

ATRIAL MYXOMA AND ASSOCIATED CUSHING SYNDROME: CARNEY COMPLEX

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Abstract A 33-year-old woman with a history of high blood pressure since she was 8 years old, hypothyroidism, polycystic ovary syndrome, metabolic syndrome, multiple nevi, and a maternal family history of death at age 50 due to malignant high blood pressure and heart failure. Cushing's syndrome secondary to a secretory pituitary microadenoma was diagnosed, being the cause of secondary arterial hypertension, and ruling out other causes such as renal stenosis and coarctation of the aorta. A transthoracic and transesophageal echocardiogram was performed, which detected a left atrial myxoma. Given the presence of an atrial myxoma, Cushing's syndrome and polycystic ovary syndrome, a diagnosis of Carney Complex was made due to the presence of positive Stratakis criteria. The cardiac tumor was resected, and pathology confirmed that it was an atrial myxoma. She evolved clinically stable in outpatient controls in a 6-month follow-up. Resection of the pituitary microadenoma is planned as a curative treatment for Cushing's syndrome and arterial hypertension.

Key words: myxoma, hypertension, Cushing syndrome, Carney complex

Resumen *Mixoma auricular y síndrome de Cushing asociado: complejo de Carney.* Mujer de 33 años, con antecedentes de hipertensión arterial desde los 8 años, hipotiroidismo, síndrome de ovario poliquístico, síndrome metabólico, nevos múltiples y antecedente familiar materno de muerte a los 50 años por hipertensión arterial maligna e insuficiencia cardíaca. Se diagnosticó síndrome de Cushing secundario a un microadenoma hipofisario secretor, siendo la causa de la hipertensión arterial secundaria, y descartándose otras causas como estenosis renal y coartación de aorta. Se realizó un ecocardiograma transtorácico y transesofágico que detectaron un mixoma auricular izquierdo. Ante la presencia de un mixoma auricular, síndrome de Cushing y síndrome de ovario poliquístico se llegó al diagnóstico de Complejo de Carney por la presencia de criterios de Stratakis positivos. Se realizó la resección del tumor cardíaco, y la anatomía patológica confirmó que se trataba de un mixoma auricular. Evolucionó clínicamente estable en controles ambulatorios en un seguimiento de 6 meses, y se planifica la resección del microadenoma hipofisario como tratamiento curativo del síndrome de Cushing y la hipertensión arterial.

Palabras clave: mixoma, hipertensión, síndrome de Cushing, complejo de Carney

Atrial myxoma (AM) is the most frequent benign cardiac tumor (CT)¹. Most AM are sporadic, although sometimes they can be familiar and associated with endocrine disorders as part of the Carney Complex (CC)¹⁻³. The diagnosis of CC is performed using the Stratakis criteria²⁻⁴.

Clinical case

A 33-year-old woman with a history of high blood pressure since she was 8 years old, hypothyroidism, polycystic ovary syndrome, metabolic syndrome, multiple nevi, and a maternal family history of death at age 50 due to malignant high blood pressure and a possible Cushing Syndrome (CS). Also, characteristically she presented multiple nevi on the face and back,

and a blue nevus. The patient was medicated with valsartan, metformin, levothyroxine, lercanidipine and atorvastatin.

Renal artery stenosis and aortic coarctation were ruled out by doppler. A transthoracic echocardiogram was performed, which showed preserved left ventricular diameters, thickness and function, and the presence of a rounded mass of 15 mm in diameter in the left atrium. Transesophageal echocardiography was made, and it confirmed the presence of this heterogeneous mass with irregular borders and independent mobility (a rounded portion of 17 × 22 × 13 mm and a filiform mobile portion of 16 mm in length), inserted in the septal face of the left atrium, compatible with AM (Fig. 1A y 1B).

The study of hypertension was completed by serum laboratory examination, which showed cortisol 1267 ug/dL (high value), adrenocorticotrophin 44 pg/ml (high value). Thyrotrophin, insulin, triglycerides, HDL-c, LDL-c, urinary ions and metanephrines were normal. The diagnosis of CS was made due to the presence of compatible clinical manifestations and serum laboratory alterations. A brain magnetic resonance detected a posterior pituitary microadenoma of 6 mm diameter (ruling out embolic events associated with AM) (Fig. 1C). Adrenal glands were normal in abdomen magnetic resonance. A gynecologic ultrasound revealed benign ovarian cysts. In

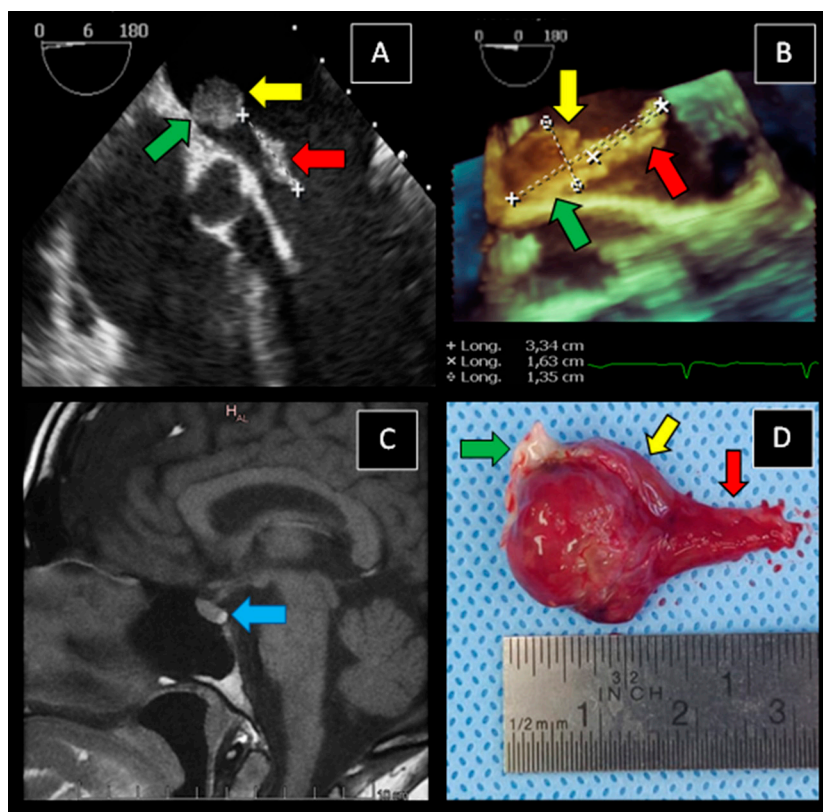
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Fig. 1.– Atrial myxoma (AM) and pituitary microadenoma in the patient with Carney Complex.

AM sited in the left atrium, assessed by bi-dimensional TEE in apical 5C view in 1A image and by three-dimensional TEE in *mid-esophageal* 0° 4C view in 1B image (the insertion site in green arrows, the rounded portion in yellow arrows, and the filiform mobile portion in red arrows). Pituitary microadenoma evaluated by brain magnetic resonance imaging in 1C (blue arrow). Resected AM in 1D (the insertion site in green arrows, the rounded portion in yellow arrows, and the filiform mobile portion in red arrows).



TEE: transesophageal echocardiogram; 5C: five-chamber; 4C: four-chamber

the presence of AM, polycystic ovary syndrome and CS due to hypersecretory pituitary microadenoma, with a family history of malignant hypertension, a diagnosis of CC was made according to the Stratakis criteria (Table 1).

Given the high embolic risk of AM, it was decided to perform surgery as soon as possible. Coronary and carotid atherosclerotic obstructions were ruled out by Doppler ultrasound and coronary tomography. AM resection without a patch was performed. It required dobutamine 5 mg/kg/min and nitroglycerin 10 µg/min in the postoperative period, without complications. Pathological anatomy confirmed that it was an AM (Figure 1D). The *PRKAR1A* gene mutation by next generation deoxyribonucleic acid sequencing techniques (Illumina technology) was negative. It was evaluated in a peripheral blood sample, and then corroborated by Sanger technique and in an external database. However, CC diagnosis was still confirmed by clinical Stratakis criteria.

The patient evolved clinically stable in outpatient controls during 6 months of follow up, and her blood pressure was controlled with valsartan 160 mg and lercanidipine 10 mg daily. Surgical resection of pituitary microadenoma will be performed as a curative treatment for CS and secondary hypertension.

Discussion

AM are the most frequent benign CT in adults, usually sporadic, but sometimes they can be associated with endocrine disorders as part of CC¹⁻³. CC was described in 1985 as a rare disease characterized by the presence of AM, skin hyperpigmentation, and endocrine hyperactivity²⁻⁴. The Mayo Clinic series reported 353 CC patients, 63% females, aged between the second and third decade of life. The presence of inactivating mutations of the *PRKAR1A* gene was detected in 73% of cases⁵. The reported patient is a young woman that present an AM, CS, skin hyperpigmentation with atypical distribution and a history of malignant secondary hypertension, so the suspicion of CC was high. CC can be inherited with an autosomal dominant pattern, and the *PRKAR1A* gene is the most frequently compromised, although this is not the

TABLE 1.– Diagnostic criteria for Carney complex (CC)

Main criteria
– Irregular skin pigmentation with typical distribution (labia, conjunctiva and inner or outer edges, vaginal and penile mucosa).
– Myxoma* (cutaneous and mucosal)
– Cardiac myxoma*
– Breast myxomatosis* or suggestive MRI findings
– Primary pigmented nodular disease, or paradoxical positive response of urinary glucocorticosteroid excretion to dexamethasone administration (Liddle's test)
– Acromegaly due to GH-secreting pituitary adenoma*
– Large cell calcifying Sertoli cell tumor*
– Thyroid carcinoma* or multiple hypoechoic nodules in a young patient
– Melanotic psammomatous schwannomas*
– Blue nevus or blue epithelioid nevus*
– Mammary ductal adenoma*
– Osteochondromyxoma*
Complementary criteria
– First-degree relative affected
– Presence of inactivating mutations of the PRKAR1A gene
– Activating variants of the PRKACA or PRKACB gene
Suggestive findings
– Multiple pigmented lesions without typical distribution
– Common blue nevus (if multiple)
– Café-au-lait spots or other "birthmarks"
– Elevated IGF-I levels, abnormal glucose tolerance test, or paradoxical GH response to thyrotropin test in the absence of clinical acromegaly
– Cardiomyopathy
– History of Cushing's syndrome, acromegaly, or sudden death in the family
– Multiple acrochordons or other skin lesions; lipomas
– Colonic polyps (usually in association with acromegaly)
– Hyperprolactinemia (mild and almost always combined with acromegaly)
– Single, benign thyroid nodule in an individual under 18 years of age; multiple thyroid nodules in an individual over 18 years of age
– Family history of thyroid, colon, pancreatic, and ovarian carcinoma

GH: growth hormone or somatotropin; IGF-1: insulin-like growth factor-1

CC Diagnosis: The diagnosis is established by the presence of 2 or more major clinical criteria. If the patient has a germline PRKAR1A mutation, genetic activating variants and/or a first-degree relative affected with CC, a single clinical manifestation is sufficient.

* Requires histological confirmation

Adapted from Stratakis⁴.

only one affected²⁻⁷. PRKAR1A gene encodes the 1-alpha regulatory subunit of protein kinase A, related to the signaling pathway of the cAMP, and it is responsible for tumorigenesis in CC⁴⁻⁷. PRKACA and PRKACB genes activating mutations have also been related with CC, the first is associated with CS and the second with acromegaly, that could be altered in our patient⁶. Diagnosis of CC is made according to the Stratakis criteria (Table 1), with the presentation of two typical manifestations confirmed by histology, laboratory or imaging tests, or with detection of the inactivating mutation of the PRKAR1A gene⁴. The main cardiovascular manifestation of CC is AM that could

be responsible for more than 50% of mortality because of embolic phenomena, heart failure or valvular occlusion, therefore surgical treatment of AM is mandatory²⁻⁴. The most frequent cutaneous manifestations are blue lentiginos and nevi around lips, conjunctiva and oral and genital mucosa. Our patient had multiple nevi and a blue nevus without classical distribution in her face²⁻⁴. The most prevalent endocrinological manifestations are acromegaly, benign thyroid tumors and CS, this last present in this case, due to an hypersecretory pituitary microadenoma²⁻⁴. Ovarian cysts are generally benign, usually polycystic ovary as in the reported case, and the ovarian adeno-

carcinoma is exceptional^{2-4, 8-10}. Although genetic study is not a necessary criterion for diagnosis, and in fact the *PRKAR1A* gene mutation was negative in the presented case, genetic screening must be performed in all index cases in order to allow family diagnosis²⁻⁴. CC requires a close follow-up due to the risk of tumor recurrence²⁻⁴. The association of AM and endocrinological disorders should lead to suspicion of the diagnosis of CC and require an interdisciplinary management for an early treatment of its manifestations.

Conflict of interest: None to declare

References

1. Zipes D, Libby P, Bonow R, Mann D, Tomaselli G. Braunwald: Tratado de Cardiología. Texto de Medicina Cardiovascular. 11a ed. España: Elsevier 2019. ISBN: 9788491134282
2. Vargas-Barrón J, Vargas G, Roldána F, Vázquez-Antona C, Vásquez Z, Erdmenger-Orellana J. Mixomas cardíacos y complejo de Carney. *Rev Esp Cardiol* 2008; 61: 1205-9.
3. Losada E, Al Kassam D, González M. Complejo de Carney. *Endocrinol y Nutr* 2011; 5 8: 308-14.
4. Stratakis C, Kirschner LS, Carney JA. Clinical and molecular features of the Carney complex: diagnostic criteria and recommendations for patient evaluation. *J Clin Endocrinol Metab* 2001; 86: 4041-6.
5. Bertherat J, Horvath A, Groussin L, et al. Mutations in regulatory subunit type 1A of cyclic adenosine 5'-monophosphate-dependent protein kinase (PRKAR1A): phenotype analysis in 353 patients and 80 different genotypes. *J Clin Endocrinol Metab* 2009; 94: 2085-91.
6. Bosco Schamun MB, Correa R, Graffigna P, de Miguel V, Fainstein Day P. Carney complex review: Genetic features. *Endocrinol Diabetes Nutr* 2018; 65: 52- 9.
7. Stratakis C, Raygada M. Carney Complex. *Gene Reviews* 2003; 1-36.
8. Berthera J. Carney Complex. *Orphanet J Rare Dis* 2006; 1: 21.
9. Stratakis C, Courcoutsakis N, Abati A, et al. Thyroid gland abnormalities in patients with the syndrome of spotty skin pigmentation, myxomas, endocrine overactivity, and schwannomas (Carney complex). *J Clin Endocrinol Metab* 1997; 82: 2037-43.
10. Papageorgiou T, Stratakis C. Ovarian tumors associated with multiple endocrine neoplasias and related syndromes. *Int J Gynecol Cancer* 2002; 12: 337-47.