Multiple Orthokeratinized Odontogenic Cysts: A Case Report

Yi-Shing Lisa Cheng · Hui Liang · John Wright ·
Tom Teenier

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Abstract The purpose of this report is to document the clinical, radiographic, pathological and molecular findings of the first case of multiple orthokeratinized odontogenic cysts (OOCs). Multiple odontogenic keratocysts are one of the major features of nevoid basal cell carcinoma syndrome (NBCCS), and loss of heterozygosity in the PTCH gene, the culprit gene for NBCCS, has recently been found in sporadic OOC cases. Therefore, in this presenting case, we also investigated the possibility that this patient might also have NBCCS, by comparing the available clinical information and the molecular findings of this case to the diagnostic criteria for NBCCS (as proposed by the First International Colloquium on NBCCS in 2011). However, this patient with multiple OOCs showed no evidence of having NBCCS. This conclusion supports the findings from previous case series based on sporadic cases that OOC does not appear to be associated with NBCCS.

Keywords Orthokeratinized odontogenic cyst · Orthokeratinized odontogenic keratocyst · Nevoid basal cell carcinoma syndrome · PTCH

Introduction

Orthokeratinized odontogenic cyst (OOC), also called orthokeratinized variant of odontogenic keratocyst (OKC),

was first described by Wright in 1981 [1]. OOC shows a different clinical behavior from OKC and most authors have concluded that it is not associated with nevoid basal cell carcinoma syndrome (NBCCS) [1–4], in which multiple OKCs are one of the major features [5]. However, all the OOC cases reported to date were sporadic cases and each patient had a single OOC. To the best of our knowledge, this is the first case report of a patient with multiple OOCs. Of further note is the fact that loss of heterozygosity of the PTCH gene, the gene that was found to be mutated in 60–75 % of NBCCS patients [6], was recently found in both sporadic OKC cases and sporadic OOC cases [7]. This knowledge naturally gives rise to a strong interest in whether a patient with multiple OOCs might also be a NBCCS patient. Here we present the clinical, radiographical and molecular findings of this multiple OOCs case in which the patient showed no evidence of having NBCCS.

Case Report

A 23-year-old Hispanic male with a chief complaint of swelling and discomfort in the posterior mandible came to the Oral Surgery clinic. His medical history was significant for multiple skin cysts removed since childhood. The patient was born in a foreign country. Despite multiple efforts trying to obtain more detailed information about these skin lesions, the diagnoses of these cysts were not known. He did not have any symptoms of medulloblastoma in the brain or lymphomesenteric cysts in the abdominal cavity.

There was no visible abnormality, such as cleft lip, macrocephaly, hypertelorism, strabismus or coloboma found in the head and neck, although some nevi and small papular lesions were seen in the skin of his face and in his

Y.-S. L. Cheng (✉) · H. Liang · J. Wright
Diagnostic Sciences, Texas A&M University-Baylor College of
Dentistry, 3302 Gaston Ave, Dallas, TX 75246, USA
e-mail: ycheng@bcd.tamhsc.edu

T. Teenier
Oral and Maxillofacial Surgery Private Practice, 5402 Holly
Road, Suite 302, Building 3, Corpus Christi, TX 78411, USA

Fig. 1 Panoramic radiograph showed four well-defined unilocular radiolucent lesions associated with the third molars in all four quadrants: around apex of #1, around the crown of impacted #16, distally and superiorly to impacted #17 and distally to impacted #32, respectively (a). A coronal reformatted CT image revealed a cystic lesion superiorly to #1 with displaced sinus floor in the right maxilla; and a large cystic lesion encompassing the un-erupted #16 in the left

maxillary sinus with osseous discontinuity of the left maxillary sinus floor (b). Another coronal CT image showed a cystic lesion associated with the un-erupted #32 at the buccal surface, with thinning of the buccal cortex, and perforation of the superior border in the right mandible; and a large cystic lesion with expansion and thinning of buccal and lingual cortices in the left mandibular ramus (c)

body. There was no palmar pitting, short fourth metacarpal, or postaxial polydactyly in his hands. Intra-oral exam revealed no cleft palate and the third molars were not visible.

A panoramic radiograph taken by the referring general dentist showed four well-defined unilocular radiolucent lesions associated with the third molars in all four quadrants: around the apex of #1, around the crown of impacted #16, distally and superiorly to #17 and distally to impacted #32. (Fig. 1a). A computed tomography (CT) was subsequently taken. The coronal reformatted CT images revealed a cystic lesion superiorly associated with the un-erupted #1 with a displaced sinus floor in the right maxilla;

and a large cystic lesion encompassing the un-erupted #16 in the left maxillary sinus with perforation of the floor of left maxillary sinus (Fig. 1b). The other section of coronal CT images showed a cystic lesion associated with the un-erupted #32 at the buccal surface, with thinning of the buccal cortex, and perforation of the superior border in the right mandible (Fig. 1c). A large cystic lesion with expansion and thinning of buccal and lingual cortices was also seen in the left mandibular ramus (Fig. 1c). No calcification was found in the falx cerebri. The clinical diagnosis was multiple OKCs.

Biopsies were performed for all four lesions and they all showed similar histological features: a cyst with a thin,

Fig. 2 Histologically, all four lesions showed a cyst with a thin, uniform lining of squamous epithelium (**a**, H&E stain, original magnification $\times 28$). Orthokeratin formation and a granular cell layer were noted in the cyst lining epithelium (**b**, H&E stain, original magnification $\times 140$)

uniform lining of squamous epithelium, with a granular cell layer and orthokeratin formation (Fig. 2a, b). The diagnoses were OOCs for all four lesions.

The patient was willing to have further genetic testing, and his peripheral blood sample was obtained and sent to a diagnostic laboratory, GeneDx, in Gaithersburg, MD, for PTCH1 gene analysis. The analysis included a bi-directional sequencing analysis of exons 1–23 and the splice sites of the PTCH1 gene, as well as a targeted array CGH analysis with exon-level resolution for evaluating a deletion or duplication of one or more exons of PTCH1 gene. The sensitivity of this combination of sequencing and deletion testing was approximately 72 % for identifying a mutation in a patient with NBCCS (information provided by GeneDx with references). The genetic analysis showed negative results for both sequencing and deletion testing of PTCH1.

The two cysts in the maxilla and the right mandible were treated with complete curettage and the larger cyst in the

left mandible was marsupialized followed by curettage with application of Carnoy's solution. No recurrence of any of the cysts was found during a follow-up period of 14 months.

Discussion

OOC is an odontogenic developmental cyst characterized histologically by a cyst lined by squamous epithelium showing orthokeratin formation [5]. It occurs in the jaw bones and about 1/2 to 2/3 of the cases have been reported to be associated with an impacted tooth [3, 8], or have presented clinically as dentigerous cysts [5]. Sporadic OOC has been recently reported to be associated with two supernumerary teeth [9]. To the best of our knowledge, the presenting case is the first case of multiple OOCs occurring in the same individual, and each of the four OOCs was associated with the impacted 3rd molar in each quadrant.

Although OOC was originally reported as “orthokeratinized variant of odontogenic keratocyst” [1], differences have been found in clinical behavior, histological features and protein expression from those seen in OKC. Clinically, OOC rarely recurs after a treatment of enucleation with curettage, in contrast to a recurrence rate of approximately 30 % found in OKC [5]. Histologically, OOC shows stratified squamous epithelium with orthokeratin production and keratohyaline granules in the superficial layer adjacent to orthokeratin [5]. Prominent palisaded and hyperchromatic nuclei in the basal cell layer are not seen in OOC. Many studies have also found different histochemical and immunohistochemical features in OOC from OKC, including significant differences in keratin profiles in the cyst lining epithelium [10], in collagen fibers, fibronectin, or numbers of myofibroblasts in the cyst wall [11–14], in expression of podoplanin [15], Ki-67, p63 [3], TGF- α , P53 [16], bcl-2 [17], KAI-1 [18], cell proliferating marker IPO-38 [19], calretinin [20], EMA, CEA, and involucrin [21]. These findings lead to the current concept that OOC is a different pathological entity from OKC.

NBCCS (Gorlin syndrome) is an autosomal-dominantly inherited syndrome characterized by several major clinical features including multiple basal cell carcinomas (BCCs), multiple OKCs, palmar or plantar pitting, and intracranial calcification [5, 6]. The causative mutations have been found to be in the sonic hedgehog pathway, including PTCH1 [22, 23], PTCH2 [24], and SUFU [25], with PTCH1 mutation being found in 60–75 % of NBCCS patients [6, 26]. Although it is a genetic disease, about 35–50 % of affected patients represent new mutations [5]. As loss of heterozygosity of the PTCH gene has also been found in the tissue of both sporadic OKC cases (5/7 = 71 %) and sporadic OOC cases (4/7 = 57 %) [7],

Table 1 Comparison of the features in the presenting case with the diagnostic criteria for NBCCS based on the consensus statement from the First International Colloquium on NBCCS [6]

Diagnostic criteria for NBCCS		Presence of the feature in the presenting case
Major criteria	BCC prior to 20 years old or excessive numbers of BCC out of proportion to prior sun exposure and skin type	Unknown
	OKCs of the jaw prior to 20 years of age	No (multiple orthoOKCs of the jaw)
	Palmar or plantar pitting	No
	Lamellar calcification of the falx cerebri	No
	Medulloblastoma	Unknown
	First degree relative with NBCCS	No
Minor criteria	Rib anomalies	Unknown
	Skeletal malformations and radiologic changes (i.e., vertebral anomalies, kyphoscoliosis, short fourth metacarpals, postaxial polydactyly)	No short fourth metacarpals. No postaxial polydactyly
	Macrocephaly	No
	Cleft lip/palate	No
	Ovarian/cardiac fibroma	Unknown
	Lymphomesenteric cysts	Unknown
	Ocular abnormalities (i.e., strabismus, hypertelorism, congenital cataracts, glaucoma, coloboma)	No

we investigated the possibility that this patient might also have NBCCS. We compared the clinical features of this case with the recently published diagnostic criteria for NBCCS, proposed by the First International Colloquium on NBCCS in 2011 [6], as listed in Table 1. In this set of diagnostic criteria, the clinical and molecular findings are categorized into major and minor criteria, and a diagnosis of NBCCS should be considered if the patient shows: (1) one major criteria and molecular confirmation; (2) two major criteria; or (3) one major and two minor criteria [6]. Based on the available clinical information, this patient does not have any clinical features that fit any of the major or minor criteria. Although epidermal cysts of the skin are found 50 % or greater frequency in NBCCS [27], the pathological diagnosis of the multiple skin cysts removed from this patient in childhood unfortunately could not be established. The OOCs found in this patient are believed to be a different pathological entity from OKC based on clinical behavior and histological, histochemical, and immunohistochemical findings (see above), despite the fact that the genetic abnormality in PTCH gene has also been

found in OOC [7]. The commercially available genetic test for Gorlin syndrome tested only the abnormalities occurring in PTCH1 which accounts for 72 % of the NBCCS patients (information provided by GeneDx). Therefore, whether this patient may have mutations in PTCH2, SUFU or other unidentified genes that may be related to NBCCS is still unknown. Although the genetic finding cannot completely exclude the possibility of NBCCS, the currently available clinical, pathological and genetic data shows no evidence suggesting that our patient has NBCCS.

In summary, we report the first case of multiple OOCs in a 23-year-old man, with the clinical, radiographic, histological and molecular findings. Based on these findings and the diagnostic criteria proposed by the First International Colloquium on NBCCS, this patient does not have NBCCS. The findings of this case report support the findings from previous case series regarding sporadic OOC cases [1–4] that OOC does not appear to be associated with NBCCS.

Conflict of interest The authors declare that they have no conflict of interest.

References

- Wright JM. The odontogenic keratocyst: orthokeratinized variant. *Oral Surg Oral Med Oral Pathol.* 1981;51(6):609–18.
- Li TJ, Kitano M, Chen XM, et al. Orthokeratinized odontogenic cyst: a clinicopathological and immunocytochemical study of 15 cases. *Histopathology.* 1998;32(3):242–51.
- Dong Q, Pan S, Sun LS, Li TJ. Orthokeratinized odontogenic cyst: a clinicopathologic study of 61 cases. *Arch Pathol Lab Med.* 2010;134(2):271–5.
- Crowley TE, Kaugars GE, Gunsolley JC. Odontogenic keratocysts: a clinical and histologic comparison of the parakeratin and orthokeratin variants. *J Oral Maxillofac Surg.* 1992;50(1):22–6.
- Neville BW, Damm DD, Allen CM, Bouquot JE. Orthokeratinized odontogenic cyst. In: Neville BW, Damm DD, Allen CM, Bouquot JE, editors. *Oral and maxillofacial pathology.* St. Louis: Saunders Elsevier; 2009. p. 687–8.
- Bree AF, Shah MR. Consensus statement from the first international colloquium on basal cell nevus syndrome (BCNS). *Am J Med Genet A.* 2011;155A(9):2091–7.
- Diniz MG, Galvao CF, Macedo PS, Gomes CC, Gomez RS. Evidence of loss of heterozygosity of the PTCH gene in orthokeratinized odontogenic cyst. *J Oral Pathol Med.* 2011;40(3):277–80.
- Macdonald-Jankowski DS. Orthokeratinized odontogenic cyst: a systematic review. *Dentomaxillofac Radiol.* 2010;39(8):455–67.
- Kasat VO, Saluja H, Kalburge JV, et al. Multiple bilateral supernumerary mandibular premolars in a non-syndromic patient with associated orthokeratinized odontogenic cyst—a case report and review of literature. *Contemp Clin Dent.* 2012;3(Suppl 2):S248–52.
- Aragaki T, Michi Y, Katsube K, et al. Comprehensive keratin profiling reveals different histopathogenesis of keratocystic odontogenic tumor and orthokeratinized odontogenic cyst. *Hum Pathol.* 2010;41(12):1718–25.
- Zhang JY, Dong A, Li TJ. Differences in collagen fibres in the capsule walls of parakeratinized and orthokeratinized odontogenic cysts. *Int J Oral Maxillofac Surg.* 2011;40(11):1296–300.

12. Vered M, Shohat I, Buchner A, Dayan D. Myofibroblasts in stroma of odontogenic cysts and tumors can contribute to variations in the biological behavior of lesions. *Oral Oncol.* 2005;41(10):1028–33.
13. da Silva MJ, de Sousa SO, Correa L, Carvalhosa AA, De Araujo VC. Immunohistochemical study of the orthokeratinized odontogenic cyst: a comparison with the odontogenic keratocyst. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2002;94(6):732–7.
14. Roy S, Garg V. Evaluation of stromal myofibroblasts expression in keratocystic odontogenic tumor and orthokeratinized odontogenic cysts: a comparative study. *J Oral Maxillofac Pathol.* 2013;17(2):207–11.
15. Caetano Ados S, Tjioe KC, Faustino SE, et al. Immunolocalization of podoplanin in benign odontogenic tumours with and without ectomesenchyme. *Arch Oral Biol.* 2013;58(4):408–15.
16. Deyhimi P, Hashemzade Z. Comparative study of TGF- α and P53 markers' expression in odontogenic keratocyst and orthokeratinized odontogenic cyst. *Dent Res J (Isfahan).* 2012;9(Suppl 1):S39–44.
17. Rangiani A, Motahary P. Evaluation of bax and bcl-2 expression in odontogenic keratocysts and orthokeratinized odontogenic cysts: a comparison of two cysts. *Oral Oncol.* 2009;45(7):e41–4.
18. Iezzi G, Piattelli A, Artese L, et al. KAI-1 protein expression in odontogenic cysts. *J Endod.* 2007;33(3):235–8.
19. Thosaporn W, Iamaroon A, Pongsiriwet S, Ng KH. A comparative study of epithelial cell proliferation between the odontogenic keratocyst, orthokeratinized odontogenic cyst, dentigerous cyst, and ameloblastoma. *Oral Dis.* 2004;10(1):22–6.
20. Piattelli A, Fioroni M, Iezzi G, Rubini C. Calretinin expression in odontogenic cysts. *J Endod.* 2003;29(6):394–6.
21. Vuhahula E, Nikai H, Ijuhin N, et al. Jaw cysts with orthokeratinization: analysis of 12 cases. *J Oral Pathol Med.* 1993;22(1):35–40.
22. Johnson RL, Rothman AL, Xie J, et al. Human homolog of patched, a candidate gene for the basal cell nevus syndrome. *Science.* 1996;272(5268):1668–71.
23. Hahn H, Wicking C, Zaphiropoulos PG, et al. Mutations of the human homolog of *Drosophila* patched in the nevoid basal cell carcinoma syndrome. *Cell.* 1996;85(6):841–51.
24. Fan Z, Li J, Du J, et al. A missense mutation in PTCH2 underlies dominantly inherited NBCCS in a Chinese family. *J Med Genet.* 2008;45(5):303–8.
25. Pastorino L, Ghiorzo P, Nasti S, et al. Identification of a SUFU germline mutation in a family with Gorlin syndrome. *Am J Med Genet A.* 2009;149A(7):1539–43.
26. Jones EA, Sajid MI, Shenton A, Evans DG. Basal cell carcinomas in gorlin syndrome: a review of 202 patients. *J Skin Cancer.* 2011. doi:[10.1155/2011/217378](https://doi.org/10.1155/2011/217378).
27. Neville BW, Damm DD, Allen CM, Bouquot JE. Nevoid basal cell carcinoma syndrome (Gorlin syndrome). In: Neville BW, Damm DD, Allen CM, Bouquot JE, editors. *Oral and maxillofacial pathology*. St. Louis: Saunders Elsevier; 2009. p. 688–91.