Title	Small cell carcinoma of the urinary bladder: a case of remarkable remission with combined chemotherapy
Author(s)	ITOH, Kiichiro; KYAKUNO, Miyaji; SAKAI, Hatsuo; KOKADO, Yukito; SAGAWA, Shiro; SHIN, Takezou
Citation	泌尿器科紀要 (1988), 34(8): 1443-1447
Issue Date	1988-08
URL	http://hdl.handle.net/2433/119666
Right	
Type	Departmental Bulletin Paper
Textversion	publisher

SMALL CELL CARCINOMA OF THE URINARY BLADDER: A CASE OF REMARKABLE REMISSION WITH COMBINED CHEMOTHERAPY

Kiichiro ITOH , Miyaji KYAKUNO, Hatsuo SAKAI, Yukito KOKADO, Shiro SAGAWA and Takezou SHIN

From the Department of Urology, Osaka Prefectural Hospital (Chief: Dr. T. Shin)

A 67-year-old man presented with asymptomatic gross hematuria. Cystoscopy and radiographic studies revealed a large tumor on the left lateral wall of the urinary bladder. Also, computer tomographic (CT) scan of the pelvic cavity showed metastasis to the left external iliac node. The light microscopic appearance of cold punch biopsy specimens for the tumor was closely akin to small cell carcinoma of the lung. Ultrastructurally, the tumor cells exhibited small numbers of neurosecretory granules in the cytoplasm. After surgical treatment, the patient was treated with combined chemotherapy using cis-diamminedichloroplatinum (CDDP) and etoposide. On CT scan, a remarkable remission was shown to have been induced at the metastatic site after three cycles of the therapy. Though the morphology of bladder tumors has not received very much attention, this report emphasizes that detailed pathological examination is of therapeutic importance.

Key words: Urinary bladder tumor, Small cell carcinoma, CDDP, Etoposide

INTRODUCTION

Small cell carcinoma arising in the urinary bladder is very rare, only 10 cases having been reported in the literature[1-5]. These tumors share histologic and ultrastructural figures, including the presence of neurosecretory granules, with small cell carcinoma of the lung. Small cell carcinoma of urinary bladder might be expected to show aggressive biologic behavior and to have a very poor prognosis as does its pulmonary counterpart[6].

Combined chemotherapy is essential in the treatment of small cell carcinoma of the lung[7]. The regimen with adriamycin, cyclophosphamide and vincristine has been most commonly used[8]. Recently, a more effective approach with CDDP and etoposide has been introduced. This regimen is superior to and is partially non-cross-resistant with the former[9]. We report one patient with small cell carcinoma of the urinary bladder who showed a remarkable effect of chemotherapy with CDDP and etoposide at the metastatic site. This is the first report of application of this regimen to small cell carcinoma of the bladder. In addition, it shows the importance of detailed pathological examination in connection with the therapeutic approach to bladder tumors.

CASE REPORT

A 67-year-old man with no remarkable past history sought medical attention because of asymptomatic gross hematuria. Cystoscopy revealed a large tumorous mass on the left side of the urinary bladder that was creating a complete obstruction of the left ureter. The left kidney could not be visualized by intravenous pyelography (IVP). Admission laboratory data and X-ray were not remarkable. The tumorous mass was biopsied and microscopically interpreted as an undifferentiated small cell carcinoma of the urinary bladder with histological resemblance to its pulmonary counterpart, that is, small cells only slightly larger than lym-

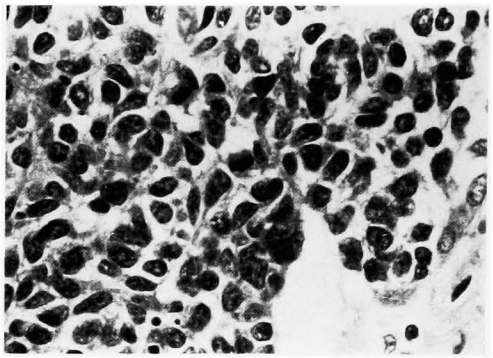

Fig. 1. Small cell carcinoma cells with small, hyperchromatic nuclei and scanty cytoplasm.

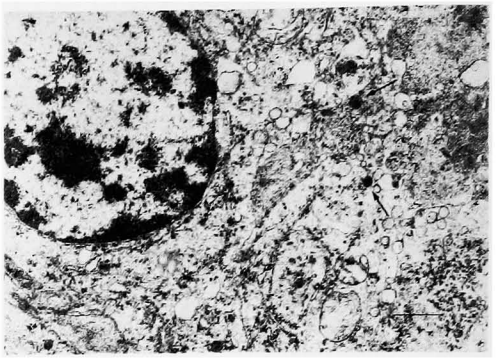

Fig. 2. Ultrastructurally, tumor cells have a few dense-core neurosecretory granules within cytoplasm (arrows).

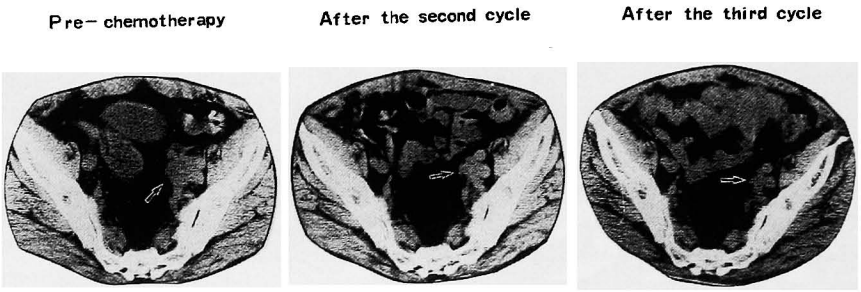

Fig. 3. CT scan of pelvic cavity before and after chemotherapy. After the second and third cycle, and remarkable remission was introduced (arrows).

phocytes, having very scanty cytoplasm and hyperchromatic nuclei, growing in sheets (Fig. 1). Though small cell carcinoma of the lung is often associated with ectopic production of various polypeptide or hormones[10], in this case, endocrinological tests were within normal limits. Metastasis was found in the left external iliac node on CT scan.

A total cystectomy, bilateral ureterocutaneostomy and biopsy of the metastazied node were well tolerated by the patient. The original tumor was necrotic and had infiltrated to the wall. In the non-tumorous areas, no significant dysplasia was noted. Postoperative tumor, node and metastasis classification was pT3b, N1 and M0, respectively. Microscopic features of both the tumor and node were compatible with that of the biopsied specimens preoperatively. Grimelius staining demonstrated numerous carcinoma cells containing granules. Ultrastructurally, tumor cells had small numbers of neurosecretory granules in the cytoplasm (Fig. 2).

Three weeks after the operation, systemic combination chemotherapy with CDDP and etoposide was started at the metastatic site. The patient received three cysles of CDDP and etoposide at the doses of 60 mg and 100 mg per whole body, respectively, on days 1~3 of each cycle with a planned interval of four weeks between the first day of each cycle. He was followed by CT scan of the pelvic cavity. No change was found after the first cycle, but a remarkable remission was introduced after the second and third ones (Fig. 3). The reduction rate was calculated on the long and short diameters of metastatic external iliac node on CT scan. After the second and third cycles, the reduction rate was 73.8 % and 88.3 %, respectively. We wanted to continue chemotherapy to induce complete re-

Table 1. Small cell carcinoma of the urinary bladder in the literature

Reference	Pt.-Age-Sex No.	Presentation	Neurosecretory Granules in Tumor Cells	Metastatic Site	Treatment	Follow Up (mos.)	Comment
Cramer et al.[1]	1-69-Male	Hematuria	+	–	Partial Cystectomy	Well (14)	In Diverticulum Hypophosphatemia
Davis et al.[2]	2-69-Male	Gross Hematuria	+	Bone Marrow, Retroperitoneal lymph node	Radical Cystectomy Chemotherapy	Died (11)	–
	3-60-Male	Hematuria	+	Left Kidney	Radical Cystectomy Chemotherapy	Well (23)	–
	4-79-Male	Gross Hematuria	+	–	Partial Cystectomy	Well (28)	In Diverticulum
Kim et al.[3]	5-77-Male	At Autopsy	–	Lung Paraaortic and Mediastinal lymph node	–	–	–
	6-83-Male	Gross Hematuria	–	–	Transurethral Resection Radiation	Died (2)	–
Reyes et al.[4]	7-64-Male	Gross Hematuria	+	Regional lymph node	Transurethral Resection	Died (5)	Hypercalcemia
	8-40-Male	At Autopsy	+	Regional, Paraaortic, Perirenal lymph node	–	–	Hypercalcemia
	9-66-Male	Gross Hematuria	+	–	Radical Cystectomy	Well (36)	–
Partanen et al.[5]	10-55-Female	At Autopsy	+	Common iliac lymph node, Bone Marrow Liver, Spinal Cord	–	–	ACTH production
Present case	11-67-Male	Gross Hematuria	+	External iliac lymph node	Radical Cystectomy Chemotherapy	Well (10)	–

mission, but the patient rejected further treatment. He was followed closely for 15 months postoperatively with repeated CT scan and X-ray. There was no evidence of regrowth at the metastatic site or of distant metastasis.

DISCUSSION

The incidence of undifferentiated carcinoma arising in the urinary bladder is less than 1.2% of all bladder carcinomas[11], and, among these, carcinomas composed of small cells have been extremely rare. Since first reported by Cramer et al.[1] in 1981, there have been only 10 cases reported in the literature (Table 1). Recognition of small cell carcinoma in a variety of extrapulmonary sites has increased in recent years[12], probably due to the more frequent use of electron microscopy in diagnostic pathology. In the cases of bladder cancer, stage has been demonstrated to be the major determinant of survival[13], and histologic type has been of little attention. The true incidence of urinary bladder small cell carcinoma may, therefore, be higher by more detailed pathological examination for bladder tumors, as Davis pointed out[2].

Morphologically, small cell carcinoma of the bladder, as well as other extrapulmonary counterparts, is very similar to pulmonary small cell carcinoma, in most cases, with nuurosecretory granules, though their presence is not essential. Kim et al.[3] reported two cases that did not manifest these granules.

Small cell carcinoma has often been shown to synthesize and secrete various polypeptide and protein hormones, occasionaly leading to clinical manifestations, the best known being ectopic adrenocorticotropic hormone (ACTH) production[10]. Partanen et al.[4] reported a patient with ACTH production. In our case, serum and urine endocrinological examinations were within normal limits and not all clinical manifestations were noted.

The histogenesis of small cell carcinoma

of the urinary bladder is controversial, and the possibilities have been thoroughly discussed by Cramer et al.[1] He suggested that these tumors may have originated from the neoplastic transformation of metaplastic cells. We have demonstrated small numbers of cells having neurosecretory granules in the basal layer of normal transitional epithelium of the urinary bladder (unpublished data), as Feyrter[14] suggested. These cells may be differentiated from normal mucosal epithelial cells, not from neural crest. Therefore, it seems that small cell carcinoma may originate from normal mucosal cells of the bladder and may have neurosecretory granules.

The prognosis of urinary bladder small cell carcinoma is difficult to evaluate because only 10 cases have been reported to date. However, considering the aggressive behavior and early distant metastasis, including pulmonary and extrapulmonary manifestations, we can assume that the prognosis of the bladder counterpart also is very poor. In small cell carcinoma of the lung, combined chemotherapy plays a central role in the treatment[7]. The regimen with adriamycin, cyclophosphamide and vincristine has been most common[8]. Recently, the regimen with CDDP and etoposide, which is superior to and is partially non-cross-resistant with the former, has been introduced and recognized to be effective[9]. The effectiveness of etoposide, a semisynthetic podophyllotoxin derivative, with or without other agents for lung small cell carcinoma, malignant lymphoma and testicular tumor has been exhibited[15]. For nonseminomatous testicular tumor, in particular, it is now an extremely important agent, mostly in combination with CDDP[16]. Davis et al[2]. reported a case of chemotherapy with adriamycin, cyclophosphamide and vincristine for bladder small cell carcinoma with bone marrow metastasis. We tried a regimen with CDDP and etoposide for the metastasized regional node after surgical treatment. Fig. 3 shows a dramatic remission after three cycles. This suggests that chemotherapy may also play an important role in the treatment of bladder small cell carcinoma as well as its pulmonary counterpart.

These observations emphasize the importance of recognizing small cell carcinoma in the urinary bladder as a distinct entity and the importance of pathological diagnosis including the use of electron microscopy for bladder tumors.

REFERENCES

1) Cramer SF, Aikawa M and Cebelin M: Neurosecretory granules in small cell invasive carcinoma of the urinary bladder. Cancer **47**: 724-730, 1981
2) Davis BH, Ludwig ME, Cole SR and Pastuszak WT: Small cell neuroendocrine carcinoma of the urinary bladder: report of three cases with ultrastructural analysis. Ultrastruct Pathol **4**: 197-204, 1983
3) Kim CR, Lin JI and Tseng CW: Small cell carcinoma of urinary bladder: ultrastructural study. Urology **24**: 384-386, 1984
4) Partanen S and Asikainen U: Oat cell carcinoma of the urinary bladder with ectopic adrenocorticotropic hormone production. Hum Pathol **16**: 313-315, 1985
5) Reyes CV and Soneru I: Small cell carcinoma of the urinary bladder. Cancer **56**:2530-2533, 1985
6) Kato Y, Ferguson TB, Bennet DE and Burford TH: Oat cell carcinoma of the lung: a review of 138 cases. Cancer **23**: 517-524, 1969
7) Aisner J, Alberto P, Bitran J, Comis R, Danieles J, Hansen H, Ikegami H and Smyth J: Role of chemotherapy in small cell lung cancer: a consensus report of the international association for the study of lung cancer workshop. Cancer Treat Rep **67**: 37-43, 1983
8) Kies MS, Mi va J, Chen T and Livingston RB: Value of chest radiation (RT) in limited small cell lung cancer after chemotherapy (CT)-induced complete disease remission. Proc Asco **1**: 141-141, 1982
9) Kim PN and Mcdonald DB: The combination of VP 16-213 and cis-platinum in the treatment of small cell carcinoma of lung. Proc Asco **1**: 141-141, 1982
10) Hande KR and Prez RMD: Current prospectives in small cell lung cancer. Chest **85**: 669-677, 1984
11) Kunze E, Schauer A and Schmitt M: Histology and histogenesis of two different types of inverted urothelial papillomas. Cancer

51: 348-358, 1983
12) Ibrahim NBN, Briggs JC and Corbishley CM: Extrapulmonary oat cell carcinoma. Cancer **54**: 1645-1661, 1984
13) Payne P: Sex, age history, tumor type, and survival. Tumours of the urinary bladder. Neoplastic diseases at various sites. Edited by Wallace DM Vol. 2, pp. 285-306, the Williams and Wilkins Co. Baltimore, 1959
14) Feyrter F: Ueber das urogenitable Helle-Zellen-System des Menschen. Zeitschrift Mikrosk Anat Forsch **57**: 324-327, 1951
15) Radice PA, Bunn PA and Ihde DC: Therapeutic trials with VP-16-213 and VM-26: active agents in small cell lung cancer, non-Hodgkins, and other malignancies. Cancer Treat Rep **63**: 1231-1239, 1979
16) Williams SD, Einhorn LH, Greco FA, Oldham R and Fletcher R: VP-16-213 salvage therapy for refractory germinal neoplasma. Cancer **46**: 2154-2158, 1980
(Accepted for publication August 26, 1987)

和文抄録

化学療法が著効を示した膀胱小細胞癌の1例

大阪府立病院泌尿器科（部長：新　武三）
伊藤喜一郎，客野　宮治，堺　　初男
小角　幸人，佐川　史郎，新　　武三

膀胱に発生する未分化癌は膀胱腫瘍の約1.2％といわれており，そのうち小細胞癌の頻度は極めて稀である．今回，われわれは，膀胱小細胞癌の1例を経験したので，治療を含め若干の文献的考察を加えて報告する．

（泌尿紀要 **34**: 1443-1447, 1988）