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A Case of Cervical Carcinoma of the Uterus Presenting with Hyperosmolar Non-ketotic Coma as a Manifestation of Ectopic Adrenocorticotropic Hormone Syndrome

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A case of advanced cervical carcinoma of the uterus with ectopic adrenocorticotrophic hormone (ACTH) syndrome is described. The patient was seen for general malaise 21 months after surgical treatment of the primary lesion whose histology was undifferentiated small cell carcinoma of the uterine cervix. She had extensive metastases in the liver and the abdominal wall. In addition to the typical clinical manifestations of Cushing's syndrome such as moon face, central obesity and acne vulgaris, hyperglycemia was so severe that she was in a hyperosmolar non-ketotic coma. Endocrinological examinations revealed elevated plasma ACTH and cortisol, and urinary excretion of 17-hydroxycorticosteroids and 17-ketosteroids, which were not suppressed by high-dose dexamethasone administration. Based on these clinical and laboratory findings, a diagnosis of ectopic ACTH syndrome was made. Among the results of other endocrinological examinations conducted to find the etiological cause of the hyperglycemic coma, which seemed to be unusual for ectopic ACTH syndrome, the plasma somatostatin level was abnormally high. Metastatic tumors in the liver obtained at the time of autopsy contained large amounts of both ACTH and somatostatin, and gel filtration studies revealed that the peptides produced by the tumor had the molecular sizes of the biologically active forms of the respective peptides. These observations suggest possible involvement of the somatostatin in deteriorating glucose intolerance to develop hyperglycemic hyperosmolar non-ketotic coma as a drastic disturbance of metabolism.

Key words: Cushing syndrome — Ectopic ACTH production — Cervical carcinoma of the uterus — Hyperglycemic hyperosmolar non-ketotic coma — Somatostatin

Adrenocorticotrophic hormone (ACTH) production by tumor cells has been a well-documented endocrinological abnormality in patients with malignant diseases since 5 cases of small cell lung carcinoma (SCLC) presenting ectopic ACTH syndrome were first described in 1962.[1] Accumulated clinical and laboratory observations concerning ectopic ACTH production by neoplastic cells may be summarized as follows: i) about half of all cases of ectopic ACTH syndrome are caused by SCLC[2]; ii) although immunoreactive (IR-) ACTH is detected in extracts of the primary lung cancer in almost all cases, clinical manifestation caused by overproduction of the hormone is very rare[3]; iii) other neoplastic diseases which often cause ectopic ACTH syndrome include thymoma, bronchial and gastro-intestinal carcinoid, pancreatic islet-cell tumor and medullary thyroid carcinoma[4,5]; iv) the concept of amine precursor uptake and decarboxylation (APUD) cells which are proposed as deriving embryologically from neural crest ectoderm, is widely accepted to explain the common feature of ACTH production by neoplasms arising from these various organs[6]; v) ACTH-producing tumors usually synthesize β-lipotropin (β-LPH), γ-LPH and β-endorphin deriving from a common precursor called proopiomelanocortin (POMC)[7,8]; vi) in addition to POMC-derived peptides, many ACTH-producing tumors produce calcitonin, gastrin-releasing peptide (GRP), somatostatin and arginine vasopressin as well, but their clinical significance is unknown.[9–12]

Although IR-ACTH has been demonstrated rather often in surgically resected specimens of undifferentiated or small cell carcinoma of the uterine cervix,[13] clinical manifestation of ACTH overproduction has been reported in only 4 cases.[14–17] We describe here a case of small cell carcinoma of the uterine cervix presenting with both ectopic ACTH syndrome and hyperglycemic hyperosmolar non-ketotic coma. Impaired glucose tolerance is one of the common features of hypercortisolemia, but hyperglycemic hyperosmolar non-ketotic coma in a patient with Cushing's syndrome is very rare.[18] We sought other pathophysiological changes which might cause deterioration of glucose tolerance, other than ACTH overproduction, and found elevated amounts of somatostatin in plasma and tumor tissue.

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CASE REPORT

A 35-year-old Japanese woman was operated for the treatment of stage I-b cervical carcinoma of the uterus on August 31, 1988, at Nihon University Hospital at Itabashi. Pathological examination revealed a small cell undifferentiated carcinoma of the uterine cervix.[19] She received 50 Gy of adjuvant radiotherapy to her lower abdomen. Laboratory tests, including those for serum electrolytes, liver and renal function and blood glucose level were normal at the time of surgery. Eight months after the operation, she experienced local recurrence with intrapelvic metastasis and received 18 Gy of intracavital radiotherapy. She was referred to our hospital in June 1989. Her blood pressure was 120/80 mmHg, and results of laboratory tests including those for serum electrolytes, and blood glucose level and urinalysis were normal. She had no family history of diabetes mellitus. One cycle of CAP (cyclophosphamide 600 mg, adriamycin 50 mg and *cis*-platinum 80 mg) was administered intravenously in August and was followed by intermittent oral administration of 50 mg of etoposide per day for 6 months. In April 1990, metastatic nodules appeared on the left lower abdominal wall and progressed rapidly. A CT scan of the liver at this time showed a huge metastatic nodule in the left lobe (Fig. 1). A biopsy specimen was taken from the skin lesion and diagnosed as metastatic small cell carcinoma from the uterine cervix. Moon face, acne vulgaris on her face and severe edema in her lower extremities were noted. Oral administration of 40 mg of furosemide per day was started on April 27, 1990. Daily urinary output was said to be 3000–4000 ml with severe polydipsia. She was admitted to our hospital on May 7, 1990, because of general malaise and loss of appetite. She was comatose and severely dehydrated. Blood glucose was 605 mg/dl; serum osmolarity, 373.8 mOsm/liter; serum Na, 164 mEq/liter; K, 3.3 mEq/liter; Cl, 112 mEq/liter. A trace amount of ketone bodies in urine was detected. A diagnosis of hyperglycemic hyperosmolar non-ketotic coma was made and insulin administration was immediately started. Based on these clinical manifestations and metabolic abnormalities, ectopic ACTH syndrome was suggested and endocrinological examinations were carried out when the hyperosmolar state was brought under control. Plasma ACTH and cortisol levels were high and diurnal rhythm was not observed (Fig. 2).

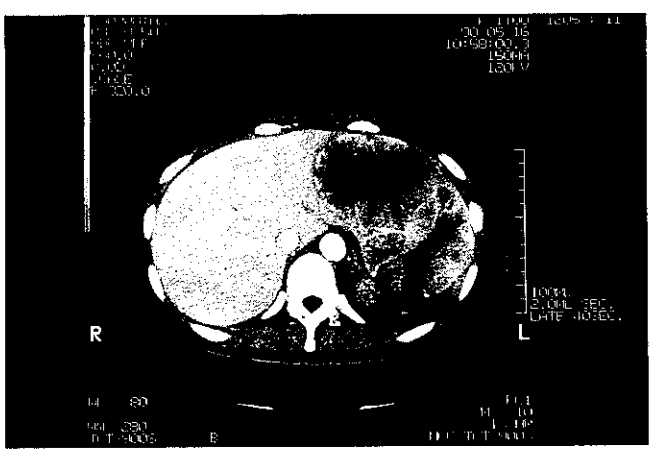

Fig. 1. Abdominal CT scan revealing a huge metastatic lesion in the left lateral segment of the liver.

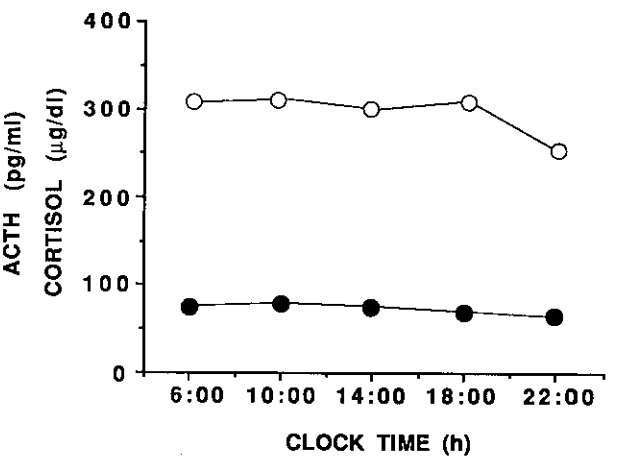

Fig. 2. Loss of diurnal rhythm of plasma ACTH (●) and cortisol (○) levels.

Table I. Results of the Standard Dexamethasone Suppression Test.

Day	Dexamethasone (mg/day)	Plasma cortisol at 6 a.m.[a)]	Urinary 17-OHCS[b)]	Urinary 17-KS[c)]
1	0	ND[d)]	38.8	21.1
2	0	68.5	39.5	21.0
3	2	60.0	46.0	18.3
4	2	76.6	31.0	22.7
5	8	76.6	33.7	19.1
6	8	59.0	23.6	20.0
7	0	64.6	24.2	19.0
8	0	ND[d)]	27.6	17.5
9	0	78.4	20.3	12.0
10	0	78.8	20.6	12.4

a) Normal range: 7–16 μg/dl.
b) Normal range: 3.9–8.6 mg/day.
c) Normal range: 4.1–12.8 mg/day.
d) Not determined.

Urinary excretion of 17-hydroxycorticosteroids (17-OHCS) and 17-ketosteroids (17-KS) was increased. The standard dexamethasone test failed to suppress plasma cortisol and urinary excretion of the cortisol metabolites (Table I). A brain CT scan and a cranial radiograph did not show an enlarged pituitary gland. These findings supported a diagnosis of Cushing's syndrome caused by overproduction of ACTH, probably from the tumor. Because hyperglycemic hyperosmolar non-ketotic coma seems to be unusual for ectopic ACTH syndrome, other diabetogenic hormones were measured. Plasma levels of glucagon, growth hormone and catecholamines were within normal ranges. The plasma level of somatostatin, however, was 505.2 pg/ml which is more than 6 times the normal value (39.4–81.6 pg/ml). The patient died of severe pneumonia on July 15, 1990, and autopsy was authorized.

The autopsy revealed bilateral hypertrophy of the adrenal cortex; the glands weighed 10.7 g (right), and 10.5 g (left). Multiple metastases were noted macroscopically in the liver and abdominal wall. Histological examination of the liver tumor revealed small cell carcinoma, metastasized from the uterine cervix. The pancreas was normal both macroscopically and microscopically. The pituitary gland was not examined.

MATERIALS AND METHODS

Tumors and their extract Metastatic tumors in the liver were obtained at autopsy and were quickly frozen and stored at −80°C. The frozen tissues were minced into small pieces and heated at 95°C for 30 min in 0.1 *M* acetic acid. The mince was homogenized with a Polytron homogenizer and centrifuged at 10,000*g* for 30 min.[20] The supernatant was frozen in aliquots at -20°C until the time of radioimmunoassay (RIA).

RIAs The ACTH RIA used anti-ACTH serum which was raised in a rabbit immunized with synthetic ACTH (1-24). Synthetic human ACTH(1-39) was used as a radioiodinated tracer and reference standard. The characteristics of the assay were reported previously.[21] Plasma ACTH and cortisol were determined with commercially available kits. The somatostatin RIA used anti-somatostatin serum (OAL-202) which was raised in a rabbit immunized with synthetic somatostatin(1-14). Synthetic Nα-Tyr-somatostatin was used as the radioiodinated tracer.

Gel filtration A Sephadex G-50 (fine) column (1×45 cm) was equilibrated with 0.1 *M* sodium phosphate buffer (pH 7.4) containing 0.1% bovine serum albumin and 0.1% sodium azide, and eluted at a flow rate of 5 ml/h at 4°C.[10] Fractions of 1 ml each were collected and stored frozen at −20°C until the time of RIA.

RESULTS

Peptide immunoreactivities in the tumor tissue The amounts of IR-ACTH and IR-somatostatin were 100.6 and 37.0 ng/g wet weight tissue, respectively. Arginine vasopressin, corticotropin-releasing factor, GRP and glucagon were not detected in the tissue extract of the liver metastases.

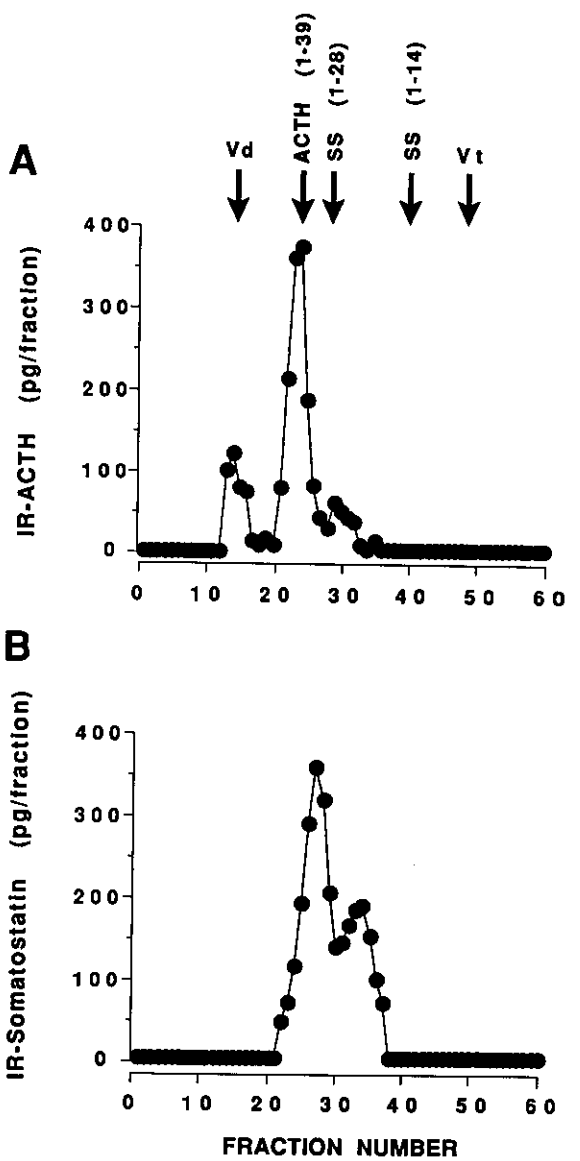

Fig. 3. Gel filtration patterns of IR-ACTH (A) and IR-somatostatin (B) in an extract prepared from metastatic lesions in the liver. Shown at the top are substances used as markers. Vd, void volume; Vt, total volume; SS, somatastatin.

Gel filtration profile of IR-ACTH and somatostatin The gel filtration profile of the tumor extract from the liver metastases is shown in Fig. 3. There are obviously 3 peaks of IR-ACTH, peak 1 in the void volume, peak 2 at the position where ACTH(1-39) was eluted and peak 3 eluted at a position slightly behind the authentic ACTH. IR-somatostatin showed 2 peaks which eluted so closely that they fused with each other. The larger molecule, coeluted at the position corresponding to that of somatostatin(1-28) was presumed to be the active form of this hormone. No IR-somatostatin was recovered in fractions where somatostatin(1-14) was eluted as a molecular size indicator.

DISCUSSION

In the present case, diagnosis of ectopic ACTH syndrome was confirmed by demonstrating elevated levels of serum ACTH and cortisol and urinary secretion of 17-OHCS and 17-KS, which were not suppressed by dexamethasone administration, and the high IR-ACTH content of the extract of liver metastases. One outstanding clinical feature of this case is that diabetes mellitus was so severe that the patient went into a hyperglycemic hyperosmolar non-ketotic coma. Although impairment of glucose tolerance is exhibited in 94% of patients with Cushing's syndrome regardless of the etiology, frank diabetes is observed in only 15% of the patients.[22] Hence, it appears that hyperglycemic hyperosmolar non-ketotic coma in patients with Cushing's syndrome is unusual. Actually, only one patient with this complication of Cushing's disease (pituitary adenoma producing ACTH) has been reported in the literature.[18] It is worth noting that somatostatin was also produced and secreted in a very large amount by the tumor and this hormone might have been involved in the pathogenesis of hyperglycemic hyperosmolar non-ketotic coma in the present case. It is known that overproduction of somatostatin by itself causes diabetes mellitus, as is observed in patients with somatostatinoma.[23, 24] Somatostatin inhibits the secretion of insulin and glucagon when administered exogenously.[25–27] Although blood glucose concentration declines sharply after somatostatin injection, owing to the inhibition of glucagon secretion, sustained inhibition of insulin secretion causes hyperglycemia in chronic somatostatin exposure and this is thought to be the cause of impaired glucose tolerance in patients with somatostatinoma.[27, 28] In the present case, somatostatin (1-28) which is presumed to be biologically active, was demonstrated in the gel filtration study of the tumor extract. The molecular size of somatostatin produced by the tumor of this patient is in good accordance with a previous report.[29] It is therefore reasonable to regard the somatostatin produced by the tumor as qualitatively intact. However, the rapid and unstable clinical course of the patient did not allow us to demonstrate impaired response of insulin secretion to glucose administration and we lack direct evidence to support the causative involvement of somatostatin in the development of hyperosmolar coma.

The gel filtration profile of IR-ACTH showed molecular size heterogeneity, which is a well-documented observation among ectopic ACTH-producing tumors.[3] The peak eluted in the void volume, presumed to have a molecular weight above 3×10^4 daltons, seems to be POMC, the precursor form of ACTH-related peptides. The second peak seems to be ACTH(1-39). The third peak appears to be a fragment of ACTH. It has been shown that ectopic ACTH-producing tumors also contain α-MSH or corticotropin-like intermediate lobe peptide (CLIP).[30, 31] Because the anti-ACTH antibody used in this study was raised by immunizing a rabbit with ACTH(1-24) and cross reacts with CLIP but not with α-MSH, the third peak may be CLIP.[21]

Cases of carcinoma of the uterine cervix presenting with ectopic ACTH syndrome are so rare that only 4 cases have been described in the literature since 1961.[14–17] Our report is the first to describe molecular size heterogeneity of ACTH in the tumor tissue of small cell carcinoma of the uterine cervix. As is observed with small cell carcinoma of the lung,[3] production of ACTH is frequently demonstrated in tumor tissues but clinical manifestation of Cushing's syndrome is rare.[13] A feature common to these 5 cases of cervical carcinoma presenting with ectopic ACTH syndrome is that the carcinomas are classified as small cell type or undifferentiated carcinoma. It is of interest to consider the biological characteristics common to small cell carcinoma of the uterine cervix and small cell carcinoma of the lung. Pearse described a type of cell which can take up and decarboxylate amino acid precursors of fluogenic amines, and named it APUD cell.[32] Tateishi *et al.*, in a study of 97 cases of invasive carcinoma of the cervix, found 5 cases of argyrophilic small cell carcinomas. Electron microscopic examination revealed that the cellular characteristics are consistent with those of neoplasms proposed to originate from APUD cells, such as medullary thyroid carcinomas, carcinoids, pancreatic islet-cell tumors and small cell carcinomas of the lung.[33]

Finally, the small cell type of cervical carcinoma of the uterus is notorious for its poor prognosis as compared with other histological types of this carcinoma.[34–36] Because there are biological features in small cell carcinoma of the uterine cervix in common with small cell carcinoma of the lung, which responds very well to combination chemotherapy, it seems to be reasonable to assess the effectiveness of chemotherapeutic agents systematically.

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