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Keratocystic Odontogenic Tumor (Odontogenic Keratocyst): Preliminary Retrospective Review of Epidemiologic, Clinical, and Radiologic Features of 261 Lesions From University of Turin

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PURPOSE

To analyze and discuss the demographic, clinical, and surgical aspects of 261 surgically treated keratocystic odontogenic tumors.

PATIENTS AND METHODS

A retrospective review was performed of all cases of treated keratocystic odontogenic tumors. Statistical analysis was used to search for associations among age, presenting symptoms, location, dimension, and locularity.

RESULTS

Keratocystic odontogenic tumors most commonly occurred in patients in the third and fourth decades of life. The ratio of males to females was 2:1. The mandibular angle region was the most frequently involved site. Significant associations were found between multilocular lesions and lesions larger than 31 mm ($P < .00000005$), a mandibular site and larger lesions ($P < .05$), patients younger than 41 years old and multilocular lesions ($P < .05$), and younger patients and larger lesions ($P < .00005$).

CONCLUSION

It is likely that most multilocular, larger (and probably aggressive) lesions are found in patients younger than 41 years of age.

Keratocystic odontogenic tumor (KCOT), or odontogenic keratocyst (OKC), is a benign neoplasm defined by the World Health Organization as a benign uni- or multicystic, intraosseous tumor of odontogenic origin, with a characteristic lining of parakeratinized stratified squamous epithelium and a potential for aggressive, infiltrative behavior. OKCs are characterized by unique and distinct histologic characteristics, an aggressive biologic behavior, and a high recurrence rate. Histologically, OKCs will have parakeratinized stratified cell layers, thickened squamous epithelium, daughter cysts, budding proliferation of the epithelium, and the formation of islands of odontogenic epithelium. OKCs are of great interest because of its high recurrence potential. The published data have reported a recurrence rate of 0% to 62%. The OKC has the ability to expand through bony walls and invade deeper structures. OKCs show a high proliferative potential, balanced by apoptotic cell death.

Radiographically, the lesion appears as a unilocular or multilocular radiolucency, surrounded by smooth or scalloped margins with sclerotic borders. However, other lesions can exhibit similar features.
The treatment of OKCs remains controversial. Various treatment modalities, both conservative and aggressive, have been reported. Conservative treatment has generally included enucleation, decompression, or marsupialization, and aggressive treatment has generally included peripheral ostectomy and resection.

The purpose of the present study was to analyze and discuss the demographic, clinical, and surgical aspects of 241 patients with 261 OKCs treated between 1980 and 2009 at the University of Turin.

PATIENTS AND METHODS

A retrospective chart review was performed of all cases of OKC treated at the Division of Maxillofacial Surgery, University of Turin (Turin, Italy) between 1980 and 2009.

The criterion for inclusion was surgically treated OKCs meeting the histologic criteria as outlined by Pindborg and Hansen and Browne. The exclusion criteria were the absence of surgical treatment at the University of Turin and a diagnosis of basal cell nevus syndrome. The retrospective series was exempted from review as a retrospective series by our institutional review board human studies committee.

A total of 241 patients with 261 OKCs were included.

The data collected included age at diagnosis, gender, lesion location, clinical manifestations, radiographic features, treatment modality, and recurrence.

The location of OKCs was classified as follows: maxillary incisor and canine, maxillary premolar, maxillary molar, mandibular incisor and canine, mandibular premolar, mandibular molar, and mandibular angle and ramus. The clinical manifestation at diagnosis was recorded in 2 categories: OKCs identified incidentally by routine radiography and OKCs identified in patients presenting with symptoms such as pain, swelling, inferior alveolar nerve paresthesia, infection, or drainage.

The lesions were also divided into unilocular and multilocular variants according to the radiographic findings. To assess the size of these lesions, the major axes of the lesions were measured on the panoramic radiographs. The treatment provided was also determined from a review of the operative report and recorded. Recurrences in the first 18 months after surgery were recorded after review of the follow-up hospital records.

Statistical analysis was used to search for associations among multiple variables. Such variables included age, presenting symptoms, location, dimension, and locularity. Statistical significance was determined using the $\chi^2$ or Fisher exact test, if the sample sizes were too small.

RESULTS

A total of 241 patients with 261 OKCs underwent surgical treatment during the study period. Of the 241 patients, 11 presented with synchronous cysts. The age range was 7 to 87 years (mean, 43.34; median, 43; standard deviation, 17.6). OKCs most commonly occurred in patients in the fourth decade of life (58 patients, 24%), followed by those in the third (43 patients, 17.8%; Fig 1). Of the 241 patients, 163 (67.6%) were male and 78 (32.4%) were female. Therefore, the ratio of males to females was 2:1, with a male predilection.
The maxilla was involved in 70 lesions (26.8%), and 191 OKCs (73.2%) were mandibular (ratio, 1:2.7). Of the 261 lesions, 77 (29.5%) were in the mandibular ramus and angle region, 59 (22.6%) were in the mandibular molar region, 42 (16.1%) were in the mandibular premolar region, 36 (13.8%) were in the maxillary molar region, 18 (6.9%) were in the maxillary premolar region, 16 (6.1%) were in the maxillary incisor and canine region, and 13 (5%) were in the mandibular incisor and canine region (Figure 2 and Figure 3,4). The mandibular ramus and angle region was the most frequently involved site.
Of the 241 patients, 97 (37.2%) presented with symptoms (swelling, pain, drainage, infection, and/or inferior alveolar nerve hypoesthesia), and 144 (62.8%) were asymptomatic. Their lesions were found incidentally during routine dental radiographic examination. The radiographic findings confirmed that 218 OKCs (83.5%) were unilocular and 43 (16.5%) were multilocular (Fig 5).

The mean lesion size measured on the panoramic radiographs was 31 mm (range, 10 to 80; median, 30; standard deviation, 1.377). The mean size of the mandibular OKCs was 32.4 mm (range, 10 to 80), and the mean size of the maxillary lesions was 28 mm (range, 15 to 70).

Of the 261 lesions, 250 (95.8%) were treated with surgical enucleation plus curettage and 11 (4.2%) were treated with marsupialization.

In the first 36 months after surgery, 31 recurrences (11.9%) of OKC were diagnosed. The recurrences were conservatively treated with enucleation and curettage.

Statistical analysis using the $\chi^2$ or Fisher exact test found significant associations between multilocular lesions and lesions larger than 31 mm (relative risk [RR], 10.066; 95% confidence interval [CI], 4.64 to 22.675; $P<.00000005$), a mandibular site and OKCs larger than 31 mm (RR, 2.313; 95% CI, 1.2 to 4.6; $P<.05$), patients younger than 41 years old and multilocular lesions (RR, 2.187; 95% CI, 1.1 to 4.366; $P<.05$), and patients younger than 41 years old and lesions larger than 31 mm (RR, 3.2; 95% CI, 1.834 to 5.631; $P<.000005$).

**DISCUSSION**

The approach to the treatment of OKCs is controversial. OKC requires special consideration because of its potential for aggressive, infiltrative behavior and the tendency to recur.\textsuperscript{6} and \textsuperscript{10}
Because of these characteristics and its rapid growth pattern (associated with frequent mitotic figures in the suprabasal layers), OKC is currently considered to be a tumor by the World Health Organization.\textsuperscript{11, 12} OKCs sometimes occur in patients affected by basal cell nevus syndrome (Gorlin syndrome).

The mean age of 43.34 years in the present study was similar to the mean age reported by Ahlfors et al,\textsuperscript{13} Brannon,\textsuperscript{14} and Morgan et al.\textsuperscript{15} As reported by Morgan et al,\textsuperscript{15} the exclusion of patients with Gorlin syndrome might have increased the mean age and altered the peak incidence, usually reported at the second and third decades of life. However, we found most patients were aged 31 to 40 and 41 to 50 years.

The ratio of males to females with OKC was 2:1, confirming the male predominance reported by several investigators.\textsuperscript{11, 15, 16 and 17}

The mandible was the most common OKC site (73.2\%) in our study, consistent with the results of other studies.\textsuperscript{12, 16, 17, 18 and 19} In particular, the posterior body and ramus regions have been the most frequently involved locations, as was confirmed by our series. More than one half of the whole study group (52.1\%) had OKCs in the mandibular molar, ramus, and angle regions.

The radiographic findings confirmed that most OKCs (83.5\%) were unilocular, with only 16.5\% multilocular.

The mean lesion size was 31 mm. As reported by Eryilmaz et al,\textsuperscript{18} OKCs of the maxilla are smaller than those in the mandible, measuring an average of 28 and 32.4 mm, respectively, in our study.

OKCs are generally thought to derive from either dental lamina remnants or traumatic implantation or downgrowth of the basal cell layer of the surface epithelium.\textsuperscript{20} Clinical evidence of the aggressive behavior of OKCs has been supported by reported cases involving perforation of adjacent cortical bone and extension to the adjacent soft tissues or extending to the skull base from the mandible or to the orbit and infratemporal fossa from the maxilla.\textsuperscript{19, 21, 22 and 23} The aggressive behavior, neoplastic potential, and high recurrence rate of OKCs seem to be confirmed by several features, including the high mitotic rate, intraluminal hyperosmolality, collagenolytic activity in the cyst wall, synthesis of interleukin-1 and interleukin-6 by keratinocytes, the increased expression of parathyroid hormone-related protein, and the greater frequency of proliferating cell nuclear antigen (PCNA) and Ki-67, p53, Bcl-2, and Gp38 positivity.\textsuperscript{2, 6, 10, 24, 25, 26, 27, 28, 29, 30, 31, 32 and 33} Various studies have found evidence of allelic loss of heterozygosity in the p16, p53, PTCH, MCC, TSLC1, LTAS2, and FHIT genes.\textsuperscript{34, 35 and 36}

However, as reported by Giuliani et al,\textsuperscript{19} some of these markers might be misleading if inflammation is present, although Ki-67 could be recommended as a prognostic marker.\textsuperscript{3}

As summarized by Gomes et al,\textsuperscript{24} 2 theories about the development have been proposed: the “2-hit” and the haploinsufficiency theory. According to the “2-hit” model, sporadic OKCs arise from susceptible cells in which 2 somatic “hits” have occurred. In contrast, lesions associated with Gorlin syndrome would derive from precursor cells containing a hereditary “first hit” followed by allelic loss of the second normal allele. According to the haploinsufficiency theory, OKCs arise from the loss of only 1 PTCH allele, leading to a reduction in gene dosage.\textsuperscript{24} Gomes et al\textsuperscript{24} stated that the presence of normal PTCH protein in patients with OKC with a PTCH nonsense mutation suggests the retention of 1 wild PTCH allele. Therefore, the haploinsufficiency model would appear to be supported.

Regarding recurrence, 3 different theories have been proposed: incomplete removal of the cyst lining, growth of a new OKC from small satellite cysts or odontogenic epithelial rests left behind after surgery, and the development of an unrelated OKC in an adjacent location misinterpreted as a recurrence.\textsuperscript{14 and 37} In particular, incomplete removal seems to result from technical difficulties because of the sometimes inaccessible location of the cyst or the thin, friable cystic epithelium.\textsuperscript{18}

The recurrence rate has been reported to vary from 0\% to 62.5\%.\textsuperscript{4, 5, 8, 16, 38 and 39} Differences in the reported recurrence rates have been attributed to variations in the follow-up period, treatment modalities, surgeon skill, lesion size, histopathologic findings, age and gender of the patient, and the number of cases investigated.\textsuperscript{12, 16, 40 and 41}
The mean interval of follow-up in our sample was very short (36 months), because various studies have suggested that most OKC recurrences develop during the first 5 years after the initial treatment period.\textsuperscript{14, 22 and 40} Therefore, in the present preliminary study, we have not drawn any conclusions about recurrences.

Regarding the clinical manifestations at diagnosis, 37.2\% of patients presented with symptoms (swelling, pain, drainage, infection, and inferior alveolar nerve hypoesthesia), and 62.8\% were asymptomatic, with their lesions found incidentally. Therefore, our results have not confirmed the findings of other investigators reporting an incidence of 50\% to 67\% symptomatic OKCs.\textsuperscript{14, 15, 42 and 43}

Diagnostic imaging should include panoramic radiographs. The appearance of large or multilocular lesions on the panoramic radiograph warrants additional radiographic evaluation. Computed tomography scans should be obtained to determine the hard and soft tissue involvement.\textsuperscript{19} However, a definitive diagnosis can only be made by histopathologic analysis.\textsuperscript{11 and 19}

The radiographic appearance of OKCs is of a unilocular or multilocular radiolucency with scalloped and well-defined margins.\textsuperscript{19} However, it is difficult to differentiate radiographically between OKCs and other cystic lesions of the jaws.\textsuperscript{16}

The differential diagnosis should include benign odontogenic or nonodontogenic neoplasms lacking calcification, other odontogenic cysts, and intraosseous vascular lesions.\textsuperscript{11, 16, 19, 44 and 45}

In our study, almost all lesions were treated with surgical enucleation plus curettage. The largest (>50 mm) OKCs were treated with marsupialization. The eradication of the cyst is the principal goal in the treatment of OKCs. However, minimizing the recurrence and surgical morbidity is also important.\textsuperscript{10, 19, 46, 47 and 48}

Historically, several treatment modalities have been used, including decompression alone, marsupialization alone, enucleation alone, enucleation with excision of overlying oral mucosa/soft tissue, enucleation with adjuvant therapy (mechanical curettage, chemical curettage, or cryosurgery), decompression followed by enucleation with or without curettage or adjuvant therapy, resection without a continuity defect, resection with a continuity defect, and resection with disarticulation.\textsuperscript{19} Resection offers a low rate of recurrence but results in significant morbidity that is often unacceptable to patients. Marsupialization requires longer treatment, multiple, staged procedures, and, in particular, patient co-operation.

Even if we could not draw conclusions about the best treatment of OKCs, because a randomized clinical study would be needed, we suggest the use of the enucleation plus curettage, although it might result in a high recurrence rate. Maurette et al\textsuperscript{5} reported that conservative treatment has great advantages because it is less traumatic for the patient (because of the preservation of bone structure, woven soft tissue, and teeth), eliminates the need for medication, reduces hospitalization expenses, and avoids the need for reconstruction using grafts or other extensive methods. Finally, annual radiographic follow-up of patients who have undergone surgery for OKCs has been recommended for an indeterminate time.\textsuperscript{4 and 5}

The statistical analysis of the results of our study showed significant associations between multilocular lesions and larger size, mandibular site and larger OKCs, patients younger than 41 years old and multilocular lesions, and patients younger than 41 years and larger lesions. Therefore, it is likely that most multilocular, larger (and probably aggressive) lesions will be found in patients younger than 41 years old. In our study group, OKCs were predominant in male patients and in those in the third and fourth decades of life. The mandibular ramus, angle, and molar regions were the most frequently involved sites. Most patients in our study were asymptomatic, and a unilocular radiographic appearance predominated. Finally, it is likely most multilocular, larger, and, probably, aggressive lesions will be found in younger patients.

Enucleation associated with curettage is a conservative and effective option with low morbidity, although it resulted in a quite high recurrence rate. Giuliani et al\textsuperscript{19} reported that radical resection of OKCs could be reserved for those lesions that have undergone carcinomatous transformation.
However, that is extremely rare. Close clinical and radiographic long-term follow-up is mandatory for successful treatment.

REFERENCES


2. I. Kaplan, A. Hirshberg
The correlation between epithelial cell proliferation and inflammation in odontogenic keratocyst
Oral Oncol, 40 (2004), p. 985

Prognostic factors for keratocystic odontogenic tumor (odontogenic keratocyst): analysis of clinico-pathologic and immunohistochemical findings in cysts treated by enucleation

4. A.B. Bataineh, M. Al Qudah
Treatment of mandibular odontogenic keratocysts

5. P.E. Maurette, J. Jorge, M. de Moraes
Conservative treatment protocol of odontogenic keratocyst: a preliminary study

6. L. Tolstunov, T. Treasure
Surgical treatment algorithm for odontogenic keratocyst: combined treatment of odontogenic keratocyst and mandibular defect with marsupialization, enucleation, iliac crest bone graft, and dental implants

Odontogenic keratocyst expresses vascular endothelial growth factor: an immunohistochemical study

8. J.J. Pindborg, J. Hansen
Studies on odontogenic cyst epithelium

9. R.M. Browne
The odontogenic keratocyst: histological features and their correlation with clinical behavior
10. Odontogenic keratocyst: to decompress or not to decompress?: A comparative study of decompression and enucleation versus resection/peripheral ostectomy

Relationship between the prevalence of the dentigerous cyst and the odontogenic keratocyst tumor and the current etiologic hypothesis

12. J. Madras, H. Lapointe
Keratocystic odontogenic tumour: reclassification of the odontogenic keratocyst from cyst to tumour
J Can Dent Assoc, 74 (2008), p. 165a

13. E. Ahlfors, A. Larsson, S. Sjogren
The odontogenic keratocyst: A benign cystic tumor?

14. R.B. Brannon
The odontogenic keratocyst: A clinicopathologic study of 312 cases: Part I

15. T.A. Morgan, C.C. Burton, F. Qian
A retrospective review of treatment of the odontogenic keratocyst

Odontogenic keratocyst: review of 256 cases for recurrence and clinicopathologic parameters

Odontogenic keratocyst: the northwestern USA experience

Odontogenic keratocyst: an unusual location and review of the literature

Conservative management of a large odontogenic keratocyst: report of a case and review of the literature

20. A.C. Chi, J.R. Owings, S. Muller
Peripheral odontogenic keratocyst: report of two cases and review of the literature

21. T.G. Emerson, R.I. Whitlock, J.H. Jones
Involvement of soft tissues by odontogenic keratocyst
22. M. Partridge, J.F. Towers
   The primordial cyst (odontogenic keratocyst): its tumor-like characteristics and behavior

   Penetration of the skull bases by dissecting keratocyst

24. C.C. Gomes, M.G. Diniz, R.S. Gomez
   Review of the molecular pathogenesis of the odontogenic keratocyst
   Oral Oncol, 45 (2009), p. 1011

25. T.J. Li, R.M. Browne, J.B. Matthews
   Quantification of PCNA positive cells within odontogenic jaw cyst epithelium

26. P.J. Slootweg
   p53 Protein and Ki-67 reactivity in epithelial odontogenic lesions: An immunohistochemical study

27. T.-J. Li, R.M. Browne, J.B. Matthews
   Epithelial cell proliferations in odontogenic keratocysts: a comparative immunocytochemical study
   of Ki67 in simple, recurrent and basal cell naevus syndrome (BCNS)-associated lesions

   Proliferating cell nuclear antigen staining in syndrome and nonsyndrome odontogenic keratocysts

   Expression of proliferating cell nuclear antigen in ameloblastomas and odontogenic cysts

   Expression of cell cycle and apoptosis-related proteins in sporadic odontogenic keratocysts and
   odontogenic keratocysts associated with nevoid basal cell carcinoma syndrome

   Immunohistochemical analysis of cell cycle and apoptosis-related factor in lining epithelium of
   odontogenic keratocysts

   MIB-1 expression in odontogenic epithelial rests, epithelium of healthy oral mucosa and epithelium
   of selected odontogenic cysts: An immunohistochemical study
33. Z. Kolár, M. Geierová, J. Bouchal, et al.
Immunohistochemical analysis of the biological potential of odontogenic keratocysts

34. N.P. Agaram, B. Collins, L. Barnes, et al.
Molecular analysis to demonstrate that odontogenic keratocyst are neoplastic
Arch Pathol Lab Med, 128 (2004), p. 313

Molecular evidence supporting the neoplastic nature of odontogenic keratocyst: a laser capture microdissection study of 15 cases
Histopathology, 47 (2005), p. 582

Alterations of FHIT and p53 genes in keratocystic odontogenic tumour, dentigerous cyst and radicular cyst

37. J.A. Woolgar, J.W. Rippin, R.M. Browne
A comparative study of the clinical and histological features of recurrent and nonrecurrent odontogenic keratocysts

38. R.A. Voosmit, P.J. Stoelinga, V.J. van Haelst
The management of keratocysts

39. K. Forssel, H. Forssel, K.E. Kahnberg
Recurrence of keratocysts in a long-term follow-up study

40. R.B. Brannon
The odontogenic keratocyst: a clinicopathologic study of 312 cases: part II: Histologic features

41. T.P. Williams, F.A. Connor
Surgical management of the odontogenic keratocyst: aggressive approach

42. T.E. Crowley, G.E. Kaugars, J.C. Gunsolley
Odontogenic keratocysts: A clinical and histologic comparison of the parakeratin and orthokeratin variants

Conservative or radical treatment of keratocysts: A retrospective review

44. J.G. Meara, S. Shah, K.K. Li, et al.
The odontogenic keratocyst: A 20-year clinicopathologic review
The surgical treatment of glandular odontogenic cysts

46. P.J. Stoelinga
The treatment of odontogenic keratocysts by excision of the overlying, attached mucosa, enucleation, and treatment of the bony defect with Carnoy solution

Management of odontogenic keratocysts of the jaws: A ten-year experience with 120 consecutive lesions
J Craniomaxillofac Surg (2009)

Odontogenic keratocysts: A report on cases with long-term histological review and clinical follow-up
Minerva Stomatol, 43 (1994), p. 115