Med. J. Cairo Univ., Vol. 86, No. 5, September: 2687-2695, 2018
www.medicaljournalofcairouniversity.net

Immunohistochemical Study of the Role of CK20, p53 and Ki-67 in Differentiation of Some Urothelial Lesions and Urothelial Carcinoma of the Urinary Bladder

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Abstract

Background: Bladder cancer is the most common malignancy affecting the urinary tract. Distinguishing between urothelial dysplasia and carcinoma in situ based on histopathological features alone is often difficult.

Aim of Work: The aim of the current work is to distinguish between urothelial hyperplasia, urothelial dysplasia from urothelial carcinoma by using CK20, p53 and Ki-67 immunomarkers, determine the pattern and extent of their immunoreactivity and correlate immuno-histochemical results with the clinicopathological parameters.

Material and Methods: Fifty cases of urothelial carcinoma (38 cases) and some flat urothelial lesions (12 cases) were collected retrospectively. Tissue specimens were in the form of radical cystectomy (nine specimens) and transurethral resection of the tumor (TURT) (forty one specimens). They were stained by H&E, CK20, p53 and Ki-67 for immunohistochemical study. The relationship between their expression and the available clinicopathological features were evaluated.

Results: CK20, p53 and Ki-67 expressions can significantly differentiate urothelial hyperplasia from urothelial dysplasia as the whole panel is negative in urothelial hyperplasia and positive with scattered expression in urothelial dysplasia. Also pattern of expression of CK20, p53 and Ki-67 expression are suggesting for the diagnosis of either urothelial dysplasia or urothelial carcinoma in situ as their expressions show diffuse positivity throughout the urothelium in urothelial carcinoma in situ. These markers were statistically significant in grading of urothelial carcinoma as higher tumor grade associated with decreased CK20 expression and increased p53 and Ki-67 expression. CK20 expression was statistically significant in tumor stage as higher tumor stage was associated with decreased CK20 expression.

Conclusions: Abnormal CK20 expression in urothelial cells plus overexpression of p53 and Ki-67 are indicators of dysplastic change in urothelial mucosa. A panel of CK20, p53 and Ki-67 can be a useful tool to confirm the diagnosis of CIS and can be helpful to distinguish it from dysplastic changes. Combined use of these markers may be helpful in assigning grade of urothelial carcinoma especially when histologic features are borderline.

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Key Words: *CK20 – p53 – Ki-67 – Bladder cancer – Urothelial lesions – Immunohistochemistry – Differentiation.*

Introduction

BLADDER cancer (BC) is the most common malignancy in the urinary tract and urothelial carcinoma (UC) is the predominant histological type [1]. It is the 6th most common cancer worldwide in men and the 17th most common cancer worldwide in women [2]. In Gharbia government, bladder cancer ranks the 3rd in both sexes being the 2nd in males and the 7th in females [3]. It is at least three times more common in men than women [1]. Excessive exposure to carcinogens, e.g. cigarette smoke and industrial chemicals, has been suggested to be a cause of higher incidence of bladder cancer in males [4]. Flat urothelial lesions show many varieties including urothelial hyperplasia and urothelial dysplasia. Urothelial hyperplasia is a benign urothelial lesion. It is characterized by markedly thickened mucosa with an increase in the number of cell layers, usually 10 or more. The cells do not show any significant cytologic abnormalities [5]. Urothelial dysplasia identifies urothelial dysplasia (low-grade intra urothelial neoplasia) as a premalignant lesion of the urothelium and it is defined as abnormal urothelium with distinctive cytologic and architectural changes that do not meet all the criteria for the unequivocal diagnosis of urothelial carcinoma in situ (CIS) [6]. Urothelial carcinoma in situ is a flat high grade non-invasive urothelial carcinoma with the potential for invasion and metastases [7]. Distinguishing between urothelial dysplasia and carcinoma in situ based on histopathological features alone is often difficult. Different immuno-histochemical markers such as Cytokeratin 20 (CK20), p53, and Ki-67 are important for this differential diagnosis [8].

Patients and Methods

Fifty cases were collected retrospectively from the archives of Pathology Department, Faculty of Medicine, Tanta University during the period of the research from January 2016 to April 2017, urothelial carcinoma (38 cases) and some flat urothelial lesions (12 cases). Approval from research ethics committee (REC), Faculty of Medicine, Tanta University, was taken antecedent to conducting study. Tissue specimens were in the form of radical cystectomy (9 specimens) and transurethral resection of the tumor (TURT) (41 specimens). After histopathological evaluation, tumors were graded according to the WHO 2016 of urothelial neoplasia, and they were classified as low grade and high grade urothelial carcinoma. Tumors were staged according to American Joint Committee (AJCC), TNM pathologic staging of urinary bladder. Immunohistochemical staining was performed on 10% formalin fixed, paraffin embedded tissue blocks for evaluation of CK20, p53 and Ki-67 expression. Sections were immunohistochemically stained, using primary antibodies to CK20 antibody which is a mouse monoclonal antibody (DAKO, Anti-human Cytokeratin 20, Clone Ks20.8) (dilution 1: 200), p53 antibody which is a rabbit monoclonal antibody (Kit no. MBS8507352, labvision) (dilution 1: 100) and Ki-67 antibody which is a mouse monoclonal antibody (DAKO, Anti-human Ki-67 Antigen/FITC) (dilution 1:800). Cytokeratin 20 was detected as cytoplasmic staining; expression was divided into positive and negative expression. Positive expression was called when immunoexpression was seen in deeper layers of urothelium as clusters of more than three positively stained cells or diffuse staining of urothelium. Negative expression was defined as cytokeratin 20 staining restricted to superficial cells of the urothelium or less than three cells in intermediate cells of the urothelium [9]. Positive expression of p53 was considered when ≥20% of the cells counted from most immunoreactive region of the section show nuclear staining for p53 [9]. Positive Ki-67 staining was observed as brown nuclear staining. Ki-67 was considered positive when >10% of cells showed nuclear positive expression [8]. Chi-square test and Spearman's correlation coefficient test were used as tests of significance to evaluate the association between categorized variables and p-value <0.05 was considered statistically significant.

Results

This study was carried out on 50 cases. The studied cases were classified into two major groups as shown in (Table 1).

- *Group I:* 12 cases of flat urothelial lesion.
- *Group II:* 38 cases with urothelial carcinoma.

In group I, the age of patients ranged from 40 to 80 years with a mean of 56.47 ± 12.76 years and (25%) of cases suffered from hematuria and dysuria. In group II the age of patients ranged from 42 to 78 years with a mean of 59.43 ±9.97 years and 73.7% suffered from hematuria and dysuria. The relation of clinical symptoms in the studied groups was statistically significant (p-value=0.002).

A- *Histopathologic results:*

Group I cases were divided into:

- Urothelial hyperplasia (7 cases) representing 58.3% of group I cases.

Microscopically: Thickened urothelial mucosa with increase in number of cell layers without cytologic atypia.

- Urothelial Dysplasia (5 cases) representing 41.7% of group I cases.

Microscopically: Urothelial dysplasia showed cellular crowding and loss of cellular polarity which did not present in full thickness of the urothelium.

B- *Immunohistochemical results:*

I- CK20 immunoexpression in group I cases:

CK20 expression was expressed by cytoplasmic staining and its expression as shown in Table (2), Figs. (1A,1B).

II- p53 immunoexpression in group I cases:

p53 expression was detected by nuclear staining and its expression as shown in Table (3), Figs. (2A, 2B).

III- Ki-67 immunoexpression in group I cases:

Ki-67 expression was negative in all 7 cases (100%) of urothelial hyperplasia (Fig. 3A) while all 5 cases (100%) of urothelial dysplasia were positive to ki-67 and scattered throughout the urothelium (Fig 3B).This result was statistically significant.

Results of group II (urothelial carcinoma) (38 Cases):

A- *Histopathologic results:*

1- *Histopathological types of the studied cases of group II:*

According to WHO (2016) histological classification of urothelial carcinoma (Humphrey et al.,

2016), group II cases were classified as shown in (Table 1). Group II cases were classified into 11 cases (29%) of non-infiltrating urothelial neoplasms and 27 cases (71%) of infiltrating urothelial carcinoma.

2- Tumor grading of urothelial carcinoma cases of group II:

Out of cases of urothelial carcinoma as shown in (Table 4), eight cases were low grade urothelial carcinoma formed of transitional cells with minimal degree of atypia, mitoses were rare or absent and 30 cases were high grade urothelial carcinoma formed of groups of cell masses with moderate to severe degree of cellular atypia, pleomorphism and mitotic figures were frequent

3- Tumor staging of urothelial carcinoma cases of group II:

According to American joint committee on cancer (AJCC) TNM staging of urinary bladder carcinomas, cases of group II were categorized into:

Ta: Six cases representing 15.8% of group II cases were non-invasive papillary carcinoma.

Tis: Five cases representing 13.2% of group II cases were carcinoma in situ.

T1: Nine cases representing 23.7% of group II cases. They included tumor with lamina propria invasion (Figs. 5-14, 5-15).

T2: Thirteen cases representing 34.2% of group II cases. They included tumor with invasion of muscularis propria invasion.

T3: Three cases representing 7.9% of group II cases, included tumors invading perivesical tissue.

T4: Two case of urothelial carcinoma, representing 5.3% of group II cases. They included tumor with invasion of prostate.

I- Results of immunohistochemical expression of CK20 in group II cases:

- *CK20 immunoexpression in istopathological types o*f group II cases:

CK20 expression was detected as cytoplasmic staining in 20 cases (52.6%), while 18 cases (47.4%) were negative to CK20. Four cases out of 5 cases of urothelial carcinoma in situ were positive to CK20 expression and extending diffusely throughout the urothelium, representing (80%) (Fig. 4A), one case (20 %) CK20 expression was negative. Two cases of nested variant of urothelial carcinoma were positive to CK20 (Fig. 4B) (Table 5).

- *Relation between CK20 expression and tumor grade of urothelial carcinoma cases of group II:*

There was difference in CK20 expressions between low and high grade cases. CK20 expression was positive in 7 cases (87.5%) of low grade urothelial carcinoma and Thirteen cases (46.7%) of high grade urothelial carcinoma was positive to CK20. The correlation between CK20 expression and tumor grade of urothelial carcinoma cases was statistically significant.

- *Relation between CK20 expression and tumor staging of urothelial carcinoma cases of group II:*

There was difference in CK20 expressions with increasing tumor stage; higher tumor stage associated with decreased CK20 expression. All two cases of T4 were negative to CK20 expression. The correlation between CK20 expression and tumor stage of urothelial carcinoma cases was statistically significant (p-value=0.021).

II- Results of immunohistochemical expression of p53 in group II cases:

- *Relation between p53 expression and tumor grade of urothelial carcinoma cases of group II:*

There was difference in p53 expressions between low and high grade cases .p53 expression was positive in four cases (50%) of low grade urothelial carcinoma. Twenty seven cases of high grade urothelial carcinoma (90%) were positive to p53 (Figs. 5A,5 B).

The relation between p53 expression and tumor grade of urothelial carcinoma cases was statistically significant.

- *Relation between p53 expression and tumor stage of urothelial carcinoma cases of group II:*

There was difference in p53 expressions with increasing tumor stage as higher tumor stage associated with increased p53 expression, inspite this relation was insignificant. All two cases of T4 were positive to p53 expression. All three cases of T3 were positive to p53 expression.

III- Results of immunohistochemical expression of ki-67 in group II cases:

- *Relation between Ki-67expression and tumor grade of urothelial carcinoma cases of group II:*

There was difference in Ki-67 expressions between low and high grade cases. Ki-67 expression was positive in four cases (50%) of low grade urothelial carcinoma and (83.3%) of high grade cases were Ki-67 positive (Figs. 6A,6B). The relation between ki-67 expression and tumor grade

of urothelial carcinoma cases was statistically significant (p-value=0.049).

- *Relation between Ki-67 expression and tumor stage of urothelial carcinoma cases of group II:*

There was difference in Ki-67expressions with increasing tumor stage as higher tumor stage associated with increased Ki-67 expression, inspite this relation was insignificant. All three cases of T3 and two cases of T4 were positive to Ki-67 expression. Five cases (55.6%) of T1 were positive to Ki-67 expression while four cases (44.4%) were negative to Ki-67 expression. Eleven cases (84.6%) of T2 cases were positive to Ki-67 expression and two cases (15.4%) were negative to Ki-67 expression. Four cases (66.7%) of Ta cases were positive to Ki-76 while 2 (33.3%) were negative to Ki-76 expression. Four cases (80%) out of five cases of Tis cases were Ki-67 expression positive only one was negative to Ki-67 expression.

IV- Correlation between tumor grade of urothelial carcinoma cases and different immunomarkers expression in group II cases:

Correlation of CK20, p53 and Ki-67 expression in high grade urothelial carcinoma (30 cases) (Table 6).

In high grade urothelial carcinoma CK20 expression was positive in 43.3% of cases in contrast to higher p53 expression (90% of cases) and Ki-67 expression (83.3% of cases). This relation was statistically significant.

Table (1): Histopathological distribution of the studied cases.

Histologic types	N	%
Group I:	12	24
- Hyperplasia	7	58.3
- Dysplasia	5	41.7
Group II:	38	76
Non-infiltrating urothelial carcinoma:	11	29
- CIS	5	13.2
- Non-infiltrating low grade papillary urothelial carcinoma	3	7.9
- Non-infiltrating high grade papillary urothelial carcinoma	3	7.9
Infiltrating urothelial carcinoma:	27	71
- Pure Infiltrating urothelial carcinoma	12	31.6
- With squamous differentiation	5	13.2
- With glandular differentiation	3	7.9
- Sarcomatoid	3	7.9
- Nested	2	5.3
- Plasmacytoid	1	2.6
- Clear	1	2.6
Total	50	100

Table (2): CK20 immunoexpression in group I cases.

CK20 expression in non umbrella cells	Hyperplasia	Dysplasia	Total
–ve			
N	7	2	9
%	100	40	75
+ve			
N	0	3	3
%	0	60	25
Total			
N	7	5	12
%	100.0	100.0	100.0
Chi-square			
X^2		5.602	
p-value		0.018*	

* Significant (p-value <0.05).

Table (3): p53 immunoexpression in group I cases.

p53s	Hyperplasia	Dysplasia	Total
–ve			
N	7	1	8
%	100	20.0	66.7
+ve			
N	0	4	4
%	.0	80.0	33.3
Total			
N	7	5	12
%	100	100%	100.0
Chi-square			
X^2		5.182	
p-value		0.023*	

* Significant (p-value <0.05).

Table (4): Tumor grading of urothelial carcinoma cases of group II.

Grade	N	%
Low	8	21.1
Non-infiltrating urothelial carcinoma:		
• Non-infiltrating low grade papillary urothelial carcinoma	3	7.9
Infiltrating urothelial carcinoma:	5	13.2
• Pure infiltrating urothelial carcinoma	3	7.9
• Nested variant of urothelial carcinoma	2	5.3
High	30	78.9
Non-infiltrating urothelial carcinoma:	8	21.1
• Urothelial carcinoma in situ	5	13.2
• Non-infiltrating high grade papillary urothelial carcinoma	3	7.9
Infiltrating urothelial carcinoma:	22	57.9
• Pure infiltrating urothelial carcinoma	9	23.7
• With squamous differentiation	5	13.2
• With glandular differentiation	3	7.9
• Sarcomatoid	3	7.9
• Plasmacytoid	1	2.6
• Clear	1	2.6
Total	38	100

Table (5): CK20 immunoexpression in urothelial carcinoma cases of group II.

Urothelial Carcinoma	CK20 –ve	CK20 +ve	Total
Non-infiltrating urothelial carcinoma:			
CIS:			
N	1	4	5
%	20.0	80.0	100.0
Non-infiltrating Papillary urothelial carcinoma low grade:			
N	0	3	3
%	0	100	100
Non-infiltrating Papillary urothelial carcinoma high grade:			
N	1	2	3
%	33.3	66.7	100
Infiltrating urothelial carcinoma:			
Pure infiltrating urothelial carcinoma:			
N	6	6	12
%	50.0	50.0	100
Squamous:			
N	4	1	5
%	80.0	20.0	100
Glandular:			
N	1	2	3
%	33.3	66.7	100
Sarcomatoid:			
N	3	0	3
%	100	0	100
Nested:			
N	0	2	2
%	0	100	100
Plasmacytoid:			
N	1	0	1
%	100	0	100
Clear:			
N	1	0	1
%	100	0	100
Total:			
N	18	20	38
%	47.4	52.6	100
Chi-square:			
X^2	17.237		
p-value	0.045*		

Table (6): Correlation of CK20, p53 and Ki-67 expression in high grade urothelial carcinoma cases.

High	–ve	+ve	Total
CK20:			
N	17	13	30
%	56.7	43.3	100.0
p53:			
N	3	27	30
%	10	90	100.0
Ki-67:			
N	5	25	30
%	16.7	83.3	100.0
Chi-square:			
X^2	19.053		
p-value	0.001 *		

* Significant (*p*-value <0.05).

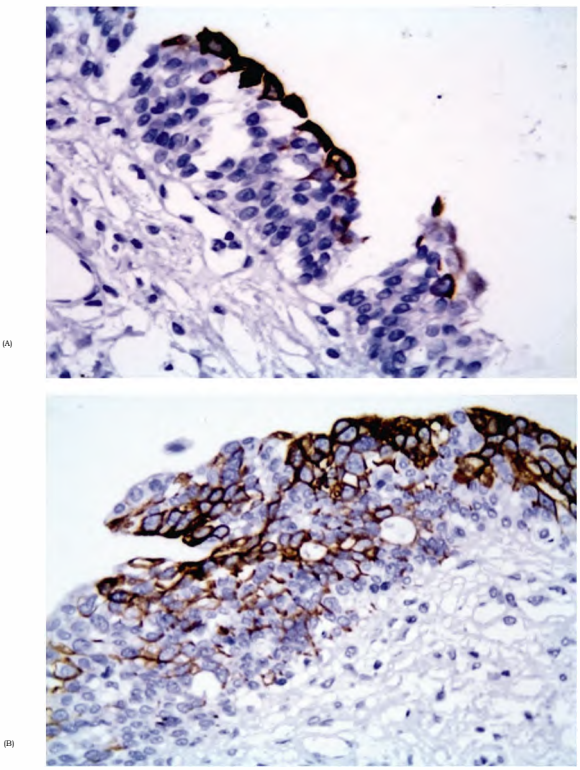

Fig. (1 A,B): (A): Urothelial hyperplasia showing positive cytoplasmic expression of CK20 in umbrella cells only and negative expression in rest of urothelial cells. (streptavidin biotin x 400) (B): Urothelial dysplasia showing positive cytoplasmic expression of CK20 scattered throughout the urothelium. (streptavidin biotin x 400).

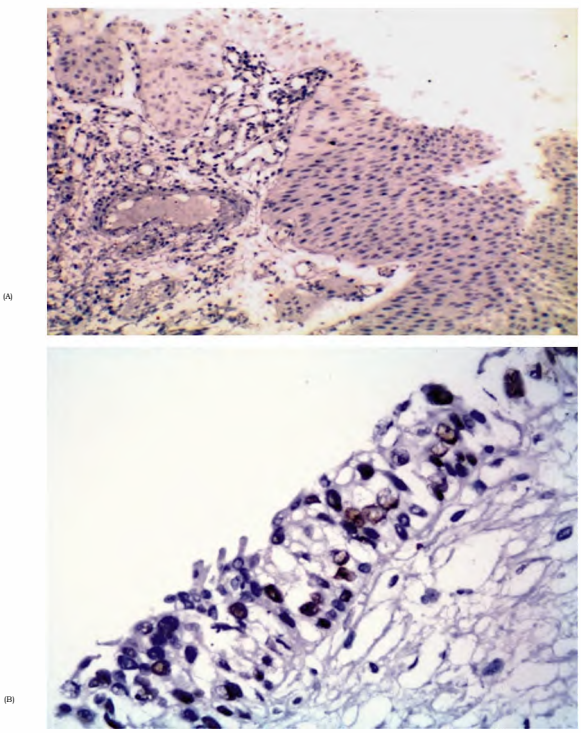

Fig. (2 A,B): (A): Urothelial hyperplasia showing negative nuclear expression of p53.(streptavidin biotin x 200) B: Urothelial dysplasia showing positive nuclear expression of p53, not in full thickness of the urothelium.(streptavidin biotin x 400).

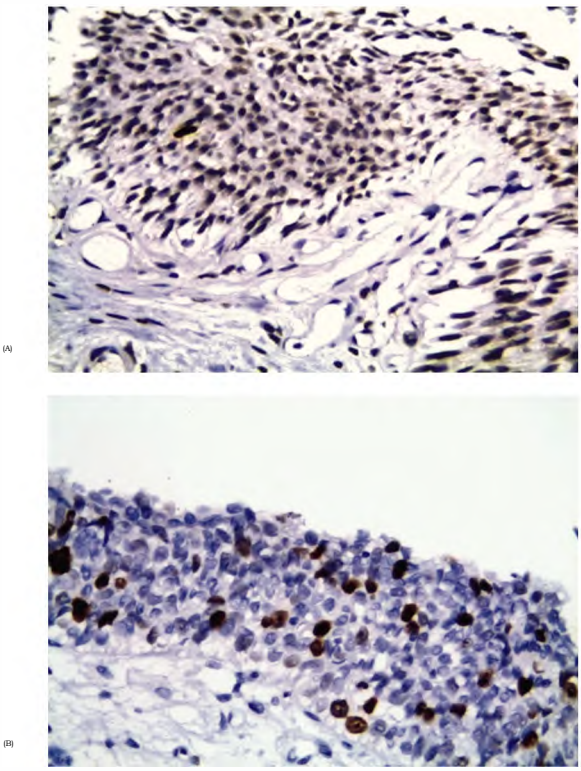

Fig. (3A,B): (A): Urothelial hyperplasia showing negative nuclear expression of ki-67.(streptavidin biotin x 200) (B): Urothelial dysplasia showing positive nuclear expression of p53, scattered throughout the urothelium.(streptavidin biotin x 400)

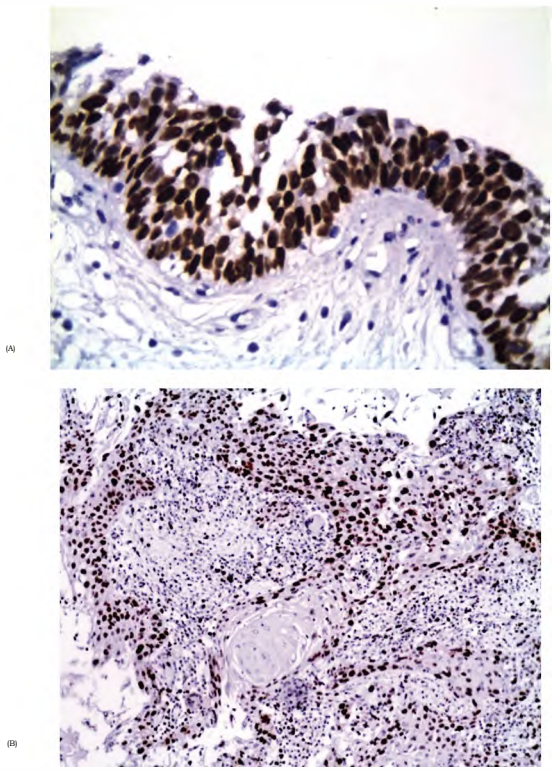

Fig. (5A,B): (A): Urothelial carcinoma in situ showing positive cytoplasmic expression of p53 diffusely in full thickness of the urothelium. (streptavidin biotin x 400) (B): Infiltrating high grade urothelial carcinoma with squamous differentiation showing positive nuclear expression of p53 (streptavidin biotin x 200).

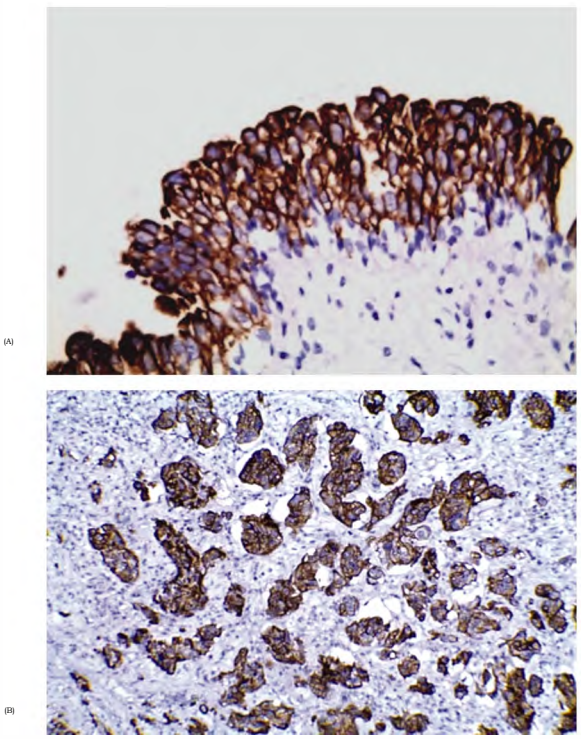

Fig. (4A,B): (A): Urothelial carcinoma in situ showing positive cytoplasmic expression of CK20 diffusely in full thickness of the urothelium. (streptavidin biotin x 400) (B): Low grade infiltrating urothelial carcinoma nested variant showing positive cytoplasmic expression of CK20. (streptavidin biotin x 200).

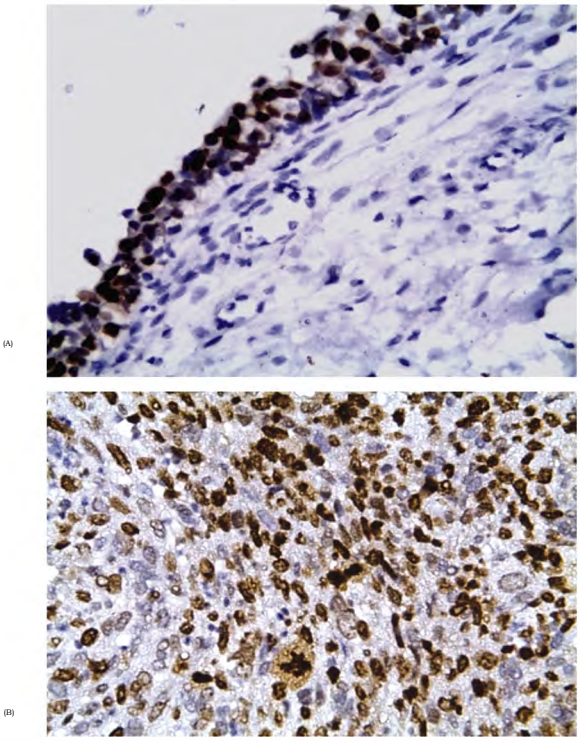

Fig. (6A,B): (A): Urothelial carcinoma in situ showing positive cytoplasmic expression of Ki-67 diffusely in full thickness of the urothelium. (streptavidin biotin x 400) (B): High grade urothelial carcinoma ,sarcomatoid variant showing positive nuclear expression of p53 (streptavidin biotin x 400).

Discussion

CK20 is considered a marker of urothelial differentiation. Cytokeratin 20 shows a limited pattern of expression in normal tissues **[10]**. In the present study, CK20 expression in urothelial hyperplasia was restricted to the umbrella cells in all cases (100%). This finding is parallel to Abdel Raheem et al., **[11]**. who found that CK20 expression restricted to the umbrella cells in all cases of urothelial hyperplasia cases (100%). In urothelial dysplasia 60% of cases showed scattered CK20 positive expression throughout the urothelium. This finding was parallel to Mallofré et al., **[12]**. who found the suspected dysplastic cells showed strong positivity in scattered cells through the epithelium in 75% of cases.

CK20 expression was positive in 80% of urothelial carcinoma in situ cases with diffuse immunoreactivity through the full thickness, which was in agreement with Yin et al., **[13]**. who found CK20 expression in urothelial carcinoma in situ in 89% and 11% failed to stain with CK2S0. Also Jung et al., **[14]** reported lower CK20 expression 61% in urothelial carcinoma in situ cases with full thickness cytoplasmic expression of CK20.

It was found that there was significant correlation between CK20 immunohistochemical expression and tumor grading of urothelial carcinoma cases; low grade (87.5%) and high grade (46.7%). The correlation between CK20 immunohistochemical expression and tumor stage of urothelial carcinoma was statistically significant.

p53 is a transcription factor(tumor suppressor gene) **[15]**. p53 expression in urothelial hyperplasia was negative in all cases but in urothelial dysplasia p53 was positive in 80% cases with scattered expression throughout the epithelium. Abdel Raheem et al., **[11]** detected p53 expression was negative in all cases of urothelial hyperplasia and positive in all cases of urothelial dysplasia with scattered expression throughout the epithelium while Mallofré et al., **[12]** found P53 expression in urothelial dysplasia 50% of cases. In the present study, urothelial carcinoma in situ cases showed p53 expression in 100% of cases with diffuse immunoreactivity throughout the urothelium. This was parallel to Mallofré et al., **[12]** who found p53 expression in 80% of urothelial carcinoma in situ in full thickness of the urothelium.

In the present study there was significant direct correlation between p53 expression and the tumor grade of urothelial carcinoma cases. Dealing with the tumor stage of urothelial carcinoma cases, the present study showed that there was no statistically significant correlation between p53 expression and tumor stage.

Ki-67 is a cellular marker for proliferation **[16]**. In the present study, Ki-67 expression was negative in all cases of urothelial hyperplasia. This is in agreement with the findings of Yin et al., **[13]**. who reported that 93% showed negative Ki-67 expression and 7% of urothelial hyperplasia showed positive Ki-67 expression and explained that by the biopsy was considered to show sufficient nuclear abnormalities to be re-diagnosed as dysplasia. In the present study, in urothelial dysplasia, Ki-67 was positive in all cases. This close to Mallofré et al., **[12]** found lower Ki-67 expression in 90% of urothelial dysplasia. Ki-67 expression in urothelial carcinoma in situ was 80%. A lower finding was reported by Asgari et al., **[8]** who found Ki-67 expression in urothelial carcinoma in situ in 65%.

In the present study there was significant direct correlation between Ki-67 expression and tumor grade of urothelial carcinoma cases. This could be explained by that progressive increase of Ki-67 in high grade may be linked to tumor aggressiveness and loss of differentiation of urothelial cancer. Dealing with tumor stage of urothelial carcinoma cases, the present study proved that there was no statistically significant correlation between Ki-67 expression with the tumor stage.

In the present study, expression of CK20, p53 and Ki-67 in urothelial carcinoma cases was positive through the full thickness of the urothelium. This was also reported by Abdel Raheem et al., **[11]**, while Arias-Stella et al., **[17]** reported that other additional markers had been less frequently evaluated for the same purpose including CD44 and Her2/Neu.

In the present study, there was difference in the expression of CK20, p53 and Ki-67 in low grade and high grade urothelial carcinoma cases as high grade cases associated with decreased CK20 expression and increased p53 and Ki-67 expressions and this is in agreement with Abdel Raheem et al., **[11]**.

In this study, p-value of p53 expression in group I and group II was 0.001 and p-value of Ki-67 expression in group I and group II was 0.025, so p53 expression was more significant than Ki-67 expression, in contrast to Mallofré et al., **[12]**. who studied the expression of CK20, p53, Ki-67 in non-neoplastic urothelial samples, carcinoma in situ and cases with atypical changes and found that Ki-67 is the most constant marker.

Conflict of interest:

None declared.

References

1- SEBASTIEN A., JACQUES F., ISABELLE S., et al.: Bladder Cancer Incidence and Mortality: A Global Overview and Recent Trends. European Urology, 71: 96-108, 2017.

2- FERLAY J.I., DIKSHIT R., ESER S., et al.: Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. International Journal of Cancer, 136 (5): E359-E386, 2015.

3- ELSHIKH E., ANAN I., EBAID A., et al.: The National Cancer Registry in Egypt: A retrospective Cross Sectional Epidemiological Study. Value in Health, 18: 437, 2015.

4- CUMBERBATCH M., ROTA M., CATTO J., et al.: The role of tobacco smoke in bladder and kidney carcinogenesis: A comparison of exposures and meta-analysis of incidence and mortality risks. Eur. Urol., 70: 458-66, 2016.

5- LOPEZ-BELTRAN A., MARQUES R.C., MONTIRONI R., et al.: Dysplasia and carcinoma in situ of the urinary bladder. Anal. Quant. Cytopathol. Histopathol., 37: 29-38, 2015.

6- HUMPHREY P.A., MOCH H., CUBILLA A.L., et al.: The 2016 WHO classification of tumours of the urinary system and male genital organs-part B: Prostate and bladder tumours. European Urology, 70 (1): 106-119, 2016.

7- CASEY R.G., CATTO J.W., CHENG L., et al.: Diagnosis and management of urothelial carcinoma in situ of the lower urinary tract: A systematic review. European Urology, 67 (5): 876-888, 2015.

8- ASGARI M., NABI MAYBODI M. and ABOLHASANI M.: Differential diagnosis of urothelial carcinoma in situ from non-neoplastic urothelia: Analysis of CK20, CD44, P53 and Ki-67: Medical Journal of the Islamic Republic of Iran, 30, 400, 2016.

9- MUMTAZ S., HASHMI A.A., HASAN S.H., et al.: Diagnostic utility of p53 & CK20 immunohistochemical expression grading urothelial malignancies. International Archives of Medicine, 7: 36, 2014.

10- NETTO G.J. and EPSTEIN J.: Immunohistology of the bladder, kidney and testis, Diagnostic Immunohistochemistry, Chapter, 17: 615-618, 2013.

11- ABDEL RAHEEM S., ABDEL NABY S., RABEE A., et al.: The Role of CK20, p53 and p63 in Differentiation of Some Urothelial Lesions of Urinary Bladder, Immunohistochemical Study. Open Journal of Pathology, 4: 181-193, 2014.

12- MALLOFRÉ C., CASTILLO M., MORENTE V., et al.: Immunohistochemical Expression of CK20, p53, and Ki-67 as Objective Markers of Urothelial Dysplasia. Mod. Pathol., 16 (3): 187, 2003.

13- YIN H., HE Q., LI T., et al.: Cytokeratin 20 and Ki-67 to Distinguish Carcinoma in Situ from Flat Non-neoplastic Urothelium. Appl Immunohistochem Mol. Morphol., 14 (3): 260-265, 2006.

14- JUNG S., WU C., ESLAMI Z., et al.: The role of immunohistochemistry in the diagnosis of flat urothelial lesions: A study using CK20, CK5/6, P53, Cd138, and Her2/Neu. Annals of Diagnostic Pathology, 18 (1): 27-32, 2014.

15- FAUSTINO V.K., JONES J. and LUIZA A.: Cloning and Characterization of p53 DNA Binding Domain, UCRiverside, 2016.

16- FASCHING A., HEUSINGER K., HAEBERLE L., et al: Ki67, chemotherapy response, and prognosis in breast cancer patients receiving neoadjuvant treatment, BMC Cancer, 11: 486, 2011.

17- ARIAS-STELLA III J.A., SHAH A.B., GUPTA N.S., et al.: CK20 and p53 Immunohistochemical Staining Patterns in Urinary Bladder Specimens With Equivocal Atypia: Correlation With Outcomes. Archives of Pathology & Laboratory Medicine, 2017.

دراسة هستوكيميائية مناعية عن دورسيتوكيراتين ٢٠ وبى ٥٣ وكى اى ٦٧ فى التفرقة بين بعض إصابات الظهارة البولية وسرطان الظهارة البولية للمثانة

تظهر آفات الظهارة البو لية المسطحة فى العديد من الأشكال ومنها فرط التنسج وخلل التنسج. ويعد فرط التنسج من الآفات الحميدة ويعرف خلل التنسج بأنه نوع غير طبيعى من الظهاره البولية مع وجود تغيرات خلوية و تهندسية ؤكنها ترقى إلى درجة السرطان اللابد كذلك يعتبر السرطان اللابد من الأنواع التى تتميز بأنها عالية التدرج وغير غزوانية لكن مع وجود إحتمالية الغزو والأنتشار. يعد انتشار سرطان المثانة من أ كثر الأورام الخبيثة فى الجهاز البولى ويعد سادس أنواع السرطان أنتشاراً فىالعالم.

يساعد تعبر السيتوكيراتين ٢٠ فى التمييز بين فرط وخلل التنسج حيث يكون سالب التعبر فى كل خلايا الظهارة البولية ومقيد فى خلايا الأمبريلا فى حالة فرط التنسج وموجب التعبر وغير مقيد على خلايا مظلة ومتناثرة فى جميع انحاء أوروثيليوم فى خلل التنسج البطانى. أما فى سرطان البطانة فى الموقع، كان سيتوكيراتين ٢٠ منتشر فى سمك كامل من أوروثيليوم. أما فى حالة بى ٥٣ فكان سالب التعبر فى حالة فرط التنسج وإيجابى فى خلايا متناثرة فى جميع انحاء أوروثيليوم فى حالة خلل التنسج وذلك فى ٨٠٪ من العينات أما فى سرطان البطانة فى الموقع، كان بى ٥٣ منتشر فى سمك كامل من أوروثيليوم. وعن كى اى ٦٧ فقد كانت سالبة فى حالة فرط التنسج وإيجابية فى خلايا متناثرة فى جميع انحاء أوروثيليوم فى حالة خلل التنسج أما فى سرطان البطانة فى الموقع كان كى اى ٦٧ منتشر فى السمك كاملا من أوروثيليوم. وقد زادت درجة التعبر كلما زادت درجة المرض فى حالة أورام الظهارة البولية. نستنتج مما سبق أن العوامل الكيميائية المناعية السيتوكيراتين ٢٠ وبى ٥٣ وكى اى ٦٧ تساعد فى التفريق بين كلا من خلل وفرط التنسج فى معرفة درجة وتطور أورام الظهارة البولية.