like domain-containing adhesion molecules. *Genomics* 2006;87:139–50.
11. Williams YN, Masuda M, Sakurai-Yageta M, Maruyama T, Shibuya M, Murakami Y. Cell adhesion and prostate tumor suppressor activity of TSLL2/IGSF4C, an immunoglobulin superfamily molecule homologous to TSLC1/IGSF4. *Oncogene* 2006;25:1446–53.
12. Yageta M, Kuramochi M, Masuda M, Fukami T, Fukuhara H, Maruyama T, Shibuya M, Murakami Y. Direct association of TSLC1 and DAL-1, two distinct tumor suppressor proteins in lung cancer. *Cancer Res* 2002;62:5129–33.
13. Tran YK, Bogler O, Gorse KM, Wieland I, Green MR, Newsham IF. A novel meber of the NF2/ERM/4.1 superfamily with growth suppressing properties in lung cancer. *Cancer Res* 1999;59:35–43.
14. Gutmann DH, Donahoe J, Perry A, Lemke N, Karen G, Kittiniyom K, Rempel AS, Gutierrez AJ, Newsham FI. Loss of DAL-1, a protein 4.1-related tumor suppressor, is an important early event in the pathogenesis of meningiomas. *Hum Mol Genet* 2000;9:1495–500.
15. Kikuchi S, Yamada D, Fukami T, Masuda M, Sakurai-Yageta M, Williams YN, Maruyama T, Asamura H, Matsuno Y, Onizuka M, Murakami Y. Promoter methylation of the DAL-1/4.1B predicts poor prognosis in non-small cell lung cancer. *Clin Cancer Res* 2005;11:2954–61.
16. Kikuchi S, Yamada D, Fukami T, Maruyama T, Ito A, Asamura H, Matsuno Y, Onizuka M, Murakami Y. Hypermethylation of the TSLC1/IGSF4 promoter is associated with tobacco smoking and a poor prognosis in primary non-small cell lung cancer. *Cancer* 2006; 106:1751–8.
17. Heller G, Fong KM, Girard L, Seidl S, End-Pfützenreuter A, Lang G, Gazdar AF, Minna JD, Zielinski CC, Zöchbauer-Müller S. Expression and methylation pattern of TSLC1 cascade genes in lung carcinomas. *Oncogene* 2006;25:959–68.
18. Heller G, Geradts J, Ziegler B, Newsham I, Filipits M, Markis-Ritzinger EM, Kandioler D, Berger W, Stiglbauer W, Depisch D, Pirker R, Zielinski CC, et al. Downregulation of TSLC1 and DAL-1 expression occurs frequently in breast cancer. *Breast Cancer Res Treat* 2007;103: 283–91.
19. Lusis E, Gutmann DH. Meningioma: an update. *Curr Opin Neurol* 2004;17:687–92.
20. Ramez M, Blot-Chabaud M, Cluzeaud F, Chanan S, Patterson M, Walensky LD, Marfatia S, Baines AJ, Chasis JA, Conboy JG, Mohandas N, Gascard P. Distinct distribution of specific members of protein 4.1 gene family in the mouse nephron. *Kidney Int* 2003;63:1321–37.
21. Yamada D, Kikuchi S, Williams YN, Sakurai-Yageta M, Masuda M, Maruyama T, Tomita K, Gutmann DH, Kakizoe T, Kitamura T, Murakami Y. Promoter hypermethylation of the potential tumor suppressor DAL-1/4.1B gene in renal clear cell carcinoma. *Int J Cancer* 2006;118: 916–23.
22. Sakurai-Yageta M, Masuda M, Tsuboi Y, Ito A, Murakami Y. Tumor suppressor CADM1 is involved in epithelial cell structure. *Biochem Biophys Res Commun* 2009;90:977–82.
23. Koma Y, Furuno T, Hagiyama M, Hamaguchi K, Nakanishi M, Masuda M, Hirota S, Yokozaki H, Ito A. Cell adhesion molecule 1 is a novel pancreatic-islet cell adhesion molecule that mediates nerve-islet cell interactions. *Gastroenterology* 2008;134: 1544–54.
24. Veigl ML, Kasturi L, Olechnowicz J, Ma AH, Lutterbaugh JD, Periyasamy S, Li GM, Drummond J, Modrich PL, Sedwick WD, Markowitz SD. Bialleic inactivation of hMLH1 by epigenetic gene silencing, a novel mechanism causing human MSI cancers. *Proc Natl Acad Sci USA* 1998;95: 8698–702.
25. Zhou Y, Du G, Hu X, Yu S, Liu Y, Xu Y, Huang X, Liu J, Yin B, Fan M, Peng X, Qiang B, et al. Nectin-like molecule 1 is a protein 4.1N associated protein and recruits protein 4.1N from cytoplasm to the plasma membrane. *Biochim Biophys Acta* 2005;1669:142–54.
26. Nickerson ML, Jaeger E, Shi Y, Durocher JA, Mahurkar S, Zaridze D, Matveev V, Janout V, Kollarova H, Bencko V, Navratilova M, Szeszenia-Dabrowska N, et al. Improved identification of von Hippel-Lindau gene alterations in clear cell renal tumors. *Clin Cancer Res* 2008;14: 4726–34.
27. Dall'Oglio MF, Antunes AA, Sarkis AS, Crippa A, Leite KR, Lucon AM, Srougi M. Microvascular tumour invasion in renal cell carcinoma: the most important prognostic factor. *BJ U Int* 2007;100:552–5.
28. Strewler GJ, Wronski TJ, Halloran BP, Miller SC, Leung SC, Williams RD, Nissenson RA. Pathogenesis of hypercalcemia in nude mice bearing a human renal carcinoma. *Endocrinology* 1986;119:303–10.
29. Dreijerink K, Braga E, Kuzmin I, Geil L, Duh FM, Angeloni D, Zbar B, Lerman MI, Stanbridge EJ, Minna JD, Protopopov A, Li J, et al. The candidate tumor suppressor gene, RASSF1A, from human chromosome 3p21.3 is involved in kidney tumorigenesis. *Proc Natl Acad Sci USA* 2001;98:7504–9.
30. Morrissey C, Martinez A, Zatyka M, Agathanggelou A, Honorio S, Astuti D, Morgan NV, Moch H, Richards FM, Kishida T, Yao M, Schraml P, et al. Epigenetic inactivation of the RASSF1A 3p21.3 tumor suppressor gene in both clear cell and papillary renal cell carcinoma. *Cancer Res* 2001;61:7277–81.
31. Dulaimi E, Caceres II, Uzzo RG, Al-Saleem T, Greenberg RE, Polascik TJ, Babb JS, Grizzle WE, Cairns P. Promoter hypermethylation profile of kidney cancer. *Clin Cancer Res* 2004;10:3972–9.
32. Murakami Y. Involvement of a cell adhesion molecule, TSLC1/IGSF4, in human oncogenesis. *Cancer Sci* 2005;96: 543–52.
33. Curto M, Cole BK, Lallemand D, Liu CH, McClatchey AI. Contact-dependent inhibition of EGFR signaling by Nf2/Merlin. *J Cell Biol* 2007;177:893–903.
34. Kunitz A, Wolter M, van den Boom J, Felsberg J, Tews B, Hahn M, Benner A, Sabel M, Lichter P, Reifenberger G, von Deimling A, Hartmann C. DNA hypermethylation and aberrant expression of the EMP3 gene at 19q13.3 in human gliomas. *Brain Pathol* 2007;17:363–70.
35. Tews B, Felsberg J, Hartmann C, Kunitz A, Hahn M, Toedt G, Neben K, Hummerich L, von Deimling A, Reifenberger G, Lichter P. Identification of novel oligodendroglioma-associated candidate tumor suppressor genes in 1p36 and 19q13 using microarray-based expression profiling. *Int J Cancer* 2006;119: 792–800.
36. Morris ZS, McClatchey A. Aberrant epithelial morphology and persistent epidermal growth factor receptor signaling in a mouse model of renal carcinoma. *Proc Natl Acad Sci USA* 2009;106:9767–72.
37. Sun CX, Robb VA, Gutmann DH. Protein 4.1 tumor suppressors: getting a FERM grip on growth regulation. *J Cell Sci* 2002; 115:3991–4000.
38. Kawano S, Ikeda W, Kishimoto M, Ogita H, Takai Y. Silencing of ErbB3/ErbB2 signaling by immunoglobulin-like Necl-2. *J Biol Chem* 2009;284:23793–805.
39. Doherty P, Walsh FS. CAM-FGF receptor interactions: a model for axonal growth. *Mol Cell Neurosci* 1996;8:99–111.
40. Surace EI, Lusis E, Murakami Y, Scheithauer BW, Perry A, Gutmann DH. Loss of tumor suppressor in lung cancer-1 (TSLC1) expression in meningioma correlates with increased malignancy grade and reduced patient survival. *J Neuropathol Exp Neurol* 2004;63:1015–27.

Osteoplastic ameloblastoma: a case report and literature review

Yuko Itoh, DDS,[a] Hirokazu Nakahara, DDS, PhD,[b] Ryota Itoh, MD, PhD,[a] Akihiko Ito, MD, PhD,[c] and Takao Satou, MD, PhD,[d] Osaka, Japan
KINKI UNIVERSITY

Ameloblastoma with bone formation is rare. We report a case of a 55-year-old woman with ameloblastoma accompanied by prominent osteoplasia. Histopathological examination exhibited an abundant stromal component between tumor nests. Therefore, she was diagnosed as the desmoplastic variant, except for the numerous bone trabeculae. The distinction between new bone formation and invasion of the bone marrow poses a problem. A thin rim of fibrous bone that can be accentuated by Masson-trichrome staining suggests the former. (Oral Surg Oral Med Oral Pathol Oral Radiol 2012;113:e23-e28)

During odontogenesis, enamel is formed by the odontogenic epithelium, whereas the dentin, cementum, dental pulp, and periodontal ligament are formed by the odontogenic ectomesenchyme.

Benign odontogenic tumors can be classified into 3 categories: odontogenic epithelium, mesenchyme/odontogenic ectomesenchyme, and odontogenic epithelium with odontogenic ectomesenchyme. Ameloblastomas are categorized as odontogenic epithelium tumors. They form nests consisting of peripheral embryologic ameloblasts and a central reticulum, showing a similar morphology to the enamel organ.[1] Despite being categorized as benign tumors, ameloblastomas have a high recurrence rate and should be treated radically.[2] They are classified into solid/multicystic type, extraosseous/peripheral type, desmoplastic type, and unicystic type according to the 2005 histologic classification of tumors by the World Health Organization (WHO). Among these clinicopathological entities, desmoplastic ameloblastoma is a relatively newly reported variant added since the 1992 histologic classification of tumors by WHO, and shows characteristic features of a predilection for the anterior mandibular region and a prominent desmoplastic stroma. The desmoplastic variant of ameloblastoma was reported to be accompanied by osteoplasia.[3-15]

[a]Assistant Professor, Department of Pathology, Kinki University, Osaka, Japan.
[b]Associate Professor, Department of Oral and Maxillofacial Surgery, Kinki University, Osaka, Japan.
[c]Professor, Department of Pathology, Kinki University, Osaka, Japan.
[d]Professor, Division of Hospital, Pathology, Kinki University, Osaka, Japan.
Received for publication Feb 17, 2011; accepted for publication Apr 21, 2011.

2212-4403/$ - see front matter
doi:10.1016/j.tripleo.2011.04.047

In this article, we report a new case of ameloblastoma accompanied by prominent osteoplasia and review previous case reports to investigate the clinical features, radiographs, histologic variants, and outcomes.

CASE REPORT

In 1999, a 55-year-old woman was referred to the Department of Oral and Maxillofacial Surgery of Kinki University Hospital with a complaint of swelling in the anterior mandible. She had noticed a small tumor on the right mandible 3 years previously, but was followed at a local hospital under the diagnosis of a bone fracture. She had suffered from rheumatoid arthritis since she was 40 years old. She underwent surgery for an unspecified brain tumor at 42 years of age.

In the oral cavity, broad swelling was observed on the buccal aspects of the mandible in the 33 to 46 region. The overlying mucosa appeared normal (Fig. 1). Panoramic radiography revealed an ill-defined trabeculalike opacity in the 35 to 46 region (Fig. 2). An ambiguous radiolucency was also observed. Teeth 44 and 45 were absent. There was root displacement of 2 and 3. Resorption was present at the roots of 31, 32, and 41 to 43. Computed tomography demonstrated reticular or ground glass sclerotic changes with a lack of periosteal reaction. A cystic radiolucent lesion was recognized. Fibrous dysplasia and an ossifying fibroma were suspected, as well as an epithelial odontogenic tumor and a desmoplastic ameloblastoma (Fig. 3). Magnetic resonance imaging was performed and the tumor displayed hypointensity on T1-weighted or T2-weighted scans. A cystic hyperintense area was also observed on T2-weighted scans. A fibrous tumor (e.g., metastatic tumor or fibrous dysplasia) was suspected (Fig. 4).

Under the clinical diagnosis of a mandibular tumor, an incisional biopsy was performed and the pathologic diagnosis was odontogenic fibroma at that time. An enucleation was performed under general anesthesia. Three fragments of 3.0, 1.0, and 0.8 cm in diameter were submitted for pathologic examination. Microscopic examination revealed epithelial tumor islands (Fig. 5). Columnar cells with a clear cytoplasm at the periphery of the islands showed palisading. The nuclei of

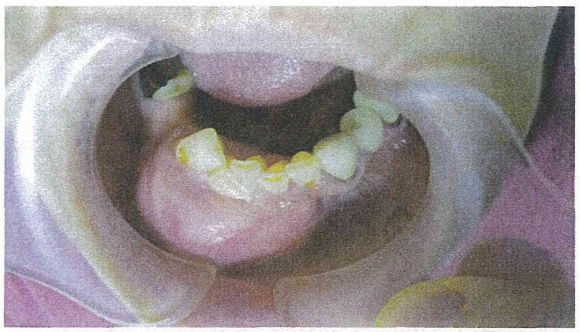

Fig. 1. Intraoral photograph.

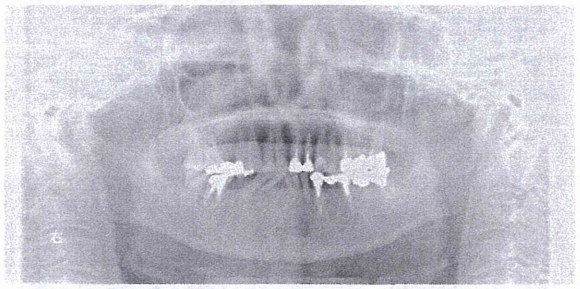

Fig. 2. Panoramic radiograph.

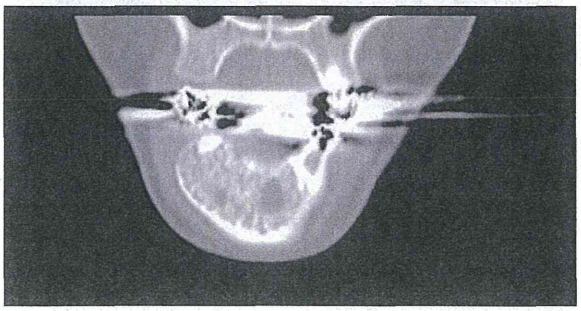

Fig. 3. Computed tomography coronal image.

these cells showed reversed polarity or localization at the opposite side to the basement membrane (Fig. 6). Cords of epithelium that appeared strangulated by stroma were also observed (Fig. 7). Nuclear atypism was not apparent. Necrosis and neural invasion were not recognized. The tumor islands were separated by an abundant stroma of fibrous connective tissue consisting of collagen fibers and fibroblast-like cells (Fig. 8). Inflammatory cell infiltration was almost imperceptible. Numerous bone trabeculae were present in the stroma. Osteoblasts partly outlined the surface of the trabeculae (Fig. 8).

Masson-trichrome staining revealed red fibrous bone at the periphery of the trabecular bone, which showed blue staining (Fig. 9). Thick fibers were inserted into the bone from the surrounding connective tissue (Fig. 10). The final diagnosis was desmoplastic ameloblastoma accompanied by prominent bone formation. There is currently no sign of recurrence at 12 months postoperatively.

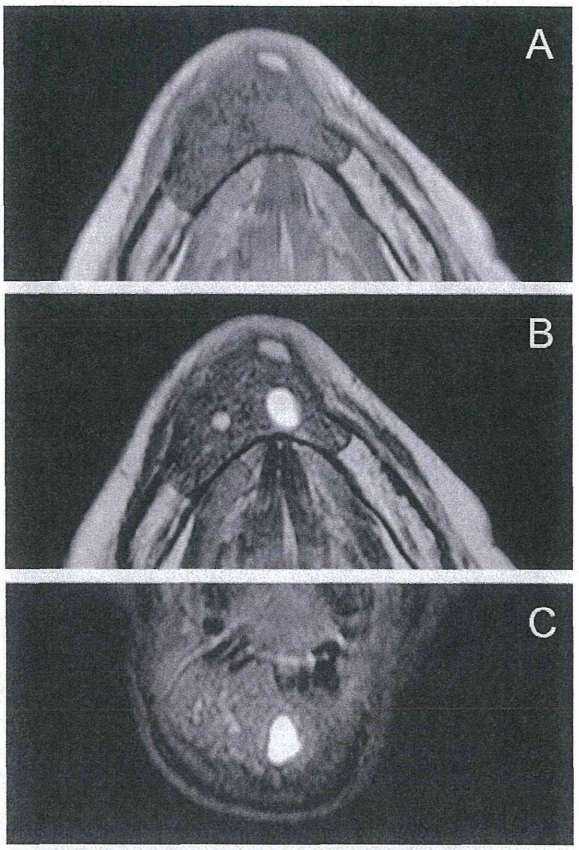

Fig. 4. Magnetic resonance images. **A**, T1-weighted axial image. **B**, T2-weighted axial image. **C**, Short-T1 inversion recovery sequence coronal image.

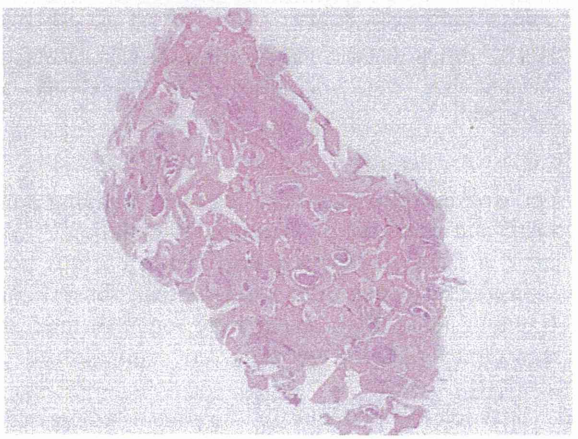

Fig. 5. Histopathologic findings (hematoxylin-eosin stain, magnification ×0.35). Epithelial tumor islands and an abundant stroma with numerous bone trabeculae are observed.

LITERATURE REVIEW

Previous case reports were retrieved from the databases MEDLINE (English literature) and Ichusi-Web (Japanese literature). The acceptance criteria were

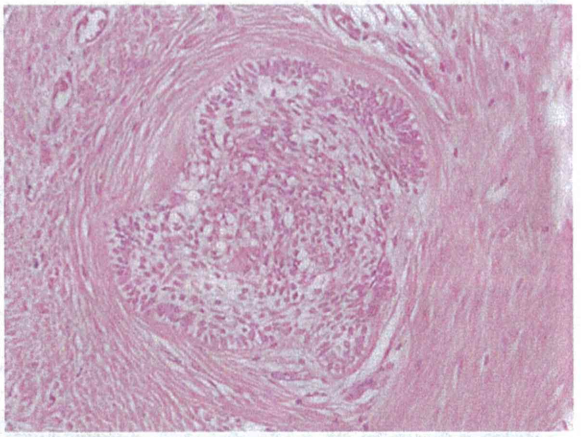

Fig. 6. Histopathologic findings (hematoxylin-eosin stain, magnification ×14). Tumor islands showing peripheral palisading and reversed nuclear polarity are observed.

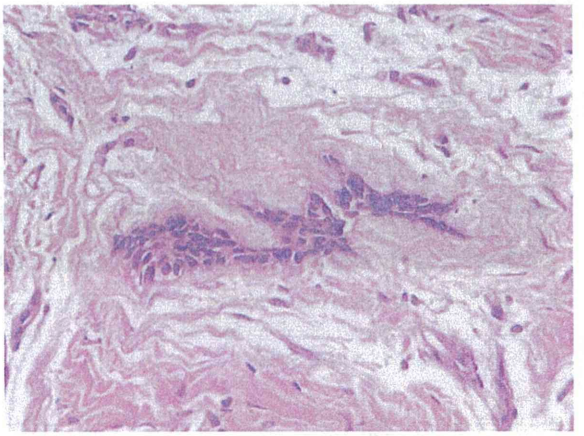

Fig. 7. Histopathologic findings (hematoxylin-eosin stain, magnification ×28). Strangulated cords of epithelium are observed.

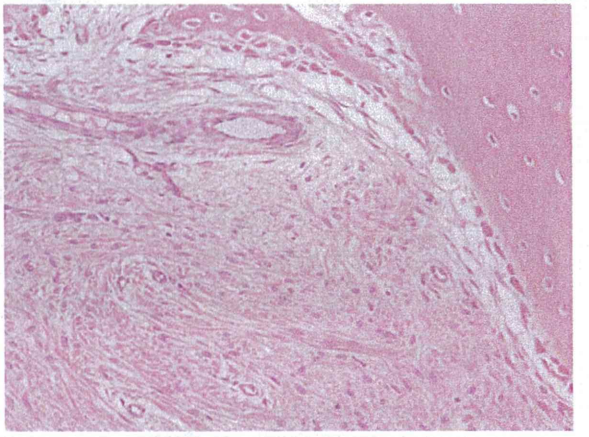

Fig. 8. Histopathologic findings (hematoxylin-eosin stain, magnification ×14). Stroma consisting of collagen fibers and fibroblastlike cells is observed.

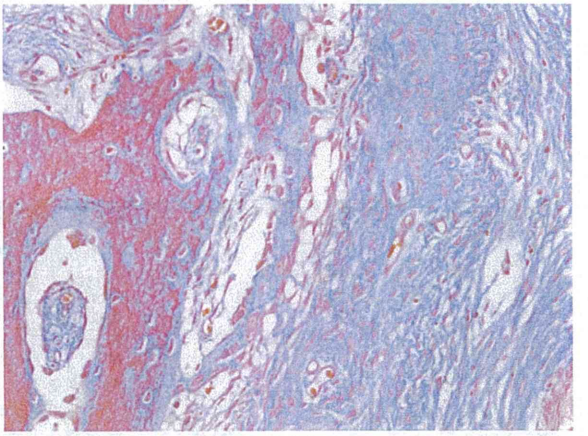

Fig. 9. Histopathologic findings (Masson-trichrome stain, magnification ×14). Red fibrous bone at the periphery of blue trabecular bone is observed.

(1) well-described clinical features, imaging findings, and microscopic pictures or pathologic findings; and (2) prominent osteoplasia to exclude bone invasion or nonspecific osteosclerosis of the surrounding bone. Eight cases were found in total and the clinicopathological data are summarized in Table I.

Including the present case, the patients comprised 5 males and 4 females who ranged in age from 28 to 74 years. The most common chief complaint was a mass or swelling. The mandible was involved in 6 cases and the maxilla in 3 cases. In one case, a tumor was found from the left molar to the right premolar and in another case from 33 to 34 by direct inspection, but there were no descriptions about the radiographic locations.[4,6] At least the anterior region seemed to be involved in all cases.

In radiographs, the lesions exhibited trabeculalike radiopacity in 5 cases, rough radiopacity in 1 case, a honeycomb pattern in 1 case, and multilocular radiolucency with floccular radiopacities in 1 case. The borders were ill defined, in whole or part, in 5 cases and well defined in 1 case.

The clinical diagnosis was a benign tumor in 3 cases, a fibro-osseous lesion in 2 cases, and an ameloblastoma in 1 cases. A biopsy was taken in only 2 case. The pathologic diagnosis was the desmoplastic variant in 2 cases. Seven cases were reported before the publication of the 1992 WHO classification, and all the cases seemed to be categorized as the desmoplastic variant from microscopic photographs or pathologic findings.

One case showed a recurrence after 9 years owing to incomplete treatment.[8] Among 6 patients who under-

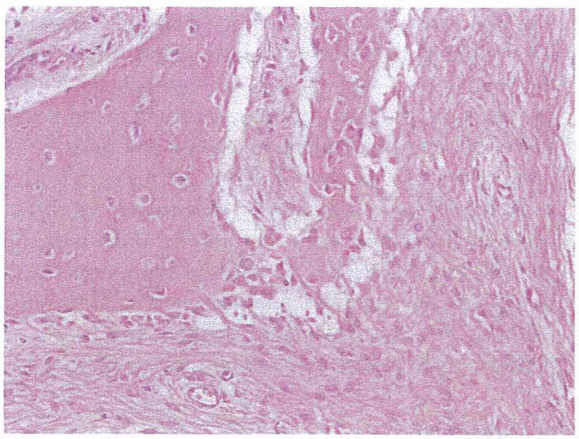

Fig. 10. Histopathologic findings (hematoxylin-eosin stain, magnification ×14). Insertion of thick fibers into the bone is observed.

went a resection, follow-up data (from 14 months to 4 years) were available for 5 patients and no recurrence was reported.

DISCUSSION

Ameloblastoma accompanied by prominent osteoplasia is rare, and only 8 previous case reports since 1983 in the English and Japanese literature fulfilled the criteria described previously.

The clinical symptoms of swelling or a mass are similar to conventional ameloblastoma. Some case reports were omitted because the osteoplasia was localized or a detailed description was absent.[11-15] All the reported cases were accompanied by desmoplasia and seemed to be categorized as desmoplastic ameloblastoma. Furthermore, the anterior region of the mandible or maxilla was involved in all cases, and this is a characteristic of desmoplastic ameloblastoma.[16]

In radiographs, only 1 case showed radiolucency, which is seen in classic ameloblastoma.[2] The other cases showed mixed radiolucent/radiopaque appearances, resembling typical desmoplastic ameloblastoma, despite the prominent osteoplasia. For this reason, it is suggested that new bone formation can be detected by extensive investigation of typical desmoplastic ameloblastoma.[10,17] There is another view that the highly invasive nature of desmoplastic ameloblastomas leads to invasion of the bone marrow space, which causes unique radiographic features and an ill-defined border.[14,18] In fact, desmoplastic ameloblastoma with peripheral osteoplasia has a well-defined border rather than an ill-defined border.[19] Peripheral-type desmoplastic ameloblastoma, in which invasion to the bone marrow space is absent by definition, was recently reported.[20,21] Although there were no detailed de-

Table I. Clinicopathologic features

Year	*Source*	*Age, y*	*Gender*	*Location*	*Clinical presentation*	*Radiograph*	*Margin*	*Clinical diagnosis*	*Variant*	*Treatment*	*Outcome*
1983	Uji et al.	28	M	33-35	Swelling	Punctate and trabeculalike opacity	Ill defined	Ameloblastoma	ND	Seg	3 y 3 m NED
1986	Okada et al.	31	F	ND	Swelling	Trabeculalike opacity	ND	Fibro-osseous lesion	ND	Par	2 y 8 m NED
1987	Fujimoto et al.	72	M	31-38, 41-46	Swelling	Punctate and trabeculalike opacity with unilocular radiolucency	Ill defined	Mandibular tumor	ND	Seg	2 y 8 m NED
1990	Takeda et al.	39	M	ND	Swelling	ND	ND	Fibro-osseous lesion	ND	Seg	14 m NED
1991	Takemoto et al.	49	M	22-25	Mass	Rough opacity	ND	Benign tumor	ND	Par	4 y NED
1991	Ishigami et al.	64	F	22-26	Mass	Honeycomb appearance	Well defined	Benign tumor	ND	Enuc + cur	ND
1992	Nakashima et al.	74	F	11-13	Swelling	Trabeculalike opacity	Ill defined	Benign tumor	ND	Enuc	4 y NED
1992	Phillipsen et al.	55	M	33-37	Slow-growing firm lesion	Multilocular radiolucency with flocular radiopacities	Well/Ill defined	ND	DA	Mar	ND
2010	Present study	55	F	31-35, 41-46	Mass	Trabeculalike opacity	Ill defined	Mandibular tumor	DA	Enuc	12 m NED

cur, curettage; *DA*, desmoplastic ameloblastoma; *Enuc*, enucleation; *mar*, marginal block resection; *par*, partial resection; *seg*, segmental resection.

scriptions about radiographs, a mixed radiolucent/radiopaque appearance was not mentioned.

Only 1 of the 9 cases could be diagnosed as ameloblastoma by diagnostic imaging. In cases with a fibro-osseous lesion in the bones of the jaw, a biopsy should be taken.[22] In such biopsies, the calcified tissue in odontogenic tumors can be enamel, dentin, cementum, or bone tissue. Enamel disappears during the decalcification process, although some acidophilic material with or without a prism boundary is occasionally left. Neoplastic enamel formation is relatively rare and almost always requires the preexistence of dentin. Dentin has tubules and a circular structure. Both cementum and bone tissue are derived from the ectomesenchyme, and it is therefore difficult to distinguish between these 2 calcified tissues. The prototypic cementum is adherent to the root of the tooth, has a solid form, and is devoid of a lamellar structure. In the present case, most of the calcified tissue was separated from the tooth and had a trabecular form with a lamellar structure, suggesting that the calcified tissue was bone.

The invasive nature of desmoplastic ameloblastoma into the bone marrow space obscures the issue of whether the bone tissue in the tumor is preexisting bone trabeculae or osteoplasia. Because the tumor border is ill defined in radiographs, the tumor size can be underestimated. In the present case, the presence of peripheral uncalcified fibrous bone gave the impression of newly forming bone rather than destroyed trabecular bone. Fibrous bone can be recognized using Masson-trichrome staining. In addition, calcified trabeculae show morphologic abnormalities, such as fusion or thickening, and dense osteoblasts, indicating newly forming bone.

Desmoplastic ameloblastoma has 2 characteristic features, namely a fibrous stoma and squeezed tumor islands,[10] and a biopsy specimen may not contain tumor islands similar to the enamel organ. Without knowledge that ameloblastoma can be accompanied by osteoplasia and with limited observations from a biopsy, pathologists may misdiagnose this lesion as odontogenic fibroma showing strands of epithelium and calcification. This differential diagnosis is important because the first choice for odontogenic fibroma is enucleation, unlike ameloblastoma.

It is well known that classic ameloblastoma or desmoplastic ameloblastoma can recur after inadequate excision.[16,22] This is also the case for ameloblastoma accompanied by osteoplasia.[8] The present patient received only enucleation and needed long-term follow-up. At least, there were no reports of recurrence after radical treatment among the 8 previous cases.

The pathogenesis of the bone formation is not clear. Tumor growth factor-beta is expressed in the tumor cells of desmoplastic ameloblastoma, and may be associated with osteoplasia, rather than only desmoplasia.[23] Interestingly, there is a case report of ameloblastic carcinoma with prominent osteoplasia.[24] Bone morphologic proteins may play a role in a similar way to heterotopic ossification in extraoral lesions.[25] Further studies on this type of tumor are necessary. However, use of immunostaining methods may be difficult because decalcification is required for bone sectioning and this process severely attenuates the immunogenicity. Newly developed techniques, such as film-transfer methods like the Kawamoto method, may solve this problem and provide insights into the pathogenesis.

REFERENCES

1. Black CC, Addante RR, Mohila CA. Intraosseous ameloblastoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;110:585-92.
2. Reichart PA, Philipsen HP, Sonner S. Ameloblastoma: biological profile of 3677 cases. Eur J Cancer B Oral Oncol 1995;31B:86-99.
3. Uji Y, Kodama K, Sakamoto A, Taen A. An ameloblastoma with interesting histological findings. Jpn J Oral Maxillofac Surg 1983;29:1512-9.
4. Okada Y, Sugimura M, Ishida T. Ameloblastoma accompanied by prominent bone formation. J Oral Maxillofac Surg 1986;44:555-7.
5. Fujimoto E, Muroki T, Sakashita H, Nakao J, Tamai K. An ameloblastoma with interesting radiographic and histological findings. Jpn J Oral Maxillofac Surg 1987;33:810-7.
6. Takeda Y, Kuroda M, Suzuki A. Ameloblastoma with prominent stromal ossification. Pathol Int 1990;40:780-4.
7. Takemoto T, Yamashita T, Ito A, Kinoshita Y, Mizuno K, Takai Y, et al. A case of ameloblastoma of maxilla with bone tissue in the tumor. Jpn J Oral Maxillofac Surg 1991;37:234-9.
8. Ishigami T, Sugihara K, Uchiyama T, Yamaguchi T, Fukumoto H, Makizumi R, et al. Ameloblastoma of the maxilla with bone tissue in the tumor: report of a case. Jpn J Oral Maxillofac Surg 1991;37:2103-4.
9. Nakashima T, Nodai T, Yamada N, Fukuyama H. A case of maxillary ameloblastoma containing bone tissue in an old woman. Jpn J Oral Maxillofac Surg 1992;38:146-7.
10. Philipsen HP, Ormiston IW, Reichart PA. The desmo- and osteoplastic ameloblastoma. Histologic variant or clinicopathologic entity? Case reports. Int J Oral Maxillofac Surg 1992;21:352-7.
11. Waldron CA, el-Mofty SK. A histopathologic study of 116 ameloblastomas with special reference to the desmoplastic variant. Oral Surg Oral Med Oral Pathol 1987;63:441-51.
12. Ng KH, Siar CH. Desmoplastic variant of ameloblastoma in Malaysians. Br J Oral Maxillofac Surg 1993;31:299-303.
13. Ludvikoya M, Michal M, Zamecnik M, Houba R, Sedlacek P, Csillagi E, et al. Desmoplastic ameloblastoma. Cesk Patol 1998;34:94-8.
14. Thompson IO, van Rensburg LJ, Phillips VM. Desmoplastic ameloblastoma: correlative histopathology, radiology and CT-MR imaging. J Oral Pathol Med 1996;25:405-10.
15. Effiom OA, Odukoya O. Desmoplastic ameloblastoma: analysis of 17 Nigerian cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:e27-31.
16. Sun ZJ, Wu YR, Cheng N, Zwahlen RA, Zhao YF. Desmoplastic ameloblastoma—a review. Oral Oncol 2009;45:752-9.
17. Philipsen HP, Reichart PA, Takata T. Desmoplastic ameloblastoma (including "hybrid" lesion of ameloblastoma). Biological

profile based on 100 cases from the literature and own files. Oral Oncol 2001;37:455-60.
18. Takata T, Miyauchi M, Ito H, Ogawa I, Kudo Y, Zhao M, et al. Clinical and histopathological analyses of desmoplastic ameloblastoma. Pathol Res Pract 1999;195:669-75.
19. Kawai T, Kishino M, Hiranuma H, Sasai T, Ishida T. A unique case of desmoplastic ameloblastoma of the mandible: report of a case and brief review of the English language literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999;87:258-63.
20. Curran AE, Byerly PD. Peripheral desmoplastic ameloblastoma: report of a rare case. J Oral Maxillofac Surg 2008; 66:820-5.
21. Smullin SE, Faquin W, Susarla SM, Kaban LB. Peripheral desmoplastic ameloblastoma: report of a case and literature review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008; 105:37-40.
22. Beckley ML, Farhood V, Helfend LK, Alijanian A. Desmoplastic ameloblastoma of the mandible: a case report and review of the literature. J Oral Maxillofac Surg 2002;60:194-8.
23. Takata T, Miyauchi M, Ogawa I, Kudo Y, Takekoshi T, Zhao M, et al. Immunoexpression of transforming growth factor beta in desmoplastic ameloblastoma. Virchows Arch 2000;436:319-23.
24. Arika T, Morita S, Nakajima M, Horii K, Okano H. Histopathological study of a malignant ameloblastoma associated with prominent new bone formation of the maxilla. Jpn J Oral Maxillofac Surg 1993;39:469-74.
25. Liu K, Tripp S, Layfield LJ. Heterotopic ossification: review of histologic findings and tissue distribution in a 10-year experience. Pathol Res Pract 2007;203:633-40.

Reprint requests:

Yuko Itoh, DDS
Department of Pathology
Kinki University
377-2 Ohnohigasi, Osakasayama
Osaka 589-8511, Japan
yukotaniguchi2011@yahoo.co.jp

J Oral Maxillofac Surg
70:1376-1379, 2012

Suppurative Arthritis of the Temporomandibular Joint Associated With Bisphosphonate: A Case Report

Akifumi Enomoto, PhD, DDS, Toshihiro Uchihashi,† Takako Izumoto,‡ Hirokazu Nakahara, PhD, DDS,§ and Suguru Hamada, PhD, DDS‖*

The prevalence of bisphosphonate-related osteonecrosis of the jaw (BRONJ) has recently increased, and this condition is difficult to manage.[1-3] A patient is diagnosed with BRONJ if the following 3 characteristics are present: *1*) current or previous treatment with a bisphosphonate (BP), *2*) exposed bone in the maxillofacial region that has persisted for more than 8 weeks, and *3*) no history of radiotherapy of the jaws.[4] BPs are potent inhibitors of osteoclastic bone resorption for the control of hypercalcemia associated with malignancy, multiple myeloma, metastatic bone disease, and bone loss resulting from breast cancer treatment. Other well-established indications are osteoporosis and Paget disease of bone.[5,6]

Suppurative arthritis of the temporomandibular joint (TMJ) is not common. It arises either from hematogenous spread of microorganisms through the highly vascularized synovial membrane or from direct extension of contiguous infection.[7,8] Several cases have been reported in the literature,[9-13] and most of them are associated with predisposing factors. Suppurative arthritis of the TMJ has multiple etiologies including trauma, head and neck infection, extraction of a third molar, TMJ arthrosis, or TMJ arthroscopy.

Suppurative arthritis of the TMJ associated with BP administration has not been previously reported. We present a rare case of suppurative arthritis of the TMJ associated with chronic BP treatment and describe our management strategy.

Received from the Department of Oral and Maxillofacial Surgery, Kinki University School of Medicine, Osaka-Sayama, Japan.

*Associate Professor.

†Resident.

‡Resident.

§Associate Professor.

‖Professor.

Address correspondence and reprint requests to Dr Enomoto: Department of Oral and Maxillofacial Surgery, Kinki University School of Medicine, 377-2, Onohigashi, Osaka-Sayama 589-8511, Japan; e-mail: enomotoa@med.kindai.ac.jp.

0278-2391/12/7006-0$36.00/0
doi:10.1016/j.joms.2011.06.215

Case Report

A 70-year-old Japanese man complaining of pain in the left TMJ and severely restricted mouth opening was referred to the Department of Oral and Maxillofacial Surgery at Kinki University School of Medicine, Osaka-Sayama, Japan, in November 2010. Obvious left-sided preauricular swelling was observed. Oral examination showed a maximal incisor opening of 10 mm. The visual analog scale score for TMJ pain on mouth opening was 8.0. Intraorally, the second and third molars of the left mandible showed periodontal disease, and the root surfaces were visible. The alveolar bone in the same region was exposed, and severe inflammation of the surrounding soft tissue was observed. Blood tests showed a C-reactive protein level of 15.1 mg/dL. His white blood cell count was 10,900/mm^3, and leukocytosis with polymorphonuclear left cell shift was evident.

Panoramic radiography showed no left condylar deformation and showed that the second and third molars of the left mandible had a periapical radiolucent region (Fig 1). The condylar head was present. Computed tomography showed little cortical erosion or periapical disease of the second and third molars of the left mandible. Magnetic resonance (MR) imaging showed a left condylar collection of intra-articular fluid with upper and lower capsular distension on the T2-weighted images. A homogeneous intermediate signal from the condylar head was evident on the proton density and T2-weighted images. MR classification of the bone marrow of the mandibular condyles was graded type I according to Sano and Westesson's classification (Fig 2).[14]

The patient's medical history included monthly intravenous infusion of zoledronate, a BP agent, for approximately 2 years, from April 2008 to March 2010, because of prostate carcinoma with distant bone metastasis. There was no recent history of TMJ trauma or invasive dental procedures. Before referral to our hospital, the patient had taken several types of antibiotics at the previous dental clinic.

We clinically diagnosed the present case as suppurative arthritis of the TMJ associated with BRONJ and treated the patient with intravenous broad-spectrum antibiotics (piperacillin and clindamycin). At the same time, aspiration of the left TMJ was performed with the patient under local anesthesia. Yellowish white fluid was obtained from the lower joint cavity and was sent for culture and histopathologic examination (Fig 3A). In addition, suppurative material obtained from the periodontal pocket at the exposed alveolar bone was sent for histopathologic examination. *Prevotella*

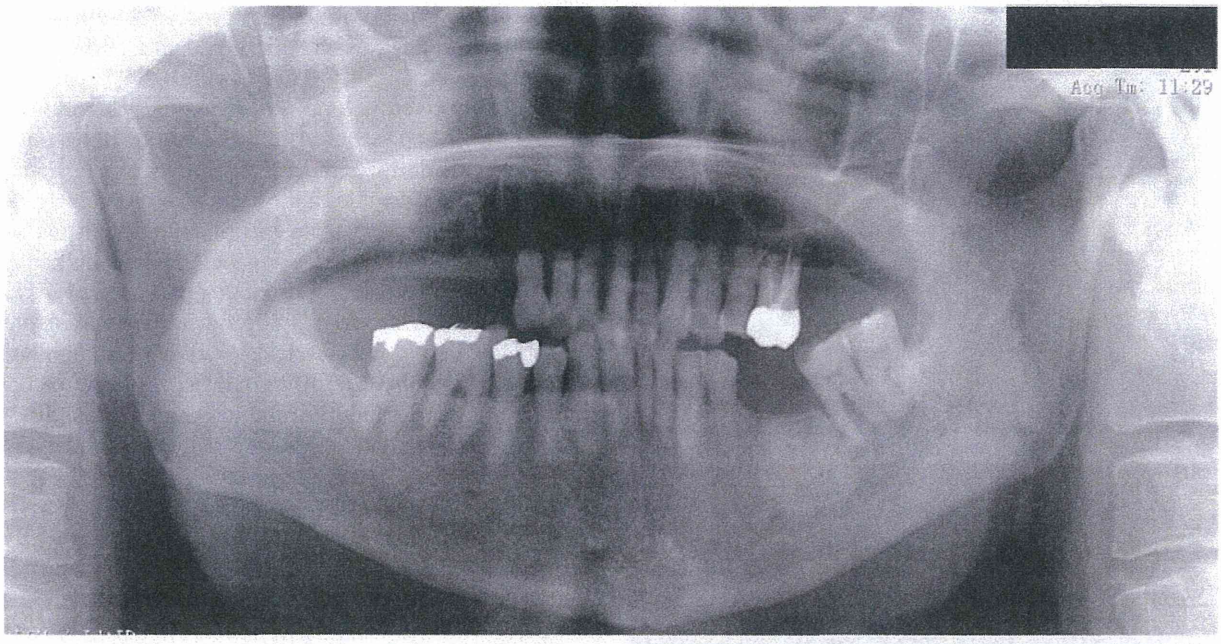

FIGURE 1. Panoramic radiograph at the initial presentation shows no deformity of the left condyle. The second and third molars of the left mandible showed periodontal disease and pathologic signs in the neighboring bone.

Enomoto et al. Suppurative Arthritis of BP-Associated TMJ. J Oral Maxillofac Surg 2012.

buccae, Haemophilus, and *Streptococcus* were cultured from both the lower joint cavity fluid and the material from the periodontal pocket. The *Streptococcus* was found to be multidrug-resistant viridans group streptococcus (MDRVS), and this organism was resistant to ampicillin, levofloxacin, gatifloxacin, azithromycin, clarithromycin, or clindamycin but was susceptible to meropenem and vancomycin. On the basis of these findings, the patient's antibiotic therapy was changed to intravenous meropenem. In addition, a preauricular lateral incision that reached the lower joint cavity was made, and daily irrigation was performed. The lower joint cavity was then drained by placement of a gauze drain. The periodontal pockets of the second and third molars of the left mandible were irrigated intraorally, and the irrigation was continued until the fluid was clear. The second and third molars of the left mandible fell out after 2 months of irrigation. The visual analog scale score for TMJ pain on mouth opening improved to 1.0. Furthermore, biopsy of the alveolar tissue was performed to rule out a primary malignancy and make a definitive diagnosis. Histopathologic examination showed mandibular sequestration with no prostate metastatic tissue.

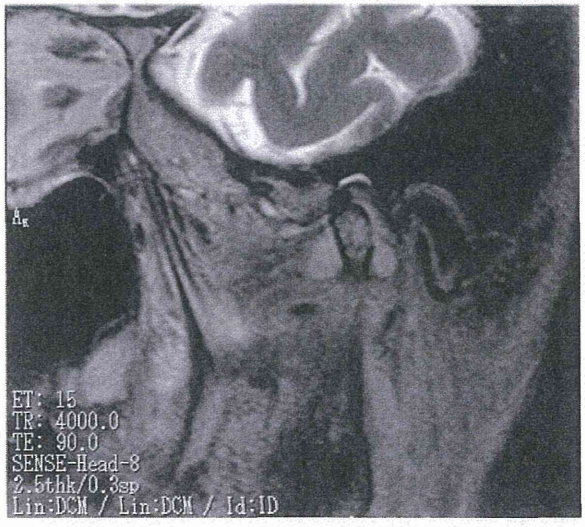

FIGURE 2. Magnetic resonance imaging showed a collection of intra-articular fluid with upper and lower capsular distension on T2-weighted images.

Enomoto et al. Suppurative Arthritis of BP-Associated TMJ. J Oral Maxillofac Surg 2012.

After 3 months, the permanent fistula in the TMJ was still present (Fig 3B), and a small amount of exposed bone was noted in the cavities of the left mandible where the 2 teeth had fallen out during irrigation. However, there was no evidence of acute infection, and the patient continued to receive local irrigation.

For this presentation, our research was approved by the review board of Kinki University School of Medicine.

Discussion

This is the first report of suppurative arthritis of the TMJ associated with chronic BP therapy. Intravenous BP therapy has been prescribed to treat patients with several different cancers that have metastasized to the bone or that are primarily present in bone. Patients with metastatic prostate cancer and other metastatic solid tumors have also been treated with intravenous BPs.

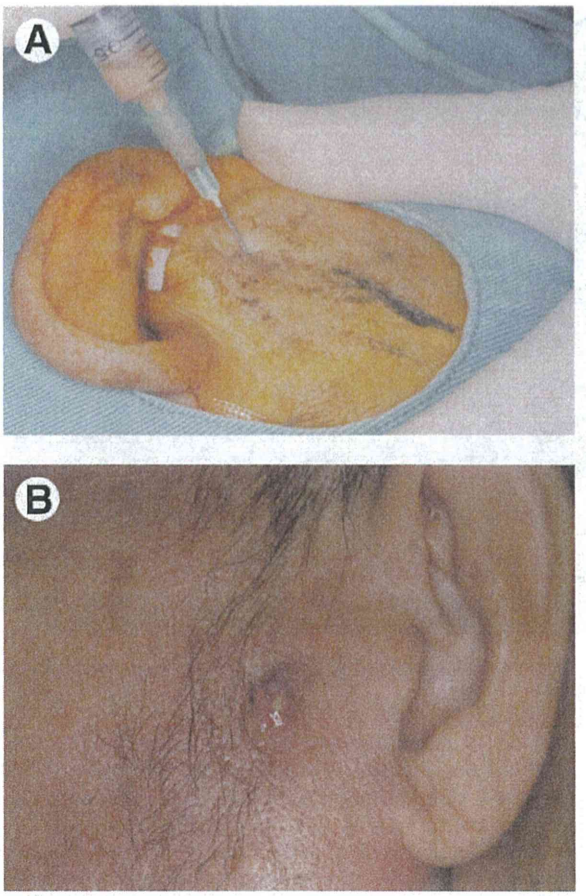

FIGURE 3. *A*, Yellowish white joint fluid was aspirated from the area with lower capsular distension of the TMJ. *B*, The permanent fistula at the TMJ was still present, even after the symptoms of inflammation had disappeared.

Enomoto et al. Suppurative Arthritis of BP-Associated TMJ. J Oral Maxillofac Surg 2012.

No clear consensus has been established on the optimal management of suppurative arthritis of the TMJ because there have only been a few reported cases.[7] Antibiotic therapy, adequate drainage, and joint immobilization are considered important components of treatment. In the acute stage, intravenous antibiotics should be started immediately when suppurative arthritis has been diagnosed. Recent studies of TMJ infection have shown that microorganisms are most commonly seeded hematogenously.[7,8] The main pathogens that have been isolated in suppurative arthritis of the TMJ include *Staphylococcus aureus*, *Neisseria*, *Haemophilus influenzae*, and *Streptococcus*.[8,11] Broad-spectrum antibiotics such as penicillin or cephalosporins are commonly used. These agents are given intravenously at first, but their administration can be changed to an oral regimen after the joint infection is under control. Once the results of the culture and antibiotic sensitivity tests have been obtained, the choice of antibiotics should be modified. In this case MDRVS was identified as a pathogen for suppurative arthritis.[15] This was probably because the patient received several different types of antibiotics for BRONJ before being referred to our department. Intravenous doripenem and vancomycin were suitable and effective. In addition, continuous local irrigation with saline solution from the preauricular fistula was performed after the symptoms of inflammation had disappeared. It has been reported that microorganisms can remain in the synovial fluid and are not completely eradicated by the bactericidal action of antibiotics.[16] Therefore sterilization of the joint space requires both antibiotics and removal of the infected synovial fluid.

In our case the exudate obtained from the periodontal pocket at the exposed alveolar bone of the second and third molars of the left mandible was sent for culture and histopathologic examination. The same type of MDRVS was also cultured in the irrigation fluid from the TMJ. Thus the route of infection could be considered hematogenous in this case. The second and third molars of the left mandible showed periodontal disease, and the alveolar bone in the same region was exposed. Inflammation of the surrounding soft tissue was observed. However, computed tomography, MR imaging, and clinical findings showed no symptoms of inflammation in the tissue between the infected molars and TMJ. Therefore it is doubtful that the route of infection was contiguous or by direct inoculation, especially because the hematogenous spread of bacteria was highly probable in this case. The synovium, which has high vascularity and no limiting basement membrane, was particularly vulnerable to hematogenous spread and induced suppurative arthritis of the TMJ associated with BP administration. A small amount of bacteria may not be sufficient to induce symptoms of suppurative arthritis of the TMJ, although bacteria are frequently present in the synovial fluid of the TMJ.[17] In this case, when immunologic balance in the host was compromised, symptoms of suppurative arthritis of the TMJ were detected. The infection subsequently progressed into the lower joint cavity surrounded by the synovial membrane, which was observed as joint fluid on MR images. The inflammation progressed into soft tissue at the preauricular area through the prominent synovial membrane.

The original infection was BRONJ. The infection of the TMJ joint due to BRONJ may not become sterile after drainage, as long as there is osteonecrosis of the mandible. Therefore the clinical treatment objectives could be to eliminate pain, control infection of the hard and soft tissue, and minimize progression or occurrence of bony necrosis to avoid TMJ adhesions. The treatment should involve the use of frequent irrigation combined with antibiotics. Current guide-