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Adrenal Black Adenoma Associated with Cushing's Syndrome

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We report a case of adrenal black adenoma associated with Cushing's syndrome. A 41-yr-old man presented to our hospital with a 6-yr history of severe hypertension and general fatigue, and a 1-mo history of diabetes mellitus. Physical examination disclosed cushingoid manifestations. His serum cortisol concentrations ranged from 14.0 to 15.4 μg/dL, with an ACTH level <5 pg/mL. Urinary free cortisol level was increased (125 μg/d). Cortisol was not suppressed on the overnight 1 mg oral dexamethasone suppression test (DST), 2-d low-dose DST, and 2-d high-dose DST. Abdominal computed tomography and magnetic resonance imaging studies revealed a solid round tumor approx 3 cm in diameter, located in the left adrenal gland. Left adrenalectomy was performed; the surgical specimen revealed a black adenoma consisting of compact cells within numerous pigments that seemed to be lipofuscin in nature.

Key Words: Cushing's syndrome; black adenoma; lipofuscin.

Introduction

Functioning black adenoma of the adrenal gland is a rare disorder, and has been reported to cause Cushing's syndrome *(1–3)*. Although most functioning adrenal cortical adenomas are mainly composed of clear cells of the fasciculata zone with abundant lipid inclusion, which appear as typical yellowish tumors on sectioning, adrenal black adenomas are composed of predominantly compact cells with numerous pigmented granules *(1,4)*. Atrophy of the adjacent nontumorous adrenal cortex is helpful for the diagnosis of functional adrenal adenoma. We report here a case of Cushing's syndrome due to functioning black adenoma of the adrenal gland; whose criteria for the diagnosis are adrenal adenoma, presence of clinical symptoms of Cushing's syndrome and chronic autoproduction of cortisol.

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Case Report

A 46-yr-old man was admitted to our hospital with progressive generalized weakness, general fatigue, easy bruisability, and weight gain. He also had severe hypertension for 6-yr and had diabetes mellitus for 1 mo, and had been receiving calcium antagonists, α- and -β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and subcutaneous insulin daily. On admission, his blood pressure was 200/140 mmHg. A physical examination revealed cushingoid features (central obesity, moon face), skin atrophy, and proximal muscle weakness. However, purple stria, buffalo hump, or peripheral edema were not observed. Endocrinological studies were consistent with adrenal Cushing's syndrome. Serum cortisol levels were normal, and diurnal cortisol variation revealed an AM cortisol of 15.4 μg/dL (normal 5–23) with a PM cortisol (at midnight) of 14.0 μg/dL, while ACTH level was <5 pg/mL (IRMA, normal range: 9.0–52 pg/mL). Diurnal variation of cortisol is minimal is this patient. Urinary free cortisol (UFC) was also increased (125 μg/d) (normal range: 20–90 μg/d). A single-dose 1-mg overnight dexamethasone suppressin test (DST) demonstrated an increase in AM cortisol from 15.4 to 16.6 μg/dL. A low-dose 2-mg DST demonsrated a decrease in AM cortisol from 15.4 to 12.5 μg/dL, and a decrease in 24-h UFC levels from 125 to 35 μg/dL. A 2-d high-dose 8-mg DST demostrated a decrease in AM cortisol from 15.4 to 14.2 μg/dL. Plasma renin activity, serum aldosterone concentrations, and urine catecholamines and its metabolites were within normal ranges. Abdominal computed tomography showed a well-demarcated solid mass (30 ↔ 30 mm) in the region of the left adrenal gland (Fig. 1). Abdominal magnetic resonance imaging (MRI) revealed a well-demarcated isointense mass measuring 30 ↔ 35 mm, located in left adrenal gland, on both T_1- and T_2-weighted seguences (Fig. 2A). Out-of-phase MR image (Fig. 2B) did not show significant signal loss in the lesion when compared with in-phase MR image (Fig. 2C).

On the basis of symptoms, laboratory findings, and imaging studies, the existence of an autonomous adenoma of the left adrenal cortex was suspected. A left adrenalectomy was performed by the transabdominal route under general anesthesia. The resected tumor was well-circumscribed, measured 30 ↔ 30 ↔ 25 mm in dimension, weighing 8.2 g and it was encapsulated. Residual adrenal gland, which was adjacent

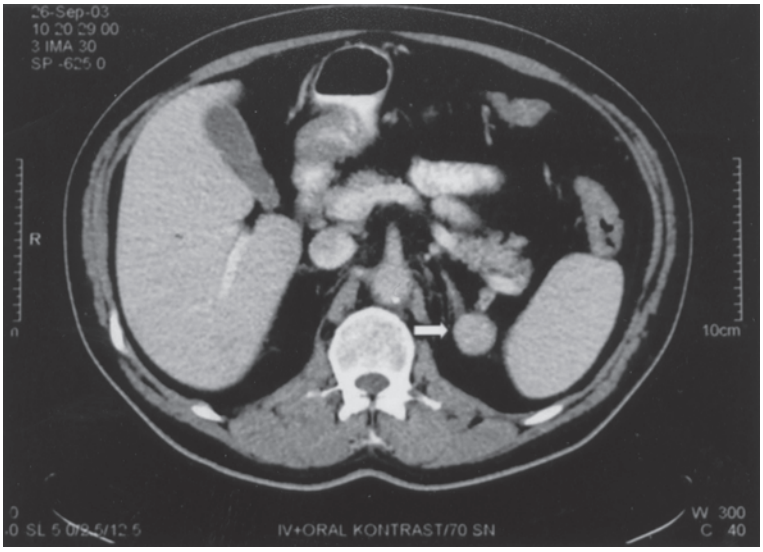

Fig. 1. Contrast-enhanced axial CT scan shows a solid homogeneous tumor at the left adrenal gland (arrow).

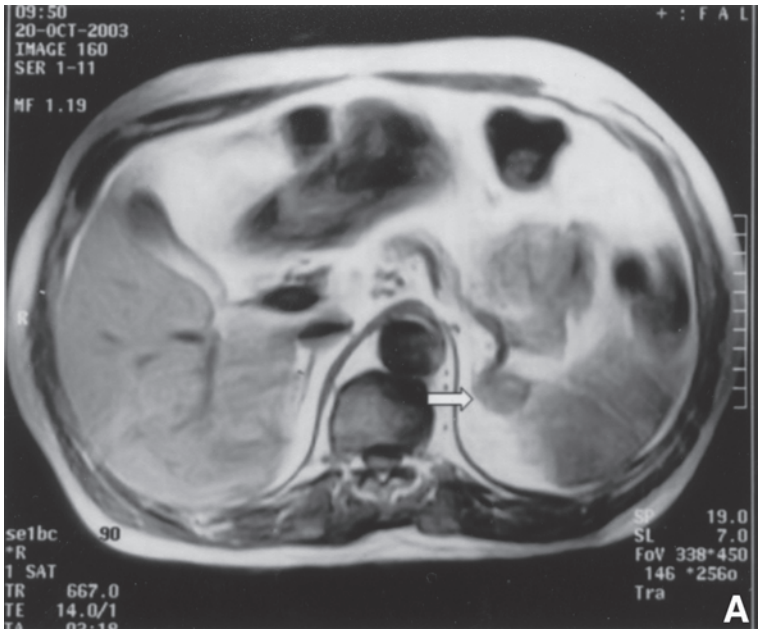

Fig. 2. T_1-weighted magnetic resonance image demonstrating round homogeneous tumor with isointensity signal at the left adrenal gland (**A**) (arrow).

to the adenoma, showed atrophic change of the cortex. The cut surface of the tumor was black color with small yellowish areas (Fig. 3). Microscopic examination of the excised specimen revealed that the tumor consisted of compact cells; in most of the cells the cytoplasm contained numerous pigment granules which appeared dark to golden brown on hematoxylin-eosin staining (Fig. 4A). The pigment granules were positive for Fontana–Masson staining (Fig. 4B), supporting the proposed lipofuscin nature of the pigment. The adenoma was divided by thin fibrovascular septa with small round cell infiltration. Tumor cells showed neither necrosis nor mitosis and there was no finding of vascular invasion.

Discussion

Adrenal black adenoma is classified into either a functional or a non-functional lesion depending on its endocrine activity *(5,6)*. Non-functioning adrenal black adenoma is occasionally encountered at autopsy, with an incidence rate ranging from 10 to 37% *(7,8)*. In contrast, functioning black adenoma of the adrenal gland is considered to be a rare dis-

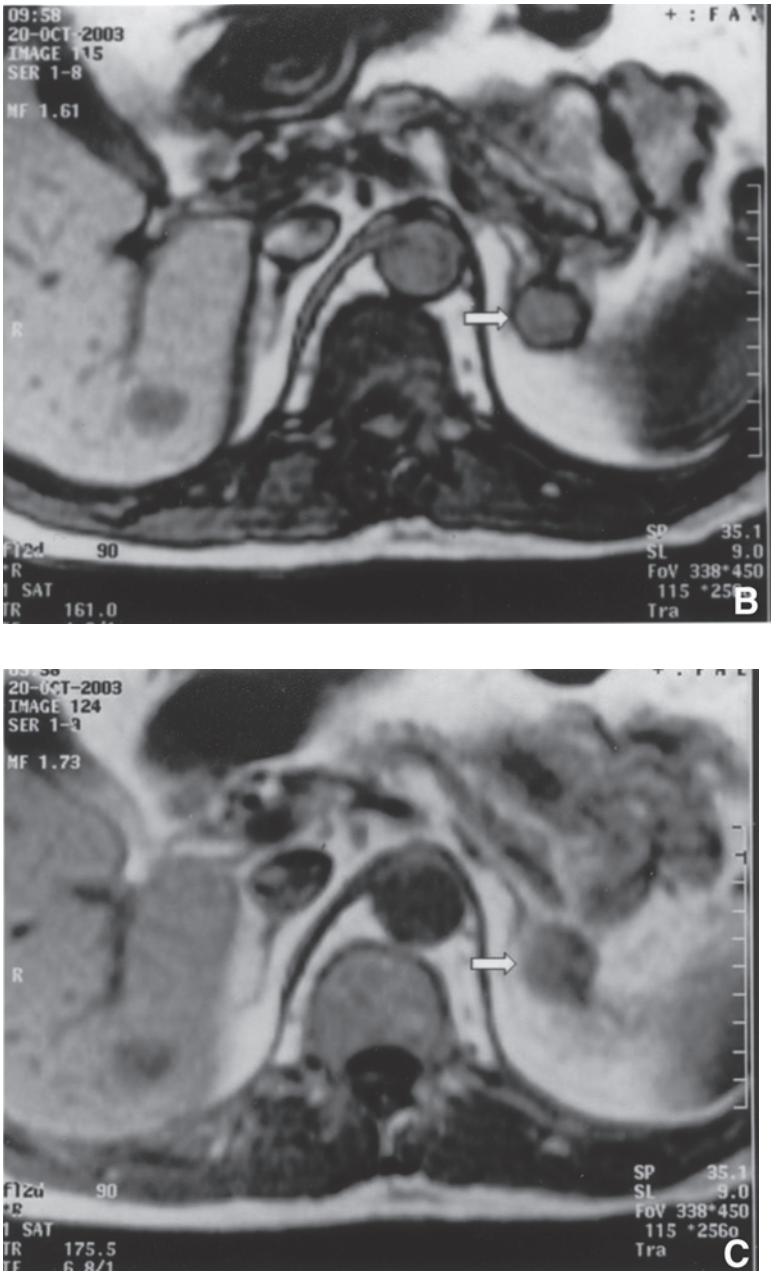

Fig. 2. Out-of-phase MR image (**B**) show no significant signal loss in the lesion when compared with in phase MR image (**C**).

ease, with approx 52 cases reported in recent years (more than 40 cases have been reported in Japan) *(1,2,6,8–10)*. In the literature, a unique case of functioning adrenal black adenoma of the adrenal gland was reported from Turkey *(10)*. To our knowledge, the present case is only the second report of functioning adrenal black adenoma from Turkey.

Functioning black adenoma has been reported to cause Cushing's syndrome and, rarely, hyperaldosteronism and virilization *(11,12)*. The clinical signs and laboratory data do not appear to differ between an ordinary "yellow" adenoma and a black adenoma *(13)*.

MRI of an adrenal mass has been proposed to have diagnostic value for the differential diagnosis between cortical adenoma and carcinoma *(14,15)*. Most adrenal cortical adenomas show signal intensities similar to those of the liver on both T_1- and T_2-weighted sequences, and the present case is in agreement. However, it is well known that most adrenal adenomas demonstrate signal loss on out-of-phase MR image. The present case does not follow this pattern because the mass did not demonstrate signal loss on out-of-phase MR image compared to in-phase MR image. Therefore, in patients with functioning black adenoma, the impor-

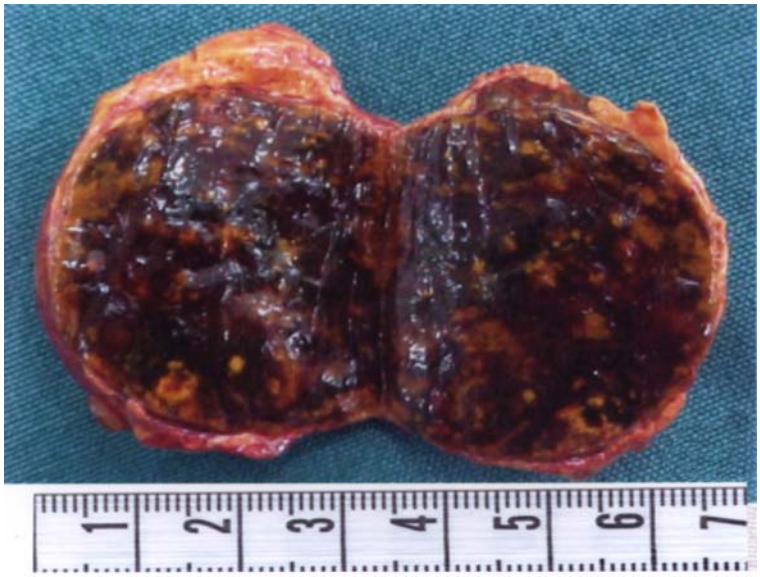

Fig. 3. The surgically resected well-circumscribed left adrenal mass measured 35 × 30 × 20 mm in dimension, The cut-surface of the adrenal adenoma had a black-brown appearance without evidence of hemorrhage or necrosis.

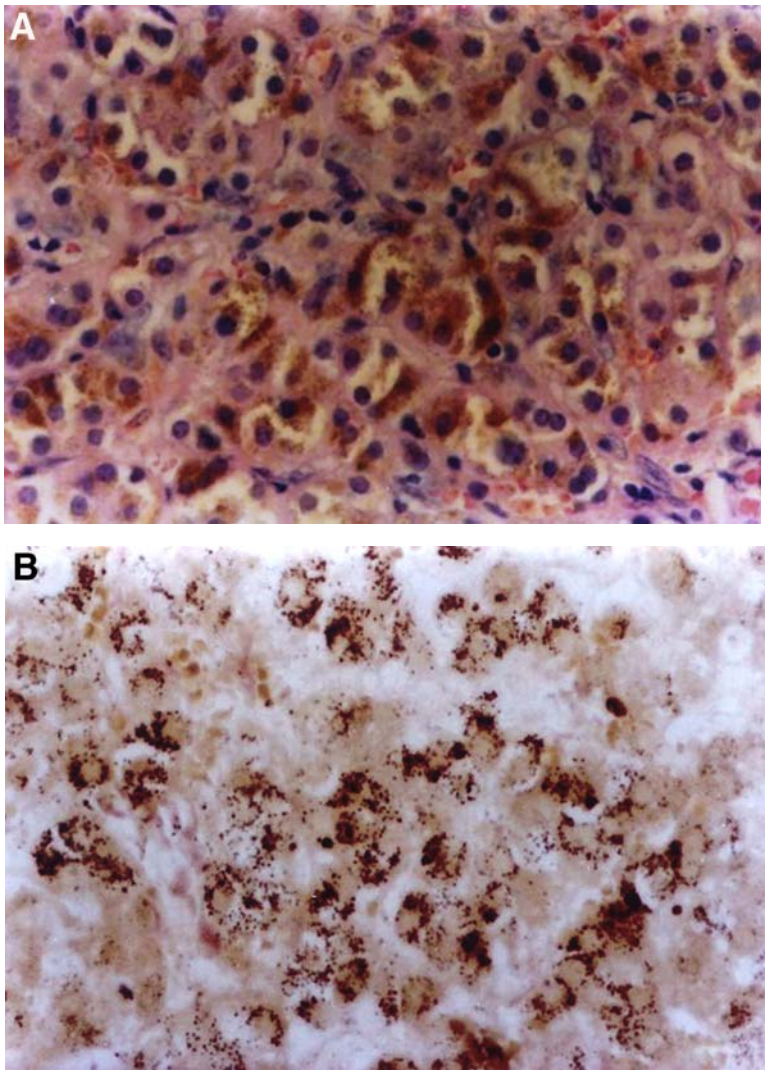

Fig. 4. (**A**) Microscopic appearance of the black adenoma The tumor cells consisted of compact cells arranged in sheets and cords. The nuclei were uniform. The cells were filled with numerous brown pigments (hematoxylin and eosin staining, original magnification ×400). (**B**) The pigmented granules were positive for Fontana–Masson staining (H&E ×400).

tant clinical problem may be the exclusion of malignancy. Moreover, absence of signal loss on out-of-phase MR image may result from the presence of abundant lipofuscin pigments in the black adenoma.

Histological observation of adrenal black adenoma revealed predominantly compact cells with few lipids. The tumor cells form pigmented nodules *(4)*. Ultrastructurally, the numbers of lysosomes, endoplasmic reticulum, mitochondria, and particularly the characterisic lipofuscin granules have been reported to be increased *(4,16)*. The pigmented granules, which appear to be lipofuscin, give the adenoma its grossly apparent black appearance. The storage of lipofuscin is based on lipoid peroxidation *(17)*. Lysosomes absorb the remaining intracellular products including the products of lipoid peroxidation. Lipofuscin accumulates as residual bodies as a result of incomplete lysosomal digestion. In the present case, a left adrenal tumor contained numerous lipofuscin granules in the tumor cells. The absence of mitosis, tumor cell necrosis, or vascular invasion generally excludes the possibility of malignancy *(18)* and the characteristics were absent in the present tumor. Therefore, we diagnosed the present case as benign functioning black adenoma.

References

1. Odanaka, M., Katabami, T., Inoue, M., and Tadokoro, M. (2003). *Pathol. Int.* **53,** 796–99.
2. Ueda, Y., Tanaka, H., Murakami, H., et al. (1997). *Intern. Med.* **36,** 398–402.
3. Takahashi, S., Liijama, H., Moriwaki, Y., et al. (2001). *J. Endocrinol. Invest.* **24,** 816–819.
4. Suzuki, K., Ojima, M., and Sasao, N. (1985). *Virchow Arch.* **405,** 161–173.
5. Visser, J. W., Boejinka, J. K., and Meer, C. D. (1974). *J. Clin. Pathol.* **98,** 13–42.
6. Komiya, I., Takasu, N., Aizawa, T. et al. (1985). *J. Endocrinol. Metab.* **61,** 711–717.
7. Robinson, M. J., Pardo, V., and Rywlin, A. M. (1972). *Hum. Pathol.* **3,** 317–325.
8. Lui, K. K., Shikata, K., and Amano, T. (1980). *Fukuaja Acta Medica* **71,** 583–591.
9. Zaniewski, M. and Sheeler, L. R. (1980). *South. Med. J.* **73,** 1410–1412.
10. Uras, A., Budak, D., Ariogul, O., Gorpe, A., and Tahsinoglu, M. (1978). *Clin. Oncol.* **4,** 181–186.
11. Sienskowski, I. K., Watkins, R. M., and Anderson, W. E. R. (1984). *J. Clin. Pathol.* **37,** 143–149.
12. Neville, A. M. and O'Hare, M. J. (1982). *Pathology and biology: an integrated approach.* Springer: New York, pp. 139–144.
13. Tseng, C. H., Chang, G. K. J., Wong, Q. Y., and Lin, J. I. (1978). *South. Med. J.* **71,** 1166–1168.
14. Higgins, C. B. and Hricak, H. (1987). *Magnetic resonance imaging of the body.* Raven Press: New York, p. 383.
15. Council on Scientific Affairs. (1989). *JAMA* **261,** 420–433.
16. Mizutani, S. and Igarashi, N. (1975). *Morphology and function of adrenal cortex.* Nankodo: Tokyo, pp. 294–299.
17. Yin, D. (1996). *Free Radic. Biol. Med.* **21,** 871–888.
18. Weiss, L. M., Medeiros, L. J., and Vickery, A. L. Jr. (1989). *Am. J. Surg. Pathol.* **13,** 202–206.