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KIAA0101 IMMUNOHISTOCHEMICAL EXPRESSION IN DIAGNOSTIC DILEMMA BETWEEN AMELOBLASTOMA AND AMELOBLASTIC CARCINOMA (IN VITRO STUDY)

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ABSTRACT

INTRODUCTION: Odontogenic tumors are a variety of oral lesions with clinical and histological variability. Some are benign, while others, like ameloblastoma, show infiltrative behavior. The most aggressive destructive odontogenic tumor is ameloblastic carcinoma. Diagnostic challenges arise in differentiating a malignant type from a classic benign ameloblastoma due to overlapping clinicopathologic features, prompting the use of immunohistochemical methods. KIAA0101, a nucleoprotein, is crucial for cell proliferation regulation, and its expression as a prognostic marker is being extensively researched in various human tumor sorts. However, its role in odontogenic tumors still needs more diagnostic research to be approved.

Aim of the study: Evaluation of KIAA0101 immunoexpression in ameloblastoma and ameloblastic carcinoma.

MATERIAL AND METHODS: Sixty blocks of human odontogenic tissues, divided equally into enamel organs (serving as a normal control), ameloblastoma, and ameloblastic carcinoma, were included in the study. Sections were stained with hematoxylin and eosin to determine an accurate histopathological diagnosis. Immunohistochemical analysis using the KIAA0101 antibody was performed using universal immunostaining techniques.

RESULTS: Different immunoexpression of KIAA0101 were expressed in enamel organs, ameloblastoma, and ameloblastic carcinoma. The enamel organs showed the lowest expression levels, while the highest were detected in ameloblastic carcinoma.

CONCLUSION: KIAA0101 produced a valuable indicator for tissue proliferation in ameloblastoma and ameloblastic carcinoma.

KEYWORDS: Ameloblastoma, Ameloblastic Carcinoma, Immunohistochemistry, KIAA0101.

RUNNING TITLE: KIAA0101 value in ameloblastoma and ameloblastic carcinoma.

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INTRODUCTION

Several distinct types of bone lesions can develop within the jaw region (1). Among oral lesions, odontogenic tumors (OTs) are remarkable because of their clinical and histological variability. They comprise a complex group of heterogeneous lesions originating from epithelium, ectomesenchyme, or both, and they exhibit various inductive degrees of interaction between the embryonic elements of the tooth germ (2). They have many histopathological types, most of which are benign; as some frequent ameloblastoma (AB), exhibit locally infiltrative action, whereas ameloblastic carcinoma (AC) is considered a primary odontogenic carcinoma which shows histological similarities with AB (3). It exhibits cytological atypia of the epithelial components within the benign histological characteristics of AB (4).

The clinical characteristics of AC frequently resemble monocystic or polycystic varieties of AB and have painless swelling, it is challenging to distinguish it from AB through clinical and radiographic data (5). As well, oral pathologists had a challenge in differentiating a benign AB from its malignant counterpart, particularly with the limited diagnostically suitable material in the biopsied specimen (6). The biological behaviors in terms of invasion, aggressiveness, and malignant transformation are exceedingly difficult to predict based solely on clinical, radiographic, and histological examination. Cell proliferative activity gives details into tissue biology and thus guides the proper diagnosis. It has been well

established that the high rates of proliferation may be a situation that predisposes to malignancy (7). Immunohistochemical (IHC) analysis offers more benefits than other methods for recognizing proliferating cells, due to the preservation of tissue morphology and the ability to see proliferating cells in relation to other histological criteria (8).

KIAA0101 is a nucleoprotein that is overexpressed in most human cancers (9). KIAA0101 has multiple biological functions that regulate the development of human cancer, including cell proliferation, cell cycle progression, DNA replication and repair, particularly in the S phase, and cell migration (10). Due to its strong interaction with PCNA, it performs a crucial function in regulating the cell cycle and DNA replication (11). It is a specific oncogene that was overexpressed in a variety of human tumors with a poor prognosis and increased proliferation of cancer cells, migration, and infiltration (12). Prior studies described its oncogenic role in several types of solid tumors, indicating that it regulates both *in vitro* and *in vivo* cell proliferation. It was found to be primarily localized in the nucleus, where it plays an important role in controlling the replication of DNA and cell survival. It has been expressed in various neoplasms, including esophageal, adrenal, pituitary, breast, and hepatocellular lesions (12-16).

Although several studies have explored the KIAA0101 overexpression in various cancers, it's worth noting that the expression of KIAA0101 in OTs remains controversial, as no known studies have evaluated its IHC expression in AB and AC. Thus, this present work aimed to evaluate KIAA0101 expression in AB and AC.

MATERIAL AND METHODS

The current study was implemented on 60 blocks of odontogenic tissues; 20 surgical specimens (group I) were taken from developmental tooth germ serving; enamel organs (EOs) as a control group obtained from the Oral Biology Department, Faculty of Dentistry, Alexandria University; and a total of 40 blocks of OTs (groups; II AB and III AC) served as study groups. The tumor tissue included 30 cases (13 AB and 17 AC) from the Oral Pathology Department's archive at Alexandria University's Faculty of Dentistry, as well as 10 cases (7 AB and 3 AC) from the Oral and Maxillofacial Pathology Department's archive at Assiut University's Faculty of Dentistry, acquired through the duration of 2018-2022.

The study has ethical approval from the Faculty of Dentistry Research Ethics Committee at Alexandria University (IRB No. 00010556-IORG 0008839). Hematoxylin and eosin (H&E) stains were used to stain serial slices of 3-4 µm thickness from the formalin-fixed paraffin-embedded tissue blocks for routine histopathological examination and confirm the tumors that were utilized in the study.

Immunohistochemical examination: Rabbit monoclonal KIAA0101 antibody Cat. # 81533 (100 ug) (Cell Signaling Technology, USA) was used for staining the tissue paraffin blocks. The manufacturer's kit manual's instructions were followed, and the staining processes were carried out in accordance with the accepted immunostaining techniques. Following that, the sections were examined, and a computer image analyzer measured the immunostaining intensity in terms of mean area percent and mean optical density. Utilizing Image J software (Anatomy and Embryology Department, Faculty of Veterinary Medicine, Assiut University). KIAA0101 was scored by multiplication of the percentage of positive tumor cells and staining intensity reported in the previous study (17). The percentage of positive cells was scored as: 0, 0%; 1+, 1–10%; 2+, 11–50%; and 3+, 51–100%. The intensity of staining was graded as follows: grade 0, negative; 1+, weak positive; 2+, moderate positive; and 3+, strong positive.

Data Management and Statistical Analysis: The IBM SPSS statistical software package, version 20.0 (Armonk, NY: IBM Corp), was used for statistical analysis of the data that were fed into the computer, with significance determined at $p < 0.05$. All findings had been presented as the mean ± standard deviation (SD). For continuous data, they were tested for normality by the Shapiro-Wilk test. For normally distributed quantitative variables, a one-way ANOVA test was used for comparing the three studied groups, and followed by a Post Hoc test (Tukey) for pairwise comparison. On the other hand, for not normally distributed quantitative variables, the Kruskal Wallis test was used to compare different groups, and followed by the Post Hoc test (Dunn's for multiple comparisons test) for pairwise comparison. They were additionally utilized to analyze the mean KIAA0101 area percentage and its optical density of the IHC findings.

RESULTS

Clinical Evaluation: At Alexandria University's Faculty of Dentistry's Oral Pathology Department, the samples were archived as EOs, AB, and AC. All patients' clinical data is condensed within (Table 1).

Histological Findings: Twenty cases of EOs showed peripherally cuboidal cells, centrally rounded cells, and supporting ectomesenchymal cells at the bud stage. Among the 20 AB, 9 conventional types (7/9 were follicular AB and 2 were plexiform), 5 unicystic cases, and aggressive AB were presented in

6 cases, which showed a mass of odontogenic epithelium formed of follicles consisting of peripheral hyperchromatic ameloblast-like cells and central stellate reticulum-like cells. Some follicles showed cystic degeneration. The follicles were separated by a delicate vascular fibrous tissue stroma. The normal architecture of the follicles was preserved. All 20 cases were AC, showing the proliferation of malignant odontogenic epithelial cells in a densely collagenized connective tissue stroma. The cell showed pleomorphism, hyperchromatism, vesicular nuclei, and basilar hyperplasia. Aberrant diffuse keratin formation with loss of architecture was seen, and abnormal mitosis was present (Figure 1).

Immunohistochemical Results: Immunoexpression of KIAA0101 in EOs showed weak positive nuclear expression, while AB showed moderately positive nuclear expression in 18 cases, and 2 cases showed strong positive nuclear expression. However, AC showed strongly positive nuclear expression in 17 cases, and 3 cases showed moderately positive nuclear expression (Figure 2). The intensity of immunoreactivity of KIAA0101 in EOs (control), AB, and AC was determined by mean area percentage and mean optical density.

The highest values of mean area percentage were recorded in AC group III, 46.33 ± 11.79%, while the lowest values were recorded in EOs group I, 1.75 ± 1.37%. An extremely statistically significant difference in the mean KIAA0101 area percent was observed ($p < 0.001$). The study findings revealed a highly statistically significant difference ($p < 0.001$) in KIAA0101 immunostaining among groups I and II or group III. Furthermore, there is a statistically significant correlation between groups II and III ($p = 0.001$). Regarding mean optical density, the highest values were recorded in AC group III, 45.98 ± 9.88, while the lowest values were recorded in EOs group I, 20.98 ± 3.05. When groups I and II or III were compared, as well as groups II and III, the differences in KIAA0101 optical density were highly significant ($p < 0.001$) (Figure 3) (Table 2).

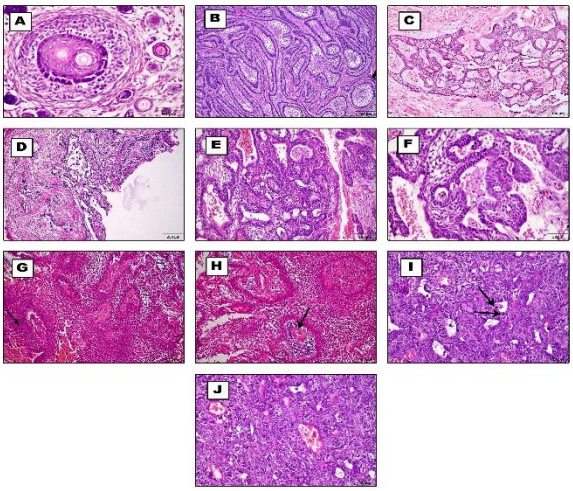

Figure 1: Histological Assessment. (A) A Photomicrograph of EOs Showing Peripherally Cuboidal Cells and Centrally Rounded Cells at Bud Stage (H&E X40). (B) A Case of Follicular Type of AB Showing Proliferation of Odontogenic Epithelium in Connective Tissue Stroma Forming Follicles (H&E X10). (C) Plexiform Type Showing Anastomosing Sheets and Strands of Proliferating Odontogenic Epithelium (H&E X20). (D) Unicystic AB Reveals a Cystic Cavity (Luminal and Mural Unicystic Variation) (H&E X10). A Case of Aggressive AB Showing (E) Peripheral Hyperchromatic Ameloblast-like Cells and Central Stellate Reticulum-like Cells (H&E X20) and (F) Some Areas of Extensive Hemorrhage (H&E X40). A Photomicrograph of AC Showing (G) Basilar Hyperplasia (Arrow) (H&E X20), (H) Diffuse Keratin Formation (Arrow) (H&E X20), (I) Hyperchromatic Nuclei (Arrows) (H&E X40), and (J) Some Areas of Extensive Hemorrhage (H&E X40).

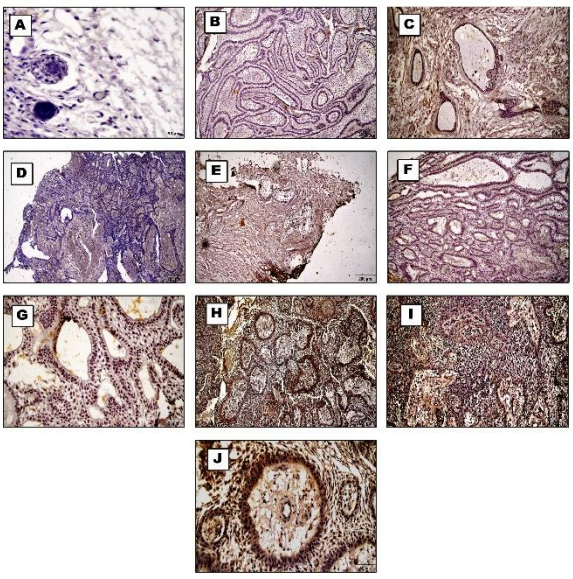

Figure 2: (A) A Case of EOs Showing Weak Positive Nuclear Expression of KIAA0101(Immuno Stain X40). Photomicrographs Showing Positive KIAA0101 Expression in Follicular AB (B) (Immuno Stain X10) and (C) (Immuno Stain X20). (D) Positive KIAA0101 Expression (Immuno Stain X10) in Plexiform AB. (E) Positive KIAA0101 Expression (Immuno Stain X10) in Unicystic AB. Positive KIAA0101 Expression in Aggressive AB (F) (Immuno Stain X10) and (Immuno Stain X40) (G). Photomicrographs Showing Positive Nuclear KIAA0101 Expression in AC Immuno Stain X10 (H), X20 (I), and X40 (J).

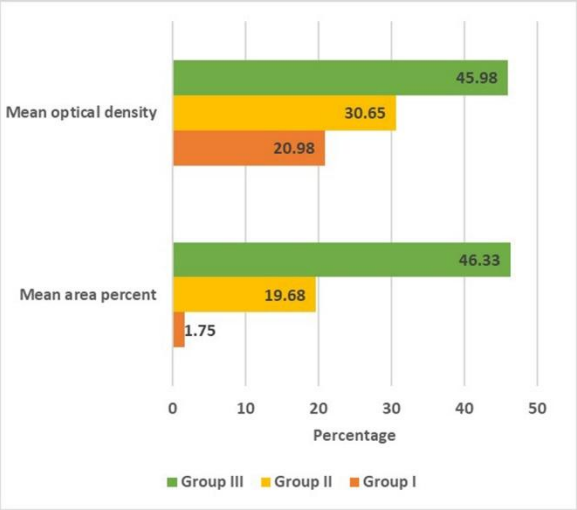

Figure 3: Column Bar Graph for Comparison Between Studied Groups According to Mean Area Percent and Optical Density (Intensity).

Table 1: Clinical data of all studied groups (N = 60).

	Group I (n = 20)		Group II (n = 20)		Group III (n = 20)	
	No.	%	No.	%	No.	%
Sex						
Male	11	55.0	14	70.0	13	65.0
Female	9	45.0	6	30.0	7	35.0
Age (years)						
<30	20	100.0	6	30.0	2	10.0
30 – 60	0	0.0	11	55.0	16	80.0
>60	0	0.0	3	15.0	2	10.0
Mean ± SD.	7.75 ± 1.80		43.60 ± 16.62		45.20 ± 15.80	
Bone/Peripheral						
Bone	20	100.0	19	95.0	15	75.0
Peripheral	0	0.0	1	5.0	5	25.0
Maxilla/Mandible						
Maxillary	12	60.0	2	10.0	3	15.0
Mandible	8	40.0	18	90.0	17	85.0
Anterior/Posterior						
Anterior	15	75.0	4	20.0	3	15.0
Posterior	5	25.0	16	80.0	17	85.0

SD: Standard deviation
Group I: Enamel organs that serve as normal controls
Group II: Ameloblastoma
Group III: Ameloblastic carcinoma

Table 2: Correlation among studied groups based on area percent and optical density (Intensity).

	Group I (n = 20)	Group II (n = 20)	Group III (n = 20)
Area percent			
Min. – Max.	0.26 – 5.06	9.55 – 50.54	17.56 – 62.37
Mean ± SD.	1.75 ± 1.37	19.68 ± 9.71	46.33 ± 11.79
Median (IQR)	1.30 (0.73 – 2.18)	17.10 (13.35 – 22.74)	45.82 (39.0 – 54.32)
significant between groups	$p_1<0.001^*$, $p_2<0.001^*$, $p_3=0.001^*$		
Optical density (Intensity)			
Min. – Max.	16.48 – 25.57	14.95 – 44.50	23.26 – 60.84
Mean ± SD.	20.98 ± 3.05	30.65 ± 7.08	45.98 ± 9.88
Median (IQR)	20.69 (18.29 – 24.42)	29.66 (26.64 – 37.03)	45.65 (42.33 – 52.86)
significant between groups	$p_1<0.001^*$, $p_2<0.001^*$, $p_3<0.001^*$		

IQR: Inter quartile range
SD: Standard deviation
p: p-value for comparing the three studied groups
p_1: p-value for comparing group I and group II
p_2: p-value for comparing group I and group III
p_3: p-value for comparing group II and group III
***:** Statistically significant at $p \leq 0.05$
Group I: Enamel organs that serve as normal controls
Group II: Ameloblastoma
Group III: Ameloblastic carcinoma

DISCUSSION

The histopathological similarities between AB and its malignant form; make some difficulty in accurate ideal diagnosis, as well as the standard histological criteria are not enough to objectively identify it, which can result in misdiagnosis and have direct implications for treatment and management outcomes (18). Examining OTs is frequently challenging; clinical findings can often greatly reduce this difficulty, but in many other situations, they may not be enough to prove a diagnosis (19). Biomarkers are among the most critical techniques for making early diagnoses of many

diseases and providing accurate prognosis (19). The IHC features of OTs, in addition to both clinical and radiological characteristics, may assist in reaching an accurate diagnosis (20).

KIAA0101 immunoexpression was assessed in EOs, AB, and AC in the current research to evaluate how it contributes to the development of those pathologies. KIAA0101 is a nucleoprotein that is mainly found in the mitochondria and nucleus of cells (21). Various researchers reported that a variety of cancerous tumor cells overexpressed KIAA0101 protein such as Lin *et al*. their bioinformatics investigation of KIAA0101 gene showed that it is a significant prognostic predictor for malignant pleura mesothelioma and that it was correlated to the prognosis of many cancers (22). Furthermore, Zhang *et al*. found that non-small cell lung cancer revealed high levels of KIAA0101 expression (23). Besides, high KIAA0101 expression was demonstrated to be positively associated with nodal spread, progressed tumor stage, and poor overall survival and this was regarded as an effective indicator of non-small cell lung cancer by Cao *et al* (24). Moreover, Xu *et al*. demonstrated that KIAA0101 expression was high in hepatitis B virus-associated hepatocellular carcinoma (HCC) tissues, indicating that KIAA0101 may be a critical factor in this carcinoma and that it is highly expressed in advanced-stage HCC and correlated with a poor outcome (25).

The best for this work is that no known research has studied the role of KIAA0101 in OTs, or AB and AC. The expression of KIAA0101 in AB and AC is shown for the first time in this current work. Immunoexpression of KIAA0101 was observed in EOs, AB, and AC; the highest expression level was in AC. The present research revealed that KIAA0101 was expressed in EOs tissues. The same result was found in the work of Liu *et al*. that KIAA0101 was expressed in some normal human tissues; however, the expression level is low, with individual variations (26). KIAA0101 expression was mainly detected in the nuclei in the present work. DNA replication and cell cycle progression primarily occur in the nucleus, which might be the main cause for KIAA0101's markedly higher expression in the nucleus and slight expression in the cytoplasm (27). This follows numerous studies in which nucleic immunostaining was observed and coincided with the findings of the study done by Liu *et al*. which reported that KIAA0101 was mostly found in the nucleus and its expression varies in different pathological types of neuroblastomas (9). Also, different studies demonstrated that glioma tissues had higher levels of KIAA0101 expression relative to normal brain tissues. It was primarily found in the nucleus, where it appears as brownish-yellow grains (28).

In this research, the expression of KIAA0101 was greater in AC than in AB, with a highly significant difference between them, confirming its crucial role in tumor aggressiveness. Several researchers have explained that KIAA0101 is a useful diagnostic tool and can distinguish between preneoplastic changes and neoplasms (9, 29). This is consistent with the study of Tantiwetrueangdet *et al*. who assessed the immunoexpression of the KIAA0101 protein in HCC and corresponding non-cancerous tissues and found that it was excessively expressed in HCC tissues, whereas it was undetected in all non-cancerous tissues analyzed (16). As well as, Zhao *et al*. results demonstrate that the level of KIAA0101 expression was significantly greater in prostate carcinoma tissues compared to normal tissues and showed important clinical significance (30). Similarly, Wang with his group, discovered that glioma tissues had greater KIAA0101 expression levels than healthy brain tissues, especially in high-grade gliomas, and had lower survival rates (31).

According to the Jin *et al*. article, high levels of KIAA0101 expression were found in tissues from ovarian cancer patients with high-grade serous lesions and were linked to a high stage and a poor overall survival rate. They suggested that KIAA0101 contributes to the oncogenic process in ovarian cancer (32). Further, Zhu *et al*. reported that gastric cancer tissue, which included both initial-stage and late-stage cancer tissues, had higher levels of KIA0101 than the matched non-cancerous tissue (17). Moreover, KIAA0101 was detected at greater levels in gastric cancer samples compared to chronic gastritis and paired surrounding non-cancerous gastric tissues.

From the results of the current work, it seems that KIAA0101 can differentiate between benign and malignant OTs due to its higher expression in the malignant variant.

CONCLUSION

It is difficult to differentiate between AB and AC based on clinical, radiographic, and histological assessment alone. KIAA0101 expression was detected in EOs, AB, and AC with variable intensities. The pattern of its immunosignals was expressed predominantly in the nucleus. Its expression was greater in AC than in AB, with a highly significant difference. The results of current research suggest that KIAA0101 provides an evaluation for the power of tissue proliferation and may aid in the diagnosis of AB and its malignant form.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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