
RELAPSE OF PHEOCHROMOCYTOMA WITH HYPERTENSIVE HEART DISEASE MILDLY REDUCED LEFT VENTRICLE EJECTION FRACTION

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ABSTRACT

Pheochromocytoma is a tumor originating from the medulla of the adrenal gland. This tumor is rare and is caused by excessive production of catecholamines. There are three classic triads of pheochromocytoma: diaphoresis, palpitations and headaches. Elevated metanephrines and normetanephrine in plasma or urine confirm the diagnosis. At the same time, radiological examination helps in the tumor's location and the presence of local invasion or metastasis. Hypertension is a health problem that is quite dangerous worldwide because it is a significant risk factor for cardiovascular diseases such as heart attack, heart failure, stroke, and kidney disease. Hypertension can cause Hypertensive Heart Disease, which is a significant cause of morbidity and mortality due to cardiovascular disease. This scientific report presents a case study of a 19-year-old woman diagnosed with relapsed pheochromocytoma and *hypertensive heart disease with mildly reduced left ventricular ejection fraction*. This patient was previously diagnosed at the age of 13 with pheochromocytoma, where the patient experienced symptoms of headache, sweating, especially in the forehead area, trembling hands, and hypertension. Hence, the patient had to be treated. The patient underwent further examination and found a right adrenal tumor, so an adrenalectomy was performed on the patient. Similar complaints appeared again in the patient, and further examination was carried out. Moreover, an increase in plasma metanephrine and normetanephrine levels was found. A CT scan of the abdomen revealed a right adrenal tumor, so this patient underwent another adrenalectomy.

Keywords: relapsed pheochromocytoma, hypertensive heart disease.

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INTRODUCTION

Pheochromocytoma is a neuroendocrine tumor originating from the chromaffin cells of the adrenal medulla gland. The incidence is 0.3% cases per million per year, and one piece of literature states that 50% are diagnosed at autopsy. The first histologically proven pheochromocytoma was diagnosed by Felix Fraenkel at the University of Freiburg in Germany, finding classic signs and symptoms of pheochromocytoma in a young woman with bilateral adrenal tumors. His colleague professor of pathology, Max Schotellus, carried out a histological investigation and was the first to notice that when the tumor was fixed with Mueller's solution containing chromate, it was reddish-gray when fresh and turned brown in Mueller's solution (Sánchez-Turcius RA, 2015); (Farrugia et al., 2017).

Manifestation of signs and symptoms of pheochromocytoma includes hypertension, palpitations, headaches, sweating, and paleness. Other symptoms that sometimes occur are weakness, nausea, weight loss, constipation, and fever (Sánchez-Turcius RA, 2015).

Pheochromocytoma is an endocrine hypertension that should be suspected if there is a family history. Other causes of endocrine hypertension are disorders of the pituitary, adrenal cortex, thyroid, and renal tumors. The incidence of pheochromocytoma is approximately 0.1% to 0.2% in the patient population suffering from hypertension. This condition can occur at any age but is more common in the 3rd to fifth decades of life. The frequency of occurrence in men is the same as in women (Sánchez-Turcius RA, 2015).

Pheochromocytoma is brown, and most tumors grow inside the adrenal glands, only 10% outside the adrenal glands (paraganglioma). Generally, it is benign, and only 10% metastasize to the bones, lungs, liver, and lymph nodes. Tumors can secrete various hormones, especially epinephrine, norepinephrine, and dopamine.

Pheochromocytoma is closely associated with high morbidity and mortality, especially cardiovascular complications (Lenders et al., 2014). Rapid and accurate diagnosis of pheochromocytoma is essential in providing optimal treatment. The following presents a relapsed pheochromocytoma with *hypertensive heart disease and mildly reduced left ventricular ejection fraction*.

RESULTS AND DISCUSSION

Case Illustrations

A woman named Ms VT, 19 years old. City address Lubuk Linggau, Palembang. The patient came to the Endocrine Metabolic Diabetes Polyclinic at RSMH Palembang on January 5, 2023, complaining of sweating all over the body, especially the forehead and chest area, and additional complaints of headaches and back pain. History of the disease in 2016. The patient complained of constant headaches, which were reduced if the patient drank. paramedik drug. The patient's vision is sometimes blurry. The patient also complained of nausea, no vomiting, and normal appetite. Patients also complain of sweating all over the body, especially the forehead area. The patient also complained of palpitations and shaking hands. The patient did not go to the hospital for treatment.

In 2017, the patient again complained of headaches, body sweating, and shaking hands. The patient went to Linggau Hospital for treatment and was suspected of hyperthyroidism. The patient was referred to RSMH Palembang. The patient was admitted to the pediatric ward and underwent a complete examination. While being treated, the patient experienced high blood pressure, which, according to the patient, was 200/180 mmHg. The patient was treated in the HCU for approximately one month. The patient underwent an ultrasound examination and CT scan of the abdomen, and the doctor said there was a mass in the adrenal gland of the right kidney. The patient underwent surgery in December 2017.

In 2018, patients complained of sweating, shaking hands, palpitations, and sometimes headaches. The patient's blood pressure began to stabilize. The patient receives routine treatment at Linggau Hospital. At the beginning of 2019, the patient complained of right hip pain. The patient still complains of headaches, trembling hands, and sweating, especially in the forehead area. The patient went to the hospital in Linggau and had another abdominal CT scan, and a mass was found. The patient was referred to RSMH Palembang. Patients do not come to RSMH; patients also do not

seek treatment and control until 2021 because patients are afraid to come to the hospital because of COVID-19.

In 2022, the patient complained of frequent sweating, especially in the forehead area, headaches, back pain, and palpitations. The patient went to the hospital in Lubuk Linggau for treatment. In early December 2022, the patient was referred to the Endocrine Polyclinic at RSMH Palembang. The patient's previous medical history did not reveal a history of hyperthyroidism and similar illnesses or a family history of the disease. Physical examination revealed sensorium compos mentis. The general condition appeared moderately ill, with BP 150/95 mmHg, pulse 100 times/minute, regular, sufficient tension, respiration 22x/minute, temperature 36.5C, BW 53 kg, TB 158 cm. Body Mass Index (BMI) 22.06% kg/cm².

The physical examination results of the head and neck organs were average. On chest examination, the cast and pulmo were regular. The abdominal region shows scars from surgical sutures, the liver and spleen are not palpable, and the tympanum and bowel sounds are normal. Normal superior and inferior extremities.

In laboratory supporting examinations, plasma-free metanephrine was found to be 26 pg/ml, free normetanephrine 7411 pg/ml, total free metanephrine, and normetanephrine 7437 pg/ml. Urine VMA examination ≤ 8 mg/hour. Left Ventricular Hypertrophy was found on electrocardiographic examination, and chest and pulmonary X-rays showed no abnormalities. Echocardiography examination showed the impression of Hypertensive Heart Disease and Mildly Reduced Left Ventricle Ejection Fraction. In this patient, a CT examination of the abdomen was carried out, and an impression of a cystic, solid mass in the right suprarenal area was obtained, measuring 46.92 mm x 40.24 mm. No intra-abdominal metastases were visible.

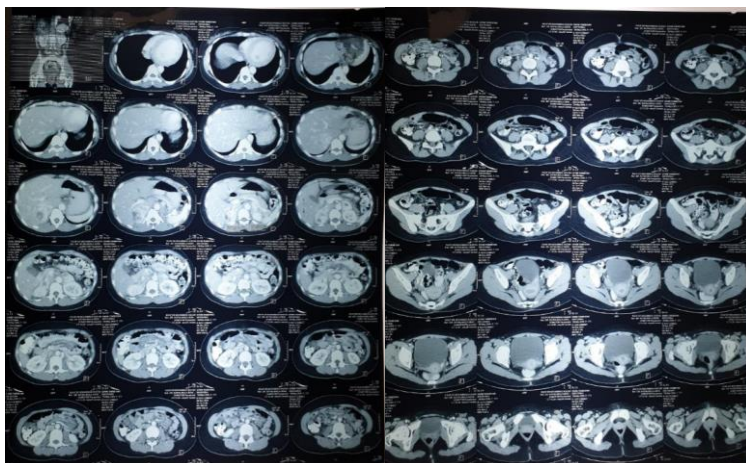


Figure 1 . Abdominal CT scan

In this patient, from the history, physical examination, laboratory results, and other supporting factors, a diagnosis of relapsed pheochromocytoma, Hypertensive Heart Disease with mildly reduced Left Ventricle Ejection Fraction, was diagnosed. This patient was then consulted by the urological surgery department and advised to undergo an open adrenalectomy due to the presence of adhesions. On July 6, 2023, the patient underwent an open right suprarenal adrenalectomy.

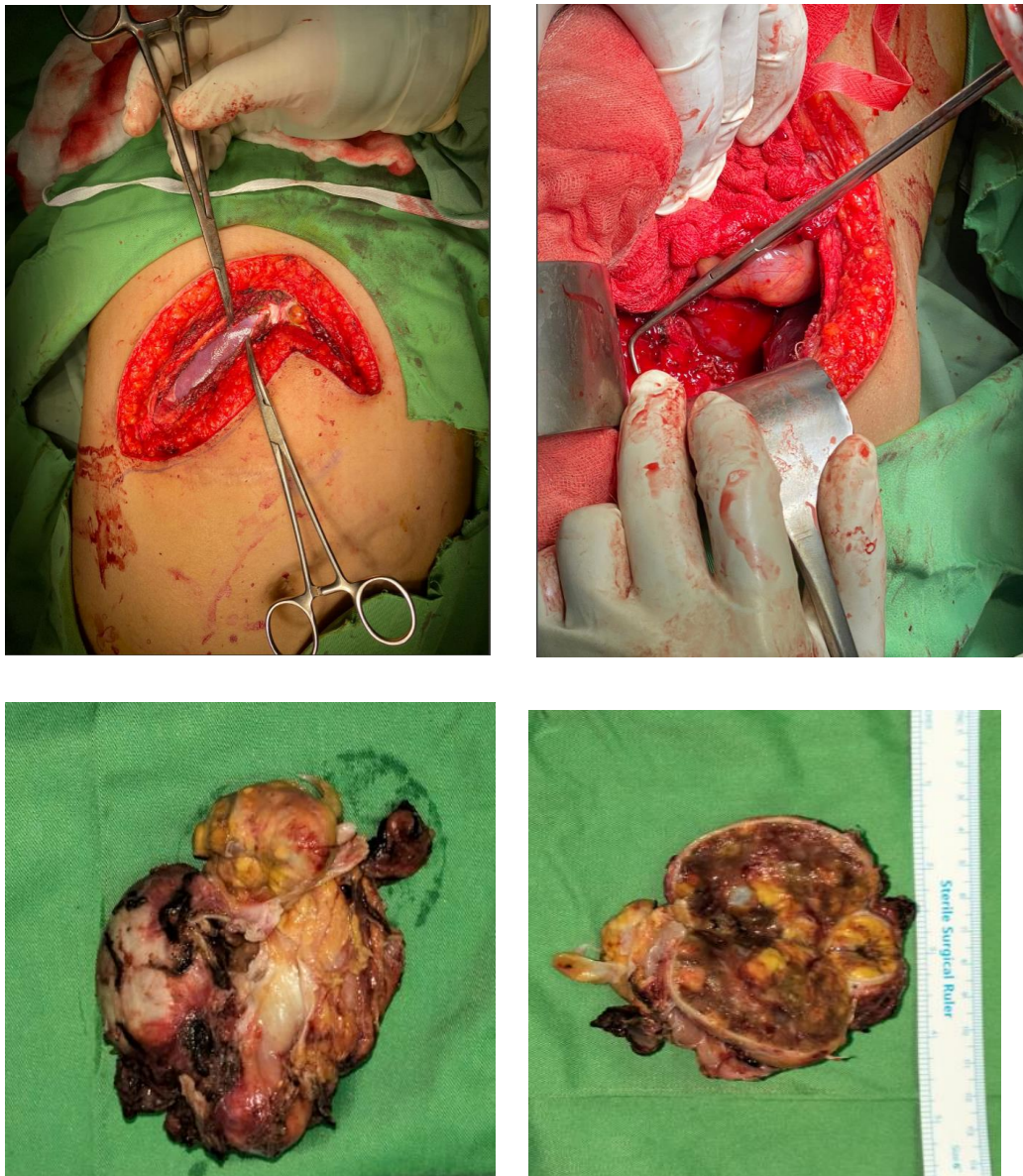


Figure 2. Open adrenalectomy operation

After surgery, the tumor from the adrenal gland was sent to the anatomical pathology department, and the histopathological examination results on July 14, 2023, showed support for pheochromocytoma of the adrenal. In 2017, this patient also underwent surgery on the right adrenal gland, and histopathology and immunohistochemistry showed benign right suprarenal pheochromocytoma.

Pheochromocytoma is a rare case with clinical manifestations related to catecholamine overproduction (headaches, sweating, palpitations), local pressure, or metastasis (Rachmat et al., 2016). In meta-analysis studies conducted by Pourian et al. in 2016 and Soltani et al. in 2017, the most significant signs and symptoms of pheochromocytoma were hypertension (80.7%), headache (60.4%), palpitations (59.3%), diaphoresis (52.4%). Other less common signs and symptoms are fatigue, nausea, vomiting, weight loss, constipation, fever, and chest and abdominal pain. The classic

triad of diaphoresis, palpitations, and headache is reported to have a sensitivity of 89% and a specificity of 67% for pheochromocytoma, and in the presence of hypertension, a sensitivity of 91% and a specificity of 94%.

Endocrine hypertension is often not diagnosed because the signs and symptoms are unclear, and no abnormalities are found in routine laboratories. For this reason, there are several clinical signs to suspect the presence of pheochromocytoma, namely (Sánchez-Turcius RA, 2015) :

1. Resistant hypertension, refractory hypertension
2. Hypertensive crisis
3. Hyperadrenergic (palpitations, diaphoresis, headache, tremor, pallor)
4. Adrenal Incidentaloma
5. Genetic history of pheochromocytoma
6. Hypertension at a young age (< 20 years)
7. Hypertension with impaired glucose tolerance and diabetes mellitus

This patient had a history of hypertension when he was 13 years old and had clinical symptoms typical of pheochromocytoma, namely diaphoresis, headaches, palpitations, and additional complaints of back pain. To confirm the diagnosis of pheochromocytoma, other supporting examinations are needed.

This patient was examined for plasma-free metanephrine and free normetanephrine, which are metabolites of catecholamines, as well as urine VMA, where free metanephrine levels were found to be 26 pg/ml (< 57 pg/ml) and free normetanephrine 7411 pg/ml (< 148 pg/ml). So, there was an increase in free metanephrine and normetanephrine levels 7437 (< 205 pg/ml). Results of urine VMA ≤ 8 mg/24 hours (N = ≤ 8 mg/24 hours). Measurement of plasma metanephrines is susceptible and is recommended for first-line examination, which has a sensitivity of 96-100% and a specificity of 89%-98% (Lenders et al., 2014) .

This patient then underwent a CT scan of the abdomen and found a right adrenal tumor. Pheochromocytoma should be evaluated with a CT scan or MRI anatomical imaging. This imaging study is essential for localizing tumors and describing the extent of the tumor as well as diagnosing several primary tumors and metastatic lesions in patients with various genetic disorders. In the study of Mantero et al., pheochromocytomas accounted for 11% of all adrenal incidentalomas. CT scans can show tumor sizes > 1 cm with a sensitivity of 87% to 100% (Farrugia et al., 2017).

This patient was referred to urological surgery for further treatment. The primary treatment modality for pheochromocytoma is surgical resection. Minimally invasive laparoscopic adrenalectomy is recommended in most cases of pheochromocytoma. Open resection laparotomy is indicated for pheochromocytoma with a large tumor size (> 9 cm) (Sánchez-Turcius RA, 2015). The urology surgeon planned an open adrenalectomy because adhesions had occurred, and the operation was carried out together with a pediatric surgeon who knew the patient's previous surgical history.

Approximately 6.5-16.5% of pheochromocytoma patients experience relapse, and 10% experience metastases. A retrospective study of 135 patients who had undergone adrenalectomy and were followed for 14 years showed that tumors measuring > 5 cm were at high risk for recurrence. Another study with 192 patients showed that age, family history, tumor location (right side, extra-adrenal), and tumor size were also predictors of recurrence in pheochromocytoma

patients. Genetic mutations such as SDHB (*succinate dehydrogenase subunit B*) are also a high risk of recurrence and malignancy in pheochromocytoma. For this reason, long-term monitoring with biochemical examination and imaging modalities is needed after the patient undergoes surgical resection (Venugopal et al., 2020) (Amar et al., 2016).

Hypertensive heart disease (HHD) is a collection of disorders that include left ventricular hypertrophy (LVH) and systolic and diastolic dysfunction, with clinical manifestations including arrhythmias and symptomatic heart failure. The classic paradigm of hypertensive heart disease is that the left ventricular (LV) wall thickens in response to increased blood pressure as a compensatory mechanism to minimize heart wall stress. The presence of left ventricular hypertrophy (LVH) is a compensation of the heart in the face of high blood pressure coupled with neurohormonal factors, which are characterized by concentric thickening of the heart muscle (concentric hypertrophy) (Yandriani & Karani, 2018). The diastolic function will be disrupted due to impaired left ventricular relaxation, followed by left ventricular dilatation (eccentric hypertrophy). Sympathetic stimulation and activation of the RAA system triggers the Frank-Starling mechanism by increasing ventricular diastolic volume to a particular stage and ultimately causing disruption of myocardial contraction (decreased/impaired systolic function). Myocardial ischemia (asymptomatic, angina pectoris, cardiac infarction, etc.) can occur due to accelerated atherosclerotic processes with increased myocardial oxygen demand resulting from LVH. The main factors of myocyte damage in hypertension are LVH, myocardial ischemia, and impaired endothelial function (Raman, 2010).

Changes in heart structure and function in HHD are caused by hypertension, which causes concentric hypertrophy, followed by dilated heart failure. Patients with hypertrophy have higher systolic blood pressure and peripheral resistance. In addition, blood pressure after outpatient treatment correlates better with left ventricular mass than blood pressure alone, and concentric hypertrophy, compared with eccentric hypertrophy, has higher ambulatory blood pressure rates (Raman, 2010); (Drazner, 2011).

This patient had developed hypertension at the age of 13 years and had been diagnosed with pheochromocytoma. The average age of pheochromocytoma in children is 11-13 years, with males being more likely to be 2:1. In hypertensive children, 1.7% had catecholamine-secreting neoplasms. Ongoing hypertension is a common symptom in 60-90% of children with pheochromocytoma. Other symptoms are headaches in up to 67% and nausea, sweating, palpitations, and pallor in 47-57% of children (Farrugia et al., 2017).

The prognosis of pheochromocytoma depends on resectability and genetic profile. If there are metastases, the 5-year survival rate in pheochromocytoma patients is 34-60%. Survival is <5 years if metastases occur in the liver or lungs and longer if there are bone metastases. If complete excision is performed, local invasion can provide long survival rates (Drazner, 2011).

CONCLUSION

Pheochromocytoma is a rare form of endocrine tumor. However, it can significantly impact the patient's health and quality of life. Although most pheochromocytomas can be removed surgically, the tumor may return or relapse after removal. Relapse rates vary depending on tumor size, location, and cell type. In relapse cases, proper diagnosis and diagnosis must be made using various diagnostic methods such as laboratory analysis, CT scan, or MRI imaging. This helps determine the tumor's location, size, and characteristics, which may differ from previous tumors.

Relapsed pheochromocytoma may worsen the symptoms and prognosis of HHD. When pheochromocytoma recurs or recurs, excessive release of the hormones epinephrine and norepinephrine can significantly increase blood pressure and worsen damage to target organs, including the heart. This may increase the risk of complications and worsen the prognosis in patients with HHD. Patients with relapsed pheochromocytoma and HHD require regular follow-up and monitoring to identify possible symptoms and complications. Regular medical examinations, blood pressure monitoring, and evaluation of the function of the heart and other target organs need to be carried out to ensure reasonable control and prevent further complications.

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