

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

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### ABSTRACT

Synchronous primary tumors of the urothelium and prostate are a diagnostic challenge among pathologists. Differentiating carcinomas of urothelial and prostatic origin requires careful assessment of histomorphology coupled with ancillary studies such as immunohistochemistry stains (IHC) to support the diagnosis. We report two cases of adult patients who underwent transurethral resection of the prostate (TURP), with two distinct morphologies noted on routine H&E sections. After a panel of immunohistochemical stains (HMWCK, CK5/6, CK7, CK20, GATA-3, p63, NKX3.1, and PSA), both cases were signed out as papillary urothelial carcinoma and prostatic acinar adenocarcinoma. Correlation of histomorphology with an IHC panel consisting of cytokeratins (CK5/6, CK7, CK20), a urothelial marker (GATA-3), and at least two prostatic markers (PSA, NKX3.1) is recommended in such cases.

*Key words: Immunohistochemistry, PSA, prostatic adenocarcinoma, urothelial carcinoma*

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### INTRODUCTION

Prostate cancer is the fifth most common malignancy and the seventh leading cause of death in the Philippines. Bladder cancer, meanwhile, has an incidence of 3.1 per 100,000 males in 2018.<sup>1,2</sup> The epidemiology of a double primary lower genital tract malignancy is not uncommon. A retrospective analysis of a single center study of radical cystectomy specimens showed a 53.1% incidence of prostate cancer. At least half had a Gleason score of 7 and above with at least pT3a on tumor staging.<sup>3</sup> In another study, a review of radical cysto-prostatectomy cases showed 45.7% incidence of prostatic adenocarcinoma in specimens with urothelial carcinoma, all of which with pN0.<sup>4</sup> However, the reporting of double primary malignancies with at least an aggressive prostatic carcinoma is infrequent with only a number of published case reports abroad.<sup>5,6</sup> After an exhaustive search on local literature (HERDIN plus and Philippine e-journals), no local published cases are available. Diagnosis of double primary prostatic and urothelial carcinomas pose a diagnostic challenge to pathologists because of likely morphologic overlap between the two tumors. The management differs for urothelial carcinomas and prostatic adenocarcinoma with different risk-stratified treatment algorithms.<sup>7,8</sup> In such cases, additional tests such as IHC may be needed to document the presence of two primary tumors. 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

A 61-year-old male who came in for regular screening at another institution, 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

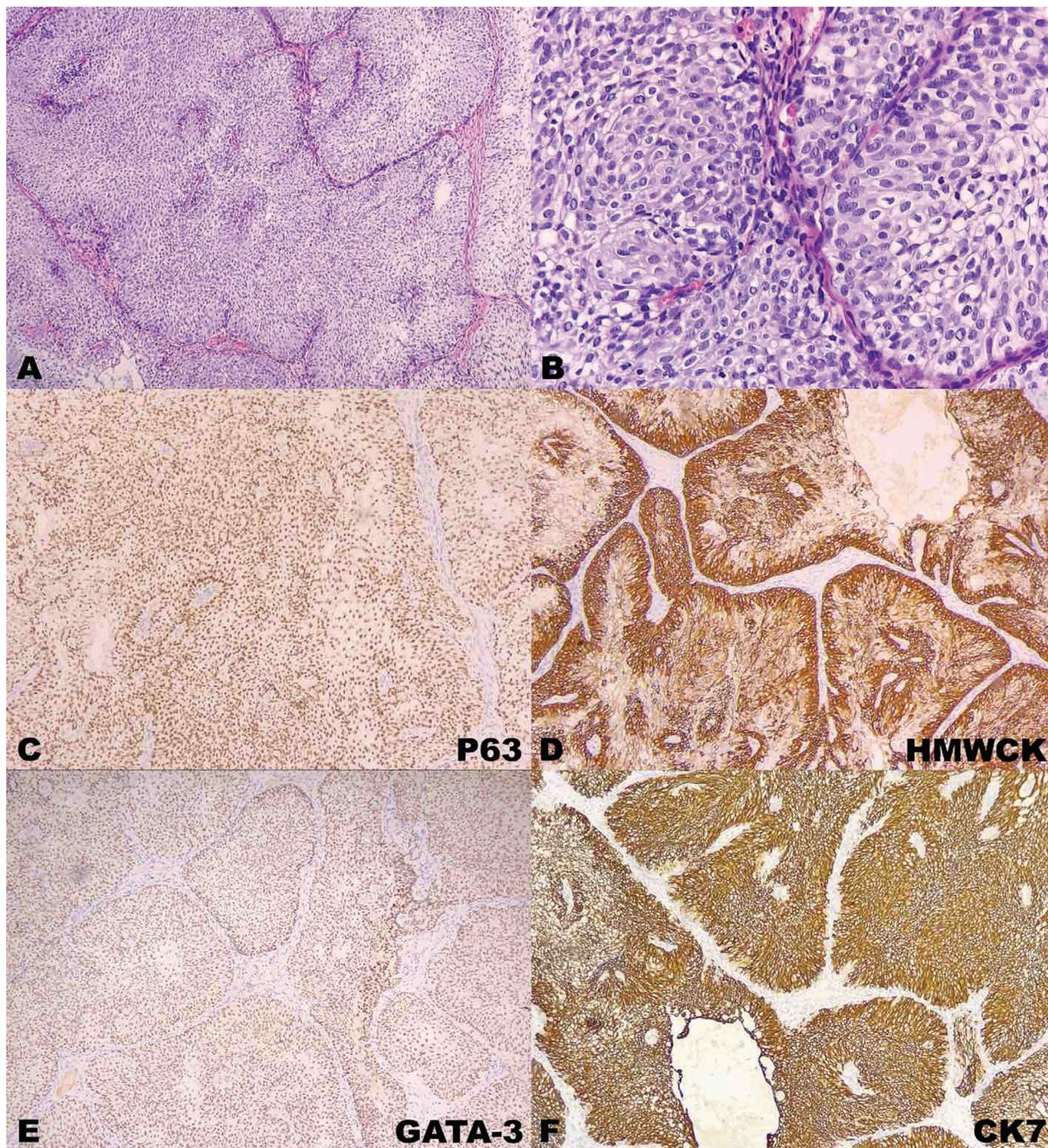


echopattern. Impression at this time was between a primary bladder mass and an intravesical extension of a primary prostatic mass. CT scan showed an additional finding of enlarged iliac nodes. The patient underwent TURP. Microscopic examination showed two distinct patterns: one consists of papillary fronds in an inverted growth pattern, lined by cells with enlarged, hyperchromatic nuclei; and the other consists of 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 (Figures 1 and 2).

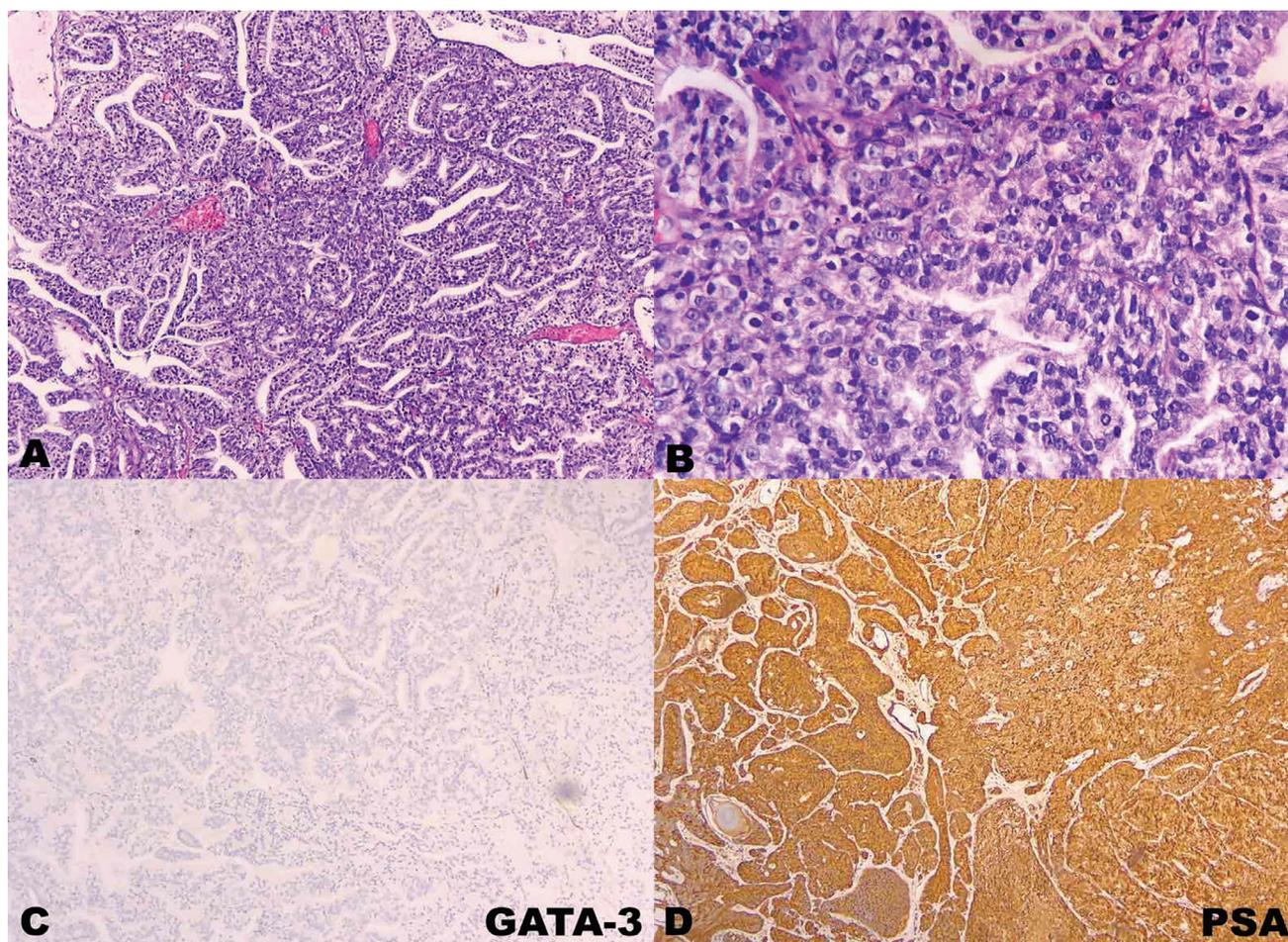
This case was signed out as low-grade papillary urothelial carcinoma, and prostatic acinar adenocarcinoma (4+4), WHO-ISUP grade group 4.

**CASE 2**

A 71-year-old male with obstructive uropathy and elevated PSA (> 100 ng/mL) was diagnosed with low-grade papillary urothelial carcinoma after TURP and transurethral resection of bladder tumor (TURBT) at another institution. He presented a month after with recurrence of difficulty in voiding. Imaging showed a



**Figure 1. Case 1 – (A)** One group of tumor cells show an inverted papillary architecture (H&E, 100X); **(B)** it is composed of cells with enlarged and hyperchromatic nuclei (H&E, 400X); **(C to F)** the IHCs show positivity for p63, HMWCK, GATA-3 and CK7 (100X).



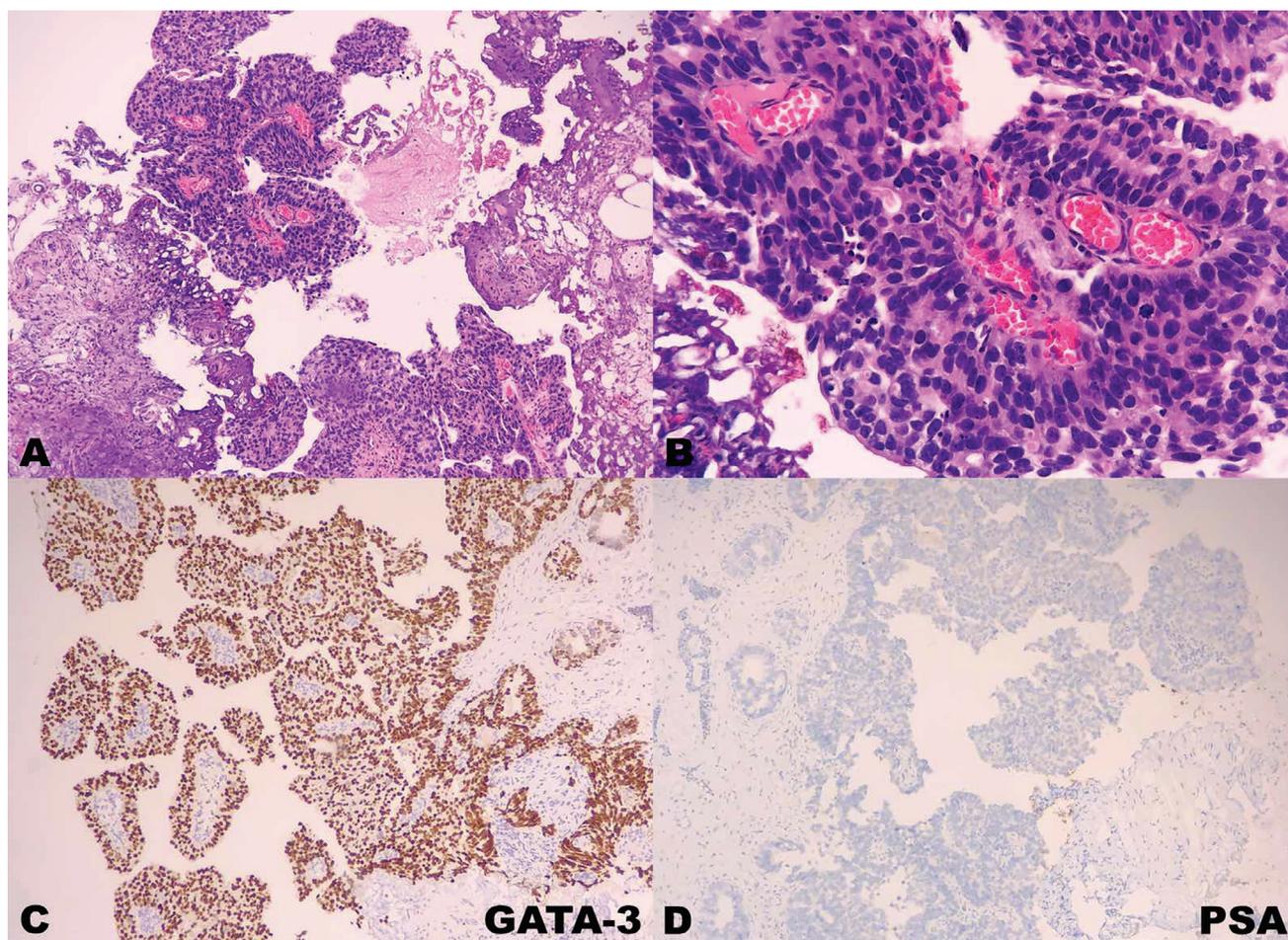
**Figure 2. Case 1** – (A) The second group of cells shows a cribriform architecture (H&E, 100X); (B) the tumor cells have vesicular nuclei and prominent nucleoli (H&E, 400X). (C) IHCs stained negative for GATA-3 (100X); (D) but they were positive for PSA (100X) and NKX3.1 (not shown).

bladder mass and diffuse cystitis. He underwent repeat TURP and TURBT. Microscopic examination showed two distinct patterns: one group consists of papillary fronds that demonstrate marked architectural disarray, and are lined by cells that exhibit marked nuclear atypia; and the other group consists of 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 (Figures 3 and 4). This case was signed out as high-grade papillary urothelial carcinoma, and prostatic acinar adenocarcinoma (5+4), WHO-ISUP grade group 5.

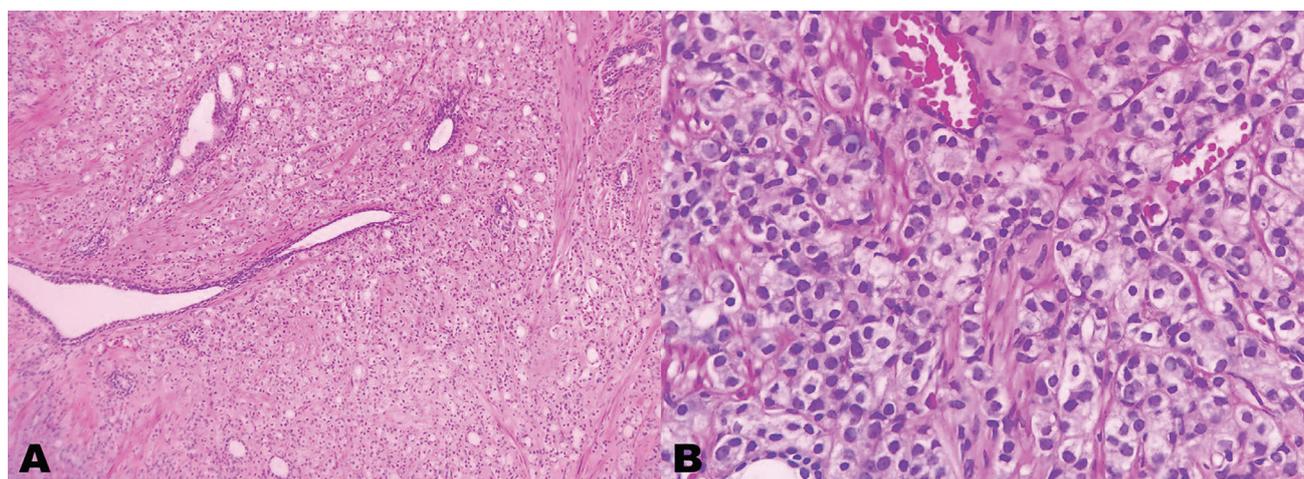
## DISCUSSION

The WHO classification of urinary tract tumors distinguishes infiltrating and non-invasive urothelial carcinomas. Infiltrating urothelial carcinomas are usually high-grade, and exhibit varied morphology. Non-invasive urothelial carcinomas are graded based on degree of architectural disarray and nuclear atypia, and frequency of mitosis. Diagnosis of prostatic acinar adenocarcinoma depends on a constellation of features, which include glandular luminal contents, cytoplasmic appearance, and nuclear features with prominent nucleoli are the most widely recognized characteristics.<sup>9</sup>

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. Non-invasive papillary urothelial carcinomas are evaluated based on order of architectural and cytological features on both low (100X) and medium-power magnification (200X). Heterogeneity of the histological features are typical of papillary urothelial carcinomas. They usually form papillary fronds with fibrovascular cores and exhibit moderate to marked pleomorphism with glassy, eosinophilic cytoplasm and enlarged nuclei.<sup>9,10</sup> On the other hand, prostatic acinar adenocarcinomas do not have a single pathognomonic feature. Major and minor criteria have been developed to aid the pathologist in assessment of prostatic specimens.<sup>11</sup> Prostatic acinar adenocarcinomas usually exhibit infiltrative small or cribriform glands and the absence of basal cell layer. Though not present in all acinar adenocarcinomas, other helpful features include intraluminal wispy blue mucin, pink amorphous secretions, intraluminal crystalloids and adjacent high-grade prostatic intraepithelial neoplasia. Cytological features include absent to minimal pleomorphism with pale to foamy cytoplasm and enlarged nuclei with prominent nucleoli. Mitotic figures may or may not be present.<sup>9-11</sup>



**Figure 3. Case 2 – (A)** One group of tumor cells exhibits papillary fronds with markedly distorted architecture (H&E, 100X); **(B)** the tumor cells have pleomorphic and hyperchromatic nuclei (H&E, 400X). **(C)** IHCs show positive cytoplasmic staining for GATA-3 (100X); **(D)** but negative for PSA (100X) and NKX3.1 (*not shown*).



**Figure 4. Case 2 – (A)** Another group of tumor cells exhibits sheets, some forming acini (H&E, 100X); **(B)** they have rounded, hyperchromatic nuclei and prominent nucleoli (H&E, 400X).

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  $\geq 8$ ) acinar adenocarcinomas and pseudopapillary features of

prostatic acinar adenocarcinomas mimicking urothelial carcinoma, IHC becomes crucial in documenting the presence of two tumors.

Urothelial and prostatic carcinomas have different classic immunophenotypes. By convention, urothelial carcinomas express cytokeratins (HMWCK, CK5/6,

CK7, CK20), and the opposite is true for prostatic carcinomas<sup>9,14</sup>. 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.<sup>15</sup>

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.<sup>9</sup> The most widely used among these urothelial markers is GATA-3, as it is widely available. Newer immunostains, such as uroplakin II, have shown high specificity (100%) but suffers from low sensitivity (65.6%), and it is still not widely available in local institutions.<sup>16</sup> 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%).<sup>17</sup> 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%).<sup>17</sup> 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.<sup>15,17</sup>

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. In our monthly evaluation of IHC diagnostic utility, the PSA antibody has been a reliable marker for prostatic tumors while GATA-3 antibody has been widely used in bladder, prostate, pleural and peritoneal fluid aspirates. 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.

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## ETHICAL CONSIDERATION

All attempts were made to obtain the consent of the patients; however, they were both lost to follow-up. This case report was written in accordance to the principles based on the Declaration of Helsinki.

## STATEMENT OF AUTHORSHIP

All authors certified fulfillment of ICMJE authorship criteria.

## AUTHOR DISCLOSURE

The authors declared no conflict of interest.

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