

[ CASE REPORT ]

## Continuous Hemodiafiltration for Pheochromocytoma Crisis with a Positive Outcome

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### Abstract:

A 38-year-old woman who consulted a local doctor with chief complaints of sudden palpitations, headaches, and chest pain is herein presented. After admission, pheochromocytoma crisis was suspected. Since the patient had a history of acute heart failure and had once survived an episode of cardiac arrest, a rapid decrease in the catecholamine levels was needed. After resuscitation, pharmacological therapy with agents such as phentolamine and landiolol was administered, and continuous hemodiafiltration (CHDF) was performed to reduce the catecholamine levels. Elective surgery was then performed, and a positive outcome was achieved. This case suggests that the preoperative use of CHDF to control pheochromocytoma crisis may therefore be effective.

**Key words:** pheochromocytoma crisis, continuous hemodiafiltration, catecholamine levels

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### Introduction

Pheochromocytoma crisis is a clinical condition with various clinical presentations, such as hypertension, headaches, nausea, or organ damage such as pulmonary edema, heart failure, and kidney dysfunction, due to the rapid and massive secretion of catecholamines (1). The onset is triggered by different causes, and it is an emergency condition with frequently fatal outcomes. Typically, the treatment involves the use of alpha-blockers to stabilize the blood pressure (beta-blockers may be used if needed), and elective surgery is performed to remove the pheochromocytoma. However, cases that are difficult to treat are sometimes encountered in which there is no or little response to pharmacological therapy during the acute phase of treatment. Other possible treatments include the administration of calcium antagonists and magnesium sulfate. When a patient is in shock, me-

chanical circulatory support may be needed using such devices as artificial heart-lung machines and intra-aortic balloon pumps.

A case of pheochromocytoma crisis in which the patient developed acute heart failure and went into temporary cardiopulmonary arrest is herein presented. In a few previous case reports, the blood catecholamine concentrations were reduced through catecholamine removal using continuous hemodiafiltration (CHDF) (2, 3). However, the detailed effects of CHDF have not yet been clarified. The general condition of the patient in this case report was stabilized by combining CHDF with pharmacological therapy to lower her catecholamine levels as quickly as possible, and a positive outcome was thus achieved after elective surgery. This case report is presented along with a review of the relevant literature, and our findings suggest that CHDF may be an effective treatment for pheochromocytoma crisis.

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**Table 1. General Laboratory Findings on Admission.**

Complete blood cell counts	White blood cells ( $\mu\text{L}$ ) [3,500 - 9,700]	20,670
	Red blood cells ( $\mu\text{L}$ ) [376 $\times 10^4$ - 516 $\times 10^4$ ]	423 $\times 10^4$
	Hemoglobin (g/dL) [11.2 - 15.2]	13.6
	Hematocrit (%) [34.3 - 45.2]	39.9
	Platelets ( $\mu\text{L}$ ) [14.0 $\times 10^4$ - 37.9 $\times 10^4$ ]	34.3 $\times 10^4$
Blood chemistry	Total protein (g/dL) [6.5 - 8.2]	7.2
	Albumin (g/dL) [3.8 - 5.2]	4.6
	Blood urea nitrogen (mg/dL) [8.0 - 22.0]	18.2
	Creatinine (mg/dL) [0.46 - 0.82]	1.00
	Uric acid (mg/dL) [2.7 - 7.0]	6.4
	Sodium (mEq/L) [135 - 145]	138
	Chloride (mEq/L) [98 - 108]	106
	Potassium (mEq/L) [3.5 - 5.0]	3.9
	Calcium (mg/dL) [8.6 - 10.2]	9.2
	Phosphorus (mg/dL) [2.5 - 4.5]	5.0
	Total bilirubin (mg/dL) [0.3 - 1.2]	0.6
	Aspartate aminotransferase (IU/L) [10 - 40]	33
	Alanine aminotransferase (IU/L) [5 - 45]	14
	Lactate dehydrogenase (IU/L) [120 - 245]	306
	Creatinine phosphokinase (IU/L) [50 - 210]	380
	Creatinine phosphokinase-MB (ng/mL) [<4.0]	18.9
	Troponin I (ng/mL) [<0.026]	4.618
	C reactive protein (mg/dL) [<0.45]	0.13
	Casual glucose (mg/dL)	231
	Hemoglobin A1c (%) [4.6 - 6.2]	6.0
Total cholesterol (mg/dL) [150 - 239]	245	
Triglycerides (mg/dL) [50 - 149]	57	

[ ]: normal reference value

## Case Report

The patient was a 38-year-old woman who had been aware of palpitations and headaches since around September 2017. The blood pressure measured at home was 190/120 mmHg, and she continued to have high blood pressure on subsequent days. On December X, she experienced sudden palpitations and a headache while seated and studying. Since she was starting to also develop chest pain, the patient decided to consult a local doctor. Since she had nausea, 10 mg of metoclopramide was administered intravenously. The patient presented with hypertension (190/110 mmHg). Abdominal computed tomography (CT) showed a 40-mm right adrenal gland tumor with a central low-density area. Because the patient was diagnosed with hypertensive crisis, she was transferred to our hospital's emergency center for further testing and treatment.

Whereas the family history was positive for diabetes mellitus (mother) and liver cirrhosis (father), there was no family history of adrenal gland disease. On admission, her consciousness level was at Glasgow Coma Scale (GCS) E3V5M6, temperature was 36.1°C, blood pressure was 167/117 mmHg, heart rate was 118 bpm, respiratory rate was 22 breaths/min, and peripheral capillary oxygen saturation

(SpO<sub>2</sub>) was 97% (room air). On physical examination, there was no jugular venous distension, and coarse crackles were heard in both lung fields. There were no heart murmurs and no abdominal abnormalities. Pitting edema of the lower limbs was observed. Marked sweating of the entire body was seen. While the blood tests did not show anemia or an impaired liver function, the white blood cell count was elevated (Table 1). Hyperglycemia, a slight elevation of creatinine, and an elevation of the cardiac enzyme level, was also observed. On the 4th hospital day, high levels of blood adrenalin and noradrenalin, and also high levels of urinary catecholamines and their metabolites, measured on admission, were identified (Table 2). The blood adrenocorticotrophic hormone (ACTH), cortisol, and plasma renin activity were also high, while the blood calcium and plasma intact parathyroid hormone (PTH) levels were within the normal ranges (Table 1 and 2).

A plain chest X-ray showed a cardiothoracic ratio of 46 %, and ground-glass opacities in both lung fields (Fig. 1). An electrocardiogram showed poor R-wave progression in V2-4 and ST depression in V4-5. The ejection fraction was about 40 %, and no abnormalities in wall motion were observed by emergent cardiac ultrasonography. A pre-surgery abdominal contrast-enhanced CT scan showed a sharply marginated, 40-mm tumor in the right adrenal gland with a

**Table 2. Hormone Profiles.**

		On admission	6th hospital day	After surgery
Plasma	Adrenocorticotrophic hormone (pg/mL) [7.2-63.3]	221.8		30.9
	Cortisol (µg/dL) [4.5-21.1]	45.1		18.0
	Renin activity (ng/mL/h) [0.3-2.9]	9.4		<0.2
	Aldosterone (pg/mL) [29.9-158.8]	103.3		64.9
	Adrenalin (ng/mL) [<0.10]	44.47	4.11	0.09
	Noradrenalin (ng/mL) [0.10-0.50]	14.31	6.69	0.14
	Dopamine (ng/mL) [<0.03]	0.25	0.04	<0.01
	Intact PTH (pg/mL) [10-65]	31		
Urine	Homovanillic acid (mg/day) [2.40-6.00]	3.92		4.64
	Vanilmandelic acid (mg/day) [1.50-4.90]	9.33		1.91
	Adrenalin (µg/day) [3.0-41.0]	771.0		33.7
	Noradrenalin (µg/day) [31.0-160.0]	1,137.8		158.6
	Dopamine (µg/day) [280.0-1100.0]	889.9		1,078.9
	Metanephrine (mg/day) [0.04-0.18]	4.50		0.15
	Normetanephrine (mg/day) [0.10-0.28]	3.11		0.32

[ ]: normal reference value

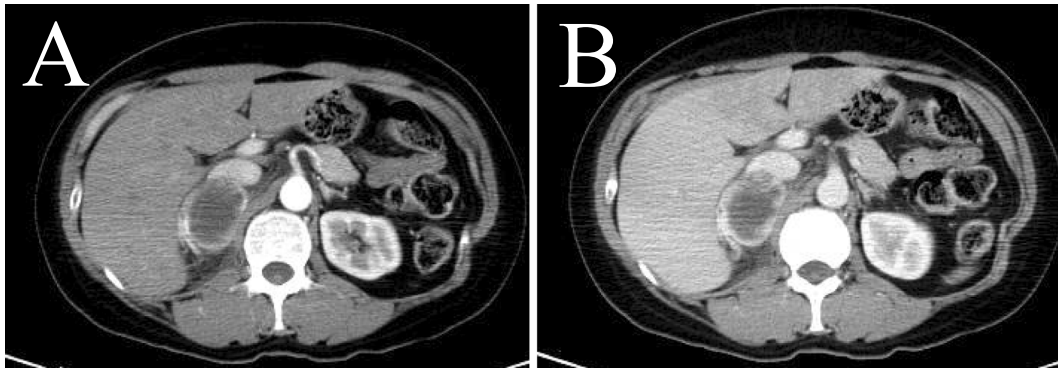
**Figure 1. Plain chest X-ray on admission.**

central low-density area. The margin was shown by a strong contrast effect in the arterial phase; however, the central low-density area showed no contrast effect (Fig. 2). A thyroid ultrasound examination showed no abnormalities of the thyroid glands and no enlargement of the parathyroid glands.

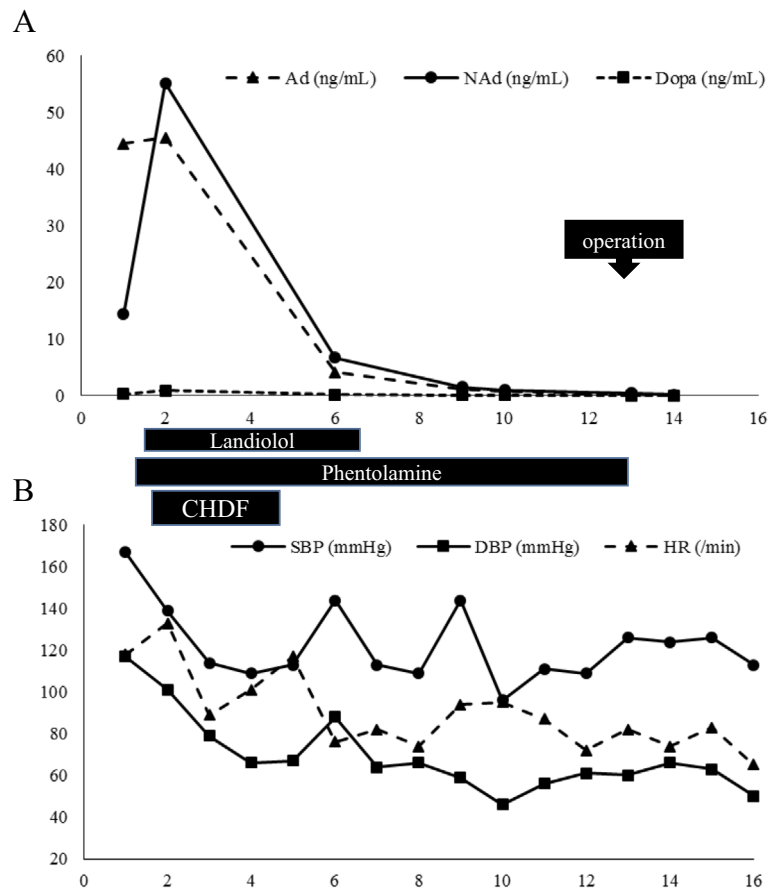
Hypertension, hyperglycemia, excessive sweating, and tachycardia on admission and the finding of a right adrenal gland tumor on abdominal CT led to us to suspect pheochromocytoma. The patient was diagnosed with clinical scenario 1 acute heart failure because the SpO<sub>2</sub> had decreased to 80 % 30 minutes after admission, with an arterial blood gas examination showing a worsening of oxygenation [partial pressure (pO<sub>2</sub>) of 63.2 mmHg], pink frothy sputum, and a worsening of coarse chest crackles (4). Non-invasive positive-pressure ventilation was started, but her oxygenation did not improve. A decline in the level of consciousness and low blood pressure were also observed. One and a half hours after admission, the patient went into cardiac arrest,

and cardiopulmonary resuscitation and tracheal intubation were performed. Adrenalin administration (1 mg) achieved a return of spontaneous circulation and an elevation of the blood pressure. Phentolamine and landiolol were started to achieve an antihypertensive effect and rate control. Five mg of phentolamine was intravenously loaded, followed by 2 mg/h of continuous infusion. Landiolol was started at a dose of 1 µg/kg/min. Although phentolamine infusion was increased to 3 mg/h, and landiolol infusion to 6 µg/kg/min, her blood pressure was as high as 182/148 mmHg, with a heart rate of 156 bpm.

While the catecholamine levels were not known at the time, pheochromocytoma crisis was strongly suspected. In order to stabilize the condition as quickly as possible, CHDF for catecholamine removal was started 3.5 hours after the start of phentolamine and landiolol infusion (Fig. 3). Using an EXCELFO AEF-10 (polysulfone membrane; membrane area 1.0 m<sup>2</sup>, Asahi Kasei Medical, Tokyo, Japan) as the membrane, CHDF was performed at a blood flow rate of 80 mL/h, filtration pump flow rate of 800 mL/h, dialysate pump flow rate of 400 mL/h, and replacement fluid pump flow rate of 400 mL/h. The patient's vital signs stabilized rapidly after the treatment was started, and with the pharmacological therapy, systolic blood pressure (110 to 140 mmHg) and diastolic blood pressure (60 to 80 mmHg) were well controlled. However, on the 4th hospital day, due to in-circuit coagulation, CHDF was discontinued after a total of 71 hours. The drainage volume after 5 hours of starting CHDF was 4,000 mL, and the catecholamine concentrations in the drainage were 12.11 ng/mL of adrenalin (total 48.4 µg) and 14.51 ng/mL of noradrenalin (total 58.0 µg). While the heart rate increased temporarily to around 120 from around 80 bpm after CHDF was discontinued, it subsequently dropped, and landiolol was discontinued on the 6th hospital day. The patient's blood catecholamine levels de-



**Figure 2.** Computed tomography (CT) of the abdomen. A: Early phase CT after contrast medium infusion. B: Delayed phase CT after contrast medium infusion. A sharply margined, 40-mm tumor is observed in the right adrenal gland with a central low-density area. The margin is shown by a strong contrast effect in the arterial phase; however, the central low-density area shows no contrast effect.



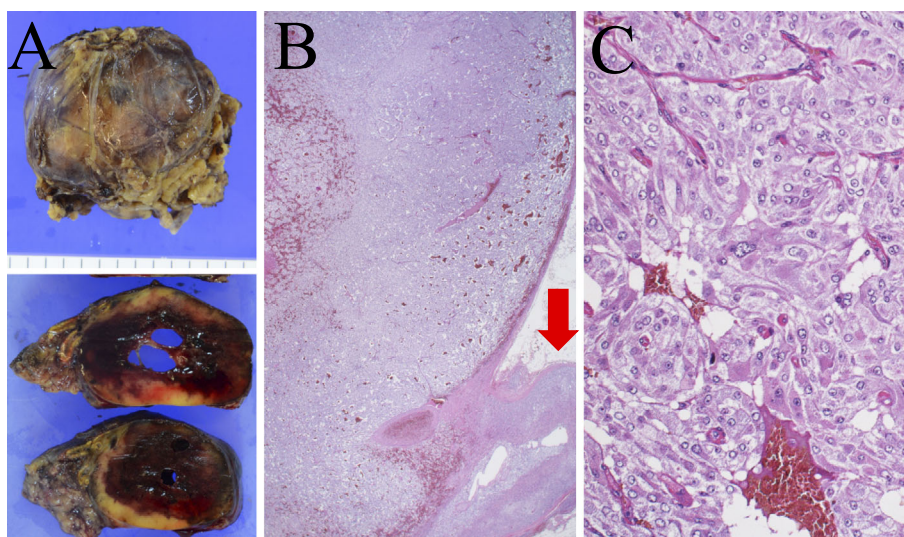
**Figure 3.** Clinical course after admission. A: Fluctuation of the blood catecholamine concentrations. B: Fluctuation of the blood pressure and heart rate. Ad: Plasma adrenalin, NAd: Plasma nor-adrenalin, Dopa: Plasma dopamine, CHDF: Continuous hemodiafiltration, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate

creased markedly by the 6th hospital day, but they still remained significantly elevated (Table 2). There was no subsequent elevation until the surgery (Fig. 3).

On the 13th hospital day, the patient underwent laparoscopic right adrenal gland resection. Even after phentolamine was discontinued after surgery, her blood pressure and

heart rate became stable. On the 14th hospital day, her blood and urinary catecholamine concentrations and urinary metabolites decreased to almost normal reference ranges (Table 2). After rehabilitation, the patient was discharged home on the 48th hospital day.

On gross examination, congestion and hemorrhaging were



**Figure 4.** Macroscopic examination and histopathology of the resected tumor. **A:** Macroscopic examination of the resected tumor. **B:** Histopathology/Hematoxylin and Eosin (H&E) staining  $\times 12.5$ . **C:** Histopathology/H&E staining  $\times 200$ . A sharply marginated solid tumor. Congestion and hemorrhaging are present in the center of the tumor. H&E staining shows the normal adrenal tissue (arrow) and the sharply marginated, encapsulated tumor. The proliferation of tumor cells with wide basophilic cytoplasm is observed, and they are arranged in an alveolar Zellballen pattern due to the vascular barrier.

present in the center of the cystic tumor (Fig. 4). The pathological findings showed a proliferation of tumor cells with wide basophilic cytoplasm arranged in an alveolar Zellballen pattern due to the vascular barrier, and a diagnosis of pheochromocytoma was thus made. The Ki67 index was below 2%. Pheochromocytoma of the adrenal gland scaled score (PASS) was 1 point, and grading system for adrenal pheochromocytoma and paraganglioma (GAPP) score was 0 point (5, 6).

## Discussion

The case of a patient with a severe pheochromocytoma crisis with temporary cardiac arrest was presented. Pharmacological therapy and CHDF stabilized the patient's general condition, and a positive outcome was achieved after elective surgery. Catecholamine removal from the blood with CHDF was found to be an effective treatment for pheochromocytoma crisis.

Pheochromocytoma crisis is induced by daily life triggers such as bending forward, sneezing, and pregnancy, mechanical stimulation such as abdominal palpation, the administration of agents such as metoclopramide and glucagon, and stress such as external injuries and surgery. Due to the rapid and massive secretion of catecholamines, pheochromocytoma crisis has the potential to cause cardiogenic shock such as our patient experienced in the present report. Whitelaw et al. proposed to classify pheochromocytoma crisis as follows: limited crisis (type A) and extensive crisis (type B) (1). Type A refers to conditions presenting with an unstable hemodynamic status, with end-organ damage or dysfunction; and

type B refers to sustained hypotension, shock, and multi-organ dysfunction. Both the cardiac and renal functions were decreased in the current case, and though the patient was type A at the beginning, she may have progressed to type B as she experienced a sharp decline in her cardiac function resulting in cardiac arrest.

As for the cause of the pheochromocytoma crisis in the current case, catecholamine secretion may have been enhanced due to the patient sitting in a forward bending posture and the metoclopramide administered by the previous doctor. The gross pathological findings showed congestion and hemorrhaging in the center of the tumor. A previous study reported the prevalence of cystic change of pheochromocytomas to be 19 %, which is not rare (7). It is believed that cystic change is caused by the hemorrhaging and necrosis of the tumor (8). In many instances, the initial symptom of pheochromocytoma crisis caused by pheochromocytoma rupture seemed to be abdominal pain followed by shock (9). While the present patient did not present with any abdominal pain, based on the pathological findings, the possibility that pheochromocytoma crisis was caused by hemorrhaging and necrosis of the tumor cannot be excluded. In fact, the catecholamine levels in our case did not increase again even after discontinuing CHDF. A forward bending posture, the administration of metoclopramide, and hemorrhaging and necrosis of the tumor are therefore considered to have had a combined effect on the onset of the pheochromocytoma crisis.

Regarding the optimal pharmacological therapy for pheochromocytoma crisis, intravenous phentolamine and, if needed, calcium antagonists and nitrovasodilators may be

administered. When patients develop tachycardia, beta-blockers should be administered. Ideally, tumor resection should be performed after stabilizing the patient's condition through these pharmacological means. According to Scholten et al., there are more complications and higher mortality rates during emergency adrenalectomies for pheochromocytoma crisis than during elective surgeries (10). Müller et al. reported that, when pheochromocytoma crisis patients with acute heart failure underwent adrenalectomy, the patients in the elective surgery group clearly had fewer postoperative complications and lower mortality rates than those in the emergency surgery group (11). In a previous study, we reported a case of pheochromocytoma crisis that was caused by a ruptured pheochromocytoma, which had a positive outcome after elective surgery (12). In the present case, a rapid decrease in catecholamine levels was needed since the patient developed acute heart failure, and she also had a history of once surviving an episode of cardiac arrest. Tumor resection is the ideal method for rapidly decreasing the catecholamine levels. However, since there are high risks associated with removing tumors by emergency surgery, it was decided to remove the catecholamines through dialysis.

While it has been shown that catecholamines can be removed by hemodialysis (13), it has also been found that, even if catecholamines are removed by hemodialysis, the blood concentration does not decrease sufficiently because pheochromocytomas continuously secrete catecholamines during the interval periods between hemodialysis sessions (14). Furthermore, the change in blood pressure during dialysis could further increase the secretion of catecholamines. Blood catecholamine concentrations can be reduced by continuously removing catecholamines through CHDF while having a minimal impact on the hemodynamic status. Furthermore, since CHDF is more suited to the removal of small to medium-sized molecules compared to regular hemodialysis, CHDF may be highly effective against catecholamines that have relatively small molecular sizes (15). In fact, there are a few studies that have reported on the effectiveness of CHDF in pheochromocytoma crisis (2, 3). According to a case report by Seo et al., the serum creatinine level increased from 1.33 mg/dL to 2.55 mg/dL within 48 hours, and the patient developed acute kidney injury (2). In addition, acute kidney injury was suspected in two cases reported by Tanigawa et al. (3), with serum creatinine levels of 2.23 and 2.35 mg/dL, respectively. While the present case did not present with acute kidney injury, CHDF was used in a similar manner. There was a marked decrease in the blood catecholamine concentrations with CHDF, and the patient's general condition was stabilized. It was estimated that CHDF removed 48.4 µg of adrenalin and 58.0 µg of noradrenalin in the first 5 hours of CHDF. The estimated amount of removed adrenalin in 24 hours was about one-third of the urinary adrenalin, indicating that it is an effective method for quickly removing catecholamines. Since CHDF was performed for 71 hours, it is possible that there were even more benefits. In fact, there was good con-

trol of the blood pressure and pulse rate during CHDF. If the marked increase in the blood catecholamine levels is transient as in the present case, then CHDF could be an effective method. However, if such catecholamine release is not transient, then there is a possibility of re-elevation of the blood catecholamine levels after the cessation of CHDF. Much more experience is necessary to establish the clinical utility of CHDF for pheochromocytoma crisis.

In conclusion, pheochromocytoma crisis may cause multi-organ failure, and it could also lead to fatal outcomes. From the perspective of complications and the mortality rate, elective surgery is recommended, and it is important that the patient's general condition is stable prior to surgery. CHDF quickly removes catecholamines and reduces the effects of excessive catecholamines. CHDF may therefore become an effective method for the preoperative control of pheochromocytoma crisis even in the absence of acute kidney injury.

**The authors state that they have no Conflict of Interest (COI).**

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