Bladder cancer in patients with HIV infection: a retrospective study of 14 cases

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Abstract

Purpose: This study was intended to determine whether differences existed between bladder cancers in HIV-infected patients compared to those in the general population.

Patients and methods: In this study, 14 patients with HIV infection were found also to have bladder cancer, treated in Beijing Ditan Hospital and Beijing You 'an Hospital from 2013 to 2021. The retrospective study parameters analyzed included HIV infection route, regular treatment, viral load and number of CD4+T lymphocytes prior to surgery, and preoperative laboratory examination. Details specific to bladder cancer included pathological stage and grade, treatment, recurrence at 3 months and longer-term follow-up.

Results: The study comprised 13 males (93%) and 1 female (7%), with a median age of 50.5 years, of whom only 9 patients received regular antiretroviral therapy after HIV infection. The median value of $CD4^+$T lymphocytes detected before surgery was 368 cells/μL (range: 147cells/μL-759cells /μL). Other preoperative laboratory results were as follows (median counts): WBC, 6.165×10^9 /L; erythrocytes, 4.16×10^{12} /L; hemoglobin, 214.5 g/L; platelets, 143×10^9 /L; creatinine, 70.85μmol/L; and serum albumin, 41.5 g/L. All patients were treated surgically, 11 of whom had non-muscle invading bladder cancer that underwent localized tumor resection (plus epirubicin bladder infusion) , and the remaining 3 patients had tumor invasion of the muscle that required radical resection (plus postoperative chemotherapy). The cancers were all urothelial, 5 high-grade and 9 low-grade histologically. At three months postoperatively, 3 cases had recurred and were re-excised, 7 had no evidence of recurrence, and 4 had not undergone reevaluation. On subsequent longer-term follow-up (median, 40 months), 2 patients had died[1] of unrelated causes, 10 were alive[2] including 1 with liver metastasis, and 2 were lost to follow-up.

Conclusions: The clinical characteristics of HIV-positive patients with bladder cancer were similar to those of the general population with the exception of a significant earlier onset of disease. The type and stages of the bladder cancer, treatment, and outcomes of these patients were also similar to the general population. However, the cause of earlier onset of bladder cancer in HIV positive patients remains to be further elucidated.

Introduction

Globally, there are approximately 38 million people living with HIV, with 1.7 million new infections each year [1]. HIV principally impacts the immune system, specifically targeting $CD4^+$T lymphocytes, mononuclear macrophages, and dendritic cells. The result is ongoing reduced numbers of $CD4^+$T lymphocytes, markedly elevated blood HIV viral load, symptoms including fever, lymphadenopathy, sore throat, myalgias/arthralgias, headache, and mucocutaneous ulcerations, among others. Eventually, profound cellular immune deficiency can lead to development of various opportunistic infections and tumors [2]. With the widespread application of high-efficiency combined anti-retroviral therapy (ART), the life span of HIV patients has been significantly prolonged, and the incidence of other diseases

superimposed on HIV has gradually increased. Non-Hodgkin lymphomas and Kaposi sarcoma are well-known HIV-related malignancies, but the relationship between HIV and urinary malignancies has not been fully clarified. As the most common malignant tumor in urology, bladder cancer is also the tenth most common cancer in the world [3]. Bladder lymphoma has an increased incidence in people with a compromised immune system. Precisely because HIV invades CD4 + T lymphocytes thereby crippling the immune system, the correlation between bladder cancer and HIV infection seemed a worthy topic for investigation.

The aim of this investigation was to determine whether differences existed between bladder cancers in HIV-infected patients compared to those in the general population. The parameters utilized were general clinical characteristics, important HIV disease criteria, cancer treatments, and pathology.

Patients And Methods

The study comprised 14 HIV-infected patients with bladder cancer who were admitted to Beijing Ditan Hospital and Beijing You 'an Hospital affiliated to Capital Medical University from 2013 to 2021. Clinical information was retrieved from patient medical records and retrospectively analyzed, including: (1) general clinical data: age, sex, route of infection, ART regimen and duration of administration, CD4 + T lymphocyte count, and viral load; (2) laboratory examination: preoperative white blood cells, red blood cells, hemoglobin, platelets, creatinine, and albumin; (3) bladder cancer information: TNM stage, pathological grade, surgical management and adjuvant therapy; and (4) follow-up status including 3-month and longer-term outcomes. Descriptive methods were used for statistical analysis.

Results

Basic information and HIV status

Among the 14 patients, there were 13 males (93%) and 1 female (7%), and the age at diagnosis of bladder cancer ranged from 28-73 years (median, 50.5 years). Infection occurred through homosexual transmission in 6 cases, 3 through heterosexual transmission, and in 5 cases the cause was unknown. Nine patients received antiretroviral therapy following HIV infection, whereas 5 did not receive regular antiretroviral therapy. The viral load was tested preoperatively in 11 patients: viral load <40 copies/mL in 7; 1 with 56 copies/mL; 4 with no detection; 3 were not tested. The $CD4^+$T lymphocyte count was greater than 200 /μL in 12 patients, only 1 had a $CD4^+$T lymphocyte count below 200, and 1 was not tested. The median CD4+T lymphocyte count was 368 cells/μL (Table 1).

Table 1 Basic information of the cases and HIV related data

Case	Age	Sex	Infection way	Regular ART before surgery	CD4 count (cells/μL)	Viral load (copies/mL)
1	31	Male	Homosexual behavior	Yes	281	TND
2	73	Male	Heterosexual behavior	Yes	288	TND
3	44	Female	Heterosexual behavior	Yes	433	NT
4	52	Male	Heterosexual behavior	Yes	721	56
5	51	Male	-	-	527	<40
6	72	Male	-	-	202	TND
7	50	Male	-	-	459	<40
8	59	Male	-	No	227	TND
9	31	Male	Homosexual behavior	No	759	NT
10	48	Male	Homosexual behavior	-	293	TND
11	51	Male	Homosexual behavior	Yes	368	TND
12	39	Male	Homosexual behavior	Yes	634	NT
13	56	Male	-	-	147	TND
14	28	Male	Homosexual behavior	Yes	-	NT

Abbreviations: NT not tested; TND target not detected; ART anti-retroviral therapy

Blood tests

Blood tests below the lower limit of the reference values were as follows: WBC in 3 patients (WBC <4.0×10^9 /L; overall median WB, 6.165×10^9 /L); erythrocyte counts in 6 cases (<4×10^{12}/L; overall median erythrocyte count, 4.16×10^{12}/L); hemoglobin in only 1 case (<120g/L; overall median hemoglobin, 214.5 g/L); platelet count in 1 patient (<100×10^9/L; overall median platelet count, 143×10^9/L); creatinine in only 1 case (>97μmol/L; overall median value of creatinine, 70.85μmol/L); albumin in 4 patients (<40g/L; overall median albumin value, 41.5 g/L; Table 2).

Table 2 Preoperative laboratory tests

Case	WBC	Hb	Plt	Scr	Albumin
1	7.11	225	148	70.7	50.6
2	3.9	136	137	68.4	39.9
3	5.63	305.7	122.8	50	38.7
4	6.76	216	135	52.8	41.4
5	6.99	181	156	72	41.7
6	2.98	213	43	71	29.7
7	8.01	216	147	73	40
8	6.19	224	155	82	41.6
9	6.54	123	139	61	41.2
10	6.14	280	134	114	35
11	3.4	159	154	71	42.3
12	5.32	220	131	68	46.7
13	7.5	78	155	67	49.1
14	5.28	209	149	92	43.7

Treatment, follow-up and outcome

The surgical treatment of the bladder cancers was guided by the depth of tumor invasion into the bladder wall. In the 11 patients whose cancers had not invaded the bladder muscle (non-muscular invasion of bladder cancer; NMIBC), transurethral resection of the bladder tumor (TURBT) was performed with subsequent intravesical infusion of epirubicin. In the 3 remaining patients that did have muscle invasion (muscle invasion of bladder cancer; MIBC), radical bladder resection was undertaken followed postoperatively with chemotherapy. The urothelial carcinomas were high-grade in 5, and low-grade in 9 cases. At the recommended 3-month postoperative evaluation, there were 3 cases of local recurrence, 7 had no evidence of disease, and 4 did not undergo review. With a median longer-term follow-up of 40 months (range, 8 to 78 months), 2 patients had died, 10 had survived (1 with liver metastasis and 1 with progression from NMIBC to MIBC), and 2 patients were lost to follow-up. (Table 3).

Table 3 Pathology, treatment, and outcomes of HIV patients with bladder cancer

Case	Depth of invasion	Pathological level	Surgery	Follow-up 3 months after surgery	Outcomes
1	NMIBC	High	TURBT	Recurrence	Alive
2	NMIBC	High	TURBT	Recurrence	Alive
3	NMIBC	Low	TURBT	No recurrence	Lost to follow-up
4	NMIBC	Low	TURBT	Recurrence	Alive Progress to MIBC
5	NMIBC	Low	TURBT	No recurrence	Lost to follow-up
6	NMIBC	Low	TURBT	-	Dead
7	MIBC	High	Radical surgery	-	Alive Liver metastases
8	MIBC	High	Radical surgery	No recurrence	Alive
9	NMIBC	Low	TURBT	No recurrence	Alive
10	MIBC	High	Radical surgery	No recurrence	Dead
11	NMIBC	Low	TURBT	-	Alive
12	NMIBC	Low	TURBT	No recurrence	Alive
13	NMIBC	Low	TURBT	-	Alive
14	NMIBC	Low	TURBT	No recurrence	Alive

Discussion

HIV positive patients with bladder cancer are quite rare. Chawki et al. [4] reported only 15 HIV positive patients with bladder cancer of 2200 overall patients with bladder cancer (<1%) evaluated at a university hospital in Paris from 1998 to 2013. They also conducted a systematic review and only found 13 additional cases. Hentrich et al. [5] also briefly described bladder cancer in their study of HIV-related urinary malignancies. Therefore, the present study of 14 HIV-infected patients with bladder cancer represents a comparatively large experience and also the first such systematic study reported at home.

In the present study, the majority of the 14 patients were male (13 cases), which is consistent with the incidence of both bladder cancer and HIV infection being more common in men [6,7]. In a study in the UK, the median age of muscularized invasive bladder cancer was 76 years old [8]; a study from the United States reported the median age of bladder cancer was 73 years old, and the median age of death was 79 years old [9]. Additionally, a meta-analysis of 1340 cases of metastatic bladder cancer determined the median age of males was 71 years, and 74 for females [10]. In striking contrast, in this study the median age was 50.5 years, significantly lower than the studies previously described, and raised considerable

probability that the young age of onset could relate directly to HIV infection. Notably, a Canadian study showed [11] that the median age of HIV infected patients was 40 years old.

The HIV virus attacks the human immune system, principally destroying $CD4^+$ T lymphocytes, which leads to human immune deficiency, thereby raising the risk of tumor occurrence. This elevated risk of malignancy was documented by Poizot-Martin et al. [12] who reported that compared with the general population, HIV-infected people indeed had a higher risk of cancer. Oh et al. [13] extracted T cells from human bladder tumors and non-malignant tissues and sequenced single cell RNA and paired the T cell receptors (TCR) of T cells, and found that more cytotoxic $CD4^+$ T cells were present in the bladder cancer tissues. These $CD4^+$ T cells can kill MHC Class II dependent autologous tumors. However, in our study, we found no evidence of a relationship between $CD4^+$ T cell count, viral load, and tumor progression in patients not taking regular ART. This apparent discrepancy may reflect the small number of patients in this study.

The characteristic blood analysis of HIV-infected patients has shown that HIV infection can cause hematopoietic system abnormalities such as anemia, thrombocytopenia and granulocytopenia [14]. In the present study, the median values of all blood components were within the normal range, with only a few patients that had values lower or higher than the normal reference range. Domestic and foreign literature review showed that some experts believed the alterations in peripheral blood indices of AIDS patients were related to HIV RNA viral load and whether they received antiviral therapy [15]. In the present study, most patients received regular ART, and even those who did not, had a low viral load, probably accounting for the laboratory tests of our study patients being relatively normal.

Bladder cancer is one of the most common malignancies in the urinary system [16,17], and its pathological type is mainly urothelial carcinoma [18], approximately 75% of which are NMIBC [19]. All 14 study patients had urothelial carcinoma, and 11 of the 14 patients (78%) had NMIBC, indicating that HIV infection appeared to have no effect on the pathological type or invasiveness of the bladder cancer. As noted, the surgical treatment for NMIBC was transurethral resection of the bladder tumor (TURBT), with postoperative bladder infusion using epirubicin. For MIBC, radical bladder surgery was performed followed by 2-3 cycles of gemcitabine + cisplatin chemotherapy. Three months postoperatively, 2 patients developed recurrent NMIBC, there were no recurrent cases of MIBC, and 4 patients did not follow the recommendation for reexamination. For patients with recurrence of the NMIBC, repeat transurethral resection of bladder was performed, followed by epirubicin infusion, 8 times a week continuously. Unlike the usual follow-up routine for NMIBC patients, because of the concern of HIV infection, cystoscopy was recommended at 3 months postoperatively, and 3 cases of local recurrence were detected. In the longer-term follow-up, with a median of 40 months, 10 patients were surviving (1 progressed from NMIBC to MIBC, 1 developed liver metastasis), 2 patients died (1 patient was 72 years old, 1 was 48 years old; deaths due to other causes with no evidence of disease), and 2 patients were lost to follow-up. Prior studies have documented that approximately 15% of NMIBC have progressed to MIBC [20], although in this study, only 1 case of NMIBC progressed to MIBC, perhaps related to the short follow-up.

Conclusions

In the present study, the HIV-positive patients with bladder cancer were similar to the general population in terms of clinical characteristics, treatment, and pathology, with the exception that the median age of our cohort was significantly younger than most published series of bladder cancer. Despite the rarity of bladder cancer in HIV-positive patients, we should be alert to the risk of bladder cancer in younger HIV patients. Regarding the impact of HIV on the molecular mechanism of bladder cancer, further research will need to be undertaken.

Declarations

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Authors' contributions

Yu Zhang and Wenrui Xue and Xuyu Li contributed research design, data collection, manuscript writing/editing. Xudong Wang and Pengfei Yuan contributed statistic analysis.Qingjun Liu contributed table1.Zhixing Han contributed table2.Haijian Zhang contributed table3.Shiqi Ji revised the manuscript. The authors read and approved the final manuscript.Corresponding author Email:urology_dt@163.com

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Declarations

Ethics approval and consent to participate the research was reviewed and approved by the Ethics Committee of Beijing Ditan Hospital Capital Medical University. All the participants provided informed consent.

Consent for publication

Written informed consent for publication was obtained from all participants.

Competing interests

The authors declare that they have no competing interests

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