Histopathological study on basal cell carcinoma and squamous cell carcinoma of the skin

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Abstrak

Penelitian kanker kulit Indonesia - Jepang dilaksanakan untuk menelaah faktor risiko dan karakteristik gambaran klinikopatologi pada orang Indonesia dan Jepang. Pada penelitian ini, dilakukan analisa gambaran histopatologik tumor ganas kulit non-melanoma yaitu karsinoma sel basal (KSB) dan karsinoma sel skuamosa (KSS) pada penderita di Indonesia. Menyadari bahwa radiasi sinar ultraviolet (UV) memegang peranan pada terjadinya kanker kulit non-melonoma, dicari hubungan antara gambaran histopatologik dengan lokasi tumor, yang berhubungan dengan daerah yang terpajan sinar matahari. Pada umumnya, ukuran tumor penderita di Indonesia lebih besar dari pada di Jepang. Karena itu dalam penelitian ini ditinjau pula hubungan antara besar tumor dengan gambaran histopatologik. Selama tahun 1996 sampai 1998 dikumpulkan 40 kasus karsinoma sel basal dan 16 kasus karsinoma sel skuamosa. Berdasarkan diferensiasi sel, dari 40 kasus karsinoma sel basal, 28 kasus dari jenis solid, 5 kasus jenis adenoid, 2 kasus jenis keratotik dan 5 kasus jenis campuran (solid-adenoid atau keratotik-adenoid). Dari 16 kasus karsinoma sel skuamosa, 12 kasus merupakan derajat I (berdiferensiasi baik) dan sisanya 4 kasus dengan derajat II (berdiferensiasi sedang). Karena dari 40 kasus, 39 diantaranya terdapat pada daerah yang terpajan matahari, maka perbandingan antara jenis histopatologik dengan perbedaan lokasi tumor berdasarkan pajanan sinar matahari tidak dapat dinilai. Dari 16 kasus karsinoma sel skuamosa, 9 kasus terdapat pada daerah yang terpajan sinar matahari, 7 kasus lainnya pada daerah yang terlindung dari sinar matahari. Tidak terdapat perbedaan yang nyata yang dapat dibuktikan dengan jumlah kasus yang terbatas ini. Berdasarkan ukuran tumor dari 40 kasus karsinoma sel basal, 9 kasus berdiameter 1 cm atau kurang (KSB kecil) dan 31 kasus berdiameter lebih dari 1 cm (KSB besar). 13 kasus diantara KSB besar ini menunjukkan tipe pertumbuhan infiltratif dengan seklerosis. Agaknya karsinoma sel basal dengan ukuran besar sering berhubungan dengan sifat pertumbuhan infiltratif dengan seklerosis. Diantara 16 kasus karsinoma sel skuamosa, 7 kasus berdiameter 1 cm atau kurang (KSS kecil) dan 9 lainnya berdiameter lebih dari 1 cm (KSS besar). Ke dua jenis ini tidak menunjukkan perbedaan tingkat diferensiasi sel yang jelas. Pengaruh sinar ultraviolet pada perubahan patologik kanker kulit non-melanoma akan diteliti lebih lanjut dengan menggunakan jumlah kasus yang lebih banyak.

Abstract

A collaborative study on skin cancer has been conducted to analyze the risk factors and clinico-pathological characteristics of skin cancers among both the Indonesian and the Japanese. In this study, we have analyzed the histopathological features of non-melanoma skin cancer (NMSC), basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of Indonesian patients. Considering the fact that ultraviolet light (UV) radiation is the major cause of NMSC, we focus on studying the relationship between the histopathological finding and the location of the tumors, whether they were developed on sun-exposed sites or sun-protected sites. In addition, because it has been revealed that the size of NMSC in Indonesian was larger than those in Japanese, we also attempted to find the relationship between the tumor size of NMSC and the pathological characteristics. From period of 1996 to 1998, we could analyze the histopathological features in 40 cases of BCC and 16 cases of SCC. Among BCC, the pathological typing according to the differentiation revealed that 28 cases were solid, 5 cases were adenoid, 2 cases were keratotic and the remaining 5 cases were mixed type (solid-adenoid or keratotic-adenoid). Among SCC, 16 cases were classified as well-differentiated type in 12 cases and moderate-differentiated type in 4 cases. Since 39 of 40 cases of BCC developed on sun-exposed sites, the comparison of pathological findings in relation to the effect of UV-exposure was not possible. Of 16 SCC, 9 cases were from sun-exposed sites (face and arm) and 7 cases were from sun-protected sites. No clear difference of pathological findings between SCC on sun-exposed sites and SCC on sun-protected was found. Of 40 cases of BCC, 9 cases were 1 cm or less in diameter (small BCC) and 31 cases were more than 1 cm (large BCC). Large BCC included 13 cases sclerosing infiltrative type. It seems that large sized BCC were frequently associated with

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sclerosing infiltrative type pathologically. The effect of UV on pathological changes in NMSC will be further examined using a higher number of cases. Of 16 cases of SCC, 7 cases were 1 cm or less in diameter (small SCC) and 9 cases were more than 1 cm (large SCC). There was no difference in differentiation of the cells between small SCC and large SCC.

Keywords: *skin cancer, basal cell carcinoma, squamous cell carcinoma, histopathological type*

In Indonesia, according to a nearly nation-wide data collected from 13 Pathology Laboratories by the National Cancer Registry, the non-melanoma skin cancer (NMSC) ranked the first among males and the fourth among females in 1988 until 1992.[1] The incidence of NMSC in 1988-1989 was obtained based on a population-based cancer registry in Semarang, Middle Java. It ranked second among males (6.62 per 100,000) and third among females (16.54 per 100,000).[2] Histologically, BCC and SCC were the most common types. Many studies, including ours, showed that ultraviolet light (UV) is an important factor in the carcinogenesis of NMSC due to mutagenic effect on cells and imunosuppresive effect on host.[3]

The collaborative study on skin cancer has been conducted to analyze the risk factors and clinico-pathological characteristics of skin cancer of both the Indonesian and the Japanese. This study has revealed that the amount of UV exposure was fairly high in Indonesia compared to that in Japan.[4] Taken together, it is postulated that UV exposure might also be crucial for skin cancer development among the Indonesian. As a matter of fact, the size of NMSC of Indonesian's are often larger compared with those of Japanese.

In this study, we analyzed the histopathological features of NMSC in Indonesian, i.e. 40 cases of BCC and 16 cases of SCC, by focusing on unveiling the relationships of pathological findings, the sites of tumor (sun-exposed vs. sun-protected) and tumor size.

MATERIALS AND METHODS

During the period of 1996 to 1998, we observed 40 cases of BCC and 16 cases of SCC. Formalin-fixed, paraffin-embedded tissues were sectioned and stained with hematoxylin-eosin.

Microscopic examination for squamous cell carcinoma included the description of the type of cells and grading of malignancy.[5]

Grade I : *well differentiated (mild anaplasia, pearl formation and intercellular bridges)*

Grade II : *moderately differentiated (pearl formation and individual cell keranitization)*

Grade III : *poorly differentiated (severe anaplasia and a few individual cell keratinization)*

Grade IV : *undifferentiated (severe anaplasia and no individual cell keratinization)*

The diagnosis of basal cell carcinoma was confirmed by describing the differentiation of the cell and growth pattern of the tumor. According to the differentiation of the cells, the tumor was classified into solid type if it was undifferentiated, adenoid type if it was differentiated toward ecrine gland, cystic type if it was differentiated to sebaceous gland, and keratotic type if it was differentiated to hair folicle.

The nature of growth in relation to the possibility of recurrence after the excision was also described, namely nodular, nodular with invasive feature in the peripheral area, infiltrative sclerosing, infiltrative non-sclerosing, and multifocal type.[6] We have to describe whether the margin of the operation was free from the tumor cells or not.

RESULTS

Forty cases of BCC were analyzed in this study, 18 were males and 22 were females. The results of the histopathological analyzes are given in Table 1.

Classification according to differentiation pattern showed that 28 cases (70%) were solid type, 2 cases were keratotic type (5%), 5 cases were adenoid type (12.5%) and 5 cases were mixed type (12.5%).

There was no significant difference of tumor types of BCC between males and females, and between the young and the old cases.

The growth type of BCC (Table 2) was classified as follows: 8 cases of nodular, 4 cases of nodular infiltrative, 14 cases of sclerosing infiltrative, 11 cases of non-sclerosing infiltrative and 3 cases of multifocal types. No difference was found between males and females and between the young and the old groups.

The location of BCC and the type of tumor according to differentiation are shown in Table 3. Since almost all of the cases developed on sun-exposed sites, characteristics of pathological features related to the UV-exposure was not determined.

When BCC was divided into small BCC (diameter less than 1 cm) and large BCC, 9 cases were small BCC and 31 cases were large BCC (Table 4).

Table 1. Distribution of Basal Cell Carcinoma according to histological type in relation to sex and age

Histological Type	Sex		Age (year)										Total
			30-39		40-49		50-59		60-69		70-79		
	M	F	M	F	M	F	M	F	M	F	M	F	
Solid	12	16	2	-	4	2	2	6	2	7	2	1	28 (70%)
Cystic	-	-	-	-	-	-	-	-	-	-	-	-	0 (0%)
Keratotic	2	-	-	-	1	-	-	-	1	-	-	-	2 (5%)
Adenoid	2	3	-	-	-	-	-	1	1	1	1	1	5 (12.5%)
Mixed	2	3	-	-	1	-	1	1	-	1	-	1	5 (12.5%)
Total	18	22	2	0	6	2	3	8	4	9	3	3	40
%	(45)	(55)	(5)	(0)	(15)	(5)	(7.5)	(22.5)	(10)	(20)	(7.5)	(7.5)	(100)

Table 2. Distribution of Basal Cell Carcinoma according to growth pattern in relation to sex and age

Growth Pattern	Sex		Age (year)										Total
			30-39		40-49		50-59		60-69		70-79		
	M	F	M	F	M	F	M	F	M	F	M	F	
Nodular	3	5	-	-	2	-	1	1	-	1	-	3	8 (20%)
Nodular Infiltrative	2	2	-	-	-	-	-	1	2	1	-	-	4 (10%)
Sclerosing Infiltrative	5	9	2	-	1	1	-	5	1	3	1	-	14 (35%)
Non-sclerosing Infiltrative	5	6	-	-	-	1	2	1	1	4	2	-	11 (27.5%)
Multifocal	3	-	-	-	3	-	-	-	-	-	-	-	3 (7.5%)
Total	18	22	2	0	6	2	3	8	4	9	3	3	40
%	(45)	(55)	(5)	(0)	(15)	(5)	(7.5)	(22.5)	(10)	(20)	(7.5)	(7.5)	(100)

Table 3. Distribution of Basal Cell Carcinoma according to location and histological type

Location	**Histological type**					**Total**
	Solid	**Adenoid**	**Keratotic**	**Cystic**	**Mixed**	
Eyelid	4	-	-	-	-	**4**
Other part of the face	23	5	2	0	5	**35**
Palm	1	-	-	-	-	**1**

Table 4. Basal Cell Carcinoma growth pattern in relation to its size

Growth Pattern	**Size (cm)**			**Total**
	1 or less	**> 1- 5**	**more than 5**	
Nodular	3	4	1	8
Nodular Inf.	1	3	-	4
Sclerosing Inf.	1	12	1	14
Non-sclerosing Inf.	3	8	-	11
Multifocal	1	1	1	3
Total	**9**	**28**	**3**	**40**
%	**(22.5)**	**(70)**	**(7.5)**	**(100)**

Large BCC consisted of 5 cases of nodular type, 3 cases of nodular infiltrative type, 13 cases of sclerosing infiltrative type, 8 cases of non-sclerosing infiltrative type, and 2 cases of multifocal type.

In contrast, small BCC consisted of 3 cases of nodular type, 1 case of nodular sclerosing type, 1 case of sclerosing infiltrative type, 3 cases of non-sclerosing infiltrative type, and 1 case of multifocal type.

The relationship between age, sex and the pathological types of SCC are shown in Table 5. Among the 16 cases, 12 cases were well-differentiated type (grade I) and 4 cases were moderate-differentiated type (grade II).

In respect to the sun exposure, 9 cases were from sun-exposed sites and 7 cases were from sun-protected sites (Table 6). No pathological differences were found between SCC from sun-exposed sites and those from sun-protected sites.

When the cases of SCC were divided into small SCC (less than 1 cm in diameter) and large SCC (more than 1 cm), there was no difference in differentiation of the cells between small SCC and large SCC (Table 7).

Table 5. Distribution of Squamous Cell Carcinoma according to histological grading in relation to sex and age

Grade	Age (year)																Total
	sex		20-29		30-39		40-49		50-59		60-69		70-79		80-89		
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	
Grade I	6	6	-	1	-	-	-	-	1	1	3	2	2	1	-	1	12 (75%)
Grade II	1	3	-	-	-	1	-	-	-	-	1	-	-	1	-	1	4 (25%)
Grade III	0	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Grade IV	0	0	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Total (%)	7 43.75	9 56.25	0 (0)	1 (6.25)	0 (0)	1 (6.25)	0 (0)	0 (0)	1 (6.25)	1 (6.25)	4 (25.0)	2 (12.5)	2 (12.5)	2 (12.5)	0 (0)	2 (12.5)	16 (100)

Table 6. Distribution of Squamous Cell Carcinoma according to location and histological grading

Location	**Histological grading**				**Total**
	Grade I	**Grade II**	**Grade III**	**Grade IV**	
Face	4	3	0	0	**7**
Arm	2	0	0	0	**2**
Foot	1	1	0	0	**2**
Trunk	3	0	0	0	**3**
Penis	1	0	0	0	**1**
Leg	1	0	0	0	**1**

Table 7. Distribution of Squamous Cell Carcinoma according to histological grading and size

Grade	**Size (cm)**			**Total**
	1 or less	**> 1- 5**	**more than 5**	
Grade I	6	3	3	12 (75%)
Grade II	1	2	1	4 (25%)
Grade III	-	-	-	-
Grade IV	-	-	-	-
Total	**7**	**5**	**4**	**16**
%	**(43.75)**	**(31.25)**	**(25.00)**	**(100)**

DISCUSSION

Basal cell carcinoma is locally invasive, slowly spreading tumor which rarely metastasize. Histopatologically, the characteristic cell of the basal cell carcinoma, have a large, oval or elongated nucleus and relatively little cytoplasm. For a long time, basal cell carcinoma has been considered to be developed from basal cell of epidermis, but nowadays, it has been suggested that basal cell carcinoma might be developed from a more pluripotent stem cell.

According to the differentiation of cells, BCC is divided into solid type if it is undifferentiated, adenoid type if it is differentiated toward ecrine gland, cystic type, with differentiation to sebaceous gland, and keratotic type if it is differentiated to area of keratinization like the hair follicle. Formerly, this classification was believed to be a good criteria for predicting the prognosis of the tumor, since usually there is correlation between the grade of malignancy and the differentiation of tumor cells, as seen in other malignancies.

Recently, classification of basal cell carcinoma according to the growth pattern has been considered to be more correlated to the aggressiveness of the tumor and is potential to recurrence.

Squamous cell carcinoma may show considerable variation. The cells usually show grade variation in size. Variants of squamous cell carcinoma are adenoid squamous cell carcinoma and spindle cell type squamous cell carcinoma.
Brodérs has divided squamous cell carcinoma using the percentage of the undifferentiated cells into grade I, II, III and IV. However, it is not easy to count the cells, so in later publication the criteria was modified.

Sun-exposure is a crucial carcinogen of NMSC. CC to TT mutations and C to T mutations at dipyrimidine sites are frequently observed in p53 tumor suppressor gene of NMSC developed on sun-exposed sites.[7]

In the current study, we attempted to analyze the pathological characteristics of BCC and SCC, in relation to the effect of sun-exposure. In previous report, adenoid type (pseudoglandular, acantholytic type) of SCC has been suggested to be associated with sun-exposure.[5] However, we did not find this type of SCC in this study.

Our data showed that sclerosing infiltrative type of BCC was frequently found in large BCC. This is consistent with the previous study that showed that the sclerosing infiltrative type of BCC was more aggressive as measured by the high number of AgNOR and PCNA positivity.[8, 9]

Larger number of the cases of NMSC will be necessary for evaluating the histopathological characteristics associated with UV exposure. In addition to morphological analysis on HE stained section, study on p53 or Ki67 by immunohistochemistry may help to distinguish the difference in relation to uv-induced molecular changes.

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