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Hemorrhagic Cystitis Induced by Low-Dose Cyclophosphamide: Case report

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***Abstract* — Cyclophosphamide (CP) is known to cause hemorrhagic cystitis (HC), and this adverse effect is more commonly seen in patients receiving high doses used in the treatment of several malignancies, on an average long duration. There are a few reported cases of HC in doses used for breast cancer. We report the case of a 52-year-old lady with a recurrent nasopharyngeal cancer who has undergone treatment with low dose CP, 150 mg per day in one shot for 21 days monthly. After two cycles, the patient presented to the hospital with a dysuria and burning sensation during urination. She went on mesna and hydration. She did not develop any further episodes of hematuria. We review the literature pertaining to our case, and also compare the characteristics of the patient in our case with previously described cases of other cancer locations who developed HC with low-dose CP.**

***Index terms*— Hemorrhagic cystitis, Low-dose cyclophosphamide, Uromitexan, Nasopharyngeal cancer**

I. INTRODUCTION

Hemorrhagic cystitis (HC) is a major but rare side effect known in treatment with high doses of cyclophosphamide (CP) and ifosfamide. However, a few cases of HC occurring with low-dose CP therapy have been reported.
We describe the case of a patient who had manifested a HC after her low-dose CP based nasopharynx cancer treatment.

II. CLINICAL CASE REPORT

It is a 52 year-old woman who was diagnosed with an undifferentiated carcinoma of nasopharynx type (UCNT) in 2021 for which she has undergone chemo-radiotherapy.
In March 2023, she had a disease metastatic recurrence showed by a CT-scan, in her liver and spleen. A first line treatment with carboplatin-based chemotherapy has been prescribed. After four rounds, the patient progressed, following which a treatment with cyclophosphamide was indicated, at a dose of 150 mg per day in single shot, for 21 days monthly, starting from January 2024. Two months later, the patient presented to the hospital with a dysuria and burning sensation during urination. Urine testing did not show any infection, and symptomatic treatment with hydration were prescribed. 4 days later, the patient shows up in the emergency unit with hematuria, pelvic pain, and worsening of previously reported urinary symptoms. A new urine testing has been done, remaining sterile. Serum electrolytes were normal, and albumin dosage showed a value of 44,66 g/l (normal values : 35 – 52).
The cyclophosphamide was interrupted and the patient underwent rehydration protocol and Uromitexan intravenous administration, with clinical improvement and disappearance of urinary symptoms.

III. DISCUSSION

Hemorrhagic cystitis is a known complication of high-dose cyclophosphamide treatment, generally occurring at doses greater than 100 g. There are few reports of hemorrhagic cystitis occurring with low-dose cyclophosphamide therapy 1. Among patients with confirmed HC, the mean dosage of CP was 100 g over a period of 30 months 2.
The few cases described in the literature were mostly with breast and gynecological cancers. Marshall et al, describes a patient who experienced HC following a single 600 mg/m2 dose of CP along with docetaxel used for breast cancer, which was subsequently prevented with uromitexan and hydration 1. Wong et al illustrates a case of severe HC in ovarian cancer after a single 600 mg/m2 dose 3. Tanaka et al reported two cases of HC in breast cancer patients following cumulative dosage of 60.8 and 74.8 g of CP 4.
CP undergoes hepatic microsomal breakdown to hydroxycyclophosphamide, then to aldophosphamide which is eventually broken down into phosphoramide mustard and acrolein. While phosphoramide mustard is the active antineoplastic metabolite, acrolein has no particular therapeutic activity 6. Acrolein is toxic to the entire urinary tract, but the bladder is the most effected as it is exposed to the metabolite the longest 7. Acrolein acts as a proinflammatory irritant that activates tumor necrosis factor alpha, interleukin 1 beta and endogenous nitric oxide (NO) 8. All of this in a dose and time dependent manner causes necrosis, sloughing, ulceration, leucocytic infiltration and eventually hemorrhage of the bladder wall mucosa 9. CP is also associated with bladder wall fibrosis and an increased risk of urothelial cancer. In a study done in Wegener's granulomatosis patients treated with CP, the incidence of bladder cancer was around 5% 7.

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The drug sodium 2-mercaptoethanesulfonate, also known as uromitexan has been used in the prevention of HC caused by both ifosfamide and CP 10. Uromitexan can be administered as both IV and oral forms. The sulfhydryl groups of uromitexan bind with the urotoxic elements of acrolein and prevent it from acting on the bladder wall 11, 12. The efficacy of uromitexan, especially in CP patients is controversial and HC still occurs in 10-40% of uromitexan -treated patients 13. Liberal hydration before and several hours after administration of CP is recommended to prevent HC 11. A single institutional study was done by Saito Y et al who showed that patients receiving low and intermediate doses of CP (< 1,500 mg/m2/day) would benefit from > 125 mL/h of fluids to prevent HC, and those getting high dose CP (> 1,500 mg/m2/day) should receive both uromitexan and vigorous hydration to prevent HC 14.

In our patients, it is sometimes common to witness the occurrence of this CP side effect particularly in high dosed regimens or with cumulative effect, however our current experience is one of exceptional HC cases induced by a very low-dose CP in a brief duration from treatment initiation. Its clinical symptomatology and therapeutic management are similar to those described in the several case series of literature, they all have shown that uromitexan and hydration have been effective to treat and most importantly prevent recurrence.

More case reports and clinical trials are needed to establish standard guidelines to treat HC especially in cancer patients, induced by much lower doses of CP, and patients should always be informed and aware of this side effect and the occurrence risk of HC even with low dose based CP regimens.

Table 1. Comparison of Baseline Patient Characteristics in Reported Cases of Low-Dose CP and HC

	Case 1 (current case)	Case 2 [5]	Case 3 [1]	Case 4 [4]	Case 4 [4]
Age in years	52	63	62	67	65
Treatment initiated	CP	CP and docetaxel	CP and docetaxel	CP and adriamycin, followed by CP and capecitabine	CP and capecitabine
Total dose received prior to symptoms	300 mg (150 mg once a day x 21 days every 21 days)	600 mg/m^2	600 mg/m^2	60.8 g (600 mg/m^2 for six cycles followed by 100 mg/day)	78.4 g (100 mg/day × 14 days every 3 weeks)
Time from initiation of CP therapy to duration of symptoms	2 months	Within 24 h	2 days	30 months	39 months
Treatment of HC	Continuous hydration and uromitexan perfusion	Continuous bladder irrigation and cystoscopic fulguration	Resolved spontaneously	Bladder irrigation with drainage, hyperbaric oxygen therapy and bilateral ureterostomy	Trans-urethral electric coagulation, continuous bladder irrigation, hyperbaric oxygen therapy
Subsequent CP use	No	Yes, three cycles with uromitexan infusion	Yes, three cycles with uromitexan infusion	No	No
Post treatment follow-up	No recurrence	No recurrence	No recurrence	No recurrence for 2 years	No recurrence for 6 months

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