Bisphosphonate-Related Osteonecrosis of the Jaw: The Role of Actinomyces

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The etiology of bisphosphonate-related osteonecrosis of the jaw is unknown but was initially postulated to be mediated by bisphosphonate accumulation within the jaws, resulting in avascular necrosis. Bisphosphonates may not be the primary cause. Actinomyces are an underrecognized agent in pathogenesis, and timely actinomycosis-specific treatment may improve outcome.

Actinomyces are anaerobic or microaerophilic, filamentous, non–spore-forming gram-positive bacteria that colonize the mouth, colon, and vagina. Actinomycosis is an indolent infection that can involve nearly every site of the body. Mucosal disruption is the key step in pathogenesis. During tissue invasion, actinomyces form clumps called sulfur granules. Common in the preantibiotic era, today the incidence and timely recognition of actinomycosis is diminished. Even when considered, actinomycosis presents a diagnostic challenge because of difficulties with microbiological isolation. Even a single dose of antimicrobials can interfere with their isolation. General features of this unique infection include (1) the combination of chronicity, progression across tissue boundaries, and masslike features that mimic malignancy; (2) development of a sinus tract(s), which may spontaneously resolve and recur; and (3) refractory or relapsing infection after a short course of therapy. Cure of established actinomycosis requires prolonged treatment.

[1] An awareness of specific associations is also of value for diagnosing actinomycosis, such as infection of the pelvis with use of an intrauterine contraceptive device. Recently, a new association with actinomycosis has been recognized.

Oral-cervicofacial disease is most common, and a newly recognized form of actinomycosis at this site has emerged. Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a condition defined by the presence of exposed mandibular or maxillary bone that does not heal within 8 weeks in a patient exposed to bisphosphonates who has not received radiation therapy directed to the jaws [2]. A typical presentation includes some combination of a painful, nonhealing dental extraction site or exposed bone associated with swelling and drainage. Intra- or extraoral fistulas may develop [3, 4]. BRONJ was originally believed to be a direct, noninfectious complication of bisphosphonate therapy. However, recent historical and microbiological data strongly support that actinomyces play a critical role in the pathogenesis of this disorder [5–10]. In a patient with BRONJ, the timely recognition that most (if not all) cases represent a bisphosphonate-facilitated actinomycotic infection involving bone and the surrounding soft tissues is critical. Stopping bisphosphonate therapy plus or minus debridement without appropriate management for actinomycosis is unlikely to result in improvement [11].

Case. A 56-year-old man was evaluated for drainage from the site of an extracted upper dental implant that had been placed 5.5 years earlier. Five years ago, he received a diagnosis of multiple myeloma. Initial treatment consisted of chemotherapy, a peripheral autologous stem cell transplant, and pamidronate (90 mg) monthly. Two years ago, pain and drainage developed at the site of the implant. These symptoms continued despite 3 attempted surgical repairs, implant extraction, and multiple short courses of oral antibiotics. Persistent exposure of maxillary bone developed. Although his myeloma was in remission, treatment with pamidronate continued. Examination revealed a fistulous opening with exposed bone in the left anterior maxilla. The affected area was debrided, and bone was sent for pathological analysis and culture. Histological analysis of the maxillary bone revealed sulfur granules within the bone accompanied by an infiltrate of inflammatory cells (Figure 1). Cultures grew Actinomyces viscosus, establishing the diagnosis of actinomycosis. Subsequent treatment consisted of intrave-
nous penicillin G (18 MU/day) with intravenous metronidazole (1.5 g/day) for 6 weeks followed by oral amoxicillin (1.5 g/day) for 6 months. At the completion of intravenous antibiotics, the maxillary aperture had stopped draining. Four months after antibiotics were discontinued, he continued to have exposed bone; however, he remained asymptomatic.

**Discussion.** BRONJ has been increasingly described. Its pathogenesis is incompletely defined but appears to be related to multiple factors. Originally it was believed that bisphosphonates alone were responsible for this syndrome. Because the jaws were usually affected, it was postulated that these bones underwent repeated microtrauma, resulting in active bone remodeling and selective bisphosphonate accumulation [12]. The bisphosphonates were hypothesized to impede the repair process, resulting in avascular osteonecrosis [12–14]. However, other observations put this hypothesis into question and suggested that bisphosphonate use facilitates actinomycotic infection, resulting in osteonecrosis. First, osteonecrosis due solely to bisphosphonates has not been described in animals or humans with normal bone [15]. Second, the concomitant occurrence of *Actinomyces* infection with BRONJ has been seen in an increasing number of cases [5–10]. Histological studies have shown a near-universal presence of the actinomyces-like organisms from affected bone (32 of 32 patients [6], 8 of 8 patients [8], 2 of 3 patients [10], 10 of 11 patients [5], 28 of 30 patients [9], and 26 of 26 patients [7]). Furthermore, actinomyces can instigate bone resorption [16], and histologically, in the setting of BRONJ, sulfur granules have been regularly noted to occur at the location of osteonecrotic bone [7, 8]. In fact, it is likely that actinomycosis has been underrecognized in this clinical setting because of the challenges in isolating and identifying actinomyces microbiologically. Of note, one would predict that many different bones would be affected if bisphosphonates alone were capable of mediating osteonecrosis. In fact, except for 4 cases of the hip in patients who also received treatment with steroids (thereby raising the possibility of steroid-mediated avascular necrosis) [17] and a single case involving the external auditory meatus (an area readily accessible by actinomyces) [18], BRONJ is essentially a syndrome that affects the mandible and maxilla. Actinomyces colonizes the mucosa adjacent to these bones. Taking these data together, the following sequence of events is biologically plausible. First, bisphosphonate use impedes oral cavity host defenses and/or establishes a niche for actinomyces within the bone when it is subsequently introduced. Next, most (but not all) affected patients have overt mucosal disruption—a critical step in the pathogenesis of actinomycosis—due to antecedent dental procedures, trauma, oncological surgery, or underlying dental disease [4, 9, 15, 19]. Bisphosphonate inhibition of the life cycle of keratinocytes may further perpetuate mucosal breakdown and prevent repair [8]. Prior disruption of bone may facilitate

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**Figure 1.** Maxillary osteomyelitis due to *Actinomyces viscosus*. A sulfur granule is seen within the bone.
infection. Subsequent entry of actinomyces results in the development of actinomycosis. That living osteocytes have been noted in the bones of some patients lends credence to the idea that actinomyces infect living bone and do not secondarily infect already-necrotic bone [8, 19].

The timely recognition that BRONJ represents an actinomycotic infection in most if not all cases is critical. In the absence of appropriate treatment directed against actinomycosis, improvement is unlikely [11]. Controlled trials evaluating specific antimicrobials or studies designed to define the duration of therapy for actinomycosis have not been performed. As a result, treatment decisions are based on the collective clinical experience. However, 2 principles have evolved. Both high doses of antimicrobials and a prolonged course are needed to effect a definitive cure, presumably because of difficulties with antimicrobials penetrating thick-walled masses associated with many cases of actinomycosis and/or the sulfur granules themselves. It is customary to use 2–6 weeks of intravenous therapy, followed by oral therapy for 6–12 months for serious infections and bulky disease. The optimal regimen and duration of treatment for BRONJ is unknown, but BRONJ has proved challenging to cure. Although non–BRONJ-associated cases of oral-facial actinomycosis with less extensive disease have been successfully treated with shorter courses of therapy, these data do not seem applicable to BRONJ. Specific details on the duration of antimicrobial therapy (if administered) in the treatment of BRONJ are lacking in most reports. However, treatment for “at least 7 days” resulted in uniform relapse (n = 11) [5]. Another report described poor outcomes when “long-term or intermittent antibiotics” were used for a minimum of 6 months without surgical debridement (n = 12) [20]. In one retrospective study, however, 82 (90%) of 97 patients remained pain free while receiving a regimen of oral penicillin VK (500 mg 4 times a day) and 0.12% chlorhexidine oral rinse for at least 1 year [4]. Another small retrospective study demonstrated the best outcome when “long-term antimicrobial therapy (duration not defined)” was combined with stopping bisphosphonates and surgery (n = 7) [21]. Therefore, given the reported difficulties with effective treatment for BRONJ, it seems prudent to treat BRONJ with a customary, prolonged, combined intravenous-oral regimen for 9–12 months until more data are available. It is also reasonable to remove foreign bodies if possible and to debride necrotic tissue and bone sequestra. If the duration of therapy is extended beyond the resolution of measurable disease, then relapses—one of the hallmarks of actinomycosis—will be minimized. Computed tomography and magnetic resonance imaging studies may assist with this goal [1]. A timely actinomycosis-specific management approach holds promise to significantly improve outcomes in BRONJ, which to date have been less than excellent.

Patients receiving bisphosphonates should be monitored carefully for the development of actinomycosis. The majority of BRONJ cases develop with the use of intravenous bisphosphonates, but BRONJ also occurs with oral bisphosphonates. The risk of BRONJ in patients receiving high-potency bisphosphonates is estimated to be 1–10 cases per 100 patients [3]. The increasing use of bisphosphonates both for patients with various tumors that affect bone (eg, multiple myeloma and breast, lung, or prostate cancer) and for the prevention of osteoporosis makes it possible that actinomycosis may experience another renaissance to an even larger degree than was seen with the use of intrauterine devices that facilitated pelvic actinomycosis.

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References


