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CASE REPORT

Bosutinib-induced osteonecrosis of the jaw in a patient with chronic myeloid leukemia: a case report

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Abstract

Medication-related osteonecrosis of the jaw (MRONJ) is an uncommon adverse drug reaction that can be induced by certain therapeutic drugs, including antiresorptive and antiangiogenic agents. Here, we describe the first case of ONJ induced by bosutinib, a tyrosine kinase inhibitor, in a patient with chronic myeloid leukemia (CML) who was not taking an antiresorptive agent. A 65-year-old male with no history of either antiresorptive treatment or dental surgery but diagnosed with CML had been undergoing treatment with bosutinib for 2 years. He developed right mandibular stage 2 osteonecrosis. The patient eventually underwent extensive surgery consisting of removal of the necrotic bone and infected soft tissue in combination with nasolabial flap reconstruction. He obtained complete resolution of MRONJ at 12 months postoperatively. As new cancer therapies become available, it is important that clinicians are aware of this novel case of bosutinib-induced ONJ in a patient undergoing CML treatment.

Keywords Bosutinib · Medication-related osteonecrosis of the jaw · Chronic myeloid leukemia · Local flaps

Introduction

Medication-related osteonecrosis of the jaw is a rare adverse drug reaction that is characterized by progressive destruction of the bone and that lowers the quality of life of affected individuals [1]. The current definition of medication-related osteonecrosis of the jaw (MRONJ) is the presence of exposed devitalized bone in the maxillofacial region for longer than 8 weeks in an individual who is currently undergoing or has previously undergone treatment with an antiresorptive or antiangiogenic agent, but who has no history of craniofacial radiotherapy [1]. Although most cases of MRONJ develop after exposure to antiresorptive agents such as bisphosphonates and denosumab [1], some recent MRONJ cases occurred following the treatment of cancer patients with tyrosine kinase inhibitors (TKIs), a mammalian target of rapamycin (mTOR) inhibitor, or monoclonal antibodies against vascular endothelial growth factor (VEGF), each of which has antiangiogenic effects [2–7]. Many MRONJ cases occur after dental trigger events such as tooth extraction, denture sore spots, and dentoalveolar surgery, but other cases develop spontaneously adjacent to periodontal infection, periapical lesions, or dental implants [2, 3].

Bosutinib is a second-generation TKI of the Src/Abl signaling pathway for the treatment of chronic myeloid leukemia (CML) in patients who are resistant and/or intolerant to prior therapy [8, 9]. We here describe the first case of a patient receiving bosutinib for CML who developed MRONJ with no history of antiresorptive treatment and who was successfully treated with surgery.

Case report

In September 2018, a 65-year-old man was referred to the Department of Oral Surgery from the Department of Hematology of our institution for the evaluation of his long-standing gingival pain in the right posterior mandible. He had

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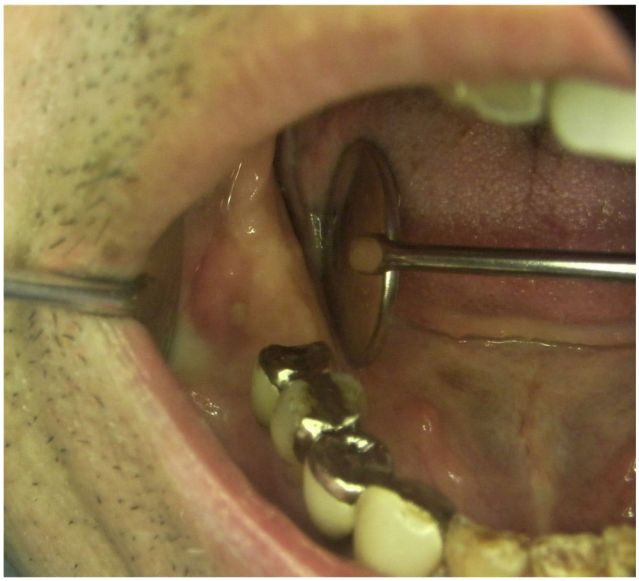

Fig. 1 Clinical view at presentation revealing exposed necrotic bone with gingival swelling

been diagnosed with CML in September 2015 and had been treated with 400 mg of imatinib once daily as first-line chemotherapy for 1 year. Subsequently, due to an insufficient response of imatinib to CML, the patient had been subjected to second-line chemotherapy with 500 mg of bosutinib once daily for 2 years at the time of presentation. He had never been exposed to antiresorptive agents such as bisphosphonates and denosumab or radiotherapy during his chemotherapy. In addition, he took no other medications that could affect bone remodeling, such as a steroid, during that time course.

At the time of the patient's initial referral, the clinical examination revealed exposed necrotic bone in the lower right molar region with an oval area 3 mm in diameter. There was a purulent discharge and the surrounding gingiva was swollen and erythematous (Fig. 1). A microbiological examination revealed the presence of *Streptococcus* species that were sensitive to amoxicillin. The patient had no related past dental history other than an extraction of the right first and second molars 10 years earlier. A panoramic radiograph revealed sequestra, osteolysis, and a periapical lesion of the second premolar in the right posterior mandible (Fig. 2). These findings were supported by computed tomography (CT) scans. Osteonecrosis of the jaw was diagnosed, and the patient was given a 1-week course of amoxicillin (250 mg orally 4 times per day) with 0.5% povidone-iodine mouthwash. The infected area was irrigated with a povidone-iodine rinse and injected with 2% minocycline hydrochloride once a week.

Over the next 2 months, 2 courses of amoxicillin administration and root canal treatment on the second premolar were conducted, but the exposed bone did not improve. The clinicoradiographic findings suggested MRONJ related to bosutinib, which was classified as stage 2 based on the American Association of Oral and Maxillofacial Surgeons (AAOMS) criteria [1]. However, due to the patient's development of arrhythmia, moderate pericardial and pleural effusion, and fatigue during the chemotherapy for CML, he was unable to undergo radical surgery at that time. The patient was referred to a cardiologist and started receiving 60 mg of edoxaban, 5 mg of amlodipine, and 40 mg of furosemide once daily. The above-described conservative treatments were also continued.

In June 2019, after cardiovascular treatment, the patient was admitted to the hospital and the bosutinib was temporarily stopped for 3 weeks during the subsequent surgery. Under general anesthesia, the second premolar with the periapical lesion was extracted, and the necrotic bone was completely removed. The periapical lesion was related to the osteolytic lesion. The debridement of the infected soft tissue was performed, causing a medium-sized defect (2 cm × 4 cm) in the mandible (Fig. 3a). Since the poorly vascularized mucoperiosteal tissue around the necrotic bone was inadequate for stable wound closure and for the prevention of the relapse of MRONJ, a nasolabial flap was prepared to provide sufficient well-vascularized soft tissue over the decorticated bone for wound closure (Fig. 3b) [10].

The patient's postoperative phase was uneventful after oral intake was started. As the second stage, the division and inset of the flap were performed 3 weeks after the initial operation, and bosutinib administration was resumed. A histopathological examination of the removed tissue confirmed the clinical

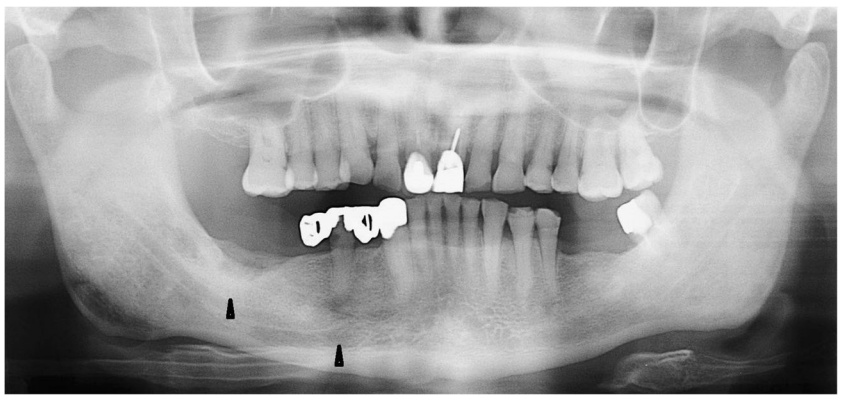

Fig. 2 Panoramic radiographic view at presentation revealing sequestrum, osteolysis, and periapical lesion of the second premolar in the mandible (arrowheads)

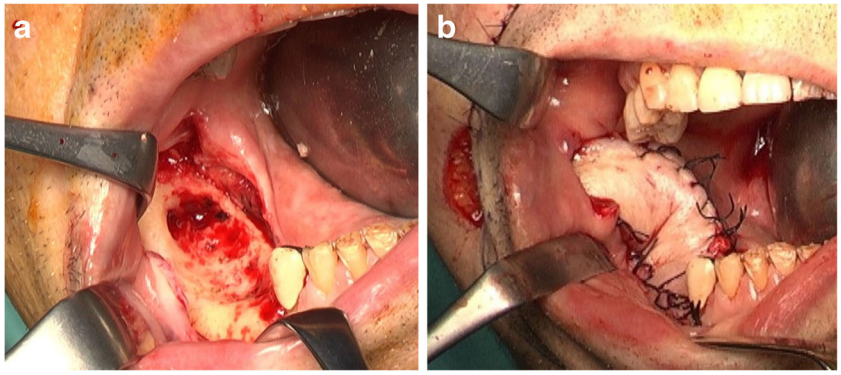

Fig. 3 Operative view. **a** Removal of the necrotic bone and soft tissue. **b** Nasolabial flap inset

diagnosis of osteonecrosis and the absence of neoplastic cells. At 12 months postoperatively, complete healing was observed in the treated area (Fig. 4). On a CT scan, osteolytic lesions were not identified in the posterior areas of the mandible. The patient has been successfully continuing chemotherapy with bosutinib for CML.

Discussion

There are currently three main classes of medications that are capable of inducing ONJ independently of antiresorptive agents such as bisphosphonates and denosumab. These are monoclonal antibodies against VEGF (including bevacizumab), TKIs (sunitib, sorafenib, lenvatinib, imatinib, and dasatinib), and an mTOR inhibitor (everolimus); all these agents are thought to have antiangiogenic effects and to cause impaired healing of the bone [2–7]. In the reported cases of TKI-induced ONJ, sunitib, sorafenib, lenvatinib, and dasatinib were found to inhibit the TKs of VEGF receptors, whereas imatinib inhibited the TK of platelet-derived growth factor (PDGF) receptors as an antiangiogenic agent [2–7].

Bosutinib is a potent second-generation TKI of the non-receptor tyrosine kinase Src/Abl pathway [11]; it is used for the treatment of CML in patients who are resistant and/or intolerant to prior therapy including imatinib or dasatinib [8, 9]. There are four reported cases in which MRONJ may have been associated with imatinib and two reported cases in which MRONJ may have been associated with dasatinib in patients with malignancies [2–4], but to the best of our knowledge, a causal association between bosutinib and MRONJ has not been reported. The most frequent adverse events due to bosutinib are diarrhea, nausea, thrombocytopenia, rash, anemia, fatigue, headache, hepatic toxicity, pericardial effusion, pleural effusion, and edema [6]. There are no published reports of MRONJ as an adverse event related to bosutinib.

Although our patient had received imatinib for 1 year, imatinib has a short half-life (18 h) and the patient's imatinib treatment had been discontinued 2 years before the occurrence of mandibular osteonecrosis. In addition, in other reported cases, the patients developed MRONJ during, not after, imatinib treatment [3, 5]. Hence, the likelihood that imatinib played an important role in the MRONJ of our patient may be negligible, suggesting that this is the first case report of a patient with CML who developed MRONJ during bosutinib treatment. In contrast to conventional chemotherapy, which is given in courses over a defined period, bosutinib should be given as a maintenance agent over a long period, sometimes for years [8, 9], and our patient had been treated with bosutinib for 2 years. The main mechanism by which bosutinib induces ONJ may be secondary to its cytotoxicity to osteoclasts and osteoblasts via inhibition of the tyrosine kinase Src/Abl pathway and consequent disturbance of bone remodeling [11], but whether bosutinib inhibits VEGF activity remains unclear [12].

The most common dental trigger events for MRONJ are tooth extraction and dentoalveolar surgery, but recent evidence suggests that periodontal and periapical infection may also be risk factors, especially in patients who have been

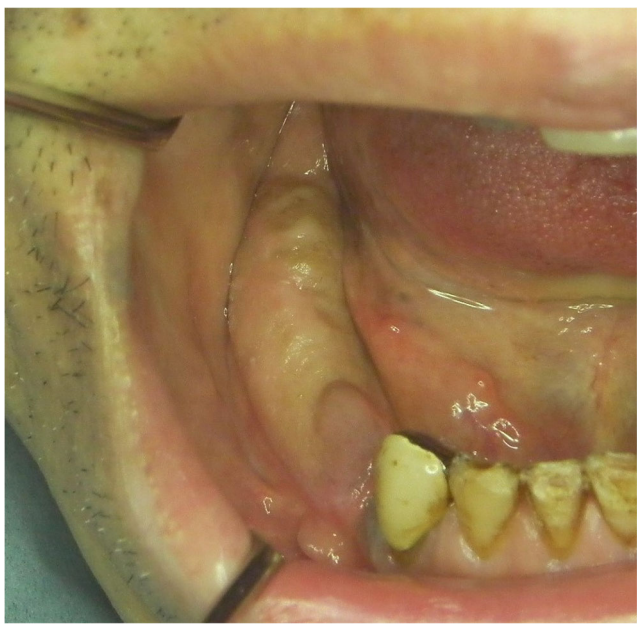

Fig. 4 Postoperative view at 12 months revealing complete healing

exposed to nonantiresorptive agents [2, 3]. Our patient had no recent history of tooth extraction, but radiographic findings revealed a periapical lesion of the second premolar close to the osteolytic lesions in the mandible.

The optimal treatment strategy for MRONJ is still controversial, but recent systematic reviews have suggested that in patients with stage 2 or 3 MRONJ, extensive surgery (defined as the removal of the necrotic bone, soft tissue, and surrounding bone) is more effective than conservative surgery (defined as the removal of only the necrotic bone) or non-surgical treatments [13]. Won et al. described the improvement of mandibular osteonecrosis induced by dasatinib in a patient with CML by non-surgical treatment, but complete healing was not observed in their case [4]. Vivano et al. reported a case of mandibular osteonecrosis related to imatinib in a patient with gastrointestinal stromal tumors; complete healing was not obtained after the removal of only the necrotic bone [5]. In contrast, a single case of dasatinib-induced mandibular osteonecrosis in a patient with acute lymphatic leukemia was reported in a retrospective cohort study; the patient underwent extensive surgery and achieved complete healing [3]. Lemound et al. recently reported that in stage 2 and stage 3 MRONJ cases, wound closure using nasolabial flaps dramatically improved the long-term results compared to mucoperiosteal flap use only, with a success rate of 68.8% vs. 18.7% [10]. In addition, another article also described the superiority of the vascularized musculomucosal flap to the mucoperiosteal flap in the surgical treatment of mandibular MRONJ [14].

Based on these reports and our previous experiences [15, 16], we believe that ensuring sufficient soft tissue coverage on the exposed bone after extensive surgery is essential to obtain a successful outcome, and in our patient's case, a nasolabial flap was prepared for wound closure, providing excellent healing under continuation of bosutinib use for CML.

In conclusion, we report what is to our knowledge the first case of bosutinib-induced MRONJ in a patient with CML in the absence of antiresorptive treatment. Since new agents with multi-target actions are applied in anticancer chemotherapy every year, oral disease control therapy and regular dental care should be an integral part of the management of patients with complex medical conditions. In particular, a recent article suggests that dentoalveolar surgery should be performed with the full mucosal coverage of the surgical site in combination with antibiotic treatment in patients receiving antiresorptive or antiangiogenic agents to prevent MRONJ [17]. We also suggest that extensive surgery might play an important role for a good bone healing process in advanced-staged MRONJ in patients with malignancies.

Authors' contributions YM and ST designed and YM wrote the paper. YM, YF, and RI performed the examination. YM and YF performed the surgery. All authors read and approved the final manuscript.

Compliance with ethical standards

Competing interests The authors declare that they have no competing interest.

Ethical approval This report was approved by the Institutional Review Board of Hiroshima Red Cross & Atomic-bomb Survivors Hospital (approval no. H 30-645).

Patient consent Written consent was obtained for publication.

References

1. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, O'Ryan F (2014) American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. J Oral Maxillofac Surg 72:1938–1956
2. Nicolatou-Galitis O, Kouri M, Papadopoulou E, Vardas E, Galiti D, Epstein JB, Elad S, Campisi G, Tsoukalas N, Bektas-Kayhan K, MASCC Bone Study Group et al (2019) Osteonecrosis of the jaw related to non-antiresorptive medications: a systematic review. Support Care Cancer 27:383–394
3. Abel Mahedi Mohamed H, Nielsen CEN, Schiodt M (2018) Medication related osteonecrosis of the jaws associated with targeted therapy as monotherapy and in combination with antiresorptives. A report of 7 cases from the Copenhagen Cohort. Oral Surg Oral Med Oral Pathol Oral Radiol 125:157–163
4. Won AM, Boddu P, Otun AO, Aponte-Wesson R, Chambers M (2018) Chronic myelogenous leukemia presenting with osteonecrosis of the jaw as a rare but debilitating toxicity of dasatinib: a case report and literature review. Oral Surg Oral Med Oral Pathol Oral Radiol 126:e208–e211
5. Vivano M, Rossi M, Cocca S (2017) A rare case of osteonecrosis of the jaw related to imatinib. J Korean Assoc Oral Maxillofac Surg 43:120–124
6. Mauceri R, Panzarella V, Morreale I, Campisi G (2019) Medication-related osteonecrosis of the jaw in a cancer patient receiving lenvatinib. Int J Oral Maxillofac Surg 48:1530–1532
7. Akkach S, Shukla L, Morgan D (2019) Everolimus-induced osteonecrosis of the jaw in the absence of bisphosphonates: a case report. Br J Oral Maxillofac Surg 57:688–690
8. Cortes JE, Apperley JF, DeAngelo DJ, Deininger MW, Kota VK, Rousselot P, Gambacorti-Passerini C (2018) Management of adverse events associated with bosutinib treatment of chronic-phase chronic myeloid leukemia: expert panel review. J Hematol Oncol 11:143
9. Cortes JE, Gambacorti-Passerini C, Deininger MW, Mauro MJ, Chuah C, Kim DW, Dyagil I, Glushko N, Milojkovic D, le Coutre P, Garcia-Gutierrez V, Reilly L, Jeynes-Ellis A, Leip E, Bardy-Bouxin N, Hochhaus A, Brümmendorf TH (2018) Bosutinib versus Imatinib for newly diagnosed chronic myeloid leukemia: results from the randomized BFORE trial. J Clin Oncol 36:231–237
10. Lemound J, Muecke T, Zeller AN, Lichtenstein J, Eckardt A, Gellrich NC (2018) Nasolabial flap improves healing in medication-related osteonecrosis of the jaw. J Oral Maxillofac Surg 76:877–885
11. Bieerkehazhi S, Chen Z, Zhao Y, Yu Y, Zhang H, Vasudevan SA, Woodfield SE, Tao L, Yi JS, Muscal JA, Pang JC, Guan S, Zhang H, Nuchtern JG, Li H, Li H, Yang J (2017) Novel Src/Abl tyrosine kinase inhibitor bosutinib suppresses neuroblastoma growth via inhibiting Src/Abl signaling. Oncotarget 8:1469–1480

12. Gover-Proaktor A, Granot G, Pasmanik-Chor M, Pasvolsky O, Shapira S, Raz O, Raanani P, Leader A (2019) Bosutinib, dasatinib, imatinib, nilotinib, and ponatinib differentially affect the vascular molecular pathways and functionality of human endothelial cells. Leuk Lymphoma 60:189–199
13. Hayashida S, Soutome S, Yanamoto S, Fujita S, Hasegawa T, Komori T, Kojima Y, Miyamoto H, Shibuya Y, Ueda N, Kirita T, Nakahara H, Shinohara M, Umeda M (2017) Evaluation of the treatment strategies for medication-related osteonecrosis of the jaws (MRONJ) and the factors affecting treatment outcome: a multicenter retrospective study with propensity score matching analysis. J Bone Miner Res 32:2022–2029
14. Mücke T, Koerdt S, Jung M, Mitchell DA, Wolff KD, Kesting MR, Loeffelbein DJ (2016) The role of mylohyoid flap in the treatment of bisphosphonate-related osteonecrosis of the jaws. J Craniomaxillofac Surg 44:369–373
15. Myoken Y, Fujita Y, Okamoto T (2020) Modified submental island flap for the surgical treatment of 4 patients with stage 3 medication-related osteonecrosis of the mandible. J Oral Maxillofac Surg 78: 29–34
16. Myoken Y, Fujita Y, Kawamoto K, Toratani S (2020) Osteonecrosis of the jaw in a metastatic lung cancer patient with bone metastases undergoing pembrolizumab+denosumab combination therapy: case report and literature review. Oral Oncol 27: 104874. https://doi.org/10.1016/j.oraloncology.2020.104874
17. Ristow O, Rückschloß T, Moratin J, Müller M, Kühle R, Dominik H, Pilz M, Shavlokhova V, Otto S, Hoffmann J et al (2020) Wound closure and alveoplasty after preventive tooth extractions in patients with antiresorptive intake-a randomized pilot trial. Oral Dis 2020: 17. https://doi.org/10.1111/odi.13556