MAXILLARY SINUSITIS AFTER BISPHOSPHONATES TREATMENT

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Abstract: *After the first report on bisphosphonates related osteonecrosis of the jaws in 2003, numerous papers have been published concerning this pathology. Medical practitioners are faced with the difficult task of managing this new disease. The therapy is time consuming. A good planned prophylaxis is very important. In advanced stages, if conservative treatment (antiseptics and antibiotics) fails, then surgical treatment is indicated. This paper reports 2 cases with maxillary sinusitis related to bisphosphonates therapy.*

Cuvinte cheie: *osteonecroza maxilarelor, sinuzită maxilară, bisfosfonați*

Rezumat: *Odată cu prima referință științifică în anul 2003 despre osteonecroza maxilară indusă de bisfosfonați au început să apară tot mai multe cazuri ce implică această patologie. De asemenea, medicii au început să se confrunte cu probleme legate de tratamentul indicat care, de cele mai multe ori este dificil și pe o perioadă lungă de timp. De aceea este necesară o profilaxie a acestor leziuni, iar dacă tratamentul medicamentos antibiotic și antiseptic nu poate controla dezvoltarea complicațiilor, atunci sunt necesare intervenții chirurgicale radicale în stadiile avansate. Sunt prezentate 2 cazuri clinice cu sinuzită maxilară indusă de osteonecroză maxilară legată de bisfosfonați și tratamentul respectiv.*

INTRODUCTION

Bisphosphonates are drugs used in the management of bone metastasis of malignant tumours of the breast, prostate, lung and multiple myeloma. They are also used in Paget disease and osteoporosis. There are delivered *off label* for osteopenia, fibrous dysplasia, Gaucher's disease and osteogenesis imperfect. Bisphosphonates are structural analogues of inorganic pyrophosphate. They inhibit bone resorption, bone turn-over and reduce calcium in serum. The most used bisphosphonates in osteoporosis are alendronate and ibandronate. When dealing with bone metastasis the most used are zoledronate and pamidronate. They are one of the most efficient drugs used in the management of bone metastasis (1) and osteoporosis.(2) They are very popular drugs, on a survey in USA in 2009 there were over 190 million prescriptions of bisphosphonates drugs.(3) In 2003 the first report of osteonecrosis of the jaw in relation with bisphosphonates usage is mentioned. Regarding their toxicity, researchers have found that any bisphosphonate will cause a level (higher or smaller) of bone toxicity.The pathology affects primary the alveoli of the jaws because of their accelerated bone turn-over: which is 10 times higher then tibia bone, 5 times higher then mandible basal bone, 3 to 5 times higher then the cortical of the mandible canal.(4) Bone turn-over is affected by the activity of the osteoclasts. The osteoclast will incorporate aged bone. The aged bone contains an amount of bisphosphonates thus these drugs will be found inside osteoclasts which will suffer an early apoptosis. The bone turn-over is slowed down, the necrotic bone is not removed from the tissue, it will be found underneath the mucosa. The mucosa lacking the so needed blood supply will eventually broke down and bone will be exposed in the oral cavity. This exposure can happen without any local cause but frequently will be triggered by surgical treatment: dental extraction, endodontic, periodontal, and preprosthetic and implantology surgery.(6)

There are also some anatomic conditions which favor the onset of the disease: the presence of mandibular tori, sharp oblique lines, and palatal torus. The systemic conditions that influence the osteonecrosis are the concomitant use of steroid drugs (especially prednisone which increase the toxicity of bisphosphonates), diabetes, renal pathology, chemotherapy and emboli. The bisphosphonates delivered IV are much more toxic then oral ones: zoledronate is the most potent and toxic bisphosphonate and alendronate is the most toxic oral bisphosphonate. In early stages osteonecrosis will be found in the alveolar process, left untreated it will spread beyond this border.(5) Once the bone is exposed in the mouth it will not be covered by soft tissue even if bisphosphonates therapy is ceased. Local surgical treatment is set to fail and the outcome will be the spread of the disease, exposing a larger amount of bone then initial.(7) Treatment consists in antiseptic mouthwashes (the most used is clorhexidine solution) and oral or iv antibiotics (penicillin, doxycycline, azithromycin) after antibiotic sensitivity tests are performed. Surgical treatment should only be reserved for late stages when the disease has crossed the border of the alveolar process with the presence of sinusitis, pathologic fractures, and fistula. In these cases, wide resections are performed with or without reconstructions.(8)

CASE PRESENTATION

Case I: A 60-year-old female patient presented to the maxillofacial surgery unit complaining of pain in the region of the edentulous ridge in the right maxilla, molar area. The patient confirmed that she has been taking zoledronate (Zometa) for over 2 years prescribed by her oncologist in order to manage bone metastasis of a breast malignant tumour. At the clinical exam there was evidence of exposed bone which was necrotic

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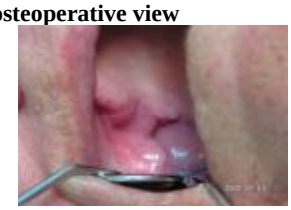
and with signs of inflammation (figure no. 1). At the x-ray exam there is a distinct opaque image of the maxillary sinus on the same side (figure no. 2). The diagnosis is osteonecrosis of the jaw related to bisphosphonate treatment and maxillary sinusitis.

Figure no. 1. Preoperative view. Necrotic bone exposed in the right superior molar area

Figure no. 2. Skull x-ray showing an opaque right maxillary sinus

The oncologist did not stop the drug administration. Treatment consisted in clorhexidine mouthwashes 0, 2%, 3 times/day and antibiotic therapy (penicillin) delivered in IV form. After 10 days when the inflammation process is ceased a surgical resection of the necrotic bone is performed and the remaining bleeding bone is covered with a vestibular flap. The histological report confirms the diagnosis of osteonecrosis. At 3 weeks the surgical site is healed (figure no. 3).

Figure no. 3. Posteoperative view

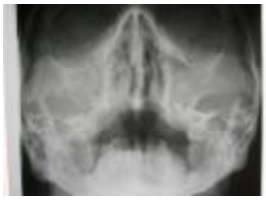


Case II: A-64-year-old male patient presented to the maxillofacial surgery unit, accusing pain in the upper jaw. From the patient history it is noted the bisphosphonates treatment for over 2 years with zoledronate for multiple myeloma. The patient was subjected to dental extraction 3 moths ago in the upper jaw. At the clinical exam there was a wide area of exposed bone from the upper right canine until the second molar area (figure no. 4). At the x-ray exam there was a specific opaque image of the right maxillary sinus (figure no. 5).

Figure no. 4. Preoperative view. Necrotic bone exposed from the right canine to the right molar area

The diagnosis is osteonecrosis of the jaw related to bisphosphonate treatment and maxillary sinusitis. Conservative treatment was started with chlorhexidine 0,2% oral washes 3 times/day and doxycycline 100mh/day and metronidazole 500 mg 3times/day for 10 days. After 10 days when inflammation processes were stopped a surgical intervention was planned. The necrotic bone was removed and the remaining bleeding bone was covered with local flaps.

Figure no. 5. Skull x-ray showing an opaque right maxillary sinus



The histological report confirms the diagnosis of osteonecrosis. At 1 moth follow up the surgical site is healed with no signs of relapse (figure no. 6).

Figure no. 6. Posteoperative view

CONCLUSIONS

Oncologic patients who are taken bisphosphonates are more likely to develop osteonecrosis of the jaw due to increased toxicity of the drugs involved, IV delivery mode, and impossibility to stop the treatment. Osteonecrosis may appear spontaneous but in over 60% of the cases it is a cause of oral surgery procedures, most implied being dental extraction. In early stages it is advisable to use conservative treatment. Surgical treatment should be employed for late stages (stage 3) which does not respond to nonsurgical approaches.

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