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British Journal of Oral and Maxillofacial Surgery 57 (2019) 271–274

BRITISH Journal of Oral and Maxillofacial Surgery

www.bjoms.com

Short communication

Spontaneous bilateral osteonecrosis of the mandible in a bisphosphonate-naive patient

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Available online 14 February 2019

Abstract

Medication-related osteonecrosis of the jaw is a well-described, yet poorly understood disease of bone that is commonly associated with antiresorptive and antiangiogenic drugs. We report a case of spontaneous bilateral osteonecrosis of the mandible in a patient with no previous exposure to either.

Keywords: osteonecrosis; MRONJ; ONJ; oral pathology; medication-related osteonecrosis of the jaw

Case report

A 61-year-old woman with no history of smoking presented to our oral and maxillofacial surgery clinic with a five-week history of spontaneous pain and swelling in both sides of the jaw that were associated with bilateral paraesthesia of the inferior alveolar nerve (Fig. 1).

She had rheumatoid arthritis that was being managed by her rheumatologist, and concurrent medications included prednisolone, hydroxychloroquine, pregabalin, and methotrexate. Coinciding with the onset of her symptoms, she had doubled her dose of methotrexate from 10 mg to 20 mg weekly. Over the last year, she had had several oral pulse doses of prednisolone of up to 30 mg. She had no history of radiotherapy to the head and neck, and had taken neither antiresorptive nor antiangiogenic drugs.

On examination, a draining sinus was noted on the left side, which extended to the underlying bone on probing, and was consistent with the clinical presentation of Stage 0 medication-related osteonecrosis of the jaw (MRONJ). Extraoral examination confirmed a non-fluctuant mild swelling in the submandibular region bilaterally.

Previous magnetic resonance imaging had shown patchy abnormal enhancement within the bone marrow of the mandibular body, and technetium–99 m bone scintigraphy showed radio-uptake that was suggestive of osteonecrosis or bilateral osteomyelitis (Fig. 2).

After consultation with the patients' rheumatologist, we stopped both the methotrexate and prednisolone, and gave her antibiotics intravenously. A bilateral biopsy examination of the mandibular bone showed active chronic inflammation with histological signs that were consistent with a diagnosis of osteonecrosis of the jaw. Osteomyelitis was considered to be an unlikely diagnosis in light of the bilateral presentation and the lack of key histological features. Microscopy, culture, and sensitivity samples that had been taken intraoperatively showed normal oral flora.

Her symptoms improved after cessation of the methotrexate and prednisolone, and were completely resolved by week four.

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https://doi.org/10.1016/j.bjoms.2019.01.015

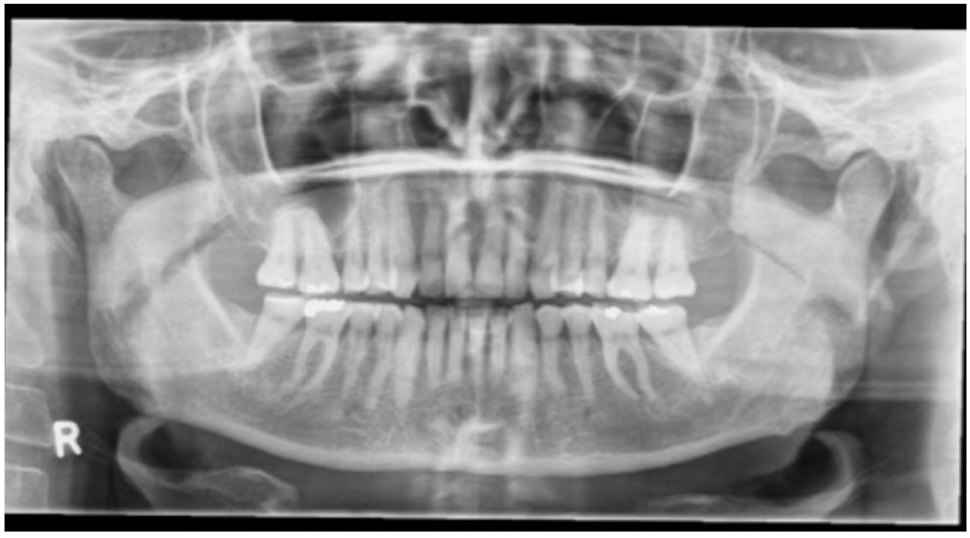

Fig. 1. Panoramic radiograph of patient's dentition.

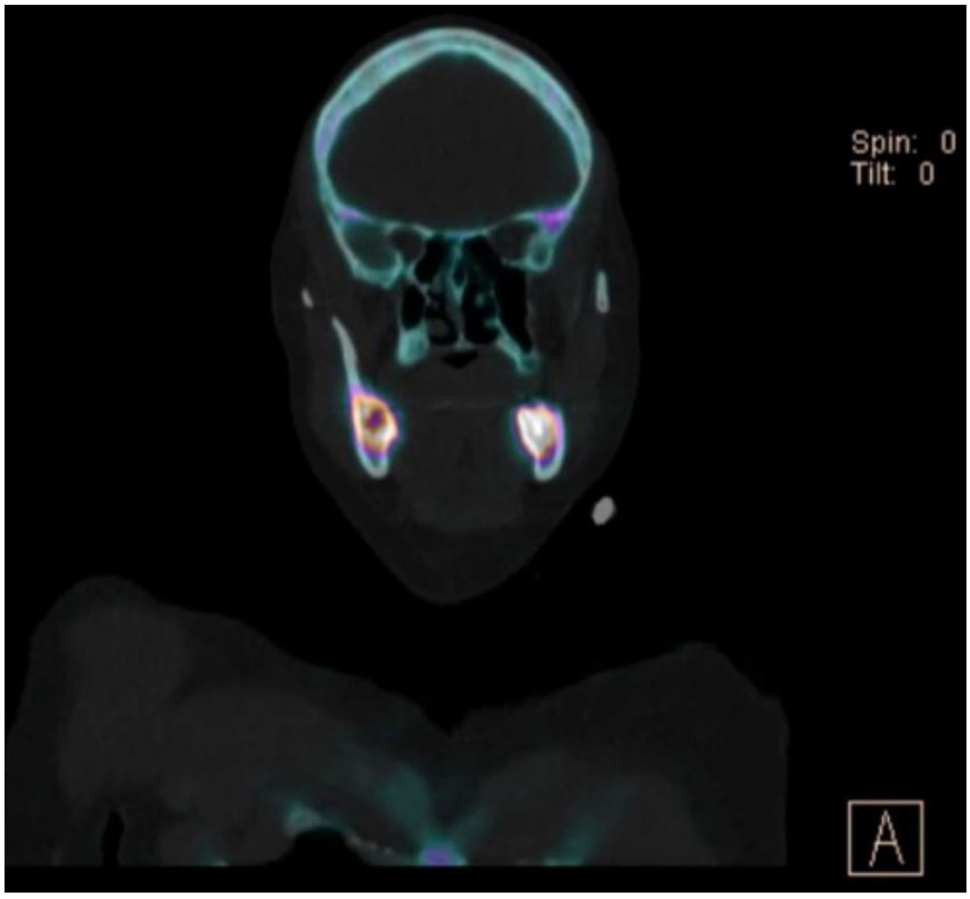

Fig. 2. Bone scintigraphy showing radio-uptake that is suggestive of osteonecrosis or bilateral osteomyelitis.

Table 1
Reports on the possible association between methotrexate and osteonecrosis of the jaw with no previous exposure to antiangiogenic or antiresorptive drugs.

First author and reference	Age	Sex	Disease	Dose of methotrexate/week	Precipitating event	Location(s)	Stage	Treatment	Outcome
Sklavos, 2019 (current paper)	61	F	Rheumatoid arthritis	20 mg	Unknown	Lower right and left third molar regions	I	Cessation of methotrexate, antibiotics	Resolution after 4 weeks
Aghaloo, 2017[4]	83	F	Rheumatoid arthritis	20 mg	Periodontal disease	Right posterior maxilla	III	Antibiotics and hyperbaric oxygen therapy, no cessation of methotrexate	Resolution after more than 6 months
Henien, 2017[5]	66	F	Rheumatoid arthritis	20 mg	Extraction	Left posterior maxilla	I	Conservative hydrogen peroxide mouthwash	Patient remained asymptomatic with no progression
	54	M	Psoriatic arthritis	20 mg	Periodontal disease	Right mandibular third molar region	II	Removal of LR6, LR8, curettage, clindamycin 300 mg 4 times/day 7/7	Resolution

Discussion

It has been well established that antiresorptive medications such as bisphosphonates and denosumab (a monoclonal RANK-ligand that targets antibodies)[1] are implicated in the development of MRONJ. More recently, antiangiogenic medications such as sunitinib and bevacizumab have been associated with an increased risk of developing MRONJ in patients on antiresorptive therapy, and the development of MRONJ in antiresorptive-naive patients.[2] These drugs inhibit growth factors such as vascular-endothelial growth factor and platelet-derived growth factor, to inhibit angiogenesis in the formation of tumours.[2] Osteonecrosis is rarely reported in bones other than the maxilla and mandible.[3] Current models for the pathophysiology of MRONJ include the inhibition of bony remodelling through a reduction in the function of osteoclasts, infection or inflammation, and the inhibition of angiogenesis.[2]

Most cases of MRONJ are precipitated by dental extractions, injury, or infection,[1,2] but some instances of its spontaneous development have also been described.[2] Largely, it has a predilection for the mandible over the maxilla, and exposure to high doses of glucocorticoids, diabetes mellitus, malignancy, smoking, infection, and dental extractions have also been associated with an increased risk.[2]

Methotrexate can be used in the treatment of neoplastic conditions, rheumatoid arthritis, and severe cases of psoriasis. To the best of our knowledge, only two previous reports have described the association between methotrexate and osteonecrosis of the jaw in three patients with no previous exposure to antiangiogenic or antiresorptive treatments.[4,5] As far as we know there are no previously published cases of bilateral osteonecrosis of the jaw in an antiresorptive and antiangiogenic-naive patient with no known initiating factors (Table 1).

Methotrexate exhibits effect through the competitive inhibition of dihydrofolate reductase (an enzyme required for the synthesis of DNA and cellular reproduction) and its potential role in the development of MRONJ is multifactorial. It has immunosuppressive and anti-inflammatory effects that reduce the host's response to oral flora, and could lead to the inflammation and breakdown of mucosa. It has also been proposed that high doses of methotrexate can inhibit the formation of bone, fibroblast growth factor, and vascular-endothelial growth factor.[6] The combination of these effects may lead to decreased angiogenesis, susceptibility to infection, and a reduced bony turnover, which in turn develops into MRONJ.

There is some disagreement as to whether osteoradionecrosis, medication-related osteonecrosis, and osteomyelitis can be differentiated histopathologically. Marx and Tursun conducted a blinded comparison study and concluded that there were distinct histological differences between the three conditions in the pattern of inflammation, level of osteoclastic activity, and the degree and type of bacterial colonisation.[7] This conclusion was inconsistent with previous studies,[8] and a subject of ongoing debate.[9] More recently, Shuster et al completed a larger histological study with a similar protocol, and concluded that there were no distinct microscopic characteristics that could be used to differentiate between osteomyelitis and osteonecrosis.[10]

The macroscopic features of the mandibular bone in our patient did not resemble an osteomyelitic process. Osteosclerosis and sequestra were both seen intraoperatively, and the bilateral presentation was not consistent with typical osteomyelitis. Irrespective of the lack of clarity in histopathological diagnosis, we think that this case adds to the growing body of evidence that methotrexate may be involved in the development of an osteonecrosis-like condition in mandibular bone.

Conclusion

Oral and maxillofacial surgeons, dentists, and rheumatologists should consider MRONJ to be a potential complication of the use of methotrexate. In our patient cessation of the drug and additional antimicrobial treatment resulted in a full recovery.

Conflict of interest

We have no conflicts of interest.

Ethics statement/confirmation of patient's permission

No ethics approval or patients' permission was required for this paper as no identifying information is included.

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