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Case Report

Management of Renal Malignancies in Von Hippel–Lindau Syndrome: Lessons Learned from a Series of Six Patients from Sri Lanka

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ABSTRACT. Management of renal malignancies in Von Hippel–Lindau (VHL) is challenging. We present six patients [mean age = 35.1 years (range: 24–54), males = 5] with VHL syndrome with multiple bilateral renal malignancies and the lessons learned during their management. The number of tumors at the time of presentation ranged from 1 to 6, while the number of new lesions varied from 1 to 3. Different combinations of radical nephrectomy (n = 2), partial nephrectomy (n = 7), and focal therapy (n = 6) were used appropriately. Median follow-up was 36 months (range: 12–72). Two patients developed new lesions which were managed with focal therapy. Nephron-sparing approaches are successful even in bilateral, multifocal, large, and recurring renal tumors associated with VHL. Awareness about the availability of efficacious surgical and minimally invasive measures would reduce psychosocial problems faced by patients and their families due to the social stigma associated with malignancies running in a family and burden of renal replacement therapy.

Introduction

Von Hippel–Lindau (VHL) syndrome is a familial cancer syndrome with the incidence of 1:36,000 live births.[1] It develops as a result of germline mutations in the VHL tumor suppressor gene in the short arm of chromosome 3.[2,3] In the majority, autosomal dominant inheritance through familial transmission is seen. However, around 20% of the patients may develop this syndrome due to sporadic mutations.[4] Its manifestations include central nervous system tumors (such as hemangioblastomas in cerebellum and retina), renal tumors, pheochromocytomas, endolymphatic sac tumors, pancreatic lesions and cystadenomas in epididymis and broad ligament.[1]

Management of renal malignancies in VHL is challenging due to its multifocal nature, bilateral involvement, and high tendency to develop new malignancies. Here we present a case series of six patients with VHL syndrome with bilateral and multiple renal malignancies and the lessons learned during the management of

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initial lesions as well as those developed during the follow-up period.

Case Report

Clinical details of the six patients are summarized in Table 1. The average age was 35.1 years and five were men. Number of tumors at the time of presentation ranged from 1 to 6, while number of recurrences varied from 1 to 3. Different combinations of radical nephrectomy (RN) (n = 2), partial nephrectomy (PN) (n = 7), and focal therapy (n = 6) were used to treat the tumors appropriately (Figures 1 and 2). Two of them developed new lesions which were managed with focal therapy. Patient 3 underwent synchronous right RN and left PN. He developed postoperative oliguria and the serum creatinine level rose to 3 mg/dL, requiring renal replacement therapy (RRT) in the form of three sessions of hemodialysis. His renal functions recovered after 2 weeks and serum creatinine reached a nadir of 1.5 mg/dL. Patient 5 had PN first and RN 3 months later and had no postoperative renal impairment. All patients had clear cell renal cell carcinoma (RCC) without any poor prognostic histopathological characteristics such as rhabdoid or sarcomatoid differentiation.

Patient 3 was offered bilateral nephrectomies followed by RRT elsewhere and patient attempted to commit suicide by jumping from a three storied building. Patient 5 had defaulted surgery for 3 years elsewhere due to possibility of requiring RRT after surgery. At the end of a median follow-up of 36 months, all six patients were alive with normal or near-normal and stable renal functions and were free of any renal malignancies.

Discussion

We describe the successful management of six patients with VHL syndrome having multiple

Table 1. Summary of clinicopathological details.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age at diagnosis	29	24	32	24	54	48
Family history	Yes	Yes	Yes	Yes	Yes	No
Tumors	Cerebellum Retina Kidney Pancreatic cysts	Cerebellum Kidney	Cerebellum Kidney	Cerebellum Kidney	Cerebellum Kidney	Cerebellum Pancreatic cysts Kidney
Initial tumor	Brain	Brain	Kidney	Retina	Kidney	Brain
Surgery for kidney	R/NSS, L/NSS, R/RFA, R/MWA	L/NSS, R/RFA, R/RFA	R/RN, L/NSS, L/RFA	L/NSS, R/RFA	L/NSS, R/RN	L/NSS
Laterality	Bilateral	Bilateral	Bilateral	Bilateral	Bilateral	Unilateral
Size of tumors (cm	3.5, 3, 1.9 2, 3	1.6 3	4.4, 1.9, 1.7 3.8, 3.4, 2.4	1.4 3.8, 2.3	6.4, 6.3, 2 6, 3, 6, 2	3.9
Grading	ISUP grade I and II	ISUP grade	ISUP grade II	ISUP grade II	ISUP grade IV, III and III	ISUP grade III
Stage	pT1a	pT1a	pT1, pT3	pT1a	pT1b	pT1
New lesions	Yes	Yes	No	No	No	No
Renal impairment	Perioperative AKI	Normal	Normal	Normal	Normal	Normal
Total follow-up after initial surgery (months)	72	60	36	36	24	12

R: Right, L: Left, NSS: Nephron-sparing surgery, RFA: Radiofrequency ablation, MWA: Microwave ablation, RN: Radical nephrectomy, ISUP: International Society of Urological Pathology, AKI: Acute kidney injury.

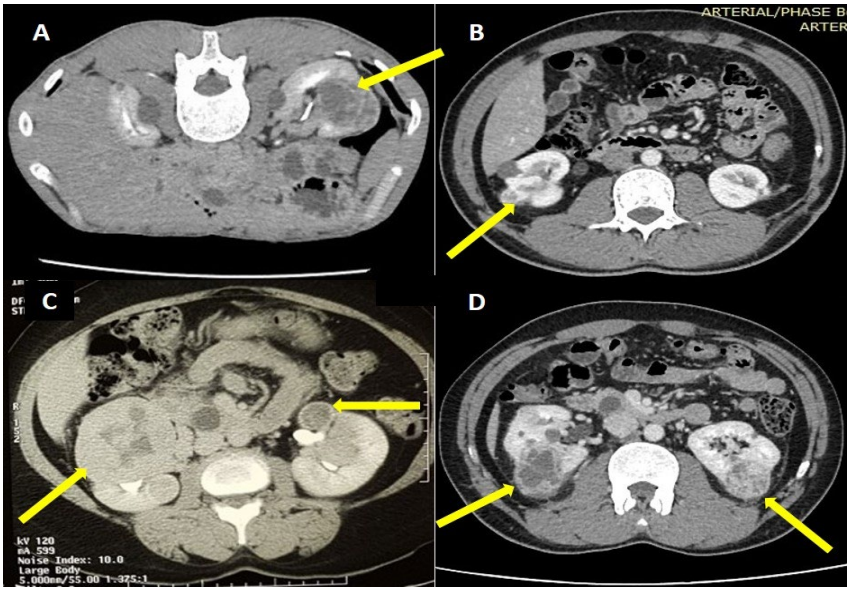

Figure 1. Computed tomography images showing multiple renal tumors (arrow) of patients 6, 2, 5, and 3 are shown in (a-d) respectively.

ablation was used appropriately to achieve optimum outcomes. All patients had normal or near-normal renal functions which were stable during the available follow-up period.

During this study, there were 285 RCCs treated in the same unit with a mean age of 56.6 years.[5] Hence, the proportion of VHL syndrome among RCC was 2.1%.

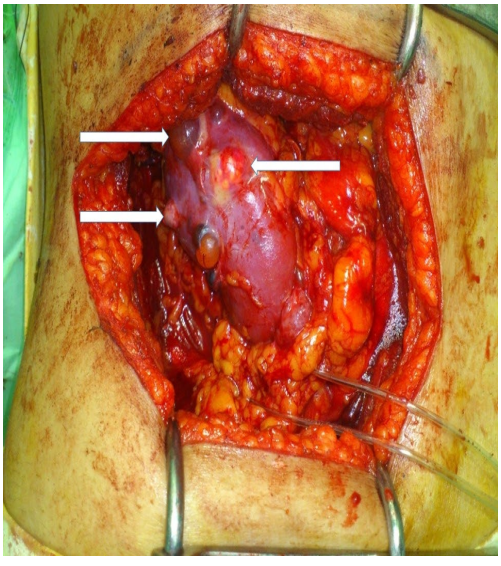

Figure 2. Intraoperative image of multiple renal tumors and cysts (arrow) in the right kidney of patient 1.

Due to the nonavailability of VHL gene analysis, we used the well-accepted clinical criteria for diagnosis.[6] The criteria for the clinical diagnosis of VHL syndrome depends on the presence of a family history. In those with a family history of VHL, one or more of the following lesions such as retinal hemangioblastoma, cerebellar or spinal cord hemangioblastoma, phaeochromocytoma, renal clear cell carcinoma or multiple renal or pancreatic cysts would suffice. In patients without a family history, two or more of the following groups of lesions should be present. These include (1) ≥2 retinal, spinal cord, or brain hemangioblastomas, or a single hemangioblastoma in addition to visceral organ lesions (multiple renal or pancreatic cysts); (2) renal clear cell carcinoma; (3) adrenal or extra-adrenal pheochromocytoma and (4) rare lesions including internal lymphoma, papillary cystadenoma of the epididymis and broad ligament, and neuroendocrine tumors of the pancreas.[6] VHL genetic test is warranted in those with atypical manifestations without a family history. All our patients fulfilled the clinical criteria for the diagnosis of VHL syndrome.

Renal malignancies are the most challenging to manage in patients with VHL syndrome due to the multifocal and bilateral involvement with frequently occurring new lesions. However, majority of the tumors are less aggressive (Grade I/II) and lower stage (stage pT1) as shown in our cohort. Bad prognostic factors such as sarcomatoid or rhabdoid differentiation were not seen. Renal preservation was possible even with extensive multifocal disease. PN could be utilized for larger tumors and focal therapy is useful for smaller lesions. This combined approach avoids unnecessary morbidity and the need for RRT which is not preferred by the patients. However, clinically challenging scenarios with large, multiple tumors that require surgery may be encountered. Patient 1 had large bilateral tumors requiring RN on one side and partial nephrotomy on the other. Performing bilateral surgeries in the same setting resulted in postoperative acute kidney injury requiring hemodialysis. Subsequently staged nephrectomies avoided this complication. Therefore, we suggest performing the PN first and allowing few weeks for healing and recovery of the remaining renal tissue and subsequently performing the contralateral RN (similar to patient no. 5). This protocol appears to be effective in avoiding postoperative renal functional impairment and RRT. Focal therapy such as radiofrequency ablation and microwave ablation is effective for recurrences or new tumors during follow-up.

Due to the epidemic of chronic kidney disease of uncertain origin in Sri Lanka, demands for RRT are high and patients dislike RRT due to the financial toll it imposes on the family. Running a cancer in the family and possibility of RRT as the available treatment option leads to psychosocial disturbances and stigma. In our practice, we noticed that patients were initially reluctant to divulge information regarding positive family history and to bring their family members for screening. When patient 5 realized that her son was doing well after surgery without requiring RRT, she agreed to surgery after refusing surgery 3 years ago. Therefore, clinicians should be empathetic toward these psychosocial issues. The availability of effective treatment in the form of surgery and minimally invasive procedures would reduce the worry and stigma associated with a chronically disabling illness.

Conclusion

Nephron-sparing approaches are successful even in bilateral, multifocal, large, and recurring renal tumors associated with VHL. In patients with large tumors and bilateral disease requiring RN on one side, nephron-sparing surgery should be performed first, and RN at a later date. Awareness about the availability of efficacious surgical and minimally invasive measures would reduce psychosocial problems faced by patients and their families due to social stigma.

Conflict of interest: None declared.

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