INTERNAL MEDICINE

□ CASE REPORT □

Pneumocystis Pneumonia Concomitant with Ectopic ACTH Syndrome Caused by a Large Cell Neuroendocrine Carcinoma of the Thymus

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Abstract

We herein report the case of a 44-year-old man who was diagnosed with pneumocystis pneumonia (PCP) concomitant with ectopic adrenocorticotropic hormone (ACTH) syndrome, which had been caused by a large cell neuroendocrine carcinoma of the thymus. Chest computed tomography revealed ground-glass opacities in the lungs. PCP was diagnosed by a polymerase chain reaction with bronchoalveolar lavage. The levels of cortisol were slowly corrected with an adrenal enzyme inhibitor, and the exacerbation of PCP was successfully avoided. Our case indicates that in addition to prophylaxis, the early diagnosis of PCP and the slow correction of hypercortisolemia should be considered in order to prevent an exacerbation due to the reconstitution of the immune function in patients with ectopic ACTH syndrome.

Key words: ectopic ACTH syndrome, Cushing's syndrome, thymus, neuroendocrine tumor, large cell neuroendocrine carcinoma, pneumocystis pneumonia

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Introduction

Ectopic adrenocorticotropic hormone (ACTH) syndrome is an endocrine disorder that is caused by excessive levels of the endogenous corticosteroid hormone cortisol arising from an ACTH-producing tumor that was located outside the pituitary. The most common cause of ectopic ACTH syndrome is small cell lung cancer (45%), followed by thymic (15%), bronchial (15%), and pancreatic neuroendocrine tumors (10%) (1). Among these tumors, large cell neuroendocrine carcinoma (LCNEC) of the thymus is a very rare cause of ectopic ACTH syndrome, and only one case has ever been reported in the literature (2).

Ectopic ACTH syndrome comes with a high risk of opportunistic infection, such as pneumocystis pneumonia (PCP), which has a significant impact on the prognosis of ectopic ACTH syndrome (3-5). We herein report a case of PCP concomitant with ectopic ACTH syndrome that had been caused by LCNEC of the thymus, in which PCP was successfully treated and the patient's hypercortisolemia was corrected.

Case Report

A 44-year-old man had been diagnosed with LCNEC of the thymus with bone metastasis at a different hospital 3 years previously. The serum levels of ACTH and cortisol were elevated, but brain magnetic resonance imaging revealed that his pituitary gland was normal. However, immunohistochemical staining of the thymic tumor tissue revealed partial anti-ACTH antibody positivity. The tumor was there-

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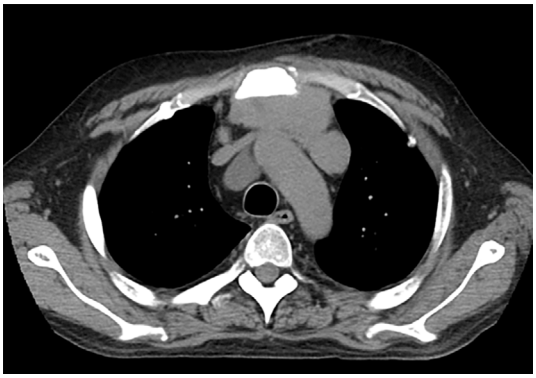

Figure 1. Chest computed tomography (CT) on admission showing an 8-cm-sized tumor in the anterior mediastinum.

fore determined to be ectopically producing ACTH. The patient underwent chemotherapy with cisplatin and irinotecan, but the continuation of chemotherapy was problematic due to a lack of tolerance. Treatment for hypertension and diabetes caused by the ectopic ACTH syndrome was initiated, as was treatment with zoledronic acid for bone metastasis.

The patient was referred to the Endocrine Center at our hospital after 3 months due to a sensation of weakness and the worsening of his hyperglycemia. A physical examination revealed hypertension, a subcutaneous mass that was palpable in the anterior chest, and redness and swelling of the left lower leg without fever, respiratory symptoms, hypoxemia, or abnormal chest sounds. The oxygen saturation by pulse oximeter in room air and was 97% and his respiratory rate was 13 breaths per minute. Among the laboratory findings, the white blood cell and neutrophil counts, and blood sugar, triglyceride, and low-density lipoprotein cholesterol levels were found to be elevated, and the patient's potassium level was decreased to 2.8 mEq/L. The patient's lactate dehydrogenase (468 IU/L), beta-D glucan (370.8 pg/mL), ACTH (354.1 pg/mL), and cortisol (49.1 μg/dL) levels were also elevated. The patient's serum was negative for aspergillus, candida, and cryptococcus antigens; a cytomegalovirus pp65 antigenemia test also yielded a negative result. These data suggested that the increased production of ACTH by the tumor, along with the progression of the disease, had promoted the elevation of the patient's serum levels of ACTH and cortisol.

Computed tomography (CT) revealed the progression of the disease in the both thymic and metastatic bone lesions, along with the multiple ground-glass opacities in both lungs (Fig. 1, 2). The patient underwent bronchoalveolar lavage (BAL) in the right B^5 segment with 150 mL saline, and 62.7% of the BAL fluid was recovered. The cell count in the BAL fluid was 0.61×10^5 per mL, and the cell differentiation in the BAL fluid was 17.0% macrophages, 81.0% lymphocytes, and 2.0% neutrophils, with a CD 4/8 ratio of 0.57. Gram, Ziehl-Neelsen, and Grocott staining were all negative. A polymerase chain reaction revealed that the patient's BAL fluid was positive for *Pneumocystis jirovecii*. PCP was diagnosed based on the above results.

The patient was treated with sulfamethoxazole/trimethoprim (12 g/day) for 3 weeks. Anti-cortisol therapy with metyrapone was also initiated at the same time with a small dose to slowly correct the hypercortisolemia. Intensive insulin therapy, potassium supplementation were initiated, while cefazolin was administered to treat cellulitis of the left lower leg. The patient's PCP fully improved without the exacerbation of his respiratory status. Thereafter, we continued to administer sulfamethoxazole/trimethoprim at a prophylactic dose.

The metyrapone dosage was gradually increased from 250 mg/day, and the blood cortisol value was observed to decline slowly (Fig. 3). In order to prevent hypocortisolemia, the patient was temporarily treated with hydrocortisone. After an improvement of his left lower leg cellulitis, PCP, and hyperglycemia, the patient underwent laminectomy and radiation therapy for spinal cord compression, which had been caused by a metastatic spinal tumor. Octreotide therapy was initiated, and he was discharged on the 68th day of hospitalization.

Discussion

Thymic neuroendocrine tumors are very rare, and are reported to comprise 0.4% of carcinoids, and less than 5% of anterior mediastinal tumors (1). There has only been one reported case in which an LCNEC of the thymus caused ectopic ACTH syndrome (2); our case is, to the best of our knowledge, the first report of PCP concomitant with ectopic ACTH syndrome due to an LCNEC of the thymus (Table 1). The risk of opportunistic infection that accompanies ectopic ACTH syndrome increases in cases that exhibit marked hypercortisolemia (6, 7). PCP, in particular, remains one of the most prevalent opportunistic infections and has a significant impact on the prognosis of patients with ectopic ACTH syndrome (4, 5).

In the present case, the patient had a high serum cortisol level, and was diagnosed with a superinfection of PCP. Interestingly, 11 out of the 12 previously reported cases were treated with adrenal enzyme inhibitors in order to correct their high serum levels of cortisol; the patients subsequently experienced a rapid respiratory deterioration due to the exacerbation of subclinical PCP (8-17) (Table 2). Ten cases required mechanical ventilation, and five did not survive. In all of these cases, endogenous cortisol had suppressed the local inflammatory reaction in the lungs, resulting in subclinical PCP. However, the immune reaction might be rapidly reconstituted following treatment for hypercortisolemia, and an exacerbation of PCP might therefore be induced as the level of serum cortisol decreases. Patients with acquired immune deficiency syndrome also show the similar exacerbation of subclinical PCP when the initiation of antiretroviral therapy induces immune reconstitution against inflammation (18). In the present case, the diagnosis of PCP caused by ectopic ACTH syndrome was made before the correction of the high serum cortisol levels. In addition, metyrapone,

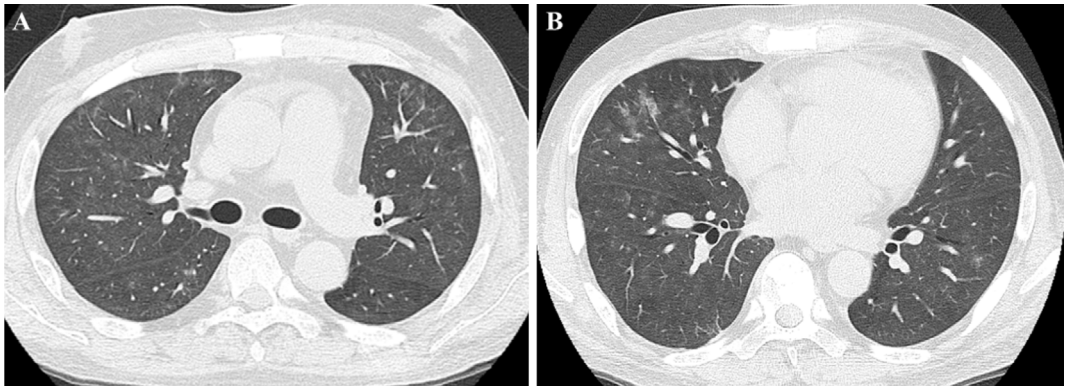

Figure 2. **Chest CT on admission showing multiple ground-glass opacities in both lungs.**

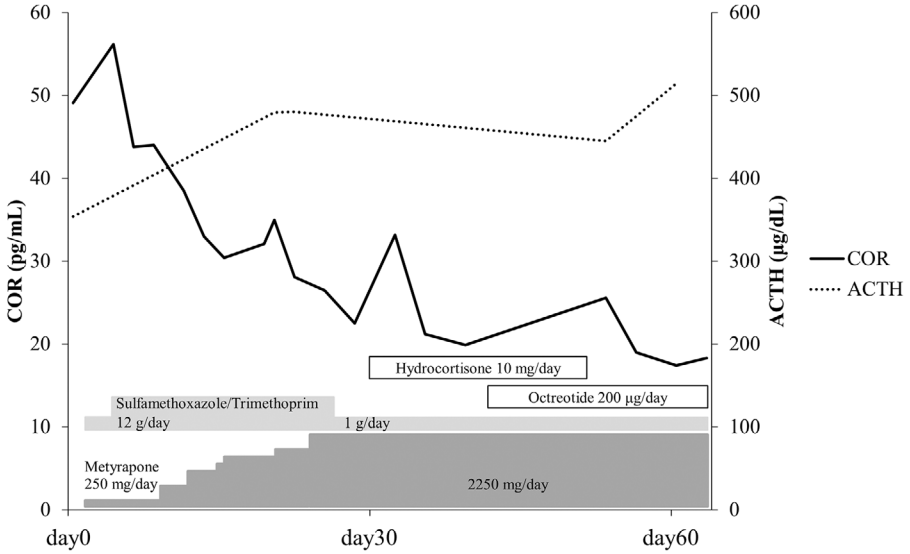

Figure 3. **The clinical course. COR: cortisol, ACTH: adrenocorticotropic hormone**

Table 1. **Literature Review of PCP Cases Caused by Ectopic ACTH Syndrome and Their Clinical Findings.**

No.	Year	Reference number	Age	Sex	COR (μg/dL)	ACTH (pg/mL)	Primary site	Histology	PCP prophylaxis
1	1981	(8)	24	M	110	902	bronchial	cartinoid	−
2	1984	(9)	38	F	114	1,750	unknown	ND	−
3	1998	(10)	56	M	198	315	unknown	ND	−
4	2000	(11)	60	F	80	460	unknown	ND	−
5	2003	(12)	21	F	145	735	pancreas	islet cell carcinoma	−
6	2006	(13)	26	F	47	204.5	unknown	ND	−
7	2007	(14)	62	F	70	296	lung	cartinoid	−
8	2007	(14)	57	F	86	318	pancreas	endocrine tumor	+
9	2008	(15)	36	M	79	1,118	kidney	well-differentiated neuroendocrine carcinoma	−
10	2011	(16)	60	F	114	250	unknown	ND	−
11	2011	(16)	20	M	50	300	unknown	high-grade endocrine carcinoma	−
12	2012	(17)	48	F	106	296	pancreas	high-grade neuroendocrine carcinoma	−

PCP: pneumocystis pneumonia, ACTH: adrenocorticotropic hormone, COR: cortisol, ND: not described

an adrenal enzyme inhibitor, was started at the same time as the initiation of PCP therapy, and the dosage was gradually increased from a small dose to slowly correct hypercortisolemia and prevent sudden immune reconstitution. Consequently, we were able to prevent the exacerbation of PCP. Thus, it is important to correct hypercortisolemia slowly in cases of PCP induced by ectopic ACTH syndrome. This is important even in cases where a diagnosis of PCP has not been made, because subclinical PCP may still exist and the exacerbation of PCP may be enhanced due to a delayed diagnosis or by the medication that is used to treat hypercortisolemia.

It has been reported that preventive medication for PCP was useful in patients with Cushing's syndrome accompa-

Table 2. Literature Review of PCP Cases Caused by Ectopic ACTH Syndrome and Their Clinical Findings.

No.	Anti-cortisol therapy (starting dose)	Measurement of COR levels after anti-cortisol therapy		PCP		Respiratory failure	Outcome
		Levels (μg/dL)	When	Development*	Treatment		
1	metyrapone (1,500 mg/day)	18	1 month later	1 month later	ST	+	alive
2	metyrapone (3,000 mg/day)	ND	ND	1 day later	ST	+	dead
3	ketoconazol (400 mg/day)	36	4 days later	13 days later	ST, steroid	+	dead
4	ketoconazol (600 mg/day)	16.2	6 days later	3 days later	ST, steroid	+	dead
5	metyrapone (3,000 mg/day)	ND	ND	before	ST	+	alive
6	ketoconazol (400 mg/day), metyrapone (1,500 mg/day)	11	ND	14 days later	ST, steroid	−	alive
7	mifepristone (400 mg/day)	ND	ND	a few days later	ST	+	alive
8	mifepristone (400 mg/day), ketoconazole	ND	ND	2 days later	ST	+	alive
9	metyrapone (1,500 mg/day)	35	6 days later	14 days later	ST, steroid	+	dead
10	ketoconazol, ethomidate	44	ND	4 days later	ST	+	alive
11	ketoconazol, ethomidate	15	4 days later	later	ST	+	alive
12	ketoconazol	ND	ND	later	−	+	dead

*: Development of PCP following initiation of anti-cortisol therapy.
COR: cortisol, ACTH: adrenocorticotropic hormone, ND: not described, ST: sulfamethoxazole/trimethoprim

nied by hypercortisolemia of ≥90 μg/dL (10). Another study showed that severe infections were more prone to occur in ectopic ACTH syndrome with serum cortisol levels of ≥40 μg/dL, daily urine cortisol excretion of ≥ 2,000 μg/day, and daily urine 17-hydroxysteroid/g creatinine excretion of ≥35 mg/g creatinine. Moreover, the increased susceptibility to infection due to exogenous glucocorticoids not only affected the dosage of glucocorticoids but also the dosing period (19). In the present case, the level of serum cortisol was increased to 49.1 μg/dL and the disease was active over a period of a few years. The length of morbidity in the present case may have also affected the patient's susceptibility to infection. Most of the previously reported cases of ectopic ACTH syndrome, including the present case, did not receive PCP prophylaxis, despite their serum cortisol levels being elevated. Although the precise prevalence of PCP in ectopic ACTH syndrome is unclear, there is often an association with subclinical PCP. Most of the previously reported cases were not recognized as having subclinical PCP. Although the present case was not a subclinical case, the patient had no respiratory symptoms and CT and bronchoscopy were required for its diagnosis. The early diagnosis of PCP in patients with ectopic ACTH syndrome might not be easy; thus, PCP prophylaxis should be considered to prevent PCP infection and fatal respiratory failure.

We encountered a rare case of PCP concomitant with ectopic ACTH syndrome, which had been caused by an LCNEC of the thymus. Ectopic ACTH syndrome associated with a malignant tumor carries a high risk of PCP during the course of the disease and is often fatal. Thus, the prevention and early diagnosis of PCP is important. When treating ectopic ACTH syndrome with concomitant PCP, the therapeutic management should gradually correct hypercortisolemia and prevent immune reconstitution and the exacerbation of PCP.

The authors state that they have no Conflict of Interest (COI).

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