

Non-Melanoma Skin Cancer in Ha'il Region in the Kingdom of Saudi Arabia: A Clinicopathological Study

Laila Seada, Nouf Al Gharbi, Shaimaa Dawa

Abstract—Although skin cancers are prevalent worldwide, it is uncommon in Ha'il region in the Kingdom of Saudi Arabia, mostly non-melanoma sub-type. During a 4-year period from 2014 to 2017, out of a total of 120 cases of skin lesions, 29 non-melanoma cancers were retrieved from histopathology files obtained from King Khalid Hospital. As part of the study, all cases of skin cancer diagnosed during 2014 -2017 have been revised and the clinicopathological data recorded. The results show that Basal cell carcinoma (BCC) was the most common neoplasm (36%), followed by cutaneous lymphomas (mostly mycosis fungoides 25%), squamous cell carcinoma (SCC) (21%) and dermatofibrosarcoma protuberans (DFSP) (11%). Only one case of metastatic carcinoma was recorded. BCC nodular type was the most prevalent, with a mean age 57.6 years and mean size 2.73 cm. SCC was mostly grade 2, with mean size 1.9 cm and an older mean age of 72.3 cm. Increased size of lesion positively correlated with older age ($p = 0.001$). Non-melanoma skin cancer in Ha'il region is not frequently encountered. BCC is the most frequent followed by cutaneous T-cell lymphomas and SCC. The findings in this study were in accordance with other parts of, but much lower than other parts of the world.

Keywords—Non melanoma skin cancer, Hail Region, histopathology, BCC.

I. INTRODUCTION

NON melanoma skin cancers (NMSC) are considered the most common malignancies in human beings. According to the American Cancer Society, more than 1 million new basal and SCC of the skin have been reported in 2008 in the United States. BCC and SCC represent approximately 80% and 20% of non-melanoma skin cancer, respectively [1].

Development of NMSC is considered to be a result of several factors including genetic, phenotypic and environmental. Exposure to ultraviolet (UV) light is an established risk factor with a known increase incidence in environments with extreme sun exposure, lower incidence in dark-skinned individuals and occurrence of most neoplasms in sun-exposed areas. Moreover, chronic exposure to UV rays was mostly associated to development of SCC, while discontinuous exposure being related to BCC development. Neuroendocrine factors as well as psychological stress have been also been attributed to development of this type of cancer [2]-[4].

Approximately 90% of BCCs occur on sun-exposed areas such as the face, neck, ears, scalp, and arms where the nose

being the most common site. For SCCs, head or neck, back, forearms, and dorsum of the hand are the commonest sites [5].

Typical BCC appears as a slowly growing, shiny, skin-colored to pink translucent papules with telangiectasia and a "pearly" rolled border. Clinically, SCC looks as discrete scaly erythematous papule on an indurated base on normal-appearing skin or on an actinic keratosis [6].

Type of treatment in NMSC depends on the risk stratification of the tumor, patient preference or suitability, and availability of local services. However, High-risk tumors have greater risk of recurrence and require more aggressive treatment. High risk NMSC management is through micrographic surgery (MMS) whenever available. The other alternative is an excision, with a wide safety margin or even radiotherapy [7].

II. MATERIAL AND METHODS

Cases of non-melanoma skin cancer have been retrieved from histopathology files of King Khalid Hospital, Ha'il, in the Kingdom of Saudi Arabia, during the years 2013-2017. Clinicopathological data for each patient were recorded whenever available. For each patient age, gender, localization of tumor, morphological subtype, histopathological diagnosis, grade and ulceration were recorded. We divided BCCs into four subtypes as follows: pigmented, nodular, adenoid and mixed [8]. Grades of SCC have been divided into grade 1 (well differentiated tumors), grade 2 (moderately differentiated tumors), grade 3 (poorly differentiated tumors), and grade 4 (anaplastic or undifferentiated tumors), based on the classification of the College of American Pathologists (CAP) and the TNM Classification of Malignant Tumor's (International Union Against Cancer 2009) [9].

All specimens were formalin-fixed and paraffin embedded. Conventional H&E was used to diagnose all cases. Antibody against CD34 was used to confirm cases of DFSP. Immunostainings for CD3, CD4, CD20 and Ki-67 antibodies were used to confirm Mycosis Fungoides and B-cell lymphoma.

III. STATISTICAL ANALYSIS

Microsoft Excel and an IBM SPSS 23 were used to calculate and compare variants. A p -value < 0.05 was considered significant.

IV. RESULTS

A total of 29 cases of non-melanoma skin cancer were studied during a 4-year period, which were 28 primary and one metastatic skin carcinoma. BCC was observed in 10 (35.7%), SCC in six (21.4%) patients, mycosis fungoides (MF) in seven (25%), DFSP in four (10.7 %), B-cell lymphoma, chronic lymphocytic leukemia (B-CLL) in one (3.6%) and one metastatic skin cancer (3.6%) (Fig. 2).

BCC was the most common skin tumor and constituted 10/28 (35.7%) of all primary cases studied (Fig. 1). Seven males were affected and three females (M:F ratio: 2.3:1). Mean age was 57.6 years (range: 29-57 years).

Localization of BCC was on the face (cheek and nasolabial folds) in eight (80%) while two cases were located in the back and flanks (Fig. 1). Mean size in centimeters was 2.73 cm, while the largest lesion measured 7 cm in its greatest diameter and was located in the flanks, while the smallest was 0.8 cm and located on the face. The nodular type predominated in all cases, being adenoid in three cases and pigmented in two other cases (Fig. 2). Ulceration was the presenting symptom in seven (70%) of the cases, while in three cases there was only a

nodular, solid mass. Stroma showed a variable lymphoid infiltrate being moderate in 60% of cases, mild in 20% and pseudo myxoid in one case. One case showed marked necrosis (Table II). Surgical margins were free in 70% of cases, while in 30% of cases the margin was involved (Table I).

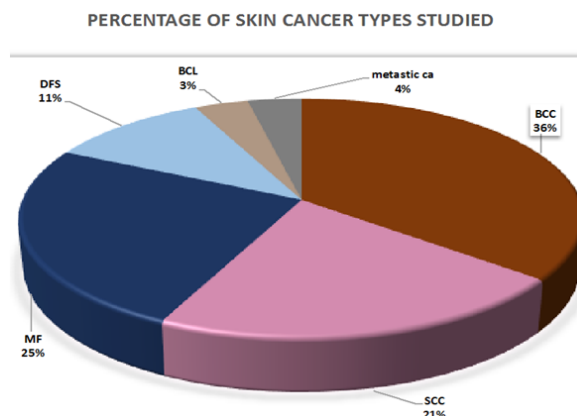


Fig. 1 Types of Skin Cancer Studied

TABLE I
CLINICOPATHOLOGICAL FEATURES OF 28 PRIMARY SKIN CANCER STUDIED

No.	type	age	gender	site	Size in cm	Subtype/grade	ulcer	stroma	margins
1	BCC	49	M	face	5.5	Nodular/solid	absent	necrosis	Free
2	BCC	60	M	scalp	2	Nod/adenoid	present	Pseudo myxoid	Free
3	BCC	60	M	face	1	Nodular/solid	Present	Lymphoid(mod)	positive
4	BCC	49	M	back	2	Nodular/solid	present	Lymph/mild	Positive
5	BCC	29	F	face	0.8	Nodular/pigmented	present	Lymph/mod	Free
6	BCC	64	F	cheek	2	Nodular/solid	present	Lymph/mod	Free
7	BCC	53	M	Nasolabial.	1.5	Nodular/solid	absent	mild	positive
8	BCC	74	F	cheek	1.5	Nodular/pigmented	absent	mod	Free
9	BCC	65	M	flank	7	Nodular/adenoid	present	mod	Free
10	BCC	73	M	Face nevus	4	Nodular/adenoid	present	Lymph/++	free
11	SCC	67	M	big toe	2	2	present	Necr/lymph	Free
12	SCC	39	M	neck	5	2	present	Necrotic	positive
13	SCC	82	M	hip	1	2	present	Lymph/++	Positive
14	SCC	80	F	cheek	0.8	3	present	Lymph/+++	free
15	SCC	87	M	cheek	1	2	absent	+++	Near
16	SCC	79	M	forehead	1.5	1	-ve	+++	+ve
17	DFSP	30	F	scar	3	-	-	spindle	+ve
18	DFSP	27	M	shoulder	4	-	-	spindle	+ve
19	DFSP	39	M	back	3	-	-	spindle	+ve
20	DFSP	30	F	scar	3	-	-	spindle	+ve
21	B-CLL/Richter B=immunoblastic	63	M	face	1	High grade B	-	-	-
22	MF	54	F	skin	0.3	Low grade T	-	-	-
23	MF	10	M	skin	0.2	Low grade T	-	-	-
24	MF	21	F	skin	0.3	Low grade T	-	-	-
25	MF	24	F	skin	0.4	Low grade T	-	-	-
26	MF	60	M	skin	0.5	Low grade T	-	-	-
27	MF	36	M	skin	0.4	Low grade T	-	-	-
28	MF	54	F	skin	0.5	Low grade T	-	-	-

Age

Mean age of all patients was 53.9 ± 20.4 (range: 11-87) years. Mean ages of the cases diagnosed as BCC, SCC, MF and DFSP were 58.1 ± 13.2 and 72.8 ± 17.2 , 37.7 ± 19.1 and

32.0 ± 6.2 years, respectively. The median age detected in men for BCC was 60 years, and in women was 65 years. For SCC, median ages were 80 years for men, and 8 years for women. No statistically significant difference was found between age

groups and skin cancer types.

Gender

In all cases studied, 18 (64.2 %) were males and 10 (35.8 %) were females. BCC was observed in 7 (25%) men and 3 (10.7 %) women. SCCs were detected in five (15.06%) males and one (3.6%) female. Out of MF patients there were four (14.3%) males and three (10.7 %) females. For DFS there were two (7.1%) males and one (3.6%) female. We found one (3.6%) female case of B-cell lymphoma, and one female case of metastatic skin cancer (3.6%) (Fig. 2). A borderline significant difference was found between gender and grade in SCC ($P = 0.070$).

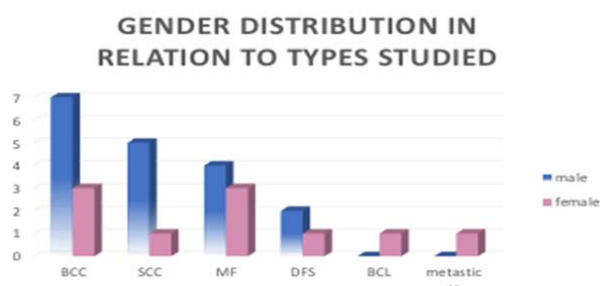


Fig. 2 Gender distribution in Relation to types studied

Site

In our study, we discovered that up to 80% of all lesions of BCC are found on the head and neck, whereas approximately 15% developed on the back or chest. For SCC, four cases were observed in the head and neck region, and two in the lower limb. Three cases of DFS were observed in the head and neck region, and one in the upper limb. As regards MF, two cases on the back, two on the trunk, and two on the face were recorded. One case of B-CLL was found in the head and neck area (Table III).

TABLE II
LOCALIZATION OF DIFFERENT TUMORS STUDIED

Diagnosis	Head & Neck	Upper Limb	Lower Limb	Trunk	Back	Total
BCC	8	0	0	1	1	10
SCC	4	0	2	1	0	7
DFS	2	1	0	0	1	4
MF	0	2		2	2	6
B-CL	1	0	0	0	0	1
Total %	50%	7.1%	3.6%	14.3%	14.3%	28

MF=mycosis fungoides.

Size

Tumors were divided according to their greatest dimensions into: 0 cm to 2 cm (67.9%), 2.1 cm to 4 cm (17.9%), ≥ 4.1 -6 cm (10.7%). Mean diameter of all types tumors was 1.2 cm. Mean tumor diameters for BCC and SCC, DFS, MF and B-CL were 2.7 cm (range 0.8 to 7), 1.9 cm (range: 0.8 to 5), 3.3 cm (range: 3 to 4) 0.4 cm (range: 0.2 to 0.5), respectively. A statistically significant correlation was found between age and tumor size in SCC ($P = 0.001$), and another border-line significance in MF ($P = 0.070$).

Ulceration

BCC presented with an ulcerated mass in seven (70%) of the cases, while only in four (66.7%) of the SCC cases presented with ulceration (Fig. 3).



Fig. 3 An ulcerated BCC on upper nasolabial fold

V. SURGICAL MARGINS

Of the BCC specimens, 30% had surgical margins involvement, while the rest (70%) were free. SCC had surgical margins involvement in 66.7% of cases, while 33.3% were free. All specimens of DFSP had surgical margins involvement. No statistically significant difference was found between surgical margins and cancer types ($P > 0.05$).

VI. HISTOPATHOLOGY

Main histological type detected in BCC was the nodular type (Fig. 4). Adenoidal BCC, which can be classified as a variant of nodular BCC, was characterized by basaloid cells with a reticulated configuration extending into the dermis. Solid and pigmented types were also seen, where upper dermal nodules of basaloid cells are shown with well-defined borders, depicting peripheral palisading of cells and a typical clefting. Some cells showed melanin pigmentation (Fig. 5). Mitotic activity was not so evident.

SCC was characterized by atypical cells in the dermis, showing enlarged and pleomorphic nuclei with atypical mitotic activity (Fig. 6). Inflammation was present in ulcerated lesions (in 4/6 cases) and consisted of lymphocytes, plasma cells, and neutrophils. Well differentiated tumors showed keratinous pearls typically present on the dermis, surrounded by nests of atypical cells and reduced stroma with lymphocytes.

SCC was mainly moderately differentiated (grade 2) in four cases, where islands of squamoid cells were seen with no evidence for keratin pearls (Fig. 6). Well differentiated grade 1 tumors were found in one case and poorly differentiated in another case.

Mycosis fungoides represented 25% of all tumors studied, with a mean age of 37 years, and a male to female ratio 0.75:1. Epidermotropic infiltrate of T-cells was seen in all cases with intraepithelial cerebrated T-lymphocytes. The infiltrate was positive for CD3 and CD4 with sparse or absent CD20. Ki-67 proliferation rate was $<10\%$.

A single case of B-Chronic lymphocytic leukemia (B-CLL)

was seen on the face of a 63-year old male patient, where a dense, diffuse infiltrate of B-lymphocytes was present in the dermis (Fig. 7). CD20 showed a strong membranous positivity in most of lymphocytes. In focal areas, a simultaneous transformation into a high grade, immunoblastic lymphoma (Richter Syndrome) was recognized, where aggregates of immunoblasts with a central prominent nucleolus were seen with an increased ki-67 proliferation rate.

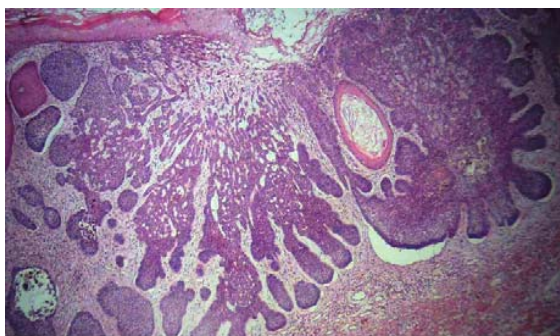


Fig. 4 Adenoid BCC with clefting, H&E X100

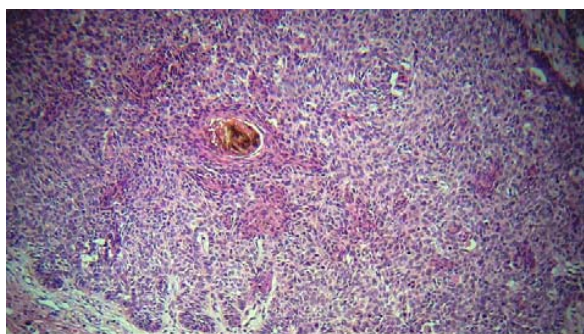


Fig. 5 Pigmented BCC, H&E X100

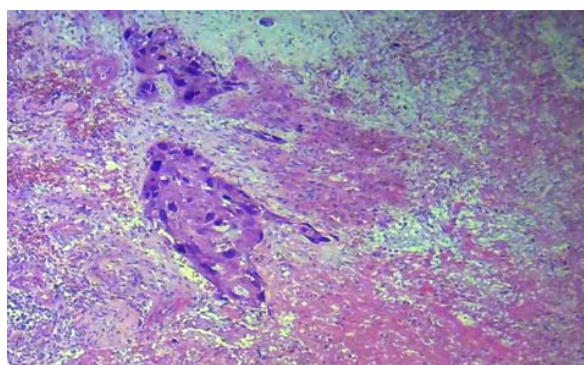


Fig. 6 Moderately differentiated SCC, H&E X400

VII. DISCUSSION

Although non-melanoma skin cancer is common in many parts of the world [10], in our series it is a relatively uncommon neoplasm. In Ha'il region, skin cancer in general represented 7% of all male cancers, ranking as the 8th more common malignancy (unpublished data). In females it

constituted only 2% of all skin cancers in the region [11].

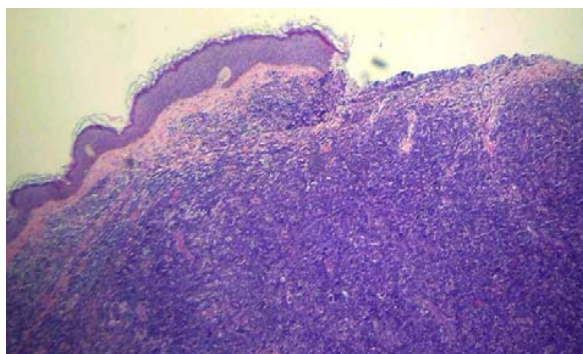


Fig. 7 Dermal infiltrate of B-CLL. H&E X100

In our series, as in other parts of the world, BCC was most prevalent especially the adenoid type with mean size 2.73 cm. Males were more affected than females. The mean age was 57.6 years. It is interesting that cutaneous T-cell lymphoma mainly MF ranked the second most common malignancy before SCC. Patients were young, with a mean age of 37 years. Females were more affected than males. One case of cutaneous B-cell lymphoma was retrieved. The patient was 36 years old.

SCC is reported to be within the top five most costly cancers in the USA [12]. It accounts for about 20% of all cutaneous malignancies. In addition, SCC accounts for the most of NMSC-related mortality and metastatic disease. It is assumed that in the future, SCC incidence will drastically increase, due to an increment in sun exposure, increased UV exposure, aging of the population, enhanced public awareness of skin cancer, and more frequent skin examinations by physicians [13].

In our series SCC accounted for 21% of cases of primary cutaneous carcinoma. Patients with SCC had an older age (mean 72.3 years), with male to female ratio was 5:1. Mean size was smaller than BCC (1.9 cm) with 50% of cases showing positive surgical margins.

Mycosis fungoides constituted 25% of our cases with a mean age of 37 years. DFSP constituted 11% of cases with a mean age of 31.5 years. These findings were in accordance with a study in the Western region of the Kingdom [14].

To conclude from our study, non-melanoma skin cancer is infrequent in Ha'il region. It accounts for 7% of all male malignancies ranking as the 4th most common, preceded by colorectal carcinoma, lymphoma, and soft tissue tumors [15]. In females, cutaneous cancer accounts for 2% of all cancers and is the 7th in frequency after breast, thyroid, colorectal, endometrial carcinoma, lymphoma and soft tissue tumors [16].

This low incidence is in accordance with other parts of the Kingdom and contrasts with incidence worldwide [17]. It might have resulted from genetic factors, the protective influence of the melanin pigment against sun rays, daily lifestyle with less daytime outdoors activities, less sun-exposure as well as traditional customs and clothing as protective factors against harmful rays.

VIII. CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

REFERENCES

- [1] Guy GP Jr, Machlin SR, Ekwueme DU, Yabroff KR: Prevalence and costs of skin cancer treatment in the U.S., 2002-2006 and 2007-2011. *Am J Prev Med.* 2015 Feb;48(2):183-187. Epub 2014 Nov 10.
- [2] Lupu M, Caruntu A, Caruntu C, Papagheorghe LML, Ilie MA, Voiculescu V, Boda D, Constantin C, Tanase C, Sifaki M, Drakoulis N, Mamoulakis C, Tzanakakis G, Neagu M, Spandidos DA, Izotov BN, Tsatsakis AM. Neuroendocrine factors: The missing link in non-melanoma skin cancer (Review). *Oncol Rep.* 2017 Sep;38(3):1327-1340. doi: 10.3892/or.2017.5817. Epub 2017 Jul 13.
- [3] Stenehjem JS, Røsbjerg TE, Bråttveit M, Samuelsen SO, Kirkeleit J, Grimsrud TK: Ultraviolet radiation and skin cancer risk in offshore workers. *Occup Med (Lond).* 2017 Oct 1; 67(7):569-573.
- [4] Azizova TV, Bannikova MV, Grigoryeva ES, Rybkina VL: Risk of malignant skin neoplasms in a cohort of workers occupationally exposed to ionizing radiation at low dose rates. *PLoS One.* 2018 Oct 5;13(10).
- [5] Rao P, Liegeois NJ, McNiff JM, Nghiem P, Prieto VG, Smith MT, Smoller BR, Wick MR, Frisberg D: Protocol for the Examination of Specimens From Patients With Squamous Cell Carcinoma of the Skin. Washington: College of American Pathologists (CAP), 1996-2010. September 2012.
- [6] Koyuncuer A. Histopathological evaluation of non-melanoma skin cancer. *World J Surg Oncol.* 2014 May 21;12:159. doi: 10.1186/1477-7819-12-159.
- [7] Ibrahim O, Gastman B, Zhang A: Advances in diagnosis and treatment of nonmelanoma skin cancer. *Ann Plast Surg.* 2014 Nov;73(5):615-9.
- [8] Arora A, Attwood J. Common skin cancers and their precursors. *Surgical Clinics of North America.* 2009 Jun 30;89(3):703-12.
- [9] AlSalman SA, Alkaff TM, Alzaid T, Binamer Y: Nonmelanoma skin cancer in Saudi Arabia: single center experience. *Ann Saudi Med.* 2018 Jan-Feb;38(1):42-45.
- [10] Paolino G, Donati M, Didona D, Mercuri SR, Cantisani C : Histology of Non-Melanoma Skin Cancers: An Update. *Biomedicine.* 2017 Dec; 5(4): 71.
- [11] Newlands C , Currie R, Memon A, Whitaker S, Woolford T: Non-melanoma skin cancer: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol.* 2016 May; 130(Suppl 2): S125–S132.
- [12] Diepgen TL, Mahler V. The epidemiology of skin cancer. *British Journal of Dermatology.* 2002 Apr 1;146(s61):1-6.
- [13] Saudi Cancer Registry, cancer incidence report, Saudi Arabia, 2010.
- [14] Albasri AM, Borhan WM: Histopathological pattern of skin cancer in Western region of Saudi Arabia, an 11 years experience. *Saudi Med J.* 2018 Oct; 39(10):994-998.
- [15] Seada LS, Al Rashid F, Negm A: A 4 year study of thyroid carcinoma in Ha'il Region. *World Academy of Science, Engineering and Technology International Journal of Medical and Health Sciences Vol:10, No:12,* 2016.
- [16] Seada LS, Al Rashid F, Ibrahim A: Changing pattern of Colorectal Cancer in Ha'il Region. *World Academy of Science, Engineering and Technology International Journal of Medical and Health Sciences Vol:8, No:10,* 2017.
- [17] Scotto J, Kopf AW, Urbach F. Non-melanoma skin cancer among caucasians in four areas of the United States. *Cancer.* 1974 Oct 1;34(4):1333-8.