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CASE REPORT

Skeletal dissemination in Paget's disease of the spine

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Abstract

Purpose Paget's disease of bone (PDB) is a common skeletal disorder that is associated with locally increased bone turnover, skeletal deformity and pain. We report a case of skeletal dissemination in PDB of the spine.

Methods Case report.

Results A 46-year-old former professional athlete suffered from disseminated PDB throughout the spine and hips after various surgical interventions including spondylodesis, bone grafting and bone morphogenetic protein (rhBMP-2) administration. Only intravenous zoledronic acid prevented the further progression of skeletal dissemination, which was expressed by a normalization of (bone-specific) alkaline phosphatase levels. The biopsy obtained from the lumbar spine confirmed the diagnosis of PDB in the absence of malignant transformation.

Conclusions We outline skeletal dissemination as a possibly surgery-related complication in a patient with PDB in the lumbar spine. Bisphosphonates remain the treatment of first choice in PDB and surgical interventions should be considered very carefully.

Keywords Paget's disease of bone · Dissemination · Bisphosphonates · Alkaline phosphatase · Spondylodesis

Introduction

Paget's disease of bone (PDB) was first described by Sir James Paget in 1876 [1]. After osteoporosis, it represents the second most common primary bone disease [2] and is characterized by localized excessive osteoclastic bone resorption followed by a compensatory increase in osteoblastic activity leading to unstructured, fibroblastic, and biomechanically unstable bone [3]. Its etiology is believed to be multifactorial, with both genetic and environmental factors [4, 5], and its overall prevalence has declined during the past few decades [6]. Malignant transformation towards Paget's sarcoma has been reported in 0.8% of the affected patients [7, 8]; however, extended dissemination of PDB has not been documented in the literature to date.

The spine, especially the lumbar spine, has been recognized as a common skeletal site for PDB [9]. Apart from bisphosphonate administration, which is the therapy of first choice [10], neurological deficits and refractory pain are the indications for additional spinal surgery [11–13]. We present iatrogenic dissemination of Paget's disease as a novel surgery-related complication in PDB of the spine.

Case report

A 46-year-old former professional athlete was admitted to the hospital because of sudden lower back pain. Radiography indicated a fragility fracture of the L4 and L5 lumbar vertebral bodies (Fig. 1a). Dorsal spondylodesis was initially performed due to a fragility fracture of L4 and L5 (first surgery, Fig. 1a, b). This was an emergency surgery utilizing a posterior instrumentation with pedicular screws in L2 and S1. Two months later, a total replacement of the L4 and L5 lumbar vertebral bodies including cage implantation was performed for further stabilization. This surgery was conducted via an anterior approach only and using an Ulrich

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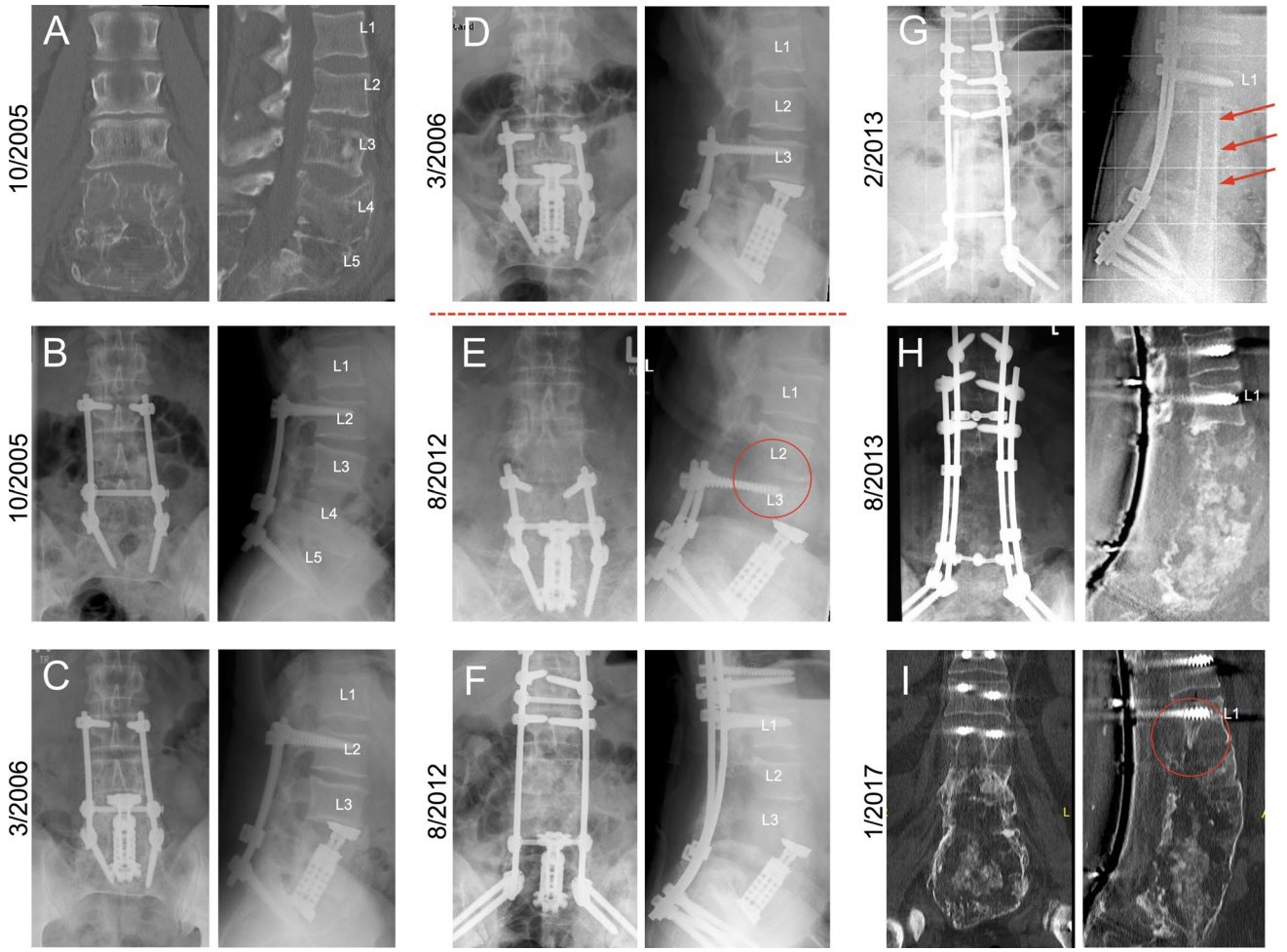

Fig. 1 Radiographic progression of spinal PDB in a 46-year-old man. **a** Coronal and sagittal reformat of the initial CT scan indicate a fragility fracture of L4 and L5. **b**–**i** Anteroposterior and lateral radiographies indicate the progression of Paget's disease from 2005 to 2017 (total 12 years follow-up). The surgical interventions that were used included, **b** initial dorsal spondylodesis, **c**, **d** cage implantation, **e**, **f** cage dislocation, **g** allogeneic bone grafting using a cadaveric femur (red arrows), **h** autologous bone transplantation and the use of rhBMP-2, and **i** osteolytic change of L1 at present

Obelisc CS292053 Cage (Ulrich Medical, Ulm, Germany) with a 15° angled base and top plate, 26 mm diameter (second surgery, Fig. 1c). Grafton® putty demineralized bone matrix was used as a bone graft. After another 3 months, the spondylodesis was moved from L2–S1 to L3–S1 to release the segment L2, since initially an affection of L3 was suspected (third surgery, Fig. 1d). A biopsy was performed, and the diagnosis of PDB was histologically determined. The patient received 70 mg of oral alendronate, weekly. A comprehensive anamnesis revealed that no other family members of the patient were affected by PDB.

Six years later, the patient presented with severe refractory pain after the previous years had been uneventful. Radiography indicated an osteolytic change in L3 and dislocation of the implanted cage (Fig. 1e). Therefore, revision spondylodesis was performed, in which the instrumentation was moved to T12/L1–S1 (fourth surgery, Fig. 1f). Both allogeneic bone transplant (fibula) and ceramic bone substitutes (Stryker® Vitoss) were used. Due to persistent cage dislocation, a femur bone graft from a human cadaver combined with an autogenous cancellous bone graft was implanted. However, this procedure did not achieve sufficient stability of the lumbar spine either (fifth surgery, Fig. 1g). Due to a dislocation of the femur graft, a complete dorsal material removal and subsequent reinstrumentation T12-ilium was performed in a sixth surgery. On the next day, the femur graft was removed in an anterior approach and cancellous bone grafting and bone morphogenetic proteins (BMP, rhBMP-2) administration was performed (seventh surgery, Fig. 1h).

When the patient presented at our outpatient clinic in 2013, the depicted revision surgeries had already been performed. PDB was confirmed in another biopsy that was conducted in 2013, in which prominent pagetic osteoclasts

with increased size and an increased number of nuclei were observed (Fig. 2). Bone scintigraphy confirmed PDB via marked tracer uptake in the lumbar spine (Fig. 3). At that time, the alkaline phosphatase level was elevated to 862 U/L, and the bone-specific alkaline phosphatase (BAP) level was 340 µg/L (Fig. 4). The BMD of the hip, as measured by dual energy X-ray absorptiometry (DXA), was within the normal range (T-score: 0.3). The patient received 20,000 IU of vitamin D weekly and 500 mg of calcium gluconate daily to balance the calcium and 25-hydroxyvitamin D levels (> 30 µg/L) and prevent the occurrence of hypocalcaemia after bisphosphonate administration. Subsequently, 5 mg of intravenous zoledronic acid (Aclasta®) was given according to the endocrine society clinical practice guideline [14], which led to a rapid reduction in the AP and BAP levels indicating the disease activity as well as marked reduction of pain levels (Fig. 4). Although the patient did not have any signs of renal dysfunction (i.e., normal glomerular filtration rate), the intravenous infusion was given slowly with prior administration of 500 mL of Ringer's solution.

Three years later, the patient's AP and BAP levels had increased again, as the patient had not attended any of the follow-up appointments until then. A CT scan and bone scintigraphy indicated progressive dissemination towards the thoracic spine and into the pelvis, including the sacrum and both hips (Figs. 1i, 3b). Another infusion of intravenous

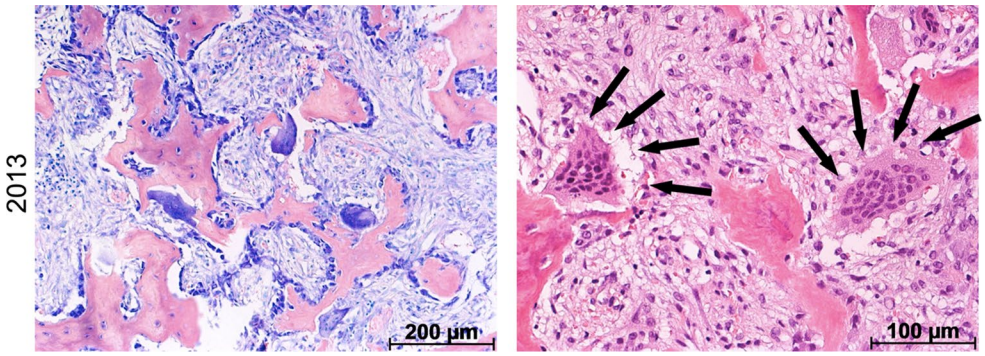

Fig. 2 Histologic findings. Hematoxylin and eosin staining (left: magnification ×10, right ×20) demonstrates multiple multinucleated giant osteoclasts (black arrows)

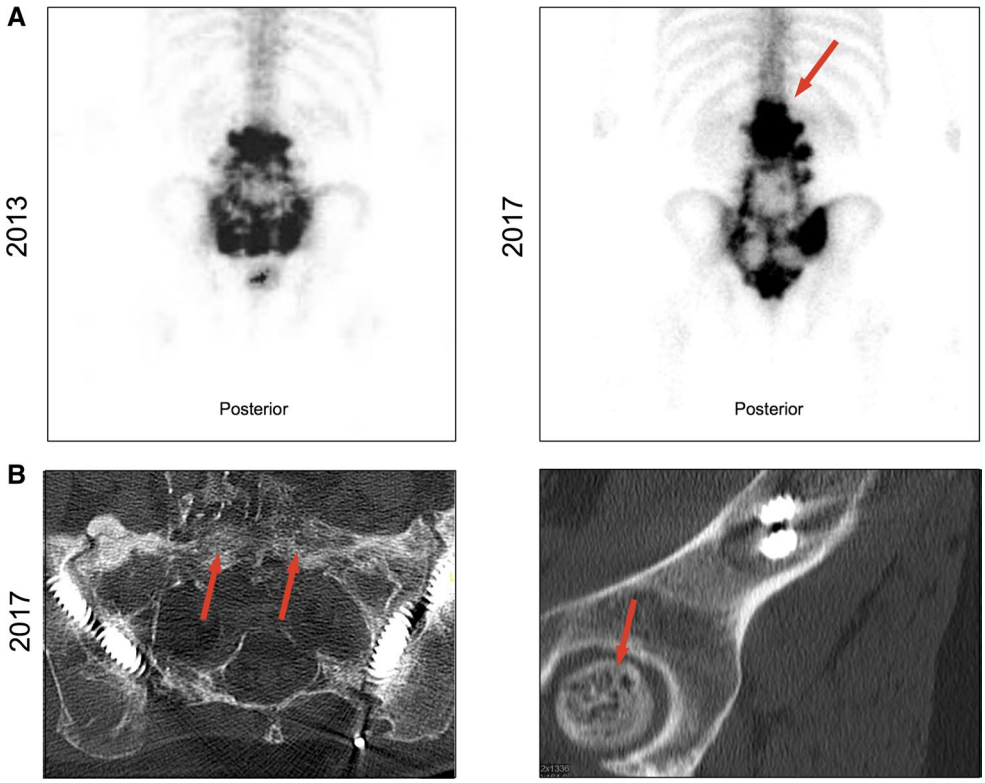

Fig. 3 Skeletal dissemination at present. **a** ^{99m}Tc-MDP bone scintigraphy indicates increased tracer uptake in the lumbar spine in 2017 compared to 2013 (red arrow). **b** Computed tomography revealed a progression into the sacrum and both hips in 2017 (red arrows)

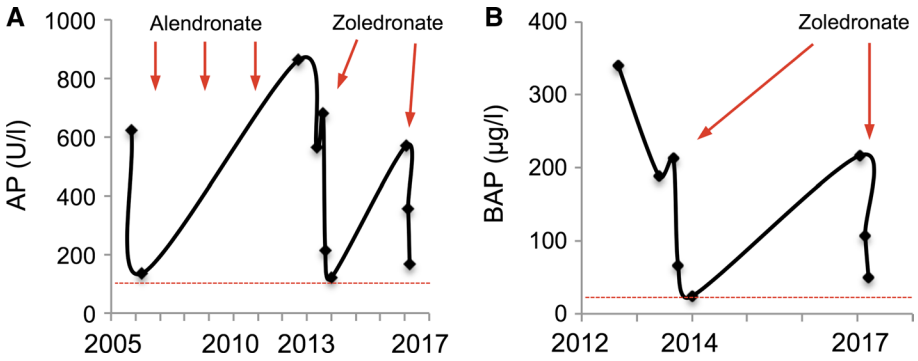

Fig. 4 Biochemical findings. **a** Changes of alkaline phosphatase (AP) levels in the course of the time indicate disease activity and treatment response. **b** Parallel curve progression of bone-specific alkaline phosphatase (BAP) levels. Red lines indicate the upper reference limit for AP and BAP

zoledronic acid led to the normalization of AP and BAP levels. The patient was advised to attend regular follow-up examinations, including extended bone turnover analyses, and to not miss the next zoledronate administration, which is used to avoid further dissemination.

Discussion

Here, we describe the possibility of a progressive dissemination of Paget's disease of the spine that could ultimately be prevented only by the administration of intravenous zoledronic acid. In this case, the disease progressed following multiple surgeries and spread into the lumbar spine, sacrum and hips. Malignant transformation (Paget's sarcoma) was excluded by radiographic and histopathologic analyses.

Several major clinical implications can be drawn from this case. First, anti-resorptive drugs (i.e., intravenous bisphosphonates) should be considered a treatment option before any surgical interventions are performed [14–16]. Bisphosphonate therapy for PDB is not novel, and its administration is seemingly simple. However, its effectiveness in the treatment of PDB is often not known, and other treatment options such as surgery are preferred. Second, neither autologous (i.e., iliac crest) or allogeneic (i.e., femur, fibula) bone transplantation nor BMPs seem to be suitable treatment options, and these may promote the progression of PDB. Since BMPs are considered to be growth factors and BMP-2 and BMP-7 have been shown to induce bone formation [17], it can be assumed that they promoted the further progression of PDB instead of bony consolidation. Potential necrosis of the transplant and both sclerotic and resorptive changes of the bone graft or the host bone tissue can mimic and hide the progression of the disease, with or without malignant transformation. Third, reaming, nailing and intralesional osteosynthesis should be performed with caution in PDB cases because it is possible that these procedures might also contribute to the spread of the disease.

We have essentially outlined a series of seven surgeries in total including the use of various graft materials and recurrent instabilities. The complexity of these events makes it difficult to determine which of the materials and/or interventions may have contributed to the disease dissemination, also given a possible non-compliance regarding the oral bisphosphonate medication. In this case, the main focus obviously lied on the surgical stabilization itself rather than the treatment of the underlying disease.

The progression of PDB in the spine 10 years after spondylodesis has been described in a single case [18]. Furthermore, strut allograft invasion has been reported in another case of PDB of the femur [19]. The dissemination of PDB from the L4/L5 lumbar vertebral body into the entire lumbar spine, as well as into the hips and sacrum, illustrates the invasiveness of PDB after its possible spreading through surgery.

In our case, the progressive dissemination of PDB apparently occurred during the time when no anti-resorptive drugs were given or when oral bisphosphonates (i.e., alendronate) initially seemed to be insufficient for preventing disease progression. The latter indicates that PDB might not respond to oral bisphosphonates and that it must be treated by intravenous zoledronic acid, which is known to be the most potent bisphosphonate regarding its inhibition of the target enzyme of this drug class, farnesyl pyrophosphate synthase [20]. Apart from the notion that in older patients with PDB, a single intravenous zoledronate infusion may achieve disease suppression for the rest of their lives [21], we provide evidence that the lifelong monitoring of bone turnover and multiple zoledronate infusions is necessary. AP and BAP levels are appropriate markers for disease and treatment monitoring [22].

Conclusions

We present a case of unusual progressive non-malignant PDB in the spine, which had a catastrophic course over 12 years and seven surgeries. This report indicates that bisphosphonates remain the treatment of first choice and that surgical interventions should be considered very carefully. The relationship between surgical treatment and disease extension should be evaluated in larger series. In the future,

in addition to the identification of environmental factors that trigger PDB, it will be of interest to determine which genetic variants are involved in the susceptibility to severe and disseminated forms of PDB.

Compliance with ethical standards

Conflict of interest None of the authors has any potential conflict of interest.

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