Successful neoadjuvant chemotherapy for primary invasive small-cell carcinoma of the ureter

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Cite as: *Can Urol Assoc J* 2015;9(5-6):E393-6. <http://dx.doi.org/10.5489/cuaj.2372>
Published online June 18, 2015.

Abstract

We report a case of invasive small-cell carcinoma (SCC) of the ureter successfully treated by neoadjuvant chemotherapy and laparoscopic nephroureterectomy. SCC of the ureter is an extremely rare condition characterized by aggressive behaviour. A 70-year-old male presented with left flank pain; he was diagnosed with SCC of the ureter, cT3N0M0, by ureteroscopic biopsy. The patient received 3 cycles of neoadjuvant chemotherapy with cisplatin and irinotecan (IP) and underwent laparoscopic nephroureterectomy. The pathological diagnosis was urothelial carcinoma, high grade, without a small-cell component. The pathological stage was downstaged to pT2N0M0. Adjuvant chemotherapy was not performed. The patient has been free of local recurrence or distant metastasis for 38 months postoperatively. This is the first reported case of primary invasive SCC of the upper urinary tract treated by neoadjuvant chemotherapy followed by nephroureterectomy.

Introduction

Extrapulmonary small-cell carcinoma (SCC) is a rare neoplasm and has been described in various organs. The urinary bladder and prostate are the major sites for this tumour of the genitourinary tract.¹ SCC of the upper urinary tract has been sporadically reported in case reports and its prognosis is poor.² Recently, the effectiveness of neoadjuvant chemotherapy in SCC of the urinary bladder (SCCUB) was reported.³ The present case is the first reported of successful treatment of primary invasive SCC of the upper urinary tract by neoadjuvant chemotherapy and nephroureterectomy.

Case report

A 70-year-old male with a complaint of left flank pain was referred to our hospital. His medical history included smok-

ing. Computed tomography (CT) showed a 26×11-mm tumour in the middle portion of the left ureter and left hydronephrosis (Fig. 1). Magnetic resonance imaging (MRI) revealed tumour invasion into periureteral tissue. The tumour showed low signal intensity in a T1-weighted sequence and slightly high signal intensity in a fat-suppression T2-weighted sequence. Urine cytology test result was negative.

The patient underwent ureteroscopy and tumour biopsy under general anesthesia. Endoscopically, the tumour was nodular in shape and white in colour. Upon histological examination, atypical small cells with a high nuclear:cytoplasmic ratio were observed. The tumour cells were immunohistochemically positive for cytokeratin (CK) AE1/AE3, CK7, synaptophysin and CD56. The pathological diagnosis was SCC. Neuron-specific enolase (NSE) was 12.8 ng/mL (range: 0–12) and pro-gastrin-releasing peptide (ProGRP) was 72.9 pg/mL (range: 0–70). Chest CT scan, head MRI, and bone scintigraphy showed no evidence of metastases. The clinical stage was cT3N0M0.

Percutaneous left nephrostomy was performed to improve renal function before chemotherapy. Antegrade pyelography revealed complete obstruction of the left ureter (Fig. 2a). The patient received 3 cycles of neoadjuvant chemotherapy with cisplatin/irinotecan. Cisplatin at 60 mg/m² was infused on day 2. Irinotecan at 60 mg/m² was infused on days 1, 8 and 15. This 4-week regimen was administered to the patient. After one cycle of chemotherapy, NSE and ProGRP decreased to 10.6 ng/mL and 46.2 pg/mL, respectively. Antegrade pyelography showed contrast medium flow to the lower portion of the ureter and bladder (Fig. 2b). The patient experienced chemotherapy-related toxicities of grade 1 diarrhea, grade 2 anemia and grade 3 pyelonephritis (Common Terminology Criteria for Adverse Events [CTCAE] ver. 4.0).

Macroscopically, the surgical specimen was cicatrized. Upon microscopic examination, the tumour was composed of urothelial carcinoma without a small-cell component and lymphatic invasion was positive. Immunohistochemically, negative stains were observed for CD56 and synaptophysin

Fig. 1. Computed tomography showing a 26-mm tumour (arrows) in the middle portion of the left ureter and left hydroureter.

(Fig. 3). The pathologic stage was downstaged to pT2N0M0. No adjuvant therapy was given. The patient has been free of recurrence or metastasis for 38 months postoperatively.

Discussion

There are no standard treatments for SCC of the upper urinary tract because there have been no large randomized trials due to the limited number of cases. Ouzzane and

Fig. 2a. Antegrade pyelography. Complete obstruction with left ureteral tumour before chemotherapy.

Fig. 2b. Urine flow to the lower portion of the ureter and bladder after 1 cycle of chemotherapy.

Fig. 3. Microscopic findings and immunohistochemical staining are shown. Tumour cells were positive for synaptophysin.

colleagues reported 39 cases of SCC of the upper urinary tract.² All patients underwent initial surgical treatment. The median overall survival (OS) was only 15 months. The 1- and 3-year survival rates were 58.4% and 23.8%, respectively. The only predictive factor for OS was pathological T stage ($\geq pT3$). Adjuvant chemotherapy was not significantly associated with survival. Most cases were diagnosed after curative surgical treatment. SCC of the urinary tract is similar to that of the lung cancer in terms of pathological and immunohistological findings.⁴

SCC of the urinary bladder is also a chemosensitive disease.¹ Among the types of SCC of the upper urinary tract, SCC of the urinary bladder is the most common and often reported. Radtke and colleagues first reported a markedly improved clinical outcome in patients who had pathologic downstaging by neoadjuvant chemotherapy of the urinary bladder.³ Lynch and colleagues compared clinical outcomes between 48 patients with SCC of the urinary bladder who received neoadjuvant chemotherapy and 47 with initial cystectomy; they found that neoadjuvant chemotherapy resulted in pathologic downstaging at surgery and contributed to a marked improvement in long-term survival.⁵ There was a suggestion that neuroendocrine regimens, such as cisplatin-based regimens, were more effective for a small-cell component than regimens used in urothelial tumours.³

In our case, the patient received neoadjuvant chemotherapy in accordance with the treatment strategies of SCC of the urinary bladder since the tumour was diagnosed as SCC by ureteroscopic biopsy. Chemotherapy regimens involved irinotecan/cisplatin, which is standard for small-cell lung cancer.⁶ After 3 cycles of chemotherapy, the tumour disappeared on CT scan. The pathological findings of the resected specimen were urothelial carcinoma without a small-cell component. These findings indicated that the tumour was composed of SCC and urothelial carcinoma. The patient

received regular examinations by CT scan and cystoscopy and no adjuvant chemotherapy was given. He has been free of recurrence and metastasis 38 months postoperatively.

Diagnosis before curative surgery is essential in SCC of the urinary tract. It is not clear whether neoadjuvant chemotherapy is also effective for upper urinary tract tumours, but good prognosis has been reported in patients with pathological downstaging.⁷ Lynch and colleagues reported that neoadjuvant chemotherapy was associated with improved OS and disease-specific survival (DSS) compared with initial cystectomy (median OS 159.5 vs. 18.3 months, $p < 0.001$; 5-year DSS 79% vs. 20%, $p < 0.001$). Lynch and colleagues also reported that, in patients with initial cystectomy, adjuvant chemotherapy had no impact on OS.³ Localized SCC of the upper urinary tract may be a good indication for neoadjuvant chemotherapy because it is also chemosensitive. With regard to the upper urinary tract, Ahsaini and colleagues reported a case of SCC of the urinary bladder and concomitant ureter treated by neoadjuvant chemotherapy, in which the patient was free of disease for 2 years.⁸ However, there have been no reports of primary SCC of the upper urinary tract treated by neoadjuvant chemotherapy.

In our case, the disappearance of small-cell components by neoadjuvant chemotherapy might have resulted in long-term survival. Ureteroscopic biopsy should be performed before curative surgical treatment to obtain a pathological diagnosis in the treatment of urothelial tumour.

Conclusion

The pathological downstaging and long-term survival in our case support the usefulness of neoadjuvant chemotherapy in treating primary SCC of the upper urinary tract.

Competing interests: The authors declare no competing financial or personal interests.

This paper has been peer-reviewed.

References

1. Mackey JR, Au HJ, Hugh J, et al. Genitourinary small cell carcinoma: Determination of clinical and therapeutic factors associated with survival. *J Urol* 1998;159:1624-9. <http://dx.doi.org/10.1097/00005392-199805000-00058>
2. Ouzzane A, Ghoneim TP, Udo K, et al. Small cell carcinoma of the upper urinary tract (UUT-SCC): Report of a rare entity and systematic review of the literature. *Cancer Treat Rev* 2011;37:366-72. <http://dx.doi.org/10.1016/j.ctrv.2010.12.005>
3. Siefker-Radtke AO, Dinney CP, Abrahams NA, et al. Evidence supporting preoperative chemotherapy for small cell carcinoma of the bladder: A retrospective review of the M.D. Anderson cancer experience. *J Urol* 2004;172:481-4. <http://dx.doi.org/10.1097/01.ju.0000132413.85866.fc>
4. van Hoesel KH, Artymszyn RL. Cytology of small cell carcinoma of the urinary bladder. *Diagn Cytopathol* 1996;14:292-7. [http://dx.doi.org/10.1002/\(SICI\)1097-0339\(199605\)14:4<292::AID-DC3>3.0.CO;2-I](http://dx.doi.org/10.1002/(SICI)1097-0339(199605)14:4<292::AID-DC3>3.0.CO;2-I)
5. Lynch SP, Shen Y, Kamat A, et al. Neoadjuvant chemotherapy in small cell urothelial cancer improves pathologic downstaging and long-term outcomes: Results from a retrospective study at the MD Anderson Cancer Center. *Eur Urol* 2013;64:307-13. <http://dx.doi.org/10.1016/j.eururo.2012.04.020>
6. Noda K, Nishiwaki Y, Kawahara M, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 2002;346:85-91. <http://dx.doi.org/10.1056/NEJMoa003034>
7. Cordier J, Sonpavde G, Stief CG, et al. Oncologic outcomes obtained after neoadjuvant chemotherapy for the treatment of urothelial carcinomas of the upper urinary tract: a review. *World J Urol* 2013;31:77-82. <http://dx.doi.org/10.1007/s00345-012-0960-8>
8. Ahsaini M, Riyach O, Tazi MF, et al. Small cell neuroendocrine carcinoma of the urinary tract successfully managed with neoadjuvant chemotherapy. *Case Rep Urol* 2013;2013:598325. Epub 2013 Aug 18. <http://dx.doi.org/10.1155/2013/598325>

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