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

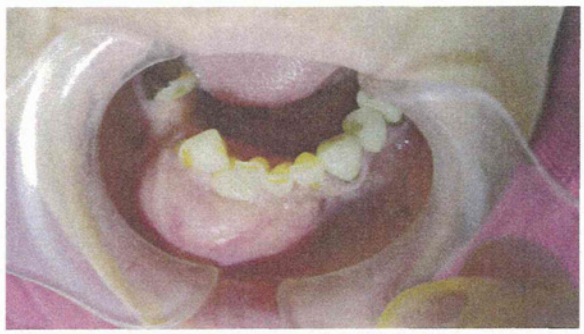


Fig. 1. Intraoral photograph.

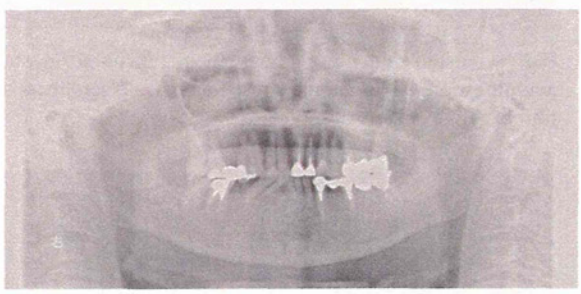


Fig. 2. Panoramic radiograph.

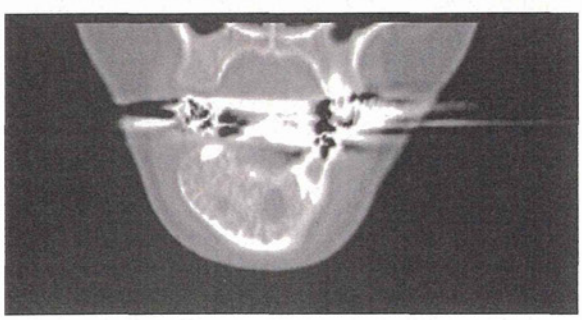


Fig. 3. Computed tomography coronal image.

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.

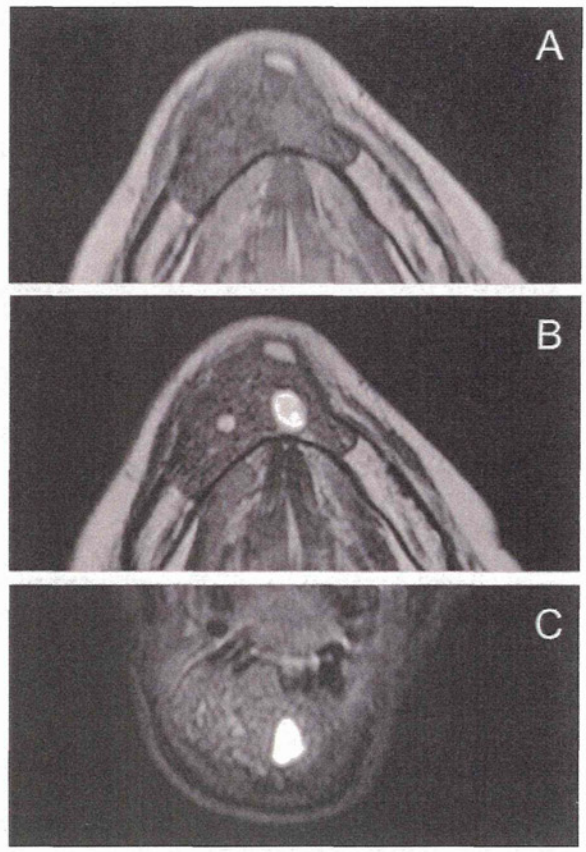


Fig. 4. Magnetic resonance images. **A**, T1-weighted axial image. **B**, T2-weighted axial image. **C**, Short-T1 inversion recovery sequence coronal image.

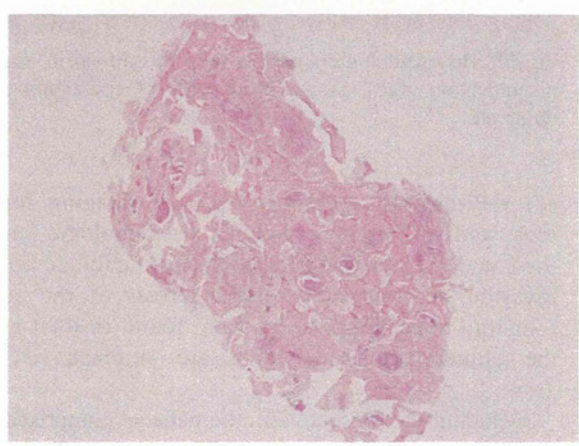


Fig. 5. Histopathologic findings (hematoxylin-eosin stain, magnification ×0.35). Epithelial tumor islands and an abundant stroma with numerous bone trabeculae are observed.

LITERATURE REVIEW

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

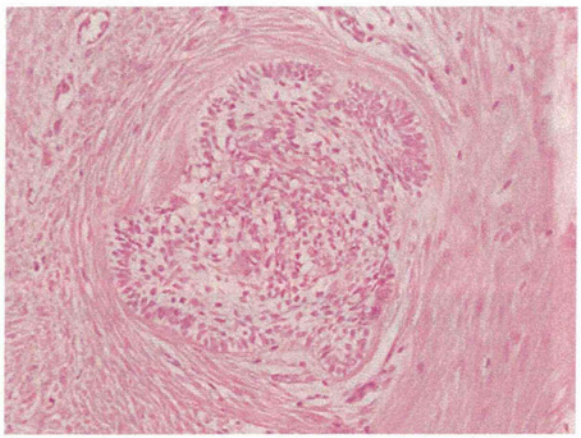


Fig. 6. Histopathologic findings (hematoxylin-eosin stain, magnification ×14). Tumor islands showing peripheral palisading and reversed nuclear polarity are observed.

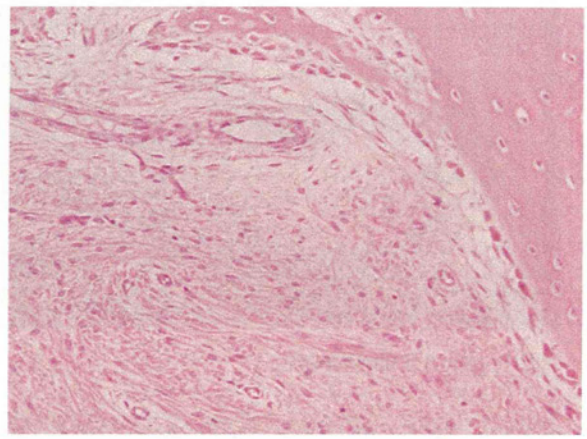


Fig. 8. Histopathologic findings (hematoxylin-eosin stain, magnification ×14). Stroma consisting of collagen fibers and fibroblastlike cells is observed.

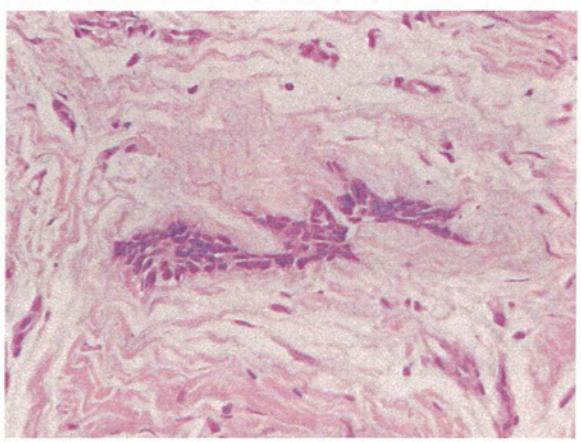


Fig. 7. Histopathologic findings (hematoxylin-eosin stain, magnification ×28). Strangulated cords of epithelium are observed.

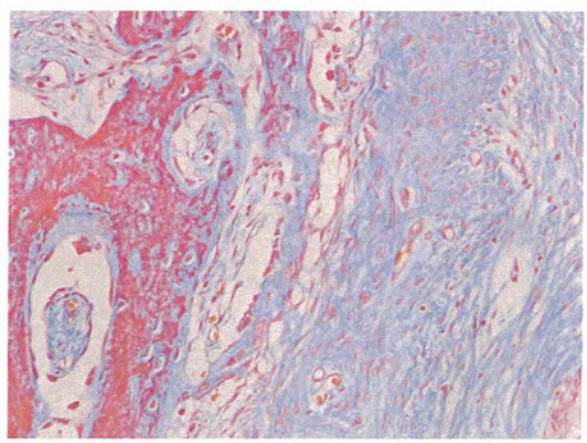


Fig. 9. Histopathologic findings (Masson-trichrome stain, magnification ×14). Red fibrous bone at the periphery of blue trabecular bone is observed.

(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-

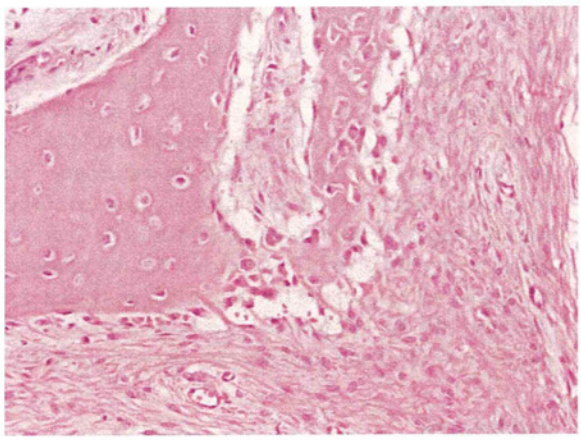


Fig. 10. Histopathologic findings (hematoxylin-eosin stain, magnification ×14). Insertion of thick fibers into the bone is observed.

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 floccular 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*

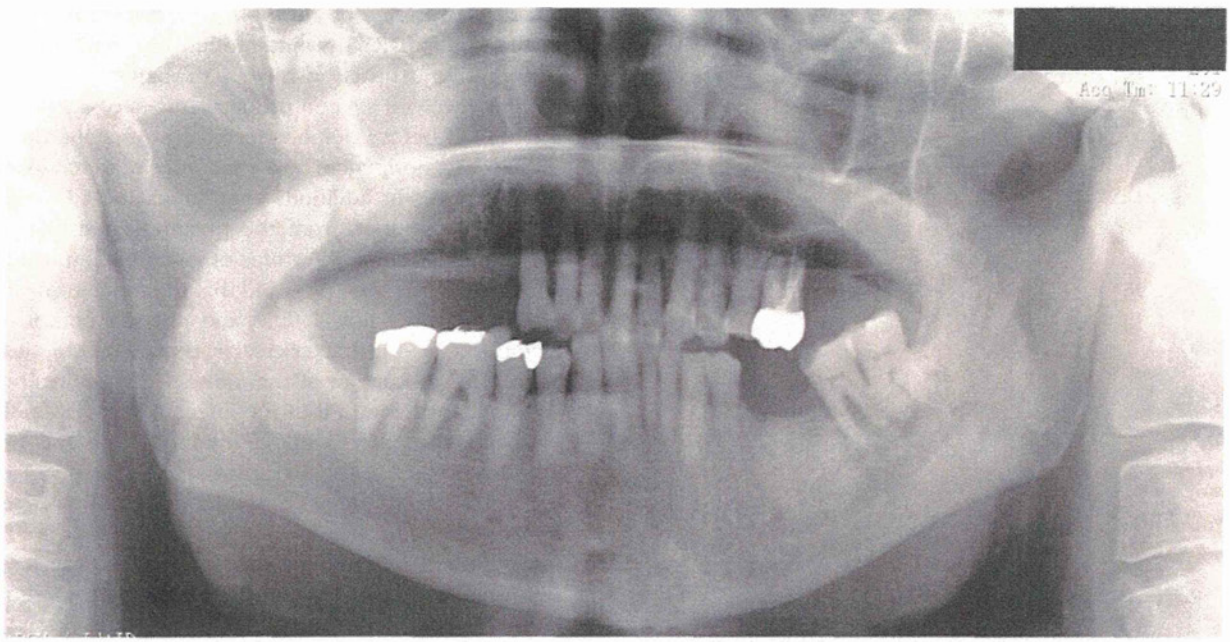


FIGURE 1. Panoramic radiograph at the initial presentation shows no deformity of the left condyle. The second and third molars of the left mandible showed periodontal disease and pathologic signs in the neighboring bone.

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.

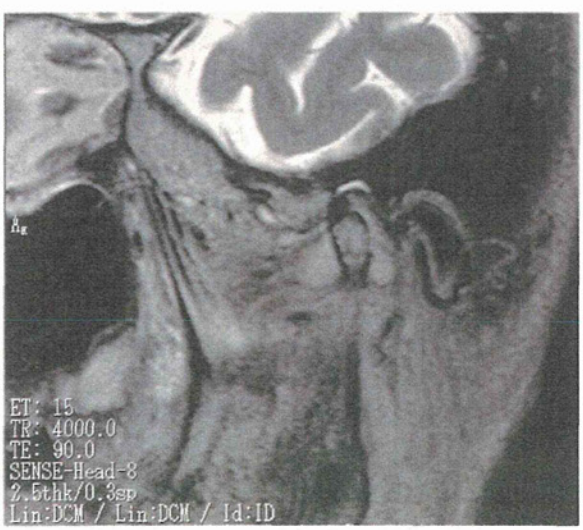


FIGURE 2. Magnetic resonance imaging showed a collection of intra-articular fluid with upper and lower capsular distension on T2-weighted images.

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.

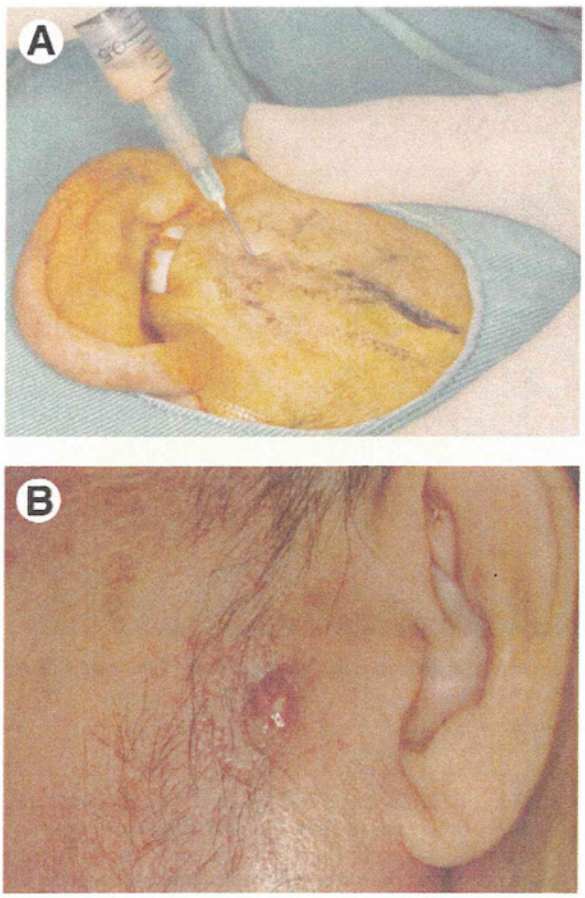


FIGURE 3. *A*, Yellowish white joint fluid was aspirated from the area with lower capsular distension of the TMJ. *B*, The permanent fistula at the TMJ was still present, even after the symptoms of inflammation had disappeared.

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-

lines discourage tooth extraction in patients at high risk of BRONJ.[18] However, tooth decay with periapical or periodontal disease causes infection and is a major risk factor for BRONJ.[19] Therefore extraction of infected teeth may be preferable.[20,21] We continued to irrigate the periodontal pockets of the second and third molars even after the teeth fell out, and invasive surgical tooth extraction was avoided.

For suppurative arthritis of the TMJ caused by BRONJ, the diagnosis should be determined by the clinical presentation, imaging findings, joint fluid analysis, and laboratory findings. Adequate antibiotic therapy and joint immobilization can be recommended in the acute stage by examination of the suppurative material. Continuous local irrigation at the TMJ from the preauricular fistula could be necessary, even after the symptoms of inflammation have disappeared.

References

1. Filleul O, Crompot E, Saussez S: Bisphosphonate-induced osteonecrosis of the jaw: A review of 2,400 patient cases. J Cancer Res Clin Oncol 136:1117, 2010
2. Nawata H, Soen S, Takayanagi R, et al: Guidelines on the management and treatment of glucocorticoid-induced osteoporosis of the Japanese Society for Bone and Mineral Research (2004). J Bone Miner Metab 23:105, 2005
3. Yoneda T, Hagino H, Sugimoto T, et al: Bisphosphonate-related osteonecrosis of the jaw: Position paper from the Allied Task Force Committee of Japanese Society for Bone and Mineral Research, Japan Osteoporosis Society, Japanese Society of Periodontology, Japanese Society for Oral and Maxillofacial Radiology, and Japanese Society of Oral and Maxillofacial Surgeons. J Bone Miner Metab 28:365, 2010
4. Ruggiero SL, Dodson TB, Assael LA, et al: American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws—2009 update. J Oral Maxillofac Surg 67:2, 2009
5. Hubner RA, Houston SJ: Bisphosphonates' use in metastatic bone disease. Hosp Med 66:414, 2005
6. Migliorati CA: Bisphosphanates and oral cavity avascular bone necrosis. J Clin Oncol 21:4253, 2003
7. Cai XY, Yang C, Zhang ZY, et al: Septic arthritis of the temporomandibular joint: A retrospective review of 40 cases. J Oral Maxillofac Surg 68:731, 2010
8. Goldschmidt MJ, Butterfield KJ, Goracy ES, et al: Streptococcal infection of the temporomandibular joint of hematogenous origin: A case report and contemporary therapy. J Oral Maxillofac Surg 60:1347, 2002
9. Amos MJ, Patterson AR, Worrall SF: Septic arthritis of the temporomandibular joint in a 6-year-old child. Br J Oral Maxillofac Surg 46:242, 2008
10. Kito S, Hirashima S, Yoshioka I, et al: A case of chronic infectious arthritis of the temporomandibular joint associated with osteomyelitis without malocclusion. Open Dent J 4:29, 2010
11. Leighty SM, Spach DH, Myall RW, et al: Septic arthritis of the temporomandibular joint: Review of the literature and report of two cases in children. Int J Oral Maxillofac Surg 22:292, 1993
12. Moses JJ, Lange CR, Arredondo A: Septic arthritis of the temporomandibular joint after the removal of third molars. J Oral Maxillofac Surg 56:510, 1998
13. Parmar J: Case report: Septic arthritis of the temporomandibular joint in a neonate. Br J Oral Maxillofac Surg 46:505, 2008
14. Sano T, Westesson PL, Larheim TA, et al: The association of temporomandibular joint pain with abnormal bone marrow in the mandibular condyle. J Oral Maxillofac Surg 58:254, 2000
15. Ang JY, Asmar BI: Multidrug-resistant viridans streptococcus (MDRVS) osteomyelitis of the mandible successfully treated with moxifloxacin. South Med J 101:539, 2008
16. Mathews CJ, Weston VC, Jones A, et al: Bacterial septic arthritis in adults. Lancet 375:846, 2010
17. Kim SJ, Park YH, Hong SP, et al: The presence of bacteria in the synovial fluid of the temporomandibular joint and clinical significance: Preliminary study. J Oral Maxillofac Surg 61:1156, 2003
18. Khosla S, Burr D, Cauley J, et al: Bisphosphonate-associated osteonecrosis of the jaw: Report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 22:1479, 2007
19. Hoff AO, Toth BB, Altundag K, et al: Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. J Bone Miner Res 23:826, 2008
20. Lodi G, Sardella A, Salis A, et al: Tooth extraction in patients taking intravenous bisphosphonates: A preventive protocol and case series. J Oral Maxillofac Surg 68:107, 2010
21. Saia G, Blandamura S, Bettini G, et al: Occurrence of bisphosphonate-related osteonecrosis of the jaw after surgical tooth extraction. J Oral Maxillofac Surg 68:797, 2010

Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology 25 (2013) 74–78

Contents lists available at SciVerse ScienceDirect

Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology

journal homepage: www.elsevier.com/locate/jomsmp

Oral Pathology/Case report

A case of malignant melanoma discovered as a result of metastatic disease of the temporomandibular joint☆

Yasunari Morimoto[a,*], Suguru Hamada[b], Takafumi Ogura[c], Hirokazu Nakahara[b], Akifumi Enomoto[b], Takayuki Uchihashi[b], Shin-ichiro Hiraoka[a], Mikihiko Kogo[a]

[a] The First Department of Oral and Maxillofacial Surgery, Osaka University Graduate School of Dentistry, 1-8, Yamadaoka, Suita, Osaka 565-0871, Japan
[b] Department of Oral and Maxillofacial Surgery, Kinki University School of Medicine, Osaka, Japan
[c] Department of Dentistry, Oral and Maxillofacial Surgery, Sakai Municipal Hospital, Osaka, Japan

ARTICLE INFO

Article history:
Received 31 August 2011
Received in revised form
21 November 2011
Accepted 20 December 2011
Available online 3 February 2012

Keywords:
Malignant melanoma
Temporomandibular disorder
Metastatic tumor
Temporomandibular joint
Primary malignant melanoma of the lung

ABSTRACT

We report the case of a patient with malignant melanoma discovered upon her experiencing pain when opening her mouth. In 2009, a 42-year-old female patient was referred to the Sakai Municipal Hospital because of preauricular pain when opening her mouth. We suspected a malignant tumor because a simple X-ray showed a radiolucent lesion in the mandibular condyle, and this was confirmed after computed tomographic (CT) and magnetic resonance imaging (MRI) scans. We also detected fluorine-18-deoxyglucose accumulation in the left mandibular condyle, right inferior lobe of lung, and lymph nodes throughout the body during a positron emission tomography PET-CT scan. We performed a biopsy on the bronchoscopic tissue and malignant melanoma was confirmed by histopathology. The patient was subsequently treated at another hospital with systemic chemotherapy along with radiotherapy applied to the left mandibular condyle, but the lymph node tumor enlarged. Accordingly, palliative therapy was given, and the patient died from the tumor 10 months after her first consultation. We could find the malignant melanoma by identifying the radiolucent lesion in the TMJ on panoramic X-ray. Hence, it is crucial not to overlook images indicating bone destruction in the mandibular condyle if there is a malignant tumor in the TMJ.

1. Introduction

Malignant melanoma occurs in 1.5% of all cancers [1]. It is comparatively rare in the oral mucosa and mucus membrane of the maxillary sinus [2], and a few reports have indicated that it can metastasize into the mouth. Seven cases of metastatic melanoma have reported that occurred in the posterior mandible [3]. On the other hand, metastases to the oral cavity only account for 1–8% of all oral malignancies [4–6]. Because of the sparse blood flow in the mandibular condyle, it is rare for a malignant tumor to metastasize here. We have identified 52 cases similar to the current one [7]. However, most of these cases involved adenocarcinomas and only 2 involved metastatic malignant melanoma [8,9]. This report details the case of a patient with malignant melanoma that was found as a result of investigations made because the patient experienced pain upon opening her mouth.

2. Case report

The patient was a 49-year-old female. She was referred to the Department of the Oral and Maxillofacial surgery at Sakai Municipal Hospital, for pain in the left temporomandibular joint (TMJ) upon opening of the mouth in 2009. Since the beginning of June 2009, the patient felt pain radiating to the top of her head when chewing food. She also had difficulty in opening her mouth immediately after waking. She did not feel any pain when she was at rest.

Medical history included undifferentiated spondylarthritis which was diagnosed and treated in 2004. She smoked 10 cigarettes per day and drank alcohol occasionally. She was medium build, and had good nutritional status. Other than that, there was no special findings systematically.

The woman's face was symmetrical, and we did not observe any mandibular deviation when her mouth was open. As a symptom outside the oral region, we found slight oppressive pain in the left TMJ when the distance between the incisors was 25 mm (maximum opening width, 42 mm), but no swelling or lumps were observed.

☆ Asian AOMS: Asian Association of Oral and Maxillofacial Surgeons; ASOMP: Asian Society of Oral and Maxillofacial Pathology; JSOP: Japanese Society of Oral Pathology; JSOMS: Japanese Society of Oral and Maxillofacial Surgeons; JSOM: Japanese Society of Oral Medicine; JAMI: Japanese Academy of Maxillofacial Implants.

* Corresponding author. Tel.: +81 6 6879 2936; fax: +81 6 6876 5298.
E-mail address: y_mori@dent.osaka-u.ac.jp (Y. Morimoto).

2212-5558/$ – see front matter © 2011 Asian AOMS, ASOMP, JSOP, JSOMS, JSOM, and JAMI. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.ajoms.2011.12.006

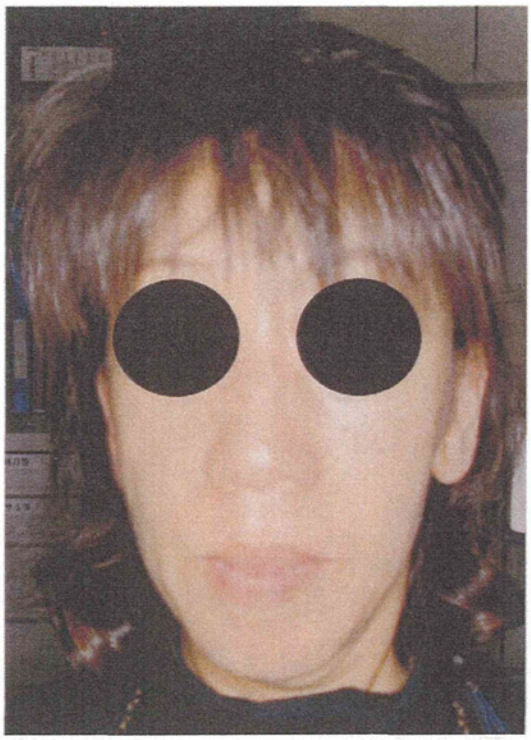


Fig. 1. Extra oral findings: no trismus and no aneurysm in the preauricular region.

The skin over the TMJ was normal, and there was no blistering or rubefaction of her earlobe and external auditory canal (Fig. 1).

We observed slight oppressive pain in the transition area between the maxilla molar part and buccal gingiva as symptoms within the oral region, but the mucous membrane in this area was normal. The patient was able to bite with her molars and no distortion was observed during closed and open biting. The movement of the mandibular condyle appeared to be normal upon palpation.

Panoramic and frontal head X-ray detected a round radiolucent lesion in the area of the left mandibular condyle. No indication of osteolysis in the articular eminence and glenoid cavity of the temporal bone was found (Fig. 2a).

The computed tomography (CT) scans showed bone resorption imaging, which confirmed destruction of the cortical bone at the outside of the left front mandibular condyle (Fig. 2b).

The hemogram was normal in her blood test. C-reactive protein and rheumatoid factor tests were also negative.

Therefore our clinical diagnosis was a malignant tumor on the left mandibular condyle. We prescribed an anti-inflammatory drug and a magnetic resonance imaging (MRI) examination, which revealed the destruction of cortical bone of the front mandibular condyle and infiltration of the lateral pterygoid muscle, and as a result, a malignant tumor was suspected (Fig. 2c).

Accordingly, a positron emission tomography (PET)-CT scan was undertaken because there was a possibility of metastasized malignant melanoma. We detected fluorine-18-deoxyglucose accumulation in the left mandibular condyle, right inferior lobe of lung, bronchial lymph node, liver, right common iliac artery lymph node, and around the hip joint (Fig. 3). Therefore, we consulted with the department of medical oncology about the possibility of lung cancer in the inferior lobe.

Blood tests were also performed, which showed that carcinoembryonic antigen, carbohydrate antigen 19-9, and cytokeratin fragments were within the normal range, and levels of Neuron-specific enolase were high.

We subsequently performed bronchoscopic and histopathologic examination in July (Fig. 4a–c). Microscopically, outgrowth of uniform tumor cells under the mucous membrane of the bronchiole was confirmed. These cells were atypical cell with small densely stained nuclei and pigment-producing cells with brown granules. Epidermal markers were negative while S100 protein and HMB-45 were positive. HMB-45 was stained Premelanosome, showing a positive marker in 80% of malignant melanoma. HMB-45 was positive for the parenchyma of the tumor. Melan-A antigen is specific for the melanocyte lineage, found in normal skin, the retina, and melanocytes, but not in other normal tissues. It is thus useful as a marker for melanocytic tumors (melanomas) with the caveat that it is normally found in benign nevi as well. Melan-A was weak positive. NKI/C3 initially was reported as a marker for a formalin-resistant, melanoma-associated antigen. NKI-C3 was positive. We diagnosed the condyle tumor was metastatic malignant melanoma of the lung.

After the examination, the patient went to the department of dermatology in a cancer center. She was given 2 cycles of chemotherapy with dacarbazine, nimustine, and cisplatin along with 28 Gy irradiation of the tumor on the left TMJ at the cancer center. Although the diameter of the tumor on the mandibular condyle was observed to have reduced on a CT scan performed after radiotherapy, treatment was switched to best supportive care because pathological changes in the lung had progressed despite chemotherapy. The patient was then referred to the affiliated hospital of Kinki University, Faculty of Medicine for palliative care.

Pleural drainage was performed for pleural effusion, and malignant melanoma cells were confirmed in the pleural cell block. Subsequently, we administered picibanil and transferred the patient to palliative care.

A CT scan performed in March 2010 indicated that the left mandibular condyle had been absorbed and had disappeared, (Fig. 5) and preauricular swelling had enhanced. The patient died from her disease 10 months after her first consultation.

3. Discussion

It is very likely that preauricular pain upon opening of the mouth and during mastication will be diagnosed as temporomandibular joint disorder (TMD) because these symptoms are the most common complaints relating to TMD in daily dental and oral surgery practice. However, other possible causes should also be considered as several reports have indicated that patients suffering the exact same symptoms as TMD were diagnosed with malignant melanoma [3,7,10,11].

Malignant tumors in the TMJ are roughly classified into those originating in the TMJ, those caused by a neighboring organ invading the TMJ, and metastasized tumors that have spread to the TMJ [12]. Although the occurrence of a tumor originating in the TMJ is extremely rare, osteosarcoma, chondrosarcoma, and giant cell malignant tumors have been reported. The parotid gland is the most likely neighboring organ from which a malignant tumor can be derived, but oral, maxillary, and pharyngeal tumors are also possible. A metastasized tumor is the most common cause of a malignant tumor detected in the TMJ. On the other hand, malignancy in the TMJ is extremely rare with only 52 other cases identified between 1954 and 2010 [7]. A total of 73% of these cases were adenocarcinomas, which are frequent in bone metastasis from the prostate, mammary glands, lungs, and thyroid glands; there were only 2 cases of malignant melanoma. Hence we can say that this case is very unusual.

Malignant melanoma is a malignant tumor originating in melanocytes although the reason for its occurrence remains

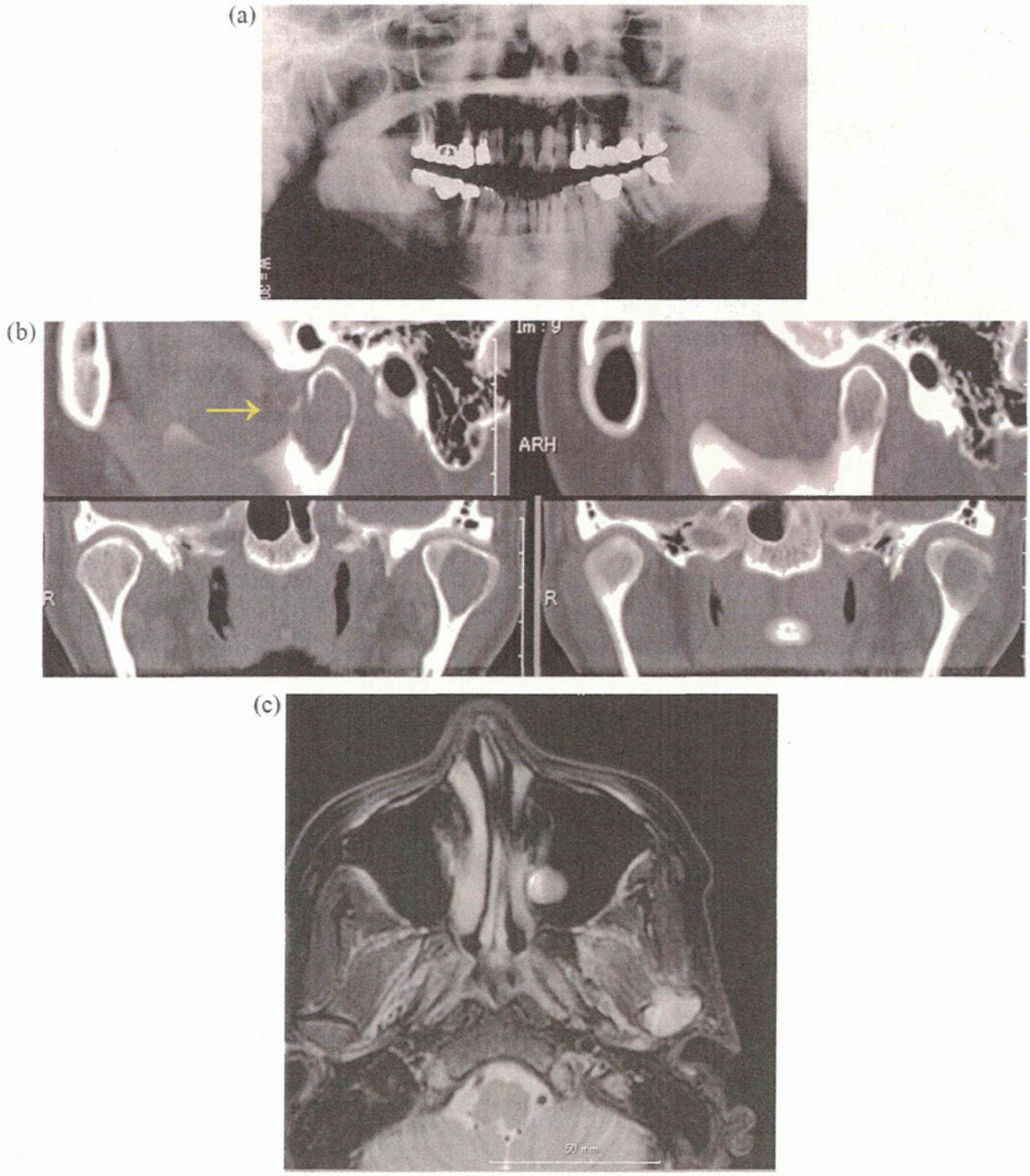


Fig. 2. (a) Panoramic radiographs of the patient at first examination showing a radiolucent lesion in the mandibular condyle. (b) Coronal and sagittal CT (bone window setting) revealed osteolysis of the left mandibular condyle. (c) Axial and sagittal MRI (short time inversion recovery) revealed destruction of the left mandibular condyle and invasion of the lateral pterygoid muscle. (Hydrocele revealed in the left maxillary sinus.)

unknown. Malignant melanoma affects approximately 1500–2000 patients annually in Japan and this number is increasing; 52.4% of patients are female and 47.6% are male, and the incidence of this disease is greatest in those aged 40 years or older.

Malignant melanoma commonly originates in the foot (sole) (27.0%), trunk (13.8%), face and neck (13.8%), upper limbs, nails, and lower limbs [13]. Malignant melanoma has also been reported to occur at the mucosa. Ariyoshi et al. [2] reported the incidence of malignant melanoma as 0.7% of malignant tumors in the oral and maxillofacial region, and a few reports have indicated that it can metastasize into the mouth. For 7 examples of which have reported that occurred in the posterior mandible [3].

Because we found fluorine-18-deoxyglucose accumulation in the bronchi and regional lymph nodes during a PET scan, as for the primary lesion of the malignant melanoma, there was no sign of malignant melanoma including the black lesion which disappeared in the skin. Moreover, because PET-CT scan showed uptakes in the temporomandibular joint, lungs, iliac bone and inguinal lymph node, it was unlikely to be the malignant melanoma that was originated in bone. Also, there are no reports of the cases of malignant melanoma originated in bone to date as much as I can collect, so that we suspected the malignant melanoma that was originated in lungs which I could find a large number of case reports. Metastasis to the TMJ in this case appears to have originated from a tumor

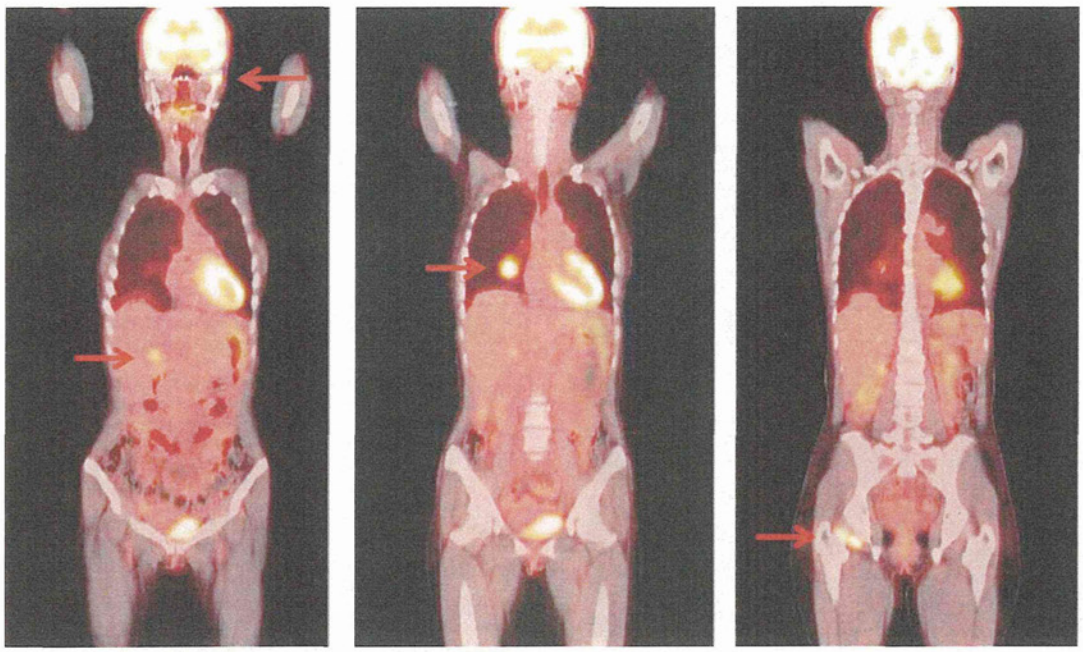


Fig. 3. (Right) Whole body fluorine-18-deoxyglucose PET-CT revealed a density anomaly mass in the liver and left mandibular condyle with increased glucose metabolism. (Center) Increased glucose metabolism in the lower left lobe, (left) increased glucose metabolism in the right common iliac artery lymph node.

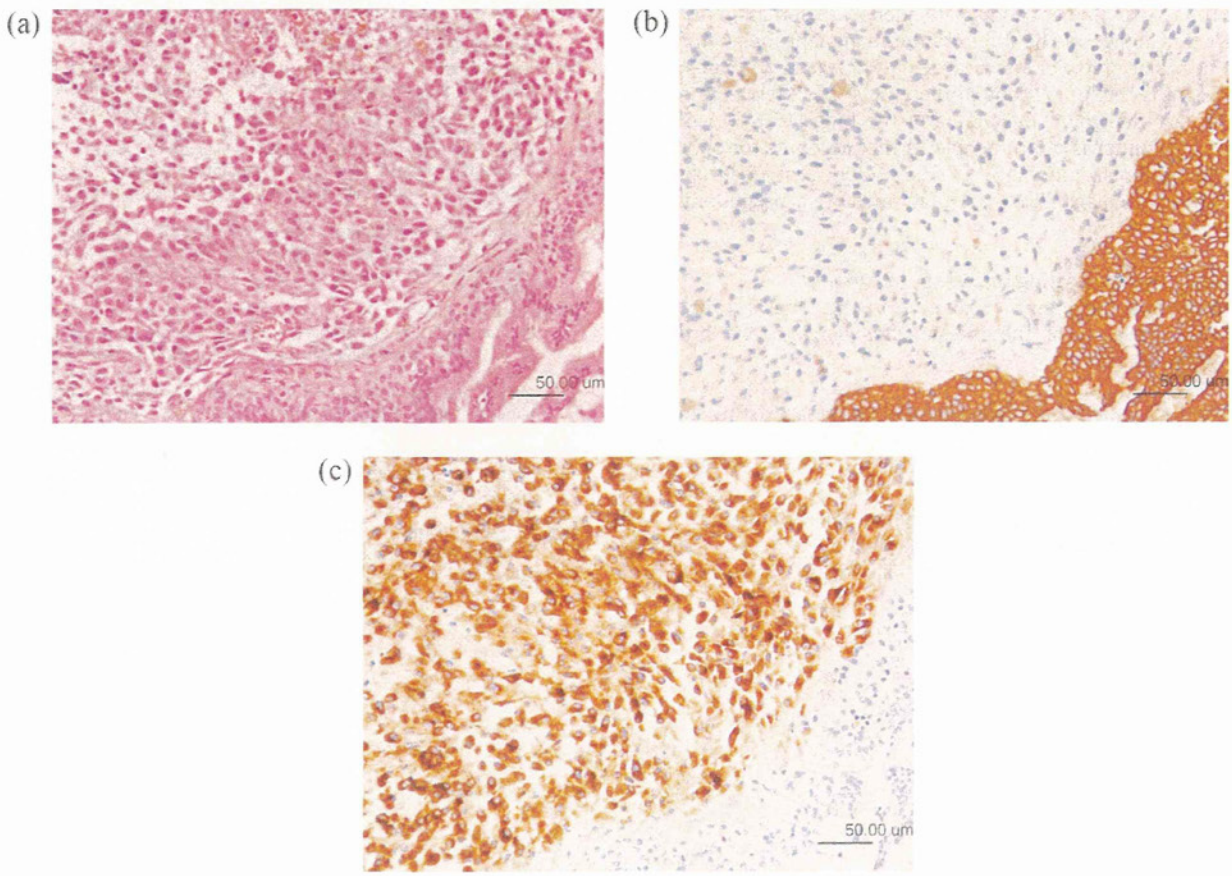


Fig. 4. Histopathological features compatible with those of malignant melanoma. (a) Hematoxylin and eosin stain confirmed outgrowth of uniform tumor cells under the mucous membrane of the bronchiole. Atypical cells with small densely stained nuclei and pigment-producing cells with brown granules were identified (original magnification ×100). (b) Immunohistochemical staining for MNF116 was negative (original magnification ×100). (c) Immunohistochemical staining for HMB 45 was positive (original magnification ×100).

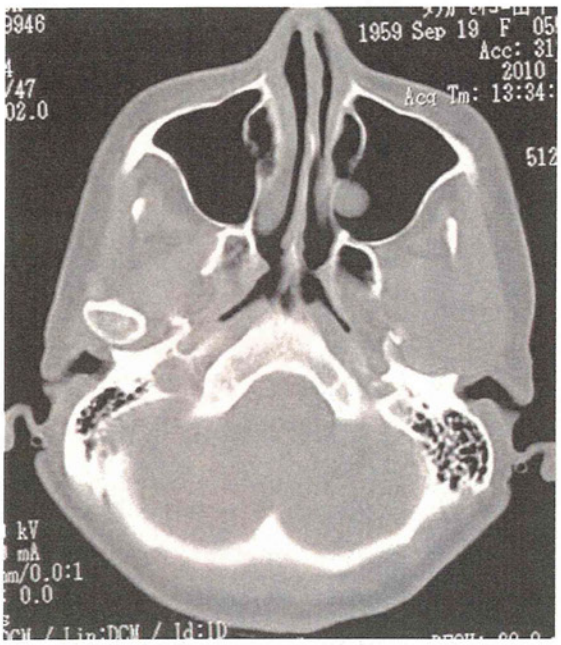


Fig. 5. CT (bone window setting) demonstrated an expansive soft tissue mass and resorption of the left mandibular condyle.

in the inferior lobe of lung because 72% of tumors that metastasize to the mandibular condyle are adenocarcinomas [7,14]. There was no clear sign of the origin of the malignant melanoma, such as a clear black mole or appearance of skin lesions. The most likely candidate is the lung although there have been few case reports of primary malignant melanoma of the lung [15,16]. A primary malignant tumor is a rare neoplasm that accounts for only 0.01% of primary lung tumors [17]. We did not perform an autopsy, but we arrived at a diagnosis of malignant melanoma originating in the lung because:

(a) there was no existing malignant melanoma;
(b) malignant melanoma originating in the lung is a malignant transformation of the melanocytes beneath the bronchial epithelial cells.

The argument remains whether melanocytes, existing since the embryonic period, result from metaplasia in bronchial epithelial cells or are a specialized part of intraneural secretory cells (Kulchitsky cell).

The prognosis of malignant melanoma originating in the lung is generally poor [16]. This patient died despite undergoing chemotherapy. There was no clear lower jaw distortion or limitation to opening the mouth initially, and her symptoms were identical to those of TMD.

We were able to find the malignant melanoma because of the radiolucent lesion in the TMJ identified on panoramic X-ray. In other words, it is crucial not to overlook images indicating bone destruction in the lower mandibular condyle that appear on simple X-rays if there is evidence of a malignant tumor in the TMJ.

References

[1] Cutler SJ, Young Jr JL. Third national cancer survey, incidence data monograph 41. 2nd ed. Washington, DC: U.S. Dept. Health, Education, Welfare; 1975.
[2] Ariyoshi Y, Shimahara M, Omura K, Yamamoto E, Mizuki H, Chiba H, et al. Epidemiological study of malignant tumors in the oral and maxillofacial region: survey of member institutions of the Japanese Society of Oral and Maxillofacial Surgeons, 2002. Int J Clin Oncol 2008;13:220–8.
[3] Rivera RD, Diamante M, Kasten SJ, Ward BB. Metastatic melanoma to the mandible: case report and review of the literature. J Oral Maxillofac Surg 2010;62:2903–6.
[4] Meyer I, Shklar G. Malignant tumors metastatic to mouth and jaws. Oral Surg 1965;20:350–62.
[5] Zachariades N. Neoplasms metastatic to the mouth, jaws and surrounding tissues. J Craniomaxillofac Surg 1989;17:283–90.
[6] Hirshberg A, Leibovich P, Buchner A. Metastatic tumors to the jaws: analysis of 390 cases. J Oral Pathol Med 1994;23:337–41.
[7] Kruse ALD, Luebbers HT, Obwegeser JA, Edelmann L, Graetz KW. Temporomandibular disorders associated with metastases to the temporomandibular joint: review of the literature and 3 additional cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;110:e21–8.
[8] Thoma KH. Tumors of the condyle and temporomandibular joint. Oral Surg Oral Med Oral Pathol 1954;7:1141–9.
[9] Nortjé CJ, van Rensburg LJ, Thompson IO. Case report. Magnetic resonance features of metastatic melanoma of the temporomandibular joint and mandible. Dentomaxillofac Radiol 1996;25:292–7.
[10] Freudlesperger C, Kurth R, Werner MK, Hoffmann J, Reinert S. Condyler metastasis from prostatic carcinoma mimicking temporomandibular disorder: a case report. J Oral Maxillofac Surg 2010:1–4 [Epub adead of print].
[11] Boniello R, Gasparini G, D'Amato G, Petrillo AD, Pelo S. Case report TMJ metastasis: a unusual case report. Head Face Med 2008;4:8–11.
[12] Omura K, Harada H, Maeda A. Malignant tumor of the temporomandibular joint diagnosis and treatment. J Jpn Soc Oral Tumor 2000;12:391–5 [article in Japanese].
[13] Ishihara K, Saida T, Otsuka F, Yamazaki N. Prognosis and statistical investigation committee of the Japanese skin cancer society statistical profiles of malignant melanoma and other skin cancers in Japan: 2007 update. Int J Clin Oncol 2008;13:33–41.
[14] Tabib R, Elias S, Tal Y, Ben-Yehuda A, Abu-Tair J. Temporomandibular joint-related symptoms as initial presentation of lung carcinoma in a patient with Takayasu's arteritis. J Oral Maxillofac Surg 2011;69:226–9.
[15] Neri S, Komatsu T, Kitamura J, Otsuka K, Katakami N, Takahashi Y. Malignant melanoma of the lung: report of two cases. Ann Thorac Cardiovasc Surg 2011;17:170–3.
[16] Scolyer RA, Bishop JF, Thompson JF. Primary melanoma of the lung. In: Raghaban D, Brecher ML, Johnson DH, Meropol NJ, Moots PL, et al., editors. Textbook of uncommon cancer. West Sussex: John Wily & Sons Ltd.; 2006. p. 293–8.
[17] Wilson RW, Moran CA. Primary melanoma of the lung: a clinicopathologic and immunohistochemical study of eight cases. Am J Surg Pathol 1997;21:196–202.

モーニングセミナーから

下顎骨に発生した良性歯原性腫瘍および悪性腫瘍の鑑別

内橋俊大　中原寛和　榎本明史　内橋隆行　栗本聖之
泉本貴子　濱田　傑

近畿大学医学部附属病院歯科口腔外科

抄　録

歯原性腫瘍は歯を形成する組織由来の腫瘍で，一般に顎骨内に発生する．大部分が良性腫瘍であり，無痛性の膨隆をきたし発見されたり，レントゲン撮影にて偶然発見される場合も多い．歯原性腫瘍は良性腫瘍が多いものの，局所再発傾向の強い腫瘍があることや，頻度は低いものの悪性腫瘍も存在するため，正確な診断と適切な処置が必要とされる．今回，当科で経験した良性歯原性腫瘍と顎骨内に発生した悪性腫瘍を提示し，その鑑別診断について検討する．

緒　言

歯原性腫瘍とは歯を形成する組織，すなわち外胚葉由来のエナメル質を作る細胞，中胚葉由来の象牙質，歯髄またはセメント質を形成する細胞を発生母地とする腫瘍で，その多くが良性腫瘍である．良性腫瘍が大部分を占めるが，その代表的な腫瘍であるエナメル上皮腫は良性腫瘍に分類されているものの，局所再発傾向の強い腫瘍として知られている．一方，顎骨に発生する腫瘍には頻度は高くないものの悪性腫瘍が存在する．言うまでもなく，悪性腫瘍の場合は迅速な診断，処置を要する．今回，当科にて経験したエナメル上皮腫と顎骨中心性の扁平上皮癌症例の初診時の症状，パノラマX線所見より鑑別診断について検討し，その診断・治療について考察する．

症　例　1

患者：61歳，男性
主訴：左側下顎部の腫脹
現病歴：平成20年12月頃より左側下顎部の腫脹を自覚するも放置していた．平成21年3月近歯科医院を受診し，パノラマX線にて左側下顎部の透過像を指摘され，精査目的で当科へ紹介となった．
現症：左側下顎部に腫脹を認めるものの，疼痛等の著明な症状は認めなかった（図1A）．
画像所見：パノラマX線所見では下顎左側第1大臼歯遠心から筋突起前縁にかけて境界明瞭な透過像を認めた（図1B）．CT所見（冠状断）では下顎左側第1大臼歯遠心から下顎枝にかけて頬舌的に膨隆した透過像を認めた（図2A）．CT所見（軸位断）頬舌側の骨は非薄化しており，下顎管は下方に圧平さ

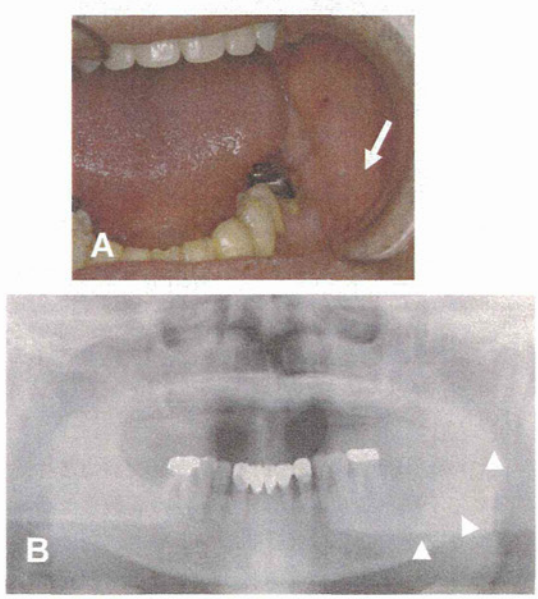


図1　A：症例1口腔内写真，左側下顎臼歯部に腫脹が認められた（白矢印）．B：症例1パノラマX線：下顎左側第1大臼歯遠心から筋突起前縁にかけて境界明瞭な透過像を認めた（白矢頭）．

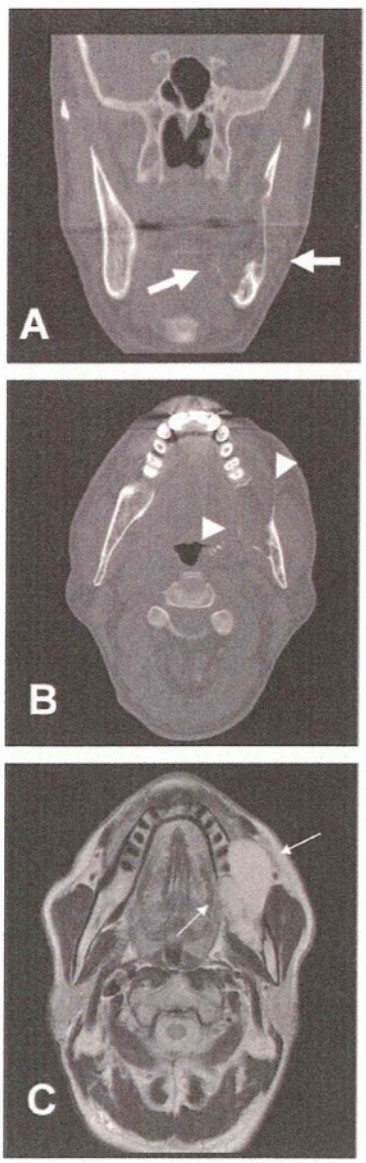


図2 A：症例1 CT 冠状断，頬舌側の骨は非薄化しており，下顎管は下方に圧平されていた（白矢印）．B：症例1 CT 軸位断，下顎左側第1大臼歯遠心から下顎枝にかけて頬舌的に膨隆した透過像を認めた（白矢頭）．C：症例1 MRI 軸位断，T2 強調像にて下顎左側第1大臼歯遠心に多房性の高信号を認め，病変は左側咬筋とは境界明瞭であった（細白矢印）．

れていた（図2 B）．MRI 所見においては T2 強調画像にて下顎左側6番遠心に多房性の高信号を認め，病変は左側咬筋とは境界明瞭であった（図2 C）．
臨床診断：左側下顎骨歯原性腫瘍
生検：外来にて局所麻酔下で生検術を施行した．
病理組織所見：腫瘍実質は歯胚のエナメル器に類似する島状の胞巣よりなる（弱拡大，図3 A）．腫瘍細胞は内腔面では類円形核を持っており，嚢胞内腔に

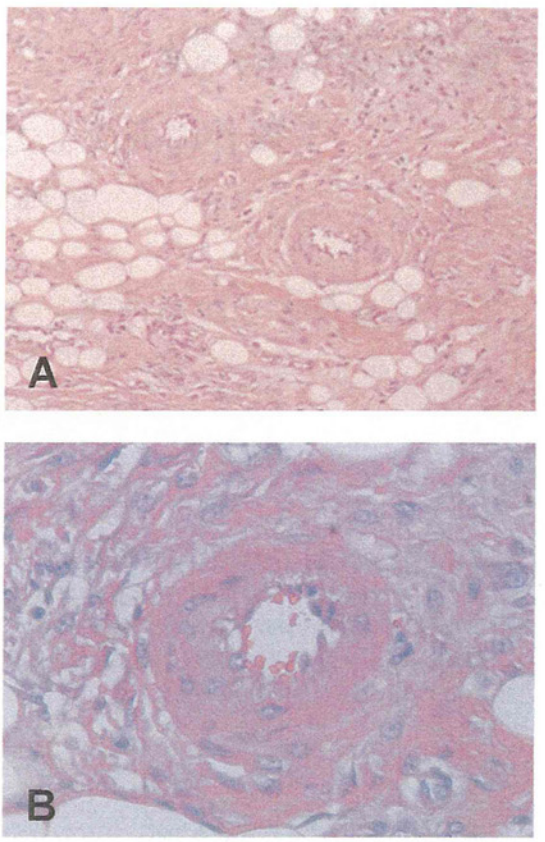


図3 A：症例1病理組織像（弱拡大）腫瘍実質は歯胚のエナメル器に類似する島状の胞巣よりなる．B：（強拡大）腫瘍細胞は内腔面では類円形核を持っており，嚢胞内腔に微小な乳頭状構造をとっている．

微小な乳頭状構造をとっている（強拡大，図3 B）．
病理組織診断：乳頭状角化エナメル上皮腫（papilliferous keratoameloblastoma）
処置および経過：平成21年5月，全身麻酔下にて腫瘍摘出開窓術を施行した．手術から2年経過しているが，経過良好である．

症 例 2

患者：68歳，男性
主訴：左側下唇麻痺
現病歴：平成22年7月頃より左側下唇の麻痺を認め，近耳鼻科を経て，本院耳鼻科を受診した．画像検査にて左側下顎部の透過像を認め，顎骨腫瘍疑いにて当科を紹介された．
既往歴：特記事項なし．
画像所見：パノラマX線所見では左側下顎第2大臼歯遠心に，下顎枝上方に至る智歯を含む辺縁不整な透過像を認めた（図4 A）．また，MRIT2 強調像にて左下顎角部に充実性信号を示した（図4 B）．

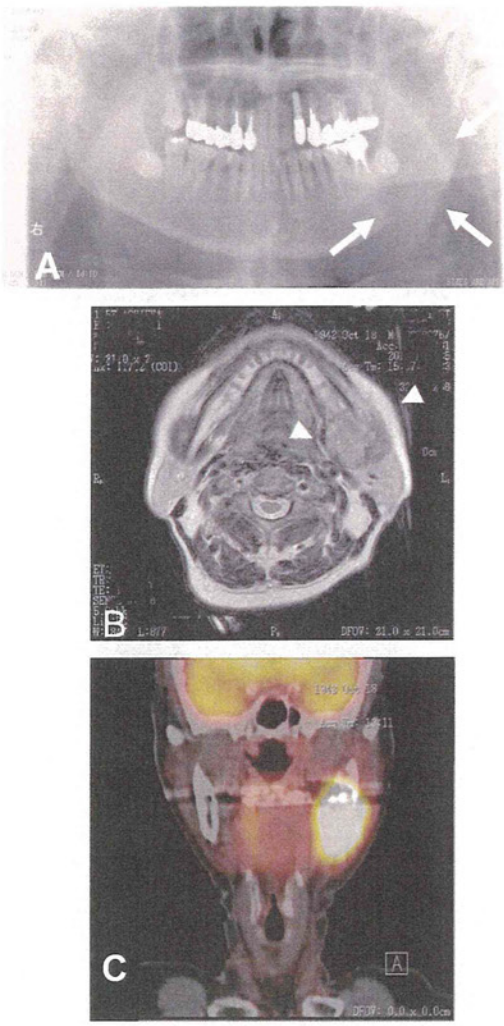


図4　A：症例2パノラマX線：左側下顎第2大臼歯遠心に，下顎枝上方に至る智歯を含む辺縁不整な透過像を認めた．B：症例2 MRI軸位断T2強調像にて左下顎角部に充実性信号を示した．C：症例2 PET-CT所見にて左側下顎骨および左頚部リンパ節に集積を認め，左側頚部リンパ節転移を疑った．

現症：左側下顎部に知覚異常を認めるものの，その他の著明な症状は認めなかった．
生検：平成22年8月，外来にて局所麻酔下に生検を施行した．
病理組織検査：未分化な扁平上皮細胞の増殖を認めた（弱拡大，図5）．
診断：顎骨中心性扁平上皮癌
PET-CT所見：左側下顎骨および左頚部リンパ節に集積を認め，左側頚部リンパ節転移を疑った（図4C）．
処置および経過：平成22年9月，全身麻酔下に下顎骨区域切除，左側頚部郭清術，ならびに下顎骨プレート再建術を施行した（図6A，B，C）．手術より1年経過しているが，再発もなく経過良好である（図7A，B）．

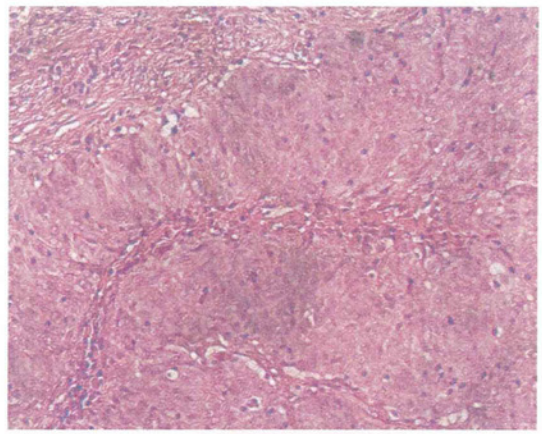


図5　症例2病理組織像（弱拡大）未分化な扁平上皮細胞の増殖を認めた．

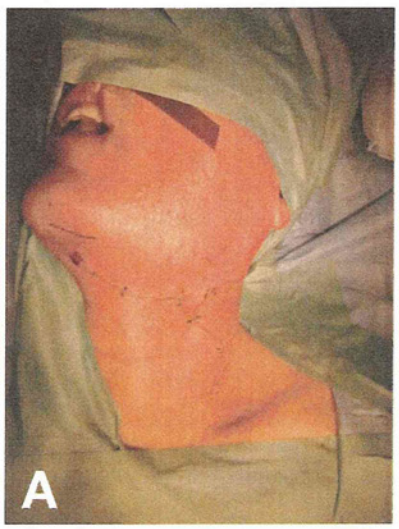
考　察

歯原性腫瘍とは歯胚を形成する組織，すなわち外胚葉由来のエナメル質を作る細胞，中胚葉由来の象牙質，歯髄またはセメント質を形成する細胞を発生母地とする腫瘍で，病理学的に複雑な組織像を示す[1]．歯原性腫瘍はその多くが良性腫瘍であり，その特徴として，初期に臨床症状が乏しく，無痛性に進行し顎骨の膨隆，変形を訴えて来院することが多く，パノラマX線撮影によって偶然発見されることも多い[1]．

歯原性腫瘍は良性腫瘍が大多数を占めるものの，局所浸潤性が高く，再発傾向が高いとされる．エナメル上皮腫や角化嚢胞性歯原性腫瘍の発生頻度が高い[1,2]．大阪大学歯学部附属病院検査部で歯原性腫瘍821例を検索した報告によると，角化嚢胞性歯原性腫瘍が293例（35.7%），エナメル上皮腫が219例（26.7%）であった[3,4]．

エナメル上皮腫は歯原性腫瘍でありながら，局所浸潤・再発傾向の高い腫瘍とされている．一方，角化嚢胞性歯原性腫瘍は2005年のWHO歯原性腫瘍の分類変更に伴い，腫瘍に再編された腫瘍で，以前は嚢胞に分類されながら，娘嚢胞が存在し，再発傾向の高い疾患である[2,4,5]．

原発性下顎骨中心性扁平上皮癌はWHOにより，顎骨内に生じ，初期には口腔粘膜と連続性がなく，歯原性上皮遺残から発生したと推定され，かつ他臓器からの転移でない扁平上皮癌と定義されている[2]．その診断は初期では困難であり，発見時はすでに下顎骨内で広範囲に進展していることが多く，一



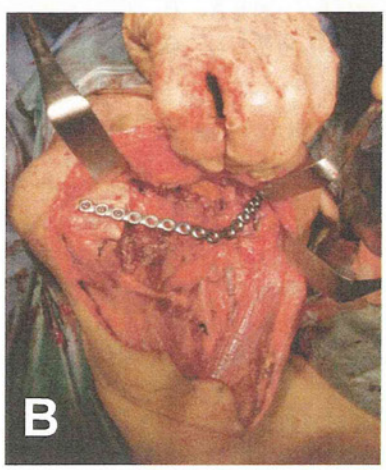


図6　A：症例2手術直前　B：左側頚部郭清および顎骨腫瘍切除後，チタンプレートにて再建．C：左側頚部リンパ節組織と顎骨腫瘍を一塊に切除．

般的に予後不良とされている[1,2,6,7]．

今回，顎骨に発生した良性の歯原性腫瘍であるエナメル上皮腫と顎骨中心性扁平上皮癌のX線所見，

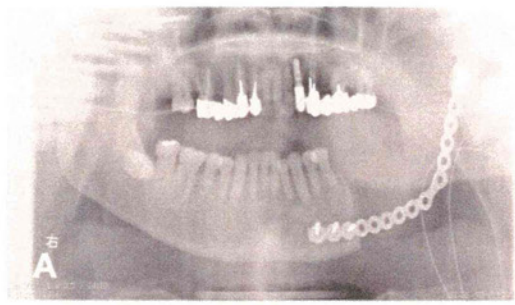


図7　A：症例2術後パノラマX線，B：症例2術後頭部正面像，顎骨腫瘍切除後チタンプレートにて再建されている．

表1　症例1，症例2のパノラマX線所見，臨床所見，病理組織診断，治療法の比較

	症例1	症例2
X-P所見	顎骨の透過像	顎骨の透過像
多胞，単胞	多房性	多房性
歯の存在	なし	埋伏歯
辺縁	比較的明瞭	不明瞭
臨床症状	無痛性膨隆	下唇に麻痺
病理組織診断	エナメル上皮腫	扁平上皮癌
治療法	腫瘍摘出開窓術	顎骨区域切除＋プレート再建

初診時の症状，診断，治療法を比較し，表1に示した．

症例1，2を比較すると，顎骨内に腫瘍が存在することから両者ともパノラマ写真にてX線透過像が認められた．パノラマX線写真は歯科で高頻度に撮影され，顎骨病変の描写には極めて有効である．透過像と顎骨との境界に関して，良性のものが比較的明瞭であったのに対し，悪性のものは境界不明瞭であった．境界不明瞭な像を呈するのは，浸潤性の強い悪性腫瘍の特徴であるといえる．臨床症状も鑑別の指標となり，良性のものが無症状であることが多いのに対し，悪性のものは知覚異常などの神経症状