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Variants of Bladder Cancer: The Pathologist's Point of View

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Abstract

Pathologic evaluation of bladder cancer typically reveals great tumor heterogeneity and, therefore, the common observation of urothelial carcinoma exhibiting a wide variety of histopathologic patterns is not surprising. Some of these patterns are so distinctive that they have been recognized as specific variants of urothelial carcinoma. Classifications have recently been revised in the 2016 World Health Organization Classification of Tumors of the Urinary System and Male Genital Organs. The current World Health Organization classifications clarify terminological issues and provide better definition criteria, but also incorporates some new entities. Many of these variants have important prognostic or therapeutic implications worth knowing by the urologist and oncologist, but also represent diagnostic challenges in daily practice of pathology. This review will discuss the features of pathologic variants of bladder cancer in the context of our current clinical practice.

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1. Introduction

Urothelial carcinoma has a propensity for divergent differentiation. Virtually the whole spectrum of bladder cancer variants described below may be seen, in variable proportions, in otherwise conventional urothelial carcinoma or in its pure forms [1–8] (Table 1). The phenotype of these histologic variants likely reflects underlying diversity in molecular composition [9–12]. In recent years, improved pathologic recognition and clinical understanding of these entities opened a novel paradigm in bladder cancer management which has impacted the process of therapy selection for patients, based on the current understanding of how distinct variant categories can affect patient prognosis [13–20].

The proper identification of bladder carcinoma with variant histology has important clinical implications, because misdiagnosis may result in improper or unnecessarily aggressive treatment [8].

Despite pathologic criteria being described for most of these variants, the diagnosis remains challenging in daily

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Table 1 – Histologic variants of infiltrating urothelial carcinoma according to World Health Organization Classification of Tumors of the Urinary Tract [1]

Urothelial carcinoma with divergent differentiation
-With squamous cell differentiation
-With glandular differentiation
-With trophoblastic differentiation
-Other
Nested urothelial carcinoma (including large nested)
Microcystic urothelial carcinoma
Micropapillary urothelial carcinoma
Lymphoepithelioma-like urothelial carcinoma
Plasmacytoid/signet ring cell/diffuse urothelial carcinoma
Sarcomatoid urothelial carcinoma
Giant cell urothelial carcinoma
Lipid-rich urothelial carcinoma
Clear cell (glycogen-rich) urothelial carcinoma
Poorly differentiated urothelial tumors

practice, a fact that frequently requires consultation to specialized genitourinary pathologists [1–8]. However, some variants may be under-recognized or misclassified due to evolving inclusion criteria for diagnostic and the frequent interobserver variability. Of great assistance is the use of differentially expressed immunohistochemical markers acting as ancillary tests to confirm variant diagnosis. An additional confounding factor can be found in a subset of patients in which multiple variant patterns may occur concurrently and at differing proportions [1–8,21]. The recently released 2016 World Health Organization Classification of Tumors of the Urinary System and Male Genital Organs presents better definition criteria of pathologic features useful in the establishment of a correct diagnosis and updates terminology and molecular characteristics of these important subtypes of bladder cancer (Table 2) [1].

Table 2 – Variants of urothelial carcinoma and their potential clinical significance

Pathologic category	Variant type	Clinical scenario and differential diagnosis	Molecular alteration
Urothelial carcinoma with divergent differentiation	With squamous cell differentiation	Primary or secondary squamous cell carcinoma	Common basal molecular classification; most unrelated to HPV
	With glandular differentiation	Primary or secondary adenocarcinoma	Unknown
	With trophoblastic differentiation	Trophoblastic cells present in urothelial carcinoma. Choriocarcinoma either primary or secondary. β-HCG (serum/tissue) in 30% of high stage urothelial carcinoma	True choriocarcinoma either primary or secondary shows high copy number of isochromosome 12p
Urothelial carcinoma with deceptively benign features	Nested urothelial carcinoma (including large nested)	Von Brunn's hyperplasia, nephrogenic adenoma	TERT promoter mutation
	Microcystic urothelial carcinoma	Cystitis cystica, cystitis glandularis, adenocarcinoma	TERT promoter mutation
Differential diagnosis with metastases to the bladder	Micropapillary urothelial carcinoma	Serous carcinoma of the ovary; micropapillary carcinomas from other sites; micropapillary morphology in carcinoma in situ or in NMIBC carcinoma seems less aggressive than invasive micropapillary carcinoma	Variable HER2-neu (*ERBB2*) gene amplifications or mutations. Basal molecular classification in 50% of cases. TERT promoter mutation. Luminal genotype.
	Plasmacytoid/signet ring cell/ diffuse urothelial carcinoma	Plasmacytoma; lymphoma; metastases from adenocarcinoma of stomach (poorly cohesive/diffuse); plasmacytoid morphology in carcinoma in situ or in NMIBC carcinoma seems less aggressive than invasive plasmacytoid carcinoma	CDH1 loss (mutation or methylation) in >80% of cases. E-cadherin loss in >70% of cases. Some with *HER2* gene amplification and alterations in genes such as *PI3K* and *TSC1*.
	Sarcomatoid urothelial carcinoma (carcinosarcoma)	Inflammatory myofibroblastic tumor (inflammatory pseudotumor); metastatic sarcomatoid carcinoma; sarcoma either primary or metastatic	Altered EMT protein expression by immunohistochemistry
	Giant cell urothelial carcinoma	Highly bizarre pleomorphic tumor giant cells similar to giant cell carcinoma of lung	Unknown
	Clear cell (glycogen-rich) urothelial carcinoma	Clear cell carcinomas from kidney or gynecologic organs; other	Similar to conventional urothelial carcinoma
	Urothelial carcinoma, lipid-cell variant	Liposarcoma; carcinosarcoma (heterologous sarcomatoid carcinoma)	Similar to conventional urothelial carcinoma
	Poorly differentiated tumors (undifferentiated carcinoma NOS, osteoclast-rich undifferentiated carcinoma, other)	Large cell carcinoma of lung; giant cell tumor of bone	Unknown
Marked immune cell response	Lymphoepithelioma-like urothelial carcinoma	Metastases from other sites; may be missed in small biopsies due to marked inflammatory background	Mostly unrelated to Epstein-Barr virus

b-HCG = beta-human chorionic gonadotropin; HPV = human papilloma virus; NMIBC = Nonmuscle invasive bladder cancer; NOS = not otherwise significant.

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