Double Trouble: Establishing Synchronous Primary Tumors of the Urothelium and Prostate by Immunohistomorphology: A Report of Two Cases

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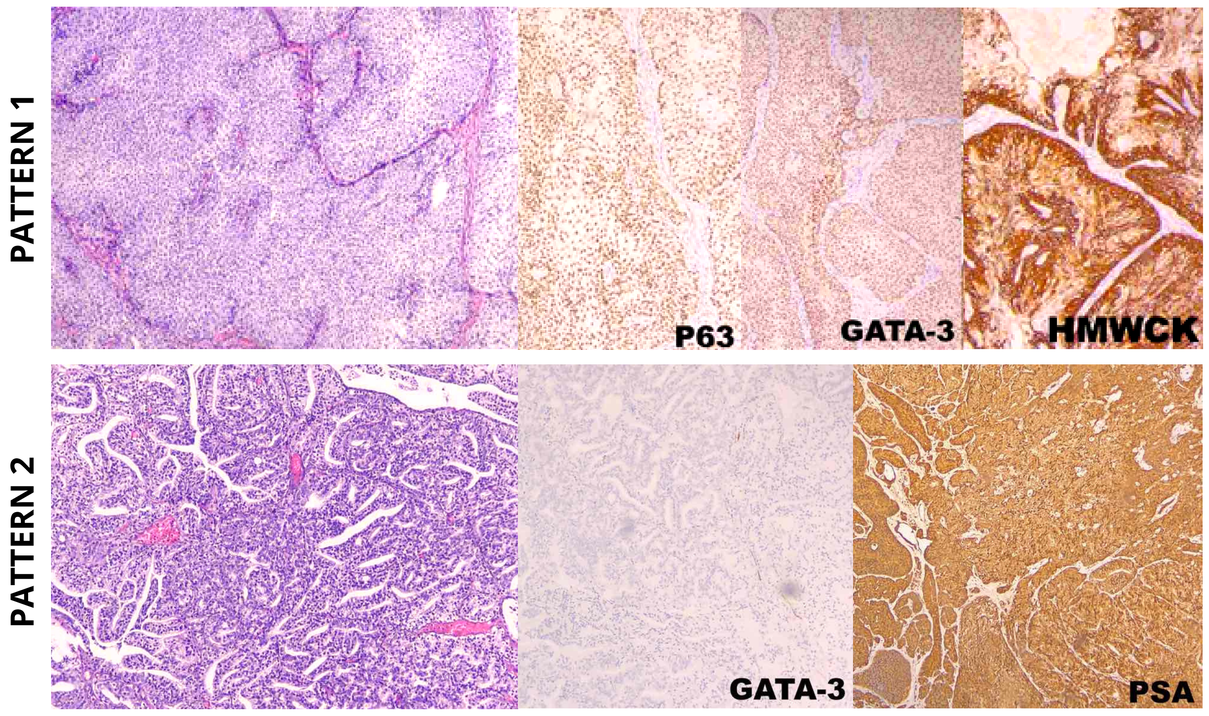
INTRODUCTION

Double primary malignancy of the lower genital tract is not uncommon. Reporting of double primary malignancies with at least an aggressive prostatic carcinoma is infrequent with only a number of published case reports abroad. Diagnosis of double primary carcinomas of the bladder and prostate in transuretheral resection of the prostate (TURP) specimens is usually straightforward, except when there is significant morphologic overlap. The management differs for urothelial carcinomas and prostatic adenocarcinoma with different risk-stratified treatment algorithms. We report two cases of double primary urothelial and prostatic carcinoma to give insights on the approach to their diagnosis and to address paucity of local data.

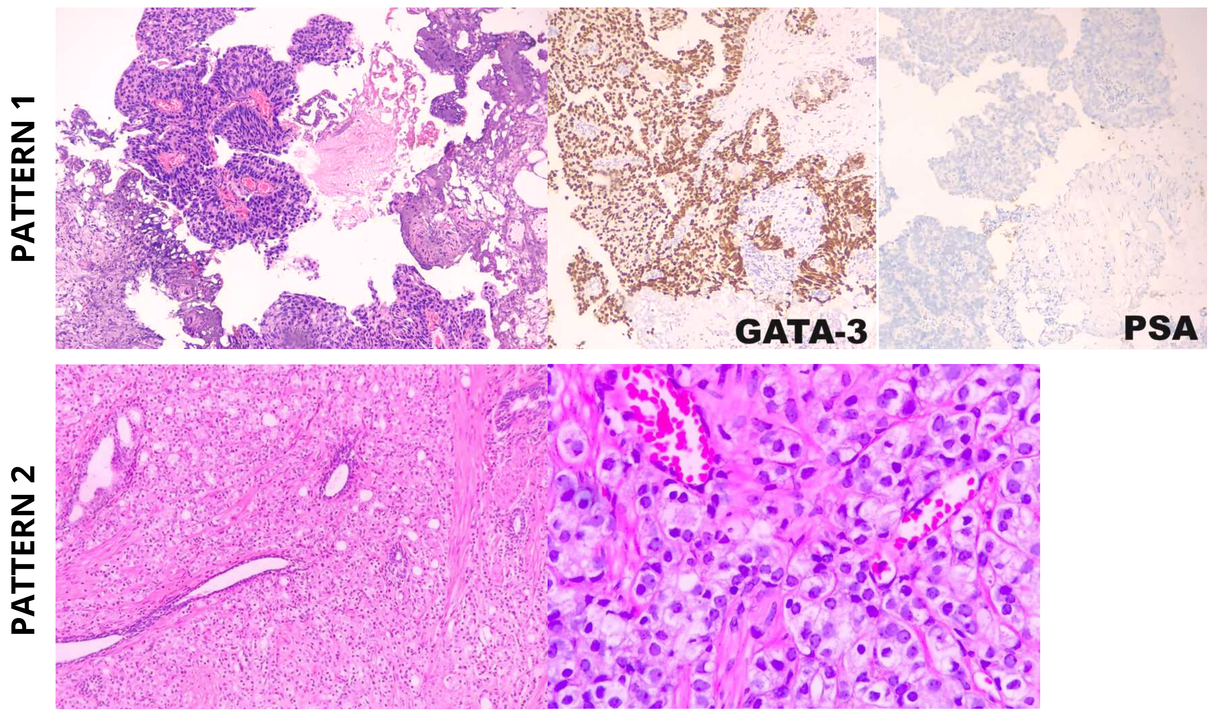
CASE 1

Clinical Data: A 61-year-old male had an elevated PSA (> 40 ng/mL). Ultrasound showed an intraluminal lobulated focus at the urinary bladder that is adherent to the bladder base, and an enlarged prostate with homogeneous echopattern. CT scan showed an additional finding of enlarged iliac nodes. The patient underwent TURP.
Microscopy: Two patterns are appreciated: (1) papillary fronds in an inverted growth pattern, lined by cells with enlarged, hyperchromatic nuclei; (2) cribriform glands lined by cells with vesicular nuclei and prominent nucleoli. The tumor cells of the former stained positive for HMWCK, CK7, GATA-3, and p63, while the those of the latter stained positive for PSA and NKX3.1
Diagnosis: Low-grade papillary urothelial carcinoma, and prostatic acinar adenocarcinoma (4+4), WHO-ISUP grade group 4.



CASE 2

Clinical data: A 71-year-old male with obstructive uropathy and elevated PSA (> 100 ng/mL) He presented a month after with recurrence of difficulty in voiding. Imaging showed a bladder mass and diffuse cystitis. He underwent repeat TURP and TURBT.
Microscopy: Two patterns are appreciated: (1) papillary fronds that demonstrate marked architectural disarray, and are lined by cells that exhibit marked nuclear atypia; (2) nests and sheets of cells with hyperchromatic to vesicular nuclei with prominent nucleoli. IHC stains were done on the former group of tumor cells which showed diffuse positivity for GATA-3, focal positivity for CK 5/6 but negative for PSA and NKX3.1
Diagnosis: High-grade papillary urothelial carcinoma, and prostatic acinar adenocarcinoma (5+4), WHO-ISUP grade group 5.



DISCUSSION

The difference in architecture and cytomorphology allows distinction between non-invasive urothelial carcinomas and prostatic acinar adenocarcinomas in cases of their co-existence, such is what the two cases demonstrated. The morphologies of the two tumors in both cases are distinct; however, one must exercise caution in signing out double primary tumors by H&E alone. In cases of morphologic overlap between the two tumors such as morphologic variants of infiltrating urothelial carcinomas, poorly-differentiated (Gleason score of at least 8) acinar adenocarcinomas and pseudopapillary features of prostatic acinar adenocarcinomas mimicking urothelial carcinoma, IHC becomes crucial in documenting the presence of two tumors.

By convention, urothelial carcinomas express cytokeratins (HMWCK, CK5/6, CK7, CK20), and the opposite is true for prostatic carcinomas. However, aberrant expression of these markers may complicate diagnosis. There are some cases of prostatic carcinomas that stain positive for CK5/6, CK7, and CK20. Some poorly differentiated prostatic adenocarcinomas have overlapping CK7/CK20 profiles with urothelial carcinomas. To circumvent this problem, it is prudent to employ additional IHCs to distinguish between the two tumors. Suggested IHCs for urothelial carcinoma include the following: p63, thrombomodulin, and GATA-3. The most widely used among these urothelial markers is GATA-3, as it is widely available. Newer immunostains, such as uroplakin II, is still not widely available in local institutions. GATA-3 remains superior in terms of sensitivity (84.8%) when compared against other urothelial markers such as p63 (73.9%), CK34βE12 (75.4%) and thrombomodulin (45.7%) despite having comparable specificities (96.4-100%).

Suggested IHCs for prostatic carcinomas include PSA, PSAP, NKX3.1, P501S, PSMA, and AR. The most established among the said immunostains is PSA, because of its high sensitivity (100%) and specificity (90.6%). However, problems encountered with PSA include decreased staining among poorly differentiated prostatic adenocarcinomas and nonspecific background staining. NKX3.1 has become more popular due to its high sensitivity (88.3%) and specificity (100%) as a prostatic marker. It is now being recommended as a prostatic marker of choice in some institutions.

Cytokeratin stains alone must not be interpreted independently since it is not sufficient in establishing the origin of both tumors. Though there is a caveat of aberrant expression, cytokeratin can still be used as part of a panel to document the tumor immunoprofile. To give more credence to the diagnosis of a prostatic tumor, especially those with higher Gleason scores, a combination of two prostatic markers is needed. Hence, a panel approach is beneficial in documenting a double primary prostate and urothelial carcinoma with a cytokeratin, at least two prostatic markers (NKX3.1 and PSA) and a urothelial marker (GATA-3).

CONCLUSION

Correlation of histomorphologic and immunohistochemistry studies is crucial to the diagnosis of suspected double primary urothelial and prostatic carcinomas because management of the two tumors is completely different. Aberrant expression must be kept in mind when requesting for IHC stains, particularly in cytokeratin and PSA. An IHC panel with a cytokeratin (CK5/6, CK7, CK20) may still be performed with at least two prostatic markers (PSA, NKX3.1), and a urothelial marker (GATA-3) to demonstrate the presence of two primary tumors.

**References available upon request*

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