Ki-67 Expression to Differ Histopathological Variant Basal Cell Carcinoma

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ABSTRACT
Basal cell carcinoma (BCC) is a common skin malignancy in humans. Cancer rarely metastasizes but it is locally destructive and recurrent, particularly an aggressive variant. Various risk factors are associated with the behavior of BCC, leading to DNA damage resulting in an increase in cell proliferation. The proliferation is a key tumor progression as assessed by Ki-67 expression. Previous studies have shown there is a relationship between the proliferation marker Ki-67 and histopathological variants BCC, but it is not clearly understood. Objectives: This study assesses Ki-67 expression in histopathology variants BCC. Methods: The sample using 40 cases consisted of 20 samples of aggressive BCC and 20 samples of non-aggressive BCC. Each sample was stained by immunohistochemical and assessed by Ki-67 proliferation index. Result: This study shows that 90% of aggressive BCC have a positive 2 proliferation index of Ki-67 and 75 % non-aggressive BCC with positive 1 Ki-67 expression. The Ki-67 expression has a significant correlation to histopathological variants of BCC, in which an aggressive variant has higher index proliferation than a non-aggressive variant. Conclusion: Expression of Ki-67 plays a role in different aggressive from non-aggressive BCC.

Keywords: *Varian histopathology of BCC, aggressive BCC, non aggressive BCC, Ki-67, proliferation index.*

1. INTRODUCTION

Basal cell carcinoma (BCC) is a group of malignant cutaneous tumors characterized by the presence of lobules, columns, bands or cords of basaloid cells (germinative cells) [1]. Basal cell carcinoma is the most common malignant cutaneous tumor which occupies approximately 70% of all malignant cutaneous tumors [2].

Basal cell carcinoma is mainly found in the Caucasian race and usually occurs in the elderly, with a male-female ratio of 2: 1,1 [1][3]. From 1960 to 2009, the incidence of BCC in the Caucasian population increased by 3 to 8 percent each year [4]. In the United States, there are 500,000 new cases of BCC in 1996, and increased to 900,000 in 2001 and 1,000,000 in 2005 [5]. The incidence of BCC in Asia is relatively low, such as in Japan (0.131%), Korea (0,048%) and Taiwan (0.015%) [6].

Histopathologic data of Registration Agency Cancer Association of Pathology Indonesia and the Ministry of Health of the Republic of Indonesia in 2011 showed malignant cutaneous tumors as fourth of 10 primary malignant tumors most common in males and sixth of 10 primary malignant tumors most common in women. Histopathologic data of Registration Agency Cancer Association of Pathology Indonesia in 2011 recorded malignant tumors of skin at the top list of 10 most common primary malignant tumors in men and ranked 5th out of 10 most common primary malignant tumors in women. From this data, obtained the highest incidence of malignant tumors of the skin is BCC (49%), followed by squamous cell carcinoma (44%) and melanoma malignum (7%) [7].

Basal cell carcinoma usually grows slowly and rarely metastasize, but it is feared for its ability to local destruction [8][9]. The tumors cause local invasion and recurrence after treatment.[1,10] Recurrence BCC is relatively common in dermatologist practice every day [11]. According to Selim et al.[12] five years recurrence rate is 10%, of which 2/3 of its happening is in the first 3 years after therapy [12].

Histopathologic picture and classification of BCC are important to determine variants. The BCC classification depends on the pattern of growth that can describe the behavior of this tumor and be a prognostic marker of biological temperament and decisive management, as a result, the pattern of growth of BCC must be stated in the pathology report [1][13]. According to WHO 2006, classification consists of eight variants, they are superficial, nodular, micronodular, infiltrating, fibroepithelial, metatypical/basosquamous, BCC with adnexal differentiation, keratotic and five other variants such as cystic, adenoid, infundibulocystic, pigmented, sclerosing/morpheiform [1].

The growth pattern of BCC is divided into high risk/aggressive and was listed on BCC high risk/low risk of aggressive and non-aggressive BCC [14]. Aggressive BCC is high-risk, locally invasive, easy to excise with local recurrence. In histopathological variants micronodular, infiltrating, sclerosing/ morpheiform and metatypical/basosquamous are included in aggressive BCC. Non-aggressive BCC low-risk, non-invasion, with surgical excision gives excellent results and a good prognosis. Non-aggressive BCC consists of nodular, cystic, adenoid, BCC with adnexal differentiation, superficial and pigmented [1][14][15].

Based on histopathological examination, aggressive BCC tends to recur, increasing rapidly in the range of 65% [16]. There is a strong relationship between aggressive BCC and infiltrative into surrounding tissue. Clinically, this will increase morbidity with a poor prognosis [17].

The mechanism of growth and development of BCC is still in long controversy and debate. Various studies of risk factors associated with aggressiveness are intrinsic and extrinsic risk factors. The intrinsic risk factors are genetic, age, race and gender, while extrinsic ones are UV light, ionizing radiation, carcinogenic substances and mechanical trauma to the skin [10]. All these factors lead to DNA damage (Deoxyribose Nucleic Acid) that results in the proliferation of basal cells to cause uncontrolled cell growth and eventually the cell will be a malignant tumor [18].

Cell proliferation is the main key for tumor progression. Ki-67 is one marker of cell proliferation that is easy and can be trusted [12]. Characteristics of Ki-67 is generally expressed in cells that are proliferating and will not be found in cells that are at rest, thus giving clues about the activity of the growth and progression of tumors, therefore it determines prognosis and as the basis for correct therapy [8][19].

Healey et al [20] described the relationship between Ki-67 to cell proliferation and histopathological variants of primary or recurrent BCC. This study shows that primary BCC has a high proliferation rate which is expressed by Ki-67, but there is no correlation between histopathological variants with the expression of Ki-67.20 Selim et al.12 and Khodaeiani et al [21] gained Ki-67 expression is high on aggressive and recurrent BCC [12][21]. In contrast Kramer et al [22] reported there is no strong relationship between the proliferation of cells with the histopathologic aggressive variant [22].

Some researchers have analyzed the prognostic value of Ki-67 and concluded it is important to distinguish the type of malignant tumor cells, but these results are still controversial [19]. The aim of the present study was to examine the relationship between Ki-67 expression and histopathological variant BCC.

2. MATERIALS AND METHODS

In order to answer the reset question we conducted cross sectional comparative study. The population was all cases that have been diagnosed with BCC in Anatomic Pathology laboratories located in West Sumatra from January 2012- December 2014.

The samples were all populations who already met the inclusion criteria. The inclusion criteria were thecase of BCC which has complete data (medical record, slides and paraffin blocks). 40 cases were obtained as samples, respectively 20 cases aggressive and 20 cases of nonaggressive by systematic random sampling.

The BCC case was reviewed by using the WHO classification of 2006. Aggressive BCC's are micronodular, sclerosing/morpheiform, metatypical/ basosquamous, whereas non aggressive BCC's are nodular, cystic, adenoid, BCC with adnexal differentiation, superficial and pigmented.

Paraffin blocks were performed with immunohistochemical staining for Ki-67. Immunohistochemical staining technique using the Ki-67 labeled streptavidin biotin complex method was performed by manual procedures. Primary antibodies used were Ki-67 Dako, Glostrup, Denmark with a 1: 100 dilution. The expression of Ki-67 proliferation index based is negative if the cell nucleus is not stained, and it becomes positive 1 if the cell nucleus stained less than <10% and positive 2 if the cell nucleus stained more than >10% [23].

The data were analyzed with appropriate statistical methods. Univariate analysis, a description of common characteristics and histopathological variants of BCC and the expression of Ki-67. The bivariate analysis using Chi Square statistical test to analyze the relationship between the expression of Ki-67 with histopathological variant BCC.

3. RESULT

Table 1 Overview common characteristic

Characteristic	f (n=40)	%
Sex		
Man	13	32,5
Woman	27	67,5
Age		
21-30 years	0	0
31-40 years	1	2,5
41-50 years	0	0
51-60 years	15	37,5
61-70 years	11	27,5

71-80 years	7	17,5
81-90 years	6	15
≥ 91 years	0	0
Tumor location		
Face	33	82,5
Head & Neck	5	12,5
Body	2	5

In table 1 more female was found (67.5%). The largest age group is 51-70 years (65%) with the youngest of 40 and the oldest 87 years old. Most tumor site are at the face (82.5%).

Table 2 Histopathological variants BCC

Histopathological variant	f (n=20)	%
Aggressive BCC		
Basosquamous	16	80
Morheaform	2	10
Infiltrative	2	10
Non aggressive BCC		
Nodular	13	65
Adenoid	4	20
Pigmented	3	15

Table 2 shows the most aggressive types of variants BCC is basosquamous (80%) and non aggressive is nodular (65%).

Table 3 Relation Ki-67 expression with histopathological variant of BCC

Histopathological variant of BCC	Ki-67 expression		Total	*p*
	Positive 1 f (%)	Positive 2 f (%)		
Aggressive Non Aggressive	2 (10,0) 15 (75,0)	18 (90,0) 5 (25,0)	20 (100,0) 20 (100,0)	0,001
Total	17 (42,5)	23 (57,5)	40 (100,0)	

Table 3 shows aggressive BCC expressing 90% Ki-67 positive 2, while non-aggressive BCC expressed Ki-67 positive 1 (75%). Departing from the statistical test, we found a significant association between the expression of Ki-67 and histopathological variant BCC (p = 0.001). Pictures of Ki-67 positive 1 and 2 can be seen in Figure 1 A and B.

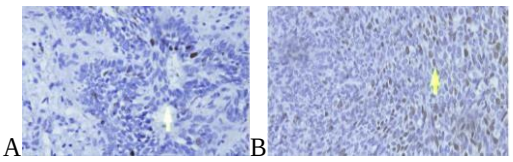

Figure 1. A Ki-67 positive 1. B Ki-67 positive 2

Table 4 The difference of Ki-67 expression with histopathological variants aggressive BCC

Aggressive BCC	Ki-67 expression		Total
	Positive 1 f (%)	Positive 2 f (%)	
Basosquamous	2 (12,5)	14 (87,5)	16 (100,0)
Morpheiform	0 (0,0)	2 (100,0)	2 (100,0)
Infiltrative	0 (0,0)	2 (100,0)	2 (100,0)
Total	2 (10,0)	18 (90,0)	20 (100)

Table 4 shows almost all kinds of variants aggressive BCC expressed Ki-67 positive 2, while positive 1 was found in basosquamous.

Table 5 The Difference of Ki-67 expression with histopathological variant non aggressive BCC

Non aggressive BCC	Ki-67 expression		Total
	Positive 1 f (%)	Positive 2 f (%)	
Nodular	12 (92,3)	1 (7,9)	13 (100,0)
Adenoid	3 (75,0)	1 (25,0)	4 (100,0)
Pigmented	0 (0,0)	3 (100,0)	3 (100,0)
Total	15 (75,0)	5 (25,0)	20 (100,0)

Table 5 shows almost all variants of non aggressive BCC expressed Ki-67 positive 1, except the pigmented variants that have a positive 2 expression of Ki-67.

4. DISCUSSION

This study shows more females with the percentage of 67.5% and 37.5% of men, with a ratio of male and female 1: 1.8. Most age groups were 51-70 years (65%) with the youngest 40 and the oldest 87 years old, the average age of 63.5 years.

The incidence of BCC increased according to age. In some epidemiological studies, only 1-3% BCC was found in patients under the age of 35 years. Basal cell carcinoma is more common in men than women, but gender differences have become less meaningful because of the changes in lifestyle and work, women have some work that used to be done by men. Women are also consulted more often to dermatologists, so when skin disorder occurs, they know it earlier [24].

Rassch et al in Australia there is an increased incidence of BCC because more people are trying to darken the skin (tanning) and use revealing clothes. The use of sunscreen can be trusted to protect the skin from disease caused by UV [25]. According to the American Cancer Society (2015) sunscreen can protect the skin from UV rays, but it has a function just as a sunscreen filter for it cannot inhibit radiation UV [26].

The location of most tumors in this study were the face (82.5%), followed by the head and neck (12.5%) and the body (5%). According to the literature

location of BCC most commonly found on the face and the body rather than extremity [3][27]. Basal cell carcinoma is closely related to UVB radiation so that the face is the area of the body that is most often exposed to the sun and become the most common site of this malignant tumor [13].

In this study, we found the most aggressive type of BCC variant is basosquamous (80%) and non-aggressive is nodular (65%). According to Yah based on the histopathological picture of 103 cases of nodular BCC, variants obtained as much as 54%, followed by successive superficial 16%, 8.7% infiltrative, micronodular 4%, keratotic 3.9%. Adenoids, infundibulocystic, mopheiform and metatypical each as much as 1% [27].

Some studies in Singapore, based on histopathology BCC, have overviewed that 30 cases and most variants are nodular (70%), morpheiform (13,3%), pigmented and infiltrative respectively 6,7% and superficial (3,3%), while in Malaysia it was found they are mostly nodular variant 81.3%, pigmented (14,7%), superficial (4%).28 In Australia, of 7,831 cases of nodular BCC variant is 48.1% at most, followed by 26.2% superficial, infiltrative 14.2%, and pigmented as much of 1.7% [25].

According to BCC histopathology, Pa lembang Yahya et al.[3] found 58 cases and the most variants were nodular in 39 cases (67.2%), superficial in 6 cases (10.3%), infiltrative in 5 cases (8.6%), pigmented in 4 cases (6.9%), metatypical in 3 cases (5.2%) and morpheiform in 1 case (17%) [3]. However, many of the above researchers do not distinguish variants of aggressive and non-aggressive BCC with the same number of samples.

Based on the literature, nodular is the most common variant of BCC as 60-80%, but there has beenno literature or research that can explain this [1] carcinoma of basosquamous/metatypical is a rare formof BCC, ranging from 0.4 to 5%. This variant of BCC behavior endangers the lives of patients but is rarely recognized quickly by the clinician, because the clinical picture is similar to BCC of other variants [29]. Incident basosquamous/metatypical should be higher, but it israrely mentioned in the report due to a lack of understanding of the clinician about this variant andperhaps also because of the lack of a pathologist in that area. It is recommended to clinicians to be more cautious in assessing the clinical picture of BCC, mainlysuspected BCC aggressive as it can help determine prognosis and therapy

Pigmented variants can occur in several variants such as nodular, micronodular, superficial and keratotic. Melanocytes appear scattered among the tumor islands [1]. Recently pigmented variants are still controversial, then, some researchers classify them into aggressive variant BCC and other non-aggressive variants mostly. Therefore, researchers are needed to see the picture of pigmented relationship with aggressiveand non-aggressive variants of BCC [17].

According to Selim et al BCC generally has indolent behavior, although sometimes it can be aggressive and destructive. This behavior is usually associated with this type of variant morpheiform, metatypical/basosquamous and micronodular [12].

In this study, it was found that aggressive BCC was expressing more of positive 2 Ki-67 as much as 90,0%, while non-aggressive BCC was expressing more of positive 1 Ki-67 as much as 75,0%. Statistically,there is a significant relationship between the expressionof Ki-67 and the histopathological variant of BCC with p <0.05.

Ki-67 expression levels was associated with tumor prognosis, metastasis potential and survival rate.[21] Barret et al and Khodaeiani et al stated that aggressive variants generally have a higher proliferation rate compared to non-aggressive, so they concluded that Ki 67 positive can be used as a predictor of prognosis in malignant tumor [21][30]. It was Healey et al who examined the relationship between Ki-67 as proliferation index and variant of histopathological BCC and recurrence BCC. Primary tumors have higher proliferation compared to non-recurrent BCC [20].

This is contrary to the results of Lee et al.[31] andTilli et al.[32] who concluded that there was no significant correlation between Ki-67 and histopathological a variant of BCC [31][32]. These is confirmed by Kramer et al.[22] that there was no real connection between the index of proliferation with histopathological variant of aggressive BCC. A low proliferation index can be found in biologically silent tumors, whereas a high proliferation index was indicated for malignant tumors [22].

Proliferation activity in BCC showed the biological behavior of tumor cells. Basal cell carcinoma is characterized by the high proliferation activity of tumor cells, which can be detected by Ki-67 staining. Differences in biological behavior and progressive BCC are caused by an imbalance between cell proliferation and apoptosis mechanisms of tumor [8][32].

In this study, it appears that the expression of positive 2 Ki-67 was found in aggressive BCC variants namely basosquamous in 14 cases, 2 cases of morpheiform and 2 infiltrative, whereas the positive 1 was only found in 2 cases of basosquamous. The expression of positive 1 Ki-67 can be found in almost all kinds of non-aggressive variants namely nodular BCC with 12 cases, adenoid with 3 cases, 1 case in nodular and adenoids, whereas pigmented variants have all positive 2 expressions of Ki-67 in 3 cases.

Bartos et al found varied Ki-67 expression, 70% in primary lesion 2 and 60% in recurrent lesion 5. There were no cases of absolute negative BCC with Ki- 67 staining. Bartos et al reported that Ki-67 was expressed to be a high in morpheiform, infiltrative and superficial, while Ki-67 was expressed low on the nodular BCC with differentiation adnexa variant [11]. Barret et al.[30] also get high proliferation rate in infiltrative variant, multiple sclerosis and metatypical/basosquamous compared with nodular [30].

Chuprov got the significant relationship between the elevation of the Ki-67 proliferation index with infiltrative variants, while Mateoiu et al gained high Ki-67 expression in the morpheiform/sclerosing compared with nodular and superficial [33][34]. Bathenia et al reported an increase in the expression of hyaluronan, Ki-67 and PCNA as the stromal reaction of infiltrative and superficial compared with nodular. This study proved that an increase in three biological molecules makes an indication of aggressive BCC and can be used in the selection of therapy [35].

In contrast to Correa research et al where nodular, superficial and morpheiform equally express high Ki-67, Kramer et al supported Correa research et al.[8] which suggested that there is no statistically significant correlation between the index of proliferation and histopathological variants [8][22].

There are difficulties in assessing the CPI growth factor of BCC because tumor cell proliferation has irregular and heterogeneous distribution. Besides that BCC has a combination of morphology consistingof a combination of several histopathological variants [11].

Interestingly, the area with a high Ki-67proliferation index often shows sporadic Ki-67 positive cells [32][36]. Some literature found Ki-67 positive cells may exist between the boundaries of the tumor cells or diffuse peripheral spreads along the nests of tumor cells. Many researchers suggest that Ki-67 has different expressions on the type of BCC variants, although the tumor is still in the same variant [32].

Cabral et al distinguished two patterns of Ki67 immunoreactive in the nodular variant of BCC. In the BCC variant nodular with a small-sized tumor, the pattern of cell proliferation is confined to the basal cells in the palisade, while the nodular variant with larger tumor size pattern of proliferation is not only found in the basal membrane, but also throughout the tumor cells. Hypothesis Cabral et al stated this is probably caused by lost tumor differentiation, and some mutations can cause loss of control microarchitecture and cellular proliferation associated with the interaction of tumor cells with stromal surrounding them [36].

Until now, the role of Ki-67 as a prognostic factor is still controversial, some researchers assert that the expression of Ki-67 is an indicator to determine the severity of the disease and can be used as a prognosis parameter [12][33]. Other researchers have concluded that there was no statistically significant difference between the proliferation cells of BCC with prognosis and proliferation index of Ki-67 [8][19][36]. The results support previous literature that there is a relationship between Ki-67 expression and histopathological variant BCC

5. CONCLUSION

This study shows that the Ki-67 expression has a significant relationship with histopathological variant in which the aggressive variant expresses higher Ki-67 than non aggressive one.

AUTHORS' CONTRIBUTIONS

Conceptualizacion S.Y, P.M, M.Z.O And H.N. Methodology S.Y and P.M, Writing-Review and Editing M.Z.O and H.N

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