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Case Report

Amelioration of Paget Disease of Bone After Denosumab for Osteopenia

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ABSTRACT

Background/Objective: Denosumab is a monoclonal antibody that inhibits bone resorption and is indicated for the treatment of osteoporosis, bone metastases, and giant cell tumor of bone. We describe a woman with symptomatic Paget disease of the skull whose headaches and monostotic disease of the skull improved after receiving denosumab for concomitant low bone density.
Case Report: A 75-year-old woman presented with unremitting headache of 1 month. She had a medical history of polymyalgia rheumatica, osteopenia, hypothyroidism, and gastroesophageal reflux disease. She reported taking prednisone 1 to 20 mg daily for polymyalgia rheumatica for 1 year and received a dose of denosumab 60 mg for osteopenia 1 month before presentation. The calcium, alkaline phosphatase, and bone-specific alkaline phosphatase levels were 8.2 mg/dL (reference range [RR], 8.5-10.5 mg/dL), 132 U/L (RR, 40-129 U/L), and 17.8 μg/L (RR, 7-22.4 μg/L), respectively. Skull radiography revealed sclerosis/hyperostosis, lytic lesions, and expansion of bone, consistent with Paget disease of bone (PDB). Five months after the initial presentation, her headache resolved, and her calcium and alkaline phosphatase levels were 9.7 U/L and 96 U/L, respectively.
Discussion: Denosumab neutralizes the receptor activator of nuclear factor-kappa B ligand. To date, there have been 2 case reports reported in the English literature of denosumab used successfully in patients with PDB who could not tolerate or were not eligible for bisphosphonates. This case report describes a patient with PDB treated with denosumab for osteopenia who experienced improvement in PDB-related symptoms.
Conclusion: Although denosumab was originally approved for the treatment of osteoporosis, the inhibition of bone resorption via inhibition of the receptor activator of nuclear factor-kappa B ligand may be potentially effective in the treatment of PDB.

Introduction

Paget disease of bone (PDB) is characterized by abnormal remodeling of lamellar bone.[1] It is typically diagnosed in middle-aged and elderly people and may involve single (monostotic) or multiple (polyostotic) bones.[2] PDB is often asymptomatic but can cause various symptoms and complications, including bone pain, skeletal deformities, pathologic fracture, hearing loss, headache, and nerve root compression.[2]

Currently, intravenous (IV) bisphosphonates are the first-line treatment for PDB.[2,3] However, bisphosphonates may be contraindicated in patients with severe renal insufficiency, hypocalcemia, or severe vitamin D deficiency.[4] Some reports have shown that oral and IV bisphosphonates can worsen hypocalcemia in patients with pre-existing renal insufficiency and may contribute to worsening renal function with chronic use.[5,6] Additionally, some patients cannot tolerate bisphosphonates because of side effects such as hypocalcemia, esophagitis, bone/joint pain, and flu-like symptoms.[4] Alternative treatments to IV bisphosphonates, such as denosumab, for PDB have not been studied. Denosumab is a human monoclonal antibody that blocks the receptor activator of nuclear

Abbreviations: ALP, alkaline phosphatase; IV, intravenous; JPD, juvenile Paget disease; RANKL, receptor activator of nuclear factor-kappa B ligand; RR, reference range; PDB, Paget disease of bone.

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factor-kappa B ligand (RANKL), the primary factor regulating osteoclast recruitment. Denosumab has been shown to be highly effective in managing osteoporosis and oncological bone disease.[7] There have been 2 case reports reported in the English literature of denosumab used in patients with PDB who could not tolerate or were not eligible for bisphosphonates.[7,8]

Herein, we describe a patient with PDB and osteopenia who experienced remission of PDB of the skull 5 months and 3 weeks after administration of denosumab that was prescribed for her osteopenia.

Case Report

A 75-year-old woman presented to the Emergency Department with persistent headache of approximately 1 month. Her medical history included polymyalgia rheumatica, osteopenia, hypothyroidism, and gastroesophageal reflux disease. She reported taking prednisone 1 to 20 mg for polymyalgia rheumatica over the previous year and levothyroxine for hypothyroidism. The headache presented as a radiating pain that started from the occipital area and ended near the left temporal/peritubal region. She denied hearing loss or bone pain in the spine or upper or lower extremities. Physical examination revealed no focal neurologic deficits or skeletal deformities. The alkaline phosphatase (ALP), bone-specific ALP, and calcium levels were 132 U/L (reference range [RR], 35-104 U/L), 17.8 μg/L (RR, 7-22.4 μg/L), and 8.2 mg/dL (RR, 8.5-10.5 mg/dL), respectively. The erythrocyte sedimentation rate and C-reactive protein level were both normal, and temporal artery biopsy was negative for giant cell arteritis. Brain magnetic resonance imaging and skull radiography (Fig. 1) revealed sclerosis/hyperostosis, lytic lesions, and expansion of the frontal bone bilaterally. Bone scintigraphy revealed diffusely increased uptake throughout the calvarium consistent with PDB (Fig. 2). The patient could not be started on IV bisphosphonate therapy because of hypocalcemia. Therefore, the patient was asked to increase dietary calcium intake along with starting calcium supplementation. Two months after the initial presentation, the patient's ALP level decreased to 94 U/L, the bone-specific ALP level trended down to 11.4 μg/L (Fig. 3), and the serum calcium level increased to 8.9 mg/dL. It was then discovered that the patient received an injection of denosumab 60 mg by her primary care provider 3 weeks before her presentation in the Emergency Department for osteopenia. The patient no longer complained of headaches, tenderness in the left temporal area, or bone pain.

Five months after the initial presentation, the patient continued to be asymptomatic, and the ALP, serum calcium, and 25-hydroxyvitamin D levels were 96 U/L, 9.7 mg/dL, and 42 ng/mL (RR, 20-80 ng/mL), respectively. The patient was then started on low-dose

Highlights

- Hypocalcemia is a contraindication to initiating bisphosphonate therapy
- Intravenous bisphosphonates are the first line to treat Paget disease of bone
- Denosumab may be an alternative treatment for Paget disease of bone in patients for whom bisphosphonates are contraindicated

Clinical Relevance

A patient with Paget disease of bone (PDB) treated with denosumab for osteopenia experienced improvement in PDB despite not receiving bisphosphonates. There is scant literature supporting the use of denosumab in PDB. This case report suggests that denosumab is an alternative treatment for PDB in patients with contraindications for bisphosphonates.

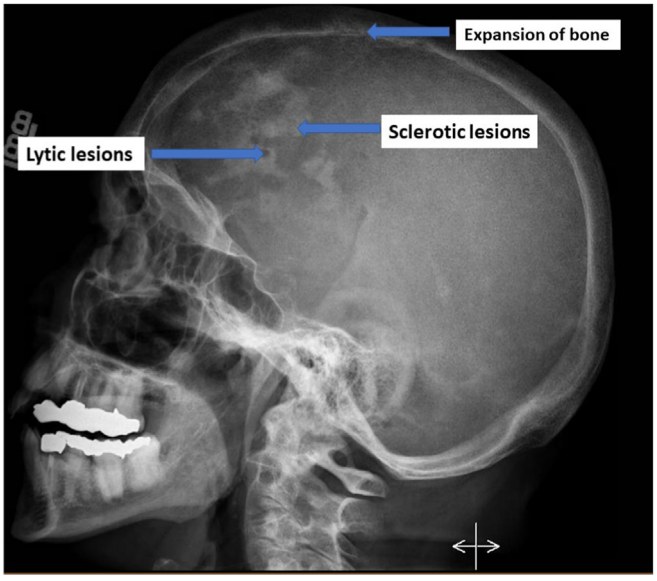

Fig 1. Radiography of the skull, lateral view. Mixed sclerotic/hyperostotic lesions, lytic lesions, and expansion of bone. These are radiographic findings characteristic of Paget disease of bone.

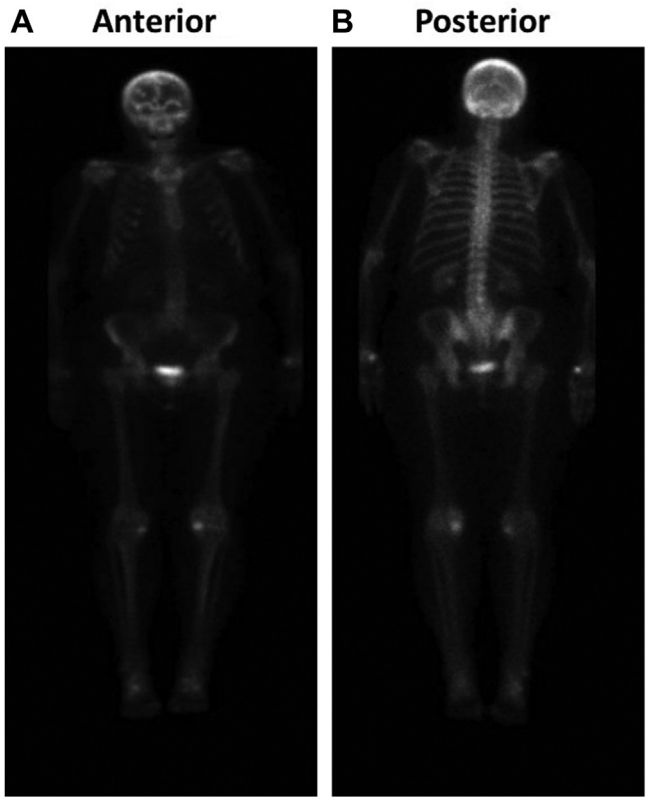

Fig 2. Nuclear bone scan of the whole body. *A*, Anterior view. *B*, Posterior view. Bone scan demonstrated diffusely increased radiotracer uptake in the whole calvarium, suggestive of Paget disease of bone.

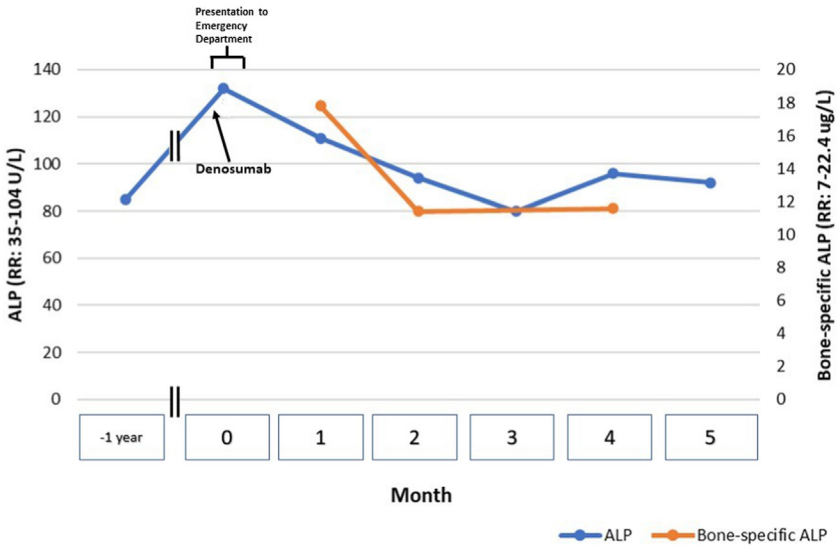

Fig 3. Alkaline phosphatase (ALP) and bone-specific ALP levels. The serum ALP and bone-specific ALP levels over the course of the patient's treatment from the initial presentation to 5 −month follow-up. *RR* = reference range.

alendronate, as initially planned, based on a previous dual x-ray absorptiometry scan that showed osteopenia.

Discussion

PDB is a nonmalignant disorder characterized by disorganized osteoclastic and osteoblastic activity leading to abnormal bone architecture. PDB is the second most common bone remodeling disease after osteoporosis with the current estimates of prevalence ranging between 1% and 3% of adults aged >40 years.[1] The most frequently affected bones are the pelvis (70%), spine (53%), skull (42%), and long bones of the lower extremities.[9] PDB involving the skull is of special importance because of its proximity to the central nervous system, which may cause headaches and, less frequently, dementia, brain stem and cerebellar dysfunction, and compressive cranial neuropathies.[10,11] Nearly one third of patients remain asymptomatic, typically being diagnosed because of high ALP levels or abnormal bone radiographic results.[10] Typically, patients with PDB are treated when symptomatic or in the setting of complications (eg, pathologic fractures). In asymptomatic patients, therapy is needed if surgery is planned near a pagetic bone, active disease is present in weight-bearing bones, and/or there is a high risk of compressive neurologic complications, such as hearing impairment.[10,11] Currently, IV bisphosphonates are the first-line treatment for PDB. They inhibit osteoclast activity, thereby reducing bone resorption and promoting the deposition of the normal lamellar bone. Bisphosphonates are highly efficacious, producing biochemical remission in 89% of patients and improving quality of life.[12] Although bisphosphonates achieve near-total disease remission, they are contraindicated in patients with renal insufficiency or low serum calcium levels.[4]

Denosumab is a human monoclonal antibody that binds to the RANKL, inhibiting osteoclast activity.[13] Denosumab is highly effective in the treatment of osteoporosis, another disease characterized by aberrant osteoclast activity.[13] Although denosumab was originally approved for the treatment of osteoporosis, the inhibition of bone resorption via RANKL inhibition may be potentially effective in the treatment of PDB. However, the efficacy of denosumab in treating PDB remains unestablished and far less studied. To date, the authors are aware of 2 published case reports of denosumab in patients in whom bisphosphonates were either poorly tolerated or contraindicated.[7,8] Schwarz et al[8] demonstrated in a patient with PDB of the pelvis and chronic kidney disease that 5 doses of denosumab 60 mg administered over a 15-month period moderately improved bone pain. Bone scintigraphy demonstrated reduced activity by 41% at 15 months. Notably, the patient was initially trialed on calcitonin, without effect on disease activity as evaluated by clinical pain, plasma total-ALP, and markers of bone turnover.[8] Similarly, Reid et al[7] demonstrated that 2 60-mg denosumab injections administered 2 years apart normalized the ALP levels and resulted in symptomatic improvement in a woman with PDB of the calvarium. However, after the second treatment, bone scintigraphy continued to show intense uptake in the calvarium and increasing ALP levels 4 months after treatment. Importantly, this patient received 2 doses of alendronate 40 mg 3 months before receiving denosumab but was not continued on this regimen because of severe musculoskeletal pain.[7] These case reports suggest that denosumab treatment is not as effective as bisphosphonate therapy, which has been shown to reduce nearly all scintigraphic activity.[14] Of note, patients in the prior 2 case reports were trialed on calcitonin or bisphosphonates, which may have potentiated the effect of subsequent treatment with denosumab. The present report described a case of initial improvement in PDB after denosumab treatment for the indication of osteopenia without prior exposure to other agents targeting the bone.

Additionally, denosumab has been experimentally trialed in juvenile Paget disease (JPD), a rare-inherited loss-of-function alteration leading to osteoprotegerin deficiency.[15,16] Although the pathogenesis may be different, both JPD and PDB in adults have similar clinical phenotypes. Two case reports in 7-, 35-, and 67-year-old individuals demonstrated that low-dose denosumab administered in a range of 1 to 6 months was successful in producing complete biochemical remission and alleviation of bone pain in patients with JPD. However, its effect on nonskeletal complications remains to be elucidated.[15,16]

Despite the demonstrated efficacy of bisphosphonates on achieving disease remission in PDB, it is currently contested whether the aggressive treatment of PDB and normalization of ALP levels versus symptomatic treatment has a significant effect on quality of life and overall body pain. One large randomized controlled trial demonstrated in 1324 patients with PDB that there were no significant differences in overall body pain, pagetic bone pain, hearing thresholds, fractures, or quality of life between a group treated aggressively with bisphosphonates and a group treated symptomatically.[17] Overall, available data suggest that clinical end points, such as normalization of ALP levels, in the treatment of PDB are not optimal

and warrant further attention. This may hinder any future head-to-head comparisons between denosumab and bisphosphonates. Given current evidence, denosumab should not be recommended as a first-line treatment for PDB.

A potential limitation of the present case report is the difficulty in evaluating the long-term efficacy of denosumab because the patient was started on alendronate, a bisphosphonate, 5 months after the initial presentation for osteopenia. Alendronate could potentially help sustain remission of PDB. Current evidence suggests that zoledronic acid achieves higher rates of biochemical remission and sustains a longer duration of suppression after a single dose.[18] The evidence is inconsistent regarding the efficacy of different oral bisphosphonates in achieving symptomatic and biochemical remission in PDB. However, it appears that the nitrogen-containing bisphosphonates have been shown to achieve higher biochemical remission rates, ranging from 75% to 95% at 6 to 12 months after treatment.[19]

Conclusion

The patient described in this case report experienced remission of PDB of the skull 5 months and 3 weeks after administration of denosumab 60 mg for the treatment of osteopenia. The observation indicating healing of PDB in this patient may have been coincidental or may reflect hitherto unrecognized beneficial effects of RANKL inhibition in PDB. This report adds to the literature suggesting a beneficial effect of denosumab in PDB, especially in patients with contraindications to bisphosphonates.

Disclosure

The authors have no multiplicity of interest to disclose.

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