Recurrent Pheochromocytoma associated with Glucagonoma.  
A Case Report

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Abstract

We treated a hypertensive patient with recurrent pheochromocytoma (paraganglioma) associated with glucagonoma. No clinical symptom of glucagonoma was found and it could be detected only by a slight elevation of plasma immunoreactive glucagon (IRG) while the extirpated pancreatic tumor contained much IRG. This case could not be classified as either multiple endocrine neoplasia (MEN) type I or type II.

Pheochromocytoma associated with islet cell tumor of the pancreas is uncommon and only 12 cases, including 3 familial cases, with such a MEN had been reported up to 1982 (Anderson and Bergdahl, 1976; Mori et al., 1977; Heikkinen and Akerblom, 1977; Probst et al., 1978; Janson et al., 1978; Hull et al., 1979; Carney et al., 1980; Alberts et al., 1980; Zeller et al., 1982).

In all these reported cases, no pancreatic tumor was identified as a glucagonoma. We now report a case of recurrent pheochromocytoma associated with glucagonoma.

Case report

A 26-year old Japanese man was first admitted to Kyushu University Hospital in 1967 with nausea and diarrhea. His blood pressure was 210/170 mmHg and urinary excretion of catecholamines was excessive (norepinephrine 2200 μg/day and epinephrine 300 μg/day). An intravenous pyelogram and retroperitoneal air insufflation suggested bilateral adrenal tumors. The left and subtotal right adrenal gland were excised and blood pressure and urinary excretion of catecholamines reverted to normal. Histological examination of the tumors revealed pheochromocytoma. In 1978 he was re-admitted with an acute viral hepatitis. At that time his blood pressure was 130/102 mmHg and urinary excretion of catecholamines was within normal limits (norepinephrine 43.2 μg/day and epinephrine 4.4 μg/day).

In 1981, his blood pressure was markedly elevated but there were no symptoms of palpitation, excessive sweating, weight loss, skin rash, polyuria or polydipsia.

On admission (Sept. 2nd, 1981), his blood pressure was 174/120 mmHg. Plasma norepinephrine concentration was 680 pg/ml and epinephrine 20 pg/ml (normal ranges: 190–250 pg/ml for norepinephrine and 20–60 pg/ml for epinephrine). Urinary excretion of norepinephrine was 141.5 μg/day and
epinephrine below 1 μg/day. Fifty gram oral glucose tolerance test was fasting 87 mg/dl, 1-hour 159 mg/dl and 2-hour 84 mg/dl. Fasting plasma immunoreactive glucagon (IRG) was 240 pg/ml (normal 40–140 pg/ml). The thyroid scintigram revealed no abnormalities. Serum calcium was 9.7 mg/dl and serum calcitonin 15.7 pg/ml (normal range: below 300 pg/ml). Computed tomography revealed two tumors in the abdomen. These tumors were hypervascular and were located in the left infrarenal region and in the body of the pancreas, as seen on the abdominal aortogram (fig. 1). Blood was sampled serially from the caval and renal veins for measurement of catecholamines. The highest level of norepinephrine concentration was demonstrated in the caval blood at the height of the 12th thoracic vertebra. Under the diagnosis of recurrent pheochromocytoma with pancreatic tumor, abdominal surgery was done and three tumors were excised. Two tumors arose from the nerve ganglions in the left paraaortic region and the other was from the body of the pancreas.

One month later the blood pressure decreased to 136/90 mmHg. Both the plasma glucagon and norepinephrine concentration were normalized (norepinephrine 170 pg/ml, IRG 145 pg/ml).

Histological examination revealed the two tumors from the paraaortic region to be chromaffin cell tumors (paragangliomas) (fig. 2) and the pancreatic tumor was an islet cell tumor (fig. 3). Some cells of the pancreatic tumor were reactive to specific antibodies to glucagon (fig. 4). IRG concentration of the pancreatic tumor was 1 μg/g tissue (the tumor weighed 159 g). OAL-123 was used for IRG assay and immunoperoxidase staining.

**Discussion**

Our patient had recurrent pheochromocytoma associated with islet cell tumor of the pancreas, such considered to be a MEN. The family history is not contributory. Plasma glucagon concentration was slightly elevated to 240 pg/ml, but much lower than in the 47 patients with glucagonoma reported by Higgins et al. (1979). The increase in plasma glucagon concentration may be due to an increase in plasma catecholamines (Unger, 1974). In our patient, an immunostaining method demonstrated glucagon producing cells in the tissue specimen of the extirpated pancreatic tumor, and the tissue contained large amounts of IRG, thus indicating a glucagonoma. Only slight elevation of plasma IRG may have produced no clinical symptom of glucagonoma such as necrolytic migratory erythema or diabetes mellitus.

Multisystem endocrine disorder (neoplasia or hyperplasia) termed “MEN” is divided into type I and type II. Type I involves the anterior lobe of the pituitary, parathyroid, and islet cells of the pancreas, the genetic aspects of which were described by Wermer (1954). Type II or Sipple’s syndrome (Sipple, 1967) consists of pheochromocytoma, multiple unrelated endocrine tumors, and hereditary fasting hypoglycemia.
Fig. 2. The tumor cells are polygonal or fusiform like those of normal adrenal medullary cells and lie in sheets intervened by fine fibrovascular stroma. (H & E, ×200)

Fig. 3. The uniform and small-sized tumor cells are arranged in nests or strands separated by vascularized stroma. (H & E, ×200)

Fig. 4.

a) An electronmicrograph showing the granules in the cell of pancreatic tumor. (×20000)
b) Immunoperoxidase staining of islet cell tumor of the pancreas with specific antibodies to glucagon. (OAL-123), (×360)
Pheochromocytoma and islet cell tumor of the pancreas are an atypical combination, overlapping between MEN type I and type II. Such a combination should be classed as a mixed type (Hansen et al., 1976) or as a new pattern of MEN (Berg et al., 1976). Pearse and Polak (1969 and 1974) proposed that chromaffin cells of the adrenal medulla and islet cells of the pancreas were derived from APUD (Amine Precursor Uptake and Decarboxylation) series. Fujita (1977) felt that both types of cells are paraneurons. The findings in our patient may support such a theory concerning the common origin of endocrine tumors. Therefore, MEN cannot always be classed into only two types.

Acknowledgements

We thank Dr. A. Funakoshi for glucagon determination, Ohtsuka Assay Laboratory for the gift of glucagon-antiserum and M. Ohara for editing the manuscript.

References
