

Osteonecrosis of the mandible due to anti-angiogenic agent, bevacizumab

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Abstract

Background Osteonecrosis of the jaw (ONJ) is defined by areas of tissue breakdown and exposure of bone in the maxillofacial region that fail to heal within 8 weeks after identification by a health provider in a patient who has not received radiation of the jaws. The disease affects the quality of life and produces significant morbidity in afflicted patients. ONJ is correlated with such risk factors as treatment with bisphosphonates, dental extraction-related trauma, chemotherapy, corticosteroids, renal osteodystrophy and infections. Although the use of bisphosphonates is associated with osteonecrosis of the jaw, the pathophysiology of bisphosphonate-associated ONJ is still unknown. It has been assumed that bisphosphonates lead to the inhibition of capillary angiogenesis and disturbances in the activities of both osteoblasts and osteoclasts, thereby impairing bone remodelling. Currently, inhibitors of angiogenesis used in the treatment of cancer patients are implicated in isolated cases of ONJ.

Case report This manuscript reports a case of ONJ in a female patient who received bevacizumab (Avastin®, Roche), a humanised monoclonal antibody that recognises and blocks vascular endothelial growth factor (VEGF)-A.

Conclusion The anti-angiogenic agent, bevacizumab, may increase the risk of osteonecrosis of the jaw. This agent inhibits VEGF and, therefore, also presumably represses the vascularisation of the jaw, which leads to healing complications. Due to increasing use of bevacizumab, patients receiving this agent should be closely monitored for possible side effects.

Keywords Osteonecrosis · Jaw · Anti-angiogenic agents · Bisphosphonates

Introduction

The anti-angiogenic agent, bevacizumab, is an established component of cancer therapy. Since 2003, reports of bisphosphonate-related osteonecrosis have been increasing [1, 2], following infections, oral surgical interventions, long-term intake of corticosteroids or chemotherapy being reported to increase the risk of osteonecrosis. Studies have shown that anti-angiogenic agents can increase the risk for osteonecrosis, particularly when combined with bisphosphonates. Anti-angiogenic agents are being prescribed with increasing frequency to inhibit vascular endothelial growth factor (VEGF) [3–6] and may increase the risk of osteonecrosis of the jaw.

Case report

A 53-year-old female patient was referred to our department with a painful area of bone exposure in the left posterior lingual mandible with an area of 15×3 mm mainly located on the alveolar crest. The bone appeared necrotic with fistulae to the vestibular and lingual regions, and the surrounding tissue revealed signs of inflammation (Fig. 1).

The history from the patient revealed pancreatic carcinoma, which had been diagnosed 16 months before the referral. Palliative surgery was performed, and the patient was subsequently treated with gemcitabine (Gemzar®, Lilly Deutschland) and erlotinib (Tarceva®, Roche) from March 2009 until August 2009 and with folic acid, 5-fluorouracil

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Fig. 1 Bone exposure in the left posterior lingual mandible

and oxaliplatin) from September 2009 until January 2010. A combination of paclitaxel (Taxol[®], Bristol-Myers Squibb GmbH), bevacizumab (Avastin[®], Roche) and sorafenib (Nexavar[®], Bayer AG) was administered from February 2010 until May 2010.

At this time, the patient developed a swelling in the left mandible, and her dentist drained an abscess in region 036 and prescribed an oral antibiotic. Due to the persistence of the swelling, chemotherapy was discontinued, and the patient was referred to our clinic. Up to this time, she had worn a total prosthesis in the lower jaw and an overdenture prosthesis in the upper jaw.

Cone beam computer tomography revealed osteolysis of the left mandible with two punctiform areas of radiodensity, composed of foreign bodies, appearing in the left posterior mandible. Emphysema was observed in the surrounding soft tissue, and the cancellous bone was fragmented. Furthermore, a unilateral opacity of the maxillary sinus was observed on the right side (Fig. 2).

Decortication was performed in the area of osteonecrosis, wherein the bone was soft; the surrounding soft tissue was carefully closed, and a biopsy of the bone was taken

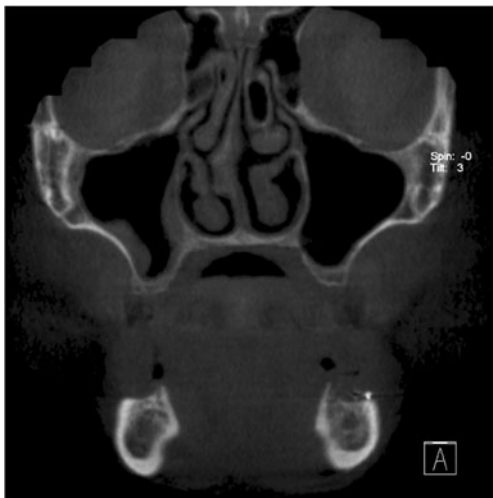


Fig. 2 Cone beam computer tomography revealed osteolysis of the left mandible

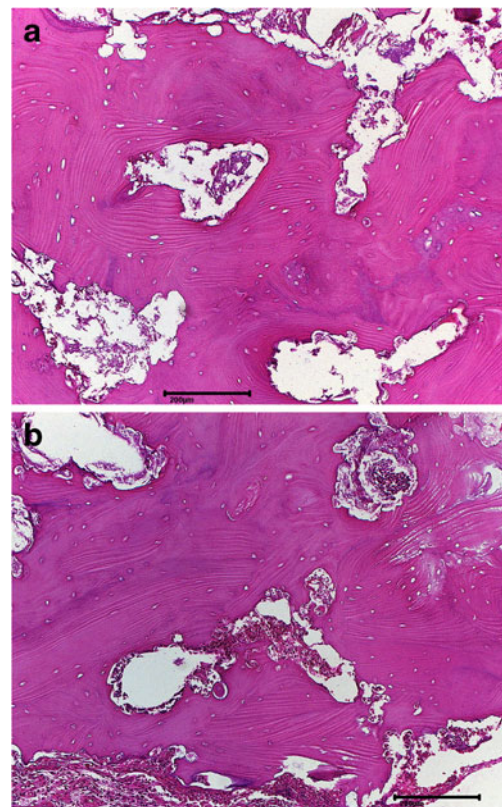


Fig. 3 a, b Pathological analysis presenting fibrosis of the bone marrow and areas of devitalised necrotic bone

intraoperatively. Pathological analysis verified the clinical diagnosis of osteonecrosis of the posterior lingual mandible, showing chronic osteomyelitis with fibrosis of the bone marrow and areas of devitalised necrotic bone. An infiltration of cancer was excluded (Fig. 3 a, b). The patient was administered with amoxicillin and clavulanic acid (Augmentin[®], HEXAL AG) 2.2 gr, 1:1:1 intravenously and chlorhexidine 0.12 % (Hexoral[®], Pfizer CHC GmbH) as an oral rinse. A nasogastric tube was inserted to avoid postoperative, mechanical disturbance of the wound (Fig. 4). A wound healing deficit was observed after the operation with dehiscence and exposed bone in the place of the original



Fig. 4 Postoperative orthopantomogram of the patient with nasogastric tube



Fig. 5 Two months after treatment, tissue repair was evident, and no exposed bone was visible

lesion, which measured approximately 10 mm in diameter. Due to a slow response, chemotherapy was stopped after consulting the oncologist, and the wound healing was treated conservatively. After 2 months of conservative treatment with daily lavage, local debridement and administration of a cream (Solcoseryl®, Meda Pharma GmbH & Co. KG), tissue repair was evident, and no exposed bone was visible (Fig. 5).

Discussion

Osteonecrosis is defined as a non-healing wound of the bone, which arises because of dental extractions or oral surgical interventions, either spontaneously or due to poor oral hygiene [3], and is often associated with bisphosphonate therapy [1, 4, 7]. Bisphosphonate-induced osteonecrosis is a non-inflammatory drug side effect [8], wherein the mandible is affected more frequently than the upper jaw [9]. This effect could be attributed to the relatively poor vascularisation of the mandible compared to the maxilla.

The incidence of osteonecrosis in tumour patients is 11 % or lower, and this complication is often associated with the intake of bisphosphonates [4]. Bisphosphonates block angiogenesis by modulating cell proliferation and lower VEGF levels [7]. Infections, oral surgical interventions, long-term intake of corticosteroids or chemotherapy are risk factors for osteonecrosis. Often osteonecrosis originates after local infections which can be caused by tooth extractions, dental medical treatments or pressure sores from prostheses [10].

Above all, the intake of bisphosphonates is often associated with osteonecrosis of the jaw. Studies show that anti-angiogenic agents can raise the risk for osteonecrosis, particularly when combined with bisphosphonates [1, 11]. Additionally, increased risk is also observed with therapy with sunitinib, a tyrosine kinase inhibitor possessing an anti-angiogenic effect, which is administered for osteomyelitis of the lower jaw [5].

In the current report, we describe a case of osteonecrosis in a cancer patient treated with bevacizumab without any prior bisphosphonate exposure. Osteonecrosis of the lower jaw [4, 6] due to bevacizumab therapy has been described in the literature, with the first case being described by Estilo in 2008 [12].

Bevacizumab is a humanised monoclonal IgG1 antibody, which works as an angiogenesis inhibitor of all endothelial growth factors and is prescribed for the treatment of advanced cancer. The above-mentioned wound healing defects, haemorrhage, thromboembolic complications, arterial hypertension and proteinuria constitute some of the side effects of bevacizumab [3, 6, 13].

In the case presented above, osteonecrosis was caused by interference in angiogenesis [3, 4]. Our patient underwent an incision and surgical drainage in the area of the necrotic bone. Furthermore, the patient developed a mouth ulcer as a side effect after treatment with gemcitabine, erlotinib, 5-fluorouracil, oxaliplatin and paclitaxel. The vulnerable mucosa represents another risk factor for bone exposure [1]. Studies have shown that the intake of bisphosphonates and such anti-angiogenic agents as bevacizumab is associated with increased incidence of osteonecrosis [1, 11].

Bevacizumab may increase the risk for osteonecrosis of the jaw while it modulates angiogenesis and inhibits the vascular endothelial growth factor [3, 4], which plays an important role in the differentiation and formation of bone [8]. Clinicians involved in the care of patients receiving anti-angiogenic agents should be aware that inhibition of VEGF might compromise the vascularisation of the jaw and lead to healing complications, especially after trauma, as in the case of tooth extraction. With increasing numbers of anti-angiogenic therapeutic agents entering clinical practice, further studies are needed to investigate any possible correlation between bevacizumab and osteonecrosis.

References

1. Aragon-Ching JB, Ning YM, Chen CC, Latham L, Guadagnini JP, Gulley JL, Arlen PM, Wright JJ, Parnes H, Figg WD, Dahut WL (2009) Higher incidence of osteonecrosis of the jaw (ONJ) in patients with metastatic castration resistant prostate cancer treated with anti-angiogenic agents. *Cancer Invest* 27: 221–226
2. Marx RE (2003) Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* 61:1115–1117
3. Disel U, Beşen AA, Özyilkan Ö, Er E, Canpolat T (2012) A case report of bevacizumab-related osteonecrosis of the jaw: old problem, new culprit. *Oral Oncol* 48:e2–e3
4. Ngamphaiboon N, Frustino JL, Kossoff EB, Sullivan MA, O'Connor TL (2011) Osteonecrosis of the jaw: dental outcomes in metastatic breast cancer patients treated with bisphosphonates with/without bevacizumab. *Clin Breast Cancer* 11:252–257

5. Hoefert S, Eufinger H (2010) Sunitinib may raise the risk of bisphosphonate-related osteonecrosis of the jaw: presentation of three cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 110:463–469
6. Hopp RN, Pucci J, Santos-Silva AR, Jorge J (2012) Osteonecrosis after administration of intravitreal bevacizumab. *J Oral Maxillofac Surg* 70:632–635
7. Guarneri V, Miles D, Robert N, Dieras V, Glaspy J, Smith I, Thomssen C, Biganzoli L, Taran T, Conte P (2010) Bevacizumab and osteonecrosis of the jaw: incidence and association with bisphosphonate therapy in three large prospective trials in advanced breast cancer. *Breast Cancer Res Treat* 122:181–188
8. Marx RE, Tursun R (2012) Suppurative osteomyelitis bisphosphonate induced osteonecrosis, osteoradionecrosis: a blinded histopathologic comparison and its implications for the mechanism of each disease. *Int J Oral Maxillofac Surg* 41:283–289
9. Sanna G, Preda L, Bruschini R, Cossu Rocca M, Ferretti S, Adamoli L, Verri E, Franceschelli L, Goldhirsch A, Nolè F (2006) Bisphosphonates and jaw osteonecrosis in patients with advanced breast cancer. *Ann Oncol* 17:1512–1516
10. Otto S, Schreyer C, Hafner S, Mast G, Ehrenfeld M, Stürzenbaum S, Pautke C (2012) Bisphosphonate-related osteonecrosis of the jaws—characteristics, risk factors, clinical features, localization and impact on oncological treatment. *J Craniomaxillofac Surg* 40:303–309
11. Christodoulou C, Pervena A, Klouvas G, Galani E, Falagas ME, Tsakalos G, Visvikis A, Nikolakopoulou A, Acholos V, Karapanagiotidis G, Batziou E, Skarlos DV (2009) Combination of bisphosphonate and antiangiogenic factors induces osteonecrosis of the jaw more frequently than bisphosphonates alone. *Oncology* 76:209–211
12. Estilo CL, Fornier M, Farooki A, Carlson D, Bohle G, Hury JM (2008) Osteonecrosis of the jaw related to bevacizumab. *J Clin Oncol* 26:4037–4038
13. Traina TT, Norton L, Drucker K, Singh B (2006) Nasal septum perforation in a bevacizumab-treated patient with metastatic breast cancer. *Oncologist* 11:1070–1071