ESC European Society of Cardiology

European Heart Journal - Case Reports (2022) **6**(3), 1–6
https://doi.org/10.1093/ehjcr/ytac098

CASE SERIES
Arrhythmias/electrophysiology

Adrenal pheochromocytoma as a rare cause of reversible left ventricular systolic dysfunction and malignant arrhythmias: a case series

Dominik Jenča [1,2]*, Miloš Kubánek[1], Michal Kudla [3], Nevenka Solar[4], and Josef Kautzner [1,5]

[1]Department of Cardiology, Institute for Clinical and Experimental Medicine, Vídeňská 1958/9, Prague, Czech Republic; [2]Third Faculty of Medicine, Charles University, Prague, Czech Republic; [3]Department of Transplant Surgery, Institute for Clinical and Experimental Medicine, Prague, Czech Republic; [4]Department of Nuclear Medicine, Institute for Clinical and Experimental Medicine, Prague, Czech Republic; and [5]Faculty of Medicine and Dentistry, Palacký University, Olomouc, Czech Republic

Received 20 August 2021; first decision 21 September 2021; accepted 12 January 2022; online publish-ahead-of-print 7 March 2022

For the podcast associated with this article, please *visit https://academic.oup.com/ehjcr/pages/podcast*

Background Pheochromocytoma is a neuroendocrine tumour originating from the chromaffin cells of adrenal glands or sympathetic paraganglia. It produces most frequently norepinephrine, epinephrine, and dopamine. As a result of non-specific and variable clinical presentation, pheochromocytoma is difficult to diagnose.

Case summary A 37-year-old female without medical history and 57-year-old male patient with diabetes, arterial hypertension, and aortic valve replacement with a mechanical prosthesis were admitted to the hospital after successful cardiopulmonary resuscitation due to ventricular fibrillation. In both patients, coronary angiography demonstrated a normal finding, and echocardiography showed left ventricular (LV) contractile dysfunction with improvement in the subsequent examination. In the first patient, the diagnosis of stress-induced cardiomyopathy was considered as the most probable cause. She was later admitted to hospital due to acute pulmonary oedema with hypertensive crisis. Echocardiography documented reversible LV systolic dysfunction with improvement after 3 days. The course of hospitalization of the male was complicated by multiorgan dysfunction syndrome comprising renal failure, paralytic ileus, and pancreatic irritation, which normalized after 2 weeks. The diagnosis of pheochromocytoma was confirmed by laboratory tests and imaging methods. After pharmacological pre-treatment with doxazosin in both patients and bisoprolol in the female, successful adrenalectomies were performed with no relapse of tumour.

Discussion We describe an atypical clinical presentation of pheochromocytoma with initial cardiac arrest due to ventricular fibrillation and reversible LV systolic dysfunction. Our cases underline that clinical suspicion of pheochromocytoma as a potentially correctable cause should be raised in unexplained cases of severe heart failure, ventricular arrhythmias, and cardiac arrest.

Keywords Pheochromocytoma • Catecholamines • Adrenergic cardiomyopathy • Ventricular arrhythmia • Cardiac arrest • Case report

ESC Curriculum 2.2 Echocardiography • 6.4 Acute heart failure • 5.6 Ventricular arrhythmia

* Corresponding author. Tel: +420261365047, Fax: +420 261362989, Email: dominik.jenca@ikem.cz
Handling Editor: Ching-Hui Sia
Peer-reviewers: Andriana Anagnostopoulou; Richard Ang
Compliance Editor: Reshma Amin
Supplementary Material Editor: Nida Ahmed

Learning points

- Pheochromocytoma is a neuroendocrine tumour that produces a spectrum of biologically active substances, most frequently norepinephrine, epinephrine, and dopamine.
- Clinical presentation of pheochromocytoma is variable: arterial hypertension is a leading manifestation, other cardiovascular presentations include atrial or ventricular tachyarrhythmias, adrenergic cardiomyopathy, cardiogenic shock, and stroke.
- Pheochromocytoma should be considered in any cardiomyopathy, cardiac arrest, or cardiogenic shock of uncertain aetiology as a potentially correctable cause.

Introduction

Pheochromocytoma is a neuroendocrine tumour originating from the chromaffin cells of adrenal glands or sympathetic paraganglia. The tumour most frequently produces norepinephrine, epinephrine, and dopamine. Occasionally, it remains biochemically silent. With an incidence of 2–8 cases per 1 000 000 adults, pheochromocytoma is a rare disease.[1] It most often affects women with a mean age of 46 years.[2] Recent genetic analysis has revealed epigenetic aberrations in a substantial proportion of patients with pheochromocytoma and paraganglioma.[3]

Clinical presentation of pheochromocytoma depends on the quantity and composition of hormones produced. Most symptoms are non-specific, like headaches, palpitations, sudden paleness, excessive sweating, and weight loss. Arterial hypertension is a principle manifestation of pheochromocytoma and can occur in paroxysmal form only. Other cardiovascular presentations include atrial or ventricular tachyarrhythmias (VT), cardiogenic shock due to adrenergic cardiomyopathy, and stroke.[4] As a result, pheochromocytoma is difficult to diagnose. Clinical suspicion of pheochromocytoma should be raised in unexplained cases of severe heart failure and ventricular arrhythmias.

In our case reports, we describe an atypical clinical presentation of pheochromocytoma with initial cardiac arrest due to ventricular fibrillation (VF) and reversible left ventricular (LV) systolic dysfunction. The subsequent evaluation established the correct diagnosis, resulting in successful treatment by adrenalectomy.

Timeline

	Date	Description
Case 1	Index date	Index hospitalization after successful cardiopulmonary resuscitation due to ventricular fibrillation
	1 months	Implantation of implantable cardioverter-defibrillator (ICD)
	13 months	Hospitalization due to acute pulmonary oedema and hypertensive crisis
	14 months	Diagnosis of pheochromocytoma of the left adrenal gland
	15 months	Laparoscopic adrenalectomy after pharmacological pre-treatment, histological confirmation of pheochromocytoma
	4 years 1 month	Last interrogation of ICD with no arrhythmia detected to this date, tumour is in remission
Case 2	Index date	Index hospitalization due to cardiac arrest caused by refractory ventricular fibrillation
	Index date	Diagnosis of pheochromocytoma of right adrenal gland, implantation of ICD
	2 months	Adrenalectomy of right adrenal gland
	6 months	One episode of polymorphic ventricular tachyarrhythmias successfully treated by 1 36 J shock, tumour is in remission
	3 years 7 months	Upgrade to cardiac resynchronization therapy-defibrillator (CRT-D) due to heart failure
	4 years 9 months	Last interrogation of CRT-D with no ventricular arrhythmias
	4 years 9 months	Death of patient due to respiratory failure caused by pneumonia and heart failure

Case presentations

Case 1

A 37-year-old female was admitted to a regional hospital after successful cardiopulmonary resuscitation due to VF. Her medical history was negative except for paroxysms of palpitations, which prompted echocardiographic examination and electrocardiographic Holter monitoring resulting in normal findings. Emergency medical services were called to attend to the patient due to sudden weakness and palpitations. Prior to arrival, the patient experienced cardiac arrest. Fast polymorphic VT was the first documented rhythm, degenerating into VF. Two defibrillations and 300 mg of intravenous amiodarone resulted in the return of spontaneous circulation after 4 min of resuscitation. On admission, the patient was sedated, her blood pressure was 123/84 mmHg. Besides small excoriation of the right frontal area, physical examination showed normal findings. Electrocardiogram

revealed 1- to 2-mm descendent ST-segment depressions in the inferolateral leads with normal QTc interval. Echocardiography showed moderate LV contractile dysfunction with an end-diastolic diameter of 55 mm (upper reference limit) and a LV ejection fraction (EF) of 40%. Hypokinaesia of the basal and middle segments of the LV was observed with hypercontractility of the apex. Coronary angiography demonstrated a normal finding on coronary arteries. Laboratory tests revealed leucocytosis (initially 13.8, maximum 20.1 $\times$ 10^9/L) and mild metabolic acidosis. Dynamics of troponin I pointed to a significant myocardial lesion (2.73 μg/L, 37.29 μg/L, 21.19 μg/L, 6.08 μg/L; upper reference limit of 0.04 μg/L). The patient was extubated on the 3rd day. Subsequent echocardiographic examination revealed normalization of LV systolic function (EF of 62%) and only mild hypokinaesia of the basal segments. Magnetic resonance imaging (MRI) showed only a thin sub-epicardial strip of late gadolinium enhancement in the basal part of the LV inferior wall. Programmed ventricular stimulation induced only short bursts of polymorphic VT. Stress-induced cardiomyopathy was considered the most probable diagnosis. A single-chamber implantable cardioverter-defibrillator (ICD) was implanted for secondary prevention of sudden cardiac death. The patient was discharged on bisoprolol and ivabradine.

After 13 months, she developed acute pulmonary oedema with blood pressure of 230/130 mmHg with a spontaneous drop to normal values. Echocardiography documented a recurrence of LV systolic dysfunction with EF of 30% and preserved contractility of the apex, indicating an inverted form of stress cardiomyopathy. Her clinical status improved following intravenous administration of diuretics. Within 3 days, LV systolic function had improved, with EF increasing to 45–50%. Upon discharge, B-type natriuretic peptide and high-sensitivity cardiac troponin T had elevated to 539 ng/L (reference range 10–89 ng/L) and 33 ng/L (reference range 0–10 ng/L), respectively.

To test for suspected pheochromocytoma, serial plasma levels of metanephrine and normetanephrine were assessed over the next 2 weeks. The level of normetanephrine increased four- and five-fold in repeat examinations to 3.25 nmol/L and 3.914 nmol/L, respectively (reference values were 0.130–0.790 nmol/L). Abdominal ultrasound indicated a tumour of the left adrenal gland. A computed tomography (CT) scan confirmed an ovoid tumour with a diameter of 27 mm $\times$ 36 mm $\times$ 39 mm. Iodine-123 meta-iodobenzylguanidine (^{123}I-MIBG) single-photon emission computed tomography and low-dose CT (SPECT/CT) scans identified an accumulation of the tracer in the left adrenal gland (*Figure 1*). Laparoscopic adrenalectomy (LA) was performed after pharmacological pre-treatment with doxazosin and bisoprolol. Macroscopic observation revealed a circumscribed tumorous mass (3 cm in diameter) that did not invade neighbouring organs (*Figure 2A*). Perioperative hypertension was managed by intravenous administration of sodium nitroprusside and phentolamine. Hydrocortisone substitution was administered over 3 post-operative weeks. Nine days after surgery, plasma levels of (nor)metanephrines had returned to normal. Histology confirmed the diagnosis of pheochromocytoma (*Figure 2B* and *C*). After surgery, follow-up involved plasma metanephrine analysis every 6 months over a 2-year period and subsequently every 9 months. Abdominal ultrasound was performed annually. The tumour is currently in remission.

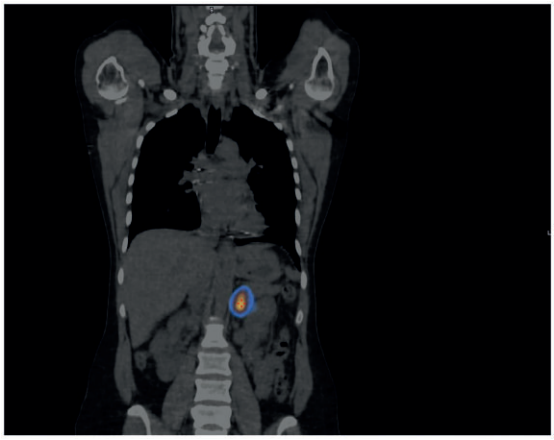


Figure 1 Hyperaccumulation of iodine-123 meta-iodobenzylguanidine in the left adrenal gland.

Case 2

A 57-year-old male patient with a history of type 2 diabetes, arterial hypertension, and aortic valve replacement with a mechanical prosthesis was admitted to our hospital after an out-of-hospital cardiac arrest caused by refractory VF. Prior to admission, his medication had included glimepiride, betaxolol, perindopril, amlodipine, and warfarin. Treatment involving 10 defibrillations supplemented with intravenous amiodarone (total dose of 450 mg) terminated the arrhythmia and recovered spontaneous circulation within 30 min. On admission, the patient was sedated, blood pressure was 110/70 mmHg. Physical examination revealed dilated pupils with sluggish reaction to light and right basal pulmonary crackles, all other findings were normal. Electrocardiogram showed an accelerated idioventricular rhythm (*Figure 3*). Bedside echocardiography revealed the normal function of the aortic valve prosthesis, moderate systolic dysfunction of the non-dilated LV with diffuse hypokinaesia, and an LV EF of 35% (*Videos 1* and *2*). Coronary angiography excluded a significant stenosis, with a brain CT scan revealing no signs of significant pathology. Laboratory tests showed significant leucocytosis (first value 29.6; peak level 33.7 $\times$ 10^9/L), metabolic acidosis, hyperglycaemia as well as elevated levels of aminotransferases, creatinine, and pancreatic amylase. Dynamic elevation of high-sensitivity cardiac troponin T suggested myocardial injury (initially 53.67 ng/L, the peak level of 1398 ng/L; upper referential limit of 14 ng/L). Therapeutic hypothermia was maintained for 24 h, with the patient extubated on the 3rd day. The course of hospitalization was complicated by multi-organ dysfunction syndrome comprising renal failure, paralytic ileus, and pancreatic irritation. Importantly, abdominal ultrasound detected a pathological mass between the liver and the right kidney. Urine analysis discovered a significant increase (9739 nmol/day—four-fold elevation) in the normetanephrines and a high plasma concentration of chromogranin A (317.1 ng/mL; reference values 0–85 ng/mL), a non-specific marker of a neuroendocrine tumour. Urine metanephrine and dopamine values were normal. A CT scan confirmed a large tumour of the right adrenal gland (38 mm $\times$ 35 mm $\times$ 43 mm) with a

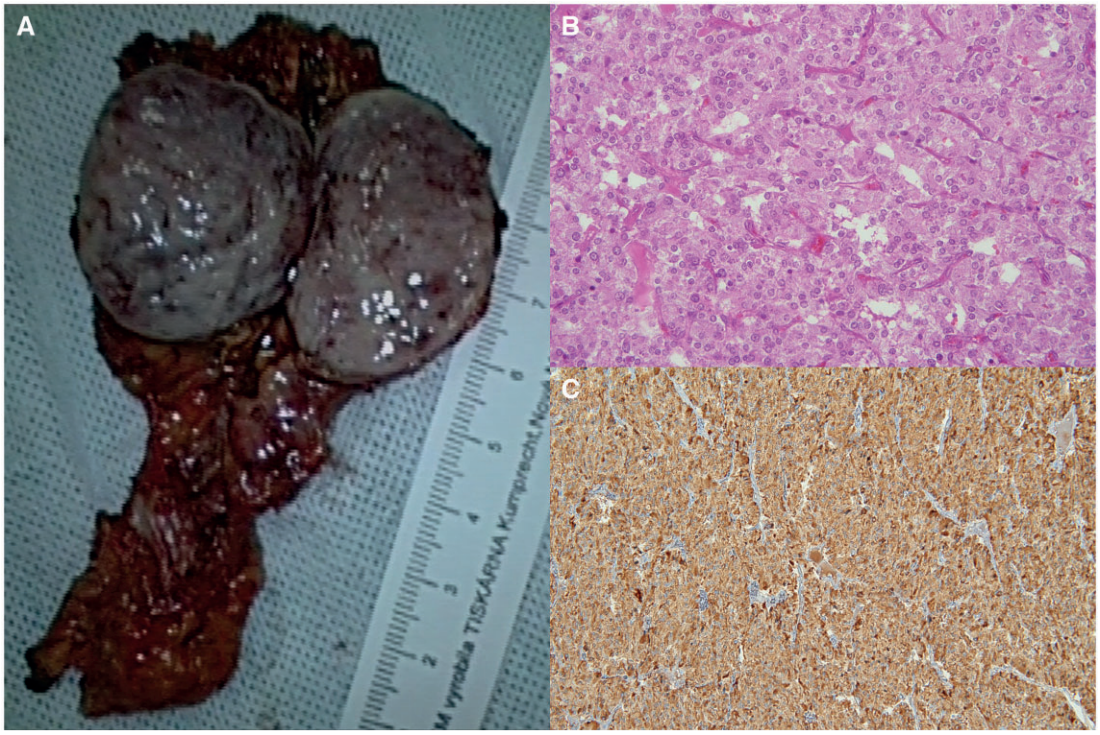


Figure 2 Microscopic and macroscopic findings from Case 1. (*A*) Pheochromocytoma in the explanted left adrenal gland; (*B*) haematoxylin and eosin staining; (*C*) chromogranin A staining.

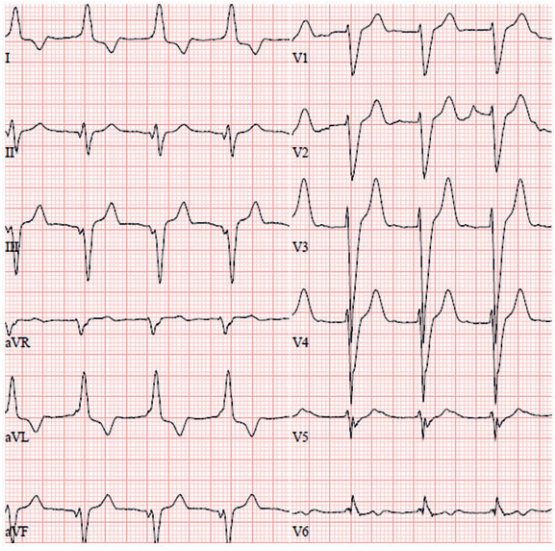
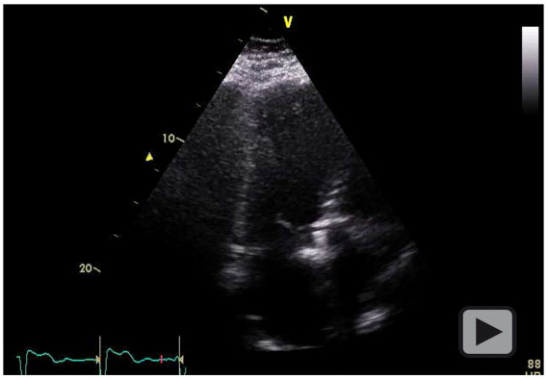


Figure 3 Accelerated idioventricular rhythm.

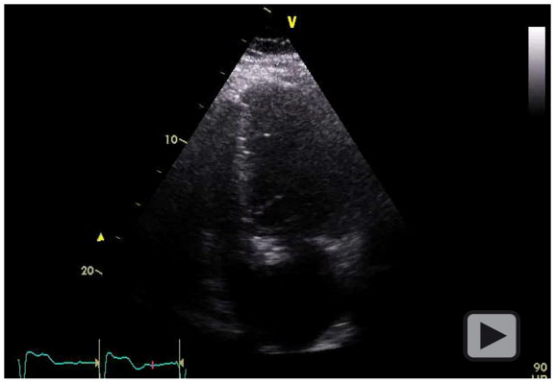


Video 1 Left ventricular systolic dysfunction with ejection fraction 35%.

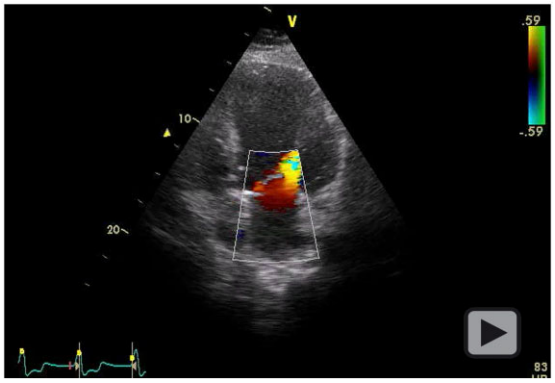
hyperaccumulation of ^{123}I-MIBG on SPECT. These findings were consistent with a diagnosis of pheochromocytoma.

After 2 weeks, the patient was normotensive and LV systolic function had normalized (*Video 3*). The only documented arrhythmia was a short paroxysm of atrial fibrillation. Although the cause of cardiac arrest was attributed to catecholamines, the patient had a history of aortic valve disease. Therefore, an ICD was implanted.

After doxazosin pre-treatment, the patient underwent LA, which was converted to open surgery due to patient habitus and anatomic conditions. Following surgery, concentrations of metanephrines and chromogranin A normalized and compensation of diabetes improved. Four months later, one episode of rapid polymorphic VT



Video 2 Left ventricular systolic dysfunction with ejection fraction 35%.



Video 3 Normalization of left ventricular systolic function.

(frequency 315/min) causing a presyncope was detected by ICD in the VF zone and subsequently was terminated by 1 shock (36 J). Follow-up consisted of metanephrine examination and abdominal ultrasound every 6 months, with no tumour relapse during this time. After 3 years and 7 months, the patient underwent an upgrade to cardiac resynchronization therapy with a defibrillator due to worsening systolic dysfunction and heart failure. The patient died 57 months after index hospitalization due to respiratory failure caused by pneumonia and decompensated heart failure.

Discussion

In our case series, we describe rare clinical presentations of pheochromocytoma with initial cardiac arrest due to VF and reversible LV systolic dysfunction. To our knowledge, this is the first series documenting two clinical cases of predominant cardiac manifestation of pheochromocytoma. Both patients exhibited LV systolic dysfunction, which was reversed within several days. The first case presented as an inverted form of takotsubo cardiomyopathy, with the second showing diffuse hypokinaesia of the non-dilated LV. Due to the absence of arterial hypertension at disease manifestation, pheochromocytoma was diagnosed in the first case 14 months after the initial presentation when the LV systolic dysfunction recurred; the diagnosis was accidental in the second case. Diagnostic procedures led to the correct diagnosis and successful adrenalectomy.

At least one in four patients with pheochromocytoma has a certain level of cardiac impairment with different phenotypes.[5] However, evidence of cardiac arrests in patients with pheochromocytoma is rare. Since 2000, only four case reports of pheochromocytoma linked to cardiac arrest have featured in the PubMed database. Two patients with ventricular arrhythmias had extremely high levels of adrenaline or its metabolites (25 and 30 times above the upper referential limit, respectively) as well as three- and five-fold increases of noradrenaline and normetanephrine.[6,7] In contrast, the patients from our case series had four- to five-fold elevations of normetanephrine levels, exhibited normal metanephrine levels, did not require any mechanical support, and were extubated early. We assume that the massive catecholamine excess observed in patients from these previous reports[6,7] explains the more serious course of hospitalization after cardiac arrest necessitating implantation of mechanical circulatory support.

Diagnostics of pheochromocytoma

Pheochromocytoma is diagnosed using biochemical and imaging methods. A four-fold or higher increase in urinary or plasma metanephrines confirms diagnosis.[8] In the case of borderline values, it is recommended to repeat testing and discontinue interfering medication and nutrients. The clonidine suppression test is helpful in cases where results are indistinct. Computed tomography and MRI both offer high sensitivity, but MRI is preferable for the detection of extra-adrenal tumours.[8] The SPECT with MIBG is essential for the identification of metastases and extra-adrenal neoplasia.

Management of pheochromocytoma

Fourteen-day pharmacological pre-treatment with non-selective phenoxybenzamine or selective alpha-1 blockers (doxazosin, terazosin) reduces the occurrence and severity of periprocedural hypertensive crises. Beta-blockers are suitable in cases of arrhythmias or insufficient blood pressure correction by alpha-blockers. However, administration of beta-blockers without alpha antagonists can provoke a hypertensive crisis caused by the unopposed suppression of beta-2-mediated vasodilation.[8] Calcium channel blockers may be used in the case of hypertension or in normotensive patients to mitigate the side effects of alpha-blockers. Pre-operative fluid expansion by infusion of crystalloids corrects hypovolaemia and reduces post-operative hypotension.

Laparoscopic adrenalectomy is a method of choice for tumours smaller than 6 cm. It is associated with lower complication rates and shorter hospitalization stays.[9] While LA may also be used for larger tumours, the odds of conversion to open procedures increase. Substantial damage of the capsule typically results in early conversion to open adrenalectomy.[9] Hypertensive crises are managed by

intravenous administration of short-acting phentolamine or by sodium nitroprusside; arrhythmias by esmolol.[9]

Rates of recurrence vary from 6.5% to 16.5% of patients.[10] A tumour size greater than 5 cm is an independent predictor of recurrence.[10] After adrenalectomy, lifelong follow-up of patients is recommended. This monitoring should involve annual CT scans and measurement of metanephrines at 1, 6, and 12 months and then annually.[10,11]

Secondary prevention of sudden cardiac death

Implantable cardioverter-defibrillator implantation in patients with cardiac arrest and pheochromocytoma is controversial. On the one hand, this tumour can be viewed as a reversible cause of cardiac arrest. On the other hand, myocardial fibrosis can arise after repeated excessive catecholamine exposure leading to an arrhythmogenic substrate. The male patient from our case series had an aortic valve replacement and impaired LV systolic function, which, in our view, necessitated ICD implantation. This decision proved correct, as one episode of fast VT occurred 4 months after adrenalectomy (while pheochromocytoma was in remission) and was successfully treated using one shock. In the female patient, an ICD was implanted before pheochromocytoma was correctly diagnosed, which underscores the need for pheochromocytoma to be included as a differential diagnosis for cardiac arrests of unknown origin.

Conclusion

Pheochromocytoma is a rare disease with heterogeneous clinical presentation. A combination of non-specific symptoms such as headaches, palpitations, sudden paleness, excessive sweating as well as other signs including weight loss, hyperglycaemia, and leucocytosis should alert clinicians to the possibility of such a diagnosis. Pheochromocytoma should also be considered in any cardiomyopathy, cardiac arrest, or cardiogenic shock of uncertain aetiology as a potentially correctable cause. The reversibility of LV systolic dysfunction and the unusual oscillation of systemic blood pressure can be diagnostic. Provided the tumour is treated early, heart impairment is reversible in 96% of cases.[2]

Lead author biography

Dr. Dominik Jenča graduated at Charles University in Prague. After spending 3 years at Internal department in Beroun he started working at Cardiology Department of Institute for Clinical and Experimental Medicine. He is an author of review article about heart failure after myocardial infarction, which is his area of focus.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent to submit and publish this case report, including images and associated documents, has been obtained from the patients in line with COPE guidance.

Conflict of interest: M.K. has received speaker honoraria from Boehringer Ingelheim, Biosense Webster, Biotronik, Boston Scientific, Daiichi Sankyo, Medtronic, Merck Sharp & Dohme, Pfizer, and St. Jude Medical (Abbott); and has served as a consultant for Bayer, Boehringer Ingelheim, Biosense Webster, Medtronic, Merit Medical, and St. Jude Medical (Abbott).

Funding: The research grant of the Ministry of Health, Czech Republic (NV19-08-00122) and by the project of Ministry of Health, Czech Republic for development of research organization 00023001 (IKEM, Prague, Czech Republic)- Institutional support.

References

1. Harari A, Inabnet WB 3rd. Malignant pheochromocytoma: a review. *Am J Surg* 2011;**201**:700–708.
2. Zhang R, Gupta D, Albert SG. Pheochromocytoma as a reversible cause of cardiomyopathy: analysis and review of the literature. *Int J Cardiol* 2017;**249**:319–323.
3. Björklund P, Backman S. Epigenetics of pheochromocytoma and paraganglioma. *Mol Cell Endocrinol* 2018;**469**:92–97.
4. Tsirlin A, Oo Y, Sharma R, Kansara A, Gliwa A, Banerji MA. Pheochromocytoma: a review. *Maturitas* 2014;**77**:229–238.
5. Gil-Barrionuevo E, Balibrea JM, Caubet E, Gonzalez O, Vilallonga R, Fort JM et al. Adrenergic cardiomyopathy and cardiogenic shock as initial presentation of pheochromocytoma. A case report and review of the literature. *Int J Surg Case Rep* 2018;**49**:145–148.
6. Chiu CC, Chen YC, Teng TH, Yang LH, Chen YP, Siao FY. Sudden cardiac arrest after minor abdominal trauma: a successful resuscitation in a patient with haemorrhagic phaeochromocytoma. *Resuscitation* 2009;**80**:1323–1324.
7. Mita K, Tsugita K, Yasuda Y, Matsuki Y, Obata Y, Matsuki Y et al. A successfully treated case of cardiac arrest after Caesarean section complicated by pheochromocytoma crisis and amniotic fluid embolism. *J Anesth* 2017;**31**:140–143.
8. Martucci VL, Pacak K. Pheochromocytoma and paraganglioma: diagnosis, genetics, management, and treatment. *Curr Probl Cancer* 2014;**38**:7–41.
9. Zografos GN, Vasiliadis G, Farfaras AN, Aggeli C, Digalakis M. Laparoscopic surgery for malignant adrenal tumors. *JSLS* 2009;**13**:196–202.
10. Press D, Akyuz M, Dural C, Aliyev S, Monteiro R, Mino J et al. Predictors of recurrence in pheochromocytoma. *Surgery* 2014;**156**:1523–1527; discussion 7–8.
11. Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, et al.; Endocrine Society. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2014;**99**:1915–1942.