Iatrogenic urothelial malignancy subsequent to adjuvant chemotherapy in breast oncology: A case report and brief review of the literature

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Abstract. Cyclophosphamide is an alkylating agent used in the treatment of solid tumors, including breast cancer. Cyclophosphamide therapy is associated with genitourinary side-effects, such as hemorrhagic cystitis and bladder cancer. The duration of drug exposure and the total dose used have an impact on the probability of developing cancer associated with therapy. The present study describes the case of a 54-year-old female patient who was diagnosed with left-sided breast cancer in 2015 and underwent a left-sided mastectomy, followed by chemoradiation with cyclophosphamide and docetaxel as the chemotherapeutic regimen. However, 7 years later, the patient developed hematuria and was diagnosed with a bladder tumor. On the whole, as demonstrated herein, the risk of cyclophosphamide-related malignancy increases with the cumulative dose and duration of exposure. Long-term follow-up is, therefore, necessary.

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Introduction

Breast cancer stands as the most prevalent malignancy affecting women, exhibiting the highest incidence rates within developed nations. While notable advances in screening and therapy have improved the survival outcomes of patients, the complexity of breast cancer biology continues to challenge clinical management. Breast cancer is a heterogeneous disease, and both inter-tumor and intra-tumor variability affect prognosis and the therapeutic response. This heterogeneity, although critical, also underscores the need to individualize therapy and monitor for diverse treatment outcomes, including adverse effects (1,2).

A crucial, yet often overlooked complication of systemic therapy is the development of secondary malignancies (3,4). Chemotherapy-induced tumor progression and secondary genitourinary malignancies have become more clinically relevant as survival rates improve (5). Among the agents used in adjuvant and neoadjuvant regimens, cyclophosphamide, an alkylating agent, has long been a cornerstone in breast cancer treatment protocols, such as cyclophosphamide, methotrexate and 5-fluorouracil (CMF) and fluorouracil, epirubicin and cyclophosphamide (FEC) (6,7). Cyclophosphamide has been demonstrated in certain trials to increase the breast cancer pathological complete response rate, whereas other investigations have found no differences (8).

Cyclophosphamide functions as a prodrug metabolized in the liver into active alkylating agents and inactive byproducts, such as acrolein. Acrolein is known to irritate the urothelium and has been implicated in the generation of reactive oxygen species, which compromise the antioxidant defense of the bladder and contribute to urothelial damage (9,10). The first

reported case of bladder transitional cell carcinoma linked to cyclophosphamide was published in 1971 (5,11,12). The cumulative dose and duration of exposure are key risk factors for developing such malignancies. This highlights the importance of long-term urological surveillance for patients treated with cyclophosphamide.

The present study describes the case of a patient with iatrogenic muscle-invasive urothelial carcinoma occurring 7 years following adjuvant cyclophosphamide-based chemotherapy for breast cancer; the patient was without any other known risk factors. The case described herein underscores the need for heightened clinical awareness of secondary bladder malignancies in long-term breast cancer survivors.

Case report

A 54-year-old woman was diagnosed with breast cancer in 2015. The histopathological examination revealed invasive lobular carcinoma grade I with metastases in six lymph nodes. It should be noted that the initial microscopic evaluation of this patient is not retrievable due to the lack of proper documentation beforehand, although the formal report and description on the findings remain available in the offline medical records system. A mastectomy was performed in the authors' center (Haji Adam Malik General Hospital, Medan, Indonesia), followed by chemoradiation (six rounds of chemotherapy and 27 rounds of radiation) which was completed in 2016 at Haji Adam Malik General Hospital, Medan, Indonesia. Cyclophosphamide at a dose of 600 mg/m^2 and docetaxel (Brexel) at a dose of 75 mg/m^2 per cycle were administered as part of the chemotherapeutic regimen. Based on a body surface area (1.6 m^2), the estimated total cumulative dose of cyclophosphamide was ~5,760 mg. During chemotherapy, the patient did not suffer from any side-effects, such as or hemorrhagic cystitis; however, the patient experienced dysuria. The patient received hormonal therapy, such as tamoxifen 20 mg daily between 2015 and 2017, followed by exemestane 25 mg daily until 2020, as part of standard endocrine management for hormone receptor-positive breast cancer.

In June 2022, the patient experienced both hematuria and dysuria and reported back to the Haii Adam Malik General Hospital, Medan, Indonesia. Vital signs and clinical examination were normal. An ultrasonography revealed tumors in the bladder (Fig. 1). The patient underwent a cystoscopy in September 2022; a bladder tumor was discovered on the inferior wall of the bladder and was completely removed by transurethral resection. From the histopathological analysis shown in Figs. 2 and 3, the majority of the tumor cells observed in the fragmented tissue from the base of the bladder were organized in an infiltrative, solid growth pattern. All procedures were performed in the Department of Surgical Pathology, Haji Adam Malik General Hospital, Medan, Indonesia following a standardized protocol. Tissue samples were paraffin-embedded and sectioned at a thickness of 4-5 μm, then fixed in 10% neutral buffered formalin at room temperature for 24 h. Staining was carried out using hematoxylin and eosin reagents (MilliporeSigma) under standardized conditions according to the manufacturer's instructions, including maintaining reagent concentrations according to the manufacturer's specifications, staining at room temperature (20-25˚C), and using consistent incubation times (hematoxylin, 5-7 min; eosin, 1-2 min) to ensure uniform staining and reproducible microscopic results. Microscopic evaluation was performed using a light microscope (Olympus BX53, Olympus Corporation). This protocol reflects the routine, validated staining and analysis procedures established in our laboratory.

With their large irregular nuclei, numerous nucleoli and thick chromatin, the tumor cells exhibited notable pleomorphism. Throughout the sample, numerous mitotic figures, including unusual forms, were observed. Tumor cells infiltrated the muscularis propria, indicating muscle invasion. There were interstitial bleeding and necrotic areas. The final diagnosis was that of low-grade muscle-invasive urothelial carcinoma (MIBC). A contrast computed tomography scan of the abdomen indicated focal inferior bladder thickening, suggestive of a malignancy of the bladder (Fig. 4). The patient was then diagnosed with a bladder tumor T2N0M0. Radical cystectomy with chemoradiation was initially recommended; however, the patient declined surgery due to concerns over its invasiveness and impact on quality of life, opting instead for bladder-preserving trimodal therapy. The patient received four cycles of gemcitabine-cisplatin and radiation (60-70 Gy) in 33 fractions, which was completed in December 2022. The patient underwent routine cystoscopy every 3 months beginning from February 2023 (Fig. 5). The patient does not have any risk factors for bladder cancer, such as smoking or a family history of cancer, apart from treatment with cyclophosphamide.

Discussion

Mechanisms of cyclophosphamide-induced carcinogenesis. Cyclophosphamide is an alkylator of the nitrogen mustard group, which causes alkylation in DNA, thereby inhibiting DNA synthesis and function. B- and T-cells are equally inhibited by cyclophosphamide, although the toxicity is greater for B-cells (6). Cyclophosphamide is a prodrug which is converted to both active and inactive metabolites by the hepatic P450 enzymatic system. Cyclophosphamide is transformed into 4-hydroxy-cyclophosphamide and its tautomer aldophosphamide in the liver via the cytochrome p-450 monooxygenase system. During β elimination, aldophosphamide releases acrolein and the alkylating chemical phosphoramide mustard (Fig. 6) (13,14).

The inactive (non-alkylating) metabolite acrolein is considered to cause cystitis. Although there is no concrete evidence, acrolein is deemed to be a likely contributor to bladder cancer as well. Similar to idiopathic bladder cancers, the vast majority of bladder cancers that develop following treatment with cyclophosphamide are transitional cell carcinomas; nevertheless, there have been a few isolated occurrences of sarcomas and other forms of bladder carcinoma documented (13). The patient in the present study was diagnosed with bladder transitional cell carcinoma after 7 years of terminating the use of cyclophosphamide as a breast cancer therapy. In a previous study, a review of 54 cases of breast cancer with bladder metastasis revealed that the median interval from breast cancer diagnosis to bladder metastasis was 5.6 years. The majority of these instances pertained to invasive ductal carcinoma, and the bladder metastases were histologically congruent with the initial breast cancer (15).

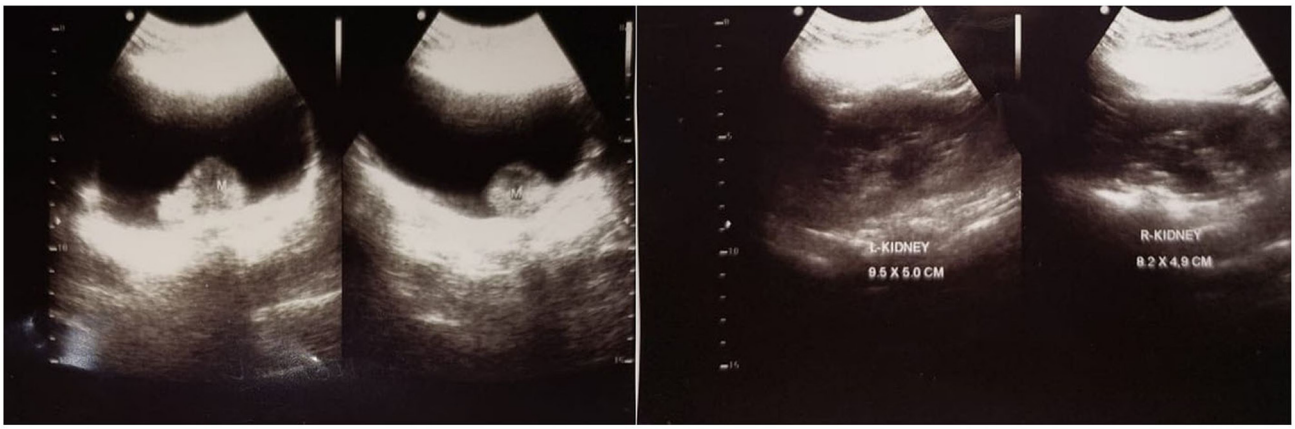

Figure 1. Ultrasonography of the bladder. (Far left and left images) Ultrasonography findings of the bladder revealing bladder tumor with malignant suspicion. (Right and far right images) Ultrasonography findings of right and left kidney, respectively, suggesting normal morphology of the kidneys.

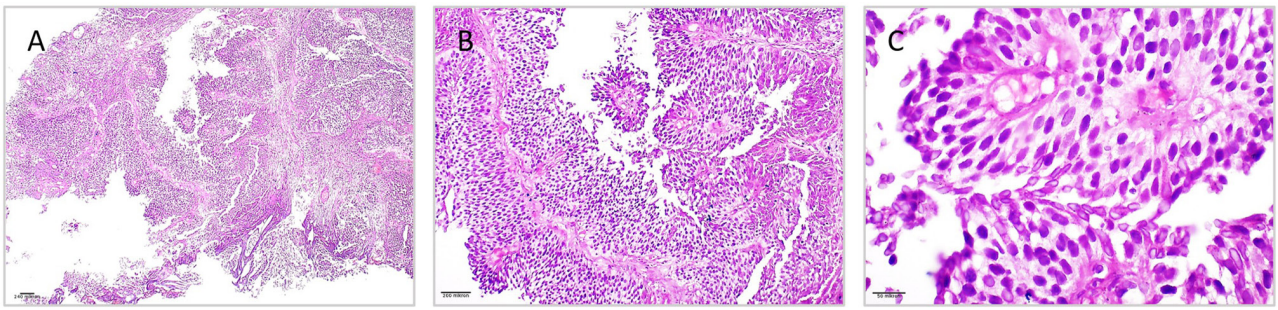

Figure 2. Histopathological features of low-grade papillary urothelial carcinoma in the base of the urinary bladder, illustrating (A) papillary fronds with fibrovascular cores lined by urothelial cells in a noninvasive growth pattern (H&E staining; magnification, x40); (B) orderly arranged urothelial cells with minimal architectural disarray and preserved polarity (H&E staining; magnification, x100); (C) mild nuclear atypia, uniform nuclear size, and low mitotic activity consistent with low-grade features (H&E staining; magnification, x400). H&E, hematoxylin and eosin.

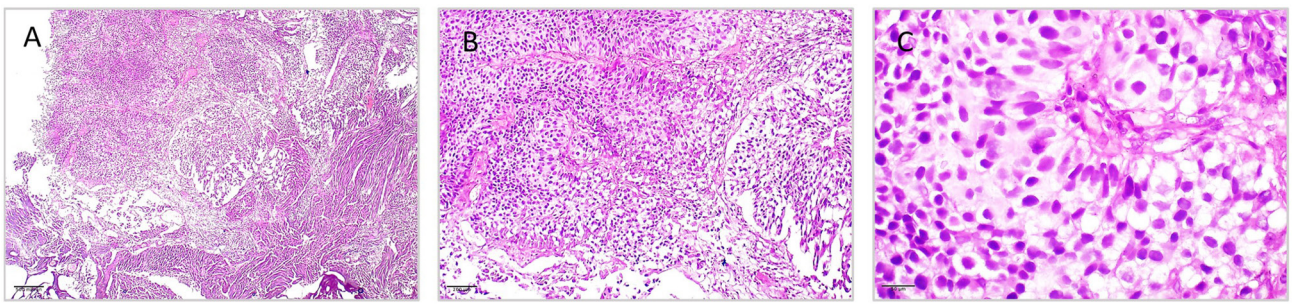

Figure 3. Histopathological features of low-grade papillary urothelial carcinoma from tumor mass of the urinary bladder, illustrating (A) delicate papillary architecture with fibrovascular cores lined by multiple layers of urothelial cells, without evidence of stromal invasion (H&E staining; magnification, x40); (B) mild nuclear pleomorphism, preserved polarity and orderly cell arrangement (H&E staining; magnification, x100); (C) tumor cells with uniform round-to-oval nuclei, fine chromatin, inconspicuous nucleoli, and low mitotic activity, consistent with low-grade morphology (H&E staining; magnification, x400). H&E, hematoxylin and eosin.

Cyclophosphamide therapy is a known risk factor for carcinogenesis due to its mutagenic qualities, particularly in the development of bladder cancer. When cyclophosphamide is administered, its active metabolite, 4-hydroxy-cyclophosphamide, diffuses into cancer cells and is responsible for the alkylating ability of cyclophosphamide. The alkylating effects of cyclophosphamide, such as mutations in the p53 tumor suppressor gene, are more likely to be the molecular changes that mediate the carcinogenic consequences (9,16).

Epidemiology and risk factors. The mode of cyclophosphamide administration that has generated the most concern with regards to bladder toxicity is daily oral dosing, as the duration of treatment and the total cumulative exposure are generally higher compared with intermittent intravenous dosing (11,13). The main risk factor is a cumulative dose >20 g, and the median time from treatment to bladder cancer diagnosis is 7 years (11). The study by Yilmaz *et al* (10) identified 17 cases of hemorrhagic cystitis and 2 cases of

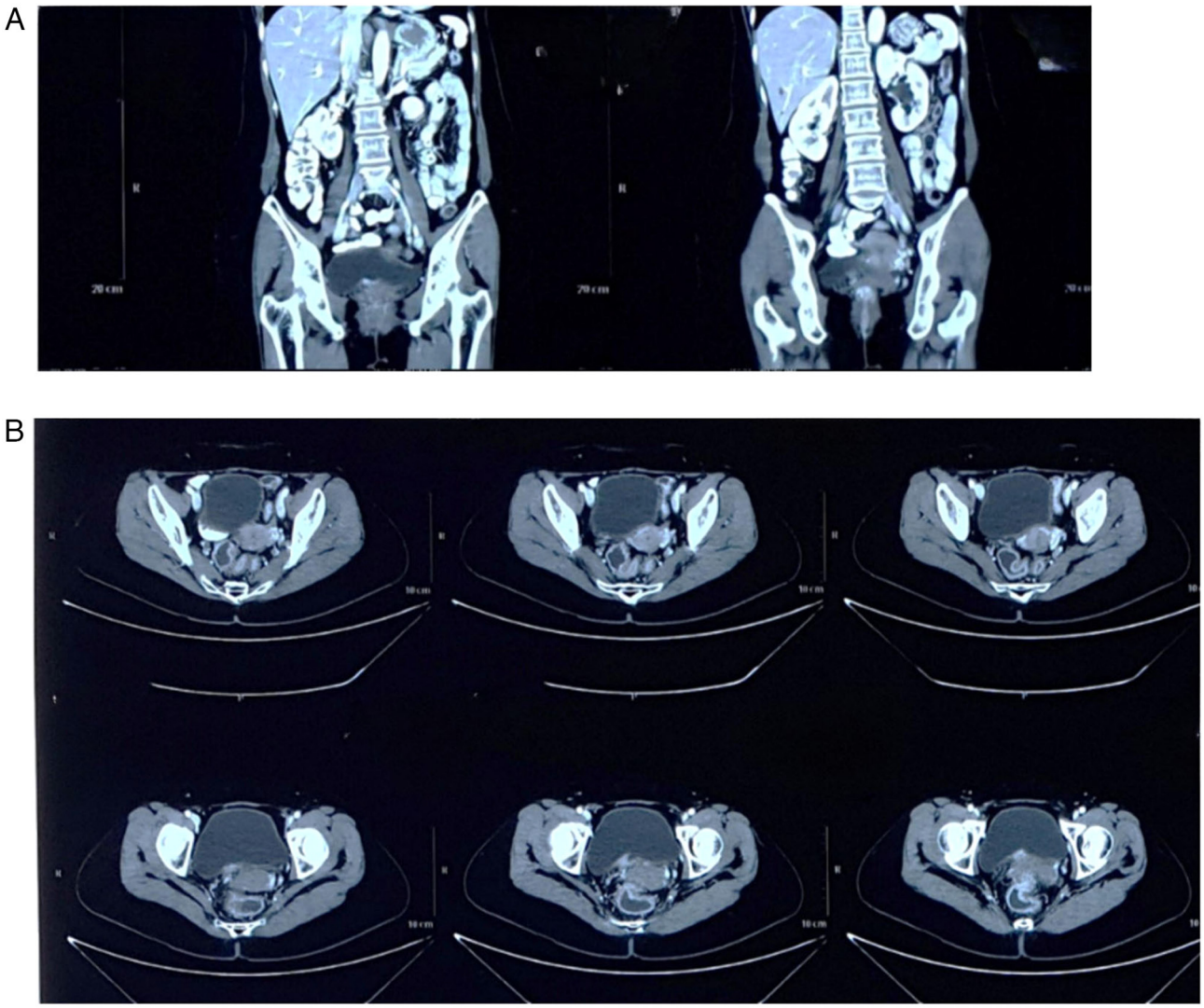

Figure 4. Abdominal CT scan. (A) Coronal view of the CT scan illustrating focal inferior bladder thickening suggestive malignancy of the bladder. (B) Axial slices of the CT scan illustrating focal inferior bladder thickening suggestive malignancy of the bladder. CT, computed tomography.

bladder cancer among 1,018 patients treated with cyclophosphamide for autoimmune diseases. The median time from initial diagnosis to the onset of hemorrhagic cystitis was 10 months, while the median time to the development of bladder cancer was 8 years. The median cumulative dose of cyclophosphamide in their cystitis patients was 10 g. The only significant risk factor for hemorrhagic cystitis identified in the risk factor analysis was cumulative cyclophosphamide dosage (10).

In the case in the present study, the bladder cancer was diagnosed 7 years after receiving cyclophosphamide therapy. However, cyclophosphamide was not administered orally; it was instead used as a chemotherapeutic regimen for breast cancer treatment. Research has also demonstrated the association between cyclophosphamide therapy and bladder cancer (17). Such cases of bladder cancer occurring years after cyclophosphamide therapy in breast cancer patients are rare.

The administration of cyclophosphamide, particularly via oral dosage, has elicited considerable apprehension regarding its long-term impact on the bladder; nevertheless, other factors, including preoperative hydronephrosis and renal insufficiency, may also significantly influence the advancement of bladder cancer. Increased blood urea nitrogen and serum creatinine values, indicative of renal impairment, have been identified as independent predictors of locally progressed bladder cancer, highlighting the necessity for thorough renal function monitoring in patients undergoing cyclophosphamide treatment (18).

In a previous study, it was demonstrated that ~50% of 145 patients with Wegener's granulomatosis who received cyclophosphamide experienced hematuria, and 7 of these individuals went on to develop bladder cancer (19). Among those who subsequently developed bladder cancer, the median cumulative dose reached ~113 g over a median treatment duration of 86 months, compared with only 25 g in patients without bladder cancer. Each additional 10 g of cyclophosphamide was associated with a doubling of the risk of developing bladder cancer (19).

In another study by Stillwell *et al* (20), only 5 of the 100 patients in a trial with cyclophosphamide-induced hemorrhagic cystitis went on to develop bladder cancer. For these

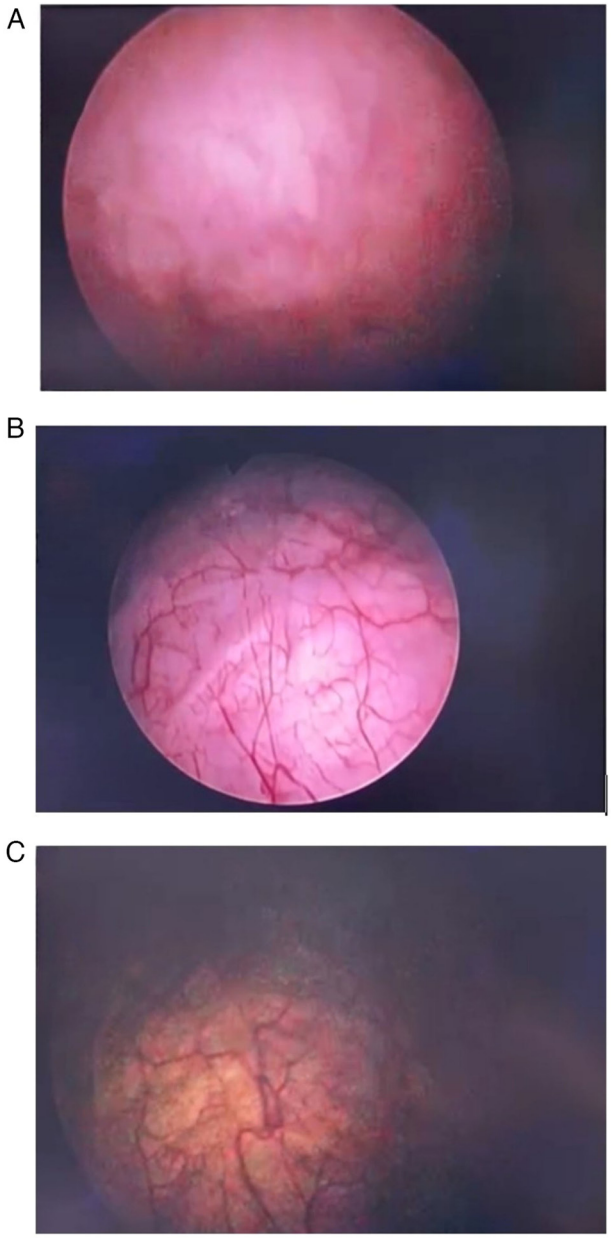

Figure 5. Routine cystoscopy performed on (A) February 2023, (B) May 2023 and (C) August 2023.

5 patients, the average dose of cyclophosphamide was 195 g for 60 months, which was significantly greater than the dosage for the other patients (20). Hemorrhagic cystitis and bladder cancer were related in each of these investigations (9).

The risk of cyclophosphamide-induced bladder cancer is associated with the high dose and long duration of therapy. Exposure to cyclophosphamide for a period >13 months has been shown to be associated with an almost 8-fold increased risk of developing bladder cancer (21). In the study by Radis *et al* (22), 9 of the 50 cancers observed in 37 of the 119 individuals with rheumatoid arthritis who received cyclophosphamide were bladder cancers, and 19 of the cancers were skin cancers, as opposed to no bladder cancers and six skin cancers in the control group. Cyclophosphamide had stopped being used for 14, 16, and 17 years when three bladder tumors developed. The patients who developed cancer received a median cumulative dose of 100 g. However, it is not known whether it was a superficial or a muscle-invasive bladder tumor (22).

Table I. Risk factors of urothelial cancer.

Risk factors for urothelial cancer
Cigarette smoking
Exposure to aryl amines (workers in organic chemical, dye, rubber, paint industries)
Phenacetin abuse
Familial history
Cyclophosphamide therapy
Nonglomerular hematuria

In the patient in the present study, although she received only six cycles of cyclophosphamide at 600 mg/m^2 per cycle, an estimated cumulative dose well below the established risk threshold, she developed MIBC 7 years later. This suggests that even lower cumulative doses, in the absence of acute urinary toxicity, may contribute to carcinogenesis in susceptible individuals.

Latency to diagnosis has been found to range from 0 to 14 years, with a median of 2.7 years. Saoji (9) reported a latency of 5 and 9 years in 2 cases, while Volm *et al* (5) documented bladder cancer 18 years following the termination of therapy. The case in the present study falls within this window. These findings underscore the need for long-term urologic surveillance in cancer survivors treated with cyclophosphamide, as bladder cancer may emerge many years after therapy ends (5,9).*Surveillance recommendations and clinical implications*. The incidence of bladder carcinoma is considered to be lower in patients receiving intravenous cyclophosphamide, likely due to the lower total cumulative dose used with this form of therapy (10,11). In the study conducted by Saoji (9), 3 patients all had advanced disease when they were first seen, and they all received more than 50 g of oral cyclophosphamide over a 3-year period. In fact, 2 of the patients needed a higher dose of cyclophosphamide (100 g) to control their disease. None of these 3 patients ever expressed any complaints about urinary symptoms while receiving treatment. While undergoing treatment and throughout the follow-up period, they underwent routine examinations, including urine analyses. In addition to the risk of bladder cancer, cyclophosphamide is associated with the risk of developing other malignancies, such as lymphoma, leukemia and squamous cell carcinoma (9).

The risk factors for bladder cancer are demonstrated in Table I (4). In the case in the present study, cyclophosphamide therapy may be the cause of bladder cancer when considering the risk factors for bladder cancer development.

It is recommended that all patients treated with cyclophosphamide undergo routine urinalysis every 3 to 6 months, even after completing treatment, as hematuria is often the first sign of cyclophosphamide-induced cystitis or bladder cancer. Although outcome data to support this level of surveillance are currently lacking, early detection may be critical. In the event that a patient presents with microscopic or gross hematuria, a cystoscopy should be performed (5). In cases where no visible lesion is detected but hematuria persists, repeat

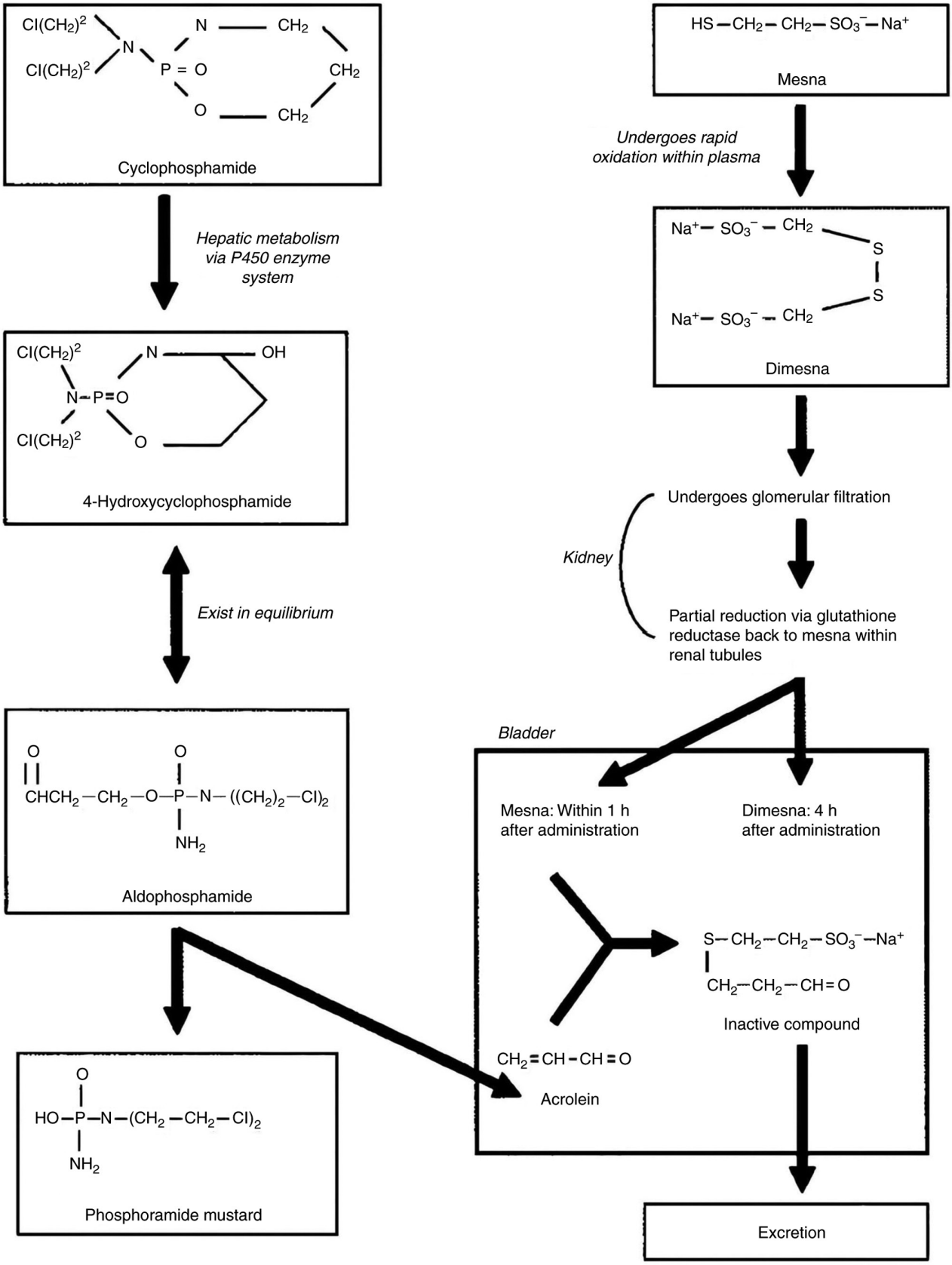

Figure 6. Schematic diagram illustrating the mechanisms of cyclophosphamide metabolism.

cystoscopy every 1 to 2 years is advisable. Stillwell *et al* specifically recommended that all patients exposed to cyclophosphamide and with microscopic hematuria undergo a cystoscopic evaluation. Persistent microscopic hematuria has been associated with progressive thickening of the bladder wall (22,23).

In the case in the present study, the patient did not report hematuria during cyclophosphamide therapy, although mild dysuria was noted. At 7 years after completing chemotherapy, including cyclophosphamide treatment, the patient developed hematuria and dysuria. Cystoscopy revealed a bladder tumor, which was completely resected via transurethral resection. As the patient declined radical cystectomy and chemoradiation, bladder-preserving trimodal therapy was administered, followed by surveillance cystoscopy every 3 months.

In conclusion, due to its mutagenic characteristics, notably in the development of bladder cancer, cyclophosphamide therapy is a known risk factor for carcinogenesis. The high dose and prolonged length of therapy are linked to an increased risk of bladder cancer caused by cyclophosphamide. Several years following the start of treatment, cyclophosphamide-induced bladder cancer may develop. Consequently, ongoing monitoring is necessary.

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Data and materials availability

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

SMW, MHW, RR and DH conceived and designed the study. The methodology was initiated by SMW, GPS, DDK and ZZT. The software-based analysis was performed by MHW, RR, MIS and DISS. Data validation was performed by SMW, DH and GPS and FFP. Formal analysis was performed by RR, DH, CTM, GPS and FFP. Investigation of the patient's data was performed by SMW, MHW, RR, MIS and DISS. Resources were provided by SMW, MHW and ZZT (providing institutional access to databases, computing or mathematical analysis software, and also sharing reference management tools). Data curation was performed by SMW, CTM, MHW and RR. SMW, CTM and RR analyzed the data. The manuscript was drafted by SMW, MHW, DH and RR. SMW, MHW, DH, GPS, DDK, FFP and CTM. Visualization was initiated by CTM, MIS and DISS. The study was supervised by SMW, GPS and FFP. Lastly, project administration was performed by MHW, RR and ZZT. All authors have read and approved the final manuscript. RR, CTM, MIS and DISS confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Ethical approval for the present study was obtained from the Health Research Ethics Committee of Universitas Sumatera Utara under the issued ID with no. 330/KEPK/USU/2025 (approving institution email: komiteetik@usu.ac.id) and the ethics committee agreed with consent for this investigation being obtained verbally. Verbal informed consent was obtained from the patient for their participation in the present study.

Patient consent for publication

Verbal informed consent was obtained from the patient for their anonymized information, and any related images to be published in the present study ('I understand that my data will be published in this article. I consent to this publication, provided that my identity remains confidential and no identifying information is disclosed').

Competing interests

The authors declare that they have no competing interests.

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