Case Report

J Chin Med Assoc
2004;67:360-365

Recurrent Pulmonary Embolism in an Elderly Patient with Cushing's Syndrome, Adrenocortical Adenoma, Pheochromocytoma and Prostate Adenocarcinoma

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Key Words
adrenocortical adenoma;
Cushing's syndrome;
pheochromocytoma;
prostate adenocarcinoma;
pulmonary embolism

Pulmonary embolism (PE) is a major health problem. Mortality in untreated PE is high, but with adequate (anticoagulant) treatment, can be reduced. Multiple primary and secondary risk factors are responsible for PE. But there is rare association of mixed adrenal tumor with PE. Here, we report a case of adrenocortical adenoma with Cushing's syndrome coexistent with pheochromocytoma with recurrent PE in an elderly patient with prostate adenocarcinoma. A 78-year-old Taiwanese retired veteran was admitted in July, 2002 with the presentation of syncope. Three years before, he was diagnosed with prostate adenocarcinoma and had received Androcur therapy since then. Five months later, he was admitted with Cushingoid appearance and hypertension. Abdominal imaging studies revealed a left adrenal tumor. Laparoscopic adrenalectomy revealed an adrenocortical adenoma. Two years later, a recurrent left adrenal tumor was found. Repeated laparoscopic adrenalectomy revealed pheochromocytoma. One month after the repeat laparoscopic surgery, the patient was admitted due to syncope. Chest X-ray revealed cardiomegaly with pulmonary venous congestion. Echocardiogram showed impaired right ventricle global systolic function. Perfusion lung scan showed a high probability of PE. Heparin and coumadin were given but stopped 5 weeks later due to the development of severe skin ecchymosis. In December 2002, the patient was admitted again with consciousness disturbance. Chest computed tomography (CT) revealed bilateral PE, and he died 5 hours later due to cardiogenic shock. In conclusion, in elderly patients with Cushing's syndrome with pheochromocytoma and prostate carcinoma, there is probability of pulmonary embolism.

Pulmonary embolism (PE) is a major health problem. The diagnosis of PE includes clinical syndromes, deep vein thrombosis, symptoms and signs (dyspnea, tachypnea, syncope, hypotension, cyanosis, pleuritic pain, cough, hemoptysis), and diagnostic modalities. The diagnostic modalities include nonimaging (blood tests, electrocardiogram), noinvasive imaging (venous ultrasonography, lung scanning, echocardiography), and invasive (pulmonary angiography, contrast phlebography) methods.[1] Mortality in untreated PE is approximately 30%, but with adequate (anticoagulant) treatment, this can be reduced to 2-8%. The prevalence of PE at autopsy is approximately 12-15% in hospitalized patients.[2] Primary therapy for PE includes medical, catheter-based, and surgical therapy. The main risk factors responsible for PE include primary and secondary.[2] But there is rare association of mixed adrenal tumor with PE. Here, we report a case of Cushing's syndrome with adrenocortical adenoma and pheochromocytoma and prostate adenocarcinoma which was in association with recurrent PE.

CASE REPORT

A 78-year-old Taiwanese retired veteran was admitted in July 2002 with the presentation of syncope. In January

Received: July 3, 2003.
Accepted: January 12, 2004.

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2000, he had had symptoms of urinary urgency, incomplete emptying and incontinence. He visited our urology section. Prostate adenocarcinoma had been diagnosed and confirmed by needle biopsy. He had been treated with hormone therapy (Androcur oral 50 mg each day) since then.

In June 2000, the patient was admitted to our endocrine section due to Cushingoid appearance with hypertension. Iatrogenic Cushing's syndrome due to hormone therapy (Androcur) was suspected. High plasma cortisol and 24-hour urine free cortisol and 24-hour urine 17-hydroxycorticoids (17-OHCs) were checked. Low-dose and high-dose dexamethasone suppression tests showed nonsuppression of plasma cortisol. Plasma corticotropin (ACTH) showed low level (1 pg/mL, normal 9-52 pg/mL). Sella magnetic resonance image (MRI) showed empty sella. Abdominal computed tomography (CT) and MRI revealed a 3.0 × 2.5 cm left adrenal tumor (Fig. 1A, 1C). Laparoscopic adrenalectomy was performed, and pathology revealed an adrenocortical adenoma. Cushing's syndrome due to adrenocortical adenoma was diagnosed. After the operation, the patient received prednisolone 5 mg each day due to decreased plasma cortisol level, and stopped this treatment 13 months later due to recovery of plasma cortisol level.

Two years later, in June 2002, due to refractory high blood pressure and progressively elevated plasma cortisol level, he was admitted to our urology section. Plasma ACTH still showed low level (7.2 pg/mL). Brain CT showed no evidence of intracranial abnormality. Recurrent left adrenal tumor with size 2 × 1 cm (Fig. 1B, 1D) was found, and he received repeat laparoscopic adrenalectomy. The pathology revealed pheochromocytoma (Fig. 2).

Unfortunately, in July 2002, 1 month after repeat laparoscopic adrenalectomy, he was again admitted due to syncope. Physical examination revealed Cushingoid appearance, with moon face and plethora over bilateral cheeks, supraclavicular fullness and dorsocervical fat pad accumulation, limb tremor, diffuse skin ecchymosed, pedal edema, and proximal muscle atrophy, but without central obesity and purple striae. His pulse rate was fast (120/min), and other physical examinations were within normal limits.

Hematological investigation showed normal find-

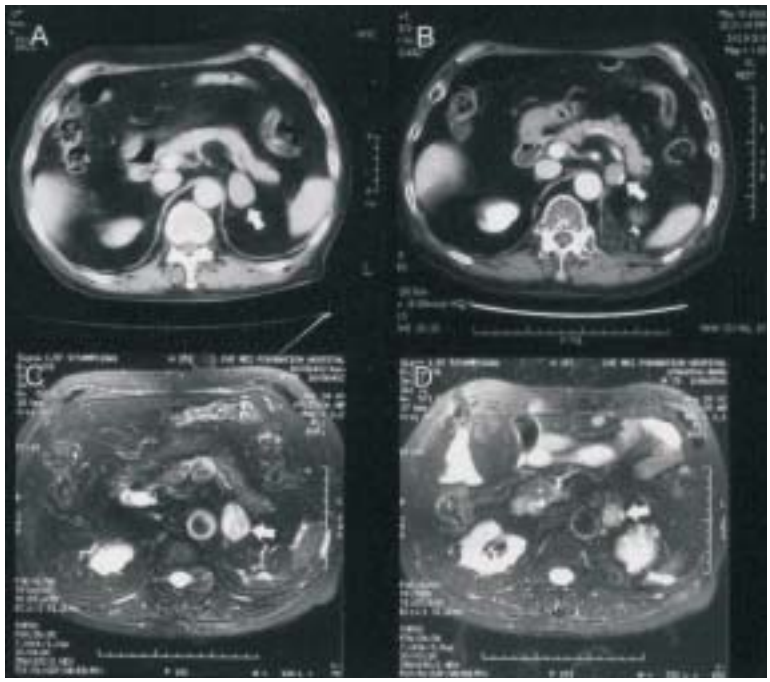

Fig. 1. Computed tomography (CT) of the abdomen and pelvis without and with contrast enhancement shows: (**A**) a 3.0 × 2.5-cm soft tissue nodule at the left suprarenal region (arrow), compatible with adrenal tumor; (**B**) a 2 × 1-cm well defined soft tissue nodule with no obvious enhancement after contrast injection at the left suprarenal region (arrow), compatible with recurrent adrenal tumor. Magnetic resonance image (MRI) of the upper abdomen without and with intravenous Gd-DTPA enhancement shows: (**C**) a well-defined nodular lesion with high signal intensity in T2WI in left adrenal gland (arrow); (**D**) a nodular lesion shows intermediate signal intensity in T2WI in the left adrenal gland (arrow).

ings except for low platelet count of 139,000/mm^3 (normal, 150,000-450,000). Biochemistry was normal except for elevated glucose of 127 mg/dL (normal, 70-110 mg/dL) and elevated troponin I of 0.5 mg/mL (normal, < 0.1 mg/dL). Room air arterial blood gas (ABG) data showed pH 7.494 (normal, 7.34-7.44), PaO_2 56.8 mmHg (normal, 75-100 mmHg), $PaCO_2$ 22.3 mmHg (normal, 35-45 mmHg), HCO_3^- 16.7 mmol/L (normal, 22-26 mmol/L) and O_2 saturation 92.4% (normal 95-98%). Endocrine study revealed plasma cortisol of 18.47 μg/dL (normal, 6-22 μg/dL) at 8 a.m. and 16.78 μg/dL at 4 p.m. (normal, 3-16 μg/dL). Electrocardiogram (EKG) showed clockwise rotation. Echocardiogram revealed impaired right ventricle (RV) global systolic function and moderate tricuspid regurgitation (TR) with estimated right ventricle systolic pressure (RVSP) over 50 mmHg. Lung perfusion study showed multiple segmental and subsegmental perfusion defects (Fig. 3), and pulmonary embolism was suggested.

Heparin and coumadin were given. The patient's condition improved and he was discharged after 3 weeks hospitalization. Unfortunately, severe skin ecchymosis developed after coumadin use and he stopped taking the medication 2 weeks later, after which his skin condition improved.

In December 2002, he arrived at our emergency ser-

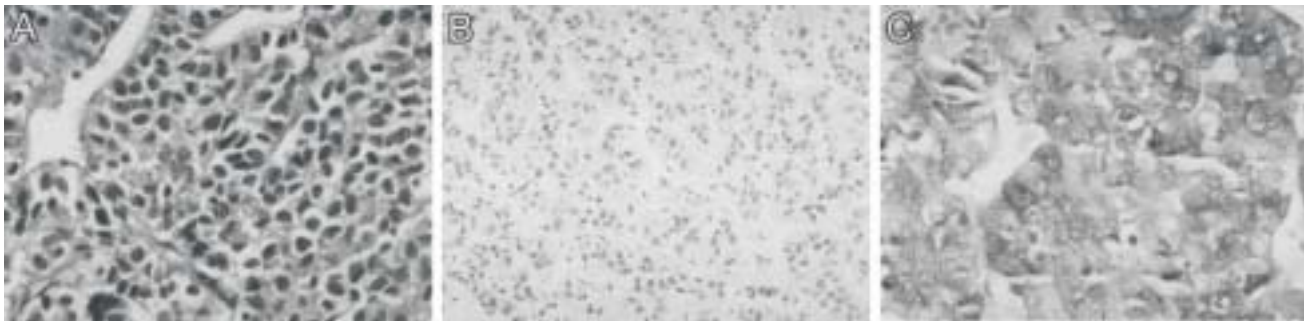

Fig. 2. Pathology of pheochromocytoma shows: (**A**) HE stain; (**B**) negative for AE1/AE3 immunohistochemical (IHS) stain; (**C**) positive IHS stain for synaptophysin reveals polygonal cells with granular cytoplasm and pleomorphic nuclei.

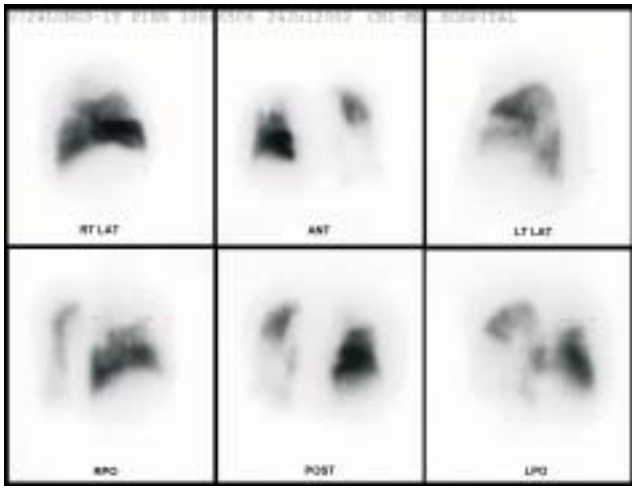

Fig. 3. Lung perfusion study in multiple views of the lungs obtained 5 minutes after the intravenous injection of 5 mCi of Tc-99m MAA shows multiple segmental and subsegmental perfusion defects. The scintigraphic findings are suggestive of pulmonary embolism.

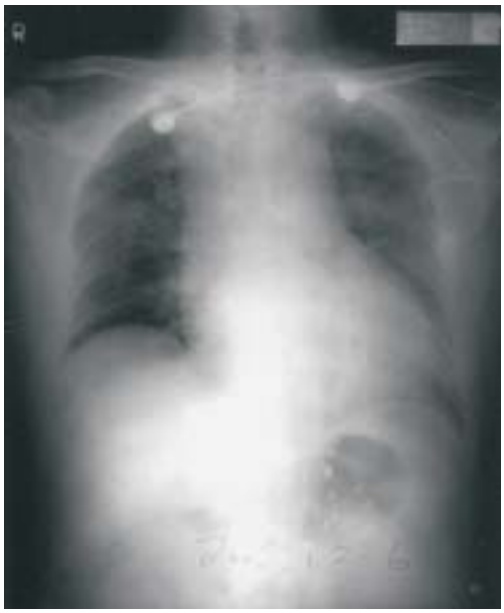

Fig. 4. Chest film obtained in the supine position shows tortuous aortic arch with intimal calcification as well as cardiomegaly with pulmonary venous congestion.

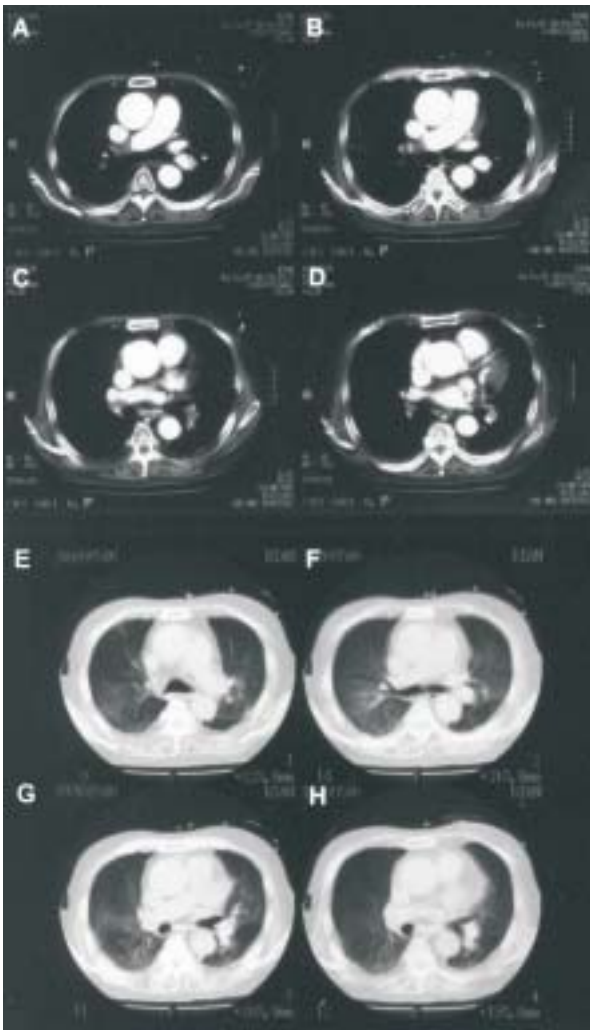

Fig. 5. Computed tomography of the chest with and without intravenous contrast enhancement: (A-D) show evidence of filling defects on pulmonary arteries (centrally) of both sides and their descending branches, indicative of pulmonary embolism; (E-H) lung window images, show avascular zones in right middle lobe and left lower lobe.

vice by ambulance due to 2 episodes of consciousness disturbance within 1 week. Physical examination revealed left lung basal rale and irregular heart rhythm. Neurological examination showed impaired mental status with disorientation to person, place and time, and bilateral muscle weakness.

Hematological study was normal except for low platelet count of 145,000/mm^3. Biochemistry revealed elevated aspartate aminotransferase of 297 IU/L (normal, < 40 IU/L), alanine aminotransferase 288 IU/L (normal, < 39 IU/L), blood urea nitrogen (BUN) 42.7 mg/dL (normal, 6-22 mg/dL), and low potassium of 3.26 mEq/L (normal, 3.5-5.0 mEq/L). Room air ABG data showed pH 7.5, PaO_2 83.9 mmHg, $PaCO_2$ 27.1 mmHg, HCO_3^- 20.8 mmol/L, and O_2 saturation 97%. Endocrine study showed elevated plasma cortisol of 20.39 μg/dL (normal, 3-16 μg/dL). EKG revealed left axis deviation with sinus tachycardia, atrial premature beat and ventricular premature beat.

Chest X-ray revealed cardiomegaly with pulmonary venous congestion (Fig. 4). Brain CT showed brain atrophy change. Chest CT revealed bilateral PE (Fig. 5).

Pheochromocytoma and Cushing's syndrome with recurrent pulmonary embolism was diagnosed. His condition deteriorated rapidly and he died 5 hours after hospitalization due to recurrent PE with cardiogenic shock.

DISCUSSION

The diagnosis of PE is frequently missed, and the symptoms are usually atypical. On physical examination, young and previously healthy individuals may simply appear anxious but otherwise seem deceptively well, even with an anatomically large PE. Dyspnea is the most frequent symptom of PE, and tachypnea is its most frequent sign. Dyspnea, syncope, hypotension, or cyanosis indicate a massive PE.[1] This patient was a 78-year-old man and was admitted after the development of syncope and consciousness disturbance. So, his symptoms were rather typical. The symptom of syncope indicates that he had a massive PE.

Mixed tumors of pheochromocytoma and adrenocortical adenoma have been reported. Akai *et al.* reported a 61-year-old woman with mixed tumor of the right adrenal gland presenting as diabetes mellitus and hypertension, and reviewed 21 cases of pheochromocytoma associated with Cushing's syndrome.[3] Yotsuyanagi *et al.* reported a 58-year-old male with pheochromocytoma in the right adrenal gland and contralateral non-functioning adrenocortical adenoma.[4] Miyazawa *et al.* also reported a 49-year-old male with hypertension due to coexisting pheochromocytoma and aldosterone-producing adrenal cortical adenoma.[5] But there were no reports of mixed adrenal tumors associated with PE. This patient presented with unilateral adrenal tumors. Adrenocortical adenoma with Cushing's syndrome was diagnosed and laparo-

scopic resection of the tumor had been performed. Two years later, repeat surgery identified a pheochromocytoma. He presented with hypertension, normal glucose level, and PE, which was different from other reported cases.

Reported causes of death in patients with pheochromocytoma and Cushing's syndrome vary, including hypertensive crisis, acute myocardial infarction, cerebrovascular accident, ventricular arrhythmias, irreversible shock, renal failure, and dissecting aortic aneurysm.[6] Regarding the association of Cushing's syndrome with PE, it is hypothesized that the glucocorticoid excess in Cushing's syndrome results in a hypercoagulable state which increases thromboembolic propensity that increases four-fold the incidence of PE, deep vein thrombosis, and mortality.[7] Our patient was in mildly impaired coagulable state with low platelet count but normal prothrombin time (PT), activated partial thromboplastin time (APTT), and liver function. After anticoagulant therapy, his PT and APTT prolonged obviously. Dicke *et al.* reported that pheochromocytoma rarely exhibits direct extension into the inferior vena cava causing symptoms of PE.[8] So, in case of Cushing's syndrome with pheochromocytoma, there is probability of PE, as in this patient.

Many risk factors may precipitate PE. Congenital predisposition to thrombosis is considered to be a rare condition. The primary risk factors of venous thromboembolism include factor V Leiden (APC-R) deficiency, prothrombin 20210A mutation, protein C deficiency, protein S deficiency, anti-thrombin deficiency, plasminogen deficiency, factor XII deficiency, hyperhomocysteinemia, anti-phospholipid antibodies syndrome, and high plasma factor VIII.[2,9] Our patient was a 78-year-old male, who had no primary risk factors of PE. He had no trauma history, stroke, smoking, oral contraceptives, heart failure, platelet abnormalities, or deep vein thrombosis. Possible secondary causes of PE in this case included advanced age, obesity, malignancy, and surgery.

The incidence of PE increase with age, but this trend may be due to an underlying relationship between age and other co-morbidities, which are the actual risk factors for PE (e.g. cancer, myocardial infarction).[2] This patient was a case of prostate carcinoma. Prostate adenocarcinoma has been reported in association with widespread microscopic PE causing respiratory failure.[10] Advanced prostatic cancer treated with chemotherapy or Iodine-125 seeds also can cause thrombotic complication.[11,12] This patient did not receive chemotherapy or iodine therapy, but he had received hormone therapy with Androcur (cyproterone acetate) for 2 years. Androcur is a potent antiandrogenic hormone. Kesteren *et al.* reported cases of treatment with Androcur in transsexual subjects causing of mortality and morbidity.[13] Other hormone replacement therapy has been reported in association with venous thromboembolism. The Heart and Estrogen/progestin Replacement Study (HERS) showed that treatment for 6.8 years with estrogen plus progestin in older women with coronary disease increased threefold the rates of venous thromboembolism.[14] This patient had prostate carcinoma and had received Androcur (anti-androgen) therapy for about 2 years, which increased the risk of PE.

Laparoscopic surgery has been well known to be associated with PE, including adrenalectomy.[15] The mechanism was hypothesized to be that abdominal insufflation causes venous stasis accompanied by elevated venous pressures during the laparoscopic surgical procedure, so that patients undergoing laparoscopic surgical procedures are at risk for deep vein thrombosis and PE.[16] This patient had received laparoscopic adrenalectomy 2 times within 2 years. The first episode of PE occurred 1 month after the second operation. So, there is possibility that the first episode of PE had some relationship with the repeat laparoscopic surgery.

Lung scintigraphy has a pivotal role to play in the diagnostic management of suspected PE. It is non-invasive, safe, and with few allergic reactions.[2,17] Pulmonary angiography is the method of choice for patients in whom non-invasive tests are either inconclusive or not available. Angiography may also be indicated in the rare situation of an extremely high bleeding risk with high probability lung scan, and in patients with contraindications for thrombolytic or heparin therapy.[2] Modern CT imaging (electron beam tomography and spiral CT angiography) has revolutionized the approach to the evaluation of patients with suspected PE, enabling the direct visualization of pulmonary emboli within the pulmonary arteries. Spiral CT is used as a primary screening test for PE or in combination with lung scan and ultrasonography.[2] Echocardiogram might be useful for the differential diagnosis. It has non-invasive character and high emergence availability. Echocardiography may suggest or reinforce clinical suspicion of PE if right ventricular overload and dysfunction are found.[2] This pa-

tient had combination tests with lung scan and CT imaging study that confirmed the diagnosis of PE.

The treatment of acute PE includes hemodynamic and respiratory support, thrombolytic therapy, anticoagulant therapy, inferior vena cava (IVC) filters, and surgical embolectomy.[2] The use of thrombolytic and anticoagulant agents with recombinant tissue plasminogen activator (rtPA), unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), warfarin, and alteplase can improve the clinical course and prevent clinical deterioration.[2,18] Patients who have a first episode of venous thromboembolism are often treated with anticoagulant therapy for more than 3 months. Such patients may benefit from long-term, low intensity warfarin therapy for 3 to 12 months as they appear to have an increased risk of recurrence after anticoagulant therapy is stopped.[18,19] This patient only received 2 weeks of anticoagulation therapy with heparin and 5 weeks with warfarin in the first episode of PE. He stopped anticoagulation therapy due to the development of severe skin ecchymosis, which increased risk of recurrence of PE and mortality.

In conclusion, in elderly patients with Cushing's syndrome with pheochromocytoma and prostate carcinoma and other secondary risk factors, there is probability of PE.

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