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What do we expect to visualize on the radiographs of mronj patients?

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Abstract

Medication related osteonecrosis of the jaws (MRONJ) is a common complication of the bisphosphonates and other anti-resorptive drugs which are mainly used for osteoporosis, malignancy related hypercalcemia and distant bone metastases. While some imaging modalities are not successful at detecting Stage 0 MRONJ patients, some modalities such as Magnetic Resonance Imaging (MRI), can detect early MRONJ lesions. Early diagnosed MRONJ lesions are relatively easier to maintain and treat; thus, early diagnosis plays huge role in treatment. In this review main imaging modalities which are used in dentistry were evaluated regarding MRONJ.

Keywords: bisphosphonate-associated osteonecrosis of the jaw, cone-beam computed tomography, magnetic resonance imaging, multidetector computed tomography, panoramic radiography, positron-emission tomography, single photon emission computed tomography

1. Introduction

Medication related osteonecrosis of the jaws (MRONJ) is a progressive necrosis of the maxilla and mandible due to bone-modifying agents, angiogenic drugs and other medications. Clinical features of MRONJ are reported as: Presence of an exposed bone area which does not heal within eight weeks (Ruggiero et al., 2014; Unsal et al., 2017; Dunphy et al., 2020; Kim et al., 2020; Limones et al., 2020; Morishita et al., 2020). Also, the patient must have a history of bone-modifying agents (BMAs) such as bisphosphonates, denosumab or angiogenic inhibitor drugs (AID) and the patient must not have any radiotherapy at the maxillofacial region. Although the pathogenesis of MRONJ is not completely understood there are hypothesizes which suggest that MRONJ is related in remodeling and healing of the jaws. Mechanisms that frequently mentioned are inhibition of osteoclast differentiation, inhibition of angiogenesis, induced apoptosis of osteoclasts, reduction of bone turnover (Ristow et al., 2015; Berg et al., 2016; Brierly et al., 2019). Oral malodor, erythema, soft tissue ulceration, which is persisted for more than 8 weeks, neuropathy, jaw pain, mucosal swelling, trismus, exposed bone or a non-healing extraction socket, paresthesia and suppuration are the common clinical signs and symptoms of MRONJ (Brierly et al., 2019; Rao et al., 2019; Sarmiento, 2019; Steel, 2019; Dunphy et al., 2020; Jasper et al., 2020; Limones et al., 2020; Morishita et al., 2020; Wadia, 2020).

Five different hypotheses were suggested for the pathophysiology of the MRONJ since the first osteonecrosis of the jaws cases were reported; however, the exact pathophysiology is not determined yet (Marx, 2003; Aghaloo et al., 2015). Proposed hypotheses were regarding; the inhibition of bone remodeling process, infection/inflammation hypothesis which tries to find an answer to if exposed bone induces bacterial biofilm or if bacteria induced the exposed bone and infection, angiogenesis inhibition, toxicity of soft tissues and acquired immunity dysfunction (Christodoulou et al., 2009; Sedghizadeh et al., 2009; Filleul et al., 2010; Kumar et al., 2010; Santos-Silva et al., 2013; Bae et al., 2014; Aghaloo et al., 2015).

The clinical signs of the MRONJ are well reported in the literature, however, only several studies concentrated on the early radiographic signs of MRONJ. This manuscript focuses on MRONJ's radiographic appearances in various imaging modalities (Berg et al., 2016; Subramanian et al., 2017; Wazzan et al., 2018; Shibahara, 2019; Zirk et al., 2019).

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2. Imaging modalities and MRONJ

2.1. Orthopantomography (OPG)

OPG which has relatively lower radiation dose, comparing to 3D imaging techniques, is useful especially for routine radiographic examinations. The most common radiological findings that can be visualized at early MRONJ defects are widening of the periodontal ligament space, thickening of the lamina dura, narrowing of the mandible canal and sclerosis of the trabecular bone. If MRONJ occurs after tooth extraction, a persistent non-healing extraction socket (Fig. 1.) is often seen at OPG image. Advanced MRONJ defects induce sequestrum formation which indicates necrotic bone island. Sequestrum is seen as a radiopaque calcified area within a radiolucent lesion which is completely separated from the healthy trabecular bone (Fig. 2.). Periosteal new bone formations can also be seen on OPGs. Osseous sclerosis is found at almost all MRONJ patients and increased mandibular inferior cortical bone thickness is also another significant parameter in MRONJ patients (Berg et al., 2016).

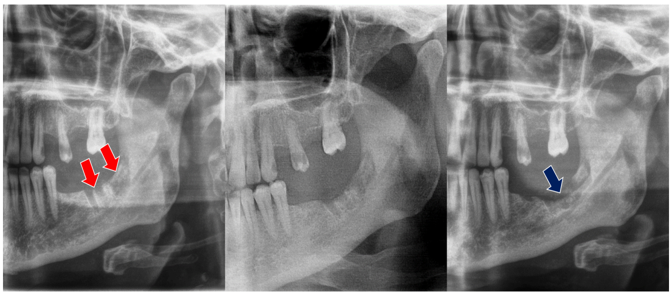

Fig. 1. Cropped panoramic radiographs of a 49-year-old female patient. Persistent non-healing extraction socket's (red arrows) transformation to sequestrum (blue arrows) is seen at mandibular left molar region

Stockmann et al. (2010) stated that the detectability of MRONJ is 96% for CT while 54% for OPGs, thus, it should not be forgotten that MRONJ may be detected on some OPGs, but advanced assessments should be done with.

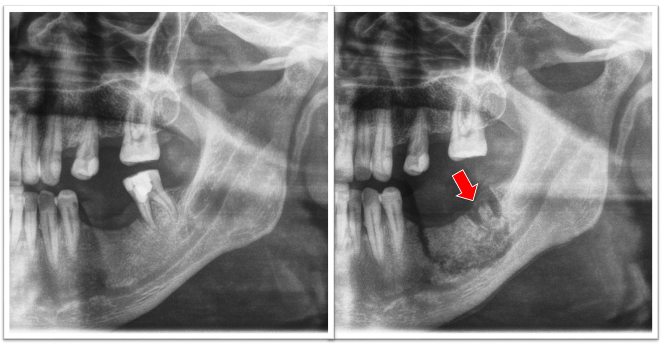

Fig. 2. Cropped panoramic radiographs of a 60-year-old female patient. Sequestrum formation as a radiopaque calcified area within a radiolucent lesion (red arrow) which is separated from the healthy trabecular bone is seen

2.2. Cone-beam computed tomography (CBCT)

CBCT, which has conical X-rays instead of fan beam X-rays, has high diagnostic quality images with lower radiation dose than CT. CBCT is also superior to OPG since there is no superpositions of adjacent anatomical structures and bucco-lingual evaluations can be performed. CBCT is better at visualizing early changes in both trabecular and cortical bone comparing to all 2D imaging modalities (Berg et al., 2016; Subramanian et al., 2017; Unsal et al., 2017; Goller-Bulut et al., 2018; Zirk et al., 2019).

CBCT can demonstrate increased bone density which is the most common initial change in MRONJ patients (Fig. 3). Since the slice thicknesses of CBCT images are usually thinner than CT images, small bone alterations can be easily detected with CBCT. CBCT images does not have diagnostic soft tissue contrast which makes it impossible to evaluate associated thickening and edema of soft tissues (Subramanian et al., 2017; Goller-Bulut et al., 2018; Zirk et al., 2019).

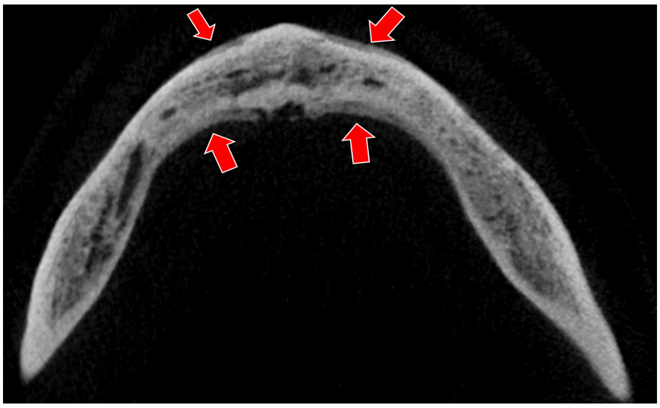

Fig. 3. Osteosclerosis is seen at axial CBCT slice. Parallel/solid periosteal reactions are also seen at buccal and lingual cortical plates (red arrows)

Common CBCT findings of initial MRONJ lesions are (Berg et al., 2016; Subramanian et al., 2017; Goller-Bulut et al., 2018; Zirk et al., 2019):

- Narrowing of bone marrow space
- Osteolysis with sclerosis at surrounding trabecular bone
- Parallel/solid periosteal reactions

Common CBCT findings of advanced MRONJ lesions are (Fig. 4.) (Berg et al., 2016; Subramanian et al., 2017; Goller-Bulut et al., 2018; Zirk et al., 2019):

- Cortical bone erosion and trabecular bone destruction.
- Pathologic fractures
- Buccal and lingual cortical plate destructions at advanced stages
- Parallel/solid periosteal reactions

2.3. Computed tomography (CT)

Relatively higher radiation dose and longer scanning process are the limitations of CT comparing to CBCT. However, CT images have diagnostic soft tissue contrast, thus, edema and thickening of soft tissues can be evaluated with CT. It should not be forgotten that most of the CT units have bigger voxel sizes than CBCT units which makes it almost impossible to evaluate minor alterations at trabecular bone (Berg et al., 2016).

2.4. Magnetic resonance imaging (MRI)

Following the studies by Lauterbur and Mansfield, MRI was developed for clinical use in 1980s. The principle of MRI relies on a large magnet which affects hydrogen nuclei in the human body and aligns them in the active magnetic field. After a radiofrequency pulse is directed to patient some hydrogen nuclei will resonate and after this radiofrequency is taken away the energy will be released from the patient. This energy is detected by the coils and a distribution pattern of those nuclei, an image will be reconstructed (Orhan and Rozylo-Kalinowska, 2019).

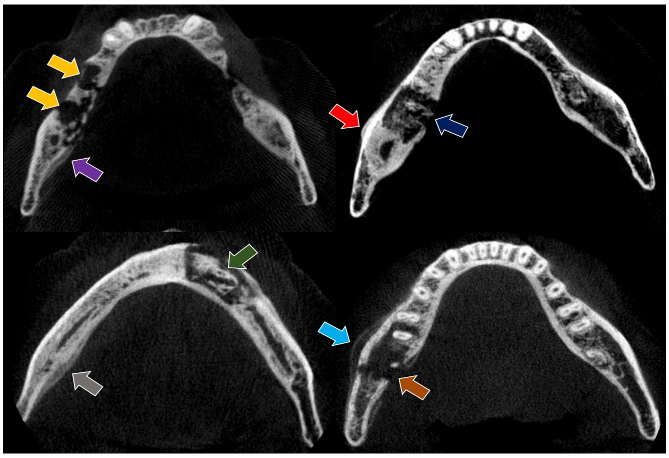

Fig. 4. Axial CBCT slices of four different MRONJ patients. A: Non-healing extraction sockets (yellow arrows), cortical destruction and parallel periosteal reaction (purple arrow) at lingual cortical plate are seen. B: Parallel periosteal reaction (red arrow) at buccal cortical plate, cortical destruction at lingual cortical plate and sequestrum (blue arrow) formation are seen. C: Osteosclerosis, sequestrum formation (green arrow), cortical destruction at buccal cortical plate and parallel periosteal reaction (gray arrow) at lingual cortical plate are seen. D: Cortical destruction at lingual cortical plate (brown arrow), parallel periosteal reaction (cyan arrow) at both lingual and buccal cortical plates are seen

Comparing to other imaging modalities MRI has a high soft tissue contrast which makes it superior in TMJ disc evaluations and other examination regarding soft tissues. However, due to long scanning times, possible injuries due to ferromagnetic objects and high installation costs it is still less common than other imaging modalities in dentistry (Orhan et al., 2005; Orhan et al., 2006; Orhan and Rozylo-Kalinowska, 2019).

Although MRONJ mainly involves the jaws which are hard tissues, exposed bone areas show hypointense regions in T1/T2 weighted images and inversion recovery (IR) images since those osteonecrotis areas have lower water content. However, unexposed, and affected areas show hypointense regions in T1 and hyperintense regions in T2-IR images since those osteomyelitic areas have higher inflammation content (Fig. 5.). In other words, it is possible to state that early MRONJ defects will have hyperintense areas in T2 sections and after osteonecrosis those areas will have hypointense areas due to lack of water content. Contrast-enhanced MRI sections reveal more extensive alterations comparing with CBCT and clinical examination (Stockmann et al., 2010; Berg et al., 2016).

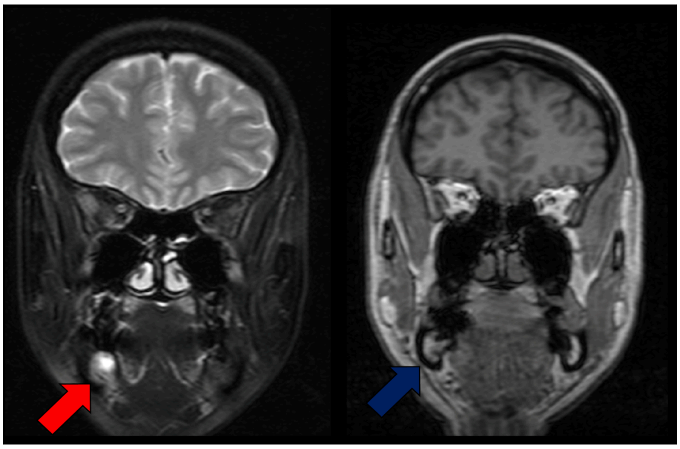

Fig. 5. Coronal T2-W (a) and T1-W (b) MRI images of a 64-year-old female patient. As it is seen in early MRONJ patients, T2-W slice reveals hyperintense osteomyelitic areas with high inflammation content (red arrow). Relevant area was seen hypointense in T1-W slice (blue arrow)

Early MRI finding of MRONJ is the loss of T1 hyperintensity of fatty bone marrow both in maxilla and mandible. Advanced MRI findings of MRONJ are soft tissue edema, bone destruction and inferior alveolar nerve thickening. MRI with contrast agents has high detectability for MRONJ lesions but extent of the detection is a concerning area (Stockmann et al., 2010; Berg et al., 2016).

2.5. Ultrasonography (USG)

Although USG is an advanced imaging modality that has superiority for superficial soft tissues examination, it is not possible to evaluate MRONJ cases since exposed bone areas lack soft tissues. No USG study has yet been done for stage 0 MRONJ cases with USG.

2.6. Single photon emission computed tomography (SPECT)

SPECT is an advanced nuclear imaging technique which is a combination of computed tomography images and signals which were gained from scintigraphy. SPECT scans the distribution of radionuclides such as Tc-99m within both hard and soft tissues with gamma cameras (White and Pharoah, 2014). This allows the distribution of the radionuclide to be displayed in a three-dimensional manner offering better detail, contrast, and spatial information than planar nuclear imaging alone.

SPECT imaging is a functional imaging which is useful especially for bone scans. Several studies were done for MRONJ patients with SPECT and common findings were reported as (Miyashita, et al., 2015; Berg et al., 2016; Miyashita et al., 2019; Miyashita, et al., 2019):

- MRONJ lesions showed focal abnormal activity with an increased radionuclide uptake at periphery and decreased radionuclide uptake at the center of the defect.
- 99Tcm-MDP and 99Tcm-DPD did not show any significant differences in detecting pathologies, so,

both nuclides can be used for MRONJ.

- MRONJ should not show an uptake in the necrotic zone, but due to associated infection, a nuclide uptake may be seen.
- Clinically asymptomatic MRONJ lesions showed significant nuclide uptake which is a promising improvement for SPECT.
- A study showed that 65.7% of the MRONJ patients have increased nuclide uptake so it should not be forgotten that SPECT is not as dependable as CBCT-MDCT or MRI images.

2.7. Positron emission tomography/computed tomography (PET/CT)

PET is also an advanced nuclear imaging modality which relies on radionuclides which emit positrons. In this modality, positron-source radionuclides given to the body lose their substance properties due to the annihilation and F-18, C-11, N-13, and O-15 radionuclides that emit positrons are generally used. The most used radionuclide is F-18 it is used for labeling FDG. Since FDG is a metabolic analogue of glucose the uptake is higher in tissues which requires more energy like cancer cells. But malignant cells do not always have high FDG uptakes which should be considered in differential diagnosis. Higher uptakes can also be seen in active infections and inflammations such as MRONJ, collagen diseases and granulomatous lesions. PET is a common imaging modality for detecting primary bone tumours, osteomyelitis, and metastases (Koenig, 2011; White and Pharoah, 2014; Kitagawa et al., 2019).

PET has limitations in MRONJ patients since the necrotic areas without blood flow and hypermetabolism will not show increased glucose metabolism; however, infected areas can be seen because of inflammatory processes. In other words, early detection and assessment of inflammatory processes can be imagined which may visualize an initial MRONJ (Fig. 6.). PET/CT can detect diffuse and local metabolic changes and these changes can be compared with the contralateral side of the mandible or maxilla for the reference (Berg et al., 2016; Fleisher et al., 2016).

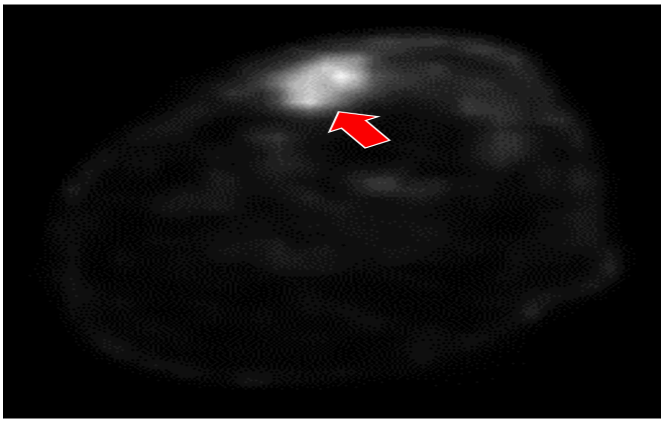

Fig. 6. PET image of a 44-year-old female Stage-0 MRONJ patient. Note the increased glucose metabolism at mandibular right molar region (red arrow)

2.8. Fluorescence-guided bone resection/visually enhanced lesion scope (VELscope)

This newly technique is published as: 100 mg of doxycycline will be received by the patient twice a day for 10 days. This will let the bone to have a high doxycycline uptake which will appear as green at VELscope images. Necrotic bone will not have an uptake therefore no/very little fluorescence is shown. Even in a patient who received only a single 100 mg shot of doxycycline one hour pre-operatively, it was possible to distinguish between necrotic and healthy bone using the VELscope. This technique is used as a guide especially before surgical procedures such as resection (Berg et al., 2016).

Tomo et al. (2020) conducted a review in which they evaluated 18 different studies (218 patients) regarding the VELscope-guided surgical management of MRONJ patients and stated that this method is promising at delimitating the surgical margins of MRONJ resections. It was also reported that inadequate necrotic bone debridement can be avoided with using VELscope.

2.9. Key differential diagnosis

2.9.1. Chronic suppurative osteomyelitis

Chronic suppurative osteomyelitis, osteoradionecrosis and MRONJ share same radiographic features since all of them are characterized with necrotic bone lesions. Medical anamnesis of chronic suppurative osteomyelitis patients lack history of head and neck radiotherapy and BMA/AID drug usage. Radiographs of these patients mostly reveal an odontogenic infection such as apical lesions (Koenig, 2011; White and Pharoah, 2014).

2.9.2. Osteoradionecrosis (ORN)

ORN is a complication of head and neck radiotherapy which is characterized by exposed necrotic bone. As it was mentioned above, radiographic features are same with MRONJ. Medical anamnesis is key in differential diagnosis (Koenig, 2011; White and Pharoah, 2014).

2.9.3. Distant metastasis to jaws

Distant metastases to jaws are unique and present only 1-3% of all oral malignant neoplasms. They can occur in jawbones or oral soft tissues. The main difference between metastatic lesions and MRONJ is metastatic lesions are characterized with ill-defined osteolytic lesions usually without osteosclerosis. Breast and prostate cancers metastases occasionally appear as purely sclerotic changes which may cause a diagnostic challenge. Irregular soft tissue mass is frequently seen with metastatic lesions (Koenig, 2011; White and Pharoah, 2014).

3. Conclusion

Since osteosclerosis is the first radiographic finding in OPG/CT and CBCT images, patients with intense osteosclerosis should be followed-up routinely. If any functional imaging was performed, for follow-up or diagnostic purposes, it should not be forgotten that high nuclide uptake is one of the findings of clinically asymptomatic MRONJ lesions. Also, unexposed MRONJ lesions show hypointense regions in

T1 images and hyperintense regions in T2-IR images due to higher inflammation content. Various imaging modalities have different radiographic findings for initial MRONJ lesions; thus, dentists should be aware of these alterations in order to take preventive measures.

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