Journal of Korean Medical Science
Vol. 9, No. 6, 450-457 December 1994

Bilateral Primary Pigmented Nodular Adrenocortical Disease

—A case report describing a rare cause of Cushing's Syndrome—

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A case of Cushing's syndrome due to bilateral pigmented nodular adrenal disease in a 35-year-old male is presented. The adrenals showed multiple, black, variable sized nodules. Histologically the cells contained lipofuscin and either had a clear cytoplasm or an eosinophilic cytoplasm with a prominent nucleus. Lymphocytic infiltration and fatty metaplasia within the nodules are two of the prominent histological features. There is extreme internodular atrophy which suggests that primary pigmented nodular adrenocortical disease is a non-adrenocorticotropic hormone dependent condition. Since the disorder appears to involve primarily the cortex of both adrenals, the treatment of choice is bilateral adrenalectomy followed by steroid replacement. The characteristic clinicopathological manifestations that separate this diagnosis from other types of adrenal disease are also discussed. This is the first reported case in Korea to be documented with the pertinent clinicopathological findings.

Key Words : *Adrenal gland, Nodular adrenocortical disease, Cushing's syndrome.*

INTRODUCTION

Non-iatrogenic Cushing's syndrome has been associated primarily with three entities : 1) pituitary-dependent processes due to pituitary adenomas or microadenomas causing adrenal hyperplasia ; 2) pituitary-independent primary adrenal causes, predominantly unilateral adenomas, rarely multiple adenomas or adrenal carcinoma ; 3) ectopic sources of adrenocorticotropic hormone (ACTH) production.

Although non-neoplastic bilateral adrenal disease generally has been ascribed to extra-adrenal stimulation, a rare cause of Cushing's syndrome that involves bilateral adrenal nodular formation independent of pituitary stimulation has been identified. The bilateral primary pigmented adrenocortical nodular disease is a disorder in which cortisol is autonomously secreted from hyperplastic adrenocortical nodules(McArthur et al., 1982). Although the usual clinical manifestations of Cushing's syndrome are generally present, Ruder et al.(1974) report that some patients have mild signs and that the most striking feature of the disease may be osteopenia.

Cutaneous pigmentation and pituitary abnormalities are absent, and patients have low plasma levels of ACTH. This disorder occurs most frequently in the pediatric age group and has been noted in both infants(Goldblatt and Snaith 1958 ; Klevit et al., 1966), and adolescents (Meador et al., 1967), it has also been described in adults(Ruder et al., 1974).

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We describe a case of bilateral primary pigmented nodular adrenocortical disease with electron microscopic findings to determine the cell type responsible for the adrenal nodule formation and its color.

CASE HISTORY

A 35-year-old male patient was admitted to Kyunghee University Hospital for the evaluation of hypertension. In his past medical history, he had especially felt facial flushing and excessive sweating on walking upstairs. Two months before admission, he had been diagnosed with hypertension on his routine check-up. On admission, blood pressure was 200/110 mmHg. Abdominal ultrasonography and adrenal computed tomographic(CT) scan were performed. Pituitary gland CT showed no abnormality. Basal plasma catecholamine levels were high.

Plasma epinephrine and norepinephrine levels were 1.68 (normal 0.04 to 0.2) and 2.12 (normal 0.07 to 0.4) ng/ml, respectively. Twenty-four hour urine epinephrine (24.3 μg/day ; normal up to 20.0 μg/day) and norepinephrine (106.4 μg/day ; normal up to 80 μg/day) levels were also higher than normal upper range. Plasma ACTH levels were undetectable on both diurnal samples. On the third hospital day, a dexamethasone suppression test was done for differential diagnosis of Cushing's syndrome(Table 1). Serum cortisol, 24-hour urine 17-hydroxycorticosteroid (17-OHCS) and 17-ketosteroid (17-KS) were not suppressed with low and high dexamethasone suppression tests. This finding was suggestive of adrenal Cushing's syndrome. From selective venous sampling, we got higher cortisol levels in both adrenal veins (right adrenal vein : 125 μg/dl, left adrenal vein 120 μg/dl) than from an inferior vena caval sampling. Serum cortisol level of the inferior vena cava was still higher(46.2 μg/dl) than that of the peripheral vein(24.3 μg/dl). Furosemide stimulation test showed normal responses of plasma renin and serum aldosterone levels(data not shown). Under the impression of bilateral functioning adrenal nodules, bilateral adrenalectomy was performed on the 14th hospital day. The patient showed good tolerance for 44 months after surgery with a maintenance dose of steroid administration.

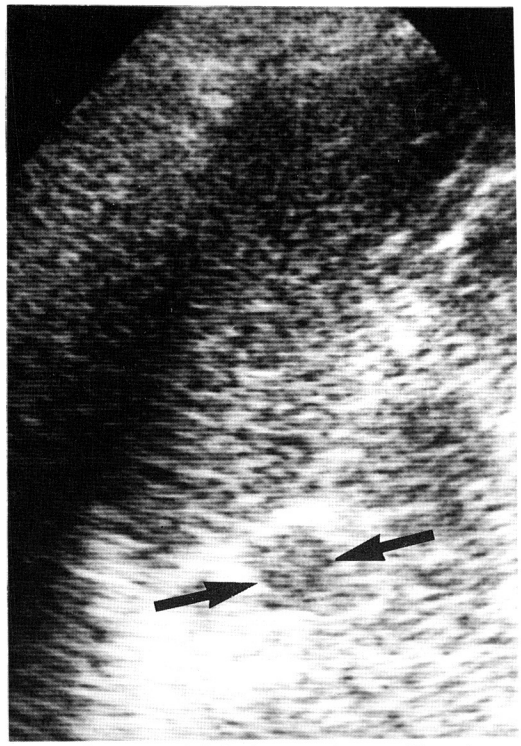

Fig. 1. Sonogram, left flank coronal scan : Mass (arrows) shows isoechogenicity with the spleen located medial to the spleen and superomedial to left kidney.

Table 1. Dexamethasone Suppression Test

	p-ACTH (pg/ml)	s-Cortisol (μg/dl)	24 hours Urine		
			17-OHCS (mg)	17-KS (mg)	Cr (mg)
Basal					
8 A.M.	15.5	29.9	17.4	6.2	1900
4 P.M.	16.8	27.9			
LDS(8 A.M.)	UD	26.4	17.4	7.6	1400
HDS(8 A.M.)	UD	29.5	13.4	6.7	700

*17-OHCS : 17-hydroxycorticosteroid, 17-KS : 17-ketosteroid
Cr : creatinine, p : plasma, s : serum, UD : undetectable
LDS : Low dose suppression test(0.5mg×4, daily 2.0 mg)
HDS : High dose suppression test(2.0mg×4, daily 8.0 mg)

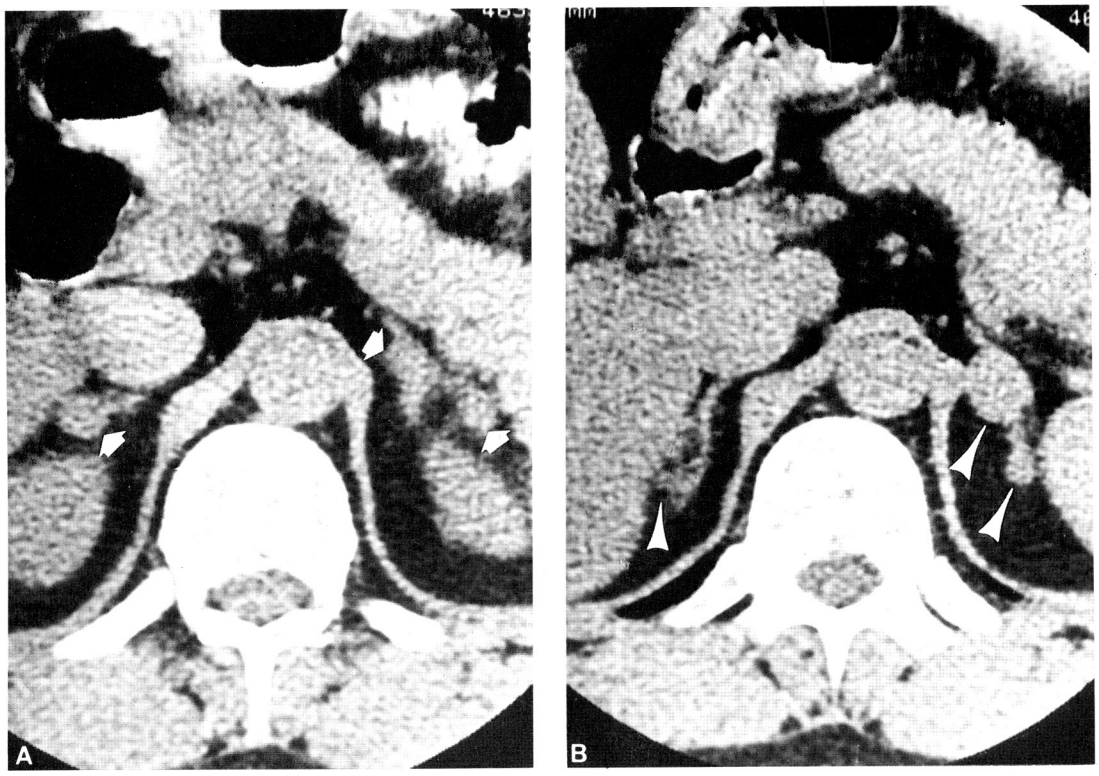

Fig. 2. CT scan shows multiple adrenal masses arrows(Fig. 2A) and arrow heads(Fig. 2B) demonstrating isodensity with the liver noting in both adrenal glands.

Radiologic findings

Sonography of the left abdomen on flank coronal scan revealed a l.7 cm mass with a well defined margin medial to the spleen and superomedial to the left kidney(Fig. 1). The echogenicity of the mass showed an iso-echoic condition to the spleen. Sonographically, the right adrenal gland was not visualized by attenuation of beam due to fatty infiltration of the liver. Computed tomograph(CT) of both the adrenal glands showed three nodules in the right adrenal gland and five nodules in the left. The adrenal nodules revealed isodensity with the liver. The largest nodule measured about 2 cm in the left adrenal gland and the smallest nodule measured 0.8 cm in the right adrenal gland(Fig. 2A, B).

Pathologic findings

Gross findings :

The right adrenal gland was 6.5X2X0.5cm in size and 5.5 grams in weight. The outer surface was smooth and glistening with multiple nodules of varying size having a dark black appearance. The cut surface of the right adrenal gland showed numerous well delineated round black nodules located in the cortical area(Fig. 3). The largest nodule was 1.0 cm in diameter. The left adrenal gland was 7.3X3X1.2cm in size and 9 grams in weight. The outer surface was nodular in appearance. The cut surface showed multiple nodules with dark black pigmentation(Fig. 4). The largest nodule measured 1.7 cm in diameter.

The cortical nodules of both adrenal glands were round to oval, relatively well-circumscribed but not encapsulated. The nodules were largely confined by the adrenal capsule, but occasionally the nodules were found to have capsular extrusion with broad-based projection into the surrounding adipose tissue. Smaller nodules were usually seen at or near the corticomedullary junction.

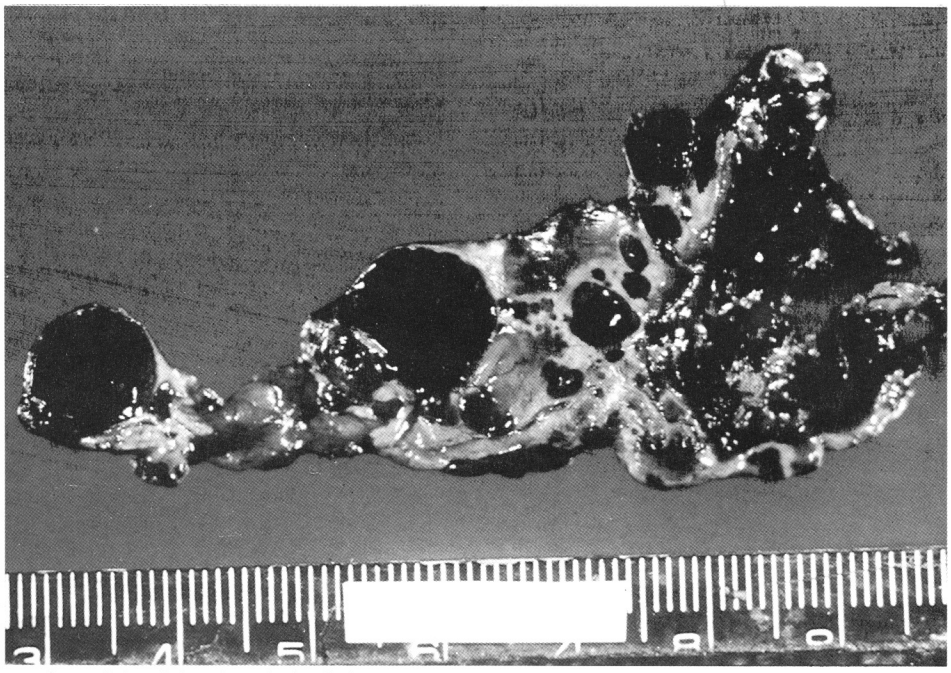

Fig. 3. Cut surface of the right adrenal gland shows numerous well delineated round black nodules located in the cortical area.

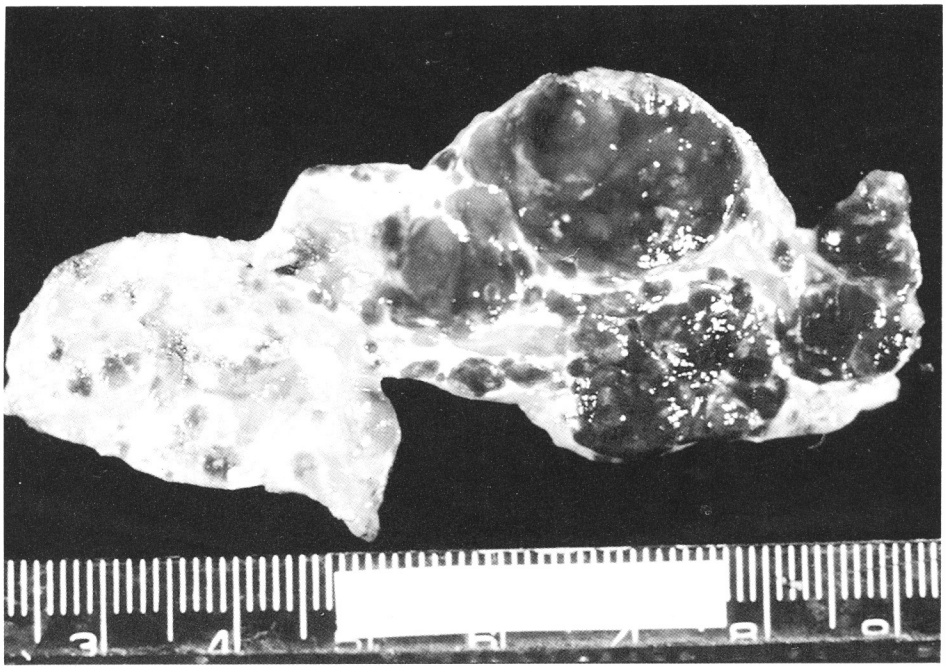

Fig. 4. The left adrenal gland shows multiple nodules with dark black pigmentation.

Light microscopic findings :

The grossly visible nodules corresponded to unencapsulated, circumscribed aggregates of altered cortical cells(Fig. 5). Most of the nodules were of round to oval configuration and sharply demarcated from the adjacent cortex. Most of the cells in the nodules were large and globular. The cells had eosinophilic cytoplasm ; varied from light and finely granular to deep and coarsely granular. Admixed with these eosinophilic cells, were large cells with voluminous, clear, granular, or vacuolated cytoplasm. Many cells contained moderate to copious amounts of coarsely granular brown pigments that were diffusely distributed throughout or focally aggregated in the cytoplasm. The pigment was lipofuscin on the basis of its staining characteristics(positive reaction with Periodic Acid-Schiff, but not with Fontana-Masson and Prussian blue technique). Some of the nodules exhibited slight to moderate fatty or myeloid transformation(Fig. 6). In area, polypoid intravenous protrusions of the nodules covered only by a single layer of endothelial cells were seen. The nuclei of the cells in the nodules were vesicular and medium sized and usually regular ; they were located eccentrically in the cells with inconspicuous nucleoli. Chromatin was finely stippled. The cortex between the nodules was markedly atrophic. In such atrophic areas, the cells were greatly reduced in size. The internodular cortex exhibited disarray-that is, loss of normal zonation. The adrenal medulla appeared normal.

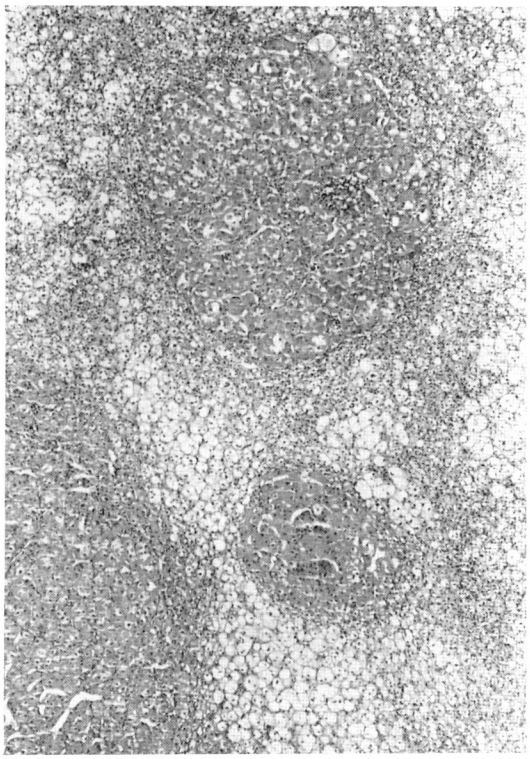

Fig. 5. There are several visible nodules unencapsulated, circumscribed aggregates of altered cortical cells.

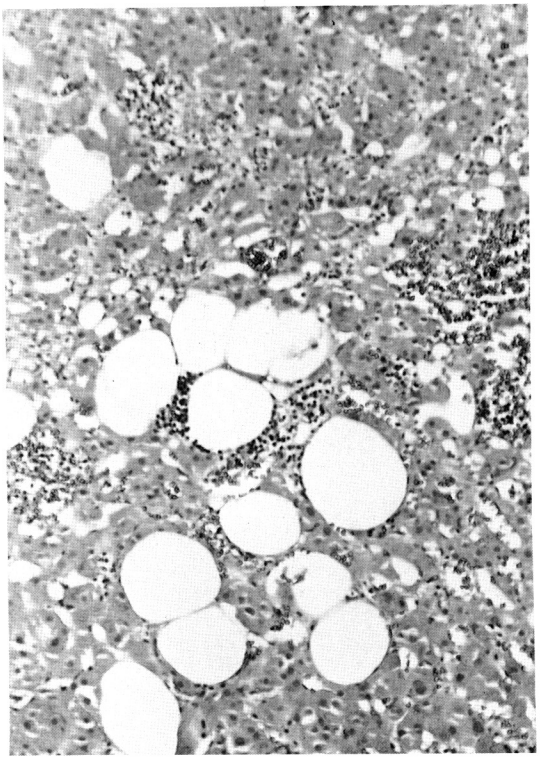

Fig. 6. There is fatty and myeloid transformation.

Electron microscopic findings :

Paraffin embedded tissue was used for electron microscopic examination. The polygonal cells composing the nodules were surrounded by a plasma membrane that was partly straight, partly folded and interdigitated. The nuclei were spherical in shape with narrow rims of peripheral condensed chromatin. The lysosomes and lipid vacuoles were commonly congregated in different areas of the cytoplasm. Some cells were entirely stuffed with tubulovesicular mitochondria. Lysosomes and pigment

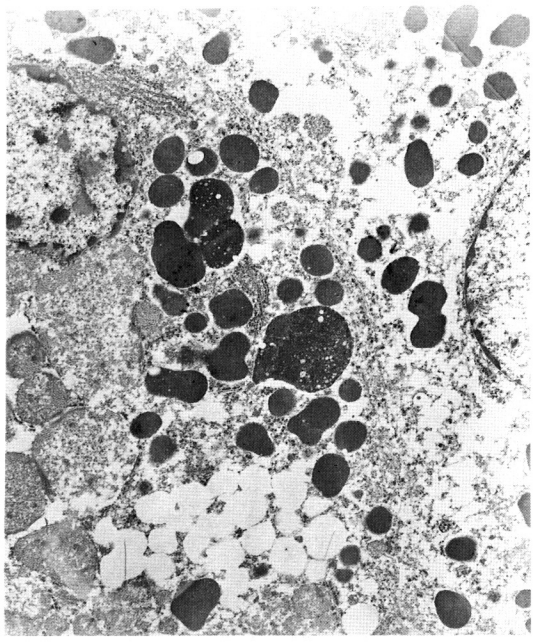

Fig. 7. Electron microscopic finding of a tumor cell shows numerous lysosomes and pigment bodies in the cytoplasm.

bodies were prominent and innumerable in the majority of cells(Fig. 7). The lipid vacuoles were sometimes delineated by a fine membrane.

DISCUSSION

Bilateral primary pigmented nodular adrenocortical disease(PPNAD) is a very rare but fascinating endocrinologic disease. The variety of terms coined for this lesion, has contributed to confusion. These terms included bilateral adenomatous adrenal hyperplasia(Levin, 1966), primary adrenocortical nodular dysplasia(Meador et al., 1967 ; McArthur et al., 1982 ; Schweizer-Cagianut et al., 1982 ; Larsen et al., 1986), micronodular adrenal disease(Ruder et al., 1974), microadnomatosis(Schweizer-Cagianut et al., 1980), primary adrenal hyperplasia, micronodular and macronodular types(Donaldson et al., 1981 ; Joffe and Brown, 1983 ; May et al., 1983 ; Smals et al., 1984), microadenomatous adrenal with hypercortisolism(Page et al., 1986), and bilateral primary pigmented nodular adrenocortical disease(Shenoy et al., 1984; Lack, 1990). This inconsistency in nomenclature reflects the uncertainties in the nature and pathogenesis of the disorder.

PPNAD is an unusual cause of Cushing's syndrome. Whereas Chute et al.(1949) were the first to report a case of Cushing's syndrome associated with small pigmented nodules of the adrenal gland in children, Ruder et al.(1974) first suggested that such a condition represented an entity distinct from the more common pituitary dependent Cushing's syndrome with micro- and macronodular adrenocortical hyperplasia.

The patient described herein presented a rare form of primary adrenal disease producing ACTH-independent Cushing's syndrome. The following biochemical findings supported the autonomous nature of PPNAD : 1) increased plasma cortisol levels, 2) plasma ACTH levels which were undetectable or low, 3) lack of suppression with low-dose or high-dose dexamethasone. Thus, low or undetectable ACTH levels, the absence of dexamethasone suppression aided in making a diagnosis. However, lack of dexamethasone suppression has also been described in adrenal nodular hyperplasia caused by pituitary ACTH overproduction(Smals et al., 1984). In this case, the ACTH value was inappropriately high to the corresponding cortisol concentration. Likewise, lack of dexamethasone suppression could also occur with adrenal adenoma ; in this case, ACTH would be expected to be suppressed just as in PPNAD. In 1988 Hermus et al.(1988) described a case of transition from pituitary dependent to adrenal dependent Cushing's syndrome. In that case, the plasma ACTH was suppressed and at most times undetectable immunoassayable levels, and the responsiveness of the pituitary-adrenal axis to dexamethasone. Histologically, it showed macronodular hyperplasia with foci of micronodular hyperplasia. However, this present case differed from that case in sense of dexamethasone suppression test. Ruder et al.(1974) and Larsen et al. (1986) suggested that a small subset of these conditions with nodular adrenal glands should be set apart for the following reasons: 1) the disease is distinct due to both the degree of nodule pigmentation and the cortical atrophy between the nodules as opposed to hyperplasia seen in other nodular disorders ; 2) Cushing's symptoms are frequently so mild that a long interval between onset of symptoms and diagnosis is not uncommon ; 3) the condition usually presents in a younger age group and rarely in adults(McArthur et al., 1982 ; Shenoy et al., 1984) ; 4) the treatment of this disorder requires

bilateral adrenalectomy, as it is functionally independent of the pituitary and has never been associated with pituitary adenomas or microadenomas, in contrast to other forms of nodular hyperplasia.

Computed tomographic scanning of the abdomen and the surgical specimen itself should demonstrate the adenoma or PPNAD(Larsen et al., 1986). However, due to the rarity of PPNAD, imaging studies have only been reported in a few patients. Doppman et al.(1988, 1989) demonstrated unilateral or bilateral nodularity in five of six patients examined by CT and/or magnetic resonance. Sonographic diagnosis of adrenal mass is usually difficult because of bowel gas, small size of mass and obesity in Cushing's syndrome. CT could detect a 5 mm nodule if the mass protruded from a margin of the adrenal gland. However, a 3 to 5 mm nodule in the adrenal gland can be obscured if the medial limb of the right adrenal gland measures up to 5 mm. This case showed 8 to 20 mm nodules and was easily detectable on CT. The echogenicity of adrenal adenoma is usually more hypoechoic than pheochromocytoma. CT density of adrenal adenoma is usually lower than pheochromocytoma and adrenal hyperplasia(Doppman et al, 1988 ; Doppman et al., 1989).

Although certain historic and diagnostic clues may lead a clinician to suspect this unusual condition, the pathologic features of the adrenal glands themselves confirm it. Grossly, the glands may be small to slightly enlarged but never as large as seen with long-standing hyperplasia. The average combined weight of 29 pairs of resected adrenal glands was 9.5 grams(range 4 to 21 grams)(Lack, 1990). The nodules may not be apparent on gross examination, but they usually are visible as focal pigmentation on cut section. The nodules have been described as up to 5 mm in size, but they are usually microscopic to 3 mm. The largest cortical nodules described by Shenoy et al.(1984) measured 1.8 cm in diameter and appeared to result from a confluence of several smaller nodules. However, in this case, the largest one was 1.7 cm in diameter and both adrenal glands weighed 14.5 grams.

Microscopically, it is difficult to be sure about the precise site of origin since some nodules fill the entire thickness of the cortex and out on the capsule, whereas others show no apparent involvement of zona reticularis(Lack, 1990). Most micronodules are composed of cells with compact eosinophilic cytoplasm and abundant granular brown pigment. A lipomatous or myelolipomatous component is seen in some micronodules(Shenoy et al., 1984 ; Lack, 1990). The pigment is lipofuscin and has been described as yellow-brown, green-black or dark red brown(Larsen et al., 1986). However, as demonstrated in the recent study by Damron et al.(1987) of incidental pigmented nodules, a component of neuromelanin could be present. In this case, the pigments were regarded as lipofuscin. There is also internodular cortical atrophy.

Ultrastructurally, the cells were arranged in groups with a convoluted plasma membrane and prominent large tubulovesicular mitochondria. Many lysosomes were present in the cytoplasm of the cells. The tubulovesicular appearance of the mitochondria seen in our case is nearly always seen in cells producing steroids. These features are those of the zona fasciculata and are compatible with those of Hasleton et al.(1982).

Interestingly in a number of instances, PPNAD has a familial predilection with involvement of more than one family member(Arce et al., 1978 ; Schweizer-Cagianut et al., 1980 ; Bohm et al., 1983) and there is a possibility that cardiac myxoma and peculiar Sertoli cell tumors of the testis may be associated with this PPNAD(Proppe and Scully, 1980). This case showed no other clinical manifestations or family history. Differentiation of primary pigmented nodular adrenocortical disease from Cushing's disease is important therapeutically. Recent evidence suggests that the treatment of Cushing's disease should be directed at the pituitary gland(McArthur et al., 1979 ; Lansen et al., 1986), whereas the treatment of choice for PPNAD is adrenalectomy followed by replacement therapy with glucocorticoids and mineralocorticoids.

In this report, we discussed the clinical characteristics and pathologic features of PPNAD in conjunction with pigment nature and cellular origin.

ACKNOWLEDGMENTS

The authors would like to thank Sung-Woon Kim, M.D., Section of Endocrinology, Department of Internal Medicine, School of Medicine, Kyunghee University, Seoul, Korea for his critical review of this manuscript.

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