A rare case report of hypertrophic cardiomyopathy induced by catecholamine-producing tumor

Federica Olmati, MD, Luigi Petramala, MD, PhD, Valeria Bisogni, MD, Antonio Concistré, MD, Vincenza Saracino, MD, Gaia Oliviero, MD, Maria Bonvicini, MD, Martina Mezzadri, MD, Antonio Ciardi, MD, Gino Iannucci, MD, Giorgio De Toma, MD, Andrea Frustaci, MD, PhD, Claudio Letizia, MD, PhD*

Abstract

Rationale: Catecholamine-producing tumors are rare, occurring in less than 0.2% of patients with hypertension, but can have relevant cardiovascular morbidity and mortality.

Patient concerns: A 37-year-old woman presented with a history of dyspnea, chest pain, palpitations, and paroxysmal hypertension. Electrocardiogram, echocardiogram, and cardiac magnetic resonance showed severe LVH with a prevalent involvement of the anterior portion of interventricular septum. Endomyocardial biopsy found severe hypertrophy with disarray of cardiomyocytes and ultrastructural evidence of contraction and necrosis of myocytes. Hormone investigations revealed high values of 24-hours urinary metanephrines. Abdominal computed tomography (CT) showed an enlarged left adrenal gland with a strong uptake of 123I−metaiodobenzylguanidine at scintigraphy scan.

Interventions: Thus, the adrenal tumor was surgically removed.

Diagnosis and lessons: We report a rare case of catecholamine-induced cardiomyopathy due to an adrenal adenoma mixed with nodules enriched in epinephrine-types secreting granules.

Abbreviations: 123I−MIBG = 123I−Metaiodobenzylguanidine, BP = blood pressure, CT = computed tomography, DXM = dexamethasone, HCM = hypertrophic cardiomyopathy, HR = heart rate, IVS = interventricular septum, LV = left ventricle, LVEF = left ventricular ejection fraction, LVH = left ventricular hypertrophy, MR = magnetic resonance, PHEO = Pheochromocytoma, SAM = systolic anterior motion.

Keywords: adrenal adenoma, catecholamine-induced cardiomyopathy, endomyocardial biopsy, pheochromocytoma

1. Introduction

Pheochromocytoma (PHEO), literally “tumor that is colored with salts chromium”, is a rare neuroendocrine neoplasm arising from chromaffin cells, which is typically found in the adrenal medulla.[1] The PHEOs originate from sympathetic nervous system, synthetize and secrete catecholamines and their metabolites. Clinical presentation is characterized by extreme variability, and most frequent symptoms are palpitations, headaches, and diaphoresis, associated with high blood pressure values.[2,3]

The cardiovascular effects of the excessive catecholaminergic states can range from mild to dramatic or catastrophic. Compared to individuals with essential hypertension, those with PHEO have a 14-fold higher rate of cardiovascular events, including myocardial infarction, stroke, and cardiomyopathy.[4] In particular, PHEO has been attributed to cause types of cardiomyopathies, including peri-partum, dilated, Takotsubo, and hypertrophic forms.[5] It has been suggested that PHEO-related cardiomyopathy is caused by the excessive levels of plasmatic catecholamines, which are released from the tumor.[5]

However, the precise histological features of reversible cardiomyopathy in PHEO-patients are today not completely known. In this paper, we report a rare case of a patient with hypertrophic cardiomyopathy (HCM) due to an adrenal adenoma mixed with nodules enriched in adrenaline-types secretory granules.

2. Case report

A 37-year-old woman with a history of arterial hypertension and cutaneous B-follicular lymphoma presented with a history of dyspnea, chest pain, palpitations, and paroxysmal hypertension. Her current medications included irbesartan and hydrochlorothiazide. On admission, her blood pressure (BP) values were 170/100 mm Hg and her heart rate (HR) was 70 beats/min and

Editor: N/A.

The authors have no funding and conflicts of interest to disclose.

* Secondary Hypertension Unit, Department of Internal Medicine and Medical Specialties, University of Rome; 2 Department of Radiological, Oncological and Anatomical-Pathological Sciences, University of Rome; 3 Department of Surgery “P. Vaiudz”, University of Rome; 4 Department of Cardiovascular, Respiratory, Nephrology, Anesthesiology and Geriatric Sciences, University of Rome “La Sapienza” Rome, Italy.

Correspondence: Claudio Letizia, Department of Internal Medicine and Medical Specialties, Policlinico “ Umberto I”, University “Sapienza”, Rome 00155, Italy (e-mail: claudio.letizia@uniroma1.it).

Copyright © 2018 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-No Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Medicine (2018) 97:50(e13369)

Received: 4 August 2018 / Accepted: 31 October 2018

https://dx.doi.org/10.1097/MD.0000000000013369

100 mm Hg and her heart rate (HR) was 70 beats/min and
regular. Her respiratory rate was 20 breaths/min and her lungs were clear at the auscultation. The electrocardiogram (ECG) showed sinus rhythm; there were signs of left ventricular hypertrophy (LVH) with negative T waves in lateral leads, V5 and V6. The plasma proBNP concentration was 87 pg/mL, which was in normal range (normal values < 100 pg/ml). Other data, including electrolytes, troponin, creatinine kinase, creatinine were within the normal range. The chest X-ray film no revealed enlargement of the cardiac silhouette. A 2D transthoracic echocardiogram showed a dilatation of the left atrium (24 cm²) with severe LVH (end-diastolic intraventricular septum thickness—17 mm) and preserved left ventricular ejection fraction (LVEF—60%). Suspecting the presence of a cardiomyopathy a cardiac magnetic resonance (MR) imaging with gadolinium was performed and showed symmetric LVH with a prevalent involvement of the anterior portion of interventricular septum. A minimum left ventricular outflow obstruction was reported without an atypical systolic anterior motion of the mitral valve. A supposed diagnosis of HCM was made (Fig. 1). Heart muscle impairment was investigated by cardiac catheterization and angiography. Coronary angiography revealed no coronary artery stenosis. Catheterization was followed by a left ventricle endomyocardial biopsy extracting 4 fragments, which were processed for histology and electron microscopy. At the left ventricle endomyocardial biopsy myocytes demonstrated features of hypercontraction of myofilaments with formation of contraction bands and occasional cellular necrosis. Wide intracellular and perivascular fibrosis was seen. A significant number of arterioles showed thickened tunica with resulting vessel lumen reduction. Further, the endocardium was thickened with prominence of smooth muscle cells (Fig. 2). An electron microscopy showed at higher magnification the catecholamine-induced diffuse contraction band necrosis. This data was suggestive of catecholamine-induced LVH (Fig. 2).

A hormonal screening test for secondary arterial hypertension revealed an abnormal increase of 24-hours urinary metanephrines

Figure 1. Cardiac magnetic resonance (MR) showing moderate symmetric left ventricular hypertrophy (LVH), which mostly involves the anterior section of interventricular septum (IVS) in its basal and medial part (sectal thickness of anterior-basal part is 19 mm; inferior-basal part is 14 mm; anterior-medial part is 16 mm; inferior-basal part is 14 mm) and in middle portion of lateral wall (thickness 16 mm). The remaining part of myocardium has a thickness between 10 and 15 mm. This hypertrophy is responsible for a mild tightening-obstruction of the left ventricular outflow tract and a modest acceleration of flow, without an atypical systolic anterior motion of the mitral valve (SAM). Mild aortic and mitral valve regurgitation can been seen. LVH = left ventricular hypertrophy, IVS = interventricular septum, MR = magnetic resonance.

Figure 2. Microscopic findings of biopsy specimen from the endomyocardium of left ventricle showing markedly hypertrophied fibers, contraction bands and replacement fibrosis.
suggesting the presence of a PHEO (Table 1). A computed tomography (CT) scan showed an enlargement of the left adrenal gland with globe shape. The strongest uptake of $^{123}$I—Metaiodobenzylguanidine ($^{123}$I—MIBG) by the left adrenal lesion was observed in $^{123}$I—MIBG scintigraphy (Fig. 3).

Pre-operative management was begun with fluids and alpha-adrenergic receptor blockers, resulting in BP control. The patient underwent left laparoscopic adrenalectomy with no significant hemodynamic alterations during the procedure. The adrenal gland measured 3.5 x 2.5 x 2.0 cm and it had an altered profile due to the presence of a yellow nodule surrounded by a subtle fibrous capsule. Nodule was made of 2 cell populations arranged in nests of trabeculae: 1 minor cell line had eosinophilic granular cytoplasm, the other had clear vacuolated cytoplasm. The remaining left adrenal gland showed areas of cortical hyperplasia (Fig. 4). On the basis of these findings a histological diagnosis of cortical adenoma with adrenocortical hyperplasia was primarily made. Secondly, immunohistochemical staining revealed diffused positivity for synaptophysin and chromogranin. At electron microscopy the tumor cells contained lipid vacuoles and smooth endoplasmic reticulum, consisted with adrenocortical differentiation, along multiple intracytoplasmatic adrenaline-type, dense core neurosecretory granules (Fig. 5).

Considering these results a diagnosis of adrenocortical adenoma with mixed nodules enriched in adrenaline-type secretory granules was made.

The patient was discharged medicated with irbesartan 150 mg/day, amlodipine 5 mg/day, and hydrochlorothiazide 12.5 mg/day.

At 6 months follow up, the patient’s 24-hours urinary metanephrines levels were normalized (143 µg/24h) and the transthoracic echocardiography after surgery showed a reduction of end-diastolic intraventricular septum thickness (14 mm) (Table 2) associated to normalization of BP values (130/80 mm Hg).

### Discussion

This is a unique case, to our knowledge, of a catecholamine-induced HCM induced by a cortical adrenal adenoma with...

#### Table 1

|                      | At diagnosis | After surgery | Normal values          |
|----------------------|--------------|---------------|------------------------|
| **PLASMA**           |              |               |                        |
| Plasma renin activity| 2.0          | 2.7           | 0.2–2.7 ng/mL/h        |
| Plasma aldosterone concentration | 141         | 207           | 30–160 pg/mL         |
| Plasma cortisol      | 9            | 11.1          | 4.5–21 µg/dL         |
| Plasma cortisol post-overnight DXM-test | 12          | –             | < 50 pg/mL          |
| **URINE**            |              |               |                        |
| Free cortisol        | 126.3        | 78.3          | 58–403 µg/24h        |
| Urine aldosterone concentration | 19.0        | 30.7          | 2.8–34 µg/24h       |
| Metanephrines        | 396; 421∗    | 143           | 0–350 µg/24h        |
| Vanillyl mandelic acid | 6.7; 5.1∗  | 3.2           | 1–10 µg/24h         |

DXM = dexamethasone: 1 mg at 11:00 pm

∗Second sample collection

---

**Figure 3.** Scintigraphy with $^{123}$I-metaiodobenzylguanidine ($^{123}$I—MIBG) showed raised activity within the left adrenal gland, concordant with the mass.
adrenaline-neurosecretory granules inside. The appearance of these metabolites, stored into nodules enriched in multiple secretory granules, explains the strongest uptake of the left adrenal lesion in 123I-MIBG scintigraphy. Previously, false-positive results of MIBG imaging were reported in adrenal adenomas showing augmented tracer uptake.[6,7,8] We support that our case cannot be listed in those previously described because we demonstrated, by using electron microscopy, the existence of a complex network of neurosecretory granules, that are directly responsible of this clinical scenario.

Left ventricular endomyocardial biopsy has been crucial, in this case, to testify catecholamine-induced LVH. Use of endomyocardial biopsy in HCM is still controversial and is recommended only in infiltrative or storage diseases.[9] In patients with true HCM, left ventricular endomyocardial biopsy can be specifically useful to analyze the underlying causes of cardiac deterioration to demonstrate histological changes during the course of the disease, and finally to provide myocardial tissue for research purposes.[11]

Catecholamine-induced cardiomyopathy is defined by a reversible left ventricular dysfunction without evidence of obstructive coronary artery disease. Acute and chronic myocardial damage are the results of an exogenous or endogenous catecholamine excess.

Overactivation of the sympatho-adrenergic system is an essential process to support cardiovascular system during stressful conditions in critical illnesses.[12] Although, its prolonged and excessive stimulation is detrimental to cardiovascular system. Abnormal amounts of catecholamines, via the beta-1 adrenoceptor transduction pathway, induce directly intracellular calcium overload in cardiomyocytes.[13] Furthermore, these metabolites can also indirectly damage the heart, in particular via their oxidation during stressful situations, which generate oxygen radicals that provoke coronary artery spasm, arrhythmias and cardiac dysfunction.[14] On the other hand, long-term exposure to catecholamines down-regulate the expression of beta-adrenergic receptors, inducing the suboptimal function of myofibers and decreasing the number of contracting units. As the consequent result, PHEO-associated cardiomyopathy is histologically characterized by contraction band necrosis, neutrophil infiltration, and fibrosis.[15]

Similar mechanisms of myocardial toxicity, which originate from a hyper catecholaminergic state, have been described in case of cocaine abuse, including marked oxidative stress and mitochondrial dysfunction. Instead, chronic use of cocaine may results in various degrees of systolic and diastolic dysfunction, cardiac hypertrophy and dilatation. Histological features, such as in those cases of endogenous excess of

| Table 2 | Comparison of 2D Echocardiographic features before and 6 months after laparoscopy surgical treatment. |
|-----------------|-----------------------------------------------|
| At diagnosis    | After surgery                                |
| Left Ventricle (LV) posterior wall thickness in diastole (mm) | 13.0 | 12.2 |
| Interventricular septum (IVS) thickness in diastole, (mm)    | 17.0 | 15.0 |
| Systolic anterior motion of the mitral valve (SAM)            | Absent | Absent |
| Mitral regurgitation                                         | Mild  | Absent |
| Mean LV outflow gradient (mm Hg)                             | 35    | 22   |
| Ejection fraction (%)                                        | 60    | 60   |

NS = Interventricular septum, LV = Left Ventricle, SAM = Systolic anterior motion.
catecholamines, include loss of myofibrils, multiple foci of band contraction necrosis and fibrosis.[17]

Treatment of PHEO-associated cardiomyopathy is curative surgical resection of catecholamine-producing tumor. After the appropriate excision of PHEO, cardiomyopathy may definitely reverse. [18]

In summary, we have described a rare case of catecholamine–induced cardiomyopathy due to an adrenal adenoma mixed with nodules enriched in epinephrine-type secreting granules. The patient has provided informed consent for publication of this case report.

Author contributions

Data curation: Federica Olmati, Gaia Oliviero, Maria Bonvicini, Antonio Ciardi, Gino Iannucci.

Investigation: Vincenza Saracino, Martina Mezzadri.

Methodology: Valeria Bisogni, Antonio Concistré.

Supervision: Giorgio de Toma, Claudio Letizia.

Validation: Giorgio de Toma, Andrea Frustaci, Claudio Letizia.

Writing – original draft: Luigi Petramala, Andrea Frustaci, Claudio Letizia, Federica Olmati.

Writing – review & editing: Luigi Petramala, Federica Olmati.

References

[1] Plouin PF, Gimenez-Roqueplo AP. Pheochromocytomas and secreting paragangliomas. Orphanet J Rare Dis 2006;1:49.

[2] Sever PS, Roberts JC, Snell ME. Phaeochromocytoma. Clin Endocrinol Metab 1980;9:543–68.

[3] Bravo EL, Gifford RWJr. Current concepts. Pheochromocytoma: diagnosis, localization and management. N Engl J Med 1984;311:1298–303.

[4] Stolk RF, Bakx C, Mulder J, et al. Is the excess cardiovascular morbidity in pheochromocytoma related to blood pressure or to catecholamines? J Clin Endocrinol Metab 2013;98:1100–6.

[5] Batisse-Lignier M, Pereira B, Morteff P, et al. Acute and chronic pheochromocytoma-induced cardiomyopathies: different prognoses?: a systematic analytical review. Medicine [Baltimore] 2015;94:e2198.

[6] Alsabe R, Mazoujian G, Goates J, et al. Adrenal cortical tumors clinically mimicking pheochromocytoma. Am J Clin Pathol 1995;104:382–90.

[7] Sone H, Okuda Y, Nakamura Y, et al. Radioiodinated metaiodobenzylguanidine scintigraphy for pheochromocytoma. A false-positive case of adrenocortical adenoma and literature review. Horm Res 1996;46:138–42.

[8] Letizia C, De Toma G, Massa R, et al. False-positive diagnosis of adrenal pheochromocytoma on iodine-123-MIBG scan. J Endocrinol Invest 1998;21:779–83.

[9] Isabelle M, Vergeade A, Moritz F, et al. NADPH oxidase inhibition prevents cocaine-induced up-regulation of xanthine oxidoreductase and cardiac dysfunction. J Mol Cell Cardiol 2007;42:326–32.

[10] Frustaci A, Verarido R, Calderaru M, et al. Myocarditis in hypertrophic cardiomyopathy patients presenting acute clinical deterioration. Eur Heart J 2007;28:733–40.

[11] Cooper LT, Vaughman KL, Feldman AM, et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Circulation 2007;116:2216–33.

[12] Kassum TA, Clarke DD, Mai VQ, et al. Catecholamine-induced cardiomyopathy. Endocr Pract 2008;14:1137–49.

[13] Adamova A, Abdellatif Y, Dhalia NS. Role of the excessive amounts of circulating catecholamines and glucocorticoids in stress-induced heart disease. Can J Physiol Pharmacol 2009;87:493–514.

[14] Schwartz BG, Rezkalla S, Klomner RA. Cardiovascular effects of cocaine. Circulation 2010;122:2558–69.

[15] Chimenti C, Frustaci A. Contribution and risks of left ventricular endomyocardial biopsy in patients with cardiomyopathies: a retrospective study over a 28-year period. Circulation 2013;128:1531–41.

[16] Llaudet I, Calderari B, Pacher P. Pathophysiological mechanisms of catecholamine and cocaine-mediated cardiotoxicity. Heart Fail Rev 2014;19:815–24.

[17] de Miguel V, Arias A, Passan A, et al. Catecholamine-induced myocarditis in pheochromocytoma. Circulation 2014;129:1348–9.

[18] Zielen P, Klisiewicz A, Januszewicz A, et al. Pheochromocytoma-related ’classic’ takotsubo cardiomyopathy. J Hum Hypertens 2010;24:363–6.