

Short communication

Everolimus-induced osteonecrosis of the jaw in the absence of bisphosphonates: a case report

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Abstract

Osteonecrosis of the jaw (ONJ) is a rare, but severe, condition that has traditionally been associated with the use of bisphosphonates. We report what is, to our knowledge, the first case of ONJ secondary to the use of everolimus, in the absence of treatment with bisphosphonates in a 65-year-old man who was given it for immunosuppression after a renal transplant. After 18 months of treatment, he was diagnosed with severe ONJ and underwent radical debridement of the palate and complete dental clearance of the maxilla.

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Introduction

Osteonecrosis of the jaw (ONJ) is a rare, but severe, condition that is characterised by exposed, necrotic bone in the maxillofacial region, and is typically associated with the use of bisphosphonates.¹ Everolimus is an inhibitor of mammalian target of rapamycin (mTOR), a serine-threonine kinase, which, when taken orally, regulates cell-signalling pathways that are crucial in the pathogenesis of several malignant tumours and the control of immunological reactions.²

Case report

A 65-year-old man was referred to our clinic from the renal unit for the evaluation of possible ONJ. He had had a kidney transplant two years previously for end-stage renal failure, for which he was given everolimus, 10 mg twice daily, mycophe-

nolate mofetil, 1 g twice daily, and prednisolone, 10 mg daily, as part of an immunosuppressive regimen (Table 1). He had never been exposed to bisphosphonates and had had no recent trauma or teeth extracted. At the time of initial referral, clinical examination showed exposed necrotic bone in the right and left upper premolar and molar regions (16, 17, 24, 25, 26) (Fig. 1). Multiple teeth were absent in all four quadrants (14, 15, 25, 36, 45, 46).

On review, six months later, he presented with severe pain in his upper jaw. Clinical examination showed considerable destruction of alveolar bone and the adjacent maxilla. Computed tomography (CT) of the facial bones showed advanced osteonecrosis of the maxilla and palate (Figs. 2 and 3). He was admitted to hospital, and everolimus was stopped (after 18 months of treatment). Two weeks later he had radical debridement of the palate and complete dental clearance of the maxilla. A specimen from the maxilla was sent for histopathological analysis and subsequently showed extensive necrosis. There was considerable improvement in his pain, and the remainder of his postoperative course was unremarkable.

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Table 1

List of all the drugs the patient was prescribed in both primary and tertiary care in the preceding four years.

Drug	Start date	End date
Amlodipine	05/06/2004	Ongoing
Bactrim	24/10/2015	Ongoing
Calcitriol	13/10/2015	Ongoing
Calcium	10/10/2014	Ongoing
Clindamycin	05/06/2018	05/09/2018
Ciprofloxacin	05/06/2018	05/09/2018
Everolimus	24/10/2015	21/05/18
Magnesium	05/01/2016	Ongoing
Mircera	10/09/2014	Ongoing
Mycophenolate mofetil	24/10/2015	Ongoing
Omeprazole	07/05/2010	Ongoing
Oxycodone	Intermittent use	Intermittent use
Paracetamol	Intermittent use	Intermittent use
Prazosin	06/06/2018	Ongoing
Prednisolone	24/10/2015	Ongoing
Simvastatin	01/06/2002	Ongoing
Tapentadol	Intermittent use	Intermittent use
Valganciclovir	30/08/18	07/09/2018
	24/10/2015	25/01/2016



Fig. 1. Intraoral clinical photograph showing exposed necrotic bone in the right upper premolar and molar region.

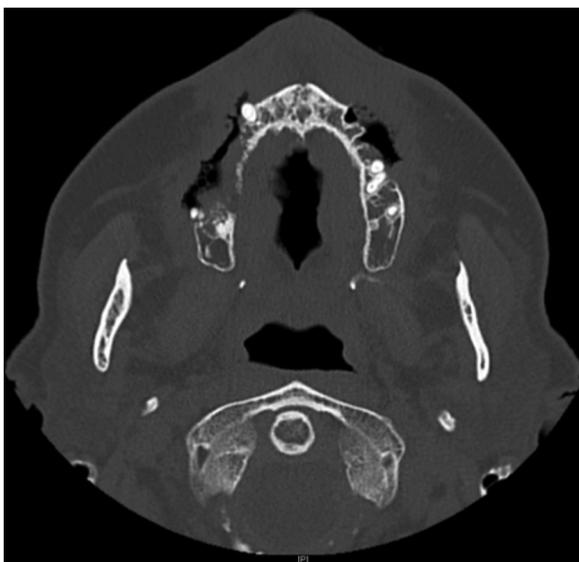


Fig. 2. Computed tomogram of the facial bones (axial view) showing extensive bony destruction with cortical erosion and permeative lucency of the entire maxilla that is consistent with osteonecrosis of the maxilla.



Fig. 3. Computed tomogram of the facial bones (coronal view) showing severe osteonecrosis of the maxilla that has resulted in destruction of part of the floor of the right maxillary sinus.

Discussion

While there have been four other reports on the possible association of ONJ with everolimus, all patients involved were also taking other medications, including bisphosphonates, which may have led to the development of ONJ.^{3–6} The causal association therefore between everolimus and ONJ cannot be concluded with certainty in any of these cases.

There are three main classes of medication capable of inducing ONJ independent of bisphosphonates: monoclonal antibodies (bevacizumab and denosumab); tyrosine kinase inhibitors (sunitinib, sorafenib, and cabozantinib); and mTOR inhibitors (temsirolimus and everolimus).⁷ Everolimus is an mTOR inhibitor that intervenes in cell-signalling pathways of growth factors and protein transcription, and is indicated for the treatment of several types of malignant tumours and the prevention of solid-organ rejection.⁷ The main mechanism of ONJ induced by mTOR inhibitors is thought to be secondary to their antiangiogenic effect, and results in impaired healing of bone.^{7,8} This is because vascular endothelial growth factors (VEGF) play an essential role in healing bone, and consequently, any anti-VEGF activity could theoretically cause ONJ, even in the absence of bisphosphonates.⁷ An inciting event such as recent trauma may therefore result in ONJ in patients being treated with everolimus.

Steroids are associated with an increased risk of developing ONJ (as well as expediting its onset and worsening its severity) in combination with other causative agents such as bisphosphonates.^{9–12} However, the role of steroids in causing ONJ directly remains controversial. It is thought to be rare and

almost never produces exposed bone.¹³ In the limited reports of ONJ that have been associated with the use of steroids, patients presented with exposed bone after recent extractions of teeth, which were likely to have triggered non-healing.^{14,15}

Three other cases of ONJ in patients who were given steroids were described in a case series, but the authors were uncertain of the causation. They reported that the comorbidities of the patients and the medications used to treat them were implicated in impaired bony healing that resulted in lesions that were clinically and radiographically identical to ONJ.¹⁶ There are no reported cases of ONJ associated with any of the other medications to which this patient was exposed (Table 1).

We therefore report what is to our knowledge the first case of ONJ secondary to everolimus in the absence of bisphosphonate treatment. Steroid use may have increased the likelihood of its occurrence and could possibly have potentiated the everolimus in this case. Clinicians must therefore be aware of this association to prevent potentially irreversible damage to maxillofacial bones.

Conflict of interest

We have no conflicts of interest.

Ethics statement/confirmation of patient's permission

Because of the retrospective nature of this case report, it was granted an exemption in writing by The Alfred Hospital IRB. The patient's consent was obtained for publication.

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