Surgical and Experimental Pathology

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Carcinomas in the bladder with papillary and pseudopapillary morphology - not always urothelial

Daniel Abensur Athanazio[1,2*], Maiara Ferreira de Souza[2] and Maria Estela Pompeu do Amaral[2]

Abstract

Background: Urothelial carcinoma shows wide plasticity and broad morphologic spectrum. In many instances, the presence of papillary morphology is reassuring of the urothelial histogenesis of a high-grade invasive lesion but is not pathognomonic.

Case presentation: We reported herein four cases of carcinomas in the bladder with papillary morphology that had a final diagnosis different from urothelial carcinoma (3% of cases in a 42-month period). In high-grade tumors involving the urinary tract, the presence of papillary/pseudopapillary morphology is not sufficient to render a diagnosis of papillary urothelial carcinoma. Prostate adenocarcinoma, primary bladder adenocarcinoma or metastasis must be excluded in selected case scenarios.

Keywords: Urologic neoplasms, Bladder cancer, Pathology

Background

Invasive urothelial carcinoma is well known to show wide plasticity and broad morphologic spectrum. It develops from two pathways: urothelial carcinoma in situ (flat) and noninvasive urothelial carcinoma (papillary). In some instances (such as invasive carcinomas with extensive squamous or sarcomatoid differentiations), the presence of noninvasive papillary component is usually used by pathologists to reassure the urothelial histogenesis of the lesion.

From the period of January 2017 to August 2020, our Service examined 118 invasive carcinomas in the bladder (diagnosed as invasive carcinoma or with this diagnosis prior to consultation). Cases clinically suspicious of bladder involvement by prostate adenocarcinoma were excluded. Of those 118 cases, 4 (3%) had papillary/pseudopapillary morphology and had a final diagnosis different from urothelial carcinoma. In all four cases, papillary/pseudopapillary morphology led to a primary diagnosis of urothelial carcinoma (sent for review) or yielded consideration of urothelial carcinoma during diagnostic work up. We review four illustrative cases that should alert the pathologist of potential differential diagnoses when dealing with carcinomas in the urinary tract showing papillary or pseudopapillary features.

Case presentation

Case 1

An 86-year old male patient presented hematuria for 1 month prior to consultation in the urology clinic. Ultrasonography and cystoscopy and showed an exophytic tumor in the vesical left lateral wall and trigone measuring 4.7 × 4.1 × 3.8 cm. The clinical impression was bladder cancer. Serum PSA levels were not informed by the time of biopsy evaluation. Retrospectively, it was retrieved that the patient had a serum PSA of 17.5 ng/ml 10 months earlier, and a new measure after transurethral resection was 31 ng/ml 15 days after the procedure. At microscopy, multilayered atypical cell covering fibrovascular cores were observed. In other areas, the tumor was

* Correspondence: dathanazio@gmail.com
[1]Hospital Universitário Professor Edgard Santos, R. Augusto Viana, s/n - Canela, Salvador 40301-155, Brazil
[2]Imagepat Laboratory, Rua Lucaia, 209 - Edf. EventusEmpresarial, Rio Vermelho, Salvador 41940-660, Brazil

solid and cribriform. Mitotic activity and foci of coagulative necrosis were easily detected. Tumor cells expressed strongly and diffusely PSA and prostein (P501S) while negative for p63 and GATA3. Cytokeratin 7 expression was focal. There was focal expression of neuroendocrine markers chromogranin (< 5% of tumor cells), CD56 (< 5% of tumor cells) and synaptophysin (< 1% of tumor cells). Final diagnosis was high-grade acinar prostate adenocarcinoma with pseudopapillary features (see discussion below). Illustrative images are seen in Fig. 1.

Case 2

An 87-year old male patient presented with hematuria for 2 months. Digital rectal exam revealed a prostate with hard consistency. Cystoscopy showed a large exophytic mass in vesical trigone with extension to prostatic urethra and left ureteral opening. Serum PSA was 15.3 ng/ml by the time of surgery. Transurethral resection (TUR) specimens of the prostate and bladder showed a high-grade and high-volume carcinoma with cribriform morphology and foci of comedonecrosis. In the prostate TUR specimen, morphologic findings were highly suspicious of a prostate primary high-grade acinar adenocarcinoma. In one focus, a small area of well differentiated adenocarcinoma (Gleason pattern 3) was observed. The tumor specimen in the bladder raised the possibility of concurrent urothelial papillary carcinoma due to pseudopapillary morphology. In both prostate and vesical samples, the tumor was strongly and diffusely positive for PSA and prostein (P501S) and did not stain for GATA3 and P63. Cytokeratin 7 expression was focal. Illustrative images are seen in Fig. 2.

Case 3

A 71-year old male patient presented recurrent unilateral (right) hydrothorax. A pleural biopsy showed an adenocarcinoma with the following immunophenotype: cytokeratin 7 positive, P63 and GATA3 focally positive, and absent expression of cytokeratin 20, TTF1, napsin A, PSMA and prostein (P501S). Cystoscopy showed a large tumor involving prostate and the bladder. Both prostate and bladder transurethral resection specimens showed a high-grade adenocarcinoma resembling a colonic type tumor with dirty necrosis, signet ring cell component and surface villous architecture. Immunophenotype showed cytokeratin 7 strong and diffuse, focal CDX2 expression, diffuse villin expression (brushborder pattern), membranous beta-catenin and absent expression of cytokeratin 20, P63, GATA3, PSA and prostein (P501S). Upper endoscopy and colonoscopy were normal. Final diagnosis favored a primary adenocarcinoma of the bladder. Illustrative images are seen in Fig. 3.

Case 4

A 47-year old male patient presented with a tumor in the bladder dome. A previous diagnosis of muscle-invasive urothelial carcinoma with glandular differentiation was rendered in other service. Slides and blocks were referred for second opinion. The lesion showed villous architecture with intestinal type epithelium and

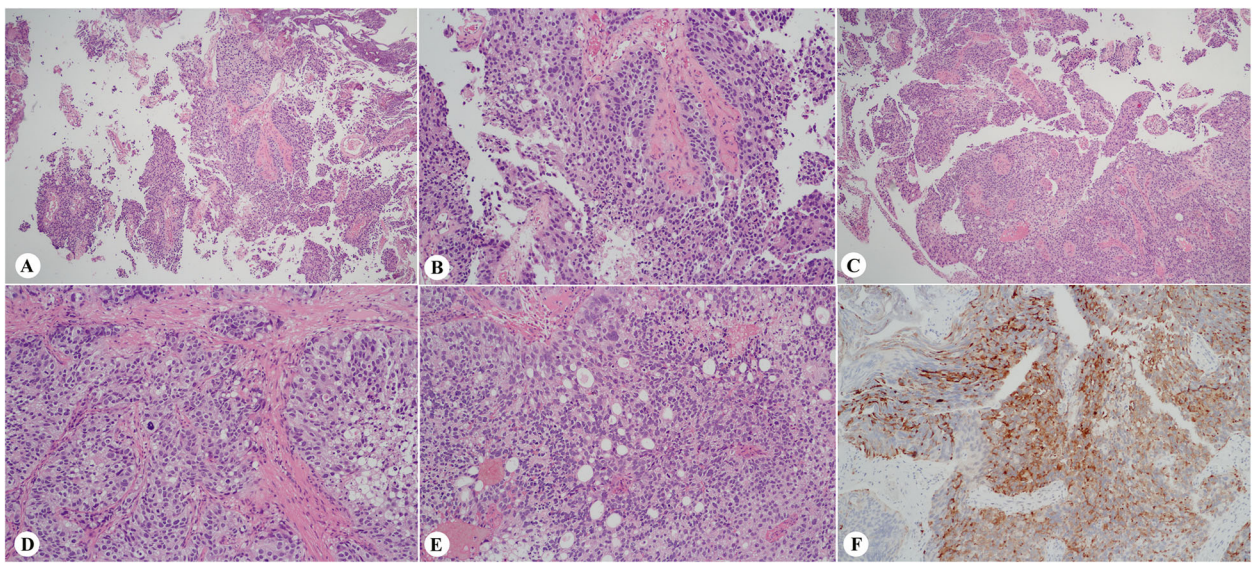

Fig. 1 Case 1. High-grade prostate adenocarcinoma with pseudopapillary features (**a**: HE stain 40x; **b**: HE stain100x, and **c**: HE 40x). Solid areas with large sheets of atypical cells (HE stain, 100x) and focal cribriform morphology (HE stain, 100x). PSA expression was strong and diffuse (PSA immunostain 100x)

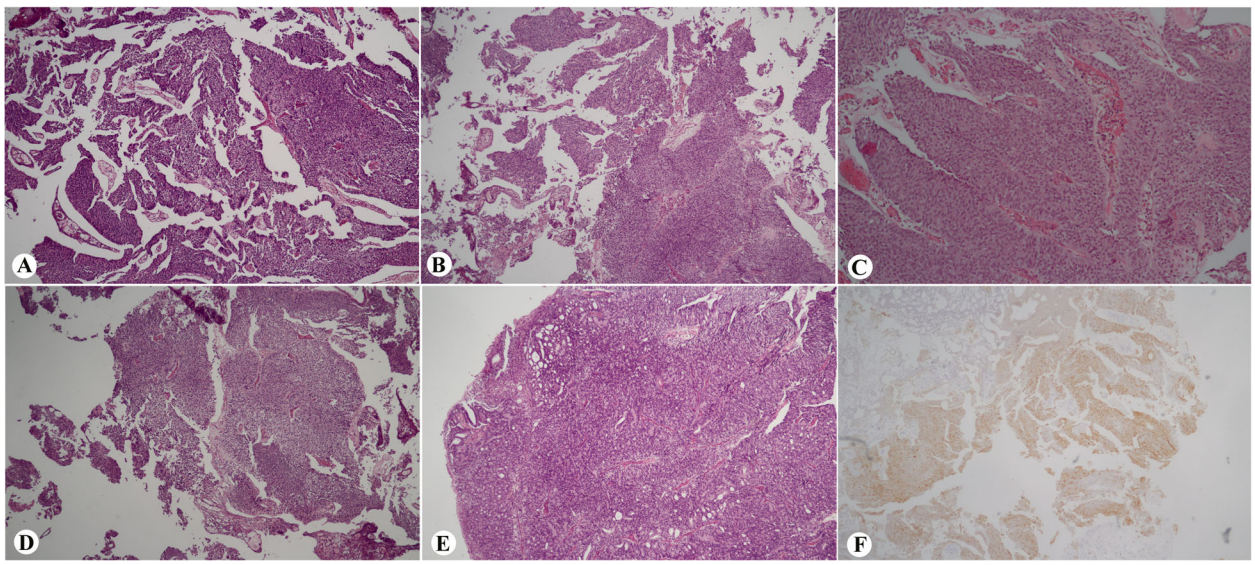

Fig. 2 Case 2. High-grade prostate adenocarcinoma with pseudopapillary features in transurethral resection specimen of the bladder (HE stain – **a**, **b**, **c** and **d**: 40x). In other areas, tumor was solid or extensively cribriform (**e**: HE, 40x). PSA expression was strong and diffuse in all areas including pseudopapillary areas in the bladder specimen (PSA immunostain 40x)

high-grade nuclear atypia. No definitive destructive / invasive foci were seen. Some glands were observed within fibromuscular stroma with morphology not diagnostic of muscularis propria and were interpreted as urachal remnants. Final diagnosis was villous adenoma with high-grade dysplasia (adenocarcinoma in situ) arising in urachal remnants. A multidisciplinary panel opted for partial cystectomy. The patient is at 18 months of follow up with no symptoms or cystoscopic signs of recurrence. Illustrative images are seen in Fig. 4.

Discussion

In high-grade tumors involving the urinary tract, the presence of papillary/pseudopapillary morphology is not sufficient to render a diagnosis of papillary urothelial carcinoma. As illustrated in cases 1 and 2, attention on location,

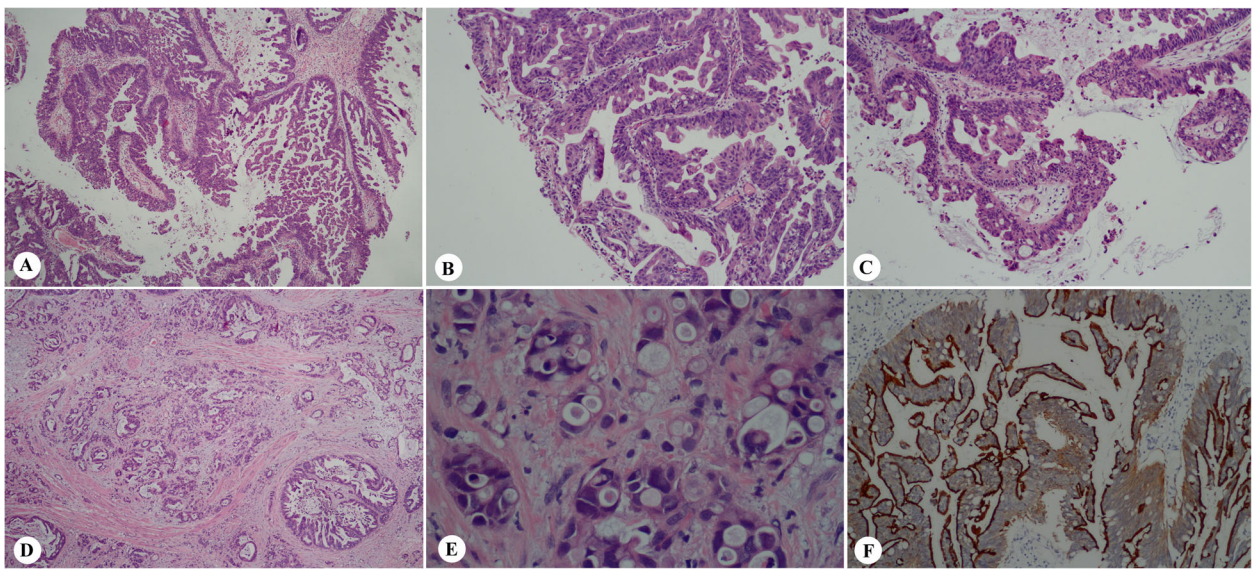

Fig. 3 Case 3. Primary adenocarcinoma of the bladder. Villous architecture with true fibrovascular cores (**a**: HE stain, 40x) showing pseudostratified columnar and goblet cells (**b** and **c**: HE stain, 100x). The tumor invades prostatic stroma showing extracellular mucin and dirty necrosis (**d**: HE stain, 40x). Signet-ring component is evident (**e**: HE stain, 100x). Villin expression in brushborder pattern (**f**: villin immunostain, 100x)

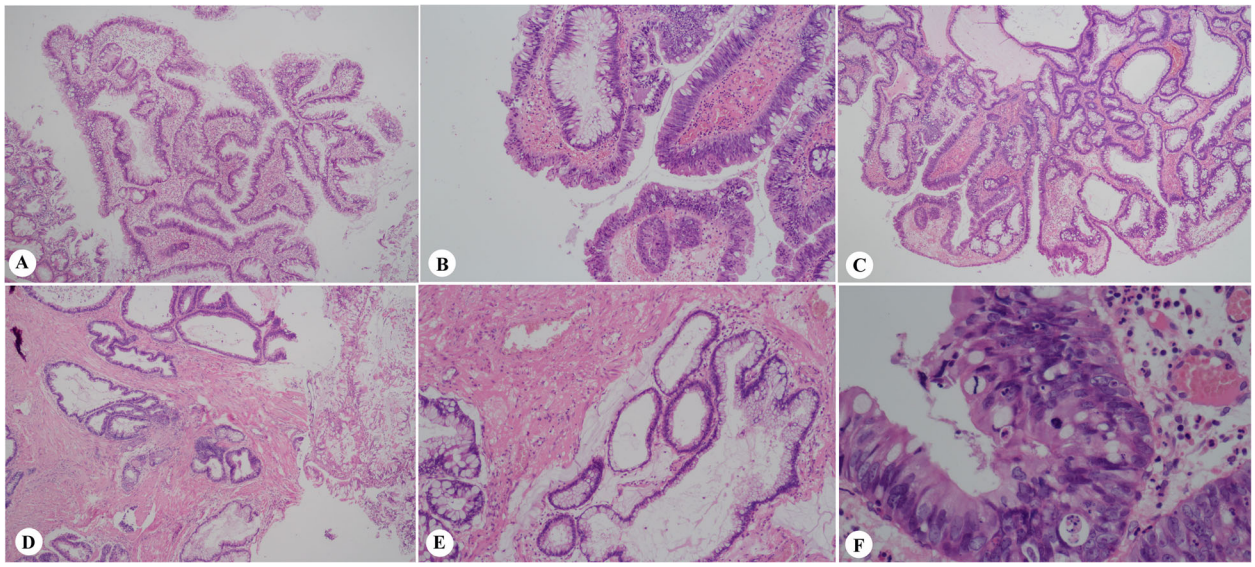

Fig. 4 Case 4. Villous adenoma /Adenocarcinoma in situ of the bladder. Villous architecture with true fibrovascular cores showing pseudostratified columnar and goblet cells (**a**: HE stain, 40x; **b**: HE stain 100x; and **c**: HE stain, 100x). Urachal remnants in fibromuscular stroma – no infiltrative pattern or desmoplastic reaction (**d**: HE stain, 40x; **e**: HE stain 100x). High-grade atypia of adenocarcinoma in situ (HE stain, 400x)

advanced age and cribriform morphology should alert the pathologist for the requirement of immunostains to exclude prostate adenocarcinoma. Recently, it has been described that pseudopapillary morphology may occur in high-grade prostate adenocarcinoma leading to a potential diagnostic pitfall (Gordetsky and Epstein 2014).

As a rule, high-grade prostate adenocarcinoma shows more uniform cytology with prominent nucleoli diffusely present in tumor cells, while high-grade urothelial carcinoma exhibits striking nuclear pleomorphism. Microacinar/rosette differentiation as well as low grade areas of acinar adenocarcinoma favor prostate as primary site but it does not exclude the possibility of concomitant/collision tumors. In a series of seven cases of high-grade prostate adenocarcinomas with pseudopapillary features, Gordetsky and Epstein interpreted this finding as tumor fragmentation in poorly cohesive areas (tumor preservation around vessels simulating fibrovascular cores). Clear-cut distinction in such cases relies on the high index of suspicious by the pathologist and a low threshold to perform immunostains (Gordetsky and Epstein 2014).

Primary adenocarcinoma of the bladder is rare and its differential diagnosis with secondary adenocarcinoma is problematic. Primary bladder adenocarcinoma and colonic cancer usually share expression of CDX2, cytokeratin 20, villin and CEA. Even the peculiar brushborder pattern of villin expression (illustrate in case 3) is also reported in primary bladder adenocarcinoma (Roy et al. 2012). Villous architecture is seen in glandular precursors of adenocarcinoma (adenocarcinoma in situ / villous adenoma with dysplasia) and may also occur as a consequence of mucosal colonization by metastatic adenocarcinoma (Epstein and Netto 2014). Villous architecture with severe dysplasia may be difficult to distinguish from a high-grade papillary urothelial carcinoma particularly when high-grade features obscures identification of intestinal type mucosa.

Villous adenoma is a rare neoplasm of the urinary bladder and location of dome and urachus are the most common. Readily recognition of villous adenoma on cystoscopy is difficult because gross findings are unspecific with few reports available. Therefore, it is difficult to differentiate from papillary urothelial neoplasms. At microscopy, they are characterized by blunt finger-like papillary architecture with pseudostratified columnar epithelium and may show goblet cells. In high-grade areas, hyperchromatic nuclei and prominent nucleoli may invoke the differential diagnosis with high-grade papillary urothelial carcinoma. In addition, glandular or villoglandular differentiation of a noninvasive papillary urothelial neoplasm must be excluded by the absent of characteristic urothelial areas (Miller and Epstein 2009; Lim et al. 2009). Villous adenomas of the bladder usually coexist with in situ and invasive adenocarcinoma (Siebel et al. 2002).

Urachal remnants are sometimes found in biopsies from dome or anterior wall of the bladder. They are recognized as cystic structures lined by urothelium or by glandular or flattened epithelium (Zhou and Magi-Galluzzi 2015). They are surrounded by thin fibromuscular stroma (Begg 1930). Importantly, this surrounding stroma does not have thick, arranged in parallel, compacted, muscle fibers with regular outline which is diagnostic of muscularis propria. Proper recognition of urachal remnants is important to avoid the diagnosis of muscle invasive disease, as illustrated in case 4.

Conclusion

In high-grade tumors involving the urinary tract, the presence of papillary/pseudopapillary morphology is not sufficient to render a diagnosis of papillary urothelial carcinoma. We report two cases that emphasizes location, advanced age and cribriform morphology as red flags for the requirement of immunostains to exclude prostate adenocarcinoma. Villous architecture and intestinal-type dysplasia should raise consideration for true glandular neoplasms.

Abbreviation

TURB: Transurethral resection of the bladder

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Adherence to national and international regulations

Not applicable.

Authors' contributions

DAA conceived the idea. DAA was the major contributor to the writing of the manuscript. DAA, MFS and MEPA diagnosed all cases. MFS and MEPA were major contributors for critically revising the manuscript for important intellectual content. All authors read and approved the final manuscript.

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All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

This study was approved by the Human Research Ethics Committee of the Faculty of Medicine, Federal University of Bahia (approval number: 3.709.215).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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