

Histological Variants of Urothelial Bladder Carcinoma

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ABSTRACT The purpose of this study was to identify and histopathological analysis of cases of urothelial carcinoma with mixed differentiation. The study included a total of 260 cases which were classic processed and histopathologically analyzed, appreciating the presence and type of differentiation and also the degree and tumor stage. In 68.8% of cases, urothelial carcinoma showed different histological differentiation, most commonly was observed areas with squamous, clear type and glandular cells. These tumors had low degrees of differentiation and invasion was more advanced. The prognosis of patients can be improved by recognizing and properly quantify the tumor differentiation areas.

KEY WORDS *urothelial carcinoma, differentiation, stage*

Introduction

Urothelial carcinomas are frequently diagnosed lesions of the bladder, representing approximately 90% of all malignancies with this location (2). One of the important features of these lesions is the ability to differentiate to a large spectrum of histopathological variants (10). In general, pure forms of non-urothelial carcinomas are more aggressive and the diagnosis moment occur at an advanced stage, decreasing the survival of patients (7). Also, in 7-44% of urothelial carcinoma cases, mixed histological features are present (3, 9). The significance of urothelial carcinomas differentiation remains unclear in the relationship with patient survival.

Materials and methods

The study included 260 cases of urothelial carcinoma diagnosed within 5 years, between 2005-2009. The biological material was represented by cystectomy pieces from Urology Clinic of Emergency County Hospital Craiova. The pieces were fixed in 10% formalin, included in paraffin followed by sectioning at 3-5 mm, and standard Hemalaun-Eosin staining (Bio-Optica kit). Also, to highlight some particular featuread we used PAS staining (Bio-Optica kit). The criteria for inclusion in the study were the needed histopathologic features for the urothelial carcinoma diagnosis elaborated in 2004 by the working group of WHO for tumors of the urinary tract (5).

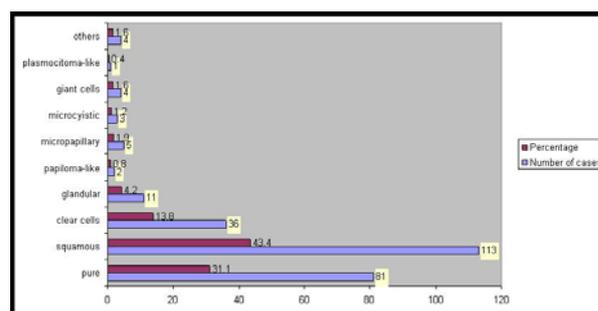
Histopathological analysis followed the presence and differentiation type and also the tumoral degree and stage. Urothelial carcinomas were classified as having a certain type of

differentiation only if those areas were less than 10% of the tumor section.

Results

Analysis of cases distribution by type of differentiation showed that in 81 cases, which represented 31.1% of carcinomas included in the histopathological study, it was pure urothelial type (Fig. IA). The cases were well or moderately differentiated, with invasion of the chorion or in the internal half of muscularis propria.

In 68.8% of cases, urothelial carcinoma showed different histological differentiation (Graphic 1).



Graphic 1: Analysis of cases distribution according to histological differentiation.

Urothelial carcinoma with **squamous differentiation** was present in 113 cases, representing 43.4% of the tumors investigated (Fig. IB). Areas of differentiation showed squamous transformed tumor cells with evident intercellular bridges and keratinization presence with unicellular and/or beads of keratin. In 71 cases was a moderate degree of differentiation, invasion was present especially in the muscularis

propria and the distribution pattern of areas with squamous differentiation was heterogeneous, with high value range limits (20-60%).

Urothelial carcinoma with **clear cells** (glycogen rich) was found in 36 cases, which represented 13.8% (Fig. IC). Lesions were characterized by the presence of cells with clear cytoplasm which became pink-red in PAS staining, demonstrating the accumulation of glycogen (Fig. ID). Carcinomas were papillary or nonpapillary, were usually moderately differentiated (27 cases), with muscle invasion or in the whole bladder wall.

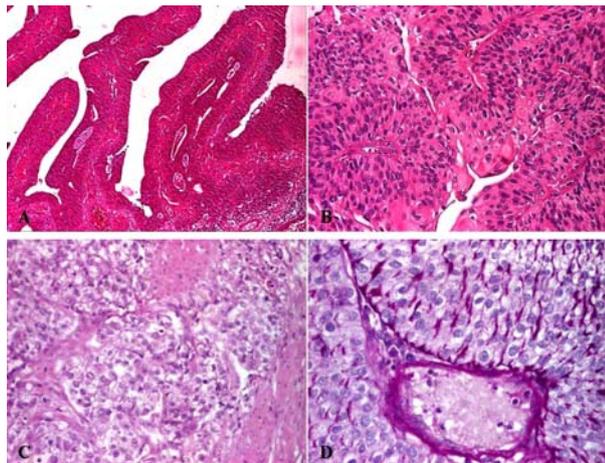


Figure 1: Urothelial carcinomas; A. Conventional type (pure), x40, HE stain; B. Squamous differentiation, x100, HE stain; C. Clear cells (glycogen rich), x200, HE stain; D. Clear cells (glycogen rich), x200, PAS stain.

Urothelial carcinoma with **glandular differentiation**. This pattern was present in 11 cases, representing 4.2% of the injuries included in the study (Fig. IIA). Histological appearance was characterized by the presence of glandular tumor cells arranged on several layers without papillary projections within the lumen, the differentiation being located at the front of invasion. The tumors were moderately or poorly differentiated, with variable depth of invasion, in muscle or the whole wall.

Urothelial carcinoma with **inverted papilloma** appearance (papilloma-like). In two cases (0.8%) urothelial carcinomas showed this pattern of differentiation characterized by an increased nuclear pleomorphism, mitotic figures and architectural abnormalities (Fig. IIB). Tumors were moderately differentiated and invasive to internal half of muscularis propria.

Urothelial carcinoma with **micropapillary differentiation**. In 5 cases (1.9%) tumors had delicate processes, filiform, or small groups looking papillary architecture of cells with small buds (Fig. IIC). Degree of tumoral differentiation

was moderate or weak and invasion was present to 1/2 external half of muscularis propria.

Urothelial carcinoma with **microcystic differentiation**. This was identified in 3 (1.2%) cases of moderately differentiated papillary carcinoma, with invasion in whole bladder wall. The lesion was characterized by the presence of microcystic and tubular structures, which sometimes showed necrotic content (Fig. IID).

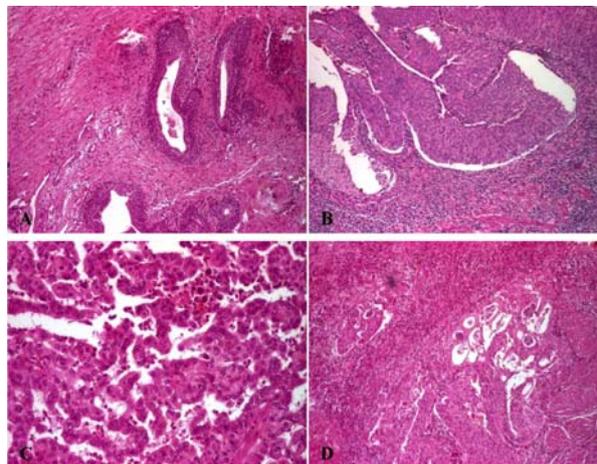


Figure 2: Urothelial carcinomas; A. Glandular differentiation, x40, HE stain; B. Papilloma-like carcinoma, x100, HE stain; C. Micropapillary differentiation, x100, HE stain; D. Microcystic differentiation, x100, HE stain.

Plasmacytoma-like carcinoma. In a case of urothelial poorly differentiated carcinoma (0.4%), with serous invasion, was present in relatively large areas a component consists of nests and islands of undifferentiated cells with large nuclei and prominent pleomorphic nucleoli (Fig. IIIA). Cytoplasmic boundaries appeared poorly defined, sometimes with a syncytial aspect.

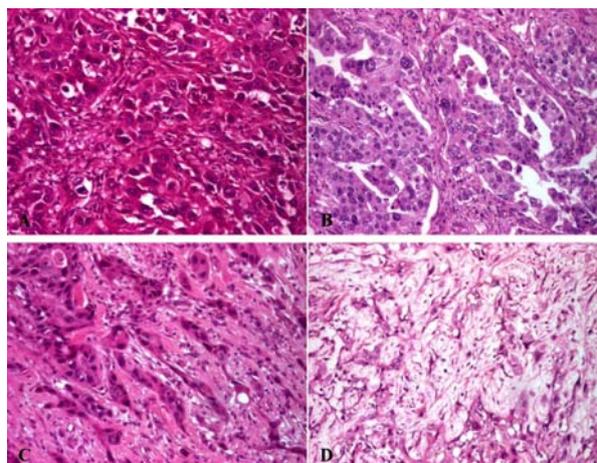


Figure 3: Urothelial carcinomas; A. Plasmacytoma-like carcinoma, x200, HE stain; B. Urothelial carcinoma with giant cells, x100, HE stain; C. Urothelial carcinoma, discohesive pattern, x100, HE stain; D. Urothelial carcinoma with myxoid stroma, x100, HE stain.

Urothelial carcinoma with **giant cells**. In 4 cases (1.6%) of poorly differentiated urothelial carcinoma, with invasion in whole bladder wall, epithelial component showed giant cell tumor in a considerable number, some with multiple nuclei (Fig. IIIB).

Other observed histopathological aspects was the arrangement of tumor cells in a discoesive, unicellular, diffuse growth pattern (1 case) or pseudosarcomatos appearance of stroma with myxoid areas (three cases), all this tumors being poorly differentiated, with invasion of whole wall (Fig. IIIC,D).

Discussion

In our study, the squamous differentiation was present most commonly in 113 cases, followed by clear cell in 36 cases and the glandular one, in 11 cases, pure urothelial carcinoma being identified in 81 cases.

These cases must be classified as urothelial tumors, indicating the type and the percentage of differentiation present in conventional urothelial carcinoma (2). Only when the differentiation is pure tumor can be classified as such, except the forms with small cell and neuroendocrine type (4).

Approximately one fifth of urothelial carcinomas containing areas of squamous or glandular differentiation (2). Their frequency increases with tumor grade and stage and the tumors with squamous or glandular component had a worse treatment response than conventional urothelial carcinoma (8). In this study we found that the squamous and glandular differentiations were present in more aggressive carcinomas with moderate or poor differentiation and deeper invasion.

Some studies have shown that two thirds of cases of urothelial carcinomas shows clear cell areas, due to accumulation of glycogen. In a study of 7 cases it was found that all patients are older people and average age of diagnosis was 74 years (9).

Also, other differentiations, such as the papilloma-like, micropapillary, microcystic, plasmacytoma-like, with giant cells, along with other special aspects (discoesive pattern, myxoid stroma) enriched the histopathological features of these lesions.

Urothelial carcinoma with papilloma-like appearance can often be confused with inverted papilloma. Data from literature shows that until just moments in which such lesions are not accompanied by destructive stromal lesions, the risk of metastases is minimal and the basal membrane is not really penetrated (1).

In this study, we identified 5, respectively 3 lesions with micropapillary and microcystic differentiation, the tumors being moderately or poorly differentiated and with invasion at least until muscularis propria level. Also, the plasmacytoma-like, giant cell differentiation and discoesive pattern was present in nonpapillary carcinomas, poorly differentiated, with invasion of all bladder wall.

In 80% of cases, micropapillary component is found in association with non-invasive or invasive typically papillary carcinoma. 25% of cases have glandular differentiation, and some authors consider this lesion as a variant of urothelial adenocarcinoma (6). Some studies have demonstrate that in cases with less than 10% micropapillary component and a surface micropapillary component area have a higher proportion of diagnoses in early stages of lesion (11).

Although controversial, the microcystic pattern should be delimited from the nested variant of urothelial carcinoma with glandular differentiation and from urothelial carcinoma with small tubes (14).

In another study that included 6 cases of urothelial carcinoma with plasmacytoma-like differentiation, the average survival of patients was 23 months, which demonstrates the aggressive nature of the lesion (12).

Data from the literature demonstrated that the presence of large, giant cells in case of urothelial carcinoma is associated with a poor prognosis of patients, the lesions being extremely aggressive (13).

All cases included in our study which showed differentiations were moderate or poorly differentiated and invasive at least up to internal half of the muscularis propria.

In 2004, Matthew J. Wasco made a study that analyzed the impact of tumor differentiation on tumor behavior. This study showed that any histopathological differentiation that may occur in the bladder urothelial carcinomas is associated with increased aggressiveness of the lesion (10). Such tumors are almost always high grade and invasive tumors. Logistic analysis showed that mixed forms increases 2.6 times the risk of extravezical involvement. It was also found that mixed forms have a phenotype more aggressive and less responsive to treatment.

Conclusions

In the case of bladder urothelial carcinoma, histological differentiation spectrum can be highly variable, and their presence should be reported

due to increased aggressiveness and the evolutive possibility of these forms. The prognosis of patients can be improved by recognizing and properly quantify the tumor differentiation areas.

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