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LETTER TO THE EDITOR

# A case of subclinical Cushing syndrome due to primary pigmented nodular adrenocortical disease associated with adrenocortical adenoma

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To the Editor,

Primary pigmented nodular adrenocortical disease (PPNAD) is a rare disorder associated with ACTH-independent Cushing syndrome (CS). Most patients with PPNAD present with clinically overt CS until young adulthood, and the condition is sometimes associated with Carney complex (CNC) [1, 2].

We report a case of a 58-year-old man who was initially diagnosed with subclinical CS because of a solitary adrenal tumor. Histological findings revealed the coexistence of a cortisol-producing adenoma and PPNAD nodules. He had no apparent Cushingoid features (height, 163 cm; weight, 73 kg). He had no family history and clinical manifestation of CNC. He received medication for hypertension, hyperlipidemia, hyperuricemia, diabetes, and liver dysfunction; his blood pressure, HbA1c level, LDL cholesterol level, and triglyceride level were 169/94 mmHg, 6.7%, 120 mg/dl, and 606 mg/dl, respectively. Computed tomography (CT) revealed a right adrenal mass (16 × 15 mm). Endocrinological tests showed subclinical hypercortisolism [3]; the morning plasma ACTH and cortisol levels were 11.0 pg/ml and 15.1 μg/dl, respectively. At 2300 h, the cortisol level was slightly high (5.5 μg/dl). Dexamethasone suppression tests (DSTs) (1 and 8 mg) showed that the morning cortisol levels were not fully suppressed (3.9 and 6.8 μg/dl, respectively).

The right adrenal gland was extirpated laparoscopically; the resected adrenal showed multiple cortical nodules. The largest nodule was an adrenocortical adenoma, and the others histopathologically corresponded to PPNAD. This adenoma consisted of numerous clear and compact cells, whereas PPNAD-like nodules mainly consisted of eosinophilic compact cells. Steroidogenic enzymes such as 3$\beta$-hydroxysteroid dehydrogenase, 17$\alpha$-hydroxylase, 21-hydroxylase, and cholesterol side-chain cleavage enzyme were abundantly expressed in both cortical adenoma and the PPNAD nodules [4]. Dehydroepiandrosterone-sulfotransferase (DHEA-ST) immunoreactivity was markedly detected in all PPNAD-like nodular cells, whereas it was detected only in small foci in the tumor cells of the adenoma. DHEA-ST expression is usually not observed in Cushing adenoma [5]. Therefore, this heterogeneous expression pattern suggests that this adenoma has some association with PPNAD. The DHEA-ST immunoreactivity in the non-neoplastic adrenals was much weaker than that in the PPNAD-like nodules, indicating continuous suppression of the hypothalamo–pituitary–adrenal axis in the present case, because DHEA-ST expression is strongly dependent on ACTH [5]. Notably, in the zona reticularis of the non-neoplastic region, a few small clusters of cortical cells consisting of

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DHEA-ST-positive cells were identified; this finding suggests that these cells are immature PPNAD nodules capable of synthesizing cortisol [4].

We reviewed the CT scan; multinodular lesions were present in both adrenal glands. The left adrenal nodules were considered as functioning adenoma, because 8 mg DST failed to suppress the morning cortisol level (3.5 μg/dl) after surgery. These clinical and histological findings were consistent with those of PPNAD, although the mutations of all coding regions and exon–intron boundaries of the cAMP-dependent protein kinase A subunit 1α (*PRKAR1A*) gene were not identified. In addition to a 5-kg weight reduction, the metabolic parameters (levels of liver enzymes, triglyceride, uric acid, and HbA1c) improved after surgery. This is a rare case of PPNAD coexisting with cortisol-producing adrenocortical adenoma in the same adrenal gland.

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