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Original article

Immuno-expression analysis of VEGF and CD34 related to histological types of mandibular ameloblastoma

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ABSTRACT

Background: *Increased expression of vascular endothelial growth factor (VEGF) and cluster of difference 34 (CD34) in ameloblastoma has been noted. Both proteins are markers of angiogenesis that play a role in supporting the growth of ameloblastoma. The existence of histopathological types of ameloblastoma allows for differences in behavioral and growth characteristics.* ***Purpose:*** *To evaluate the differences and correlation of VEGF and CD34 expression in histological types of ameloblastoma.* ***Methods:*** *This laboratory cross-sectional study uses total sampling from histological slides of mandibular ameloblastoma. Two observers manually quantified the immunohistochemical expression. The comparative data were analyzed statistically with the Kruskal–Wallis test ($p < 0.05$), while the correlative data were analyzed with Spearman's rho ($p<0.01$).* ***Results:*** *32 samples were obtained according to the inclusion criteria. The Kruskal–Wallis test showed significant differences in VEGF expression ($p = 0.003$) and CD34 expression ($p = 0.026$). The pairwise comparison test showed that VEGF expression in follicular ameloblastoma significantly differed from plexiform ($p = 0.001$) and combination ($p = 0.002$). The pairwise comparison test for CD34 expression showed a significant difference between follicular and combination ameloblastoma ($p = 0.007$). Spearman's rho test showed a positive correlation ($p = 0.001$, $r = 0.565$) between markers.* ***Conclusion:*** *Follicular ameloblastoma expressed higher VEGF than plexiform and combination ameloblastoma. Follicular ameloblastoma expressed higher CD34 than combination types. CD34 expression is associated with VEGF in histological types of ameloblastoma.*

Keywords: *ameloblastoma; cluster of difference 34; follicular type; immunohistochemistry; medicine; vascular endothelial growth factor*
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INTRODUCTION

Ameloblastoma is an odontogenic benign tumor that is slow-growing and locally aggressive. The World Health Organization (WHO) defines ameloblastoma as a locally aggressive benign tumor with a high risk of recurrence, consisting of odontogenic epithelium in the fibrous stroma.[1–3] The causative factors of ameloblastoma are the same as those of other neoplasms, which are generally not known.[4,5] Based on the histologic pattern, ameloblastoma shows two main patterns: follicular and plexiform, which are both common. Ameloblastoma also shows a combination of two or more types of histology patterns.[6,7] These different histology types allow for differences in the clinical properties of the tumor between ameloblastoma histology types in terms of recurrence, expansion, destruction, and prognosis.[8,9]

Efforts to determine the correlation between the histological type of ameloblastoma and the nature of the tumor are still underway. Six hallmarks of cancer, or six distinctive complementary abilities of tumors to enlarge and spread, have been used as the basis for studying the biological properties of tumors. The six hallmarks are: (1) the ability to release continuous proliferative signals; (2) the ability to minimize growth suppressors; (3) the ability to induce angiogenesis; (4) the ability to survive apoptosis;

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(5) the ability to replicate perpetually; and (6) the ability to invade and metastasize.[8,10,11] Previous studies have found that follicular types are more aggressive and have a higher recurrence ratio than plexiform types.[12,13] Recent research has discovered a higher expression of hypoxia-related proteins in the follicular type, indicating their significant role in this type of ameloblastoma.[14]

One of the factors in tumor growth is the process of angiogenesis. The role of angiogenesis is to support the growth of ameloblastoma. The primary factor that plays an essential role in tumor angiogenesis is vascular endothelial growth factor (VEGF). This stimulates the breakdown of the extracellular matrix surrounding endothelial cells, promoting endothelial cell migration and proliferation and aiding in the formation of blood vessel structures. These actions start angiogenesis and contribute to the high proliferative capacity of epithelial cells.[15–19] The process of angiogenesis can also be measured by assessing new blood vessels. Cluster of difference 34 (CD34) is a specific marker of micro vessels that differentiates old and newly formed blood vessels and may act as an agent of epithelial mitosis in odontogenic tumors.[16,17,20] Angiogenesis markers such as VEGF and CD34 have been studied in various tumors to determine the prognosis of tumor development.[21–24] This study aims to determine the difference in the expression of VEGF and CD34 as markers of the angiogenic process based on the histological types of ameloblastoma.

MATERIALS AND METHODS

This type of research is observational analysis, using a retrospective study with a cross-sectional approach. The Commission for Ethical Clearance of Health Research, Faculty of Dental Medicine, Universitas Airlangga, has approved the ethical clearance of the methods used in this study (519/HRECC.FODM/VIII/2022). The minimum sample size for research on the different tests was four per group, using the formula from Lemeshow and Lwanga.[25] The calculation results in this study's power test, based on the Analysis of Variance test, were 0.999 at a confidence level (alpha) of 0.05 with a beta accuracy level of 80%. In this study, the power test based on the correlation test was 0.9315 at a confidence level (alpha) of 0.05 with a beta accuracy level of 80%. The inclusion and exclusion criteria were determined before study identification. The inclusion criteria were as follows: surgical specimens from patients with a histopathological diagnosis showing follicular, plexiform, or a combination of follicular and plexiform type, and operation time from 2015 to 2022. The exclusion criteria were as follows: surgical specimens from patients with a histopathological diagnosis showing ameloblastic carcinoma or metastasizing ameloblastoma and samples that did not show representative sections of ameloblastoma in the form of tumor parenchyma and stroma. Thirty-eight paraffin-embedded tissue blocks of ameloblastoma specimens were acquired from Universitas Airlangga Hospital and Dr. Suwandi Regional General Hospital. The samples comprised five follicular, 11 plexiform, 16 combination, and four ameloblastic carcinomas. Four ameloblastic carcinoma samples were excluded from the analysis. The histological types were determined by hospital anatomical pathology based on WHO criteria.

The tissue was cut to a thickness of 4 mm into two slides for each sample, and then an immunohistochemical examination was carried out. After deparaffinization in xylene and dehydration in alcohol, slides were treated with 0.3% hydrogen peroxide in methanol for 20 minutes. Antigen retrieval was performed using sodium citrate buffer, and then slides were microwaved twice for five minutes. The sections were blocked with unspecific proteins with 5% fetal bovine serum containing 0.25% Triton X-100. After being washed with phosphate-buffered saline (PH = 7.4) three times for five minutes, the slides were incubated using primary antibodies (VEGF *mouse monoclonal* 11B5 ab38909 Abcam, Cambridge, UK; CD34 *mouse monoclonal* sc-19621 Santa Cruz Biotechnology, Dallas, TX, USA) for 60 minutes at room temperature. After being rinsed with phosphate-buffered saline, slides were incubated with biotinylated secondary antibodies. Then, the slides were washed again and incubated with streptavidin-horseradish peroxidase conjugate. The slides were then dripped with a chromogen-substrate solution (3–3′-diaminobenzidine tetrahydrochloride). Finally, the sections were counterstained with Mayer's hematoxylin. The slides were rinsed under running water, dried, and covered with a cover slip. Two observers blinded to the clinical data evaluated the stained slides, and possible disagreements were resolved by consensus. Quantitative calculations were obtained by counting the brown-colored endothelial cells from an average of 20 HPF with 400x magnification using a light microscope (Olympus BX53).

All statistical analyses were conducted using SPSS software version 26.0 (IBM, Armonk, NY, USA). The research data were tested for normality using the Shapiro–Wilk test and expressed as a mean ± SD. The Kruskal–Wallis test was used to determine differences in VEGF and CD34 expression among all groups and was considered statistically significant if it was less than 0.05. Spearman's rho was carried out to analyze the correlation between VEGF and CD34 expression, which was considered statistically significant if it was less than 0.01.

RESULTS

Thirty-two samples met the inclusion criteria, consisting of 17 (53%) females and 15 (47%) males with mean ages of 32 years (ranging from 16 to 66 years). The most common histological type was combination, followed by plexiform and follicular. Based on age, the youngest patient with ameloblastoma at the time of surgery was 13 years old, and the oldest was 66 years old, with an average age of 32 years. Those age between 10 to 20 and 21 to 30 were the most

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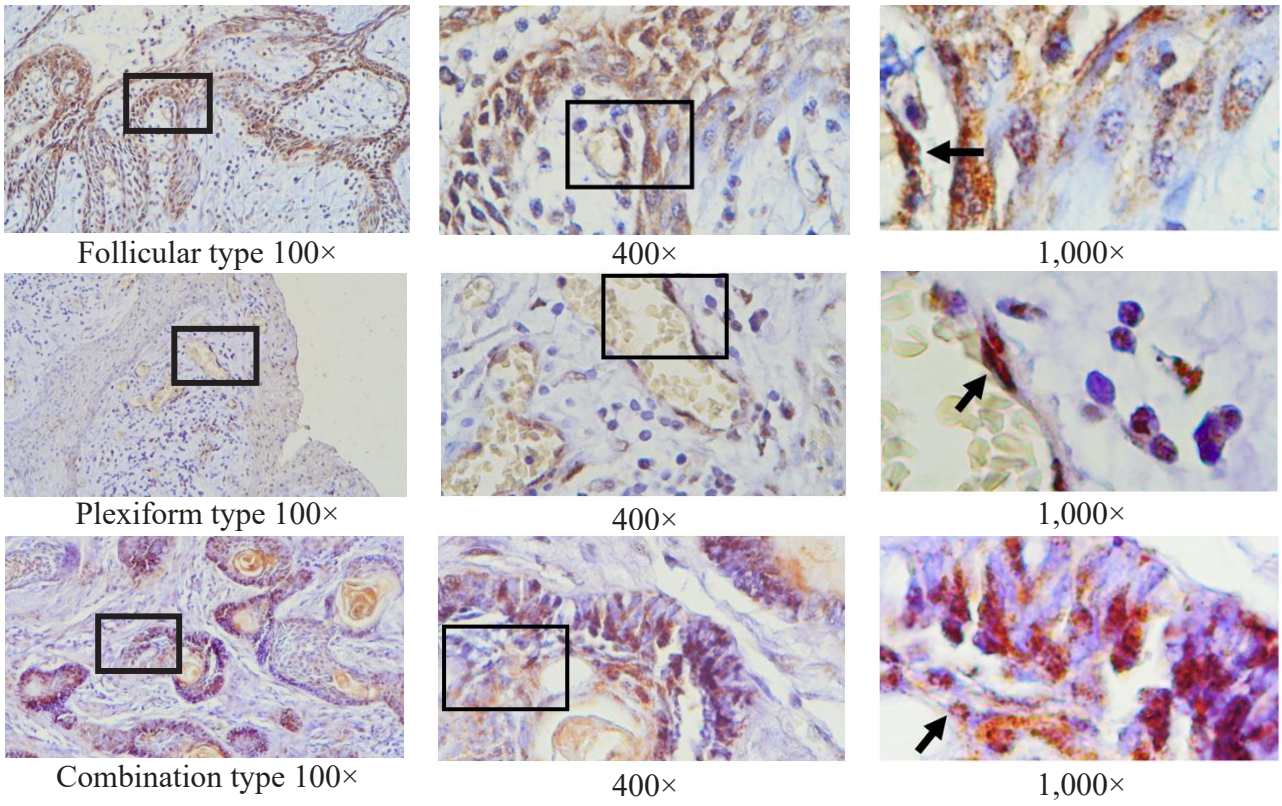

Figure 1. VEGF immunostaining on samples. VEGF is expressed by vascular endothelial cells in the tumor stroma. Black squares show magnified colored areas. Arrows indicate cells that are brown on staining.

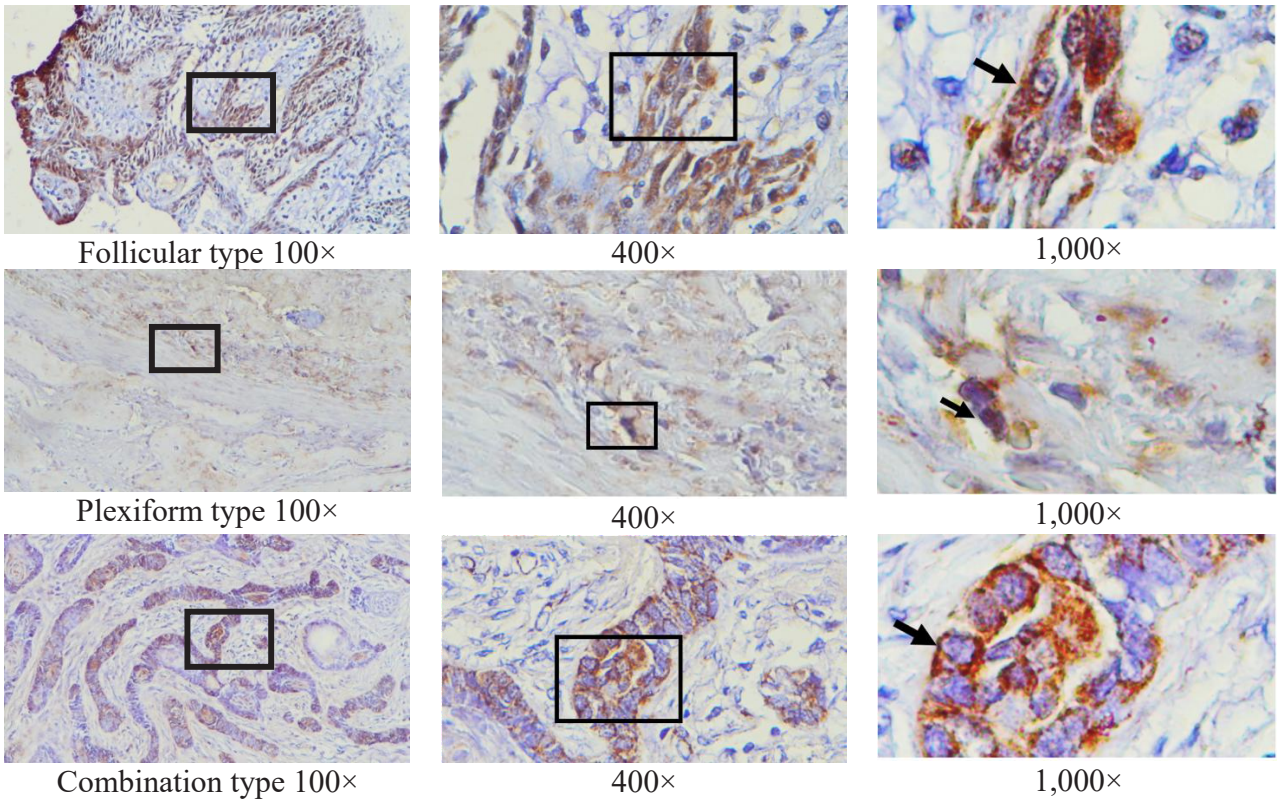

Figure 2. CD34 immunostaining on samples. CD34 is expressed by vascular endothelial cells in tumor stroma. Black squares show magnified colored areas. Arrows indicate cells that are brown on staining.

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common age group with eight patients (25%), followed by 31 to 40 age group with seven patients (21.87%), the 51 to 60 age group with four patients (12.5%), the 41 to 50 age group with three patients (9.38%), and there were two patients over 60 years old (6.25%). Of the plexiform ameloblastoma variant, most cases occurred in the 10 to 20 age group (four patients), the combined ameloblastoma variant had the most cases in the 31 to 40 age group (five patients), and the follicular ameloblastoma variant was evenly distributed. All 32 samples occurred in the mandible.

In this study, VEGF and CD34 were expressed by vascular endothelial cells in the tumor stroma (Figures 1 and 2). The highest amount of VEGF expression was found in the follicular type (13.8 ± 1.643), followed by the combination (6.63 ± 4.365) and plexiform type (6 ± 3.406). CD34 antibody expression was highest in the follicular type (12 ± 4.062), followed by the plexiform (7 ± 3.715) and combination type (5.25 ± 4.435).

Statistical tests showed that VEGF expression in follicular ameloblastoma significantly differed from plexiform (p = 0.001) and combination (p = 0.002). A statistical test of CD34 expression showed a significant difference between follicular and combination (p = 0.007) (Figure 3). The VEGF and CD34 expression correlation test used Spearman's rho because the data were not normally distributed. The test results showed a significant positive correlation between the expression of VEGF and CD34 (p < 0.001; r = 0.565; Table 1).

Table 1. Correlation of CD34 expression with VEGF in ameloblastoma

		CD34 expression
VEGF expression	r	0.565
	p	0.001*
	N	32

*Correlation significancy < 0.01

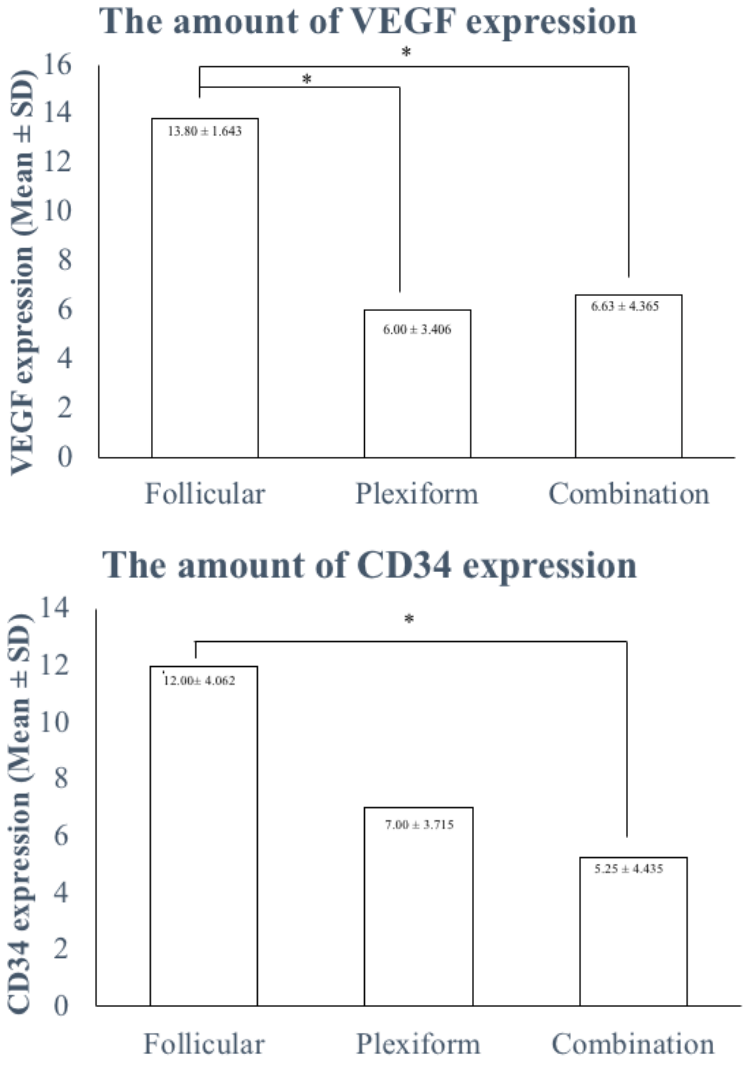

Figure 3. Immuno-expression of (a) VEGF and (b) CD34 differences among types of ameloblastoma. The * indicates a significant difference (p < 0.05).

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DISCUSSION

The enigmatic nature of ameloblastoma is manifested by its slow growth rate, similar to benign tumors, but it has locally invasive characteristics with a high recurrence rate and metastatic potential resembling malignant tumors.[26] Factors associated with the nature of these lesions include increased proliferative potential, altered expression of tumor suppressor genes, and abnormal expression of cell adhesion regulatory protein molecules. The VEGF marker in ameloblastoma shows higher expression than in odontogenic adenomatoid tumors, so it is concluded that the angiogenesis process is involved in developing ameloblastoma tumors. Mithogen-activated protein kinase pathway mutations in ameloblastoma are currently thought to result in abnormal cell regulation because the signaling process occurs perpetually, so proliferation becomes uncontrolled.[27,28]

The VEGF is expressed by vascular endothelial cells in the tumor stroma. Interactions between ameloblast cells and surrounding stromal cells also contribute to the growth of ameloblastoma. In this study, the average amount of VEGF expression in the follicular ameloblastoma was significantly higher than in the plexiform and combination types. The angiogenesis process can be associated with hypoxia-inducible factor 1-alpha (HIF-1α) induced by hypoxic conditions, so it contributes enormously to the growth of ameloblastoma.[29] As proliferation increases in the peripheral cell layers of ameloblastoma, cells in the center lack oxygen because the supply of epithelial cells depends on the surrounding tissue stroma for nutrition.[30] HIF-1α expression is known to be slightly higher in follicular ameloblastoma compared to plexiform, so it is thought to contribute to differences in VEGF expression.[24] In the process, angiogenesis is influenced by the degradation of the extracellular matrix, which is triggered by matrix metalloproteinase activity and proteolytic enzymes. These enzymes cause the release of angiogenic growth factors from the basement membrane of blood vessels.[31] The expression of MMP-2 is highest in the follicular type, followed by plexiform and combination. Matrix metalloproteinase activity in the bone matrix degradation process activates existing growth factors, including VEGF, and with the matrix's sequestering properties, signaling causes the proliferation process to occur.[18,32]

Hypoxia also causes macrophages to produce more VEGF and suppresses the immune response. VEGF signaling can have a significant effect on vessel permeability and neovascularization and also supports tumor cell proliferation and migration. VEGF expression has been widely studied as a prognosis of the severity of various tumors. Previous studies have shown higher VEGF expression in ameloblastoma than odontogenic keratocyst.[33] Studies in patients with laryngeal squamous cell carcinoma and osteosarcoma with high VEGF expression found there to be a high recurrence rate and a smaller chance of disease-free survival.[34,35]

Angiogenesis can also be measured indirectly by microvascular quantification and assessed as mean microvascular density. The CD34 antibody used to determine tumor microvascular density can confirm the role of VEGF in the angiogenesis process in benign and malignant ameloblastoma.[31] The formation of new tumor blood vessels, which are primarily the product of activation of cell division from pre-existing blood vessels, is characterized by the expression of CD34 on the cell surface.[36]

The results of this study show that the highest expression of CD34 is found in the follicular type of ameloblastoma compared to the plexiform and combination types. This is in line with previous studies that also found that CD34 expression in follicular ameloblastoma was significantly higher than in plexiform, although this was not statistically significant.[37,38] Previous research on micro vessel density found that the more aggressive the tumor growth of the tissue, the higher the micro vessel density value of the tissue. The increased density of micro-blood vessels in ameloblastoma indicates the need for blood supply in the neoplasmic tissue.[31] High CD34 expression is also associated with a worse prognosis and cure ratio for malignant tumors. In lung carcinoma, high CD34 expression is followed by cancer cell invasion into the surrounding tissue. CD34 expression is also closely related to the severity of brain glioma and is a prognostic factor.[39,40] Positive CD34 staining results in ameloblastoma indicate that, although ameloblastoma is an infiltrative benign tumor, micro vessel density values in certain types can be suspected of invasive behavior such as malignancy.[41]

This study shows positive correlation results between VEGF expression and CD34 expression on ameloblastoma histological types. High VEGF expression is also accompanied by high CD34 expression in the same type. High expression of these two angiogenesis markers may be correlated with higher tissue metabolism, more aggressive biological behavior, and higher rates of recurrence and growth. Angiogenesis can be used as an indicator to determine the nature of the growth and invasive behavior of ameloblastoma because of its role as a supporter of the ameloblastoma pathogenesis process. The VEGF and CD34 are potential markers for identifying patients with ameloblastoma, and they are independent indicators of the presence of disease and prognosis of overall survival.[31,38,42]

This research still has limitations, namely that it cannot explain with certainty the relationship between angiogenesis and other characteristics of ameloblastoma growth and development, such as proliferative behavior, local invasiveness, and the tumor's ability to degrade the bone matrix. Furthermore, the limited sample size and absence of data on patient sample follow-up, such as tumor-free survival time and recurrence, as a result of the study's retrospective design, are regarded as research limitations. Nevertheless, it can be concluded that, within the study's limitations, the follicular type shows the highest

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expression of VEGF and CD34 compared to the plexiform and combination types of mandibular ameloblastoma. A positive correlation is found in VEGF–CD34 expression, whereby CD34 expression is influenced by VEGF expression in the growth of ameloblastoma of the mandible. High CD34 expression in one histopathological type of ameloblastoma is also followed by high VEGF expression. Further study is required to validate the association between CD34 and VEGF expression and the clinical manifestation of mandibular ameloblastoma.

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