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First Case of Paget's Disease in the Kingdom of Bahrain: A Case Report

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ABSTRACT

Background: Paget's disease of bone is a disorder of bone remodeling, it can affect a single bone or multiple bones at the same time what is known as monostotic and polyostotic involvement respectively. The disease is of undetermined etiology and its prevalence increases with age with a slight predominance in males. It is most common among European countries and rare in the Middle East. No other cases were reported from Bahrain in local and international journals before.
Clinical presentation: we present a case of classic Paget's disease but unique to the region. This is a 48-year-old Yemeni male resigning in the Kingdom of Bahrain and presenting with localized hip pain and chronic back pain. He was promptly diagnosed via clinical picture, biochemical markers, and radiographic images. He was then given injections of zoledronic acid which showed dramatic improvement with excellent follow-up. Out of interest, during his recent follow up he complained of hematuria and found to have Nutcracker Syndrome.
Conclusion: Paget's disease indeed exists in Bahrain and should be considered in similar scenarios.

Keywords: Paget's disease, hip, zoledronic acid

INTRODUCTION

Paget disease of bone (PDB) is a localized disorder that is characterized by excessive osteoclastic bone resorption which is then compensated by an increase in osteoblastic bone formation, this leads to the formation of a structurally disorganized mosaic of bone (woven bone), although it is new, it is weak, wide, and highly vascular, making it more prone to pathological fractures, deformities, and complications as osteoarthritis [1].

Although any bone can be affected, Paget's disease has a predilection for the axial skeleton as the spine, pelvis, femur, sacrum, and skull [2]. After that, the disease may progress and get worse in the affected bone without spreading to adjacent bones [3].

Paget disease is more prevalent in older individuals with slight male predominance [4]. It is often diagnosed incidentally by elevated serum alkaline phosphatase (ALP), or abnormal X-ray for an unrelated condition [5].

The most common clinical presentations in symptomatic patients include bone pain, pathological fractures, and deformities. Complications may be local as malignant changes, osteoarthritis, and neurovascular compressions, or systemic like cardiac insufficiency [6].

There is a major geographical variation in the prevalence of PDB. Where it is most common in Western Europe and North America. Followed by Australia and New Zealand. Despite that, its occurrence among

Middle East countries is very low [7]. In the kingdom of Bahrain, the
prevalence of the disease is believed to be extremely rare. Through an extensive literature review, we found no reported cases in local journals.

This study aims to increase physicians' awareness in this region of this "rare" disease and to highlight its clinical presentation, diagnostic studies, potential misdiagnosis, and treatment modalities, contributing to the understanding of this condition and its implications for patient care.

CASE REPORT

This is a 48-year-old Yemeni patient residing in Bahrain with a known case of bronchial asthma and hyperlipidemia. He was referred to the rheumatology department in our hospital in 2023 for chronic lower back pain for 15 years and localized left hip pain for 1 year. The pain radiates to his left leg and is associated with numbness. History revealed no prior trauma, He reported no other joint pain, skeletal deformities, or fractures. Physical examination was remarkable for lumbar spine tenderness and the lasagne test was positive bilaterally. A neurological examination was conducted which showed no weakness, no saddle paraesthesia, and only mild numbness over the affected area. Radiological studies included an X-ray pelvis (figure 1) that showed coarse trabeculae of the left ischial bone. Laboratory investigations provided results

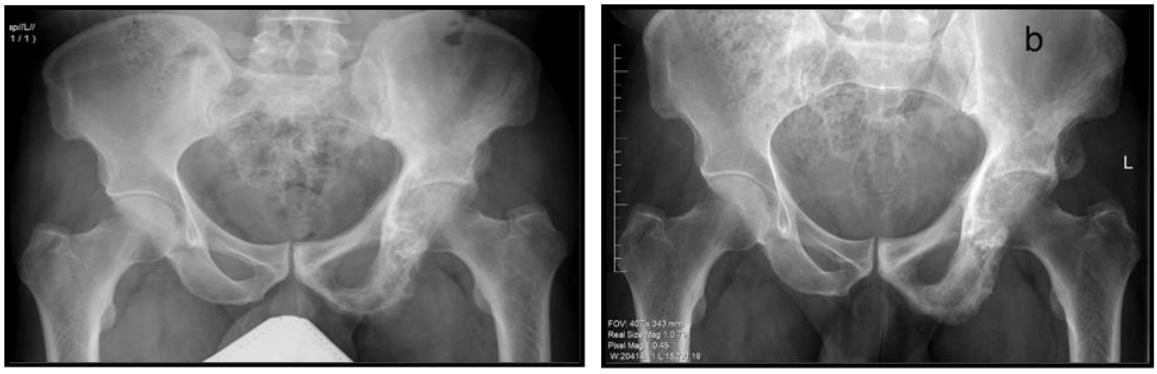

Figure 1- Plain radiograph of the pelvis showing thickening and sclerosis of the right ischiopubic ramus with cortical thickening, and thickening of the ilioischial line. Note the stability after two years (image b), which is consistent with Paget's disease of bones.

within the normal range except for a markedly elevated alkaline phosphatase (ALP) 212 U/L (normal range, 50-120 U/L) and the more specific bone marker procollagen type 1 N-terminal peptide 241 µg/l (normal range, 23.1-70.7µg/l). Consideration was given to the possibility of metabolic bone disease, metastases of undetermined origin, or parathyroid disorder and so investigations were done to rule them out which included serum calcium was 2.08 mmol/L (normal range, 2.1-2.60 mmol/L) and phosphate was 1.5 mmol/L (normal range, 0.8-1.45 mmol/L). Parathyroid hormone was normal at 7 ng/ dL (normal range, 15-65 ng/dL), and 25-OH vitamin D was 23 nmol/L (normal range, 22-116 nmol/L). Lastly, an MRI was done, and an impression of a case of probably Paget's disease, involving the left iliac wing, left acetabulum, and left ischial tuberosity, with extension in the left pubic tubercle (progressive disease). A bone scan revealed a diffuse intense uptake on delayed images with associated bony expansion which corresponds to PDB (figure 2), and then a biopsy was taken from it to further confirm the condition. And so, a diagnosis of Paget's disease of bone was established and the patient was started on zoledronic acid 4 mg injection over 6 months. 1 year follow-up, the patient significantly improved clinically, and his ALP dropped to 46 U/L (normal range, 50-120 U/L) (figure 3). But he complained of painless hematuria, and he

was referred to urology for a KUB CT scan and found to have Nutcracker Syndrome.

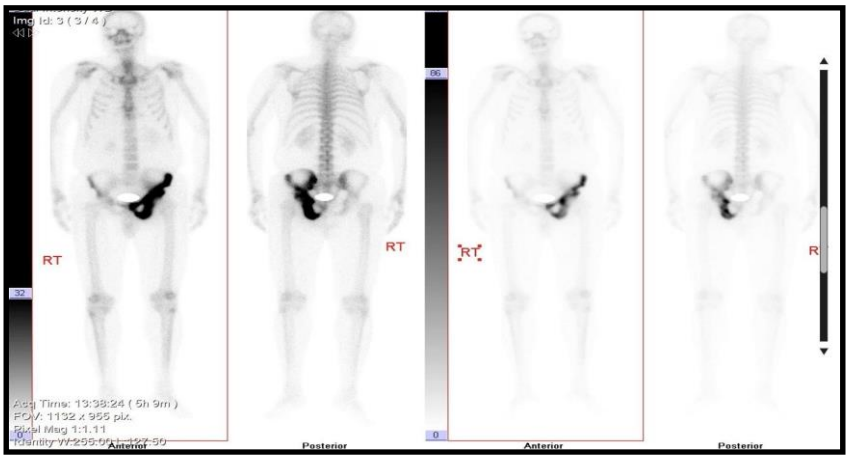

Figure 2- bone scan, after administration of 99mTC-HDP, shows intense and increased homogeneous radionuclide uptake in the right clavicle.

DISCUSSION

The 15-year delay in the diagnosis of our case is mostly attributed to the disease being rare in the region, as it is more common in European countries and where people of British descent[8]. This factor coupled with the age of our patient which is not in line with the typical age of presentation in Paget's disease prolonged the diagnosis process.

Although it is fairly uncommon in this region of the world, it is the second most common bone disorder after osteoporosis affecting 1–2% of adults over the age of 55 years [9]. A Retrospective Cohort Study of 3592 cases of Paget's disease in the UK between 1999 and 2015, showed that the prevalence increased with age. In women and men, respectively, the crude incidence increased from 0.037 and 0.074/10 000 population per year among those 45–49 years of age to 3.7 and 6.3/10 000 population per year among those ≥85 years [10].

PDB was first described as "osteitis deformans" By Sir James Paget, who published his findings in 1877 [11].

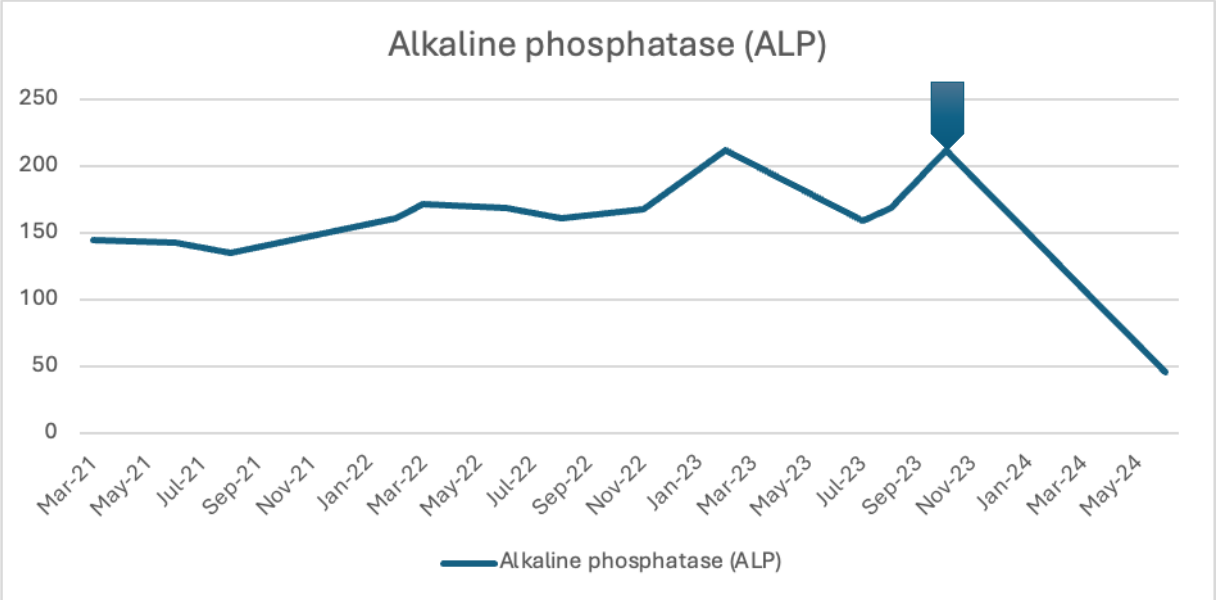

Figure 3- Serum ALP of the patient over the course of two years with dramatic decline of its level after receiving a single injection of zoledronic acid.

The exact cause of the disease is still unknown but it is believed to be multi-factorial as it is triggered by an environmental factor such as paramyxoviral infections in genetically predisposed individuals. To date, 7 loci have been associated with PDB, with SQSTM1 mutations found by Genome-wide association studies (GWAS) in 20-50% of the patients that tend to develop the disease at an earlier age and have more extensive illness than other patients [12]. However, our case did not exhibit any infectious or genetic background.

Paget's disease of bone is characterized by increased osteoclast activity that in turn increases bone resorption, which recruits osteoblasts and produces a new bone matrix. Disorganized bone tissues develop from rapid bone resorption and formation[13]. Clinically, Paget's bone can look completely normal if the changes are early or mild. However, in more advanced stages, the bone may become enlarged and significantly deformed. Areas where bone turnover is high like the tibia or skull may feel warm due to increased blood flow. While most patients do not experience symptoms, some may have issues related to bone involvement, such as bone pain, secondary arthritis, and traumatic or pathological fractures. Additionally, the expansion of the bone can lead to compression of nearby neural structures, causing further complications which could be sensory or motor deficits [14].

Due to the disease character being asymptomatic in most cases, many patients were diagnosed via persistently raised alkaline phosphatase levels found in routine laboratory tests. In a 2004 study of 4,406 individuals in the Netherlands, radiographic confirmation of Paget's disease was found in 20.5% of those with elevated alkaline phosphatase levels. In contrast, only 2.3% of patients with Paget's disease exhibited normal biochemical values. This highlights the significance of this specific laboratory finding in identifying Paget's disease in individuals over 50 [15]. ALP also provides good indices of disease activity and an immediate index of response to therapy as it is one of the markers of increased bone turnover which is expected in active disease. However, it is important to note that many patients with monostotic and, in some cases, polyostotic disease may exhibit a mild increase or even normal serum alkaline phosphatase [16].

In agreement with the literature, our work observed a higher frequency of monostotic disease in the left hip.

Plain radiographic imaging is sufficient to diagnose Paget's disease of bone showing the characteristic mixture of lysis along with sclerosis areas caused by osteoclasts and osteoblasts respectively [17].

A systemic review was conducted in the UK where they gave diagnostic recommendations for PDB which included that radionuclide bone scans, in addition to targeted radiographs, can be used to accurately identify the lesion's site and demonstrate the extent of the metabolic activity of the disease in patients with PDB [18]. These changes are usually characteristic, but occasionally other disorders need to be ruled out like sclerotic or lytic metastases [19]. The latter can be considered when there is involvement in new areas after years, or there are new radiographic findings that are not explained by PDB. This prompts a bone biopsy which is not typically necessary to diagnose Paget's disease of bone.

Bone scintigraphy using Tc-99m-MDP shows an area of intense radionuclide uptake coinciding with increased bone turnover is a more sensitive tool. A Brazilian study about the diagnosis of PDB demonstrated that bone scan is positive even before the earliest changes become apparent on plain radiography. Hence, about 10-15% of lesions identified by scintigraphy appear normal on plain radiographs. Comparing results from both methods, bone scintigraphy, and radiography show alterations 56 to 86% of the time, with 2-23% of the cases showing alterations only in the scintigrams, and 11-20% only in the radiographs. With treatment, the disease activity declines, and therefore

the uptake goes back to normal contradicting the plain X-ray findings thus both methods when combined enhance the accuracy of the diagnosis [20].

CT and MRI are limited to when complications of PDB are suspected, such as fractures or sarcomatous transformation [18].

The mainstay of treatment for Paget's disease of bone is to control the patient's symptoms and prevent or stop the disease progression and complications.

Bisphosphonates are the first-line treatment, effectively reducing bone turnover and alleviating pain. A systematic review of 20 studies done in the UK found moderate-quality evidence that bisphosphonates improved pain associated with PDB [21]. Also, a randomized trial of 502 subjects was conducted to study the efficacy of intensive versus symptomatic treatment. This showed favorable outcomes towards zoledronic acid which normalizes bone turnover in comparison to bisphosphonates which only provides symptomatic relief and thus improves the overall patient's quality of life [22]. Zoledronic acid is a third-generation nitrogen-containing bisphosphonate that transformed the treatment of Paget's disease by sustaining remission in patients with no contraindication to it. Our patient received an intravenous injection of 4mg zoledronic acid and showed marked clinical and biochemical improvement.

CONCLUSION

In conclusion, we have presented a typical case of Paget disease in a Bahraini resident in whom the diagnosis was not suspected primarily due to the global impression of the rarity of the disease in this region of the world. Although this study does not reflect the exact prevalence of the disease in society, it suggests that this disease should be considered as one of the differential diagnosis in patients with bone pain especially in elderly individuals, or those with mildly elevated ALP. Further research should be directed toward the pathophysiology and treatment options for a better understanding of the disease and so to enhance the patient's overall quality of life.

Declaration by Authors

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