

Aggressive denosumab-related jaw necrosis – a case series

M. Badr,¹ E. Kyriakidou,² A. Atkins³ and S. Harrison⁴

In brief

Presents four case reports showing progressive and increasingly severe presentations of the disease.

Dental practitioners are more likely to recognise early stages and appropriate actions might limit the severity.

The condition is a potential material risk and the patient needs to be adequately informed.

Medication related osteonecrosis of the jaw is becoming a repeatedly seen complication in cancer patients. Stage 0 of the disease is more likely to be seen by the patients' general dental practitioners. We are presenting four cases of MRONJ related to denosumab treatment showing increasingly aggressive pictures of the disease. Nevertheless, we also present a good response to a drug holiday arranged by the patients' treating oncologists.

Background

Our skeletal system is constantly remodeling to maintain its health. The balance between bone formation and resorption can be disrupted in a number of pathological and metabolic conditions predisposing to disease progression and significant skeletal related events such as pathological fractures and severe pain.¹

Bisphosphonates are one of the first anti-resorptive drugs to be discovered. Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is one major complication that, in spite of its low incidence rate, can significantly affect patients' quality of life.² A new generation of anti-resorptive medication was required to overcome bisphosphonates' shortcomings.

Denosumab is a human monoclonal antibody that inhibits bone resorption. In contrast to bisphosphonates, it does not get

incorporated inside the mineral bone matrix. Denosumab acts through binding with receptor activator of nuclear factor kappa b ligand (RANKL) which is found as a cell surface molecule on osteoblasts. Blocking RANKL inhibits the osteoblastic effect on osteoclasts and osteoclast progenitors and obstructs their activation and differentiation respectively.³

Osteonecrosis of the jaw (ONJ) that is related to anti-resorptive medications (MRONJ) continues to be reported with denosumab. The available published information is suggesting an increased risk of ONJ with denosumab, compared to bisphosphonates and proposing a similar clinical course with all four stages (Table 1) of the disease presented.^{4,5}

This report discusses four cases of

denosumab-related MRONJ and shows a possibly more aggressive picture of the disease.

Case 1

A 55-year-old woman was referred by her general dental practitioner (GDP) to our nerve injury clinic for management of her left sided inferior alveolar nerve (IAN) paraesthesia. The patient presented with numbness and constant pain in the left sided IAN distribution following removal of tooth LL5 in July 2014. A year later, removal of tooth LL6 was undertaken after recurrent infections and pain.

Medically she was diagnosed with breast cancer in 2011 and had a wide local excision followed by chemotherapy and was placed on denosumab intravenous injections.

Table 1 Medication-related osteonecrosis of the jaw (MRONJ) staging from subclinical to extensive form of the disease.

Stage	Characteristic
0	No clinical or radiographic evidence of bone necrosis in presence of non-specific clinical findings and symptoms.
1	Exposed and necrotic bone in asymptomatic patients.
2	Exposed and necrotic bone associated with infection, pain, and/or erythema.
3	Stage 2 plus:
	(i) Bone lesions extending beyond the region of alveolar bone. Or
	(ii) Osteolysis extending to inferior border of mandible or sinus floor.

¹Academic Clinical Lecturer in Oral Surgery; ²Academic Clinical Fellow/ Specialty Registrar in Oral Surgery; ³Senior Clinical Lecturer/Honorary Consultant Oral Surgeon; ⁴Senior Specialist Clinical Teacher and Honorary Consultant in Oral Surgery, University of Sheffield, School of Clinical Dentistry, 19 Claremont Crescent, S10 2TA
*Correspondence to: M. Badr
Email: medodont@hotmail.com

Refereed Paper. Accepted 23 May 2017
DOI: 10.1038/sj.bdj.2017.573

Clinical examination revealed a grossly mobile anterior mandible with widespread bony necrosis, osteomyelitis and submental swelling. Sensory testing revealed complete numbness in the left sided IAN distribution. This represents a stage 3 MRONJ.

A panoramic radiograph revealed an extensive patchy area of ill-defined bone loss in the anterior mandible extending posteriorly to the premolar/molar areas bilaterally. Cone beam computed tomography (CBCT) demonstrated extensive bony destruction together with periosteal reaction in keeping with a spreading chronic bony infection (Fig. 1).

Due to the patient's area of residence she requested to be seen at her local hospital. The patient was referred to her local oral and maxillofacial surgery unit for management and follow up.

Case 2

A 76-year-old woman was referred by her GDP with a three month history of a non-healing socket of tooth LL4. The patient was treated with two courses of antibiotics prior to referral which provided only temporary relief to her symptoms.

Medically, she was diagnosed with breast cancer ten years before and recently commenced intravenous denosumab for metastatic disease. She also receives hormonal therapy and palliative radiotherapy to the spine.

Clinically, there was a partially healed socket of tooth LL4 with granulomatous appearance and tenderness. There was no discharge from the area. Radiographs confirmed the absence of bony infill of the socket (Fig. 2). Local debridement and biopsy of the granulomatous tissue was performed to exclude any potential malignancy.

The lesion was treated conservatively with long-term antibiotic cover and oral hygiene. After liaison with the oncology team, denosumab was stopped for four months. Significant clinical improvement was seen on subsequent review appointments and signs of bony infill could also be noted (Fig. 2).

Case 3

A 66-year-old woman was referred to our oral surgery department by her GDP with delayed healing of extraction socket of tooth LL7. The patient reported having had an extraction about four months prior to her review and a previous episode of infection which was treated with antibiotics.

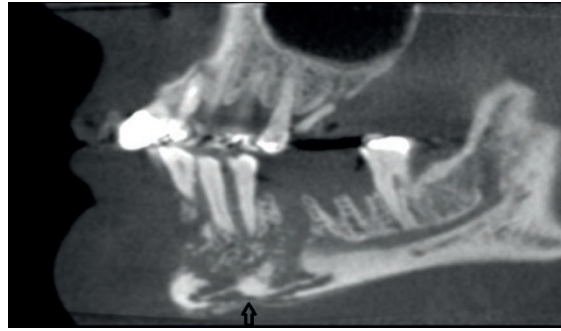


Fig. 1 A sagittal CT view showing extensive bone destruction in anterior mandible extending to the inferior border (arrow)

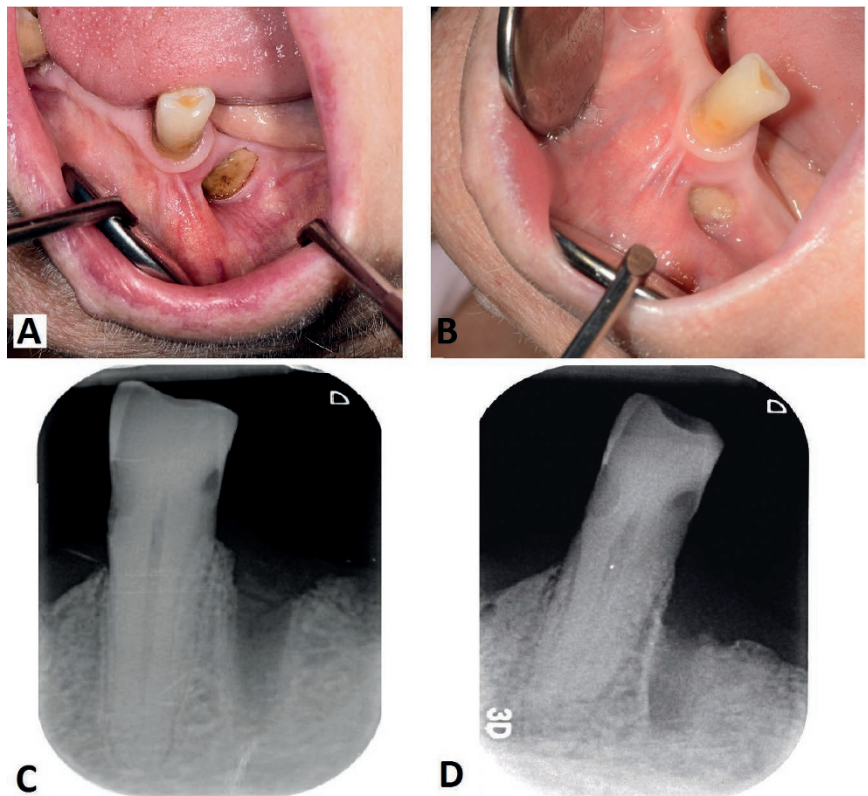


Fig. 2 Picture A shows an exposed bone area at tooth LL4 position and absence of bony infill is shown in picture C. Picture B shows the gradual process of granulation four months subsequent to stopping denosumab. Some bony infill is shown in picture D

This patient was being managed by her oncologist for metastatic deposits of breast carcinoma in bone, liver, and peritoneum for the past three years after ten years of her primary tumour resection and chemotherapy. Denosumab was given in the form of 120 mg injections every six weeks over the past two and half years. No previous history of radiotherapy or other anti-resorptive treatment was noted. The patient was also on chemotherapy and opioids for pain.

On first presentation, the socket area in the lower left quadrant showed incomplete gingival healing with a central area of granulation

with no exposed bone. The patient also reported discomfort from the lower right jaw quadrant with no clinical or radiological abnormalities which is suggestive of stage 0 of the disease. The patient had a heavily restored dentition and generalised deteriorating periodontal condition and bone loss.

The patient suffered repeated infections from both quadrants and severe and progressive periodontal disease leading to loss of teeth LR4, LR5, and LR6 within six weeks. Gingival breakdown and failure of extraction sockets to heal was noted leading to areas of exposed bone (Fig. 3). All areas

were managed conservatively with antibiotics, chlorhexidine mouth wash and oral hygiene instructions. A CBCT was undertaken which showed lytic lesions in the inferior mandibular border possibly denoting stage 3 MRONJ.

Denosumab injections were discontinued after liaising with the patient's treating oncologist and signs of a developing sequestrum were noted five months subsequently (Fig. 4). Loose symptomatic sequestra were removed under local anaesthetic leaving granulated beds. Histopathologic examination confirmed ONJ with no metastatic jaw deposits.

Case 4

A 66-year-old woman was referred by her GDP with non-healing ulcers in the palatal midline and upper right buccal sulcus. The patient was recently provided with a new full upper denture which has been uncomfortable and the patient had to go back to her old denture.

Medically, the patient was diagnosed with bone metastasis three years after breast cancer treatment. The patient was previously on Zometa (Zoledronic acid) injections before she was managed with monthly denosumab injections. She also receives hormonal therapy and opioids for pain management.

Clinical examination revealed exposed bone and draining sinuses extending from the upper right premolar area to the upper left canine position. A central ulcer in the anterior hard palate was noted. Denosumab was stopped by her treating oncologist. The area has been treated conservatively with long-term amoxicillin and chlorhexidine irrigation. Signs of sequestration were seen in subsequent reviews and a maturing sequestrum is shown in Figure 5. The CBCT images in Figure 5 shows involvement of the anterior margin of the right maxillary antrum, as well as the lateral margin of the nasal cavity denoting stage 3 of the disease.

A stage 0 of the disease is believed to have preceded this clinical picture with uncomfortable upper right and left buccal sulci and erythematous palatal midline seen by her GDP four month prior to this review with absence of any exposed bone or radiographic abnormalities.

Discussion

Bone is a common site of metastatic deposits for a number of oncological diseases like prostate and breast cancer.⁶ Such bone disease is often associated with disrupted bone homeostasis leading to progressive bone loss and bone pain.



Fig. 3 Intraoral picture showing an extensive area of exposed bone affecting the alveolar process following dental extraction of teeth LR4, LR5, and LR6

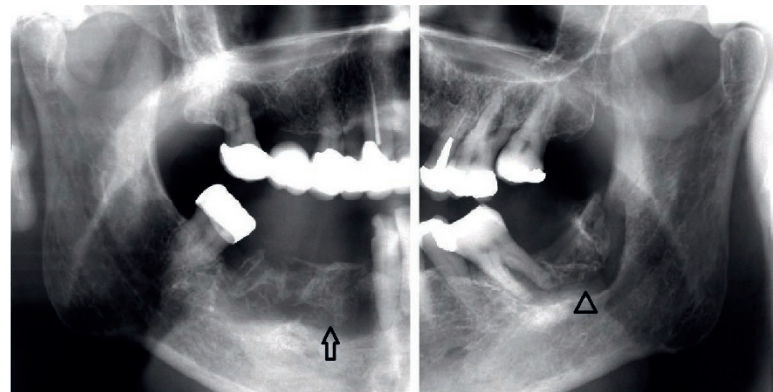


Fig. 4 Sectional orthopantomograms showing developing bony sequestra in mandibular right (arrow) and left (arrow head) quadrants. The left side showing more maturation

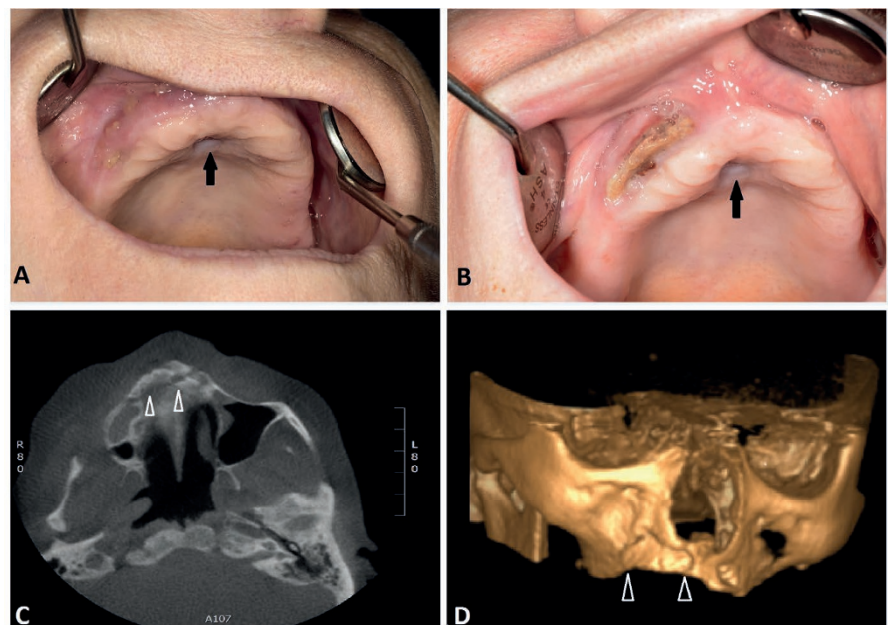


Fig. 5 A and B shows a developing sequestrum of the anterior maxilla and ulcer in the anterior mid palate (Arrows). Picture B was taken two month after picture A. Arrow heads in pictures C and D shows sinus and nasal involvement in CBCT and 3D images

Anti-resorptive medications such as bisphosphonates and more recently denosumab can significantly improve metastatic cancer patients' quality of life by counteracting skeletal-related events (for example, pathologic fracture, spinal cord compression, and pain). Due to the encouraging results of denosumab, more patients are being prescribed the drug.

The mechanism of MRONJ development is still not clear. However, direct cytotoxic effects, the role of microbial environment, the affected remodelling and angiogenic capacity continue to form the main theories of disease pathogenesis.⁷

Dental extraction remains a major risk factor for MRONJ, however, we also highlight the risk of this aggressive disease developing with no previous surgical intervention. Minor denture related trauma and/or periodontal disease may have played a part in the disease process in the cases presented.

An aggressive and progressive nature of denosumab-related MRONJ is shown in this report with either several teeth being lost in a short period of time, vital structures being affected and spontaneous lesions, or lesions developing secondary to minor denture trauma. Taking this into consideration, the importance of prevention cannot be overemphasised, which can be achieved through cooperation between the patients' general dentists and their treating oncologists.

Oncologists have frequently stopped anti-resorptive medications (drug holidays) in an

attempt to limit the disease progression. The benefit of a denosumab drug holiday is shown in this report which is in agreement with previously published reports and reflects the difference between denosumab and bisphosphonates pharmacology mode of action.⁸

Conclusion

An increasing number of patients are presenting at stage 0 of the disease. This report shows disease progression from stage 0 to 1, 2 or 3. This is consistent with previous reports and emphasises stage 0 as a disease variant and thus highlights the importance of early recognition and full liaison with treating oncologists to achieve an optimum patient outcome.

Jaw osteonecrosis secondary to denosumab treatment can be a material risk and needs to be thoroughly discussed with patients and considered by oncologists. Although comprehensive dental assessment is always recommended prior to starting any anti-resorptive medication, it should be carried out as early as possible if the former was not possible.

General dental practitioners are advised to undertake:

- Thorough dental and periodontal examination, patient education and follow up
- A pre-emptive approach towards existing dental and/or periodontal problems before the start of anti-resorptive medication and a conservative approach after

- Contemporaneous and accurate note keeping and early reporting of any vague or unexplained jaw symptoms
- Appropriate and early referral to the secondary care services should that be necessary.

Anti-resorptive medications will continue to be prescribed for metastatic cancer patients especially with their promising results, and with teamwork it is our aim to try to minimise their side effects.

1. Tsuzuki S, Park S H, Eber M R, Peters C M, Shiozawa Y. Skeletal complications in cancer patients with bone metastases. *Int J Urol* 2016; **23**: 825–832.
2. Miksad R A, Lai K C, Dodson T B *et al*. Quality of life implications of bisphosphonate-associated osteonecrosis of the jaw. *Oncologist* 2011; **16**: 121–132.
3. Qi W X, Tang L N, He A N *et al*. Risk of osteonecrosis of the jaw in cancer patients receiving denosumab: a meta-analysis of seven randomized controlled trials. *Int J Clin Oncol* 2014; **19**: 403–410.
4. Ruggiero S L, Dodson T B, Fantasia J *et al*. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws 2014 update. *J Oral Maxillofac Surg* 2014; **72**: 1938–1956.
5. Saad F, Brown J E, Van P C *et al*. Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. *Ann Oncol* 2012; **23**: 1341–1347.
6. Hiraga T. Targeted Agents in Preclinical and Early Clinical Development for the Treatment of Cancer Bone Metastases. *Expert Opin Investig Drugs* 2016; **25**: 319–334.
7. Reid I R, Cornish J. Epidemiology and pathogenesis of osteonecrosis of the jaw. *Nat Rev Rheumatol* 2012; **8**: 90–96.
8. Malan J, Ettinger K, Naumann E *et al*. The relationship of denosumab pharmacology and osteonecrosis of the jaws. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012; **114**: 671–676.