Original paper

Vimentin 3 expression in odontogenic keratocysts – a molecular and immunohistochemical study

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Odontogenic keratocysts (OKC) are locally aggressive jaw lesions characterized by a high recurrence rate. Vimentin 3 (VIM3), a truncated splice variant of full-length vimentin (VIMFL), has recently emerged as a potential biomarker in odontogenic tumors. However, its role in OKC and association with recurrence remain unexplored. Formalin-fixed paraffin-embedded samples from OKC ($n = 25$) and dentigerous cysts (DC) ($n = 25$) were analyzed. Immunohistochemical staining for VIM3, VIMFL, p53, and Ki-67 was performed. In parallel, reverse transcription-quantitative polymerase chain reaction was used to assess mRNA expression levels of VIM3, VIMFL, and p53. While VIM3 expression did not significantly differ between OKC and DC, recurrent OKC exhibited significantly higher VIM3 labeling indices compared to non-recurrent cases ($p = 0.040$).
This study demonstrates, for the first time, the expression of VIM3 in OKC. Although the findings are promising, further research with larger cohorts and functional validation is required to clarify the mechanistic role of VIM3 in odontogenic cyst biology.

Key words: odontogenic keratocysts, recurrence, RT-qPCR, vimentin 3 (VIM3).

Introduction

An odontogenic keratocyst (OKC) is a distinctive jaw cyst characterized by local aggressiveness, significant growth potential, and a high tendency for recurrence. First defined as "cholesteatoma", OKC has undergone multiple revisions in nomenclature and classification, most recently being categorized as a jaw cyst in the latest classification of the World Health Organization of 2022 [1, 2]. Although histopathological diagnosis is relatively straightforward, the clinical management of OKC remains challenging due to variable recurrence rates reported as 2–62% [3]. Numerous studies have explored molecular markers to predict recurrence, with Ki-67 and p53 being the most commonly investigated. These markers reflect cellular proliferation and have shown increased expression in OKC compared to other odontogenic cysts [4–6]. However, despite their frequent use, these markers lack specificity and standardization, and no reliable prognostic biomarker for recurrence has yet been established for OKC.

Vimentin 3 (accession number ACA06103.1, referred as VIM3) is a truncated isoform of full-length vimentin (VIMFL), generated through miR-498 – mediated cleavage, resulting in a unique C-terminal ending encoded by intronic sequences [7, 8]. Initially described in the differential diagnosis of renal oncocytomas and chromophobe renal cell carcinomas, VIM3 has gained attention for its diagnostic utility and distinct expression profile compared to VIMFL [8]. Vimentin 3 expression has also been demonstrated

in highly proliferative cells such as colon crypt epithelium, inflammatory cells, and spermatozoa [7–12]. In short, VIM3 expression tends to be elevated in cells with high proliferative activity, suggesting its potential association with cellular turnover rather than a specific signaling pathway. Recent evidence has highlighted VIM3 expression in odontogenic tumors, suggesting a potential role in tumor behavior and recurrence. Unlike classical VIMFL, which is broadly mesenchymal, VIM3 has been detected in epithelial contexts with high proliferative activity, such as ameloblastomas [13]. Given that OKC also exhibit a high proliferation index and a propensity for recurrence, the present study evaluated VIM3 expression in OKC, alongside Ki-67 and p53, two widely used proliferation markers, in these lesions. Ki-67 and p53 were included to serve as reference biomarkers for comparison, rather than to explore mechanistic interactions.

Therefore, the aim of this study was to evaluate VIM3 expression in OKC using immunohistochemistry (IHC) and reverse transcription-quantitative polymerase chain reaction (RT-qPCR), and to assess its potential as a biomarker for recurrence.

Material and methods

Patients

Formalin-fixed paraffin-embedded (FFPE) tissue samples diagnosed as OKC and dentigerous cyst (DC) between 2000 and 2022 were retrieved from the archives of the Oral Pathology Department. Cases that underwent only incisional biopsies or were treated with marsupialization were excluded. A total of 50 patients were included in the study: 25 OKC and 25 DC. Among the OKC group, 10 patients had recurrent lesions. For these cases, both the primary (OKC1) and recurrent (OKC2) specimens were available, yielding 20 OKC samples from 10 patients. The remaining 15 non-recurrent OKC patients contributed one representative sample each, resulting in a total of 35 OKC specimens.

For immunohistochemical evaluation, 60 FFPE tissue blocks were analyzed: 35 blocks from 25 OKC patients (with recurrent cases providing more than one block) and 25 blocks from DC. Reverse transcription-quantitative polymerase chain reaction analysis was performed on the same 60 FFPE samples. All patient data (age, gender, lesion site, recurrence history) were recorded.

Immunohistochemistry

The 4–6 μm thick sections were cut from FFPE blocks and prepared manually for IHC staining. Deparaffinization was performed using xylene and graded ethanol. Antigen retrieval was carried out in citrate buffer (pH 6.0), followed by blocking with 10% bovine serum albumin (BSA). Primary antibody against VIM3 (provided by Brandenstein/Fries, patent number EP13160876.2–1405) was diluted in phosphate buffered saline containing 1% BSA. The other antibodies (Ki-67, p53, and VIMFL) were prepared according to the manufacturers' protocols. All primary antibodies were incubated for 1 hour at room temperature. Table I provides details regarding the antibodies. Visualization was performed using a 3, 3'-diaminobenzidine substrate (Thermo Fisher Scientific, USA) and slides were counterstained with hematoxylin.

Vimentin 3 detection was performed using an antibody that specifically targets the unique C-terminal sequence encoded by intron 7 of the truncated VIM3 isoform. Unlike VIMFL, which includes the C-terminal epitope recognized by clone V9, VIM3 lacks this domain and terminates in an 8-amino acid extension. This epitope specificity has been validated by von Brandenstein *et al*. [8] (EP13160876.2–1405), distinguishing VIM3 from VIMFL and allowing selective detection in IHC. This antibody has been successfully applied in odontogenic tumors and renal neoplasms.

Immunostaining was assessed using QuPath v0.5.1. For each sample, three random fields at 200× magnification were analyzed. Nuclear staining was recorded for Ki-67 and p53, cytoplasmic staining for VIMFL, and nuclear/perinuclear staining for VIM3:

- Ki-67 was evaluated using the labeling index (LI): (positive nuclei/total nuclei) × 100,
- p53 and VIMFL were evaluated semi-quantitatively using the H-score,

Table I. Antibodies

Antibody	Clone	Host	Origin	Positive control tissue (human)	Dilution
p53	DO-1	Mouse monoclonal	Santa Cruz, Heidelberg, Germany	Squamous cell carcinoma	1 : 100
Ki-67	EP5	Rabbit monoclonal	Bio SB, Santa Barbara, USA	Tonsil	1 : 100
VIMFL	V9	Mouse monoclonal	Santa Cruz, Heidelberg, Germany	Fibroepithelial hyperplasia	1 : 200
VIM3	–	Rabbit polyclonal	EZBiolab, Carmel, USA	Oncocytoma	1 : 500

- H-score was calculated by multiplying the percentage positivity score (0 = 0–5%, 1 = 6–25%, 2 = 26–50%, 3 ≥ 50%) by the staining intensity score (0 = no staining, 1 = weak, 2 = moderate, 3 = strong), yielding a total score of 0–9.

For VIM3, both LI and H-score were calculated due to its novel use in this context.

Reverse transcription-quantitative polymerase chain reaction

RNA was extracted from three 10-μm FFPE curls per case using the NucleoSpin totalRNA FFPE kit (Macherey-Nagel, Germany). RNA concentration and purity were verified *via* spectrophotometry (Nano-400A, Allsheng). cDNA synthesis was performed using the QuantiTect Reverse Transcription Kit (Qiagen, Germany). qPCR reactions were prepared using SYBR Green Master Mix (Vazyme, China) and run on a Rotor-Gene Q device (Qiagen). The primer sequences for p53, VIMFL, VIM3, and β-actin (housekeeping gene) used in this study were identical to those published in earlier studies [8, 9], where their specificity and efficiency had been thoroughly validated. Results were analyzed *via* the 2–ΔΔCT method.

Statistical analysis

Statistical analysis was conducted using SPSS v28 and GraphPad Prism v5. Descriptive statistics (mean, SD, median, range) were reported. Normality was assessed using the Shapiro-Wilk test. As data were non-normally distributed, non-parametric tests were used:

- Mann-Whitney *U* test and Kruskal-Wallis test for group comparisons,
- Spearman's rank correlation for associations between variables,
- receiver operating characteristic (ROC) curve analysis was applied to determine the diagnostic utility of VIM3 expression (LI and H-score) in differentiating recurrent vs. non-recurrent OKC. Area under the curve (AUC) values, sensitivity, and specificity were calculated.

95% confidence intervals (CI) were reported where appropriate. A p-value < 0.05 was considered statistically significant. Given the small number of recurrent OKC cases ($n = 10$), all p-values related to subgroup comparisons should be interpreted as exploratory.

Results

Patients

Demographic, clinical, and radiological characteristics of all cases are summarized in Table II. Recurrence was observed in 10 out of 25 OKC cases (40%). Among these, 2 cases (8%) were associated with nevoid basal cell carcinoma syndrome. Syndromic patients experienced up to five recurrences over a 7.5-year average follow-up, affecting both the maxilla and mandible. The recurrence group was followed for a minimum of 1 year and a maximum of 10 years

Table II. Patients' results (demographic, clinical, and radiological data)

PARAMETERS	OKC ($N = 25$)		DC ($N = 25$)		χ^2		p-value
	N	%	*N*	%			
Gender					3.779		0.052
Female	10	40	5	19.2			
Male	15	60	20	80.8			
Location							
Mandible posterior	19	76	22	84			
Mandible anterior	4	16	2	8	4.144		0.246
Maxilla posterior	1	4	2	8			
Maxilla anterior	1	4	0	0			
Radiography	9	42.9	25	100.0	16.48		0.000049*
Unilocular	12	57.1	0	0.00			
	Mean	SD	Mean	SD	Z	*p*-value	
Multilocular							
Radiographic dimension [cm^2]	3.93	4.53	2.08	2.70	1.64	0.101	
Gross dimension [cm^3]	4.33	6.78	1.98	2.49	1.51	0.132	

** $p < 0.05$ (statistically significant)*
DC – dentigerous cysts, OKC – odontogenic keratocysts

(mean: 4.53 years), whereas non-recurrent cases were followed for at least 5 years (mean: 5.3 years).

Immunohistochemistry

Comparison of immunohistochemical staining between DC and OKC groups revealed significantly higher Ki-67 labelling indices in OKC ($p < 0.05$), while p53 H-scores showed no significant differences ($p > 0.05$). A variant of full-length vimentin staining was predominantly observed in the connective tissue of both lesions. Although 24% of DC cases showed epithelial VIMFL positivity, none of the OKC exhibited VIMFL expression in the epithelial lining.

When the comparison was limited to OKC subgroups, non-recurrent OKCs demonstrated significantly higher p53 H-scores than recurrent OKCs ($p < 0.05$). No statistically significant differences were found between primary and recurrent specimens in the recurrent OKCs group for Ki-67 or p53 staining ($p > 0.05$). Representative images are presented in Figure 1.

Vimentin 3 expression

Vimentin 3 expression appeared as nuclear and perinuclear brown staining in both epithelial and stromal components (Figure 2A–H). In OKC, nuclear positivity was observed in the basal layer, approximately 1 in 30 cells, while suprabasal cells showed more intense expression. Stromal fibroblasts and plasma cells also demonstrated strong VIM3 staining. In DC, VIM3 positivity was evident mainly in odontogenic epithelial rests, to a lesser extent in the cyst lining epithelium, and was minimal in hyperplastic epithelium.

Quantitative assessment of VIM3 expression across all OKC and DC cases showed no statistically significant difference ($p > 0.05$). However, among OKC, recurrent cases had significantly higher VIM3 labelling indices compared to non-recurrent cases ($p = 0.0404$) (Figure 2I). No significant differences were observed based on H-score evaluation ($p > 0.05$) (Figure 2J). Although VIM3 expression tended to increase following recurrence, the difference was not statistically significant. Among the recurren-

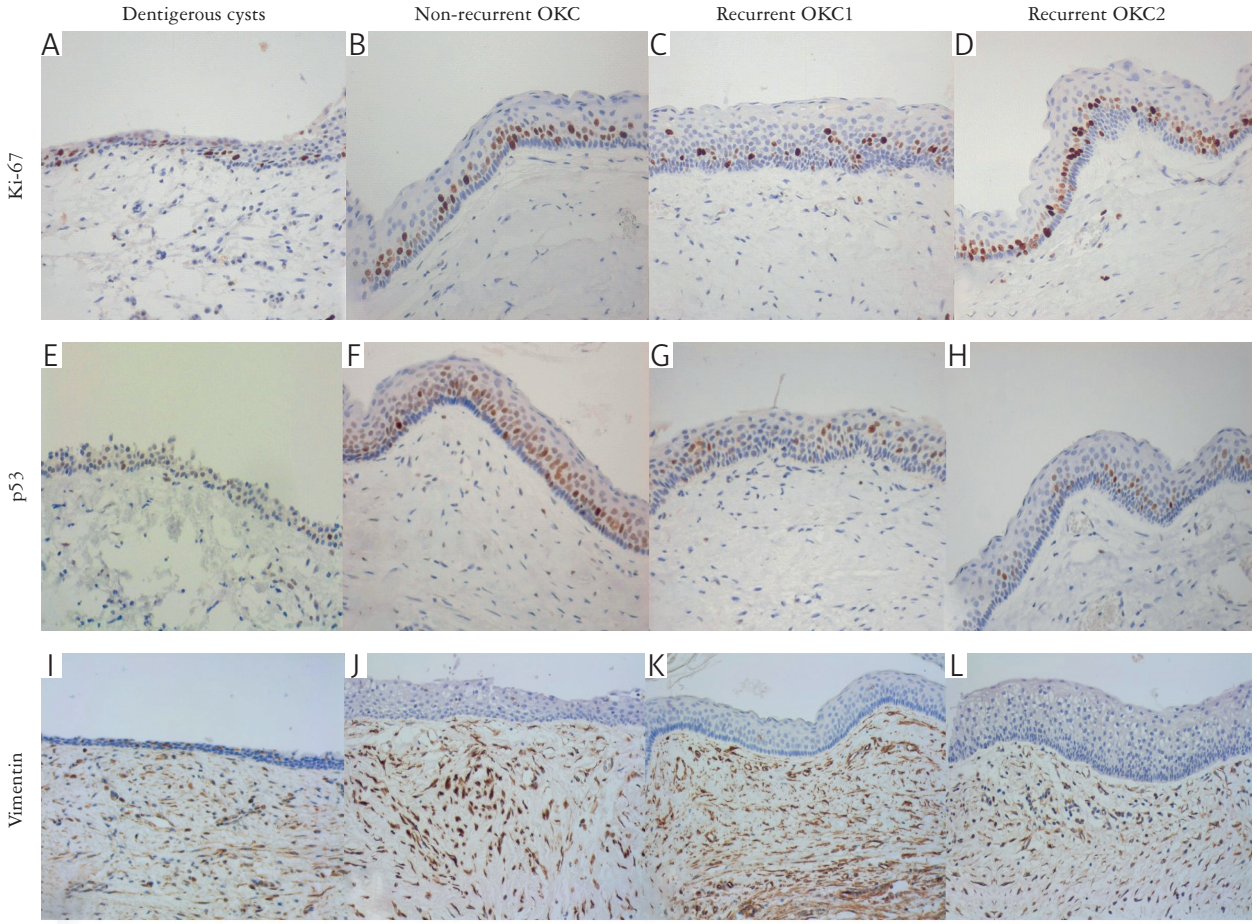

Figure 1. Representative immunohistochemical staining patterns of Ki-67, p53, and full-lenght vimentin (VIMFL) in dentigerous cysts (**DC**), non-recurrent odontogenic keratocyst (OKC), and recurrent OKC. **A**) Ki-67 staining: occasional suprabasal nuclear positivity in DC. **B**) Increased positivity in suprabasal epithelial cells of non-recurrent OKC. **C**) Recurrent OKC1. **D**) Recurrent OKC2. **E**) p53 staining: limited nuclear positivity in DC epithelium. **F–H**) Stronger basal and suprabasal nuclear staining in OKC, most intense in the suprabasal layer. **I–L**) VIMFL staining: no positivity in the epithelial lining across groups; strong cytoplasmic expression observed in the connective tissue

Scale bar = 100 μm

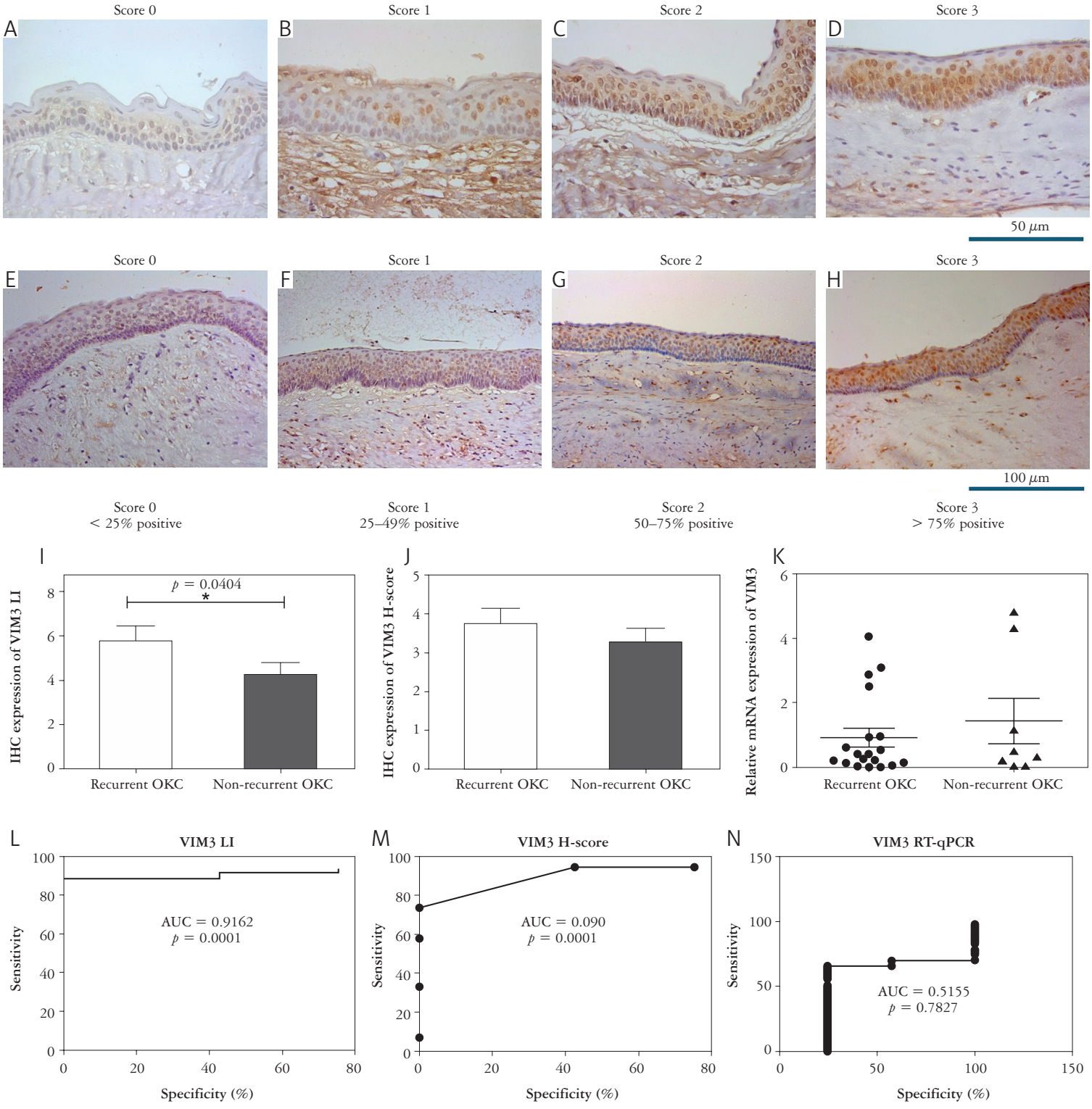

Figure 2. Representative immunohistochemical staining images of vimentin 3 (VIM3) in odontogenic keratocyst (OKC). **A–D**) VIM3 staining intensity scores of 0–3. **E–H**) VIM3 positivity scores based on the percentage of stained epithelial cells (< 25 to > 75%). **I–J**) Immunohistochemical expression of VIM3 in recurrent and non-recurrent OKC, presented as labelling index (LI) and H-score, respectively. A statistically significant difference was observed in LI values (*$p = 0.0404$). **K**) Relative mRNA expression of VIM3 determined by reverse transcription-quantitative polymerase chain reaction (RT-qPCR); no significant difference was found between groups. **L–M**) Receiver operating characteristic (ROC) curve analysis shows good performance of VIM3 immunohistochemistry (LI and H-score) in predicting recurrence. **N**) ROC curve of VIM3 RT-qPCR shows low accuracy (area under the curve = 0.5155; $p = 0.7827$)

AUC – area under the curve, IHC – immunohistochemistry, LI – labeling index, VIM3 – vimentin 3, OKC – odontogenic keratocysts, RT-qPCR – reverse transcription-quantitative polymerase chain reaction

tOKC group, syndromic cases exhibited significantly higher VIM3 LI values than sporadic cases ($p < 0.05$).

Reverse transcription-quantitative polymerase chain reaction

No statistically significant differences were detected between OKC and DC groups for VIM3, VIMFL, or p53 mRNA expression levels ($p > 0.05$). When OKC subgroups were analyzed, p53 mRNA levels were significantly higher in non-recurrent OKC compared to recurrent OKC ($p < 0.05$), whereas VIMFL mRNA levels were elevated in the recurrent group ($p < 0.05$). Vimentin 3 mRNA expression showed no significant difference between recurrent and non-recurrent OKC groups ($p > 0.05$) (Figure 2K). Interestingly, syndromic cases demonstrated significantly higher VIM3 mRNA levels compared to other recurrent cases ($p < 0.05$).

Receiver operating characteristic curve analysis

The diagnostic utility of VIM3 expression for predicting recurrence in OKC was assessed using ROC curve analysis. Immunohistochemistry-based VIM3 LI demonstrated good discriminative performance (AUC = 0.9162; 95% CI: 0.8544–0.9779; $p < 0.0001$). The optimal cutoff value identified by ROC analysis was 0.1365, yielding a sensitivity of 93.18% and a specificity of 92.84%. Similarly, the VIM3 H-score showed high accuracy (AUC = 0.9090; 95% CI: 0.8506–0.9673; $p < 0.0001$), with an optimal cutoff of 0.50 providing 94.74% sensitivity and 90.28% specificity. In contrast, RT-qPCR analysis of VIM3 expression demonstrated poor discriminatory ability (AUC = 0.5155; 95% CI: 0.3926–0.6385; $p = 0.7827$), and no meaningful cutoff could be identified (Figure 2L–N).

Discussion

Odontogenic keratocysts represent a unique group of developmental cysts that often exhibit aggressive behavior and a high recurrence rate. Recent advancements in molecular pathology have increasingly focused on the identification of biomarkers capable of predicting such behavior, thereby informing both diagnosis and treatment. Within this context, VIM3, a truncated isoform of VIMFL, has emerged as a novel marker with potential diagnostic and prognostic utility. Our current study is the first to comprehensively evaluate VIM3 expression in odontogenic cysts and to explore its relevance in predicting recurrence in OKC. We observed that VIM3 immunoreactivity was significantly elevated in recurrent OKC compared to non-recurrent cases. Statistical analysis demonstrated good accuracy (AUC > 0.9), suggesting that IHC-based VIM3 quantification may serve as a promising marker for recurrence. These findings are consistent with our previous research on ameloblastomas, where VIM3 showed markedly elevated expression compared to dental follicles, supporting its role in odontogenic epithelial dynamics [13]. Notably, VIM3 expression was particularly intense in the suprabasal epithelial layers and connective tissue, regions typically active in epithelial-mesenchymal signaling and inflammation.

Conversely, VIM3 expression analyzed by RT-qPCR failed to demonstrate significant differences between recurrent and non-recurrent OKC. This discrepancy may reflect the limitations of RNA extraction from FFPE tissues, or the lack of microdissection, which could have diluted epithelial signals with stromal RNA. Furthermore, post-transcriptional regulatory or miRNA-mediated mechanisms might contribute to differential protein translation, as previously discussed by von Brandenstein *et al*. [8].

Since VIM3 was applied for the first time in odontogenic cysts, we considered it appropriate to evaluate the protein using two scoring systems. An intriguing finding was that VIM3 H-scores did not differ significantly between recurrent and non-recurrent OKC, whereas both the LI and ROC analysis demonstrated clear discrimination. This discrepancy likely reflects the different aspects captured by each method. Labeling index measures only the proportion of positively stained cells and is therefore more sensitive to shifts in positivity. In contrast, the H-score incorporates both positivity and staining intensity; when intensity values remain relatively similar across cases, this composite measure may underrepresent differences, resulting in a non-significant Mann-Whitney *U* test [14]. Receiver operating characteristic curve analysis, however, focuses on how well specific threshold values separate groups rather than evaluating the entire distribution [15]. The clustering of recurrent OKC at higher VIM3 values produced a threshold effect that yielded a high AUC despite overlapping H-score distributions. Because these three analytical approaches emphasize different features of the data, such discrepancies are expected in biomarker research.

A particularly interesting finding was the higher VIM3 expression observed in syndromic OKC compared with sporadic cases. Although this subgroup consisted of only two patients, necessitating cautious interpretation, the pattern is noteworthy. As a possible biological explanation, previous studies have shown that endothelin-1 (ET-1), a regulator of keratinocyte proliferation and an activator of the Sonic Hedgehog (SHH) pathway [16], may influence VIM3 expression. This mechanism is especially relevant in syndromic OKC, where *PTCH1* mutations and SHH pathway dysregulation are well documented. The potential link between ET-1, SHH signaling pathway, and VIM3 [17], remains speculative but biologically plausible, underscoring the need for future studies exploring this pathway in odontogenic lesions.

In our previous study on ameloblastomas, we demonstrated that VIM3 expression was significantly higher in solid/multicystic ameloblastomas compared to unicystic types and dental follicles [13]. The immunostaining pattern revealed strong cytoplasmic and perinuclear positivity in odontogenic epithelial islands, with higher intensity in more proliferative and recurrent cases. When considered alongside the current findings in OKC, a broader pattern emerges in which VIM3 is consistently associated with aggressive biological behavior across distinct odontogenic entities. While ameloblastomas represent true odontogenic neoplasms with a well-established tendency for recurrence, OKC lie on the cyst-tumor continuum. The shared feature of VIM3 overexpression may reflect a common biological mechanism involving epithelial plasticity, proliferative signaling, or epithelial-mesenchymal interactions. Collectively, these observations strengthen the notion that VIM3 is not merely a structural variant of VIMFL but may serve as a potential biomarker indicative of increased biological activity within odontogenic tissues. Further comparative studies encompassing a wider spectrum of odontogenic cysts and tumors are warranted to elucidate the underlying mechanisms and clarify the diagnostic and prognostic value of VIM3.

Among additional markers evaluated; p53 expression showed a tendency towards association with recurrence. Both IHC and mRNA levels of p53 were lower in recurrent OKCs, in line with previous studies suggesting that reduced p53 activity may contribute to the aggressive biological behavior of OKC [18–20]. Although reports in the literature remain inconsistent [6, 19], our combined findings indicate that p53 downregulation could be related to recurrence risk. Previous research has also linked *TP53* alterations with *PTCH1* mutations and SHH pathway dysregulation, which are frequently implicated in syndromic OKC [21, 22].

Regarding VIMFL, our RT-qPCR results revealed a statistically significant increase in recurrent OKCs, despite the absence of epithelial VIMFL staining on IHC. Given that VIMFL is typically expressed during early odontogenesis within the mesenchymal compartment [23], its elevated transcript levels may reflect enhanced stromal activity in recurrent cases. This finding could indicate epithelial-mesenchymal interactions rather than a true EMT process, suggesting that stromal VIMFL overexpression may contribute to the locally aggressive behavior of OKC.

Previous studies have suggested a possible interplay between p53 and VIMFL isoforms. Nohl *et al*. [24] reported that wild-type and mutant p53 may form distinct complexes with VIMFL variants, potentially influencing downstream molecular pathways. The inverse expression pattern of p53 and VIM3 observed in our study might be consistent with such regulatory interactions [21, 22, 25, 26], although this hypothesis requires further molecular validation.

Limitations of the present study include the relatively small size of the recurrent OKC subgroup, which may affect statistical power, and the lack of tissue microdissection in molecular analysis. Moreover, RNA extraction from long-term archived FFPE samples may compromise RNA integrity, potentially affecting qPCR accuracy. Future studies with larger cohorts, inclusion of microdissection, and protein quantification in fresh-frozen tissue may provide a more refined understanding of the biological role of VIM3 in odontogenic lesions.

Conclusions

Vimentin 3 appears to be a promising marker associated with recurrence in OKC when evaluated by IHC. The observed differences between IHC and qPCR results emphasize the importance of methodological and tissue-specific factors in biomarker research. Further studies with larger sample sizes are needed to validate these findings and clarify the clinical relevance of VIM3 in odontogenic cysts.

Disclosures

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