Reumatologia 2019; 57, 3: 167–172
DOI: https://doi.org/10.5114/reum.2019.86428

Monostotic Paget's disease of bone – literature review and case report

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Abstract

Paget's disease of bone (PDB) is a localized, chronic bone metabolic disorder, characterized by an osteoclastic malfunction, causing increased bone resorption and subsequent compensatory creation of new bone with a defective microstructure. Monostotic cases of PDB are less common than asymmetrical polyostotic PDB cases. The radiological diagnosis of PDB is usually straightforward, but monostotic cases can cause diagnostic difficulties.

We report a case of monostotic PDB in a 64-year-old man. He experienced pain of the left lower extremity and radiological investigations revealed irregular areas of bone destruction in the left femur. Bone biopsy findings indicated PDB. Treatment with bisphosphonates was initiated, but after about three years of treatment left hip arthroplasty was required due to a large area of bone destruction. Presentation of this case report aims to discuss diagnostic challenges of monostotic cases of PDB and present guidelines of treatment.

Key words: bisphosphonates, bone metabolism, Paget's disease of bone.

Introduction

Paget's disease of bone (PDB) was first described in 1877, by Sir James Paget at St Bartholomew's Hospital in London. In his paper he wrote about cases of patients whose "bones enlarge and soften, and those bearing weight yield and become unnaturally curved and misshapen". The current definition of PDB or osteitis deformans states that it is a localized chronic bone metabolic disorder, characterized by an osteoclastic malfunction, causing increased bone resorption and subsequent compensatory creation of new bone with a defective microstructure [1, 2].

Paget's disease of bone is often incidentally diagnosed, from an elevated serum alkaline phosphatase (ALP) or an incidental radiographic finding [3].

Most common symptoms of the disease include bone pain, skeletal deformities, symptoms of fractures, hearing loss, symptoms of nerve root compression, and headache. The disease may involve multiple bones (polyostotic variant) or only one bone (the monostotic variant) [3].

The radiological diagnosis of PDB is usually straightforward, but monostotic cases can cause diagnostic difficulties [4]. We present case of monostotic femoral Paget's disease (MFPD), to discuss the problem.

Case report

A 64-year-old man, with no relevant past diseases, complained of left hip pain and numbness of the left lower extremity. He had experienced these symptoms for the last several years, but their intensity was low. The patient was taking paracetamol and over-the-counter nonsteroidal anti-inflammatory drugs periodically, and all this time he did not report to the doctor. The pain had been getting worse for about one month, so finally the patient reported to the doctor. There was no history of trauma reported. Anteroposterior hip radiograph was performed, which revealed bone destruction in the greater trochanter area, and decreased bone density in the head and neck of the femur. Besides a slightly elevated level of alkaline phosphatase (1.5 × over upper limit of normal), there were no significant laboratory findings.

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Submitted: 28.02.2019; **Accepted:** 10.06.2019

The patient was referred to the Orthopedics Department, where CT scan of left hip was performed, which showed irregular areas of bone destruction in trochanters, head, neck and body of the left femur, lower density of bone trabeculae, while remaining ones were thickened and sclerotized. No further investigations were performed for the next eight months, when another CT scan of the left hip was carried out. It showed a similar image to the last CT scan, and soon a biopsy was taken. Histopathological findings indicated Paget's disease of bone. Bone scintigraphy was performed to assess the extent of the disease (Fig. 1). It revealed areas of unevenly increased radioisotope uptake in the proximal part of the left femur, but no other focal changes consistent with Paget's disease of bone were found. The patient was referred to the Metabolic Bone Diseases Outpatients Clinic. Due to the high intensity of bone pain, despite only a slightly elevated level of alkaline phosphatase, treatment with bisphosphonates was initiated. The patient was receiving pamidronic acid at 90 mg every three months.

After two years of treatment a high level of prostate cancer antigen (PSA) was revealed in a routine blood test (the patient was having the PSA level checked once a year). Per rectal biopsy indicated prostate adenocarcinoma. Treatment with bisphosphonates was periodically stopped. No metastases were found and the patient underwent radical surgical resection of the prostate gland. Pamidronic acid at 90 mg every 3 months was again initiated. However, eight months after the diagnosis of prostate cancer, left hip arthroplasty was required due to a large area of bone destruction in the femur (Fig. 2). Antiresorptive therapy was continued for the next 9 months until the Metabolic Bone Diseases Outpatient Clinic, where the patient was attending, closed. The patient did not report to any other clinic for the next eight months.

After this time the patient was admitted to our department, with strong pain in the left hip. Alkaline phosphatase and acute phase reactants were normal. Bone scintigraphy and CT scan of the left hip revealed findings which might be consistent with loosening of hip endoprosthesis. Preoperative treatment with bisphosphonates (once again pamidronic acid at 90 mg) was indicated, and the patient was referred to the orthopedics department, where replacement of hip arthroplasty was performed. Due to presence of bone pain the patient received another two doses of pamidronic acid at 90 mg every three months, which strongly relieved symptoms. At the moment the patient does not experience bone pain or any other symptoms of PDB and the serum level of alkaline phosphatase is normal. He is being followed in the outpatient clinic of our department, and possible

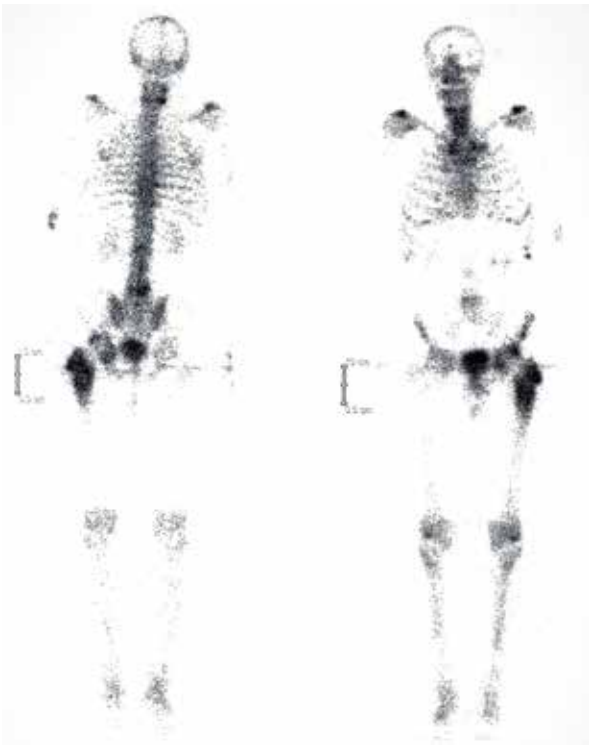

Fig. 1. Bone scintigraphy, with unevenly increased radioisotope uptake in proximal part of left femur.

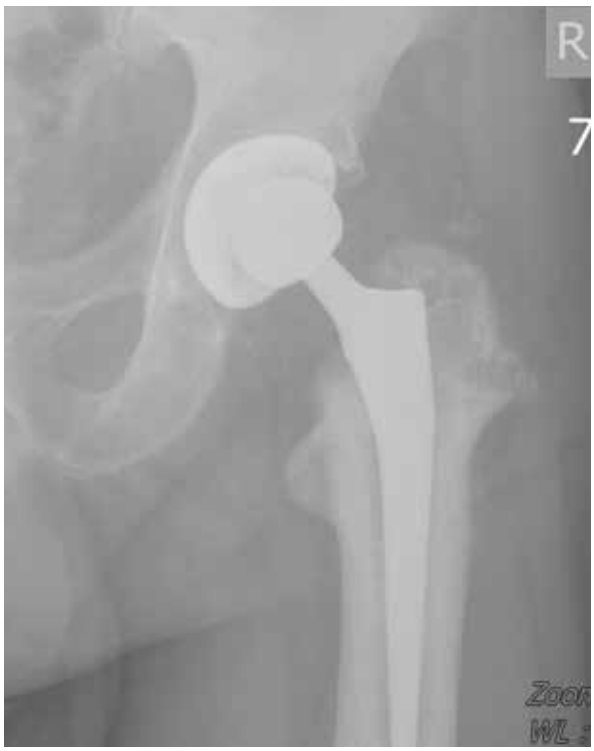

Fig. 2. Anteroposterior left hip radiograph after first performed arthroplasty.

re-initiation of antiresorptive therapy is dependent on presence of symptoms of the disease and the level of alkaline phosphatase.

Discussion

Paget's disease of bone is the second most frequent metabolic disorder of bone after osteoporosis [3]. Prevalence of PDB in higher in males than females (at proportion of 3 : 2) and in older patients. It is very uncommon under the age of 25, slightly more frequent before the age of 40, and it occurs five times more often in patients over the age of 85 than in those under 60 years old [5]. The prevalence of PDB varies according to ethnic origin and geographical location. It is more frequent in people of British ancestry. Paget's disease of bone is most prevalent in the UK, Australia, New Zealand and North America. In contrast, it is rare in Scandinavia, Asia, the Middle East and Africa. The global prevalence is approximately 0.3%, and has slowly been decreasing over recent years [5]. There are no data describing epidemiology of PDB in Poland.

Although the exact cause of PDB is unknown, the most probable hypothesis is that the cause of the disease is paramyxoviral infection in people who are genetically vulnerable [3]. The hypothesis is backed up by in vivo research which showed that co-expression of the measles virus nucleocapsid gene and mutation in sequestosome 1 – $p62^{P394L,}$ in mice is connected with development of severe pagetic bone lesions. Results of the survey suggest that $p62^{P394L}$ mutation and IL-6 induction by the measles virus nucleocapsid gene have a very important role in pathogenesis of PDB [6].

Paget's disease of bone is a focal disorder of bone metabolism, whose natural course consists of three phases. In the first phase, osteolytic, intense bone resorption and hypervascularization occur. In the intermediate (mixed osteoblastic/osteolytic) phase, bone resorption by osteoclasts is parallel to increased production of new bone by osteoblasts. Due to ineffective mineralization of newly created bone matrix, normal lamellar bone is replaced with chaotic bone, which structure is weak and prone to deformities and fractures. In the late osteosclerotic "burnt-out" phase, osteoclastic activity is reduced, but formation of ineffectively mineralized bone matrix persists. All three phases may occur at the same time in different parts of the skeletal system [3, 5].

Diagnosis is often made incidentally, either when an elevated ALP level is noted on a routine blood test or when characteristic radiographic changes are revealed on X-rays performed for some other reason. However, it does not mean that patients with PDB do not present any symptoms of the disease. Most cases are symptomatic, but the manifestations are not specific. Nevertheless, at least 20–25% of patients are asymptomatic [3, 7].

The most common presentation of PDB is bone pain, which often occurs at night, is worse at rest, and eased by movement. Studies have demonstrated that the level of bone pain is proportional to the level of disease activity [1, 3, 8]. Other symptoms include musculoskeletal disorders (bending of long bones, enlarged skull, osteoarthritis of joints adjacent to pagetic lesions, bone fractures), neurological disorders (decreased hearing, platybasia, spinal stenosis, vascular steal syndromes, increased cerebral spinal fluid pressure, rare cases of cranial nerve deficits), cardiovascular disorders (cardiac failure due to the high cardiac output, aortic stenosis, conduction abnormalities and increased vascular calcification) and malignant transformation (mainly sarcomas – 1% of PDB cases, but transformation to giant cell tumors of bone (GCTB), lymphoma, multiple myelomas, carcinomas and parathyroid tumors may also occur) [3, 5].

Investigations useful in diagnosing PDB are serum biochemical markers of bone resorption and radiography. The most commonly raised biochemical marker is the alkaline phosphatase level, which reflects osteoblast activity. As it comes to radiological investigations, CT shows similar findings to classical radiography, but it is useful when localization is hard to assess by X-ray scan. The radiological picture varies, depending on which stage of the natural course of disease predominates – osteolytic, mixed osteoblastic/osteolytic or late phase [3, 5]. Bone scintigraphy is the most sensitive method to detect pagetic lesions [3, 9, 10] and is recommended in all patients to evaluate the extent of the disease [11].

In management of PDB the treatment of choice is bisphosphonates. There is good evidence that suppressing bone turnover with bisphosphonate treatment is highly effective; it heals radiological lesions and restores normal histology of bone [12]. Nevertheless, most patients are asymptomatic and there was a discussion whether this group needs treatment. Paget's disease of bone: a randomized trial of intensive versus symptomatic management (PRISM) study, was carried out in a group of 1,324 patients with PDB, to compare results of treatment with bisphosphonates only in symptomatic patients and in every patient whether symptomatic or not. In the symptomatic treatment group if bone pain occurred, analgesics and anti-inflammatory drugs were used, and if there was no response, treatment with bisphosphonates was initiated. In the intensive treatment group patients were treated with repeated courses of bisphosphonates whether they had symptoms or not and the goal was to keep the alkaline phosphatase level in the normal range. There were no significant differences between the groups in quality of life, in overall bodily

pain, in pagetic bone pain, hearing thresholds, occurrence of fractures or number of patients who required orthopedic surgery. The conclusion was that there is no clinical advantage of intensive treatment regardless of symptoms over symptom based therapy [13, 14].

The most common side effects of therapy with bisphosphonates are gastrointestinal side-effects when administered orally, and acute phase responses when administered intravenously. There are also two rare but severe adverse effects of bisphosphonates which are atypical femoral fractures and osteonecrosis of the jaw [15]. Atypical fractures of the femur is very rare [16]; in the study by Meier et al. [17] it was 32 cases per million person-years and increased by 10.7% per year of bisphosphonate therapy on average, while according to Dell et al. [18] it was 1.78/100,000/year in patients with bisphosphonates treatment duration from 0.1 to 1.9 years, and increased to 113.1/100,000/year with duration from 8 to 9.9 years. Osteonecrosis of the jaw mainly develops in oncological patients during bisphosphonate therapy, and research shows that occurrence is less than 1/10,000 among patients who use bisphosphonates for osteoporosis [19].

Denosumab is a RANKL inhibitor which inhibits bone resorption by prevention of the development of osteoclasts. There have been a number of reports showing that denosumab has some clinical value in treatment of patients with PDB [20–22]. Possibly it may become a second-line therapy among patients with contraindications to bisphosphonates, although very limited clinical data are available and at the moment denosumab is not approved by the FDA for this indication [23].

The latest available guidelines of treatment of PDB were developed by committees and members of the Endocrine Society and the European Society of Endocrinology in 2014. The recommendations are as follows [24]:

- Plain radiographs should be obtained of the pertinent regions of the skeleton in patients with suspected Paget's disease.
- If the diagnosis is confirmed, a radionuclide bone scan should be done to determine the extent of the disease.
- After diagnosis of Paget's disease, measurement of serum total alkaline phosphatase should be performed or, when warranted, a more specific marker of bone formation or bone resorption to assess the response to treatment or evolution of the disease in untreated patients.
- Treatment with a bisphosphonates is recommended for most patients with active Paget's disease who are at risk for future complications. A single 5 mg dose is of *i.v.* zoledronate is suggested as the treatment of choice in patients who have no contraindications.
- In patients with monostotic disease who have normal serum total alkaline phosphatase, a specific marker of bone formation and bone resorption should be measured, although these may still be normal. Serial radionuclide bone scans may determine the response to treatment if the markers are normal.
- Bisphosphonate treatment may be effective in preventing or slowing the progress of hearing loss and osteoarthritis in joints adjacent to Paget's disease and may reverse paraplegia associated with spinal Paget's disease.
- The patient should receive treatment with a bisphosphonate before surgery on pagetic bone.

Not earlier than three months after the start of treatment with bisphosphonates, ALP level should be measured. Its normalization is a good indicator of remission. Usually short courses with potent bisphosphonates are capable to obtain biochemical remission and prolonged treatment with bisphosphonates is unnecessary [11]. Due to high efficiency and achieved long-term remissions, single intravenous infusion of zoledronate 5 mg is, at the moment, regarded as the treatment of choice [11]. Some patients may require surgical management; the main indications for it are presence of fracture, deformity, compression neuropathies, arthritis and malignancy [5] (Table I).

Femur (25–46%) is the second most common location of skeletal involvement in PDB after pelvis (21–75%). However, monostotic cases of PDB are less common (about 10–35% of patients) than asymmetrical polyostotic PDB cases – about 65–90% of patients. Due to this fact, monostotic femoral Paget's disease (MFPD) is not such a widespread finding [5].

Table I. Doses of bisphosphonates in treatment of Paget's disease of bone. Based on the information from [25]

Medication	Dose
Zoledronic acid	A single intravenous infusion of 5 mg at a constant rate over at least 15 min
Pamidronate	30 mg intravenously over 4 h for 3 consecutive days for a total dose of 90 mg
Alendronate	40 mg orally daily for 6 months
Risedronate (immediate release)	30 mg orally once daily for 2 months

According to the Bachiller-Corral et al. study [4], when compared with other monostotic locations of PDB, MFPD patients more frequently had normal alkaline phosphatase levels and a higher percentage of MFPD cases presented symptoms such as bone pain, bone deformities or development of a fracture. These findings led the authors to the conclusion that MFPD causes considerably more morbidity than other locations of monostotic PDB [4]. Moreover, bone biopsy was needed in 29% of patients to establish the diagnosis of MFPD [4]. It proves that MFPD raises more diagnostic difficulties than cases of polyostotic PDB, in which bone biopsy is rarely needed [4, 26].

An explanation of this fact is that, depending on the phase of the natural course of PDB (lesions in the early stage may not have typical appearance) and location of changes (those located in the distal part of the femur have a less characteristic radiological picture than those located in the proximal part of the femur), establishing the diagnosis only on the basis of radiological investigations may not be possible in certain cases. In polyostotic form one is more likely to find at least one lesion with a specific radiographic appearance, and establish the diagnosis of PDB without taking a bone biopsy [4].

In the present case, consistently with the results of research described above, serum ALP level was only slightly elevated (over 1.5 × upper limit of normal), yet the intensity of bone pain was high. Radiological investigations have not provided reliable diagnosis, so bone biopsy was needed. Due to severe symptoms, treatment with bisphosphonates and subsequent hip arthroplasty were required. After two years of remission, loosening of hip endoprosthesis required another therapy with bisphosphonates as preoperative treatment, to reduce the increased blood flow and excessive bleeding [11].

Conclusions

Paget disease of bone can be seen in clinical practice occasionally. Monostotic femoral Paget's disease is a less common form of PDB. Due to lower levels of ALP and often a less characteristic radiological picture, it is usually more difficult to establish the diagnosis of MFPD than in polyostotic PDB. Bisphosphonates are currently the treatment of choice of all forms of PDB. Therapy is usually effective and leads to achievement of long-term clinical and biochemical remission.

The authors declare no conflict of interest.

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