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Surgical anesthesia in a patient with a pheochromocytoma crisis supported by ECMO: a case report

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Abstract
Pheochromocytoma is rare in clinical practice, with patients typically presenting with headache, high blood pressure and sweating. Patients who develop a pheochromocytoma crisis are particularly rare. This report describes the case of a patient in a pheochromocytoma crisis who presented with severe cardiogenic shock, acute respiratory failure, and acute coronary syndrome. The patient underwent surgery under general anesthesia with ECMO support and was discharged in good health.

Introduction

Pheochromocytoma is a rare endocrine tumor in which pheochromocytoma cells in the adrenal medulla or paraganglia secrete large amounts of catecholamines. The typical clinical manifestations are persistent or flareup hypertension, severe headache, palpitations and excessive hormone-induced sweating. However, in clinical practice, the symptoms of pheochromocytoma can easily be confused with those of other diseases, leading to a misdiagnosis or missed diagnosis. Missing the optimal treatment window poses a significant risk of death.

Clinical data

The patient was a 64-year-old female with no previous history of heart disease, hypertension, diabetes, or other significant conditions. She suddenly experienced palpitations, accompanied by nausea, vomiting, and pain radiating in both lower limbs without an obvious cause. She was initially treated at a local hospital. The patient suddenly experienced nausea and vomiting, chest tightness, obvious shortness of breath, headache, and dizziness and gradually became confused. Her oxygenation was difficult to maintain, requiring assisted ventilation with tracheal intubation. Enhanced abdominal CT revealed a mass in the left adrenal area is with a rich blood supply, suggesting pheochromocytoma. It was difficult to maintain the stability of the patient's circulatory system after administering large doses of vasoactive drugs, so she was transferred to our hospital for further treatment (Fig. 1).

Upon admission, the patient's heart rate was 148 breaths/min, her blood pressure was 108/68 mmHg (epinephrine at 1.5 μg/kg/min and norepinephrine at 1.2 μg/kg/min were continuously pumped). With ventilator support treatment, her blood oxygen saturation was 93% (the oxygen concentration was 100%). Blood gas analysis and blood tests showed the following results: pH, 7.27; plasma lactate, 10.5 mmol/L; bicarbonate concentration, 14.4 mmol/L; oxygen partial pressure, 65 mmHg; oxygenation index, 65 mmHg (Table 1); NTproBNP, 14,079

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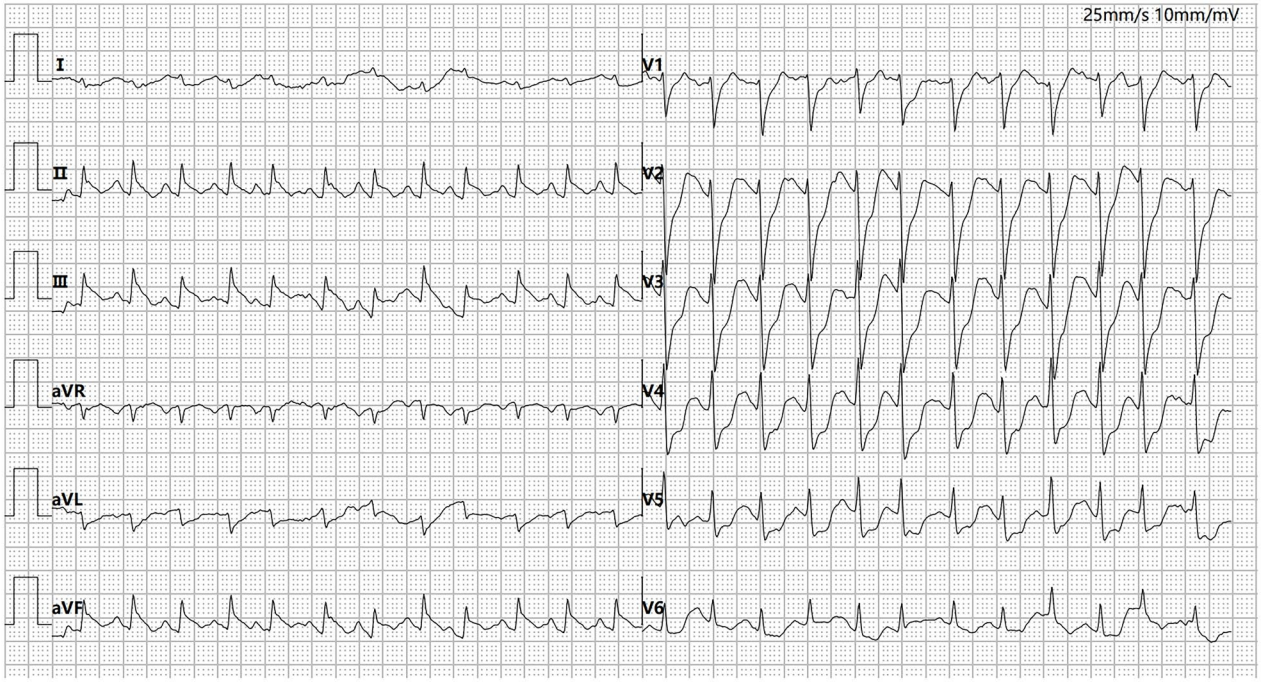

Fig. 1 A 12-lead electrocardiogram of the patient upon admission

Table 1 Blood gas analysis values of the patient at different time points

	Glucose(mmol/L)	Ph	$PaCO_2$(mmHg)	PaO_2(mmHg)	PaO_2/FiO_2(mmHg)	BE(mmol/L)	Lac(mmol/L)	FiO_2(%)
At admission	24.9	7.27	32	65	65	-11.3	10.5	100
Before the operation	6.7	7.46	37	149	373	1.8	0.9	40
During the operation	9.5	7.382	40.7	291.6	296	-1.4	1.66	100
15 days after surgery	5.4	7.42	42	146	355	1.8	0.7	40

pg/ml; glucose, 26.02 mmol/L; creatinine, 233 μmol/L; free methoxynorepinephrine, 15511.60 ng/L; free methoxyepinephrine, 4205.70 ng/L; and free methoxyadrenaline substance, 18717.30 ng/L. A bedside color Doppler ultrasound indicated left ventricular enlargement and reduced left cardiac function with an LVEF of 20%. Coronary angiography showed normal LM, LAD, LCX, and RCA arteries. The patient developed severe cardiogenic shock, and despite 100% inspired oxygen, high positive end-expiratory pressure, and deep sedation, profound hypoxemia persisted. ECMO treatment was initiated.

Patients continued to require high doses of vasoactive drugs despite ECMO support. Given that surgical resection of the tumor or subtumor embolization was the most appropriate treatment at this stage, a multidisciplinary consultation was conducted. The patient was taken to the operating room with ECMO support. After anesthesia induction, an increase in blood pressure was observed during patient transfer and tumor removal. phentolamine was administrated to maintain circulatory stability during this period. The operation lasted for 4 h, the cumulative blood loss was 1000 ml, and a total of 800 ml of red blood cell suspension and 910 ml of fresh frozen plasma were transfused. Pathology confirmed the presence of pheochromocytoma, and the patient's postoperative circulatory status stabilized (Figs. 2 and 3). Her postoperative LVEF was 57%. The ECMO cannulas were removed on the second day after surgery. Due to a lung infection, the patient received two bedside alveolar lavages. Sputum culture results of alveolar lavage tested positive for Klebsiella pneumoniae. Following anti-infective treatment, the tracheal catheter was removed on the tenth day after surgery, and the patient was transferred to a general ward. She eventually recovered and was discharged from the hospital with no lasting complications.

Discussion

Pheochromocytoma and paraganglioma (PPGL) tumors are rare endocrine tumors characterized by the secretion of catecholamines. PPGLs store a large amount of catecholamines, with some patients having tumor content of more than 3 million pg/g of catecholamines. When catecholamines are released into the bloodstream, plasma catecholamine concentration can increase approximately 1000-fold. Nearly 80% of pheochromocytomas originate

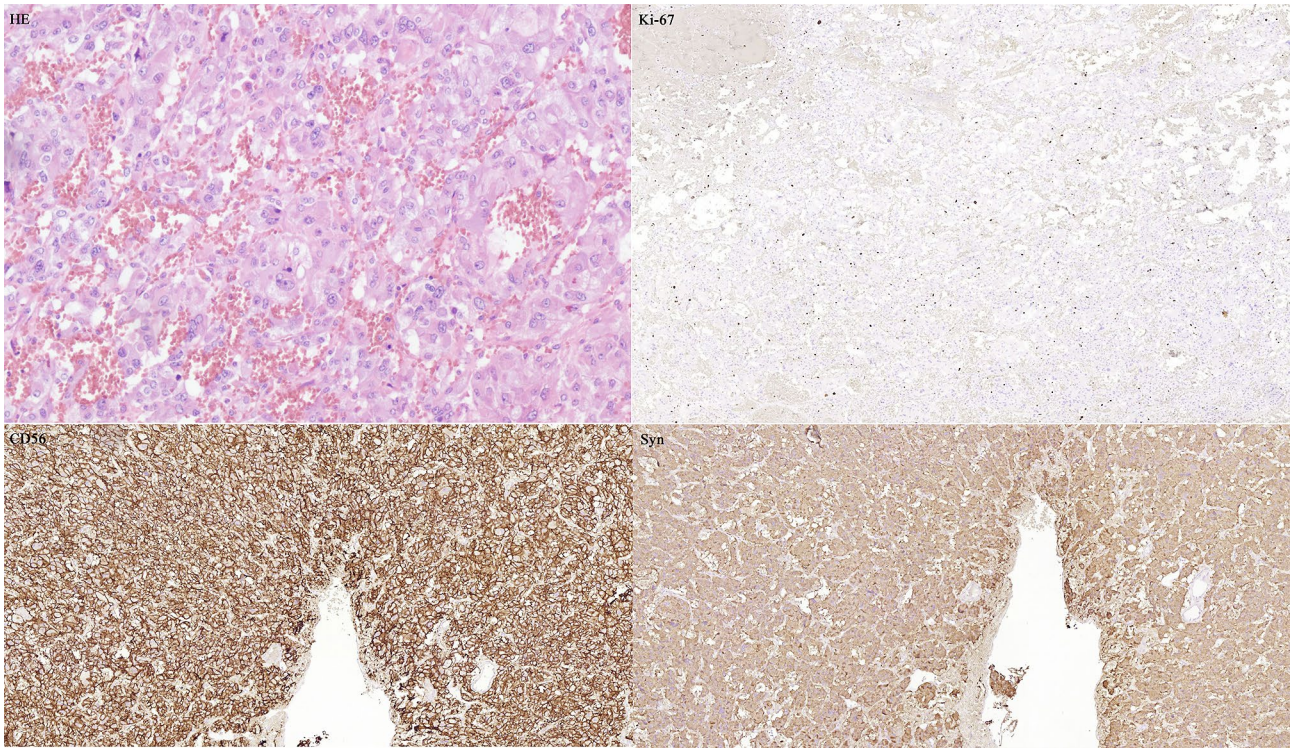

Fig. 2 H&E staining and immunohistochemistry of the tumors

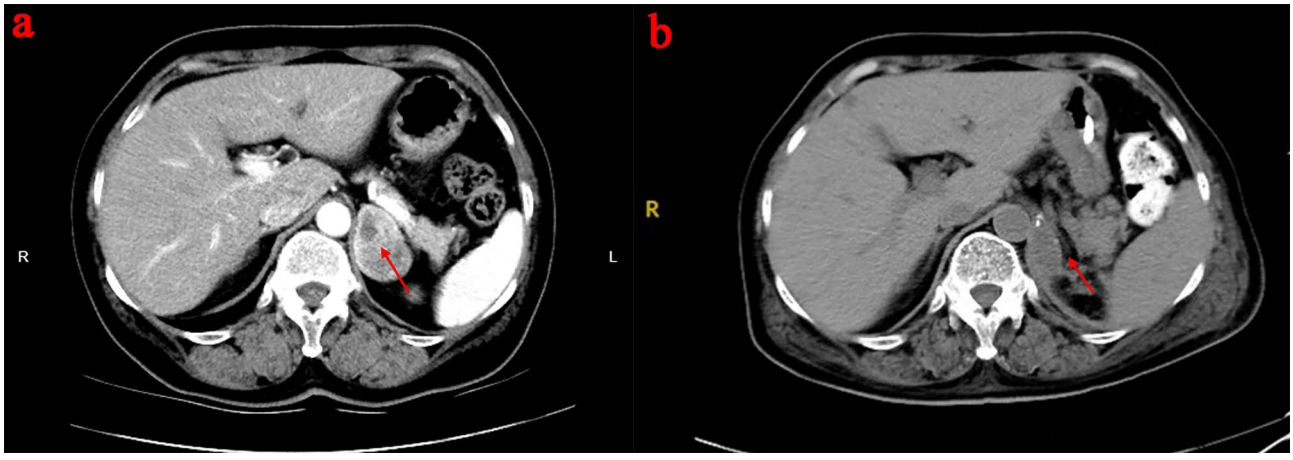

Fig. 3 (**a**)Preoperative abdominal CT image. The marked area is pheochromocytoma (**b**) Postoperative abdominal CT image. The marked area is after tumor resection

from the adrenal medulla, whereas only 10-15% of tumors originate outside adrenal tissues [1, 2]. Paragangliomas originating outside adrenal glands mostly arise from nonfunctional parasympathetic ganglia or functional catecholamine-secreting sympathetic ganglia [3]. Pheochromocytomas can be divided into three main molecular clusters. Tumors related to the Krebs cycle/VHL/EPAS1 are primarily norepinephrine-secreting phenotypes and are more prone to metastasis and recurrence, necessitating close follow-up. Tumors associated with kinase signaling predominantly involve adrenaline-secreting phenotype and are generally less severe. To date, a few phenotypes related to Wnt signaling have been detected in clinical studies, and further research is required to explore their relevance [4].

The typical clinical manifestations of pheochromocytoma are headache, increased blood pressure due to peripheral vascular contraction from catecholamines binding to vascular α receptors, rapid heart rate, and sweating due to β adrenergic receptor simulation. Among these symptoms, seizures, hypertension, palpitations, syncope, anxiety, and hyperglycemia are more common

in pheochromocytoma patients who have tumors that secrete adrenaline. Headache, sweating, and persistent hypertension are more frequently associated with norepinephrine-secreting PPGLs [5]. However, extreme clinical manifestations, such as cardiogenic shock, catecholamine cardiomyopathy, and acute coronary syndrome, can also occur in patients with PPGLs. These severe cases are often due to the condition being overlooked by both doctors and patients [6]. The manifestations of the case in this report were also due to insufficient attention by both the doctors and the patient during the initial visit, resulting in a delay in diagnosis and a missed opportunity for optimal treatment. PPGL-induced cardiomyopathies occur in up to 11% of cases and are most often associated with an adrenal pheochromocytoma (90%) and rarely with a paraganglioma derived from the sympathetic ganglia (10%) and can be fatal when it occurs. It is the leading cause of preoperative death in patients with PPGLs and is most commonly observed in patients with adrenal pheochromocytoma (approximately 90%). Excessive catecholamines can directly irritate and eventually damage the heart (causing cardiac diseases such as myocarditis) and the vascular system (causing vascular diseases such as coronary artery vasoconstriction leading to myocardial infarction), regardless of the severity of hypertension [2]. This patient had no previous history of hypertension, and her life-threatening acute cardiomyopathy was caused by the massive secretion of catecholamines by the pheochromocytoma, consistent with the case descriptions in the literature. Pheochromocytoma cardiomyopathy can present acutely or chronically. The most common type of acute PPGL cardiomyopathy is Takotsubo syndrome, characterized by arterial vasoconstriction and severe left ventricular dysfunction [5], whereas patients with chronic disease mainly exhibit dilated or hypertrophic cardiomyopathy [7]. Patients with acute stress cardiomyopathy (Takotsubo type) may have a normal ECG (11%), show ST/T wave changes (39%), ST segment elevations (39%), a transient left bundle branch block (4%), or arrhythmias (atrial tachycardia, heart block, and ventricular arrhythmia) (7%) [8]. Upon admission, the electrocardiogram of the patient in this case indicated sinus tachycardia, frequent atrial premature beats, lambda waves, an indoor block, and ST-T changes. Color Doppler ultrasound indicated left ventricular enlargement and reduced left cardiac function, with an LVEF of 20%. The clinical manifestations of acute left heart failure, which closely resemble Takotsubo cardiomyopathy, along with the absence of significant coronary artery abnormalities on coronary angiography, further confirmed that the patient had acute PPGL cardiomyopathy. The rapid and massive secretion of catecholamines by a pheochromocytoma led to paroxysmal or persistent hypertension, which can damage organ functions throughout body. In this case, the electrocardiogram and myocardial enzyme spectrum of the patient were abnormal. However, coronary angiography revealed no obvious abnormalities, and the myocardial enzyme levels significantly decreased after surgery. The previous increase in the patient's myocardial enzyme levels before surgery may have been caused by coronary artery constriction induced by catecholamines. Acute PPGL cardiomyopathy is caused by temporary myocardial ischemia [9] and must be distinguished from organic coronary atherosclerotic heart disease. In a retrospective study, increased platelet count and combined secretion were identified as independent risk factors for cardiovascular complications in PPGL patients. Most PPGL patients mainly secrete norepinephrine, but combined secretion occurs mainly in patients with coexisting cardiovascular complications. In addition to intravascular volume depletion, other sequelae that can occur in PPGL patients include sudden cessation of catecholamine secretion due to tumor necrosis, adrenal receptor desensitization, and hypocalcemia because these tumors normally secrete adrenaline, which may also lead to hypotension and shock [10]. According to a multivariate regression model based on 200 studies, nausea or vomiting are not typical clinical manifestations of pheochromocytoma but are associated with increased mortality. However, there is no significant difference in mortality between patients with severe hypertension and those without severe hypertension [11]. In this case, nausea and vomiting at the early stage of the disease also indicate a poor prognosis and a high risk of death. Therefore, the author hopes to share details regarding the successful treatment of this patient through this case report.

The author suggested that the successful treatment and good prognosis of this patient are closely related to the support of ECMO technology. The use of extracorporeal membrane oxygenation (ECMO) is increasing worldwide, with 48% of these patients requiring noncardiac surgery, creating new challenges for both surgeons and anesthesiologists. Adequate preoperative preparation and evaluation are the keys to ensuring the smooth operation of anesthesia. The ECMO parameters should be accurately recorded to evaluate the patient's coagulation function and to determine whether there are complications. In this case, the induction of anesthesia may only require a small amount of anesthetic drugs, and intravenous anesthesia should be the first choice for maintenance. Monitoring of the intraoperative anesthetic depth and echocardiographic monitoring are also necessary. For patients receiving ECMO support, a negative fluid balance should usually be maintained. Volumetric therapy may be considered unless massive acute blood loss is accompanied by a decrease in pulse oxygen saturation. In this case, volume management itself is challenging. Considering the characteristics of pheochromocytomas,

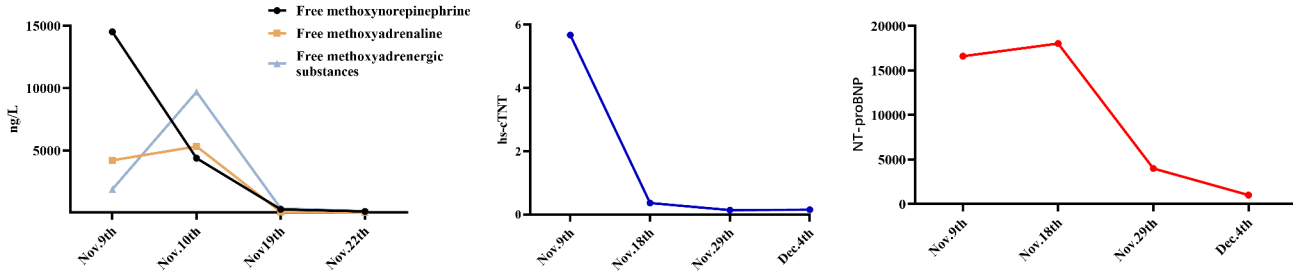

Fig. 4 Changes in the catecholamine hormone test results at different time points

preoperative dilatation is needed in these patients. If the volume is insufficient, the patient's circulation may be difficult to maintain after tumor removal. However, in this case, the patient's cardiac function was significantly reduced; her LVEF was 20%, and the diagnosis of PPGL cardiomyopathy was clear. An excessive volume load can burden the heart and further aggravate myocardial damage. Therefore, under real-time transesophageal echocardiography monitoring, we chose to supplement an appropriate volume and administer the positive inotropic drug epinephrine to regulate the patient's blood pressure and maintain satisfactory perfusion. It has also been suggested that in ECMO-supported patients, the use of "ultraprotective ventilation" setting the VT to a predicted body weight of less than 4 ml/kg and a P Plat of less than 25 cmH2O, can reduce pulmonary edema, inflammatory marker levels, and ventilator-induced lung injury (VILI). Due to the absence of anticoagulation therapy in patients receiving perioperative ECMO, the amount of membrane clot formed by the oxygenator increases, and membrane function decreases. Therefore, oxygenator replacement should be considered before surgery [12]. The successful treatment of this patient confirms the importance of ECMO in the clinical management of a pheochromocytoma crisis and provides a new perspective for the future treatment of pheochromocytoma crises.

Currently, surgical resection of the tumor is the main treatment method for PPGLs. In this case, the patient's respiratory circulation tended to be stable after tumor resection, all indicators returned to normal, and the patient experienced a steep decrease in her catecholamine levels after tumor resection (Fig. 4). Studies have shown that 15-25% of patients still have a poor prognosis due to postoperative metastasis. There are many methods for predicting the metastasis and recurrence of pheochromocytoma, but they are not consistent. Currently, experts and scholars agree that the proliferation of cells expressing Ki67 (>3-5%) and mutations in the succinate dehydrogenase (SDHB) gene are strongly correlated with the metastasis and recurrence of pheochromocytoma [13]. The pathological outcome of this patient was Ki-67 (5%), making genetic testing highly important. However, this patient refused genetic testing, and close follow-up is necessary to prevent recurrence.

Conclusion

We report an extremely rare case of a pheochromocytoma crisis complicated by catecholamine cardiomyopathy. This patient was admitted to the hospital with a cardiogenic shock, an LVEF of 20%, difficulty maintaining oxygenation, the need for ECOM to maintain life, and a significant increase in her plasma levels of norepinephrine and epinephrine. She was intubated and received ventilator-assisted ventilation. After the primary lesion was removed under ECOM maintenance, the patient's vital signs were stable, and her cardiac function returned to normal. However, this type of tumor has a risk of metastasis and recurrence. Based on the pathological classification of the patient's tumor, it is recommended that the patient undergo genetic testing and close long-term follow-up.

Limitations

There are several deficiencies in the handling of this case. First, this patient's hormone levels, cardiac function, genetic factors, and imaging findings should have been carefully evaluated before she underwent elective pheochromocytoma resection. Adequate preoperative preparation is necessary, as catecholamines may be released in large amounts during anesthesia induction, endoscopic pneumoperitoneum establishment, and tumor resection. Patients may develop severe hypertension and cardiovascular complications during the perioperative period [14]. Alpha-adrenergic blockers should be used for at least 7 to 14 days when alpha-blockers cannot effectively control the patient's blood pressure. In addition to the use of calcium channel blockers, treatment should also include the inhibition of clinical symptoms caused by a functional PPGL, the restoration of the patient's intravascular blood volume loss after alpha-adrenergic receptor blockade through a high-salt diet and fluid intake (1000–2000 ml/day), and the strict control of the patient's blood pressure and heart rate. Additionally, the patient's blood pressure should be stable and less than 140/90 mmHg before surgery. The optimal heart rate is 60–70 beats/min

when sitting and 70–80 beats/min when standing [11, 15, 16]. Because beta-blockers tend to cause catecholamine overdose, leading to hypertensive crises, beta-blockers should not be used as first-line therapy and should only be used for the treatment of tachycardia in PPGL patients [16]. However, due to the urgent change in this patient's condition, there were only 9 days from hospitalization to surgery, and no formal preoperative preparation was carried out. Therefore, the perioperative management of this patient was highly limited, and the patient's circulation fluctuated sharply, which may have caused potential harm. Second, the choice of treatment, especially whether to surgically resect the tumor or intervene with subtumor embolization, is warrants further discussion. This hospital is a prefecture city hospital that lacks experience in interventional tumor embolization, so laparoscopic tumor resection was the only option in this case. However, laparoscopic surgery requires changing the body position, injecting a certain amount of carbon dioxide to maintain pneumoperitoneum, and inducing hypercapnia after carbon dioxide absorption to further stimulate the release of hormones from the tumor mass. These factors present further challenges for the perioperative management of these patients. CRRT is particularly useful in pheochromocytoma crisis since it continuously removes catecholamines from the systemic circulation. Due to the emergency situation at that time, we did not consider CRRT, which is also worth reflecting on.

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Author contributions
All authors contributed to the writing of the manuscript and read and approved the final manuscript.

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Data availability
Data archiving is not mandated but data will be made available upon reasonable request.

Declarations

Ethics approval and consent to participate
The research was prospectively reviewed and approved by Zhejiang Taizhou Hospital, China. This study was approved by Ethics Committee of Zhejiang Taizhou Hospital [No.KL20240110], and all participants provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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