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Correlation of Ki-67 Expression as Tumor cell Proliferation Activity Marker with Cutaneous Squamous Cell Carcinoma Grading

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Abstract

Cutaneous Squamous Cell Carcinoma (cSCC) is a malignant keratinocyte tumour that develops through the suprabasal epidermis. This malignant tumour is the second most common skin malignancy after Basal Cell Carcinoma (BCC). The increased incidence of cSCC is directly proportional to increasing age. Generally, the predisposing factor of cSCC is exposure to recurrent sunlight for a long time, so localisation of cSCC is a part of the body that often exposed to direct sunlight, such as the forehead, face, ears, scalp, neck, and back of the hand. The carcinogenesis process of cSCC is a cumulation of a series of events, one of which plays an important role is the proliferation index assessed by Ki-67. Forty-eight tissue paraffin blocks were diagnosed histopathologically as cutaneous squamous cell carcinoma from the Anatomical Pathology Laboratory of the Faculty of Medicine, Universitas Sumatera Utara and the Anatomical Pathology Unit of Haji Adam Malik General Hospital Medan, as the research sample. The results of protein expression from Ki-67 were assessed based on area. There was no significant correlation between cSCC grading and Ki-67 expression ($p > 0.05$). Ki-67 antigen tumour marker, widely used to determine the level of tumour cell proliferation.

Introduction

Cutaneous Squamous Cell Carcinoma (cSCC) is a malignant keratinocyte tumour that develops through the suprabasal epidermis [1]. This malignant tumour is the second most common skin malignancy after Basal Cell Carcinoma (BCC), with an amount of 20% of all malignancy in the skin. The American Cancer Society noted a comparison between cSCC and BCC of 1:3 [2]. It was in line with the data on the number of cases at the Polyclinic of Department of Dermatology and Venereology at the Dr Cipto Mangunkusumo, Central General Hospital, Jakarta, who reported the number of cases of BCC as many as 261 cases and followed by 69 cases of cSCC in 2000-2009. However, epidemiological data from the Dharmais Cancer Hospital during 2005-2007 noted that the most common skin cancer was cSCC followed by BCC [3]. The research conducted by Edi Kerina at the Haji Adam Malik General Hospital, Medan in 2012-2015 also placed cSCC as the most common type of skin malignancy above BCC with 59 cases of cSCC, while the number of BCC cases was only 29 cases [4]. The increasing incidence of cSCC is directly proportional to increasing age [2]. In general, a predisposing factor for cSCC is repeated sun exposure over a long period in the older age group. People with cSCC with a younger age usually have a brown skin colour. The impact of race on the incidence of cSCC appears to be at a less frequent incidence rate in black groups [5].

Sun exposure predisposes to cSCC, so localisation of cSCC is the part of the body most often exposed to direct sunlight, such as the forehead, face, ears, scalp, neck, and back of the hand. Other locations that also often experience malignant transformation from keratinocytes are the lower lip vermilion [5].

The process of carcinogenesis to become cutaneous squamous cell carcinoma is the cumulation of a series of events in a cell which then undergoes malignant transformation. Each stage of the event primarily influenced by various factors, both genetic, environmental, and food patterns [6].

One of a series of events in a cell that plays an important role in the carcinogenesis process is a cell proliferation index that can be assessed by Ki-67. Ki-67 expression is associated with the proliferative activity of intrinsic cell populations of malignant tumours, thus allowing the use of these markers in evaluating tumour aggressiveness [7].

This study aims to assess tumour cell proliferation in cutaneous squamous cell carcinoma through Ki-67 expression. Therefore, the researchers were interested in investigating the level of cell proliferation (Ki-67 proliferation index) in Squamous Cell Carcinoma using histopathological tissue preparations obtained from biopsy or excision that were fixed with formalin and planted in paraffin blocks.

Material and Methods

This study is a descriptive-analytic study with a cross-sectional design which aims to assess tumour cell proliferation in cutaneous Squamous Cell Carcinoma through Ki-67 expression.

This research was conducted at the Anatomical Pathology Laboratory of the Faculty of Medicine, Universitas of Sumatera Utara and the Anatomical Pathology Unit of Haji Adam Malik General Hospital Medan. This research is conducted for 16 months, starting from June 2017 to October 2018, which includes library studies, data collection, data processing and writing research reports.

Samples size in this study were calculated based on the sample formula for testing hypotheses in one population. Calculations are carried out using a confidence level of 95% and 80% power. Based on the formula, the samples size of at least 47 was found.

The sample in this study were 48 tissue paraffin blocks diagnosed histopathologically as cutaneous squamous cell carcinoma that met the inclusion criteria. Sampling is done using consecutive sampling technique.

Product data marker Ki-67 antibody biology option listed in the core with clone MIB-1; Monoclonal antibodies; Dako and dilution of 1:300. Ki-67 are proliferating cell nuclear antigen (PCNA) that indirectly may reflect the proliferation of tumour cells. Ki-67 expression assessment using the method semiquantitative.

The percentage of tumor cells at all stained: - Score 0 = ≤ 5% positive cells; - Score 1 = 6-25% positive cells; - Score 2 = 26-50% positive cells; - Score 3 = 51-75% positive cells; - Score 4 = > 76% positive cells.

We examine the complete clinical data needed. Re-reading of all slides from skin tissue was diagnosed as cSCC with Hematoxylin Eosin staining by two pathologists together with the researcher to determine the variance and histology grade. Then the serial slides of paraffin blocks were repeated in three slides to proceed with each examination with Ki-67 immunohistochemical staining.

Results

The expression of protein from Ki-67 was considered broad-based. There was no significant correlation between cSCC grading and Ki-67 expression ($p > 0.05$)

Table 1: Correlation Cutaneous Squamous Cell Carcinoma Grading with Ki-67

No	Grading	Ki-67			P
		Median	Mean	SD	
1	Well Differentiated	2	33.4	43.1	
2	Moderately Differentiated	85.5	61.8	42.4	0.167
3	Poorly Differentiated	50	53.8	37.6	

Discussion

Histopathological examination is still the primary support in establishing the diagnosis of cSCC in addition to holding on to the clinical picture. Histopathologically the cSCC found the irregular mass of epidermal cells that had proliferated and invaded the dermis layer. Cell proliferation rates at cSCC can be a consideration in determining cSCC differentiation so that it can establish grading from cSCC used to develop appropriate prognosis and management. It's also found in a study that states that cells from the outer layer of cSCCtumor mass will continue to proliferate. In contrast, cells in the layer of tumour mass will experience differentiation [8].

As a tumour marker, the Ki-67 antigen has been widely used to determine the level of

proliferation of tumor cells which were most commonly used in breast tumors. The Ki-67 antigen encodes two isoform proteins with molecular weights 345 and 395 kDa initially identified by Scholzer and Gerden in the early 1980s. This protein appears in all active phases of the cell cycle, namely G1, S, G2, and M, but does not appear in the G0 phase [9], [10]. Ki-67 is at a low level in the G1 and S phases and reaches a peak at the beginning of the mitotic phase, but in the next phase of mitosis (i.e., during anaphase and telophase), there is a decrease in Ki-67 levels. The amount of Ki-67 that appears in the cell cycle will be governed by the right balance between synthesis and degradation which is characterised by a short Ki-67 half-life, i.e., 1-1.5 hours. The Ki-67 expression is associated with the proliferative activity of intrinsic cell populations of malignant tumours, thus allowing the use of these markers in assessing tumour aggressiveness [7].

Marinescu et al., (2015) found that the highest expression of Ki-67 was found in low differentiated cSCC, after conducting p53, p16, and Ki-67 Immunoexpression studies on cutaneous squamous cell carcinoma and precursor lesions [11]. Referring to tumour grading currently used than conventionally, cSCC is divided subjectively into three histological degrees based on nucleus atypia and tumour-formed keratinisation [5], namely cSCC well-differentiated, cSCC moderately differentiated, and cSCCpoorly differentiated, so in this study, the highest Ki-67 expression was found in cSCC with poor differentiation. Accordance with Marinescu et al., (2015) who found that the highest Ki-67 expression was found cSCC with poorly differentiated [11].

In conclusion, the expression of tumour marker activity, Ki-67, found no significant correlation in establishing cSCC grading.

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