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RETROSPECTIVE EVALUATION OF THE CLINICAL COURSE OF PAGET'S DISEASE OF BONE

KEMİĞİN PAGET HASTALIĞININ KLİNİK SEYRİNİN RETROSPEKTİF OLARAK DEĞERLENDİRİLMESİ

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ABSTRACT

Objective: Paget's disease of bone (PDB) is a focal, chronic, metabolic disorder of bones and causes complications such as bone deformity, fractures, and heart failure. This study aimed to evaluate the clinical characteristics of patients with PDB and patients' responses to antiresorptive treatments.

Material and Methods: In the study, we retrospectively evaluated the medical records of patients who were followed up with PDB at the Istanbul Faculty of Medicine and treated with antiresorptive therapy.

Results: A total of 26 patients (12 females/14 males) with PDB were evaluated. The mean age at diagnosis was 62.9±13.5 years. The median time from the onset of symptoms to diagnosis was 17.5 months (range 1-480). The symptoms were as follows: pain in 16, swelling in 3, rubor in 2, bone fracture in 1, nephrolithiasis in 1, and hearing loss in 1 patient. Laboratory tests revealed the following results (mean±SD); Alkaline phosphatase (ALP) 512±557 U/L, bone-specific ALP 81.2±51.4 µg/L, and the mean ALP was 4.12±4 times of upper limit of the normal range. The distribution of the disease was as follows: pelvis in 58%, vertebra in 46%, skull in 35%, femur in 23%, tibia in 11.5%, humerus in 3.8% of the patients. Of 26 patients, 21 were treated with zoledronic acid alone. Relapse occurred in four patients; the mean duration from therapy to relapse was 72.25±28.7 months.

Conclusion: Zoledronic acid is a very potent antiresorptive drug and provides long-term remission of the disease even with a single dose of therapy.

Keywords: Paget's disease of bone, zoledronic acid, alkaline phosphatase

ÖZ

Amaç: Kemiğin Paget hastalığı (KPH), fokal, kronik, metabolik bir kemik hastalığıdır ve kemik deformitesi, kırıklar ve kalp yetmezliği gibi komplikasyonlara neden olur. Bu çalışma, KPH hastalarının klinik özelliklerini ve hastaların antiresorptif tedavilere yanıtlarını değerlendirmeyi amaçladı.

Gereç ve Yöntemler: Bu çalışmada İstanbul Tıp Fakültesi'nde KPH tanısı ile takip edilen ve antirezorptif tedavi uygulanan hastaların tıbbi kayıtları retrospektif olarak değerlendirildi.

Bulgular: KPH olan toplam 26 hasta (12 kadın/14 erkek) değerlendirildi. Ortalama tanı yaşı 62.9±13.5 idi. Semptomların başlangıcından tanıya kadar geçen medyan süre 17.5 aydı (1-480 arası). Belirtilerden ağrı 16 hastada, şişlik 3 hastada, kızarıklık 2 hastada, kırık 1 hastada, nefrolitiazis 1 hastada, işitme kaybı 1 hastada mevcuttu. Laboratuvar incelemesinde ortalama alkalen fosfataz (ALP) 512±557 U/L, kemiğe özgü ALP 81.2±51.4 µg/L ve ALP üst limitin 4.12±4 katı idi. Hastalığın tutulum yerleri %58 pelvis, %46 vertebra, %35 kafatası, %23 femur, %11.5 tibia, %3.8 humerus şeklinde idi. Toplam 26 hastanın 21'i tek başına zoledronik asit ile tedavi edilmişti. Dört hastada nüks meydana geldi ve tedaviden nükse kadar geçen ortalama süre 72.25±28.7 aydı.

Sonuç: Zoledronik asit çok güçlü bir antirezorptif ilaçtır ve tek doz tedavi ile bile hastalığın uzun süreli remisyonunu sağlar.

Anahtar Kelimeler: Kemiğin Paget hastalığı, zoledronik asit, alkalen fosfataz

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INTRODUCTION

Paget's disease of bone (PDB) is a focal and chronic disorder of bones. It is characterized by increased bone resorption by osteoclast and followed by accelerated osteoblast activity, bone remodeling, and overgrowth (1). The disease may occur in a single site (monostotic) or multiple sites (polyostotic). The most affected sites include the pelvis, spine, femur, tibia, and skull. The prevalence of the disease is higher in the UK and in countries where the British population has migrated, such as the United States. The prevalence is 1-2% in the United States, but it is declining (2,3). It is rare for Paget's disease of bone to present before the age of 50, and it is seen equally in men and women however, some studies have reported that it is more common in men (4-6).

Although the exact cause is not known, genetic factors and environmental factors such as a slow virus infection are involved in the development of the Paget disease The majority of patients are sporadic (7). The most important gene responsible for the disease is the SQSTM1 (8,9).

Most of the patients are asymptomatic and they are diagnosed during the evaluation of incidentally detected lesions or elevated serum alkaline phosphatase (ALP) levels. Pain and deformity are two important clinical manifestations. Complications related to Paget's disease include heart failure, deformity, hearing loss, bone fracture, nerve compression, and sarcoma.

The diagnosis of PDB is made by clinical features, and typical findings of the disease in radiological and scintigraphic examination. In laboratory analysis bone turnover markers including ALP, bone-specific ALP (BALP), procollagen type 1 N-terminal propeptide (P1NP), serum C-telopeptide (CTx), and urinary N-telopeptide (NTx) are frequently elevated. If there are typical findings in radiographs, scintigraphy is taken to evaluate the extent of the disease. Computerized tomography (CT) or magnetic resonance imaging (MRI) is used to evaluate suspicious lesions. Treatment options for PDB include calcitonin, bisphosphonates, and denosumab. Current guidelines recommend a single dose of 5 mg intravenous zoledronic acid if there is no contraindication for use (10,11). Although the response to treatment is different, it was shown that a single dose of zoledronic acid provided remission for 5-6 years (12).

This study aimed to evaluate the clinical characteristics of patients with PDB and patients' responses to the treatments.

MATERIAL and METHODS

In the study, we retrospectively evaluated medical records of patients who were followed up with the diagnosis of PDB and treated with antiresorptive therapy in the Department of Endocrinology and Metabolic Diseases of Istanbul Faculty of Medicine between 1980 and 2023.

Clinical and demographic features of patients, age, gender, family history, symptoms, duration from symptom onset to diagnosis, disease involvement, distribution of disease on bone scintigraphy, and additional imaging methods for diagnosis were evaluated. Before the treatment serum levels of creatinine, adjusted calcium, phosphorus, albumin, magnesium, parathyroid hormone (PTH), 25 OH vitamin D, total serum ALP, and BALP were analyzed. ALP level was expressed as the upper limit of the normal range (ULNR).

Patients' responses to treatment, duration of remission and time to relapse, and major side effects related to treatment were assessed in patients who were treated with only zoledronic acid for PDB.

Remission was defined as the normalization of ALP or BALP. If ALP was normal before the therapy, BALP was monitored to assess the patient's responses to therapy. Relapse was defined as the elevation of ALP (or BALP) above the normal range or increased by more than 25% from the nadir ALP value in patients who did not achieve ALP normalization.

The study protocol was approved by the Clinical Ethics Committee of Istanbul University, Istanbul Faculty of Medicine (Date: 21.07.2023, No: 15). Written informed consent was waived due to the nature of this retrospective study. Statistical analyses were performed using SPSS version 21.0. Categorical variables were presented as percentage and frequency, whereas numerical variables were presented as mean±standard deviation (SD).

RESULTS

In this study, a total of 26 patients with Paget's disease of bone were evaluated. There were 12 females and 14 males, male/female ratio was 1.17. The mean age at diagnosis was 62.9±13.5 years (median 65.5, range 33-84). The mean age of the females was 70±10.9 years (median 71.5, range 53-84), and the mean age of the males was 56.6±12.6 years (median 58.5 range 33-72).

The median duration from the onset of symptoms to diagnosis was 17.5 months (range 1-480). The symptoms were as follows: pain in 16 (61.5%), swelling in 3 (11.5%), rubor in 2 (7.7%), bone fracture in 1 (3.8%), nephrolithiasis in 1 (3.8%), and hearing loss in 1 (3.8%) patient. The diagnosis of PDB was made during the evaluation of elevated ALP levels in 3 asymptomatic patients. In one patient, pagetic lesions were detected in cranial computed tomography performed to evaluate post-accident head trauma. Two patients had similarly affected siblings and both of them were involved in this study. These two patients were diagnosed by family screening for PDB.

Laboratory tests revealed the following results (mean±SD): Plasma creatinine 0.89±0.24 mg/dL (normal range 0.7-1.4), GFR 82.1±19.4, phosphorus 3.6±0.45 mg/dl (normal range 2.7- 4.5), adjusted calcium 9.3±0.45 mg/dL (normal range 8.5-10.5), PTH 55.6±24 pg/ml (normal range 15-65), 25 OH D 34±30 ng/mL (normal range 30-80), ALP 512±557 U/L (median 296, range 70-2339) (normal range 40-120), BALP 81.2±51.4 µg/L (median 63, normal range 4-22). The mean ALP was 4.12±4 ULNR (median 2.6 range 1.01-16.5).

Table 1: Distribution of bone involvement of Paget's disease on scintigraphy imaging

Localization	Number of patients
Skull	9
Vertebra	12
Servical	1
Dorsal	7
Lomber	9
Sacrum	5
Humerus	1
Right	1
Scapula	2
Right	1
Left	1
Pelvis	15
Right	6
Left	12
Femur	6
Right	4
Left	5
Tibia	3
Right	1
Left	2

Bone scintigraphy was performed to determine the extent of the disease in all patients at initial evaluation. The distribution of the disease was; pelvis in 15 patients (15/26, 58%), vertebra in 12 patients (12/26, 46%), skull in 9 patients (9/26, 35%), femur in 6 patients (6/26, 23%), tibia in 3 patients (3/26, 11.5%), scapula in 2 patients (2/26, 7.7%), humerus in 1 patient (1/26, 3.8%). The distribution of PDB is summarized in Table 1. Eleven patients (42.3%) had polyostotic disease (7 females, 4 males). We performed bone biopsies on 3 patients to confirm the diagnosis due to suspicious lesions.

Of 26 patients, 21 were treated with zoledronic acid alone, and 3 patients were treated with pamidronate followed by zoledronic acid. The remaining two patients were treated with pamidronate or ibandronate. The patients treated with only zoledronic acid for PDB were evaluated for the efficiency of therapy. The mean duration from therapy to normalization of ALP was 4.37±3.6 months (range 1-13). The nadir ALP level was 64.76±19.21 and achieved after 17.3±12.9 months (median 13). The mean duration of follow-up was 53.4±38.3 months after zoledronic acid therapy. Fourteen patients were in remission after a single dose of zoledronic acid and the mean duration of follow-up was 51.3±30.6 months. We could not assess remission because of the short follow-up time in Case 5 and Case 20 (Table 2). In 1 patient (Case 6), the ALP value decreased

Table 2: Baseline characteristics and treatment responses of patients treated with zoledronic acid

	Gender	Age at diagnosis	ALP	ALP (ULNR)	BALP	Distribution of disease	Duration of followed up (month)	Presence of remission/relapse
Case 1	M	62	107	*	25	Monostotic	69	Remission
Case 2	F	73	338	2.75	123	Polyostotic	24	Remission
Case 3	F	54	292	2.78	75	Monostotic	66	Relapse
Case 4	M	67	245	1.88	163	Monostotic	60	Remission
Case 5	M	72	459	3.53	51	Monostotic	3	**
Case 6	F	70	1740	16.5	>90	Polyostotic	12	***
Case 7	F	64	202	1.94	46.9	Polyostotic	43	Remission
Case 8	M	52	403	3.1	>90	Monostotic	33	Remission
Case 9	F	58	183	1.74	56	Monostotic	54	Remission
Case 10	M	33	131	1.01	32	Monostotic	14	Remission
Case 11	M	58	337	2.59	84	Polyostotic	64	Remission
Case 12	F	84	70	*	20	Monostotic	36	Remission
Case 13	F	53	667	5.13	>90	Polyostotic	104	Remission
Case 14	F	75	613	5.8	NA	Polyostotic	93	Relapse
Case 15	M	59	504	3.87	>90	Polyostotic	93	Relapse
Case 16	M	47	296	2.27	>90	Monostotic	108	Remission
Case 17	M	41	195	1.5	59,9	Polyostotic	8	Remission
Case 18	F	68	281	2.18	178	Monostotic	133	Relapse
Case 19	M	46	139	1.1	37	Monostotic	50	Remission
Case 20	F	84	1232	11.7	>90	Polyostotic	1	**
Case 21	M	71	213	1.63	68	Monostotic	18	Remission

NA: Not available, ALP: Alkaline phosphatase (normal range 40-120 U/L), ULNR: Upper limit of the normal range, BALP: Bone specific Alkaline phosphatase (normal range 4-22 µg/L), * It was not calculated because of ALP value was normal, **Short follow-up time limited to assess remission, ***The decline of ALP was not enough to define remission.

significantly from 1740 to 169 U/L in the first year after zoledronic acid therapy, although it was above the upper limit of normal. Relapse occurred in four patients; the mean duration from therapy to relapse was 72.25±28.7 months (range 30-94). The characteristics of the patients and patient's responses to zoledronic acid therapy were summarized in Table 2.

Bisphosphonate-related major side effects were not present in the patients treated with zoledronic acid. However, osteonecrosis of the jaws occurred in 1 patient who was treated with ibandronate. PDB-related complications were as follows: hearing loss in 6 patients, nerve compression in 3 patients, and bone fracture in 1 patient. Bone malignancy did not occur in any of the patients.

DISCUSSION

In this study, we reviewed patients' demographic and clinical features and also assessed the effect of a single dose of zoledronic acid in the treatment of PDB. PDB is more common in people over the age of 55 years, it rarely presents before age 40. The mean age of our study group is compatible with the literature, however, seven patients were younger than 55 years at diagnosis and one of them was 33 years old. The male/female ratio was 1.17, and as in similar studies, there was a small male predominance (2).

Most patients with PDB are asymptomatic, but in our study, the majority of patients were symptomatic, and only five patients were asymptomatic (10). Bone pain is one of the most common clinical manifestations. In the study of Tan et al., it was reported in 73.8% of patients. Similarly, the most common symptom in our study was pain and it was present in 61.5% of the patients (13).

The pelvis is reported to be the most common site of involvement in PDB. In the study of Guyer et al., pelvis involvement was present in 74-76% of the patients and there was a tendency to the involvement of the right side. Similarly, the most common site of involvement was the pelvis in our study. However, left-side involvement was more common than right (14).

Multiple genetic loci associated with PDB have been identified and the inheritance of the disease seems to be autosomal dominant. The most important gen is SQSTM1. It encodes a protein which is called p62 and has a role in the activation of the transcription factor NF-κB (15,16). There were siblings from two different families in the present study, but the genetic analysis could not be performed.

Treatment is recommended in patients with active PDB to prevent the development of complications. Treatment options include three antiresorptive groups: bisphosphonates, denosumab, and calcitonin. Recommended bisphosphonates are zoledronic acid, pamidronate, and oral bisphosphonates such as alendronate, and risedronate. First-choice treatment is zoledronic acid because it is the most potent agent (10,11). It was reported that a single dose provided biochemical remission in 96% of patients with PDB and the duration of remission was longer than 5 years (12,17). Relapse developed in 4 of 21 patients treated with a single dose of zoledronic acid. Similar to the studies in the literature, the time from zoledronic acid treatment to relapse was longer than 5 years in our study.

CONCLUSION

PDB is a common metabolic bone disorder that causes complications and has a negative long-term physical impact. Zoledronic acid improves symptoms and prevents complications. It is a potent antiresorptive agent and provides long-term remission as shown in our study

Ethics Committee Approval: This study was approved by Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 21.07.2023, No: 15).

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REFERENCES

1- Meunier PJ, Coindre JM, Edouard CM, Arlot ME. Bone histomorphometry in Paget's disease. Quantitative and dynamic analysis of pagetic and nonpagetic bone tissue. Arthritis Rheum 1980;23(10):1095-103.

2- Altman RD, Bloch DA, Hochberg MC, Murphy WA. Prevalence of pelvic Paget's disease of bone in the United States. J Bone Miner Res 2000;15(3):461-5.

3- Husseini JS, Oganesyan R, Staffa SJ, Huang E, Habibollahi S, Hemke R, et al. Prevalence of Paget's disease of bone: review of consecutive abdominopelvic CT scans and literature. Acta Radiol 2023;64(3):1086-92.

4- Cook MJ, Pye SR, Lunt M, Dixon WG, Ashcroft DM, O'Neill TW. Incidence of Paget's disease of bone in the UK: evidence of a continuing decline. Rheumatology (Oxford) 2021;60(12):5668-76.

5- Mays S. Archaeological skeletons support a northwest European origin for Paget's disease of bone. J Bone Miner Res 2010;25(8):1839-41.

6- Guañabens N, Garrido J, Gobbo M, Piga AM, del Pino J, Torrijos A, et al. Prevalence of Paget's disease of bone in Spain. Bone 2008;43(6):1006-9.

7- Reddy SV, Singer FR, Roodman GD. Bone marrow mononuclear cells from patients with Paget's disease contain measles virus nucleocapsid messenger ribonucleic acid that has mutations in a specific region of the sequence. J Clin Endocrinol Metab 1995;80(7):2108-11.

8- Hocking LJ, Herbert CA, Nicholls RK, Williams F, Bennett ST, Cundy T, et al. Genomewide search in familial Paget disease of bone shows evidence of genetic heterogeneity with candidate loci on chromosomes 2q36, 10p13, and 5q35. Am J Hum Genet 2001;69(5):1055-61.

9- Cronin O, Subedi D, Forsyth L, Goodman K, Lewis SC, Keerie C, et al. Characteristics of early Paget's disease in SQSTM1 mutation carriers: Baseline analysis of the ZiPP study cohort. J Bone Miner Res 2020;35(7):1246-52.

10- Singer FR, Bone HG 3rd, Hosking DJ, Lyles KW, Murad MH, Reid IR et al. Endocrine Society. Paget's disease of bone: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2014;99(12):4408-22.

11- Ralston SH, Corral-Gudino L, Cooper C, Francis RM, Fraser WD, Gennari L, et al. Diagnosis and Management of Paget's Disease of Bone in Adults: A Clinical Guideline. J Bone Miner Res 2019;34(4):579-604.

12- Reid IR, Lyles K, Su G, Brown JP, Walsh JP, del Pino-Montes J, el al. A single infusion of zoledronic acid produces sustained remissions in Paget disease: Data to 6.5 years. J Bone Miner Res 2011;26(9):2261-70.

13- Tan A, Ralston SH. Clinical presentation of Paget's disease: evaluation of a contemporary cohort and systematic review. Calcif Tissue Int 2014;95(5):385-92.

14- Guyer PB. Paget's disease of bone: the anatomical distribution. Metab Bone Dis Relat Res 1981;3(4-5):239-41.

15- Hocking LJ, Lucas GJ, Daroszewska A, Mangion J, Olavesen M, Cundy T, et al. Domain specific mutations in Sequestosome 1 (SQSTM1) cause familial and sporadic Paget's disease. Hum Mol Genet 2002;11(22):2735-9.

16- Moscat J, Diaz-Meco MT. p62 at the crossroads of autophagy, apoptosis, and cancer. Cell 2009;137(6):1001-4.

17- Reid IR, Miller P, Lyles K, Fraser W, Brown JP, Saidi Y, et al. Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. N Engl J Med 2005;353(9):898-908.