



# Factors Influencing the Aggressive Behavior of Odontogenic Keratocyst: A Narrative Review

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## Abstract

During odontogenesis, the dental lamina disintegrates, leaving behind the remnants. Odontogenic pathologies such as cysts and tumors can arise from these remnants. The odontogenic keratocyst (OKC) arises from dental lamina remnants. Among the cysts, the odontogenic keratocyst is the most controversial. There is convincing evidence that inflammation plays a significant role in the pathogenesis and expansion of OKCs. Several factors mediate the proliferative capacity of the epithelial lining. The presence of mast cells close to the epithelial lining, cystic pressure build-up by vascular endothelial growth factors (VEGFs), and other cytokines contribute to the cystic expansion. Fibroblast activation by inflammation in the connective tissue stroma and changes in the epithelial lining are responsible for the aggressive nature of OKC. The use of molecular methodologies gives more profound insights into the factors influencing the progression of the lesion and helps develop newer treatment modalities for OKC. This review describes the characteristics that determine the aggressive behavior of this unique cyst.

## Keywords

- ▶ odontogenic keratocyst
- ▶ host response
- ▶ aggressiveness

## Introduction

The classification of odontogenic cysts and tumors accurately reflects these lesions restricted only to the jaws. The World Health Organization 2017 classification of odontogenic lesions, reverted the original term odontogenic keratocyst (OKC) from the earlier terminology of keratocystic odontogenic tumor given in 2005. The literature review shows that patched gene (*PTCH*) mutation is also present in other non-neoplastic lesions such as developmental cysts. The intrusive nature of OKC and recurrences has many theories for the cyst to be considered a tumor.<sup>1,2</sup> The proliferative potential of the epithelial lining is also a reason. OKCs occur sporadically and in nevoid basal cell carcinoma syndrome as well.<sup>3</sup> Under the

microscope, this unique odontogenic cyst has some salient features representing the clinical behavior that is different from that of other cysts of the jaws.<sup>4,5</sup> In 1967, Toller mentioned that the OKCs behave like a neoplasm with the expansion of the cortical plates due to their growth potential and low protein content, which affects the cyst's osmotic pressure. The transformation in the parakeratinized epithelial lining is related to growth factors, and cytokines released by inflammatory infiltrates, which are responsible for the proliferative activities of the basal epithelium, making OKCs aggressive.<sup>6–8</sup>

This review describes the factors that modulate the changes in the connective tissue stroma and the proliferation of the epithelial lining in odontogenic keratocysts.

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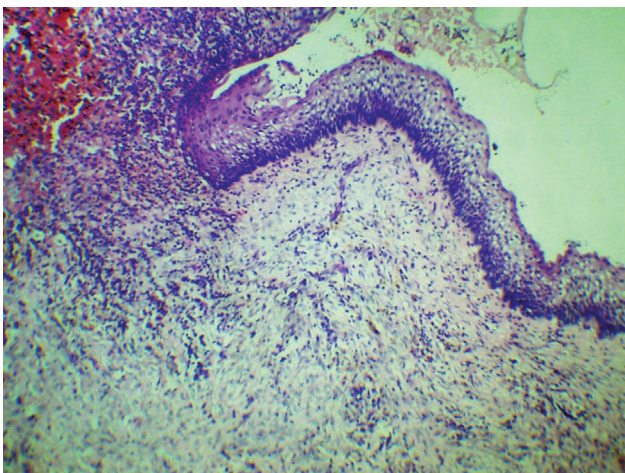
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## Origin of OKC

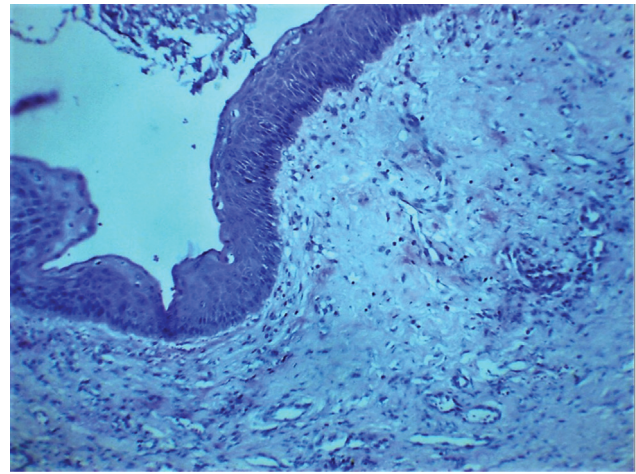
Tooth formation involves a sequence of epithelial–mesenchymal molecular communications. Experimental studies show that the oral epithelium is critical in initiating molecular encoding; the underlying ectomesenchyme takes over later.<sup>9</sup> The rudimentary successional lamina posterior to the permanent tooth germ implies further odontogenesis is aborted among diphyodonts.<sup>10</sup> Dental lamina disintegrates by cell migration, epithelial–mesenchymal transformation, and apoptosis after its role is over. OKCs arise from the remnants of the inactivated dental lamina, found close to the mucosa. Many studies have reported that cases found more commonly involving the ascending ramus.<sup>11–13</sup> The dental lamina has an enormous capacity to initiate odontogenesis. It is active until it induces tooth bud formation. The entire dental lamina can form a tooth but has triggering centers at specific sites. Successive tooth formation lies in the mesenchyme, adjacent to the dental lamina. Teeth grow continuously in some mammals, but in diphyodonts, the dental epithelium becomes inactive after completion of the tooth formation.<sup>14,15</sup>

## Changes in the Cystic Epithelium

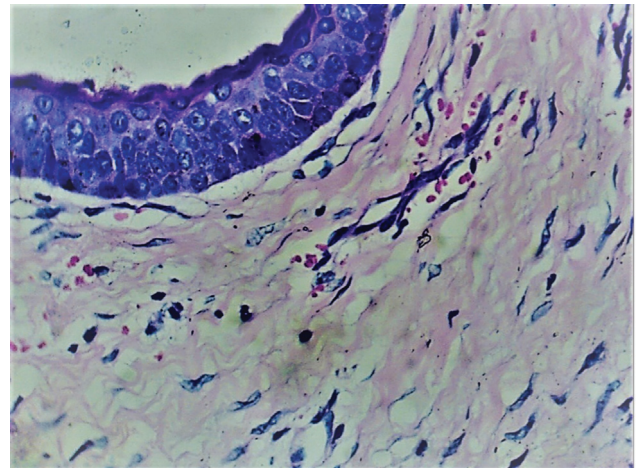
Cytokeratin expression alters the epithelial lining if inflammation is present in the connective tissue wall. (► **Fig. 1**) A study on mice demonstrated changes in the cystic epithelium related to the underlying stroma and epithelium interaction.<sup>15</sup> Lysosomal activity is the cause of the break-up as observed in 70 to 80% of the cases and not in any other cysts (► **Figs. 2–4**). Studies imply the tendency for recurrence because of the presence of satellite cysts and proliferative activity in the epithelial lining (► **Figs. 5 and 6**).<sup>16</sup> Rodu et al stated that ~76% of their cases had inflammation associated with transforming the cyst lining to a nonkeratinized one.<sup>16,17</sup> Vasculature in the area of infiltrative growth provides the essential nutrient supply. Previous studies point to



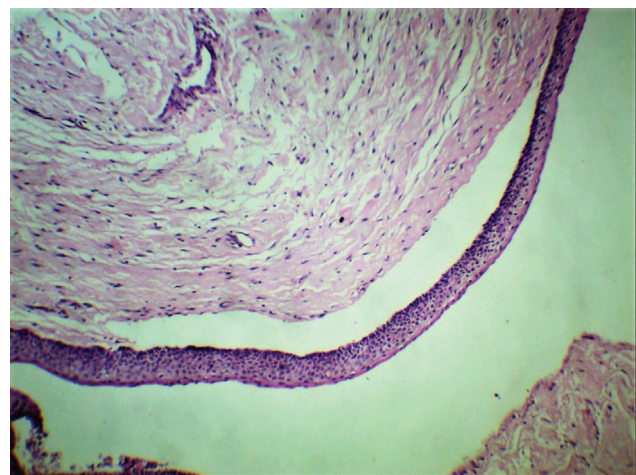
**Fig. 1** Palisaded, hyperchromatic basal layer with subepithelial hyalinization with transition of parakeratotic epithelium changing into nonkeratinized epithelium with dense infiltration of inflammatory cells (magnification X10).



**Fig. 2** Photomicrograph of hematoxylin and eosin staining (H&E) in OKC show corrugated parakeratinized, stratified squamous epithelium, palisading basal cells with hyperchromatic nuclei (magnification X40).

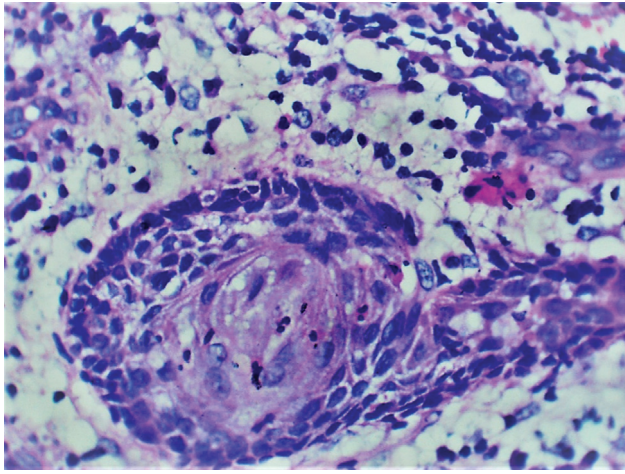


**Fig. 3** OKCs with large round basal and suprabasal cells (magnification X40).



**Fig. 4** Photomicrograph of H&E show OKC lining that are 6 to 8 cells thick, with epithelial lining separated from the underlying connective tissue capsule (magnification X10).





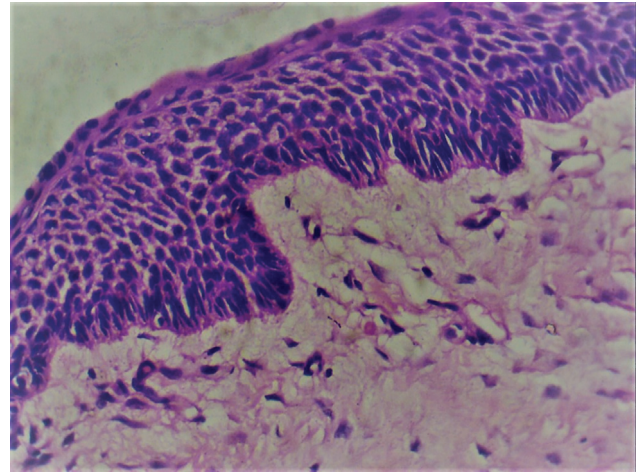
**Fig. 5** Photomicrographs of H&E show OKC with satellite cyst with keratin in the connective tissue capsule (magnification X40).

the vascular endothelial growth factor (VEGF) in the lining epithelium concerning proliferation activities. VEGF in endothelial cells is responsible for increased cystic pressure; thus, an autocrine loop induces proliferation.<sup>18</sup> Accumulating cystic fluid containing serum proteins from the vasculature elevates the hydrostatic pressure helping to expand. Smith et al considered histamine release from mast cells a significant event. Expansion continues as extracellular matrix breakdown with an increase in the osmotic pressure leading to bone resorption. Epithelial changes in the OKCs are more active than other odontogenic cysts. Studies have shown that the OKCs in most cases show inflammation.<sup>19</sup>

### Eosinophils and Mast Cells

Mast cells play an essential role in the pathogenesis of OKC, with cytoplasmic granules rich in proteoglycans, proteases, and other substances. Mature mast cells are found close to the epithelium, blood vessels, nerves, other tissues, mucous glands, and within epithelia. They participate in many inflammatory, immunologic, and neoplastic reactions. Mast cells can stimulate fibroblasts to produce collagen, angiogenic growth factor, fibroblastic growth factor, and mitogenic polypeptides. There is a relationship between mast cells, blood vessels, and nerve axons. The tumor necrosis factor- $\alpha$  and cytokines recruit effector cells in the inflammatory reaction. The hydrolytic enzymes released by mast cells directly influence the degradation of cystic connective tissue capsule. They contribute to the osmotic pressure by draining the lumen because there is a lack of lymphatic drainage. By releasing granule-associated stem cell factors, mast cells regulate bone loss, and osteoclast activity. Mast cells enhance bone resorption by heparin production and TNF- $\alpha$  stimulating osteoclast activity.<sup>20,21</sup> Mast cell heterogeneity in different anatomical sites is responsible for differences in biochemical and functional properties accordingly to the biological requirements of that particular site of involvement.

Eosinophil chemo-attractant factor and histamine released by mast cells attract eosinophils. Both cells can stimulate the production of prostaglandins, important in



**Fig. 6** OKC with cystic epithelium exhibiting proliferative activity into the underlying connective tissue capsule (magnification X40).

bone resorption, and aid in cyst growth.<sup>20-22</sup> Osteolytic cytokines interleukin-1 and interleukin-6 in OKC are crucial in reaching large-sized bone destruction by matrix metalloproteinases and prostaglandins activating osteoclast-like cells. Interleukin levels in OKC fluids are higher than in any other dentigerous and radicular cysts.<sup>23,24</sup>

### Fibroblasts

The fibroblasts directly impact the production and activity of collagens, proteolytic enzymes, and growth factors in response to local or systemic stimuli. Studies indicate that OKC's biological behavior depends on the epithelium and the underlying stroma. Epithelial and mesenchymal interactions are part of maintaining equilibrium in tissues. Fibroblasts are one of the primary connective tissue cells that change in response to an alteration in the extracellular matrix and the epithelial transformations. The presence of inflammatory cells in the OKCs capsule depends on the epithelial lining and connection to the outer oral mucosa. In inflammation cases, there is a difference in epithelial behavior from parakeratinized to nonkeratinization. Fibroblasts actively recruit inflammatory cells during a normal response to tissue disruption. Inflammation initiates tissue destruction, wound healing responses, and eventually fibrosis. The stromal myofibroblasts in OKC are more common than in other developmental odontogenic cysts. Studies show that the presence of myofibroblasts is responsible for the aggressive behavior of OKC. Epithelial-mesenchymal interaction generates changes in the collagen structure from loosely packed fibers to more tightly packed collagen. Myofibroblasts are fibroblasts with smooth muscle-like features characterized by contractile apparatus. The transforming growth factor  $\beta$ -1 cytokine is essential in differentiating fibroblasts into myofibroblasts. Platelet-derived growth factor cytokine is responsible for maturation. Myofibroblasts synthesize the extracellular matrix responsible for tissue contraction during wound healing and promote tumor invasion. There are also collagen bundles

staining similar to other odontogenic neoplasms, proving that the stroma is also a part of unusual cystic behavior.<sup>23–25</sup>

## Proliferative Markers

Cell cycle-associated proteins determine cell proliferation. The consequences of pathological behavior in various odontogenic cysts and tumors are identified using antibodies against these proteins. Various methods help analyze the information on expression patterns, gene sequence, and protein-to-protein interactions. These new methods for studying cell proliferation-associated proteins improve patient treatment options.<sup>26</sup> They are targets for cell proliferation studies and can be localized in the nucleus, cell membrane, or the cytoplasm. The expression of proliferative cell nuclear antigen (PCNA) and Ki-67 in OKCs and other odontogenic cysts indicate their intrinsic growth potential. Likewise, in the case of radicular cysts, the Ki-67 expression shows a positive increase in the severity of inflammation in the connective tissue.<sup>8,27,28</sup> Ki-67 expression indicates cell proliferation but is influenced by fixation, radiation, and salt concentration. Detailed cell cycle analysis has demonstrated that the Ki-67 antigen is expressed in all phases except G0 and early G1. Ki-67 is an effective cell proliferation marker extensively studied in many standard and neoplastic disorders. The relatively new marker minimicrosome proteins (MCM) are present in high levels in proliferating cells. MCM-2 expression in the radicular cyst is more than observed in OKCs and correlates with inflammation. MCM proteins are present in all cell cycle phases and absent from differentiated cells and during quiescence. MCM-2 can be demonstrated in the early G1 phase when Ki-67 cannot be detected. This protein can be observed in cells coming out of the cell cycle and during the cellular proliferation in the normal, premalignant, and neoplastic cells.<sup>28,29</sup>

## Recurrences

Research shows that recurrence in OKC is more likely to occur over a 5 to 37 years span. The epithelium of the cyst in areas difficult to explore, such as the angle or ramus of the mandible, is a challenge in OKC treatment. More precisely, the recurrences are related to treatment methods, but the presence of daughter cysts, tooth involvement in the cyst, inflammation, and epithelial islands close to oral mucosa influence cyst aggressiveness.<sup>30,31</sup> Also, collagenolytic activity is observed in a few OKCs separating the epithelial lining from the connective tissue capsule. Some studies highlight that extracellular matrix proteins tenascin and fibronectin interact more in the OKC capsule and basement membrane than in other odontogenic cysts. Tenascin is produced by both epithelial and mesenchymal cells. These proteins are present in embryonic cells and help in cell to cell, cell to extracellular matrix, migration, and proliferation activities. They are the initial interactions of the odontogenesis apparatus; other elements are syndecan collagen types I and IV, heparin sulfate, and laminin. These proteins thus indicate that the lining and capsule equally participate in the odon-

togenic cyst expansion.<sup>3,32</sup> The treatment outcome in the case of the OKCs depends on the location or size of the lesion. Treatment options such as decompression to lessen the morbidity with resectioning and using Carnoy's solution have got good results. Literature studies show fewer recurrences with the removal of the part of the mucosa in the cyst roof, especially when there is perforation of the cortical bone. New methods in the future, such as SHh pathway inhibitors, can bring hope to the treatment of OKC.<sup>33–35</sup>

## Conclusion

It is evident that the main interactions between epithelial and mesenchymal cells are those of the primitive embryonic cell phase, which help in differentiation and proliferation. Basal cell budding from the surface oral epithelium has been a hindrance in the prognosis of the treatment. Aggressive modulating factors influence the behavior and proliferation of OKCs. Research on OKCs through IHC markers helps predict those factors and reduce recurrence. Therefore, depending on the clinicopathological characteristics, treatment options can be modified to improve the prognosis.

### Funding

None.

### Conflict of Interest

None declared.

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