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91 Osteoporosis Patients Affected with Bisphosphonate Related Osteonecrosis of the Jaw: A Case Series

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Abstract

PURPOSE—Bisphosphonate-related osteonecrosis of the jaw (BRONJ) presents with necrotic bone in the mouth in the setting of bisphosphonate (BP) exposure. It has been studied in cancer patients taking high-dose BP, but BRONJ has also been noted in patients taking lower dose BP for osteoporosis. The purpose of this study is to characterize the phenotypes and outcomes in a large series of patients with osteoporosis and BRONJ in the setting of BP exposure.

METHODS—The investigators conducted a retrospective case series. The sample was composed of subjects with BRONJ and osteoporosis. Subjects with a history of BP treatment for myeloma or metastatic cancer to the bones were excluded. Descriptive statistics were computed for the study variables.

RESULTS—Ninety one cases of BRONJ met the inclusion criteria. Subjects had a median age of 71 years and were predominately female (94.5%). The median time of BP exposure was 60 months and ranged from 2 to 120 months. Most subjects were treated with alendronate (82.4%). The mandible was involved more frequently (58.2%) than the maxilla (37.3%). Subjects commonly (65.9%) but not universally reported pain. For subjects with treatment outcome data (n = 40), most reported improvement (80.0%).

CONCLUSION—Although BRONJ is an uncommon condition, the absolute number of cases is fairly large due to the very large number of patients taking BPs for osteoporosis. The findings of this study confirm that BRONJ primarily affects the mandible, a substantial minority present without pain and that patients typically improve with treatment.

Keywords

Osteoporosis; bisphosphonate; osteonecrosis of the jaw; risk factors

INTRODUCTION

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a condition in which maxillary or mandibular bone becomes necrotic in the setting of bisphosphonate (BP) exposure.[1–3] Bisphosphonates (including etidronate, alendronate, pamidronate, risedronate, zoledronic acid, and ibandronate) belong to a class of drugs that increase bone density by inhibiting osteoclast activity thereby altering the balance of bone resorption and deposition in favor of deposition.[4] BPs are used to treat osteoporosis, primary bone malignancies, as well as

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metastatic bone lesions from cancer. In 2007, Ruggiero and colleagues proposed a case definition for BRONJ that includes the following three elements: history of BP exposure, exposed bone visible in the mouth for at least 8 weeks, and no history of head or neck radiation and this is the definition adopted by the American Association of Oral and Maxillofacial Surgery (AAOMS).[5, 6] While reports of BRONJ have been circulating in the literature for approximately a decade, it was not recognized with a formal ICD-9-CM diagnosis code until 2007 (ICD 733.45 and an E code, 933.6 and 933.7, osteonecrosis of the jaw in the setting of BP exposure).

The precise molecular mechanisms underlying BRONJ remain unclear, and epidemiologic studies may help characterize this condition. BRONJ has been associated with the use of both intravenous and oral BPs. High dose intravenous BPs, used to treat metastatic cancer and malignancies with skeletal manifestations, have been linked to BRONJ with an incidence rate of 3%–15%.[7] BRONJ has also been observed in patients taking lower dosages of BPs for osteoporosis, but there have been few large case series with the largest published to date comprising 30 patients.[8]; Manfredi, 2011 #3465; O’Ryan, 2012 #3466} The incidence rate of BRONJ among osteoporosis users has been estimated at between 0.03% to 4.3%.[9, 10]

The widespread use of BPs for osteoporosis and ongoing media attention on their potential side effects demands further study of this relationship. It is important to continue to identify and implement preventative measures, identify risk factors, and improve treatments. Clinicians need to be able to advise patients on the relative safety of BP use. Given that incidence rates have been difficult to estimate precisely because of small numbers and varying case definitions, it is useful to examine osteoporosis-related BRONJ as a case series. To date, there have been a number of case series in cancer patients that have outlined the patient characteristics and risk factors for BRONJ.[11–14] However, the majority of BP users are not cancer patients, but instead receive the medication at much lower doses for osteoporosis. Much less is known about the epidemiology and treatment outcomes of BRONJ in osteoporosis patients.

We describe here a very large case series of osteoporosis-related BRONJ from two academic hospital-based practices in Boston, MA and one oral and maxillofacial pathology laboratory.

METHODS

Study population

Non-oncology cases of BRONJ were collected from two hospital-based specialty practices (oral medicine and oral and maxillofacial surgery) in Boston, MA and from one oral and maxillofacial pathology laboratory in MA between 2003 and 2012. Cases from the clinical practices were considered for study inclusion if they met the case definition of BRONJ as determined by the treating clinician, using American Association of Oral and Maxillofacial Surgeons definition [15] which requires: 1) current or previous treatment with a BP; 2) exposed, necrotic bone visualized in the maxillofacial region that persisted for more than 8 weeks; and 3) no history of radiation therapy to the jaws. Cases from the oral and maxillofacial pathology laboratory were considered if they were identified as BP users, the clinicians provided a clinical diagnosis of BRONJ and the histopathologic diagnosis was consistent with BRONJ. For the purposes of this study, cases were excluded if a patient had undergone intravenous (IV) BP therapy as part of cancer therapy. Stage 0 cases where there was no bone exposure were also excluded. Subjects who had a history of cancer, but were being treated with a BP for non-oncologic reasons were not excluded.

Data collection

Data were collected using a structured format that differed slightly for the clinical and pathology cases. Data elements included demographics, dental and medical history, possible triggering events, stage of BRONJ per AAOMS,[6] BRONJ treatment and outcomes, and type and duration of BP use. This information was extracted by two authors (TN and EM) onto structured forms which were then reviewed by the dental specialists who cared for the patients (NT, TD, SBW).

We attempted to collect the same information for all cases. However, some data elements were not available for the cases collected from the pathology laboratory. We were able to review the clinical information provided on the requisitions for all pathology cases and we attempted to get further information from clinicians submitting the specimens. Letters were sent and followed-up with further correspondence.

This study protocol was reviewed and approved by the Partners Healthcare Institutional Review Board.

Analysis

Descriptive statistics were computed for all study variables including measures of frequency, central tendency, and variance after accounting for missing data. No formal comparisons were attempted between the two cohorts as slightly different information was available.

RESULTS

Assembly of the case series

We identified 135 clinical cases from our clinicians. After reviewing cases individually, 44 of these cases were excluded because the patient was treated with a BP for cancer. Thus, 91 non-oncology cases of BRONJ were identified in the population surveyed: 18 clinical cases and 73 pathology cases. These two sources of patients are described separately and as a group below.

Clinical cases (Table 1)

The sample of clinical cases was composed of 18 subjects with a mean age of 67.4 years, and 88.9% were female. The most frequently used BP was alendronate which was used in 16 of 18 patients (88.9%). It was the only BP used in 14 cases (77.7%) and 2 cases also had used ibandronate. One patient received ibandronate alone (5.6%) and 1 patient received pamidronate alone (5.6%). The median duration of BP therapy was 60 months (range 2 to 120).

Precipitating risk factors for BRONJ were identified in 12 (66.7%) subjects who had undergone a previous dental extraction or had received an implant. The location of BRONJ was mandible for 9 patients (50.0%), maxilla in 7 patients (38.9%), and both in 2 (11.1%) cases. The distribution of BRONJ stages were stage 1 in 7 (39.5%) patients, stage 2 in 8 (44.4%), and stage 3 in 3 patients (16.7%). Fourteen patients reported pain (77.8%). Nine patients underwent surgery or non-surgical sequestrectomy (50.0%) to manage BRONJ and 9 did not (50.0%). Lastly, we reviewed each patient's notes to see if they had improved at the time of their last visit. Thirteen patients had improved (72.2%) and 4 patients had not (33.3%). This information was missing for 1 patient (5.6%)

Oral and maxillofacial pathology laboratory cases (Table 2)

The sample of oral and maxillofacial pathology laboratory cases was composed of 73 subjects with a mean age of 72.2 years and 96.0% were female. The most frequently used BP was alendronate which was used in 59 patients (80.0%); it was used alone in 55 cases (75.3%) and in combination with another BP in 4 cases (5.5%). One patient received ibandronate alone (1.5%), 2 patients received pamidronate alone (2.7%), 3 patients received risedronate alone (4.1%), and 3 patients received zoledronic acid alone (4.1%).

Possible triggers included a previous dental extraction or implant in 26 patients (35.6%). The most common location for BRONJ was the mandible noted in 44 (60.3%) patients. Pain was noted in 15 of 26 patients where this information was available (57.7%). All subjects had a single sample submitted; however, we only have complete treatment information available for 27 patients in the pathology laboratory group. Focusing on cases with data available, 22 (81.5%) patients underwent a surgical treatment and 5 did not (18.5%). Of the 23 patients with treatment outcome information, 19 (82.6%) had improved and 4 patients had not (17.4%).

Combined Case Series (Table 3)

Information for the clinical and laboratory cases is summarized in Table 3 and largely reflects the results described for the two cohorts.

DISCUSSION

We collected 91 cases of osteoporosis related BRONJ from one metropolitan US city between 2003 and 2012. From the available case information, patients presented with BRONJ after use of all available BPs used for osteoporosis with a median duration of use of 5 years. The mandible was the most common site of presentation and painless presentations occurred in approximately one-third of cases. Most patients noted an extraction prior to their BRONJ and the vast majority clinically improved.

BRONJ has been understudied given the number of patients using BPs, particularly at low doses for osteoporosis. While a case series has important limitations in methods that preclude strong inferences (such as the lack of a clear denominator), it often provides vital information about poorly studied drug adverse events that may be uncommon and require characterization before large scale epidemiologic studies can be successfully carried out.

Several other case series have examined cases of BRONJ in the osteoporosis patient populations.[16–18] These prior case series included between 11 and 85 patients and found that the median time until BRONJ appeared was between 1–5 years. Prior case series report that BRONJ had been associated with all BPs and the current case series notes similar results. As well, we report on treatments and treatment outcomes, which were generally effective. We also found that some cases appeared to occur very early after the start of BPs.

Cases from the clinical practices completely fulfilled the guidelines for diagnosis as proposed by the AAOMS. Cases identified from the oral and maxillofacial pathology laboratory, by their nature, had limited clinical and medical history. The diagnosis of BRONJ relied entirely on the fact the patients were on a BP for osteoporosis, had no history of radiation and had developed clinical evidence of necrotic bone confirmed by biopsy. Nevertheless, it is highly unlikely that these cases could represent a non-BP associated osteonecrotic process such as steroid-associated osteonecrosis which is extremely rare in the jawbones. Although no inter-rater reliability was performed, the clinical manifestation of BRONJ is very well-recognized now by most dentists and dental specialists and the diagnosis is generally unambiguous using the criteria set out by AAOMS.

We did not have complete treatment information on many of the pathology laboratory cases, but it appears that most patients improve or demonstrate complete resolution from BRONJ. This agrees with prior literature; when follow-up information was collected, 80.0% of patients, similar to the 70.1%–81.8% that had been reported in the past, improved.[17, 19]

Even though the number of cases reported here is the largest to date, it is likely that BRONJ is unlikely an under-reported condition because of several factors. Many dentists in the community now feel comfortable managing these lesions, so not all cases are referred to specialists. Not all cases of necrotic bone that are removed by non-surgical sequestrectomy are sent for histopathologic evaluation. The inclusion of a new category of Stage 0 lesions where there is no exposed bone contributes to under-estimation [6]. Furthermore, not all prior epidemiologic studies have queried dental practices. The oral and maxillofacial pathology laboratory that participated in this study is one of the largest in the country, accessioning more than 13,000 specimens annually, working with more than 100 dentists and dental specialists and this large pool of material may explain why we have such a large cohort.

In a prior study, we attempted to conduct formal epidemiologic analyses of risk factors for BRONJ among patients with osteoporosis.[8] Several methodologic factors limited the success of this prior work. We used large claims databases to increase the yield of BRONJ cases. However, BRONJ only received its own formal ICD diagnosis code in 2007. Further limiting this method was the fact that dental insurance claims do not routinely contain diagnoses codes but rather only CPT codes without reasons for visits included. While it appears that BRONJ related to osteoporosis is uncommon, the incidence of this adverse event is not clear based on prior literature. This case series adds some information to the literature, but it largely confirms smaller prior studies.[1, 16, 17, 19] In future studies, it would be helpful if patients could be stratified according to whether they were on an oral or IV preparation. In addition, we were unable to assess BP compliance in this study, but this would be an important area for future studies since it is well-known that compliance in taking oral medications long-term falls.[20]

In conclusion, the large number of cases identified in the current series strongly supports a true relationship between ONJ and BPs, even at osteoporosis dosages. Patients using all available BPs presented with BRONJ. Painful mandible lesions were most common, but some cases presented without pain. The vast majority of cases demonstrated clinical improvement. Clinicians prescribing BPs for osteoporosis need to be vigilant for this possible adverse event. Better epidemiologic data could be collected if a registry of BRONJ for patients with osteoporosis were developed. This might be sponsored by the manufacturers of BPs and run by oral medicine or oral surgery societies and/or osteoporosis provider groups. Such a registry would likely enhance our understanding of which patients are at risk, the typical course of BRONJ, and optimal management. BRONJ remains epidemiologically confusing, as it is difficult to identify and confirm cases. However, collecting a unified case series allows for further epidemiologic analysis of the risk of BRONJ.

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Table 1
Non-oncological patients affected by BRONJ on oral bisphosphonates: clinical features and medication history

Patient	Gender	Age	Mandible, maxilla, both	Exposed bone, 8 weeks	Stage	Pain at ONJ site	Dental extraction/ dental implants	Surgery	Bisphosphonate type	Duration BP use (mos)	Improved
1	M	69	Mandible	Yes	3	Yes	Yes	Yes	Alendronate, bandronate	60	Yes
2	F	62	Mandible	Yes	1	No	No	Yes	Alendronate, Ibandronate	60	Yes
3	F	57	Maxilla	Yes	1	Yes	No	Yes	Alendronate	66	Yes
4	F	74	Maxilla	Yes	1	No	Yes	No	Alendronate	72	No
5	F	71	Maxilla	Yes	2	Yes	Yes	Yes	Alendronate	>24	Yes
6	F	69	Mandible	Yes	3	Yes	Yes	Yes	Alendronate	42	Yes
7	F	55	Mandible	Yes	1	Yes	Yes	No	Alendronate	18	No
8	F	61	Both	Yes	2/3	Yes	Yes	Yes	Alendronate	...	Yes
9	F	64	Mandible	Yes	2	Yes	Yes	No	Alendronate	120	Yes
10	M	62	Maxilla	Yes	2	Yes	Yes	No	Alendronate	24	Yes
11	F	85	Mandible	Yes	2	No	No	No	Alendronate	6	Yes
12	F	62	Maxilla	Yes	2	Yes	Yes	No	Alendronate	24	Yes
13	F	76	Both	Yes	1	Yes	Yes	No	Alendronate	120	Yes
14	F	90	Maxilla	Yes	1	No	No	Yes	Alendronate	84	...
15	F	57	Maxilla	Yes	1	Yes	Yes	Yes	Alendronate	24	Yes
16	F	84	Mandible	Yes	2	Yes	No	No	Alendronate	96	No
17	F	51	Mandible	Yes	2	Yes	No	Yes	Ibandronate	33	Yes
18	F	64	Mandible	Yes	2	Yes	Yes	No	Pamidronate	2	No

The ellipse (...) denotes missing data from the record review.

Non-oncological patients from pathology reports affected by BRONJ on oral bisphosphonates: clinical features and medication history

Table 2

Patient	Gender	Age	Quadrant of mouth	Exposed bone, 8 weeks	Pain at ONJ site	Dental extraction/dental implants	Bisphosphonate type	Duration of BP use (mos)	Surgery	Improved
1	F	63	Mandible	...	Yes	Yes	Pamidronate	...	Yes	Yes
2	F	81	Mandible	...	Yes	...	Alendronate	24	...	Yes
3	F	91	Maxilla	...	Yes	Yes	Risedronate	...	Yes	Yes
4	M	61	Mandible	...	...	...	Zoledronic	...	...	...
5	F	71	Mandible	...	...	...	Bisphosphonate	...	...	...
6	F	71	Maxilla	...	...	...	Alendronate	120	...	...
7	F	82	Mandible	...	Yes	...	Alendronate	60	Yes	Yes
8	F	64	Mandible	...	No	Yes	Alendronate	3	Yes	Yes
9	F	52	Maxilla	...	Yes	Yes	Alendronate	5	...	No
10	F	88	Maxilla	...	Yes	No	Risedronate	...	Yes	Yes
11	F	78	Mandible	...	No	...	Alendronate	24	Yes	Yes
12	F	79	Mandible	Yes	Yes	...	Pamidronate	24	Yes	Yes
13	F	84	Maxilla	Yes	No	No	Alendronate	120	No [*]	Yes
14	F	56	Mandible	...	...	...	Alendronate	24	Yes	...
15	F	69	Mandible	No	Yes	Yes	Alendronate	30	Yes	No
16	F	57	Mandible	...	No	No	Zoledronic	4	No	Yes
17	F	56	Mandible	...	...	...	Ibandronate	...	...	...
18	F	80	Mandible	...	...	...	Alendronate	84	...	...
19	F	78	Maxilla	...	Yes	No	Alendronate	120	...	Yes
20	F	64	Mandible	Yes	...	...	Alendronate	...	...	...
21	F	79	Mandible	...	...	...	Alendronate	108	...	...
22	F	64	Mandible	...	...	No	Alendronate, pamidronate	120	...	...
23	M	89	Mandible	...	...	...	Alendronate	30	...	...
24	M	71	Mandible	Yes	...	Yes	Alendronate	...	...	No
25	F	77	Mandible	No	Yes	Yes	Alendronate	24	Yes	No
26	F	83	Maxilla	...	No	No	Alendronate	120	No [*]	Yes
27	F	56	Mandible	...	...	...	Bisphosphonate	...	...	...

Patient	Gender	Age	Quadrant of mouth	Exposed bone, 8 weeks	Pain at ONJ site	Dental extraction/ dental implants	Bisphosphonate type	Duration of BP use (mos)	Surgery	Improved
28	F	70	Mandible	No (2wks)	Yes	No	Alendronate	120	Yes	Yes
29	F	66	Mandible	No (1 wk)	No	Yes	Alendronate	60	...	Yes
30	F	82	Maxilla	No (6wks)	No	No	Alendronate	168	No	...
31	F	69	Mandible	...	Yes	Yes	Alendronate	96	No	Yes
32	F	67	Mandible	...	...	Yes	Alendronate, ibandronate	60	...	...
33	F	65	Mandible	...	No	Yes	Alendronate	48	Yes	Yes
34	F	64	Maxilla	...	...	Yes	Alendronate	...	...	...
35	F	78	Maxilla	...	Yes	Yes	Alendronate	72	Yes	...
36	F	56	Mandible	...	No	Yes	Alendronate	...	...	Yes
37	F	89	Maxilla	...	Yes	Yes	Alendronate	36	Yes	...
38	F	74	Maxilla	...	No	Yes	Alendronate	60	Yes	Yes
39	F	53	Mandible	...	...	...	Alendronate	48	...	...
40	F	52	Maxilla	...	...	...	Alendronate	60	...	...
41	F	84	Mandible	...	...	...	Bisphosphonate	...	...	...
42	F	66	Maxilla	...	No	No	Alendronate	24	Yes	Yes
43	F	72	Mandible	Yes	...	...	Bisphosphonate	120	Yes	...
44	F	83	Mandible	...	...	...	Alendronate	36	...	...
45	F	92	Maxilla	...	...	...	Alendronate	...	...	...
46	F	89	Maxilla	...	...	...	Alendronate, risedronate	...	...	...
47	F	71	Mandible	...	...	...	Alendronate	30	...	...
48	F	78	Mandible	...	...	...	Alendronate	...	...	...
49	F	89	Mandible	Yes	...	Yes	Alendronate	72	...	...
50	F	84	Mandible	...	...	...	Alendronate	...	...	...
51	F	84	Maxilla	Yes	...	Yes	Alendronate	...	...	...
52	F	52	...	...	...	...	Alendronate	...	...	...
53	F	80	...	...	...	Yes	Alendronate	24	...	...
54	F	80	Maxilla	...	...	...	Alendronate	192	Yes	...
55	F	60	Mandible	...	...	...	Risedronate	...	...	...
56	F	65	Maxilla	...	...	...	Alendronate	24	...	...
57	F	53	Maxilla	...	...	Yes	Alendronate	60	...	...

Patient	Gender	Age	Quadrant of mouth	Exposed bone, 8 weeks	Pain at ONJ site	Dental extraction/ dental implants	Bisphosphonate type	Duration of BP use (mos)	Surgery	Improved
58	F	91	Mandible	...	...	...	Alendronate	120	...	...
59	F	83	Maxilla	...	...	...	Alendronate	84	Yes	...
60	F	72	Maxilla	...	...	...	Alendronate	240	...	...
61	F	61	Mandible	...	...	...	Alendronate	48	...	...
62	F	58	Mandible	...	...	Yes	Alendronate	...	...	...
63	F	74	Maxilla	...	...	Yes	Bisphosphonate	...	Yes	...
64	F	71	Maxilla	...	...	...	Alendronate	...	...	...
65	F	64	Mandible	...	...	...	Zoledronic	...	...	...
66	F	71	Maxilla	...	...	...	Alendronate	...	...	...
67	F	68	Mandible	...	...	Yes	Alendronate	...	...	...
68	F	75	Mandible	...	...	...	Alendronate	66	...	...
69	F	60	Maxilla	...	...	...	Alendronate	120	...	...
70	F	82	Mandible	...	...	Yes	Alendronate	...	...	...
71	F	86	Mandible	...	...	...	Alendronate	...	...	...
72	F	71	Mandible	...	Yes	Yes	Alendronate	...	Yes	...
73	F	72	Maxilla	...	...	Yes	bisphosphonate	...	Yes	...

The ellipse (...) denotes missing data from the record review. Some bisphosphonates were not specified in the records.

* Non-surgical bone removal

Table 3

Selected patient characteristics of 91 subjects with osteoporosis and BRONJ

Characteristics	Total cohort		Excluding subjects with missing data	
	N (%) or Median (IQR)		N (%) or Median (IQR)	
Gender				
male	5	(5.4%)	5	(5.4%)
female	86	(94.5%)	86	(94.5%)
Median age at presentation, years	71.0	(19.0)	71.0	(19.0)
Bisphosphonate type *				
alendronate	75	(77.3%)	75	(82.4%)
ibandronate	5	(5.2%)	5	(5.5%)
risedronate	4	(4.1%)	4	(4.4%)
pamidronate	4	(4.1%)	4	(4.4%)
zoledronic	3	(3.1%)	3	(3.3%)
missing	6	(6.2%)	0	(0.0%)
Median duration BP use (months)	60.0	(78.0)	60.0	(78.0)
Area of mouth affected by ONJ				
maxilla	34	(37.3%)	34	(37.5%)
mandible	53	(58.2%)	53	(60.2%)
both	2	(2.2%)	2	(2.3%)
missing	2	(2.2%)		
Pain at ONJ Site				
yes	28	(30.8%)	28	(65.1%)
no	15	(16.5%)	15	(34.9%)
missing	48	(52.7%)		
Highest ONJ stage †				
stage 0	0	(0.0%)	0	(0.0%)
stage 1	7	(7.6%)	7	(38.9%)
stage 2	8	(8.8%)	8	(44.4%)
stage 3	3	(3.3%)	3	(16.7%)
missing	73	(80.2%)		
Extraction or Implant				
yes	38	(41.8%)	38	(71.7%)
no	15	(16.5%)	15	(28.3%)
missing	38	(41.8%)		
Treatment Type				
surgical	31	(34.1%)	31	(68.9%)
non-Surgical	14	(15.4%)	14	(31.1%)
missing	46	(50.5%)		
ONJ Improved				

Characteristics	Total cohort		Excluding subjects with missing data	
	N (%) or Median (IQR)		N (%) or Median (IQR)	
yes	32	(35.1%)	32	(80.0%)
no	8	(8.8%)	8	(20.0%)
missing	51	(56.0%)	0	(0.0%)

* Totals more than 91; some patients on more than 1 bisphosphonate.

† Data from Table 1 only

Abbreviations: ONJ, osteonecrosis of the jaw; IQR; Interquartile range