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Digital Pathology-Based Quantitative Assessment of Cytokeratin-19 Expression Across Challenging Odontogenic Lesions: Differentiating Ameloblastoma from Dentigerous Cysts and Odontogenic Keratocysts from Orthokeratinized Odontogenic Cysts

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Abstract

Background: Histopathological differentiation of odontogenic cysts and tumors is often challenging due to similar morphological features. Cytokeratin-19 (CK19), a marker of odontogenic epithelium, aids in evaluating epithelial differentiation; however, conventional semi-quantitative Immunohistochemistry (IHC) is limited by observer variability. Digital pathology offers a more objective approach to quantification.

Methods: This retrospective study included 30 formalin-fixed, paraffin-embedded archival cases: ameloblastoma (n=5), dentigerous cyst (n=10), odontogenic keratocyst (n=10) and orthokeratinized odontogenic cyst (n=5). Diagnoses were confirmed using hematoxylin and eosin staining based on WHO criteria. CK19 IHC (mouse monoclonal, clone RCK108; Dako; 1:100) was analyzed using QuPath (v0.6.0). Region-specific analysis was performed by defining epithelial compartments: basal, suprabasal and superficial layers in cysts and peripheral and central cells in ameloblastoma. Positive cell detection was based on cytoplasmic DAB staining.

Results: CK19 expression was significantly higher in ameloblastoma peripheral cells (66.2%) compared to dentigerous cyst basal cells (52.2%), while ameloblastoma central cells showed lower expression (14.8%) than dentigerous cyst superficial cells (31.3%). Odontogenic keratocyst demonstrated uniformly high CK19 expression (basal 98.3%, suprabasal 93.2%, superficial 91.1%), in contrast to minimal expression in orthokeratinized odontogenic cyst (0-1.3%). Receiver operating characteristic analysis showed excellent diagnostic performance (AUC: 0.82 for ameloblastoma vs. dentigerous cyst; 0.99 for odontogenic keratocyst vs. orthokeratinized odontogenic cyst). Inter-observer agreement was strong (κ=0.87).

Conclusion: QuPath-based quantification of CK19 reveals distinct, layer-specific expression patterns that enable objective differentiation of odontogenic lesions. These findings support CK19 as a reliable biomarker in odontogenic pathology.

Keywords: Cytokeratin-19; Ameloblastoma; Dentigerous Cyst; Odontogenic Keratocyst; Orthokeratinized Odontogenic Cyst; Digital Pathology; Qupath; Immunohistochemistry

Introduction

Odontogenic cysts and tumors develop from remnants of odontogenic epithelium, such as the dental lamina, reduced enamel epithelium and epithelial rests of Malassez. These lesions show a broad range of biological behavior, varying from slow-growing cysts to aggressive, recurring neoplasms, which highlight the intricate epithelial-mesenchymal interactions inherent in tooth development [1,2].

Among keratinizing odontogenic cysts, the Odontogenic Keratocyst (OKC) and Orthokeratinized Odontogenic Cyst (OOC) originate from the same tissue but differ greatly in their behavior and microscopic features [3-6]. OKC features a parakeratinized epithelial layer with a corrugated appearance and palisaded basal cells and it is recognized for its aggressive behavior and high likelihood of recurrence. Conversely, OOC displays an orthokeratinized lining with a granular cell layer, does not have basal palisading and demonstrates a less aggressive nature with infrequent recurrence, justifying its categorization as a separate entity [7,8].

Likewise, the dentigerous cyst and ameloblastoma are both odontogenic lesions with some overlapping characteristics, yet they exhibit different biological potentials. The dentigerous cyst is a prevalent, benign lesion associated with the crown of an unerupted tooth and usually takes a non-aggressive course. In contrast, ameloblastoma is a locally aggressive tumor with a high recurrence rate, often requiring extensive surgical management. Histopathological differentiation, particularly in unicystic variants, can sometimes be challenging [4,6].

Immunohistochemistry serves as a valuable adjunct in such cases by revealing molecular and cellular characteristics not evident on routine staining. Cytokeratin 19 (CK19), a low molecular weight epithelial marker, is expressed in odontogenic tissues such as dental lamina, reduced enamel epithelium and ameloblasts, making it a useful indicator of odontogenic epithelial origin and differentiation [3-6].

Prior research has shown varying levels of CK19 expression across different odontogenic lesions. The Odontogenic Keratocyst (OKC) generally exhibits a stronger expression in both the basal and suprabasal layers compared to the Odontogenic Oncocytoma (OOC), whereas the dentigerous cyst shows only limited staining in its basal layer. On the other hand, ameloblastoma reveals a robust and widespread positivity in both the peripheral and central tumor cells, which is associated with its increased proliferative capacity and aggressive characteristics [4-8]. However, most studies rely on subjective, semi-quantitative assessment methods. The advent of digital pathology, particularly image analysis software such as QuPath, enables objective and reproducible quantification of immunohistochemical staining, reducing observer bias and improving accuracy [15-19].

Therefore, the present study aims to quantitatively evaluate CK19 expression in odontogenic keratocyst, orthokeratinized odontogenic cyst, dentigerous cyst and ameloblastoma using QuPath-based digital image analysis. By comparing layer-specific and cell-specific expression patterns, this study seeks to enhance diagnostic accuracy and better understand the biological behavior of these lesions.

Materials and Methods

Study Design and Ethical Approval

This retrospective observational immunohistochemical study was conducted in the Department of Oral and Maxillofacial Pathology, Tagore Dental College and Hospital, Chennai, India. Archival Formalin-Fixed Paraffin-Embedded (FFPE) tissue specimens were retrieved from departmental records. Ethical approval was obtained from the Institutional Ethics Committee (IEC/TDCH/63/2025; Approval No. 05092502). As anonymized archival samples were used, the requirement for informed consent was waived. The study adhered to the Declaration of Helsinki and followed REMARK guidelines for reporting tumor marker studies.

Case Selection and Histopathological Confirmation

Histopathologically confirmed cases of odontogenic lesions were included, comprising:

- Dentigerous cyst (n = 10)
- Ameloblastoma (n = 5)

- Odontogenic keratocyst (n=10)
- Orthokeratinized odontogenic cyst (n=5)

Inclusion Criteria
- FFPE tissue blocks with adequate epithelial lining
- Complete histopathological and clinical records

Exclusion Criteria
- Poorly preserved or autolyzed tissues
- Sections with necrosis, artefacts or incomplete epithelium
- Cases with ambiguous or overlapping histopathological features

All Hematoxylin and Eosin (H&E) stained slides were independently reviewed by two oral pathologists according to WHO criteria and discrepancies were resolved by consensus.

Tissue Sectioning and Preparation
FFPE blocks were sectioned at 3-4 μm thickness using a rotary microtome. Sections were mounted on silane- or poly-L-lysine-coated slides and incubated overnight at 37°C. Slides were further heated at 60-65°C prior to staining. One section per case was stained with H&E to reconfirm the diagnosis.

Immunohistochemical Staining Protocol
Immunohistochemistry for Cytokeratin-19 (CK19) was performed using a polymer-based detection system.

Deparaffinization and Rehydration
Sections were deparaffinized in xylene and rehydrated through graded alcohols to distilled water.

Antigen Retrieval
Heat-induced epitope retrieval was carried out using either Tris-EDTA buffer (pH 9.0) in a pressure cooker or citrate buffer (pH 6.0) in a microwave, followed by cooling and rinsing in buffer solution.

Blocking
Endogenous peroxidase activity was blocked using 3% hydrogen peroxide. Non-specific binding was minimized using protein blocking solution/normal serum.

Primary Antibody
Sections were incubated with mouse monoclonal anti-CK19 antibody (Clone RCK108, Dako; dilution 1:100) for 1 hour at room temperature.

Secondary Antibody and Detection
Slides were incubated with HRP-labeled secondary antibody followed by chromogen development using Diaminobenzidine (DAB).

Counterstaining and Mounting
Sections were counterstained with Mayer's hematoxylin, dehydrated, cleared and mounted.

Controls
Positive controls (normal oral mucosa/reduced enamel epithelium) and negative controls (omission of primary antibody) were included.

Conventional Microscopic Evaluation

CK19-positive cytoplasmic staining was assessed under light microscopy at 400x magnification. In cystic lesions, evaluation was performed in three epithelial layers: basal, suprabasal and superficial layers. In ameloblastoma, staining was assessed in peripheral ameloblast-like cells and central stellate reticulum-like cells. Both strong and weak cytoplasmic staining were considered positive (Fig. 1).

Digital Image Analysis Using QuPath

To minimize observer bias, digital image analysis was performed using QuPath software (versions 0.4.3-0.6.0). Digitized images were imported for quantitative evaluation (Fig. 2).

Region of Interest (ROI) Annotation

Representative epithelial regions were manually annotated by a blinded pathologist.

- OKC and OOC: basal, suprabasal and superficial epithelial layers
- Dentigerous cyst: basal, suprabasal and superficial layers
- Ameloblastoma: peripheral ameloblast-like cells and central stellate reticulum-like cells

Cell Detection and Quantification (Fig. 3)

A positive cell detection algorithm was applied with the following parameters:

- DAB threshold: 0.15
- Cell size: 10-100 μm^2
- Detection type: cytoplasmic staining

The software generated:

- Total cell count
- CK19-positive cell count
- Percentage positivity
- Mean Optical Density (MOD)

Algorithm Validation

To ensure reliability, 10% of annotated regions were independently evaluated by a second oral pathologist. Agreement between manual and automated analysis was assessed using Cohen's kappa statistic.

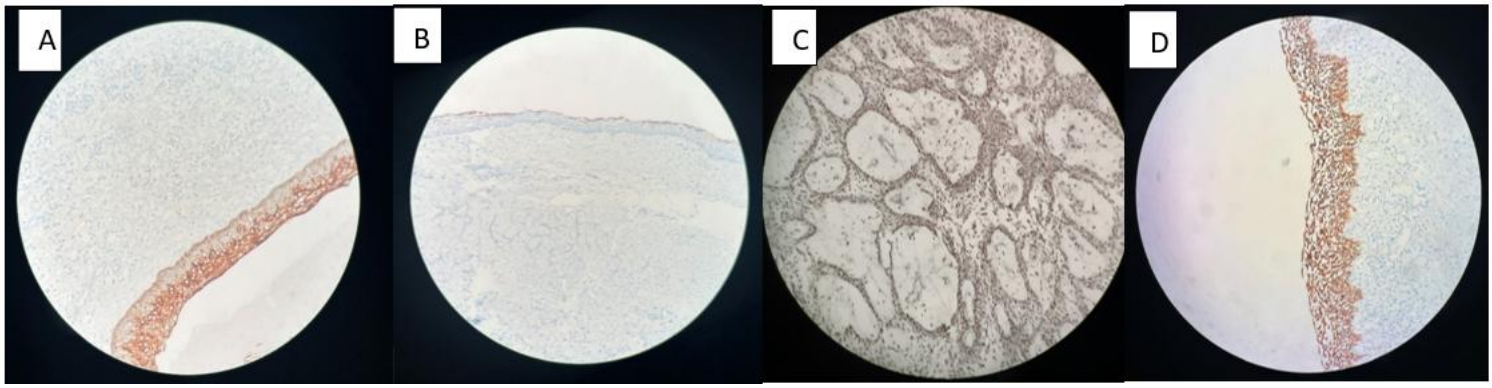

Figure 1: Microscopic image of CK19 immunohistochemical staining in odontogenic lesion showing positive epithelial expression (IHC, ×40). A: CK19 immunohistochemical staining in OKC; B: CK19 immunohistochemical staining in OOC; C: CK19 immunohistochemical staining in ameloblastoma; D: CK19 immunohistochemical staining in DC.

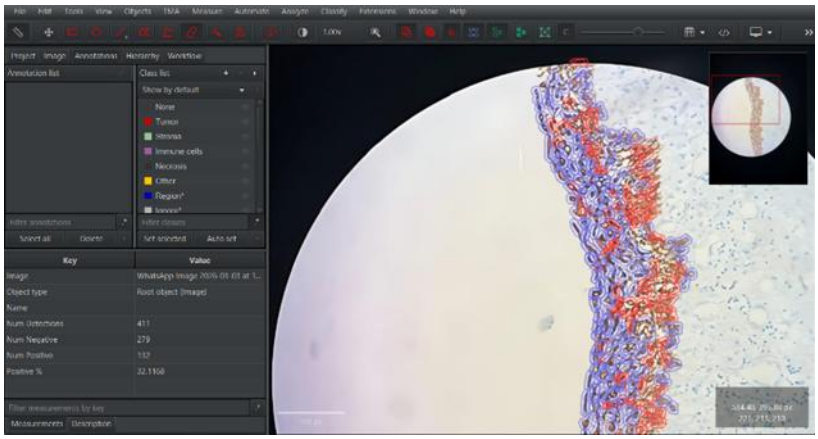

Figure 2: "QuPath-based digital annotation of CK19 immunohistochemical expression in DC showing positive epithelial cell detection.

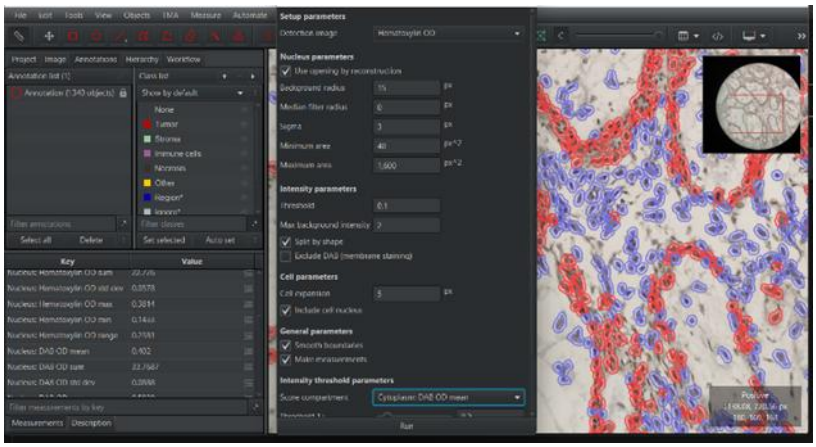

Figure 3: QuPath-assisted digital annotation and cell detection of CK19 immunohistochemical staining in odontogenic lesion epithelium for quantitative analysis.

Results

Case Distribution

A total of 30 cases were analyzed, comprising dentigerous cyst (n = 10), ameloblastoma (n = 5), Odontogenic Keratocyst (OKC) (n = 10) and Orthokeratinized Odontogenic Cyst (OOC) (n = 5).

The distribution revealed a predominance of cystic lesions, with dentigerous cyst and OKC collectively accounting for 66.6% of the study sample, whereas ameloblastoma and OOC represented 33.4% (Table 1). This proportional representation facilitated a balanced comparative assessment between cystic and neoplastic odontogenic lesions.

Layer-wise CK19 Expression

The quantitative evaluation of CK19 immunoexpression demonstrated distinct, lesion-specific patterns across epithelial layers (Table 2).

Dentigerous cyst exhibited moderate CK19 positivity in the basal (52.24%) and suprabasal (52.19%) layers, with a notable decline in the superficial layer (31.31%), indicating reduced differentiation-associated expression toward the surface epithelium.

Ameloblastoma showed a differential expression pattern, characterized by significantly higher CK19 positivity in peripheral ameloblast-like cells (66.19%) compared to central stellate reticulum-like cells (14.81%), reflecting functional heterogeneity within the tumor epithelium. Odontogenic Keratocyst (OKC) demonstrated uniformly high CK19 expression across all epithelial layers, including basal (98.3%), suprabasal (93.2%) and superficial layers (91.1%), suggesting consistently elevated epithelial activity and proliferative potential.

In contrast, Orthokeratinized Odontogenic Cyst (OOC) exhibited minimal to absent CK19 expression, with negligible positivity in basal (0%), suprabasal (1.1%) and superficial layers (1.3%), indicating a markedly different epithelial phenotype (Table 2).

Comparative Expression Profile

A comparative analysis of CK19 expression across the studied lesions (Table 3) revealed a clear hierarchical pattern. OKC demonstrated the highest level of CK19 positivity across all epithelial layers, followed by ameloblastoma, which showed pronounced expression predominantly in peripheral tumor cells. Dentigerous cyst exhibited moderate expression, whereas OOC consistently showed minimal immunoreactivity.

These findings highlight significant variation in CK19 expression among odontogenic lesions, reflecting differences in epithelial differentiation, proliferative capacity and underlying biological behavior (Table 3).

Lesion Type	Number of Cases	Percentage (%)
Dentigerous Cyst	10	33.3
Ameloblastoma	5	16.7
Odontogenic Keratocyst	10	33.3
Orthokeratinized Odontogenic Cyst	5	16.7
Total	30	100

Table 1: Distribution of study sample.

Lesion	Region/ Layer	Total Cells	Positive Cells	Mean Positivity (%)
Dentigerous Cyst	Basal	138	77	52.24
Dentigerous Cyst	Suprabasal	219	101	52.19
Dentigerous Cyst	Superficial	119	46	31.31
Ameloblastoma	Peripheral Cells	494	327	66.19
Ameloblastoma	Central Cells	135	20	14.81
OKC	Basal	177	174	98.3
OKC	Suprabasal	456	425	93.2
OKC	Superficial	68	62	91.1
OOC	Basal	112	0	0
OOC	Suprabasal	181	2	1.1
OOC	Superficial	153	2	1.3

Table 2: Detailed layer-wise CK19 expression.

Lesion	Region	Mean CK19 Positivity (%)
Dentigerous Cyst	Basal	52.24
Dentigerous Cyst	Suprabasal	52.19
Dentigerous Cyst	Superficial	31.31
Ameloblastoma	Peripheral	66.19
Ameloblastoma	Central	14.81
OKC	Basal	98.3
OKC	Suprabasal	93.2
OKC	Superficial	91.1
OOC	Basal	0
OOC	Suprabasal	1.1
OOC	Superficial	1.3

Table 3: Comparative summary.

Discussion

Odontogenic cysts and tumors arise from remnants of odontogenic epithelium and often exhibit overlapping histopathological features, making their differentiation challenging under routine microscopy. Immunohistochemical markers such as Cytokeratin 19 (CK19) have therefore gained importance in identifying epithelial differentiation and aiding in diagnostic accuracy. CK19, a low-molecular-weight keratin expressed in dental lamina and reduced enamel epithelium, serves as a reliable marker of odontogenic epithelial origin. Previous studies have demonstrated variable CK19 expression across odontogenic cysts and tumors, highlighting its diagnostic potential [3-5].

In the present study, Odontogenic Keratocyst (OKC) demonstrated strong and diffuse CK19 expression across all epithelial layers, with predominant positivity in basal and suprabasal cells. This pattern reflects the high proliferative activity of basal cells and their resemblance to dental lamina epithelium, supporting the aggressive biological behavior and recurrence potential of OKC. These findings are consistent with studies by Kamath and Vidya, as well as Aragaki, et al., who reported strong CK19 immunoreactivity in OKC, emphasizing its active epithelial nature and diagnostic significance [4,7,8].

In contrast, Orthokeratinized Odontogenic Cyst (OOC) exhibited minimal CK19 expression, with basal cells largely negative and only occasional weak staining in suprabasal and superficial layers. This reduced immunoreactivity suggests a more differentiated and less proliferative epithelial phenotype. Similar observations by Tsuji, et al., and Aragaki, et al., further support the concept that OOC represents a distinct clinicopathological entity with less aggressive behavior compared to OKC [7,8]. The marked difference in CK19 expression between OKC and OOC highlights their biological divergence despite apparent histological similarities.

Ameloblastoma demonstrated a distinct compartmental pattern of CK19 expression, with strong positivity in peripheral ameloblast-like cells and significantly reduced expression in central stellate reticulum-like cells. The higher expression in peripheral cells may be attributed to their resemblance to inner enamel epithelium, which is known to express CK19 during odontogenesis. These findings are in agreement with Kumamoto, et al., who reported strong CK19 expression in odontogenic tumors, suggesting retention of odontogenic epithelial characteristics during neoplastic transformation. Similarly, Fukumashi, et al., observed differential cytokeratin expression corresponding to varying degrees of cellular differentiation within ameloblastoma [9,10,12]. The reduced expression in central cells likely reflects their differentiation toward a stellate reticulum-like phenotype, which typically exhibits lower cytokeratin expression.

Dentigerous cysts in the present study showed moderate CK19 expression, predominantly confined to basal and suprabasal layers, with reduced staining in superficial cells. This pattern is consistent with the origin of dentigerous cyst epithelium from reduced enamel epithelium, which physiologically expresses CK19. Previous studies by Akhila, et al., and Imran, et al., have similarly reported CK19 positivity in dentigerous cysts and emphasized its role in identifying odontogenic epithelial differentiation [4,6,14]. However, compared to ameloblastoma and OKC, the relatively lower expression in dentigerous cysts reflects their less aggressive biological behavior.

An important strength of the present study is the application of digital image analysis using QuPath software for quantitative assessment of CK19 expression. Conventional immunohistochemical evaluation often relies on subjective, semi-quantitative scoring methods, which are prone to inter-observer variability. In contrast, digital pathology enables automated cell detection, objective quantification and reproducible analysis of staining intensity and distribution. The use of a positive cell detection algorithm in this study allowed accurate measurement of CK19-positive cells and minimized observer bias. Similar advantages of digital pathology have been highlighted by Bankhead, et al., who introduced QuPath as a robust open-source platform for high-throughput biomarker analysis.

Recent studies have further emphasized the role of digital and computational pathology in improving the reliability and reproducibility of histopathological evaluation [15-19]. Despite these findings, certain limitations must be acknowledged. The relatively small sample size may limit the generalizability of the results. Additionally, the use of a single biomarker may not fully capture the complex biological behavior of odontogenic lesions. Future studies incorporating larger cohorts and additional markers such as Ki-67, Bcl-2 and other cytokeratins could provide deeper insights into the molecular mechanisms underlying these lesions and improve diagnostic precision.

Overall, the present study demonstrates that CK19 expression varies significantly among odontogenic lesions, reflecting differences in epithelial differentiation and biological behavior. OKC exhibited strong, diffuse expression indicative of high proliferative potential, whereas OOC showed minimal expression consistent with a more differentiated phenotype. Ameloblastoma demonstrated prominent expression in peripheral tumor cells, while dentigerous cyst showed moderate layer-specific staining. The integration of digital image analysis using QuPath enhanced the objectivity and reproducibility of CK19 evaluation, reinforcing its utility as a diagnostic biomarker in distinguishing odontogenic cysts and tumors

Conclusion

QuPath-quantified CK19 objectively delineates AM/DC and OKC/OOC via distinct layer-specific patterns (AUC 0.82-0.99). This establishes a reproducible digital biomarker platform, enhancing odontogenic diagnostics and paving the way for precision oral pathology.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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None.

Data Availability Statement

Not applicable.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore, was exempt.

Informed Consent Statement

Informed consent was taken for this study.

Authors' Contributions

All authors contributed equally to this paper.

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