

Histopathologic findings in bone from edentulous alveolar ridges: A Role in Osteonecrosis of the Jaws?

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ABSTRACT

Bisphosphonate-related osteonecrosis of the jaws (BONJ) is characterized by a breach in the oral mucosa with exposure of necrotic bone. Although bisphosphonates impact multiple biologic processes, including bone turnover and vascularity, factors contributing to the pathogenesis of BONJ remain poorly understood. In this retrospective analysis, the histopathologic findings from 154 alveolar bone specimens obtained during osteotomy preparation for dental implant placement were reviewed from 147 consecutively treated patients [male (79); female (68); Caucasian (141); African-American (6)]. The alveolar ridge sites had been edentulous for 1 year or longer. None of the patients in this study had a history of bisphosphonate therapy or clinical evidence of BONJ. Two pathologists, masked, using predetermined criteria, reviewed and substantiated the pathology reports provided by the licensed pathology service. In selected cases, special stains had been conducted to help establish the presence of bacteria. The histopathologic findings for the core specimens were as follows: 76 viable bone (49.4%); 54 nonviable bone (35.0%); and 24 osteomyelitis (15.6%). These histopathologic findings indicate that the edentulous jaw can contain regions of nonviable bone and microbial biofilm formation for 1 year or more after tooth extraction and mucosal healing. Regions of necrotic bone and subclinical infection may contribute to the development of untoward clinical events, such as BONJ and early implant failure.

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Introduction

Bisphosphonate-related osteonecrosis of the jaws (BONJ) is clinically characterized by a nonhealing breach in the oral mucosa with exposure necrotic bone [1–4]. The most important risk factors for developing BONJ appear to be potency of the drug and cumulative dose [5], implicating direct cellular toxicity in bone and soft tissue [1]. Although the pathogenesis of BONJ remains poorly understood, local micro-damage secondary to physiologic function, physical trauma, or infection appear to be significant contributing factors in the presence of drug-induced alterations in bone metabolism and vasculature [6,7]. Exposure of bone has been widely attributed to alterations in bone metabolism culminating in the necrosis; however, it is unclear whether a breach in the oral mucosa is necessary for the development of BONJ [8]. Bisphosphonates have been shown *in vitro* to inhibit the proliferation of mucosal cells, which might also contribute to the pathogenesis of BONJ [9].

Although the majority of patients developing BONJ report a history of tooth extraction or injury, these factors do not fully account for the occurrence of BONJ [10]. The development of BONJ at edentulous sites without an apparent history of injury, for example, suggests that factors

other than normal mechanical loading may contribute to pathogenesis. Indeed, the latter cases suggest the possibility that pre-existing conditions, such as subclinical infection or regions of necrotic bone may set the stage for the development of BONJ. Of particular interest, here, is the recognition that (1) dental extractions often occur in the presence of chronic periradicular infection and (2) dental extractions result in fracture of alveolar bone, with occasional retention of bone and root fragments. Anecdotal reports of poor alveolar bone “quality” discovered during dental implant surgery are common, suggesting that gingival and mucosal healing following tooth extraction may occur in the presence of subclinical infection and regions of nonviable bone in the subjacent alveolus. Such regions, therefore, could provide foci for the development of BONJ in the absence of other risk factors.

The purpose of this retrospective study was to examine the histopathologic features of alveolar bone specimens obtained from edentulous ridges during dental implant therapy.

Methods

In this retrospective analysis, approved by the Institutional Review Board at the University of Maryland Baltimore, pathology reports on alveolar bone specimens obtained during osteotomy preparation for dental implant placement were reviewed from a total of 154 consecutively treated patients [male (79); female (68); Caucasian (141); African-American (6)]. The 82 maxillary and 72 mandibular alveolar

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ridge sites, all post-tooth extraction, had been edentulous for a minimum of 1 year. Four patients had a history of wearing removable dentures. All specimens were submitted by a single practitioner, as part of normal practice, from all patients undergoing implant surgery over a 5-year period. All surgeries were performed at least 1 year after tooth extraction. A limited chart review was conducted to identify any patients with a history of bisphosphonate therapy or removable dentures. All specimens were accessioned by a licensed oral and maxillofacial pathology service at the University of Maryland, which provided access to the slides and reports. In selected cases, special stains had been conducted to help establish the presence of bacteria. Two pathologists, masked, using specific criteria, reviewed and substantiated the pathology reports provided by the pathology service. Diagnosis was based on the most prominent histopathologic feature, using the following criteria.

- (a) *Viable bone*: normal appearing bone that is remodeling with the presence of osteoclasts, osteoblasts, and osteocytes. Occasional empty osteocytic lacunae (≤ 10 –20% of lacunae per high power field) may be present in the absence of an inflammatory reaction.
- (b) *Non-viable bone*: presence of empty osteocytic lacunae and absence of osteoblasts. Osteoclasts and bacterial colonies may be present; however, the inflammatory reaction is minimal, if present.
- (c) *Fibrosis*: presence of dense fibrous connective tissue without inflammation within the tissue.
- (d) *Osteomyelitis*: prominent inflammatory cell infiltration in fibrous marrow, with osteoblastic and osteoclastic activity creating irregular bony trabeculae. Necrotic bone (sequestrum) and bacterial colonies are often present. Acute or chronic designation used to identify specimens with inflammatory cell infiltrate characterized by either polymorphonuclear leukocytes or plasma cells and lymphocytes, respectively.

Results

The diagnostic pathology reports for the 154 alveolar specimens were as follows: 76 viable bone (49.4%); 54 nonviable bone (35.0%); and 24 osteomyelitis (15.6%). Of the 82 maxillary cases, 26 were diagnosed nonviable bone (31.7%) and 11 were diagnosed osteomyelitis (13.4%). Of the 72 mandibular cases, 28 were diagnosed nonviable bone (38.9%) and 13 were diagnosed osteomyelitis (18.1%). With the exception of 2 cases, the reviewers were in agreement and substantiated each diagnosis in the pathology reports. The 2 exceptions involved specimens originally diagnosed as nonviable bone, where one pathologist diagnosed the cases as osteomyelitis. After review, the tissue specimens were found not to meet the criteria for osteomyelitis, confirming the original diagnosis.

Viable bone, when present, was typically a dense mature compact bone with sparse marrow and viable osteocytes occupying numerous lacunas, often with multiple remodeling reversal lines, consistent with normal healing of an extraction site (Fig. 1A). The composition of bone marrow, when present, was predominately fatty in nature (Fig. 1B).

Multiple specimens (35%) were also found to contain regions of mixed viable and nonviable bone (Fig. 2A) or purely nonviable bone (Fig. 2B). In other specimens, acute or chronic osteomyelitis was present (Fig. 3A and B). Fig. 3 illustrates acute suppurative osteomyelitis with mature nonviable bone showing empty lacunae, reduced osteoblastic activity, increased osteoclastic activity, and the presence of polymorphonuclear neutrophils filling the marrow spaces. Bacterial colonies were often observed in association with osteomyelitis (Fig. 4).

Discussion

The histopathologic findings in this case series provide compelling evidence that the edentulous jaw can contain regions of bacterial

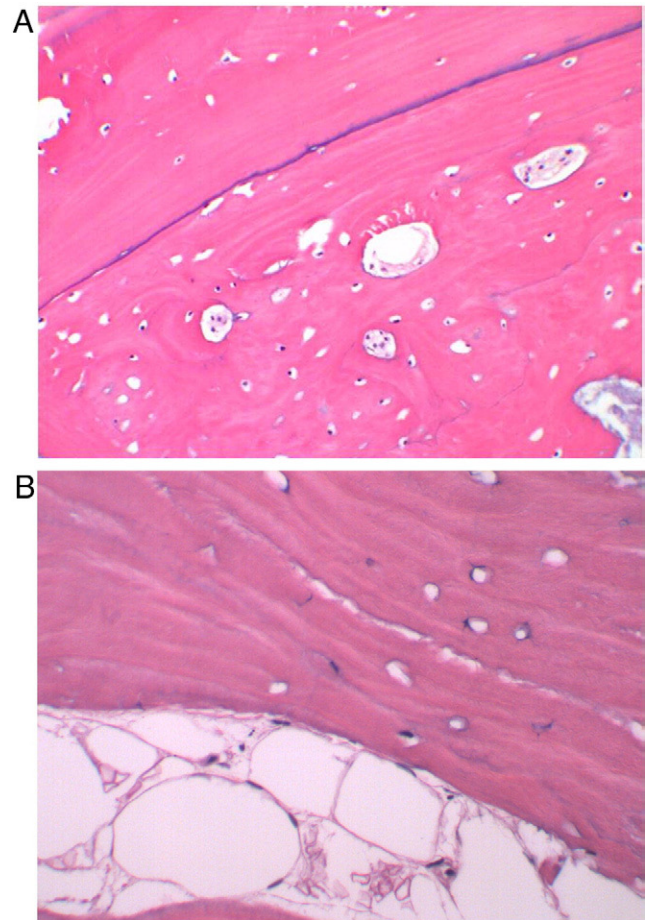


Fig. 1. (A) Dense mature compact bone, showing remodeling reversal lines, with sparse marrow and osteocytes occupying lacunae in viable bone, $\times 40$. (B) Bone specimen illustrates the composition of bone marrow, which was predominately fatty in nature, $\times 40$.

biofilm formation and nonviable alveolar bone for 1 year or more following tooth extraction and mucosal healing. Although BONJ may result from direct toxicity to cells of bone and soft tissue from high potency bisphosphonates [1], the presence of subclinical bacterial infection and regions of nonviable bone prior to drug therapy may represent important risk factors for the development of BONJ. Regions of nonviable alveolar bone may mimic injury secondary to physical trauma, which is considered a key feature in the pathophysiology of BONJ [11–14]. Recent evidence suggests that bisphosphonates may also alter or promote biofilm formation [15], which could alter the balance of a subclinical bacterial infection. Regions of nonviable bone, therefore, could provide foci for the development of BONJ in the absence of other risk factors, consistent with the hypothesis that bone necrosis precedes a clinically evident breach in the oral mucosa [8,16].

The present findings might also provide insight into anecdotal reports of poor alveolar bone “quality” discovered at edentulous sites during implant surgery. Aseptic necrosis of bone has been reported as manifestation of selected systemic conditions as well as following surgery, trauma, and immunosuppressive therapy [17–19]. The development of aseptic necrosis has been documented in the maxilla and mandible, most notably following osteotomies [19,20]. Moreover, in a large nested case-control study, Etminan and coworkers [21] observed an association between oral bisphosphonate use and nonspecific aseptic osteonecrosis in a cohort of elderly cardiovascular patients. Barragan-Adjemian and coworkers [22] identified necrotic bodies or “involucrums,” often expanding into large areas of the jaws, within the BONJ lesions of cancer patients using cone beam computerized tomography. The foregoing studies suggest a role for aseptic

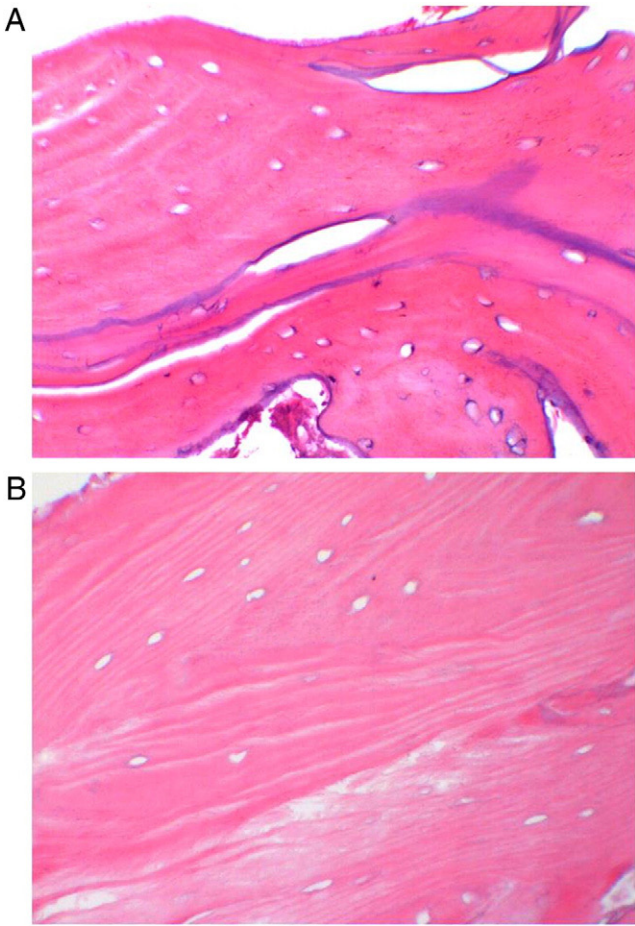


Fig. 2. (A) Specimen shows transition from an area of viable mature compact bone with sparse marrow and viable osteocytes occupying numerous lacunae (bottom) to an area of nonviable bone where the lacunae lack osteocytes (top). Note the region of viable bone shows prominent reversal lines indicating bony deposition, $\times 40$. (B) Nonviable bone shows all lacunae devoid of osteocytes with, $\times 40$.

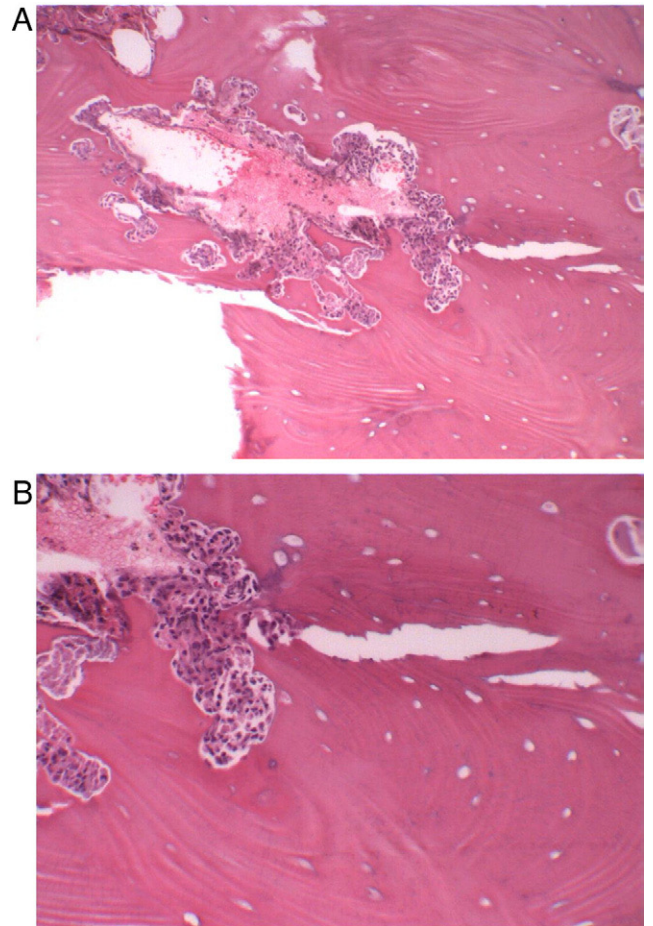


Fig. 3. (A) Nonviable mature bone shows lack of osteocytes in lacunae, absence of fatty marrow, and dense inflammatory cell infiltrate in acute (suppurative) osteomyelitis, $\times 10$. (B) Higher magnification shows empty lacunae and marrow spaces occupied primarily by polymorphonuclear neutrophils. Bone trabeculae show irregular contours due to osteoclast resorption, $\times 40$.

necrosis secondary to injury or drug therapy in the pathophysiology of BONJ.

The bacterial colonies observed in these specimens were generally well organized and confined largely within marrow spaces. Contamination during osteotomy preparation, in contrast, would have been associated with isolated cells or disrupted colonies on the surface of the specimens. Biofilms develop preferentially on inert surfaces and occur commonly on medical devices and fragments of dead tissue, such as sequestra of necrotic bone [23,24], and slow-growing small-colony variants often remain undetected and respond poorly to standard antibiotic treatment [25]. Nelson and Thomas [26] analyzed tissue fluid and bone samples from 56 osteotomies with a minimum 3-month healing at fixture placement in 32 private practice patients and found that 21% of sites were culture positive. These investigators concluded that bacteria can persist as a contaminant in apparently healed alveolar bone following extraction of teeth with apical or radicular pathology, consistent with the findings of this study. Residual pathology following extraction secondary to prior endodontic infection has been implicated in retrograde peri-implantitis [27–29] and may also contribute to early implant failure, which has been associated with impaired healing, mechanical injury, and infection [30].

In summary, the histopathologic findings in this study document that the edentulous jaw can contain regions of microbial biofilm formation and nonviable bone for 1 year or more after tooth extraction and mucosal healing. Such regions of subclinical infection and necrotic bone may represent significant risk factors for the development of BONJ, early dental implant failure, and other bony conditions.

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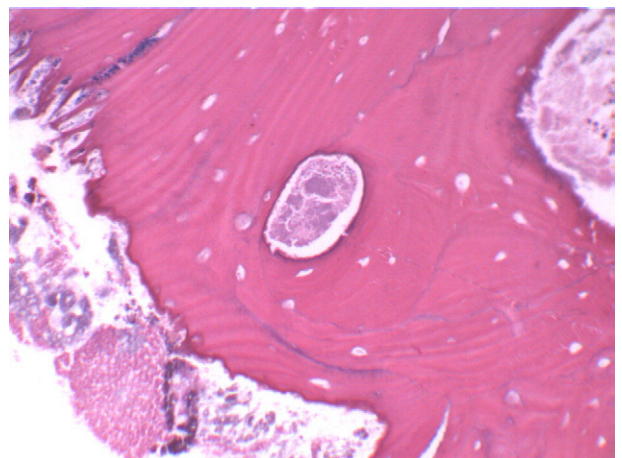


Fig. 4. (a) Abundant bacterial colonies and chronic inflammatory infiltrate are shown proximal to nonviable mature bone, $\times 20$.

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