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TISSUE MICROARRAY ANALYSIS OF THE DIAGNOSTIC VALUE OF P53, KI-67, CK 5/6, COX-2 AND STAG2 EXPRESSION IN UROTHELIAL CARCINOMAS OF NEUROGENIC BLADDER

Hypothesis / aims of study

Patients with a neurogenic bladder (i.e. neuro-urological patients) develop UCB (urothelial carcinoma of bladder) with a frequency which has been reported to be at least equivalent to that among the general population [1]. However, the urothelial carcinogenesis in neuro-urological patients has been poorly investigated so far [2]. The aim was to characterize the pathology of urothelial carcinoma of neurogenic bladder (UCNB).

Study design, materials and methods

Tissue samples from UCNB (n=20) were retrieved and compared to control samples (n= 46 UCB tissue samples from non neuro-urological patients and n=11 samples without UCB from neuro-urological patients). The expression of p53, Ki-67, CK 5/6, Cox-2 and STAG2 was analysed via immunohistochemistry of micro-array sections. The associations between the previous biomarker expression, gender, tumour stage and histological differentiation were assessed using Fisher's exact test

Results

Among the neuro-urological patients with UCB included, 15 men were and 5 women, median age 54.5 years (IQR 48.2-66.2). Muscle-invasive bladder cancers were found in 13 patients. Squamous cell differentiation was observed in 10 UCNB samples. Median follow-up was 22 months (IQR 3.5-59.7). At last follow-up, 15 patients died, among them 13 because of the evolution of the oncological disease. In UCNB, p53, Ki-67, CK 5/6, Cox-2 and STAG2 were expressed in 2, 9, 6, 3 and 3 patients respectively. None of the biomarker was significantly associated with patients' gender, with the histological differentiation or with the invasive stage (table 1). The positive expression of p53 was more frequent in UCNB with squamous cell differentiation (p53 expression in non-squamous cell differentiation: UCNB n=16/16, UCB n=0/2, p=0,006). No other correlation has been found between the expression of these biomarkers and the neurological status (table 2).

Interpretation of results

The present study investigated a panel of potential diagnostic biomarkers of UCNB. However, none of the investigated biomarkers (p53, Ki-67, CK 5/6, Cox-2 and STAG-2) were identified as being overexpressed in UCNB.

As the previous biomarkers have been classically reported to have a potential role in the carcinogenesis of UCB in sporadic cases, and as UCNB are often invasive and display squamous differentiation, our preliminary results suggest that the carcinogenesis pathways involved in UCB in neuro-urological patients are different. The development of UCNB predominantly occurs after a long period of progression of their neuro-urologic disease (frequently 15-20 years). Various risk factors, such as smoking, indwelling or supra-pubic catheterisation, chronic urinary tract infections and bladder stones, have been identified [3]. Consequently, a specific type of chronic inflammation appears to be involved in the development of UCB in this patient group.

Concluding message

p53, Ki-67, CK 5/6, Cox-2 and STAG2 were not specifically identified in UNCB, emphasizing the need to investigate other markers to characterize this particular population.

Table 1. Association of the studied biomarkers with the clinico-pathological characteristics of neuro-urological patients with UCNB

Cohort of neuro-urological patients with UCNB N= 20 patients	**N (%)**	**P53 expression**			**Ki-67 expression**			**CK 5/6 expression**			**Cox-2 Expression**			**STAG2 Expression**		
		Positive	**Negative**	**P value**	**Positive**	**Negative**	**P value**	**Positive**	**Negative**	**P value**	**Positive**	**Negative**	**P value**	**Positive**	**Negative**	**P value**
Gender																
Male	15 (75%)	1 (5%)	14 (70%)	0.45	5 (25%)	10 (50%)	0.13	4 (20%)	11 (55%)	0.61	2 (10%)	13 (65%)	1.00	2 (10%)	13 (65%)	1.00
Female	5 (25%)	1 (5%)	4 (20%)		4 (20%)	1 (5%)		2 (10%)	3 (15%)		1 (5%)	4 (20%)		1 (5%)	4 (20%)	
T Stage																
NMIBC (pTa, PT1)	7 (35%)	0	7 (35%)	0.52	3 (15%)	4 (20%)	1.00	1 (5%)	6 (30%)	0.35	1 (5%)	6 (30%)	1.00	1 (5%)	6 (30%)	1.00
MIBC (pT2, pT3, pT4)	13 (65%)	2 (10%)	11 (55%)		6 (30%)	7 (35%)		5 (25%)	8 (40%)		2 (10%)	11 (55%)		2 (10%)	11 (55%)	
Histological differentiation																
Squamous	10 (50%)	2 (10%)	8 (40%)	0.47	3 (15%)	7 (35%)	0.37	5 (25%)	5 (25%)	0.14	2 (10%)	8 (40%)	1.00	2 (10%)	8 (40%)	1.00
Non squamous	10 (50%)	0	10 (50%)		6 (30%)	4 (20%)		1 (5%)	9 (45%)		1 (5%)	9 (45%)		1 (5%)	9 (45%)	

* Fisher's exact test, UCNB: urothelial carcinoma of neurogenic bladder; NMIBC: non muscle-invasive bladder cancer; MIBC: muscle- invasive bladder cancer

Table 2. Comparison of the studied biomarkers with the clinico-pathological characteristics of neuro-urological with UCNB and non neuro-urological patients with UCB

Cohort of neuro-urological and non neuro-urological patients with UCB	Positive P53 expression			Positive Ki-67 expression			Positive CK 5/6			Positive Cox-2 Expression			Positive STAG2 Expression		
	Neuro-urological	Non neuro-urological	P value	Neuro-urological	Non neuro-urological	P value	Neuro-urological	Non neuro-urological	P value	Neuro-urological	Non neuro-urological	P value	Neuro-urological	Non neuro-urological	P value
Gender															
Male	1 (5%)	14 (30%)	0,31	5 (25%)	24(52%)	0,20	4 (20%)	9 (20%)	1,00	2 (10%)	15(33%)	0,49	2 (10%)	13 (28%)	1,00
Female	1 (5%)	2 (4%)		4 (20%)	6 (13%)		2 (10%)	4 (21%)		1 (5%)	3 (7%)		1 (5%)	7 (27%)	
T Stage															
NMIBC (pTa, PT1)	0	9 (20%)	0,47	3 (15%)	13(28%)	0,71	1 (5%)	4 (9%)	1,00	1 (5%)	6 (13%)	1.000	1 (5%)	6 (13%)	1,00
MIBC (pT2, pT3, pT4)	2 (10%)	7 (15%)		6 (30%)	17 (37%)		5 (25%)	9 (20%)		2 (10%)	12(26%)		2 (10%)	14 (30%)	
Histological differentiation															
Squamous	2 (10%)	0	0,006	3 (15%)	3 (7%)	0,12	5 (25%)	5 (11%)	0,14	2 (10%)	3(7%)	0,13	2 (10%)	3 (7%)	0,11
Non squamous	0	16 (35%)	*	6 (30%)	27 (59%)		1 (5%)	8 (17%)		1 (5%)	15(33%)		1 (5%)	17 (37%)	

* Fisher's exact test, UCNB: urothelial carcinoma of neurogenic bladder, UCB : urothelial carcinoma of bladder, NMIBC: non muscle-invasive bladder cancer; MIBC: muscle- invasive bladder cancer

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