Micropapillary Variant of Urothelial Carcinoma: A Report of 4 Cases and Literature Review

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Micropapillary variant of urothelial carcinoma (MPUC) is an uncommon variant of urothelial carcinoma with high metastatic potential. The cases reported in the literature were associated with high grade and advanced stages of the disease at presentation and had a poor prognosis. Four patients were diagnosed with MPUC at our center. One patient had an MPUC located in the urinary bladder, and the other three had MPUC originating from the kidney and/or the ureter respectively. All these lesions were confirmed pathologically and treated by radical surgery. Three of the four patients were found to be in the advanced stages of the disease. Although adjuvant chemotherapy was administered, the first and second patients died after 15 and 10 months, respectively. The third and fourth patients are being followed up at our hospital 5 and 27 months after surgery, respectively. Clinically, MPUC is far more aggressive than conventional urothelial carcinoma. Patients with MPUC should be diagnosed promptly and treated aggressively. *(Chang Gung Med J 2010;33:461-5)*

Key words: micropapillary variant, urothelial carcinoma, bladder cancer, ureteral cancer

Micropapillary variant of urothelial carcinoma (MPUC) is a rare form of cancer that was first described at the University of Texas M. D. Anderson Cancer Center in 1994.[1] Previous reports have estimated that micropapillary bladder cancer accounts for 0.7% to 5.8% of all cases of urothelial cancer.[1-3] MPUC is often associated with an aggressive course and a poor prognosis. It is often presented as invasive and metastatic disease at the time of diagnosis.[4] Surgery, radiotherapy, and chemotherapy, either alone or as part of combined therapy, have been used to treat MPUC. We present 4 cases of MPUC and review the literature relevant to this disease.

CASE REPORT

Case 1

A 66-year-old male, living in the area affected by the black foot endemic in Taiwan,[5] was initially diagnosed with metastatic carcinoma in the left supraclavicular lymph node. Invasive left renal tumor was suspected on the basis of the results from fluorodeoxyglucose positron emission tomography (FDG-PET) and magnetic resonance imaging (MRI) studies (Fig. 1). The initial diagnosis made on the basis of a fine needle biopsy of the left renal lesion was renal cell carcinoma. Therefore, radical nephrec-

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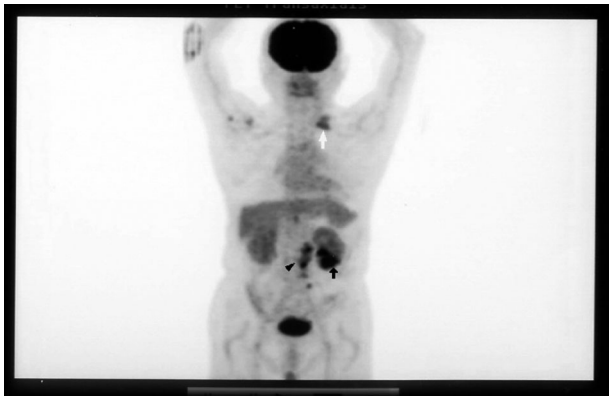

Fig. 1 Fluorodeoxyglucose positron emission tomography (FDG-PET) study demonstrating multiple hypermetabolic lesions in the left supraclavicular lymph node, classical Virchow's node (white arrow), low pole of the left kidney (black arrow), and the para-aortic lymph node (black arrowhead).

tomy was performed on the patient. The tumor was found to be located in the lower portion of the kidney and showed a characteristic infiltration (Fig. 2). However, final pathological diagnosis confirmed MPUC, and the stage was found to be T4N2. Although adjuvant chemotherapy was administered with gemcitabine 1000 mg/m^2 on days 1, 8 and 15, and cisplatin 70 mg/m^2 on day 1 in a 28-day cycle, the disease still progressed and the patient died 15 months after surgery.

Case 2

A 70-year-old male, living in the area affected by the black foot endemic in Taiwan,[5] presented with acute renal failure secondary to invasive bladder cancer. Rectal invasion was suspected (Fig. 3), and the patient underwent total pelvic exenteration with double barrel urine and stool diversion. However, MPUC was diagnosed later, and the stage was found to be T4N2. Adjuvant chemotherapy with gemcitabine and carboplatin was administered. In spite of aggressive surgery, the disease still progressed, and the patient died 10 months after surgery.

Case 3

A 60-year-old male diagnosed with ureteral infiltrative urothelial cancer by ureteroscopic biopsy was referred to our institute from another hospital. He received hand-assisted retroperitoneoscopic

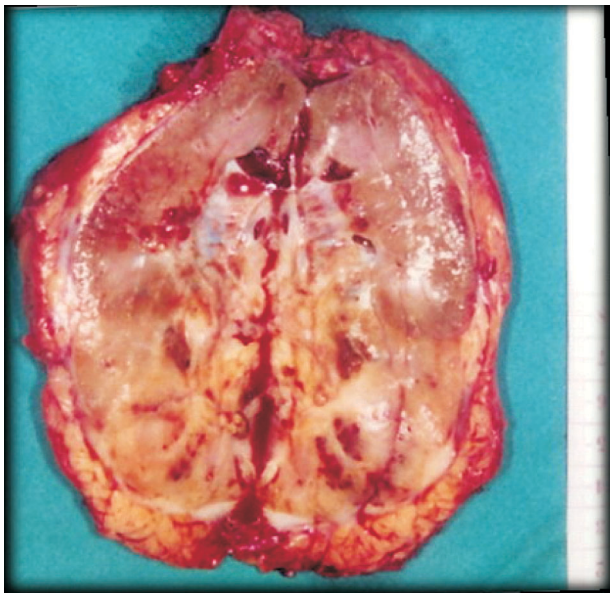

Fig. 2 Gross morphology of the renal tumor: the tumor appeared hard and yellowish and showed infiltration in the lower pole of the left kidney.

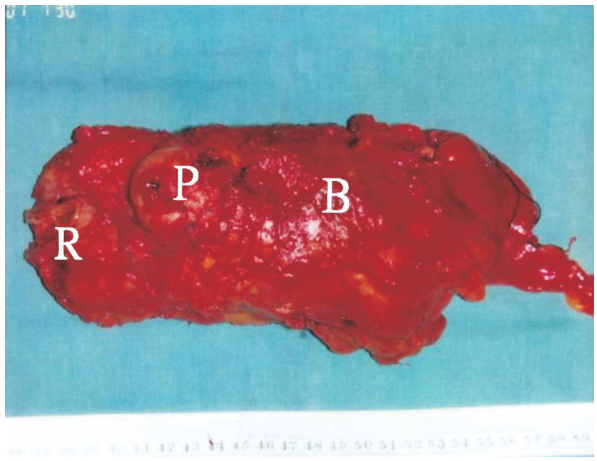

Fig. 3 Total pelvic exenteration of urinary bladder (B), prostate (P), and rectum (R) in the second case.

nephroureterectomy (HARNU) at our hospital. The final pathologic report confirmed MPUC with invasion of the periureteral fat (Fig. 4), which implied that the stage was T3N0. This patient is receiving adjuvant chemotherapy (cisplatin and gemcitabine) and has, so far, been followed up for 5 months after the surgery.

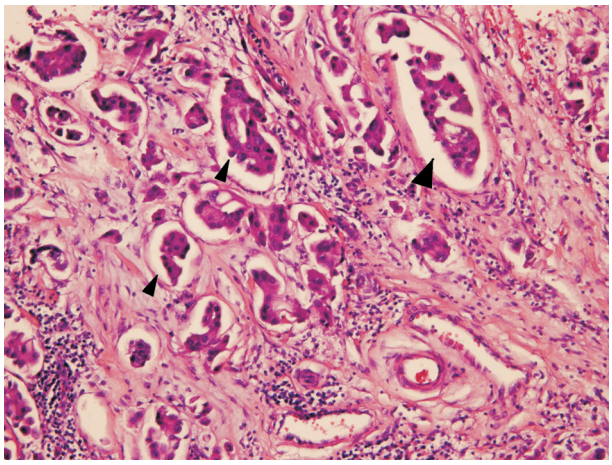

Fig. 4 Microscopic examination of case 3 shows the presence of a secondary micropapillary bud in the stroma of the ureter (black arrow head). (200×)

Case 4

A 67 year-old-female had gross hematuria for 1 month. Retrograde pyelography and CT imaging were used to detect a papillary tumor occupying the renal pelvis of the right kidney. This patient then received HARNU at our hospital. The final pathologic report showed MPUC involving the mucosal layer, which implied that the stage was TaN0. There was no evidence of disease progression during follow-up. However, a papillary urinary bladder tumor was found 27 months after nephroureterectomy, and transurethral resection was performed. The pathological diagnosis of this bladder lesion was invasive, superficial, squamous cell carcinoma of stage T1N0.

DISCUSSION

Medline searches yielded less than 300 cases of MPUC and only 33 cases involving the upper urinary tract. To the best of our knowledge, we report the first four cases in Taiwan. In three cases, the tumor originated in the upper urinary tract. This form of MPUC is especially rare, compared to those reported in other series. It is noteworthy that patients in cases 1 & 2 are both residents of the area affected by the black foot endemic in Taiwan. This area has been reported to have a high prevalence of invasive upper urinary tract tumors.[5-7] DNA analysis by flow cytometry revealed that 79% of the non-diploid patterns were present in the black foot endemic area, whereas only 22% appeared in patients living in other areas of Taiwan.[5]

There is no specific feature that allows definite clinical diagnosis of MPUC. Painless gross hematuria was the most common symptom. It may also result in ulcerative lesions, which may be infiltrated or identical to the typical exophytic papillary lesions characteristic of conventional urothelial carcinoma (CUC). The diagnosis of MPUC is based on the presence of a secondary micropapillary bud in the stroma beneath the urothelium in microscopic studies.[1] It is easily confused with nephrogenic adenoma because of the presence of low-to-intermediate grade cuboidal epithelium with a focal hobnail appearance.[4] Immunohistochemical staining with cytokeratin (CK) 7, CK 20, epithelial membrane antigen, carcinoembryonic antigen, and cytokeratin 34βE12 is positive in both MPUC and CUC. In renal lesions, the high nucleus-to-cytoplasm ratio and tumor mitotic activity may lead to the diagnosis of renal cell carcinoma as in our first case. Such misdiagnosis may occur if the pathological specimen is not examined carefully, because it is usually mosaic in CUC. In the first report by Amin et al.,[1] only 3 of the 18 cases of urinary carcinoma of the urinary bladder were found to contain a micropapillary component of over 90% in the tumor. Therefore, accurate diagnosis is dependent on the experience of the pathologist.

While patients in most reported cases already have locally advanced or metastatic disease at the time of diagnosis, an accurate diagnosis allows for a proper choice of therapy. Treatment of patients with MPUC cannot be performed using protocols similar to those for managing CUC. Kamat et al. have conducted the only studies on patients presenting with MPUC of the bladder with a sufficiently large sample size; they reported that the overall 5-year survival rate was 51%.[8] Bladder-sparing therapy–transurethral resection combined with intravesical Bacille Calmette-Guérin (BCG) instillation–was attempted in 27 of 44 patients of nonmuscle-invasive disease, but the disease progressed in 67% of the patients, and 22% of the patients developed metastatic disease. Because of poor prognosis and ineffectiveness of intravesical therapy, it is suggested that radical surgery be performed once MPUC is diagnosed, even in the early stages.

Alvarado-Cabrero et al.[3] reported that 38 patients with a micropapillary component of more

than 50% had a relative mortality risk 2.4 times higher than that of CUC.[3] MPUC patients with a micropapillary component less than 50% did not have a significantly increased mortality risk. However, we cannot find such a trend in these four cases. The first and second cases had a MPUC component of 40% and 10% respectively, whereas both the third and fourth cases had a MPUC component of 95%. Holmang et al. reported that out of 26 patients who had MPUC of the upper urinary tract,[9] 20 patients (77%) died of the disease and only 7 survived for longer than 5 years. Radiotherapy and chemotherapy have also been reported to yield poor response, and should be applied only for salvage treatment.

We prescribed chemotherapy for our first two patients with metastatic lesions. However, the patients died 15 and 10 months after the diagnosis, respectively. The response of MPUC patients to chemotherapy seems to be poor. The fourth patient suffered from a recurrence of urinary bladder squamous cell carcinoma, which is also known as a highly malignant form of urothelial cancer. It is important to perform further studies to identify the genetic defects in such patients and to determine the biobehavior of this tumor. In southern Taiwan, which has a high prevalence of invasive urothelial cancer, it is a critical issue for pathologists and urologists to identify this disease and to provide aggressive surgery to improve the chances of the patient's survival.

In conclusion, early diagnosis of MPUC and an understanding of its nature have important clinical implications in treatment. Early radical surgery is suggested and should be performed promptly after diagnosis of MPUC.

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微乳突變異之尿路上皮癌；四案例報告及文獻回顧

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微乳突變異之尿路上皮癌 (MPUC) 是尿路上皮癌中一種少見但高惡性度的變異，文獻上曾報告過的案例大多於診斷時呈現高惡性度癌細胞及高癌症分期。本院近 3 年有四位患者診斷爲微乳突變異之尿路上皮癌 (MPUC)，其中一例腫瘤位於膀胱，另外 3 例的腫瘤位於腎臟和 (或) 輸尿管。全部 4 位患者皆接受根治性外科手術並由病理診斷確認分期，而當中有 3 位患者屬於高癌症分期，雖然輔以輔助性化學治療，第一及第二位患者分別死於診斷後 15 及 10 個月。第 3 和第 4 位病患在手術後分別追蹤了 5 及 27 個月。微乳突變異之尿路上皮癌 (MPUC) 較之於一般尿路上皮癌 (CUC) 有更高度侵犯性，患者若有此變異，必須儘快正確診斷並給予積極外科治療。(長庚醫誌 2010;33:461-5)

關鍵詞：微乳突變異，尿路上皮癌，膀胱癌，輸尿管癌

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