The Management of Urothelial Bladder Carcinoma with Synchronous and Bilateral Urothelial Carcinoma of the Upper Tractus at Saint Clair Hospital, South of France

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ABSTRACT

Introduction and Objectives. Urothelial carcinomas can arise throughout the entire urinary tract, the urinary bladder being the predominant point of origin. Synchronous multifocal non-muscle invasive urothelial carcinomas of the bladder (UCB) are not a rare finding. Although rare, the incidence of concomitant bladder and upper urothelial tract tumors (UTUC) is 8–17% and mostly found in recurrences after initial treatment. The aim of this article is to share our individual experience regarding the case management of a patient with synchronous bilateral UTUC and UCB, at presentation, for a better understanding and optimization of future patient care.

Materials and Methods. A late November 2022 evening, Mr. V.J.M, an 81-year-old male patient, is brought into our emergency room at the request of his general practitioner for suspicion of acute ischemic stroke. A kidney and bladder ultrasound (US) scan was performed, finding bilateral hydronephrosis and the presence of a tumor mass measuring almost 3 centimeters on the right lateral wall of the bladder. A non-contrast CT scan confirmed the bilateral hydronephrosis as well as the presence of an endo-ureteral tissue density mass at L4 level on the right side and another an endo-ureteral tissue density mass in regard to the iliac vessels on the left side, highly in favor of urothelial lesions

Results. An urgent urine drainage was granted, the patient undergoing surgery for a bilateral retrograde stent insertion. A second intervention consisting in a transurethral resection of the bladder and bilateral rigid and flexible diagnostic ureteroscopy (URS) was performed. The histopathological examination reported a non-muscle invasive low-grade papillary urothelial carcinoma (NMIBC) for all the lesions of the upper tractus as well as the bladder lesion. The patient then underwent surgery allowing the laser vaporization of all urothelial masses and bilateral double J stents were left in place as to ensure good kidney drainage.

Conclusions. Although the incidence of concomitant bladder and upper urothelial tract tumors is very rare, it is something that we may stumble upon in everyday clinical practice. The management of multifocal and synchronous locations is difficult, requiring a multidisciplinary approach with a meticulous preoperative and postoperative planning as to offer the most adapted treatment plan, where minimal invasive treatment might be offered in highly selected cases as this one. If radical invasive treatment cannot be proposed, a more rigorous follow-up may be useful as not to compromise the oncological results.

Key-words: bilateral UTUC, bladder carcinoma, synchronous, upper urinary tract, urothelial carcinoma

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INTRODUCTION AND OBJECTIVES

Urothelial carcinomas can arise throughout the entire urinary tract, the urinary bladder being the predominant point of origin. Synchronous multifocal non-muscle invasive urothelial carcinomas of the bladder (UCB) are not a rare finding. Although rare, the incidence of concomitant bladder and upper urothelial tract tumors (UTUC) is 8–17% and mostly found in recurrences after initial treatment[1,2]. However, synchronous bilateral UTUC are quite rare and even rarer at the first hospital admission of the patient due to urothelial carcinoma, with 80% of patients in one population-based study having urothelial carcinoma of the bladder diagnosed either before or following diagnosis of UTUC[3]. At the time of diagnosis, almost two thirds of UTUC patients have an invasive tumor, therefore a poor prognosis, with a 5-year overall survival rate of less than 40%[4]. Therefore, being a rare condition, very often the medical and surgical management of these cases requires a multidisciplinary approach with extensive preoperative planning and a tailored treatment conduit.

Thus, the aim of this article is to share our individual experience regarding the case management of a patient with synchronous bilateral UTUC and UCB, at presentation, for a better understanding and optimization of future patient care.

MATERIALS AND METHODS

A late November 2022 evening, Mr. V.J.M, an 81-year-old male patient, is brought into our emergency room at the request of his general practitioner for suspicion of acute ischemic stroke. His personal history consists in moderate obesity (BMI 34.7 kg/m^2), stage three NYHA hypertension with secondary hypertrophic cardiomyopathy, ischemic left parietal lobe stroke with sensory sequelae and stage three smoking related chronic obstructive pulmonary disease (COPD). He also has a family history of malignancies with a father deceased due to a colorectal cancer and a brother due to a metastatic cancer of unknown origin.

The presenting symptoms were, as follows: altered general status, acute onset spatial and temporal disorientation, abnormal gait, nausea with multiple vomiting and cramping in the lower abdomen. During the general physical examination, the patient showed a bilateral costovertebral angle tenderness with suprapubic tenderness and no signs of infection or neurological deficit.

Laboratory investigations showed elevated creatinine levels (472 micromole/l), moderate anemia (hemoglobin = 9.7 g/dL) and a moderately elevated C-reactive protein (62 mg/L). The urine culture was sterile. Acute kidney injury was confirmed (the patient having a creatinine level of 78 umol/l 2 years prior to the current presentation) and an obstructive etiology was suspected.

A kidney and bladder ultrasound (US) scan was performed, finding bilateral hydronephrosis and the presence of a tumor mass measuring almost 3 centimeters on the right lateral wall of the bladder. A non-contrast CT scan confirmed the bilateral hydronephrosis as well as the presence of an endo-ureteral tissue density mass at L4 level on the right side and another an endo-ureteral tissue density mass in regard to the iliac vessels on the left side, highly in favor of urothelial lesions (*fig. 1*).

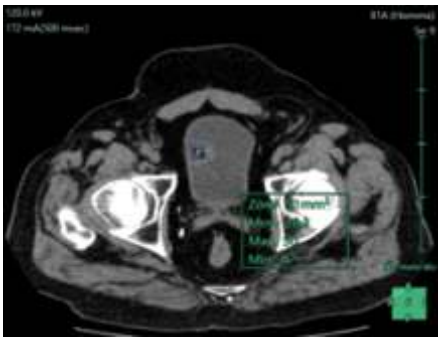


Figure 1. CT aspect of the bladder mass

The bladder had moderately thickened walls with the presence of a dense tissue-like nodular mass of the right lateral portion, measuring 25 mm in diameter, showing no peri vesical fat infiltration. A prior abdominal and pelvic contrast CT scan from 2020 showed no suspect tumor masses in the bladder nor the upper urinary tractus.

RESULTS

An urgent urine drainage was granted, the patient undergoing surgery for a bilateral retrograde stent insertion. The initial cystoscopy found a bladder tumor that at least macroscopically seemed to be non-muscle invasive, without involvement of the ureteral ostiums. The postoperative evolution was favorable.

A second intervention consisting in a transurethral resection of the bladder and bilateral rigid and flexible diagnostic ureteroscopy (URS) was scheduled afterwards. We thus confirmed the presence of the lesions described on the prior CT scan and further characterized them as follows: on the right side, a polypoid stenotic lesion over four centimeters of the lumbar portion of the ureter and a solitary polypoid lesion in the superior calyx. On the left side, a papillary stenotic lesion over two centimeters of the iliac portion of the ureter and a solitary papillary lesion in the renal pelvis. Multiple biopsies were harvested as well as "in situ" urinary cytology samples, subsequently the bladder tumor was resected in an "en bloc" manner as recommended by the recent guidelines[5]. There were no peri operative complications.

The histopathological examination reported a non-muscle invasive low-grade papillary urothelial carcinoma (NMIBC) for all the lesions of the upper tractus as well as the bladder lesion. The urinary cytology found atypical urothelial elements (AUH) and no sign of high-grade urothelial carcinoma using the new PARIS 2022 terminology[6].

No other suspect lesion was revealed using a non-contrast thoracic abdominal and pelvic CT scan (Stage four chronic kidney disease with 28 ml/min estimated filtration rate not permitting contrast use). No other complementary imaging was demanded because of the lack of metastatic symptomatology.

The final diagnostic revealed a non-metastatic non-muscle-invasive urothelial bladder carcinoma with synchronous and bilateral superficial urothelial carcinoma of the upper tractus (pTaN0M0 – using the 2017 TNM classification). The multifocality of the disease, the tumor size (> 2 cm) as well as the bilateral hydronephrosis classified the disease as high-risk [7]. On its own, the bladder carcinoma was classified as low to intermediate risk. The pre-operative evaluation of the kidney function using renal scintigraphy showed a symmetric relative renal function with 54% for the left kidney and 46% for the right kidney for an estimated filtration rate at 39 ml/min (CKD-Epi).

The advanced age of the patient, his multiple comorbidities and a G8 (Geriatric 8) score of 13 prompted us to ask for a comprehensive geriatric assessment (CGA) as part of the pre-operative planning[8]. The CGA showed pathological aging with a 65% risk of mortality at 4 years (LEE score of 9), a CHARLSON comorbidity index of 11 (estimated 10-year survival estimated at 0%)[9,10].

Given the complex nature of the case, a multi-disciplinary tumor board has been assembled to discuss the treatment plan and try to choose a proper therapeutic conduit of the case. The proposed the following theoretical treatment options were, as follows:

1. radical bilateral nephroureterectomy followed by intravesical instillation of mitomycin ad one post-operative dose of intravesical chemotherapy.
2. right radical nephroureterectomy and left kidney-sparing surgery (rigid and flexible ureteroscopy - f-URS - with laser vaporization of the tumors) with eight intravesical instillation of mitomycin and one post-operative dose of intravesical chemotherapy.
3. bilateral kidney-sparing surgery (bilateral rigid and flexible URS - f-URS - with laser vaporization of the tumors) followed by intravesical instillation of mitomycin and one post-operative dose of intravesical chemotherapy.
4. palliative symptomatic treatment by programmed bilateral retrograde stent insertion or nephrostomy in case of stent mounting failure.

The more invasive procedures showed little to no interest because of the patient's poor pre-operative

status with a high complication (24.8- 32%) and mortality (3.7- 7%) risk, as well as the necessity of long-term dialysis[11].

We concluded that the bilateral kidney-sparing surgery was the most suitable treatment option in this particular case. Thus, we opted for a two-time approach abording the left side first (the smallest tumor size and the best relative renal function) and the right side later. The patient, being considered unfit because of his poor global status and a stage 3B chronic kidney disease, was not eligible for neo-adjuvant or adjuvant chemotherapy.



Figure 2. Papillary lesion in the left renal pelvis (before and after vaporization)

days following the last surgery. The patient will be receiving 8 additional weekly intravesical chemotherapy with mitomycin C.

With a high risk of recurrence and death evolving during the follow-up period after surgery, follow-up regimens are mainly based on endourological surveillance and urinary cytology but seeing the high-risk nature of the disease, we opted for a more extensive surveillance involving cystoscopy, bilateral URS with "in situ" urinary cytology and also CT urography and chest CT at 3 and 6 months, and then yearly[12,13].

DISCUSSIONS

While the surgical part of the treatment showed no technical difficulties, the particularities of this case were primarily related to the bilateral and multifocal nature of the upper urothelial tract tumors associated with the synchronous bladder tumor, the patient having no personal history of neither UCB, nor UTUC prior to the diagnostic. Furthermore, an abdominal and pelvic contrast CT scan from

In January 2023, the patient underwent surgery allowing the laser vaporization (Holmium-YAG) of all urothelial masses and bilateral double J stents were left in place as to ensure good kidney drainage. There was no peri operative or anesthesia related complication
The total operative time was 65 minutes for the left side f-URS and 95 for the right-side f-URS. Standard laser parameters were used (using a 272 µm single use laser fiber, 10 Hz frequency, 1 J energy and a pulse width of 800 µs) (*fig.2 and fig.3*).

A single post-operative dose of intravesical chemotherapy (mitomycin C) was administered 10

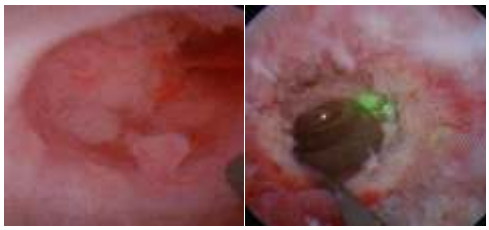


Figure 3. Papillary lesion in the right lumbar ureter (before and after vaporization).

2020 showed no suspect mass in the bladder or the upper urinary tractus at that moment. Another particularity of the above-mentioned case was the advanced age and altered performance status of the patient requiring an extensive geriatric assessment to better adapt the treatment plan, not uncommon seeing that UTUCs have a peak incidence in individuals aged 70-90 years old[14]. At the time of surgery, we considered that upper urinary tract instillation of topical agents could have been interesting for this patient, but we could not follow through seeing that there were no clinical trials involving adjuvant endocavitary treatment at our center or any other centers in our proximity. However, we opted for an early single dose adjuvant intracavitary instillation of mitomycin C as to reduce the risk of local recurrence in the bladder[15].

Taking into consideration that the patient was deemed un-fit for neo-adjuvant or adjuvant cisplatin-based chemotherapy because of his fragility and altered renal function, the research of PD-1 and PDL-1 tumor expression has been demanded as to offer immunotherapy (pembrolizumab or atezolizumab) as alternative treatment[16,17].

We also considered that the patient and his family may benefit from a genetic consultation as to search for an underlying Lynch syndrome (HNPPC - Hereditary Nonpolyposis Colorectal Cancer Syndrome) taking into account the patient's personal and family history of malignancies and the increased risk for upper tract urothelial carcinoma described in patients with Lynch syndrome[18].

Even though we opted for a kidney-sparring surgery, we chose a more frequent and more stringent follow-up compared to radical nephroureterectomy in order not to compromise the oncological results.

CONCLUSIONS

Although the incidence of concomitant bladder and upper urothelial tract tumors is very rare, it is something that we may stumble upon in everyday clinical practice. The management of multifocal and synchronous locations is difficult, requiring a multidisciplinary approach with a meticulous preoperative and postoperative planning as to offer the most adapted treatment plan, where minimal invasive treatment might be offered in highly selected cases as this one. If radical invasive treatment cannot be proposed, a more rigorous follow-up may be useful as not to compromise the oncological results.

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