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Welcome to the Int J Cancer and Biomedical Research (IJCBR)**!**

It is with great pleasure that I write this editorial to welcome you to the IJCBR. This journal provides a platform for publication of original and reviews research articles, short communications, letter to editor, thesis abstract, conference report, and case studies. These types of publication are directed at the interface of the fields of cancer and biomedical research.

The IJCBR relies on a distinguished expert of the Advisory and Editorial Board Members from the top international league covering in depth the related topics. They timely review all manuscripts and maintain highest standards of quality and scientific methodology and ethical concepts. Meanwhile, we take all possible means to keep the time of the publication process as short as possible.

I take this chance to welcome your contributions to the IJCBR and have every expectation that it will soon become one of the most respected journals in both the fields of cancer and biomedical research.

Mohamed L. Salem,

Editor in Chief

INTERNATIONAL JOURNAL OF CANCER AND BIOMEDICAL RESEARCH (IJCBR)

RESEARCH ARTICLE

Assessment of PD-L1 and p53 expression in urinary bladder carcinoma: Association with different clinicopathologic characteristics

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ABSTRACT

Background: Urinary bladder carcinoma is the most common urologic malignancy that includes phenotypically and genotypically diverse tumors. The development of new treatment modalities is essential to improve the outcomes and increase the overall survival of urinary bladder carcinoma patients'. Among these modalities, comes the PD-L1 inhibitors, as promising immunotherapy. P53 may also play a role in these treatment strategies. **Aim:** This study aimed to evaluate PD-L1 and p53 expression in urinary bladder carcinoma, and its available variants, and relate PD-L1 and p53 expression to each other and the available clinicopathological features. **Materials and methods:** This study included 60 cases of urinary bladder carcinoma, with no history of radiotherapy or chemotherapy, classified as follows: 32 cases of urothelial carcinoma, 25 squamous cell carcinomas, and 3 adenocarcinomas. Immunohistochemical staining of all cases using PD-L1 and p53 was done. **Results:** Positive PD-L1 expression was detected in 51.7% of all cases. PD-L1 expression was significantly associated with the histopathological types, high tumor grade and muscle invasion. High p53 expression was detected in 50% of the studied cases. P53 expression was significantly associated with high tumor grade, advanced stage, vascular invasion and lymph node metastasis. PD-L1 and p53 co-expression was detected in 33.3% of the cases. PD-L1 positivity was significantly associated with p53 expression. **Conclusions:** PD-L1 and p53 could be considered as predicting biomarkers for aggressive bladder carcinoma and their immunohistochemical expression may aid in identifying suitable patients for target therapy.

Keywords: Urinary bladder carcinoma; immune checkpoints; PD-L1; P53

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INTRODUCTION

Urinary bladder carcinoma is a major worldwide health problem with a high death rate (Siegel *et al.,* 2019). The development of new treatment modalities is crucial to improve the outcomes and increase the overall survival of urinary bladder carcinoma patients' (Patel and Kurzrock, 2015).

Immunotherapy is a promising strategy for the treatment of different cancers. Cancer immunotherapy starts with a proper understanding of tumor immuno-biology (Bellmunt *et al.,* 2017). Study of the tumor microenvironment revealed the importance of immune checkpoints in facilitating tumor immunological escape, leading to the development of multiple novel therapeutics targeting the PD-1/PD-L1 (programmed cell death protein 1, CD279; programmed death-ligand 1, CD274) immune checkpoints (Brahmer *et al.,* 2012 and Topalian *et al.,* 2012).

PD-1 is a T-cell immune inhibitory checkpoint that dampens T-cell activation and contributes to the immunosuppressive tumor microenvironment. PD-1 is also expressed on activated B cells and NK cells (Pardoll, 2012). PD-1 is activated by binding to its ligand; PD-L1, which is a cell surface glycoprotein. Many cell types express PD-L1, including placenta, vascular endothelium, hepatocytes and mesenchymal stem cells, also B cells, T cells, dendritic cells, macrophages, and mast cells (Sharpe *et al.,* 2007).

The binding of PD-L1 on the tumor cells to PD-1 on T cells- leads to the generation of a tumor that evades immune surveillance by multiple immuno-inhibitory mechanisms, as well as, contributes to the development of T-cell exhaustion and peripheral immunologic tolerance. This binding also decreases immunogenic antigen presentation by the tumor and creates an immunosuppressive state via a process termed "immune-editing" (Kawahara *et al.,* 2018 and Ding *et al.,* 2019).

The blockage of the PD-1/PD-L1 interaction led to good clinical responses in several cancer types. Yet, determining which patients gain benefit from PD-1/PD-L1–directed immunotherapy remains an important clinical question. Data suggest that patients whose tumors overexpress PD-L1 by IHC have improved responses with anti-PD-1–directed therapy, but the strong responses in some patients with low expression of these markers make this process controversy (Patel and Kurzrock, 2015).

Most human cancers result from mutations of cell-cycle regulatory genes, which control DNA synthesis and replication. In bladder carcinoma, the most studied cell-cycle molecule is p53 a tumor suppressor gene on chromosome 17p13 that prevents genomic mutation. Mutations of p53 lead to tumor generation (Favaretto *et al.,* 2018).

P53 status is considered a biomarker of progression, disease-free and disease-specific survival in both non-muscle invasive (NMI) and muscle-invasive (MI) bladder carcinoma. In NMI bladder carcinoma, p53 overexpression is associated with higher progression rates, while in MI bladder carcinoma, it's associated with increasing tumor stage (Rodriguez-Alonso *et al.,* 2002 and Shariat *et al.,* 2010). P53 expression may also impair the response to cisplatin-based chemotherapy in advanced bladder cancer, so p53-negative patients exhibit a more favorable response (Jankevicius *et al.,* 2002). P53 plays a role in controlling PD-L1 expression and regulating the immune responses (Braun and Iwakuma, 2016; Muñoz-Fontela *et al.,* 2016). Cortez *et al.* (2016) revealed that wild-type p53 decreases PD-L1 expression via up-regulating miR-34, in non-small cell lung cancer cell lines. Members of the miR-34 family are effector molecules, induced by wild-type p53, and act as a link between PD-L1 and p53 (Heinemann *et al*., 2012).

However, little is known about the role of PD-L1 and its relation to p53 in urinary bladder carcinoma including its different histopathological variants. In this study, we aimed to evaluate PD-L1 and p53 expression in urinary bladder carcinoma, and its available variants, and relate PD-L1 and p53 expression to each other, and the available clinicopathological features.

MATERIALS AND METHODS

This retrospective study was carried out on 60 biopsies of primary bladder carcinomas. Formaline fixed paraffin-embedded blocks were collected from the archives of the Pathology Department, Faculty of Medicine, Tanta University during the period of the study (from May 2019 to June 2020). Tissue specimens were in the form of 40 transurethral resections of bladder tumors (TURBT) and 20 radical cystectomy specimens. The cases were categorized as follows: 32 cases of urothelial carcinoma, 25 cases of squamous cell carcinoma and 3 cases of adenocarcinoma. Cases are classified and graded according to 2016 WHO classification of bladder tumors (Humphery *et al.,* 2016).

All specimens were fixed in 10% formalin solution and embedded in paraffin for routine histopathologic examination. The clinicopathological characteristics assessed for each case- included: the age, sex, histologic type, tumor grade, concomitant carcinoma in situ (CIS), lymphovascular and perineural invasion, and TNM staging. Tumor staging was done according to the American Joint Committee on Cancer (AJCC) -TNM classification of bladder tumors (eighth edition) (Amin *et al.,* 2017). We took the approval of the Local Research Ethics Committee, Faculty of Medicine, Tanta University, before conducting this study.

Immunohistochemistry: Representative tissue sections were deparaffinized in xylene, rehydrated in descending alcohol grades then incubated with an anti PD-L1 antibody, a mouse

monoclonal antibody (clone 1C10: sc-293425, Santa Cruz Biotechnology, INC, USA) at 1:100 dilution, and an anti-p53 antibody, a mouse monoclonal antibody (clone DO-1: sc-126, Santa Cruz Biotechnology, INC, USA) at 1:100 dilution. This is done after antigen retrieval by microwave incubation in 6.1 PH citrate buffer for 20 minutes and blocking endogenous peroxidase by H_2O_2. Visualization was obtained by the streptavidin-biotin ABC detection kit (Catalog # TA-015-HP, Lab-Vision Corporation Fremont, USA). Colour development was done using 3,3 diaminobenzidines and Meyer Hematoxylin as a counterstain. Slides were mounted with DPX and coverslipped. Negative control was done by omitting the step of the primary antibody.

Assessment of PD-L1 and P53 immunohistochemical staining

Positive PD-L1 immunostaining was defined by the presence of ≥5% membranous staining of the tumor cells (Bellmunt *et al.,* 2015). P53 positivity was seen as nuclear staining. The percentage of immunopositive cells was calculated by counting at least 1000 tumor cells in areas of maximum positivity. The results were interpreted taking the cutoff value as 20% and divided into 0 as negative, <20% as low, and >20% as high p53 expression (Thakur *et al.,* 2017). For Statistical purposes, cases were grouped as low expression (negative & <20%) and high expression (>20%).

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Science (SPSS version 23.0). Data were presented as mean ± SD for numerical variables and frequencies for categorical ones. For comparing categorical data, Chi-square ($\chi 2$) test was used as a test of significance. Fisher's exact test or Monte Carlo was used when one or more cells have an expected frequency of five or less. P values of < 0.05 were considered statistically significant.

RESULTS

Clinicopathological data

The clinicopathologic characteristics of the studied cases are summarized in Table 1.

Immunohistochemical staining results of PD-L1

Positive PD-L1 expression was demonstrated as membranous staining in 31 cases (51.7%). The relation between the immunohistochemical staining results of PD-L1 expression and different clinicopathological parameters is summarized in Table 2. Among the 32 urothelial carcinomas, 10 cases (31.2%) showed PD-L1 positive expression: 2/12 (16.7%) high grade infiltrating urothelial carcinoma, 6/10 (60%) urothelial carcinoma with squamous differentiation and 2/2 (100%) sarcomatoid urothelial carcinoma. Eighteen cases (72%) out of 25 SCC cases were PD-L1 positive. All the 3 adenocarcinoma cases showed PD-L1 positivity (Figure 1). There was a statistically significant relation between PD-L1 expression and the various histopathological types (P = 0.001), high tumor grade (P = 0.023) and advanced stage (P = 0.01). No significant relation was detected between PD-L1 expression and patients' sex, associated carcinoma in situ, lymph node status and vascular and perineural invasion.

Immunohistochemical staining results of p53

High p53 expression was demonstrated as brownish nuclear staining in 30 (50%) out of the 60 studied cases. The relation between the immunohistochemical staining results of p53 expression and the different clinicopathological parameters is summarized in Table 3.

Among the 32 urothelial carcinomas, 17 cases (53.1%) showed high p53 expression: 2/8 (25%) low grade non infiltrating papillary urothelial carcinoma, 6/12 (50%) high grade infiltrating urothelial carcinoma, 7/10 (70%) urothelial carcinoma with squamous differentiation and 2/2 (100%) sarcomatoid urothelial carcinoma. Ten cases (40%) out of 25 SCC cases showed high p53 expression. All the 3 adenocarcinoma cases showed high p53 expression (Figure 2).

There was a statistically significant relation between p53 expression and high tumor grade (P = 0.003), advanced tumor stage (P = 0.032), the presence of vascular invasion (P = 0.0078) and lymph node metastasis (P = 0.012). No significant relation was detected between p53 expression and patients' sex, histopathological types, associated carcinoma in situ and perineural invasion.

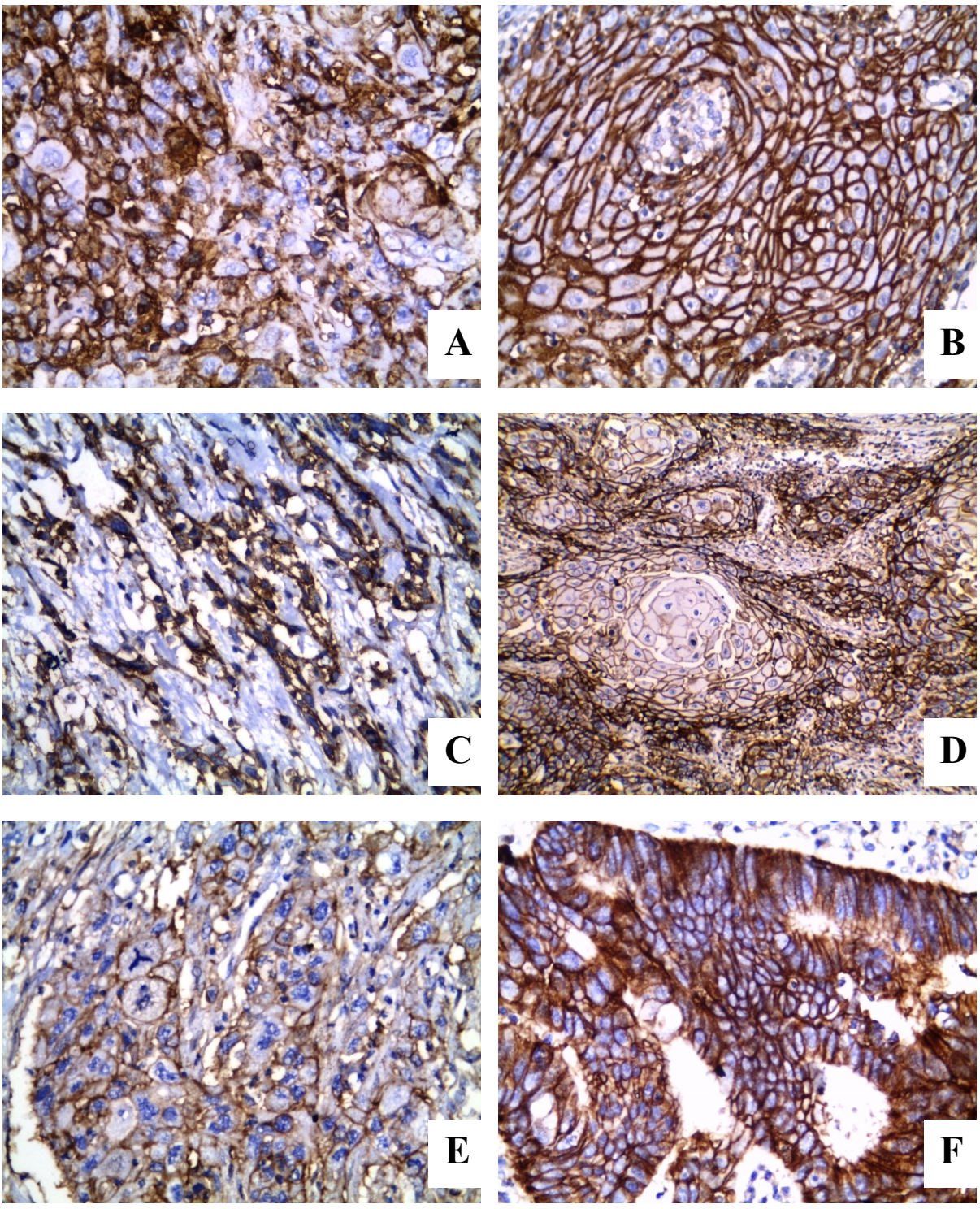

Figure 1. High grade infiltrating urothelial carcinoma 'x400'(A), High grade infiltrating urothelial carcinoma with squamous differentiation 'x400'(B), Sarcomatoid urothelial carcinoma 'x400'(C), Moderately differentiated squamous cell carcinoma 'x200'(D), Poorly differentiated squamous cell carcinoma 'x400'(E), Moderately differentiated adenocarcinoma 'x400'(F), cases from (A-F) show positive membranous PD-L1 expression.

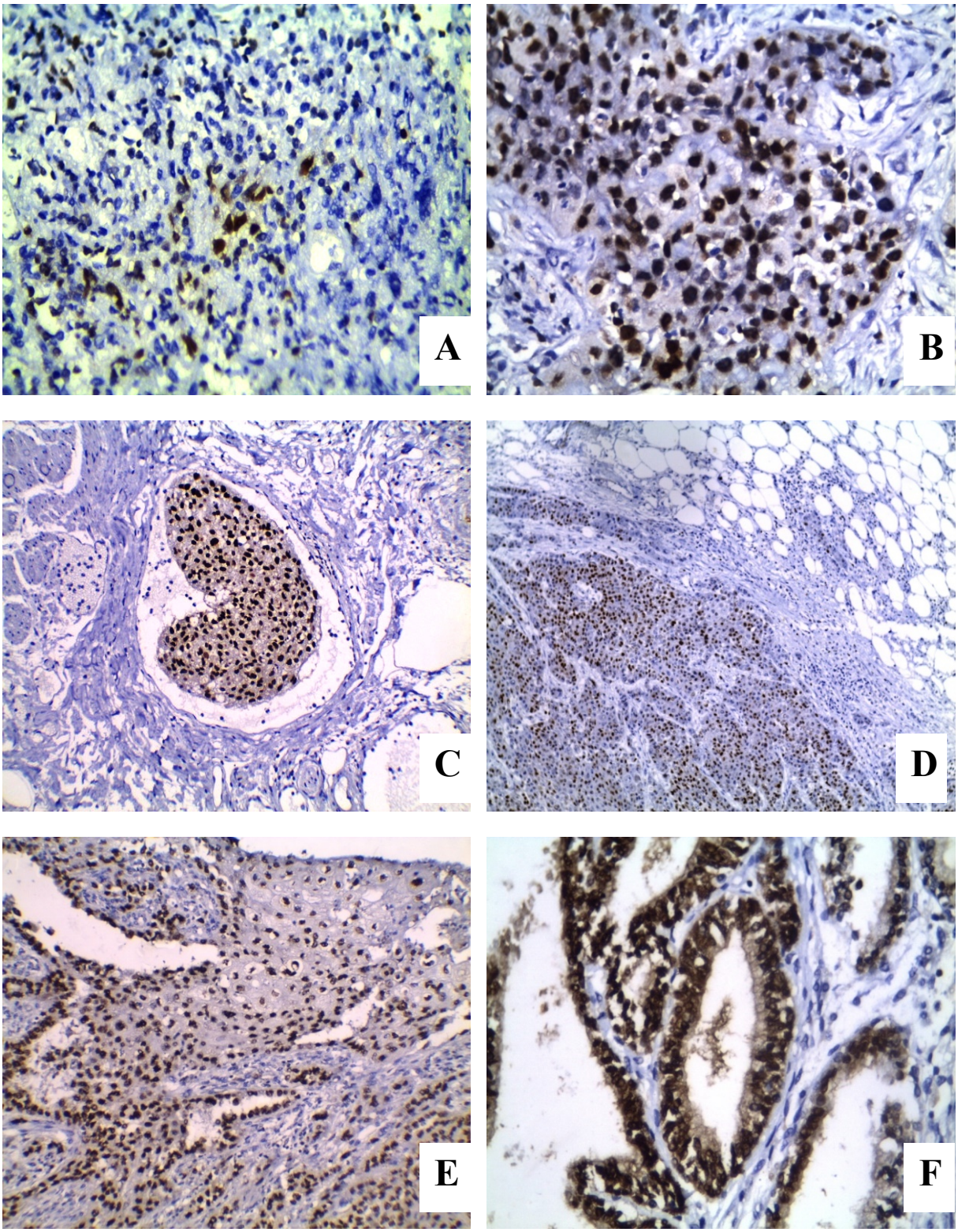

Figure 2. High grade infiltrating urothelial carcinoma showing low p53 expression 'x400'(A), High grade infiltrating urothelial carcinoma 'x400'(B), High grade infiltrating urothelial carcinoma with vascular emboli 'x200'(C), Lymph nodal metastasis of urothelial carcinoma 'x100'(D), Moderately differentiated squamous cell carcinoma 'x200' (E), Moderately differentiated adenocarcinoma 'x400'(F), cases form (B-F) show high p53 expression.

Table 1. The clinicopathological characteristics of the studied cases

Clinicopathological characteristics	Cases (No.)	%
Sex		
Male	47	78.3%
Female	13	21.7%
Histopathological types		
Urothelial carcinoma (Total)	32	53.3%
Low grade non-infiltrating papillary urothelial carcinoma	8	13.3%
High grade infiltrating urothelial carcinoma	12	20%
Urothelial carcinoma with squamous differentiation	10	16.7%
Sarcomatoid urothelial carcinoma	2	3.3%
Squamous cell carcinoma	25	41.7%
Adenocarcinoma	3	5%
Grade		
Low	21	35%
High	39	65%
Stage		
NMI[1] (pTa & pT1)	20	33.3%
MI[2] (pT2, pT3 & pT4)	40	66.7%
Associated carcinoma in situ		
Absent	45	75%
Present	15	25%
Vascular invasion		
Positive	9	15%
Negative	51	85%
Perineural invasion:		
Positive	9	15%
Negative	51	85%
Lymph node status		
Involved	17	28.3%
Not involved	43	71.7%

1= NMI, Non-muscle invasive, 2= MI, Muscle-invasive.

Relation between PD-L1 and p53 expressions

There was a significant relation between PD-L1 and p53 expressions (P = 0.012) (Table 4). PD-L1 and p53 co-expression was detected in 20 cases out of 60 (33.3%).

DISCUSSION

Urinary bladder carcinoma is the most common malignancy of the urinary tract and includes phenotypically and genotypically diverse tumors (Charlton *et al.,* 2014).

In this work, we studied the expression of PD-L1 and p53 in tumor cells of urothelial carcinoma and its squamous and sarcomatoid variants-, squamous cell carcinoma and adenocarcinoma, and we related their expression to different clinicopathological parameters.

PD-L1 recently catches the attention because of its critical role in immunosuppression, facilitating tumor immunologic escape. Only a few studies have investigated the role of PD-L1 expression in urinary bladder carcinoma and its histologic variants and the role of PD-1/PD-L1 inhibitors for treating advanced bladder carcinoma, with inconclusive results. IHC-based detection of PDL-1 helps to determine which tumor histologies may get benefit from PD-1/PD-L1 blockage, which is an important step in cancer immunotherapy.

In the current study, positive PD-L1 expression was present in 31.2% of the urothelial carcinomas, 72% of the SCCs and 100% of the adenocarcinomas. Regarding urothelial carcinomas with squamous differentiation, 60% of cases showed PD-L1 positive expression, and the 2 sarcomatoid urothelial carcinoma cases were also PD-L1 positive.

Our results matched those of Gatalica *et al.* (2014) who found that 55% of their bladder carcinoma cases showed PD-L1 positivity. Morsch *et al.* (2020) found that positive PD-L1 staining was detected in 51.2% of their cases and that its expression was higher in urothelial carcinoma with squamous differentiation and squamous cell carcinomas, compared with conventional urothelial tumors and stated that

Table 2. Relation of PD-L1 expression with the different clinicopathological parameters

Clinicopathological parameters	Cases (No.)	Positive PD-L1 expression N = 31(%)	Negative PD-L1 expression N = 29 (%)	P value
Sex				
Male	47	26 (55.3)	21 (44.7)	0.282
Female	13	5 (38.5)	8 (61.5)	
Histopathological types				
Urothelial carcinoma (Total)	32	10 (31.2)	22 (68.8)	
Low grade non-infiltrating papillary urothelial carcinoma	8	0(0)	8(100)	
High grade infiltrating urothelial carcinoma	12	2(16.7)	10(83.3)	
Urothelial carcinoma with squamous differentiation	10	6(60)	4(40)	0.001*
Sarcomatoid urothelial carcinoma	2	2(100)	0(0)	
Squamous cell carcinoma	25	18 (72)	7 (28)	
Adenocarcinoma	3	3 (100)	0 (0)	
Grade				
Low	21	6 (28.6)	15 (71.4)	0.023*
High	39	25 (64.1)	14 (35.9)	
Stage				
NMI[1] (pTa & pT1)	20	3 (15)	17 (85)	0.01*
MI[2] (pT2, pT3 & pT4)	40	28 (70)	12 (30)	
Associated carcinoma in situ				
Absent	45	22 (48.9)	23 (51.1)	0.456
Present	15	9 (60)	6 (40)	
Vascular invasion				
Positive	9	6 (66.7)	3 (33.3)	0.44
Negative	51	25 (49)	26 (51)	
Perineural invasion				
Positive	9	7 (77.8)	2 (22.2)	0.4
Negative	51	24 (47)	27 (53)	
Lymph node status				
Involved	17	8 (47)	9 (53)	0.1
Not involved	43	23 (53.5)	20 (46.5)	

*****Statistically significant (P < 0.05), 1= NMI, Non-muscle invasive, 2= MI, Muscle-invasive.

those patients may get benefit from PD-L1 inhibition. Pichler *et al.* (2017) and Davick *et al.* (2018) stated that high PD-L1 expression on the tumor cells was more frequently seen in histologic subtypes of urothelial cancer- especially the squamous and sarcomatoid subtypes- compared to pure urothelial cancers (46.2% *vs.* 20.8%). Our results were higher than those of Patel and Kurzrock (2015) who found that PD-L1 expression, was detected in 21% of their cases (22% of urothelial carcinomas and 37% of squamous carcinomas).

Few studies compared PD-L1 expression among urothelial, SCC and adenocarcinoma cases. Necchi *et al.* (2020) found significant differences in PD-L1 expression among these major subtypes. SCC had the highest frequency of them all, followed by urothelial carcinoma and then adenocarcinoma. The difference in our adenocarcinoma cases results may be related to our small sample size, so we recommend further studies to investigate PD-L1 expression in bladder adenocarcinomas and determine their chance to get benefit from anti PD-L1 therapy.

Immune checkpoint markers are affected by the molecular subtypes and histologic variants of the tumors. Guo and Czerniak (2019) explained the low expression of PD-L1 among conventional urothelial carcinoma and the high PD-L1 expression among squamous and sarcomatoid variants by their molecular subtypes. The expression of PD-L1 is moderately elevated in luminal conventional urothelial carcinoma subtype. Meanwhile, the basal/squamous subtype is associated with a strong expression of PD-L1 and more likely to respond to immune checkpoint therapy.

Table 3. Relation of p53 expression with different clinicopathological parameters

Clinicopathological parameters	Cases (No.)	High p53 expression N = 30	Low p53 expression N = 30	P-value
Sex				
Male	47	23 (48.9)	24 (51.1)	0.754
Female	13	7 (53.8)	6 (46.2)	
Histopathological types				
Urothelial carcinoma (Total)	32	17 (53.1)	15 (46.9)	
Low grade non-infiltrating papillary urothelial carcinoma	8	2(25)	6(75)	
High grade infiltrating urothelial carcinoma	12	6(50)	6(50)	0.153
Urothelial carcinoma with squamous differentiation	10	7(70)	3(30)	
Sarcomatoid urothelial carcinoma	2	2(100)	0(0)	
Sqaumous cell carcinoma	25	10 (40)	15 (60)	
Adenocarcinoma	3	3 (100)	0 (0)	
Grade				
Low	21	5 (23.8)	16 (76.2)	0.003*
High	39	25 (64.1)	14 (35.9)	
Stage				
NMI[1] (pTa & pT1)	20	5 (25)	15 (75)	0.032*
MI[2] (pT2, pT3 & pT4)	40	25 (62.5)	15 (37.5)	
Associated carcinoma in situ				
Absent	45	23 (51.1)	22 (48.9)	0.766
Present	15	7 (46.7)	8 (53.3)	
Vascular invasion				
Positive	9	9 (100)	0 (0)	0.0078*
Negative	51	21 (41.2)	30 (58.8)	
Perineural invasion				
Positive	9	6 (66.7)	3 (33.3)	0.45
Negative	51	24 (47)	27 (53)	
Lymph node status				
Involved	17	12 (70.6)	5 (29.4)	0.012*
Not involved	43	18 (41.9)	25 (58.1)	

*Statistically significant (P<0.05), 1=NMI, Non-muscle invasive, 2=MI, Muscle-invasive.

Table 4. Relation between PD-L1 and P53 expressions

PD-L1 (n=60)	P53 (n=60)	
	High expression (n=30) N (%)	low expression (n=30) N (%)
+ve (n=31)	20 (33.3%)	11 (18.3%)
-ve (n=29)	10 (16.7%)	19 (31.7%)
P	**0.012***	

*Statistically significant (P<0.05).

Li *et al.* (2020) also found that non-invasive papillary urothelial carcinoma was significantly lower in PD-L1 expression than invasive UC, mainly in the squamous and sarcomatoid histologies, compared to the other variants. Mak *et al.* (2016) and Lerner *et al.* (2017) stated that the basal/squamous subtype is much sensitive to anti-PD-L1/PD-1 compared with papillary luminal tumors.

So, we support that certain histological variants (squamous and sarcomatoid) and molecular subtypes (basal/squamous) tend to show positive PD-L1, and therefore may be appropriate for anti PD-L1 immune checkpoint therapy. Further researches involving the different variants and molecular subtypes may provide a benefit for urinary bladder carcinoma patients'.

In our study, positive PD-L1 expression was significantly associated with high grade and muscle-invasive cases.Our results match those of Huang *et al.* (2015) and Kawahara *et al.* (2018) who stated that PD-L1 expression on bladder carcinoma tumor cells was related to high tumor grade, muscle-invasive disease, increased resistance to Bacillus Calmette-Guerin (BCG) therapy and worse overall survival.

Ding *et al.* (2019) found no significant relation between PD-L1 expression on bladder carcinoma tumor cells and higher tumor grade, lymph node and distant metastases, but it was associated with muscle-invasion, suggesting that positive PD-L1 expression could be a potential prognostic marker for patients with bladder cancer. Also, Davick *et al.* (2018) and Owyong *et al.* (2019) reported that high PD-L1, was significantly associated with higher tumor stage, distant metastasis and poor overall survival, but not with sex, tumor grade, lymph node status, and multifocality.

P53 -the guardian of the genome- is one of the most widely studied molecular markers in bladder carcinoma. Regarding p53 immunohistochemical results, high p53 expression was found in 50% of our studied cases. There was a statistically significant relation between p53 expression and high tumor grade (64.1% of high-grade cases), advanced tumor stage (62.5% of muscle-invasive cases), the presence of vascular invasion and lymph node metastases. No statistically significant difference -in p53 expression- was found between urothelial, SCC and adenocarcinoma cases.

Our results were in agreement with Thakur *et al.* (2017) who stated that high p53 expression was significantly associated with high tumor grade, muscle-invasion, decreased disease-free (DFS), cancer-specific (CSS), and overall survival (OS), suggesting that p53 is an independent poor prognostic factor in urinary bladder carcinoma patients'. P53 regulates immune responses by targeting immune checkpoints, including PD-L1. PD-L1 expression is lost or shows decreased expression in cells that have wild-type p53, suggesting that induction of wild-type p53 down-regulates PD-L1 expression (Cortez *et al.,* 2016).

Few studies explored the relation between PD-L1 and p53 expression in urinary bladder carcinoma. Previous studies focused mainly on their relationship in non-small cell lung cancer (NSCLC). In our study, there was a statistically significant relation between PD-L1 and p53 expression.

Dong *et al.* (2017), Kadara *et al.* (2017), Wieser *et al.* (2018) and Kang *et al.* (2020) stated that p53 mutation is associated with elevated PD-L1 expression in lung and ovarian cancinoma. Jiang *et al.* (2015) and Yu *et al.* (2018) studied PD-L1 and p53 expression in pulmonary lymphoepithelioma-like carcinoma patients, and detected high PD-L1 expression levels in p53-mutated tumors, compared to the p53-negative group. They also stated that PD-L1 and P53 may predict benefit from adjuvant therapy in these cases.

Cortez *et al.* (2016) supported the inverse relationship of p53 and PD-L1 expression in vivo, using p53-wild type and p53-mutated NSCLC samples. NSCLC tumors with mutated p53, showed a statistically significant higher PD-L1 expression than wild-type p53 tumors. Cha *et al*. (2016) also, studied PD-L1 and p53 expression in lung adenocarcinoma, and found that PD-L1 positive tumors were significantly associated with mutant p53 expression. Tojyo *et al.* (2019) found a significant positive association between PD-L1 and p53 expressions in oral squamous cell carcinoma.

On the contrary, Rashed *et al.* (2017) found no significant association between p53 and PD-L1 expression in their study on NSCLCs Egyptian patients. Despite these previous studies, the relation between PD-L1 and p53 is still poorly understood (Shen *et al.,* 2019).

CONCLUSIONS

This study coclude that PD-L1 and p53 are considered predicting antibodies for high grade muscle-invasive urinary bladder carcinoma, and that their immunohistochemical expression could be affected by the histological types and may aid in identifying suitable patients for target therapy. Nevertheless, we recommend additional studies to evaluate the expression of PD-L1 in different histopathological bladder carcinoma variants and molecular subtypes, and the mechanisms that link p53 mutation and PD-L1 expression in urinary bladder carcinoma for establishing new therapeutic modalities.

CONFLICT OF INTEREST

Authors declare that they have no conflicts of interest.

FUDING

There is no financial support for this study.

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