

# Cardiac Involvement in Von Hippel-Lindau Disease

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## Key Words

Cardiomyopathy · Cardiovascular disease · Pheochromocytoma · Von Hippel-Lindau disease · Screening

## Abstract

**Objective:** The aim of this case report was to highlight the importance of ruling out pheochromocytoma in a patient with Von Hippel-Lindau disease (VHL) and cardiovascular manifestations. **Clinical Presentation and Intervention:** A 22-year-old woman with type IIb VHL presented with signs and symptoms of acute decompensated heart failure. Transthoracic echocardiography showed a dilated left ventricle with severely depressed ejection fraction, confirmed by MRI. Urinary catecholamine and metanephrine tests had elevated levels and an abdominal MRI showed the presence of two cystic masses at the left hypochondrium. Surgical resection of both masses was performed, confirming the diagnosis of pheochromocytoma and clear cell renal carcinoma on histology. Six-month echocardiography showed a left ventricle with normal diameters and preserved ejection fraction. Genetic analysis revealed a germline mutation (exon 3 deletion of VHL). As there was no family history of VHL, it was determined to be a de novo mutation. **Conclu-**

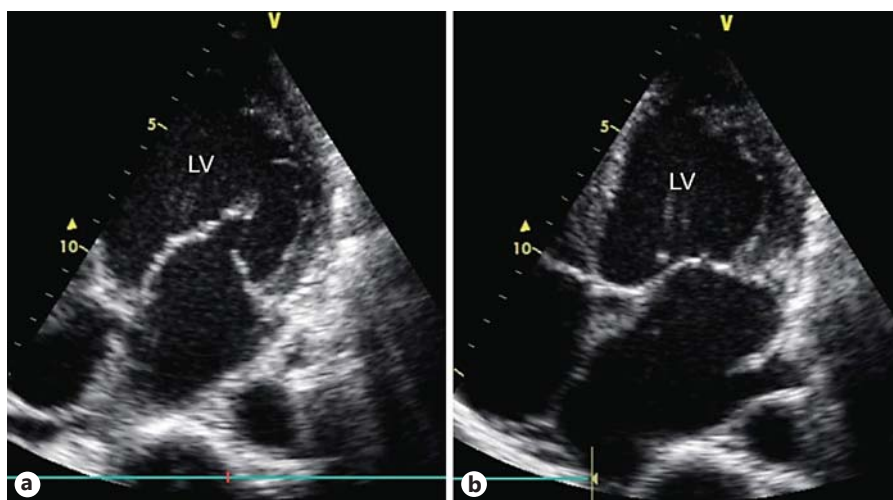
**sion:** This case report showed an atypical manifestation in a patient with VHL and underlines the importance of screening for pheochromocytoma in such patients.

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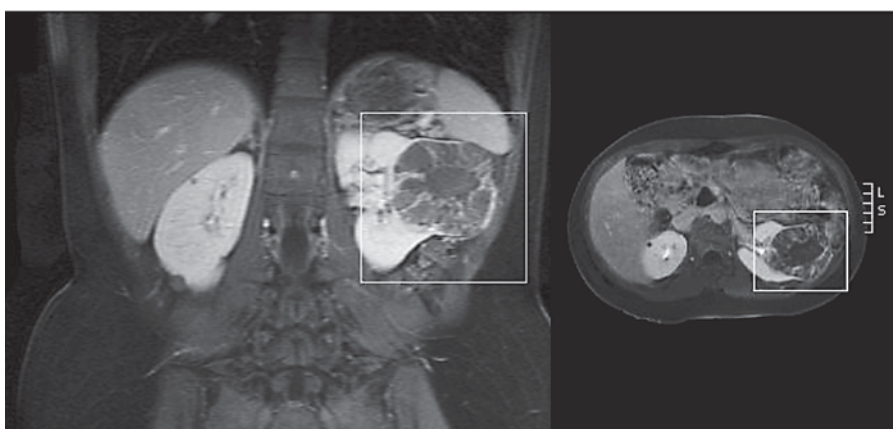
## Introduction

Von Hippel-Lindau disease (VHL) is a rare genetic syndrome that increases the risk of developing various benign and malignant tumors of the central nervous system, kidneys, adrenal glands and pancreas [1, 2]. Its association with pheochromocytoma has been described in approximately 20% of the cases [3], but its presentation in the form of dilated cardiomyopathy and acute heart failure is not common [4]. Classically, VHL has been grouped into 2 different familial types according to phenotype. Type I families have a reduced risk of presenting with pheochromocytomas, but can develop all the other tumor types associated with the disease. Type II families have pheochromocytomas and are subclassified into 3 different types according to the risk of developing renal cell carcinomas: type IIa (low-risk), type IIb (high-risk) and type IIc (pheochromocytomas only, with no other neoplastic finding) [1]. Therefore, this case was reported

**Fig. 1.** Transthoracic echocardiography. **a** Apical view showing a dilated left ventricle (LV) with severely depressed ejection fraction at diagnosis. **b** Apical view showing normalization of the LV diameters with preserved ejection fraction 6 months after surgical resection.



**Fig. 2.** Abdominal MRI showing two cystic masses (white boxes) at the left hypochondrium.



in order to emphasize the importance of ruling out pheochromocytoma in all patients with VHL presenting with cardiovascular manifestations.

### Case Report

We present the case of a 22-year-old woman who was diagnosed in childhood with type IIb VHL, with known multiple retinal angiomas, pancreatic cysts, and spinal and cerebellar hemangioblastomas. She was admitted to our hospital complaining of progressive dyspnea and palpitations. On examination, her blood pressure was 159/119 mm Hg and her pulse was 123 bpm. Physical examination revealed a systolic murmur at the mitral focus with irradiation to the axilla and pulmonary rales. Electrocardiography revealed no remarkable findings, except for sinus tachycardia. Laboratory tests showed an elevated N-terminal pro-brain natriuretic peptide and chest X-ray showed signs of pulmonary interstitial edema. The patient was admitted to the Department of Cardiology with the diagnosis of acute decompensated heart failure. Transthoracic echocardiography showed a dilated left ventricle with severely depressed ejection fraction due to generalized hypokinesia and

a mild mitral regurgitation (fig. 1a). During admission, the patient had several episodes of paroxysmal dyspnea despite treatment with  $\beta$ -blockers and diuretics. Due to the clinical suspicion of adrenal gland disease, 24-hour urinary catecholamine and metanephrine tests were requested. Cardiac MRI was performed in order to complete the cardiomyopathy study, and confirmed the echocardiographic findings as well as revealed an incidental finding of a great left renal mass. The 24-hour urine laboratory tests showed markedly elevated levels of norepinephrine, total catecholamines, normetanephrine and metanephrine with normal epinephrine values: 24-hour norepinephrine 468  $\mu\text{g}$  (normal range: 23–105), 24-hour epinephrine 13  $\mu\text{g}$  (normal range: 4–20), 24-hour total catecholamines 658  $\mu\text{g}$  (normal range: 217–575), 24-hour normetanephrine 2,988  $\mu\text{g}$  (normal range: 105–354), 24-hour total metanephrine 3,013  $\mu\text{g}$  (normal range: 0–1,000). Therefore, an abdominal MRI was performed, which showed the presence of two cystic masses (fig. 2) located at the left hypochondrium. Surgical resection of both masses was performed (after  $\alpha$ -blockade with phenoxybenzamine and  $\beta$ -blockade with propranolol) through a laparoscopic approach, confirming the diagnosis of pheochromocytoma and clear cell renal carcinoma on histology. During follow-up, blood pressure and heart rate values normalized (124/77 mm Hg, 78 bpm), 24-hour urinary catecholamine values returned to nor-

mal range (norepinephrine 69 µg/24 h, total catecholamine 221 µg/24 h, normetanephrine 202 µg/24 h and total metanephrine 259 µg/24 h) and the patient had no new episodes of palpitations or dyspnea. Six months after surgical resection, echocardiography was repeated and showed a left ventricle with normal diameters and preserved ejection fraction (fig. 1b). Genetic analysis revealed a germline mutation (exon 3 deletion) of the VHL tumor suppressor gene on the short arm of chromosome 3. As the patient had no family history of VHL, it was concluded that it was a de novo mutation.

## Discussion

This case report showed an atypical manifestation in a patient with VHL and the importance of screening for pheochromocytoma in such patients.

Clinical expression of pheochromocytoma may involve numerous cardiovascular manifestations (as in this case), but it classically presents as sustained or paroxysmal hypertension associated with other signs and symptoms of catecholamine excess, such as the triad of episodic headaches, palpitations and increased sweating [5, 6]. Most of the life-threatening cardiovascular manifestations of pheochromocytoma (e.g. hypertensive emergencies, ventricular arrhythmias or even shock) result from a rapid and massive release of catecholamines from the tumor [4]. More rarely, patients present with acute decompensated heart failure and dilated cardiomyopathy due to a sustained secretion of catecholamines leading to left ventricular dysfunction [4]. This dilated cardiomyopathy is known to be transient and reversible after surgical re-

section in most of the cases; however, there are cases described in the literature showing no improvement in ejection fraction after surgical resection of pheochromocytomas associated with VHL [7]. However, the management of cardiac complications in these patients is not easy [8] and the use of  $\alpha$ - and  $\beta$ -blockade before surgery is usually recommended [5].

As the cardiovascular complications of pheochromocytoma can be life-threatening, all patients with VHL who present with manifestations that even remotely suggest excessive catecholamine secretion should be screened for the disease [5]. Clinical manifestations of pheochromocytoma in VHL are different from those occurring in isolated pheochromocytoma and are more difficult to detect because they usually have less catecholamine secretion. Screening for pheochromocytoma with annual chemical blood and urine tests is recommended for all subjects diagnosed with VHL [5].

## Conclusion

This case report showed an atypical manifestation in a patient with VHL and the importance of screening for pheochromocytoma in such a patient, especially when cardiovascular manifestations are involved.

## Disclosure Statement

The authors reported no conflicts of interest.

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