Journal of Cancer Research and Practice

journal homepage: https://www.ovid.com/jnls/jcrp

Case Report

Unearthing the Synergy: How *Actinomyces* and Bisphosphonates Fuel BRONJ—A Case Report

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Abstract

Bisphosphonate induced osteonecrosis of the jaw (BRONJ) is a severe debilitating bone condition with an unclear etiopathogenesis. Here we present a case of actinomycotic osteomyelitis of the jaw in a patient of metastatic carcinoma breast treated with intravenous bisphosphonates. This case report tries to analyze the role of actinomyces in the etiopathogenesis of BRONJ and to reflect upon on various risk factors associated with BRONJ. The criteria used for diagnosis and management options are discussed briefly. As this condition significantly compromises overall health status of the patient leading to increase morbidity, timely diagnosis and treatment is vital to achieving cure and improving patient QOL (quality of life).

Keywords: Actinomycotic osteomyelitis, bisphosphonate, bisphosphonate-related osteonecrosis of the jaw, case report, mandible, osteonecrosis

Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is a well-recognized side effect of certain medications, including bisphosphonates, denosumab, and antiangiogenic agents.[1] This condition was previously referred to as bisphosphonate-related osteonecrosis of the jaw (BRONJ).[2]

In 2014, the American Association of Oral and Maxillofacial Surgeons defined MRONJ as meeting all of the following criteria: (1) current or previous bisphosphonate, denosumab, or antiangiogenic therapy; (2) the presence of exposed jawbone or bone that can be probed through at least one intraoral or extraoral fistula, persisting for more than 8 weeks; and (3) no history of radiation therapy to the jaw or evident metastatic disease affecting the jaw.[2]

Here, we report an intriguing case of actinomycotic osteomyelitis of the mandible in a breast cancer patient undergoing intravenous bisphosphonate therapy. By examining this unique case, we aim to gain a deeper understanding of the potential relationship between BRONJ and *Actinomyces* infection. By elucidating the underlying mechanisms, we hope to enhance the overall quality of care in similar clinical scenarios.

Submitted: 03-Oct-2025 **Revised:** 27-Dec-2025
Accepted: 05-Feb-2026 **Published:** 21-Sep-2026

Access this article online

Quick Response Code:

Website: https://www.ovid.com/jnls/jcrp

DOI: 10.4103/ejcrp.eJCRP-D-25-00054

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How to cite this article: Thakur V, Singh K, Preet K, Negi RR. Unearthing the synergy: How *Actinomyces* and bisphosphonates fuel BRONJ—A case report. J Cancer Res Pract 2026;13:118-21.

Case Report

A 50-year-old diabetic and hypertensive woman with ER/PR-positive, HER2-negative breast carcinoma (cT4N1M1) and skeletal metastases at the S1 and S2 vertebrae identified on whole-body fluorodeoxyglucose positron emission tomography (FDG-PET) reported to our outpatient department for management. As she was symptomatic for bone metastasis, she was started on palliative chemotherapy upfront with single-agent taxane and intravenous bisphosphonates (zoledronic acid 4 mg, administered every 3 weeks).

Due to a lack of response to taxane-based chemotherapy and treatment-related neuropathy, the treatment was changed to a combination of adriamycin and cyclophosphamide while continuing zoledronic acid injections. After completing four cycles of adriamycin and cyclophosphamide, she was asymptomatic, and a repeat FDG-PET scan indicated a partial response. Thus, she was switched to an oral endocrine therapy comprising palbociclib and letrozole, along with the administration of zoledronic acid every 4 weeks.

The patient received a cumulative dose of 92 mg of zoledronic acid through 23 infusions. She received eight cycles of zoledronic acid on a 3-weekly schedule with intravenous chemotherapy followed by 13 cycles of zoledronic acid on a 4-weekly schedule with oral palbociclib and letrozole. After 21 cycles of zoledronic acid and 13 cycles of palbociclib and letrozole, spontaneous rupture occurred and part of a tooth fell from her right jaw, for which she received a 7-day course of antibiotics and removal of the remaining tooth by a dentist. Zoledronic acid was subsequently withheld and resumed 6 months after the dental procedure. Oral chemotherapy with palbociclib and letrozole was resumed 1 month after the dental procedure when the dental wound had completely healed. Neutropenia did not occur during oral chemotherapy before or after the dental procedure.

Two months after resuming zoledronic acid, she developed dull, aching pain in the right lower jaw. The pain progressively increased, was poorly localized, and radiated to the preauricular and temporal regions. Upon examination, unhealed sockets with exposed necrotic bone were noted in the right lower jaw, accompanied by pus discharge. Orthopantomography of the patient showed lytic lesions and bony resorption on the right side of the body of the mandible [Figure 1].

Surgical debridement was performed and a bone biopsy was sent for the analysis. The histopathology report indicated the presence of trabeculae of cortical bone with empty lacunae. In addition, the report identified colonies of filamentous organisms surrounded by amorphous eosinophilic material in a radiating pattern, a finding associated with the Splendore-Hoeppli phenomenon. These colonies were seen eroding into the bone matrix and showed no atypical cells [Figure 2].

The final diagnosis was actinomycotic osteomyelitis based on the histopathology. She underwent a surgical intervention to remove the necrotic bone and received intravenous antibiotics

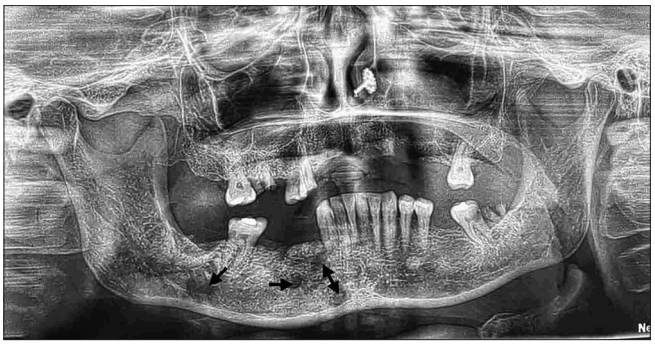

Figure 1: Orthopantomogram showing lytic lesions (black arrow heads) with buccal surface irregularity and bony resorption on the right side of the body of the mandible

in the form of amoxicillin and clavulanic acid for 2 weeks followed by same oral antibiotics for the next 3 months, to which she responded favorably. Her condition was assessed monthly, with a radiographic evaluation scheduled for 6 months later.

Discussion

This report discusses a rare case of actinomycotic osteomyelitis of the jaw in a breast cancer patient on intravenous bisphosphonates. *Actinomyces* are soil saprophytes and commensals found in the oral cavity, with *Actinomyces israelii* being the species most commonly associated with cervicofacial actinomycosis.[3] This infection is primarily endogenous and can result from trauma, such as dental procedures. It is often referred to as the "great masquerader of head and neck disease" due to its ability to mimic granulomatous diseases and tumors.[4] Successful isolation of *Actinomycetes spp.* from a culture is often not useful as most patients are under antibiotic treatment before a surgical intervention. Thus histopathology plays a key role in making an exact diagnosis.

Bisphosphonates are the analogs of pyrophosphates and exhibit a strong affinity for hydroxyapatite crystals. They play a significant role in the treatment of various bone conditions, including bone metastasis, osteoporosis, osteolytic bone disorders, and Paget's disease.[5,6] They are also frequently used in cancer patients and are known to reduce the local release of tumor growth factors, making the bone less favorable for metastasis.[7] Zoledronate and pamidronateinduced osteonecrosis of jaw was first reported as avascular necrosis of the jaw by Marx in 2003, who also reported that it was a growing epidemic.[8] The precise mechanism behind BRONJ is not entirely understood, but is thought to be multifactorial.[1]

Bisphosphonates have been hypothesized to interfere with bone immunity via the mevalonate pathway or by their direct effect on neovascularization, leading to increased susceptibility to osteomyelitis.[9] Several risk factors for the development of BRONJ have been identified, including poor oral hygiene, smoking, diabetes, age over 65 years, use of steroids, renal insufficiency, periodontal disease, and a history of previous osteonecrosis.[1]

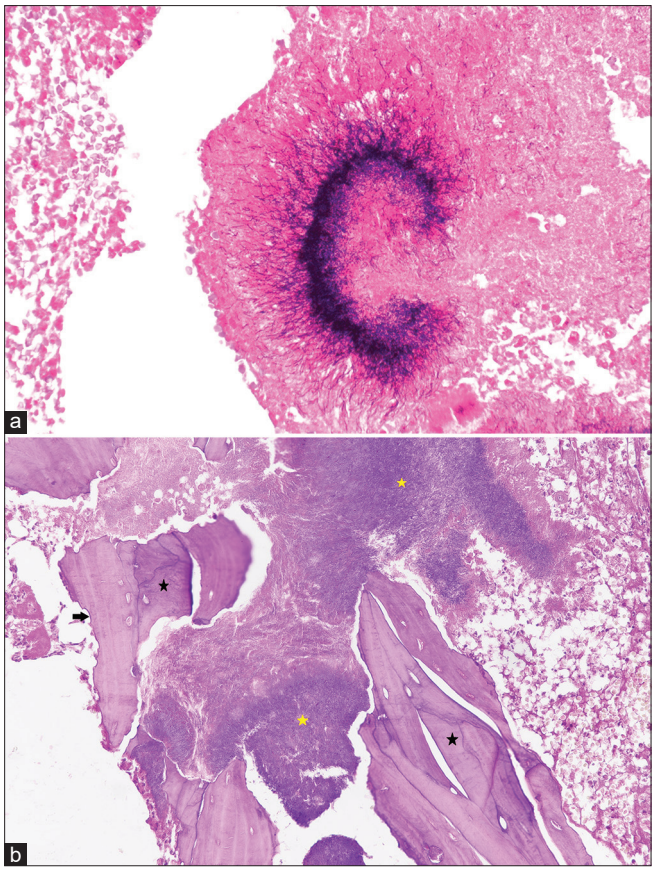

Figure 2: (a) ×60, Gram stain: Colony of Gram-positive filamentous bacteria (black C-shaped structure with radiating filaments) surrounded by inflammatory cells (pink background), (b) Histopathology examination: ×20, Hematoxylin and eosin: Large, basophilic bacterial aggregates (yellow asterisk) accompanied by inflammatory cells lying in between the bony trabeculae (black asterisk). The trabeculae were thinned out and eroded (black arrow)

BRONJ has been predominantly identified in the mandible, accounting for two-thirds of cases, compared to one-third in the maxilla.[10] The distinctive nature of the oral cavity and jawbone makes BRONJ specific to the jaw region. The remodeling period of the jawbone is shorter than that of other bones in the body. In addition, the jawbone is in close proximity to oral pathogens, where it is only protected by the periosteum, epithelium, and a thin layer of connective tissue, while other bones benefit from the deeper soft tissues and skin for protection.[11]

The revised Henle-Koch postulates state that the simultaneous presence of an organism and chronic disease appearing in a correct sequence and the specificity of the effect of the organism on the development of disease are required to establish a causal relationship between a micro-organism and a chronic disease.[12] It has been postulated that BRONJ may be a bisphosphonate-induced *Actinomyces* infection of the jaw, in line with modified Koch's postulates. Supporting factors for this hypothesis include a high prevalence of *Actinomyces* isolated from BRONJ lesions (73.2% in a retrospective series).[13] In addition, pathologically, BRONJ and *Actinomyces* osteomyelitis appear very similar, and cases of BRONJ associated with active *Actinomyces* show a favorable response to treatment against *Actinomyces* infection.[13] Previous Russian studies have suggested the role of bisphosphonates or phosphorus in the regulation of virulence of *Actinomyces* species by demonstrating a correlation between filamentous growth mode with increased secretion of exoproteins.[14,15]

Our patient had several significant risk factors for the development of BRONJ, including a high cumulative dose of bisphosphonates, diabetes mellitus, and a minor dental procedure prior to the onset of BRONJ. The presence of these risk factors and isolation of *Actinomyces* species from the debrided pathology specimen collectively led to the diagnosis of *Actinomyces*-related BRONJ.

Once developed, BRONJ is difficult to cure and lacks ideal treatment. Surgical interventions range from conservative (debridement, curettage, and sequestrectomy) to radical (marginal or segmental resection).[10] However, surgery is likely to produce more exposed bone. Previous observational studies on BRONJ have shown a good clinical response to *Actinomyces*-directed antibiotic regimens with symptomatic relief for the patient.[9] *Actinomyces spp.* are highly susceptible to penicillins and macrolide antibiotics (in patients allergic to penicillin), and a treatment duration ranging from 3 to 12 months has been reported to lead to successful outcomes and prevent relapse.[16] Our patient also showed a favorable subjective and clinical response to *Actinomyces*-directed therapy, with healing of the diseased site and no signs of infection at 12 months of follow-up.

This case report supports the hypothesis that BRONJ may be a form of *Actinomyces* osteomyelitis. Given the potential therapeutic implications, the role of *Actinomyces* in the etiopathogenesis of all cases of BRONJ should be excluded, and an optimal management strategy including surgery with long-term antibiotics for better therapeutic outcomes and prevention of relapse should be developed.

Declaration of patient consent

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and its amendments. The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Author contributions

All authors contributed to the article conception. Data collection and first draft of the manuscript was written by Dr. Vandna Thakur. All authors reviewed the manuscript and provided valuable insights and changes on initial draft of the manuscript. All authors read and approved the final manuscript.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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