

Invasive Bladder Cancer after Cyclophosphamide Administration for Nephrotic Syndrome- A Case Report

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ABSTRACT

We report a case of invasive bladder cancer after cyclophosphamide administration for nephrotic syndrome, and briefly discuss the association of bladder cancer and cyclophosphamide.

A 6-year-old boy, who was diagnosed as having nephrotic syndrome, was treated with oral administration of prednisolone and cyclophosphamide for 4 years, receiving a total dose of 49.5 g cyclophosphamide. At age 27, a gross hematuria with bloody clots appeared and he presented with postrenal renal failure. He underwent a radical cystourethrectomy and ileal conduit for stage a pT3a pN0 M0 transitional cell carcinoma of the bladder. He was not given any adjuvant treatments because of his renal insufficiency, and he died from the disease 14 months after radical surgery.

Key words: *Bladder cancer, Cyclophosphamide, Nephrotic syndrome*

Cyclophosphamide, a cytotoxic alkylating agent, is widely used in various malignancies, immune disorders and organ transplantation¹⁾. Cyclophosphamide is known to cause hemorrhagic cystitis and, rarely, bladder fibrosis and has also been associated with urothelial malignancies, both upper urinary tract cancer as well as bladder cancer²⁾. We report a case of invasive bladder cancer after cyclophosphamide administration for nephrotic syndrome, and briefly discuss the association of bladder cancer and cyclophosphamide.

CASE REPORT

A 6-year-old boy, who was diagnosed as having nephrotic syndrome in 1974, was treated by oral administration of prednisolone and cyclophosphamide for 4 years, receiving a total dose of 49.5 g cyclophosphamide. Although the disease was clinically well-controlled by methylprednisolone, he sometimes complained of gross hematuria.

In December 1996 when the patient was aged 27, the gross hematuria developed to produce a discharge of bloody clots, but he was not referred to a urologist because the discharge was considered to be caused by his hematuria, with the result that his nephrotic syndrome became worse. Since the gross hematuria with bloody clots did not disappear and a general tiredness and an elevation of serum creatinine occurred, he presented

at the Department of Nephrology, Hiroshima University Hospital on April 25, 1997. An abdominal ultrasound revealed bilateral hydronephrosis and a large mass on the posterior of the bladder. He was presented to our Department and immediately underwent right percutaneous nephrostomy.

Physical examination revealed a moon face and striae atrophicae on the abdomen. Blood pressure was 130/80mmHg, and endogenous creatinine clearance (CCr) was 42.9 ml/min. An abdominal computed tomography (CT scan) demonstrated left hydronephrosis and a muscle-invasive bladder tumor on the posterior wall of the bladder. A chest X-ray, CT scan and bony survey revealed no evidence of distant metastases or lymphadenopathy. Cystoscopy showed a hen egg-sized, broad-based, solid tumor on the trigone of the bladder and biopsy demonstrated a muscle-invasive transitional cell carcinoma grade 3, ly (-), v (-), INF β .

On June 16, he underwent radical cystourethrectomy and ileal conduit for the muscle-invasive bladder cancer. The removed bladder contained a 4 × 3 cm tumor with irregular ulceration (Fig. 1). Microscopic examination revealed a transitional cell carcinoma grade 3, pT3a pN0 pL2 pV1, INF β (Fig. 2A, 2B).

He did not received any adjuvant therapy because his endogenous CCr was less than 50 ml/min and he was eager to go back to his job as

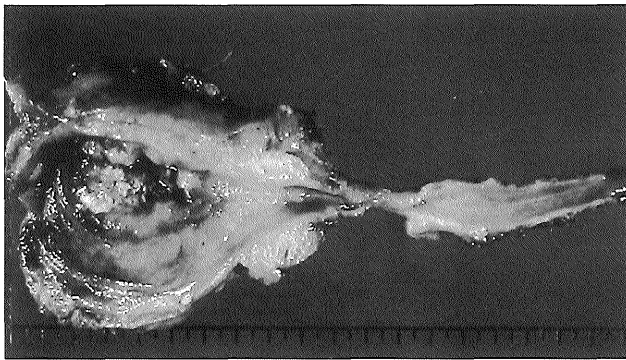


Fig. 1. The removed bladder contained a 4 × 3 cm tumor with irregular ulceration.

soon as possible. Unfortunately, local recurrence was found in April 1998, and he died from the disease on August 8, 1998.

DISCUSSION

Cyclophosphamide is a biologically inactive nitrogen mustard compound that is absorbed by the gastrointestinal tract and metabolized in the liver into its active metabolites, 4-ketocyclophosphamide, carboxyphosphamide, acrolein and phosphoramidate. The later two metabolites are excreted into the urine and they are responsible for cytotoxic and mutagenic effects on the urothelium¹⁾. Therefore, cyclophosphamide is known to cause hemorrhagic cystitis and has also been associated with urothelial malignancies⁹⁾.

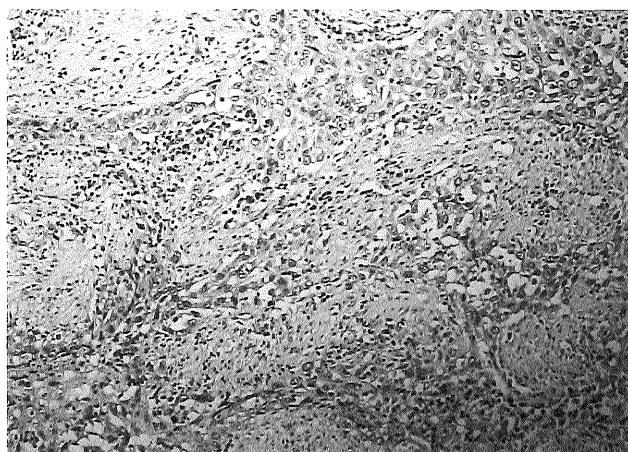
Since Worth et al reported the first two cases of cyclophosphamide related bladder cancer in 1971⁹⁾, many cases of cyclophosphamide associated urinary bladder cancers have been reported^{2,7)}, with the suggestion that cyclophosphamide may have induced bladder cancer. Both animal experiments⁶⁾ and epidemiological investigations^{3,5,8)} have shown that the risk of bladder cancer is directly related to the duration and total administered dose of

cyclophosphamide, and that this risk might persist for longer than 10 years after termination of therapy⁷⁾. Patients receiving more than 50 g cyclophosphamide, for longer than 12 months, and those with a history of cyclophosphamide cystitis appear to be a high-risk group. Therefore, Stein et al advocated that annual urinalysis should be performed on all patients in the high-risk group. If hematuria is detected, further evaluation with excretory urography, urine cytology and cystoscopy with biopsy of any suspicious lesion is indicated⁷⁾.

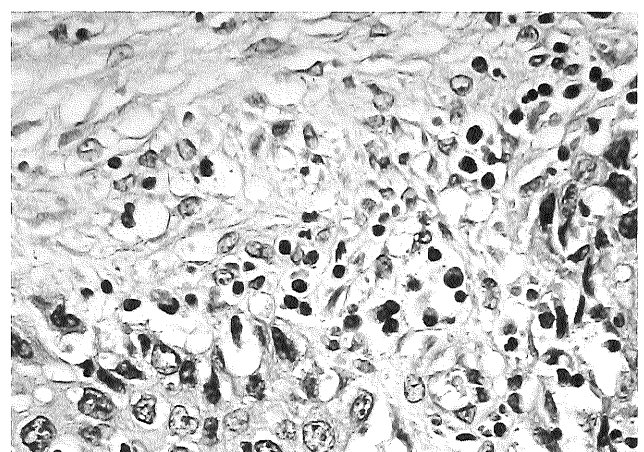
Fernandes et al reviewed 12 cases of cyclophosphamide-associated bladder cancer and found the characteristics of these cancers⁴⁾. Cyclophosphamide induced tumors frequently appear in younger patients and occur equally in both sexes. Frequently, these tumors are of high grade, rapidly growing and invasive. Even when the tumors are initially of low grade and stage, the recurrence rate is high and progression to a higher stage is common after transurethral resection, probably because these neoplasms frequently occur in patients with a potentially damaged immune system. For this reason, radical cystectomy is generally appropriate for bladder cancers showing any sign of invasion and for recurrent high grade cancers, even if noninvasive⁴⁾.

To prevent epithelial injury by acrolein, good hydration and adequate, frequent emptying of the bladder minimizes contact with acrolein, though use of substances such as 2-mercaptoethane sulfonate (mesna) that specifically bind acrolein may be more effective. However, alkylating agents can cause direct deoxyribonucleic acid damage and concurrent use of mesna does not guarantee protection against tumor formation⁴⁾.

The present case corresponded to the high-risk group, because the duration of oral ingestion of cyclophosphamide was 4 years and the total dose



A



B

Fig. 2. Microscopic examination revealed that tumor cells containing hyperchromatic pleomorphic nuclei were growing in a solid pattern forming a sheet arrangement. These findings indicated transitional cell carcinoma grade 3, pT3a pN0 pL2 pV1, INF β (2A: × 100, 2B: × 400).

reached approximately 50 g. Unfortunately, since he was diagnosed as having nephrotic syndrome, which can cause gross hematuria, and was treated with cyclophosphamide, cyclophosphamide-induced bladder cancer was not taken into consideration although gross hematuria sometimes occurred. He was finally diagnosed when postrenal renal failure, caused by invasive bladder cancer, developed.

Therefore, careful observation is undoubtedly important for patients treated with cyclophosphamide. However, for patients with hematuria, urological evaluation with excretory urography, urine cytology and cystoscopy should be completed, in case another disease that may cause gross hematuria, such a nephrotic syndrome, is also present.

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