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PROGRAMMED DEATH- LIGAND 1 EXPRESSION IN UROTHELIAL CARCINOMA

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ABSTRACT

*Background :*Urothelial bladder cancer is a disease of significant morbidity and mortality. It is ninth most common malignancy worldwide. It is the 7th most common cancer worldwide in men and the 17th most common cancer worldwide in women.*Methods*: The present study was undertaken in the Department of Pathology, after getting approval from Institutional Ethical Committee . Samples were collected from the department of urology with their clinical details. The study design was Retrospective and Prospective Cross-sectional study.*Results*: Majority of the cases were Conventional UC (83.8%), other common types were Squamoid, Glandular and Signet ring (5.0%, 6.3% & 2.5%). Apart from these, 1 (1.3%) case each was differentiated as Sarcomatoid and Sarcomatoid with glandular variant.*Conclusions*: Majority of cases with tumour recurrence showed strong positive PD-L1 expression and this association was found to be significant suggesting that degree of PD-L1 expression may be a crucial determinant of tumour invasiveness not only for primary tumours but also for recurrent tumours.

Keywords: urothelial bladder carcinoma; glandular; histopathological

INTRODUCTION

Urothelial bladder cancer is a disease of significant morbidity and mortality. It is ninth most common malignancy worldwide(1). It is the 7th most common cancer worldwide in men and the 17th most common cancer worldwide in women. Approximately 75% of newly diagnosed urothelial bladder carcinomas are non-invasive. Males are more often affected than females. Each year, approximately 1,10,500 men and 70,000 women are diagnosed with new cases(2). In India, as per the National Cancer Registry Programme, the overall incidence rate of the urinary bladder cancer is 2.25% (per 100,000 annually): 3.67% among males and 0.83% for females(3). Age of onset is most often between 65 and 85 years of age(4). Smoking is the most common risk factor and accounts for approximately half of all urothelial bladder cancers(5). Occupational exposures to aromatic amines and polycyclic aromatic hydrocarbons are also some of important risk factors.Other causal factors include chronic irritation, indwelling catheters, Schistosoma haematobium infestation, and pelvic irradiation(6). The main aim of this study is to assess the utility of PD-L1 immunohistochemical expression and its correlation with clinicopathological parameters in urothelial carcinomas.

Material and Methods

The present study was undertaken in the Department of Pathology, after getting approval from Institutional Ethical Committee . Samples were collected from the department of urology with their clinical details. The study design was Retrospective and Prospective Cross-sectional study with study sample being TURBT (Transurethral resection of bladder tumor) and/or Radical cystectomy specimens diagnosed as cases of urothelial carcinomas of 80 patients with

INCLUSION CRITERIA:

A. Histologically diagnosed cases of bladder cancer
B. Patients who gave consent to enroll in the study .
C. Availability of clinical details at presentation.

EXCLUSION CRITERIA:

A. Patients who were not willing to give consent to be a part of the study
B. Cases in which tissue may be lost during antigen retrieval or insufficient tumor tissue.
C. Poorly preserved tumor tissue.

Results

The present study was conducted in the Department of Pathology in collaboration with Department of Urology in urothelial carcinoma cases diagnosed after analysis of TURBT (Transurethral resection of bladder tumor) and/or Radical cystectomy specimens to explore the Immunohistochemical (IHC) expression of Programmed death-ligand 1 (PD-L1) marker in urothelial carcinomas, in different variants of urothelial carcinoma and find any correlation between IHC expression of PD-L1 marker and clinico-pathological parameters of urothelial carcinomas.A total of 80 cases of urothelial carcinoma fulfilling the inclusion criteria were included in the study after taking an informed consent. Profile of patients enrolled in the study was as under.

Age of patients enrolled in the study ranged between 18 to 86 years. Mean age was 55.25±12.65 years. Majority of the patients were aged 51-75 years (66.3%), only 3 (3.8%) were aged >75 years and 4 (5.0%) ≤25 years of age, rest were aged 25-50 years (25.0%).

Of 80 patients enrolled in the study only 14 (17.5%) were females and rest 66 (82.5%) were males. Male: Female ratio was 4.71:1.

Most common clinical feature of the study population was Hematuria (86.3%) followed by Dysuria (62.5%) and Urinary frequency (42.5%). Majority of the patients presented with more than one clinical symptoms (n=48; 60.0%).

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Case-sheet records for Location of tumour were available only for 63 patients. No records regarding tumour location could be retrieved for remaining 17 cases. Out of 63 cases, in majority of the cases tumour was located at lateral wall (76.2%) while that in bladder neck in only 6.3% of cases and in rest of the 17.5% cases tumour was located at other sites.

Majority of the tissue specimens analysed in the present study were of TURBT (92.5%) and rest were of Radical cystectomy (including 1 partial cystectomy).

Majority of the specimens were graded as Low grade tumours (58.8%). Only 41.3% tissue specimens were graded as High Grade tumours.

None of the patient was found to be stage pT3/T4. Most common pathologic stage of tumour was pT1 (42.5%), followed by pT2 (32.5%) while least common pathologic tumour stage was pTa (7.5%), followed by pTis (17.5%).

No lymphocytic infiltration was observed in 19 (23.8%) cases. Focal infiltration and diffuse infiltration were observed in 38.8% and 37.5% cases, respectively.

Majority of the cases were Conventional UC (83.8%), other common types were Squamoid, Glandular and Signet ring (5.0%, 6.3% & 2.5%). Apart from these, 1 (1.3%) case each was differentiated as Sarcomatoid and Sarcomatoid with glandular variant.

Expression of PD-L1 was found to be negative (≤1% tumour cells expressing PD-L1) for one-fourth of the cases (25.0%). Weak expression (2%-50% tumour cells expressing PD-L1) was observed for 48.8% cases and Strong expression (51%-100%tumour cells expressing PD-L1) for only 26.3% cases.

Out of 80 (100.0%) cases of Urothelial carcinoma enrolled in the study, 23 (28.8%) expired during the study period, rest were alive.

Out of 80 cases of Urothelial carcinoma 23 expired during the study and 57 remained the part of the study till completion. Of these 57 cases recurrence of urothelial carcinoma was observed in 9 (15.8%) cases only.

Strong expression of PD-L1 was observed among higher proportion of cases of lower age groups *i.e.* aged ≤25 years (14.3% vs. 0.0% negative & 2.6% weak) while Weak expression was observed in higher proportion of patients of older age *i.e.* 51-75 age (74.4% vs. 60.0% negative & 57.1% Strong). Proportion of negative expression of PD-L1 was higher among age extremely older patients *i.e.* >75 years (15.0% vs. 0.0% Weak & strong each). This association was found to be statistically significant (p=0.020).

Though Strong expression of PD-L1 as compared to negative expression and Weak expression was observed in higher proportion of females (28.6% vs. 15.0% & 12.8%) but this association was not found to be statistically significant (p=0.292).

Among cases presenting with hematuria proportion of Weak expression of PD-L1 was higher as compared to negative and Strong expression (87.2% vs. 85.0% & 85.7%) but statistically this difference was found to be comparable (p=0.971). Similar findings were observed for patients presenting with Other clinical features (5.1% weak vs. 5.0% negative & 0.0% strong), this association too was not found to be significant statistically (p=0.574).

Proportion of PD-L1 strong expression was higher as compared to negative expression and weak expression among cases presenting with dysuria (71.4% vs. 55.0% & 61.5%) and Urinary frequency (47.6% vs. 40.0% & 41.0%), none of the above associations were found to be significant statistically (p>0.05).

Weak expression of PD-L1 was observed in higher proportion as compared to negative and strong expression in tumours located at lateral wall (82.76% vs. 68.7% & 72.2%), while strong expression of PD-L1 was observed in higher proportion of tumours located at Bladder neck (11.1% vs. 6.25% negative, 3.45% weak). Among patients with tumour located at other sites negative expression was higher as compared to weak and strong expression (25.0% vs. 13.79% & 16.7%). This association too was not found to be statistically significant (p=0.718).

Among High grade tumours Strong PD-L1 expression was more prevalent as compared to Negative and Weak expression (100.0% vs. 10.0% negative& 25.6% weak). This association was found to be significant statistically (p=0.003).

Strong PD-L1 expression was observed in higher proportion of pT2 stage tumours (61.9% vs. 15.0% negative & 25.6% Weak). Weak PD-L1 expression was observed in higher proportion of pT1 stage tumours (51.3% vs. 35.0% negative & 33.3% strong) and pTa (10.3% vs. 10.0% negative & 0.0% strong) while proportion of Negative PD-L1 expression was higher among patients of tumour stage pTis (40.0% vs. 12.8% weak & 4.8% strong). Association of Tumour stage was found to be significant statistically (p=0.003). Majority of patients of pT1 and pT2 stage had weak (76.9%) or strong level of expression (95.2%).

All the cases with strong PD-L1 expression had diffuse tumour lymphocytic infiltration. Majority of the cases with Weak expression had Focal tumour lymphocytic infiltration (76.9%) and rest had diffuse tumour lymphocytic infiltration (20.5%). While majority of the cases with negative PD-L1 expression had no tumour lymphocytic expression (90.0%). This association was found to be statistically highly significant (p<0.001).

No statistically significant association of PD-L1 expression with nuclear pleomorphism, mitosis, necrosis and LVI was observed.

Negative expression was observed in higher proportion of Sarcomatoid & Sarcomatoid with glandular variants (5.0% vs. 0.0% weak & 0.0% strong).
Weak expression was observed in higher proportion of Conventional UC cases (92.3% vs. 90.0% negative vs. 61.9% strong).
Strong expression was observed in higher proportion as compared to negative and weak expression in cases of Signet ring (4.8% vs. 2.6% weak & 0.0% negative), Squamoid (9.5% vs. 0.0% negative and 5.1% weak) and Glandular variants (23.8% vs. 0.0% weak & 0.0% negative).
Association of PD-L1 expression and differentiation of tumours was found to be statistically significant (p=0.006).
Proportion of Strong PD-L1 expression as compared to negative and weak expression was higher in expired cases (47.6% vs. 30.0% negative& 17.9% weak), but this association was not found to be statistically significant (p=0.053).
Proportion of Strong PD-L1 expression as compared to negative and weak expression was higher in cases with recurrence of urothelial carcinoma (45.5% vs. 7.1% negative& 9.4% weak), this association was found to be statistically significant (p=0.011).

DISCUSSION

In the beginning an unknown co-stimulatory molecule was identified known to be involved in the negative regulation of immune mediated responses, which was later studied and defined by *Dong H et al.* (1999)[19] as PD-L1 (Programmed Death-Ligand 1) in 1999. Since then, PD-L1 is emerging as a potential biomarker in various carcinomas including urothelial carcinomas. Various studies have been carried out addressing PD-L1 expression in urothelial carcinomas.
and immunohistochemical markers. Thus, keeping in mind the above fact we have conducted our present study where correlation of PD-L1 expression with various clinic-pathologic parameters of urothelial carcinomas has been analysed.
This study included a total of 80 cases of urothelial carcinoma whose histopathology and PD-L1 immunohistochemistry was performed and assessed in The Department of Pathology, King George's Medical University.
Majority (70%) patients were aged >50 years. The median age was **56** years (Age range 18-86 years). The study had predominantly males (82.5%) as compared to females (17.5%) with a Male: Female ratio of 4.71:1.
The most common clinical feature was Hematuria (86.3%) amongst the study population, followed by dysuria (62.5%). Majority (76.2%) of the tumours were located at the lateral wall of the urinary bladder and were received predominantly as TURBT (Transurethral Resection of Bladder Tumour) specimens (92.5%).

CONCLUSION

Majority of cases with tumour recurrence showed strong positive PD-L1 expression and this association was found to be significant suggesting that degree of PD-L1 expression may be a crucial determinant of tumour invasiveness not only for primary tumours but also for recurrent tumours.

Ethical clearance- Taken from ethical committee of institution

Source of funding- Self

Conflict of Interest – Nil

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