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Patient with Von Hippel-Lindau disease diagnosed with Renal Cell Carcinoma

Paciente com doença de Von Hippel-Lindau diagnosticado com Carcinoma de Células Renais

Paciente con enfermedad de Von Hippel-Lindau diagnosticado con Carcinoma de Células Renales

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Abstract
Von Hippel-Lindau disease is an autosomal dominant hereditary disorder caused by a germline mutation in the VHL gene. Those mutations lead to the development of multiple benign and malignant tumors, including renal cell carcinoma (RCC). VHL disease is the most common risk factor for hereditary RCC, presenting in 1 in 36,000 live births. Patients with VHL disease are at high risk of early and multiple clear cell RCC; approximately two-thirds will present several renal cysts and RCC during their lifetimes. RCCs are the leading cause of death in patients with VHL, and median overall survival in these patients is around 50 years. The purpose of the present study is to present a clinical case report of a 54-year-old Indonesian male patient who had a stiff neck, followed by constant tingling in the right arm. The patient was subsequently diagnosed with VHL disease based on clinical diagnostic criteria, which included central nervous system (CNS) hemangioblastoma, pancreatic cyst, and RCC. Early recognition and treatment remain the mainstay of VHL disease management. Treatment decisions for RCC in VHL depend on tumor size and growth kinetics of each lesion, as those parameters determine the risk of metastatic disease. The main therapeutic goal to deal with RCCs in patients with VHL disease is to remove as many RCCs as possible while preserving renal function.
Keywords: VHL disease; Autosomal dominant; Renal cell carcinoma.

Resumo
A doença de Von Hippel-Lindau é um distúrbio hereditário autossômico dominante causado por uma mutação germinativa no gene VHL. Essas mutações levam ao desenvolvimento de múltiplos tumores benignos e malignos, incluindo o carcinoma de células renais (CCR). A doença VHL é o fator de risco mais comum para o CCR hereditário, apresentando-se em 1 a cada 36.000 nascimentos vivos. Pacientes com a doença de VHL têm alto risco de desenvolver CCR de células claras de forma precoce e múltipla; aproximadamente dois terços apresentarão múltiplos cistos renais e CCR ao longo da vida. O CCR é a principal causa de morte em pacientes com VHL, e a sobrevida geral mediana desses pacientes é em torno de 50 anos. O objetivo do presente estudo é apresentar um relato de caso clínico de um paciente masculino indonésio de 54 anos, que se apresentou com rigidez no pescoço, seguida de formigamento constante no braço direito. O paciente foi subsequentemente diagnosticado com a doença de VHL com base nos critérios diagnósticos clínicos, incluindo hemangioblastoma do sistema nervoso central (SNC), cisto pancreático e CCR. O reconhecimento precoce e o tratamento continuam sendo a principal estratégia no manejo da doença de VHL. As decisões de tratamento para o CCR na VHL dependem tanto do tamanho do tumor quanto da cinética de crescimento de cada lesão, pois esses parâmetros determinam o risco de doença metastática. O principal objetivo terapêutico no manejo do CCR em pacientes com a doença de VHL é remover o maior número possível de CCRs, preservando a função renal.
Palavras-chave: Doença VHL; Autossômica dominante; Carcinoma de células renais.

Resumen
La enfermedad de Von Hippel-Lindau es un trastorno hereditario autosómico dominante causado por una mutación germinal en el gen VHL. Estas mutaciones conducen al desarrollo de múltiples tumores benignos y malignos, incluido el carcinoma de células renales (CCR). La enfermedad VHL es el factor de riesgo más común para el CCR

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hereditario, presentándose en 1 de cada 36,000 nacimientos vivos. Los pacientes con enfermedad de VHL tienen un alto riesgo de desarrollar CCR de células claras de manera temprana y múltiple; aproximadamente dos tercios presentarán múltiples quistes renales y CCR a lo largo de su vida. El CCR es la principal causa de muerte en pacientes con VHL, y la supervivencia global media en estos pacientes es de alrededor de 50 años. El propósito del presente estudio es presentar un informe de caso clínico de un paciente masculino indonesio de 54 años, que presentó rigidez en el cuello, seguido de hormigueo constante en el brazo derecho. El paciente fue diagnosticado posteriormente con enfermedad de VHL basado en los criterios diagnósticos clínicos, que incluyen hemangioblastoma del sistema nervioso central (SNC), quiste pancreático y CCR. El reconocimiento temprano y el tratamiento siguen siendo la piedra angular del manejo de la enfermedad de VHL. Las decisiones de tratamiento para el CCR en VHL dependen tanto del tamaño del tumor como de la cinética de crecimiento de cada lesión, ya que estos parámetros determinan el riesgo de enfermedad metastásica. El principal objetivo terapéutico en el manejo del CCR en pacientes con enfermedad de VHL es eliminar el mayor número posible de CCR, preservando la función renal.
Palabras clave: Enfermedad VHL; Autosómica dominante; Carcinoma de células renales.

1. Introduction

Von Hippel-Lindau (VHL) disease is a hereditary condition inherited in an autosomal dominant manner, characterized by cysts, benign tumors, and malignant tumors in various organs, with a prevalence of approximately 1 in 39,000 to 1 in 91,000 individuals (Akioka et al., 2022). Tumors associated with VHL disease are typically diagnosed in adulthood, although they can be found at younger ages, depending on the type of VHL and the clinical manifestations that arise. The spectrum of clinical manifestations of VHL disease is broad, including hemangioblastomas of the central nervous system (CNS), retinal hemangioblastomas, renal cell carcinoma (RCC), pheochromocytomas (Pheo), pancreatic cystic lesions, endolymphatic sac tumors (ELST), and epididymal cystadenomas (Zhang et al., 2015; Binderup et al., 2022; Cinque et al., 2022).

VHL disease is classified into several types and subtypes based on the presence or absence of pheochromocytomas (Pheo) and clear cell renal cell carcinoma (ccRCC): Type 1 is the most common form and does not involve pheochromocytomas, whereas Type 2 is associated with pheochromocytomas. Type 2 VHL is further classified into Type 2A (presence of pheochromocytoma without RCC), Type 2B (presence of both RCC and pheochromocytoma), and Type 2C (pheochromocytoma is the only manifestation of the disease) (Cinque et al., 2022; Kim & Zschiedrich, 2018)

Hereditary cancer syndromes related to the kidney account for about 5-8% of cases. VHL disease is the most common hereditary risk factor for RCC, with an incidence rate of 1 in 36,000 live births (Northrup et al., 2012). Patients with VHL have a predisposition to develop renal cysts and RCC. RCC is found in 40-70% of patients with VHL, with an average age of diagnosis between 39 and 44 years. This disease is rare before the age of 20, though it can occur between the ages of 15 and 75 (Cinque et al., 2022; Chahoud et al., 2021).

RCC is one of the leading causes of death in VHL disease. An important risk factor related to the decreased life expectancy in VHL patients is the high prevalence and recurrence rate of RCC (Carrion et al, 2020). Evaluation and management of RCC are critical, as these tumors can significantly impact both survival rates and the quality of life for patients and their families. In recent years, the incidence and mortality rates of RCC related to VHL have significantly decreased due to the implementation of guidelines for routine screening for RCC (Cinque et al, 2022; Carrion et al., 2020).

The purpose of the present study is to present a clinical case report of a 54-year-old Indonesian male patient who had a stiff neck, followed by constant tingling in the right arm.

2. Methodology

This research is a qualitative, descriptive study or case report (Estrela, 2018; Pereira et al., 2018) and was prepared following the CARE Guidelines. It studied a 54-year-old male arriving at the hospital with a case of Von Hippel-Lindau disease and renal cell carcinoma. We also performed a secondary literature review to help readers better understand how to

diagnose and treat RCC in VHL patients. Ethical approval is waived from this study by our IRB.

3. Case Report

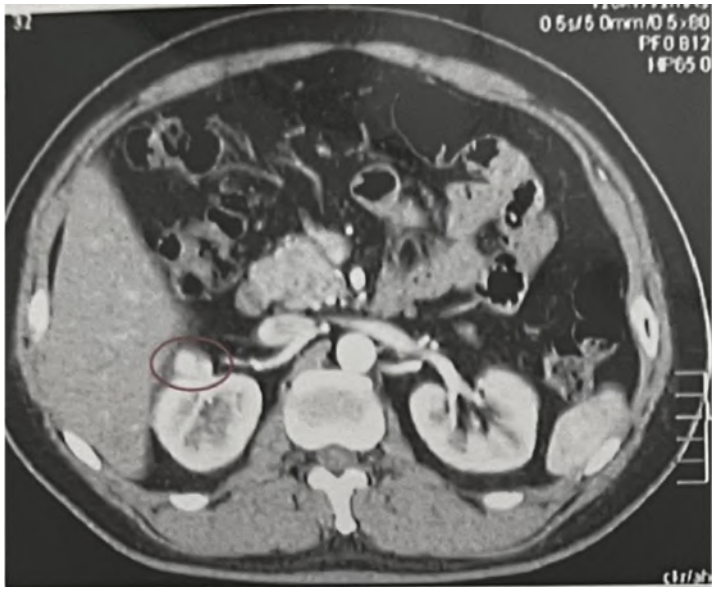
A 54-year-old male patient initially presented with pain and stiffness in the back of his head and neck in 2004, describing the sensation as though being cut by a sharp object. The complaint was nearly constant throughout the day, causing significant discomfort. The patient consulted several specialists, but the symptoms persisted. In 2005, he sought treatment in Singapore, where it was suggested that there was an issue with the nerves in his neck.

Four years after the initial complaints, the patient began experiencing additional symptoms, including involuntary movement of his right little finger and persistent neck pain. He underwent multiple physiotherapy sessions, but the symptoms continued. The patient then had an MRI of the spine at a private hospital, which revealed an issue with the C5-C6 disc. In 2014, he developed tingling and pain in his right hand, with decreased strength, making it difficult to perform tasks like writing. He also experienced tingling and pain in both legs.

The patient subsequently resumed treatment in Singapore. An MRI of the brain revealed a tumor in the posterior cervical-medullary junction, measuring 2.8 x 2 x 1.8 cm, with a cyst in front of it. The patient underwent a sub-occipital craniectomy, C1 laminectomy, and tumor excision in March 2014. Histopathological examination showed morphology consistent with hemangioblastoma. Immunohistochemistry testing was performed, with GFAP and CD10 being negative, and the Ki67 proliferation index at 1-2%. The immunohistochemical profile was consistent with hemangioblastoma. The patient was then suspected of having Von Hippel-Lindau disease.

Two months later, the weakness in his right hand improved, and the tingling sensations also subsided. A follow-up MRI of the brain showed no evidence of hemangioblastoma. A CT scan of the abdomen revealed a mass in the pancreas (measuring 3.5 x 3.7 x 3 cm) and a mass in the upper pole of the right kidney (measuring 1.5 x 1.5 x 1.7 cm). The patient was advised to undergo surgery but refused. At that time, he was also referred to an ophthalmologist to see the evaluation of retinal angioma, but no retinal angioma was found. The CT scan can be seen in Figure 1.

Figure 1 - The right kidney mass was measured having: 1.5 x 1.5 x 1.7 cm on the abdominal CT scan.



Source: Authors.

Figure 1 shows a right kidney mass of 1.5 x 1.5 x 1.7 cm indicated inside the circle.

In August 2014, the patient sought treatment in Guangzhou, which included radioactive therapy for the pancreatic tumor and interventions such as embolization, cryotherapy, and microwave ablation for the kidney mass. The patient then continued these treatments each 6 months, combined with immunotherapy. In early 2018, a follow-up evaluation showed that the kidney mass had grown to 4.3 x 3.8 x 3.7 cm.

In September 2019, the patient underwent another surgery on the right kidney in Singapore. Due to the COVID-19 pandemic, the patient did not continue treatment at that time, though the patient had no symptoms. In January 2023, an MRI revealed lung metastasis with a mass size of approximately 6 cm. The patient then resumed treatment with immunotherapy in Bali. The patient is currently undergoing the sixth series of pembrolizumab immunotherapy and regularly taking lenvatinib 10 mg once a day.

The patient is the second of four siblings. The patient's older sister was diagnosed with breast cancer before the patient experienced symptoms. No malignancy or family history was found in the parents or the two younger siblings.

4. Discussion

Von Hippel-Lindau (VHL) disease is a hereditary syndrome inherited in an autosomal dominant manner, caused by a germline mutation in the VHL gene located on the short arm of chromosome 3 (3p25-26) (Zhang et al., 2016). The VHL gene mutation leads to the development of both benign and malignant tumors affecting various organ systems. Hemangioblastomas of the central nervous system (CNS) are the most common tumors in VHL disease, found in 60-80% of patients (Thulung et al., 2020). In this case, the patient was initially diagnosed with a hemangioblastoma of the central nervous system (CNS), so VHL disease should be considered as one of the differential diagnoses.

The diagnosis of VHL disease is based on clinical criteria. The first diagnostic criteria, established in 1964, include: a) a family history of VHL disease with at least one hemangioblastoma or a typical tumor associated with VHL, or b) a patient without a family history of VHL disease who presents with two typical tumors associated with VHL, which may include two hemangioblastomas or one hemangioblastoma along with a visceral manifestation of VHL disease (Thulung et al, 2020; Reddy et al., 2020); Maher et al., 2022). Clinical findings included in the diagnostic criteria for VHL disease include hemangioblastomas of the central nervous system (CNS), retinal hemangioblastomas, renal cell carcinoma (RCC), pheochromocytomas, pancreatic cystic lesions, endolymphatic sac tumors (ELST), and epididymal cystadenomas.[3] In this case, there is no family history of VHL disease, but the patient has a hemangioblastoma of the central nervous system (CNS) along with visceral tumors, including a pancreatic tumor and RCC. Therefore, the patient meets the clinical criteria for a diagnosis of VHL disease, even though genetic testing was not performed.

VHL disease is classified into several types and subtypes based on the presence or absence of pheochromocytomas (Pheo) and clear cell renal cell carcinoma (ccRCC): Type 1 is the most common form and does not involve pheochromocytomas, while Type 2 is associated with pheochromocytomas. Type 2 VHL is further subdivided into Type 2A (presence of pheochromocytoma without RCC), Type 2B (presence of both RCC and pheochromocytoma), and Type 2C (pheochromocytoma is the only manifestation of the disease) (Cinque et al., 2022; Kim and Zschiedrich et al, 2018). In this case, the patient does not show manifestations of pheochromocytoma, only RCC, so the patient can be classified as having VHL type 1.

Approximately 5-8% of RCC cases have a hereditary basis, with VHL being the most common cause (Zhang et al., 2015; Cinque et al., 2022). In general, RCC develops in 40-70% of patients with VHL disease, with an average age of diagnosis between 39 and 44 years (Cinque et al., 2022; Zhang et al., 2016; Kim et al., 2013). The dominant histological type of VHL-related RCC is clear cell carcinoma, accounting for approximately 75-91% of cases. However, kidney biopsy is not routinely performed in patients with VHL disease (Zhang et al., 2015; Cinque et al., 2022). A kidney biopsy is indicated when

imaging findings are atypical, there is a history of extrarenal malignancy that may have spread to the kidney, or if there is suspicion of recurrence after surgery or ablation procedures (Cinque et al., 2022; Chahoud et al., 2021). Clear cell RCC (ccRCC) associated with VHL is typically multiple and bilateral in over 75% of cases. It tends to be low-grade, with low rates of local spread, and does not metastasize when the tumor size is less than 3 cm (Zhang et al., 2015; Cinque et al., 2022).

ccRCC associated with VHL has a high recurrence rate. The diagnosis of RCC is often delayed due to the asymptomatic natural course of the disease. As a result, typical symptoms and signs of RCC, such as hematuria, flank pain, and a palpable mass in the flank region, often indicate more advanced disease, although these findings are rare. The first-line diagnostic technique in suspected RCC is an abdominal CT scan with contrast, which helps determine the location, number, size, and appearance of solid lesions (Zhang et al., 2015; Cinque et al., 2022). In this case, the classic triad of RCC symptoms was not present in the patient. However, a renal tumor was discovered through imaging performed as part of the workup for the patient's VHL disease. This suggests that the RCC in this patient may represent an early stage of the disease, which remains asymptomatic.

The primary goal of managing RCC in VHL disease is to reduce tumor size while preserving kidney function. Treatment options depend on the tumor size and growth rate, as these factors determine the risk of metastasis.[7] If the tumor size is < 3 cm, active surveillance is generally the approach, with periodic MRI or contrast-enhanced CT scans of the abdomen every 3-6 months during the first year to assess the tumor's growth rate (Chahoud et al., 2021). If the tumor remains stable after three MRI scans, the interval between follow-up MRIs may be extended to two years. Conversely, if the tumor exceeds 3 cm in size, the patient should be referred to the urology surgery department for further management (Chahoud et al., 2021).

Surgical intervention is the standard management for lesions larger than 3 cm, as this size is associated with an increased risk of metastasis. Surgical options include radical nephrectomy and nephron-sparing surgery (NSS). NSS or partial nephrectomy is currently the standard therapy for RCC associated with VHL and can be performed using either a laparoscopic or open approach (Carrion et al., 2020; Bhuyan et al., 2020; National Comprehensive Cancer Network, 2023). NSS can preserve kidney function and reduce the risk of metastasis, while also having a lower risk of bleeding compared to radical nephrectomy. NSS is now widely performed in patients with T1a and T1b renal tumors (size < 7 cm) and in cases where the contralateral kidney is normal, with outcomes equivalent to those of radical nephrectomy (National Comprehensive Cancer Network, 2023). Radical nephrectomy is the surgical procedure of choice when the tumor has extended into the inferior vena cava or as an alternative when NSS cannot be performed. However, this approach is associated with an increased risk of chronic kidney disease, as well as higher cardiovascular morbidity and mortality (National Comprehensive Cancer Network, 2023).

Ablative techniques such as cryoablation, radiofrequency ablation (RFA), and microwave ablation (MWA) can be alternatives for patients with smaller tumors, approximately 2-3 cm in size, located away from blood vessels, and at high risk for surgical procedures (Chahoud et al., 2021). NCCN guidelines recommend ablative techniques only for patients with stage I RCC (T1a) (National Comprehensive Cancer Network, 2023). Ablative techniques provide good short-term results, but the long-term outcomes are still unknown (Akioka et al., 2022). In this patient, microwave ablation was performed as the initial treatment for RCC, given that the tumor size was < 3 cm at the time of discovery. Upon follow-up, the tumor size had increased to 4.3 x 3.8 x 3.7 cm, prompting the decision to perform nephron-sparing surgery (NSS) via laparoscopy on the patient's right kidney.

After surgery, 20-30% of patients with localized tumors will experience recurrence. Pulmonary metastasis is the most common site of distant spread, affecting 50-60% of patients, with the highest recurrence rates occurring within 3 years post-surgery (National Comprehensive Cancer Network, 2023). Several systemic therapies can be considered for recurrent RCC or stage IV RCC, including targeted therapies, immune checkpoint inhibitors, and anti-angiogenic agents (National

Comprehensive Cancer Network, 2023). In this case, the patient showed evidence of mass spread to the lungs, so management was continued with systemic therapy using a combination of lenvatinib and pembrolizumab. Lenvatinib is a second-generation tyrosine kinase inhibitor (TKI) that acts as an anti-angiogenic agent by targeting the vascular endothelial growth factor (VEGF) receptor. Pembrolizumab, on the other hand, is a monoclonal antibody that selectively binds to programmed death (PD)-1 and inhibits its interaction with programmed death ligands 1 and 2 (PD-L1 and PD-L2) (Choueiri et al., 2021). In August 2021, the U.S. Food and Drug Administration (FDA) approved the combination of lenvatinib and pembrolizumab as first-line systemic therapy for patients with advanced clear cell renal cell carcinoma (ccRCC) (National Comprehensive Cancer Network, 2023). A phase 3 study comparing the combination of lenvatinib and pembrolizumab with sunitinib monotherapy found that the combination of lenvatinib and pembrolizumab was significantly associated with longer progression-free survival (PFS) and overall survival (OS) in patients with advanced RCC compared to sunitinib monotherapy (Motzer et al., 2021).

5. Conclusion

This study reports the case of a patient with von Hippel-Lindau (VHL) disease who developed renal cell carcinoma (RCC). The diagnosis of VHL in this case was made based on clinical criteria, with the discovery of a central nervous system (CNS) hemangioblastoma, accompanied by typical visceral manifestations of VHL, including pancreatic cystic lesions and RCC. The evaluation and management of RCC are crucial, as RCC is one of the leading causes of death in VHL disease. The primary goal of RCC management in VHL is to remove as much of the RCC as possible while preserving kidney function. However, treatment options largely depend on tumor size and growth rate.

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