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Diffuse pulmonary hemorrhage as a rare presentation of pheochromocytoma: a case report with review of the literature

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Abstract

A 37-year-old male patient with a past history of fluctuating hypertension and insulin-treated diabetes mellitus presented to our clinic with a 1-year history of sudden-onset cough, dyspnea, and frank hemoptysis. Examination showed asthenia, moderate anemia, uncontrolled blood pressure, and a past history of one admission for management of hemoptysis and cardiac failure. The evaluation showed mild anemia, azotemia, low ejection fraction, contrast-enhanced computed tomography (CECT) of the chest, and sputum suggestive of pulmonary hemorrhage. Investigation during current admission revealed proteinuria, left suprarenal mass on USG, and clear lung parenchyma on chest X-ray and CECT. Autoimmune workup for vasculitis was negative and 24-h urinary catecholamine levels were elevated with CECT abdomen confirming pheochromocytoma. His blood pressure was controlled and he underwent laparoscopic left adrenalectomy with confirmation on histopathology. Postoperatively he is doing well with minimal requirement of antihypertensive, and diabetes is controlled with diet and exercise only. This case highlights diffuse alveolar hemorrhage as a rare presentation of pheochromocytoma. This case also highlights that secondary cause of hypertension should always be ruled out in case of uncontrolled hypertension in young patients to prevent devastating complications.

Keywords Pheochromocytoma, Pulmonary hemorrhage, A rare presentation of pheochromocytoma

Main points

1. Immune-mediated disorders constitute the most common etiology for diffuse alveolar hemorrhage. DAH is characterized by the accumulation of intra-alveolar RBCs and hemosiderin-laden macrophages resulting from injury to alveolar microcirculation as a rare presentation.
2. Pheochromocytoma should be considered as one of the differential diagnosis in patients of uncontrolled hypertension and hemoptysis. Hemoptysis in pheochromocytoma is attributed to elevated BP and pulmonary venous hypertension leading to pulmonary edema and hemorrhage.
3. In addition vascular injury from catecholamines may result in abnormalities of the coagulation system, specifically activation of the coagulation cascade. The most common histologic finding is "capillaritis."
4. Patients who are managed surgically with the removal of the catecholamine-secreting tumor followed by a good outcome, as in our case. The case

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where surgery could not be done due to the critical condition of the patient had a poor outcome and died. Thus, though rare, catecholamine-secreting tumors can present as pulmonary hemorrhage, and delay in diagnosis or management can have fatal outcomes

Introduction

Pheochromocytoma is a rare neuroendocrine tumor, occurring in 0.1 to 0.6% of patients with hypertension. Clinical presentation varies widely with headache, palpitations, diaphoresis being the most common symptoms, and hypertension most common sign. Paragangliomas are also neuroendocrine tumors but developed in the extra-adrenal sympathetic and parasympathetic nervous systems with a lower incidence (< 1 per 300,000 inhabitants per year). These tumors may occur sporadically or secondarily due to germline mutations of several tumor-susceptibility genes [1]. Diffuse alveolar hemorrhage (DAH) is a clinical condition characterized by hemoptysis, anemia, and dyspnea. DAH is characterized by the accumulation of intra-alveolar RBCs and hemosiderin-laden macrophages resulting from injury to alveolar microcirculation as a rare presentation. The radiological pattern of this disease is defined by ground-glass consolidations and interlobular septal thickening (crazy-paving pattern). The most common histologic finding is "capillaritis." However, bland DAH without capillaritis can also occur [2]. Hemoptysis in pheochromocytoma is attributed to elevated BP and pulmonary venous hypertension leading to pulmonary edema and hemorrhage. Severe systemic hypertension can also lead to pulmonary venous hypertension, which may predispose these patients to hemoptysis similar to patients with mitral stenosis and pulmonary hypertension [3]. In addition, vascular injury from catecholamines may result in abnormalities of the coagulation system, specifically activation of the coagulation cascade. The definitive cause of hemoptysis in patients with pheochromocytoma is not known; however, various mechanisms have been proposed. Immune-mediated disorders constitute the most common etiology for DAH. BAL shows progressively bloody aliquots on sequential samples, and ≥ 20% hemosiderin-laden macrophages in lavage fluid. Pulmonary hemorrhage has been attributed to the presence of lung metastasis, pulmonary venous hypertension secondary to severe paroxysmal hypertension [4] and coagulopathy [5]. On rare occasions, pheochromocytoma can present with atypical manifestations such as hemoptysis, acute coronary syndrome with normal coronary catheterization, or dilated cardiomyopathy. Pathophysiological mechanisms most often involved in hemoptysis are lung metastases and coagulation disorders. When all of these have been ruled out, hemoptysis may be related to the hypertensive crisis triggered by chromaffin tumor secretion [2].

There is a paucity of literature regarding pheochromocytoma presenting as diffuse alveolar hemorrhage with only a meager number of cases reported in literature as discussed in Table 1. So it is very important to rule out DAH in patients of pheochromocytoma presenting with such presentation to tackle this life-threatening complication at the earliest.

Case report

A 37 years old male was doing well till about 2 and half years back when he was detected to have severe hypertension (systolic BP of 200 mm Hg) during a routine medical check-up and was prescribed amlodipine 5 mg daily without any further evaluation in view of absence of any symptoms and clues to a secondary cause. Two months later, he developed generalized weakness, fatigability, and weight loss (3–4 kg over 4 months) and was documented

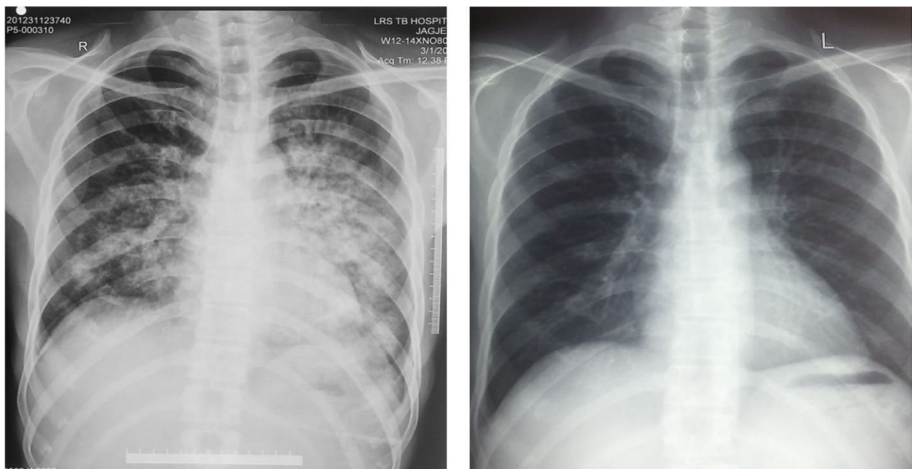
Table 1 Showing comparison of summary of published reports

	Author	Year	Journal	Presentation	Treatment	Outcome
1	Park M et al	2009	*J Clin Hypertens (Greenwich)*	40 year/M, hemoptysis, LV dysfunction	Surgical removal of pheochromocytoma	LVEF improved to 50% at discharge
2	Yoshida T and Ishihara H	2009	*American Journal of Emergency Medicine*	33 year/M, dyspnea, hemoptysis	Surgical removal of pheochromocytoma	Not available
3	Querol Ripoll R et al	2014	*Arch Bronconeumol*	68 year/M, hemoptysis, ↑BP, NSTEMI	Laparoscopic left adrenalectomy	Asymptomatic on follow-up
4	Makuuchi Y et al	2015	*Intern Med*	21 year/M, dyspnea, DAH on bronchoscopy	Surgical removal of paraganglioma	Stable on follow-up
5	Shijubou N et al	2021	*Respirology Case Reports*	60 year/M, dyspnea	Left adrenalectomy	Stable on follow-up
6	Masahiro Nezu et al	2021	*Intern Med*	46 year/F DAH, started on steroids and developed a hypertensive crisis	Left adrenalectomy	Stable on follow-up

to have diabetes mellitus (fasting plasma glucose 180 mg/dl). He was treated by metformin 1 g daily in addition to amlodipine. With erratic compliance to medication, 1 year later he had an episode of sudden onset cough, dyspnea, and frank hemoptysis. Evaluation revealed moderate anemia, mild azotemia, and bilateral alveolar infiltrates with peripheral sparing of lung fields (Fig. 1a). Urine routine and microscopic examination showed mild proteinuria but no active sediments. Bronchoscopy revealed normal upper respiratory tract, with erythematous changes in segmental bronchi on both sides and hemorrhagic bronchoalveolar lavage (BAL) from the right middle, right lower, and left lower lobes. BAL fluid cytopathology showed cellular smears, scattered alveolar macrophages, a few neutrophils, and bronchial epithelial cells suggestive of diffuse alveolar hemorrhage was made. Acid-fast bacillus (AFB) stain was negative and autoimmune workup including rheumatoid factor/antinuclear antibody (ANA)/c-ANCA/GBM antibody was non-reactive. Ultrasonography abdomen incidentally detected left suprarenal mass with cystic components; both kidneys were normal. CT abdomen confirmed the left suprarenal mass and had features suggestive of pheochromocytoma (Fig. 3). Twenty-four-hour urinary catecholamines were elevated. The patient was treated with intravenous methylprednisolone to prevent pulmonary fibrosis and discharged on calcium channel blocker, alpha-blocker, oral steroids, and basal-bolus regimen of insulin (80 U per day). On follow-up, hemoptysis and cough had subsided with the control of BP. Subsequently, after BP control and proper preparation including the addition of beta-blocker, he was planned for robotic left adrenalectomy. The patient was lost to follow-up as surgery was postponed due to poor glycemic control.

Nine months later, he got readmitted again to the same hospital with a history of nonproductive cough, wheezing, dyspnea at rest, and orthopnea. The patient did not have further episodes of hemoptysis, however, and accepted withdrawal of prescribed medication. Investigations revealed anemia, azotemia, transaminitis, and nephrotic range proteinuria. Viral markers for hepatitis were negative. Chest X-ray and high-resolution computed tomography (HRCT) chest showed significant improvement compared to previous scans (Figs. 1a and b, 2a and b). 2-D echocardiography showed mild concentric left ventricular hypertrophy (LVH), severe global left ventricular (LV) hypokinesia, normal right ventricular systolic function, and LV ejection fraction (LVEF) ~ 15%. He was treated for heart failure and 10 days later 2-D echocardiography was repeated which showed global hypokinesia with LVEF ~ 40%. He was discharged on alpha- and beta-blockers and calcium channel blockers along with insulin. The patient continued to have fluctuation in BP owing to poor compliance to medication till he was referred to our institution and got admitted for further management.

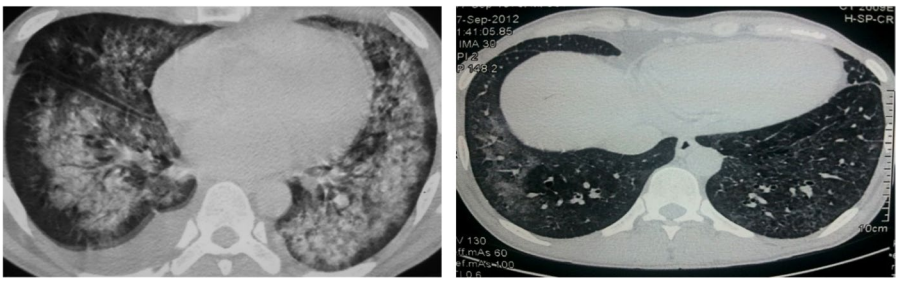
At the time of admission under us, he had persistent dyspnea and orthopnea but no further episodes of hemoptysis. There was no history suggestive of multiple endocrine neoplasias (MEN) 2 syndrome and he denied any family history of similar problems, sudden unexpected death, coronary artery disease, or stroke.



a. Chest X-Ray PA view showing bilateral alveolar infiltrates with peripheral sparing.

b. Chest X-Ray PA view showing clearing of the infiltrates (9 months later)

Fig. 1 **a** Chest X-ray PA view showing bilateral alveolar infiltrates with peripheral sparing. **b** Chest X-ray PA view showing clearing of the infiltrates (9 months later)



a CT chest showing bilateral alveolar infiltrates

b Fig. 1b CECT chest X-Ray after 9 months showing clearing of the infiltrates

Fig. 2 **a** CT chest showing bilateral alveolar infiltrates. **b** CECT chest X-ray after 9 months showing clearing of the infiltrates

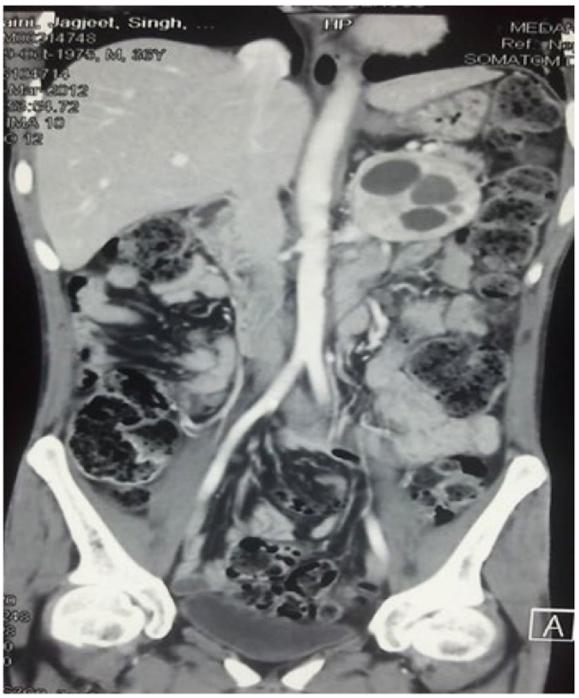


Fig. 3 CT abdomen showing left suprarenal mass

Examination showed tachycardia, markedly elevated BP, pallor, and signs of heart failure. He had anterior staphyloma in the right eye and phthisis bulbi on left. The vision was limited to light perception in the right eye and no vision in the left. The thyroid gland was normal. There were no neurofibromas or café au lait spots. Systemic examination was unremarkable.

On investigations, he was found to have anemia, azotemia, and bilateral alveolar infiltrates with peripheral sparing. Urine routine and microscopic examination showed proteinuria but no active sediments. CT abdomen confirmed left suprarenal mass with features suggestive of pheochromocytoma (Fig. 3). Twenty-four-hour urinary catecholamines were elevated [vinyl mandelic acid = 65.71 mg/g creatinine (normal range 1.6–4.2), normetanephrine = 7560.38 mcg (normal range 88–444), and metanephrine = 82 mcg (normal range 52–341)]. MIBG/SPECT-CT revealed the presence of 6.2 × 6.9 cm left suprarenal mass with solid and cystic components with mild heterogeneous MIBG uptake in the solid component. 68 Ga DOTANOC PET/CT whole-body scan showed somatostatin receptor-expressing left adrenal mass measuring 5.7 × 6.5 × 6.5 cm with areas of central necrosis and nonuniform tracer uptake. The rest of the body shows physiological radiotracer distribution. Morning serum cortisol, serum testosterone, and thyroid function tests were normal. The coagulation profile was normal.

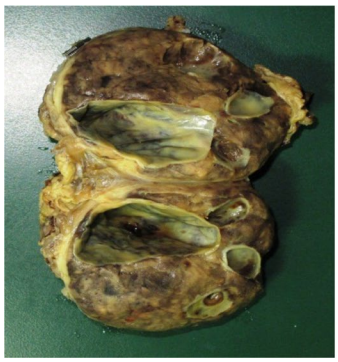
Management

The patient was prepared for left adrenalectomy. Diabetes was managed with insulin (~ 20 units/day). Liberal salt and fluid could not be given in view of heart failure. BP control was achieved with prazosin 5 mg every six-hourly, carvedilol 75 mg daily, and amlodipine 10 mg twice daily. The patient was started on iron supplements and 2 packed RBCs were transfused. With adequate BP and glycemic control, the patient underwent laparoscopic left adrenalectomy. Intra-operatively left adrenal mass was found in close relation to the tail of pancreas and left renal hilum but separate from it. The postoperative course was uneventful.

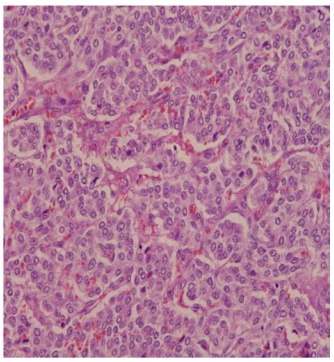
Gross pathologic examination (Fig. 4a) of the lesion showed a grayish brown tumor measuring 12 × 6 × 3 cm with areas of cystic degeneration (1 × 1–3 × 2 cm) and hemorrhage. The capsule was intact. Microscopic examination (Fig. 4b) was consistent with a diagnosis of pheochromocytoma.

Outcome and follow-up

In the postoperative period, requirement of antihypertensive drugs came down and BP was well controlled on the tab. Amlodipine 5 mg twice daily and prazosin



a. Gross pathologic examination of the lesion showing greyish brown tumor measuring 12×6×3 cm with areas of cystic degeneration and hemorrhage with intact capsule.



b. Microscopic examination consistent with diagnosis of pheochromocytoma.

Fig. 4 **a** Gross pathologic examination of the lesion showing grayish brown tumor measuring 12×6×3 cm with areas of cystic degeneration and hemorrhage with intact capsule. **b** Microscopic examination consistent with diagnosis of pheochromocytoma

2.5 mg daily. Diabetes was well controlled only by lifestyle modifications.

Discussion

Pheochromocytoma/paragangliomas are one of the common causes of secondary hypertension. They are associated with increased mortality and morbidity if not diagnosed at the earliest. Diffuse alveolar hemorrhage is a lethal complication associated with various lung diseases, autoimmune disorders, and certain malignancies. However, DAH presenting as initial presentation in pheochromocytoma is very rare as per the literature with only meager case reports. Although rare, pheochromocytoma should be one of the differential diagnoses in patients presenting with DAH. Park et al. [6] described a 40-year-old patient with pheochromocytoma with hemoptysis and left ventricular (LV) dysfunction, whose symptoms resolved after surgical removal. Another case of adrenal pheochromocytoma that presented with hemoptysis, hypertension, and non-ST elevation myocardial infarction was presented by Querol Ripoll et al. [3] with marked improvement in symptomatology after adrenalectomy.

Similarly, there are a few more examples of case reports [7–9] in the literature that presented dyspnea and hemoptysis with severe hypertension proved biochemically and radiologically as pheochromocytoma or paraganglioma like our case. Mostly they were managed surgically with the removal of catecholamine tumor followed by a good outcome, as in our case. Although rare, catecholamine-secreting tumors can present as pulmonary hemorrhage, and delay in diagnosis or management can have fatal outcomes. Steroids are one of the important forms of treatment for DAH but should be used with caution. Nezu et al. [10] published an interesting case that had a typical presentation of DAH as per symptomatology and was started on glucocorticoids. The patient presented with a hypertensive crisis after starting steroids and on evaluation was found to have pheochromocytoma. So it is necessary to rule out pheochromocytoma in a case of DAH before starting steroids.

From the above cases, it becomes important to rule out secondary causes of hypertension in young resistant cases of hypertension as early as possible to prevent life-threatening complications as was found in our case and timely management of such cases can prevent lethal cardiovascular and renal consequences as found in the literature [11].

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All contributed equally.

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Declarations

Ethics approval and consent to participate
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Consent for publication
Appropriate written informed consent was obtained for publication of this case report and accompanying images.

Competing interests
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