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Case Report Open Access

Unusual and Challenging Presentation of Hereditary Pheochromocytoma: Physicians Should Not Be Fooled - A Case Report

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Abstract

We present the case of a 45-year-old woman admitted to our hospital with acute heart failure and cardiogenic shock requiring stabilization with an intra-aortic balloon pump, inotropes and vasopressors. Nevertheless, the patient developed a multi organ failure. Firstly, diagnosed as an acute myocarditis, bilateral pheochromocytoma was discovered with MRI scan and confirmed with urine and plasma metanephrines. Bilateral adrenalectomy was performed. The genetic testing revealed a mutation in the Neurofibromatosis type 1 gene. Given the life-threatening complications and the good prognosis after radical surgery, the diagnosis of pheochromocytoma should be quickly considered in patients presenting with unexplained cardiovascular compromise.

Keywords: Pheochromocytoma; Neurofibromatosis 1; Cardiovascular diseases; Neuroendocrine tumors; Hypertension

Introduction

Pheochromocytoma (PCC) and paraganglioma (PGL) are rare tumors arising from adrenomedullary cells and from sympathetic or parasympathetic ganglia respectively. About 80-85% of chromaffin cell tumors are PCCs, whereas 15-20% is PGLs. The prevalence of pheochromocytoma and paraganglioma (PPGL) in hypertensive patients varies between 0.2% and 0.6%, while PCC is observed in 5% of patients with adrenal incidentaloma. PCCs and sympathetic PGLs commonly produce catecholamines: epinephrine, norepinephrine and dopamine, while parasympathetic PGLs are often silent [1].

The rule that 10% of chromaffin tumors are paragangliomas, malignant, associated to genetic muta-tions, affect patients without arterial hypertension, have bilateral adrenals involvement and pediatric onset is not epidemiologically correct anymore. In fact, recent series reported that PPGL are associated to genetic mutation in up to 40% of cases [2]. 16 different PPGL susceptibility genes have been reported: NF1, RET, VHL, SDHD, SDHC, SDHB, SDHA, SDHAF2, FH, MDH2, EGLN1/PHD2, KIF1, SDH5/IDH1, TMEM127, MAX and HIF2α. SDHB, MAX and FH mutations are also considered good markers of aggressive clinical behavior. For these reasons, Endocrine Society and European Society of Endocrinology Guidelines recommend considering genetic tests in all patients with PPGL [1,3]. Many mutations in susceptibility genes for development of PPGLs have been identified in last years and research in this field has advanced our understanding in cancer biology.

PPGL were the first human tumor model found to carry an inherited mutation of a gene encoding a metabolic enzyme (SDHD). They are also pioneer models of genetic-based personalized medical care for example, in the management of multiple endocrine neoplasia type 2 (MEN2). In this pathology, the identification of a high-risk germline RET mutation can guide the need for early thyroidectomy to prevent medullary thyroid carcinoma, which is a co-occurring tumour in this disorder. PPGL also became the first tumors known to carry activating mutations of HIF2α, which had long been implicated in multiple human cancers and was suspected, but had never been genetically proved, to function as a bona fide oncogene [4].

Case Report

A 45-year-old woman was admitted to our emergency care unit presenting with rapidly worsening dyspnoea, orthopnoea and fatigue. In anamnesis there is neither prior cardiologic disease nor chronic medical treatment. At first medical contact, she presented severe hypotension (systolic blood pressure 80 mmHg) and oliguria. ECG showed rapid atrial fibrillation (150 bpm) of unknown date, with non-specific repolarization alterations. A first echocardiogram showed a non-dilated left ventricle (LV) with severely depressed ejection fraction (LVEF) of about 20%, characterized by diffuse hypokinesia. Laboratory findings showed a slight increase in myocardial necrosis markers without a significant curve, leucocytosis along with signs of acute renal and hepatic failure, and acidosis with lactate increasing.

The patient was immediately referred to the Cath lab and underwent coronary angiography that excluded significant coronary disease. Suspecting an acute myocarditis, an intra-aortic balloon pump (IABP) was positioned, with a sudden mild improvement in hemodynamic conditions, mean blood pressure and urine output. Acute renal failure was managed with a transient dialytic support. The patient, on the first day, developed a coagulopathy characterized by spontaneous INR increasing, fibrinogen and anti-thrombin III reduction, severe platelet reduction and bilirubin increase, both direct and indirect, consistent with intravascular disseminated coagulation. Massive melena developed, requiring red blood cells transfusion. The coagulopathy was treated with plasma and platelet transfusion for 10 days, and a progressive normalization was finally noted. At the same time, hemodynamic condition progressively improved: IABP was removed on the third day, LVEF progressively recovered until reaching

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50% ten days after the acute presentation. AF was treated with rate control and oral anticoagulation, due to the documentation of a large LV apical thrombus. During the management of acute complications, the geneticist suggested a clinical diagnosis of Neurofibromatosis type 1 (based on café-au-lait spots, small skin fibromas, axillary and inguinal freckling).

However, despite normalization of coagulation parameters, renal function and LVEF, high levels of direct bilirubin persisted, and patient developed sub-icterus. An abdominal echo scan was then performed, identifying dilated biliary ducts, without hepatic masses or alterations; kidneys were normal, but a right adrenal incidentaloma was discovered. To confirm the diagnosis for biliary tract pathology, an MRI diagnosed the presence of an ampulloma (20 mm) but it also evidenced left (6 mm) and right (40 mm) masses of adrenal glands (Figures 1, 2 and 3). High concentrations of urine and plasma free metanephrines (p-normetanephrines: 1518 and 2480 pmol/L, p-metanephrines: 3313 and 4222 pmol/L, u24h-normetanephrines: 437 and 509 mcg/die, u24h-metanephrines: 1386 and 1830 mcg/die), high Chromogranin A (>1100 ng/mL) and neuron specific enolase (19.6 ng/mL) levels suggested the diagnosis of pheochromocytoma (PCC). The presence of distant metastasis was excluded with brain-neck-thoracic CT scan and with 123I-MIBG and 111In-Pentetreotide Scintigraphies. Both imaging methods showed surprisingly a more intense tracers' uptake from left PCC without visualizing the ampulloma.

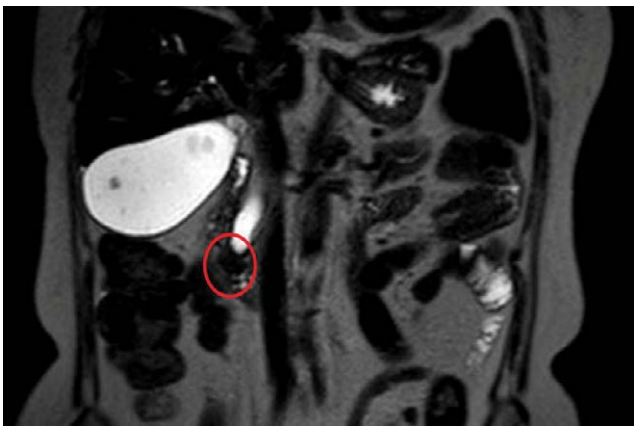

Figure 1: MRI image of 20 mm ampulloma (Pathological examination: Neuroendocrine tumor, G2 with muscular invasion – pT2 N0 M0).

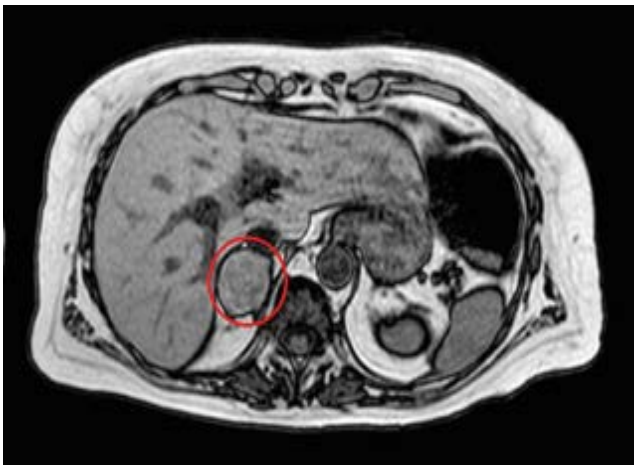

Figure 2: MRI image of right 40 mm PCC (Pathological examination: Ki67 2%).

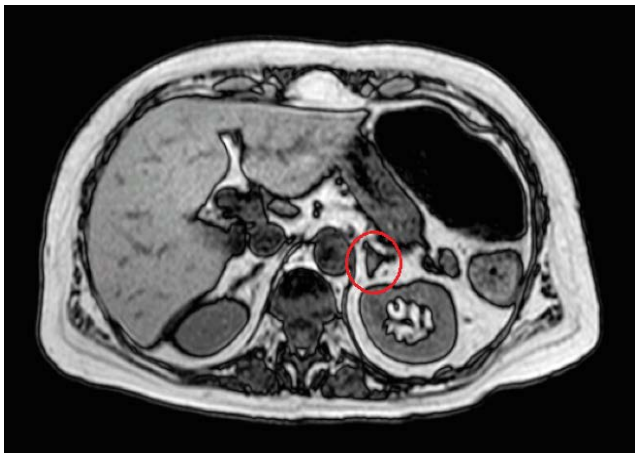

Figure 3: MRI image of left 6 mm PCC (Pathological examination: Vascular invasion, profound nuclear pleomorphism, mitosis 6x 10 HPF, Ki67 9%).

All tumors were surgically removed without complications. Pathologist confirmed the diagnosis of bilateral PCC (right adrenal gland: PCC of 40 mm, Ki67 2%; left adrenal gland: PCC of 5 mm with vascular invasion, profound nuclear pleomorphism, mitosis 6x 10 HPF, Ki67 9%) and of ampullary neuroendocrine tumor (G2 with muscular invasion – pT2 N0 M0). Results from genetic analysis confirmed the mutation in *NF-1* gene. After 3 year of regular follow-up, the patient presents good clinical conditions and has neither biochemical nor radiological evidence of disease recurrence.

Discussion

The present case describes a rare case of bilateral PCC in NF-1, presenting with acute heart failure and cardiogenic shock. It is important to early recognize this tumor to reduce related cardiovascular morbidity/mortality, prevent growth and extension into adjacent tissues, development of metastases and address syndromic forms. In our case, because of the clinical presentation, all diagnostic exams were directed towards acute myocarditis. The patient required hemodynamic support. Renal and hepatic failure, along with coagulopathy and melena, were considered as consequences of the cardiogenic shock.

Medical approach to PCC heterogeneous biochemical, pathological and clinical presentations is an example of precision medicine [2,3]. Genetic testing is a crucial moment of the PPGL management. In this case, the diagnosis of PCC and therefore the appropriate surgical treatment was established only after few weeks, when the patients, after recovering from the acute phase, presented persistent altered hepatic function, along with new diagnosis of hypertension. A prompt diagnosis could have directed the treatment properly in a faster time interval, avoiding time and diagnostic exams.

Some previous case reports described an acute presentation of PCC as a Tako-Tsubo-like cardiomyopathy sometimes accompanied by acute heart failure and cardiogenic shock [5-7]. However, in these series, patients presented with chest pain before symptoms of heart failure, not present in our patient. More relevant, our patient did not present ECG and echocardiographic features usually described in Tako-Tsubo cardiomyopathy, not only primary but also PCC-related. This original and myocarditis-mimicking presentation has already been reported among patients with PCC in single case reports [8-10]. Following these reports, PCC has been described as a possible cause of Tako-Tsubo cardiomyopathy, due to the effect of adrenergic stress deriving from massive catecholamine release from the tumor [11].

In the present case, PCC didn't mimic a typical or inverted Tako-Tsubo cardiomyopathy but presented similarly to an acute fulminant myocarditis [12]. The high inflammatory markers were consistent with this presentation. However, the patient didn't experience fever or chest pain. In this case, the diagnostic work-up was driven by the persistence of elevated cholestasis indices, suggesting an abdominal disease. In fact, PCC was identified through diagnostic exams performed to define the nature of the biliary duct mass.

Conclusion

We discuss a very rare case. In fact, bilateral PCC occurs only in 0.6% of patients with NF-1 [13]. Ampullary NET is a further clinical manifestation of the syndrome.

PPGLs should be quickly considered in patients with unexplained left ventricular failure, multi-or-gan failure, hypertensive crises, shock and without coronary artery disease. The diagnosis of PPGL is commonly based on measurements of metanephrines in plasma or urine. Waiting for diagnostic test results may delay rapid decisions on patient management or therapeutic interventions. The acute emergency situation is the only exception to the rule where imaging studies to search for a PPGL may be undertaken without biochemical evidence of a catecholamine producing tumour.

Conflict of Interest

The authors report no conflict of interest in this work.

References

1. Lenders JWM, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SKG, et al. (2014) Pheochromocytoma and paraganglioma: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 99: 1915-1942.
2. Mannelli M, Ianni L, Cilotti A, Conti A (1999) Pheochromocytoma in Italy: A multicentric retrospective study. Eur J Endocrinol 141: 619-624.
3. Björklund P, Pacak K, Crona J (2016) Precision medicine in pheochromocytoma and paraganglioma: Current and future concepts. J Int Med 280: 559-573.
4. Plouin PF, Amar L, Dekkers OM, Fassnach M, Gimenez-Roqueplo AP, et al. (2016) European society of endocrinology clinical practice guideline for long-term follow-up of patients operated on for a phaeochromocytoma or a paraganglioma. Eur J Endocrinol 174: 1-10.
5. Dahia PLM (2014) Pheochromocytoma and paraganglioma pathogenesis: Learning from genetic heterogeneity. Nat Rev Cancer 14: 108-119.
6. Lassnig E, Weber T, Auer J, Nömeyer R, Eber B (2009) Pheochromocytoma crisis presenting with shock and tako-tsubo-like cardiomyopathy. Int J Cardiol 134: 138-140.
7. Steppan J, Shields J, Lebron R (2011) Pheochromocytoma presenting as acute heart failure leading to cardiogenic shock and multiorgan failure. Case Rep Med 2011: 1-4.
8. Di Palma G, Daniele GP, Antonini-Canterin F, Piazza R, Nicolosi GL (2010) Cardiogenic shock with basal transient left ventricular ballooning (Takotsubo-like cardiomyopathy) as first presentation of pheochromocytoma. J Cardiovasc Med 11: 507-510.
9. Tanriver Y, Betz MJ, Nibbe L, Pfluger T, Beuschlein F, et al. (2010) Sepsis and cardiomyopathy as rare clinical manifestations of pheochromocytoma-two case report studies. Exp Clin Endocrinol Diab 118: 747-753.
10. Brukamp K, Goral S, Townsend RR, Silvestry FE, Torigian DA (2007) Rapidly reversible cardiogenic shock as a pheochromocytoma presentation. Am J Med 120: 1-2.
11. Nef HM, Möllmann H, Kostin S, Troidl C, Voss S, et al. (2007) Tako-Tsubo cardiomyopathy: Intraindividual structural analysis in the acute phase and after functional recovery. Eur Heart J 28: 2456-2464.
12. Ferner RE, Huson SM, Thomas N, Moss C, Willshaw H, et al. (2007) Guidelines for the diagnosis and management of individuals with neurofibromatosis. J Med Genet 44: 81-88.
13. Bausch B, Borozdin W, Neumann HPH (2006) Clinical and genetic characteristics of patients with neurofibromatosis type 1 and pheochromocytoma. New Eng J Med 354: 2729-2731.