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The Dental Oncology Complication that Wouldn't go Away

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ABSTRACT

Background: Bone modifying agents are used throughout cancer care and their utilisation can optimise advanced stage cancer cases with bone metastases, by reducing skeletal-related events, treatment-induced bone loss and treatment hypercalcaemia. They are also used in patients with a curative intent such as early breast cancer, reducing recurrence and increasing survival rates. Medication-related osteonecrosis of the jaw (MRONJ) is a potential complication following bone modifying agents (BMAs). It represents exposed bone in the maxillofacial region which significantly compromises the quality of life for these patients. Dental disease is the most common initiating factor of MRONJ. We report a case in which MRONJ has dominated cancer care despite its successful treatment.

Case presentation: A 69-year-old female was diagnosed with a breast cancer (grade 1, infiltrating ductal carcinoma, pT1c pN1mi(sc) Mx), for which she was treated with a wide local excision and axillary lymph-node clearance. Seven years after initial presentation, the patient presented with metastatic disease involving the left supraclavicular fossa, bone, peritoneum, and liver. Her BMA regime included zoledronic acid intravenous (IV) every month for 12 months and switched to oral zoledronic acid for a subsequent year due to poor venous access.

Two years after her diagnosis of metastatic disease, the patient presented with exposed bone in her anterior maxilla, which represented advanced stage MRONJ (AAOMS 3). The exposed bone in the maxilla was treated surgically by sequestrectomy and fistula closure. Three years later (12 years after initial breast cancer diagnosis), the patient was re-admitted with a cervical fascial space infection involving the right mandible. The patient developed another site of advanced- stage MRONJ (AAOMS 3) in the right mandible associated with an orocutaneous fistula. The patient had a marginal resection of her mandible, fistula closure and extraction of the remaining teeth under general anesthetic.

Conclusion: The practicing oncologist needs to be cognisant of the possibility of MRONJ in both the curative and palliative setting. Traditionally, oncology care has required a significant degree of self-reliance on patients to navigate dental treatment pathways. Integration of dental clinics into oncology pathways would help eliminate this need for self-reliance. MRONJ is an inevitable risk for a large cohort of oncology patients and active engagement of dental-oncology specialities will ensure optimal care for patients.

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INTRODUCTION

Medication related osteonecrosis of the jaw (MRONJ) was diagnosed originally by Marx twenty years ago, following the administration of bisphosphonates.[1] It includes a spectrum of osteonecrosis ranging from innocuous exposure of regions of the maxilla or mandible to extensive

necrosis with risk pathological fractures and orocutaneous fistula.[2] Over the past two decades, there has been an increased integration of bisphosphonates into the guideline based management of metastatic, and now early stage breast cancer.[3–5] Bone Modifying Agents (BMAs) are also implicated monoclonal antibodies, antiangiogenics, immunomodulators, folate antagonists and some chemotherapeutic agents in the development of MRONJ.[6–11]

For the practicing oncologist, quantifying MRONJ risk in the clinic is challenging. The risk of MRONJ in patients with metastatic disease ranges from 0 – 12%.[2,12] The risk with antiresorptive therapy varies from 1.5-6%[2], and with RANK-ligand inhibitors from 0.7% - 6.7% of patients. The prevalence of MRONJ in the adjuvant, early stage breast cancer setting was noted from a total of eight clinical trials between 0 – 2.1%. Incomplete recording of MRONJ was noted in 2 of the above studies in the adjuvant setting.[13–20] Secondary osteoporosis can be a consequence of aromatase inhibitors which also relies upon BMAs. The risk of MRONJ is also relevant to this cohort of breast cancer patients.[21,22]

Dental disease remains the most non-communicable diseases worldwide and is the most common initiating factor of MRONJ.[23] The World Health Assembly resolution WHA 74.5 in May 2021 as a global strategy to combat oral disease. Dental infection and inflammation remain worrisome predictors of further MRONJ development.[24–27] Factors predisposing patients to the development of MRONJ include infectious and inflammatory dental diseases such as advanced periodontitis, dental caries and periapical disease.[28,29] Invasive dentoalveolar procedures, and contaminant corticosteroids have also been reported as predisposing factors of MRONJ.[30,31] Variations in anatomical factors such as the mandible compared to the maxilla or ill-fitting removable prostheses can be associated with MRONJ development.[6,31] MRONJ is 2.7 times more common in the mandible compared to the maxilla due to the more complex vascular network and blood supply to the maxilla.[31,32]

We report a case in which MRONJ has dominated cancer care despite its successful treatment. We discuss the management and learning points regarding this case and the impact of BMAs on long-term cancer patient care. The case has prompted us to modify our treatment pathways for patients receiving MRONJ implicated agents.

CASE PRESENTATION

A 69-year-old female was diagnosed with breast cancer (grade 1, infiltrating ductal carcinoma, pT1c pN1mi(sc) Mx), for which she was treated with a wide local excision and axillary lymph-node clearance. Her post operative staging was pT1N1(mi). The tumor was hormone sensitive and HER2 negative. She received adjuvant radiation therapy (50Gy in 25 fractions and boost to tumor bed 10gy in 5 fractions). The patient commenced adjuvant hormone therapy (tamoxifen followed by anastrozole) for the subsequent 7 years. Adjuvant bisphosphonate therapy was not prescribed.

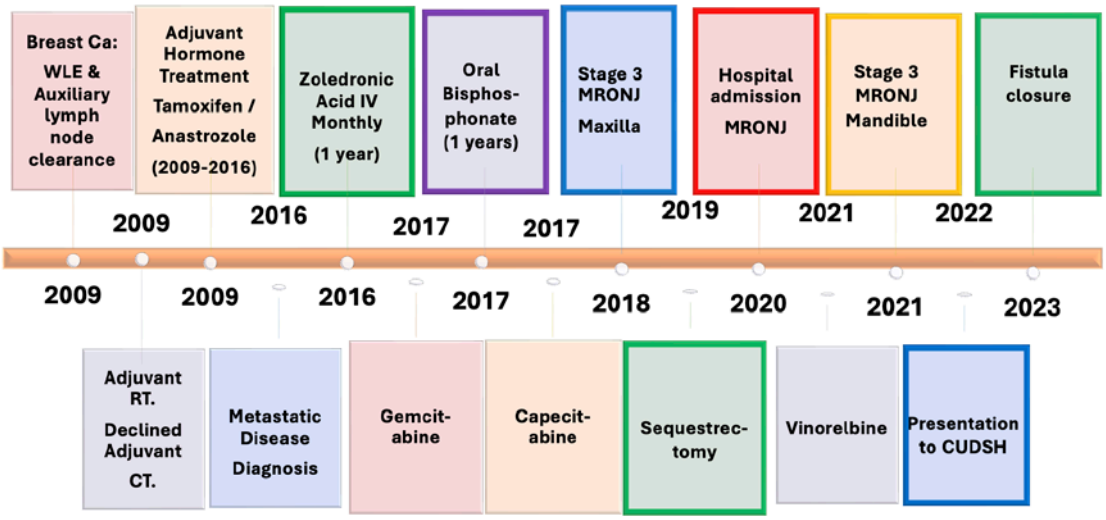

Figure 1. A timeline of the patient's concurrent oncological and dental history

Seven years after initial presentation, the patient presented with metastatic disease involving the left supraclavicular fossa, bone, peritoneum, and liver. She was commenced on gemcitabine and subsequently capecitabine, in combination with a regime of zoledronic acid intravenous (IV) every

month for 12 months. She was switched to oral bisphosphonate for a further year secondary to poor IV access.

Two years post her diagnosis of metastatic disease, the patient presented with exposed bone in her anterior maxilla in 2018. MRONJ AAOMS stage 3[2] (oronasal fistula) was diagnosed, and bisphosphonate therapy was stopped indefinitely. The exposed bone was treated surgically by sequestrectomy and fistula closure (Figure 2).

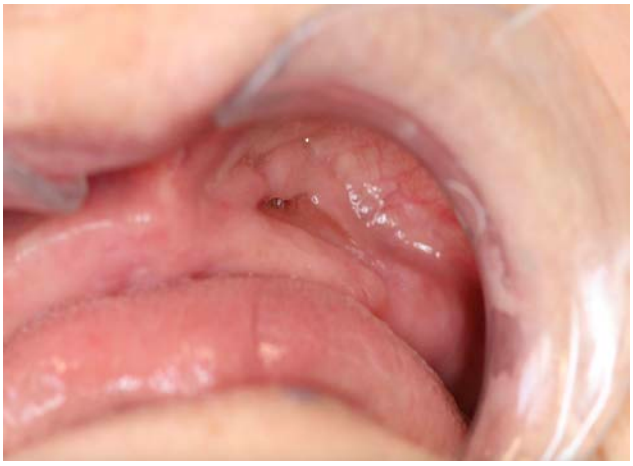

Figure 2. The remnants of an oronasal fistula in the left anterior maxilla

Three years later (12 years after initial breast cancer diagnosis), the patient was admitted with a cervical fascial space infection involving the right submandibular/sublingual spaces. This acute infection was the first presentation of mandibular stage 3 MRONJ with an orocutaneous fistula (figure 3 and 4). A CT mandible confirmed extensive bony destruction of the mandible with sequestration. The acute infection subsided with antibiotic therapy. Two years later (5 years after the cessation of all antiresorptive therapy), the patient re-presented to the Cork Dental Hospital with stage 3 MRONJ in the right mandible.

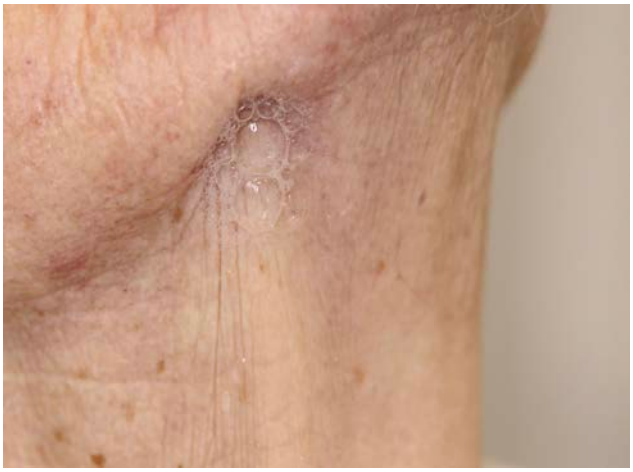

Figure 3. Saliva extruding through the orocutaneous fistula in the right mandible

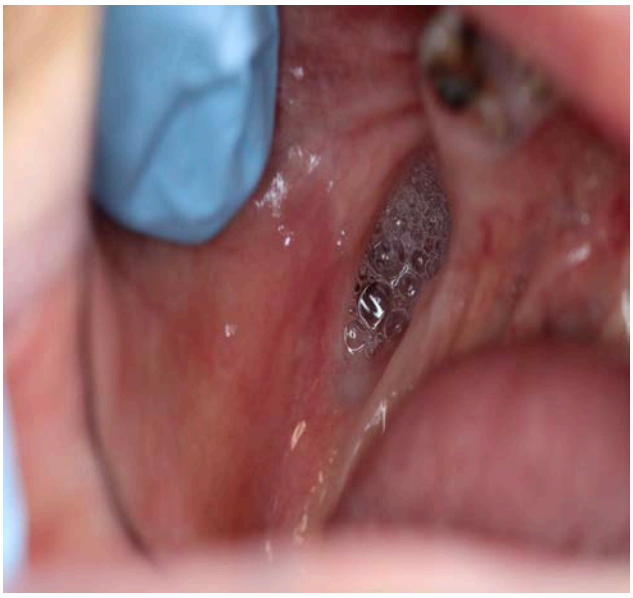

Figure 4. An intraoral aspect of the orocutaneous fistula in the right body of mandible

There was a significant impact to both the patient's functional and psychological well-being, due to constant leakage of saliva and oral liquid contents from her orocutaneous fistula. The patient was advised to stop cigarette smoking and was treated with a marginal mandibular resection and closure of the fistula. The patient remains a high-risk candidate for additional MRONJ development due to her remaining, poorly maintained dentition.

DISCUSSION

This case highlights a common occurrence in the oncological–dental interface; MRONJ. Predisposition for this condition is noted in high risk categories, such as oncology patients receiving regimes of antiresorptive therapy. This clinical consequence of a productive fistula in her mandible has severely affected the patient's quality of life from both a functional and psychological perspective, irrespective of her successful cancer treatment. Early detection of dental disease and MRONJ throughout the course of BMA treatment can reduce requirements for invasive procedures, which result in more predictable, optimal clinical outcomes.[33] The pathophysiology includes site-specific jaw involvement attributed to bone remodelling inhibition, inflammation, infection, direct cellular toxic effects, angiogenesis inhibition and immune dysfunction.[25,34,35]

Cessation of BMAs does not preclude patients from the risk of MRONJ following therapy. The half-life of such medications precludes patients from the risk of MRONJ for over one decade in the case of intravenous zoledronic acid. Drug holidays have yet to be proven as definitively effective strategies to prevent MRONJ, their benefits are unclear, and the literature is divided.[2,33,36]

Table 1 depicts a summary of MRONJ exacerbation factors.

Table 1. A summary of MRONJ exacerbation factors[6,28,30,31]

Domain	Exacerbation factor
Dental disease	Periodontitis Periapical disease
Invasive dental procedure	Tooth extraction
Immunosuppression	Concurrent corticosteroids Chemotherapy
Systemic factors	Uncontrolled diabetes
Anatomical	Mandible
Prosthetic	Ill-fitting prosthesis
Social factors	Tobacco use

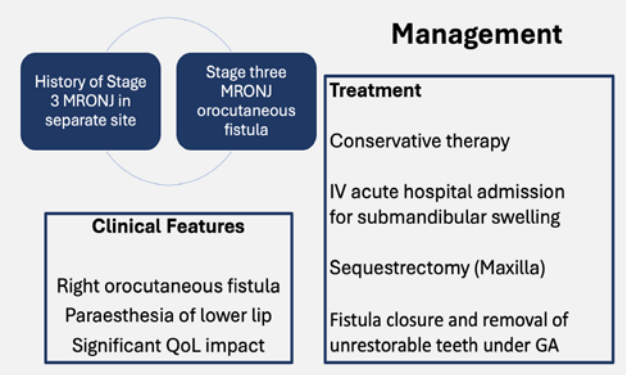

Figure 5. The clinical features and management regimes

The foundation of a drug holiday is that despite the 11.2 year half-life oral bisphosphonate or 6 month half-life of denosumab, alongside oncology regimes for BMAs, effective drug holidays cannot be achieved. The bone marrow stem cells and osteoclast precursors do not have the ability to regenerate to sufficient numbers to remodel and renew bone during the healing phase. An effective bone modifying agent drug holiday is not effectively achievable in cancer patients because of the rapid depletion of osteoclast precursor cells and potency of the bone modifying agent in the oncology setting.[37] This complicates the long-term dental care of patients after cancer treatment. Dental extractions are a common initiating factor for MRONJ.[2] However, as seen in our case, advanced stage MRONJ was noted in both the maxilla and the mandible. Poor dental health, repetitional micro-trauma from an ill-fitting upper denture, concurrent chemotherapy and smoking were exacerbating factors. Integrated dental care into cancer treatment programmes can address modifiable factors such as dental infection and periodontal disease prior to and after BMA therapy.[24,25]

Management strategies for MRONJ have not progressed significantly towards predictable curative treatments. The literature has offered suggestive medical adjuvants to manage MRONJ, such as systemic recombinant human parathyroid replacement therapy (teriparatide), and PENTE regime (pentoxifylline, tocopherol), hyperbaric oxygen, low intensity laser, and medical ozone therapy.[38] However, no definitive evidence has concluded their ability to cure or stop progression.[39]

Surgical management was initially employed to palliate MRONJ which was unresponsive to conservative and medical management. However, recent trends are towards earlier surgical interventions including superficial debridement, sequestrectomy, and alveoloplasty/marginal resection, with primary mucosal closure. Radical surgery with segmental resection of the mandible and free tissue transfer are offered in selective advanced stage MRONJ cases. [40–42] The literature has produced an array of cohort and retrospective studies to assist management strategies. Preventative strategies have a significant role to play in combating MRONJ prevalence and reducing the requirement for unpredictable therapies in this group.[43,44]

Preventative dental therapy prior to bone modifying agents (BMA) is an effective strategy to reduce the incidence of MRONJ.[43,45,46] Removal of teeth with poor prognosis and elimination of dental infection should be complete at least 4-6 weeks prior to administration of a BMA to allow for mucosal healing.[37] Secondary prevention and earlier detection of MRONJ reduce the requirement for further invasive surgeries compared to the population without a pre-therapeutic preventative dental programme.[43–45] The role of BMAs in the oncology setting has expanded into the curative setting in breast cancer.

The practicing oncologist needs to be cognisant of the possibility of MRONJ in both the curative and palliative setting. Traditionally, oncology care has required a significant degree of self-reliance on patients to navigate dental treatment pathways.[47,48] Integration of dental clinics into oncology pathways would help eliminate this need for self-reliance. It would also assist in ensuring equity of access for those who already have poorer cancer outcomes due to their socioeconomic status and would be concordant with the European Code of Cancer Practice 2020 . Dental oncology clinics for patients on BMA regimes are a suitable strategic integration to ensure optimal healthcare in cancer patients and facilitate interdisciplinary care.

The Global Breast Cancer Initiative was established by the World Health Organisation in 2021 to reduce breast cancer mortality.[42] It has 3 pillars: health promotion for early detection, timely diagnostics and comprehensive breast cancer

management which includes support services such a psycho-oncology. Our experience with this and other cases has prompted a situational analysis through a grant funded dental oncology clinic to prospectively assess dental issues in oncology patients and integrate this care into routine breast cancer management. We have learnt from this and other cases that dental oncology should be integrated into the 3rd pillar of breast cancer care.

CONCLUSION

MRONJ is an unavoidable risk following BMA therapy, which requires vigilance from the prescriber and oncology team. BMAs are an integral part of breast cancer care both in palliative and curative settings. This case highlights potential pitfalls and consequences of BMA therapy. Our understanding of the pathophysiology has progressed over the past twenty years since its original documentation[1], but predictable management of MRONJ still presents challenges for the treating clinicians.[2,12] Dental preventative measures play an integral role in reducing the prevalence of MRONJ.[33,53] Active engagement and integration of dental oncology services is an important element of breast cancer care for patients at risk of MRONJ.

ETHICAL CONSIDERATIONS

Written and informed consent was obtained legally from the patient documented in this case report.

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CONFLICTS OF INTEREST

None.

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