A Case of Islet Cell Tumor of the Pancreas

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Abstract: This report deals with a case of an islet cell tumor of the pancreas with surrounding direct lung and liver metastases in a 79-year-old male patient who showed hematemesis, melena, hypergastrinemia and multihormone hypersecretion. However, gastric acid secretion was normal and the secretin stimulation test was equivocal. The plasma insulin (IRI), and glucagon (IRG) levels were markedly elevated as well as gastrin, ACTH and PTH. Also, glucagon, secretin and somatostatin were detected in the tumor tissue whereas C-peptide, ACTH, β-MSH, VIP, motilin, gastrin and pancreatic polypeptide were not detected in that tissue. In the autopsy study, no adenoma, carcinoma and carcinoid were observed in the parathyroid, thyroid, adrenal cortex and renal cortex. Unfortunately, we could not obtain permission for the skull opening from his family. In addition, squamous cell carcinoma was found in the upper lobe of the right lung. Therefore, we came to the conclusion that the case was a multi-hormone producing islet cell carcinoma of the pancreas.

Key words: multi-hormone producing tumor, islet cell tumor.

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Introduction

In 1954, Wermer first reported a case of multiple endocrine adenomatosis as a familial syndrome.

Subsequently, this syndrome, so-called Wermer's syndrome, was classified as the islet cell tumor of the pancreas with which usually pituitary adenoma and parathyroid adenoma, and occasionally adrenal cortical adenoma, renal cortical adenoma, thyroid adenoma and carcinoid tumor were associated.

Some authors (Stacpoole et al., 1981) call this syndrome a multiple endocrine neoplasia type 1 (MEN-I).

Our case was a pancreatic islet cell carcinoma with multiple metastases, multiple petic ulcer, hypergastrinemia, hyperglucagonemia, hyperinsulinemia and high plasma levels of ACTH and PTH.

Although histologically, the direct invasion and metastases issued from primary lesion
of the islet cell carcinoma of the pancreas was recognized and the malignancy could not be observed in other endocrine organs, kidney and gastrointestinal tract, we were able to detect the three kinds of hormone including glucagon, secretin and somatostatin in the tumor tissues.

Therefore, we concluded that the case was a multi-hormone producing islet cell tumor of the pancreas.

Case Report

A 79-year-old Japanese man was admitted to our University Hospital on October 29, 1980, for evaluation and treatment of hematemesis. He was healthy until only a month previously, when general malaise, anorexia and paleness appeared and gradually increased in severity.

After the first attack of hematemesis resulting in a glass of blackish brown blood at ca. 4:00 A.M. and the second vomiting of a similar volume of old sanguineous fluid concomitantly with tarry stool at ca. 6:00 A.M. on Oct. 29, he visited our hospital as an out-patient at ca. 10:00 o'clock. No remarkable weight loss was reported and he was not suffering from diarrhea.

Two members in his family, his grandfather and son, suffered from a gastric ulcer.

In 1975, at age 74, the patient received an endoscopy examination by a doctor and abnormalities were diagnosed. After a month, he received a cholecystectomy because of cholecystitis.

On admission the skin was pale and cool, the conjunctivias were not icteric but markedly anemic. The hair was thin and dry with parietal recession. The visual field was full and the optic fundi were normal. The neck was supple and cervical veins were flat. There was no struma, lymphadenopathy or tendency to bleed. The heart and lungs were normal. The abdomen was soft, and muscular defense was not noticed but there was a slight tenderness at the epigastrium. The liver and spleen were not palpable. The extremities were normal, and the neurologic examination was negative.

The urine test was negative for protein and sugar; the sediment contained 10 to 20 erythrocytes and occasional epithelial cells per high-power field, and strongly positive occult blood was found in the stool.

The hemoglobin was 7.0 g/100 ml, and the white cell count 9,500/mm³ with 79 percent neutrophils, 12 percent lymphocytes, 5 percent monocytes, 3 percent eosinophils and 1 percent basophils. The hematocrit was 21.3 percent, the red cell count 2,200,000/mm³, platelet count 151,000/mm³ and erythrocyte sedimentation rate (ESR) 15 mm/hr.

The blood urea nitrogen level was 61 mg/100 ml, creatinine 1.0 mg/100 ml, sodium 138 mEq/l, potassium 4.7 mEq/l, chloride 98 mEq/l, calcium 8.8 mg/100 ml inorganic phosphorus 3.2 mEq/l.

The total protein was 5.3 g/100 ml (albumin 3.3 g/100 ml), total bilirubin 0.3 mg/100 ml (direct bil. 0.2 mg/100 ml), S-GOT 14 IU/l, S-GPT 6 IU/l, LDH 149/l, Al-P 4.4
(K-A) U/l, LAP 42 IU/l and γ-GTP 13 IU/l.

The total cholesterol was 103 mg/100 ml, triglyceride 108 mg/100 ml, TTT 0.7 KU, ZnTT 7.2 KU and ChE 0.4 μpH/hr.

The serological tests revealed negative HBsAg and positive anti HBs.

1. Clinical course after the admission

Urgent gastrointestinal endoscopy on admission showed two hemorrhagic shallow ulcers on the posterior wall of angles and one similar ulcer at the antrum (Fig. 1).

Since the second hospital day (Oct. 30), he had received a blood transfusion of two packs (400 ml) every day for three days, epigastic pain and discomfort were gradually decreased. Blood counting revealed an improvement, namely, the red blood cells was 3,590,000/mm³ hemoglobin 10.7 g/100 ml and hematcrit 33.2% on Nov. 16.

On the 14th hospital day (Nov. 11), he could go to the bathroom without any trouble, and the second gastroendoscopy was carried out on the 15th hospital day (Nov. 12). The examination showed a little improvement and the biopsy obtained from gastric mucosa

![Fig. 1. The gastrofiberscopic findings show two hemorrhagic shallow ulcers on the posterior wall of angles and one similar ulcer at the antrum.](image)

| Table 1. Gastric secretion assay (tetragastrin stimulation) |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Before No. 1    | No. 2           | No. 3           | No. 4           | No. 5           | No. 6           | After 10'       | 20'             | 30'             | 40'             | 50'             | 60'             |
| Color           | yellowish green | +               | +               | +               | +               | +               | watery clear    | +               | +               | +               | +               | +               |
| Mucus           | +               | +               | +               | ±               | ±               | ±               | -               | -               | -               | -               | -               | -               |
| Occult blood    | ++              | ++              | ++              | ++              | ++              | ++              | ++              | ++              | ++              | ++              | ++              | ++              |
| Volume          | 22              | 11              | 43              | 22              | 9               | 37              | 30             | 44              | 40              | 28              | 35              | 43              |
| pH              | 2.8             | 2.1             | 3.2             | 3.3             | 3.4             | 2.0             | 3.1            | 1.2             | 1.1             | 0.5             | 0.7             | 1.3             |
| Acidity         | 13              | 18              | 8               | 7               | 5               | 20              | 11             | 86              | 93              | 117             | 103             | 68              |
| Acid secretion  | 0.29            | 0.20            | 0.34            | 0.15            | 0.05            | 0.74            | 0.33           | 3.78            | 3.72            | 3.28            | 3.6             | 12.92           |

BAO 1.77 mEg/hr MAO 17.64 mEg/hr
revealed no malignancy.

On the 17th hospital day (Nov. 14), plasma gastrin level showed 705.5 pg/ml (N: 30–150), and carcinoembryonic antigen (CEA) revealed 49.0 ng/ml (N: below 2.0 ng/ml).

Therefore, we suspected firstly that he suffered from Zollinger-Ellison syndrome.

General malaise, itching and icterus began at the beginning of December, the total bilirubin was 8.4 mg/100 ml (direct bil. 7.0 mg/100 ml), S-GOT 1,392 IU/l, S-GPT 806 IU/l, HBsAg negative and he was diagnosed as having post-transfusion hepatitis.

On the 70th hospital day (Jan. 6, 1981), a gastric juice examination was carried out, and the result revealed a normoacidity as shown in Table 1.

Therefore, Zollinger-Ellison syndrome was ruled out for the diagnosis.

On the 80th hospital day (Jan. 16), an echography of the abdomen was carried out and the result showed no remarkable change.

On the 93th hospital day (Jan. 29), he underwent the secretin stimulation test for a correct evaluation.

### Table 2. Secretin stimulation test

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>10'</th>
<th>20'</th>
<th>30'</th>
<th>60'</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of gastric juice (ml)</td>
<td>9</td>
<td>3</td>
<td>8</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>pH</td>
<td>1.6</td>
<td>3.8</td>
<td>6.6</td>
<td>1.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Serum gastrin level (pg/ml)</td>
<td>774.3</td>
<td>908</td>
<td>765.7</td>
<td>1038</td>
<td>732</td>
</tr>
</tbody>
</table>

**Fig. 2-1.** Secretin stimulation test.
(the first trial)

**Fig. 2-2.** Secretin stimulation test.
(the second trial)
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The serum gastrin levels were elevated and reached maximum (1,087 pg/ml) at 30 min after the beginning of the intravenous drip-infusion of the secretin (3 unit/kg) which took about 60 min from the starting until the end, whereas the gastrin levels were usually decreased in normal adults (Table 2, Fig. 2-1, 2).

Therefore, we concluded a positive result for the secretin stimulation test at first. However, when we tried the test again on Feb. 25, 1981, we got a negative result as the result in normal controls.

On the 93th hospital day, liver function tests revealed an improvement, namely, the total bilirubin was 8.4 mg/100 ml (direct bil. 1.6 mg/100 ml), S-GOT 83 IU/ℓ and S-GPT 58 IU/ℓ.

On the 107th hospital day (Feb. 12), we carried out the barium enema examination and we obtained a normal finding. A thumb-sized soft tumor had been projecting out from the operation scar at the upper portion of the umbilicus since the beginning of February, accompanied by increasingly severe pain at the tumor.

On the 108th hospital day (Feb. 13), the patient was transferred to the surgical unit to undergo an operation for removal of the tumor.

Histological studies revealed that the tumor was a metastasis caused by an islet cell carcinoma of the pancreas (Fig. 3).

As the abnormal shadow in the mid-portion of the right lung on the chest X ray was enlarged, a bronchography test was carried out on Feb. 19, and it revealed deteriorating branches of the right bronchus, B3, B4, B5.

On the 114th hospital day (Feb. 19), a bronchofiberscopy was carried out to establish a correct diagnosis, and it revealed only an extrabronchial oppression with a trivial intrabronchial disturbance.

So, we concluded that the abnormal shadow of the right lung was a metastasis from the pancreatic islet cell cancer.

On the 122th hospital day (Feb. 27), a computed tomography of the whole body was carried out and no pathological changes were observed.

On the 125th hospital day (Mar. 2), a hepato-pancreatico-scintigraphy was done and

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**Fig. 3.** The histological findings show the metastasis caused by an undifferentiated islet cell adenocarcinoma.
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1980
11
12
1981
1
2
3
4
General fatigue
Epigastric pain
Hematemesis
Tarry stool
Soft stool
Jaundice
Cough
Dyspnea

Gastrin (pg/ml) 705.5 548 547 757.9
ACTH (pg/ml) 207 182.7
Glucagon (pg/ml) 982 1913
Insulin (mU/ml) 137.2 3.6
PTH (ng/ml) 2.25
AFP (ng/ml) < 5
CEA-Z (ng/ml) -

Fig. 4. Clinical course after admission.

Table 3. Hormone levels in plasma and tumor tissues

<table>
<thead>
<tr>
<th>Blood</th>
<th>Gastrin 705.5 pg/ml</th>
<th>Secretin 50.0 pg/ml</th>
<th>ACTH 182.7 pg/ml</th>
<th>Insulin 137.2 mU/ml</th>
<th>Glucagon 982.0 pg/ml</th>
<th>PTH 2.54 ng/ml</th>
<th>GH 2.0 ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>↑</td>
<td>&gt;</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>=&gt;</td>
</tr>
<tr>
<td></td>
<td>(N: 30–150)</td>
<td>(N: &lt; 50)</td>
<td>(N: 10–100)</td>
<td>(N: 5–23)</td>
<td>(N: 40–160)</td>
<td>(N: 0.2–1.0)</td>
<td>(N: &lt; 5)</td>
</tr>
</tbody>
</table>

Tumor tissues (ng/g(wet-w))

<table>
<thead>
<tr>
<th></th>
<th>Pancreatic tumor</th>
<th>Abdominal wall meta.</th>
<th>Lung meta.</th>
<th>Mesocolon’s meta.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucagon</td>
<td>3.4</td>
<td>12.3</td>
<td>U. D.</td>
<td>U. D.</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>9.1</td>
<td>2.1</td>
<td>3.7</td>
<td>U. D.</td>
</tr>
<tr>
<td>Secretin</td>
<td>U. D.</td>
<td>14.5</td>
<td>U. D.</td>
<td>U. D.</td>
</tr>
</tbody>
</table>

Undetected hormones
Gastrin, VIP, Motilin, C-peptide, Pancreatic polypeptide, Insulin, ACTH, β-MSH
no abnormal findings were obtained.

Also, on the 127th hospital day (Mar. 4), an anangiography, superior mesenteric and selective coeliac arteriography, were carried out and no malignant changes were discovered.

Since the beginning of March, the patient had complained of a general malaise and a slight case of jaundice appeared. Subsequently the icterus was abruptly increased with the serum total bilirubin level being 5.2 mg/100 ml on March 14, and 18.6 mg/100 ml on March 19.

On the 143th hospital day (Mar. 20), it was discovered that the intrahepatic bile ducts were markedly dilated by an echography of the abdomen. The echogram also showed a cystic tumor surrounding the pancreas tail.

On the 150th hospital day (Mar. 27), an operation, and external bile fistula formation, was carried out, and postoperatively, 700 to 1000 ml of bile was secreted out continuously.

On the 166th hospital day (Apr. 12), he died due to a large hematemesis (Fig. 4).

After the autopsy was carried out, the hormone assay which included a bioassay and a radioimmunoassay for the ten kinds of gastrointestinal and other hormones in tumor tissues was done (Table 3).

2. Autopsy studies

(1) Major findings

1) Islet cell carcinoma which was originated from the subcapsular portion of the pancreas head (Fig. 5).

   The histological finding of the tumor was an undifferentiated or poorly differentiated adenocarcinoma.

2) Metastases

   i) In the middle lobe of the right lung

   The tumor formed a cavity in which the branch of the right bronchus called B communicated, and the histological finding showed a large cell carcinoma of a

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Fig. 5. The macroscopic findings show the pancreas cancer originated from the subcapsular portion of the pancreas head.

Fig. 6. The histological findings show a large cell carcinoma of giant cell type and partly sarcomatous appearance in the middle lobe of the right lung.
giant cell type and partly sarcomatous appearance (Fig. 6).

ii) In the lower lobe of the right lung
   The histological finding showed moderately differentiated tubular adenocarcinoma and so-called scar carcinoma with an indentation to subpleural portion in Segment No. 9 (Sq).

iii) In the hepatic hilus
   The tumor infiltrated into both the hepatic bile duct and the common duct and then made an obstruction of both bile ducts.

iv) In the liver, left adrenal and mesenterium at the transverse colon

v) Lymph nodes
   In surrounding area of the pancreas, aorta and retroperitoneum.
   These metastases of iii) – v) were histologically similar to islet cell carcinoma of the pancreas head.

3) Well differentiated and infiltrative squamous cell carcinoma in the upper lobe of the right lung (B region) (Fig. 7).

(2) Minor findings
1) Gastroduodenal ulcers
   Multiple ulcers in the stomach and duodenum and extensive gastrointestinal bleeding (Fig. 8).

2) Bronchopneumonia in the right lung with fresh and old organized pneumonia (right lung 1,150 g, left lung 350 g).

3) Obstructive jaundice caused by the infiltration of the neoplasm in the extrahepatic bile duct.

4) Renal tubular degeneration caused by bile nephrosis and shock kidney.

5) Spindle-shaped aneurysm of the abdominal aorta with thrombus and arteriosclerotic dilatation of iliac artery.

Fig. 7. The histological findings show a well differentiated and infiltrative squamous cell carcinoma in the upper lobe of the right lung (B region).

Fig. 8. The macroscopic findings show multiple ulcers in stomach and duodenum which caused extensive gastrointestinal bleeding before death.
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Comment

Following the first observation made by Mc Gavran et al. (1966) of a glucagon-secreting pancreatic tumor, others have reported islet cell tumors producing glucagon, insulin and gastrin (Murray-Lyon et al., 1968; Vance et al., 1969), and other extrapancreatic hormones (polyglandular adenoma syndrome) (Croisier et al., 1971; Croughs et al., 1972; Cassano et al., 1973; Belchetz et al., 1973).

Due to the presence of the pancreatic islet-cell tumor associated with gastrin, insulin, glucagon, ACTH and parathyroid hormone (PTH) hypersecretion, the patient described can probably be classified as having a case of multiple endocrine adenomatoses.

Through the recent studies on gastrointestinal hormones, it has become well-known that the factors which promote the release of antral gastrin, such as mechanical stimulation, motor activity, food or products by digestion, augmented by high pH are not operative in the islet cell for the gastrin secretion whereas cholinergic stimulation and calcium ion may be effective in both the antrum and islet cell.

On the other hand, it is a well-known fact that glucagon, secretin and calcium ion, which have little effect on the antral G cell, or in inhibiting release, cause a marked secretion of gastrin by gastrinomas.

Also, when gastric acid enters the duodenum, secretin decreases antral gastrin release but increases the release of tumor gastrin, which would further stimulate acid production.

Although it is still uncertain in this case whether glucagon production and release from the islet cell tumor took place, because of the detection of the glucagon, secretin and somatostatin in the tumor tissues (Table 3), the possibility is present.

So, we may conclude that the secreted glucagon issued from the islet cell tumor promoted the gastrin secretion from the tumor which produced a small amount of gastrin.

We may also suppose that the released secretin originating in the islet cell tumor also promoted the gastrin release from the tumor.

In the case, diabetes mellitus, weight loss, stomatitis, glossitis and skin lesions which include pemphigoid, pruritic and exudative dermatitis were all lacking presumably because of the little higher than normal plasma level of glucagon (982 pg/ml).

High plasma insulin levels (138 zU/ml) observed in this case may be thought of as the hormonal biological response to the high plasma glucagon by which the beta (β) cells were stimulated. No abnormal values of blood sugar due to fasting were recognized through the clinical course of the patient.

It should also be regarded that an insulin determined by the radioimmunologic method (IRI) is, to a great extent, a proinsulin, which lacks the biologic properties of an insulin.

Although slight elevations of plasma PTH levels were observed in this patient, no hyperfunction could be found in clinical pictures and laboratory findings.

As described above, neither adenoma nor carcinoma were detected in the parathyroid glands during autopsy studies.

Therefore, the case could not be thought of as a case of multiple endocrine adenomatoses,
type I (MEA-I) or multiple endocrine neoplasia, type I (MEN-I).

As for the relatively lower levels of plasma glucagon, insulin and gastrin in this case when compared with the data of the other previous reports, one should consider the significance of the tumor tissue somatostatin which was detected in the autopsy materials, because a somatostatin induces a prompt, partial suppression of glucagon, insulin and gastrin levels as described in a previous report (Tiengo et al., 1976).

Furthermore, the case was thought very rare since squamous cell carcinoma was found in the upper lobe of the right lung combined with the metastasis originated from islet cell carcinoma of the pancreas.

In conclusion, we deduced that this case was a multi-hormone producing tumor, which produced glucagon, secretin and somatostatin, and presumably promoted the production and release of gastrin, and insulin in tumor tissues from the source of the pancreatic islet cell which produced a scanty amount of these hormones originally.

And it may be possible that ectopic parathormone was produced, except in the parathyroid glands, in other tissues in this patient.

The cause of high plasma ACTH levels is unknown.

(We presented this case at the 37th Seasonal Meeting of Kyushu Association of Gastroenterology, July, 1981, Beppu.)

Acknowledgement

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脾島由来ホルモン産生腫瘍の一例

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要旨: われわれは脾島由来と思われるホルモン産生腫瘍の一例を経験した。本例は79才の男子で吐下血を主訴として急性入院、内視鏡により胃角後壁に2ヶ、前庭部小嚢に1ヶのU-I-III多発性潰瘍を認めた。血中ガストリノム値は705.5pg/mlと高値で最初Zollinger-Ellison症候群を疑ったが、胃液検査ではBAO1.77mEq/hr, MAO17.64mEq/hrと正常であり本症候群は否定した。一方、血中の各種ホルモンを測定したところインスリン、グルカゴン、ACTH、PTHなどいずれも高値を示し多発性内分泌腫瘍の疑いが強くなった。入院後施行したセクレチン負荷試験は陽性を示しガストリノーオマの存在を考えた