Primary signet cell adenocarcinoma of bladder

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ABSTRACT
Primary signet cell cancer of the urinary bladder is a relatively rare entity. Since there is no mucinous epithelium in the bladder, it is proposed that the tumor arises from metaplastic urothelium. Two thirds of the tumors are mucin secreting, in most of which the site of the deposition is either extracellular or intracellular displacing the nucleus to a peripheral crescent, giving the cells a signet ring appearance. The tumors are most often infiltrative and diffusely involving the majority of the bladder akin to its name sake in stomach. It is essential to distinguish this carcinoma from gastrointestinal metastases as different therapeutic strategies are often necessary.

KEY WORDS: Bladder, metastasis, signet cell carcinoma

INTRODUCTION
Signet cell adenocarcinoma is an uncommon histological variant of carcinoma of urinary bladder, accounting for 0.5%–2% of primary malignant tumors of the bladder.¹ The tumor either arises from the bladder wall or urachus remnants or is a metastatic tumor originating in the stomach, colon, or breast.² The rarest of these is a primary variant arising from the bladder.

This tumor initially presents as a high-grade, high-stage lesion and diffusely invades the bladder wall without forming intraluminal growth. The patients have no specific symptoms, which leads to delayed diagnosis and poor prognosis. As histopathological and immunohistochemical (IHC) findings do not aid in the definite diagnosis of primary signet-ring cell adenocarcinoma of the bladder, the extensive workup is essential to prove the primary site. The patient survival is usually poor, with a reported mean 5-year survival rate of 27%–30%.³ Less than 100 cases were described after Saphir reported the first two cases in 1955.⁴ Here, we present the case of primary signet-ring cell adenocarcinoma of urinary bladder in a 36-year-old male.

CASE REPORT
A 36-year-old male presented with bilateral flank pain radiating to thighs, burning micturition, and retention of urine for 1 month. There was no history of hematuria or mass per abdomen. Abdominal examination revealed no organomegaly. Ultrasonography (USG) abdomen revealed a 3-mm calculus in both kidneys with a bladder mass and prostatomegaly. On computed tomography (CT) urogram, a 7.2 cm × 5.3 cm × 9.5 cm irregular polypoidal mass was seen in the urinary bladder, involving vesicoureteral junctions, seminal vesicles, and prostate [Figure 1a]. Chest X-ray, upper gastrointestinal (GI) endoscopy, and colonoscopy were normal. Positron emission tomography-CT scan revealed metabolically active lesion in the bladder extending into prostate with extensive nodal metastasis and a solitary skeletal metastasis involving the left ischiium [Figure 1b]. Clinically, he was staged as T⁴N₂M₁ (IV). Tumor markers such as alpha-fetoprotein, CA125, CA19-9, and prostate-specific antigen (PSA) were within the normal range. Carcinoembryonic antigen (CEA) was at 22.78 ng/ml against a normal range of <5 ng/ml. A transurethral resection biopsy of the bladder tumor was done. A repeat colonoscopy and CT scan did not show any tumor in the GI tract.

Gross and microscopy findings
A multiple transurethral resection of bladder tumor chips measuring 3 ml in volume was received in the laboratory. Microscopy revealed a tumor composed of signet-ring cells with peripherally pushed hyperchromatic nucleus, intracytoplasmic mucin, and lakes of extracellular mucin [Figure 2a and b]. Tumor cells were arranged in lobules, separated by fibrovascular septae. About

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1–2 mitoses/hpf and areas of tumor necrosis were seen. Tumor was seen infiltrating the underlying stroma and muscle. Transitional lining of the bladder appeared normal; however, the underlying tumor could be seen merging with the urothelium. Periodic acid–Schiff stain showed intense pink staining of the cytoplasmic vacuoles of the tumor cells. A differential diagnosis of metastatic signet cell carcinoma of colon/stomach, urachal carcinoma, and primary signet cell carcinoma of bladder was entertained. IHC of biopsy revealed tumor cells to be strongly and diffusely positive for CK20 and CDX2. CK7 was focally positive and PSA was negative.

**DISCUSSION**

Primary signet-ring cell carcinoma (PSRCC) of the urinary bladder is a relatively rare subtype of adenocarcinoma and comprises only 0.24%–2% of all primary epithelial urinary bladder tumors.\(^5\) The histopathogenesis of primary mucin-producing adenocarcinomas, including signet-ring cell carcinomas, remains unclear because the normal bladder contains neither columnar nor mucus-secreting glandular epithelium. Many investigators proposed that the metaplastic potential of the urothelium has two distinct patterns. Progressive invagination of hyperplastic epithelial buds into the lamina propria (Von Brunn’s nest) leads to the formation of cystitis cystica. Subsequent metaplasia of the urothelial lining within these cysts to columnar mucin-producing cells results in the production of cystitis glandularis, which is a premalignant lesion. Alternatively, cuboidal or columnar metaplasia of the surface epithelium can occur without downward invagination, with chronic vesical irritation and infection being the predisposing factors of these changes. Most of these tumors are mucin secreting, but the passage of mucus during micturition is uncommon. The mucin deposition is either seen extracellular or intracellular. Intracellular mucin deposition leads to a typical signet ring appearance due to pushing out of nuclei.\(^6\) Primary signet cell carcinoma term is generally used when at least 25% area of the entire tumor shows signet cell pattern.\(^7\) In general, this neoplasm occurs in middle age and is usually diagnosed at an advanced stage, usually demonstrating a subsequently poor prognosis. The common presenting symptoms are irritative voiding symptoms and hematuria. Urinary retention and flank pain due to ureteral obstruction are less common. Rare symptoms such as mucusuria, acute renal failure, and acute duodenal obstruction mimicking retroperitoneal fibrosis have been reported.\(^8\) Our case presented only with dysuria and flank pain.

Signet-ring cell carcinomas of the bladder are most often infiltrative and diffusely involving the majority of the bladder akin to its name sake in the stomach. The lesion is described in cystoscopy as pedunculated, polypoid, sessile, and ulceroinfiltrative. Cystoscopy may only reveal edematous, bullous, or erythematous mucosa.\(^9\)

Bladder adenocarcinoma may arise in any region of the bladder, but it is usually found in the bladder dome. It may be very difficult to rule out urachal carcinoma as it has the same histological features. Several criteria for classifying a tumor as urachal in origin have been suggested as follows: (1) tumor in the bladder (dome), (2) a sharp demarcation between the tumor and the surface epithelium, and (3) exclusion of primary adenocarcinoma located elsewhere that spreads secondarily to the bladder.\(^3\) The present case showed no sharp demarcations between the tumor and the surface epithelium. There was a pedunculated mass seen on cystoscopy unlike urachal carcinoma which is common within the bladder wall.

It is essential to distinguish this carcinoma from metastases, as different therapeutic strategies are often necessary. PSRCC of the urinary bladder has the same histology as that of the GI tract, breast, lung, gallbladder, and prostate; therefore, further evaluations for other primary sites are mandatory to exclude metastasis.\(^9\) In our case, the GI evaluation included esophagogastroduodenoscopy and colonoscopy, but we found no other tumor lesions. Serum PSA levels, PSA IHC on tissue, and transrectal USG in our case ruled out prostatic primary
adenocarcinoma. Although there is no established serum marker of PSRCC of the urinary bladder, elevated CEA has often been reported. Yamamoto et al. reported that the serum level of CEA is normalized postoperatively and gradually increases as the disease progresses. They have suggested, therefore, that CEA might be used for determining the malignant potential and for monitoring signet-ring cell carcinoma. In our case, serum CEA was mildly elevated. CDX2, a primary IHC marker of intestinal origin tumors, has also been documented in bladder adenocarcinomas; hence, it cannot be used to differentiate the two. In our case, the CK7 showed positivity which is unusual in colonic cancer.

Treatment modalities for signet-ring cell carcinomas include surgery, radiotherapy, and chemotherapy. Surgical options range from transurethral resection to radical cystectomy with urinary diversion. Several effective treatments including intra-arterial chemotherapy with cisplatin and methotrexate and radiation therapy or only radiotherapy after cystectomy are reported in the literature. To date, some patients fail to respond to standard platinum-based regimens but derive a significant clinical benefit from colon cancer-type regimens such as 5-fluorouracil-based regimens of capecitabine. Unfortunately, no standard chemotherapy exists for PSRCCs of the bladder because of their rarity.

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Conflicts of interest
There are no conflicts of interest.

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