Case Report

Mandibular fracture in a patient treated with long-term antiangiogenic therapy and previous bisphosphonate exposure

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Bisphosphonate-related osteonecrosis of the jaw (ONJ) has been reported in the literature since 2003,[1,2] with more than 90% of the events attributed to treatment with bisphosphonate agents, such as zoledronic acid (Zometa) and pamidronate, which are used to treat hypercalcemia of malignancy and to reduce the risk of skeletal-related events due to bone metastases.[3–5] Patients with ONJ generally present with exposed necrotic bone that does not heal for 6–8 weeks, often leading to significant morbidity. The pathogenic mechanism for osteonecrosis is unclear, but, in addition to inhibiting bone resorption, preclinical data have demonstrated thrombotic microangiopathy and potent inhibition of angiogenesis,[6] which may lead to avascular necrosis and poor wound healing after dental procedures.

Angiogenesis is a critical step in tumor growth, and agents that block neovascularization by targeting vascular endothelial growth factor (VEGF) or its receptor (VEGFR) have been used successfully for a variety of solid tumors. Bevacizumab (Avastin) is a monoclonal antibody that inhibits angiogenesis by binding to VEGF,[7] and sorafenib (Nexavar) is a multiple-kinase inhibitor that inhibits several intracellular and cell-surface kinases, including VEGFR.[8] Osteonecrosis of the jaw or femoral heads has been increasingly recognized in patients treated with antiangiogenic therapies, even without concurrent bisphosphonate use.[9–12] Previous data on combining bisphosphonates with antiangiogenic agents are conflicting, with some reports indicating a similar risk of ONJ compared with the use of bisphosphonates alone[13,14] and others showing significantly higher rates (18% vs 1% with bisphosphonates alone).[15,16]

In this paper, we describe the case of a patient with metastatic prostate cancer and a history of ONJ from use of zoledronic acid who developed a mandibular fracture while he was off zoledronic acid for 15 months but undergoing treatment with paclitaxel and bevacizumab plus sorafenib on a clinical trial. The case may help explain the temporal relationship between therapy and the occurrence of jaw fracture, as well as the link between ONJ and the risk of fractures with sequential use of bisphosphonates and antiangiogenic agents.

Case presentation

A 65-year-old man was diagnosed with stage IIB (T2cN0M0) prostate cancer and initially treated with prostatectomy in 1997. He developed a biochemical recurrence, with a rise in prostate-specific antigen (PSA) level, in 2000 and was treated with local radiotherapy followed by bicalutamide. In February 2004, he had another recurrence, this time with bone metastases, and was treated with six cycles of docetaxel plus estramustine and started on zoledronic acid, 4 mg IV every 4 weeks, until December 2004, when a bone scan showed no evidence of disease and treatment with zoledronic acid was stopped. Subsequently, he developed PSA elevations and was treated with ketoconazole, followed by pemetrexed (Alimta).

Zoledronic acid therapy was resumed in November 2005, when a bone scan showed progressive metastases. At that point, he received multiple lines of therapy on clinical trials, including paclitaxel with PTK787 (vatalanib, a pan-VEGFR/tyrosine kinase inhibitor), given between April 2006 and May 2007; a pan-PI3K/mTOR inhibitor SF1126, given

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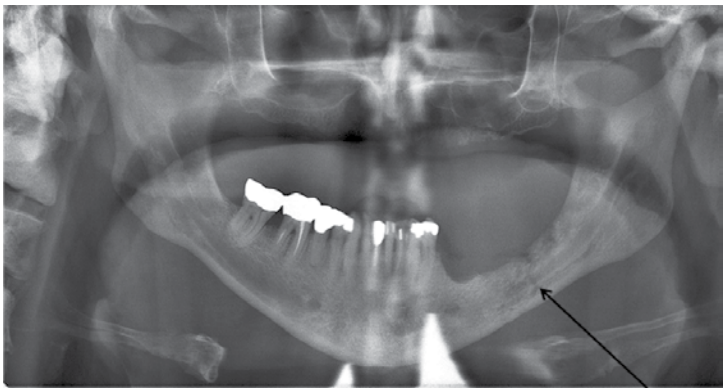

FIGURE 1 Panoramic radiograph of the jaw showing a fracture of the left mandible (arrow). Note the loss of bone mineralization and dentition, supporting the diagnosis of osteonecrosis of the jaw.

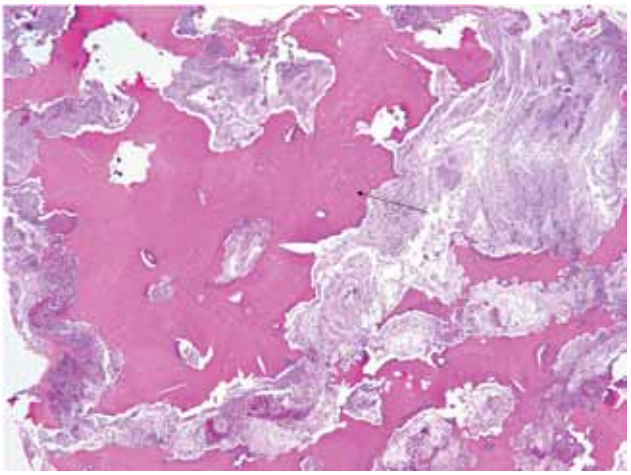

FIGURE 2 Slide illustrating bone necrosis (arrow). In this 40× image, all visualized bone is dead. The basophilic areas between bony trabeculae represent bacterial colonies.

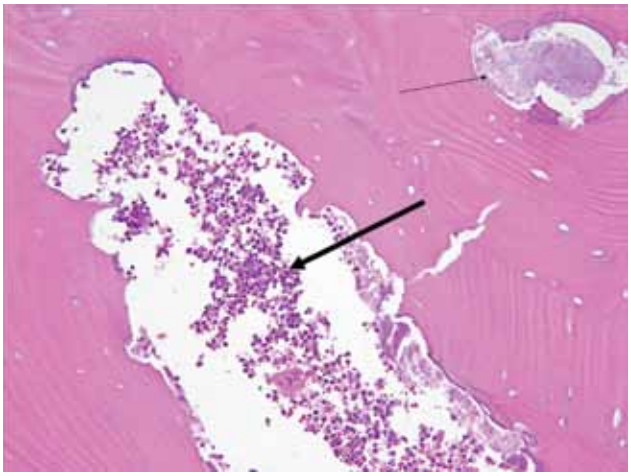

FIGURE 3 Medium-power (200×) image illustrating dead bone and areas of inflammation, with neutrophil infiltration (thick arrow) and bacterial colonies (thin arrow).

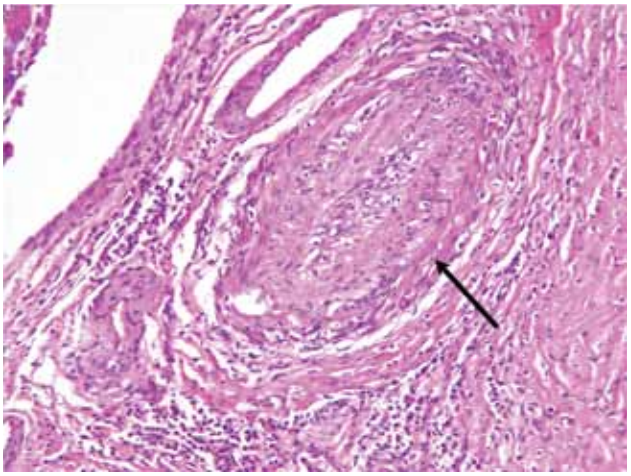

FIGURE 4 Medium-power (200×) image of mandibular resection showing obliterative endarteritis. The vessel in the center (arrow) demonstrates medial and intimal thickening and is almost occluded. Inflammation, in the form of lymphocytes and plasma cells, is also evident.

between July and December 2007; and paclitaxel 80 mg/m^2 three times a week every 4 weeks, bevacizumab 5 mg/kg every 2 weeks, and sorafenib 200 mg/day orally 5 days/week, given from May 2008 to June 2010.

In May 2008, baseline CT scans showed evidence of mediastinal adenopathy; and the bone scan showed diffuse metastases in the thoracolumbar spine, bilateral ribs, distal left femur, proximal left humerus, and the calvarium, with no uptake in the mandibles. In December 2008, the patient required the extraction of an infected left mandibular molar. All treatment was withheld for 3 weeks before the procedure, and bevacizumab was withheld for an additional 4 weeks after the tooth extraction. Although dental notes indicate slow healing, the patient had no residual discomfort, but with a clinical diagnosis of ONJ, treatment with zoledronic acid was discontinued.

In September 2009, a routine bone scan identified increased radiotracer uptake in the left mandible and, coinciding with another left molar infection, the patient developed an erosion of the left mandibular area. He was treated with oral antibiotics (amoxicillin/clavulanic acid) but did not require any dental procedures. Because of the patient's overall response of his metastatic disease to the study treatment, he continued on protocol coupled with frequent dental follow-ups. Repeat bone scans every 2 months showed stable radiotracer uptake in the left mandible through June 2010, and he remained asymptomatic.

On July 2, 2010, the patient developed left jaw pain, which was self-treated with antibiotics. Nine days later, the pain acutely exacerbated, and he developed jaw swelling, prompting him to go to the hospital emergency room. A panoramic x-ray demonstrated a non-

displaced comminuted fracture of the mid-left mandible (Figure 1). His last study treatment with paclitaxel and bevacizumab was on June 29 and for sorafenib, on July 2. In September 2010, after pain control and optimization of his nutritional status via a gastroesophageal tube, the patient underwent segmental mandibular resection, with reconstruction with a fibular free flap and microvascular anastomosis. The length of the mandible defect was estimated at 3.5 cm. The pathology report indicated devitalized, thickened, sclerotic bony trabeculae with empty lacunes, and soft tissue with mixed inflammatory response accompanied by necrosis, but no evidence of malignancy (Figures 2 and 3). There was evidence of isolated obliterative endarteritis (Figure 4). The patient recovered well from surgery and remained off any cancer therapy, but suffered rapid disease progression in December 2010 and died from metastatic disease in May 2011.

Discussion

This patient clearly developed ONJ with significant morbidity after the prolonged use of zoledronic acid for about 37 months, coupled with concurrent use of two antiangiogenic agents, bevacizumab and sorafenib, for 7 months. His tooth extraction seems to have been the precipitating event for the development of ONJ.

Dental surgery and tooth extraction are known to increase the risk of developing ONJ.[17] The average length of time from initiation of bisphosphonate therapy to development of ONJ is about 2–3 years, but that estimate is confounded by the fact that ONJ may be asymptomatic for weeks or months.[18,19] Osteonecrosis associated with antiangiogenic agents has been reported to occur anywhere between 1 and 16 months after starting treatment.[13] There is debate on whether the addition of antiangiogenic therapy compounds the risk of ONJ from bisphosphonates, because both may affect bone angiogenesis and healing.

In our patient, the ONJ occurred 3 years after starting bisphosphonate therapy, and after zoledronic acid was discontinued, he remained on treatment with antiangiogenic agents and chemotherapy for another 18 months. This treatment very likely exacerbated his ONJ and caused the mandibular fracture more than 2 years from starting study treatment and 18 months after stopping the use of zoledronic acid. We reviewed the jaw resection pathologic specimen and identified bone necrosis and obliterative endarteritis (Figure 4), and although the surgical specimen dated from 2 months after he had stopped anti-VEGF therapy, it is consistent with the profound effects of antiangiogenic agents, which may have precluded long-term bone healing.

The jaw fracture we describe in our patient with a previous diagnosis of ONJ, despite discontinuing treatment with bisphosphonates, represents an alarming complication of VEGF blockade. Clinical providers caring for patients with bony metastatic disease who are using bisphosphonates and antiangiogenic drugs in combination or sequentially need to be aware of the link between these drugs and ONJ and the risk of both exacerbating existing ONJ and precipitating further bone fractures. Finally, it is important for providers to limit, where possible, the duration of treatment with bisphosphonates and/or antiangiogenic agents, emphasize to patients the importance of oral care and hygiene while they are on these agents, and recognize the early signs of ONJ and stress fractures, all of which could improve their quality of life.

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