RESEARCH ARTICLE

Image findings of bisphosphonate related osteonecrosis of jaws comparing with osteoradionecrosis

¹Kenichi Obinata, ¹Shinichi Shirai, ¹Hitoshi Ito, ²Motoyasu Nakamura, ³Marco Carrozzo, ⁴Iain Macleod, ⁴Andrew Carr, ⁵Yutaka Yamazaki and ⁶Kanchu Tei

¹Omni Dentix, Dartmouth, Sapporo, Hokkaido, Japan; ²Nakamura Dental Clinic, Sapporo, Hokkaido, Japan; ³Department of Oral Medicine, University of Newcastle upon Tyne, Newcastle upon Tyne, UK; ⁴Department of Dental Radiology, University of Newcastle upon Tyne, Newcastle upon Tyne, UK; ⁵Department of Oral Medicine, Center for Dental Clinics, Hokkaido University Hospital, Sapporo, Hokkaido, Japan; ⁶Department of Oral Surgery, Center for Dental Clinics, Hokkaido University Hospital, Sapporo, Hokkaido, Japan

Objectives: The aim of this study was to evaluate image characteristics of bisphosphonate-related osteonecrosis of the jaws (BRONJ) and compare these with osteoradionecrosis (ORN).

Methods: 34 patients with BRONJ and 16 patients with ORN were included in this study. We investigated the CT and dental panoramic radiograph (DPR) images for osteolysis, osteosclerosis, sequestration, periosteal reaction, pathological fracture and spread of soft tissue inflammation around the jaws.

Results: Osteolysis, osteosclerosis, sequestration and spread of soft tissue inflammation around the jaws were common radiological features in both BRONJ and ORN. Osteolysis and spreading of soft tissue inflammation around the jaws were predominant in ORN, and by contrast osteosclerosis was predominant in BRONJ. Periosteal reaction was established in 15 of the 34 BRONJ cases, but none in the ORN cases. Pathological fractures were observed in 6 of 16 ORN cases, but none in BRONJ cases. CT was better for detection than DPR for osteolysis, osteosclerosis, sequestration and periosteal reactions.

Conclusions: Image findings of BRONJ were characterized as a severe sclerotic change combined with osteolysis, sequestration, periosteal reaction and spread of soft tissue inflammation around the jaws.

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Keywords: bisphosphonate-related osteonecrosis of the jaw; osteoradionecrosis; CT; panoramic radiography

Introduction

Bisphosphonate (BP) is used to treat osteoporosis, bone metastases, hypercalcaemia of malignancies and multiple myelomas and shows good benefits.^{1–3} Bisphosphonate-related osteonecrosis of the jaws (BRONJ) was first reported by Marx⁴ (2003). The author reported 36 cases of BRONJ who received i.v. infusions of zoledronate for multiple myelomas, hypercalcaemia of metastatic breast

cancer and osteoporosis. The BRONJ is defined as exposed necrotic bone in the maxillofacial area that persists for more than 8 weeks in patients with a history of nitrogen-containing BP use without a history of radiation exposure.⁵ The BRONJ affects the quality of life including giving rise to pain, swelling, purulent secretions, paresthesia, difficulty of eating and deformation after breaking away or surgical resection of necrotic bone.⁶ Increasingly, many studies of BRONJ have been published in the recent decade. The studies are mostly case reports and focus on treatment strategies and the

Correspondence to: Kenichi Obinata. E-mail: obikenca@yahoo.co.jp

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treatment outcomes.^{7,8} Several reports have described image diagnoses of BRONJ including CT, MRI and plain radiographs.^{9–12} Osteoradionecrosis (ORN) of the jaw is one of the most severe chronic side effects of radiation therapy for head and neck malignancies, and often the result of high total dose or large fraction size of radiation therapy or large irradiated volume. Typical osseous findings of ORN on CT scans include cortical disruption, disorganization of trabeculation and osseous fragmentation. ORN can be associated with significant soft tissue thickening and enhancement in the adjacent masticator muscles.¹³ Image findings of BRONJ and ORN have something in common and specific, but quantitative and comparative evaluation has not been performed.

The present study investigates image findings of BRONJ by CT and dental panoramic radiograph (DPR) and analyzes the detectability of the features. Further, we compared the image characteristics with ORN, which has also been known as refractory osteonecrosis of the jaws.

Methods and materials

This study included 34 patients referred to the Division of Oral Medicine or Oral Surgery at the Centre for Dental Clinics, Hokkaido University Hospital, and diagnosed with BRONJ between 2007 and 2013. The inclusion criteria were: obtaining patient medical/dental history and availability of both CT scans and DPRs. At our institution, DPR and CT are routine examinations for the patients with osteomyelitis and osteonecrosis of the jaws. For some cases, MRI, radioisotope and positron emission tomography are additionally performed. The patients examined in this study underwent DPRs with a Veraviewepocs® (Morita, Tokyo, Japan; at 60–80 kV and 1–10 mA) and underwent multislice helical CT scans with Aquilon PRIME (Toshiba Medical, Toyo, Japan) at 0.5-mm slice thickness. The patients were classified in accordance with the BRONJ stage guidelines provided by the American Association of Oral and Maxillofacial Surgeons (Table 1). 16 patients with ORN where the medical/dental records, CT scans and DPRs were available were selected for the comparisons. Each case was assessed on both the CT scans and DPRs for the following radiographic details: osteolysis, osteosclerosis, presence of sequestrum, periosteal reaction and pathological fractures. The spread of soft tissue inflammation around the jaws was assessed on the CT scans. Grading of image features was performed based on the following criteria (Table 2):

- osteolysis/osteosclerosis: Grade 0: none; Grade 1: localized in the alveolar bone of the jaws; Grade 2: extended beyond the mandibular canal (mandible) or the maxillary sinus (maxilla) (Figure 1)
- sequestration, periosteal reaction and pathological fracture: Grade 0: not observed; Grade 1: observed (Figure 2)

Table 1 Stage of bisphosphonate-related osteonecrosis of the jaws

Stage 0	No apparent necrotic/exposed bone Hypaesthesia or anaesthesia of lower lip (Vincent's symptom) Intraoral fistula Deep periodontal pocket Small osteolytic lesions on radiograph
Stage I	Necrotic/exposed bone Asymptomatic No infection
Stage II	Necrotic/exposed bone Infection (pain, erythema) With or without purulent discharge
Stage III	Stage II plus Extending necrotic/exposed bone Pathologic fractures Extraoral fistula Oral antral/oral nasal communication Extending osteolysis

- spreading of soft tissue inflammation around the jaws: Grade 0: not observed; Grade 1: localized around the alveolar bone; Grade 2: extended into the masticatory muscles, masticatory space, subcutaneous adipose tissue and nasal/paranasal cavities in the cases of maxilla (Figure 3).

Mean values were calculated for each grade of the image feature. Images were all evaluated by two dental radiologists with 15 and 25 years' experience who were not aware of the grade assigned by the other. If the image interpretation of the dental radiologists differed, discussion was made including an oral medicine specialist who was experienced in the diagnosis of osteomyelitis of the jaws, and an interpretation was agreed upon. Differences in detectability of image features between the CT and DPR were analyzed. We evaluated the frequency of image feature appearances and its grading and analyzed the differences between BRONJ and ORN with the non-parametric Mann–Whitney *U* test. The relationship among image features in BRONJ and ORN was evaluated with a Spearman rank correlation test. Comparisons were made, and statistical analyses were carried out using Stat® view v. 5 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL). Values of $p < 0.05$ were considered to indicate statistical significance.

Table 2 Criteria of image diagnosis (grading)

Osteolysis and osteosclerosis (DPR/CT)
0: not observed
1: located in alveolar bone
2: extended into mandibular canal (mandible)/maxillary sinus (maxilla)
Sequester, periosteal reaction and pathological fracture (DPR/CT)
0: not observed
1: observed
Spread into soft tissue (CT)
0: not observed
1: spread into alveolar (buccolingual)
2: spread into masticator muscles or subcutaneous adipose tissue or maxillary sinus
DPR, dental panoramic radiograph.

Figure 1 Feature images of osteolysis and osteosclerosis: osteolysis and osteosclerosis are observed, extending beyond the mandibular canal (arrow) (Grade 2). Dental panoramic radiograph (DPR) image (a) and CT image (b) of bisphosphonate-related osteonecrosis of the jaws (BRONJ) osteolysis, DPR image (c) and CT image (d) of osteoradionecrosis osteolysis, DPR image (e) and CT image (f) of BRONJ osteosclerosis.

Results

The patient characteristics of the study are summarized in Tables 3 and 4. The patients with BRONJ were 9 males and 25 females (mean age 68 years; age range 40–88 years). Of the 34 patients, 20 patients were administered i.v. BP and 14 patients had oral administration of BP. 2 patients were classified as Stage 0, 11 patients as Stage I, 18 patients as Stage II and 3 patients as Stage III. 20 cases were developed in the mandible, 12 cases in the maxilla and 2 cases in both the mandible and maxilla, arising from 30 molar and 6 incisor regions. As background to the BRONJ development, 20 cases occurred after tooth extraction, 10 cases were with severe periodontitis and/or after teeth falling out, 2 cases were spontaneous and 2 cases were unknown. In the patients with ORN, 13 patients were males and 3 patients were females (mean age 69 years; age range 49–90 years). There were six oropharyngeal cancers, five tongue cancers, two parotid gland cancers, a cheek cancer, a maxillary sinus cancer and an ethmoid sinus cancer given radiotherapy doses ranged from 50 Gy to 70 Gy, and seven cases were combined with chemotherapy. Of the 34 BRONJ cases, osteolysis was observed in 14 (41.2%) cases on the DPRs and 29 (85.3%) cases on the CT, giving mean grades of 0.59 and 1.24, respectively. Of the 16 ORN cases, osteolysis was observed in 15 (93.8%) cases on the DPRs and 16 (100%) cases on the CT, giving mean grades of 1.69 and 1.88, respectively. Osteosclerosis was observed in 19 (55.9%) cases on the DPRs and 31 (91.2%) cases on the CT, giving mean grades of 0.82 and 1.68 in BRONJ. In ORN, osteosclerosis was observed in 9 (56.3%) cases on the DPRs and 10 (62.5%) cases on the CT, giving mean grades of 0.94 and 1.13. Sequestration was observed in 9 of the 34 (26.5%) cases on the DPRs and in 25 (73.5%) cases on the CT for BRONJ, giving mean grades of 0.27 and 0.74. With ORN, sequestration was observed in 6 of

16 (37.5%) cases on the DPRs and in 15 (93.8%) cases on the CT, giving mean grades of 0.38 and 0.94. A periosteal reaction was observed in 1 of the 34 (2.9%) cases on the DPRs and 15 (44.1%) cases on the CT for BRONJ, giving mean grades of 0.03 and 0.44, but none among the ORN. Pathological fractures were observed in 5 of the 16 (31.3%) cases on both the DPRs and CT in ORN, giving mean grades of 0.31, but none among the BRONJ. Spreading of soft tissue inflammation was observed in 21 of the 34 (61.8%) cases of the BRONJ and in 16 of the 16 (100%) cases of the ORN, giving mean grades of 0.94 and 1.63, respectively. There was a statistically significant difference in image feature detectability of BRONJ between the DPR and CT ($p < 0.05$). Statistically significant correlations were indicated between the spread of soft tissue inflammation and osteolysis in both BRONJ and ORN, and further between pathological fractures and osteolysis in ORN ($r = 0.66$) (Table 5).

Discussion

The patients receiving BP therapy either intravenously or by oral administration is growing, because patients with cancer and osteoporosis are increasing in number owing to the ageing of society. BP inhibits osteoclasts and can effectively control bone resorption resulting in alleviating patient disadvantages. In this decade, BP has impacted on dentistry. Since Marx reported the first cases of osteonecrosis of the jaws, many case reports, epidemiological surveys and position papers have been published worldwide.^{5–7} A greater incidence of BRONJ has been reported in patients receiving i.v. BP administration than in those administered BP orally. Mavrokokki *et al*⁶ reported the frequency of BRONJ as 0.01–0.04% with patients administered oral BP and 0.88–1.15% for patients administered i.v. BP in

Figure 2 Feature images of sequestration, periosteal reaction and pathological fracture (arrow): sequestration is observed on dental panoramic radiograph (DPR) (a) and CT (b) in the bisphosphonate-related osteonecrosis of the jaws (BRONJ) case (Grade 1). Sequestration is observed on DPR (c) and CT (d) in the osteoradionecrosis (ORN) case (Grade 1). Periosteal reaction is observed on DPR (e) and CT (f, g) in the BRONJ case (Grade 1). Pathological fracture is observed on DPR (h) and CT (i) in the ORN case (Grade 1).

Figure 3 Feature images of spread of soft tissue inflammation around the jaws: swelling of the right buccinator and mylohyoid muscle (arrowheads) is observed on CT in the bisphosphonate-related osteonecrosis of the jaws case (a) (Grade 2). Swelling of the right masseter and medial pterygoid muscle (arrowheads) is observed, and increase of CT number of the right buccal adipose tissue is observed (arrows) on CT in the osteoradionecrosis case (b) (Grade 2), which means inflammation is spreading into the subcutaneous tissue.

Australia. In the study here, with 34 patients, 20 patients received i.v. BP and 14 patients received oral BP. As described in the Japanese survey of BRONJ, more patients with osteoporosis receiving oral BP developed BRONJ in Japan than in other developed countries. In the study here, BRONJ lesions were noted for 22 patients in the mandible and for 14 patients in the maxilla, and for 30 patients in the posterior and for 6 patients in the anterior regions, which is in agreement with previous reports.^{7,8} ORN occurred more frequently in the mandible. The higher incidence of mandibular involvement has been attributed to its lower blood supply compared with the maxilla and the compact bone structure.¹⁴ It has been the agreed consensus that dentoalveolar trauma is the most common risk factor for BRONJ and ORN development. We found that 20 of the 34 patients developed BRONJ after tooth extractions. There are several reports of image findings of BRONJ, which describe that DPR, CT, MRI and radioisotope imaging can be useful for identifying BRONJ.⁹⁻¹² The radiologic findings of BRONJ are not specific and also involve other conditions such as osteomyelitis and ORN. The DPR is taken as the initial radiologic screening for BRONJ and the observations include osteolysis, diffuse sclerosis and poor or non-healing of the extraction site.⁹

Imaging of bisphosphonate-related osteonecrosis of the jaws

Bianchi et al¹¹ reported that sequestrum and periosteal reactions were observed with CT, and that CT is superior to DPR. This was consistent with our result that image feature detectability of BRONJ was significantly better in CT than in DPR. Osteosclerosis was a predominant feature, and periosteal reaction was a characteristic feature of BRONJ. BP affects osteoclasts selectively, and bone remodelling involves more bone formation, which might result in osteosclerosis and periosteal reaction. Bagan et al¹² reported that the degree of sclerosis increased with the clinical stage of BRONJ and was correlated with the depth of

Table 3 Bisphosphonate-related osteonecrosis of the jaws case characteristics

Patient number	Age (years), gender	Stage	Location	BP type	Pre-existing medical conditions
1	79, M	II	Mandible posterior	Zoredronate	Lung cancer
2	63, F	II	Mandible posterior	Zoredronate	Breast cancer
3	78, F	III	Maxilla anterior and posterior	Alendronate	Osteoporosis
4	81, F	II	Mandible posterior	Alendronate	Osteoporosis
5	78, F	III	Mandible posterior	Risedronate	Osteoporosis
6	68, M	II	Mandible anterior and posterior	Zoredronate	Prostate cancer
7	59, M	II	Mandible posterior	Zoredronate	Prostate cancer
8	64, F	I	Mandible anterior	Zoredronate	Breast cancer
9	69, F	0	Mandible posterior	Zoredronate	Breast cancer
10	69, M	II	Mandible posterior	Zoredronate	Renal cancer
11	75, M	I	Mandible posterior	Zoredronate	Prostate cancer
12	77, M	II	Maxilla anterior	Zoredronate	Renal cancer
13	56, F	II	Maxilla anterior	Zoredronate	Breast cancer
14	67, F	I	Mandible posterior	Zoredronate	Breast cancer
15	67, F	II	Maxilla posterior	Alendronate	Breast cancer, osteoporosis
16	76, F	II	Mandible posterior	Risedronate	Osteoporosis, rheumatoid
17	53, F	III	Mandible posterior	Alendronate	SLE
18	68, F	0	Maxilla anterior and mandible posterior	Alendronate	Osteoporosis, rheumatoid
19	67, F	I	Maxilla posterior	Zoredronate	Breast cancer
20	58, F	I	Mandible posterior	Zoredronate	Breast cancer
21	66, F	II	Mandible posterior	Risedronate	Rheumatoid, SjS
22	84, F	II	Maxilla posterior	Alendronate	Osteoporosis, DM
23	86, F	II	Maxilla posterior	Alendronate	Osteoporosis
24	58, F	II	Maxilla posterior	Zoredronate	Renal cancer
25	59, M	I	Maxilla posterior	Zoredronate	Prostate cancer
26	58, F	II	Maxilla (torus palatinum)	Zoredronate	Breast cancer
27	57, F	II	Mandible posterior	Zoredronate	Breast cancer
28	44, M	I	Maxilla posterior	Zoredronate	Endocrine tumour, bone metastasis
29	80, M	II	Mandible posterior	Alendronate	Osteoporosis, rheumatoid, DM
30	79, F	II	Maxilla and mandible, anterior and posterior	Risedronate	Osteoporosis, rheumatoid, DM
31	86, F	I	Mandible posterior	Risedronate, alendronate	Osteoporosis
32	40, F	I	Maxilla posterior	Zoredronate	Breast cancer, bone and liver metastasis
33	70, F	I	Mandible posterior	Alendronate	Osteoporosis, rheumatoid
34	88, F	I	Mandible posterior	Alendronate	Steroid induced-osteoporosis

BP, bisphosphonate; DM, diabetes mellitus; F, female; M, male; SLE, systemic lupus erythematosus; SjS, Sjögren syndrome.

radiolucency. It has been reported that thickening of the lamina dura is observed on periapical radiographs in BRONJ.¹⁵ There were a few cases which showed thickening of the lamina dura on the DPRs or in periapical radiographs in our BRONJ cases, but the findings were not consistent. Before BP was used as a pharmacological agent for osteoporosis and bone metastasis, it was previously used as a macrophage apoptosis experimental model *in vivo*.¹⁶ As Hoefert et al¹⁷ reported that the pathogenesis of BRONJ may be associated with an immune compromise, something that was evident from observation of actinomycotic clusters histopathologically in this study.

Imaging of osteoradionecrosis

Reports of images of ORN have been published well before BRONJ. The localization and extent of the bone destruction can be better evaluated with CT than with conventional occlusal or panoramic films. The typical osseous findings of mandibular ORN on CT scans are cortical disruption, disorganization of trabeculation and osseous fragmentation (sequestration).¹³

In the study here, bone destruction due to osteolysis and spreading of soft tissue inflammation were

Table 4 Osteoradionecrosis (ORN) case characteristics

Patient number	Age (years), gender	Tumour site	Irradiation dose	Chemotherapy
1	64, M	Parotid	66 Gy	—
2	70, M	Tongue and OP	Tongue/50 Gy and OP/70 Gy	—
3	62, M	Parotid	66 Gy	—
4	61, M	Tongue	70 Gy	—
5	70, M	OP	66 Gy	+
6	75, F	Maxillary sinus	66 Gy	+
7	77, F	Tongue	70 Gy	—
8	73, M	Cheek	70 Gy	—
9	83, M	Tongue	70 Gy	—
10	66, M	Ethmoid sinus	66 Gy	+
11	80, F	OP	70 Gy	+
12	77, M	OP	66 Gy	+
13	90, M	OP	66 Gy	—
14	49, M	OP	66 Gy	+
15	55, M	OP	66 Gy	+
16	64, M	OP	66 Gy	+

F, female; M, male; OP, oropharynx.

Table 5 Result

Image feature detectability and grade	BRONJ		ORN	
	DPR	CT	DPR	CT
Osteolysis	14/34 (41.2%) 0.59 ^a	29/34 (85.3%) 1.24 ^{a,b}	15/16 (93.8%) 1.69 ^b	16/16 (100%) 1.88 ^b
Osteosclerosis	19/34 (55.9%) 0.82 ^a	31/34 (91.2%) 1.68 ^a	9/16 (56.3%) 0.94	10/16 (62.5%) 1.13
Sequestration	9/34 (26.5%) 0.27 ^a	25/34 (73.5%) 0.74 ^a	6/16 (37.5%) 0.38	15/16 (93.8%) 0.94
Periosteal reaction	1/34 (2.9%) 0.03 ^a	15/34 (44.1%) 0.44 ^a	0/16 (0%) 0	0/16 (0%) 0
Pathological fracture	0/34 (0%) 0	0/34 (0%) 0	5/16 (31.3%) 0.31 ^b	5/16 (31.3%) 0.31 ^b
Spread of soft tissue inflammation	— —	21/34 (61.8%) 0.94 ^b	— —	16/16 (100%) 1.63 ^b

BRONJ, bisphosphonate-related osteonecrosis of the jaws; DPR, dental panoramic radiograph; ORN, osteoradionecrosis.

^aStatistically significant difference ($p < 0.05$).

^bStatistically significant correlation ($p < 0.05$).

predominant in ORN, more so than for BRONJ. Hermans *et al*¹⁸ described that the bone abnormalities in mandibular ORN were often associated with a soft tissue mass. It may be speculated that once the defence of the cortical bone is absent, soft tissue inflammation spreads from the jaws into masticator space and subcutaneous adipose tissue. In this study, pathological fractures were observed only in ORN and were thought to be associated with severe osteolysis. Significant correlation was indicated between pathological fracture and osteolysis in ORN. The radiosensitivity of osteogenic cells is different. Osteocytes are post-mitotic differentiated cells and considered to belong to the radioresistant cell group. Osteoclasts belong to a somewhat radiosensitive cell group, but osteoblasts and periosteum cells are considered more radiosensitive than osteoclasts.¹⁹ The facts that osteolysis was more common in ORN and periosteal reaction was not observed in ORN might have resulted from apoptosis of highly radiosensitive osteoblastic and periosteal cells. Osteosclerosis of ORN can be attributed to surviving osteoblasts from lethal doses of irradiation in the irradiated field. Radiation affects all osteogenic cells, while BP affects osteoclast selectively.

Conclusions

Detectability of the image features of BRONJ was significantly superior for CT than for DPR. Image features of BRONJ were osteolysis, osteosclerosis, sequestration, periosteal reaction and spreading of soft tissue inflammation, while those of ORN were osteolysis, osteosclerosis, sequestration, pathological fracture and spreading of soft tissue inflammation. Osteolysis was a predominant image finding of ORN, while osteosclerosis was a predominant image finding of BRONJ. In this study, periosteal reaction was the characteristic finding of BRONJ and pathological fracture was the characteristic finding of ORN, respectively.

Image feature detection of early stage BRONJ (Stage 0–1) is necessary for the prediction and prevention of BRONJ development. Image findings especially CT will be also useful for therapy evaluations of BRONJ in further investigations.

This study was partly presented at the 17th congress of clinical imaging for oral and maxillofacial lesions held on the 25–27 October 2012 in Osaka, Japan.

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