Paraganglioma Associated with Hypoglycemia

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A 63-year-old female had frequent attacks of palpitations with sweating and occasional loss of consciousness for 7 years before admission. These symptoms and documented hypoglycemia (blood glucose: 46 mg/dl) suggested insulinoma, but computed tomography demonstrated a retroperitoneal tumor which was diagnosed as a paraganglioma by histological examination of the resected specimen.

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Key words: retroperitoneal tumor, pheochromocytoma, insulin-like growth factor

Introduction

Retroperitoneal nonfunctioning paraganglioma is a rare tumor and is difficult to detect while still small. We found a retroperitoneal tumor (3 cm in diameter) by imaging studies in a woman who had hypoglycemic symptoms. The tumor was confirmed to be a paraganglioma by histological examination after resection.

Case Report

A 63-year-old housewife developed palpitations, sweating, and fatigue in 1982. Two years later, a pacemaker was implanted after a diagnosis of sick sinus syndrome with paroxysmal atrial fibrillation was made when the patient developed syncope following admission. After this, the syncopal attacks disappeared but she continued to have occasional palpitations. However, detailed examination of the heart showed no significant evidence of sick sinus syndrome. At the time when her symptoms were present, the blood glucose level was 46 mg/dl and the plasma immunoreactive insulin level was 7 μU/ml. The oral glucose tolerance test showed a normal pattern. In addition, insulin secretion in the glucagon test and the C-peptide response to insulin-induced hypoglycemia were within the normal range. Her hypoglycemic attacks were induced by hunger, and the hypoglycemia was treated symptomatically by the oral intake of sugar.

Cortisol and aldosterone levels were normal. Urinary noradrenaline (220 μg/day) and dopamine (1,469 μg/day) excretion were slightly elevated. Blood pressure and plasma catecholamine levels were normal, and there were no abnormal responses in the metoclopramide test, the glucagon test, and insulin-induced hypoglycemia.

Ultrasound and computed tomography detected a tumor located at the upper pole of the left kidney (Figs. 1 and 2). Angiography demonstrated that the left upper, middle, and lower adrenal arteries were distorted and compressed by this tumor, and a tumor stain was observed in the venous phase (Fig. 3).

Fig. 1. Abdominal echography. The tumor (arrow) is located at the upper pole of the left kidney.
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**Findings at operation**

She underwent surgery on January 10, 1991. An incision was made in the left subcostal region and the retroperitoneal structures were approached transperitoneally. The tumor was found to be attached to the left adrenal gland. It was covered by a brownish capsule and there was no evidence of invasion into the surrounding organs, but because of thick adhesions to the left adrenal gland, the tumor and the gland were excised en bloc. The resected tumor measured $2.7 \times 2.5 \times 3.3$ cm and was composed of solid tissue (Fig. 4). The insulin, insulin-like growth factor I (IGF-I) and IGF-II concentrations in the tumor tissue were not measured.

**Histological appearance**

The tumor was covered with a fibrous capsule and the proliferating tumor cells formed nests. The spaces between the nests were filled with interstitial tissue containing tiny vessels (Fig. 5). The tumor cells were irregularly shaped and their borders were not clear. The cytoplasm was abundant and light in color, while the nuclei were round but varied in size and color (Fig. 6). Following resection of the tumor, hypoglycemia and the associated symptoms have not occurred again (17 months follow up).

**Discussion**

The World Health Organization (WHO) (1) classifies

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**Fig. 2.** Abdominal computed tomography. The tumor (arrow) is located at the upper pole of the left kidney.

**Fig. 3.** Abdominal angiography. A tumor stain (arrow) is observed in the venous phase.

**Fig. 4.** Cut surface of the tumor. The lesion measured $2.7 \times 2.5 \times 3.3$ cm (arrow) and is composed of solid tissue.

**Fig. 5.** Photomicrograph of the tumor (silver stain, x100). Proliferating tumor cells form nests and the spaces between the nests are filled by interstitial tissue.
paraganglioma as 1) pheochromocytoma, 2) chemodectoma (nonchromaffin paraganglioma), and 3) unclassified paraganglioma. On the other hand, Glenner and Grimley (2) classified paraganglioma as 1) brachio- metric, 2) intravagal, 3) aorto-sympathetic, and 4) visceral autonomc, with the subclassification of functioning and nonfunctioning tumor. Our patient had a nonfunctioning aorto-sympathetic paraganglioma according to Glenner’s classification. Paragangliomas are characteristically composed of nests of tumor cells with lightly stained cytoplasm and chromatophilic nuclei (2), just as the tumor in our patient. The resected left adrenal gland showed no abnormalities on histological examination and the diameter of the resected tumor was about 3 cm, which suggests that it was not malignant.

In one series, retroperitoneal paraganglioma was reported to comprise 1.8% of all retroperitoneal tumors (3). In Japan, reports of retroperitoneal paraganglioma without catecholamine hypersecretion include the following: the first case was reported by Kanei et al (4) in 1965, 5 cases were reported by Sakurai et al (5), 15 cases by Ikeuchi et al (6), and 52 cases by Sawai et al (7). These patients included 28 males and 24 females aged from 13 to 80 years (average: 49.6 years). Abdominal mass and abdominal distension were frequent presenting features of these tumors without abnormal catecholamine secretion.

Mesothelioma, fibrosarcoma, neurofibrosarcoma, and smooth muscle sarcoma are all sometimes associated with hypoglycemia. Such hypoglycemia has been reported to be caused by abnormalities of glucose metabolism (8, 9), tumor production of insulin (10) or substances immunologically cross-reactive with insulin (11), non-suppressible insulin-like activity (IGF-I/II) (12), or tumor-induced cytokines (13). In pheochromocytoma and neural crest tumor, high concentrations of IGF-I/II are observed in the plasma (14, 15) and in tumor tissue (15, 16). These peptides, though not measured in the present study, might have been an important factor in the hypoglycemia that occurred in our patient, because paraganglioma is a neural crest-derived tumor. As far as we know, this is the first report of paraganglioma associated with hypoglycemia.

Diagnosis of a nonsecretory paraganglioma is difficult, but a secretory tumor can usually be detected by imaging after abnormal catecholamine levels are noted. Surgical resection of paraganglioma is recommended, but fine tumor vessels may sometimes cause profuse bleeding. In our case, the paraganglioma was found when it was still small enough to be resected completely, because frequent hypoglycemic attacks prompted the search for a lesion.

References