Human Immunodeficiency Virus Related Renal Cell Carcinoma: a Retrospective Study of 19 Cases

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Abstract

Purpose: We aimed to investigate basic information, clinical findings, treatments for tumor, pathology and outcomes of HIV-positive patients diagnosed renal cell carcinoma(RCC).

Patients and Methods: We collected 19 patients from 2012 to 2020 who diagnosed RCC with HIV- positive. A retrospective analyze was performed on their hospitalization course and tumor related parameters, including basic information, clinical findings, HIV associated datas, pathology, treatments for tumor and outcomes.

Results: In our study, patients were diagnosed RCC at the median age 51. Males took a great part(17 males,89%) in all patients, while only 2 females were diagnosed. The median CD4⁺ T-lymphocyte cell count was 462 cells/ul when diagnosed RCC(range from 111 cells/ul to 1536 cells/ul). 11 patients diagnosed RCC and HIV infection at the same time, who may have high viral load and low CD4⁺ T-lymphocyte cell count. 8 patients accepted a median HAART for 30 months(range from 11 months to 108months) prior to diagnosis of RCC. All the patients performed operations successfully, and 4 of them performed partial nephrectomy. Only 1 patient was identified with chromophobe cell carcinoma, 1 with partially clear cell and partially papillary carcinoma, and 17 with clear cell carcinoma. 2 of the patients with Fuhrman grade2-3 accepted cytokine therapy with IL-2 and IFN- α . 2 patients died of lung metastasis one year and six months after surgery respectively, even though 1 patient accepted full dose targeted therapy (Sorafenib) for 3 months, and one refused adjuvant therapy. The remaining 17 patients are still alive at a median follow-up of 34 months, however 1 patient live with lung and brain metastases at last follow-up of 3 years after surgery.

Conclusions: RCC Patients with HIV-positive were similar to general population in terms of clinical characters, treatment measures, and pathology. RCC patients with HIV- positive seemed like to obey the same clinical practice guideline as in general population. The outcomes of HIV-positive patients with partial nephrectomy are not inferior to patients with radical nephrectomy. Further more experience in targeted therapy and immunal therapy(PD-1/ PD-L1 inhibitors) needs to be learned.

1. Introduction

Human immunodeficiency virus (HIV) infects body's dendritic cells (DCs),macrophages, and activates CD4⁺ T-cells, causing destructions of immunal system, and leading to a significant increasement of incidence of certain cancers. So medical scientists focus on these acquired immune deficiency syndrome (AIDS)- defining cancers (Kaposi's sarcoma, non-Hodgkin lymphoma [NHL] and invasive cervical carcinoma) [1]. Following widely used and great advances in highly active antiretroviral therapy(HAART), up to date the situation has been well controlled. In addition to this, an increasement in the incidence of other non- AIDS-defining cancers along with improved survival was noted [2]. Renal cell carcinoma(RCC) has become one of the most common genitourinary tumors, and it is the sixth and eighth common cancer representing 5% and 3% of all cancers respectively in males and females in the United States in 2019[3]. Few cases diagnosed RCC with HIV infection were reported worldwide in recent years. The cases from the United States, Africa, Europe and India take accounts for the most, although the latest cases were reported in Australia[4]. In 1984, Gardenswartz et al. firstly reported a case of RCC associated with HIV infection. The patient was a 38-year-

old African American man who had Kaposi's sarcoma and CMV infection at the same time. They considered that the onset of RCC was associated with immunodeficiency caused by HIV infection[5]. France surgeons reported 1 renal adenocarcinoma and 1 renal angiosarcoma, and introduced their clinical course, treatment measures and outcomes of the malignancies[6]. Increased prevalence of RCC in local HIV patients was documented in the United States. The report revealed that the prevalence of RCC in HIV-positive patients was 8.5 times greater than non-HIV population, with a mean age of occurrence approximately 15 years younger than general population. Similar conclusions were found in Nigeria and Uganda[7]. In India 1 RCC patient was screened from 2880 HIV infected individuals with good prognosis[8]. A transatlantic case report showed no difference on the clinical presentation and behavior of RCC between HIV-positive patients and HIV-negative patients, and it seemed like that chronic immunosuppression played a lesser role than age and exposure to risk factors in this setting[9]. A statewide report from Australia retrospectively reviewed 9 patients with HIV and RCC in a HIV referral center. The report revealed that patients with HIV and RCC should be treated with the same guideline as the general population, taking into account poor prognosis of HIV[4].

However, the cases diagnosed RCC with HIV infection were not widely reported worldwide nowadays. We presented 19 cases of patients HIV infection who diagnosed RCC, and preliminarily attempted to learn if there was obvious difference between HIV-positive and general population diagnosed RCC on clinical characters, treatment measures, pathology, specially on outcomes obeying the same guideline as the general population.

2. Patients And Methods

The cases diagnosed RCC with HIV infection were screened from the patients who were treated at the department of Urology in Beijing Youan hospital affiliated to Capital Medical University from 2012 to 2020. Hospital records were checked out, in order to collect patients' basic information, HIV status, and RCC relevant datas. Patients' basic information included demographics, diagnosis, and comorbidity. The datas of HIV status included CD4⁺ T-lymphocyte cell count, HIV viral load at diagnosis of RCC, treatment duration of HAART. RCC relevant datas included clinical presentation, treatment measures, pathology, and survival outcomes. Descriptive statistical analysis was used for the acquired data.

3. Results

3.1 Basic information and HIV status

19 patients diagnosed RCC with HIV infection were identified from our department of Urology in all from 2012 to 2020. Males took account for the majority(89.5%,17cases), while the females were rare(10.5%, 2cases).The median age was 51 years old(range from 30 to 72years). The most common comorbidity was hypertension, which occurred in four patients. 1 patient was co-infected with HIV and syphilis. 5 patients(26.3%) had been smoking for more than 10 years. 15 patients(79%) presented with incidental findings on imaging examination, 1 presented with flank pain and hematuria, 1 presented with flank pain, and 2 presented with hematuria. 11 patients diagnosed RCC and HIV infection at the same time. 8 patients accepted a median HAART for 30 months(range from 11 months to 108months) prior to diagnosis of RCC.

13 patients underwent viral load measurements when diagnosed RCC,5 of whom had viral load of target not detected (TND). The median CD4⁺ T-lymphocyte cell count was 462 cells/ul when diagnosed RCC(range from 111cells/ul to 1536cells/ul).

Table 1
Basic information of the cases and HIV related datas

Case	Gender	Age	Comorbidity	Presentation	CD4 count (cells/ μ L)	Viral load (copies/mL)	Regular HAART before surgery	HAART duration (months)
1	Male	59	Hypertension	Incidental	614	NT	No	-
2	Male	61	None	Incidental	288	102130	No	-
3	Male	43	None	Incidental	390	NT	Yes	12
4	Male	58	None	Incidental	1536	386	No	-
5	Male	45	Hypertension	Incidental	628	NT	No	-
6	Male	51	Diabetes	Incidental	611	NT	Yes	12
7	Male	54	Hypertension Diabetes	Incidental	880	TND	Yes	36
8	Male	51	None	Hematuria	190	6495	No	-
9	Male	34	None	Hematuria	462	NT	Yes	24
10	Male	72	Diabetes insipidus	Flank pain	378	< 40	Yes	108
11	Male	54	None	Incidental	535	63188	No	-
12	Female	51	None	Incidental	111	409601	No	-
13	Male	53	Hypertension	Incidental	328	TND	No	-
14	Male	30	Meniere's Disease	Incidental	604	TND	Yes	36
15	Male	39	None	Incidental	296	NT	No	-
16	Male	50	None	Incidental	151	73907	No	-
17	Male	50	None	Incidental	327	4909	No	-
18	Female	54	None	Hematuria Flank pain	665	TND	Yes	11
19	Male	48	Syphilis	Incidental	589	TND	Yes	60

Abbreviations: NT = not tested; TND = Target not detected

3.2 Pathology

The tumors' median diameter was only 4.1cm, due to early tumor stage and low degree of malignancy. Pathologic analysis showed that 17(89.5%) patients had clear cell carcinoma(1 was cystic renal carcinoma), 1 had chromophobe cell carcinoma(Fig. 1), and 1 had partially clear cell and partially papillary carcinoma (Fig. 2).

Tumor grade classification showed that 1 patient had Fuhrman grade 1 disease, 3 had grade1-2 disease, 5 had grade 2 disease, 2 had grade 2–3, and 4 had grade 3(4 patients were not recorded). 14 patients(73.7%) were identified with stage pT1, and 9 of them were with stage pT1a, Only 2 patients were identified with locally advanced malignancy at stages pT3a and pT3b respectively. The remaining 3 patients were identified with pT2.

3.3 Treatments and outcomes

Operations were performed on each patient, 4 patients had partial nephrectomy, and 15 had radical nephrectomy(1 had removal of inferior vena cava cancerous suppository). Acknowledging the immunal deficiency, we recommended that all the patients with fuhrman grade 2–3 or 3 accepted cytokine therapy, but only 2 patients with Furman grade 2–3(histological type: clear cell carcinoma, partially clear cell and partially papillary carcinoma) accepted cytokine therapy including IL-2 and IFN. During the median follow-up of 35 months(range from 14 months to 96 months), no patients occurred tumor recurrence. 2 patients died of lung metastasis one year and six months after surgery respectively, even though 1 accepted full dose targeted therapy(Sorafenib) for 3 months, and 1 refused adjuvant therapy. The remaining 17 patients are still alive at a median follow-up of 34 months, however 1 patient live with lung and brain metastases at last follow-up of 35 years after surgery who underwent radical nephrectomy. This patient accepted sorafenib for 4 months, sunitinib for 6 months, and then axitinib for 3 months when diagnosed lung metastasis 3 months after surgery, but he refused the immunal therapy(PD-1/ PD-L1 inhibitors) considering the side effects and economic factors.

Table 2
Pathology, treatment, and outcomes of HIV related RCC

Case	Surgery	TNM stage	Pathology	Adjuvant therapy	Follow-up duration (months)	Outcomes
1	RN	pT1a N0 M0	Clear cell Grade1-2	NT	96	Alive
2	PN	pT1a N0 M0	Chromophobe cell NR	NT	78	Alive
3	RN	pT1a N0 M0	Clear cell NR	NT	76	Alive
4	RN	pT2a N0 M0	Clear cell Grade1-2	NT	68	Dead
5	RN	pT2b N0 M0 (cystic renal carcinoma)	Clear cell NR	NT	65	Alive
6	PN	pT1a N0 M0	Clear cell Grade 3	NT	61	Alive
7	RN	pT1a N0 M0	Clear cell Grade1-2	NT	47	Alive
8	RN	pT3b N0 M0 (inferior vena cava cancerous suppository)	Partially clear cell Partially papillary Grade2-3	IFN + IL-2	35	Alive
9	RN	pT2a N0 M0	Clear cell Grade2-3	IFN Sorafenib 4M Sunitinib 6M Axitinib 3M	35	Alive (Lung and brain metastases)
10	RN	pT3a N0 M0 (perirenal adipose sac invaded)	Clear cell Grade 2	Sorafenib 3M	35	Dead
11	RN	pT1b N0 M0	Clear cell Grade 3	NT	34	Alive
12	RN	pT1a N0 M0	Clear cell Grade 2	NT	34	Alive
13	RN	pT1b N0 M0	Clear cell NR	NT	33	Alive
14	PN	pT1a N0 M0	Clear cell Grade 2	NT	33	Alive

Abbreviations: RN = radical nephrectomy; PN = partial nephrectomy; NR: not recorded; IFN = interferon; IL = interleukin; NT = no treatment

Case	Surgery	TNM stage	Pathology	Adjuvant therapy	Follow-upduration (months)	Outcomes
15	RN	pT1b N0 M0	Clear cell Grade 2	NT	32	Alive
16	RN	pT1b N0 M0	Clear cell Grade 3	NT	29	Alive
17	RN	pT1a N0 M0	Clear cell Grade 2	NT	28	Alive
18	RN	pT1b N0 M0	Clear cell Grade 3	NT	20	Alive
19	PN	pT1a N0 M0	Clear cell Grade 1	NT	14	Alive
Abbreviations: RN = radical nephrectomy; PN = partial nephrectomy; NR: not recorded; IFN = interferon; IL = interleukin; NT = no treatment						

4. Discussion

We reviewed 19 cases diagnosed RCC with HIV infection in Beijing Youan Hospital which is the largest HIV follow-up center in China. Our study is the largest published series about this kind of crew at present.

The average onset age of RCC in the general population is more than 60 with a male preponderance[10], while our study shows an earlier age of 51. Similarly, in an Australian statewide series of 7 HIV-positive patients, the median age of RCC diagnosis was also slightly younger at 52 years old[4]. Smoking seemed like a risk factor in A Transatlantic Case Series report, in which 7 of 9 patients had smoking history[9]. However we did not find conclusive evidence in our series, due to only 5 patients had long smoking history. We can not draw the conclusion that hypertension is the risk factor, because only 4 patients complicated with hypertension, while smoking, obesity, hypertension, and chronic kidney disease had already been identified as risk factors in general population[11]. The majority of cases presented as incidental findings screened out by imaging examination, while no patients presented typically triad syndrome (hematuria, flank pain, and abdominal mass), and only 1 patient presented hematuria and flank pain. This phenomenon was consistent with the general population because of the adhibition and diversity of screening methods[12]. In our study we investigated patients' immunal status in terms of CD4⁺ T-lymphocyte cell count and HIV viral load, and we found no evidence on the relationship between immunal deficiency and tumor progression, even though the cases with no regular HAART treatment.

To our surprise, 73.7% of the patients had stage pT1 tumors in the case of immunal deficiency, which may predict better outcomes, and this proportion was close to that of the general population (75%)[13]. In our series, patients with pathological classification of clear cell carcinoma accounting for 89.5% of all cases was slightly higher than the proportion of general population (70%-85%)[14]. Fuhrman grade is the most widely accepted histologic prognostic factor[15]. A large-sample study of 5453 patients in the United States showed that patients with Fuhrman grade 2 and 3 jointly accounted for 71.4%, and grade 1, 2, 3 all had good

outcomes[16]. In our report, 11 patients (73.3%) with Fuhrman grade 2 and 3 which was close to the above research also had good outcomes.

All the patients underwent operations successfully which were selected in accordance with general population, and 15 patients with radical nephrectomy and 4 with partial nephrectomy. The 4 patients who underwent partial nephrectomy are still alive without local recurrence or distant metastasis with mean follow-up of 43 months, the same outcome as in general patients[17]. There were a large number of literatures on radical versus partial nephrectomy for cT1 renal cell carcinoma. A recent study consisted of a total number of 2459 adults in the United States who were treated with radical or partial nephrectomy. It was documented that radical nephrectomy was associated with an increased risk of chronic kidney disease compared with partial nephrectomy, but there were no statistically significant difference in cancer-specific mortality (CSM) or all-cause mortality (ACM) among patients with cT1 RCC between radical nephrectomy and partial nephrectomy[18]. We can not draw the same conclusions as the above study because of inherent defects of our study, but the 4 patients with partial nephrectomy did have good outcomes considering the immunodeficiency. More randomized controlled studies are necessary to confirm the good prognosis of partial nephrectomy versus radical nephrectomy in HIV-positive population, so as to reduce concerns that partial nephrectomy may predispose to recurrence and metastasis because of immunodeficiency special for young HIV-positive population.

We have little experience to share on adjuvant treatment selection, due to good outcomes of our cases. We recommended patients with Fuhrman grade 2–3 and grade 3 accepted cytokine therapy, however only 2 patients agree to the scheme considering of side effects. We used targeted therapy in 2 patients with lung metastasis, but 1 patient still occurred brain metastasis and 1 died of lung metastasis. Checkpoint inhibitors have been identified to induce significant responses in RCC[19]. However, due to the role of PD-1⁺ T cells in HIV transcription in treated aviremic individuals and concerns of unforeseen side effects[20], the cases of cancers with HIV infection were rarely reported. In a recent literature, 16 HIV-positive nivolumab recipients were identified, including 8 non-small-cell lung cancer patients, 2 Hodgkin lymphoma patients, 2 RCC patients, and 4 off-label cancer patients. 1 of RCC patients was unable to assess side effects, response to treatment and outcomes. The other RCC patient received 3 doses of Nivolumab with poor outcome, and occurred grade 3 pneumonitis[21]. The latest study including 17 HIV-positive cancer patients showed that Checkpoint inhibitors seemed like to have comparable efficacy and tolerable adverse effects, and CD4⁺ T-lymphocyte cell count and viral load were not affected. In this study, the only one RCC patient with stage III responded to immunotherapy with stable disease, and had slight side effects[22].

5. Conclusions

In our study, RCC Patients with HIV-positive were similar to general population in terms of clinical characters, treatment measures, and pathology. RCC Patients with HIV positive seemed like to obey the same clinical practice guideline as in general population. To our delight, the outcomes of patients with partial nephrectomy is not inferior to patients with radical nephrectomy. Young HIV-positive patients with early-stage tumors would benefit so much from the nephron sparing surgery, and it is no need to worry about the local recurrence and distant metastasis caused by immunodeficiency. Further study are still warranted to

investigate RCC features in HIV-positive population. Checkpoint inhibitors are revolutionizing cancer therapy, however more experience still need to be learned in HIV-positive population.

Declarations

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Authors' contributions

Mengmeng Zhang and Zhiqiang Zhu contributed research design, data collection, manuscript writing/editing. Wenrui Xue contributed statistic analysis. Yu Zhang revised the manuscript. Hui Liu was responsible for pathological analysis.

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Ethics approval and consent to participate

The research was reviewed and approved by the Ethics Committee of Beijing Youan Hospital Capital Medical University. The Ethics Committee archive number is LL-2019-176-K, and the approval number is [2020]035.

All the participants provided informed consent.

Consent for publication

Written informed consent for publication was obtained from all participants.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests

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Figures

Figure 1

Case 2 with chromophobe cell carcinoma HE×200

Figure 2

Case 8 with partially clear cell and partially papillary carcinoma HEx40