BULLETIN OF STOMATOLOGY AND MAXILLOFACIAL SURGERY
Volume 21, Issue 8

DOI: 10.58240/1829006X-2025.21.8-27

ORIGINAL RESEARCH

DIFFERENCES EXPRESSION OF SYNDECAN-1 (SDC-1) AND E-CADHERIN (E-CAD) IN HISTOPATHOLOGICAL TYPES OF FOLLICULAR, PLEXIFORM, AND MIXED AMELOBLASTOMA (FOLLICULAR-PLEXIFORM)

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Received: *Jul 21. 2025;* ***Accepted:*** *Aug. 27, 2025;* ***Published:*** *Sep. 3, 2025*

ABSTRACT

Background: Ameloblastoma is a benign tumor that can cause deformity and functional disorders in the craniomaxillofacial region. The invasion process of ameloblastoma requires degradation of the extracellular matrix (ECM) and basement membrane to support tumor cell proliferation. SDC-1 (CD-138) functions as a heparan sulfate proteoglycan that regulates cellular adhesion and extracellular matrix attachment, while E-Cadherin (E-Cad) serves as a calcium-dependent transmembrane glycoprotein critical for epithelial morphogenesis and homotypic cellular adhesion.

Aim: The present study was designed to evaluate differences in SDC-1 and E-Cad expression patterns according to ameloblastoma histopathological classification.

Materials and Methods: This research is an analytical observational study with a cross-sectional approach. The research sample used 24 post-operative paraffin blocks from ameloblastoma patients from the period 2015–2023 who were histopathologically diagnosed. SDC-1 and E-Cad expression was analyzed using immunohistochemical methods. Statistical analysis used the Tukey HSD test. This research has received ethical approval from the local ethics committee.

Results: The lowest expression of SDC-1 and E-Cad was found in the follicular type, while the mixed type (follicular-plexiform) showed the highest expression values. The Tukey HSD test showed significant differences in SDC-1 expression between the mixed type and the plexiform type (p=0.040) and follicular type (p=0.032). E-Cad expression also showed significant differences between the follicular type and mixed type (p=0.032).

Conclusion:
There are significant differences in SDC-1 and E-Cad expression between follicular type and mixed type ameloblastoma, while no significant differences were found between follicular type and plexiform type. These results indicate that histopathological variation is related to cell adhesion molecule expression in ameloblastoma.

***Keywords*:** Ameloblastoma, Syndecan-1, E-Cadherin, Immunohistochemistry, Histopathology.

INTRODUCTION

Ameloblastoma is classified as a benign tumor, but it can have serious clinical consequences due to its aggressive, expansive, and locally invasive development pattern. Large ameloblastoma can result in deformity and functional disorders in the craniomaxillofacial region.[1] The recurrence rate in ameloblastoma cases is around 64% after conservative therapy and 12% after tumor removal.[2,3] Ameloblastoma can be classified based on clinical, radiological, and histological characteristics. The plexiform and follicular histological varieties of ameloblastoma are the most frequently observed forms, whereas the follicular-plexiform type is the most frequently observed in mixed type.[4] Compared to plexiform or unicystic forms, follicular ameloblastoma has been reported to have a higher recurrence rate.[5] The prognosis of ameloblastoma can be determined by understanding cellular changes that are impacted by tumor growth factors and tumor biology, ranging from proliferation, differentiation, apoptosis, angiogenesis, tumor invasive properties, and tumor histomorphology using immunohistochemical examination.[6]

The high recurrence rate despite surgical intervention indicates that conventional clinical and histopathological assessment is not sufficient to accurately predict tumor behavior.[7,8] Therefore, identification of molecular markers that can reflect the biological aggressiveness of ameloblastoma is important for improving prognosis and determining more appropriate management strategies.[9]

The invasion process of ameloblastoma is characterized by disruption of the basement membrane and extracellular matrix (ECM) and loss of adhesion to surrounding cells. Syndecan-1 (SDC-1) and E-Cadherin (E-Cad) levels can be used as indicators of cellular alterations in the process. Known also as CD-138, SDC-1 is a transmembrane heparan sulphate proteoglycan that regulates several biological processes, such as cytoskeleton organization, growth factor signalling, cell adhesion, and attachment to the extracellular matrix. E-Cad, a calcium-dependent transmembrane glycoprotein, is essential for both epithelial morphogenesis and homotypic cell adhesion, which are essential for organogenesis, morphogenesis, and the maintenance of epithelial tissue. Reduced expression of E-Cad also correlates with tumor invasiveness and metastasis in malignant tumors, while loss of expression of SDC-1 in carcinoma is also associated with tissue invasion, metastatic processes, and poor prognosis (recurrence and metastasis).[10,11] Although SDC-1 and E-Cadherin have been extensively studied in malignant tumors, their role in benign but locally aggressive tumors such as ameloblastoma remains unclear.

Not much research has been done comparing the expression of SDC-1 in the stroma, epithelium, and E-Cad in ameloblastoma. Therefore, it is crucial to conduct more thorough research to help manage ameloblastoma with different levels of aggressiveness and to provides insight into the prognosis and recurrence potential of each type of ameloblastoma that has received surgical treatment. Understanding the differential expression of these molecules can provide deeper insights into the biological behavior of various histological subtypes of ameloblastoma, thus potentially serving as a basis for determining prognosis and planning therapeutic strategies. Therefore, this study aims to analyze and compare SDC-1 expression in stroma and epithelium, as well as E-Cadherin expression in ameloblastoma. This study hypothesizes that decreased expression of these adhesion molecules correlates with higher levels of aggressiveness and greater potential for recurrence.

METHODS

This study was an observational analytical study to analyze differences in E-cad and SDC-1 expression based on the histology of ameloblastoma. The research instruments were 24 post-operative paraffin blocks for ameloblastoma post-operative patients. The operative paraffin blocks were taken from patient's specimen who had been operated on by the Oral and Maxillofacial Surgery Team and were stored in the Anatomical Pathology section of Airlangga University and Dr. Mohammad Soewandhie Hospital Surabaya in the period 2015–2023. Ethical approval was obtained from the Ethics Committee of the Faculty of Dental Medicine, Universitas Airlangga, with number 1324/HRECC.FODM/XII/2023.

Paraffin blocks are of four follicular types, twelve plexiform types, and eight follicular-plexiform types. The histopathological findings were evaluated by immunohistochemistry. For immunohistochemical analyses, 4 μm-thick sections were prepared and mounted on slides. Deparaffinization of the sections was performed using distilled water followed by phosphate-buffered saline (PBS, pH 7.4) treatment for 2 minutes. The prepared samples then underwent overnight incubation (12 hours) with specific antibodies: anti-E-Cad (DECMA-1: sc-59778, rat monoclonal, concentrated and prediluted, human reactive, Santa Cruz Biotechnology, Europe) and anti-SDC-1 (CD-138) (DL-101: sc-12765, mouse monoclonal, concentrated and prediluted, human reactive, Santa Cruz Biotechnology, Europe). Each slide was assigned random codes and numbers for

blinded evaluation, followed by quantification of tumor epithelial cells displaying brown cytoplasmic staining. Statistical analysis was performed using the Shapiro-Wilk test with significance set at $P < 0.05$, utilizing IBM SPSS Statistics Version 48.0 (IBM Corporation, Armonk, New York, USA).

RESULTS

The 24 paraffin blocks of ameloblastoma patients have been collected during resections by the Oral and Maxillofacial Surgery team at Universitas Airlangga Hospital and Dr. Mohammad Soewandhie Hospital Surabaya between 2015 and 2023. Table 1 shows the gender distribution of the samples, which are divided into 12 (50%) and 12 (50%) males, with the most dominant type of ameloblastoma based on sex being plexiform type, which accounts for 7 (29.2%) males and 5 (20.8%) females.

Table 1. Data distribution of histological type of ameloblastoma based on gender

	Follicular	Plexiform	Mixed-type (follicular-plexiform)	Total
Gender				
Male	1 (4,1%)	7 (29,2%)	4 (16,7%)	12 (50%)
Female	3 (12,5%)	5 (20,8%)	4 (16,7%)	12 (50%)
Age				
< 20	0	3	1	4 (16,7%)
21-30	2	5	3	10 (41,7)
31-40	1	1	3	5 (20,8%)
41-50	0	1	0	1 (4,2 %)
51-60	0	1	1	2 (8,3%)
> 60	1	1	0	2 (8,3%)

The distribution sample based on age was categorized into five categories: <20 years, 21–30 years, 31–40 years, 41–50 years, 51–60 years, and >60 years, with the dominant age range being 21–30 years, there are 10 (41.7%) patients.

The results of observing their expression in all samples show the highest expression of SDC-1 and E-cad in the follicular-plexiform type. The expression of SDC-1 from highest to lowest in sequence, as shown in figure 1 and 2, is ameloblastoma type follicular-plexiform (13.13), plexiform (10.50), and follicular (9.75), while the results of E-cad expression are follicular-plexiform (7.13), plexiform (6.25), and follicular (4.00).

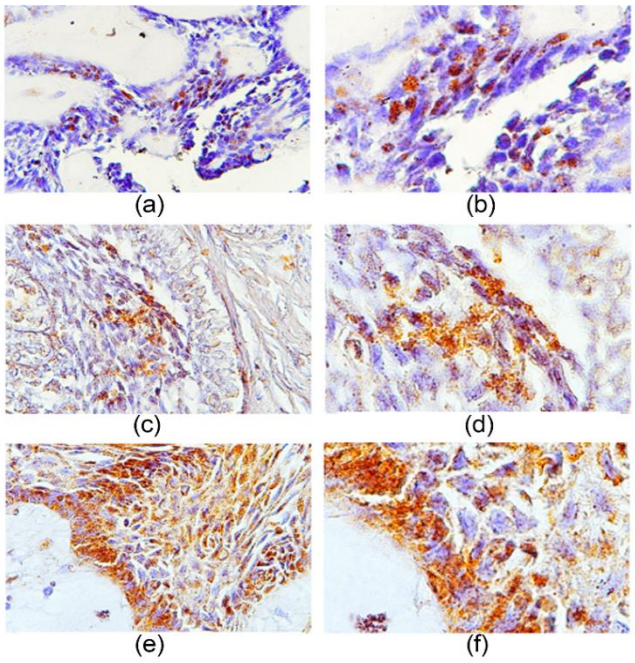

Figure 1. Expression rate of Syndecan-1 based on histological type of ameloblastoma. (A) Follicular type (400x magnification). (B) Follicular type (1000x magnification). (C) Plexiform type (400x magnification). (D) Plexiform type (1000x magnification). (E) Follicular-Plexiform (400x magnification). (F) Follicular-Plexiform (1000x magnification).

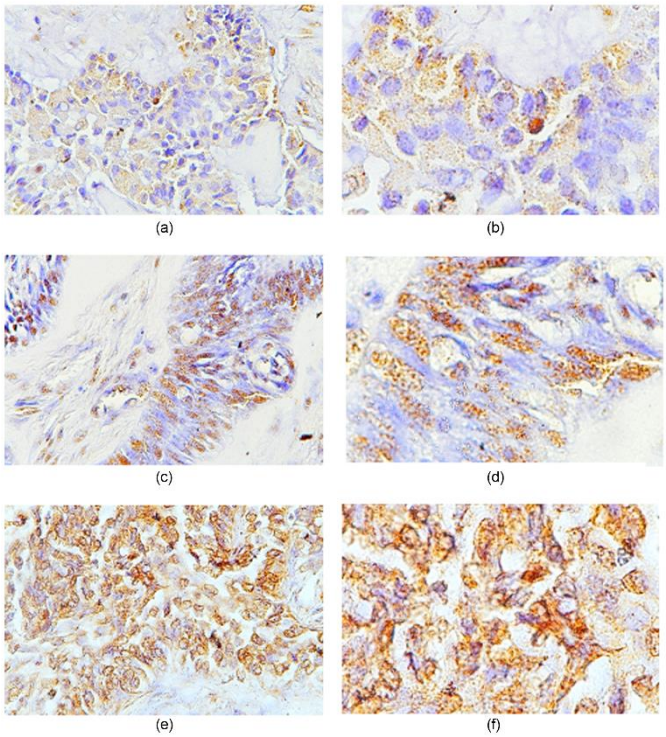

Figure 2. Expression rate of E-Cadherin based on histological type of ameloblastoma. (A) Follicular type (400x magnification). (B) Follicular type (1000x magnification). (C) Plexiform type (400x magnification). (D) Plexiform type (1000x magnification). (E) Follicular-Plexiform (400x magnification). (F) Follicular-Plexiform (1000x magnification).

Table 2 shows a *One-Way Anova* test of the three groups of ameloblastoma types, showing significant differences ($p<0.05$) in SDC-1 and E-Cad expression.

Table 2. Expression rate of Syndecan-1 and E-Cadherin based on histological type of ameloblastoma

Histological type	Number of cases	Mean ± SD	
		SDC-1	E-Cad
Follicular	4	9,75 ± 0,95	4,00 ± 1,41
Plexiform	12	10,50 ± 1,78	6,25 ± 1,85
Follicular-Plexiform	8	13,13 ± 2,80	7,13 ± 2,10

Post-hoc Tukey was used in the comparison test to compare the ameloblastoma types according to these two characteristics. The results of the comparison test between variables on SDC-1 expression showed that significant values ($p<0.05$) were found between the follicular-plexiform type and the follicular and plexiform groups. E-Cad expression showed that the comparison test between variables was significant only in the follicular-plexiform group and the follicular group ($p<0.05$), the results shown in table 3.

Table 3. Differences in expression of Syndecan-1 and E-Cadherin among follicular, plexiform, and mixed type ameloblastoma (follicular-plexiform)

Histopathological Type		SDC-1 **p value (sig.)*	E-Cad **p value (sig.)*
Follicular	Plexiform	0,812	0,116
Plexiform	Follicular – Plexiform	0,032*	0,568
Follicular	Follicular– Plexiform	0,040*	0,032*

*Multiple comparison Post Hoc Tukey HSD, statistical significance at $p < 0,05$. SDC-1 = Syndecan-1; E-Cad = E-Cadherin.

DISCUSSION

Ameloblastoma is classified histopathologically according to the specimen's dominant architectural characteristic; however, it is not uncommon to find a combination of two or more distinct architectural traits. The 12 patients (50%) in this study were plexiform type; followed by 8 (33.3%) mixed type patients and 4 (16.7%) follicular type patients. The distribution of histopathology categories in this study contrasts with the study of Cadavid et al. (2019), which found that the follicular type was the most common.[4] This may be attributed to the limited number of samples, which increases the possibility of distortion in the final data results. This study shows that the expression of SDC-1 and E-Cad is lowest in the follicular type of ameloblastoma compared to the plexiform and mixed types, indicating that the follicular variant may represent the most aggressive biological behavior. Ameloblastoma can locally expand into the surrounding area. Cellular invasion of the tumour requires the breakdown of the basement membrane and ECM around the tumour, followed by the growth and proliferation of tumour cells. A study conducted by Hashimoto et al. (2008) on colorectal adenocarcinoma revealed that a decrease in SDC-1 in the tumour epitel indicated progression and showed more aggressive biological activity. SDC-1 also regulates the activity of α2β1integrin, which plays a role in cell attachment, inhibition of cell migration, and tumour-invasive behaviour in squamous cell carcinoma.[12–14]

The study's data distribution results showed that ameloblastoma epithelial and stromal cells expressed SDC-1, with the follicular type exhibiting the lowest mean expression of SDC-1 in the epithelium (9.75) compared to the plexiform (10.50) and mixed (follicular-plexiform) types (13, 13). This is in line with the research of Setyawan who found the average amount of SDC-1 in the epithelium was lower in the follicular type compared to plexiform, which the follicular has the highest expression of MMP-2, MMP-9, and IL-1α.[15] The release of proteolytic enzymes, such MMP, is the primary cause of the reduction in SDC-1 expression. This is since SDC-1 can cleave MMP, which results in syndecan being shed and MMP accumulated in the stroma. This is possible as MMP's primary substrate target is SDC-1 (syndecan sheddase).[16] Loss of SDC-1 expression decreases cell-cell adhesion, as well as adhesion to the extracellular matrix, where in the development of ameloblastoma, cell invasion requires the breakdown of the basal membrane and the surrounding extracellular matrix, followed by cell growth and proliferation. Therefore, decreased cell-cell adhesion and changes in the composition of the basal membrane affect the growth of neoplasia. In addition, decreased syndecan-1 expression also occurs in cases of recurrent ameloblastoma.[17] From a clinical perspective, decreased SDC-1 expression has the potential to function as a biomarker for identifying ameloblastoma with higher invasive potential. This information can help clinicians in selecting more aggressive surgical management and better follow-up strategies for patients with the follicular subtype.

The association between decreased SDC-1 expression and tumor hypoxia in ameloblastoma occurs when high metabolic demands for energy and oxygen by tumor cells establish intratumoral hypoxic zones. Consequently, this hypoxic environment induces the expression of hypoxia-inducible factor 1-alpha (HIF-1α) as part of the cellular adaptive response to oxygen deficiency.[18] Furthermore, HIF-1α regulates endothelial cell migration toward hypoxic areas by modulating vascular endothelial growth factor (VEGF) synthesis. Through direct interaction with VEGF gene regulatory sequences, hypoxia-inducible factor-1 promotes transcriptional upregulation and enhanced VEGF expression.[19] HIF-1α expression levels have been reported to be moderately elevated in follicular ameloblastoma compared to the plexiform subtype, potentially accounting for the observed variations in VEGF expression between these histological types.[20] During angiogenesis, extracellular matrix remodeling occurs via matrix metalloproteinase and proteolytic enzyme activity, which triggers the release of angiogenic stimulatory factors from the basement membranes of blood vessels.[21] Hypoxic conditions are also linked to enhanced tumor aggressiveness, influencing both angiogenic processes and invasive cellular behavior.[22]

Observations of E-Cad in the three types also showed a similar pattern, with the follicular type having the lowest mean expression of E-Cad (4.00) compared to the plexiform type (6.25) and the mixed (follicular-plexiform) type (7.13). The results of multiple comparison analysis on E-Cad expression showed that there were significant differences in E-Cad expression between the follicular type and the mixed type (follicular-plexiform) with the plexiform type and the mixed type (follicular-plexiform). Most epithelial cells express E-Cad, a type I calcium-dependent transmembrane glycoprotein that contributes to the maintenance of epithelial tissue integrity through homophilic cell-to-cell adhesion of adherent junctions in all epithelial cells and cell polarity. The tumor suppressor gene CDH-1 encodes E-cadherin, which plays a role in adhesion between cells at adherent junctions through a complex with catenin called the Cadherin-Catenin Complex (CCC). Decreased

adhesion between epithelial cells in ameloblastoma may result from mutations in this CDH-1 gene, which may lead to decreased expression of E-Cad during the tumor development process.[23]

Another process that is also affected is the Wnt signaling pathway. Loss of expression of E-Cad causes the inability to degrade β-catenin, which causes the accumulation of β-catenin in the cytoplasm. After entering the nucleus, β-catenin translocate itself to T-cell factor/lymphoid enhancer-binding factor-1 (TCF/LEF-1), a protein related to both tumor development and proliferation of cells.[20] These results are also supported by research conducted by Hao et al. on the expression of E-Cad, Vimentin, and β-catenin based on their clinicopathological characteristics, showing a decrease in E-Cad expression in clinically aggressive ameloblastoma.[23] These findings expand current knowledge by reinforcing the role of adhesion molecules in ameloblastoma biology.[24] Combined evaluation of SDC-1 and E-Cad expression provides a more comprehensive understanding of tumor aggressiveness and may help refine prognostic assessment in the future. Hertog et al. reported that among ameloblastoma cases treated with conservative therapy, follicular type demonstrated the highest recurrence rate (7/10), while mixed type showed intermediate recurrence (3/7), and plexiform type exhibited the lowest recurrence rate (4/11).[25] This may be related to a decrease in E-Cad expression, where the follicular type shows reverse nuclear cell polarity and palisading cell configuration. However, the generalizability of these research findings is still limited. The patient group in this study represents a single-center population, which may not fully capture the biological diversity of ameloblastoma across different ethnic or geographic groups. Larger multicenter studies are needed to validate these observations.

The results of this study show that ameloblastoma of the follicular and plexiform types could be more aggressive than the mixed type (follicular-plexiform). The absence of a linear relationship between SDC-1 and E-Cad expression in every investigation group in this study indicates that there is no correlation between the decreasing processes of SDC-1 and E-Cad expression, indicating that the processes are caused by the same entity differently but having the same effect on tumor cell adherence to the extracellular matrix. Because this study is retrospective, this study is restricted by a small number of participants and lacks details on the long-term outcomes of patients, such as survival without cancer recurrence. The strengths of this study include the use of immunohistochemical evaluation of SDC-1 and E-Cad across different histopathological subtypes, which allows for detailed comparison of their expression profiles. Nevertheless, future prospective studies with larger sample sizes and long-term clinical follow-up, including recurrence and survival data, are needed to confirm the prognostic value of these biomarkers and to explore their potential integration into clinical decision-making.

The findings of this study reinforce the role of cell adhesion molecules, SDC-1 and E-Cadherin, in determining the biological characteristics of ameloblastoma. Decreased SDC-1 expression in the follicular type indicates that reduced cell interaction with the extracellular matrix can facilitate proteolytic activity, particularly by MMPs, which leads to basement membrane degradation and increased invasive capacity. Similarly, low E-Cad expression in the follicular type reflects weakening of the cadherin-catenin complex that functions to maintain polarity and cohesion of epithelial tissue. The loss of these adhesion molecules not only disrupts tissue stability but also activates signaling pathways such as Wnt/β-catenin that promote proliferation and phenotypic transition toward more invasive properties. The synergism of these molecular changes most likely explains why follicular ameloblastoma exhibits more aggressive biological behavior compared to other subtypes.

From a clinical perspective, low expression of SDC-1 and E-Cad has the potential to serve as prognostic indicators for determining more appropriate management strategies, whether through more radical surgical options or long-term follow-up plans for high-risk patients. Integration of these biomarkers into clinical practice can support risk stratification and therapy personalization. However, the generalizability of these research findings is still limited by the retrospective design, small sample size, and absence of clinical outcome data such as recurrence rates and disease-free survival. Therefore, prospective multicenter studies with larger sample sizes and long-term clinical follow-up are urgently needed. The combination analysis of SDC-1 and E-Cad together with other biomarkers, such as Ki-67, p53, Bcl-2, or angiogenesis markers, is expected to expand understanding of ameloblastoma biology while opening opportunities for developing more accurate clinical prediction models and potential molecular therapeutic targets in the future.

CONCLUSION

Based on the research results, there are significant differences in SDC-1 and E-Cad expression between follicular type and mixed type (follicular-plexiform) ameloblastoma. SDC-1 and E-Cad expression in follicular type ameloblastoma is lower compared to plexiform type and mixed type (follicular-plexiform), indicating that the

follicular type has higher aggressive potential. This study provides novelty by linking the differences in SDC-1 and E-Cad expression to ameloblastoma histopathological subtypes, thus providing new understanding regarding tumor biological behavior. These findings have practical significance as they have the potential to serve as additional markers in predicting ameloblastoma aggressiveness and can help clinicians in determining appropriate therapeutic strategies. Further research is recommended to explore the application of SDC-1 and E-Cad as prognostic biomarkers in routine clinical practice.

DECLARATIONS

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

Funding

This research received no external funding.

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