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PREMALIGNANT LESIONS OF URINARY BLADDER MUCOSAE

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Summary. *Premalignant lesions of mucosae urinary bladder are flat, noninvasive lesions of urothelium such as atypical hyperplasia/dysplasia and nonpapillary carcinoma in situ (CIS). The aim of this study was to identify association between premalignant lesions and subsequent invasive carcinoma. The study includes 60 patients with diagnosed noninvasive superficial and invasive bladder tumors. Our examination suggested that atypical hyperplasia/dysplasia and in situ carcinoma were more frequent in the higher grade and pathologic staging. In our material we had three patients with this concomitant lesions. Essential events in evaluation bladder urothelial carcinoma is grading, pathological staging and identification of premalignant lesions of mucosae urinary bladder. The authors suggest that the identification of patients with urothelial CIS and atypical hyperplasia/dysplasia is a particularly important event, representing the locus minoris resistentiae for the development of invasive bladder cancer.*

Key words: *Atypical hyperplasia/dysplasia, carcinoma in situ, mucosa urinary bladder*

Introduction

We know less about premalignant lesions of urothelium than about the premalignant lesions of the cervix, since the cervix has been more thoroughly studied. Premalignant lesions of mucosae urinary bladder are flat, noninvasive lesions of urothelium such as atypical hyperplasia and nonpapillary carcinoma in situ (1). This lesions are the common source of invasive bladder carcinoma. Atypical hyperplsia/dysplasia describes histological changes between normal and carcinoma in situ. It is defined as having some or all of the characteristics of urothelial dysplasia. An increase in the thickness of the urothelium is not always present (2, 3). In situ cancer, evolving from epithelial atypia or hyperplasia, is the early phase in the development of invasive bladder cancer. In situ cancer is a generalized urothelial malignancy that very often involves ureteral, prostatic as well as all bladder musoca (2).

The aim of this study was to identify association between premalignant lesions and subsequent invasive carcinoma.

Material and Methods

The study includes 60 patients with diagnosed nonivasive superficial and invasive bladder tumors. 51 specimens were transurethrally resected, 6 were partial cystectomy specimens and 3 had completely cystectomised. Median age was 60,4 years; range, 39 to 85 years. Paraffin sections were used and slides stained with hematoxylin and eosin (HE) showing tumor in resection specimens were examined. Tumor was classified from Grade I to Grade IV as follows: Grade I, well - differentiated tumor; Grade II, moderately differentiated; Grade III, poorly differentiated; and Grade IV, very poorly differentiated or anaplastic. Tumors were also staged from Ta to T_4 using the new TNM clasiffication proposed by the International Union Against Cancer (UICC) as shown in Table 1 (4).

Table 1. Comparison of Local Extent of Tumor According to the Jewett-Strong-Marshall and the American Joint Committee Classifications

Jewett-Strong-Marshall	American Joint Committee
O - Epithelial	TIS, Ta (Papillary carcinoma confined to mucosa)
A - Lamina propria	T_1
B_1 - Superficial muscle	T_2
B_2 - Deep muscle	T_{3a}
C - Perivesical fat	T_{3b}
D_1 - Adjacent organs Lymph nodes	T_4 - Adjacent organs N+ - Pelvic lymph nodes metastases M+ - Metastatic lesions other than nodes. Where used, "p" indicates Pathological stage specifically.

The significance of the parameters were determined by chi square testing.

Results

In this retrospective study 60 transitional cell tumors of urinary bladder were analysed. The mean age of the patients was 60,4 years with a range between 39 years and 85 years. There were 51 males and 9 females, for a ratio of 5.66 : 1.

Microscopic examination showed 12 of 60 cases (20%) in situ carcinoma. The characteristic cellular abnormality of in situ cancer is confined to the nucleus, which is disproportionately large and has deeply stained, coarse chromatin, prominent nucleoli and mitotic activity. The cell layers of mucosa in some cases was increased numerically and exist in a disorderly array, but there are no extensions beyond the basement membrane. In the submucosal layer, there is a striking inflammatory infiltrate of lymphocytes, plasma cells, and monocytes (Fig. 1 and 2). Those intraepithelial lesions developed in association with coincident bladder neoplasms and were interpreted as secondary CIS. In situ carcinoma was obtained in group of invasive carcinoma grade II two cases (16.6%), grade III seven cases (58.3%) and grade IV three cases (25%) (Table 2). These lesions were not found in group of patients with noninvasive carcinomas.Two (16.6%) CIS were in group of superficial invasive (pT_1) and 10 (83.3%) were in group of deeply invasive (pT_2 , pT_3 and pT_4) (Table 3). In the later group the most numerous CIS were in the pT_3 stage.

Examination showed atypical hyperplasia/dysplasia in 8 of 60 cases (13,3%). Part of mucosae urinary bladder with atypical hyperplasia/dysplasia had a: deviation of nuclear size, shape and staining, loss of orderly cell arrangement with focus clumping of cells and nuclei, increased nuclear to cytoplasmic ratio resulting in the appearance of cell crowding, loss of the cell polarity, increase in nuclear hyperchromasia and increase in the thickness of the urothelium. The changes were seen in the basal and intermediate cells (Fig.3). Atypical hyperplasia/dysplasia were obtained predominantly in group of invasive carcinoma grade II 2 cases (25%) and grade III 5 cases (62.5%). One case (12.5%) was in group of noninvasive papillary carcinoma grade I (pTa). In group of deeply invasive (pT_3 and pT_4) were 4 cases (50%) , and 3 patients (37.5%) with pT_1. Three bladder specimens showed zones of mucosal atypia, which were about the borders of in situ cancer (Table 2 and 3). Analysing the group with the invasive carcinoma grade II-IV by using the chi square test, statisticaly significant differences between carcinoma in situ and atypical hyperplasia appearances were not found ($\chi^2 = 2.17 < \chi^2 = 5.991$, $p>0.05$). Comparing the deepness of invasion with premalignant lesions, there were no statisticaly significant difference too ($\chi^2 = 4.41 < \chi^2 = 9.488$, $p>0.05$). Therefore, bouth carcinoma in situ and atypical hyperplasia can be found with equal probability around neoplasm of mucosae urinary bladder. Eight cases of transitional cell carcinoma had part of mucosae with simple or papillary hyperplasia without signs of atypia. Flat lesions with the presence of more than six layers of epithelium (simple hyperplasia) were seen in 5 specimens mucosae of the urinary bladder and 3 specimens with zone of papillary hyperplasia. These lesions were seen in transitional cell carcinoma with pTa (6 cases) and 2 cases with invasive bladder carcinoma. There were no simultaneous presence of atypical hyperplasia or in situ carcinoma with simple/papillary hyperplasia. In thirty two cases (of 60) urinary bladder mucosa had histologycaly normal appearance.

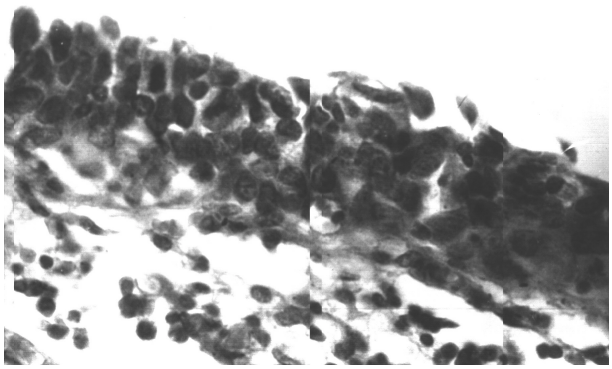

Fig. 1. Carcinoma in situ. The cells have hyperchromatic nuclei that vary in size, shape, and orientation. The basement membrane is still intact (HE, x 180).

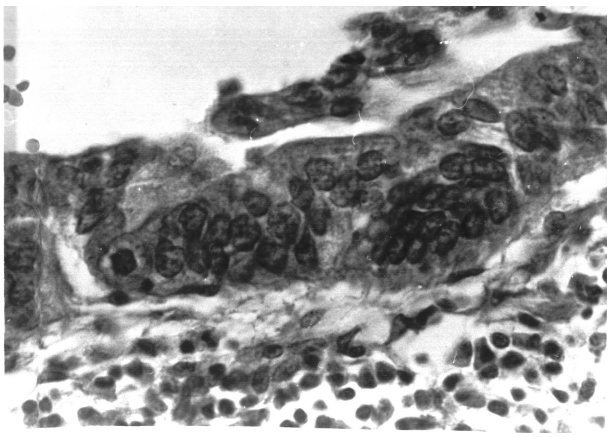

Fig. 2. Carcinoma in situ of bladder urothelium with the dense inflammatory infiltrate in the lamina propria (HE, x 180).

Table 2. Comparison of histologic grade and premalignant lesions of mucosae urinary bladder

Histologic grade		Premalignant lesions		Hyperplasia	
		Carcinoma in situ	Atypical hyperplasia/ dysplasia	Simple	Papillary
Noninvasive carcinoma	G I	0	1(12.5%)	1	2
	G II	0	0	2	1
	G III	0	0	0	0
Invasive carcinoma	G I	0	0	0	0
	G II	2(16.6%)	2(25%)	1	0
	G III	7(58.3%)	5(62.5%)	0	0
	G IV	3(25%)	0	1	0

Table 3. Comparison of pathologic stage and premalignant lesions of mucosae urinary bladder

Pathologic stage	Premalignant lesions		Hyperplasia	
	Carcinoma in situ	Atypical hyperplasia/ dysplasia	Simple	Papillary
Ta , Tis	0	1(12.5%)	3	3
T_1	2(16.6%)	3(37.5%)	0	0
T_2	3(25%)	0	1	0
T_3	5(41.7%)	3(37.5%)	1	0
T_4	2(16.6%)	1(12.5%)	0	0

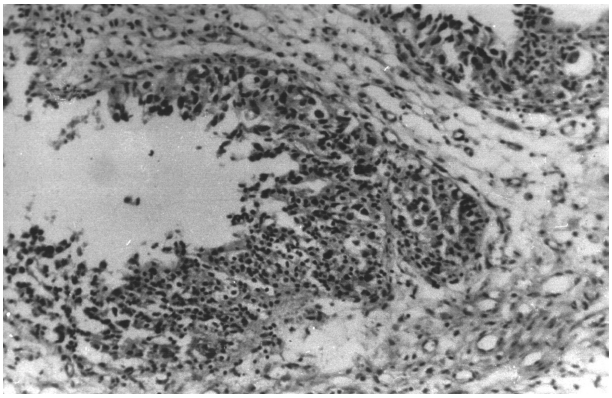

Fig. 3. Atypical hyperplasia of bladder urothelium (HE, x 120)

Discussion

The results of the current study are similar to the other reports in the literature. The biologic changes associated with the development of bladder cancer presumes that the some malignant potential is present in the residual epithelium. There is the possibility that removal or disruption of a circumscibed lesion has completly eliminated the only problem area (1). The incidence of the premalignant lesions of mucoase urinary bladder in our material was 33.3%. Our examination suggested that atypical hyperplasia /dysplasia were more frequent in the higher grade and pathologic staging, i.e. the possibility of finding atypical lesions was higher in cases with more advanced staging. Escanhoela - CA and authors (5) suggest similar finding of atypical lesions in patients with multiple biopsies in bladder urothelial carcinomas. They had a higher incidence of atypical lesions among patients with more than one tumor at cystoscopy, the higher grade and clinical staging. Kiemeney - LA at al. (6) confirmed that the 3 - year risk of reccurence in patients with dysplasia or carcinoma in situ in macroscopically normal-looking urothelium was only slightly higher than the risk in patients without dysplastic changes. Concomitant dysplasia and CIS significantly increased the 3 - year risk of disease progresion. In our material we had three patients with this concomitant lesions which suggested a gradual and progressive transition of premalignant atypia into cancer in situ.

Carcinoma in situ of the urinary bladder is a neolasm of uncertain biologic behaviour. It rarely occurs as the primary disease and exists the most often as secondary disease in association with high grade, invasive tumor, that was also found in this study. Orozco - RE et al. (7) suggested that progression or death from disease is unusual among patients presenting with primary CIS, but common among individuals with CIS associated with other bladder cancers.

This study confirmed that invasive carcinomas with infiltration of tunica muscularis, perivesical fat and adjacent organs had higher degree of anaplasia as well as higher frequency of CIS and atypical hyperplasia. Noninvasive carcinomas, except in one case, revealed no appearance of this premalignant lesions.

Hadži-Đokić et al. (8) pointed out that patients with histological grade II , pathological stage B-D (pT_2-pT_4) and presence of CIS, must be considered as high risk group.

Conclusion

Essential events in evaluation bladder urothelial carcinomas are grading, pathological staging and identification of premalignant lesions of mucosae urinary bladder. The authors suggest that the identification of patients with urothelial CIS and atypical hyperplasia/dysplasia is a particularly important event, representing the locus minoris resistentiae for the development of invasive bladder cancer. The presence of these lesions has an important impact on prognosis as weel as on therapeutic approach.

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PREMALIGNE LEZIJE SLUZOKOŽE MOKRAĆNE BEŠIKE

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Kratak sadržaj: *Premaligne lezije sluzokože mokraćne bešike su ravne, neinvazivne promene u urotelu kao što su atipična hiperplazija/displazija i nepapilarni karcinom in situ. Cilj ovog rada je bio utvrđivanje povezanosti između premalignih lezija sluzokože mokraćne bešike i invazivnog karcinoma. Analizirano je 60 pacijenata sa papilarnim tranziciоćelijskim neinvazivnim i invazivnim karcinomom mokraćne bešike. Ovo ispitivanje je potvrdilo veću učestalost atipične hiperplazije/displazije i karcinoma in situ kod pacijenata sa većim histološkim gradusom i dubljom infiltrcijom zida mokraćne bešike, tj. većim patološkim stadijumom. Istovremenu pojavu ovih premalignih promena registrovali smo u tri pacijenta. Autori zaključuju da je esencijalni proces u evaluaciji pacijenta sa karcinomom mokraćne bešike, pored određivanja histološkog gradusa i patološkog stadijuma, i utvrđivanje premalignih promena sluzokože mokraćne bešike u okolini malignih tumora. Prepoznavanjem ovih lezija utvrđujemo mesto smanjene rezistencije iz koga se može razviti invazivni karcinom a što može uticati na prognozu i terapeutski pristup kod tih pacijenata.*

Ključne reči: *Atipična hiperplazija-displazija, karcinom in situ, sluzokoža mokraćne bešike*

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