

Adrenocorticotrophic hormone (ACTH)-producing pheochromocytoma presented as Cushing syndrome and complicated by invasive aspergillosis

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Adrenocorticotrophic hormone (ACTH)-producing pheochromocytoma has been rarely reported, whereas only a few cases of Cushing syndrome accompanied by opportunistic infections have been reported. We experienced a patient with pheochromocytoma with ectopic Cushing syndrome complicated by invasive aspergillosis. A 35-year-old woman presented with typical Cushingoid features. Her basal plasma cortisol, ACTH, and 24-hour urine free cortisol levels were significantly high, and 24-hour urine metanephrine and catecholamine levels were slightly elevated. The endogenous cortisol secretion was not suppressed by either low- or high-dose dexamethasone. Abdominal computed tomography (CT) revealed a heterogeneous enhancing mass measuring approximately 2.5 cm in size in the left adrenal gland. No definitive mass lesion was observed on sellar magnetic resonance imaging. On fluorine-18 fluorodeoxyglucose positron emission tomography/CT, a hypermetabolic nodule was observed in the left upper lung. Thus, we performed a percutaneous needle biopsy, which revealed inflammation, not malignancy. Thereafter, we performed a laparoscopic left adrenalectomy, and its pathologic finding was a pheochromocytoma with positive immunohisto-staining for ACTH. After surgery, the biochemistry was normalized, but the clinical course was fatal despite intensive care because of the invasive aspergillosis that included the lungs, retina, and central nervous system.

Keywords: ACTH syndrome; Ectopic; Cushing syndrome; Pheochromocytoma; Aspergillosis

INTRODUCTION

Ectopic adrenocorticotrophic hormone (ACTH)-dependent Cushing syndrome comprises approximately 10% of Cushing syndrome [1]. The most common causes of ectopic ACTH syndrome are malignancies that include small cell lung cancer (SCLC), bronchial carcinoids, islet cell tumors of the pancreas, thymic carcinoids, and medullary thyroid cancer. ACTH-producing pheochromocytoma is one cause of ectopic ACTH syndrome, which has been reported to range from 2% to 25% [2-8], fewer than 30 cases globally and only 3 cases have been reported in Korea [9-12].

Endogenous and iatrogenic hypercortisolism is known to impair cell-mediated immunity, making patients with Cushing syndrome susceptible to opportunistic infections such as mucocutaneous and invasive fungal infections, viral infections, bacterial infections, reactivation of tuberculosis, and post-operative wound infections [13,14]. However, invasive aspergillosis is rarely reported in patients with Cushing syndrome. This case is the first report of invasive aspergillosis complicated by ACTH-producing pheochromocytoma.

CASE

A 35-year-old woman was admitted to our hospital due to headache for 2 months. She also suffered from proximal muscle weakness and ocular pain. She had not had any other disease, but 2 months before her admission, she was diagnosed with hypertension and treated with 3 kinds of anti-hypertensive drugs (an α 1-receptor blocker, a calcium antag-

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onist, and an angiotensin-2 receptor blocker). On physical examination, she presented typical Cushingoid features, including centripetal obesity with slim extremities, a buffalo hump, a moon face, and hirsutism. She had gained over 6 kg in weight from 2 months earlier. Her weight was 56 kg; height, 155 cm (body mass index, 23.31 kg/m²); body temperature, 37.2°C; pulse, 70 beats/min; and blood pressure, 140/90 mmHg.

The laboratory findings at presentation were severe hypercortisolism with loss of diurnal variation, hypokalemia, and glucose intolerance. The basal plasma cortisol levels were over 49 µg/dL at both 8:00 a.m. and 4:00 p.m. (normal range [NR], 5-25 µg/dL at 8:00 a.m. and 3-13 µg/dL at 4:00 p.m.), and the plasma ACTH levels were 357.89 pg/mL (NR, 10-60 pg/mL) and 289.54 pg/mL (NR, 6-30 pg/mL) at 8:00 a.m. and 4:00 p.m., respectively. However, the plasma epinephrine (48.24 pg/mL; NR, <120 pg/mL) and norepinephrine (210.04 pg/mL; NR, 0-410 pg/mL) levels were not elevated. The 24-hour urine free cortisol level (5,600 µg/day; NR, 20-90 µg/day) was significantly elevated; the 24-hour urine epine-

phrine (44.3 µg/day; NR, 0-20 µg/day), norepinephrine (121.6 µg/day; NR, 15-80 µg/day), and metanephrine (1.8 mg/day; NR, <0.8 mg/day) levels and the plasma dehydroepiandrosterone-sulfate level (379.82 µg/dL; NR, 30-333) were slightly elevated; and the 24-hour urine vanillylmandelic acid (VMA) level (2.6 mg/day; NR, 0-8 mg/day) was not elevated. The serum potassium level was 2.4 mEq/L (NR, 3.5-5.5 mEq/L); the plasma glucose level, 197 mg/dL (NR, 72-110 mg/dL); and the glycohemoglobin (HbA1c) level, 6.4% (NR, 4.4%-6.3%). Endogenous cortisol secretion was not suppressed by either the standard low-dose (0.5 mg every 6 hours for 2 days) or high-dose dexamethasone (2 mg every 6 hours for 2 days) suppression tests, which led to the diagnosis of ectopic ACTH syndrome. The results of the endocrinologic study are summarized in Table 1.

On abdominal computed tomography (CT), a heterogeneous enhancing round mass measuring approximately 2.5 cm in size was observed in the left adrenal gland (Fig. 1). To exclude ACTH overproduction by the pituitary gland, sellar magnetic resonance imaging (MRI) was performed, which found no evidence of pituitary adenoma (Fig. 2). To search for a source of ectopic ACTH production, fluorine-18 fluorodeoxyglucose positron emission tomography (F-18 FDG PET)/CT was performed, on which a focal hypermetabolic nodule was observed in the left upper lung. Enlargement of both adrenal glands and a mass in the left adrenal gland with FDG uptake were also observed on PET/CT (Fig. 3). A cavitory nodule measuring approximately 1.2 cm in size with a sur-

Table 1. Endocrinologic studies before and after surgery (16 weeks)

Hormonal profiles	Reference range	Before surgery	After surgery
Serum cortisol (µg/dL)			
Basal (8:00 a.m.)	5-25	>49	24
Basal (4:00 p.m.)	3-13	>49	
After low-dose suppression		>49	
After high-dose suppression		>49	
Serum ACTH (pg/mL)			
Basal (8:00 a.m.)	10-60	357.89	47
Basal (4:00 p.m.)	6-30	289.54	
Serum epinephrine (pg/mL)	<120	48.24	
Serum norepinephrine (pg/mL)	0-410	210.04	
Serum DHEA-S (µg/dL)	30-333	379.82	
24-hr urine free cortisol (µg/day)			
Basal	20-90	5,600	298
After low-dose suppression		>5,000	
After high-dose suppression		5,565	
24-hr urine epinephrine (µg/day)	0-20	44.3	
24-hr urine norepinephrine (µg/day)	15-80	121.6	
24-hr urine VMA (mg/day)	0-8	2.6	
24-hr urine metanephrine (mg/day)	<0.8	1.8	

ACTH, adrenocorticotropic hormone; DHEA-S, dehydroepiandrosterone-sulfate; VMA, vanillylmandelic acid.



Fig. 1. Abdominal computed tomography scan showing a heterogeneous enhancing round mass (arrow) measuring approximately 2.5 cm in the left adrenal gland (32 Hounsfield units in the left adrenal gland in the non-contrast phase).

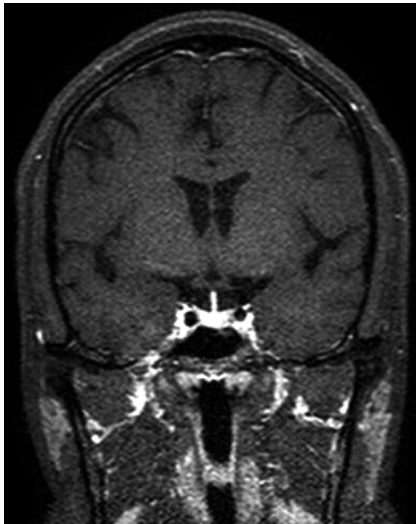


Fig. 2. Sellar magnetic resonance imaging scan showing no definite evidence of abnormal lesions in the pituitary gland.

rounding ground glass appearance in the left upper lung was observed on chest CT (Fig. 4). At first, we considered ectopic ACTH-producing lung cancer; therefore, we performed a percutaneous needle biopsy of the lung nodule. However, the pathologic result was inflammation, not malignancy. Based on these findings, we diagnosed ectopic ACTH syndrome of the adrenal adenoma and performed laparoscopic left adrenalectomy.

In examination of the resected specimen, the left adrenal gland measured 6.0×4.3×2.3 cm and weighed 22 g. We found a solid round tumor with a diameter of approximately 2.4 cm. The cut surface of the tumor showed a dark brown to gray color and focal hemorrhage (Fig. 5A). The histological finding was pheochromocytoma with oval to polygonal cells and abundant acidophilic cytoplasmic granules, a round nucleus, a clear vacuolated cytoplasm, and increased vascularity. Mitosis or capsular invasion was not seen. The left adrenal gland showed mild cortical hyperplasia (Fig. 5B). Immunohistochemistry showed that the tumor cells were strongly positive-stained for ACTH (Fig. 5C) and negative-stained for inhibin.

After surgery, the biochemistry normalized (Table 1), but the clinical course was fatal due to the complication of invasive aspergillosis in the lung, retina, and central nervous system. The day after surgery, fever developed; and 2 days later, the patient complained of dyspnea. The chest X-ray showed multifocal dense consolidation and partial cavity for-

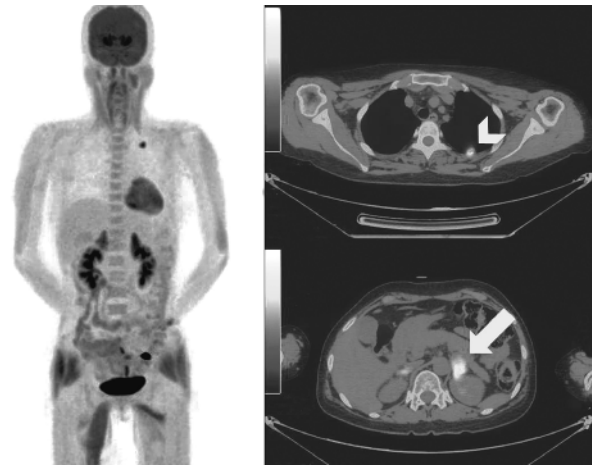


Fig. 3. Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography scan showing a focal hypermetabolic nodule in the left upper lung (arrowhead) and a mass in the left adrenal gland (arrow).



Fig. 4. Chest computed tomography scan showing a cavitary nodule (arrow) measuring approximately 1.2 cm with a surrounding ground glass appearance in the left upper lung.

mation in both lungs. On the 5th post-operative day, the chest CT showed more aggravated multifocal patchy consolidation, a ground glass appearance, and new formation of cavities in both lungs (Fig. 6A). The sputum cultures revealed the *Aspergillus* species, and the result of aspergillus antigen test was positive. The patient was treated with intravenous voriconazole. On the 6th post-operative day, the patient complained of visual disturbance of the right eye. Fundus photography revealed inflammatory ball-like lesions in the vitreous cavity and neovascular fibroproliferation that demonstrated fungal retinitis (Fig. 6B). On the 10th post-operative day, the patient became stuporous. Brain CT showed multifocal low-density areas in both cerebral hemispheres and the right

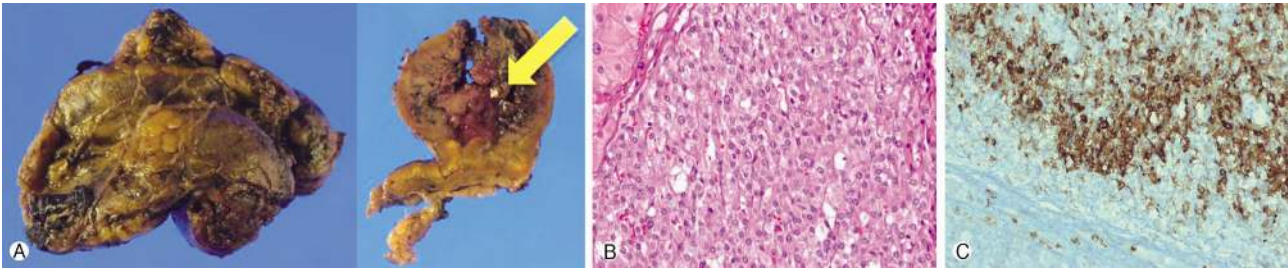


Fig. 5. (A) Gross finding. The left adrenal gland shows a dark brown colored mass measuring approximately 2.4 cm in size (arrow). (B) Histological findings. The tumor is composed of oval to polygonal cells with round nuclei and abundant acidophilic or clear vacuolated cytoplasm (H&E stain, $\times 200$). (C) The tumor cells are positive for adrenocorticotropic hormone (immunohistochemical stain, $\times 100$).

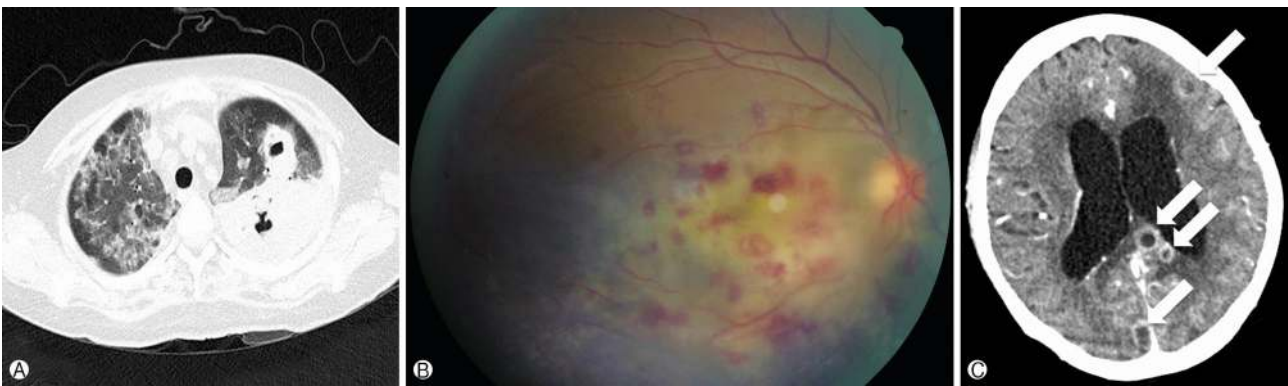


Fig. 6. (A) Chest computed tomography (CT) scan showing pulmonary aspergillosis, including multifocal patchy consolidation, a ground glass appearance, and formation of cavities in both lungs. (B) Fundus photograph showing inflammatory ball-like lesions and neovascular fibroproliferation in the right eye indicative of fungal retinitis. (C) Brain CT scan showing multiple ring enhancing masses (arrows) from the cerebral aspergillosis.

cerebellum. Despite continuous antifungal treatment, the patient's mental status showed further deterioration. Brain CT was performed repeatedly, which showed multiple ring enhancing masses from the cerebral aspergillosis (Fig. 6C). Despite administration of antifungal and broad-spectrum antibiotics therapy, the patient died on the 233th day of her hospitalization.

DISCUSSION

Cushing syndrome is a rare disorder with an annual incidence of 0.7-2.4 per million population. Overall, ACTH-dependent causes account for approximately 80%-85% of all cases, and of these, 80% are due to pituitary adenomas (Cushing disease), and the remaining 20% are due to ectopic ACTH syndrome. Approximately 10%-15% of cases are caused by an ACTH-independent adrenal source [1]. The most common causes of ectopic ACTH syndrome are malignancies

that include SCLC, bronchial carcinoids, islet cell tumors of the pancreas, thymic carcinoids, and medullary thyroid cancer. Of these, bronchial carcinoids seem to be by far the most common tumors. Because the SCLC patients' condition, they did not have time to go to a reference center [8]. Pheochromocytoma accounts for 2%-25% of overt cases of ectopic ACTH-secreting tumors [2-8]. Fewer than 30 cases have been reported globally. Nijhoff et al. [9] reviewed 24 cases of Cushing syndrome caused by pheochromocytoma reported between 1977 and 2009. Only 3 cases have been reported in Korea. Hong et al. [10] were the first to report on a patient with ACTH-producing pheochromocytoma in 1997. However, to the best of our knowledge, this is the first report of a patient with ACTH-producing pheochromocytoma complicated by invasive aspergillosis.

Due to the highly variable phenotype, clinical diagnosis of ACTH-producing pheochromocytoma is very difficult. Some cases have no typical Cushingoid symptoms, and some have

no typical features of catecholamine excess. Chen et al. [15] proposed the following diagnostic criteria for Cushing syndrome caused by pheochromocytoma: (1) clinical and laboratory evidence of hypercortisolism; (2) elevated plasma ACTH levels; (3) evidence of pheochromocytoma in the urinary catecholamine, metanephrine, or VMA levels, or MRI evidence of an adrenal mass with a bright T2 signal; (4) resolution of symptoms/signs of adrenocorticoid and catecholamine excess after unilateral adrenalectomy; and (5) rapid normalization of the plasma ACTH levels after adrenalectomy. In our patient, the normal plasma catecholamine and 24-hour urine VMA levels, and the slightly elevated 24-hour urine catecholamine and metanephrine levels, led us initially to reject the possibility of pheochromocytoma as the ectopic source of the ACTH secretion. The cause of the low levels of urinary metanephrine and VMA was speculated as the negative effect of the hypercortisolism or ectopic ACTH production on the detection of urinary metanephrine excretion or the metabolic process of catecholamine that includes monoamine oxidase or catechol-O-methyltransferase activation [16]. Therefore, a high index of suspicion is required for early diagnosis of adrenal pheochromocytoma as the source of ectopic Cushing syndrome, together with a laboratory study, imaging findings, invasive procedures (such as sampling of ACTH in the adrenal veins), and clinical characteristics.

Excessive corticosteroid impairs cell-mediated immunity. Thus, patients with Cushing syndrome are susceptible to opportunistic infections [14]. Patients with endogenous Cushing syndrome have the same spectrum of infections as patients with iatrogenic Cushing syndrome. The risk of infection is correlated with the degree of cortisol excess [13]. Therefore, the fatality rate for endogenous Cushing syndrome is higher than that for iatrogenic Cushing syndrome [14]. Furthermore, the type of infection depends on the degree of cortisol excess. For example, Graham and Tucker [13] reported that cryptococcosis occurred with a less than 1,933 nmol/L morning plasma cortisol level. However, the *Pneumocystis jirovecii* pneumonia (PJP) threshold was much higher, as morning cortisol levels above 3,342 nmol/L are associated with pneumocystosis. In immunocompetent hosts, there are normally 2 lines of defense against inhaled molds. First, the resident lung macrophages facilitate phagocytosis, and, second, polymorphonuclear leukocytes destroy the hyphae. Glucocorticoids negatively affect this mechanism, and thus, produce an immuno-

suppressive condition.

Several invasive fungal infections, including cryptococcosis, PJP, invasive aspergillosis, invasive candidiasis, and histoplasmosis, have been reported in endogenous Cushing syndrome [17]. Invasive aspergillosis is the most common invasive mold infection associated with glucocorticoids [14]. Cases of invasive aspergillosis in ectopic ACTH syndrome have been reported. Among them, Naylor et al. [18] reported pulmonary aspergillosis and endophthalmitis in ectopic ACTH syndrome caused by bronchial carcinoids, and Walsh and Mendelsohn [19] reported pulmonary and disseminated aspergillosis in ectopic ACTH syndrome caused by prostate carcinoma.

The prognosis of ACTH-producing pheochromocytoma is worse than that of bronchial carcinoids. The observed mortality rate was 20% [2,3,5]. Rapid control of hypercortisolism is crucial for survival. In our patient, the biopsy-confirmed inflammatory left lung nodule was considered a source of invasive aspergillosis, which was disseminated after surgery.

In summary, we presented a patient with ectopic ACTH-producing pheochromocytoma complicated by invasive aspergillosis. These invasive fungal infections have fatal outcomes because of their immunosuppressive condition due to hypercortisolism. Thus, careful attention and prompt management are needed in treatment of these patients.

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