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Catecholamine-induced cardiomyopathy triggered by pheochromocytoma

Miocardiopatía catecolamínica desencadenada por un feocromocitoma

Pheochromocytoma is a catecholamine-secreting tumor arising in the chromaffin cells of the sympathetic nervous system. Its prevalence is not well known. It is estimated to occur in 1-2/100, adults/year, and represents 0.3%-1.9% of secondary causes of arterial hypertension in the general population. Pheochromocytoma is a common cause of adrenal incidentaloma, accounting for 6.5% of such tumors[1].

Increased blood catecholamine levels have multiple effects in different organs. The typical clinical presentation of pheochromocytoma includes headache, palpitations, sweating, and arterial hypertension. Other signs, such as abdominal pain, shock, respiratory distress syndrome, pulmonary edema, and hyperthermia occur less frequently. Increased catecholamine levels may cause structural and biochemical damage to the myocardium. This involvement is called catecholamine-induced cardiomyopathy.

We report a pheochromocytoma which was diagnosed based on a catecholamine-induced cardiomyopathy, and briefly review cardiac impairment caused by catecholamines.

A 48-year-old female patient, a former smoker with a history of difficult to control hypertension and dyslipidemia on treatment, was admitted to the department of endocrinology and nutrition of our hospital for work-up and management of a pheochromocytoma.

In April 2008, the patient attended the emergency room of another hospital reporting tight, non-radiating retrosternal pain over the previous few days. The pain did not change on deep inspiration or with postural changes, nor after sublingual nitroglycerin administration. She reported symptoms consistent with upper respiratory tract infection over the previous three weeks, with no dysthermic sensation or fever measured. Physical examination (PE) findings were normal, and an ECG revealed sinus rhythm at 75 bpm with pointed T waves from V3 to V5 and negative T wave in aVL. Laboratory test results included: a WBC count of 20.1 x 10^9/L, high fibrinogen levels (447 mg/dL), blood glucose 219 mg/dL, creatinine 1.63 mg/dL and calculated clearance (GFR) of 36 mL/min, urea 56 mg/dL, CK 491 U/L, troponin T 3,63 ng/mL, total cholesterol 283 mg/dL, HDL-C 85 mg/dL, LDL-C 183.6 mg/dL and triglycerides 72 mg/dL. The patient was admitted to the ICU with a diagnosis of acute coronary syndrome. An echocardiogram showed global hypokinesis of the left ventricle, more marked in the anteroseptal, medioapical, and posteromedial segments, with an EF of 40%. Heart catheterization showed normal coronary arteries and an EF of 42%. ECG findings, myocardial damage markers, and kidney function normalized during her stay at the ICU.

An echocardiogram performed one week later showed full recovery, and the patient was discharged from hospital with the diagnoses of myopericarditis, hypertension, and dyslipidemia. Enalapril 5 mg/day and simvastatin 20 mg/day were prescribed.

In June 2009, the patient returned to the emergency room of the same hospital reporting malaise, nausea, vomiting, joint pain, and a temperature of 37.8ºC for the previous two days, and palpitations and tight retrosternal pain radiating to both upper limbs for the previous 24 hours. During the previous year she had experienced several crises of difficult to control hypertension, alternating with occurrences of a fainting sensation coinciding with blood pressure (BP) values of 90/60 mmHg. The patient also reported palpitations, insomnia, restlessness, headache, asthenia, and a weight loss of 5 kg over the previous 4 months. She had no piloerection or sweating.

PE revealed a poor general appearance and skin pallor. BP was 170/110 mmHg. An ECG showed sinus rhythm at 90 bpm with ST depression in the anterior and inferior aspects. The results of emergency laboratory tests included CK 757 U/L, troponin T 3.37 ng/mL, CK-MB 82 IU/L, and creatinine 1.4 mg/dL (GFR: 43 mL/min). Chest X-rays revealed hilar engorgement with vascular redistribution.

An echocardiogram showed severe hypokinesis of anterior septal, basal, inferior, and posterior segments with normal systolic function. During her stay at the ICU the patient remained clinically stable, with a disappearance of pain and a trend to hypotension. Cardiac enzymes and kidney function normalized. Anti-inflammatory treatment was started for a suspected new episode of myopericarditis, and the patient was discharged to internal medicine, where a contrast-enhanced computed tomography of the chest and abdomen was requested to rule out a tumor. CT disclosed a heterogeneous mass in the right adrenal gland, 44 mm in largest diameter. A ^{123}I-MIBG scan showed increased uptake in the right adrenal gland and no significant changes in other locations.

Based on these results, the patient was referred to our center for work-up and management of a possible pheochromocytoma. At our department, PE findings were normal. The results of 24-hour urine tests included:

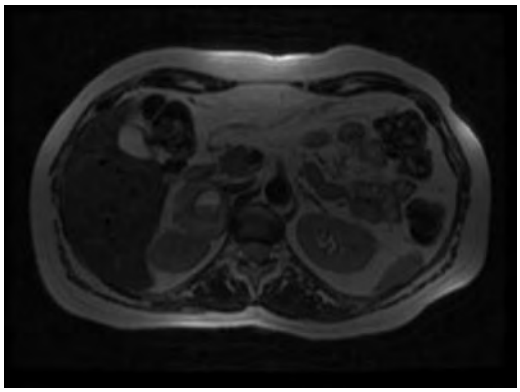

Figure 1 Abdominal MRI. Axial section in T2 showing a heterogeneous 5 x 4 cm space-occupying lesion located in the right adrenal gland, with a cystic-necrotic 25-mm central area which displaces the upper pole of the right kidney posteriorly, contacts the vena cava, and is only a few millimeters away from the right renal hilum. No changes in the left adrenal gland.

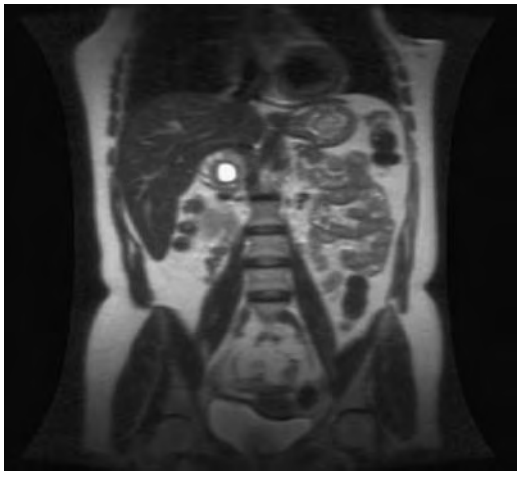

Figure 2 Abdominal MRI. Coronal section in T2 showing a heterogeneous 5 x 4 cm space-occupying lesion located in the right adrenal gland. No changes in the left adrenal gland.

vanilmandelic acid 25.4 mg/24 h (2.9-11), normetanephrine 3,615.3 µg/24 h (105-354), metanephrines 4,376.7 µg/24 h (74-297), total metanephrines 8,380.8 µg/24 h (0-1,000), norepinephrine 186.3 µg/24 h (23-105), epinephrine 224.1 µg/24 h (4-20), dopamine 189 µg/24 h (190-450), total catecholamines 599.4 µg/24 h (217-575). The following plasma levels were measured: norepinephrine 1,284 pg/mL (135-300 pg/mL), epinephrine 856 pg/mL (20-60 pg/mL), dopamine 10 pg/mL (10-50 pg/mL), and chomogranin A 871 ng/mL (19.4-98.1 ng/mL).

ECG, echocardiogram, chest X-rays, and liver ultrasound were normal. Abdominal magnetic resonance imaging showed a heterogeneous 5 x 4 cm mass located in the right adrenal gland, with a cystic-necrotic 25-mm central area, which had displaced the upper pole of the right kidney, contacted the vena cava, and was only a few millimeters away from the right renal hilum. The left adrenal gland was not affected and the rest of examination was normal (Fig. 1 and Fig. 2).

Treatment was started with phenoxybenzamine 10 mg/12 h. Subsequently, enalapril was discontinued and phenoxybenzamine dosage was increased to 20 mg/12 h. During admission, the patient remained symptom-free, with a normal heart rate. The patient experienced tachycardia a few days following discharge, and was therefore prescribed propranolol 10 mg/8 h by the oral route, which normalized heart rate. Laparoscopic right adrenalectomy was performed some weeks later with no complications.

At the time of writing, the patient was stable and asymptomatic, with normal BP values, and had experienced no new episodes of chest pain.

Catecholamines and their oxidation products may have a toxic effect upon the myocardium, either directly or mediated by the beta-adrenergic receptor[2], as occurred in our patient. Myocardial oxygen consumption is increased, and coronary artery spasm may occur[3]. Long-term catecholamine elevation leads to the down-regulation of beta-adrenergic receptors, with a suboptimal myofiber function and a decrease in the number of contractile units[4]. All of these result in catecholamine-induced cardiomyopathy. The etiology of catecholamine-induced cardiomyopathy includes, in addition to pheochromocytoma, catecholamine elevation secondary to stress, solvent abuse, chronic overuse of epinephrine inhalers (asthma), long-term amphetamine use, Tako-Tsubo syndrome, cardiotoxicity of scorpion venom, septic cardiomyopathy, and baclofen withdrawal[5].

The clinical characteristics of cardiomyopathy related to pheochromocytoma include: arterial hypertension, hypertrophic or dilated cardiomyopathy, acute lung edema due to cardiogenic and non-cardiogenic factors (by a direct effect of catecholamines in the lungs increasing pulmonary capillary permeability and pulmonary venous tone, and damaging the pulmonary capillary endothelium), myocardial stunning, ECG changes, cardiac arrhythmia, and cardiac arrest.

ECG changes include right axis deviation, poor R wave progression, non-specific ST segment and T wave changes, prominent U waves, arrhythmia (sinus tachycardia and bradycardia, supraventricular tachycardia, ventricular extrasystole, and sick sinus syndrome), and conduction disorders (right and left bundle branch block)[3].

Myocardial stunning caused by catecholamines has been implicated in the pathogenesis of stress-induced cardiomyopathy[6]. Autopsy studies in patients who died from pheochromocytomas revealed active myocarditis with left ventricular failure and pulmonary edema in half of them[7]. Structural changes include local degeneration and band necrosis of myocytes, infiltration by inflammatory cells, media thickening in medium-sized and small coronary arteries, and interstitial fibrosis. There may also be defective storage of endogenous amines and increased levels of free fatty acids in the myocyte[8].

The lack of adequate criteria for establishing a diagnosis of catecholamine-induced cardiomyopathy and the low incidence and prevalence of pheochromocytomas make this clinical condition difficult to diagnose, as occurred in the reported patient, in whom diagnosis was delayed by at least one year.

Cardiac involvement may be the main clinical manifestation of a pheochromocytoma. The prognosis of catecholamine-induced cardiomyopathy associated with a pheochromocytoma depends on its early identification and medical and surgical treatment. In addition, recognition of catecholamine-induced cardiomyopathy, particularly in patients with a pheochromocytoma, is important not only because the myocardium returns to normal within a few months of treatment, but also to avoid factors that may trigger a catecholaminergic crisis.

When a pheochromocytoma is suspected, there is no agreement as to what the most accurate diagnostic test is. A multicenter study concluded that the most sensitive parameter is plasma metanephrine level (99%), followed by fractionated urinary metanephrines (97%), with statistically significant differences versus all other parameters (urinary catecholamines, 86%; plasma catecholamines, 84%; total urinary metanephrines, 77%; and vanilmandelic acid, 64%). The most specific test is measurement of vanilmandelic acid (95%), followed by levels of total urinary metanephrines, plasma metanephrines (89%), urinary catecholamines (88%), plasma catecholamines (81%), and fractionated urinary metanephrines (69%)[9]. To confirm diagnosis, hormone levels should be at least twice the upper normal limit.

A pheochromocytoma is a very serious clinical condition and, based on these results, measurements of plasma metanephrine and fractionated urinary metanephrine levels are considered to be the most sensitive biochemical tests, and are therefore the tests of choice for diagnosis in order to avoid false negative results. Measurement of fractionated urinary metanephrines was sufficient for diagnosis of our patient. However, plasma catecholamine and plasma and urine metanephrine levels were measured to compare the sensitivity and specificity of the procedure at our laboratory.

Surgery is the treatment of choice for a pheochromocytoma. Preoperative drug preparation is a key factor for mortality reduction. While it has been suggested that long-term use of alpha-adrenergic blockade with drugs such as phenoxybenzamine is not always required for surgical preparation, the effectiveness of other types of treatment such as calcium channel blockers or captopril has not been investigated in patients with coexistent pheochromocytoma and catecholamine-induced cardiomyopathy[10].

To sum up, we report a case of a pheochromocytoma with an atypical clinical presentation in which cardiac involvement with an acute coronary syndrome led to diagnosis.

Conflict of interest

The authors state that they have no conflict of interest.

References

1. Mantero F, Terzolo M, Arnaldo G, Osella G, Masini AM, Ali A, et al, Study group in adrenal tumours of the Italian Society of Endocrinology. A survey on adrenal incidentaloma in Italy. J Clin Endocrinol Metab. 2000;85:637-44.
2. Brouri F, Findji L, Mediani O, Mougenot N, Hanoun N, Le Naour G, et al. Toxic cardiac effects of catecholamines: role of beta-adrenoceptor downregulation. Eur J Pharmacol. 2002;456:69-75.
3. William F, Young Jr, editors. Williams Textbook of Endocrinology. 9.a ed. Saunders Elsevier p. 705–7.
4. Fripp RR, Lee JC, Downing SE. Inotropic responsiveness of the heart in catecholamine cardiomyopathy. Am Heart J. 1981;101:17-21.
5. Dickinson BD, Altman RD, Deitchman SD, Champion HC. Safety of over-the-counter inhalers for asthma: report of the council on scientific affairs. Chest. 2000;118:522-6.
6. Kassim TA, Clarke DD, Mai VQ, Clyde PW, Mohamed Shakir KM. Catecholamine- induced cardiomyopathy. Endocr Pract. 2008;14:1137-49.
7. Rona G. Catecholamine cardiotoxicity. J Mol Cell Cardiol. 1985;17:291-306.
8. Westaby S, Shahir A, Sadler G, Flynn F, Ormerod O. Mechanical bridge to recovery in pheochromocytoma myocarditis. Nat Rev Cardiol. 2009;6:482-7.
9. Lenders JW, Pacak K, Walter MM, Linehan WM, Mannelli M, Friberg P, et al. Biochemical diagnosis of pheochromocytoma. Which test is best? JAMA. 2002;287:1427-34.
10. Pacak K. Preoperative management of the pheochromocytoma patient. J Clin Endocrinol Metab. 2007;92:4069-79.

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Carcinoid tumor and patent foramen ovale

Tumor carcinoide y foramen oval permeable

Carcinoid tumors are derived from neuroendocrine cells. They are uncommon (2-5 cases per 100,000 inhabitants/year)[1], but their incidence has increased in recent decades, partly as the result of increasingly perfected diagnostic procedures. Locally invasive or metastatic tumors usually cause a carcinoid syndrome. Once this is established, symptoms of heart involvement (carcinoid heart disease), generally affecting the right valves, occur in more than half of all cases[2].

We report the case of a 73-year-old male patient who attended for diarrhea and episodes of flushing and hot flashes. He had a history of smoking, arterial hypertension, diabetes mellitus, and clinically stable ischemic heart disease. Physical examination revealed facial telangiectasis,