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Evaluation of Histopathological and Prognostic Significance of Programmed Death Ligand 1 (PD-L1) Expression of Cutaneous Squamous Cell Carcinoma and Basal Cell Carcinoma

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Abstract:

Basal cell carcinoma and Cutaneous squamous cell carcinoma are the most common malignancies in humans. Five-year survival rates of these tumors are considerably high, and classical treatment methods, such as surgery and radiotherapy, are generally sufficient. However, additional systemic treatment may be required for high-risk, locally advanced, and metastatic BCC and CSCC. PD-L1 activation plays an important role in the tumor's avoidance of immune surveillance. PD-L1 expression has been studied in different tumor types. However, data on PD-L1 expression in BCC and CSCC are limited. The aim of this study is to evaluate the immunohistochemical expression of PD-L1 in CSCC and BCC cases and detect its relationship with other clinicopathological parameters as a prognostic factor. A total of 47 formalin fixed paraffin embedded skin biopsies of patients with CSCC (19) and BCC (28) were collected and studied immunohistochemically for PD-L1. All biopsies were scored for the PD-L1 expression in tumor cells and TILs. PD-L1expression was positive in 14 (73.7%) of the included CSCC cases, while 5 (26.3%) were negative. Score 0 was seen in 5 cases (26.3%), Score +1 was seen in 6 cases (31.6%), score +2 was seen in 8 cases (42.1%). PD-L1 score in tumor cells showing significant correlation with tumor size, PD-L1 expression in TILs and PD-L1 scores in TILs. According to 28 BCC cases, 27 (96.4%) showed negative PD-L1 expression in tumor cells while only one case (3.6%) has positive expression, however according to PD-L1 expression in TILs 11(39.3%) cases were negative but 17(60.7%) cases showed positive expression.

Keywords: Cutaneous squamous cell carcinoma, Basal cell carcinoma, PD-L1 expression.

1. Introduction:

Skin cancer remains the most common group of cancers globally and the incidence continues to rise. There are three main types of skin cancers, melanoma, basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (CSCC). Non-melanoma skin cancer (NMSC) principally comprises BCC and CSCC **(6)**, it represents about 98% of all skin cancers **(23)**. In Egypt, the incidence rate of NMSC was 1.35% of all cancers in males and 1.24% of all cancers in females **(6).** BCC is the most common type of skin cancer; it represents approximately about 80% of all skin carcinomas **(8)**. The incidence of BCC increases with age, and it occurs more often in the elderly population **(16)**. BCCs grow slowly and metastasize rarely, their mortality rate is < 0.1% **(8)**. The second most common type of skin cancer is CSCC representing less than 20% of all skin malignancies **(28).** It predominantly occurs in old age and is more common in men than women and increase with age. Approximately 1.9–4.9 % of CSCC metastasize to regional lymph nodes or more distant sites **(16)**. Surgery is the first-line therapy for BCC **(5)** and in CSCC is the therapy of choice and mostly curative in early stage **(28)**. Some cases can progress to locally advanced or a metastatic state, so other nonsurgical local and systemic treatment options are required **(5)**.

Programmed death-ligand 1 (PD-L1) is a cell surface glycoprotein that functions as an inhibitor of T-cells and plays a major role in suppression of the cellular immune responses **(2)**. The antibodies blocking PD-1 and PD-L1 on tumor binding site could locally inhibit the downregulation of the T cell activation and restore the immune response **(26)** Therefore, it is hypothesized that the PD-1/PD-L1 signaling pathway plays an important role in immune system escape by tumors **(2)**. The PD-L1 expression levels have been associated with response to treatment, with PD-1 inhibition in numerous tumor types. For instance, the degree of PD-L1 expression in tumor cells predicts response in melanoma and the degree of PD-L1 expression in TILs predicts response in non–small cell lung cancer and metastatic bladder cancer. PD-L1 expression status is important for anti-PD-L1 therapies **(14)**, but Studies on PD-L1 expression in non-melanocytic skin cancers are limited **(18)**.

2. Materials and Methods :

Tumor tissue sections from 47 patients of CSCC (19) and BCC (28) specimens were collected who underwent excisional biopsy. Ethical approval was sought from the university Ethical Committee (approval No.: FMBSUREC\07062022\ Alian). For the sake of data confidentiality and to ensure that it will be used only for scientific research, the patient's identity was taken from each case and replaced with a number. Also, these samples

were studied immunohistochemically for PDL-1 using monoclonal PDL-1 antibody. The expression of positively stained tumor cells was evaluated.

2.1 Histopathological evaluation:

Paraffin blocks of the tumors were sectioned at 4μm thickness. Then, they were stained with routine Hematoxylin and Eosin stain for pathological examination and morphologic classification of CSCC and BCC according to the recommendations of the World Health Organization (WHO) including TILs response, histopathological grade and pathologic stage for CSCC cases and histological variant , TILs response for BCC cases

2.2 Immunohistochemical examination:

Section from each case was mounted on positively charged slide and stained by immunohistochemical stain Monoclonal rabbit anti PD-L1 clone (ZR3) for in vitro diagnostic use, Catalog Number 438R-28 (7.0 ml) predilute ready- to- use from (CELL MARQUE, USA).

2.3 Interpretation of PD-L1 positivity:

PD-L1 staining was detected as brownish staining in the cell membrane of tumor cells and as brownish staining in cytoplasm of TILs. The extent of positivity was scored according to the percentage of immunopositive cells relative to the total number of neoplastic cells.

PD-L1 score for tumor cells in CSCC cases as follows :

-Score (0): negative; no staining

-Score (+1): Positive cells were <10% PD-L1 positivity of tumor cells

-Score (+2): Positive cells were ≥10% PD-L1 positivity of tumor cells

Most studies consider PD-L1 staining of >1% of tumor cells as positive, So, both scores of +1 and +2 were considered positive.

PD-L1 scores for tumor cells in BCC cases as follows:

-Score (0): negative; no staining up to < 5% staining

-Score (+1): Positive cells were ≥ 5% PD-L1 positivity of tumor cells

-Score (+2): Positive cells were >10% PD-L1 positivity of tumor cells

Cases demonstrating at least 5% membranous (cell surface) expression of PD-L1 were considered positive (Lipson et al., 2017 and Gompertz-Mattar et al., 2021).

TILs response was assessed in Hematoxylin and eosin-stained slides and recorded as absent (0), focal (1), mild (2), moderate (3), and marked (4) with score 0 or 1 considered negative. The extent of PD-L1- positive TILs was also assessed using the same scoring scale (0–4) and samples with a score of 2–4 were considered PD-L1-positive.

2.4 Slide examination and imaging:

Slides were examined by Olympus BX53 light microscope and images were captured using Leica digital pathology slide scanners (Aperio LV1 IVD).

Statistical methodology

The statistical software for the social sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA) was used to code and enter the data. The following metrics were used to summarize the data: frequency (count) and relative frequency (%) for categorical data; mean, standard deviation, median, minimum, and maximum for quantitative data. The non-parametric Mann-Whitney test was used to compare quantitative variables.

An analysis using the Chi square (2) test was done to compare categorical data.

Statistics were considered significant for p-values under 0.05.

3. Results:

Our research conducted 47 cases of CSCC (19), and BCC (28) were collected as formalin fixed Paraffin embedded tissue blocks, received as specimens from skin lesions in pathology Lab at Specialized Medical Centre, faculty of medicine Beni-Suef University in the period from January 2018 to September 2022.

Exclusion criteria included marked tumor autolysis, Poor fixation and widely necrotizing tumor tissue.

In our study the patient′s age of CSCC cases ranged from 11 to 75 years old with mean age was 56 years ± 18.62 SD and more than half (57.9%) of cases were > 60 years. Most studied cases (63.2%) were males with male: female ratio 1.7:1. About tumor size of studied cases, the size ranged from 1.6 to 8 cm with mean size 3.87 ±1.74 SD and the most of cases (84.2%) > 2cm. Regarding the pathological stage (pT) of our cases, most of the cases were pT2 and pT3 (89.5%). There were variable amounts of peri and intra-tumoral TILs, groups based on inflammatory response revealed that 31.6% of cases had an intensive inflammatory response, 36.8% had moderate, and 31.6% had a mild inflammatory response. No studied cases have negative or focal inflammatory response.

Regarding the expression of PD-L1 most of cases (73.7%) were positive in both tumor cells and TILs. About half of cases (42.1%) showed PD-L1 score +2 in tumor cells.

According to our thesis, there was a positive correlation between PD-L1 score in tumor cells and tumor size however, there was no significant relationship with age, gender, histopathological grade, pathological stage and TILs response. There was a statistically significant relationship between PD-L1 score in tumor cells with both PD-L1expression and score in TILs as illustrated in **table (1)**.

There was no statistically significant difference between PD-L1 expression in TILs with age, sex, tumor size, TILs response histopathological grade and pT stage in studied cases as illustrated in **table (2)**.

The age of BCC cases; it was ranged from 36 to 85 years old with mean age 59 years ± 11.65 SD and more than half (57.1%) of cases were > 60 years. Regarding gender more than

half of cases (57.1%) were males with male: female ratio 1.3:1. About tumor size of studied cases, the size ranged from 0.50 to 8.1 cm with mean size 1.96 ± 1.54 SD and most of cases (71.4%) were ≤ 2cm. Concerning the histopathological variant, the studied cases were divided into low risk and high risk. More than half of cases (60.7%) were low risk cases. According to inflammatory response, the studied cases revealed that 21.4% of cases showed mild TILs response, 46.4% have moderate response and 32.1% exhibited marked response.

Regarding the expression of PD-L1 in tumor cells, most cases (96.4%) were negative, only one case showing positive expression, however the expression of PD-L1 in TILs showed that more than half of cases (60.7%) showed positive PD-L1 expression and positive expression scored as negative score (39.3%),mild score (35.7%), moderate score (10.7%) and marked score (14.3%). There was no statistically significant relationship between PD-L1 expression in TILs with age groups, gender tumor size, histopathological variant and TILs response in studied cases as illustrated in **table(3)**

Table (1) Correlation between PD-L1 score in tumor cells among CSCC cases with clinicopathological parameters (N=19):

SCC		PDL1 score in tumor cells						p.value
		Score 0		Score +1		Score +2		
		Count	%	Count	%	Count	%	
Age groups	≤60	3	60%	3	50%	2	25%	0.622
	>60	2	40%	3	50%	6	75%	
Gender	Male	3	60%	3	50%	6	75%	0.413
	Female	2	40%	3	50%	2	25%	
Tumor size	≤2 cm	0	0.0%	3	50%	0	0.0%	0.021
	>2 cm	5	100.0%	3	50%	8	100.0%	
Histopathological grade	Well differentiated	3	50%	1	16.7%	2	33.3%	0.52
	Moderate differentiated	1	11.2%	4	44.4%	4	44.4%	
	Poorly differentiated	1	25%	1	25%	2	25%	
pathological stage (pT).	T1	0	0.0%	2	100.0%	0	0.0%	0.07
	T2	2	22.3%	4	44.4%	3	33.3%	
	T3	3	37.5%	0	0.0%	5	62.5%	
TILs response	Mild	2	33.3%	3	50.0%	1	16.7%	0.178
	Moderate	2	28.6%	3	42.8%	2	28.6%	
	Marked	1	16.7%	0	0.0%	5	83.3%	
PD-L1 expression in TILs cells	Negative	4	80.0%	1	20.0%	0	0.0%	0.003
	Positive	1	7.1%	5	35.7%	8	57.2%	
PD-L1 score in TILs	Negative	4	80.0%	1	20.0%	0	0.0%	0.009
	Mild	0	0.0%	3	50.0%	3	50.0%	
	Moderate	1	25.0%	2	50.0%	1	25.0%	
	Marked	0	0.0%	0	0.0%	4	100.0%	

Table (2) Correlation between PD-L1 expression in TILs among CSCC cases with clinicopathological parameters (N=19):

SCC		PDL1 expression in TILs				p.value
		Positive		Negative		
		Count	%	Count	%	
Age group	<60	5	62.5%	3	37.5%	0.603
	>60	9	81.8%	2	18.2%	
Gender	Male	9	75.0%	3	25.0%	1.0
	Female	5	71.4%	2	28.6%	
Tumor size	≤2 cm	1	7.1%	2	40.0%	0.084
	>2 cm	13	92.9%	3	60.0%	
TILs response	Mild	3	50.0%	3	50.0%	0.196
	Moderate	5	71.4%	2	28.6%	
	Marked	6	100.0%	0	0.0%	
Histopathological grade	Well differentiated	3	50.0%	3	50.0%	0.286
	Moderately differentiated	1	11.1%	8	88.9%	
	Poorly differentiated	1	25.0%	3	75.0%	
Pathological stage (pT)	T1	0	0.0%	2	100.0%	0.798
	T2	2	22.2%	7	77.8%	
	T3	3	37.5%	5	62.5%	

Table (3) Correlation between PD-L1 expression in TILs among BCC cases with clinicopathological parameters (N=28):

BCC		PD-L1 expression in TILs				p.value
		Positive		Negative		
		Count	%	Count	%	
Age groups	≤ 60	7	58.4%	5	41.6%	1.0
	> 60	10	62.5%	6	37.5%	
Gender	Male	11	68.7%	5	31.3%	0.441
	Female	6	50.0%	6	50.0%	
Tumor size	≤ 2 cm	12	70.6%	8	72.7%	0.903
	> 2 cm	5	29.4%	3	27.3%	
Histopathological variant	Low risk	11	64.7%	6	35.3%	0.701
	High risk	6	54.5%	5	45.5%	
TILs response	Mild	2	33.3%	4	66.7%	0.098
	Moderate	7	53.8%	6	46.2%	
	Marked	8	88.9%	1	11.1%	

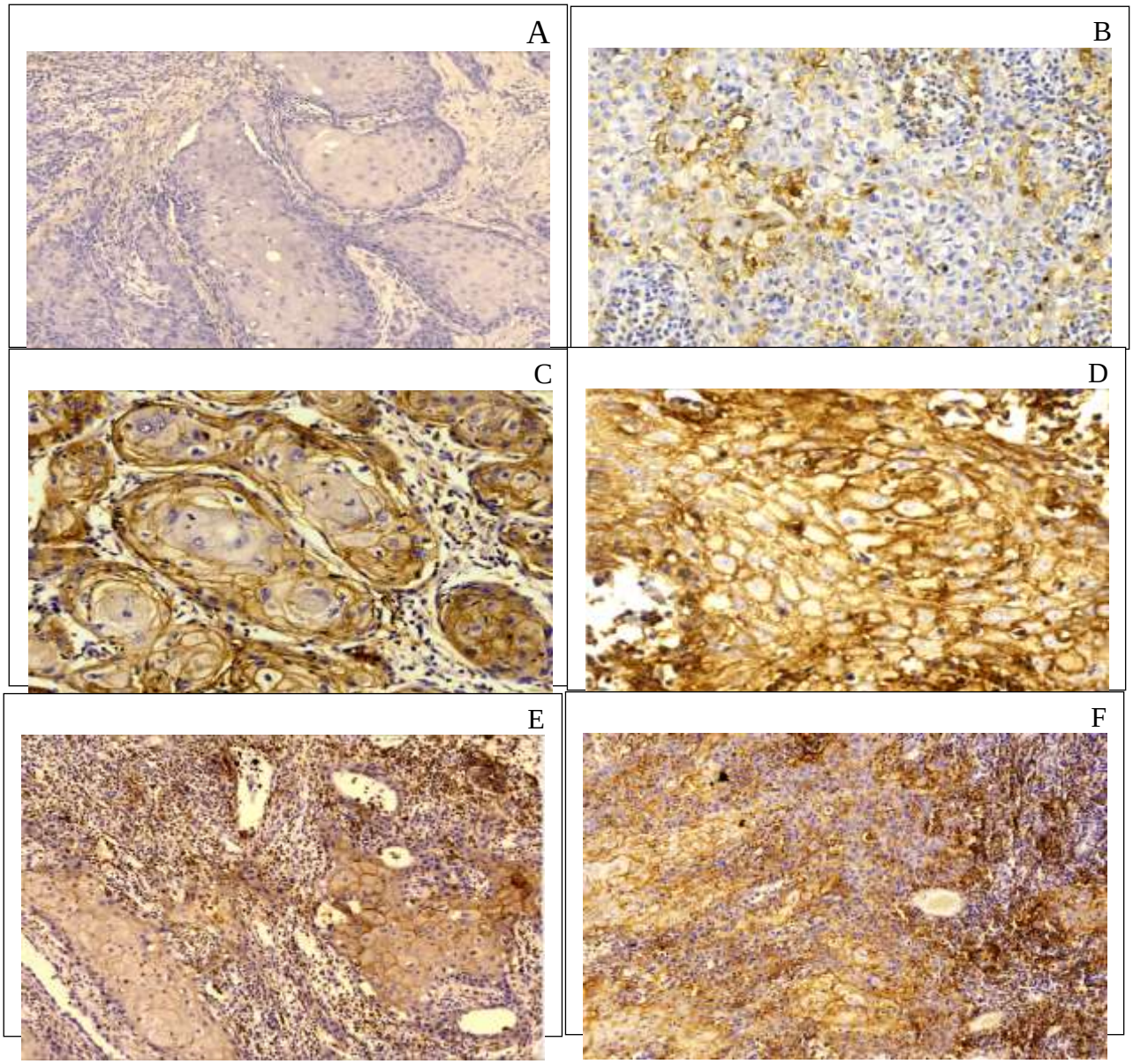

Figure (A) Negative PD-L1Expression in tumor cells and in TILs of moderately differentiated SCC (IHC x100).

Figure (B) Positive PD-L1 expression in tumor cells of poorly differentiated SCC (score +1) (IHC x200).

Figure (C) Positive PD-L1 expression in tumor cells (score +2) and in TILs (mild score) of well differentiated SCC (IHC x200).

Figure (D) Positive PD-L1 expression in tumor cells of moderately differentiated (score +2) (IHC x400).

Figure (E) Positive PD-L1 Expression (score +2) in tumor cells and TILs (score+4) (star) of poorly differentiated SCC (IHC x100).

Figure (F) Positive PD-L1 Expression(score +2) in tumor cells and TILs (score +3) of poorly differentiated SCC (IHC x100).

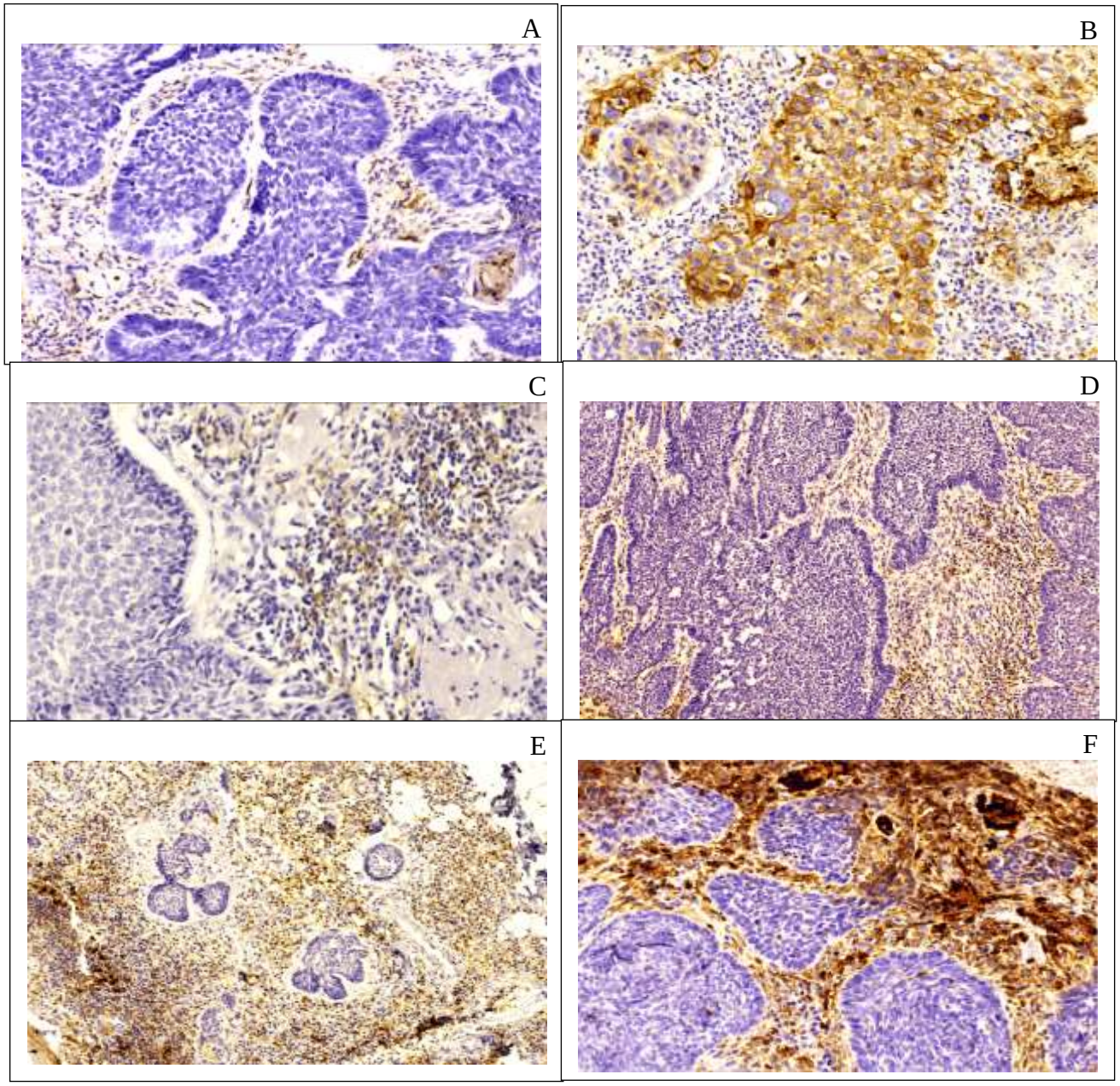

Figure (A) Micronodular BCC, showing negative PD-L1 expression in tumor cells (IHC x200).

Figure (B) Positive PD-L1 expression in tumor cells (the only positive case) and in TILs (score +2) of nodular BCC (IHC x200).

Figure (C) Nodular BCC, showing negative PD-L1 expression in tumor cells and Positive expression in TILs (score +2), (IHC x200).

Figure (D) Nodular BCC, showing negative PD-L1 expression in tumor cells and positive expression in TILs (score +3), (IHC x100).

Figure (E) Micronodular BCC, showing negative PD-L1 expression in tumor cells and Positive expression in TILs (score +4), (IHC x100).

Figure (F) Another case of nodular BCC BCC, showing negative PD-L1expression in tumor cells and Positive expression in TILs (score +4), (IHC x200).

4. Discussion:

Regarding our work, the mean age of 19 CSCC cases was 56 years. These results were compatible with ***(20)*** which reported a mean age 59 years, however ***(29)*** reported a higher mean age (83 in men and 91 in women). These differences could be explained by lifestyle variations.

As regards the gender, males (63.2%) were more predominant than females in our study and male to female ratio was 1.7:1 and that was related to results obtained by ***(4)*** and ***(20)*** who reported male predominance (60%) and (66.7%) respectively, however **(10), (1)** ***and*** **(15)** reported higher male predominance (78%, 81%, 71.7% and 82.9%, respectively).

The majority of our studied cases (84.2%) had tumors larger than ≥2cm, while 15.8% had tumors smaller than < 2cm.That is different from study reported by **(27)** and **(17),** whereas 59% and 93% of cases respectively were ≤ 2cm in size. This difference could be due to the delay in seeking medical advice.

Regarding the histopathological grade in this thesis, (31.6%) of cases were well differentiated, (47.4%) were moderately differentiated and (21.1%) were poorly differentiated**.** These results were approximating those found by **(27),** who noted poorly differentiated in (20%) of total cases**.** According to the results reported by **(30)**, 48% of cases were well differentiated, 48% were moderately differentiated, and 4% were poorly differentiated. About the histopathological grade in study done by **(15),** 91.3% of cases were well and moderately differentiated, 8.7% were poorly differentiated. Both studies were different from our study in percentage of poorly differentiated cases. This may be due to a delay in discovering the disease or due to the difference in the number of studied cases in our study.

In this work, according to the pathological tumor stage, 10.5% of cases presented at pT1, 47.4% of cases presented at the pT2 stage, and 42.1% of cases presented at the pT3 stage, as indicated by. According to **(25),** reported that 50% of cases had pT1 stage and this does not correlate with our result. This difference in pathological tumor stage could be due to the delay in seeking medical care or maybe limited financial resources of the families in different countries.

There were variable amounts of TILs response; TILs response in studied cases revealed (31.6%) of cases presented mild response, (36.8%) showing moderate response and (31.6%) exhibiting marked TILs, there were little variation between different degrees of response. That differs from the results found by **(30),** 18.2% had a mild inflammatory response, 31.8% had moderate inflammatory response and about half (50%) of cases had a marked inflammatory response and this is higher than our cases with marked TILs. This difference is due to their cases being more advanced than our cases. Regarding the

relationship between different prognostic parameters there was a relationship between TILs response and tumor size (*p.value= 0.021)*, whereas the moderate and marked TILs response present exclusively with cases had tumor size > 2cm and this may denote bad prognostic value. Furthermore, there was a statistically significant difference between gender and histopathological grade *(p.value= 0.047)*, whereas poorly differentiated cases present only in male, but this is possible due to the small number of studied cases and male gender more exposed to sun. Those findings are not supported or declined by any available previous studies. As regards the PD-L1 expression in tumor cells of studied cases, (26.3%) of cases showed negative expression, however most of the cases (73.7%) were positive. According to PD-L1 score in tumor cells, (31.6%) of cases were PD-L1 score +1 and (42.1%) of cases showed PD-L1 score +2 in tumor cells. The study done by **(12),** were in line with our findings who measured the expression of PD-L1 in 40 cases of CSCC, revealed about 67.5% of cases presented with positive PD-L1. Those findings were different from the results reported by **(30)** who stated that (44%) of cases showing positive PD-L1 expression in tumor cells and this is less than our percentage in our study, while 32% of their cases had score +1 and 12% had score +2. In our study, the percentage of cases with score +2 are higher than cases with score +1. Also, the study differs from our study done by **(9)** showed that 26.9% of cases with positive PD-L1 expression. This discrepancy in the expression pattern of PD-L1 could be explained by the variety of antibodies clones used in each study, different methodology (manual vs automated), PD-L1 heterogeneity in the tumor, different cutoff values in various studies and number of studied cases. Another issue that we considered assessing in this study is PD-L1 expression and score in TILs in studied cases, (26.3%) of cases showing negative expression, however most of cases (73.7%) presented positive expression and this is the same percentage appears in PD-L1 expression in tumor cells. PD-L1 scoring in TILs was divided into 26.3% of cases showing negative score, 31.6% of cases showing mild score, 21.1% of cases showing moderate score and 21.1% of cases showing marked score**.** Our findings correlated with the studies performed by **(22)** who reported that (70.2%) of cases showed positive PD-L1 expression in TILs, however **(9)** reported that the percentage of PD-L1 positive expression in TILs was 34.6% and this is less than our findings.

About the similarity of positive PD-L1 expression in tumor cells and TILs in our study, this correlated with result done by **(9)** showing PD-L1 positive expression in tumor cells and TILs in KA (33.3% and 33.3%, respectively) and in CSCC (26.9% and 34.6% respectively).

In our study, there was a positive correlation between PD-L1 score and tumor size

(p.value= 0.021), whereas 100% of cases with score +2 have tumor size > 2cm. Our findings do not agree with studies done by ***(24), (15) and (30),*** which reported that there was no statistical relationship between PDL1 score in tumor cells and tumor size. ***(25)*** reported in their study that the PD-L1 expression score in tumor cells showing positive relationship with tumor size more than 2cm and this compatible with our study.

Additionally, we noted in this thesis, that there was no statistically significant relation between PD-L1 score in tumor cells and histopathological grade or pathological stage (pT) (p.values=0.52 and 0.07, respectively)**.** Our findings agreed with studies done by ***(24) and (30),*** which concluded that there was no statistical relationship between PDL1 score in tumor cells with both histopathological grade and pathological stage (pT), however regarding to study done by ***(25)***, there was significant relationship between PDL1 score in tumor cells and histopathological grade and histological stage (pT) by increasing PD-L1 positive expression in the higher pathological stage. This difference may be due to the distribution of histopathological grade among studied cases differ from our cases and their cases had metastatic CSCC as well as the number of study cases they have is greater than the number of our cases.

As shown in, there was no significant relationship between PD-L1 score in tumor cells and TILs response (p.value= 1.0). According to results reported by ***(30),*** there was no statistically significant difference between PD-L1 score in tumor cells and the TILs response and this closely matched to our study, however according to ***(24)*** reported positive correlation between TILs response and the PD-L1 score in tumor cells and this result is incompatible with our result. This difference may be due to the increased number of the studied cases (78) in their research.

In the presented study, there was statistically significant correlation between PD-L1 score in tumor cells and both PD-L1 expression and scoring in TILs (p.values= 0.003 and 0.009, respectively). 100% of cases with PD-L1 score +2 showed positive PD-L1 expression in TILs. According to ***(9)*** reported positive correlation between the PD-L1 score of tumor cells and the PD-L1 expression and scoring of TILs. According to ***(30),*** there was no significant importance between the PD-L1 score of tumor cells and the PD-L1 expression and scoring of TILs. This disagrees with our result due to difference in TILs response distribution and distribution of positive PD-L1expression among his studied cases from our study.

Our current study found no statistically significant correlation between expression of PD-L1 in TILs and the following prognostic parameters (age, gender, tumor size, TILs response and histopathological grades, pathological stage) (p.values= 0.603, 1.0, 0.084, 0.196, 0.286 and 0.798, respectively)

and this correlate with study reported by ***(15)and (30).***

Regarding our study, the mean age of 28 BCC studied cases was 59 years and more than half (57.1%) of cases were > 60 years . These results were compatible with ***(3), (21)*** *and* ***(11)*** which reported a mean age of 58, 69 and 65 years respectively, However, **(25)** reported a higher mean age 76 years. These differences could be explained by lifestyle variations.

Regarding the gender, more than half of cases (57.1%) were males with male: female ratio 1.3:1. This is agreed with result reported by ***(13) and (21)***, who reported male predominance (٧٥% and 7٠%, respectively), however, according to study reported by ***(11),*** which presented that 52.6% of cases were females and 47.4% were males does not correlate with our study.

About tumor size of studied cases, the size ranged from 0.5 to 8.1 cm with mean size 1.96 ± 1.54 SD and the most of cases (71.4%) were ≤ 2cm. The study done by ***(19)*** revealed that the tumor size among 40 cases ranged from 2 to 15 cm. Regarding the histopathological variant, the studied cases were divided into low-risk and high-risk variants, and more than half of cases (60.7%) were low risk**.** According to study reported by ***(7)*** **,** they divided histopathological variants into low risk and high-risk variants depending on the risk of recurrence.

In this thesis, there was no statistically significant difference between histopathological variant and age group, gender, or TILs response *(p.values=0.441, 0.441, 0.33 and 0.421, respectively)***.** According to ***(7),*** their study revealed that there was no significant relationship between TILs response and histopathological variants, and this correlated with our study. Other findings are not supported or declined by any available previous studies.

Regarding the expression of PD-L1 in tumor cells, only one case, which had a positive PD-L1 expression, and our findings agreed with studies done by ***(30)***, which reported that one of the 42 cases with BCC was PD-L1 positive. According to a study done by ***(11),*** morphea and superficial types in his study did not show any PD-L1 expression, which is also match with our study. In the case of PD-L1 expression, which is the opposite to our result, ***(3)*** have shown that patients with BCC have a high level of expression of PD-L1 (89.9%) in tumor cells in their study. Another study done by ***(19)*** revealed PD-L1 positivity in BCC was 22% and this finding was far from our study. This difference could be explained by the variety of antibodies clones used in each study or because of the variety of histopathological variants in each study.

Additionally, A second focus of our study was TILs, the expression of PD-L1 in TILs, more than half of cases (60.7%) showed positive PD-L1 expression**.** The prevalence of PD-L1

positivity in studies reported by ***(19)and (3),*** that (82% and 94.9%, respectively) of cases showing PD-L1 positivity in TILs, that is higher than our prevalence of PD-L1 positivity in TILs. This may be contradiction due to the difference in number of cases, or their cases were more locally advanced than our cases.

In this thesis, there was no significant relationship between PD-L1 expression in TILs and the following parameters (age, gender, tumor size, TILs response and histopathological variant) (p.values=1.0, 0.441, 0.903, 0.701, and 0.098, respectively).Those findings are not supported or declined by any available previous studies. The small sample size in this study limits the conclusions that we can draw. Further research that includes a greater number of patients is needed.

5. Conclusion and Recommendations

-The current research including 47 cases;

19 cases were CSCC, about 74% of cases showed positive PDL-1 expression in tumor cells and TILs. These findings suggest that immune-targeted therapy against PD-L1 could be an effective therapy.

Our study demonstrated that all positive CSCC cases for PD-L1 in TILs showed also positive PDL-1 in tumor cells.

According to 28 BCC cases, only one case showed positive PD-L1 expression, however (60.7%) of cases have positive PD-L1 expression in TILs.

There was no significant relationship between PD-L1 expression in TILs in BCC cases with (age, gender, tumor size, histopathological variant and TILs response).

-Further studies with larger samples are recommended to establish the prognostic significance of PD-L1 and its role in Metastatic and locally advanced CSCC and BCC tumors which have poor response to surgery or radiotherapy to provide targeted therapy.

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