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A Rare Case: Primary Signet Ring Cell Carcinoma of Urinary Bladder

Nadir Bir Vaka: Mesanenin Primer Taşlı Yüzük Hücreli Karsinomu

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Abstract

Primary signet ring cell carcinoma of the urinary bladder is a very rare tumor. At the time of diagnosis, patients are usually in an advanced stage and have a poor prognosis. It is a very rare tumor, case report presentations are important in the management of these patients. We report to a 41-year-old patient who presented with painless gross hematuria and abdominal pain for three months and was diagnosed with a bladder tumor. The patient was considered to have advanced stage disease due to the presence of liver metastasis at the time of diagnosis and was followed up with chemotherapy. After medical treatment, the patient died after a survival of more than 30 months.

Keywords: bladder, adenocarcinoma, signet ring cell

Özet

Mesanenin primer taşlı yüzük hücreli karsinomu çok nadir görülen bir tümördür. Tanı anında hastalar genellikle ileri evrededir ve kötü prognoza sahiptir. Çok nadir görülen bir tümördür, olgu sunumları bu hastaların yönetiminde önemlidir. Üç aydır ağrısız makroskopik hematüri ve karın ağrısı ile başvuran ve mesane tümörü tanısı alan 41 yaşında bir hastayı sunuyoruz. Hasta tanı anında karaciğer metastazı varlığı nedeniyle ileri evre hastalık olarak kabul edildi ve kemoterapi ile takip edildi. Medikal tedavi başlangıcının ardından hasta 30 aydan uzun bir süre hayatta kaldıktan sonra hayatını kaybetmiştir.

Anahtar kelimeler: mesane, adenokarsinom, taşlı yüzük hücre

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Introduction

Primary signet-ring cell carcinoma (PSRCC) is a rare tumor of the urinary bladder [1,2]. The most common type of bladder cancer is urothelial carcinoma, which occurs in 90% of all cases [3,4]. Cases of adenocarcinoma of the bladder are extremely low (2%) [3]. PSRCC of the bladder accounts for 0.12–0.6% among the different histological subtypes of bladder carcinomas [3,5].

PSRCC of the bladder was first described in 1955 by Otto Saphire [6]. To the present day, data on just over 300 cases with such a finding have been published [3]. In a research that has been performed between Sept 1991 and Aug 2016, and included a total of 2778 bladder cancer patients, only five (0.18%) patients were diagnosed with PSRCC [2].

Signet ring cell carcinoma (SRCC), classified as a subtype of adenocarcinoma, most commonly occurs in the colon and stomach. Evaluation of clinical, radiological and immunohistochemical findings of involvement of other systems is important in the differential diagnosis to determine the primary origin of cancer. Here, we aimed to share a rare case of PSRCC of the bladder who had a longer survival time than the median overall survival reported in the literature.

Case

A 41-year-old male referred to internal medicine outpatient clinic with intermittent painless gross hematuria and abdominal pain ongoing for three months. The medical history of the patient included diabetes mellitus and thyroidectomy. The patient was using oral anti-diabetic and thyroid replacement therapies. Systemic examination was grossly normal.

The abdominal ultrasound revealed 63x45 mm protruding cystic lesion in the bladder lumen and two solid lesions in the liver, the largest of which is 28 mm in size. Computed tomography scan revealed a 73x49x51 mm lesion with exophytic extension in the bladder **(Figure 1)**, three metastatic lesions in the liver, the largest of which was 31 mm in segment 2 **(Figure 2)**, and a 16 mm lymphadenopathy in the right external iliac chain. Trucut biopsy was performed from the lesion in the segment 2 of the liver. The pathology report showed carcinoma infiltration in extracellular mucin with diffuse appearance of signet-ring cells and glandular structures **(Figure 3)**. The immunohistochemical findings included positivity for CK7, CK20, CDX2, and SATB2 with negative results for PAX8 and GATA3. Liver function tests were unremarkable. Upper gastrointestinal endoscopy and colonoscopy were not performed because no findings indicated a primary gastrointestinal cancer. Serum prostate-specific antigen (PSA) was 1,6 ng/ml (reference range(RR): 0,4 ng/ml), CA 19-9 2 U/ml (RR:0-37 U/ml), and carcinoembryonic antigen (CEA) 19.9 ng/ml (RR: <5 ng/ml). No other primary focus was detected in other system scans, so the bladder was considered as the primary site of the tumor.

As a result of the current findings, first-line gemcitabine plus cisplatin regimen was initiated. CEA level was 64 ng/ml at the initiation date of chemotherapy (CTh). After the third cycle of CTh, cisplatin was discontinued due to acute kidney injury (creatinine level increased to 2.5 mg/dl from its basal level of 0,8 mg/dl). After creatinine level decreased to 1.4 mg/dl and remained stable, it was decided to continue the treatment with carboplatin and gemcitabine combination. After three cycles of this CTh regimen, partial response was detected on positron emission tomography-computerized tomography (PET-CT) scan and CEA level decreased to 5,3 ng/ml. Therefore, additional three CTh cycles was planned. After the sixth cycle, CTh was discontinued due to grade 3 thrombocytopenia. After the complete blood count results normalized, it was decided to continue the treatment with single agent capecitabine. Due to chronic kidney disease, capecitabine was initiated after renal

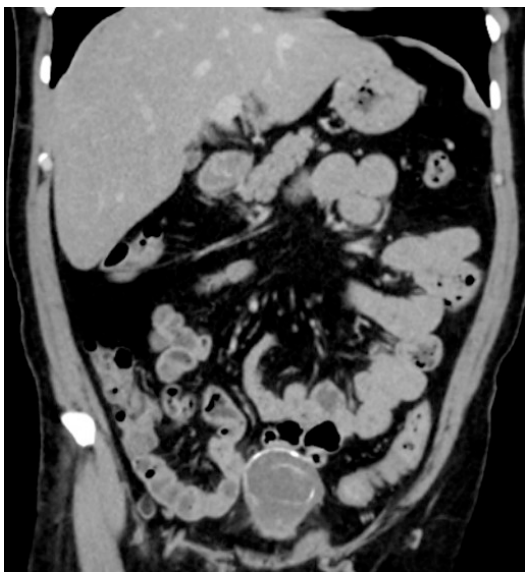

Figure 1. Primary tumour at the time of diagnosis

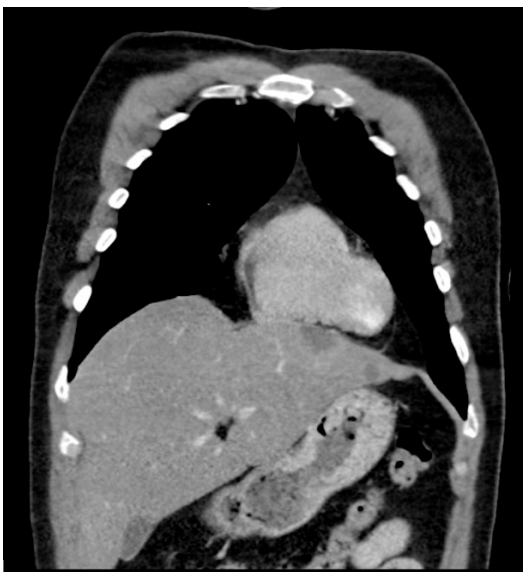

Figure 2. Liver metastases at the time of diagnosis

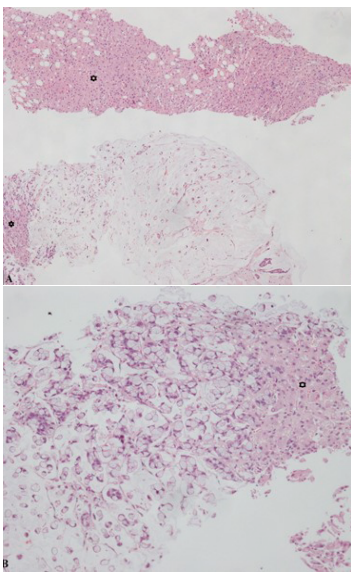

Figure 3. Carcinoma infiltration (H&E, Ax40, Bx100) forming glandular structures in the focal area with signet ring cell appearance in a large area within the liver tissue (stellate)

dose adjustment. After two months of treatment, CEA level increased to 50 ng/ml and macroscopic hematuria occurred. PET-CT scan was ordered after these findings. Although the primary lesion in the bladder was stable, a new metastatic lesion in the liver was detected. Because of the good response with first-line gemcitabine-platin combination, re-challenge with carboplatin and gemcitabine regimen was preferred. After three cycles of treatment, PET-CT imaging showed progression in metastatic liver lesions and new conglomerated lymphadenopathies in the external iliac region, although the primary lesion in the bladder was stable. After palliative radiotherapy (RT) was applied to the lesions in the bladder, liver, and external iliac region, it was decided to continue the treatment with second-line paclitaxel and carboplatin combination. CEA level was found as 22 ng/ml at the initiation of CTh. After two cycles of CTh, new metastatic lesions in the liver and lung were detected on PET-CT scan and third-line single agent docetaxel regimen was planned. After the third cycle of docetaxel, treatment was discontinued due to grade 3 anemia. PET-CT imaging was performed and new metastases were detected in the lung, liver and sacrum. Single agent vinorelbine was initiated after palliative RT to the sacral metastasis. One month after the 3rd cycle vinorelbine was administered, the patient was referred for cardiology consultation upon complaints of dyspnea and peripheral edema which had been present for one week. The patient was diagnosed as heart failure with low ejection fraction and was interned to the coronary intensive care unit. Acute decompensated heart failure treatment was started. Unfortunately, the patient died of acute decompensated heart failure in June 2023. Despite all interventions, the patient died 30 months after diagnosis.

Discussion

Less than 2% of all primary bladder neoplasms are of the adenocarcinomas [4]. PRSCC of the urinary bladder is an extremely rare tumor as a subtype of adenocarcinoma, accounting for 0.24% of all bladder malignancies [3,5]. After the first two cases published in 1955, approximately 300 patients have been described in the English literature [2,6]. The disease is usually diagnosed at an incurable disease. Due to asymptomatic progression, advanced disease is present at the time of diagnosis, so the prognosis is poor. Also, the tumor is considered resistant to CTh and RT. [3,7].

The clinical presentations of PSRCC of the bladder are similar to those of bladder malignant tumors. Common presenting symptoms were hematuria and irritative voiding symptoms. Hong et al. investigated 32 patients with SRCC of the bladder, reported macroscopic hematuria in 59% of patients, bladder irritation symptoms in 25% [8]. The current information on diagnosis and treatment is based on case reports and small non-randomized studies [3]. Identification of the primary localization requires the collaboration of radiology, pathology, urology and internal medicine. Hong et al. reported that SRCC of the bladder shows diffuse and infiltrative growth and therefore neoplastic lesions are often not recognized in the early stage of SRCC on cystoscopy [8]. On cystoscopy, the lesion is characterized as pedunculated, polypoid, sessile, or ulceroinfiltrative. Two thirds of the tumors secreted mucin and most accumulated in the interstitial area. Less frequently, mucin is secreted within the lumen of the acinus and rarely, excess intracellular mucin shifts the nucleus into a peripheral crescent, giving the cells the appearance of a signet ring [9].

When diagnosing SRCC of the bladder, it is recommended to rule out a primary tumor that arises from outside the bladder [3]. Metastatic SRCC of bladder, the primary lesion is likely to originate from gastrointestinal tract. Patients should be examined for abdominal pain, nausea, vomiting, bloddy diarrehea and constipasion. Contrast CT of the abdomen/pelvis and gastrointestinal endoscopy can be used for clinical diagnosis. Immunohistochemistry is very useful in determining the origin of unknown primary site. Until now, there is no commonly accepted agreement on the immunohistochemical findings of primary SRCC of the bladder. CK20 is a cytokeratin typically expressed in the lower gastrointestinal tract, urothelium and Merkel cells. CK7 is expressed in lung, ovarian, endometrial and breast cancers [10]. CK20-positive/CK7-positive combination is seen in urothelial carcinomas and pancreatic/biliary cancers. Thomas et al. found positive expression of CK20 (78%), CK7 (67%), CDX2(33%) and β-catenin (78%) [11]. Hong et al. found positive expression GATA3 (72%), Ki-67 (63%), CEA (44%) and CK20 (28%) [8]. SRCCs of the gastrointestinal tract and bladder have similar immunohistochemical staining patterns. So immunohistochemistry is insufficient to distinguish between primary bladder tumor and metastasis of gastrointestinal origin [11]. In addition, the absence of nuclear positivity for β-catenin in the absence of an endoscopically visible lesion in the gastrointestinal tract supports a urinary bladder origin [1]. β-catenin positivity is detected to the cell membrane, confirming a primary bladder origin [1]. Despite the lack of an identified serum marker for PSRCC of the urinary bladder, elevated CEA has been frequently reported. There is evidence that an increase in CEA level after surgery in SRCC patients is closely associated with disease progression and CEA is recommended to determine the degree of malignancy and to monitor the follow-up of SRCC [9]. In our case, we observed CEA elevation and we used in evaluation of treatment response.

Patients with SRCC present at a younger age, higher histologic grade and more advanced tumor stage than other bladder tumor subtypes [3]. Patients with SRCC have worse responses to RT and CTh than patients with urothelial carcinoma [4]. In the absence of consensus guidelines for the management of PSRCC, diagnosis in a multidisciplinary setting and input from relevant clinical subspecialties is required. Treatment options for SRCCs include surgery, RT and CTh. Surgical methods range from transurethral resection to radical cystectomy with urinary diversion. Currently, there is no standard CTh for PSRCCs of the bladder due to their rarity. In a case report of 12 cases of bladder SRCC treated with adjuvant CTh or CTh for metastatic disease, regimens containing carboplatin, cisplatin, gemcitabine, capecitabine and 5-fluoro-uracil were used [12]. We preferred cisplatin and gemcitabine, a standard combination for transitional carcinoma of the urinary bladder. Due to progression during follow-up, capecitabine, paclitaxel and docetaxel CTh agents were administered. When progression was detected on the last imaging, vinorelbine was initiated. Acute kidney injury and thrombocytopenia, which were thought to be related to chemotherapy, developed during treatment. In a retrospective study of 32 SRCC patients, 1-year and 2-year

survival rates were %53.1 and %9.4 respectively [8]. The same study also showed that GATA3 was an independent protective factor for prognosis ($p < 0.05$) and T stage was an independent risk factor ($p < 0.05$) [8]. In a series of 54 patients, 46% had stage 4 disease, with an overall survival rate of 43% at 2 years, in addition, no patient with stage 4 disease at diagnosis was alive 2 years later [7]. Liu et al found that the 3-year median survival for PSRCC of the bladder was 25.3% [13] . Thirty months after the diagnosis, the patient died of acute decompensated heart failure. The patient's 30-month survival month survival exceeds the typical survival reported for PSRCC patients. This is attributed to the favorable response to initial chemotherapt and the absence of serious systemic complications in the early period.

Conclusion

PSRCCs of the bladder is very rare. When a diagnosis of SRCC is made, other sites, especially the gastrointestinal tract, should be investigated. Due to the rarity of the tumor and the lack of randomized trials, optimal treatment has not yet been determined. Treatment is usually similar to the traditional radical treatment of the bladder cancer. Consequently, further work is needed to investigate and consider potential barriers to the provision of appropriate care for these patients.

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