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# Pheochromocytoma crisis presenting with cardiogenic shock

Pheochromocytoma is a neuroendocrine tumor composed of chromaffin cells that secrete catecholamines [1]. It can be clinically silent but occasionally may present with hypertension when catecholamine release is triggered by exogenous stimuli [2, 3]. In this report, we describe a case of pheochromocytoma crisis presenting with cardiogenic shock and we discuss the diagnostic and therapeutic challenges.

## Case report

A 55-year-old man was admitted to our department with diffuse abdominal pain and vomiting. His past medical history was notable for non-Hodgkin's lymphoma treated with chemotherapy 15 years previously. Over the last 3 years, he had headaches characterized by increasing frequency and severity. The headaches were attributed to anxiety disorder and the patient was started on mirtazapine. Mirtazapine was interrupted by the patient 20 days before his admission to our department. On admission, the patient's blood pressure was 155/90 mmHg. Physical examination revealed mild abdominal distention. The rest of the physical examination and the psychiatric evaluation were unremarkable. Initial laboratory tests demonstrated leukocytosis (WBC =19,200/μl, 78% neutrophils) and hyperglycemia (glucose =294 mg/dl). All the other laboratory results, including markers of myocardial necrosis (troponin, CK-MB, LDH, SGOT) and left ventricular dysfunction (BNP) were unremarkable.

The following day the patient complained of intense chest pain with diaphoresis and signs of peripheral hypoperfusion. His vital signs were: blood pressure, 65/40 mmHg on both arms; heart rate, 126 beats/min; respiratory rate, 26 breaths/min with oxygen saturation at 90%; and body temperature, 36.3°C. EKG showed transient ST elevations in all precordial leads V1–V6 (**Fig. 1**). On the basis of the clinical and EKG findings, the initial differential diagnosis included acute coronary syndrome vs. aortic dissection and the patient was transferred to the coronary care unit for further management. A transthoracic echocardiogram showed normal biventricular size and systolic function without evidence of regional wall motion abnormalities, normal biatrial size, and mild calcific aortic stenosis. Urgent coronary angiography demonstrated normal arteries and aortography showed no evidence of aortic dissection. The renal arteries were normal on angiography. Of note, during the first contrast injection the patient complained of worsening chest pain and his blood pressure raised abruptly from 80/50 mmHg to 204/102 mmHg and then returned back to the baseline 70/45 mmHg; heart rate remained increased at 130 beats/min. This abrupt fluctuation of blood pressure raised the suspicion of pheochromocytoma, which was further supported by the markedly elevated vanillylmandelic acid in urine (42 mg/24 h, normal: 4–7 mg/24 h) and by abdominal computed tomography (CT) that demonstrated a large (7.1×6.6 cm), heterogeneous, left suprarenal mass (**Fig. 2**).

The patient was started on propranolol i.v. and subsequently on labetalol i.v. that effectively increased the blood pressure to normal levels and also controlled the heart rate (**Fig. 3**). Intravenous fluids and phenoxybenzamine 10 mg qd per os were also commenced. The following day the patient was asymptomatic with well-controlled blood pressure and heart rate. Two weeks after combined treatment with phenoxybenzamine 10 mg qd per os and propranolol 40 mg b.i.d. per os, the patient underwent surgical tumor resection (**Fig. 4a**).

Immunostaining of the resected tumor with chromogranin-A and CD56 (neural cell adhesion molecule, N-CAM), which is a marker of neuroendocrine activity, confirmed the diagnosis of pheochromocytoma. Histopathology showed areas of extensive tumor necrosis as shown on the CT scan. The Pheochromocytoma of the Adrenal Gland Scaled Score (PASS) [4] was greater than 4 suggestive of aggressive tumor behavior (**Fig. 4b, c, d**). The patient was discharged uneventfully with-

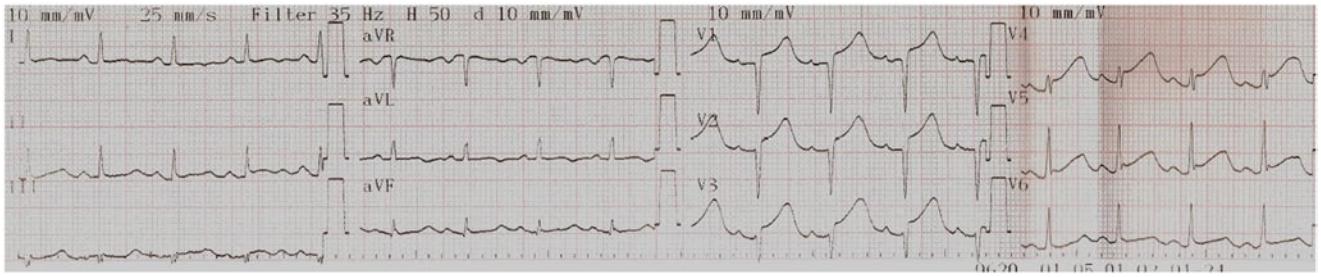


**Fig. 1** ▲ EKG showed mild ST elevation in leads V1–V6

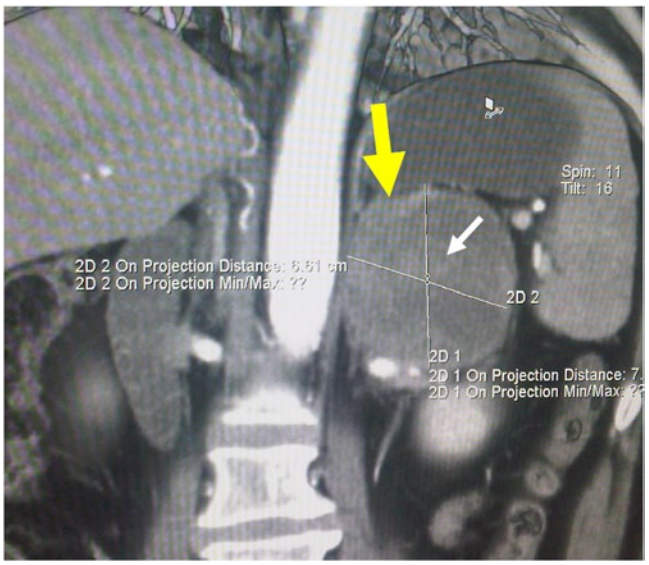


**Fig. 2** ◀ Abdominal computed tomography scan demonstrated a large (7.1×6.6 cm) left-sided, heterogeneous adrenal mass (*yellow arrow*) with a hypodense central area likely representing necrosis or hemorrhage (*white arrow*)

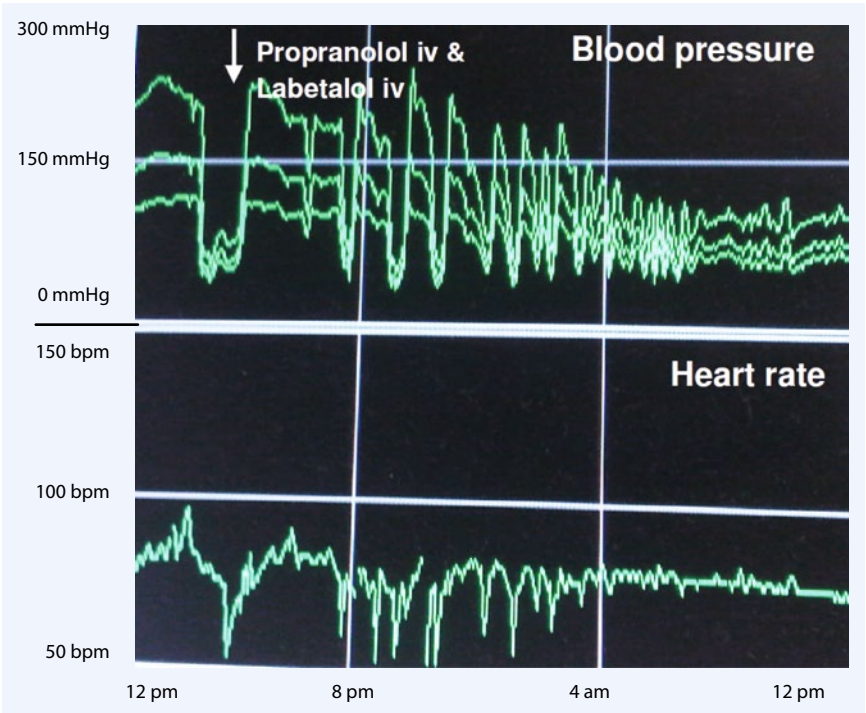


**Fig. 3** ▲ Blood pressure and heart rate waveforms showed marked fluctuations during the first 24 h. Gradual stabilization of blood pressure and heart rate was achieved with administration of propranolol i.v and labetalol i.v.

out any medication 10 days after the operation and he remained normotensive and asymptomatic in the ensuing months.

## Discussion

Pheochromocytoma is a rare catecholamine-producing tumor of chromaffin cells. Usually it presents with the classic triad of headache, palpitations, and diaphoresis [5]. Chest pain, abdominal pain with nausea, vomiting, and diarrhea are also frequent symptoms, as in our patient. Psychiatric disorders may also occur that can be easily misdiagnosed as anxiety or somatization disorders as initially happened in our case [6]. Weight loss or unexpected development of diabetes mellitus could also be associated with pheochromocytoma [7]. Cardiovascular manifestations of pheochromocytoma include hypertension, arrhythmia, transient left ventricular apical ballooning, acute myocardial infarction, congestive heart failure, dilated cardiomyopathy, and aortic dissection [8]. The patient may even present with ischemic EKG changes. Catecholamines may alter ion transport across cell membranes, thereby leading to ischemic EKG changes [9]. In addition, during a pheochromocytoma crisis, the supply–demand mismatch caused by the catecholamine-driven tachycardia may precipitate true ischemia, leading to EKG abnormalities even in the absence of coronary atherosclerosis [10].

There have been reported cases of pheochromocytoma patients presenting with takotsubo syndrome with normal coronary arteries, regional wall motion abnormalities, and troponin leak [11, 12, 13]. In contrast to these cases, there was no evidence of takotsubo-like myocardial response in our patient. The ST elevations were transient and brief and there

was no troponin leak or left ventricular dysfunction.

The most profound effect of the catecholamine surge in the current case was a marked, transient, peripheral vasodilation resulting in cardiogenic shock. Although pheochromocytoma usually induces hypertension, 20% of the patients may present with hypotension and 2% with cardiogenic shock [2]. Several mechanisms are responsible for the reduction of peripheral resistances by pheochromocytoma. The predominant catecholamine secretion appears to play a key role. Epinephrine- or dopamine-secreting pheochromocytomas may manifest with hypotension, since epinephrine acts mostly on $\beta_2$-adrenergic receptors located on smooth muscle cells of the peripheral arteries, whereas norepinephrine-secreting tumors may present with hypertension secondary to the $\alpha_1$-adrenergic receptor-mediated peripheral vasoconstriction [7, 14]. In the current case, we did not assess directly the catecholamine levels during the cardiogenic shock and therefore only assumptions can be made regarding the predominant secretion by the tumor. An imbalance in catecholamine secretion by the tumor in favor of epinephrine could likely explain the clinical events in our case.

Intriguingly, during the coronary angiography, the patient's blood pressure status altered abruptly from hypotension to severe hypertension. It is most likely that contrast injection triggered hypertension [15]. Fluctuation of blood pressure in pheochromocytoma is quite rare and is believed to be associated with tumors that primarily secrete epinephrine [3]. Although the precise mechanism of this hemodynamic instability remains unclear, baroreflex failure appears to play a key role [16].

Our patient was treated with mirtazapine because of a suspected anxiety disorder. The medication was interrupted abruptly by the patient without any medical consultation. The interaction of mirtazapine with pheochromocytoma-secreted catecholamines could be considered. Mirtazapine is a noradrenergic and specific serotonergic antidepressant that is primarily used for the treatment of depression. Experimental data show that mirtazapine can inhibit various catecholamine transporters, thereby increasing the synaptic cleft that subsequently increases the likelihood of adrenergic receptor activation. Theoretically, mirtazapine could accentuate the catecholamine surge in the presence of pheochromocytoma. However, unlike most conventional antidepressants, clinically used doses of mirtazapine have no appreciable affinity for the serotonin, norepinephrine, or dopamine transporters and have minimal effect as a reuptake inhibitor of these neurotransmitters [17] Approximately 10% of pheochromocytomas are malignant. The diagnosis of malignant pheochromocytoma can be made only in the presence of metastases [18]. Although there are no specific metabolic, radiologic, or histopathologic features of malignant pheochromocytoma, there are several postoperative features that determine the likelihood of malignancy or recurrence, such as a PASS greater than 4, increased tumor weight, high perioperative dopamine levels, and postoperative persistent hypertension [19]. Patients with these characteristics should have more thorough follow-up. In our case the tumor appeared to be benign despite having indirect markers of malignancy (e.g., PASS >4 with tumor necrosis, increased tumor weight). The benign nature of the tumor was supported by the absence of clear tissue invasion on CT and macroscopically during the resection, as well as by the uneventful postoperative course of our patient. However, given the increased PASS our patient continues to be followed up.

The therapeutic management of a pheochromocytoma has two major objectives: (a) to control the pheochromocytoma crisis in order to prevent major and potentially lethal cardiovascular complications, such as myocardial injury and malignant arrhythmias, and (b) to prepare the patient for surgical intervention. In the present case, in the setting of severe hypotension, we decided to administer propranolol i.v. However, administration of a nonselective β-blocker, like propranolol, would induce hypertension without prior α-blockade [20]. This occurs because nonselective β-blockers antagonize the catecholamine

## Abstract · Zusammenfassung

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### Pheochromocytoma crisis presenting with cardiogenic shock

**Abstract**

Pheochromocytoma is a catecholamine-secreting tumor of the adrenal glands whose typical presentation includes the triad of headache, palpitations, and diaphoresis. Pheochromocytoma crisis is an urgent medical condition whose diagnosis and management constitute a challenge for physicians. We present the case of a 55-year-old man who developed cardiogenic shock in the setting of a pheochromocytoma crisis. After stabilizing blood pressure with combined administration of α- and β-blockers, the tumor was surgically removed. Our diagnostic and therapeutic challenges are discussed.

**Keywords**

Pheochromocytoma · Cardiogenic shock · Catecholamines · Adrenergic blockers · Surgery

### Phäochromozytomkrise mit kardiogenem Schock

**Zusammenfassung**

Ein Phäochromozytom ist ein katecholaminsezernierender Tumor der Nebennieren, dessen typische Symptomatik aus der Trias von Kopfschmerzen, Herzklopfen und Schweißausbrüchen besteht. Die Phäochromozytomkrise ist ein medizinischer Notfall, dessen Diagnostik und Behandlung eine Herausforderung für Ärzte darstellt. Wir präsentieren den Fall eines 55-jährigen Mannes, der während einer phäochromozytombedingten Krise einen kardiogenen Schock entwickelte. Nach Stabilisierung des Blutdrucks mit kombinierter Verabreichung von α-und β-Blockern wurde der Tumor operativ entfernt. Unsere diagnostischen und therapeutischen Ansätze werden vorgestellt und diskutiert.

**Schlüsselwörter**

Phäochromozytom · Kardiogener Schock · Katecholamine · Adrenozeptorenblocker · Chirurgie

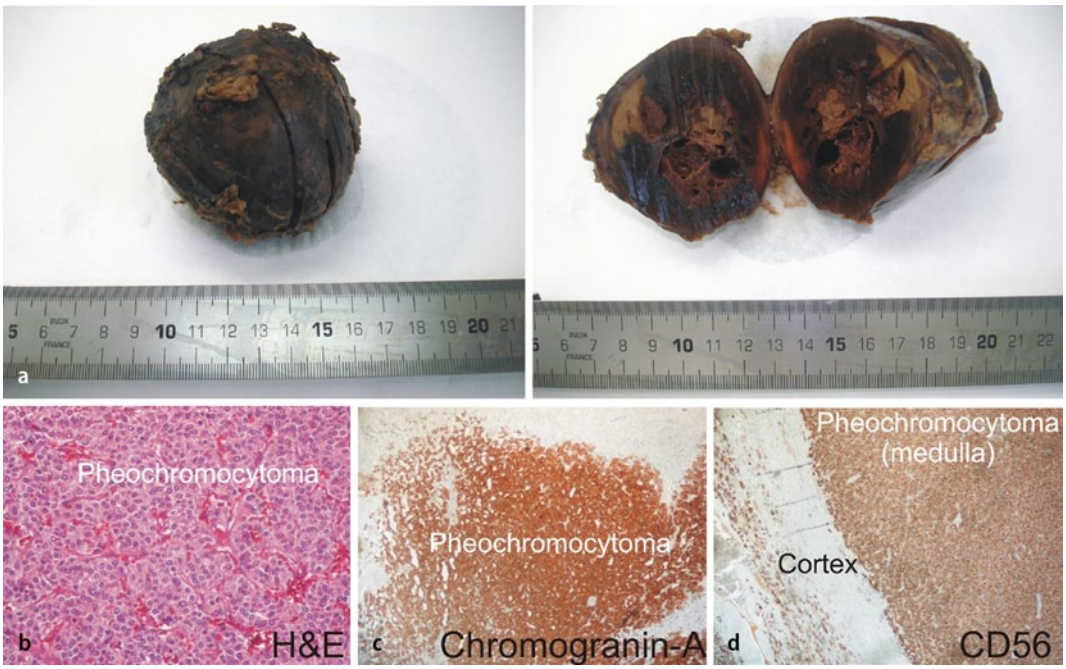


**Fig. 4** ◀ **a** Macroscopic appearance of the resected tumor. **b** H&E staining showed nests of tumor cells (*zellballen*) surrounded by a discontinuous layer of sustentacular cells and fibrovascular stroma. There were blood vessels surrounding tumor nests that were composed of round-to-oval cells. There was evidence of extensive tumor necrosis. **c** Immunostaining for chromogranin-A was positive in pheochromocytoma cells. **d** CD56 (neural cell adhesion molecule, N-CAM) immunostaining was positive in pheochromocytoma cells, as well as in normal cortical cells of the zona glomerulosa but not in cells of the zona fasciculata or zona reticularis

β2-mediated vasodilation while leaving the α-mediated vasoconstriction intact, thereby resulting in increased vascular resistance, hypertension, and increased cardiac afterload. For this reason, we also used labetalol hydrochloride, which is a combination of α1-adrenergic and nonselective β-adrenergic receptor blocking agent [21]. Even though labetalol has been used in the treatment of pheochromocytoma crisis, it is not yet recommended as first-line treatment because it has weak α-blocking activity [21, 22]. Moreover, labetalol reduces significantly the uptake of metaiodobenzylguanidine (MIBG), and therefore, it needs to be interrupted about 2 weeks before MIBG uptake scanning [23]. In our case we switched labetalol to phenoxybenzamine, a long-acting, noncompetitive, irreversible α-adrenergic blocking agent, which is the mainstay of therapy in pheochromocytoma. Because of its noncompetitive blockade effect, it is more difficult for the circulating catecholamines secreted by the pheochromocytoma to overcome the blocking effects of phenoxybenzamine. Collectively, the most effective pharmacological approach to pheochromocytoma crisis should involve the administration of an α-blocker for a few days followed by a β-blocker.

As in our case, surgical resection of the tumor is the only effective radical treatment of pheochromocytoma [24]. With regard to the preoperative preparation, it is advisable that the patient remains asymptomatic and normotensive for at least 7–14 days before the surgery, as long as this is clinically feasible [25]. It has been recommended that the following criteria should be met prior to tumor removal: (a) blood pressure less than 160/90 mmHg for 24 h before surgery, (b) no postural hypotension, (c) absence of ST or T abnormalities for 1 week, and (d) no more than one premature ventricular contraction every 5 min [26].

## Conclusion

**In conclusion, in the current report we present a case of a pheochromocytoma crisis presenting with transient cardiogenic shock due to catecholamine (most likely epinephrine) surge. Administration of propranolol, labetalol, and phenoxybenzamine was effective in stabilizing the blood pressure prior to surgical resection of the tumor. Early recognition of the tumor is crucial, as pheochromocytoma patients presenting with shock may have a poor prognosis.**


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**Conflict of interest.** On behalf of all authors, the corresponding author states that there are no conflicts of interest.


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