

Case Report

Microcystic urothelial carcinoma: a case report

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Abstract: Microcystic urothelial carcinoma (MUC) is a rare variant of urothelial carcinoma that is highly aggressive with poor prognosis. Due to the scarcity of cases, its histologic morphology and immunohistochemical characteristics are still not clear. This paper reports a 71-year old female patient with gross hematuria and abdominal pain. Imaging examination showed that the bladder wall was thickened, and rough. A soft tissue mass was seen in the bladder and the left lower ureter, and the boundary between the bladder and the uterus and bilateral adnexa was not clear. Multiple enlarged lymph nodes were seen around the abdominal aorta and left iliac artery. Cystoscopy showed diffuse thickening and edema of the left wall of the bladder, local rough bleeding, and histopathologic results showed that the lesions were consistent with high-grade invasive urothelial carcinoma. Radical cystectomy and bilateral ovariectomy were performed. By microscopic observation the tumor showed infiltrative growth with cystic structures of different sizes. Mitotic figures were frequent and a large amount of mucus was in the stroma. The same type of cancer was found in the left ovary. Immunohistochemistry showed CK5/6 +, p63 +, Pax-8, MUC5AC, CK7, and Ki67 was 50%. Postoperative pathology confirmed that MUC involved the left ureter with ovarian metastasis. Two months after the operation, the patient died of vascular invasion. Because tumor cells were bland in morphology and had no specific immunohistochemical markers, they were easily missed and misdiagnosed by pathologists. Here, we describe this case and analyze it with relevant literature to deepen understanding of MUC.

Keywords: Bladder tumor, urothelial carcinoma, microcystic, immunohistochemistry

Introduction

Urothelial carcinoma is the most common histologic type of bladder carcinoma, and accounts for more than 90% of bladder cancers [1, 2]. In recent years, it has been found that there are many variants of urothelial carcinoma in addition to common types. These new variants are recognized in the 2016 World Health Organization (WHO) classification of urothelial neoplasms [3]. It is of great significance to fully understand these variants for correct pathologic diagnosis and prognosis.

Microcystic urothelial carcinoma (MUC) is a rare and special subtype of urothelial carcinoma, which was first reported by Young in 1991 [4]. The main microscopic features of MUC are saccular structures of different sizes, with high invasive and metastatic ability, high recurrence rate, and poor prognosis. In this paper, a rare case of MUC with infiltrative growth, ureteral invasion and left ovarian metastasis is reported.

Clinical summary

A 71-year old woman was admitted to hospital due to gross hematuria with pain in her lower abdomen for 10 days. There was no obvious inducement for hematuria, which manifested as gross hematuria, blood clot, no tissue debris, and pain in the lower abdomen. The nature of the pain was intermittent colic, no frequency of urination, urgency and pain in urination, no difficulty in urination, and no other special discomfort. The patient had a history of hypertension and cerebral infarction. Through physical examination the abdomen was flat and soft without varicose veins of abdominal wall, tenderness of lower abdomen, no rebound pain and muscle tension, no percussion pain in bilateral kidney area, no tumor palpated in bilateral ureter area, no tenderness and fullness in bladder area, and normal bowel sounds. There was no abnormality in blood tests and routine biochemical tests: TAP: ++; TAM: 132 U/ml, SCCA: 70 ng/ml, CYFRA: 7.67 ng/ml. Con-

Microcystic urothelial carcinoma

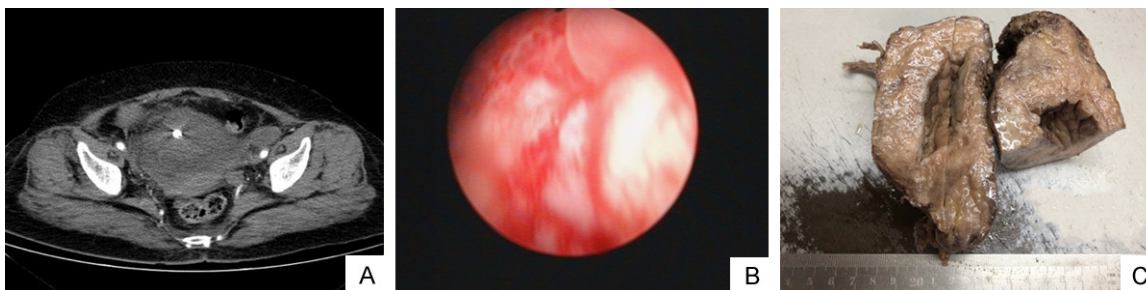


Figure 1. A. Contrast-enhanced CT shows obvious thickening of the left anterior wall of the bladder. B. Cystoscopy shows irregular protuberance with erosion and hemorrhage. C. Gross specimen shows thickening of bladder wall.

trast enhanced CT and CTA showed that the bladder was not well-filled, the wall was thickened and rough, and soft tissue mass shadows could be seen in the bladder and the lower left ureter, with a maximum cross-section of 6.4 cm * 8.5 cm and 1.6 cm * 1.8 cm respectively. The contrast-enhanced examination showed slight enhancement, and unclear boundary with the uterus and bilateral appendages. The left renal pelvis, calyces, and ureters were dilated and hydrous, and the contrast agent still filled well. Multiple enlarged lymph nodes were seen around the abdominal aorta and left iliac artery. The larger one was about 1.9 cm in diameter, and the enhancement was uneven. The wall of the left renal artery was thickened and the lumen was slightly narrowed (**Figure 1A**). Preliminary clinical diagnosis: 1. Bladder cancer; 2. Left hydronephrosis; 3. Hypertension; 4. Cerebral infarct. Further improvement of cystoscopy showed that old blood clots and fresh bleeding were found in the bladder, diffuse thickening and edema were found in the left wall of the bladder, there was local rough bleeding, smooth right wall, and unclear ureteral orifices on both sides (**Figure 1B**). Pathologic examination showed the lesions of high grade invasive urothelial carcinoma. After exclusion of contraindications, the patient was operated in our hospital on August 28, 2019. Laparoscopic examination showed that the bladder was significantly enlarged, rigid fixation, diffuse thickening of the left bladder wall, part of the bladder wall and the surrounding tissue were closely adherent, difficult to separate. The left lower ureter was invaded by tumor, and the ovaries on both sides were suspected to be involved. The bladder and ovaries were removed completely, the lymph nodes around the iliac vessels were cleaned, and a histopathologic examination was performed.

Pathologic findings

The specimens received by formalin included one specimen of the whole bladder, 12.0 cm * 11.0 cm * 6.0 cm in size. The bladder was dissected. The mucosal surface of the anterior wall was rough, the range was about 5.0 cm * 3.0 cm. The bladder muscle layer had a diffuse infiltrating mass, involving the whole bladder. Cross-section was gray and red, some areas were slightly gelatinous, sticky and slippery. Some serous surface of the mass was rough; the range was about 7.0 cm * 4.0 cm. The left ovary was a piece of gray red irregular tissue, 6.5 cm * 3.5 cm * 2.5 cm, with hard gray white matter on the section. The right ovary was a piece of gray red irregular tissue, 3.0 cm * 1.5 cm * 1.3 cm, with slightly tough gray yellow gray red matter on section (**Figure 1C**).

The tumor cells diffusely infiltrated and were arranged in nests. There were several cysts with different sizes, circles or ovals, mucus, and the walls of cysts were covered with multi-layer or single-layer cuboid tumor cells. The shape of tumor cells was the same, the nucleus was round, the nucleolus was not obvious, and mitotic figures frequent. The tumor infiltrated into serosa, and extensive tumor thrombi were seen in the vessels. Microscopically, the tumor involved the left ovary. No cancer was found in the right ovary (**Figure 2**).

Immunohistochemistry showed CK5/6 (+), p63 (+), pax-8 (scattered +), Muc5AC (partial +), CK7 (weakened +), p53 (-), Syn (-), CgA (-), GATA-3 (-), CK20 (-), SALL-4 (-), and Ki67 value-added index was about 50% (**Figure 3**).

Morphology and immunohistochemical results under the microscope, were consistent with microcystic urothelial carcinoma of the bladder.

Microcystic urothelial carcinoma

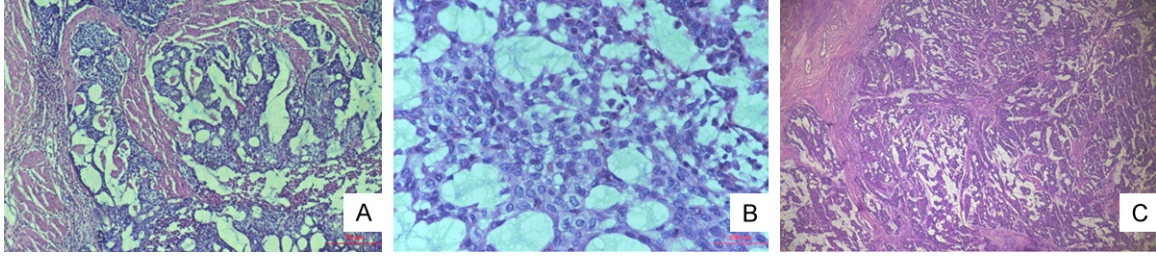


Figure 2. A. Under the microscope, there are cysts or oval of different sizes in the tumor tissue, infiltrating the muscular layer (10×). B. The wall is covered with single or multiple layers of urothelium. The tumor cells have the same morphology and relatively low atypia (40×). C. Tumor cells infiltrate ovarian tissue.

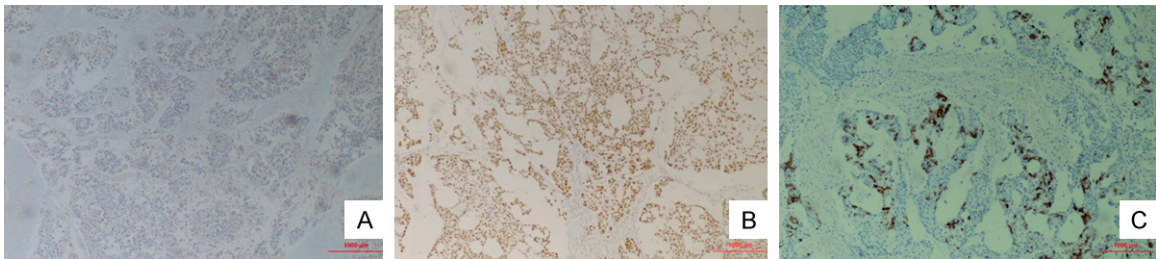


Figure 3. A. CK7 protein is weakly positive. B. p63 expressed strongly in tumor cells. C. MUC5AC is focally positive.

The carcinoma tissue invaded the serosal layer of the bladder wall and invaded the left ureter. Metastatic carcinoma was seen in the left ovary. After operation, the patient was discharged from the hospital, but he was not treated with the normal chemoradiotherapy or radiotherapy. He died of vascular invasion 2 months later.

Discussion

Microcystic type is a very rare subtype of urothelial carcinoma (MUC). It is recognized in the 2004 WHO classification of urothelial neoplasms, accounting for about 1% of urothelial carcinoma. In addition to the bladder, it can also occur in the upper urinary tract such as the renal pelvis [5, 6]. At present, the etiology of MUC is not clear. Some scholars have proposed that the aetiology of the microcystic variant of urothelial carcinoma includes the following: (1) cystic structures may come from the capability of urothelium to line spaces as occurs in the URI. (2) cysts may result from cell regeneration which is based upon presence of luminal debris and necrotic cells [3]. The specific etiology and pathogenesis still need in-depth study. The imaging findings show a thickened bladder wall or mass protruding into the lumen. Clinical symptoms of MUC are nonspecific and similar

to other types of bladder cancer. Most patients have painless gross hematuria as the main clinical manifestation, a few patients have bladder irritation symptoms and dysuria, and a few get abdominal pain, urinary retention, anaemia, and other symptoms [7].

Due to the lack of specific clinical manifestations of MUC, the final diagnosis depends on histopathology and immunohistochemistry. The tumor can be polypoid, papillary, nodular, or diffuse through the wall, sometimes with bladder wall thickening and hardening [8]. The specific microscopic features of tumor cells are as follows: 1. There are obvious sac-like structures in invasive tumors, the size of which varies from 1 to 2 mm in diameter; 2. The sacs are round, oval, sometimes elongated, filled with necrosis or pale pink secretions, or accompanied by calcification; 3. The cysts are lined with flat urothelium, which is bland in shape, accompanied by mucinous cell differentiation, and some of the wall epithelium can fall off; 4. Usually lack of an interstitial reaction; 5. The microcapsule structure shows infiltrative growth, which can invade the intrinsic muscle layer; 6. Some of the tumor can be transformed into small nest or large nest variant urothelial carcinoma components [9-12].

Microcystic urothelial carcinoma

Due to the low incidence of MUC, there is no international standard for immunohistochemistry. According to literature review, similar to common urothelial carcinoma, MUC tumor cells often express GATA3, p63, 34 β E12, CK7, and CK20, and some of them express uroplakin and thrombomodulin. Ki-67 and p53 are high in high grade cancers [13-15]. According to Lopez and his colleagues' research on many cases of MUC, CK7/20, MUC1, MUC5AC, p63 and GATA3 can be expressed positively in tumor cells. The overexpression rates of Ki-67, p53 and p27-*kip1* in tumor cells are 20-60%, 10-40% and 10-30% respectively. In this case, as mentioned above, the tumor morphology and most of the immunohistochemical expression are consistent with the literature.

According to the current classification of WHO, there are nearly 20 subtypes of tissue variants of urothelial carcinoma, including nested subtype, micropapillary subtype, and plasmacytoid subtype. The morphology of MUC is not specific, which leads to MUC being easily misdiagnosed as benign lesions or other bladder lesions, especially in biopsy specimens with little tissue [7]. Therefore, we need to distinguish MUC from the following diseases: 1. Infiltrative urothelial carcinoma with adenocarcinoma differentiation: there are real glandular components in the tumor. These components can be mucus-secreting tubules or intestinal type glandular tubes. MUC5AC and CK8/18 can be used as immunohistochemical markers of this kind of tumor. 2. Nested variant of urothelial carcinoma: it is a kind of tumor with a "pseudo benign" appearance similar to the inherent layer of Brunner's nest infiltration. It can have a small lumen, and the tumor cells infiltrate irregularly to the deep muscular layer. With the increase of the depth of tumor invasion, the cell atypia gradually increases. 3. Cystitis glandularis: a kind of metaplasia of bladder mucosa on the basis of chronic inflammation or long-term stimulation. Under the microscope, it is mainly manifested as Brunner nests, cysts, and glands formed in the mucosal layer, which are superficial non-infiltrative growth. The main difference with MUC lies in the existence of an infiltrative growth pattern. 4. Nephrogenic adenoma: the tumor is composed of tubules, sacs, and papillary structures covered with cuboidal or columnar cells and hobnail cells. The tumor has the following microscopic features: clear boundaries, limited to the lamina propria, no

infiltration, and no transitional cells around the tubules. Immunohistochemistry showed that P504S, PAX2, and Pax8 were positive, and 34 β E12 and p63 were negative in most cases, and Ki-67 index was generally low.

MUC is highly invasive, with infiltrative growth, often invades the muscular layer and spreads out in the bladder, and is prone to distant metastasis [4, 10-12]. The first report of MUC cases by Young et al. showed that the four cases of MUC were deeply invasive, two were of grade 2, and two were of grade 3. Similarly, Lopez found that the tumors were all deeply invasive in 20 patients, and four of them had peripheral infiltration. Therefore, the aggressiveness of MUC is very strong. Sari and Barresi each reported a case of MUC metastasis to the penis. Both patients died 6 months after operation. One patient developed penile metastasis 5 months after diagnosis of MUC. Despite radical operation and chemotherapy, the patient died of lung and liver metastasis 6 months after operation [1, 11].

Although it has been reported that there is no significant difference between the prognosis of MUC and that of common urothelial carcinoma of the same stage, MUC tends to be of high grade and high stage, and the clinical stage is often late at the time of diagnosis. The overall prognosis of patients is poor [7, 15, 16]. Venyo reported 17 patients, and only two survived. Lopez reported 20 patients with MUC undergoing surgery, 11 of whom died of disease at 11-56 months (mean 30 months), with a mortality rate of more than 50%. All these reports support that this tumor subtype is related to the low survival rate [7, 17].

This case was found to have ureteral involvement and ovarian metastasis during imaging examination and operation. Despite radical operation, the patient died of vascular invasion 2 months later. At present, the literature reports agree that radical cystectomy and neoadjuvant chemotherapy are the primary choice for the treatment of MUC. Although the prognosis of patients with MUC is not very optimistic, there is evidence that active and effective treatment can alleviate and control the disease [18, 19].

Conclusion

MUC is a rare variant of bladder urothelial carcinoma, which has high metastasis, high recur-

rence rate, and poor prognosis. It is more invasive than ordinary invasive urothelial carcinoma. Early detection, and early diagnosis and treatment are of great significance to improve the survival rate. Its bland histologic appearance and non-characteristic immunohistochemical phenotype easily lead to misdiagnosis and missed diagnosis of tumor. Therefore, it is of great significance for clinicians to fully understand its histopathologic characteristics and make a correct pathologic diagnosis to judge the prognosis and treatment.

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The case report and any accompanying report pictures were with signed informed consent from the patient's family members.

Disclosure of conflict of interest

None.

Abbreviations

MUC, Microcystic urothelial carcinoma; WHO, Epithelioid World Health Organization.

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References

- [1] Barresi V, Ieni A, Magno C and Barresi G. High-grade urothelial carcinoma of the urinary bladder showing acquisition of microcystic histology in the penile metastasis: histogenetic considerations. *Pathol Res Pract* 2009; 205: 568-571.
- [2] Lopez-Beltran A, Henriques V and Montironi R. Variants and new entities of bladder cancer. *Histopathology* 2019; 74: 77-96.
- [3] Humphrey PA, Moch H, Cubilla AL, Ulbright TM and Reuter VE. The 2016 WHO classification of tumours of the urinary system and male genital organs-part B: prostate and bladder tumours. *Eur Urol* 2016; 70: 106-119.
- [4] Young RH and Zukerberg LR. Microcystic transitional cell carcinomas of the urinary bladder. A report of four cases. *Am J Clin Pathol* 1991; 96: 635-639.
- [5] Leroy X, Leteurtre E, De La Taille A, Augusto D, Biserte J and Gosselin B. Microcystic transitional cell carcinoma: a report of 2 cases arising in the renal pelvis. *Arch Pathol Lab Med* 2002; 126: 859-861.
- [6] Pacchioni D, Bosco M, Allia E, Mussa B, Mikuz G and Bussolati G. Microcystic urothelial cell carcinoma with neuroendocrine differentiation arising in renal pelvis. Report of a case. *Virchows Arch* 2009; 454: 223-227.
- [7] Lopez Beltran A, Montironi R and Cheng L. Microcystic urothelial carcinoma: morphology, immunohistochemistry and clinical behaviour. *Histopathology* 2014; 64: 872-879.
- [8] Rolim I and Henriques V. Clinicopathologic analysis of upper urinary tract carcinoma with variant histology. *Virchows Arch* 2020; 477: 111-120.
- [9] Sasaki Y, Shiozaki K, Miyake T, Izumi K, Kishimoto T, Yamanaka M, Kawanishi Y, Jinno M and Hayashi T. Microcystic variant of urothelial carcinoma in urinary bladder: a case report. *Nihon Hinyokika Gakkai Zasshi* 2017; 108: 101-105.
- [10] Paz A, Rath-Wolfson L, Lask D, Koren R, Manes A, Mukamel E and Gal R. The clinical and histological features of transitional cell carcinoma of the bladder with microcysts: analysis of 12 cases. *Virchows Arch* 1997; 79: 722-725.
- [11] Sari A, Uyaroglu MA, Ermete M, Oder M, Girgin C and Dincer C. Microcystic urothelial carcinoma of the urinary bladder metastatic to the penis. *Pathol Oncol Res* 2007; 13: 170-173.
- [12] Triki M, Ayadi L, Kallel R, Charfi S, Saguem I, Mhiri N, Boudawara TS and Gouiaa N. Microcystic transitional cell carcinoma: a rare tumor of the urinary bladder. *Pathologica* 2017; 109: 151-155.
- [13] Paner GP, Annaiah C, Gulmann C, Rao P, Ro JY, Hansel DE, Shen SS, Lopez-Beltran A, Aron M, Luthringer DJ, De Peralta-Venturina M, Cho Y and Amin MB. Immunohistochemical evaluation of novel and traditional markers associated with urothelial differentiation in a spectrum of variants of urothelial carcinoma of the urinary bladder. *Hum Pathol* 2014; 45: 1473-1482.
- [14] Mai KT, Truong LD, Ball CG, Williams P, Flood TA and Belanger EC. Invasive urothelial carcinoma exhibiting basal cell immunohistochemical markers: a variant of urothelial carcinoma associated with aggressive features. *Pathol Res Pract* 2015; 211: 610-618.

Microcystic urothelial carcinoma

- [15] Mai KT, Hakim SW, Ball CG, Flood TA and Belanger EC. Nested and microcystic variants of urothelial carcinoma displaying immunohistochemical features of basal-like urothelial cells: an immunohistochemical and histopathogenetic study. *Pathol Int* 2014; 64: 375-381.
- [16] Alvarado-Cabrero I, Perez-Montiel D and Hes O. Multicystic urothelial carcinoma of the bladder with gland-like lumina and with signet-ring cells. A case report. *Diagn Pathol* 2008; 3: 36.
- [17] Venyo AK. Microcystic variant of urothelial carcinoma. *Adv Urol* 2013; 2013: 654751.
- [18] Radopoulos D, Kalyvas K, Kotakidou R, Panagiotopoulou K, Katsikas V and Papathanasiou M. Case report: microcystic transitional cell carcinoma of the urinary bladder. *Int Urol Nephrol* 2005; 37: 291-293.
- [19] Lobo N, Shariat SF, Guo CC, Fernandez MI, Kassouf W, Choudhury A, Gao J, Williams SB, Galsky MD, Taylor JA 3rd, Roupret M and Kamat AM. What is the significance of variant histology in urothelial carcinoma? *Eur Urol Focus* 2020; 6: 653-663.