Primary Signet Ring Cell Mucinous Adenocarcinoma of the Urinary Bladder: A Rare Case Report

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Abstract: Primary ‘signet ring mucinous adenocarcinoma’ is most commonly located in the stomach. The bladder is an uncommon presentation site for the primary location of this tumor. Mucinous signet-ring adenocarcinoma with urinary bladder as the primary origin is uncommon, accounting for fewer than two percent of all upper urinary tract carcinomas. The presence of signet ring cells, which is caused by compression and displaced nucleus of the cell into a crescent placed in the periphery along the cell wall, is a distinguishing feature of signet ring cell carcinoma. These cells are loaded with cytoplasmic mucus-containing vacuoles. Lower than one-third of primary bladder signet ring cell carcinoma cases show this gross morphology showing linitis plastica pattern with subepithelial infiltration without producing an exophytic mass in a pure signet ring cell carcinoma. Because this tumor shares histological features with the adenocarcinomas originating in several other sites, such as the prostate, digestive tract, and reproductive system, immunohistochemistry tests are required to confirm the bladder as the primary origin. Owing to the paucity of the neoplasm and the difficulty in locating the underlying tumor, site identification is frequently prolonged, leaving palliative care as the only choice for roughly half of the patients. This study depicts a rare case report of primary vesicular signet ring cell mucinous adenocarcinoma that considerably invades the pelvis and retroperitoneum’s prostate and lymph nodes. This case emphasizes the significant characteristics of bladder mucinous adenocarcinoma, such as the sequence of tumor spread, the propensity for preliminary diagnostic errors, the microscopic pattern, and the significance of immunohistochemistry for defining its primary root from the bladder and selecting the most suitable intervention from the start.

Keywords: Signet-ring cells, bladder, adenocarcinoma bladder, immunohistochemistry, mucinous adenocarcinoma.
1. INTRODUCTION

A rare kind of mucus-producing adenocarcinoma, primary signet-ring cell carcinoma of the urinary bladder accounts for less than two percent of all the primary bladder neoplasms. This neoplasm diffusely invades the bladder wall without the development of intraluminal growth. This neoplasm usually has higher grading and higher staging at the time of diagnosis. Lack of distinct symptoms among the patients causes delayed diagnosis and a bad prognosis. Signet-ring cell carcinoma with a primary origin in the bladder is a very uncommon tumor. Following the initial two cases reported by Saphir, less than a hundred cases were described. Only 0.24% to 2% of all primary epithelial urinary bladder tumors are primary signet-ring cell carcinomas, a relatively uncommon form of adenocarcinoma. It is frequently found to have resistance to chemotherapy and radiotherapy and has poor disease-free survival. The presence of signet ring cells, which is caused because of compression and displaced nucleus of the cell into a crescent placed in the periphery along the cell wall, is a distinguishing feature of signet ring cell carcinoma. These cells are loaded with cytoplasmic mucus-containing vacuoles. Lower than one-third of primary bladder signet ring cell carcinoma cases show this gross morphology showing limitis plastica pattern with subepithelial infiltration without producing an exophytic mass in a pure signet ring cell carcinoma. Signet ring cell carcinoma frequently joins forces with another cancer subtype to create an exophytic intraluminal tumor. Although most of these tumors secrete mucin, it is unusual for mucus to pass during micturition. Most mucin deposition sites were extracellular; two-thirds of the tumors secreted mucin (interstitial). Infrequently, abundant intracellular mucin pushes the nucleus to a peripheral crescent, giving the cells a signet-ring appearance. Less frequently, mucin is produced within the lumen of the acini. This tumor typically develops during 30-50 yrs is usually diagnosed at an advanced stage with a poor outcome. Compared to other bladder cancers, the typical clinical appearance is not much different. Although bladder adenocarcinoma can develop anywhere in it, it is typically discovered in the dome of the bladder. Given that it exhibits the same histopathology as immunohistochemistry as that of urachal carcinoma, it might be challenging to rule it out. Additionally, urachal-derived adenocarcinomas contain signet-ring cells. Several factors can determine a tumor's urachal origin: 1) a bladder tumor (dome); 2) a distinct boundary separating the neoplasm from the epithelial surface; 3) the omission of a primary adenocarcinoma with other sites as the primary origin with metastasis to the bladder. The tumor and the surface epithelium did not separate in the current situation. As a result, we could rule out a urachal tumor as the cause. Mucinous signet-ring adenocarcinoma with urinary bladder as the primary origin is uncommon, accounting for fewer than two percent of all upper urinary tract carcinomas. Histological variations like 'mucinous' and 'signet-ring cells' are far more uncommon. The invasive behavior and poor response towards the first radiation or chemotherapy differentiate the primary neoplasm of the bladder. Because this tumor shares histological features with the adenocarcinomas originating in several other sites, such as the prostate, digestive tract, and reproductive system, immunohistochemistry tests are required to confirm the bladder as the primary origin. It is crucial to differentiate this carcinoma from metastases since different therapy techniques are frequently required. Because primary signet-ring cell carcinoma of the urinary bladder shares histopathological characteristics with those of the gastrointestinal system, breast, lung, gallbladder, and prostate, additional studies are required to rule out metastasis from other primary sites. Owing to the paucity of the neoplasm and the difficulty in locating the underlying tumor, site identification is frequently prolonged, leaving palliative care as the only choice for roughly half of the patients. There is no additional proven serum marker of primary signet ring cell carcinoma of the urinary bladder, but some research studies have found higher carcinoembryonic antigen levels.

2. CASE PRESENTATION

- History and clinical examination: A sixty-year-old male presented with signs and symptoms of burning during voiding urine and blood in the urine for four months. In addition, the patient developed a right-sided hydrocele and grade 1 prostatomegaly. The patient also complained of urine incontinence and extreme difficulty during micturition. An enlarged prostate was discovered during a digital rectal examination, but no prostate nodules were found.

- Medical History: No significant medical or surgical history was found.

- Family History: No relevant family history was found.

- Special tests and investigations: Prostate Specific Antigen levels were 0.41 ng/mL. Ultrasonography of the abdominal area and pelvis revealed substantial chronic urine retention with a post-void remnant of about 230 cu.cm and verified prostate, which was enlarged without any worrisome abnormalities. Additionally, enlargement of the bladder and minor hydro-nephrosis came into observation, initially related to benign prostatic hyperplasia. According to the existing situation, the patient underwent transurethral resection of the prostate. A further histological investigation revealed that ninety percent of the tissue removed had prostatic adenocarcinoma with a Gleason score of ten (5+5). There was no sign of regional lymphadenopathy or viscero-megaly on clinical examination.
Fig 1: Magnetic resonance imaging showing urinary bladder wall thickening associated with an exophytic lesion.

T2WGb-enhanced abdomino-pelvic MRI scan indicated hypointense patches in the left-sided apex. The prostatic base showed significant contrast enhancement on both sides. A solitary internal iliac lymph node measured 1.2 cm and had an uneven appearance. A considerably thickened bladder with a mild ballooning of the proximal ureters was also seen bilaterally (Figure 1). One month later, a radical prostatectomy with lymphadenectomy was performed.

Fig 2: Mucinous adenocarcinoma of the bladder with signet ring cells - Low power view (20x magnification)
Fig 3: High power view (40x magnification) showing well-differentiated bladder mucinous adenocarcinoma with signet ring cells and mucin at few places.

- **Diagnosis:** Histopathological investigation gave the final diagnosis as “mucinous adenocarcinoma with signet-ring cells” (Figure 2, 3). Figures 2 and 3 show histopathological features of a well-differentiated bladder mucinous adenocarcinoma with signet ring cells showing discohesive round cells with large intracellular mucin vacuoles displacing nuclei to the periphery with extravasated mucin at few places.

Tumour had already invaded the prostate capsule, and the excised tumor’s margins showed positive infiltration by infiltration. However, as previously said, determining the origin of a tumor is frequently challenging; hence an immunohistochemistry analysis was required.

As depicted in figure 4, the tumor demonstrated a strong immunoreactivity to the immunohistochemical markers CDX2, cytokeratin 7 and cytokeratin 20. Still, it was found to be negative for carcinoembryonic antigen, CA 9-19, NKX3.1, and prostate specific antigen. This immunohistochemistry panel did not imply primary prostatic adenocarcinoma but corresponded more to a primary vesical or colonic adenocarcinoma.

- **Management:** A subsequent abdominopelvic MRI scan revealed an increased volume of the retroperitoneal and aortic-iliac lymph nodes. Furthermore, the magnetic resonance imaging revealed thickened bladder, which was more noticeable near the bottom of the bladder, also linked with an exophytic lesion. The patient underwent a vesical biopsy and histological analysis of the patient, which
immunohistochemistry is performed correctly, due to the immunohistochemistry studies. Furthermore, even when the clinical studies, radiological workups, and autopsy findings are not conclusive, a high diagnostic accuracy can be achieved by incorporating mutations into the diagnostic workup. For example, mutations in the KRAS gene (in particular, the G12V mutation) might cause the diagnosis to be delayed even longer.

Rutten et al. studied primary mucinous adenocarcinoma of the bladder with cytokeratin-7 negative as well as CK20 positive expression. The usual colonic cancer markers, such as carcinoembryonic antigen (CEA), cytokeratin-20 (CK20), MUC-1, MUC-2, and MUC-3, in addition to CK7 and CDX2, are typically positive in colonic adenocarcinoma, is generally positive for "CEA, CDX 2, MUC-1, MUC-2, and MUC-3", in addition to CK7 and CK20. The usual colonic adenocarcinoma immunohistochemically profile, on the other hand, is CK7 negative as well as CK20 positive. It is a case of primary mucinous adenocarcinoma of the bladder with histopathological similarities to colonic adenocarcinoma. The mutations might cause the diagnosis to be delayed even longer. A high diagnostic accuracy can be achieved by incorporating clinical studies, radiological workups, and immunohistochemistry studies. Furthermore, even when the immunohistochemistry is performed correctly, due to the rareness of this tumor and the propensity for initial diagnostic error, approximately forty-five percent of subjects have stage four tumors (including "lymph node positivity, T4b stage, and distant metastases") at the time of diagnosis, necessitating the use of palliative chemotherapy. A radical cystectomy is the treatment of choice for an operable tumor. According to Akamatsu et al., tumor stage and elevated CEA levels are significant prognostic variables. In this instance, the patient's metastatic condition necessitated palliative chemotherapy; therefore, gemcitabine with Taxol was given as first-line therapy; however, no clinical response was observed. Because primary vesical adenocarcinoma has a histopathological resemblance to colon cancer, some scientists in recent times proposed that chemotherapeutic regimens often used for gastrointestinal malignancies may be evaluated as alternate management options. Only four cases in the literature describe the use of combined chemotherapeutic regimens (folinic acid, fluorouracil, and oxaliplatin) in primary metastatic adenocarcinoma of the bladder. Yamamoto et al. conducted a study in which the carcinoembryonic antigen serum level showed normal levels in the operated site, gradually increasing with the disease progression. Their study suggested that CEA serum levels may be useful to determine the aggressiveness and monitor the signet-ring cell carcinoma. According to the research work of Erdogru et al., only total cystectomies may lead to a better outcome in some cases. Multiple efficacious management techniques like intra-arterial chemotherapy with cisplatin and methotrexate combined with radiation therapy or post-cystectomy-only radiotherapy were found in the literature. Continuous research studies are essential to reveal the severity of this neoplasm and set standards for the diagnostic workup and therapeutic strategy of upper urinary tract primary signet ring mucinous adenocarcinoma.

A novel survival chemotherapeutic protocol involving FOLFOX was scheduled to be administered; however, the treatment was postponed because of the patient's poor overall condition. About after 8 weeks, the patient was hospitalized with a severe urinary tract infection, which was most likely caused by the disease's progression, and deceased within three weeks of being admitted.

3. DISCUSSION

There are several histological subtypes of primary adenocarcinoma of the urinary bladder, including signet-ring cell type, clear cell type, colonic type, hepatoid, mucinous type, and adenocarcinoma not otherwise characterized. As mentioned above, each histological variation is categorized into urachal and non-urachal variants. Adenocarcinoma developing from remnants of the urachus is the most frequent kind of "vesical adenocarcinoma," reckoning for twenty to thirty-four percent of all bladder adenocarcinomas. It is usually more prevalent in males and occurs in the anterior wall or vesical dome. Many studies suggest that non-urachal adenocarcinoma develops from an intestinal metaplasia triggered by prolonged inflammation. We had to cope with a non-urachal 1° signet ring cell mucinous adenocarcinoma of the bladder. Because the initial magnetic resonance imaging scan revealed a significantly thickened bladder but no exophytic lesions, this radiographic observation was attributed primarily to the effect of persistent urine retention. Immunohistochemically analysis was critical in determining the main cause of the tumour and ruling out other adenocarcinomas, particularly prostate and colonic metastatic adenocarcinomas. The immunohistochemically profile was positive for Cytokeratin-20, Epithelial Membrane Antigen, and CDX2 but negative for Prostate Specific Antigen, Cytokeratin-7, and NKX3.1, not indicating primary prostate adenocarcinoma but a primary vesical or colonic adenocarcinoma. Vesical adenocarcinoma, like metastatic colonic adenocarcinoma, is generally positive for "CEA, CDX-2, MUC-1, MUC-2, and MUC-3", in addition to CK7 and CK20. The usual colonic cancer immunohistochemically profile, on the other hand, is cytokeratin-7 negative as well as CK20 positive. It is a case of primary mucinous adenocarcinoma of the bladder with histopathological similarities to colonic adenocarcinoma. The mutations might cause the diagnosis to be delayed even longer. A high diagnostic accuracy can be achieved by incorporating clinical studies, radiological workups, and immunohistochemistry studies. Furthermore, even when the immunohistochemistry is performed correctly, due to the rareness of this tumor and the propensity for initial diagnostic error, approximately forty-five percent of subjects have stage four tumors (including "lymph node positivity, T4b stage, and distant metastases") at the time of diagnosis, necessitating the use of palliative chemotherapy. A radical cystectomy is the treatment of choice for an operable tumor. According to Akamatsu et al., tumor stage and elevated CEA levels are significant prognostic variables. In this instance, the patient's metastatic condition necessitated palliative chemotherapy; therefore, gemcitabine with Taxol was given as first-line therapy; however, no clinical response was observed. Because primary vesical adenocarcinoma has a histopathological resemblance to colon cancer, some scientists in recent times proposed that chemotherapeutic regimens often used for gastrointestinal malignancies may be evaluated as alternate management options. Only four cases in the literature describe the use of combined chemotherapeutic regimens (folinic acid, fluorouracil, and oxaliplatin) in primary metastatic adenocarcinoma of the bladder. Yamamoto et al. conducted a study in which the carcinoembryonic antigen serum level showed normal levels in the post-operated site, gradually increasing with the disease progression. Their study suggested that CEA serum levels may be useful to determine the aggressiveness and monitor the signet-ring cell carcinoma. According to the research work of Erdogru et al., only total cystectomies may lead to a better outcome in some cases. Multiple efficacious management techniques like intra-arterial chemotherapy with cisplatin and methotrexate combined with radiation therapy or post-cystectomy-only radiotherapy were found in the literature. Continuous research studies are essential to reveal the severity of this neoplasm and set standards for the diagnostic workup and therapeutic strategy of upper urinary tract primary signet ring mucinous adenocarcinoma.

4. CONCLUSION

Urinary primary adenocarcinoma is a rare malignancy. An immunohistochemical examination of the gastrointestinal and gynecological tracts should be undertaken as soon as possible to rule out adenocarcinomas from other primary sites and determine the best therapy. Radical cystectomy is the treatment of choice for non-urachal adenocarcinoma of the bladder. In instances of early cystectomy, neoadjuvant chemotherapy may increase long-term survival. Recent research suggests that an oxaliplatin plus fluoropyrimidine regimen should be explored if first-line chemotherapy fails.

5. AUTHORS CONTRIBUTION STATEMENT

Dr. Ketki Wajpeyi collected information, conceptualized the study, and prepared the draft of the manuscript. Dr. Kishor Hiwale has done histopathological and immunohistochemical reporting of the case. Dr. Sunita Vagha has supervised the case and guided the study. Dr. Kishor Hiwale and Dr. Sunita Vagha have thoroughly reviewed the manuscript. All the authors have read and agreed to the manuscript.

6. CONFLICT OF INTEREST

Conflict of interest declared none.
7. REFERENCES


