Osteonecrosis of the jaw and bisphosphonates: Imaging features

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Abstract

Purpose. 1) To review the pathophysiology of osteonecrosis of the jaw in patients receiving bisphosphonates. 2) To review the imaging findings of osteonecrosis of the jaw and attempt to define pathognomonic imaging features.

Materials and methods. Retrospective study of 15 patients with metastatic disease treated with bisphosphonates. All available imaging studies including orthopantomograms, CT and bone scans were reviewed simultaneously by two radiologists (FO, DB).

Results. The most frequent imaging finding was osteolysis. Signs of bisphosphonate impregnation were frequently observed: areas of osteosclerosis or heterogeneous demineralization due to abnormal bone remodeling. The outer cortex appeared duplicated in one case. Complications including fracture, sequestra, oroantral fistula and sinusitis may also occur.

Conclusion. The imaging features of osteonecrosis remain fairly nonspecific. Drug-related osteonecrosis of the jaw should nonetheless be suggested in the appropriate clinical setting in the presence of osteolysis associated with osteosclerosis. Imaging is helpful to assess the extent of the disease and detect complications for improved patient management.

Key words: Osteonecrosis. Bisphosphonates. CT. Orthopantomogram.

Bisphosphonates (BPs) reduce bone resorption by inhibiting osteoclastic activity. BPs have anti-fracture effects by increasing bone mineralization and mechanical resistance. They also have anti-angiogenic properties causing a decrease in vascularization (1). The indications for BPs have increased with the demonstration of their efficacy in the management of metastatic bone disease. Classically used in patients with Paget’s disease and osteoporosis, BPs are now frequently used by oncologists in the management of patients with lytic bone metastases secondary to any solid tumor or multiple myeloma (2).

Osteonecrosis of the jaw (ONJ) is an undesirable complication of BPs that was first described in 2003 by Marx, et al. (3). ONJ is characterized by an impaired bone repairation process at the alveolar ridge with exposed bone of abnormal quality. Bleeding and pain may be present. Based on a review of 15 diagnosed cases, we illustrate the main imaging features of ONJ to familiarize radiologists with this “new entity”. Early detection of the relationship with BP therapy is important to ensure optimal dental care. Therefore, it is important for radiologists to be aware of this entity.

Patients and methods

Retrospective study of 15 patients, aged 56 to 86 years, with bone metastases treated with BPs, referred to maxillofacial surgeons due to oral and dental symptoms. Patient characteristics, duration and type of treatments and clinical presentation are summarized in table I. All patients had one or more orthopantomograms (OPGs), and 13 examinations were available for review. CT of the maxilla was performed in 5 cases, and bone scan
The imaging findings on OPGs are summarised and illustrated in figures 1 to 3.

### Results

The imaging findings on OPGs are summarized in **table II** and illustrated in figures 1 to 3.

### Discussion

BP-related ONJ is characterized by the presence of exposed bone in the mouth which fails to heal after appropriate intervention over a period of 3 or 6 weeks in a patient taking BPs (fig. 5). Exposed bone

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**Table I**

Patient characteristics.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>15</th>
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<tbody>
<tr>
<td>Age</td>
<td>68.2 years (56-86 years)</td>
</tr>
<tr>
<td>Sex</td>
<td>10 females, 5 males</td>
</tr>
<tr>
<td>Primary malignancy</td>
<td>Breast: 5, Kidney: 1, Kidney and prostate: 2, Prostate: 1, Thyroid: 1, Myeloma: 4, Endometrium: 1</td>
</tr>
<tr>
<td>Bisphosphonates prescribed</td>
<td>Zoledronic acid: 8, Pamidronate and zoledronic acid: 4, Alendronic acid: 2, Not specified: 1</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>29 months (11-48 months)</td>
</tr>
<tr>
<td>Delay to onset of ONJ</td>
<td>26 months (10-48 months)</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Pain: 1 case, Tooth loosening/flocc : 7 cases, Delayed healing: 3 cases, Fracture: 1 case, Sinusitis: 3 cases, Not specified: 4 cases</td>
</tr>
<tr>
<td>Clinical findings</td>
<td>Exposed bone: 9 cases, Osteitis, necrosis: 3 cases, Not specified: 2 cases</td>
</tr>
<tr>
<td>Triggering event</td>
<td>Tooth extraction: 8 cases</td>
</tr>
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</table>

On CT, osteolysis was present in 2 cases. A bone sequestrum was present in 1 case (fig. 1). In addition to osteolysis, areas of sclerosis and cortical thickening with duplicated appearance and mandibular fracture were present in 1 case (fig. 4). Maxillary sinus opacification was present next to bone lesions with one case of oroantral fistula. In the 3 available bone scans, non-specific inflammatory type increased tracer uptake was present (fig. 2).

BP-related ONJ is characterized by the presence of exposed bone in the mouth which fails to heal after appropriate intervention over a period of 3 or 6 weeks in a patient taking BPs (fig. 5). Exposed bone...
Fig. 1: Delayed healing after tooth extraction after 22 months of zoledronate therapy for myeloma.

\(a\) Areas of osteolysis of the maxilla at the site of extraction.

\(b, c\) CT, axial and sagittal reformatted images: presence of a sequestrum (white arrows).

Fig. 2: Delayed healing after tooth extraction in a 68 year old patient treated for 3 years with pamidronate and zoledronate for prostate cancer.

\(a\) Orthopantomogram: lamina dura thickening indicating BP impregnation.

\(b\) Bone scan: inflammatory like increased tracer uptake of the right mandible.
is not encountered with other types of inflammatory or infectious osteitis or radiation induced osteonecrosis (6). Three criteria are needed for diagnosis: no history of radiation therapy to the affected bone, no evidence of underlying metastasis and absence of healing after 3 to 6 weeks of appropriate treatment (9). Since the first published cases in 2003 (3), several studies have been published. The incidence of BP related ONJ remains difficult to estimate, ranging between 4 and 11% in small series (10-13). In the series by Hoff et al. on 4019 patients receiving BPs intravenously, it was estimated at 1-3% (14). In the literature, mandibular involvement occurs in 59% of cases, maxillary involvement in 27% of cases, and combined mandibular and maxillary involvement in 8% of cases (4). While spontaneous ONJ may occur, a triggering event such as dental extraction or surgery is reported in 61.5% of cases (15). The type of BP and mode of administration have an impact on the disease: a few cases have been described in osteoporotic patients receiving oral BPs. The vast majority of published cases occurred in patients receiving high doses of BPs intravenously for metastatic disease, with doses 12 fold larger. The risk appears increased for patients receiving zoledronate alone compared to pamidronate alone or in combination with zoledronate (4). Studies show an increased incidence with treatment duration, from 1.5% in patients treated for less than 1 year to 7.7% in patients treated between 37 to 48 months (9). The role of chemotherapy and radiation therapy remains controversial. While Marx, et al. (3) recognize these as factors of comorbidity, the series by Bamias (9) and Ruggiero (6) describe cases in patients without history of chemotherapy or radiation therapy. Histology reveals nearly complete absence of bone cells and signs of active remodeling suggesting an appearance of “frozen bone” (fig. 6). Very active bone resorption is noted. The loss of osteoclasts could be the result of repeated administration of BPs, and the loss of bone cells could be the result of osteonecrosis. Signs of inflammation are associated to the acellular necrotic bone. A mixed inflammatory cellular infiltration is present that may indicate infection. The outcome of treated ONJ has not extensively been studied. While clinical improvement often occurs with medical treatment, persistent zones of necrosis frequently are observed. Based on data from our series, early diagnosis and management combining improvement in dental hygiene, antibiotics and conservative surgical management could improve the local prognosis. Discontinuation of BPs would not appear to have an impact on outcome (16). The best treatment would be prevention, with restoration of dental and oral health as best as possible, prior to BP treatment. The role of imaging includes 4 elements:

- OPG, prior to BP treatment, allows detection of infected teeth, periapical cysts and granulomas.
- OPG allows early detection of asymptomatic foci of non-exposed necrotic bone.
- At the time of diagnosis, OPG, complemented by CT, depicts areas of osteosclerosis with or without osteolysis. The presence of complications such as fracture, bone sequestrum, oroantral fistula and sinusitis may be detected and direct management. The presence of alveolar bone sclerosis as a result of BP impregnation is an inconstant finding. Bone expansion with “double contour” of the cortex was present in one patient with severe disease. While our small patient sample precludes us from confirming the specific nature of this finding, it could be an indicator of severe disease. Imaging was integrated in 2008 in the classification of ONJ by a group of French experts (table III) (17). Their classification is used for patient follow-up, to determine prognostic clinical and/or imaging features. It was established based on currently available data, and will undoubtedly evolve with time. Indeed, the significance of bone sclerosis which is observed in nearly all cases remains indeterminate: does it indicate BP impregnation or osteonecrosis (17)?
- Finally, OPG is used for follow-up after treatment, and to assess bone healing after conservative surgical management. Unfortunately, the imaging features are
Fig. 4: **Spontaneous tooth loss and parasymphyseal pain in a 68 year old patient with renal cancer treated with zoledronate and pamidronate for 44 months.**

- **a** Osteolysis and sclerosis. Heterogeneous appearance of the bone.
- **b** CT, axial images showing outer cortex duplication.
- **c** Coronal reformatted CT images: mandibular fracture (white arrow).
- **d** 3D VRT image: Duplication of the outer cortex.
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Fig. 5: Osteonecrosis, clinical findings: exposed bone without healing at 3 to 6 weeks in a patient receiving BPs.

Table III
Classification of ONJ.

<table>
<thead>
<tr>
<th>Clinical findings</th>
<th>CT findings</th>
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<tr>
<td>A absence of exposed bone</td>
<td>0 Absence of sclerosis</td>
</tr>
<tr>
<td>A bis fistula and/or infection</td>
<td>1 Sclerosis</td>
</tr>
<tr>
<td>B exposed bone</td>
<td>2 Sclerosis and duplicated cortex</td>
</tr>
<tr>
<td>C exposed bone + infection</td>
<td>3 Sclerosis + sequestrum without cortical thickening</td>
</tr>
<tr>
<td>D cutaneous fistula</td>
<td>4 Sclerosis + cortical thickening + sequestrum</td>
</tr>
<tr>
<td>S pain, heaviness, dysesthesia</td>
<td>L: focal involvement</td>
</tr>
<tr>
<td>Ns asymptomatic</td>
<td>E: diffuse involvement</td>
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Fig. 6: Osteonecrosis as a complication of BP therapy: histology.

a Normal bone (Goldner x10).
b Osteonecrosis. (Goldner x2.5). Calcified bone without cells (pink). No sign of bone remodeling. Mixed inflammatory cell infiltrate (arrow).

not specific, and correlation with an appropriate clinical context is needed for diagnosis: biopsy is not recommended in these patients with poor healing for whom invasive procedures should be avoided. With regards to differential diagnosis, radiation induced osteonecrosis occurs after local radiation therapy or brachytherapy. Metastases frequently are associated with a surrounding soft tissue mass next to the zone of osteolysis. They may be associated with neuralgia related to perineural involvement.

Conclusion

Osteonecrosis of the jaw as a complication of BP therapy is relatively rare. While this would not deter from using BP therapy in patients with bone metastases, it might limit the treatment duration to two years. A Mayo Clinic consensus statement (18) suggested that BP therapy should be suspended after two years in patients with multiple myeloma. Even though no specific treatment exists for ONJ, knowledge of this clinical entity may improve clinical and dental management. OPG should be obtained in all patients before starting BP therapy. CT of the maxilla should be obtained at the time of diagnosis to further characterize the extent of disease and detect potential complications.

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References


