Pathological fracture of the femur in a patient with Paget’s disease of bone: a case report

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Abstract

Paget’s disease of bone is a benign disease characterized by exaggerated remodeling of the bone matrix after osteoclast-mediated bone destruction. Its etiology is still unknown, despite the fact that it was discovered and described in 1877, but genetic factors and environmental triggers were shown to play their part in the pathogenesis of the disease. The main clinical presentations of the disease are related to bone pain and deformities. Radiological diagnosis is the main detection tool, though many monostotic Paget’s disease cases may remain undiagnosed. We present the case of an 81-year-old male patient admitted to the Clinic of Orthopedics, Emergency County Hospital, Timisoara, Romania, with intense pain and deformity of the upper left thigh. Radiological examination performed shows a complete fracture of the upper third diaphysis of the left femur with suggestive signs for Paget’s disease of the bone therefore a biopsy was taken and the patient was treated by surgical realignment with favorable evolution. He was discharged 13 days after surgery. The biopsy of the bone revealed extensive bone remodeling with numerous osteoclasts and extensive bone matrix deposition, unevenly stained and unevenly mineralized and reverse cement lines, which are consistent with the diagnosis of Paget’s disease of the bone. Histomorphometric analysis show intense matrix deposition with a highly active remodeling process. Computed tomography (CT) scans were performed three years later and show the extension of the disease into the lower half of the left femur.

Keywords: Paget’s disease, radiological diagnosis, pathological fracture, histomorphometrical analysis.

Introduction

Paget’s disease of the bone (also known as ostitis deformans) is a remodeling defect of the bone tissue after hyper-activated osteoclast-mediated bone destruction, resulting in exuberant bone tissue formation with low mechanical resistance and prone to pathological fractures. Although described by Sir James Paget, in 1877, its etiology is still unknown. Recent studies show a consistent genetic background involvement in the pathogenesis of the disease, particularly mutations in the sqstm1/p62 and valosin-containing protein (VCP) genes [1–8], overexpression of Dickkopf-1 and sclerosin in pagetoid osteoclasts [9], overexpression of secreted phospholipase A2 type II and mutations up-regulating FGF2-RANKL-NF-κB signaling pathway [10–12]. Environmental factors may be involved in the pathogenesis of the disease, as suggested by the changing epidemiology [13].

Although benign in evolution, it sometimes causes bone pain, deformities, fractures and in a small percentage of the cases gives rise to malignant tumors such as Paget’s sarcoma and osteosarcoma, with a prevalence of malignant transformation in men [14–17].

The diagnosis of the disease is mostly radiological, with limited efficacy, completed by computed tomography (CT) scans, scintigraphic scans and serum levels of alkaline phosphatase [18–21]. Care must be taken in monostotic Paget’s disease, as radiological exams and biological tests may be inconclusive [20], association with hyperparathyroidism [22, 23], and in patients with malignant tumors metastatic to the bone, as it can lead to misdiagnosis of Paget’s disease as cancer metastasis [24, 25].

In our study, we present the case of a patient with femur Paget’s disease of bone, complicated by a fracture, which caused problems of differential diagnosis with bone tumor.

Case presentation

We present the case of an 81-year-old male patient with a history of ankylosing spondylitis, admitted to the Clinic of Orthopedics, Emergency County Hospital, Timișoara, Romania, with intense pain and deformity of
the soft parts around the fracture focus, for the histobioptical samples that included both the bone tissue and the femur fracture. There was performed a large opening of the fracture focus, the bone synthesis being performed with 12 screws. During bone synthesis, there were taken biopsy samples that included both the bone tissue and the soft parts around the fracture focus, for the histopathological confirmation of the disease and for establishing the differential diagnosis of a bone fracture. The wound had a favorable progress, the threads being removed after 14 days after surgery, and, as there were no complications, the patient was discharged.

The biological material harvested during surgery was fixed in 10% formalin solution and sent to the Laboratory of Pathological Anatomy for diagnosis confirmation. After bone decalcifying and paraffin inclusion, according to the classical histopathological protocol, there were performed 5 μm sections in the microtome that were stained with Hematoxylin–Eosin (HE). The microscopic examination was performed with the research microscope Nikon Eclipse 55i, equipped with an automatic camera and an adequate software for image take and processing.

The microscopic examination showed the presence of an intense process of bone remodeling, extended all over the biopsy structure, with numerous large-sized osteoclasts, with an abundant cytoplasm and various nuclei (Figures 1 and 2). Bone remodeling, produced both by bone resorption processes and bone synthesis processes, determined the formation of a mixture between trabecular bone tissue and haversian bone, with heterogeneous bone trabecules, placed “in a mosaic” (Figure 3). The general aspect of the bone tissue was spongy, bone remodeling leading to an almost total replacement of the compact harvesian bone tissue, characteristic to the diaphysis of long bone with the spongy bone tissue. Quite often, there were observed heterogeneous bone trabecule fragments, more or less demineralized, with osteoid-covered surfaces or not. Between the bone trabecules, there appeared various shape areolas, mostly covered by fibrous conjunctive tissue (Figure 4).

In some bone trabecules, there were identified osteocytes and osteoblasts with a normal aspect, the activity of bone synthesis being absent, the processes of demineralization and bone lysis presenting an intense expression (Figures 5 and 6). These microscopic aspects make us believe that, even though osteoclasts appear to be normal, their function is reduced or even absent. In some areas, there were identified large size trabecules with successive layers of osteoid covering their surface. Thus, in Paget’s disease there are processes of bone synthesis, but they are chaotic and do not re-establish the normal bone structure. In this way, the overall mechanic resistance of the tissue affected by the Paget’s disease is reduced and may lead to fractures.

The radiological examination results (plain Rx) prior to and after surgical treatment are shown in Figures 5 and 6.

Three years later, the patient presents to the Department of Surgery, Emergency County Hospital, Timișoara, with a stenosing tumor of the descendent colon and two other polypoid lesions closer to the proximal resection margin; pathological examination revealed the tumor as a moderately differentiated colon adenocarcinoma and the polypoid lesions were adenomatous polyps with variable degree of dysplasia. CT scan of the left thigh revealed an area with decreased bone density in the lower half of the left femur, with suggestive aspect for Paget’s disease of the bone, as shown in Figures 9–11. The fracture site healed with callus formation (Figure 12).

After pathological diagnosis, we have tried to determine the degree of matrix deposition and remodeling in bone surgical biopsies by morphometric analysis. We have used a calibration tool to transform the pixels into microns, with 0.42 μm/pixel in an 200× magnification image. Binary images were created and the bone fragments size was assessed by using the ImageJ software (imagej.nih.gov/ij/). Binary images of the corresponding HE-stained slides are presented in Figure 13 (a and b). The areas occupied by bone matrix as measured as absolute value, with an average of 0.7231518 μm², and as a ratio of the total area of the field, with values between 26% and 34%, which show increased bone matrix deposition in our case.

![Figure 1 - Microscopic image of bone spongy tissue with demineralized panes and hyperactive osteoclasts. HE staining, ×200.](image1)

![Figure 2 - Image of hyperactive osteoclasts (large sizes, abundant cytoplasm, numerous nuclei). Detail from previous figure. HE staining, ×400.](image2)
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Figure 3 – Strongly reshaped bone tissue, with a “mosaic” aspect, resulted from the destruction of the haversian bone and its replacement with bone panes of various shapes and sizes. HE staining, ×100.

Figure 4 – Reshaped areolar cavities, filled with fibrous conjunctive tissue. HE staining, ×200.

Figure 5 – Overall microscopic image of the reshaped bone area, with bone panes of different thickness and shapes, heterogeneously demineralized. HE staining, ×100.

Figure 6 – Heterogeneously demineralized bone panes, with hypertrophic osteocytes, with a low reaction of bone synthesis processes. HE staining, ×400.

Figure 7 – Initial Rx scan of the left upper third of the femur shows fracture with displacement of the bone segments that needed surgical treatment and suggestive signs of Paget’s disease of the bone.

Figure 8 – Rx scan of the upper third of the left femur after surgery.
Discussion

Paget’s disease of the bone is a relatively common condition, with benign evolution in most of the cases, although malignant transformation may occur. Most of the cases reported so far are polyostotic, affecting multiple bones, particularly the skull [26, 27], spine [27–30], and upper extremity [31, 32]. Although the femur is one of the most common sites of the disease, monostotic Paget’s disease cases of the femur are relatively rare, and can show no clinical and biological signs. In our case, the extension of the lesion almost to the entire bone has produced a pathological fracture big enough to warrant surgical treatment and biopsy, which was crucial for the diagnosis. Due to the fragility of the bones involved, biopsy is usually avoided, as it can cause serious morbidity and even fractures on the site of the biopsy. The mechanical fragility is due mainly to the mineralization defects in the bone, particularly in the newly formed one and in the cortical bone, although the increased plasticity of the pagetoid bone ensures some mechanical resistance [33].

Histological analysis of the bone in Paget’s disease found abnormal osteoclasts and bone marrow fibrosis [34], which is consistent with our findings; we have identified a high number of osteoclasts with 7–10 nuclei (they usually have 5–7 nuclei), which are known to be hyper-active (the number of the nuclei in the osteoclast correlates positively with its activity [35]). We have also identified enlarged bone cavities filled with connective tissue and a significant number of osteoprogenitor cells near the bone trabeculae. Mineralization of the bone trabeculae was uneven, with reverse cement lines easily visible on usual HE staining. Our histomorphometric study revealed higher values of the area occupied by bone matrix than other studies [16, 36] performed on Paget’s disease of the iliac crest and spine, respectively, which may be an explanation for these differences. Moreover, the fact that the patient had a fracture of the same bone may have determined this abnormal matrix deposition.

The treatment of Paget’s disease of the bone is mainly medical, with bisphosphonates as the cornerstone of the modern therapy, which produce pain relief, radiological healing and biochemical remission [37], zoledronic acid being widely used and recommended [38–40], even if it is unclear if it alters the natural history of the disease [41].

The main issue in this patient was the differential diagnosis of the newly diagnosed lesion of the lower half of the left femur between Paget’s disease of the bone and other primary tumor (osteosarcoma, Paget’s sarcoma) or a metastasis from a distant tumor. The patient had a
history of Paget’s disease of the same bone confirmed by biopsy, which is a strong argument in favor of this diagnosis. Combined with the highly suggestive CT scan aspect and the very low probability that a moderately differentiated colon carcinoma to metastasize in the lower half of the femur, all these overrule the possibility of a primary bone tumor or a metastasis. The evolution of the patient is favorable; he is alive and well three years after surgery for colon carcinoma and six years after surgery for pathological fracture of the femur.

Conclusions

Monostotic Paget’s disease of the femur is a relatively rare variant of the disease, frequently overlooked due to subtle clinical signs, lack of biological markers and to inconclusive radiological aspect. Rx and CT scans are useful for the diagnosis combined, while histological analysis is conclusive, but rarely performed due to complications. Surgical treatment is reserved only for fractures, nerve compressions and severe osteo-articular deformities. The histomorphometric analysis is a useful marker of the disease evolution and stage and may have a role in prognosis.

Conflict of interests

The authors declare that they have no conflict of interests.

Author contribution

Pompliu Horatiu Petrescu and Dragoș Andrei Izvernariu contributed equally to this work.

References


Tucci JR. Zoledronic acid therapy of patients with Paget disease of bone resistant to or with unsustained remission following prior bisphosphonate therapy. Endocr Pract, 2015, 21(10):1111–1116.


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