Case Report

Osteonecrosis of jaw associated with bisphosphonate use

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ABSTRACT
Bisphosphonates are associated with osteonecrosis of the jaw (ONJ) that is defined as an area of exposed, nonvital bone in the maxilla or mandible persisting over 6–8 weeks. We describe a case of 55-year-old female who developed ONJ after tooth extraction and had been receiving oral ibandronate for osteoporosis. Diagnosis of ONJ was confirmed on CT scan. The patient was managed conservatively as she denied teriparatide therapy because of cost constraints.

Key words: Bisphosphonates, denosumab, ibandronate osteonecrosis of the jaw, teriparatide

INTRODUCTION
Bisphosphonates are group of antiresorptive drugs most commonly used to treat osteoporosis. Recently, bisphosphonates are also being used for various metabolic bone disorders like Paget’s disease of bone, fibrous dysplasia, and osteogenesis imperfecta.[1] More potent, parenteral bisphosphonates in higher doses are used in various malignancies (multiple myeloma), to prevent and treat skeletal metastasis and other skeletal events.

The primary mechanism of action of bisphosphonates is inhibition of osteoclastic resorption of bone. Bisphosphonates are associated with unusual side effects such as thrombotic thrombocytopenic purpura, acute retinal pigment epithelitis, atrial fibrillation, and recently intravenous preparations have been associated with osteonecrosis of the jaw (ONJ).[2] ONJ is defined as an area of exposed, nonvital bone in the maxilla or mandible that persists over 6–8 weeks.[3]

We are reporting a case of 55-years-old female who developed ONJ with zoledronic acid.

CASE REPORT
A 55-year-old post menopausal women, known case of rheumatoid arthritis receiving glucocorticoids and methotrexate for past many years presented with nonhealing wound in her oral cavity after tooth extraction four months back. She was diagnosed osteoporosis for which she had been receiving oral ibandronate 150 mg once a month since 20 months. Her dual energy X-ray absorptiometry had revealed a T-score of -3.2 at lumbar vertebrae.

Biochemical investigations revealed serum calcium of 9.0 mg/dl (8.5–10.2 mg/dl), phosphate 3.2 mg/dl (3.0–4.5 mg/dl), alkaline phosphate 104 IU/l (40–132 IU/l) and albumin 3.9 gm/dl (3.5–4.5 mg/dl). Her serum iPTH was 32 pg/ml (15–65 pg/ml) and 25(OH) D 3 was 21.2 ng/ml (11.9–42.9 ng/ml).

On intraoral examination, there was a brownish blackish area at the site of left-mandibular premolar tooth extraction with the bone visible through it. Her tooth extraction sockets had not healed in the past 4 months after tooth
extraction. There were no signs of infection. The area was tender to palpation. The bone surface felt rough, without sharp edges, and was firmly attached, with no clinical evidence of sequestration [Figure 1]. Her orthopantogram was suggestive of mandibular necrosis [Figure 2a]. The diagnosis of ONJ was considered and subsequently confirmed on CT scan [Figure 2b]. The patient was advised teriparatide therapy but she denied because of cost constraints. She was therefore managed conservatively.

Discussion

ONJ is a rare and chronic debilitating illness. Bisphosphonates have recently been incremented to be associated with ONJ. ONJ is a much more common event in those patients receiving bisphosphonates for the treatment and prevention of cancer-related skeletal events (mainly intravenously), rather than in those patients receiving bisphosphonates (mainly orally) for nonmalignancy indications.[4]

The important predisposing factors for the development of bisphosphonates associated ONJ are the type and total dose of bisphosphonates and history of trauma, dental surgery, or dental infection.[5] Our patient had nonhealing lesion which developed after tooth extraction and had been receiving oral ibandronate since 20 months. Temporal correlation of the events suggested ONJ due to bisphosphonates in the present case.

Oral lesions may develop as early as 4 months after bisphosphonates therapy. However, the median duration of drug use has been reported to range from 22 to 39 months like in the present case.[6] The cumulative hazard for development of ONJ is 1% within the first year and 21% at 3 years of treatment with zolendronic acid.[6]

Bisphosphonates affect the jaw preferably because of the higher remodeling and turnover rate in this area of the skeleton. Bisphosphonates cause marked suppression of bone metabolism, which results in accumulation of physiologic micro damage in the jawbones, compromising its biomechanical properties. Trauma and infection increase demand for osseous repair that exceeds the capacity of the hypodynamic bone, resulting in localized bone necrosis.

Jawbone is prone for osteonecrosis because the jawbones are separated from a trauma-intense and microbiologically diverse oral environment by thin mucosa and periosteum. Even minor trauma causing local damage to the thin mucosa and underlying periosteum can lead to bone necrosis. Moreover teeth are separated from bone by no more than 2 mm of periodontal connective tissue, and teeth infections being common have easy access to the underlying bone.[9]

The risk for ONJs is substantially higher for patients taking zolendronic acid and increases over time, probably because of the long half-life of these drugs. However, clodronate, a nonamino bisphosphonate, has not been implicated in the development of osteonecrosis.

Teriparatide therapy has recently been used for ONJ with satisfactory healing of osteonecrosis.[7] The proposed mechanism is an increased number of remodeling units and increased bone formation within each unit which may promote healing and the removal of damaged bone. Teriparatide also stimulates Wnt signaling through its action on sclerostin and further enhances the reparative pathway. Teriparatide was offered to our patient but could not be given because of cost constraints.
Recently denosumab, monoclonal IgG2 antibody that binds selectively and with high affinity to the receptor activator of nuclear factor-κB ligand (RANK-L used for the treatment of osteoporosis, primary and metastatic bone cancer has been incriminated to be associated with ONJ.\[^8\,9\]\ Though a large trial of denosumab used for osteoporotic women did not find any increased incidence of ONJ over a period of 24 months of treatment.\[^10\]\

To conclude a careful history of recent dental procedure should be elicited before administering bisphosphonates. Patients on bisphosphonates should be subjected to thorough oral cavity examination on routine follow up, particularly if patient complains of nonhealing dental lesion.

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Cite this article as: Rastogi A, Rattan V, Bhadada SK. Osteonecrosis of jaw associated with bisphosphonate use. Indian J Endocr Metab 2012;16:450-2.

Source of Support: Nil, Conflict of Interest: None declared.