

Histopathological Study of the Urothelial Bladder Carcinomas

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ABSTRACT: **Introduction:** In this study we analysed the most important parameters necessary for the histopathologic diagnosis of urothelial carcinoma, a tumor which frequently develops at the vesical urothelial's level. **Material and methods:** It is presented a study which contained a number of 150 cases of urothelial carcinoma of the bladder, selected during year 2011. We described histopathological aspects corresponding to the growing pattern, tumoral differentiation and invasion depth, as well as the associated lesions, especially those of the urothelium adjacent to the tumors. **Results and discussions:** The urothelial carcinoma located at the bladder level had various histopathological features. The evaluation of the cytologic atypia and neoplastic configuration, as well as the identification of atypical mitosis, allowed us to grade the tumors. The analysis of biopsies allowed us to identify the invasion at muscularis propria level in most cases. The lesions associated with invasive urothelial carcinoma were represented by carcinoma in situ, dysplasia, squamous metaplasia, inflammation. **Conclusions:** The tumoral differentiation degree was correlated with the growing pattern and also with the invasion depth. Some tumors have few associated modifications, enhancing the complexity of the lesions and posing diagnosis setting problems.

KEYWORDS *urothelium, carcinomas, histopathology*

Introduction

Urothelial carcinoma is the most common tumor of the bladder, representing approximately 90% of malignancies with this origin (1, 2). It is estimated these malignant tumors accomplish 5th place in the world and is a major cause of morbidity and mortality (3-7). Histopathologically, depending on the pattern of growth, urothelial bladder carcinomas are classified in flat and papillary, most tumors are papillary, only carcinoma in situ and some invasive histological forms having a flat pattern (8-11). The papillary equivalent of flat in situ carcinoma is the high grade noninvasive papillary urothelial carcinoma (8). It is estimated that in the time of diagnosis, 60-65% of urothelial tumors are in an superficial stage, which includes Tis, Ta and T1 (12, 13).

Bladder transurethral resection of the tumor is a therapeutic procedure that ensures the material necessary for histopathological diagnosis because allows assessment of the degree of differentiation, depth of tumor invasion, parameters useful in elaboration of diagnosis and prognosis assessment (11). The friability of these tumors, as well as some technical impediments and interpretation errors, including electrocoagulation artifacts, retraction artifacts, presence of muscle fibers from the mucosa may represent difficulties to establish the differentiation degree and tumor invasion. In these cases, serial sections and special stains of

biological material in sufficient quantity, can ensure the diagnosis.

Material and Methods

Our study was performed retrospectively and included a total of 150 cases selected during 2011. The biological material came from the patients hospitalized for bladder tumors in Urology Clinic from Emergency County Hospital Craiova. The pieces were processed by common histopathological technique using 10% formalin fixation, paraffin embedding and Hematoxylin-Eosin stain.

We followed the morphological aspects of urothelial carcinoma, respectively growth pattern, degree of differentiation and depth of invasion. For assess the degree of tumor differentiation, we followed cytological atypia, the papillae architecture and the presence of atypical mitosis.

Results

This study included 150 transurethral bladder tumor resections from a total of 175 cases of urothelial carcinoma, which represented 85.1% of tumoral bladder pathology. The age of patients diagnosed with urothelial carcinoma was between 25 and 88 years, 135 of whom were over 50 years and the maximum incidence was at 65 years. We found a net predominance of malignancies in males, with 128 tumors and a male / female ratio of 6.1 / 1.

In this study we investigated the pattern of tumor growth, their degree of differentiation and progression, and the associated mucosal changes tumorale. In 148 cases, the tumors had a papillary growth pattern, with the presence of papillae usually tall and branched, with individual aspect or adhering to the base. The number of cell layers that covered these papillae

was between 6 and 11. In 15 cases, which corresponded to well differentiated carcinomas, the papillary structures were tenuous, orderly, moderately vascular and covered with well differentiated tumor cells, with pale eosinophilic cytoplasm and minimum nuclear atypia, mitosis being rare (fig. 1a).

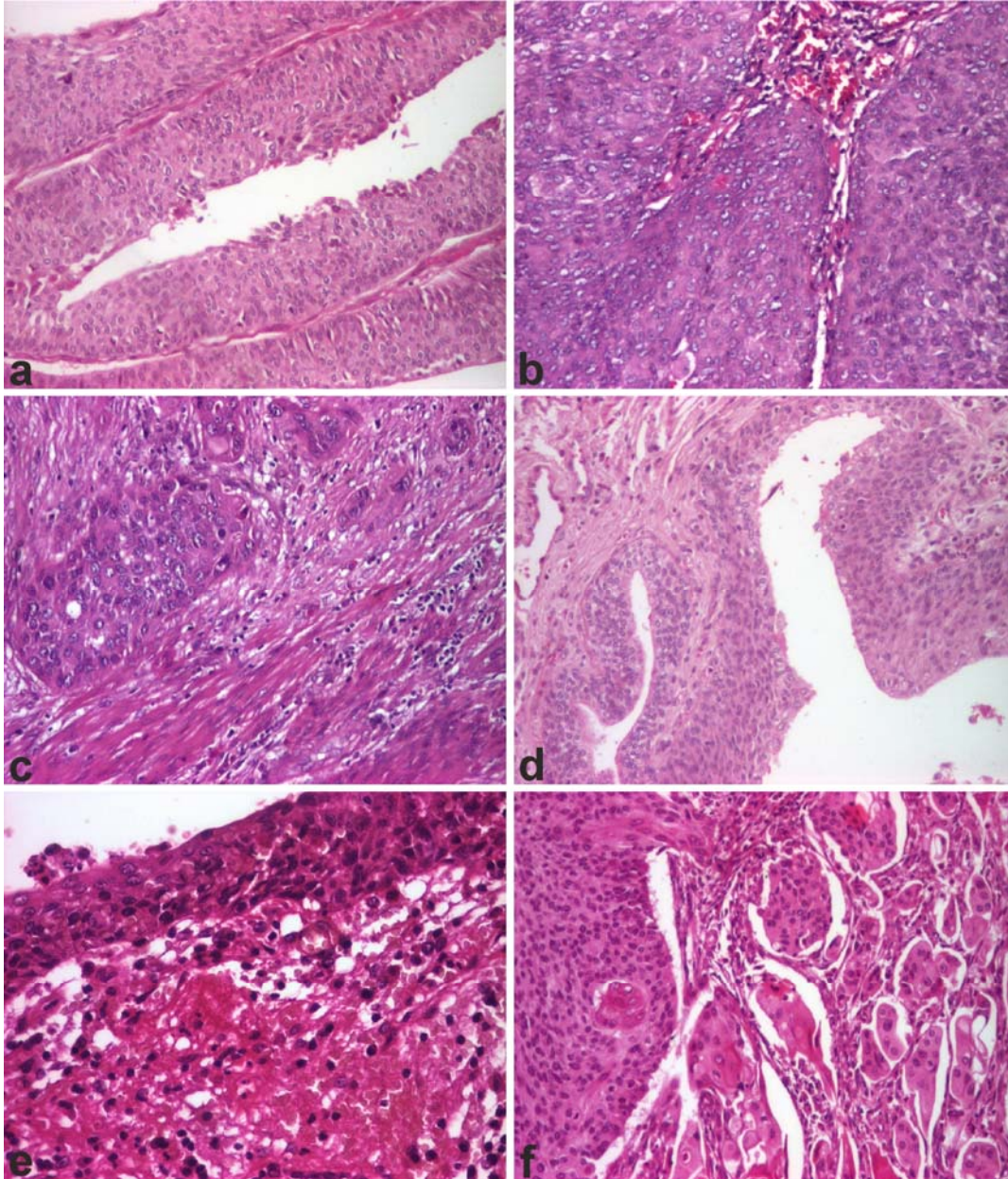


Fig.1. Urothelial carcinoma, HE stain, x100. a) Well differentiated carcinoma with lamina propria invasion; b) Moderate differentiated carcinoma with lamina propria invasion; c) Poorly differentiated carcinoma with muscularis propria invasion; d) Low grade papillary urothelial carcinoma; e) Carcinoma in situ adjacent to urothelial carcinoma; f) Squamous metaplasia in the invasion front.

In 87 cases, the carcinomas were moderately differentiated, the papillary axes with a more compact, crowded, fused at the base and unordered stratified by moderate differentiated

cell, with shape and volume changes of the nucleus, with prominent nucleoli and loss of polarity (fig. 1b).

At the deep layers level, the mitosis were frequent (1 mitosis / x40 microscopic field). Tumors were poorly differentiated in 46 cases, covering papillae fused over large areas, which formed solid areas, unordered, crossed by vascular axis. In these cases tumor cells presented high cytological atypia and a increased number of atypical mitoses (4 mitoses / x40 microscopic field) in the full thickness of epithelium (fig. 1c). It was noted the lack of cellular cohesivity in the superficial layers with their tendency to exfoliation. In some cases the papillae had particular aspects with slopes covered with cells with various degrees of differentiation and transition areas. In 2 cases the histopathological appearance of the tumor was undifferentiated with papillae hard identifiable, with atypia and increased pleiomorfism, atypical mitoses, tumor necrosis and ulceration of the urothelium.

Another aspect that we were interested was related to tumor progression, which was analyzed in relation to histological type and the degree of differentiation. We encountered one case of low grade non-invasive urothelial papillary carcinoma with thin, minimum merged papillae, slightly atypical cells and basement membrane intact (fig.1d). All studied papillary carcinomas invaded the chorion in papillary axis or on their basis. For both lamina propria and muscularis propria, the invasion pattern was by the form of small islands of solitary cells, which achieved retraction artifacts. In many cases invasion was accompanied by stromal inflammatory response and reaction sometimes by desmoplastic reaction. In some cases we observed paradoxical differentiation with eosinophilia of tumor cells from the edge of islands. The depth of invasion was established in 108 cases. The tumors that have invaded the lamina propria were well and moderately differentiated in 27 cases and poorly differentiated in 11 cases. The tumors with muscularis propria invasion (68 cases), were moderately differentiated in 42 cases, poorly differentiated in 20 cases, and well differentiated in 6 cases. As particular aspects of tumor invasion we encountered in two cases the perineural invasion and in one case the presence of vascular invasion the invasive cases corresponding to some papillary carcinoma with muscularis propria invasion and poorly differentiated. In 10 cases of invasive papillary carcinoma depth of invasion could be indicated only after serial sections.

In the group of flat lesions, we met 3 poorly differentiated urothelial carcinomas with adjacent areas of carcinoma in situ, with cytological atypia, loss of polarity and cell cohesivity (fig. 1e).

We also followed the existence of lesions associated with urothelial carcinomas. These were represented by mild dysplasia associated with the presence of cases of carcinoma in situ, squamous metaplasia and the presence of inflammatory infiltrate sometimes with gigantocellular appearance (fig. 1f). Necrosis and ulceration were observed in poorly differentiated or undifferentiated tumors. In the dysplastic areas, we noticed the increasing number of cell layers with slightly atypical cells, but cohesive, unlike carcinoma in situ. The cells from metaplastic areas were greater in size than urothelial normal cells, with intensely eosinophilic cytoplasm, fine grains and excentric nucleus.

Discussions

Our study which included a total of 150 biopsies with urothelial bladder carcinoma diagnosis, indicated a net predominance neoplasia in the sixth decade of life, with a male / female ratio of 6.9 / 1. Similar data from the literature mentions a 3-4/1 report for males, the difference obtained being due to probable exposure to a wide range of regional carcinogens, diet, genetic background (6).

Histopathological analysis followed the assessment of growth pattern, degree of differentiation

and the relationship with tumor progression. The literature indicates that papillary tumors are less aggressive than the flat ones (12). In this study, from 148 tumors with papillary pattern, in 38 cases was observed the invasion to the lamina propria. The degree of tumoral differentiation affects prognosis and literature data indicated that the tumors are better differentiated as the age of occurrence is low (14). In our study we evaluated 5 cases diagnosed under the age of 50 years, these tumors being well differentiated and invasive to the lamina propria.

The degree of tumor differentiation was correlated with the depth of invasion, well and moderately tumors presenting invasion to the lamina propria, and the majority of moderately and poorly differentiated carcinomas being invasive to muscularis propria level. It was unable to specify the depth of invasion in the muscularis propria and in some cases mucosal fine muscle fibers raised the question of the

differential diagnosis. Their differentiation has completely different therapeutic implications. In case of muscularis mucosae invasion the treatment is the biopsy itself, unlike muscularis propria invasion when the treatment is represented by total / partial cystectomy, depending on the depth of invasion (8, 10).

The specific histopathological aspects encountered in this study were the cases of papillary carcinoma with mixed areas of differentiation, the presence of intraepithelial flat lesions associated with papillary carcinoma and identification of a case of low grade, non-invasive papillary carcinoma.

Conclusion

Urothelial carcinomas are heterogeneous lesions various histological aspects that require detailed investigations of tumor areas, invasion front and adjacent apparently normal areas.

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