

## Bladder tumor associated with phenacetin abuse: A case report and a review of the literature.

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We herein report the case of a bladder tumor in an 85-year-old man who had been engaged in phenacetin abuse. He had been taking phenacetin owing to migraine headaches since he was 45 year of age. His total intake of phenacetin was approximately 7.3 to 11.5 kg over a period of years. He visited the Department of Urology in our hospital due to gross hematuria and pain on urination. IVP and a pelvic CT scan revealed a tumor mass on the right lateral wall of the urinary bladder. TUR-BT was performed. A histopathological examination of the resected specimen was diagnosed as urothelial carcinoma, grade 2~3, pT<sub>2</sub>N<sub>0</sub>M<sub>0</sub>. To our acknowledge, only 24 cases of urothelial tumors owing to phenacetin abuse have been previously reported in the Japanese literature, making this the 25 th such case to be reported in Japan.

**Key words:** phenacetin, urothelial carcinoma

### INTRODUCTION

The long term administration of analgesics, including phenacetin, sometimes leads patients to suffer from analgesic abuse. When treating patient with phenacetin abuse, urologists must not only recognize the characteristic side effects related to chronic analgesic therapy, such a methemoglobinemia and duodenal ulcers, but also interstitial nephritis, renal papillary necros and urothelial tumors [1] [2].

Although more than 120 cases of urothelial tumors due to phenacetin abuse have been reported in Europe and the US, very few reports dealing with this problem have been published in the Japanese literature [3]. To date, only 25 such cases have been reported including the present case. We encountered a case of a urinary bladder tumor associated with phenacetin abuse and herein report the clinical course with some bibliographical coments.

### CASE REPORT

The patient was an 85-year-old male who visited Nerima General Hospital due to the chief complaint of pain on urination and gross hematuria.

Regarding his past history, he was diagnosed to have schizophrenia at 20 years of age and had been on drug therapy ever since.

He began to suffer from pain during urination delete in addition to an increased frequency and thus visited a local clinic. A diagnosis of urinary tract infection was established and he was given antibiotics for two weeks. He was thereafter referred to our hospitak

because the antibiotic therapy did not improve his symptoms. Intravenous pyelography performed in the outpatient department revealed right hydronephrosis and a filling defect was disclosed on a cystgram. A pelvic CT scan showed a relatively large tumor on the right wall of the urinary bladder (Fig. 1 and 2).

Regarding the history of drug therapy, the patient had been given a daily dosage of 500~750 mg as the amount of phenacetin for about 40 years for the treatment of pers stent migraines.

The patient was admitted to Nerima General Hospital due to a diagnosis of a urinary bladder tumor associated with phenacetin abuse. The physical exam was as follows: his temperature was 37.8 °C and his pulse 90/min regular. The superficial lymph nodes were not palpable. The palpable conjunctiva appeared to be anemic. He spent almost all day in bed and his condition was compatible with a performance status 3.

The laboratory data conducted on admission showed a red blood cell count of  $344 \times 10^4 / \text{mm}^3$ , a white blood cell count of  $10100 / \text{mm}^3$ , Hb of 10.5 g/dl, Ht of 30.9%, BUN of 28 mg/dl and Creatinine of 1.9 mg/dl.

The patient underwent TUR-BT. A non-papillary tumor was observed in the region from the right wall of the urinary bladder to the trigone on a resectoscopic examination and these findings were the same as those for IVP imaging and an abdominal CT scan. A histopathological examination of a resected tissue specimen revealed an irregular arrangement of cells, which included spindle-shaped and bizarre cells.

These histological findings were classified as

urothelial carcinoma G2~3 (Fig. 3). Tumor cells had invaded the muscle layer. Although an abdominal ultrasound examination and an abdominal CT scan were performed postoperatively to detect any distant metastasis, no findings suggesting metastasis were found. As a result of the pathological manifestation, the histopathological findings were considered to indicate pT<sub>2</sub>N<sub>0</sub>M<sub>0</sub>. The postoperative course was uneventful. According to the results of a histological examination and stage classification, a total cystectomy is generally indicated in patients with bladder tumors. Considering the patient's age, however, his poor overall condition (performance status 3) and renal failure, we selected conservative therapy consisting of the instillation of Pirarubicin hydrochloride and the oral administration of Doxifluridine. Three months after being discharged, he stopped visiting our hospital and his subsequent course is presently unknown.

### DISCUSSION

Some of the characteristic side effects of phenacetin, which is an aniline analgesic and antipyretic agent, on the urinary tract worthy of particular mention include interstitial nephritis, renal papillary necrosis and urothelial tumors; the development mechanisms of these diseases have previously been discussed by several

researchers.

In general, phenacetin is metabolized by acetaminophen after dehydration in the liver and thereafter it undergoes either sulfate acid or glutamic conjugation in the kidneys; the remaining free phenacetin is then excreted into the urine. Excessive acetaminophen results in the depletion of glutathione and the accumulation of acetaminophen oxides and an activated reaction may thus occur [4] [5].

The reflux of acetaminophen into the kidneys and its concentration in the renal medulla contribute to the inhibition of prostaglandin synthesis, thus leading to renal medullary ischemia and renal papillary necrosis. The resulting tubular obstruction promotes an enlargement of the renal cortex and the formation of a histological background of interstitial nephritis. The incidence of nephropathy is said to increase when the total dosage of phenacetin exceeds 2 kg [6].

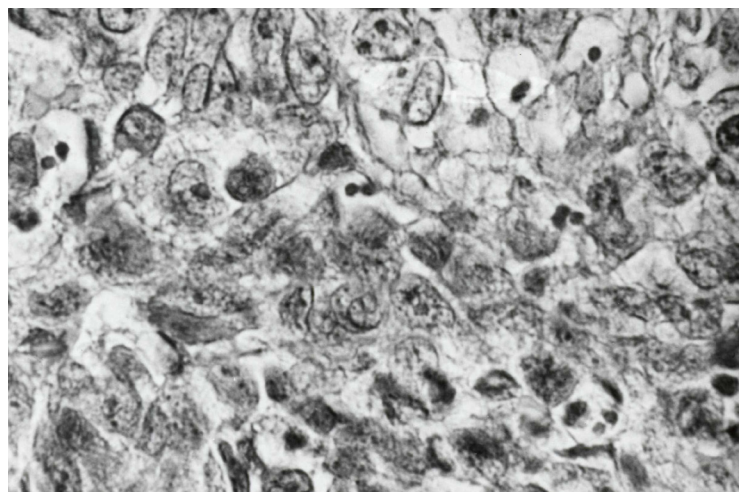
Nephropathy induced by phenacetin abuse is histologically characterized by interstitial nephritis. In these cases, tubular vitrification is generally more clearly observed than glomerular destruction. The characteristic findings obtained in clinical laboratory tests are a reduction in the urinary concentrating ability and a decrease in the PSP-15 min value. Furthermore, only a slight reaction is detected by the



**Fig. 1** IVP revealed right hydronephrosis and a filling defect in the urinary bladder.



**Fig. 2** A pelvic CT scan showed an invasive tumor in the right lateral wall of the Urinary bladder.



**Fig. 3** An HE staining specimen demonstrated urothelial carcinoma with G2~3.

screening test using a TES Tape<sup>®</sup> because of proteinuria, namely the presence of tubular protein. Cellular elements are rarely detected in urination sediment in spite of the presence of renal failure and mild proteinuria [7]-[10].

Regarding the development of urothelial tumor associated with phenacetin abuse, N-hydroxylation products, the intermediate metabolite of phenacetin such as N-hydroxy-p-phenetidine and 2-hydroxyphetidine, seemed to be potential carcinogens. The process of carcinogenesis in urothelium by exposure of the potential carcinogens in phenacetin metabolic products are considered to take at least 10 years under excessive [3]. Therefore, almost all reported cases of urothelial tumor associated with phenacetin abuse had a history of excessive phenacetin use for more than 10 years (Table 1).

Recently, several newer findings concerning genetic alterations in urothelial tumor associated with phenacetin abuse were shown by advances in molecular methods. Lee *et al.*<sup>①</sup> reported cyclin D1 gene amplification could be an essential genetic event in generation of urothelial tumor associated with phenacetin abuse. Also Petersen *et al.*<sup>②</sup> investigated 15 urothelial carcinomas from 13 patients with evidence of phenacetin abuse and screened for p53 mutation by single-strand polymorphism analysis, followed by direct sequencing of PCR amplified DNA. As a result of this molecular study, p53 mutations were detected in 8/15 primary urothelial tumors. These interested experimental results were to identify possible of genetic events in urothelial carcinomas associated with phenacetin abuse.

In 1965, Hultengen *et al.* [6] first reported a case of a urothelial tumor caused by phenacetin abuse and

over 120 reported cases have since been reported. In Japan, the first case of a urothelial tumor caused by phenacetin abuse was reported by Yamamoto *et al.* in 1984 [7]. Our preview of the Japanese literature yielded a total of 25 cases including the present case (Table 1). The patients ranged in age from 45 to 85 years. The reported cases included 13 males and 12 females, which thus suggested no significant sex-based difference. Urothelial tumors were detected at the following sites ; the renal pelvis 12, ureter 9, urinary bladder 15, and urethra 1.

Multiple urothelial tumors were detected in 7 cases. 6 cases (90%) were histologically classified as squamous cell carcinoma, adenocarcinoma sarcoma or mesonephric tumors. These results indicated that urothelial tumors due to phenacetin abuse are thus regarded as highly malignant in comparison to general urothelial tumors.

As a result of the literature review concerning the site of urothelial carcinoma associated with phenacetin abuse, there was a tendency in such reported cases, for the upper urinary tract to show more than the lower urinary tract both in Japan and in European countries.

In our literature review, the period of phenacetin administration in such cases range from 5 to 40 years. The individual who had been on phenacetin therapy for the longest period of time was our patient. The total amount of phenacetin taken by the patients ranged from 1.0 to 24.6 kg.

There are fewer reported cases of urothelial tumor cases induced by phenacetin abuse in Japan than in Europe and the US. The reason for this phenomenon can be explained due to the following facts: (1) in Japan, phenacetin is classified as a prescription anal-

**Table 1.** Reported Case of Urothelial Tumor associated with Phenacetin Abuse in the Japanese Literature after the report by Fukuhara<sup>⑤</sup>

NO	Age	Sex	origin	pathological finding	administration period(year)	total dose(kg)	microscopic finding	Cr/BUN	reference
14	53	M	bladder	UC , G2	18	12.0	P.N	2.9/26	13
15	53	M	lt renal pelvis	UC , G2	12	3.0	N.D	H.O	14
16	68	M	lt renal pelvis, bladder,urethra	UC , G2	5	2.0	N.D	N.D	15
17	60	F	bladder	UC , G3	20	1.0	N.D	N.D	16
18	60	M	lt renal pelvis,bladder	UC , G3	30	13.0	P.N , I.N	2.8/36	17
19	48	M	bladder	adenocarcinoma	24	2.6	P.N	N.D	18
20	78	F	bilateral ureter	UC , G2 > G1	40	N.D	N.D	N.D	19
21	75	F	bladder	UC , G2	35	9.6	N.D	N.D	20
22	64	F	lt ureter	UC , G2	10	2.7	I.N	N.D	21
23	66	M	bladder	UC , G3	30	24.6	N.D	Ccr.25ml/min	22
24	83	M	lt renal pelvis,lt ureter,bladder	UC , G2~3	N.D	N.D	N.D	N.D	23
25	85	M	bladder	UC , G2 > 3	40	7.3~11.0	None	1.9/28	our case

Abbreviations/ UC : Urothelial Carcinoma G : Grade HD : Hemodialysis ND : not described  
PN : Papillary Necrosis IN : Interstitial Nephritis Ccr : creatine clearance

gesic which can only be administered under the direct control of a physician; (2) according to the recommendations made between 1972 and 1982 by the Ministry of Health and Welfare, the amount of phenacetin in general drugs was reduced or the contents of prescriptions were modified [7]. As in the cases of general urothelial tumors, urothelial tumors due to phenacetin abuse have been said to show a multicentric growth and recurrence even after the withdrawal of phenacetin.

As noted, phenacetin-induced toxicity and carcinogenicity has already been recognized. Due to these adverse effects, the drug was withdrawn from the market in Western countries in the 1980s and also in Japan in 2001. Urothelial tumors have been reported in 25 Japanese patients with phenacetin abuse. In 2 of the patients tumors were noted 12 and 13 years after discontinuation of the drug, respectively, suggesting that patients with chronic use of phenacetin are still at risk of urothelial tumors even after discontinuation of the drug. Phenacetin products are no longer manufactured in Japan; however, in the future there will possibly be sporadic reports of urothelial tumors, which have been associated with phenacetin use at higher dose levels and for longer durations. Patients with a history of analgesic abuse should be evaluated for the presence of urothelial tumors, with careful follow-up.

Regarding the treatment of urothelial tumors due to phenacetin abuse, the current therapeutic approach to general urothelial tumors should be applied. In conventional adjuvant therapy, antitumor agents such as cisplatin and methotrexate are selected as first-line drugs for urothelial tumor. However, as patients with urothelial tumors associated with phenacetin abuse are frequently associated with renal function disorders the possibility of fatal complications occurring can not be ruled out when drugs with a potential to cause uremia are administered.

Grimland *et al* reported that the degree of renal function impairment is correlated with the amount of phenacetin consumption [2]. In our review, these cases of urothelial tumor along with renal lesion, such as interstitial nephritis and papillary necrosis, also had a tendency of renal function impairment. Namely, of 25 reported cases with urothelial tumor associated with phenacetin abuse, 13 showed either serum creatinine of more than 1.5 mg/dl or blood urea nitrogen of more than 25 mg/dl. Therefore, our review might confirm the evidence showing that correlation between renal function impairment and the amount of phenacetin consumption is parallel.

The patient reported in the present study was an elderly man suffering from renal failure who was judged to be performance status 3. We therefore performed the instillation of Pirarubicin hydrochloride and the oral administration of Doxifluridine instead of systemic adjuvant chemotherapy.

The prognosis for urothelial tumors due to phenacetin abuse is poor because such tumors are generally highly malignant. Regular consultations and periodic observations are thus indispensable for the early detec-

tion of this pathological condition.

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