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CASE REPORT

Microcystic Urothelial Carcinoma of the Urinary Bladder Metastatic to the Penis

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Metastatic spread of primary bladder cancer to the penis is an extremely rare event. Microcystic urothelial carcinoma is a very rare variant of urothelial carcinoma. Due to its rareness and insufficient clinical follow-up data, the prognosis of microcystic urothelial carcinoma is still not clear. Here in we report a case of a penile metastasis from microcystic urothelial carcinoma of urinary bladder, in a 56-year-old man who died 6 months after radical cystoprostatectomy and total penectomy. To the best of our knowledge this is the first case report of microcystic variant of urothelial carcinoma which has metastasized to the penis. (Pathology Oncology Research Vol 13, No 2, 170–173)

Key words: Urothelial carcinoma, microcystic variant, primary bladder cancer, penile metastasis

Introduction

Urothelial carcinoma is the most common type of bladder neoplasms accounting for about 95% of the cases. At the time of diagnosis, 15% of cases have spread to regional lymph nodes or distant sites. Metastatic spread of urothelial carcinoma of the bladder to the penis is a rare event.[1]. In a review from Memorial Sloan-Kettering Cancer Center not a single case of penile metastasis was detected in 1165 cases of bladder cancer.[2] Microcystic urothelial carcinoma (mUC) is a rare variant of urothelial carcinoma characterized by widespread and prominent cystic changes.[3,4] To date only 17 cases of mUC have been reported worldwide, and no data are available on the prognosis of mUC due to its rarity and insufficient clinical follow-up data. We present a case of mUC which has metastasized to the penis, and a review of the relevant literature.

Case Report

The 56-year-old man presented to an outside institution in July 2004 with macroscopic hematuria of one year duration. Ultrasonography (USG) revealed three solid masses on right and posterolateral walls of the urinary bladder. The patient did not return until 6 months later. Transurethral resection (TUR) of the mass was performed on February 2005. The diagnosis of the mass was reported as grade III urothelial carcinoma infiltrating the lamina propria. He had six BCG treatments intravesically. On CT scans, a mass extending all the way through the posterior wall of the bladder to the base and to the extravesical region was detected. A second TUR was performed on May 2005, and it was reported that the tumor had infiltrated the muscularis propria. Afterwards, he was referred to our hospital for further therapy. On admission he had macroscopic hematuria and pain in his penis**.** On physical examination glans penis was hyperemic and ulcerated, and painful fibrotic tissues were palpated on both corpus cavernosum. The patient's pain and penile lesions persisted in spite of the use of antibiotics. Tru-cut biopsy of the penis was performed on June 2005. The pathologic examination of the lesion confirmed the diagnosis as urothelial carcinoma. The patient's pain was intolerable. Radical cystoprostatectomy with bilateral pelvic lymphadenectomy and total penectomy was performed.

On macroscopic examination of the specimen, the tumor was located mainly in the trigone but the prostate as well as the whole body and glans of penis were widely infiltrated (*Fig. 1a*). Microscopic examination showed high-grade papillary urothelial carcinoma, of which the

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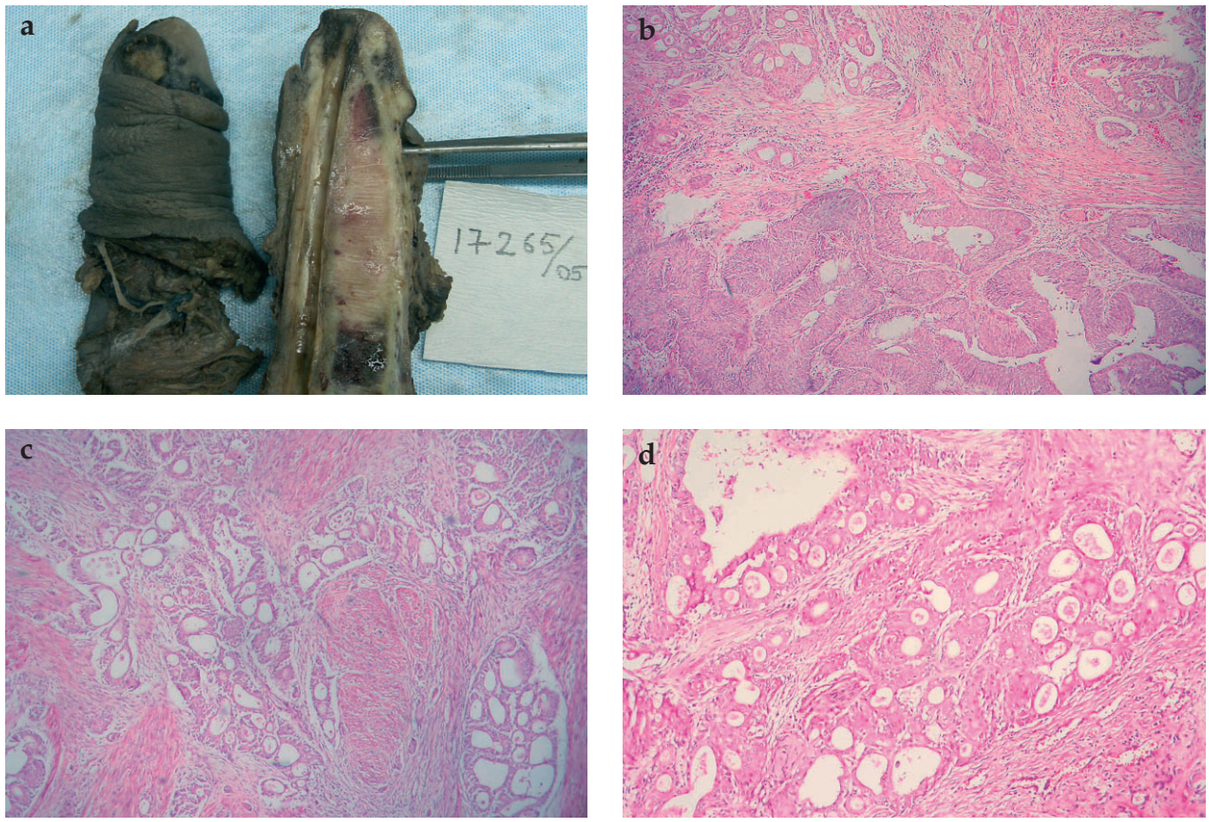

Figure 1. ***(a)*** *Whitish tumoral mass infiltrating the whole body of the penis including corpus spongiosum and glans penis.* ***(b)*** *Interface of the conventional urothelial carcinoma and microcystic part of the tumor.* ***(c)*** *Urothelial carcinoma with many cysts invading the muscularis propria.* ***(d)*** *Urothelial carcinoma with many cysts of varying sizes*

invasive part composed entirely of variable sized cysts lined by single to several layers of urothelial cells or occasionally by squamous cells (*Figs. 1b-d*). The centers of the cysts were often filled with either pale-pink to eosinophilic secretion or necrotic material that stained positive for mucin (Alcian Blue). Urothelial cells at the periphery of many large cysts were punctuated by many smaller cysts which contained a targetoid secretion that was eosinophilic (*Fig. 2a*). Immunohistochemical studies were performed using monoclonal antibodies to Ki-67, p53, cytokeratin 7 (CK7) and prostate-specific antigen (PSA). Tumor cells showed diffuse intense staining for CK7, but negative staining for PSA. Percentages of positively stained cells for Ki-67 and p53 were 15% and 70%, respectively. The tumor extensively infiltrated the muscularis propria, penetrated into the perivesical fat tissue and extended through the whole penis including the body as well as corpus spongiosum and glans penis (*Fig. 2b,c*). One out of five obturator lymph nodes removed showed metastasis. Chemotherapy including Gemcitabine and Cisplatinum were given to the patient. There was no metastatic spread elsewhere**.** Although there was no distant metastasis in the first metastatic work-up, CT scan performed 3 months after the chemotherapy revealed multiple metastases to lung and liver. The patient died of disseminated disease 6 months after the operation.

Discussion

Microcystic urothelial carcinoma is one of the rarest variants of urothelial carcinoma, exhibiting extensive and prominent cysts within nests of urothelial carcinoma.[3,4] To date only 17 cases of this variant have been reported in the literature. Its characteristic features were first described comprehensively on four cases by Young and Zukerberg.[4] Twelve of the other cases published by Paz et al[5] in the proceeding years have been debated by Leroy et al[6] who described mUC in renal pelvis. Leroy et al claimed that the microphotographs presented in Paz et al's study were papillary urothelial carcinoma with glandular metaplasia rather than microcystic carcinoma described by Young and Zukenberg.

Histologically, mUC consists of round, oval or sometimes elongated microcysts ranging between 1 to 2 mm in

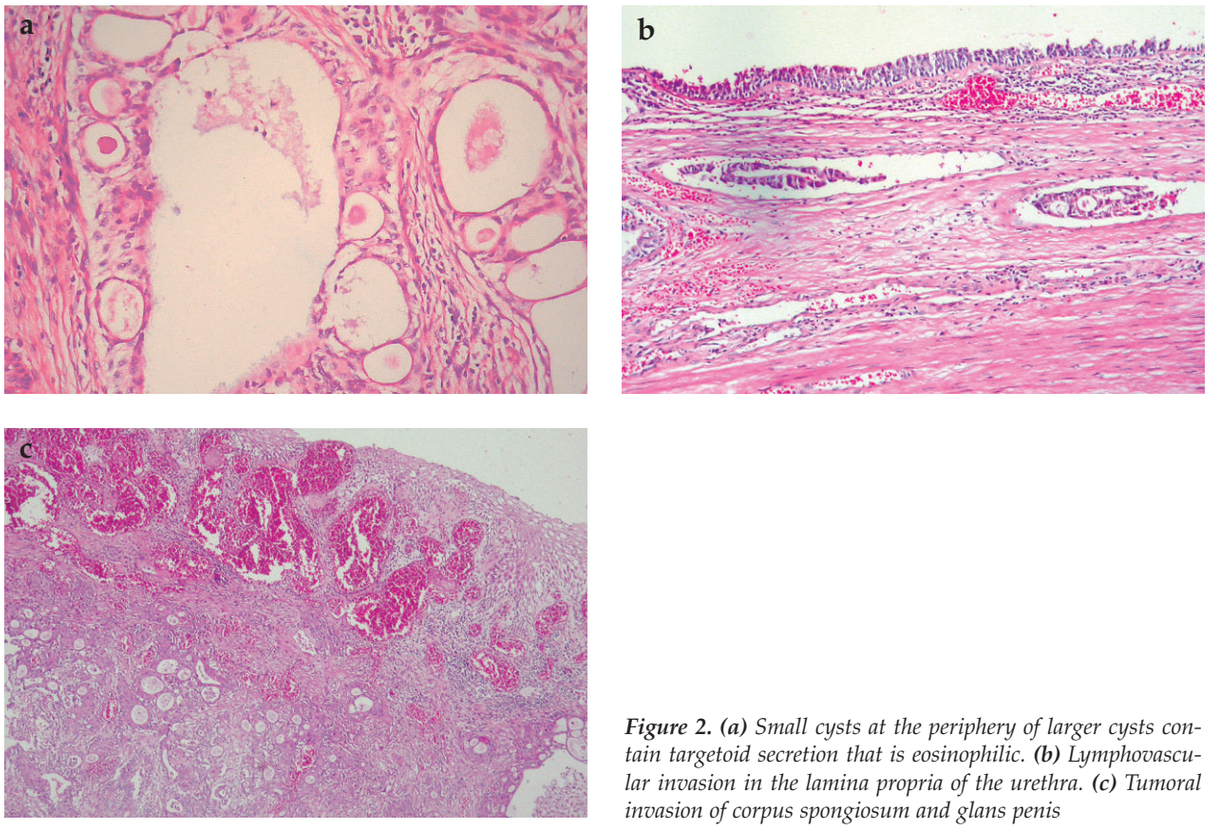

Figure 2. (a) *Small cysts at the periphery of larger cysts contain targetoid secretion that is eosinophilic.* ***(b)*** *Lymphovascular invasion in the lamina propria of the urethra.* ***(c)*** *Tumoral invasion of corpus spongiosum and glans penis*

diameter. The cysts are usually lined by urothelial cells, but in large cysts epithelium may be denuded or lined by flattened cells. A pink-pale, eosinophilic secretion which is usually positive with mucin stains may be present in the centers of the cysts or there may be detached clusters of urothelial cells as well as necrotic material.[3,4] A striking feature, as in our case, is the presence of targetoid eosinophilic secretion in small cysts at the periphery of larger cysts.[3]

In cystectomy specimens, it is unlikely to misdiagnose these tumors, but in smaller specimens it is always possible to confuse mUC with adenocarcinoma and more importantly with benign lesions such as cystitis glandularis or cystitis cystica. Irregular, variably sized and shaped cysts are exceptional in cystitis cystica. Furthermore, deep location in the muscle and/or association of cystic foci with the typical nests of invasive carcinoma are the most important clues to diagnosis of malignancy.[3,4] The cytologic criteria may not always be helpful because sometimes the neoplastic cells lining the periphery of the large cysts have minimal atypia.[4]

There is no information regarding Ki-67 and p53 reactivity in mUC. The neoplastic cells in our case showed high Ki-67 and p53 expression (15% and 70%, respectively). Although there is a need for a larger number of cases to determine the immunohistochemical profile of mUC, given the high Ki-67 and p53 values observed, immunohistochemical detection of Ki-67 and p53 proteins could be helpful in diagnosing malignancy in small biopsy specimens.

Differential diagnosis of mUC with adenocarcinoma is mainly based on the nature of the cells comprising the cyst wall; glandular cells are seen in adenocarcinoma versus urothelial cells in mUC.[3,4]

According to the limited number of studies, this tumor commonly has invasive behavior. Data on survival rates of these patients from three studies demonstrate that only two patients, both of whom had muscle invasion, were reported to be alive 3 and 6 years after the diagnosis.[4,7] Our case followed an aggressive course and presented with penile metastases 11 months after the initial diagnosis of tumor on USG, only 5 months after the initial pathologic diagnosis. In spite of treatment with radical surgery and chemotherapy, he died of disseminated disease with lung and liver metastases 6 months after the operation.

Despite abundant blood supply, tumors metastatic to the penis are not common, with approximately 300 cases reported since 1970.[8] Bladder carcinomas only very rarely metastasize to the penis, however, 75% of the cases with penile metastases originate from genitourinary organs,

with bladder being the most frequent site accounting for 32% of the cases.[9]

Approximately one-third (30%) of all penile metastases are detected concomitantly with the primary tumor, whereas the remaining two-thirds present within a mean interval of 18 months after detection of the primary tumor.[9] In our case there was an approximately 11-month period between the detection of primary tumor and penile metastases. Although the route by which the tumor spreads to the penis is not clear, it may spread by local invasion, growth into the adjacent tissues or by the hematogenous, lymphatic or retrograde venous routes. Even tumor spillage by instrumentation is conceivable.[10,11]

There is no universally accepted treatment for metastatic penile malignancies. Apparent differences in survival seem to be related to the extent of the penile lesion rather than to the treatment used.[11] After the diagnosis the prognosis is usually poor as a result of disseminated disease. The average survival is 3.9 months after the detection of penile metastases.[12] However, total penectomy seems to offer the best chance of survival; there are studies reporting overall survival of 9.2 months to 5 years in the literature.[11,12]

In conclusion, due to the limited number of cases reported in the literature it would be difficult to estimate the prognosis of mUC. We believe that our case supports current knowledge that mUC is a highly aggressive variant of urothelial carcinoma. Therefore, it is crucial not to underdiagnose mUC as a benign process, and keeping this variant of urothelial carcinoma in mind is necessary as it might be seen as a metastatic lesion in any part of body, including the penis.

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