CASE REPORT

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Denosumab Experience in a Patient with End-Stage Renal Disease and Paget's Disease of the Bone

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ABSTRACT Paget's disease of the bone (PDB) is a chronic bone disease which is characterized by accelerated bone turnover and disorganized bone remodeling. Diagnosis and treatment of PDB is particularly challenging in patients with chronic kidney disease (CKD). Denosumab administered subcutaneously at a single dose of 60 mg every 3 months reduced both serum total and bone-specific alkaline phosphatase (ALP) levels to near normal range in a 47-year-old male with CKD was suspected of having PDB due to very high serum total ALP levels and imaging findings suggestive of poliostotic involvement. Elevated serum total ALP levels detected at 3 months after denosumab suggests that serum total ALP starts to increase after 60 days of treatment but it is difficult to exactly determine the day when serum total ALP started to increase. It seems wise to administer denosumab at an interval of 60-120 days to maintain serum total ALP level within normal limits.

Keywords: Chronic kidney disease; Paget's disease of the bone; denosumab; hypocalcemia

Paget's disease of the bone (PDB), is a chronic bone disease involving one or more bones locally which is characterized by increased bone turnover and disorganized bone remodeling.[1] Although PDB can affect almost all bones, the skull, pelvis, sacrum, vertebra, femur, tibia, humerus and clavicle bones are most commonly involved.[1,2]

In general, PDB is discovered incidentally when an elevated serum total alkaline phosphatase (ALP) is detected and diagnosed based on typical radiological imaging findings in patients presenting with bone and joint pain.[3,4] Increased serum total ALP is used both for the diagnosis of the disease and to monitor disease activity and response to treatment.[5]

Bisphosphonates are the first-line treatment for PDB and are highly effective. Bisphosphonates reduce pain and slow bone turnover.[5] Recently, case reports have been published, showing good results with denosumab, a human monoclonal antibody that binds to the receptor activator of nuclear factor kappa-B ligand in a number of PDB patients who were deemed unsuitable for treatment with bisphosphonates due to comorbidities such as renal failure, atrial fibrillation or advanced age.[6-8]

Here, we present our experience with denosumab in a patient with end-stage chronic renal failure who was subsequently diagnosed with PDB.

CASE REPORT

A 47-year-old male patient with chronic kidney disease (CKD) undergoing hemodialysis 3 days a week presented to our outpatient clinic with complaints of severe pain in his joints and bones. On physical examination, he seemed uremic and unusually pale. His height was 165 cm, body weight was 75 kg, arterial blood pressure was 140/90 mmHg and body mass index was 27.5 kg/m^2. An arteriovenous fistula was present in his left antecubital region, which was created for use in hemodialysis. His current medications were calcium acetate (3x1, 400 mg/day), metoprolol (50 mg tb 1x1) and acetyl salicyclic acid (100 mg tb 1x1).

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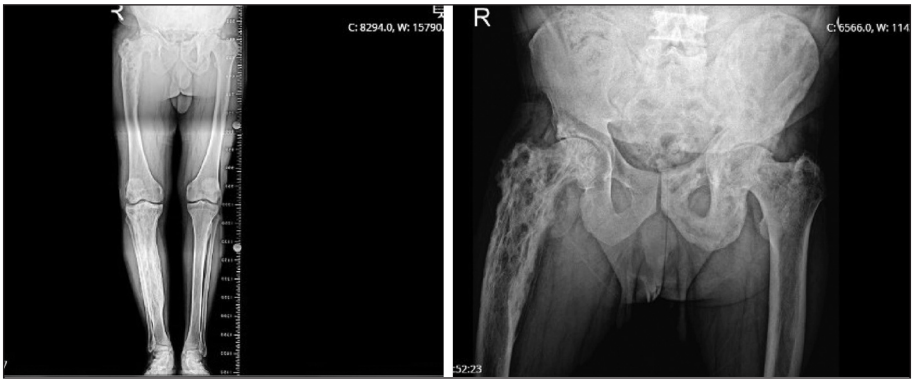

FIGURE 1: a) Plain X-ray view of the lower limbs. b) X-ray view of the pelvis and proximal femur.

Laboratory workup showed the following results: Calcium (Ca): 9.3 mg/dL, Phosphorous: 5.5 mg/dL, albumin: 4.3 g/dL, parathyroid hormone: 501 pg/mL, serum total alkaline phosphatase (ALP): 1,693 IU/L (40-129), bone-specific ALP: 244 mcg/L (3.7-20.9), urea: 82 mg/dL, creatinine: 6.6 mg/dL, Sodium: 143 mmol/L, Potassium: 5.2 mmol/L, alanine transaminase: 19 IU/L, aspartate transaminase: 23 IU/L, gamma-glutamyltransferase: 36 IU/L, thyroid-stimulating hormone: 1.1 mIU/L, hemoglobin: 13.8 g/dL, white blood cell: 7,000/ uL, platelets: 345,000/uL, 25-hydroxyvitamin D_3: 34 ng/mL.

ASSESSMENTS

Plain Radiographs: Bilateral bone deformities, mixed osteolytic-osteosclerotic areas, loss of corticomedullary differentiation, trabecular thickening and irregular bone expansion were observed particularly in the left iliac bone, right femur and tibia (Figure 1a, 1b).

Bone Scintigraphy: Areas of increased activity detected in the calvarium, left hemipelvis, left femur trochanter major, right femur and right tibia were suggestive of involvement of multiple sites (Figure 2).

Dual-energy X-ray absorptiometry: L1-L4 T-score was-1.7 and total femur T-score was 0.9.

Clinical Follow-up: Poliostotic PDB was considered because of very high serum levels of total and bone-specific ALP for this patient who was receiving hemodialysis treatment on a regular basis for CKD. Direct radiographs, bone magnetic resonance imaging (MRI) and bone scintigraphy findings supported the diagnosis of PDB.

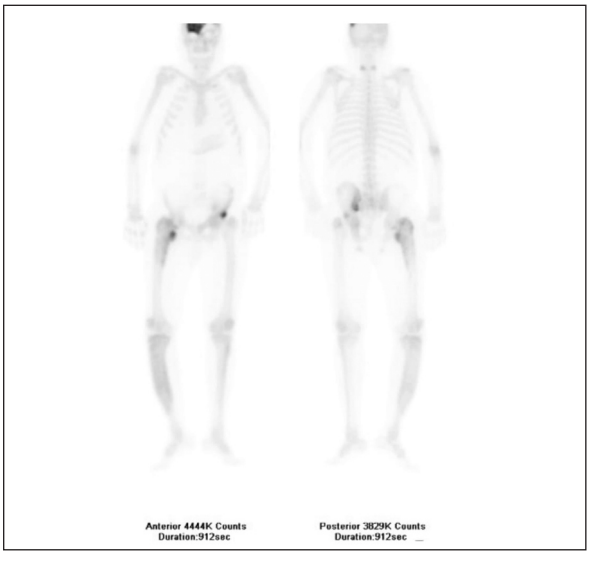

FIGURE 2: Bone scintigraphy.

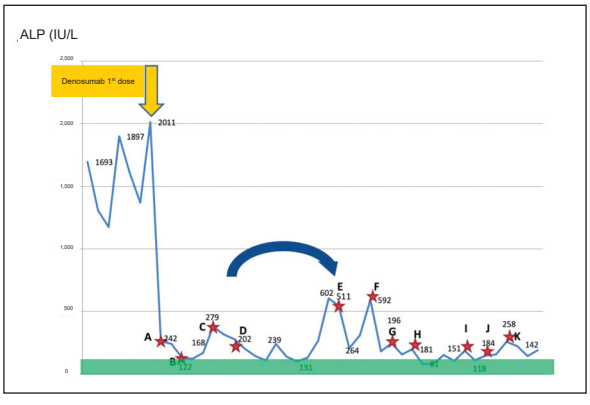

FIGURE 3: Changes in serum total ALP levels at denosumab dosage intervals.

TABLE 1: Follow-up levels of bone-specific ALP.

Date	Bone-Specific ALP (mcg/L)*
24.4.2015	244
20.7.2016	124
7.12.2016	24.3
12.7.2019	14

* Reference range for bone-specific ALP=3.7-20.9 mcg/L; ALP: Alkaline phosphatase.

Since the patient was unable to receive bisphosphonate therapy due to CKD, denosumab was initiated at a dose of 60 mg subcutaneously. At the follow-up visit one week after denosumab administration, the patient reported general weakness, which was worse in the lower extremities. His calcium level measured at the time of that visit was 6.4 mg/dL. Calcium supplementation was given and once weekly intravenous calcitriol was started by his dialysis physician. During the follow-up visits, although calcium levels were not as high as after the first dose, the patient was started on dialysis with a high calcium dialysate (Ca: 1.75 mmol/L) since his post-dialysis Ca levels fell down to 7.9-8.2 mg/dL. Dangerously low calcium levels were not detected thereafter.

While a marked reduction occurred in serum total ALP levels after the initial dose of denosumab, serum total ALP elevations were observed when denosumab could not be given (Figure 3).

The bone-specific ALP level of the patient obtained at the time of diagnosis was quite high and found to be reduced on occasional repeat measurements compared to baseline during the treatment periods (Table 1).

In Türkiye, denosumab is not routinely covered by the national health insurance system for the treatment of PDB and "consent for off-label use" is required by the Turkish Ministry of Health for its reimbursement. In this patient, elevations in serum total ALP levels up to 500-600 mcg/L were seen when denosumab could not be administered due to difficulty in accessing the drug. At the end of 2-year treatment with denosumab, serum total ALP levels decreased to 81 mcg/L. Denosumab treatment was interrupted at that timepoint and serum total ALP level was followed on a monthly basis. Three months after withdrawal of the drug, serum total ALP levels were found to increase again. The patient currently receives denosumab treatment every 3 months and his follow-up serum total ALP levels are close to normal range.

Written informed consent was obtained from the patient to publish his case (including case history, data and images).

DISCUSSION

It is challenging to differentiate PDB from CKD-related mineral and bone disease (MBD) since CKD-MBD may have phases with high or low bone turnover. Bone biopsy, the gold standard method used for the differential diagnosis of these two conditions, is no longer recommended by the 2017 The Kidney Disease: Improving Global Outcomes guidelines due to its invasive nature.[9] Therefore, we considered the diagnosis of poliostotic PDB for our patient based on very high serum total ALP and bone-specific ALP values and images from direct radiographs, bone MRI and bone scintigraphy which were consistent with PDB. The patient was started on denosumab because he was not suitable for bisphosphonate treatment due to the presence of Stage V CKD.

Hypocalcemia is a recognized side effect of denosumab. It has been stated that denosumab is liable to cause severe hypocalcemia especially in patients with renal dysfunction.[10,11] Similarly, severe hypocalcemia developed in our patient following the initial denosumab dose, which was managed by corrective measures including calcium supplementation during subsequent administrations and using a high calcium dialysate in hemodialysis sessions.

In our patient, serum total ALP showed an initial reduction after denosumab administration, followed by a resurge after about 2 months. Monthly follow-up of serum total ALP level was performed for the patient and therefore, it was not possible to exactly determine the day when serum total ALP started to increase. We considered that this peculiarity observed on clinical follow-up is noteworthy. For this reason, efforts were made to give deno-

sumab treatment every 3 months. Looking at the relevant literature data, as with denosumab therapy, elevations in serum total ALP levels were reported to also occur after 3 months of bisphosphonate treatment.[12] In some cases, denosumab was administered as a single 60 mg dose every 6 months for the treatment of PDB.[7,8] The guidelines recommend that serum total ALP level be kept within normal range in order to achieve remission in PDB.[5] Thus, it seems to be more appropriate to administer denosumab at an interval of 60-120 days to maintain serum total ALP level in the normal range.

Denosumab is an effective and safe therapeutic option in PDB patients with CKD. However, caution is advised to minimize the risk of hypocalcemia following denosumab administration. In addition, it seems plausible to administer denosumab at a frequency of 60-120 days to maintain serum total ALP level within the normal reference range.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Gülşah Elbüken;* ***Design:*** *Gülşah Elbüken;* ***Control/Supervision:*** *Gülşah Elbüken;* ***Data Collection and/or Processing:*** *Ogün İrem Bilen, Hünkar Ağgül;* ***Analysis and/or Interpretation:*** *Ogün İrem Bilen, Gülşah Elbüken;* ***Literature Review:*** *Ogün İrem Bilen, Hünkar Ağgül;* ***Writing the Article:*** *Ogün İrem Bilen, Gülşah Elbüken;* ***Critical Review:*** *Gülşah Elbüken;* ***References and Fundings:*** *Gülşah Elbüken;* ***Materials:*** *Ogün İrem Bilen.*

REFERENCES

1. Corral-Gudino L, Borao-Cengotita-Bengoa M, Del Pino-Montes J, Ralston S. Epidemiology of Paget's disease of bone: a systematic review and meta-analysis of secular changes. Bone. 2013;55(2):347-52. [Crossref] [PubMed]
2. Davie M, Davies M, Francis R, Fraser W, Hosking D, Tansley R. Paget's disease of bone: a review of 889 patients. Bone. 1999;24(5 Suppl):11S-12S. [Crossref] [PubMed]
3. Cundy T. Paget's disease of bone. Metabolism. 2018;80:5-14. [Crossref] [PubMed]
4. Appelman-Dijkstra NM, Papapoulos SE. Paget's disease of bone. Best Pract Res Clin Endocrinol Metab. 2018;32(5):657-68. [Crossref] [PubMed]
5. 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. [Crossref] [PubMed] [PMC]
6. Reid IR, Sharma S, Kalluru R, Eagleton C. Treatment of Paget's disease of bone with denosumab: case report and literature review. Calcif Tissue Int. 2016;99(3):322-5. [Crossref] [PubMed]
7. Schwarz P, Rasmussen AQ, Kvist TM, Andersen UB, Jørgensen NR. Paget's disease of the bone after treatment with Denosumab: a case report. Bone. 2012;50(5):1023-5. [Crossref] [PubMed]
8. Kuthiah N, Er C. Effective treatment of Paget's disease of the bone in a Chinese woman. Ann Acad Med Singap. 2018;47(12):528-30. [PubMed]
9. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2017;1-59. [Crossref]
10. Jalleh R, Basu G, Le Leu R, Jesudason S. Denosumab-induced severe hypocalcaemia in chronic kidney disease. Case Rep Nephrol. 2018;2018:7384763. [Crossref] [PubMed] [PMC]
11. Gopaul A, Kanagalingam T, Thain J, Khan T, Cowan A, Sultan N, et al. Denosumab in chronic kidney disease: a narrative review of treatment efficacy and safety. Arch Osteoporos. 2021;16(1):116. [Crossref] [PubMed]
12. Panuccio VA, Tripepi R. Paget's disease and secondary hyperparathyroidism: ıs healing possible? Front Cell Dev Biol. 2020;8:399. [Crossref] [PubMed] [PMC]