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Case Report

# Safety of preoperative carvedilol in a patient with recent atenolol-induced pheochromocytoma crisis and cardiomyopathy: A case report

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ABSTRACT

*Introduction:* Beta-adrenergic blockade without adequate alpha blockade is an established trigger of pheochromocytoma crisis (PC). Carvedilol is a nonselective beta-adrenergic and alpha 1-adrenergic blocking agent, and its use for preoperative preparation of pheochromocytoma patients with prior cardiomyopathy secondary to PC resulting from unopposed beta-blocker therapy has never been reported.

*Case presentation:* A 48-year-old woman was admitted to the Urology Department for evaluation of a huge right upper abdominal mass. She developed hypertensive crisis with acute pulmonary edema resulting in respiratory failure after administration of atenolol to treat hypertension and tachycardia. Transthoracic echocardiogram revealed global hypokinesia. The patient was managed with intravenous nicardipine, furosemide, and prazosin because of the clinical suspicion of pheochromocytoma that was subsequently confirmed by elevated plasma and urine catecholamine levels. Within 3 days of alpha-adrenergic blockers treatment, there was rapid amelioration of hypertension and pulmonary congestion, as well as normalization of left ventricular function by echocardiography. However, tachycardia persisted after 1 month of adequate alpha-adrenergic blockade. Given the benefit of beta-adrenergic blockers in patients with systolic dysfunction, we slowly titrated carvedilol while carefully monitoring the patient's condition in the intensive care unit. Tachycardia was controlled without inducing PC. Surgical resection was successful without perioperative complications.

*Conclusion:* Clinicians should be cautious when prescribing beta-adrenergic blocker in patients with hypertension and upper quadrant mass of unknown etiology. The mass may be pheochromocytoma. Preoperative use of carvedilol after sufficient alpha-adrenergic blockade for control of tachycardia in a patient with prior cardiomyopathy associated with atenolol-induced PC is safe and effective.

## 1. Introduction

The classic symptoms of pheochromocytoma are paroxysmal headache, diaphoresis, and palpitations. However, the clinical presentations of these tumors are extremely variable, ranging from an absence of symptoms to hemodynamic instability and end-organ dysfunction to pheochromocytoma crisis (PC), which has a significant mortality rate. PC can manifest spontaneously or be triggered by certain factors, including surgical procedures, general anesthesia, and beta-adrenergic blockade without prior adequate alpha-adrenergic blockade [1].

Transient cardiomyopathy secondary to hypertensive crisis after beta-blocker therapy is a rarely reported presentation of pheochromocytoma [2]. Furthermore, using carvedilol, a nonselective beta-blocker and selective alpha-1 blocker, to treat tachycardia in a patient who has previously presented with hypertensive crisis after beta-blocker therapy has never been reported. We present a pheochromocytoma patient who presented with transient left ventricular dysfunction secondary to hypertensive crisis after receiving a single dose of atenolol. After the hypertensive crisis had been successfully treated by alpha-adrenergic blockade, carvedilol was administered to control the patient's heart rate (HR) before tumor resection. The operation was successfully performed without any complications. This study has been reported in line with the SCARE 2018 criteria [3].

*Abbreviations:* PC, Pheochromocytoma crisis; HR, heart rate; BP, blood pressure; CT, Computed tomography; ECG, Electrocardiogram.

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## 2. Case report

A 48-year-old Thai woman, farmer, complained of epigastric pain lasting 4 years. She was treated with proton pump inhibitors without further abdominal imaging. Her symptom progressively worsened. Her past medical history revealed she completed treatment for pulmonary tuberculosis 12 years earlier. She is non-smoker and has no other medical history. A month earlier, she had been admitted to another hospital for severe headache and forceful heartbeat. Her blood pressure (BP) was 224/190 mmHg and HR was 120 beats/min. On physical examination, she had normal cardiopulmonary and neurological systems. She was treated with amlodipine 10 mg/day and hydralazine 75 mg/day. The symptoms improved and the systolic BP decreased to 160–170 mmHg. Abdominal computed tomography (CT) scan was performed to evaluate the chronic epigastric pain. The CT scan showed a large heterogeneous enhancing mass (9.9 × 12.7 × 14.7 cm) with central necrosis in the right upper abdomen. The differential diagnosis included renal or suprarenal tumors (Fig. 1). Therefore, antihypertensive agents were continued and she was referred to the department of Urology for further management.

On this admission, physical examination revealed BP of 170/100 mmHg, HR 120 beats/min, regular rhythm. She was well looking with mildly pale conjunctiva, without peripheral edema. The point of maximal impulse was at the 5$^{th}$ intercostal space and left midclavicular line. There was no heaving or thrill, S1 and S2 were normal. On bimanual palpation, no abdominal mass was detected. Initial blood laboratory test results indicated mild anemia and hyponatremia (Table 1). The cardiothoracic ratio on the chest radiograph was 0.55 (Fig. 2A). Electrocardiogram (ECG) showed sinus tachycardia, left ventricular hypertrophy, and normal axis.

Twelve hours after admission, she complained of palpitations. Her BP and HR were 160/90 mmHg and 120 beats/min, respectively. She was treated with 50 mg of atenolol. Twelve hours after receiving this single dose of atenolol, she presented with sudden dyspnea and agitation. Her BP rose to 220/120 mmHg, HR was 150 beats/min, respiratory rate was 40 breath/min, and oxygen saturation was 85% with ambient air. High jugular venous pressure was observed, and she presented with bilateral lung crepitations. An urgent chest radiograph (Fig. 2B) showed new bilateral patchy infiltrates compatible with acute pulmonary edema. Urgent ECG revealed sinus tachycardia, without definite ST-T changes. Therefore, she was diagnosed with hypertensive crisis and acute pulmonary edema. Intubation and positive pressure ventilation were initiated immediately. Moreover, she received a total dose of nicardipine 30 mg and furosemide 160 mg intravenously.

A transthoracic echocardiography showed global hypokinesia of the left ventricular wall and the overall estimated left ventricular ejection fraction was 36%. There was no significant valvular disease. She had elevated cardiac markers (Table 1). Based on the onset of hypertensive crisis after a single dose of atenolol and the huge right upper quadrant mass, a diagnosis of pheochromocytoma was suspected. Therefore, an alpha adrenergic antagonist (prazosin) was administered and titrated until the BP normalized at approximately 12 hours after the onset of hypertensive crisis. Seventy-two hours later, her clinical status had improved dramatically. She was extubated and able to breathe without support. She received prazosin 6 mg/day and furosemide 40 mg/day, and her BP was 130/80 mmHg. Further, the HR was 86 beats/min. Intravenous nicardipine was tapered and eventually discontinued. A repeated echocardiography 72 hours after hypertensive crisis indicated completed resolution of the affected wall and a normal ejection fraction of 63%.

**Table 1**
Laboratory investigations in this patient.

| | Result | Normal value |
|---|---|---|
| Hematocrit (%) | 29.7 | 36–48 |
| Sodium (mmol/L) | 134 | 135–145 |
| Troponin T (ng/ml) | 0.259 | 0–0.1 |
| Creatinine kinase (ng/ml) | 9.49 | 0–5 |
| Free plasma metanephrine (nmol/L) | 8.5 | 0–0.9 |
| Free plasma normetanephrine (nmol/L) | 46 | 0–0.5 |
| Urine metanephrine (μg/day) | 154.87 | 52–341 |
| Urine normetanephrine (μg/day) | 548.72 | 88–444 |
| Urine vanillylmandelic acid (mg/day) | 77.7 | 1.5–10 |

The biochemical markers of pheochromocytoma were significantly elevated except urine metanephrine (Table 1). Iodine-131 meta-iodobenzylguanidine (I-131 MIBG) scintigraphy revealed a sizable, intense, heterogeneous uptake in the right upper abdomen. Single-photon emission CT images also showed inhomogeneous tracer uptake in the right retroperitoneal mass. It was suggestive of pheochromocytoma without evidence of distant metastases. We switched from treatment with prazosin to doxazosin for greater pharmacokinetic results.

One week after doxazosin administration, the BP was well controlled at 120/80 mmHg with doxazosin 8 mg/day. The patient had neither orthostatic hypotension nor paroxysmal symptoms. However, she had sinus tachycardia (100 beats/min). Thus, carvedilol was added to control her HR. We slowly titrated the dose of carvedilol and closely monitored her symptoms in the intensive care unit. Two weeks later, the carvedilol dose reached 25 mg/day, and her HR was 60–70 beats/min. The patient had no signs or symptoms of heart failure and was ready to undergo surgery by an experienced urological surgeon.

During open right adrenalectomy, the intraoperative BP varied between 120/80 and 160/90 mmHg controlled with nitroprusside. She had no congestive symptoms or hypoglycemia. The operative findings revealed a large right adrenal mass (Fig. 3). The left adrenal gland

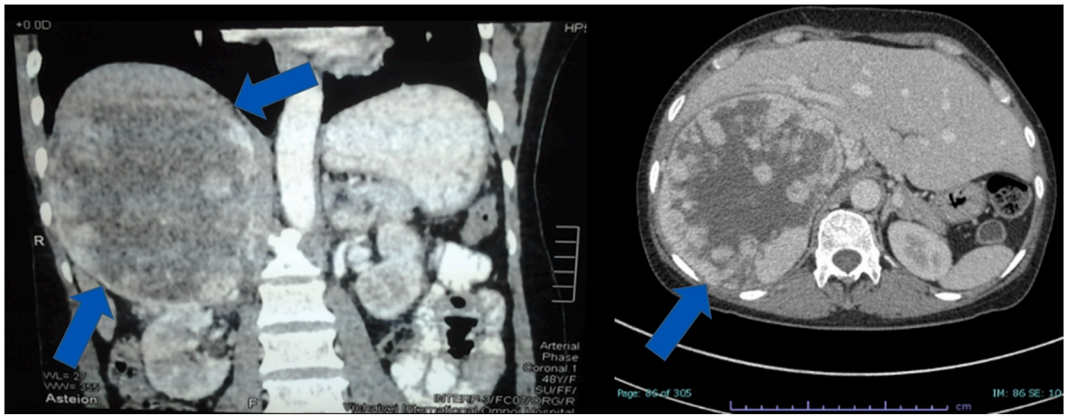


**Fig. 1.** CT scan of the abdomen in the coronal and axial planes show a large right suprarenal mass 9.9 × 12.7 × 14.7 cm with central necrosis (arrow). The mass was exerting pressure on the liver, inferior vena cava, and right renal vein. There was no definite evidence of intraabdominal metastasis.

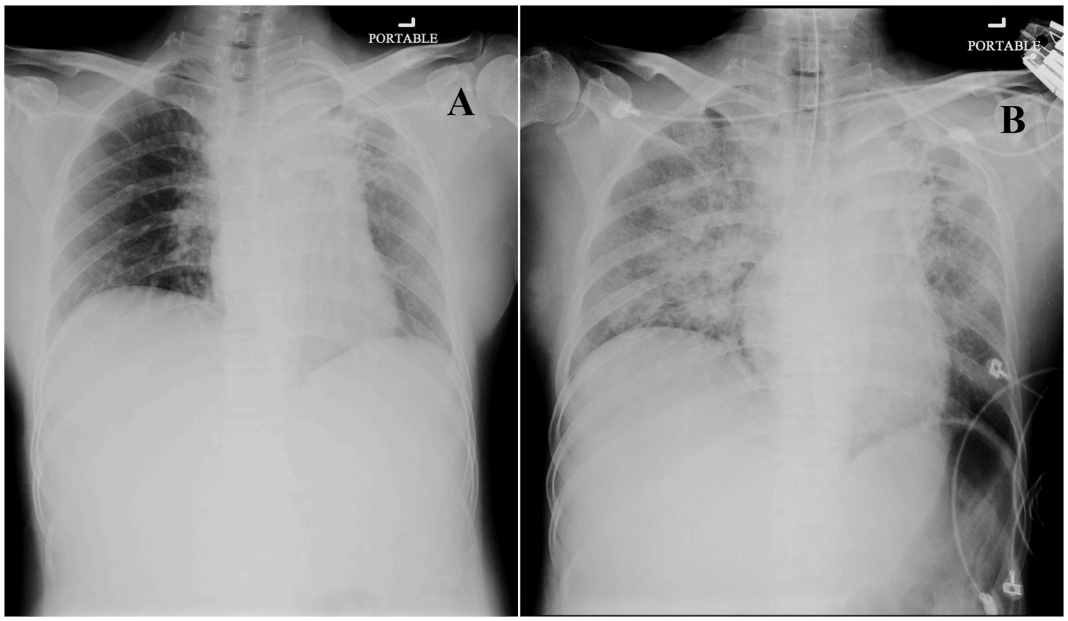


**Fig. 2.** A chest radiograph 12 hours before (A) hypertensive crisis showed decreased lung volume and fibrosis in the left upper lung field corresponding with a history of pulmonary tuberculosis. And a chest radiograph 6 hours after (B) hypertensive crisis showed a rapid change in bilateral patchy alveolar infiltrates compatible with acute pulmonary edema.

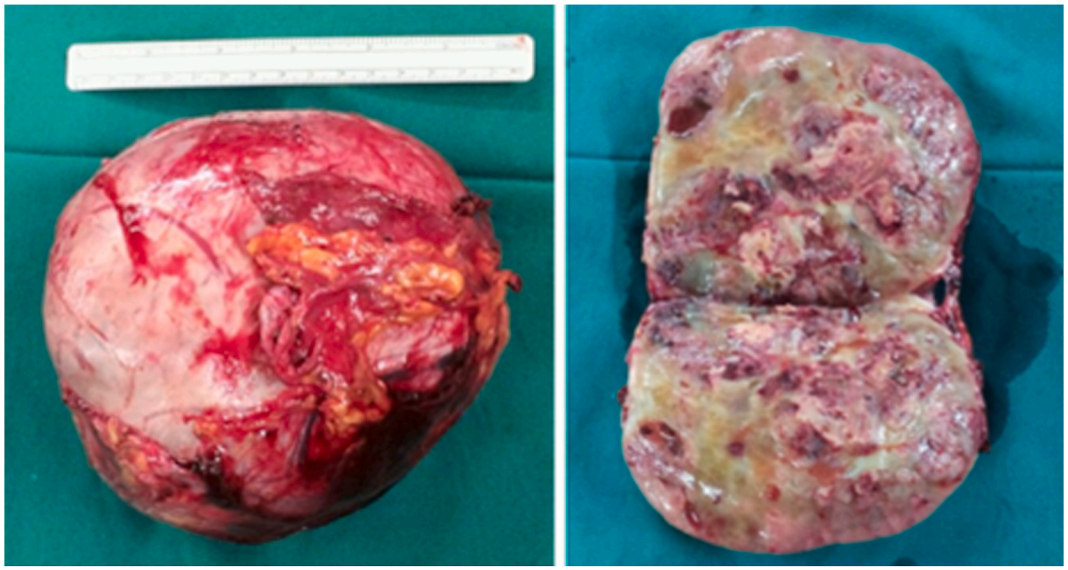

**Fig. 3.** Right adrenal mass measuring 13.5 × 13 × 9 cm.

appeared normal. No extra-adrenal nodules were seen. The pathological report of the right adrenal gland revealed a mass weighing 819 g. Focal hemorrhage and geographic necrosis were noted without evidence of extra-adrenal extension or positive margins. Furthermore, the mass was positive to chromogranin that was compatible with pheochromocytoma.

The immediate postoperative BP was 110/80 mmHg without antihypertensive agents. Seventy-two hours postoperatively, the BP rose to 150/90 mmHg without any symptoms. She received doxazosin 2 mg/day. Subsequently, the urinary vanillylmandelic acid (VMA) level returned to normal within 4 weeks after the tumor resection. Moreover, the follow-up I-131 MIBG scintigraphy revealed no I-131 avid lesions. The genetic testing for pheochromocytoma, including *VHL*, *RET*, and *SDH* genes were negative. She is healthy after surgery. To date, the patient has been treated with doxazosin 1 mg/day, and has not presented with any spells or congestive symptoms. She has been followed up at endocrinology clinic for three years and has normal result of urine metanephrine and normetanephrine.

## 3. Discussion

Pheochromocytoma is a catecholamine producing tumor the adrenal medulla with an annual incidence of 2–8 per million [4]. Clinical manifestations of pheochromocytoma are highly variable, ranging from asymptomatic forms to life-threatening cardiovascular events. This tumor can mimic other disorders because of its gastrointestinal, neurological, and metabolic manifestations [2,5]. Because pheochromocytoma can lead to hypertensive crisis and is curable by surgical resection, it is important to have clinical suspicion when faced with a potential case, and to confirm the diagnosis and resect the tumor promptly. Catecholamines affect many cardiovascular and metabolic processes by

activation of three types of adrenergic (α, β, and dopamine) receptors. The α1-adrenoreceptors mediate vascular and smooth muscle contraction; their activation causes vasoconstriction and increased BP. The vasodilatation in skeletal muscle from stimulation of β2-adrenoreceptors is important because it protects against catecholamine excess. If this protection is blocked, unopposed α1-adrenoreceptors stimulation may lead to a hypertensive crisis [1,6,7]. The present case illustrates the onset of hypertensive crisis and pulmonary edema after the administration of atenolol, a β1-antagonist, during a 12-h period without previous administration of α-adrenergic blocker. Furthermore, left ventricular dysfunction and elevated cardiac markers are consequences of acute catecholamine excess. Several mechanisms of acute myocardial damage associated with catecholamines have been proposed. One mechanism is that catecholamines have a direct toxic effect on the myocardium by enhanced lipid mobility, calcium overload, and free radical production [2]. Another mechanism is catecholamine-induced myocardial stunning [8] and coronary vasoconstriction that lead to focal myocardial necrosis [9]. The left ventricular dysfunction patterns associated with pheochromocytoma have been heterogeneous including reversible or irreversible dilated cardiomyopathy [2], hypertrophic cardiomyopathy, Takotsubo, and atypical (inverted) Takotsubo cardiomyopathies [2,8,10]. Fortunately, most of them are reversible after treatment with alpha adrenergic antagonists or complete excision of the tumor. Reportedly, it may take a few days to several months for complete resolution after treatment [2]. As in this patient, the global left ventricular wall hypokinesia returned to its normal function after a 72-h alpha adrenergic blockade treatment.

The diagnosis of pheochromocytoma must be confirmed by the presence of high concentrations of fractionated catecholamines (metanephrine, normetanephrine, VMA) in urine or plasma. According to a literature review, there is a positive linear correlation between the level of 24-h urine VMA and the size of tumor mass [11] because the metabolism of catecholamines is primarily intratumoral and VMA is its final metabolite. This patient had high levels of 24-h urine VMA and slightly elevated 24-h urinary normetanephrine excretion corresponding to the remarkable tumor size.

Surgical removal is the gold standard of treatment of pheochromocytoma. There were approximately 140 cases of pheochromocytoma in our hospital during the past ten years. Every case was managed by multidisciplinary team and surgically operated by experienced surgeons. Before the operation, alpha adrenergic blockers should be administered to control BP and restore vascular volume. Beta blockers may be used as an alternative in patients unable to achieve the target BP with at least 3 days of treatment with alpha blockers [1,12]. Reportedly, patients with PC, triggered by the administration of beta blockers alone without alpha blockade use, can be rechallenged with beta blockers after adequate treatment with alpha adrenergic blockade for control of the increased HR. This could be caused by either the high levels of circulating catecholamines or the alpha adrenergic blockade therapy [13,14]. Further, there was no hypertensive crisis during the rechallenging with beta blockers. In general, combined alpha and beta adrenoreceptor antagonists (labetalol and carvedilol) are not recommended for the first choice of preoperative adrenergic blockade because they have a ratio of alpha to beta antagonist activity of approximately 1:5, which may cause hypertensive crisis from the surge of alpha adrenergic activity [1,12]. However, carvedilol has been proven to reduce the risk of death and hospitalization from cardiovascular causes in patients with heart failure [15]. Therefore, we prescribed the non-selective beta and selective alpha-1 blocker (carvedilol) to control HR after hypertensive crisis was controlled with the adequate dose of alpha blocker therapy. There were no complications because α1-adrenoreceptors were blocked completely before starting carvedilol. Postoperative BP is usually reduced to normal limits. However, our patient's BP remained elevated. The probable reasons are coincident essential hypertension, long-standing hypertension with structural changes of blood vessels and resetting of baroreceptors.

## 4. Conclusion

Beta-adrenergic blocker should be used cautiously in patients with hypertension and upper quadrant mass. The mass may be pheochromocytoma for which beta-blockers without appropriate alpha-receptor blockade are contraindicated. Preoperative use of carvedilol after sufficient alpha-adrenergic blockade for control of reflex tachycardia in a patient with prior cardiomyopathy associated with PC was safe and effective.

## Data availability

The data that support the findings of this case report are available from the corresponding author on reasonable request.

## Patient confidentiality

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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## Declaration of competing interest

All authors have no financial or non-financial conflicts of interest related to this report.

This case report was presented as a poster presentation at International Symposium on pheochromocytoma and paraganglioma 2014 in Japan.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2020.11.014.

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The following information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned. If you have nothing to declare in any of these categories then this should be stated.

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All authors have no financial or non-financial conflicts of interest related to this report.

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**Ethical approval**

The case report is exempt from ethical approval in our institution.

**Consent**

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

**Author contribution**

Dr. Wannachalee conceptualized, drafted, reviewed and revised the manuscript. Dr. Chunharojrith contributed to the concept of the report, critical manuscript review and approval. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Paweena Chunharojrith

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