Case Report

Unexpected massive bleeding caused by extensive maxillary osteonecrosis in a breast cancer patient: a case report

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Abstract: Diphosphonate application is routinely recommended to treat bone metastasis (BM) in cancer patients. However, the severe side effects of diphosphonate, especially after long-term use, are often overlooked by clinicians. In this article, we describe a case in which a heavily-treated breast cancer patient, suffered from massive bleeding as a result of maxillary osteonecrosis by zoledronic acid (ZA) and apatinib. In October 2018, a 48-year-old Chinese female with breast cancer presented at our department with brain metastases. The patient had experienced progression multiple times and had received several lines of systemic interventions. ZA was administered monthly for a rather long period of 37 months. She also took 250 mg of apatinib, a small molecular tyrosine kinase inhibitor (TKI) that targets vascular endothelial growth factor receptor 2, daily for 11 days. However, massive bleeding from the oral and nasal cavity occurred that could not be alleviated by conventional means. Computed tomography revealed severe destruction and loss of the right maxillary bone and maxillary sinus wall. A pathological examination of the exfoliated bone tissue further confirmed that the patient was suffering from necrosis rather than metastasis. An emergency interventional embolization was performed, and the bleeding was stopped. In this case, maxillary osteonecrosis developed from the antiresorptive agents. Antiangiogenesis drugs should be avoided whenever possible. In clinical practice, the high risk of osteonecrosis needs to be carefully considered. Further, care needs to be taken to ensure osteonecrosis is not misdiagnosed as BM, especially in stage IV patients. Pathology is a prerequisite for the timely and correct diagnosis and management. Life-threatening toxicity such as massive bleeding, should be avoided to ensure that patients receive adequate antitumor treatments.

Keywords: Massive bleeding; osteonecrosis; zoledronic acid (ZA); antiangiogenesis; case report

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Introduction

Due to their efficacy in reducing osteolysis, bisphosphonates (BPs) are attractive agents for bone metastasis (BM) in malignant tumors. Zoledronic acid (ZA), a third-generation nitrogen-containing BP has been reported to exert pleiotropic antitumor effects *in vitro* (1). Thus, the long-term application of BP is very common in clinical settings. Antiangiogenetic drugs, including both monoclonal antibodies and small molecule tyrosine kinase inhibitors (TKIs), produce promising effects when used in monotherapy or combined with other antitumor approaches, such as chemotherapy, immune checkpoint inhibitors, and radiotherapy. In metastatic and refractory settings, the combined application of antiresorptive and antiangiogenetic agents is common. However, the severe

complications this combination causes, have been largely ignored. Previous studies have shown that the use of BPs to prevent and treat bone-related events in patients with tumor or osteoporosis can cause medicine-related osteonecrosis of the jaw (MRONJ), which may increase when used in combination with antiangiogenic drugs (2). In the case presented here, massive bleeding resulted from osteonecrosis in a heavily treated breast cancer patient. Additionally, the mechanism by which BP and the antiangiogenetic drugs induced osteonecrosis was analyzed. This case study suggests that clinicians should make further efforts to ensure the early detection and appropriate management of osteonecrosis. We believe that this case raises the issue of whether severe osteonecrosis can be avoided in heavily-treated cancer populations. We present the following case in accordance with the CARE reporting checklist (available at https://dx.doi.org/10.21037/tcr-21-404).

Case presentation

In May 2014, a 44-year-old Chinese woman presented with a 3-year history of a painless mass in her left breast. Her past medical and family history was unremarkable. The mass progressed from 1.5×1.5 to 4.0×4.0 cm in size at the physical examinations. Ultrasound demonstrated an irregular hypoechoic lesion measuring about 39.1 mm × 25.9 mm in size located in the outer upper quadrant of the left breast. Additionally, several axillary lymph nodes were found in the left, some of which had lost normal structure, and the largest of which was about 13.8 mm × 10.5 mm in size. A subsequent biopsy of the breast tumor verified invasive ductal breast carcinoma with immunohistochemical results of estrogen receptor (ER) (80%+), progesterone receptor (PR) (80%+), human epidermal growth factor receptor 2 (HER2) (3+), and Ki-67 (20%+). A biopsy of the left axillary lymph node also indicated metastasis. The patient underwent a mastectomy at a tertiary hospital with a postoperative stage of T3N2 (primary tumor: 7 cm × 5 cm × 3.5 cm; axillary lymph nodes: 4/10), followed by 6 cycles of adjuvant chemotherapy (pirarubicin 60 mg, cisplatin 100 mg, and 5-Fu 2.5 g). The patient refused radiotherapy and endocrine therapy.

In March 2015, the patient suffered from disease progression with pulmonary, pleural, and sternal metastasis, but declined target therapy and chemotherapy. The treatment strategy was switched to a bilateral oophorectomy followed by letrozole and ZA. In February 2017, the patient experienced a second progression of pulmonary metastases. She was then enrolled in the HLX02-BC01 clinical trial and underwent 8 cycles of HLX02 (trastuzumab made in China, 8 mg/kg first dose and 6 mg/kg in maintenance) plus docetaxel (75 mg/m^2) every 3 weeks.

In November 2017, the patient showed further disease progression of pulmonary metastasis. At this time, her HER-2 status was rechecked and was found to be positive. She was then enrolled into the BO29919 clinical trial. The patient underwent 12 cycles of trastuzumab emtansine (TDM-1). Her response was evaluated as partial remission (PR), but TDM-1 was suspended due to grade 3 thrombocytopenia.

In October 2018, the patient complained of progressive sensory disturbance and a mobility disorder in a right limb. Subsequent brain magnetic resonance imaging (MRI) revealed metastases. Local radiotherapy to the metastatic brain lesions was initiated from October 18, 2018, at a dose of 45 Gy/5 Gy/9 f. The patient also took 250 mg of apatinib, a small-molecular TKI that targets intracellular segments of vascular endothelial growth factor receptor 2 (VEGFR2), daily from October 15, 2018. However, surprisingly, in October 26, 2018, massive bleeding from the oral and nasal cavity occurred. A computed tomography (CT) scan revealed severe destruction and loss of the right maxillary bone and maxillary sinus medial and lateral wall (see *Figure 1A-1C*). A pathological examination of the exfoliated bone tissue demonstrated bone necrosis, and BM was excluded (see *Figure 1D*). The bleeding continued despite aggressive medical hemostasis and tamponade treatment. Embolization hemostasis treatment was then recommended. Intraoperative arteriography revealed the presence of contrast agent dispersion from the upper alveolar branch of the right internal mandibular artery. An emergency interventional embolization was performed, and the bleeding was stopped. Anti-infective treatment was given after the operation. The patient received ZA regularly (once a month) from March 2015 to April 2018 and denied any history of tooth extraction, oral operation, or local debridement. However, in 2016, she suffered from a toothache and underwent analgesic treatment and took an antibiotic (ornidazole). Thus, the ZA and apatinib treatment was ceased. Fulvestrant was administered from October 30, 2018, to April 26, 2019. This patient was heavily treated and her prognosis was poor.

Follow-up and outcomes

In May 2019, the patient's intracranial metastasis had

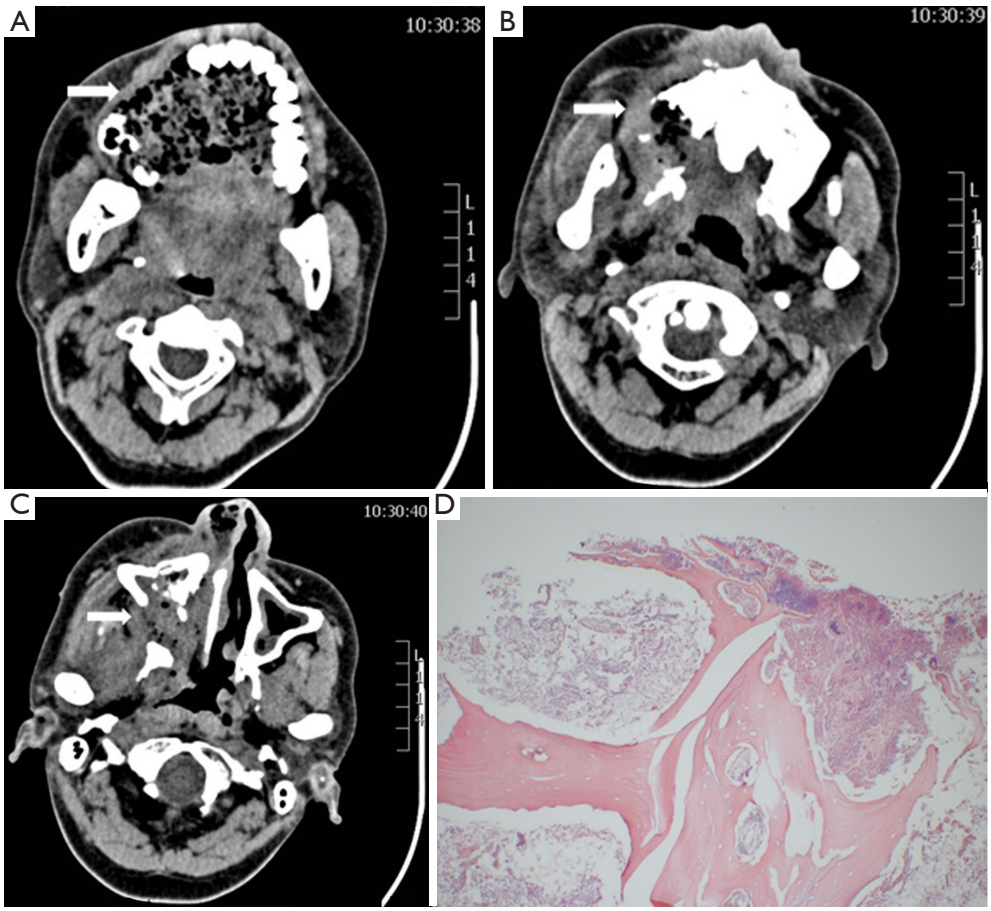

Figure 1 Maxillofacial computed tomography (CT) and pathological findings. Maxillofacial CT demonstrated severe destruction and loss of the right maxillary bone and maxillary sinus medial and lateral wall. (A) Right maxillary bone image. (B) Right maxillary bone image. (C) Right maxillary sinus medial and lateral wall image. White arrow (A-C) indicated bone defect. (D) The pathology of the exfoliated bone tissue showed no osteocytes in the lacunae, indicating bone necrosis (HE staining after decalcification, original magnification, 100×).

progressed. A brain MRI showed metastasis of the left temporal parietal lobe. The lesion of the left parietal lobe appeared to be enlarged. A new treatment strategy of chemotherapy with pirlotinib and capecitabine was employed. In August 2019, the patient refused any antitumor management. The local necrosis and defects became progressively aggravated, causing the mouth and nasal cavity to communicate. She found it difficult to eat and drink and often choked after drinking. The patient died on July 24, 2020 (see *Figure 2*).

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's son for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Bone is one of the most common metastatic sites for solid tumors (3). Bone metastases develop in approximately 54–81% of prostate cancer patients (4,5), 55% of breast cancer patients (6), 20–40% of lung cancer patients, and 17.4% of renal cell carcinoma patients (7,8). Skeletal-related events caused by BM include pathologic fracture, spinal cord compression, hypercalcemia, and local pain (3). These events not only seriously reduce patients' quality of life but also negatively affect their prognosis (3). Antiresorptive

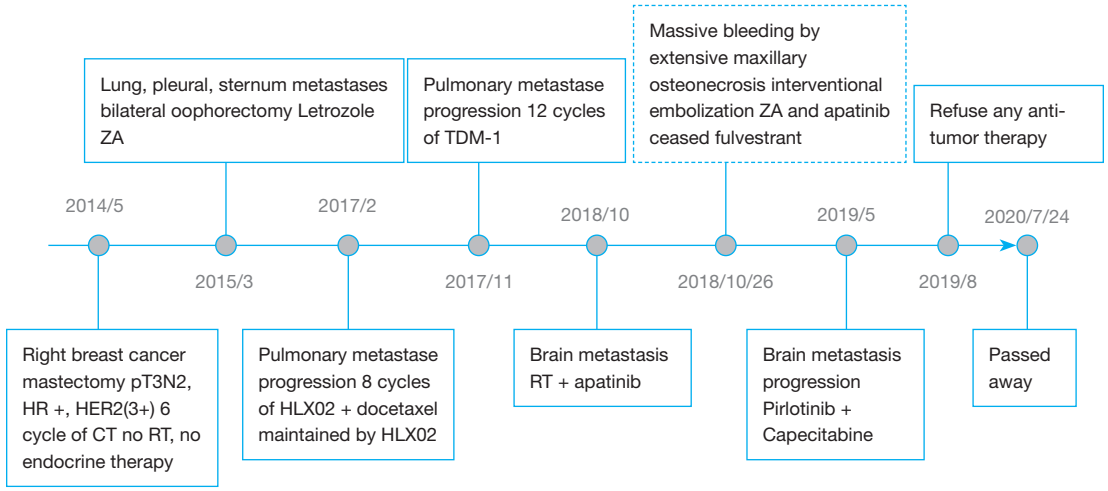

Figure 2 The timeline of diagnosis, treatment, and follow-up.

agents, such as ZA, are the standard option for treating BM.

With an occurrence rate of 1%, ZA-related osteonecrosis of the jaw (ONJ) is rare (9). In cancer patients, the incidence of ONJ related to BP therapy has been reported to be between 0.8–3.1% (10-14); however, its incidence increases when it is used combination with antiangiogenic drugs (2) (see *Table 1*). The incidence of ONJ differs in various tumors. In a retrospective study, the incidence of BP-related ONJ in patients with multiple myeloma and breast cancer was higher than that in patients with prostate cancer, lung cancer, kidney cancer, and other tumors (12). To be diagnosed with ONJ, a patient must meet the following criteria proposed by the American Association of Oral and Maxillofacial Surgeons (AAOMS): (I) a persistently nonhealing mandible or maxillary bone for longer than 8 weeks, (II) treatment with antiresorptive agents and/or antiangiogenesis, (III) no history of previous radiation to this region, and (IV) no tumor invasion or metastasis in this site (13,15,16).

Our patient was differentiated from BM, suppurative osteomyelitis, and radiation osteomyelitis. The patient had no obvious symptoms, such as a high fever or chills, and the results of the laboratory examination excluded suppurative osteomyelitis. Radiation osteomyelitis was also excluded, as the patient had no history of radiotherapy in the maxillofacial region. MRONJ patients have a clear history of related drug use. In our case, a CT scan revealed obvious destruction and loss of the right maxillary bone and maxillary sinus walls. The patient had taken ZA for a long period (37 months) and had also taken apatinib. The pathology of the exfoliated bone tissue confirmed bone necrosis. Thus, the patient was diagnosed with osteonecrosis.

Qi *et al.* retrospectively reviewed 2,214 individuals with advanced BM cancer from 3 phase III clinical trials. The multivariate analysis revealed that old age (≥66; P=0.007), anemia (P=0.006), and a long duration of ZA application (1–2 years; P=0.01; ≥2 years; P<0.001) were closely associated with a high risk of osteonecrosis (13). Our patient had used ZA for a rather long period (37 months), which contributed greatly to the severe osteonecrosis and results in massive bleeding. In the OPTIMIZE-2 clinical trial, 2 patients developed ONJ in the every-4-week group, while no patient developed ONJ in the every-12-week group (17). The question of whether tooth extraction leads to a high risk of developing ONJ remains controversial. Hasegawa *et al.* suggested that tooth extraction is a major risk factor of ONJ (18). Similarly, Kyrgidis *et al.* found that tooth extraction led to a 16-fold increase in the risk of ZA-related ONJ (19). Despite having no history tooth extraction, a history of oral infection in our patient partly aggravated the development of osteonecrosis. Lipopolysaccharide, a bacterial cell wall constituent, has been shown to enhance the direct necrotic effects of ZA (20). Over 800 kinds of bacteria inhabit the human oral mucosa (21). If oral mucosal damage occurs, these bacteria can easily reach the jaw bones and contribute to bone necrosis.

Antiresorptive and antiangiogenetic agents may share a common pathological process in inducing osteonecrosis. The key mechanism includes blocking the VEGF/VEGFR

Table 1 The incidence of ONJ related to BP therapy in cancer patients in previous studies

Author	Year	Num	Disease	Treatment	Risk factors	Outcome
Thumbigere-Math V (12)	2012	576	Cancer	Pamidronate 90 mg every 4 to 5 weeks; Zoledronate 4 mg every 4 to 6 weeks	Doses and long-term BP treatment, type of BP, diabetes, hypothyroidism, smoking, and previous dental extractions	BRONJ: 18 patients (3.1%) Healed completely: 2 (11%) Healed partially: 5 (28%) Stable: 5 (28%) Progressed: 6 (33%)
Saad F (11)	2011	5,723	Bone metastases secondary to solid tumors or myeloma	37 (1.3%) received zoledronic acid 4 mg Q4W; 52 (1.8%) received denosumab 120 mg Q4W	Tooth extraction: 55 (61.8%) Coinciding oral infection: 43 (48.3%) Jaw pain: 73 (82.0%)	ONJ: 89 patients (1.6%) Zoledronic acid group: 37 (1.3%) Denosumab group: 52 (1.8%)
Kizub DA (14)	2021	6,018	Breast cancer	Zoledronic acid 4 mg IV monthly for 6 months, then 1,600 mg of oral clodronate every 3 months daily, or 50 mg of oral ibandronate for 3 years	Infection: 21 (43.8%) Moderate/severe periodontal disease, dental calculus, gingivitis, and periodontitis >4 mm	BRONJ: 48 (0.8%) Median duration to onset: 2.3 years (range 0.1–6.3)
Qi WX (13)	2019	2,214	Cancer	Median duration of ZA treatment: 347.5 days (3–1,117 days)	Older age, anemia, and duration of ZA exposure	BRONJ:25(1.1%) Grade 1: 3 Grade 2: 9 Grade 3: 11 Unknown: 2
Hoff AO (10)	2008	3,994	Cancer	Pamidronate: 2,288 Zoledronic acid: 1,180 Pamidronate followed by zoledronic acid: 526	Dental extractions (P<0.0001) zoledronic acid (P=0.0004)	BRONJ: Breast cancer: 16 (1.2%) Multiple myeloma: 13 (2.4%)
Christodoulou C (2)	2009	116	Cancer	Zoledronic acid: 62; Ibandronic acid: 29; Zoledronic acid+ antiangiogenic therapy: 16; Ibandronic acid + antiangiogenic therapy: 9	NA	BRONJ: Bisphosphonates with or without antiangiogenic agents: (4/25) 16% and (1/91) 1.1% (P=0.008)

pathway, which results in the inhibition of proliferation, migration, permeability, and the survival of vascular endothelial cells (VEC). Allegra *et al.* found that application of BP resulted in a decrease in circulating endothelial progenitor cells (EPCs) and thus interfered with endothelial cell proliferation (20,22). Additionally, BP administration has been shown to induce endothelial cell apoptosis (20,23). Nitrogen-containing bisphosphonates (NBPs) can also inhibit the expression of osteopontin in the mandible, which in turn promotes the proliferation of endothelial cells (24).

NBPs inhibit the number and function of γδ T lymphocytes in circulation and reduce the serum levels of interleukin 17, which plays a critical role in the stimulation of VEC migration and the secretion of proangiogenic factors (20,24,25). Further, NBPs directly inhibit the messenger RNA (mRNA) expression of VEGF and thus reduce the production of VEGF (26). NBPs inhibit the activity of osteoclasts, preventing osteoclast from releasing stored VEGF and indirectly inhibiting VEGF production (27). NBPs inhibit the activity of matrix metalloproteinase 9 in the extracellular matrix, thereby reducing VEGF-VEGFR binding and inhibiting angiogenesis (28).

In 2008, Estilo *et al.* were first to report a patient with breast cancer and a patient with glioblastoma multiforme developing ONJ after receiving the antiangiogenic drug, bevacizumab (29). A subsequent retrospective study found that patients receiving BP combined with antiangiogenic drugs had a higher incidence of ONJ than did patients receiving BP alone (16% *vs.* 1.1%; P=0.008) (2). Lescaille *et al.* reviewed 42 ONJ patients and found that ZA combined with bevacizumab was associated with an increased risk of spontaneous ONJ (odds ratio: 6.07; 95% confidence interval: 1.3–28.2; P<0.05) (30). Ngamphaiboon *et al.* found that patients receiving BPs combined with antiangiogenic drugs had more severe symptoms, such as pain, abscesses, and loose teeth than patients with BPs alone (31). Apatinib, a potent small-molecule inhibitor of VEGFR2 signaling, undoubtedly exerts a synergistic action on BP in avascular necrosis. Additionally, local infection and trauma can also aggravate ONJ.

The treatment of ONJ is rather challenging, and no standard paradigm has thus far been established. According to the AAOMS, ONJ has 4 stages (9). Conservative treatments, such as antibiotics and analgesics, are generally applied to patients in the early stage (stage 0–1), while surgery has been shown to be superior to supportive management alone in more advanced patients (in stages 2–3) (9). However, the complete removal of the necrotic bones and closure of the wound are critical to the success of surgery (32,33). In our case, the involved region was so extensive that the complications caused by the surgery were severe. Providing new insights into their role in ONJ, Steller *et al.* reported that platelet-rich plasma and platelet-rich fibrin full of growth factors, such as platelet-derived growth factor, transforming growth factor, and insulin-like growth factor, reduce the negative effects of ZA on cell viability, proliferation, and migration (34).

The findings of our case are noteworthy in many respects. First, the combined use of NBP and angiogenetic drugs is rather common in clinical practice, but the subsequent disastrous complications, such as osteonecrosis, which occurred in our patient, have failed to attract sufficient attention. Populations at high-risk of osteonecrosis should be identified, and the intensity and duration of treatments should be adjusted correspondingly to ensure that severe side effects are avoided where possible. An oral inspection should be performed before BP or antiangiogenesis drugs are administered and unnecessary oral procedures should be avoided during treatment. Second, we analyzed the mechanism of osteonecrosis induced by NBP and angiogenetic agents. In the future, novel drugs targeting the key link in osteonecrosis development should be addressed to solve the current therapeutic dilemmas facing patients with osteonecrosis. Third, care needs to be taken to ensure that osteonecrosis is not mistakenly diagnosed as BM in heavily-treated cancer patients with a definite history of metastases in the bone and/or other sites. Pathology is essential to ensuring the correct diagnosis and management.

In conclusion, given the common application of antiresorptive and antiangiogenetic agents, severe side effects, such as the extensive osteonecrosis shown in our case, should be avoided. The high-risk patients, causes, underlying molecular mechanism, and best intervention for drug-related osteonecrosis need to be further clarified. Pathology is a prerequisite for excluding BM, especially in refractory and metastatic settings. This issue should be given more attention, as it seriously affects patients' quality of life.

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Footnote

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