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Correlation between Matrix Metalloproteinase-9 (MMP-9) Immunohistochemical Expression and Histopathological Subtypes of Basal Cell Carcinoma

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ABSTRACT

Background
Basal cell carcinoma (BCC) is a non-melanocytic skin cancer originating basal layer of the epidermis and/or hair follicles that shows an increasing global incidence. Disease growth is slow, rarely metastasizes but has the ability to invade and destroy deeper surrounding tissues. Low mortality, but high morbidity. Matrix metalloproteinases are enzymes that can degrade various extracellular matrix components. In skin, MMP-9 expression may be increased by prolonged ultraviolet exposure. UV radiation is one of the causes of BCC.

Method
Analytic study with a cross sectional approach on 40 surgical samples diagnosed as BCC and then performed with MMP-9 immunohistochemical staining. The data obtained were processed with statistical software and the relationship between the immunohistochemical expression of MMP-9 with histopathological subtypes of basal cell carcinoma was used the Somers'd statistical test.

Results
The expression of MMP-9 in the lower risk BCC group with the weakest expression was 37.5%, the most common nodular BCC subtype was 27.5%. The higher risk BCC group with the strongest expression was 20.0%, the most common infiltrating BCC was 17.5%. There was a significant relationship between the immunohistochemical expression of MMP-9 with histopathological subtypes of basal cell carcinoma, p value <0.0001 ($p<0.05$).

Conclusion
This study proves that there is a significant relationship between the expression of MMP-9 with histopathological subtypes of basal cell carcinoma, so it can be considered as an additional marker to predict the recurrence.

Keywords: Basal cell carcinoma, matrix metalloproteinase-9, recurrence, immunohistochemistry, subtype.

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INTRODUCTION

Basal cell carcinoma (BCC) is a non-melanocytic skin cancer and is the most common malignancy involving the skin and shows an increasing global incidence.[1,2] The incidence begins to increase in the fourth decade of life and is more common in men. The disease is slow growing and rarely metastasizes, but has the ability to invade and infiltrate the surrounding tissue and can destroy the deeper skin structures. BCC shows a high mortality and morbidity rate. Several studies reported an increase in the incidence of this malignancy by 2% annually. In Indonesia, in 2012 there were 1,530 cases of skin cancer and the most cases were BCC, it was 39.93%.[2-6] This is still relatively small when compared to other countries. The main risk factor is exposure to ultraviolet (UV) rays, so these lesions often appear on areas of the body that are frequently exposed to UV rays, such as the face, ears, neck. BCC shows great variability in morphology, aggressiveness, and response to treatment.[7] One of the molecules involved in tumor aggressiveness is matrix metalloproteinases (MMPs). In the skin, MMPs expression increases in response to various stimuli, including UV radiation. MMPs have been linked to UV-associated carcinogenesis by modulating various processes associated with tumor growth.[1,3,4,6,8]

Matrix metalloproteinase (MMP) is a molecule that can degrade extracellular matrix proteins. Increased expression of MMPs in tumor cells and adjacent tissues has been associated with more aggressive tumor behavior. MMP sources can be released by stromal cells, tumor cells or circulating cells. Degradation of components of the extracellular matrix and basement membrane is an important event in tumor invasion.[6,8] In particular, MMP-9 plays a role in tumor invasion and increased expression of MMP-9 has been frequently observed in several types of malignant tumors. Many studies have explored MMP-9 as a biomarker in various cancers, but it is still very rare in BCC.[9] MMP-9 as a promoter of tumor invasion plays a role in degrading type IV collagen, laminin and fibronectin so that cancer cells can migrate outside the tumor and even form distant metastases.[6,8,9] Increased expression of MMP-9 correlated with a more aggressive phenotype also plays an important role in the process of neo-angiogenesis.[6,8,10] In Indonesia, there are still very few studies with MMP-9, even in the city of Medan, research on the relationship between MMP-9 expression in BCC has never been studied. This is what prompted the author to conduct this research at the Haji Adam Malik General Hospital in Medan.

METHOD

This study used an analytic research design with a cross-sectional research methodology conducted at the Haji Adam Malik Hospital in Medan/Anatomic Pathology Unit at the Haji Adam Malik General Hospital in Medan. This research was conducted from December 2021 to October 2022 after obtaining permission from the Health Research Ethics Committee, Faculty of Medicine, University of North Sumatra. The samples in this study were H&E slides and paraffin blocks of 40 samples from patients who were histopathologically diagnosed as BCC and were taken by consecutive sampling. Data on age, sex, tumor size and location were obtained from medical record data. Exclusion criteria were incomplete patient data, paraffin slides/block preparations which after review were inadequate/could not be reprocessed for H&E and IHK staining. Each slide was stained with hematoxylin-eosin staining and immunohistochemical staining of matrix metalloproteinase-9 rabbit polyclonal antibody (BZ-0898450-AP, dilution 1:200, overnight). The location of the tumor is the tumor area and is divided into the upper face (forehead), middle face (orbita, lids, cheeks, nose, ears), and lower face (lips). The histopathological subtypes of BCC were assessed by microscopic examination based on WHO Classification of Skin Tumors 4th edition of 2018 and grouped into: lower risk BCC (nodular BCC, superficial BCC, pigmented BCC, BCC with adnexal differentiation, fibroepithelial BCC) and higher risk BCC (sclerosing/morphoeic BCC, infiltrating BCC, micronodular BCC, basosquamous carcinoma, BCC with sarcomatoid differentiation).[2]

MMP-9 immunohistochemical expression was identified by brownish color in the cytoplasm and adjacent stroma. The results of the expression analysis were assessed semiquantitatively using the immunohistochemical staining index (ISI) which was obtained by multiplying the percentage of

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positive cells (PPC) and the staining intensity (SI), where PPC is the percentage of cells stained positively and SI is the staining intensity. The percentage of cells stained positively was assessed by looking at 10 large fields of view (100 times magnification) and taking the average number of the ten large fields of view. To see the intensity of staining on positively stained cells using a strong magnification of 400 times.[11] The PPC score is divided into: 0=no positive cells, 1=>1-10% positive cells, 2=>10%-50% positive cells, and 3=>50% positive cells. The SI score is divided into: 0=not stained, 1=weakly stained, 2=moderately colored, 3=strongly colored. The final expression results by multiplying the cell percentage proportion score and intensity score, and interpreted as follows: Score 0=not expressed, score 1-3=weakly expressed, score 4-6=moderately expressed, and score 9=strongly expressed. Evaluation of MMP-9 expression was assessed semiquantitatively by researchers and 2 pathology specialists blindly.[9]

The data obtained was processed and analyzed using statistical software. Data analysis was performed using the somers'd correlation test. The value of p<0.05 was stated to be statistically significant.

RESULTS

Of the 40 BCC samples, the most BCC ages were the age group 50-59 years old and ≥70 years old, namely 13 cases (32.0%) each, the average age was 63 years old and most were found in women with a total sample of 26 cases (65 ,0%). The most common location was in the middle face in 35 cases (87.5%) and the most tumor size was ≤2 cm in 27 cases (67.5%). The histopathological subtype of BCC in this study was found to be the lower risk subtype, namely nodular BCC in 19 cases (47.5%). Expression of MMP-9 immuno-histochemical stains that appeared in the adjacent cytoplasm and stroma, found weak expression in 15 cases (37.5%) of the lower risk BCC group where the most common subtype in this group was nodular BCC in 11 cases (27.5%) %). In the higher risk histopathological subtype group, the most common BCC was strong expression, totaling 8 cases (20.0%) where infiltrating BCC was the most common subtype, namely 7 cases (17.5%). A significant association was found between the expression of matrix metalloproteinase-9 immuno-histochemistry to the histopathological subtype of basal cell carcinoma with a p-value<0.0001. This shows that the more aggressive the BCC subtype, the stronger the expression of MMP-9.

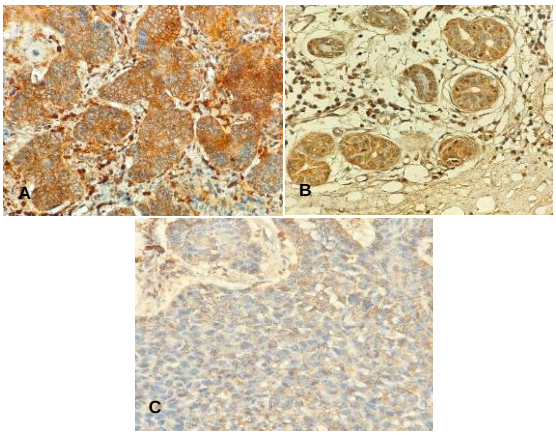

Figure 1. MMP-9 immunohistochemical expression. A. Strong expression (400 times). B. Moderate expression (400 times). C. Weak expression (400 times).

Table 1. Distribution of BCC patients based on age, sex, location, and tumor size, histopathological subtype.

Variable (n=40)	Frequency (f)	Percentage (%)
Age		
30-39 years old	2	5.0
40-49 years old	0	0.0
50-59 years old	13	32.5
60-69 years old	12	30.0
≥70 years old	13	32.5
Gender		
Male	14	35.0
Female	26	65.0
Tumour Location		
Upper face	3	7.5
Middle face	35	87.5
Lower face	2	5.0
Tumour size		
≤2 cm	27	67.5
>2 cm	13	32.5
MMP-9 Expression		
Weak	15	37.5
moderate	14	35.0
Strong	11	27.5

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Table 2. Frequency distribution of matrix metalloproteinase-9 immunohistochemical expression in lower risk and higher risk BCC histopathological subtypes.

Variabel	BCC Subtype						Total f (%)
	Lower Risk BCC*			Higher Risk BCC**			
	Nodular f (%)	Superficial f (%)	Pigmented f (%)	Sclerosing f (%)	Infiltrating f (%)	Micro nodular f (%)	
MMP-9 Expression							
Weak	11 (27.5)	2 (5.0)	2 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	15 (37.5)
Moderate	6 (15.5)	3 (7.5)	0 (0.0)	1 (2.5)	2 (5.0)	2 (5.0)	14 (35.0)
Strong	2 (5.0)	1 (2.5)	0 (0.0)	0 (0.0)	7 (17.5)	1 (2.5)	11 (27.5)

*lower risk BCC: nodular, superfisial, pigmented
**higher risk BCC: sclerosing, infiltrating, mikronodular

Table 3. Correlation between matrix metalloproteinase-9 (MMP-9) immunohistochemical expression and lower risk and higher risk BCC subtypes.

Variabel	BCC Subtype		Total	Value	p*
	Lower Risk BCC f (%)	High Risk BCC f (%)			
MMP-9 Expression					
Weak	15 (37.5)	0 (0.0)	15 (37.5)		
Moderate	9 (22.5)	5 (12.5)	14 (35.0)	0.476	<0.0001
Strong	3 (7.0)	8 (20.0)	11 (27.5)		

*Uji Somers'd

DISCUSSION

In this study, out of 40 samples, the most BCC was found in the age group 50-59 years old and ≥70 years old, namely 13 cases (32.0%) and 13 cases (32.0%) respectively, followed by the 60-69 years old age group with 12 cases (30.0%), and the least in the age group of 30-39 years old, namely 2 cases (5.0%). The mean age of BCC patients in this study was 63 years old with the highest incidence in the fifth to seventh decades of life. This finding is in line with research conducted by Yogiswara, at Sanglah Hospital (2014-2018), out of 39 samples the most found were aged ≥70 years old, namely 13 cases (33.33%), followed by ages 60-69 years old, namely 11 cases (28.21%) and the least, namely the age of 30-39 years old amounted to 1 case (2.56%).[3] Not much different from Demirseren et al's study of 320 BCC patients, the most common was the age group of 40-79 years old with an average age of 62 years old.[10] Research conducted by Wibawa, BCC is most often found at the age of >60 years old. BCC often occurs at an older age and more than half of patients occur between the ages of 50-80 years old.[11,12] Wardhana et al obtained results that were not much different, most cases were found at the group of >50 years old.[12]

Cumulative exposure to sunlight over many years, especially UVB rays, which are the most carcinogenic, can trigger skin cancer through photochemical damage to DNA, injury to DNA repair mechanisms and partial suppression of cell-mediated immunity. Increasing age will cumulatively increase the risk of UV exposure and reduce the capacity and ability to repair DNA damage as well as decrease the efficiency of immune surveillance and DNA repair mechanisms due to the aging process. A decrease in the density of skin melanocytes in old age causes UV penetration into the dermis to become more extensive and cause more extensive damage.[13,14] The damaging effects of sun exposure can start at an early age and results can't be seen in 20-30 years old. Cases of BCC are rare in the young population but there are reported rates of occurrence and increasing incidence in children and young adults. In this study, patients <40 years old were 5%. In line with the studies of Birch-JF, Callens J and Apalla that there is an increased incidence at the age of <40 years old. This is thought to be caused by changes in lifestyle, clothing style, and UV exposure due to outdoor activities without UV protection which increases the incidence rate to 5 times higher for exposure to BCC.[3,15-18]

In this study, BCC was found to be more common in women, namely 26 cases (65.0%), while in men there were 14 cases (35.0%). In line with research conducted by Fonny Josh in Makassar (January 2017-December 2019), it is said that there are more

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BCC incidents in women.[25] Chow et al also reported the same incidence of BCC as our study, which is higher in women. This can happen due to lifestyle changes, differences in behavior in seeking medical care where women tend to be quicker and more concerned so that more cases in women will be recorded. These results are different from what is written in the WHO book and a study conducted by Demirseren et al in 320 BCC patients reported that men generally have a risk of BCC 2 times higher than women. The study conducted by Aandani and Ganatra also reported that the incidence of BCC was dominated by males with a ratio of 1.4: 1.2. Chinem and Miot found that men are more often affected by this cancer than women (1.5-2: 1). This can happen due to the fact that men are more often exposed to sunlight by working outdoors.[10,15,19-21]

BCC is usually found in the head and neck area, especially the eyelids and nose areas which are areas that are often exposed to UV exposure, especially in the elderly, in males who are frequently and intensively exposed to UV exposure throughout their lives.[22] In this study, the most BCC locations were in the midface area with 35 cases (87.5%); namely in the region of the nose, eyelids, cheeks and ears. The rarest location in the upper-face area, such as the forehead, was 3 cases (7.5%). In line with a study conducted by Fonny Josh where the most frequent predilection was in the nasal region (30.6%), which was the midface area and the least common was in the frontotemporal region (2%), namely the upper-face area.[27] Chow et al reported that the nasal was the most frequent predilection then the cheek region which is the midface area.[19-22]

Based on the findings of Demirseren et al, more than half of the cases were found in the nasal (32.3%), orbital (19.1%), and cheek areas (18.1%) which are the most central and prominent parts of all is in the head and neck. And more susceptible to chronic sun exposure too.[12] This is because the BCC in the midface region is prone to perineural spread with high recurrence compared to other places. Aggressive BCC is reported to occur in the midface area. Tumor predilection is critical for the spread of BCC. Tumors in the ala nasi region may spread without symptoms to the perichondria. The periorbital region (canthus) may spread around the ethmoid sinuses resulting in enucleation and death, whereas spread over the tarsal plate involving the conjunctival mucosa may promote recurrence in the eyelids.[23] The pre-auricular region, especially the tragus, is an important area of embryonic fusion, if there is extension to the perichondria, the tumor will be difficult to trace, while the post-auricular sulcus is an area of embryonic fusion where tumors often grow aggressively. Anatomical location is divided based on Baker's classification which divides facial predilection into 3 groups, namely the upper face (upper face), mid face (middle face and ears), and lower face (lower face).[23-24]

From this study, cases of BCC with a tumor size ≤2 cm in diameter were found in 27 cases (67.5%) and >2 cm in 13 cases (32.5%). These results differ from a study conducted by Fonny Josh where the most cases were found in tumors >2 cm in diameter, 38 cases (77.6%) of 49 samples.[19] Similar to the research conducted by Toha SS, 10 samples (52.6%) had a tumor diameter of 2 cm. Tumor size in BCC can play a role in determining metastatic potential. The recurrence rate is approximately 2% for all BCCs (primary and recurrent) <2 cm in diameter and increases to approximately 8% for BCCs >5 cm.[13,19]

The most common histopathological subtype was nodular BCC in 19 cases (47.5%), belonging to the lower risk BCC subtype, and the least was sclerosing BCC in 1 case (2.5%) belonging to the higher risk BCC group. This study is in line with research conducted by Fonny Josh where the most frequent histopathological subtype in their study was the nodular subtype, namely 26 cases (53.1%), the least was the morpheaform subtype, 1 case (2%).[19] This finding is also the same as that reported in the study of Abbas et al where nodular BCC was the most common subtype with 69.11% and the least common subtype was basosquamous with 2.3%. Similar to a study conducted by Darmayani P.R et al, the results showed that the most frequent subtype was nodular BCC in 22 cases (47.8%), and the least was the morpheaform / sclerosing subtype in 1 case (2.2%). In contrast to the research conducted by Nurlela et al at Adam Malik Haj Center General Hospital in Medan (2016), the results showed that the most subtypes were micronodular subtypes, 17 cases (42.5%) and the least basosquamous subtypes, 1 case (2.5%). Based on the literature, the

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histopathologic subtype of nodular BCC is the most common BCC subtype.[2,24,25] In this study we did not find subtypes of BCC with adnexal differentiation, fibroepithelial BCC, baso-squamous BCC, BCC with sarcomatoid differentiation.

Based on the immunohistochemical expression of MMP-9 in the lower risk histopathology group, the most commonly found weakly expressed BCC was 15 cases (37.5%), with nodular BCC subtype being the most common, 11 cases (27.5%). In this study we also found strong expression of MMP-9 in the lower risk histopathological subtype group, namely the nodular BCC and superficial BCC subtypes. This shows that the tumor phenotype is becoming more aggressive than before so that it can increase the recurrence rate. We suspect this is related to a tumor measuring ≥2 cm and the location of the tumor in the middle-face area, where this area is the most susceptible to perineural spread with a high recurrence rate.[24] Further research is needed to see the relationship between MMP-9 expression and tumor size and location in BCC. The highest expression of MMP-9 immunohistochemistry in the higher risk BCC group was strong expression in 8 cases (20.0%) where infiltrating BCC was the most common subtype in 7 cases (17.5%), while weak expression was not found. These results are almost the same as a study conducted by Zlatarova et al where the most expressed MMP-9 was nodular BCC in 29 cases of 49 BCC cases, but with a different intensity of expression, moderate or strong in 82% of cases. BCC significantly related to sun exposure. MMPs, particularly MMP-9, were reported as enzymes shown to be involved in extracellular matrix degradation and tumor invasion, being upregulated in tumor cells and surrounding stroma in varying intensities across all BCC subtypes. [4,26]

After statistical analysis using the Somers'd test, a significant relationship was found between Matrix Metalloproteinase-9 (MMP-9) immunohistochemical expression and BCC histopathological subtype with a value of p=0.0001 (p<0.05). The test results obtained a significant correlation, the direction of the positive correlation where the more aggressive the subtype, the stronger the expression of MMP-9, and vice versa. Anna et al's study stated that MMP-9 expression in nodular BCC was much lower than infiltrative BCC and obtained significant results with a p value <0.001. Infiltrating BCC proved to be more invasive than nodular BCC, suggesting that MMP-9 may be used as a prognostic factor for BCC. Increased MMP-9 expression has been shown to correlate with the clinical stage of BCC and a more aggressive phenotype of this cancer. ECM undergoes constant remodeling catalyzed by proteolytic enzymes, including metalloproteinases. A number of previous studies demonstrated increased expression of MMP-9 in various malignancies, and this enzyme was proposed as a potential cancer marker.[4] Very little research has been done on the relationship between MMP-9 expression and BCC histopathological subtypes, especially in Medan. However, few studies have been conducted on other malignancies. Research conducted by Triastuti et al with the result that there is a perfect fit with a p value <0.001 so that the examination results can be used.[26,27]

CONCLUSION

Skin cancer in Indonesia, especially BCC, the incidence tends to increase. MMP-9 is expected to play an important role in predicting aggressive tumor behavior so that cancer treatment, especially BCC, can make MMP-9 a prognostic factor for recurrence. It is necessary to educate the public about the importance of protecting oneself from exposure to direct sunlight to reduce the incidence of basal cell carcinoma (such as more closed clothing and sunscreen) and to immediately check oneself if any lesions are found on the skin.

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