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RESEARCH

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Immunohistochemical assessment of the potential behavior of glandular odontogenic cyst and inflammatory periodontal cyst using E-cadherin and N-cadherin

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Abstract

Background This study is done to evaluate the immunohistochemical expression of E-cadherin and N-cadherin in glandular odontogenic cysts (GOC), inflammatory periodontal (IPDL) cysts, and dental follicles (DF), and if there is a correlation with their biological behavior GOC, IPDL cysts, and DF cases were collected and investigated by immunohistochemistry. The area percent of immunoexpressed markers was calculated by SPSS version 25.

Results The statistical analysis revealed a clear, statistically significant difference between the studied groups regarding the area percentage of the two immune-expression markers (p value = 0.000). The highest area percentage of the mean value of E-cadherin was recorded in IPDL cysts group with the most negligible value recorded in the group of GOC. On the other hand, the highest area percentage of the mean value of N-cadherin was documented in the group of GOC with the least recorded value was noted in the group of DF.

Conclusion We noted that the cadherin switch mechanism in the epithelial lining of odontogenic cysts is a critical step in the epithelial mesenchymal transition process which may associates with clinical behavior and may also impact the mode of treatment.

Keywords EMT, Cadherin switch, Radicular cysts, N-cadherin, E-cadherin, Glandular odontogenic cyst

1 Background

The glandular odontogenic cyst (GOC) is a relatively rare cystic lesion clinically found in the mandibular jaw more than the maxillary jaw; it usually poses a diagnostic and treatment challenge [1]. Despite its histological resemblance between odontogenic tumors and some salivary gland tumors, it was named a sialo-odontogenic cyst as previously confirmed by immunohistochemical analysis, and it has an odontogenic origin [2]. Periapical lesions initiated by inflammatory stimulus followed by periapical infection clinically appeared as radicular cysts or periapical granulomas. This category of lesions epitomizes the most frequent pathologies in jaw bones [3, 4]. An inflammatory periodontal cyst (IPDL cyst) is the most well-known type of odontogenic cyst in the inflammatory category. The IPDL cyst occurs as a result of inflammatory stimulus causing proliferation of the epithelial rests of malassez that leads to the occurrence of the inflammatory type of odontogenic cysts. On the opposite side, the pathogenesis of the developmental lateral periodontal cyst is attributed to an unknown stimulus that stimulates the proliferation of Epithelial Rests of Serre's [5]. Radiographically, cases of IPDL cysts usually look like

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an osteolytic lesion with a well-defined unilocular radiolucent appearance at the periapical area of a non-vital tooth. Surgical removal and proper endodontic treatment of involved teeth are considered the best line of treatment with an excellent prognosis for such cases [6–8].

According to the classification of head and neck tumors by the world health organization (WHO) 2017, the GOC is a development cyst with epithelial features that simulate glandular differentiation and is characterized by variable histological structures [9].

The histological diagnosis of such GOC cases is challenging and not straightforward, unlike the IPDL cysts. Diagnosis of GOC usually depends on fulfilling at least seven out of the criteria indicated by the WHO 2017 [9]. The WHO criteria include variable thickness of the epithelial lining, multiple cystic compartments, plaque-like epithelial thickening and tufting. In addition, intra epithelial microcysts, clear cells, mucous cells, apocrine cells, hobnail cells and cilia. Also solid islands of odontogenic epithelium detected in connective tissue cystic wall. Therefore, it is a critical decision to confirm the histopathological diagnosis of GOC due to its unfavorable prognosis in some cases. In addition, as previously known from the scientific literature, there is a challenge regarding the histopathological differentiation between GOC and intra-osseous mucoepidermoid carcinoma facing oral pathologists [9]. The intra-osseous mucoepidermoid carcinoma is a rare salivary gland malignant neoplasm which occurs inside the jaw bones. It usually composed of sheets or masses of mucous cells and dysplastic epidermoid cells. Moreover, cystic spaces and duct like structures filled with mucin are usually found in this neoplasm. Thus depending on the previously mentioned histological clues will guide any pathologist to reach a correct definitive diagnosis regarding GOC. According to the scientific literature, the GOC is known to have aggressive clinical behavior, a high incidence of loss of the cortical plate integrity, and an elevation in the recurrence frequency if treated by a conservative approach [3]. Therefore, the surgical decision of jaw en-bloc resection with a longer follow-up duration, even for small lesions, is the best treatment option compared to other odontogenic cysts [4]. However, little information about GOC histogenesis is available in the literature due to its rare occurrence [8, 9].

The epithelial-mesenchymal transition (EMT) is a complicated mechanism by which the epithelial cells lose their polarity and alter their cytoskeleton [10], gaining a mesenchymal cellular morphology that assists their migration through the extracellular matrix [11–13]. As mentioned in old literature, EMT shares a role in several embryonically and pathological conditions, mainly fibrosis and carcinogenesis [14, 15]. Moreover, modern research embraced EMT's pivotal role in regulating growth, migration, and the invasive mechanisms of many odontogenic cystic lesions and tumors [9–13].

Cadherins and integrins usually control cellular motility and morphology by facilitating cellular and extracellular matrix interactions [16, 17]. One of the most studied cell–cell adhesion molecule is the E-cadherin which governs the invasion properties by altering cytoskeletal and cell junctional association. N-cadherin is a non-epithelial type of cadherin predominantly located in mesenchymal and stromal tissues and principally considered a critical diagnostic immunohistochemical marker for EMT [16, 17].

Aberrant immunohistochemical expression of N-cadherin has been reported to be pro-oncogenic and enhances tumor cell invasion and migration, according to recent research in oncology [18]. Adhesion-blocking by reducing E-cadherin and increasing N-cadherin immune expression elevates cells' invasive tendency [19]. Previously it was proven by scientific evidence that there was a down-regulation of essential adhesion molecules such as E-cadherin and up-regulation of N-cadherin in the studied cases of aggressive odontogenic cysts and tumors. This observation signifies the vital role of EMT and its association with the clinical behavior and the recurrence frequency of odontogenic lesions [9–13].

This study aimed to evaluate the E-cadherin and N-cadherin immunohistochemical expression as a fundamental portion of EMT in GOC which may correlate with the invasion potential and aggressiveness of such lesions. For comparative purposes, IPDL cyst cases (as non-aggressive odontogenic cysts) and DF (as morphologically healthy odontogenic tissue) were involved in this study.

2 Methods

The protocol for this study was accepted by the Research and Ethics Committee of the Faculty of Dentistry, (xxxxxx) University. The files of the patients who visited our oral and maxillofacial pathology department between 2010 and 2020 were reviewed for cases selection. All our research cases were obtained from a bank of paraffin blocks in the oral and maxillofacial pathology department, as these excised tissues are stored and kept in certain conditions approved by the ethical committee in our faculty. Therefore, we have the ethical committee's approval registered with no. (14 2 22), to use these preserved tissues without patient consent.

The paraffin blocks included in this study were prepared from tissues taken as biopsies from patients suffering from oral swellings diagnosed as GOC, IPDL cysts, and normal DF cases. All H&E stained slides obtained from the previously prepared paraffin blocks related to study cases were reviewed, and the diagnosis was reconfirmed based on the latest WHO histological criteria by two blinded pathologists.

The clinicopathological presentation of IPDL cases varied from slight asymptomatic intraoral swelling related to a non-vital tooth with well-defined unilocular radiolucency in the x-ray to significant intraoral swelling with eggshell crackling sensation. Some of them were painful and contained pus related to the non-vital tooth. Upon histological examination of different IPDL cysts cases, all of them appeared to be cystic lesions lined by hyperplastic stratified squamous epithelium. Cases showed some variations in the cyst lining and intense infiltration of the chronic inflammatory cells in the connective tissue wall. Also, the clinicopathological presentation of most of the GOC cases were prominent intraoral swelling related to vital teeth with well-defined multilocular radiolucency presentation in the x-ray associated with thinning, destruction or perforation of the cortical jaw bones and numbness in the affected area. Upon histological examination of different GOC cyst cases, they all fulfilled seven of the previously mentioned histological criteria.

Only total excised samples (with full medical, radiographic and clinical data) were included in this current study, and improperly processed samples were excluded. Forty-five cases were selected for immunohistochemical staining, including fifteen cases of recurrent lesions of GOCs, fifteen cases of IPLC, and fifteen cases of DF. This sample size was approved and accepted by the ethical committee in our institute due the rarity of the GOC cases which was reported in scientific literature [20].

Three-micrometer sections were cut from the paraffin-embedded tissue blocks for immunohistochemistry protocol. All slides were deparaffinized and then rehydrated in decreasing concentrations of ethanol. The antigen retrieval step was performed using microwave heating for 20 min and then slides underwent endogenous peroxidase activity blocking step, followed by immersing the glass slides in 3% hydrogen peroxide considered as a mandatory step. Then washing the prepared slides with PBS was done. The monoclonal antibodies of E & N-cadherin immune markers were diluted by phosphate buffer saline (PBS) in a dilution of 1:100 to be used in this study (E-cadherin (G-10); sc-8426 and N-cadherin (H-2): sc-393933; Santa Cruz Biotechnology Inc., Dallas, TX, USA). Both immune markers were utilized fully automated on a Ventana Benchmark Ultra platform following the Ultra View DAB detection kit procedure (cat #760-500, Ventana Medical Systems/Roche Diagnostics). After that, the sections were immersed and incubated with the antibodies in a moist chamber, followed by two PBS washing cycles. The necessary treatment was done at room temperature with a polymer-based complex anti-N-cadherin and anti-E-cadherin antibodies. Peroxidase activity was developed by immersing the tissue sections in diaminobenzidine (liquid DAB + substrate; Dako), resulting in a brown reaction product. Finally, the sections were counterstained with Harris's hematoxylin and were finally covered by slips.

Immunohistochemical analysis was performed using a leica light microscope supported by microscopic camera of 12 MP to inspect all the stained sections for histological examination by two well-trained blinded pathologists as external examiners, and using the software Leica Qwin 500 (Germany) for image analysis. The area percent of E-cadherin and N-cadherin immune expression was measured in a measuring frame of 61,934 μm^2. Five fields were measured from every slide of each case using a magnification (×400); this method was described before by Pinheiro et al. [19]. First, areas of the most intense immunoreaction (brown stained) were automatically selected then the computerized system converted the area into a green binary color that could be precisely calculated.

Data were acquired from computer image analysis for statistical analysis, followed by checking the data distribution using normality tests of the Statistical Package for the Social Sciences software (SPSS version 25; IBM ® Company). Then parametric data were presented in the form of mean and standard deviation (± SD) values for each group of cases. Next, one Way Analysis of Variance (ANOVA) test was utilized for statistical comparison between the different groups, followed by Tukey's Post-Hoc Test for pairwise comparison between the means when the ANOVA test was significant. Finally, study hypotheses were tested, adopting a significance level of 5%, with p values ≤ 0.05 considered significant.

3 Results

As regards the H&E stained sections, the histopathological diagnosis of all the cases was reconfirmed according to WHO classification (2017). GOC cases showed a cystic cavity lined with odontogenic epithelium. Hobnail cells, clear vacuolated cells (Fig. 1a), plaque-like thickening (Fig. 1b), and variable thickness of cyst lining (Fig. 1c) were observed in all the stained sections. Mucous cells (Fig. 1a), intraepithelial cysts (Fig. 1c), cilia (Fig. 1a), and epithelial papillary projections (Fig. 1c) were also detected in some areas of all the examined samples. The underlying fibrous connective tissue stroma showed chronic inflammatory cell infiltration in a small number of GOC cases.

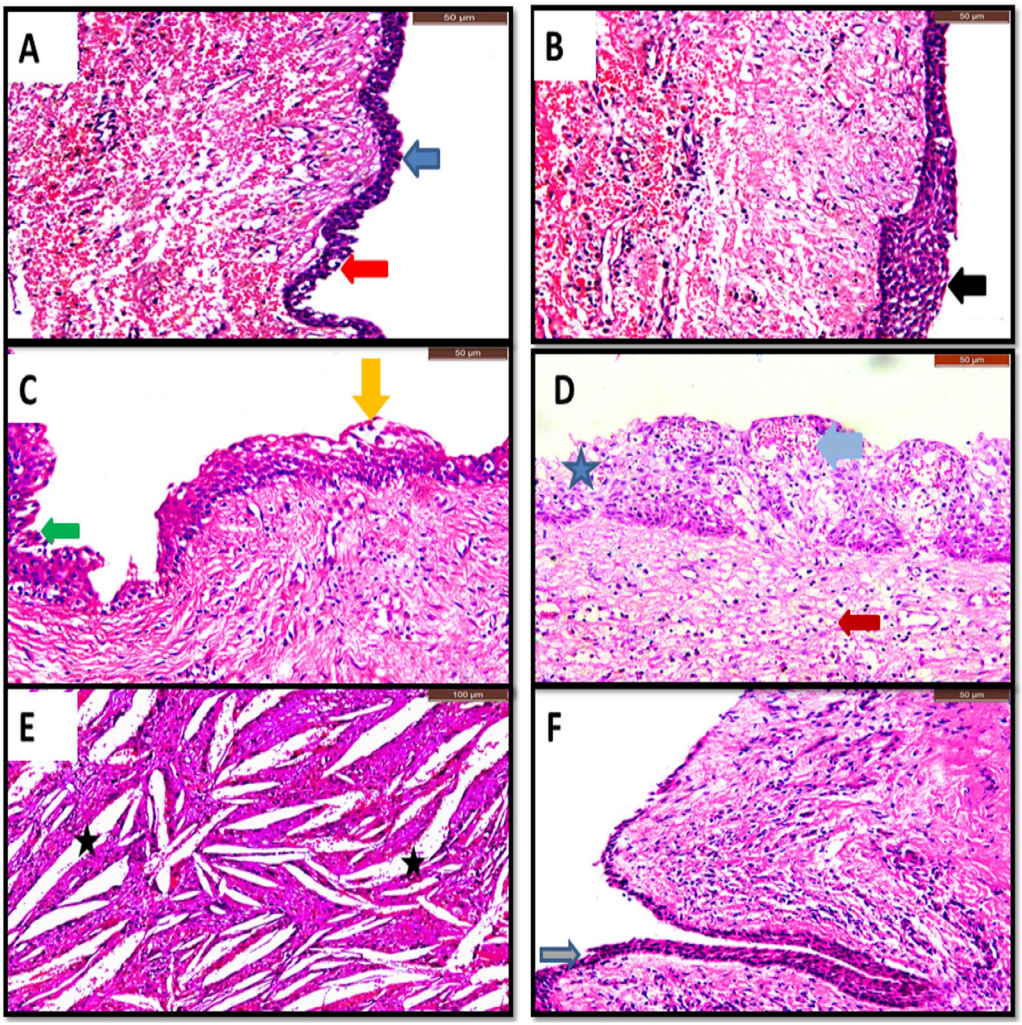

Fig. 1 Photomicrographs of H&E stained sections **a** showing a cystic cavity lined by epithelium containing clear cells (red arrow) and showing luminal hobnail cells (blue arrow) superficially in GOC, magnification × 200. **b** Variable thickness of the epithelial lining of GOC and plaque like thickening (black arrow) were also observed, magnification × 200. **c** Intraepithelial microcysts (orange arrow) and tufting (green arrow) were detected in the epithelial lining of GOC, magnification × 200. **d** A cystic cavity lined by hyperplastic stratified squamous epithelium (blue star) showing arcades (light blue arrow), also chronic inflammatory cells and foam cells (dark red arrow) could be seen in the connective tissue wall of IPDLcyst, magnification × 200. **e** Cholesterol clefts (black star) were seen in the connective tissue wall of IPDL cyst, magnification × 100. **f** The dental follicle tissue showing the covering epithelium composed of 1–2 layers of cuboidal cell (reduced enamel epithelium) (gray arrow) and underneath the true dental follicle with thick layer of connective tissue stroma (CT), magnification × 200

IPDL cyst cases revealed a cystic cavity lined by hyperplastic stratified squamous epithelial, which showed arcades in some cases (Fig. 1d). The underlying connective tissue wall was infiltrated with chronic inflammatory cells in all the cases. Some cases showed cholesterol clefts (Fig. 1e) and foam cells (Fig. 1d). DF cases showed the reduced enamel epithelium formed of 2 or 3 layers of cuboidal cells underlined by a thick connective tissue (Fig. 1f).

Concerning the immunohistochemically stained sections, 80% of GOC cases showed weak E-cadherin cytoplasmic immune reactivity in the epithelium's basal half. At the same time, moderate membranous expression was limited to the epithelium's upper half (Fig. 2a). The rest of the cases of GOC showed weak E-cadherin immune expression in the whole thickness of the epithelial lining. On the other hand, strong E-cadherin membranous and cytoplasmic immune reactivity was

observed in the basal half of the epithelium. However, moderate membranous expression was noted in superficial cells in about 90% of the cases of IPDL cyst (Fig. 2b). Contrarily, in all the DF cases, there was a solid heterogeneous membranous and cytoplasmic E-cadherin immunoreaction observed throughout the whole epithelial thickness extending from the basal cell layer to the surface layer (Fig. 2c).

As to N-cadherin immune-expression, in all cases of GOC, N-cadherin immune expression was observed to be moderate to strong diffuse cytoplasmic and membranous, through most of the thickness of epithelial lining and also in some stromal cells in the connective tissue wall (Fig. 2d). Regarding IPDL cyst cases, N-cadherin was detected as a weak scattered cytoplasmic expression in the epithelial lining and the connective tissue stroma (Fig. 2e). But in DF cases showed no immunoreaction across the whole epithelium (Fig. 2f).

3.1 Statistical analysis

Upon comparing the area percentage of E-cadherin among cases of GOC, IPDL cyst, and DF, there was an evident statistically significant difference. The highest area percent value of E-cadherin was detected and recorded in a group of IPDL cysts to be 12.16, followed by the DF group to be 6.04 with the least value recorded in the group of GOC equal to 1.58. The one-way ANOVA test showed a statistically significant difference between the groups, and mean values with different superscript letters were significantly different depending on Tukey's post hoc test. All these values are represented in Table 1

Statistical linking of the area percentage of N-cadherin among cases of GOC, IPDL cyst, and DF showed a notable statistically significant difference. The highest area percent value of N-cadherin was documented in group GOC to be 2.75, followed by the IPDL cyst group to be 2.07, with the least value noted in a group of DF equal to 1.12. The one-way ANOVA test showed a statistically

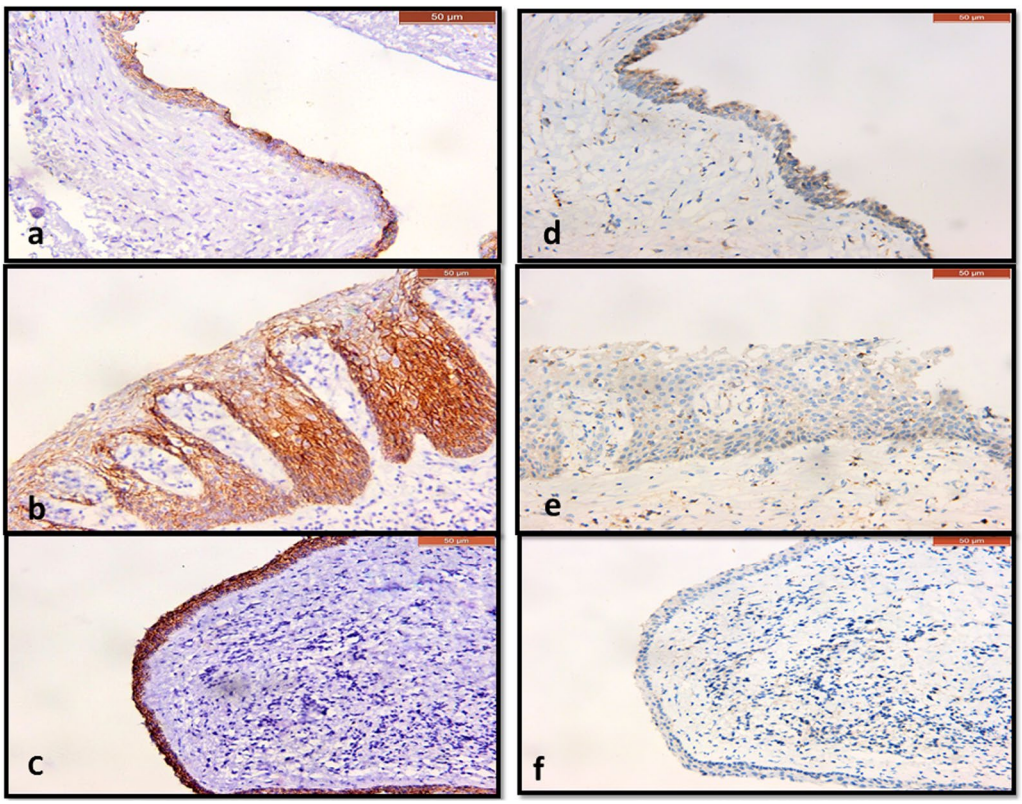

Fig. 2 Photomicrographs of immunohistochemical staining of E-cadherin and N-cadherin representing **a** weak cytoplasmic expression of E-cadherin in the basal half and moderate membranous immunoexpression in the superficial half of the epithelial lining in GOC. **b** Strong E-cadherin cytoplasmic and membranous immunoexpression in the basal half and moderate to weak E-cadherin immunoexpression in the superficial half of the epithelium in IPDL cyst. **c** Strong cytoplasmic and membranous immunoexpression of E-cadherin in the whole thickness of the epithelial lining of the DF. **d** Strong and diffuse N-cadherin immunoexpression in most of the epithelial lining and stromal cells of GOC. **e** Weak and scattered N-cadherin immune-expression in the epithelial lining and stromal cells of IPDL cyst. **f** No immunoreaction was noted across the whole thickness of the epithelium in most of DF cases

Table 1 The area percentage of E-cadherin immunoexpression in the study groups

Study groups	E-cadherin area %				
	Mean	SD	SE	95% confidence interval for mean	
				Lower bound	Upper bound
DF group	6.04[a]	1.12	0.50	4.64	7.43
IPDL Cyst group	12.16[b]	2.34	1.04	9.25	15.06
GOC group	1.58[c]	0.93	0.41	0.42	2.73
P value	0.000				

Means with different superscript letters are significantly different. (Tukey's post hoc test)

*Significant at $P < 0.05$

Table 2 The area percentage of N-cadherin immunoexpression in the study groups

Study groups	N-cadherin area%				
	Mean	SD	SE	95% confidence interval for mean	
				Lower bound	Upper bound
DF group	1.12[a]	0.097	0.04	0.99	1.24
IPDL Cyst group	2.07[b]	0.37	0.16	1.61	2.53
GOC group	2.75[c]	0.35	0.16	2.31	3.19
P value	0.000				

Means with different superscript letters are significantly different. (Tukey's post hoc test)

*Significant at $P < 0.05$

significant difference between the groups, and mean values with different superscript letters were significantly different depending on Tukey's post hoc test. All these values are represented in Table 2.

4 Discussion

Odontogenic cysts are a heterogeneous group of lesions with a broad spectrum of varied clinical behavior and histopathological characteristics. They are classified according to their origin into developmental and inflammatory subtypes [9]. The inflammatory subtype of the odontogenic cysts (IPDL cysts) usually results from the inflammatory stimulus in the epithelial rests of malassez. The developmental subtype of odontogenic cysts as GOC has a similar odontogenic epithelial origin; it is noteworthy that they exhibit different levels of invasion and biological behaviors than other types. Unfortunately, little research was elucidated about GOC as one of the developmental odontogenic cysts in the jaw concerning its onset, progression, and all-over pathogenesis due to its rarity.

Substantiation of the contribution of the process of EMT in inducing invasiveness and recurrences has not been well inspected in most of odontogenic tumors and cysts especially GOC. Cadherins are calcium-dependent cell adhesion molecules involved in several physiological events such as cell adhesion, migration, and morphogenesis [21]. In the present study, the expression of E-cadherin and N-cadherin immune markers were investigated to discover the link between the cadherin switch process as a vital step in EMT and the biological behavior of the odontogenic cysts as GOC &IPDL. This switch allows the seeding of the cells in the surrounding tissues; this may be a primary cause of aggressive biological behavior and the high recurrence rate of odontogenic cysts.

Concerning the E-cadherin immunohistochemical expression, 80% of the recurrent GOC cases showed weak expression, mainly in the basal half or in the whole thickness of their epithelial lining. On the other hand, examining the N-cadherin immunohistochemical expression in all recurrent cases of GOC, it was detected to be strong cytoplasmic and membranous immunoexpression in the cyst lining. Therefore, the proper explanation of this observation is that the epithelial cells undergo the cadherin switch process, especially in the basal part of the epithelial lining of the GOC, cause elevation in its rate of recurrence. A similar finding was noted in another study investigating ameloblastoma cases, proving a link between the aggressiveness of ameloblastoma and the cadherin switch mechanism [22]. Another earlier study also reported elevated N-cadherin and reduced E-cadherin immunoexpressions in the epithelial lining of odontogenic keratocyst cases. These empirical findings confirm that the cadherin switch mechanism is a vital step in controlling the biological behavior of odontogenic cysts [10].

On the other hand, strong E-cadherin and weak N-cadherin immune reactivity in the epithelial lining of most cases of IPDL cyst were noted and documented in our study. Our explanation for this observed finding is that IPDL cyst cases are usually indolent with non-aggressive behavior and a very low recurrence rate. Thus, the cell adhesion molecules between epithelial cells in IPDL cysts are prominent compared to epithelial cells in other aggressive odontogenic lesions such as GOC, ameloblastoma, and odontogenic keratocysts. Similar previously published results by Özcan et al. [23] reported elevated E-cadherin expression in IPDL cysts more than in odontogenic keratocyst cases. Their observation suggests that the E-cadherin protein regulates the cell adhesion and controlling the behavior of these odontogenic cysts. Also, Zhong et al. [24] documented that N-cadherin has reduced immune expression in IPDL cysts compared to aggressive odontogenic keratocysts. Those findings also

confirm that the idea of biological behavior of any odontogenic cyst is usually linked to the EMT process that allows the seeding of odontogenic epithelial cells in the surrounding tissue. Contrasting immunohistochemical findings were detected in previous immunohistochemical research by Pinheiro et al. [16]. They confirmed the lack of statistical significance difference between E-cadherin expression of non-aggressive IPDL cysts and the aggressive odontogenic keratocyst in most cases without clearly discussing their observed finding. However, another study by Aborisade et al. [25] noted that the Cadherin switching mechanism could not finally predict the biological behavior of ameloblastomas (most common locally agrressive odontogenic tumor).

Contrarily in all the DF cases, strong heterogeneous membranous and cytoplasmic E-cadherin immunoreaction was observed throughout the whole epithelial thickness extending from the basal cell layer to the surface layer. However, N-cadherin expression was almost negative in the epithelial part covering the dental follicle. Driesen et al. [26] discussed earlier that strong positive E-cadherin immunostaining was found in the epithelial remnants of Hertwig's epithelial root sheath in the dental follicle area. In addition, Porto et al. [10] illustrated that nuclear staining with N-cadherin was only apparent in cases of neoplastic epithelium and not found in the epithelial part covering the dental follicle. Thus the novelty of our presented study is to ensure that there is a strong relation between cadherin switch mechanism and the behavior (regarding prognosis and recurrence) of the GOC cases, which is not previously investigated in any other published studies until now. Our novel introduced study can participate to understand the nature of GOC, as a rare entity and try to find the best line of treatment of such cases. Exploring the proteins involving in EMT process, could guide surgeons to choose the best line of treatment which suits the biological behavior of each odontogenic lesion. This finally will minimize the rate of recurrence of these oral cysts and also improve patient life style.

5 Conclusions

In conclusion, and by taking the previously discussed findings into our consideration, we noted that the cadherin switch mechanism (reducing E-cadherin immune expression and gaining N-cadherin immune expression) is a vital and critical step in the EMT process which probably associates with behavior of odontogenic cysts especial those of variable clinical findings. Finally, it may impact the mode of treatment and alter patient life style. Hence inspecting cadherin proteins in the cases of odontogenic cysts of variable clinical findings as GOC could give the surgeon better guidance regarding their behavior in each case. Moreover, it will direct surgeons for the proper treatment strategy of odontogenic cysts, either enucleation or en-bloc resection in each case. Finally, limitations of our research must be clearly stated as the small number of involved cases of GOC in our study, this is attributed to the rarity of the GOC and also excluding the cases with incomplete data available from our work. In addition, we did not investigate the immune reaction of another more proteins involved in EMT reaction as vimentin and fibronectin. Thus, further studies are recommended to investigate the effect of other proteins involved in the EMT process in GOC and in different odontogenic tumors.

Abbreviations

DF	Dental follicle
EMT	Epithelial mesenchymal transition
GOC	Glandular odontogenic cyst
IPDL	Inflammatory periodontal cyst
WHO	World Health Organization
PBS	Phosphate buffered saline

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Author contributions

Conceptualization: AE; methodology: HS and DM Formal analysis and investigation: HS, writing—original draft preparation: AE and DM. Writing—review and editing: HS, supervision: DM, all authors commented on previous versions of the manuscript, All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available until this work is accepted in the journal but are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study followed the ethical standards of the Research Ethical Committee, Faculty of Dentistry, Cairo University. This study required the utilization of removed cysts from patients in the last years and stored them for research studies per the institution's ethical standards. Therefore, the Research Ethics Committee of the faculty of dentistry, Cairo University approved the study (Protocol No. 14.2.22). Also, the Research Ethics Committee of the faculty of dentistry, Cairo University approved the use of these preserved tissues without patient informed consent. Not required for this study, as we have the ethical committee's approval to use these preserved tissues without patient consent. All our research cases were obtained from a bank of paraffin blocks in the oral and maxillofacial pathology department, as these excised tissues are stored and kept in certain conditions approved by the ethical committee in our faculty.

Consent for publication

Not applicable.

Competing interests
All the authors declare that they have no conflict of interest regarding this submitted manuscript.

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