A novel treatment approach prolonging survival in an uncommon metastatic primary bladder adenocarcinoma

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Primary bladder adenocarcinoma (PBA) is an epithelial malignancy with pure glandular differentiation, without evidence of typical urothelial (transitional cell) carcinoma. PBA is rare, accounting for 0.5%-2% of all malignant bladder neoplasms, and it is seen more frequently in men than in women and is commonly diagnosed in the sixth decade of life.[1-3] Clinical presentation includes hematuria and symptoms of bladder irritation.[2] PBA is common in schistosomiasis-endemic regions and among patients with congenital bladder exstrophy (ectopia vesicae); it mostly arises in the trigone and posterior bladder wall.[4] In contrast, urachal adenocarcinomas arise within urachal remnants (residual tissues from the embryonic allantoic stalk connecting the umbilicus and bladder), close to the dome and anterior wall of the bladder. Morphologically, PBA is classified into enteric and nonenteric types, which includes mucinous, signet-ring cell variant, clear-cell type, hepatoid, and mixed forms.[2] Currently, there is no standard of care in the management of PBA. We present the case of a patient with metastatic PBA with intestinal differentiation and wild-type KRAS, who was treated with colorectal cancer regimens.

Case presentation and summary

A 54-year-old man with no significant medical history was admitted with urinary retention. He had experienced urinary urgency and hematuria for 6 weeks, which progressively worsened to urinary retention. A digital rectal exam revealed an enlarged prostate. A Foley catheter was placed, and he failed the voiding trial. The results of a computed-tomography (CT) scan of the abdomen and pelvis revealed right hydroureteronephrosis, bladder wall thickening, and an enlarged prostate. A cystoscopy revealed prostatomegaly with partial obstruction of prostatic urethra. Ureteral orifices were seen, the bladder mucosa appeared trabeculated, and there was no obvious bladder tumor. The patient underwent transurethral resection of prostate (TURP), with improvement in his symptoms.

The pathology of the TURP showed invasive moderate to poorly differentiated adenocarcinoma (Figure 1). Immunostains were positive for cytokeratin (CK)20, CDX2 and negative for CK7, p504s (alpha-methylacyl CoA racemase, or AMACR), uroplakin, thrombomodulin, prostate-specific antigen (PSA), and prostatic-specific acid phosphatase (PSAP) favoring colorectal origin (Figure 2).

Levels of the tumor markers, PSA, and carcinoembryonic antigen, were within normal limits. Pelvic magnetic-resonance imaging (MRI) showed asymmetric thickening of the right posterior wall of urinary bladder with increased enhancement along the mucosa. This was contiguous with enlarged right seminal vesicle (with abnormal low T2 signal), suggesting a suspicious mass lesion extending toward the distal right ureterovesical junction causing obstruction. No colorectal masses or pelvic/abdominal lymphadenopathy were identified. The results of a sigmoidoscopy were also unremarkable. The results of a colonoscopy (for symptoms of rectal discomfort

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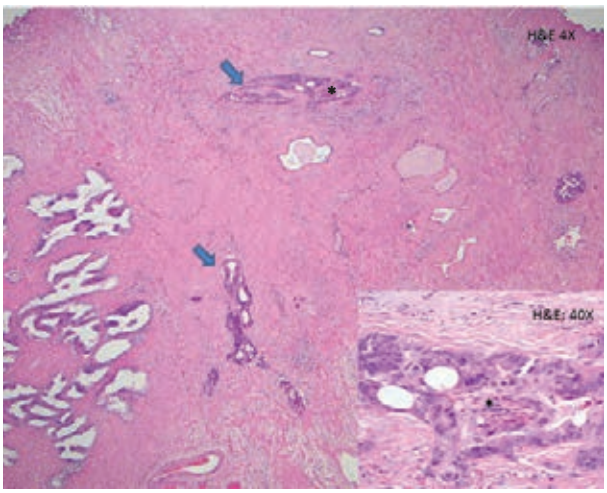

FIGURE 1 Prostate gland showing normal and atrophic glands with admixed infiltrating adenocarcinoma (arrows) with perineural invasion (asterisk).

and constipation) he had a few months before the presentation described here were negative for suspicious lesions. These features were suggestive of a primary bladder adenocarcinoma with intestinal differentiation extending into the prostate and toward the right ureterovesical junction. The results of a repeat cystoscopy demonstrated effaced right trigonal architecture and multiple attempts to catheterize the right ureter were unsuccessful. The patient then underwent right percutaneous nephrostomy and antegrade ureteral stenting.

A positron-emission tomography scan, done to complete staging, showed avid pleural-based pulmonary nodules suspicious for metastasis. A pleural biopsy guided by video-assisted thoracoscopic surgery confirmed metastatic adenocarcinoma (positive for CK20 and CDX2, and negative for CK7 and TTF-1).

Because of the presence of intestinal differentiation, we decided to initiate the colorectal chemotherapy regimen FOLFOX (5-fluorouracil, folinic acid, oxaliplatin) plus bevacizumab (Bev). After 12 cycles of FOLFOX-Bev, computed-tomography imaging showed a decrease in the bladder wall thickening (Figure 3) and stable disease in the lungs. Subsequent imaging 3 months later showed enlargement of the pulmonary metastases, so we changed the oxaliplatin to irinotecan (FOLFIRI-Bev). The patient received about 28 cycles of FOLFIRI-Bev with intermittent chemotherapy breaks and had radiographic progression in the bladder. The Bev was then replaced with cetuximab, because the patient's original tumor biopsy was tested wild type (for KRAS [exon 2/exon 3]). His metastases are currently stable on FOLFIRI-cetuximab and his urinary symptoms have improved. Overall, he received 3 lines of colorectal cancer regimens, with stable disease for 2.2 years.

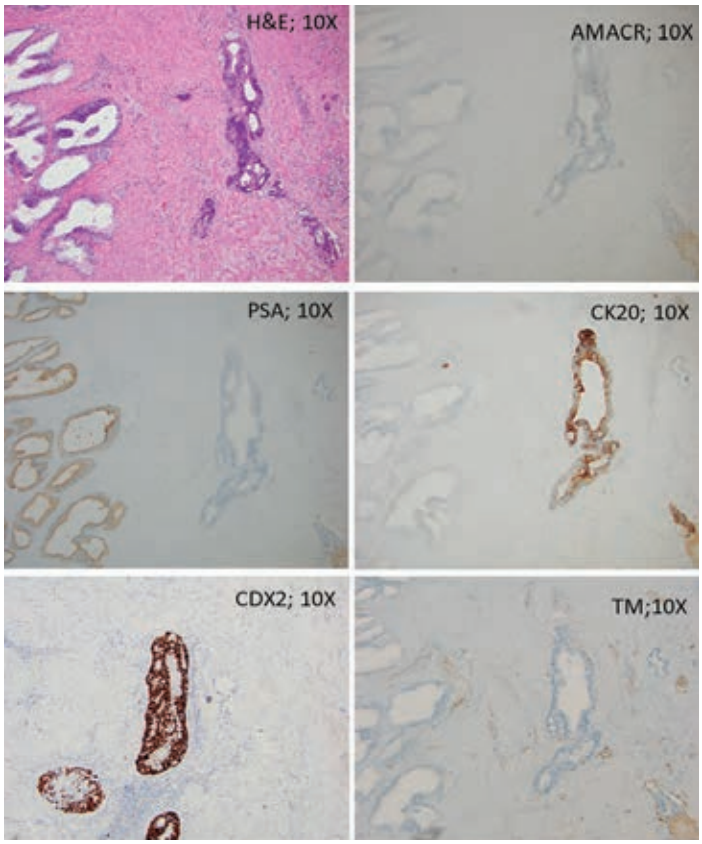

FIGURE 2 The infiltrating neoplastic glands were positive for CK20 and CDX2 and negative for prostate-specific antigen, thrombomodulin, and AMACR, which was suggestive of lower gastrointestinal or bladder origin.

Discussion

It is challenging for clinicians to distinguish PBA from the more common secondary adenocarcinoma of bladder (metastasizing from the organs adjacent to bladder) and to tailor treatment accordingly. Colorectal adenocarcinoma is the most common secondary malignancy of bladder and is virtually indistinguishable from enteric type PBA on histomorphology. The common embryologic origin of the bladder and rectum from the cloaca may contribute to this. Wang and colleagues[3] have hypothesized that pluripotent cloacal cells undergo similar genetic changes, giving rise to both bladder and colorectal adenocarcinomas.

Immunohistochemistry, combined with extensive clinical and radiologic work-up, is required for diagnostic accuracy. CK7 negativity and CK20 positivity usually denotes colorectal origin,[5] but similar immunoprofile can be seen in 29% of PBA.[3] CDX-2 (homeobox gene implicated in differentiation of intestinal epithelial cells) positivity indicates colorectal origin, but it can also be positive in bladder adenocarcinomas.[6] Thrombomodulin, an endothelial thrombin receptor, is a sensitive urothelial marker, but is seen in only 59% of bladder adenocarcinomas.[3] So these

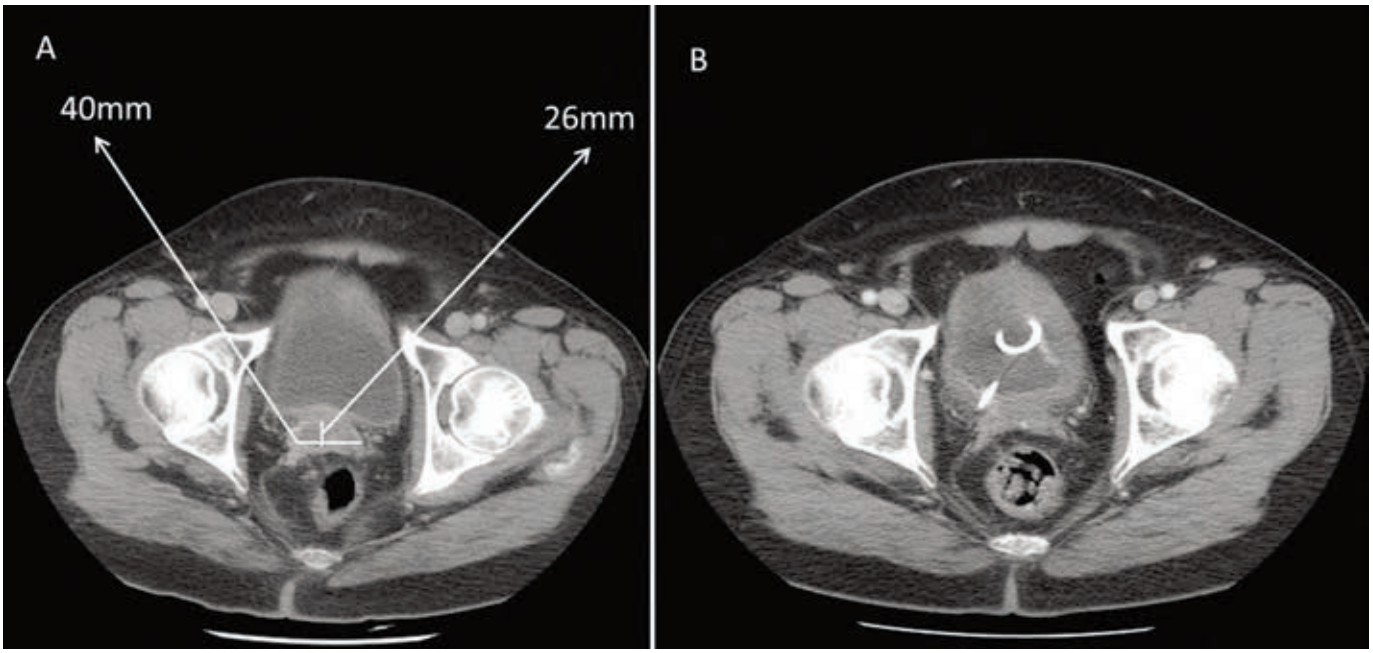

FIGURE 3 Computed-tomography scan A, before initiation of treatment showing a lobulated thickening (26 x 40 mm) along the posterior wall of urinary bladder and B, after treatment with FOLFOX and bevacizumab showing a decrease in thickening along the posterior wall of urinary bladder. Right ureteral stent can also be seen.

immunohistochemical markers are meaningful only in the light of appropriate clinical and radiologic findings. In our patient, immunoprofile was positive for CK20 and CDX-2 and negative for CK7 and thrombomodulin, suggesting adenocarcinoma with intestinal differentiation. However, our patient's pelvic MRI demonstrated a posterior bladder wall lesion and a gastrointestinal endoscopy did not reveal any suspicious colorectal lesions, indicating PBA of enteric type. In addition, his PSA and PSAP (specific prostate adenocarcinoma markers) were negative, suggesting against prostatic origin.

PBAs tend to be very aggressive; they present with metastasis in 40% cases[1,2] and are resistant to chemoradiation, resulting in poorer prognosis compared with pure urothelial bladder cancers.[7] A study of 185 patients with nonurachal primary vesical adenocarcinomas showed an overall 5-year disease-free survival of 55%.[1] Seifker and colleagues presented a median survival of 24 months for metastatic urachal carcinomas in a small retrospective analysis, suggesting better survival rates than nonurachal vesical adenocarcinomas.[8] Wright and colleagues examined the Surveillance, Epidemiology and End Results (SEER) database and showed that urachal adenocarcinomas had better overall and disease-specific mortality than did nonurachal PBA.[9]

The systemic chemotherapy regimens used for pure urothelial bladder cancers are generally not effective for pure nonurothelial bladder carcinomas such as PBA, and there are no standard strategies to treat them. Some findings have shown that 5-fluorouracil-based chemotherapy induces some sustained responses for advanced PBA patients,[10,11] whereas cisplatin-based chemotherapy did not induce any response.[11] Kasahara and colleagues from Japan reported a case of metastatic PBA, showing complete disappearance of metastatic disease (in liver, lung, and lymph nodes) after 4 courses of PMUE (cisplatin, mitomycin-C, tegafur-uracil, and etoposide) chemotherapy and a 3-year disease-free survival on follow-up.[12] Valerio and colleagues from Switzerland reported a case of metastatic primary mucinous adenocarcinoma of bladder with intestinal metaplasia treated with FOLFOX-Bev, resulting in regression of hepatic metastases and stabilization of pulmonary metastases for 15 months.[13] A similar sustained response for more than 10 months was shown in metastatic PBA using 12 cycles of FOLFOX-Bev.[14] Similar to these cases, our patient with metastatic PBA and intestinal differentiation, responded well to colorectal palliative chemotherapy regimens,[15] with stable disease for more than 2 years. The exon 2 KRAS gene mutations (codon 12/13) in metastatic colorectal cancers have been shown to be insensitive to epidermal growth factor receptor inhibitors such as cetuximab.[16] Our patient was found to have wild-type KRAS prior to initiation of cetuximab.

Conclusion

There is a need for the development of therapies for uncommon cancers such as PBA. The present case underscores the art of individualizing therapy based on his-

tology. It suggests that PBA responds well to colorectal adenocarcinoma treatment regimens, strengthening the hypothesis that both bladder and colorectal adenocarcinomas arise from pluripotent cloacal cells undergoing identical genetic changes and that they have similar clinical behaviors. Nonurothelial histologies are greatly underrepresented in larger trials of metastatic bladder cancer, and our collective experience could serve as a rationale for prospective clinical trials using colon cancer regimens in PBA. With the advent of sophisticated molecular technologies in the era of precision medicine, studies evaluating the genome sequence of these rare malignancies are also needed, to identify potential biomarkers and therapeutic targets.

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