Exposed Bone in Oral Cavities

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Case Study

Ms. N is a 54-year-old woman initially diagnosed in 2002 with stage IIIB non-small cell lung cancer, for which she received radical pneumonectomy followed by chemotherapy with carboplatin and gemcitabine. After a period of stability (i.e., approximately nine months) in which no further lesions were discovered, in a follow-up visit, she complained of lower abdominal pain, leading to the discovery of several large sclerotic lesions in her pelvis. Ms. N was diagnosed with metastatic lung cancer to the bone and began monthly therapy with zolendronic acid, a bisphosphonate approved for the treatment of metastatic lesions from lung cancer. In 2003, the patient presented with a complex ovarian mass and elevated cancer antigen 125 and began therapy for presumed ovarian cancer. Ms. N received liposomal doxorubicin and continued the monthly infusions of zolendronic acid. Her quality of life was good, and she was able to participate in her usual activities.

In 2004, Ms. N began to complain of diffuse jaw pain. The pain was unresponsive to analgesics administered over several months. On examination, the gum looked edematous with mild erythema, and the initial differential diagnosis included oral abscess. After consultation with a dentist, a full panoramic radiographic study was taken of the affected area of her jaw. The patient then presented to the clinic with a complaint of exposed bone in her jaw and gum line (see Figure 1). Ms. N was started on oral clindamycin and oral chlorhexidine 0.12% mouth rinses three times a day. She was referred to an oral surgeon for further evaluation, where avascular necrosis or osteonecrosis of the jaw (ONJ) was diagnosed.

Literature Review

Osteonecrosis of bony areas, most frequently the head of the femur, has been associated with long-term or chronic corticosteroid use and is well known in the rheumatology literature (Koo et al., 2002; Zalavras, Shah, Birnbaum, & Frenkel, 2003). Excessive alcohol use also has been implicated in osteonecrosis of the femoral head (Hirota et al., 1993). One report described osteonecrosis of the femoral head after long-term, low-dose, inhaled corticosteroid therapy (Kistelinski, Niedhart, Schneider, & Neithard, 2004). Osteonecrosis has been found in patients on various chemotherapy drugs, bone marrow transplant recipients, and patients with inflammatory bowel disease (probably related to steroid use) or HIV disease (Klingerstein, Lev, Kornbluth, Shah, & Present, 2005; Siddiqui, Smith, Mashoo, & Bryk, 2004; Tauchmanova et al., 2003). In transplant recipients, avascular necrosis is believed to be related to the ability of bone marrow stromal stem cells to repopulate after stem cell transplantation (Tauchmanova et al.).

ONJ or avascular necrosis of the jaw is a condition in which the jaw’s bone tissue fails to heal, usually after minor trauma such as a dental procedure involving tooth extraction. ONJ may occur in patients who have received radiation therapy to the head and neck. In the case of radiation therapy patients, the condition is termed osteoradionecrosis and usually occurs in the mandible, with approximately 50% of the cases subsequent to tooth extraction (Bagan et al., 2005; Ruggiero, Mehrotra, Rosenberg, & Engroff, 2004). Osteoradionecrosis of the mandible occurs in 5%–15% of patients receiving radiation therapy (Balogh & Sutherland, 1989) and can present with asymptomatic lesions that remain stable for several months to years. The condition may heal with conservative
management, but some patients develop severe necrosis of the jaw that requires surgical reconstruction (Mendenhall, 2004). Hyperbaric oxygen has been used to treat osteoradionecrosis of the mandible; however, in a randomized clinical trial, Annane et al. (2004) failed to slow disease progression or improve pain relief.

Recently, the literature has reported a possible connection between bisphosphonate therapy and ONJ. Although the case reports typically have involved patients receiving IV bisphosphonates, oral bisphosphonates have been implicated as well. Nitrogen-containing bisphosphonates are an integral component of the treatment of bone metastases and hypercalcemia in patients with cancer and include the IV agents pamidronate and zoledronic acid (Melo & Obeid, 2005). Oral bisphosphonates are an important part of the treatment of some patients with osteoporosis or Paget disease of the bone and may include non-nitrogen-containing bisphosphonates such as alendronate and risedronate (Melo & Obeid).

A retrospective review of 63 cases found that the common denominator in the increased number of patients with ONJ in one oral surgery service was the use of bisphosphonates (Ruggiero et al., 2004). Fifty-six patients had been receiving IV bisphosphonates for at least one year, and seven patients were on chronic oral bisphosphonate therapy. In all patients, ONJ appeared to be very similar to the clinical and radiographic features of osteoradionecrosis, a previously uncommon complication. The patients in the retrospective review usually presented with a nonhealing extraction socket, or exposed bone, in the jaw; debridement and antibiotic therapy were not helpful. The study participants had different diagnoses, including breast, lung, and prostate cancer, as well as multiple myeloma, and seven patients without malignancies were receiving oral bisphosphonates for treatment of osteoporosis. All except two required surgery to remove the affected area of the bone (Ruggiero et al.).

In a recent European report of ONJ in association with cancer chemotherapy, different agents used in the treatment of 10 patients were analyzed (Bagan et al., 2005). Six patients had breast cancer, and the remaining four had multiple myeloma. ONJ primarily affected the mandible, but some maxillary involvement existed. In seven patients, a tooth extraction predated the ONJ diagnosis. Eight of the 10 patients received drug combinations containing cyclophosphamide, whereas four received dexamethasone as part of their drug therapy. The common denominator for all 10 patients was bisphosphonate therapy, pamidronate and zoledronic acid, which they received for metastatic bone disease. The treating surgeons believed the patients’ jaw bones became exposed to oral flora after tooth extraction and were unable to heal, thus producing pain and ultimately infection; however, three patients had no previous dental extraction (Bagan et al.).

Migliorati (2003) described five patients who were on pamidronate or zoledronic acid and had intraoral bone necrosis, with exposure of the necrotic bone and associated pain. Melo and Obeid (2005) reported a case involving a 72-year-old woman with metastatic breast cancer and a nonhealing extraction socket in her upper left maxilla following a tooth extraction. The patient was on oral capcitabine and trastuzumab, as well as zoledronic acid. After several months of delayed healing, the site was debrided surgically, the granulation tissue removed, and the surgical site was closed and allowed to heal by secondary intention, although an area of oroantral communication in the sinus remained open. Another case report discussed three patients with multiple myeloma on IV bisphosphonates with severe osteomyelitis requiring antibiotic therapy (Lugassy, Shaham, Nemets, Ben-Dor, & Nahlieli, 2004). Treatment with prolonged penicillin therapy for extensive actinomycosis infection resolved one case; the second required hyperbaric oxygen and antibiotic therapy to achieve treatment success (Lugassy et al.).

ONJ was found in three patients with breast cancer receiving taxoid chemotherapy and pamidronate therapy; two patients showed the condition related to tooth extraction, whereas the third patient developed the complication spontaneously (Wang, Googer, & Pogrel, 2003). In addition, Marx (2003) reported that 36 patients who received either pamidronate or zoledronic acid for metastatic bone disease or osteoporosis developed ONJ. Although most of the patients had a previous tooth extraction, approximately 30% spontaneously developed the complication.

Whether the duration of therapy correlates to the development of ONJ is unknown, but that information may emerge as patients receive chronic bisphosphonate therapy over longer periods of time, as in the case of the patients with multiple myeloma (Lugassy et al., 2004). Healthcare providers must be cognizant of ONJ as a potential complication of this drug class (i.e., bisphosphonates).

**Pathophysiology**

IV bisphosphonates have been used to treat bone metastases since 1994 and are a crucial part of therapy for affected patients. Bisphosphonates help to decrease the severity of and pain associated with bone metastases and are effective in reducing the incidence of skeletal-related complications such as fractures (Maxwell, Swift, Goode, Doane, & Rogers, 2003). Bisphosphonates are analogs of pyrophosphate, a natural compound in the body that helps to regulate calcium, and the agents work by reducing bone resorption by the osteoclasts that break down bone.

Normal bone remodeling is a balanced process involving osteoclasts, which are responsible for bone resorption, and osteoblasts, which are responsible for bone growth; however, in patients with bone metastases, this process becomes unbalanced with increased osteoclast and/or osteoblast activity, resulting in bony complications (Viale & Yamamoto, 2003). The bisphosphonate drugs work by inhibiting the activity of osteoclast cells that resorb or break down bone and may help to reduce tumor burden. Bisphosphonates have been shown to inhibit tumor cells, possibly by inducing apoptosis (Melo & Obeid, 2005; Viale & Yamamoto). The agents also have antiangiogenic properties (Melo & Obeid). This quality helps the drugs to make changes in the bone microenvironment that are unfavorable for tumor cells but may make healthy bone cells less effective (Melo & Obeid; Migliorati, 2003). However, no clear causal relationship has been established between the diagnosis of ONJ and administration of bisphosphonates (Robinson & Yeo, 2004). Further research needs to be conducted to accurately identify the role of bisphosphonates in ONJ.

**Assessment and Diagnosis**

An expert panel consisting of oral surgeons and oral medicine, oral oncology, endocrinology, and medical oncology clinicians convened in 2004 to develop recommendations regarding ONJ. The panel determined that patients on bisphosphonates should be assessed for the presence of swelling in the oral cavity, infection, pain, tooth loss or loosening, drainage, and exposed bone (Damato et al., 2005). Although ONJ may occur spontaneously, it often is related to tooth extractions. Radiologic studies to confirm suspected ONJ, including panoramic and computed axial tomography imaging, may be performed to rule out other possible etiologies. If metastatic disease is suspected, biopsies should be performed. Potential risk factors for the condition include concomitant therapy with steroids, chemotherapy and bisphosphonates, and dental procedures including extractions.

The panel recommended the avoidance of any elective jaw procedure that requires
bone to heal and suggested dental examinations to determine preexisting infections or the need for preventive dentistry procedures prior to the start of bisphosphonate therapy. Oncologists, healthcare providers, and oncology nurses should be cognizant of oral complaints from patients, and a brief visual oral inspection should be performed at each visit (Damato et al., 2005).

Once ONJ is diagnosed, consultation with an oral surgeon or dental oncologist is necessary. Both nonsurgical and surgical approaches may be considered. Intermittent or continuous antibiotic therapy may be helpful for patients with ONJ. Hyperbaric oxygen therapy is not recommended. Bisphosphonate therapy may be interrupted or completely halted in some cases, especially if ONJ is severe (Damato et al., 2005).

Discussion

Although surgical resection of her mandible and hyperbaric oxygen therapy were considered, Ms. N currently is on observation only, and her bisphosphonate therapy has been discontinued.

ONJ has been implicated as a possible complication in the treatment of patients taking bisphosphonates, and all oral complaints in this population should be evaluated comprehensively. As bisphosphonates increasingly are used in patients with cancer who develop bone metastatic disease, heightened awareness of possible complications such as ONJ is important. Oncology nurses should be aware of ONJ and are in an ideal position to assess and report oral problems. Future research is needed to further establish the pathophysiology of ONJ and its possible connection to bisphosphonates; more data are needed to evaluate the incidence of ONJ in patients receiving bisphosphonate therapy.

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References


