CASE REPORT

Bisphosphonate-Associated Osteonecrosis of Jaw and Osteomyelitis

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Abstarct

We describe three patients with bisphosphonate-associated osteonecrosis of the jaw and mandibular osteomyelitis due to oral microflora. All patients required surgical debridement with fixation and prolonged antibiotic therapy. We review the pathology and treatment of this relatively new clinical entity. A high degree of suspicion for infection is needed as well as a collaborative management approach.

Key Words

Osteonecrosis, Osteomyelitis, Bisphosponates, Jaw, Mandible

Introduction

Osteonecrosis of the jaw (ONJ), defined as chronically exposed bone within the oral cavity in the absence of malignancy or radionecrosis, was noted with phosphorous exposure as early as the 1830's (1). The reappearance of ONJ was seen in association with bisphosphonate use at the start of the new millennium (1, 2). Since then, there has been a dramatic increase in reported cases (3-5) and accumulating evidence that infection may complicate this clinical condition (4, 6, 7). We describe three patients with bisphosphonate-associated ONJ and mandibular osteomyelitis seen within a two-month period at our institution. Our report highlights the need for increased awareness of this condition and a collaborative approach to care.

Case Report

Patient 1: is a 74-year-old woman who received risedronate for osteoporosis after prolonged corticosteroid therapy for pemphigus vulgaris. Subperiosteal dental implants were placed while on bisphosphonate therapy; eight years later she developed osteonecrosis of her left mandible. After a trial of conservative treatment and removal of hardware, she suffered a pathological fracture requiring debridement and operative fixation. Histopathology revealed acute osteomyelitis of the anterior mandible. Bone and tissue cultures grew *Streptococcus anginosus-constellatus, Prevotella intermedia, P. melaninogenica, Fusobacterium* species, and *Peptostreptococcus magnus*. The patient reported multiple antibiotic allergies and intolerances and was treated with moxifloxacin 400 mg intravenous daily for one week, followed by oral therapy. During her fourth week of therapy she developed a mandibular fistula and exudative drainage (*Fig-1*). Operative tissue cultures grew only *P. intermedia*. The patient refused alternative antibiotics and was again treated with oral moxifloxacin. A course of adjuvant hyperbaric oxygen (HBO) was initiated pre-operatively and continued post-operatively. After a course of 20 HBO dives, she underwent surgical removal of her deep hardware, mandibular debridement with osteotomies, reconstruction with plating, and excision of extraoral and intraoral fistulas (*Fig-2*). Cultures grew multiple anaerobes: *P. intermedia, F. nucleatum* and *P. micros*. The patient was treated with oral clindamycin 300 mg every 8 hours and had no recurrence of infection following eight weeks of therapy. *Patient 2* is a 61-year-old woman with osteoporosis, diabetes mellitus, and multiple sclerosis who had been receiving alendronate for more than 10 years. She presented with left mandibular pain and a draining submandibular fistula. Clinical findings were consistent with ONJ and superimposed infection.

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The patient underwent open exploration with debridement of necrotic tissue and bone. Histopathology demonstrated necrotic bone with extensive acute inflammation. Operative bone and tissue cultures grew *Streptococcus mitus*, *S. intermedius*, and *Abiotrophia/Granulicatella* species. The patient was treated as an outpatient with oral cefuroxime 500 mg every 12 hours for six weeks with clinical resolution of her infection.

Patient 3 is an 88-year-old man with a history of prostate cancer with multiple bone metastases. He had been treated with pamidronate for over five years and was receiving corticosteroids and ketoconazole. The patient presented with a pathologic fracture of the left mandible that was debrided and surgically stabilized with internal rigid fixation (*Fig-3*). Histology revealed non-viable bone with acute inflammation and many filamentous bacterial colonies consistent with *Actinomyces*. Operative cultures were not obtained. The patient was treated with a 12-week course of oral amoxicillin 500 mg every 8 hours and had complete healing of the fracture. He had no evidence of recurrent infection three months after completion of therapy.

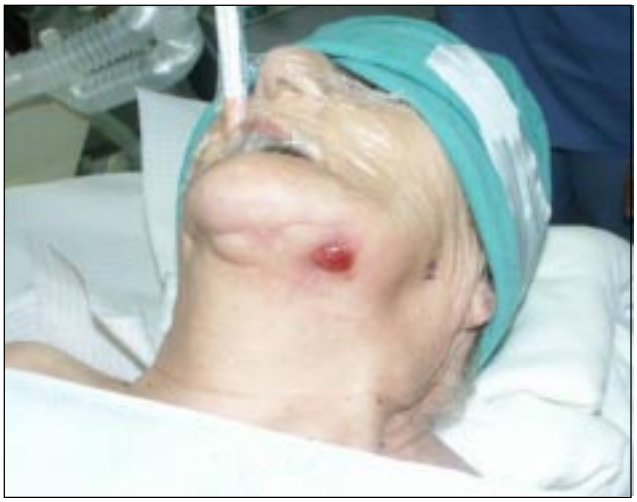

Fig 1. Draining Left Mandibular Fistula in a Patient with Underlying Osteonecrosis and Osteomyelitis

Discussion

Mandibular osteomyelitis is an uncommon clinical condition, but one that may be increasingly recognized in patients with bisphosphonate-associated ONJ. Risk factors for ONJ are related to the use of bisphosphonates as well as the patient's dental health. Intravenous bisphosphonates appear to carry a higher risk than oral formulations. There also appears to be increased risk with higher cumulative doses, longer duration of therapy,

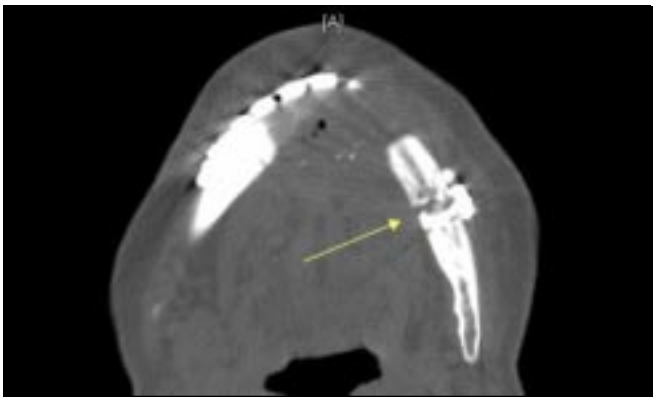

Fig 2. Noncontrast CT Scan of the Left Mandible Showing Osteolysis & Inflammation Adjacent to the Implant

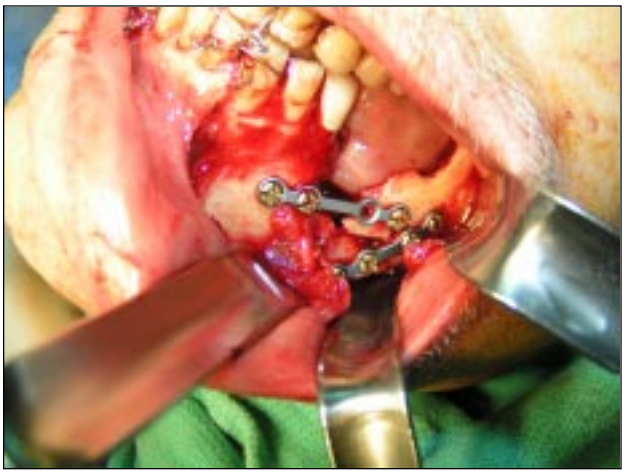

Fig 3. Intraoperative Debridement of the Left Mandible and Subsequent Rigid Fixation of the Resulting Pathologic Fracture of a Patient with Osteonecrosis & Actinomycosis

and immunosuppression, such as diabetes mellitus or use of corticosteroids [3, 6-8]. In a recent review, 75% of cases were attributable to local trauma, 30% of which also had extensive dental comorbidities including periodontitis, carries, dental abscesses, and prior root canal procedures (4).

ONJ is a largely clinical diagnosis and it may be difficult to recognize superimposed infection, particularly since bacterial colonization is commonly present (5). Computed tomography, technetium bone scanning, and indium-labeled white blood cell scans often cannot differentiate between ONJ and active infection (6). Infection in patients with underlying ONJ can be deep seated with the presence of sinus tracts and foul-smelling drainage (7), or may present indolently, as was the case with our third patient. *Actinomyces* is often implicated in

odontogenic infections, but caution must be exercised as the organism commonly colonizes dental plaque. All oral flora, including anaerobes, are potential pathogens and polymicrobial infection is common (9).

Effective treatment requires adequate surgical debridement and prolonged antimicrobial therapy. Empiric therapy should cover the spectrum of potential oral pathogens; including coverage for ß-lactamase-producing anaerobes and aerobic or microaerophilic streptococci. Ampicillin-sulbactam is an excellent choice for empiric intravenous therapy. Alternatively, penicillin G with oral metronidazole, clindamycin, second-generation cephalosporins, piperacillin-tazobactam or carbapenems may be used. Ideally, the selection of antimicrobials should be guided by cultures obtained from deep tissue and bone (10). Consideration should be given to both the cost and side effects of oral therapy as the duration is prolonged. We chose to use moxifloxacin in our first patient due to her multiple antibiotic allergies and intolerances. The drug has the required spectrum of activity and achieves excellent bone penetration. It has been used successfully for the treatment of multidrug-resistant viridans osteomyelitis of the mandible (11). Although, it is possible our patient failed therapy with moxifloxacin due to antimicrobial resistance, persistent infection was most likely due to the extensive nature of her sequestered bone infection. Hyperbaric oxygen has been used as adjunctive therapy for osteomyelitis and osteoradionecrosis of the mandible and may be beneficial in some patients (10, 12). However, the use of hyperbaric oxygen in ONJ is limited and is not currently recommended as standard therapy (5-7).

Bisphosphonate-associated ONJ is a condition that is best prevented, rather than treated. Patients should be screened for dental comorbidities and invasive dental procedures performed prior to initiation of bisphosphonate therapy (5, 13). When ONJ does occur, antiseptic rinses should be routinely used to prevent infection and appropriate antibiotics given during and continued after dental surgery for at least 10 days (5). When osteomyelitis does occur, surgical debridement and prolonged antimicrobial therapy are usually required for successful outcomes.

Conclusion

Bisphosphonate associated osteonecrosis of the jaw and mandibular osteomyelitis is relatively new clinical entity,a high degree of suspicion must be kept in mind for those patients on ling term bisphosphonates therapy so that it can prevented before it devlops.

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