Case report

# Pheochromocytoma-induced diffuse alveolar hemorrhage after cholecystectomy: A case report and literature review

Xinlian He [a], Ruchun Dai [b], Liming Zhou [a], Lingbo Lv [a], Mingzheng Li [a], Jianxin Deng [a,*], Dewen Yan [a,**]

[a] Department of Endocrinology, Shenzhen Second People's Hospital, the First Affiliated Hospital of Shenzhen University, Health Science Center of Shenzhen University, Shenzhen Clinical Research Center for Metabolic Diseases, Shenzhen Center for Diabetes Control and Prevention, No. 3002, Sungang West Road, Futian District, Shenzhen, 518035, Guangdong Province, China
[b] Department of Endocrinology and Metabolism, Hunan Provincial Key Laboratory of Metabolic Bone Diseases, National Clinical Research Center for Metabolic Disease, The Second XiangYa Hospital, Central South University, 139 Renmin Middle Road, Changsha, 410011, China

ARTICLE INFO

ABSTRACT

Diffuse alveolar hemorrhage (DAH) can be caused by various conditions, categorized as autoimmune and non-autoimmune. Immunofactor-mediated vasculitis, such as Wegener granulomatosis, microscopic polyangiitis, Goodpasture syndrome, connective tissue disorders, and antiphospholipid antibody syndrome, are common autoimmune causes. Non-autoimmune factors include infectious or toxic exposures and neoplastic conditions. The diagnosis of DAH, resulting from excessive catecholamine release from an adrenal pheochromocytoma or extra-adrenal paraganglioma, can present diagnostic challenges and necessitate prompt treatment. In this report, we present a case of pheochromocytoma that manifested as an adrenal incidentaloma (diagnosed during the management of sudden-onset DAH after cholecystectomy). **Case report**: A 39-year-old female patient with adrenal incidentaloma developed DAH following a cholecystectomy procedure, presenting with sudden-onset hemoptysis and dyspnea. Administration of glucocorticoids, known to precipitate pheochromocytoma crisis (PCC), was required before the cause was determined. Intubation and mechanical ventilation were necessary due to persistent hypoxemic respiratory failure and acute respiratory distress syndrome (ARDS). The patient in this case experienced two epidoses of PCC while she was on mechanical ventilation. Subsequent workup revealed a 26 × 25 mm left adrenal adenoma with hormonal confirmation of catecholamine hypersecretion. A laparoscopic adrenalectomy was done eight months later to excise the left adrenal gland. Subsequent examination of the tissue revealed pheochromocytoma, thereby validating the initial diagnosis. **Conclusion**: Adrenal incidentalomas may be pheochromocytomas (adrenal incidentalomas can manifest as pheochromocytomas), even without adrenergic symptoms. It is recommended that adrenal incidentalomas undergo evaluation for pheochromocytoma before undergoing invasive surgery or receiving corticosteroid treatment. When considering

potential causes of DAH without further elucidation, including a pheochromocytoma or para-ganglioma (PPGLs) in the differential diagnosis is important.

## 1. Introduction

Pheochromocytomas originate from chromaffin cells located in the adrenal medulla, while paragangliomas arise from extra-adrenal sympathetic paravertebral ganglia. Both are rare neuroendocrine tumors that often exhibit similar or identical morphology and share a mostly identical neuroendocrine phenotype, sometimes even having the same genetic predisposition [1]. These tumors, collectively known as PPGLs, can manifest comparable symptoms due to the excessive release of catecholamines. Differential diagnosis between pheochromocytomas and paragangliomas relies primarily on the assessment of the tumor's anatomical location. Data indicate that approximately 5.1 % of incidental adrenal masses are found to be pheochromocytomas [2]. Pheochromocytomas have the potential to be fatal even in asymptomatic cases, often leading to a condition known as pheochromocytoma crisis (PCC) [3,4]. PCC is characterized by a sudden onset of hemodynamic instability, severe hyper- or hypotension, and cardiac failure, which can result in the development of multiorgan dysfunction and mortality rates ranging from 6 % to 18 % [5]. PCC may occur spontaneously or be triggered by factors such as trauma, surgical procedures, anesthesia, and pharmacological interventions, including glucocorticoids [6]. Various medications, particularly glucocorticoids, can induce PCC in patients with pheochromocytoma [7].

Diffuse alveolar hemorrhage (DAH) is a clinical syndrome frequently leading to respiratory failure and typically has severe consequences [8]. The etiology of DAH includes both autoimmune and nonautoimmune illnesses [8]. Standard treatment for DAH often involves the use of corticosteroids, immunosuppressive medications, and, in some cases, plasmapheresis [8]. Although the occurrence of DAH with PPGLs is rare, this report presents a case of pheochromocytoma manifesting as an adrenal incidentaloma and identified during the management of sudden-onset DAH following cholecystectomy. The patient did not exhibit typical symptoms associated with pheochromocytoma, but a phenomenon of PCC was observed after glucocorticoid therapy. The identification of a left adrenal incidentaloma and hypercatecholaminemia strongly indicated the presence of pheochromocytoma, which was later confirmed through postoperative pathology.

## 2. Case report

A 39-year-old female patient arrived at our medical facility with a history of recurring right upper abdomen pain caused by cholelithiasis and cholecystitis for the past five years. The patient expressed a desire to undergo a cholecystectomy and was thereafter admitted to the hepatobiliary surgery department for hospitalization. Approximately three months before admission, the patient experienced persistent cramping discomfort in the upper right quadrant of the abdomen, along with nausea and retching, after consuming high-fat meals. The pain radiated to the back but was relieved after receiving antibiotic treatment. This occurred around three months before admission. An ultrasound scan and magnetic resonance cholangiopancreatography (MRCP) verified the presence of a thicker gallbladder wall, chronic cholecystitis, and gallstones stuck in the neck of the gallbladder. The patient's medical history included the excision of an endometrial polyp, a cesarean section, and the development of gestational diabetes mellitus, which resolved after giving birth. No similar medical history was found in her family. The patient displayed normal blood pressure and showed no symptoms, save for occasional sudden upper abdomen pain. Before the cholecystectomy treatment, the abdominal computed tomography scan revealed a left adrenal incidentaloma with dimensions measuring 26 × 25 × 31mm (Fig. 1). The tumor was initially classified as a nonfunctional adenoma because it did not exhibit the usual triad of symptoms associated with
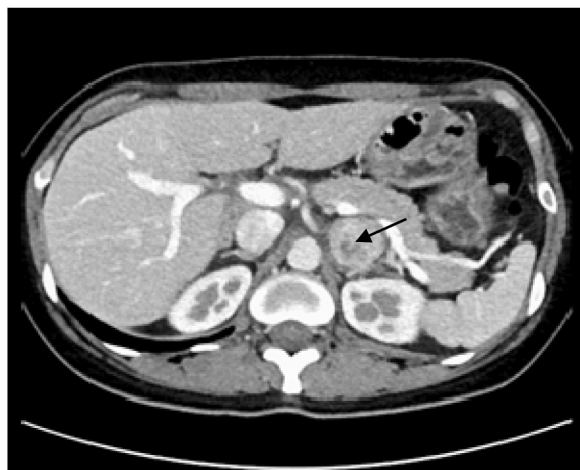


Fig. 1. Adrenal contrast-enhanced CT revealed a left adrenal region measuring approximately 26 × 25 mm, with a CT value 37 Hounsfield units.

pheochromocytoma, nor did it show other common symptoms related to excessive catecholamine production. Additionally, there were no signs of cushingoid characteristics or hypokalemia. The patient underwent laparoscopic cholecystectomy on the fifth hospital day with an unremarkable intra- and post-operative course with stable blood pressure, cardiac, and respiratory rates. Subsequently, 6-h post-surgery, she had a sudden onset of hemoptysis, cough, dyspnea, nausea, and vomiting. During the examination of the chest using a stethoscope, crackling noises were detected in all areas of the right lung and the lower parts of the left lung.

However, the patient's health status deteriorated significantly and rapidly 6 h after undergoing cholecystectomy (changes in the vital signs before and after surgery are shown in Supplementary Table 1). This was characterized by the abrupt onset of symptoms including hemoptysis (coughing up blood), dyspnea (difficulty in breathing), nausea, vomiting, chest tightness, and coughing. During the physical examination, the patient displayed lucid consciousness but presented signs of mental tiredness, including a pale face and cyanotic lips. The patient's vital signs were as stated: a heart rate (HR) of 135 BPM (preoperative HR was 74 BPM, with a normal range of 60–100 BPM), the blood pressure (BP) was 140/80 mmHg (preoperative was 104/78 mmHg, with a normal range of 90–135/60–85 mmHg), a respiratory rate (RR) of 44 BPM (breaths per minute) (preoperative was 20 BPM, with a normal range of 16–20 BPM), and percutaneous oxygen saturation was 80–85 % (when breathing room air, with a normal range of 95–100 %), arterial blood gas analysis suggested hypoxemic respiratory failure and metabolic acidosis. This was shown by a pH level of blood 7.182 (normal range 7.35–7.46), a partial pressure of oxygen ($PO_2$) of 59.1 mmHg (normal range 80–100 mmHg), a partial pressure of carbon dioxide ($PCO_2$) measurement of 30.4 mmHg (normal range 35–45 mmHg), a bicarbonate ($HCO_3^-$) level of 11.0 mmol/L (normal range 21–28 mmol/L), an alkali residue (BE) level of −16.3 mmol/l (normal range -3-+3), and a lactic acid concentration of 6.8 mmol/L (normal range 0.7–2.5 mmol/L). The examination of the heart using a stethoscope revealed tachycardia and bigeminal beats. The concentration of N-terminal-pro β-type natriuretic peptide (NT-proBNP) in the serum was 845 pg/mL (with a normal range of 0–125 pg/mL). The electrocardiogram (ECG) results indicated frequent ventricular premature beats. Additionally, the ECG showed a shortened PR interval, substantial ST depression, and inverted T waves. It is worth noting that the preoperative ECG was within normal limits. The chest computed tomography scan demonstrated diffuse bilateral alveolar infiltrates, with the right side exhibiting more severe involvement. These data suggest that the individual had DAH (Fig. 2), which progressively increased and led to the development of more extensive infiltrates within 48 hours (Fig. 3A and B). The transthoracic echocardiography scan successfully ruled out valvular disease and revealed signs of compromised left ventricular function, indicated by a significantly decreased ejection fraction of 40 %.

To address the patient's medical condition, the administration of glucocorticoids (particularly dexamethasone at a dosage of 20 mg within a 48-h timeframe), furosemide injection, deslanoside injection, nitroglycerin injection, and antibiotics were commenced. Nevertheless, it is crucial to acknowledge that despite these interventions, the patient's condition exhibited a rapid and worsening trend. The patient developed a low-grade fever (38 °C) on the second day following cholecystectomy, which increased to a maximum of 39 °C as the illness worsened. Both blood culture and sputum culture tests yielded negative results. A multitude of organ malfunctions were determined with the implementation of blood collection protocols. The white blood cell count was measured to be $28.10 \times 10^9$/L, while the level of hemoglobin was assessed at 10.9 g/dL (compared to a preoperative hemoglobin level of 14.0 g/dL). The test findings revealed elevated levels of alanine aminotransferase (603 U/L), lipase (191 U/L), and amylase (327 U/L), respectively. The patient experienced a transient episode of acute renal injury, indicated by an elevated blood urea nitrogen level of 165.6 mg/dL (normal range: 50.4–111.6 mg/dL) and a serum creatinine level of 1.9 mg/dL (normal range: 0.5–1.5 mg/dL). The patient exhibited a reduction in plasma albumin levels (27.4 g/L) compared to the preoperative plasma albumin levels (44.1 g/L). In addition, there was slight swelling in the lower limbs. The patient's coagulation system exhibited anomalies, as shown by the following laboratory results: a plasma fibrinogen level of 1.34 g/l (below the normal range of 2.0–4.0 g/l), a D-dimer level of 28.22 mg/L (beyond the typical threshold of <0.55 mg/L), and a positive result on the 3P test. During that timeframe, there was a continued decline in cardiac function, as indicated by increased levels of troponin I, myoglobin, and creatine kinase isoenzyme. Specifically, the levels of troponin I, myoglobin, and creatine kinase isoenzyme were measured at 27.4 ng/mL (normal range: 0–0.02 ng/mL), 291.0 ng/mL (normal range: 0–46.6 ng/mL), and 94.6 ng/mL (normal range: 0–0.02 ng/mL), respectively. The concentration of NT-proBNP showed a statistically
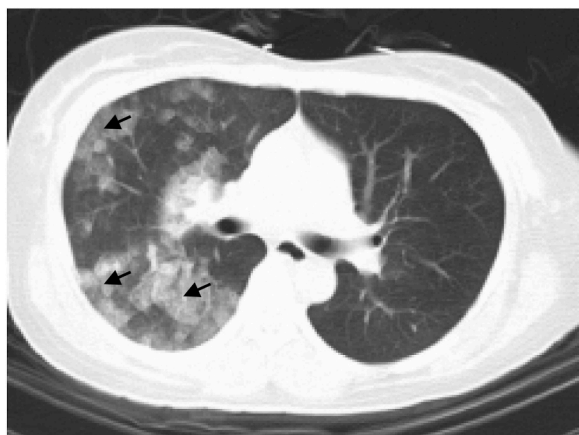


**Fig. 2.** 6 hours after the cholecystectomy procedure, a chest CT scan revealed DAH, with the right side being particularly evident.
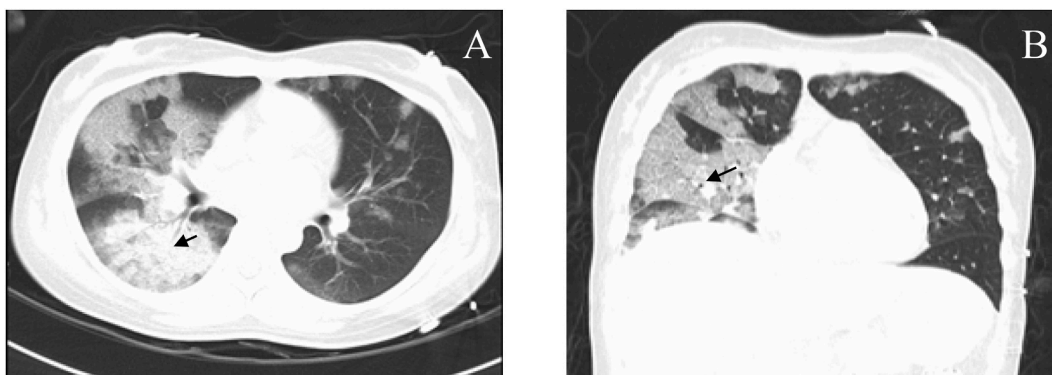
Finally, she was discharged from the hospital after being hospitalized for twenty-two days. No drugs were maintained.

The patient was rehospitalized after eight months to have a comprehensive diagnostic assessment for pheochromocytoma. Before the surgical intervention, the laboratory examination of the blood samples and urinary specimens indicated consistently high levels of catecholamine, as shown in result 2 of Table 1. However, the patient's ABPM result was normal, and she showed no signs of hypertension or any other issues. This case study offered additional support for the concept that the levels of catecholamines and their metabolites in the plasma and urine may be elevated even in the absence of hypertension. She exhibited a mild impairment in the oral glucose tolerance test. During this period, the patient's respiratory and cardiovascular systems were fully recovered, with no subsequent complications.

Following two weeks of administering oral phenoxybenzamine, the dosage was increased from 20 to 40 mg/day. Additionally, 2000 ml of rehydration fluids were given daily before three days of the left adrenalectomy. Subsequently, the blood volume was fully replenished. A laparoscopic procedure was performed to remove the left adrenalectomy without any complications. Throughout the treatment, the patient's vital signs remained steady and within the expected range. The patient's recuperation following the surgery progressed smoothly without any notable incidents. A pathological examination confirmed the diagnosis of pheochromocytoma. Under light microscopy, the study revealed that the tumor cells were arranged in nested clusters that had a slightly basophilic and granular look. The immunohistochemical results show that the left adrenal mass is a pheochromocytoma because it stained positively for Syn, CgA, CD56, NSE, S100 (focal), Vim, and Ki67 (<1 %). Following the surgical procedure, no signs of malignancy or recurrence were detected for six years.

## 3. Discussion

This study provides a detailed case report of an atypical clinical progression of pheochromocytoma in a patient who did not exhibit symptoms associated with excessive release of catecholamine. The patient presented with an adrenal incidentaloma. Even if there are no symptoms, it is necessary to conduct hormonal tests for the adrenal incidentaloma to exclude the possibility of different types of secreting adenomas, such as primary aldosteronism and autonomous cortisol secretion [9,10]. However, it is essential to rule out pheochromocytoma, as this is crucial for someone who will undergo surgery. This case highlights the need to emphasize the exclusion of pheochromocytoma as the first step in addressing adrenal incidentalomas. Failure to detect this condition can lead to serious and harmful consequences [7].

Pheochromocytoma is a rare neuroendocrine tumor that accounts for a modest percentage (0.1–0.6 %) of hypertension observed in routine outpatient clinics [11]. Many cases stay concealed and are exclusively detected by post-mortem examination [11]. The traditional clinical trio is comprised of periods of headache, palpitations, and sweating, frequently accompanied by persistent or intermittent hypertension [12]. However, the clinical presentations of pheochromocytoma are complex, showing considerable variation and lacking specificity. This can lead to confusion with over 30 different medical diseases, which poses big challenges to physicians [13]. Therefore, pheochromocytomas have been referred to as 'the great mimic' [14] and 'the great masquerader' [15], resulting in frequent instances of missed and delayed diagnoses.

DAH typically presents with symptoms such as hemoptysis, dyspnea, reduced hemoglobin levels, hypoxemia, and diffuse radiographic pulmonary infiltrates [8]. Other symptoms, such as cough and fever, are not specific to DAH. DAH can occur at any stage of life and is frequently observed in conjunction with a pre-existing medical condition. Furthermore, it can act as the earliest indication of an underlying systemic disease. Once a diagnosis of DAH is made, it's crucial to identify the root cause to initiate the appropriate treatment [8]. However, the occurrence of DAH as the primary or worsening presentation of previously undiagnosed PPGLs is rare and often goes unnoticed. When attempting to establish a correlation between PPGLs as a causative factor in DAH, clinicians face difficulties.

Thirteen cases of PPGL-induced alveolar hemoptysis were reported in the scientific literature from 2006 to 2021 [16–28]. Alveolar hemoptysis and PPGLs have only been linked through case reports, with hidden PPGLs triggering alveolar hemoptysis independently or in response to environmental or psychological stress in a few cases. Aside from our patient, no case reports of surgically induced alveolar hemoptysis in PPGLs have been published, indicating that surgical intervention is not an appropriate motivator. Table 3 provides a comprehensive overview of all reported cases, including our own.

After examining all of the aforementioned cases, including our own, we found eight male and six female patients, with ages ranging from 14 to 72 at the time of diagnosis. In the cohort of patients who underwent surgical treatment for PPGLs, alveolar bleeding was observed in 13 cases, with 11 patients having pheochromocytomas. Among these, ten had tumors in the left adrenal gland and one in

**Table 2**

Laboratory test results of plasma and urinary catecholamines.

| Test | Result 1 | Result 2 | Reference range |
| --- | --- | --- | --- |
| Plasma epinephrine | 1155.44 | 174.73 | 0.00–100.00 (pg/ml) |
| Plasma norepinephrine | 573.69 | 560.52 | 0.00–100.00 (pg/ml) |
| Plasma dopamine | 510.77 | 57.09 | 0.00–100.00 (pg/ml) |
| Urinary epinephrine | 70.19 | 40.29/52.75 | 0.00–20.00 (μg/d) |
| Urinary norepinephrine | >450.00 | 170.81/179.48 | 0.00–90.00 (μg/d) |
| Urinary dopamine | | 171.81/250.23 | 0.00–600 (μg/d) |

Result 1: after a PCC in ICU, Result 2: before pheochromocytoma resection.

**Table 3**
Case series of PPGLs with DAH.

| Case | Age | Gender | Main symptoms | Ventilator support | Blood pressure (mmHg) | Tumor localization | Tumor size (mm) | Used glucocorticoid |
|------|-----|--------|---------------|--------------------|-----------------------|--------------------|-----------------|---------------------|
| Ref. [16] | 46 | F | Hemoptysis, Dyspnea | No | 80/40 | Left adrenal | 70 × 55 | Yes |
| Ref. [17] | 22 | M | Hemoptysis, Dyspnea | Yes | / | Extra-adrenal abdomen | 28 × 30 × 50 | No |
| Ref. [18] | 30 | M | Hemoptysis | No | 107/80 | Left adrenal | 69 × 61 × 62 | No |
| Ref. [19] | 60 | M | Dyspnea | Yes | / | Left adrenal | / | No |
| Ref. [20] | 21 | M | Dyspnea | No | 140/80 | Extra-adrenal abdomen | / | No |
| Ref. [21] | 72 | M | Dyspnea | Yes | 260-290/100 | Left adrenal | 28 × 24 | No |
| Ref. [22] | 51 | F | Hemoptysis, Dyspnea, | No | 175/120 | Left adrenal | Diameter 40 | No |
| Ref. [23] | 68 | M | Chest pain Dyspnea Hemoptysis | No | 180/100 | Left adrenal | 46 × 40 | Yes |
| Ref. [24] | 33 | M | Dyspnea Hemoptysis | Yes | 150/100 | Left adrenal | 80 × 80 × 60 | No |
| Ref. [25] | 40 | M | Hemoptysis | Yes | 208/106 | Left adrenal | Diameter 80 | Yes |
| Ref. [26] | 52 | F | Fever, Hypotension Periodic, Fluctuations in BP | Yes | Periodic blood pressure fluctuation | Left adrenal | Diameter 27 | Yes |
| Ref. [27] | 39 | F | Dyspnea Hemoptysis | No | / | Left adrenal | 20 × 16 | No |
| Ref. [28] | 14 | F | Dyspnea Hemoptysis | No | 72/50 | Bilateral adrenal gland | Left: 40 × 50 × 30 Right: 60 × 40 × 30 | Yes |
| Our cases | 39 | F | Dyspnea Hemoptysis | Yes | 140/80 | Left adrenal | 26 × 28 | Yes |

PPGL: pheochromocytoma and paraganglioma, DAH: diffuse alveolar hemorrhage,/: Data not available. The patient died in Reference 19.

the bilateral adrenal glands, while two had extra-adrenal paragangliomas. During the surgical procedure, one 72-year-old male patient with a history of ischemic heart disease, and interstitial pneumonitis experienced rapid deterioration, including hard breathing, acute hypertension, and hemoptysis, leading to the patient's death. The autopsy revealed the lungs had fibrosis, there was bleeding in the alveoli on both sides without capillaritis, signs of high blood pressure in the pulmonary arteries, and a pheochromocytoma on the right side of the kidney [21].

In these 14 cases, DAH predominantly presented as hemoptysis and/or dyspnea, accompanied by different levels of hypoxemia. Out of these cases, seven patients (including one who died) developed hypoxic respiratory failure, requiring ventilator support. Before receiving surgical removal of a pheochromocytoma located in the left adrenal gland, a patient developed DAH and required therapy with mechanical ventilation [19]. In 3 cases, respiratory and cardiovascular symptoms, as well as abnormal exams, were promptly alleviated with basic treatment and did not require ventilator support or oxygen therapy. Ultimately, the analysis of the 14 cases showed that the severity of alveolar hemorrhage caused by PPGLs exhibited variability. 13 patients experienced a positive outlook after surgery, suggesting that we should strive for surgery when encountering similar patients.

Workups commonly identify dysfunction in systems other than the respiratory system, with hypertension and left ventricular systolic dysfunction being the most prevalent. Out of the total of fourteen patients, six of them had mild renal impairment, and three of those six cases were further aggravated by liver dysfunction. The level of both lipase and amylase values was markedly increased in two cases. A patient with myoglobinuric renal failure and developing erythrocytosis (hematocrit, 59.8 %) [25] exhibited elevated levels of erythropoietin. Notably, we have identified a significant coagulation issue in our case.

Three male adolescents presented with two episodes of acute dyspnea and/or hemoptysis before the diagnosis of pheochromo-cytoma/paraganglioma was made. The doctors only suspected and identified PPGLs, which included a pheochromocytoma and two paragangliomas, after the second occurrence. All of them had a familial predisposition to the disease and exhibited symptoms after engaging in strenuous physical exertion. A 33-year-old male who tested positive for glycosuria presented with complaints of nausea, vomiting, and headache before being admitted. Doctors diagnosed him with gastroenteritis. Two of the fourteen patients had aberrant electrocardiograms and high myocardial enzymes, which led to the suspicion of acute coronary syndrome [23,25]. However, after urgent cardiac catheterization, the patient was found to have fully normal coronary anatomy [25]. The above data suggests that the first nonspecific and varied symptoms of PPGLs-induced DAH facilitated the tendency to overlook and delay diagnosis. The initial step in identifying PPGLs is to acknowledge their potential. It may aid our early diagnosis of PPGLs without typical symptoms if we maintain a state of heightened sensitivity and attention toward them.

Six of the fourteen cases of paroxysmal hypertension or hypotension were observed during treatment. Among these cases, three occurred after intubation, and in two of these patients, the combination of intubation and glucocorticoid usage appeared to cause periodic fluctuations in blood pressure [26]. Six patients exhibited sinus tachycardia. A 14-year-old female patient, who had Moraxella-catarrhalis cultured in her sputum, was one of three cases in which infection preceded the onset of alveolar hemoptysis [28]. Nine out of the fourteen cases had echocardiogram results available; of those, six described abnormal echocardiography abnormalities, including a decline in left ventricular function and ejection fraction. DAH was confirmed in 8 patients through bronchoscopy and bronchoalveolar lavage fluid analysis.

It is challenging to figure out a clear pathophysiological relationship between PPGLs and alveolar hemoptysis because the process that causes alveolar hemoptysis in people has not been fully identified [16]. Previous evidence [29] suggests that severe hypertension can precipitate the onset of alveolar bleeding. When catecholamines rise, they mostly act on α-adrenergic receptors. This leads to systemic arterial hypertension, an increase in total peripheral resistance (TPR), pulmonary venous hypertension, and, as a result, an increase in pulmonary capillary pressure. Pulmonary congestion occurs when there is an increase in left ventricular afterload, which is caused by systemic hypertension due to vasoconstriction [15]. Furthermore, elevated plasma catecholamines alter pulmonary capillary permeability [22]. Alveolar hemorrhage happens in people with PPGLs because of high pulmonary venous pressure, higher pulmonary capillary pressure, and changes in the permeability of the pulmonary capillaries. Direct cardiotoxicity, myocardial catecholamine-receptor signaling, microvascular ischemia, and transitory coronary artery vasospasm are all potential causes of catecholamine-driven cardiac dysfunction [5,20], which can appear as hypokinesia [20]. In people with PCC, the fundamental mechanism underlying organ failure is a decreased intravascular volume, which in turn causes decreased end-organ perfusion and tissue ischemia. In addition, we found that two patients had hypotension at admission, whereas one remained normotensive during the whole course of treatment. This indicated that other causes than hypertension were at work during DAH in PPGL patients. Cate-cholamine synthesis has been associated with both endothelial dysfunction and irregular coagulation [30]. As seen in our case, excessive catecholamine secretion can also lead to coagulation abnormalities. Further investigation is required to gain a deeper un-derstanding of the relationship between hemodynamic changes and DAH in PPGLs.

In this study, we explored the potential correlation between laparoscopic cholecystectomy and the development of DAH in our patient. Our hypothesis suggests that the increase in abdominal pressure caused by the surgical procedure, combined with the stimulation of pheochromocytoma, results in excessive catecholamine secretion and a subsequent elevation of blood pressure after cholecystectomy. It has been established that glucocorticoids activate enzymes necessary for catecholamine production. Glucocorti-coids are essential in the normal adrenal medulla and pheochromocytoma cells for the metabolism, synthesis, and release of cate-cholamines in normal adrenal medulla and pheochromocytoma cells [31]. Glucocorticoids are also reported to have an increased risk of triggering PCC in patients with PPGLs [32]. Prompt administration of glucocorticoids may be necessary to determine the causes of DAH, as seen in some cases, including the one we encountered [16]. Notably, in five of the other thirteen cases, glucocorticoids were involved. Adverse reactions to glucocorticoids in these patients included paroxysmal hypertension, headache, sweating, and palpi-tations, as well as abdominal pain, chest tightness, and tachycardia. Tumor sizes greater than 30 mm and glucocorticoid dosages exceeding 60 mg/day of hydrocortisone in the majority of cases of PCC are attributed to glucocorticoids [32]. However, in our

investigation, glucocorticoid dosages were not present, even though tumor diameters were less than 30 mm in four cases and less than 20 mm in two cases.

Concerning the occurrence of PCC episodes, a notable association was found between corticosteroid therapy, mechanical ventilation, and PCC. Yet, the specific component with a greater impact on PCC initiation remains uncertain. Overall, the cases presented illustrate that DAH caused by PPGLs follows an unpredictable and variable course, with severity seemingly uncorrelated with tumor size but always requiring vigilant medical attention. Despite the challenges posed by multi-organ failure, intensive treatment led to the successful reversal of DAH caused by PPGLs, as evidenced by the thirteen patients who underwent tumor removal.

## 4. Conclusion

In this report, we present a case of DAH, a rare and potentially life-threatening condition that occurred abruptly after cholecystectomy and was caused by a left adrenal pheochromocytoma. It is vital to rule out the possibility of a clinically silent pheochromocytoma in the adrenals before any invasive surgery or administration of corticosteroids. Clinical manifestations of PCC are variable, and DAH can be considered one of them. In the absence of other explanations, a PPGL should be included in the differential diagnosis of DAH, even if there are no symptoms of excessive catecholamine release. When receiving glucocorticoids, patients with unexplained DAH should be treated with caution, and PPGLs should be ruled out as soon as possible using accurate testing.

## Ethics approval and consent to participate

This case report was approved by the ethical committee of Shenzhen Second People's Hospital. The patients/participants provided written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Funding

## Data availability statement

All data were included in article/supplement.

## CRediT authorship contribution statement

**Xinlian He:** Writing – original draft, Formal analysis, Data curation. **Ruchun Dai:** Writing – review & editing. **Liming Zhou:** Data curation. **Lingbo Lv:** Data curation. **Mingzheng Li:** Data curation. **Jianxin Deng:** Writing – review & editing, Funding acquisition. **Dewen Yan:** Writing – review & editing, Funding acquisition, Conceptualization.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Jianxin Deng reports financial support was provided by Shenzhen Science and Technology Program. Dewen Yan reports financial support was provided by Shenzhen Clinical Research Center for Metabolic Diseases. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgement

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e34218.

## References

[1] A.S. Tischler, Pheochromocytoma and extra-adrenal paraganglioma: updates, Arch. Pathol. Lab Med. 132 (2008) 1272–1284.
[2] W.F. Young Jr., Management approaches to adrenal incidentalomas. A view from Rochester, Minnesota, Endocrinol Metab. Clin. N. Am. 29 (2000) 159–185.

[3] M.G. Sutton, S.G. Sheps, J.T. Lie, Prevalence of clinically unsuspected pheochromocytoma. Review of a 50-year autopsy series, Mayo Clin. Proc. 56 (1981) 354–360.

[4] E.L. Bravo, Tagle R. Pheochromocytoma, state-of-the-art and future prospects, Endocr. Rev. 24 (2003) 539–553.

[5] B.C. Whitelaw, J.K. Prague, O.G. Mustafa, K.M. Schulte, P.A. Hopkins, J.A. Gilbert, et al., Phaeochromocytoma [corrected] crisis, Clin. Endocrinol. 80 (2014) 13–22.

[6] A.L. Rosas, A.A. Kasperlik-Zaluska, L. Papierska, B.L. Bass, K. Pacak, G. Eisenhofer, Pheochromocytoma crisis induced by glucocorticoids: a report of four cases and review of the literature, Eur. J. Endocrinol. 158 (2008) 423–429.

[7] D.W. Yi, S.Y. Kim, D.H. Shin, Y.H. Kang, S.M. Son, Pheochromocytoma crisis after a dexamethasone suppression test for adrenal incidentaloma, Endocrine 37 (2010) 213–219.

[8] A.R. Lara, M.I. Schwarz, Diffuse alveolar hemorrhage, Chest 137 (2010) 1164–1171.

[9] E. Kebebew, Adrenal incidentaloma, N. Engl. J. Med. 384 (2021) 1542–1551.

[10] M. Fassnacht, S. Tsagarakis, M. Terzolo, A. Tabarin, A. Sahdev, J. Newell-Price, et al., European Society of Endocrinology clinical practice guidelines on the management of adrenal incidentalomas, in collaboration with the European Network for the Study of Adrenal Tumors, Eur. J. Endocrinol. 189 (2023) G1–G42.

[11] Medical Masterclass contributors, J. Firth, Endocrinology: phaeochromocytoma, Clin. Med. 19 (2019) 68–71.

[12] J.W. Lenders, G. Eisenhofer, M. Mannelli, K. Pacak, Phaeochromocytoma, Lancet. 366 (2005) 665–675.

[13] S. Melmed, K.S. Polonsky, R. Larsen, H.M. Kronenberg, Williams Textbook of Endocrinology, twelfth ed., 2012.

[14] C. Yucha, Blakeman N. Pheochromocytoma, The great mimic, Cancer Nurs. 14 (1991) 136–140.

[15] N. Reisch, M. Peczkowska, A. Januszewicz, H.P. Neumann, Pheochromocytoma: presentation, diagnosis and treatment, J. Hypertens. 24 (2006) 2331–2339.

[16] M. Nezu, H. Kobayashi, M. Shiozaki, M. Katsumata, S. Takizawa, T. Tsutsui, et al., Pheochromocytoma diagnosed during the treatment of diffuse alveolar hemorrhage, a diagnostic necessity before using high-dose glucocorticoids, Intern. Med. 60 (2021) 2825–2830.

[17] Y. Endo, M. Kitago, M. Shinoda, H. Yagi, Y. Abe, S. Hori, et al., Extra-adrenal pheochromocytoma with initial symptom of haemoptysis: a case report and review of literature, BMC Surg. 21 (2021) 13.

[18] Q. Zhai, C. Tian, Z. Deng, C. Liu, Q. Ma, Case report: an unusual first manifestation of a pheochromocytoma, Front. Endocrinol. 12 (2021) 697202.

[19] N. Shijubou, T. Sumi, K. Kamada, Y. Yamada, H. Nakata, H. Chiba, Diffuse alveolar haemorrhage due to pheochromocytoma crisis, Respirol Case Rep 9 (2021) e00722.

[20] Y. Makuuchi, M. Wada, A. Kawashima, Y. Kataoka, M. Miyahara, M. Ikusaka, et al., Paraganglioma-induced alveolar hemorrhage, Intern. Med. 54 (2015) 487–489.

[21] L. Garcia-Ferrer, R. Calvo, M.J. Broch, [Pheochromocytoma as a cause of massive hemoptysis], Arch. Bronconeumol. 44 (2008) 396.

[22] N. Bourvis, M. Fartoukh, S. Christin-Maitre, T. Francois, A. Parrot, C. Mayaud, [Intra-alveolar hemorrhage revealing pheochromocytoma], Rev. Pneumol. Clin. 62 (2006) 43–48.

[23] R. Querol Ripoll, M.I. del Olmo Garcia, R. Camara Gomez, J.F. Merino-Torres, Diffuse alveolar hemorrhage as first manifestation of a pheochromocytoma, Arch. Bronconeumol. 50 (2014) 412–413.

[24] T. Yoshida, H. Ishihara, Pheochromocytoma presenting as massive hemoptysis and acute respiratory failure, Am. J. Emerg. Med. 27 (2009) 626 e3–e4.

[25] M. Park, K. Hryniewicz, J.F. Setaro, Pheochromocytoma presenting with myocardial infarction, cardiomyopathy, renal failure, pulmonary hemorrhage, and cyclic hypotension: case report and review of unusual presentations of pheochromocytoma, J. Clin. Hypertens. 11 (2009) 74–80.

[26] Y. Uehira, H. Yamaguchi, N. Matsumoto, M. Nakazato, Periodic blood pressure fluctuations in undiagnosed pheochromocytoma, Intern. Med. 60 (2021) 491–492.

[27] S. El Aoud, F. Mnif, N. Lassoued, M. Mnif Feki, N. Rekik, N. Charfi, et al., [An unusual cause of hemoptysis], Rev. Med. Interne 38 (2017) 150–151.

[28] R. Wu, N. Tong, X. Chen, S. Xu, F. Zhang, L. Tang, et al., Pheochromocytoma crisis presenting with hypotension, hemoptysis, and abnormal liver function: a case report, Medicine (Baltim.) 97 (2018) e11054.

[29] A. Suzuki, N. Nakagawa, K. Maruyama, M. Matsuki, N. Hasebe, Diffuse alveolar hemorrhaging with hypertensive emergency: a rare but important cause of hemoptysis, Intern. Med. 58 (2019) 1511–1516.

[30] J.R.U. Santos, A. Brofferio, B. Viana, K. Pacak, Catecholamine-induced cardiomyopathy in pheochromocytoma: how to manage a rare complication in a rare disease? Horm. Metab. Res. 51 (2019) 458–469.

[31] G.A. Geva, D.J. Gross, H. Mazeh, K. Atlan, I.Z. Ben-Dov, M. Fischer, Adrenocorticotropic hormone secreting pheochromocytoma underlying glucocorticoid induced pheochromocytoma crisis, Case Rep Endocrinol 2018 (2018) 3963274.

[32] C. Barrett, S.H. van Uum, J.W. Lenders, Risk of catecholaminergic crisis following glucocorticoid administration in patients with an adrenal mass: a literature review, Clin. Endocrinol. 83 (2015) 622–628.