



Original Article



Comparative Study on Histochemical Expression of CD34 in Different Variants of Ameloblastoma

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ABSTRACT

Ameloblastoma is a benign, locally aggressive, tumor of the oral cavity having a high propensity for recurrence. The growth potential of the tumor is linked to the proliferation of preexisting vasculature and is reflected in CD34 expression. has been rephrased as "Mean Vascular Density (MVD) which measures CD34 expression, aids in predicting this proliferation. **Objectives:** To evaluate the biological behavior of different variants of Ameloblastoma according to expression of CD34 and to correlate it with age and gender. **Methods:** The present study was analytical, cross-sectional study composed of total 40, already diagnosed cases of ameloblastoma. Immuno-histochemical expression of CD34 was analyzed. **Results:** Follicular variant has more growth potential in females 21(62%) and males reveal more vascular growth in plexiform 19(80%) acanthomatous (50%) and unicystic variant (50%). More endothelial proliferation in age group of > 40 years was seen in follicular variant, whereas, in age group of < 40 years, plexiform type was more dominant. However, relationship between the age groups and MVD scores were found to be insignificant ($p > 0.05$). Relationship between CD34 expression in ameloblastoma and its histological variants were also found to be statistically non-significant ($p=0.9$). **Conclusions:** All variants display highest Mean Vascular Density (MVD) score in posterior mandible. Follicular variant has more growth potential in females while in males it is found more in plexiform, acanthomatous and unicystic variants. More epithelial proliferation in the follicular variety is observed in the age group over 40, whereas more plexiform type was shown in the age group below 40.

INTRODUCTION

Ameloblastoma (AM) is recognized as a benign oral cavity tumor and has a strong propensity for local invasion. It is ranked second among tumors of odontogenic origin accounting for <1% of the tumors arising in the head and neck area [1, 2]. Ameloblastoma is of epithelial origin having mature, fibrous stroma [1]. Mostly the tumor arises in the third to fifth decades of life and is equally common in both genders, with 80% occurrence in mandible and 20% in maxilla [3, 4]. Global estimation of the incidence is 0.5 cases per million populations, however slightly higher incidence has been reported in South Africa [5]. Asians and Africans are more commonly affected as compared to Latin Americans and Europeans [6]. The aggressive nature of its behavior has compelled the researchers to seek more deepened knowledge about the mechanism that could help

prevent its progression [2]. Proliferating vessels have an important role to play in predicting the biological behavior of different pathologies including tumors of odontogenic origin, as well as a therapeutic guide for the said conditions. The connective tissue stroma facilitates epithelial changes by providing the environment that is needed for the fibroblasts and blood vessels to become active resulting in neoplastic growth [7]. A cascade of events is involved in angiogenesis resulting in the proliferation of already existing vessels. The most searched mechanisms include multiplication and degradation of extracellular matrix, endothelial cell migration, and capillary formation [8]. The process is controlled by inhibitory biomarkers and growth factors [7]. It was initially discovered that CD34 was expressed as antigen on the surface of 1% to 2% of normal



bone marrow and in the myeloblastic cell line [9]. It marks cells that act as precursors for a wide range of cells and tissues like vascular endothelial lining, connective tissue stroma, dermal epithelium, and keratinocytes [10]. The increased growth potential of ameloblastoma reflects higher expression of CD34 in this odontogenic tumor. Mean Vascular Density (MVD) is estimated to help predict the behavior of the lesions that express CD34 [11]. Depending on its accessibility and ease of use, CD34 can be employed as a specific marker that can reveal proliferating vessels in a variety of lesions. Immunohistochemical labeling is used to identify this antigen [12]. Ameloblastoma is known for its aggressive nature having variable recurrence for histologically different patterns [13-15]. Therefore, the current study was designed to assess the proliferative potential of histological variants of ameloblastoma to see if they may provide a clue for a difference in the organic behavior of these variants.

Ameloblastoma is a locally aggressive odontogenic tumor with variable recurrence potential, yet reliable biological markers to predict the proliferative behavior of its histological variants remain insufficiently explored. Although CD34-mediated mean vascular density (MVD) has been recognized as an indicator of angiogenesis and tumor aggressiveness, limited regional data exist comparing CD34 expression across different ameloblastoma variants while simultaneously correlating these findings with age, gender, and anatomical site. This study addressed this gap by evaluating the histochemical expression of CD34 in follicular, plexiform, acanthomatous, and unicystic ameloblastoma variants to better understand their comparative growth potential and biological behavior, particularly within the Pakistani population. The primary aim was to assess whether differences in vascular proliferation could contribute to improved prognostic stratification and individualized management of ameloblastoma patients.

METHODS

This analytical cross-sectional study consisted of 40 diagnosed cases of ameloblastoma of different ages and gender groups. Sample size calculation was done using Epi-tool with the estimated true proportion of 0.01 (1% prevalence), confidence interval of 95%, and precision of 0.05 about a study carried out by Nazir H and Usman I [16]. A non-probability purposive sampling technique was applied. Formalin-fixed paraffin-embedded (FFPE) blocks were recruited from the archives of the histopathology Department of Peshawar Medical College (PMC) and Pakistan Institute of Medical Sciences (PIMS). Blocks with insufficient tissue and excessive hemorrhage were excluded from the study. Before the study started, ethical approval was obtained (Prime/IRB/2022-420) from the

review board of the Prime Foundation Peshawar. Already prepared slides of selected cases of ameloblastoma were examined. Following confirmation of the diagnosis, blocks with adequate tissue were chosen for immunohistochemistry. Six slides (3+3) from representative blocks, each of 4-5 microns' thin sections were made. For each case Hematoxylin and Eosin (H and E) stain was applied on one slide, one was utilized for Immunohistochemistry (IHC), and one of each case was kept aside for future use. Tonsillar tissue was taken as a positive control. One slide of positive control was used for each batch. The procedure of IHC was carried out using Mouse Anti-Human CD 34 Monoclonal Antibody (DAKO, Denmark). Scoring was carried out following the method proposed by Hosseini S et al., [17]. MVD was then measured by evaluating the IHC-stained slides under the microscope. Under low magnification, four hot spots or regions with the greatest degree of vascularization were chosen. At ($\times 40$) magnification number of the vessels showing staining was counted. The mean of stained blood vessels in the four selected hot spots was taken as MVD. Cases having MVD scores of 0-19.9 were categorized as low, scores of 20-29.9 as moderate, and scores more than 40 as high. The statistical analysis was carried out using the Statistical Program for Social Sciences (SPSS) version 20. Continuous variable like age was presented as mean and standard deviation. Categorical variables like the site, gender, age group, and MVD were presented as percentages, and a chi-square test was applied to age groups and variants of ameloblastoma to find its relationship with MVD. A p-value of less than 0.05 was deemed statistically significant.

RESULTS

The study consisted of a total 40 cases of ameloblastoma. Among all cases 19/40 (47.5%) were found in males and 20/40 (50%) in females with a ratio of 0.95:1. Ameloblastoma patients ranged in age from 12 to 80 years, with a mean age of 36.13 ± 12.8 . The age group under 40 years had the highest number of instances. The posterior mandible was found to be the most preferred site followed by the anterior mandible, posterior maxilla, anterior maxilla, and maxillary sinus comprising 72%, 15%, 5%, 2.5%, and 2.5% of cases respectively. Histologically, the follicular variant was most common, making 72.5% of ameloblastomas, followed by plexiform ameloblastoma 12.5%, acanthomatous ameloblastoma 10% and unicystic ameloblastoma 05%. In posterior mandible maximum number of follicular variant presented with moderate MVD score 50% followed by low 35% and high score 15%. In anterior mandible follicular variant presented 60% high MVD score and 40% moderate score. In posterior and anterior maxilla, only follicular variant showed moderate 100% MVD score as seen in figure 1.

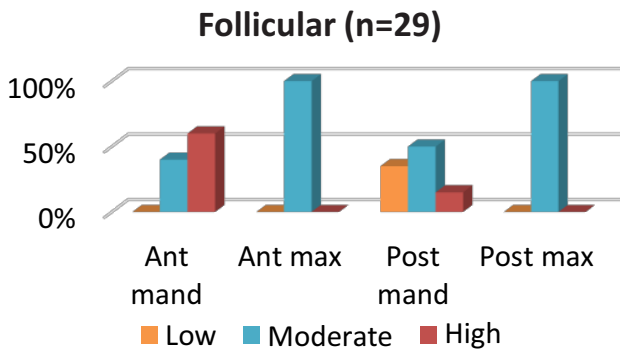


Figure 1: MVD Score of Follicular Variant with Respect to Site

In posterior mandible Plexiform variant presented with 50% each of high and low score. Only plexiform variant presented with 100% moderate MVD score in maxillary sinus shown in figure 2.

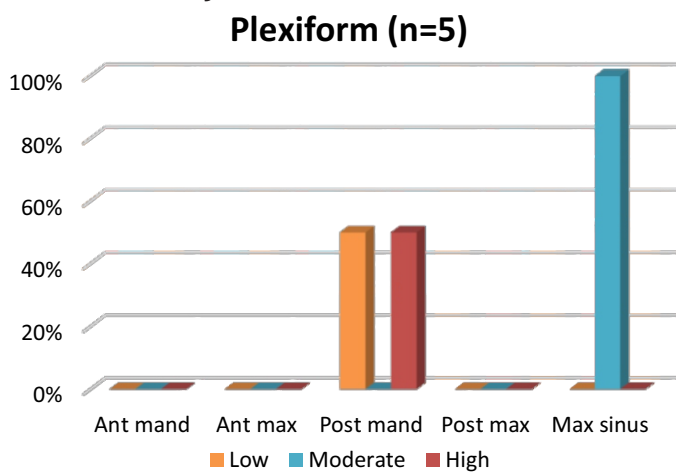


Figure 2: MVD Score of Plexiform Variant with Respect to Site

In posterior mandible acanthomatous variant presented with moderate MVD score 50% followed by 25% each of low and high score as seen in Figure 3.

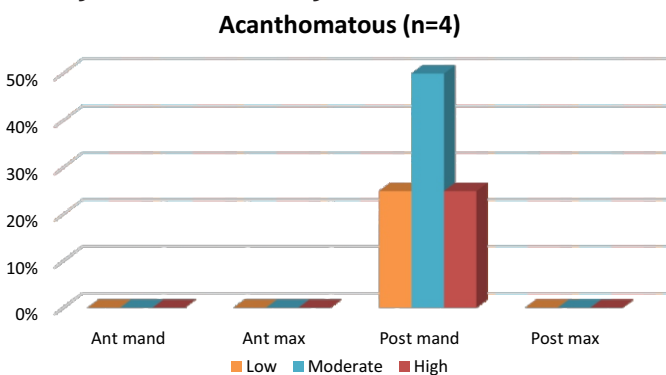


Figure 3: MVD Score of Acanthomatous Variant with Respect to Site

In posterior mandible acanthomatous variant presented with moderate MVD score 50% followed by 25% each of low and high score as seen in Figure 3.

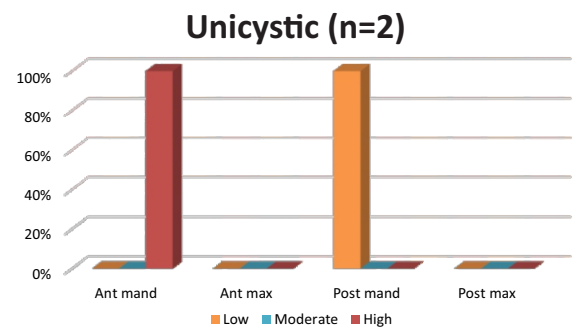


Figure 4: MVD Score of Unicystic Variant with Respect to Site

Out of 29 cases of follicular variant 11 (37.9%) of cases were present in males and 18 (62%) in females. In male patients, maximum number of follicular variant presented with moderate MVD score 63.6% followed by 27.2% of low and 9.1% of high MVD score. In female's maximum number of follicular variants showed moderate MVD score 44.4% followed by high 33.3% and low 22.2% score. Out of 5 cases of plexiform variant 4 (80%) of cases were present in males and 1 (20%) in females. In males, 50% of plexiform variant presented with high MVD score and 25% each of low and moderate score. In females only one case of plexiform variant was present showing low MVD score 100%. Among 4 cases of acanthomatous ameloblastoma equal distribution 50% was found in both genders. Males presented with 50% each of low and high MVD score while in females both the cases 100% were of moderate MVD score. Unicystic ameloblastoma in male presented with 50% each of low and high score. Whereas in female there was no case of unicystic variant as shown in the following Table 1.

Table 1: MVD Score of Ameloblastoma Variants in both the Genders (n=69)

MVD Score	Gender	
	Male n (%) (n=19)	Female n (%) (n=21)
Follicular (n=21)	11 (37.9%)	18 (62%)
Low	3 (27.2%)	4 (22.2%)
Moderate	7 (63.6%)	8 (44.4%)
High	1 (9.1%)	6 (33.3%)
Plexiform (n=5)	4 (80%)	1 (20%)
Low	1 (25%)	1 (100%)
Moderate	1 (25%)	-
High	2 (50%)	-
Acanthomatous (n=4)	2 (50%)	2 (50%)
Low	1 (50%)	-
Moderate	-	2 (100%)
High	1 (50%)	-
Unicystic (n=2)	2 (100%)	-
Low	1 (50%)	-
Moderate	-	-
High	1 (50%)	-
Total (n=40)	19	21

Regarding age, cases with maximum number 51.7% of follicular variant with 53.3% of the patients above 40 years

of age presented with moderate MVD score followed by low 33.3% and high 13.3% score. In cases below 40 years of age, follicular variant presented with maximum number of moderate MVD score 50% followed by high 35.7% and low 14.2% score. In patients above 40 years of age, the only plexiform 100% variant presented with moderate MVD score while in patients below 40 years it presented with 50% each of low and high score. Acanthomatous presented with 50% each of low and moderate score in the patients above 40 years and 50% each of moderate and high MVD score in cases below 40 years. One case each of unicystic ameloblastoma was present in both the groups showing high MVD in age group above 40 and low MVD in below 40 years as seen in table 2.

Table 2: MVD Score of Ameloblastoma Variants in both Age Groups

MVD Score	Age (Years) n (%)		p-value
	>40 (n=19)	<40 (n=21)	
Follicular (n=29)	15 (51.7%)	14 (48.2%)	0.27
Low	5 (33.3%)	2 (14.2%)	-
Moderate	8 (53.3%)	7 (50%)	
High	2 (13.3%)	5 (35.7%)	
Plexiform (n=5)	1 (20%)	4 (80%)	0.08
Low	-	2 (50%)	-
Moderate	1 (100%)	-	
High	-	2 (50%)	
Acanthomatous (n=4)	2 (50%)	2 (50%)	0.36
Low	1 (50%)	-	-
Moderate	1 (50%)	1 (50%)	
High	-	1 (50%)	
Unicystic (n=2)	1 (50%)	1 (50%)	0.36
Low	-	1 (100%)	-
Moderate	-	-	
High	1 (100%)	-	
Total (n=40)	19	21	-

The follicular variant showed 24.1% cases of low, 51.7% cases of moderate and 24.1% cases of high MVD. The plexiform variant showed 40 % cases of low, 20% cases of moderate and 40 % cases of high MVD. The acanthomatous variant had 25% cases of low, 50% cases of moderate and 25% cases of high MVD. In unicystic variant 50% of cases presented with low and 50% with high MVD while there was no case with moderate MVD. Relationship between CD34 expression in ameloblastoma and its histological variants were found to be statistically non-significant (p-value 0.74) table 3.

Table 3: Expression of CD34 in Different Variants of Ameloblastoma

Variants	MVD Score n (%)			Total n (%)	p-value
	Low	Moderate	High		
Follicular	7 (24.1%)	15 (51.7%)	7 (24.1%)	29 (72.5%)	0.74
Plexiform	2 (40%)	1 (20%)	2 (40%)	5 (12.5%)	

Acanthomatous	1 (25%)	2 (50%)	1 (25%)	4 (100%)
Unicystic	1 (50%)	-	1 (50%)	2 (05%)
Total	11 (27.5%)	18 (45%)	11 (27.5%)	40 (100%)

Photomicrographs of Ameloblastoma showing hematoxylin and eosin (H & E) staining (A, C, and E) and immunohistochemical staining for CD34 (B, D, and F) at low, moderate, and high microvascular density (MVD) in blood vessels, respectively. Arrowheads indicate CD34-stained blood vessel as shown in figure 5.

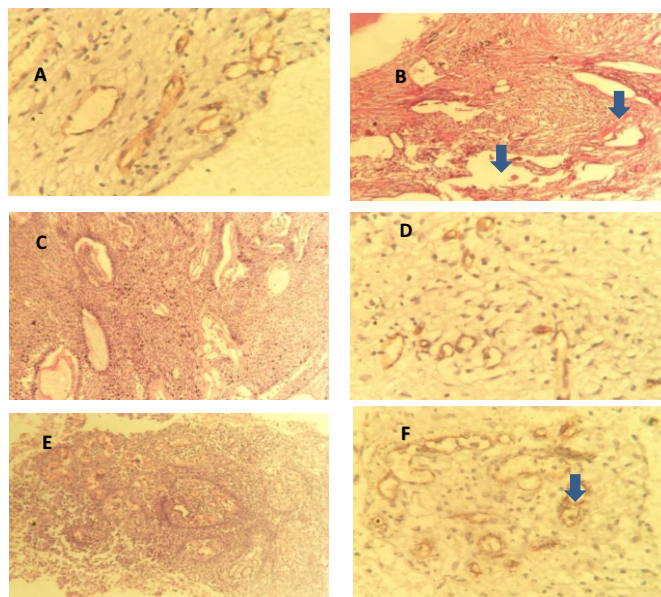


Figure 5: Photomicrograph of Ameloblastoma with H & E staining (A, C and E) and immunohistochemical staining (B, D and F) with CD 34 of low, moderate and high MVD in blood vessels respectively. Arrow heads showing CD 34 stained blood vessels.

DISCUSSION

A total of 40 cases of ameloblastoma were evaluated in the present study. The most common age group was the second and third decades of life with a mean age of 36.13 ± 12.8 . The findings are similar to the previously reported studies conducted in Pakistan but different from the findings of Stefan Vila S et al [18, 19]. This variation may be explained based on the differences observed between different ethnic groups. Almost equal predilection was found for both the genders which is consistent with other studies [20, 21]. However, some national and international studies have demonstrated slight male predilection [18, 19]. A Pakistani study has also observed female predominance [22]. This minor discrepancy in ratio might be due to the difference in sample size. In this study, the mandible was found to be the commonest 82.5% site for ameloblastoma which is similar to Egyptian and Iranian studies and the posterior region to be the favorite site as compared to the anterior region in both the mandible and maxilla [21, 22]. The maxillary sinus was the least affected site. The results are similar to that of a Pakistani study but

in contrast to study of Treville Pereira, who demonstrated the anterior region to be the commonest affected site [23, 13]. Follicular ameloblastoma was found to be the most common type. Plexiform was the second followed by acanthomatous and unicystic ameloblastoma. These results are in agreement with already existing data in the literature [24-26]. However, plexiform and unicystic ameloblastoma have been reported to be the most frequently occurring variants in studies conducted in Thailand and India [27-29]. The possibility for this contrast might be the variability in geographic locations, genetics, differences in cultural habits, and sample size. The importance of angiogenesis as a major player in increased neoplastic changes, invasion and aggressive behavior in multicystic ameloblastoma has been demonstrated in the literature. MVD score determines the tumor's aggressiveness which validates the angiogenesis as an important prognosticator that can assist clinicians in designing more effective treatment strategies [30]. CD 34 expression has already been identified as an effective tool to quantify vascular proliferation in a tumor [31]. Regarding CD34 expression in histological variants, the current study found that the follicular type has the highest MVD score in the posterior mandible. Anterior mandible, posterior maxilla, and anterior maxilla are then affected respectively. The maxillary sinus and posterior jaw had the highest MVD scores for the Plexiform variety. Similarly, acanthomatous and unicystic variants also expressed maximum MVD score in the posterior mandible. Based on these findings it is revealed that in the posterior mandible, all variants of ameloblastoma exhibit maximum vascular proliferation in comparison to other sites. Different researchers discovered that Solid Multicystic Ameloblastoma (SMA) had higher MVD scores than desmoplastic and unicystic types based on which they suggested its behavior to be more aggressive than the other two [30, 32, 33]. Hande AH et al., also concluded the same increased angiogenesis in SMA while doing a comparison between the three and reported unicystic and desmoplastic ameloblastoma as second and third in the list [34]. In contrast, Jamshedi S et al., reported the same aggressive nature for both solid multicystic and unicystic ameloblastoma [22]. All the above-mentioned studies did not compare MVD in variants of ameloblastoma with respect to sites as is done in the present study. While comparing CD34 expression status in both genders, it was discovered that the follicular variant has more growth potential in females while plexiform, acanthomatous and unicystic type proliferate violently in males. Due to scant available data in the literature investigating endothelial proliferation in ameloblastoma variants for site and gender, comparison with other studies is hampered. The present study evaluated endothelial proliferation in two age groups i.e. above and below 40 years. Follicular ameloblastoma

was found to have a higher MVD score in the group of more than 40 years. In contrast plexiform variant showed more vascular growth in the group of less than 40 years whereas acanthomatous and unicystic type were equally proliferative in both age groups. These findings are in line with a Pakistani study [7]. According to Koizumi et al., plexiform type is common among the younger population and the follicular type is among older people. This led to the suggestion that in addition to affecting tumor growth pattern, angiogenesis is also modulated by the patient's age. [35]. However current study could not find significant relationship with age groups ($p > 0.05$). Since vasculogenesis is important for the tumor to grow and metastasize, measurement of MVD can help in its prediction together with treatment outcome [22]. Although ameloblastoma is known for its aggressive behavior, this study is the first one to correlate different variants of ameloblastoma with age, gender, and site on basis of CD34 expression or vascular proliferation. This might provide a help in further stratification of the patients having differential growth potentials in accordance with clinicopathological features. Relationship of CD 34 expression with histological variants of ameloblastoma revealed insignificant relationship which is in contrast to studies carried out in India and Iran [13, 22]. Large sample size of their study might be responsible for this difference. Although present study pointed towards insignificant relationship between variants and angiogenesis but report of high MVD score in females, in specific age group and in mandible suggest evaluation of endothelial proliferation while planning treatment specifically for the groups just mentioned.

The study was limited by its relatively small sample size, single-region retrospective tissue selection, and non-probability purposive sampling, which may reduce generalizability and statistical power. Additionally, the absence of long-term clinical follow-up restricted evaluation of CD34 as a predictor of recurrence or treatment outcomes. Future studies should include larger multicenter cohorts, longitudinal follow-up, and integration of additional molecular angiogenic markers to validate CD34's prognostic significance and strengthen personalized therapeutic planning for ameloblastoma variants.

CONCLUSIONS

All variants displayed the highest MVD score in the posterior mandible. The follicular variant has more growth potential in females while in males it is found more in plexiform, acanthomatous and unicystic variants. More epithelial proliferation in the follicular variety is observed in the age group over 40, whereas more plexiform type was shown in the age group below 40. Further investigations

regarding angiogenesis in variants of ameloblastoma are needed. Stratification according to different variants, each strata containing a large number of patients is recommended. Additionally, follow-up of the patients is recommended for further exploration of MVD as a predictive factor in ameloblastoma cases.

Authors' Contribution

Conceptualization: NB, FI

Methodology: MO, HM

Formal analysis: MO

Writing and Drafting: HM, TN, ASK, NB, FI

Review and Editing: HM, TN, ASK, NB, FI

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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