DENOSUMAB-RELATED OSTEONECROSIS OF THE JAW IN A METASTATIC PROSTATE CANCER PATIENT: CASE REPORT

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ABSTRACT. Osteonecrosis of the jaw (ONJ) is a clinical condition characterized by the presence of exposed necrotic bone in the maxillofacial region. Its pathogenesis is still undetermined, but may be associated with risk factors such as bisphosphonates. The aim of this paper is to report a case of ONJ in a patient with metastatic prostate cancer and a history of Denosumab use.

KEY WORDS: osteonecrosis of the jaw (ONJ), human RANKL monoclonal antibody, bisphosphonates, dental extraction, metastases.

INTRODUCTION

Osteonecrosis of the jaw (ONJ) is a well-known complication in cancer patients taking intravenous bisphosphonate drugs for the prevention of fractures due to bone metastases (Marx, 2005).

To date there is no diagnostic test to determine if an individual patient is at increased risk for ONJ. The condition itself is diagnosed only by the presence of exposed bone, lasting more than 8 weeks (AAOMS, 2007). Patients typically complain of pain, which is often related to infection, soft tissue swelling, drainage and exposed bone (Grenberg, 2003). ONJ most often develops after an invasive (surgical) dental procedure such as dental extraction (Ruggiero, 2004).

ONJ has been reported in patients taking other strong antiresorptive therapies such as RANKL (receptor activator of nuclear factor-κB ligand) inhibitors (Aghaloo, 2010). Recent papers sustained equal ONJ incidence for patients treated with bisphosphonates vs. human RANKL monoclonal antibody therapy for management of bone metastases (Epstein, 2012).

We present here a case of osteonecrosis following dental extractions in a patient diagnosed with metastatic prostate cancer, taking Denosumab, a human RANKL monoclonal antibody.

CASE REPORT

A 78 year-old man was referred to our Oro-Maxillofacial Surgery Clinic of UMF „Carol Davila” Bucharest with a chief complaint of painful exposed bone on the right side of the mandible area with pus discharge and paresthesia in the inferior alveolar nerve territory. His mandibular right first and second molar had been extracted 10 weeks previously, and he had experienced persistent pain due to the unhealed extraction socket.

Patient’s medical history included diabetes type 2, peptic ulcer disease, hypertension atrial fibrillation and depression. He was diagnosed with metastatic prostate cancer two years ago. At this time he was placed on bicalutamide (Casodex) 150 mg a dayly and Dexamethasone 0.5mg daily. Eight months ago the patient complained lumbar pain with elevated PSA level (6.83 ng/ml) and was the bone scintigraphy with (99m)Tc-MDP demonstrated intense uptake on lumbar spine. Since then he was placed on Denosumab 120 mg injection every four weeks and Tramadol 25 mg qds.

Oral examination revealed erythema, mucosal swelling, and exposed necrotic alveolar bone in the area of the right mandibular molars. The bone surface felt rough, with sharp edges, but with no clinical evidence of sequestration (Figure 1).

Based on patient history coupled with the clinical evaluation we established a working diagnosis of ONJ.
Initial treatment consisted of administration of oral clindamycin for 20 days and 0.12% chlorhexidine oral rinses twice daily.

The patient was referred to oncologist to evaluate the potential risks and benefits of the patient’s anti-cancer therapy; consequently, the current regime of drugs was continued.

The patient was seen three weeks after the initial presentation with no change in the clinical severity of exposed bone but without pain and discomfort.

Three months later, the patient presented to for follow-up with minimal change in the area of exposed bone. Evaluation of panoramic radiographs showed decreased bone density and sequestrum on right mandibular area (Figure 2).

We decided to remove the necrotic bone (Figure 3), because it was a source of infection and was unresponsive to antibiotic therapy and 0.12% chlorhexidine irrigation.

Biopsy from the bony lesion demonstrated sequestrum infiltrated with chronic inflammatory cell as well as bacterial flora.

During 3 months follow-up period, there was no recurrence sign.

DISCUSSIONS

Many systemic antiprostate cancer therapies such as chemotherapy and hormonal therapy have been shown to reduce bone complications (Tannock, 2004). The use of antiresorptive therapies reduces bone destruction by inhibiting osteoclast function and survival. Until recently the most widely used osteoclast-inhibiting class of agents in castration-resistant prostate cancer metastatic to bone were bisphosphonates (Smith, 2004).

Bisphosphonates use has a couple of disadvantages, such the need for intravenous administration and dose adjustments to prevent acute renal failure, acute phase reactions and osteonecrosis of the jaws (Fizazi, 2011, Durie, 2005).

Denosumab, a human monoclonal antibody to RANKL, represents a treatment option for the prevention of skeletal complications in patients with metastatic castration-resistant prostate cancer. Denosumab suppresses osteoclast formation in humans by binding to RANKL, which in turn inhibits RANK activation (Kostenuik, 2009). Denosumab is given subcutaneously, has no effect on renal function and is not associated with acute phase reactions (Smith, 2009).

Studies showed superiority of denosumab to bisphosphonates for the prevention or delay of bone metastases in patients with prostate cancer and the deacresing the risk of skeletal complications (Shore, 2012).

In patients with prostate cancer, Fizazi K et al. reported a relatively low incidence of ONJ in patients receiving bisphosphonates (1.3%); a similar incidence was observed for patients receiving Denosumab (2.3%) (Fizazi, 2010).

In patients with established ONJ, intermittent antibiotic together with surgical removal of a sequestrum can be beneficial to palliate this kind of lesion (Vescovi, 2010).

Due to its molecular structure, bisphosphonates are accumulated in high in the resorption lacunae. Because bisphosphonates are not metabolized, high concentrations are maintained within the bone for a long period of time (Woo, 2006). On the other hand, interruption of bisphosphonates can produce hypercalceymia associated with tumour or skeletal-related events in metastatic cancer (Ruggiero, 2006).

Discontinuing Denosumab therapy as a mean of risk reduction for ONJ could be considered though the mean elimination half-life of Denosumab is 28 days (Amgen Incorporated, 2010); no detectable amounts of denosumab were traced 6 months after a single dose (Amgen Incorporated, 2012). The oncologist in consultation with oral and maxillofacial surgeon should be in the best position to consider the benefits versus risks of discontinuation of Denosumab therapy.

The concurrent prescribing of corticosteroids and human RANKL monoclonal antibody therapy is becoming more common in metastatic castration resistant prostate cancer. The patient in this case had a short course of Dexamethasone.

Osteonecrosis of the jaws has not been associated with glucocorticoids (Sarin, 2008). However, a few mechanisms of corticosteroid-induced osteonecrosis have been described, such as suppression of gonadal steroids, suppression of osteoblast function or induction of apoptosis of osteoclasts (Patschan, 2001). Combine these molecular mechanisms with the suppression of immune mechanisms, glucocorticoids could play key role in the development of ONJ. In order to clarify the possibility of corticosteroids treatment synergistically enhancing Denosumab activity and ONJ development, accumulated clinical practice will be necessary.

CONCLUSIONS

Although the definitive role of human RANKL monoclonal antibody therapy remains to be elucidated, the alteration in bone metabolism together with invasive dental treatment appears to be key factors in the development of osteonecrosis of the jaws.

Although discontinuation of iv bisphosphonates in cancer patients has been suggested, discontinuation of Denosumab prior to dental surgery should be investigated ongoing clinical trials.

REFERENCES


IMAGES:

Figure 1 – Clinical view of pus formation and exposed necrotic bone
Figure 2 - Plain radiographic examination showed affected bony area; notice the sequestrum on the right mandibular alveolar process

Figure 3 – Clinical view after sequestrectomy

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