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Osteonecrosis of the jaws in patients assuming bisphosphonates and sunitinib: two case reports

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Abstract. – Osteonecrosis of the jaw (ONJ) is an unremitting adverse outcome associated with bisphosphonate therapy, primarily intravenously administered, in patients with bone metastases from solid tumors, multiple myeloma and osteometabolic diseases. From 2003 many cases of bisphosphonates related osteonecrosis of the jaw (BRONJ) have been reported in literature.

Sunititnib is a novel anticancer agent used in gastrointestinal cancers and renal cancers resistant to imatinib.

Recent reports describe the onset of ONJ in patients treated with both sunitinib and bisphosponates.

A case of osteonecrosis of the jaw related to sunitinib, without association of bisphosphonate (BP) medications has been recently reported.

A recent hypothesis suggests that antiangiogenic drugs such as sunitinib could cause ONJ even without the association with BPs.

We describe a case of two patients affected by renal carcinoma under BP and sunitinib medication who developed stage III bisphosphonates-related osteonecrosis of the jaw (BRONJ).

Key Words:

Osteonecrosis, Jaws, Antiangiogenic, Bisphosphonates, Sunitinib.

Introduction

Avascular osteonecrosis of the jaw (ONJ) is a consequence of bone infarction deriving from an ischemic episode. However, pathology-related diseases are several including bacterial or viral osteomyelitis[1-3], radiotherapy side effects[2-5], chemotherapy including intravenously bisphosphonates (IVBP) such as pamidronate and zoledronic acid.

Despite the amount of bisphosphonates related osteonecrosis (BRONJ) cases reported in literature, the pathogenesis is still not completely elucidated. Four main theories prevail. The principal popular BRONJ hypothesis is the manifestation of necrotic bone resulting from bisphosphonate-induced remodeling suppression[6,7]. An other hypothesis includes the toxic effect of bisphosphonates on oral mucosa[8,9].

Several studies suggest that the antiangiogenic effect of bisphosphonates have a fundamental role in the pathophysiology of BRONJ[10,11]. Koch et al[12] report that the antiangiogenic effect on maxillary bones seems to be exerted by anticancer drugs as sunitinib that could lead to a jaw osteonecrosis similar to BRONJ.

Several Authors suggest a possible cumulative effect of antiangiogenic drugs with BPs[13-17].

Sunitinib is a tyrosine kinase inhibitor that amplifies bone remodeling process exerted by BP and antagonizes the mucosal healing process by inhibiting surrounding fibroblasts and endothelial cells, causing bone exposition to infective agents during the treatment. Soft tissues and endothelial damage could play a key role in the pathogenesis of ONJ[8,9].

Sunitinib is used in the treatment of non-operable and metastatic stromal cancers of the gastrointestinal tract after failure of a treatment with Imatinib mesilate due to resistance or intolerance. It is also indicated in the treatment of advanced/metastatic renal carcinoma. The use of sunitinib in the last years and his association with aminoBPs seems to be related to an higher incidence of BRONJ[13-16].

We report the cases of two patients with renal carcinoma under BP medication who developed stage III BRONJ[18] during and after sunitinib administration. One of them presented additional suppurative maxillary sinusitis extending to anterior skull base with meningitis as complication.

Case 1

A 65 years old male underwent to total nefrectomy for renal cell cancer in May 2008. Considering the advanced stage of disease with lung and lumbosacral metastases, a cycle of sunitinib (50 mg/die for 4 weeks every 6 weeks) was start-

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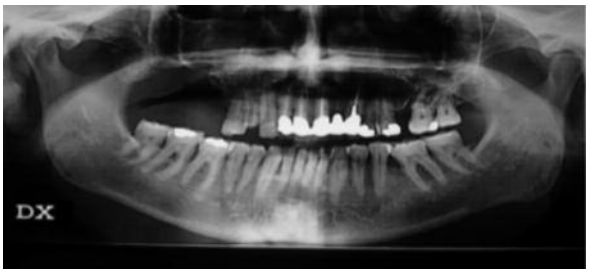

Figure 1. Patient 1, extent of the lesion of the upper jaw.

ed but shortly decreased to 37.5 mg/die for the observation of intermittent mucositis and gengivitis in different areas of the oral cavity associated with nausea and diarrhea. At the same time the patient started intravenous zoledronic acid (4 mg every 4 weeks). In June 2009, after one year of treatment, zoledronic acid was discontinued for the appearance of painful swelling of the right maxilla that didn't progress with macrolids. The clinical examination showed a painful exposed bone lesion (20 × 20 mm) of the right maxilla with oro-antral communication treated with surgical therapy (Figures 1, 2). Five months after surgery the patient showed again bone exposition and suppurative maxillary sinusitis with extent to the sphenoidal sinuses (Figures 3, 4). After a cycle of ozone therapy and beta lactam antibiotics the patient underwent to an ulterior surgical intervention in July 2009. The following controls showed a progression of ONJ lesion. The CT images pointed the interest of pterygoid processes and part of the right parasellar region. In addition the patient developed an episode of meningitis that worsened importantly his general condition. Although the pharmacological therapy was efficient in treating meningitis, the patient died in the following weeks for oncological complications.

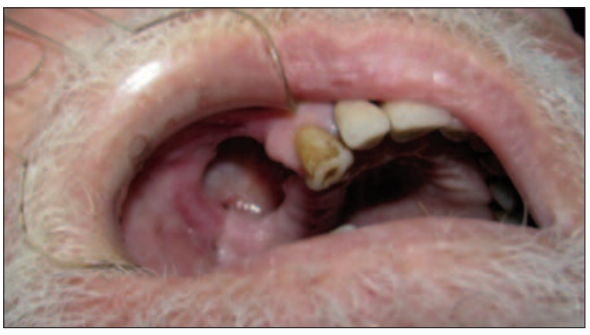

Figure 2. Patient 1, important loss of maxillary bone tissue with posterior oro-antral fistula.

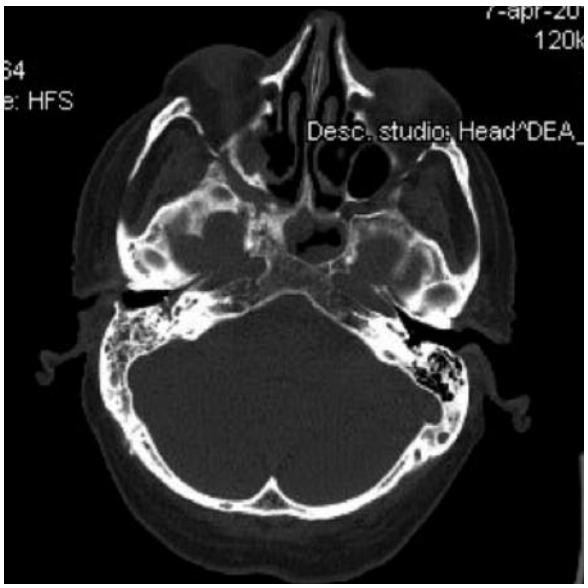

Figure 3. Assial CT scan of patient 1 showing the interest of maxillary pterygoid junction and sphenoidal pterygoid processes until skull base area.

Case 2

A 67 years old male, affected by clear cell renal cancer underwent radical nefrectomy in March 1995.

In January 2003 were reported pulmonary and osseous metastases; in February 2003 received 3 cycles of chemotherapy with Methotrexate, Doxorubicin and Adriamycin; furthermore in June 2003 received immunotherapy for three months.

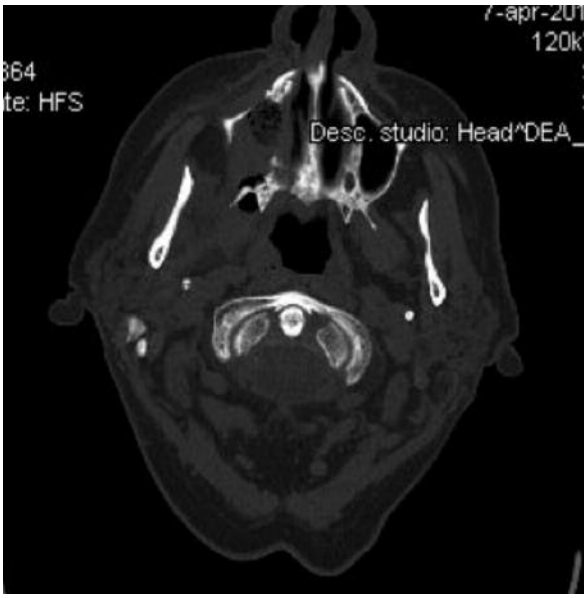

Figure 4. The CT scan showes sphenoidal sinusitis and a small bone sequestration.

In October 2004, 6 cycles of gemcitabine and vinorelbine were administered. In January 2005 the patient presented progression of metastases of cervico-dorsal spine and a cycle of chemotherapy with Roferon-A and fluorouracil was begun. From August 2005 to September 2006 zoledronic acid was introduced in therapy. The interruption was due to the onset of painful swelling of the left mandible with bone exposition and teeth instability. In September 2006 was anyway executed a cycle of sunitinib (50 mg/die for 4 weeks every 6 weeks). In January 2007 the total body CT showed progression of osteolitic lesions and, therefore, sunitinib was administered in association with 7 cycles of temsirolimus.

In February 2008 a painful swelling of the left mandible with exposed bone was observed and purulent material was drained (Figure 5). In addition, in the submandibular region was visible a cutaneous fistula. Antimicrobial rinses combined with antibiotic therapy (penicillin) were prescribed. The CT showed a pathological fracture associated with the osteolitic lesion and wide bone sequestration (Figure 6). The patient underwent to emimandibulectomy and then was positioned a rigid titanium plate for jaw's.

After few months he died for progression of the oncological pathology.

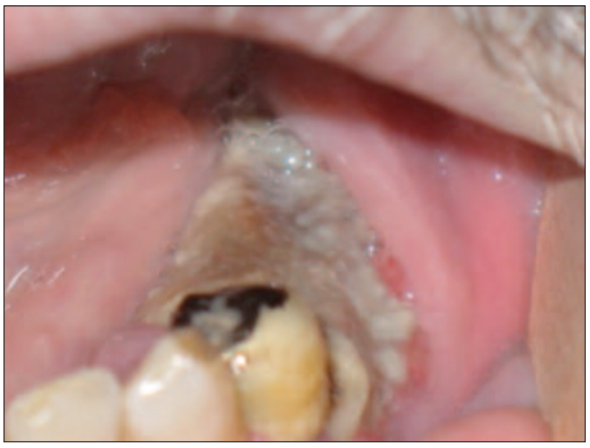

Figure 5. Endo oral examination of patient 2 showes exposed osteonecrotic bone.

Discussion

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a relatively rare but potentially serious complication of therapy with nitrogen-containing bisphosphonates (NBPs).

The first cases of ONJ associated with the use of nitrogen-containing bisphosphonates were presented by Ruggiero et al in 2003[19]. Only few cases of their original patients series took oral bisphosphonates. Because oral NBPs are less potent than intravenous NBPs, their opposing effect on bone healing may be incomplete with limited jawbone involvement.

Despite the amount of bisphosphonates related osteonecrosis (BRONJ) cases reported in literature, the pathogenesis is still unclear. Four main theories prevail. The first hypothesis mantains that BRONJ would be induced by an over-suppression of bone turnover. Bisphosphonates (BP)

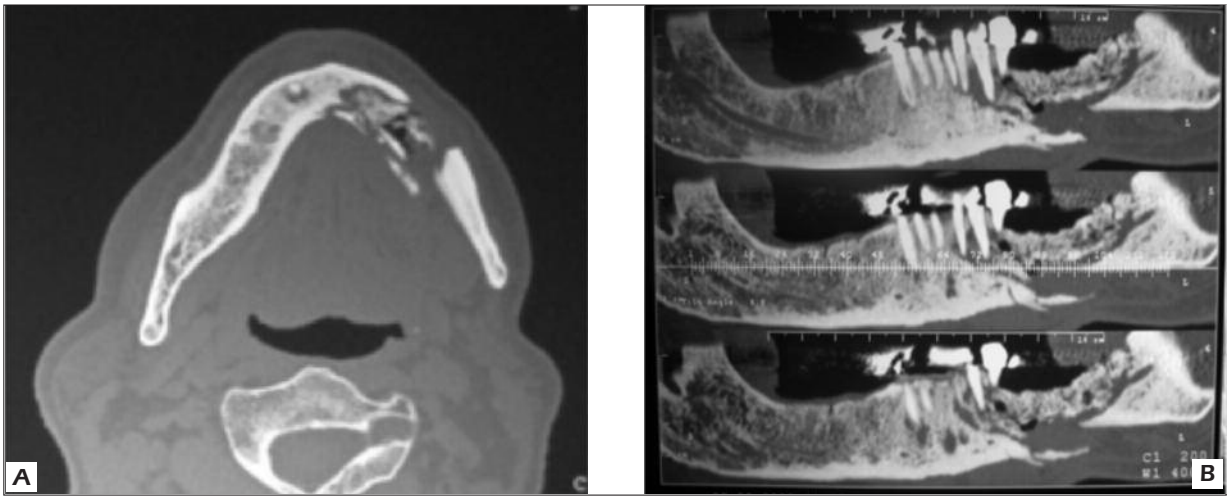

Figure 6. ***A*** and ***B,*** Patient 2: Assial CT and Dentascan sections of the mandible showing litic lesion of the left emimandible associated to wide bone sequestra and pathological fracture.

have great affinity for bone, are able to inhibit osteoclast function and bone remodeling[6-7].

The second theory suggests that BRONJ could be a response to infection. BPs are known to modulate the immune response of different cell types[13,14]. This may decrease the immune response predisposing to several infections mainly sustained by multimicrobial colonies forming biofilm with the prevalence of Actinomyces[10,15].

BRONJ is also a possible result of ischemia due to the antiangiogenic effects of BPs. Although the description of BRONJ as avascular necrosis and the antiangiogenic effect in BPs in tumor tissues suggest a role in the pathogenesis of BRONJ[10,11], the angiogenesis during bone formation seems to be unaltered by bisphosphonates[20,21].

The last hypothesis underlines the importance of BP's toxicity toward different cell types, including mucosal tissue. Accumulation of BPs may, in combination with other cancer therapy medications, lead to mucosal injury followed by exposed bone and BRONJ[8,9].

Otto et al[22] underline the possible importance in the pathogenesis of an acid pH that would increase the dissociation between BP and hydroxyapatite.

Despite the presence of bacterial conglomerates, above all Actynomices, in many patients with BRONJ, there is no clear evidence to address the question of whether infection is a primary or secondary event in BRONJ pathophysiology[14]. The infective role of microbial oral species is of great interest, not only for the pathogenesis but only for the infective complications which sometimes represent a great complication[8,9].

Several works suggest the antiangiogenic effect of bisphosphonates as a key role in the pathophysiology of BRONJ)[10,11]. This effect seems to be confirmed by the role on maxillary structures of the novel antiangiogenic drugs like Sunitinib which, as recently reported by Koch et al[12], could lead to a jaw osteonecrosis mimicking a BRONJ.

Sunitinib is a molecule orally administered that inhibits cellular signaling by targeting multiple receptor tyrosine kinases. Of the receptors, PDGF-Rs (receptors for platelet-derived growth factor) and VEGFRs (vascular endothelial growth factor) have a key role to both angiogenesis and tumor cell proliferation. Simultaneous inhibition of these targets leads to reduction of tumor vascularization and cancer cell death and finally tumor shrinkage.

Sunitinib also inhibits other receptors as KIT (stem cell factor receptor), RET (glial cell-derived neurotrophic receptor), (CSF-1R) colony-stimulating factor type 1, FLT3 (Fms-like tyrosine chinase 3).

The fact that sunitinib targets a large variety of receptors implies several side effects as: fatigue, hand-foot syndrome, stomatitis, proteinuria, neuro-toxicity, coagulation disorders with epistaxis, hypothyroidism, diarrhea, nausea, anorexia, dyspepsia, constipation, hypertension, yellow skin discoloration[24-26].

Usually most side effects result to be reversible and do not lead to sunitinib discontinuation and can be solved with dose adjustments even if interruption of therapy is sometimes suggested[25].

A decrease in left ventricular ejection fraction is a rare but potentially life-threatening side effect[25].

Long term side effect are not yet known and are currently under investigation.

Koch et al[12] report the case of a 59-year-old male patient that had contracted renal cell carcinoma operated by nephrectomy in 2003. Soft tissue metastases occurred. After initial therapy with interferon and vinblastine, a relapse occurred and the therapy was changed to sorafenib, followed by sunitinib. Osteonecrosis of the lower jaw appeared 1 year after initial and exclusive therapy with sunitinib. In this patient BPs had never been applied.

Osteonecrosis of the jaws has been associated even with other antiangiogenic drugs as bevacizumab without association with BPS. Guarnieri et al[17] report the case of a 51-year-old patient with mammary breast cancer that developed ONJ during therapy with bevacizumab in combination with capecitabine. She had previously received doxorubicin, cyclophosphamide, and then letrozole in the adjuvant setting and albumin-bound nanoparticle paclitaxel in the metastatic setting, but had no history of bisphosphonate exposure. Six weeks after the eight dose of bevacizumab, the patient presented with a small area of bone exposure, which appeared necrotic.

Greuter et al[27] describe another breast cancer patient who developed ONJ after treatment with bevacizumab. She had no history of bisphosphonate exposure. Two infected teeth were extracted and 1 month later ONJ was diagnosed.

In addition to the two cases described above, a retrospective analysis of patients receiving bisphosphonates for bone metastases from breast,

colon, or renal cell cancers was reported recently by Christodoulou et al[14]. Of the 116 bisphosphonate-treated patients included in the analysis, 25 had received concurrent treatment with anti-angiogenic agents (bevacizumab in 22 patients, sunitinib in two patients and sorafenib in one patient). In this subgroup four (16%); three receiving bevacizumab, one receiving sunitinib) developed ONJ.

Individual cases of ONJ have been reported in the literature among zoledronate-exposed patients treated with sunitinib for renal cell carcinoma[13,15,16].

Ayllon et al[15] report two cases of ONJ observed in patients that received i.v. zoledronate for the treatment of bone metastases in female breast cancer patient (patient 1) and of hypercalcemia in male renal cell carcinoma patient (patient 2). Patient 1 was switched to oral clodronate after 4 months on zoledronate. She had been on clodronate for 15 months and patient 2 had been on zoledronate for 19 months when ONJ occurred. Patient 1 had received bevacizumab for 2-3 months and patient 2 had received sunitinib for 14 months before diagnosis of ONJ. Both died with ongoing ONJ.

Bedogni et al[16] describe the case of a 59 year-old patient affected by metastatic renal cell carcinoma (RCC) and established BRONJ experienced consecutive episodes of painful jaw infection with cutaneous fistula and bone sequestration which occurred during active treatment with sunitinib, improved after discontinuation and antibiotic therapy and rapidly worsened with resumption of sunitinib.

Hoefert et al[13] report three patients with renal cell carcinoma under BP medication who developed BRONJ during and after sunitinib medication. In two patients, BRONJ was linked to the occurrence of mucositis after sunitinib intake. The third patient showed relapse of completely healed BRONJ lesions shortly after resumption of a sunitinib therapy.

According to other Authors experience we report here two cases of patients affected by renal cancer and treated with both sunitinib and ivBPs. In both cases the patient developed stage 3 BRONJ. Patient 1 showed oro-antral communication with suppurative maxillary sinusitis and cranial base involvement that did not progress either with antibiotics or surgical treatment; was instead complicated by a meningitis episode; the patient died with ongoing BRONJ. Patient 2 in treatment with sunitinib and other chemoterapics and zoledronic acid manifested wide bone sequestration, pathological fracture and cutaneous fistula; conditions that worsened significantly the patient's quality of life.

We suggest a careful monitoring of oral health in patients treated with sunitinib, especially in those with an history of BPs therapy.

Conclusions

The increase of reports which describe the onset of ONJ in patients treated with bisphosphonates and antiangiogenic drugs and with sunitinib alone confirms the role of antiangiogenic effect on ONJ.

Further studies are needed to clarify the incidence of antiangiogenic agents on ONJ, and, as reported for BRONJ, to make a primary prevention to reduce the incidence of ONJ.

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