

# The Multifocal Nature of Odontogenic Keratocysts

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## ABSTRACT

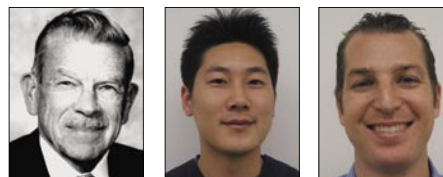
The odontogenic keratocyst, OKC, is a very aggressive intraosseous lesion with a recurrence rate of approximately 25 percent to 60 percent.<sup>1</sup> The tendency for this lesion to "return" after surgical treatment has prompted studies to obtain more information concerning the inherent nature of the lesion. The OKC lesions are usually treated with enucleation of the soft tissue lining, curettage and ostectomy of the bony margins, or with more aggressive block resection. The purpose of this study was to characterize the multifocal aspect of the OKC and to demonstrate the presence of cystic lesions remote from the margins of the primarily diagnosed cyst itself. A retrospective chart review was conducted of seven patients who had sustained a long history of recurrent OKCs.

Three types of documentation were reviewed for each patient:

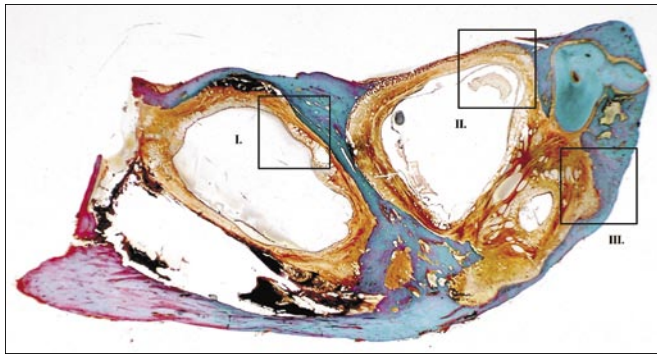
- Orthopantomograms, cephalograms, and CT scans, which had been taken over the long-term course of the disease,
- Detailed operation reports of surgical procedures to treat the OKC lesions, and
- Large histologic specimens from the six patients who received total resection of the involved mandibular bodies.

These hemimandibulectomy slides offered a unique opportunity to observe OKC activity throughout a wide osseous area.

All patients had been operated multiple times over a period of 10 to 21 years, coming eventually to mandibular resection. The operating surgeon in all of the cases was one of the authors, Philip J. Boyne, DMD, MS, DSc. All patients exhibited the multifocal nature of OKCs with demonstrable cyst formation at distant sites in the mandible. Two patients had local recurrences at the margins of the primary lesion in addition to cyst formation at distant sites. The authors concluded that clinicians should respect the multifocal nature of OKCs. The "recurrences" observed in OKCs may not necessarily be due to the degree of skill of the surgeon or the technique used to eradicate the primary cyst, but instead are probably a reflection of the multifocal nature of the pathologic lesion itself. The OKC is a very aggressive intraosseous lesion of the jaws, which not infrequently clinicians detect in the process of routine oral examination.<sup>2</sup>



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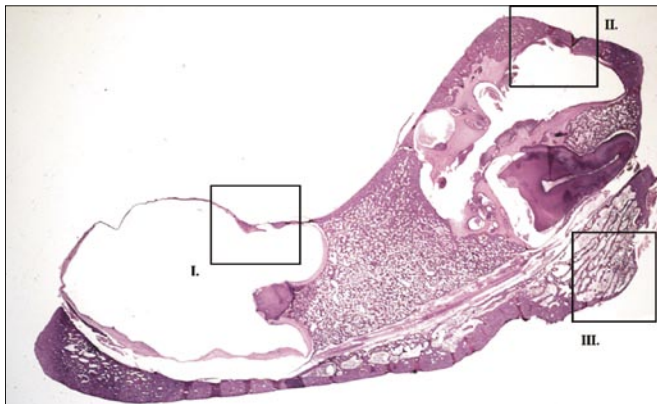


**Figure 1.**

**Box I.** Shows the lining of the large primarily diagnosed OKC lesion.

**Box II.** Shows the area of an additional secondary proliferating OKC separate from the primary lesion.

**Box III.** Shows an area containing small early proliferating OKCs, again separate from the primarily diagnosed OKC lesion.

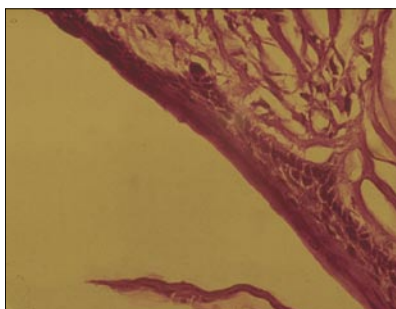


**Figure 2a.**

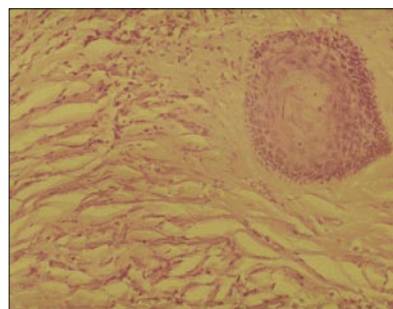
**Box I.** The lining of a large primarily diagnosed OKC is shown.

**Box II.** The lining of large mature secondarily diagnosed OKC is shown. (The space surrounding the crown of the impacted tooth represents a dentigerous cyst, which is separate from the surrounding OKCs.)

**Box III.** An area of additional epithelial cell nests and small developing OKCs separate from the other larger OKCs is shown at the angle of the mandible.



**Figure 2b.** The thin epithelial lining of the primary OKC lesion shown in Figure 2a Box I at a higher magnification. The existence of a basal cell layer with high mitotic activity is characteristic of an OKC, along with a marked sloughing of keratin into the lumen of the cyst.



**Figure 2c.** This view shows a magnified view of Figure 2a Box III, where a small cyst is developing into a characteristic OKC. The existence of a basal layer with high mitotic activity is shown.

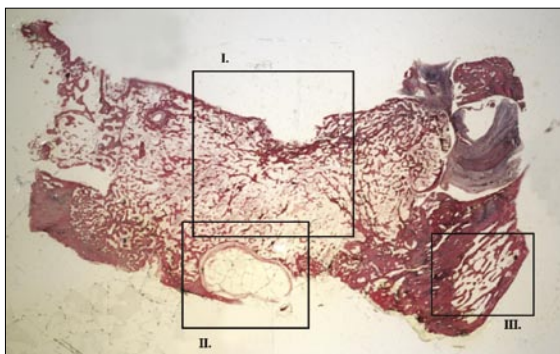
There are two types of OKCs: nonsyndromic or sporadic, and syndromic Nevroid Basal Cell Carcinoma, NBCCs. The NBCCs Gorlin-Goltz syndrome is characterized by multiple OKCs, nevoid basal cell carcinomas of the skin, bifid ribs, calcification of the fax cerebri, and other findings.<sup>1</sup>

The most commonly involved areas for occurrence of OKCs are the angle of the mandible and the ascending ramus.<sup>3</sup> The symphyseal area is also frequently a locus for this lesion. The current treatment modalities of OKCs range from conservative enucleation to more radical partial en bloc resection. The cause of recurrence has been attributed in some reports to the type of surgical treatment of the bony margins as well as the skill and experience of the surgeon.<sup>4</sup>

The epithelial lining of OKCs is thought to be a source of the recurrence. "Disruption of the epithelial lining was documented in 50 percent of the cases of recurrence and 45 percent of all cysts, leading to the belief that new cysts form from remaining fragments of cyst walls."<sup>5</sup>

More recent research has shown that "differences in proliferative activity in OKCs suggest an alteration of the cell's cycle control" producing "an increase in cell proliferation that could explain the biological behavior of OKCs."<sup>6</sup>

The goal of this study was to demonstrate the presence or absence of additional cysts proliferating in areas not necessarily adjacent to the primary cystic lesion. This study is felt to be of clinical importance since OKC patients are usually treated to "prevent" recurrence at the margins of the initially presenting lesion. If there are additional cysts present at some distance from the original lesion, then drastic treatment of the original cyst's bony margin may not be helpful in preventing the persistence of the lesion.

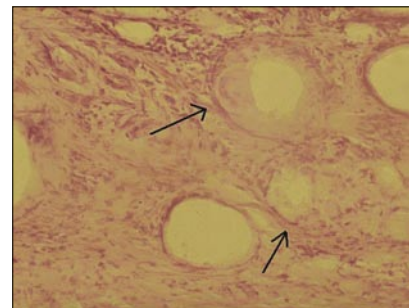


**Figure 3a.**

**Box I.** The lines indicate the borders of a previous block resection for an OKC, followed by a bone graft. There is no OKC recurrence in the bone grafted area.

**Box II.** This area shows the presence of a secondarily occurring OKC at the inferior border of the mandible.

**Box III.** The presence of additional developing OKCs is shown in the MV spaces at the angle of the mandible.



**Figure 3b.** This is a magnified view of Figure 3a Box III showing the presence of young developing OKCs.

The authors' study is unique because of the availability in the cases of histologic single-sectioned slides of the entire horizontal mandible. These specimens were procured from the resected hemimandibles of six of the seven patients. These large slides offer a view of the entire mandible not usually obtained from routine pathologic specimens, which usually are multisectioned cuts through the lesion's margins. A literature search revealed no other investigation has presented such histologic material.

### Materials and Methods

A retrospective chart review was completed of seven patients having a long history of recurrent OKCs, and who eventually came to resection of the mandible because of continual recurrence of the lesions. Three types of documentation were studied and reviewed for each patient:

- Orthopantomograms, cephalograms, and CT scans, which had been taken over the long-term course of the disease,

- Reports of the patients' history and physical examination, and surgical procedures throughout the entire treatment of the OKC lesions, and

- A review of large pathologic specimens from the hemisections of the mandibular body.

### Results

It was found that all of the patients in the study experienced multiple surgical operations for treatment of OKCs over a period of 10 to 21 years. Operations included curettage of bony margins, enucleation of cysts, block resection, and hemisection of the mandible.

In treating the lesion, six patients came to complete surgical unilateral resection of their horizontal mandible due to continual recurrences of aggressive cysts. These resections were performed after multiple failed attempts to control the recurrences. In all patients, the osseous defect created by the surgery was restored by an autogenous iliac crest bone graft. In these patients receiving resection, no recurrences of OKCs were noted in the bone grafted areas or in the surrounding native bone.

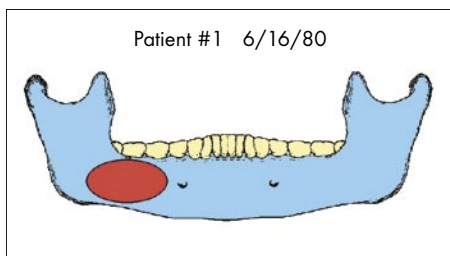
All of the patients exhibited the multifocal nature of OKCs. Initially, a single cyst was discovered and surgically treated, followed by "secondary" cyst formations at distant sites in the mandible (Figures 4a-b; Figures 5a-d). The authors' study showed that all the patients had evidence of multifocal OKCs (Figures 1-5). These histologic findings revealed collections of epithelial cells at distant sites in the marrow vascular spaces of the mandible. Some of these epithelial cells demonstrated

a central lumen, while others showed actual cyst formation with characteristic OKC keratin desquamation (Figures 2a-c; Figures 3a-b). Two patients had local recurrences at the margins of the primary lesion in addition to cyst formations at distant sites (Figure 5d).

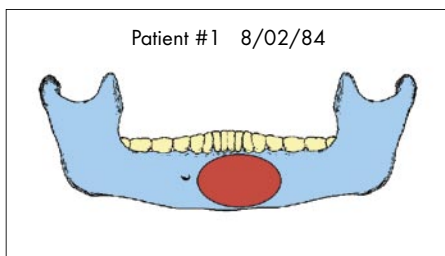
### Discussion

Successful treatment of OKCs is usually attributed to the use of techniques which address the margins of the initially presenting cyst, with the objective of removing all of the epithelial lining.<sup>7-9</sup> In the background literature review, the term "recurrence" was used to describe cysts that recurred near the bony margin of the originally treated cyst.<sup>10</sup> It could be proposed that rather than "recurrences" of the original cystic lesion, many OKC patients are actually experiencing separate "occurrences" at distant sites. Although this study was only based upon seven patients, the availability of histopathologic review of the entire body of the mandible, on the involved side, has given interesting information on this problem area. It could be assumed from this review that aggressive surgical treatment of the bony margins of the primary lesion would not necessarily preclude a second occurrence.

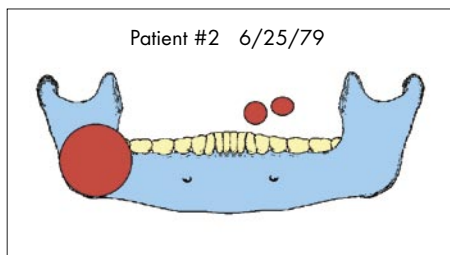
It is of interest that the observations made in this paper may corre-



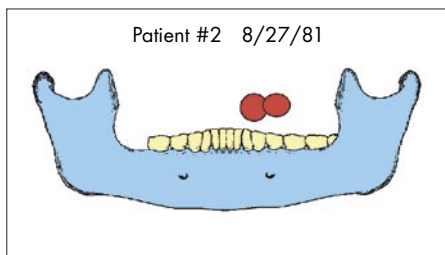
**Figure 4a.** Patient No. 1 presented with a large OKC lesion near the right angle of the mandible. The lesion was treated with enucleation, peripheral ostectomy, and iliac crest autogenous particulate bone graft. The area healed completely.



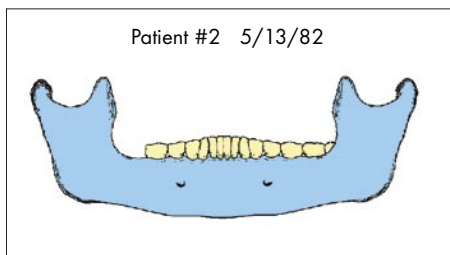
**Figure 4b.** Four years later, Patient No. 1 showed healed bone at the right angle of the mandible. However, the patient now presents with a large OKC lesion toward the left symphysis area. This OKC is separate and distinct from the primary lesion that was treated four years previously. This new lesion clearly illustrates the multifocal nature of OKCs.



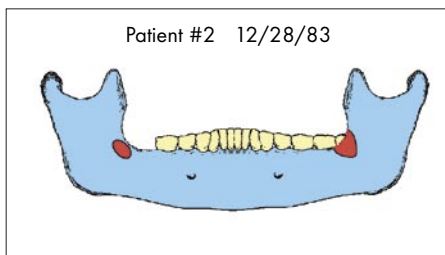
**Figure 5a.** Patient No. 2 presented with a large OKC lesion at the right angle of the mandible, along with two other OKCs in the left maxillary incisor and canine areas.



**Figure 5b.** Patient No. 2 was treated by curettage for the large OKC lesion at the right angle of the mandible. This depiction of the radiographs, taken two years later, showed osseous healing in that area.



**Figure 5c.** Patient No. 2 was treated for the maxillary OKCs. Radiographs taken a year later show good postoperative bone healing.



**Figure 5d.** Four years after initial treatment of the mandible OKC, the patient presents with a local OKC recurrence in the right mandibular area, along with a new OKC lesion at the left third molar area of the mandible. The new lesion in the left mandible is representative of the multifocal nature of this lesion.

**Figures 4a and b** and **5a-d** are two-dimensional representations of the radiographs that were reviewed for these two patients. The presence of OKCs (depicted in red) were derived from orthopantomograms, cephalograms, and CT scans.

late with the results of recent genetic research. A tumor suppressor gene has been shown to be associated with the nevoid basal cell carcinoma syndrome or NBCCS. Alterations in this tumor suppressor gene, which is also called the patched gene or PTCH, may be the first important step in the pathogenesis of the OKC. It is possible that OKC epithelial cells remain in a “resting state” in the mandible for an indeterminate amount of time, under the protective influence of the PTCH tumor suppressor gene. Any mutations in the favorable influence of this tumor suppressor gene, could lead to rapid OKC cell proliferation and a change from a dormant state to a more aggressive form. Recent immunocytochemical studies have shown that the PTCH gene is also present and exerting its protective influence in the case of sporadic OKCs, as well as in the case of the syndromic NBCCS cysts. This dramatic mutation of the PTCH gene in sporadic OKCs, as well as the syndromic OKCs, is very important in understanding the nature of this aggressive lesion. If the PTCH gene undergoes mutation, its protective influence may be lost through a subsequent immunologic “hit” and the OKC resting cells may become neoplastically aggressive.<sup>11-13</sup>

This genetic change could help to explain the aggressive behavior of the OKC cells just as the loss of the tumor suppression produces aggressive behavior in other forms of neoplastic disease. In fact, Shear, in 2002, stated that the “loss of tumor suppressor genes supports the view that OKC is a benign neoplasm.”<sup>11</sup>

The histological sections, which demonstrated the presence of clusters of epithelial cells and secondary cysts, show the multifocal characteristics of OKCs. In fact, many of these distant cysts were too small to be shown by

radiographic imaging. Clinicians should be aware that these small cystic areas can exist in OKC patients without detection.

Literature has shown that patients sustaining large resections of the mandible have the lowest recurrence rate of OKCs compared with other surgical techniques.<sup>14,15</sup> The authors' study illustrated a possible reason for this observation. These patients demonstrated the presence of additional cysts and epithelial clusters at distant sites in the large mandibular histological sections. The reported low OKC recurrence rate following mandibular resections could possibly be explained by the fact that the multifocal lesions have become part of the large resected specimen.

In the authors' study, two of the seven patients were syndromic. It was reported that a characteristic of syndromic patients, NBCCS, was a high multifocal occurrence of OKCs, along with a high recurrence rate.<sup>16</sup> The authors showed that nonsyndromic or sporadic OKCs also can exhibit multifocal OKCs. Additionally, the authors' sporadic OKC cases also had recurrences that were highly destructive and aggressive (Figure 1).

The distant lesions were seen to be in various stages of maturation from single collections of epithelial cells to lumen development and cyst formation. Pathologic specimens viewed microscopically showed that the remote cysts tended to begin around a keratin pearl leading to lumen formation.

## Conclusions

■ Clinicians should respect the multifocal characteristics of OKCS.

■ OKCS exhibit highly aggressive behavior, and persistence of the lesion can lead to mandibular resections.

■ In all of the mandibular resected

patients, no "recurrences" were noted to date in the bone-grafted surgical site or elsewhere in the native bone. The one patient who did not receive hemiresection experienced "recurrence" of the OKCs.

■ Syndromic patients, along with nonsyndromic or sporadic patients, tend to present with multifocal lesions.

■ The recurrence of OKCs may not necessarily be due to the degree of skill of the surgeon or the technique used to eradicate the primarily diagnosed cyst, but instead is probably a reflection of the multifocal nature of the lesion itself. **CDA**

**References** / 1. Sapp PJ, Eversole LR, Wysocki GP, Contemporary Oral and Maxillofacial Pathology, St. Louis, Mo., pg. 54, 2004.

2. Myoung H, Hong S, et al, Odontogenic keratocyst, review of 256 cases for recurrence and clinicopathologic parameters. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 91(3):3280-33, 2001.

3. El-hajj G, Anneroth G, Odontogenic keratocysts, A retrospective clinical and histologic study. *Int J Oral Maxillofac Surg* 25:124-9, 1996.

4. Kakarantza-Angelopoulou E, Nicolatou O, Odontogenic keratocysts: Clinicopathologic study of 87 cases. *J Oral Maxillofac Surg* 48(12):1353-4, 1990.

5. Anand VK, Arowood JP, Krolls SO, Odontogenic keratocysts: A study of 50 patients. *Laryngoscope* 105(1):14-6, 1995.

6. Piatelli A, Fioroni M, et al, Protein expression in odontogenic cysts. *J Endod* 27(7):459-61, 2001.

7. Ephros H, Lee HY, Treatment of a large odontogenic keratocyst using the Brosch procedure. *J Maxillofac Surg* 49(8):871-4, 1991.

8. Meara JG, Shah S, et al, The odontogenic keratocyst: A 20-year clinicopathologic review. *Laryngoscope* 108(2):280-3, 1998.

9. Gryfe A, Gryfe JH, Isolated odontogenic keratocyst. *Canadian Med Assoc J* 117:1392-4, 1977.

10. Hsun-Tau C, Odontogenic keratocyst: A clinical experience in Singapore. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 86(1):573-7, 1998.

11. Shear M, The aggressive nature of the odontogenic keratocyst: is it a benign cystic neoplasm? Part 2 proliferation and genetic studies, *Oral Oncol* 38(4):323-31, 2002.

12. Barreto DC, Bale AE, et al, Immunolocalization of PTCH protein in odontogenic cysts and tumors. *J Dent Res* 81(11):757-60, 2002.

13. Barreto DC, Gomez RS, et al, PTCH gene mutations in odontogenic keratocysts. *J Dent Res* 79(6):1418-22, 2000.

14. Blanas N, Freund B, et al, Systematic review of the treatment and prognosis of the odontogenic keratocyst. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 90(5):553-8, 2000.

15. Zhao YF, Wei JX, Wang SP, Treatment of odontogenic keratocysts: a follow-up of 255 Chinese patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 94(2):151-6, 2002.

16. McGrath CJR, Myall RWT, Conservative management of recurrent keratocysts in basal-cell naevus syndrome. *Aust Dent J* 42(6):399-403, 1997.

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