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Case Report

Primary urinary bladder adenosquamous carcinoma complicated with lower limb deep venous thromboses: a case report

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Abstract: Primary urinary bladder adenosquamous carcinoma is extremely rare and only a few cases have been reported in English literatures. Its biological behavior remains unclear. Here we reported a 60-year-old male patient with lower limb deep venous thromboses associated with primary urinary bladder adenosquamous carcinoma. A color ultrasonography showed right stock total venous thrombosis and right great saphenous vein thrombosis of lower limb. Contrast-enhanced computed tomography (CT) scan confirmed a 3.17 × 3.33 × 3.84 cm enhancing mass within the urinary bladder along the right lateral and posterior wall. Histopathological examination revealed adenosquamous carcinoma of urinary bladder, with extensive infiltration of the muscle layer. To the best of our knowledge, this is the first report of primary urinary bladder adenosquamous carcinoma complicated with deep venous thromboses in lower limb.

Keywords: Urinary bladder adenosquamous carcinoma, deep venous thromboses, hypercoagulability, hematuria

Introduction

Primary urinary bladder adenosquamous carcinoma is an extremely rare disease and only 9 cases with primary urinary bladder adenosquamous carcinoma (from 1992 to 2014) have been reported in PubMed (6 cases) and China National Knowledge Internet (5 cases). Cancer-associated thromboembolism is a clinically severe paraneoplastic syndrome, which will accelerate the deterioration of disease [1]. The most common malignancies responsible for venous thrombosis are lung, pancreatic, gastrointestinal and ovarian cancers [2].

We, for the first time, reported a case of primary urinary bladder adenosquamous carcinoma complicated with lower limb deep venous thromboses. The main points of interest in this case were that venous thromboses were the primary clinical manifestation of this urinary bladder adenosquamous carcinoma, which is an extremely rare condition. The pathogenesis and treatment of cancer-associated venous thromboembolism is also focused from this point of view.

Materials and methods

The tissue specimens were routinely fixed in 10% buffered formalin, embedded in paraffin, and serially sectioned into 5-μm-thick sections. Paraffin sections were stained with hematoxylin and eosin for routine histology. Additional immunohistochemical staining was performed on formalin-fixed, paraffin-embedded tissue sections. The primary antibodies used in this study were shown in the **Table 1**.

Case report

Clinical findings

A 60-year-old male patient was admitted to hospital with his right lower limb pain for one month, which was spontaneous swelling within 1 day. Then the patient had painless intermittent gross hematuria for two months. On admis-

Table 1. Antibodies and summary of immunohistochemical results

Antibody	Source	Dilution	AC	SCC
Cytokeratin (AE1/AE3)	Invitrogen, USA	1:200	+++ Cytoplasmic staining	+++ Cytoplasmic staining
Cytokeratin 5/6	Biocare, USA	1:150	Negative	+++ Cytoplasmic and membranous staining
Cytokeratin 7	Invitrogen, USA	1:150	+++ Cytoplasmic and membranous staining	++ Cytoplasmic staining
Cytokeratin 8	Leica, USA	1:150	+++ Cytoplasmic and membranous staining	+++ Cytoplasmic and membranous staining
Cytokeratin 18	Invitrogen, USA	1:150	+++ Cytoplasmic and membranous staining	Negative
Cytokeratin 8/18	Invitrogen, USA	1:100	+++ Cytoplasmic and membranous staining	+ Cytoplasmic staining
Cytokeratin 14	Eptomics, USA	1:150	Negative	+++ Cytoplasmic staining
Cytokeratin 17	CM, USA	1:100	++ Cytoplasmic staining	+++ Cytoplasmic and membranous staining
Cytokeratin 19	Invitrogen, USA	1:150	+++ Cytoplasmic and membranous staining	Negative
Cytokeratin 20	EPI, USA	1:150	Negative	Negative
CK-H	Cell Marque, USA	1:150	++ Cytoplasmic staining	+++ Cytoplasmic and membranous staining
CK-L	CM, USA	1:150	+ Cytoplasmic staining	Negative
PSA	Leica, USA	1:100	Negative	Negative
CEA	Leica, USA	1:150	++ Cytoplasmic staining	Negative
CDX2	EPI, USA	1:100	Negative	Negative
P63	Origene, USA	1:100	Negative	++ Nuclear staining
P53	Invitrogen, USA	1:150	Negative	Negative
TTF-1	Zeta, USA	1:150	Negative	Negative
S-100	Leica, USA	1:100	Negative	Negative
EMA	Leica, USA	1:200	Negative	Negative
Ki-67 labeling index (%)	Origene, USA	1:200	Nuclear staining: 5-10%	Nuclear staining: 5-10%

Abbreviations: AC: adenocarcinoma component. SCC: squamous cell carcinoma component. CK-H: high molecular weight cytokeratin. CK-L: low molecular weight cytokeratin. PSA: prostate-specific antigen. CEA: carcinoembryonic antigen. CDX2: Caudal-related homeobox 2. TTF-1: thyroid transcription factor-1. EMA: Epithelial Membrane Antigen.

sion, the patient's vital signs were stable. His family history was negative for malignancy. He had no history of any other diseases.

Physical examination was essentially normal. Hematologic work-up revealed red blood count, 4.13×10^{12}/L; leukocyte count, 10.49×10^{9}/L; platelet count, 261×10^{9}/L; sodium, 139.6 mmol/L; potassium, 3.42 mmol/L; bicarbonate, 26.2 mmol/L; blood urea nitrogen (BUN), 2.9 mmol/L; creatinine, 78 μmol/L; and calcium, 2.09 mmol/L. Hemoglobin was 128.10 g/L with MCV 95.36 fL and MCH 31.06 pg. The partial pressure of oxygen was 59 mmHg and of carbon dioxide 29.4 mmHg. Blood pH was 7.557, with an oxygen saturation of 94%. The levels of the majority of the tumor markers were promoted: Carcinoembryonic antigen (CEA), 6.34 ng/mL; cancer antigen (CA) 125, 36.60 U/mL; CA19-9, 160.62 U/mL. The results of anti-double stranded DNA antibody, rheumatic factor, anti-SSA, anti-SSB, anti-glomerular basement membrane, myeloperoxidase, proteinase 3, cytoplasmic antineutrophil cytoplasmic antibody, perinuclear antineutrophil cytoplasmic antibody, antineutrophilic antibody (ANA), hepatitis panel, and human immunodeficiency virus antibody tests were negative.

Urine protein of 24-hour was 575.64 mg. Urine output of 24-hour was 1950 mL. Urine showed red blood cells under microscopy. Urine and blood were sterile on culture. Routine urinalysis showed that RBC in urine was 200/uL and WBC

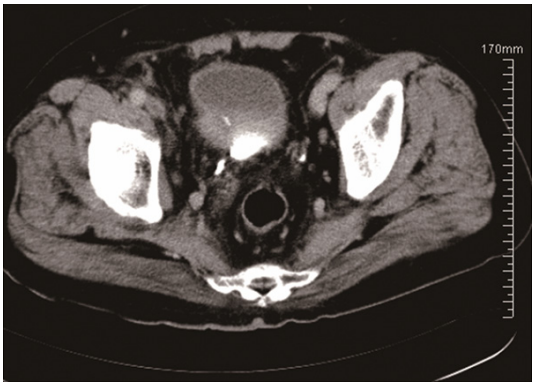

Figure 1. The result of Contrast-enhanced pelvic. CT scan depicting enhancing lesion on the right lateral wall and posterior wall of the urinary bladder.

in urine was 70/uL. Urine cytology showed that a small number of malignant cells could be observed.

He presented weight loss 5 kg, lower limb edema for one day. There was no palpable abdominal tumor and digital rectal examination was normal.

The chest X-ray and liver function tests were within normal limits.

A color ultrasonography showed right stock total venous thrombosis (formation of complete thrombosis) and right great saphenous vein thrombosis of lower limb (incomplete thrombosis).

An abdominal ultrasound revealed a solitary 5.4 × 2.6 cm bladder mass.

Contrast-enhanced computed tomography (CT) scan confirmed a 3.17 × 3.33 × 3.84 cm enhancing mass within the bladder along the right lateral and posterior wall (**Figure 1**). An abdominal CT demonstrated that the back of the right iliac artery appeared fusion of multiple swollen lymph nodes with the largest diameter as 5.98 cm. There were multiple enlarging of lymph nodes beside abdominal aorta.

The patient received inferior vena cava filter placement on the fifth day after admission. Then the patient was transferred to urinary surgery due to painless intermittent gross hematuria, suspected as urinary bladder cancer.

The therapeutic strategy was explained to the patient, who decided to undergo a surgical resection. He received partial urinary bladder resection and right ureter re-implantation. Histopathological examination of the resected specimens revealed adenosquamous carcinoma of urinary bladder, with extensive infiltration of the muscle layer. The patient refused chemotherapy or radiotherapy management and was discharged.

Histopathological and immunohistochemical findings

The surgical specimen contained the urinary bladder along the right lateral and posterior wall, measuring 3.2 × 3.3 × 3.8 cm. Microscopic examination revealed a moderate to poor-differentiated, adenosquamous carcinoma of urinary bladder with invasion to the muscle layer (**Figure 2**). The squamous cell component of the tumor was about 40-50% (**Figure 2A**) and the rest was adenocarcinoma (**Figure 2B**). Adenocarcinoma components were moderate to poorly differentiated, and squamous carcinoma component were poorly differentiated. Mitotic figures were observed (> 5/10 high-power fields). In addition, muscle layer invasion was prominent.

The results of immunohistochemical studies were summarized in the **Table 1**. Histopathologic and immunohistochemical findings of the urinary bladder adenosquamous carcinoma were showed in the **Figures 2**, **3**.

Discussion

Adenosquamous carcinoma is an extremely rare primary tumor of urinary bladder. Until 2014, only 6 cases of primary urinary bladder adenosquamous carcinoma have been reported in the English literatures [3-6]. Its biological behavior remains uncertain. To our knowledge, we, for the first time, reported a case of urinary bladder adenosquamous carcinoma complicated with venous thromboses, which is extremely rare.

Vascular thrombosis requires the presence of one or more of the following factors: endothelial damage, alteration of blood flow and/or hypercoagulability of the blood. Activated clotting factors in areas of sluggish or turbulent blood flow precipitate platelet aggregation, which in turn initiates the thrombotic process [2]. Hypercoagulability is a common paraneoplastic occurrence. The most common malignancies

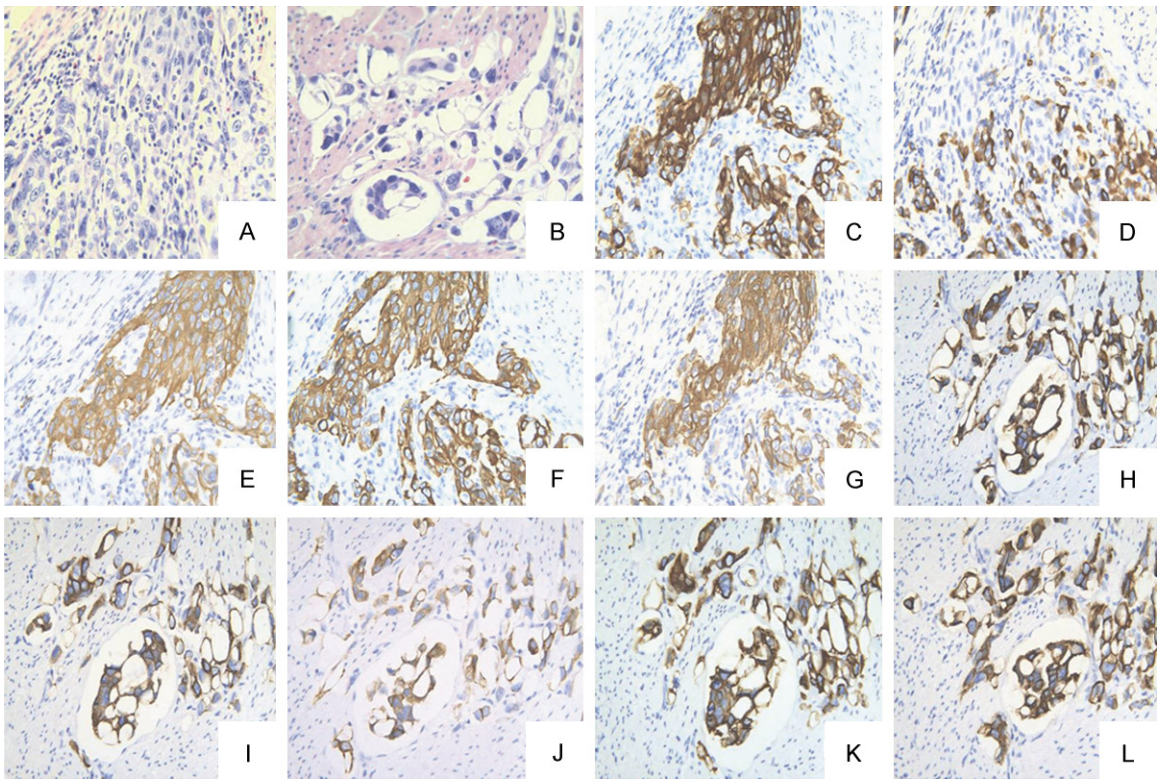

Figure 2. Histopathologic and immunohistochemical findings of the urinary bladder adenosquamous carcinoma. A. Poorly differentiated squamous cell carcinoma component composed of irregular nests with central necrosis. Mitotic figures were observed (> 5/10 high-power fields). B. Moderate to poorly differentiated adenocarcinoma component with tubular and cribriform patterns composed of uniform tumor cells with bland nuclei. Muscle layer invasion. C-G, CK-H, CK8, CK14, CK17 and CK5/6 were expressed in the poorly differentiated squamous cell carcinoma component. H-L, CK8, CK8/18, CK18, CK19 and CK7 were expressed in the adenocarcinoma component (hematoxylin and eosin: A, B; immunohistochemistry: C-L, original magnification × 400).

often occur venous thrombosis with lung, pancreatic, gastrointestinal and ovarian cancers [2]. However, report of bladder cancer with venous thrombosis is relatively uncommon. According to the study of Sandhu et al, patients with urinary bladder cancer had a 1.9% 2-year incidence of venous thromboembolism [7]. In another study of 2,011,000 patients with bladder cancer between 1979 and 1999, patients who were hospitalized with urinary bladder cancer had a venous thromboembolic events (VTE) incidence of 1.0% [8]. Clinically apparent thrombosis occurs in 1-11% of patients with cancer and the incidence is much higher in post-mortem studies [9]. In addition, deep venous thrombosis contributed a worse prognosis upon cancer patients [10]. Although uncommon, hypercoagulability associated with a distant malignancy may result in deep venous thrombosis of even the internal jugular vein [2]. The clinical manifestations of cancer-associated thrombosis include spontaneous recurrent migratory venous thrombosis, arterial thrombosis, microangiopathy, non-bacterial thrombotic endocarditis and acute and chronic disseminated intravascular coagulation [1]. Thus, cancer-association thrombosis must be comprehensive inspection and handling in time, otherwise it will affect the patient outcome.

Primary urinary bladder adenosquamous carcinoma is rare. If it is poorly differentiated carcinoma, it is often difficult to distinguish them from metastatic adenosquamous carcinoma morphologically.

Immunohistochemical analysis using a panel of specific markers is an important alternative for etiological differentiation of these tumors. Our immunohistochemical results showed that CK-H, CK8, CK14, CK17 and CK5/6 were positive expressed in the poorly differentiated squamous cell carcinoma component. CK8/18, CK18, CK19, CK7 and CK8 were positive

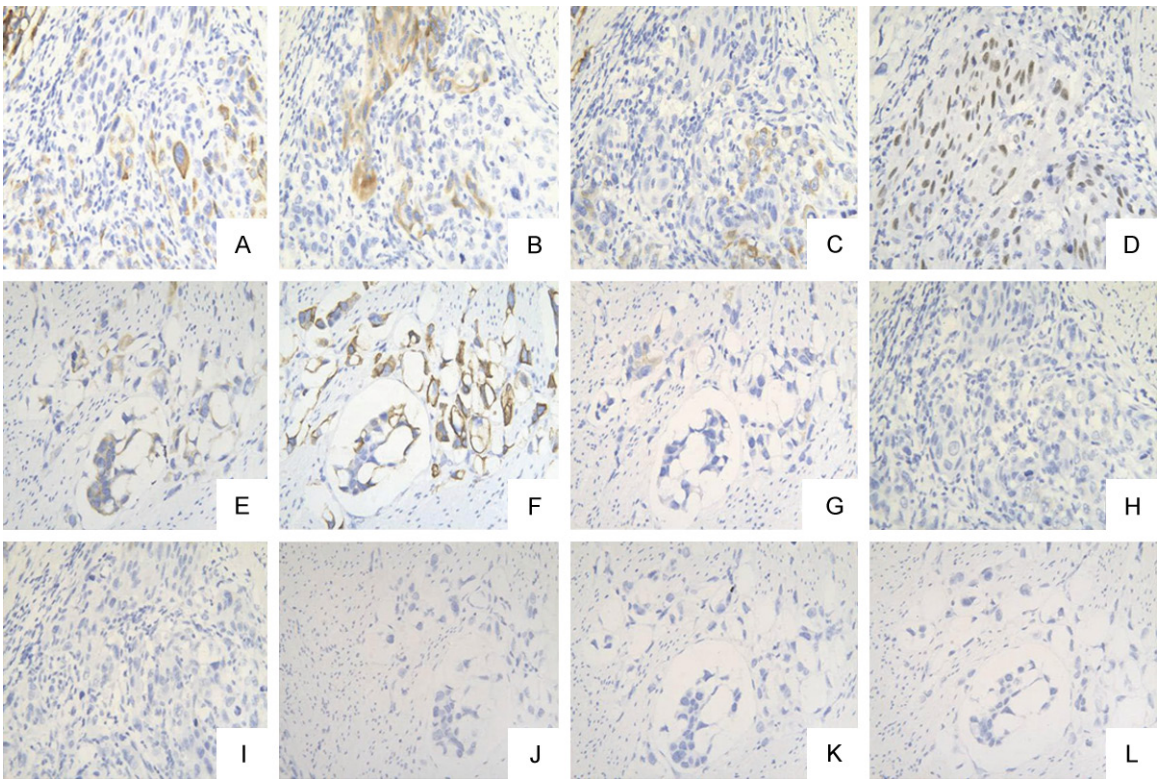

Figure 3. Immunohistochemical findings of the urinary bladder adenosquamous carcinoma. A-D. Poorly differentiated squamous cell carcinoma component: CK7, CK19, CK8/18 and p63 were positive. E-G. Moderate to poorly differentiated adenocarcinoma component: CK-H, CK17 and CK-L were positive. H-I. CK-L and CK18 in the poorly differentiated squamous cell carcinoma component were negative. J-L. CK20, CK5/6 and CK14 are negative expression in the adenocarcinoma component (immunohistochemistry, original magnificantion × 400).

expressed in the adenocarcinoma component. A CDX2, CK20-positive and CK7-negative profile is indicative of digestive tract adenocarcinoma, particularly colorectal carcinoma. It is rare in urothelial tumors, which normally express CK7 alone or together with CK20 [11] and are negative for CDX2. No studies on the expression of the cytokeratins CK20 and CK7 in primary urinary bladder adenocarcinoma cases are available in the literature. Torenbeek et al [12] observed that CK7 and CK20 were expressed at least focally in 82% and 73% of 22 primary urinary bladder adenocarcinomas, respectively. Our results of immunohistochemistry showed that CDX2 and CK20 were negative while CK7 was positive. The results of immunohistochemistry together with the negativity of abdominal CT excluded the possibility of tumor origin from the digestive tract.

An early study by Abenoza et al. [13] showed that nearly all primary adenocarcinomas of the urinary bladder were immunoreactive for pan-CK. It was consistent with our results.

No primary tumor was identified upon examination of the entire prostate, and ancillary immunohistochemical studies clearly showed a complete absence of immunoreactivity for prostate-specific antigen in this component of the tumor, further excluding the possibility of origin from the prostate.

The above pathological microscopy, immunohistochemical results and CT results together showed that it was primary adenosquamous carcinoma of urinary bladder.

The histogenesis of adenosquamous cell carcinoma of the urinary bladder remains undefined, and several different hypotheses have been offered: 1) a preexisting adenocarcinoma undergoing squamous cell transformation; 2) heterotopic squamous epithelium undergoing a malignant change; and 3) a stem cell capable of differentiating into either a squamous or glandular cell undergoing a malignant change. In summary, this case suggests that each patient with spontaneous thromboembolism

should undergo a cautious clinical history, a complete physical examination and a thorough investigation to avoid missing or delaying the diagnosis of a hidden malignancy.

Disclosure of conflict of interest

None.

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