Adrenomedullary Hyperplasia Associated with Cortisol Producing Adenoma

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Abstract. We report a case of a 58-year-old man with adrenal medullary hyperplasia associated with cortisol producing adenoma. Preoperative examination showed both adrenocortical and adrenomedullary hyperfunction. No Cushingoid sign was present and pheochromocytoma-like symptoms were predominant. Abdominal computarized tomography revealed a left adrenal tumor stained by contrast medium. Histologically, the adrenal tumor was found to be a cortical adenoma, and medullary hyperplasia was observed in the remaining parenchyma.

Key words: Adrenomedullary hyperplasia, Pheochromocytoma, Cortisol producing adenoma.

ADRENAL medullary hyperplasia has recently been recognized as an independent disease entity [1–4]. This pathologic condition bears a symptomatic resemblance to pheochromocytoma, and usually occurs bilaterally, occasionally occurring as a component of type 2 multiple endocrine neoplasia, with sporadic cases of unilateral involvement sometimes being reported [5]. With recent advances in diagnostic imaging techniques, on the other hand, the number of incidentally detected adrenal tumors and of asymptomatic cortisol-producing tumors has increased [6–9]. We recently saw a patient with an adrenal tumor who had clinical symptoms compatible with pheochromocytoma. Pathological examination demonstrated an adrenocortical tumor and coexisting adrenal medullary hyperplasia. We describe this case in detail herein.

Case Report

In 1990, a 58-year-old male was admitted to our hospital to examine the cause of muscle weakness. Paroxysmal hypertension had occurred since 1987, and was poorly controlled by antihypertensive drugs. In 1989, a sense of heaviness, perspiration, palpitation, and facial redness were noted. On admission, he was 170 cm tall and weighed 63 kg, which was similar to his body weight in 1983. There were no Cushingoid signs such as central obesity, skin striae, or acne. His blood pressure range was 140–170/90–110 mmHg. The hemoglobin level was 11.1 g/dl, a white blood cell count was 7100/µl with eosinophils 0%, serum sodium was 141 meq/l, potassium was 4.0 meq/l, chloride was 109 meq/l, total protein was 6.1 g/dl, and glucose tolerance test was normal. The thyroxine binding globulin (TBG) was very low (5.4 µg/dl). Levels of urinary catecholamines were increased, especially that of dopamine (3,071 µg/day). The blood cortisol value was increased, with the disappearance of circadian rhythm (0800 h, 21.8 µg/dl; 2000 h, 18.4 µg/dl). Overnight dexamethasone suppression test elicited no sup-
Expression of cortisol. The ACTH level was 13.7 pg/ml (0800 h; ACTH was measured with an ACTH IRMA kit) (Table 1). The plasma aldosterone concentration was normal. Plasma calcitonin and carcinoembryonic antigen (CEA) were also within the normal range. Abdominal computed tomography (CT) demonstrated a 2.5 cm-diameter tumor which was uniformly stained by contrast medium in the left adrenal gland (Fig. 1a) but there was no tumor or enlargement of the right adrenal gland (Fig. 1b). Prazosin administration induced a decrease in blood pressure and a sensation of light-headedness. The patient was diagnosed as having a pheochromocytoma with increased cortisol secretion and no cortisol suppression after dexamethasone administration. On August 21, 1990, the left adrenal gland was resected.

Pathological examination

The tumor was 3 cm in diameter, and the cut surface was dark brown mixed with yellowish-brown. The histological type of the tumor was cortical adenoma, and the cortex other than the cortical adenoma was atrophic. The medulla was abnormally wide and the cortico-medullary border was irregular. Medullary cells varied in size and alveolar arrangement (Fig. 2a, 2b, 2c).

Discussion

Adrenal medullary hyperplasia has recently been recognized as a clinical entity that causes a syndrome which clinically resembles that of pheochromocytoma. However, clinical and morphological diagnoses are very difficult. In our present case, as the cortex contained an encapsulated tumor, the medulla/cortex ratio and the weight of the adrenal medulla could not be accurately determined. Histologically, adrenal medullary hyperplasia was observed in the remaining parenchyma. Removal of the affected adrenal gland resulted in complete disappearance of the clinical signs and symptoms, and urinary catecholamines returned to normal. These findings were also clinically consistent with adrenal medullary hyperplasia. The most prominent feature in our case was the coexistence of an adrenal cortical tumor. To the best of our knowledge, there have been only two similar cases reported. In one case, described by Kazama et al. [10], the clinical symptoms and physical findings of Cushing's syndrome were apparent, while the clinical symptoms of pheochromocytoma were lacking. The lack of clinical symptoms of pheochromocytoma in their case may be due to the fact that mainly norepinephrine was secreted. In the second case, reported by Borrero et al. [11], though endocrine examination was not complete, mild pheochromocytoma-like symptoms were the only manifestation. In the present case, pheochromocytoma-like symptoms were predominant and no Cushingoid sign was present. This was partly due to oversecretion of dopamine causing typical symptoms of adrenomedullary hyperplasia, and, because of insufficient secretion of cortisol, the signs and symptoms of Cushing's syndrome were not produced in spite of the presence of autonomous cortisol secretion. However, it should be noted in this connection that a fair number of cases of clinically silent cortisol producing tumor have recently been observed [6-9].

Hyperfunction of both the medulla and the cortex of the adrenal gland is more commonly seen when a pheochromocytoma secretes ACTH or corticotropin-releasing factor (CRF) ectopically [12–15]. Bilateral adrenocortical hyperplasia should have been observed in these cases. Ectopic ACTH production by the adrenal medulla in our case can be ruled out because the remainder of the...
cortex was atrophic and the plasma ACTH level was low.

There was a concurrent decrease in TBG in our patient. It is generally known that Cushing’s syndrome is usually associated with decreased TBG. However, in our case, TBG remained low both before and after operation, and the accompanying decrease in TBG was considered to be accidental.

It is more than 30 months since the operation, and the patient is free from recurrent pheochromocytoma-like symptoms. Replacement therapy with hydrocortisone at a dose of 5 mg/day is still being carried out, because anorexia and general malaise had returned in a few days when this regimen was discontinued (the latest ACTH level was 15.8 pg/ml). We cannot deny the possibility of the presence of medullary hyperplasia in the right

Fig. 1. a: Enhanced computed tomography (CT) scan shows a 2.5 cm homogeneous mass in the left adrenal gland. b: No tumor or enlargement of the right adrenal gland.
side also. On the basis of the clinical and laboratory data obtained to date, we propose that this is a case with sporadic unilateral adrenal medullary hyperplasia associated with cortisol producing adenoma.

References


Fig. 2. a: Survey photograph showing cortical adenoma and the remaining parenchyma (arrow). b: Medulla which is positive by Grimelius’ reaction is abnormally wide and the cortico-medullary border is irregular (Grimelius’ method. × 29). c: Medullary cells showing variety in size and alveolar arrangement (Hematoxylin and eosin. × 290).