CASE REPORT

Medication-related osteonecrosis of the jaw: a dentist's nightmare

Arvind Muthukrishnan, Laliytha Bijai Kumar, Gomathi Ramalingam

Department of Oral Medicine and Radiology, Saveetha University, Saveetha Dental College, Chennai, Tamil Nadu, India

Correspondence to
Dr Arvind Muthukrishnan, arvindmuthukrishnan@yahoo.com

Accepted 21 March 2016

SUMMARY

Medication-related osteonecrosis of the jaw (MRONJ) is a complication in patients who are on anti-bone resorptive drugs. These drugs are prescribed for patients with multiple myeloma, osteoporosis, metastatic carcinoma and Paget's disease. Common anti-bone resorptive drugs such as bisphosphonate and monoclonal antibodies such as denosumab are prescribed for these patients to prevent bone resorption. Although very effective in preventing bone resorption, a complication arising from these groups of drugs is the development of osteomyelitis of the jaw. This medication-related osteonecrosis occurs only in the jaw bones. It could mimic a metastatic jaw tumour when a patient reports to the dental surgeon with pain and swelling in the jaw. This case report describes MRONJ in a 50-year-old Indian woman. This possible painful drug-induced complication of jaw bones can be prevented if proper medical history is taken and management protocol is followed in these patients.

BACKGROUND

Medication-related osteonecrosis of the jaw (MRONJ) is increasing in frequency among patients who are on bisphosphonate therapy and other anti-bone-resorbing drugs such as denosumab, and antiangiogenic medications such as sunitinib and sorafenib.[1 2] MRONJ has been reported in 1 of 30 metastatic carcinoma patients and in 1 f 2000–3000 patients with osteoporosis who were on bisphosphonate therapy. Several cohort and case–control studies have reported MRONJ incidence to be from 0.8% to 12%.[2] These patients usually report to the dental surgeon after a sudden onset of painful jaw swelling, mobility of teeth, halitosis and exposed jaw bone. There are certain guidelines and management strategies for patients who are (1) about to start antiresorptive and anti-angiogenic drugs for cancer management or osteoporosis, (2) asymptomatic patients already on antiresorptive drugs and (3) patients with established MRONJ. According to the literature, the occurrence of osteonecrosis of the jaw after tooth extraction among patients with cancer exposed to intravenous bisphosphonates ranges from 1.6% to 14.8%.[2] Globally, more than 300 million prescriptions of bisphosphonates are given per year and about 5% of patients with cancer on intravenous bisphosphonates develop MRONJ with a mean period for the development of osteonecrosis being 1.8 years.[3] Owing to increasing global usage of bisphosphonates and other antiresorptive drugs, there is an increased incidence of MRONJ. Hence knowledge of this is essential for dental surgeons and medical practitioners.

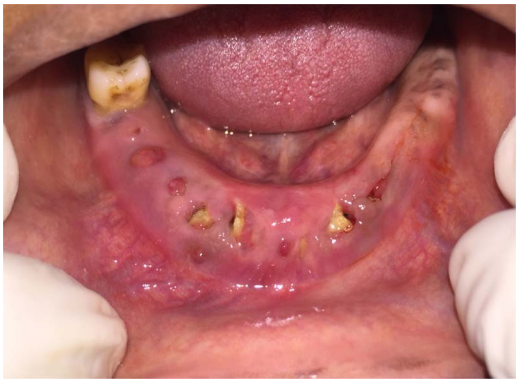

Figure 2 Inraoral swelling with exposed necrotic bone.

CASE PRESENTATION

A 50-year-old Indian woman presented with pain and swelling in the mandibular anterior tooth

Figure 1 Extraoral swelling on the mandibular symphysis region.

To cite: Muthukrishnan A, Bijai Kumar L, Ramalingam G. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2016-214626

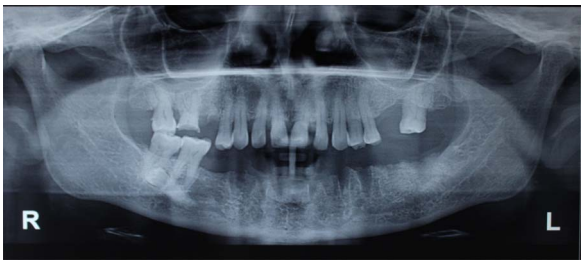

Figure 3 Orthopantomograph revealed altered trabecular pattern with fragments of bone.

region of 1-week duration. The pain was continuous and severe in intensity (visual analogue scale score: 7) and the swelling had gradually increased since onset. A radical mastectomy had been performed in May 2013 after the patient was diagnosed with medullary carcinoma (T2 N2M0 Stage III A). Subsequently, within 4 months, she developed skeletal and brain metastasis for which she received radiotherapy (30 Gy). No radiation was given to the neck or jaw region. Following radiotherapy and chemotherapy with trastuzumab (interferes with HER2 receptor), monthly intravenous injection of zoledronic acid (nitrogenous-based bisphosphonate group of drug) was started and 20 cycles had been completed when the patient reported to us. During this period, she had developed mobility of her teeth in the mandibular anterior region for which she visited her primary care dentist. Suspecting a localised periodontal problem, extraction of mobile 41, 42, 31 and 32 was carried out without consulting with her physician on the patient's drug and medical history. The patient's personal, social and family history was unremarkable.

On clinical examination, there was a localised, mildly firm, tender swelling in the submandibular and submental region, extending from right parasymphysis region to left parasymphysis region. The skin over the swelling was erythaematous (figure 1). Intraorally, there was an obliteration of buccal sulcus from regions 44 to 34. Tender necrotic bone with multiple draining sinuses was present in the alveolar ridge regions 42, 41, 31 and 32 (figure 2).

On the basis of history and clinical findings, a provisional diagnosis of MRONJ was made.

INVESTIGATIONS

Orthopantomograph revealed sclerosis in extraction sockets and surface irregularity in relation to the mandibular anterior region. The trabecular pattern in the extraction socket appeared altered with loose fragments of bone within it. Periosteal reaction was evident on the inferior border of the mandible in the symphysis region (figure 3).

There was bone sequestration in the mandibular symphysis region with a breach on the lingual cortical plate and a

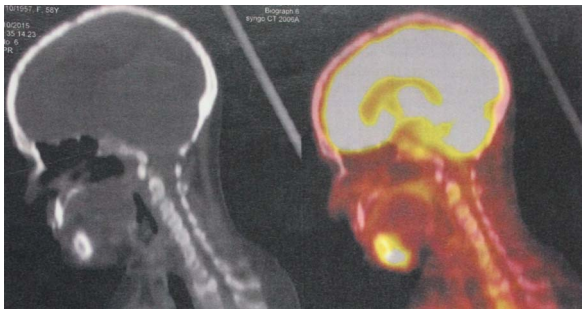

Figure 5 ^{18}F-fludeoxyglucose (FDG) positron emission tomography CT scan revealed increased FDG concentration in symphysis menti and adjacent body of mandible with cortical breach.

periosteal reaction was evident on the inferior border of the mandible in the symphysis region on cone beam CT (figure 4).

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography CT scan showed increased FDG concentration in symphysis menti and adjacent body of the mandible with cortical breach (figure 5).

An incisional biopsy of the exposed bone revealed fragments of infracted bone, regenerating wide sheets of fibrous tissue with proliferating fibroblast, patchy area of lymphocytes, plasma cells and increased vascularity. Dense chronic inflammation was also seen (figure 6).

On the basis of medical history, drug history, clinical findings, imaging findings and histopathological correlation, a final diagnosis of MRONJ was made.

DIFFERENTIAL DIAGNOSIS

1. Metastatic carcinoma: as the patient developed brain and skeletal metastasis, this could be a possible metastatic carcinoma to the mandible. Metastatic lesions to the mandible are common from a primary lung, breast, prostrate and cervical carcinoma.[4]
2. Second primary tumour (SPT): the second differential could be a second primary tumour because it was more than 2 years since the patient developed a primary stage III A medullary carcinoma with subsequent metastasis and it was symptomatic for more than 13 months following treatment for the metastatic lesions. SPT's can develop either synchronously or metachronously more than 6 months after detecting the primary tumour.[5]
3. Chronic suppurative pyogenic osteomyelitis: a persistent periodontal infection could have caused inflammation of the soft tissue components of bone, namely marrow spaces of cancellous bone and the Haversian system of cortical bone, leading to osteomyelitis with clinical evidence of localised swelling, bone tenderness, exposed necrotic bone intraorally and multiple draining sinuses.[6]

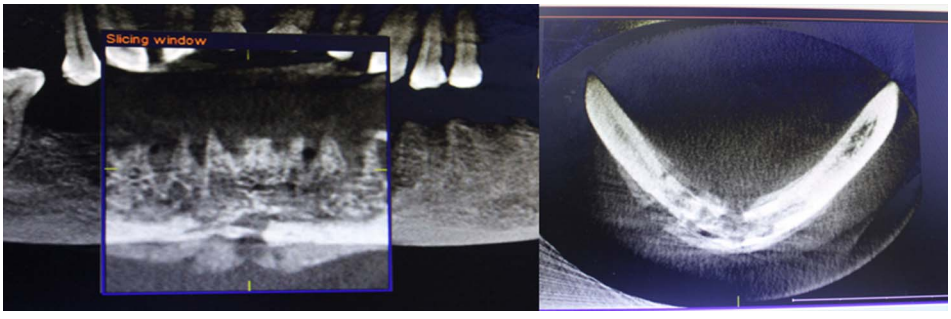

Figure 4 Cone beam CT revealed patchy areas of radiolucency in mandibular symphysis region with breach on lingual cortical plate.

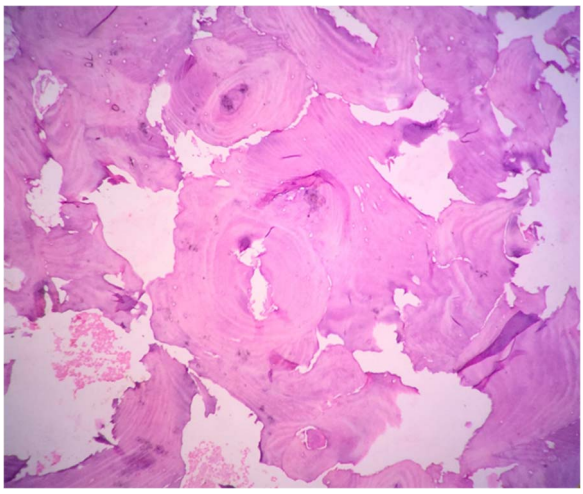

Figure 6 Histopathological section revealed fragments of infracted bone, regenerating wide sheets of fibrous tissue with proliferating fibroblast, patchy area of lymphocytes, plasma cells and increased vascularity.

TREATMENT

The patient was started on clindamycin 300 mg two times a day, metronidazole 200 mg three time a day and ibuprofen 200 mg three times a day for 14 days. The patient was put on clindamycin as it has better bone penetration capacity into avascular tissues. The patient was also put on chlorhexidine gluconate mouth rinse and advised to use it three times a day. After medical consultation, the intravenous zoledronic acid was discontinued for a month after which, under general anaesthesia, peripheral osteotomy leaving the lower border of the mandible intact was performed. The same preoperative medication of clindamycin, metronidazole and ibuprofen was continued 14 days postoperatively. The patient was asked to regularly continue the chlorhexidine mouth rinse.

OUTCOME AND FOLLOW-UP

No complications were encountered postoperatively and follow-up for up to 3 months postsurgery did not reveal any complications.

DISCUSSION

MRONJ is considered in patients if all of the following characteristics are present: current or previous treatment with antiresorptive or antiangiogenic agents; exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for more than 8 weeks and no history of radiation therapy to the jaws and no obvious metastatic disease to the jaws.[2] Therapeutics not only help in curing diseases but in rare instances therapy for a particular disease itself could induce a new disease. The best example for this is MRONJ. Bisphosphonates inhibit osteoclastic activity by interfering with osteoclast metabolism through disruption of the mevalonate pathway, which leads to apoptosis.[7 8] Patients with intravenous bisphosphonates or denosumab have increased risk of developing osteonecrosis of the jaw following dental extraction;[2] but reports also suggest a spontaneous occurrence of osteonecrosis of the jaw in patients who were on antiresorptive drugs.

The bisphosphonates group of drugs are either nitrogenous based or non-nitrogenous based, which can be administered orally or intravenously. The oral route of administration is usually given for osteoporosis, whereas the intravenous bisphosphonates are used to prevent the spread and growth of osteolytic lesions that could metastasise as seen in multiple myeloma, breast cancer or prostrate cancer. This disease was first described in 2003 by a maxillofacial surgeon, Marx, when he described 36 cases of exposed necrotic bone in patients receiving intravenous bisphosphonate therapy.[9] More than 300 000 patients annually receive the intravenous bisphosphonate, zoledronate, to prevent hypercalcaemia of malignancy.[10] The correlation between osteonecrosis induced by bisphosphonates is deduced from the data stating that between 33% and 86% of reported cases had undergone surgical treatment in the period before diagnosis and that the area of osteonecrosis was coincident with the area of treatment.[11]

Table 1 shows the updated 2014 staging and treatment protocol for MRONJ proposed by the American Association of Oral and Maxillofacial Surgeons (AAOMS).[2]

Our patient was on intravenous zolendronate after she developed metastasis following treatment for breast carcinoma. The site of occurrence was also in the mandibular symphysis region. The clinical signs and symptoms corresponded with stage II of the AAOMS protocol.[2]

Table 1 Staging and treatment protocol for medication-related osteonecrosis of the jaw from the Association of Oral and Maxillofacial Surgeons

MRONJ staging	Treatment
At risk category. No apparent necrotic bone in patients who have been treated with either oral or intravenous bisphosphonates.	▶ No treatment indicated ▶ Patient education
Stage 0: No clinical evidence of necrotic bone, but non-specific clinical findings and symptoms.	Systemic management, including the use of pain medication and antibiotics
Stage 1: Exposed and necrotic bone in patients who are asymptomatic and have no evidence of infection.	▶ Antibacterial mouth rinse ▶ Clinical follow-up on a quarterly basis ▶ Patient education and review of indications for continued bisphosphonate therapy
Stage 2: Exposed and necrotic bone associated with infection as evidenced by pain and erythaema in the region of the exposed bone with or without purulent drainage.	▶ Symptomatic treatment with oral antibiotics ▶ Oral antibacterial mouth rinse ▶ Pain control ▶ Superficial debridement to relieve soft-tissue irritation
Stage 3: Exposed and necrotic bone in patients with pain, infection and one or more of the following: exposed and necrotic bone extending beyond the region of the alveolar bone, (ie, inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathological fracture, extraoral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible of sinus floor.	▶ Antibacterial mouth rinse ▶ Antibiotic therapy and pain control ▶ Surgical debridement/resection for long term palliation of infection and pain

In conclusion, with the increasing number of elderly patients with osteoporosis, multiple myeloma and metastatic carcinoma, use of antiresorptive drugs, for them, is inevitable. While treating these patients for any invasive dental treatment, proper drug history has to be taken by the dental surgeon. For those patients on antiresorptive medication, the physician should advise a routine oral evaluation to assess for any medication-related osteonecrosis of the jaw and mucosal changes. The dentist treating these patients should also be well updated on the complications that could arise from this group of drugs. Management of these patients who have developed complications should always be carried out in liaison with their physician. The decision to discontinue an antiresorptive drug for any dental procedure should be taken in consultation with the patient's physician. Prevention, risk reduction and treatment strategies of MRONJ need to be further improved for an accurate judgement on the risk, prognosis, treatment selection and outcome for patients with MRONJ.[2]

Learning points

- Medication-related osteonecrosis of the jaw (MRONJ) is a complication that could arise in patients on antiresorptive medications.
- Primary care dentists should be aware of oral side effects, signs and symptoms of MRONJ.
- The dentist should be aware of dental operative protocol for patients on these groups of drugs.
- The physician should refer those patients on antiresorptive drugs to the dentist for frequent evaluation and assessment for any drug-related jaw changes.
- In these categories of patients, prevention is always better than cure.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Arrain Y, Masud T. A current update on osteonecrosis of the jaw and bisphosphonates. *Dent Update* 2011;38:672–6, 678.
2 Ruggiero SL, Dobson TB, Fantasia J, *et al*. American Association of Oral and Maxillofacial Surgeons Position Paper on Medication-related Osteonecrosis of the Jaw. 2014.
3 Scully's medical problems in dentistry, 7th edn. Churchill Livingstone Elsevier 2014, ISBN: 978-0-7020-5401-3, pp. 431.
4 Lenz M, Freid JR. Metastases to the skeleton, brain and spinal cord from cancer of the breast and the effect of radiotherapy. *Ann Surg* 1931;93:278–93.
5 Warren S, Gates O. Multiple primary malignant tumors: a survey of the literature and a statistical study. *Am J Cancer* 1932;16:1358–414.
6 Baltensperger M, Eyrich G. Osteomyelitis of the jaws: definitions and classification. In: Baltensperger M, Eyrich G, eds. *Osteomyelitis of jaws*. Berlin: Springer, 2009:5–56.
7 Van Beek ER, Löwik CWGM, Papapoulos SE. Bisphosphonates suppress bone resorption by a direct effect on early osteoclast precursors without affecting the osteoclastic capacity of osteogenic cells: the role of protein geranylgeranylation in the action of nitrogen containing bisphosphonates on osteoclast precursors. *Bone* 2002;30:64.
8 Rogers MJ, Gordon S, Benford HL, *et al*. Cellular and molecular mechanism of action of bisphosphonates. *Cancer* 2000;88(12 Suppl):2961–78.
9 Marx RE. Letters to editor. Pamidronate (Aredia) and zoledronate (Zometx) induced vascular necrosis of jaw: a growing epidemic. *J Oral Maxillofac Surgery* 2003;61:1115–17.
10 HellStein JW, Marek CL. Bisphosphonate osteoradionecrosis (bis-phossy jaw): is this phossy jawof the 21st century. *J Oral Maxillofac Surg* 2005;63:682–9.
11 Mc Leod NM, Davies BJ, Brenan PA. Bisphosphonates osteonecrosis of the jaws; an increasing problem for the dental practioner. *Br Dent J* 2007;203:641–4.