# The role of molecular testing in diagnosing recurrent prostatic adenocarcinoma when immunohistochemistry and morphological evaluation are not enough

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## Case Report

A 75-year-old man with history of high-risk, Grade Group (GG) 5 prostatic adenocarcinoma status post radiation therapy, on androgen deprivation, developed urinary retention and gross hematuria six years after his initial diagnosis.

Laboratory analyses yielded a serum prostate specific antigen (PSA) of <0.01 ng/mL.

CT abdomen and pelvis with contrast revealed thickened bladder wall with markedly enlarged prostate, and perivesical/periprostatic soft tissue infiltration/stranding.

Urine cytology was positive for malignancy.

On cystoscopic examination, nonspecific low-lying papillary-appearing erythematous lesions were noted along the left lateral wall of the bladder, which were resected, as well as friable prostate tissue, which was fulgurated.

Histologic sections showed rare clusters of focally columnar neoplastic cells with moderate to abundant cytoplasm, and enlarged, markedly irregular nuclei with prominent nucleoli, on a background of benign bladder mucosa with cystitis cystica et glandularis.

The neoplastic cells did not show immunophenotypical evidence of either prostatic or bladder origin (resulting negative for NKX3.1, GATA-3, p63, PSA, and PSAP), or other "organ-specific" derivation. They were also negative for markers of neuroendocrine differentiation (synaptophysin and chromogranin A), ultimately leading to a diagnosis of high-grade carcinoma with glandular features of uncertain origin, differential diagnoses including bladder/urethral primary and post-treatment prostatic adenocarcinoma.

The initial diagnostic needle biopsy specimen was reviewed. Stains performed on the archived material revealed the tumor on the biopsy to diffusely and strongly express nuclear NKX3.1 and patchy positive cytoplasmic PSAP, and again negative neuroendocrine and urothelial marker immunoreactivity (Fig 1-2).

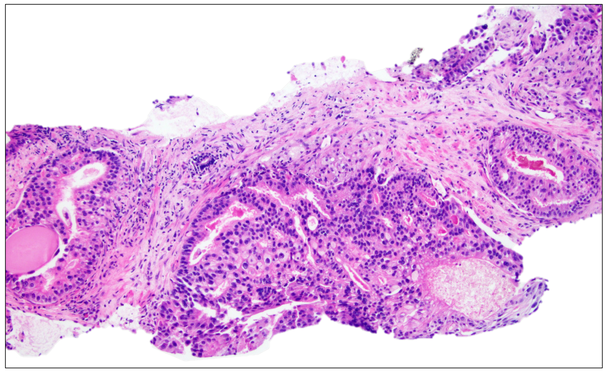

**Figure 1.** Prostatic adenocarcinoma initially diagnosed at transrectal ultrasound-guided needle biopsy (Hematoxylin&Eosin, H&E, 100x)

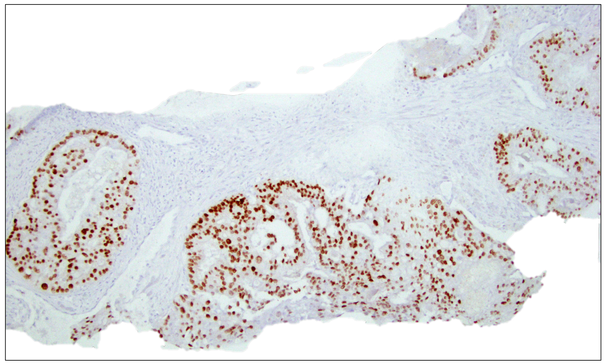

**Figure 2.** Neoplastic cells show diffuse nuclear positivity for NKX3.1 immunostain, supporting prostate origin. (Original magnification, OM, 100x)

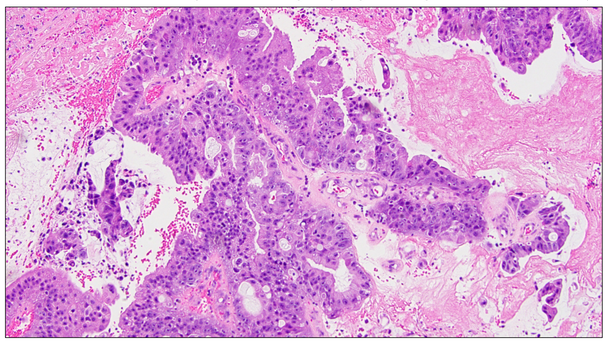

**Figure 3.** Transurethral resection of recurrent tumor showing adenocarcinoma (H&E, OM 100x)

The initial diagnosis of high-grade (GG5) prostatic adenocarcinoma was thus confirmed.

The patient underwent a repeat transurethral resection (TUR) of bladder, with additional prostate sampling, yielding an increased amount of neoplastic tissue (Fig 3), which showed the same morphology and immunohistochemical features of the prior TUR (including negative NKX3.1 immunostain).

Targeted next-generation sequencing (NGS) was carried out on the TUR sample, and, simultaneously, on stored samples from the initially diagnosed prostatic adenocarcinoma needle biopsy.

The molecular analyses revealed overlapping genomic alterations between the two tumors, including *PTEN* loss and identical mutations in *TP53*, *NF1*, and *BCOR* genes, with additional mutations in the most recent tumor, confirming clonal relationship between the initial and recurrent tumor and, ultimately, allowing the diagnosis of post-treatment recurrence of the patient's known prostatic adenocarcinoma.

## Key Diagnostic Point

- High-stage prostate cancer can involve the urinary bladder and manifest with hematuria.
- The diagnosis of prostate cancer involving bladder relies primarily on morphological evaluation, with or without the aid of immunohistochemistry, the latter assisting in the differential diagnosis with primary glandular and glandular-appearing urothelial lesions, or other adenocarcinomas secondarily spreading to the bladder.
- Loss of prostatic marker expression has been reported in post-treatment prostatic adenocarcinoma and can make the determination of prostatic origin challenging in this setting.
- Molecular testing may represent a valuable ancillary tool in establishing clonal relationship between primary and secondary (recurrent/ metastatic) tumors with discordant immunophenotype.