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Original contribution

Immunohistochemical profile to distinguish urothelial from squamous differentiation in carcinomas of urothelial tract

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Summary Urothelial neoplasms with squamous morphology raise the differential diagnosis between pure primary squamous cell carcinoma, urothelial carcinoma with squamous differentiation and secondary involvement by squamous cell carcinoma, for example, from uterine cervix. Accurate identification between these entities is critical due to differing prognosis and therapeutic strategies. We evaluated the utility of an immunohistochemical panel of 3 urothelial-associated antibodies (uroplakin III, S100P, and GATA3) and two squamous-associated antibodies (CK14 and desmoglein-3) in 50 primary urothelial neoplasms: 15 pure urothelial carcinomas, 12 pure squamous cell carcinomas and 23 urothelial carcinomas with squamous differentiation. Squamous differentiation was defined by intercellular bridges or evidence of keratinization. Pure squamous cell carcinomas were positive for CK14 (100%) and desmoglein-3 (75%), negative for GATA3 and uroplakin III; one case was S100P positive (9%). Pure urothelial carcinomas had an opposite pattern and were positive for S100P (93%), GATA3 (93%), and uroplakin III (67%) and were negative for desmoglein-3; CK 14 was positive in 27% of cases; 74% of urothelial carcinomas with squamous differentiation had expression of urothelial and squamous associated markers (S100P, 83%; GATA3, 35%; uroplakin III, 13%; CK14, 87%; and desmoglein-3, 70%), although reactivity for individual markers within some tumors did not always correspond with morphologic differentiation. Of the remaining 26%, 4 showed an overall "squamous" immunoprofile, whereas 2 cases showed a "urothelial" immunoprofile. Our study showed that a panel of five antibodies identifies squamous and urothelial differentiation in most instances suggesting potential diagnostic utility.

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1. Introduction

Urothelial carcinoma, the predominant epithelial malignancy of the urothelial tract [1], has a marked propensity for divergent differentiation [2]. Urothelial carcinoma with squamous differentiation is the most common variant morphology and is seen in up to 40% to 60% of cases of urothelial carcinoma [3–5]. Pure squamous cell carcinoma is much less common representing only 2% to 5% of primary bladder malignancies in most Western countries [6–9]. The differential diagnosis for a urothelial tract tumor with squamous morphology includes pure primary squamous cell carcinoma of urothelial tract, urothelial carcinoma with frank squamous differentiation, and secondary involvement by squamous cell carcinoma from adjacent organs, for example, the uterine cervix, vagina, or anal canal. Accurate classification is clinically important as investigations, management and prognosis differ between urothelial carcinoma, pure primary squamous cell carcinoma and secondary squamous cell carcinoma [2,6,10–16].

The distinction between poorly differentiated squamous and urothelial carcinomas, however, can be challenging as there is morphological overlap [17]. A particularly problematic issue is identification of urothelial differentiation in a high-grade neoplasm with predominant squamous morphology. In routine practice, pathologists are often confronted by this morphologically challenging scenario particularly in limited or crushed tissue samples (eg, urethral biopsy). Immunomarkers that reliably distinguish urothelial and squamous phenotypes would therefore be useful.

In this study, we tested a panel of five contemporary antibodies with putative specificity for urothelial epithelium (uroplakin III, GATA-3 and S100P) and squamous epithelium (CK14, Desmoglein-3). The aim was to determine whether this panel of markers can distinguish pure urothelial carcinoma, pure squamous cell carcinoma and urothelial carcinoma with squamous differentiation.

2. Materials and methods

2.1. Materials

Fifty cases of primary urothelial tract carcinomas, which included 12 pure squamous cell carcinomas, 15 pure urothelial carcinomas, and 23 urothelial carcinomas with squamous differentiation were retrieved from the archival surgical pathology files of Cedars-Sinai Medical Center, Cleveland Clinic, The Methodist Hospital, and University Hospital Cordoba, Spain. The study had institutional review board approval. Squamous differentiation was defined by intracellular keratin, keratin pearls and intercellular bridges [2,17]. Pure squamous cell carcinoma was defined by lack of invasive or in-situ urothelial carcinoma or history of urothelial carcinoma [18–20]. Details of cases are given in Table 1. Urothelial carcinomas included 8 high-grade (6 invasive and 2 non-invasive) and 7 low-grade (all non-invasive) tumors. Urothelial carcinoma with squamous differentiation included 22 high grade (all invasive) and 1 low grade (non-invasive) tumors. All 12 cases of pure squamous cell carcinoma were invasive and included 3 well, 6 moderately, and 3 poorly differentiated tumors.

2.2. Methods

One block from each case was chosen; in cases with more than 1 block, the block chosen was the most representative

Table 1 Details of cases

		Urothelial carcinoma	Squamous cell carcinoma	Urothelial carcinoma with squamous differentiation
Number		15	12	23
Gender	Male	10	6	15
	Female	5	6	8
Age; average (min − max); years		75.6 (56–90)	73.1 (34–96)	71.1 (42–87)
Site	Bladder	15	11	21
	Other	0	1 prostatic urethra	1 prostatic urethra1 renal pelvis
Differentiation	High-grade	8	9	22
	Low-grade	7	3	1
Specimen type	TUR	15	8	22
	Resection	0	4	1
Stage [a]	Tis	9	2	1
	T1	5	1	13
	T2	1	7	8
	T3	0	2	1

[a] TUR specimens exclude definitive pathological staging.