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Case Report

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# Rare Presentation of Von Hippel Lindau Disease in a 33-Year-Old Female

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## Abstract
*Von Hippel Lindau (VHL) disease is rare disorder that causes the formation of tumors and cysts due to mutation of the VHL gene. This case is about a 33-year-old female who presented with heart failure secondary to VHL. The patient had a rare presentation of VHL as she had bilateral pheochromocytomas needing a total adrenalectomy and was subsequently found to have a de-novo mutation causing VHL disease.*

**Keywords:** Von Hippel Lindau, Ophthalmologist, Retinal Angiomatosis, Pheochromocytomas, Endolymphatic Sac Tumors, Renal Cell Carcinomas

## Abbreviations
CHF: Chronic heart failure
ED: Emergency department
VMA: Vanillylmandelic acid
VHL: Von Hippel Lindau

## 1.Introduction
In the early 20th century, a German ophthalmologist Eugene von Hippel described the retinal angiomatosis part and a Swedish pathologist Arvid Lindau studied the cerebellar tumor component of a disease that was eventually termed after their names as Von Hippel–Lindau (VHL) disease [1,2]. Later on, several studies found that the VHL is a tumor suppressor gene, located on chromosome 3p25-26 and that the *VHL* disease occurs due to germline mutations in the *VHL* gene [3,4]. Accordingly, VHL patients are at high risk of presenting visceral cysts and tumors throughout their body. While cystadenomas are found in the epididymis and broad ligament, simple cysts are more common in the pancreas, liver, and kidney [5,6]. Therefore, the prototypical lesions of VHL disease include simple cysts, pheochromocytomas, endolymphatic sac tumors, clear cell renal cell carcinomas, pancreatic serous cystadenomas, pancreatic neuroendocrine tumors, and hemangioblastomas of the retina and central nervous system [7-11]. Common tumors associated with this disease are usually benign but can be malignant. Moreover, sometimes VHL patients die due to complications from the central nervous system (CNS) and renal tumors. Here, we delineate a unique case of VHL in a 33-year-old female.

## 2. Case Presentation
Patient is a 33-year-old female who presented to the emergency department (ED) 4 years ago with abdominal pain and vomiting. She was found to have acute hypoxic respiratory failure secondary to chronic heart failure (CHF) exacerbation with a proBNP of 11,800. She exhibited an elevated blood pressure of 145/83 and an increased plasma normetanephrine level of 30.8nmol/L (normal range 0-0.89 nmol/L). Analysis of her urine collected at 24 h showed an astronomically high level of normetanephrine of 15,677 µg/d (normal range 109-393 µg/d). Although her plasma metanephrine was 0.28 nmol/L and was within the normal limits, she had elevated metanephrine in 24 hr urine collection of 218 µg/d (normal range 39-143 µg/d).

Upon MRI analysis, it was found that she displayed bilateral adrenal nodules suggesting the presence of malignant bilateral adrenal pheochromocytomas. Since the nodules were very large, she went through a bilateral adrenalectomy. Post-surgery, patient's plasma normetanephrine level came down to 0.28 nmol/L and metanephrine level was less than 0.1 nmol/L.

Patient needed to be on steroid replacement therapy for life and was started on prednisone 20 mg and is currently on prednisone 5 mg. She underwent genetic testing and was found to have a mutation in the VHL gene, confirming that she had VHL disease. Interestingly, she did not have any family history of VHL, indicating that she had a de novo mutation. However, as expected, both her daughters tested positive for VHL gene mutation. She is currently only on prednisone 5 mg. During her second pregnancy which was post bilateral adrenalectomy, patient had

preeclampsia and had to deliver her baby before 30 weeks. She did not have any other issues with hypertension and no longer needed to be on blood pressure management. Patient regularly gets DHEA levels checked, which have been very low (10-20, normal range<100) due to lack of adrenal function. Patient needs yearly whole-body MRIs to monitor for any tumors. Further suggestions are starting her on fludrocortisone and liberal salt intake to prevent dehydration.

## 2. Discussion

Although VHL is a rare disease, this case is unique due to the following: First, this patient had a de novo mutation and only had bilateral pheochromocytomas, which is a rare finding with VHL. VHL affects 1 in 36,000 and only 10-20% of those cases arise from de novo mutation. The most common tumor found with this syndrome are hemangioblastomas, which are seen in 44-72% of patients with VHL. Pheochromocytomas [12] are rarer and are found in only 10-20% of patients. Only, 10% of pheochromocytomas are bilateral and found more often in younger patients. Therefore, this combination of findings is rare in someone with VHL.

Second, this young patient presented with heart failure. Heart failure is a rare and life-threatening complication of pheochromocytoma. Pheochromocytomas cause increased catecholamine release that leads to vasoconstriction. This decrease in blood flow to the heart and increases in cardiac contractility and oxygen demand result in heart failure. Cardiac complications usually occur in 20% of patients. Other cardiac complications include myocardial infarction, dilated cardiomyopathy, and arrhythmias. Third, common lab findings with pheochromocytomas are elevated plasma and 24hr urine collection catecholamine metabolites such as metanephrines and normetanephrines, and elevated end-product of metabolites, vanillylmandelic acid (VMA). This patient only had elevated normetanephrines, not metanephrines, which is not a common finding.

Fourth, this patient is also at risk of developing adrenal insufficiency due to the bilateral adrenalectomy. Common symptoms of adrenal insufficiency are fatigue, weight loss, loss of appetite, etc., however, until now, she did not exhibit these symptoms due to well management with her regular use of prednisone.

Welireg is the only FDA approved treatment which reduces transcription and expression of hypoxia inducible factor 2 alpha genes [13] associated with cell proliferation, angiogenesis, and tumor growth [14]. If this patient's needs further management due to progression of her disease, she could be started on Welireg.

## 4. Conclusion

In summary, we have presented a distinctive case of VHL disease in a 33-year-old female with de-novo mutation, heart failure, elevated urine level of only normetanephrines, and bilateral adrenalectomy. Identification of clinical cases of VHL with unique symptoms and features may help the scientists and clinicians to find a more coherent approach for better understanding of physiological and pathological processes of VHL and defining a prototype, but an effective, therapeutic approach against VHL.

## Availability of Data and Materials

Not applicable.

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