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BILATERAL RENAL CELL CARCINOMA ASSOCIATED WITH VON HIPPEL LINDAU DISEASE: CASE REPORT AND REVIEW OF LITERATURE

Oncology

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ABSTRACT

Von Hippel Lindau disease is an autosomal dominant inherited disorder and is associated with bilateral multifocal clear cell renal cell carcinomas and other extrarenal manifestations like CNS hemangioblastomas, retinal hemangiomas, pheochromocytomas, multiple pancreatic cysts etc. Management of RCCs in VHL patients is challenging as they require lifelong surgeries eventually leading to death due to chronic kidney disease. Active surveillance, nephron sparing surgeries, ablation, antiangiogenic drugs are various available treatment options. We report a case of young man who was evaluated for back pain and was found to have multiple hemangioblastomas on MRI and incidentally detected bilateral multifocal RCC. He underwent laporoscopic right nephrectomy and excision of symptomatic intramedullary hemangioblastoma and then started on adjuvant Sunitinib. He is on active surveillance for left RCC.

KEYWORDS

Bilateral RCC, VHL, Nephrectomy, Surveillance, Sunitinib

INTRODUCTION:

Von Hippel Lindau (VHL) disease is a raare autosomal dominant inherited disorder caused by germline mutations in VHL gene located on 3p chromosome. These VHL patients may present with multiple bilateral renal cell carcinomas (RCC) along with extrarenal manifestations like CNS hemangioblastomas, pancreatic cysts, retinal hemangiomas, pheochromocytomas. Renal cell carcinoma in VHL is mostly bilateral and of clear cell histology. Usual age of presentation of RCC in VHL is 39 years [1]. Median overall survival is 50years. RCC in VHL rarely metastasize. Lesions less than 3cm size associated with low risk of metastasis [2] and active surveillance can be offered for those. Nephron sparing surgeries or ablation are done if size is more than 3cm [3] and adjuvant use of TKI against VEGF can control the growth of residual lesions. Occasionally if there are multiple lesions in the same kidney located at varying distances from each other nephron sparing surgery becomes potentially difficult and complex.

Here we report an interesting case of a young man who presented with the chief complaints of back pain and was found to have multifocal non metastatic RCC on detailed evaluation.

Case Presentation:

A 29 year old male, non smoker, non alcoholic presented with complaints of upper back pain of 4 years duration which was insidious in onset and gradually progressive in nature. He also complained of neck pain and tingling sensation over both lower limbs of 1year duration. He had no bowel or bladder disturbances. He had no medical comorbidities. His father had history of lung cancer. Physical examination was normal and there were no signs of sensory, motor or cranial nerve deficits. Power was 5/5 in all 4 limbs.

MRI whole spine screening was done which showed multiple hemangioblastomas at various levels of dorsal lumbar vertebra (figure 1) and multiple cystic lesions in pancreas and all poles of both kidneys with suspicious solid lesions in both kidneys- likely multifocal Renal cell carcinoma. PET CT with contrast enhanced triphasic and delayed abdominal phases was performed for staging. There were three FDG avid solid cystic heterodense lesions in the cortex of the right kidney (largest- 4.4x3.4cm, max SUV-3.11 in superior pole), other two endophytic lesions measuring 2x2cm each located in the inter polar region and lower pole. There was also one FDG avid solid cystic heterodense lesion noted in the inter polar region of the left kidney measuring 2.2x2.6x2.5cm with multiple fluid attenuating cystic lesions noted in bilateral kidneys (figure 2). The largest RCC located in the right upper pole was also abutting segment VI of liver with ill defined fat planes. Multiple cysts noted in entire extent of pancreas. No evidence of any other metastasis. In view of multiple hemangioblastomas, multiple renal and pancreatic cysts, suspicion of Von Hippel Lindau syndrome was made. Image guided biopsy from the right upper pole of kidney was done and it was suggestive of Clear cell RCC, WHO histological grade 1 with no evidence of sarcomatoid or rhabdoid areas.

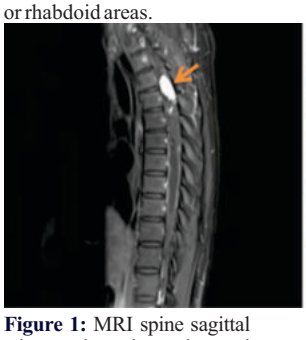

Figure 1: MRI spine sagittal view showing dorsal hemangioblastomas at D3-D4 level shown in orange arrow.

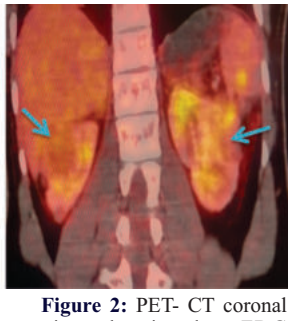

Figure 2: PET- CT coronal view showing low FDG uptake bilateral renal lesions (shown in blue arrows)

This case was discussed in our multi-disciplinary tumour board. In view of B/L RCC, possibility of B/L Nephron sparing surgery was considered. However, as the right kidney had multifocal 3 RCCs along with multiple cystic lesions and superior pole lesion was abutting liver with loss of fat planes, nephron sparing surgery was not technically feasible. Since left kidney had <3cm lesion, active surveillance and radiofrequency ablation were valid options. After discussing with patient, laparoscopic right nephrectomy was done for right RCC and active surveillance for left RCC. As there is only limited literature regarding neoadjuvant TKI or immunotherapy, they were not offered for this patient. He also underwent D3-D4 Laminectomy and excision of intramedullary hemangioblastoma that was causing severe backpain. Postoperative histopathology report suggestive of multiple clear cell carcinoma grade 1 (figure 3,4) and Hemangioblastoma grade 1 (figure 5,6). His postoperative course was uneventful. He recovered

well from both surgeries. Currently he is on sunitinib since 3months and on active surveillance of the left renal RCC.

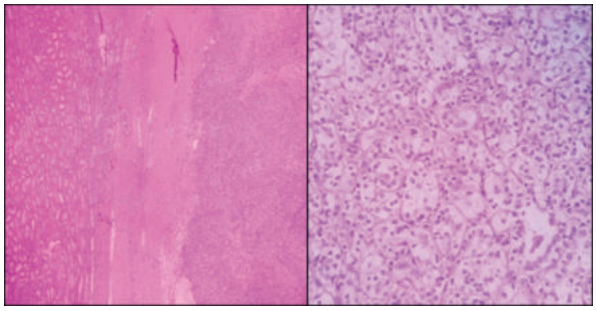

Fig 3- H&E 4x (scanner) – Normal renal parenchyma with tumor.

Fig 4- H&E 40x- Individual tumor cells with abundant clear cytoplasm, round to oval nuclei and nucleoli

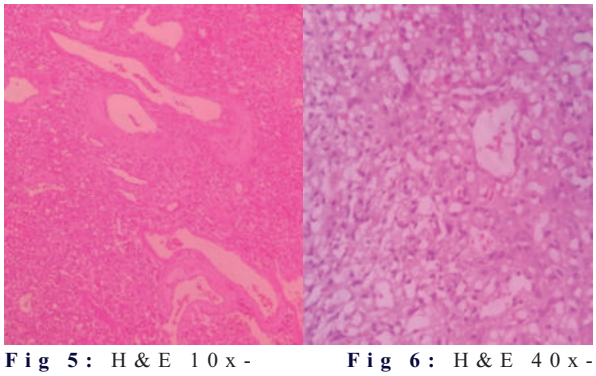

Fig 5: H&E 10x- Hemangioblastoma Moderately cellular tumor composed of neoplastic stromal cellinterspersed with numerous blood vessels in diffuse sheets

Fig 6: H&E 40x- Hemangioblastoma Stromal cells with mild nuclear pleomorphism, clear foamy cytoplasm

DISCUSSION:

There are many inherited renal cancer syndromes in which Von Hippel-Lindau (VHL) disease is the most common hereditary renal cell carcinoma (RCC) cancer syndrome [4]. They are usually bilateral. Due to young age at diagnosis of RCC in VHL patients and their lifelong risk of developing RCCs, they require multiple and repeated surgeries and interventions in each kidney during their lifetime. This will eventually result in chronic kidney disease (CKD) with high chances of death and they may survive until 50 years of age maximum.[5] So the main goal in managing RCCs in VHL patients is to preserve renal function as much as possible while treating RCCs. Active surveillance can be offered for small lesions of size less than 3cm as the risk of metastasis is low. For lesions more than 3cm, nephron sparing surgeries are preferred. In some cases, radiofrequency ablation is also an option.

Pathogenesis of VHL syndrome includes mutation in VHL which results in accumulation of Hypoxia inducible Factor (HIF). This leads to activation of HIF pathway and expression of VEGR, PDGF etc.[6] These factors cause upregulation of angiogenesis and increased cellular proliferation that lead to formation of highly vascular tumours both benign and malignant in retina, CNS, kidneys, pancreas etc. Tyrosine kinase inhibitors (TKI) that target VEGF pathway and inhibit angiogenesis have a significant role in the treatment of RCC. These TKIs such as Sunitinib, Axitinib can cause either tumor downstaging or can delay progression of residual RCC lesions that lead to delay in repeat surgeries and eventually can delay the development of CKD in those patients.

In Kaifang Ma et al [7] retrospective study of 32 patients, 12 patients (38%) received sunitinib, 11 (34%) received sorafenib, 6 patients (19%) axitinib and 3 patients (9%) pazopanib. After a median follow up of 31.5 months, 28% patients had partial response, 47% showed stable disease and 25% progressive disease with TKI therapy overall. Among Sunitinib treated patients, 33% showed partial response, 33% stable disease and 33% progressive disease. 27% had partial response, 36% stable disease and 36% disease progression in Sorafenib group. Out of 6 axitinib treated patients, 33% showed partial response and 67% stable disease. All patients who received Pazopanib (100%) had stable disease. Complete response was not seen with any TKI. In this study, Axitinib showed best response followed by Sunitinib and Sorafenib. Median OS was 72 months and 66 months (p= 0.89) and median PFS was 70 months and 57 months (p=0.44) for sunitinib and sorafenib treated patients respectively. There was no statistically significant difference between them. We chose Sunitinib to treat our patient based on his profile.

Belzutifan is the newer exciting drug which is US FDA approved for managing Von Hippel Lindau disease without performing immediate surgery.[8] It targets HIF-2α which is involved in the pathophysiology of VHL disease. It has been studied in upfront, refractory and adjuvant settings and found to have activity in patients with RCCs and non RCC neoplasms associated with VHL disease. It has more favourable safety profile than antiangiogenic TKIs. But it is not widely available. Various other HIF-2α inhibitors are also under study.

CONCLUSION :

Managing young patients with VHL can be a clinical challenge as they often require multiple surgeries. RCCs in VHL tend to be clear cell histology and rarely metastasize and nephron sparing surgery is ideal for them. However multifocal RCCs in the background of multiple cysts of the kidney can pose a surgical challenge for nephron sparing surgery. Neoadjuvant use of TKIs may favour nephron sparing surgeries and adjuvant TKIs can delay further surgeries. Newer drugs like Belzutifan seems to have potential role in VHL disease and may avoid multiple surgeries in near future.

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