendronate), calcium and vitamin D supplements.

OUTCOME AND FOLLOW-UP

At 6-month follow-up, sister and brother were symptomatically better and the alkaline phosphatase were 98 and 142 U/L (reference interval 40–125 U/L), respectively.

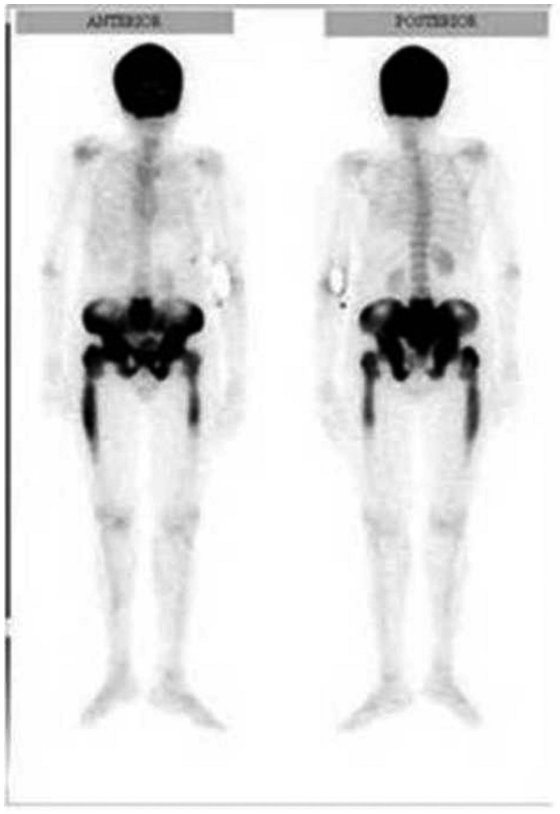

Figure 4 Technetium pyrophosphate bone scan showing intense increase in tracer uptake in the skull, pelvic bone and proximal in the sibling (male).

DISCUSSION

PDB is a common treatable disorder affecting older individuals. About 15–20% of those affected have a family history of Paget's disease. The familial nature of this disease has been reported in the literature and various environmental and genetic factors contributing to familial aggregation of this disease have been studied.[1]

An increased frequency of DQW1 and DR2 antigens (class II histocompatibility leucocyte antigen) was initially described. However, they have not been further replicated in other studies. Various susceptibility loci have been identified, these include: class II major histocompatibility complex on chromosome 6p21.3 (PDB 1), 18q21-22 (PDB 2) sequestrosome gene (SQSMT1) on chromosome 5q35 (PDB 3), 5q31 (PDB 4), 2q36 (PDB 5), 10p13 (PDB 6) and a locus at 18q23.[2 3] Mutation in

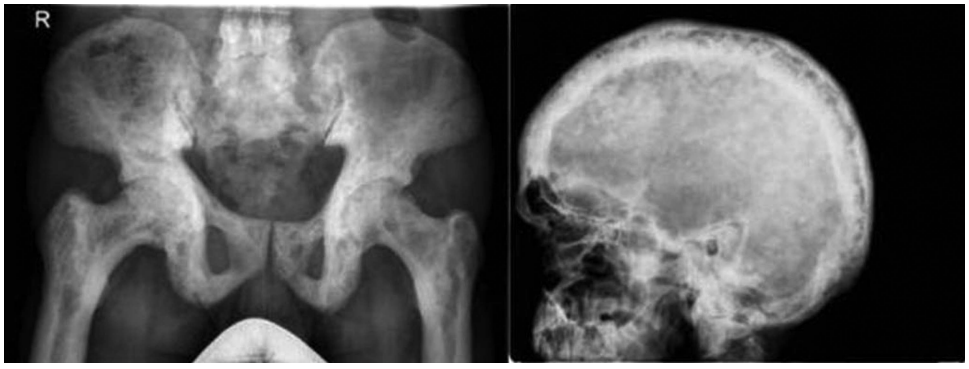

Figure 3 X-ray of the pelvis and skull showing osteosclerotic and lytic lesions in the sibling (male).

SQSMT1 gene primary affect around the ubiquitin-binding domain and the more common type of mutation is at codon P392L.[2]

The clinical behaviour of familial PDB resembles that of classic PDB except that these patients more often have severe sequelae with fractures and deformities. The diagnosis and management of familial PDB is similar to that of classic PDB. Serum alkaline phosphatase is the most useful screening test and is a marker of disease activity, but normal alkaline phosphatase level does not exclude Paget's disease.[4]

Potent second and third generation bisphosphonates are the treatment of choice. These include alendronate, risedronate and zoledronic acid.[4]

Disease activity can be monitored by measuring alkaline phosphatase levels every 3 months. Treatment can be stopped when the serum alkaline phosphatase level returns to the normal reference range or when there is no further reduction on successive measurements.[1]

First-degree relatives of patients with PDB should be screened periodically for early detection and treatment of the disease to prevent complications such as hearing loss, fractures and high-output cardiac failure. Identification of several susceptibility loci have led to better understanding of this disease. However this understanding needs to be translated into developing newer modalities of therapy to help patients resistant to conventional bisphosphonate therapy.

Learning points

- Paget's disease of bone can run in many members of the same family.
- A high index of clinical suspicion is necessary if members of the same family present with skeletal symptoms such as bone pains and other system involvement such as hearing loss.
- Early diagnosis and treatment will help this group of individuals to prevent complications.

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Competing interests None.

Patient consent Obtained.

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