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## LETTER TO THE EDITOR

# BISPHOSPHONATES AND OSTEONECROSIS OF THE JAW: A CASE REPORT

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## INTRODUCTION

The incidence of bone metastases is high among patients with advanced cancer. Bone metastases occur in about 80% of men with advanced prostate cancer,[1] 75% of patients with metastatic breast cancer[2] and 30% to 60% of patients with advanced metastatic lung cancer,[3] and are present in 35% of patients with renal cell carcinoma at the time of diagnosis[4].

Bone metastases cause considerable skeletal morbidity with severe bone pain in some cases, pathologic fractures, spinal cord compression and hypercalcemia. In addition, patients frequently need radiotherapy or surgery to treat bone pain or to prevent pathological fractures.[3,5] Because of this, complications from bone metastases heavily impact the quality of life of patients with cancer. Therefore, the prevention or delay of these complications would be of significant benefit to patients with advanced cancer.[6]

The bisphosphonates represent a major advance in helping patients with bone metastases.[7] They have been largely used in the treatment of this condition, since they inhibit osteoclastic activity, proliferation of tumor cells and angiogenesis. Bisphosphonates are also used in the treatment of other bone diseases, such as osteoporosis, Paget's disease and malignancy-related hypercalcemia.[8-10]

In 1995, intravenous pamidronate was approved for treating patients with multiple myeloma or metastatic breast cancer based on study findings that pamidronate reduces the risk of skeletal complications. In 2002, intravenous zoledronic acid was approved for the treatment and prevention of skeletal complications in patients with multiple myeloma or with bone metastases from any solid tumor type.[11,12] This was the first bisphosphonate with proven efficacy in the treatment of bone metastases from solid tumors, in addition to breast carcinoma.[6] Currently, therapy with bisphosphonates is considered standard in the prevention of skeletal complications in patients with bone metastases.[13]

Although serious side-effects have been reported, including acute renal failure after intravenous administration and gastrointestinal toxicities such as esophagitis when used orally, these drugs are generally well tolerated[14]. Recently, however, a new complication associated with the use of bisphosphonates has been described: osteonecrosis of the jaw. This condition was initially associated with the use of zoledronic acid, but occurrences after pamidronate use have also been reported.[15, 16]

## CASE REPORT

A 57-year-old male patient sought medical help for progressive lumbar pain. Tomographic studies revealed lytic lesions in L1, L2 and L3, and a hypodense lobulated mass in the left kidney. The patient underwent radiotherapy on the lumbar column, followed by a left nephrectomy (renal clearance after this procedure was 80 mL/min) and treatment with 5 MU/m² interferon, three times a week, and 4 mg of intravenous zoledronic acid administered as a 15-minute infusion every 4 weeks. After one year of therapy with no evidence of active disease, the patient required invasive dental treatment due to intense pain in his left molar tooth. Fifteen days after this procedure, he developed an ulcerated lesion in his lower jaw with local purulent secretion (Figure 1). In a radiological evaluation, osteonecrosis with bone rarefaction in the regional jaw was discovered (Figure 2).

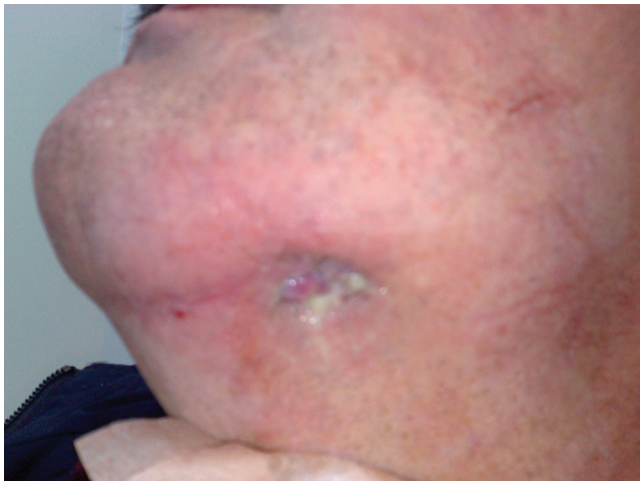

**Figure 1 -** Ulcered jaw lesion with local purulent secretion due to osteonecrosis after zoledronic acid treatment

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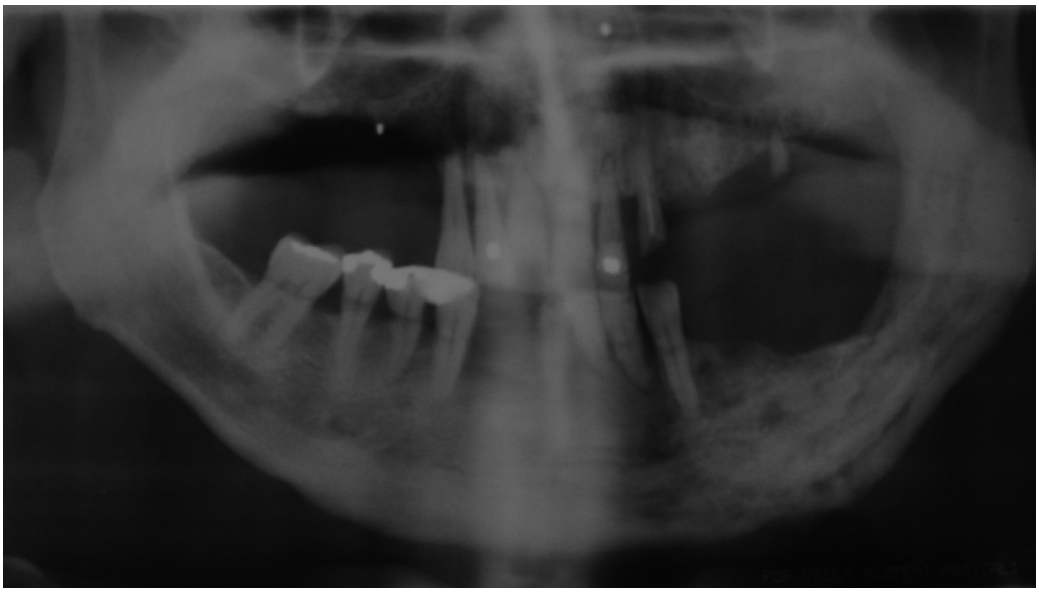

**Figure 2 -** Panoramic x-ray showing bisphosphonate-induced osteonecrosis in the left jaw

## DISCUSSION

Bisphosphonates are analogous to synthetic pyrophosphate, a natural regulator of bone metabolism that is abundant in the bone matrix.[17] These compounds inhibit the differentiation of osteoclastic precursors, lead to osteoclast apoptosis and stimulate the release of osteoclastic inhibitory factor from osteoblasts.[18] Numerous clinical studies have shown that bisphosphonates can reduce the incidence of pathological fractures, bone pain, episodes of hypercalcemia and the need for radiotherapy and surgery in patients with osteolytic bone metastases.[19-21]

In addition to adverse effects previously associated with the use of bisphosphonates, a new complication has recently been described: avascular osteonecrosis of the jaw.[15,16,22-24] The incidence of this complication is around 0.03% to 6.2%. This variation mainly depends on the type of analysis.[16,22,25] Osteonecrosis has been associated with a wide range of conditions, including corticosteroid usage, alcoholism, infections, hyperbaric events, storage disorders, marrow infiltrating diseases, coagulation defects and some autoimmune diseases. However, a large number of idiopathic cases of osteonecrosis have been described without an obvious etiologic factor.[26]

The osteoclastic function is part of the cycle of bone turnover. If osteoclastic function is too severely impaired, dead and dying osteocytes are not replaced, and the capillary network in the bone is not maintained, resulting in avascular bone necrosis.[27]

Zoledronic acid was the most powerful bisphosphonate investigated in pre-clinical tests of bone resorption.[7] However, extended treatments with bisphosphonates increase the risk of osteonecrosis, which is greater with the use of zoledronic acid than with the use of pamidronate in treatments exceeding 36 months.[28,29]

Reports have shown that the majority of patients (69%) had teeth pulled before the development of osteonecrosis. This seems to confirm the importance of this type of trauma in causing the complication,[30] and can be explained by the fact that when local defenses are overwhelmed by infection, trauma or surgery, diverse microorganisms may invade the bone marrow. Additionally, the inhibition of angiogenesis can aggravate this process by compromising the vascular supply through tissue cicatrisation.[31]

A study that included 225 patients showed that the most common symptom of osteonecrosis is pain (94), followed by purulent secretion (10), oroanthral fistula (7), swelling (3) and fever (1). Data was available for only 115 (51.1%) of these patients. In 14 other patients (12.2%), osteonecrosis was asymptomatic and was discovered through routine tests.[30]

Therefore, to avoid osteonecrosis of the jaw, it is recommended that patients who are about to start bisphosphonate therapy have a complete dental exam in order to identify possible existing infections, compromised teeth and dentures that do not fit properly. If therapy with bisphosphonates can be delayed, preventive surgery to eliminate possible infections must be performed. In addition, any jaw or elective maxillary procedure requiring healing should be avoided. Proper dental health during treatment is crucial, and all patients should be informed of the importance of good oral hygiene. In addition, a regular visual inspection by an oncologist and a routine evaluation by a dentist are important.[30]

If osteonecrosis develops, non-surgical access can achieve benefits through antibiotic therapy. Interruption of bisphosphonate therapy can be considered in severe cases if the benefits outweigh the risks of skeletal events, although no improvements have been observed in cases published so far.[31] Similarly, therapy with hyperbaric oxygen did not prove to be effective.[30]

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