Silent Hypertensive Crisis in an Adolescent: First Case Report of Pediatric Pheochromocytoma from Indonesia

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Abstract
Secondary hypertension in children, to the rare extent, can be caused by endocrine factors such as pheochromocytoma, an adrenal tumor that secretes catecholamine. Only a few cases have been reported in the past 3 decades. To the best of our knowledge, this is the first case report of pediatric pheochromocytoma from Indonesia. We reviewed a case of a 16-year-old Indonesian boy with history of silent hypertensive crisis who was referred from a remote area in an island to the pediatric nephrology clinic at Cipto Mangunkusumo Hospital, Jakarta, Indonesia. Despite medications, his symptoms persisted for 14 months. At the pediatric nephrology clinic, pheochromocytoma was suspected due to symptoms of catecholamine secretion presented, which was palpitation, diaphoresis, and weight loss. However, as the urine catecholamine test was unavailable in Indonesia, the urine sample was sent to a laboratory outside the country. The elevated level of urine metanephrine, focal pathological uptake in the right adrenal mass seen on ¹³¹I-MIBG, and histopathology examination confirmed the suspicion of pheochromocytoma. Following the tumor resection, he has been living with normal blood pressure without antihypertensive medications. This case highlights that pheochromocytoma should always be included in the differential diagnoses of any atypical presentation of hypertension. In limited resources setting, high clinical awareness of pheochromocytoma is required to facilitate prompt referral. Suspicion of pheochromocytoma should be followed by measurement of urine metanephrine levels. Early diagnosis of pheochromocytoma would fasten the optimal cure, alleviate the symptoms of catecholamine release, and reverse hypertension.

Keywords
blood pressure, MIBG, epinephrine, norepinephrine, metanephrine, adrenal glands

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Introduction
The prevalence of pediatric hypertension has been reported to be approximately 3.5% worldwide.¹ It commonly occurs in chronic kidney disease patients and complicates majority of pediatric end-stage kidney disease cases in our center.² A secondary cause of pediatric hypertension is kidney parenchymal disease (78%-80%) and it can also be rarely associated with endocrine causes (0.06%-6%) such as pheochromocytoma, which is a rare adrenal catecholamine secreting tumor.¹

Herein, we described the case of a 16-year-old boy with hypertensive crisis who had presumably been silently hypertensive for 2 years without any complications, and the condition was later discovered to be caused by pheochromocytoma. Although pheochromocytoma has been rarely reported, especially in Indonesia, it was suspected on the basis of catecholamine secretion

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symptoms, such as palpitations, tachycardia, diaphoresis, and weight loss. To the best of our knowledge, this is the first report of pediatric pheochromocytoma from Indonesia.

**Case Description**

A 16-year-old Indonesian boy with uncontrolled hypertension was referred from a remote area in an island to the pediatric nephrology clinic at Cipto Mangunkusumo Hospital, Jakarta, Indonesia. Twenty months prior to admission to our clinic, he experienced palpitation, diaphoresis, and left-sided chest pain without radiation, because of which he was brought to the emergency room. He experienced neither shortness of breath nor blurry vision. His blood pressure was 200/120 mmHg. The internist initiated the administration of 20 mg furosemide per oral (PO) and 12.5 mg captopril PO twice daily, together with 10 mg nifedipine PO 4 times daily. However, the patient’s symptoms and hypertension persisted, due to which his parents turned to herbal treatment and skipped further medical follow-up, although oral medications were continued.

As the boy’s palpitations persisted for 14 months, he was taken to another internist who prescribed 30 mg nebivolol PO every morning and 80 mg telmisartan PO every evening. Echocardiography revealed normal cardiac function. Kidney Doppler ultrasound disclosed a suspicion of right adrenal mass and kidney artery stenosis, therefore, he was referred to the pediatric nephrology clinic at our center.

At the clinic, he complained of palpitations with diaphoresis. We also discovered that he had lost a weight of 10 kg in the past 4 months. His BMI was 16.5 kg/m² (undernourished with normal stature), and no skin lesions were noted (Figure 1). He was hypertensive (blood pressure [BP] 140/83 mmHg) and tachycardic (heart rate [HR] 107 times/minute), with similar BP and HR values in all limbs. Other physical examinations, including neurological examinations and funduscopy, revealed normal findings. Complete blood count, random glucose levels, hepatic enzyme levels, kidney functions, urinalysis, chest X-ray, and electrocardiography were unremarkable. Pheochromocytoma was suspected due to symptoms of catecholamine secretion. However, as the urine catecholamine test was unavailable in Indonesia, the urine sample was sent to a laboratory outside the country. Simultaneously, the patient underwent abdominal magnetic resonance imaging (MRI) (Figure 2a and b) and ¹³¹I-meta-iodobenzylguanidine (MIBG) scintigraphy (Figure 2c and d) were ordered. ¹³¹I-MIBG scintigraphy demonstrated the uptake of pathological tracer in the right suprarenal region corresponding to an adrenal tumor without metastatic lesions. The results of urine catecholamine test, which were received subsequently, confirmed our suspicion of pheochromocytoma (Table 1), after which the administration of terazosin was initiated.

The boy had always been healthy with no recorded history of high BP, chest pain, or palpitations. He was the first of 3 children in his family. His father had hypertension with obesity. Hereditary diseases were not acknowledged in the family. Since the past 2 years, he had stayed at a boarding school in a remote area. He denied smoking, alcohol use, and the intake of regular medications.

One week prior to the surgery, bisoprolol was added to his treatment regimen. Surgery was performed using the posterior retroperitoneoscopic right adrenalectomy approach for removing the tumor (Figure 3a and b). Administration of 1 mg terazosin PO was maintained until 1 week after the surgery. As his hypertension gradually resolved, terazosin was then discontinued. The results of pathological examination suggesting pheochromocytoma are presented in Figure 3c to g. A follow-up examination conducted 6 months after the surgery showed normal and stable BP without the use of any antihypertensive medications, and no other persistent signs associated with pheochromocytoma were noted.

![Figure 1. Patient’s appearance upon visitation to Pediatric Nephrology Clinic, Cipto Mangunkusumo Hospital. He was undernourished (BMI 16.5 kg/m²) with normal stature. No skin lesions were noted.](image-url)
Figure 2. Magnetic resonance imaging (MRI) demonstrating a circular, well-defined mass with heterogeneous high signal intensity on right suprarenal. Enhancement was seen post-contrast. (a) Pre-contrast view. (b) Post-contrast view. $^{131}$I-metaiodobenzylguanidine (MIBG) results. (c) Anterior and posterior (24 hours and 48 hours) planar whole body images of $^{131}$I-MIBG scintigraphy showed pathological uptake in the right adrenal tumor (as seen on MRI) compatible with pheochromocytoma. No other pathological uptake considered as metastases were seen. (d) $^{131}$I-MIBG SPECT/CT image showed focal pathological uptake in the right adrenal mass as seen on planar images.
The incidence rate of pheochromocytoma has been reported to be approximately 0.3 cases/million/year, and only 20% of cases are diagnosed in childhood. In Indonesia, only one case of adult pheochromocytoma has been reported till date.

Our case had persistent hypertension and elevated urine metanephrine levels, indicating the secretory characteristic of pheochromocytoma. The presence of gremlin mutations could not be confirmed because of the unavailability of specific genetic tests in Indonesia. In fact, genetic tests are strongly advised to disclose any relationship between pheochromocytoma and other diseases such as multiple endocrine neoplasia (MEN) type 2, an autosomal dominant hereditary disorder which is characterized by the growth of 2 or more endocrine gland tumors in an individual. MEN type 2A is more prevalent and consists of pheochromocytoma, medullary thyroid carcinoma, and parathyroid adenoma or hyperplasia, which is indicated by mutations in the RET gene. In the present case, for excluding the possibility of MEN type 2A, tests for thyroid and parathyroid function were conducted, which showed normal results.

At early presentation, the presence of palpitation along with persistent hypertension in our case was believed to be associated with cardiac abnormalities. An earlier study reported a patient presenting with hypertension, tachycardia, diaphoresis, and negative T waves on electrocardiography, who was subsequently diagnosed with non-ST-elevation myocardial infarction, but it was later found to be pheochromocytoma. In addition, 76% of pheochromocytoma cases were discovered during autopsy, implying that pheochromocytoma had not been considered in differential diagnoses. The persistent hypertension in our patient may have been caused due to incorrect choice of antihypertensive medication, which was supposed to be an alpha blocker combined with a beta blocker.

A clinical suspicion of pheochromocytoma should be followed by measurements of plasma free metanephrines and 24-hour urinary fractionated metanephrines. An elevation of more than fourfold of the upper limit of normal value, which is comparable to the level in our patient, is indicative of a catecholamine-secreting tumor. However, due to the unavailability of this test in Indonesia, the urine sample had to be sent overseas, costing the patient IDR 3 121 000 (USD $223) for assessing 24-hour urinary fractionated metanephrines and IDR 2 342 000 (USD $ 167) for assessing random urine metanephrines. Diagnosing rare diseases in Indonesia has been challenging due to unavailability of supporting laboratories. Another limitation of healthcare in Indonesia is that there were only 3700 pediatricians whereas the pediatric population had reached 90 million, resulting in a doctor-to-population ratio of 1:24000 in 2017. Moreover, Indonesia consists of

### Table 1. Laboratory Results.

| Parameter                                      | Results          | Normal value                  |
|------------------------------------------------|------------------|-------------------------------|
| Blood test                                     |                  |                               |
| Urea                                           | 4.23 mmol/L      | 2.99-7.49 mmol/L              |
| Creatinine                                     | 0.06 mmol/L      | 0.02-0.05 mmol/L              |
| eGFR (New Schwartz):                          | 97.35 mL/min/1.73 m² |                          |
| FT4                                            | 10.94 pmol/L     | 11.46-17.63 pmol/L            |
| T3                                             | 2.61 nmol/L      | 1.44-2.40 nmol/L              |
| TSHs                                           | 0.766 µU/mL      | 0.35-4.94 µU/mL               |
| PTH intact                                     | 2.47 pmol/L      | 1.06-6.89 pg/mL               |
| Phosphate                                      | 1.68 mmol/L      | 1.29-2.26 mmol/L              |
| Ca++                                          | 1.19 mmol/L      | 1.01-1.31 mmol/L              |
| Vitamin D 25-OH                                | 56.41 nmol/L     | 74.88-249.60 nmol/L           |
| Urine test                                     |                  |                               |
| Normetanephrine                                | 10 539           | 69-531 µmol/day               |
| Metanephrine                                   | 54 030.99        | 542.49-3,756.87 µmol/day      |
| Epinephrine                                    | <2               | ≤11 µmol/day                  |
| Norepinephrine                                 | 2332             | 12-88 µmol/day                |
| Total catecholamine (norepinephrine + epinephrine) | 2332            | 13-90 µmol/day                |
| Dopamine                                       | 417              | 51-645 µmol/day               |

Abbreviations: FT4, free thyroxine; T3, triiodothyronine; PTH, parathyroid hormone; Ca++, ionized calcium; Vitamin D 25-OH, 25-hydroxy vitamin.

### Discussion

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more than 17,000 islands, engendering it as the largest archipelago country in the world with a population of more than 260 million people. These inevitable limitations justified the initial treatment received from the internist rather than from a pediatrician. In addition, 131I-MIBG scintigraphy is available only in Jakarta, the capital city of Indonesia, requiring referral from the remote area. The distance from local health facilities to advanced medical services has been a major problem in the management of complex cases in Indonesia. Additionally, poor compliance to medical advice aggravates the previously mentioned condition, similar to this case. Consequently, multiple complications have already emerged upon admission to the tertiary referral centers.

The results of pathological examination in this case reinforced the diagnosis of pheochromocytoma, indicating the presence of tumor cells in a typical alveolar or nestling “Zellballen” pattern, moderate-to-marked pleomorphism, coarse chromat, and amphilic-to-basophilic granules. Moreover, numerous periadrenal brown fat cells were noted that are typically found in pheochromocytoma. Cytological variations of pheochromocytoma could imitate infiltrating carcinoma, vascular neoplasms,
and melanoma, necessitating a more challenging diagnostic approach.\textsuperscript{15} In the present case, the results of immunohistochemistry (IHC) staining for chromogranin, synaptophysin, and CD56 were positive, and S100 demonstrated positivity only in sustentacular cells, consistent with the pathology of pheochromocytoma.\textsuperscript{16}

Complete surgical resection is the gold standard cure for pheochromocytoma.\textsuperscript{16} However, the probability of the occurrence of hypertensive crisis requires careful perioperative management by a multidisciplinary team (endocrinologist, nephrologist, urologist, and anesthesiologist) for preventing catecholamine release during the procedure.\textsuperscript{16} Administration of an alpha blocker at 10-14 days before surgery is recommended as a perioperative treatment.\textsuperscript{16} Subsequently, a beta blocker could be administered to prevent reflex tachycardia at 3 days before surgery.\textsuperscript{3} In the present case, the patient received terazosin and bisoprolol.

Since 2017, the World Health Organization has favored the Phaeochromocytoma of the Adrenal gland Scaled Score (PASS) to determine the risk of metastasis.\textsuperscript{17} A PASS $\geq$4 is considered as likely to metastasize.\textsuperscript{17} The PASS score in our patient was 6, which was caused due to high cellularity [2], cellular monotony [2], profound nuclear pleomorphism [1], and hyperchromasia [1]. Approximately 38% of cases had recurrence during a period of 25 years.\textsuperscript{18} Therefore, we support the recommendation to test serum/urinary metanephrines annually, followed by MIBG/MRI/CT scans, in the presence of any symptoms or indicated by an increase in serum/urinary metanephrine levels.\textsuperscript{19}

**Conclusion**

Pheochromocytoma should always be included in the differential diagnoses of any atypical presentation of hypertension. In limited resources setting, high clinical awareness of pheochromocytoma is required to facilitate prompt referral. Early diagnosis of pheochromocytoma would fasten the optimal cure, alleviate the symptoms of catecholamine release, and reverse hypertension.

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**Authors’ Contributions**

CGA and AG performed the literature search, data collection, analysis, and interpretation, and wrote the first draft of the manuscript. HFW and ASH performed data collection and analysis. ELH, BT, and CAM critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

**Declaration of Conflicting Interests**

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**Ethics Statement**

Written informed consent for the publication of this case report and accompanying images was obtained from the patient’s guardian. A copy of the written consent is available for review from the editor of this journal.

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