Tokai J Exp Clin Med., Vol. 30, No. 1, pp. 35-39, 2005

A Pheochromocytoma Causing Limited Coagulopathy with Hemoptysis

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(Received November 4, 2004; Accepted December 7, 2004)

We treated a 59-year-old woman presenting with hemoptysis, a rare symptom of pheochromocytoma. Multiple factors including hypertension caused by sudden catecholamine release may result in pulmonary edema. It should be noted that the increased activation of coagulation cascade, which was demonstrated by increased thrombin-antithrombin III complex (TAT) and prothrombin fragment factor 1 and 2 (F1+2), as well as endothelial or platelet stimulation evidenced by the increased plasma von Willebrand factor, may have contributed to hemoptysis. These abnormalities were normalized after adrenalectomy. Our case indicates the important role of catecholamine in coagulopathy and possibly in vasculopathy.

Key words : pheochromocytoma, hemoptysis, catecholamines

INTRODUCTION

Pheochromocytomas are chromaffin cell tumors that arise in the adrenal medulla and sympathetic ganglia. Pheochromocytoma is diagnosed based on clinical manifestation, plasma and urine catecholamine determination, and abdominal ultrasonography, radiologic assessment, and finally intraoperative findings. Signs and symptoms of pheochromocytoma include hypertension, tachycardia, palpitations and sweating, all attributable to excessive release of catecholamines [1, 2]. Few reports describe the abnormality in coagulation [3]. We show here that a case of pheochromocytoma, whose increased activity of coagulation was reversed by adrenalectomy. Of note, rare symptom of hemoptysis in this patient appears to correlate with abnormality in coagulation.

CASE PRESENTATION

A 59-year-old woman with an 8-year history of hypertension was treated with medication by her family doctor. About 3 months prior to admission, she complained of palpitations, excessive sweating and weight loss (6 kg in 3 months). Five days before admission, the anti-hypertensive agent was changed to a β-adrenergic antagonist, because the patient complained of palpitations again. On January 18, 2001, the patient developed massive hemoptysis of fresh blood and was transported to the emergency room at Tokai University Oiso Hospital. She was admitted for diagnostic and therapeutic interventions.

Physical examination showed a blood pressure of 190/100 mmHg and pulse rate of 108 beats/min. Ejection type systolic murmur was evident in the second interspace along the left sternal border. A fourth sound was audible. Chest auscultation revealed moist rales in both lungs. Laboratory data on admission indicated liver dysfunction and hypoxemia (Table 1). A chest radiograph on admission demonstrated patchy infiltration centrally in both lungs as well as in periphery (Fig. 1). The perihilar infiltrates

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Table 1 Laboratory data on admission

	Patient data	Normal ranges
Complete blood count		
WBC count (10^9/L)	7.5	4.0 - 8.0
RBC count (10^{12}/L)	5.1	4.1 - 5.3
Platelet count (10^9/L)	153	140 - 400
Biochemistry		
Urea nitrogen (mmol/L)	4.5	2.9 - 7.2
Creatinine (μ mol/L)	60	53 - 84
Aspartate aminotransferase (U/L)	130	11 - 29
Alanine aminotransferase (U/L)	158	9 - 37
Lactate dehydrogenase (U/L)	774	230 - 410
Creatine kinase (U/L)	188	48 - 187
Sodium (Na, mmol/L)	141	136 - 144
Potassium (K, mmol;/L)	4.4	3.4 - 4.8
Total protein (g/L)	59	65 - 80
Albumin (g/L)	39	41 - 50
Plasma glucose (mmol/L)	6.2	3.9 - 6.1
CRP (mg/dl)	0.1	< 0.3
Atrial blood gas at room air		
pH	7.343	7.36 - 7.44
pCO_2 (torr)	47.0	36 - 44
pO_2 (torr)	36.8	80 - 90
HCO_3 (mmol/L)	25.0	22 - 26
Base excess (mmol/L)	-1.2	-2.5 - +2.5

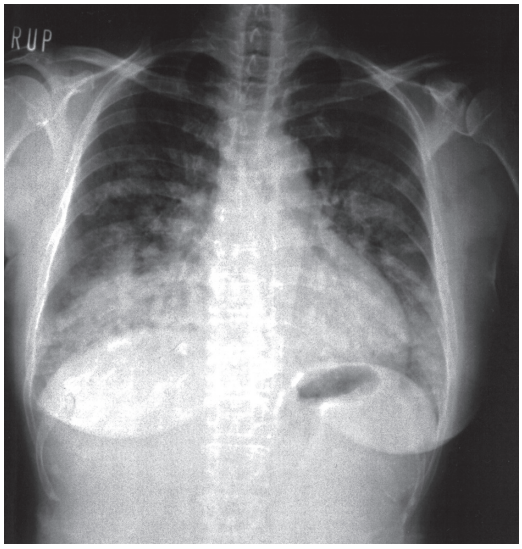

Fig. 1 Chest X-ray on the admission day
Alveolar consolidation with air bronchogram is embeded mainly in the central portion of the lung, while Kerly's B lines, interstitial components, are observed at periphery of right lower lung.

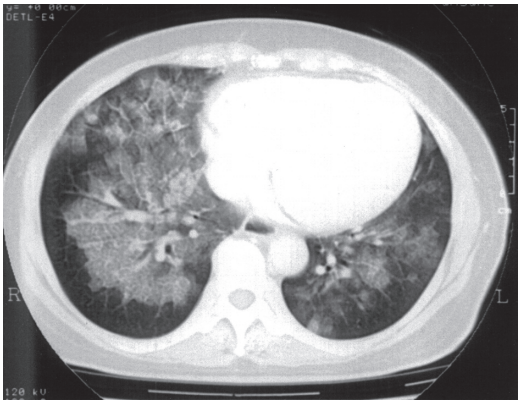

Fig. 2 Thoracic CT on admission
Patchy and geographic air-space filling are seen in the bilateral lungs.

consisted of alveolar consolidation associated with air bronchogram, while the interstitial components was associated with Kerley's B lines. Thoracic computed tomography revealed bilateral diffuse perihilar infiltration including air bronchograms, a periphery scattered infiltrates in the lung (Fig. 2). One day after admission, the infiltrates had resolved almost completely with supportive therapy, including supplemental oxygen and intravenous antihypertensive agents (Fig. 3). A laryngogram as well as bronchoscope performed subsequently did not identify the site of bleeding. Hemoptysis no longer occurred after the admission.

Further laboratory assessment is summarized in Table 2. Plasma adrenaline, noradrenaline, and dopamine concentrations were elevated to 560 ng/ml, 5671 ng/ml,

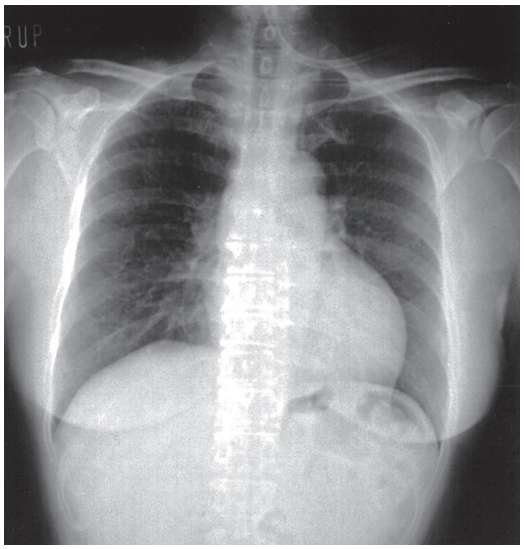

Fig. 3 Chest X-ray (one day after admission)
Infiltrates disappeared almost completely within one day.

Table 2 Laboratory and urinary evaluations of catecholamine products

	before surgery	after surgery	normal range
serum adrenaline	560	18	0-100
serum noradrenaline	5671	751	100-450
serum dopamine	37	27	0-20
urinary HVA	10.4	2.6	1.5-6.6
urinary VMA	125	3.0	1.3-5.1

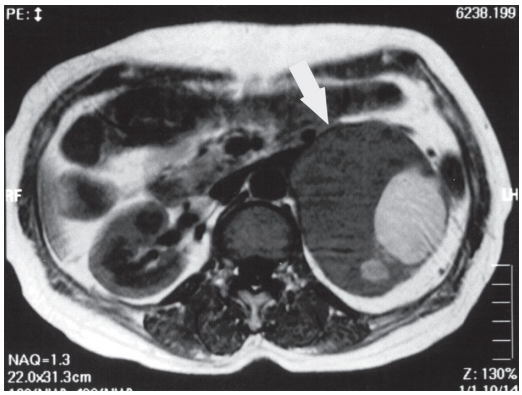

Fig. 4 Axial T1-weighted image of pheochromocytoma
Axial T1-weighted image shows a large left-sided adrenal lesion with central area of hyperintensity. The small focus of hyperintensity may reflect hemorrhage and necrosis.

and 37 ng/ml respectively. Thrombin-antithrombin III complex, von Willebrand factor, and prothrombin fragment factor 1 and 2 increased to 22.7 ng/ml, 224%, and 1.62 nmol/L, respectively (Table 3). Furthermore 24-h urinary excretion of homovanillic acid and vanillymandelic acid were increased 10.4 ng/ml/day and 125 ng/ml/day, respectively (Table 2). Magnet resonance imaging (Fig. 4) confirmed the presence of a large mass about $8 \times 8 \times 9$ cm. The mass arose from the left adrenal grand, and focal signal abnormalities written in the tumor suggested hemorrhage and necrosis. ^{131}I – metaiodobenzylguanidine using scintigraphy, adrenaline analogue, localized uptake to the left adrenal gland, ruling out multiple, extra-adrenal, and metastatic pheochromocytoma (Fig. 5). Accordingly, we diagnosed the patient with secondary hypertension caused by pheochromocytoma.

The adrenal tumor was resected successfully on February 15, 2001. It measured $8.5 \times 9.5 \times 7.5$ cm, and was encapsulated

(Fig. 6). The cut surface was reddish, with areas of hemorrhage. The microscopic and histochemical findings were compatible with pheochromocytoma.

Postoperatively, the patient had only mild hypertension without paroxysms. High serum concentrations of adrenaline and noradrenaline, and increased urinary homovanillic acid and urinary vanillymandelic acid excretion normalized after operation from 560 ng/ml, 5671 ng/ml, 10.4 mg/day and 125 mg/day to 18 ng/ml, 751 ng/ml, 2.6 mg/day and 3.0 mg/day, respectively (Table 2). Elevated thrombin-antithrombin III complex, von Willebrand factor, and prothrombin fragment factor 1 and 2 decreased 22.7 ng/ml, 224%, and 1.62 nmol/L to 3.4 ng/ml, 133% and 1.43 nmol/L, respectively

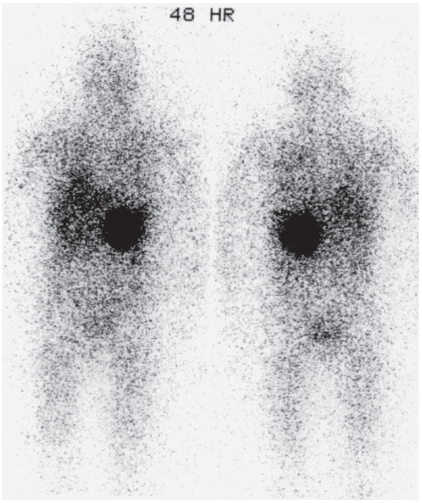

Fig. 5 Metaiodobenzylguanidine (MIBG) scintigraphy
MIBG selectively accumulates more rapidly in pheochromocytoma than in normal tissue. MIBG localized uptake to the left adrenal gland, ruling out multiple, extra-adrenal and metastatic pheochromocytoma.

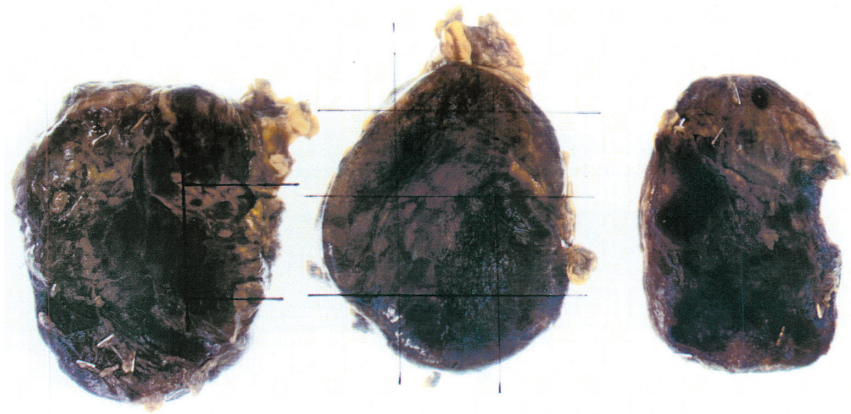

Fig. 6 Pheochromocytoma
The adrenal tumor measured 8.5 × 9.5 × 7.5 cm, and was encapsulated.

Table 3 Coagulant factors before and after surgery

	before surgery (day 27)	after surgery (post 2 months)	normal range
TAT (ng/ml)	22.7	3.4	0-3
vWf (%)	224	133	50-155
PT·F1+2 (nmol/L)	1.62	1.43	0.4-1.4

(Table 3).

DISCUSSION

The present case demonstrated rare symptom of hemoptysis as well as increased coagulation activity, which is reversed by the resection of pheochromocytoma using orthodox method [1]. Previously, Frymoyer *et al*. [4] have demonstrated the possible causes and suspected mechanisms of hemoptysis in a patient with pheochromocytoma, although the combined abnormalities in coagulation were not reported.

Based on the previous report, first, marked paroxysmal elevation of blood pressure induced by sudden catecholamine release may precipitate pulmonary venous hypertension, leading to pulmonary edema and hemoptysis [4]. In our patient, substituting β-adrenergic blockade for the previous antihypertensive strategy may have enhanced pressor response to endogenous noradrenaline. Occurrence of pulmonary edema in our patient is supported by the nearly complete resolution within 24 hours initially present in radiograph.

Second, catecholamines released from the tumor may cause vascular injury resulting in abnormalities of the coagulation system. Ljungner *et al*. [3] reported significantly higher circulating concentrations of plasminogen activator before pheochromocytoma surgery than after, and these had normalized at 6 months. Increased synthesis of plasminogen activator in response to elevations of endogenous catecholamines was postulated. We not only assessed fibrinolytic activity in our case, but also examined coagulant parameters including augmented partial thromboplastin time, prothrombin time, antithrombin III, prothrombin fragment factor 1 and 2, von Willebrand factor, thrombin-antithrombin complex, protein C, thrombomodulin. Plasma thrombin-antithrombin complex, prothrombin fragment factor 1 and 2, which directly indicate thrombin formation were greatly increased on admission and returned to the normal range after resection of the pheochromocytoma. This finding strongly suggests the activity of coagulation cascade by catecholamine, although the mechanisms are still to be elucidated. Moreover, our findings suggest the role of catecholamine in endothelial dysfunction, which was supported by increased von Willebrand factor before adrenalectomy and its reverse by operation. Adrenaline has been found to stimulate exocytosis of von Willebrand factor from endothelial Weibel-Palade bodies [5, 6]. Our finding of a marked increase in plasma von Willebrand factor is suggestive of such stimulated exocytosis. Increases in plasma thrombin-antithrombin III complex, prothrombin fragment factor 1 and 2, and von Willebrand factor imply that adrenaline-induced secretory activity in endothelial cells. However, it is not clear why catecholamine effects were limited to these as opposed to other coagulant factors. Further work is needed to clarify the consequences of coagulant factor increases in response to catecholamines released by pheochromocytomas.

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