

A 70-year-old male presenting with a papillary urethral tumor

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Clinical history

The patient is a 70-year-old gentleman with a history of benign prostatic hyperplasia who presented with hematuria. Cystoscopic evaluation revealed a papillary urethral mass that was subsequently excised by trans-urethral resection.

Histology

The histology reveals a complex glandular proliferation with both exophytic and endophytic components. The architecture includes foci of papillary infoldings around fibrovascular cores intermixed with cribriform areas (Fig. 1).

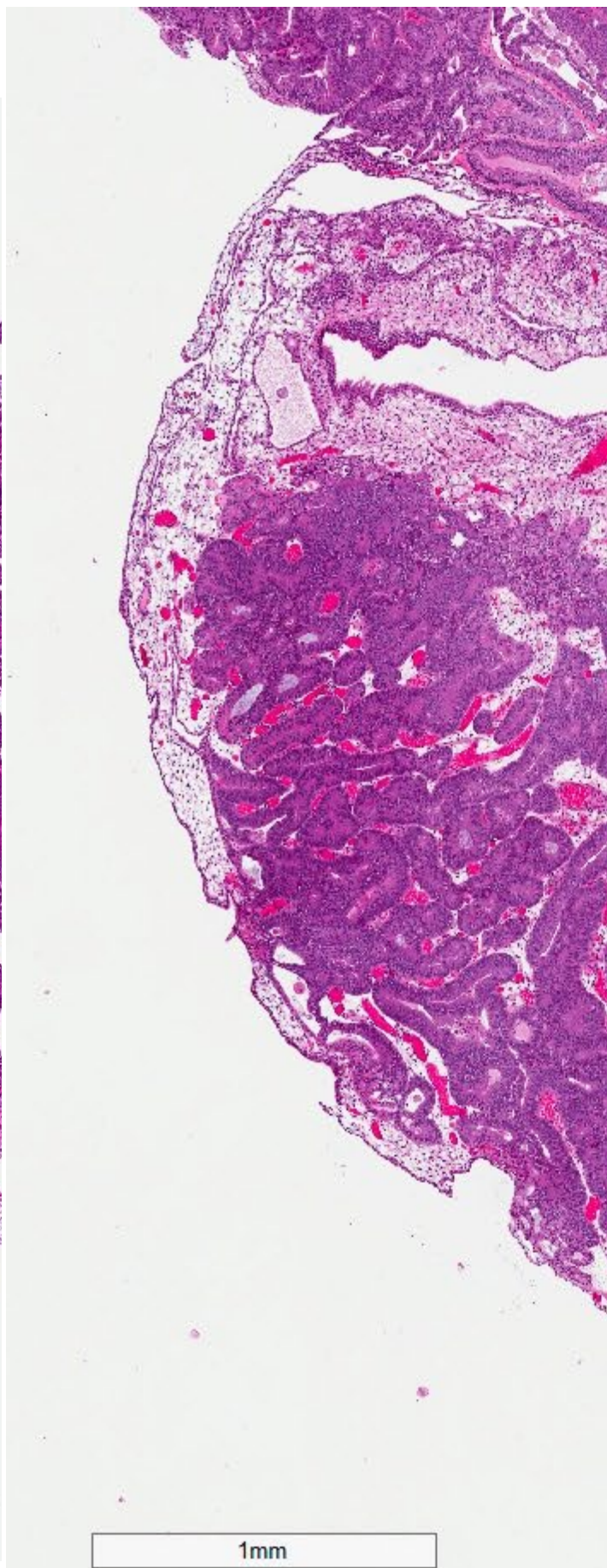
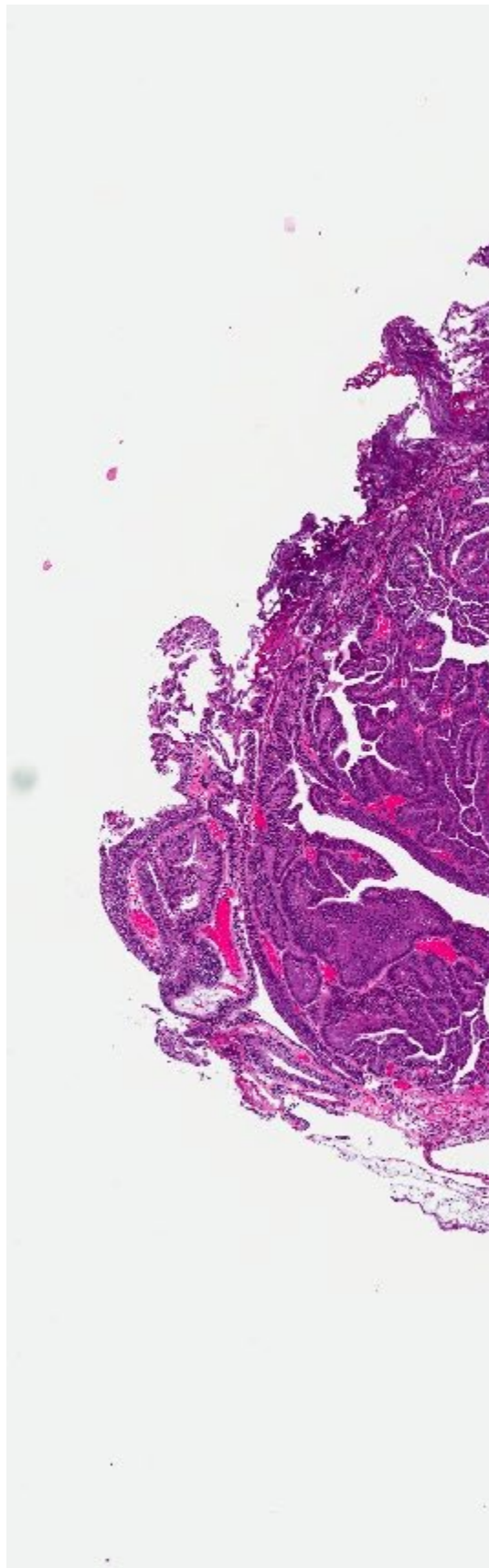
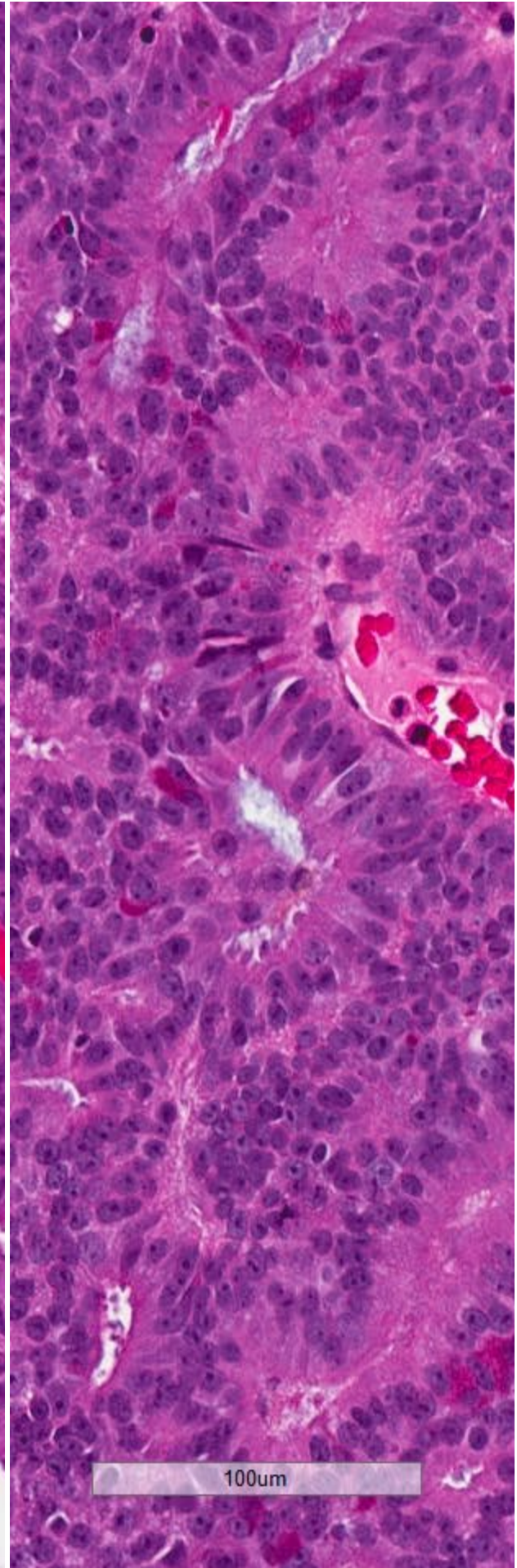
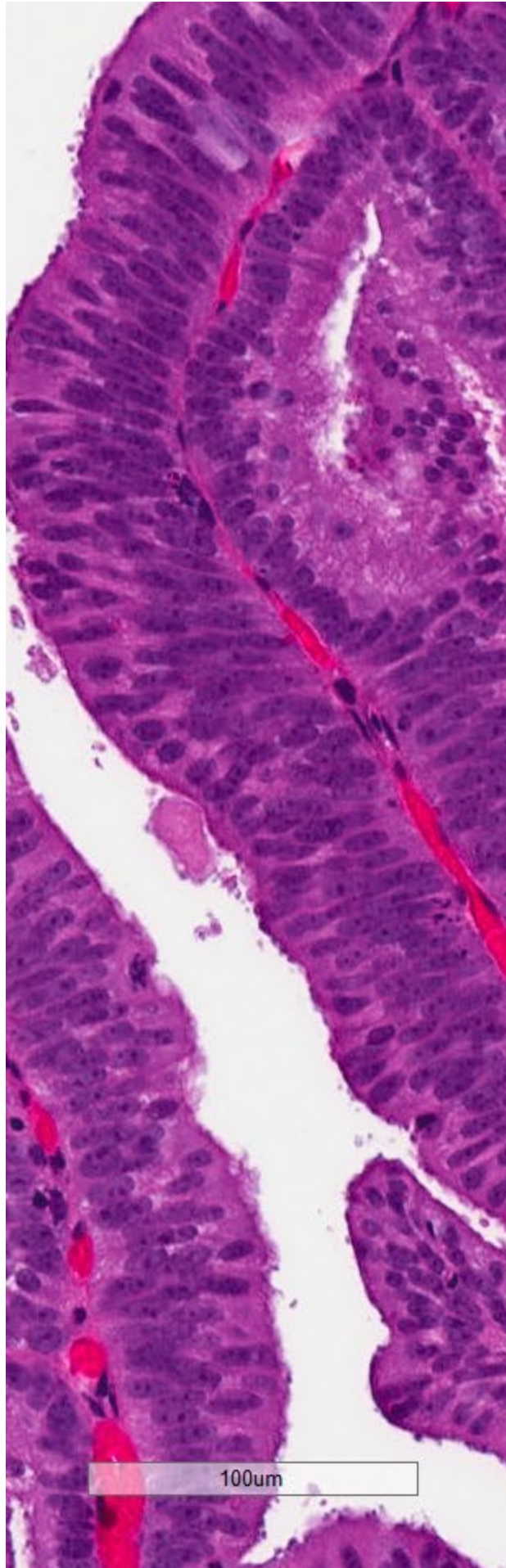


Fig. 1A Low magnification reveals multiple nodules with complex malignant glands growing in papillary and cribriform patterns (H&E, 2X)

Fig. 1B Areas of cribriform growth are seen in the lamina propria underlying normal urethral epithelium (H&E, 2X)

The glands are lined by tall columnar cells with amphophilic cytoplasm and pseudostratified elongated nuclei. Prominent nucleoli with coarse chromatin and numerous mitotic figures are observed (Fig. 2). Islets of tumor cells are seen growing under the urothelium of the urethra, invading into lamina propria and surrounding muscle tissue (Fig. 3). No in situ or invasive usual urothelial carcinoma components are identified in the specimen.



A

B

Fig. 2 Malignant glands in papillary (A) and cribriform (B) arrangements are lined by tall columnar epithelium with pseudostratified nuclei and prominent nucleoli. Multiple mitoses are identified. (H&E, 20X)

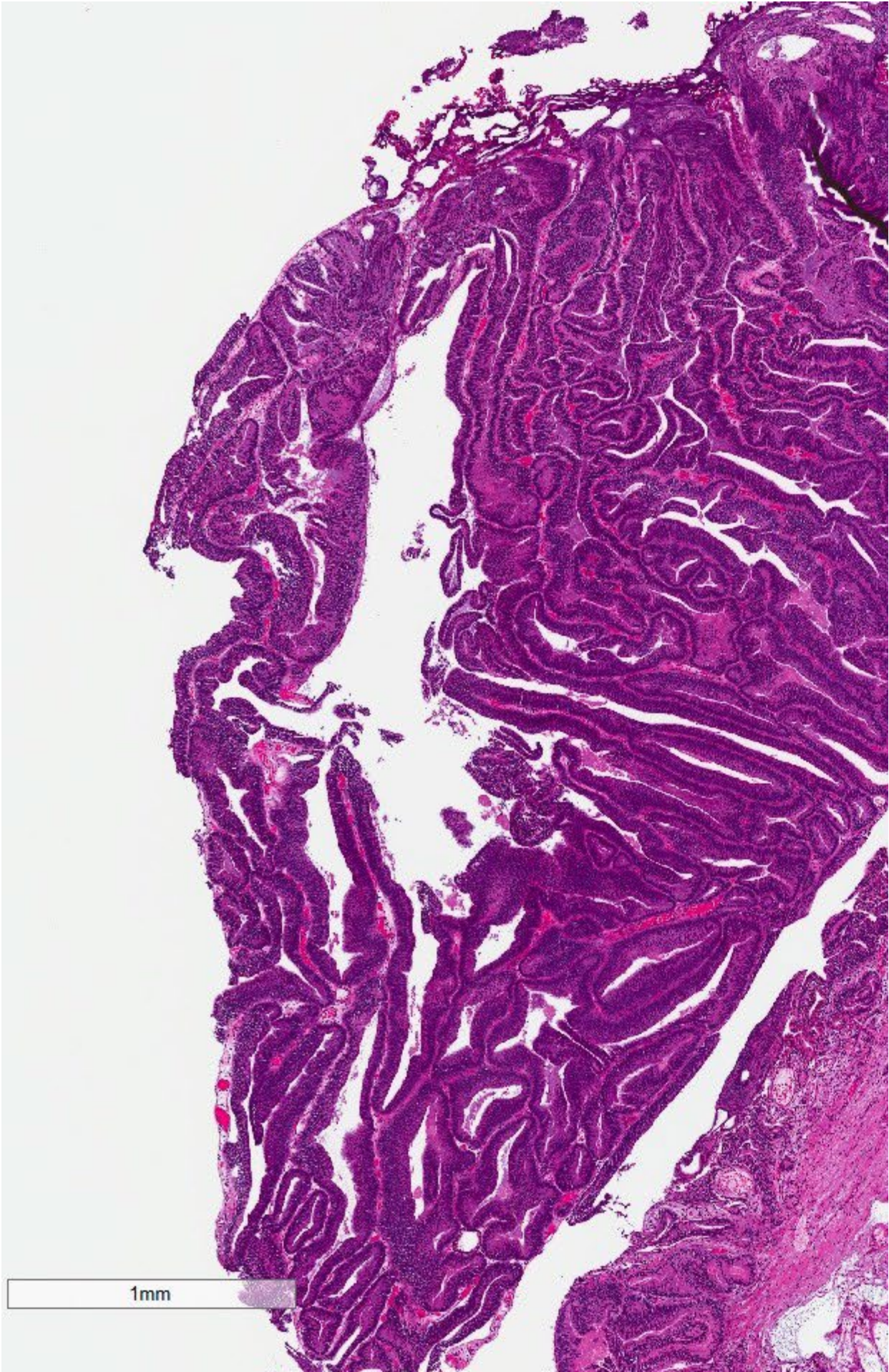


Fig. 3 Islets of malignant cells invade into muscular tissue (H&E, 2X)

Differential Diagnosis

Focal glandular differentiation can be seen in up to 18% of invasive urothelial carcinoma (1). However, purely gland-forming lesion should raise the possibility of primary urothelial adenocarcinoma. Specifically, the enteric subtype recapitulates the features of its gastrointestinal counterpart by demonstrating tall columnar mucin-secreting cells with variable pleomorphism and central necrosis. In parallel with the morphology, tumor cells tend to acquire the enteric immunophenotype and thus show immunoreactivity for CDX2 and CK20, while GATA3 nuclear labeling is lost in up to 50% of cases (2, 3). Expression of a more recently described colorectal adenocarcinoma biomarker SATB2 has likewise been reported in primary urothelial lesions (4). Membranous rather than nuclear pattern of beta-catenin immunoreactivity can be used as an argument in favour of urothelial origin (2). These lesions are also less likely to express villin in comparison to colorectal adenocarcinoma (5). Clinico-radiological correlation remains imperative to exclude a gastrointestinal metastasis.

Particularly in this case, secondary involvement of urethral and periurethral tissue by prostatic carcinoma should be considered. Tall columnar pseudostratified epithelium is specifically characteristic of a morphologically distinct variant of prostatic adenocarcinoma, the ductal type. Alike its acinar counterpart, prostatic ductal carcinoma stains positive for PSA, PSAP, NKX3.1 and AMACR, while urothelial markers are negative.

Indeed, in this case the nature of the neoplastic cells was determined by immunohistochemistry, demonstrating marked reactivity with NKX3.1 and negative GATA3 staining (Fig. 4).

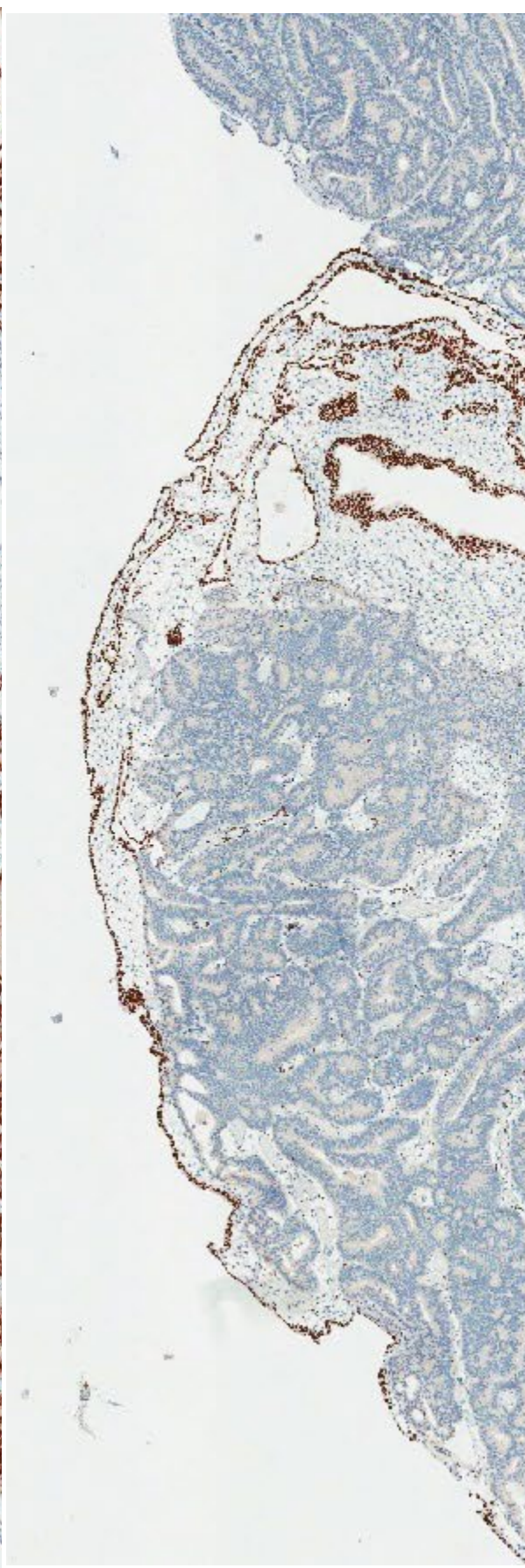
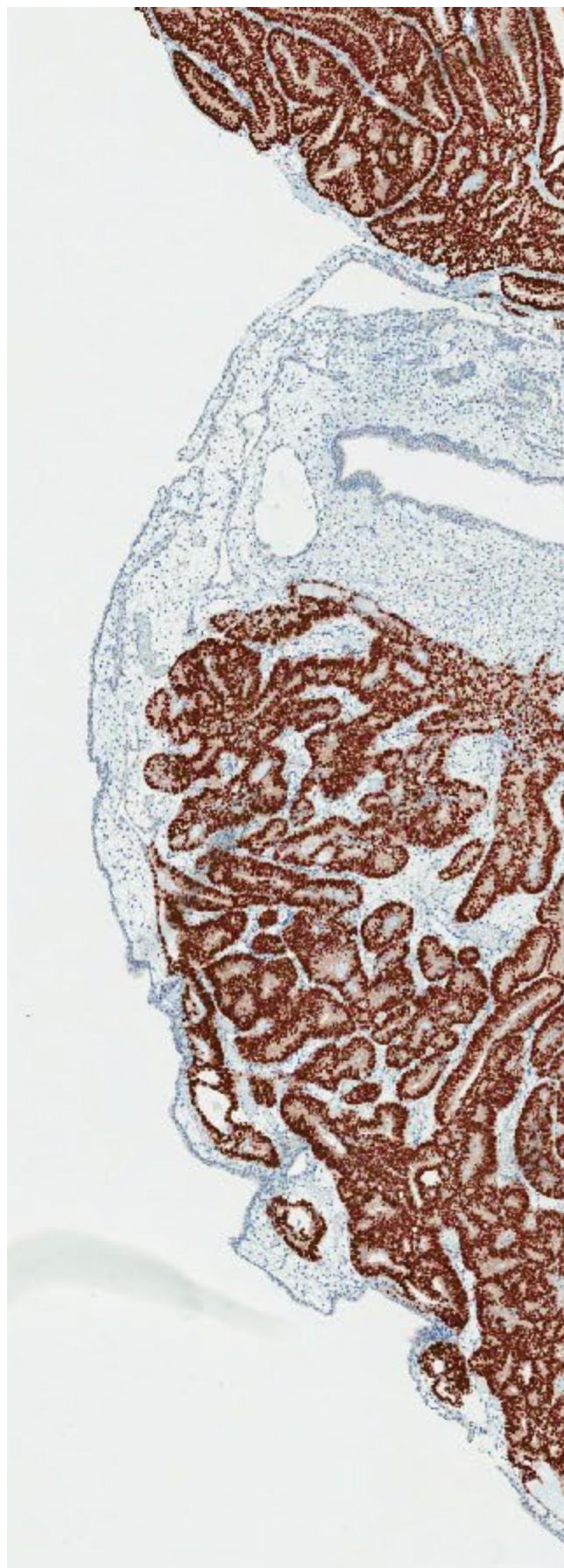


Fig.4A Tumor cells show strong and diffuse immunoreactivity for NKX3.1 thereby confirming their prostatic origin (NKX3.1, 2X)

Fig. 4B GATA3 staining highlights the remaining urethral lining but is negative in malignant cells (GATA3, 2X)

Final Diagnosis: Prostatic Ductal Adenocarcinoma.

Discussion

Prostatic ductal adenocarcinoma (PDA) was first described as “endometrioid carcinoma” by Melicow and Patcher in 1967, given the tumor morphological resemblance to endometrial carcinoma (6). It was initially thought to originate from a remnant of Müllerian duct – the prostatic utricle –, but in reality, this malignancy arises from prostatic duct epithelium, often expanding along the ducts and eventually invading into prostatic stroma and surrounding tissue (1). Although rare, PDA is still the second most common histological variant of prostatic carcinoma with diverse incidence in prostatectomy and biopsy specimens. Its incidence varies from 0.4% to 0.8% in a pure ductal form and up to 3% to 12.7% in a mixed ductal-acinar adenocarcinoma form (7). PDA mainly occurs in elderly men with the age of 63 to 72 years old (range: 41 to 89 years old). PDA is predominantly located in the periurethral zone of prostate, but can also be found in the peripheral zone. The patients with PDA in the periurethral zone may present with urinary obstruction, urinary urgency, urinary frequency and hematuria, symptoms related to an exophytic growth of tumor into the urethra. The cystoscopy examination usually reveals an exophytic, villous or polypoid mass, as in our case. In that context, the tumor may be mistaken for an urothelial papillary neoplasm, both clinically and histologically. Moreover, patients with PDA may have normal digital rectal examination, particularly when tumors originate from the larger periurethral prostatic ducts, and most patients have normal serum prostate-specific antigen (PSA) level (< 4.0 ng/mL) which may result in its delayed diagnosis or misdiagnosis (7). The other presentation is in the context of prostatic biopsies performed for elevated PSA. Typically, in that context the tumor shows mixed acinar and ductal morphologies. Importantly, PDA is associated with higher stage at presentation, greater risk of recurrence and increased mortality than average acinar adenocarcinoma (7). Metastatic spread can involve lymph nodes, bone, penis, testis and lung. Moreover, serum PSA level is not associated with tumor staging, recurrence and metastasis, and is therefore not an ideal marker for risk assessment and prediction of recurrence in PDA (7). The conventional therapies, including hormonal therapy and radiotherapy, and newer anti-androgen therapies such as Abiraterone may be less effective for patients with PDA, but the evidence is very limited due to its rarity. Pure PDA, however, may be a different biologic and clinical entity than mixed PDA. Clinical biological behavior of mixed ductal and acinar adenocarcinoma is considered to be depended on the proportion of ductal component as well as the Gleason score of acinar component (7).

Histologically, a proliferation of complex glands with tall columnar pseudostratified epithelium as seen in the current case is characteristic of this entity. Multiple architectural patterns have been described, with papillary and cribriform growths being the most common. The current case exemplifies both of these with regions composed of papillary fronds along with areas of crowded back-to-back glands with intraglandular epithelial bridging creating slit-like lumina. Otherwise,

solid, glandular, prostatic intraepithelial neoplasia (PIN)-like and other rarer patterns, including micropapillary, mucinous, foamy gland, and cystic papillary patterns, can be seen (7). Notably, the PIN-like ductal adenocarcinoma is characterized by individual infiltrating glands with tall columnar cell lining that can be easily mistaken for flat or tufted high grade PIN. The distinguishing features include extensive crowded growth, often with cystic dilation and flat lining, as well as absence of basal cells. Most patterns of PDA are assigned a Gleason pattern 4, with the exception of the PIN-like variant (Gleason pattern 3) and the solid variant (Gleason pattern 5) (8). Presence of comedonecrosis likewise upgrades the lesion to a Gleason pattern 5.

While its unique histological features help distinguish the ductal variant from the usual acinar carcinoma, the diagnostic challenges may arise when the tumor originates in the large primary periurethral prostatic ducts and grows as an exophytic lesion into the urethra. This is seen most commonly in and around verumontanum, and may constitute a potential diagnostic pitfall when evaluating urethral specimens. It is important to remember that in addition to infrequency of primary urethral neoplasms, the primary adenocarcinoma constitutes an exceedingly rare entity among malignant neoplasms of the urothelial tract, accounting for 0.5-2% of malignant bladder tumors (1). These neoplasms are thought to arise in the context of chronic irritation through intestinal metaplasia of urothelium and resulting chromosomal abnormalities (9). As aforementioned, pure glandular morphology is required for diagnosis. In addition to the enteric type previously described, the mucinous variant is characterized by lakes of extravasated mucin containing nests of malignant cells. Most commonly a mixture of these histological patterns is observed. Uncommon variants may include signet ring cell, clear cell and hepatoid morphology (10). Given the rarity of this entity, it is important to remember that glandular lesions in urothelial tract are more likely to be of secondary rather than primary nature, the most common origin being colorectal and prostatic. Documenting an in situ component constitutes the strongest evidence of urothelial origin but can be challenging in transurethral resection specimens given the presence of cautery artefacts and incomplete sampling. Moreover, true carcinoma in situ must be distinguished from colonization of native epithelium by metastatic carcinoma. Careful interpretation of immunohistochemistry, as previously discussed, and review of clinical history must be integrated to reach the final diagnosis. The distinction is critical given the divergent staging methods, therapeutic approaches and prognosis.

In conclusion, PDA is rare but the second most common histological variant of prostatic carcinoma. It has unique origin, histological and clinical features, and biological behavior. Due to its aggressive clinical course and high risk of disease progression, it is crucial to differentiate PDA from other mimickers.

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