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Case Report

Primary Adenocarcinoma of the Urinary Bladder: Report of Two Cases with a Literature Review

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Abstract

Urothelial carcinoma is the most discussed form of bladder cancer. However, there are also other histological subtypes, such as adenocarcinoma, which have different presentations, treatment strategies, and prognosis. Primary adenocarcinoma of the urinary bladder can be classified as urachal adenocarcinoma and nonurachal adenocarcinoma. The average age of patients with urachal adenocarcinoma is about one decade younger than those with the nonurachal subtype, and the prognosis of urachal adenocarcinoma is better. Complete surgical resection is the standard treatment, but adjuvant therapy is always needed due to the high relapse rate. Due to the rareness, research about this malignancy is limited. Herein, we report two cases with different primary adenocarcinomas of the urinary bladder and perform a literature review.

Keywords: Chemotherapy, nonurachal bladder adenocarcinoma, primary bladder adenocarcinoma, treatment, urachal adenocarcinoma

Introduction

Bladder cancer is the fourth most common cancer in men, with an estimated 81,190 new cases and 17,240 deaths in the United States in 2018.[1] Based on histological differences, bladder cancer can be divided into urothelial and nonurothelial. Approximately, 75% of cases of these cancers are classified as urothelial carcinoma, and the remaining 25% of cases consist of other histological variants.[2] Most nonurothelial bladder cancers are epithelial in origin, including squamous cell carcinoma, adenocarcinoma, and small cell carcinoma. Tissue metaplasia and chronic urinary tract infections are believed to be factors in tumorigenesis; however, the actual pathogenesis is still unknown.[3]

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Among nonurothelial bladder cancers, adenocarcinoma is the second most common after squamous cell carcinoma. Primary adenocarcinoma of the urinary bladder accounts for only 0.5%–2% of bladder cancers in the United States.[4,5] It can be further classified by location (urachal and nonurachal) or histological subtype (glandular, mucinous, papillary, signet ring, clear cell, mixed patterns, and others). Urachal adenocarcinoma of the urinary bladder is localized in the midline of the bladder,

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the dome, or anterior wall of the bladder, and it develops from fibrotic remnants of the urachus. It constitutes <1% of all bladder tumors and approximately 10% of all primary bladder adenocarcinomas.[5] In contrast, nonurachal adenocarcinoma of the urinary bladder usually arises from the trigone or posterior wall of the bladder. Both demonstrate similar histologic features, but they can be distinguished on careful pathologic examination.[4] However, the prognosis and treatment strategy for urachal and nonurachal adenocarcinoma are different, so distinguishing one from the other is crucial.

Here, we report two cases of primary bladder adenocarcinoma, one with urachal adenocarcinoma and the other with nonurachal primary adenocarcinoma. Due to the rareness, we also performed a literature review to identify other cases. Ethical approval for this study was given by Kaohsiung Medical University Chung-Ho Memorial Hospital (IRB number KMUHIRB-E (I)-20200059).

Case Report

Case 1

A 53-year-old male presented with hypertension and benign prostate hyperplasia with regular medical control. He came to our urology clinic with chief complaints of frequency, dysuria, and weak stream for days. A bladder mass with right ureterovesical junction (UVJ) invasion was noted in sonographic images. Abdomen computed tomography and magnetic resonance imaging (MRI) revealed urinary bladder cancer in the posterior wall with the involvement of bilateral UVJs, distal ureter, and prostate gland (cT4aN0M0, Stage III). Transurethral resection of the bladder tumor was performed, and the pathological results revealed mucinous bladder adenocarcinoma. He received extensive workup, including colonoscopy, bone scan, and positron emission tomography (PET) scan, to rule out the possibility of metastasis. As no other possible lesions were found, the diagnosis of primary urinary bladder adenocarcinoma was made. Radical cystectomy was suggested, but the patient refused. Therefore, he started chemotherapy with paclitaxel + carboplatin + gemcitabine and received a total of three courses initially. Residual tumor was noted in follow-up pelvic MRI and PET scans. Cystectomy was suggested again, but he still refused. Due to a poor response to chemotherapy alone, radiotherapy (total dose 6600 cGy/33fx) was added concurrently with further chemotherapy (paclitaxel + carboplatin + gemcitabine). However, the disease still progressed with new metastatic peritoneal carcinomatosis. Due to his refractory metastatic status, he was given checkpoint inhibitor immunotherapy with pembrolizumab and atezolizumab. Unfortunately, peritoneal carcinomatosis developed with abdominal lymphadenopathy, and disease progression was diagnosed.

Case 2

A 41-year-old male presented with whitish urethral discharge for 1 month accompanied with mild voiding pain and low abdomen discomfort. Sonography showed a heterogeneous echogenicity lesion below the umbilicus. Abdominal computed tomography disclosed a heterogeneous 9 cm urachal tumor with some calcifications which had invaded into the bladder dome. Cystoscopy showed a papillary tumor at the bladder dome, near the anterior wall. Radical tumor excision, partial cystectomy, and bilateral pelvic lymph node dissection were performed, and urachal mucinous adenocarcinoma, Grade 2, pT3bN0M0, Stage IIIA, invasion to the bladder dome, was diagnosed. The surgical margin was free of tumor cells. He then received a total of six courses of adjuvant chemotherapy with a combination of cisplatin and 5-fluorouracil. He tolerated the chemotherapy well and is now under regular follow-up with complete remission status.

Discussion

Adenocarcinoma of the urinary bladder can be primary or secondary. It is necessary to investigate other sources of cancer if adenocarcinoma of the urinary bladder is diagnosed, since secondarily from other organs such as the colorectal, prostate, endometrium, and cervix are much more common. Secondary adenocarcinomas involve the bladder either by direct extension or by metastasis from a distant site.[4] It usually occurs late in the clinical course, and the primary tumor is usually either symptomatic or easily detectable through examinations. Immunomarkers have some value in differentiating metastatic adenocarcinoma and primary urinary bladder adenocarcinoma. Nuclear staining of β-catenin and CK20 suggests a colorectal origin, whereas CK7, thrombomodulin, and membranous β-catenin staining pattern suggest primary urinary bladder adenocarcinoma.[6] Prostate-specific antigen, prostate-specific acid phosphatase, and other prostate-specific markers including prostate-specific membrane antigen (PSMA), prostein (P501S), and NKX3.1 are expressed in most prostatic adenocarcinomas.[4] Ca-125, vimentin, and Pax-8 are useful to diagnose endometrial carcinoma.[6] Endocervical adenocarcinoma is less likely to be confused with primary bladder adenocarcinoma due to distinct complex glandular structures with mucin-containing columnar cells.[4] After primary bladder adenocarcinoma is diagnosed, the urachal origin needs to be distinguished from nonurachal origins. Although the location of the tumor can be indicated, the differential diagnosis can still be difficult because some nonurachal bladder adenocarcinomas are confined to the dome of the bladder.

The urachus is a fibrous remnant of the allantois, which connects the bladder to the umbilical cord during embryogenesis and is usually obliterated after birth. Urachal carcinomas develop from the fibrotic remnants of the urachus, and most are composed of adenocarcinoma. As with the urachus, urachal adenocarcinoma of the urinary bladder is localized in the midline, dome, or anterior wall of the bladder. Urachal adenocarcinoma is most common in the fourth to sixth decades of life with virtually the same distribution in males and females.[5,7,8] Clinical presentations include hematuria, abdominal pain, irritative symptoms, mucusuria, and umbilical

pain or discharge, but it is usually asymptomatic in the early stage.[8] Many patients present with locally advanced disease with a high risk of distant metastasis, of which peritoneal carcinomatosis is a frequent finding.[9] The prognosis of urachal carcinoma depends mostly on the pathologic stage and the presence or absence of metastatic disease.[10] In general, a urachal origin is associated with a more favorable prognosis than a nonurachal origin.[5]

Different from urachal adenocarcinoma, nonurachal adenocarcinoma of the urinary bladder is derived from the urothelium of the bladder and usually arises from the trigone and posterior wall. It usually occurs at an older age than urachal carcinoma in the sixth and seventh decades of life, with male predominance. It shares common clinical symptoms with other bladder cancers, such as hematuria and irritative symptoms.[4] Nonurachal bladder adenocarcinoma exhibits several different histologically patterns, and the signet-ring cell type has a poorer prognosis compared with other types.[11] In addition, a number of benign glandular lesions should also be considered in the differential diagnosis of bladder adenocarcinoma, including cystitis cystica et glandularis, intestinal metaplasia, endometriosis, endocervicosis, and endosalpingiosis.[4] According to a previous study, when the tumor is confined to the bladder, the survival rate can be more than 75%; however, fewer than 30% of patients are diagnosed at an early stage.[12]

Due to the rareness, there are no randomized trials and no established treatment algorithms for this histology, and therapeutic decisions are usually based on retrospective data. Surgery is currently the most effective treatment option for urachal and nonurachal adenocarcinoma of the urinary bladder, since the response to chemotherapy and radiation is poor.[13,14] In urachal adenocarcinoma, partial cystectomy with margin-negative *en bloc* resection of the median umbilical ligament with the bladder dome and umbilicus is most commonly recommended. In contrast, radical cystectomy is suggested for nonurachal adenocarcinoma.[5]

The role of radiotherapy in bladder adenocarcinoma is still under debate. One study demonstrated a positive effect on the adjuvant setting through best local disease control,[15] whereas another study found no survival benefit, either using radiotherapy alone or in combination with surgery.[14] There are still no conclusive data. Radiotherapy is mostly used as an adjuvant strategy, especially in patients who are ineligible for cystectomy or have positive surgical margins. For chemotherapy, there are also no conclusive data to support the use of neoadjuvant or adjuvant chemotherapy for primary bladder adenocarcinoma including urachal adenocarcinoma. Neoadjuvant chemotherapy has been reported to decrease the frequency of nonorgan-confined disease but with no overall survival benefit.[16] However, due to the high risk of relapse, individualized adjuvant chemotherapy is still favored. Colorectal regimens are mostly considered, such as FOLFOX (oxaliplatin, leucovorin, and 5-fluorouracil) and XELOX (capecitabine and oxaliplatin). Gem-FLP (5-fluorouracil, leucovorin, gemcitabine, and cisplatin) is another choice. A combination of 5-fluorouracil and cisplatin has been reported to be beneficial for urachal adenocarcinoma.[9] Other regimens, including ITP (ifosfamide, paclitaxel, and cisplatin)[17] and a combination of paclitaxel with platinum, may also be applicable. In Case 1, surgical resection would have been the best treatment choice; however, the patient refused due to personal reasons. He then received chemotherapy and radiotherapy; however, the response was poor, and the disease progressed. This demonstrates that chemotherapy and radiotherapy should not be used as first-line treatment. Chemotherapy in an adjuvant setting is more appropriate as with our Case 2.

Several target agents for advanced urothelial bladder cancer are currently being studied, including agents targeting epidermal growth factor receptor signaling, angiogenesis, and PI3K/Akt/mTOR signaling.[18] The benefits of immune checkpoint inhibitors, PD-L1 inhibitor and PD-1 inhibitor, in locally advanced or metastatic urothelial cell bladder carcinoma have also been proven and approved by the US Food and Drug Administration. However, due to the rareness, no clinical trials have been conducted for adenocarcinoma of the urinary bladder, so the benefits of target agents and immune checkpoint inhibitors remain unclear. A previous article reported that the addition of bevacizumab, cetuximab, or panitumumab in urachal adenocarcinoma could be considered owing to the similarity with colorectal cancer.[7] Furthermore, urachal adenocarcinoma has been associated with high microsatellite instability and mutated Kirsten rat sarcoma viral oncogene homolog (KRAS), neuroblastoma RAS viral oncogene homolog (NRAS), and V-raf Murine Sarcoma Viral Oncogene Homolog B1 (BRAF),[19] so theoretically, immune checkpoint inhibitors may have a role in treatment. However, in Case 1, the effect of immune checkpoint inhibitors was not that promising.

Conclusion

When primary bladder adenocarcinoma, either the urachal or nonurachal type, is diagnosed, extensive workup to rule out a secondary cause is mandatory. Surgical intervention is the best first-line treatment due to a poor response to chemotherapy or radiotherapy. Individualized adjuvant chemotherapy and additional radiotherapy are favored, and chemotherapy with a colorectal regimen (mostly 5-fluorouracil based) is suggested. In the urachal type, the combination of 5-fluorouracil and cisplatin can also be considered. As for other treatment choices, the role of target agents or immune checkpoint inhibitors in primary bladder adenocarcinoma is still unknown.

Ethical statement

Ethical approval (IRB number KMUHIRB-E (I)-20200059) for this study was given by Kaohsiung Medical University Chung-Ho Memorial Hospital. The informed patient consent was waived by IRB.

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Conflicts of interest

There are no conflicts of interest.

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