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Derinin Skuamöz Hücreli Karsinomunda ve Liken Planusta PDL-1, PD-1 Ekspresyonlarının Değerlendirilmesi

Evaluation of PD1 and PDL1 expressions in Squamous Cell Carcinoma and Lichen Planus

Gamze ERKILINÇ[1], Onur ERTUNÇ[1], Mehmet KIRAN[1], Nermin KARAHAN[1], Havva Hilal AYVAZ ÇELİK[2], Dudu Dilek YAVUZ[3], Zümrüt Arda KAYMAK[4]

[1]Department of Pathology, Suleyman Demirel University Faculty of Medicine, Isparta, Turkey.
[2]Department of Dermatology, Suleyman Demirel University Faculty of Medicine, Isparta, Turkey.
[3]Department of Plastic, Reconstructive and Aesthetic Surgery, Suleyman Demirel University Faculty of Medicine, Isparta, Turkey.
[4]Department of Radiation Oncology, Suleyman Demirel University Faculty of Medicine, Isparta, Turkey.

ÖZET

Amaç: Programlı hücre ölümü 1 (PD1) T hücre ailesinde olan immün sistemi "down" regüle eden bir proteindir. PD ligandı 1 (PDL1) T hücre proliferasyonunu ve sitokin üretimini inhibe eden PD1 reseptör proteinidir. Dermiste lenfositik reaksiyon Liken Planusta (LP) lezyonun özelliği iken Skuamöz Hücreli Karsinomada (SHK) tümör hücrelerine karşı gelişen bir cevap olarak da izlenebilir. Çalışmamızda SHK ve LP'de PD1, PDL1'in epidermis ve lenfositik hücrelerdeki ekspresyonunu karşılaştırmayı amaçladık. Materyal ve Method: Retrospektif randomize olarak dermiste LHİ (lenfositik hücre infiltrasyonu) yaygın olan 31 SCC ve 38 LP tanılı olgu çalışmamıza dahil edildi. PD1, PDL1'in; SHK, LP' lerde dermisteki LHİ ekspresyonu ve epidermisteki hücrelerdeki ekspresyonları skorlandı. Bulgular: PD1'in LHİ skoru LP'lerde anlamlı şekilde skor 1 ve 2 sık görülür iken (sırasıyla %44.7, %34.2), SHK'larda çoğunlukla skor 0 (%67.7) idi. PD1'in LP, SHK'da skor 3 hiç görülmez iken her iki grupta skor 0 çoğunlukta saptandı (LP: %76.3, SHK %87.1). PDL1'in LHİ skoru LP, SHK'da çoğunlukla skor 2, 3 olarak saptandı. PDL1'in deri skoru LP'lerde skor 2 ve 3 hiç görülmezken SHK'larda skor 2 %9.7, skor 3 %6.5 oranında görüldü. Sonuç: PD1, PDL1 ile LP'lerin SHK'lara göre anlamlı şekilde lenfositik hücrelerde ekspresyonu, neoplastik durumlarda kullanımı sonrası yan etki olarak görülen LP ve benzeri deri reaksiyonlarını açıklayabileceğini düşünmekteyiz.

Anahtar Kelimeler: PDL1, PD1, Skuamöz Hücreli Karsinoma, Liken Planus

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ABSTRACT

Aim: Programmed cell death 1(PD1) is a protein in the T cell family that down regulates the immune system. PD ligand 1(PDL1) is a PD1 receptor protein that inhibits T cell proliferation and cytokine production. There is often a prominent lymphocytic cell infiltration(LCI) in the dermis in Squamous Cell Carcinoma of the skin(SCC), and pathognomonically in Lichen Planus (LP). In this study, it is aimed to compare the expression of PD1 and PDL1 in epidermis and lymphocytic cells in SCC and LP.
Materials and Methods: Retrospectively randomly selected 31 cases with common LCI in the dermis and 38 cases with a diagnosis of LP were included in the study. PDL1, PD1 expression in LCI and epithelial cells in SCC and LP cases were evaluated by scoring the expressions.Results: While the LCI score of PD1 was significantly higher in LP (44.7%, 34.2%), the score was mostly 0 (67.7%) in SCC. PD1 expression in the epidermis in LP and SCC was not seen as score 3, while the score was 0 in both groups (LP: 76.3%, SCC 87.1%). While score 2, 3 expressions of PDL1 weren't seen LP cases, in SCC cases score 2 was seen at a rate of 9.7% and score 3 was was seen at a rate of 6.5%.Conclusion: Expression score of PD1, PDL1 in LCI in LP was significantly higher than that in SCC. We think that it can explain the LP and similar skin reactions seen as side effects after use in neoplastic cases.

Keywords: PDL1, PD1, Squamous Cell Carcinoma, Lichen Planus

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ARAŞTIRMA MAKALESİ

**Corresponding author:* gamzecirak@gmail.com

1. Introduction

Programmed death 1 (PD1) is a protein in the CD28/CTLA-4 T cell family that down-regulates the immune system through a dual mechanism of inhibition (1). Programmed death ligand 1 (PDL1) is a PD1 receptor protein that inhibits T cell proliferation and cytokine production (2). PD1 is expressed in T cells, B cells, macrophages and dendritic cells. However, PDL1, which has proven expression in tumor cells and immune cells, can be expressed in endothelial, pancreatic and muscle cells as well as T cells, B cells, macrophages and dendritic cells (3).

Today, immunotherapy modality targeting (PD1) / PDL1 pathway has become important among treatment options in the field of oncology (4).

It has been reported that the use of PD1 and PDL1, which are the treatment options for neoplastic conditions, may cause dermatological non-neoplastic side effects (5). Case series in the literature reported side effects such as lichenoid, perivascular and vacuolar dermatitis on the skin after the use of anti-cancer agents that block the anti-tumor T cell response, such as T-cell receptors PD1 and CTLA-4 (6, 7).

Lichen Planus (LP) is a recurrent and mostly chronic benign dermatosis that affects mucosal membranes and displays characteristic clinical and histological properties and is reported to exist in 0.5-4% of the general population (8, 9).

The lymphocytic reaction in the dermis layer in the skin may be a characteristic of the LP lesion or it may occur as a response to tumor cells in malignant conditions such as Squamous Cell Carcinoma (SCC).

SCC is a malignant disease in the group of non-melanocytic skin cancers, with a reported rate of metastasis of 2-5% (10,11). The tumor microenvironment regulated by inflammatory cells developed against tumor cells, has an important role in the immunological response (12). PD1 has two receptor ligands namely PDL1 and PD-L2, associated with the suppression of reactive T cells in the tumor and the aggregation of immunosuppressive T cells. This interaction may consequently cause adverse effects in the regulation of T cell activation, as in autoimmune diseases (12). The aberrant expression of PDL1 on tumor cells has been shown to have impeding effects on antitumoral immunity (13).

There are studies that compare the expression of PD1 and PDL1 in actinic cheilitis and SCC in order to guide the treatment of SCC (14,15).

Previous studies have compared premalignant and malignant conditions in the skin (15). However, no study evaluating LP, a benign dermatosis, and SCC, a malignant skin tumor has been encountered in literature. Although lymphocytic infiltration is observed in both diseases, in previous studies, this effect of PD1 and PDL1 was used as a treatment option in patients with SCC and was reported as a side effect in patients with LP (13). The demonstration of the expression of PDL1 and PD1 in neoplastic and non-neoplastic cells are expected to guide the future studies on the use of target agents. There is a limited number of studies on this issue.

In this study, we aimed to compare the expression of PD1 and PDL1 in epidermis and lymphocytic cells in SCC and LP.

2. Materials and Methods

Patients and tissue samples

100 SCC diagnosed randomly selected cases in which the patients underwent incisional or excisional biopsy between January 2007 and June 2019 by the doctor working for Department of Plastic and Reconstructive Surgery in our hospital were retrospectively reevaluted. Samples of 31 of these cases determined to have extensive lymphocyte infiltration in the dermis were included in this study. Samples of 38 cases diagnosed LP where the patient had no clinical history of medication and underwent punch biopsy at the Department of Dermatology between January 2007 and June 2019 in our hospital were also

included in the study. Age and gender data was obtained from the pathology reports of patients diagnosed with SCC. Tumor differentiation was reevaluated for the patients with SCC.

The clinical information including age, gender, and localization of the lesion in patients with LP, was obtained from pathology reports.
Ethics committee approval was obtained from the local ethics committee of our institution (date: 07/01/2020 and protocol number: 3032).

Immunohistochemistry

Hematoxylin and eosin (H&E) stained slides were retrospectively reassessed and PDL1 and PD1 antibodies were applied to the eligible paraffin blocks using the immunohistochemical method. PD1 (Biocare Medical CA USA, Concentrated and Prediluted Monoclonal Antibody, API 3137 AA, Clone NAT105) ready to use antibody positive control tonsillar tissue, 4 µm thin adhesive obtained from formalin-fixed paraffin embedded blocks with sample sent with negative control antibody. It was processed in an automatic immunohistochemistry device along with the working samples taken into the slides.

The PDL1 (Dako, Monoclonal Mouse Antibody, Clone 22C3) antibody was then prepared according to the instructions provided in the data sheet. The antibody positive control tonsillar tissue was processed in an automatic immunohistochemistry device together with the sample sent with the negative control antibody and the working samples taken on 4 µm thin adhesive slides obtained from formalin fixed paraffin embedded blocks.

Evaluation of Immunohistochemical Staining

Immunohistochemically stained preparations were evaluated by pathologists who were experienced in dermatopathology but had no knowledge of the cases.

Considering cytoplasmic membrane staining in immunohistochemical stained preparations as positive, the expressions of PD1 and PDL1 in lymphocytic cells in the dermis, epidermis tumor cells in patients with SCC, and epidermis cells in patients with LP were scored and assessed.

The scores were determined as: score 0: no positive staining, score 1: positive staining in less than 1% of cells; score 2: positive staining in 1 to 5%, and score 3: positive staining in more than 5%. In another study on PD1 and PDL1 expressions, a positive staining in less than 1% of cells was considered negative PD1 or PDL1 expression, where positive staining scores ranged from 1 to 5%, 5 to 50%, and above 50% (16). However, in the current study, although no expression was observed in some cases in the evaluation, less than 1% was added as a subgroup considering that this situation might have a different meaning since expression was observed below 1% in at least some of the cases. In addition, expression above 50% was not created as a subgroup in scoring because no such cases were encountered in the cases under investigation in this study (Figure 1-7).

Furthermore, the relationship between the expression scores of PD1 and PDL1 and tumor differentiation in patients with SCC was evaluated. An incisional biopsy was performed for the cases with SCC. Besides, the effects of perineural and lymphovascular invasion on prognosis are excluded from the study. Expression of PD1 and PDL1 in lymphocytic infiltration in epidermis and dermis in patients with LP and in lymphocytic infiltration in tumor cells and dermis in patients with SCC were compared statistically.

Statistical analysis

The differences in age, gender and PD1 and PDL1 scores between patients diagnosed with LP and SCC were compared by the Chi-Square test. The relationship between PD1 and PDL1 scores and tumor differentiation in patients with SCC was examined by Spearman's correlation test. For all statistical analysis, SPSS version 21.0 (IBM, Chicago, IL, USA) was used and a p value of <0.05 was considered statistically significant.

3. Results

Clinical findings:

In 50% of 38 patients with LP, the lesion was detected in the upper extremity (On the wrist in 12 patients, on the forearm in 5 patients, on the elbow in 1 patient, on the hand in 1 patient, on the anterior chest wall in 3 patients, in the lumbar region in 1 patient, in the pubic region in 1 patient, in the inguinal region in 1 patient, on the knee in 1 patient, on the anterior surface of the tibia in 6 patients and on the dorsal side of the foot in 6 patients).

In 31 patients with SCC, the lesion was detected on the auricle in 11 patients, on the hand in 5 patients, on the nose in 4 patients, on the mandible in 4 patients, in the temporal region in 2 patients, in the malar region in 1 patient, on the anterior chest wall in 1 patient, in the nasolabial region in 1 patient, on the dorsal surface of the foot in 1 patient, and on the ankle in 1 patient.

The patients with LP were mostly <60 years old while the majority of patients with SCC were ≥60 years old (The percentages of <60 years old patients were 89.5% and 6.5%, respectively; p <0.001). The distribution of females and males was almost equal among patients with LP (females, 52.6% and males, 47.4%), whereas the percentage of males was higher among the patients with SCC (females, 29% and males, 71%) (Table 1).

Table 1. Comparison of age and gender between patients with LP and SCC

	LP (n = 38) (%)	SCC (n = 31) (%)	*P value*
Age			
<60 years	34 (89.5)	2 (6.5)	<0.001
≥60 years	4 (10.5)	29 (93.5)	
Gender			
Female	20 (52.6)	9 (29)	0.041
Male	18 (47.4)	22 (71)	

LP: Lichen Planus, SCC: Squamous Cell Carcinoma

Immunohistochemical findings

The difference in the LCI score of PD1 and epidermis cells score of PDL1 between patients with LP and SCC was statistically significant (p <0.001 and p = 0.012, respectively). However, there was no significant difference in the epidermis cells score of PD1 and LCI score of PDL1 between the two groups (p = 0.189 and p = 0.246, respectively). Considering the LCI score of PD1, patients with LP had a higher rate of 1 and 2 score (44.7% and 34.2%, respectively), while patients with SCC had a higher rate of 0 score (67.7%). Considering the epidermis cells score of PD1, there were no patients who scored score 3 in both groups, whereas there was a higher rate of 0 score in both groups (LP, 76.3% and SCC, 87.1%) (Figure 8).

Similarly, LCI score of PDL1 was mostly score 2 and 3 in both groups. Considering the epidermis cells score of PDL1, none of the patients with LP received score 2 and 3, while the rate of score 2 in SCC patients was 9.7% and the rate of score 3 was 6.5% (Figure 8). Comparison of PD1 and PDL1 scores between patients with LP and SCC is given in detail in Tables 2 and 3.

Table 2: Comparison of PDL1 scores in between patients with LP and SCC

	PDL1									
	LCI				*P value*	Epidermis Cells				*P value*
Score	0 (%)	1 (%)	2 (%)	3 (%)	0.246	0 (%)	1 (%)	2 (%)	3 (%)	0.012
LP	3(7.9)	11(28.9)	20(52.6)	4(10.5)		30(78.9)	8(21.1)	0(0)	0(0)	
SCC	5(16.1)	12(38.7)	10(32.3)	4(12.9)		18(58.1)	8(25.8)	3(9.7)	2(6.5)	

LP: Lichen Planus, SCC: Squamous Cell Carcinoma, PDL1: Programmed cell death ligand 1, LCI: Lymphocytic cell infiltration

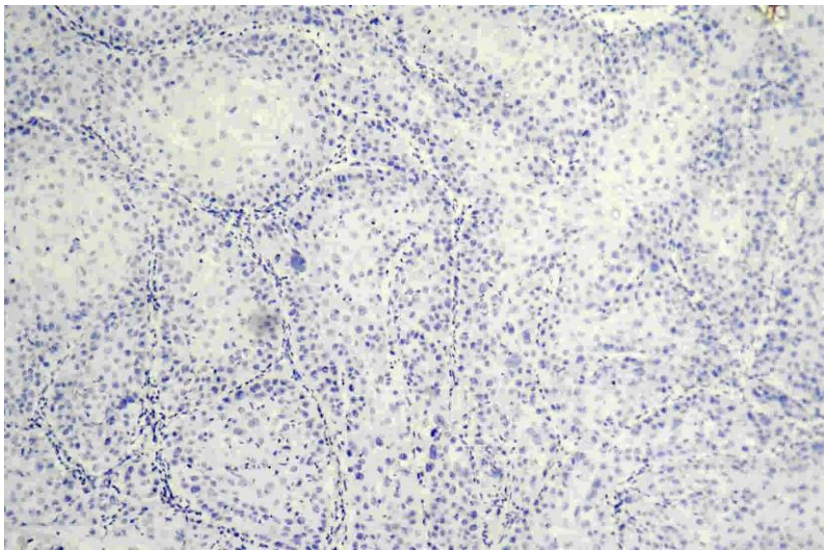
Table 3: Comparison of PD1 scores between patients with LP and SCC

	PD1									
	LCI				*P value*	Epidermis Cells				*P value*
Score	0	1	2	3	<0.001	0	1	2	3	0.189
SCC	21 (67.7)	8 (25.8)	2 (6.5)	0 (0)		27(87.1)	2 (6.5)	2 (6.5)	0 (0)	
LP	7 (18.4)	17(44.7)	3(34.2)	1 (2.6)		29(76.3)	8(21.1)	1 (2.6)	0 (0)	

LP: Lichen Planus, SCC: Squamous Cell Carcinoma, PD1: Programmed cell death 1, LCI: Lymphocytic cell infiltration

The correlation of PD1 and PDL1 scores with tumor differentiation in patients with SCC was examined. The Spearman's correlation test did not give a statistically significant correlation between tumor differentiation and PD1 skin and lymphocyte scores or PDL1 epidermis and lymphocyte cells scores (p = 0.843, 0.814, 0.155 and 0.083, respectively).

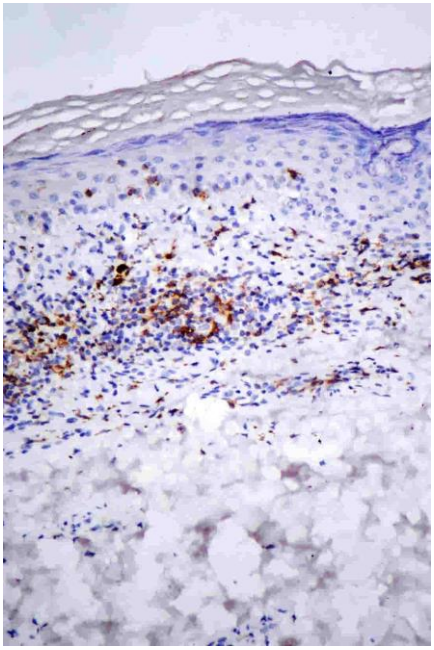
Figure 1: Squamous cell carcinoma epithelium score: 0,lymphocytic cell infiltration score: 0 (PD1x200)



4.Discussion

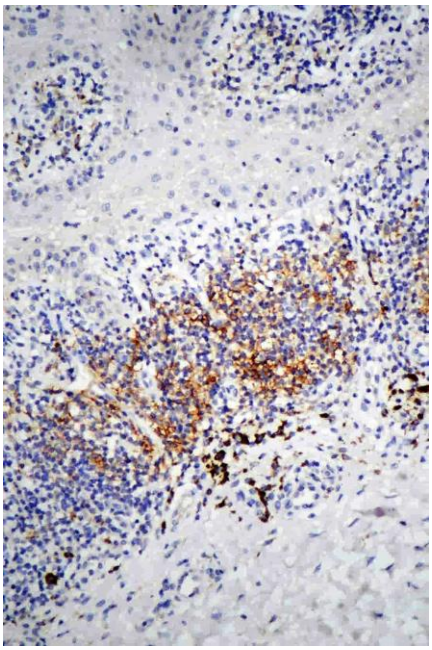
Lichen planus is a dermatosis with HLA (Human leukocyte antigen) antigens in genetic predisposition, having classic and idiopathic forms frequently seen in women affecting 30-60 years of age (9). LP treatment choices vary in a wide range from topical steroids to PUVA. The mechanism of action in the use of immunomodulators is probably achieved by restoring the balance between T helper and T cytotoxic (17). The use of immunotherapy in cancer treatment such as PD1, PDL1 blockade has led to several different immune-related conditions. In cancer cases using PD1, PDL1 blockade, a drug reaction of LP-like and even more severe skin necrosis and spongiosis was observed (18-19). In dermatoses, where lichenoid inflammation in the dermoepidermal junction like LP is seen, continuous activation of CD8 T lymphocytes against epidermal cells takes an important place in pathophysiology. Therefore, robust PD1 / PDL1 interaction is thought to be essential to maintain T cell homeostasis in the skin (19). In our study, it is proposed that frequent rate of scores 1 and 2 (44.7% and 34.2%, respectively) for LCI rate of PD1 in LP cases, high score 0 rate (67.7%) in SCC cases revealed that the homeostatic balance was impaired in the development of LP cases. The fact that PD1 expression was never seen for score 3 in both groups in the skin and that the score 0 was observed in the majority of the cases caused the suspicion that the situation was as such because of the inflammatory cells in LP cases.

Figure 2: Lichen planus skin score: 1, lymphocytic cell infiltration score: 3 (PD1 x200)



The fact that the LCI score of PDL1 was similarly determined mostly as scores 2 and 3 in both groups, and that there were no scores 2 and 3 in LP cases suggest that the situation originated rather from inflammatory cells. In a similar way, the LCI score of PDL1 was mostly found to be score 2 and 3 in both groups, and the absence of score 2, 3 in the epidermis cells of LP cases conveys that the situation is mostly caused by inflammatory cells.

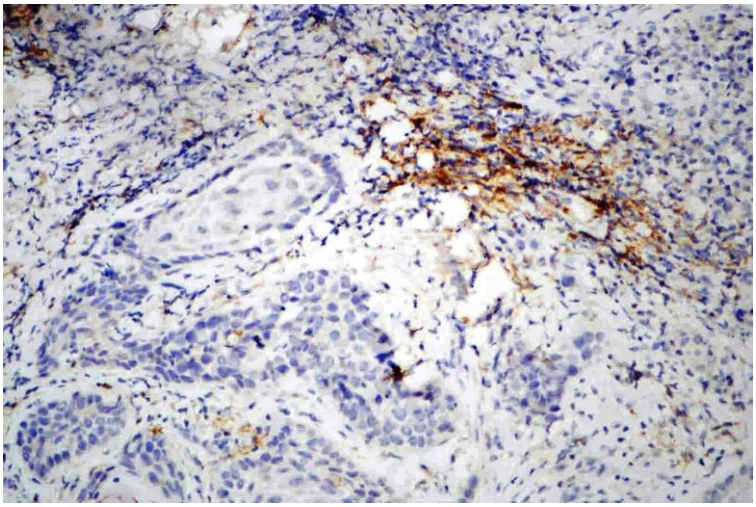
Figure 3: Lichen Planus skin score: 1, lymphocytic cell infiltration score: 3 (PD1 x200)



At the beginning of this study, the PD1 and PDL1 expression observed in both epidermis and inflammatory cells in SCC and significant surplus expression in inflammatory cells of LP cases made the researchers think that immune checkpoint inhibitors may be favorable in chronic severe inflammatory cell infiltration in non-neoplastic disease.

However, revisiting the literature, it was found that many types of drug reactions such as lichenoid, spongiotic, etc. on the skin were reported after the use of immunomodulators in case series, apart from treatment (20, 21).According to the immune checkpoint literature, PD1 deficient mice can develop autoimmune disorders beside lichenoid reactions (19), and there are several studies showing the expression of PD1, PDL1 in preneoplastic and neoplastic diseases (22).

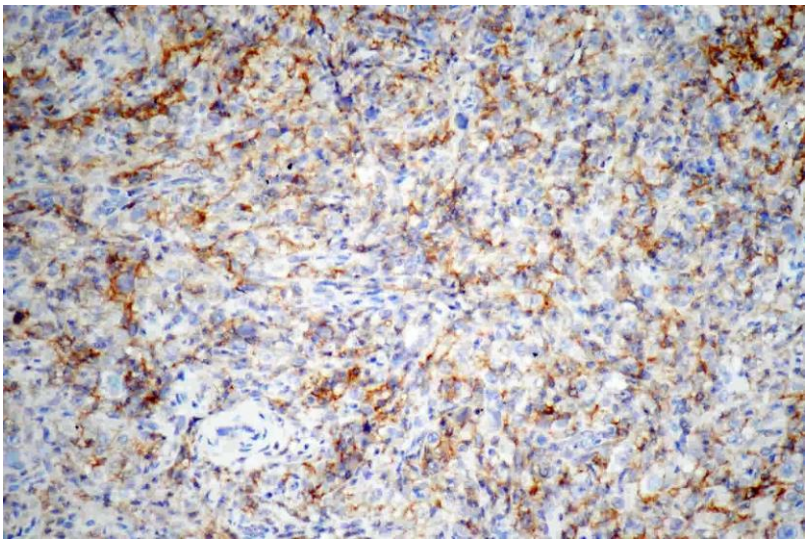
Figure 4: Squamous Cell Carcinoma skin score:0, lymphocytic cell infiltration score: 2 (PDL1 x200)



Although the mechanism has not been clarified thoroughly, the lymphocytic cell response in the skin might occur in a malignant process such as Malign Melanoma, SCC as well as in nonneoplastic skin diseases such as LP (23).
The effect of immune checkpoint inhibitors on CNS and MSI colorectal tumors has been studied, and tumor-infiltrating lymphocyte (TIL) and immune checkpoint inhibitors were found to be dramatically

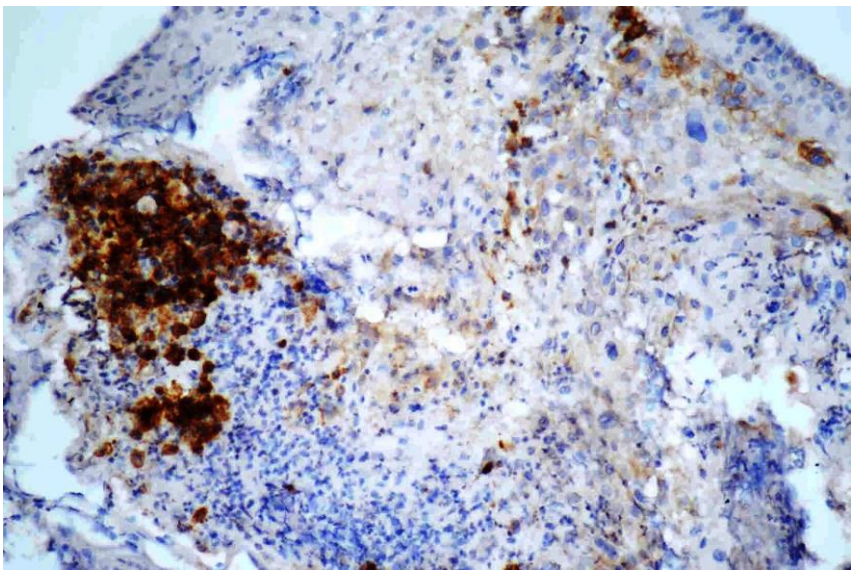
higher, especially in tumors with microsatellite instability (24). It was emphasized that the infiltrate in the tumor microenvironment was rich in granulocyte series alongside deficient in lymphocytes, negatively affecting the response to the treatment (25). Immunological tolerance-mediated PDL1, PDL2, PD1, and CTLA-4 have been investigated in autoimmune diseases as they are therapeutic targets (26, 27).

Figure 5: Squamous Cell Carcinoma skin score: 3, lymphocytic cell infiltration score:1 (PDL1 x200)



Examining the interface dermatitis observed among patients using immune checkpoint inhibitors and reported as side effects, a preliminary evaluation may be considered before the use of these immune modulators in patients with autoimmune disease.The literature remains limited on the use of PD1, PDL1 as a treatment option in non-neoplastic conditions. In the studies mentioned, whether there is a predisposition for an autoimmune skin reaction or previous medications that cause sides effects in cases of LP and similar skin reactions observed secondary to treatment, plus many drugs might cause lichenoid-style skin eruptions, and it is not known which causes the other (28, 29).

Figure 6: Squamous Cell Carcinoma skin score: 3, lymphocytic cell infiltration score: 3 (PDL1 x200)



In the light of all these observations, considering the susceptibility to autoimmune diseases in the circumstances, it is thought that patients with a malignancy requiring the use of immune check point

inhibitor drugs, especially those with 5% or more PD1 and PDL1 immunohistochemical expression, will have less side effects like interface dermatitis.

Figure 7: Squamous Cell Carcinoma skin score: 3, lymphocytic cell infiltration score: 3 (PDL1 x200)

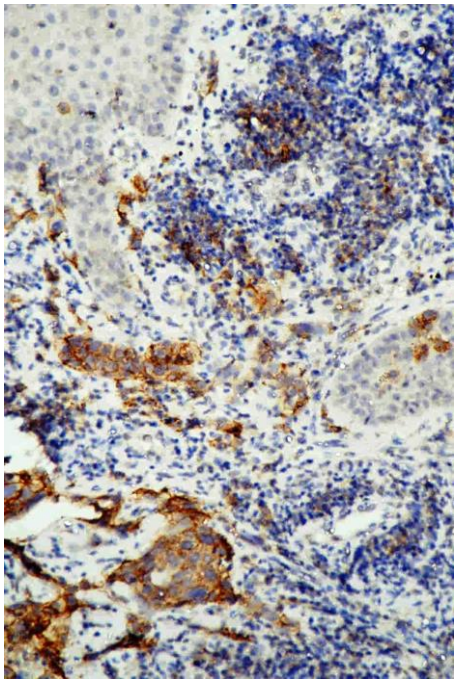
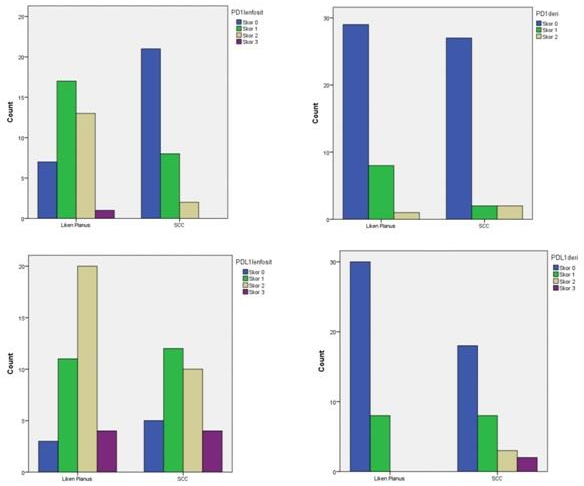


Figure 8: Comparison of PD1 lymphocytic cell infiltration, PD1 skin, PDL1 lymphocytic cell infiltration and PDL1 skin scores between patients with LP and SCC.



5.Conclusion

In our study, immunohistochemical expression of PD1 and PDL1 which is often utilized in neoplastic situations for the tumor microenvironment response in advance tumor for immune check point inhibitor therapy, in SCC and LP is questioned. Significantly higher immunohistochemical expression of PD1 and PDL1 in lymphocytic cells in LP compared to SCC may explain the side effects of the usage of checkpoint inhibitors.

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