

TRANSITIONAL CELL CARCINOMA OF THE RENAL PELVIS IN A PATIENT WITH CYCLOPHOSPHAMIDE THERAPY FOR MALIGNANT LIMPHOMA: A CASE REPORT AND LITERATURE REVIEW

Yoshiyuki SHIGA, Koichiro SUZUKI, Masakazu TSUTSUMI and Satoru ISHIKAWA

From the Department of Urology, Hitachi General Hospital

Cyclophosphamide is considered to be a bladder carcinogen and there are many reports of secondary bladder cancer, while only a few cases of upper urothelial cancer have been described.

A 59-year-old man, who had received cyclophosphamide therapy for malignant lymphoma, was suffering from gross hematuria and consulted our institute. Computerized tomography (CT), intravenous pyelography (IVP) and retrograde pyelography (RP) revealed a left renal pelvic tumor. Urinary cytology showed class V and radical left nephroureterectomy was performed. Histopathological diagnosis of the left renal pelvic tumor was transitional cell carcinoma, invading the renal parenchyma. He is free from recurrence eight months after surgery. To our knowledge, this is the third case of cyclophosphamide-induced upper urothelial carcinoma reported in Japan, and the twelfth reported in the English literature.

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Key words: Renal pelvic tumor, Cyclophosphamide, Secondary cancer

INTRODUCTION

Cyclophosphamide is an alkylating chemotherapeutic agent that is widely used to treat many neoplasms. It is also used in patients with non-neoplastic diseases, such as serious autoimmune diseases and to prevent rejection of organ allografts. Hemorrhagic cystitis and secondary cancer in the bladder are well-recognized complications of cyclophosphamide therapy¹⁾, however, cyclophosphamide-induced upper urothelial tumors have rarely been described. We report a case of transitional cell carcinoma of the renal pelvis in a patient who had received cyclophosphamide therapy for malignant lymphoma. To our knowledge, this is the third case in Japan, and the twelfth case in the English literature of cyclophosphamide-induced upper urothelial carcinoma.

CASE REPORT

A 59-year-old man with no history of tobacco smoking, who had received 4.9 gm cyclophosphamide and adjuvant radiation of 50 Gy as therapy for malignant lymphoma in 1996, was suffering from gross hematuria and consulted our institute. Initial blood counts and blood chemistry were normal, except for slight anemia and a mild elevation of alanine-aminotransferase.

An enhanced computerized tomography (CT) demonstrated a solid mass, measuring 2 cm in diameter, in the renal pelvis of the left kidney without lymphadenopathy, suggesting no recurrence of malignant lymphoma (Fig. 1). An intravenous

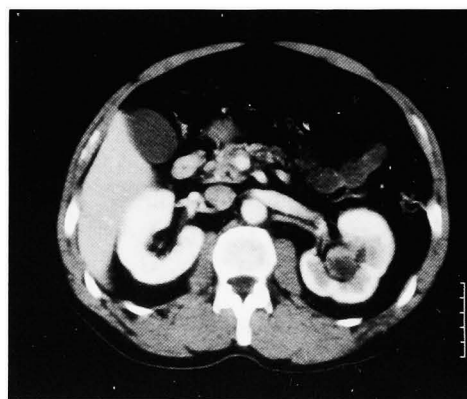


Fig. 1. An enhanced CT demonstrated a solid mass, measuring 2 cm in diameter, in the renal pelvis of the left kidney without lymphadenopathy.

pyelography (IVP) showed a non-visualized left kidney and retrograde pyelography (RP) revealed a filling defect in the upper calyx of the left kidney (Fig. 2). Cystoscopy revealed no bladder tumors. Urinary washing cytology of the renal pelvis showed class V. A left radical nephroureterectomy was subsequently performed in May, 2000. A cross section of the specimen showed a pedunculated papillary tumor, measuring 2 cm in diameter, in the upper calyx and no tumor in the other urinary tract. Histopathological diagnosis was transitional cell carcinoma, grade 2 (G2), pT2, pR0, pL0, pV0 and pNx (Fig. 3). No adjuvant therapy was administered. He is free from recurrence eight months after surgery.

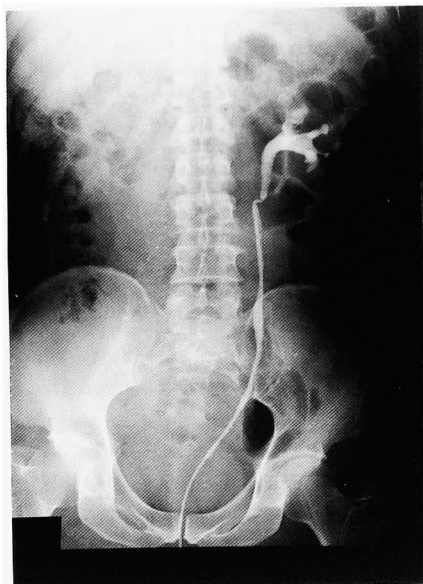


Fig. 2. Retrograde Pyelography revealed a filling defect in the upper calyx of the left kidney.

DISCUSSION

Since Worth et al.¹⁾ reported secondary bladder cancer in patients given cyclophosphamide therapy in 1971, over one hundred cases have been reported. In 1981, McDougal²⁾ reported the first case of cyclophosphamide-induced renal pelvic tumor and Inagaki et al.³⁾ described the first case report in Japan in 1998. Cyclophosphamide-induced upper urothelial tumors are rare. To our knowledge, this is the third case in Japan, and only 11 cases⁴⁻¹¹⁾ have

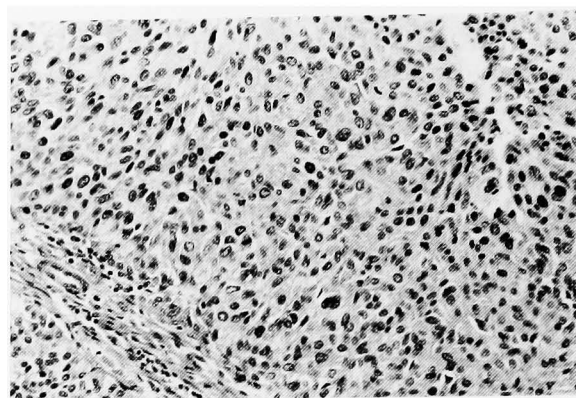


Fig. 3. Microscopic appearance of the renal pelvic tumor. Grade 2 (G2) transitional cell carcinoma invades to renal parenchyma.

previously been reported in the world. We reviewed all cases of cyclophosphamide-induced upper urothelial tumors as shown in Table 1. The cumulative dose ranged from 4.9 gm in this case to 275 gm and the average dose was 138.7 gm. The latency period, defined as the time from the initiation of cyclophosphamide therapy to the diagnosis of renal pelvic tumor, ranged from 27 months to 23 years. The most common histological type was high grade or invasive transitional cell carcinoma, except for squamous cell carcinoma in one case²⁾ Consequently, most prognoses are poor because of the high-grade cancer. Neither previous radiation therapy nor gross hematuria as hemorrhagic cystitis was found to be a significant risk factor for the development of upper urothelial cancer. In this

Table 1. Reported cases of cyclophosphamide-induced upper urothelial cancer

No.	Author	Age/Sex	Original disease	Cyclophosphamide total dose (g)/Latency	Pathological diagnosis	Prognosis	Tumor location
1	McDougal (1981)	47/F	Cerebral vasculitis	182/5 y	SCC	2 m dead	Rt ureter
2	Fuchs (1981)	56/M	Lymphoma	150/9 y	TCC G3	8 w dead	Lt renal pelvis
3	Fuchs (1981)	52/M	Reticular cell sarcoma	275/8 y	TCC G3	2 m dead	(?) renal pelvis
4	Schiff (1982)	81/F	Interstitial pneumonia	230/27 m	TCC G4 invasive/CIS	3 m dead	Lt ureter/renal pelvis
5	Brenner (1987)	68/F	Non-Hodgkin's lymphoma	60/10 y	TCC poorly	5 m dead	Lt ureter/renal pelvis
6	Shetty (1987)	61/F	Ovarian cancer	116/8 y	TCC moderate	Not described	Rt ureter
7	Cannon (1991)	43/M	Hodgkin's lymphoma	146/23 y	TCC non-invasive	Not described	Lt ureter
8	Levine (1992)	20/M	Malignant hemangiopericytoma	29/6 y	TCC G2 invasive	4 m alive	Rt renal pelvis
9	Inagaki (1998)	57/F	Non-Hodgkin's lymphoma	290/17 y	TCC G3 pT3	6 m alive	Lt renal pelvis
10	Rhode (1998)	46/F	Hodgkin's lymphoma	not described/14 y	TCC G 2-3 pT3b	12 m dead	Lt ureter
11	Yoshimura (1998)	24/M	Rhabdomyosarcoma	43/14 y	TCC G2 pT1	17 m alive	Lt renal pelvis
12	Present case (2001)	59/M	Non-Hodgkin's lymphoma	4.9/4 y	TCC G2 pT2	8 m alive	Lt renal pelvis

TCC: transitional cell carcinoma, SCC: squamous cell carcinoma.

case, he had received a lower dose of cyclophosphamide compared to other cases, and had no history of hemorrhagic cystitis or tobacco smoking.

In 1979, Fairchild et al.¹²⁾ reported that cyclophosphamide use creates a 9-fold increased risk of bladder cancer and a 45-fold increased risk of urothelial cancers. Travis et al.¹³⁾ reported that with a cumulative dose of 20 to 49 gm, cyclophosphamide use creates a 6-fold increased risk of bladder cancers and a 14.5-fold increased risk of urothelial cancers. Stain et al.¹⁴⁾ mentioned oncogenic doses greater than 50 gm. Doses as small as 4 gm have been implicated, although the average in the reported cases of bladder cancer was 152 gm¹⁵⁾. It is thought that our case is the third lowest dose in cyclophosphamide-induced secondary urothelial cancers previously reported. In 1978, Pearson and Soloway¹⁶⁾ reported a case of adenocarcinoma of the bladder associated with malignant lymphoma after cyclophosphamide therapy with 3 gm as the total dose. Four years after the initial tumor, the patient experienced gross hematuria. Cystoscopy and biopsy of the bladder revealed adenocarcinoma. A radical cystectomy and bilateral pelvic lymphadenectomy with ileal loop urinary diversion was performed. The patient is well without evidence of metastatic disease or lymphoma thirty-three months postoperatively. The second lowest dose case was suggested in a previous report¹⁵⁾, but it was not confirmed.

On the other hand, neither the total dose of cyclophosphamide nor the cumulative time of receiving cyclophosphamide therapy was found to be a significant risk factor for the development of bladder cancer¹⁷⁾. Moreover, there is no difference between cyclophosphamide-induced carcinoma and usual urothelial carcinoma, and it may be difficult to directly relate cyclophosphamide-induced tumors in each case. Our case with low cyclophosphamide without cystitis cannot be excluded as a secondary cancer, because the incidence of cyclophosphamide-induced cystitis and its relation to the development of bladder cancer have not been defined in the literature.

In the mechanism of bladder carcinogenesis by cyclophosphamide, acrolein, a byproduct of metabolized cyclophosphamide in the liver, has been investigated for its relation to carcinogenesis in the bladder of rats^{14,17)}. Patients with a history of smoking in the immunosuppressive conditions of receiving cyclophosphamide developed early bladder cancer with a lower total dose of cyclophosphamide¹⁷⁾. In the upper urothelial cancers reviewed, smoking was not described in any cases and is unconfirmed as a risk factor for the development of upper urothelial cancer. Upper urothelial tumors associated with cyclophosphamide have previously been rarely reported compared to secondary tumors

in the bladder. In general, renal pelvic tumors are considered to account for approximately 5% of all urothelial tumors. It is thought that the reason for the low incidence of secondary upper urinary tract cancer is related with the passage time of urine. Prompt passage of urine may minimize contact between acrolein and urothelial mucosa.

Talar-Williams et al.¹⁸⁾ described that the incidences of bladder cancer after previous exposure to cyclophosphamide were 2% at 5 years, 5% at 10 years, and 16% at 15 years. Close follow-up is necessary for the early detection and treatment of urinary tract cancers in cyclophosphamide-treated cases. The prognosis will be improved when initial radical cystectomy is performed for cyclophosphamide-induced cancer with any sign of invasion, but, these tumors are high grade, rapidly growing and invasive, with a high recurrence rate¹⁵⁾.

It is important that good hydration, and adequate and frequent emptying of the bladder are employed to decrease residual urine for protection against tumor formation. The use of 2-mercaptoethane sulfonate (MESNA), that specifically binds acrolein, is also an effective management for the prevention of hemorrhagic cystitis and secondary cancer¹⁵⁾. The best way to monitor patients with cyclophosphamide is unclear, but routine yearly cystoscopy, intravenous pyelography, and urinalysis of cytology is recommended for those with hematuria or significant irritative symptoms.

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和文抄録

Malignant lymphoma に対する Cyclophosphamide 投与後に
発症した腎盂腫瘍の 1 例

日立総合病院泌尿器科（部長：石川 悟）

志賀 淑之，鈴木康一郎，堤 雅一，石川 悟

Cyclophosphamide（以下 CPM）は膀胱発癌のひとつの因子として考えられ，膀胱癌については多くの報告があるが，上部尿路発癌に関しては散見するにすぎない。症例は59歳，男性。Malignant lymphoma に対して CPM が投与され，肉眼的血尿を主訴に当科紹介受診した。CT，IVP，RP にて左腎盂腫瘍を認め，尿細胞診はクラスVで 根治的左腎尿管全摘除術が施行された。病理組織学的診断は移行上皮癌，G2，

pT2，pR0，pL0，pV0，pNx であったため，追加治療は行わなかった。われわれが調べたかぎりでは，本症例は CPM に誘発された上部尿路腫瘍としては本邦3例目と考えられ，尿路2次発癌の CPM 投与量としては3番目に低い投与量で文献的考察を加え報告した。

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