

Original Article

Evaluating histopathological factors of predicting the recurrence rate of odontogenic keratocyst

Gholam Reza Jahanshahi¹, Forooz Keshani², Zahra Mirkazemi³, Hossein Mirkazemi⁴

¹Department of Oral Maxillofacial Pathology, Dental Research Center, Dental Research Institute, School of Dentistry, Isfahan University of Medical Sciences, ²Department of Oral and Dental Pathology, Dental Research Center, Dental Research Institute, School of Dentistry, Isfahan University of Medical Sciences, ³Department of Oral Maxillofacial Pathology, Dental Students' Research Committee, School of Dentistry, Isfahan University of Medical Sciences, Isfahan, ⁴Department of Orthodontics, Dental School, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran

ABSTRACT

Background: Odontogenic keratocyst (OKC) is one of the most common jaw cysts with high recurrence rate. Some possible factors affecting recurrence that have not been evaluated in previous studies are examined in this study. This study aimed to predict the recurrence rate of OKC and more viable treatment of OKC.

Materials and Methods: In this descriptive, analytical, and cross-sectional study, 10 recurrent OKCs, which both slides before and after recurrence were accessible, were collected from oral and maxillofacial pathology department's archive. First, they were evaluated based on common histopathologic features. In the second phase, the frequency of these findings in 36 OKCs (24 samples with recurrence and 12 without recurrence after 5 years) was evaluated based on clinical, radiological, and histopathologic features. Data were analyzed by SPSS, Wilcoxon signed-rank test, McNamara, *t*-test, Chi-square, Mann-Whitney, Fisher's exact test, Cohen's kappa coefficient, and odds ratio ($P < 0/05$).

Results: According to this study, OKC in women, with multilocular radiolucency and mitosis in basal layer of epithelium as well as diffused inflammation, were statistically associated with probability of recurrence ($P = 0.05, 0.035, 0.033, \text{ and } 0.045$, respectively). The corrugated surface, reverse polarity, hypercellularity in parabasal, and satellite cysts can affect the recurrence of OKC with odds ratios = 2.364, 2.364, 1.190, and 1.500, respectively).

Conclusion: Gender (women), multilocular radiolucency, diffused inflammation in stroma, and mitosis in basal layer of epithelial lining, can statically predict the possibility of recurrence rate. In addition, findings regarding the age (in younger patients), corrugated surface, reverse polarity, and sub-basal cleft can be helpful in predicting recurrence.

Key Words: Odontogenic cysts, pathology, recurrence

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Address for correspondence:
Dr. Forooz Keshani,
Department of Oral and
Dental Pathology, Dental
Research Center Dental
Research Institute, School of
Dentistry, Isfahan University
of Medical Sciences, Isfahan,
Iran.
E-mail: f_keshani@dnt.mui.
ac.ir

INTRODUCTION

Odontogenic keratocyst (OKC) is a distinct benign cystic odontogenic lesion, known for its aggressive behavior and high recurrence rate.^[1] It was reported

that this complication constitutes between 1.8% and 21.5% of odontogenic jaw cysts^[2] and affects more men than women at a mean age range of 37 years

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and older.^[3] Furthermore, relevant studies have identified odontogenic cysts and reported that the most common locations involved in the mandible are the posterior sextant, the angle, and ascending ramus.^[2,4] In general, although nevoid basal cell carcinoma syndrome (NBCCS) is associated with multiple OKCs, an OKC usually occurs as a single lesion^[1] and penetrates locally into cortical bones and surrounding soft tissues.^[3] In addition, numerous studies have reported a recurrence rate of up to 62.5%.^[1,5,6] OKCs often occur during the first 5 years after initial treatment.^[1] OKCs were grouped as benign odontogenic tumors by the World Health Organization in 2005,^[7] and they were again placed into the same group of odontogenic cysts in the new classification in 2017.^[8]

In general, there are high prevalence and recurrence rates for OKCs, and several studies have detailed different and separated manifestations about factors affecting the recurrence of these cysts. Accordingly, the present study aimed to understand the possible prognostic factors related to the recurrence of OKCs through histopathological evaluation of their features.

MATERIALS AND METHODS

This descriptive, analytical, and cross-sectional study had two stages. At the first stage, 10 slides which have both before and after recurrence slides were collected from the archive of the Pathology Department in Isfahan University of Medical Sciences. Cases with multiple cases with or without NBCCS were excluded from the study. It should be noted that several low-quality slides were re-prepared from the block and stained with hematoxylin and eosin. Since the type of surgery may affect the recurrence rate, all samples were excised with curettage.

Then, samples were evaluated in terms of differences and similarities according to some characteristics [Table 1] by two oral pathologists with light microscope (Olympus, Tokyo, Japan). According to these differences and similarities, factors that may be highly likely effective on recurrence rate were extracted. At the second stage, 34 recurrent OKCs and 12 nonrecurrent slides (which were followed up for at least 5 years, and then, it was ensured that there was no recurrence following contacting patients and doing radiographic tests) were selected and assessed. Demographic information related to age, sex, lesion’s location, and radiographic features was first extracted from the Pathology Department’s records. After that, histopathological evaluations were performed on epithelial tissue, connective stroma, and lumen of the possible cysts by two oral pathologists using light microscope (Olympus, Tokyo, Japan) in the blind condition, ignorance of the recurrent or nonrecurrent samples. Data were analyzed by SPSS software (version 25) (IBM, Armonk, NY, United States of America), ultimately. Descriptive results were presented as the number, percentage, average, median, and standard deviation. Plus, the Wilcoxon signed-rank test, McNamara’s test, *t*-test, Chi-square, Mann–Whitney, Fisher’s exact test, Cohen’s kappa coefficient, and odds ratio were used to compare the mean of the data.

RESULTS

The significant histopathologic findings in the recurrent OKCs, slides before and after recurrence at the first stage, included corrugated surface, reverse polarity, and increased cellularity in the parabasal area, which were observed in 50% of the cases in both before and after recurrence. Mitosis (more than 3) was present in 30% of the cases in both slides in the basal region. Inflammation was observed in all slides, and diffused inflammation was observed in 50% of the

Table 1: Comparative analysis of histopathologic findings in the odontogenic keratocysts with recurrence which are evaluated before and after recurrence in the first stage in the first stage

Histopathology features	Being in keratocysts with recurrence (before and after recurrence)	Absence in keratocysts with recurrence (before and after recurrence)	Being in keratocysts with recurrence (before recurrence)	Being in keratocysts with recurrence (after recurrence)	Analysis test	<i>P</i>
Wavy surface	50	10	10	30	McNemar	0.625
Reverse polarity	50	0	40	10	McNemar	0.375
Increasing cellularity in the parabasal region	50	20	20	10	McNemar	1
Odontogenic epithelial remnants	0	50	20	30	McNemar	1
Foreign body reaction	0	80	0	20	McNemar	0.5

cases in both slides. Furthermore, 30% of the cases had dense collagen in both slides. The mentioned histopathological features probably show that influential factors for the recurrence. However, some features, including odontogenic epithelial remnants and foreign body reaction and keratin layer thickness, were not involved in increasing the recurrence [Table 1].

In addition, the thickness of the keratin layer was thin in 80% of the cases in both slides, and the keratin type was parakeratin in 90% of the cases in both slides. Hence, since keratin in OKC is usually parakeratin and thin, these features were not considered a recurrence factor. Tables 1 and 2 show some significant histopathologic findings of the first stage.

According to the results of the second stage, in which the recurrent and nonrecurrent OKCs were compared, the patients' age varied between 11 and 76 years, though most patients were between 20 and 30 years of age. The age (mean ± standard deviation) was higher in nonrecurrent patients (36.75 ± 18.45) compared with recurrent patients (32.04 ± 13.32). Despite the lower mean age of recurrent patients, the difference was not significant according to the *t*-test ($P = 0.397$). 69.44% of the participants were male, and 30.55% of them were female. The recurrence rate was 90.90% in women and 56% in men, which showed a significant difference based on Fisher's exact test ($P = 0.05$). The odds ratio is 7.857, which indicates that the female-to-male ratio is 7.857-fold in the recurrent patient group compared with the nonrecurrent patient group (95% confidence interval of the odds ratio: 0.869–71.059). Results of this study showed that the posterior mandible (85.3%) is the most commonly involved area, followed by the posterior maxilla (8.8%). Fisher's exact test showed no significant difference between the two groups in terms of the frequency distribution of the lesion site ($P = 0.319$). Regarding radiographic findings, Fisher's exact test showed a multilocular as a

significant factor for recurrence ($P = 0.035$). Charts 1-3 summarize the comparison of different histopathologic features between the recurrent and nonrecurrent OKCs at the second stage.

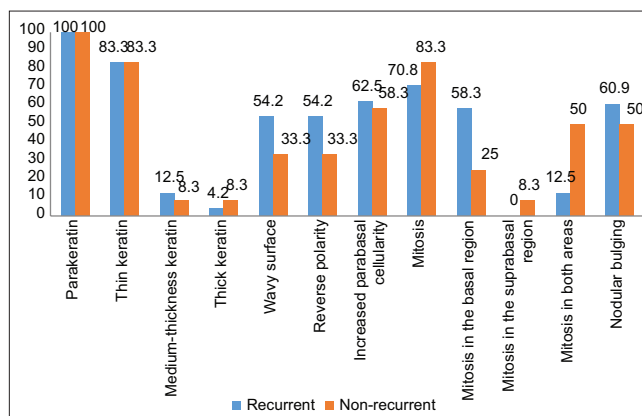


Chart 1: Frequency distribution of the epithelial histopathological features in recurrent and nonrecurrent keratocyst odontogenic cases at the second stage.

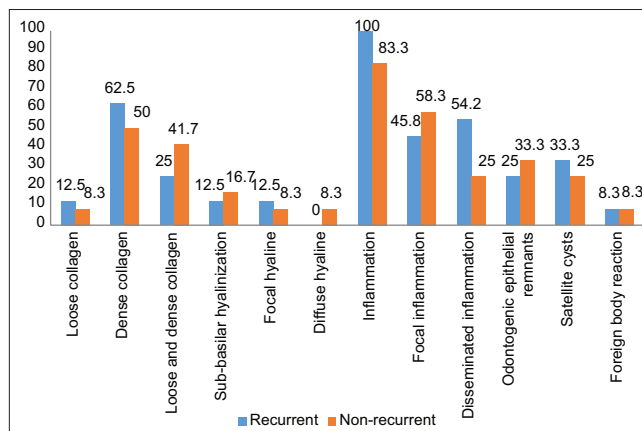


Chart 2: Frequency distribution of histopathological features of connective stroma in recurrent and nonrecurrent keratocyst odontogenic cases in the second stage.

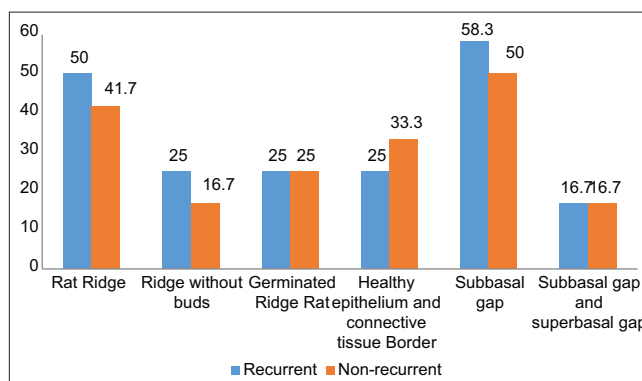


Chart 3: Frequency distribution of other types of histopathological changes in recurrent and nonrecurrent keratocyst odontogenic cases in the second stage.

Table 2: Comparative analysis of inflammation in the stroma of the odontogenic keratocysts with recurrence which are evaluated before and after recurrence at the first stage

Inflammation The first slide (before recurrence)	The second slide (after recurrence)		
	Local (%)	Diffuse (%)	No (%)
Local	30	10	0
Diffuse	10	50	0
No	0	0	0

The histopathological findings of the second stage show that in all OKCs, parakeratin was observed in the epithelial cyst wall. The test was not done due to similar data. On the epithelium surface of the cyst wall, the keratin layer thickness was mostly thin (83.3% among the recurrent patients and 83.3% among the nonrecurrent patients), and no statistically significant difference was observed between them ($P = 0.959$). The corrugated surface was observed more frequently among the recurrent patients (54.2%) compared with nonrecurrent patients (33.3%), though the difference was not statistically significant ($P = 0.238$) with an odds ratio of 2.364.

The presence of reverse polarity was observed more in the group with recurrence (54.2%); however, this feature was not statistically significant between the two groups ($P = 0.238$) and its odds ratio is equal to 2.364. The increased parabasal cellularity was more prominent in the recurrent patients (62.5%), yet the difference was not statistically significant ($P = 1$) with an odds ratio of 1.190. Results of the present study indicated that the mitotic activity rate was not different between the two groups, though the mitosis position was different; in the recurrent patients, the mitosis mostly occurred in the basal region (58.3%), while in nonrecurrent patients, mitosis mostly occurred in in basal and suprabasal regions (50%). Fisher's exact test showed that mitosis occurrence was significantly different between the two groups ($P = 0.033$). Nodular bulging was more commonly observed in the recurrent cases (60.9%), though the difference was not statistically significant ($P = 0.537$) [Chart 1]. The present study indicated a higher amount of dense collagen in the OKC's connective tissue in the recurrent cases (62.5%) compared with nonrecurrent cases (50%), yet collagen arrangement did not show a statistically significant difference between the two groups ($P = 0.592$). Sub-basilar hyalinization is an unusual finding in three recurrent cases (12.5%) in focal form and one nonrecurrent case (8.3%) in focal form, and one nonrecurrent case in the diffused form (8.3%). This feature was not statistically different between the two groups ($P = 0.675$). Inflammation has been evident in all slides of the recurrent patients. Moreover, inflammation in the recurrent patient was mostly diffuse (54.2%), and in the nonrecurrent patients was mostly focal (58.3%), which shows a statistically significant difference ($P = 0.045$). Odontogenic epithelial remnants were observed most

commonly in the nonrecurrent cases (25%) compared with the recurrent patients (33.3%), though the difference is not statistically significant ($P = 0.7$).

Satellite cysts were observed more frequently in the recurrent cases (33.3%), though the difference was not statistically significant ($P = 0.715$) with an odds ratio of 1.500 [Figure 1]. The foreign body reaction was an unusual finding found in two recurrent cases (8.3%) and one nonrecurrent case (8.3%). Statistically, the groups were not significantly different in this regard ($P = 1$) [Chart 2]. Rete ridge was more common in the recurrent OKCs (50%) compared with nonrecurrent cases (41.7%), yet the difference was not statistically significant ($P = 0.898$). Regarding the border between epithelium and connective tissue, the sub-basal gap was seen as more common among the recurrent cases (58.3%). Furthermore, the suprabasal gap was not observed in any of the slides, and the suprabasal gap was always accompanied by the sub-basal gap. The difference is not statistically significant between the two groups in this regard ($P = 0.889$) [Chart 3].

DISCUSSION

According to the results of this study, recurrent OKCs could be seen in the lower mean age compared with nonrecurrent patients, which is in line with many studies and may be attributed to the conservative treatment method used for young patients compared to the elderly.^[2,7,9] In this study, similar to many studies, the OKC incidence was higher among the men.^[1,7,10,11] The recurrence rate was higher among women, which was statistically significant. Considering the odds ratio, it also shows that the female-to-male ratio is 7.857-fold in the recurrent patient group compared with the nonrecurrent patient group. In González-Alva *et al.*'s study, the recurrences rate was

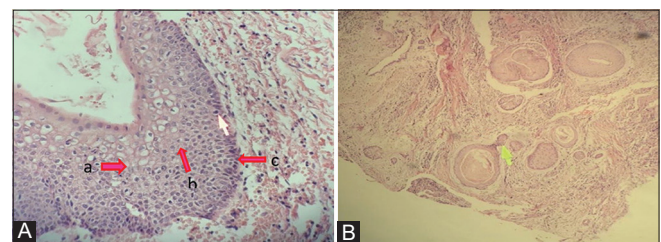


Figure 1: Basal layer (a) germination and the female cyst (b) and epithelial remnants (c) at $\times 100$ magnification (A), and mitosis in the basal layer of a keratocyst odontogenic (arrow) at $\times 400$ magnification (B). Odontogenic keratocyst with Hematoxylin and Eosin staining under the light microscope.

higher among women,^[7] yet some studies, including Razavi *et al.*, Habibi *et al.*, and Selvi *et al.*'s studies, proved no significant gender difference.^[2,9,12] This inconsistency between the results of these studies may probably be due to the difference in the sample size of the recurrent and nonrecurrent groups. In the current study, similar to many other studies, most slides belonged to the posterior mandible (85.3%).^[4,6,10,12] Furthermore, the second common area in this study was the molar region and maxillary tuberosity, which was consistent with many studies.^[7,11] In this study, the lesion site was not significantly different between the recurrent and nonrecurrent groups. The multilocular radiolucency was observed more common among the recurrent patients compared with nonrecurrent patients, and the difference was statistically significant ($P = 0.035$), in line with Forssell *et al.*'s study,^[13] which may be attributed to the penetration of cysts among the bone trabeculae and the possibility of leaving cyst remnants. OKC is a benign lesion that is relatively stable, both clinically and radiographically, though presenting a wide range of histopathological changes.^[11] The most observed OKCs at the epithelial wall surface were thin parakeratin in the present study, which is similar to Azevedo *et al.* and Cottom *et al.*'s studies.^[3,11] At the first stage, wavy surface, parakeratinization, reverse polarity, and increased cellularity in the parabasal region were observed in 50% of the recurrent patients, in both pre- and postrecurrence slides. The second stage showed that all three features are present more frequently in the recurrent cases compared with nonrecurrent, and they are likely to affect the recurrence, although these differences are not statistically significant, probably due to the number of samples. In Cottom *et al.*'s study, all these three features were more commonly reported in the recurrent group compared with the nonrecurrent group.^[3] The first stage showed mitosis in the basal area in 30% of the recurrent patients in both slides before and after recurrence. Further examinations in the second stage showed that mitosis mostly occurs in the basal area in the recurrent patients and in both basal and suprabasal areas of the nonrecurrent ones, which showed a statistically significant difference. In line with the present study, Cottom *et al.*'s study showed that the rate of mitotic activity was not different between recurrent and nonrecurrent patients, though the mitosis site is different.^[3] Nodular bulging of the cyst was more common in the recurrent OKCs compared with nonrecurrent cases, though

this difference was not statistically significant, and this feature is less likely to affect OKC recurrence. Yet, further evaluation is required due to the lack of previous studies. In the connective tissue of the recurrent group, the amount of dense collagen was higher than loose collagen, though this difference was not significant. It may be attributed the probably the lesion's chronicity in the recurrent cases before being treated, and it may be stated that patients who receive treatment earlier are less likely to experience recurrence. While Cottom *et al.* showed that the amount of dense and loose collagen was nearly the same between the two groups.^[3] In the current study, sub-basilar hyalinization is an uncommon finding. Hyaline bodies have been rarely found in Azevedo *et al.* and González-Alva *et al.*'s studies.^[7,11] In the present study, the recurrent cases had a higher hyalinization rate compared with nonrecurrent cases. Similar to this study, Cottom *et al.* reported a higher rate of focal hyalinization in the recurrent case.^[3] Given that higher sample size may further show the difference in hyalinization in the recurrent cases compared with nonrecurrent, hyalinization is probably considered a potentially effective factor in OKC recurrence. Daughter cysts were observed slightly more in the recurrent patients. Similarly, Naruse *et al.* considered daughter cysts to cause recurrence, though not reporting significant results.^[14] This study does not rule out the presence of odontogenic epithelial remnants as a factor in recurrence. Naruse *et al.* considered epithelial islands as a cause of recurrence, but their results were not significant.^[14] In all samples with recurrence, inflammation was observed (in the group with more recurrence as diffuse and in the group without recurrence as more focal) which was statistically significant. Inflammation may increase recurrence due to increased fragility and rupture of the cyst wall.^[13] Foreign body reaction was unusual, and similar to the study of Cottom *et al.*, no significant difference was observed between the two groups.^[3] The presence of rete ridges did not show a statistically significant difference between the two groups with recurrence and no recurrence, and basal layer germination was not related to recurrence rate. However, the number of rete ridges was higher in cases with recurrence and is probably not a factor in predicting recurrence. Similar to the present study, in the study of Cottom *et al.*, the presence of rete ridge and basal layer germination was not significantly different between the two groups with and without recurrence.^[3] Sub-basal clefts were reported in the

most recurrent groups, although the difference was not statistically significant, but this feature is likely to be effective in OKC recurrence. This cleft may also contribute to an increased risk of the cyst epithelial lining's rupture, persisting in the area being treated surgically, thereby increasing the likelihood of the recurrence.

CONCLUSION

According to the results of the study, OKCs in female patients with multilocular radiographs, diffuse inflammation, and mitosis in the basal region are more likely to have a recurrence. However, at the next probability level, the presence of reverse polarity, infrabasal cleft, parakeratinized wave surface, increased cellularity in the epithelial lining of the cyst, the presence of satellite cysts, dense collagen, nodular protrusion in the epithelium, and the presence of infra-basilar hyalinization can predict recurrence. It is hoped that the data will be helpful in predicting recurrence and more appropriate OKC treatment.

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Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or nonfinancial in this article.

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