

Radiographic Findings in Bisphosphonate-Treated Patients With Stage 0 Disease in the Absence of Bone Exposure

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Purpose: Radiographic features in patients with bisphosphonate-related osteonecrosis of the jaw (BRONJ) are well described, but less is known in bisphosphonate-exposed individuals with stage 0 disease (clinical symptoms without exposed necrotic bone) considered at risk for BRONJ. We sought to characterize radiographic findings in a subgroup of patients with concerning clinical symptoms and bisphosphonate exposure to identify imaging features that may presage development of BRONJ.

Materials and Methods: A dental symptom survey was returned by 8,572 Kaiser Permanente Health Plan members receiving chronic oral bisphosphonate therapy, and 1,005 patients reporting pertinent dental symptoms or complications after dental procedures were examined. Those without BRONJ but with concerning symptoms were referred for clinical evaluation, including imaging. Among the subset who received maxillofacial imaging, we identified those with stage 0 disease and abnormal radiographic features.

Results: There were a total of 30 patients without exposed bone but with concerning symptoms who received maxillofacial imaging (panoramic radiography or computed tomography) in the context of clinical care. Among these 30 patients, 10 had stage 0 disease with similar radiographic features of regional or diffuse osteosclerosis in clinically symptomatic areas, most with extension beyond the involved site. Other findings in these 10 patients included density confluence of cortical and cancellous bone, prominence of the inferior alveolar nerve canal, markedly thickened and sclerotic lamina dura, uniform periradicular radiolucencies, cortical disruption, lack of bone fill after extraction, and a persisting alveolar socket. None had exposed bone develop during 1-year follow-up. The remaining 20 patients had normal or localized radiographic findings consistent with odontogenic pathology.

Conclusion: In 10 of 30 symptomatic patients referred for clinical evaluation and imaging, a consistent finding was conspicuous osteosclerosis in clinically symptomatic areas characteristic of stage 0 disease. These data support the need to better understand radiographic features associated with bisphosphonate exposure and to determine whether osteosclerosis is a specific finding indicative of the risk for progression to BRONJ.

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The nitrogen-containing oral bisphosphonates (alendronate, risedronate, and ibandronate) are potent inhibitors of osteoclast function and have been shown to be highly effective in reducing the risk of osteoporotic fractures.¹ As such, oral bisphosphonate drugs are considered one of the main pharmacologic options in the treatment of postmenopausal osteoporosis. Recently, however, bisphosphonate-related osteonecrosis of the jaw (BRONJ), a condition characterized by persistent (>8 weeks) exposed bone in the maxillofacial region, has been reported in patients with bisphosphonate exposure.^{2,5} Among patients receiving chronic high-dose intravenous bisphosphonate drugs, the prevalence of BRONJ is in the range of 1% to 5%.⁶⁻⁸ In contrast, the prevalence of BRONJ is extremely low, in the range of 0.01% to 0.1%, among population cohorts with exclusive oral bisphosphonate exposure.⁹⁻¹¹

The diagnostic criteria for BRONJ developed by the American Association of Oral and Maxillofacial Surgeons include a history of bisphosphonate use, absence of radiotherapy to the head/neck, and presence of exposed bone in the maxilla or mandible persisting for more than 8 weeks.^{12,13} The guidelines were revised in 2009 to include patients with stage 0 disease, characterized as those with no evidence of necrotic bone but with: 1) nonspecific symptoms such as pain or odontalgia not explained by odontogenic causes or dull aching bone pain; 2) clinical findings including loosening of teeth not explained by chronic periodontal disease and/or periapical/periodontal fistula not associated with pulpal necrosis due to caries; or 3) radiographic findings including alveolar bone loss not attributable to chronic periodontal disease, trabecular bone alterations including dense woven bone, and persistent unremodeled bone in extraction sites, thickening of the lamina dura, and inferior alveolar canal narrowing.¹³ Given the extremely low prevalence of BRONJ in patients treated with oral bisphosphonates, the clinical and radiographic features that precede stages 1 to 3 BRONJ remain largely unknown. Hence we sought to describe concerning radiographic patterns in a subset of symptomatic stage 0 patients identified in a large surveillance study of health plan members receiving chronic oral bisphosphonate therapy. Supported by recent case series describing similar findings in bisphosphonate-exposed patients,¹³⁻¹⁶ this study contributes to an ongoing effort to characterize radiographic patterns that may presage development of BRONJ in at-risk populations.

Materials and Methods

The Predicting Risk of Osteonecrosis with Bisphosphonate Exposure (PROBE) Study was conducted by

Kaiser Permanente Northern California in 2007 to ascertain the prevalence of BRONJ among adult members with a history of chronic oral bisphosphonate therapy, excluding those with known exposure to intravenous bisphosphonates.¹⁰ Among 8,572 mailed survey respondents, 2,159 individuals reporting osteonecrosis, exposed bone, gingival sores, moderate periodontal disease, persistent dental symptoms, or complications after invasive dental procedures were contacted.¹⁰ Of these, 1,005 patients underwent screening oral examinations to determine the presence or absence of BRONJ-related findings or conditions suspicious for possible progression to BRONJ. The study was approved by Institutional Review Boards at the Kaiser Foundation Research Institute and the Food and Drug Administration.

Patients found to have BRONJ features, overt osteomyelitis, osteoradionecrosis, or implant complications are reported separately.^{10,17} Among the remaining examined cohort, those with findings for development of BRONJ, including persisting bone pain without an apparent odontogenic cause, delayed healing after extraction, infection or periodontal fistula not associated with caries, and unexplained tooth mobility, were referred for further clinical evaluation (including relevant imaging) in maxillofacial surgery clinics. The radiologic records of these individuals were reviewed to determine whether there were features concerning for BRONJ, excluding abnormalities related to underlying dental disease.

Patient characteristics, dental history, and cumulative oral bisphosphonate treatment duration were obtained from health plan databases, patient interviews, and health records as previously described.¹⁰ Follow-up was continued 1 year from initial study examination to confirm that these cases did not develop into classified stages 1 to 3 BRONJ. Imaging studies reviewed included panoramic radiographs, computed tomography (CT), and/or cone beam computed tomography (CBCT). Maxillofacial CT scans were evaluated by health plan radiologists, and a secondary review of all images (panoramic radiographs and CT and CBCT scans) was conducted jointly by an oral and maxillofacial surgeon (F.O.) and a maxillofacial radiologist (D.C.H.). Radiographic abnormalities were documented, particularly evidence of osteosclerosis, cortical disruption, periosteal proliferation, abnormalities of the lamina dura and inferior alveolar nerve (IAN) canal, and persisting alveolar sockets with unremodeled bone. Osteosclerosis was characterized qualitatively as flocculent or densely sclerotic, and differentiation between the cortical and submedullary endosteal bone was also evaluated. Evidence of odontogenic pathosis (periapical inflammatory lesions) was also noted.

For comparison, we also reviewed 14 consecutive noncontrast CT scans of women aged 50 years or older, without bisphosphonate exposure, undergoing maxillofacial surgery for odontogenic cyst or tumor ($n = 5$), temporomandibular joint disorder ($n = 5$), oral antral fistula ($n = 2$), facial fractures ($n = 1$), and maxillary sinus disease ($n = 1$); only uninvolved quadrants were reviewed.

Results

Among the 1,005 patients undergoing clinical examination (excluding BRONJ, osteomyelitis, or implant complications),¹⁰ there were a total of 30 individuals with findings concerning for development of BRONJ (persisting bone pain, delayed healing after extraction, infection or periodontal fistula not related to caries, or unexplained tooth mobility), who underwent radiographic imaging during clinical follow-up. Within this subset, 10 patients had radiographic evidence of regional or diffuse osteosclerosis in clinically symptomatic areas, as well as uniform periradicular radiolucencies, a prominent IAN canal (ipsilateral), or a persisting alveolar socket. Clinical complaints among these 10 patients included delayed healing (>8 weeks) after extractions or persisting pain (Table 1). The remaining 20 patients showed no evidence of regional sclerotic changes or any of the previously mentioned findings.

PATIENT CHARACTERISTICS

All 10 patients with stage 0 disease and radiographic abnormalities that included osteosclerosis were women, with a mean age of 68.5 ± 6.4 years at study examination (Table 1). All had received alendronate (prescribed in 95% of the entire study cohort) for osteoporotic fracture prevention; none had Paget's disease. The median total duration of bisphosphonate therapy was 3.0 years (interquartile range, 2.4-4.7). Relevant comorbidities included polymyalgia rheumatica treated with chronic or intermittent glucocorticoid therapy (cases 4 and 10), diabetes mellitus (case 6), and current smoking (case 3). Over the 1-year follow-up, all patients either discontinued bisphosphonate therapy or had a temporary drug holiday.

CLINICAL FEATURES AND DENTAL ANTECEDENTS

As described in Table 1, all 10 patients had involvement of either the posterior mandible ($n = 9$) or the posterior maxilla ($n = 1$). Nine patients reported localized pain and/or delayed healing (>8 weeks to mucosal healing) after one or more dental procedures including dental extractions, endodontic therapy of one or more teeth, or restorative procedures. One patient had chronic focal periodontitis with gingival

inflammation and associated tooth mobility that became apparent during follow-up care. Seven patients had dental extractions 3 to 31 months before presentation; among these, 5 had persistent pain in the area at the time of examination (despite the extractions occurring >6 months prior), 4 reported delayed healing, and 3 required one or more procedures to remove bony spicules or sequestra. Six of the 7 post-extraction patients had intact mucosa, whereas 1 had a non-draining pinpoint fistula in the extraction area at the time of examination (case 10). Two patients had root canal therapy on teeth in the symptomatic region; of these, 1 had subsequent extraction of an adjacent tooth, whereas the other had thrice-repeated root canal treatment for unresolved localized pain. In 1 patient constant pain developed surrounding a tooth that was previously restored without complication. No patients had drainage, purulence, bony spicules, or exposed bone at the time of examination. Table 1 summarizes the clinical history and radiographic findings in each case, including information pertaining to the time interval from the initial study visit to the date of imaging. Imaging studies were obtained 3 to 35 months after extraction or dental treatments.

RADIOGRAPHIC FINDINGS

Imaging studies included one or more of the following: panoramic radiographs ($n = 1$), CBCT scans ($n = 2$), and conventional CT scans ($n = 9$). Bony sclerosis in symptomatic areas was seen in all cases and ranged from focal alveolar sclerosis to extensive involvement of almost half the mandible or maxilla (Table 2). Density in the sclerotic areas ranged from flocculent to densely sclerotic with irregular compact and disorganized trabeculation. In cases with diffuse sclerosis ($n = 5$), thickened buccal and lingual cortices with reduced contrast definition between the endosteal cortex and subjacent medullary bone (density confluence) was evident (Figs 1-5). The sclerosis encroached on the margins of the IAN resulting in a prominent IAN canal ($n = 7$) (Figs 1-4). In cases with more focal findings ($n = 3$), dense osteosclerosis of the alveolar margins and lamina dura, as described by Arce et al,¹⁸ was seen in symptomatic dentate and extraction site areas (Figs 6, 7). Lack of bone fill ($n = 2$) and a persisting alveolar socket ($n = 1$) after extraction were also found; these findings were notable because the extractions occurred 13 to 26 months before imaging (Figs 5B, 7). Four patients showed uniform periradicular radiolucencies without focal periapical pathology (Figs 2, 4). Three patients showed cortical disruption in the affected areas (Figs 1, 4). Periosteal proliferation was not seen in any patients.

Table 1. CLINICAL AND RADIOGRAPHIC FEATURES OF PATIENTS WITH CONCERNING SYMPTOMS

Case	BP (yr)*	Location	Symptoms	Dental History/Predisposing Factors	Imaging†	Radiographic Findings
1	4.6	Left posterior mandible	Persistent pain	RCT of left mandibular first molar, 37 mo before examination; EXT of left mandibular second molar, 31 mo before examination	CT scan 31 mo postoperatively	Osteopenia of right mandible, diffuse flocculent sclerosis of left posterior mandible, periradicular lucency of left mandibular first molar, prominent IAN, buccal cortical disruption
2	3.3	Right posterior mandible	Persistent pain	Chronic periodontitis of right mandibular second molar with mobility, focal gingival inflammation	CT scan	Diffuse sclerosis of right hemi-mandible to mental foramen, prominent IAN, periradicular lucency of right mandibular second molar
3	2.7	Right posterior maxilla	Persistent pain, bony spicules	EXT of right maxillary first molar and first premolar, 26 mo before examination; sequestrectomy of right maxillary first molar extraction site, 14 mo before examination	CT scan 26 mo postoperatively	Diffuse sclerosis of right posterior maxilla, dense lamina dura, lack of bone fill with large cortical defect of right maxillary first molar
4	5.6	Right posterior mandible	Persistent pain	Restoration of right mandibular second molar, 32 mo before examination; chronic glucocorticoid therapy	CT scan 32 mo postoperatively	Diffuse sclerosis of right posterior mandible, periradicular lucency of right mandibular second molar, lingual cortical perforation, prominent IAN
5	2.4	Right posterior mandible	Delayed healing	EXT of right mandibular second molar with immediate bone graft 2.5 mo before examination	CT scan 3 mo postoperatively	Sclerosis of right posterior mandible, prominent IAN
6	1.5	Right posterior mandible	Persistent pain	EXT of right mandibular third molar, 19 mo before examination	CT scan 19 mo postoperatively	Sclerosis of right posterior mandible
7	2.5	Left posterior mandible	Delayed healing, pain, bony spicules	EXT of left mandibular second molar, 18 mo before examination; sequestrectomy of left mandibular second molar extraction site, 13 mo before examination	CBCT 25 mo postoperatively	Sclerosis of left posterior mandible, lingual cortical perforation of left mandibular first molar, prominent IAN
8	4.7	Right posterior mandible	Persistent pain	RCT of right mandibular second molar × 3, approximately 18 mo before examination	CBCT 35 mo postoperatively	Sclerosis right posterior mandible, prominent IAN
9	2.1	Right posterior mandible	Delayed healing, pain	EXT of right mandibular third molar, 18 mo before examination	CT scan 19 mo postoperatively	Diffuse sclerosis of right posterior mandible, periradicular lucency of right mandibular second molar, prominent IAN
10	4.1	Right posterior mandible	Delayed healing, bony spicules	EXT of right mandibular first molar, 7 mo before examination; alveolar osteitis 6 mo before examination; chronic glucocorticoid therapy	Panoramic radiograph 13 mo postoperatively	Focal sclerosis of right mandibular second molar to second premolar area, dense lamina dura with lack of bone fill and persisting alveolar socket in right mandibular first molar extraction site

Abbreviations: BP, bisphosphonate; EXT, extraction; RCT, root canal therapy.

*Nitrogen-containing oral bisphosphonate treatment duration up until the time of study examination.

†Timing of imaging study in relation to tooth extraction or root canal therapy if relevant.

Hutchinson et al. *Radiographic Patterns in Stage 0 BRONJ*. *J Oral Maxillofac Surg* 2010.

Table 2. SUMMARY OF RADIOGRAPHIC FINDINGS (n = 10)

Radiographic Findings	No. of Patients
Sclerosis	10
Focal	5
Diffuse	5
Prominent IAN canal	7
Uniform periradicular radiolucency	4
Cortical disruption	3
Increased lamina dura thickness and density	2
Lack of bone fill in extraction sites	2
Persisting alveolar sockets	1

Hutchinson et al. Radiographic Patterns in Stage 0 BRONJ. *J Oral Maxillofac Surg* 2010.

Among the 20 patients without regional sclerotic changes, there were no bony inflammatory or reactive changes that could not be readily attributed to identified dental pathology. There was also no radiographic enhancement of the IAN canal or evidence of persisting alveolar sockets.

Among the non-bisphosphonate-exposed individuals undergoing routine maxillofacial surgery, CT images in 3 patients showed inflammatory bone loss and thickened lamina dura, but these changes were localized only to the areas immediately adjacent to the root apices of the involved mandibular teeth, suggesting a dental origin. Sclerosis, if evident, was subtle and confined to a narrow band around the area of disease, consistent with typical reactive bone formation; none showed the broad zone of regional or diffuse bony sclerosis observed in the bisphosphonate-exposed pa-

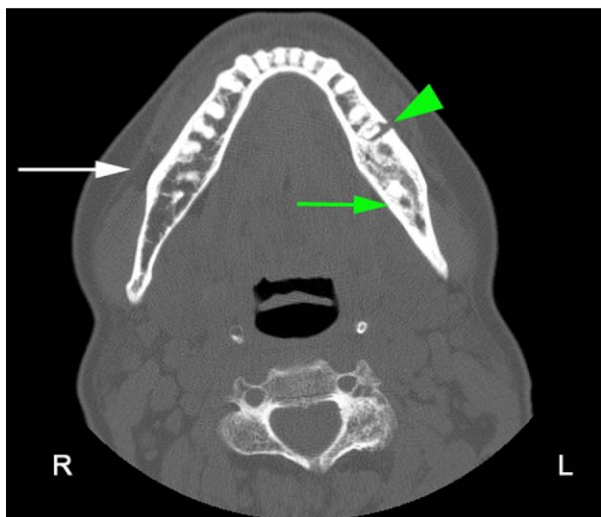


FIGURE 1. Case 1. Osteopenic right mandible (white arrow), diffuse flocculent sclerosis, and prominent IAN (green arrow), with buccal cortical disruption (triangle).

Hutchinson et al. Radiographic Patterns in Stage 0 BRONJ. *J Oral Maxillofac Surg* 2010.

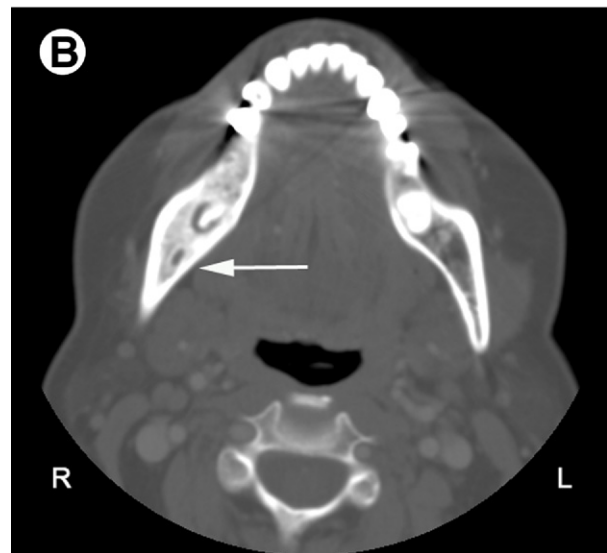
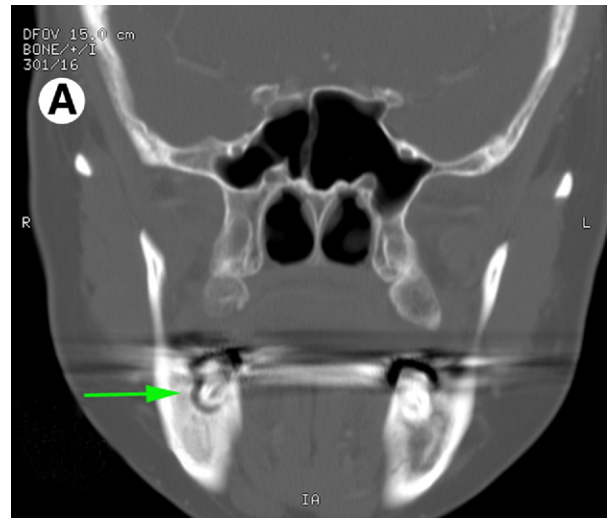


FIGURE 2. Case 2. A, Diffuse osteosclerosis of right mandible and periradicular lucency (arrow). B, Axial view with prominent IAN (arrow).

Hutchinson et al. Radiographic Patterns in Stage 0 BRONJ. *J Oral Maxillofac Surg* 2010.

tients. All had normal cortical and medullary definition, and there was no prominence of the lamina dura or IAN canal.

Discussion

A wide spectrum of radiographic features have recently been reported in BRONJ, with the emergence of typical patterns now readily identifiable in affected patients.¹⁸⁻²⁴ These include osteosclerosis, thickened and disorganized medullary trabeculation, cortical disruption, increased thickness of the lamina dura and IAN canal margins, periosteal bone formation, and sequestration.¹⁸⁻²⁴ In our cohort of stage 0 patients with radiographic abnormalities, a consistent finding

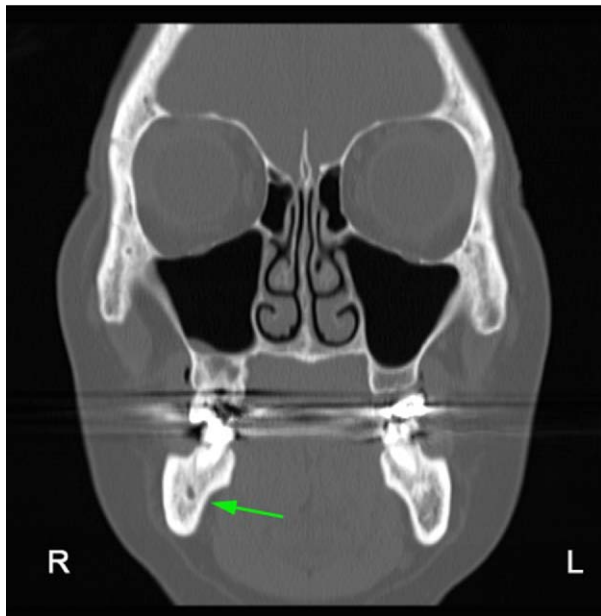


FIGURE 3. Case 9. Diffuse sclerosis and prominent IAN with narrowing of canal margins (arrow).

Hutchinson et al. Radiographic Patterns in Stage 0 BRONJ. J Oral Maxillofac Surg 2010.

was the presence of osteosclerosis in clinically symptomatic areas, ranging from distinct focal density of the surrounding alveolar bone to more widespread involvement. In most patients the posterior mandible was involved, and prominence of the IAN canal, increased trabecular density, and lack of differentiation between cortical and medullary bone were common findings. Uniform periradicular radiolucencies were noted in almost half the mandibular cases, and one third had evidence of buccal or lingual cortical disruption. Two patients had thickened lamina dura with lack of bone fill in areas of prior (>1 year) extraction.

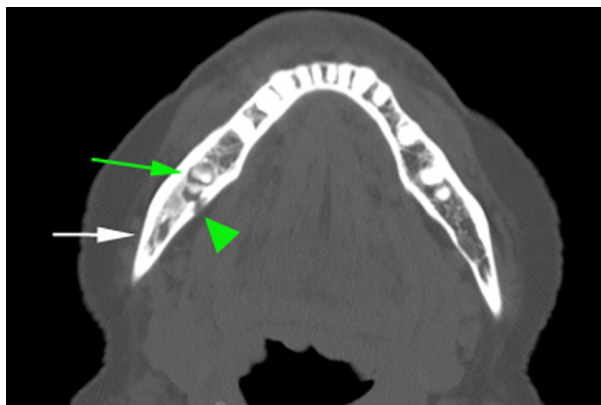


FIGURE 4. Case 4. Diffuse sclerosis, prominent IAN (white arrow), periradicular lucency (green arrow), and lingual cortical disruption (triangle).

Hutchinson et al. Radiographic Patterns in Stage 0 BRONJ. J Oral Maxillofac Surg 2010.

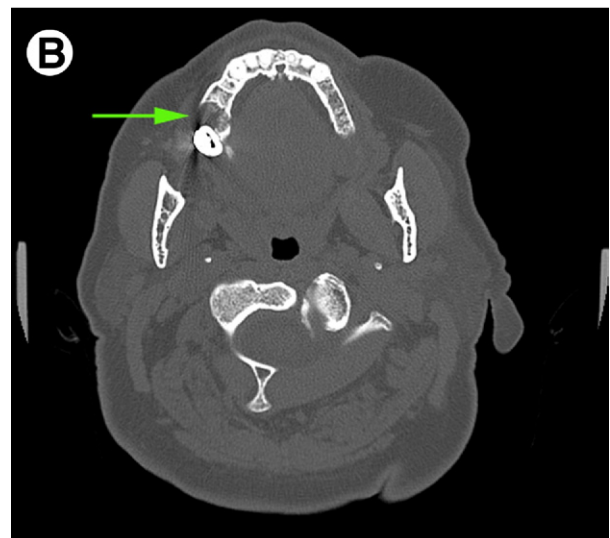
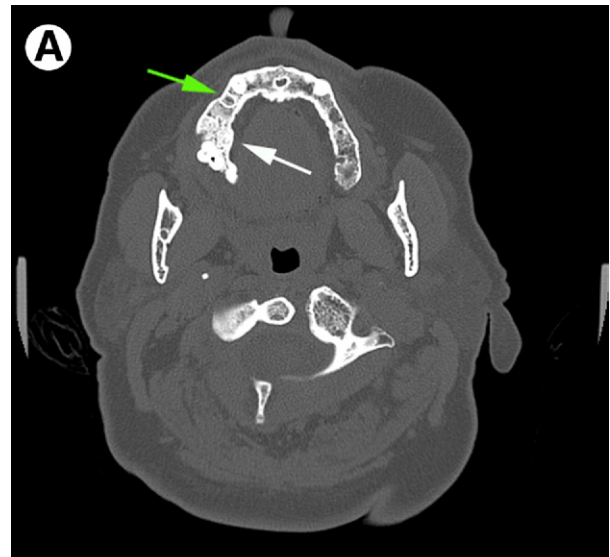


FIGURE 5. Case 3. A, Diffuse osteosclerosis of right hemi-maxilla (white arrow) with thickened lamina dura (green arrow). B, Lack of bone fill in extraction site (26 months before this scan) (arrow).

Hutchinson et al. Radiographic Patterns in Stage 0 BRONJ. J Oral Maxillofac Surg 2010.

These imaging findings are similar to those seen in stages 1 to 3 BRONJ with exposed bone and have also been reported in stage 0 disease.^{14,18-25} In the series by Bisdas et al,²¹ all 32 patients with histologic evidence of osteonecrosis had sclerotic lesions on unenhanced CT, including 4 with early symptoms of tooth loosening or delayed extraction site healing, where the only notable CT finding was osteosclerosis in the suspected necrotic site. Groetz and Al-Nawas²⁵ reviewed radiographic features in a series of BRONJ cases and postulated that persisting alveolar sockets might be an early radiographic sign of preclinical BRONJ. Although our data do not directly address whether bisphosphonate exposure contributed to

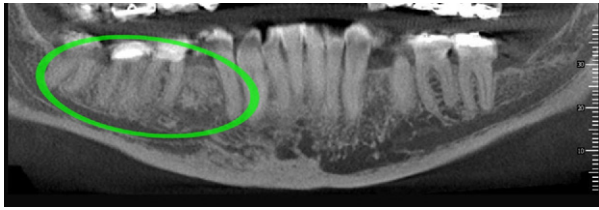


FIGURE 6. Case 8. CBCT scan showing focal osteosclerosis (circle) of alveolar margins and periodontal region similar to cases described by Arce et al.¹⁸

Hutchinson et al. *Radiographic Patterns in Stage 0 BRONJ*. *J Oral Maxillofac Surg* 2010.

these radiographic findings, a broader recognition of early radiographic patterns in symptomatic individuals may ultimately help identify patients potentially at risk for BRONJ.

Oral bisphosphonates reduce osteoclast bone resorption through cellular actions causing increased osteoclast apoptosis and diminished osteoclast function. These pharmacologic effects have led many investigators to consider disorders of impaired osteoclast function as potential models in understanding the pathogenesis of BRONJ.^{26,27} Osteopetrosis is a bone disorder resulting from defects in osteoclast function that presents with radiographic features similar to BRONJ.²⁷ Impaired osteoclast action and abnormal bone remodeling in patients with osteopetrosis result in increased bone mass/density with dense trabecular and cortical bone, findings that may vary by skeletal site because of known osteoclast heterogeneity.²⁸ Thickening of the cortical structures of the jaws, including the lamina dura and walls of the mandibular canal, with loss of corticommedullary interfaces, has been reported²⁹; the compromised osteopetrotic bone may be brittle, has reduced vascularity, and is susceptible to infection/osteomyelitis.³⁰⁻³² Of additional interest are transgenic rodent models showing that normalizing osteoclast function in long bones does not necessarily result in normalization of osteoclast function in the jaws, suggesting that susceptibility to osteoclast suppression may be site specific.²⁸ Indeed, the high rate of alveolar bone remodeling, coupled with chronic exposure to local dental inflammatory stimuli and local microbial factors, might provide one explanation as to why the jaws are the site for BRONJ.^{2,33}

Among the 7 patients with dental extraction as a prior antecedent, it is of interest that 4 reported delayed healing. Recent data from Hikita et al³⁴ show that bisphosphonate administration before tooth extraction increases bone formation in rats but delays initial healing of the extraction socket. In histomorphometric analyses of non-necrotic sites adjacent to BRONJ, Favia et al³⁵ found abnormal bone remodeling with increased deposition of newly woven bone that

had smaller Haversian canals, increased trabecular thickness, reduced marrow spaces, and scarce osteoclastic activity. They concluded that increased appositional osteogenesis coupled with reduced bone remodeling may be a distinct pathologic process in bisphosphonate-exposed patients.³⁵ It has also been postulated that bisphosphonate exposure may predispose to microcracks or inhibit their repair, another theory proposed in the pathogenesis of BRONJ.³⁶

In our reported patients a salient radiographic feature was the absence of a periosteal response (no periosteal thickening or “onion skinning” and no evidence of periosteal or parosteal bone formation), similar to what is seen in chronic low-grade or sclerosing osteomyelitis. Other authors have noted these radiographic similarities in patients with BRONJ.^{18,37} If stage 0 BRONJ patients represent an earlier phase along the spectrum of bony disease progression, this might explain the apparent lack of a periosteal response, as would ordinarily be seen in patients with overt osteomyelitis.

Our study has several limitations. First, we did not evaluate all symptomatic patients in our cohort,¹⁰ and thus these data cannot be used to infer the frequency of stage 0 disease. Second, because we only enrolled patients who received bisphosphonate therapy, we do not have a broader control population of symptomatic individuals without bisphosphonate exposure and are thus unable to address causality. However, we did not see any atypical patterns of



FIGURE 7. Case 10. Persisting alveolar socket with lack of bone fill 13 months after extraction.

Hutchinson et al. *Radiographic Patterns in Stage 0 BRONJ*. *J Oral Maxillofac Surg* 2010.

osteosclerosis in patients without bisphosphonate exposure who underwent maxillofacial CT imaging, where bony sclerosis, if evident, was confined to a narrow band and consistent with local reactive bone formation. Nevertheless, we cannot exclude the possibility that the radiographic findings in our cohort are related to underlying dental conditions or reflect anatomic variations, particularly because the pre-bisphosphonate oral health status was not known. That only patients with particular symptoms of concern received additional clinical evaluation may also have introduced bias in our study. Finally, these manifestations may simply be due to physiologic changes in bone architecture induced by bisphosphonates. The consistent finding of regional bony sclerosis in symptomatic areas, similar to cases of chronic osteomyelitis and stages 1 to 3 BRONJ, is supported by other reports characterizing stage 0 BRONJ and points to the need for further investigation.

Previous studies have attempted to elucidate radiographic changes that occur in BRONJ patients with a history of intravenous bisphosphonate use.¹⁹⁻²³ Not only is determination of radiographic changes of interest to the clinician, but establishing the predictive value of these findings for BRONJ development is also important because they may bear directly on oral health decisions in these individuals. Osteoporosis remains a major health problem both globally and nationally.³⁸ Given the known efficacy of oral bisphosphonate drugs in reducing osteoporotic fracture risk in numerous clinical trials,¹ widespread use of these therapies is expected to increase. Within the treated population, the frequency of adverse jaw complications is exceedingly small.¹⁰ However, a clearer understanding of the significance of early radiographic manifestations may assist identification of patients at increased risk for BRONJ. Although none of the 10 patients developed exposed bone (BRONJ stages 1-3) during follow-up observation (albeit most discontinued bisphosphonate therapy), these data contribute to the growing body of knowledge regarding maxillofacial findings in symptomatic patients with prolonged bisphosphonate exposure.

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