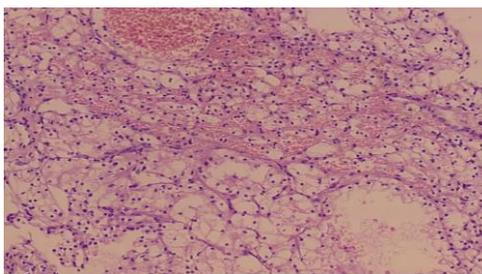


Clinical diagnosis and treatment of advanced renal cell carcinoma associated with von Hippel-Lindau syndrome: a rare case report and review of literature

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Abstract: Investigate the clinical characteristics of advanced renal cell carcinoma associated with von Hippel-Lindau syndrome to improve the clinicians' understanding and reduce the incidence of missed diagnosis and misdiagnosis. Retrospective analysis of clinical data of 1 patient which suffered VHL syndrome complicated with advanced renal cell carcinoma in urology of Yantai Yuhuangding Hospital Affiliated to Qingdao University, review with the literature. **Results:** This case of patients without renal mass family history, which multiple mass were found in the pancreas and kidney, several Suspicious mass Scattered in Bilateral kidney, one of the mass located in left renal was performed biopsy under the guidance of ultrasound, and the Histological analysis confirmed after operation were left renal clear cell carcinoma. Surgical is obviously not suitable for treatment due to the number of the tumor. Therefore sunitinib has been used as molecular targeted drug to treatment in 2 years, and regular Computed tomography (CT) scan found the tumor was significantly reduced in follow-up period. VHL syndrome can occur in multiple systems, renal cell carcinoma is a common cause of late death, accurate clinical diagnosis and treatment, can improve the late survival rate of patients with VHL syndrome.



Keywords: Von Hippel-Lindau syndrome; Renal cell carcinoma; Targeted therapy

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1. Introduction

Von Hippel-Lindau (VHL) syndrome is a rare autosomal dominant hereditary disease [1], the syndrome is a group of benign and malignant neoplasms involving systemic systems, Involved organs include the brain, retina, spinal cord, pancreas, kidney, adrenal gland, etc [2]. Research has shown [3] that most patients with kidney disease will eventually progress to renal cell carcinoma eventually if the survival time is long enough. Seven kinds of the gene are known to be associated with renal cell carcinoma, including Von-Hippel-Lindau (VHL), fumarate hydratase (FH) and succinate dehydrogenase (SDH) and so on [4]. Among all kidney cancers, clear cell renal cell carcinoma (ccRCC) accounts for more than 80% of the cases of renal cell carcinoma and is the most common with a molecularly distinct phenotype [5] and contain up to 91% nonfunctional VHL mutations [4]. ccRCC is the most frequent malignant tumours to occur in patients with von Hippel-Lindau (VHL) disease, and VHL disease is the primary cause of inherited renal cancer [6]. Clinically VHL syndrome mostly seen in patients with hereditary, sporadic VHL syndrome is uncommon which approximately 20% of VHL patients demonstrate negative family history [7], with disease resulting from a de novo mutation and its clinical manifestations are very complex due to the

different parts of the disease.

The incidence of VHL disease has been estimated by the molecular genetic testing to be 1 in 36,000 live births in the population of Eastern England and prevalences of 1/39000 in South-West Germany and 1/53 000 in Eastern England [8,9], with gradually more apparent clinical manifestations occurring between ~18 and 30 years of age [10]. Clinical diagnosis is more difficult and easy misdiagnosed to sporadic VHL syndrome without a positive family history. Retrospective analyze the clinical data and treatment plan of a case of de novo VHL disease in a female patient with advanced bilateral multifocal RCC involvement in our hospital, and to improve the knowledge and diagnosis ability of VHL syndrome and reduce the misdiagnosis and misdiagnosis. Written informed consent was obtained from the patient. The relevant literature is also reviewed.

2. Case

A 21-year-old female parent was admitted to Yuhuangding Hospital, Qingdao University (Yantai, China) with a six-day history of found double kidney tumor. She has found an unknown mass in right abdomen inadvertently a month ago, however it has been ignored because there have no discomfort. One Urinary ultrasonography checked in outside our

hospital discovery the multiple renal solid mass, right kidney capsule solid mass, double kidney cysts. The patient comes to our hospital for further diagnosis and treatment. The image of CT uveography and CT angiography were showed: kidney and pancreas have multiple lesions, consider the VHL syndrome, bilateral renal multi-cystic mass, consider the possibility of renal clear cell carcinoma, combined with renal pancreas Multiple cysts. The patient had a negative family history of renal tumors. All the relative in her family have no found a relative clinical performance about VHL syndrome. She has no previous medical history and was Unwed during this time. Admission diagnosis: 1) bilateral kidney tumor; 2) multiple renal cysts; 3) pancreatic cyst. The left renal biopsy was performed under the guidance of ultrasound, and the pathological changes after operation were left renal clear cell carcinoma (Figure 1). Postoperative diagnosis: 1) multiple renal cysts, pancreatic cysts, VHL syndrome; 2) renal clear cell carcinoma .After consultation with patient and their families, the targeted therapy using sunitinib were implement because there were too many lesions to doing surgical operation. 50mg/day for oral administration, 4 weeks after the drug withdrawal for 2 weeks. This 4/2 program were continued treatment for up to 2 years which kept review of renal CT. The good news that

bilateral renal tumor was found to be atrophic (Figure 2) and no new symptoms were appearance.

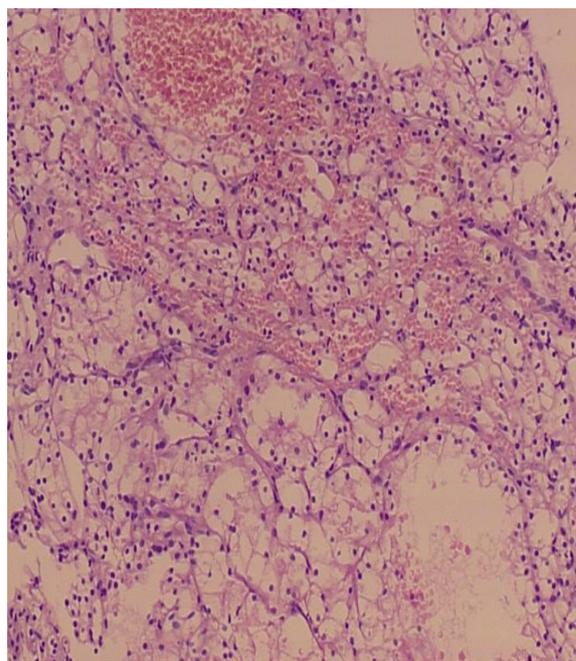


Figure 1. Renal clear cell carcinoma was confirmed histologically (x20; HE).

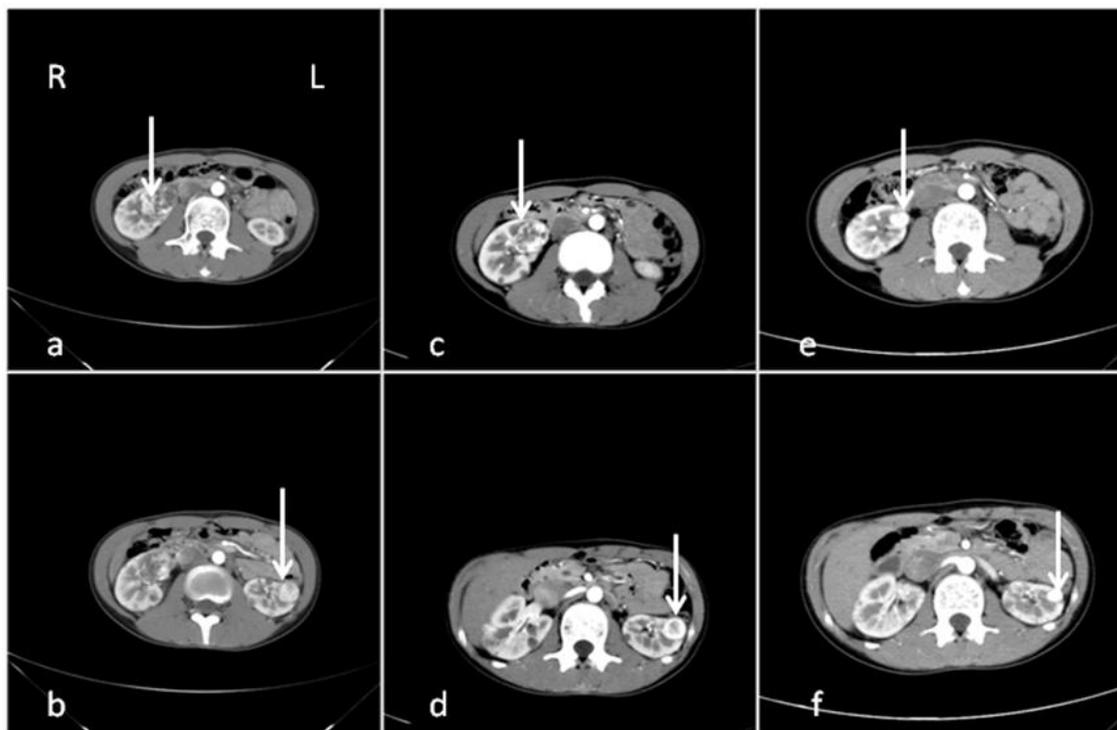


Figure 2. The contrast-enhanced abdominal CT imaging at the period of before (a and b), during (c and d) and after (e and f) used of Sunitabine, The arrow points to the largest diameter of the mass.

3. Discussion

VHL syndrome is caused by a germline mutation in the VHL gene where located in chromosome 3 short

arm [11,12], the VHL gene is a tumor suppressor gene normally, and a normal VHL protein cannot be synthesized by vascular endothelial growth factor (VEGF) expression increased when the gene had been

mutated or deleted, all of pathophysiological changes induced the Hemangioblastoma [13]. VHL syndrome is an autosomal dominant genetic disease. The mutational VHL gene can originate from anyone of parents, all the patients with familial hereditary VHL syndrome would have gene mutation; but there is still have one kind of VHL syndrome without familial history, which called sporadic VHL syndrome, induced by the non penetrance or mosaicism, remutations and other mechanisms [14].

The earliest reported of the VHL syndrome can be traced back to the early 20th-century, the first report of the retinoblastoma family hereditary was written by Von Hippel, a German ophthalmologist, and since then the disease is named after both when the Swedish ophthalmologist Lindau published retinoblastoma associated with renal and pancreatic tumors reported. Later, some scholars have found that these patients can also be associated with pheochromocytoma. In 1970s, Dr. Melmon first named the comprehensive disease of benign and malignant tumor of the kidney, pancreas and other organs which associated with hemangioblastomas of the central nervous system as Von Hippel-Lindau (VHL) syndrome [15]. The incidence of VHL syndrome has been estimated to be 1 in 36,000 live births and has over 90% penetrance by the age of 65 [16]. The average survival age <50 years because poor prognosis and the most common cause of death is rupture of CNS hemangioblastoma, renal cell carcinoma and pheochromocytoma induced malignant hypertension [17]. So early diagnosis is very necessary for the subsequent treatment.

The complex clinical manifestations of VHL syndrome make it difficult to diagnose. VHL syndrome includes clinical diagnosis and gene diagnosis. At present, the commonly used clinical diagnostic criteria [18, 19] include: 1) multiple retinal and central nervous system hemangioblastoma; 2) a kind of retinal and central nervous system hemangioblastoma concured visceral lesions; (3) with VHL syndrome positive family history and one of the standard above. Although many studies suggest that gene diagnosis is the gold standard for the diagnosis of VHL syndrome [20], it is not widely used in clinical practice. Therefore VHL syndrome is mainly based on clinical diagnosis presently. In this study, we found this patient have double kidney tumor, multiple renal cysts and pancreatic cyst. The left renal biopsy was performed under the guidance of ultrasound, and the histological analysis revealed clear cell carcinomas. According to the above diagnostic criteria, she can be diagnosed as VHL syndrome. Further diagnosed should be made as family hereditary VHL syndrome due to positive family history.

Surgical and targeted therapy are the main treatment for VHL syndrome. Research has shown [3] that most patients will occur in renal cell carcinoma eventually if the survival time is long enough, other additional complication such as pancreas, epididymis, liver disease always have no clinical symptoms and have a

good prognosis. The surgery, radiofrequency ablation and targeted therapy for renal tumors underwent when advanced kidney cancer have metastasized [21], while preserving surgery in the treatment of larger than 3cm in diameter, can reduce the transfer of risk, protect the renal function of [22], However, studies have revealed that the majority of patients with VHL-associated RCC eventually develop local recurrence with the concomitant requirement for repeated renal surgery [23], so long-term follow-up is very necessary. Currently, no definitive guidelines and unified consensus are available with regard to the timing and surgical approach for these multicentric bilateral tumors. However, the main goal of treatment should be to control the progress of cancer, to protect residual kidney function and to avoid kidney or adrenal gland-related diseases rather than cure [14]. Related studies have reported that the majority of RCCs in VHL syndrome exhibit a low pathological grade [23]. But in this case which have multiple renal mass and uneven enhancement. Renal clear cell carcinoma was confirmed by biopsy. The size of the larger mass was 4.0cmx3.5cm in right kidney and 2.0cmx2.0cm in left kidney. Thus, surgical treatment program was excluded and targeted therapy was treated as the first choice. The commonly targeted drug are listed below: 1) Antiangiogenic drugs such as bevacizumab, sunitinib and pazopanib, Sola Fini, it has been proved that can earn a significant efficacy in the treatment of metastatic renal cell carcinoma; 2) Hypoxia inducible factor inhibitor, VHL gene mutation leads to overexpression of hypoxia inducible factor and this increases the formation of erythropoietin (EPO) which induced cell proliferation, chemotaxis and angiogenesis, and inhibit apoptosis [24]; 3) gene therapy [25]. Sunitinib was administered (50 mg every day for 4 weeks then withdrawal for 2 weeks) for 2 years. Computed tomography (CT) was used to detect the gradually atrophic renal masses in the period of follow-up.

In conclusion, VHL syndrome have different clinical manifestations because incidence of non synchronization of different organs. This easily leads to misdiagnosis, missed diagnosis. The contrast-enhanced abdominal CT imaging can be used as one standard method for the detection of renal involvement in patients with VHL. Most patients will suffered renal lesions in the late survival and nephron-sparing surgery (NSS) can be considered for patients with renal cell carcinoma. For patients with advanced renal cell carcinoma, Sunitinib can be used as an alternative to surgical treatment to prolong the survival of patients with VHL syndrome.

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