CASE REPORT

Alendronate-Associated Osteonecrosis of the Hard Palate After Harvesting of a Connective Tissue Graft: A Case Report

John K. Brooks,* Justin W. Kleinman,†‡ Rania H. Younis,* and Mark A. Reynolds†

Introduction: Much attention has been given to the development of osteonecrosis of the jaws, concomitant with a history of bisphosphonate usage, particularly regarding inciting dental procedures. This report describes a case of bisphosphonate-related osteonecrosis of the hard palate after the harvesting of a subepithelial connective tissue (CT) graft for treatment of gingival recession (GR) in the mandible.

Case Presentation: A 60-year-old female sought periodontal therapy for GR. Her medical history revealed the use of alendronate for osteopenia, hypothyroidism, sulfa allergy, and >18 regimens of steroid formulations (oral, inhaled, and topical) for various upper respiratory and dermatologic disorders. The hard palate was selected as the donor site for the subepithelial CT graft. At a 4-month postoperative evaluation, osteonecrosis was evident in the palatal site. Successful clinical outcome was achieved after conservative debridement, antibiotics, and use of chlorhexidine gluconate.

Conclusions: It is advised that a patient’s medical history include current and past intake of bisphosphonates and comorbidities that could predispose to the development of osteonecrosis of the jaws. Attempts should be instituted to achieve primary wound closure of the donor site in patients who have taken bisphosphonates. Postoperative follow-up of the donor site of CT grafts should continue for at least 6 months for surveillance of bisphosphonate-related osteonecrosis.

Key Words: Alendronate; bone and bones; diphosphonates; osteonecrosis; tissue transplantation.

Background

Oral and intravenous bisphosphonates are used for the treatment of a variety of diseases of bone.1 The primary mechanisms of action of bisphosphonates are to alter osteoclastic signaling enzymes and suppress bone turnover rates, thereby promoting osteoblastogenesis and maturation and resulting in improved bone strength and mineral density.2 Use of these agents has led to the development of bisphosphonate-related osteonecrosis of the jaw (BRONJ), which is seen in 0.8% of patients with oral administration and up to 12% of patients when given parenterally.3

An array of surgical procedures have been implicated with the onset of BRONJ. Marx et al.4 conducted a retrospective analysis of 119 cases of BRONJ and identified the most frequent precipitating factors as tooth extraction (37.8%) and, to a lesser extent, dental implant surgery (3.4%) and apicoectomy (0.8%). With regard to the periodontium, 28.6% of the patients studied were diagnosed with concurrent periodontal disease, and 4.2% received unspecified periodontal surgery (the percentage of affected patients who had undergone unspecified periodontal surgery was presented as five of 119 [11.2%] and corrected to 4.2%; of note, 25.2% of this cohort developed BRONJ spontaneously without other definable oral etiologies.
The edentulous jaw can contain regions of non-viable bone and microbial biofilm formation for 1 year or more after tooth extraction and mucosal healing, which may provide a basis of osteonecrosis in some cases.\(^5\) Repetitive oral trauma to tori, such as that caused by ill-fitting dentures, has also been found to promote BRONJ.\(^6\)

Case reports of BRONJ attributable to periodontal surgery are rare.\(^7\) To the best of the authors’ knowledge, the development of BRONJ in a donor graft site has not been documented previously. This report describes a case of BRONJ of the hard palate after the harvesting of a subepithelial connective tissue (CT) graft for treatment of gingival recession (GR) in the mandible.

### Clinical Presentation

A 60-year-old female was referred on July 7, 2010 to a private practice (JWK) limited to periodontics in Owings Mills, Maryland for evaluation of root exposure. Her medical history was significant for osteopenia, as determined by a bone mineral density \(^T\) score of \(-1.8\) (normal \(^T\) score \(\geq -1.0\), osteopenia from \(-1.0\) to \(-2.5\), and osteoporosis \(-2.5\) or below) in the cervical neck after a dual-energy \(^x\)-ray absorptiometry scan. The patient had been prescribed 70 mg alendronate weekly for >9 years; intake was discontinued 7 months before the initial oral assessment. Other pertinent health issues were hypothyroidism and \(>18\) regimens of steroid formulations (oral, inhaled, and topical) for various upper respiratory and dermatologic disorders. The patient also reported an allergy to sulfa. Current medications consisted of levothyroxine and daily supplements of vitamins, calcium, and vitamin D. The patient denied any other bone diseases, blood dyscrasias, diabetes, and use of tobacco, cocaine, or oral contraceptives; alcohol consumption was limited. The periodontal examination was remarkable for GR, ranging from 1 to 6 mm, with several sites manifesting inadequate attached keratinized gingiva. Probing depths and tooth mobilities were within normal limits. The dentition was in good condition with the exception of multiple areas of cervical abfractions of varying depths. Subepithelial CT grafts were treatment planned to augment root surface coverage for multiple teeth.

### Case Management

Oral consent was obtained, including the review of the potential risk of osteonecrosis because of a history of bisphosphonate usage. The initial treatment sites involved teeth \#27 through \#30, with 3 to 5 mm of facial recession and minimal attached keratinized gingiva (Fig. 1). Tooth \#27 also exhibited facial cervical abfraction. Local anesthesia was achieved with infiltration into the buccal and lingual regions. Tooth \#27 was then prepared with root etching and applications of adhesive agents,\(^\text{\textdagger}\) restored with a dual-cure ionomer/composite,\(^\text{\textdaggerdouble}\) and smoothed with finishing burs and stones. Teeth \#27 through \#30 were wetted with citric acid formulated with 2 g/mL water\(^\star\) for 1 minute and then copiously irrigated with sterile water. Preparation of the recipient bed was initiated with double horizontal incisions, with a no. 15 scalpel blade connecting adjacent cemento-enamel junctions and at the apical extent of the recession. A partial-thickness flap was elevated while maintaining CT coverage over the subjacent bone and root surfaces.

A \(20 \times 15\) mm subepithelial CT graft was obtained from the hard palate (as described by Hürzeler and Weng\(^8\)). A greater palatine nerve block with local anesthesia was administered posterior to the confines of the intended donor tissue. From the palatal aspects of teeth \#3 through \#6, a single horizontal incision was performed with a no. 15 scalpel blade at a 90-degree angulation to the bone and \(\approx 4\) mm from the gingival margins. The scalpel blade was then advanced throughout the incision line, paralleling the underlying palatal bone. While the overlying gingiva was retained, a partial-thickness CT flap down to periosteum was detached with a periosteal elevator and excised to bone along the mesial, distal, and medial sides. After the palatal graft was removed, positive pressure was

---

\(^{\text{\textdagger}}\) Prime & Bond NT, DENTSPLY Caulk, Milford, DE.

\(^{\text{\textdaggerdouble}}\) Geristore, DenMat, Lompoc, CA.

\(^{\star}\) Kaye’s Epic Pharmacy, Baltimore, MD.
immediately applied. A moistened unfilled gauze, saturated with sterile water, was then draped over the palate while the recipient graft site was prepared.

The donor graft was trimmed of adipose tissue and thinned and was then secured to the recipient bed with 5-0 resorbable gut sutures. The mucosal flap was coronally positioned to cover the donor tissue and secured with 5-0 synthetic absorbable sling sutures. Cyanoacrylate tissue adhesive was applied in droplets at the interproximal papillae with a disposable pipette to optimize wound stability. A surgical dressing was placed along the lingual aspects of teeth #27 through #30 to reduce patient awareness of the suture material and avoid possible factitial injury. The palatal margins were closely approximated with 4-0 resorbable gut sling and interrupted sutures. The estimated time to suture the palatal incision was 15 minutes. The hard palate was protected with a custom-fitted plastic stent, and the patient was advised to wear it for 1 week postoperatively.

The patient was given discharge prescriptions (600 mg ibuprofen, every 6 hours daily, for 7 days; 500 mg penicillin V potassium, four times daily, for 7 days; and 5 mg hydrocodone/500 mg acetaminophen, every 4 to 6 hours [16 pills] as needed for pain). Additionally, the patient was instructed to rinse twice daily with 0.12% chlorhexidine gluconate. At 2 weeks, normal healing was evident and residual sutures were removed. The patient was subsequently referred back to her general dentist for comprehensive care.

**Clinical Outcomes**

Four months later, the patient returned to her general dentist for periodic recall and prophylaxis. The patient was referred back to the attending periodontist (JWK) for assessment of a conspicuous palatal ulceration in the previous donor site. The periodontist denoted the presence of necrotic bone, measuring 9 × 5 mm (Fig. 2). The patient was symptom free and unaware of any oral changes. Local anesthesia was given via a greater palatine block as described previously. Using a back-action chisel, superficial non-vital bone was

---

*# Henry Schein Dental, Melville, NY.
** Vicryl, Ethicon, Johnson & Johnson, Somerville, NJ.
†† PeriAcryl, GluStitch, Delta, BC, Canada.
‡‡ Coe-Pak, GC America, Alsip, IL.
§§ Henry Schein Dental.
‖‖ DENTSPLY Raintree Essix, Sarasota, FL.*
easily mobilized (Fig. 3), exposing highly vascular cancellous bone (Fig. 4). Histopathologic examination of the surgical specimens was consistent with BRONJ (Fig. 5).

For the ensuing week, the patient was prescribed 250 mg amoxicillin, four times daily, advised to rinse twice daily with 0.12% chlorhexidine gluconate, and to avoid masticatory contact with this site. The patient was then seen postoperatively for 6 consecutive weeks and experienced an uneventful course. At each of these follow-up appointments, the palatal site was swabbed with 0.12% chlorhexidine gluconate. By 4.5 months, palatal reepithelialization was complete and without inflammation or exposed bone. At 35 months, no recurrence of osteonecrosis was seen; interestingly, focal hyperpigmentation, consistent with post-inflammatory melanosis or possibly amalgam tattoo, was noted in the palatal site (Fig. 6). The patient will continue to be observed for any pigmentary changes.

Discussion

Numerous grafting techniques have been implemented for the management of GR, restoration of implant coverage, and enhancement of edentulous defects. The mucosa of the hard palate is the most common site for harvesting tissue grafts, offering favorable, long-term stability. Complications in the donor site typically include pain, swelling, and prolonged bleeding.9 Predictive risk factors for adverse sequelae in the donor site have been associated with the duration of the surgical procedure, ischemia, infection, diabetes, and smoking.9-11 To the best of the authors’ knowledge, the development of BRONJ has not been reported previously in the palatal donor site subsequent to harvesting of a CT graft.

Harris et al.12 reviewed surgical records of 500 consecutive CT grafts obtained from the hard palate and were unable to discover any cases of BRONJ. The postoperative period of their study had not been disclosed and perhaps could have failed to identify any cases of BRONJ because of a reduced follow-up interval. Del Pizzo et al.13 evaluated palatal donor-site healing in 36 patients and found no instances of osteonecrosis at 8 weeks. In the current case report, at 4 months postoperatively to the harvesting of a palatal graft, the presented patient likely developed BRONJ as a result of taking alendronate for > 9 years. Successful clinical outcome was accomplished after conservative surgical debridement, antibiotics, and use of an antimicrobial oral rinse. Overall, the emergence of BRONJ in the hard palate is infrequent and usually consequent to repeated trauma to the palatal torus.14

The pathogenesis of BRONJ is attributed to the disruption of physiologic bone remodeling, leading to inhibition of resorptive and angiogenic osteoclastic activity and apoptosis, and culminating in bone death.3 BRONJ shares
microscopic findings with chronic osteomyelitis and typically displays islands of non-vital bone, fibrous exudates, and an inflammatory cell infiltration consisting of neutrophils, histiocytes, eosinophils, and plasma cells. Moreover, an assortment of oral pathogenic biofilms has been recovered surrounding foci of necrotic bone, the most common species of which is *Actinomyces*, although it is unclear whether this isolate simply represents a commensal relationship or a true secondary infection. Recently, an animal model investigation suggested that the incidence of BRONJ could be diminished by maintaining primary mucoperiosteal closure after surgical procedures, thereby reducing oral contaminants. Nevertheless, the patient in the current case report developed BRONJ after the harvesting of a CT graft, despite the minimal length of time needed to achieve satisfactory palatal closure with sutures.

A diversity of comorbidities has been reported with non-bisphosphonate-related osteonecrosis, namely malignant and benign diseases affecting bone, coagulation disorders, sickle cell disease, lupus erythematosus, pharmacologic agents (cancer chemotherapeutics, glucocorticoids, oral contraceptives), radiotherapy, ischemia, anorexia nervosa, substance abuse (alcohol, tobacco, and cocaine), and crush injuries. Various iatrogenic dental procedures can lead to osteonecrosis, including excessive application of an acid etchant for adhesive bonding, traumatic extractions, ischemia from excessive local anesthesia, sodium hypochlorite irrigation, and hyperthermic heat formation when performing trephination for implant placement. Repetitive trauma to the oral mucosa in regions of reduced vascularity (i.e., lingual aspect of the posterior body of the mandible) has also resulted in localized osteonecrosis.

In addition to the long-term bisphosphonate usage, the patient in this case report had other identifiable risks that may have contributed to the development of osteonecrosis. The patient’s chronic history of hypothyroidism could be considered an etiologic cofactor, because this disorder has been associated with the induction of aseptic necrosis of the knee, hip, and wrist. Furthermore, Thumbigere-Math et al. reported an increased incidence of BRONJ in patients with hypothyroidism receiving intravenous bisphosphonates. One could certainly speculate whether hypothyroidism could potentiate osteonecrosis of the jaws in patients taking oral bisphosphonates, such as alendronate, as seen with the presented patient.

Another possible comorbidity was the >18 regimens of steroid formulations (oral, inhaled, and topical) taken for various upper respiratory and dermatologic disorders. Glucocorticoids are known immunosuppressive agents capable of promoting osteonecrosis of the extremities and in some cases with the jaws. It seems less likely that any one of the patient’s total dosages of steroids (≤300 mg/month) could have played any intrinsic role in the palatal osteonecrosis, particularly because each was well below 1,000 to 1,800 mg/month, generally regarded as the threshold needed to induce osteonecrosis. Powell et al. cautioned that the cumulative dosing of steroids could also increase the risk of osteonecrosis, proposing a “multi-hit theory in a predisposed host.” In conclusion, it is extremely important for attending clinicians to be aware of all of the patient’s comorbidities, in the context of osteonecrosis of the jaws, when treatment planning surgical procedures involving bone.
Summary

<table>
<thead>
<tr>
<th>Why is this case new information?</th>
<th>To the best of the authors’ knowledge, this is the first case of bisphosphonate-related osteonecrosis of the hard palate after harvesting of a CT graft.</th>
</tr>
</thead>
<tbody>
<tr>
<td>What are the keys to successful management of this case?</td>
<td>- The patient should be provided with an informed consent concerning the possible complication of BRONJ when performing osseous surgery.</td>
</tr>
<tr>
<td></td>
<td>- Clinicians need to elucidate past and present intake of bisphosphonates and ascertain other possible comorbidities associated with osteonecrosis.</td>
</tr>
<tr>
<td></td>
<td>- Conservative surgical debridement, antibiotics, and antimicrobial rinses should be used.</td>
</tr>
<tr>
<td></td>
<td>- Efforts should be attempted to achieve primary closure of the donor site.</td>
</tr>
<tr>
<td>What are the primary limitations to success in this case?</td>
<td>- Clinicians need to be aware of the risk of BRONJ when treatment planning periodontal surgery, particularly with osseous procedures.</td>
</tr>
<tr>
<td></td>
<td>- Patients who undergo CT grafting harvested from the hard palate, and elicit a history of bisphosphonate intake, should be monitored postoperatively for at least 6 months to ensure complete healing and to check for signs of osteonecrosis.</td>
</tr>
</tbody>
</table>

Acknowledgments

The authors thank Dr. Sushma Sidh, private practice, Westminster, Maryland, for providing pertinent bone density records. The authors report no conflicts of interest related to this case report.

CORRESPONDENCE:
Dr. John K. Brooks, Department of Oncology and Diagnostic Sciences, Baltimore College of Dental Surgery, Dental School, University of Maryland, Baltimore, 650 W. Baltimore St., Baltimore, MD 21201-1586. E-mail: jbrooks@umaryland.edu.
References


indicates key references.