NOTE

Marked Increase in Plasma ACTH with Tumor Reduction after Chemotherapy in Ectopic ACTH Syndrome

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Abstract. We report on a case of rapid and marked hormone release as a result of rapid tumor reduction due to chemotherapy in a 36-year-old woman with ectopic ACTH syndrome due to small cell lung cancer. Treatment of the cancer with cisplatin and etoposide resulted in an 80% reduction in tumor size on computed tomographic scan within two weeks. Concurrently, plasma ACTH exhibited an unexpected and astonishing increase from 373 pg/ml before treatment to more than 1200 pg/ml. There were no biochemical characteristics observed in tumor lysis syndrome of solid tumors such as azotemia, increased LDH and hyperkalemia. The present case indicates that anticancer chemotherapy instituted in patients with ectopic ACTH syndrome could result in an acute increase of plasma ACTH and exacerbation of hypercortisolism, similar to tumor lysis syndrome, which is a potentially fatal complication following anti-cancer chemotherapy.

Key words: Small cell lung carcinoma, Ectopic ACTH syndrome, Tumor lysis syndrome

THE association of Cushing's syndrome with small cell lung cancer (SCLC) was first described by Brown in 1928 [1]. Ectopic ACTH syndrome occurs in approximately 2% of SCLC [2, 3]. In most cases, plasma ACTH decreases in patients who respond to chemotherapy. In this report we present a patient with ectopic ACTH syndrome resulting from SCLC, in whom treatment with cisplatin and etoposide resulted in a rapid and marked increase in plasma ACTH and cortisol, in spite of significant tumor reduction. The present case consequently indicated that careful observation of hormonal response was important when anti-cancer chemotherapy is instituted in patients with ectopic ACTH syndrome. Furthermore, the possibility of a variant form of tumor lysis syndrome in an ectopic hormone producing tumor is discussed.

Case report

A 36-year-old woman was admitted to the hospital because of dry cough, hypertension and edema in July, 1995. She had been well until hypertension was first noted a year before admission. Physical examination revealed palpable left axillary lymph nodes and bilateral pretibial edema. Typical cushingoid features were not present. Blood pressure was 190/110 mm Hg. Urinary excretion of free cortisol was greatly increased (1127 μg/day). High plasma ACTH levels ranging from 255 to 393 pg/ml were noted without normal diurnal variation (Table 1). Serum cortisol at 08:00 h was 17.6 μg/dl after an overnight 8 mg dexamethasone suppression test (Table 1). Plasma ACTH showed a blunted response to corticotropin-releasing hormone (100 μg i.v.) test (Table 1). Both a computed tomographic (CT) scan and a magnetic resonance imaging scan revealed a normal pituitary gland. A CT scan of the chest showed a solid mass in the pulmonary hilum and stenotic left main bronchus. Bronchoscopy with
biopsy confirmed SCLC, and the authors finally diagnosed the patient as SCLC with ectopic ACTH production. Initial treatment with a combination of cyclophosphamide, doxorubicin and vincristine (CAV) failed to reduce the tumor. Although metyrapone was also administered to ameliorate hypercortisolism, it was discontinued because of the development of liver dysfunction. A second therapeutic trial with cisplatin and etoposide (PVP) (cisplatin 80 mg/m² d.i.v. day 1 and etoposide 100 mg/m² d.i.v. day 1, 2 and 3) was initiated, and an approximately 80% reduction in the size of the tumor was confirmed by CT scan obtained on the 11th day after PVP treatment (Fig. 1). After the treatment, and coincident with tumor reduction, plasma ACTH and cortisol exhibited an unexpected and astonishing increase from 373 pg/ml and 13.7 μg/dl before treatment, to 687 pg/ml and 59.6 μg/dl on the 5th day after PVP treatment and exceeded 1200 pg/ml and 99.4 μg/dl on the 12th day after PVP, respectively. These hormone data on 5th and 12th day were revealed on the 11th day and after death, respectively. Some relevant biochemical laboratory data before and after PVP treatment are shown in Table 3. On the 5th and 12th days, hypokalemia and alkalosis were noted. At that time, she became depressed, possibly due to severe hypercortisolism. Although metyrapone was readministered immediately after confirming the rise in plasma ACTH and this unusual sudden exacerbation of hypercortisolism, she committed suicide on the 18th PVP treatment day (Fig. 2). The tumor tissues obtained at autopsy were strongly positive for ACTH immunostaining, and also positive for chromogranin.

**Discussion**

PVP and CAV regimen are widely applied for SCLC. In the present case, PVP resulted in an 80%
reduction in the size of the tumor as seen on CT scan although CAV was not effective. There have been few reports in the literature regarding the impact of chemotherapy in patients with SCLC and ectopic ACTH syndrome.

In hormone producing tumors, monitoring the plasma hormone levels, in addition to radiological evaluation, can be a useful in determining tumor response to chemotherapy. It is generally thought that reduction of the tumor size finally results in a decrease in the plasma hormone level, although it may exhibit a transient rise in the process of disruption [4–7]. Gropp et al [7] reported that serial determinations of ACTH revealed a simple decline in the hormone level in patients with ACTH-producing SCLC after successful chemotherapy. In the present case we also expected a decrease in plasma ACTH when the 80% reduction in tumor size was noted, but we unexpectedly found 3 to 4 fold increases in plasma ACTH levels after the treatment for about two weeks. A few other similar cases, although mild, are described in the literature [6, 8, 9]. Hoffman et al [8] reported, in a patient with ectopic ACTH syndrome due to SCLC, a transient increase in plasma ACTH from 440 pg/ml to 760 pg/ml despite tumor reduction after the treatment with etoposide for a week. Furthermore, in a case of SCLC with simultaneous production of ACTH and ADH reported by Abeloff et al [9], the ACTH excess symptom developed when the tumor had significantly regressed and SIADH had clinically disappeared due to combined chemotherapy with CAV. Based on these findings, they

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**Fig. 1.** Axial computed tomographic scans of the chest, showing the tumor, small cell lung carcinoma. A: 2 days before cisplatin and etoposide treatment. B: 11 days after cisplatin and etoposide treatment.

**Fig. 2.** Changes in plasma ACTH and cortisol levels. CAV: Treatment with cyclophosphamide, doxorubicin and vincristine. PVP: Treatment with cisplatin and etoposide.
postulated that the cytotoxic chemotherapy was successful in eradicating a population of cells that produced ADH, but that another group of cells, which had the capacity to produce biological active ACTH, persisted or emerged.

Tumor lysis syndrome is a potentially fatal complication of anti-cancer therapy that is usually seen in patients with bulky, rapidly proliferating, treatmentsensitive tumors [10]. The biochemical and clinical hallmarks of tumor lysis syndrome occur as a result of rapid tumor necrosis with release of intracellular ions and metabolic byproducts due to the initiation of effective chemotherapy [11]. Although the majority of cases of tumor lysis syndrome have been reported in hematologic malignancies, about 25 cases of tumor lysis syndrome due to solid tumors, including 5 cases of SCLC, have been reported [10, 12-15], but there have been no reports on tumor lysis syndrome in ectopic hormone producing tumors. The present case did not exhibit any biochemical characteristics of tumor lysis syndrome observed in solid tumor, that is, azotemia, increased LDH, hyperkalemia, hypocalcemia and metabolic acidosis, excluding hyperuricemia and hyperphosphatemia which were not measured (Table 2). Although it remains to be possible that hypercortisolemia due to a rise in plasma ACTH might mask hyperkalemia and acidosis, the present case was not a case of typical tumor lysis syndrome, but it seems likely that the abrupt increase in plasma ACTH in the present case, which resulted in a clinically serious condition, is caused by lysis of tumor cells so that tumor lysis in an ectopic hormone(s) producing tumor due to chemotherapy could result in serum hormone increase alone. And the present case could be such a condition, a variant form of tumor lysis syndrome. On the other hand, it is expected that high plasma ACTH due to tumor reduction finally reaches the normal range, but it is very difficult to explain the prolonged (2 weeks) increased plasma ACTH, taking into account the very short half life of plasma ACTH. There was no specific pathological findings in the present case. The incidence of tumor lysis syndrome with SCLC after chemotherapy was very low; one in 86-300 patients [12, 13], and no specific histological findings have not been reported in previous papers. Tumor size, hormone content and other unknown factors might be associated with such a phenomenon, but mechanism remains to be clarified.

In conclusion, it is clinically important to note the possibility of prolonged very high plasma ACTH and exacerbation of hypercortisolism when anti-cancer chemotherapy is instituted in patients with ectopic ACTH syndrome. In such cases, hypokalemia and metabolic alkalosis must be early clinical hallmarks, since it takes several days for the determination of hormone data.

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References