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A Case of Ectopic ACTH Syndrome Associated with Small Cell Lung Cancer

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= 국문초록 =

소세포폐암에 동반된 이소성 ACTH 증후군 1예

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송현주 · 유금혜 · 김수현 · 윤수진 · 김도연 · 임석아 · 성주명 · 구혜수* · 이순남

이소성 ACTH(adrenocorticotropic hormone)증후군은 ACTH를 분비하는 비뇌하수체종양으로 고코르티졸혈증을 보인다. 소세포폐암에서 ACTH를 분비하는 부종양 증후군은 비교적 흔하지만, 임상적으로 의미있는 고코르티졸혈증은 1~5% 정도로 매우 드물다. 이소성 ACTH 증후군은 소세포폐암이 전형적인 쿠싱증후군이 나타나기도 전에 빨리 진행하므로 전형적인 월상안, 복부비만, 골다공증 등의 증상을 나타낼 때까지 생존하는 경우가 매우 드물며, 체중 감소, 부종, 근위축 등 비전형적인 임상 양상을 나타내어 신속히 진단하여 치료하기가 어렵다. 또한 이소성 ACTH 증후군에 의한 고코르티졸혈증은 항암제에 잘 반응하지 않고 치료 중에 소화기 궤양, 출혈, 천공, 폐렴 등의 치명적인 합병증이 동반되므로 평균 수명이 4개월 미만으로 예후가 매우 불량하다. 따라서, 소세포폐암에서 이소성 ACTH 증후군의 조기 발견 및 치료는 예후 향상을 위해 매우 중요하다. 이에 저자들은 61세의 비전형적인 쿠싱 증후군의 증상으로 발현된 진행성 소세포폐암의 환자에서 급격히 악화되는 임상 경과를 보인 1예를 경험하였기에 문헌 고찰과 함께 보고하는 바이다.

중심 단어 : 이소성 ACTH 증후군 · 소세포폐암 · 쿠싱 증후군.

Introduction

In small cell lung cancer(SCLC), the ectopic productions of antidiuretic hormone(ADH) and corticotropin(adrenocorticotropic hormone ; ACTH) are seen most frequently[1]. However, the biochemical evidence of hypercortisolism can be detected in up to 50% of partients, clinical Cushing's syndrome secondary to ectopic ACTH production is rare, approximately 1−5% of all SCLC patients[1)2)].

The clinical manifestrations of ectopic ACTH syndrome(EAS) are muscle weakness, weight loss, marked edema, glucose intolerance and hypokalemic metabolic alkalosis[2)]. Classical "Cushingoid" eatures may be abset in parients with SCLC and EAS due to the fact patients do not live long enough to develop the classical signs, such as moon faces, truncal obesity and red striae[1)]. Patients with EAS and SCLC have adverse porgnosis due to their large tumor burdens, the relative

lack of responsiveness of the tumors to cytotoxic chemotherapy and life threatening complications, mostly related to severe infection, gastrointestinal bleeding or ulceration[3].

Since first reported case of EAS associated with SCLC[4], several cases have reported in Korea and they were all died early (Table 1)[5-7]. We report a 61-year-old man who had rapidly progressive EAS associated with SCLC who presented with atypical Cushing's syndrome to emphasize on the early diagnosis and treatment of hypercortisolosm as well as SCLC.

Case Report

A 61-year-old man was referred to our hospital with generalized edema and cough which had started 1 week before admission. He had a history of heavy smoking (60pack years) and poorly controlled type II diabetes mellitus with insulin therapy for five years. He was 170cm in height and weighed 78kg, however, he did not lose in weight. His blood pressure was 110/70mmHg and his pulse rate was 80/min. The respiratory rate was 18/min and the body temperature was 36.5℃. Physical examination revealed acute ill-looking appearance, slightly anemic conjunctivae and no icteric sclerae. There was no lymphadenopathy. Coarse breathing sounds with rhonchi and crackles were audible in both lung fields. The heart rhythm was regular without murmurs. His abdomen was soft and distended with shifting dullness. He didn't have Cushingoid appearance nor hyperpigmentations, but had generalized edema.

Laboratory data revealed hemoglobin 9.3g/dL, hematocrit 26.7%, white blood cell count 9,100/mm^3 (polymorphoneuclear leukocytes 90.7%, lymphocytes 8.0%, monocytes 0.8%, eosinophils 0.1%) and platelet 71,000/mm^3, respectively. The peripheral blood smear showed normocytic normochromic anemia. Arterial blood gases with the patient breathing room air revealed severe metabolic alkalosis with profound hypoxemia and hypercapnea (pH 7.571, PaO_2 51.3mmHg, $PaCO_2$ 51.3mmHg, HCO_3 47.5mmol/L and SaO_2 89.7%). The serum sodium level was 141mmol/L ; potassium, 2.4mmol/L ; chloride, 90mmol/L ; bicarbonate, 43mEq/L ; serum albumin, 3.2g/dL ; total calcium, 8.4mg/dL ; ionized calcium, 3.9mg/dL ; fasting glucose, 239mg/dL ; blood urea nitrogen, 21.5mg/dL ; and creatinine, 1.2 mg/dL. 24hour urine protein was 460mg/day and 24 hour urine creatinine was 1,225mg/day. The porfiles of disseminated ingravascular coagulation were positive (prothrombin time, 104% ; aPTT, 24.6sec ; fibrinogen, 407mg/dL ; FDP, above 20μg/mL ; and D-dimer, above 1 μg/mL). Tumor markers were increased ; NSE (neuron specific enolase) was 189.19 (normal 4.7−14.7) ng/mL ; CEA, 38.7 (normal 0−5) ng/mL ; CA19−9, 248.5 (normal 0−37) U/mL ; and LDH (lactate dehydrogenase), 2,882 (normal 100−450) U/L.

Plasma renin (0.2ng/mL/h, normal 0.2−2.8ng/mL/h) and aldosterone (7.5ng/dL, normal 1−16ng/dL) levels

Table 1. Clinical characteristics of ectopic ACTH syndrome associated with small cell lung cancer in Korea

Case	Sex/ age	Presenting symptom	K^+ (mEq/L)	ACTH (pg/ml)	Treatment	Outcome
Kim et al[4] (1987)	M/65	Dyspnea, generalized edema	1.2	550	Spironolactone, K^+ supply	Against discharge due to poor cooperation
Kim et al[5] (1990)	F/58	Generalized edema, muscle weakness, hyperpigmentation	2.0	1172.3	Spironolactone, K^+ supply	Expired on the 12th day of admission due to sepsis
Kwak et al[6] (1995)	M/59	Hemoptysis, dyspnea, general weakness, weight loss	2.7	11.5	K^+ supply Ketoconazol, CAV chemotherapy	Expired 1 month after admission due to ARDS
Kim et al[7] (1997)	M/69	Chest discomfort, dyspnea, facial edema	1.9	195	VIP chemotherapy	Expired 2 month after chemotherapy due to sepsis
Present case[4] (2003)	M/61	Gereralized edema, dyspnea	2.4	288.9	Spironolactone, K^+ supply	Exipired on the 17th day of admission due to ARDS

CAV : Cyclophosphamide, doxorubicin, vincristine, VIP : Etoposide, ifosfamide, cisplatin, ARDS : Acute respiratory distress syndrome

were within the normal range. However, plasma ACTH (288.9pg/mL, normal 6−60pg/mL) and cortisol (245.1 μg/dL, normal 5−251 μg/dL) levels were markedly increased. These findings suggested ectopic ACTH productions. Therefore no high dose dexamethasone suppression test nor 24 hour free cortisol level were performed.

On admission, the chest X-ray showed emphysematous changes with ill-defined primary lung lesion in right lower lung zone masked by liver shadow. Chest CT scan taken two days before admission showed ill-defined mass-like lesions in the right lower lung and ascites were seen in abdomen CT scan. Both adrenal glands and pancreas showed normal findings. Further evaluations like brain CT scan and bone scan were impossible, because he rapidly fell down to acute respiratory distress.

Lung biopsy was not available due to acute respiratory failure. But bone marrow biopsy was done on the 4th day of admission, for suspicious bone marrow involvement with normocytic anemia and thrombocytopenia. Atypical, multifocal, small round and hyperchromatic cells occupied bone marrow suggesting metastatic small cell lung cancer (Fig. 1A). Immunohistochemical staining for ACTH showed positive findings which confirmed the productions of ACTH by the metastatic tumor cells in the bone marrow (Fig. 1B).

On the 4th day of admission, he fell to acute respiratory distress and required mechanical ventilation. A chest radiography showed normal sized cardiac shadow, but new bilateral reticulonodular infiltrates in both lung fields were definitely suggestive of acute respiratory destress syndrome. Metabolic alkalosis, hypokalemia and generalized edema were somewhat controlled by spironolactone, which was increased dose from 100 mg/day to 200mg/day via the nasogastric tube. In addition, 200 mmols of intravenous potassium per day were supplied during the ventrilator care. After the diagnosis, even he was still on ventilator, cytotoxic chemotherapy was under consideration. But pneumonia and sepsis with the fever made it impossible. In spite of conservative management like antibiotic and mechanical ventilator, life threatening complications were beyond control. After all, he died on the 17th day of admission due to rapid progressive respiratory distress, pneumonia, upper gastrointestinal bleeding and disseminated intravascular coagulation before the initiation of chemotherapy.

Discussion

In 1928, Brown first reported oat-cell lung carcinoma associated with Cushing's syndrome, presented as hyperpigmentation, hyperglycemia, hypertension, weakness and numbness of the legs and adrenal hyperplasia[8]. At that time, no pathogenic explanation was offered between the neoplasm and the other disorder. The term "EAS" was introduced in 1696 when Liddle, et al. demonstrated the presence of corticotropin in the blood[9].

EAS with Cushing's syndrome is associated with mostly neuroendocrine tumors. Bronchial carcinoid was the most frequent cause of EAS, followed by islet cell

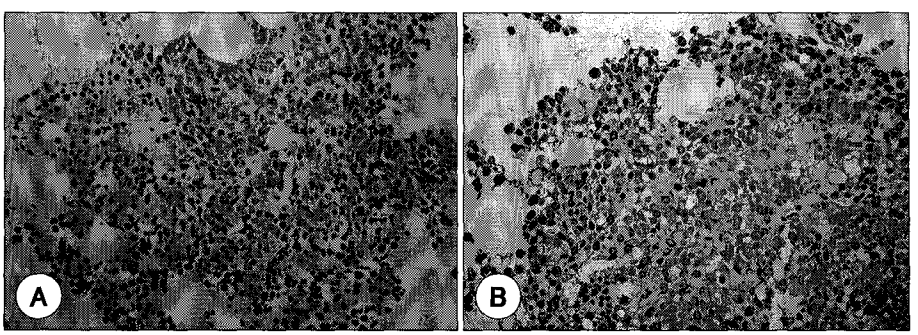

Fig. 1. A : Bone marrow biopsy shows diffusely scattered, mutifocal, small round and hyperchromatic cells, which are suggestive of metastatic small cell lung cancer (H & E ×400). B : ACTH immunohistochemical stain shows purplish brown cytoplasmic granules of the tumor cells in the bone marrow (×400).

cancer(16%), SCLC(11%), medullary thyroid carcinoma(8%), disseminated neuroendocrine tumor of unknown primary origin(7%), thymic carcinoid(5%), pheochromocytoma(3%), disseminated gastrointestinal carcinoid(1%), and other tumors(8%). No tumor was found in 16% of patients[10].

Gender distribution showed male to female is about 2 to 1[1], but in Korea more predominant in male at the ration of 4 to 1[4-7]. The clinical presentations of Cushing's syndrome is atypical with muscle wasting and weight loss being more frequently observed than the classic signs of hypercortisolism, such as moon faces, trucal obesity and red striae due to the fact the patients do not live long enough to develop the classical signs[11]. If the patients with SCLC have muscle weakness, weight loss, marked edema, glucose intolerance of hypokalemic metabolic alkalosis, he should be highly suspicious of EAS[11].

If EAS is suspicious, radiologic and biochemical confirmations are essential to detect the extrapituitary source of ACTH[11]. The clinical criterias that support the diagnosis of EAS are 1) signs and symptoms of Cushing's syndrome, 2) increased serum and urine cortisol levels, 3) increased or high-normal plasma concentration of ACTH, and 4) absence of other know cause of Cushing's syndrome(e.g., pituitary tumor)[10]. The definitive diagnosis requires positive immunostaining for ACTH in a nonpituitary neoplasm or cure of Chshing's syndrome after resection of nonpituitary neoplasm[10]. In our case, uncontrolled hyperglycemia, generalized edema, hypokalemia and metabolic alkalosis were en-ough to doubt about EAS. Plasma ACTH and cortisol levels were increased and positive immunohistochemical staining for ACTH of metastatic tumor cells in bone marrow biopsy confirmed EAS. ACTH producing primary pituitary tmor can be ruled out for the differences of histologic findings and adrenal gland tumor also ruled out. Plasma ACTH level does not necessarily correlate directly with tumor burden, and relapse of hormine secreting tumor after response is not always accompanied by resmption of hormone secretion, so ACTH can not be used as as tumor marker[1].

Most frequent sites of metastasis in SCLC with paraneoplastic syndrome were lymph nodes(100%), other sites within lungs(86%), liver(82%). Bone marrow (71%), adrenal glands(50%) and others. Compared with patients who did not have paraneoplastic syndromes, those with paraneoplastic syndrome had significantly more extensive metastases to bone marrow, but the metastasis to central nervous system was less frequent and less extensive[12]. We couldn't confirm metastasis to central nervous system, because he was on ventilator.

The ideal treatment of the EAS is removal of the ectopic source of ACTH. However, the malignant ACTH-secreting tumors are mostly unresectable, treatments of targeting the adrenal glands(bliateral adrenalectomy or adrenolytic drugs) are necessary when the source of ACTH cannot be removed[10][11]. Control of cortisol secretion at least 1 to 2 weeks before chemotherpy may improve the prognosis[2][11]. The use of high doses of inhibitors of steroid biosynthesis should be considered as the first line of treatment given a few weeks before cytotoxic chemotherapy[11]. Ketoconazole can be expected clinical improvement in hypokalemia, metabolic alkalosis, diabetes mellitus and hypertension in most patients with EAS. Alternative therapy for Cushing's syndrome include metyrapone, aminoglutethimide, somatostatin analogs, adrenal ablation by mitotane, or embolization. But ketoconazole is most effective and fewer toxicites than these treatments[13]. Combined threatment of ketoconazole and octreotide had an additive effect in treatment of severe adrenocorticotropin-dependent hypercortisolism[14].

Patients with the EAS at initial presentation of SCLC had shorter survivial(median, 4 months) than did those diagnosed later during the course of their SCLC(median, 11.9 months)[11][15]. Eventhough the reason for the short survivial of patients with SCLC and EAS is not clear, hypercortisolism may play an important role in the poor outcome and the early mortality[15]. Complications include gastrointestinal ulceration, bleeding or perforation, pneumonia, septic shock and fungal infections[1]. Opportunistic infections with simultaneuos *Pneumocystis carnii* pneumonitis, *cytomegalovirus* pneumonitis and disseminated aspergillosis were reported[16]. Poor prognosis factors include uncontrolled Cushing's syndrome, poor performance status, reduced hemglobin con-

cerntraions, increased LDH level, stage of disease and bone marrow involvement[2]. After all, early treatment of hypercortisolism in patients with EAS and SCLC may prolong survivial and impove the quality of life[17].

Summary

We report a case of extensive stage SCLC with EAS confirmed by immunohistochemical stain of ACTH in tumor cells who died early due to rapidly progressive acute respiratory distress and pneumonia before the start of chemotherapy and corticosteroid blocking agent. Through our case, we learn how important early diagnosis and treatment of EAS associated with SCLC are and hope to apply to other cases from now on.

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