Are ministerial recommendations sufficient to avoid bisphosphonate related osteonecrosis of the jaw? A case report

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Abstract

Bisphosphonate related osteonecrosis of the jaw (BRONJ) can occur in patients affected by malignancy associated hypercalcemia, bone metastases of solid tumors or multiple myeloma intaking amino-bisphosphonates or other bone resorption inhibitors.
BRONJ occurs initially with alveolar bone radiographic alterations, with peripheral facial neurological symptoms and thereafter with bone exposition and necrosis
Drug related ONJ were also reported in oncologic patients intaking angiogenesis inhibitors or monoclonal antibodies that inhibit bone resorption (e.g. Denosumab).
In the present case report, Denosumab has been administered to treat bone lesions related to invasive ductal breast cancer.
Before starting therapy with Denosumab, in order to restore oral and periodontal health, dental extractions were performed without any modifications to surgical protocols and waiting the complete healing of extraction sites (6 weeks).
Even if ministerial recommendations were followed, even if we waited the biologic healing and even if denosumab therapy started without symptoms, BRONJ occurred in this patient.
The mistake made in the management of the present case is that we did not carefully evaluated early radiological signs (alveolar crest thickening, bone sclerosis, persistent alveolar post-extraction socket, periodontal space widening, formation of bone sequestrum) that could bring the clinician to the diagnostic suspect of BRONJ before the onset of clinical signs (fistula, and bone exposure).
Identifying early radiological signs could bring the clinician to an early diagnosis and consequently a better prognosis.

Introduction

Bisphosphonate related osteonecrosis of the jaw (BRONJ) is an adverse effect characterized by a progressive bone necrosis of the jaws in patients intaking bisphosphonates or resorption inhibitors without previous exposition to radiation therapy. Table 1 reports diagnostic criteria for BRONJ. The reason of the exclusive occurrence of BRONJ in the jaws is unknown.
To this regard some hypotheses were proposed:

- the bone turnover is physiologically faster in the jaws;
- the lower jaw has a terminal vascularization
- presence of a thin mucoperiosteal layer that protects the underlying bone tissue;
- oral biofilm
- dento-alveolar interface that predispose to bone exposition in case of oral surgery.

Table 1. BRONJ Diagnostic criteria.

Diagnostic Criteria
Current or previous therapy with: • Bisphosphonates • Denosumab • Antgiogenesis inhibitors • Clinical or radiological diagnosis of progressive bone destruction or bone necrosis
Exclusion Criteria
• Previous or simultaeous radiation theraphy head and neck region
Doubt Criteria
• Primary bone neoplasm primitiva and/or bone jaw metastasis

The literature Medication-related ONJ as (1-8) :
1) BRONJ
2) NON BRONJ: ONJ related non-bisphosphonates drugs.
Two groups of resorption inhibitor drugs are described: bisphosphonates and denosumab. Bisphosphonates bind to the hydroxyapatite crystals of bone and include aminobisphosphonates and non-aminobisphosphonates. Aminobisphosphonates were mainly associated to BRONJ (56). These drugs are prescribed to treat bone metastases secondary to solid neoplasms o multiple myeloma and osteo-metabolic deseases.
Aminobisphosphonates are also prescribed to prevent drug induced osteoporosis after hormonal therapy for breast or prostate cancer (61-63).
Denosumab is monoclonal antibody that temporary inhibits osteoclasts recruitment and activation with a consequent bone turnover reduction.

First cases of denosumab related ONJ were described in 2010 (26-99-100-132-13).
Three studies compared ONJ prevalence between denosumab and zoledronic acid treatment in patients with bone metastases secondary to solid tumors (26-99-100). These studies showed that ONJ prevalence after the intake of these drugs is similar (1-2%) (27-70-24-135-134). The Italian society of Maxillo-Facial Surgery (SICMF) and the Italian society of oral medicine and pathology (SIPMO) noticed the need of defining the medication-related ONJ on the basis of clinical and radiological criteria different from the only observation of exposed necrotic bone (39-173).
Even if necrotic bone exposition remains the main indicator of ONJ, the clinician should identify other clinical and instrumental signs that can place the suspect of ONJ also without bone exposition (175-178) These signs are reported in table 2. SICMF e SIPMO stated that X-rays exams are fundamentals to a diagnostic confirm of medication-related ONJ (mainly without bone exposition).
Without x-rays imaging and only following classifications based on clinical signs, there are 25% of false negative with negative consequences on prognosis and on world health care cost (40).

Table 2. Clinical criteria for the diagnosis of medication-related ONJ.

Symptoms and clinical signs
• Halitosis
• Dental abscess
• Mandibular asymmetry
• Pain originated form teeth or bone
• NECROTIC BONE EXPOSITION
• Mucous Fistola
• Extra-oral Fistula
• Hyperemic mucosae
• Absence of complete healing of extraction sites
• Dental mobility
• Abnormal mandibular range of motion
• Labial Paresthesia/disesthesia
• Exudate emission from the nose
• Purulent secretion
• Bone fragments spontaneous Sequestrum
• Trisma
• Soft tissues tumefaction

The ONJ suspect should induce the clinician to perform a complete anamnesis with first and second line x-rays investigations.
Orthopantomography (OPM) and endoral x-rays are the first line investigations (190-191), while the computed tomography (CT) represents the second lie investigation (192-193). First line investigations are useful in order to identify bone sequestrum and osteolytic areas. These investigations permit to evaluate some osteonecrosis subclinical signs such as periodontal space widening, lamina dura sclerosis and alteration of spongious bone, but do not permit to discern between generic osteolytic lesions and bone metastases.
With the OPM it is possible to identify an osteolytic lesion only when there is a bone mineral loss over 30-40% (192-194). However, the OPM is very useful as first approach in patients with a suspect of ONJ. The CT provides detailed information about the number and the nature of osteolytic osteosclerotic lesions (188-192). The CT permits to investigate cortical and spongious bone and to discern between healthy and pathologic bone giving information about the extension of pathologic process (193-186-192-198-199-200). Table 3 reports the radiological criteria for the diagnosis of medication-related ONJ.

Table 3. radiological criteria for the diagnosis of medication-related ONJ.

Medication-related ONJ non-specific signs

OPM
Early signs
Increased thickness of alveolar crest
Lamina dura sclerosis
Post-extractive site presistance.
Sequestrum
Widening of periodontal space
Late signs
Pathologic fracture
Increased thickness of alveolar nerve canal
Widespread osteosclerosis
Radiopacity maxillary sinus
Periostal reaction
CT
Early signs
Cortical Erosion
Increased thickness of alveolar crest and lamina dura
Increased thickness of spongious bone
Focal midollar osteonecrosis
Post-extractive site presistance.
Sequestrum
Widening of periodontal space
Late signs
Oro-antral, oro-nasal and muco-cutaneous fistula
Pathologic fracture
Increased thickness of alveolar nerve canal
Osteolysis extended to maxillary sinus.
Widespread osteosclerosis
Zygomatic and hard palate osteosclerosis
Periostal reaction
Sinusitis

Nowadays the preventive approach represents the more effective strategy in the management of patients that will intake ONJ-related drugs (4-10).
The aim of primary prevention is the control of risk factors in order to reduce the chance to develop infections and inflammatory events that do not respond to conservative therapy, while secondary prevention is based on the early diagnosis throughout clinical and radiological signs and associated symptoms identification
Following current ministerial recommendations (19) the patients that are candidates to therapy with ONJ-related drugs must undergo a dental examination and to treatment of oral pathologies before starting drug therapy.
If dental surgical therapies are indicated to solve oral pathologies (e.g. dental extractions), the onset of the ONJ-related drugs therapy should be 4-6 weeks after the

surgical procedures or however not before the complete epithelialization of extraction site.
In the clinical case the we will present despite all the ministerial recommendations have been followed, some mistakes brought to a bad management of the patients with consequent late diagnosis.
The aim of the present case report is to underline that following the ministerial recommendation should be not sufficient in order to avoid the ONJ risk. Furthermore the present work aims at the importance of early radiological signs that should bring the clinician to the suspect of ONJ before the onset of clinical signs in order to have an early diagnosis and a consequent better prognosis.

Case report

A female aged 70 affected by bone metastases secondary to ductal invasive breast cancer was waiting to start the therapy with resorption inhibitor drugs (DENOSUMAB) and undergone a dental clinical evaluation that underlined the need of some dental extractions (1.2-2.2-3.2-3.3-4.2-4.3).
26.11.2018: dental extractions were performed following appropriate surgical protocols (29-79-89) and prescribing antibiotic therapy (Amoxicillin 1gr 3 times a day started 3 days before the surgery and stopped 1 week after the surgery) (29-79-82-84-85-88-90). Dental extractions were performed after a rinse with a 0.2% chlorhexidine mouthwash without alcohol for 1 minute. After the local anesthesia, the extractions of teeth were performed with the minimum intrusiveness for the bone after removing granulation tissue. The wounds were sutured in order to obtain a healing by primary intention.

03.12.2018 After one week the sutures were removed and the post-surgical control was planned after one month

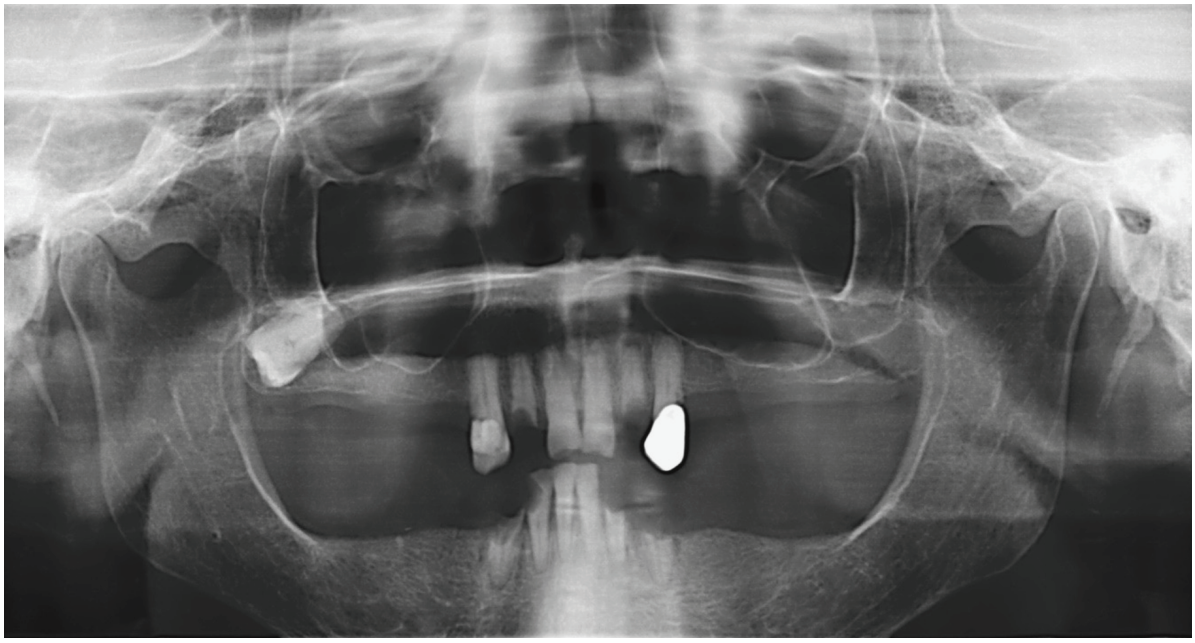
07.01.2019 Complete healing of the tissues. Absence of symptoms. The therapy with Denosumab started.

14.06.2019 Dental evaluation: absence of acute or chronic inflammation. Further x-rays investigations were not prescribed.

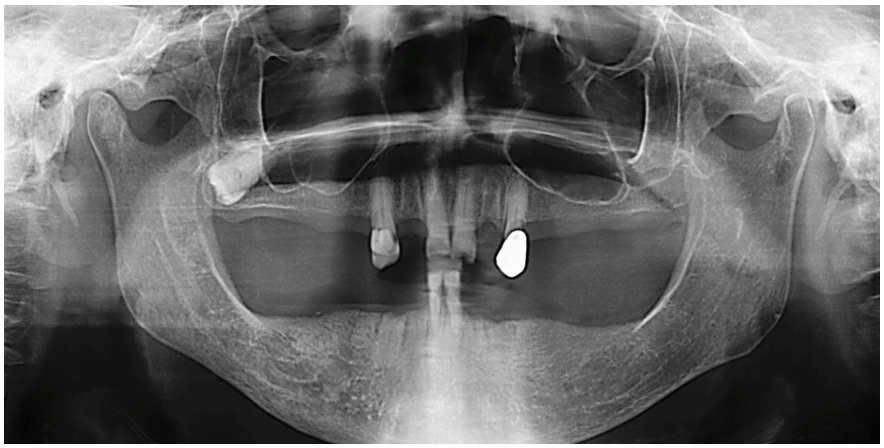
10.10.2019 The patient refers pain during chewing in the 4th quadrant. The clinician decided to modify the lower removable prostheses in order to eliminate areas of pressure.

15.11.2019 After an initial improvement, the symptoms get worse and a new OPM was prescribed.

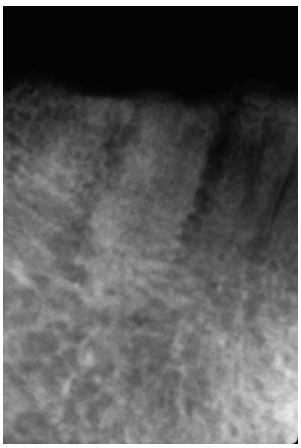
The OPM is significant concerning early ONJ signs. In this case these signs were misinterpreted by the dentist and the radiologist and were confused with root residuals in the 43-44 area. In 41-42 area a late healing was detected (the extractions were performed 1 year before). Endoral x-rays were performed in order to confirm the radiological suspect (presence of root residuals) but these investigations show the presence of a bone thickening caused by the denosumab therapy.
Therefore, we decided to further modify the lower prosthesis in order to remove pressure areas.
Actually, the OPM and the endoral x-rays show evident signs of ONJ: post-extractive socket persistence after more than 1 year from the extraction; widespread osteosclerosis and spongious thickening in the extraction areas; bone sequestrum in 44-45 areas.
The progressive bone thickening is more clear if this area of osteosclerosis is compared to the bone density of adjacent or contralateral areas (187-203).
These radiological signs were ignored or misinterpreted as late healing caused by resorption inhibitors drugs.



OPM 16.11.2018



OPM 15.11.2019

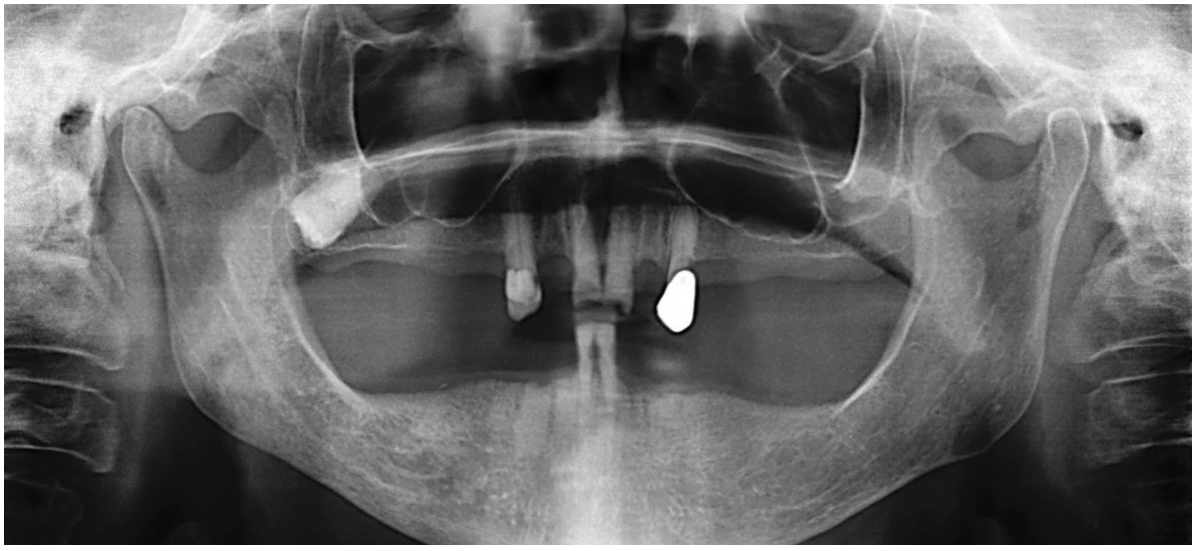


OPM 15.11.2019 (detail)

This contributed to a delayed diagnosis and to a consequent worst prognosis.
28.11.2019 After about 2 months the patient come back for a dental control because of persistent pain. The clinical examination showed the presence of a fistula in the 43-44 area. Therefore we decided with the oncologist to suspend the therapy with Denosumab and to refer the patient to the maxilla-facial section in order to treat a possible medication-related ONJ.

Conclusion

In this case the pain referred by the patient was underestimated and misinterpreted. Furthermore, since all steps of the management protocols were followed, the early radiological signs were not recognized.
The results of the present clinical experience aim to underline that detecting early signs of medication-related ONJ could be difficult. Furthermore, we would like to



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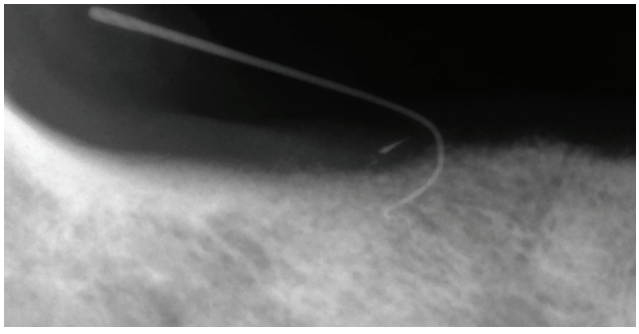

ENDORAL x-rays: FISTULA

highlight that this pathology can occur even if all ministerial recommendation are followed.
Osteonecrosis diagnosis and treatment need a specific knowledge and a careful evaluation of clinical and radiological signs (even if not specific).
The management of the oncologic patient require a coordination among different specialists in order to intercept this pathology in the early stage and to improve the treatment that could be invasive. The specialists involved should be: the oncologist (management of oncologic pathology), the dentist (management of oral pathology), the general physician and the radiologist (management of the comorbidity).

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