INTRODUCTION

On rare occasions, pheochromocytoma and ganglioneuroma develop together within a single adrenal medullary tumor. It is apparent that composite tumors of that type may display symptoms referable to hormonal hypersecretion by either portion of the tumor. Yet, pheochromocytomas commonly act in the typical manner and presented as cardiomyopathy or ganglioneuroma, and both have been rarely documented. The non-specific nature of its manifestations may render prompt recognition elusive. We recently experienced a case of a composite adrenal medullary tumor of pheochromocytoma and ganglioneuroma that was incidentally discovered and masquerading as acute relapsing pancreatitis. To our knowledge, it may be the first case in medical literature.

CASE REPORT

A 48-year-old male was referred to our endocrinologic clinic for the evaluation of an adrenal incidentaloma. Two months ago, he had been admitted to our gastroenterologic clinic at which time he complained of acute, severe, intense abdominal discomfort. He claimed that the discomfort had a rapid onset reaching a maximum in 10 to 20 minutes. Further, he had band-like radiation on/to the back. He consumed small amounts of alcohol but had no significant medical and family history. Laboratory data revealed elevated serum pancreatic amylase and lipase levels (reference range shown parenthetically) of 98.8 U/L (8~53) and 603.4 U/L (0~60), respectively. A diagnosis of acute alcoholic pancreatitis was suggested. He was managed with conservative treatments including restriction of caloric...
intake. Ten days later, he was discharged with significant clinical improvements.

However, seven days after he was discharged, the same symptoms and signs redeveloped at which time he also described palpitation, facial flushing and resting hand tremor in the previous five months that were developed slightly, briefly and occasionally. On admission, the patient’s body temperature was 36.6°C while blood pressure was 110/70 mmHg. The pulse rate was 72 beats/minute and the respiratory rate was 19/minute. His height and body weight were 158 cm and 52 kg, respectively. The physical examination was unremarkable except for direct tenderness in the epigastric area. Laboratory data revealed normal blood cell counts, plasma glucose and serum electrolyte levels. The results of liver and renal function tests were also within the normal ranges. However, serum pancreatic amylase and lipase levels were elevated to 81.4 U/L (8~53) and 100.9 U/L (0~60), respectively. The serum calcium level was 2.22 mmol/L (2.15~2.50) and triglyceride level was 0.66 mmol/L (<2.83). The serum CPK-MB (creatine phosphokinase-MB isoform) level was 1.8 μg/L (0.7~3.8) and the troponin-I level was 0.3 μg/L (0~0.5). The findings of a chest roentgenogram, electrocardiogram, and 24-hour holter monitor showed nothing significant. Echocardiographic findings were normal except for mild concentric left ventricular hypertrophy. An abdominal computed tomographic scan showed a mildly enlarged pancreatic change without abnormal fluid collection and necrosis. In addition, he showed a left adrenal mass, 3×3 cm in diameter, which was heterogeneously low attenuated and enhanced after intravenous contrast administration (Figure 1A).

About one month after the second discharge, we performed medical tests for discriminating the functional status of the adrenal incidentaloma. The urinary metanephrine level was elevated to 24.7 μmol/24h (0.5~8.1) and the urinary VMA (vanillylmandelic acid) level was normal at 27.5 μmol/24h (7~33). The results of plasma catecholamines, baseline plasma ACTH and cortisol, urinary-free cortisol, uplight plasma renin activity and aldosterone and serum DHEA-S (dehydroepiandrosterone sulfate) levels were also within normal ranges. The results of 5-HIAA (5-hydroxyindoleacetic acid) and thyroid function tests were also normal. 131I-MIBG (Metaiodobenzyl guanidine) scintigraphy was performed for the confirmation of the provisional diagnosis and localization of additional extra-adrenal tumors. 131I-MIBG scintigraphic findings showed a marked uptake in a single location corresponding to the left adrenal mass (Figure 1B). Ultrasonographic findings of the neck were unremarkable and serum intact PTH and calcitonin levels were 14.39 pg/mL (15~65) and 1.4 ng/mL (0~10), respectively. Therefore, we could exclude pheochromocytoma from familial association of multiple endocrine neoplasia type II. An α-adrenoceptor blocker (doxazocin mesylate 4mg qd for 11 days) was prescribed preoperatively to prevent an operative adrenal crisis. Then, the left adrenal gland was surgically removed trans-abdominally through a subcostal incision.

On pathologic examination, a composite adrenal medullary tumor of pheochromocytoma and ganglioneuroma was confirmed. On gross examination, a well-defined solid tumor measuring 2.8×2.5×2.5 cm was found within the adrenal gland and cut surface of the tumor was yellowish brown. The microscopic appearance of the tumor showed an abrupt transition of two different patterns of typical pheochromocytoma and a large area of ganglioneuroma (Figure 2A).
Figure 2. (A) Light micrograph of the tumor showed abrupt transition of two different patterns of typical pheochromocytoma and large area of ganglioneuroma (H&E stain, ×40). (B) Light micrograph of the pheochromocytoma component. Organoid nest called “Zellballen” pattern, granular basophilic or amphophilic cytoplasm, intracytoplasmic hyaline globules, and round or oval nuclei with prominent nucleoli are noted (H&E, ×400). (C) Light micrograph of the ganglioneuroma component. Uncapsulated clusters of fully matured ganglion cells surrounded by fascicles of spindle (Schwann-like) cells are noted (H&E stain, ×100).

DISCUSSION

Although pheochromocytoma may occur at multiple sites and in association with a number of other tumors, the presence of both pheochromocytoma and ganglioneuroma within a single tumor is extremely rare. Only a few cases have been described previously. While pheochromocytoma is a tumor that originated from the adrenal medullary chromaffin cells, ganglioneuroma represents a tumor from autonomic ganglion cells or their precursors. Embryologically, both chromaffin and ganglion cells are derived from neural crest cells and migrate to somatic areas. It is apparent that a composite tumor of pheochromocytoma and ganglioneuroma may display symptoms referable to hormonal hypersecretion by either portion of the tumor, and Moore et al. described hormonal hypersecretion in approximately three-fourths of the reported cases. Clinically active pheochromocytoma may produce the classic symptoms of headache, palpitation, and excessive perspiration in 50% of the cases. In addition, hypertension, either sustained or paroxysmal, is the cardinal feature of pheochromocytoma. In our case, while the 24-hour urinary metanephrine level was
elevated to 24.7 mol/24h (reference range, 0.5~8.1), no definite manifestations referable to catecholamine hypersecretion were identified prior to diagnosis. In other words, the patient had no hypertension or any classic symptoms of pheochromocytoma. He only complained of palpitation, facial flushing and hand tremor which developed only slightly, briefly and occasionally. Further, there were no episodes during the hospitalized days. Reviews have placed frequency of hypertension at 72.4%, with that of sustained hypertension at only 47.9% in pheochromocytomas\(^\text{12}\), and Moore et al.\(^\text{2}\) noted that only four of the 13 patients had associated hypertension in composite adrenal medullary tumors. The reason for a lack of endocrine abnormalities and symptoms of pheochromocytoma component in some composite adrenal action of circulating catecholamines has not been shown conclusively. One possible hypothesis is the autoregulation of the pheochromocytoma cells by the ganglion cells in the ganglioneuroma component\(^\text{15}\).

Pheochromocytomas commonly do not behave in the classic manner, which may render prompt recognition elusive\(^\text{15}\). The signs and symptoms are often absent and can be unusually presented as catecholamine-induced cardiomyopathy\(^\text{4-6}\) or hyperamylasemia\(^\text{7-11}\). In review of the literature, the amylase was almost exclusively of the S-type in the pheochromocytoma cells by the ganglioneuroma component. The provisional diagnosis seemed reasonable because of the acute onset of abdominal intense discomfort, elevated serum pancreatic enzyme levels and a mildly enlarged pancreas on image. We did not perform an analysis of amylase isoenzyme by the electrophoretic method, but pancreatic amylase, not total amylase, was assayed by a enzymatic photometric test, which is based on the method of monoclonal antibodies to inhibit the salivary enzyme and which distinguish pancreatic and salivary amylase sufficiently\(^\text{17, 18}\). Therefore, it could be suggested that the pancreatitis was caused by the pheochromocytoma in our case. The mechanism of this was considered to be ischemic damage of the pancreas itself by vasoconstrictive action of circulating catecholamines\(^\text{16}\). The second suggested mechanism was dysfunction of the sphincter of Oddi caused by adrenergic action of circulating catecholamines. This possibility was low because the sphincter of Oddi was relaxed by adrenergic stimulation in general\(^\text{19}\). However, paradoxical contraction by down regulation of adrenoceptors was as probable as circulatory collapse or hypotension seen in pheochromocytoma.

In conclusion, pheochromocytoma can be present in a variety ways without hypertension and classic symptoms. Therefore, it is vital to recognize the rare presentations of pheochromocytoma to avoid an unsuspected lethal course. We recently experienced a case of 48-year-old male with incidentally discovered a composite adrenal medullary tumor of pheochromocytoma and ganglioneuroma that was manifested as catecholamine-induced relapsing pancreatitis without hypertension. Herein, we described the case with the review of the literature.

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