A Rare Case of Ectopic Antidiuretic Hormone-Producing Pancreatic Adenocarcinoma: New Diagnostic Approach

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We describe a 73-year-old man with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) due to an ectopic ADH-producing pancreatic adenocarcinoma. His laboratory findings showed marked hyponatremia, and the water load test showed uncontrolled ADH secretion. The imaging studies revealed pancreatic body cancer. Histological examination revealed an adenocarcinoma of the pancreas, which was positive for ADH immuno-staining. The ADH in the tumor extract was 53.3 pg/g wet weight. In attempt to diagnose ADH-production from the tumor, the ADH in his pancreatic juice was measured and found to be 2.1 pg/ml. We conclude that it is valid to measure the ADH in pancreatic juice to diagnose ectopic ADH production by tumors. (Internal Medicine 35: 280-284, 1996)

Key words: syndrome of inappropriate antidiuretic hormone secretion (SIADH), ectopic hormone secretion, pancreatic cancer, hyponatremia

Introduction

Malignancy-associated syndrome of inappropriate antidiuretic hormone secretion (SIADH) is most commonly seen in patients with small cell carcinoma of the lung. We describe here a rare case who presented SIADH induced by an ectopic ADH producing pancreatic adenocarcinoma. Furthermore, this is the first report in which ADH detected in pancreatic juice proved ectopic ADH production by the tumor.

Case Report

A 73-year-old man was admitted to our hospital in June 1994, because of body weight loss and sense of lassitude. He lost about 10 kg in the previous three months. His past history and family history were noncontributory.

His height was 150 cm and weight was 38 kg. His blood pressure was 110/70 mmHg, and pulse rate 80 beats/min. On physical examination, no abnormal skin pigmentation was noted. There was no edema over the lower extremities. The chest auscultation was normal. The heart sounds were normal. There was a mass, approximately 3x8 cm in diameter, with slight pulsation in the umbilical region. The ultrasonographic examination revealed that it was the abdominal aorta.

Hemoglobin level was 12.8 mg/dl, red blood cell count 416x10^6/mm^3, white blood cell count 4,800/mm^3 with 73% neutrophils, platelet count 14.4x10^4/mm^3. Serum sodium concentration was 119 mEq/l, potassium 3.7 mEq/l, and chloride 83 mEq/l, that revealed marked hyponatremia and hypochloridemia. Serum proteins were 6.1 g/dl, of which 3.7 g was albumin. Blood urea nitrogen and serum creatinine were normal. There were no abnormal findings in liver function tests except for a slight decrease in cholinesterase, 0.35 ΔpH. There were also no abnormal findings in several tumor marker tests including CA19-9. The urine volume was about 1,500 ml/day, and the urine was negative for protein and glucose, and had a specific gravity 1.017. The urine sediment was unremarkable. Urinary sodium excretion was excessive (130–160 mEq/day) in view of his hyponatremia.

The basal plasma adrenocorticotropic hormone (ACTH) and serum cortisol levels at 8:00 A.M. were high, 72 pg/ml and 22 μg/dl, respectively. The intravenous bolus injection of 250 μg ACTH₄₋₉ increased the serum cortisol level to 32.7 μg/dl at 30 minutes. Therefore, his adrenal gland was considered to be stimulated under the stressed condition, but not to be deficient. The serum levels of free T3, free T4, and thyrotropin were 1.0 pg/ml, 1.3 ng/dl and 0.73 μU/ml, respectively, consistent with findings of low T3 syndrome. Since there was no evidence of renal, adrenal
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or thyroidal dysfunction, SIADH was suspected as the cause of the hyponatremia.

The serum osmolality was low, 233 mOsm/kg·H₂O. The urine osmolality was 378 mOsm/kg·H₂O, that was higher than the plasma osmolality. Plasma ADH was 18.5 pg/ml, which was a high level in view of his hyponatremia. To diagnose SIADH, the water load test was performed with 5% glucose which was infused at 10 ml/kg B.W.·h for 2 hours, and blood samples were collected before and 30, 60, 90 and 120 minutes after the start of the infusion. The response of ADH to the osmotic changes are shown in Fig. 1. The ADH level did not decrease and kept an above-normal concentration under the condition of the suppression of serum osmolality. These results indicated that this case had SIADH (1).

A computed tomographic (CT) scan of the abdomen enhanced with contrast medium revealed a hypodense mass located in the pancreatic body, 4x2 cm in a diameter with irregular margin, infiltrating into the surrounding tissues, and the enlargement of para-aortic lymphonodi (Fig. 2). An endoscopic retrograde cholangiopancreatography (ERCP) revealed that the main pancreatic duct was cut off at the pancreatic body. Therefore, these findings suggested pancreatic body cancer.

The CT scans of the brain showed no evidence of metastatic lesions. But X-ray films and CT scans of the chest showed multiple nodules throughout both lung fields, indicating metastatic lesions of the lung. We considered this case not to be operable. The patient started water restriction with less than 1,000 ml of fluid per day, and the serum sodium concentration increased. He died in September 1994, and postmortem examination was performed.

Material and Method

Subjects

We performed ERCP in the present case, in two patients with cholelithiasis and in one with pancreatic adenocarcinoma. Before the regular procedure of ERCP, we collected 0.5–1 ml of pancreatic juice.

Treatment of samples

We measured ADH levels in plasma, pancreatic juice, and tumor extract. Each sample was pretreated as follows. 1) Blood sample for ADH was collected into a tube containing EDTA·2Na, immediately centrifuged at 4°C and stored at -20°C until extraction. The plasma was applied to a Sep-Pak-C 18 cartridge, washed with 4% acetic acid, eluted with methanol, and dried under nitrogen stream. 2) The pancreatic juice collected was immediately mixed with 10 mg EDTA-2Na and 500U aprotinin per ml sample, to protect the immunoreactivity of ADH from the proteolytic enzyme of the pancreatic juice. The extraction procedure of the pretreated pancreatic juice was the same as that of plasma. 3) Tumor tissues of the pancreas were obtained during the postmortem examination. A frozen section weighed about 100 mg was boiled in 1 ml of 1 N acetic acid to denature the endogenous proteolytic enzyme. It was homogenized and centrifuged at 4°C at 10,000 g for 30 minutes. The supernatant was collected in a glass tube and lyophilized. The dried extract was reconstituted with radioimmunoassay (RIA) buffer and subjected to a serial dilution and a gel filtration chromatography.
Gel filtration chromatography of tumor ADH

The gel filtration was performed using a 20 ml glass column packed with Sephadex G-25 resin (Pharmacia Fine Chemicals, Uppsala, Sweden) equilibrated earlier with RIA buffer. The sample containing the tumor extract was applied on this column in a single pass. The RIA buffer was used as the elution buffer, and 500 µl effluent fractions from the column were collected into tubes. The ADH levels of the fractions obtained were measured by ADH-RIA.

Measurement

The ADH RIA was performed using specific rabbit antiserum against arginine vasopressin. The minimum detection limit of the assay was 0.05 pg/tube (2).

Immunohistochemical staining

Tumor tissues obtained during the postmortem examination were fixed in 10% formalin and embedded in paraffin. Immunohistochemical staining were performed by the streptavidin-biotin method (Histofine, Nichirei Co., Ltd, Tokyo, Japan). Sections of 5 µm thickness were deparaffinized and then incubated for 20 minutes with the antiserum against ADH, which was also used for RIA and diluted at 1:1,000. Immunohistochemical staining with normal rabbit serum was also performed as a negative control, and a normal human pituitary gland obtained at another autopsy was stained with anti-ADH antiserum as a positive control.

Result

Autopsy findings

The tumor was located in the body of the pancreas with direct invasion of abdominal aortic adventitia and measured 5 cm in the largest diameter. The cut surface of the tumor showed marked fibrosis and necrosis. Metastasis to a peripancreatic lymph node was detected.

Histological findings

Microscopically, the tumor was composed of moderately differentiated tubular adenocarcinoma with marked fibrosis and necrosis, and numerous areas of perineural invasion were observed (Fig. 3). The immunohistochemical examination revealed that the tumor cells were positively stained for ADH in their cytoplasts (Fig. 4), and the staining of the tumor cells was a little weaker than that of normal posterior pituitary cells (data not shown). In addition, the staining of the same tumor cells with normal rabbit serum were negative (data not shown).

ADH in pancreatic juice

The ADH level in the pancreatic juice was 2.1 pg/ml; as shown in Table 1, the ADH level of three other control cases was less than 0.1 pg/ml. Therefore, the ADH level in pancreatic juice of the present case was considered to be elevated.

ADH in tumor

The ADH concentration in the pancreatic tumor extract was 53.3 pg/g wet weight, and its serial dilution was parallel to synthetic ADH standard curve (Fig. 5). The ADH concentration of the metastatic peripancreatic lymphnodus was 59.8 pg/g wet weight. Figure 6 shows the results of gel filtration chromatography of the pancreatic tumor extract. We detected two peaks of
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Figure 5. Immunoreactive ADH in tumor extract. The tumor was extracted as described in Materials and Methods, and diluted serially. Synthetic arginine vasopressin was used as the standard.

Figure 6. Gel filtration chromatography of the tumor extract. The tumor was extracted as described in Materials and Methods, and the extract was applied onto a Sephadex G-25 column. In order to determine the molecular weight, bovine serum albumin (BSA) and 125I-ADH were eluted separately.

IR-ADH. The latter large peak was identical to the fraction of 125I-ADH. From these results, we concluded that the tumor produced authentic ADH.

Discussion

The present case met the criteria for SIADH (1), and was diagnosed as ectopic ADH-producing pancreatic adenocarcinoma based on the ADH detected in the tumor tissue by both radioimmunoassay and immunohistochemistry.

Since Schwartz WB. et al first described SIADH associated with bronchial carcinoma (3), more than 50 cases of ectopic ADH-producing tumors have been reported in the last twenty years in Japan (4). In these reports, most of the malignancy-associated SIADH cases were caused by oat cell carcinoma of the lung, supporting “the amine precursor uptake and decarboxylation (APUD) concept” proposed by Pearse AGE in 1980 (5). In this concept, the carcinoma originates from APUD cells, for example, oat cell carcinoma of the lung, malignant thymoma, carcinoid, thyroid medullary carcinoma, and islet cell carcinoma, is often associated with the ectopic production of the APUD hormone of the same origin. This is one of the theories how tumor cells acquire the ability of hormone production (5, 6).

Among the twelve cases of SIADH with a malignant tumor of the digestive organs reported since 1970 in Japan (7–12), only five cases were associated with pancreatic carcinoma (10–12). Furthermore, in only one of these five cases, the ADH production was detected in the pancreatic tumor cells; in the other four cases, the situation that ADH may be released from the normal posterior pituitary rather than from the tumor, for example, involvement of the hypothalamus or stimulation of volume receptors by lung metastasis, is suspected (13). In a literature search, we could find only a few reports of ADH-producing pancreatic tumors (2, 14). Takabayashi K. et al reported an ectopic ADH production from undifferentiated small cell carcinoma of the pancreas which belongs to APUDoma (12). On the other hand, the pathological findings of the present case showed adenocarcinoma. Although there have been case reports of ADH-producing adenocarcinoma of the stomach, rectum or colon (7–9), an ADH-producing adenocarcinoma of pancreas has never been reported.

Diagnosis of the ectopic production of ADH from tumor tissue during lifetime is very difficult, because it requires ADH determination in the tumor tissue. Due to the prognosis, pancreatic carcinoma is often unresectable, and it is very difficult to obtain a tumor specimen in the lifetime of the patient. Therefore, various monitoring markers have been examined as possible useful indicators of an early diagnosis of the ectopic ADH production from tumor cells. It has been reported that the monitoring of the plasma level of atrial natriuretic peptides or neurophysin in a hyponatremic patient suspected to be associated with an ADH-producing tumor, was useful for early diagnosis of the tumor (6, 15). We first tried to measure the ADH level in pancreatic juice of the patient to diagnose the ADH production from the pancreas tumor cells. In the present case, the ADH level in the pancreatic juice was high enough, because the proteolytic enzymes of pancreatic juice, especially trypsin, digest ADH, and ADH must be undetectable. In fact, the ADH levels in the pancreatic juice of patients with other disorders were undetectable. The ADH level in the pancreatic juice of the present case was lower than that of his plasma level. Some reasons are raised to explain this contradiction. First, the pretreatment of the pancreatic juice might not be sufficient, and the proteolytic enzymes of the pancreatic juice may destroy the immunoreactivity of ADH. Secondly, the carcinoma cells secrete a relatively lesser amount of ADH into the pancreatic duct than into blood stream, and there may be no correlation between
the ADH levels in exocrine product of the tumor-associated organ and plasma, as reported between the tumor extract and plasma levels (16).

In summary, we described the first case of an ectopic ADH-producing pancreatic adenocarcinoma by detecting the ADH in pancreatic juice. It is valid in diagnosing an ectopic ADH-producing pancreatic tumor to measure the ADH level in pancreatic juice, when it is difficult to obtain a tumor specimen.

References