

Figura 1 Gammagrafía tiroidea con ^{99m}Tc : exploración de baja calidad por inadecuada captación tiroidea del trazador. La causa puede atribuirse a repetidas curas con povidona yodada, por lesiones en los pies.

escape que normaliza la producción hormonal. A pesar de ello, el exceso de yodo también puede producir un hipertiroidismo (efecto Jod-Basedow), debido a la hiperproducción y liberación brusca de hormonas tiroideas en respuesta a la administración de grandes cantidades de yodo. Este fenómeno afecta más frecuentemente (aunque no de forma exclusiva) a personas con afección tiroidea previa como, por ejemplo, bocio endémico, bocio multinodular tóxico o déficit de yodo³.

No obstante, la sobrecarga de yodo es una causa poco frecuente de hipertiroidismo; por ello, la historia clínica detallada es fundamental para su detección, incluyendo datos sobre el consumo de medicamentos o suplementos dietéticos⁴ con elevado contenido de dicho elemento, la utilización de soluciones antisépticas como la povidona yodada o la realización de pruebas de imagen con contraste. La mayoría de casos de hipertiroidismo inducido por yodo son autolimitados y se resuelven con el cese de la exposición⁵.

En resumen, se presenta un caso de hipertiroidismo subclínico inducido por un exceso de yodo tóxico en un paciente

sin enfermedad tiroidea previa, que se resolvió tras sustituir la povidona yodada por una solución antiséptica exenta de yodo. La aplicación de antisépticos yodados es una práctica muy extendida en el ámbito hospitalario, especialmente en pacientes sometidos a cirugía o en aquellos con úlceras, tanto de origen arterial como venoso⁶. En caso de exposición prolongada, es importante tener presente la posible disfunción tiroidea dado que, como en el caso presentado, puede no ser excepcional aún sin antecedentes de afección tiroidea.

Bibliografía

1. Brotfain E, Koyfman L, Frenkel A, Smolikov A, Zlotnik A, Klein M. Iodine-induced hyperthyroidism-an old clinical entity that is still relevant to daily ICU practice: A case report. *Case Rep Endocrinol.* 2013;2013:792745.
2. Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, DC: National Academy Press; 2001.
3. Nobukuni K, Hayakawa N, Namba R, Ihara Y, Sato K, Takada H, et al. The influence of long-term treatment with povidone-iodine on thyroid function. *Dermatology.* 1997;195 Suppl 2: S69-72.
4. Salas Coronas J, Cruz Caparrós G, Laynez Bretones F, Díez García F. Hipertiroidismo inducido por consumo de algas marinas. *Med Clin (Barc).* 2002;118:796-9.
5. Pagliaricci S, Lupatelli G, Mannarino E. Hyperthyroidism due to the improper use of povidone-iodine. *Ann Ital Med Int.* 1999;14:124-6.
6. Shetty KR, Duthie EH Jr. Thyrotoxicosis induced by topical iodine application. *Arch Intern Med.* 1990;150:2400-1.

María José Burchés-Feliciano*, María Argente-Pla, Katherine García-Malpartida, Matilde Rubio-Almanza y Juan Francisco Merino-Torres

Departamento de Endocrinología y Nutrición, Hospital Universitario y Politécnico La Fe, Valencia, España

* Autor para correspondencia.

Correo electrónico: mjburches@yahoo.com
(M.J. Burchés-Feliciano).

<http://dx.doi.org/10.1016/j.endonu.2015.05.012>

Black adrenal adenoma causing Cushing's syndrome: 40 years ago and today



Adenoma suprarrenal Negro causar el síndrome de Cushing: Hace 40 años y hoy

Dear Editor,

Black adrenal adenomas are adrenal cortical tumors that are black or dark brown on cut sections. The first case of black adrenal adenoma was reported in 1938.¹ Autopsy studies

published in the early 1970s suggest that the pigments in black adrenal adenomas are made of lipofuscin, a lysosomal material, and that these tumors are common autopsy findings (10% on random adrenal sections and 37% on fine sections) but do not secrete hormones.² In 1973, two of us (G.D.B. and R.R.E.) cared for and studied a patient with a black adrenal adenoma that caused ACTH-independent Cushing's syndrome. We here describe the case and discuss it in historical background and in light of the literature on this topic in the last 40 years.

A 42-year-old Caucasian female had been well until 1966 when she developed hypertension, edema, and hyperglycemia during her third pregnancy. In 1969, she developed

right femoral head aseptic necrosis. She also noted a 40-pound weight gain, rounding of face, the development of a dorsal fat pad, ruddy complexion, facial hair, weakness, easy fatigability, emotional lability, irregular menses, and easy bruising. In January 1973, she was seen at Harbor General Hospital (now Harbor-UCLA Medical Center). She denied skin darkening, exogenous steroid ingestion, or family history of endocrine diseases. Physical examination revealed a hypertensive, Cushingoid female. Endocrine evaluation revealed absence of suppression of plasma or urinary 17-hydroxysteroids by both low (2 mg) and high (8 and 12 mg) doses of dexamethasone administration. Her plasma 17-hydroxysteroids failed to increase after metopirone (more commonly called "metyrapone" now) administration

or synthetic ACTH (Cortrosyn) infusion. ACTH-independent Cushing's syndrome was diagnosed and the presence of a functional adrenal lesion deemed probable. Adrenal androgen levels were not measured. The patient underwent an exploratory laparotomy through which the right adrenal gland was found to be grossly normal but the left adrenal to harbor a mass. A left adrenalectomy was performed. Her post-operative course was uncomplicated and the Cushingoid features gradually regressed in the ensuing 2 months. She developed adrenal insufficiency postoperatively and was treated with corticosteroids with tapered doses.

The left adrenal mass appeared well circumscribed and measured 3 × 2 cm (Fig. 1). The tumor was homogeneously

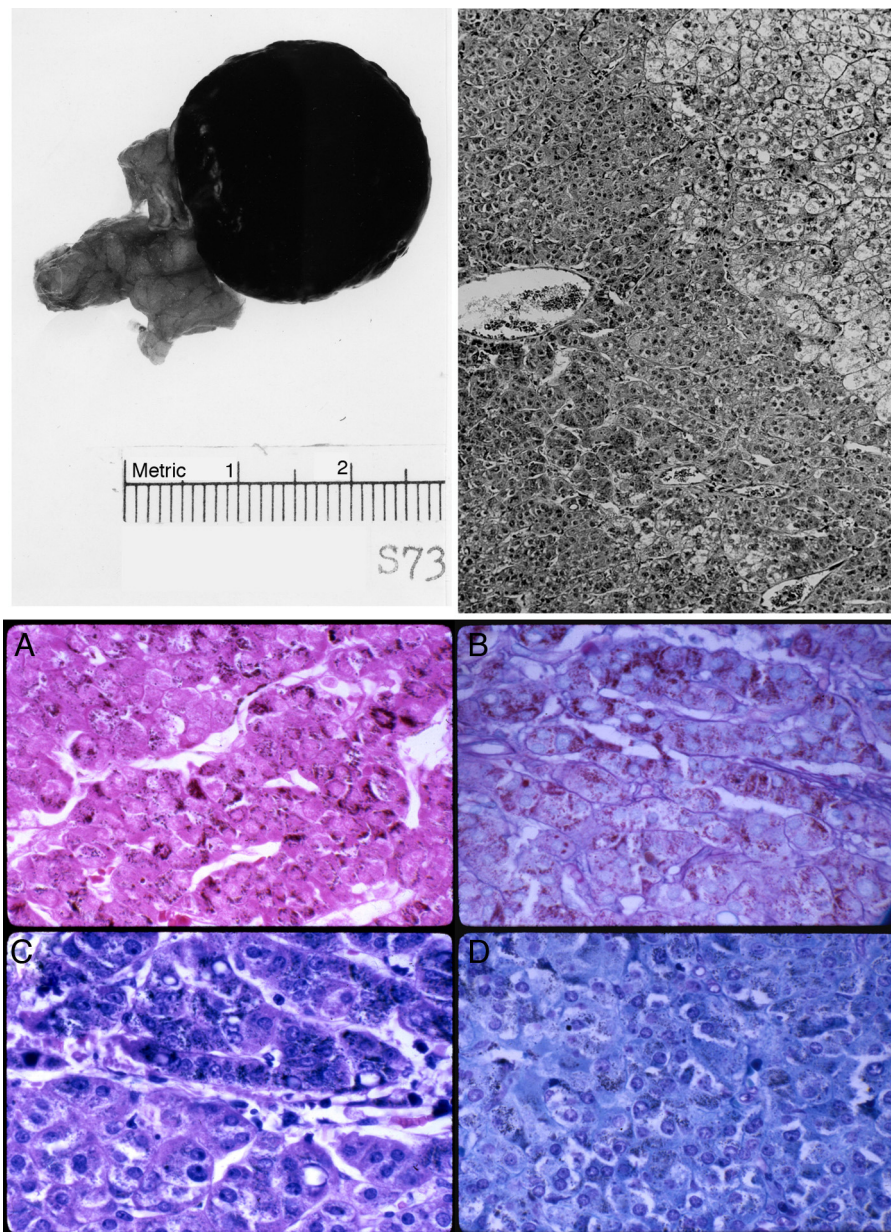


Figure 1 Top left: gross photograph of the black adrenal adenoma with atrophic adrenal seen in the adipose tissue to the left. Top right: margin of zona reticularis with pigmented tumor cells below and to the left. Hematoxylin and eosin. Magnification, 120×. Bottom: lipofuscin pigments as stained by (A) Fontana; (B) Alcian blue-PAS; (C) Giemsa; and (D) Luxol fast blue. Magnification, 480×.

dark brown to black throughout (Fig. 1, top left). Microscopically, the mass consisted of large, polygonal, eosinophilic cells resembling those of the zona reticularis. The tumor cells abutted directly on but did not invade into the non-pigmented cells of the gland (Fig. 1, top right). The majority of these cells contained heavy deposits of golden brown, slightly refractile, granular, pigments which were localized predominantly at the cell periphery. The pigments were visible also with Congo Red, Gomori iron, and in even in unstained slides (Fig. 1, bottom). It reacted weakly with Sudan black and negatively with acid fast stains. Fontana stain was strongly positive and the pigment assumed a reddish coloration with the periodic acid-Schiff's technique. The pigments appeared green with Giemsa stain and greenish blue with Luxol fast blue stain, thus indicating that they consisted of lipofuscin. Mitotic figures were very rare. The tumor cells did not exhibit nuclear atypia, necrosis, or atypical mitotic figures.

To assess how frequent the black adrenal adenoma is, we examined our pathology database between 1998 and 2014. One hundred and fourteen adrenal cortical tumors were found. The average age of patients was 53 years (range 23–70). Forty-one of the adenomas were aldosterone-secreting, 23 cortisol-secreting, 1 androgen-secreting, and 49 nonfunctional. The average adenoma size was 3.1 cm (range 0.2–27). Twenty-three of the adenomas were ≤ 1.5 cm and 91 larger. The tumor color ranged from yellow, orange, tan, red, to brown. None of the 114 adenomas was predominantly black or dark brown.

Our study of the frequency of black adrenal adenoma here and the work of others in the last 40 years advance our understanding of this interesting tumor. Black adrenal adenomas may be more common on post-mortem adrenals but they are certainly rare in surgical adrenal samples. In our own series of 115 adrenal cortical tumors from surgical adrenal samples, not a single black adrenal adenoma was encountered. Although the incidence of black adrenal adenomas has not been formally addressed in other surgical series, the mostly single-case reports of this unique-colored tumor even recently suggest that they are indeed rare in surgical adrenal samples.³ The discrepancy between the high frequency of incidental black adrenal adenomas in autopsy findings and their exceptionally low incidence in surgical series may be due to the small size and non-functional nature of the adenomas which avoid the surgery in spite of the tumors' radiological features. Most of black adrenal adenomas, like in this case, cause ACTH-independent Cushing's syndrome, some cause primary hyperaldosteronism, and a few even result in masculinization.^{3–5} Less frequently reported are nonfunctional black adrenal adenomas which present as incidentalomas.⁶ With the introduction of CT, MRI, and FDG-PET, the imaging characteristics of adrenal adenomas in general and the distinct imaging features of black adrenal adenomas in particular have now been well described. Unlike most other adrenal adenomas, the black ones exhibit high Hounsfield units (>30) on CT, high T2 signal and lack of drop of signal on out-of-phase imaging on MRI, and high standard uptake value (higher than that of liver) on FDG-PET, which all indicate less tumor lipid content but higher tissue density and blood supply, features suspicious of pheochromocytoma, interstitial tumors, and malignancy.^{6–8} Furthermore, the black adrenal adenomas

are often not visualized by radiocholesterol scintigraphy.^{9,10} Biologically, however, the black adrenal adenomas are benign without histological evidence of aggressiveness or invasiveness, as our patient's tumor. Black adrenal adenomas should now be considered as one subtype of adrenal adenomas with atypical imaging characteristics. The clinical significance of lipofuscin pigments in black adrenal adenomas remains unclear.¹¹ Black adrenal adenomas are unilateral, solitary adrenal cortical tumors; they are in contrast to primary pigmented nodular adrenocortical disease (PPNAD) which involves diffuse nodular enlargement of both adrenal glands.¹² PPNAD can occur as part of the Carney complex and is associated with a genetic defect, PRKAR1A mutation. The pigments in PPNAD are also due to lipofuscin. Patients with PPNAD can exhibit a paradoxical increase of cortisol levels after administration of dexamethasone.

In summary, black adrenal adenomas appear to derive from the zona reticularis and their black color is due to lysosomal lipofuscin. Clinically very rare tumors, they mainly present as Cushing's syndrome or other syndromes of adrenocortical hormone hypersecretion. Although biologically benign, they exhibit atypical imaging characteristics suspicious of malignancy. The main difference between black adrenal adenomas and other adrenal cortical tumors is just the appearance to the naked or aided eye.

References

1. Baker MR. A pigmented adenoma of the adrenal. *Arch Pathol.* 1938;26:845–52.
2. Robinson MJ, Pardo V, Rywlin AM. Pigmented nodules (black adenomas) of the adrenal An autopsy study of incidence, morphology, and function. *Hum Pathol.* 1972;3:317–25.
3. Ueda Y, Tanaka H, Murakami H, Ninomiya T, Yamashita Y, Ichikawa M, et al. A functioning black adenoma of the adrenal gland. *Intern Med.* 1997;36:398–402.
4. Cohen RJ, Brits R, Phillips JI, Botha JR. Primary hyperaldosteronism due to a functional black (pigmented) adenoma of the adrenal cortex. *Arch Pathol Lab Med.* 1991;115:813–5.
5. Tanaka S, Tanabe A, Aiba M, Hizuka N, Takano K, Zhang J, et al. Glucocorticoid- and androgen-secreting black adrenocortical adenomas: unique cause of corticotropin-independent Cushing syndrome. *Endocr Pract.* 2011;17:e73–8.
6. Prince EA, Yoo DC, DeLellis RA, Mayo-Smith WW. CT and PET appearance of a pigmented black adrenal adenoma in a patient with lung cancer. *Clin Radiol.* 2007;62:1229–31.
7. Nakajo M, Nakajo M, Kajiya Y, Tani A, Tsuruta M, Sugita S, et al. A black adrenal adenoma difficult to be differentiated from a malignant adrenal tumor by CT, MRI, scintigraphy and FDG PET/CT examinations. *Ann Nucl Med.* 2011;25:812–7.
8. Pitts A, Ih G, Wei M, Dhall D, Nissen NN, Waxman A, et al. Clinical utility of FDG-PET for diagnosis of adrenal mass: a large single-center experience. *Hormones (Athens).* 2013;12:417–27.
9. Ambrosi B, Colombo P, Faglia G. Cushing's syndrome due to a black adenoma of the adrenal gland: lack of tumour visualization by radiocholesterol scintigraphy. *Eur J Nucl Med.* 1994;21:1367–8.
10. Reschini E1, Baldini M, Cantalamessa L. A black adrenocortical adenoma causing Cushing's syndrome not imaged by radiocholesterol scintigraphy. *Eur J Nucl Med.* 1990;17:185–7.
11. Jung T, Bader N, Grune T. Lipofuscin: formation, distribution, and metabolic consequences. *Ann NY Acad Sci.* 2007;1119:97–111.

12. Stratakis CA. Adrenocortical tumors, primary pigmented adrenocortical disease (PPNAD)/Carney complex, and other bilateral hyperplasias: the NIH studies. *Horm Metab Res.* 2007;39:467-73.

Run Yu^{a,*}, Meng Wei^b, Xuemo Fan^c, Richard R. Ellis^d, Glenn D. Braunstein^a

^a Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA 90048, United States

^b Cedars-Sinai Medical Care Foundation, Beverly Hills, CA 90211, United States

^c Department of Pathology, Cedars-Sinai Medical Center, Los Angeles, CA 90048, United States

^d Providence Little Company of Mary Medical Center, San Pedro, CA 90732, United States

* Corresponding author.

E-mail address: run.yu@cshs.org (R. Yu).

<http://dx.doi.org/10.1016/j.endonu.2015.05.002>

Síndrome de insensibilidad parcial a andrógenos con restos müllerianos. Descripción de un caso



Partial androgen insensitivity syndrome with persistent müllerian remnants. A case report

El síndrome de insensibilidad parcial a andrógenos (PAIS) es un trastorno de la diferenciación sexual 46 XY en el que existe una pérdida de función del receptor de andrógenos (RA). Se trata de una enfermedad causada por mutaciones en el gen AR (Xq11-12) que codifica para el RA.

Presentamos el caso de un recién nacido a término producto de un embarazo controlado sin complicaciones, segundo hijo de padre de origen italiano y madre dominicana, sanos y no consanguíneos. Ecografías prenatales normales con diagnóstico de sexo femenino. Peso al nacimiento 2.862 g (-0,12 DE), longitud 46,5 cm (-0,62 DE), perímetro cefálico 35 cm (1,16 DE), con Apgar 8-9. Presentaba genitales ambiguos, hiperpigmentados, con un tubérculo genital de 1,5 cm con meato urinario hipospádico, rodetes de labios escrotales simétricos, fusionados en su porción posterior, sin abertura vaginal ni testes a la palpación, correspondiente a Prader 4-5 (fig. 1). Presentó un distrés respiratorio leve, secundario a una hipertensión pulmonar con una miocardiopatía hipertrófica no obstructiva, que se resolvió en 2 semanas. El equilibrio ácido-base y los niveles de sodio y potasio fueron normales. La ecografía abdominal realizada el primer día de vida demostró una estructura compatible con útero y una cavidad endometrial rellena de líquido, no visualizándose ovarios ni testes.

El estudio hormonal en la primera semana de vida mostró LH < 0,1 UI/ml, FSH 0,4 mUI/ml, testosterona 152 ng/dl, cortisol 7 µg/ml, ACTH 23,3 pg/ml, androstendiona 5,5 ng/ml, DHEAS 159 µg/ml, aldosterona 1.428 pg/ml, 17-hidroxi-progesterona 9 ng/ml, renina 12,2 ng/ml/h y estradiol 17-beta < 12 pg/ml, dihidrotestosterona 28,2 ng/dl, todos dentro de valores normales. Posteriormente se solicitó: 11-desoxicortisol 6,15 ng/ml, desoxicorticosterona 3 ng/ml, inhibina B 99 pg/ml y hormona antimülleriana 18,8 ng/ml, también en valores normales para la edad.

El cariotipo fue 46 XY, compatible con trastorno de la diferenciación sexual 46 XY con genitales ambiguos y el estudio de la microdelección del gen SRY resultó normal. Se solicitó estudio del gen del receptor de los andrógenos y del

gen SRD5A2, asociado al déficit de 5-alfa-reductasa, ya que la madre nació en la comarca de la República Dominicana donde se describió este síndrome.

La cistouretrografía miccional seriada evidenció una uretra de morfología masculina con un seno urogenital y un nuevo control ecográfico a los 10 días de vida reveló la presencia de estructuras paravesicales compatibles con gónadas sin folículos en su interior, de 0,8 y 1 cm. Ante el hallazgo del sexo genético 46 XY, la producción de testosterona en niveles normales por una estructura ajena a la suprarrenal (en un probable tejido testicular posiblemente en la gónada), uretra de longitud y trayecto de características masculinas, y la existencia de un pene de tamaño aceptable y tras el acuerdo multidisciplinar entre endocrinología infantil, cirugía infantil, neonatología y la familia, a los 18 días de vida se le asignó sexo masculino.

A los 36 días de vida fue sometido a cirugía por una hernia inguino-escrotal izquierda, realizándose orquidopexia y biopsia gonadal. La biopsia testicular evidenció hipoplasia germinal marcada (tipo II de Nistal et al.¹) y cariotipo gonadal 46 XY.

Ante el hallazgo de un recién nacido con genitales ambiguos y una estructura compatible con útero en ecografía de urgencia, el diagnóstico más probable es una virilización de una mujer 46 XX, siendo la causa más frecuente la hiperplasia suprarrenal congénita por el déficit de 21-hidroxi-lasa. Al demostrarse un sexo genético 46 XY, el trastorno de la diferenciación sexual 46 XY es más complejo de filiar². El estudio del gen SRY, principal gen implicado



Figura 1 Genitales ambiguos al nacimiento.