Morphological Characteristics and Differential Diagnosis of Urothelial Bladder Carcinomas: A Literature Review

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Abstract

Cancer of the bladder occupies the seventh place among the most common malignancies in the world and also represents the most frequent malignancy of the urinary system, characterized by a tendency to relapse and a specific course of development. Urothelial carcinoma (UC) of the bladder is three times more common in men. By the age of 40, the tumor is sporadic. After the 5th decade, however, the incidence increased sharply. The complications caused by UC worsen the quality of life of patients. UC is the second most common neoplasm of the urogenital system after prostate cancer and is one of the biggest challenges that the World Health Organization (WHO) faces.

Keywords: Bladder Carcinoma, Urothelial Carcinoma, Histology.

1. Introduction

In the last two or three years, with the introduction of new trends in oncology for the application of innovative therapeutic approaches in the treatment of patients with bladder cancer, special attention is paid to the detailed macroscopic and histological description, including lesion topic, tumor size, histological variant, degree of invasion, grading and staging.

2. Macroscopical characteristics of urothelial bladder carcinomas

Macroscopically, UC of the bladder can be presented as flat tumor formations, exophytic (papillary or nodular) lesions, or ulcers. The described macroscopic types of bladder cancer can be solitary or multifocal growth [ZhouM et al., 2012; MohanH et al., 2000]. The most common localizations of bladder UC are the lateral walls of the bladder - in about 25% of cases, the posterior wall - 20%, the trigonum - 20%, and the anterior wall and fundus - about 10%.

Moreover, bladder UC represents 90% of the cases described in the literature, while the remaining 10% are carcinomas of the urethra, ureters, and urachus [Stenehjem DD et al., 2018].
The pathohistological features of bladder UC possess significant heterogeneity with a pronounced tendency for divergent differentiation. This leads to the occurrence of urothelial neoplasms with mixed histological features [Epstein JI et al., 1998]. Some of those variants have specific morphological characteristics. They are classified as specific histological subtypes described in the WHO classification of 2016 (2016 WHO Classification of Tumors of the Urinary System and Male Genital Organs) [Beltran LA et al., 2017; Moch H et al., 2016].

The WHO 2016 classification of bladder carcinomas clarifies terminological issues and provides more detailed criteria for definition, including some new options. Many of them are of particular prognostic or therapeutic importance to the urologist and oncologist, but also represent diagnostic challenges in the daily practice of the pathologist [Beltran LA et al., 2017].

The most common bladder cancer is UC (transitional cell carcinoma) - in over 90% of cases. They are followed by the significantly rarer squamous cell carcinoma, adenocarcinoma, small cell carcinoma, and others [Carneiro AB et al., 2014].

3. Low-grade papillary urothelial carcinoma of the bladder (LGPUC)
The typical histological characteristics of LGPUC are well-formed papillary structures with central fibrovascular core, discrete branching and minimal fusion of the papillae, slight loss of cell polarity, and mild atypia. The nuclei are uniform, elongated with moderate polymorphism (including differences in shape, contours, and chromatin dispersion), and single nucleoli and atypical mitoses can be found [1]. Low grade bladder UCs often recur, in 50 to 70% of patients, and rarely progress to invasive carcinomas - less than 5% of cases [Grignon DJ et al., 2014].

**Differential diagnosis of LGPUC:**

3.1 *Papillary urothelial neoplasia of low malignant potential* (PUNLMP) - it is more common in male (65 years of age, ± 14 years) with a ratio of m:f/5:1. This neoplasia rarely invades and metastasizes and has an excellent prognosis after the excision of the lesion. Macroscopic characteristics: 1-2 cm regular polypoid tumor, while histologically is very difficult to distinguish from transitional cell papilloma, with the difference that the papillae in papillary urothelial neoplasia with low malignant potential are slightly "thicker," with increased nuclear–cytoplasmic ratio, pronounced hyperchromasia, without the presence of nucleoli and without mitotic figure or single ones, usually confined to basal layer [Grignon DJ et al., 2014].

3.2 *Nephrogenic adenoma of the urinary bladder* (NAUB) - represents rare benign tubulo-papillary lesions of the bladder. Nephrogenic adenoma is more common in adults but it has been reported that about 10% of nephrogenic adenosomas affect children in a ratio m:f/2:1. The NAUB can be induced and associated with persistent inflammation, irritation caused by the surgery in the area of the bladder, kidney transplantation, diverticulitis, gallstones, and intravesical administration of Bacillus Calmette-Guérin (BCG) therapy. Morphologically NAUB is characterized by the meta-plastic changes of the transitional cell epithelium with papillary growth and Small hollow tubules similar to mesonephric tubules, surrounding eosinophilic or basophilic secretions (Fig. 1A and 1B). Both structures are lined by single layer of cuboidal or hobnail cells with minimal mitotic figure [Venyo KGA et al., 2015].
3.3 Polypoid / papillary cystitis - is a benign polypoid or papillary inflammatory lesion affecting the mucous of the bladder seen commonly in patients with indwelling catheter. Histologically polypoid / papillary cystitis is characterized by thin, finger-like papillae with highly edematous fibrovascular core with indistinct branching of the papillae - without anastomosis and fusion, as in some instances can be found and reactive epithelial atypia, but with no abnormal mitotic figures [Ozaki K et al., 2014; Kwok JL et al., 2019].

4. High-grade papillary urothelial carcinoma of the bladder (HGPUC)

The typical histological characteristic of the papillary UC of the bladder with a high degree of malignancy is the fusion of the papillary structures, in some areas with a difficult to detect transitional cell character of the epithelium, with superficial loosening and fragmentation. There is also variable thickening of the urothelium, upholstering the tumor papillae, with more than ten cell layers, with moderate to severe cellular atypism, polymorphism and polychromasia. The nuclei of the cells are enlarged and elongated with an irregular contour and protruding, often numerous nucleoli. Often detected numerous atypical mitoses and in individual cases, it is possible to establish different types of differentiation (the most common are squamous cell and glandular) [Zhou M et al., 2012; Amen BM et al., 2009]. Bladder cancer with a high degree of malignancy progresses to invasive carcinoma in 15% to 40% of patients [Zhou M et al., 2012].

The differential diagnosis of HGPUC [Grignon DJ et al., 2014]:

4.1 LGPUC;

4.2 Invasive UC.

In most cases, invasive bladder cancers are highly malignant. In them, the invasion can be presented in the form of individual cells or nests of tumor cells.

The differential diagnostic plan for invasive bladder cancers includes [Grignon DJ et al., 2014]:

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Figure 1A and 1B. Nephrogenic adenoma of the urinary bladder. HES x100, x200
4.2.1 **Benign urothelial proliferation** (Florid von Brunn Nests, cystitis cystica and cystitis glandularis and pseudocarcinomatous epithelial hyperplasia of the bladder).

4.2.2 **Inverted urothelial papilloma of the bladder (Bruner's adenoma)** is a rare benign endophytic tumor with focal papillary growth and low malignant potential. It is observed more often in male between the ages of 60-70, in the ratio m:f/7.3:1. This tumor is characterized by a solitary (rarely multiple), polypoid tumor with a diameter of about 3 cm. Histologically, inverted papillomas are of two types: trabecular and glandular. May be associated with urothelial carcinoma[PicozziS et al., 2012].

4.2.3 **Paraganglioma** is very rare sporadic functional bladder tumor (0.06-0.1% of all bladder tumors) derived from paraganglion cells, similar to counterpart at other sites. The age range it affects is from 10 to 78 years (median age 40 years), it is more common in female, in the ratio m:f/2:3. Paraganglioma arises from chromaffin cells in the muscularis propria and can occur anywhere in the bladder. Macroscopic paraganglioma is small lesion or represents a single seal of the mucosa. The morphological features do not differ from that of paragangliomas with other localizations. In paraganglioma, the stromal reaction is absent, while necrosis and mitoses were observed rarely [PriyadarshiV et al., 2015; Iwamoto G et al., 2017; Epstein JI et al., 1998].

4.2.4 **Acinar adenocarcinoma of the prostate, Gleason pattern 5.**

We can also establish the auxiliary diagnostic and prognostic criteria in the daily practice of the pathologist:

- In cases where more than 5% of the tumor component with the morphological characteristics of high-grade urothelial neoplasia is observed, the lesion should be classified as high-grade UC and vice versa - in cases of UC with high malignancy, where this component is less than 5% - the tumor is diagnosed as low-grade UC [Zhou M et al., 2012].
- In cases where high-grade bladder UC is combined with low-grade, histological grading is in favor of a high degree of malignancy [Zhou M et al., 2012].
- In cases where the UC of the bladder is built focally of the component with high-grade and less than 5% low-grade carcinoma, can be graded as: Lowgrade UC occupying <5% by Highgrade UC [Zhou M et al., 2012].

5. **Conclusion**

Since bladder cancer ranks 7th among the world's most dangerous malignancies, the complications arising from UC deteriorate patients’ quality of life. UC is the second most prevalent urogenital system neoplasm after prostate cancer, and it remains one of the world’s most critical issues.

However, the auxiliary diagnostic and prognostic criteria in the daily practice of the pathologist are determined by the percentages of tumor components with the morphological characteristics of high-grade or low-grade urothelial neoplasia.

**References**


Moch H, Cubilla AL, Humphrey PA, Reuter VE, Ulbright TM. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part A: Renal, Penile, and Testicular Tumours


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