Case Report

DOI: 10.7860/JCDR/2016/19411.8289

Dentistry Section

Non-Syndromic Familial Keratocystic Odontogenic Tumour: A Rare Case Report in Japanese Identical Twins

YASUYUKI SHIMADA[1], YUTAKA MARUOKA[2], IENA YAMAJI[3], SHIGEO KAWAI[4]

ABSTRACT

Keratocystic Odontogenic Tumour (KCOT) is unicystic or multicystic intraosseous benign tumour of odontogenic origin that recurs due to locally destructive behaviour. KCOTs are usually the first manifestation of Nevoid Basal Cell Carcinoma Syndrome (NBCCS), an autosomal dominant disorder also known as Gorlin's syndrome and they are most frequently observed familial symptom regardless of patients' nationality. In addition, the recurrence rate and multiplicity of KCOTs is relatively high as compared to that of other sporadic carcinomas. KCOT has been considered as a non-hereditary lesion and its familial onset is an extremely rare event in non-NBCCS cases. Here, we describe previously unreported non-syndromic multiple KCOT cases in identical twins in a Japanese family. The subjects were female Japanese identical twins who were 26 and 27 years old, respectively, at the time of diagnosis for KCOT. They had no major or minor features of NBCCS other than KCOT. Although there were lesions that were likely to be dentigerous cysts based on radiographic findings, one of them was KCOT. This case report highlights the importance of precise diagnosis, choice of surgical method and careful observation for multiplicity or familial onset in sporadic KCOT cases without NBCCS.

Keywords: Dentigerous cyst, Gorlin syndrome, Nevoid basal cell carcinoma syndrome

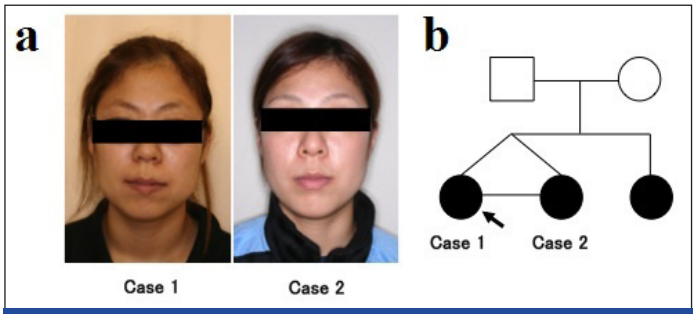
CASE REPORT

The patients were two Japanese identical twins. The twins were 26 years old at the time first sister was evaluated in May 2010 and 27 years old at the time second sister was evaluated in September 2011. The former (Case 1) was the third daughter in the family and the proband in this study. The latter (Case 2) was the second daughter in this family [Table/Fig-1a,1b].

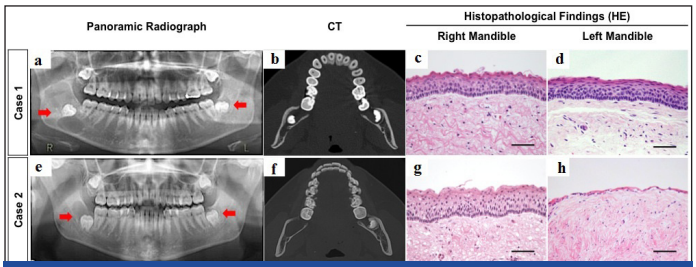
Clinical, Radiological and Histopathological Findings: The chief complaint of these patients was a repeated sense of incongruity in the gingiva of right mandible. Intra-oral examination revealed slight pain on pressure in the right mandibular posterior region, but no gingival swelling, tooth mobility, or pus discharge. The molars were vital. No neurological symptoms associated with the trigeminal nerve domain were observed.

Case 1

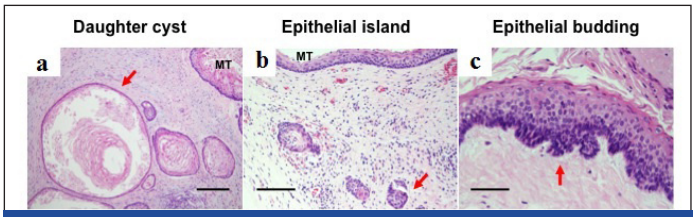
Panoramic radiography and CT revealed two separate radiolucent lesions: (1) a well-defined 68mm X 40mm scalloped radiolucency with mild cortical plate expansion in the right mandible, extending from the first molar to the mandibular ramus, involving an impacted third molar and contacting the first and second molars, and (2) a well-defined 17mm X 15mm radiolucency without cortical plate expansion in the left mandible, involving an impacted third molar and contacting the second molar [Table/Fig-2a,2b]. We suspected an odontogenic benign tumour in the right mandible and enucleated. We also performed bone excavation around the tumour cavity to prevent recurrence [1]. The histopathological diagnosis was Keratocystic Odontogenic Tumour (KCOT), showing parakeratinised stratified squamous epithelium of uniform 6–8 cell thickness and a palisaded basal layer [Table/Fig-2c] accompanied by tumour recurrence-associated histopathological variations [2,3], such as epithelial islands and epithelial budding [Table/Fig-3]. The impacted third molar was extracted. The first and second molars were not extracted because of the patient's age and to maintain occlusal function. Although we suspected that the left mandibular lesion was a dentigerous cyst and recommended for surgical removal at the time of the first radiological examination, we decided to follow-up as per patients' wish. However, we performed cystectomy two years later due to the expansion of the radiolucency [Table/Fig-4]. Contrary to our expectation, the pathological diagnosis was KCOT [Table/Fig-2d] with daughter cysts, epithelial islands and budding [Table/Fig-3]. We followed up



[Table/Fig-1a,b]: Complexion photographs and a family tree of non-syndromic KCOT patients of the present study.
Filled symbols indicate patients with KCOT and blank symbols indicate unaffected individuals. The arrow indicates a proband. Case 1 and Case 2 are identical twins who visited our hospital. There was no NBCCS within at least the first-degree relatives in this family, and only a diagnosis of KCOT was accepted for these sisters.



[Table/Fig-2]: (a,b,e,f) Panoramic radiograph and CT at the first visit. Panoramic radiographs exhibit radiolucent lesions in the posterior region of the mandible, with scalloped, well-defined margins, involving impacted third molars (arrows). Mild cortical plate expansion was found in the right mandible. **(c,d,g,h)** Hematoxylin–Eosin (H&E) staining of surgical specimens. c, d, and g show KCOT with a parakeratinized squamous epithelial lining and a palisaded basal layer (Scale bars = 30 μm). h) shows a dentigerous cyst in Case 2, showing a 2-3-cell-layer-thick non-keratinized epithelium by H&E staining (Scale bar = 30 μm).



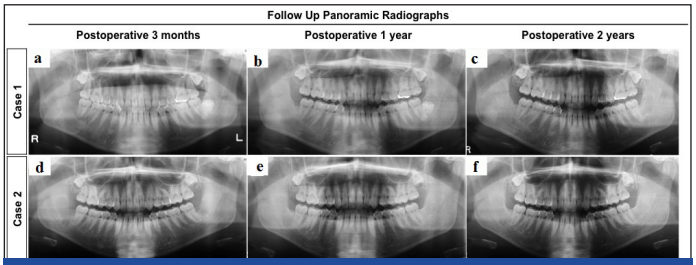
[Table/Fig-3]: Histopathological variations in KCOT surgical specimens from Case 1.
(a) A daughter cyst is a small keratin-filled cystic cavity, located far from the main tumor (MT). Scale bars = 100 μm
(b) An epithelial island is a detached lump of epithelial cells, located far from the main tumor (MT). Scale bars = 60 μm
(c) Epithelial budding is distinct mural invagination from the basal layer into the underlying fibrous connective tissue. Scale bars = 30 μm

the left mandibular region without additional treatment such as bone excavation due to the wishes of the patient.

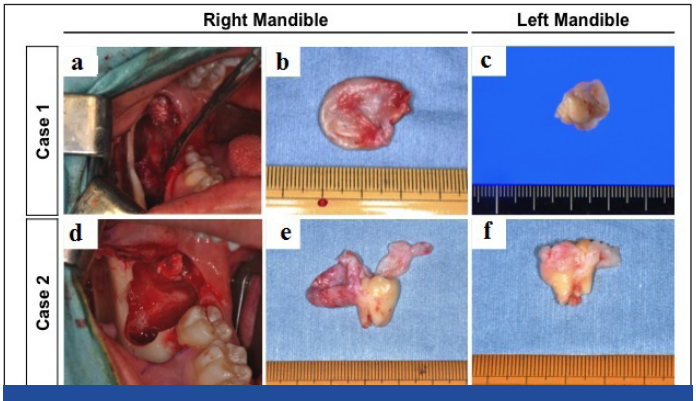
Case 2

Revealed a well-defined, scalloped 35mm X 18mm radiolucency with mild cortical plate expansion in the right mandible extending from the second molar to the mandibular ramus and a well-defined 10mm X 10mm radiolucency without cortical plate expansion in the left mandible, involving an impacted third molar and contacting the second molar [Table/Fig-2e,2f]. We suspected KCOT in the right mandibular lesion and performed enucleation and bone excavation, as with Case 1. The histopathological diagnosis was KCOT [Table/Fig-2g] accompanied by daughter cysts and epithelial islands. The second molar was not extracted for the same reasons as for Case 1. The left impacted third molar and cystic lesion was also removed and pathologically diagnosed as a dentigerous cyst, as predicted, showing a 2–3 cell layer thick non-keratinised epithelium [Table/Fig-2h]. These patients are being monitored regularly, with no evidence of recurrence [Table/Fig-4]. At least two examiners, including a specialist in oral pathology, independently assessed the microscopic findings and confirmed each evaluation. Photographs of the operation and surgical specimen are shown in [Table/Fig-5].

A physical examination, combined with careful investigations of the medical records, showed no features of NBCCS other than KCOT in the present cases. Although complete exclusion of the rare NBCCS-associated features is clinically difficult, based on Kimonis criteria [4], a diagnosis of NBCCS could not be established for the



[Table/Fig-4]: Follow-up panoramic radiographs in Case 1 and Case 2.



[Table/Fig-5]: Surgical findings of jaw lesions regarding Case 1 and Case 2.

sisters. From detailed interviews, it was clear that their parents had no history of NBCCS diagnosis or jaw surgery.

Authors (et al.,)	Song YL	Wang X	Shimada Y
Year	2006	2011	2016
Nationality	China	China	Japan
No. of KCOT cases	5	5	3
No. of families	1	1	1
No. of tumours	7≤	8≤	4
Mean age (years)	48	30	27
Sex ratio (M:F)	4 : 1	2 : 3	0 : 3
Proband (Age, Sex)	12, M	29, F	26, F
Symptoms agree with Kimonis criteria other than KCOT	-	-	-

[Table/Fig-6]: Relative frequencies of non-syndromic familial KCOT cases compared with other countries.

DISCUSSION

Most KCOTs arise sporadically; in contrast, only approximately 10% of all KCOT cases meet the major diagnostic criteria for NBCCS [5], which is a rare autosomal dominant disorder also known as Gorlin's syndrome [6,7]. Although familial onset of KCOT usually occurs as a component of NBCCS, it is an extremely rare event in non-NBCCS cases. Only two non-syndromic families with KCOT have been reported from Asia [Table/Fig-6] [8,9]. Similar to previous reports, KCOT showed a tendency for multifocality, and the probands were young, in the first or second decade of life. The eldest daughter in the family of the twin sisters described here [Table/Fig-1b] was diagnosed with KCOT at another hospital. Similar to Cases 1 and 2, she did not show any other symptoms of NBCCS. Thus, no NBCCS was observed in the first-degree relatives, and only a diagnosis of KCOT was established. To the best of our knowledge, ours is the first report to present a family with non-syndromic KCOTs in Japan and particularly in identical twins. Although non-syndromic familial KCOT is extremely rare, we recommend careful observation for multiplicity or familial onset for patients with sporadic KCOT without NBCCS.

In the present case, clinical manifestations in both cases were similar except for the presence of a dentigerous cyst that developed in Case 2 [Table/Fig-2h]. As mentioned earlier, we suspected a dentigerous cyst in the left mandible in Case 1 as well. Dentigerous cyst is the second most common odontogenic cyst associated with the crowns of permanent unerupted teeth. It is usually single in occurrence and located in the mandible. It commonly manifests in the second and third decades of life [10]. Regarding the radiological findings, although KCOT is associated with a broad range of bone resorption and cortical plate expansion visible on CT [11], a dentigerous cyst rarely shows expansive growth [12]. Therefore, the occurrence of benign tumours in the left mandibular lesion in both cases seemed unlikely at the first radiological screening. However, Case 1 was diagnosed with KCOT, contrary to our expectations. From the perspective of recurrence, the recommended surgical method for KCOT is different as compared to dentigerous cysts because of its locally destructive behaviour and tendency to recur [1,13]. For dentigerous cysts, most dental surgeons choose conservative treatment—defined as enucleation with any part of the included root left within the cyst cavity—and recurrence is rarely observed [10,13]. In contrast, conservative treatment has a relatively high risk of recurrence for KCOTs, and no tumour recurrence has been reported following radical treatment, which is defined as the enucleation of KCOTs with the extraction of all teeth or the resection of all roots that are included in or are in contact with the tumour [1,14]. Therefore, a biopsy should be performed for precise diagnosis and determination of the appropriate treatment plan before surgery, even if the radiological findings indicate a dentigerous cyst. The presence of tumour recurrence-associated histopathological variations and enforced

surgical techniques indicates the possibility of recurrence, which necessitates continuous monitoring in the present cases.

CONCLUSION

Dental surgeons have additional opportunities for detecting KCOTs compared to other specialists. Therefore, dental surgeons must make a precise diagnosis and follow an optimal treatment plan for KCOTs and rule out NBCCS. Further longitudinal studies and genetic investigations are warranted.

Author Contributions: YS, IY, and YM conceived and designed the study; YS and SK analyzed the data; YS wrote the paper; all authors read and made a final approval of the version to be submitted.

Ethical approval: This case report was reviewed and approved by the ethical committee of National Centre for Global Health and Medicine (NCGM-G-001778-00). We also conducted this study in accordance with the current revision of the 1975 Helsinki Declaration. For those agreeing to participate in this study, written consent was obtained.

Conflict of interest: None of the authors has any conflict of interest in this work.

ACKNOWLEDGMENTS

This work was supported in part by Grants-in-Aid for Research from the National Centre for Global Health and Medicine (26A-201). We would like to thank Editage (www.editage.jp) for English language editing.

REFERENCES

[1] Mendes RA, Carvalho JF, Van Der Waal I. Characterization and management of the keratocystic odontogenic tumor in relation to its histopathological and biological features. *Oral Oncol*. 2010;46(4):219-25.
[2] Ahlfors E, Larsson A, Sjogren S. The odontogenic keratocyst: a benign cystic tumor? *J Oral Maxillofac Surg*. 1984;42(1):10-19.
[3] Shimada Y, Katsube K, Kabasawa Y, Morita K, Omura K, Yamaguchi A, et al. Integrated genotypic analysis of hedgehog-related genes identifies subgroups of keratocystic odontogenic tumor with distinct clinicopathological features. *PLoS* One. 2013;8(8):e70995.
[4] Kimonis VE, Goldstein AM, Pastakia B, Yang ML, Kase R, DiGiovanna JJ, et al. Clinical manifestations in 105 persons with nevoid basal cell carcinoma syndrome. *Am J Med Genet.* 1997;69(3):299-308.
[5] Taguchi T, Morita K, Shimada Y, Omura K. A clinical study on recurrence of keratocystic odontogenic tumor. *J Jpn Soc Oral Tumors*. 2012;24:9-19. (in Japanese)
[6] Gorlin RJ, Goltz RW. Multiple nevoid basal cell epithelioma, jaw cysts and bifid rib: a syndrome. *N Engl J Med*. 1960;262:908-12.
[7] Gorlin RJ. Nevoid basal cell carcinoma (Gorlin) syndrome. *Genet Med*. 2004;6(6):530-39.
[8] Song YL, Zhang WF, Peng B, Wang CN, Wang Q, Bian Z. Germline mutations of the PTCH gene in families with odontogenic keratocysts and nevoid basal cell carcinoma syndrome. *Tumor Biol.* 2006; 27(4):175-80.
[9] Wang X, Lu Y, Shen G, Chen W. One germline mutation of PTCH gene in a Chinese family with non-syndromic keratocystic odontogenic tumors. *Int J Oral Maxillofac Surg*. 2011;40(8):829-33.
[10] Motamedi MH, Talesh KT. Management of extensive dentigerous cysts. *Br Dent J.* 2005;198(4):203-06.
[11] Apajalahti S, Hagström J, Lindqvist C, Suomalainen A. Computerized tomography findings and recurrence of keratocystic odontogenic tumor of the mandible and maxillofacial region in a series of 46 patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2011;111(3):e29-37.
[12] Weber AL. Imaging of cysts and odontogenic tumors of the jaw. Definition and classification. *Radiol Clin North Am*. 1993;31(1):101-20.
[13] Cakarer S, Selvi F, Isler SC, Keskin C. Decompression, enucleation, and implant placement in the management of a large dentigerous cyst. *J Craniofac Surg*. 2011;22(3):922-24.
[14] Shimada Y, Morita K, Kabasawa Y, Taguchi T, Omura K. Clinical manifestations and treatment for keratocystic odontogenic tumors associated with nevoid basal cell carcinoma syndrome: a study in 25 Japanese patients. *J Oral Pathol Med*. 2013;42(3):275-80.

PARTICULARS OF CONTRIBUTORS:
1. Fellow, Department of Oral and Maxillofacial Surgery, Center Hospital of the National Center for Global Health and Medicine, Tokyo, Japan.
2. Director, Department of Oral and Maxillofacial Surgery, Center Hospital of the National Center for Global Health and Medicine, Tokyo, Japan.
3. Resident, Department of Oral and Maxillofacial Surgery, Center Hospital of the National Center for Global Health and Medicine, Tokyo, Japan.
4. Assistant Director, Department of Pathology, Musashino Red Cross Hospital, Tokyo, Japan.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Yasuyuki Shimada,
1-21-1, Toyama, Shinjuku-ku, Tokyo, Japan.
E-mail: yasuyuki.shimada.ys@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: As declared above

Date of Submission: **Feb 12, 2016**
Date of Peer Review: **Apr 07, 2016**
Date of Acceptance: **Apr 26, 2016**
Date of Publishing: **Aug 01, 2016**